

Substitutions at the Carbonyl Group

REACTIONS OF CARBOXYLIC ACIDS AND DERIVATIVES

CHAPTER

19

THE PREVIOUS CHAPTER discussed the attack of nucleophiles at the electrophilic carbonyl carbon of aldehydes and ketones. In most of the reactions this resulted in the addition of the nucleophile to the carbon and a proton to the oxygen of the carbonyl group. In this chapter the electrophile is the carbonyl carbon of a carboxylic acid or a related derivative such as an acyl chloride, anhydride, ester, or amide. The reactions in this chapter begin in exactly the same way as those in the last chapter—that is, by attack of a nucleophile at the carbonyl carbon. Here, however, the presence of the other heteroatom (an atom other than carbon or hydrogen, such as oxygen, nitrogen, or chlorine) on the carbonyl carbon causes the reaction to diverge at this point. Rather than the addition reactions of Chapter 18, the heteroatom group leaves, resulting in a substitution.

First, the general mechanisms for these reactions are presented. Then the reactivity of these carboxylic acid derivatives is discussed. As expected, the factors that control the reactivity are very similar to those that affect the addition reactions of Chapter 18. Next, reactions with nucleophiles that interconvert all of the members of the carboxylic acid family are presented. Finally, the reactions of hydride and organometallic nucleophiles with these electrophiles are discussed.

19.1 THE GENERAL MECHANISM

As was the case for nucleophilic additions to aldehydes and ketones, two mechanisms occur for the reactions in this chapter: one under basic conditions and one under acidic conditions. Both of these start in the same manner as the addition reaction mechanisms. The basic conditions mechanism is shown in Figure 19.1. First the nucleophile

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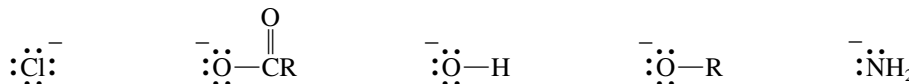
- ▶ Predicting the Products of Nucleophilic Substitutions at Carbonyl Groups
- ▶ Understanding the Mechanisms for These Reactions
- ▶ Predicting the Effect of the Structure of the Reactant on the Position of the Equilibrium for These Reactions
- ▶ Using These Reactions to Interconvert Any of the Carboxylic Acid Derivatives and to Prepare Aldehydes, Ketones, Alcohols, and Amines
- ▶ Using These Reactions to Synthesize Compounds

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attacks the carbonyl carbon, generating an intermediate that is very similar to that produced by nucleophilic attack on an aldehyde or ketone. The major difference between this intermediate and that produced from an aldehyde or ketone is the ability of L to act as a leaving group in this case. In the second step, L leaves in a reaction that looks very much like the reverse of the first step. The overall result is a substitution of the nucleophile for the leaving group. Although this reaction is a substitution, it is important to note that the mechanism is quite different from the S_N2 mechanism that occurs at sp^3 -hybridized carbons. This mechanism occurs in two steps, with the nucleophile bonding to the carbon first. Such a mechanism is impossible at an sp^3 -hybridized carbon because the intermediate would have five bonds to the carbon and would violate the octet rule. At a carbonyl carbon a pair of electrons can be displaced onto the oxygen when the nucleophile bonds, resulting in the formation of an sp^3 -hybridized carbon in the intermediate (often called the **tetrahedral intermediate** because of its geometry).

For this mechanism to occur for an aldehyde or ketone, hydride ion or a carbanion would have to act as the leaving group. These species are much too basic to leave under normal circumstances. In the case of carboxylic acid derivatives the leaving group is one of the following less basic species:



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Click Mechanisms in Motion to view the Mechanism of Nucleophilic Substitution at a Carbonyl Group under Basic Conditions.

