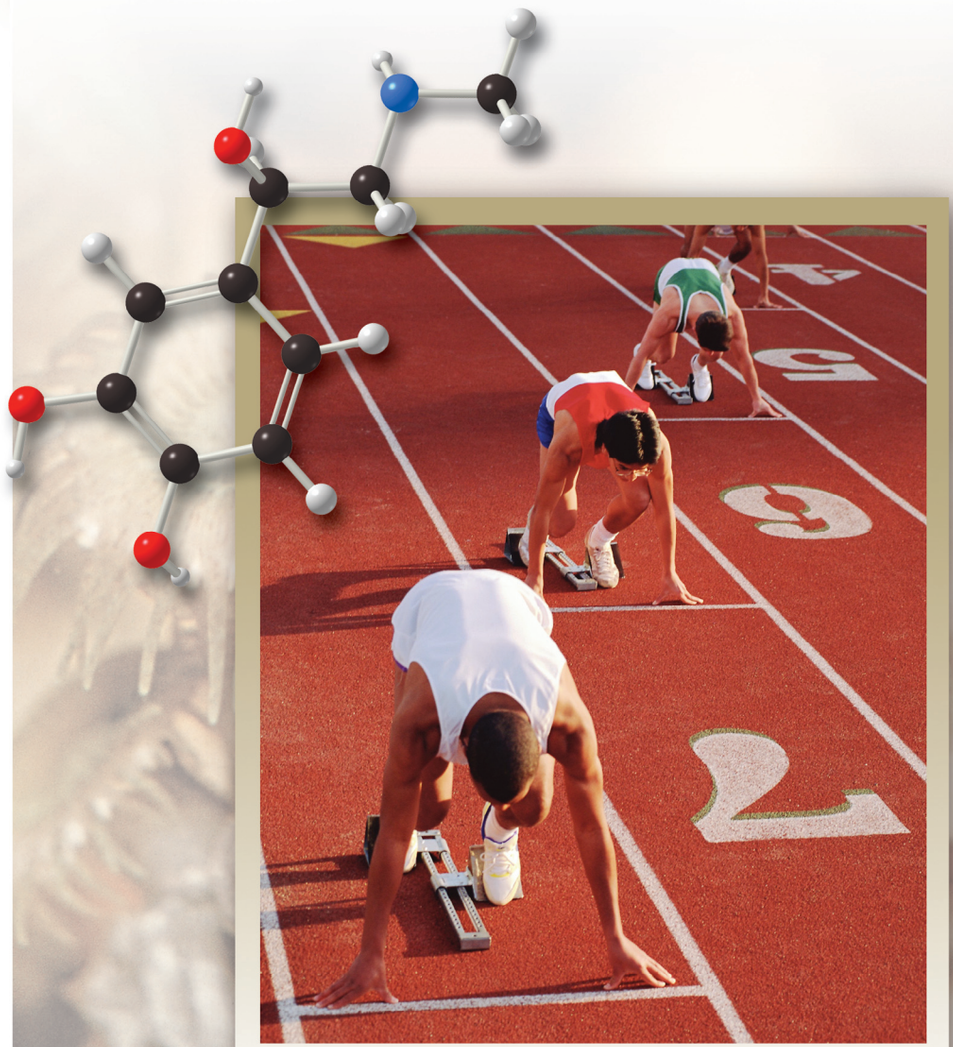
smi97462_ch07.qxd 11/4/04 2:51 PM Page 220

CHAPTER

7

Alkyl Halides and Nucleophilic Substitution

Adrenaline (or **epinephrine**), a hormone secreted by the adrenal gland, increases blood pressure and heart rate, and dilates lung passages. Individuals often speak of the "rush of adrenaline" when undertaking a particularly strenuous or challenging activity. Adrenaline is made in the body by a simple organic reaction called **nucleophilic substitution.** In Chapter 7 you will learn about the mechanism of nucleophilic substitution and how adrenaline is synthesized in organisms.



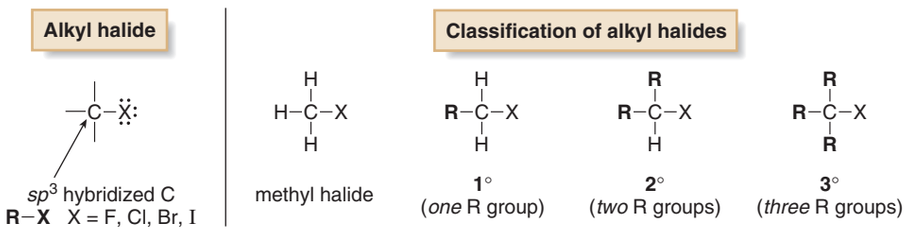
smi97462_ch07.qxd 11/22/04 2:34 PM Page 221

This is the first of three chapters dealing with an in-depth study of the organic reactions of compounds containing C–Z σ bonds, where Z is an element more electronegative than carbon. In Chapter 7 we learn about **alkyl halides** and one of their characteristic reactions, **nucleophilic substitution.** In Chapter 8, we look at **elimination,** a second general reaction of alkyl halides. We conclude this discussion in Chapter 9 by examining other molecules that also undergo nucleophilic substitution and elimination reactions.

7.1 Introduction to Alkyl Halides

Alkyl halides are organic molecules containing a halogen atom X bonded to an sp^3 hybridized carbon atom. Alkyl halides are classified as **primary (1°), secondary (2°),** or **tertiary (3°)** depending on the number of carbons bonded to the carbon with the halogen.

Alkyl halides have the general molecular formula $C_nH_{2n+1}X$, and are formally derived from an alkane by replacing a hydrogen atom with a halogen.



Whether an alkyl halide is 1°, 2°, or 3° is the *most important factor* in determining the course of its chemical reactions. Figure 7.1 illustrates three examples.

Four types of organic halides having the halogen atom in close proximity to a π bond are illustrated in Figure 7.2. **Vinyl halides** have a halogen atom bonded to a carbon–carbon double bond, and **aryl halides** have a halogen atom bonded to a benzene ring. These two types of organic halides with X directly bonded to an sp^2 hybridized carbon atom do ***not*** undergo the reactions presented in Chapter 7, as discussed in Section 7.18.

Allylic halides and benzylic halides have halogen atoms bonded to sp^3 hybridized carbon atoms and ***do*** undergo the reactions described in Chapter 7. **Allylic halides** have X bonded to the carbon atom *adjacent* to a carbon–carbon double bond, and **benzylic halides** have X bonded to the carbon atom *adjacent* to a benzene ring. The synthesis of allylic and benzylic halides is discussed in Sections 13.10 and 18.13, respectively.

Figure 7.1 Examples of 1°, 2°, and 3° alkyl halides

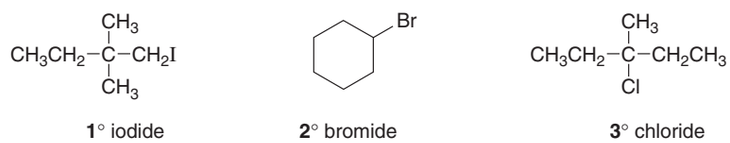
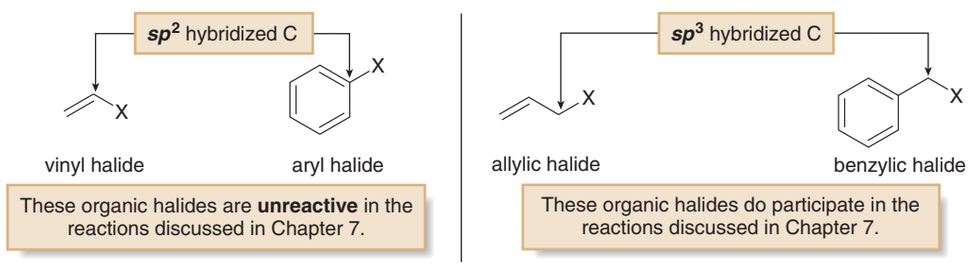
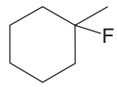
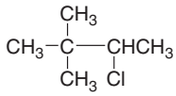
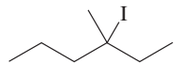


Figure 7.2 Four types of organic halides (RX) having X near a π bond



smi97462_ch07.qxd 11/22/04 2:35 PM Page 222

PROBLEM 7.1 Classify each alkyl halide as 1°, 2°, or 3°.

a. $CH_3CH_2CH_2CH_2CH_2-Br$ b.  c.  d. 

7.2 Nomenclature

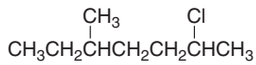
The systematic (IUPAC) method for naming alkyl halides follows from the basic rules described in Chapter 4. The common method is also discussed in Section 7.2B, because many low molecular weight alkyl halides are often referred to by their common names.

7.2A IUPAC System

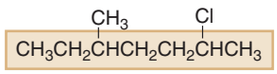
An alkyl halide is named as an alkane with a halogen substituent—that is, as a ***halo alkane.*** To name a halogen substituent, change the ***-ine*** ending of the name of the halogen to the suffix ***-o*** (chlor*ine* → chlor*o*).

How To Name an Alkyl Halide Using the IUPAC System

Example **Give the IUPAC name of the following alkyl halide:**



Step [1] **Find the parent carbon chain containing the halogen.**



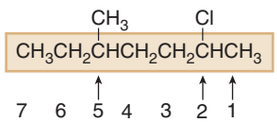
7 C's in the longest chain

7 C's ⟶ **heptane**

- Name the parent chain as an ***alkane,*** with the halogen as a substituent bonded to the longest chain.

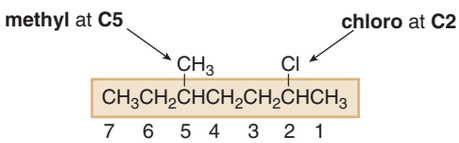
Step [2] **Apply all other rules of nomenclature.**

[a] **Number** the chain.



- Begin at the end nearest the first substituent, either alkyl or halogen.

[b] **Name** and **number** the substituents.



[c] **Alphabetize: c** for **c**hloro, then **m** for **m**ethyl.

ANSWER: 2-chloro-5-methylheptane

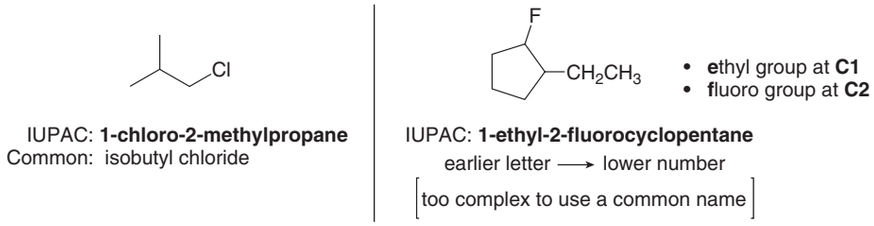
7.2B Common Names

Common names for alkyl halides are used only for simple alkyl halides. To assign a common name:

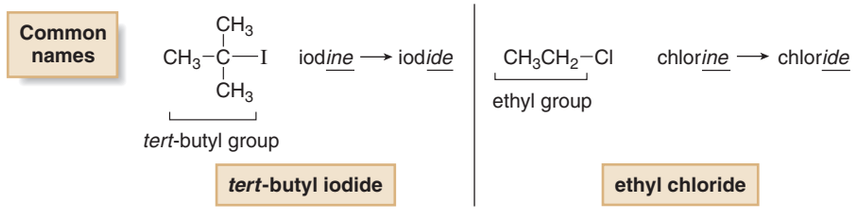
- Name all the carbon atoms of the molecule as a single **alkyl group.**
- Name the halogen bonded to the alkyl group. To name the halogen, change the ***-ine*** ending of the halogen name to the suffix ***-ide;*** for example, **brom*ine* → brom*ide.***

smi97462_ch07.qxd 11/22/04 2:36 PM Page 223

Figure 7.3 Examples: Nomenclature of alkyl halides

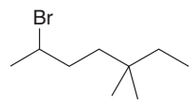
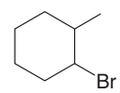
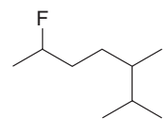


◆ Combine the names of the alkyl group and halide, separating the words with a space.



Other examples of alkane nomenclature are given in Figure 7.3.

PROBLEM 7.2 Give the IUPAC name for each compound.

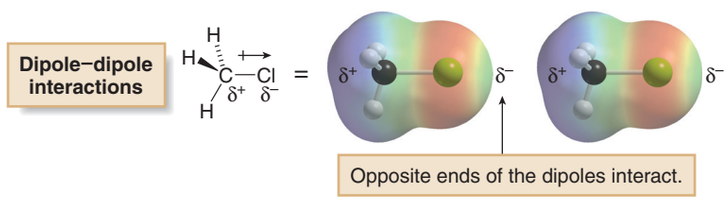
a. $(CH_3)_2CHCH(Cl)CH_2CH_3$ b.  c.  d. 

PROBLEM 7.3 Give the structure corresponding to each name.

a. 3-chloro-2-methylhexane
b. 4-ethyl-5-iodo-2,2-dimethyloctane
c. *cis*-1,3-dichlorocyclopentane
d. 1,1,3-tribromocyclohexane
e. propyl chloride
f. *sec*-butyl bromide

7.3 Physical Properties

Alkyl halides are weakly polar molecules. They exhibit **dipole–dipole** interactions because of their polar C−X bond, but because the rest of the molecule contains only C−C and C−H bonds they are incapable of intermolecular hydrogen bonding. How this affects their physical properties is summarized in Table 7.1.



PROBLEM 7.4 Rank the compounds in each group in order of increasing boiling point.

a. $CH_3CH_2CH_2I$, $CH_3CH_2CH_2Cl$, $CH_3CH_2CH_2F$
b. $CH_3(CH_2)_4CH_3$, $CH_3(CH_2)_5Br$, $CH_3(CH_2)_5OH$

smi97462_ch07.qxd 11/4/04 2:51 PM Page 224

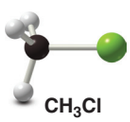
TABLE 7.1 Physical Properties of Alkyl Halides

Property	Observation
Boiling point and melting point	• Alkyl halides have higher bp's and mp's than alkanes having the same number of C carbons. **CH_3CH_3** bp = –89 °C and **CH_3CH_2Br** bp = 39 °C • Bp's and mp's increase as the size of R increases. **CH_3CH_2Cl** mp = −136 °C, bp = 12 °C and **$CH_3CH_2CH_2Cl$** mp = −123 °C, bp = 47 °C ← **larger surface area—higher mp and bp** • Bp's and mp's increase as the size of X increases. **CH_3CH_2Cl** mp = −136 °C, bp = 12 °C and **CH_3CH_2Br** mp = −119 °C, bp = 39 °C ← **more polarizable halogen—higher mp and bp**
Solubility	• RX is soluble in organic solvents. • RX is insoluble in water.

7.4 Interesting Alkyl Halides

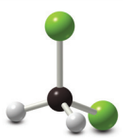
Many simple alkyl halides make excellent solvents because they are not flammable and dissolve a wide variety of organic compounds. Compounds in this category include **$CHCl_3$** (chloroform or trichloromethane) and **CCl_4** (carbon tetrachloride or tetrachloromethane). Large quantities of these solvents are produced industrially each year, but like many chlorinated organic compounds, both chloroform and carbon tetrachloride are toxic if inhaled or ingested. Other simple alkyl halides are shown in Figure 7.4.

Synthetic organic halides are also used in insulating materials, plastic wrap, and coatings. Two such compounds are **Teflon** and **polyvinyl chloride (PVC).**



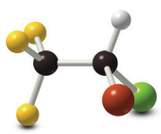
CH_3Cl

- **Chloromethane (CH_3Cl)** is produced by giant kelp and algae and also found in emissions from volcanoes such as Hawaii's Kilauea. Almost all of the atmospheric chloromethane results from these natural sources.



CH_2Cl_2

- **Dichloromethane (or methylene chloride, CH_2Cl_2)** is an important solvent, once used to decaffeinate coffee. Coffee is now decaffeinated by using supercritical CO_2 due to concerns over the possible ill effects of trace amounts of residual CH_2Cl_2 in the coffee. Subsequent studies on rats have shown, however, that no cancers occurred when animals ingested the equivalent of over 100,000 cups of decaffeinated coffee per day.



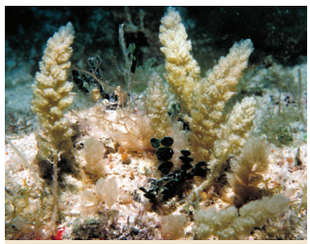
$CF_3CHClBr$

- **Halothane ($CF_3CHClBr$)** is a safe general anesthetic that has now replaced other organic anesthetics such as $CHCl_3$, which causes liver and kidney damage, and $CH_3CH_2OCH_2CH_3$ (diethyl ether), which is very flammable.

Figure 7.4 Some simple alkyl halides

smi97462_ch07.qxd 11/4/04 2:51 PM Page 225

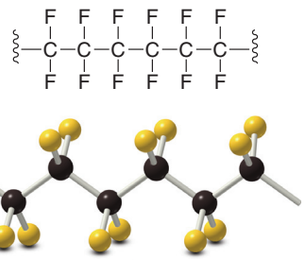
PVC was used at one time for the plastic sheets used to store and display baseball cards and other archival papers. Residual acid from its preparation, however, seeped into the paper over time, eventually destroying it.



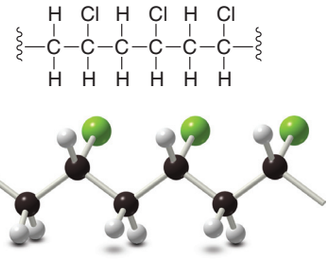
Asparagopsis taxiformis is an edible red seaweed that grows on the edges of reefs in areas of constant water motion. Almost 100 different organic halides have been isolated from this source.

Time Magazine, June 30, 1947.

Winston Churchill called DDT a "miraculous" chemical in 1945 for the many lives it saved during World War II. Fewer than 20 years later, as prolonged use of large quantities of this nonspecific pesticide led to harmful environmental effects, Rachel Carson called DDT the "elixir of death" in her book *Silent Spring.* DDT use was banned in the United States in 1973, but because of its effectiveness and low cost, it is still widely used to control insect populations in developing countries.



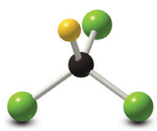
Teflon
(nonstick coating)



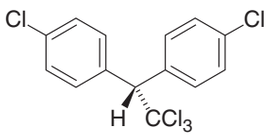
polyvinyl chloride (PVC)
(plastic used in films, pipes, and insulation)

Organic halides constitute a growing list of useful naturally occurring molecules, many produced by marine organisms. Some have irritating odors or an unpleasant taste and are synthesized by organisms for self-defense or feeding deterrents. Examples include $Br_2C{=}CHCHCl_2$ and $Br_2C{=}CHCHBr_2$, isolated from the red seaweed *Asparagopsis taxiformis,* known as *limu kohu* (supreme seaweed) in Hawaii. This seaweed has a strong and characteristic odor and flavor, in part probably because of these organic halides.

Although the beneficial effects of many organic halides are undisputed, certain synthetic chlorinated organics such as the **chlorofluorocarbons** and the pesticide **DDT** have caused lasting harm to the environment.

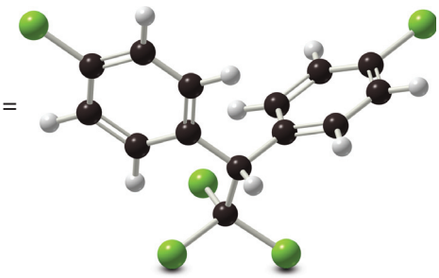


$CFCl_3$
CFC 11
Freon 11



DDT

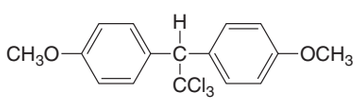
=



Chlorofluorocarbons (**CFCs**) have the general molecular structure $\mathbf{CF_xCl_{4-x}}$. Trichlorofluoromethane [$CFCl_3$, CFC 11, or Freon 11 (trade name)] is an example of these easily vaporized compounds, having been extensively used as a refrigerant and an aerosol propellant. CFCs slowly rise to the stratosphere, where sunlight catalyzes their decomposition, a process that contributes to the destruction of the ozone layer, the thin layer of atmosphere that shields the earth's surface from harmful ultraviolet radiation as discussed in Section 13.9. Although it is now easy to second-guess the extensive use of CFCs, it is also easy to see why they were used so widely. **CFCs made refrigeration available to the general public.** Would you call your refrigerator a comfort or a necessity?

The story of the insecticide **DDT** (***d***ichloro***d***iphenyl***t***richloroethane) follows the same theme: DDT is an organic molecule with valuable short-term effects that has caused long-term problems. DDT kills insects that spread diseases such as malaria and typhus, and in controlling insect populations, DDT has saved millions of lives worldwide. DDT is a weakly polar and very stable organic compound, and so it (and compounds like it) persist in the environment for years. Because DDT is soluble in organic media, it accumulates in the fatty tissues of most animals. Most adults in the United States have low concentrations of DDT (or a degradation product of DDT) in their bodies. The long-term effect on humans is not known, but DDT has had a direct harmful effect on the eggshell formation of certain predator birds such as eagles and hawks.

