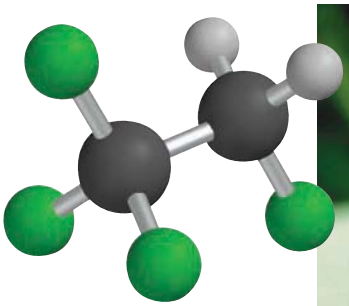
07

Haloalkanes



Asthma patient using a metered-dose inhaler to deliver the drug albuterol. The drug is propelled by haloalkanes such as 1,1,1,2-tetrafluoroethane. Inset: A molecule of 1,1,1,2-tetrafluoroethane (HFA-134a). (Carolyn A. McKeone/Photo Researchers, Inc.)

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

COMPOUNDS CONTAINING a halogen atom covalently bonded to an sp^3 hybridized carbon atom are named **haloalkanes** or, in the common system of nomenclature, *alkyl halides*. The general symbol for an **alkyl halide** is R—X, where X may be F, Cl, Br, or I:

A haloalkane (An alkyl halide)

Alkyl halide A compound containing a halogen atom covalently bonded to an sp^3 hybridized carbon atom; given the symbol RX.

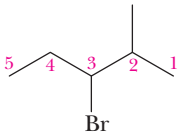
In this chapter, we study two characteristic reactions of haloalkanes: nucleophilic substitution and β-elimination. Haloalkanes are useful molecules because they can be converted to alcohols, ethers, thiols, amines, and alkenes and are thus versatile molecules. Indeed, haloalkanes are often used as starting materials for the synthesis of many useful compounds encountered in medicine, food chemistry, and agriculture (to name a few).

7.1 How Are Haloalkanes Named?

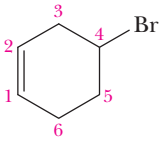
A. IUPAC Names

IUPAC names for haloalkanes are derived by naming the parent alkane according to the rules given in Section 3.3A:

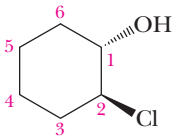
- Locate and number the parent chain from the direction that gives the substituent encountered first the lower number.
- Show halogen substituents by the prefixes *fluoro-*, *chloro-*, *bromo-*, and *iodo-*, and list them in alphabetical order along with other substituents.
- Use a number preceding the name of the halogen to locate each halogen on the parent chain.
- In haloalkenes, the location of the double bond determines the numbering of the parent hydrocarbon. In molecules containing functional groups designated by a suffix (for example, *-ol*, *-al*, *-one*, *-oic acid*), the location of the functional group indicated by the suffix determines the numbering:



3-Bromo-2-methylpentane



4-Bromocyclohexene

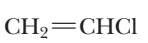


(1*S*,2*S*)-2-Chlorocyclohexanol
or
trans-2-Chlorocyclohexanol

B. Common Names

Common names of haloalkanes consist of the common name of the alkyl group, followed by the name of the halide as a separate word. Hence, the name **alkyl halide** is a common name for this class of compounds. In the following examples, the IUPAC name of the compound is given first, followed by its common name, in parentheses:

2-Fluorobutane
(*sec*-Butyl fluoride)



Chloroethene
(Vinyl chloride)

Several of the polyhalomethanes are common solvents and are generally referred to by their common, or trivial, names. Dichloromethane (methylene chloride) is the most widely used haloalkane solvent. Compounds of the type CHX_3 are called **haloforms**. The common name for $CHCl_3$, for example, is *chloroform*. The common name for CH_3CCl_3 is

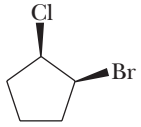
methyl chloroform. Methyl chloroform and trichloroethylene are solvents for commercial dry cleaning.

CH_2Cl_2	$CHCl_3$	CH_3CCl_3	$CCl_2{=}CHCl$
Dichloromethane (Methylene chloride)	Trichloromethane (Chloroform)	1,1,1-Trichloroethane (Methyl chloroform)	Trichloroethylene (Trichlor)

HOW TO 7.1 Name Cyclic Haloalkanes

(a) First, determine the root name of the cycloalkane.

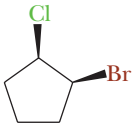
the root name of a 5-carbon ring is "cyclopentane"



Cyclopentane

(b) Name and number the halogen substituents.

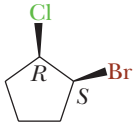
in rings, multiple halogens are listed alphabetically and numbered in alphabetical order



1 -Bromo-2-chlorocyclopentane

(c) Don't forget to indicate stereochemistry.

see Chapter 6 for rules on assigning R/S configurations

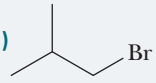


(1*S*,2*R*)-1-Bromo-2-chlorocyclopentane
or
cis -1-Bromo-2-chlorocyclopentane

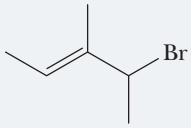
EXAMPLE 7.1

Write the IUPAC name for each compound:

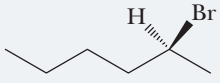
(a)



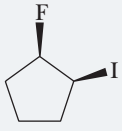
(b)



(c)



(d)



STRATEGY

First look for the longest chain of carbons. This will allow you to determine the root name. Then identify the atoms or groups of atoms that are not part of that chain of carbons. These are your substituents. Remember to include stereochemical configurations, *E*/*Z* or *R*/*S*, where applicable.

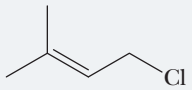
SOLUTION

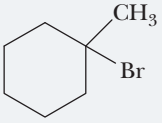
(a) 1-Bromo-2-methylpropane. Its common name is isobutyl bromide.
(b) (*E*)-4-Bromo-3-methyl-2-pentene.
(c) (*S*)-2-Bromohexane.
(d) (1*R*,2*S*)-1-Fluoro-2-iodocyclopentane or *cis*-1-fluoro-2-iodocyclopentane.

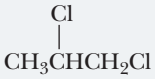
See problems 7.9–7.12

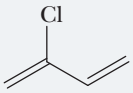
PROBLEM 7.1

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

(d) 

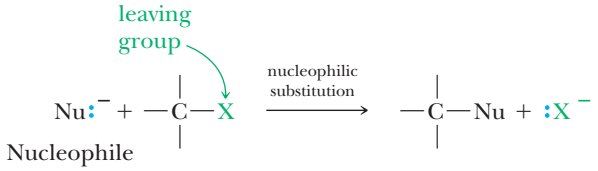
Of all the haloalkanes, the **chlorofluorocarbons (CFCs)** manufactured under the trade name Freon® are the most widely known. CFCs are nontoxic, nonflammable, odorless, and noncorrosive. Originally, they seemed to be ideal replacements for the hazardous compounds such as ammonia and sulfur dioxide formerly used as heat-transfer agents in refrigeration systems. Among the CFCs most widely used for this purpose were trichlorofluoromethane (CCl_3F, Freon-11) and dichlorodifluoromethane (CCl_2F_2, Freon-12). The CFCs also found wide use as industrial cleaning solvents to prepare surfaces for coatings, to remove cutting oils and waxes from millings, and to remove protective coatings. In addition, they were employed as propellants in aerosol sprays. They are now, however, banned from use in most developed countries (see Chemical Connections 7A).

7.2 What Are the Characteristic Reactions of Haloalkanes?

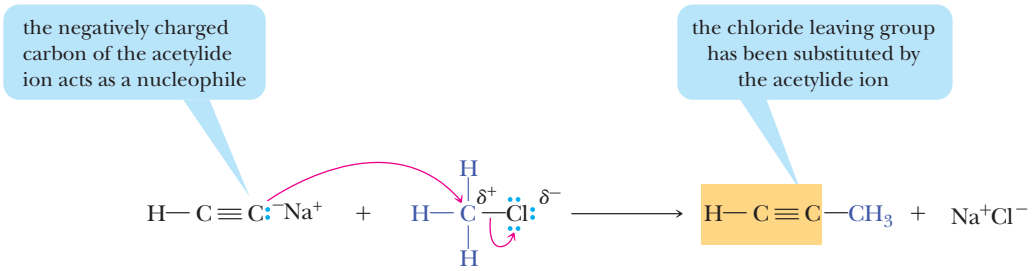
A **nucleophile** (nucleus-loving reagent) is any reagent that donates an unshared pair of electrons to form a new covalent bond. **Nucleophilic substitution** is any reaction in which one nucleophile is substituted for another. In the following general equations, $Nu:^-$ is the nucleophile, X is the leaving group, and substitution takes place on an sp^3 hybridized carbon atom:

Nucleophile An atom or a group of atoms that donates a pair of electrons to another atom or group of atoms to form a new covalent bond.

Nucleophilic substitution A reaction in which one nucleophile is substituted for another.



Halide ions are among the best and most important leaving groups. Recall from Section 5.7 that nucleophilic substitution occurs in the alkylation of an acetylide ion:



Chemical Connections 7A

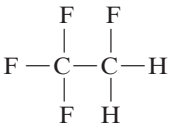
THE ENVIRONMENTAL IMPACT OF CHLOROFLUOROCARBONS

Concern about the environmental impact of CFCs arose in the 1970s when researchers found that more than 4.5×10^5 kg/yr of these compounds were being emitted into the atmosphere. In 1974, Sherwood Rowland and Mario Molina announced their theory, which has since been amply confirmed, that CFCs catalyze the destruction of the stratospheric ozone layer. When released into the air, CFCs escape to the lower atmosphere. Because of their inertness, however, they do not decompose there. Slowly, they find their way to the stratosphere, where they absorb ultraviolet radiation from the sun and then decompose. As they do so, they set up a chemical reaction that leads to the destruction of the stratospheric ozone layer, which shields the Earth against short-wavelength ultraviolet radiation from the sun. An increase in short-wavelength ultraviolet radiation reaching the Earth is believed to promote the destruction of certain crops and agricultural species and even to increase the incidence of skin cancer in light-skinned individuals.

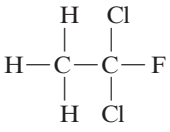
The concern about CFCs prompted two conventions, one in Vienna in 1985 and one in Montreal in 1987, held by the United Nations Environmental Program. The 1987 meeting produced the Montreal Protocol, which set limits on the production and use of ozone-depleting CFCs and urged the complete phase-out of their production by the year 1996. Only two members of the UN have failed to ratify the protocol in its original form.

Rowland, Molina, and Paul Crutzen (a Dutch chemist at the Max Planck Institute for Chemistry in Germany) were awarded the 1995 Nobel Prize for chemistry. As the Royal Swedish Academy of Sciences noted in awarding the prize, "By explaining the chemical mechanisms that affect the thickness of the ozone layer, these three researchers have contributed to our salvation from a global environmental problem that could have catastrophic consequences."

The chemical industry responded to the crisis by developing replacement refrigerants that have a much lower ozone-depleting potential. The most prominent replacements are the hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs), such as the following:



HFC-134a



HCFC-141b

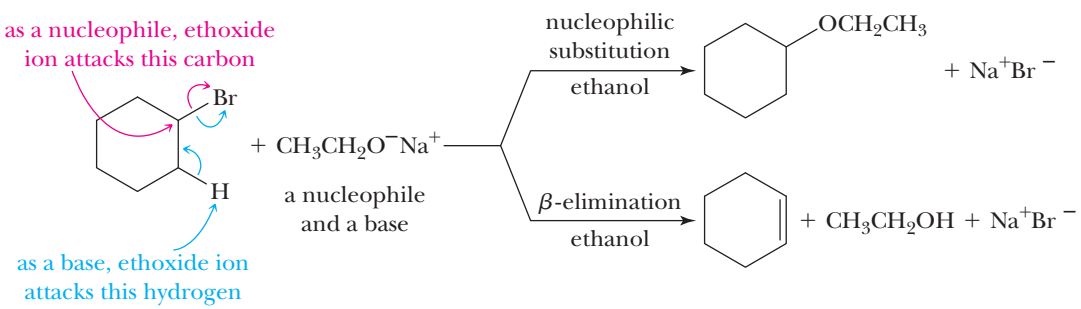
These compounds are much more chemically reactive in the atmosphere than the Freons are and are destroyed before they reach the stratosphere. However, they cannot be used in air conditioners in 1994 and earlier model cars.

Question

Provide IUPAC names for HFC-134a and HCFC-141b.

β-Elimination reaction
The removal of atoms or groups of atoms from two adjacent carbon atoms, as for example, the removal of H and X from an alkyl halide or H and OH from an alcohol to form a carbon–carbon double bond.

Because all nucleophiles are also bases, nucleophilic substitution and base-promoted **β-elimination** are competing reactions. The ethoxide ion, for example, is both a nucleophile and a base. With bromocyclohexane, it reacts as a nucleophile (pathway shown in red) to give ethoxycyclohexane (cyclohexyl ethyl ether) and as a base (pathway shown in blue) to give cyclohexene and ethanol:



HOW TO 7.2

Recognize Substitution and β-Elimination Reactions

(a) Substitution reactions always result in the replacement of one atom or group of atoms in a reactant with another atom or group of atoms.

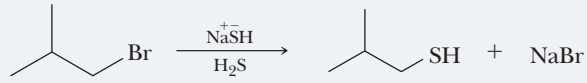
(b) β-Elimination reactions always result in the removal of a hydrogen and an atom or group of atoms on adjacent carbon atoms and in the formation of a C—C double bond.

In this chapter, we study both of these organic reactions. Using them, we can convert haloalkanes to compounds with other functional groups including alcohols, ethers, thiols, sulfides, amines, nitriles, alkenes, and alkynes. Thus, an understanding of nucleophilic substitution and β-elimination opens entirely new areas of organic chemistry.

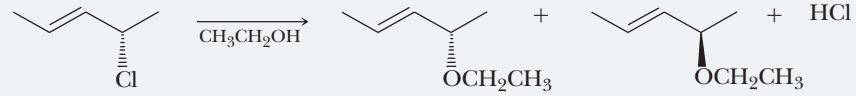
EXAMPLE 7.2

Determine whether the following haloalkanes underwent substitution, elimination, or both substitution and elimination:

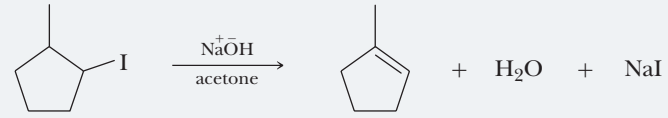
(a)



(b)



(c)



STRATEGY

Look for the halogen in the reactant. Has it been replaced by a different atom or group of atoms in the product(s)? If so, the reaction was a substitution reaction. If the carbon that was once bonded to the halogen is now part of a C—C double bond in the product(s), an elimination reaction has occurred.

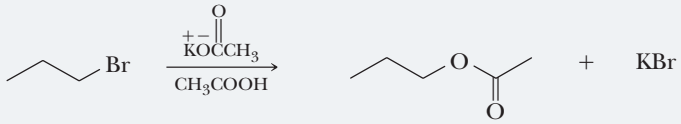
SOLUTION

(a) Substitution; the bromine was replaced by a thiol group.
(b) Substitution; in both products, an ethoxyl group replaces chlorine.
(c) β-Elimination; a hydrogen atom and an iodo group have been removed, and an alkene forms as a result.