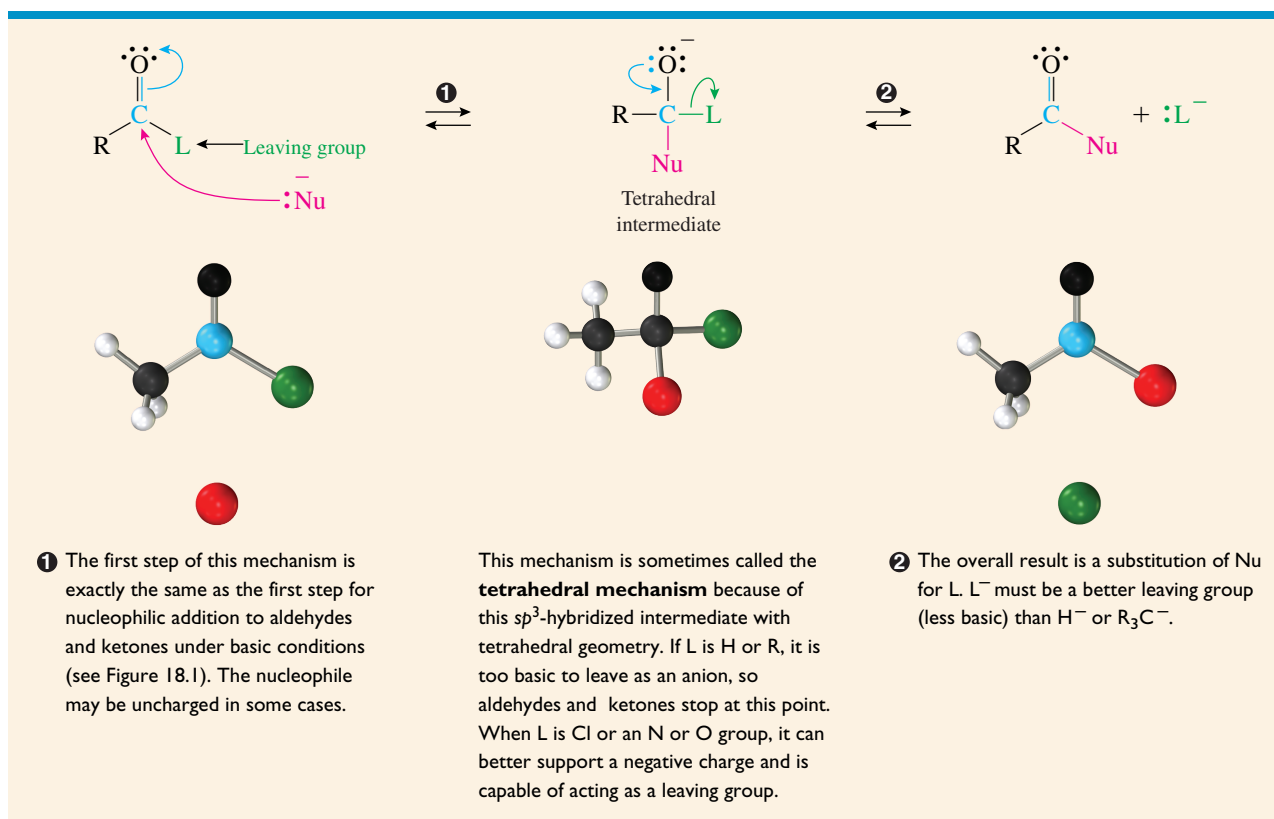


Figure 19.1

MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT A CARBONYL GROUP UNDER BASIC CONDITIONS.

Except for chloride anion, these anions are too basic to act as leaving groups in the S_N2 reaction. However, poorer leaving groups can be used in this reaction because the first step, attack of the nucleophile, is usually the rate-determining step. The leaving group is lost in the subsequent step, which is favored by entropy because it is intramolecular.

As was the case for the addition reaction of Chapter 18, another version of the mechanism operates under acidic conditions. In this version the carbonyl oxygen is protonated before the nucleophile attacks. Because this makes the carbonyl carbon more electrophilic, weaker nucleophiles can be used (often the conjugate acids of those used under basic conditions). In addition, the leaving group may be protonated before it leaves. Examples of the acidic conditions mechanism are provided in later sections.

Now let's address the reactivity of these compounds—that is, how the rate and the position of the equilibrium for the reaction are affected by the structure of the compound. The first step, attack of the nucleophile, is usually the rate-determining step. Because this step is the same as the first step in the mechanism for additions to aldehydes and ketones, steric, resonance, and inductive effects control the rate of this reaction in exactly the same manner as was described in Sections 18.3 and 18.4. These effects can be summarized as follows:

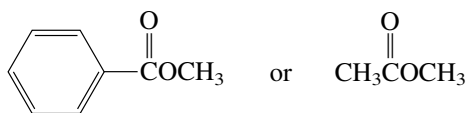
Steric effects: Steric hindrance slows the approach of the nucleophile and causes a decrease in the reaction rate. (However, the position of the equilibrium is not affected if the starting material and the substitution product have similar steric interactions.)

Inductive effects: Electron-withdrawing groups make the carbonyl carbon more electrophilic and increase the reaction rate; electron-donating groups make the carbonyl carbon less electrophilic and decrease the reaction rate.

Resonance effects: Resonance electron-withdrawing groups make the carbonyl carbon more electrophilic and increase the rate; resonance electron donors make the carbonyl carbon less electrophilic and decrease the reaction rate.