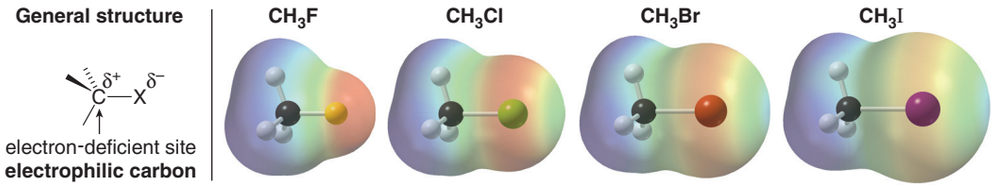
PROBLEM 7.5 Although nonpolar compounds tend to dissolve and remain in fatty tissues, polar substances are more water soluble, and more readily excreted into an environment where they may be degraded by other organisms. Explain why methoxychlor is more biodegradable than DDT.



methoxychlor

smi97462_ch07.qxd 11/4/04 2:51 PM Page 226

Figure 7.5 Electrostatic potential maps of four halomethanes (CH_3X)



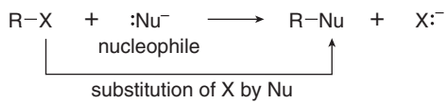
- The polar C−X bond makes the carbon atom *electron deficient* in each CH_3X molecule.

7.5 The Polar Carbon–Halogen Bond

The properties of alkyl halides dictate their reactivity. The electrostatic potential maps of four simple alkyl halides in Figure 7.5 illustrate that the electronegative halogen X creates a polar C−X bond, making the carbon atom electron deficient. **The chemistry of alkyl halides is determined by this polar C–X bond.**

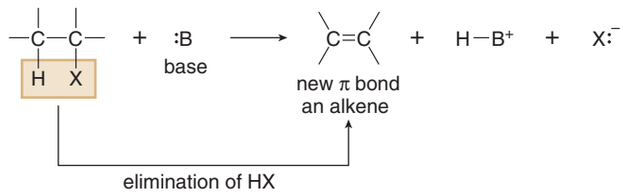
What kind of reactions do alkyl halides undergo? **The characteristic reactions of alkyl halides are substitution and elimination.** Because alkyl halides contain an electrophilic carbon, they react with electron-rich reagents—Lewis bases (nucleophiles) and Brønsted–Lowry bases.

◆ Alkyl halides undergo substitution reactions with nucleophiles.



In a substitution reaction of RX, **the halogen X is replaced by an electron-rich nucleophile :Nu⁻.** The C−X σ bond is broken and the C−Nu σ bond is formed.

◆ Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

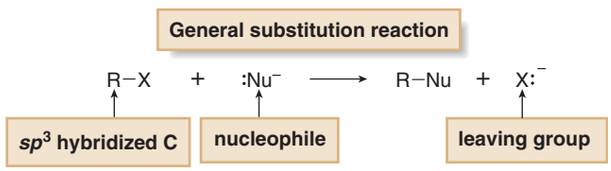


In an elimination reaction of RX, the **elements of HX are removed by a Brønsted–Lowry base :B.**

The remainder of Chapter 7 is devoted to a discussion of the substitution reactions of alkyl halides. Elimination reactions are discussed in Chapter 8.

7.6 General Features of Nucleophilic Substitution

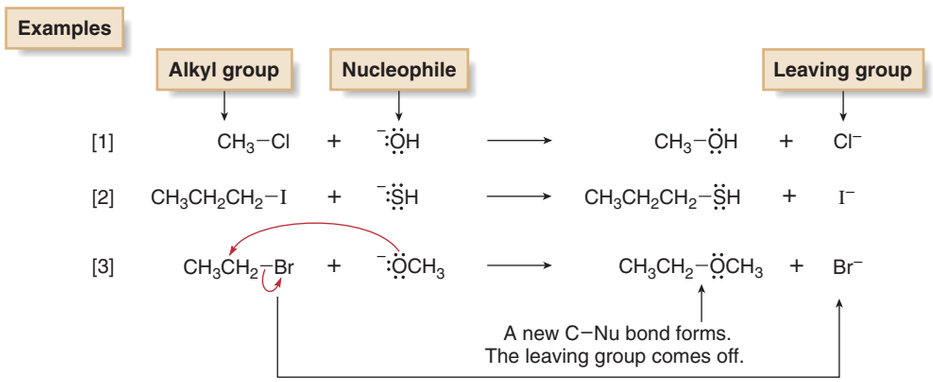
Three components are necessary in any substitution reaction.



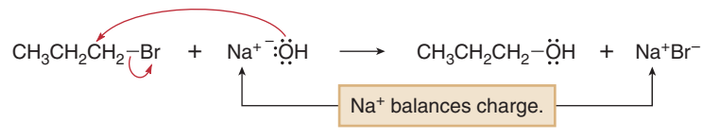
smi97462_ch07.qxd 11/22/04 2:36 PM Page 227

[1] **R**—An alkyl group R containing an sp^3 hybridized carbon bonded to X.
[2] **X**—An atom X (or a group of atoms) called **a leaving group,** which is able to accept the electron density in the C−X bond. The most common leaving groups are halogen atoms (−X), but $-OH_2^+$ and $-N_2^+$ are also encountered.
[3] **:Nu⁻**—A **nucleophile.** Nucleophiles contain a lone pair or a π bond but not necessarily a negative charge.

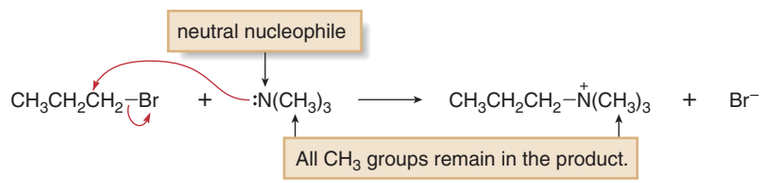
Because these substitution reactions involve electron-rich nucleophiles, they are called ***nucleophilic* substitution reactions.** Examples are shown in Equations [1]–[3]. **Nucleophilic substitutions are Lewis acid–base reactions.** The nucleophile donates its electron pair, the alkyl halide (Lewis acid) accepts it, and the C−X bond is heterolytically cleaved. Curved arrow notation can be used to show the movement of electron pairs, as shown in Equation [3].



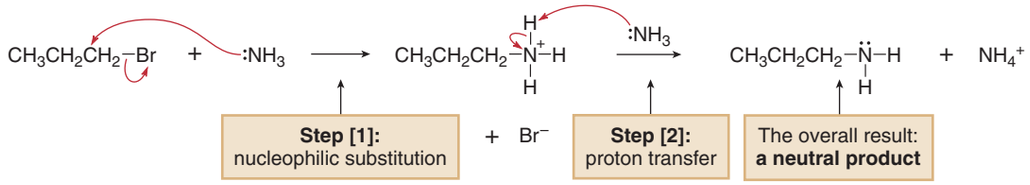
Negatively charged nucleophiles like ⁻OH and ⁻SH are used as **salts** with Li^+, Na^+, or K^+ counterions to balance charge. The identity of the cation is usually inconsequential, and therefore it is often omitted from the chemical equation.



When a neutral nucleophile is used, the substitution product bears a positive charge. **Note that all atoms bonded to the nucleophile originally, stay bonded to it after substitution occurs.** All three CH_3 groups stay bonded to the N atom in the given example.



Furthermore, when the substitution product bears a positive charge and also contains a proton bonded to O or N, the initial substitution product readily loses a proton in a Brønsted–Lowry acid–base reaction, forming a neutral product.

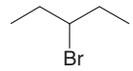


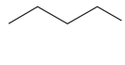
All of these reactions are nucleophilic substitutions and have the same overall result—**replacement of the leaving group by the nucleophile,** regardless of the identity or charge of the nucleophile. To draw any nucleophilic substitution product:

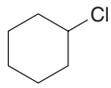
smi97462_ch07.qxd 11/4/04 2:51 PM Page 228

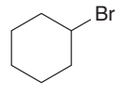
- **Find the sp^3 hybridized carbon** with the leaving group.
- **Identify the nucleophile,** the species with a lone pair or π bond.
- **Substitute the nucleophile for the leaving group** and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

PROBLEM 7.6 Identify the nucleophile and leaving group and draw the products of each reaction.

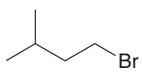
a.  + $^-OCH_2CH_3$ ⟶

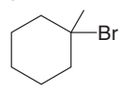
c.  + N_3^- ⟶

b.  + NaOH ⟶

d.  + NaCN ⟶

PROBLEM 7.7 Draw the product of nucleophilic substitution with each neutral nucleophile. When the initial substitution product can lose a proton to form a neutral product, draw that product as well.

a.  + $:N(CH_2CH_3)_3$ ⟶

c.  + $CH_3\ddot{O}H$ ⟶

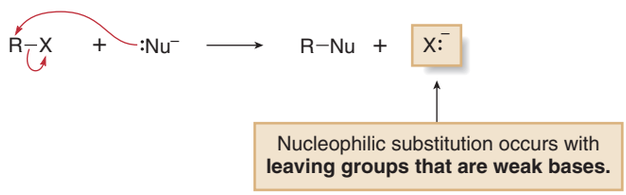
b. $(CH_3)_3C-Cl$ + $H_2\ddot{O}:$ ⟶

7.7 The Leaving Group

Nucleophilic substitution is a general reaction of organic compounds. Why, then, are alkyl halides the most common substrates, and halide anions the most common leaving groups? To answer this question, we must understand leaving group ability. **What makes a good leaving group?**

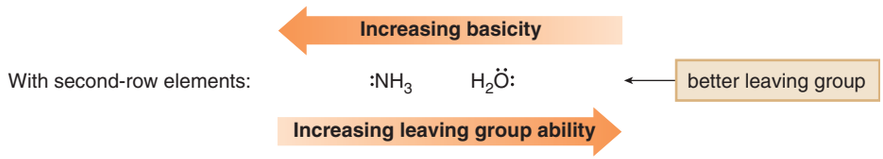
In a nucleophilic substitution reaction of R−X, the C−X bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming $X:^-$. **The more stable the leaving group $X:^-$, the better able it is to accept an electron pair,** giving rise to the following generalization:

- **In comparing two leaving groups, the better leaving group is the weaker base.**



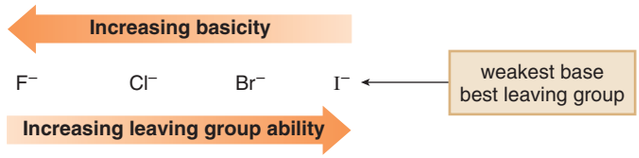
For example, H_2O is a better leaving group than ^-OH because H_2O is a weaker base. Moreover, the periodic trends in basicity listed in Section 2.9 can now be used to identify **periodic trends in leaving group ability:**

- **Left-to-right across a row of the periodic table, basicity *decreases* so leaving group ability *increases.***



- **Down a column of the periodic table, basicity *decreases* so leaving group ability *increases.***

smi97462_ch07.qxd 11/22/04 2:37 PM Page 229



All good leaving groups are weak bases with strong conjugate acids having low pK_a values. Thus, all halide anions except F^- are good leaving groups because their conjugate acids (HCl, HBr, and HI) have low pK_a values. Tables 7.2 and 7.3 list good and poor leaving groups for nucleophilic substitution reactions, respectively. Nucleophilic substitution does not occur with any of the leaving groups in Table 7.3 because these leaving groups are strong bases.

TABLE 7.2 Good Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK_a
R—Cl	Cl^-	HCl	–7
R—Br	Br^-	HBr	–9
R—I	I^-	HI	–10
R—OH_2^+	H_2O	H_3O^+	–1.7

These molecules undergo nucleophilic substitution. — good leaving groups

TABLE 7.3 Poor Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK_a
R—F	F^-	HF	3.2
R—OH	^-OH	H_2O	15.7
R—NH_2	$^-NH_2$	NH_3	38
R—H	H^-	H_2	35
R—R	R^-	RH	50

These molecules do *not* undergo nucleophilic substitution. — poor leaving groups

PROBLEM 7.8 Which is the better leaving group in each pair?
a. Cl^-, I^- b. NH_3, $^-NH_2$ c. H_2O, H_2S

PROBLEM 7.9 Which molecules contain good leaving groups?
a. $CH_3CH_2CH_2Br$ b. $CH_3CH_2CH_2OH$ c. $CH_3CH_2\overset{+}{O}H_2$ d. CH_3CH_3

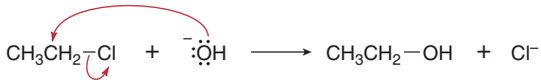
Given a particular nucleophile and leaving group, how can we determine whether the equilibrium will favor products in a nucleophilic substitution? We can often correctly predict the direction of equilibrium by comparing the basicity of the nucleophile and the leaving group.

◆ **Equilibrium favors the products of nucleophilic substitution when the leaving group is a weaker base than the nucleophile.**

Sample Problem 7.1 illustrates how to apply this general rule.

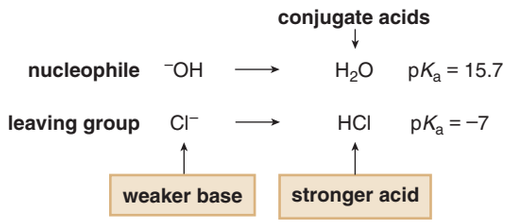
smi97462_ch07.qxd 11/4/04 2:51 PM Page 230

SAMPLE PROBLEM 7.1 Will the following substitution reaction favor formation of the products?



SOLUTION

Compare the basicity of the nucleophile ($^-$OH) and the leaving group (Cl^-) by comparing the pK_a values of their conjugate acids. **The stronger the conjugate acid, the weaker the base, and the better the leaving group.**

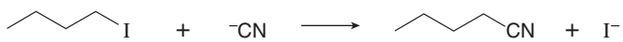


ANSWER

Because Cl^-, the leaving group, is a weaker base than $^-$OH, the nucleophile, the reaction favors the products.

PROBLEM 7.10 Does the equilibrium favor the reactants or products in each substitution reaction?

a. $CH_3CH_2{-}NH_2 + Br^- \longrightarrow CH_3CH_2{-}Br + {}^-NH_2$

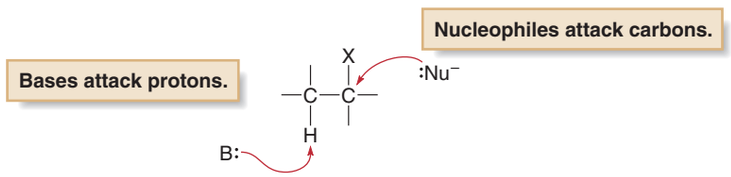
b. 

7.8 The Nucleophile

Nucleophiles and bases are structurally similar: both have a lone pair or a π bond. They differ in what they attack.

We use the word *base* to mean *Brønsted–Lowry* base and the word *nucleophile* to mean a *Lewis base* that reacts with electrophiles *other than protons.*

◆ Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).



Although nucleophilicity and basicity are interrelated, they are fundamentally different. **Basicity** is a measure of how readily an atom donates its electron pair to a proton; it is characterized by an equilibrium constant K_a in an acid–base reaction, making it a **thermodynamic property. Nucleophilicity** is a measure of how readily an atom donates its electron pair to other atoms; it is characterized by the rate constant, *k,* of a nucleophilic substitution reaction, making it a **kinetic property.**

7.8A Nucleophilicity Versus Basicity

How is **nucleophilicity** (nucleophile strength) related to **basicity?** Although it is generally true that **a strong base is a strong nucleophile,** nucleophile size and steric factors can sometimes change this relationship.

Nucleophilicity parallels basicity in three instances:

[1] **For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.**

◆ The relative nucleophilicity of $^-$OH and CH_3COO^-, two oxygen nucleophiles, is determined by comparing the pK_a values of their conjugate acids (H_2O and CH_3COOH). CH_3COOH (pK_a = 4.8) is a stronger acid than H_2O (pK_a = 15.7), so $^-$OH is a stronger base and stronger nucleophile than CH_3COO^-.

[2] **A negatively charged nucleophile is always stronger than its conjugate acid.**

◆ $^-$OH is a stronger base and stronger nucleophile than H_2O, its conjugate acid.

smi97462_ch07.qxd 11/4/04 2:51 PM Page 231

[3] **Right-to-left across a row of the periodic table, nucleophilicity increases as basicity increases.**

For second-row elements with the same charge:

CH_3^- $^-NH_2$ ^-OH F^-

Increasing basicity
Increasing nucleophilicity

PROBLEM 7.11 Identify the stronger nucleophile in each pair.

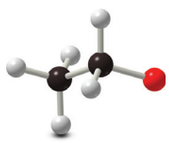
a. NH_3, $^-NH_2$ b. CH_3^-, HO^- c. CH_3NH_2, CH_3OH d. CH_3COO^-, $CH_3CH_2O^-$

7.8B Steric Effects and Nucleophilicity

All steric effects arise because two atoms cannot occupy the same space. In Chapter 4, for example, we learned that **steric strain** is an increase in energy when big groups (occupying a large volume) are forced close to each other.

Nucleophilicity does not parallel basicity when **steric hindrance** becomes important. ***Steric hindrance* is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.**

For example, although pK_a tables indicate that *tert*-butoxide [$(CH_3)_3CO^-$], is a stronger base than ethoxide ($CH_3CH_2O^-$), **ethoxide is the *stronger* nucleophile.** The three CH_3 groups around the O atom of *tert*-butoxide create steric hindrance, making it more difficult for this big, bulky base to attack a tetravalent carbon atom.



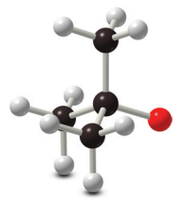
= $CH_3CH_2-\ddot{O}:^-$

ethoxide

stronger nucleophile

$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-\ddot{O}:^-$

tert-butoxide



stronger base

Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile.**

Steric hindrance decreases nucleophilicity but *not* basicity. Because bases pull off small, easily accessible protons, they are unaffected by steric hindrance. Nucleophiles, on the other hand, must attack a crowded tetrahedral carbon, so bulky groups decrease reactivity.

Sterically hindered bases that are poor nucleophiles are called *nonnucleophilic bases*. Potassium *tert*-butoxide [$K^+\ ^-OC(CH_3)_3$] is a strong, nonnucleophilic base.

7.8C Comparing Nucleophiles of Different Size—Solvent Effects

Atoms vary greatly in size down a column of the periodic table, and in this case, **nucleophilicity depends on the solvent used in a substitution reaction.** Although solvent has thus far been ignored, most organic reactions take place in a liquid solvent that dissolves all reactants to some extent. Because substitution reactions involve polar starting materials, polar solvents are used to dissolve them. There are two main kinds of polar solvents—**polar *protic* solvents and polar *aprotic* solvents.**

Polar Protic Solvents

In addition to dipole–dipole interactions, **polar *protic* solvents are capable of intermolecular hydrogen bonding,** because they contain an O−H or N−H bond. The most common polar protic solvents are water and alcohols (ROH), as seen in the examples in Figure 7.6. **Polar protic solvents solvate *both* cations and anions well.**

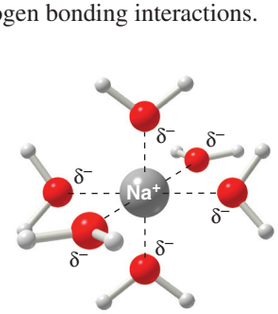
- Cations are solvated by ion–dipole interactions.
- Anions are solvated by hydrogen bonding.

smi97462_ch07.qxd 11/22/04 12:46 PM Page 232

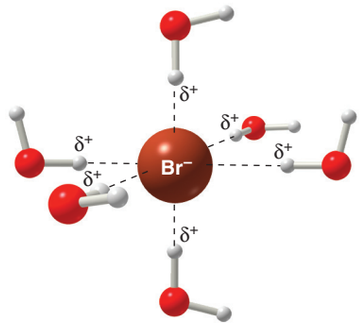
Figure 7.6 Examples of polar protic solvents

H_2O	CH_3OH	CH_3CH_2OH	$(CH_3)_3COH$	CH_3COOH
	methanol	ethanol	*tert*-butanol	acetic acid

For example, if the salt NaBr is used as a source of the nucleophile Br^- in H_2O, the Na^+ cations are solvated by ion–dipole interactions with H_2O molecules, and the Br^- anions are solvated by strong hydrogen bonding interactions.



Na^+ is solvated by ion–dipole interactions with H_2O.



Br^- is solvated by hydrogen bonding with H_2O.

How do polar protic solvents affect nucleophilicity? **In polar protic solvents, nucleophilicity *increases* down a column of the periodic table as the size of the anion increases. This is *opposite* to basicity.** A small electronegative anion like F^- is very well solvated by hydrogen bonding, effectively shielding it from reaction. On the other hand, a large, less electronegative anion like I^- does not hold onto solvent molecules as tightly. The solvent does not "hide" a large nucleophile as well, and the nucleophile is much more able to donate its electron pairs in a reaction. Thus, **nucleophilicity increases down a column** even though basicity decreases, giving rise to the following trend in polar protic solvents:

I^- is a weak base but a strong nucleophile in polar protic solvents.

Down a column of the periodic table

F^- Cl^- Br^- I^-

Increasing nucleophilicity in polar protic solvents

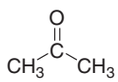
Polar Aprotic Solvents

Polar *aprotic* solvents also exhibit dipole–dipole interactions, but they have no O–H or N–H bond so they are **incapable of hydrogen bonding.** Examples of polar aprotic solvents are shown in Figure 7.7. **Polar aprotic solvents solvate only cations well.**

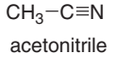
- Cations are solvated by ion–dipole interactions.
- Anions are not well solvated because the solvent cannot hydrogen bond to them.

Figure 7.7 Examples of polar aprotic solvents

Abbreviations are often used in organic chemistry, instead of a compound's complete name. A list of common abbreviations is given in Appendix A.