PROBLEM 7.2

Determine whether the following haloalkanes underwent substitution, elimination, or both substitution and elimination:

(a)



(b)

7.3 What Are the Products of Nucleophilic Aliphatic Substitution Reactions?

Nucleophilic substitution is one of the most important reactions of haloalkanes and can lead to a wide variety of new functional groups, several of which are illustrated in Table 7.1. As you study the entries in this table, note the following points:

1. If the nucleophile is negatively charged, as, for example, OH^- and RS^-, then the atom donating the pair of electrons in the substitution reaction becomes neutral in the product.
2. If the nucleophile is uncharged, as, for example, NH_3 and CH_3OH, then the atom donating the pair of electrons in the substitution reaction becomes positively charged in the product. The products then often undergo a second step involving proton transfer to yield a neutral substitution product.

TABLE 7.1 Some Nucleophilic Substitution Reactions

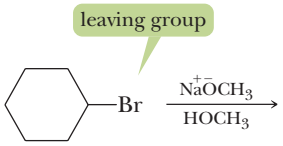
Reaction: $Nu:^- + CH_3X \longrightarrow CH_3Nu + :X^-$

Nucleophile	Product	Class of Compound Formed
$HO:^-$	CH_3OH	An alcohol
$RO:^-$	CH_3OR	An ether
$HS:^-$	CH_3SH	A thiol (a mercaptan)
$RS:^-$	CH_3SR	A sulfide (a thioether)
$:I:^-$	$CH_3I:$	An alkyl iodide
$:NH_3$	$CH_3NH_3^+$	An alkylammonium ion
HOH	$CH_3\overset{+}{O}(H)H$	An alcohol (after proton transfer)
CH_3OH	$CH_3\overset{+}{O}(H)CH_3$	An ether (after proton transfer)

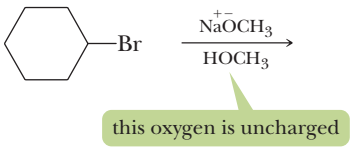
notice that a nucleophile does not need to be negatively charged

HOW TO 7.3 Complete a Substitution Reaction

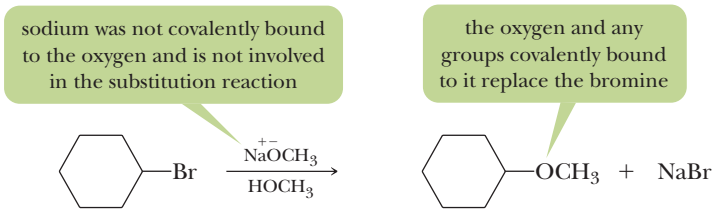
(a) Identify the leaving group.



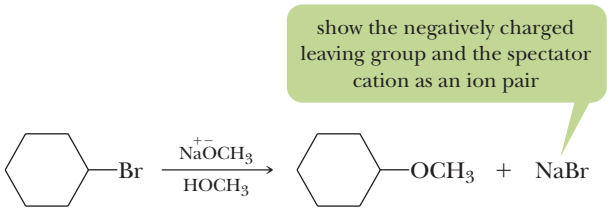
(b) Identify the nucleophile and its nucleophilic atom. The nucleophilic atom will be the negatively charged atom or the atom with a lone pair of electrons to donate. If both a negatively charged atom and an uncharged atom with a lone pair of electrons exist, the negatively charged atom will be the more nucleophilic atom. In the following example, CH_3O^- is a better nucleophile than $HOCH_3$.



(c) Replace the leaving group in the reactant with the nucleophilic atom or group. Any groups connected to the nucleophilic atom through covalent bonds will remain bonded to that atom in the product.

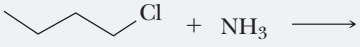


(d) Spectator ions will usually be shown as part of an ion pair with the negatively charged leaving group.



EXAMPLE 7.3

Complete these nucleophilic substitution reactions:

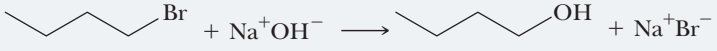
(a)  **(b)** 

STRATEGY

First identify the nucleophile. Then break the bond between the halogen and the carbon it is bonded to and create a new bond from that same carbon to the nucleophile.

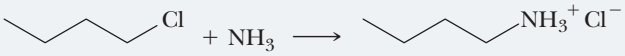
SOLUTION

(a) Hydroxide ion is the nucleophile, and bromine is the leaving group:



1-Bromobutane — Sodium hydroxide — 1-Butanol — Sodium bromide

(b) Ammonia is the nucleophile, and chlorine is the leaving group:

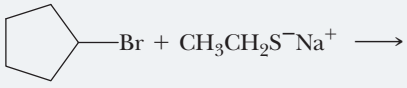
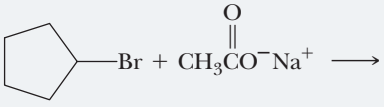


1-Chlorobutane — Ammonia — Butylammonium chloride

See problems 7.21, 7.22, 7.26

PROBLEM 7.3

Complete these nucleophilic substitution reactions:

(a)  **(b)** 

7.4 What Are the S_N2 and S_N1 Mechanisms for Nucleophilic Substitution?

On the basis of a wealth of experimental observations developed over a 70-year period, chemists have proposed two limiting mechanisms for nucleophilic substitutions. A fundamental difference between them is the timing of bond breaking between carbon and the leaving group and of bond forming between carbon and the nucleophile.

A. S_N2 Mechanism

Two processes occur in the S_N2 mechanism: (1) the reaction of an electrophile and a nucleophile to form a new covalent bond and (2) the breaking of a bond to form a stable ion or molecule. At one extreme, the two processes are *concerted*, meaning that bond breaking and bond forming occur simultaneously. Thus, the departure of the leaving group is assisted by the incoming nucleophile. This mechanism is designated **S_N2**, where *S* stands for *S*ubstitution, *N* for *N*ucleophilic, and 2 for a ***bi*molecular reaction**. This type of substitution reaction is classified as bimolecular because both the haloalkane and the nucleophile are involved in the rate-determining step. That is, both species contribute to the rate law of the reaction:

Bimolecular reaction
A reaction in which two species are involved in the reaction leading to the transition state of the rate-determining step.

k is the rate constant for the reaction

$$\text{Rate} = k[\text{haloalkane}][\text{nucleophile}]$$

Following is an S_N2 mechanism for the reaction of hydroxide ion and bromomethane to form methanol and bromide ion:

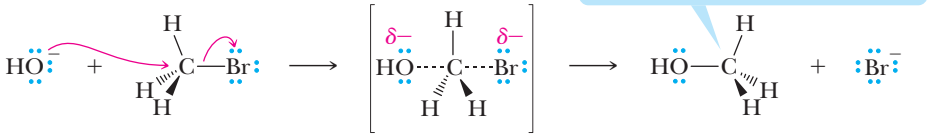
Mechanism

An S_N2 Reaction

The nucleophile attacks the reactive center from the side opposite the leaving group; that is, an S_N2 reaction involves a backside attack by the nucleophile. **(1) The reaction of an electrophile and a nucleophile to form a new covalent bond and (2) the breaking of a bond to form a stable ion or molecule** occur simultaneously.

Inversion of configuration
The reversal of the arrangement of atoms or groups of atoms about a reaction center in an S_N2 reaction.

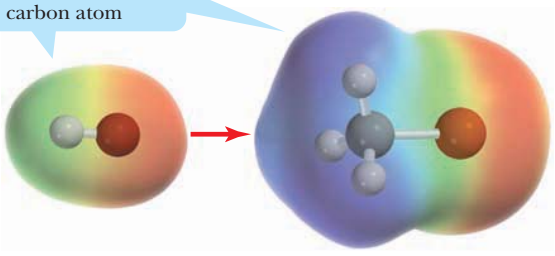
note inversion of the reactive center



Reactants | Transition state with simultaneous bond breaking and bond forming | Products

Figure 7.1 shows an energy diagram for an S_N2 reaction. There is a single transition state and no reactive intermediate.

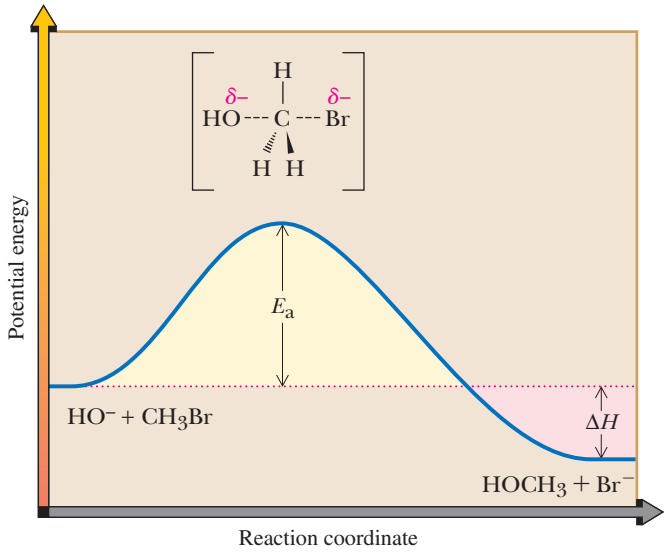
the negatively charged (red) oxygen atom is attracted to the electropositive (blue) carbon atom



Nucleophilic attack from the side opposite the leaving group

An S_N2 reaction is driven by the attraction between the negative charge of the nucleophile (in this case the negatively charged oxygen of the hydroxide ion) and the center of positive charge of the electrophile (in this case the partial positive charge on the carbon bearing the bromine leaving group).

FIGURE 7.1
An energy diagram for an S_N2 reaction. There is one transition state and no reactive intermediate.



B. S_N1 Mechanism

In the other limiting mechanism, called S_N1, bond breaking between carbon and the leaving group is completed before bond forming with the nucleophile begins. In the designation **S_N1**, *S* stands for *S*ubstitution, *N* stands for *N*ucleophilic, and *1* stands for a ***uni*molecular reaction**. This type of substitution is classified as unimolecular because only the haloalkane is involved in the rate-determining step; that is, only the haloalkane contributes to the rate law governing the rate-determining step:

$$\text{Rate} = k[\text{haloalkane}]$$

An S_N1 reaction is illustrated by the **solvolysis** reaction of 2-bromo-2-methylpropane (*tert*-butyl bromide) in methanol to form 2-methoxy-2-methylpropane (*tert*-butyl methyl ether). You may notice that the second step of the mechanism is identical to the second step of the mechanism for the addition of hydrogen halides (H—X) to alkenes (Section 5.3A) and the acid-catalyzed hydration of alkenes (Section 5.3B).

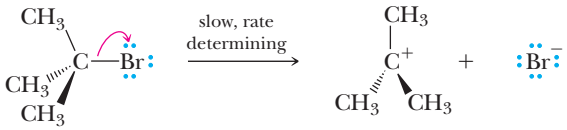
Unimolecular reaction A reaction in which only one species is involved in the reaction leading to the transition state of the rate-determining step.

Solvolysis A nucleophilic substitution reaction in which the solvent is the nucleophile.

Mechanism

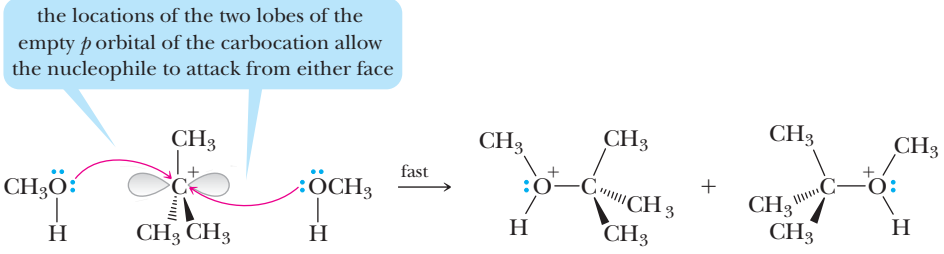
An S_N1 Reaction

STEP 1: Break a bond to form a more stable ion or molecule. The ionization of a C—X bond forms a 3° carbocation intermediate:



A carbocation intermediate; carbon is trigonal planar

STEP 2: Reaction of a nucleophile and an electrophile to form a new covalent bond. Reaction of the carbocation intermediate (an electrophile) with methanol (a nucleophile) gives an oxonium ion. Attack by the nucleophile occurs with equal probability from either face of the planar carbocation intermediate.



STEP 3: Take a proton away. Proton transfer from the oxonium ion to methanol (the solvent) completes the reaction and gives *tert*-butyl methyl ether:

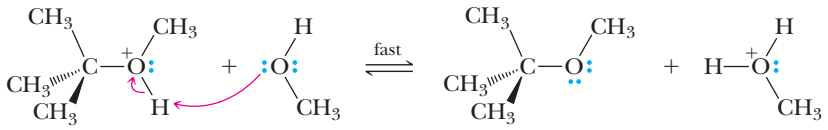
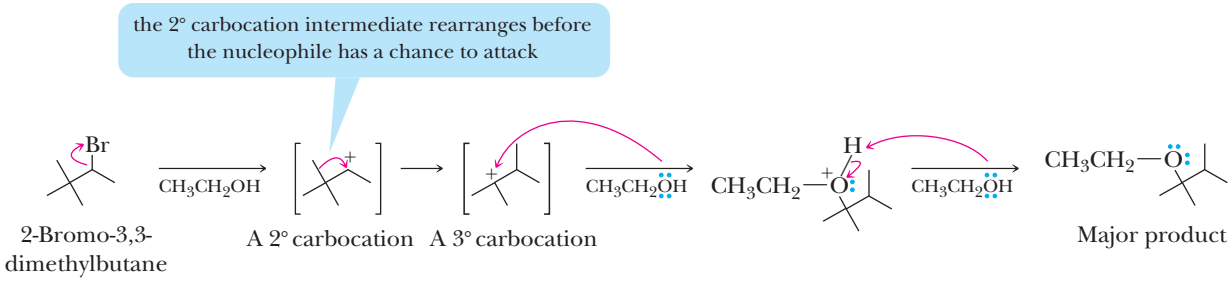


Figure 7.2 shows an energy diagram for the S_N1 reaction of 2-bromo-2-methyl propane and methanol. There is one transition state leading to formation of the carbocation intermediate in Step 1 and a second transition state for reaction of the carbocation intermediate with methanol in Step 2 to give the oxonium ion. The reaction leading to formation of the carbocation intermediate crosses the higher energy barrier and is, therefore, the rate-determining step.

If an S_N1 reaction is carried out on a 2° haloalkane, a 2° carbocation is formed as an intermediate. Recall from Section 5.4 that a 2° carbocation can undergo a rearrangement to form a more stable 3° carbocation. This is illustrated in the solvolysis reaction of 2-bromo-3,3-dimethylbutane in ethanol.



