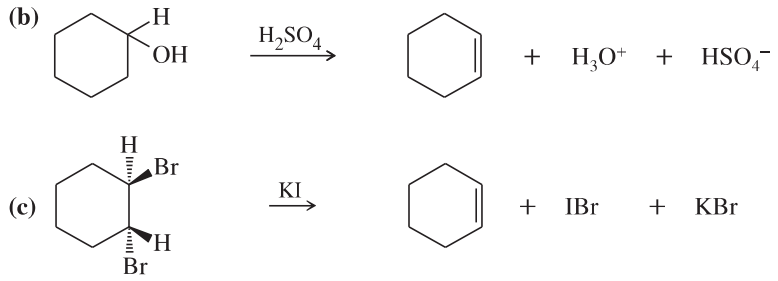


PROBLEM-SOLVING HINT

Many common nucleophiles are also bases, so the same species might react both as Nuc:$^-$ (giving substitution) and B:$^-$ (giving elimination) in the same reaction. We study substitutions in Chapter 6, then add eliminations in Chapter 7.

PROBLEM 6-12

Give the structures of the substitution products expected when 1-bromohexane reacts with
(a) $NaOCH_2CH_3$ **(b)** KCN **(c)** NaOH

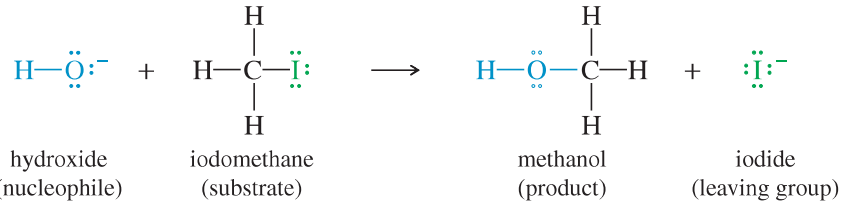
6-8 Bimolecular Nucleophilic Substitution: The S_N2 Reaction

A nucleophilic substitution has the general form

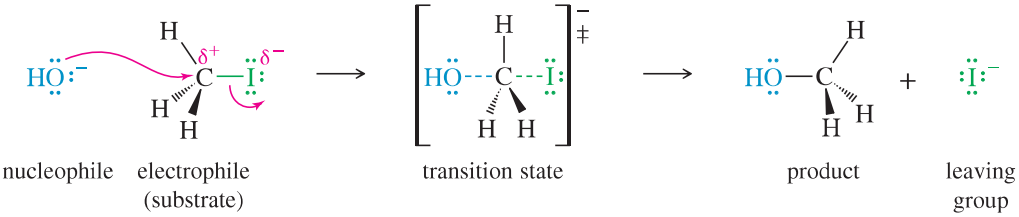
General nucleophilic substitution:

where Nuc:$^-$ is the nucleophile and :X:$^-$ is the leaving halide ion. An example is the reaction of iodomethane (CH_3I) with hydroxide ion. The product is methanol.

Example:



Hydroxide ion is a strong **nucleophile** (donor of an electron pair) because the oxygen atom has unshared pairs of electrons and a negative charge. Iodomethane is called the **substrate,** meaning the compound that is attacked by the reagent. The carbon atom of iodomethane is electrophilic because it is bonded to an electronegative iodine atom. Electron density is drawn away from carbon by the halogen atom, giving the carbon atom a partial positive charge. The negative charge of hydroxide ion is attracted to this partial positive charge.



Hydroxide ion attacks the back side of the electrophilic carbon atom, donating a pair of electrons to form a new bond. (In general, nucleophiles are said to attack electrophiles, not the other way around.) Notice that curved arrows are used to show the movement of electron pairs—from the electron-rich nucleophile to the electron-poor carbon atom of the electrophile. Carbon can accommodate only eight electrons in its valence shell, so the carbon–iodine bond must begin to break as the carbon–oxygen bond begins to form. Iodide ion is the leaving group; it leaves with the pair of electrons that once bonded it to the carbon atom.

This one-step mechanism is supported by kinetic information. We can vary the concentrations of the reactants and observe the effects on the reaction rate (how much methanol is formed per second). The rate is found to double when the concentration of *either* reactant is doubled. The reaction is therefore first order in each of the reactants and second order overall. The rate equation has the following form:

$$\text{second-order rate} = k_r[CH_3I][^-OH]$$

This rate equation is consistent with a mechanism that requires a collision between a molecule of methyl iodide and a hydroxide ion. Both of these species are present in the transition state, and the collision frequency is proportional to both concentrations. The rate constant k_r depends on several factors, including the energy of the transition state and the temperature (Section 4-9).

This one-step nucleophilic substitution is an example of the **S_N2 mechanism.** The abbreviation S_N2 stands for *Substitution, Nucleophilic, bimolecular*. The term *bimolecular* means that the transition state of the rate-limiting step (the only step in this reaction) involves the collision of *two* molecules. Bimolecular reactions usually have rate equations that are second order overall.

The S_N2 reaction of methyl iodide (iodomethane) with hydroxide ion is a **concerted reaction,** taking place in a single step with bonds breaking and forming at the same time. The middle structure is a **transition state,** a point of maximum energy, rather than an intermediate. In this transition state, the bond to the nucleophile (hydroxide) is partially formed, and the bond to the leaving group (iodide) is partially broken. Remember that a transition state is not a discrete molecule that can be isolated; it exists for only an instant.

PROBLEM-SOLVING HINT

A transition state is unstable and cannot be isolated. It exists for only an instant. In contrast, an intermediate exists for a finite length of time.

The reaction-energy diagram for this substitution (Figure 6-5) shows only one transition state and no intermediates between the reactants and the products. The

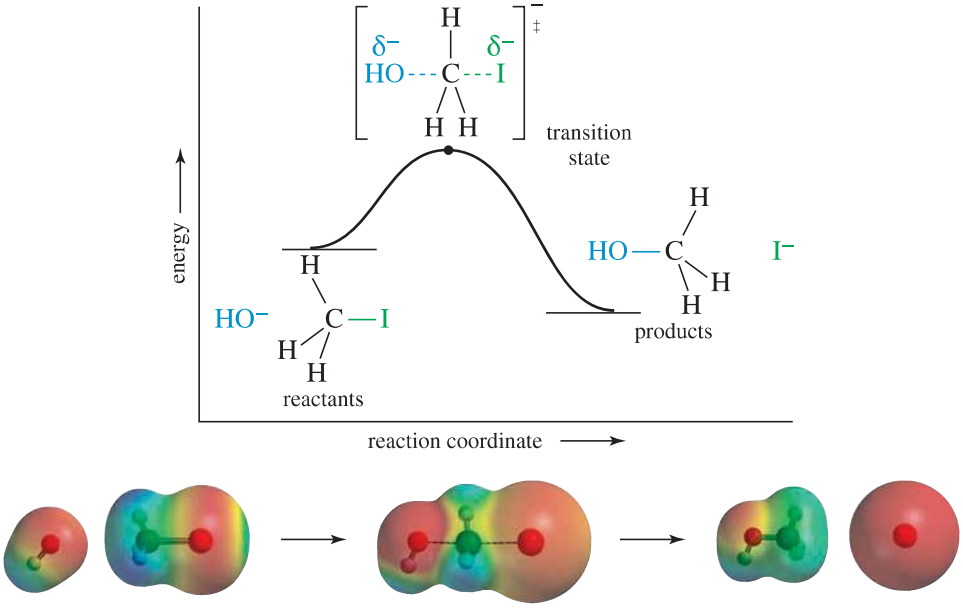


FIGURE 6-5
The reaction-energy diagram for the S_N2 reaction of methyl iodide with hydroxide shows only one energy maximum: the transition state. There are no intermediates.

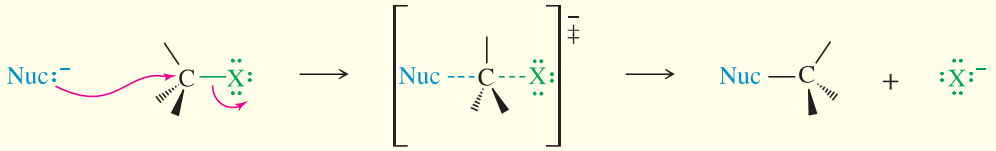
The electrostatic potential maps of the reactants, transition state, and products show that the negatively charged nucleophile (red) attacks the electrophilic (blue) region of the substrate. In the transition state, the negative charge (red) is delocalized over the nucleophile and the leaving group. The negative charge leaves with the leaving group.

reactants are shown slightly higher in energy than the products because this reaction is known to be exothermic. The transition state is much higher in energy because it involves a five-coordinate carbon atom with two partial bonds.

Key Mechanism 6-2 shows a general S_N2 reaction. A nucleophile attacks the substrate to give a transition state in which a bond to the nucleophile is forming at the same time the bond to the leaving group is breaking.

KEY MECHANISM 6-2 The S_N2 Reaction

The S_N2 reaction takes place in a single (concerted) step. A strong nucleophile attacks the electrophilic carbon, forcing the leaving group to leave.

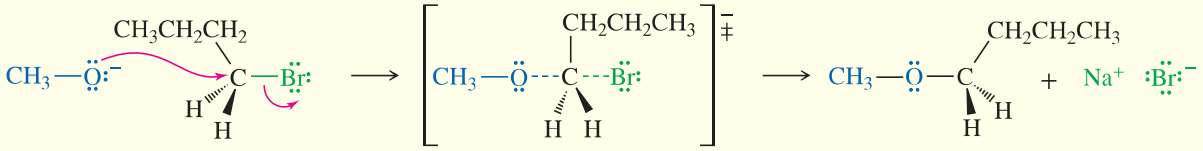


nucleophile | substrate (electrophile) | transition state | product | leaving group

The order of reactivity for substrates is $CH_3X > 1° > 2°$. (3° alkyl halides cannot react by this mechanism.)

EXAMPLE: Reaction of 1-bromobutane with sodium methoxide gives 1-methoxybutane.

$$\underset{\text{sodium methoxide}}{NaOCH_3} + \underset{\text{1-bromobutane}}{CH_3CH_2CH_2CH_2Br} \longrightarrow \underset{\text{1-methoxybutane}}{CH_3CH_2CH_2CH_2OCH_3} + NaBr$$



nucleophile | electrophile (substrate) | transition state | product | leaving group

PROBLEM 6-13

(a) Under certain conditions, the reaction of 0.5 M 1-bromobutane with 1.0 M sodium methoxide forms 1-methoxybutane at a rate of 0.05 mol/L per second. What would be the rate if 0.1 M 1-bromobutane and 2.0 M $NaOCH_3$ were used?

(b) Consider the reaction of 1-bromobutane with a large excess of ammonia (NH_3). Draw the reactants, the transition state, and the products. Note that the initial product is the salt of an amine (RNH_3^+ Br^-), which is deprotonated by the excess ammonia to give the amine.

(c) Show another S_N2 reaction using a different combination of an alkoxide and an alkyl bromide that also produces 1-methoxybutane.

6-9 Generality of the S_N2 Reaction

Many useful reactions take place by the S_N2 mechanism. The reaction of an alkyl halide, such as methyl iodide, with hydroxide ion gives an alcohol. Other nucleophiles convert alkyl halides to a wide variety of functional groups. The following table summarizes some of the types of compounds that can be formed by nucleophilic displacement of alkyl halides.

