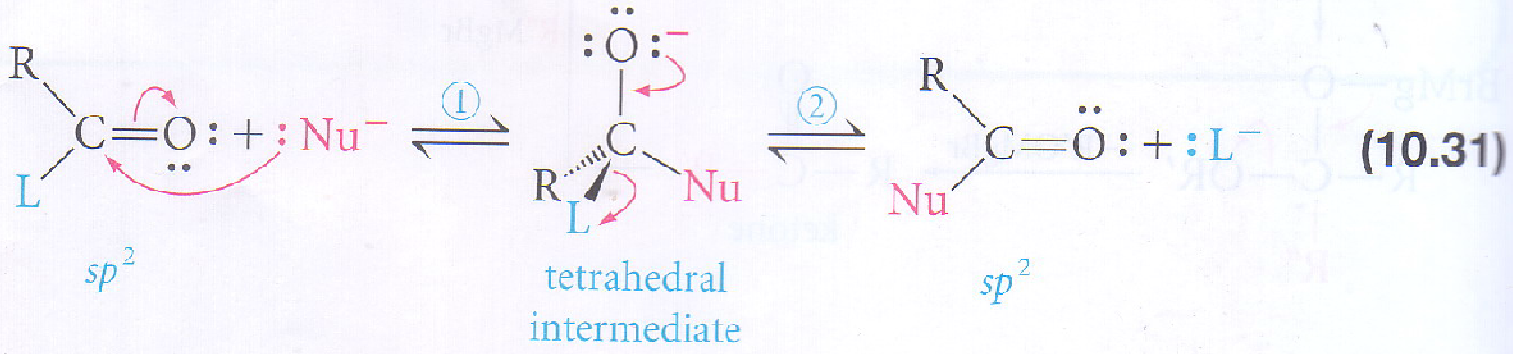
10.17 The Need for Activated Acyl Compounds

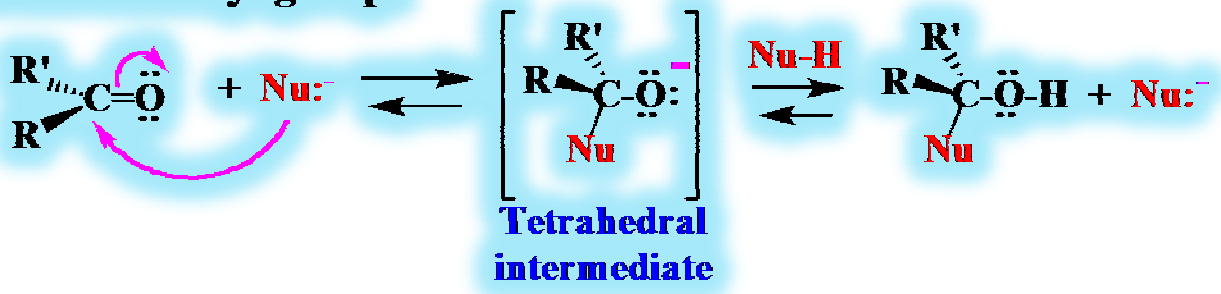
As we have seen, most reactions of carboxylic acids, esters, and related compounds involve, as the first step, nucleophilic attack on the carbonyl carbon atom. Examples are Fischer esterification, saponification and ammonolysis of esters, and the first stage of the reaction of esters with Grignard reagents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



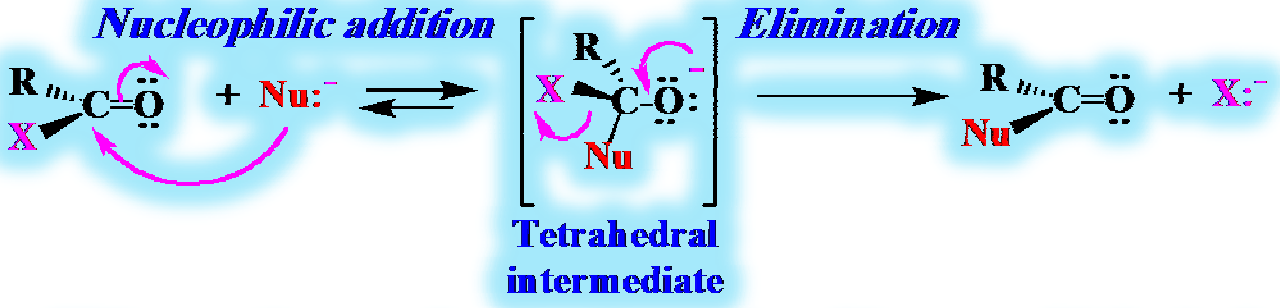
(10.31)

Nucleophilic Addition-Elimination at Acyl Carbon

Aldehydes and ketones undergo **nucleophilic additions** to the carbonyl group:

