

Ionic Reactions

NUCLEOPHILIC SUBSTITUTION AND ELIMINATION REACTIONS OF ALKYL HALIDES

Not all substitutions are a good thing; for instance, we wouldn't want to accidentally use salt in place of the needed amount of sugar in a batch of chocolate chip cookies. But with some substitutions, we get something even better. In organic chemistry that is often the case, since nucleophilic substitution reactions (which we will learn about in this chapter) allow the conversion of functional groups within a given molecule into entirely different functional groups, leading to new compounds with distinct properties. Moreover, nature utilizes a number of specific substitution reactions that are required for life.

IN THIS CHAPTER WE WILL CONSIDER:

- what groups can be replaced (i.e., substituted) or eliminated
- the various mechanisms by which such processes occur
- the conditions that can promote such reactions

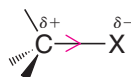
[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will show an example where just a few substitution reactions can convert table sugar into a sweetener that has no calories—a sugar substitute that is not salty, but is in fact 600 times sweeter than sugar itself!

PHOTO CREDIT: (sugar bowl) Sylvie Shirazi Photography/Getty Images (salt pouring) Tom Grill/Getty Images (sugar pouring) Tom Grill/Getty Images

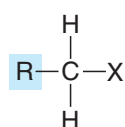
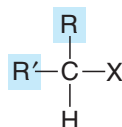
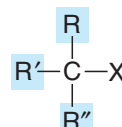


6.1 ALKYL HALIDES

- An **alkyl halide** has a halogen atom bonded to an sp^3 -hybridized (tetrahedral) carbon atom.
- The carbon–halogen bond in an alkyl halide is polarized because the halogen is more electronegative than carbon. Therefore, the carbon atom has a partial positive charge (δ^+) and the halogen has a partial negative charge (δ^-).



- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°) according to the number of carbon groups (R) directly bonded to the carbon bearing the halogen atom (Section 2.5).

Primary (1°)Secondary (2°)Tertiary (3°)

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 (see Table 6.1) 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.

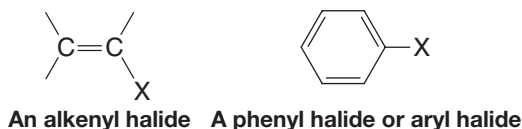
In the laboratory and in industry, alkyl halides are used as solvents for relatively nonpolar compounds, and they are used as the starting materials for the synthesis of many compounds. As we shall learn in this chapter, the halogen atom of an alkyl halide can be easily replaced by other groups, and 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 alkene carbon are called **alkenyl halides**. In older nomenclature these were called vinylic halides. Compounds having a halogen bonded to an aromatic ring are called **aryl halides**. When the aromatic

TABLE 6.1 CARBON–HALOGEN BOND LENGTHS AND BOND STRENGTHS

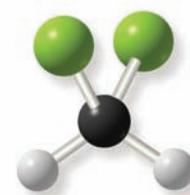
C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol ⁻¹)	472	350	293	239

ring is specifically a benzene ring these compounds are called **phenyl halides**. The reactivity of compounds in which a halogen is bonded to an sp^2 carbon, as in alkenyl, aryl, and phenyl halides, is markedly different than when a halogen is bonded to an sp^3 carbon, as in an alkyl halide. The reactions that we discuss in this chapter will pertain to alkyl halides, not alkenyl, aryl, or phenyl halides.



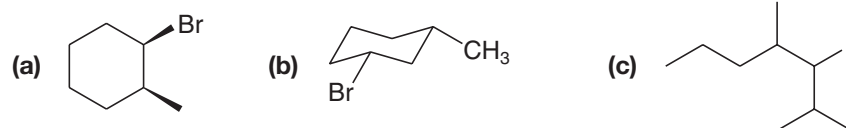
6.1A Physical Properties of Alkyl Halides

Most alkyl 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 CH_2Cl_2 , CHCl_3 , and CCl_4 , have cumulative toxicity and are carcinogenic, however, and should therefore be used only in fume hoods and with great care.



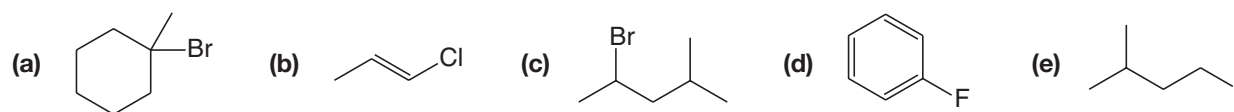
Dichloromethane (CH_2Cl_2), a common laboratory solvent

Give IUPAC names for each of the following.



PRACTICE PROBLEM 6.1

Classify each of the following organic halides as primary, secondary, tertiary, alkenyl, or aryl.



PRACTICE PROBLEM 6.2

6.2 NUCLEOPHILIC SUBSTITUTION REACTIONS

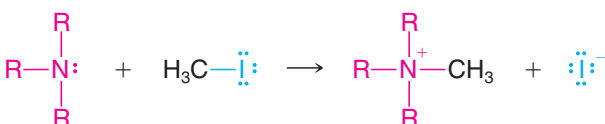
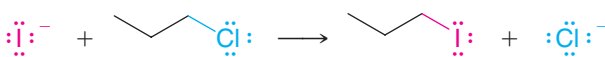
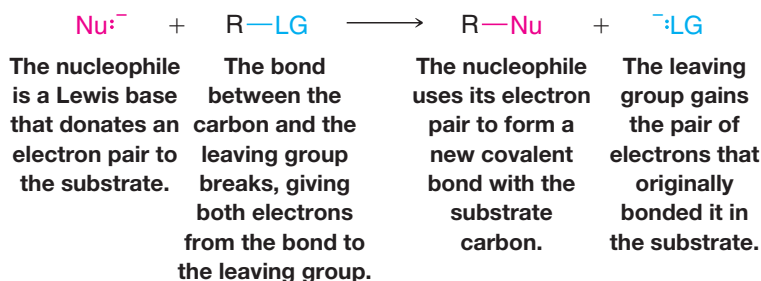
Nucleophilic substitution reactions are among the most fundamental types of organic reactions. In a **nucleophilic substitution reaction** a nucleophile (Nu^-) displaces a leaving group (LG) in the molecule that undergoes the substitution (the substrate).

- The **nucleophile** is always a Lewis base, and it may be negatively charged or neutral.
- The **leaving group** is always a species that takes a pair of electrons with it when it departs.

Often the **substrate** is an alkyl halide ($\text{R}-\ddot{\text{X}}:$) and the leaving group is a halide anion ($:\ddot{\text{X}}:^-$). The following equations include a generic nucleophilic substitution reaction and some specific examples.

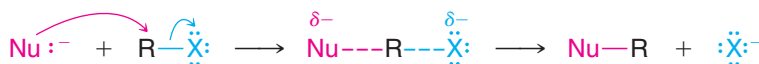
Helpful Hint

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

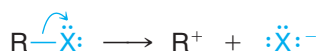


In nucleophilic substitution reactions the bond between the substrate carbon and the leaving group undergoes *heterolytic* bond cleavage. The unshared electron pair of the nucleophile forms the new bond to the carbon atom.

A key question we shall want to address later in this chapter is this: when does the bond between the leaving group and the carbon break? Does it break at the same time that the new bond between the nucleophile and carbon forms, as shown below?



Or, does the bond to the leaving group break first?



Followed by



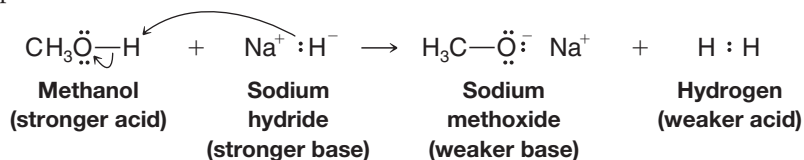
We shall find in Sections 6.9 and 6.14A that the answer depends greatly on the structure of the substrate.

SOLVED PROBLEM 6.1

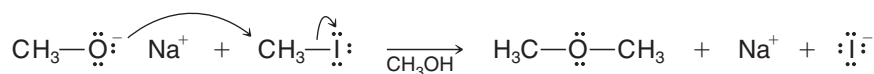
- (a) A solution containing methoxide ions, CH_3O^- ions (as NaOCH_3), in methanol can be prepared by adding sodium hydride (NaH) to methanol (CH_3OH). A flammable gas is the other product. Write the acid–base reaction that takes place.
 (b) Write the nucleophilic substitution that takes place when CH_3I is added and the resulting solution is heated.

STRATEGY AND ANSWER:

- (a) We recall from Section 3.15 that sodium hydride consists of Na^+ ions and hydride ions (H^- ions), and that the hydride ion is a very strong base. [It is the conjugate base of H_2 , a very weak acid ($\text{p}K_a = 35$, see Table 3.1).] The acid–base reaction that takes place is



- (b) The methoxide ion reacts with the alkyl halide (CH_3I) in a nucleophilic substitution:



6.3 NUCLEOPHILES

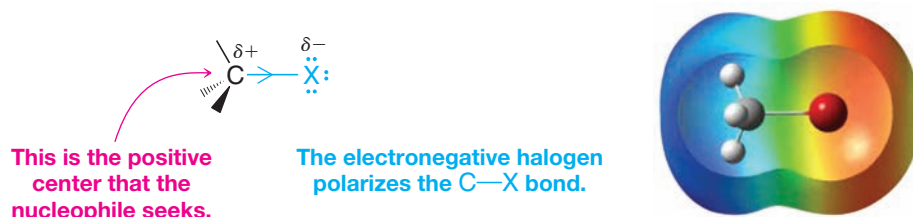
A nucleophile is a reagent that seeks a positive center.

- Any negative ion or uncharged molecule with an unshared electron pair is a potential nucleophile.

When a nucleophile reacts with an alkyl halide, the carbon atom bearing the halogen atom is the positive center that attracts the nucleophile. This carbon carries a partial positive charge because the electronegative halogen pulls the electrons of the carbon-halogen bond in its direction.

Helpful Hint

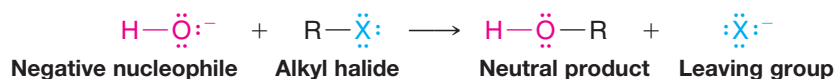
You may wish to review Section 3.3A, "Opposite Charges Attract."



Let us look at two examples, one in which the nucleophile is a negatively charged Lewis base, and one in which the nucleophile is a neutral Lewis base.

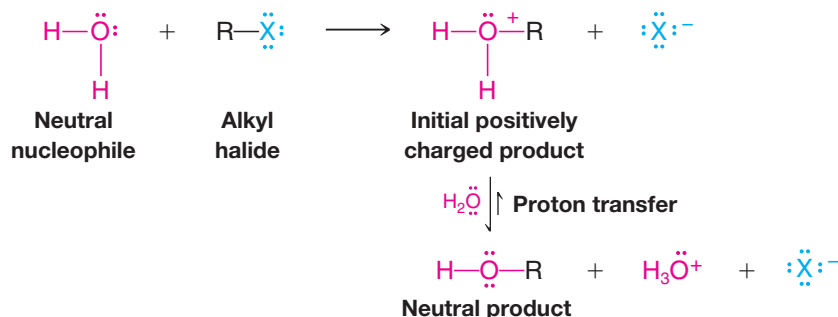
- Use of a **negatively charged nucleophile** (hydroxide in this case) **results in a neutral product** (an alcohol in this case). Formation of the covalent bond between the negative nucleophile and the substrate neutralizes the formal charge of the nucleophile.

Nucleophilic Substitution by a Negatively Charged Nucleophile Results Directly in a Neutral Product



- Use of a **neutral nucleophile** (water in this case) **results initially in a positively charged product**. The neutral nucleophile gains a positive formal charge through formation of the covalent bond with the substrate. A neutral product results only after a proton is removed from the atom with the formal positive charge in the initial product.

Nucleophilic Substitution by a Neutral Nucleophile Results Initially in a Positively Charged Product

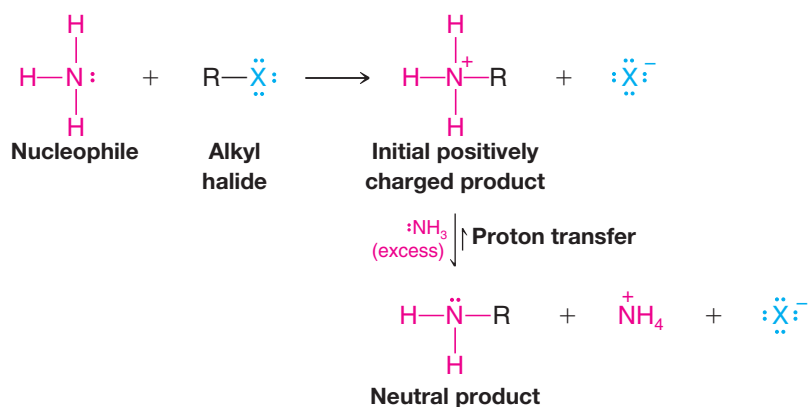


Helpful Hint

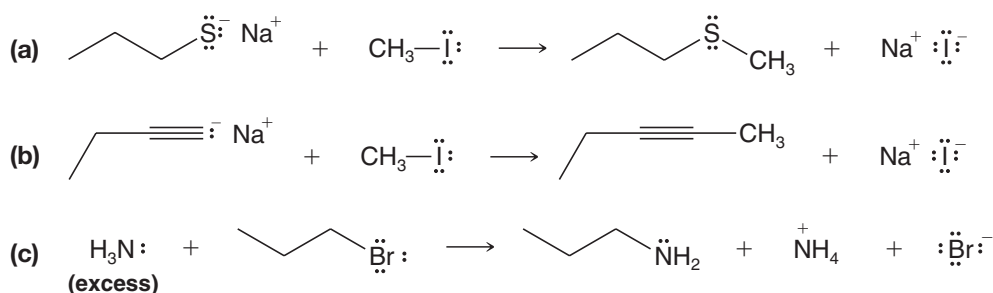
A deprotonation step is always required to complete the reaction when the nucleophile was a neutral atom that bore a proton.

In a reaction like this the nucleophile is a solvent molecule (as is often the case when neutral nucleophiles are involved). Since solvent molecules are present in great excess, the equilibrium favors transfer of a proton from the alkyloxonium ion to a water molecule. This type of reaction is an example of solvolysis, which we shall discuss further in Section 6.12B.

The reaction of ammonia (NH_3) with an alkyl halide, as shown below, provides another example where the nucleophile is uncharged. An excess of ammonia favors equilibrium removal of a proton from the alkylammonium ion to form the neutral amine.


SOLVED PROBLEM 6.2

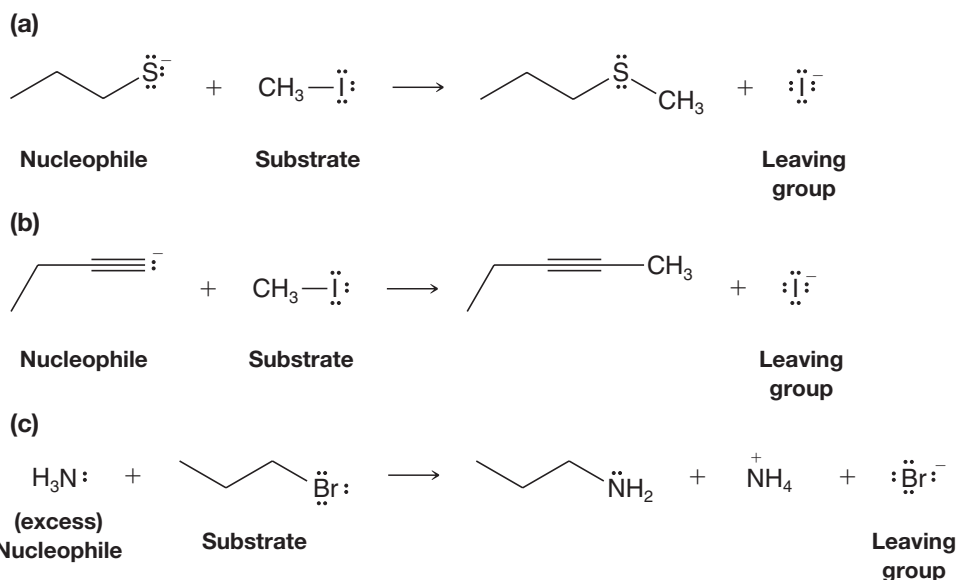
Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each case.



STRATEGY: A net ionic equation does not include spectator ions but is still balanced in terms of charges and the remaining species. Spectator ions are those ions that have not been involved in covalent bonding changes during a reaction, and that appear on both sides of a chemical equation. In reactions (a) and (b) the sodium ion is a spectator ion, thus the net ionic equation would not include them, and their net ionic equations would have a net negative charge on each side of the arrow. Equation (c) has no ions present among the reactants, and thus the ions found with the products are not spectator ions—they have resulted from covalent bonding changes. Equation (c) cannot be simplified to a net ionic equation.