If an S_N1 reaction is carried out at a tetrahedral stereocenter, the major product is a racemic mixture. We can illustrate this result with the following example: Upon ionization,

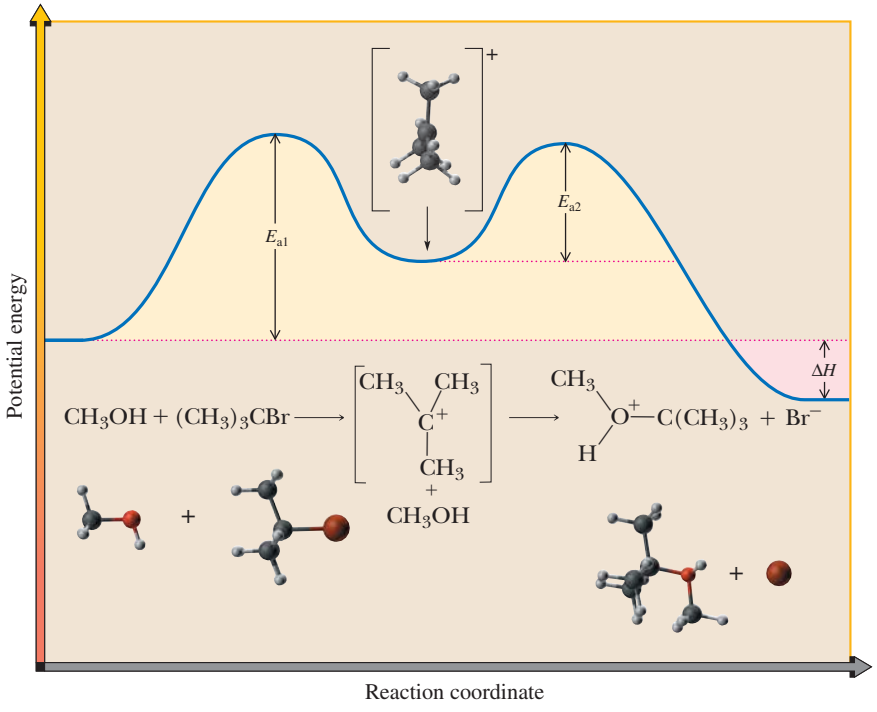
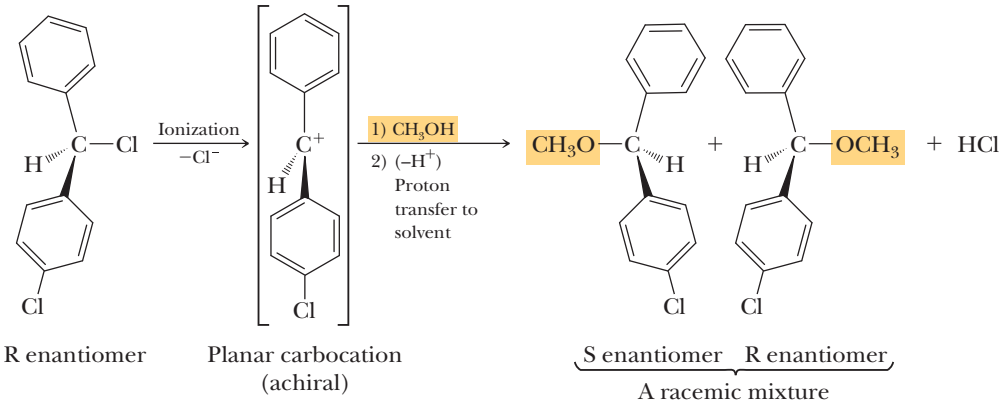


FIGURE 7.2
An energy diagram for the S_N1 reaction of 2-bromo-2-methylpropane and methanol. There is one transition state leading to formation of the carbocation intermediate in Step 1 and a second transition state for the reaction of the carbocation intermediate with methanol in Step 2. Step 1 crosses the higher energy barrier and is, therefore, rate determining.

the R enantiomer forms an achiral carbocation intermediate. Attack by the nucleophile from the left face of the carbocation intermediate gives the S enantiomer; attack from the right face gives the R enantiomer. Because attack by the nucleophile occurs with equal probability from either face of the planar carbocation intermediate, the R and S enantiomers are formed in equal amounts, and the product is a racemic mixture.



7.5 What Determines Whether S_N1 or S_N2 Predominates?

Let us now examine some of the experimental evidence on which these two contrasting mechanisms are based. As we do so, we consider the following questions:

1. What effect does the structure of the nucleophile have on the rate of reaction?
2. What effect does the structure of the haloalkane have on the rate of reaction?
3. What effect does the structure of the leaving group have on the rate of reaction?
4. What is the role of the solvent?

A. Structure of the Nucleophile

Nucleophilicity is a kinetic property, which we measure by relative rates of reaction. We can establish the relative nucleophilicities for a series of nucleophiles by measuring the rate at which each displaces a leaving group from a haloalkane—for example, the rate at which each displaces bromide ion from bromoethane in ethanol at 25 °C:

$$CH_3CH_2Br + NH_3 \longrightarrow CH_3CH_2NH_3^+ + Br^-$$

From these studies, we can then make correlations between the structure of the nucleophile and its **relative nucleophilicity**. Table 7.2 lists the types of nucleophiles we deal with most commonly in this text.

Relative nucleophilicity The relative rates at which a nucleophile reacts in a reference nucleophilic substitution reaction.

Because the nucleophile participates in the rate-determining step in an S_N2 reaction, the better the nucleophile, the more likely it is that the reaction will occur by that mechanism. The nucleophile does not participate in the rate-determining step for an S_N1 reaction. Thus, an S_N1 reaction can, in principle, occur at approximately the same rate with any of the common nucleophiles, regardless of their relative nucleophilicities.

B. Structure of the Haloalkane

S_N1 reactions are governed mainly by **electronic factors**, namely, the relative stabilities of carbocation intermediates. S_N2 reactions, by contrast, are governed mainly by **steric factors**, and their transition states are particularly sensitive to crowding about the site of reaction. The distinction is as follows:

Steric hindrance The ability of groups, because of their size, to hinder access to a reaction site within a molecule.

1. *Relative stabilities of carbocations.* As we learned in Section 5.3A, 3° carbocations are the most stable carbocations, requiring the lowest activation energy for their formation,

TABLE 7.2 Examples of Common Nucleophiles and Their Relative Effectiveness

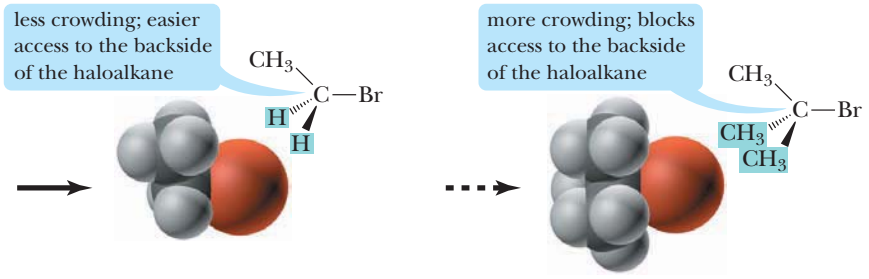
Effectiveness as a Nucleophile	Nucleophile
good	Br^-, I^-
	CH_3S^-, RS^-
	HO^-, CH_3O^-, RO^-
moderate	Cl^-, F^-
	CH_3CO^-, RCO^-
	CH_3SH, RSH, R_2S
	NH_3, RNH_2, R_2NH, R_3N
poor	H_2O
	CH_3OH, ROH
	CH_3COH, $RCOH$

Increasing nucleophilicity

the table shows that negatively charged species are better nucleophiles than neutral species

whereas 1° carbocations are the least stable, requiring the highest activation energy for their formation. In fact, 1° carbocations are so unstable that they have never been observed in solution. Therefore, 3° haloalkanes are most likely to react by carbocation formation; 2° haloalkanes are less likely to react in this manner, and methyl and 1° haloalkanes never react in that manner.

2. *Steric hindrance.* To complete a substitution reaction, the nucleophile must approach the substitution center and begin to form a new covalent bond to it. If we compare the ease of approach by the nucleophile to the substitution center of a 1° haloalkane with that of a 3° haloalkane, we see that the approach is considerably easier in the case of the 1° haloalkane. Two hydrogen atoms and one alkyl group screen the backside of the substitution center of a 1° haloalkane. In contrast, three alkyl groups screen the backside of the substitution center of a 3° haloalkane. This center in bromoethane is easily accessible to a nucleophile, while there is extreme crowding around the substitution center in 2-bromo-2-methylpropane:



Bromoethane (Ethyl bromide) 2-Bromo-2-methylpropane (*tert*-Butyl bromide)

Given the competition between electronic and steric factors, we find that 3° haloalkanes react by an S_N1 mechanism because 3° carbocation intermediates are particularly stable and because the backside approach of a nucleophile to the substitution center in a 3° haloalkane is hindered by the three groups surrounding it; 3° haloalkanes never react by an S_N2 mechanism. Halomethanes and 1° haloalkanes have little crowding around the substitution center and react by an S_N2 mechanism; they never react by an S_N1 mechanism, because methyl and primary carbocations are so unstable.

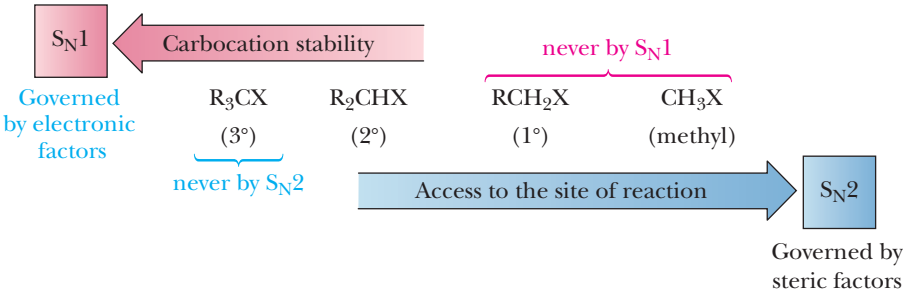
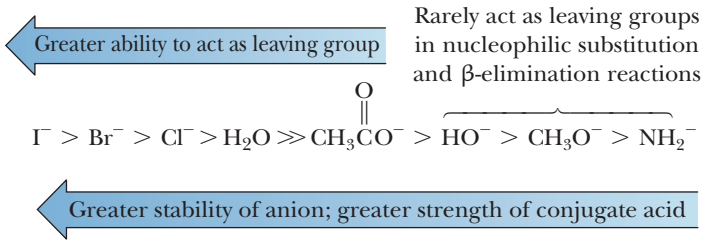


FIGURE 7.3
Effect of electronic and steric factors in competition between S_N1 and S_N2 reactions of haloalkanes.

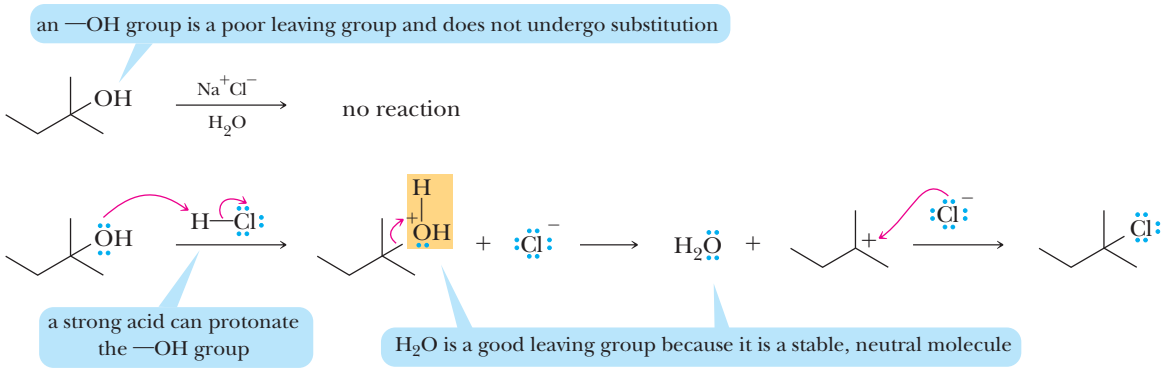
Secondary haloalkanes may react by either an S_N1 or an S_N2 mechanism, depending on the nucleophile and solvent. The competition between electronic and steric factors and their effects on relative rates of nucleophilic substitution reactions of haloalkanes are summarized in Figure 7.3.

C. The Leaving Group

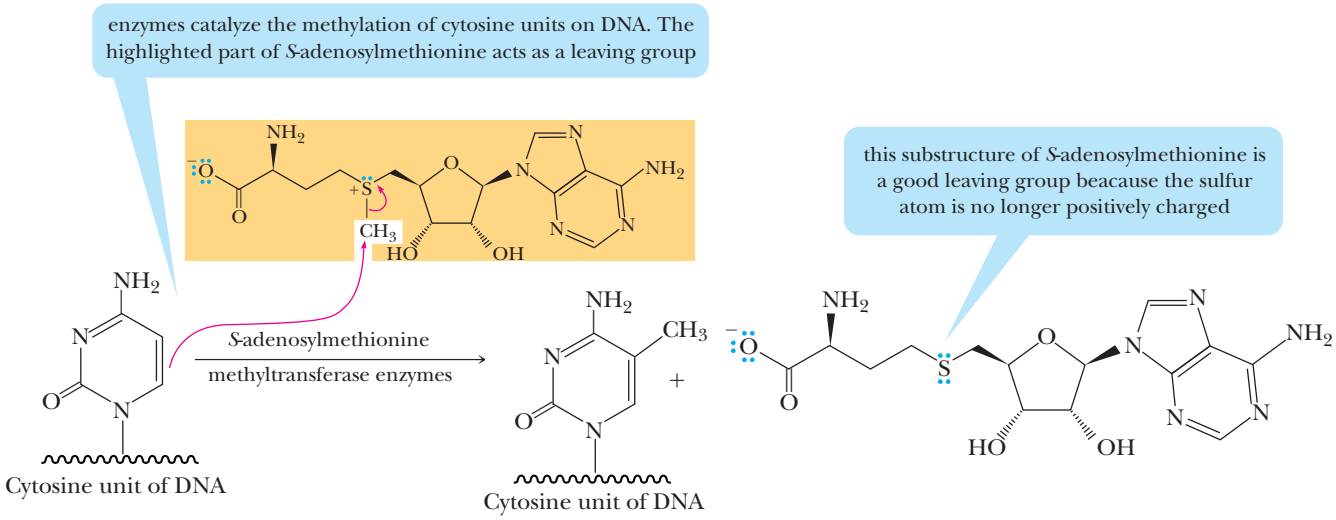
In the transition state for nucleophilic substitution on a haloalkane, the halogen leaving group develops a partial negative charge in both S_N1 and S_N2 reactions. The halogens Cl^-, Br^-, and I^- make good leaving groups because their size and electronegativity help to stabilize the resulting negative charge. Thus, the ability of a group to function as a leaving group is related to how stable it is as an anion. The most stable anions and the best leaving groups are the conjugate bases of strong acids. We can use the information on the relative strengths of organic and inorganic acids in Table 2.1 to determine which anions are the best leaving groups:



The best leaving groups in this series are the halogens I^-, Br^-, and Cl^-. Hydroxide ion (OH^-), methoxide ion (CH_3O^-), and amide ion (NH_2^-) are such poor leaving groups that they rarely, if ever, are displaced in nucleophilic aliphatic substitution reactions. H_2O can act as a leaving group if an —OH group of an alcohol is first protonated by an acid.



One important example of leaving group stability is found in the methylation of DNA, a process common in all mammals and involved in a variety of biological processes including X-chromosome inactivation in females, inheritance, and carcinogenesis. In DNA methylation, enzymes catalyze the attack of a cytosine unit of DNA on the methyl group of *S*-adenosylmethionine (SAM). All but the methyl group of SAM acts as a leaving group and is able to do so because the positive sulfur atom initially bonded to the methyl group becomes uncharged, making the sulfur atom more stable than before.



