8.2 REACTION MECHANISMS

As introduced in Chapter 4, a reaction mechanism shows how the nuclei and the electrons move and how the bonds change as the reaction proceeds. It shows the individual steps in a reaction—that is, the order in which the bonds are made and broken. For example, the nucleophilic substitution reaction involves breaking one bond, the bond between the carbon and the leaving group, and forming one bond, the bond between the nucleophile and the carbon. There are three possible timings for these events—three possible mechanisms: (1) the bond to the leaving group may be broken first, followed by formation of the bond to the nucleophile; (2) the bond to the nucleophile may be formed first, followed by breaking the bond to the leaving group; or (3) bond breaking and bond formation may occur simultaneously. Pathways (1) and (3) both occur. Mechanism (2) does not occur, because the intermediate that would form when the nucleophile bonds first has five bonds to the carbon and cannot exist because the valence of the carbon would be exceeded.

Although certain mechanisms for a reaction can be eliminated on the basis of experimental evidence, it is never possible to prove that the reaction follows a particular mechanism. It can only be demonstrated that all the experimental facts are consistent with that mechanism. One piece of experimental information that is of primary importance is the rate law that the reaction follows. The rate law predicted by a possible mechanism must be consistent with the rate law determined in the laboratory. If the two are not consistent, that mechanism can be ruled out. In the case of these nucleophilic substitution reactions, experimental studies have shown that two different rate laws are followed, depending on the substrate (R—L), the nucleophile, and the reaction conditions. This means that there must be two different mechanisms for the reaction. Let's look at each.

8.3 **BIMOLECULAR NUCLEOPHILIC SUBSTITUTION**

Consider the reaction of hydroxide ion with chloroethane:

$$HO^- + CH_3CH_2 - CI \longrightarrow CH_3CH_2 - OH + CI^-$$

Investigation of this reaction in the laboratory has shown that the reaction rate depends on the concentration of hydroxide ion and on the concentration of chloroethane (EtCl), that is, the reaction follows the second-order rate law:

rate =
$$k$$
[EtCl][OH⁻]

From general chemistry you might recall that the dependence of the rate law on the concentration of a particular species requires that species to be involved in the slowest step of the reaction or a step before the slowest step. Therefore, in this case, both hydroxide ion and chloroethane must be present in the slowest step of the reaction.

This rate law is consistent with mechanism (3), in which the bond to the leaving group (chloride) is broken and the bond to the nucleophile (hydroxide) is formed simultaneously, in the same step. A reaction that occurs in one step is termed a **concerted reaction**. Because two species (hydroxide ion and chloroethane) are involved in this step, the step is said to be bimolecular. This reaction is therefore described as a **bimolecular nucleophilic substitution** reaction, or an $S_N 2$ reaction.

Diagrams that show how the free energy changes as a reaction proceeds were introduced in Chapter 4 and are very useful. Figure 8.1 shows such a diagram for the $S_N 2$ reaction. Recall that the free energy, G, of the system is shown on the *y*-axis in these diagrams, and the progress of the reaction, which is just a measure of how much the reaction has proceeded from reactants toward products, is shown along the *x*-axis. The reactants are shown on the left-hand side of the diagram and the products on the right-hand side.

In this case the products are lower in energy than the reactants, so ΔG° is negative (the reaction is **exergonic**). Such reactions proceed spontaneously to the right. (Reactions in which the free-energy change is positive are **endergonic** and are not spontaneous. The terms **exothermic** and **endothermic** refer to reactions in which the enthalpy change [ΔH°] is negative and positive, respectively.)

Of more importance in terms of the mechanism is what happens to the energy of the system as the reaction progresses from the reactants to the products. As the reaction starts, the bond to the chlorine begins to break and the bond to the hydroxide ion begins to form. Initially, breaking the bond costs more energy than is returned by forming the other bond, so the energy of the system increases. The energy of the system continues to increase until it reaches a maximum where both bonds are approximately half formed (or broken). The structure of the complex at this energy decrease from forming the new bond outweighs the energy increase from breaking the bond to the leaving chlorine. The energy difference between the transition state and the reactants is the **free energy of activation**, ΔG^{\ddagger} .

The free energy versus reaction progress diagram shown in Figure 8.1 is typical for a concerted reaction. There is only one energy maximum; there is one transition state, between reactants and products; and there is no minimum between them.

What does the transition state for the S_N^2 reaction look like? Because it is a maximum on the free energy versus reaction progress diagram and any change, either forward to products or backward to reactants, is downhill in energy, the transition state has no appreciable lifetime. Because of this, it cannot be observed directly and any information



Figure 8.1

Free energy versus reaction progress diagram for the $\ensuremath{S_N2}$ reaction of chloroethane and hydroxide ion.

about its structure must be obtained by indirect means. However, we do know that the transition state must have a five-coordinate carbon—that is, a carbon with five bonds: three normal bonds and two partial bonds. The geometry of these bonds in the transition state has been determined by investigation of the stereochemistry of the reaction.

8.4 Stereochemistry of the $S_N 2$ Reaction

What happens in the $S_N 2$ reaction if the leaving group is attached to a carbon that is a chirality center, that is, one that is bonded to four different groups (the leaving group and three other, different groups)? *Possible* stereochemical outcomes are illustrated in Figure 8.2 for the reaction of hydroxide ion with (*S*)-2-chlorobutane. In possibility 1 the product has the same relative configuration as the reactant. In such a case we say that the reaction has occurred with **retention of configuration**. In possibility 2 the product has the opposite relative configuration. In possibility 3, complete randomization of stereochemistry has occurred in the product. The reaction has occurred with **racemization**, or 50% inversion and 50% retention. (Of course, partial racemization, resulting in different ratios of inversion to retention, is also possible.)

