CHAPTER

7

The gases released during volcanic eruptions contain large amounts of organohalides, including chloromethane, chloroform, dichlorodifluoromethane, and many others.

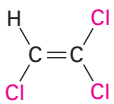
Organohalides: Nucleophilic Substitutions and Eliminations

Now that we've covered the chemistry of hydrocarbons, it's time to start looking at more complex substances that contain elements in addition to just C and H. We'll begin by discussing the chemistry of **organohalides**, compounds that contain one or more halogen atoms.

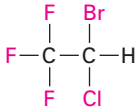
Halogen-substituted organic compounds are widespread in nature, and more than 5000 organohalides have been found in algae and various other marine organisms. Chloromethane, for instance, is released in large amounts by ocean kelp, as well as by forest fires and volcanoes. Halogen-containing compounds also have a vast array of industrial applications, including their use as solvents, inhaled anesthetics, refrigerants, and pesticides. The modern electronics industry, for example, relies on halogenated solvents such as trichloroethylene for cleaning semiconductor chips and other components.

OWL

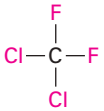
Online homework for this chapter can be assigned in OWL, an online homework assessment tool.



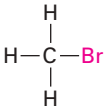
Trichloroethylene (a solvent)



Halothane (an inhaled anesthetic)



Dichlorodifluoromethane (a refrigerant)



Bromomethane (a fumigant)

A large variety of organohalides are known. The halogen might be bonded to an alkynyl group (C≡C—X), a vinylic group (C=C—X), an aromatic ring (Ar—X), or an alkyl group. We'll be concerned in this chapter primarily with **alkyl halides**, compounds with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

WHY THIS CHAPTER?

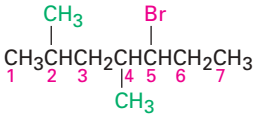
Alkyl halides (R—X) are encountered much less frequently than their oxygen-containing relative alcohols (R—OH), but some of the *kinds* of reactions they undergo—nucleophilic substitutions and eliminations—*are* encountered frequently. Thus, alkyl halide chemistry acts as a relatively simple model for many mechanistically similar but structurally more complex reactions. We'll begin with a look at how to name and prepare alkyl halides, and we'll then make a detailed study of their substitution and elimination reactions—two of the most important and well-studied reaction types in organic chemistry.

7.1 Naming Alkyl Halides

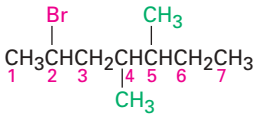
Although commonly called *alkyl halides,* halogen-substituted alkanes are named systematically as *haloalkanes* (Section 2.3), treating the halogen as a substituent on a parent alkane chain. There are three steps.

STEP 1 **Find the longest chain, and name it as the parent**. If a multiple bond is present, the parent chain must contain it.

STEP 2 **Number the carbons of the parent chain beginning at the end nearer the first substituent, whether alkyl or halo**. Assign each substituent a number according to its position on the chain. If there are substituents the same distance from both ends, begin numbering at the end nearer the substituent with alphabetical priority.

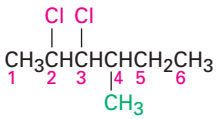


5-Bromo-2,4-dimethylheptane



2-Bromo-4,5-dimethylheptane

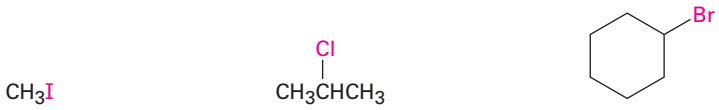
STEP 3 **Write the name**. List all substituents in alphabetical order, and use one of the prefixes *di-*, *tri-*, and so forth if more than one of the same substituent is present.



2,3-Dichloro-4-methylhexane

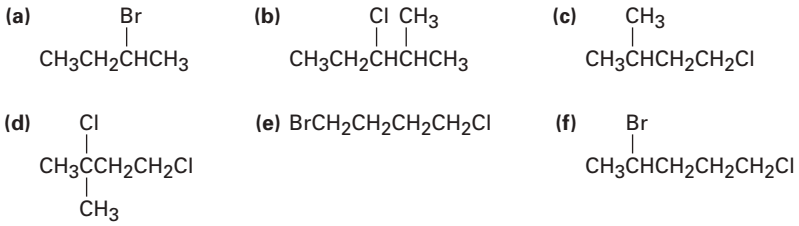
In addition to their systematic names, many simple alkyl halides are also named by identifying first the alkyl group and then the halogen. For example,

CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.



Iodomethane (or methyl iodide) | **2-Chloropropane (or isopropyl chloride)** | **Bromocyclohexane (or cyclohexyl bromide)**

Problem 7.1 Give the IUPAC names of the following alkyl halides:

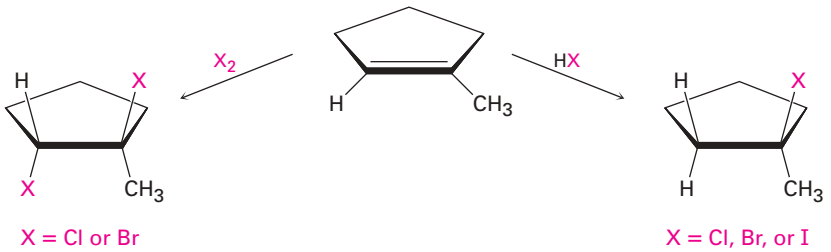


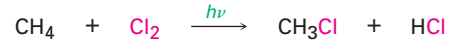
Problem 7.2 Draw structures corresponding to the following names:

(a) 2-Chloro-3,3-dimethylhexane **(b)** 3,3-Dichloro-2-methylhexane
(c) 3-Bromo-3-ethylpentane **(d)** 2-Bromo-5-chloro-3-methylhexane

7.2 Preparing Alkyl Halides

We've already seen several methods for preparing alkyl halides, including the addition reactions of HX and X_2 with alkenes in electrophilic addition reactions (Sections 4.1 and 4.4) and the reaction of an alkane with Cl_2 (Section 2.4).

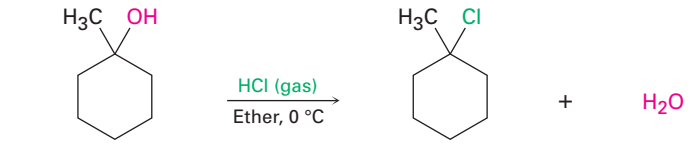




Methane **Chloromethane**

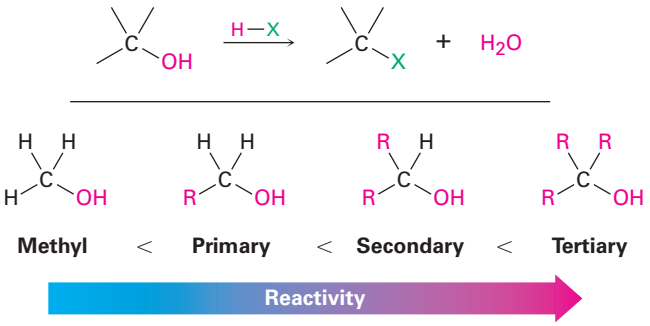
The most generally useful method for preparing alkyl halides is to make them from alcohols, which themselves are easily obtained from carbonyl compounds. The reaction can often be carried out simply by treating the alcohol

with HCl or HBr. 1-Methylcyclohexanol, for example, is converted into 1-chloro-1-methylcyclohexane by treating with HCl.

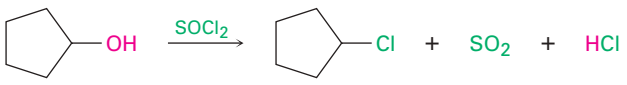


1-Methylcyclohexanol **1-Chloro-1-methylcyclohexane (90%)**

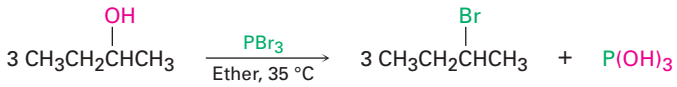
For reasons that will be discussed in Section 7.6, the HX reaction works best with tertiary alcohols. Primary and secondary alcohols react much more slowly.



Primary and secondary alcohols are best converted into alkyl halides by treatment with either thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3). These reactions normally take place in high yield.

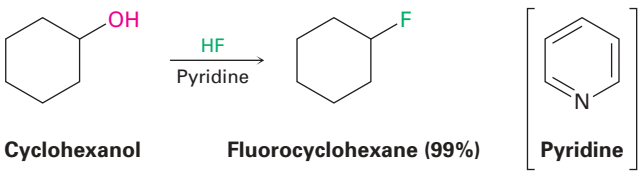


Cyclopentanol **Chlorocyclopentane**



Butan-2-ol **2-Bromobutane (86%)**

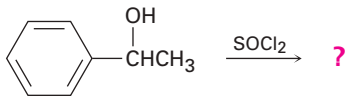
Alkyl fluorides can also be prepared from alcohols. Numerous alternative reagents are used for the reaction, including diethylaminosulfur trifluoride [$(CH_3CH_2)_2NSF_3$] and HF–pyridine, where pyridine is the nitrogen-containing analog of benzene.



Cyclohexanol **Fluorocyclohexane (99%)** **Pyridine**

Worked Example 7.1 **Synthesizing an Alkyl Halide**

Predict the product of the following reaction:

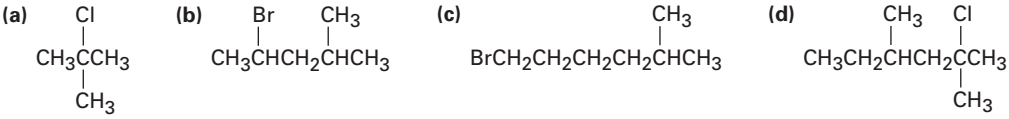


Strategy A big part of learning organic chemistry is remembering reactions. Ask yourself what you know about alcohols, and then recall that alcohols yield alkyl chlorides on treatment with $SOCl_2$.

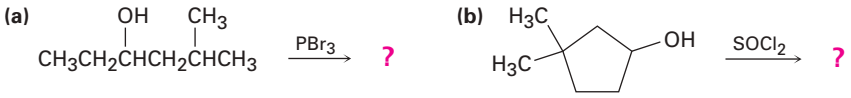
Solution

Problem 7.3 Alkane chlorination can occur at any position in the alkane chain. Draw and name all monochloro products you might obtain from radical chlorination of 3-methylpentane. Which, if any, are chiral?

Problem 7.4 How would you prepare the following alkyl halides from the appropriate alcohols?

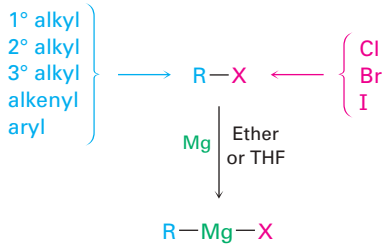


Problem 7.5 Predict the products of the following reactions:

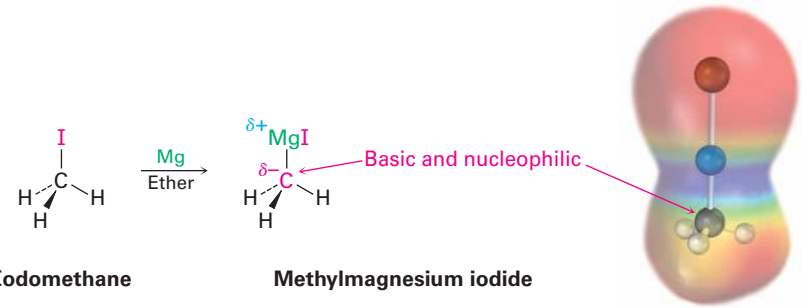


7.3 Reactions of Alkyl Halides: Grignard Reagents

Alkyl halides, RX, react with magnesium metal in ether solvent to yield alkylmagnesium halides, RMgX. The products, called **Grignard reagents** after their discoverer, Victor Grignard, are examples of *organometallic* compounds because they contain a carbon–metal bond. In addition to alkyl halides, alkenyl (vinylic) and aryl (aromatic) halides also react with magnesium to give Grignard reagents. The halogen can be Cl, Br, or I, but not F.