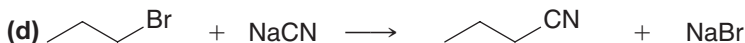
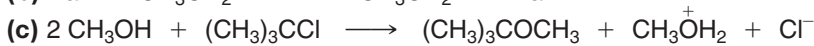
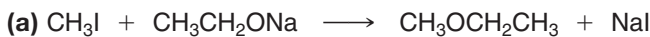
Nucleophiles use a pair of electrons to form a covalent bond that is present in a product molecule. In all of the above reactions we can identify a species that used a pair of electrons in this way. These are the nucleophiles. **Leaving groups** depart from one of the reactant molecules and take a pair of electrons with them. In each reaction above we can identify such a species. Finally, the reactants to which the nucleophiles became bonded and from which the leaving groups departed are the **substrates**.

ANSWER: The net ionic equations are as follows for (a) and (b), and there is no abbreviated equation possible for (c). Nucleophiles, substrates, and leaving groups are labeled accordingly.



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

PRACTICE PROBLEM 6.3



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 ion.

In the examples shown above (Sections 6.2 and 6.3) the leaving group has been a halogen. Halide anions are weak bases (they are the conjugate bases of strong acids, HX), and therefore halogens are good leaving groups.

Some leaving groups depart as neutral molecules, such as a molecule of water or an alcohol. For this to be possible, the leaving group must have a formal positive charge while it is bonded to the substrate. When this group departs with a pair of electrons the leaving group's formal charge goes to zero. The following is an example where the leaving group departs as a water molecule.



As we shall see later, the positive charge on a leaving group (like that above) usually results from protonation of the substrate by an acid. However, use of an acid to protonate the substrate and make a positively charged leaving group is feasible only when the nucleophile itself is not strongly basic, and when the nucleophile is present in abundance (such as in solvolysis).

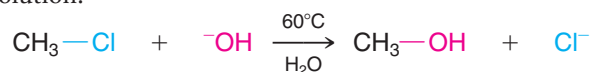
Let us now begin to consider the mechanisms of nucleophilic substitution reactions. How does the nucleophile replace the leaving group? Does the reaction take place in one step or is more than one step involved? If more than one step is involved, what kinds of intermediates are formed? Which steps are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

Helpful Hint

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.

6.5A How Do We Measure the Rate of This Reaction?

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 HO^- 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 6.2.

Experiment Number	Initial $[\text{CH}_3\text{Cl}]$	Initial $[\text{HO}^-]$	Initial Rate ($\text{mol L}^{-1} \text{s}^{-1}$)
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}

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 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,

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

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

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

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.)

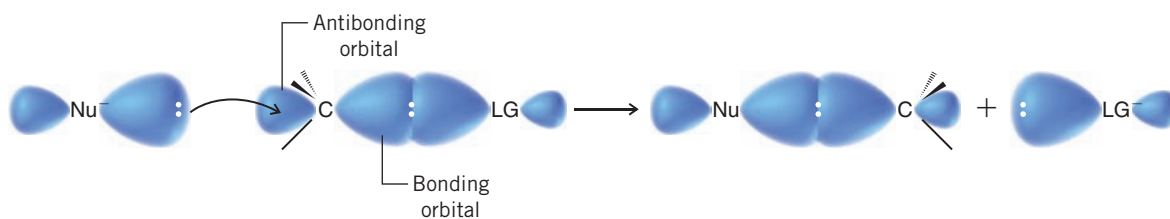
6.5B What Is the Order of This Reaction?

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 **$\text{S}_{\text{N}}2$ reaction**, meaning **substitution, nucleophilic, bimolecular**.

6.6 A MECHANISM FOR THE $\text{S}_{\text{N}}2$ REACTION

A schematic representation of orbitals involved in an $\text{S}_{\text{N}}2$ reaction—based on ideas proposed by Edward D. Hughes and Sir Christopher Ingold in 1937—is outlined below.

*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 $[\text{A}]$, first order with respect to $[\text{B}]$, and third order overall.



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.

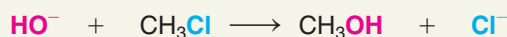
- As the nucleophile forms a bond and the leaving group departs, the substrate carbon atom undergoes **inversion***—its tetrahedral bonding configuration is turned inside out.

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 “Mechanism for the S_N2 Reaction” box below.

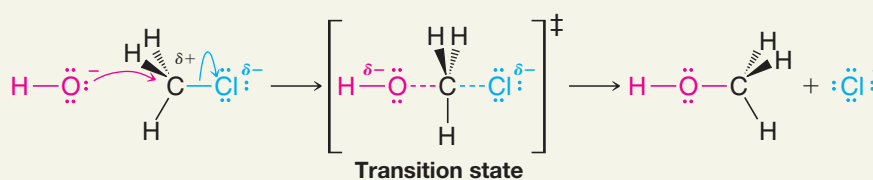
- The S_N2 reaction proceeds in a single step (without any intermediates) through an unstable arrangement of atoms called the **transition state**.

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.

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.

*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.

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.

- The S_N2 reaction is said to be a **concerted reaction**, because bond forming and bond breaking occur in concert (*simultaneously*) through a single transition state.

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.

6.7 TRANSITION STATE THEORY: FREE-ENERGY DIAGRAMS

- A reaction that proceeds with a negative free-energy change (releases energy to its surroundings) is said to be **exergonic**; one that proceeds with a positive free-energy change (absorbs energy from its surroundings) 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, 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 the energy changes in a reaction using a graph called a **free-energy diagram**, where we plot the free energy of the reacting particles (y -axis) against the reaction coordinate (x -axis). Figure 6.1 is an example for a generalized S_N2 reaction.

- The **reaction coordinate** indicates the progress of the reaction, in terms of the conversion of reactants to products.
- The top of the energy curve corresponds to the **transition state** for the reaction.
- The **free energy of activation** (ΔG^\ddagger) for the reaction is the difference in energy between the reactants and the transition state.
- The **free energy change for the reaction** (ΔG°) is the difference in energy between the reactants and the products.

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

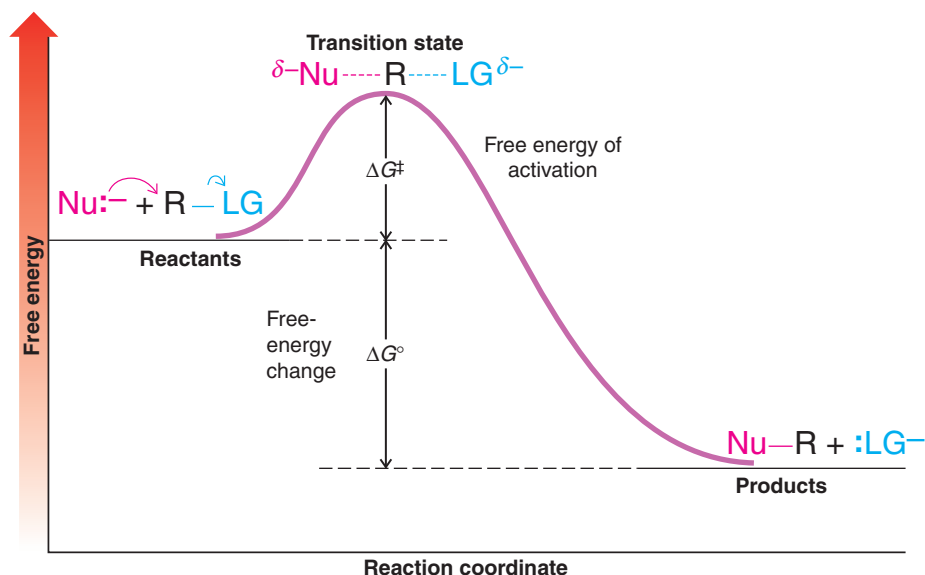


FIGURE 6.1 A free-energy diagram for a hypothetical exergonic $\text{S}_{\text{N}}2$ reaction (i.e., that takes place with a negative ΔG° , releasing energy to the surroundings).

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.

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.

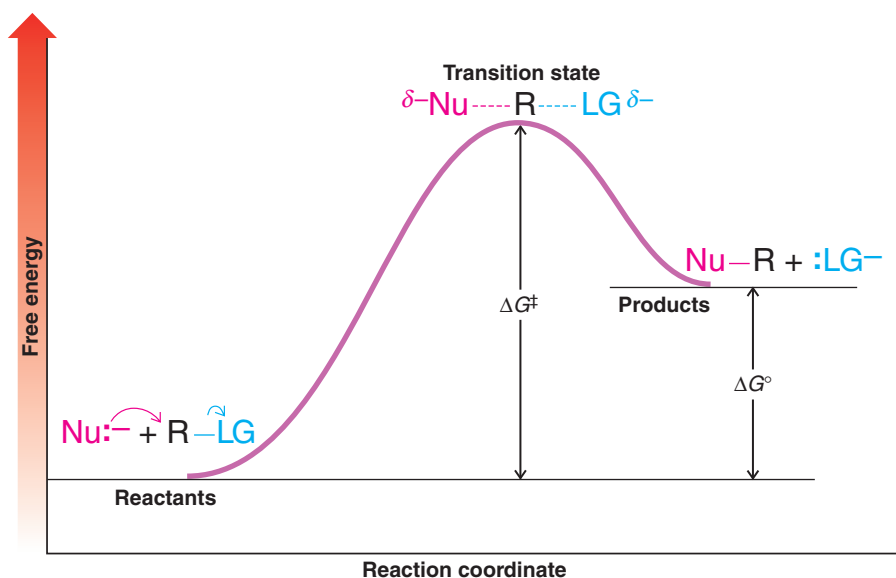


FIGURE 6.2 A free-energy diagram for a hypothetical endergonic $\text{S}_{\text{N}}2$ reaction (i.e., that takes place with a positive ΔG° , absorbing energy from the surroundings).

6.7A Temperature and Reaction Rate

Most chemical reactions occur much more rapidly at higher temperatures. The increase in reaction rate for $\text{S}_{\text{N}}2$ reactions relates to the fact that at higher temperatures the number of collisions between reactants with sufficient energy to surmount the activation energy (ΔG^\ddagger) increases significantly (see Fig. 6.3).

- A 10°C increase in temperature will cause the reaction rate to double for many reactions taking place near room temperature.

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.

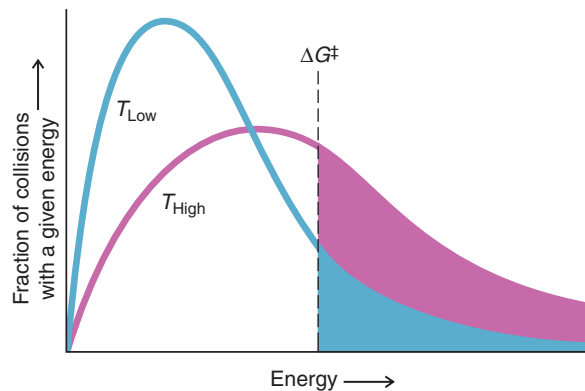


FIGURE 6.3 The distribution of energies at two different temperatures, T_{Low} and T_{High} . The number of collisions with energies greater than the free energy of activation is indicated by the corresponding shaded area under each curve.

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.

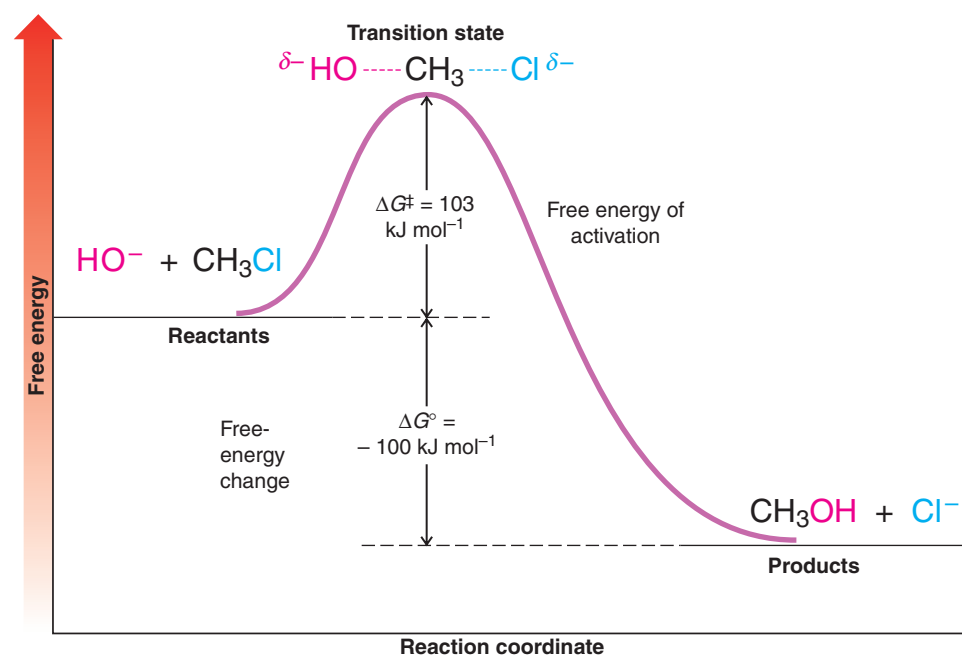


FIGURE 6.4 A free-energy diagram for the reaction of chloromethane with hydroxide ion at 60°C .

PRACTICE PROBLEM 6.4

Draw a hypothetical free-energy diagram for the $\text{S}_{\text{N}}2$ reaction of iodide anion with 1-chlorobutane. Label the diagram as in Fig. 6.4, and assume it is exergonic but without specific values for ΔG^\ddagger and ΔG° .

6.8 THE STEREOCHEMISTRY OF S_N2 REACTIONS

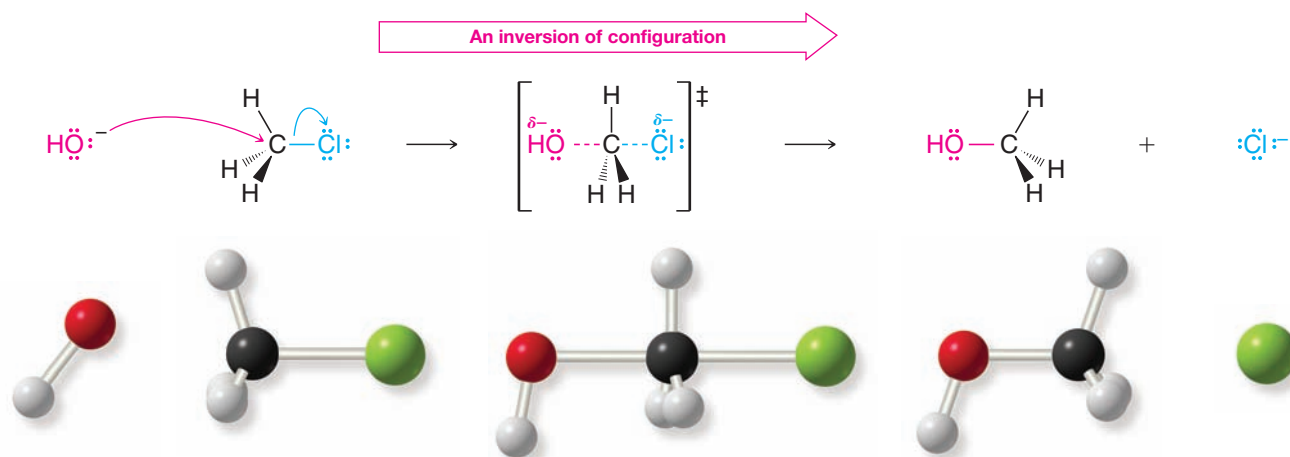
The **stereochemistry** of S_N2 reactions is directly related to key features of the mechanism that we learned earlier:

- **The nucleophile approaches the substrate carbon from the back side with respect to the leaving group.** In other words, the bond to the nucleophile that is forming is opposite (at 180°) to the bond to the leaving group that is breaking.
- Nucleophilic displacement of the leaving group in an S_N2 reaction causes **inversion of configuration** at the substrate carbon.

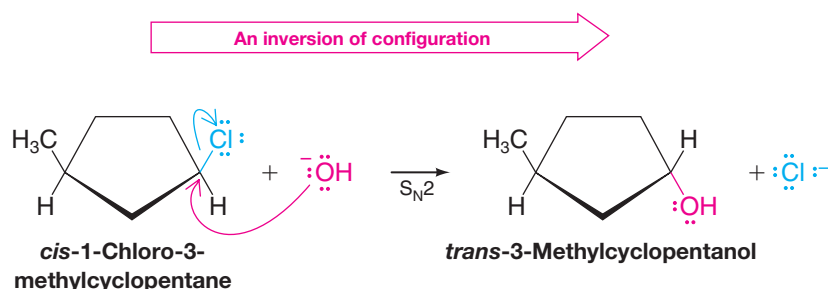
We depict the inversion process as follows. It is much like the way an umbrella is inverted in a strong wind.