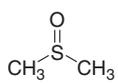


acetone

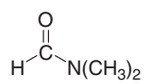


acetonitrile

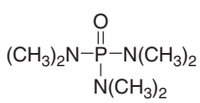
tetrahydrofuran
THF



dimethyl sulfoxide
DMSO



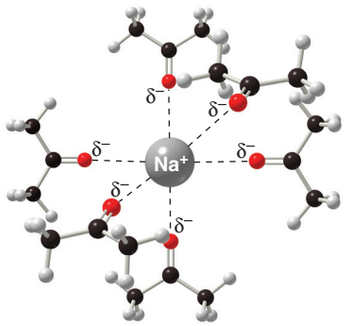
dimethylformamide
DMF



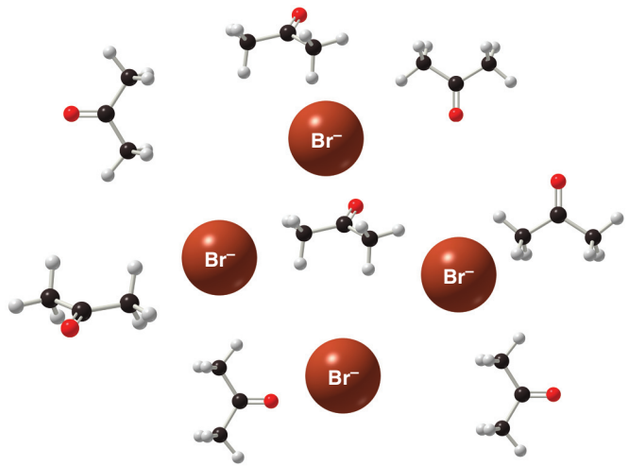
hexamethylphosphoramide
HMPA

smi97462_ch07.qxd 11/22/04 12:47 PM Page 233

When the salt NaBr is dissolved in acetone, $(CH_3)_2C{=}O$, the Na^+ cations are solvated by ion–dipole interactions with the acetone molecules, but, with no possibility for hydrogen bonding, the Br^- anions are not well solvated. Often these anions are called **naked anions** because they are not bound by tight interactions with solvent.



$(CH_3)_2C{=}O$ solvates Na^+ well by ion–dipole interactions.



Br^- anions are surrounded by solvent but not well solvated by the $(CH_3)_2C{=}O$ molecules.

How do polar aprotic solvents affect nucleophilicity? Because anions are not well solvated in polar aprotic solvents, there is no need to consider whether solvent molecules more effectively hide one anion than another. Nucleophilicity once again parallels basicity and **the stronger base is the stronger nucleophile.** Because basicity decreases with size down a column, nucleophilicity decreases as well:

Down a column of the periodic table

F^- Cl^- Br^- I^-

Increasing nucleophilicity in polar aprotic solvents

PROBLEM 7.12 Classify each solvent as protic or aprotic.

a. $HOCH_2CH_2OH$ b. $CH_3CH_2OCH_2CH_3$ c. $CH_3COOCH_2CH_3$

PROBLEM 7.13 Identify the stronger nucleophile in each pair of anions.

a. Br^- and Cl^- in a polar protic solvent
b. HO^- and Cl^- in a polar aprotic solvent
c. HS^- and F^- in a polar protic solvent

7.8D Summary

This long discussion of nucleophilicity has brought together many new concepts, such as steric hindrance and solvent effects, both of which we will meet again in our study of organic chemistry. Keep in mind, however, the central relationship between nucleophilicity and basicity in comparing two nucleophiles.

- It is generally true that the *stronger* base is the *stronger* nucleophile.
- In polar protic solvents, however, nucleophilicity increases with increasing size of an anion (opposite to basicity).
- Steric hindrance decreases nucleophilicity without decreasing basicity, making $(CH_3)_3CO^-$ a stronger base but a weaker nucleophile than $CH_3CH_2O^-$.

Table 7.4. lists some common nucleophiles used in nucleophilic substitution reactions.

smi97462_ch07.qxd 11/4/04 2:51 PM Page 234

TABLE 7.4 Common Nucleophiles in Organic Chemistry

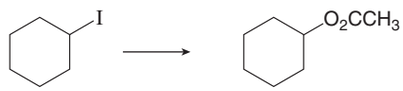
	Negatively charged nucleophiles			Neutral nucleophiles	
Oxygen	^-OH	^-OR	CH_3COO^-	H_2O	ROH
Nitrogen	N_3^-			NH_3	RNH_2
Carbon	^-CN	$HC\equiv C^-$			
Halogen	Cl^-	Br^-	I^-		
Sulfur	HS^-	RS^-		H_2S	RSH

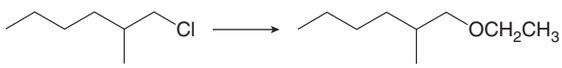
PROBLEM 7.14 Rank the nucleophiles in each group in order of increasing nucleophilicity.

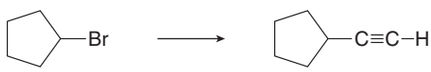
a. ^-OH, $^-NH_2$, H_2O b. ^-OH, Br^-, F^- (polar aprotic solvent) c. H_2O, ^-OH, CH_3COO^-

PROBLEM 7.15 What nucleophile is needed to carry out each reaction?

a. $CH_3CH_2CH_2{-}Br \longrightarrow CH_3CH_2CH_2{-}SH$

b. 

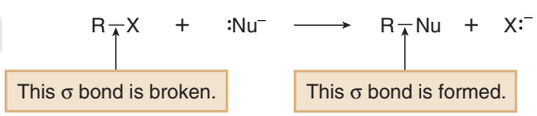
c. 

d. 

7.9 Possible Mechanisms for Nucleophilic Substitution

Now that you know something about the general features of nucleophilic substitution, you can begin to understand the mechanism.

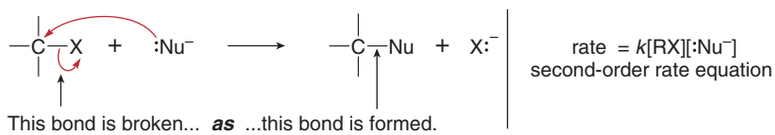
Overall reaction



Nucleophilic substitution at an sp^3 hybridized carbon involves two σ bonds: the bond to the leaving group, which is broken, and the bond to the nucleophile, which is formed. To understand the mechanism of this reaction, though, we must know the timing of these two events; that is, **what is the order of bond breaking and bond making?** Do they happen at the same time, or does one event precede the other? There are three possibilities.

[1] **Bond breaking and bond making occur at the *same* time.**

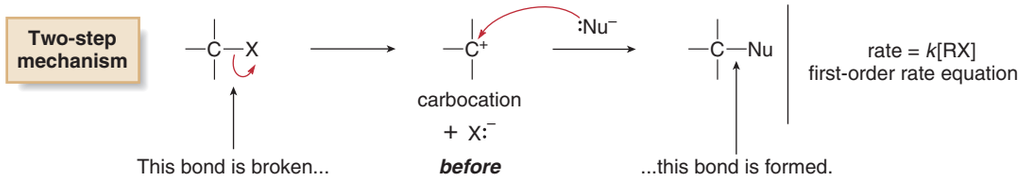
One-step mechanism



- If the C–X bond is broken ***as*** the C–Nu bond is formed, the mechanism has **one step.** As we learned in Section 6.9, the rate of such a bimolecular reaction depends on the concentration of both reactants; that is, the rate equation is **second order.**

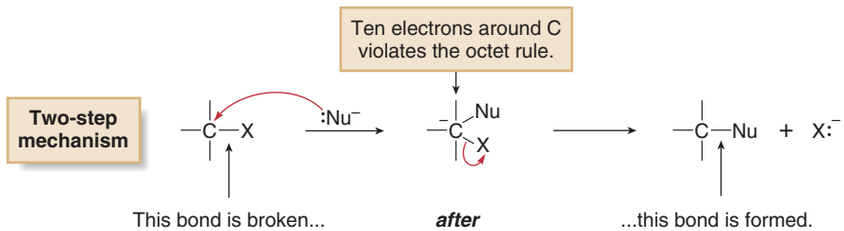
smi97462_ch07.qxd 11/22/04 12:48 PM Page 235

[2] **Bond breaking occurs *before* bond making.**



- If the C−X bond is broken ***first*** and then the C−Nu bond is formed, the mechanism has **two steps** and a **carbocation** is formed as an intermediate. Because the first step is rate-determining, the rate depends on the concentration of RX only; that is, the rate equation is **first order.**

[3] **Bond making occurs *before* bond breaking.**



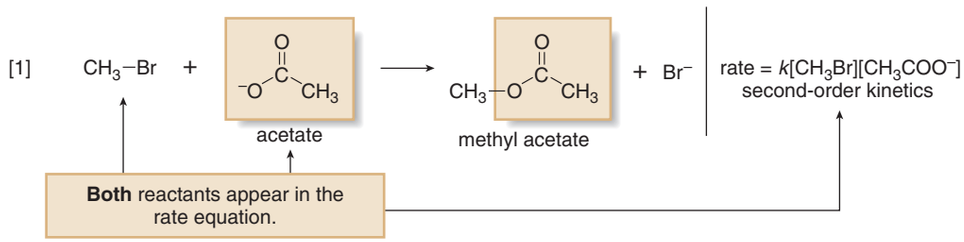
- If the C−Nu bond is formed ***first*** and then the C−X bond is broken, the mechanism has **two steps,** but this mechanism has an inherent problem. The intermediate generated in the first step has 10 electrons around carbon, violating the octet rule. Because two other mechanistic possibilities do not violate a fundamental rule, this last possibility can be disregarded.

The preceding discussion has generated two possible mechanisms for nucleophilic substitution: **a one-step mechanism in which bond breaking and bond making are simultaneous, and a two-step mechanism in which bond breaking comes before bond making.** In Section 7.10 we look at data for two specific nucleophilic substitution reactions and see if those data fit either of these proposed mechanisms.

7.10 Two Mechanisms for Nucleophilic Substitution

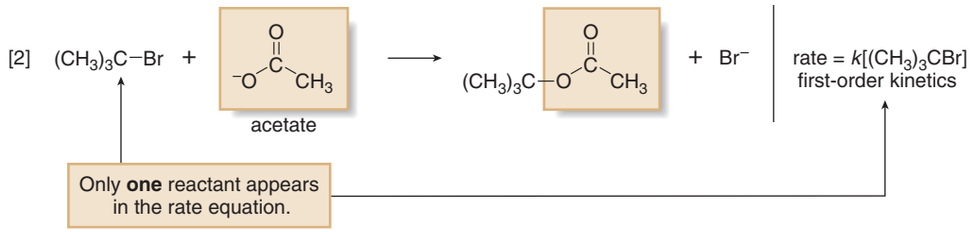
Rate equations for two different reactions give us insight into the possible mechanism for nucleophilic substitution.

Reaction of bromomethane (CH_3Br) with the nucleophile acetate (CH_3COO^-) affords the substitution product methyl acetate with loss of Br^- as the leaving group (Equation [1]). Kinetic data show that the reaction rate depends on the concentration of *both* reactants; that is, the rate equation is **second order.** This suggests a **bimolecular reaction with a one-step mechanism** in which the C−X bond is broken *as* the C−Nu bond is formed.



Equation [2] illustrates a similar nucleophilic substitution reaction with a different alkyl halide, $(CH_3)_3CBr$, which also leads to substitution of Br^- by CH_3COO^-. Kinetic data show that this reaction rate depends on the concentration of only *one* reactant, the alkyl halide; that is, the rate equation is **first order.** This suggests a **two-step mechanism in which the rate-determining step involves the alkyl halide only.**

smi97462_ch07.qxd 11/22/04 2:37 PM Page 236



How can these two different results be explained? Although these two reactions have the same nucleophile and leaving group, **there must be two different mechanisms** because there are two different rate equations. These equations are specific examples of two well known mechanisms for nucleophilic substitution at an sp^3 hybridized carbon:

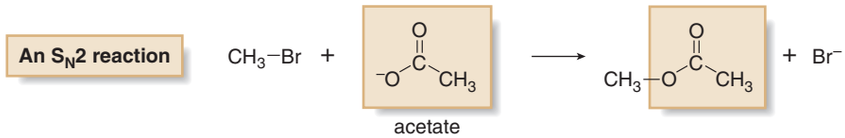
- The **S_N2 mechanism (substitution nucleophilic bimolecular),** illustrated by the reaction in Equation [1].
- The **S_N1 mechanism (substitution nucleophilic unimolecular),** illustrated by the reaction in Equation [2].

We will now examine the characteristics of the S_N2 and S_N1 mechanisms.

The numbers **1** and **2** in the names S_N1 and S_N2 refer to the kinetic order of the reactions. For example, S_N2 means that the kinetics are **second** order. The number *2* does *not* refer to the number of steps in the mechanism.

7.11 The S_N2 Mechanism

The reaction of CH_3Br with CH_3COO^- is an example of an **S_N2 reaction.** What are the general features of this mechanism?



7.11A Kinetics

An S_N2 reaction exhibits **second-order kinetics;** that is, the reaction is **bimolecular** and both the alkyl halide and the nucleophile appear in the rate equation.

- **rate = $k[CH_3Br][CH_3COO^-]$**

Changing the concentration of *either* reactant affects the rate. For example, doubling the concentration of *either* the nucleophile or the alkyl halide doubles the rate. Doubling the concentration of *both* reactants increases the rate by a factor of four.

PROBLEM 7.16 What happens to the rate of an S_N2 reaction under each of the following conditions?

a. [RX] is tripled, and [:Nu⁻] stays the same.
b. Both [RX] and [:Nu⁻] are tripled.
c. [RX] is halved, and [:Nu⁻] stays the same.
d. [RX] is halved, and [:Nu⁻] is doubled.

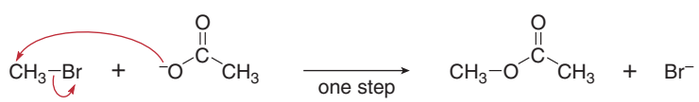
7.11B A One-Step Mechanism

The most straightforward explanation for the observed second-order kinetics is a **concerted reaction—bond breaking and bond making occur at the *same* time,** as shown in Mechanism 7.1.

MECHANISM 7.1

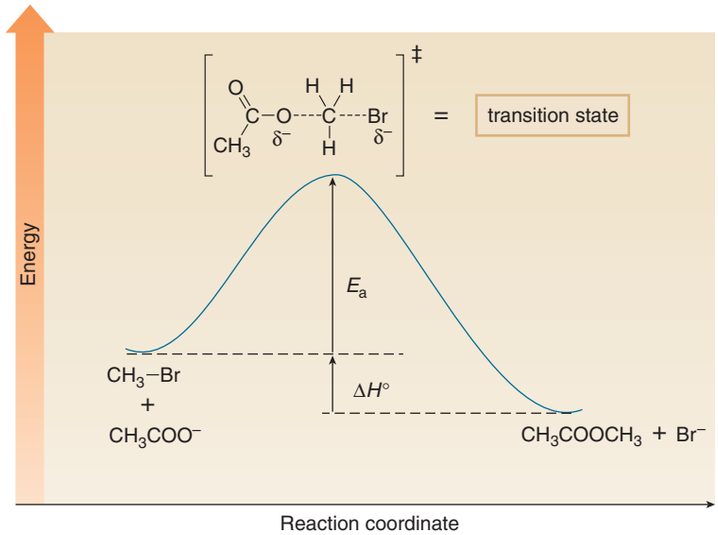
The S_N2 Mechanism

One step **The C–Br bond breaks *as* the C–O bond forms.**



smi97462_ch07.qxd 11/23/04 3:38 PM Page 237

Figure 7.8 An energy diagram for the S_N2 reaction: $CH_3Br + CH_3COO^- \rightarrow CH_3COOCH_3 + Br^-$

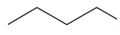
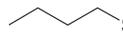


- In the transition state, the C—Br bond is partially broken, the C—O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

An energy diagram for the reaction of $CH_3Br + CH_3COO^-$ is shown in Figure 7.8. The reaction has one step, so there is one energy barrier between reactants and products. Because the equilibrium for this S_N2 reaction favors the products, they are drawn at lower energy than the starting materials.

PROBLEM 7.17 Draw the structure of the transition state in each of the following S_N2 reactions.

a. $CH_3CH_2CH_2$—Cl + $^-OCH_3$ ⟶ $CH_3CH_2CH_2$—OCH_3 + Cl^-

b.  + ^-SH ⟶  + Br^-

PROBLEM 7.18 Draw an energy diagram for the reaction in Problem 7.17a. Label the axes, the starting material, the product, and the transition state. Assume the reaction is exothermic. Label $\Delta H°$ and E_a.

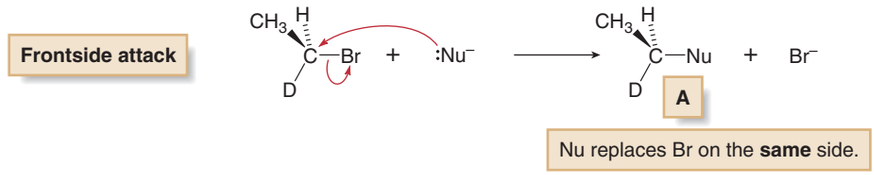
7.11C Stereochemistry of the S_N2 Reaction

From what direction does the nucleophile approach the substrate in an S_N2 reaction? There are two possibilities.

- **Frontside attack:** The nucleophile approaches from the ***same*** side as the leaving group.
- **Backside attack:** The nucleophile approaches from the side ***opposite*** the leaving group.

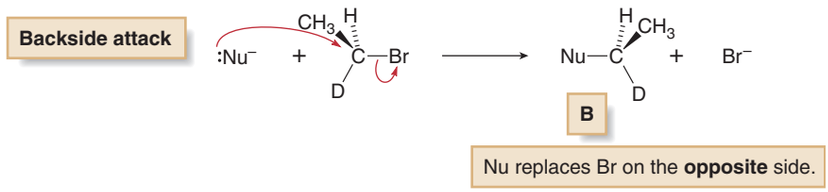
The results of frontside and backside attack of a nucleophile are illustrated with $CH_3CH(D)Br$ as substrate and the general nucleophile $:Nu^-$. This substrate has the leaving group bonded to a stereogenic center, thus allowing us to see the structural difference that results when the nucleophile attacks from two different directions.

In **frontside attack,** the nucleophile approaches from the **same** side as the leaving group, forming **A.** In this example, the leaving group was drawn on the right, so the nucleophile attacks from the right, and all other groups remain in their original positions. Because the nucleophile and leaving group are in the same position relative to the other three groups on carbon, frontside attack results in **retention of configuration** around the stereogenic center.

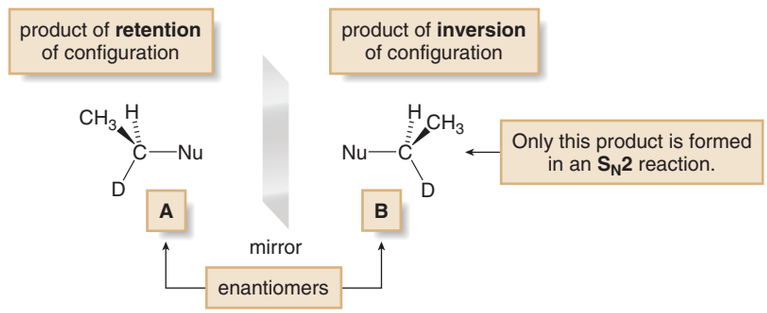


smi97462_ch07.qxd 11/22/04 12:59 PM Page 238

In **backside attack,** the nucleophile approaches from the **opposite** side to the leaving group, forming **B.** In this example, the leaving group was drawn on the right, so the nucleophile attacks from the left. Because the nucleophile and leaving group are in the opposite position relative to the other three groups on carbon, backside attack results in **inversion of configuration** around the stereogenic center.



The products of frontside and backside attack are *different* compounds. **A** and **B** are stereoisomers that are nonsuperimposable—they are **enantiomers.**



Inversion of configuration in an S_N2 reaction is often called **Walden inversion,** after Latvian chemist Dr. Paul Walden, who first observed this process in 1896.

Which product is formed in an S_N2 reaction? When the stereochemistry of the product is determined, **only B, the product of backside attack, is formed.**

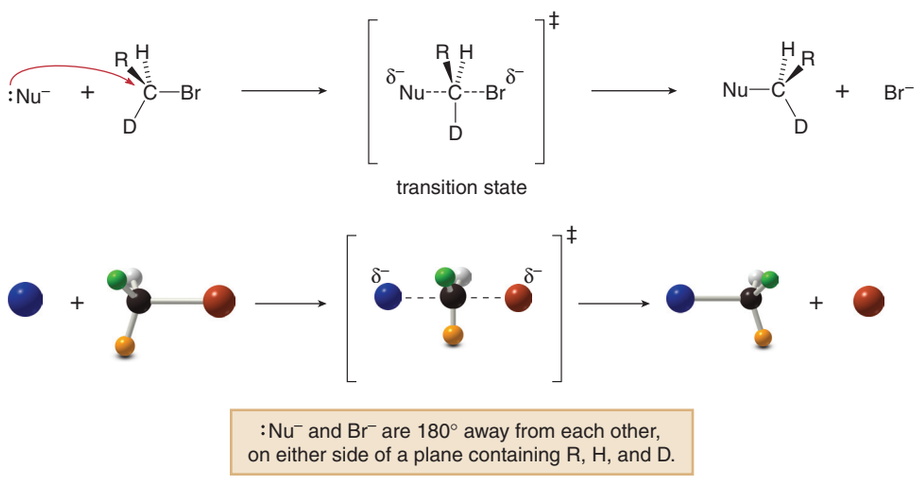
◆ **All S_N2 reactions proceed with backside attack of the nucleophile, resulting in *inversion* of configuration at a stereogenic center.**

Backside attack resulting in inversion of configuration occurs in all S_N2 reactions, but we can observe this change only when the leaving group is bonded to a stereogenic center.