SUMMARY S_N2 Reactions of Alkyl Halides

$$Nuc:^- + R{-}X \longrightarrow Nuc{-}R + X^-$$

Nucleophile		Product	Class of Product
R—X + $:\ddot{\underset{\cdot\cdot}{I}}:^-$	⟶	R—$\ddot{\underset{\cdot\cdot}{I}}:$	alkyl halide
R—X + $:\ddot{\underset{\cdot\cdot}{O}}H^-$	⟶	R—$\ddot{\underset{\cdot\cdot}{O}}H$	alcohol
R X + $:\ddot{\underset{\cdot\cdot}{O}}R'^-$	⟶	R—$\ddot{\underset{\cdot\cdot}{O}}R'$	ether
R—X + $:\ddot{\underset{\cdot\cdot}{S}}H^-$	⟶	R—$\ddot{\underset{\cdot\cdot}{S}}H$	thiol (mercaptan)
R—X + $:\ddot{\underset{\cdot\cdot}{S}}R'^-$	⟶	R—$\ddot{\underset{\cdot\cdot}{S}}R'$	thioether (sulfide)
R—X + $:NH_3$	⟶	R—NH_3^+ X^-	amine salt
R—X + $:\ddot{N}{=}\overset{+}{N}{=}\ddot{N}:^-$	⟶	R—$\ddot{N}{=}\overset{+}{N}{=}\ddot{N}:^-$	azide
R—X + $:C{\equiv}C{-}R'^-$	⟶	R—C≡C—R′	alkyne
R—X + $:C{\equiv}N:^-$	⟶	R—C≡N:	nitrile
R—X + $:\ddot{O}{-}\overset{\ddot{O}:}{\overset{\|\|}{C}}{-}R'^-$	⟶	R—$\ddot{O}{-}\overset{\ddot{O}:}{\overset{\|\|}{C}}{-}R'$	ester
R—X + $:PPh_3$	⟶	$[R{-}PPh_3]^+$ X^-	phosphonium salt

Halogen Exchange Reactions The S_N2 reaction provides a useful method for synthesizing alkyl iodides and fluorides, which are more difficult to make than alkyl chlorides and bromides. Halides can be converted to other halides by **halogen exchange reactions,** in which one halide displaces another.

Iodide is a good nucleophile, and many alkyl chlorides react with sodium iodide to give alkyl iodides. Alkyl fluorides are difficult to synthesize directly, and they are often made by treating alkyl chlorides or bromides with KF under conditions that use a crown ether (Section 14-2D) to dissolve the fluoride salt in an aprotic solvent, which enhances the normally weak nucleophilicity of the fluoride ion (see Section 6-10).

$$R{-}X + I^- \longrightarrow R{-}I + X^-$$

$$R{-}X + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} R{-}F + KX$$

Examples

$$\underset{\text{allyl chloride}}{H_2C{=}CH{-}CH_2Cl} + NaI \longrightarrow \underset{\text{allyl iodide}}{H_2C{=}CH{-}CH_2I} + NaCl$$

$$\underset{\text{ethyl chloride}}{CH_3CH_2Cl} + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} \underset{\text{ethyl fluoride}}{CH_3CH_2F} + KCl$$

PROBLEM 6-14

Predict the major products of the following substitutions.

(a) CH_3CH_2Br (ethyl bromide) + $(CH_3)_3CO^-\ K^+$ (potassium *tert*-butoxide) ⟶

(b) $HC{\equiv}C{:}^-\ Na^+$ (sodium acetylide) + $CH_3CH_2CH_2CH_2Cl$ (1-chlorobutane) ⟶

(c) $(CH_3)_2CHCH_2Br$ + excess NH_3 ⟶
(d) $CH_3CH_2CH_2I$ + NaCN ⟶
(e) 1-chloropentane + NaI ⟶
(f) 1-chloropentane + KF $\xrightarrow[CH_3CN]{\text{18-crown-6}}$

PROBLEM 6-15

Show how you might use S_N2 reactions to convert 1-chlorobutane into the following compounds.

(a) butan-1-ol
(b) 1-fluorobutane
(c) 1-iodobutane
(d) $CH_3—(CH_2)_3—CN$
(e) $CH_3—(CH_2)_3—C{\equiv}CH$
(f) $CH_3CH_2—O—(CH_2)_3—CH_3$
(g) $CH_3—(CH_2)_3—NH_2$

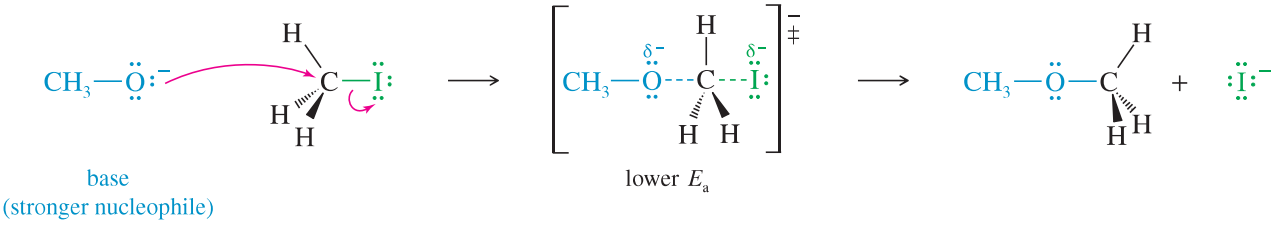
6-10 Factors Affecting S_N2 Reactions: Strength of the Nucleophile

We will use the S_N2 reaction as an example of how we study the factors that affect the rates and products of organic reactions. Both the nucleophile and the substrate (the alkyl halide) are important, as well as the type of solvent used. We begin by considering what makes a good nucleophile.

A "stronger" nucleophile is an ion or a molecule that reacts faster in the S_N2 reaction than a "weaker" nucleophile under the same conditions. A strong nucleophile is much more effective than a weak one in attacking an electrophilic carbon atom. For example, both methanol (CH_3OH) and methoxide ion (CH_3O^-) have easily shared pairs of nonbonding electrons, but methoxide ion reacts with electrophiles in the S_N2 reaction about 1 million times faster than methanol. It is generally true that a species with a negative charge is a stronger nucleophile than a similar, neutral species.

Methoxide ion has nonbonding electrons that are readily available for bonding. In the transition state, the negative charge is shared by the oxygen of methoxide ion and by the halide leaving group. Methanol, however, has no negative charge; the transition state has a partial negative charge on the halide but a partial positive charge on the methanol oxygen atom. We can generalize the case of methanol and the methoxide ion to say that

> a base is always a stronger nucleophile than its conjugate acid.



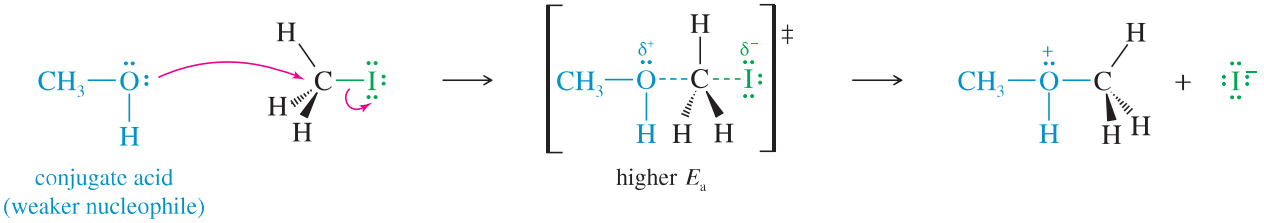
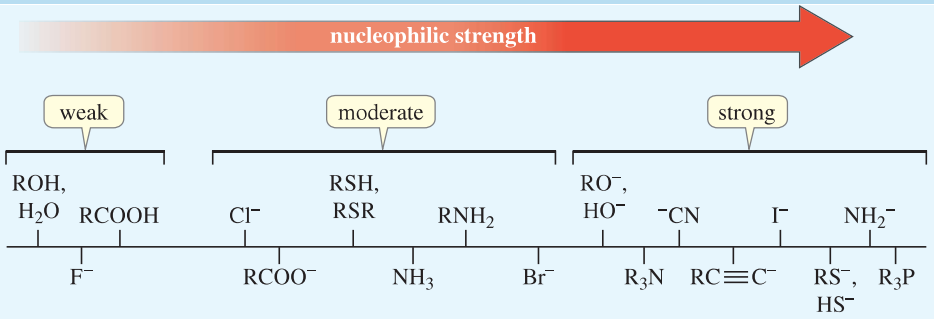


TABLE 6-3
Some Common Nucleophiles
Listed in increasing order of nucleophilicity in polar solvents such as water and alcohols



We might be tempted to say that methoxide is a much better nucleophile because it is much more basic. This would be a mistake because basicity and nucleophilicity are different properties. **Basicity** is defined by the *equilibrium constant* for abstracting a *proton*. **Nucleophilicity** is defined by the *rate* of attack on an electrophilic *carbon atom*. In both cases, the nucleophile (or base) forms a new bond. If it forms a new bond to a proton, it has reacted as a **base;** if it forms a new bond to carbon, it has reacted as a **nucleophile.** Predicting which way a species will react may be difficult; most (but not all) good nucleophiles are also strong bases, and vice versa.

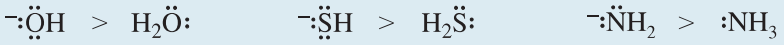
Basicity: equilibrium for abstracting a proton

Nucleophilicity: rate of attacking a carbon atom

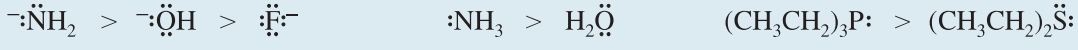
Table 6-3 lists some common nucleophiles in increasing order of their nucleophilicity in polar solvents such as water and alcohols. The strength of nucleophiles in these solvents shows three major trends, as described in the Summary below.

SUMMARY Trends in Nucleophilicity

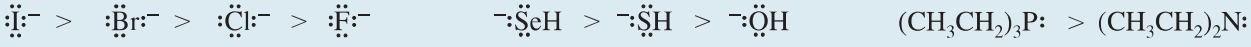
1. A species with a negative charge is a stronger nucleophile than a similar neutral species. In particular, a base is a stronger nucleophile than its conjugate acid.



2. Nucleophilicity decreases from left to right in the periodic table, following the increase in electronegativity from left to right. The more electronegative elements have more tightly held nonbonding electrons that are less reactive toward forming new bonds.



3. Nucleophilicity increases down the periodic table, following the increase in size and polarizability and the decrease in electronegativity.



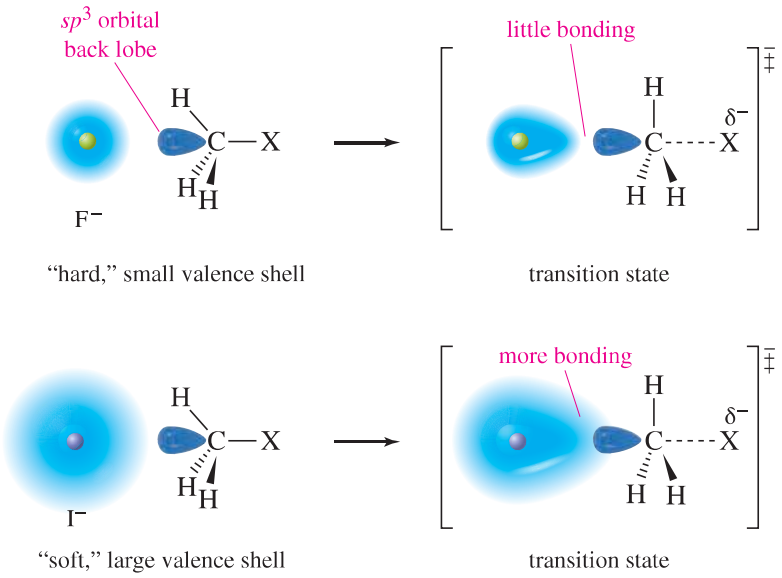


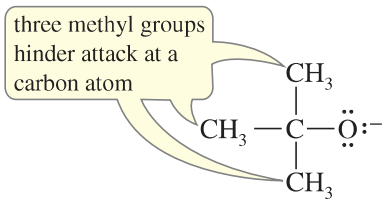
FIGURE 6-6
Comparison of fluoride ion and iodide ion as nucleophiles in the S_N2 reaction. Fluoride has tightly bound electrons that cannot begin to form a C—F bond until the atoms are close together. Iodide has more loosely bound outer electrons that begin bonding earlier in the reaction.

The third trend (size and polarizability) reflects an atom's ability to engage in partial bonding as it begins to attack an electrophilic carbon atom. As we go down a column in the periodic table, the atoms become larger, with more electrons at a greater distance from the nucleus. The electrons are more loosely held, and the atom is more **polarizable:** Its electrons can move more freely toward a positive charge, resulting in stronger bonding in the transition state. The increased mobility of its electrons enhances the atom's ability to begin to form a bond at a relatively long distance.

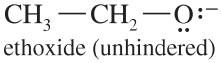
Figure 6-6 illustrates this polarizability effect by comparing the attack of iodide ion and fluoride ion on a methyl halide. The outer shell of the fluoride ion is the second shell. These electrons are tightly held, close to the nucleus. Fluoride is a "hard" (low-polarizability) nucleophile, and its nucleus must approach the carbon nucleus quite closely before the electrons can begin to overlap and form a bond. In the transition state, there is little bonding between fluorine and carbon. In contrast, the outer shell of the iodide ion is the fifth shell. These electrons are loosely held, making the iodide ion a "soft" (high-polarizability) nucleophile. The outer electrons begin to shift and overlap with the carbon atom from farther away. There is a great deal of bonding between iodine and carbon in the transition state, which lowers the energy of the transition state.