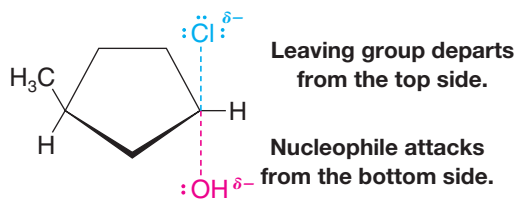
Transition state for an S_N2 reaction



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 hydroxyl group ends up bonded on the opposite side of the ring from the chlorine it replaces:*



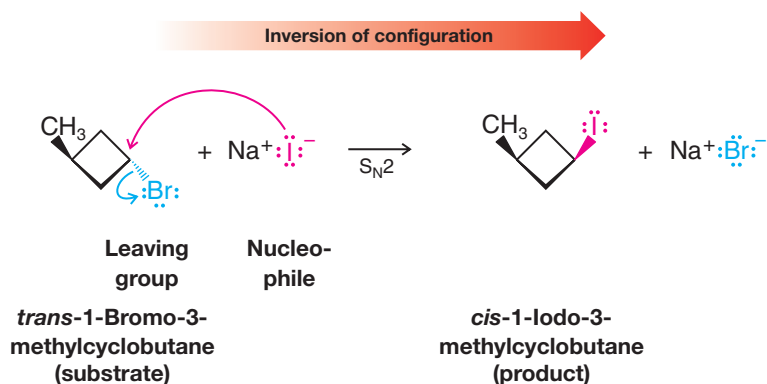
Presumably, the transition state for this reaction is like that shown here.



SOLVED PROBLEM 6.3

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 back side of the substrate carbon atom that bears the leaving group, causing an inversion of configuration at that carbon, write the structure of the product.

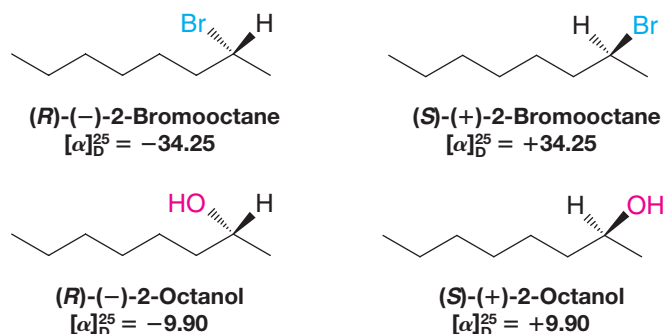


PRACTICE PROBLEM 6.5

Using chair conformational structures (Section 4.11), 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.)

• S_N2 reactions always occur with inversion of configuration.

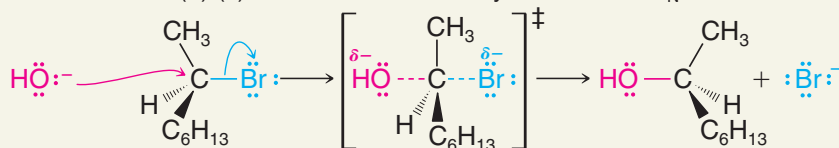
We can also observe inversion of configuration when an S_N2 reaction occurs at a chirality center in an acyclic molecule. The reaction of (*R*)-(-)-2-bromooctane with sodium hydroxide provides an example. We can determine whether or not inversion of configuration occurs in this reaction because the configurations 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 ($[\alpha]_D^{25} = -34.25$) has been converted to enantiomerically pure (*S*)-(+)-2-octanol ($[\alpha]_D^{25} = +9.90$).

A MECHANISM FOR THE REACTION — The Stereochemistry of an S_N2 Reaction

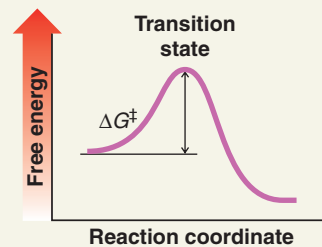
The reaction of (*R*)-(-)-2-bromooctane with hydroxide is an S_N2 reaction and takes place with *inversion of configuration*:



An inversion of configuration

(*R*)-(-)-2-Bromooctane
 $[\alpha]_D^{25} = -34.25^\circ$
 Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol
 $[\alpha]_D^{25} = +9.90^\circ$
 Enantiomeric purity = 100%

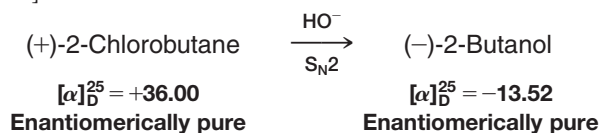


An S_N2 reaction has one transition state.

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.

PRACTICE PROBLEM 6.6

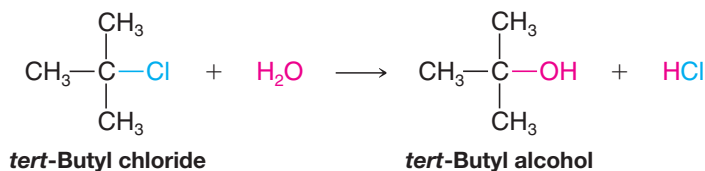
- (a) Illustrate how this is true by assigning *R,S* configurations to the 2-chlorobutane enantiomers based on the following data. [The configuration of (-)-2-butanol is given in Section 5.8C.]



- (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?

6.9 THE REACTION OF *TERT*-BUTYL CHLORIDE WITH WATER: AN S_N1 REACTION

Let us now consider another mechanism for nucleophilic substitution: the S_N1 reaction. When Hughes (Section 6.6) and co-workers studied the reaction of *tert*-butyl chloride with water they found the kinetics leading to formation of *tert*-butyl alcohol to be quite different than for other substitution reactions that they had studied.



Hughes found that the rate of *tert*-butyl chloride substitution was the same whether the reaction was run at pH 7, where the hydroxide ion concentration is 10^{-7} M and the predominant nucleophile is water, or in 0.05 M hydroxide, where the more powerful hydroxide nucleophile is present in roughly 500,000 times higher concentration. These results suggest that neither water nor hydroxide ions are involved in the rate-determining step of the reaction. Instead, the rate of substitution is dependent only on the concentration of *tert*-butyl chloride. The reaction is thus first order in *tert*-butyl chloride, and first order overall.

$$\text{Rate} = k[(\text{CH}_3)_3\text{CCl}]$$

The reaction rate is first order in *tert*-butyl chloride and first order overall.

Furthermore, these results indicate that the transition state governing the rate of reaction involves only molecules of *tert*-butyl chloride, and not water or hydroxide ions. The reaction is said to be **unimolecular** (first-order) in the rate-determining step, and we call it an **S_N1 reaction (substitution, nucleophilic, unimolecular)**. In Section 6.15 we shall see that elimination reactions can compete with S_N1 reactions, leading to the formation of alkenes, but in the case of the conditions used above for the experiments with *tert*-butyl chloride (moderate temperature and dilute base), S_N1 is the dominant process.

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:

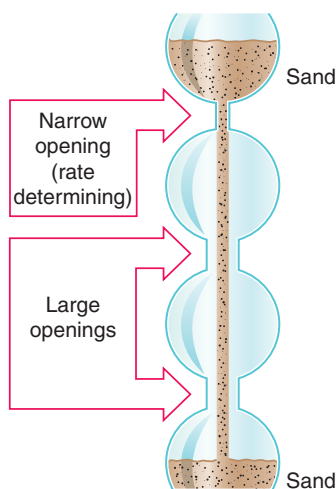
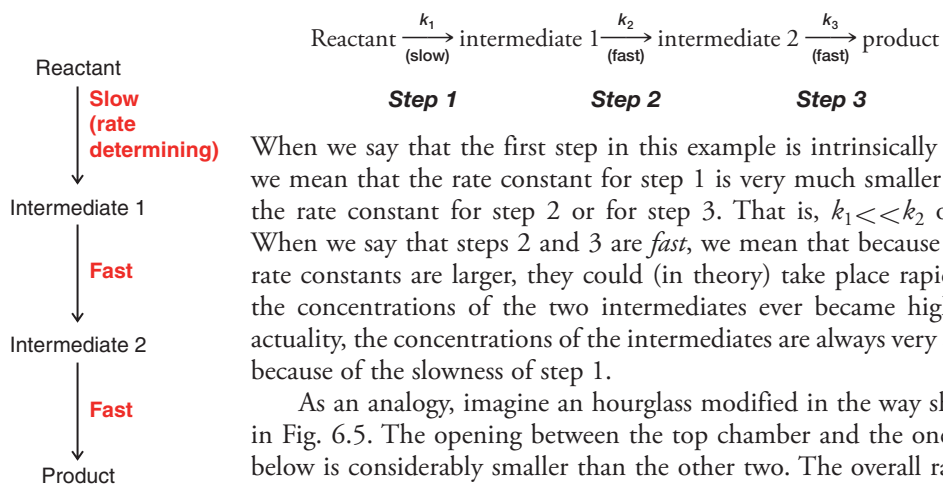


FIGURE 6.5 A modified hourglass that serves as an analogy for a multistep reaction. The overall rate is limited by the rate of the slow step.

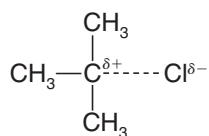


When we say that the first step in this example is intrinsically slow, we mean that the rate constant for step 1 is very much smaller than the rate constant for step 2 or for step 3. That is, $k_1 \ll k_2$ or k_3 . When we say that steps 2 and 3 are *fast*, we mean that because their rate constants are 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 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) can be described in three steps. See the box “Mechanism for the S_N1 Reaction” below, 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:



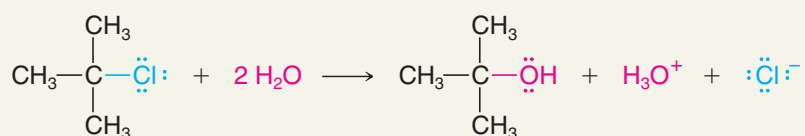
The solvent (water) stabilizes these developing ions by solvation. Carbocation formation, in general, takes place slowly because it is usually a highly endothermic process and is uphill in terms of free energy.

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 2.13D).

In the second step the intermediate *tert*-butyl cation reacts rapidly with water to produce a *tert*-butyloxonium ion, (CH₃)₃COH₂⁺, which in the third step, rapidly transfers a proton to a molecule of water producing *tert*-butyl alcohol.

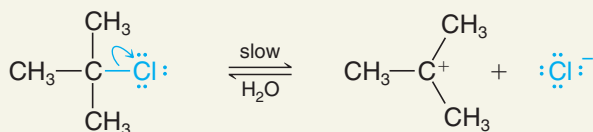
A MECHANISM FOR THE REACTION — Mechanism for the S_N1 Reaction

Reaction



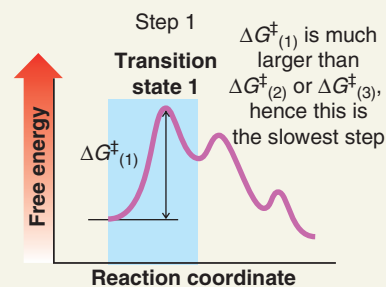
Mechanism

Step 1

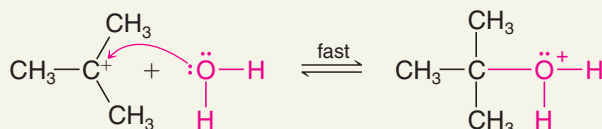


Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the 3° carbocation intermediate and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.

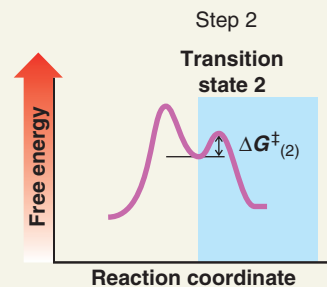


Step 2

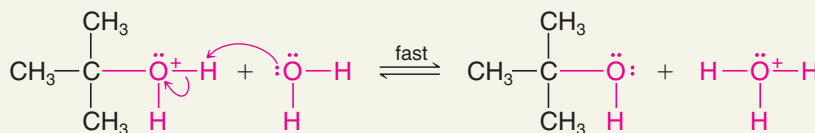


A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

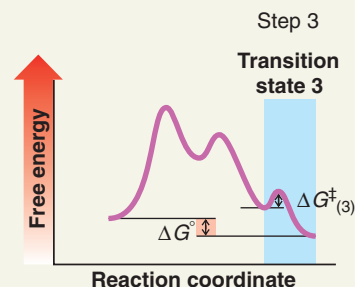


Step 3



A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.



6.11 CARBOCATIONS



GEORGE A. OLAH WAS awarded the 1994 Nobel Prize in Chemistry.

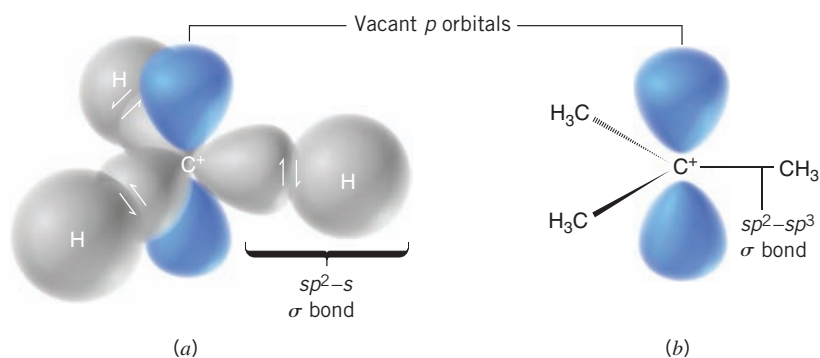
Beginning in the 1920s much evidence began to accumulate implicating simple alkyl cations as intermediates in a variety of ionic reactions. However, because alkyl cations are highly unstable and highly reactive, they were, in all instances studied before 1962, very short-lived, transient species that 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.

6.11A The Structure of Carbocations

- 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.



- The central carbon atom in a carbocation is electron deficient; it has only six electrons in its valence shell.

In our model (Fig. 6.6) these six electrons are used to form three sigma (σ) covalent bonds to hydrogen atoms or alkyl groups.

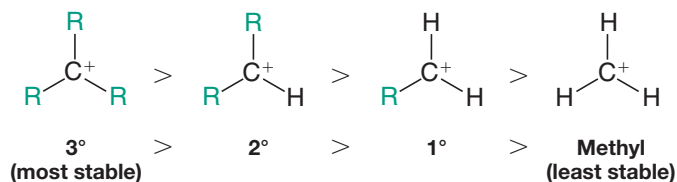
- The p orbital of a carbocation contains no electrons, but it can accept an electron pair when the carbocation undergoes further reaction.

Not all types of carbocations have the same relative stability, as we shall learn in the next section.

6.11B The Relative Stabilities of Carbocations

The relative stabilities of carbocations are related to the number of alkyl groups attached to the positively charged trivalent carbon.

- Tertiary carbocations are the most stable, and the methyl carbocation is the least stable.
- The overall order of stability is as follows:



This order of carbocation stability 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).

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

Helpful Hint

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

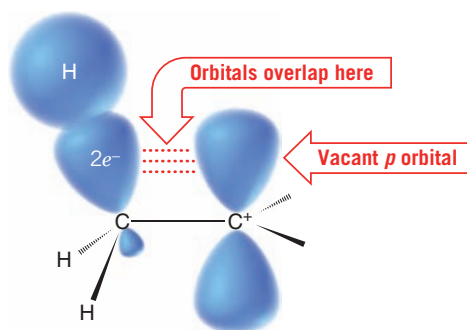


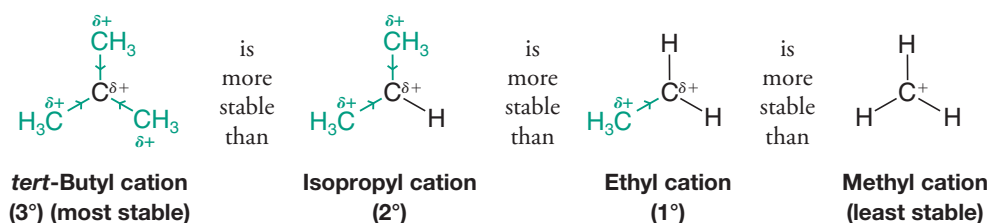
FIGURE 6.7 How an adjacent sigma bond helps stabilize the positive charge of a carbocation. Electron density from one of the carbon–hydrogen sigma bonds of the methyl group flows into the vacant p orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way 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.

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 by hyperconjugation, inductive effects, or resonance, 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.

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:



In summary:

- **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).

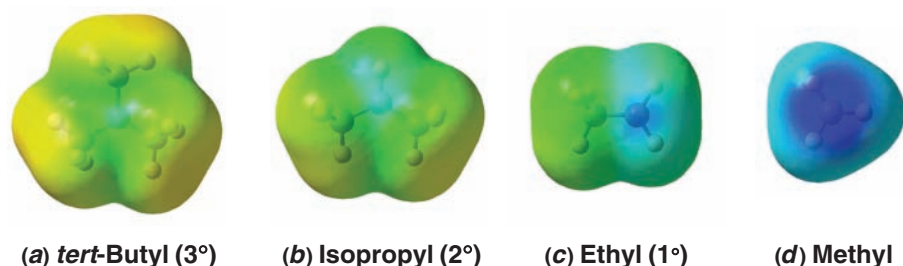
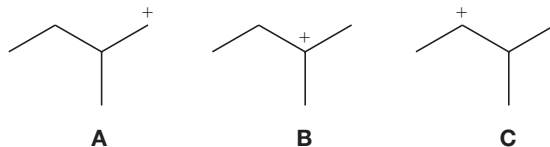


FIGURE 6.8 Maps of electrostatic potential for (a) *tert*-butyl (3°), (b) isopropyl (2°), (c) ethyl (1°), and (d) methyl carbocations show the trend from greater to lesser delocalization (stabilization) of the positive charge in these structures. Less blue color indicates greater delocalization of the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

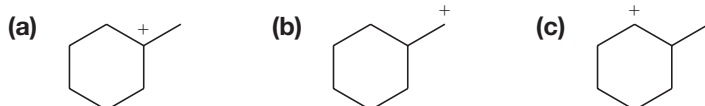
SOLVED PROBLEM 6.4

Rank the following carbocations in order of increasing stability:



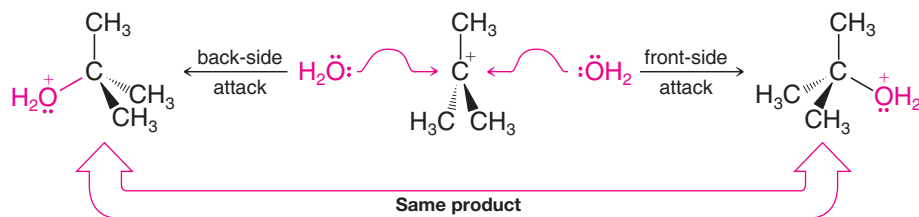
STRATEGY AND ANSWER: Structure **A** is a primary carbocation, **B** is tertiary, and **C** is secondary. Therefore, in order of increasing stability, $A < C < B$.

PRACTICE PROBLEM 6.7 Rank the following carbocations in order of increasing stability:



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.

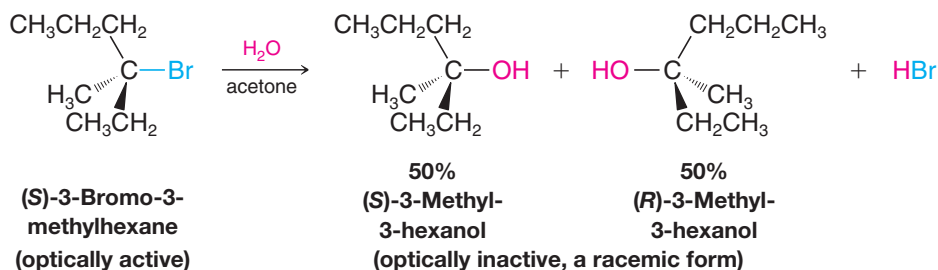
6.12A Reactions That Involve Racemization

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

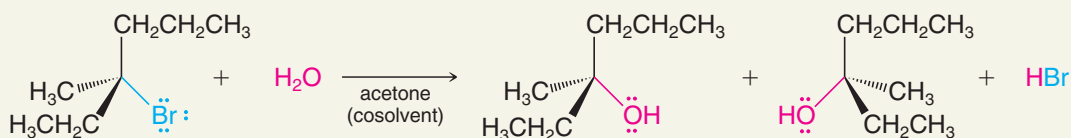
with aqueous acetone results in the formation of 3-methyl-3-hexanol as a mixture of 50% (*R*) and 50% (*S*).



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.

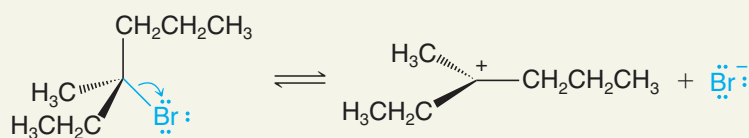
A MECHANISM FOR THE REACTION — The Stereochemistry of an S_N1 Reaction

Reaction



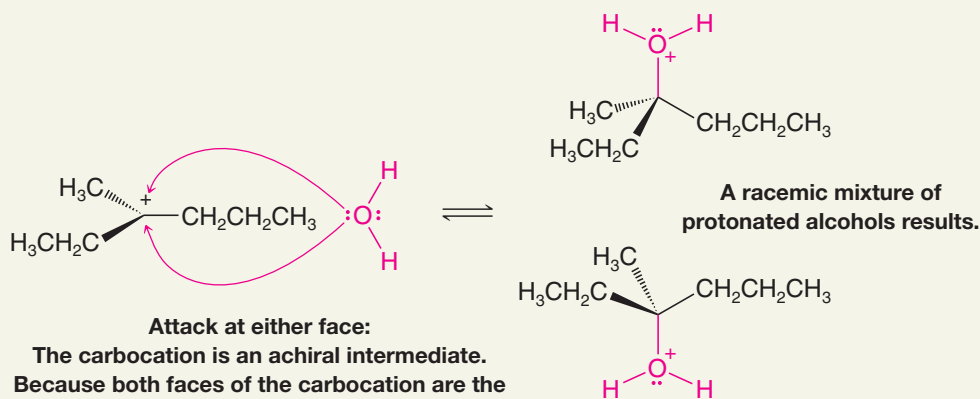
Mechanism

Step 1



Departure of the leaving group (assisted by hydrogen bonding with water) leads to the carbocation.

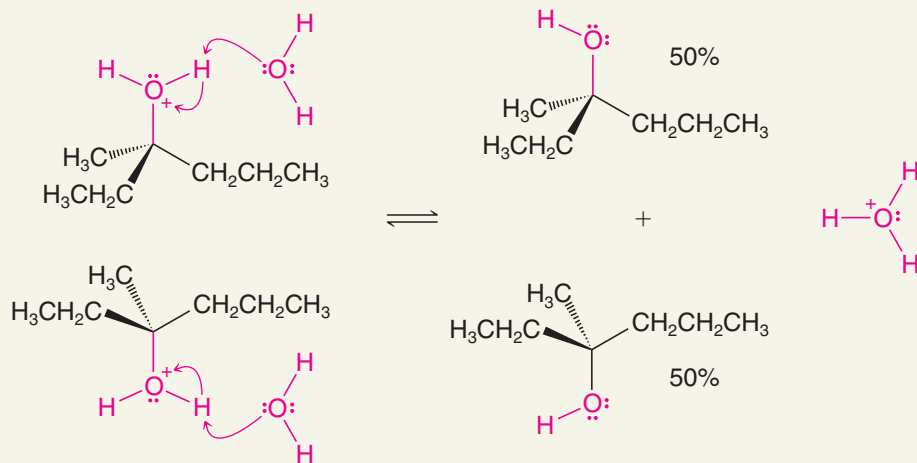
Step 2



Attack at either face:

The carbocation is an achiral intermediate. Because both faces of the carbocation are the same, the nucleophile can bond with either face to form a mixture of stereoisomers.

(mechanism continues on the next page)



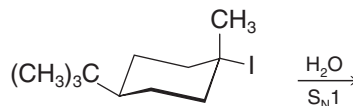
Additional solvent molecules (water) deprotonate the alkyloxonium ion.

The product is a racemic mixture.

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.

PRACTICE PROBLEM 6.8

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 reaction of iodocyclohexane in water:

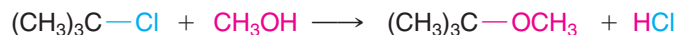
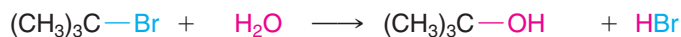


6.12B Solvolysis

- A **solvolysis reaction** is a nucleophilic substitution in which *the nucleophile is a molecule of the solvent* (*solvent + lysis*: cleavage by the solvent). The S_N1 reaction of an alkyl halide with water is an example of **solvolysis**.

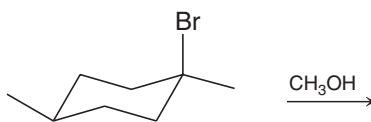
When the solvent is water, we could also call the reaction a **hydrolysis**. If the reaction had taken place in methanol, we would call it a **methanolysis**.

Examples of Solvolysis

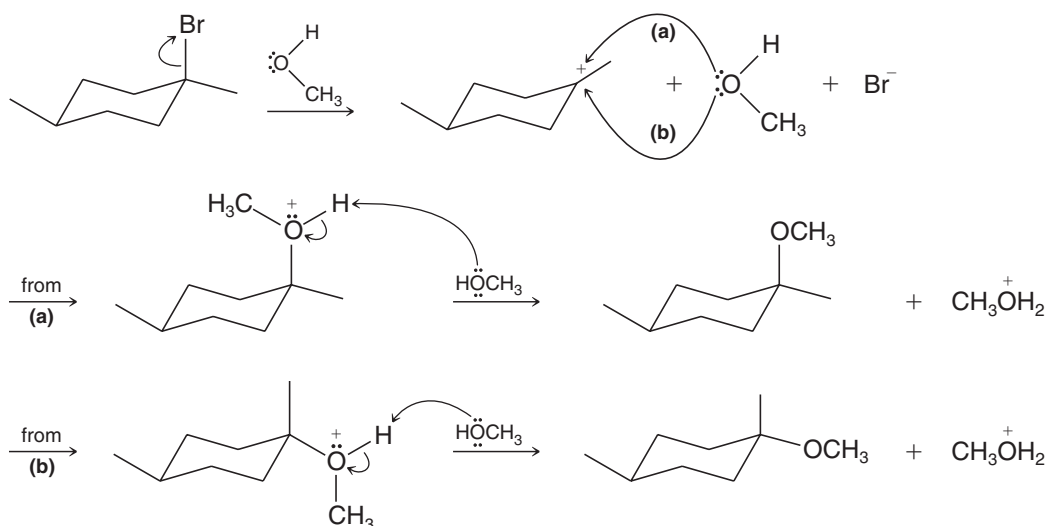


SOLVED PROBLEM 6.5

What product(s) would you expect from the following solvolysis?



STRATEGY AND ANSWER: We observe that this cyclohexyl bromide is tertiary, and therefore in methanol it should lose a bromide ion to form a tertiary carbocation. Because the carbocation is trigonal planar at the positive carbon, it can react with a solvent molecule (methanol) to form two products.



What product(s) would you expect from the methanolysis of the iodocyclohexane derivative given as the reactant in Practice Problem 6.8?

PRACTICE PROBLEM 6.9

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.

- 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 S_N2 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:

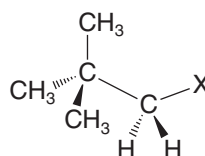


Methyl halides react most rapidly, and tertiary halides react so slowly as to be unreactive by the S_N2 mechanism. Table 6.3 gives the relative rates of typical S_N2 reactions.

TABLE 6.3 RELATIVE RATES OF REACTIONS OF ALKYL HALIDES IN S_N2 REACTIONS

Substituent	Compound	Approximate Relative Rate
Methyl	CH ₃ X	30
1°	CH ₃ CH ₂ X	1
2°	(CH ₃) ₂ CHX	0.03
Neopentyl	(CH ₃) ₃ CCH ₂ X	0.00001
3°	(CH ₃) ₃ CX	~0

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, and in this case, steric hindrance.

- A **steric effect** is an effect on the relative rates caused by the space-filling properties of those parts of a molecule attached at or near the reacting site.
- **Steric hindrance** is when the spatial arrangement of atoms or groups at or near a 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). Nearby bulky groups cause the free energy of an S_N2 transition state to be higher and, consequently, the free energy of activation for the reaction is larger, and the rate of reaction is slower. 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.)

Helpful Hint

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

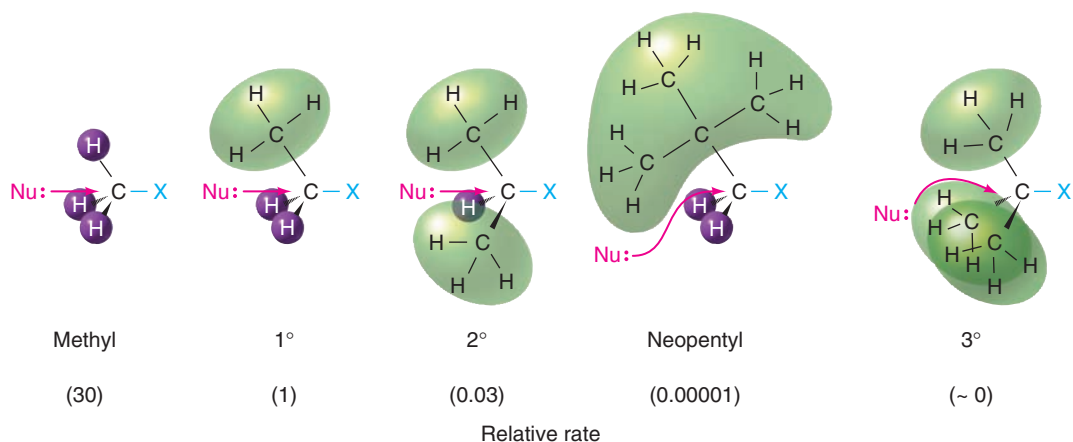
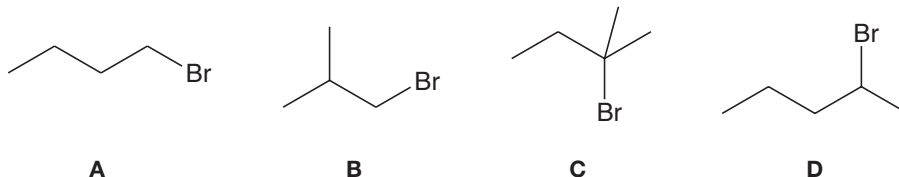


FIGURE 6.9 Steric effects and relative rates in the S_N2 reaction.


SOLVED PROBLEM 6.6

Rank the following alkyl bromides in order of decreasing reactivity (from fastest to slowest) as a substrate in an S_N2 reaction.



STRATEGY AND ANSWER: We examine the carbon bearing the leaving group in each instance to assess the steric hindrance to an S_N2 reaction at that carbon. In **C** it is 3° ; therefore, three groups would hinder the approach of a nucleophile, so this alkyl bromide would react most slowly. In **D** the carbon bearing the leaving group is 2° (two groups hinder the approach of the nucleophile), while in both **A** and **B** it is 1° (one group hinders the nucleophile's approach). Therefore, **D** would react faster than **C**, but slower than either **A** or **B**. But, what about **A** and **B**? They are both 1° alkyl bromides, but **B** has a methyl group on the carbon adjacent to the one bearing the bromine, which would provide steric hindrance to the approaching nucleophile that would not be present in **A**. The order of reactivity, therefore, is **A** > **B** > **D** \gg **C**.

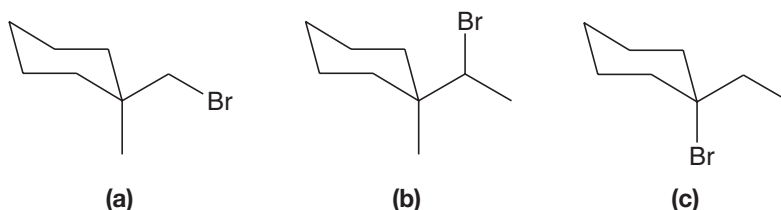
S_N1 Reactions

- 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.

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

Which of the following alkyl halides is most likely to undergo substitution by an S_N1 mechanism?



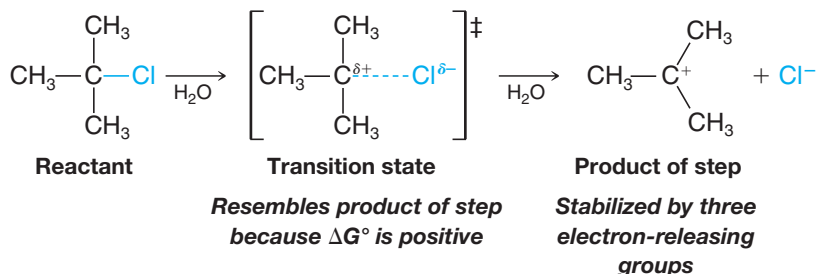
PRACTICE PROBLEM 6.10

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 the **Hammond–Leffler postulate**, 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

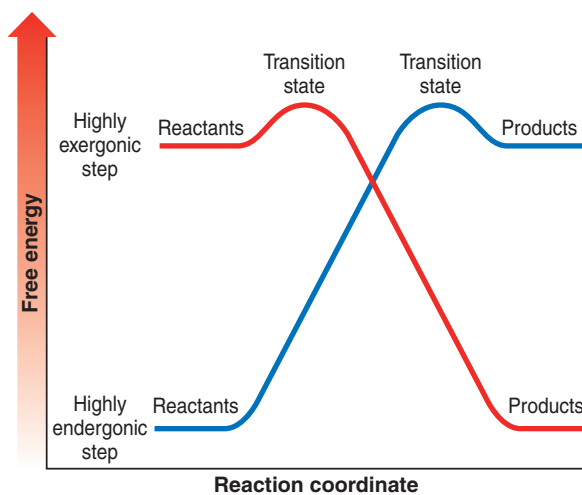


A methyl, primary, or secondary alkyl halide would have to ionize to form a methyl, primary, or secondary carbocation to react by an S_N1 mechanism. These carbocations, however, are much higher in energy than a tertiary carbocation, and the transition states leading to these carbocations are even higher in energy.

- The activation energy for an S_N1 reaction of a simple methyl, primary, or secondary halide is so large (therefore the reaction is so slow) that, for all practical purposes, an S_N1 reaction with a methyl, primary, or secondary halide 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 reactants in free energy, and we assume, therefore, that **it resembles the reactants in structure** as well. Conversely, in a highly **exergonic** step (red 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**. 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.

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. (Reprinted with permission of the McGraw-Hill Companies from Pryor, W., *Free Radicals*, p. 156, copyright 1966.)



PRACTICE PROBLEM 6.11 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.

- Is each of these reactions likely to be S_N1 or S_N2 ?
- Provide an explanation for the relative reactivities that are observed.

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

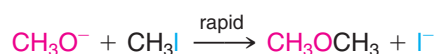
- The rate of an S_N1 reaction is unaffected by either the concentration or the identity of the nucleophile, because the nucleophile does not participate in the rate-determining step of an S_N1 reaction.
- The rate of an S_N2 reaction depends on *both* the concentration *and* the identity of the attacking nucleophile.

We saw in Section 6.5 how increasing the concentration of the nucleophile increases the rate of an S_N2 reaction. We can now examine how the rate of an S_N2 reaction depends on the identity of the nucleophile.

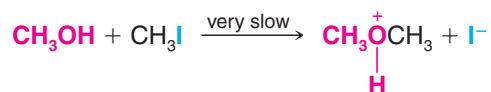
- The relative strength of a nucleophile (its **nucleophilicity**) is measured in terms of the relative rate of its S_N2 reaction with a given substrate.

A good nucleophile is one that reacts rapidly in an S_N2 reaction with a given substrate. A poor nucleophile is one that reacts slowly in an S_N2 reaction with the same substrate under comparable reaction conditions. (As mentioned above, we cannot compare nucleophilicities with regard to S_N1 reactions because the nucleophile does not participate in the rate-determining step of an S_N1 reaction.)

Methoxide anion, for example, is a good nucleophile for a substitution reaction with iodomethane. It reacts rapidly by an S_N2 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 three structural features:
 1. **A negatively charged nucleophile is always a more reactive nucleophile than its conjugate acid.** Thus HO[−] is a better nucleophile than H₂O 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 (RCO₂[−]), and so on.

3. **When the nucleophilic atoms are different, nucleophilicities may not parallel basicities.** For example, in protic solvents HS[−], N≡C[−], and I[−] are all weaker bases than HO[−], yet they are **stronger nucleophiles** than HO[−].

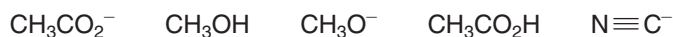


Nucleophilicity versus Basicity While nucleophilicity and basicity are related, they are not measured in the same way.

- Basicity, as expressed by pK_a, is measured *by the position of an equilibrium* in an acid–base reaction.
- Nucleophilicity is measured *by the relative rates of substitution reactions*.

For example, the hydroxide ion (HO^-) is a stronger base than a cyanide ion ($\text{N}\equiv\text{C}^-$); 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.

PRACTICE PROBLEM 6.12 Rank the following in terms of *decreasing* nucleophilicity:



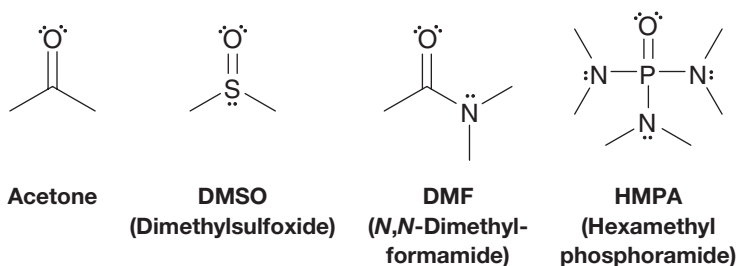
6.13C Solvent Effects in $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ Reactions

- $\text{S}_{\text{N}}2$ reactions are favored by **polar aprotic solvents** (e.g., acetone, DMF, DMSO).
- $\text{S}_{\text{N}}1$ reactions are favored by **polar protic solvents** (e.g., EtOH, MeOH, H_2O).

Important reasons for these **solvent effects** have to do with (a) minimizing the solvent's interaction with the nucleophile in $\text{S}_{\text{N}}2$ reactions, and (b) facilitating ionization of the leaving group and stabilizing ionic intermediates by solvents in $\text{S}_{\text{N}}1$ reactions. In the following subsections we will explain these factors in further detail.

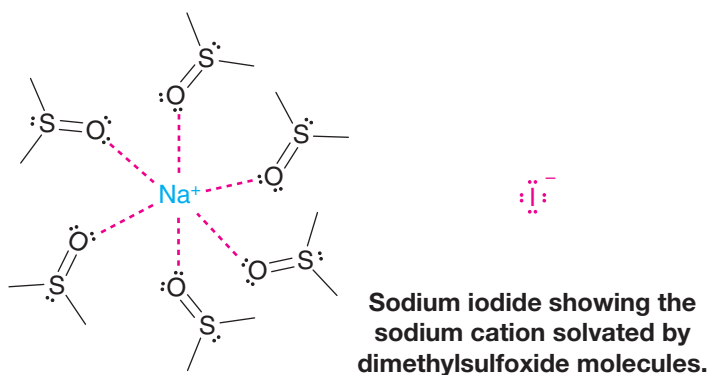
Polar Aprotic Solvents Favor $\text{S}_{\text{N}}2$ Reactions

- An aprotic solvent does not have hydrogen atoms that are capable of hydrogen bonding.
- Polar, aprotic solvents such as acetone, DMF, DMSO, and HMPA are often used alone or as co-solvents for $\text{S}_{\text{N}}2$ reactions.



- The rates of $\text{S}_{\text{N}}2$ 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.

Polar aprotic solvents solubilize cations well using their unshared electron pairs, but do not interact as strongly with anions because they cannot hydrogen bond with them and because the positive regions of the solvent are shielded by steric effects from the anion. This differential solvation leaves anions more free to act as nucleophiles because they are less encumbered by the cation and solvent, thus enhancing the rate of $\text{S}_{\text{N}}2$ reaction. Sodium ions of sodium iodide, for example, can be solvated by DMSO as shown here, leaving the iodide anion more free to act as a nucleophile.



“Naked” anions in polar aprotic solvents are also more reactive as bases, as well as in their capacity as nucleophiles. In DMSO, for example, the relative order of halide ion basicity is the same as their relative order of nucleophilicity. Halide basicity is opposite to nucleophilicity in protic solvents, however, as we shall explain shortly.

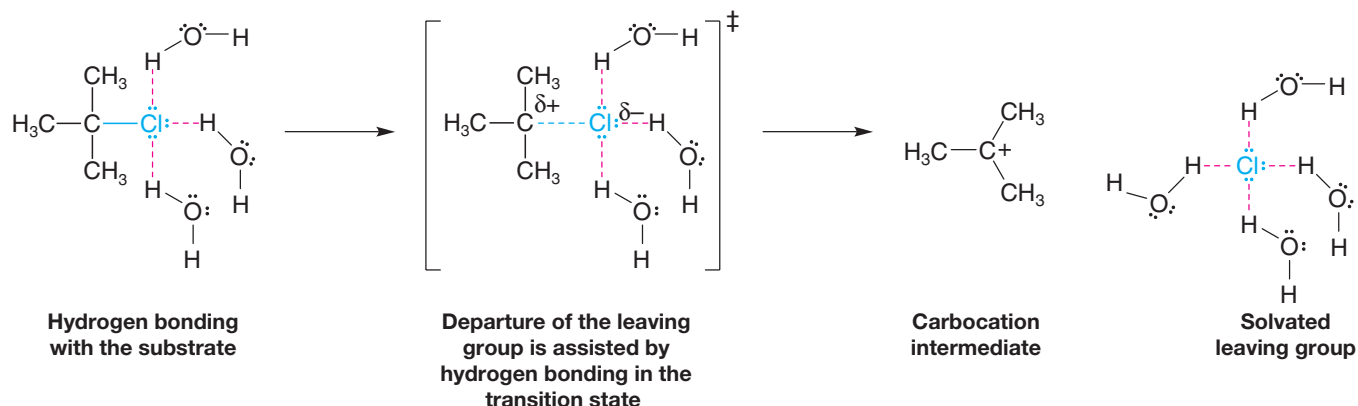


Helpful Hint

Polar aprotic solvents increase S_N2 rates.

Polar Protic Solvents Favor S_N1 Reactions

- A protic solvent has at least one hydrogen atom capable of participating in a hydrogen bond.
- Protic solvents, such as water, EtOH, and MeOH, facilitate formation of a carbocation by forming hydrogen bonds with the leaving group as it departs, thereby lowering the energy of the transition state leading to a carbocation.



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 6.4 gives the dielectric constants of some common solvents.

TABLE 6.4 DIELECTRIC CONSTANTS OF COMMON SOLVENTS

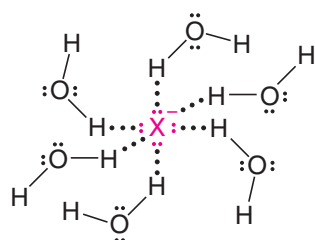
	Solvent	Formula	Dielectric Constant
↑ Increasing solvent polarity ↓	Water	H ₂ O	80
	Formic acid	HCO ₂ H	59
	Dimethyl sulfoxide (DMSO)	CH ₃ SOCH ₃	49
	<i>N,N</i> -Dimethylformamide (DMF)	HCON(CH ₃) ₂	37
	Acetonitrile	CH ₃ C≡N	36
	Methanol	CH ₃ OH	33
	Hexamethylphosphoramide (HMPA)	[(CH ₃) ₂ N] ₃ P=O	30
	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.

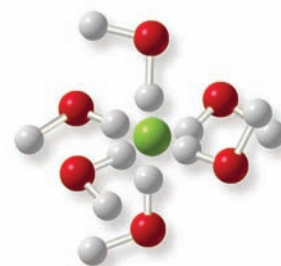
Protic Solvents Hinder the Nucleophile in S_N2 Reactions

A solvated nucleophile must shed some of its solvent molecules to react with the substrate. In a polar aprotic solvent, the nucleophile is less unencumbered by solvent molecules because hydrogen bonding between the solvent and the nucleophile is not possible.

- Hydrogen bonding with a protic solvent such as water, EtOH, or MeOH, encumbers a nucleophile and hinders its reactivity in a nucleophilic substitution reaction.



Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.



- The extent of hydrogen bonding with the nucleophile varies with the identity of the nucleophile. Hydrogen bonding with a small nucleophilic atom is stronger than to a larger nucleophilic atom 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 a protic solvent, the general trend in *nucleophilicity* among the halide anions 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

PRACTICE PROBLEM 6.13 Rank the following in terms of decreasing nucleophilicity in a protic solvent.



PRACTICE PROBLEM 6.14 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, $\text{HOCH}_2\text{CH}_2\text{OH}$.

PRACTICE PROBLEM 6.15 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.

Which would you expect to be the stronger nucleophile in a polar aprotic solvent?

- (a) CH₃CO₂⁻ or CH₃O⁻ (b) H₂O or H₂S (c) (CH₃)₃P or (CH₃)₃N

PRACTICE PROBLEM 6.16

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.

PRACTICE PROBLEM 6.17

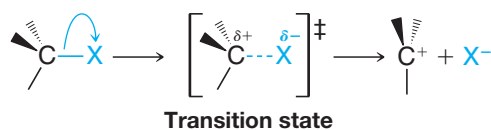
6.13D The Nature of the Leaving Group

- 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.

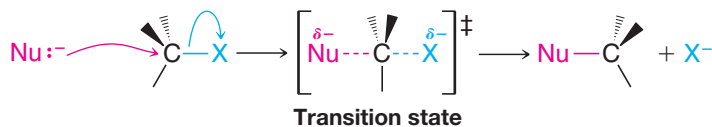
First, let us consider leaving groups that become anions when they separate from the substrate. Because weak bases stabilize a negative charge effectively, leaving groups that become weak bases are good leaving groups.

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

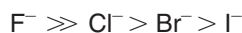


Stabilization of this developing negative charge at the leaving group stabilizes the transition state (lowers its free energy); this lowers the free energy of activation and thereby increases the rate of the reaction.

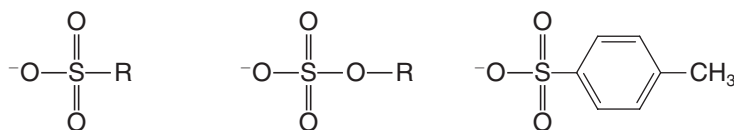
- Among the halogens, an iodide ion is the best leaving group and a fluoride ion is the poorest:



The order is the opposite of the basicity in an aprotic solvent:



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

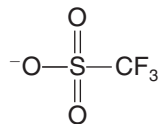
p-Toluenesulfonate ion

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

Helpful Hint

Good leaving groups are weak bases.

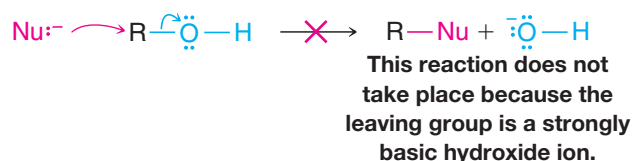
The trifluoromethanesulfonate ion (CF_3SO_3^- , commonly called the **triflate ion**) is one of the best leaving groups known to chemists. It is the conjugate base of $\text{CF}_3\text{SO}_3\text{H}$, an exceedingly strong acid ($\text{p}K_a \sim -5$ to -6):



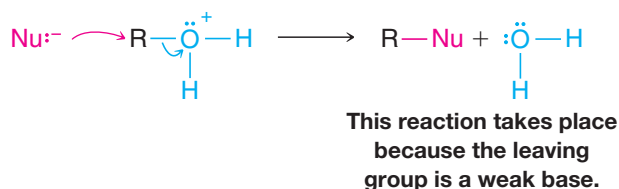
Triflate ion
(a “super” leaving group)

- 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 $-\text{OH}$ group of the alcohol, the leaving group 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:

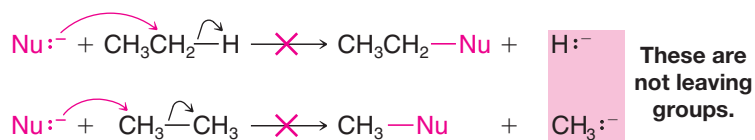


PRACTICE PROBLEM 6.18

List the following compounds in order of decreasing reactivity toward CH_3O^- in an $\text{S}_{\text{N}}2$ reaction carried out in CH_3OH : CH_3F , CH_3Cl , CH_3Br , CH_3I , $\text{CH}_3\text{OSO}_2\text{CF}_3$, $^{14}\text{CH}_3\text{OH}$.

- Very powerful bases such as hydride ions (H^-) and alkoxide ions (R^-) virtually never act as leaving groups.

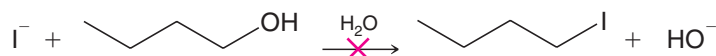
Therefore, **reactions such as the following are not feasible:**



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

SOLVED PROBLEM 6.7

Explain why the following reaction is not feasible as a synthesis of butyl iodide.



STRATEGY AND ANSWER: The strongly basic HO^- ion (hydroxide ion) virtually never acts as a leaving group, something this reaction would require. This reaction would be feasible under acidic conditions, in which case the leaving group would be a water molecule.

SUMMARY OF S_N1 VERSUS S_N2 REACTIONS

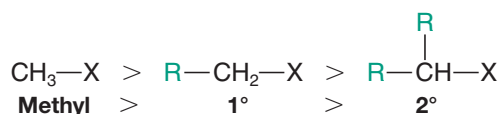
S_N1: The Following Conditions Favor an S_N1 Reaction

1. A substrate that can form a relatively stable carbocation (such as a substrate with a leaving group at a tertiary position)
2. A relatively weak nucleophile
3. A polar, protic solvent such as EtOH, MeOH, or H₂O

The S_N1 mechanism is, therefore, important in solvolysis reactions of tertiary alkyl halides, especially when the solvent is highly polar. In a solvolysis reaction the nucleophile is weak because it is a neutral molecule (of the polar protic solvent) rather than an anion.

S_N2: The Following Conditions Favor an S_N2 Reaction

1. A substrate with a relatively unhindered leaving group (such as a methyl, primary, or secondary alkyl halide). The order of reactivity is



Tertiary halides do not react by an S_N2 mechanism.

2. A strong nucleophile (usually negatively charged)
3. High concentration of the nucleophile
4. A polar, aprotic solvent

The trend in reaction rate for a halogen as the leaving group is the same in S_N1 and S_N2 reactions:



Because alkyl fluorides react so slowly, they are seldom used in nucleophilic substitution reactions.

These factors are summarized in Table 6.5.

TABLE 6.5 FACTORS FAVORING S_N1 VERSUS S_N2 REACTIONS

Factor	S _N 1	S _N 2
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 _N 1 and S _N 2 (the weaker the base after the group departs, the better the leaving group)	

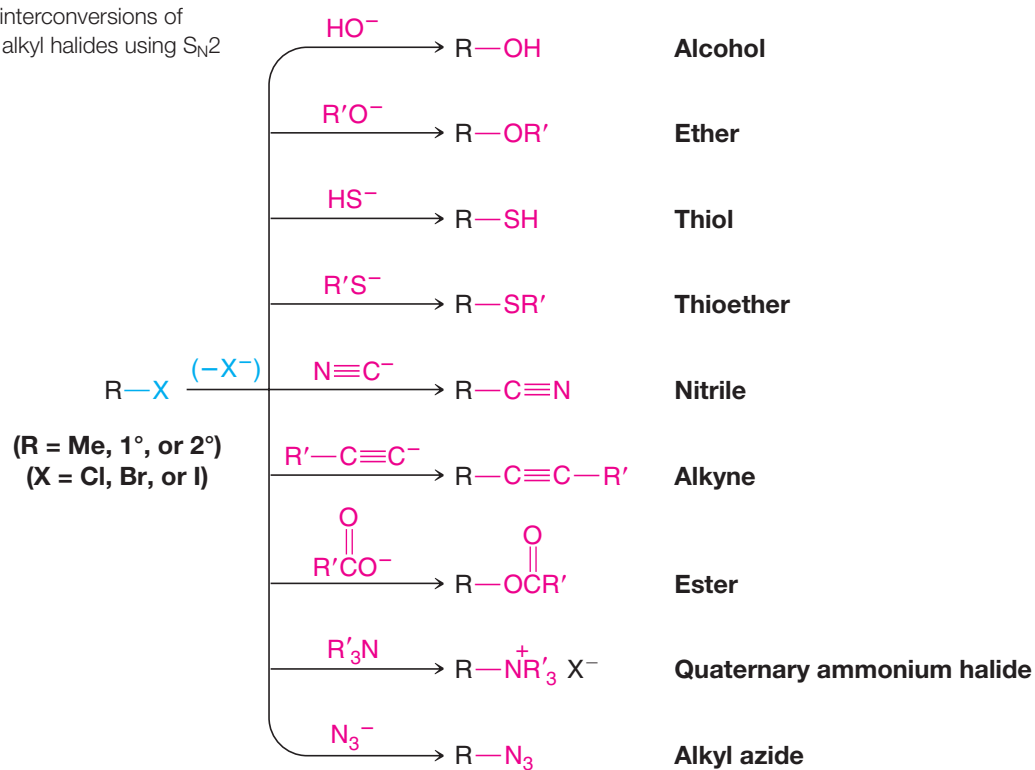
6.14 ORGANIC SYNTHESIS: FUNCTIONAL GROUP TRANSFORMATIONS USING S_N2 REACTIONS

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, methyl, primary, or secondary alkyl halides can be transformed into alcohols, ethers, thiols, thioethers, nitriles, esters, 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.)

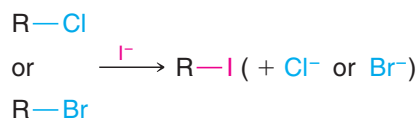
Helpful Hint

S_N1 versus S_N2.

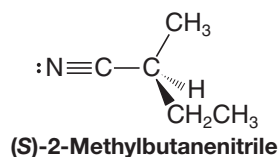
FIGURE 6.11 Functional group interconversions of methyl, primary, and secondary alkyl halides using S_N2 reactions.



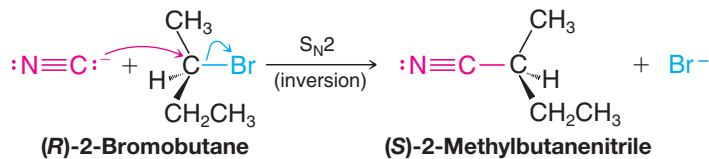
Alkyl chlorides and bromides are also easily converted to alkyl iodides by nucleophilic substitution reactions.



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:



PRACTICE PROBLEM 6.19

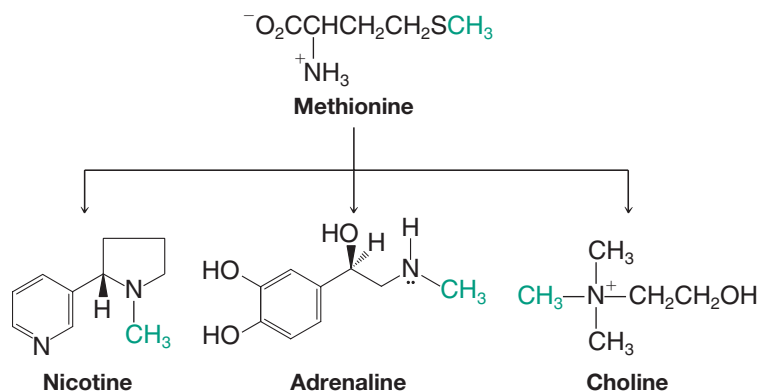
Starting with (*S*)-2-bromobutane, outline syntheses of each of the following compounds:

- | | |
|---|--|
| <p>(a) $(R)-CH_3CH(OCH_2CH_3)CH_2CH_3$</p> | <p>(c) $(R)-CH_3CH(SH)CH_2CH_3$</p> |
| <p>(b) $(R)-CH_3CH(OC(=O)CH_3)CH_2CH_3$</p> | <p>(d) $(R)-CH_3CH(SCH_3)CH_2CH_3$</p> |

THE CHEMISTRY OF... Biological Methylation: A Biological Nucleophilic Substitution Reaction

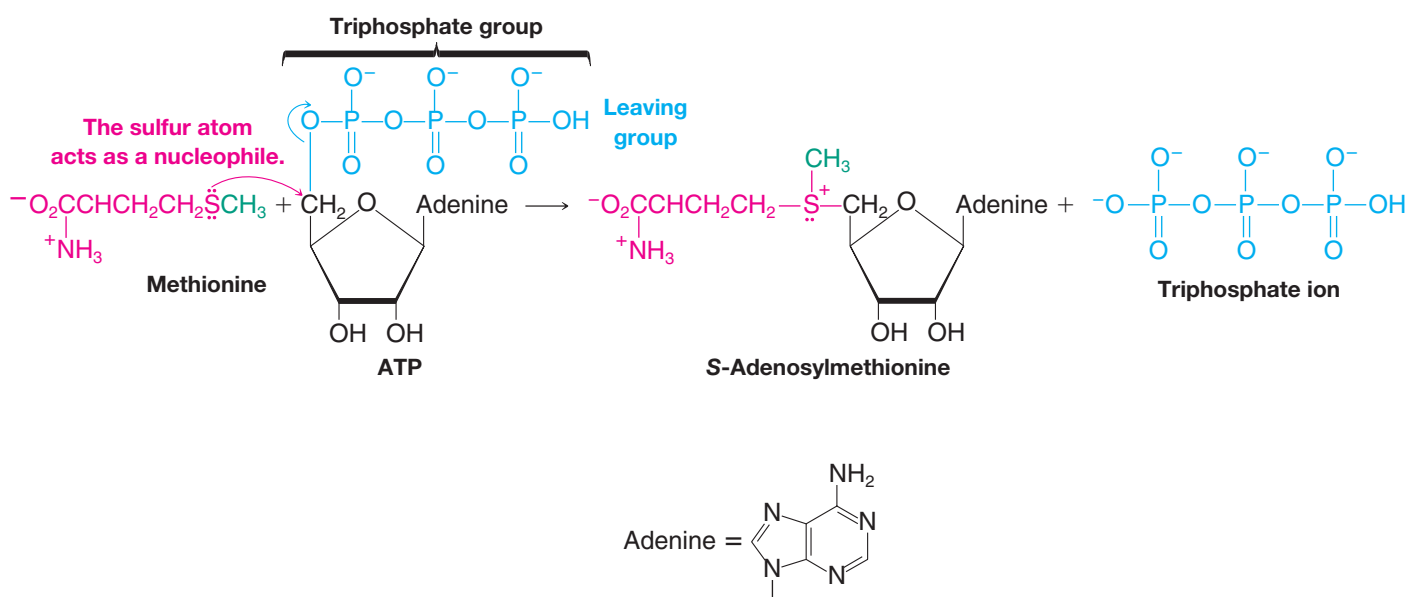
The cells of living organisms synthesize many of the compounds they need from smaller molecules. Often these biosyntheses resemble the syntheses organic chemists carry out in their laboratories. Let us examine one example now.

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., ¹³C or ¹⁴C) 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.)

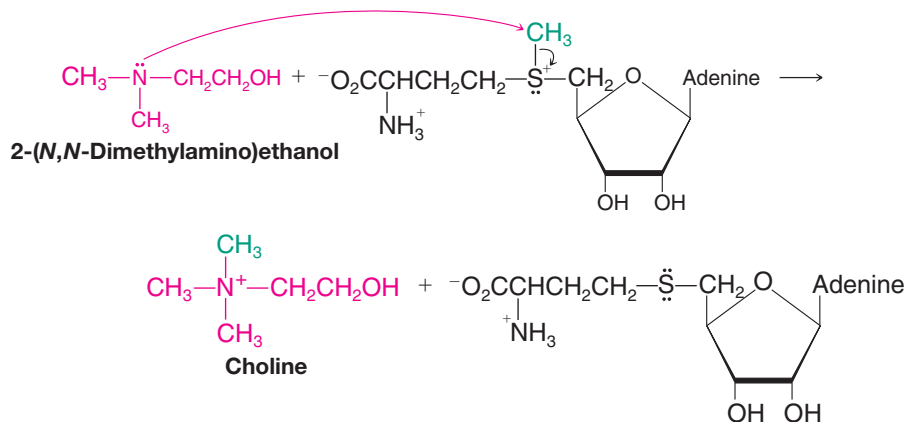
The transfer of the methyl group from methionine to these other compounds does not take place directly. The actual methylating agent is not methionine; it is *S*-adenosylmethionine,* a compound that results when methionine reacts with adenosine triphosphate (ATP):



*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."

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 methyl-sulfonium group, $\text{CH}_3\text{-S}^+$.

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:



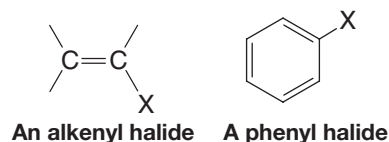
These reactions appear complicated only because the structures of the nucleophiles and substrates are complex. Yet conceptually they are simple, and they illustrate many of the principles we have encountered thus far in Chapter 6. In them we see how nature makes use of the high nucleophilicity of sulfur 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 $-\text{OH}$ group. And when a nucleophile attacks *S*-adenosylmethionine, we see that the attack takes place at the less hindered CH_3- group rather than at one of the more hindered $-\text{CH}_2-$ groups.

Study Problem

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

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 **alkenyl** or **vinylic halides**; those that have a halogen atom attached to a benzene ring are called **aryl** or **phenyl halides**:

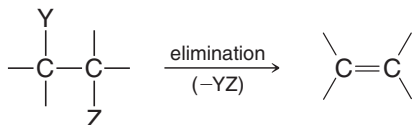


- Alkenyl and phenyl halides are generally unreactive in $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ reactions.

They are unreactive in $\text{S}_{\text{N}}1$ reactions because alkenyl and phenyl cations are relatively unstable and do not form readily. They are unreactive in $\text{S}_{\text{N}}2$ reactions because the carbon-halogen bond of an alkenyl 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.

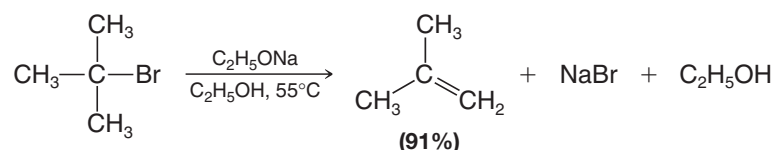
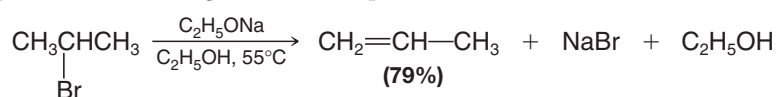
6.15 ELIMINATION REACTIONS OF ALKYL HALIDES

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:

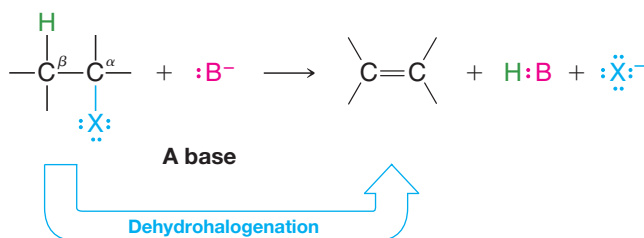


6.15A Dehydrohalogenation

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:

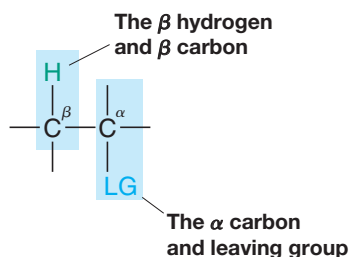


Reactions like these are not limited to the elimination of hydrogen bromide. Chloroalkanes also undergo the elimination of hydrogen chloride, iodoalkanes undergo the elimination of hydrogen iodide, and, in all cases, alkenes are produced. When the elements of a hydrogen halide are eliminated from a haloalkane 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.

Chemists often call the carbon atom that bears the leaving group (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**.

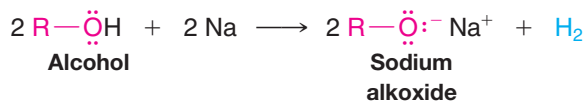


We shall have more to say about dehydrohalogenation in Chapter 7, but we can examine several important aspects here.

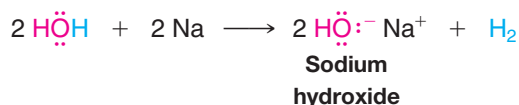
6.15B Bases Used in Dehydrohalogenation

Various strong bases have been used for dehydrohalogenations. Potassium hydroxide dissolved in ethanol (KOH/EtOH) is a reagent sometimes used, but the conjugate bases of alcohols, such as sodium ethoxide (EtONa), 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:



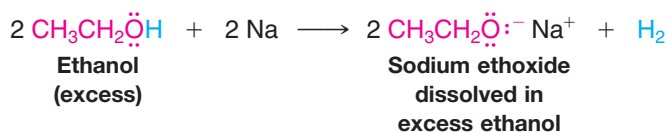
This reaction is an **oxidation–reduction reaction**. Metallic sodium reacts with hydrogen atoms that are bonded to oxygen atoms to generate hydrogen gas, sodium cations, and the alkoxide anion. The reaction with water is vigorous and at times explosive.



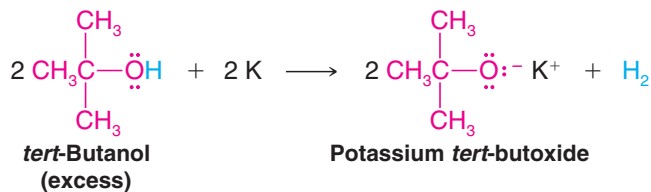
Sodium alkoxides can also be prepared by allowing an alcohol to react with sodium hydride (NaH). The hydride ion (H^-) is a very strong base. (The $\text{p}K_a$ of H_2 is 35.)



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 using excess ethanol.



Potassium *tert*-butoxide (*t*-BuOK) is another highly effective dehydrohalogenating reagent. It can be made by the reaction below, or purchased as a solid.



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 $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ 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:

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

- From the reaction order 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. We call this type of elimination an E2 reaction.

Considerable experimental evidence indicates that an E2 reaction takes place in the following way:

Helpful Hint

EtONa/EtOH is a common abbreviation for sodium ethoxide dissolved in ethanol.

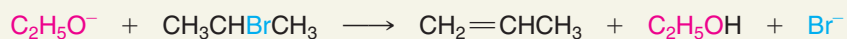
Helpful Hint

t-BuOK/*t*-BuOH represents potassium *tert*-butoxide dissolved in *tert*-butanol.

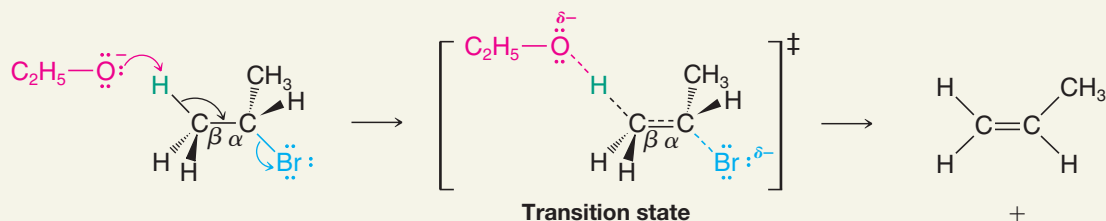
A MECHANISM FOR THE REACTION

Mechanism for the E2 Reaction

Reaction



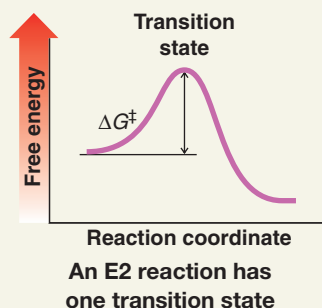
Mechanism



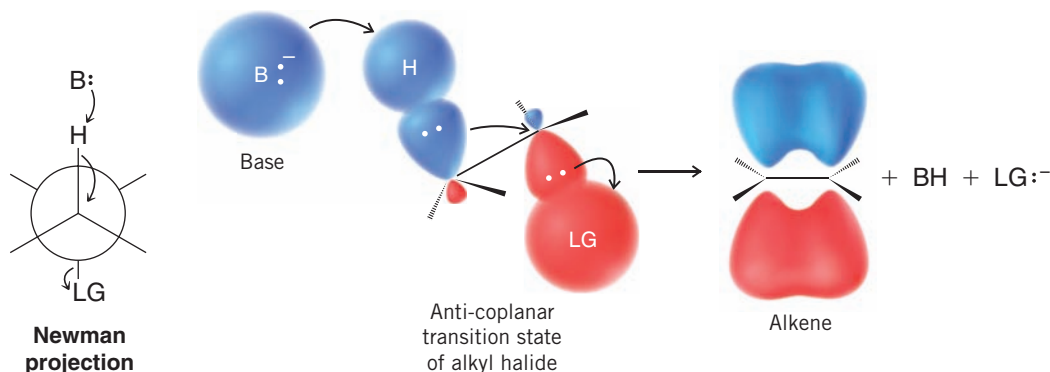
The basic ethoxide ion begins to remove a proton from the β carbon using its electron pair to form a bond to it. At the same time, the electron pair of the β C—H bond begins to move in to become the π bond of a double bond, and the bromine begins to depart with the electrons that bonded it to the α carbon.

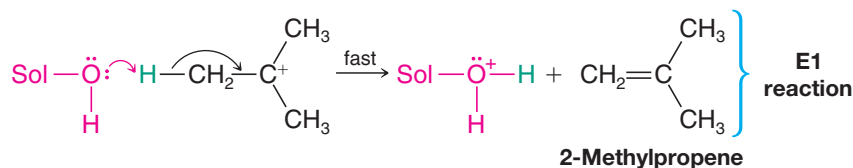
Partial bonds in the transition state extend from the oxygen atom that is removing the β hydrogen, through the carbon skeleton of the developing double bond, to the departing leaving group. The flow of electron density is from the base toward the leaving group as an electron pair fills the π bonding orbital of the alkene.

At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.



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

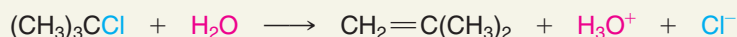




E1 reactions almost always accompany S_N1 reactions.

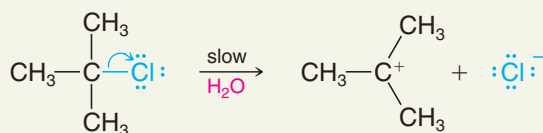
A MECHANISM FOR THE REACTION — Mechanism for the E1 Reaction

Reaction



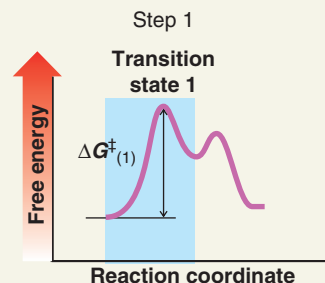
Mechanism

Step 1

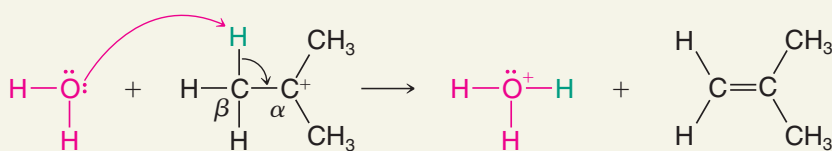


Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

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

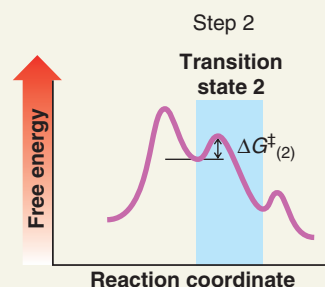


Step 2



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 HOW TO DETERMINE WHETHER SUBSTITUTION OR ELIMINATION IS FAVORED

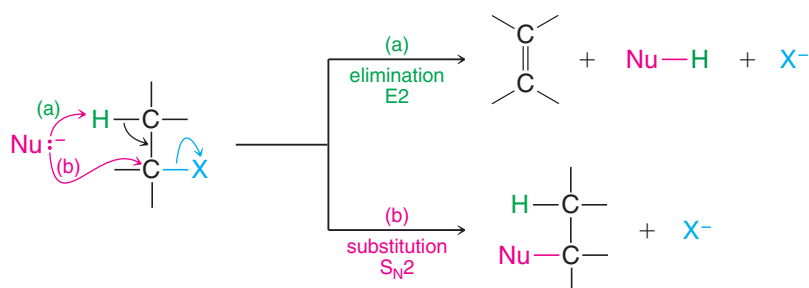
All nucleophiles are potential bases and all bases are potential nucleophiles. This is because the reactive part of both nucleophiles and bases is an unshared electron pair. It should not be surprising, then, that nucleophilic substitution reactions and elimination reactions often compete with each other. We shall now summarize factors that influence which type of reaction is favored, and provide some examples.

Helpful Hint

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

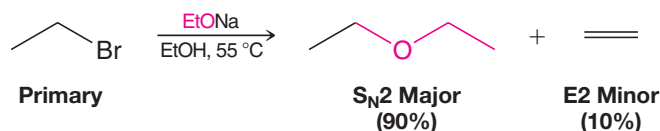
6.18A S_N2 versus E2

S_N2 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:

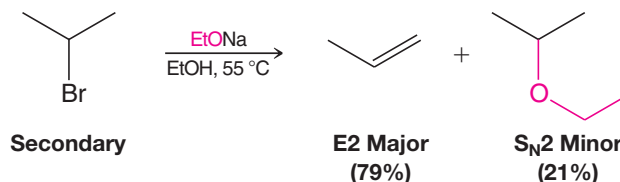


The following examples illustrate the effects of several parameters on substitution and elimination: relative steric hindrance in the substrate (class of alkyl halide), temperature, size of the base/nucleophile (EtONa versus *t*-BuOK), and the effects of basicity and polarizability. In these examples we also illustrate a very common way of writing organic reactions, where reagents are written over the reaction arrow, solvents and temperatures are written under the arrow, and only the substrate and major organic products are written to the left and right of the reaction arrow. We also employ typical shorthand notations of organic chemists, such as exclusive use of bond-line formulas and use of commonly accepted abbreviations for some reagents and solvents.

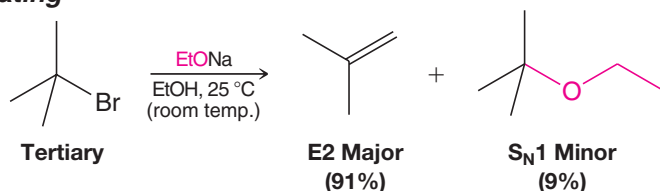
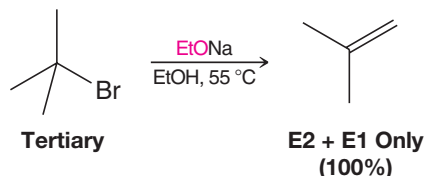
Primary Substrate When the substrate is a *primary* halide and the base is strong and unhindered, like ethoxide ion, substitution is highly favored because the base can easily approach the carbon bearing the leaving group:



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

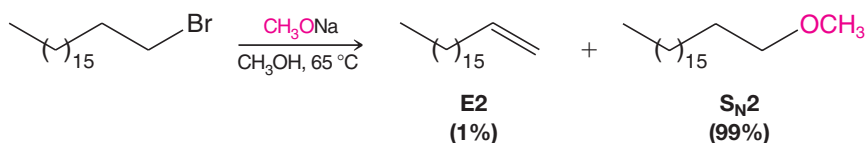
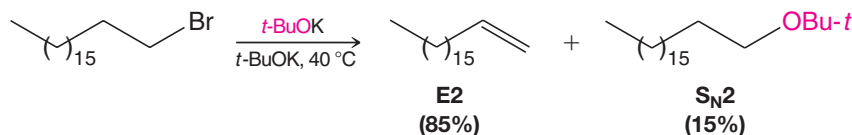


Tertiary Substrate With *tertiary* halides, steric hindrance in the substrate is severe and an S_N2 reaction cannot take place. Elimination is highly favored, especially when the reaction is carried out at higher temperatures. Any substitution that occurs must take place through an S_N1 mechanism:

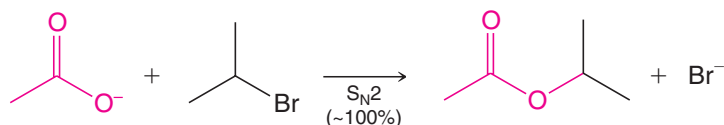
Without Heating**With Heating**

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 reaction 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 hydroxide ion, amide ion (NH_2^-), 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 (CH_3CO_2^-) 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.

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 an elimination product is desired from a tertiary substrate, it is advisable to use a strong base so as to encourage an E2 mechanism over the competing E1 and S_N1 mechanisms.

6.19 OVERALL SUMMARY

The most important reaction pathways for the substitution and elimination reactions of simple alkyl halides are summarized in Table 6.6.

Helpful Hint

Use this table as an overall summary.

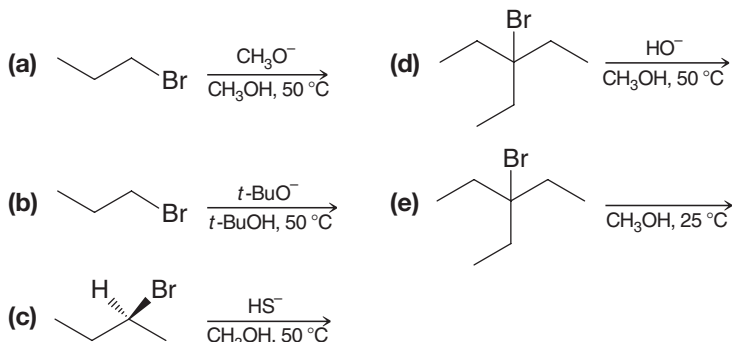
TABLE 6.6 OVERALL SUMMARY OF S_N1, S_N2, E1, AND E2 REACTIONS

CH ₃ X			
Methyl	1°	2°	3°
	Bimolecular (S _N 2/E2) Reactions Only		S _N 1/E1 or E2
Gives S _N 2 reactions	Gives mainly S _N 2 except with a hindered strong base [e.g., (CH ₃) ₃ CO ⁻] and then gives mainly E2.	Gives mainly S _N 2 with weak bases (e.g., I ⁻ , N≡C ⁻ , RCO ₂ ⁻) and mainly E2 with strong bases (e.g., RO ⁻).	No S _N 2 reaction. In solvolysis gives S _N 1/E1, and at lower temperatures S _N 1 is favored. When a strong base (e.g., RO ⁻) is used, E2 predominates.

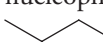
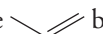
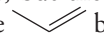
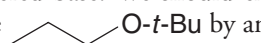
Let us examine several sample exercises that will illustrate how the information in Table 6.6 can be used.

SOLVED PROBLEM 6.8

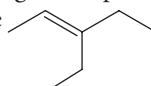
Give the product (or products) that you would expect to be formed in each of the following reactions. In each case give the mechanism (S_N1, S_N2, E1, or E2) by which the product is formed and predict the relative amount of each (i.e., would the product be the only product, the major product, or a minor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



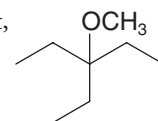
STRATEGY AND ANSWER:

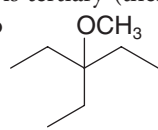
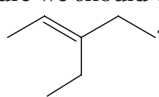
- (a) The substrate is a 1° halide. The base/nucleophile is CH_3O^- , a strong base (but not a hindered one) and a good nucleophile. According to Table 6.6, we should expect an $\text{S}_{\text{N}}2$ reaction mainly, and the major product should be . A minor product might be  by an E2 pathway.
- (b) Again the substrate is a 1° halide, but the base/nucleophile, $t\text{-BuO}^-$, is a strong hindered base. We should expect, therefore, the major product to be  by an E2 pathway and a minor product to be  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 HO^- , a strong base and a strong nucleophile. 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 $\text{S}_{\text{N}}1$ solvolysis, product,

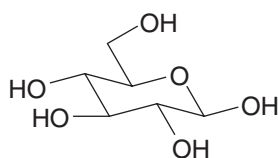
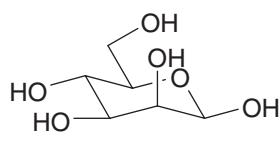
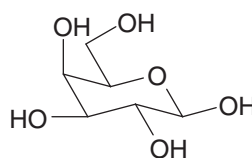
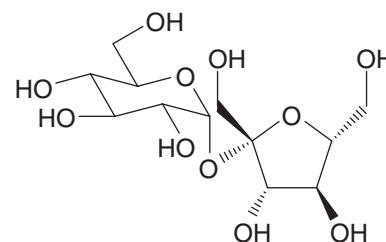


- (e) This is solvolysis; the only base/nucleophile is the solvent, CH_3OH , which is a weak base (therefore, no E2 reaction) and a poor nucleophile. The substrate is tertiary (therefore, no $\text{S}_{\text{N}}2$ reaction). At this lower temperature we should expect mainly an $\text{S}_{\text{N}}1$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

[WHY Do These Topics Matter?

SUBSTITUTING THE CALORIES OF TABLE SUGAR

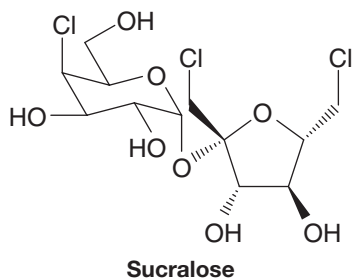
As we shall see in more detail in Chapter 24, simple carbohydrates, or monosaccharides, can exist in the form of a six-membered ring system with a chair conformation. The name carbohydrate derives from “hydrated carbon” since most carbon atoms have an H and OH attached. In the examples below, the structural differences of the monosaccharides glucose, mannose, and galactose are based on the change of one or more chirality centers through what we could formally consider to be an inversion reaction. As such, all of these carbohydrates are diastereomers of each other. Based on what you already know about torsional strain from Chapter 4, it should come as no surprise that D-glucose is the most common monosaccharide: D-glucose has the least strain because all of its substituents are in equatorial positions. All other six-carbon sugars have at least one axial group, and thus possess some 1,3-diaxial strain. Standard table sugar, or sucrose, is a disaccharide, since it combines a molecule of D-glucose with the slightly less common carbohydrate called D-fructose.


D-glucose

D-mannose

D-galactose

Sucrose

All carbohydrates taste sweet, though not equally so. D-Fructose, for example, tastes approximately 1.5 times sweeter than the same amount of simple table sugar, while D-glucose is only about 0.75 times as sweet. Irrespective of their individual degrees of sweetness, however, it is the fact that they are all sweet that lets us perceive their presence in foods whether they are found naturally or have been added (often from corn syrup or cane sugar) to create a more unique flavor profile. Either way, their

(continues on next page)

sweet taste always comes at a cost: calories that can be converted into fat in our bodies. At present, it is estimated by some that Americans consume well over 100 pounds of sugar per person per year from sources both natural and unnatural. That amounts to a lot of calories! What is amazing is that organic chemistry can come to the rescue and knock those calories out. Shown below is the structure of a popular artificial (or synthetic) sweetener known as sucralose, or Splenda. It is the product of some of the chemistry that you have learned in this chapter. Can you guess what that chemistry is?



Absolutely right—it is the replacement of three alcohol groups within sucrose, two of them primary and one of them secondary, with chloride through an inversion reaction. Achieving these events in a laboratory setting is quite difficult, since it means selective reaction of only certain hydroxyls in the presence of many others, but it is possible over several steps under the right conditions, including solvent, temperature, and time. What results is a compound that, when ingested, is sensed by our taste receptors as being sweet like table sugar—in fact, 600 times as sweet! What is perhaps even more amazing, however, is that sucralose has, in effect, no calories. We have metabolic pathways that can, in principle, carry out the reverse reactions and replace those chlorines with alcohols through inversion chemistry, thereby re-creating table sugar and leading to calories. But those replacements do not happen fast enough physiologically. As a result, sucralose leaves our bodies before it can be converted into energy and/or stored as fat. Pretty amazing what just a few substitutions can do!



Media Bakery

SUMMARY AND REVIEW TOOLS

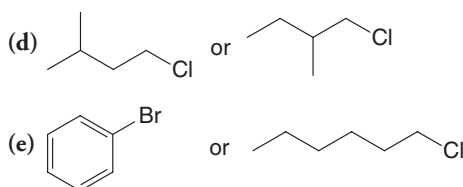
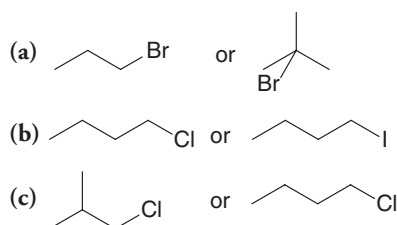
The study aids for this chapter include Key Terms and Concepts (which are highlighted in bold, blue text within the chapter and defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying *WileyPLUS* course (www.wileyplus.com), and a Mechanism Review regarding substitution and elimination reactions.

PROBLEMS

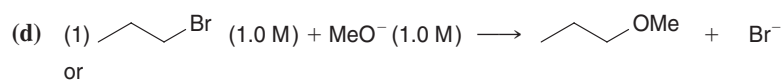
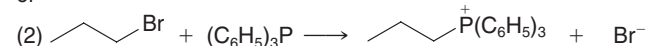
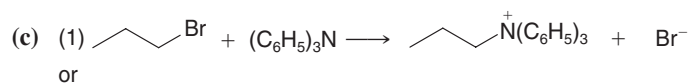
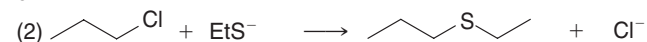
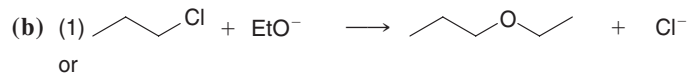
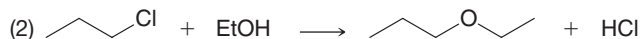
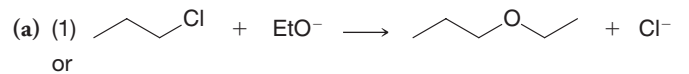
Note to Instructors: Many of the homework problems are available for assignment via *WileyPlus*, an online teaching and learning solution.

RELATIVE RATES OF NUCLEOPHILIC SUBSTITUTION

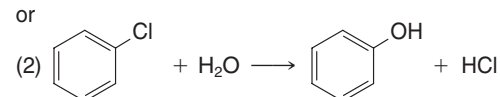
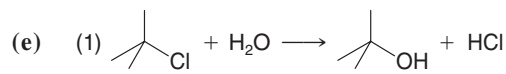
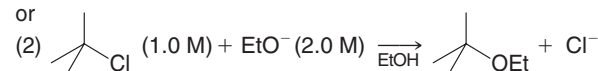
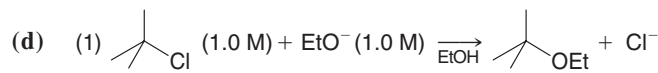
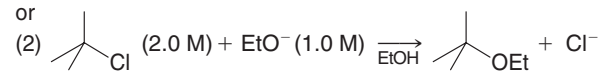
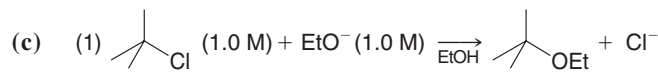
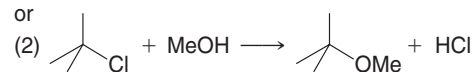
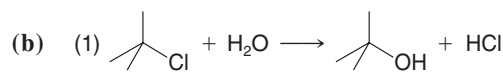
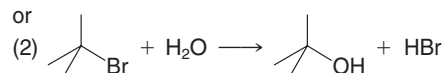
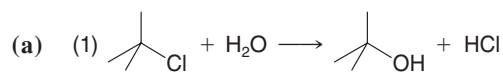
6.20 Which alkyl halide would you expect to react more rapidly by an S_N2 mechanism? Explain your answer.



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

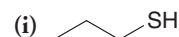
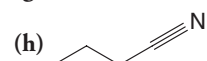
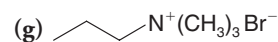
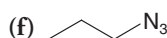
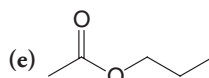
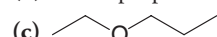
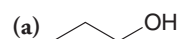


6.22 Which S_N1 reaction of each pair would you expect to take place more rapidly? Explain your answer.

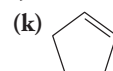
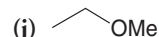
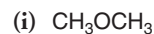
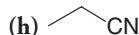
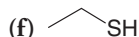
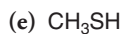
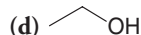


SYNTHESIS

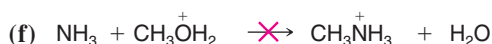
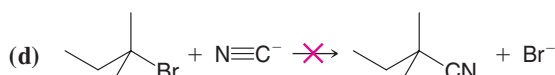
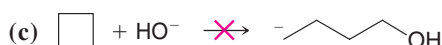
6.23 Show how you might use a nucleophilic substitution reaction of 1-bromopropane to synthesize each of the following compounds. (You may use any other compounds that are necessary.)



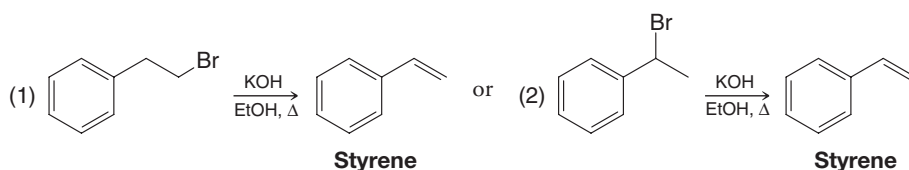
6.24 With methyl, ethyl, or cyclopentyl halides as your organic starting materials and using any needed solvents or inorganic reagents, outline syntheses of each of the following. More than one step may be necessary and you need not repeat steps carried out in earlier parts of this problem.



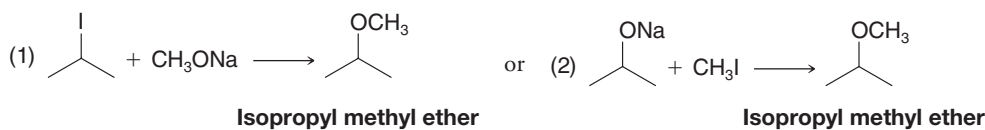
6.25 Listed below are several hypothetical nucleophilic substitution reactions. None is synthetically useful because the product indicated is not formed at an appreciable rate. In each case provide an explanation for the failure of the reaction to take place as indicated.



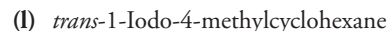
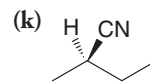
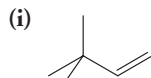
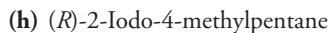
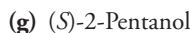
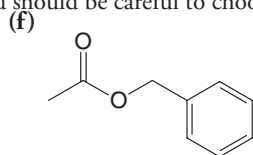
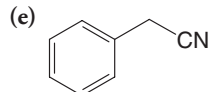
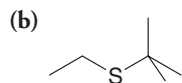
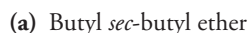
6.26 Your task is to prepare styrene by one of the following reactions. Which reaction would you choose to give the better yield of styrene? Explain your answer.



6.27 Your task is to prepare isopropyl methyl ether by one of the following reactions. Which reaction would give the better yield? Explain your answer.

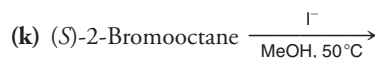
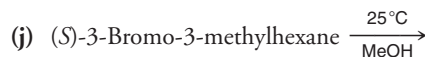
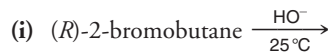
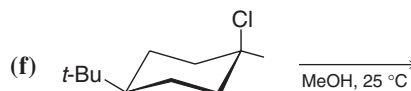
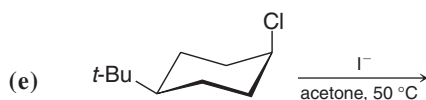
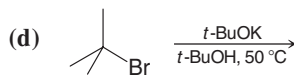
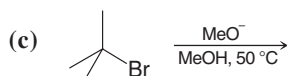
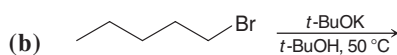
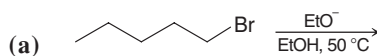


6.28 Starting with an appropriate alkyl halide and using any other needed reagents, outline syntheses of each of the following. When alternative possibilities exist for a synthesis, you should be careful to choose the one that gives the better yield.

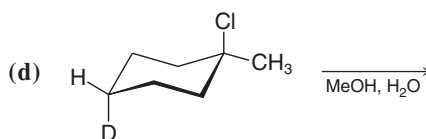
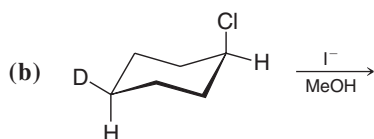
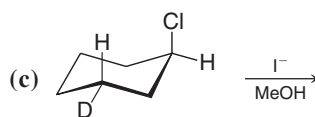
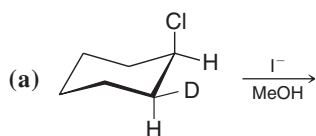


GENERAL $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, AND ELIMINATION

6.29 Which product (or products) would you expect to obtain from each of the following reactions? In each part give the mechanism ($\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, 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.).



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



6.31 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 (EtO^-), 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?

6.32 Consider the reaction of I^- with $\text{CH}_3\text{CH}_2\text{Cl}$.

(a) Would you expect the reaction to be S_N1 or S_N2 ? The rate constant for the reaction at 60°C is $5 \times 10^{-5} \text{ L mol}^{-1} \text{ s}^{-1}$.

(b) What is the reaction rate if $[\text{I}^-] = 0.1 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.1 \text{ mol L}^{-1}$?

(c) If $[\text{I}^-] = 0.1 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.2 \text{ mol L}^{-1}$?

(d) If $[\text{I}^-] = 0.2 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.1 \text{ mol L}^{-1}$?

(e) If $[\text{I}^-] = 0.2 \text{ mol L}^{-1}$ and $[\text{CH}_3\text{CH}_2\text{Cl}] = 0.2 \text{ mol L}^{-1}$?

6.33 Which reagent in each pair listed here would be the more reactive nucleophile in a polar aprotic solvent?

(a) CH_3NH^- or CH_3NH_2

(d) $(\text{C}_6\text{H}_5)_3\text{N}$ or $(\text{C}_6\text{H}_5)_3\text{P}$

(g) H_2S or HS^-

(b) CH_3O^- or CH_3CO_2^- ($^- \text{OAc}$)

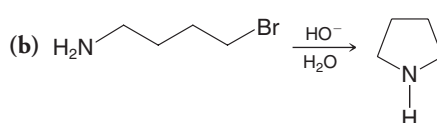
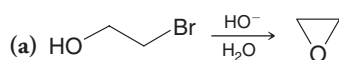
(e) H_2O or H_3O^+

(h) CH_3CO_2^- ($^- \text{OAc}$) or HO^-

(c) CH_3SH or CH_3OH

(f) NH_3 or $^+\text{NH}_4$

6.34 Write mechanisms that account for the products of the following reactions:



6.35 Draw a three-dimensional representation for the transition state structure in the S_N2 reaction of $\text{N}\equiv\text{C}^-$ (cyanide anion) with bromoethane, showing all nonbonding electron pairs and full or partial charges.

6.36 Many S_N2 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.

6.37 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.

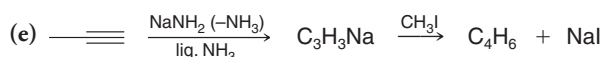
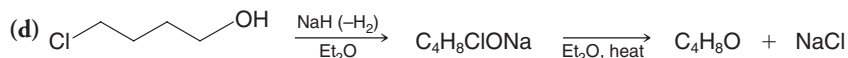
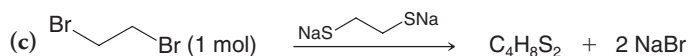
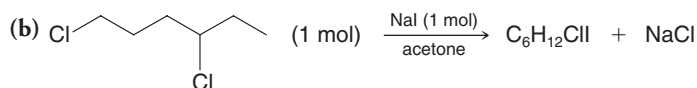
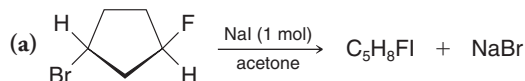
6.38

- (a) 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?
- (b) 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?

6.39 1-Bromobicyclo[2.2.1]heptane is extremely unreactive in either S_N2 or S_N1 reactions. Provide explanations for this behavior.

6.40 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.

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



6.42 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 $(\text{C}_6\text{H}_5)_2\text{CHBr}$ undergoes S_N1 hydrolysis, adding NaBr retards the reaction. Given that the $(\text{C}_6\text{H}_5)_2\text{CH}^+$ cation is known to be much more stable than the $(\text{CH}_3)_3\text{C}^+$ cation (and we shall see why in Section 15.12A), provide an explanation for the different behavior of the two compounds.

6.43 When the alkyl bromides (listed here) were subjected to hydrolysis in a mixture of ethanol and water (80% $\text{EtOH}/20\% \text{H}_2\text{O}$) at 55°C , the rates of the reaction showed the following order:



Provide an explanation for this order of reactivity.

6.44 The reaction of 1° alkyl halides with nitrite salts produces both RNO_2 and RONO . Account for this behavior.

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



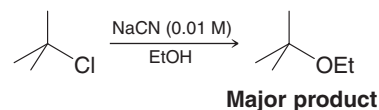
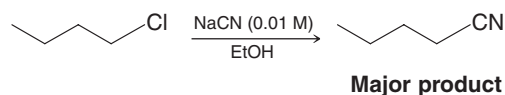
6.46 Competition experiments are those in which two reactants at the same concentration (or one reactant with two reactive sites) compete for a reagent. Predict the major product resulting from each of the following competition experiments:



6.47 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 following:



CHALLENGE PROBLEMS

6.48 The reaction of chloroethane with water *in the gas phase* to produce ethanol and hydrogen chloride has $\Delta H^\circ = +26.6 \text{ kJ mol}^{-1}$ and $\Delta S^\circ = +4.81 \text{ J K}^{-1} \text{ mol}^{-1}$ at 25°C .

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

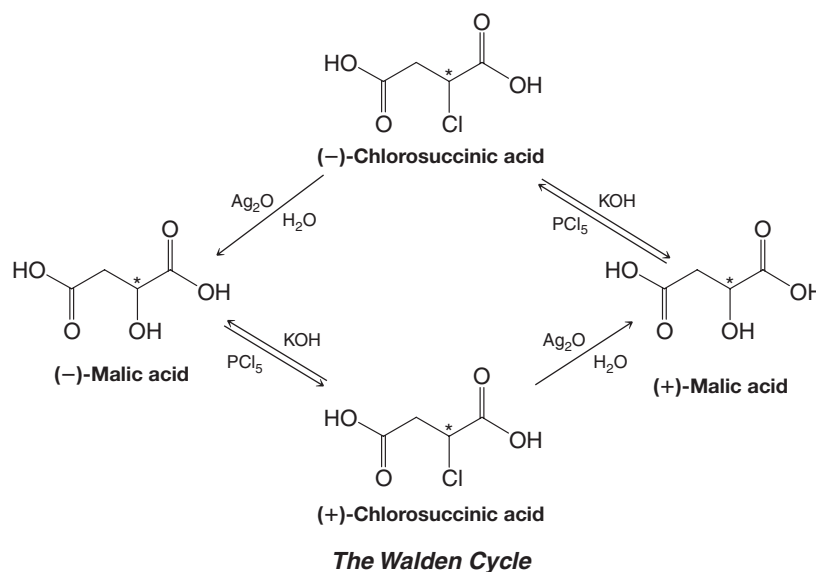
(b) Calculate ΔG° for the reaction. What can you now say about whether the reaction will proceed to completion?

(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?

6.49 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.

6.50 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?

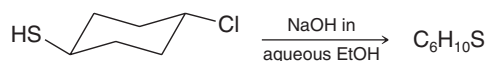
(d) Assuming that the reaction of (-)-malic acid and thionyl chloride has the same stereochemistry, outline a Walden cycle based on the use of thionyl chloride instead of PCl₅.

6.51 (*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?

6.52 Predict the structure of the product of this reaction:



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

6.53 *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**.

6.54 1-Bromo[2.2.1]bicycloheptane is unreactive toward both S_N2 and S_N1 reactions. Open the computer molecular model at the book's website 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?

6.55 Open the computer molecular model titled "1-Bromo[2.2.1]bicycloheptane LUMO" at the book's website for the lowest unoccupied molecular orbital (LUMO) of this compound. Where is the lobe of the LUMO with which the HOMO of a nucleophile would interact in an S_N2 reaction?

6.56 In the previous problem and the associated molecular model at the book's website, you considered the role of HOMO's and LUMO's 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 at the book's website 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

1. 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.

2. 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 structures 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.

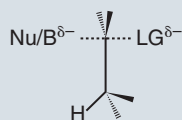
[SUMMARY AND REVIEW TOOLS]

Mechanism Review: Substitution versus Elimination

S_N2

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



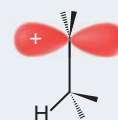
S_N2 and E2

Secondary or primary substrate
Strong unhindered base/nucleophile leads to S_N2
Strong hindered base/nucleophile leads to E2
Low temperature (S_N2) / high temperature (E2)

S_N1 and E1

Tertiary substrate
Carbocation intermediate
Weak nucleophile/base (e.g., solvent)

Unimolecular in rate-determining step
Racemization if S_N1
Removal of β -hydrogen if E1
Protic solvent assists ionization of LG
Low temperature (S_N1) / high temperature (E1)



E2

Tertiary or secondary substrate
Concerted anti-coplanar transition state
Bimolecular in rate-determining step
Strong hindered base
High temperature