One explanation for backside attack is based on an electronic argument. Both the nucleophile and leaving group are electron rich and these like charges repel each other. Backside attack keeps these two groups as far away from each other as possible. In the transition state, the nucleophile and leaving group are 180° away from each other, and the other three groups around carbon occupy a plane, as illustrated in Figure 7.9.

Two additional examples of inversion of configuration in S_N2 reactions are given in Figure 7.10.

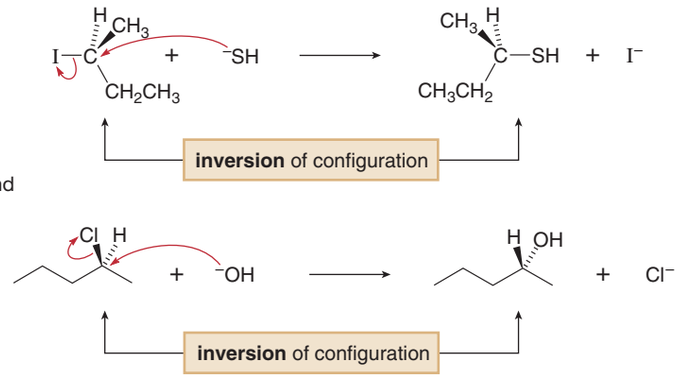
Figure 7.9 Stereochemistry of the S_N2 reaction



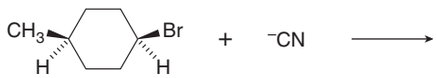
smi97462_ch07.qxd 11/4/04 2:51 PM Page 239

Figure 7.10 Two examples of inversion of configuration in the S_N2 reaction

- The bond to the nucleophile in the product is always on the **opposite side** relative to the bond to the leaving group in the starting material.

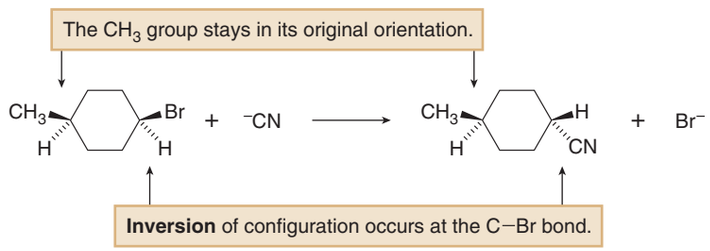


SAMPLE PROBLEM 7.2 Draw the product (including stereochemistry) of the following S_N2 reaction.



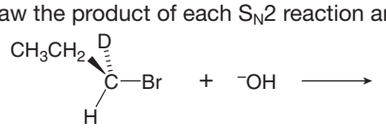
SOLUTION

Br^- is the leaving group and ^-CN is the nucleophile. Because S_N2 reactions proceed with **inversion** of configuration and the leaving group is drawn above the ring (on a wedge), the nucleophile must come in from below.

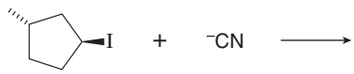


Note how the stereochemistry of the starting material and product compares. Backside attack converts the starting material, which has two groups **cis** to each other, to a product with two groups **trans** to each other because the nucleophile (^-CN) attacks from below the plane of the ring.

PROBLEM 7.19 Draw the product of each S_N2 reaction and indicate stereochemistry.

a. 

b. 

c. 

7.11D The Identity of the R Group

How does the rate of an S_N2 reaction change as the alkyl group in the substrate alkyl halide changes from CH_3 ⟶ 1° ⟶ 2° ⟶ 3°?

◆ As the number of R groups on the carbon with the leaving group *increases,* the rate of an S_N2 reaction *decreases.*

CH_3-X	RCH_2-X	R_2CH-X	R_3C-X
methyl	**1°**	**2°**	**3°**

Increasing rate of an S_N2 reaction

smi97462_ch07.qxd 11/4/04 2:52 PM Page 240

- Methyl and 1° alkyl halides undergo S_N2 reactions with ease.
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides *do not* undergo S_N2 reactions.

This order of reactivity can be explained by steric effects. As small H atoms are replaced by larger alkyl groups, **steric hindrance caused by bulky R groups makes nucleophilic attack from the back side more difficult,** slowing the reaction rate. Figure 7.11 illustrates the effect of increasing steric hindrance around the carbon bearing the leaving group in a series of alkyl halides.

The effect of steric hindrance on the rate of an S_N2 reaction is reflected in the energy of the transition state, too. Let's compare the reaction of ^-OH with two different alkyl halides, CH_3Br and $(CH_3)_2CHBr$. Steric hindrance around the 2° halide $(CH_3)_2CHBr$ is greater, making attack of the nucleophile more difficult, and *destabilizing* the transition state. This is shown in the energy diagrams for these two reactions in Figure 7.12.

- The *higher* the E_a, the *slower* the reaction rate. Thus, any factor that increases E_a (i.e., destabilizes the transition state), decreases the reaction rate.

Figure 7.11 Steric effects in the S_N2 reaction

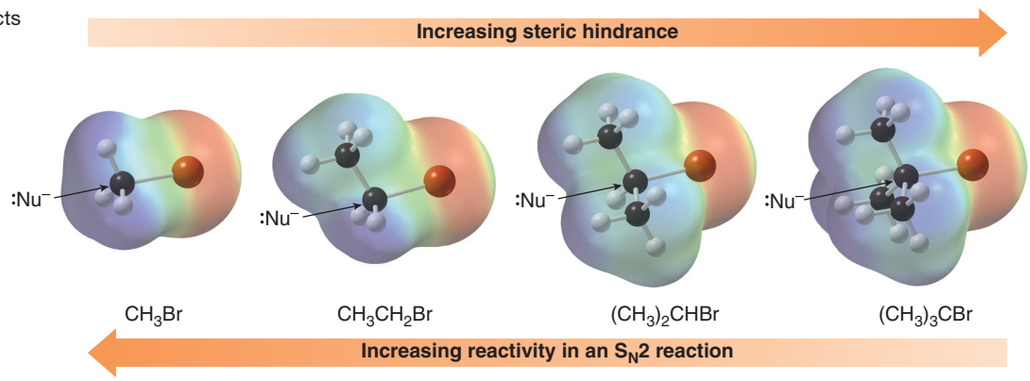
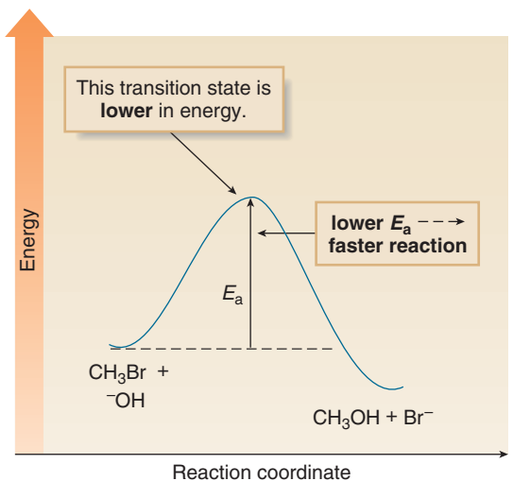
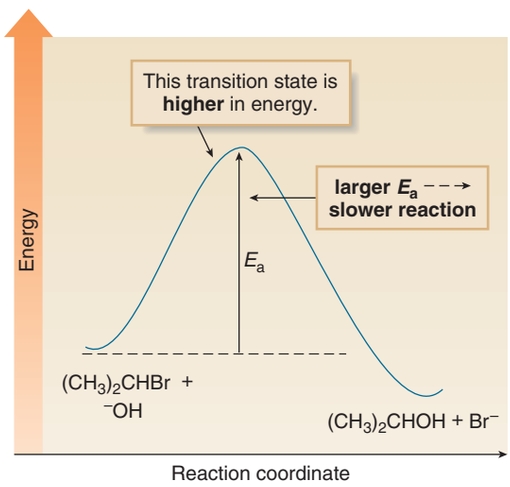


Figure 7.12 Two energy diagrams depicting the effect of steric hindrance in S_N2 reactions



[a]: $CH_3Br + {}^-OH \rightarrow CH_3OH + Br^-$

- CH_3Br is an unhindered alkyl halide. The transition state in the S_N2 reaction is lower in energy, making E_a lower and increasing the reaction rate.

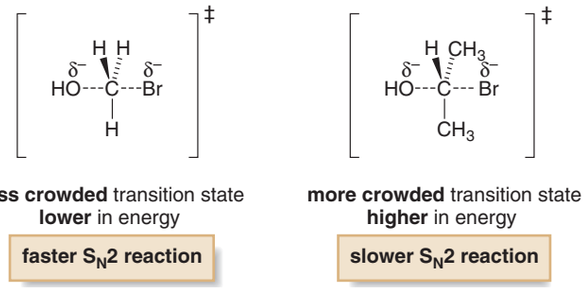


[b]: $(CH_3)_2CHBr + {}^-OH \rightarrow (CH_3)_2CHOH + Br^-$

- $(CH_3)_2CHBr$ is a sterically hindered alkyl halide. The transition state in the S_N2 reaction is higher in energy, making E_a higher and decreasing the reaction rate.

smi97462_ch07.qxd 11/4/04 2:52 PM Page 241

Why does steric hindrance destabilize the transition state, making it higher in energy? The transition state of an S_N2 reaction consists of five groups around the central carbon atom—three bonds to either H or R groups and two partial bonds to the leaving group and the nucleophile. **Crowding around the central carbon atom increases as H atoms are successively replaced by R groups,** so the central carbon is much more sterically hindered in the transition state for $(CH_3)_2CHBr$ than for CH_3Br. This increased crowding in the transition state makes it higher in energy (increases E_a), so the rate of the S_N2 reaction decreases.



less crowded transition state
lower in energy

faster S_N2 reaction

more crowded transition state
higher in energy

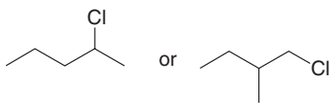
slower S_N2 reaction

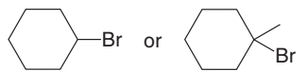
- **Increasing the number of R groups on the carbon with the leaving group *increases crowding* in the transition state, *decreasing* the rate of an S_N2 reaction.**

- **The S_N2 reaction is fastest with unhindered halides.**

PROBLEM 7.20 Which compound in each pair undergoes a faster S_N2 reaction?

a. $CH_3CH_2{-}Cl$ or $CH_3{-}Cl$

b.  or

c. 

PROBLEM 7.21 Explain why $(CH_3)_3CCH_2Br$, a 1° alkyl halide, undergoes S_N2 reactions very slowly.

Table 7.5 summarizes what we have learned thus far about an S_N2 mechanism.

TABLE 7.5 Characteristics of the S_N2 Mechanism

Characteristic	Result
Kinetics	• Second-order kinetics; rate = k[RX][:Nu^-]
Mechanism	• One step
Stereochemistry	• Backside attack of the nucleophile • Inversion of configuration at a stereogenic center
Identity of R	• Unhindered halides react fastest. • Rate: $CH_3X > RCH_2X > R_2CHX > R_3CX$

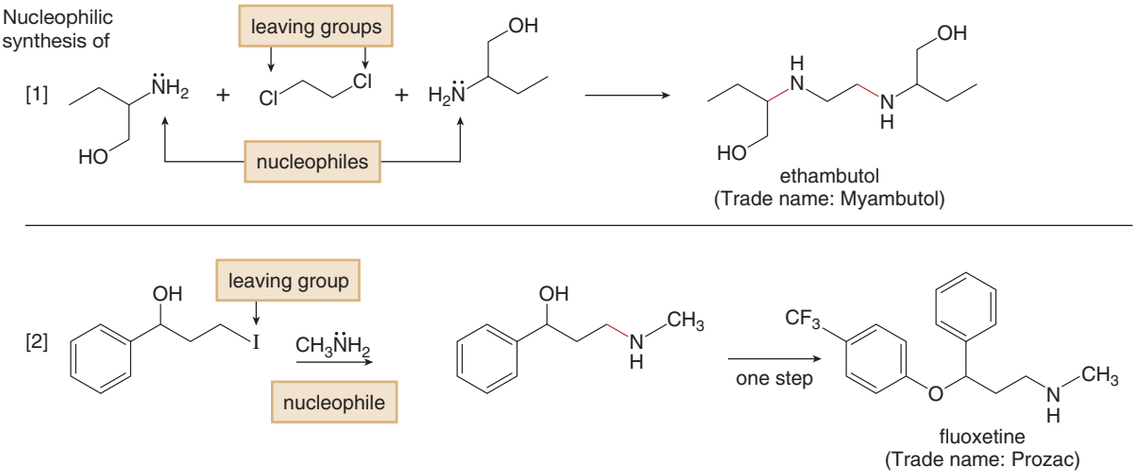
7.12 Application: Useful S_N2 Reactions

Nucleophilic substitution by an S_N2 mechanism is common in the laboratory and in biological systems.

The S_N2 reaction is a key step in the laboratory synthesis of many drugs including **ethambutol** (trade name: Myambutol), used in the treatment of tuberculosis, and **fluoxetine** (trade name: Prozac), an antidepressant, as illustrated in Figure 7.13.

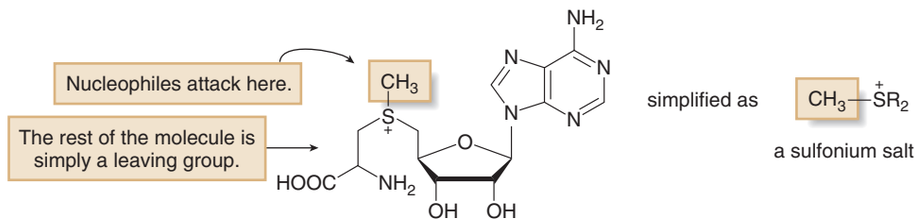
smi97462_ch07.qxd 11/22/04 2:38 PM Page 242

Figure 7.13 Nucleophilic substitution in the synthesis of two useful drugs



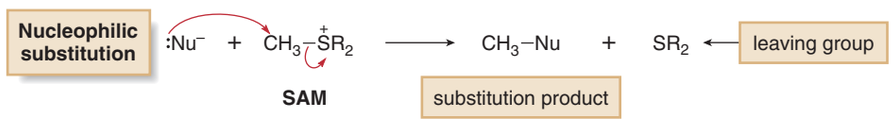
In both syntheses, the NH_2 group serves as a neutral nucleophile to displace halogen. The new bonds formed by nucleophilic substitution are drawn in red in the products.

Nucleophilic substitution reactions are important in biological systems as well. The most common reaction involves nucleophilic substitution at the CH_3 group in *S*-adenosylmethionine, or **SAM.** SAM is the cell's equivalent of CH_3I.



S-adenosylmethionine
SAM

The CH_3 group in SAM [abbreviated as $(CH_3SR_2)^+$] is part of a sulfonium salt, a positively charged sulfur species that contains a good leaving group. Nucleophilic attack at the CH_3 group of SAM displaces R_2S, a good neutral leaving group. This reaction is called **methylation,** because a CH_3 group is transferred from one compound (SAM) to another ($:Nu^-$).

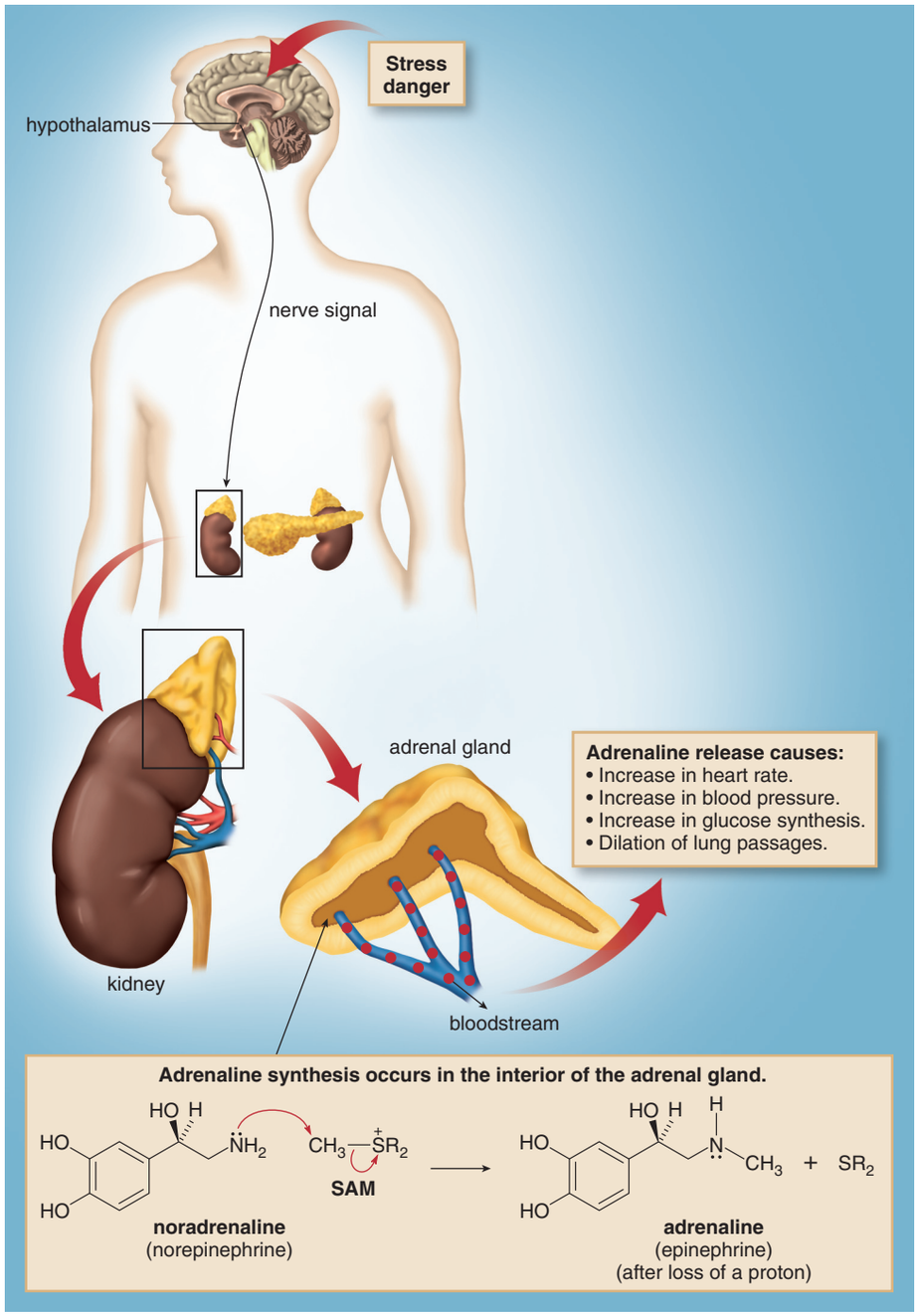


Cells use SAM, $(CH_3SR_2)^+$, instead of alkyl halides such as CH_3I in nucleophilic substitution reactions because alkyl halides are insoluble in the predominantly aqueous environment of the cell. In biological nucleophilic substitutions, therefore, the leaving group contains additional polar functional groups that make SAM, $(CH_3SR_2)^+$, water soluble.

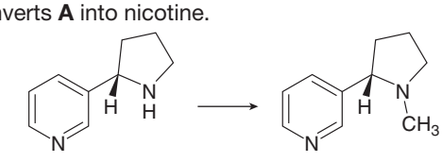
Adrenaline (epinephrine), the molecule that opened Chapter 7, is a hormone synthesized in the adrenal glands from noradrenaline (norepinephrine) by nucleophilic substitution using SAM (Figure 7.14). When an individual senses danger or is confronted by stress, the hypothalamus region of the brain signals the adrenal glands to synthesize and release adrenaline, which enters the bloodstream and then stimulates a response in many organs. Stored carbohydrates are metabolized in the liver to form glucose, which is further metabolized to provide an energy boost. Heart rate and blood pressure increase, and lung passages are dilated. These physiological changes prepare an individual for "fight or flight."

smi97462_ch07.qxd 11/22/04 2:39 PM Page 243

Figure 7.14 Adrenaline synthesis from noradrenaline in response to stress



PROBLEM 7.22 Nicotine, a toxic and addictive component of tobacco, is synthesized from **A** using SAM. Write out the reaction that converts **A** into nicotine.



smi97462_ch07.qxd 11/4/04 2:52 PM Page 244

7.13 The S_N1 Mechanism

The reaction of $(CH_3)_3CBr$ with CH_3COO^- is an example of the second mechanism for nucleophilic substitution, the **S_N1 mechanism.** What are the general features of this mechanism?

An S_N1 reaction

7.13A Kinetics

The S_N1 reaction exhibits **first-order kinetics.**

- rate = $k[(CH_3)_3CBr]$

As we learned in Section 7.10, this suggests that the S_N1 mechanism involves **more than one step,** and that the slow step is **unimolecular,** involving *only* the alkyl halide. **The identity and concentration of the nucleophile have no effect on the reaction rate.** For example, doubling the concentration of $(CH_3)_3CBr$ doubles the rate, but doubling the concentration of the nucleophile has no effect.

PROBLEM 7.23 What happens to the rate of an S_N1 reaction under each of the following conditions?

a. [RX] is tripled, and [:Nu$^-$] stays the same.
b. Both [RX] and [:Nu$^-$] are tripled.
c. [RX] is halved, and [:Nu$^-$] stays the same.
d. [RX] is halved, and [:Nu$^-$] is doubled.

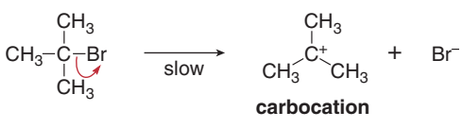
7.13B A Two-Step Mechanism

The most straightforward explanation for the observed first-order kinetics is a **two-step mechanism** in which **bond breaking occurs *before* bond making,** as shown in Mechanism 7.2.