6-10A Steric Effects on Nucleophilicity

To serve as a nucleophile, an ion or a molecule must get close to a carbon atom to attack it. Bulky groups on the nucleophile hinder this close approach, and they slow the reaction rate. For example, *tert*-butoxide ion is a stronger *base* (for abstracting protons) than ethoxide ion, but *tert*-butoxide ion has three methyl groups that hinder any close approach to a more crowded carbon atom. Therefore, ethoxide ion is a stronger nucleophile than *tert*-butoxide ion. When bulky groups interfere with a reaction by virtue of their size, we call the effect **steric hindrance.**



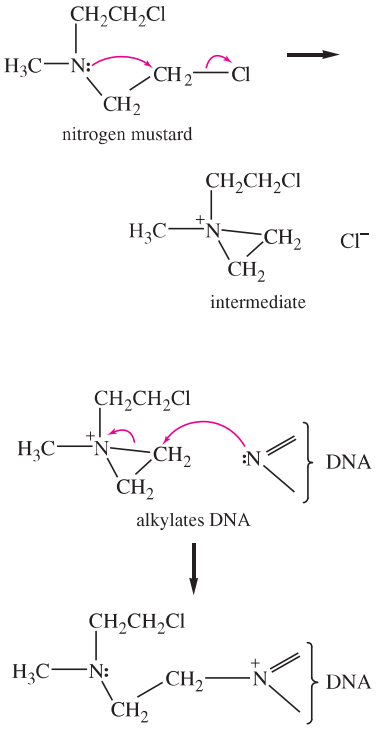
tert-butoxide (hindered)
stronger base, yet weaker nucleophile



ethoxide (unhindered)
weaker base, yet stronger nucleophile

Application: Biochemistry

The "nitrogen mustard" anticancer drugs are believed to alkylate DNA using two S_N2 reactions. First, the nitrogen nucleophile displaces chloride on the primary alkyl chloride portion to generate a reactive intermediate. Second, the intermediate alkylates a nitrogen atom of DNA. The process is repeated, linking the two strands of the double-helix DNA, and thereby preventing replication of the DNA.



Steric hindrance has little effect on *basicity* because basicity involves attack on an unhindered proton. When a *nucleophile* attacks a carbon atom, however, a bulky nucleophile cannot approach the carbon atom so easily. Most bases are also nucleophiles, capable of attacking either a proton or an electrophilic carbon atom. If we want a species to act as a base, we use a bulky reagent such as *tert*-butoxide ion. If we want it to react as a nucleophile, we use a less hindered reagent such as ethoxide.

PROBLEM-SOLVING HINT

Steric hindrance (bulkiness) hinders nucleophilicity (S_N2) more than it hinders basicity.

PROBLEM 6-16

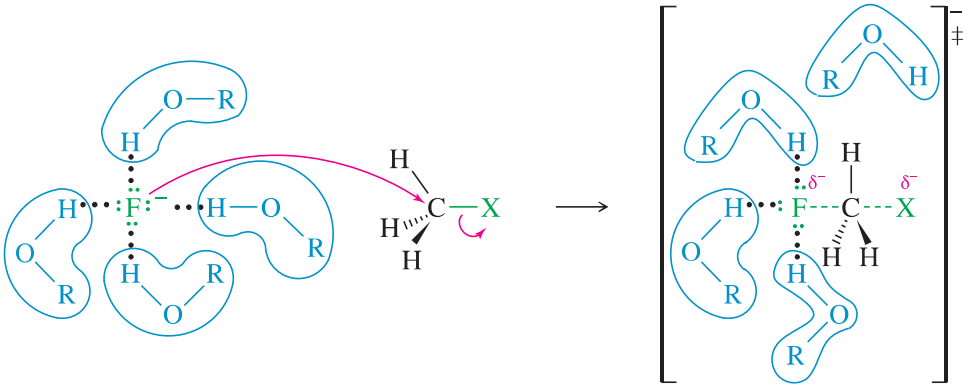
For each pair, predict the stronger nucleophile in the S_N2 reaction (using an alcohol as the solvent). Explain your prediction.

(a) $(CH_3CH_2)_3N$ or $(CH_3CH_2)_2NH$
(b) $(CH_3)_2O$ or $(CH_3)_2S$
(c) NH_3 or PH_3
(d) CH_3S^- or H_2S
(e) $(CH_3)_3N$ or $(CH_3)_2O$
(f) CH_3COO^- or CF_3COO^-
(g) $(CH_3)_2CHO^-$ or $CH_3CH_2CH_2O^-$
(h) I^- or Cl^-

6-10B Solvent Effects on Nucleophilicity

Another factor affecting the nucleophilicity of these ions is their solvation, particularly in protic solvents. A **protic solvent** has acidic protons, usually in the form of O—H or N—H groups. Those with O—H groups are often called **hydroxylic solvents.** These groups form hydrogen bonds to negatively charged nucleophiles. Protic solvents, especially alcohols, are convenient solvents for nucleophilic substitutions because the reagents (alkyl halides, nucleophiles, etc.) tend to be quite soluble.

Small anions are solvated more strongly than large anions in a protic solvent because the solvent molecules approach a small anion more closely and form stronger hydrogen bonds. When an anion reacts as a nucleophile, energy is required to "strip off" some of the solvent molecules, breaking some of the hydrogen bonds that stabilized the solvated anion. More energy is required to strip off solvent from a small, strongly solvated ion such as fluoride than from a large, diffuse, less strongly solvated ion such as iodide.



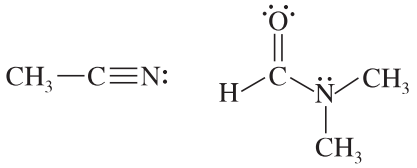
solvent partially stripped off in the transition state

The enhanced solvation of smaller anions in protic solvents, requiring more energy to strip off their solvent molecules, reduces their nucleophilicity. This trend reinforces the trend in polarizability: The polarizability increases with increasing atomic number, and the solvation energy (in protic solvents) decreases with increasing atomic number. Therefore, nucleophilicity (in protic solvents) generally increases down a column in the periodic table, as long as we compare similar species with similar charges.

In contrast with protic solvents, **aprotic solvents** (solvents without O—H or N—H groups) enhance the nucleophilicity of anions. An anion is more reactive in an aprotic solvent because it is not so strongly solvated. There are no hydrogen bonds to be broken when solvent must make way for the nucleophile to approach an electrophilic carbon atom. The relatively weak solvating ability of aprotic solvents is also a disadvantage: Most polar, ionic reagents are insoluble in simple aprotic solvents such as alkanes.

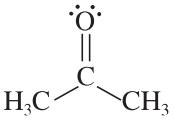
Polar aprotic solvents have strong dipole moments to enhance solubility, yet they have no O—H or N—H groups to form hydrogen bonds with anions. Examples of useful polar aprotic solvents (shown below) are acetonitrile, dimethylformamide (DMF), acetone, and dimethyl sulfoxide (DMSO). Changing from a hydroxylic solvent to a polar aprotic solvent often enhances the rate of an S_N2 reaction, sometimes by a factor of 1000 or more. In some cases, we can add specific solvating reagents to enhance solubility without affecting the reactivity of the nucleophile. For example, the "crown ether" 18-crown-6 solvates potassium ions. Using the potassium salt of a nucleophile and solvating the potassium ions causes the nucleophilic anion to be dragged along into solution.

Examples of polar aprotic solvents:

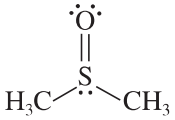


acetonitrile

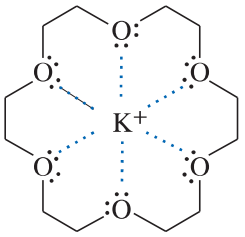
dimethylformamide (DMF)



acetone

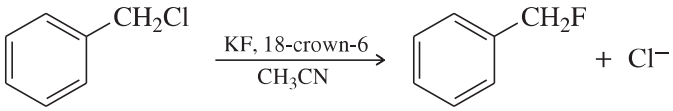


dimethyl sulfoxide (DMSO)



18-crown-6 solvates K^+ ions

The following example shows how fluoride ion, normally a poor nucleophile in hydroxylic (protic) solvents, can be a good nucleophile in an aprotic solvent. Although KF is not very soluble in acetonitrile, 18-crown-6 solvates the potassium ions, and the poorly solvated fluoride ion follows. This poorly solvated fluoride ion is nucleophilic, and it attacks carbon more readily than it would in a protic solvent.



6-11 Reactivity of the Substrate in S_N2 Reactions

Just as the nucleophile is important in the S_N2 reaction, the structure of the alkyl halide is equally important. We will often refer to the alkyl halide as the **substrate:** literally, the compound that is being attacked by the reagent. Besides alkyl halides, a variety of other types of compounds serve as substrates in S_N2 reactions. To be a good substrate for S_N2 attack by a nucleophile, a molecule must have an electrophilic carbon atom with a good leaving group, and that carbon atom must not be too sterically hindered for a nucleophile to attack.

6-11A Leaving-Group Effects on the Substrate

A leaving group serves two purposes in the S_N2 reaction:

1. It polarizes the C—X bond, making the carbon atom electrophilic.
2. It leaves with the pair of electrons that once bonded it to the electrophilic carbon atom.

To fill these roles, a good leaving group should be

1. electron-withdrawing, to polarize the carbon atom,
2. stable (not a strong base) once it has left, and
3. polarizable, to stabilize the transition state.

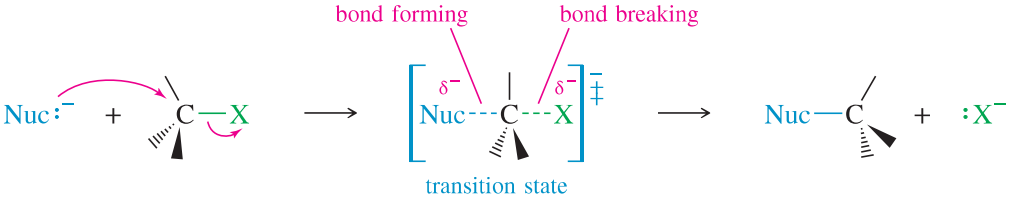
1. The leaving group must be *electron-withdrawing* to create a partial positive charge on the carbon atom, making the carbon electrophilic. An electron-withdrawing leaving group also stabilizes the negatively charged transition state. Halogen atoms are strongly electronegative, so alkyl halides are common substrates for S_N2 reactions. Oxygen,

nitrogen, and sulfur also form strongly polarized bonds with carbon; given the right substituents, they can form the basis for excellent leaving groups.

Strongly polarized

$C^{\delta+}-X^{\delta-}$ (X = halogen) $C^{\delta+}-O^{\delta-}$ $C^{\delta+}-N^{\delta-}$ $C^{\delta+}-S^{\delta-}$

2. The leaving group must be *stable* once it has left with the pair of electrons that bonded it to carbon. A stable leaving group is needed for favorable energetics. The leaving group is leaving in the transition state; a reactive leaving group would raise the energy of the transition state, slowing the reaction. Also, the energy of the leaving group is reflected in the energy of the products. A reactive leaving group would raise the energy of the products, driving the equilibrium toward the reactants.

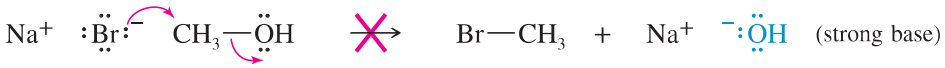


PROBLEM-SOLVING HINT

Strong bases make poor leaving groups. Do not write S_N2 reactions that show hydroxide ions, alkoxide ions, or other strong bases serving as leaving groups.

Good leaving groups should be *weak bases*; therefore, they are the conjugate bases of strong acids. The hydrohalic acids HCl, HBr, and HI are strong, and their conjugate bases (Cl^-, Br^-, and I^-) are all weak bases. Other weak bases, such as sulfate ions, sulfonate ions, and phosphate ions, can also serve as good leaving groups. Table 6-4 lists examples of good leaving groups.

Hydroxide ions, alkoxide ions, and other strong bases are poor leaving groups for S_N2 reactions. For example, the —OH group of an alcohol is a poor leaving group because it would have to leave as hydroxide ion.



