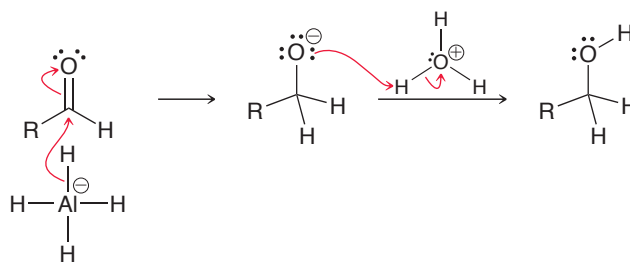




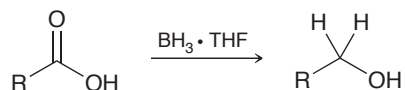
Carboxylic Acids and Their Derivatives

Klein, D. (2012). Carboxylic Acids and Their Derivatives. En *Organic Chemistry* (pp. 979-983). USA: Wiley.

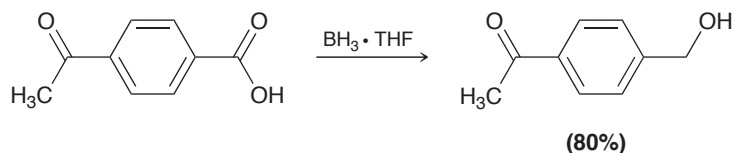
Under these conditions, the aldehyde cannot be isolated. Instead, it is further attacked by LAH to form an alkoxide, which is then protonated when H_3O^+ is added to the reaction flask.



An alternative method for reducing carboxylic acids involves the use of borane (BH_3).

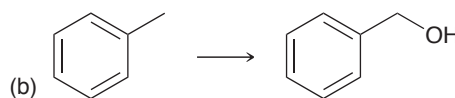
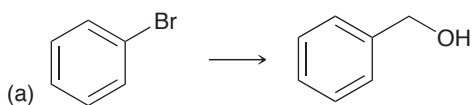


Reduction with borane is often preferred over reduction with LAH, because borane reacts selectively with a carboxylic acid moiety in the presence of another carbonyl group. As an example, if the following reaction were performed with LAH instead of borane, both carbonyl groups would be reduced.



CONCEPTUAL CHECKPOINT

21.11 Identify the reagents you would use to achieve each of the following transformations:



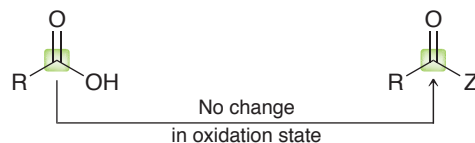
21.6 Introduction to Carboxylic Acid Derivatives

Classes of Carboxylic Acid Derivatives

In the previous section, we learned about the reaction between a carboxylic acid and LAH. This reaction is a reduction, because the carbon atom of the carboxylic acid moiety is reduced in the process:



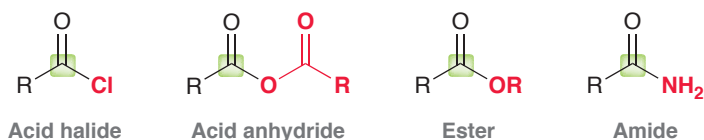
Carboxylic acids also undergo many other reactions that do not involve a change in oxidation state.



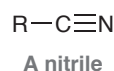
LOOKING BACK

For a review of oxidation states, see Section 13.4.

Replacement of the OH group with a different group (Z) does not involve a change in oxidation state if Z is a heteroatom (Cl, O, N, etc.). Compounds of this type are called **carboxylic acid derivatives**, and they will be the focus of the remainder of this chapter. The four most common types of carboxylic acid derivatives are shown below.



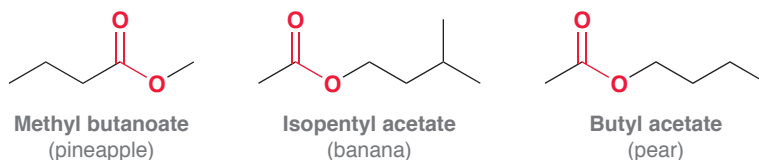
Notice that in each case there is a carbon atom (highlighted in green) with three bonds to heteroatoms. As a result, each of these carbon atoms has the same oxidation state as the carbon atom of a carboxylic acid. Although all of these derivatives exhibit a carbonyl group, the presence of a carbonyl group is not a necessary requirement to qualify as a carboxylic acid derivative. Any compound with a carbon atom that has three bonds to heteroatoms will be classified as a carboxylic acid derivative. For example, consider the structure of nitriles.