MECHANISM 7.2

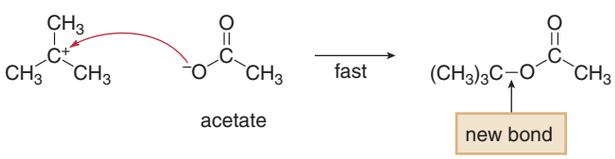
The S_N1 Mechanism

Step [1] The C–Br bond is broken.



- **Heterolysis of the C–Br bond** forms an intermediate **carbocation.** This step is rate-determining because it involves only bond cleavage.

Step [2] The C–O bond is formed.



- **Nucleophilic attack of acetate** on the carbocation forms the new C–O bond in the product. This is a **Lewis acid–base reaction;** the nucleophile is the Lewis base and the carbocation is the Lewis acid. Step [2] is *faster* than Step [1] because no bonds are broken and one bond is formed.

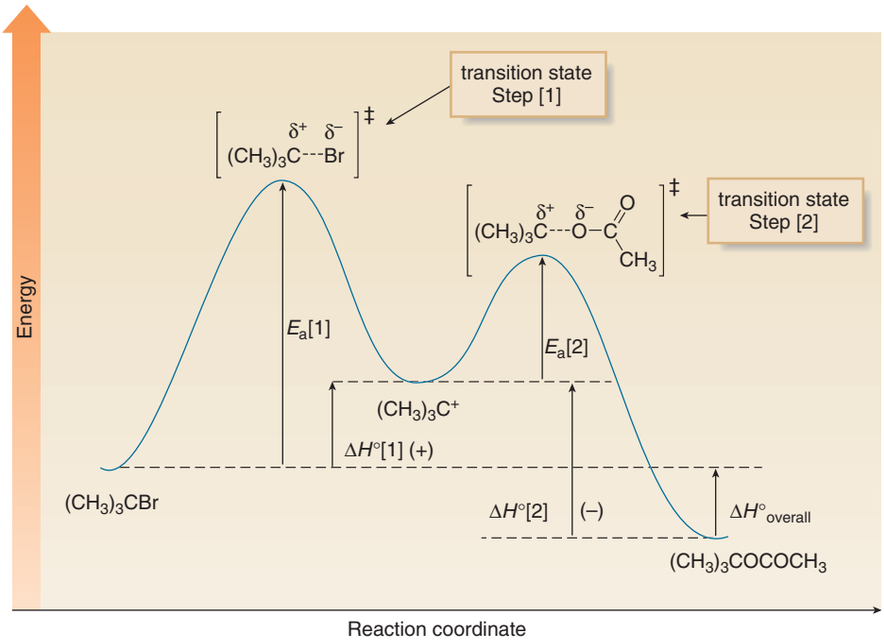
The key features of the S_N1 mechanism are:

- The mechanism has two steps.
- Carbocations are formed as reactive intermediates.

An energy diagram for the reaction of $(CH_3)_3CBr + CH_3COO^-$ is shown in Figure 7.15. Each step has its own energy barrier, with a transition state at each energy maximum. Because Step [1]

smi97462_ch07.qxd 11/4/04 2:52 PM Page 245

Figure 7.15 An energy diagram for the S_N1 reaction: $(CH_3)_3CBr + CH_3COO^- \rightarrow (CH_3)_3COCOCH_3 + Br^-$



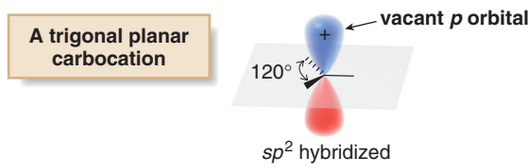
- Since the S_N1 mechanism has two steps, there are two energy barriers.
- Step [1] is rate-determining; $E_a[1] > E_a[2]$.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn with $\Delta H°_{overall}$ as a negative value, since the products are lower in energy than the starting materials.

is rate-determining, its transition state is at higher energy. $\Delta H°$ for Step [1] has a positive value because only bond breaking occurs, whereas $\Delta H°$ of Step [2] has a negative value because only bond making occurs. The overall reaction is assumed to be exothermic, so the final product is drawn at lower energy than the initial starting material.

PROBLEM 7.24 Assume the following reaction has an S_N1 mechanism and draw the two steps.

7.13C Stereochemistry of the S_N1 Reaction

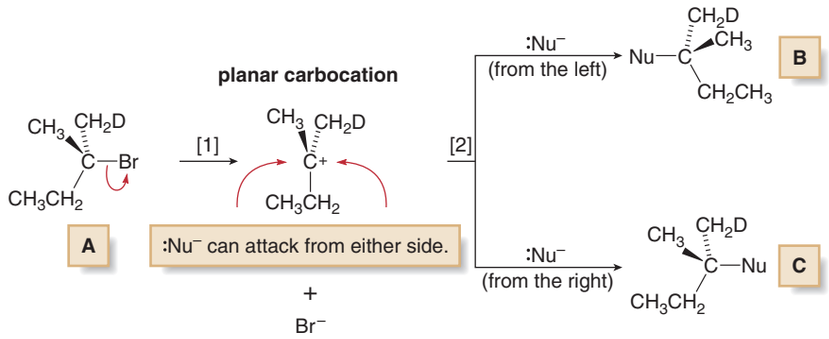
To understand the stereochemistry of the S_N1 reaction, we must examine the geometry of the carbocation intermediate.



◆ **A carbocation (with three groups around C) is sp^2 hybridized and trigonal planar, and contains a vacant *p* orbital extending above and below the plane.**

To illustrate the consequences of having a trigonal planar carbocation formed as a reactive intermediate, we examine the S_N1 reaction of a 3° alkyl halide **A** having the leaving group bonded to a stereogenic carbon.

smi97462_ch07.qxd 11/4/04 2:52 PM Page 246



Loss of the leaving group in Step [1] generates a planar carbocation that is now achiral. Attack of the nucleophile in Step [2] can occur from either side to afford two products, **B** and **C.** These two products are *different* compounds containing one stereogenic center. **B** and **C** are stereoisomers that are not superimposable—they are **enantiomers.** Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a **racemic mixture.** We say that ***racemization*** has occurred.

Nucleophilic attack from both sides of a planar carbocation occurs in S_N1 reactions, but we see the result of this phenomenon only when the leaving group is bonded to a stereogenic center.

- ***Racemization*** **is the formation of equal amounts of two enantiomeric products from a single starting material.**
- **S_N1 reactions proceed with *racemization* at a single stereogenic center.**

Two additional examples of racemization in S_N1 reactions are given in Figure 7.16.

SAMPLE PROBLEM 7.3 Draw the products (including stereochemistry) of the following S_N1 reaction.

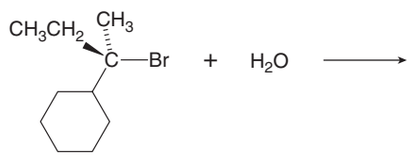
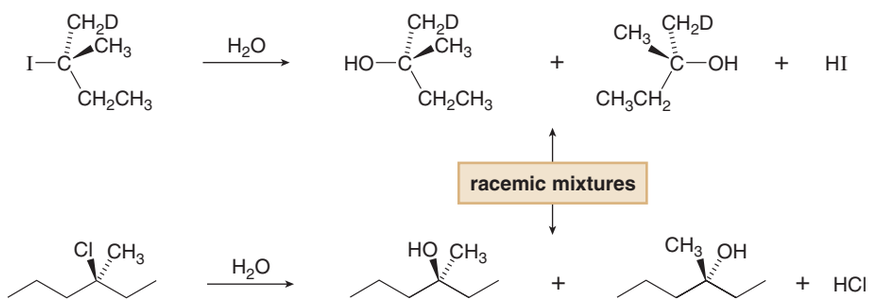


Figure 7.16 Two examples of racemization in the S_N1 reaction

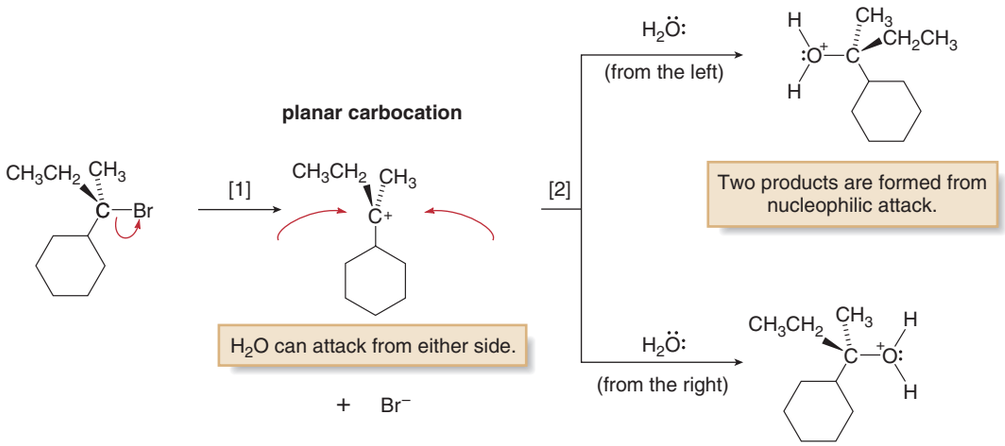


- Nucleophilic substitution of each starting material by an S_N1 mechanism forms a **racemic mixture** of two products.
- With H_2O, a neutral nucleophile, the initial product of nucleophilic substitution (ROH_2^+) loses a proton to form the final neutral product, ROH (Section 7.6).

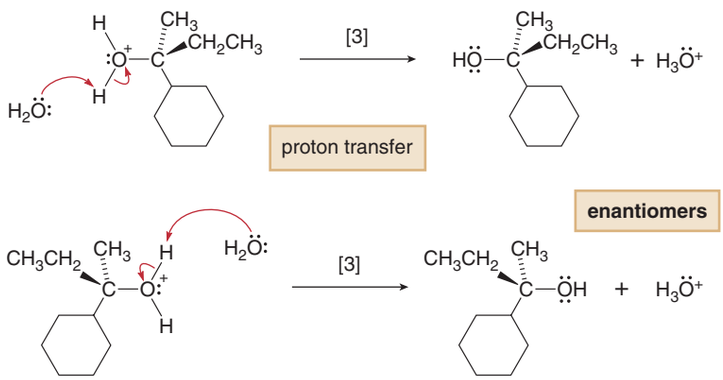
smi97462_ch07.qxd 11/4/04 2:52 PM Page 247

SOLUTION

Br^- is the leaving group and H_2O is the nucleophile. Loss of the leaving group generates a trigonal planar carbocation, which can react with the nucleophile from either direction to form two products.

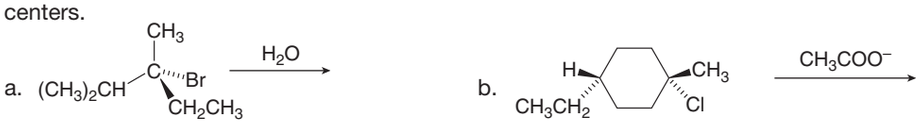


In this example, the initial products of nucleophilic substitution bear a positive charge. They readily lose a proton to form neutral products. The overall process with a neutral nucleophile thus has **three steps:** the first two constitute the **two-step S_N1 mechanism** (loss of the leaving group and attack of the nucleophile), and the third is a **Brønsted–Lowry acid–base reaction** leading to a neutral organic product.



The two products in this reaction are nonsuperimposable mirror images—**enantiomers.** Because nucleophilic attack on the trigonal planar carbocation occurs with equal frequency from both directions, a **racemic mixture is formed.**

PROBLEM 7.25 Draw the products of each S_N1 reaction and indicate the stereochemistry of any stereogenic centers.



7.13D The Identity of the R Group

How does the rate of an S_N1 reaction change as the alkyl group in the substrate alkyl halide changes from CH_3 ⟶ 1° ⟶ 2° ⟶ 3°?

smi97462_ch07.qxd 11/4/04 2:52 PM Page 248

- As the number of R groups on the carbon with the leaving group *increases,* the rate of an S_N1 reaction *increases.*

CH_3-X	RCH_2-X	R_2CH-X	R_3C-X
methyl	**1°**	**2°**	**3°**

Increasing rate of an S_N1 reaction

- 3° Alkyl halides undergo S_N1 reactions rapidly.
- 2° Alkyl halides react more slowly.
- Methyl and 1° alkyl halides do *not* undergo S_N1 reactions.

Table 7.6 summarizes the characteristics of the S_N1 mechanism.

This trend is exactly opposite to that observed for the S_N2 mechanism. To explain this result, we must examine the rate-determining step, the formation of the carbocation, and learn about the effect of alkyl groups on **carbocation stability.**

TABLE 7.6 Characteristics of the S_N1 Mechanism

Characteristic	Result
Kinetics	• First-order kinetics; rate = k[RX]
Mechanism	• Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More substituted halides react fastest. • Rate: $R_3CX > R_2CHX > RCH_2X > CH_3X$

7.14 Carbocation Stability

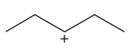
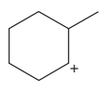
Carbocations are classified as **primary (1°), secondary (2°), or tertiary (3°)** by the number of R groups bonded to the charged carbon atom. As the number of R groups on the positively charged carbon atom increases, the stability of the carbocation **increases.**

$\overset{+}{C}H_3$	$R\overset{+}{C}H_2$	$R_2\overset{+}{C}H$	$R_3\overset{+}{C}$
methyl	**1°**	**2°**	**3°**

Increasing carbocation stability

When we speak of carbocation stability, we really mean *relative* stability. Tertiary carbocations are too unstable to isolate, but they are more stable than secondary carbocations. We will examine the reason for this order of stability by invoking two different principles: **inductive effects** and **hyperconjugation.**

PROBLEM 7.26 Classify each carbocation as 1°, 2°, or 3°.

a. $CH_3\overset{+}{C}HCH_2CH_3$ b.  c. $(CH_3)_3C\overset{+}{C}H_2$ d.  e. 

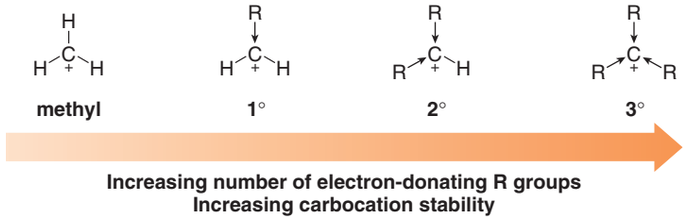
7.14A Inductive Effects

Inductive effects are electronic effects that occur through σ bonds. They stabilize a species when electron density is dispersed over a larger volume. In Section 2.5B, for example, we learned that more electronegative atoms stabilize a negative charge by an electron-withdrawing inductive effect.

smi97462_ch07.qxd 11/4/04 2:52 PM Page 249

Electron donor groups (Z) stabilize a (+) charge; $Z \rightarrow Y^+$. Electron-withdrawing groups (W) stabilize a (–) charge; $W \leftarrow Y^-$.

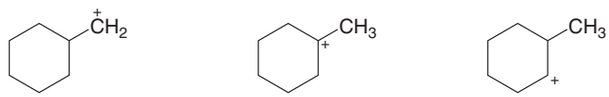
To stabilize a positive charge, **electron-donating groups** are needed. **Alkyl groups are electron donor groups that stabilize a positive charge.** Because an alkyl group has several σ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and more able to donate electron density. Thus, as R groups successively replace the H atoms in CH_3^+, **the positive charge is more dispersed on the electron donor R groups, and the carbocation is more stabilized.**



Electrostatic potential maps for four different carbocations in Figure 7.17 illustrate how the positive charge on carbon becomes less concentrated (more dispersed) as the number of alkyl groups increases.

PROBLEM 7.27 Rank the following carbocations in order of increasing stability.

a. $(CH_3)_2\overset{+}{C}CH_2CH_3$ $(CH_3)_2CHCH_2\overset{+}{C}H_2$ $(CH_3)_2CH\overset{+}{C}HCH_3$

b. 

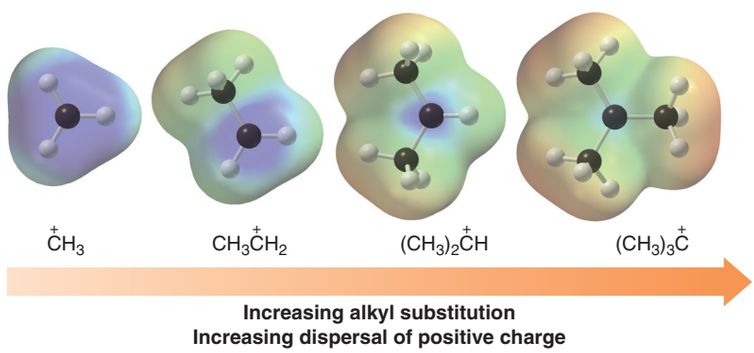
PROBLEM 7.28 Which of the following 1° carbocations is more stable: $CH_3CH_2^+$ or $CCl_3CH_2^+$?

7.14B Hyperconjugation

A second explanation for the observed trend in carbocation stability is based on orbital overlap. A 3° carbocation is more stable than a 2°, 1°, or methyl carbocation because the positive charge is delocalized over more than one atom.

◆ **Spreading out charge by the overlap of an empty *p* orbital with an adjacent σ bond is called *hyperconjugation.***

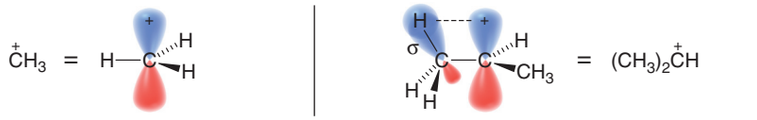
Figure 7.17 Electrostatic potential maps for different carbocations



- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.

smi97462_ch07.qxd 11/4/04 2:52 PM Page 250

For example, CH_3^+ cannot be stabilized by hyperconjugation, but $(CH_3)_2CH^+$ can:



This carbocation has no opportunity for orbital overlap with the vacant *p* orbital.

Overlap of the C—H σ bond with the adjacent vacant *p* orbital stabilizes the carbocation.

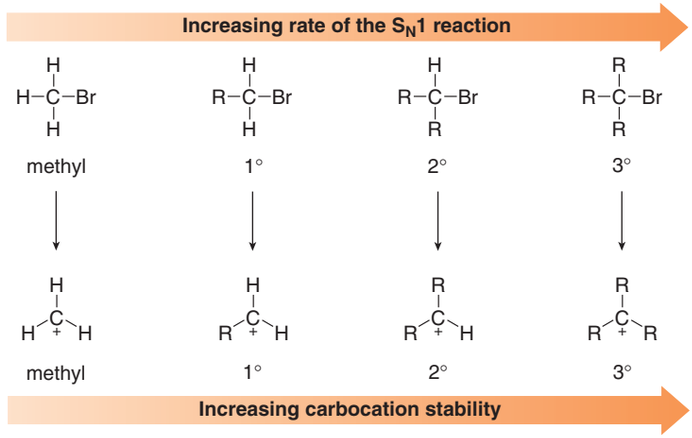
Both carbocations contain an sp^2 hybridized carbon, so both are trigonal planar with a vacant *p* orbital extending above and below the plane. There are no adjacent C−H σ bonds with which the *p* orbital can overlap in CH_3^+, but there *are* adjacent C−H σ bonds in $(CH_3)_2CH^+$. This overlap (the **hyperconjugation**) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.

The larger the number of alkyl groups on the adjacent carbons, the greater the possibility for hyperconjugation, and the larger the stabilization. Hyperconjugation thus provides an alternate way of explaining why **carbocations with a larger number of R groups are more stabilized.**

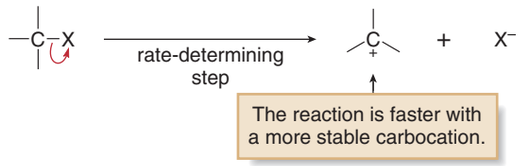
7.15 The Hammond Postulate

The rate of an S_N1 reaction depends on the rate of formation of the carbocation (the product of the rate-determining step) via heterolysis of the C−X bond.

- The rate of an S_N1 reaction *increases* as the number of R groups on the carbon with the leaving group *increases.*
- The stability of a carbocation *increases* as the number of R groups on the positively charged carbon *increases.*



- Thus, the rate of an S_N1 reaction *increases* as the stability of the carbocation *increases.*



The rate of a reaction depends on the magnitude of E_a, and the stability of a product depends on $\Delta G°$. The **Hammond postulate,** first proposed in 1955, **relates rate to stability.**

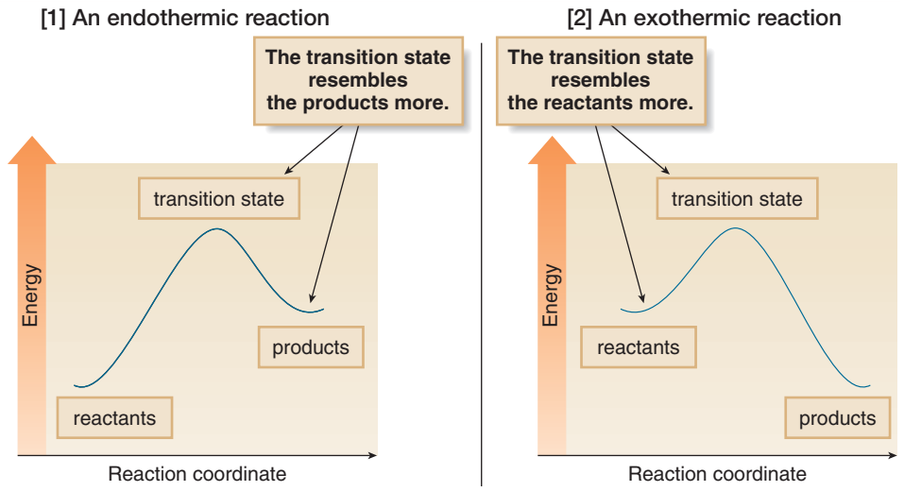
smi97462_ch07.qxd 11/4/04 2:52 PM Page 251

7.15A The General Features of the Hammond Postulate

The Hammond postulate provides a qualitative estimate of the energy of a transition state. Because the energy of the transition state determines the energy of activation and therefore the reaction rate, predicting the relative energy of two transition states allows us to determine the relative rates of two reactions.