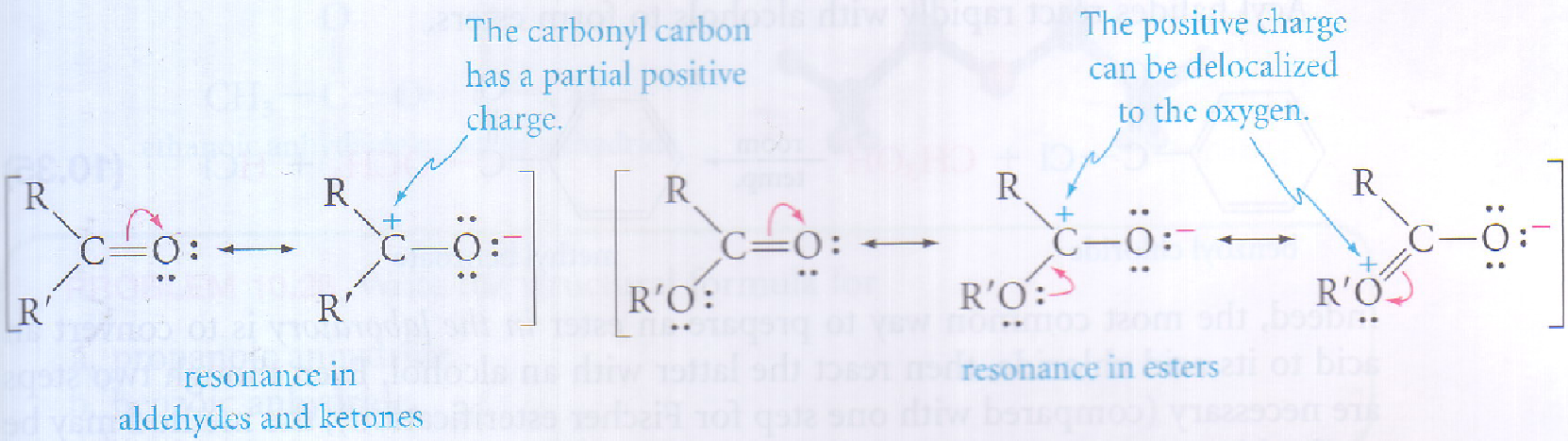


A typical reaction of carboxylic acids and their derivatives is **nucleophilic addition-elimination**. The first step is nucleophilic addition to the carbonyl to give a tetrahedral intermediate, but the presence of a good **leaving group (X)** at this site results in an elimination that regenerates the trigonal carbonyl.



This reaction mechanism is employed in many biological systems, and biochemists call them **acyl transfer reactions**.

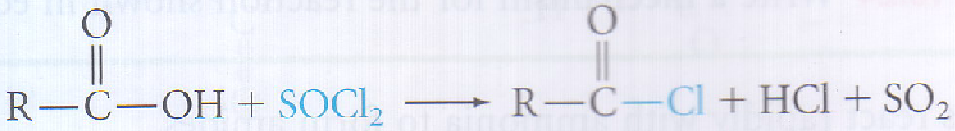
In general, esters are *less* reactive toward nucleophiles than are aldehydes or ketones because the positive charge on the carbonyl carbon in esters can be delocalized to the oxygen atom. Consequently, the ester is more stable and less prone to attack.



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

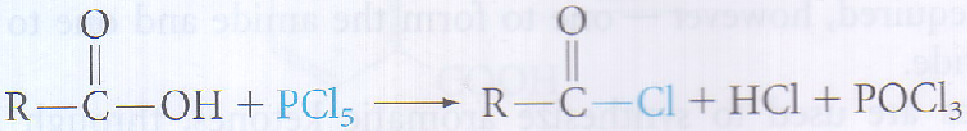
10.18 Acyl Halides

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



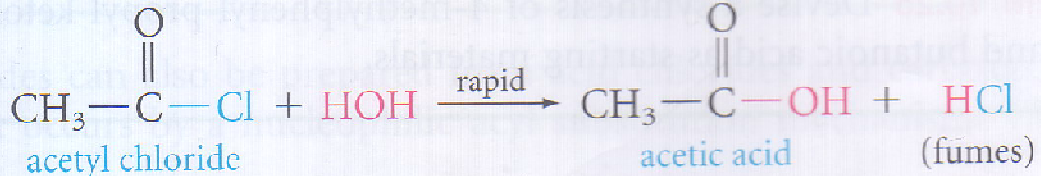
$$R-\overset{\overset{O}{\|}}{C}-OH + SOCl_2 \longrightarrow R-\overset{\overset{O}{\|}}{C}-Cl + HCl + SO_2 \qquad \textbf{(10.32)}$$