Ions that are strong bases and poor leaving groups:

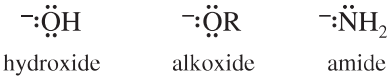
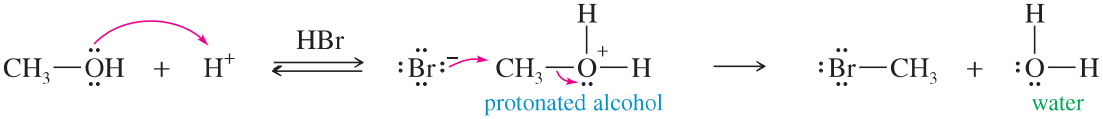


Table 6-4 also lists some neutral molecules that can be good leaving groups. A neutral molecule often serves as the leaving group from a *positively charged* species. For example, if an alcohol is placed in an acidic solution, the hydroxy group is protonated. Water then serves as the leaving group. Note that the need to protonate the alcohol (requiring acid) limits the choice of nucleophiles to those few that are weak bases, such as bromide and iodide. A strongly basic nucleophile would become protonated in acid.



3. Finally, a good leaving group should be *polarizable* to maintain partial bonding with the carbon atom in the transition state. This bonding helps stabilize the transition state and reduce the activation energy. The departure of a leaving group is much like the attack of a nucleophile, except that the bond is breaking rather than forming. Polarizable nucleophiles and polarizable leaving groups both stabilize the transition state by engaging in more bonding at a longer distance. Iodide ion, one of the most polarizable ions, is both a good nucleophile and a good leaving group. In contrast, fluoride ion is a small, "hard" ion. Fluoride is both a poor nucleophile (in protic solvents) and a poor leaving group in S_N2 reactions.

TABLE 6-4
Weak Bases That Are Common Leaving Groups

Ions:	$^-:\ddot{Cl}:$ $^-:\ddot{Br}:$	$^-:\ddot{I}:$	$^-:\ddot{O}-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R$	$^-:\ddot{O}-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-\ddot{O}R$	$^-:\ddot{O}-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{P}}-\ddot{O}R$
	halides		sulfonate	sulfate	phosphate
Neutral molecules:	$H-\ddot{O}-H$	$H-\ddot{O}-R$	$R-\ddot{N}(R)-R$	$R-\ddot{S}-R$	
	water	alcohols	amines	sulfides	

PROBLEM 6-17

When diethyl ether ($CH_3CH_2OCH_2CH_3$) is treated with concentrated HBr, the initial products are CH_3CH_2Br and CH_3CH_2OH. Propose a mechanism to account for this reaction.

6-11B Steric Effects on the Substrate

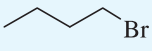
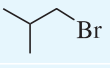
Different alkyl halides undergo S_N2 reactions at vastly different rates. The structure of the substrate is the most important factor in its reactivity toward S_N2 displacement. The reaction goes rapidly with methyl halides and with most primary substrates. It is more sluggish with secondary halides. Tertiary halides fail to react at all by the S_N2 mechanism. Table 6-5 shows the effect of alkyl substitution on the rate of S_N2 displacements.

For simple alkyl halides, the relative rates for S_N2 displacement are

Relative rates for S_N2: $CH_3X > 1° > 2° \gg 3°$

The physical explanation for this order of reactivity is suggested by the information in Table 6-5. All the slow-reacting compounds have one property in common: The back side of the electrophilic carbon atom is crowded by the presence of bulky groups. Tertiary halides are more hindered than secondary halides, which are more hindered

TABLE 6-5
Effect of Substituents on the Rates of SN2 Reactions

Class of Halide	Example	Structure	Relative Rate
methyl	CH_3-Br		>1000
primary (1°)	CH_3CH_2-Br		50
secondary (2°)	$(CH_3)_2CH-Br$		1
tertiary (3°)	$(CH_3)_3C-Br$		<0.001
n-butyl (1°)	$CH_3CH_2CH_2CH_2-Br$		20
isobutyl (1°)	$(CH_3)_2CHCH_2-Br$		2
neopentyl (1°)	$(CH_3)_3CCH_2-Br$		0.0005

Note: Two or three alkyl groups, or even a single bulky alkyl group, slow the reaction rate. The rates listed are compared to the secondary case (isopropyl bromide), assigned a relative rate of 1.

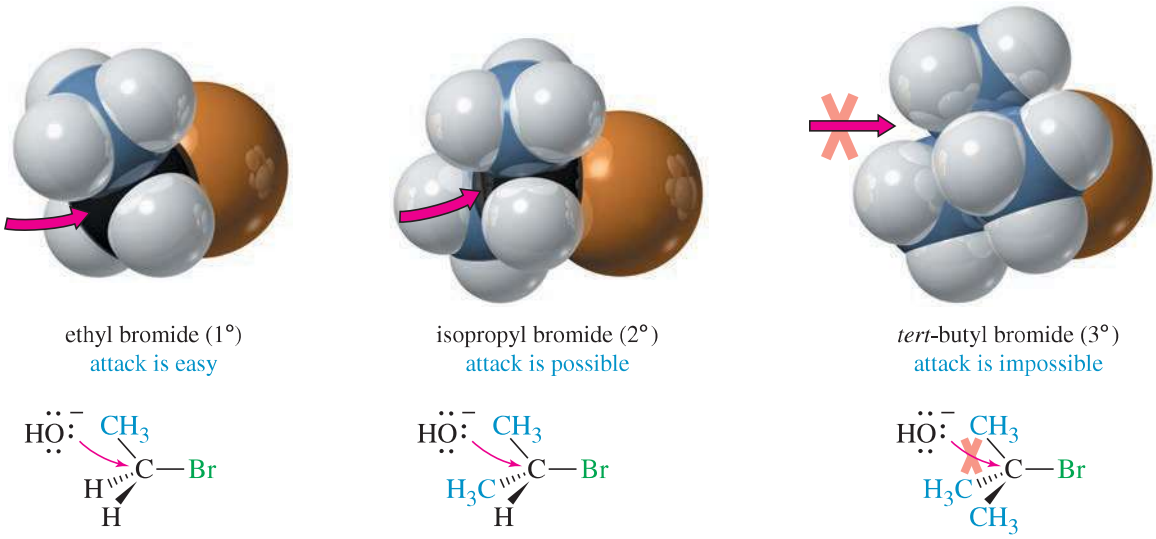


FIGURE 6-7
S_N2 attack on a simple primary alkyl halide is unhindered. Attack on a secondary halide is hindered, and attack on a tertiary halide is impossible.

than primary halides. Even a bulky primary halide (like neopentyl bromide) undergoes S_N2 reaction at a rate similar to that of a tertiary halide. The relative rates show that it is the bulk of the alkyl groups, rather than an electronic effect, that hinders the reactivity of bulky alkyl halides in the S_N2 displacement.

This effect on the rate is another example of **steric hindrance.** When the nucleophile approaches the back side of the electrophilic carbon atom, it must come within bonding distance of the back lobe of the C—X sp^3 orbital. If two alkyl groups are bonded to the carbon atom, this process is difficult. Three alkyl groups make it impossible. Just one alkyl group can produce a large amount of steric hindrance if it is unusually bulky, such as the *tert*-butyl group of neopentyl bromide.

Figure 6-7 shows the S_N2 reaction of hydroxide ion with ethyl bromide (1°), isopropyl bromide (2°), and *tert*-butyl bromide (3°). The nucleophile can easily approach the electrophilic carbon atom of ethyl bromide. In isopropyl bromide, the approach is hindered, but still possible. In contrast, S_N2 approach to the tertiary carbon of *tert*-butyl bromide is impossible because of the steric hindrance of the three methyl groups. Make models of ethyl bromide, isopropyl bromide, and *tert*-butyl bromide, and compare the ease of bringing in an atom for a back-side attack.

PROBLEM-SOLVING HINT

Do not write S_N2 reactions occurring on tertiary alkyl halides.

PROBLEM 6-18

Rank the following compounds in decreasing order of their reactivity toward the S_N2 reaction with sodium ethoxide ($Na^+ {}^-OCH_2CH_3$) in ethanol.

methyl chloride	*tert*-butyl iodide	neopentyl bromide
isopropyl bromide	methyl iodide	ethyl chloride

PROBLEM 6-19

For each pair of compounds, state which compound is the better S_N2 substrate.

(a) 2-methyl-1-iodopropane or *tert*-butyl iodide
(b) cyclohexyl bromide or 1-bromo-1-methylcyclohexane
(c) 2-bromobutane or isopropyl bromide
(d) 1-chloro-2,2-dimethylbutane or 2-chlorobutane
(e) 1-iodobutane or 2-iodopropane

6-12 Stereochemistry of the S_N2 Reaction

As we have seen, the S_N2 reaction requires attack by a nucleophile on the back side of an electrophilic carbon atom (Figure 6-8). A carbon atom can have only four filled bonding orbitals (an octet), so the leaving group must leave as the nucleophile bonds to the carbon atom. The nucleophile's electrons insert into the back lobe of carbon's sp^3 hybrid orbital in its antibonding combination with the orbital of the leaving group (because the bonding MO is already filled). These electrons in the antibonding MO help to weaken the C—Br bond as bromide leaves. The transition state shows partial bonding to both the nucleophile and the leaving group.

Back-side attack literally turns the tetrahedron of the carbon atom inside out, like an umbrella caught by the wind (Figure 6-8). In the product, the nucleophile assumes a stereochemical position opposite the position the leaving group originally occupied. We call this result an **inversion of configuration** at the carbon atom.

In the case of an asymmetric carbon atom, back-side attack gives the opposite configuration of the carbon atom (Mechanism 6-3). The S_N2 displacement is the most common example of a **Walden inversion,** a step (in a reaction sequence) where an

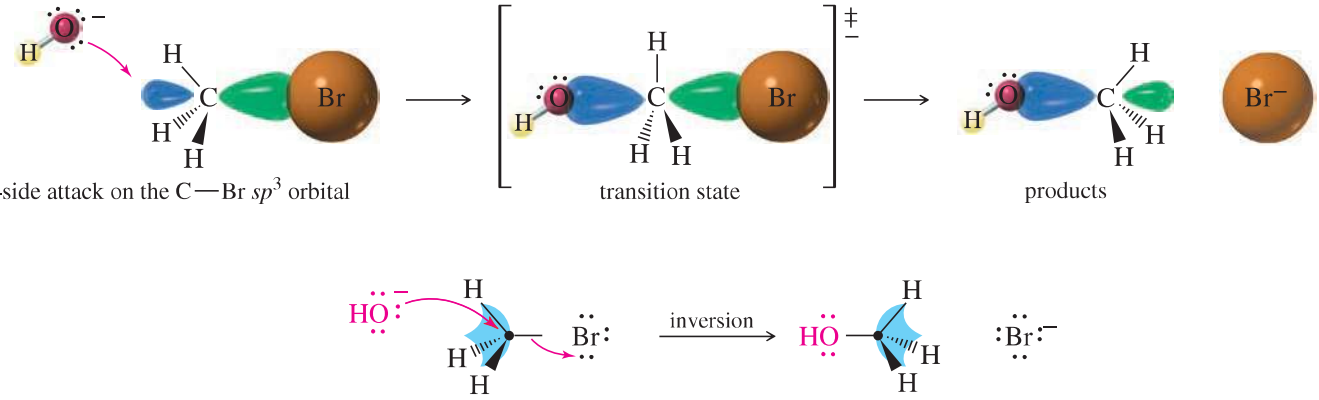
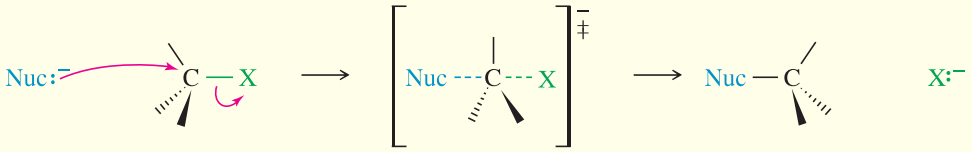


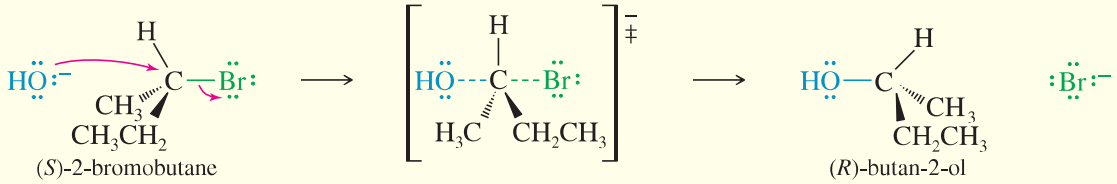
FIGURE 6-8
Back-side attack in the S_N2 reaction. The S_N2 reaction takes place through nucleophilic attack on the back lobe of carbon's sp^3 hybrid orbital. This back-side attack inverts the carbon atom's tetrahedron, like a strong wind inverts an umbrella.