As you might expect from the discussion of electronegativity in Section 1.9, a carbon–magnesium bond is polarized, making the carbon both nucleophilic and basic. An electrostatic potential map of methylmagnesium iodide, for instance, indicates the electron-rich (red) character of the carbon bonded to magnesium.

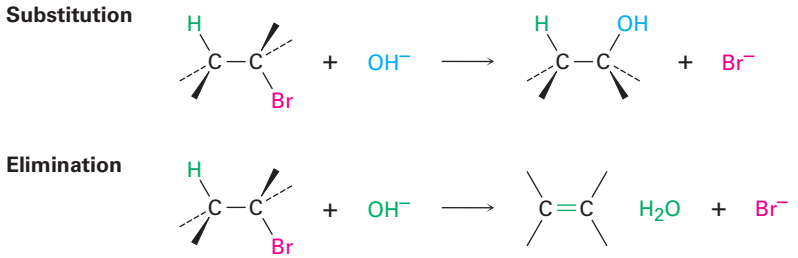


A Grignard reagent is formally the magnesium salt, $R_3C^{-+}MgX$, of a carbon acid, $R_3C—H$, and is thus a carbon anion, or **carbanion**. But because hydrocarbons are such weak acids, carbon anions are very strong bases. Grignard reagents must therefore be protected from atmospheric moisture to prevent their being protonated and destroyed in an acid–base reaction: $R—Mg—X + H_2O \rightarrow R—H + HO—Mg—X$.

Grignard reagents themselves don't occur in living organisms, but they are useful carbon-based nucleophiles in important laboratory reactions, as we'll see in the next chapter. In addition, they act as a simple model for other, more complex carbon-based nucleophiles that *are* important in biological chemistry. We'll see examples in Chapter 17.

7.4 Nucleophilic Substitution Reactions

Because they are electrophiles, alkyl halides do one of two things when they react with nucleophiles/bases, such as hydroxide ion: either they undergo *substitution* of the X group by the nucleophile or *elimination* of HX to yield an alkene.



Let's look first at substitution reactions. The discovery of the nucleophilic substitution reaction of alkyl halides dates back to 1896 when the German chemist Paul Walden discovered that (+)- and (−)-malic acids could be interconverted. When Walden treated (−)-malic acid with PCl_5, he isolated (+)-chlorosuccinic acid. This, on reaction with wet Ag_2O, gave (+)-malic acid. Similarly, reaction of (+)-malic acid with PCl_5 gave (−)-chlorosuccinic acid,

which was converted into (−)-malic acid when treated with wet Ag_2O. The full cycle of reactions reported by Walden is shown in Figure 7.1.

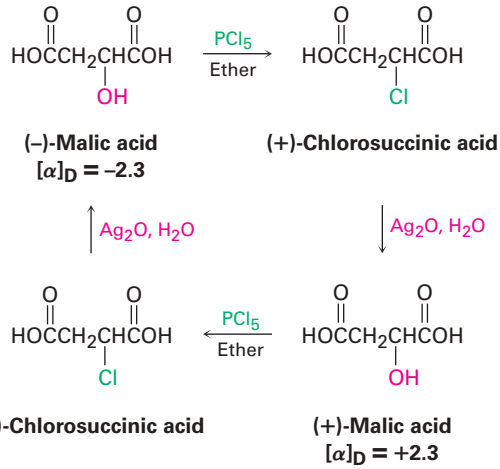
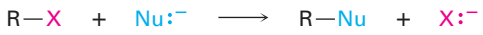


Figure 7.1 Walden's cycle of reactions interconverting (+)- and (−)-malic acids.

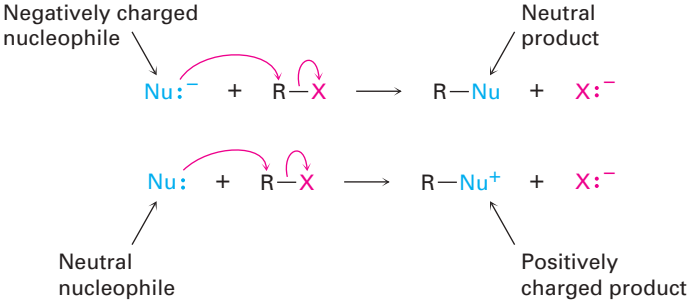
At the time, the results were astonishing. Since (−)-malic acid was converted into (+)-malic acid, *some reactions in the cycle must have occurred with an inversion, or change, in the configuration of the chirality center.* But which ones, and how? Remember from Section 6.5 that you can't tell the configuration of a chirality center from the sign of optical rotation.

Today we refer to the transformations taking place in Walden's cycle as **nucleophilic substitution reactions** because each step involves the substitution of one nucleophile (chloride ion, Cl^-, or hydroxide ion, OH^-) by another. Nucleophilic substitution reactions are one of the most common and versatile reaction types in organic chemistry.

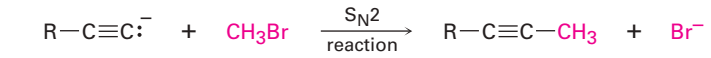


Following the work of Walden, further investigations were undertaken during the 1920s and 1930s to clarify the mechanism of nucleophilic substitution reactions and to find out how inversions of configuration occur. These investigations showed that nucleophilic substitutions occur by two major pathways, named the S_N1 *reaction* and the S_N2 *reaction*. In both cases, the "S_N" part of the name stands for *substitution, nucleophilic.* The meanings of *1* and *2* are discussed in the next two sections.

Regardless of mechanism, the overall change during all nucleophilic substitution reactions is the same: a *nucleophile* (symbolized Nu**:** or Nu**:**$^-$) reacts with a *substrate* R—X and substitutes for a *leaving group* X**:**$^-$ to yield the product R—Nu. If the nucleophile is neutral (Nu**:**), then the product is positively charged to maintain charge conservation. If the nucleophile is negatively charged (Nu**:**$^-$), the product is neutral.



A wide array of substances can be prepared using nucleophilic substitution reactions. In fact, we've already seen examples in previous chapters. The reaction of an acetylide anion with an alkyl halide (Section 4.11), for instance, is an S_N2 reaction in which the acetylide nucleophile replaces halide. Table 7.1 lists other examples.



An acetylide anion

Table 7.1 Some Nucleophilic Substitution Reactions with Bromomethane

$$Nu:^- + CH_3Br \rightarrow CH_3Nu + Br^-$$

Nucleophile		Product	
Formula	**Name**	**Formula**	**Name**
H_2O	Water	$CH_3OH_2^+$	Methylhydronium ion
$CH_3CO_2^-$	Acetate	$CH_3CO_2CH_3$	Methyl acetate
NH_3	Ammonia	$CH_3NH_3^+$	Methylammonium ion
Cl^-	Chloride	CH_3Cl	Chloromethane
HO^-	Hydroxide	CH_3OH	Methanol
CH_3O^-	Methoxide	CH_3OCH_3	Dimethyl ether
I^-	Iodide	CH_3I	Iodomethane
^-CN	Cyanide	CH_3CN	Acetonitrile
HS^-	Hydrosulfide	CH_3SH	Methanethiol

Worked Example 7.2

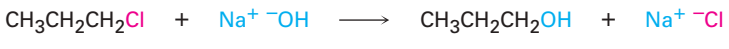
Predicting the Product of a Substitution Reaction

What is the substitution product from reaction of 1-chloropropane with NaOH?

Strategy

Write the two reactants, and identify the nucleophile (in this instance, OH^-) and the leaving group (in this instance, Cl^-). Then, replace the –Cl group by –OH and write the complete equation.

Solution



1-Chloropropane **Propan-1-ol**

Worked Example 7.3

Using a Substitution Reaction in a Synthesis

How would you prepare propane-1-thiol, $CH_3CH_2CH_2SH$, using a nucleophilic substitution reaction?

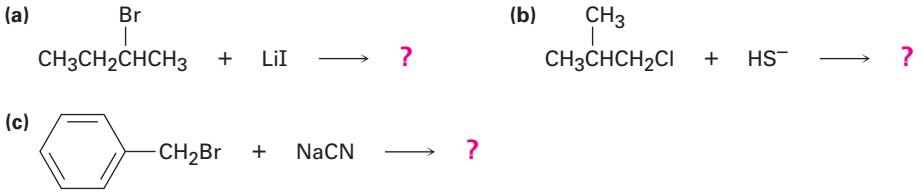
Strategy

Identify the group in the product that is introduced by nucleophilic substitution. In this case, the product contains an –SH group, so it might be prepared by reaction of SH^- (hydrosulfide ion) with an alkyl halide such as 1-bromopropane.

Solution

1-Bromopropane **Propane-1-thiol**

Problem 7.6 What substitution products would you expect to obtain from the following reactions?



Problem 7.7 How might you prepare the following substances by using nucleophilic substitution reactions?

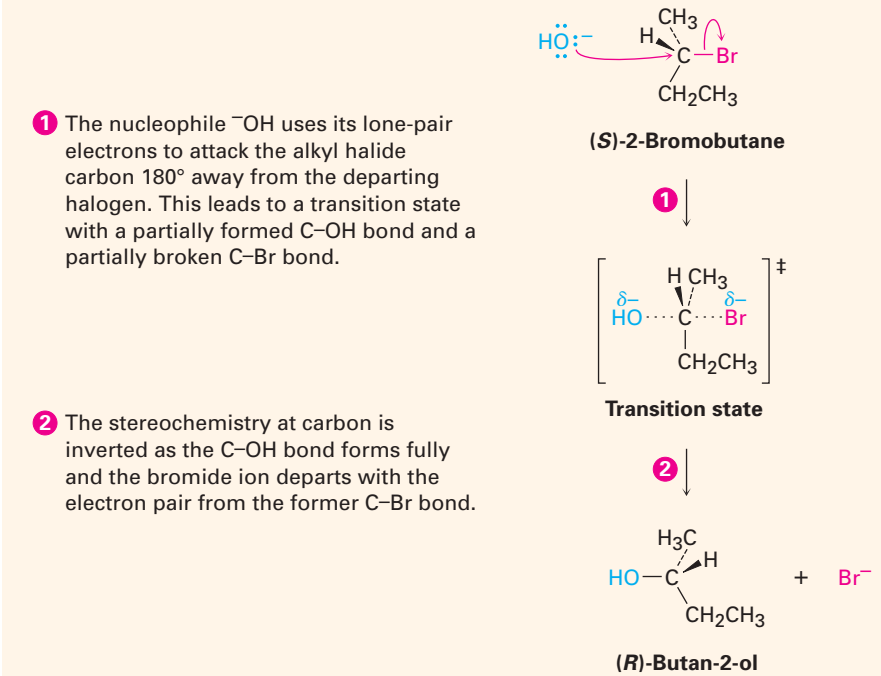
(a) $CH_3CH_2CH_2CH_2OH$ **(b)** $(CH_3)_2CHCH_2CH_2N_3$

7.5 Substitutions: The S_N2 Reaction

An **S_N2 reaction** takes place in a single step without intermediates when the entering nucleophile approaches the substrate from a direction 180° away from the leaving group. As the nucleophile comes in on one side of the molecule, an electron pair on the nucleophile Nu:$^-$ forces out the leaving group X:$^-$, which departs from the other side of the molecule and takes with it the electron pair from the C–X bond. In the transition state for the reaction, the new Nu–C bond is partially forming at the same time the old C–X bond is partially breaking, and the negative charge is shared by both the incoming nucleophile and the outgoing leaving group. The mechanism is shown in Figure 7.2 for the reaction of OH^- with (*S*)-2-bromobutane.

MECHANISM

Figure 7.2 The mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.



Let's see what evidence there is for this mechanism and what the chemical consequences are.

Rates of S_N2 Reactions

In every chemical reaction, there is a direct relationship between the rate at which the reaction occurs and the concentrations of the reactants. The S_N2 reaction of CH_3Br with OH^- to yield CH_3OH, for instance, takes place in a single step when substrate and nucleophile collide and react. At a given concentration of reactants, the reaction takes place at a certain rate. If we double the concentration of OH^-, the frequency of collision between the two reactants doubles and we find that the reaction rate also doubles. Similarly, if we double the concentration of CH_3Br, the reaction rate doubles. Thus, the origin of the "2" in S_N2: S_N2 reactions are said to be **bimolecular** because the rate of the reaction depends on the concentrations of *two* substances—alkyl halide and nucleophile.