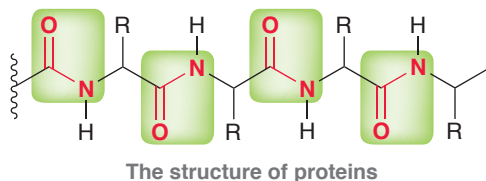
Nitriles exhibit a carbon atom with three bonds to a heteroatom (nitrogen). As a result, the conversion of a nitrile into a carboxylic acid (or vice versa) is neither a reduction nor an oxidation. Nitriles are therefore considered to be carboxylic acid derivatives, and they will also be discussed in this chapter.

Carboxylic Acid Derivatives in Nature

As we will soon see, acid halides and acid anhydrides are highly reactive and are therefore not very common in nature. In contrast, esters are more stable and are abundant in nature. Naturally occurring esters, such as the following three examples, often have pleasant odors and contribute to the aromas of fruits and flowers.



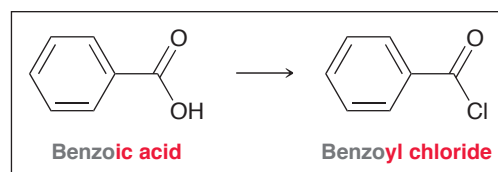
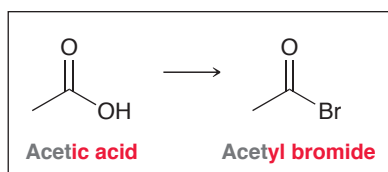
Amides are abundant in living organisms. For example, proteins are comprised of repeating amide linkages.



Chapter 26 will focus on the structure of proteins as well as the central role that proteins play in catalyzing most biochemical reactions.

Naming Acid Halides

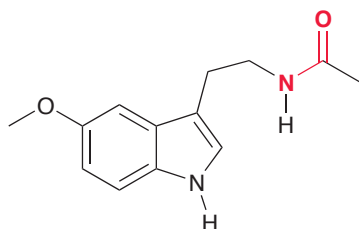
Acid halides are named as derivatives of carboxylic acids by replacing the suffix “ic acid” with “yl halide”:



MEDICALLY SPEAKING)))

Sedatives

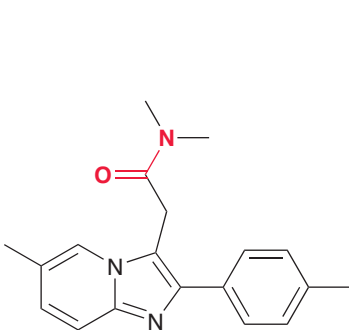
Sedatives are compounds that reduce anxiety and induce sleep. Our bodies utilize many natural sedatives, including melatonin.



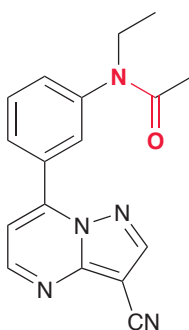
Melatonin

There is much evidence suggesting that melatonin plays an important role in regulating the body's natural sleep-wake cycle. For example, it has been observed that levels of melatonin for most people increase at night and then decrease in the morning. For this reason, many people take melatonin supplements to treat insomnia.

Notice the amide moiety in the structure of melatonin (shown in red). This moiety is a common feature in many drugs that are marketed as sedatives, for example,

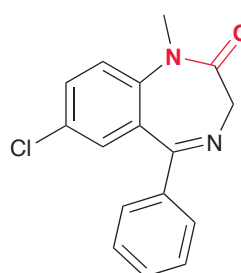


Zolpidem
(Ambien™)

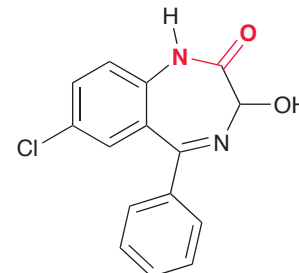


Zaleplon
(Sonata™)