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



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

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



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

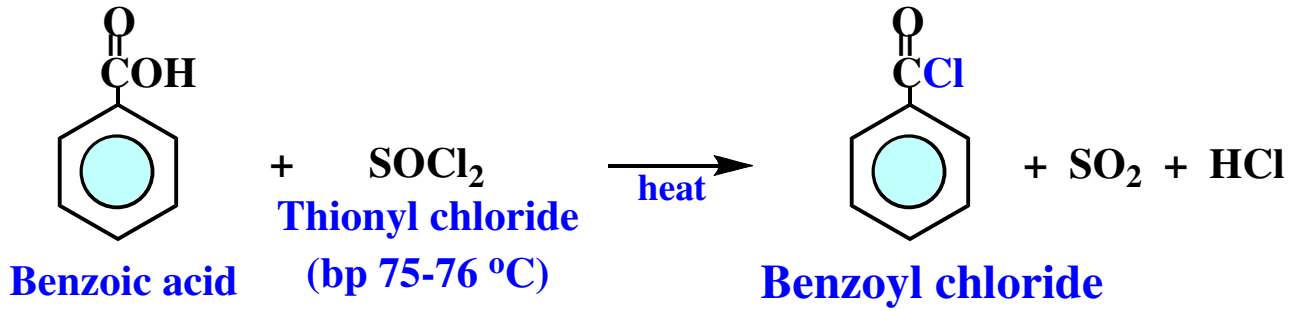
acetyl chloride — acetic acid — (fumes)

Synthesis of Acyl Chlorides

Because of their reactivity, acyl chlorides must be prepared under conditions that exclude exposure to good nucleophiles like water. Common reagents that convert carboxylic acids into acyl chlorides are phosphorus trichloride (PCl_3) phosphorus pentachloride (PCl_5), and thionyl chloride ($SOCl_2$).

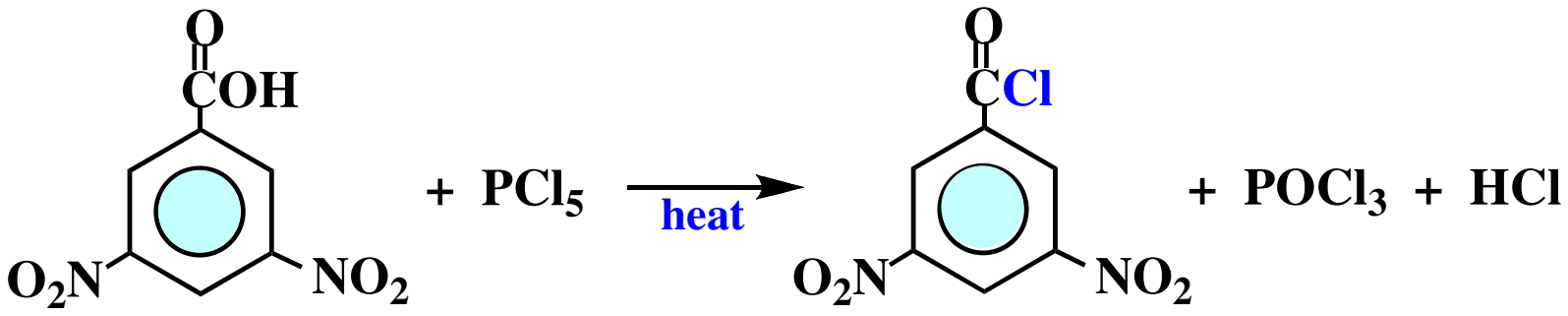
Typical Synthetic Procedures

The carboxylic acid is heated with the reagent, with or without the presence of an inert solvent.



Thionyl chloride is an especially convenient reagent because the byproducts are gases and easily removed. Excess thionyl chloride is easy to remove by distillation.

Use of Phosphorus Pentachloride



3,5-Dinitrobenzoic acid

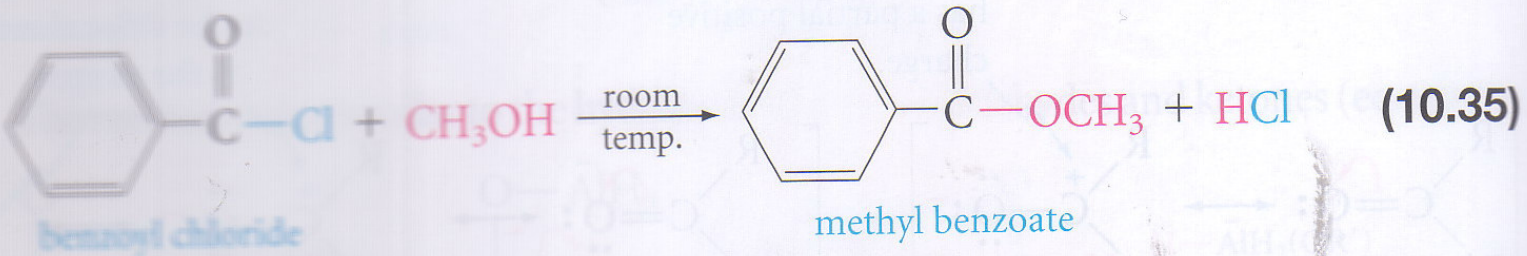
3,5-Dinitrobenzoyl chloride

Phosphorus oxychloride

The acyl chlorides are usually isolated and purified, often by distillation. They are reasonably stable in the absence of water and other nucleophiles.