Problem 7.8 What effects would the following changes have on the rate of the S_N2 reaction between CH_3I and sodium acetate?

(a) The CH_3I concentration is tripled.
(b) Both CH_3I and CH_3CO_2Na concentrations are doubled.

Stereochemistry of S_N2 Reactions

Look carefully at the mechanism of the S_N2 reaction shown in Figure 7.2. As the incoming nucleophile attacks the substrate and begins pushing out the leaving group on the opposite side, the configuration of the molecule *inverts* (Figure 7.3). (*S*)-2-Bromobutane gives (*R*)-butan-2-ol, for example, by an inversion of configuration that occurs through a planar transition state.

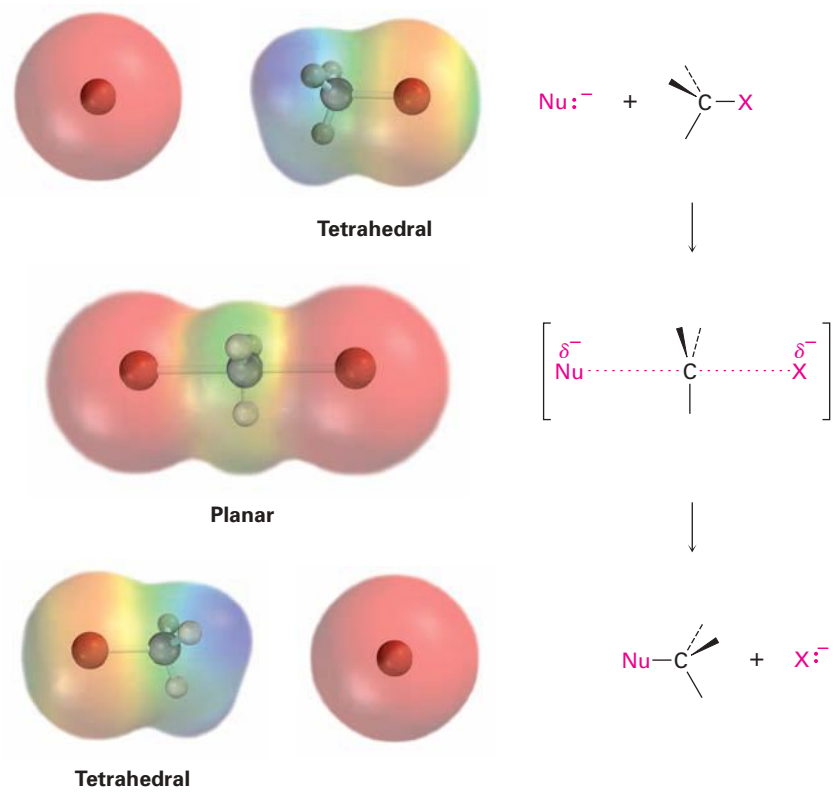


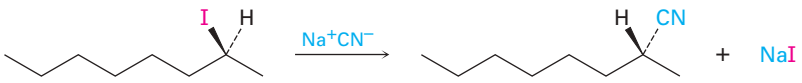
Figure 7.3 The transition state of the S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups. Electrostatic potential maps show that the negative charge (red) is shared by the incoming nucleophile and the leaving group in the transition state. (The dotted red lines indicate partial bonding.)

Worked Example 7.4 Predicting the Product of a Substitution Reaction

What product would you expect to obtain from the S_N2 reaction of (*S*)-2-iodooctane with sodium cyanide, NaCN?

Strategy Identify the nucleophile (cyanide ion) and the leaving group (iodide ion). Then carry out the substitution, inverting the configuration at the chirality center. (*S*)-2-Iodooctane reacts with CN^- to yield (*R*)-2-methyloctanenitrile.

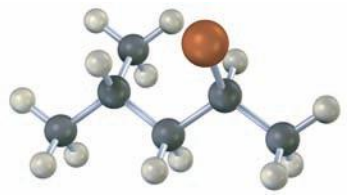
Solution



(*S*)-2-Iodooctane **(*R*)-2-Methyloctanenitrile**

Problem 7.9 What product would you expect to obtain from the S_N2 reaction of (*S*)-2-bromohexane with sodium acetate, CH_3CO_2Na? Show the stereochemistry of both product and reactant.

Problem 7.10 Assign configuration to the following substance, and draw the structure of the product that would result on nucleophilic substitution reaction with HS^- (reddish brown = Br):



Steric Effects in S_N2 Reactions

The ease with which a nucleophile can approach a substrate to carry out an S_N2 reaction depends on steric accessibility to the halide-bearing carbon. Bulky substrates, in which the halide-bearing carbon atom is difficult to approach, react much more slowly than those in which the carbon is more accessible (Figure 7.4).

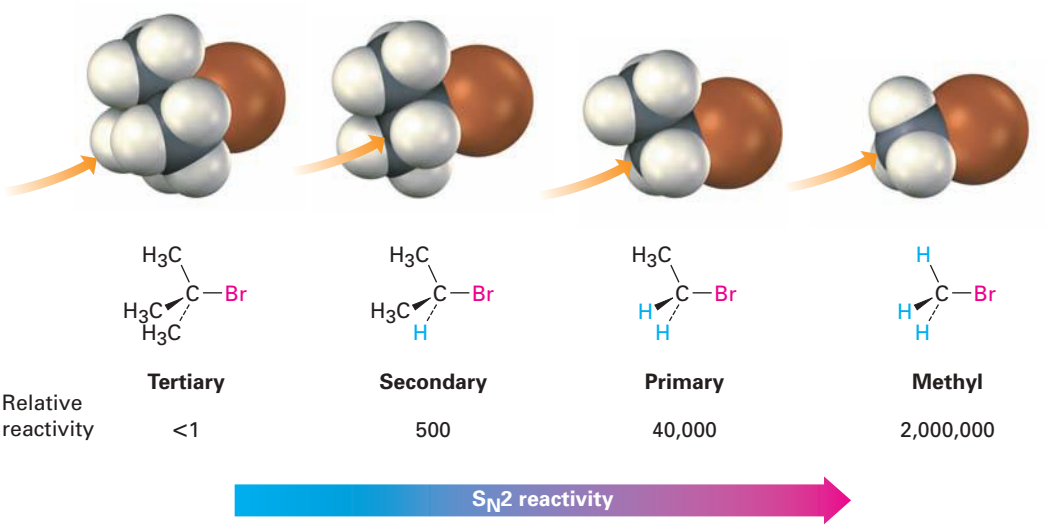
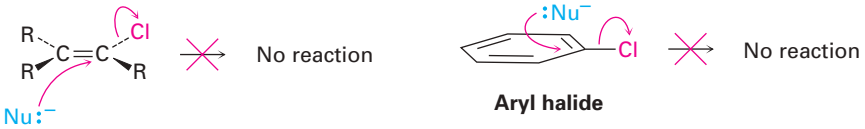


Figure 7.4 Steric hindrance to the S_N2 reaction. The carbon atom in bromomethane is readily accessible, resulting in a fast S_N2 reaction, but the carbon atoms in bromoethane (primary), 2-bromopropane (secondary), and 2-bromo-2-methylpropane (tertiary) are successively less accessible, resulting in successively slower S_N2 reactions.

Methyl halides (CH_3X) are the most reactive substrates, followed by primary alkyl halides (RCH_2—X) such as ethyl and propyl. Alkyl branching next to the leaving group slows the reaction greatly for secondary halides (R_2CH—X), and further branching effectively halts the reaction for tertiary halides (R_3C—X).

Vinylic (R_2C=CRX) and aryl (Ar—X) halides are not shown on this reactivity list because they are completely unreactive toward S_N2 displacements. This lack of reactivity is due to steric hindrance: the incoming nucleophile would have to burrow through part of the molecule to carry out a displacement.



Vinylic halide **Aryl halide**

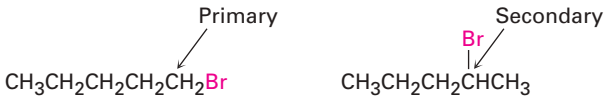
Worked Example 7.5 Predicting the Rates of Substitution Reactions

Which would you expect to be faster, the S_N2 reaction of OH^- ion with 1-bromopentane or with 2-bromopentane?

Strategy

Decide which substrate is less hindered. Since 1-bromopentane is a 1° halide and 2-bromopentane is a 2° halide, reaction with the less hindered 1-bromopentane is faster.

Solution



1-Bromopentane **2-Bromopentane**

Problem 7.11 Which of the following S_N2 reactions would you expect to be faster?

(a) Reaction of CN^- (cyanide ion) with $CH_3CH(Br)CH_3$ or with $CH_3CH_2CH_2Br$?

(b) Reaction of I^- with $(CH_3)_2CHCH_2Cl$ or with H_2C=CHCl?

The Leaving Group in S_N2 Reactions

Another variable that can affect the S_N2 reaction is the nature of the leaving group displaced by the attacking nucleophile. Because the leaving group is expelled with a negative charge in most S_N2 reactions, the best leaving groups are those that give the most stable anions (anions of strong acids). A halide ion (I^-, Br^-, or Cl^-) is the most common leaving group, although others are also possible. Anions such as F^-, OH^-, OR^-, and NH_2^- are rarely found as leaving groups.

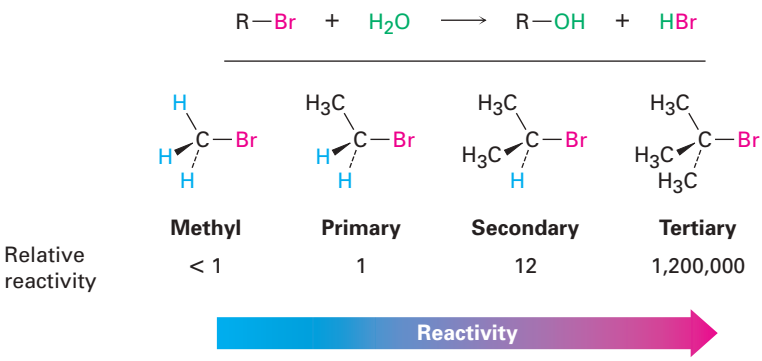
	OH^-, NH_2^-, OR^-	F^-	Cl^-	Br^-	I^-
Relative reactivity	<<1	1	200	10,000	30,000

Leaving group reactivity

Problem 7.12 Rank the following compounds in order of their expected reactivity toward S_N2 reaction: CH_3I, CH_3F, CH_3Br.

7.6 Substitutions: The S_N1 Reaction

Most nucleophilic substitutions take place by the S_N2 pathway just discussed, but an alternative called the **S_N1 reaction** can also occur. In general, S_N1 reactions take place only on *tertiary* substrates and only under neutral or acidic conditions in a hydroxylic solvent such as water or alcohol. We saw in Section 7.2, for example, that alkyl halides can be prepared from alcohols by treatment with HCl or HBr. Tertiary alcohols react rapidly, but primary and secondary alcohols react far more slowly.



What's going on here? Clearly, a nucleophilic substitution reaction is taking place—a halogen is replacing a hydroxyl group—yet the reactivity order 3° > 2° > 1° is backward from the normal S_N2 order. Furthermore, an –OH group is being replaced, although we said in the previous section that OH^- is a poor leaving group. These reactions can't be taking place by the S_N2 mechanism we've been discussing but are instead taking place by the S_N1 mechanism shown in Figure 7.5.

Unlike what occurs in an S_N2 reaction, where the leaving group is displaced at the same time that the incoming nucleophile approaches, an S_N1 reaction occurs by spontaneous loss of the leaving group *before* the incoming nucleophile approaches. Loss of the leaving group gives a carbocation intermediate, which then reacts with the nucleophile in a second step to yield the substitution product.