MECHANISM 6-3 Inversion of Configuration in the S_N2 Reaction

Back-side attack inverts the configuration of the carbon atom.

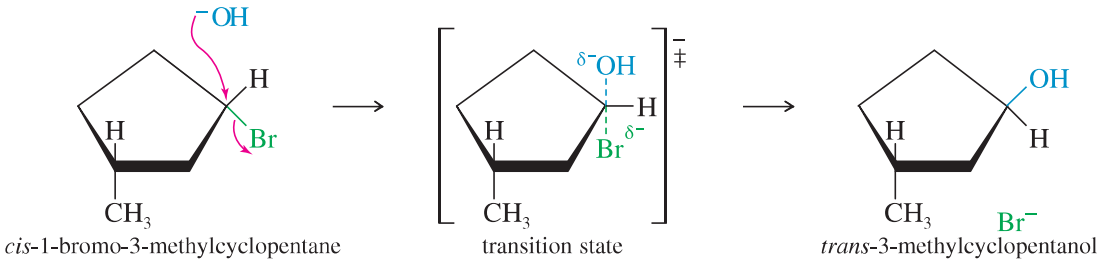


EXAMPLE:



asymmetric carbon atom undergoes inversion of configuration. In the 1890s, Paul Walden, of the University of Tübingen (Germany), was one of the first to study reactions giving inversion of configuration.

In some cases, inversion of configuration is readily apparent. For example, when *cis*-1-bromo-3-methylcyclopentane undergoes S_N2 displacement by hydroxide ion, inversion of configuration gives *trans*-3-methylcyclopentanol.



cis-1-bromo-3-methylcyclopentane transition state *trans*-3-methylcyclopentanol

The S_N2 displacement is a good example of a **stereospecific reaction:** one in which different stereoisomers react to give different stereoisomers of the product. To study the mechanism of a nucleophilic substitution, we often look at the product to see if the reaction is stereospecific, with inversion of configuration. If it is, the S_N2 mechanism is a good possibility, especially if the reaction kinetics are second order. In many cases (no asymmetric carbon or ring, for example), it is impossible to determine whether inversion has occurred. In these cases, we use kinetics and other evidence to help determine the reaction mechanism.

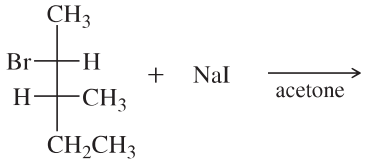
PROBLEM 6-20

Draw a perspective structure or a Fischer projection for the products of the following S_N2 reactions.

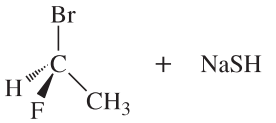
(a) *trans*-1-bromo-3-methylcyclopentane + KOH

(b) (*R*)-2-bromopentane + KCN

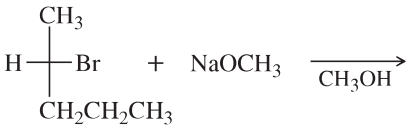
(c)



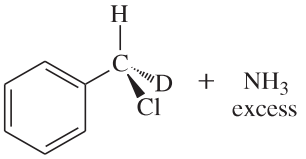
(d)



(e)



(f)



PROBLEM-SOLVING HINT

(*R*) and (*S*) are just names, and they vary with changing priorities of the substituents. Don't rely on names to determine the stereochemistry of a reaction.

PROBLEM 6-21

Under appropriate conditions, (*S*)-1-bromo-1-fluoroethane reacts with sodium methoxide to give pure (*S*)-1-fluoro-1-methoxyethane.

$$\underset{(S)}{CH_3CHBrF} + NaOCH_3 \longrightarrow \underset{(S)}{CH_3CHFOCH_3} + NaBr$$

(a) Why is bromide rather than fluoride replaced?

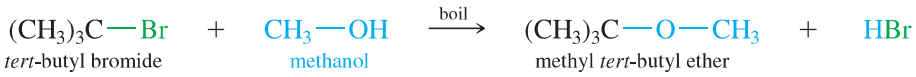
(b) Draw perspective structures (as shown on the previous page for 2-bromobutane) for the starting material, the transition state, and the product.

(c) Does the product show retention or inversion of configuration?

(d) Is this result consistent with reaction by the S_N2 mechanism?

6-13 Unimolecular Nucleophilic Substitution: The S_N1 Reaction

When *tert*-butyl bromide is placed in boiling methanol, methyl *tert*-butyl ether can be isolated from the reaction mixture. Because this reaction takes place with the solvent acting as the nucleophile, it is called a **solvolysis** (*solvo* for "solvent," plus *lysis*, meaning "cleavage").



This solvolysis is a substitution because methoxide has replaced bromide on the *tert*-butyl group. It does not go through the S_N2 mechanism, however. The S_N2 requires a strong nucleophile and a substrate that is not too hindered. Methanol is a weak nucleophile, and *tert*-butyl bromide is a hindered tertiary halide—a poor S_N2 substrate.

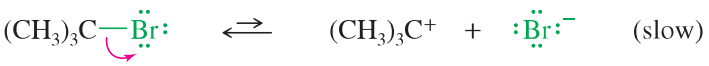
If this substitution cannot go by the S_N2 mechanism, what kind of mechanism might be involved? An important clue is kinetic: Its rate does not depend on the concentration of methanol, the nucleophile. The rate depends only on the concentration of the substrate, *tert*-butyl bromide.

$$\text{first-order rate} = k_r[(CH_3)_3C{-}Br]$$

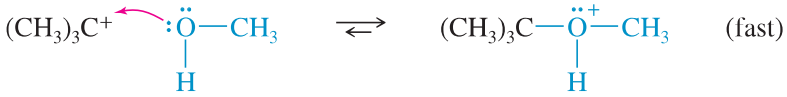
This rate equation is first order overall: first order in the concentration of the alkyl halide and zeroth order in the concentration of the nucleophile. Because the rate does not depend on the concentration of the nucleophile, we infer that the nucleophile is not present in the transition state of the rate-limiting step. The nucleophile must react *after* the slow step.

This type of substitution is called an **S_N1 reaction,** for *Substitution, Nucleophilic, unimolecular*. The term *unimolecular* means there is only one molecule involved in the transition state of the rate-limiting step. The mechanism of the S_N1 reaction of *tert*-butyl bromide with methanol is shown here. Ionization of the alkyl halide (first step) is the rate-limiting step.

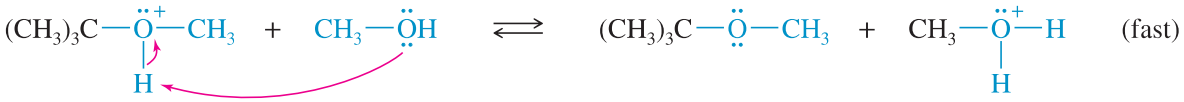
Step 1: Formation of carbocation (rate limiting)



Step 2: Nucleophilic attack on the carbocation



Final Step: Loss of proton to solvent



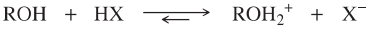
The S_N1 mechanism is a multistep process. The first step is a slow ionization to form a carbocation. The second step is a fast attack on the carbocation by a nucleophile. The carbocation is a strong electrophile; it reacts very quickly with nucleophiles, including weak nucleophiles. The nucleophile in S_N1 reactions is usually weak, because a strong nucleophile would be more likely to attack the substrate and force some kind of second-order reaction. If the nucleophile is an uncharged molecule such as water or an alcohol, the positively charged product must lose a proton to give the final uncharged product. The general mechanism for the S_N1 reaction is summarized in Key Mechanism 6-4.

PROBLEM-SOLVING HINT

Strong acids such as HCl, HBr, and HI are completely dissociated in solutions of alcohols or water. Consider the pK_a values:

HI	−10
HBr	−9
HCl	−7
$CH_3OH_2^+$	−2.5
$CH_3CH_2OH_2^+$	−2.4
H_3O^+	−1.7

These pK_a values show that the equilibrium

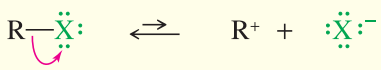


lies far to the right. When we write "HBr (aq)" or "HBr in ethanol," we actually mean the dissociated ions. The values also show that alcohols and water are much more basic than halide ions, so they are more likely than halide ion to serve as the base in the final deprotonation in the S_N1 reaction and similar reactions under acidic conditions.

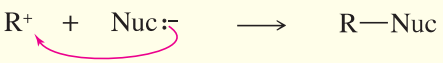
KEY MECHANISM 6-4 The S_N1 Reaction

The S_N1 reaction involves a two-step mechanism. A slow ionization gives a carbocation that reacts quickly with a (usually weak) nucleophile. Reactivity: 3° > 2° > 1°.

***Step 1*:** Formation of the carbocation (rate-limiting).



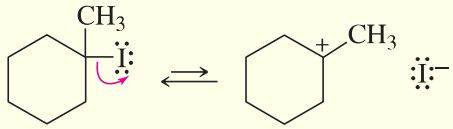
***Step 2*:** Nucleophilic attack on the carbocation (fast).



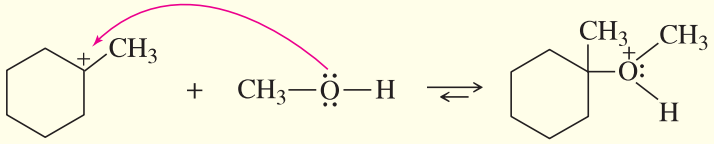
If the nucleophile is water or an alcohol, a third step is needed to deprotonate the product.

EXAMPLE: Solvolysis of 1-iodo-1-methylcyclohexane in methanol.

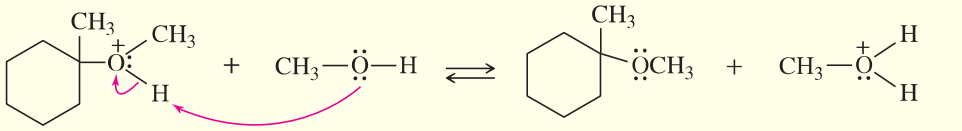
***Step 1*:** Formation of a carbocation (rate-limiting).



***Step 2*:** Nucleophilic attack by the solvent (methanol).



***Step 3*:** Deprotonation to form the product.



product (protonated methanol)

PROBLEM 6-22

Propose an S_N1 mechanism for the solvolysis of 3-bromo-2,3-dimethylpentane in ethanol.

PROBLEM-SOLVING HINT

Never show a proton falling off into thin air. Show a possible base (often the solvent) abstracting the proton.

The reaction-energy diagram of the S_N1 reaction (Figure 6-9) shows why the rate does not depend on the strength or concentration of the nucleophile. The ionization (first step) is highly endothermic, and its large activation energy determines the overall reaction rate. The nucleophilic attack (second step) is strongly exothermic, with a lower-energy transition state. In effect, a nucleophile reacts with the carbocation almost as soon as it forms.

The reaction-energy diagrams of the S_N1 mechanism and the S_N2 mechanism are compared in Figure 6-9. The S_N1 has a true intermediate, the carbocation. The intermediate appears as a relative minimum (a low point) in the reaction-energy diagram. Reagents and conditions that favor formation of the carbocation (the slow step) accelerate the S_N1 reaction; reagents and conditions that hinder its formation retard the reaction.