Both $SOCl_2$ and PCl_5 are strong electrophiles that transform the hydroxyl into a much better leaving group, thereby promoting substitution at the acyl carbon.

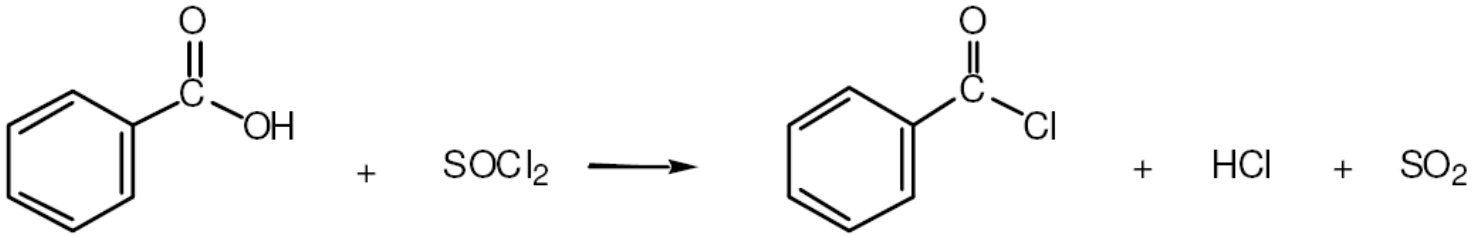
Acyl halides react rapidly with alcohols to form esters.



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

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

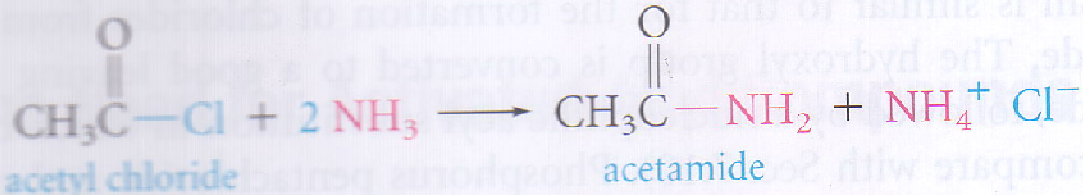
10.22



benzoic acid benzoyl chloride

10.23 When acyl halides come in contact with the moist membranes of the nose, they hydrolyze, producing HCl, a severe irritant.

Acyl halides react rapidly with ammonia to form amides.



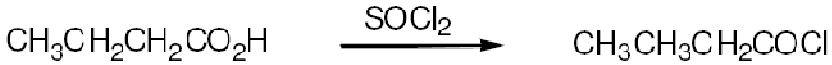
(10.36)

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

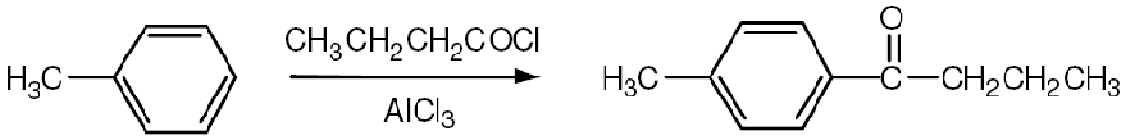
Acyl halides are used to synthesize aromatic ketones, through Friedel–Crafts acylation of aromatic rings (review Sec. 4.9.d).