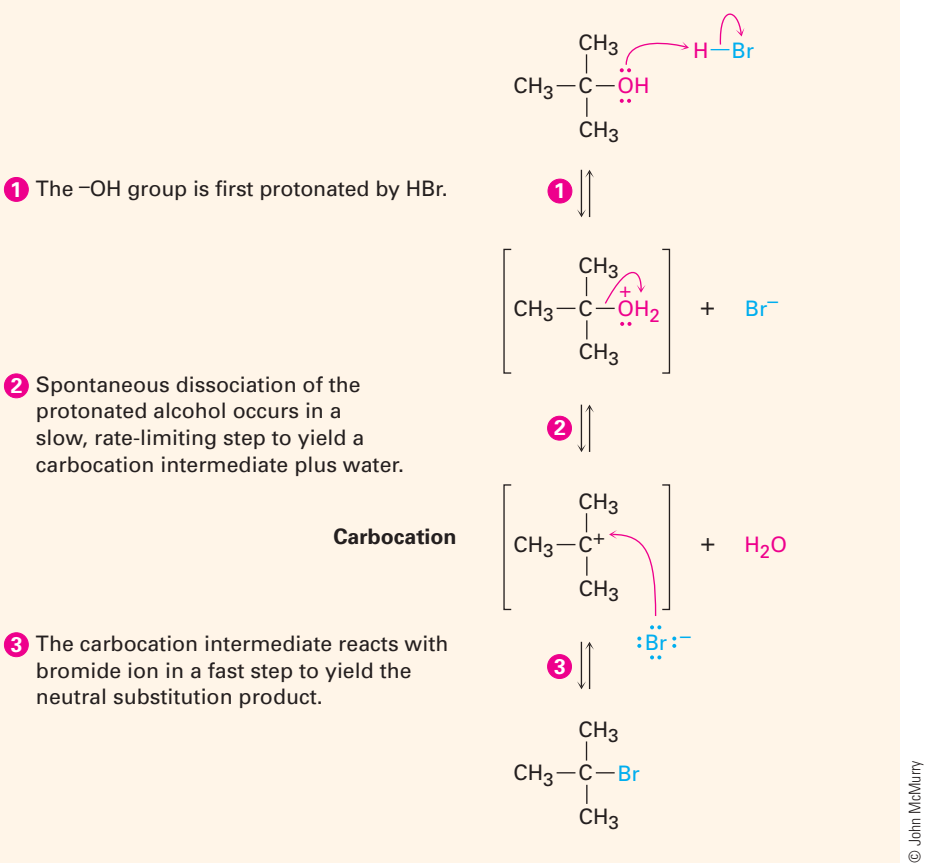
This two-step mechanism explains why tertiary alcohols react with HBr so much more rapidly than primary or secondary ones do: S_N1 reactions can occur only when stable carbocation intermediates are formed. The more stable the carbocation intermediate, the faster the S_N1 reaction. Thus, the reactivity order of alcohols with HBr is the same as the stability order of carbocations (Section 4.2).

Rates of S_N1 Reactions

Unlike an S_N2 reaction, whose rate depends on the concentrations of both substrate and nucleophile, the rate of an S_N1 reaction depends only on the concentration of the substrate and is independent of the nucleophile concentration. Thus, the origin of the "1" in S_N1: S_N1 reactions are **unimolecular** because the rate of the reaction depends on the concentration of only *one* substance—the substrate. The observation that S_N1 reactions are unimolecular means that the substrate must undergo a spontaneous reaction without involvement of the nucleophile, exactly what the mechanism shown in Figure 7.5 accounts for.

MECHANISM

Figure 7.5 The mechanism of the S_N1 reaction of *tert*-butyl alcohol with HBr to yield an alkyl halide. Neutral water is the leaving group.



Problem 7.13 What effect would the following changes have on the rate of the S_N1 reaction of *tert*-butyl alcohol with HBr?

(a) The HBr concentration is tripled.
(b) The HBr concentration is halved, and the *tert*-butyl alcohol concentration is doubled.

Stereochemistry of S_N1 Reactions

Because an S_N1 reaction occurs through a carbocation intermediate, as shown in Figure 7.5, its stereochemistry is different from that of an S_N2 reaction. Carbocations, as we've seen, are planar, sp^2-hybridized, and achiral. The positively charged carbon can therefore react with a nucleophile equally well from either side, leading to a 50:50 (racemic) mixture of enantiomers (Figure 7.6). In other words, if we carry out an S_N1 reaction on a single enantiomer of a chiral substrate and go through an achiral carbocation intermediate, the molecule momentarily loses its chirality so the product is optically inactive.

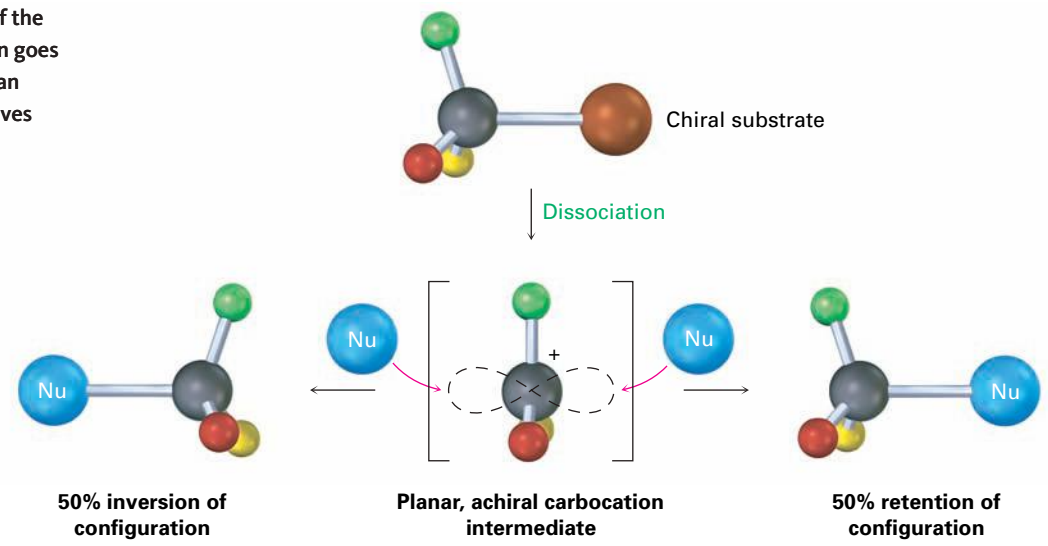
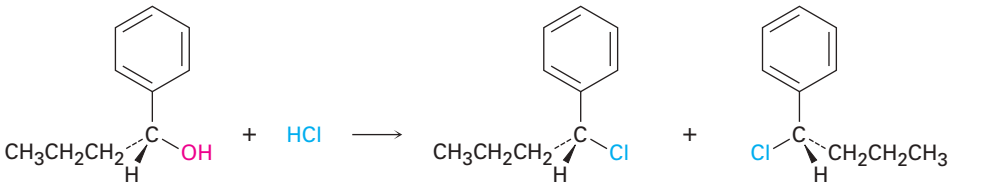


Figure 7.6 A Stereochemistry of the S_N1 reaction. Because the reaction goes through an achiral intermediate, an enantiomerically pure reactant gives a racemic product.

An example of an S_N1 reaction on a chiral substrate occurs on treatment of (*R*)-1-phenylbutan-1-ol with HCl: a racemic alkyl chloride product is formed.



(*R*)-Phenylbutan-1-ol

(*R*)-1-Phenyl-1-chlorobutane (50%, retention)

(*S*)-1-Phenyl-1-chlorobutane (50%, inversion)

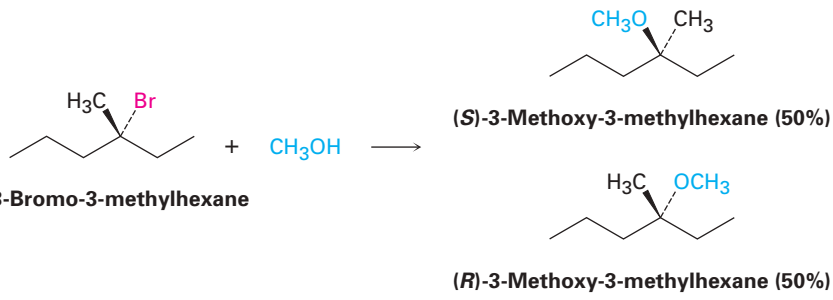
Worked Example 7.6

Predicting the Stereochemistry of a Substitution Reaction

What stereochemistry would you expect for the S_N1 reaction of (*R*)-3-bromo-3-methylhexane with methanol to yield 3-methoxy-3-methylhexane?

Strategy First draw the starting alkyl halide, showing its correct stereochemistry. Then replace the –Br with a methoxy group ($-OCH_3$) to give the racemic product.

Solution



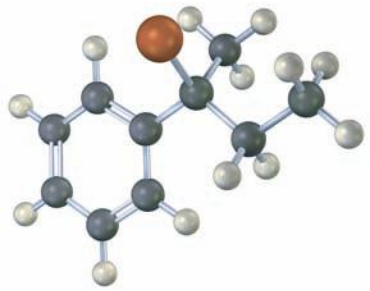
(*R*)-3-Bromo-3-methylhexane

(*S*)-3-Methoxy-3-methylhexane (50%)

(*R*)-3-Methoxy-3-methylhexane (50%)

Problem 7.14 What product would you expect from the S_N1 reaction of (*S*)-3-methyloctan-3-ol [(*S*)-3-hydroxy-3-methyloctane] with HBr? Show the stereochemistry of both starting material and product.

Problem 7.15 Assign configuration to the following substrate, and show the stereochemistry and identity of the product you would obtain by S_N1 reaction with H_2O (reddish brown = Br):



The Leaving Group in S_N1 Reactions

The best leaving groups in S_N1 reactions are those that give the most stable anions, just as in S_N2 reactions. Note that if an S_N1 reaction is carried out under acidic conditions, as occurs when a tertiary alcohol reacts with HX to yield an alkyl halide (Figure 7.5), neutral water is the leaving group. The S_N1 reactivity order of leaving groups is

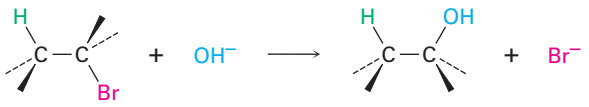
$$HO^- < Cl^- < Br^- < I^- \approx H_2O$$

Leaving group reactivity

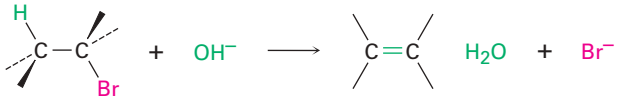
7.7 Eliminations: The E2 Reaction

Thus far, we've looked only at substitution reactions, but in fact two kinds of reactions can happen when a nucleophile/base reacts with an alkyl halide. The nucleophile/base can either substitute for the halide in an S_N1 or S_N2 reaction, or it can cause elimination of HX, leading to formation of an alkene.

Substitution



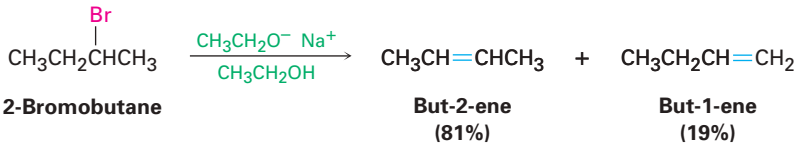
Elimination



The elimination of HX from an alkyl halide is a very useful method for preparing alkenes, but the topic is complex for several reasons. One complication is the problem of regiochemistry. What products result by loss of HX from an unsymmetrical halide? In fact, elimination reactions almost always give mixtures of alkene products, and the best we can usually do is to predict which will be the major product.

According to **Zaitsev's rule**, a predictive guideline formulated in 1875 by the Russian chemist Alexander Zaitsev, base-induced elimination reactions generally give the more highly substituted alkene product—that is, the alkene with the larger number of alkyl substituents on the double bond. Treatment of 2-bromobutane with KOH in ethanol, for instance, gives primarily but-2-ene (disubstituted; two alkyl group substituents on the double-bond

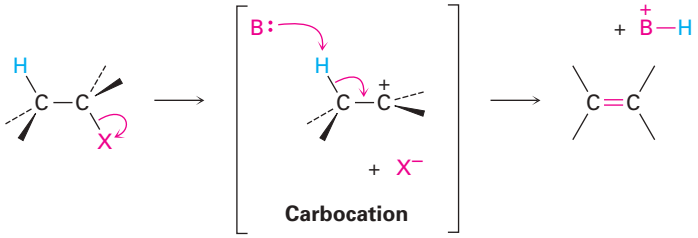
carbons) rather than but-1-ene (monosubstituted; one alkyl group substituent on the double-bond carbons).



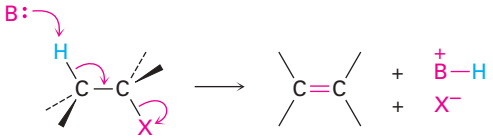
ZAITSEV'S RULE In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.

A second complication is that eliminations can take place by several different mechanisms, just as substitutions can. We'll consider the three most common mechanisms—the E1, E2, and E1cB reactions—which differ in the timing of C–H and C–X bond-breaking. In the E1 reaction, the C–X bond breaks first to give a carbocation intermediate that undergoes subsequent base abstraction of H^+. In the E2 reaction, base-induced C–H bond cleavage is simultaneous with C–X bond cleavage, giving the alkene in a single step. In the E1cB reaction (cB for "conjugate base"), base abstraction of the proton occurs first, giving a carbanion ($R:^-$) intermediate that loses X^- in a subsequent step. All three mechanisms occur frequently in the laboratory, but the E1cB mechanism predominates in biological pathways.

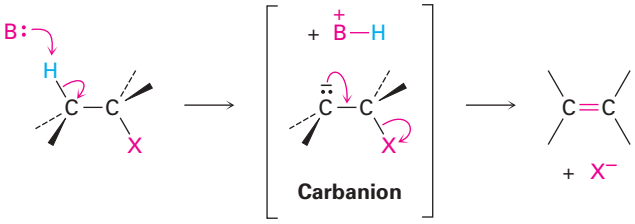
E1 Reaction: C–X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.



E2 Reaction: C–H and C–X bonds break simultaneously, giving the alkene in a single step without intermediates.



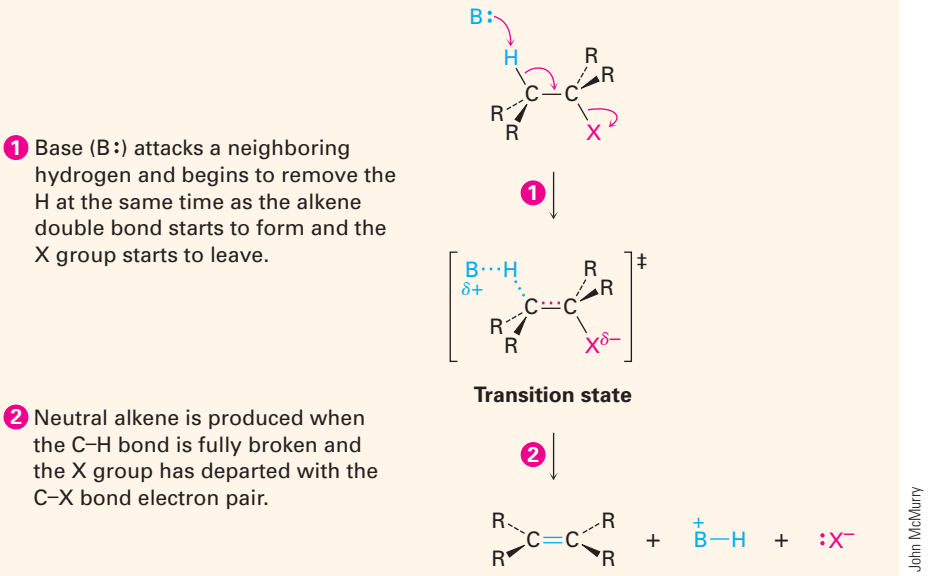
E1cB Reaction: C–H bond breaks first, giving a carbanion intermediate that loses X^- to form the alkene.



Let's look first at the most common elimination pathway—the **E2 reaction** (for *elimination, bimolecular*). The process takes place when an alkyl halide is treated with a strong base, such as hydroxide ion or alkoxide ion (RO^-), and occurs by the mechanism shown in Figure 7.7.

MECHANISM

Figure 7.7 Mechanism of the E2 reaction. The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving. Red dotted lines indicate partial bonding in the transition state.



Like the S_N2 reaction discussed in Section 7.5, the E2 reaction takes place in one step without intermediates. As the attacking base begins to abstract H^+ from a carbon atom next to the leaving group, the C–H and C–X bonds begin to break and the C=C double bond begins to form. When the leaving group departs, it takes with it the two electrons from the former C–X bond.

Worked Example 7.7

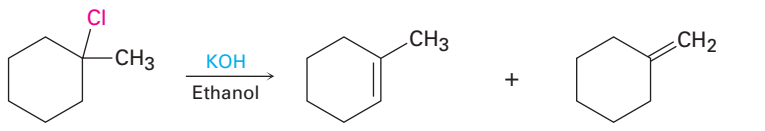
Predicting the Product of an Elimination Reaction

What product would you expect from reaction of 1-chloro-1-methylcyclohexane with KOH in ethanol?

Strategy

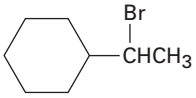
Treatment of an alkyl halide with a strong base such as KOH yields an alkene. To find the products in a specific case, draw the structure of the reactant and locate the hydrogen atoms on neighboring carbons. Then generate the potential alkene products by removing HX in as many ways as possible. The major product will be the one that has the most highly substituted double bond—in this case, 1-methylcyclohexene.

Solution

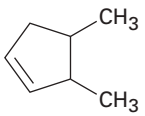


1-Chloro-1-methylcyclohexane | 1-Methylcyclohexene (major) | Methylenecyclohexane (minor)

Problem 7.16 Ignoring double-bond stereochemistry, what products would you expect from elimination reactions of the following alkyl halides?

(a) $CH_3CH_2CH(Br)CHCH_3$ (b) $CH_3CHCH_2-C(Cl)(CH_3)-CHCH_3$ (with CH_3 below) (c) 

Problem 7.17 What alkyl halides might the following alkenes have been made from?

(a) $CH_3CHCH_2CH_2CHCH{=}CH_2$ (with CH_3 groups) (b) 

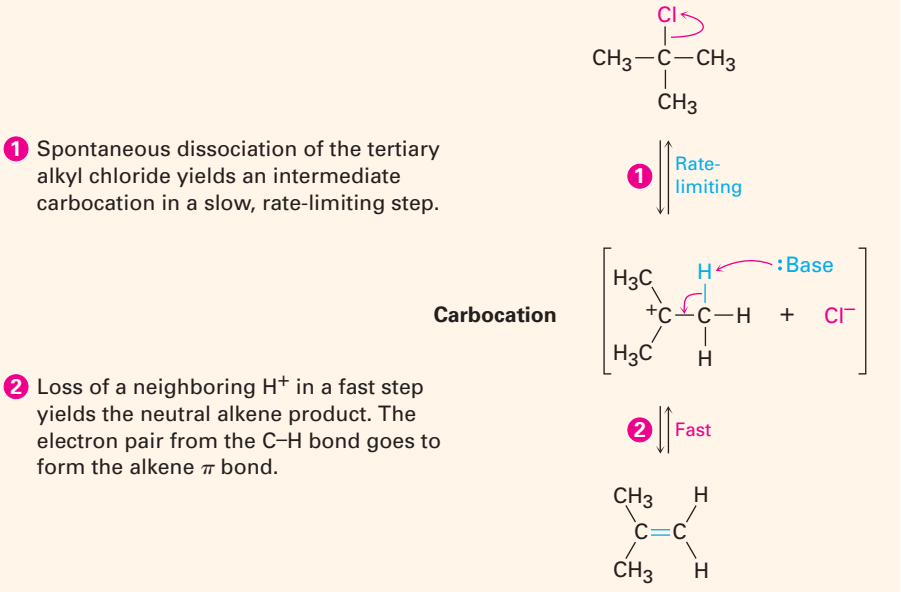
7.8 Eliminations: The E1 and E1cB Reactions

The E1 Reaction

Just as the E2 reaction is analogous to the S_N2 reaction, the S_N1 reaction has a close analog called the **E1 reaction** (for *elimination, unimolecular*). The E1 mechanism is shown in Figure 7.8 for the elimination of HCl from 2-chloro-2-methylpropane.

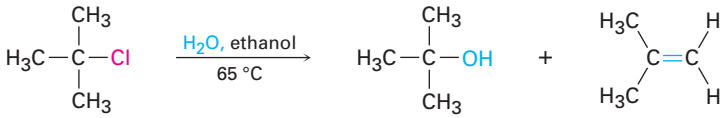
MECHANISM

Figure 7.8 Mechanism of the E1 reaction. Two steps are involved, and a carbocation intermediate is present.



E1 eliminations begin with the same unimolecular dissociation to give a carbocation that we saw in the S_N1 reaction, but the dissociation is followed by loss of H^+ from the adjacent carbon rather than by substitution. In fact, the E1 and S_N1 reactions normally occur together whenever an alkyl halide is treated in a hydroxylic solvent with a nonbasic nucleophile. Thus, the best E1 substrates are also the best S_N1 substrates, and mixtures of substitution and elimination products are usually obtained. For example, when

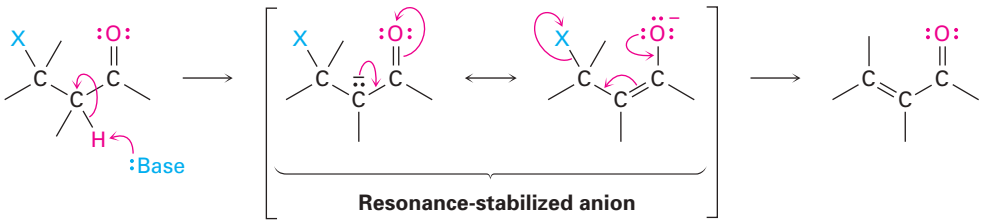
2-chloro-2-methylpropane is warmed to 65 °C in 80% aqueous ethanol, a 64:36 mixture of 2-methylpropan-2-ol (S_N1) and 2-methylpropene (E1) results.



2-Chloro-2-methylpropane — **2-Methylpropan-2-ol (64%)** — **2-Methylpropene (36%)**

The E1cB Reaction

In contrast to the E1 reaction, which involves a carbocation intermediate, the **E1cB reaction** takes place through a *carbanion* intermediate. Base-induced abstraction of a proton gives an anion, which immediately expels a leaving group on the adjacent carbon. The reaction is particularly common in substrates that have a poor leaving group, such as –OH, two carbons removed from a carbonyl group, HO—C—CH—C=O. The poor leaving group disfavors the alternative E1 and E2 possibilities, and the carbonyl group makes the adjacent hydrogen unusually acidic by resonance stabilization of the anion intermediate. We'll look at this acidifying effect of a carbonyl group in Section 11.4. Note that the carbon–carbon double bond in the product is conjugated to the carbonyl, C=C—C=O, a situation similar to that in conjugated dienes (Section 4.8).



Problem 7.18 What effect on the rate of an E1 reaction of 2-chloro-2-methylpropane would you expect if the concentration of the alkyl halide were tripled?

7.9 A Summary of Reactivity: S_N1, S_N2, E1, E1cB, and E2

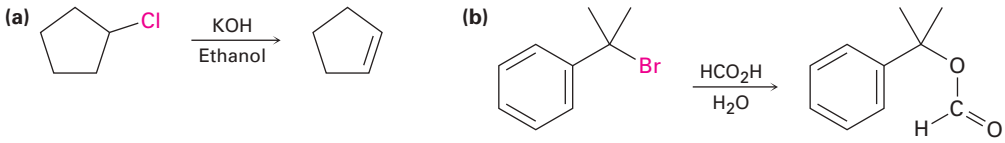
Now that we've seen five different kinds of nucleophilic substitution/elimination reactions, you may be wondering how to predict what will take place in any given case. Will substitution or elimination occur? Will the reaction be unimolecular or bimolecular? There are no rigid answers to these questions, but it's possible to recognize some trends and make some generalizations.

- **Primary alkyl halide (RCH_2X)** S_N2 substitution occurs if a nucleophile such as I^-, Br^-, RS^-, NH_3, or CN^-, is used; E2 elimination occurs if a strong base such as OH^- or an alkoxide ion (RO^-) is used; and E1cB elimination occurs if the leaving group is two carbons away from a carbonyl group (HO—C—CH—C=O).
- **Secondary alkyl halide (R_2CHX)** S_N2 substitution predominates if a weakly basic nucleophile is used; E2 elimination predominates if a strong base is used; and E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group (HO—C—CH—C=O).

- **Tertiary alkyl halide (R_3CX)** E2 elimination occurs when a base is used, but S_N1 substitution and E1 elimination occur together under neutral or acidic conditions. E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group (HO—C—CH—C=O).

Worked Example 7.8 Predicting the Mechanism of a Reaction

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2:



Strategy Look to see whether the substrate is primary, secondary, or tertiary, and determine whether substitution or elimination has occurred. Then apply the generalizations summarized above.

Solution

(a) The substrate is a secondary alkyl halide, a strong base is used, and an elimination has occurred. This is an E2 reaction.

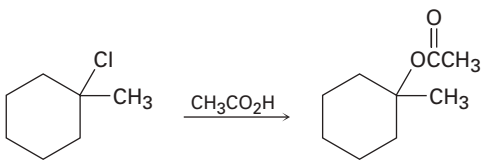
(b) The substrate is a tertiary halide, an acidic solvent is used, and a substitution has occurred. This is an S_N1 reaction.

Problem 7.19 Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2:

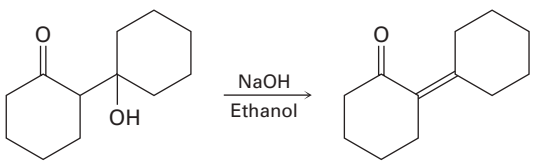
(a) $CH_3CH_2CH_2CH_2Br \xrightarrow[\text{Ether}]{NaN_3} CH_3CH_2CH_2CH_2N{=}N{=}N$

(b) $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[\text{Ethanol}]{KOH} CH_3CH_2CH{=}CHCH_3$

(c)



(d)

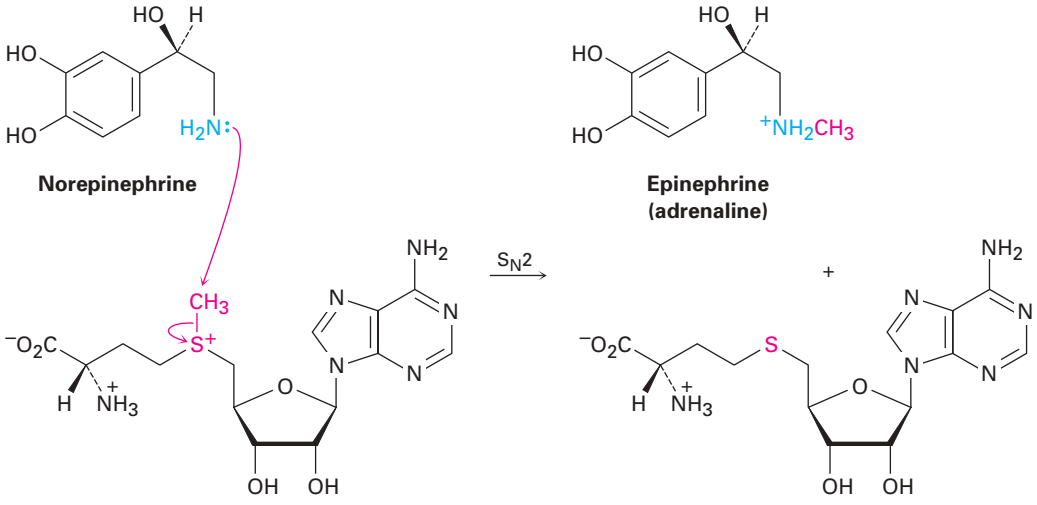


7.10 Substitution and Elimination Reactions in Living Organisms

All chemistry, whether carried out in flasks by chemists or in cells by living organisms, follows the same rules. Biological reactions therefore occur by the same addition, substitution, elimination, and rearrangement mechanisms

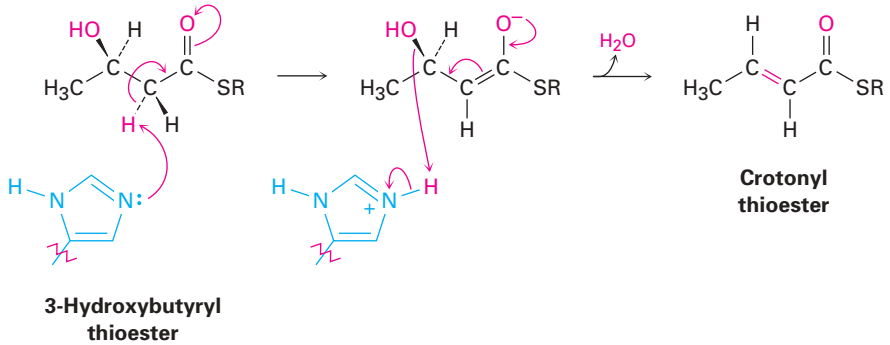
encountered in laboratory reactions. Both S_N1 and S_N2 reactions, for instance, are well-known in biological chemistry.

Among the most common biological substitution reactions is *methylation,* the transfer of a $-CH_3$ group from an electrophilic donor to a nucleophile. A laboratory chemist might choose CH_3I for such a reaction, but living organisms use the complex molecule *S*-adenosylmethionine (abbreviated SAM) as the biological methyl donor. Because the sulfur atom in *S*-adenosylmethionine has a positive charge (a *sulfonium* ion, R_3S^+), it is a highly reactive leaving group for S_N2 displacements on the methyl carbon. In the biosynthesis of epinephrine (adrenaline) from norepinephrine, for instance, the nucleophilic nitrogen atom of norepinephrine attacks the electrophilic methyl carbon atom of *S*-adenosylmethionine in an S_N2 reaction, displacing *S*-adenosylhomocysteine.



After dealing only with simple halides such as CH_3I up to this point, it's a shock to encounter a molecule as complex as *S*-adenosylmethionine. From a chemical standpoint, however, CH_3I and *S*-adenosylmethionine do exactly the same thing: both transfer a methyl group by an S_N2 reaction.

Eliminations, like substitutions, also occur frequently in biological pathways, with the E1cB mechanism particularly common. The substrate is usually an alcohol, and the H atom removed is usually adjacent to a carbonyl group, just as in laboratory reactions. A typical example occurs during the biosynthesis of fats when a 3-hydroxybutyryl thioester is dehydrated to the corresponding unsaturated (crotonyl) thioester. The base in this reaction is an amine functional group in the enzyme.

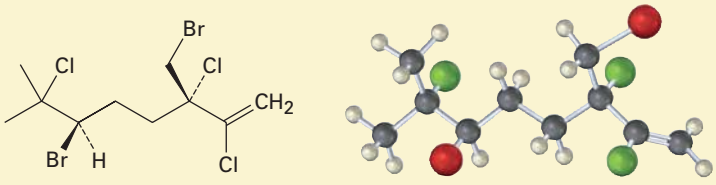


INTERLUDE

Naturally Occurring Organohalides

Marine corals secrete organohalide compounds that act as a feeding deterrent to starfish.

As recently as 1970, only about 30 naturally occurring organohalides were known. It was simply assumed that chloroform, halogenated phenols, chlorinated aromatic compounds called PCBs, and other such substances found in the environment were industrial pollutants. Now, a bit more than a third of a century later, the situation is quite different. More than 5000 organohalides have been found to occur naturally, and tens of thousands more surely exist. From a simple compound like chloromethane to an extremely complex one like vancomycin, a remarkably diverse range of organohalides exists in plants, bacteria, and animals. Many even have valuable physiological activity. The pentahalogenated alkene halomon, for instance, has been isolated from the red alga *Portieria hornemannii* and found to have anticancer activity against several human tumor cell lines.



Halomon

Some naturally occurring organohalides are produced in massive quantities. Forest fires, volcanoes, and marine kelp release up to *5 million tons* of CH_3Cl per year, for example, while annual industrial emissions total about 26,000 tons. Termites are thought to release as much as 10^8 kg of chloroform per year. A detailed examination of the Okinawan acorn worm *Ptychodera flava* found that the 64 million worms living in a 1 km^2 study area excreted nearly 8000 pounds per year of bromophenols and bromoindoles, compounds previously thought to be nonnatural pollutants.

Why do organisms produce organohalides, many of which are undoubtedly toxic? The answer seems to be that many organisms use organohalogen compounds for self-defense, either as feeding deterrents, as irritants to predators, or as natural pesticides. Marine sponges, coral, and sea hares, for example, release foul-tasting organohalides that deter fish, starfish, and other predators from eating them. Even humans appear to produce halogenated compounds as part of their defense against infection. The human immune system contains a peroxidase enzyme capable of carrying out halogenation reactions on fungi and bacteria, thereby killing the pathogen. And most remarkable of all, even free chlorine—Cl_2—has been found to be present in humans.

Much remains to be learned—only a few hundred of the more than 500,000 known species of marine organisms have been examined—but it is clear that organohalides are an integral part of the world around us.

Summary and Key Words

Alkyl halides are not often found in terrestrial organisms, but the kinds of reactions they undergo are among the most important and well-studied reaction types in organic chemistry. In this chapter, we saw how to name and prepare alkyl halides, and we made a detailed study of their substitution and elimination reactions.

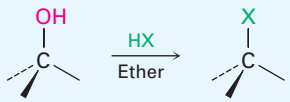
Alkyl halides are usually prepared from alcohols by treatment either with HX (for tertiary alcohols) or with $SOCl_2$ or PBr_3 (for primary and secondary alcohols). Alkyl halides react with magnesium metal to form organomagnesium halides, called **Grignard reagents (RMgX)**. Because Grignard reagents are both nucleophilic and basic, they react with acids to yield hydrocarbons.

Treatment of an alkyl halide with a nucleophile/base results either in substitution or elimination. **Nucleophilic substitution reactions** occur by two mechanisms: S_N2 and S_N1. In the **S_N2 reaction,** the entering nucleophile attacks the substrate from a direction 180° away from the leaving group, resulting in an umbrella-like inversion of configuration at the carbon atom. S_N2 reactions are strongly inhibited by increasing steric bulk of the reagents and are favored only for primary substrates and simple secondary substrates. In the **S_N1 reaction,** the substrate spontaneously dissociates to a carbocation, which reacts with a nucleophile in a second step. As a consequence, S_N1 reactions take place with racemization of configuration at the carbon atom and are favored only for tertiary substrates.

Elimination reactions occur commonly by three mechanisms—E2, E1, and E1cB—which differ in the timing of C–X and C–H bond-breaking. In the **E2 reaction**, a base abstracts a hydrogen at the same time that the adjacent halide group departs. The E2 reaction usually gives a mixture of alkene products in which the more highly substituted alkene predominates (**Zaitsev's rule**). In the **E1 reaction**, C–X bond-breaking occurs first. The substrate spontaneously dissociates to form a carbocation, which subsequently loses H^+ from a neighboring carbon. In the **E1cB reaction**, C–H bond-breaking occurs first. A base removes H^+ to give a **carbanion** intermediate, followed by loss of the leaving halide group from the adjacent carbon. Biological elimination reactions typically occur by this E1cB mechanism.

Summary of Reactions

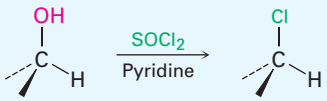
1. Synthesis of alkyl halides from alcohols (Section 7.2)
   (a) Reaction of alcohols with HX, where X = Cl, Br

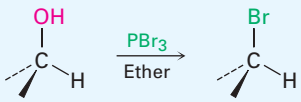


Reactivity order: 3° > 2° > 1°

continued

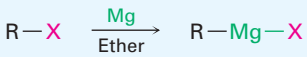
(b) Reaction of primary and secondary alcohols with $SOCl_2$ and PBr_3



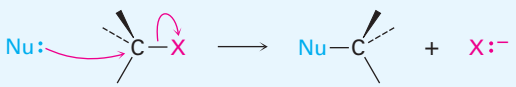


2. Reactions of alkyl halides

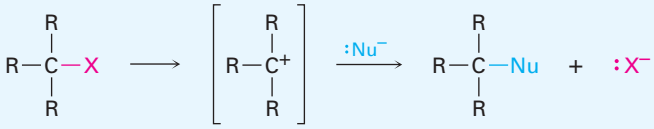
(a) Formation of Grignard reagents (Section 7.3)



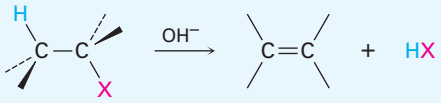
(b) S_N2 reaction: backside attack of nucleophile on alkyl halide (Section 7.5)



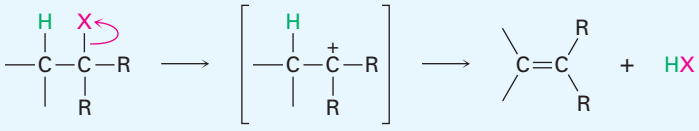
(c) S_N1 reaction: carbocation intermediate is involved (Section 7.6)



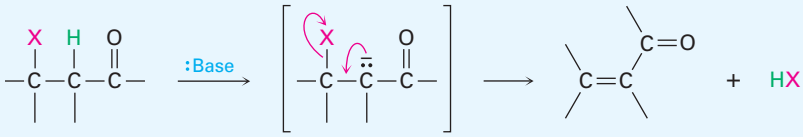
(d) E2 reaction (Section 7.7)



(e) E1 reaction (Section 7.8)



(f) E1cB reaction (Section 7.8)



Exercises

Visualizing Chemistry

(Problems 7.1–7.19 appear within the chapter.)

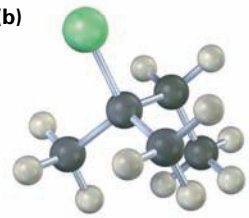
OWL

Interactive versions of these problems are assignable in OWL.

7.20 Write the product you would expect from reaction of each of the following alkyl halides with (i) $Na^+ \ ^-SCH_3$ and (ii) NaOH (yellow-green = Cl):

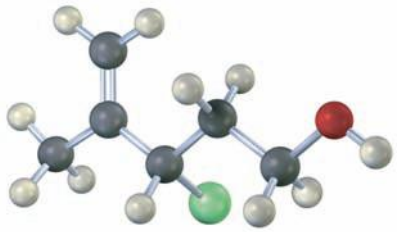
(a)

(b)

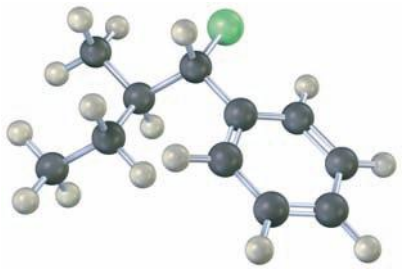


(c)

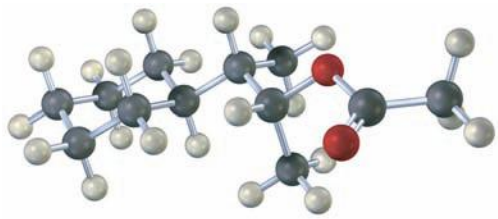
7.21 Assign *R* or *S* configuration to the following molecule, write the product you would expect from S_N2 reaction with NaCN, and assign *R* or *S* configuration to the product (red = O, yellow-green = Cl):



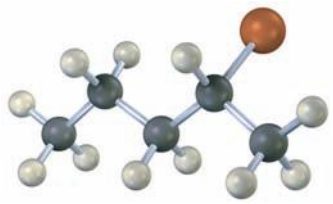
7.22 Draw the structure of the product you expect from E2 reaction of the following molecule with NaOH (yellow-green = Cl):



7.23 From what alkyl bromide was the following alkyl acetate made by S_N2 reaction? Write the reaction, showing all stereochemistry.



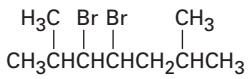
7.24 The following alkyl bromide can be prepared by reaction of the alcohol (*S*)-pentan-2-ol with PBr_3. Name the compound, assign (*R*) or (*S*) stereochemistry, and tell whether the reaction of the alcohol with PBr_3 occurs with retention of the same stereochemistry or with a change in stereochemistry (reddish brown = Br).

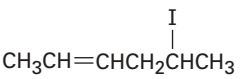


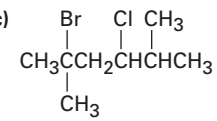
Additional Problems

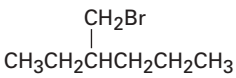
NAMING ALKYL HALIDES

7.25 Name the following alkyl halides:

(a) 

(b) 

(c) 

(d) 

(e) $ClCH_2CH_2CH_2C{\equiv}CCH_2Br$

7.26 Draw structures corresponding to the following IUPAC names:
(a) 2,3-Dichloro-4-methylhexane
(b) 4-Bromo-4-ethyl-2-methylhexane
(c) 3-Iodo-2,2,4,4-tetramethylpentane

7.27 Draw and name the monochlorination products you might obtain by reaction of 2-methylpentane with Cl_2. Which of the products are chiral?

CHARACTERISTICS OF S_N1 AND S_N2 REACTIONS

7.28 Describe the effects of the following variables on both S_N2 and S_N1 reactions:
(a) Substrate structure **(b)** Leaving group

7.29 Which ion in each of the following pairs is a better leaving group?
(a) F^- or Br^- **(b)** Cl^- or NH_2^- **(c)** OH^- or I^-

7.30 Which alkyl halide in each of the following pairs will react faster in an S_N2 reaction with OH^-?
(a) Bromobenzene or benzyl bromide, $C_6H_5CH_2Br$
(b) CH_3Cl or $(CH_3)_3CCl$
(c) $CH_3CH{=}CHBr$ or $H_2C{=}CHCH_2Br$

7.31 What effect would you expect the following changes to have on the S_N2 reaction of CH_3Br and CN^- to give CH_3CN?
(a) The concentration of CH_3Br is tripled and that of CN^- is halved.
(b) The concentration of CH_3Br is halved and that of CN^- is tripled.
(c) The concentration of CH_3Br is tripled and that of CN^- is doubled.
(d) The reaction temperature is raised.
(e) The volume of the reacting solution is doubled by addition of more solvent.

7.32 What effect would you expect the following changes to have on the S_N1 reaction of $(CH_3)_3CBr$ with CH_3OH to give $(CH_3)_3COCH_3$?

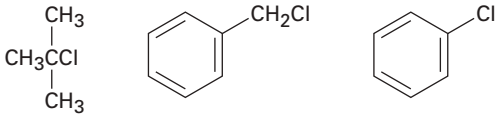
(a) The concentration of $(CH_3)_3CBr$ is doubled and that of CH_3OH is halved.

(b) The concentration of $(CH_3)_3CBr$ is halved and that of CH_3OH is doubled.

(c) The concentrations of both $(CH_3)_3CBr$ and CH_3OH are tripled.

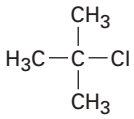
(d) The reaction temperature is lowered.

7.33 Order the following compounds with respect to both S_N1 and S_N2 reactivity:

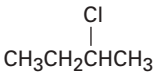


7.34 Order each set of compounds with respect to S_N2 reactivity:

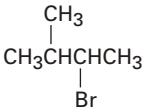
(a)

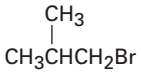


$CH_3CH_2CH_2Cl$



(b)





CH_3Br

SYNTHESIS

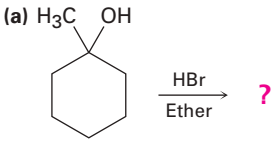
7.35 How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?

(a) Chlorocyclopentane **(b)** Cyclopentanol

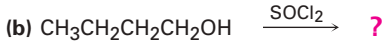
(c) Cyclopentylmagnesium chloride **(d)** Cyclopentane

7.36 Predict the product(s) of the following reactions:

(a)



(b)



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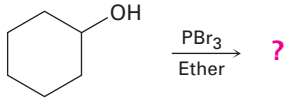
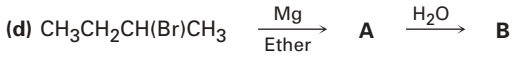


(d)



7.37 How might you prepare the following molecules using a nucleophilic substitution reaction at some step?

(a) CH_3CH_2Br **(b)** $CH_3CH_2CH_2CH_2CN$ **(c)** $CH_3OC(CH_3)_3$

(d) $CH_3CH_2CH_2\overset{+}{N}{=}N{=}N^-$ **(e)** CH_3CH_2SH **(f)** CH_3COCH_3

7.38 What products do you expect from reaction of 1-bromopropane with the following reagents?

(a) NaI **(b)** NaCN **(c)** NaOH **(d)** Mg **(e)** $NaOCH_3$

7.39 None of the following reactions take place as written. What is wrong with each?

(a) $CH_3CH_2C(Br)(CH_3)CH_2CH_3 \xrightarrow{NaCN} CH_3CH_2C(CN)(CH_3)CH_2CH_3$

(b) $CH_3CH(CH_3)CH_2CH_2CH_2OH \xrightarrow{NaBr} CH_3CH(CH_3)CH_2CH_2CH_2Br$

(c) $CH_3CH_2C(OH)(CH_3)CH_3 \xrightarrow{HBr} CH_3CH{=}C(CH_3)CH_3$

Substitutions and Eliminations

7.40 Propose a structure for an alkyl halide that can give a mixture of three alkenes on E2 reaction.

7.41 Heating either *tert*-butyl chloride or *tert*-butyl bromide with ethanol yields the same reaction mixture: approximately 80% *tert*-butyl ethyl ether [$(CH_3)_3COCH_2CH_3$] and 20% 2-methylpropene. Explain why the identity of the leaving group has no effect on the product mixture.

7.42 What effect would you expect the following changes to have on the rate of the reaction of 1-iodo-2-methylbutane with CN^-?

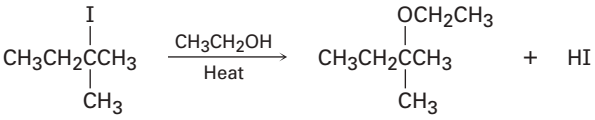
$$CH_3CH_2CH(CH_3)CH_2I + CN^- \longrightarrow CH_3CH_2CH(CH_3)CH_2CN$$

1-Iodo-2-methylbutane

(a) CN^- concentration is halved and 1-iodo-2-methylbutane concentration is doubled.

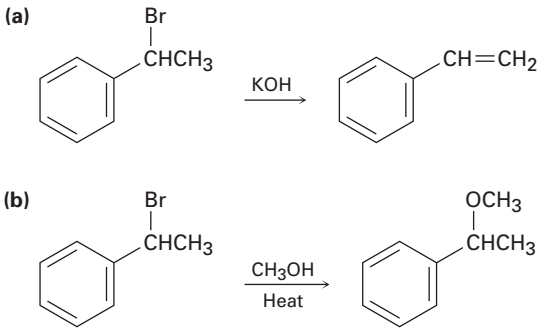
(b) Both CN^- and 1-iodo-2-methylbutane concentrations are tripled.

7.43 What effect would you expect on the rate of reaction of ethyl alcohol with 2-iodo-2-methylbutane if the concentration of the alkyl halide is tripled?

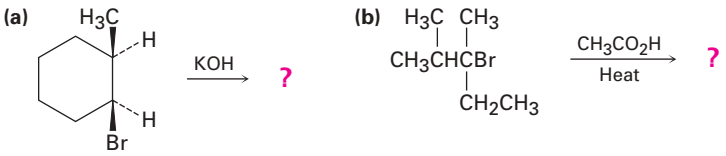


2-Iodo-2-methylbutane

7.44 Identify the following reactions as either S_N1, S_N2, E1, or E2:



7.45 Predict the major alkene product from the following eliminations:



7.46 Treatment of an alkyl chloride C_4H_9Cl with strong base gives a mixture of three isomeric alkene products. What is the structure of the alkyl chloride, and what are the structures of the three products?