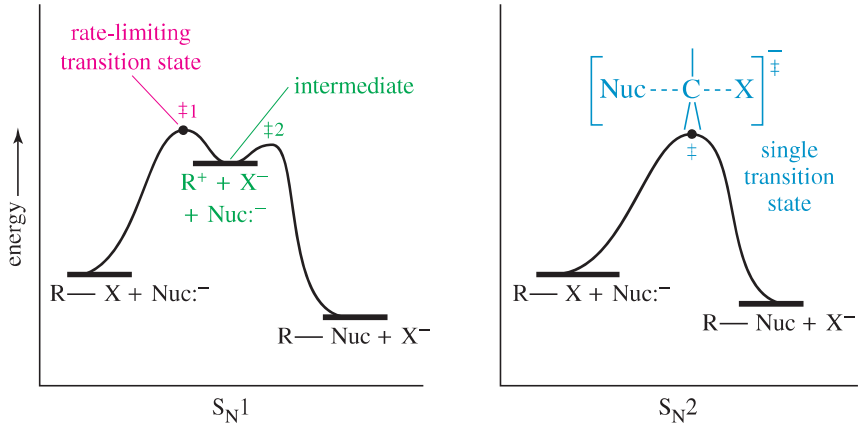
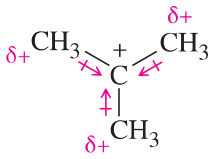


FIGURE 6-9
Reaction-energy diagrams of the S_N1 and S_N2 reactions. The S_N1 is a two-step mechanism with two transition states (‡1 and ‡2) and a carbocation intermediate. The S_N2 has only one transition state and no intermediate.

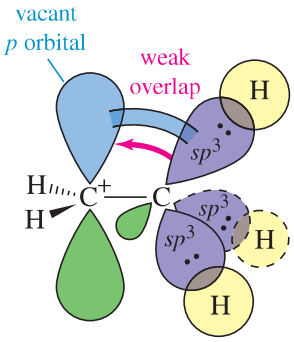
6-13A Substituent Effects

The rate-limiting step of the S_N1 reaction is ionization to form a carbocation, a strongly endothermic process. The first transition state resembles the carbocation (Hammond's postulate, Section 4-14); consequently, rates of S_N1 reactions depend strongly on carbocation stability. In Section 4-16A, we saw that alkyl groups stabilize carbocations by donating electrons through sigma bonds (the *inductive effect*) and through overlap of filled orbitals with the empty *p* orbital of the carbocation *(hyperconjugation)*. Highly substituted carbocations are therefore more stable.

carbocation stability:
$3° > 2° > 1° > {}^+CH_3$



inductive effect



carbocation alkyl group

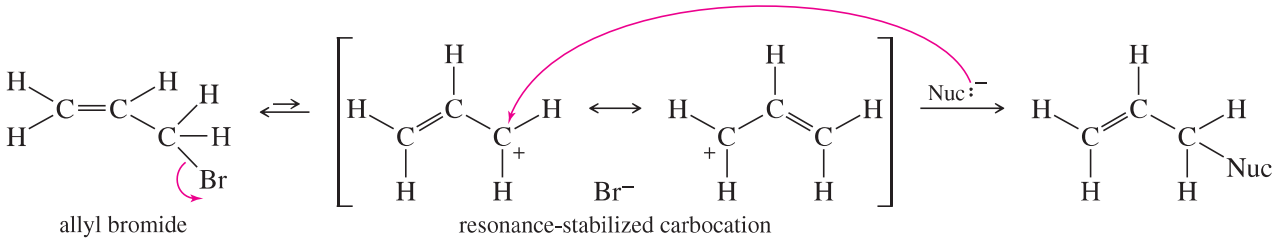
hyperconjugation

Reactivity toward S_N1 substitution mechanisms follows the stability of carbocations:

S_N1 reactivity: $3° > 2° > 1° > CH_3X$

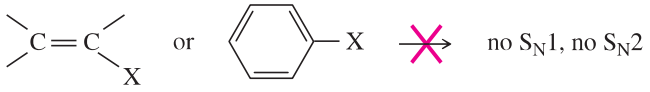
This order is *opposite* that of the S_N2 reaction. Alkyl groups hinder the S_N2 by blocking attack of the strong nucleophile, but alkyl groups enhance the S_N1 by stabilizing the carbocation intermediate. Simple primary and methyl carbocations are not normally seen in solution.

Resonance stabilization of the carbocation can also promote the S_N1 reaction. For example, allyl bromide is a primary halide, but it undergoes the S_N1 reaction about as fast as a secondary halide. The carbocation formed by ionization is resonance-stabilized, with the positive charge spread equally over two carbon atoms.



allyl bromide — resonance-stabilized carbocation

Vinyl and aryl halides generally do not undergo S_N1 or S_N2 reactions. An S_N1 reaction would require ionization to form a vinyl or aryl cation, either of which is less stable than most alkyl carbocations. An S_N2 reaction would require back-side attack by the nucleophile, which is made impossible by the repulsion of the electrons in the double bond or aromatic ring.



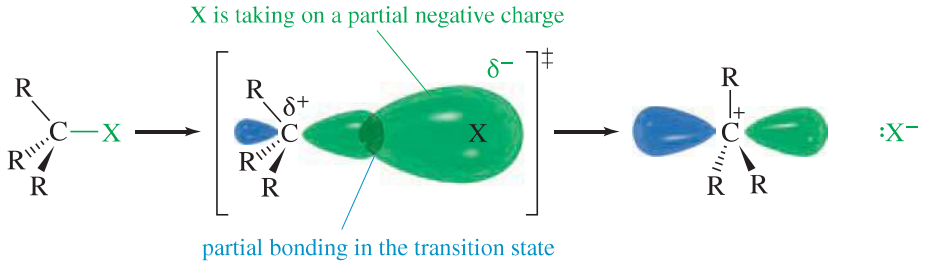
a vinyl halide — an aryl halide

6-13B Leaving-Group Effects

The leaving group is breaking its bond to carbon in the rate-limiting ionization step of the S_N1 mechanism. A highly polarizable leaving group helps stabilize the rate-limiting transition state through partial bonding as it leaves. The leaving group should be a weak base—very stable after it leaves with the pair of electrons that bonded it to carbon.

Figure 6-10 shows the transition state of the ionization step of the S_N1 reaction. Notice how the leaving group is taking on a negative charge while it stabilizes the new carbocation through partial bonding. The leaving group should be stable as it takes on this negative charge, and it should be polarizable to engage in effective partial bonding as it leaves. A good leaving group is just as necessary in the S_N1 reaction as it is in the S_N2, and similar leaving groups are effective for either reaction. Table 6-4 (page 271) lists some common leaving groups for either reaction.

FIGURE 6-10
In the transition state of the S_N1 ionization, the leaving group is taking on a negative charge. The C—X bond is breaking, and a polarizable leaving group can still maintain substantial overlap.



PROBLEM-SOLVING HINT

Primary cations are rarely formed in solution unless they are resonance-stabilized.

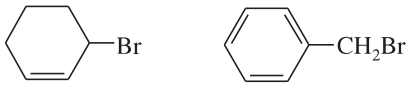
PROBLEM 6-23

Choose the member of each pair that will react faster by the S_N1 mechanism.

(a) 1-bromopropane or 2-bromopropane
(b) 2-bromo-2-methylbutane or 2-bromo-3-methylbutane
(c) *n*-propyl bromide or allyl bromide
(d) 1-bromo-2,2-dimethylpropane or 2-bromopropane
(e) 2-iodo-2-methylbutane or *tert*-butyl chloride
(f) 2-bromo-2-methylbutane or ethyl iodide

PROBLEM 6-24

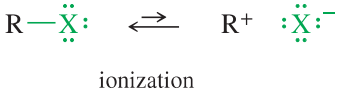
3-Bromocyclohexene is a secondary halide, and benzyl bromide is a primary halide. Both halides undergo S_N1 substitution about as fast as most tertiary halides. Use resonance structures to explain this enhanced reactivity.



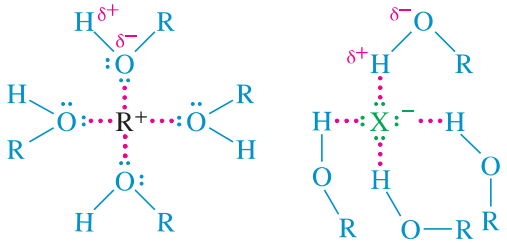
3-bromocyclohexene benzyl bromide

6-13C Solvent Effects on S_N1 Reactions

The S_N1 reaction goes much more readily in polar solvents that stabilize ions. The rate-limiting step forms two ions, and ionization is taking place in the transition state. Polar solvents solvate these ions by an interaction of the solvent's dipole moment with the charge of the ion. Protic solvents such as alcohols and water are even more effective solvents because anions form hydrogen bonds with the —OH hydrogen atom, and cations complex with the nonbonding electrons of the —OH oxygen atom.



ionization



solvated ions

Ionization of an alkyl halide requires formation and separation of positive and negative charges, similar to what happens when sodium chloride dissolves in water. Therefore, S_N1 reactions require highly polar solvents that strongly solvate ions. One measure of a solvent's ability to solvate ions is its *dielectric constant* (ε), a measure of the solvent's polarity. Table 6-6 lists the dielectric constants of some common solvents and the relative ionization rates for *tert*-butyl chloride in these solvents. Note that ionization occurs much faster in highly polar solvents such as water and alcohols. Although most alkyl halides are not soluble in water, they often dissolve in highly polar mixtures of acetone and alcohols with water.

TABLE 6-6
Dielectric Constants (ε) and Ionization Rates of *tert*-Butyl Chloride in Common Solvents

Solvent	ε	Relative Rate
water	78	8000
methanol	33	1000
ethanol	24	200
acetone	21	1
diethyl ether	4.3	0.001
hexane	2.0	<0.0001

6-14 Stereochemistry of the S_N1 Reaction

Recall from Section 6-12 that the S_N2 reaction is stereospecific: the nucleophile attacks from the back side of the electrophilic carbon atom, giving inversion of configuration. In contrast, the S_N1 reaction is not stereospecific. In the S_N1 mechanism, the carbocation intermediate is sp^2 hybridized and planar. A nucleophile can attack the carbocation from either face. Figure 6-11 shows the S_N1 solvolysis of a chiral compound, (*S*)-3-bromo-2,3-dimethylpentane, in ethanol. The carbocation is planar and achiral; attack from both faces gives both enantiomers of the product. Such a process, giving both enantiomers of the product (whether or not the two enantiomers are produced in equal amounts), is called **racemization.** The product is either racemic or at least less optically pure than the starting material.

If a nucleophile attacks the carbocation in Figure 6-11 from the front side (the side the leaving group left), the product molecule shows **retention of configuration.** Attack from the back side gives a product molecule showing **inversion of configuration.** Racemization is simply a combination of retention and inversion. When racemization occurs, the product is rarely completely racemic, however; there is often more inversion than retention of configuration. As the leaving group leaves, it partially blocks the front side of the carbocation. The back side is unhindered, so attack is more likely there.

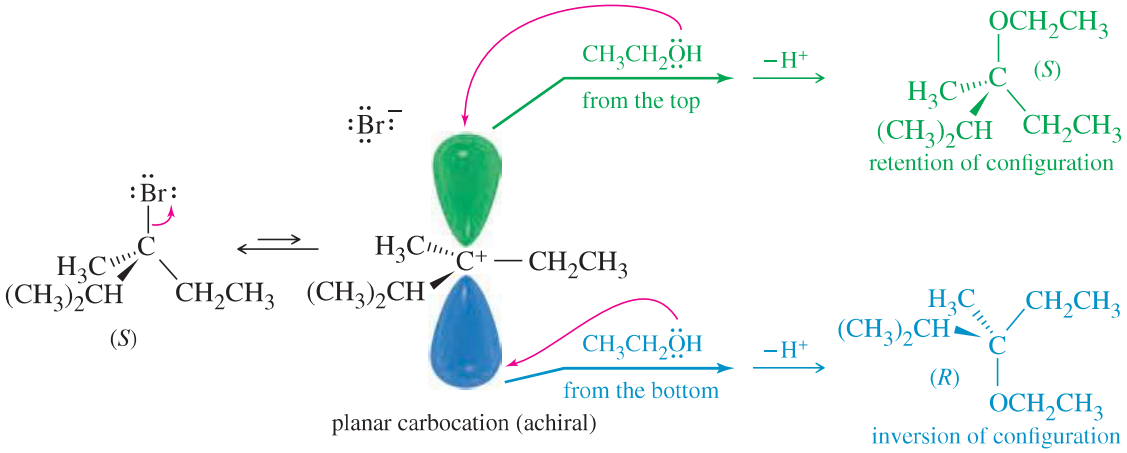


FIGURE 6-11
Racemization. An asymmetric carbon atom undergoes racemization when it ionizes to a planar, achiral carbocation. A nucleophile can attack the carbocation from either face, giving either enantiomer of the product.