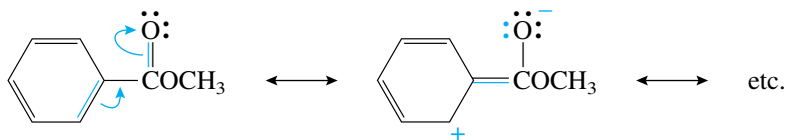
PRACTICE PROBLEM 19.1

Explain which of these compounds would have the faster rate of nucleophilic substitution at its carbonyl group:



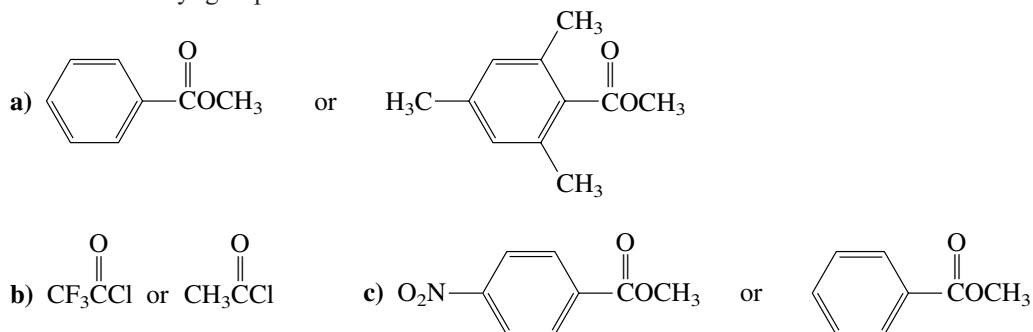
Solution

The benzene ring donates electrons to the carbonyl carbon by resonance, thus making the carbon less electrophilic and slowing the reaction rate:



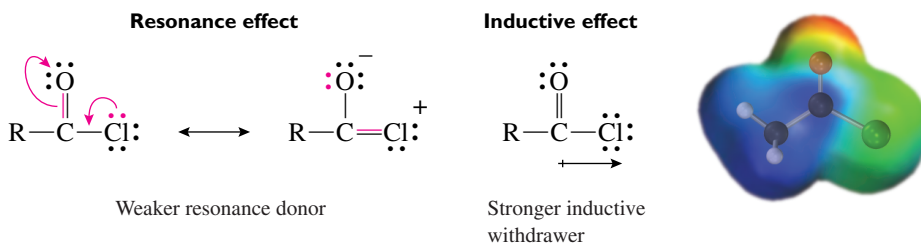
PROBLEM 19.1

Explain which compound would have the faster rate of nucleophilic substitution at its carbonyl group:

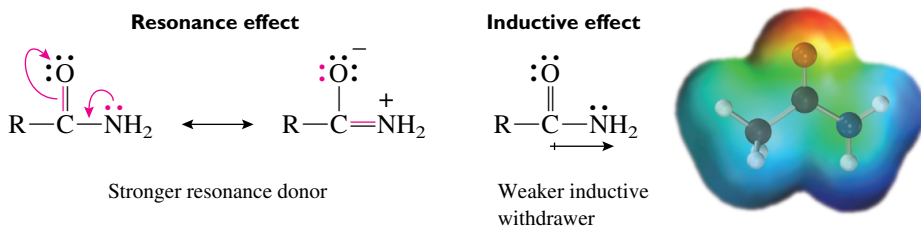


Although the leaving group does not come off during the rate-determining step, it does affect the reaction rate by its inductive and resonance effects. Furthermore, its stability after it has left affects the position of the equilibrium. Leaving groups that are weaker bases are more stable and cause the products to be more favored at equilibrium.

Consider the case of an acyl chloride. The chlorine is an inductive electron withdrawer and a resonance electron donor. As we saw in Chapter 17, the inductive effect is stronger. (Recall that chlorine is not a very strong resonance electron donor because the long C—Cl bond and the size difference between the 3*p* AO on the Cl and the 2*p* AO on the C result in poor overlap of these orbitals.) In addition, chloride anion is a very weak base. Overall, acyl chlorides are the most reactive of the carboxylic acid derivatives discussed here and are the least favored at equilibrium.



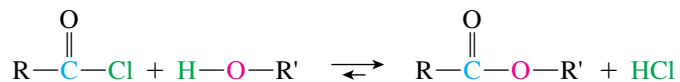
Now consider the case of an amide. The same effects are operating. The nitrogen is an inductive electron withdrawer and a resonance electron donor. As we saw in Chapter 17, the resonance effect is stronger in this case. Also, amide ion is quite basic. Overall, amides are much less reactive than acyl halides and are much more favored at equilibrium.