General Problems

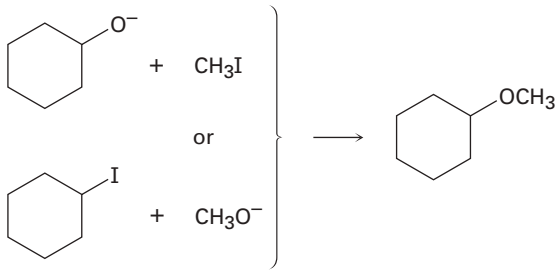
7.47 Predict the product and give the stereochemistry of reactions of the following nucleophiles with (*R*)-2-bromooctane:
(a) CN^- **(b)** $CH_3CO_2^-$ **(c)** Br^-

7.48 Draw all isomers of C_4H_9Br, name them, and arrange them in order of decreasing reactivity in the S_N2 reaction.

7.49 Although the radical chlorination of alkanes with Cl_2 is usually unselective and gives a mixture of products, chlorination of propene, $CH_3CH{=}CH_2$, occurs almost exclusively on the methyl group rather than on a double-bond carbon. Draw resonance structures of the allyl radical $CH_2{=}CHCH_2{\cdot}$ to account for this result.

7.50 Draw resonance structures of the benzyl radical $C_6H_5CH_2{\cdot}$ to account for the fact that radical chlorination of toluene with Cl_2 occurs exclusively on the methyl group rather than on the aromatic ring.

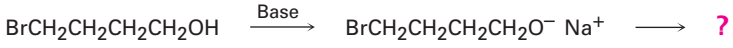
7.51 Ethers can be prepared by S_N2 reaction of an alkoxide ion with an alkyl halide: $R—O^- + R'—Br \rightarrow R—O—R' + Br^-$. Suppose you wanted to prepare cyclohexyl methyl ether. Which of the following two routes would you choose? Explain.



7.52 How could you prepare diethyl ether, $CH_3CH_2OCH_2CH_3$, starting from ethyl alcohol and any inorganic reagents needed? More than one step is needed. (See Problem 7.51.)

7.53 How could you prepare cyclohexane starting from 3-bromocyclohexene? More than one step is needed.

7.54 The S_N2 reaction can occur *intramolecularly,* meaning within the same molecule. What product would you expect from treatment of 4-bromobutan-1-ol with base?

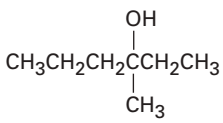


7.55 *trans*-1-Bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with KOH. What does this result tell you about the stereochemistry of E2 reactions?

***trans*-1-Bromo-2-methylcyclohexane** **3-Methylcyclohexene**

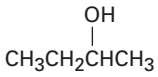
7.56 How can you explain the fact that treatment of (*R*)-2-bromohexane with NaBr yields racemic 2-bromohexane?

7.57 Reaction of HBr with (*R*)-3-methylhexan-3-ol yields (±)-3-bromo-3-methylhexane. Explain.



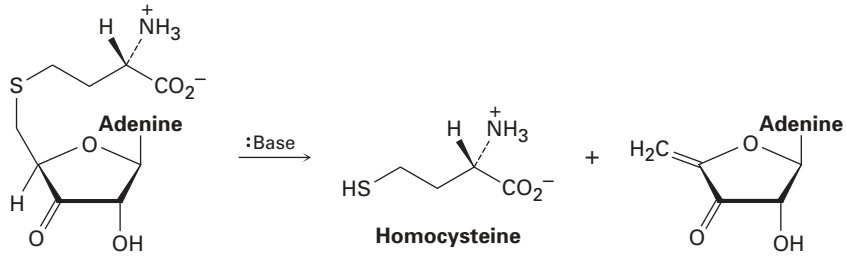
3-Methylhexan-3-ol

7.58 (*S*)-Butan-2-ol slowly racemizes to give (±)-butan-2-ol on standing in dilute sulfuric acid. Propose a mechanism to account for this observation.



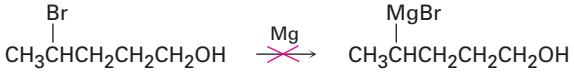
Butan-2-ol

7.59 Metabolism of *S*-adenosylhomocysteine (Section 7.10) involves the following step. Propose a mechanism.

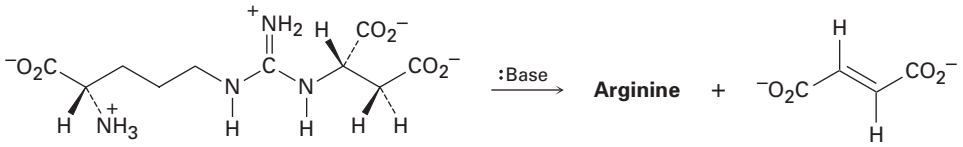


7.60 Compound **A** is optically inactive and has the formula $C_{16}H_{16}Br_2$. On treatment with strong base, **A** gives hydrocarbon **B**, $C_{16}H_{14}$, which absorbs 2 equivalents of H_2 when reduced over a palladium catalyst. Hydrocarbon **B** also reacts with acidic $KMnO_4$ to give two carbonyl-containing products. One product, **C**, is a carboxylic acid with the formula $C_7H_6O_2$. The other product is oxalic acid, HO_2CCO_2H. Formulate the reactions involved, and suggest structures for **A**, **B**, and **C**.

7.61 Why do you suppose it's not possible to prepare a Grignard reagent from a bromoalcohol such as 4-bromopentan-1-ol?

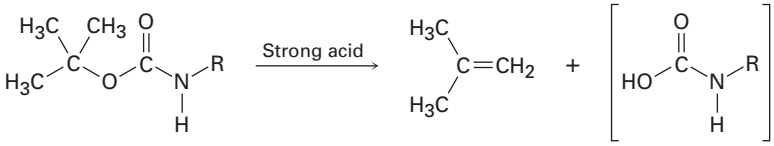


7.62 One step in the urea cycle for ridding the body of ammonia is the conversion of argininosuccinate to the amino acid arginine plus fumarate. Propose a mechanism for the reaction, and show the structure of arginine.



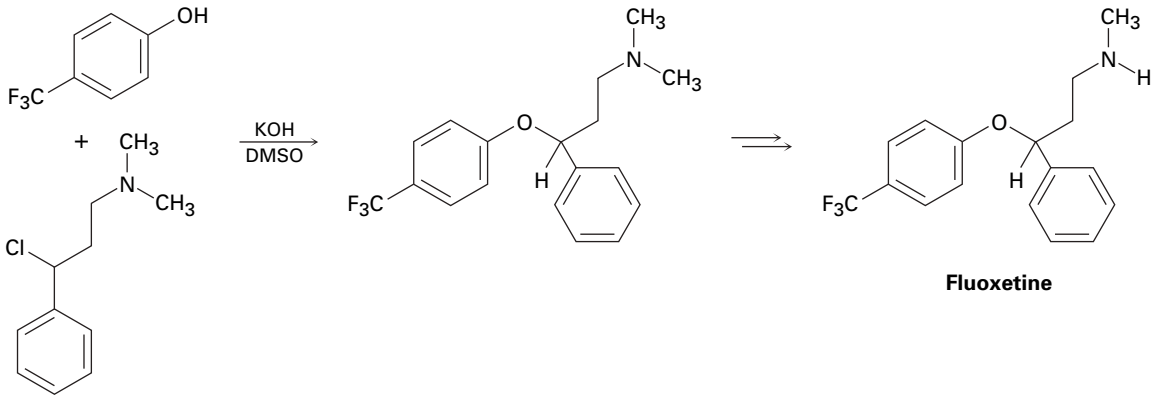
Argininosuccinate **Fumarate**

7.63 The following reaction is an important step in the laboratory synthesis of proteins. Propose a mechanism.



IN THE MEDICINE CABINET

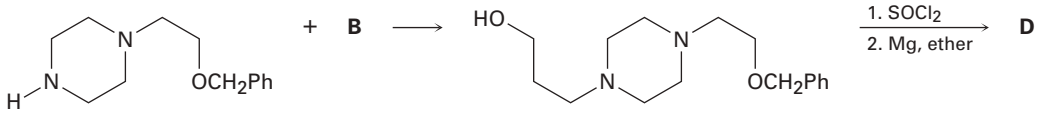
7.64 The antidepressant fluoxetine, marketed as Prozac, can be prepared by a sequence of steps that involves the substitution reaction of an alkyl chloride with a phenol, using a base to convert the phenol into its phenoxide anion.



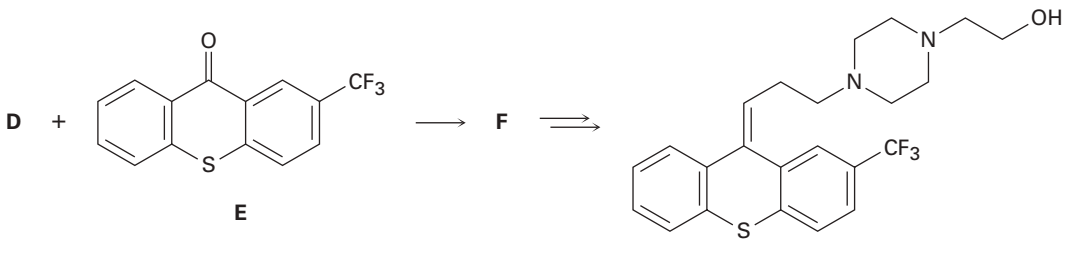
Fluoxetine

(a) Identify the nucleophile and electrophile in the reaction.
(b) The rate of the substitution reaction depends on concentrations of both the alkyl chloride and phenol. Is this an S_N1 or an S_N2 reaction?
(c) The physiologically active enantiomer of fluoxetine has (*S*) stereochemistry. Based on your answer in part **(b)**, draw the structure of the alkyl chloride you would need, showing the correct stereochemistry.

7.65 The antipsychotic drug flupentixol is prepared by the following scheme:



A **C**



E

Flupentixol

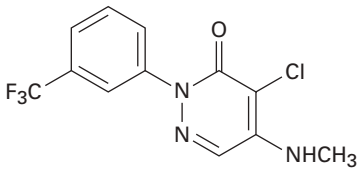
(a) What alkyl chloride **B** reacts with amine **A** to form **C**?
(b) Compound **C** is treated with $SOCl_2$, and the product is allowed to react with magnesium metal to give a Grignard reagent **D**. What is the structure of **D**?

(c) We'll see in Section 9.6 that Grignard reagents add to ketones, such as **E**, to give tertiary alcohols, such as **F**. Because of the newly formed chirality center, compound **F** exists as a pair of enantiomers. Draw both, and assign *R*,*S* configuration.

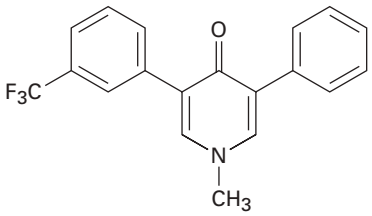
(d) Two stereoisomers of flupentixol are subsequently formed from **F**, but only one is shown. Draw the other isomer, and identify the type of stereoisomerism.

IN THE FIELD

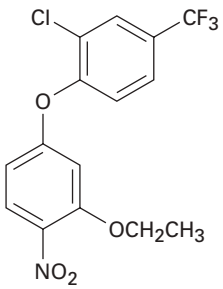
7.66 All five of the following herbicides contain a trifluoromethyl group attached to a benzene ring. This group is commonly included in many bioactive molecules because it slows down oxidative decomposition of the aromatic ring, making the $-CF_3$ containing compounds more stable than their $-CH_3$ analogs.



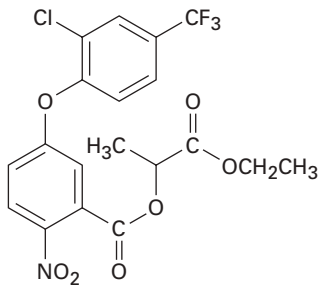
Norflurazon



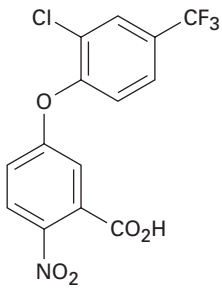
Fluridone



Oxyfluorfen



Lactofen



Acifluorfen

(a) Oxidation is defined as the loss of electrons. Is it likely to be easier to remove electrons from a benzene ring with a $-CF_3$ or $-CH_3$ group attached? Why?

(b) Two of the compounds shown inhibit pigment synthesis in plants, while three inhibit lipid synthesis. Group the compounds by their likely mechanism of action. What criteria did you use to make these groupings?