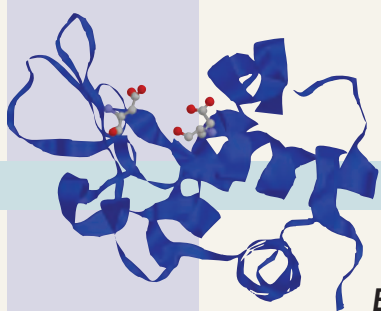


6

IONIC REACTIONS NUCLEOPHILIC SUBSTITUTION AND ELIMINATION REACTIONS OF ALKYL HALIDES



Lysozyme

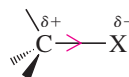
Breaking Bacterial Cell Walls with Organic Chemistry

Enzymes, nature's quintessential chemists, catalyze most reactions of life. Enzymes catalyze metabolic reactions, the flow of genetic information, and the synthesis of molecules that provide biological structure. They also help defend us against infections and disease. Although mechanisms have been elucidated for the action of many enzymes, those for which mechanistic secrets have been unlocked constitute only a fraction of all of the enzymes involved in life's processes. It is widely accepted, however, that all reactions catalyzed by enzymes occur on the basis of rational chemical reactivity. The mechanisms utilized by enzymes are essentially those that we learn about in organic chemistry. One such example involves lysozyme, a protein whose schematic structure is shown above.

Lysozyme is an enzyme that degrades bacterial cell walls. It is found in tears, saliva, nasal mucous, and egg whites. Lysozyme cleaves bacterial cell walls by a nucleophilic substitution reaction involving a mechanism we shall study in this chapter. In the first reaction of a two-reaction sequence, a covalent bond in the bacterial cell wall is broken as lysozyme forms a bond with a specific carbon of the cell wall structure. In the next reaction, a water molecule displaces the lysozyme molecule, releasing the enzyme for another catalytic cycle and completing the hydrolysis process. We shall return later in this chapter to consider the details of these nucleophilic reactions in "The Chemistry of ... Lysozyme" (Section 6.8). As you shall see, lysozyme provides a wonderful biochemical example of one type of nucleophilic substitution mechanism that we will study.

6.1 Organic Halides

The halogen atom of an alkyl halide is attached to an sp^3 -hybridized carbon. The arrangement of groups around the carbon atom, therefore, is generally tetrahedral. Because halogen atoms are more electronegative than carbon, the carbon–halogen bond of alkyl halides is *polarized*; the carbon atom bears a partial positive charge, the halogen atom a partial negative charge:



Halogen atom size increases as we go down the periodic table: fluorine atoms are the smallest and iodine atoms the largest. Consequently, the carbon–halogen *bond length increases* and carbon–halogen *bond strength decreases* as we go down the periodic table (Table 6.1). Maps of electrostatic potential at the van der Waals surface for the four methyl halides, with ball-and-stick models inside, illustrate the trend in polarity, C—X bond length, and halogen atom size as one progresses from fluorine to iodine substitution. Fluoromethane is highly polar and has the shortest C—X bond length and the strongest C—X bond. Iodomethane is much less polar and has the longest C—X bond length and the weakest C—X bond.

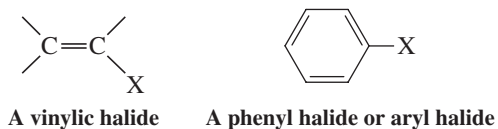
TABLE 6.1 Carbon–Halogen Bond Lengths and Bond Strengths

| | | | | |
|---|---|--|--|---|
| | | | | |
| | | | | |
| | $\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{F} \\ \\ \text{H} \end{array}$ | $\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{Cl} \\ \\ \text{H} \end{array}$ | $\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{Br} \\ \\ \text{H} \end{array}$ | $\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{I} \\ \\ \text{H} \end{array}$ |
| C—X Bond length (Å) | 1.39 | 1.78 | 1.93 | 2.14 |
| C—X Bond strength (kJ mol ⁻¹) | 472 | 350 | 293 | 239 |

In the laboratory and in industry, alkyl halides are used as solvents for relatively nonpolar compounds, and they are used as the starting materials for the synthesis of many compounds. As we shall learn in this chapter, the halogen atom of an alkyl halide can be easily replaced by other groups, and the presence of a halogen atom on a carbon chain also affords us the possibility of introducing a multiple bond.

Compounds in which a halogen atom is bonded to an sp^2 -hybridized carbon are called **vinyl halides** or **phenyl halides**. The compound $\text{CH}_2=\text{CHCl}$ has the common name **vinyl chloride**, and the group $\text{CH}_2=\text{CH}-$ is commonly called the **vinyl group**. *Vinyl halide*, therefore, is a general term that refers to a compound in which a halogen is attached to a carbon atom that is also forming a double bond to another carbon atom. *Phenyl halides* are compounds in which a halogen is attached to a benzene ring (Section 2.5B).

Phenyl halides belong to a larger group of compounds that we shall study later, called **aryl halides**.



Together with alkyl halides, these compounds comprise a larger group of compounds known simply as **organic halides** or **organohalogen compounds**. The chemistry of vinylic and aryl halides is, as we shall also learn later, quite different from that of alkyl halides, and it is on alkyl halides that we shall focus most of our attention in this chapter.

6.1A Physical Properties of Organic Halides

Most alkyl and aryl halides have very low solubilities in water, but as we might expect, they are miscible with each other and with other relatively nonpolar solvents. Dichloromethane (CH_2Cl_2 , also called *methylene chloride*), trichloromethane (CHCl_3 , also called *chloroform*), and tetrachloromethane (CCl_4 , also called *carbon tetrachloride*) are sometimes used as solvents for nonpolar and moderately polar compounds. Many chloroalkanes, including CHCl_3 and CCl_4 , have a cumulative toxicity and are carcinogenic, however, and should therefore be used only in fume hoods and with great care.

Iodomethane (bp 42°C) is the only monohalomethane that is a liquid at room temperature and 1 atm pressure. Bromoethane (bp 38°C) and iodoethane (bp 72°C) are both liquids, but chloroethane (bp 13°C) is a gas. The chloro-, bromo-, and iodoalkanes are all liquids. In general, higher chloro-, bromo-, and iodoalkanes are all liquids and tend to have boiling points near those of alkanes of similar molecular weights.

Polyfluoroalkanes, however, tend to have unusually low boiling points (Section 2.14D). Hexafluoroethane boils at -79°C , even though its molecular weight (MW = 138) is near that of decane (MW = 144; bp 174°C).

Table 6.2 lists the physical properties of some common organic halides.

TABLE 6.2 Organic Halides

| Group | Fluoride | | Chloride | | Bromide | | Iodide ^a | |
|------------------------------------|-------------------------|--|-------------------------|--|-------------------------|--|--|--|
| | bp ($^\circ\text{C}$) | Density ^a (g mL^{-1}) | bp ($^\circ\text{C}$) | Density ^a (g mL^{-1}) | bp ($^\circ\text{C}$) | Density ^a (g mL^{-1}) | bp ^{b,c} ($^\circ\text{C}$) | Density ^a (g mL^{-1}) |
| Methyl | -78.4 | 0.84 ⁻⁶⁰ | -23.8 | 0.92 ²⁰ | 3.6 | 1.73 ⁰ | 42.5 | 2.28 ²⁰ |
| Ethyl | -37.7 | 0.72 ²⁰ | 13.1 | 0.91 ¹⁵ | 38.4 | 1.46 ²⁰ | 72 | 1.95 ²⁰ |
| Propyl | -2.5 | 0.78 ⁻³ | 46.6 | 0.89 ²⁰ | 70.8 | 1.35 ²⁰ | 102 | 1.74 ²⁰ |
| Isopropyl | -9.4 | 0.72 ²⁰ | 34 | 0.86 ²⁰ | 59.4 | 1.31 ²⁰ | 89.4 | 1.70 ²⁰ |
| Butyl | 32 | 0.78 ²⁰ | 78.4 | 0.89 ²⁰ | 101 | 1.27 ²⁰ | 130 | 1.61 ²⁰ |
| sec-Butyl | — | — | 68 | 0.87 ²⁰ | 91.2 | 1.26 ²⁰ | 120 | 1.60 ²⁰ |
| Isobutyl | — | — | 69 | 0.87 ²⁰ | 91 | 1.26 ²⁰ | 119 | 1.60 ²⁰ |
| tert-Butyl | 12 | 0.75 ¹² | 51 | 0.84 ²⁰ | 73.3 | 1.22 ²⁰ | 100 dec | 1.57 ⁰ |
| Pentyl | 62 | 0.79 ²⁰ | 108.2 | 0.88 ²⁰ | 129.6 | 1.22 ²⁰ | 157 | 1.52 ²⁰ |
| Neopentyl | — | — | 84.4 | 0.87 ²⁰ | 105 | 1.20 ²⁰ | 127 dec | 1.53 ¹³ |
| $\text{CH}_2=\text{CH}-$ | -72 | 0.68 ²⁶ | -13.9 | 0.91 ²⁰ | 16 | 1.52 ¹⁴ | 56 | 2.04 ²⁰ |
| $\text{CH}_2=\text{CHCH}_2-$ | -3 | — | 45 | 0.94 ²⁰ | 70 | 1.40 ²⁰ | 102–103 | 1.84 ²² |
| C_6H_5- | 85 | 1.02 ²⁰ | 132 | 1.10 ²⁰ | 155 | 1.52 ²⁰ | 189 | 1.82 ²⁰ |
| $\text{C}_6\text{H}_5\text{CH}_2-$ | 140 | 1.02 ²⁵ | 179 | 1.10 ²⁵ | 201 | 1.44 ²² | 93 ¹⁰ | 1.73 ²⁵ |

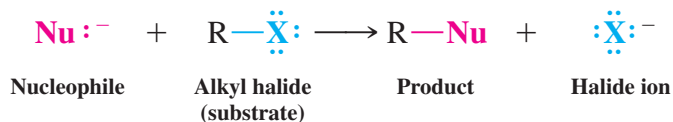
^aDensities were measured at temperature ($^\circ\text{C}$) indicated in superscript.

^bBoiling point superscripts indicate pressure (torr) when other than atmospheric pressure was used.

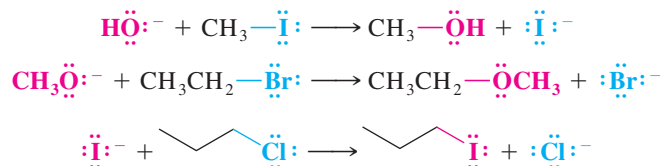
^cDecomposes is abbreviated dec.

6.2 Nucleophilic Substitution Reactions

There are many reactions of the general type shown here:



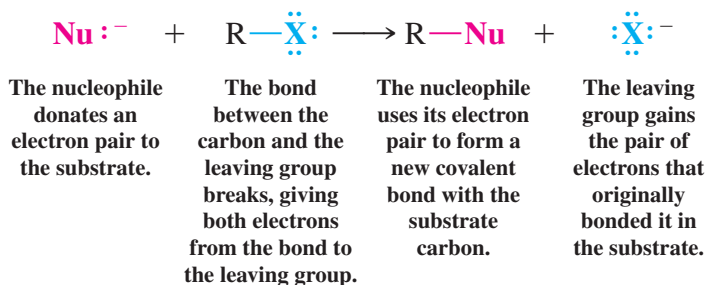
Following are some examples:



In Section 6.14 we shall see examples of biological nucleophilic substitution.

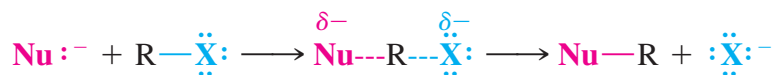
In this type of reaction a **nucleophile**, a *species with an unshared electron pair*, reacts with an alkyl halide (called the **substrate**) by replacing the halogen substituent. A **substitution reaction** takes place and the halogen substituent, called the **leaving group**, departs as a halide ion. Because the substitution reaction is initiated by a nucleophile, it is called a **nucleophilic substitution reaction**.

In nucleophilic substitution reactions the carbon–halogen bond of the substrate undergoes *heterolytic* bond cleavage, and the unshared electron pair of the nucleophile is used to form a new bond to the carbon atom:

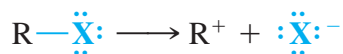


In color-coded reactions of this chapter, we will use red to indicate a nucleophile and blue to indicate a leaving group.

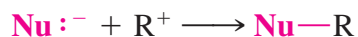
A key question we shall want to address later in this chapter is this: When does the carbon–halogen bond break? Does it break at the same time that the new bond between the nucleophile and the carbon forms?



Or does the carbon–halogen bond break first?



And then



We shall find that the answer depends primarily on the structure of the alkyl halide.

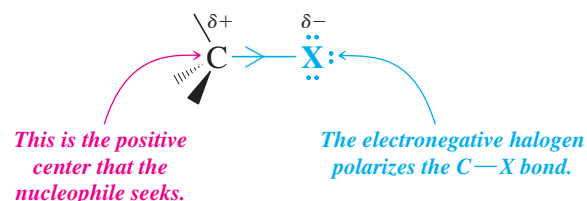
6.3 Nucleophiles



You may wish to review Section 3.2C, “Opposite Charges Attract.”

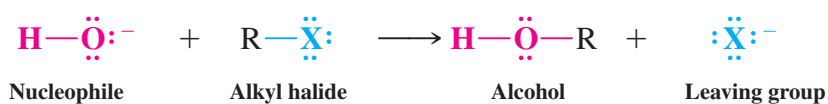
A nucleophile is a reagent that seeks a positive center. (The word nucleophile comes from *nucleus*, the positive part of an atom, plus *-phile* from the Greek word *philos*, meaning to love.) When a nucleophile reacts with an alkyl halide, the positive center that the nucleophile seeks is the carbon atom that bears the halogen atom. This carbon atom carries a par-

tial positive charge because the electronegative halogen pulls the electrons of the carbon–halogen bond in its direction (see Section 2.4):

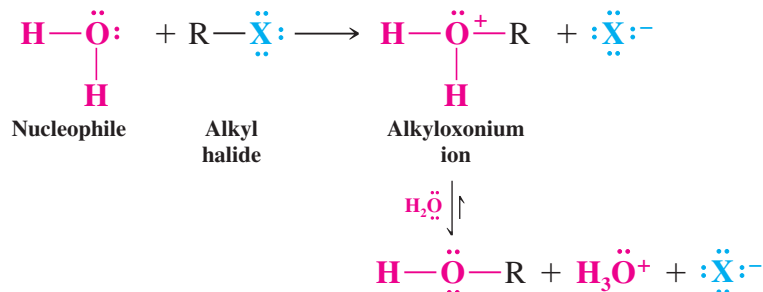


A nucleophile is any negative ion or any neutral molecule that has at least one unshared electron pair. (Later we shall see that pi bonds can be nucleophiles as well.) For example, both hydroxide ions and water molecules can act as nucleophiles by reacting with alkyl halides to produce alcohols.

General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion



General Reaction for Nucleophilic Substitution of an Alkyl Halide by Water



STUDY TIP! A deprotonation step is always required to complete the reaction when the nucleophile was a neutral atom that bore a proton.

In the second reaction, note that the first product is an alkyloxonium ion, $\text{R}-\overset{+}{\text{O}}(\text{H})_2$, which then loses a proton to a water molecule to form an alcohol.

Write the following as *net ionic reactions* and designate the nucleophile, substrate, and leaving group in each reaction:

- (a) $\text{CH}_3\text{I} + \text{CH}_3\text{CH}_2\text{ONa} \longrightarrow \text{CH}_3\text{OCH}_2\text{CH}_3 + \text{NaI}$
- (b) $\text{NaI} + \text{CH}_3\text{CH}_2\text{Br} \longrightarrow \text{CH}_3\text{CH}_2\text{I} + \text{NaBr}$
- (c) $2 \text{CH}_3\text{OH} + (\text{CH}_3)_3\text{CCl} \longrightarrow (\text{CH}_3)_3\text{COCH}_3 + \text{CH}_3\text{OH}_2^+ + \text{Cl}^-$
- (d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{NaCN} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CN} + \text{NaBr}$
- (e) $\text{C}_6\text{H}_5\text{CH}_2\text{Br} + 2 \text{NH}_3 \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2 + \text{NH}_4\text{Br}$

Review Problem 6.1

6.4 Leaving Groups

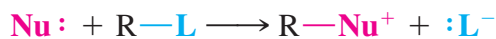
To act as the substrate in a nucleophilic substitution reaction, a molecule must have a good **leaving group**. A good leaving group is a substituent that can leave as a relatively stable, weakly basic molecule or anion. The halogen atom of an alkyl halide is a good leaving group because once departed it is a weak base and stable anion. (Alkyl halides are not the only class of compounds that can act as substrates in nucleophilic substitution reactions. We shall see later that other compounds can also react in the same way).

226 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

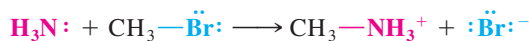
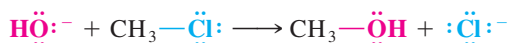
In the following examples we show nucleophilic substitution reactions first with a charged nucleophile and then with a neutral nucleophile. We use **L** to represent a generic leaving group. Note that the overall charge is balanced in the case of each equation:



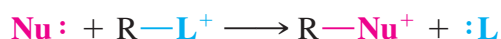
or



Specific Examples

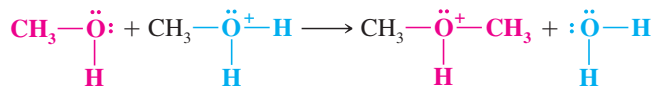


Later we shall also see reactions where the substrate bears a formal positive charge and a reaction like the following takes place:



In this case, when the leaving group departs with an electron pair, its formal charge goes to zero.

Specific Example



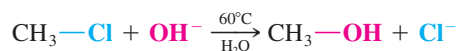
Nucleophilic substitution reactions are more understandable and useful if we know something about their mechanisms. How does the nucleophile replace the leaving group? Does the reaction take place in one step or is more than one step involved? If more than one step is involved, what kinds of intermediates are formed? Which steps are fast and which are slow? In order to answer these questions, we need to know something about the rates of chemical reactions.



Note that the net charge is the same on each side of a properly written chemical equation.

6.5 Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction

To understand how the rate of a reaction (**kinetics**) might be measured, let us consider an actual example: the reaction that takes place between chloromethane and hydroxide ion in aqueous solution:



Although chloromethane is not highly soluble in water, it is soluble enough to carry out our kinetic study in an aqueous solution of sodium hydroxide. Because reaction rates are known to be temperature dependent (Section 6.7), we carry out the reaction at a constant temperature.

The rate of the reaction can be determined experimentally by measuring the rate at which chloromethane or hydroxide ion *disappears* from the solution or the rate at which methanol or chloride ion *appears* in the solution. We can make any of these measurements by withdrawing a small sample from the reaction mixture soon after the reaction begins and analyzing it for the concentrations of CH_3Cl or OH^- and CH_3OH or Cl^- . We are interested in what are called *initial rates*, because as time passes the concentrations of the reactants change. Since we also know the initial concentrations of reactants (because we measured them when we made up the solution), it will be easy to calculate the rate at which the reactants are disappearing from the solution or the products are appearing in the solution.

We perform several such experiments keeping the temperature the same but varying the initial concentrations of the reactants. The results that we might get are shown in Table 6.3.

Notice that the experiments show that the rate depends on the concentration of chloromethane *and* on the concentration of hydroxide ion. When we doubled the concentration of chloromethane in experiment 2, the rate *doubled*. When we doubled the

TABLE 6.3 Rate Study of Reaction of CH₃Cl with OH⁻ at 60°C

| Experiment Number | Initial [CH ₃ Cl] | Initial [OH ⁻] | Initial Rate (mol L ⁻¹ s ⁻¹) |
|-------------------|------------------------------|----------------------------|---|
| 1 | 0.0010 | 1.0 | 4.9 × 10 ⁻⁷ |
| 2 | 0.0020 | 1.0 | 9.8 × 10 ⁻⁷ |
| 3 | 0.0010 | 2.0 | 9.8 × 10 ⁻⁷ |
| 4 | 0.0020 | 2.0 | 19.6 × 10 ⁻⁷ |

concentration of hydroxide ion in experiment 3, the rate *doubled*. When we doubled both concentrations in experiment 4, the rate increased by a factor of *four*.

We can express these results as a proportionality,

$$\text{Rate} \propto [\text{CH}_3\text{Cl}][\text{OH}^-]$$

and this proportionality can be expressed as an equation through the introduction of a proportionality constant (*k*) called the rate constant:

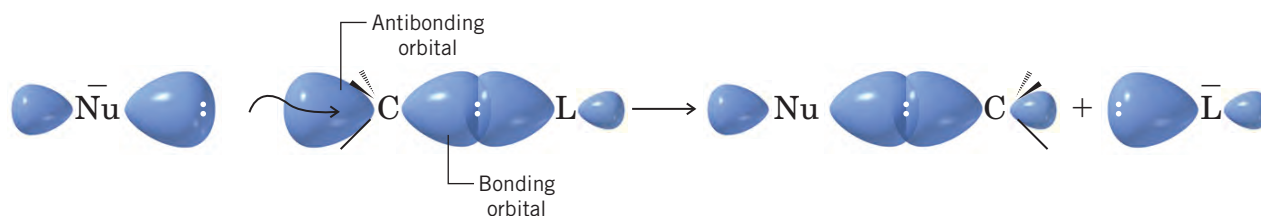
$$\text{Rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]$$

For this reaction at this temperature we find that $k = 4.9 \times 10^{-4} \text{ L mol}^{-1} \text{ s}^{-1}$. (Verify this for yourself by doing the calculation.)

This reaction is said to be **second order overall**.* It is reasonable to conclude, therefore, that *for the reaction to take place a hydroxide ion and a chloromethane molecule must collide*. We also say that the reaction is **bimolecular**. (By *bimolecular* we mean that two species are involved in the step whose rate is being measured. In general the number of species involved in a reaction step is called the **molecularity** of the reaction.) We call this kind of reaction an **S_N2 reaction**, meaning **substitution, nucleophilic, bimolecular**.