According to the Hammond postulate, the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy. A transition state is always higher in energy than both the reactants and products, so it will resemble the structure of either the reactant or product, whichever is higher in energy.

- In endothermic reactions, the transition state is closer in energy to the products.
- In exothermic reactions, the transition state is closer in energy to the reactants.



- Transition states in endothermic reactions resemble the products.
- Transition states in exothermic reactions resemble the reactants.

What happens to the reaction rate if the energy of the product is lowered? In an **endothermic reaction,** the transition state resembles the products more than the reactants, so anything that stabilizes the product stabilizes the transition state, too. **Lowering the energy of the transition state *decreases* the energy of activation (E_a), which *increases* the reaction rate.**

Suppose there are two possible products of an endothermic reaction, but one is more stable (lower in energy) than the other (Figure 7.18). According to the Hammond postulate, **the transition state to form the more stable product is lower in energy, so this reaction should occur faster.**

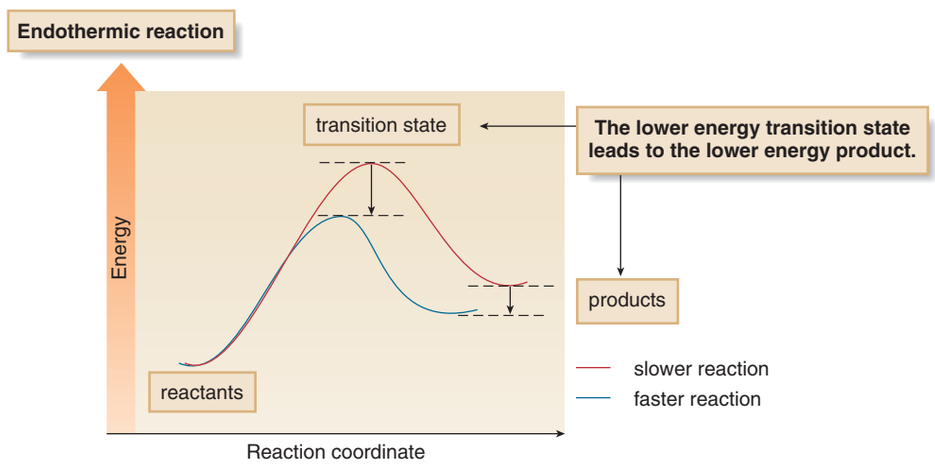


Figure 7.18 An endothermic reaction—How the energy of the transition state and products are related

smi97462_ch07.qxd 11/4/04 2:52 PM Page 252

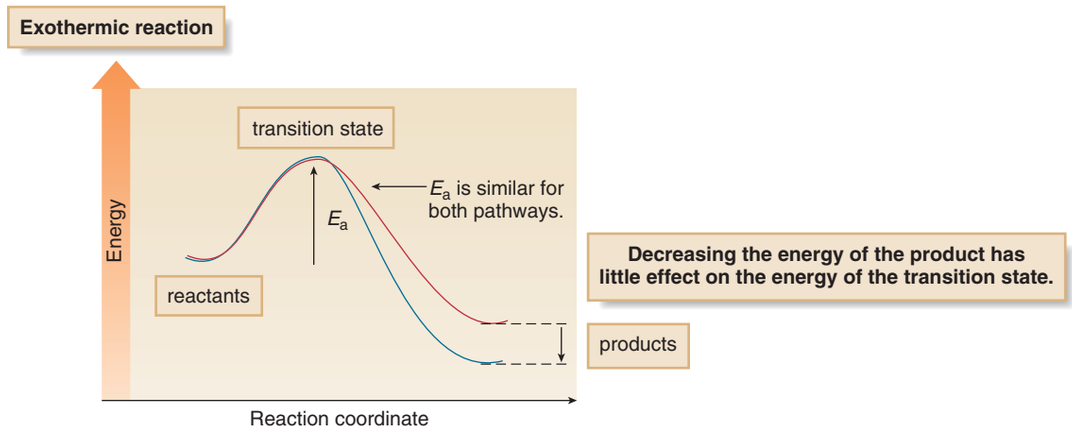


Figure 7.19 An exothermic reaction—How the energy of the transition state and products are related

◆ **Conclusion: In an endothermic reaction, the more stable product forms faster.**

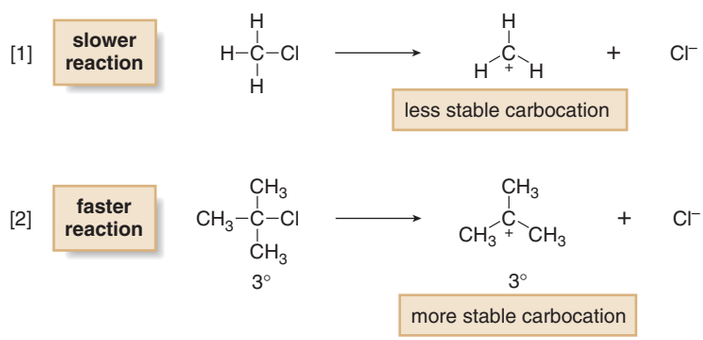
What happens to the reaction rate of an **exothermic reaction** if the energy of the product is lowered? The transition state resembles the reactants more than the products, so **lowering the energy of the products has little or no effect on the energy of the transition state.** If E_a is unaffected, then the reaction rate is unaffected, too, as shown in Figure 7.19.

◆ **Conclusion: In an exothermic reaction, the more stable product may or may not form faster because E_a is similar for both products.**

7.15B The Hammond Postulate and the S_N1 Reaction

In the S_N1 reaction, the rate-determining step is the formation of the carbocation, an *endothermic* reaction. According to the Hammond postulate, the **stability of the carbocation determines the rate of its formation.**

For example, heterolysis of the C−Cl bond in CH_3Cl affords a highly unstable methyl carbocation, CH_3^+ (Equation [1]), whereas heterolysis of the C−Cl bond in $(CH_3)_3CCl$ affords a more stable 3° carbocation, $(CH_3)_3C^+$ (Equation [2]). The Hammond postulate states that Reaction [2] is much faster than Reaction [1], because the transition state to form the more stable 3° carbocation is lower in energy. Figure 7.20 depicts an energy diagram comparing these two endothermic reactions.

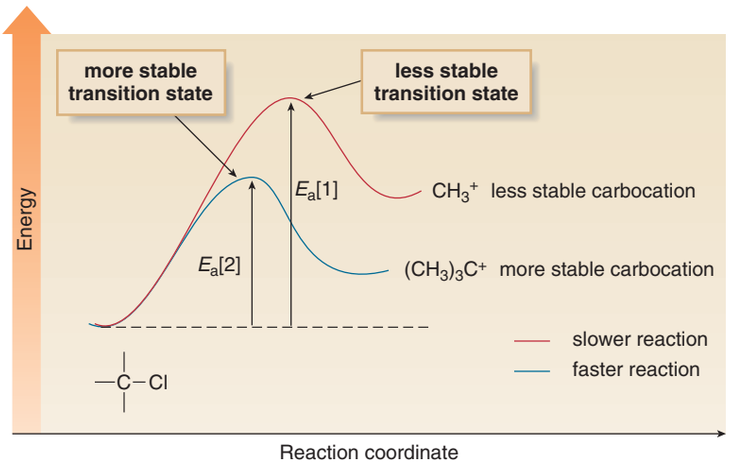


In conclusion, the Hammond postulate estimates the relative energy of transition states, and thus it can be used to predict the relative rates of two reactions.

smi97462_ch07.qxd 11/4/04 2:52 PM Page 253

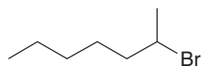
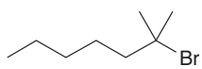
Figure 7.20 Energy diagram for carbocation formation in two different S_N1 reactions

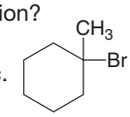
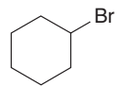
- Since CH_3^+ is less stable than $(CH_3)_3C^+$, $E_a[1] > E_a[2]$, and Reaction [1] is slower.



PROBLEM 7.29 Which alkyl halide in each pair reacts faster in an S_N1 reaction?

a. $(CH_3)_3CBr$ and $(CH_3)_3CCH_2Br$

b.  and 

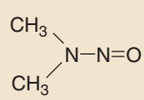
c.  and 

7.16 Application: S_N1 Reactions, Nitrosamines, and Cancer

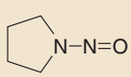
S_N1 reactions are thought to play a role in how **nitrosamines,** compounds having the general structure $\mathbf{R_2NN{=}O}$, act as toxins and carcinogens. Nitrosamines are present in many foods, especially cured meats and smoked fish, and they are also found in tobacco smoke, alcoholic beverages, and cosmetics. Nitrosamines cause many forms of cancer.

Spam, a widely consumed canned meat in Alaska, Hawaii, and other parts of the United States, contains sodium nitrite.

Examples of two common nitrosamines:



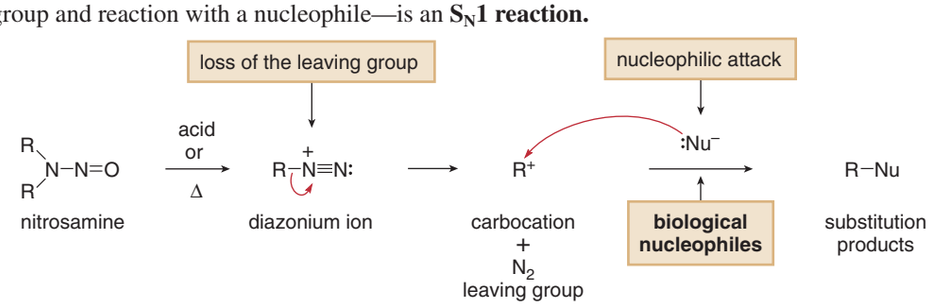
N-nitrosodimethylamine



N-nitrosopyrrolidine

Nitrosamines are formed when amines that occur naturally in food react with sodium nitrite, $NaNO_2$, a preservative added to meats such as ham, bacon, and hot dogs to inhibit the growth of *Clostridium botulinum,* a bacterium responsible for a lethal form of food poisoning. Nitrosamines are also formed in vivo in the gastrointestinal tract when bacteria in the body convert nitrates (NO_3^-) into nitrites (NO_2^-), which then react with amines.

In the presence of acid or heat, nitrosamines are converted to **diazonium ions,** which contain a very good leaving group, N_2. With certain R groups, these diazonium compounds form carbocations, which then react with biological nucleophiles (such as DNA or an enzyme) in the cell. If this nucleophilic substitution reaction occurs at a crucial site in a biomolecule, it can disrupt normal cell function leading to cancer or cell death. This two-step process—loss of N_2 as a leaving group and reaction with a nucleophile—is an **S_N1 reaction.**



smi97462_ch07.qxd 11/4/04 2:52 PM Page 254

The preparation and reactions of diazonium ions (RN_2^+) are discussed in Chapter 25.

The use of sodium nitrite as a preservative is a classic example of the often delicate balance between risk and benefit. On the one hand, there is an enormous benefit in reducing the prevalence of fatal toxins in meats by the addition of sodium nitrite. On the other, there is the added risk that sodium nitrite may increase the level of nitrosamines in certain foods. Nitrites are still used as food additives, but the allowable level of nitrites in cured meats has been reduced.

7.17 When Is the Mechanism S_N1 or S_N2?

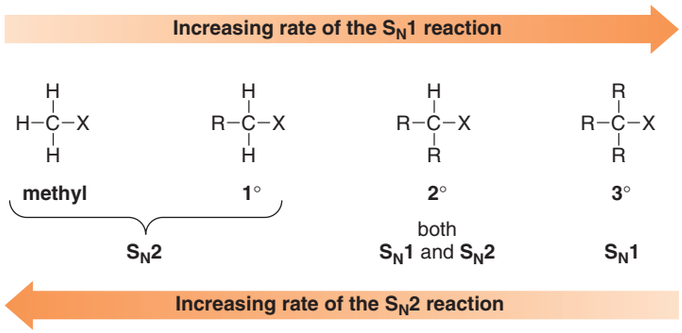
Given a particular starting material and nucleophile, how do we know whether a reaction occurs by the S_N1 or S_N2 mechanism? Four factors are examined:

- **The alkyl halide—CH_3X, RCH_2X, R_2CHX, or R_3CX**
- **The nucleophile—strong or weak**
- **The leaving group—good or poor**
- **The solvent—protic or aprotic**

7.17A The Alkyl Halide—The Most Important Factor

The most important factor in determining whether a reaction follows the S_N1 or S_N2 mechanism is the *identity of the alkyl halide.*

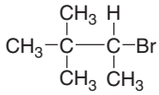
- Increasing alkyl substitution favors S_N1.
- Decreasing alkyl substitution favors S_N2.

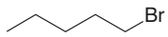


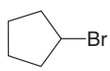
- Methyl and 1° halides (CH_3X and RCH_2X) undergo S_N2 reactions only.
- 3° Alkyl halides (R_3CX) undergo S_N1 reactions only.
- 2° Alkyl halides (R_2CHX) undergo both S_N1 and S_N2 reactions. Other factors determine the mechanism.

Examples are given in Figure 7.21.

PROBLEM 7.30 What is the likely mechanism of nucleophilic substitution for each alkyl halide?

a. 

b. 

c. 

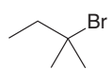
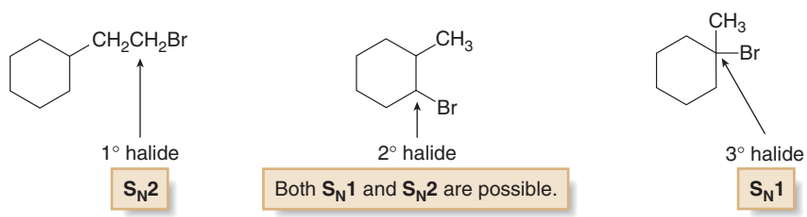
d. 

Figure 7.21 Examples: The identity of RX and the mechanism of nucleophilic substitution



smi97462_ch07.qxd 11/22/04 1:04 PM Page 255

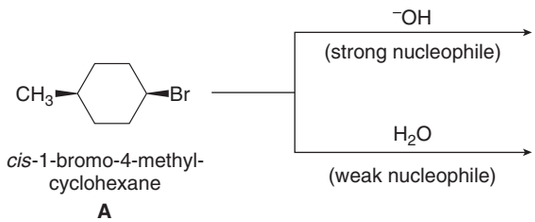
7.17B The Nucleophile

How does the strength of the nucleophile affect an S_N1 or S_N2 mechanism? The rate of the S_N1 reaction is unaffected by the identity of the nucleophile because the nucleophile does not appear in the rate equation (rate = k[RX]). The identity of the nucleophile *is* important for the S_N2 reaction, however, because the nucleophile does appear in the rate equation for this mechanism (rate = k[RX][:Nu^-]).

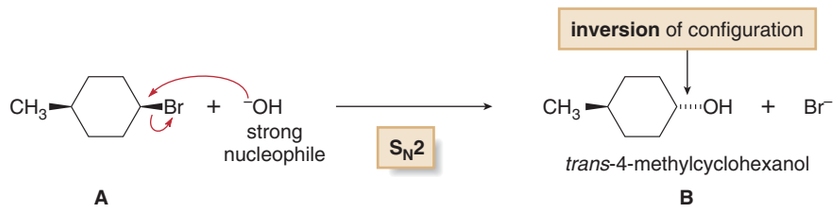
- **Strong nucleophiles present in high concentration favor S_N2 reactions.**
- **Weak nucleophiles favor S_N1 reactions by decreasing the rate of any competing S_N2 reaction.**

The most common nucleophiles in S_N2 reactions bear a net negative charge. The most common nucleophiles in S_N1 reactions are weak nucleophiles such as H_2O and ROH. The identity of the nucleophile is especially important in determining the mechanism and therefore the stereochemistry of nucleophilic substitution when 2° alkyl halides are starting materials.

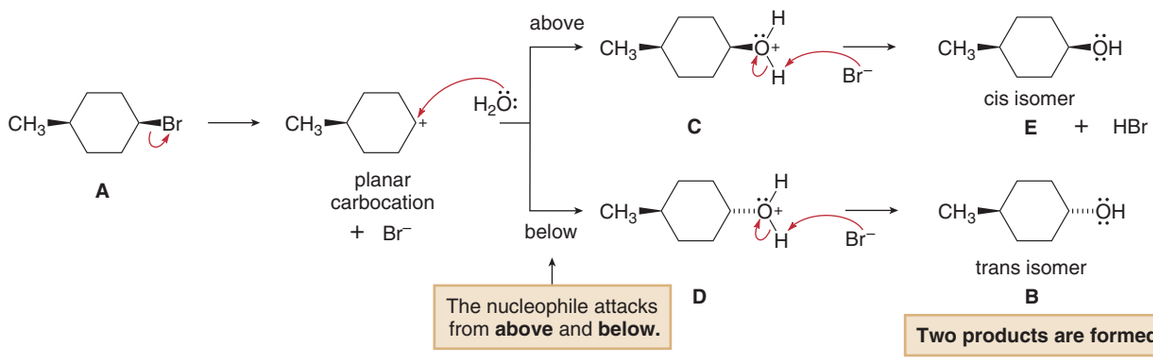
Let's compare the substitution products formed when the 2° alkyl halide **A** (*cis*-1-bromo-4-methylcyclohexane) is treated with either the strong nucleophile $^-$OH or the weak nucleophile H_2O. Because a 2° alkyl halide can react by either mechanism, the strength of the nucleophile determines which mechanism takes place.



The **strong nucleophile $^-$OH favors an S_N2 reaction,** which occurs with **backside** attack of the nucleophile, resulting in **inversion of configuration.** Because the leaving group Br^- is above the plane of the ring, the nucleophile attacks from below, and a single product **B** is formed.



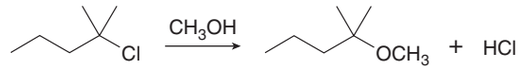
The **weak nucleophile H_2O favors an S_N1 reaction,** which occurs by way of an intermediate carbocation. Loss of the leaving group in **A** forms the carbocation, which undergoes nucleophilic attack from both above and below the plane of the ring to afford two products, **C** and **D.** Loss of a proton by proton transfer forms the final products, **B** and **E. B** and **E** are diastereomers of each other (**B** is a trans isomer and **E** is a cis isomer).

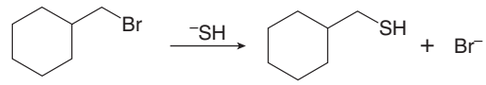


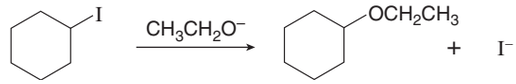
smi97462_ch07.qxd 11/22/04 1:05 PM Page 256

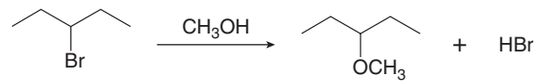
Thus, the mechanism of nucleophilic substitution determines the stereochemistry of the products formed.

PROBLEM 7.31 What is the likely mechanism (S_N1 or S_N2) for each reaction?

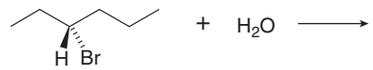
a. 

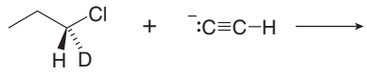
b. 

c. 

d. 

PROBLEM 7.32 Draw the products (including stereochemistry) for each reaction.

a. 

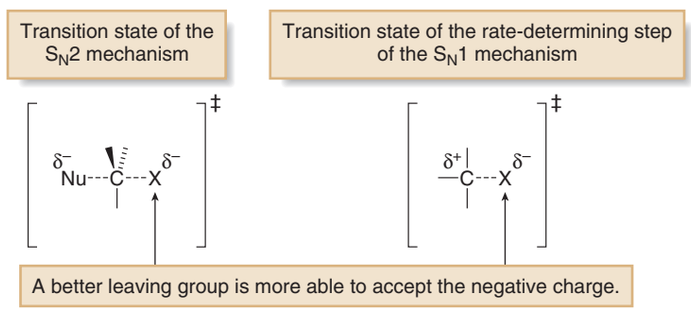
b. 

7.17C The Leaving Group

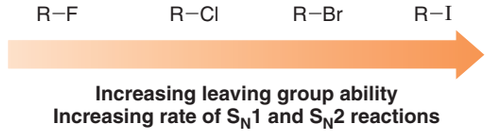
How does the identity of the leaving group affect an S_N1 or S_N2 reaction? Unlike nucleophilicity, the identity of the leaving group does *not* favor one mechanism over the other.

◆ **A better leaving group increases the rate of both S_N1 and S_N2 reactions.**

Because the bond to the leaving group is partially broken in the transition state of the only step of the S_N2 mechanism and the slow step of the S_N1 mechanism, **a better leaving group increases the rate of both reactions.** The better the leaving group, the more willing it is to accept the electron pair in the C−X bond, and the faster the reaction.