When the reaction of 2-chlorobutane with hydroxide ion is run in the laboratory, the rate is found to depend on the concentration of both species. This indicates that the re-



The hydroxide has bonded in the exact position the chlorine originally occupied. The product has the same relative stereochemistry as the reactant. The reaction has occurred with retention of configuration.

The hydroxide has bonded to the side opposite that where the chlorine was originally bonded. The stereochemistry of the product is opposite that of the reactant. The reaction has occurred with inversion of configuration.

The hydroxide has bonded equally to the same side and the opposite side as the original chlorine. A complete loss of stereochemistry has occurred. The reaction has proceeded with racemization.

Figure 8.2

(S)-2-Chlorobutane

POSSIBLE STEREOCHEMICAL OUTCOMES FOR THE REACTION OF (S)-2-CHLOROBUTANE WITH HYDROXIDE ION. Only possibility 2 actually occurs.

action is following the S_N^2 mechanism. Investigation of the stereochemistry of the reaction shows that the product is formed with inversion of configuration; that is, (*S*)-2chlorobutane produces (*R*)-2-butanol, corresponding to possibility 2 in Figure 8.2. The same result has been found for all S_N^2 reactions. S_N^2 reactions occur with inversion of configuration at the reaction center.

The fact that $S_N 2$ reactions *always* occur with inversion of configuration enables us to form a better picture of the transition state. The nucleophile must approach the carbon from the side opposite the leaving group (**back-side attack**). The structure of the transition state, with partial bonds to the entering hydroxide and the leaving chloride, is shown in the following structure. Figure 8.3 uses orbitals to show how this process occurs.



S_N2 transition state

Remember that the stereochemistry is inverted only at the reaction center. Because no bonds are made or broken except at the carbon bonded to the leaving group, the stereochemistry at any other chirality centers in the reactant remains unchanged. Some more examples of the S_N2 reaction are as follows:





(2) The nucleophile approaches the carbon from the side opposite the leaving group (back-side attack). An atomic orbital on the nucleophile, containing an unshared pair of electrons, begins to interact with the back lobe of the sp^3 orbital used by the carbon to form the sigma bond to the leaving group. As the nucleophile continues to approach, the leaving group begins to move away from the carbon, and the three other groups begin to swing to the right as the hybridization of the carbon changes.

- At the transition state, the carbon has trigonal planar geometry and is sp² hybridized. The AO of the nucleophile overlaps with one lobe of the p orbital on the carbon, and the AO of the leaving group overlaps with the other lobe of this orbital. The overall geometry is trigonal bipyramidal, with partial bonds to both Nu and L and approximate charges of negative 1/2 on each.
- G As the nucleophile continues to approach, the distance between the carbon and the leaving group continues to increase, and the other three groups continue to swing to the right. The hybridization of the carbon changes back to sp³, and its geometry returns to tetrahedral but with the nucleophile bonded to the side opposite to the one to which the leaving group was originally bonded.

Active Figure 8.3

MECHANISM OF THE S_N^2 **REACTION OF (5)-2-CHLOROBUTANE AND HYDROXIDE ION SHOWING ORBITALS.** Test yourself on the concepts in this figure at **OrganicChemistryNow.**

PROBLEM 8.1

Show the products, including stereochemistry, of these $S_N 2$ reactions:



organic Chemistry•∳•Now™

8.5 Effect of Substituents on the Rate of the $S_N 2$ Reaction

Let's now consider how the other groups that are bonded to the electrophilic carbon affect the rate of the S_N2 reaction. Table 8.1 lists the relative rates of the S_N2 reaction for a number of compounds. In this table the rate for ethyl chloride is assigned the value of 1, and the rates for the other compounds are compared to this value.

Examination of the first six entries in the table reveals an interesting trend. Methyl chloride reacts significantly faster than ethyl chloride. The other primary chlorides, propyl chloride and butyl chloride, react at nearly the same rate as ethyl chloride. However, isopropyl chloride reacts 40 times more slowly than ethyl chloride, and *tert*-butyl chloride, for all practical purposes, does not undergo the S_N2 reaction at all. (When forced, *tert*-butyl chloride will give a substitution product, but the reaction follows a different mechanism, as we will see shortly.)

You can see that the rate of the S_N^2 reaction decreases dramatically each time one of the hydrogens on the electrophilic carbon of methyl chloride is replaced with a

Name	Structure	Relative Rate
Methyl chloride	CH ₃ Cl	30
Ethyl chloride	CH ₃ CH ₂ Cl	I.
Propyl chloride	CH ₃ CH ₂ CH ₂ Cl	0.4
Butyl chloride	CH ₃ CH ₂ CH ₂ CH ₂ Cl	0.4
	CH_3	
lsopropyl chloride	CH ₃ CHCl	0.025
	CH ₃	
tert-Butyl chloride	CH ₃ CCl	0
	CH ₃	
	CH ₃	
Neopentyl chloride	CH ₃ CCH ₂ Cl	10 ⁻⁵
	CH ₃	
Allyl chloride	CH ₂ =CHCH ₂ Cl	40
Benzyl chloride	CH ₂ Cl	120
	O	
Chloroacetone	CH ₃ CCH ₂ Cl	10 ⁵

Table 8.1 Relative Rates of S_N2 Reactions for Selected Compounds

methyl group. Thus, replacing one hydrogen with a methyl group, to give ethyl chloride, causes the rate to decrease by a factor of 30. Replacing a second hydrogen with a methyl, to give isopropyl chloride, results in a further rate decrease by a factor of 40. By the time three methyl groups have been added, to give *tert*-butyl chloride, the compound is unreactive in the $S_N 2$ reaction. This effect is a result of the larger size of the methyl group (or other carbon groups) as compared to the size of hydrogen—a **steric effect.** The steric effect is a result of increasing strain energy in the transition state as the size of the groups on the electrophilic carbon increases.

Figure 8.4 illustrates this effect. It shows free energy versus reaction progress diagrams for the $S_N 2$ reactions of methyl chloride, ethyl chloride, and isopropyl chloride with hydroxide ion. In the case of methyl chloride, very little steric strain is introduced into the transition state by the interaction of the hydroxide ion nucleophile with the hydrogens. In the case of ethyl chloride, the interaction between the nucleophile and the methyl group on the electrophilic carbon generates more steric strain in the transition state, causing it to increase in energy. This results in an increase in ΔG^{\ddagger} and slows the reaction. In the case of isopropyl chloride, the interaction of the nucleophile with two methyl groups causes even more steric strain in the transition state and slows the reaction even more. When three methyl groups are present, as in the case of *tert*-butyl chloride, so much strain is present in the transition state that the rate of the $S_N 2$ reaction is extremely slow.



Figure 8.4

Free energy versus reaction progress diagrams for the S_N^2 reactions of 0 methyl chloride, 0 ethyl chloride, and 0 isopropyl chloride with hydroxide ion.

Figure 8.5 provides another view of this effect. It shows computer-generated spacefilling models of some of the molecules from Table 8.1 and illustrates the increasing difficulty the nucleophile experiences when approaching the back side of the electrophilic carbon and reaching the transition state as the number of methyl groups bonded to that carbon increases.

Other primary alkyl groups have effects similar to that of the methyl group. Replacing a hydrogen on the electrophilic carbon of methyl chloride with an ethyl group rather than a methyl group causes only a slightly larger rate decrease (compare the relative rates of ethyl chloride and propyl chloride in Table 8.1). This indicates that, as far as this mechanism is concerned, an ethyl group is only slightly "larger" than a methyl group, a result that is consistent with the axial destabilization energies of these groups discussed in Chapter 6.

To summarize, the rate of the S_N^2 reaction is controlled by steric factors at the electrophilic carbon. Steric hindrance slows the reaction. Based on the number of carbon groups attached to that carbon, the reactivity order is



Rules in organic chemistry cannot be followed blindly, because exceptions often occur. Examination of Table 8.1 shows that neopentyl chloride, a primary chloride, reacts 2500 times more *slowly* than isopropyl chloride, a secondary chloride. Closer examination of neopentyl chloride reveals the reason for this discrepancy. While the electrophilic carbon is indeed primary, the group attached to it is an extremely bulky *tert*-butyl group. A single *tert*-butyl group hinders the back-side approach of the nucleophile and raises the transition state energy even more than two methyl groups. Figure 8.5 shows a space-filling picture of this group.

Finally, Table 8.1 lists three primary alkyl chlorides—allyl chloride, benzyl chloride, and chloroacetone—that react considerably faster than other primary alkyl chlorides. This increase in reaction rate is due to resonance stabilization of the transition state. Each of these compounds has a pi bond adjacent to the reactive site and forms a transition state that is conjugated. The p orbital that develops on the electrophilic carbon in the transition state overlaps with the p orbital of the adjacent pi bond. The stabilization due to the conjugated transition state results in a significantly faster reaction. The transition state for the reaction of allyl chloride with a nucleophile is shown as follows:





PROBLEM 8.2

Explain which compound has a faster rate of $S_N 2$ reaction:



PROBLEM 8.3

Arrange these compounds in order of decreasing $S_N 2$ reaction rate:



8.6 UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION

Now consider the reaction of acetate ion with tert-butyl chloride:

$$\begin{array}{c} O \\ H_{3}C - \stackrel{\frown}{\bigcirc} \stackrel{\bullet}{\vdots} + H_{3}C - \stackrel{C}{\overset{\bullet}{\bigcirc} -Cl} \\ H_{3}C - \stackrel{O}{\underset{CH_{3}}{\overset{\bullet}{\frown}}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\frown}}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\frown}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\frown}}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\frown}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\bullet}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\frown}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{\bullet}} + H_{3}C - \stackrel{C}{\underset{CH_{3}}{\overset{\bullet}{$$

This reaction looks very similar to the reaction of hydroxide ion with methyl chloride presented earlier, but with the negative oxygen of the acetate anion acting as the nucleophile. (The CH_3CO_2H shown over the arrow is the solvent for the reaction.) However, investigation of this reaction in the laboratory has shown that the reaction rate depends only on the concentration of *tert*-butyl chloride (*t*-BuCl). It is totally independent of the concentration of acetate anion. The reaction follows the first-order rate law:

rate =
$$k[t-BuCl]$$

Because the reaction follows a different rate law from the $S_N 2$ mechanism, it must also proceed by a different mechanism.

The fact that the rate law depends only on the concentration of *tert*-butyl chloride means that only *tert*-butyl chloride is present in the transition state that determines the rate of the reaction. There must be more than one step in the mechanism because the acetate ion must not be involved until after the step with this transition state. Because only one molecule (*tert*-butyl chloride) is present in the step involving the transition state that determines the rate of the reaction, this step is said to be unimolecular. The reaction is therefore described as a **unimolecular nucleophilic substitution** reaction, or an S_N1 reaction.

The S_N1 mechanism proceeds by the following two steps:





Figure 8.6

FREE ENERGY VERSUS REACTION PROGRESS DIAGRAM FOR THE S_N I REACTION OF *TERT*-BUTYL CHLORIDE (2-CHLORO-2-METHYLPROPANE) AND ACETATE ANION.

In this mechanism, the bond to the chloride is broken in the first step and the bond to the acetate is formed in the second step. A free energy versus reaction progress diagram for the $S_N I$ mechanism is shown in Figure 8.6. In this reaction, each of the two steps has an energy maximum or transition state separating its reactant and product, which are both at energy minima. The transition state for the first step is at higher energy in this case. Once a molecule makes it over the higher-energy barrier of the first step, it has enough energy to proceed rapidly over the lower-energy barrier of the second step. The first step is called the **rate-limiting** or **rate-determining step** because it determines the rate of the reaction. It acts as a kind of bottleneck for the reaction. The rate of this reaction should depend only on the concentration of *tert*-butyl chloride because it is the only molecule involved in the rate-determining step. Therefore, this mechanism is consistent with the experimentally determined rate law.