Although the rate of reaction of a carboxylic acid derivative depends on the inductive and resonance effects of the leaving group and the position of the equilibrium de-

depends on the stability of the leaving group, both of these effects are related to the basicity of the leaving group. Acid derivatives with leaving groups that are weaker bases react faster and are less favored at equilibrium. Table 19.1 lists the reactivity order for all of these compounds. Note that aldehydes and ketones have been included in this reactivity scale, but for the rate of nucleophilic attack only. The second step, in which the leaving group comes off, does not occur for these compounds.

The reactivity scale of Table 19.1 is very important. Not only does it tell where a nucleophile will react when faced with a choice between two different carbonyl groups, but it also enables the position of the equilibrium to be predicted for many reactions. For example, a compound that has both an aldehyde and an ester group is more likely to be attacked by a nucleophile at the aldehyde carbonyl carbon. The table also indicates that the equilibrium in the reaction



favors the products because the ester is lower on the reactivity scale than is the acyl chloride. Any carboxylic acid derivative can readily be prepared by reaction of the appropriate nucleophile with a derivative that is higher on the scale. For example, an ester is often prepared by reaction of an acyl chloride with an alcohol, as shown in the preceding equation. Let's examine the details of how to prepare acid derivatives.

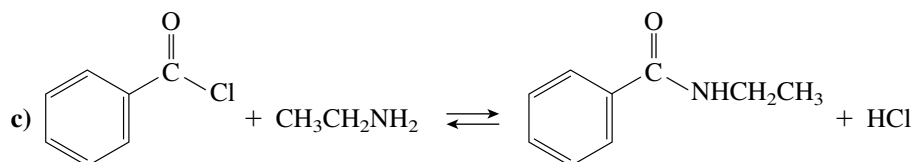
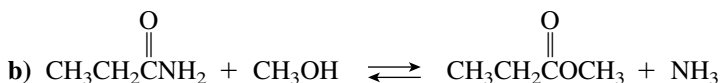
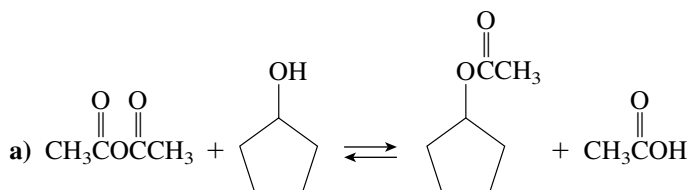
Table 19.1 Reactivity Scale for Carbonyl Compounds

Compound	Structure	Leaving Group	Comment
Most reactive compound ↑ Acyl chloride	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Cl}$	Cl^-	Less favored at equilibrium
Anhydride	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$	$\overset{-}{\text{O}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$	
Aldehyde	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$		First step only
Increasing reaction rate ↑ Ketone	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$		First step only
Ester	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{R}'$	$\overset{-}{\text{O}}-\text{R}'$	Esters and acids are very similar in both rate and equilibrium position
Acid	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{H}$	$\overset{-}{\text{O}}-\text{H}$	
Amide	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2$	$\overset{-}{\text{N}}\text{H}_2$	Increasing equilibrium constant ↓ More favored at equilibrium
Least reactive compound ↓ Carboxylate anion	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{-}{\text{O}}$	O^{2-}	

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 for more practice using Table
 19.1 to predict the position of
 the Equilibrium in
**Carbonyl Group
 Substitutions.**

PROBLEM 19.2

Explain whether these equilibria favor the reactants or the products:

**PROBLEM 19.3**

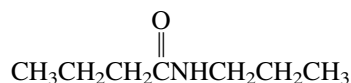
Explain which of these reactions is faster:



or

**PROBLEM 19.4**

Suggest a reaction that could be used to prepare this amide:



19.2 PREPARATION OF ACYL CHLORIDES

Because they are readily available from a number of synthetic reactions, carboxylic acids are the most common starting materials for the preparation of the other members of this family. Conversion of a carboxylic acid to an acyl chloride provides access to any of the other derivatives because the acyl chloride is at the top of the reactivity scale. But how can the acyl chloride be prepared from the acid when the acid is lower on the reactivity scale? This can be accomplished by using an even more reactive compound to drive the equilibrium in the desired direction. The reagent that is employed in the vast majority of cases is thionyl chloride, SOCl_2 . Phosphorus trichloride, PCl_3 , and phosphorus pentachloride, PCl_5 , are also used occasionally. Examples are provided in the following equations: