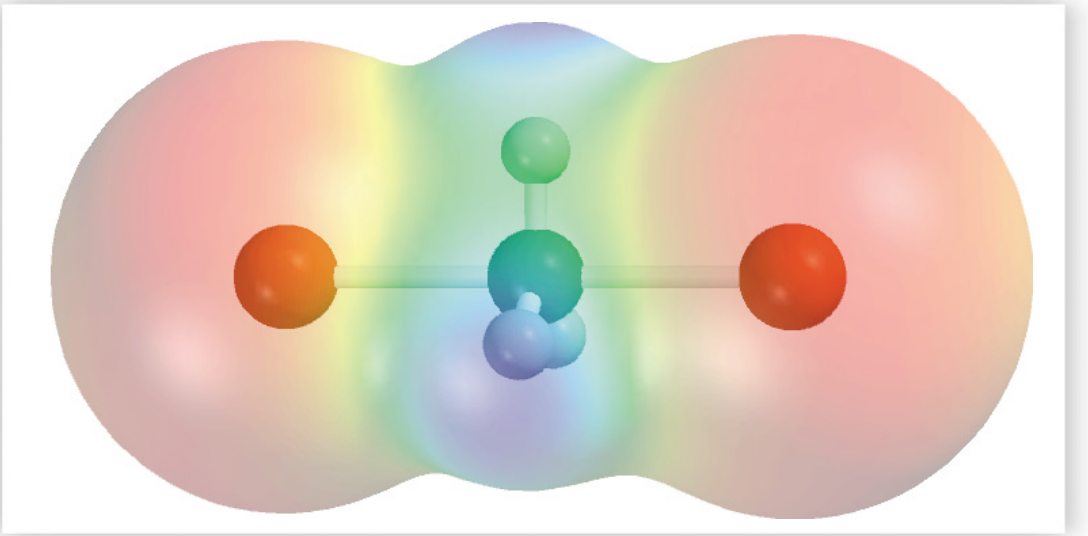
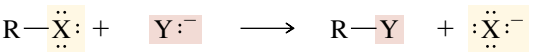


CHAPTER 8

NUCLEOPHILIC SUBSTITUTION

When we discussed elimination reactions in Chapter 5, we learned that a Lewis base can react with an alkyl halide to form an alkene. In the present chapter, you will find that the same kinds of reactants can also undergo a different reaction, one in which the Lewis base acts as a **nucleophile** to substitute for the halide substituent on carbon.



Alkyl halide | Lewis base | Product of nucleophilic substitution | Halide anion

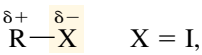
We first encountered nucleophilic substitution in Chapter 4, in the reaction of alcohols with hydrogen halides to form alkyl halides. Now we'll see how alkyl halides can themselves be converted to other classes of organic compounds by nucleophilic substitution.

This chapter has a mechanistic emphasis designed to achieve a practical result. By understanding the mechanisms by which alkyl halides undergo nucleophilic substitution, we can choose experimental conditions best suited to carrying out a particular functional group transformation. The difference between a successful reaction that leads cleanly to a desired product and one that fails is often a subtle one. Mechanistic analysis helps us to appreciate these subtleties and use them to our advantage.

8.1 FUNCTIONAL GROUP TRANSFORMATION BY NUCLEOPHILIC SUBSTITUTION

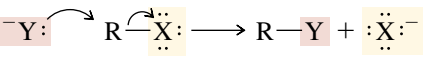
Nucleophilic substitution reactions of alkyl halides are related to elimination reactions in that the halogen acts as a leaving group on carbon and is lost as an anion. The carbon–halogen bond of the alkyl halide is broken **heterolytically:** the pair of electrons in that bond are lost with the leaving group.

The carbon–halogen bond in an alkyl halide is polar



X = I, Br, Cl, F

and is cleaved on attack by a nucleophile so that the two electrons in the bond are retained by the halogen



The most frequently encountered nucleophiles in functional group transformations are anions, which are used as their lithium, sodium, or potassium salts. If we use M to represent lithium, sodium, or potassium, some representative nucleophilic reagents are

MOR (a metal *alkoxide,* a source of the nucleophilic anion $RO:^-$)

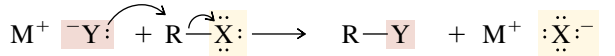
MOCR (a metal *carboxylate,* a source of the nucleophilic anion RCO_2^-)

MSH (a metal *hydrogen sulfide,* a source of the nucleophilic anion $HS:^-$)

MCN (a metal *cyanide,* a source of the nucleophilic anion $:C{\equiv}N:^-$)

MN_3 (a metal *azide,* a source of the nucleophilic anion $:N{=}N^+{=}N:^-$)

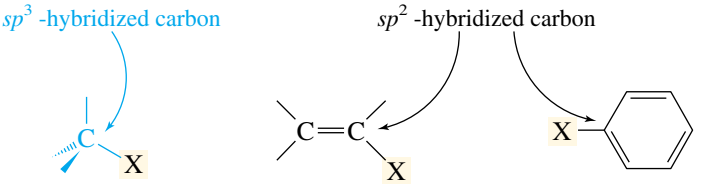
Table 8.1 illustrates an application of each of these to a functional group transformation. The anionic portion of the salt substitutes for the halogen of an alkyl halide. The metal cation portion becomes a lithium, sodium, or potassium halide.



Nucleophilic reagent	Alkyl halide	Product of nucleophilic substitution	Metal halide

Notice that all the examples in Table 8.1 involve **alkyl halides,** that is, compounds in which the halogen is attached to an sp^3-hybridized carbon. **Alkenyl halides** and **aryl halides,** compounds in which the halogen is attached to sp^2-hybridized carbons, are essentially unreactive under these conditions, and the principles to be developed in this chapter do not apply to them.

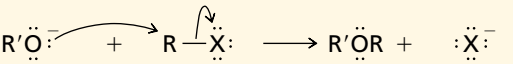
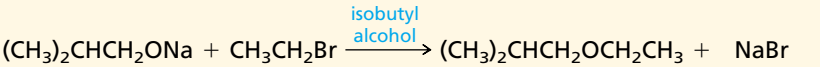
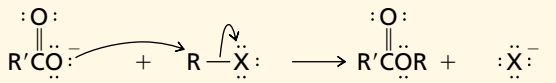
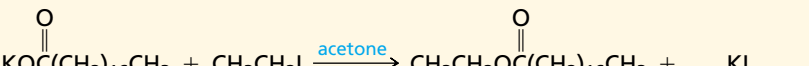
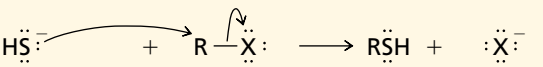
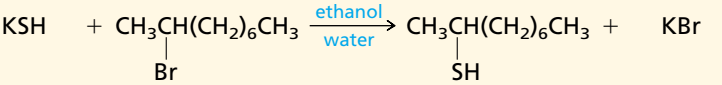
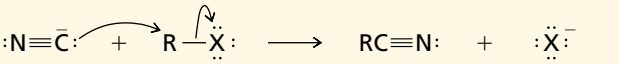
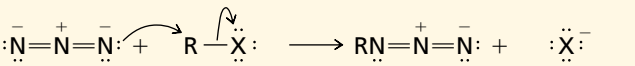
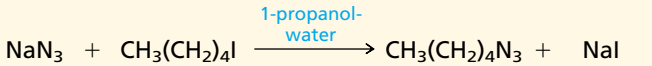
Alkenyl halides are also referred to as *vinylic halides.*



To ensure that reaction occurs in homogeneous solution, solvents are chosen that dissolve both the alkyl halide and the ionic salt. The alkyl halide substrates are soluble in organic solvents, but the salts often are not. Inorganic salts are soluble in water, but alkyl halides are not. Mixed solvents such as ethanol–water mixtures that can dissolve enough of both the substrate and the nucleophile to give fairly concentrated solutions are frequently used. Many salts, as well as most alkyl halides, possess significant solubility in dimethyl sulfoxide (DMSO), which makes this a good medium for carrying out nucleophilic substitution reactions.

The use of DMSO as a solvent in *dehydrohalogenation* reactions was mentioned earlier, in Section 5.14.

TABLE 8.1 Representative Functional Group Transformations by Nucleophilic Substitution Reactions of Alkyl Halides

Nucleophile and comments	General equation and specific example
Alkoxide ion ($RO:^-$) The oxygen atom of a metal alkoxide acts as a nucleophile to replace the halogen of an alkyl halide. The product is an *ether.*	 Alkoxide ion · Alkyl halide · Ether · Halide ion  Sodium isobutoxide · Ethyl bromide · Ethyl isobutyl ether (66%) · Sodium bromide
Carboxylate ion (RCO_2^-) An *ester* is formed when the negatively charged oxygen of a carboxylate replaces the halogen of an alkyl halide.	 Carboxylate ion · Alkyl halide · Ester · Halide ion  Potassium octadecanoate · Ethyl iodide · Ethyl octadecanoate (95%) · Potassium iodide
Hydrogen sulfide ion (HS^-) Use of hydrogen sulfide as a nucleophile permits the conversion of alkyl halides to compounds of the type RSH. These compounds are the sulfur analogs of alcohols and are known as *thiols.*	 Hydrogen sulfide ion · Alkyl halide · Thiol · Halide ion  Potassium hydrogen sulfide · 2-Bromononane · 2-Nonanethiol (74%) · Potassium bromide
Cyanide ion ($:C\equiv N:^-$) The negatively charged carbon atom of cyanide ion is usually the site of its nucleophilic character. Use of cyanide ion as a nucleophile permits the extension of a carbon chain by carbon–carbon bond formation. The product is an *alkyl cyanide,* or *nitrile.*	 Cyanide ion · Alkyl halide · Alkyl cyanide · Halide ion  Sodium cyanide · Cyclopentyl chloride · Cyclopentyl cyanide (70%) · Sodium chloride
Azide ion ($:N=N^+=N:^-$) Sodium azide is a reagent used for carbon–nitrogen bond formation. The product is an *alkyl azide.*	 Azide ion · Alkyl halide · Alkyl azide · Halide ion  Sodium azide · Pentyl iodide · Pentyl azide (52%) · Sodium iodide

(Continued)

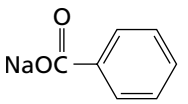
TABLE 8.1 Representative Functional Group Transformations by Nucleophilic Substitution Reactions of Alkyl Halides *(Continued)*

Nucleophile and comments	General equation and specific example
Iodide ion ($:\ddot{I}:^-$) Alkyl chlorides and bromides are converted to *alkyl iodides* by treatment with sodium iodide in acetone. NaI is soluble in acetone, but NaCl and NaBr are insoluble and crystallize from the reaction mixture, driving the reaction to completion.	$:\ddot{I}:^- + R-\ddot{X}: \xrightarrow{\text{acetone}} R-\ddot{I}: + :\ddot{X}:^-$ Iodide ion; Alkyl chloride or bromide; Alkyl iodide; Chloride or bromide ion CH_3CHCH_3 (Br) + NaI $\xrightarrow{\text{acetone}}$ CH_3CHCH_3 (I) + NaBr (solid) 2-Bromopropane; Sodium iodide; 2-Iodopropane (63%); Sodium bromide

PROBLEM 8.1 Write a structural formula for the principal organic product formed in the reaction of methyl bromide with each of the following compounds:

(a) NaOH (sodium hydroxide)

(b) $KOCH_2CH_3$ (potassium ethoxide)

(c)  (sodium benzoate)

(d) LiN_3 (lithium azide)

(e) KCN (potassium cyanide)

(f) NaSH (sodium hydrogen sulfide)

(g) NaI (sodium iodide)

SAMPLE SOLUTION (a) The nucleophile in sodium hydroxide is the negatively charged hydroxide ion. The reaction that occurs is nucleophilic substitution of bromide by hydroxide. The product is methyl alcohol.

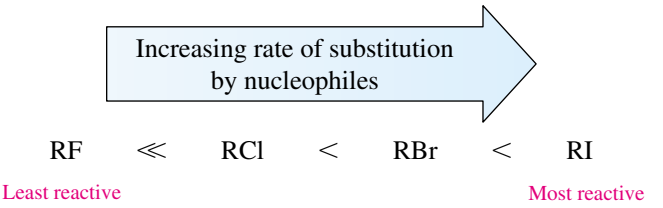
$HO:^- + CH_3-Br: \longrightarrow CH_3-OH + :Br:^-$

Hydroxide ion (nucleophile); Methyl bromide (substrate); Methyl alcohol (product); Bromide ion (leaving group)

With this as background, you can begin to see how useful alkyl halides are in synthetic organic chemistry. Alkyl halides may be prepared from alcohols by nucleophilic substitution, from alkanes by free-radical halogenation, and from alkenes by addition of hydrogen halides. They then become available as starting materials for the preparation of other functionally substituted organic compounds by replacement of the halide leaving group with a nucleophile. The range of compounds that can be prepared by nucleophilic substitution reactions of alkyl halides is quite large; the examples shown in Table 8.1 illustrate only a few of them. Numerous other examples will be added to the list in this and subsequent chapters.

8.2 RELATIVE REACTIVITY OF HALIDE LEAVING GROUPS

Among alkyl halides, alkyl iodides undergo nucleophilic substitution at the fastest rate, alkyl fluorides the slowest.



The order of alkyl halide reactivity in nucleophilic substitutions is the same as their order in eliminations. Iodine has the weakest bond to carbon, and iodide is the best leaving group. Alkyl iodides are several times more reactive than alkyl bromides and from 50 to 100 times more reactive than alkyl chlorides. Fluorine has the strongest bond to carbon, and fluoride is the poorest leaving group. Alkyl fluorides are rarely used as substrates in nucleophilic substitution because they are several thousand times less reactive than alkyl chlorides.

PROBLEM 8.2 A single organic product was obtained when 1-bromo-3-chloropropane was allowed to react with one molar equivalent of sodium cyanide in aqueous ethanol. What was this product?

The relationship between leaving group ability and basicity is explored in more detail in Section 8.14.

Leaving-group ability is also related to basicity. A strongly basic anion is usually a poorer leaving group than a weakly basic one. Fluoride is the most basic and the poorest leaving group among the halide anions, iodide the least basic and the best leaving group.

8.3 THE S_N2 MECHANISM OF NUCLEOPHILIC SUBSTITUTION

The mechanisms by which nucleophilic substitution takes place have been the subject of much study. Extensive research by Sir Christopher Ingold and Edward D. Hughes and their associates at University College, London, during the 1930s emphasized kinetic and stereochemical measurements to probe the mechanisms of these reactions.

Recall that the term "kinetics" refers to how the rate of a reaction varies with changes in concentration. Consider the nucleophilic substitution in which sodium hydroxide reacts with methyl bromide to form methyl alcohol and sodium bromide:

$$\underset{\text{Methyl bromide}}{CH_3Br} + \underset{\text{Hydroxide ion}}{HO^-} \longrightarrow \underset{\text{Methyl alcohol}}{CH_3OH} + \underset{\text{Bromide ion}}{Br^-}$$

The rate of this reaction is observed to be directly proportional to the concentration of both methyl bromide and sodium hydroxide. It is first-order in each reactant, or *second-order* overall.

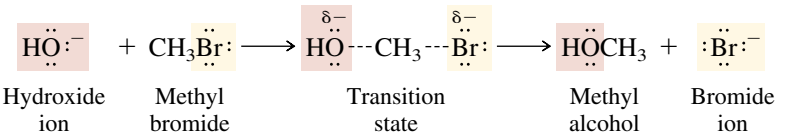
$$\text{Rate} = k[CH_3Br][HO^-]$$

Hughes and Ingold interpreted second-order kinetic behavior to mean that the rate-determining step is *bimolecular,* that is, that both hydroxide ion and methyl bromide are involved at the transition state. The symbol given to the detailed description of the mechanism that they developed is S_N2, standing for **substitution nucleophilic bimolecular.**

The S_N2 mechanism was introduced earlier in Section 4.13.

The Hughes and Ingold S_N2 mechanism is a single-step process in which both the alkyl halide and the nucleophile are involved at the transition state. Cleavage of the bond between carbon and the leaving group is assisted by formation of a bond between carbon and the nucleophile. In effect, the nucleophile "pushes off" the leaving group from

its point of attachment to carbon. For this reason, the S_N2 mechanism is sometimes referred to as a **direct displacement** process. The S_N2 mechanism for the hydrolysis of methyl bromide may be represented by a single elementary step:



Carbon is partially bonded to both the incoming nucleophile and the departing halide at the transition state. Progress is made toward the transition state as the nucleophile begins to share a pair of its electrons with carbon and the halide ion leaves, taking with it the pair of electrons in its bond to carbon.

PROBLEM 8.3 Is the two-step sequence depicted in the following equations consistent with the second-order kinetic behavior observed for the hydrolysis of methyl bromide?

$$CH_3Br \xrightarrow{\text{slow}} CH_3^+ + Br^-$$

$$CH_3^+ + HO^- \xrightarrow{\text{fast}} CH_3OH$$

The S_N2 mechanism is believed to describe most substitutions in which simple primary and secondary alkyl halides react with anionic nucleophiles. All the examples cited in Table 8.1 proceed by the S_N2 mechanism (or a mechanism very much like S_N2—remember, mechanisms can never be established with certainty but represent only our best present explanations of experimental observations). We'll examine the S_N2 mechanism, particularly the structure of the transition state, in more detail in Section 8.5 after first looking at some stereochemical studies carried out by Hughes and Ingold.

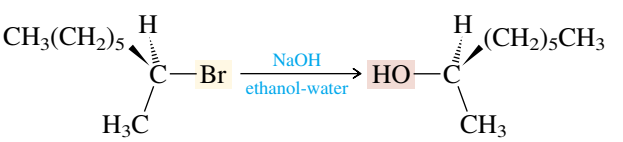
8.4 STEREOCHEMISTRY OF S_N2 REACTIONS

What is the structure of the transition state in an S_N2 reaction? In particular, what is the spatial arrangement of the nucleophile in relation to the leaving group as reactants pass through the transition state on their way to products?

Two stereochemical possibilities present themselves. In the pathway shown in Figure 8.1*a,* the nucleophile simply assumes the position occupied by the leaving group. It attacks the substrate at the same face from which the leaving group departs. This is called "front-side displacement," or substitution with **retention of configuration.**

In a second possibility, illustrated in Figure 8.1*b,* the nucleophile attacks the substrate from the side opposite the bond to the leaving group. This is called "back-side displacement," or substitution with **inversion of configuration.**

Which of these two opposite stereochemical possibilities operates was determined in experiments with optically active alkyl halides. In one such experiment, Hughes and Ingold determined that the reaction of 2-bromooctane with hydroxide ion gave 2-octanol having a configuration opposite that of the starting alkyl halide.



(*S*)-(+)-2-Bromooctane (*R*)-(−)-2-Octanol

Although the alkyl halide and alcohol given in this example have opposite configurations when they have opposite signs of rotation, it cannot be assumed that this will be true for all alkyl halide/alcohol pairs. (See Section 7.5)

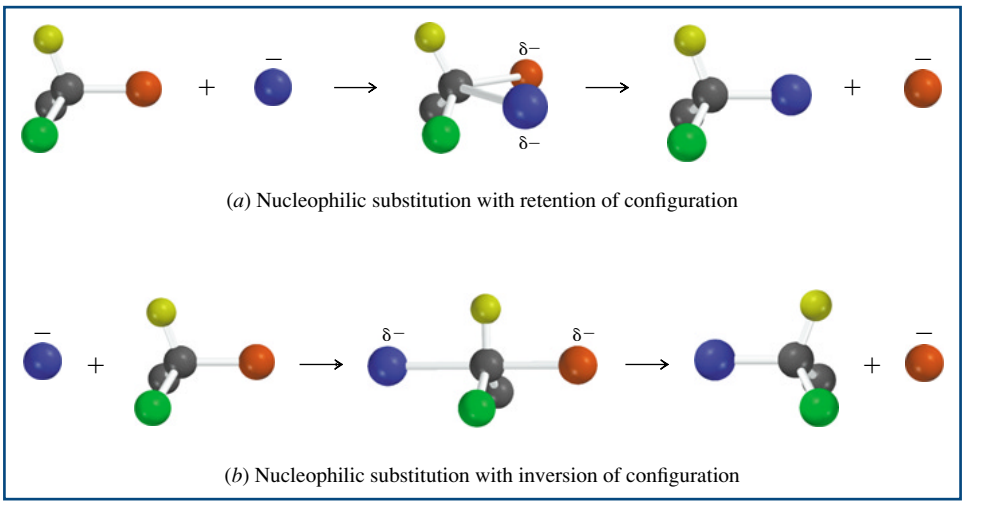
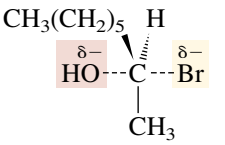


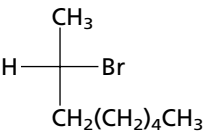
FIGURE 8.1 Two contrasting stereochemical pathways for substitution of a leaving group (red) by a nucleophile (blue). In (*a*) the nucleophile attacks carbon at the same side from which the leaving group departs. In (*b*) nucleophilic attack occurs at the side opposite the bond to the leaving group.

Nucleophilic substitution had occurred with inversion of configuration, consistent with the following transition state:



For a change of pace, try doing Problem 8.4 with molecular models instead of making structural drawings.

PROBLEM 8.4 The Fischer projection formula for (+)-2-bromooctane is shown. Write the Fischer projection of the (−)-2-octanol formed from it by nucleophilic substitution with inversion of configuration.



PROBLEM 8.5 Would you expect the 2-octanol formed by S_N2 hydrolysis of (−)-2-bromooctane to be optically active? If so, what will be its absolute configuration and sign of rotation? What about the 2-octanol formed by hydrolysis of racemic 2-bromooctane?

The first example of a stereoelectronic effect in this text concerned anti elimination in E2 reactions of alkyl halides (Section 5.16).

Numerous similar experiments have demonstrated the generality of this observation. Substitution by the S_N2 mechanism is stereospecific and proceeds with inversion of configuration at the carbon that bears the leaving group. *There is a stereoelectronic requirement for the nucleophile to approach carbon from the side opposite the bond to the leaving group.* Organic chemists often speak of this as a **Walden inversion,** after the German chemist Paul Walden, who described the earliest experiments in this area in the 1890s.

8.5 HOW S_N2 REACTIONS OCCUR

When we consider the overall reaction stereochemistry along with the kinetic data, a fairly complete picture of the bonding changes that take place during S_N2 reactions emerges. The potential energy diagram of Figure 8.2 for the hydrolysis of *(S)*-(+)-2-bromooctane is one that is consistent with the experimental observations.

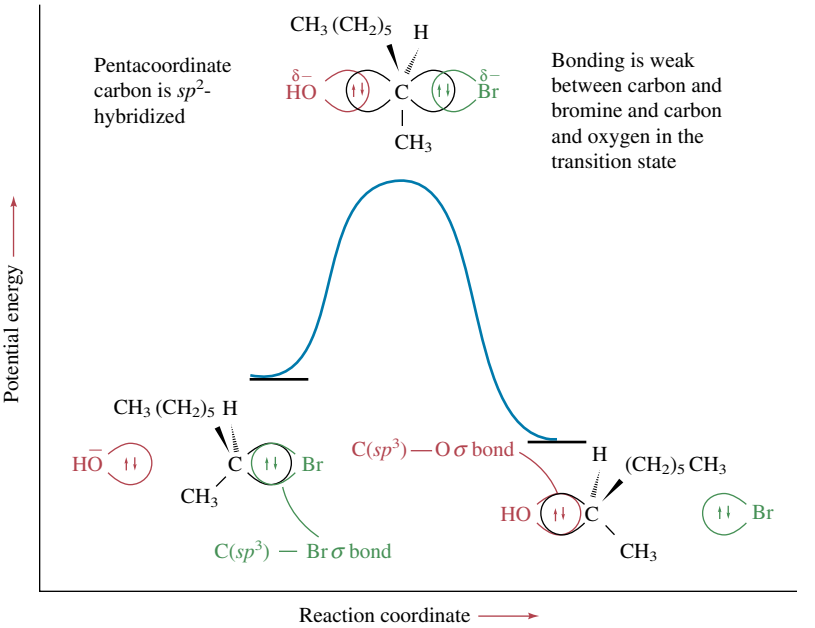


FIGURE 8.2 Hybrid orbital description of the bonding changes that take place at carbon during nucleophilic substitution by the S_N2 mechanism.

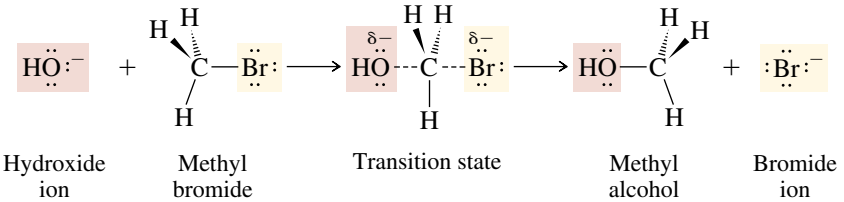
Hydroxide ion acts as a nucleophile, using an unshared electron pair to attack carbon from the side opposite the bond to the leaving group. The hybridization of the carbon at which substitution occurs changes from sp^3 in the alkyl halide to sp^2 in the transition state. Both the nucleophile (hydroxide) and the leaving group (bromide) are partially bonded to this carbon in the transition state. We say that the S_N2 transition state is *pentacoordinate;* carbon is fully bonded to three substituents and partially bonded to both the leaving group and the incoming nucleophile. The bonds to the nucleophile and the leaving group are relatively long and weak at the transition state.

Once past the transition state, the leaving group is expelled and carbon becomes tetracoordinate, its hybridization returning to sp^3.

During the passage of starting materials to products, three interdependent and synchronous changes take place:

1. Stretching, then breaking, of the bond to the leaving group
2. Formation of a bond to the nucleophile from the opposite side of the bond that is broken
3. Stereochemical inversion of the tetrahedral arrangement of bonds to the carbon at which substitution occurs

Although this mechanistic picture developed from experiments involving optically active alkyl halides, chemists speak even of methyl bromide as undergoing nucleophilic substitution with *inversion.* By this they mean that tetrahedral inversion of the bonds to carbon occurs as the reactant proceeds to the product.



For an animation of this S_N2 reaction, see *Learning By Modeling.*

We saw in Section 8.2 that the rate of nucleophilic substitution depends strongly on the leaving group—alkyl iodides are the most reactive, alkyl fluorides the least. In the next section, we'll see that the structure of the alkyl group can have an even greater effect.

8.6 STERIC EFFECTS IN S_N2 REACTIONS

There are very large differences in the rates at which the various kinds of alkyl halides—methyl, primary, secondary, or tertiary—undergo nucleophilic substitution. As Table 8.2 shows for the reaction of a series of alkyl bromides:

$$\underset{\text{Alkyl bromide}}{RBr} + \underset{\text{Lithium iodide}}{LiI} \xrightarrow{\text{acetone}} \underset{\text{Alkyl iodide}}{RI} + \underset{\text{Lithium bromide}}{LiBr}$$

the rates of nucleophilic substitution of a series of alkyl bromides differ by a factor of over 10^6 when comparing the most reactive member of the group (methyl bromide) and the least reactive member (*tert*-butyl bromide).

The large rate difference between methyl, ethyl, isopropyl, and *tert*-butyl bromides reflects the **steric hindrance** each offers to nucleophilic attack. The nucleophile must approach the alkyl halide from the side opposite the bond to the leaving group, and, as illustrated in Figure 8.3, this approach is hindered by alkyl substituents on the carbon that is being attacked. The three hydrogens of methyl bromide offer little resistance to approach of the nucleophile, and a rapid reaction occurs. Replacing one of the hydrogens by a methyl group somewhat shields the carbon from attack by the nucleophile and causes ethyl bromide to be less reactive than methyl bromide. Replacing all three hydrogen substituents by methyl groups almost completely blocks back-side approach to the tertiary carbon of $(CH_3)_3CBr$ and shuts down bimolecular nucleophilic substitution.

In general, S_N2 reactions exhibit the following dependence of rate on substrate structure:

Increasing rate of substitution by the S_N2 mechanism

R_3CX	<	R_2CHX	<	RCH_2X	<	CH_3X
Tertiary		Secondary		Primary		Methyl
Least reactive, most crowded						Most reactive, least crowded

TABLE 8.2 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N2 Mechanism*

Alkyl bromide	Structure	Class	Relative rate†
Methyl bromide	CH_3Br	Unsubstituted	221,000
Ethyl bromide	CH_3CH_2Br	Primary	1,350
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	1
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	Too small to measure

*Substitution of bromide by lithium iodide in acetone.
†Ratio of second-order rate constant k for indicated alkyl bromide to k for isopropyl bromide at 25°C.

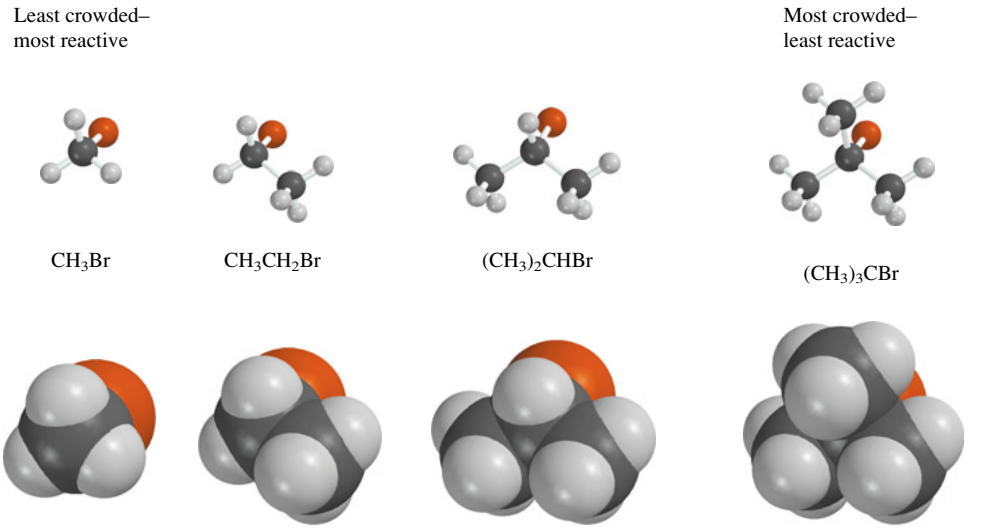
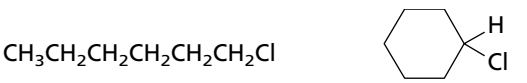


FIGURE 8.3 Ball-and-spoke and space-filling models of alkyl bromides, showing how substituents shield the carbon atom that bears the leaving group from attack by a nucleophile. The nucleophile must attack from the side opposite the bond to the leaving group.

PROBLEM 8.6 Identify the compound in each of the following pairs that reacts with sodium iodide in acetone at the faster rate:

(a) 1-Chlorohexane or cyclohexyl chloride
(b) 1-Bromopentane or 3-bromopentane
(c) 2-Chloropentane or 2-fluoropentane
(d) 2-Bromo-2-methylhexane or 2-bromo-5-methylhexane
(e) 2-Bromopropane or 1-bromodecane

SAMPLE SOLUTION (a) Compare the structures of the two chlorides. 1-Chlorohexane is a primary alkyl chloride; cyclohexyl chloride is secondary. Primary alkyl halides are less crowded at the site of substitution than secondary ones and react faster in substitution by the S_N2 mechanism. 1-Chlorohexane is more reactive.



1-Chlorohexane (primary, more reactive) — Cyclohexyl chloride (secondary, less reactive)

Alkyl groups at the carbon atom *adjacent* to the point of nucleophilic attack also decrease the rate of the S_N2 reaction. Compare the rates of nucleophilic substitution in the series of primary alkyl bromides shown in Table 8.3. Taking ethyl bromide as the standard and successively replacing its C-2 hydrogens by methyl groups, we see that each additional methyl group decreases the rate of displacement of bromide by iodide. The effect is slightly smaller than for alkyl groups that are attached directly to the carbon that bears the leaving group, but it is still substantial. When C-2 is completely substituted by methyl groups, as it is in neopentyl bromide [$(CH_3)_3CCH_2Br$], we see the unusual case of a primary alkyl halide that is practically inert to substitution by the S_N2 mechanism because of steric hindrance.

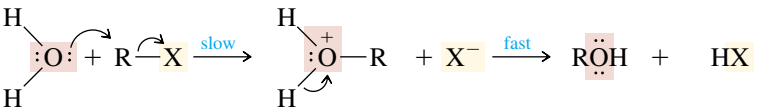
TABLE 8.3 Effect of Chain Branching on Reactivity of Primary Alkyl Bromides Toward Substitution Under S_N2 Conditions*

Alkyl bromide	Structure	Relative rate†
Ethyl bromide	CH_3CH_2Br	1.0
Propyl bromide	$CH_3CH_2CH_2Br$	0.8
Isobutyl bromide	$(CH_3)_2CHCH_2Br$	0.036
Neopentyl bromide	$(CH_3)_3CCH_2Br$	0.00002

*Substitution of bromide by lithium iodide in acetone.
†Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for ethyl bromide at 25°C.

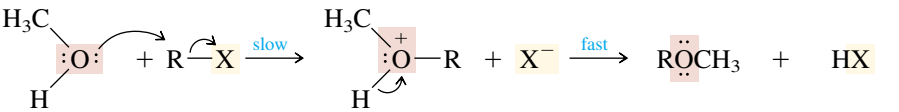
8.7 NUCLEOPHILES AND NUCLEOPHILICITY

The Lewis base that acts as the nucleophile often is, but need not always be, an anion. Neutral Lewis bases can also serve as nucleophiles. Common examples of substitutions involving neutral nucleophiles include *solvolysis* reactions. **Solvolysis** reactions are substitutions in which the nucleophile is the solvent in which the reaction is carried out. Solvolysis in *water* converts an alkyl halide to an *alcohol.*



Water — Alkyl halide — Alkyloxonium halide — Alcohol — Hydrogen halide

Solvolysis in *methyl alcohol* converts an alkyl halide to an *alkyl methyl ether.*



Methyl alcohol — Alkyl halide — Dialkyloxonium halide — Alkyl methyl ether — Hydrogen halide

In these and related solvolyses, the first stage is the one in which nucleophilic substitution takes place and is rate-determining. The proton-transfer step that follows it is much faster.

Since, as we have seen, the nucleophile attacks the substrate in the rate-determining step of the S_N2 mechanism, it follows that the rate at which substitution occurs may vary from nucleophile to nucleophile. Just as some alkyl halides are more reactive than others, some nucleophiles are more reactive than others. Nucleophilic strength, or **nucleophilicity,** is a measure of how fast a Lewis base displaces a leaving group from a suitable substrate. By measuring the rate at which various Lewis bases react with methyl iodide in methanol, a list of their nucleophilicities relative to methanol as the standard nucleophile has been compiled. It is presented in Table 8.4.

Neutral Lewis bases such as water, alcohols, and carboxylic acids are much weaker nucleophiles than their conjugate bases. When comparing species that have the same nucleophilic atom, a negatively charged nucleophile is more reactive than a neutral one.

TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

*Relative reactivity is k(nucleophile)/k(methanol) for typical S_N2 reactions and is approximate. Data pertain to methanol as the solvent.

RO^- (Alkoxide ion) is more nucleophilic than ROH (Alcohol)

RCO^- (Carboxylate ion) is more nucleophilic than RCOH (Carboxylic acid)

As long as the nucleophilic atom is the same, the more basic the nucleophile, the more reactive it is. An alkoxide ion (RO^-) is more basic and more nucleophilic than a carboxylate ion (RCO_2^-).

RO^- (Stronger base; Conjugate acid is ROH: $K_a = 10^{-16}$ ($pK_a = 16$)) is more nucleophilic than RCO^- (Weaker base; Conjugate acid is RCO_2H: $K_a = 10^{-5}$ ($pK_a = 5$))

The connection between basicity and nucleophilicity holds when comparing atoms in the *same row* of the periodic table. Thus, HO^- is more basic and more nucleophilic than F^-, and H_3N is more basic and more nucleophilic than H_2O. *It does not hold when proceeding down a column in the periodic table.* For example, I^- is the least basic of the halide ions but is the most nucleophilic. F^- is the most basic halide ion but the least nucleophilic. The factor that seems most responsible for the inverse relationship between basicity and nucleophilicity among the halide ions is the degree to which they are *solvated* by hydrogen bonds of the type illustrated in Figure 8.4. Smaller anions, because of their high charge-to-size ratio, are more strongly solvated than larger ones. In order to act as a nucleophile, the halide must shed some of the solvent molecules that surround it. Among the halide anions, F^- forms the strongest hydrogen bonds to water and alcohols, and I^- the weakest. Thus, the nucleophilicity of F^- is suppressed more than that of Cl^-, Cl^- more than Br^-, and Br^- more than I^-. Similarly, HO^- is smaller, more solvated, and less nucleophilic than HS^-.

Nucleophilicity is also related to polarizability, or the ease of distortion of the electron "cloud" surrounding the nucleophile. The partial bond between the nucleophile and the alkyl halide that characterizes the S_N2 transition state is more fully developed at a longer distance when the nucleophile is very polarizable than when it is not. An increased degree of bonding to the nucleophile lowers the energy of the transition state and

A descriptive term applied to a highly polarizable species is *soft*. Iodide is a very soft nucleophile. Conversely, fluoride ion is not very polarizable and is said to be a *hard* nucleophile.

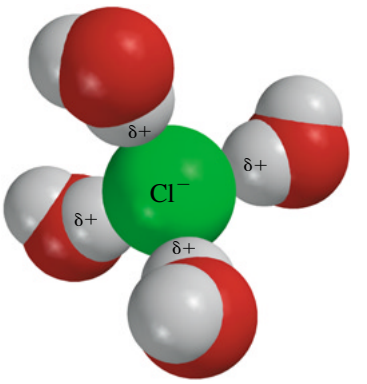


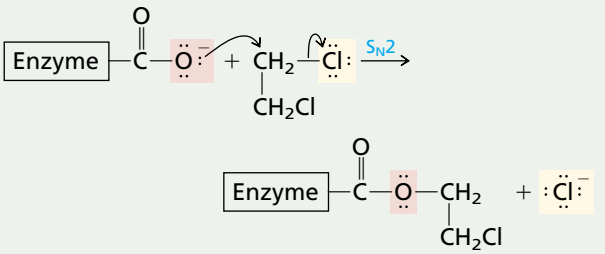
FIGURE 8.4 Solvation of a chloride by ion–dipole attractive forces with water. The negatively charged chloride ion interacts with the positively polarized hydrogens of water.

AN ENZYME-CATALYZED NUCLEOPHILIC SUBSTITUTION OF AN ALKYL HALIDE

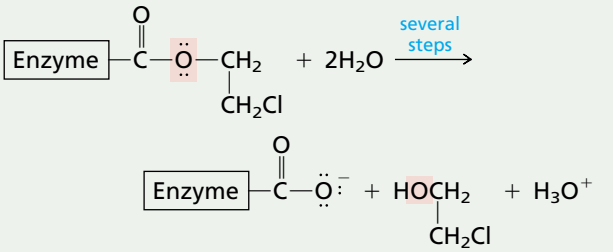
Nucleophilic substitution is one of a variety of mechanisms by which living systems detoxify halogenated organic compounds introduced into the environment. Enzymes that catalyze these reactions are known as *haloalkane dehalogenases.* The hydrolysis of 1,2-dichloroethane to 2-chloroethanol, for example, is a biological nucleophilic substitution catalyzed by a dehalogenase.

$$\underset{\text{1,2-Dichloroethane}}{ClCH_2CH_2Cl} + \underset{\text{Water}}{2H_2O} \xrightarrow[\text{enzyme}]{\text{dehalogenase}} \underset{\text{2-Chloroethanol}}{ClCH_2CH_2OH} + \underset{\text{Hydronium ion}}{H_3O^+} + \underset{\text{Chloride ion}}{Cl^-}$$

The haloalkane dehydrogenase is believed to act by using one of its side-chain carboxylates to displace chloride by an S_N2 mechanism. (Recall the reaction of carboxylate ions with alkyl halides from Table 8.1.)



The product of this nucleophilic substitution then reacts with water, restoring the enzyme to its original state and giving the observed products of the reaction.



This stage of the reaction proceeds by a mechanism that will be discussed in Chapter 20. Both stages are faster than the reaction of 1,2-dichloroethane with water in the absence of the enzyme.

Some of the most common biological S_N2 reactions involve attack at methyl groups, especially a methyl group of *S-adenosylmethionine.* Examples of these will be given in Chapter 16.

increases the rate of substitution. Among related atoms, polarizability increases with increasing size. Thus iodide is the most polarizable and most nucleophilic halide ion, fluoride the least.

PROBLEM 8.7 Sodium nitrite ($NaNO_2$) reacted with 2-iodooctane to give a mixture of two constitutionally isomeric compounds of molecular formula $C_8H_{17}NO_2$ in a combined yield of 88%. Suggest reasonable structures for these two isomers.

8.8 THE S_N1 MECHANISM OF NUCLEOPHILIC SUBSTITUTION

Having just learned that tertiary alkyl halides are practically inert to substitution by the S_N2 mechanism because of steric hindrance, we might wonder whether they undergo nucleophilic substitution at all. We'll see in this section that they do, but by a mechanism different from S_N2.

Hughes and Ingold observed that the hydrolysis of *tert*-butyl bromide, which occurs readily, is characterized by a *first-order* rate law:

$$\underset{\text{tert-Butyl bromide}}{(CH_3)_3CBr} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\text{tert-Butyl alcohol}}{(CH_3)_3COH} + \underset{\text{Hydrogen bromide}}{HBr}$$

$$\text{Rate} = k[(CH_3)_3CBr]$$

They found that the rate of hydrolysis depends only on the concentration of *tert*-butyl bromide. Adding the stronger nucleophile hydroxide ion, moreover, causes no change in the rate of substitution, nor does this rate depend on the concentration of hydroxide. Just as second-order kinetics was interpreted as indicating a bimolecular rate-determining step, first-order kinetics was interpreted as evidence for a *unimolecular* rate-determining step—a step that involves only the alkyl halide.

The proposed mechanism is outlined in Figure 8.5 and is called S_N1, standing for **substitution nucleophilic unimolecular.** The first step, a unimolecular dissociation of the alkyl halide to form a carbocation as the key intermediate, is rate-determining. An energy diagram for the process is shown in Figure 8.6.

The S_N1 mechanism was earlier introduced in Section 4.11.

PROBLEM 8.8 Suggest a structure for the product of nucleophilic substitution obtained on solvolysis of *tert*-butyl bromide in methanol, and outline a reasonable mechanism for its formation.

The S_N1 mechanism is an *ionization* mechanism. The nucleophile does not participate until after the rate-determining step has taken place. Thus, the effects of nucleophile and alkyl halide structure are expected to be different from those observed for reactions proceeding by the S_N2 pathway. How the structure of the alkyl halide affects the rate of S_N1 reactions is the topic of the next section.

8.9 CARBOCATION STABILITY AND S_N1 REACTION RATES

In order to compare S_N1 substitution rates in a range of alkyl halides, experimental conditions are chosen in which competing substitution by the S_N2 route is very slow. One such set of conditions is solvolysis in aqueous formic acid (HCO_2H):

$$\underset{\text{Alkyl halide}}{RX} + \underset{\text{Water}}{H_2O} \xrightarrow[\text{acid}]{\text{formic}} \underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX}$$

FIGURE 8.5 The S_N1 mechanism for hydrolysis of *tert*-butyl bromide.

The Overall Reaction:

$$(CH_3)_3CBr + 2H_2O \longrightarrow (CH_3)_3COH + H_3O^+ + Br^-$$

tert-Butyl bromide; Water; *tert*-Butyl alcohol; Hydronium ion; Bromide ion

Step 1: The alkyl halide dissociates to a carbocation and a halide ion.

$$(CH_3)_3C{-}\ddot{Br}: \xrightarrow{\text{slow}} (CH_3)_3C^+ + :\ddot{Br}:^-$$

tert-Butyl bromide; *tert*-Butyl cation; Bromide ion

Step 2: The carbocation formed in step 1 reacts rapidly with a water molecule. Water is a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an alkyloxonium ion.

$$(CH_3)_3C^+ + :O(H)H \xrightarrow{\text{fast}} (CH_3)_3C{-}\overset{+}{O}(H)H$$

tert-Butyl cation; Water; *tert*-Butyloxonium ion

Step 3: This step is a fast acid-base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the alkyloxonium ion to give the observed product of the reaction, *tert*-butyl alcohol.

$$(CH_3)_3C{-}\overset{+}{O}(H)H + :O(H)H \xrightarrow{\text{fast}} (CH_3)_3C{-}\ddot{O}H + H{-}\overset{+}{O}(H)H$$

tert-Butyloxonium ion; Water; *tert*-Butyl alcohol; Hydronium ion

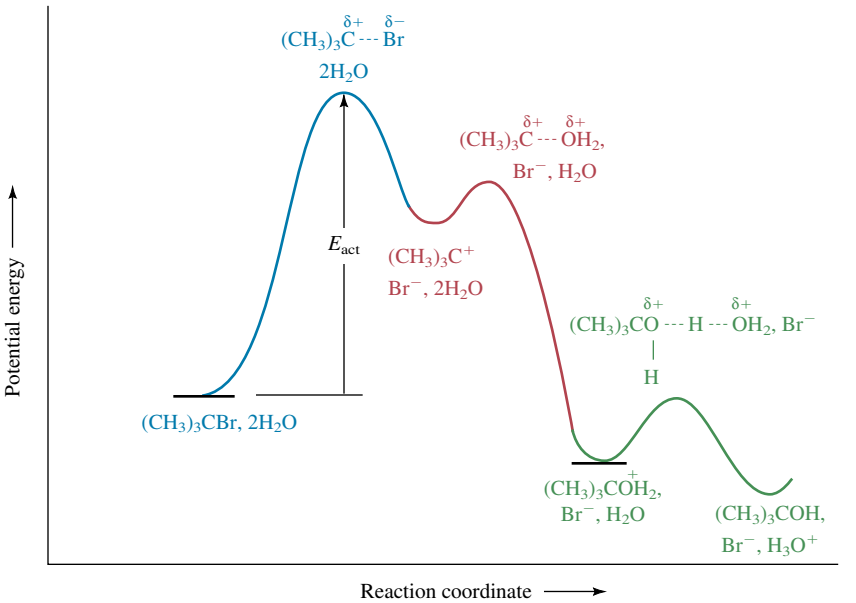


FIGURE 8.6 Energy diagram illustrating the S_N1 mechanism for hydrolysis of *tert*-butyl bromide.

Neither formic acid nor water is very nucleophilic, and so S_N2 substitution is suppressed. The relative rates of hydrolysis of a group of alkyl bromides under these conditions are presented in Table 8.5.

The relative rate order in S_N1 reactions is exactly the opposite of that seen in S_N2 reactions:

S_N1 reactivity: methyl < primary < secondary < tertiary
S_N2 reactivity: tertiary < secondary < primary < methyl

Clearly, the steric crowding that influences reaction rates in S_N2 processes plays no role in S_N1 reactions. The order of alkyl halide reactivity in S_N1 reactions is the same as the order of carbocation stability: the more stable the carbocation, the more reactive the alkyl halide. We have seen this situation before in the reaction of alcohols with hydrogen halides (Section 4.12), in the acid-catalyzed dehydration of alcohols (Section 5.9), and in the conversion of alkyl halides to alkenes by the E1 mechanism (Section 5.17). As in these other reactions, an electronic effect, specifically, the stabilization of the carbocation intermediate by alkyl substituents, is the decisive factor.

PROBLEM 8.9 Identify the compound in each of the following pairs that reacts at the faster rate in an S_N1 reaction:

(a) Isopropyl bromide or isobutyl bromide
(b) Cyclopentyl iodide or 1-methylcyclopentyl iodide
(c) Cyclopentyl bromide or 1-bromo-2,2-dimethylpropane
(d) *tert*-Butyl chloride or *tert*-butyl iodide

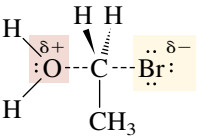
SAMPLE SOLUTION (a) Isopropyl bromide, $(CH_3)_2CHBr$, is a secondary alkyl halide, whereas isobutyl bromide, $(CH_3)_2CHCH_2Br$, is primary. Since the rate-determining step in an S_N1 reaction is carbocation formation and since secondary carbocations are more stable than primary carbocations, isopropyl bromide is more reactive than isobutyl bromide in nucleophilic substitution by the S_N1 mechanism.

Primary carbocations are so high in energy that their intermediacy in nucleophilic substitution reactions is unlikely. When ethyl bromide undergoes hydrolysis in aqueous formic acid, substitution probably takes place by a direct displacement of bromide by water in an S_N2-like process.

TABLE 8.5 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N1 Mechanism*

Alkyl bromide	Structure	Class	Relative rate†
Methyl bromide	CH_3Br	Unsubstituted	1
Ethyl bromide	CH_3CH_2Br	Primary	2
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	43
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	100,000,000

*Solvolysis in aqueous formic acid.
†Ratio of rate constant *k* for indicated alkyl bromide to *k* for methyl bromide at 25°C.

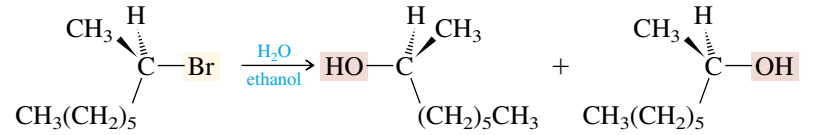


Bimolecular transition state
for hydrolysis of ethyl bromide

8.10 STEREOCHEMISTRY OF S_N1 REACTIONS

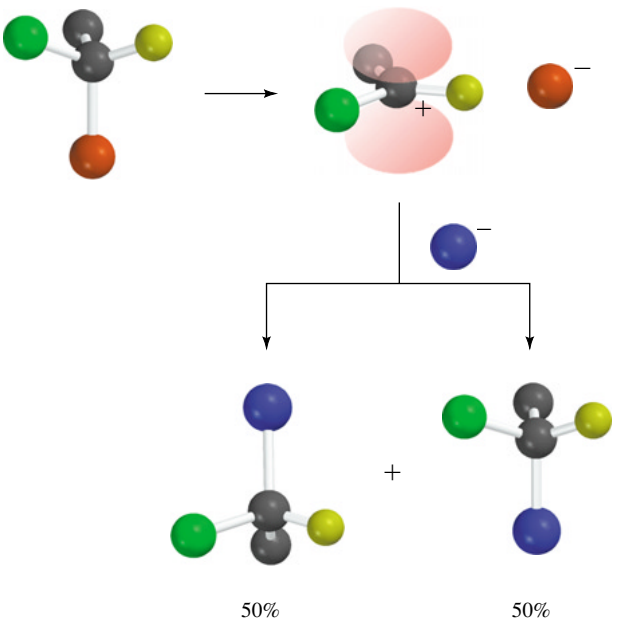
Although S_N2 reactions are stereospecific and proceed with inversion of configuration at carbon, the situation is not as clear-cut for S_N1 reactions. When the leaving group is attached to the stereogenic center of an optically active halide, ionization gives a carbocation intermediate that is achiral. It is achiral because the three bonds to the positively charged carbon lie in the same plane, and this plane is a plane of symmetry for the carbocation. As shown in Figure 8.7, such a carbocation should react with a nucleophile at the same rate at either of its two faces. We expect the product of substitution by the S_N1 mechanism to be racemic and optically inactive. This outcome is rarely observed in practice, however. Normally, the product is formed with predominant, but not complete, inversion of configuration.

For example, the hydrolysis of optically active 2-bromooctane in the absence of added base follows a first-order rate law, but the resulting 2-octanol is formed with 66% inversion of configuration.



(*R*)-(−)-2-Bromooctane (*S*)-(+)-2-Octanol (*R*)-(−)-2-Octanol

66% net inversion corresponds
to 83% *S*, 17% *R*



50% 50%

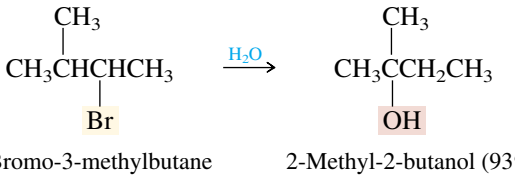
FIGURE 8.7 Formation of a racemic product by nucleophilic substitution via a carbocation intermediate.

Partial but not complete loss of optical activity in S_N1 reactions probably results from the carbocation not being completely "free" when it is attacked by the nucleophile. Ionization of the alkyl halide gives a carbocation–halide ion pair, as depicted in Figure 8.8. The halide ion shields one side of the carbocation, and the nucleophile captures the carbocation faster from the opposite side. More product of inverted configuration is formed than product of retained configuration. In spite of the observation that the products of S_N1 reactions are only partially racemic, the fact that these reactions are not stereospecific is more consistent with a carbocation intermediate than a concerted bimolecular mechanism.

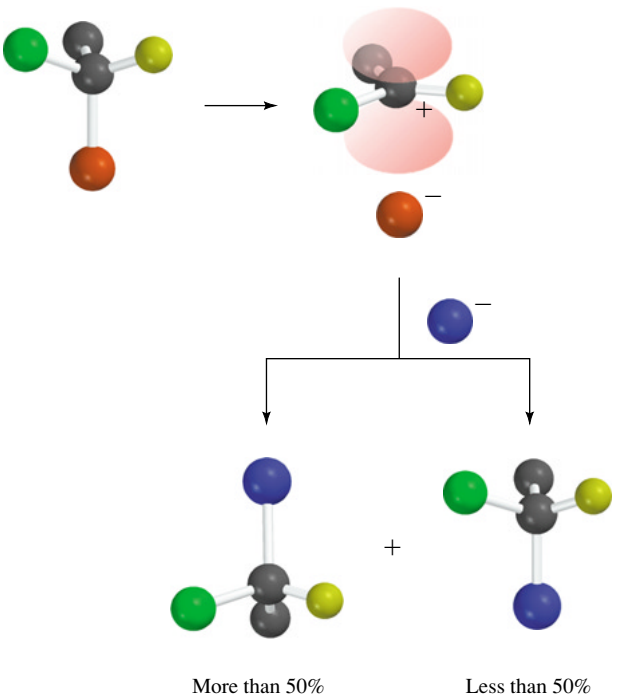
PROBLEM 8.10 What two stereoisomeric substitution products would you expect to isolate from the hydrolysis of *cis*-1,4-dimethylcyclohexyl bromide? From hydrolysis of *trans*-1,4-dimethylcyclohexyl bromide?

8.11 CARBOCATION REARRANGEMENTS IN S_N1 REACTIONS

Additional evidence for carbocation intermediates in certain nucleophilic substitutions comes from observing rearrangements of the kind normally associated with such species. For example, hydrolysis of the secondary alkyl bromide 2-bromo-3-methylbutane yields the rearranged tertiary alcohol 2-methyl-2-butanol as the only substitution product.



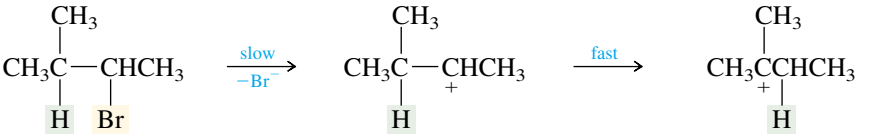
2-Bromo-3-methylbutane 2-Methyl-2-butanol (93%)



More than 50% Less than 50%

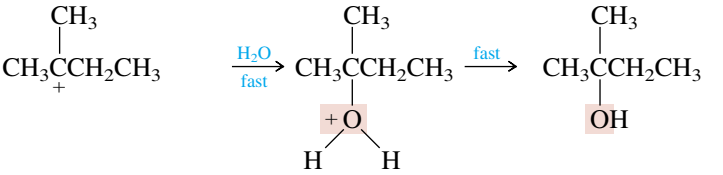
FIGURE 8.8 Inversion of configuration predominates in S_N1 reactions because one face of the carbocation is shielded by the leaving group (red).

A reasonable mechanism for this observation assumes rate-determining ionization of the substrate as the first step followed by a hydride shift that converts the secondary carbocation to a more stable tertiary one.



2-Bromo-3-methylbutane | 1,2-Dimethylpropyl cation (a secondary carbocation) | 1,1-Dimethylpropyl cation (a tertiary carbocation)

The tertiary carbocation then reacts with water to yield the observed product.



1,1-Dimethylpropyl cation | 2-Methyl-2-butanol

PROBLEM 8.11 Why does the carbocation intermediate in the hydrolysis of 2-bromo-3-methylbutane rearrange by way of a hydride shift rather than a methyl shift?

Rearrangements, when they do occur, are taken as evidence for carbocation intermediates and point to the S_N1 mechanism as the reaction pathway. Rearrangements are never observed in S_N2 reactions.

8.12 EFFECT OF SOLVENT ON THE RATE OF NUCLEOPHILIC SUBSTITUTION

The major effect of the solvent is on the *rate* of nucleophilic substitution, not on what the products are. Thus we need to consider two related questions:

1. What properties of the *solvent* influence the rate most?
2. How does the rate-determining step of the *mechanism* respond to this property of the solvent?

Because the S_N1 and S_N2 mechanisms are so different from each other, let's examine each one separately.

Solvent Effects on the Rate of Substitution by the S_N1 Mechanism. Table 8.6 lists the relative rate of solvolysis of *tert*-butyl chloride in several media in order of increasing **dielectric constant** (ϵ). Dielectric constant is a measure of the ability of a material, in this case the solvent, to moderate the force of attraction between oppositely charged particles compared with that of a standard. The standard dielectric is a vacuum, which is assigned a value ϵ of exactly 1. The higher the dielectric constant ϵ, the better the medium is able to support separated positively and negatively charged species. Solvents with high dielectric constants are classified as *polar solvents.* As Table 8.6 illustrates, the rate of solvolysis of *tert*-butyl chloride (which is equal to its rate of ionization) increases dramatically as the dielectric constant of the solvent increases.

TABLE 8.6 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	Dielectric constant ϵ	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

*Ratio of first-order rate constant for solvolysis in indicated solvent to that for solvolysis in acetic acid at 25°C.

According to the S_N1 mechanism, a molecule of an alkyl halide ionizes to a positively charged carbocation and a negatively charged halide ion in the rate-determining step. As the alkyl halide approaches the transition state for this step, a partial positive charge develops on carbon and a partial negative charge on the halogen. Figure 8.9 contrasts the behavior of a nonpolar and a polar solvent on the energy of the transition state. Polar and nonpolar solvents are similar in their interaction with the starting alkyl halide, but differ markedly in how they affect the transition state. A solvent with a low dielectric constant has little effect on the energy of the transition state, whereas one with a high dielectric constant stabilizes the charge-separated transition state, lowers the activation energy, and increases the rate of reaction.

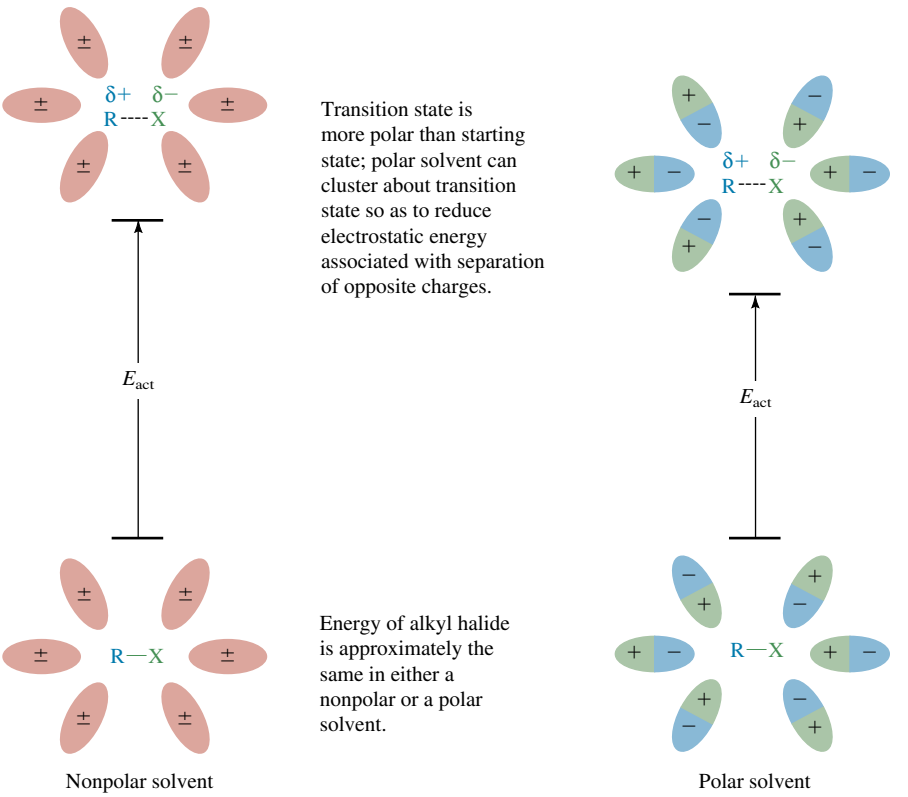


FIGURE 8.9 A polar solvent stabilizes the transition state of an S_N1 reaction and increases its rate.

Solvent Effects on the Rate of Substitution by the S_N2 Mechanism. Polar solvents are required in typical bimolecular substitutions because ionic substances, such as the sodium and potassium salts cited earlier in Table 8.1, are not sufficiently soluble in nonpolar solvents to give a high enough concentration of the nucleophile to allow the reaction to occur at a rapid rate. Other than the requirement that the solvent be polar enough to dissolve ionic compounds, however, the effect of solvent polarity on the rate of S_N2 reactions is small. What is most important is whether or not the polar solvent is **protic** or **aprotic.**

Water (HOH), alcohols (ROH), and carboxylic acids (RCO_2H) are classified as *polar protic solvents;* they all have OH groups that allow them to form hydrogen bonds to anionic nucleophiles as shown in Figure 8.10. Solvation forces such as these stabilize the anion and suppress its nucleophilicity. *Aprotic solvents,* on the other hand, lack OH groups and do not solvate anions very strongly, leaving them much more able to express their nucleophilic character. Table 8.7 compares the second-order rate constants k for S_N2 substitution of 1-bromobutane by azide ion (a good nucleophile) in some common polar aprotic solvents with the corresponding k's for the much slower reactions observed in the polar protic solvents methanol and water.

$$\underset{\text{1-Bromobutane}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{Azide ion}}{N_3^-} \longrightarrow \underset{\text{1-Azidobutane}}{CH_3CH_2CH_2CH_2N_3} + \underset{\text{Bromide ion}}{Br^-}$$

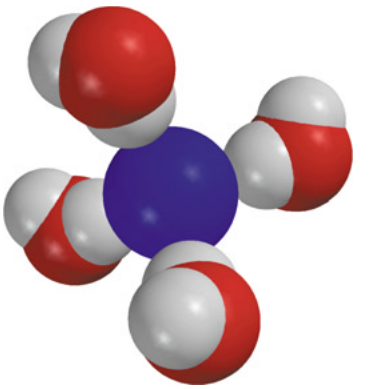


FIGURE 8.10 Hydrogen bonding of the solvent to the nucleophile stabilizes the nucleophile and makes it less reactive.

TABLE 8.7 Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(CH_3)_2S{=}O$	48.9	Polar aprotic	1300
N,N-Dimethylformamide	$(CH_3)_2NCH{=}O$	36.7	Polar aprotic	2800
Acetonitrile	$CH_3C{\equiv}N$	37.5	Polar aprotic	5000

*Ratio of second-order rate constant for substitution in indicated solvent to that for substitution in methanol at 25°C.

The large rate enhancements observed for bimolecular nucleophilic substitutions in polar aprotic solvents are used to advantage in synthetic applications. An example can be seen in the preparation of alkyl cyanides (nitriles) by the reaction of sodium cyanide with alkyl halides:

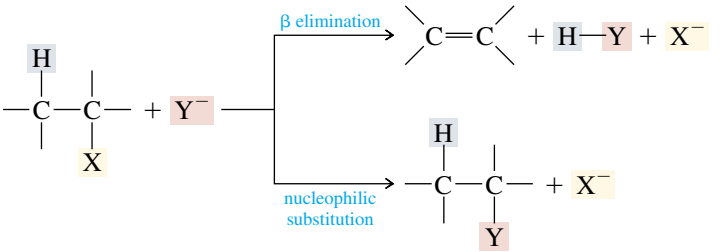
$$\underset{\text{Hexyl halide}}{CH_3(CH_2)_4CH_2X} + \underset{\text{Sodium cyanide}}{NaCN} \longrightarrow \underset{\text{Hexyl cyanide}}{CH_3(CH_2)_4CH_2CN} + \underset{\text{Sodium halide}}{NaX}$$

When the reaction was carried out in aqueous methanol as the solvent, hexyl bromide was converted to hexyl cyanide in 71% yield by heating with sodium cyanide. Although this is a perfectly acceptable synthetic reaction, a period of over *20 hours* was required. Changing the solvent to dimethyl sulfoxide brought about an increase in the reaction rate sufficient to allow the less reactive substrate hexyl chloride to be used instead, and the reaction was complete (91% yield) in only *20 minutes.*

The *rate* at which reactions occur can be important in the laboratory, and understanding how solvents affect rate is of practical value. As we proceed through the text, however, and see how nucleophilic substitution is applied to a variety of functional group transformations, be aware that it is the nature of the substrate and the nucleophile that, more than anything else, determines what *product* is formed.

8.13 SUBSTITUTION AND ELIMINATION AS COMPETING REACTIONS

We have seen that an alkyl halide and a Lewis base can react together in either a substitution or an elimination reaction.



Substitution can take place by the S_N1 or the S_N2 mechanism, elimination by E1 or E2.

How can we predict whether substitution or elimination will be the principal reaction observed with a particular combination of reactants? The two most important factors are the *structure of the alkyl halide* and the *basicity of the anion.* It is useful to approach the question from the premise that the characteristic reaction of alkyl halides with Lewis bases is *elimination,* and that substitution predominates only under certain special circumstances. In a typical reaction, a typical secondary alkyl halide such as isopropyl bromide reacts with a typical nucleophile such as sodium ethoxide mainly by elimination:

$$\underset{\text{Isopropyl bromide}}{CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3} \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} \underset{\text{Propene (87\%)}}{CH_3CH{=}CH_2} + \underset{\text{Ethyl isopropyl ether (13\%)}}{CH_3\underset{\displaystyle OCH_2CH_3}{\underset{|}{C}}HCH_3}$$

Figure 8.11 illustrates the close relationship between the E2 and S_N2 pathways for this case, and the results cited in the preceding equation clearly show that E2 is faster than S_N2 when the alkyl halide is secondary and the nucleophile is a strong base.

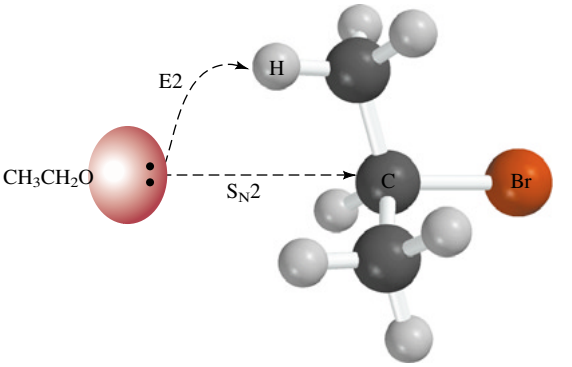


FIGURE 8.11 When a Lewis base reacts with an alkyl halide, either substitution or elimination can occur. Substitution (S_N2) occurs when the nucleophile attacks carbon to displace bromide. Elimination occurs when the Lewis base abstracts a proton from the β carbon. The alkyl halide shown is isopropyl bromide. The carbon atom that bears the leaving group is somewhat sterically hindered, and elimination (E2) predominates over substitution with alkoxide bases.

As crowding at the carbon that bears the leaving group decreases, the rate of nucleophilic attack by the Lewis base increases. A low level of steric hindrance to approach of the nucleophile is one of the special circumstances that permit substitution to predominate, and primary alkyl halides react with alkoxide bases by an S_N2 mechanism in preference to E2:

$$\underset{\text{Propyl bromide}}{CH_3CH_2CH_2Br} \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} \underset{\text{Propene (9\%)}}{CH_3CH{=}CH_2} + \underset{\text{Ethyl propyl ether (91\%)}}{CH_3CH_2CH_2OCH_2CH_3}$$

If, however, the base itself is a crowded one, such as potassium *tert*-butoxide, even primary alkyl halides undergo elimination rather than substitution:

$$\underset{\text{1-Bromooctadecane}}{CH_3(CH_2)_{15}CH_2CH_2Br} \xrightarrow[(CH_3)_3COH,\ 40°C]{KOC(CH_3)_3} \underset{\text{1-Octadecene (87\%)}}{CH_3(CH_2)_{15}CH{=}CH_2} + \underset{\textit{tert}\text{-Butyl octadecyl ether (13\%)}}{CH_3(CH_2)_{15}CH_2CH_2OC(CH_3)_3}$$

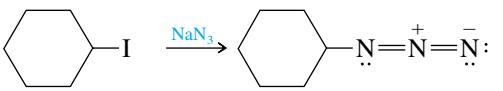
A second factor that can tip the balance in favor of substitution is weak basicity of the nucleophile. Nucleophiles that are less basic than hydroxide react with both primary and secondary alkyl halides to give the product of nucleophilic substitution in high yield. To illustrate, cyanide ion is much less basic than hydroxide and reacts with 2-chlorooctane to give the corresponding alkyl cyanide as the major product.

Cyanide is a weaker base than hydroxide because its conjugate acid HCN (pK_a 9.1) is a stronger acid than water (pK_a15.7).

$$\underset{\text{2-Chlorooctane}}{CH_3\underset{\displaystyle Cl}{\underset{|}{C}}H(CH_2)_5CH_3} \xrightarrow[DMSO]{KCN} \underset{\text{2-Cyanooctane (70\%)}}{CH_3\underset{\displaystyle CN}{\underset{|}{C}}H(CH_2)_5CH_3}$$

The conjugate acid of azide ion is called *hydrazoic acid* (HN_3). It has a pK_a of 4.6, and so is similar to acetic acid in its acidity.

Azide ion ($:\ddot{\underset{\cdot\cdot}{N}}{=}\overset{+}{N}{=}\ddot{\underset{\cdot\cdot}{N}}:^-$) is a good nucleophile and an even weaker base than cyanide. It reacts with secondary alkyl halides mainly by substitution:

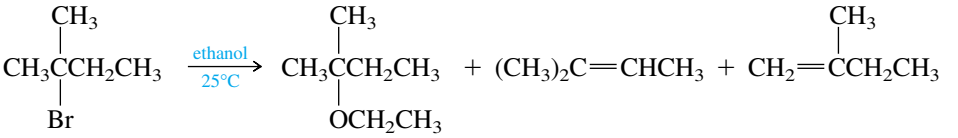


Cyclohexyl iodide Cyclohexyl azide (75%)

Hydrogen sulfide ion HS^-, and anions of the type RS^-, are substantially less basic than hydroxide ion and react with both primary and secondary alkyl halides to give mainly substitution products.

Hydrogen sulfide (pK_a 7.0) is a stronger acid than water (pK_a 15.7). Therefore HS^- is a much weaker base than HO^-.

Tertiary alkyl halides are so sterically hindered to nucleophilic attack that the presence of any anionic Lewis base favors elimination. Usually substitution predominates over elimination in tertiary alkyl halides only when anionic Lewis bases are absent. In the solvolysis of the tertiary bromide 2-bromo-2-methylbutane, for example, the ratio of substitution to elimination is 64:36 in pure ethanol but falls to 1:99 in the presence of 2 M sodium ethoxide.



2-Bromo-2-methylbutane

2-Ethoxy-2-methylbutane (Major product in absence of sodium ethoxide)

2-Methyl-2-butene

2-Methyl-1-butene

(Alkene mixture is major product in presence of sodium ethoxide)

PROBLEM 8.12 Predict the major organic product of each of the following reactions:

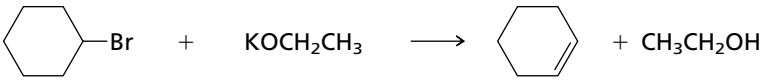
(a) Cyclohexyl bromide and potassium ethoxide

(b) Ethyl bromide and potassium cyclohexanolate

(c) *sec*-Butyl bromide solvolysis in methanol

(d) *sec*-Butyl bromide solvolysis in methanol containing 2 M sodium methoxide

SAMPLE SOLUTION (a) Cyclohexyl bromide is a secondary halide and reacts with alkoxide bases by elimination rather than substitution. The major organic products are cyclohexene and ethanol.



Cyclohexyl bromide Potassium ethoxide Cyclohexene Ethanol

Regardless of the alkyl halide, raising the temperature causes both the rate of substitution and the rate of elimination to increase. The rate of elimination, however, usually increases faster than the rate of substitution, so that at higher temperatures the proportion of elimination products increases at the expense of substitution products.

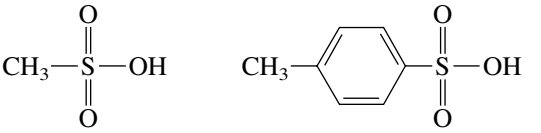
As a practical matter, elimination can always be made to occur quantitatively. Strong bases, especially bulky ones such as *tert*-butoxide ion, react even with primary alkyl halides by an E2 process at elevated temperatures. The more difficult task is to find the set of conditions that promote substitution. In general, the best approach is to choose conditions that favor the S_N2 mechanism—an unhindered substrate, a good nucleophile that is not strongly basic, and the lowest practical temperature consistent with reasonable reaction rates.

Functional group transformations that rely on substitution by the S_N1 mechanism are not as generally applicable as those of the S_N2 type. Hindered substrates are prone to elimination, and there is the possibility of rearrangement when carbocation intermediates are involved. Only in cases in which elimination is impossible are S_N1 reactions used for functional group transformations.

8.14 SULFONATE ESTERS AS SUBSTRATES IN NUCLEOPHILIC SUBSTITUTION

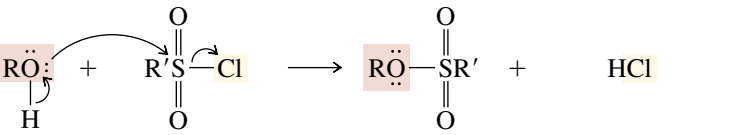
Two kinds of starting materials have been examined in nucleophilic substitution reactions to this point. In Chapter 4 we saw alcohols can be converted to alkyl halides by reaction with hydrogen halides and pointed out that this process is a nucleophilic substitution taking place on the protonated form of the alcohol, with water serving as the leaving group. In the present chapter the substrates have been alkyl halides, and halide ions have been the leaving groups. A few other classes of organic compounds undergo nucleophilic substitution reactions analogous to those of alkyl halides, the most important of these being alkyl esters of sulfonic acids.

Sulfonic acids such as methanesulfonic acid and *p*-toluenesulfonic acid are strong acids, comparable in acidity with sulfuric acid.



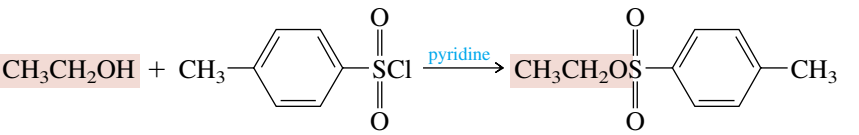
Methanesulfonic acid *p*-Toluenesulfonic acid

Alkyl sulfonates are derivatives of sulfonic acids in which the proton of the hydroxyl group is replaced by an alkyl group. They are prepared by treating an alcohol with the appropriate sulfonyl chloride.



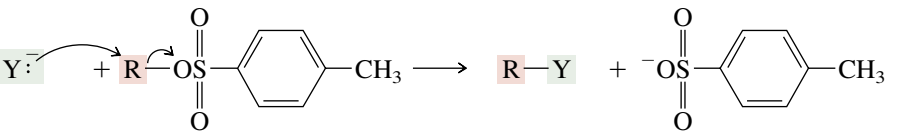
Alcohol Sulfonyl chloride Sulfonate ester Hydrogen chloride

These reactions are usually carried out in the presence of pyridine.



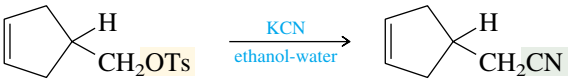
Ethanol *p*-Toluenesulfonyl chloride Ethyl *p*-toluenesulfonate (72%)

Alkyl sulfonate esters resemble alkyl halides in their ability to undergo elimination and nucleophilic substitution.



Nucleophile *p*-Toluenesulfonate ester Product of nucleophilic substitution *p*-Toluenesulfonate anion

The sulfonate esters used most frequently are the *p*-toluenesulfonates. They are commonly known as *tosylates* and given the abbreviated formula ROTs.



(3-Cyclopentenyl)methyl *p*-toluenesulfonate

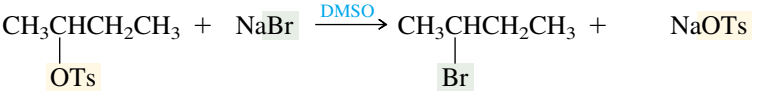
4-(Cyanomethyl)cyclopentene (86%)

p-Toluenesulfonate (TsO^-) is a very good leaving group. As Table 8.8 reveals, alkyl *p*-toluenesulfonates undergo nucleophilic substitution at rates that are even faster than those of alkyl iodides. A correlation of leaving-group abilities with carbon–halogen bond strengths was noted earlier, in Section 8.2. Note also the correlation with the basicity of the leaving group. Iodide is the weakest base among the halide anions and is the best leaving group, fluoride the strongest base and the poorest leaving group. A similar correlation with basicity is seen among oxygen-containing leaving groups. The weaker the base, the better the leaving group. Trifluoromethanesulfonic acid (CF_3SO_2OH) is a much stronger acid than *p*-toluenesulfonic acid, and therefore trifluoromethanesulfonate is a much weaker base than *p*-toluenesulfonate and a much better leaving group.

Trifluoromethanesulfonate esters are called *triflates*.

Notice too that strongly basic leaving groups are absent from Table 8.8. In general, any species that has a K_a less than 1 for its conjugate acid cannot be a leaving group in a nucleophilic substitution. Thus, hydroxide (HO^-) is far too strong a base to be displaced from an alcohol (ROH), and alcohols do not undergo nucleophilic substitution. In strongly acidic media, alcohols are protonated to give alkyloxonium ions, and these do undergo nucleophilic substitution, because the leaving group is a weakly basic water molecule.

Since halides are poorer leaving groups than *p*-toluenesulfonate, alkyl *p*-toluenesulfonates can be converted to alkyl halides by S_N2 reactions involving chloride, bromide, or iodide as the nucleophile.



sec-Butyl *p*-toluenesulfonate | Sodium bromide | *sec*-Butyl bromide (82%) | Sodium *p*-toluenesulfonate

TABLE 8.8 Approximate Relative Leaving-Group Abilities*

Leaving group	Relative rate	Conjugate acid of leaving group	K_a of conjugate acid	pK_a
F^-	10^{-5}	HF	3.5×10^{-4}	3.5
Cl^-	10^0	HCl	10^7	−7
Br^-	10^1	HBr	10^9	−9
I^-	10^2	HI	10^{10}	−10
H_2O	10^1	H_3O^+	55	−1.7
TsO^-	10^5	TsOH	6×10^2	−2.8
$CF_3SO_2O^-$	10^8	CF_3SO_2OH	10^6	−6

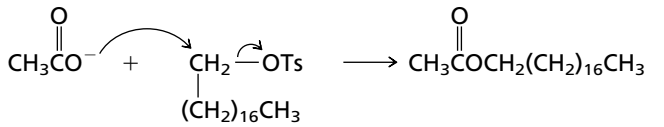
*Values are approximate and vary according to substrate.

PROBLEM 8.13 Write a chemical equation showing the preparation of octadecyl *p*-toluenesulfonate.

PROBLEM 8.14 Write equations showing the reaction of octadecyl *p*-toluenesulfonate with each of the following reagents:

(a) Potassium acetate ($KOCCH_3$, with O double-bonded to C)
(b) Potassium iodide (KI)
(c) Potassium cyanide (KCN)
(d) Potassium hydrogen sulfide (KSH)
(e) Sodium butanethiolate ($NaSCH_2CH_2CH_2CH_3$)

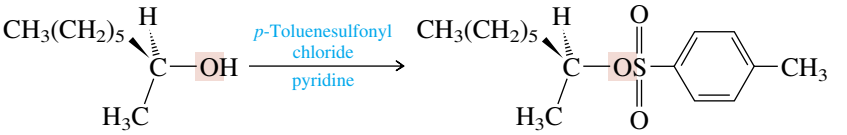
SAMPLE SOLUTION All these reactions of octadecyl *p*-toluenesulfonate have been reported in the chemical literature, and all proceed in synthetically useful yield. You should begin by identifying the nucleophile in each of the parts to this problem. The nucleophile replaces the *p*-toluenesulfonate leaving group in an S_N2 reaction. In part (a) the nucleophile is acetate ion, and the product of nucleophilic substitution is octadecyl acetate.



Acetate ion Octadecyl tosylate Octadecyl acetate

Sulfonate esters are subject to the same limitations as alkyl halides. Competition from elimination needs to be considered when planning a functional group transformation that requires an anionic nucleophile, because tosylates undergo elimination reactions, just as alkyl halides do.

An advantage that sulfonate esters have over alkyl halides is that their preparation from alcohols does not involve any of the bonds to carbon. The alcohol oxygen becomes the oxygen that connects the alkyl group to the sulfonyl group. Thus, the configuration of a sulfonate ester is exactly the same as that of the alcohol from which it was prepared. If we wish to study the stereochemistry of nucleophilic substitution in an optically active substrate, for example, we know that a tosylate ester will have the same configuration and the same optical purity as the alcohol from which it was prepared.



(*S*)-(+)-2-Octanol
$[\alpha]_D^{25}$ +9.9°
(optically pure)

(*S*)-(+)-1-Methylheptyl p-toluenesulfonate
$[\alpha]_D^{25}$ +7.9°
(optically pure)

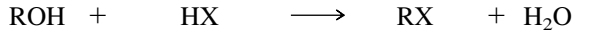
The same cannot be said about reactions with alkyl halides as substrates. The conversion of optically active 2-octanol to the corresponding halide *does* involve a bond to the stereogenic center, and so the optical purity and absolute configuration of the alkyl halide need to be independently established.

The mechanisms by which sulfonate esters undergo nucleophilic substitution are the same as those of alkyl halides. Inversion of configuration is observed in S_N2 reactions of alkyl sulfonates and predominant inversion accompanied by racemization in S_N1 processes.

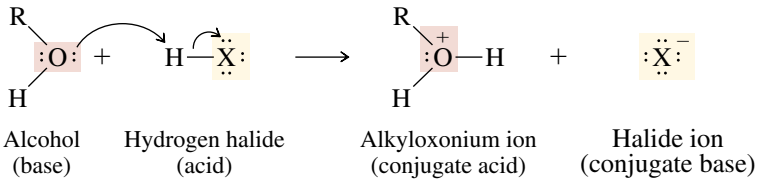
PROBLEM 8.15 The hydrolysis of sulfonate esters of 2-octanol is a stereospecific reaction and proceeds with complete inversion of configuration. Write a structural formula that shows the stereochemistry of the 2-octanol formed by hydrolysis of an optically pure sample of (S)-(+)-1-methylheptyl *p*-toluenesulfonate, identify the product as *R* or *S*, and deduce its specific rotation.

8.15 LOOKING BACK: REACTIONS OF ALCOHOLS WITH HYDROGEN HALIDES

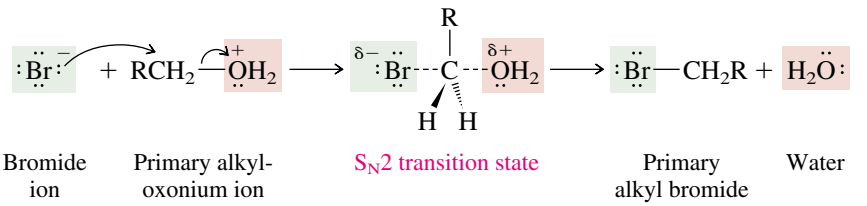
The principles developed in this chapter can be applied to a more detailed examination of the reaction of alcohols with hydrogen halides than was possible when this reaction was first introduced in Chapter 4.



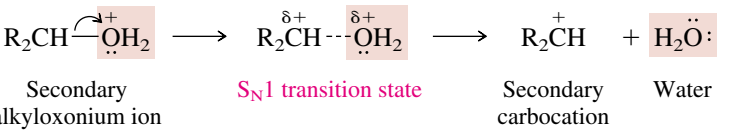
As pointed out in Chapter 4, the first step in the reaction is proton transfer to the alcohol from the hydrogen halide to yield an alkyloxonium ion. This is an acid-base reaction.



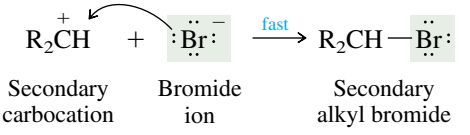
With primary alcohols, the next stage is an S_N2 reaction in which the halide ion, bromide, for example, displaces a molecule of water from the alkyloxonium ion.



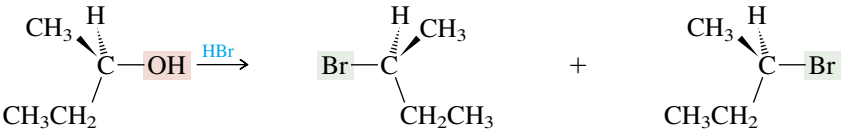
With secondary and tertiary alcohols, this stage is an S_N1 reaction in which the alkyloxonium ion dissociates to a carbocation and water.



Following its formation, the carbocation is captured by halide.



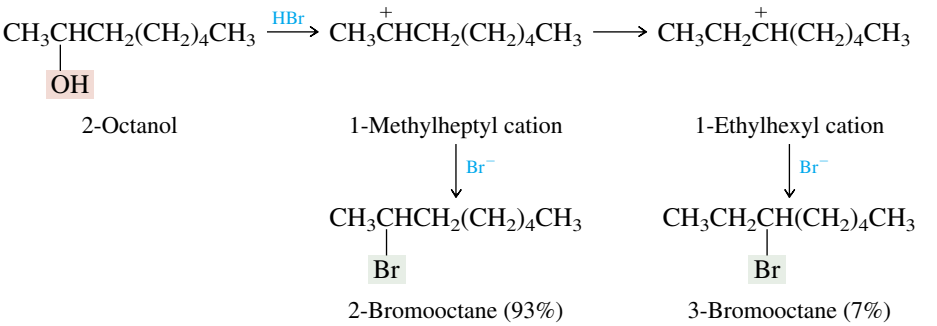
With optically active secondary alcohols the reaction proceeds with predominant, but incomplete, inversion of configuration.



(*R*)-(−)-2-Butanol (*S*)-(+)-2-Bromobutane (87%) (*R*)-(−)-2-Bromobutane (13%)

The few studies that have been carried out with optically active tertiary alcohols indicate that almost complete racemization attends the preparation of tertiary alkyl halides by this method.

Rearrangement can occur, and the desired alkyl halide is sometimes accompanied by an isomeric halide. An example is seen in the case of the secondary alcohol 2-octanol, which yields a mixture of 2- and 3-bromooctane:



PROBLEM 8.16 Treatment of 3-methyl-2-butanol with hydrogen chloride yielded only a trace of 2-chloro-3-methylbutane. An isomeric chloride was isolated in 97% yield. Suggest a reasonable structure for this product.

Unbranched primary alcohols and tertiary alcohols tend to react with hydrogen halides without rearrangement. The alkyloxonium ions from primary alcohols react rapidly with bromide ion, for example, in an S_N2 process without significant development of positive charge at carbon. Tertiary alcohols give tertiary alkyl halides because tertiary carbocations are stable and show little tendency to rearrange.

When it is necessary to prepare secondary alkyl halides with assurance that no trace of rearrangement accompanies their formation, the corresponding alcohol is first converted to its *p*-toluenesulfonate ester and this ester is then allowed to react with sodium chloride, bromide, or iodide, as described in Section 8.14.

8.16 SUMMARY

Section 8.1 Nucleophilic substitution is an important reaction type in synthetic organic chemistry because it is one of the main methods for functional group transformations. Examples of synthetically useful nucleophilic substitutions were given in Table 8.1. It is a good idea to return to that table and review its entries now that the details of nucleophilic substitution have been covered.

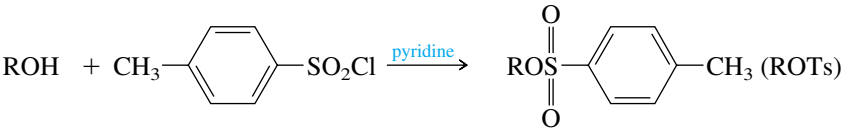
Sections 8.2–8.12 These sections show how a variety of experimental observations led to the proposal of the S_N1 and the S_N2 mechanisms for nucleophilic substitution. Summary Table 8.9 integrates the material in these sections.

TABLE 8.9 Comparison of S_N1 and S_N2 Mechanisms of Nucleophilic Substitution in Alkyl Halides

	S_N1	S_N2
Characteristics of mechanism	Two elementary steps: Step 1: $R{-}\ddot{X}: \rightleftharpoons R^+ + :\ddot{X}:^-$ Step 2: $R^+ + :Nu^- \longrightarrow R{-}Nu$ Ionization of alkyl halide (step 1) is rate-determining. (Section 8.8)	Single step: $^-Nu: + R{-}\ddot{X}: \longrightarrow Nu{-}R + :\ddot{X}:^-$ Nucleophile displaces leaving group; bonding to the incoming nucleophile accompanies cleavage of the bond to the leaving group. (Sections 8.3 and 8.5)
Rate-determining transition state	$^{\delta+}R\cdots\ddot{X}:^{\delta-}$ (Section 8.8)	$^{\delta-}Nu\cdots R\cdots\ddot{X}:^{\delta-}$ (Sections 8.3 and 8.5)
Molecularity	Unimolecular (Section 8.8)	Bimolecular (Section 8.3)
Kinetics and rate law	First order: Rate = k[alkyl halide] (Section 8.8)	Second order: Rate = k[alkyl halide][nucleophile] (Section 8.3)
Relative reactivity of halide leaving groups	RI > RBr > RCl ≫ RF (Section 8.2)	RI > RBr > RCl ≫ RF (Section 8.2)
Effect of structure on rate	$R_3CX > R_2CHX > RCH_2X > CH_3X$ Rate is governed by stability of carbocation that is formed in ionization step. Tertiary alkyl halides can react only by the S_N1 mechanism; they never react by the S_N2 mechanism. (Section 8.9)	$CH_3X > RCH_2X > R_2CHX > R_3CX$ Rate is governed by steric effects (crowding in transition state). Methyl and primary alkyl halides can react only by the S_N2 mechanism; they never react by the S_N1 mechanism. (Section 8.6)
Effect of nucleophile on rate	Rate of substitution is independent of both concentration and nature of nucleophile. Nucleophile does not participate until after rate-determining step. (Section 8.8)	Rate depends on both nature of nucleophile and its concentration. (Sections 8.3 and 8.7)
Effect of solvent on rate	Rate increases with increasing polarity of solvent as measured by its dielectric constant ϵ. (Section 8.12)	Polar aprotic solvents give fastest rates of substitution; solvation of $Nu:^-$ is minimal and nucleophilicity is greatest. (Section 8.12)
Stereochemistry	Not stereospecific: racemization accompanies inversion when leaving group is located at a stereogenic center. (Section 8.10)	Stereospecific: 100% inversion of configuration at reaction site. Nucleophile attacks carbon from side opposite bond to leaving group. (Section 8.4)
Potential for rearrangements	Carbocation intermediate capable of rearrangement. (Section 8.11)	No carbocation intermediate; no rearrangement.

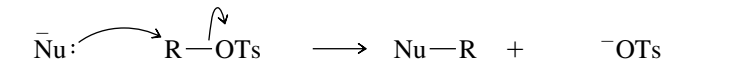
Section 8.13 When nucleophilic substitution is used for synthesis, the competition between substitution and elimination must be favorable. However, *the normal reaction of a secondary alkyl halide with a base as strong or stronger than hydroxide is elimination (E2).* Substitution by the S_N2 mechanism predominates only when the base is weaker than hydroxide or the alkyl halide is primary. Elimination predominates when tertiary alkyl halides react with any anion.

Section 8.14 Nucleophilic substitution can occur with leaving groups other than halide. Alkyl *p*-toluenesulfonates *(tosylates),* which are prepared from alcohols by reaction with *p*-toulenesulfonyl chloride, are often used.



Alcohol *p*-Toluenesulfonyl chloride Alkyl *p*-toluenesulfonate (alkyl tosylate)

Section 8.15 In its ability to act as a leaving group, *p*-toluenesulfonate is comparable to iodide.



Nucleophile Alkyl *p*-toluenesulfonate Substitution product *p*-Toluenesulfonate ion

The reactions of alcohols with hydrogen halides to give alkyl halides (Chapter 4) are nucleophilic substitution reactions of alkyloxonium ions in which water is the leaving group. Primary alcohols react by an S_N2-like displacement of water from the alkyloxonium ion by halide. Secondary and tertiary alcohols give alkyloxonium ions which form carbocations in an S_N1-like process. Rearrangements are possible with secondary alcohols, and substitution takes place with predominant, but not complete, inversion of configuration.

PROBLEMS

8.17 Write the structure of the principal organic product to be expected from the reaction of 1-bromopropane with each of the following:

(a) Sodium iodide in acetone

(b) Sodium acetate ($CH_3\overset{\overset{O}{\|}}{C}ONa$) in acetic acid

(c) Sodium ethoxide in ethanol

(d) Sodium cyanide in dimethyl sulfoxide

(e) Sodium azide in aqueous ethanol

(f) Sodium hydrogen sulfide in ethanol

(g) Sodium methanethiolate ($NaSCH_3$) in ethanol

8.18 All the reactions of 1-bromopropane in the preceding problem give the product of nucleophilic substitution in high yield. High yields of substitution products are also obtained in all but one of the analogous reactions using 2-bromopropane as the substrate. In one case, however, 2-bromopropane is converted to propene, especially when the reaction is carried out at elevated temperature (about 55°C). Which reactant is most effective in converting 2-bromopropane to propene?

8.19 Each of the following nucleophilic substitution reactions has been reported in the chemical literature. Many of them involve reactants that are somewhat more complex than those we have dealt with to this point. Nevertheless, you should be able to predict the product by analogy to what you know about nucleophilic substitution in simple systems.

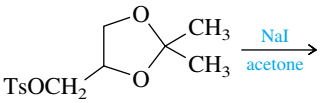
(a) $BrCH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[\text{acetone}]{NaI}$

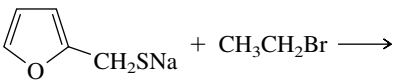
(b) $O_2N\text{-}C_6H_4\text{-}CH_2Cl \xrightarrow[\text{acetic acid}]{CH_3\overset{O}{\overset{\|}{C}}ONa}$

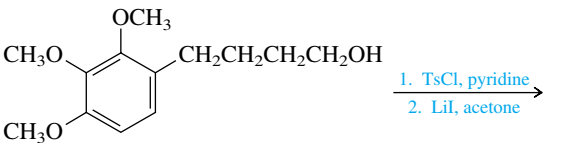
(c) $CH_3CH_2OCH_2CH_2Br \xrightarrow[\text{ethanol–water}]{NaCN}$

(d) $NC\text{-}C_6H_4\text{-}CH_2Cl \xrightarrow{H_2O,\ HO^-}$

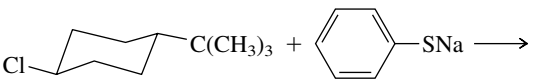
(e) $ClCH_2\overset{O}{\overset{\|}{C}}OC(CH_3)_3 \xrightarrow[\text{acetone–water}]{NaN_3}$

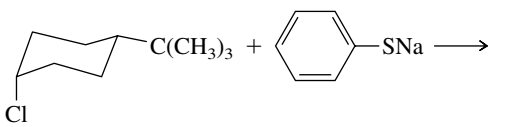
(f) 

(g) 

(h) 

8.20 Each of the reactions shown involves nucleophilic substitution. The product of reaction (a) is an isomer of the product of reaction (b). What kind of isomer? By what mechanism does nucleophilic substitution occur? Write the structural formula of the product of each reaction.

(a) 

(b) 

8.21 Arrange the isomers of molecular formula C_4H_9Cl in order of decreasing rate of reaction with sodium iodide in acetone.

8.22 There is an overall 29-fold difference in reactivity of 1-chlorohexane, 2-chlorohexane, and 3-chlorohexane toward potassium iodide in acetone.

(a) Which one is the most reactive? Why?

(b) Two of the isomers differ by only a factor of 2 in reactivity. Which two are these? Which one is the more reactive? Why?

8.23 In each of the following indicate which reaction will occur faster. Explain your reasoning.

(a) $CH_3CH_2CH_2CH_2Br$ or $CH_3CH_2CH_2CH_2I$ with sodium cyanide in dimethyl sulfoxide

(b) 1-Chloro-2-methylbutane or 1-chloropentane with sodium iodide in acetone

(c) Hexyl chloride or cyclohexyl chloride with sodium azide in aqueous ethanol

(d) Solvolysis of 1-bromo-2,2-dimethylpropane or *tert*-butyl bromide in ethanol

(e) Solvolysis of isobutyl bromide or *sec*-butyl bromide in aqueous formic acid

(f) Reaction of 1-chlorobutane with sodium acetate in acetic acid or with sodium methoxide in methanol

(g) Reaction of 1-chlorobutane with sodium azide or sodium *p*-toluenesulfonate in aqueous ethanol

8.24 Under conditions of photochemical chlorination, $(CH_3)_3CCH_2C(CH_3)_3$ gave a mixture of two monochlorides in a 4:1 ratio. The structures of these two products were assigned on the basis of their S_N1 hydrolysis rates in aqueous ethanol. The major product (compound A) underwent hydrolysis much more slowly than the minor one (compound B). Deduce the structures of compounds A and B.

8.25 The compound KSCN is a source of *thiocyanate* ion.

(a) Write the two most stable Lewis structures for thiocyanate ion and identify the atom in each that bears a formal charge of -1.

(b) Two constitutionally isomeric products of molecular formula C_5H_9NS were isolated in a combined yield of 87% in the reaction shown. (*DMF* stands for *N,N*-dimethylformamide, a polar aprotic solvent.) Suggest reasonable structures for these two compounds.

$$CH_3CH_2CH_2CH_2Br \xrightarrow[DMF]{KSCN}$$

(c) The major product of the reaction cited in (b) constituted 99% of the mixture of isomers. Its structure corresponds to attack by the most polarizable atom of thiocyanate ion on 1-bromobutane. What is this product?

8.26 Reaction of ethyl iodide with triethylamine $[(CH_3CH_2)_3N{:}]$ yields a crystalline compound $C_8H_{20}NI$ in high yield. This compound is soluble in polar solvents such as water but insoluble in nonpolar ones such as diethyl ether. It does not melt below about 200°C. Suggest a reasonable structure for this product.

8.27 Write an equation, clearly showing the stereochemistry of the starting material and the product, for the reaction of (*S*)-1-bromo-2-methylbutane with sodium iodide in acetone. What is the configuration (*R* or *S*) of the product?

8.28 Identify the product in each of the following reactions:

(a) $ClCH_2CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[acetone]{NaI\ (1.0\ equiv)} C_5H_{10}ClI$

(b) $BrCH_2CH_2Br + NaSCH_2CH_2SNa \longrightarrow C_4H_8S_2$

(c) $ClCH_2CH_2CH_2CH_2Cl + Na_2S \longrightarrow C_4H_8S$

8.29 Give the mechanistic symbols (S_N1, S_N2, E1, E2) that are most consistent with each of the following statements:

(a) Methyl halides react with sodium ethoxide in ethanol only by this mechanism.

(b) Unhindered primary halides react with sodium ethoxide in ethanol mainly by this mechanism.

(c) When cyclohexyl bromide is treated with sodium ethoxide in ethanol, the major product is formed by this mechanism.

(d) The substitution product obtained by solvolysis of *tert*-butyl bromide in ethanol arises by this mechanism.

(e) In ethanol that contains sodium ethoxide, *tert*-butyl bromide reacts mainly by this mechanism.

(f) These reaction mechanisms represent concerted processes.

(g) Reactions proceeding by these mechanisms are stereospecific.

(h) These reaction mechanisms involve carbocation intermediates.

(i) These reaction mechanisms are the ones most likely to have been involved when the products are found to have a different carbon skeleton from the substrate.

(j) Alkyl iodides react faster than alkyl bromides in reactions that proceed by these mechanisms.

8.30 Outline an efficient synthesis of each of the following compounds from the indicated starting material and any necessary organic or inorganic reagents:

(a) Cyclopentyl cyanide from cyclopentane

(b) Cyclopentyl cyanide from cyclopentene

(c) Cyclopentyl cyanide from cyclopentanol

(d) $NCCH_2CH_2CN$ from ethyl alcohol

(e) Isobutyl iodide from isobutyl chloride

(f) Isobutyl iodide from *tert*-butyl chloride

(g) Isopropyl azide from isopropyl alcohol

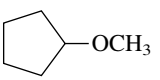
(h) Isopropyl azide from 1-propanol

(i) (*S*)-*sec*-Butyl azide from (*R*)-*sec*-butyl alcohol

(j) (*S*)-$CH_3CH_2\underset{\displaystyle SH}{\underset{|}{C}}HCH_3$ from (*R*)-*sec*-butyl alcohol

8.31 Select the combination of alkyl bromide and potassium alkoxide that would be the most effective in the syntheses of the following ethers:

(a) $CH_3OC(CH_3)_3$

(b) 

(c) $(CH_3)_3CCH_2OCH_2CH_3$

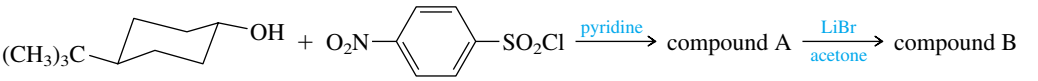
8.32 (*Note to the student:* This problem previews an important aspect of Chapter 9 and is well worth attempting in order to get a head start on the material presented there.)

Alkynes of the type $RC{\equiv}CH$ may be prepared by nucleophilic substitution reactions in which one of the starting materials is sodium acetylide ($Na^+ :\bar{C}{\equiv}CH$).

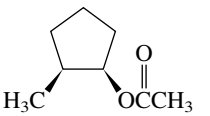
(a) Devise a method for the preparation of $CH_3CH_2C{\equiv}CH$ from sodium acetylide and any necessary organic or inorganic reagents.

(b) Given the information that K_a for acetylene ($HC{\equiv}CH$) is 10^{-26} (pK_a 26), comment on the scope of this preparative procedure with respect to R in $RC{\equiv}CH$. Could you prepare $(CH_3)_2CHC{\equiv}CH$ or $(CH_3)_3CC{\equiv}CH$ in good yield by this method?

8.33 Give the structures, including stereochemistry, of compounds A and B in the following sequence of reactions:



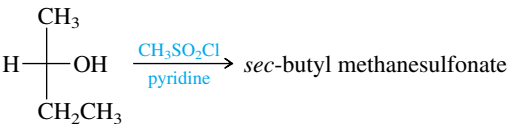
8.34 (a) Suggest a reasonable series of synthetic transformations for converting *trans*-2-methylcyclopentanol to *cis*-2-methylcyclopentyl acetate.



cis-2-Methylcyclopentyl acetate

(b) How could you prepare *cis*-2-methylcyclopentyl acetate from 1-methylcyclopentanol?

8.35 Optically pure (*S*)-(+)-2-butanol was converted to its methanesulfonate ester according to the reaction shown.



(a) Write the Fischer projection of the *sec*-butyl methanesulfonate formed in this reaction.

(b) The *sec*-butyl methanesulfonate in part (a) was treated with $NaSCH_2CH_3$ to give a product having an optical rotation α_D of $-25°$. Write the Fischer projection of this product. By what mechanism is it formed? What is its absolute configuration (*R* or *S*)?

(c) When treated with PBr_3 , optically pure (*S*)-(+)-2-butanol gave 2-bromobutane having an optical rotation $\alpha_D = -38°$. This bromide was then allowed to react with $NaSCH_2CH_3$ to give a product having an optical rotation α_D of $+23°$. Write the Fischer projection for (−)-2-bromobutane and specify its configuration as *R* or *S*. Does the reaction of 2-butanol with PBr_3 proceed with predominant inversion or retention of configuration?

(d) What is the optical rotation of optically pure 2-bromobutane?

8.36 In a classic experiment, Edward Hughes (a colleague of Ingold's at University College, London) studied the rate of racemization of 2-iodooctane by sodium iodide in acetone and compared it with the rate of incorporation of radioactive iodine into 2-iodooctane.

$$RI + [I^*]^- \longrightarrow RI^* + I^-$$

(I* = radioactive iodine)

How will the rate of racemization compare with the rate of incorporation of radioactivity if

(a) Each act of exchange proceeds stereospecifically with retention of configuration?

(b) Each act of exchange proceeds stereospecifically with inversion of configuration?

(c) Each act of exchange proceeds in a stereorandom manner, in which retention and inversion of configuration are equally likely?

8.37 The ratio of elimination to substitution is exactly the same (26% elimination) for 2-bromo-2-methylbutane and 2-iodo-2-methylbutane in 80% ethanol/20% water at 25°C.

(a) By what mechanism does substitution most likely occur in these compounds under these conditions?

(b) By what mechanism does elimination most likely occur in these compounds under these conditions?

(c) Which substrate undergoes substitution faster?

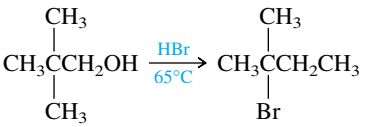
(d) Which substrate undergoes elimination faster?

(e) What two substitution products are formed from each substrate?

(f) What two elimination products are formed from each substrate?

(g) Why do you suppose the ratio of elimination to substitution is the same for the two substrates?

8.38 The reaction of 2,2-dimethyl-1-propanol with HBr is very slow and gives 2-bromo-2-methylpropane as the major product.



Give a mechanistic explanation for these observations.

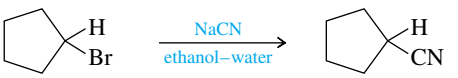
8.39 Solvolysis of 2-bromo-2-methylbutane in acetic acid containing potassium acetate gave three products. Identify them.

8.40 Solvolysis of 1,2-dimethylpropyl *p*-toluenesulfonate in acetic acid (75°C) yields five different products: three are alkenes and two are substitution products. Suggest reasonable structures for these five products.

8.41 Solution A was prepared by dissolving potassium acetate in methanol. Solution B was prepared by adding potassium methoxide to acetic acid. Reaction of methyl iodide either with solution A or with solution B gave the same major product. Why? What was this product?

8.42 If the temperature is not kept below 25°C during the reaction of primary alcohols with *p*-toluenesulfonyl chloride in pyridine, it is sometimes observed that the isolated product is not the desired alkyl *p*-toluenesulfonate but is instead the corresponding alkyl chloride. Suggest a mechanistic explanation for this observation.

8.43 The reaction of cyclopentyl bromide with sodium cyanide to give cyclopentyl cyanide



Cyclopentyl bromide Cyclopentyl cyanide

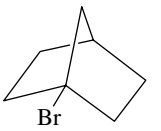
proceeds faster if a small amount of sodium iodide is added to the reaction mixture. Can you suggest a reasonable mechanism to explain the catalytic function of sodium iodide?

8.44 Illustrate the stereochemistry associated with unimolecular nucleophilic substitution by constructing molecular models of *cis*-4-*tert*-butylcyclohexyl bromide, its derived carbocation, and the alcohols formed from it by hydrolysis under S_N1 conditions.

8.45 Given the molecular formula $C_6H_{11}Br$, construct a molecular model of the isomer that is a primary alkyl bromide yet relatively unreactive toward bimolecular nucleophilic substitution.

8.46 Cyclohexyl bromide is less reactive than noncyclic secondary alkyl halides toward S_N2 substitution. Construct a molecular model of cyclohexyl bromide and suggest a reason for its low reactivity.

8.47 1-Bromobicyclo[2.2.1]heptane (the structure of which is shown) is exceedingly unreactive toward nucleophilic substitution by either the S_N1 or S_N2 mechanism. Use molecular models to help you understand why.



1-Bromobicyclo[2.2.1]heptane