For alkyl halides, the following order of reactivity is observed for the S_N1 and the S_N2 mechanisms:



PROBLEM 7.33 Which compound in each pair reacts faster in nucleophilic substitution?

a. $CH_3CH_2CH_2Cl$ and $CH_3CH_2CH_2I$
b. $(CH_3)_3CBr$ and $(CH_3)_3CI$
c. $(CH_3)_3COH$ and $(CH_3)_3COH_2^+$
d. $CH_3CH_2CH_2OH$ and $CH_3CH_2CH_2OCOCH_3$

smi97462_ch07.qxd 11/22/04 1:07 PM Page 257

See Section 7.8C to review the differences between polar protic solvents and polar aprotic solvents.

Summary of solvent effects:

- Polar protic solvents favor S_N1 reactions because the ionic intermediates are stabilized by solvation.
- Polar aprotic solvents favor S_N2 reactions because nucleophiles are not well solvated, and therefore are more nucleophilic.

7.17D The Solvent

Polar protic solvents and polar aprotic solvents affect the rates of S_N1 and S_N2 reactions differently.

- **Polar *protic* solvents are especially good for S_N1 reactions.**
- **Polar *aprotic* solvents are especially good for S_N2 reactions.**

Polar protic solvents like H_2O and ROH solvate both cations and anions well, and this characteristic is important for the S_N1 mechanism, in which two ions (a carbocation and a leaving group) are formed by heterolysis of the C−X bond. The carbocation is solvated by ion–dipole interactions with the polar solvent, and the leaving group is solvated by hydrogen bonding, in much the same way that Na^+ and Br^- are solvated in Section 7.8C. These interactions stabilize the reactive intermediate. In fact, a polar protic solvent is generally needed for an S_N1 reaction. S_N1 reactions do not occur in the gas phase, because there is no solvent to stabilize the intermediate ions.

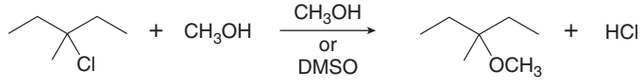
Polar aprotic solvents exhibit dipole–dipole interactions but not hydrogen bonding, and as a result, they do not solvate anions well. This has a pronounced effect on the nucleophilicity of anionic nucleophiles. Because these nucleophiles are not "hidden" by strong interactions with the solvent, they are **more nucleophilic.** Because stronger nucleophiles favor S_N2 reactions, **polar aprotic solvents are especially good for S_N2 reactions.**

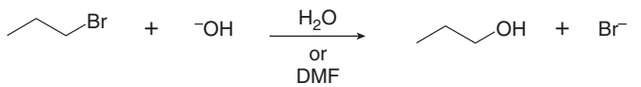
PROBLEM 7.34 Which solvents favor S_N1 reactions and which favor S_N2 reactions?

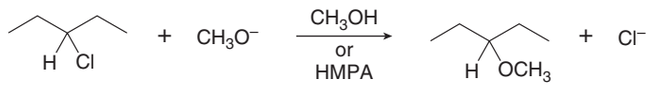
a. CH_3CH_2OH b. CH_3CN c. CH_3COOH d. $CH_3CH_2OCH_2CH_3$

PROBLEM 7.35 For each reaction, use the identity of the alkyl halide and nucleophile to determine which substitution mechanism occurs. Then determine which solvent affords the faster reaction.

a. $(CH_3)_3CBr + H_2O \xrightarrow[\text{or } (CH_3)_2C{=}O]{H_2O} (CH_3)_3COH + HBr$

b. 

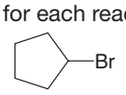
c. 

d. 

7.17E Summary of Factors that Determine Whether the S_N1 or S_N2 Mechanism Occurs

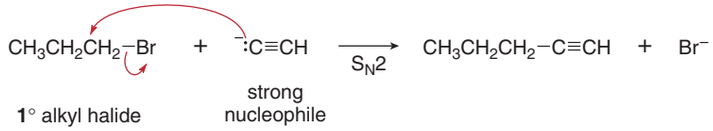
Table 7.7 summarizes the factors that determine whether a reaction occurs by the S_N1 or S_N2 mechanism. Sample Problems 7.4 and 7.5 illustrate how these factors are used to determine the mechanism of a given reaction.

SAMPLE PROBLEM 7.4 Determine the mechanism of nucleophilic substitution for each reaction and draw the products.

a. $CH_3CH_2CH_2{-}Br + {}^-{:}C{\equiv}CH \longrightarrow$ b.  $+ {}^-CN \longrightarrow$

SOLUTION

[a] The alkyl halide is 1° so it must react by an S_N2 mechanism with the nucleophile $^-{:}C{\equiv}CH$.

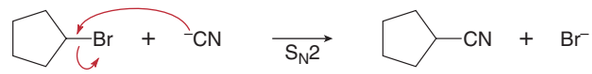


smi97462_ch07.qxd 11/22/04 2:39 PM Page 258

TABLE 7.7 Summary of Factors that Determine the S_N1 or S_N2 Mechanism

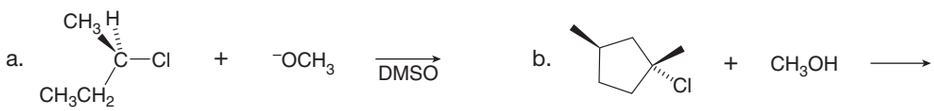
Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	**S_N2**	Favored by • **strong nucleophiles** (usually a net negative charge) • polar **aprotic** solvents
R_3CX (3°)	**S_N1**	Favored by • **weak nucleophiles** (usually neutral) • polar **protic** solvents
R_2CHX (2°)	**S_N1 or S_N2**	The mechanism depends on the conditions. • **Strong nucleophiles favor the S_N2 mechanism over the S_N1 mechanism.** For example, RO^- is a stronger nucleophile than ROH, so RO^- favors the S_N2 reaction and ROH favors the S_N1 reaction. • **Protic solvents favor the S_N1 mechanism and aprotic solvents favor the S_N2 mechanism.** For example, H_2O and CH_3OH are polar protic solvents that favor the S_N1 mechanism, whereas acetone $[(CH_3)_2C{=}O]$ and DMSO $[(CH_3)_2S{=}O]$ are polar aprotic solvents that favor the S_N2 mechanism.

[b] The alkyl halide is 2° so it can react by either the S_N1 or S_N2 mechanism. The strong nucleophile (^-CN) favors the S_N2 mechanism.



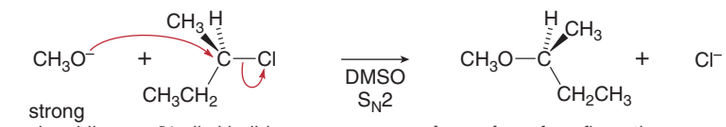
2° alkyl halide — strong nucleophile

SAMPLE PROBLEM 7.5 Determine the mechanism of nucleophilic substitution for each reaction and draw the products, including stereochemistry.



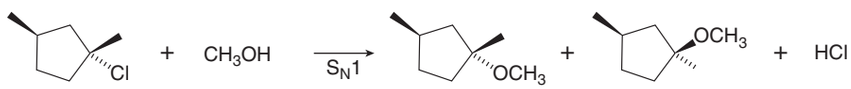
SOLUTION

[a] The 2° alkyl halide can react by either the S_N1 or S_N2 mechanism. The strong nucleophile ($^-OCH_3$) favors the S_N2 mechanism, as does the polar aprotic solvent (DMSO). S_N2 reactions proceed with inversion of configuration.



strong nucleophile — **2°** alkyl halide — **inversion** of configuration

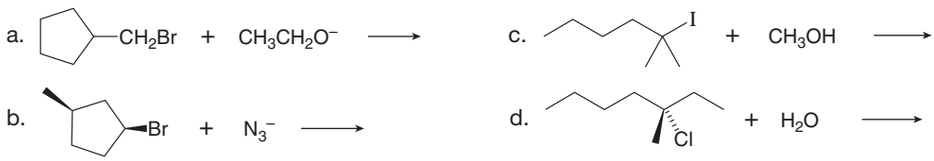
[b] The alkyl halide is 3° so it reacts by an S_N1 mechanism with the weak nucleophile CH_3OH. S_N1 reactions proceed with racemization at a single stereogenic center, so two products are formed.



3° alkyl halide — weak nucleophile — two products of nucleophilic substitution

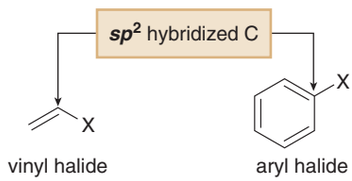
smi97462_ch07.qxd 11/22/04 1:10 PM Page 259

PROBLEM 7.36 Determine the mechanism and draw the products of each reaction. Include the stereochemistry at all stereogenic centers.



7.18 Vinyl Halides and Aryl Halides

S_N1 and S_N2 reactions occur only at sp^3 hybridized carbon atoms. Now that we have learned about the mechanisms for nucleophilic substitution we can understand why **vinyl halides** and **aryl halides,** which have a halogen atom bonded to an sp^2 hybridized C, do not undergo nucleophilic substitution by either the S_N1 or S_N2 mechanism. The discussion here centers on vinyl halides, but similar arguments hold for aryl halides as well.



Vinyl halides do not undergo an S_N2 reaction in part for electronic reasons, because the electron-rich π bond prevents backside attack by the electron-rich nucleophile. The nucleophile would have to approach the leaving group in the plane of the double bond (Figure 7.22a). Steric factors also make approach in the plane of the double bond difficult.

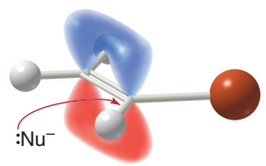
Vinyl halides do not undergo S_N1 reactions because heterolysis of the C−X bond would form a **highly unstable vinyl carbocation.** Because this carbocation has only two groups around the positively charged carbon, it is ***sp*** hybridized (Figure 7.22b). These carbocations are even less stable than 1° carbocations, so the S_N1 reaction does not take place.

PROBLEM 7.37 Rank the following carbocations in order of increasing stability.

a. $CH_3CH_2CH_2CH_2CH{=}\overset{+}{C}H$ b. $CH_3CH_2CH_2CH_2\overset{+}{C}HCH_3$ c. $CH_3CH_2CH_2CH_2CH_2\overset{+}{C}H_2$

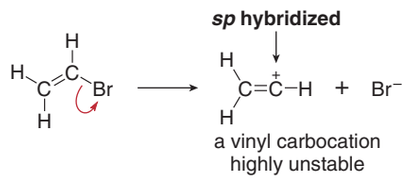
Figure 7.22 Vinyl halides and nucleophilic substitution mechanisms

[a] Vinyl halides and the S_N2 mechanism: Backside attack of the nucleophile is not possible.



Backside attack would force the nucleophile to approach in the plane of the double bond.

[b] Vinyl halides and the S_N1 mechanism: Heterolysis of the C−X bond forms a very unstable carbocation, making the rate-determining step very slow.



a vinyl carbocation highly unstable

smi97462_ch07.qxd 11/4/04 2:52 PM Page 260

7.19 Organic Synthesis

Thus far we have concentrated on the starting material in nucleophilic substitution—the alkyl halide—and have not paid much attention to the product formed. Nucleophilic substitution reactions, and in particular S_N2 reactions, introduce a wide variety of different functional groups in molecules, depending on the nucleophile. For example, when ^-OH, ^-OR, and ^-CN are used as nucleophiles, the products are alcohols (ROH), ethers (ROR), and nitriles (RCN), respectively. Table 7.8 lists some functional groups readily introduced using nucleophilic substitution.

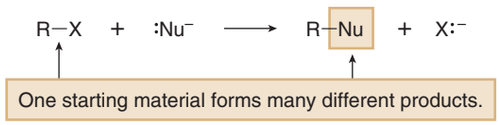
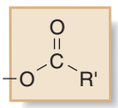


TABLE 7.8 Molecules Synthesized from R–X by the S_N2 Reaction

	Nucleophile (:Nu⁻)	Product	Name
Oxygen compounds	^-OH	R—OH	alcohol
	$^-OR'$	R—OR'	ether
			ester
Carbon compounds	^-CN	R—CN	nitrile
	$^-:C\equiv C-H$	R—C≡C—H	alkyne
Nitrogen compounds	N_3^-	R—N_3	azide
	$:NH_3$	R—NH_2	amine
Sulfur compounds	^-SH	R—SH	thiol
	$^-SR'$	R—SR'	sulfide

the products of nucleophilic substitution

By thinking of **nucleophilic substitution as a reaction that *makes* a particular kind of organic compound,** we begin to think about ***synthesis.***

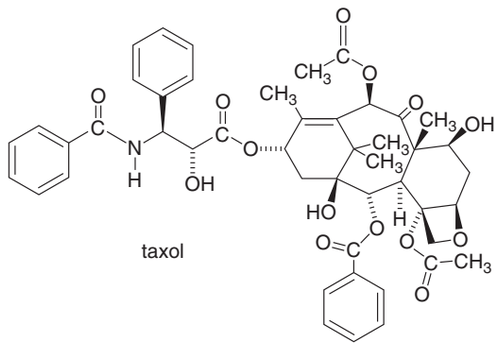
◆ Organic synthesis is the systematic preparation of a compound from a readily available starting material by one or many steps.

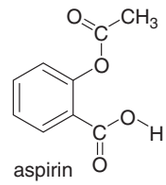
7.19A Background on Organic Synthesis

Chemists synthesize molecules for many reasons. Sometimes a **natural product,** a compound isolated from natural sources, has useful medicinal properties, but is produced by an organism in only minute quantities. Synthetic chemists then prepare this molecule from simpler starting materials so that it can be made available to a large number of people. **Taxol** (Section 5.5), the

smi97462_ch07.qxd 11/22/04 1:11 PM Page 261

complex anticancer compound isolated in small amounts from the bark of the Pacific yew tree, is one such natural product. It is now synthesized commercially from a compound isolated from the leaves and needles of the European yew.





Phenol, the starting material for the aspirin synthesis, is a petroleum product, like most of the starting materials used in large quantities in industrial syntheses. A shortage of petroleum reserves thus affects the availability not only of fuels for transportation, but also of raw materials needed for most chemical synthesis.

Sometimes, chemists prepare molecules that do not occur in nature (although they may be similar to those in nature), because these molecules have superior properties to their naturally occurring relatives. **Aspirin, or acetylsalicylic acid** (Section 2.7), is a well known example. Acetylsalicylic acid is prepared from phenol, a product of the petroleum industry, by a two-step procedure (Figure 7.23). Aspirin has become one of the most popular and widely used drugs in the world because it has excellent analgesic and anti-inflammatory properties, *and* it is cheap and readily available.

7.19B Nucleophilic Substitution and Organic Synthesis

To carry out synthesis we must think backwards. We examine a compound and ask: **What starting material and reagent are needed to make it?** If we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product. This is the simplest type of synthesis because it involves only one step. In Chapter 11 we will learn about multistep syntheses.

Suppose, for example, that we are asked to prepare $(CH_3)_2CHCH_2OH$ (2-methyl-1-propanol) from an alkyl halide and any required reagents. To accomplish this synthesis, we must "fill in the boxes" for the starting material and reagent in the accompanying equation.

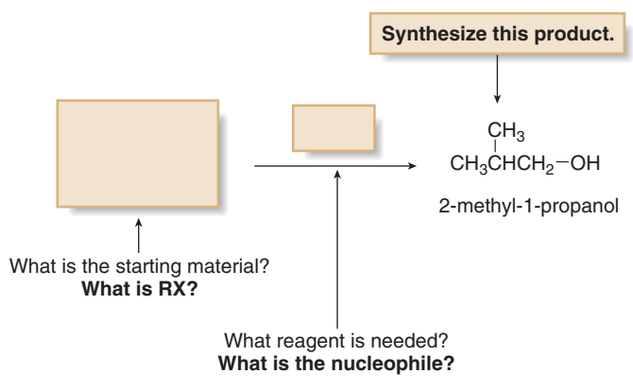
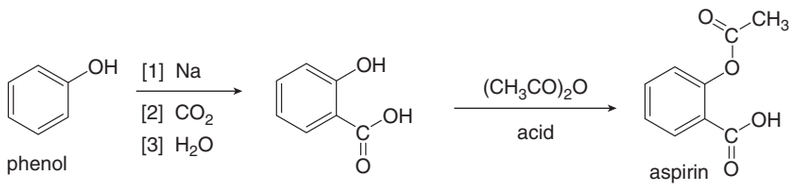


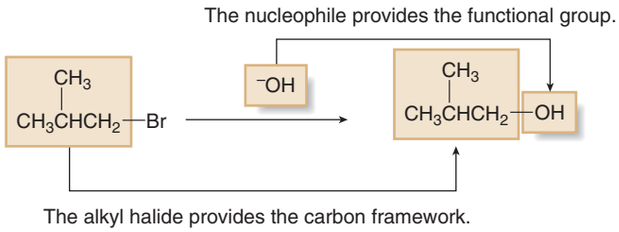
Figure 7.23 Synthesis of aspirin

- Aspirin is synthesized by a two-step procedure from simple, cheap starting materials.



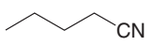
smi97462_ch07.qxd 11/4/04 2:52 PM Page 262

To determine the two components needed for the synthesis, remember that the carbon atoms come from the organic starting material, in this case a 1° alkyl halide [$(CH_3)_2CHCH_2Br$]. The functional group comes from the nucleophile, ^-OH in this case. With these two components, we can "fill in the boxes" to complete the synthesis.

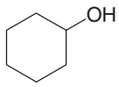


After any synthesis is proposed, check to see if it is reasonable, given what we know about reactions. Will the reaction written give a high yield of product? The synthesis of $(CH_3)_2CHCH_2OH$ is reasonable, because the starting material is a 1° alkyl halide and the nucleophile (^-OH) is strong, and both facts contribute to a successful S_N2 reaction.

PROBLEM 7.38 What alkyl halide and nucleophile are needed to prepare each compound?

a. 

b. $(CH_3)_3CCH_2CH_2SH$

c. 

d. $CH_3CH_2-C\equiv C-H$

PROBLEM 7.39 The ether, $CH_3OCH_2CH_3$, can be prepared by two different nucleophilic substitution reactions, one using CH_3O^- as nucleophile and the other using $CH_3CH_2O^-$ as nucleophile. Draw both routes.

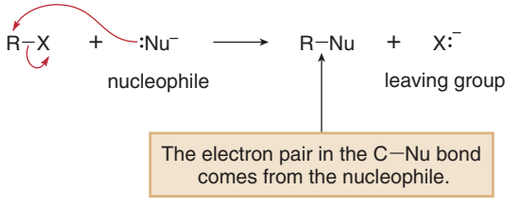
7.20 Key Concepts—Alkyl Halides and Nucleophilic Substitution

General Facts about Alkyl Halides

- Alkyl halides contain a halogen atom X bonded to an sp^3 hybridized carbon (7.1).
- Alkyl halides are named as halo alkanes, with the halogen as a substituent (7.2).
- Alkyl halides have a polar C–X bond, so they exhibit dipole–dipole interactions but are incapable of intermolecular hydrogen bonding (7.3).
- The polar C–X bond containing an electrophilic carbon makes alkyl halides reactive towards nucleophiles and bases (7.5).

The Central Theme (7.6)

- Nucleophilic substitution is one of the two main reactions of alkyl halides. A nucleophile replaces a leaving group on an sp^3 hybridized carbon.



- One σ bond is broken and one σ bond is formed.
- There are two possible mechanisms: S_N1 and S_N2.

smi97462_ch07.qxd 11/4/04 2:52 PM Page 263

S_N1 and S_N2 Mechanisms Compared

	S_N2 mechanism	S_N1 mechanism
[1] Mechanism	• One step (7.11B)	• Two steps (7.13B)
[2] Alkyl halide	• Order of reactivity: $CH_3X > RCH_2X > R_2CHX > R_3CX$ (7.11D)	• Order of reactivity: $R_3CX > R_2CHX > RCH_2X > CH_3X$ (7.13D)
[3] Rate equation	• Rate = k[RX][:Nu$^-$] • Second-order kinetics (7.11A)	• Rate = k[RX] • First-order kinetics (7.13A)
[4] Stereochemistry	• Backside attack of the nucleophile (7.11C) • Inversion of configuration at a stereogenic center	• Trigonal planar carbocation intermediate (7.13C) • Racemization at a single stereogenic center
[5] Nucleophile	• Favored by stronger nucleophiles (7.17B)	• Favored by weaker nucleophiles (7.17B)
[6] Leaving group	• Better leaving group ⟶ faster reaction (7.17C)	• Better leaving group ⟶ faster reaction (7.17C)
[7] Solvent	• Favored by polar aprotic solvents (7.17D)	• Favored by polar protic solvents (7.17D)

Important Trends

- The best leaving group is the weakest base. Leaving group ability increases left-to-right across a row and down a column of the periodic table (7.7).
- Nucleophilicity decreases left-to-right across a row of the periodic table (7.8A).
- Nucleophilicity decreases down a column of the periodic table in polar aprotic solvents (7.8C).
- Nucleophilicity increases down a column of the periodic table in polar protic solvents (7.8C).
- The stability of a carbocation increases as the number of R groups bonded to the positively charged carbon increases (7.14).

Important Principles

Principle

- Electron-donating groups (such as R groups) stabilize a positive charge (7.14A).
- Steric hindrance decreases nucleophilicity but not basicity (7.8B).
- Hammond postulate: In an endothermic reaction, the more stable product is formed faster. In an exothermic reaction, this is not necessarily true (7.15).
- Planar, sp^2 hybridized atoms react with reagents from both sides of the plane (7.13C).