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

10.25 First prepare butanoyl chloride:

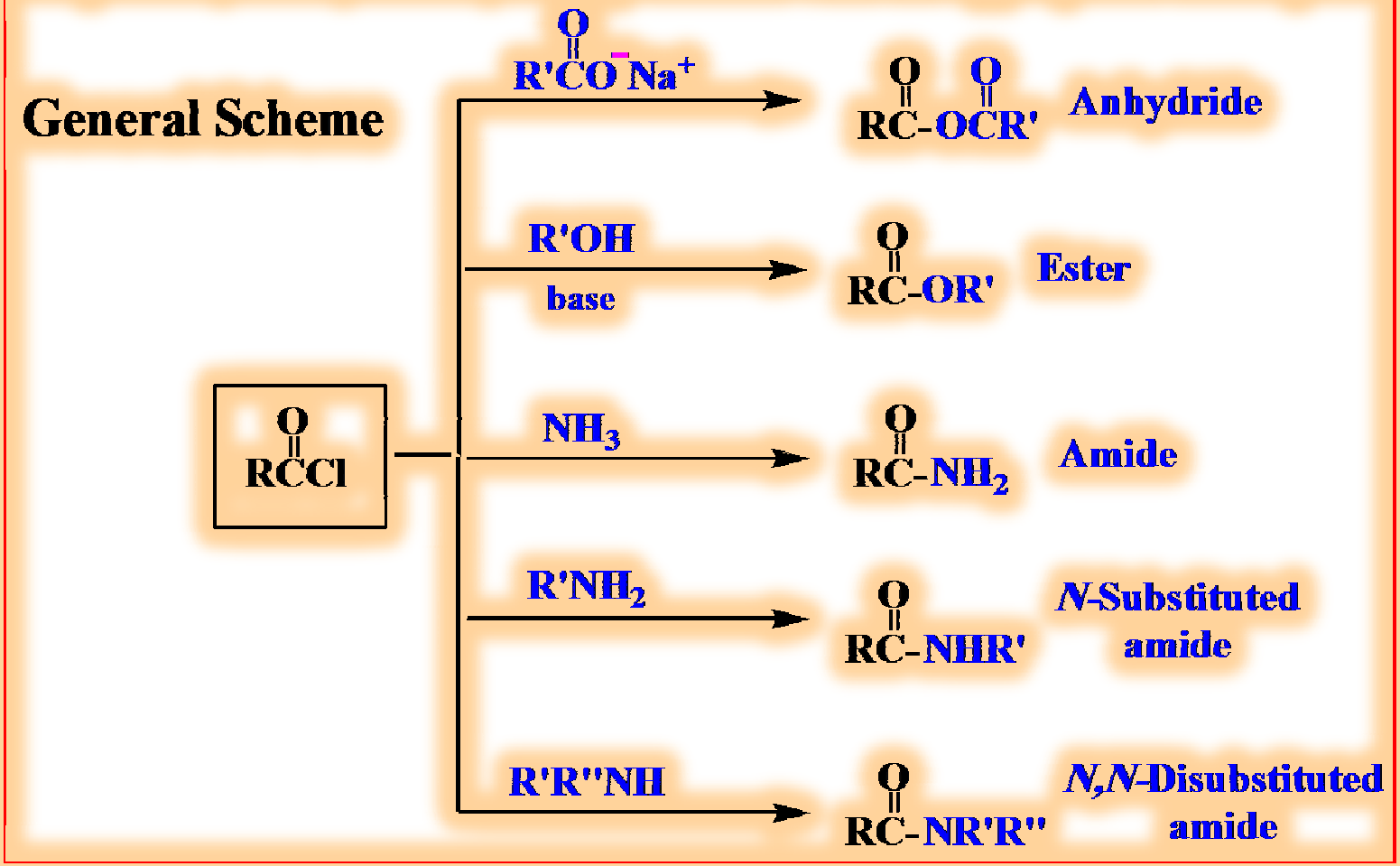


Then perform a Friedel–Crafts acylation:



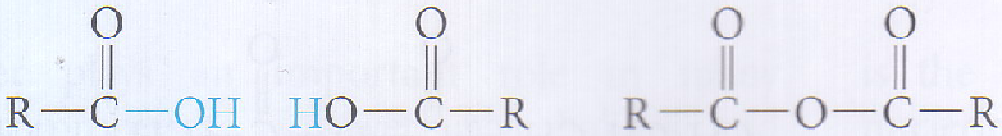
Reactions of Acyl Chlorides

Acyl chlorides are easily converted into other acyl compounds (acid anhydrides, esters, amides, etc.) by reaction with the appropriate nucleophile.



10.19 Acid Anhydrides

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

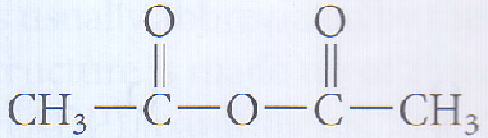


two acid molecules

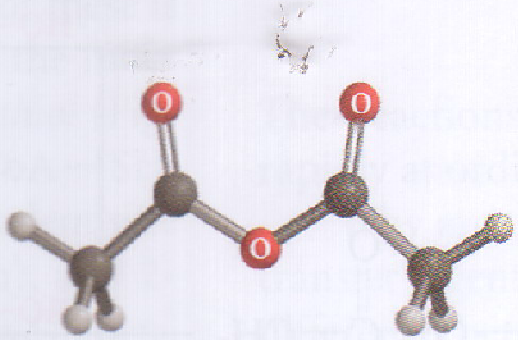
an acid anhydride

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

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



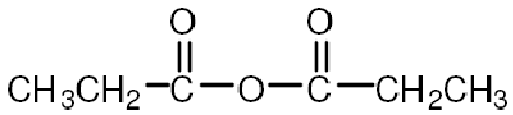
ethanoic anhydride or acetic anhydride



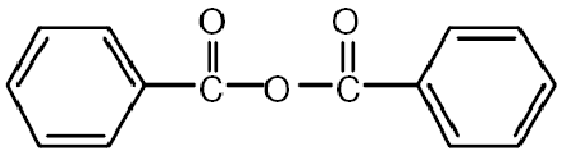
PROBLEM 10.26 Write the structural formula for

a. propanoic anhydride.
b. benzoic anhydride.