We will have more to say about leaving groups other than the halides in subsequent chapters.

D. The Solvent

Protic solvent A hydrogen bond donor solvent as, for example, water, ethanol, and acetic acid. We define hydrogen bond donors as compounds containing hydrogens that can participate in H-bonding.

Solvents provide the medium in which reactants are dissolved and in which nucleophilic substitution reactions take place. Common solvents for these reactions are divided into two groups: **protic** and **aprotic**.

Protic solvents contain —OH groups and are hydrogen-bond donors. Common protic solvents for nucleophilic substitution reactions are water, low-molecular-weight alcohols, and low-molecular-weight carboxylic acids (Table 7.3). Each is able to solvate both the

TABLE 7.3 Common Protic Solvents

Protic Solvent	Structure	Polarity of Solvent	Notes
Water	H_2O	Increasing	These solvents favor S_N1 reactions. The greater the polarity of the solvent, the easier it is to form carbocations in it because both the carbocation and the negatively charged leaving group can be solvated.
Formic acid	HCOOH		
Methanol	CH_3OH		
Ethanol	CH_3CH_2OH		
Acetic acid	CH_3COOH		

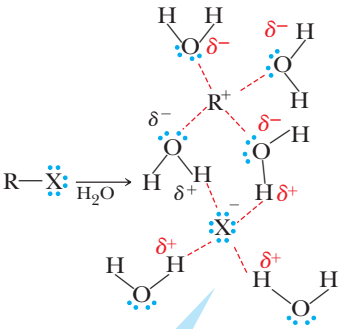
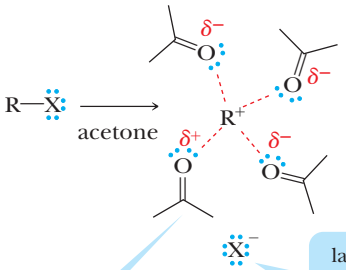


TABLE 7.4 Common Aprotic Solvents

Aprotic Solvent	Structure	Polarity of Solvent	Notes
Dimethyl sulfoxide (DMSO)	CH_3SCH_3 (O)	Increasing	These solvents favor S_N2 reactions. Although solvents at the top of this list are polar, the formation of carbocations in them is far more difficult than in protic solvents because the anionic leaving group cannot be solvated by these solvents.
Acetone	CH_3CCH_3 (O)		
Dichloromethane	CH_2Cl_2		
Diethyl ether	$(CH_3CH_2)_2O$		



lack of solvation makes the anion less stable and very reactive

polar aprotic solvents, like acetone, can only solvate cations effectively, making it *unlikely* for a leaving group to break its bond to carbon and undergo an S_N1 reaction

anionic and cationic components of ionic compounds by electrostatic interaction between its partially negatively charged oxygen(s) and the cation and between its partially positively charged hydrogen(s) and the anion. These same properties aid in the ionization of C—X bonds to give an X^- anion and a carbocation; thus, protic solvents are good solvents in which to carry out S_N1 reactions.

Aprotic solvents do not contain —OH groups and cannot function as hydrogen-bond donors. They are unable to promote the formation of a carbocation because the leaving group would be unsolvated. Therefore aprotic solvents cannot be used in S_N1 reactions. Table 7.4 lists the aprotic solvents most commonly used for nucleophilic substitution reactions. Dimethyl sulfoxide and acetone are polar aprotic solvents; dichloromethane and diethyl ether are less polar aprotic solvents. The aprotic solvents listed in the table are particularly good ones in which to carry out S_N2 reactions. Because polar aprotic solvents are able to solvate only cations and not anions, they allow for "naked" and highly reactive anions as nucleophiles when used with ionic nucleophiles such as Na^+CN^-, Na^+OH^-, and so on.

Aprotic solvent A solvent that cannot serve as a hydrogen bond donor as, for example, acetone, diethyl ether, and dichloromethane.

a polar aprotic solvent, like acetone, will solvate the cation of an ion pair, but leave the anion "naked" and therefore a highly reactive nucleophile

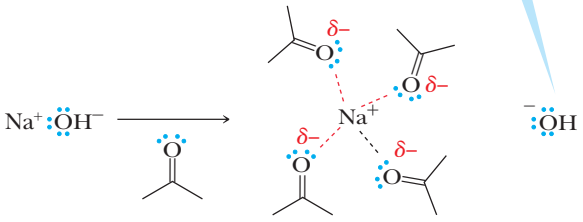


Table 7.5 summarizes the factors favoring S_N1 or S_N2 reactions; it also shows the change in configuration when nucleophilic substitution takes place at a stereocenter.

TABLE 7.5 Summary of S_N1 versus S_N2 Reactions of Haloalkanes

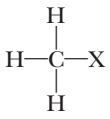
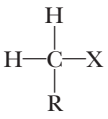
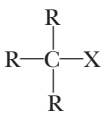
Type of Haloalkane	S_N2	S_N1
Methyl CH_3X	**S_N2 is favored.**	**S_N1 does not occur.** The methyl cation is so unstable that it is never observed in solution.
Primary RCH_2X	**S_N2 is favored.**	**S_N1 does not occur.** Primary carbocations are so unstable that they are not observed in solution.
Secondary R_2CHX	**S_N2 is favored** in aprotic solvents with good nucleophiles.	**S_N1 is favored** in protic solvents with poor nucleophiles.
Tertiary R_3CX	**S_N2 does not occur,** because of steric hindrance around the substitution center.	**S_N1 is favored** because of the ease of formation of tertiary carbocations.
Substitution at a stereocenter	**Inversion of configuration.** The nucleophile attacks the stereocenter from the side opposite the leaving group.	**Racemization.** The carbocation intermediate is planar, and attack by the nucleophile occurs with equal probability from either side.

HOW TO 7.4

Predict the Type of Substitution Reaction a Haloalkane Will Undergo

(a) Identify and assess the stability of the potential leaving group. A substitution reaction will not occur unless there is a good leaving group.

(b) Classify the structure of the haloalkane. Methyl and primary haloalkanes do not undergo S_N1 reactions, while tertiary haloalkanes do not undergo S_N2 reactions.

methyl	1°	2°	3°
			
favor S_N2		both S_N2 and S_N1	favor S_N1

(c) Identify the nucleophile and assess its relative nucleophilicity. S_N2 reactions are favored with good nucleophiles and rarely occur with poor nucleophiles. S_N1 reactions can occur with both poor and moderate nucleophiles, but receive competition from the S_N2 mechanism in the presence of good nucleophiles.

(d) Identify and classify the solvent. A polar protic solvent is required for an S_N1 reaction. Polar aprotic solvents favor S_N2 reactions, although S_N2 reactions can also occur in protic solvents.

(e) If no single factor eliminates or mandates either substitution mechanism, try to determine whether these factors collectively favor the predominance of one mechanism over the other.

EXAMPLE 7.4

Answer the following questions:

(a) The rate of a substitution reaction of a haloalkane is unchanged when the nucleophile is switched from hydroxide to ammonia. What type of substitution reaction does this haloalkane likely undergo?

(b) When (*R*)-2-bromobutane is reacted with diethylamine, $(CH_3CH_2)_2NH$, the reaction solution gradually loses optical activity. What type of substitution mechanism is in operation in this reaction?

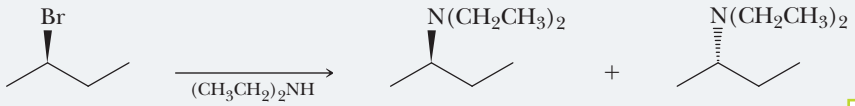
STRATEGY

It is important to remember the details that go along with each of the two substitution mechanisms. In an S_N1 reaction, look for (1) the rate of the reaction to be unaffected by the type or the concentration of the nucleophile or (2) the formation of two products (often enantiomers if stereochemistry exists at the reacting carbon). In an S_N2 reaction, look for (1) the rate of the reaction to be dependent on the type or the concentration of the nucleophile or (2) the formation of only one product.

SOLUTION

(a) S_N1. Hydroxide ion is a better nucleophile than ammonia. S_N1 reactions are unaffected by the effectiveness of the nucleophile. If the reaction were to occur by an S_N2 mechanism, we would expect reaction with the better nucleophile to result in a faster reaction.

(b) S_N1. Diethylamine is a moderate nucleophile and likely favors the S_N1 mechanism. This is confirmed by the stereochemical data, because an S_N2 reaction would yield only the S enantiomer because of the required backside attack. The loss of optical activity most likely indicates that a carbocation intermediate is formed, followed by the attack of the nucleophile to form equal amounts of the enantiomers shown.



(*R*)-2-bromobutane (*R*) (*S*)

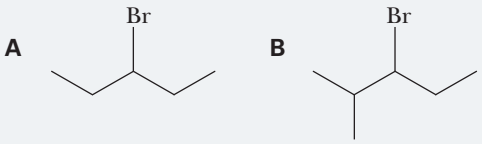
See problems 7.20, 7.23, 7.27

PROBLEM 7.4

Answer the following questions:

(a) Potassium cyanide, KCN, reacts faster than trimethylamine, $(CH_3)_3N$, with 1-chloropentane. What type of substitution mechanism does this haloalkane likely undergo?

(b) Compound A reacts faster with dimethylamine, $(CH_3)_2NH$, than compound B. What does this reveal about the relative ability of each haloalkane to undergo S_N2? S_N1?

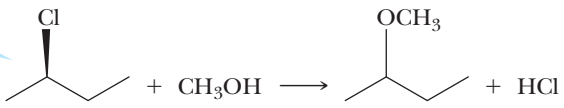


7.6 How Can S_N1 and S_N2 Be Predicted Based on Experimental Conditions?

Predictions about the mechanism for a particular nucleophilic substitution reaction must be based on considerations of the structure of the haloalkane, the nucleophile, and the solvent. Following are analyses of three such reactions:

Nucleophilic Substitution Example 1

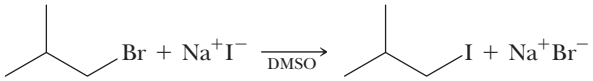
before continuing, try to predict whether these reactions proceed by an S_N1 or S_N2 mechanism



R enantiomer

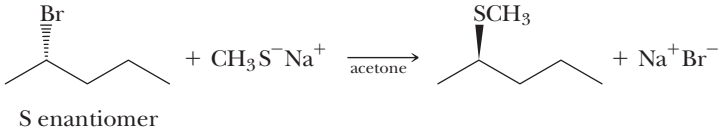
Methanol is a polar protic solvent and a good one in which to form carbocations. 2-Chlorobutane ionizes in methanol to form a 2° carbocation intermediate. Methanol is a weak nucleophile. From this analysis, we predict that reaction is by an S_N1 mechanism. The 2° carbocation intermediate (an electrophile) then reacts with methanol (a nucleophile) followed by proton transfer to give the observed product. The product is formed as a 50:50 mixture of R and S configurations; that is, it is formed as a racemic mixture.

Nucleophilic Substitution Example 2



This is a 1° bromoalkane in the presence of iodide ion, a good nucleophile. Because 1° carbocations are so unstable, they never form in solution, and an S_N1 reaction is not possible. Dimethyl sulfoxide (DMSO), a polar aprotic solvent, is a good solvent in which to carry out S_N2 reactions. From this analysis, we predict that reaction is by an S_N2 mechanism.

Nucleophilic Substitution Example 3

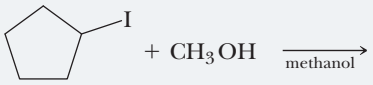


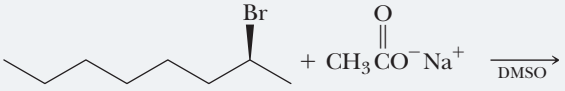
S enantiomer

Bromine ion is a good leaving group on a 2° carbon. The methylsulfide ion is a good nucleophile. Acetone, a polar aprotic solvent, is a good medium in which to carry out S_N2 reactions, but a poor medium in which to carry out S_N1 reactions. We predict that reaction is by an S_N2 mechanism and that the product formed has the R configuration.

EXAMPLE 7.5

Write the expected product for each nucleophilic substitution reaction, and predict the mechanism by which the product is formed:

(a) 

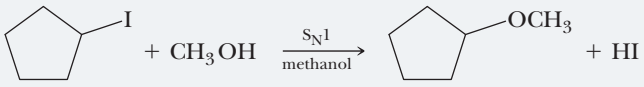
(b) 

STRATEGY

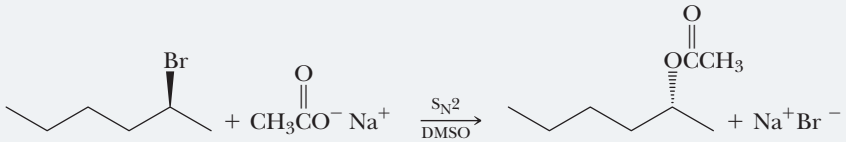
Determine whether the electrophile's reaction center is 1°, 2°, or 3°. Then assess the nucleophilicity of the nucleophile. If it is poor, then the reaction will most likely proceed by an S_N1 mechanism, provided that there exists a polar protic solvent and the reaction center is 2° or 3°. If there is a good nucleophile, then the reaction will most likely proceed by an S_N2 mechanism, provided that the reaction center is 1° or 2°. If the nucleophile is moderate, focus on the solvent polarity and reaction center of the electrophile. Remember that S_N1 mechanisms only occur in polar protic solvents.

SOLUTION

(a) Methanol is a poor nucleophile. It is also a polar protic solvent that is able to solvate carbocations. Ionization of the carbon–iodine bond forms a 2° carbocation intermediate. We predict an S_N1 mechanism:



(b) Bromide is a good leaving group on a 2° carbon. Acetate ion is a moderate nucleophile. DMSO is a particularly good solvent for S_N2 reactions. We predict substitution by an S_N2 mechanism with inversion of configuration at the stereocenter:

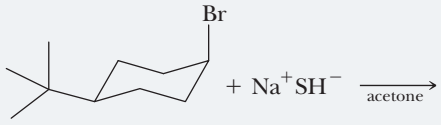


See problems 7.23, 7.25–7.28, 7.34, 7.35

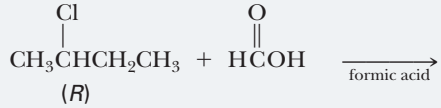
PROBLEM 7.5

Write the expected product for each nucleophilic substitution reaction, and predict the mechanism by which the product is formed:

(a)



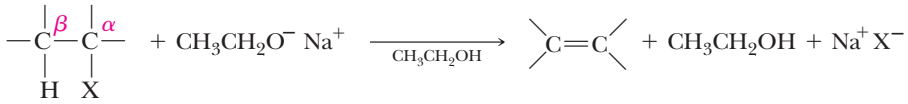
(b)



7.7 What Are the Products of β-Elimination?

Dehydrohalogenation
Removal of —H and —X from adjacent carbons; a type of β-elimination.

In this section, we study a type of β-elimination called **dehydrohalogenation**. In the presence of a strong base, such as hydroxide ion or ethoxide ion, halogen can be removed from one carbon of a haloalkane and hydrogen from an adjacent carbon to form a carbon–carbon double bond:



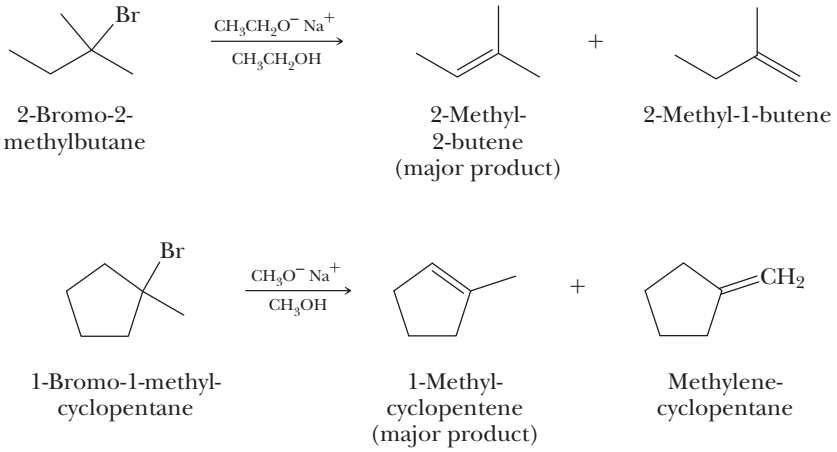
A haloalkane Base An alkene

As the equation shows, we call the carbon bearing the halogen the *α-carbon* and the adjacent carbon the *β-carbon*.

Because most nucleophiles can also act as bases and vice versa, it is important to keep in mind that β-elimination and nucleophilic substitution are competing reactions. In this section, we concentrate on β-elimination. In Section 7.9, we examine the results of competition between the two.

Common strong bases used for β-elimination are OH^-, OR^-, and NH_2^-. Following are three examples of base-promoted β-elimination reactions:

1- Bromooctane Potassium *tert*-butoxide 1- Octene

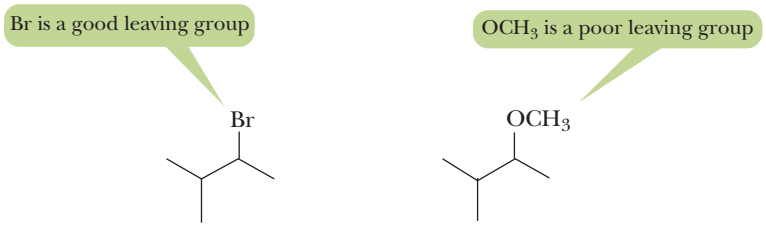


Zaitsev's rule A rule stating that the major product from a β-elimination reaction is the most stable alkene; that is, the major product is the alkene with the greatest number of substituents on the carbon–carbon double bond.

In the first example, the base is shown as a reactant. In the second and third examples, the base is a reactant, but is shown over the reaction arrow. Also in the second and third examples, there are nonequivalent β-carbons, each bearing a hydrogen; therefore, two alkenes are possible from each β-elimination reaction. In each case, the major product of these and most other β-elimination reactions is the more substituted (and therefore the more stable—see Section 5.6) alkene. We say that each reaction follows **Zaitsev's rule** or, alternatively, that each undergoes Zaitsev elimination, to honor the chemist who first made this generalization.

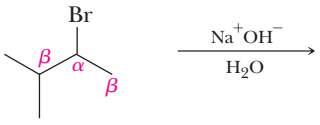
HOW TO 7.5 Complete an Elimination Reaction

(a) Identify and assess the leaving group. An elimination reaction will not occur unless there is a good leaving group.

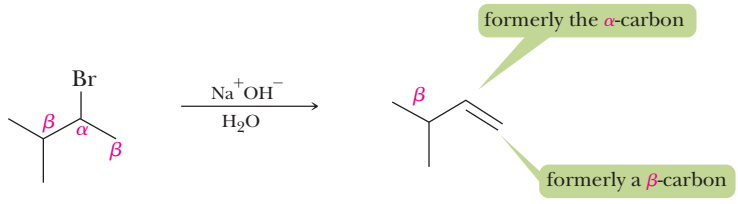


(b) Label the carbon bonded to the leaving group as "α" (alpha).

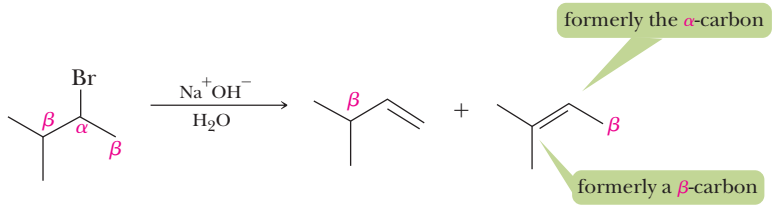
(c) Label any carbon bonded to the α-carbon as "β" (beta). *Note:* Only do so if the β-carbon is bonded to a hydrogen atom.



(d) Remove the leaving group and a β-hydrogen from the molecule and place a new double bond between the α and β carbons. This forms a β-elimination product.

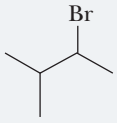


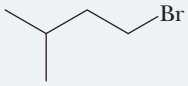
(e) Repeat Step (d) above for any other β-carbons to form a different β-elimination product.

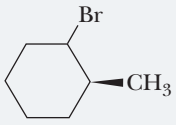


EXAMPLE 7.6

Predict the β-elimination product(s) formed when each bromoalkane is treated with sodium ethoxide in ethanol (if two might be formed, predict which is the major product):

(a) 

(b) 

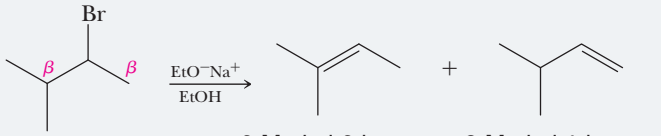
(c) 

STRATEGY

Label the carbon bonded to the halogen as α. Then label any carbons next to the α-carbon as β. If the β-carbon is bonded to at least one hydrogen, remove that hydrogen and the halogen and draw a C—C double bond between the α- and β-carbons. Start over and repeat this process for any other β-carbons that meet this criteria. Each time you are able to do this will result in an elimination product.

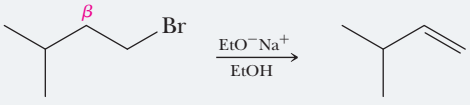
SOLUTION

(a) There are two nonequivalent β-carbons in this bromoalkane, and two alkenes are possible. 2-Methyl-2-butene, the more substituted alkene, is the major product:



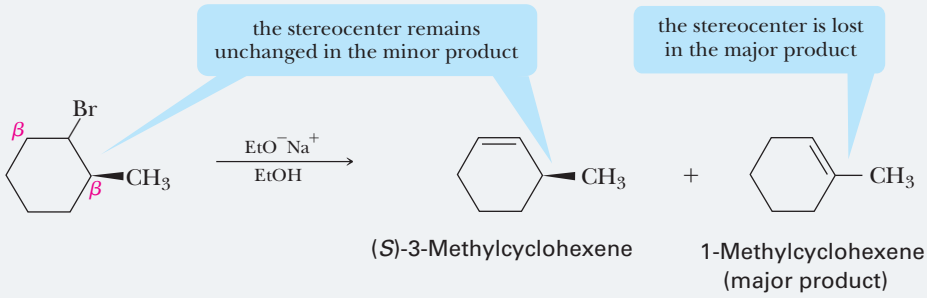
2-Methyl-2-butene (major product) 3-Methyl-1-butene

(b) There is only one β-carbon in this bromoalkane, and only one alkene is possible.



3-Methyl-1-butene

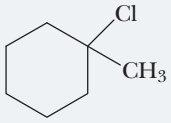
(c) There are two nonequivalent β-carbons in this cyclic bromoalkane, and two alkenes are possible. 1-Methylcyclohexene, the more substituted alkene, is the major product:

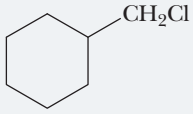


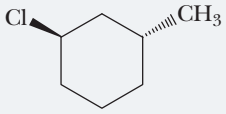
See problems 7.36–7.38

PROBLEM 7.6

Predict the β-elimination products formed when each chloroalkane is treated with sodium ethoxide in ethanol (if two products might be formed, predict which is the major product):

(a) 

(b) 

(c) 

7.8 What Are the E1 and E2 Mechanisms for β-Elimination?

There are two limiting mechanisms of β-elimination reactions. A fundamental difference between them is the timing of the bond-breaking and bond-forming steps. Recall that we made this same statement about the two limiting mechanisms for nucleophilic substitution reactions in Section 7.4.

Draw Mechanisms

HOW TO 7.6

Remember that curved arrow notation always shows the arrow originating from a bond or from a lone pair of electrons.

Correct use of curved arrows...

Incorrect use of curved arrows...

A. E1 Mechanism

At one extreme, breaking of the C—X bond is complete before any reaction occurs with base to lose a hydrogen and before the carbon–carbon double bond is formed. This mechanism is designated **E1**, where *E* stands for *e*limination and *1* stands for a *uni*molecular reaction; only *one* species, in this case the haloalkane, is involved in the rate-determining step. The rate law for an E1 reaction has the same form as that for an S_N1 reaction:

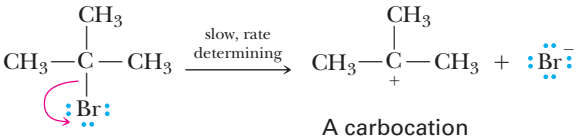
$$\text{Rate} = k[\text{haloalkane}]$$

The mechanism for an E1 reaction is illustrated by the reaction of 2-bromo-2-methylpropane to form 2-methylpropene. In this two-step mechanism, the rate-determining step is the ionization of the carbon–halogen bond to form a carbocation intermediate (just as it is in an S_N1 mechanism).

Mechanism

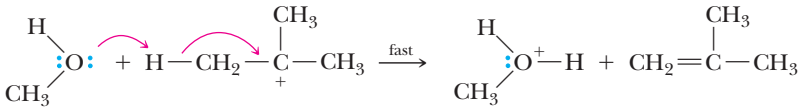
E1 Reaction of 2-Bromo-2-methylpropane

STEP 1: Break a bond. Rate-determining ionization of the C—Br bond gives a carbocation intermediate:



A carbocation intermediate

STEP 2: Take away a proton. Proton transfer from the carbocation intermediate to methanol (which in this instance is both the solvent and a reactant) gives the alkene:



B. E2 Mechanism

At the other extreme is a concerted process. In an **E2** reaction, *E* stands for *e*limination, and *2* stands for *bi*molecular. Because the base removes a β-hydrogen at the same time the C—X bond is broken to form a halide ion, the rate law for the rate-determining step is dependent on both the haloalkane and the base:

$$\text{Rate} = k[\text{haloalkane}][\text{base}]$$

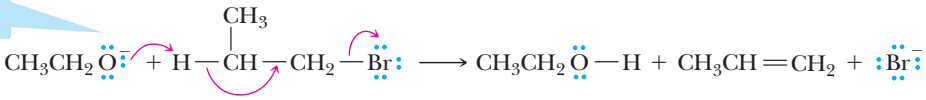
The stronger the base, the more likely it is that the E2 mechanism will be in operation. We illustrate an E2 mechanism by the reaction of 1-bromopropane with sodium ethoxide.

Mechanism

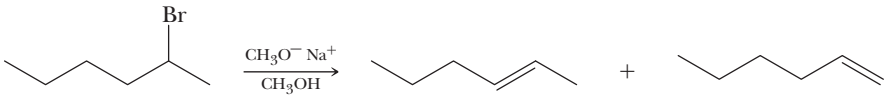
E2 Reaction of 1-Bromopropane

In the E2 mechanism we (1) take away a proton and (2) break a bond to form a stable ion or molecule. Proton transfer to the base, formation of the carbon–carbon double bond, and the ejection of bromide ion occur simultaneously; that is, all bond-forming and bond-breaking steps occur at the same time.

the E2 mechanism is concerted



For both E1 and E2 reactions, the major product is that formed in accordance with Zaitsev's rule (Section 7.7) as illustrated by this E2 reaction:



2-Bromohexane → *trans*-2-Hexene (74%) + 1-Hexene (26%)

Table 7.6 summarizes these generalizations about β-elimination reactions of haloalkanes.

TABLE 7.6 Summary of E1 versus E2 Reactions of Haloalkanes

Haloalkane	E1	E2
Primary RCH_2X	E1 does not occur. Primary carbocations are so unstable that they are never observed in solution.	E2 is favored.
Secondary R_2CHX	Main reaction with weak bases such as H_2O and ROH.	Main reaction with strong bases such as OH^- and OR^-.
Tertiary R_3CX	Main reaction with weak bases such as H_2O and ROH.	Main reaction with strong bases such as OH^- and OR^-.

HOW TO 7.7

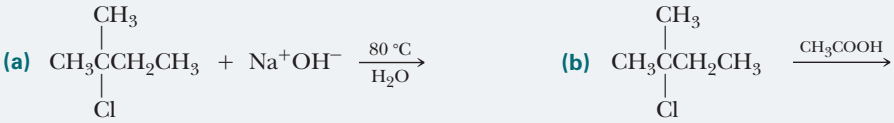
Predict the Type of β-Elimination Reaction a Haloalkane Will Undergo

(a) Classify the structure of the haloalkane. Primary haloalkanes will not undergo E1 reactions. Secondary and tertiary haloalkanes will undergo both E1 and E2 reactions.

(b) Identify and assess the base. E2 reactions are favored with strong bases and rarely occur with weak bases. E2 reactions can occur in any solvent. E1 reactions can occur with both weak and strong bases, but require polar protic solvents to stabilize the carbocation formed in the first step of the reaction.

EXAMPLE 7.7

Predict whether each β-elimination reaction proceeds predominantly by an E1 or E2 mechanism, and write a structural formula for the major organic product:

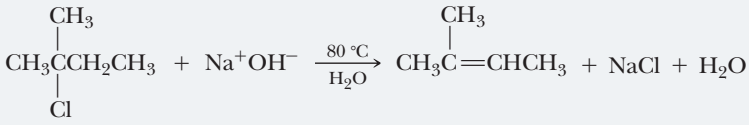


STRATEGY

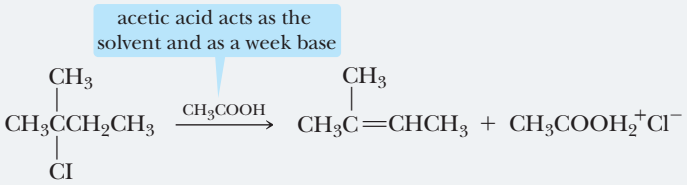
Identify the solvent and the base. If the base is strong, an E2 mechanism is favored to occur. If the base is weak and the solvent is polar protic, then an E1 mechanism is favored to occur.