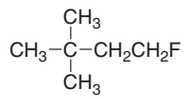
Example

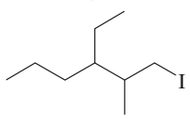
- 3° Carbocations (R_3C^+) are more stable than 2° carbocations (R_2CH^+), which are more stable than 1° carbocations (RCH_2^+).
- $(CH_3)_3CO^-$ is a stronger base but a weaker nucleophile than $CH_3CH_2O^-$.
- S_N1 reactions are faster when more stable (more substituted) carbocations are formed, because the rate-determining step is endothermic.
- A trigonal planar carbocation reacts with nucleophiles from both sides of the plane.

Problems

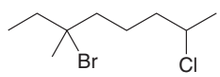
Nomenclature

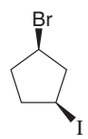
7.40 Give the IUPAC name for each compound.

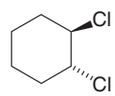
a. 

b. 

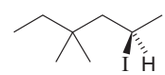
c. $(CH_3)_3CCH_2Br$

d. 

e. 

f. 

g. $(CH_3)_3CCH_2CH(Cl)CH_2Cl$

h. 

(Also, label this compound as *R* or *S*.)

smi97462_ch07.qxd 11/4/04 2:52 PM Page 264

7.41 Give the structure corresponding to each name.

a. isopropyl bromide
b. 3-bromo-4-ethylheptane
c. 1,1-dichloro-2-methylcyclohexane
d. *trans*-1-chloro-3-iodocyclobutane
e. 1-bromo-4-ethyl-3-fluorooctane

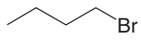
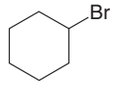
7.42 Classify each alkyl halide in Problem 7.40 as 1°, 2°, or 3°. When a compound has more than one halogen, assign each separately.

7.43 Draw the eight constitutional isomers having the molecular formula $C_5H_{11}Cl$.

a. Give the IUPAC name for each compound (ignoring *R* and *S* designations).
b. Label any stereogenic centers.
c. For each constitutional isomer that contains a stereogenic center, draw all possible stereoisomers, and label each stereogenic center as *R* or *S*.

Physical Properties

7.44 Which compound in each pair has the higher boiling point?

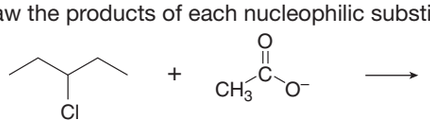
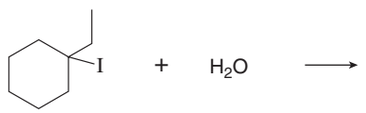
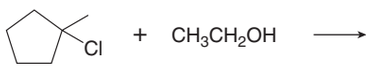
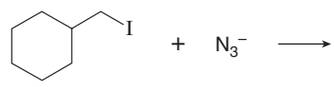
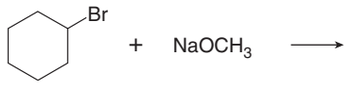
a. $(CH_3)_3CBr$ and $CH_3CH_2CH_2CH_2Br$ b.  and  c.  and 

General Nucleophilic Substitution, Leaving Groups, and Nucleophiles

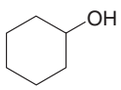
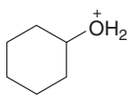
7.45 Draw the substitution product that results when $CH_3CH_2CH_2CH_2Br$ reacts with each nucleophile.

a. ^-OH
b. ^-SH
c. ^-CN
d. $^-OCH(CH_3)_2$
e. $^-C{\equiv}CH$
f. H_2O
g. NH_3
h. NaI
i. NaN_3

7.46 Draw the products of each nucleophilic substitution reaction.

a. 
b.
c. 
d. 
e. 
f. 
g. $(CH_3)_3CBr + CH_3COOH \longrightarrow$
h. 

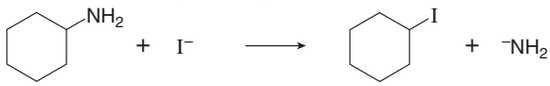
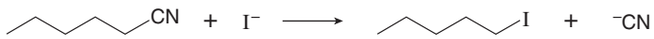
7.47 Which of the following molecules contain a good leaving group?

a.  b. $CH_3CH_2CH_2CH_2Cl$ c.  d.  e. $CH_3CH_2NH_2$ f. $CH_3CH_2CH_2I$

7.48 Rank the species in each group in order of increasing leaving group ability.

a. ^-OH, F^-, $^-NH_2$
b. H_2O, $^-NH_2$, ^-OH
c. Br^-, Cl^-, I^-
d. NH_3, H_2S, H_2O

7.49 Which of the following nucleophilic substitution reactions will take place?

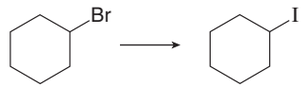
a. 
b. $CH_3CH_2I + CH_3O^- \longrightarrow CH_3CH_2OCH_3 + I^-$
c. 
d. 

smi97462_ch07.qxd 11/4/04 2:52 PM Page 265

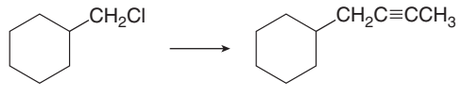
7.50 What nucleophile is needed to carry out each reaction?

a. $CH_3CH_2CH_2CH_2Br \longrightarrow CH_3CH_2CH_2CH_2OH$

b. 

c. 

d. $CH_3CH_2Cl \longrightarrow CH_3CH_2OCH_2CH_3$

e. 

f. $CH_3CH_2Br \longrightarrow CH_3CH_2\overset{+}{N}(CH_3)_3\ Br^-$

7.51 Rank the species in each group in order of increasing nucleophilicity.

a. CH_3^-, ^-OH, $^-NH_2$
b. H_2O, ^-OH, ^-SH in CH_3OH
c. $CH_3CH_2S^-$, $CH_3CH_2O^-$, CH_3COO^- in CH_3OH
d. CH_3NH_2, CH_3SH, CH_3OH in acetone
e. ^-OH, F^-, Cl^- in acetone
f. HS^-, F^-, Cl^- in CH_3OH

7.52 We have learned that nucleophilicity depends on the solvent when nucleophiles of very different size are compared. For example, in polar protic solvents nucleophilicity follows the trend $F^- < Cl^- < Br^- < I^-$, but the reverse is true in polar aprotic solvents. Predict the trend in nucleophilicity for these halide anions in the gas phase, with no solvent.

7.53 Classify each solvent as protic or aprotic.

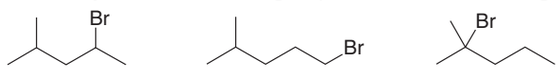
a. $(CH_3)_2CHOH$
b. CH_3NO_2
c. CH_2Cl_2
d. NH_3
e. $N(CH_3)_3$
f. $HCONH_2$

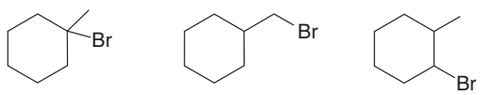
The S_N2 Reaction

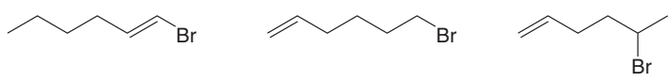
7.54 Consider the following S_N2 reaction:

a. Draw a mechanism using curved arrows.
b. Draw an energy diagram. Label the axes, the reactants, products, E_a, and $\Delta H°$. Assume that the reaction is exothermic.
c. Draw the structure of the transition state.
d. What is the rate equation?
e. What happens to the reaction rate in each of the following instances? [1] The leaving group is changed from Br^- to I^-; [2] The solvent is changed from acetone to CH_3CH_2OH; [3] The alkyl halide is changed from $CH_3(CH_2)_4Br$ to $CH_3CH_2CH_2CH(Br)CH_3$; [4] The concentration of ^-CN is increased by a factor of five; and [5] The concentrations of both the alkyl halide and ^-CN are increased by a factor of five.

7.55 Rank the alkyl halides in each group in order of increasing S_N2 reactivity.

a. 

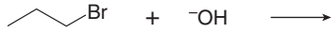
b. 

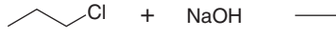
c. 

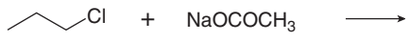
7.56 Which S_N2 reaction in each pair is faster?

a. $CH_3CH_2Br + {}^-OH \longrightarrow$

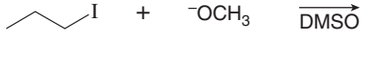
$CH_3CH_2Cl + {}^-OH \longrightarrow$

b. 

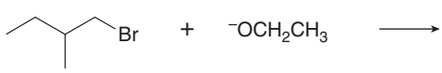
c. 



d. 

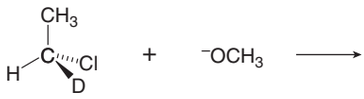


e. 

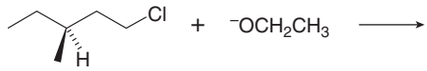


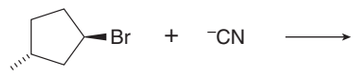
smi97462_ch07.qxd 11/22/04 1:12 PM Page 266

7.57 Draw the products of each S_N2 reaction and indicate the stereochemistry where appropriate.

a. 

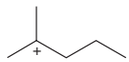
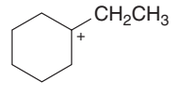
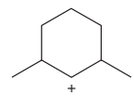
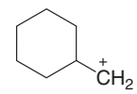
b. 

c. 

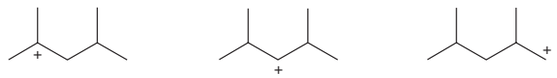
d. 

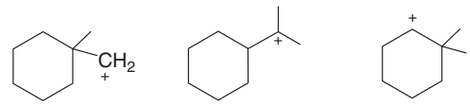
Carbocations

7.58 Classify each carbocation as 1°, 2°, or 3°.

a. $CH_3CH_2\overset{+}{C}HCH_2CH_3$ b.  c. $(CH_3)_2\overset{+}{C}HCH_2CH_2$ d.  e.  f. 

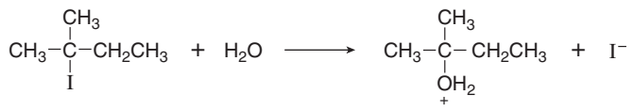
7.59 Rank the carbocations in each group in order of increasing stability.

a. 

b. 

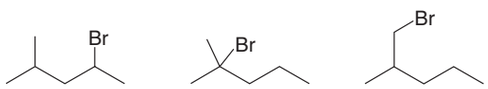
The S_N1 Reaction

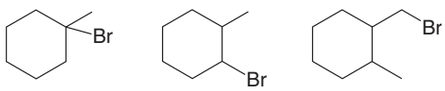
7.60 Consider the following S_N1 reaction.

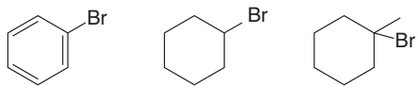


a. Draw a mechanism for this reaction using curved arrows.
b. Draw an energy diagram. Label the axes, starting material, product, E_a, and $\Delta H°$. Assume that the starting material and product are equal in energy.
c. Draw the structure of any transition states.
d. What is the rate equation for this reaction?
e. What happens to the reaction rate in each of the following instances? [1] The leaving group is changed from I^- to Cl^-; [2] The solvent is changed from H_2O to DMF; [3] The alkyl halide is changed from $(CH_3)_2C(I)CH_2CH_3$ to $(CH_3)_2CHCH(I)CH_3$; [4] The concentration of H_2O is increased by a factor of five; and [5] The concentrations of both the alkyl halide and H_2O are increased by a factor of five.

7.61 Rank the alkyl halides in each group in order of increasing S_N1 reactivity.

a. 

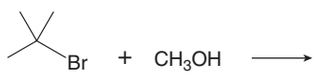
b. 

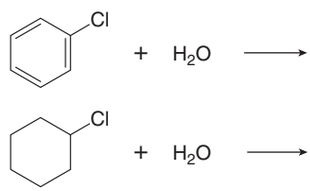
c. 

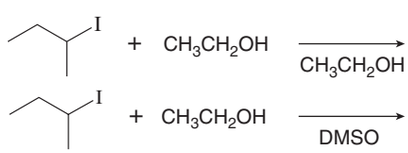
7.62 Which S_N1 reaction in each pair is faster?

a. $(CH_3)_3CCl + H_2O \longrightarrow$

$(CH_3)_3CI + H_2O \longrightarrow$

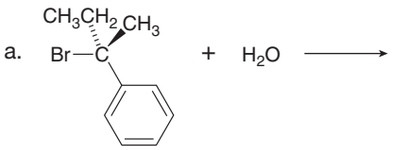
b. 

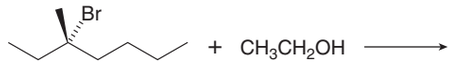
c. 

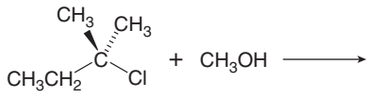
d. 

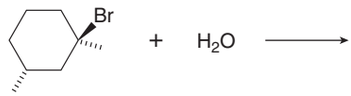
smi97462_ch07.qxd 11/22/04 1:13 PM Page 267

7.63 Draw the products of each S_N1 reaction and indicate the stereochemistry when necessary.

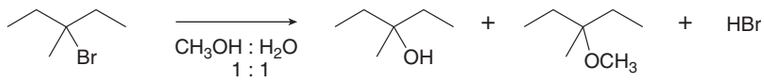
a. 

c. 

b. 

d. 

7.64 Draw a stepwise mechanism for the following reaction.



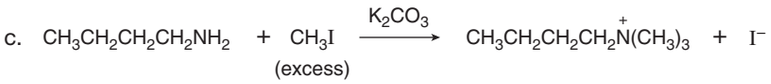
7.65 H_2O is a more polar medium than CH_3CH_2OH because the nonpolar CH_3CH_2 group of CH_3CH_2OH decreases the number of polar interactions in a given volume. Explain what happens to the rate of an S_N1 reaction as the solvent is changed from 100% H_2O to 50% H_2O/50% CH_3CH_2OH.

S_N1 and S_N2 Reactions

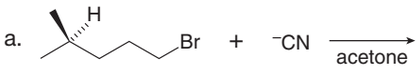
7.66 Draw a stepwise, detailed mechanism for each reaction. Use curved arrows to show the movement of electrons.

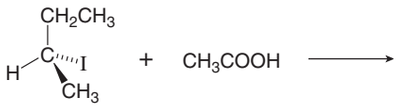
a. 

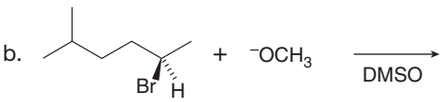
b. 

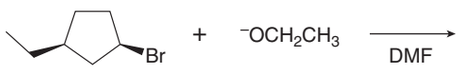
c. 

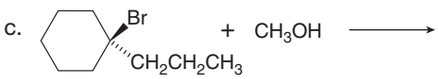
7.67 Determine the mechanism of nucleophilic substitution of each reaction and draw the products, including stereochemistry.

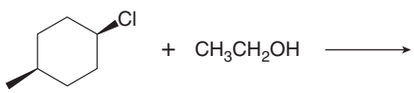
a. 

d. 

b. 

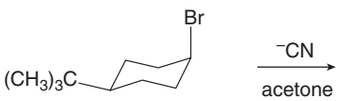
e. 

c. 

f. 

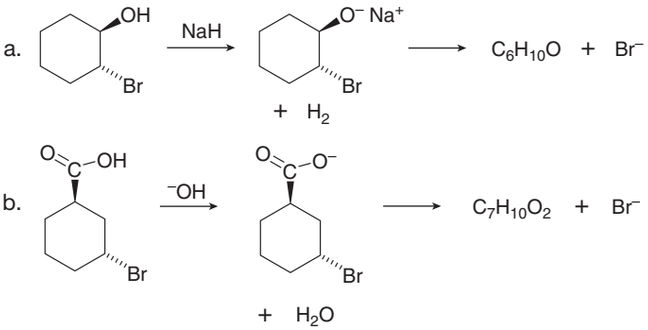
7.68 Draw the products of each nucleophilic substitution reaction.

a. 

b. 

smi97462_ch07.qxd 12/3/04 2:31 PM Page 268

7.69 When a single compound contains both a nucleophile and a leaving group, an **intramolecular** reaction may occur. With this in mind, draw the product of each reaction.



7.70 When CH_3I is reacted with $NaOCH_3$ and $NaSCH_3$, both CH_3OCH_3 and CH_3SCH_3 form, but the amount of each depends on the solvent. Predict which is the major product when CH_3OH is the solvent and when $(CH_3)_2S{=}O$ is the solvent. Explain why this happens.

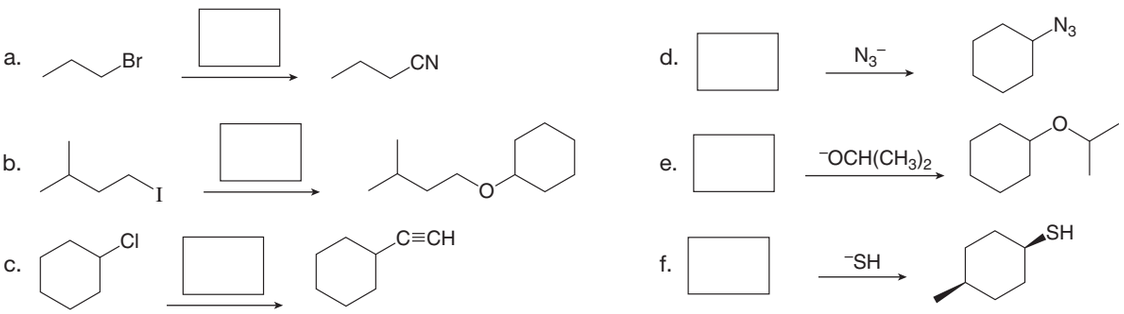
7.71 Explain each of the following statements.

a. Hexane is not a common solvent for either S_N1 or S_N2 reactions.
b. $(CH_3)_3CO^-$ is a stronger base than $CH_3CH_2O^-$.
c. $(CH_3)_3CBr$ is more reactive than $(CH_3)_2C(CF_3)Br$ in S_N1 reactions.
d. $(CH_3)_3CBr$ reacts at the same rate with F^- and H_2O in substitution reactions even though F^- has a net negative charge.
e. When optically active (*R*)-2-bromobutane is added to a solution of NaBr in acetone, the solution gradually loses optical activity until it becomes optically inactive.

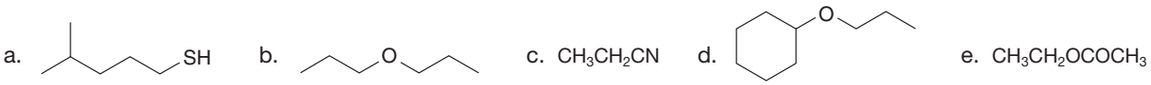
7.72 Simple organic halides like CH_3Cl and CH_2Cl_2 are slowly decomposed in the environment by reaction with H_2O. For example, the half-life (the time it takes for the initial concentration of a compound to be halved) for the conversion of CH_3Cl to CH_3OH by nucleophilic substitution is 339 days. Explain why this reaction is slow, and why CH_2Cl_2 reacts even more slowly with H_2O.

Synthesis

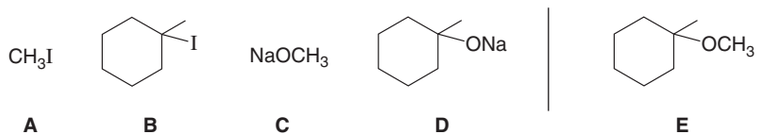
7.73 Fill in the appropriate reagent or starting material in each of the following reactions.



7.74 Devise a synthesis of each compound from an alkyl halide using any other organic or inorganic reagents.



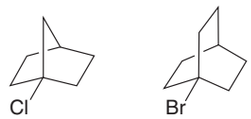
7.75 Suppose you have compounds **A**–**D** at your disposal. Using these compounds, devise two different ways to make **E.** Which one of these methods is preferred, and why?



smi97462_ch07.qxd 11/4/04 2:52 PM Page 269

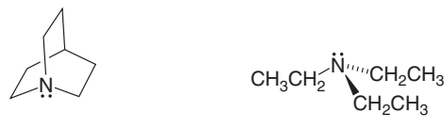
Challenge Questions

7.76 Explain why alkyl halides **A** and **B** do not undergo nucleophilic substitution by either an S_N1 or S_N2 mechanism.



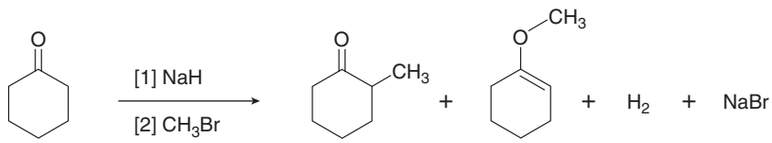
A **B**

7.77 Explain why quinuclidine is a much more reactive nucleophile than triethylamine, even though both compounds have N atoms bonded to three R groups.



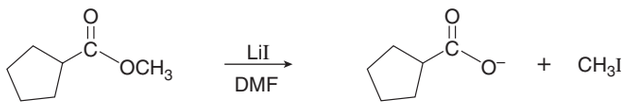
quinuclidine triethylamine

7.78 Draw a stepwise mechanism for the following reaction sequence.

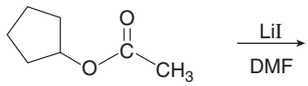


major product minor product

7.79 Explain why compound **A** reacts readily with LiI in DMF to afford products of nucleophilic substitution, but isomer **B** does not react under similar reaction conditions.



A



B

7.80 Explain why the alkyl halide $CH_3CH_2OCH_2Cl$ reacts rapidly with CH_3CH_2OH under S_N1 conditions to afford $CH_3CH_2OCH_2OCH_2CH_3$.