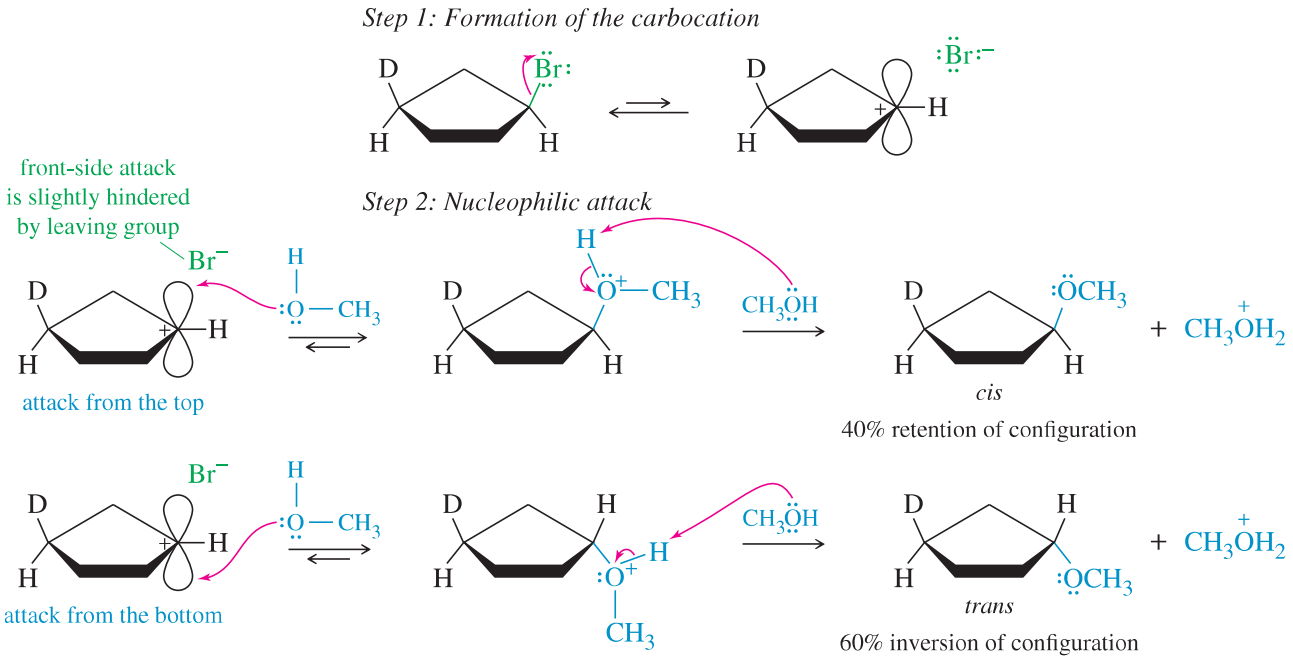


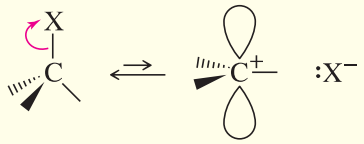
FIGURE 6-12
In the S_N1 reaction of *cis*-1-bromo-3-deuteriocyclopentane with methanol, the carbocation can be attacked from either face. Because the leaving group (bromide) partially blocks the front side as it leaves, back-side attack (inversion of configuration) is slightly favored.

Figure 6-12 shows a cyclic case where one of the faces of a cyclopentane ring has been "labeled" by a deuterium atom. Deuterium has the same size and shape as hydrogen, and it undergoes the same reactions. It distinguishes between the two faces of the ring: the bromine atom is cis to the deuterium in the reactant, so the nucleophile is cis to the deuterium in the retention product. The nucleophile is trans to the deuterium in the inversion product. The product mixture contains both cis and trans isomers, with the trans isomer slightly favored because the leaving group hinders approach of the nucleophilic solvent from the front side.

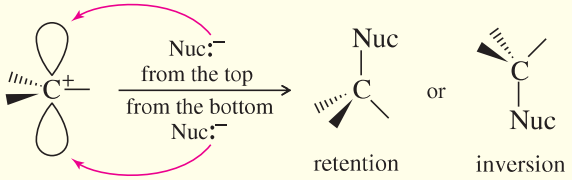
MECHANISM 6-5 Racemization in the S_N1 Reaction

The S_N1 reaction involves ionization to a flat carbocation, which can be attacked from either side.

Step 1: Ionization of a tetrahedral carbon gives a flat carbocation.



Step 2: A nucleophile may attack either side of the carbocation.



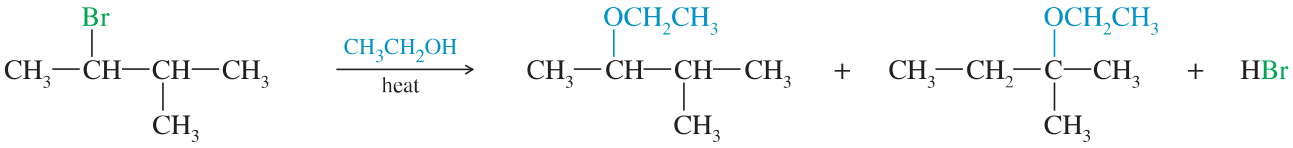
Racemization: Formation of products showing both retention and inversion of configuration.

These two products may be different if the carbon atom is stereogenic.

6-15 Rearrangements in S_N1 Reactions

Carbocations frequently undergo structural changes, called **rearrangements,** to form more stable ions. A rearrangement may occur after a carbocation has formed, or it may occur as the leaving group is leaving. Rearrangements are not seen in S_N2 reactions, where no carbocation is formed and the one-step mechanism allows no opportunity for rearrangement.

An example of a reaction with rearrangement is the S_N1 reaction of 2-bromo-3-methylbutane in boiling ethanol. The product is a mixture of 2-ethoxy-3-methylbutane (not rearranged) and 2-ethoxy-2-methylbutane (rearranged).



PROBLEM 6-25

Give the S_N1 mechanism for the formation of 2-ethoxy-3-methylbutane, the unrearranged product in this reaction.

PROBLEM-SOLVING HINT

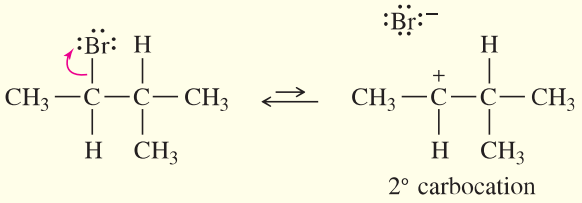
A carbocation usually rearranges just once. Most rearrangements convert the carbocation to a more stable carbocation, typically
2° ⟶ 3°
or 2° ⟶ resonance-stabliized
or 3° ⟶ resonance-stabilized.

The rearranged product, 2-ethoxy-2-methylbutane, results from a **hydride shift,** the movement of a hydrogen atom with its bonding pair of electrons. A hydride shift is represented by the symbol ~H. In this case, the hydride shift converts the initially formed secondary carbocation to a more stable tertiary carbocation. Attack by the solvent gives the rearranged product.

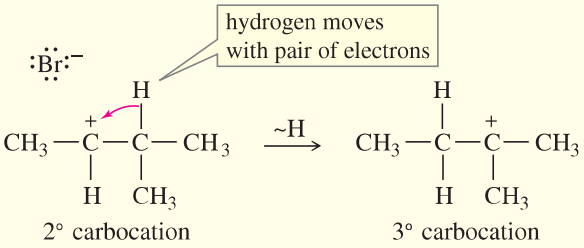
MECHANISM 6-6 Hydride Shift in an S_N1 Reaction

Carbocations often rearrange to form more stable carbocations. This may occur when a hydrogen atom moves with its bonding pair of electrons. Formally, this is the movement of a hydride ion ($H:^-$), although no actual free hydride ion is involved.

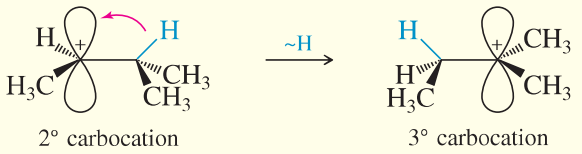
Step 1: Unimolecular ionization gives a carbocation.



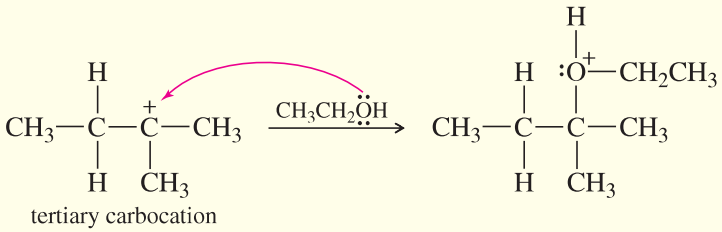
Step 2: A hydride shift forms a more stable carbocation.



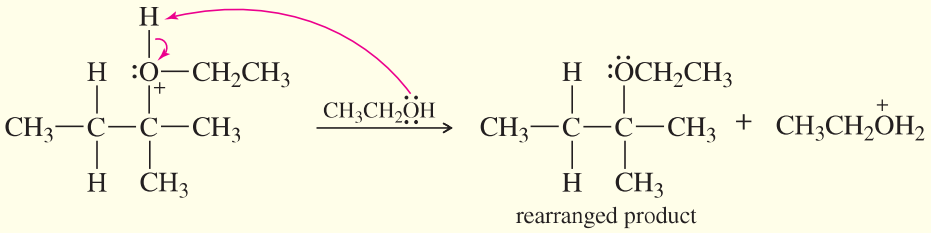
This rearrangement involves movement of a hydrogen atom with its bonding pair of electrons over to the empty *p* orbital of the carbocation. In three dimensions, the rearrangement looks like this:



Step 3: Solvent (a weak nucleophile) attacks the rearranged carbocation.



Step 4: Deprotonation gives the rearranged product.



When neopentyl bromide is boiled in ethanol, it gives *only* a rearranged substitution product. This product results from a **methyl shift** (represented by the symbol $\sim CH_3$), the migration of a methyl group together with its pair of electrons. Without rearrangement, ionization of neopentyl bromide would give a very unstable primary carbocation.

The methyl shift occurs *while* bromide ion is leaving, so that only the more stable tertiary carbocation is formed.

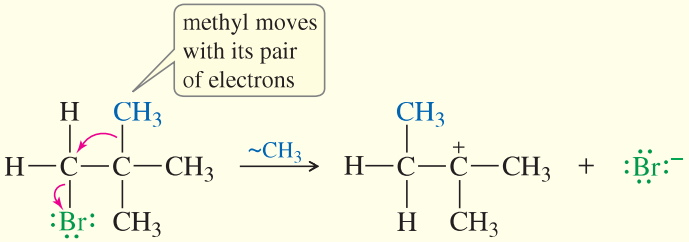
PROBLEM-SOLVING HINT

Primary halides and methyl halides rarely ionize to carbocations in solution. If a primary halide ionizes, it will likely ionize with rearrangement.

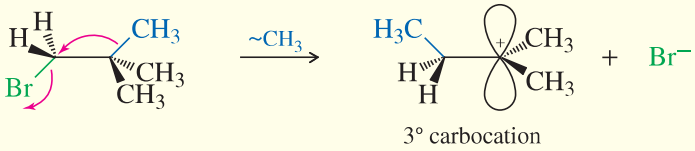
MECHANISM 6-7 Methyl Shift in an S_N1 Reaction

An alkyl group can rearrange to make a carbocation more stable.

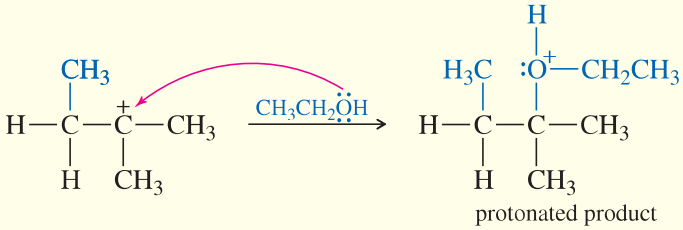
Step 1: Ionization occurs with a methyl shift.