In general, for a nonconcerted reaction, that is, a reaction that proceeds in several steps, the free energy versus reaction progress diagram has a separate transition state for each step. One or more intermediates are present along the reaction pathway, each of these located at an energy minimum. These intermediates may be located at relatively high energy and have only a transient existence, such as the carbocation formed in the S_N1 reaction, or they may be located at lower energy and have a longer lifetime. If one of the transition states is located at significantly higher energy than the others, then that step is the rate-determining step for the reaction. Molecules that become involved in the mechanism after the rate-determining step do not appear in the rate law for the reaction.

PROBLEM 8.4

Draw a free energy versus reaction progress diagram for a reaction that occurs in two steps with a relatively stable intermediate and in which the transition state for the second step is the highest-energy transition state. When the chloride ion leaves in the first step of the mechanism, a **reactive inter-mediate** is formed. This reactive intermediate is a high-energy, reactive species. Under most conditions it has a very short lifetime. However, it differs from a transition state in that it is located at a minimum on the energy curve. It has an activation barrier, al-though small, that must be surmounted for reaction in either the forward or reverse direction. Although its lifetime is short, it is significantly longer than that of a transition state. It may be possible, under certain circumstances, to obtain experimental observations of a reactive intermediate.

The particular reactive intermediate formed in this reaction is called a **carbocation**. It has a carbon with only three bonds and a positive charge. This carbon has only six electrons in its valence shell and is quite unstable because it does not satisfy the octet rule. It has trigonal planar geometry and sp^2 hybridization at the positively charged carbon.



Carbocations are one of the most important types of reactive intermediates in organic chemistry. They are encountered in many reactions in addition to the S_N1 reaction.

Let's now turn our attention to the transition state for this reaction. What is the structure of the transition state? This is an important question because a better understanding of its structure will help in predicting how various factors affect its stability and therefore will aid in predicting how these same factors affect the rate of the reaction. The transition state has a structure that is intermediate between that of the reactant, *tert*-butyl chloride, and that of the product, the *tert*-butyl carbocation. It has the bond between the carbon and the chlorine partially broken and can be represented as shown in the following structures:



It has a partial positive charge on the carbon and a partial negative charge on the chlorine. The hybridization of the carbon is between that of the reactant, sp^3 , and that of the carbocation, sp^2 .

Is the bond in the transition state more or less than half broken? The **Hammond postulate** enables questions such as this to be answered. It states that the structure of the

Exergonic Reaction

Endergonic Reaction





For an exergonic reaction, in which the reactants are at higher energy than the products, the energy of the transition state is closer to that of the reactants than that of the products. Therefore, the structure of the transition state resembles that of the reactants more than that of the products. If a bond is forming in the reaction, that bond is less than half formed in the transition state, and if a bond is breaking, it is less than half broken.



Reaction progress -----

For an endergonic reaction, in which the products are at higher energy than the reactants, the energy of the transition state is closer to that of the products. Therefore, its structure is also closer to that of the products. Any bonds that are forming in the reaction are more than half formed, and any bonds that are breaking are more than half broken.

Figure 8.7

Using the Hammond postulate to predict the structure of a transition state (2) exergonic reaction and (3) endergonic reaction.

transition state for a reaction step is closer to that of the species (reactant or product of that step) to which it is closer in energy. If the product of the step is higher in energy than the reactant, the structure of the transition state is more similar to that of the product than it is to that of the reactant. In contrast, if the reactant is higher in energy than the product, the structure of the transition state is more similar to that of the reactant than the product (see Figure 8.7). Because the carbocation is much higher in energy than the starting alkyl halide (the slow step of the mechanism in Figure 8.6 corresponds to the case on the right in Figure 8.7), the structure of the transition state for the S_N1 reaction is closer to that of the carbocation; the bond is more than half broken.

PROBLEM 8.5

Consider the free energy versus reaction progress diagram for the S_N^2 reaction shown in Figure 8.1. Does the transition state for this reaction have the C—Cl bond less than half broken, approximately half broken, or more than half broken?

8.7 Effect of Substituents on the Rate of the S_N 1 Reaction

How do the other groups bonded to the electrophilic carbon affect the rate of the $S_N I$ reaction? Table 8.2 lists the relative rates of the $S_N I$ reaction for a number of compounds, compared to the rate for isopropyl chloride taken as 1. Methyl chloride and ethyl chloride are not listed in the table because *methyl and simple primary alkyl chlorides do not react by the* $S_N I$ *mechanism.* Even under the most favorable $S_N I$ conditions, these unhindered compounds react by the $S_N 2$ mechanism.

For the S_N1 reaction, formation of the carbocation is the rate-limiting step. We have already seen that the transition state for this step resembles the carbocation. Any change that makes the carbocation more stable will also make the transition state more stable, resulting in a faster reaction. Carbocation stability controls the rate of the S_N1 reaction. Many studies have provided the following order of carbocation stabilities:



This stability order is important to remember because carbocations occur as intermediates in several other reactions.