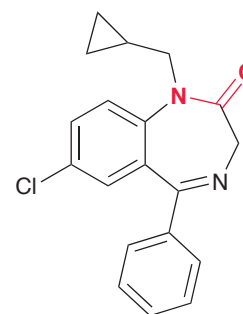
These drugs, which are similar in structure to melatonin, are used to treat insomnia. Other sedatives are used primarily in the treatment of excessive anxiety:



Diazepam
(Valium™)



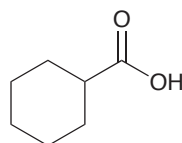
Oxazepam
(Serax™)



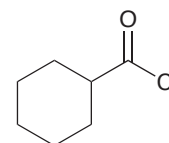
Prazepam
(Verstran™)

Drugs used in the treatment of anxiety are called anxiolytic agents. The three examples shown are all similar in structure and belong to a class of compounds called benzodiazepines. Extensive research has been undertaken to elucidate the relationship between the structure and activity of benzodiazepines. It was found that the amide moiety is not absolutely necessary, but its presence does increase the potency of these agents.

When an acid halide moiety is connected to a ring, the suffix “carboxylic acid” is replaced with “carbonyl halide”, for example,



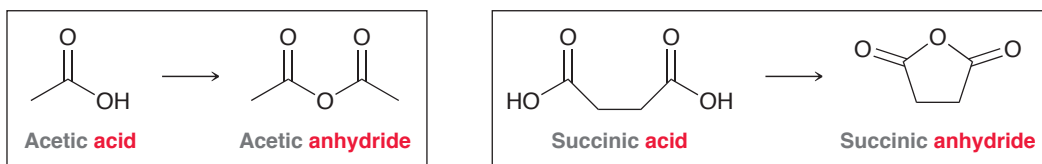
Cyclohexanecarboxylic acid



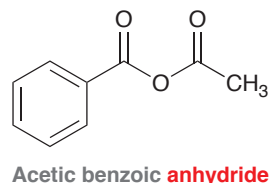
Cyclohexanecarbonyl chloride

Naming Acid Anhydrides

Acid anhydrides are named as derivatives of carboxylic acids by replacing the suffix “acid” with “anhydride.”

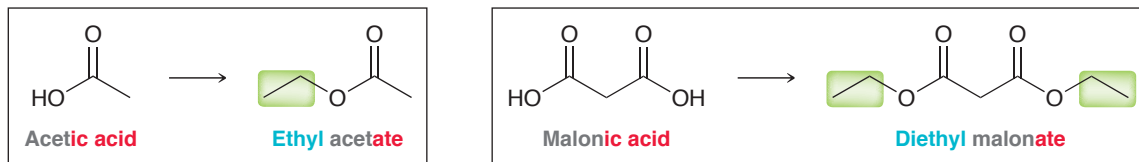


Unsymmetrical anhydrides are prepared from two different carboxylic acids and are named by indicating both acids alphabetically followed by the suffix “anhydride”:

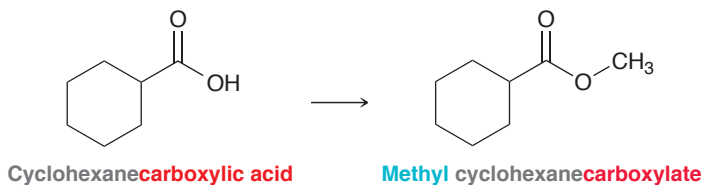


Naming Esters

Esters are named by first indicating the alkyl group attached to the oxygen atom followed by the carboxylic acid, for which the suffix “ic acid” is replaced with “ate.”

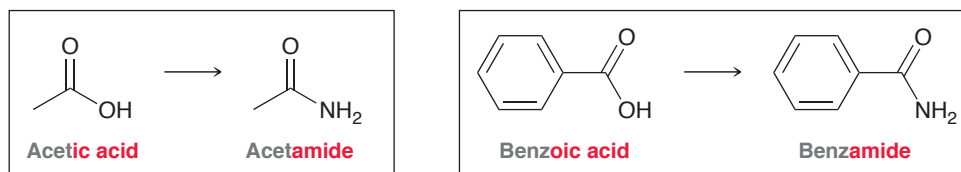


The same methodology is applied when the ester moiety is connected to a ring, for example.

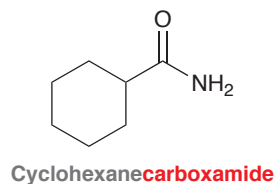


Naming Amides

Amides are named as derivatives of carboxylic acids by replacing the suffix “ic acid” or “oic acid” with “amide.”

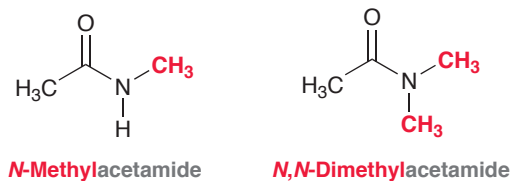


When an amide moiety is connected to a ring, the suffix “carboxylic acid” is replaced with “carboxamide.”



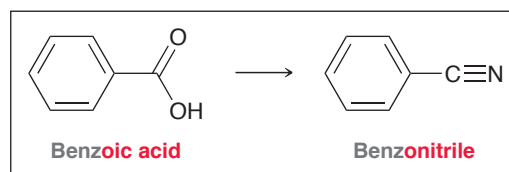
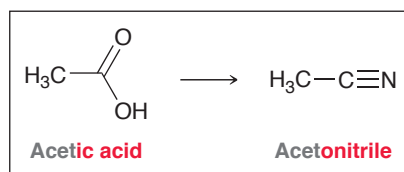


If the nitrogen atom bears alkyl groups, these groups are placed at the beginning of the name, and the letter “N” is used as a locant to indicate that they are attached to the nitrogen.



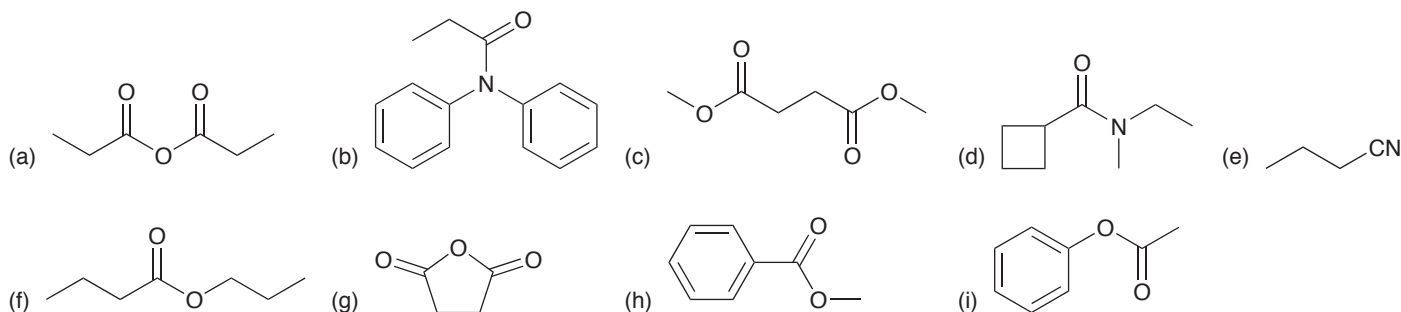
Naming Nitriles

Nitriles are named as derivatives of carboxylic acids by replacing the suffix “ic acid” or “oic acid” with “onitrile.”



CONCEPTUAL CHECKPOINT

21.12 Provide a name for each of the following compounds:



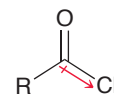
21.13 Draw a structure for each of the following compounds:

- (a) Dimethyl oxalate (b) Phenyl cyclopentanecarboxylate (c) N-Methylpropionamide (d) Propionyl chloride

21.7 Reactivity of Carboxylic Acid Derivatives

Electrophilicity of Carboxylic Acid Derivatives

In the previous chapter, we saw that the carbon atom of a carbonyl group is electrophilic as a result of both inductive and resonance effects. The same is true of carboxylic acid derivatives, although there is a wide range of reactivity among the carboxylic acid derivatives, illustrated in Figure 21.4. Acid halides are the most reactive. To rationalize this, we must consider both inductive effects and resonance effects. Let's begin with induction. Chlorine is an electronegative atom and therefore withdraws electron density from the carbonyl group via induction.



This effect renders the carbonyl group even more electrophilic when compared with the carbonyl group of a ketone.