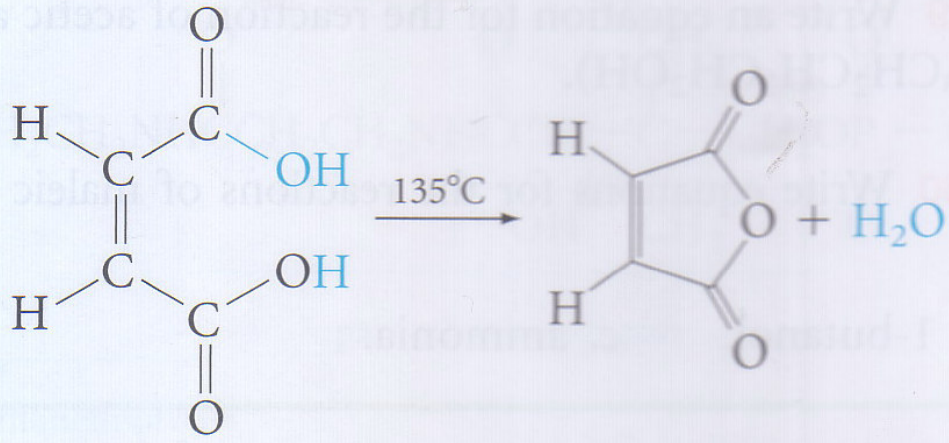
a.



b.



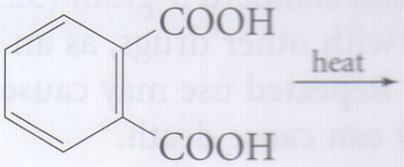
Dicarboxylic acids with appropriately spaced carboxyl groups lose water on heating to form cyclic anhydrides with five- and six-membered rings. For example,

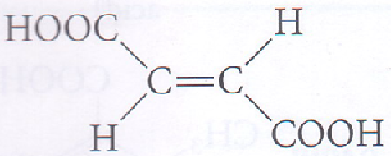


maleic acid maleic anhydride

(10.37)

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

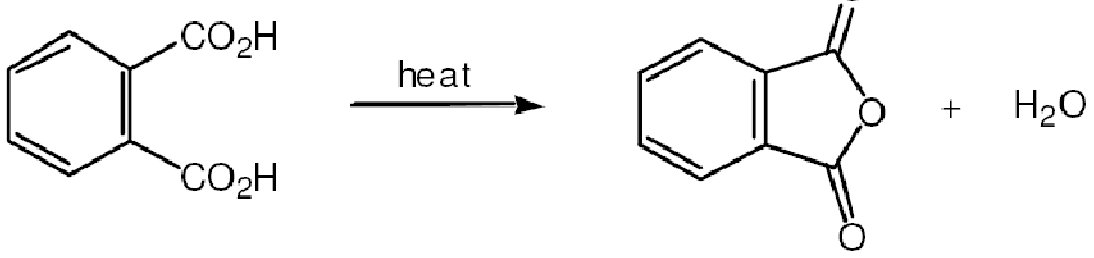




fumaric acid

PROBLEM 10.28 Do you expect fumaric acid (page 288) to form a cyclic anhydride on heating? Explain.

10.27

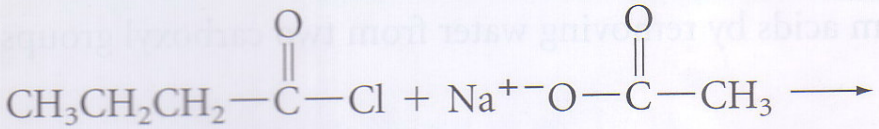


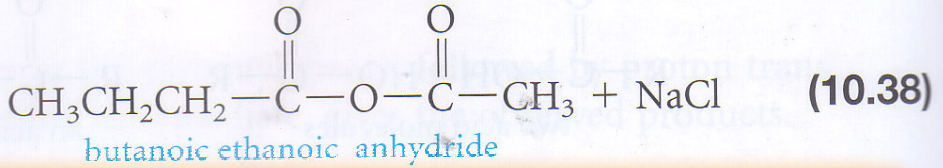
phthalic acid — phthalic anhydride

10.28 No. The two carboxyl groups are *trans* to one another and cannot interact in an intramolecular fashion.

A

method for preparing anhydrides derived from two different carboxylic acids, called **mixed anhydrides.**

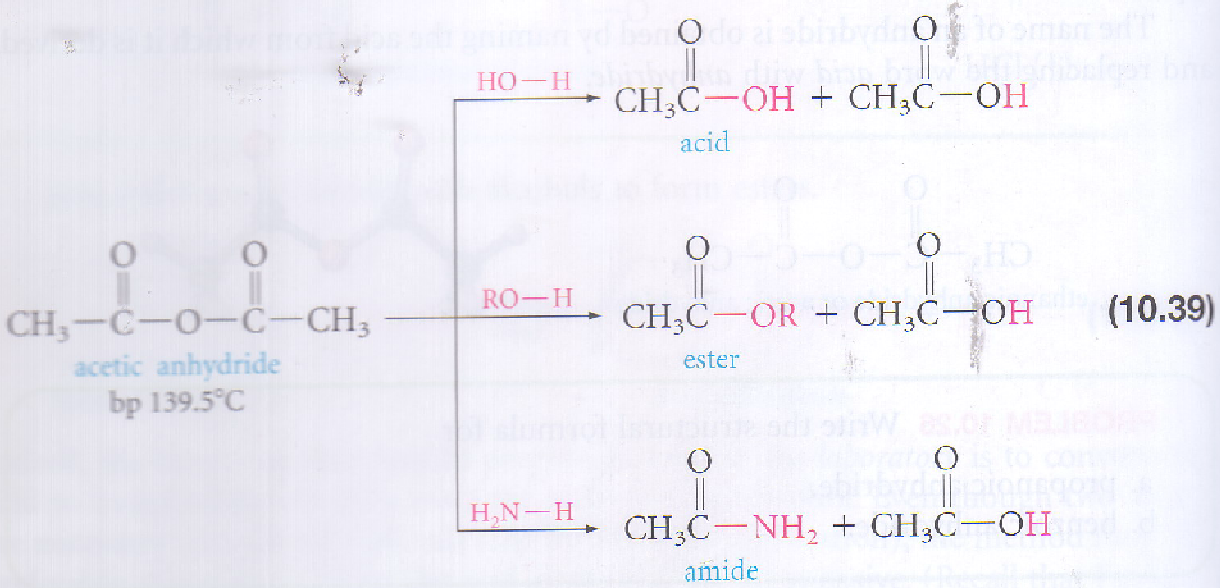




butanoic ethanoic anhydride

(10.38)

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



acetic anhydride
bp 139.5°C

acid

ester

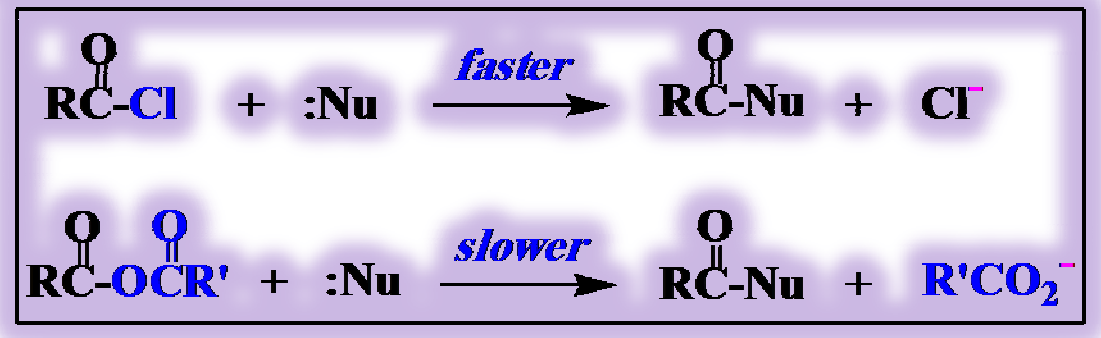
amide

(10.39)

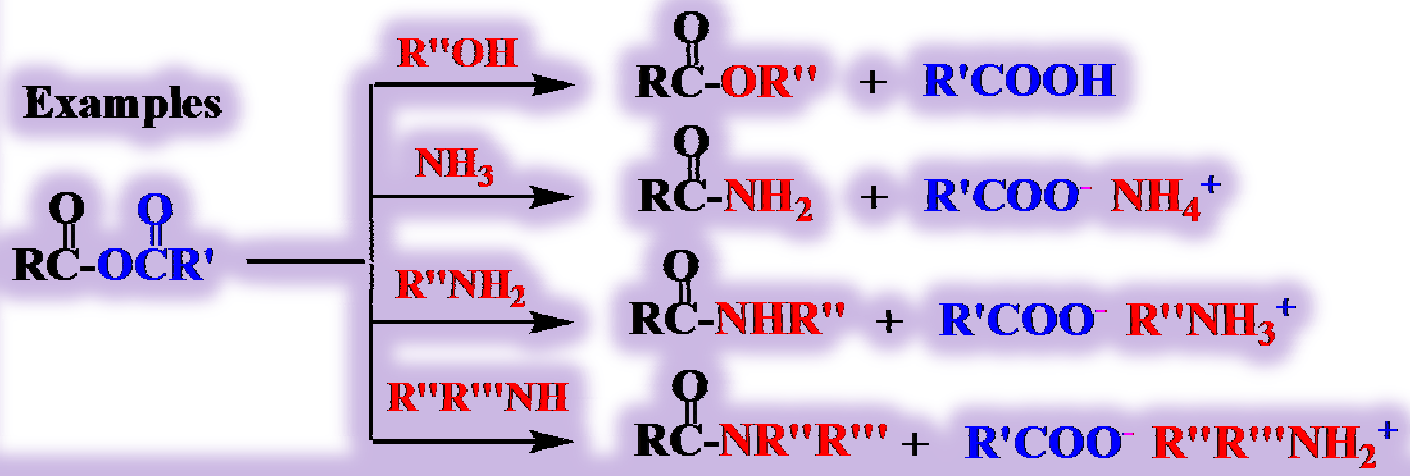
Water hydrolyzes an anhydride to the corresponding acid. Alcohols give esters, and ammonia gives amides. In each case, one equivalent of acid is also produced.