SOLUTION

(a) A 3° chloroalkane is heated with NaOH, a strong base. Elimination by an E2 reaction predominates, giving 2-methyl-2-butene as the major product:



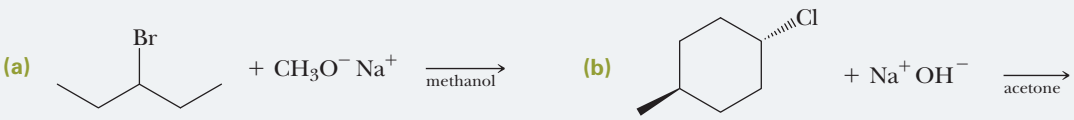
(b) A 3° chloroalkane dissolved in acetic acid, a solvent that promotes the formation of carbocations, forms a 3° carbocation that then loses a proton to give 2-methyl-2-butene as the major product. The reaction is by an E1 mechanism:



See problems 7.36–7.38

PROBLEM 7.7

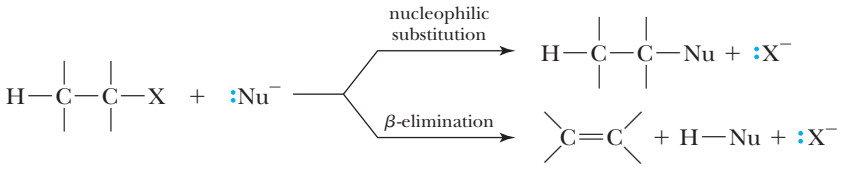
Predict whether each elimination reaction proceeds predominantly by an E1 or E2 mechanism, and write a structural formula for the major organic product:



7.9 When Do Nucleophilic Substitution and β-Elimination Compete?

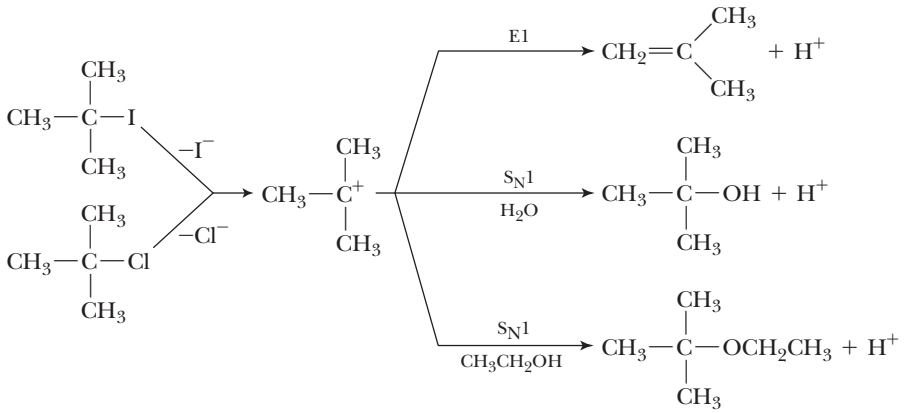
Thus far, we have considered two types of reactions of haloalkanes: nucleophilic substitution and β-elimination. Many of the nucleophiles we have examined—for example, hydroxide ion and alkoxide ions—are also strong bases. Accordingly, nucleophilic

substitution and β-elimination often compete with each other, and the ratio of products formed by these reactions depends on the relative rates of the two reactions:



A. S_N1-versus-E1 Reactions

Reactions of secondary and tertiary haloalkanes in polar protic solvents give mixtures of substitution and elimination products. In both reactions, Step 1 is the formation of a carbocation intermediate. This step is then followed by either (1) the loss of a hydrogen to give an alkene (E1) or (2) reaction with solvent to give a substitution product (S_N1). In polar protic solvents, the products formed depend only on the structure of the particular carbocation. For example, *tert*-butyl chloride and *tert*-butyl iodide in 80% aqueous ethanol both react with solvent, giving the same mixture of substitution and elimination products:



Because iodide ion is a better leaving group than chloride ion, *tert*-butyl iodide reacts over 100 times faster than *tert*-butyl chloride. Yet the ratio of products is the same.

B. S_N2-versus-E2 Reactions

It is considerably easier to predict the ratio of substitution to elimination products for reactions of haloalkanes with reagents that act as both nucleophiles and bases. The guiding principles are as follows:

1. Branching at the α-carbon or β-carbon(s) increases steric hindrance about the α-carbon and significantly retards S_N2 reactions. By contrast, branching at the α-carbon or β-carbon(s) increases the rate of E2 reactions because of the increased stability of the alkene product.
2. The greater the nucleophilicity of the attacking reagent, the greater is the S_N2-to-E2 ratio. Conversely, the greater the basicity of the attacking reagent, the greater is the E2-to-S_N2 ratio.

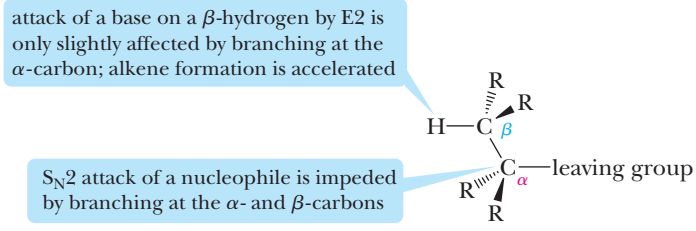


TABLE 7.7 Summary of Substitution versus Elimination Reactions of Haloalkanes

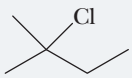
Halide	Reaction	Comments
Methyl	S_N2	The only substitution reactions observed.
CH_3X	~~S_N1~~	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
Primary RCH_2X	S_N2	The main reaction with strong bases such as OH^- and EtO^-. Also, the main reaction with good nucleophiles/weak bases, such as I^- and CH_3COO^-.
	E2	The main reaction with strong, bulky bases, such as potassium *tert*-butoxide.
	~~S_N1/E1~~	Primary cations are never formed in solution; therefore, S_N1 and E1 reactions of primary halides are never observed.
Secondary R_2CHX	S_N2	The main reaction with weak bases/good nucleophiles, such as I^- and CH_3COO^-.
	E2	The main reaction with strong bases/good nucleophiles, such as OH^- and $CH_3CH_2O^-$.
	S_N1/E1	Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.
Tertiary R_3CX	~~S_N2~~	S_N2 reactions of tertiary halides are never observed because of the extreme crowding around the 3° carbon.
	E2	Main reaction with strong bases, such as HO^- and RO^-.
	S_N1/E1	Main reactions with poor nucleophiles/weak bases.

Primary halides react with bases/nucleophiles to give predominantly substitution products. With strong bases, such as hydroxide ion and ethoxide ion, a percentage of the product is formed by an E2 reaction, but it is generally small compared with that formed by an S_N2 reaction. With strong, bulky bases, such as *tert*-butoxide ion, the E2 product becomes the major product. Tertiary halides react with all strong bases/good nucleophiles to give only elimination products.

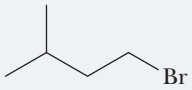
Secondary halides are borderline, and substitution or elimination may be favored, depending on the particular base/nucleophile, solvent, and temperature at which the reaction is carried out. Elimination is favored with strong bases/good nucleophiles—for example, hydroxide ion and ethoxide ion. Substitution is favored with weak bases/poor nucleophiles—for example, acetate ion. Table 7.7 summarizes these generalizations about substitution versus elimination reactions of haloalkanes.

EXAMPLE 7.8

Predict whether each reaction proceeds predominantly by substitution (S_N1 or S_N2) or elimination (E1 or E2) or whether the two compete, and write structural formulas for the major organic product(s):

(a) 

$+ Na^+OH^- \xrightarrow[H_2O]{80\ ^\circ C}$

(b) 

$+ (C_2H_5)_3N \xrightarrow[CH_2Cl_2]{30\ ^\circ C}$

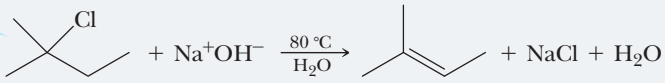
STRATEGY

First, determine whether the reagent acts predominantly as a base or a nucleophile. If it is a weak base but a good nucleophile, substitution is more likely to occur. If the reagent is a strong base but a poor nucleophile, elimination is more likely to occur. When the reagent can act equally as both a base and a nucleophile, use other factors to decide whether substitution or elimination predominates. These include the degree of substitution about the reacting center (1° haloalkanes will not undergo E1 or S_N1 reactions, 3° haloalkanes will not undergo S_N2 reactions) or type of solvent (E1 and S_N1 reactions require polar protic solvents).

SOLUTION

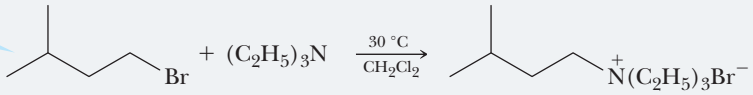
(a) A 3° halide is heated with a strong base/good nucleophile. Elimination by an E2 reaction predominates to give 2-methyl-2-butene as the major product:

a strong base/good nucleophile favors E2/S_N2. However, 3° halides cannot undergo S_N2 reactions



(b) Reaction of a 1° halide with triethylamine, a moderate nucleophile/weak base, gives substitution by an S_N2 reaction:

1° halides cannot undergo E1/S_N1 reactions. The base is not strong enough to undergo an E2 reaction

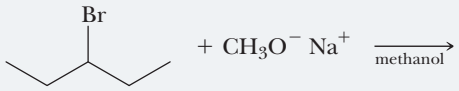


See problem 7.43

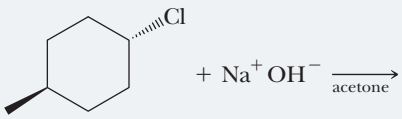
PROBLEM 7.8

Predict whether each reaction proceeds predominantly by substitution (S_N1 or S_N2) or elimination (E1 or E2) or whether the two compete, and write structural formulas for the major organic product(s):

(a)



(b)

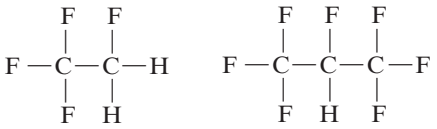


Chemical Connections 7B

THE EFFECT OF CHLOROFLUOROCARBON LEGISLATION ON ASTHMA SUFFERERS

The Montreal Protocol on Substances That Deplete the Ozone Layer was proposed in 1987 and enacted in 1989. As a result of this treaty, and its many revisions, the phaseout of CFCs and many other substances harmful to the ozone layer has been achieved in many industrialized nations. However, the Montreal Protocol provided exceptions for products in which the use of CFCs was essential because no viable alternatives existed. One such product was albuterol metered-dose inhalers, which use CFCs as propellants to deliver the drug and are used by asthma patients worldwide. In the United States, this exemption from the Montreal Protocol expired in December 2008, thanks to the Clean Air Act and the availability of another type of propellant known as hydrofluoroalkanes (HFAs). One drawback of HFA-equipped inhalers is that of cost; HFA inhalers cost three to six times as much as CFC-enabled inhalers because generic versions do not yet exist. This has sparked concerns from patients, physicians, and patients' rights groups over the ability of the nearly 23 million people in the United States who suffer from asthma to obtain treatment. Other differences include taste, smell, temperature of inhalant upon ejection, and effectiveness in colder climates and higher altitudes (HFAs are more effective under these conditions than CFCs). These practical differences are a result of the absence of chlorine in HFAs versus in CFCs, and are an excellent example of how changes in chemical structure can affect the properties of molecules and their ultimate applications in society.

Courtesy Teva USA



HFA-134a HFA-227

Hydrofluoroalkanes used in CFC-free medical inhalers

Question

Would you expect HFA-134a or HFA-227 to undergo an S_N1 reaction? An S_N2 reaction? Why or why not?

SUMMARY OF KEY QUESTIONS

7.1 How Are Haloalkanes Named?

- In the IUPAC system, halogen atoms are named as fluoro-, chloro-, bromo-, or iodo- substituents and are listed in alphabetical order with other substituents.
- In the common system, **haloalkanes** are named **alkyl halides**, where the name is derived by naming the alkyl group followed by the name of the halide as a separate word (e.g., methyl chloride).
- Compounds of the type CHX_3 are called **haloforms**.

7.2 What Are the Characteristic Reactions of Haloalkanes?

- Haloalkanes undergo **nucleophilic substitution** reactions and **β-elimination** reactions.
- In substitution reactions, the halogen is replaced by a reagent known as a **nucleophile**. A nucleophile is any molecule or ion with an unshared pair of electrons that can be donated to another atom or ion to form a new covalent bond; alternatively, a nucleophile is a Lewis base.
- In elimination reactions, the halogen and an adjacent hydrogen are removed to form an alkene.

7.3 What Are the Products of Nucleophilic Aliphatic Substitution Reactions?

- The product of a nucleophilic substitution reaction varies depending on the nucleophile used in the reaction. For example, when the nucleophile is hydroxide (HO^-), the product will be an alcohol (ROH).
- Nucleophilic substitution reactions can be used to transform haloalkanes into alcohols, ethers, thiols, sulfides, alkyl iodides, and alkyl ammonium ions, to name a few.

7.4 What Are the S_N2 and S_N1 Mechanisms for Nucleophilic Substitution?

- An **S_N2** reaction occurs in one step. The departure of the **leaving group** is assisted by the incoming nucleophile, and both nucleophile and leaving group are involved in the transition state. S_N2 reactions are stereoselective; reaction at a stereocenter proceeds with **inversion of configuration**.
- An **S_N1** reaction occurs in two steps. Step 1 is a slow, rate-determining ionization of the C—X bond to form a carbocation intermediate, followed in Step 2 by its rapid reaction with a nucleophile to complete the substitution. For S_N1 reactions taking place at a stereocenter, the major reaction occurs with **racemization**.

7.5 What Determines Whether S_N1 or S_N2 Predominates?

- The stability of the leaving group. The ability of a group to function as a leaving group is related to its stability as an anion. The most stable anions and the best leaving groups are the conjugate bases of strong acids.

- The **nucleophilicity** of a reagent. Nucleophilicity is measured by the rate of its reaction in a reference nucleophilic substitution.
- The structure of the haloalkane. S_N1 reactions are governed by **electronic factors**, namely, the relative stabilities of carbocation intermediates. S_N2 reactions are governed by **steric factors**, namely, the degree of crowding around the site of substitution.
- The nature of the solvent. **Protic solvents** contain —OH groups, interact strongly with polar molecules and ions, and are good solvents in which to form carbocations. Protic solvents favor S_N1 reactions. **Aprotic solvents** do not contain —OH groups. Common aprotic solvents are **dimethyl sulfoxide**, acetone, diethyl ether, and dichloromethane. Aprotic solvents do not interact as strongly with polar molecules and ions, and carbocations are less likely to form in them. Aprotic solvents favor S_N2 reactions.
- A nonhalogenated compound with a good leaving group can, like haloalkanes, undergo substitution reactions.
- Halogens make good leaving groups because either their size (as in I^- or Br^-) or electronegativity (Cl^-) helps to stabilize the resulting negative charge. F^- is not a good leaving group because HF is a weak acid. HCl, HBr, and HI are strong acids, making their halide anions weak bases.
- The ability of a group to function as a leaving group is related to how stable it is as an anion.
- The most stable anions and the best leaving groups are the conjugate bases of strong acids.

7.6 How Can S_N1 and S_N2 Be Predicted Based on Experimental Conditions?

- Predictions about the mechanism for a particular nucleophilic substitution reaction must be based on considerations of the structure of the haloalkane, the nucleophile, the leaving group, and the solvent.

7.7 What Are the Products of β-Elimination?

- **Dehydrohalogenation**, a type of β-elimination reaction, is the removal of H and X from adjacent carbon atoms, resulting in the formation of a carbon–carbon double bond.
- A β-elimination that gives the most highly substituted alkene is called **Zaitsev elimination**.

7.8 What Are the E1 and E2 Mechanisms for β-Elimination?

- An **E1** reaction occurs in two steps: breaking the C—X bond to form a carbocation intermediate, followed by the loss of an H^+ to form the alkene.
- An **E2** reaction occurs in one step: reaction with the base to remove an H^+, formation of the alkene, and departure of the leaving group, all occurring simultaneously.