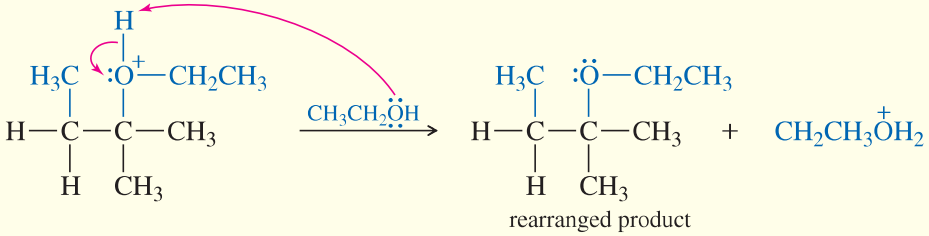
In three dimensions,



Step 2: Attack by ethanol gives a protonated version of the rearranged product.



Step 3: Deprotonation gives the rearranged product.



Because rearrangement is required for ionization of this primary halide, only rearranged products are observed.

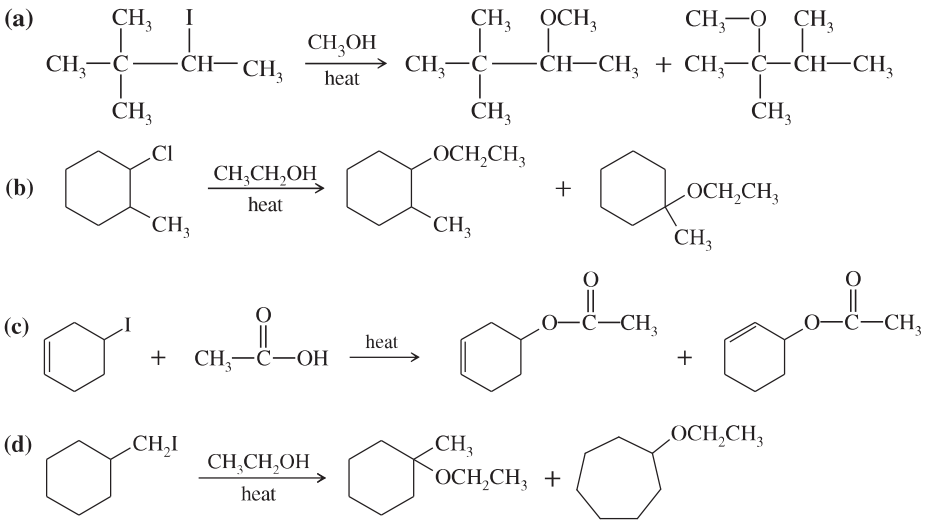
In general, we should expect rearrangements in reactions involving carbocations whenever a hydride shift or an **alkyl shift** can form a more stable carbocation. Most rearrangements convert 2° (or incipient 1°) carbocations to 3° or resonance-stabilized carbocations.

PROBLEM-SOLVING HINT

Most rearrangements convert 2° (or incipient 1°) carbocations to 3° or resonance-stabilized carbocations.

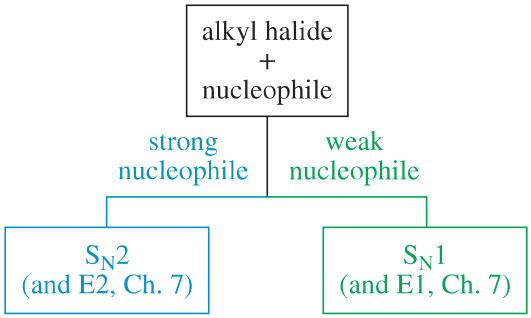
PROBLEM 6-26

Propose a mechanism involving a hydride shift or an alkyl shift for each solvolysis reaction. Explain how each rearrangement forms a more stable intermediate.



6-16 Comparison of S_N1 and S_N2 Reactions

Let's compare what we know about the S_N1 and S_N2 reactions, then organize this material into a brief table.



Effect of the Nucleophile The nucleophile takes part in the slow step (the only step) of the S_N2 reaction but not in the slow step of the S_N1. Therefore, a strong nucleophile promotes the S_N2 but not the S_N1. Weak nucleophiles fail to promote the S_N2 reaction; therefore, reactions with weak nucleophiles often go by the S_N1 mechanism if the substrate is secondary or tertiary.

S_N1:	Nucleophile strength is unimportant (usually weak).
S_N2:	Strong nucleophiles are required.

Effect of the Substrate The structure of the substrate (the alkyl halide) is an important factor in determining which of these substitution mechanisms might operate. Most methyl halides and primary halides are poor substrates for S_N1 substitutions because they cannot easily ionize to high-energy methyl and primary carbocations. They are relatively unhindered, however, so they make good S_N2 substrates.

Tertiary halides are too hindered to undergo S_N2 displacement, but they can ionize to form tertiary carbocations. Tertiary halides undergo substitution exclusively through the S_N1 mechanism. Secondary halides can undergo substitution by either mechanism, depending on the conditions.

S_N1 substrates:	$3^\circ > 2^\circ$	(1° and CH_3X are unlikely)
S_N2 substrates:	$CH_3X > 1^\circ > 2^\circ$	(3° is unsuitable)

If silver nitrate ($AgNO_3$) is added to an alkyl halide in a good ionizing solvent, the silver ion removes the halide ion to give a carbocation. This technique can force some unlikely ionizations, often giving interesting rearrangements (see Problem 6-29).

Effect of the Solvent The slow step of the S_N1 reaction involves formation of two ions. Solvation of these ions is crucial to stabilizing them and lowering the activation energy for their formation. Very polar ionizing solvents such as water and alcohols are needed for the S_N1. The solvent may be heated to reflux (boiling) to provide the energy needed for ionization.

Less charge separation is generated in the transition state of the S_N2 reaction. Strong solvation may weaken the strength of the nucleophile because of the energy needed to strip off the solvent molecules. Thus, the S_N2 reaction often goes faster in less polar solvents if the nucleophile will dissolve. Polar aprotic solvents may enhance the strength of weak nucleophiles.

S_N1:	Good ionizing solvent required.
S_N2:	May go faster in a less polar solvent.

Kinetics The rate of the S_N1 reaction is proportional to the concentration of the alkyl halide but not the concentration of the nucleophile. It follows a first-order rate equation.

The rate of the S_N2 reaction is proportional to the concentrations of both the alkyl halide [R—X] and the nucleophile [Nuc:$^-$]. It follows a second-order rate equation.

S_N1 rate $= k_r$[R—X]
S_N2 rate $= k_r$[R—X][Nuc:$^-$]

Stereochemistry The S_N1 reaction involves a flat carbocation intermediate that can be attacked from either face. Therefore, the S_N1 usually gives a mixture of inversion and retention of configuration.

The S_N2 reaction takes place through a back-side attack, which inverts the stereochemistry of the carbon atom. Complete inversion of configuration is the result.

S_N1 stereochemistry:	Mixture of retention and inversion; racemization.
S_N2 stereochemistry:	Complete inversion.

Rearrangements The S_N1 reaction involves a carbocation intermediate. This intermediate can rearrange, usually by a hydride shift or an alkyl shift, to give a more stable carbocation.

The S_N2 reaction takes place in one step with no intermediates. No rearrangement is possible in the S_N2 reaction.

S_N1:	Rearrangements are common.
S_N2:	Rearrangements are impossible.

SUMMARY Nucleophilic Substitutions

	S_N1	S_N2
Promoting factors		
nucleophile	weak nucleophiles are OK	strong nucleophile needed
substrate (RX)	3° > 2°	CH_3X > 1° > 2°
solvent	good ionizing solvent needed	wide variety of solvents
leaving group	good one required	good one required
other	$AgNO_3$ forces ionization	
Characteristics		
kinetics	first order, k_r[RX]	second order, k_r[RX][Nuc:$^-$]
stereochemistry	mixture of inversion and retention	complete inversion
rearrangements	common	impossible

	S_N1 conditions (weak nucleophile)	S_N2 conditions (strong nucleophile)
methyl halides CH_3X	No reaction. A methyl cation is too unstable.	S_N2 is unhindered and favored.
primary halides RCH_2X	Rarely any reaction unless it can form a resonance-stabilized cation.	S_N2 is favored unless the R group is exceptionally bulky.
secondary halides R_2CHX	S_N1, often with rearrangement, can occur in a good solvent.	S_N2 can occur unless the alkyl groups or the nucleophile are bulky.
tertiary halides R_3CX	S_N1 occurs readily in a good solvent.	S_N2 cannot occur because of steric hindrance.

PROBLEM-SOLVING HINT

The strength of the nucleophile (or base) usually determines the order of the reaction. Strong nucleophiles encourage bimolecular, second-order reactions, and weak nucleophiles more commonly react by unimolecular, first-order mechanisms. Also, S_N2 is unlikely with 3° halides, and S_N1 is unlikely with 1° halides unless they are resonance-stabilized.

PROBLEM 6-27

For each reaction, give the expected substitution product, and predict whether the mechanism will be predominantly first order (S_N1) or second order (S_N2).

(a) 2-chloro-2-methylbutane + CH_3COOH
(b) isobutyl bromide + sodium methoxide
(c) 1-iodo-1-methylcyclohexane + ethanol
(d) cyclohexyl bromide + methanol
(e) cyclohexyl bromide + sodium ethoxide

PROBLEM 6-28

Under certain conditions, when (*R*)-2-bromobutane is heated with water, the S_N1 substitution proceeds twice as fast as the S_N2. Calculate the e.e. and the specific rotation expected for the product. The specific rotation of (*R*)-butan-2-ol is −13.5°. Assume that the S_N1 gives equal amounts of the two enantiomers.

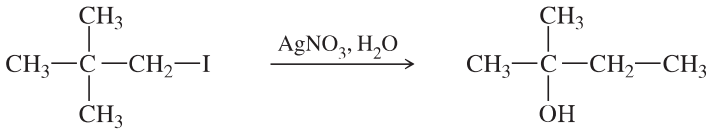
PROBLEM 6-29

A reluctant first-order substrate can be forced to ionize by adding some silver nitrate (one of the few soluble silver salts) to the reaction. Silver ion reacts with the halogen to form a silver halide (a highly exothermic reaction), generating the cation of the alkyl group.

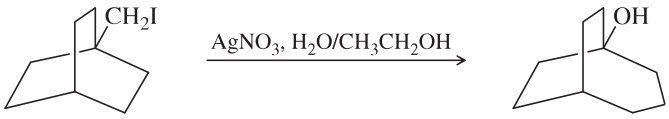
$$R{-}X + Ag^+ \longrightarrow R^+ + AgX\downarrow$$

Give mechanisms for the following silver-promoted rearrangements.

(a)



(b)



The Rest of the Story Elimination reactions often accompany nucleophilic substitutions of alkyl halides and other compounds containing good leaving groups. Under conditions that favor them, elimination reactions often predominate over substitutions. In Chapter 6, we have concentrated on the factors that favor S_N1 and S_N2 substitutions. In Chapter 7, we will cover the factors that favor eliminations. At that point, we can begin to predict the products and mechanisms of many reactions that are subject to competition between substitutions and eliminations.

SUMMARY Reactions of Alkyl Halides

Some of these reactions have not yet been covered, but they are included here for completeness and for later reference. The reactions that we have not yet covered are shown in the summary with a gray background. Notice the section numbers, indicating where each reaction is covered.

1. *Nucleophilic substitutions* (Section 6-9)

a. *Alcohol formation*

$$R{-}X + {:}\ddot{\underset{\cdot\cdot}{O}}H \longrightarrow R{-}OH + :X^-$$

b. *Halide exchange*

$$R{-}X + {:}\ddot{\underset{\cdot\cdot}{I}}{:}^- \longrightarrow R{-}I + :X^-$$

$$R{-}Cl + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} R{-}F + KCl$$

c. *Williamson ether synthesis*

$$R{-}X + R'\ddot{\underset{\cdot\cdot}{O}}{:}^- \longrightarrow R{-}\ddot{\underset{\cdot\cdot}{O}}{-}R' + :X^- \quad \text{ether synthesis}$$

$$R{-}X + R'\ddot{\underset{\cdot\cdot}{S}}{:}^- \longrightarrow R{-}\ddot{\underset{\cdot\cdot}{S}}{-}R' + :X^- \quad \text{thioether synthesis}$$

d. *Amine synthesis*

$$R{-}X + \underset{\text{excess}}{{:}NH_3} \longrightarrow R{-}NH_3^+\ :X^- \xrightarrow{:NH_3} \underset{\text{amine}}{R{-}\ddot{N}H_2} + NH_4^+\ :X^-$$

(continued)