Name	Structure	Relative Rate
lsopropyl chloride <i>tert-</i> Butyl chloride	CH_{3} $CH_{3}CH-CI$ CH_{3} $CH_{3}C-CI$ CH_{3} $CH_{3}C-CI$ CH_{3}	 × 0 ⁵
Allyl chloride	CH ₂ =CHCH ₂ -Cl	3
Benzyl chloride	PhCH ₂ —Cl	30
Diphenylmethyl chloride	Ph ₂ CH—Cl	$I imes I0^4$
Triphenylmethyl chloride	Ph ₃ C—Cl	$I \times I0^9$

Table 8.2Relative Rates of S_NI Reactions forSelected Compounds

This order shows that the substitution of a methyl group for a hydrogen on a carbocation results in considerable stabilization. (The substitution of other alkyl groups provides a similar stabilization.) This is due to the overlap of a sigma bonding MO from the adjacent carbon with the empty p orbital of the carbocation. This overlap forms a conjugated system and allows electron density to flow from the sigma bond to the electron-deficient carbon. This overlap can be illustrated for the ethyl cation as follows:



The sigma MO and the empty p AO are coplanar, so they overlap in a manner similar to a pi bond, even though they are not parallel. This overlap provides a path for the electrons of the sigma bond to be delocalized into the empty p orbital, thus helping to stabilize the carbocation. Other kinds of sigma bonds can interact with an empty p orbital in a similar fashion, as long as the sigma MO and the p AO are on adjacent carboons. Such a stabilizing interaction is termed **hyperconjugation**.

Further examination of Table 8.2 shows that allyl chloride and benzyl chloride have much faster rates for S_N1 reactions than would be expected for primary systems. Examination of the carbocations reveals that the reason for this enhanced reactivity is the significant resonance stabilization provided by the adjacent double bond or benzene ring. Resonance stabilization increases with the substitution of additional phenyl groups, as illustrated by the reaction rates of diphenylmethyl and triphenylmethyl chloride (Table 8.2).



Focus On

The Triphenylmethyl Carbocation

Most carbocations are quite unstable and have only a fleeting existence as intermediates in reactions such as the $S_N 1$ substitution. However, some, such as the triphenylmethyl carbocation, are stable enough that they can exist in significant concentrations in solution or even can be isolated as salts.

When triphenylmethanol is dissolved in concentrated sulfuric acid, a solution with an intense yellow color is formed. The yellow species is the triphenylmethyl carbocation, formed by the following reaction:



The extensive resonance stabilization of this carbocation allows it to exist in solution as long as there is no good nucleophile around to react with it.

Other examples of the stability of this carbocation abound. Triphenylmethyl chloride forms conducting solutions in liquid sulfur dioxide because of cleavage of the carbon–chlorine bond (the first step of an S_N1 reaction):

$$Ph_3C \xrightarrow{\frown} Cl \xrightarrow{SO_2} Ph_3C^+ Cl^-$$

If the anion is not very nucleophilic, solid salts containing the triphenylmethyl carbocation can actually be isolated. Thus, the tetrafluoroborate salt, $Ph_3C^+BF_4^-$, can be isolated and stored for years as a stable ionic solid and is even commercially available. The geometry of perchlorate salt, $Ph_3C^+ ClO_4^-$, has been determined by X-ray crystallography. The central carbon has planar geometry as expected for an sp^2 -hybridized carbocation but the rings are twisted out of the plane because of the severe steric crowding that would occur if they were all planar, so the cation has a shape that resembles a propeller. Note that this causes a decrease in resonance stabilization (called steric hindrance to resonance) because the *p* orbitals on the benzene rings are not exactly parallel to the *p* orbital of the central carbon. Still, there is enough resonance stabilization to make this carbocation much more stable than most others.



PROBLEM 8.6

Explain which compound has a faster rate of S_N1 reaction.



PROBLEM 8.7

Arrange these compounds in order of decreasing $S_N 1$ reaction rate.



8.8 Stereochemistry of the $S_N 1$ Reaction

What happens in the S_N1 reaction if the leaving group is attached to a carbon that is a chirality center? A common result for the S_N1 reaction is racemization; that is, the product is formed with 50% inversion and 50% retention of configuration. An example, the reaction of (*S*)-1-chloro-1-phenylethane with water to give racemic 1-phenyl-1-ethanol, is illustrated in Figure 8.8. In this reaction the stereochemical integrity of the reactant is randomized on the pathway to the product. This usually means that there is some intermediate along the reaction pathway that is not chiral. In the case of the S_N1 reaction the carbocation intermediate is sp^2 hybridized and has trigonal planar geometry. Because planar carbons are not chirality centers, this explains why the reaction results in racemization.

Although many $S_N 1$ reactions proceed with racemization, many others result in more inversion of configuration in the product than retention. This is a result of the extremely short lifetime of the carbocation. When the carbocation is first formed, the leav-



Figure 8.8

MECHANISM AND STEREOCHEMISTRY OF THE $S_N I$ reaction of (S)-1-chloro-1phenylethane in Aqueous Solution. ing group is still present on the side of the carbocation where it was originally attached, as shown in Figure 8.9. This species is called an **ion pair**. If the nucleophile attacks the ion pair, the leaving group is still blocking the front side of the carbocation and inversion is favored. After the leaving group has had time to diffuse away, generating a "free" carbocation, the nucleophile can attack equally well from either side, and equal amounts of inversion and retention result. As the lifetime of the carbocation increases, it will more likely reach the free stage, resulting in more complete racemization. The lifetime of the carbocation increases as its stability increases and also depends on the nucleophile and the solvent that are used in a particular reaction. The change of nucleophile and solvent is why the reaction of 1-chloro-1-phenylethane in water (Figure 8.8) gives a different stereochemical result than the reaction of the same compound in



- The initial species formed in this S_NI reaction, a carbocation with the chloride anion situated directly adjacent, is called an ion pair. There is a competition between reaction of the nucleophile with the ion pair and diffusion of the anion away from the carbocation.
- Onder this particular set of reaction conditions, 16% of the ion pairs react with the nucleophile, acetate ion. Because the chloride is blocking one side of the ion pair, acetate can approach only from the opposite side. Therefore, only the product with inverted configuration is formed when the nucleophile reacts at this stage.
- For the other 84% of the ion pairs, the chloride ion diffuses away before the nucleophile attacks.
- The nucleophile can approach the resulting free carbocation equally well from either side, resulting in the formation of equal amounts of product with retained and inverted configuration (42% of each). The final result is 42% retention and 16% + 42% = 58% inversion. The reaction has occurred with racemization and some excess inversion.