7.9 When Do Nucleophilic Substitution and β-Elimination Compete?

- Many of the nucleophiles we have examined—for example, hydroxide ion and alkoxide ions—are also strong bases. As a result, nucleophilic substitution and β-elimination often compete with each other, and the ratio of products formed by these reactions depends on the relative rates of the two reactions.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. An S_N1 reaction can result in two products that are stereoisomers. (7.4)
2. In naming halogenated compounds, "haloalkane" is the IUPAC form of the name while "alkyl halide" is the common form of the name. (7.1)
3. A substitution reaction results in the formation of an alkene. (7.3)
4. Ethoxide ion ($CH_3CH_2O^-$) can act as a base and as a nucleophile in its reaction with bromocyclohexane. (7.2)
5. The rate law of the E2 reaction is dependent on just the haloalkane concentration. (7.8)
6. The mechanism of the S_N1 reaction involves the formation of a carbocation intermediate. (7.4)
7. Polar protic solvents are required for E1 or S_N1 reactions to occur. (7.9)
8. OH^- is a better leaving group than Cl^-. (7.5)
9. When naming haloalkanes with more than one type of halogen, numbering priority is given to the halogen with the higher mass. (7.1)

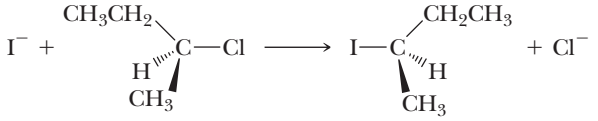
10. S_N2 reactions prefer good nucleophiles, while S_N1 reactions proceed with most any nucleophile. (7.5)
11. The stronger the base, the better is the leaving group. (7.5)
12. S_N2 reactions are more likely to occur with 2° haloalkanes than with 1° haloalkanes. (7.9)
13. A solvolysis reaction is a reaction performed without solvent. (7.4)
14. The degree of substitution at the reaction center affects the rate of an S_N1 reaction but not an S_N2 reaction. (7.5)
15. A reagent must possess a negative charge to react as a nucleophile. (7.3)
16. Elimination reactions favor the formation of the more substituted alkene. (7.7)
17. The best leaving group is one that is unstable as an anion. (7.5)
18. In the S_N2 reaction, the nucleophile attacks the carbon from the side opposite that of the leaving group. (7.4)
19. Only haloalkanes can undergo substitution reactions. (7.5)
20. All of the following are polar aprotic solvents: acetone, DMSO, ethanol. (7.5)

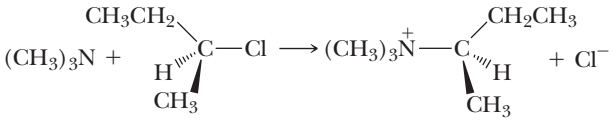
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.
Answers: (1) T (2) T (3) F (4) T (5) F (6) T (7) T (8) F (9) F (10) T (11) F (12) F (13) F (14) F (15) F (16) T (17) F (18) T (19) F (20) F

KEY REACTIONS

1. Nucleophilic Aliphatic Substitution: S_N2 (Section 7.4A)

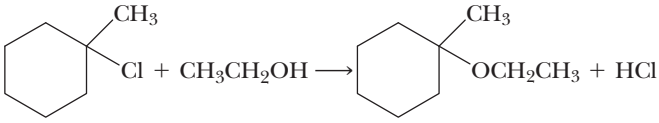
S_N2 reactions occur in one step, and both the nucleophile and the leaving group are involved in the transition state of the rate-determining step. The nucleophile may be negatively charged or neutral. S_N2 reactions result in an inversion of configuration at the reaction center. They are accelerated in polar aprotic solvents, compared with polar protic solvents. S_N2 reactions are governed by steric factors, namely, the degree of crowding around the site of reaction.





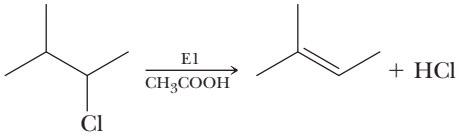
2. Nucleophilic Aliphatic Substitution: S_N1 (Section 7.4B)

An S_N1 reaction occurs in two steps. Step 1 is a slow, rate-determining ionization of the C—X bond to form a carbocation intermediate, followed in Step 2 by its rapid reaction with a nucleophile to complete the substitution. Reaction at a stereocenter gives a racemic product. S_N1 reactions are governed by electronic factors, namely, the relative stabilities of carbocation intermediates:



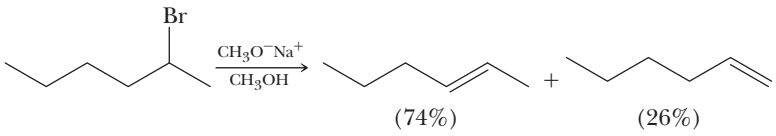
3. β-Elimination: E1 (Section 7.8A)

E1 reactions involve the elimination of atoms or groups of atoms from adjacent carbons. Reaction occurs in two steps and involves the formation of a carbocation intermediate:



4. β-Elimination: E2 (Section 7.8B)

An E2 reaction occurs in one step: reaction with base to remove a hydrogen, formation of the alkene, and departure of the leaving group, all occurring simultaneously:

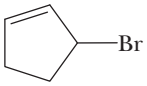
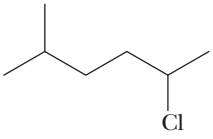


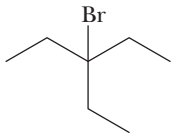
PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

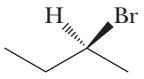
Section 7.1 Nomenclature

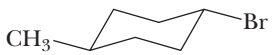
7.9 Write the IUPAC name for each compound: **(See Example 7.1)**

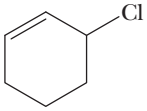
(a) $CH_2{=}CF_2$ (b)  (c)  (d) $Cl(CH_2)_6Cl$

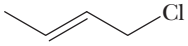
(e) CF_2Cl_2 (f) 

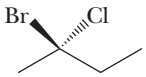
7.10 Write the IUPAC name for each compound (be certain to include a designation of configuration, where appropriate, in your answer): **(See Example 7.1)**

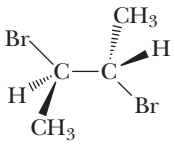
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

7.11 Draw a structural formula for each compound (given are IUPAC names): **(See Example 7.1)**

(a) 3-Bromopropene
(b) (*R*)-2-Chloropentane
(c) meso-3,4-Dibromohexane
(d) *trans*-1-Bromo-3-isopropylcyclohexane
(e) 1,2-Dichloroethane
(f) Bromocyclobutane

7.12 Draw a structural formula for each compound (given are common names): **(See Example 7.1)**

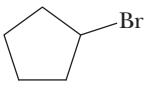
(a) Isopropyl chloride
(b) *sec*-Butyl bromide
(c) Allyl iodide
(d) Methylene chloride
(e) Chloroform
(f) *tert*-Butyl chloride
(g) Isobutyl chloride

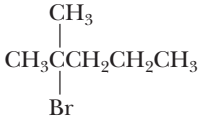
7.13 Which compounds are 2° alkyl halides?

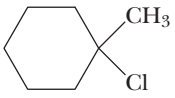
(a) Isobutyl chloride
(b) 2-Iodooctane
(c) *trans*-1-Chloro-4-methylcyclohexane

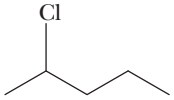
Synthesis of Alkyl Halides

7.14 What alkene or alkenes and reaction conditions give each alkyl halide in good yield? (*Hint*: Review Chapter 5.) **(See Example 5.2)**

(a) 

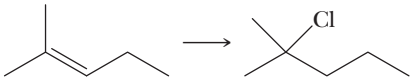
(b) 

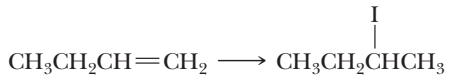
(c) 

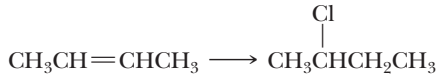
(d) 

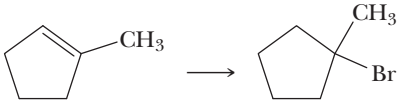
racemic

7.15 Show reagents and conditions that bring about these conversions: **(See Example 5.2)**

(a) 

(b) 

(c) 

(d) 

Sections 7.2–7.6 Nucleophilic Aliphatic Substitution

7.16 Write structural formulas for these common organic solvents:

(a) Dichloromethane
(b) Acetone
(c) Ethanol
(d) Diethyl ether
(e) Dimethyl sulfoxide
(f) *tert*-Butyl alcohol

7.17 Arrange these protic solvents in order of increasing polarity:

(a) H_2O
(b) CH_3CH_2OH
(c) CH_3OH

7.18 Arrange these aprotic solvents in order of increasing polarity:

(a) Acetone
(b) Pentane
(c) Diethyl ether

7.19 From each pair, select the better nucleophile:

(a) H_2O or OH^-
(b) CH_3COO^- or OH^-
(c) CH_3SH or CH_3S^-

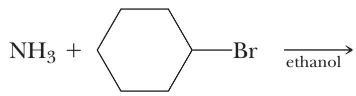
7.20 Which statements are true for S_N2 reactions of haloalkanes? **(See Example 7.4)**

(a) Both the haloalkane and the nucleophile are involved in the transition state.
(b) The reaction proceeds with inversion of configuration at the substitution center.
(c) The reaction proceeds with retention of optical activity.
(d) The order of reactivity is 3° > 2° > 1° > methyl.

(e) The nucleophile must have an unshared pair of electrons and bear a negative charge.
(f) The greater the nucleophilicity of the nucleophile, the greater is the rate of reaction.

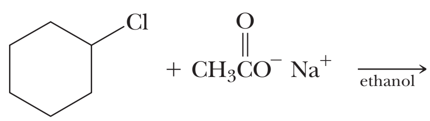
7.21 Complete these S_N2 reactions: **(See Examples 7.3, 7.5)**

(a) $Na^+I^- + CH_3CH_2CH_2Cl \xrightarrow[\text{acetone}]{}$

(b) 

(c) $CH_3CH_2O^-Na^+ + CH_2{=}CHCH_2Cl \xrightarrow[\text{ethanol}]{}$

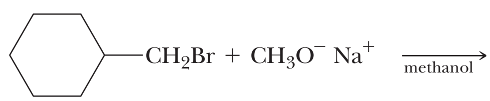
7.22 Complete these S_N2 reactions: **(See Examples 7.3, 7.5)**

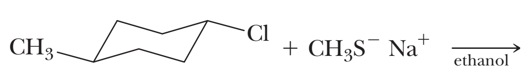
(a) 

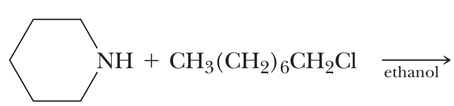
(b) $CH_3\overset{I}{\overset{|}{C}}HCH_2CH_3 + CH_3CH_2S^-Na^+ \xrightarrow[\text{acetone}]{}$

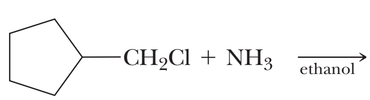
(c) $CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2Br + Na^+I^- \xrightarrow[\text{acetone}]{}$

(d) $(CH_3)_3N + CH_3I \xrightarrow[\text{acetone}]{}$

(e) 

(f) 

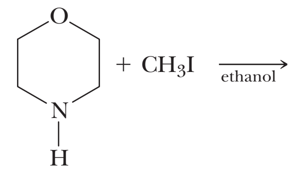
(g) 

(h) 

7.23 You were told that each reaction in Problem 7.22 proceeds by an S_N2 mechanism. Suppose you were not told the mechanism. Describe how you could conclude, from the structure of the haloalkane, the nucleophile, and the solvent, that each reaction is in fact an S_N2 reaction. **(See Examples 7.4, 7.5)**

7.24 In the following reactions, a haloalkane is treated with a compound that has two nucleophilic sites. Select the more nucleophilic site in each part, and show the product of each S_N2 reaction:

(a) $HOCH_2CH_2NH_2 + CH_3I \xrightarrow[\text{ethanol}]{}$

(b) 

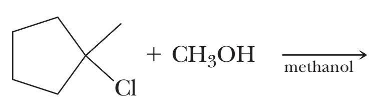
(c) $HOCH_2CH_2SH + CH_3I \xrightarrow[\text{ethanol}]{}$

7.25 Which statements are true for S_N1 reactions of haloalkanes? **(See Example 7.5)**

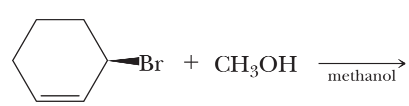
(a) Both the haloalkane and the nucleophile are involved in the transition state of the rate-determining step.
(b) The reaction at a stereocenter proceeds with retention of configuration.
(c) The reaction at a stereocenter proceeds with loss of optical activity.
(d) The order of reactivity is 3° > 2° > 1° > methyl.
(e) The greater the steric crowding around the reactive center, the lower is the rate of reaction.
(f) The rate of reaction is greater with good nucleophiles compared with poor nucleophiles.

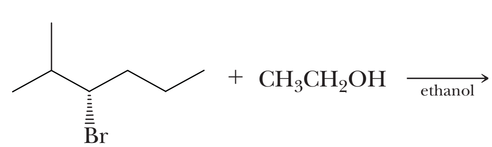
7.26 Draw a structural formula for the product of each S_N1 reaction: **(See Examples 7.3, 7.5)**

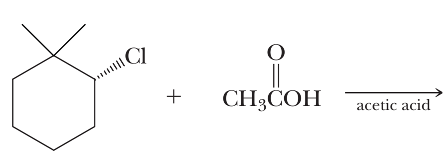
(a) $CH_3\overset{Cl}{\overset{|}{C}}HCH_2CH_3 + CH_3CH_2OH \xrightarrow[\text{ethanol}]{}$
S enantiomer

(b) 

(c) $CH_3\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}Cl + CH_3\overset{O}{\overset{\|}{C}}OH \xrightarrow[\text{acetic acid}]{}$

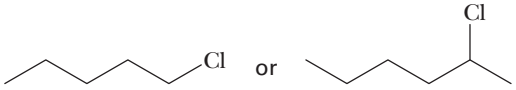
(d) 

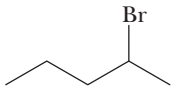
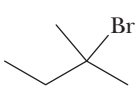
(e) 

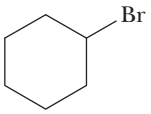
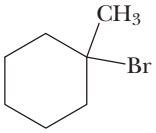
(f) 

7.27 You were told that each substitution reaction in Problem 7.26 proceeds by an S_N1 mechanism. Suppose that you were not told the mechanism. Describe how you could conclude, from the structure of the haloalkane, the nucleophile, and the solvent, that each reaction is in fact an S_N1 reaction. **(See Examples 7.4, 7.5)**

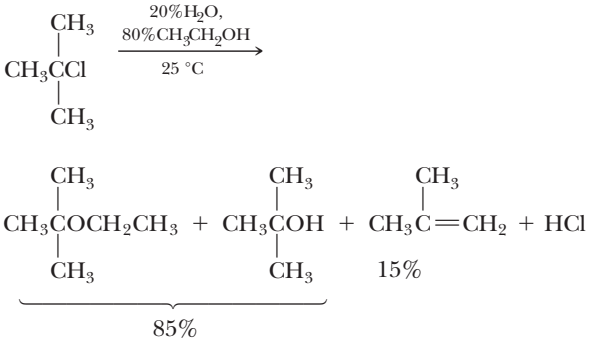
7.28 Select the member of each pair that undergoes nucleophilic substitution in aqueous ethanol more rapidly: **(See Example 7.5)**

(a)  or

(b)  or 

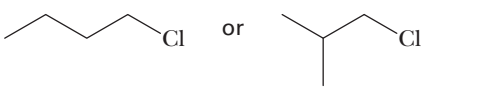
(c)  or 

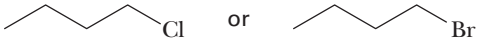
7.29 Propose a mechanism for the formation of the products (but not their relative percentages) in this reaction:

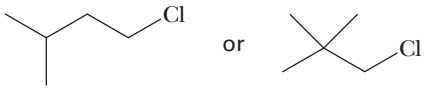


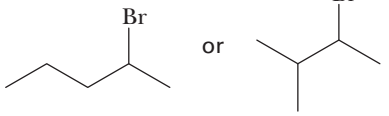
7.30 The rate of reaction in Problem 7.29 increases by 140 times when carried out in 80% water to 20% ethanol, compared with 40% water to 60% ethanol. Account for this difference.