6.6 A Mechanism for the S_N2 Reaction

A schematic representation of orbitals involved in an S_N2 reaction—based on ideas proposed by Edward D. Hughes and Sir Christopher Ingold in 1937—is outlined below.



According to this mechanism, the nucleophile approaches the carbon bearing the leaving group from the **back side**, that is, from the side directly opposite the leaving group. The orbital that contains the electron pair of the nucleophile (its highest occupied molecular orbital, or HOMO) begins to overlap with an empty orbital (the lowest unoccupied molecular orbital, or LUMO) of the carbon atom bearing the leaving group. As the reaction progresses, the bond between the nucleophile and the carbon atom strengthens, and the bond between the carbon atom and the leaving group weakens. As this happens, the carbon atom has its configuration turned inside out, it undergoes **inversion**,[†] and the leaving group is pushed

*In general, the overall order of a reaction is equal to the sum of the exponents *a* and *b* in the rate equation $\text{Rate} = k[\text{A}]^a [\text{B}]^b$. If in some other reaction, for example, we found that $\text{Rate} = k[\text{A}]^2 [\text{B}]$, then we would say that the reaction is second order with respect to [A], first order with respect to [B], and third order overall.

[†]Considerable evidence had appeared in the years prior to Hughes and Ingold's 1937 publication indicating that in reactions like this an inversion of configuration of the carbon bearing the leaving group takes place. The first observation of such an inversion was made by the Latvian chemist Paul Walden in 1896, and such inversions are called **Walden inversions** in his honor. We shall study this aspect of the S_N2 reaction further in Section 6.8.

228 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

away. The formation of the bond between the nucleophile and the carbon atom provides most of the energy necessary to break the bond between the carbon atom and the leaving group. We can represent this mechanism with chloromethane and hydroxide ion as shown in the box “A Mechanism for the S_N2 Reaction” below.

The Hughes–Ingold mechanism for the S_N2 reaction involves only one step. There are no intermediates. The reaction proceeds through the formation of an unstable arrangement of atoms called the **transition state**.

The transition state is a fleeting arrangement of the atoms in which the nucleophile and the leaving group are both partially bonded to the carbon atom undergoing substitution. Because the transition state involves both the nucleophile (e.g., a hydroxide ion) and the substrate (e.g., a molecule of chloromethane), this mechanism accounts for the second-order reaction kinetics that we observe. (Because bond formation and bond breaking occur *simultaneously* in a single transition state, the S_N2 reaction is an example of what is called a **concerted reaction**.)

The transition state has an extremely brief existence. It lasts only as long as the time required for one molecular vibration, about 10^{-12} s. The structure and energy of the transition state are highly important aspects of any chemical reaction. We shall, therefore, examine this subject further in Section 6.7.



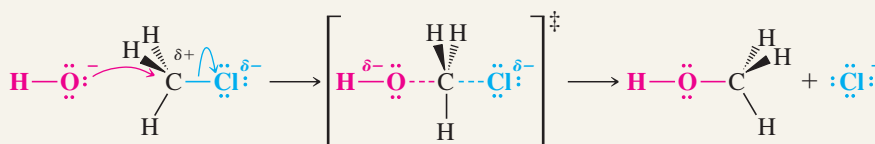
A MECHANISM FOR THE REACTION

Mechanism for the S_N2 Reaction

REACTION



MECHANISM



The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

Transition state
In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

6.7 Transition State Theory: Free-Energy Diagrams

A reaction that proceeds with a negative free-energy change is said to be **exergonic**; one that proceeds with a positive free-energy change is said to be **endergonic**. The reaction between chloromethane and hydroxide ion in aqueous solution is highly exergonic; at 60°C (333 K), $\Delta G^\circ = -100 \text{ kJ mol}^{-1}$. (The reaction is also exothermic, $\Delta H^\circ = -75 \text{ kJ mol}^{-1}$.)



The equilibrium constant for the reaction is extremely large, as we show by the following calculation:

$$\begin{aligned}\Delta G^\circ &= -RT \ln K_{\text{eq}} \\ \ln K_{\text{eq}} &= \frac{-\Delta G^\circ}{RT} \\ \ln K_{\text{eq}} &= \frac{-(-100 \text{ kJ mol}^{-1})}{0.00831 \text{ kJ K}^{-1} \text{ mol}^{-1} \times 333 \text{ K}} \\ \ln K_{\text{eq}} &= 36.1 \\ K_{\text{eq}} &= 5.0 \times 10^{15}\end{aligned}$$

An equilibrium constant as large as this means that the reaction goes to completion.

Because the free-energy change is negative, we can say that in energy terms the reaction goes **downhill**. The products of the reaction are at a lower level of free energy than the reactants.

However, considerable experimental evidence exists showing that **if covalent bonds are broken in a reaction, the reactants must go up an energy hill first**, before they can go downhill. This will be true even if the reaction is exergonic.

We can represent this graphically by plotting the free energy of the reacting particles against the reaction coordinate. A **free-energy diagram** is given in Fig. 6.1. We have chosen as our example a generalized S_N2 reaction.

The **reaction coordinate** is a quantity that measures the progress of the reaction. It represents the changes in bond orders and bond distances that must take place as the reactants are converted to products. In this instance the R–L distance could be used as the reaction coordinate because as the reaction progresses the R–L distance becomes longer.

In our illustration (Fig. 6.1), we can see that an **energy barrier** exists between the reactants and products. The height of this barrier (in kilojoules per mole) above the level of reactants is called the **free energy of activation, ΔG^\ddagger** .

The top of the energy hill corresponds to the transition state. *The difference in free energy between the reactants and the transition state is the free energy of activation, ΔG^\ddagger . The difference in free energy between the reactants and products is the free-energy change for the reaction, ΔG° .* For our example in Fig. 6.1, the free-energy level of the products is lower than that of the reactants. In terms of our analogy, we can say that the reactants in one energy valley must surmount an energy hill (the transition state) in order to reach the lower energy valley of the products.

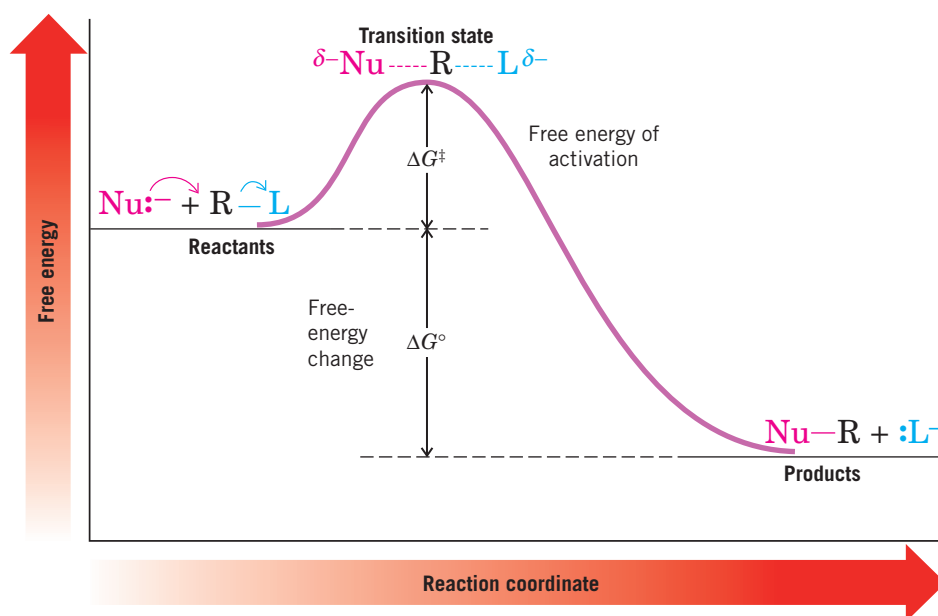
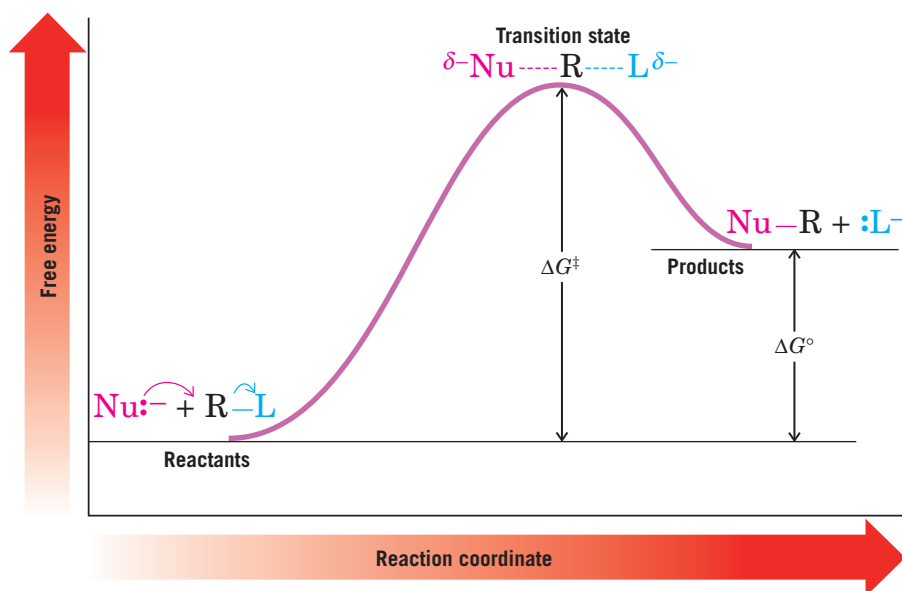


FIGURE 6.1 A free-energy diagram for a hypothetical S_N2 reaction that takes place with a negative ΔG° .

230 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

FIGURE 6.2 A free-energy diagram for a hypothetical reaction with a positive free-energy change.

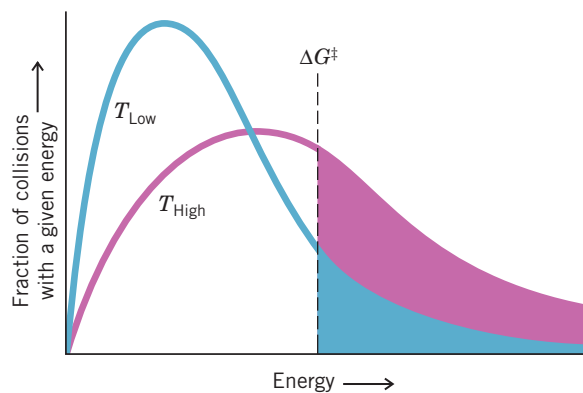


If a reaction in which covalent bonds are broken proceeds with a positive free-energy change (Fig. 6.2), there will still be a free energy of activation. That is, if the products have greater free energy than reactants, the free energy of activation will be even higher. (ΔG^\ddagger will be larger than ΔG° .) In other words, in the **uphill** (endergonic) reaction an even larger energy hill lies between the reactants in one valley and the products in a higher one.

The existence of an activation energy (ΔG^\ddagger) explains why most chemical reactions occur much more rapidly at higher temperatures. *For many reactions taking place near room temperature, a 10°C increase in temperature will cause the reaction rate to double.*

This dramatic increase in reaction rate results from a large increase in the number of collisions between reactants that together have sufficient energy to surmount the barrier at the higher temperature. The kinetic energies of molecules at a given temperature are not all the same. Figure 6.3 shows the distribution of energies brought to collisions at two temperatures (that do not differ greatly), labeled T_{Low} and T_{High} . Because of the way energies are distributed at different temperatures (as indicated by the shapes of the curves), increasing the temperature by only a small amount causes a large increase in the number of collisions with larger energies. In Fig. 6.3 we have designated an arbitrary minimum free energy of activation as being required to bring about a reaction between colliding molecules. The number of collisions having sufficient energy to allow the reaction to take place at a given temperature is proportional to the area under the portion of the curve that represents free energies greater than or equal to ΔG^\ddagger . At the lower temperature (T_{Low}) this number is relatively small. At the higher temperature (T_{High}), however, the number of collisions that take place with enough energy to react is very much larger. Consequently, a modest temperature increase produces a large increase in the number of collisions with energy sufficient to lead to a reaction.

FIGURE 6.3 The distribution of energies at two different temperatures, T_{Low} and T_{High} . The number of collisions with energies greater than the free energy of activation is indicated by the appropriately shaded area under each curve.



There is also an important relationship between the rate of a reaction and the magnitude of the free energy of activation. The relationship between the rate constant (k) and ΔG^\ddagger is an exponential one:

$$k = k_0 e^{-\Delta G^\ddagger/RT}$$

In this equation, $e = 2.718$, the base of natural logarithms, and k_0 is the absolute rate constant, which equals the rate at which all transition states proceed to products. At 25°C, $k_0 = 6.2 \times 10^{12} \text{ s}^{-1}$. Because of this exponential relationship, **a reaction with a lower free energy of activation will occur very much faster than a reaction with a higher one.**

Generally speaking, if a reaction has a ΔG^\ddagger less than 84 kJ mol⁻¹, it will take place readily at room temperature or below. If ΔG^\ddagger is greater than 84 kJ mol⁻¹, heating will be required to cause the reaction to occur at a reasonable rate.

A free-energy diagram for the reaction of chloromethane with hydroxide ion is shown in Fig. 6.4. At 60°C, $\Delta G^\ddagger = 103 \text{ kJ mol}^{-1}$, which means that at this temperature the reaction reaches completion in a matter of a few hours.

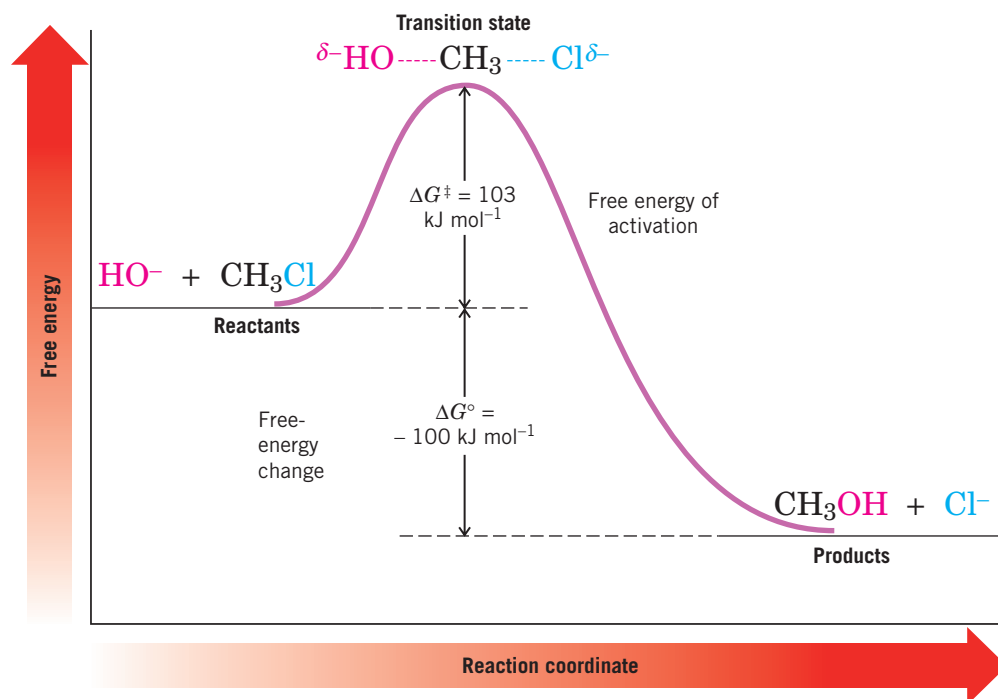
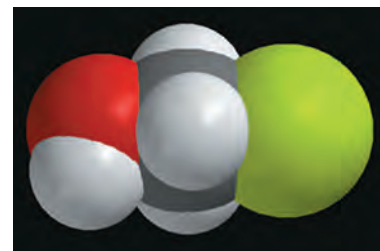
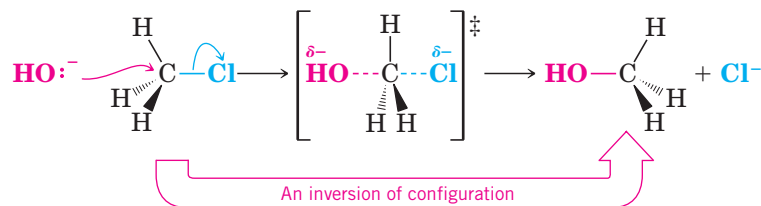


FIGURE 6.4 A free-energy diagram for the reaction of chloromethane with hydroxide ion at 60°C.

6.8 The Stereochemistry of S_N2 Reactions

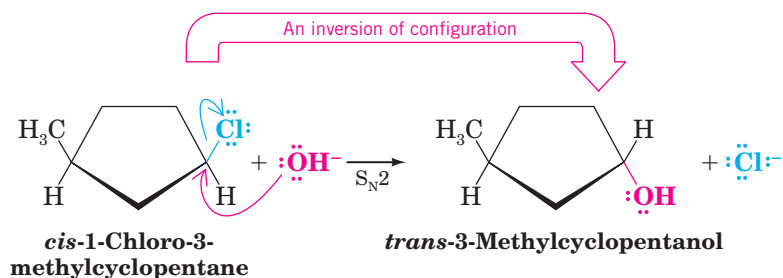
As we learned earlier (Section 6.6), in an S_N2 reaction **the nucleophile approaches from the back side, that is, from the side directly opposite the leaving group.** This mode of attack (see below) causes a **change in the configuration** of the carbon atom that is the target of nucleophilic attack. (The **configuration** of an atom is the particular arrangement of groups around that atom in space; Section 5.7.) As the displacement takes place, the configuration of the carbon atom being substituted undergoes **inversion**—it is turned inside out in much the same way that an umbrella is turned inside out, or inverts, when caught in a strong wind:



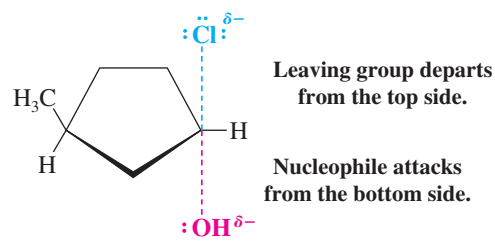
Transition state for an S_N2 reaction.

232 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

With a molecule such as chloromethane, however, there is no way to prove that attack by the nucleophile has involved inversion of configuration of the carbon atom because one form of methyl chloride is identical to its inverted form. With a molecule containing chirality centers such as *cis*-1-chloro-3-methylcyclopentane, however, we can observe the results of an inversion of configuration by the change in stereochemistry that occurs. When *cis*-1-chloro-3-methylcyclopentane reacts with hydroxide ion in an S_N2 reaction, the product is *trans*-3-methylcyclopentanol. *The hydroxide ion ends up being bonded on the opposite side of the ring from the chlorine it replaces:*



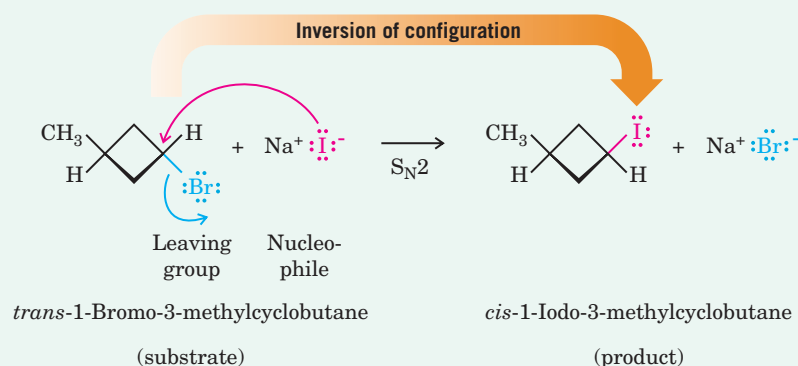
Presumably, the transition state for this reaction is like that shown here.



Study Problem

Give the structure of the product that would be formed when *trans*-1-bromo-3-methylcyclobutane undergoes an S_N2 reaction with NaI.

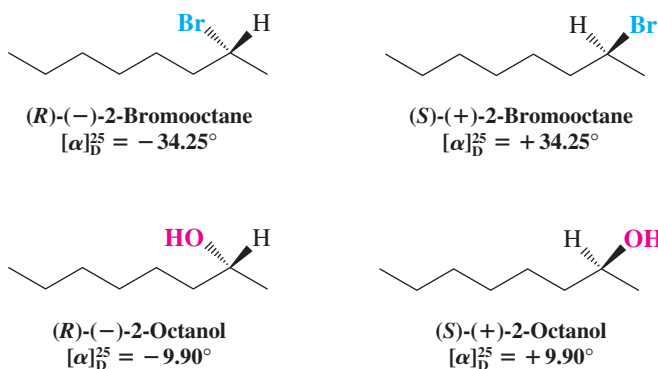
STRATEGY AND ANSWER First, write the formulas for the reactants and identify the nucleophile, the substrate, and the leaving group. Then, recognizing that the nucleophile will attack the carbon atom of the substrate that bears the leaving group from the back side, causing an inversion of configuration at that carbon, write the structure of the product.



Review Problem 6.2 Using chair conformational structures (Section 4.12), show the nucleophilic substitution reaction that would take place when *trans*-1-bromo-4-*tert*-butylcyclohexane reacts with iodide ion. (Show the most stable conformation of the reactant and the product.)

We can also observe inversion of configuration when an S_N2 reaction occurs at a chirality center in an acyclic molecule. Indeed, we find that **S_N2 reactions always occur**

with **inversion of configuration**. The reaction of (*R*)-(-)-2-bromooctane with sodium hydroxide provides an example. We can determine whether or not inversion of configuration occurs in this reaction because the configurations and optical rotations for both enantiomers of 2-bromooctane and the expected product, 2-octanol, are known.



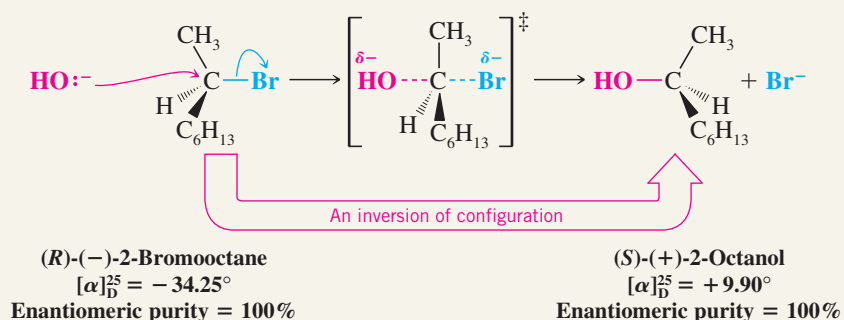
When the reaction is carried out, we find that enantiomerically pure (*R*)-(-)-2-bromooctane ([α]_D²⁵ = -34.25°) has been converted to enantiomerically pure (*S*)-(+)-2-octanol ([α]_D²⁵ = +9.90°).

A MECHANISM FOR THE REACTION



The Stereochemistry of an S_N2 Reaction

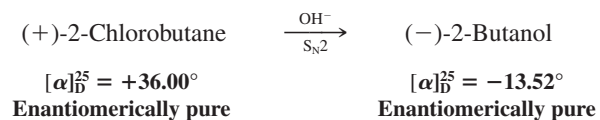
This reaction is S_N2 and takes place with *complete inversion of configuration*:



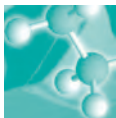
S_N2 reactions that involve breaking a bond to a chirality center can be used to relate configurations of molecules because the *stereochemistry* of the reaction is known.

Review Problem 6.3

- (a) Illustrate how this is true by assigning configurations to the 2-chlorobutane enantiomers based on the following data. [The configuration of (-)-2-butanol is given in Section 5.8C.]



- (b) When optically pure (+)-2-chlorobutane is allowed to react with potassium iodide in acetone in an S_N2 reaction, the 2-iodobutane that is produced has a minus rotation. What is the configuration of (-)-2-iodobutane? Of (+)-2-iodobutane?

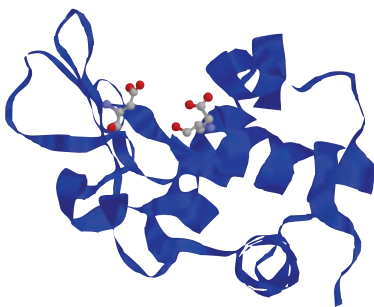


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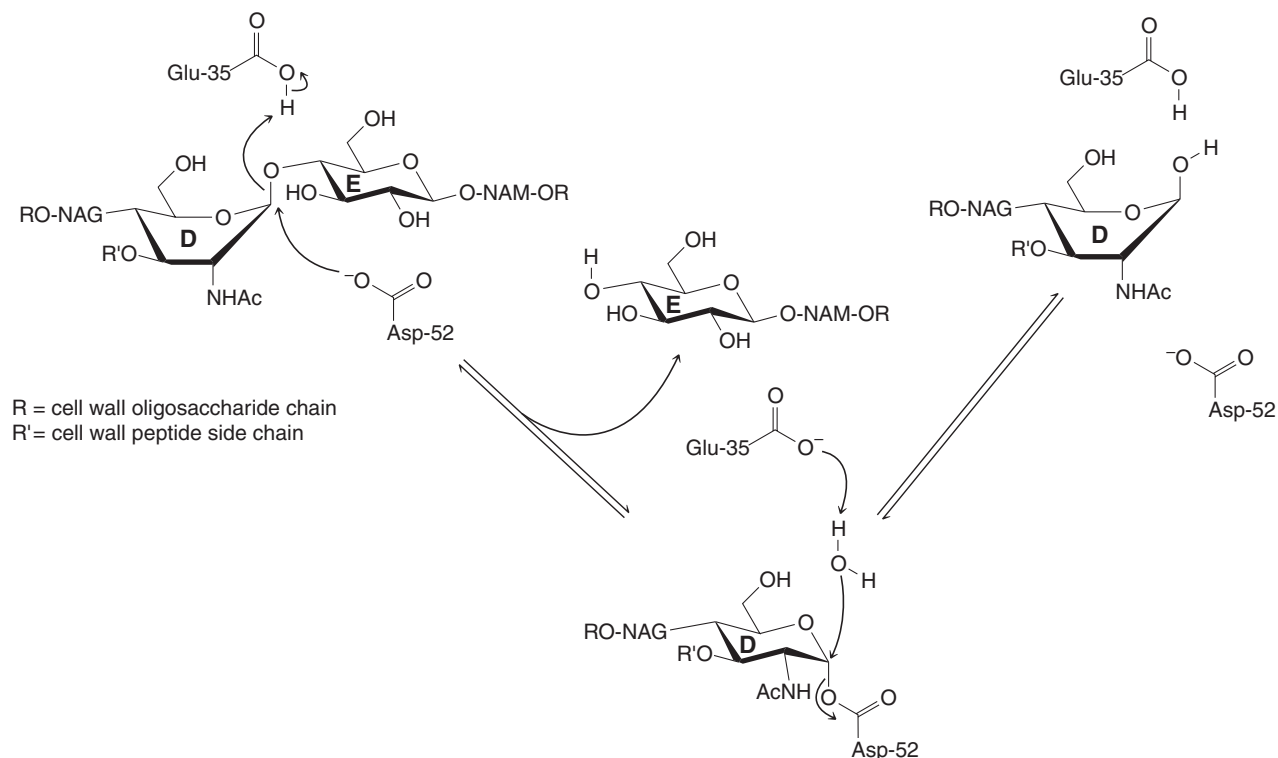
Lysozyme

In the opening essay for this chapter we briefly discussed the mechanism of lysozyme bacterial cell wall hydrolysis. Let us now look at this process in more detail.

Lysozyme is an enzyme, and therefore it is also a protein. Proteins are polymers of amino acids. Most of the amino acids that comprise enzymes have side-chain functional groups, and often some of these functional groups participate in the reactions catalyzed by enzymes. In the case of lysozyme, the amino acids involved in the mechanism are the glutamic acid at position 35 in the protein chain (Glu-35), and the aspartic acid at position 52 (Asp-52). Glu-35 (left) and Asp-52 (right) are shown in ball-stick format in the structure of lysozyme shown here. (See Chapter 24 for more information about amino acids and protein structure.)



placing an oxygen bonded to ring E. This process is an S_N2 reaction, with the expected stereochemical result of inversion at the ring D carbon. (The rings are labeled D and E because they are fourth and fifth in a six-ring repeating sequence of the cell wall oligosaccharide structure, as discussed in Section 24.10.) Note that the Glu-35 carboxylic acid group also provides a proton to the oxygen of ring E as it departs, allowing the oxygen to leave as a neutral hydroxyl group rather than an alkoxide anion. The lysozyme molecule is now covalently bonded to ring D of the cell wall structure. A water molecule then reacts by an S_N2 mechanism at the carbon of ring D where lysozyme Asp-52 is bound, resulting in another inversion of configuration at the carbon of ring D. As this occurs, the carboxylate anion of Glu-35 makes the water molecule more nucleophilic by assisting with removal of one of its protons during the reaction.



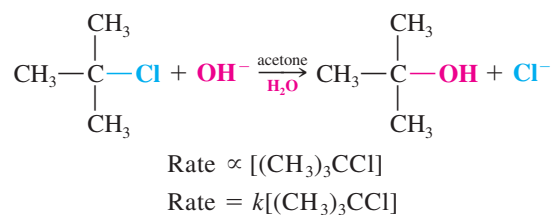
Thus, the mechanism of lysozyme involves two sequential S_N2 reactions that involve a carboxylate anion and a water molecule as nucleophiles. The stereochemistry of each reaction involves inversion, just as we would expect from S_N2 reactions, yet the net result is retention of configuration

because two inversions occur. In the overall mechanism of lysozyme we have a marvelous example of S_N2 substitution reactions in a natural context. In Chapter 24 we shall have more to say about enzymes and their prowess in organic chemistry.

6.9 The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

Let us now consider another mechanism for nucleophilic substitution: the S_N1 reaction. When *tert*-butyl chloride reacts with sodium hydroxide in a mixture of water and acetone, the kinetic results are quite different than for the reaction of chloromethane with hydroxide. The rate of formation of *tert*-butyl alcohol is dependent on the concentration of *tert*-butyl chloride, but it is *independent of the concentration of hydroxide ion*. Doubling the *tert*-butyl chloride concentration *doubles* the rate of the reaction, but changing the hydroxide ion concentration (within limits) has no appreciable effect. *tert*-Butyl chloride reacts by substitution at virtually the same rate in pure water (where the hydroxide ion is $10^{-7}M$) as it does in $0.05M$ aqueous sodium hydroxide (where the hydroxide ion concentration is 500,000 times larger). (We shall see in Section 6.10 that the important nucleophile in this reaction is a molecule of water.)

Thus, the rate equation for this substitution reaction is first order with respect to *tert*-butyl chloride and *first order overall*:



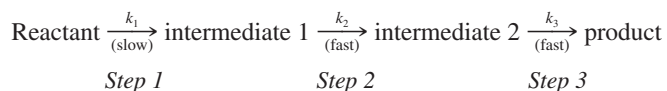
We can conclude, therefore, that hydroxide ions do not participate in the transition state of the step that controls the rate of the reaction and that only molecules of *tert*-butyl chloride are involved. This reaction is said to be **unimolecular** (first order) in the rate-determining step. We call this type of reaction an **S_N1 reaction (substitution, nucleophilic, unimolecular)**.

How can we explain an S_N1 reaction in terms of a mechanism? To do so, we shall need to consider the possibility that the mechanism involves more than one step. But what kind of kinetic results should we expect from a multistep reaction? Let us consider this point further.

6.9A Multistep Reactions and the Rate-Determining Step

If a reaction takes place in a series of steps, and if one step is intrinsically slower than all the others, then the rate of the overall reaction will be essentially the same as the rate of this slow step. This slow step, consequently, is called the **rate-limiting step** or the **rate-determining step**.

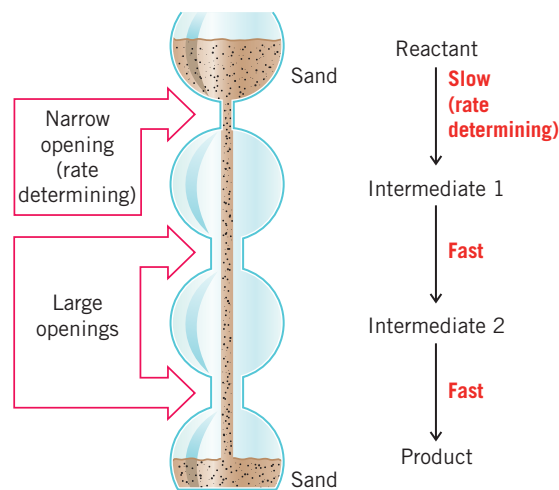
Consider a multistep reaction such as the following:



When we say that the first step in this example is intrinsically slow, we mean that the rate constant for step 1 is very much smaller than the rate constant for step 2 or for step 3. That is, $k_1 \ll k_2$ or k_3 . When we say that steps 2 and 3 are *fast*, we mean that because their rate constants are larger, they could (in theory) take place rapidly if the concentrations of the two intermediates ever became high. In actuality, the concentrations of the intermediates are always very small because of the slowness of step 1.

As an analogy, imagine an hourglass modified in the way shown in Fig. 6.5. The opening between the top chamber and the one just below is considerably smaller than the other two. The overall rate at

FIGURE 6.5 A modified hourglass that serves as an analogy for a multistep reaction. The overall rate is limited by the rate of the slow step.

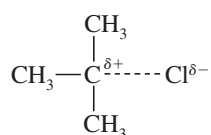


236 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

which sand falls from the top to the bottom of the hourglass is limited by the rate at which sand passes through the small orifice. This step, in the passage of sand, is analogous to the rate-determining step of the multistep reaction.

6.10 A Mechanism for the S_N1 Reaction

The mechanism for the reaction of *tert*-butyl chloride with water (Section 6.9) apparently involves three steps. See the box “A Mechanism for the S_N1 Reaction” on p. 000, with a schematic free-energy diagram highlighted for each step. Two distinct **intermediates** are formed. The first step is the slow step—it is the rate-determining step. In it a molecule of *tert*-butyl chloride ionizes and becomes a *tert*-butyl cation and a chloride ion. In the transition state for this step the carbon–chlorine bond of *tert*-butyl chloride is largely broken and ions are beginning to develop:



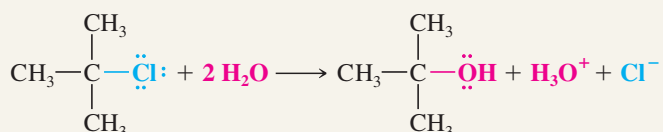
The solvent (water) stabilizes these developing ions by solvation. Carbocation formation, in general, takes place slowly because it is usually a highly endothermic process and is uphill in terms of free energy.



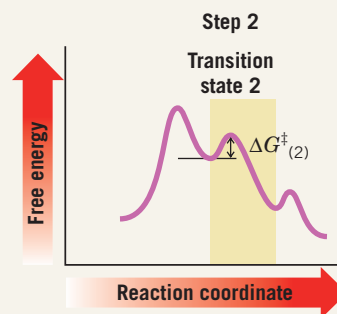
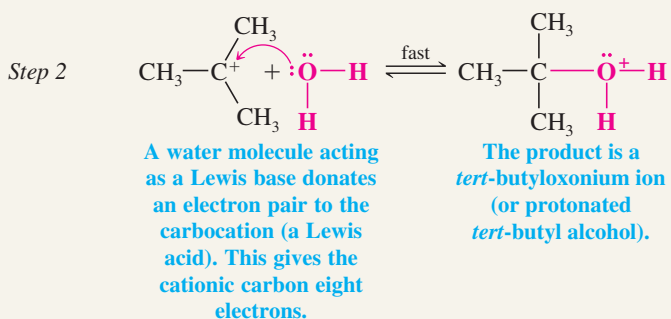
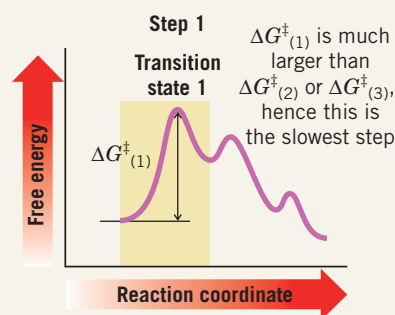
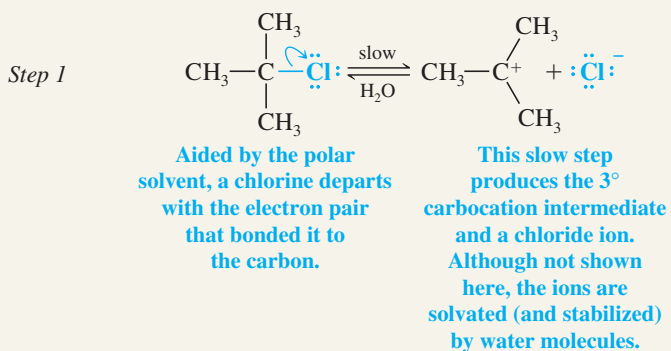
A MECHANISM FOR THE REACTION

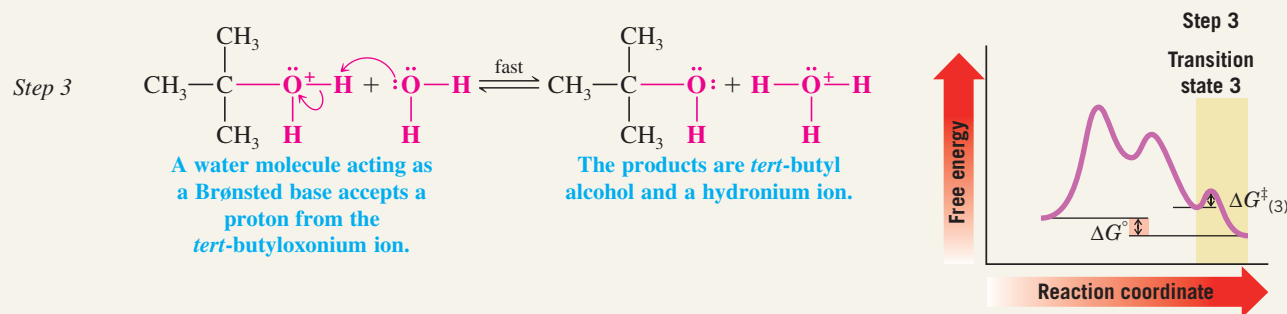
Mechanism for the S_N1 Reaction

REACTION



MECHANISM






The first step requires heterolytic cleavage of the carbon–chlorine bond. Because no other bonds are formed in this step, it should be highly endothermic and it should have a high free energy of activation, as we see in the free-energy diagram. That departure of the halide takes place at all is largely because of the ionizing ability of the solvent, water. Experiments indicate that in the gas phase (i.e., in the absence of a solvent), the free energy of activation is about 630 kJ mol^{-1} ! In aqueous solution, however, the free energy of activation is much lower—about 84 kJ mol^{-1} . Water molecules surround and stabilize the cation and anion that are produced (cf. Section 2.14E).

In the second step the intermediate *tert*-butyl cation reacts rapidly with water to produce a *tert*-butyloxonium ion, $(\text{CH}_3)_3\text{COH}_2^+$, which in the third step, rapidly transfers a proton to a molecule of water producing *tert*-butyl alcohol.

6.11 Carbocations

Beginning in the 1920s much evidence began to accumulate implicating simple alkyl cations as intermediates in a variety of ionic reactions. However, because alkyl cations are highly unstable and highly reactive, they were, in all instances studied before 1962, very short-lived, transient species that could not be observed directly.* However, in 1962 George A. Olah (University of Southern California) and co-workers published the first of a series of papers describing experiments in which alkyl cations were prepared in an environment in which they were reasonably stable and in which they could be observed by a number of spectroscopic techniques.

 Olah was awarded the 1994 Nobel Prize in chemistry.

6.11A The Structure of Carbocations

Considerable experimental evidence indicates that carbocations are trigonal planar. Just as the trigonal planar structure of BF_3 (Section 1.16D) can be accounted for on the basis of sp^2 hybridization so, too (Fig. 6.6), can the trigonal planar structure of carbocations.

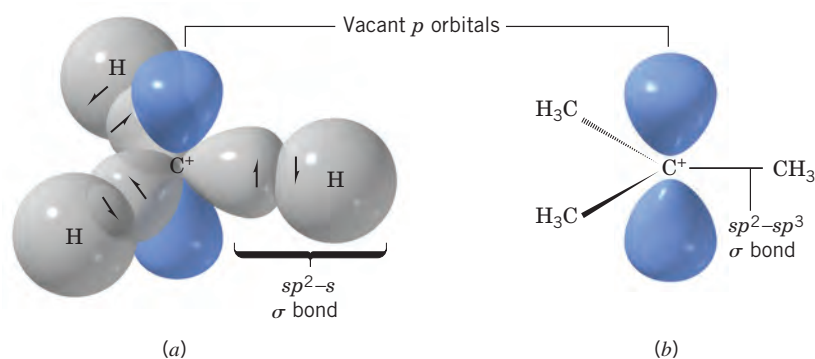


FIGURE 6.6 (a) A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 orbitals with the $1s$ orbitals of the hydrogen atoms. The p orbital is vacant. (b) A dashed line-wedge representation of the *tert*-butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl groups with sp^2 orbitals of the central carbon atom.

*As we shall learn later, carbocations bearing aromatic groups can be much more stable; one of these had been studied as early as 1901.

238 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

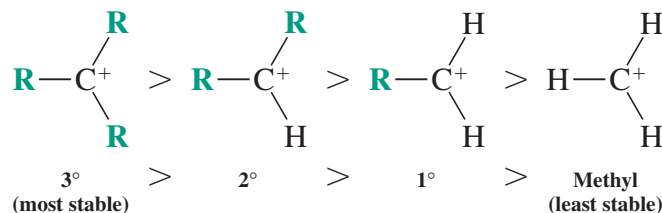
The central carbon atom in a carbocation is electron deficient; it has only six electrons in its outermost energy level. In our model (Fig. 6.6) these six electrons are used to form sigma covalent bonds to hydrogen atoms (or to alkyl groups). The p orbital contains no electrons.



STUDY TIP! An understanding of carbocation structure and relative stability is important for learning a variety of reaction processes.

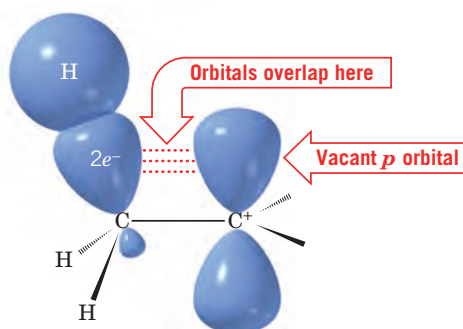
6.11B The Relative Stabilities of Carbocations

A large body of experimental evidence indicates that the relative stabilities of carbocations are related to the number of alkyl groups attached to the positively charged trivalent carbon atom. Tertiary carbocations are the most stable, and the methyl cation is the least stable. The overall order of stability is as follows:

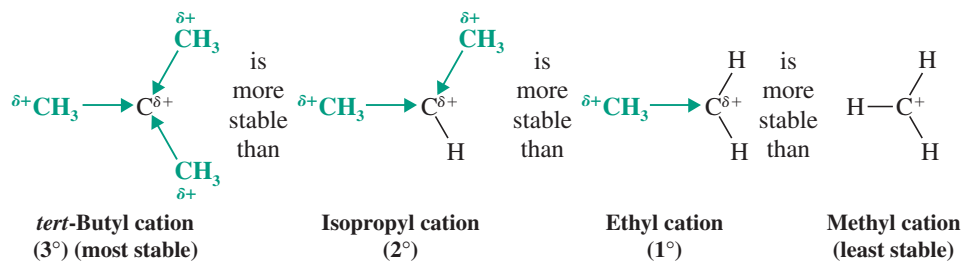


This order of stability of carbocations can be explained on the basis of **hyperconjugation**. Hyperconjugation involves electron **delocalization** (via partial orbital overlap) from a filled bonding orbital to an adjacent unfilled orbital (Section 4.8). In the case of a carbocation, the unfilled orbital is the vacant p orbital of the carbocation, and the filled orbitals are C—H or C—C sigma bonds at the carbons *adjacent* to the p orbital of the carbocation. Sharing of electron density from adjacent C—H or C—C sigma bonds with the carbocation p orbital delocalizes the positive charge. **Any time a charge can be dispersed or delocalized, a system will be stabilized.** Figure 6.7 shows a stylized representation of hyperconjugation between a sigma bonding orbital and an adjacent carbocation p orbital.

FIGURE 6.7 How a methyl group helps stabilize the positive charge of a carbocation. Electron density from one of the carbon–hydrogen sigma bonds of the methyl group flows into the vacant p orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way makes the sp^2 -hybridized carbon of the carbocation somewhat less positive, and the hydrogens of the methyl group assume some of the positive charge. Delocalization (dispersal) of the charge in this way leads to greater stability. This interaction of a bond orbital with a p orbital is called hyperconjugation.



Tertiary carbocations have three carbons with C—H bonds (or, depending on the specific example, C—C bonds instead of C—H) adjacent to the carbocation that can overlap partially with the vacant p orbital. Secondary carbocations have only two adjacent carbons with C—H or C—C bonds to overlap with the carbocation; hence, the possibility for hyperconjugation is less and the secondary carbocation is less stable. Primary carbocations have only one adjacent carbon from which to derive hyperconjugative stabilization, and so they are even less stable. A methyl carbocation has no possibility for hyperconjugation, and it is the least stable of all in this series. The following are specific examples:



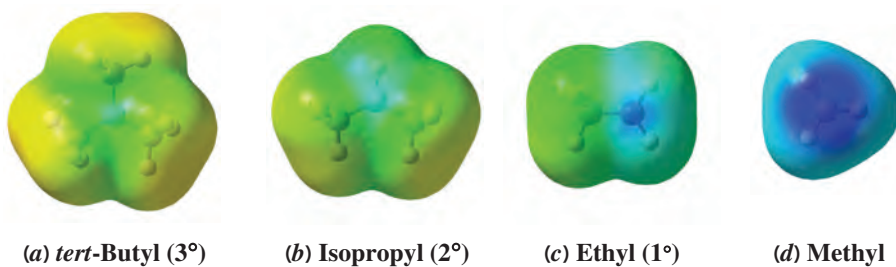
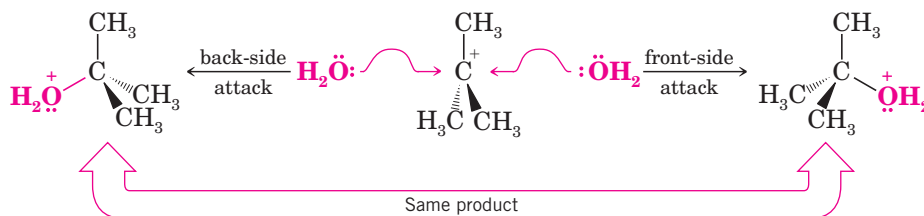


FIGURE 6.8 Maps of electrostatic potential for (a) *tert*-butyl (3°), (b) isopropyl (2°), (c) ethyl (1°), and (d) methyl carbocations show the trend from greater to lesser delocalization (stabilization) of the positive charge in these structures. Less blue color indicates greater delocalization of the positive charge. (The structures are mapped on the same scale of electrostatic potential to allow direct comparison.)

Thus, the relative stability of carbocations is $3^\circ > 2^\circ > 1^\circ > \text{methyl}$. This trend is also readily seen in electrostatic potential maps for these carbocations (Fig. 6.8).

6.12 The Stereochemistry of S_N1 Reactions

Because the carbocation formed in the first step of an S_N1 reaction has a trigonal planar structure (Section 6.11A), when it reacts with a nucleophile, it may do so from either the front side or the back side (see below). With the *tert*-butyl cation this makes no difference; since the *tert*-butyl group is not a chirality center, the same product is formed by either mode of attack. (Convince yourself of this result by examining models.)



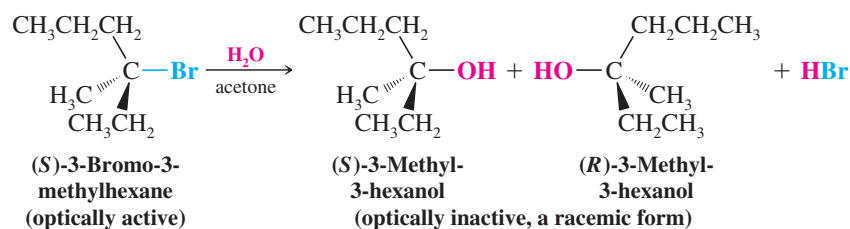
With some cations, however, stereoisomeric products arise from the two reaction possibilities. We shall study this point next.

6.12A Reactions That Involve Racemization

A reaction that transforms an optically active compound into a racemic form is said to proceed with **racemization**. If the original compound loses all of its optical activity in the course of the reaction, chemists describe the reaction as having taken place with *complete* racemization. If the original compound loses only part of its optical activity, as would be the case if an enantiomer were only partially converted to a racemic form, then chemists describe this as proceeding with *partial* racemization.

Racemization takes place *whenever the reaction causes chiral molecules to be converted to an achiral intermediate*.

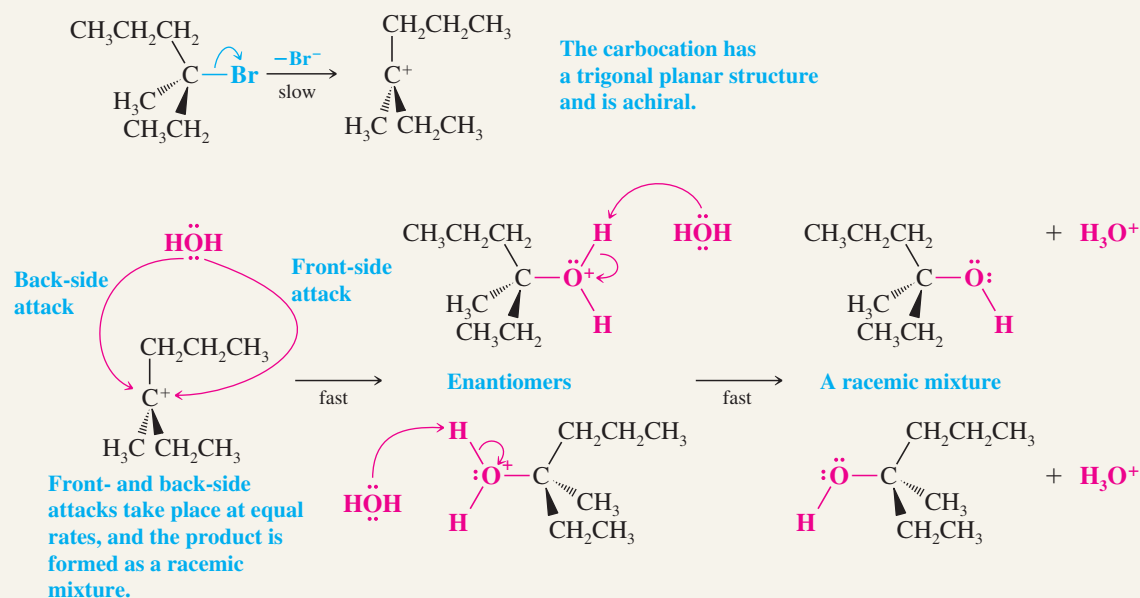
Examples of this type of reaction are S_N1 reactions in which the leaving group departs from a chirality center. These reactions almost always result in extensive and sometimes complete racemization. For example, heating optically active (*S*)-3-bromo-3-methylhexane with aqueous acetone results in the formation of 3-methyl-3-hexanol as a racemic form:



240 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

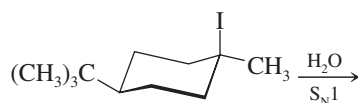
The reason: The S_N1 reaction proceeds through the formation of an intermediate carbocation and the carbocation, because of its trigonal planar configuration, is *achiral*. It reacts with water at equal rates from either side to form the enantiomers of 3-methyl-3-hexanol in equal amounts.

A MECHANISM FOR THE REACTION

The Stereochemistry of an S_N1 Reaction

The S_N1 reaction of (*S*)-3-bromo-3-methylhexane proceeds with racemization because the intermediate carbocation is achiral and attack by the nucleophile can occur from either side.

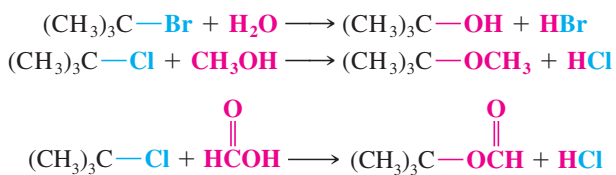
Review Problem 6.4 Keeping in mind that carbocations have a trigonal planar structure, (a) write a structure for the carbocation intermediate and (b) write structures for the alcohol (or alcohols) that you would expect from the following reaction:



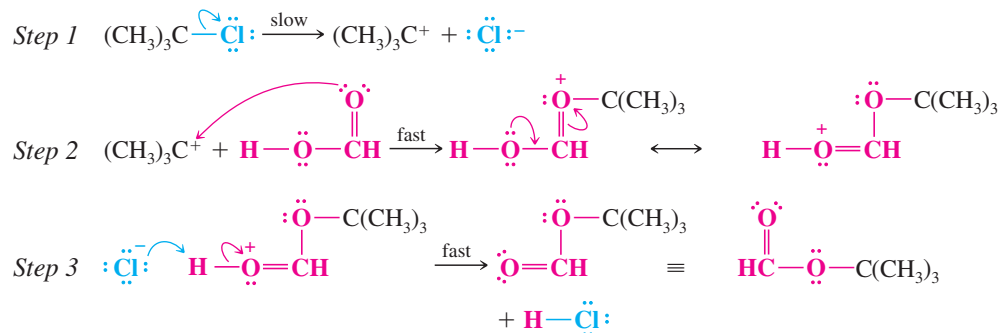
6.12B Solvolysis

The S_N1 reaction of an alkyl halide with water is an example of **solvolysis**. A solvolysis reaction is a nucleophilic substitution in which *the nucleophile is a molecule of the solvent* (*solvent + lysis*: cleavage by the solvent). Since the solvent in this instance is water, we could also call the reaction a **hydrolysis**. If the reaction had taken place in methanol, we would call it a **methanolysis**.

Examples of Solvolysis



In the last example the solvent is formic acid (HCO_2H) and the following steps take place:

6.13 Factors Affecting the Rates of S_N1 and S_N2 Reactions 241

These reactions all involve the initial formation of a carbocation and the subsequent reaction of that cation with a molecule of the solvent. Solvolysis reactions are, therefore, S_N1 reactions.

What product(s) would you expect from the methanolysis of the iodocyclohexane derivative given as the reactant in Review Problem 6.4?

[Review Problem 6.5](#)

6.13 Factors Affecting the Rates of S_N1 and S_N2 Reactions

Now that we have an understanding of the mechanisms of S_N2 and S_N1 reactions, our next task is to explain why chloromethane reacts by an S_N2 mechanism and *tert*-butyl chloride by an S_N1 mechanism. We would also like to be able to predict which pathway— S_N1 or S_N2 —would be followed by the reaction of any alkyl halide with any nucleophile under varying conditions.

The answer to this kind of question is to be found in the *relative rates of the reactions that occur*. If a given alkyl halide and nucleophile react *rapidly* by an S_N2 mechanism but *slowly* by an S_N1 mechanism under a given set of conditions, then an S_N2 pathway will be followed by most of the molecules. On the other hand, another alkyl halide and another nucleophile may react very slowly (or not at all) by an S_N2 pathway. If they react rapidly by an S_N1 mechanism, then the reactants will follow an S_N1 pathway.

Experiments have shown that a number of factors affect the relative rates of S_N1 and S_N2 reactions. The most important factors are

1. the structure of the substrate,
2. the concentration and reactivity of the nucleophile (for bimolecular reactions only),
3. the effect of the solvent, and
4. the nature of the leaving group.

6.13A The Effect of the Structure of the Substrate

S_N2 Reactions Simple alkyl halides show the following general order of reactivity in S_N2 reactions:



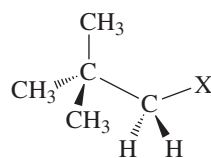
Methyl halides react most rapidly and tertiary halides react so slowly as to be unreactive by the S_N2 mechanism. Table 6.4 gives the relative rates of typical S_N2 reactions.

TABLE 6.4 Relative Rates of Reactions of Alkyl Halides in S_N2 Reactions

| Substituent | Compound | Approximate Relative Rate |
|-------------|---------------------------------------|---------------------------|
| Methyl | CH_3X | 30 |
| 1° | $\text{CH}_3\text{CH}_2\text{X}$ | 1 |
| 2° | $(\text{CH}_3)_2\text{CHX}$ | 0.03 |
| Neopentyl | $(\text{CH}_3)_3\text{CCH}_2\text{X}$ | 0.00001 |
| 3° | $(\text{CH}_3)_3\text{CX}$ | ~ 0 |

242 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

Neopentyl halides, even though they are primary halides, are very unreactive:



A neopentyl halide

The important factor behind this order of reactivity is a **steric effect**. A steric effect is an effect on relative rates caused by the space-filling properties of those parts of a molecule attached at or near the reacting site. One kind of steric effect—the kind that is important here—is called **steric hindrance**. By this we mean that *the spatial arrangement of the atoms or groups at or near the reacting site of a molecule hinders or retards a reaction*.

For particles (molecules and ions) to react, their reactive centers must be able to come within bonding distance of each other. Although most molecules are reasonably flexible, very large and bulky groups can often hinder the formation of the required transition state. In some cases they can prevent its formation altogether.

An S_N2 reaction requires an approach by the nucleophile to a distance within the bonding range of the carbon atom bearing the leaving group. Because of this, bulky substituents on or near that carbon atom have a dramatic inhibiting effect (Fig. 6.9). They cause the free energy of the required transition state to be increased and, consequently, they increase the free energy of activation for the reaction. Of the simple alkyl halides, methyl halides react most rapidly in S_N2 reactions because only three small hydrogen atoms interfere with the approaching nucleophile. Neopentyl and tertiary halides are the least reactive because bulky groups present a strong hindrance to the approaching nucleophile. (Tertiary substrates, for all practical purposes, do not react by an S_N2 mechanism.)

STUDY TIP! You can best appreciate the steric effects in these structures by building models.

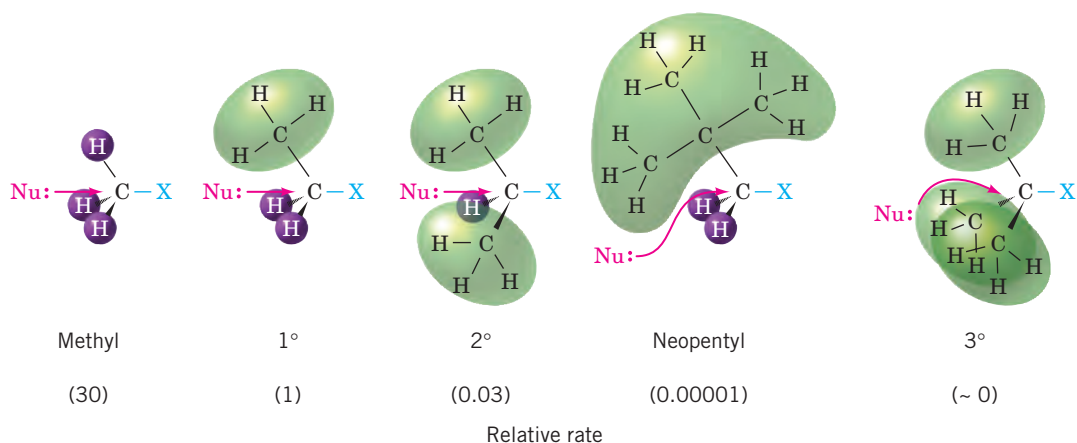


FIGURE 6.9 Steric effects in the S_N2 reaction.

STUDY TIP! The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed.

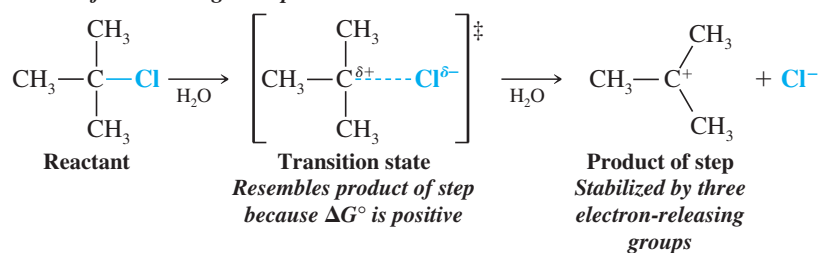
S_N1 Reactions Except for those reactions that take place in strong acids, which we shall study later, **the only organic compounds that undergo reaction by an S_N1 path at a reasonable rate are those that are capable of forming relatively stable carbocations**. Of the simple alkyl halides that we have studied so far, this means (for all practical purposes) that only tertiary halides react by an S_N1 mechanism. (Later we shall see that certain organic halides, called *allylic halides* and *benzylic halides*, can also react by an S_N1 mechanism because they can form relatively stable carbocations; see Sections 13.4 and 15.15.)

Tertiary carbocations are stabilized because sigma bonds at three adjacent carbons contribute electron density to the carbocation *p* orbital by hyperconjugation (Section 6.11B). Secondary and primary carbocations have less stabilization by hyperconjugation. A methyl carbocation has no stabilization. Formation of a relatively stable carbocation is important

6.13 Factors Affecting the Rates of S_N1 and S_N2 Reactions 243

in an S_N1 reaction because it means that the free energy of activation for the slow step of the reaction (e.g., $R-L \rightarrow R^+ + L^-$) will be low enough for the reaction to take place at a reasonable rate.

The Hammond–Leffler Postulate If you review the free-energy diagrams that accompany the mechanism for the S_N1 reaction of *tert*-butyl chloride and water (Section 6.10), you will see that step 1, the ionization of the leaving group to form the carbocation, is *uphill in terms of free energy* (ΔG° for this step is positive). It is also uphill in terms of enthalpy (ΔH° is also positive), and, therefore, this step is *endothermic*. According to a postulate made by G. S. Hammond (then at California Institute of Technology, deceased 2005) and J. E. Leffler (Florida State University), **the transition-state structure for a step that is uphill in energy should show a strong resemblance to the structure of the product of that step**. Since the product of this step (actually an intermediate in the overall reaction) is a carbocation, any factor that stabilizes the carbocation—such as dispersal of the positive charge by electron-releasing groups—should also stabilize the transition state in which the positive charge is developing.

Ionization of the Leaving Group

A methyl, primary, or secondary alkyl halide would have to ionize to form a methyl, primary, or secondary carbocation to react by an S_N1 mechanism. These carbocations, however, are much higher in energy than a tertiary carbocation, and the transition states leading to these carbocations are even higher in energy. The activation energy for an S_N1 reaction of a simple methyl, primary, or secondary halide, consequently, is so large (therefore the reaction is so slow) that, for all practical purposes, an S_N1 reaction does not compete with the corresponding S_N2 reaction.

The **Hammond–Leffler postulate** is quite general and can be better understood through consideration of Fig. 6.10. One way that the postulate can be stated is to say that *the structure of a transition state resembles the stable species that is nearest it in free energy*. For example, in a highly **endergonic** step (blue curve) the transition state lies close to the products in free energy, and we assume, therefore, that **it resembles the products of that step in structure**. Conversely, in a highly exergonic step (red curve) the transition state lies close

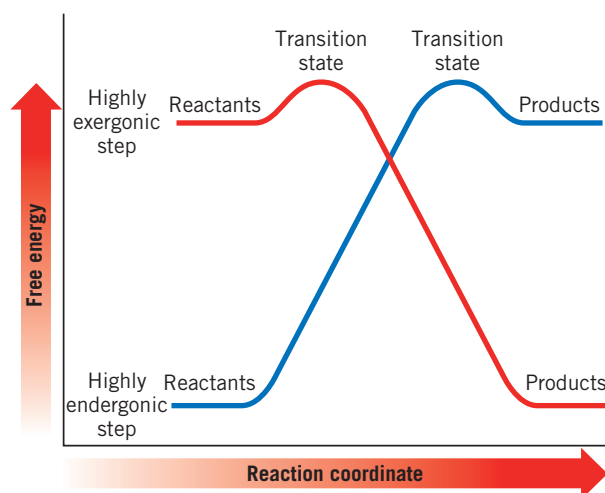


FIGURE 6.10 The transition state for a highly exergonic step (red curve) lies close to and resembles the reactants. The transition state for an endergonic step (blue curve) lies close to and resembles the products of a reaction. (Adapted from Hammond, G. J. *Amer. Chem. Soc.* **1953**, 77, 334–338; Leffler, J. E. *Science* **1952**, 117, 340–341.)

244 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

to the reactants in free energy, and we assume **it resembles the reactants in structure** as well. The great value of the Hammond–Leffler postulate is that it gives us an intuitive way of visualizing those important, but fleeting, species that we call transition states. We shall make use of it in many future discussions.

Review Problem 6.6 The relative rates of ethanolysis of four primary alkyl halides are as follows: $\text{CH}_3\text{CH}_2\text{Br}$, 1.0; $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$, 0.28; $(\text{CH}_3)_2\text{CHCH}_2\text{Br}$, 0.030; $(\text{CH}_3)_3\text{CCH}_2\text{Br}$, 0.00000042.

(a) Is each of these reactions likely to be $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$?

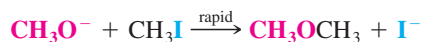
(b) Provide an explanation for the relative reactivities that are observed.

6.13B The Effect of the Concentration and Strength of the Nucleophile

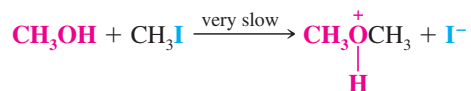
Since the nucleophile does not participate in the rate-determining step of an $\text{S}_{\text{N}}1$ reaction, the rates of $\text{S}_{\text{N}}1$ reactions are unaffected by either the concentration or the identity of the nucleophile. The rates of $\text{S}_{\text{N}}2$ reactions, however, depend on *both* the concentration *and* the identity of the attacking nucleophile. We saw in Section 6.5 how increasing the concentration of the nucleophile increases the rate of an $\text{S}_{\text{N}}2$ reaction. We can now examine how the rate of an $\text{S}_{\text{N}}2$ reaction depends on the identity of the nucleophile.

The relative strength of a nucleophile (its **nucleophilicity**) is measured in terms of the relative rate of its $\text{S}_{\text{N}}2$ reaction with a given substrate. A good nucleophile is one that reacts rapidly in an $\text{S}_{\text{N}}2$ reaction with a given substrate. A poor nucleophile is one that reacts slowly in an $\text{S}_{\text{N}}2$ reaction with the same substrate under comparable reaction conditions. (As mentioned above, we cannot compare nucleophilicities with regard to $\text{S}_{\text{N}}1$ reactions because the nucleophile does not participate in the rate-determining step of an $\text{S}_{\text{N}}1$ reaction.)

Methoxide anion, for example, is a good nucleophile for a substitution reaction with iodomethane. It reacts rapidly by an $\text{S}_{\text{N}}2$ mechanism to form dimethyl ether:



Methanol, on the other hand, is a poor nucleophile for reaction with iodomethane. Under comparable conditions it reacts very slowly. It is not a sufficiently powerful Lewis base (i.e., nucleophile) to cause displacement of the iodide leaving group at a significant rate:



The relative strengths of nucleophiles can be correlated with two structural features:

1. **A negatively-charged nucleophile is always a more reactive nucleophile than its conjugate acid.** Thus HO^- is a better nucleophile than H_2O and RO^- is better than ROH .
2. **In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicities parallel basicities.** Oxygen compounds, for example, show the following order of reactivity:



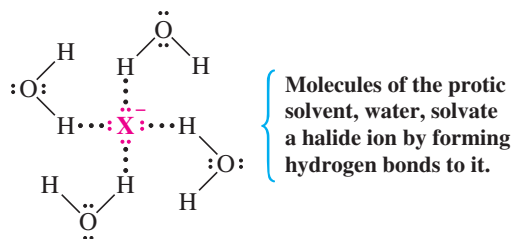
This is also their order of basicity. An alkoxide ion (RO^-) is a slightly stronger base than a hydroxide ion (HO^-), a hydroxide ion is a much stronger base than a carboxylate ion (RCO_2^-), and so on.

Nucleophilicity versus Basicity While nucleophilicity and basicity are related, they are not measured in the same way. Basicity, as expressed by $\text{p}K_{\text{a}}$, is measured *by the position of an equilibrium* involving an electron pair donor (base), a proton, the conjugate acid, and

the conjugate base. Nucleophilicity is measured *by relative rates of reaction*, by how rapidly an electron pair donor reacts at an atom (usually carbon) bearing a leaving group. For example, the hydroxide ion (OH^-) is a stronger base than a cyanide ion (CN^-); at equilibrium it has the greater affinity for a proton (the $\text{p}K_a$ of H_2O is ~ 16 , while the $\text{p}K_a$ of HCN is ~ 10). Nevertheless, cyanide ion is a stronger nucleophile; it reacts more rapidly with a carbon bearing a leaving group than does hydroxide ion.

6.13C Solvent Effects on S_N2 Reactions: Polar Protic and Aprotic Solvents

A molecule of a solvent such as water or an alcohol—called a **protic solvent** (Section 3.11)—has a hydrogen atom attached to a strongly electronegative element (oxygen). Molecules of protic solvents can, therefore, form hydrogen bonds to nucleophiles in the following way.



The effect of hydrogen bonding with the nucleophile is to encumber the nucleophile and hinder its reactivity in a substitution reaction. For a strongly solvated nucleophile to react, it must shed some of its solvent molecules so that it can approach the carbon of the substrate that bears the leaving group. This is one type of important **solvent effect** in nucleophilic reactions.

Hydrogen bonds to a small nucleophilic atom are stronger than those to larger nucleophilic atoms. This trend is borne out among elements in the *same group (column) of the periodic table*. For example, fluoride anion is more strongly solvated than the other halides because it is the smallest halide anion and its charge is the most concentrated. Hence, in a protic solvent fluoride is not as effective a nucleophile as the other halide anions. Iodide is the largest halide anion and it is the most weakly solvated in a protic solvent; hence, it is the strongest nucleophile among the halide anions. In general, the trend in *nucleophilicity* among the halide anions in a protic solvent is as follows:

Halide Nucleophilicity in Protic Solvents



The same effect holds true when we compare sulfur nucleophiles with oxygen nucleophiles. Sulfur atoms are larger than oxygen atoms and hence they are not solvated as strongly in a protic solvent. Thus, thiols (R-SH) are stronger nucleophiles than alcohols, and RS^- anions are better nucleophiles than RO^- anions.

The greater reactivity of nucleophiles with large nucleophilic atoms is not entirely related to solvation. Larger atoms have greater **polarizability** (their electron clouds are more easily distorted); therefore, a larger nucleophilic atom can donate a greater degree of electron density to the substrate than a smaller nucleophile whose electrons are more tightly held.

The relative nucleophilicities of some common nucleophiles in protic solvents are as follows:

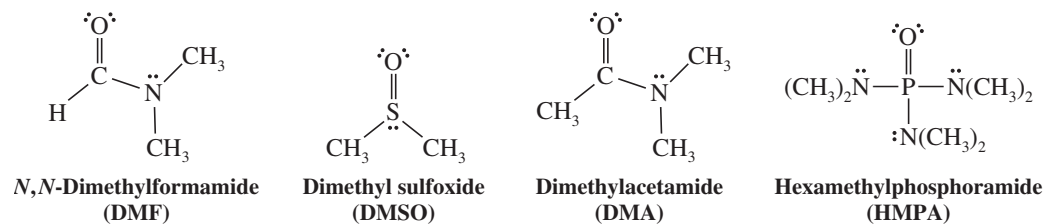
Relative Nucleophilicity in Protic Solvents



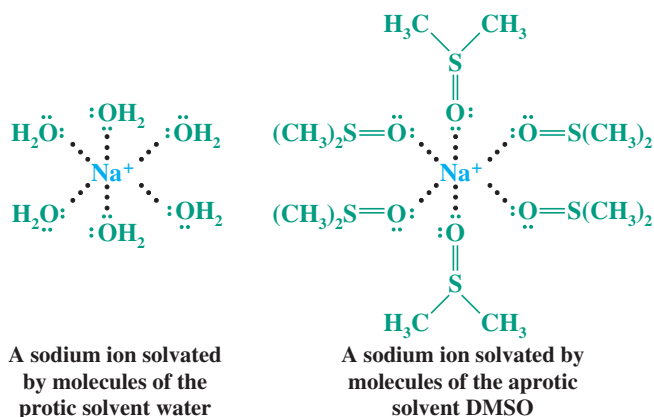
Polar Aprotic Solvents Aprotic solvents are those solvents whose molecules do not have a hydrogen atom that is attached to an atom of an electronegative element. A number

246 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

of **polar aprotic solvents** have come into wide use by chemists *because they are especially useful in S_N2 reactions*. Several examples are the following:



All of these solvents (DMF, DMSO, DMA, and HMPA) dissolve ionic compounds, and they solvate cations very well. They do so in the same way that protic solvents solvate cations: by orienting their negative ends around the cation and by donating unshared electron pairs to vacant orbitals of the cation:



However, because they cannot form hydrogen bonds and because their positive centers are well shielded by steric effects from any interaction with anions, **aprotic solvents do not solvate anions to any appreciable extent**. In these solvents anions are unencumbered by a layer of solvent molecules and they are therefore poorly stabilized by solvation. These “naked” anions are highly reactive both *as bases and nucleophiles*. In DMSO, for example, the relative order of reactivity of halide ions is opposite to that in protic solvents, and it follows the same trend as their relative basicity:

Halide Nucleophilicity in Aprotic Solvents



The rates of S_N2 reactions generally are vastly increased when they are carried out in polar aprotic solvents. The increase in rate can be as large as a millionfold.

STUDY TIP Polar aprotic solvents increase S_N2 rates.

Review Problem 6.7 Classify the following solvents as being protic or aprotic: formic acid, HCO_2H ; acetone, CH_3COCH_3 ; acetonitrile, $\text{CH}_3\text{C}\equiv\text{N}$; formamide, HCONH_2 ; sulfur dioxide, SO_2 ; ammonia, NH_3 ; trimethylamine, $\text{N}(\text{CH}_3)_3$; ethylene glycol, $\text{HOCH}_2\text{CH}_2\text{OH}$.

Review Problem 6.8 Would you expect the reaction of propyl bromide with sodium cyanide (NaCN), that is,



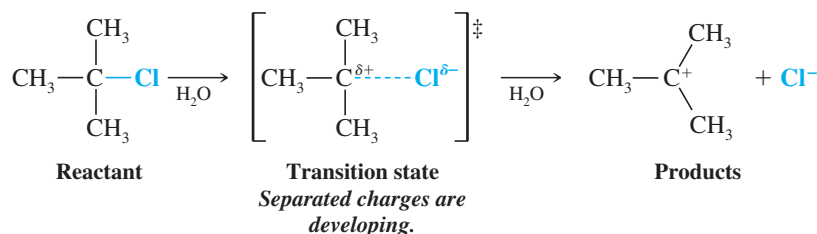
to occur faster in DMF or in ethanol? Explain your answer.

Review Problem 6.9 Which would you expect to be the stronger nucleophile in a polar aprotic solvent? (a) CH_3CO_2^- or CH_3O^- (b) H_2O or H_2S (c) $(\text{CH}_3)_3\text{P}$ or $(\text{CH}_3)_3\text{N}$

6.13D Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent

The use of a **polar protic solvent** will greatly increase the rate of ionization of an alkyl halide in any S_N1 reaction because of its ability to solvate cations and anions so effectively. It does this because solvation stabilizes the transition state leading to the intermediate carbocation and halide ion more than it does the reactants; thus the free energy of activation is lower. The transition state for this endothermic step is one in which separated charges are developing, and thus it resembles the ions that are ultimately produced:

STUDY TIP Polar protic solvents favor S_N1 reactions.



A rough indication of a solvent's polarity is a quantity called the **dielectric constant**. The dielectric constant is a measure of the solvent's ability to insulate opposite charges (or separate ions) from each other. Electrostatic attractions and repulsions between ions are smaller in solvents with higher dielectric constants. Table 6.5 gives the dielectric constants of some common solvents.

TABLE 6.5 Dielectric Constants of Common Solvents

| | Solvent | Formula | Dielectric Constant |
|--|--------------------------------|--|---------------------|
| ↑ Increasing solvent polarity | Water | H ₂ O | 80 |
| | Formic acid | HCO ₂ H | 59 |
| | Dimethyl sulfoxide (DMSO) | CH ₃ SOCH ₃ | 49 |
| | N,N-Dimethylformamide (DMF) | HCON(CH ₃) ₂ | 37 |
| | Acetonitrile | CH ₃ C≡N | 36 |
| | Methanol | CH ₃ OH | 33 |
| | Hexamethylphosphoramide (HMPA) | [(CH ₃) ₂ N] ₃ P=O | 30 |
| | Ethanol | CH ₃ CH ₂ OH | 24 |
| | Acetone | CH ₃ COCH ₃ | 21 |
| | Acetic acid | CH ₃ CO ₂ H | 6 |

Water is the most effective solvent for promoting ionization, but most organic compounds do not dissolve appreciably in water. They usually dissolve, however, in alcohols, and quite often mixed solvents are used. Methanol–water and ethanol–water are common mixed solvents for nucleophilic substitution reactions.

When *tert*-butyl bromide undergoes solvolysis in a mixture of methanol and water, the rate of solvolysis (measured by the rate at which bromide ions form in the mixture) *increases* when the percentage of water in the mixture is increased. **(a)** Explain this occurrence. **(b)** Provide an explanation for the observation that the rate of the S_N2 reaction of ethyl chloride with potassium iodide in methanol and water *decreases* when the percentage of water in the mixture is increased.

Review Problem 6.10

6.13E The Nature of the Leaving Group

Leaving groups depart with the electron pair that was used to bond them to the substrate. The best leaving groups are those that become either a relatively stable anion or a neutral molecule when they depart. First, let us consider leaving groups that become anions when

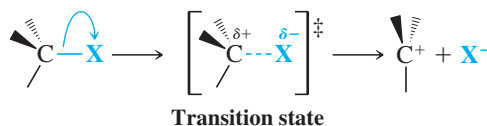
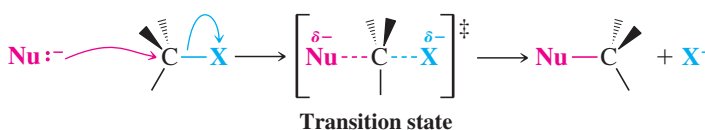
248 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides



Good leaving groups are weak bases.

they separate from the substrate. Because weak bases stabilize a negative charge effectively, leaving groups that become weak bases are good leaving groups. In general, **the best leaving groups are those that can be classified as weak bases after they depart.**

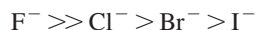
The reason that stabilization of the negative charge is important can be understood by considering the structure of the transition states. In either an S_N1 or S_N2 reaction the leaving group begins to acquire a negative charge as the transition state is reached:

 S_N1 Reaction (Rate-Limiting Step) S_N2 Reaction

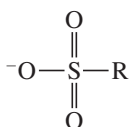
Stabilization of this developing negative charge at the leaving group stabilizes the transition state (lowers its free energy); this lowers the free energy of activation and thereby increases the rate of the reaction. Of the halogens, an iodide ion is the best leaving group and a fluoride ion is the poorest:



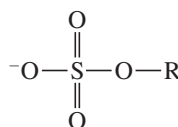
The order is the opposite of the basicity:



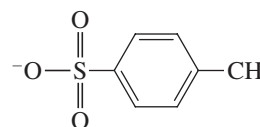
Other weak bases that are good leaving groups, which we shall study later, are alkanesulfonate ions, alkyl sulfate ions, and the *p*-toluenesulfonate ion:



An alkanesulfonate ion

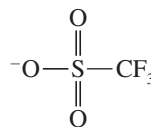


An alkyl sulfate ion

*p*-Toluenesulfonate ion

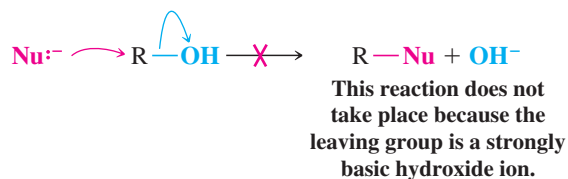
These anions are all the conjugate bases of very strong acids.

The trifluoromethanesulfonate ion (CF_3SO_3^- , commonly called the **triflate ion**) is one of the best leaving groups known to chemists. It is the conjugate base of $\text{CF}_3\text{SO}_3\text{H}$, an exceedingly strong acid ($\text{p}K_a \sim -5$ to -6):



Triflate ion
(a “super” leaving group)

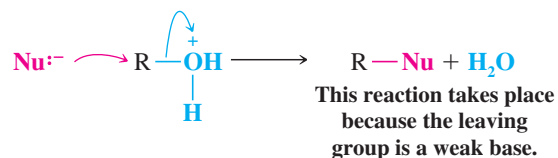
Strongly basic ions rarely act as leaving groups. The hydroxide ion, for example, is a strong base and thus reactions like the following do not take place:



However, when an alcohol is dissolved in a strong acid, it can undergo substitution by a nucleophile. Because the acid protonates the —OH group of the alcohol, the leaving group

6.13 Factors Affecting the Rates of S_N1 and S_N2 Reactions 249

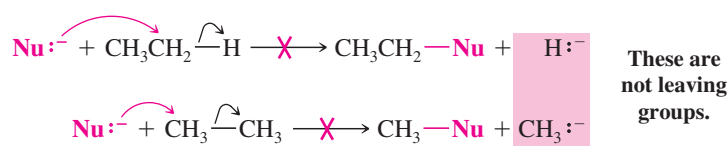
no longer needs to be a hydroxide ion; it is now a molecule of water—a much weaker base than a hydroxide ion and a good leaving group:



List the following compounds in order of decreasing reactivity toward CH_3O^- in an S_N2 reaction carried out in CH_3OH : CH_3F , CH_3Cl , CH_3Br , CH_3I , $\text{CH}_3\text{OSO}_2\text{CF}_3$, $^{14}\text{CH}_3\text{OH}$.

Review Problem 6.11

Very powerful bases such as hydride ions (H^-) and alkanide ions (R^-) virtually never act as leaving groups. Therefore, reactions such as the following are not feasible:

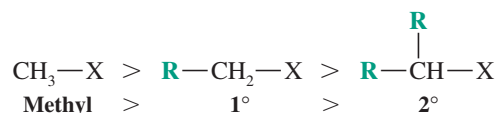


Remember: The best leaving groups are weak bases after they depart.

Summary of S_N1 versus S_N2 Reactions

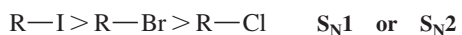
Reactions of alkyl halides by an S_N1 mechanism are favored by the use of substrates that can form relatively stable carbocations, by the use of weak nucleophiles, and by the use of highly ionizing solvents. S_N1 mechanisms, therefore, are important in solvolysis reactions of tertiary halides, especially when the solvent is highly polar. In a solvolysis reaction the nucleophile is weak because it is a neutral molecule (of the solvent) rather than an anion.

If we want to favor the reaction of an alkyl halide by an S_N2 mechanism, we should use a relatively unhindered alkyl halide, a strong nucleophile, a polar aprotic solvent, and a high concentration of the nucleophile. For substrates, the order of reactivity in S_N2 reactions is



Tertiary halides do not react by an S_N2 mechanism.

The effect of the leaving group is the same in both S_N1 and S_N2 reactions: alkyl iodides react fastest; fluorides react slowest. (Because alkyl fluorides react so slowly, they are seldom used in nucleophilic substitution reactions.)



These factors are summarized in Table 6.6.

TABLE 6.6 Factors Favoring S_N1 versus S_N2 Reactions

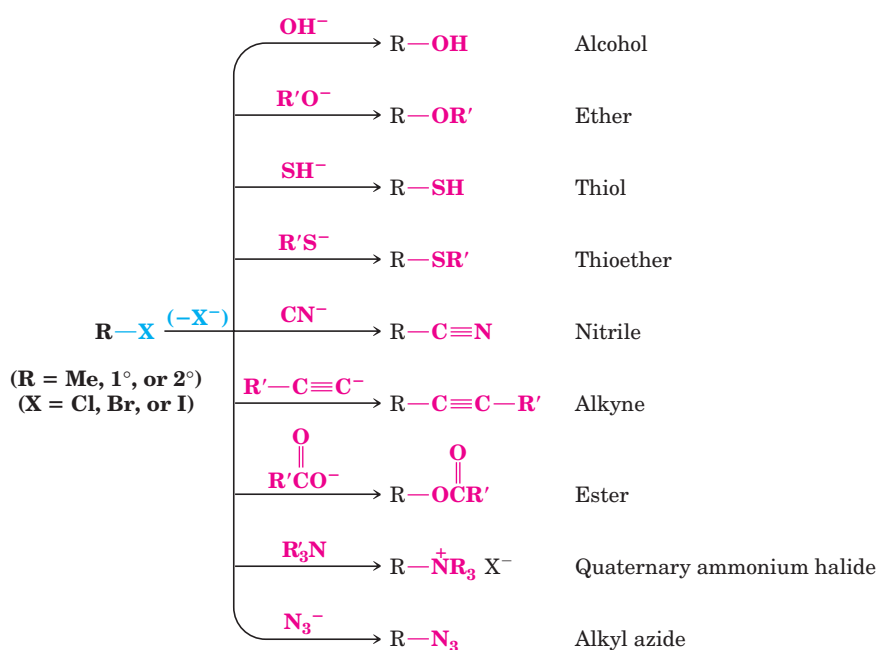
| Factor | S_N1 | S_N2 |
|---------------|---|--|
| Substrate | 3° (requires formation of a relatively stable carbocation) | Methyl > 1° > 2° (requires unhindered substrate) |
| Nucleophile | Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis) | Strong Lewis base, rate increased by high concentration of nucleophile |
| Solvent | Polar protic (e.g., alcohols, water) | Polar aprotic (e.g., DMF, DMSO) |
| Leaving group | I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after the group departs, the better the leaving group) | |



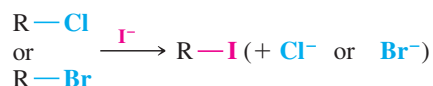
6.14 Organic Synthesis: Functional Group Transformations Using S_N2 Reactions

S_N2 reactions are highly useful in organic synthesis because they enable us to convert one functional group into another—a process that is called a **functional group transformation** or a **functional group interconversion**. With the S_N2 reactions shown in Fig. 6.11, the functional group of a methyl, primary, or secondary alkyl halide can be transformed into that of an alcohol, ether, thiol, thioether, nitrile, ester, and so on. (*Note:* The use of the prefix *thio-* in a name means that a sulfur atom has replaced an oxygen atom in the compound.)

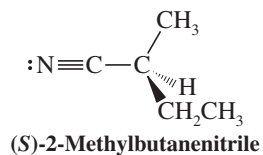
FIGURE 6.11 Functional group interconversions of methyl, primary, and secondary alkyl halides using S_N2 reactions.



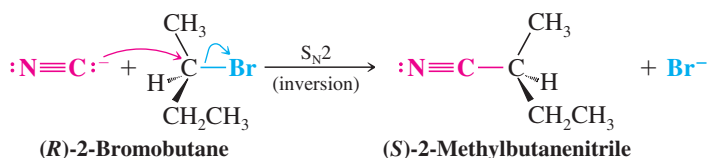
Alkyl chlorides and bromides are also easily converted to alkyl iodides by nucleophilic substitution reactions.

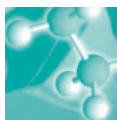


One other aspect of the S_N2 reaction that is of great importance is **stereochemistry** (Section 6.8). S_N2 reactions always occur with **inversion of configuration** at the atom that bears the leaving group. This means that when we use S_N2 reactions in syntheses we can be sure of the configuration of our product if we know the configuration of our reactant. For example, suppose we need a sample of the following nitrile with the (*S*) configuration:



If we have available (*R*)-2-bromobutane, we can carry out the following synthesis:





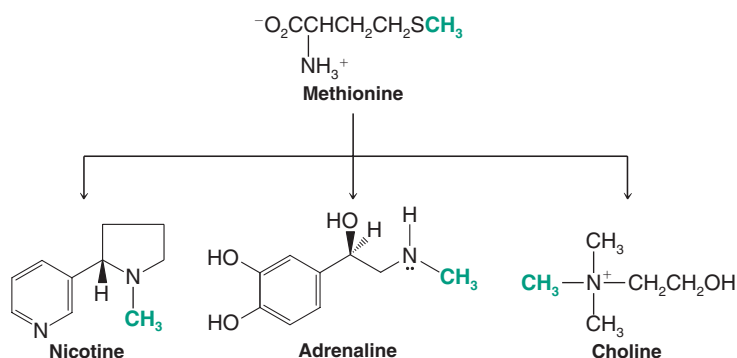
THE CHEMISTRY OF...

Biological Methylation: A Biological Nucleophilic Substitution Reaction

The cells of living organisms synthesize many of the compounds they need from smaller molecules. Often these biosyntheses resemble the syntheses organic chemists carry out in their laboratories. Let us examine one example now.

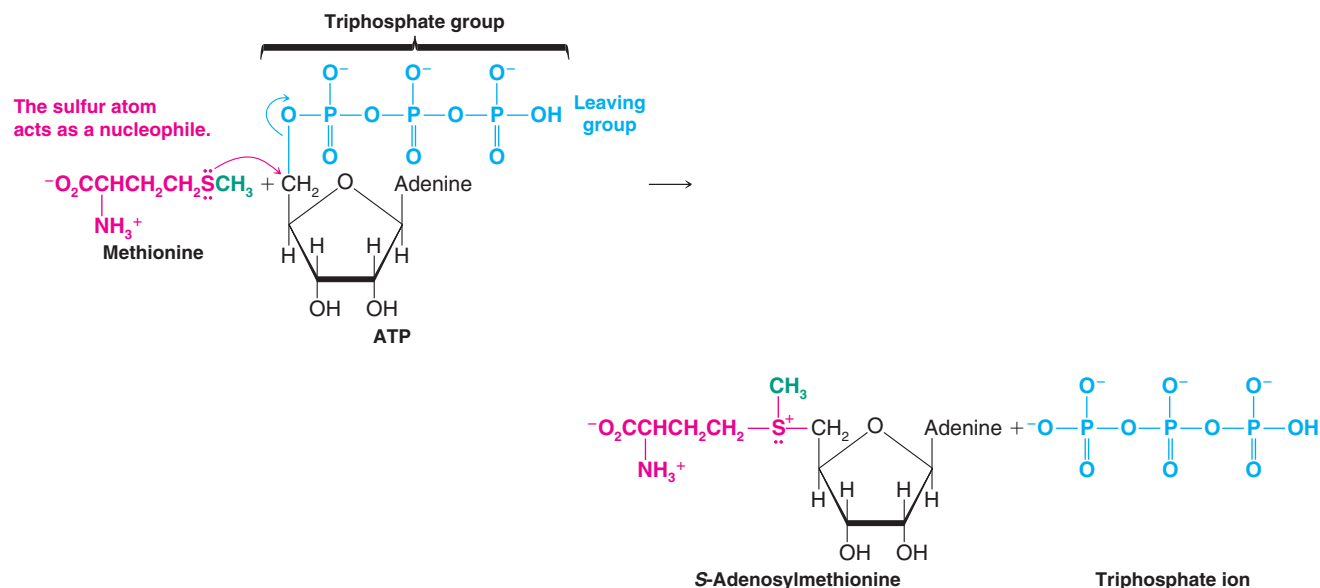
Many reactions taking place in the cells of plants and animals involve the transfer of a methyl group from an amino acid called methionine to some other compound. That this

transfer takes place can be demonstrated experimentally by feeding a plant or animal methionine containing an isotopically labeled carbon atom (e.g., ^{13}C or ^{14}C) in its methyl group. Later, other compounds containing the "labeled" methyl group can be isolated from the organism. Some of the compounds that get their methyl groups from methionine are the following. The isotopically labeled carbon atom is shown in green.



Choline is important in the transmission of nerve impulses, adrenaline causes blood pressure to increase, and nicotine is the compound contained in tobacco that makes smoking tobacco addictive. (In large doses nicotine is poisonous.)

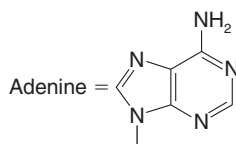
The transfer of the methyl group from methionine to these other compounds does not take place directly. The actual methylating agent is not methionine; it is *S*-adenosylmethionine,* a compound that results when methionine reacts with adenosine triphosphate (ATP):



*The prefix *S* is a locant meaning "on the sulfur atom" and should not be confused with the (*S*) used to define absolute configuration. Another example of this kind of locant is *N*, meaning "on the nitrogen atom."

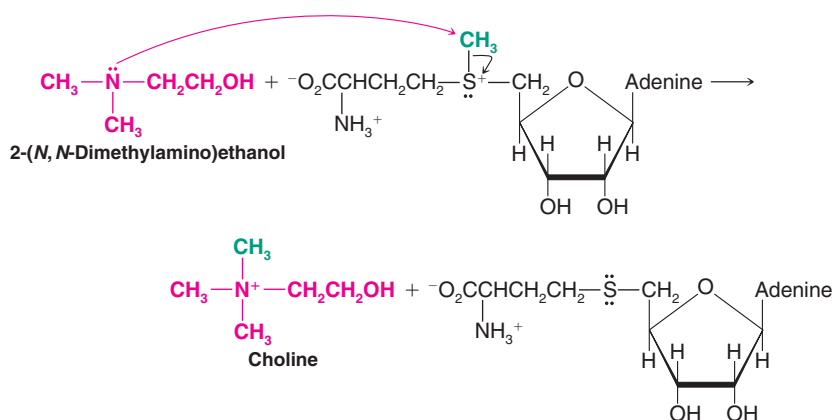
(continues on next page)

252 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides



This reaction is a nucleophilic substitution reaction. The nucleophilic atom is the sulfur atom of methionine. The leaving group is the weakly basic triphosphate group of ATP. The product, *S*-adenosylmethionine, contains a methylsulfonium group, $\text{CH}_3\text{—}\overset{\ominus}{\text{S}}\text{—}$.

S-Adenosylmethionine then acts as the substrate for other nucleophilic substitution reactions. In the biosynthesis of choline, for example, it transfers its methyl group to a nucleophilic nitrogen atom of 2-(*N,N*-dimethylamino)ethanol:

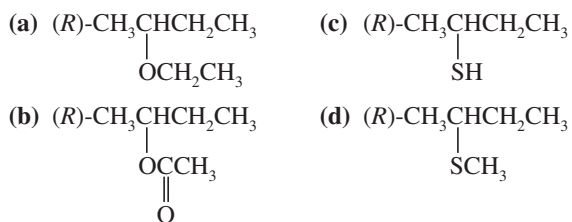


These reactions appear complicated only because the structures of the nucleophiles and substrates are complex. Yet conceptually they are simple, and they illustrate many of the principles we have encountered thus far in Chapter 6. In them we see how nature makes use of the high nucleophilicity of sulfur atoms. We also see how a weakly basic group (e.g., the triphosphate group of ATP) functions as a

leaving group. In the reaction of 2-(*N,N*-dimethylamino)ethanol we see that the more basic $(\text{CH}_3)_2\text{N—}$ group acts as the nucleophile rather than the less basic —OH group. And when a nucleophile attacks *S*-adenosylmethionine, we see that the attack takes place at the less hindered $\text{CH}_3\text{—}$ group rather than at one of the more hindered $\text{—CH}_2\text{—}$ groups.

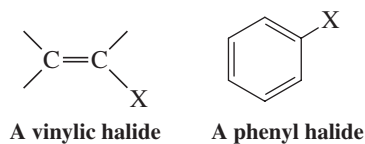
Study Problem (a) What is the leaving group when 2-(*N,N*-dimethylamino)ethanol reacts with *S*-adenosylmethionine? (b) What would the leaving group have to be if methionine itself were to react with 2-(*N,N*-dimethylamino)ethanol? (c) Of what special significance is this difference?

Review Problem 6.12 Starting with (*S*)-2-bromobutane, outline syntheses of each of the following compounds:



6.14A The Unreactivity of Vinylic and Phenyl Halides

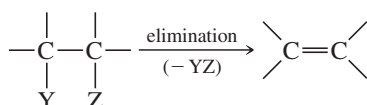
As we learned in Section 6.1, compounds that have a halogen atom attached to one carbon atom of a double bond are called **vinylic halides**; those that have a halogen atom attached to a benzene ring are called **phenyl halides**:



Vinylic and phenyl halides are generally unreactive in S_N1 or S_N2 reactions. They are unreactive in S_N1 reactions because vinylic and phenyl cations are relatively unstable and do not form readily. They are unreactive in S_N2 reactions because the carbon-halogen bond of a vinylic or phenyl halide is stronger than that of an alkyl halide (we shall see why later), and the electrons of the double bond or benzene ring repel the approach of a nucleophile from the back side.

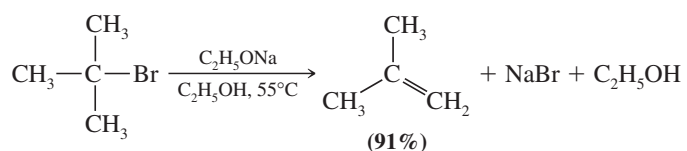
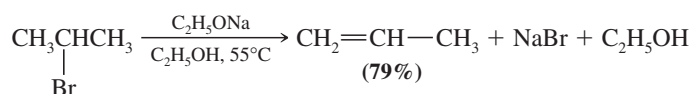
6.15 Elimination Reactions of Alkyl Halides

Elimination reactions of alkyl halides are important reactions that compete with substitution reactions. In an **elimination reaction** the fragments of some molecule (YZ) are removed (eliminated) from adjacent atoms of the reactant. This elimination leads to the creation of a multiple bond:

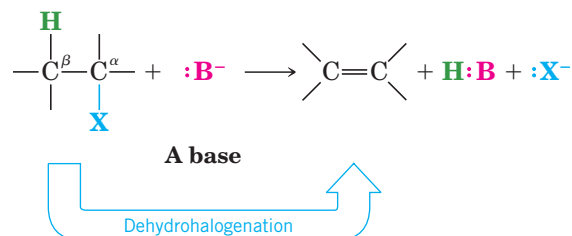


6.15A Dehydrohalogenation

A widely used method for synthesizing alkenes is the elimination of HX from adjacent atoms of an alkyl halide. Heating the alkyl halide with a strong base causes the reaction to take place. The following are two examples:



Reactions like these are not limited to the elimination of hydrogen bromide. Chloroalkanes also undergo the elimination of hydrogen chloride, iodoalkanes undergo the elimination of hydrogen iodide, and, in all cases, alkenes are produced. When the elements of a hydrogen halide are eliminated from a haloalkane in this way, the reaction is often called **dehydrohalogenation**:



In these eliminations, as in S_N1 and S_N2 reactions, there is a leaving group and an attacking Lewis base that possesses an electron pair.

254 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

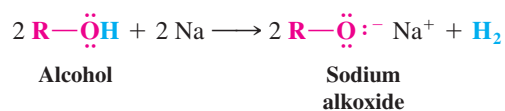
Chemists often call the carbon atom that bears the substituent (e.g., the halogen atom in the previous reaction) the **alpha (α) carbon atom** and any carbon atom adjacent to it a **beta (β) carbon atom**. A hydrogen atom attached to the β carbon atom is called a **β hydrogen atom**. Since the hydrogen atom that is eliminated in dehydrohalogenation is from the β carbon atom, these reactions are often called **β eliminations**. They are also often referred to as **1,2 eliminations**.

We shall have more to say about dehydrohalogenation in Chapter 7, but we can examine several important aspects here.

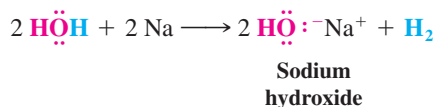
6.15B Bases Used in Dehydrohalogenation

Various strong bases have been used for dehydrohalogenations. Potassium hydroxide dissolved in ethanol is a reagent sometimes used, but the conjugate bases of alcohols, such as sodium ethoxide, often offer distinct advantages.

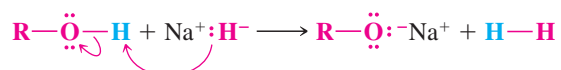
The conjugate base of an alcohol (an alkoxide) can be prepared by treating an alcohol with an alkali metal. For example:



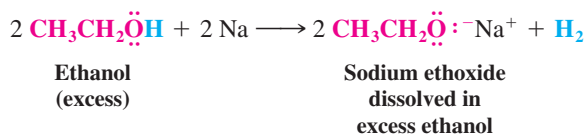
This reaction is an **oxidation–reduction reaction**. Metallic sodium reacts with hydrogen atoms that are bonded to oxygen atoms to generate hydrogen gas, sodium cations, and the hydroxide anion. The reaction is vigorous and at times explosive.



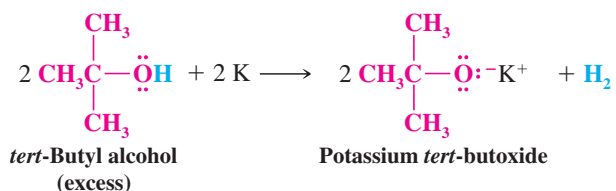
Sodium alkoxides can also be prepared by allowing an alcohol to react with sodium hydride (NaH). The hydride ion (H^-) is a very strong base. (The $\text{p}K_{\text{a}}$ of H_2 is 36.)



Sodium (and potassium) alkoxides are usually prepared by using an excess of the alcohol, and the excess alcohol becomes the solvent for the reaction. Sodium ethoxide is frequently prepared in this way.



Potassium *tert*-butoxide is another highly effective dehydrohalogenating reagent.



6.15C Mechanisms of Dehydrohalogenations

Elimination reactions occur by a variety of mechanisms. With alkyl halides, two mechanisms are especially important because they are closely related to the S_N2 and S_N1 reactions that we have just studied. One mechanism, called the **E2 reaction**, is bimolecular in the rate-determining step; the other mechanism is the **E1 reaction**, which is unimolecular in the rate-determining step.

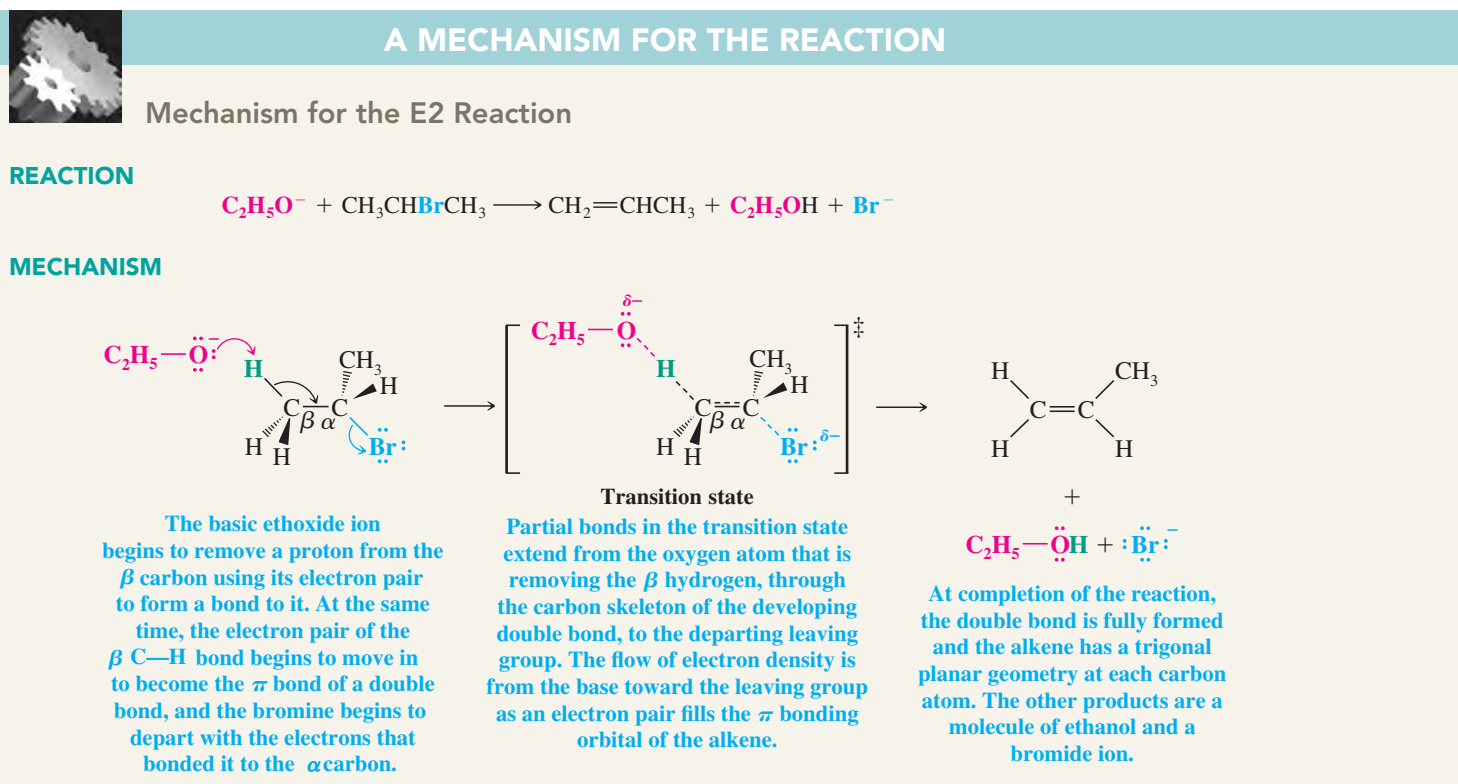
6.16 The E2 Reaction

When isopropyl bromide is heated with sodium ethoxide in ethanol to form propene, the reaction rate depends on the concentration of isopropyl bromide and the concentration of ethoxide ion. The rate equation is first order in each reactant and second order overall:

$$\text{Rate} \propto [\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

$$\text{Rate} = k[\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

From this we infer that the transition state for the rate-determining step must involve both the alkyl halide and the alkoxide ion. The reaction must be bimolecular. Considerable experimental evidence indicates that the reaction takes place in the following way:

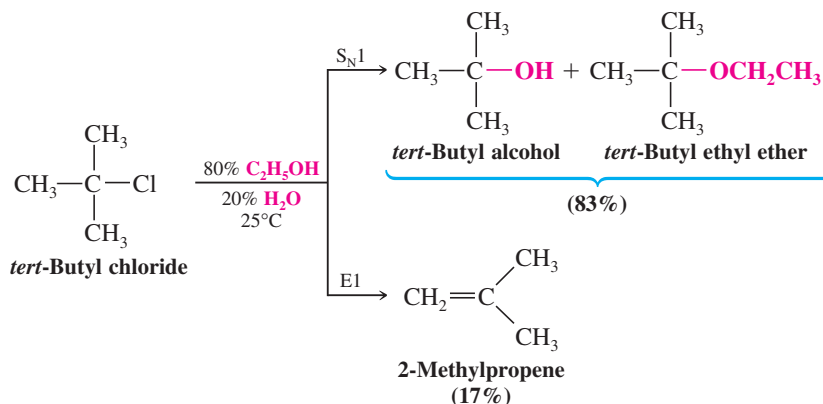


When we study the E2 reaction further in Section 7.6C, we shall find that the orientations of the hydrogen atom being removed and the leaving group are not arbitrary and that the orientation where they are all in the same plane, as shown above, is required.

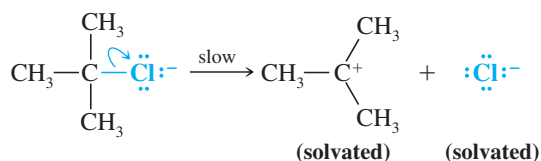
256 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

6.17 The E1 Reaction

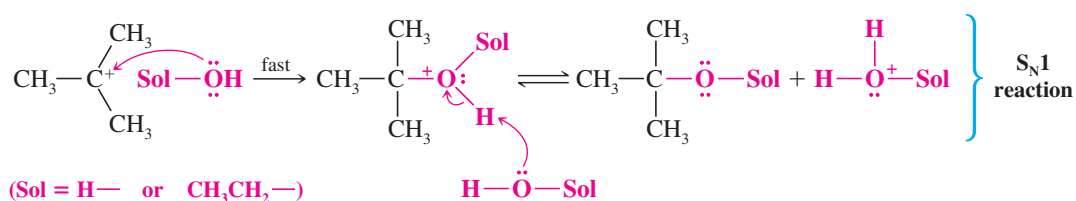
Eliminations may take a different pathway from that given in Section 6.16. Treating *tert*-butyl chloride with 80% aqueous ethanol at 25°C, for example, gives *substitution products* in 83% yield and an elimination product (2-methylpropene) in 17% yield:



The initial step for both reactions is the formation of a *tert*-butyl cation. This is also the rate-determining step for both reactions; thus both reactions are unimolecular:

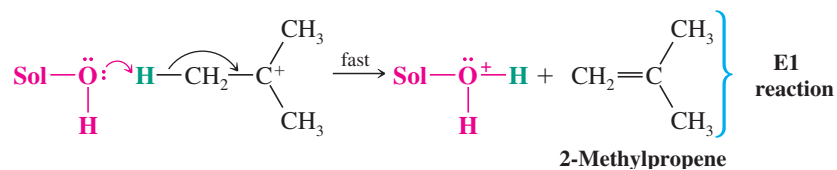


Whether substitution or elimination takes place depends on the next step (the fast step). If a solvent molecule reacts as a nucleophile at the positive carbon atom of the *tert*-butyl cation, the product is *tert*-butyl alcohol or *tert*-butyl ethyl ether and the reaction is S_N1:



If, however, a solvent molecule acts as a base and removes one of the β hydrogen atoms as a proton, the product is 2-methylpropene and the reaction is E1.

E1 reactions almost always accompany S_N1 reactions.

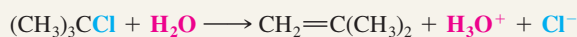




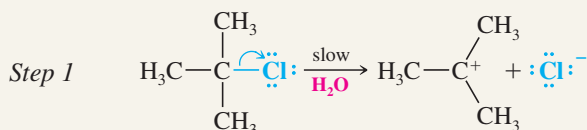
A MECHANISM FOR THE REACTION

Mechanism for the E1 Reaction

REACTION

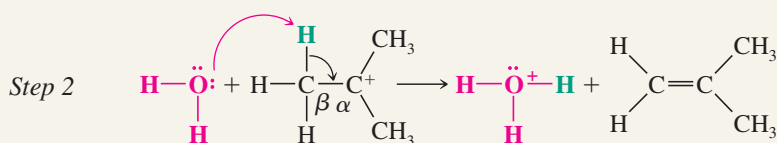


MECHANISM



Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. The ions are solvated (and stabilized) by surrounding water molecules.



A molecule of water removes one of the hydrogens from the β carbon of the carbocation. These hydrogens are acidic due to the adjacent positive charge. At the same time an electron pair moves in to form a double bond between the α and β carbon atoms.

This step produces the alkene and a hydronium ion.

6.18 Substitution versus Elimination

All nucleophiles are potential bases and all bases are potential nucleophiles. This is because the reactive part of both nucleophiles and bases is an unshared electron pair. It should not be surprising, then, that nucleophilic substitution reactions and elimination reactions often compete with each other.

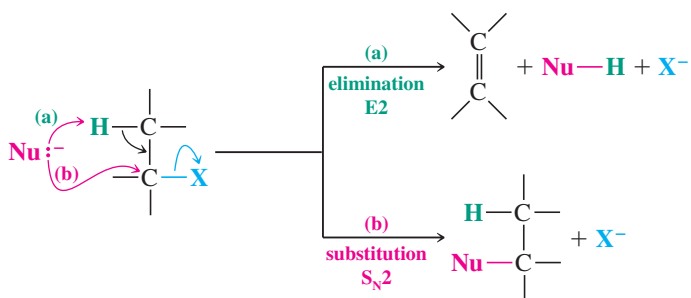
6.18A $\text{S}_{\text{N}}2$ versus E2

$\text{S}_{\text{N}}2$ and E2 reactions are both favored by a high concentration of a strong nucleophile or base. When the nucleophile (base) attacks a β hydrogen atom, elimination occurs. When the nucleophile attacks the carbon atom bearing the leaving group, substitution results:



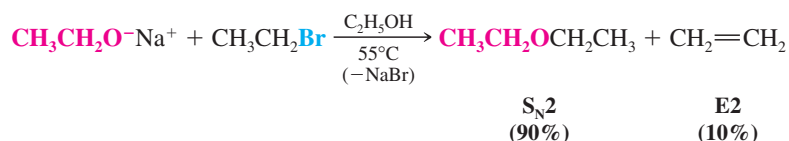
This section draws together the various factors that influence the competition between substitution and elimination.

258 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

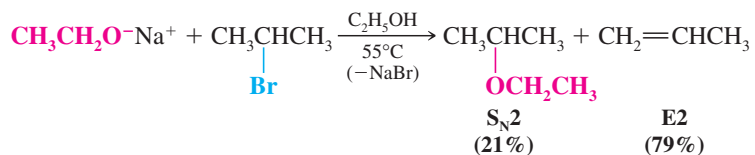


Consider the following examples with small (unhindered) nucleophiles and alkyl halides of different classes. Note the ratio of products formed in each case.

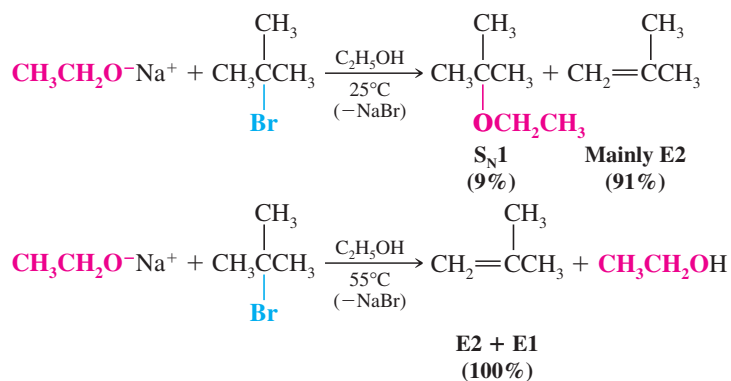
Primary Substrate When the substrate is a *primary* halide and the base is unhindered, like ethoxide ion, substitution is highly favored because the base can easily approach the carbon bearing the leaving group:



Secondary Substrate With *secondary* halides, however, a strong base favors elimination because steric hindrance in the substrate makes substitution more difficult:



Tertiary Substrate With *tertiary* halides, steric hindrance in the substrate is severe and an $\text{S}_{\text{N}}2$ reaction cannot take place. Elimination is highly favored, especially when the reaction is carried out at higher temperatures. Any substitution that occurs must take place through an $\text{S}_{\text{N}}1$ mechanism:

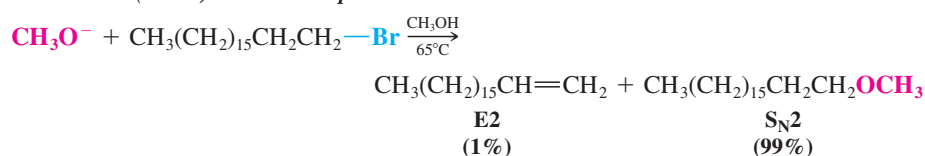


Temperature Increasing the reaction temperature favors elimination (E1 and E2) over substitution. Elimination reactions have greater free energies of activation than substitution reactions because more bonding changes occur during elimination. When higher temperature is used, the proportion of molecules able to surmount the energy of activation barrier for elimination increases more than the proportion of molecules able to undergo substitution, although the rate of both substitution and elimination will be increased. Furthermore, elimination reactions are entropically favored over substitution because the products of an elimination reaction are greater in number than the reactants. Additionally, because

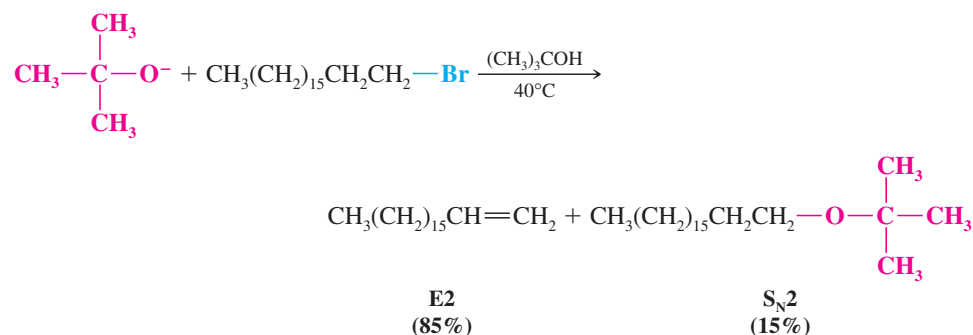
temperature is the coefficient of the entropy term in the Gibbs free-energy equation $\Delta G^\circ = \Delta H^\circ - T \Delta S^\circ$, an increase in temperature further enhances the entropy effect.

Size of the Base/Nucleophile Increasing the reaction temperature is one way of favorably influencing an elimination reaction of an alkyl halide. Another way is to use a **strong sterically hindered base** such as the *tert*-butoxide ion. The bulky methyl groups of the *tert*-butoxide ion inhibit its reacting by substitution, allowing elimination reactions to take precedence. We can see an example of this effect in the following two reactions. The relatively unhindered methoxide ion reacts with octadecyl bromide primarily by *substitution*, whereas the bulky *tert*-butoxide ion gives mainly *elimination*.

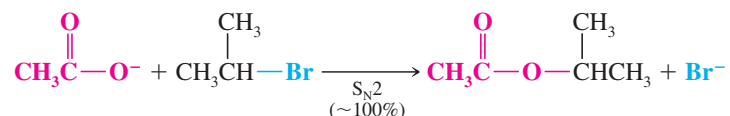
Unhindered (Small) Base/Nucleophile



Hindered Base/Nucleophile



Basicity and Polarizability Another factor that affects the relative rates of E2 and S_N2 reactions is the relative basicity and polarizability of the base/nucleophile. Use of a strong, slightly polarizable base such as amide ion (NH₂[−]) or alkoxide ion (especially a hindered one) tends to increase the likelihood of elimination (E2). Use of a weakly basic ion such as a chloride ion (Cl[−]) or an acetate ion (CH₃CO₂[−]) or a weakly basic and highly polarizable one such as Br[−], I[−], or RS[−] increases the likelihood of substitution (S_N2). Acetate ion, for example, reacts with isopropyl bromide almost exclusively by the S_N2 path:



The more strongly basic ethoxide ion (Section 6.15B) reacts with the same compound mainly by an E2 mechanism.

6.18B Tertiary Halides: S_N1 versus E1

Because E1 and S_N1 reactions proceed through the formation of a common intermediate, the two types respond in similar ways to factors affecting reactivities. E1 reactions are favored with substrates that can form stable carbocations (i.e., tertiary halides); they are also favored by the use of poor nucleophiles (weak bases) and they are generally favored by the use of polar solvents.

It is usually difficult to influence the relative partition between S_N1 and E1 products because the free energy of activation for either reaction proceeding from the carbocation (loss of a proton or combination with a molecule of the solvent) is very small.

260 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

In most unimolecular reactions the S_N1 reaction is favored over the E1 reaction, especially at lower temperatures. *In general, however, substitution reactions of tertiary halides do not find wide use as synthetic methods. Such halides undergo eliminations much too easily.*

Increasing the temperature of the reaction favors reaction by the E1 mechanism at the expense of the S_N1 mechanism. *If the elimination product is desired, however, it is more convenient to add a strong base and force an E2 reaction to take place instead.*

6.19 Overall Summary

The most important reaction pathways for the substitution and elimination reactions of simple alkyl halides are summarized in Table 6.7.

TABLE 6.7 Overall Summary of S_N1 , S_N2 , E1, and E2 Reactions

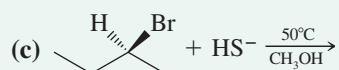
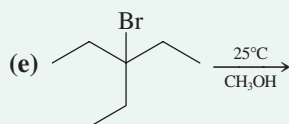
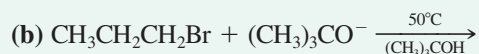
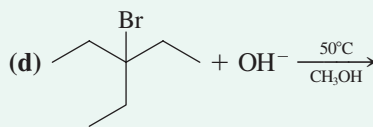
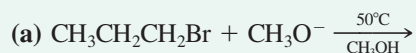
Overall summary

| | $\begin{array}{c} \text{H} \\ \\ \text{R}-\text{C}-\text{X} \\ \\ \text{H} \end{array}$ | $\begin{array}{c} \text{R} \\ \\ \text{R}-\text{C}-\text{X} \\ \\ \text{H} \end{array}$ | $\begin{array}{c} \text{R} \\ \\ \text{R}-\text{C}-\text{X} \\ \\ \text{R} \end{array}$ |
|------------------------|--|--|--|
| CH_3X | | | |
| Methyl | 1° | 2° | 3° |
| | Bimolecular (S_N2 /E2) Reactions Only | | S_N1 /E1 or E2 |
| Gives S_N2 reactions | Gives mainly S_N2 except with a hindered strong base [e.g., $(\text{CH}_3)_3\text{CO}^-$] and then gives mainly E2. | Gives mainly S_N2 with weak bases (e.g., I^- , CN^- , RCO_2^-) and mainly E2 with strong bases (e.g., RO^-). | No S_N2 reaction. In solvolysis gives S_N1 /E1, and at lower temperatures S_N1 is favored. When a strong base (e.g., RO^-) is used, E2 predominates. |

Let us examine several sample exercises that will illustrate how the information in Table 6.7 can be used.

Study Problem

Give the product (or products) that you would expect to be formed in each of the following reactions. In each case give the mechanism (S_N1 , S_N2 , E1, or E2) by which the product is formed and predict the relative amount of each (i.e., would the product be the only product, the major product, or a minor product?).

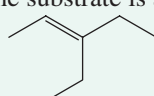


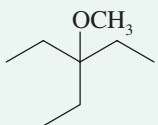
STRATEGY AND ANSWER:

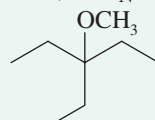
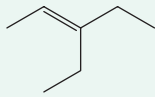
(a) The substrate is a 1° halide. The base/nucleophile is CH_3O^- , a strong base (but not a hindered one) and a good nucleophile. According to Table 6.7, we should expect an S_N2 reaction mainly, and the major product should be $\text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3$. A minor product might be $\text{CH}_3\text{CH}=\text{CH}_2$ by an E2 pathway.

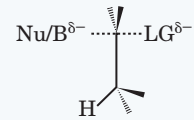
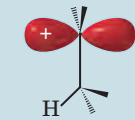
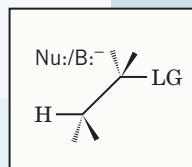
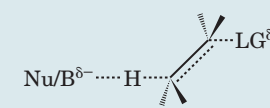
- (b) Again the substrate is a 1° halide, but the base/nucleophile, $(\text{CH}_3)_3\text{CO}^-$, is a strong hindered base. We should expect, therefore, the major product to be $\text{CH}_3\text{CH}=\text{CH}_2$ by an E2 pathway and a minor product to be $\text{CH}_3\text{CH}_2\text{CH}_2\text{OC}(\text{CH}_3)_3$ by an $\text{S}_\text{N}2$ pathway.
- (c) The reactant is (*S*)-2-bromobutane, a 2° halide and one in which the leaving group is attached to a chirality center. The base/nucleophile is HS^- , a strong nucleophile but a weak base. We should expect mainly an $\text{S}_\text{N}2$ reaction, causing an inversion of configuration at the chirality center and producing the (*R*) stereoisomer:



- (d) The base/nucleophile is OH^- , a strong base and a strong nucleophile. However, the substrate is a 3° halide; therefore, we should not expect an $\text{S}_\text{N}2$ reaction. The major product should be  via an E2 reaction. At this higher temperature and in the presence of a strong base, we should not expect an appreciable amount of the $\text{S}_\text{N}1$ product,



- (e) This is solvolysis; the only base/nucleophile is the solvent, CH_3OH , which is a weak base (therefore, no E2 reaction) and a poor nucleophile. The substrate is tertiary (therefore, no $\text{S}_\text{N}2$ reaction). At this lower temperature we should expect mainly an $\text{S}_\text{N}1$ pathway leading to . A minor product, by an E1 pathway, would be .

| Summary and Review Tools | |
|--|---|
| Mechanism Review: Substitution versus Elimination | |
| $\text{S}_\text{N}2$ | $\text{S}_\text{N}1$ and E1 |
| Primary substrate Back side attack of Nu: with respect to LG Strong/polarizable unhindered nucleophile Bimolecular in rate-determining step Concerted bond forming/bond breaking Inversion of stereochemistry Favored by polar aprotic solvent | Tertiary substrate Carbocation intermediate Weak nucleophile/base (e.g., solvent) Unimolecular in rate-determining step Racemization if $\text{S}_\text{N}1$ Removal of β -hydrogen if E1 Protic solvent assists ionization of LG Low temperature ($\text{S}_\text{N}1$) / high temperature (E2) |
|  |  |
| $\text{S}_\text{N}2$ and E2 | E2 |
| Secondary or primary substrate Strong unhindered base/nucleophile leads to $\text{S}_\text{N}2$ Strong hindered base/nucleophile leads to E2 Low temperature ($\text{S}_\text{N}2$) / high temperature (E2) | Tertiary or secondary substrate Concerted anti-coplanar TS Bimolecular in rate-determining step Strong hindered base High temperature |
|  |  |

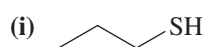
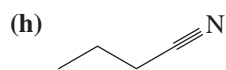
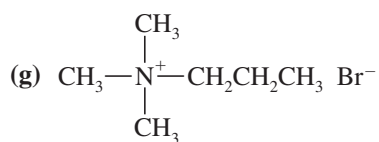
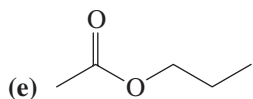
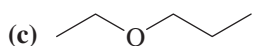
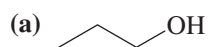
Key Terms and Concepts

Aprotic solvent Section 6.13C
Bimolecular reaction Section 6.5
Carbocation Sections 6.11, 6.12
Configuration Section 6.8
Dehydrohalogenation Section 6.15A
Delocalization Section 6.11B
E1 reaction Sections 6.15C, 6.17, 6.18B
E2 reaction Sections 6.15C, 6.16, 6.18A
Elimination reaction Sections 6.15–6.17
Endergonic reaction Section 6.7
Exergonic reaction Section 6.7
Free-energy of activation, ΔG^\ddagger Section 6.7
Free-energy diagram Section 6.7
Hammond–Leffler postulate Section 6.13A
Hyperconjugation Section 6.11
Inversion of configuration Section 6.8
Kinetics Section 6.5
Leaving group Sections 6.2, 6.4, 6.13E
Nucleophile Sections 6.2, 6.3, 6.13B

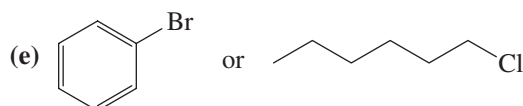
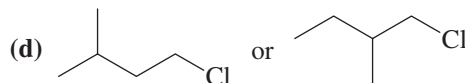
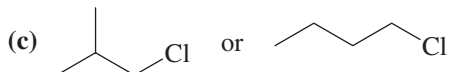
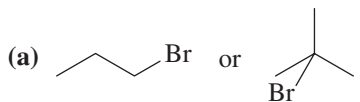
Nucleophilicity Section 6.13B
Nucleophilic substitution reaction Section 6.2
Polar aprotic solvent Section 6.13C
Polarizability Section 6.13C
Polar protic solvent Section 6.13D
Protic solvent Section 6.13C
Racemization Section 6.12A
Rate-determining step Sections 6.9, 6.9A
Reaction coordinate Section 6.7
 S_N1 reaction Sections 6.9, 6.10, 6.12, 6.13, 6.18B
 S_N2 reaction Sections 6.5–6.8, 6.13, 6.18A
Solvent effect Sections 6.13C, 6.13D
Solvolysis Section 6.12B
Steric effect Section 6.13A
Steric hindrance Section 6.13A
Substitution reaction Section 6.2
Substrate Section 6.2
Transition state Sections 6.6, 6.7, 6.10
Unimolecular reaction Section 6.9

Exercises

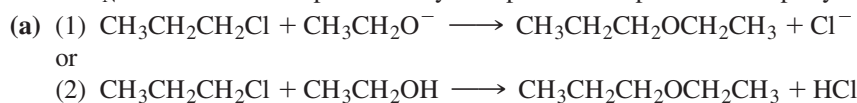
6.13 Show how you might use a nucleophilic substitution reaction of 1-bromopropane to synthesize each of the following compounds. (You may use any other compounds that are necessary.)



6.14 Which alkyl halide would you expect to react more rapidly by an S_N2 mechanism? Explain your answer.



6.15 Which S_N2 reaction of each pair would you expect to take place more rapidly in a protic solvent?



- (b) (1) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + \text{CH}_3\text{CH}_2\text{O}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3 + \text{Cl}^-$
 or
 (2) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + \text{CH}_3\text{CH}_2\text{S}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_3 + \text{Cl}^-$
- (c) (1) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + (\text{C}_6\text{H}_5)_3\text{N} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{N}(\text{C}_6\text{H}_5)_3^+ + \text{Br}^-$
 or
 (2) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + (\text{C}_6\text{H}_5)_3\text{P} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_3^+ + \text{Br}^-$
- (d) (1) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} (1.0M) + \text{CH}_3\text{O}^- (1.0M) \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 + \text{Br}^-$
 or
 (2) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} (1.0M) + \text{CH}_3\text{O}^- (2.0M) \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 + \text{Br}^-$

6.16 Which $\text{S}_{\text{N}}1$ reaction of each pair would you expect to take place more rapidly? Explain your answer.

- (a) (1) $(\text{CH}_3)_3\text{CCl} + \text{H}_2\text{O} \longrightarrow (\text{CH}_3)_3\text{COH} + \text{HCl}$
 or
 (2) $(\text{CH}_3)_3\text{CBr} + \text{H}_2\text{O} \longrightarrow (\text{CH}_3)_3\text{COH} + \text{HBr}$
- (b) (1) $(\text{CH}_3)_3\text{CCl} + \text{H}_2\text{O} \longrightarrow (\text{CH}_3)_3\text{COH} + \text{HCl}$
 or
 (2) $(\text{CH}_3)_3\text{CCl} + \text{CH}_3\text{OH} \longrightarrow (\text{CH}_3)_3\text{COCH}_3 + \text{HCl}$
- (c) (1) $(\text{CH}_3)_3\text{CCl} (1.0M) + \text{CH}_3\text{CH}_2\text{O}^- (1.0M) \xrightarrow{\text{EtOH}} (\text{CH}_3)_3\text{COCH}_2\text{CH}_3 + \text{Cl}^-$
 or
 (2) $(\text{CH}_3)_3\text{CCl} (2.0M) + \text{CH}_3\text{CH}_2\text{O}^- (1.0M) \xrightarrow{\text{EtOH}} (\text{CH}_3)_3\text{COCH}_2\text{CH}_3 + \text{Cl}^-$
- (d) (1) $(\text{CH}_3)_3\text{CCl} (1.0M) + \text{CH}_3\text{CH}_2\text{O}^- (1.0M) \xrightarrow{\text{EtOH}} (\text{CH}_3)_3\text{COCH}_2\text{CH}_3 + \text{Cl}^-$
 or
 (2) $(\text{CH}_3)_3\text{CCl} (1.0M) + \text{CH}_3\text{CH}_2\text{O}^- (2.0M) \xrightarrow{\text{EtOH}} (\text{CH}_3)_3\text{COCH}_2\text{CH}_3 + \text{Cl}^-$
- (e) (1) $(\text{CH}_3)_3\text{CCl} + \text{H}_2\text{O} \longrightarrow (\text{CH}_3)_3\text{COH} + \text{HCl}$
 or
 (2) $\text{C}_6\text{H}_5\text{Cl} + \text{H}_2\text{O} \longrightarrow \text{C}_6\text{H}_5\text{OH} + \text{HCl}$

Problems

6.17 With methyl, ethyl, or cyclopentyl halides as your organic starting materials and using any needed solvents or inorganic reagents, outline syntheses of each of the following. More than one step may be necessary and you need not repeat steps carried out in earlier parts of this problem.

- | | |
|---------------------------------------|--|
| (a) CH_3I | (g) CH_3CN |
| (b) $\text{CH}_3\text{CH}_2\text{I}$ | (h) $\text{CH}_3\text{CH}_2\text{CN}$ |
| (c) CH_3OH | (i) CH_3OCH_3 |
| (d) $\text{CH}_3\text{CH}_2\text{OH}$ | (j) $\text{CH}_3\text{OCH}_2\text{CH}_3$ |
| (e) CH_3SH | (k) Cyclopentene |
| (f) $\text{CH}_3\text{CH}_2\text{SH}$ | |

6.18 Listed below are several hypothetical nucleophilic substitution reactions. None is synthetically useful because the product indicated is not formed at an appreciable rate. In each case provide an explanation for the failure of the reaction to take place as indicated.

- (a) $\text{CH}_3\text{CH}_2\text{CH}_3 + \text{OH}^- \not\rightarrow \text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3^-$
- (b) $\text{CH}_3\text{CH}_2\text{CH}_3 + \text{OH}^- \not\rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{H}^-$
- (c) $\text{Cyclobutane} + \text{OH}^- \not\rightarrow \text{}^-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$
- (d) $\text{CH}_3\text{CH}_2-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}-\text{Br} + \text{CN}^- \not\rightarrow \text{CH}_3\text{CH}_2-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}-\text{CN} + \text{Br}^-$
- (e) $\text{NH}_3 + \text{CH}_3\text{OCH}_3 \not\rightarrow \text{CH}_3\text{NH}_2 + \text{CH}_3\text{OH}$
- (f) $\text{NH}_3 + \text{CH}_3\text{OH}_2^+ \not\rightarrow \text{CH}_3\text{NH}_3^+ + \text{H}_2\text{O}$

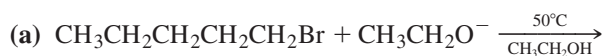
264 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

6.19 You have the task of preparing styrene ($C_6H_5CH=CH_2$) by dehydrohalogenation of either 1-bromo-2-phenylethane or 1-bromo-1-phenylethane using KOH in ethanol at reflux temperature. Which halide would you choose as your starting material to give the better yield of the alkene? Explain your answer.

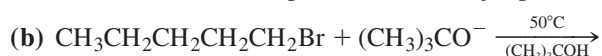
6.20 Your task is to prepare isopropyl methyl ether, $CH_3OCH(CH_3)_2$, by one of the following reactions. Which reaction would give the better yield? Explain your choice.



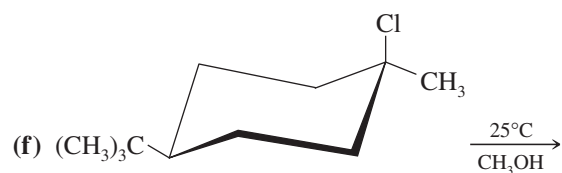
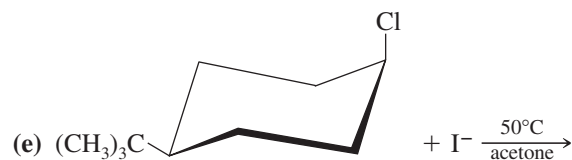
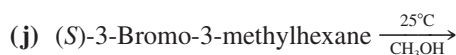
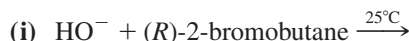
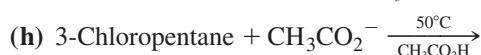
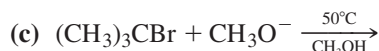
6.21 Which product (or products) would you expect to obtain from each of the following reactions? In each part give the mechanism (S_N1 , S_N2 , E1, or E2) by which each product is formed and predict the relative amount of each product (i.e., would the product be the only product, the major product, a minor product, etc.?).



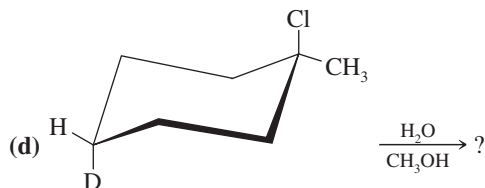
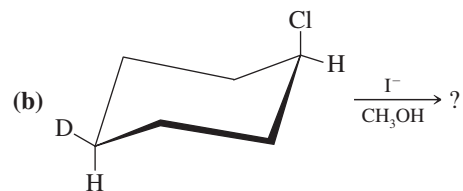
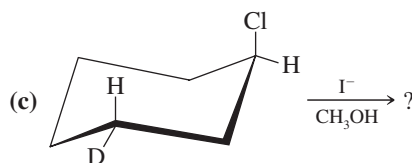
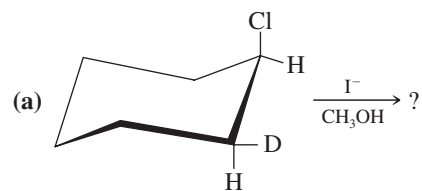
Hint: The ^{13}C NMR spectrum of the major product shows no signals in the $\delta 110$ – 150 region.



Hint: The ^{13}C NMR spectrum of the major product shows no signals in the $\delta 40$ – 85 region.



6.22 Write conformational structures for the substitution products of the following deuterium-labeled compounds:

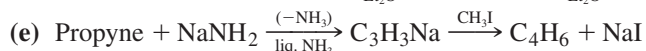
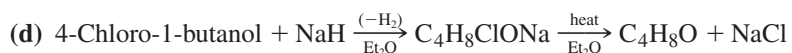
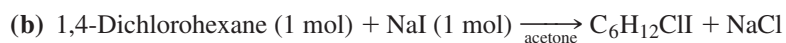
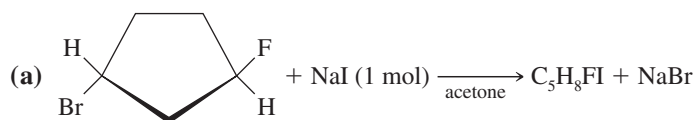


6.23 Although ethyl bromide and isobutyl bromide are both primary halides, ethyl bromide undergoes S_N2 reactions more than 10 times faster than isobutyl bromide does. When each compound is treated with a strong base/nucleophile ($CH_3CH_2O^-$), isobutyl bromide gives a greater yield of elimination products than substitution products, whereas with ethyl bromide this behavior is reversed. What factor accounts for these results?

- 6.24** Consider the reaction of I^- with $\text{CH}_3\text{CH}_2\text{Cl}$.
- Would you expect the reaction to be $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$? The rate constant for the reaction at 60°C is $5 \times 10^{-5} \text{ L mol}^{-1} \text{ s}^{-1}$.
 - What is the reaction rate if $[\text{I}^-] = 0.1 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.1 \text{ mol L}^{-1}$?
 - If $[\text{I}^-] = 0.1 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.2 \text{ mol L}^{-1}$?
 - If $[\text{I}^-] = 0.2 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.1 \text{ mol L}^{-1}$?
 - If $[\text{I}^-] = 0.2 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.2 \text{ mol L}^{-1}$?
- 6.25** Which reagent in each pair listed here would be the more reactive nucleophile in a polar aprotic solvent?
- CH_3NH^- or CH_3NH_2
 - CH_3O^- or CH_3CO^-
 - CH_3SH or CH_3OH
 - $(\text{C}_6\text{H}_5)_3\text{N}$ or $(\text{C}_6\text{H}_5)_3\text{P}$
 - H_2O or H_3O^+
 - NH_3 or NH_4^+
 - H_2S or HS^-
 - CH_3CO^- or OH^-
- 6.26** Write mechanisms that account for the products of the following reactions:
- $\text{HOCH}_2\text{CH}_2\text{Br} \xrightarrow[\text{H}_2\text{O}]{\text{OH}^-} \text{H}_2\text{C} \begin{array}{c} \diagup \\ \text{O} \\ \diagdown \end{array} \text{CH}_2$
 - $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow[\text{H}_2\text{O}]{\text{OH}^-} \text{N} \begin{array}{c} \diagup \\ \text{H} \\ \diagdown \end{array}$
- 6.27** Many $\text{S}_{\text{N}}2$ reactions of alkyl chlorides and alkyl bromides are catalyzed by the addition of sodium or potassium iodide. For example, the hydrolysis of methyl bromide takes place much faster in the presence of sodium iodide. Explain.
- 6.28** Explain the following observations: When *tert*-butyl bromide is treated with sodium methoxide in a mixture of methanol and water, the rate of formation of *tert*-butyl alcohol and *tert*-butyl methyl ether does not change appreciably as the concentration of sodium methoxide is increased. However, increasing the concentration of sodium methoxide causes a marked increase in the rate at which *tert*-butyl bromide disappears from the mixture.
- 6.29**
- Consider the general problem of converting a tertiary alkyl halide to an alkene, for example, the conversion of *tert*-butyl chloride to 2-methylpropene. What experimental conditions would you choose to ensure that elimination is favored over substitution?
 - Consider the opposite problem, that of carrying out a substitution reaction on a tertiary alkyl halide. Use as your example the conversion of *tert*-butyl chloride to *tert*-butyl ethyl ether. What experimental conditions would you employ to ensure the highest possible yield of the ether?
- 6.30** 1-Bromobicyclo[2.2.1]heptane is extremely unreactive in either $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ reactions. Provide explanations for this behavior.
- 6.31** When ethyl bromide reacts with potassium cyanide in methanol, the major product is $\text{CH}_3\text{CH}_2\text{CN}$. Some $\text{CH}_3\text{CH}_2\text{NC}$ is formed as well, however. Write Lewis structures for the cyanide ion and for both products and provide a mechanistic explanation of the course of the reaction.
- 6.32** Starting with an appropriate alkyl halide and using any other needed reagents, outline syntheses of each of the following. When alternative possibilities exist for a synthesis, you should be careful to choose the one that gives the better yield.
- Butyl *sec*-butyl ether
 - $\text{CH}_3\text{CH}_2\text{SC}(\text{CH}_3)_3$
 - Methyl neopentyl ether
 - Methyl phenyl ether
 - $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$
 - $\text{CH}_3\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$
 - (*S*)-2-Pentanol
 - (*R*)-2-Iodo-4-methylpentane
 - $(\text{CH}_3)_3\text{CCH}=\text{CH}_2$
 - cis*-4-Isopropylcyclohexanol
 - (*R*)- $\text{CH}_3\text{CH}(\text{CN})\text{CH}_2\text{CH}_3$
 - trans*-1-Iodo-4-methylcyclohexane

266 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

6.33 Give structures for the products of each of the following reactions:



6.34 When *tert*-butyl bromide undergoes S_N1 hydrolysis, adding a “common ion” (e.g., NaBr) to the aqueous solution has no effect on the rate. On the other hand, when (C₆H₅)₂CHBr undergoes S_N1 hydrolysis, adding NaBr retards the reaction. Given that the (C₆H₅)₂CH⁺ cation is known to be much more stable than the (CH₃)₃C⁺ cation (and we shall see why in Section 15.12A), provide an explanation for the different behavior of the two compounds.

6.35 When the alkyl bromides (listed here) were subjected to hydrolysis in a mixture of ethanol and water (80% C₂H₅OH/20% H₂O) at 55°C, the rates of the reaction showed the following order:



Provide an explanation for this order of reactivity.

6.36 The reaction of 1° alkyl halides with nitrite salts produces both RNO₂ and RONO. Account for this behavior.

6.37 What would be the effect of increasing solvent polarity on the rate of each of the following nucleophilic substitution reactions?



6.38 Competition experiments are those in which two reactants at the same concentration (or one reactant with two reactive sites) compete for a reagent. Predict the major product resulting from each of the following competition experiments:



6.39 In contrast to S_N2 reactions, S_N1 reactions show relatively little nucleophile selectivity. That is, when more than one nucleophile is present in the reaction medium, S_N1 reactions show only a slight tendency to discriminate between weak nucleophiles and strong nucleophiles, whereas S_N2 reactions show a marked tendency to discriminate.

(a) Provide an explanation for this behavior.

(b) Show how your answer accounts for the fact that CH₃CH₂CH₂CH₂Cl reacts with 0.01 M NaCN in ethanol to yield primarily CH₃CH₂CH₂CH₂CN, whereas under the same conditions (CH₃)₃CCl reacts to give primarily (CH₃)₃COCH₂CH₃.

Challenge Problems

6.40 The reaction of chloroethane with water *in the gas phase* to produce ethanol and hydrogen chloride has ΔH° = +26.6 kJ mol^{−1} and ΔS° = +4.81 J K^{−1} mol^{−1} at 25°C.

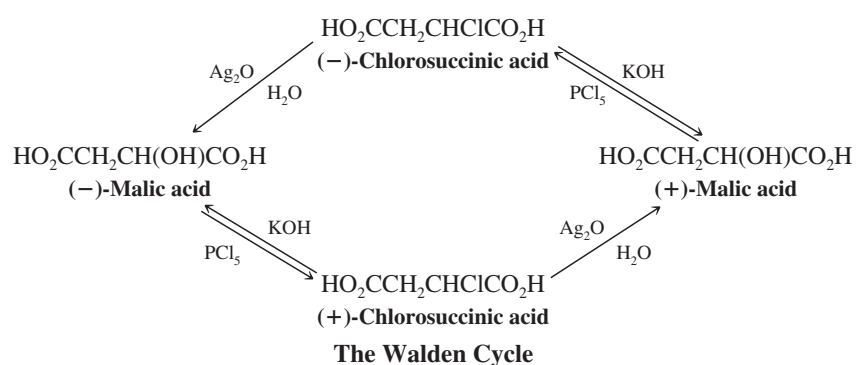
(a) Which of these terms, if either, favors the reaction going to completion?

(b) Calculate ΔG° for the reaction. What can you now say about whether the reaction will proceed to completion?

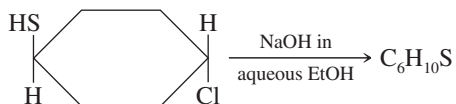
(c) Calculate the equilibrium constant for the reaction.

(d) In aqueous solution the equilibrium constant is very much larger than the one you just calculated. How can you account for this fact?

- 6.41 When (*S*)-2-bromopropanoic acid [(*S*)-CH₃CHBrCO₂H] reacts with concentrated sodium hydroxide, the product formed (after acidification) is (*R*)-2-hydroxypropanoic acid [(*R*)-CH₃CHOHCO₂H, commonly known as (*R*)-lactic acid]. This is, of course, the normal stereochemical result for an S_N2 reaction. However, when the same reaction is carried out with a low concentration of hydroxide ion in the presence of Ag₂O (where Ag⁺ acts as a Lewis acid), it takes place with overall *retention of configuration* to produce (*S*)-2-hydroxypropanoic acid. The mechanism of this reaction involves a phenomenon called **neighboring-group participation**. Write a detailed mechanism for this reaction that accounts for the net retention of configuration when Ag⁺ and a low concentration of hydroxide are used.
- 6.42 The phenomenon of configuration inversion in a chemical reaction was discovered in 1896 by Paul Walden (Section 6.6). Walden's proof of configuration inversion was based on the following cycle:




- (a) Basing your answer on the preceding problem, which reactions of the Walden cycle are likely to take place with overall inversion of configuration and which are likely to occur with overall retention of configuration?
- (b) Malic acid with a negative optical rotation is now known to have the (*S*) configuration. What are the configurations of the other compounds in the Walden cycle?
- (c) Walden also found that when (+)-malic acid is treated with thionyl chloride (rather than PCl₅), the product of the reaction is (+)-chlorosuccinic acid. How can you explain this result?
- (d) Assuming that the reaction of (-)-malic acid and thionyl chloride has the same stereochemistry, outline a Walden cycle based on the use of thionyl chloride instead of PCl₅.
- 6.43 (*R*)-(3-Chloro-2-methylpropyl) methyl ether (**A**) on reaction with azide ion (N₃⁻) in aqueous ethanol gives (*S*)-(3-azido-2-methylpropyl) methyl ether (**B**). Compound **A** has the structure ClCH₂CH(CH₃)CH₂OCH₃.
- (a) Draw wedge-dashed wedge-line formulas of both **A** and **B**.
- (b) Is there a change of configuration during this reaction?
- 6.44 Predict the structure of the product of this reaction:



The product has no infrared absorption in the 1620–1680-cm⁻¹ region.

- 6.45 *cis*-4-Bromocyclohexanol $\xrightarrow[t\text{-BuOH}]{t\text{-BuO}^-}$ racemic C₆H₁₀O (compound **C**)
- Compound **C** has infrared absorption in the 1620–1680-cm⁻¹ and in the 3590–3650-cm⁻¹ regions. Draw and label the (*R*) and (*S*) enantiomers of product **C**.

268 Chapter 6 Ionic Reactions—Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

- 6.46** 1-Bromo[2.2.1]bicycloheptane is unreactive toward both S_N2 and S_N1 reactions. Open the computer molecular model titled “1-Bromo[2.2.1]bicycloheptane” and examine the structure. What barriers are there to substitution of 1-bromo[2.2.1]bicycloheptane by both S_N2 and S_N1 reaction mechanisms?
- 6.47** The Concept Unit titled “ S_N2 Orbitals” on the book website explains the importance of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) in S_N2 reactions. Open the computer molecular model titled “1-Bromo[2.2.1]bicycloheptane LUMO” for the LUMO molecular orbital of this compound. Where is the lobe of the LUMO with which the HOMO of a nucleophile would interact in an S_N2 reaction?
- 6.48** In the previous problem and the associated  on the Web, you considered the role of HOMOs and LUMOs in an S_N2 reaction.
- What is the LUMO in an S_N1 reaction and in what reactant and species is it found?
 - Open the molecular model titled “Isopropyl Methyl Ether Carbocation LUMO.” Identify the lobe of the LUMO in this carbocation model with which a nucleophile would interact.
 - Open the model titled “Isopropyl Methyl Ether Carbocation HOMO.” Why is there a large orbital lobe between the oxygen and the carbon of the carbocation?



Learning Group Problems

- Consider the solvolysis reaction of (1*S*,2*R*)-1-bromo-1,2-dimethylcyclohexane in 80% H_2O /20% CH_3CH_2OH at room temperature.
 - Write the structure of all chemically reasonable products from this reaction and predict which would be the major one.
 - Write a detailed mechanism for formation of the major product.
 - Write the structure of all transition states involved in formation of the major product.
- Consider the following sequence of reactions, taken from the early steps in a synthesis of ω -fluorooleic acid, a toxic natural compound from an African shrub. (ω -Fluorooleic acid, also called “ratsbane,” has been used to kill rats and also as an arrow poison in tribal warfare. Two more steps beyond those below are required to complete its synthesis.)
 - 1-Bromo-8-fluorooctane + sodium acetylide (the sodium salt of ethyne)
 \longrightarrow compound **A** ($C_{10}H_{17}F$)
 - Compound **A** + $NaNH_2 \longrightarrow$ compound **B** ($C_{10}H_{16}FNa$)
 - Compound **B** + $I-(CH_2)_7-Cl \longrightarrow$ compound **C** ($C_{17}H_{30}ClF$)
 - Compound **C** + $NaCN \longrightarrow$ compound **D** ($C_{18}H_{30}NF$)
 - Elucidate the structure of compounds **A**, **B**, **C**, and **D** above.
 - Write the mechanism for each of the reactions above.
 - Write the structure of the transition state for each reaction.