Figure 8.9

Stereochemistry of the S_NI reaction of (S)-1-chloro-1-phenylethane in acetic acid containing potassium acetate.

acetic acid containing potassium acetate (Figure 8.9). The carbocation has a longer lifetime under the reaction conditions of Figure 8.8 than under those of Figure 8.9 (see problem 8.14), allowing the chloride ion time to diffuse away before the nucleophile attacks, resulting in the formation of a racemic product. The shorter-lived carbocation of Figure 8.9 reacts partly at the ion-pair stage, resulting in more inversion than retention. In summary, S_N reactions occur with racemization, often accompanied by some excess inversion. We will not attempt to predict the exact amount of each enantiomer that is produced.

PRACTICE PROBLEM 8.1

Show the product, including stereochemistry, of this reaction:



Strategy

First, identify the leaving group, the electrophilic carbon, and the nucleophile. Then decide whether the reaction follows the $S_N 1$ or $S_N 2$ mechanism because this determines the stereochemistry. If the leaving group is bonded to a tertiary carbon, then the reaction must occur by the $S_N 1$ mechanism. (Later we will learn other factors that control which substitution mechanism a reaction follows.) For an $S_N 1$ reaction, replace the leaving group on the electrophilic carbon with the nucleophile with loss of stereochemistry at the reaction center.

Solution

The leaving group is the chlorine and it is bonded to a tertiary carbon, so the reaction must follow an $S_N I$ mechanism. Because a planar carbocation is formed at the reaction center, the nucleophile, H₂O, can bond to either side of the cyclopentane ring. Stereochemistry is lost at the electrophilic carbon, but there is no change at the other chirality center because the reaction does not involve that carbon. Because the two products, one with the methyl groups cis and the other with the methyl groups trans, are diastereomers, they, along with the transition states leading to them, may have different energies. Therefore, the two alcohol products are not necessarily formed in equal amounts even if all of the carbocation makes it to the "free" stage. However, the stabilities of the products are not very different so similar amounts of both are expected.



PROBLEM 8.8

Show the products, including stereochemistry, of these S_N1 reactions:



8.9 LEAVING GROUPS

The bond to the leaving group is broken during the rate-determining step in both the S_N1 and S_N2 reactions. Therefore, the structure of the leaving group affects the rates of both of these reactions. Although the only leaving group we have seen so far is chloride, there are others that can be used. In general, the more stable the leaving group is as a free species—that is, after it has left—the faster it will leave. This stability is also reflected in the basicity of the species: the more stable it is, the weaker base it is. In general, the leaving groups that are used in the S_N1 and the S_N2 reactions are weak bases. Table 8.3 lists the most important leaving groups and provides their relative reaction rates in an S_N1 reaction. Similar rate effects are found for S_N2 reactions.

As can be seen from Table 8.3, the leaving ability of the halides increases as one goes down the column of the periodic table; that is, Cl⁻ is the slowest, Br⁻ is faster, and

Structure	Leaving Group	Name	Relative Reactivity
R—Cl	Cl	Chloride	I
R—Br	Br	Bromide	10
$\mathbf{R} \stackrel{+}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset{H}{\overset$	OH ₂	Water	10
R—I	Ī	lodide	10 ²
$\begin{array}{c} O \\ \parallel \\ R - O - \begin{array}{c} S \\ \parallel \\ O \end{array} - CH_3 \\ 0 \end{array}$	$\begin{array}{c} O\\ \parallel\\ -O-S-CH_3\\ \parallel\\ O\end{array}$	Mesylate (methane- sulfonate)	104
$\begin{array}{c} O \\ \parallel \\ R - O - S \\ \parallel \\ O \end{array} - CH_3$	$-O - S - CH_3$	Tosylate (p-toluene- sulfonate)	104

Table 8.3 Approximate Reactivities of Some Important Leaving Groups

 I^- is the fastest. This order parallels the decrease in basicity that occurs as one proceeds down a column of the periodic table. Fluoride ion (F⁻) is so slow that it is not commonly used as a leaving group.

PROBLEM 8.9

Explain whether these reactions would follow the $S_N 1$ or the $S_N 2$ mechanism and then explain which reaction is faster:

a)
$$CH_{3}CH_{2}$$
 + $OH \xrightarrow{H_{2}O} O-SO_{2}CH_{3}$
 $H_{2}O \rightarrow OH \xrightarrow{H_{2}O} OH \xrightarrow{H_{$

Because alcohols are very common and easily prepared by a variety of methods, it would be useful to be able to use OH as a leaving group in nucleophilic substitution reactions. However, OH^- is much too basic to act as a leaving group in S_N1 and S_N2 reactions. It is necessary to modify the OH, converting it to a better leaving group, to use alcohols as substrates for these reactions. Several methods have been developed to accomplish this goal. If the reaction of the alcohol is conducted in acidic solution, the oxygen becomes protonated, producing ROH_2^+ . The leaving group is now water, which is comparable to bromide in reactivity. (Of course, to use this leaving group, the nucleophile must be stable in acidic solution.) An example is provided in the following equation:



Click Mechanisms in Motion to view this S_NI Mechanism.

Another method that can be used to transform the hydroxy group of an alcohol into a leaving group is to replace the hydrogen with some other group that significantly decreases the basicity of the oxygen. A group that is commonly used for this purpose is the SO_2R group. Replacing the hydrogen of the alcohol with this group produces a sulfonate ester, such as the mesylate or tosylate ester shown in Table 8.3. As can be seen by their resemblance to the bisulfate anion (the conjugate base of sulfuric acid), sulfonate anions are weak bases and excellent leaving groups.



A sulfonate anion

Bisulfate anion

PROBLEM 8.10

a) Show all the steps in the mechanism for this reaction. Don't forget to use curved arrows to show the movement of electrons in each step of the mechanism.

$$\begin{array}{cccc} CH_{3} & CH_{3} \\ Ph & \stackrel{I}{\longrightarrow} OH & + & HI & \longrightarrow & Ph & \stackrel{I}{\longrightarrow} I & + & H_{2}O \\ & \stackrel{I}{\longrightarrow} CH_{3} & & CH_{3} \end{array}$$

b) Show a free energy versus reaction progress diagram for the reaction of part a.

Primary and secondary alcohols are readily converted to mesylate or tosylate esters by reaction with the corresponding sulfonyl chloride. The mesylate and tosylate esters derived from tertiary alcohols are too reactive and cannot be isolated. (Although we will not go into the mechanism of these reactions in detail at this point, the reactions involve the attack of the oxygen [the nucleophile] of the alcohol at the sulfur [the electrophile], ultimately displacing chloride [the leaving group].) Pyridine is often used as a solvent for these preparations in order to react with the HCl that is produced as a by-product. An example of the preparation of a methanesulfonate (mesylate) ester is shown in the following equation:





An example of the preparation of a tosylate ester is shown in the following equation:



or, in more general form:



In summary, the halide ions, Cl⁻, Br⁻, and I⁻, are common leaving groups for these nucleophilic substitution reactions. The OH of an alcohol can be converted to a leaving group by protonation in acid solution or by conversion to a mesylate or tosylate ester. The OR⁻ of an ether, like the OH⁻ of an alcohol, is too basic to leave. Likewise, NH₂⁻ (from an amine), H⁻ (from breaking C—H bonds of alkanes), and R₃C⁻ (carbanions from breaking C—C bonds of alkanes) are much too basic and *do not act as leaving groups in these reactions*.

The tosylate leaving group was used in one of the classic experiments that was used to determine the stereochemistry of the S_N2 reaction. Now that we know about this leaving group, let's look at the experiment and see how it helped establish that S_N2 reactions occur with inversion of configuration.

Designing an experiment to demonstrate that an $S_N 2$ reaction occurs with inversion of configuration is not as simple as it might appear at first glance. For example, consider using the reaction of 2-chlorobutane with hydroxide ion to produce 2-butanol to determine the stereochemistry of the $S_N 2$ reaction:



First, it must be established that this reaction proceeds by an $S_N 2$ mechanism. To do this, the experimental rate law for the reaction is determined. Because the reaction is found to follow the second-order rate law, rate = k[2-chlorobutane][hydroxide ion], it is proceeding by the $S_N 2$ mechanism. Then the stereochemistry of the product is investigated. Suppose that the starting 2-chlorobutane has $[\alpha] = +8.5$ and the 2-butanol formed in the reaction has $[\alpha] = -13.9$. What can be deduced from this information? Remember, there is no relationship between the sign of the rotation and the configuration of a compound. So, even though the starting 2-chlorobutane and the product 2-butanol have opposite signs for their rotations, we do not know whether they have the same or opposite relative configurations. Thus, it is impossible to determine whether the reaction has occurred with inversion or retention of configuration. Furthermore, unless the specific rotation of 2-butanol is known for comparison, the product can be partially racemic. Therefore, the only conclusion that can be reached on the basis of these data is that the reaction has not proceeded with complete racemization.

To determine the stereochemistry of the reaction, a method must be found to relate the configuration of the reactant to that of the product. The following experiment shows one method that has been used to accomplish this. A sample of 2-octanol with $[\alpha] = +1.12$ was converted to its tosylate ester, which had $[\alpha] = +0.90$. In this reaction the O of the alcohol displaces the Cl of *p*-toluenesulfonyl chloride. Because the carbon–oxygen bond of the alcohol is not broken in this reaction, the tosylate ester must have the same relative configuration as the alcohol.



 $^{[\}alpha] = +0.84$

The S_N2 reaction of the tosylate ester with acetate ion in acetone as solvent produced an ester with $[\alpha] = -0.83$. (Again, the configuration of the product cannot be determined solely on the basis of this experiment.)

To determine its stereochemistry, the ester was prepared by an alternate pathway. Reaction of the starting alcohol with acetyl chloride (CH₃COCl) produced the ester with $[\alpha] = +0.84$. This reaction, like the formation of the tosylate ester, does not involve breaking the carbon-oxygen bond of the alcohol, so the ester obtained in this reaction must have the same relative configuration as both the alcohol and the *p*-toluenesulfonate ester. Comparison of the rotation of this ester, ($[\alpha] = +0.84$) with that of the ester obtained as the product of the S_N2 reaction ($[\alpha] = -0.83$) demonstrated that they have opposite relative configurations. Therefore, the S_N2 reaction has occurred with complete inversion of configuration, within experimental error. It is interesting to note that it not necessary to know the absolute configuration of any of the compounds in this reaction cycle to determine that the S_N2 reaction has proceeded with inversion of configuration. Nor is it necessary that the original alcohol be enantiomerically pure—that is, that it be composed of a single enantiomer. In fact, in the experiment described here, the enantiomeric purity of the original 2-octanol was only 11%.

A large number of other experiments have been performed, and in each case the results have been the same. $S_N 2$ reactions have always been found to proceed with complete inversion of configuration.

8.10 NUCLEOPHILES

In the case of an S_N1 reaction, the nucleophile does not become involved until after the rate-determining step. Therefore, changing the nucleophile has no effect on the *rate* of an S_N1 reaction, although it may change the *product* of the reaction. In contrast, changing the nucleophile in an S_N2 reaction has a dramatic effect on the reaction rate because the nucleophile attacks in the rate-determining step.

What makes a good nucleophile? Nucleophilic substitutions are somewhat similar to acid-base reactions. In an acid-base reaction, a hydrogen is transferred from one base to another. In a nucleophilic substitution reaction, a carbon group is transferred from one nucleophile (Lewis base) to another. It is not surprising, then, that strength as a nucleophile often parallels strength as a base. However, because nucleophiles react with carbon and bases react with hydrogen, it is also not surprising that there are some differences between nucleophilicity and basicity. The following rules apply.

If the nucleophilic atoms are from the same period of the periodic table, strength as a nucleophile parallels strength as a base. For example,

$$H_2O < NH_3$$

 $CH_3OH \approx H_2O < CH_3CO_2^- < CH_3O^- \approx HO^-$
increasing base strength/increasing nucleophile strength

RULE 2

Nucleophile strength increases down a column of the periodic table (in solvents that can hydrogen bond, such as water and alcohols). For example,



In these cases the change in nucleophile strength is opposite to the change in base strength. This is due at least in part to the stronger hydrogen bonding that occurs between the smaller ions and solvent molecules of water or alcohols. The resulting tighter arrangement of solvent molecules around the nucleophile makes it more difficult for the electrophilic carbon to approach.

RULE 3

Steric bulk decreases nucleophilicity. For example,

tert-Butoxide ion Weaker nucleophile, stronger base Stronger nucleophile Weaker base

Because the presence of bulky groups at the electrophilic carbon slows the rate of $S_N 2$ reactions, it is reasonable that the presence of bulky groups on the nucleophile will also slow the reaction. The steric bulk of the *tert*-butoxide ion causes it to be a much weaker nucleophile than hydroxide ion even though it is a stronger base. Therefore, *tert*-butoxide ion is often used when a strong base that is not very nucleophilic is needed.

PRACTICE PROBLEM 8.2

Explain which reaction proceeds at a faster rate:

$$\begin{array}{c} I \\ H_{2}O \\ CH_{3}CH_{2}CH_{2} + OH \end{array} \xrightarrow{H_{2}O} Or CH_{3}CH_{2}CH_{2} + H_{2}O \xrightarrow{H_{2}O} EtOH \end{array}$$

Strategy

First identify the leaving group, the electrophilic carbon, and the nucleophile. If the leaving group is on a primary carbon, then the mechanism that the reaction follows is $S_N 2$. If the leaving group is on a tertiary carbon, then the mechanism is $S_N 1$. (We will learn how to determine the mechanism if the leaving group is on a secondary carbon in Section 8.12.) Then identify the difference between the two reactions and analyze how this difference will affect the rate.

Solution

Because the leaving group is on a primary carbon, the reaction proceeds by an S_N^2 mechanism. The left reaction will be faster because hydroxide ion is a stronger base and, thus, a better nucleophile than water.

PROBLEM 8.11

Explain which of these reactions proceeds at a faster rate:

a)
$$CH_3 C O CH_3 O CH_3 O O CH_3 O O CH_3 O O O CH_3 CO_2 H$$

 $H_3 C - Cl + CH_3 COH CH_3 CO_2 H$ or $CH_3 C - Cl + CH_3 CO^- CH_3 CO_2 H$
 $CH_3 C - Cl + CH_3 CO^- CH_3 CO_2 H$

b)
$$CH_3CH_2CH_2CH_2 + CH_3O^- \xrightarrow{CH_3OH} \text{ or } CH_3CH_2CH_2CH_2 + CH_3S^- \xrightarrow{CH_3OH}$$

c) $CH_3CH_2CH_2CH_2 + CH_3O^- \xrightarrow{CH_3OH} \text{ or } CH_3CH_2CH_2CH_2 + CH_3CO^- \xrightarrow{CH_3CO_2H}$

PROBLEM 8.12

Show the products and the mechanisms of the following reactions. Don't forget to use curved arrows to show the movement of electrons in each step of the mechanism.

a)
$$CH_{3}CH_{2}CHCH_{3} + \overrightarrow{:::H} \xrightarrow{S_{N}2}$$

b) $CH_{3}CH_{2}CCH_{3} + CH_{3}CH_{2}\overrightarrow{:CH} \longrightarrow$
Br
c) $CH_{3}CH_{2}CH_{2}CH_{2}CH_{2} + \overrightarrow{N}H_{2}CH_{3} \longrightarrow$
d) \overrightarrow{C} + $CH_{3}CH_{2}CH_{2}\overrightarrow{:CH} \xrightarrow{S_{N}2}$

PROBLEM 8.13

Show all of the steps in the mechanism for this reaction:

$$\begin{array}{cccc} CH_3 & CH_3 \\ CH_3 - C - Cl & + & CH_3OH & \longrightarrow & CH_3 - C - OCH_3 & + & HCl \\ CH_3 & & & CH_3 & - & CH_3 \end{array}$$

8.11 EFFECT OF SOLVENT

The solvent has several roles to play in an organic reaction. It must dissolve the reagents so that they can come in contact with one another. It must not react with or decompose any of the reagents. In addition, for reactions that involve ionic or polar molecules (as reactants, intermediates, or products), the polarity of the solvent often dramatically affects the reaction rate.

Polar solvents help to stabilize ions and polar molecules. To understand the effect of the solvent polarity on reaction rates, the polarity of the reactant must be compared with the polarity of the transition state. The one (reactant or transition state) that is more polar (has more charge separation) will be stabilized more by an increase in the polarity of the solvent. If the transition state is more polar than the reactants, increasing the solvent polarity will stabilize the transition state more than the reactants. This will decrease ΔG^{\ddagger} , resulting in a faster reaction. In contrast, if the reactants are more polar than the transition state, increasing the solvent polarity will stabilize the reactants more, resulting in a larger ΔG^{\ddagger} and a slower reaction.

Figure 8.10 illustrates the results of increasing the solvent polarity on the energy versus reaction progress curve for the S_N1 reaction. Because the transition state, which resembles the carbocation, is more polar than the reactant, the rate of an S_N1 reaction is much faster in a more polar solvent.