Reactions of Carboxylic Acid Anhydrides

Carboxylic acid anhydrides and acyl chlorides show parallel patterns of reactions. The latter react faster because of the better leaving group ability of Cl^-.



Examples

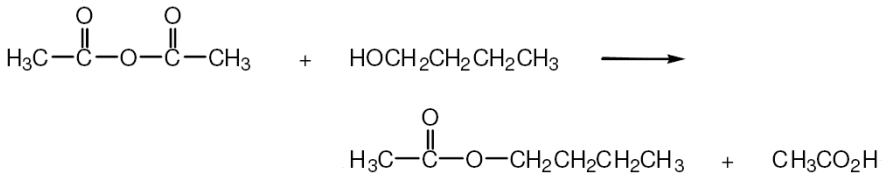


PROBLEM 10.29 Write an equation for the reaction of acetic anhydride with 1-butanol ($CH_3CH_2CH_2CH_2OH$).

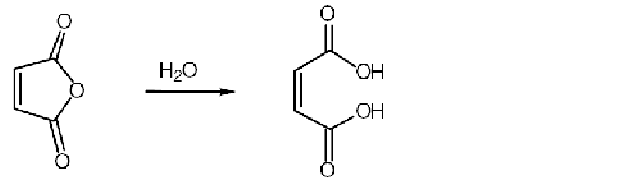
PROBLEM 10.30 Write equations for the reactions of maleic anhydride (see eq. 10.37) with

a. water. b. 1-butanol. c. ammonia.

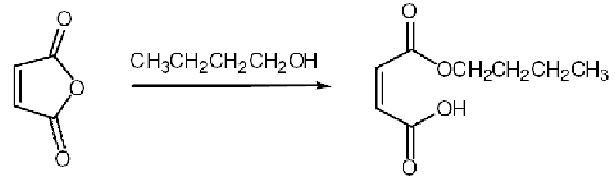
10.29 Use the middle part of eq. 10.39 as a guide:



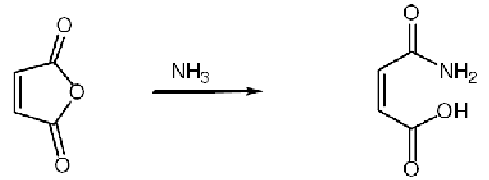
10.30 a. Use the top part of eq. 10.39 as a guide:

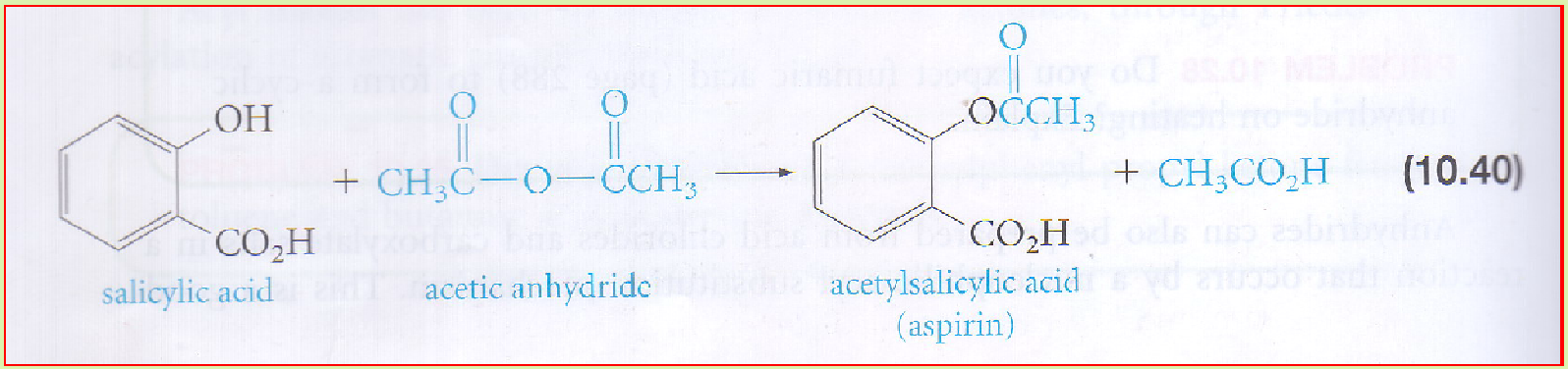


b. Use the middle of eq. 10.39 as a guide:



c. Use the bottom of eq. 10.39 as a guide:




OH
CO2H
salicylic acid
+ CH3C—O—CCH3
acetic anhydride
OCCH3
CO2H
acetylsalicylic acid
(aspirin)
+ CH3CO2H
(10.40)