7.31 Select the member of each pair that shows the greater rate of S_N2 reaction with KI in acetone:

(a) 

(b) 

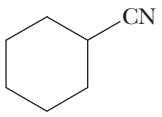
(c) 

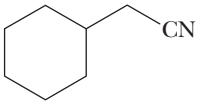
(d) 

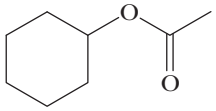
7.32 What hybridization best describes the reacting carbon in the S_N2 transition state?

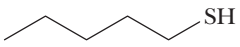
7.33 Haloalkenes such as vinyl bromide, $CH_2{=}CHBr$, undergo neither S_N1 nor S_N2 reactions. What factors account for this lack of reactivity?

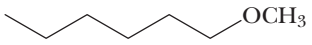
7.34 Show how you might synthesize the following compounds from a haloalkane and a nucleophile: **(See Example 7.5)**

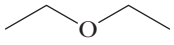
(a) 

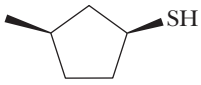
(b) 

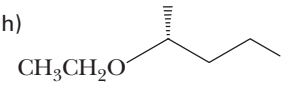
(c) 

(d) 

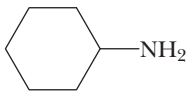
(e) 

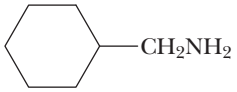
(f) 

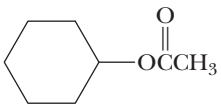
(g) 

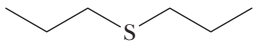
(h) 

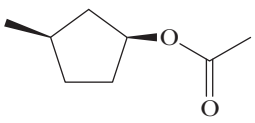
7.35 Show how you might synthesize each compound from a haloalkane and a nucleophile: **(See Example 7.5)**

(a) 

(b) 

(c) 

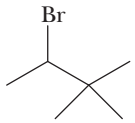
(d) 

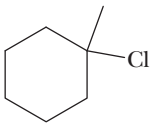
(e) 

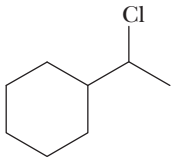
(f) $(CH_3CH_2CH_2CH_2)_2O$

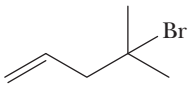
Sections 7.7–7.8 β-Eliminations

7.36 Draw structural formulas for the alkene(s) formed by treating each of the following haloalkanes with sodium ethoxide in ethanol. Assume that elimination is by an E2 mechanism. Where two alkenes are possible, use Zaitsev's rule to predict which alkene is the major product: **(See Examples 7.6, 7.7)**

(a) 

(b) 

(c) 

(d) 

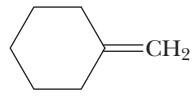
7.37 Which of the following haloalkanes undergo dehydrohalogenation to give alkenes that do not show *cis–trans* isomerism? **(See Examples 7.6, 7.7)**

(a) 2-Chloropentane (b) 2-Chlorobutane
(c) Chlorocyclohexane (d) Isobutyl chloride

7.38 How many isomers, including *cis–trans* isomers, are possible for the major product of dehydrohalogenation of each of the following haloalkanes? **(See Examples 7.6, 7.7)**

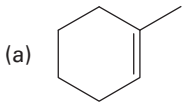
(a) 3-Chloro-3-methylhexane
(b) 3-Bromohexane

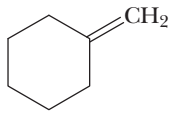
7.39 What haloalkane might you use as a starting material to produce each of the following alkenes in high yield and uncontaminated by isomeric alkenes?

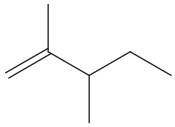
(a) 

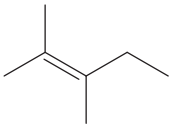
(b) $CH_3CHCH_2CH{=}CH_2$ (CH_3 branch)

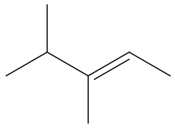
7.40 For each of the following alkenes, draw structural formulas of all chloroalkanes that undergo dehydrohalogenation when treated with KOH to give that alkene as the major product (for some parts, only one chloroalkane gives the desired alkene as the major product; for other parts, two chloroalkanes may work):

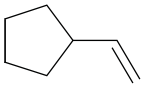
(a) 

(b) 

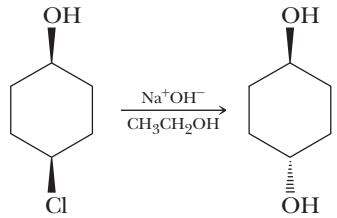
(c) 

(d) 

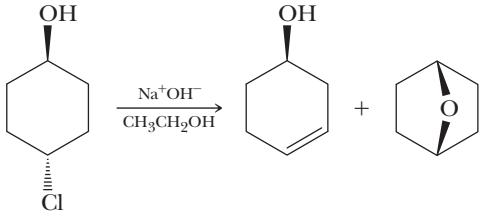
(e) 

(f) 

7.41 When *cis*-4-chlorocyclohexanol is treated with sodium hydroxide in ethanol, it gives only the substitution product *trans*-1,4-cyclohexanediol (1). Under the same experimental conditions, *trans*-4-chlorocyclohexanol gives 3-cyclohexenol (2) and product (3):



cis-4-Chloro-cyclohexanol (1)



trans-4-Chloro-cyclohexanol (2) (3)

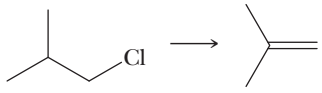
(a) Propose a mechanism for the formation of product (1), and account for its configuration.

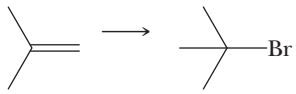
(b) Propose a mechanism for the formation of product (2).

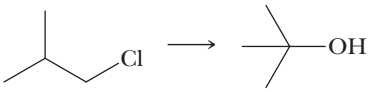
(c) Account for the fact that the product (3) is formed from the *trans* isomer, but not from the *cis* isomer.

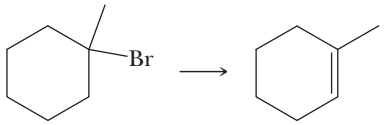
Section 7.9 Synthesis and Predict the Product

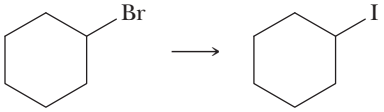
7.42 Show how to convert the given starting material into the desired product (note that some syntheses require only one step, whereas others require two or more steps):

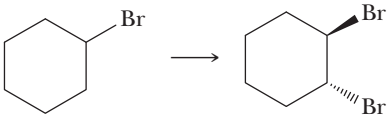
(a) 

(b) 

(c) 

(d) 

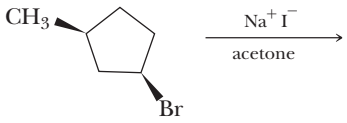
(e) 

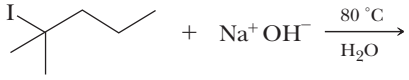
(f) 

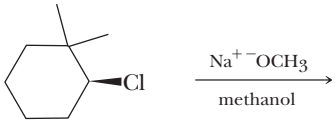
racemic

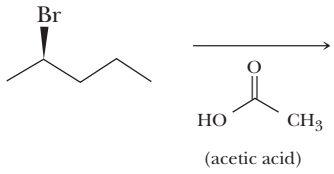
7.43 Complete these reactions by determining the type of reaction and mechanism (S_N1, S_N2, E1, or E2) that they undergo. **(See Example 7.8)**

(a) 

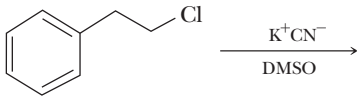
(b) 

(c) 

(d) 

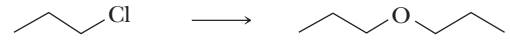
(e) 

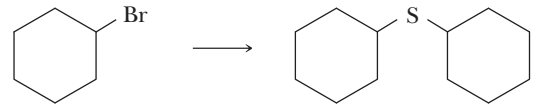
(acetic acid)

(f) 

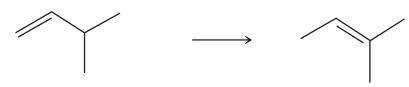
CHEMICAL TRANSFORMATIONS

7.44 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.*

(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

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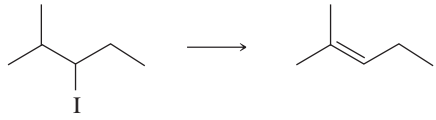
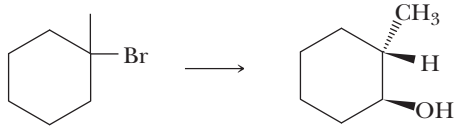
(g) 

(h) 

(i) 

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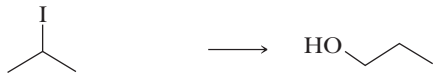
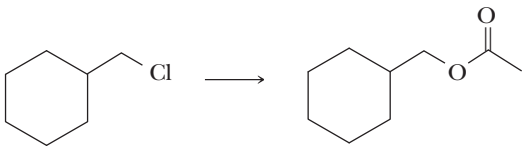
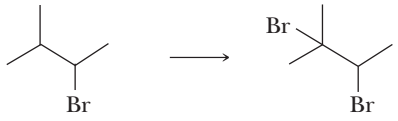
(j) 

(k) 

(l) 

(m) 

(n) 

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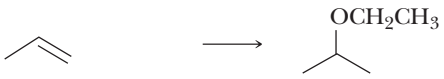
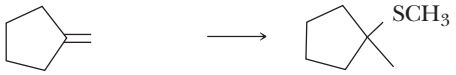
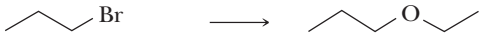
(o) 

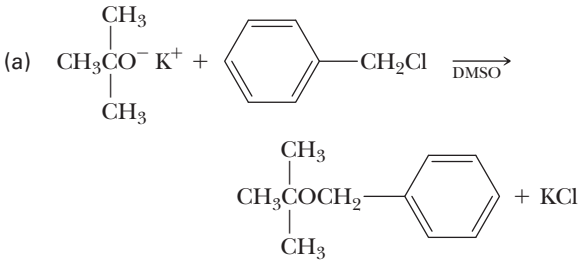
(p) 

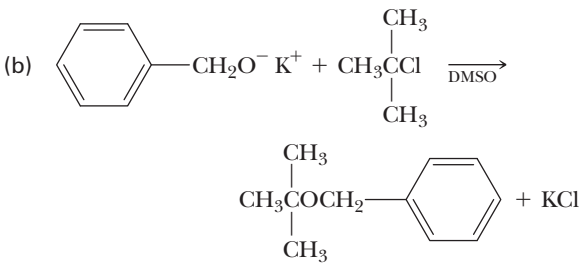
(q) 

(r) 

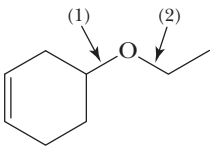
LOOKING AHEAD

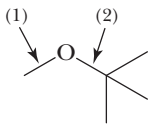
7.45 The Williamson ether synthesis involves treating a haloalkane with a metal alkoxide. Following are two reactions intended to give benzyl *tert*-butyl ether. One reaction gives the ether in good yield, the other does not. Which reaction gives the ether? What is the product of the other reaction, and how do you account for its formation?

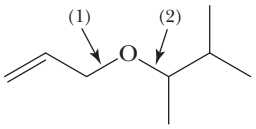
(a) 

(b) 

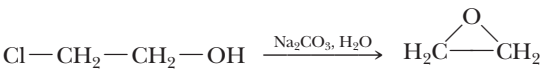
7.46 The following ethers can, in principle, be synthesized by two different combinations of haloalkane or halocycloalkane and metal alkoxide. Show one combination that forms ether bond (1) and another that forms ether bond (2). Which combination gives the higher yield of ether?

(a) 

(b) 

(c) 

7.47 Propose a mechanism for this reaction:

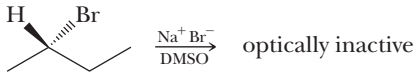


2-Chloroethanol — Ethylene oxide

7.48 An OH group is a poor leaving group, and yet substitution occurs readily in the following reaction.

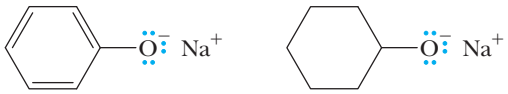
Propose amechanism for this reaction that shows how OH overcomes its limitation of being a poor leaving group.

7.49 Explain why (*S*)-2-bromobutane becomes optically inactive when treated with sodium bromide in DMSO:



optically active

7.50 Explain why phenoxide is a much poorer nucleophile and weaker base than cyclohexoxide:



Sodium phenoxide Sodium cyclohexoxide

7.51 In ethers, each side of the oxygen is essentially an OR group and is thus a poor leaving group. Epoxides are three-membered ring ethers. Explain why an epoxide reacts readily with a nucleophile despite being an ether.

An ether

An epoxide

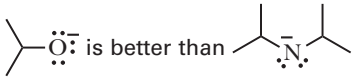
GROUP LEARNING ACTIVITIES

7.52 Discuss and come up with examples of the following:

(a) a negatively charged reagent that is a weak base
(b) a negatively charged reagent that is a poor nucleophile
(c) aside from chloride, bromide, or iodide, a negatively charged reagent that is a good leaving group

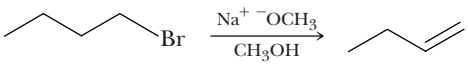
7.53 Discuss reasons why the following statements are true:

(a) although hexane is an aprotic solvent, it is a poor solvent for an S_N2 reaction
(b) $CH_3\ddot{N}\bar{H}$, is a better nucleophile than $CH_3\ddot{O}^-$, but



7.54 Discuss ways that you could speed up the following reactions without changing the products formed.

(a)



(b)