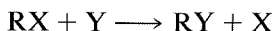


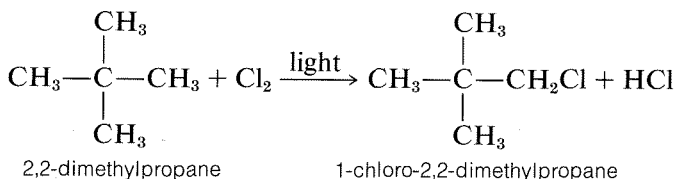
8

NUCLEOPHILIC SUBSTITUTION AND ELIMINATION REACTIONS

Substitution reactions involve the replacement of one atom or group (X) by another (Y):



We already have described one very important type of substitution reaction, the halogenation of alkanes (Section 4-4), in which a hydrogen atom is replaced by a halogen atom (X = H, Y = halogen). The chlorination of 2,2-dimethylpropane is an example:

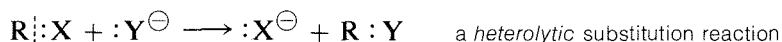


Reactions of this type proceed by radical-chain mechanisms in which the bonds are broken and formed by atoms or radicals as reactive intermediates. This

mode of bond-breaking, in which one electron goes with R and the other with X, is called **homolytic** bond cleavage:



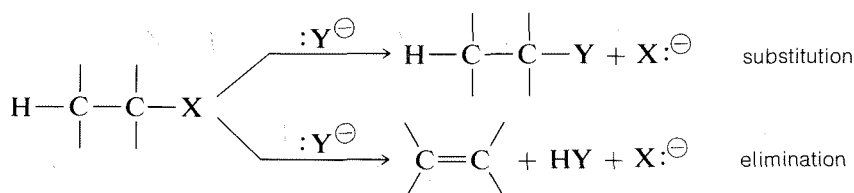
There are a large number of reactions, usually occurring in solution, that do *not* involve atoms or radicals but rather involve ions. They occur by **heterolytic** cleavage as opposed to homolytic cleavage of electron-pair bonds. In heterolytic bond cleavage, the electron pair can be considered to go with one or the other of the groups R and X when the bond is broken. As one example, Y is a group such that it has an unshared electron pair and also is a negative ion. A heterolytic substitution reaction in which the R:X bonding pair goes with X would lead to RY and X^\ominus :



A specific substitution reaction of this type is that of chloromethane with hydroxide ion to form methanol:



In this chapter, we shall discuss substitution reactions that proceed by ionic or polar mechanisms in which the bonds cleave heterolytically. We also will discuss the mechanistically related **elimination** reactions that result in the formation of carbon-carbon multiple bonds:



These reactions often are influenced profoundly by seemingly minor variations in the structure of the reactants, in the solvent, or in the temperature. It is our purpose to show how these reactions can be understood and how they can be used to prepare other useful organic compounds. But first it will be helpful to introduce the concepts of **nucleophilic** and **electrophilic** reagents, and to consider the ΔH values for heterolytic bond breaking.

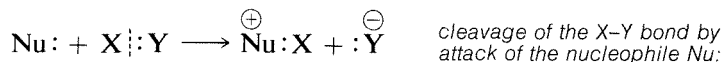
8-1 CLASSIFICATION OF REAGENTS AS ELECTROPHILES AND NUCLEOPHILES. ACIDS AND BASES

To understand ionic reactions, we need to be able to recognize whether a particular reagent will act to *acquire an electron pair* or to *donate an electron*

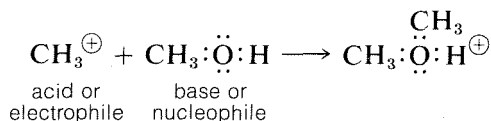
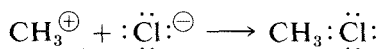
pair. Reagents that acquire an electron pair in chemical reactions are said to be **electrophilic** ("electron-loving"). We can picture this in a general way as a heterolytic bond breaking of compound X:Y by an electrophile E such that E becomes bonded to Y by the electron pair of the XY bond. Thus



Reagents that donate an electron pair in chemical reactions are said to be **nucleophilic** ("nucleus loving"). Thus the X:Y bond also can be considered to be broken by the nucleophile Nu:, which donates its electron pair to X while Y leaves as Y:[⊖] with the electrons of the X:Y bond:



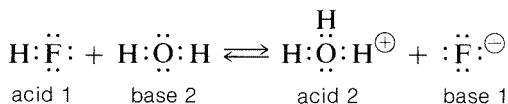
Thus, by definition, electrophiles are electron-pair acceptors and nucleophiles are electron-pair donors. These definitions correspond closely to definitions used in the generalized theory of acids and bases proposed by G. N. Lewis (1923). According to Lewis, an acid is any substance that can accept an electron pair, and a base is any substance that can donate an electron pair to form a covalent bond. Therefore acids must be electrophiles and bases must be nucleophiles. For example, the methyl cation may be regarded as a **Lewis acid**, or an electrophile, because it *accepts* electrons from reagents such as chloride ion or methanol. In turn, because chloride ion and methanol donate electrons to the methyl cation they are classified as **Lewis bases**, or nucleophiles:



The generalized Lewis concept of acids and bases also includes common proton-transfer reactions.¹ Thus water acts as a base because one of the

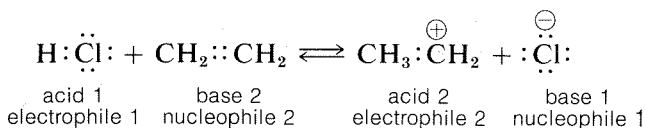
¹The concept of an acid as a **proton donor** and a base as a **proton acceptor** is due to Brønsted and Lowry (1923). Previous to this time, acids and bases generally were defined as substances that functioned by forming H[⊕] and OH[⊖] in water solutions. The Brønsted-Lowry concept was important because it liberated acid-base phenomena from the confines of water-containing solvents by focusing attention on *proton transfers* rather than the formation of H[⊕] or OH[⊖]. The Lewis concept of generalized acids and bases further broadened the picture by showing the relationship between proton transfers and reactions where an electron-pair acceptor is transferred from one electron-pair donor to another.

electron pairs on oxygen can abstract a proton from a reagent such as hydrogen fluoride:



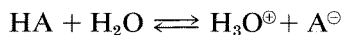
Alternatively, the hydronium ion ($\text{H}_3\text{O}^{\oplus}$) is an acid because it can accept electrons from another reagent (e.g., fluoride ion) by donating a proton.

A proton donor can be classified as an electrophile and a proton acceptor as a nucleophile. For example, hydrogen chloride can transfer a proton to ethene to form the ethyl cation. Therefore hydrogen chloride functions as the electrophile, or acid, and ethene functions as the nucleophile, or base:



What then is the difference between an acid and an electrophile, or between a base and nucleophile? No great difference until we try to use the terms in a *quantitative* sense. For example, if we refer to acid strength, or acidity, this means the position of *equilibrium* in an acid-base reaction. The equilibrium constant K_a for the dissociation of an acid HA, or the $\text{p}K_a$, is a quantitative measure of acid strength. The larger the value of K_a or the smaller the $\text{p}K_a$, the stronger the acid.

A summary of the relationships between K_a and $\text{p}K_a$ follow, where the quantities in brackets are concentrations:



$$K_a = \frac{[\text{H}_3\text{O}^{\oplus}][\text{A}^{\ominus}]}{[\text{HA}]}$$

(Notice that the concentration of water does not appear in this expression; it is the solvent and its concentration is large and constant.)

or

$$-\log K_a = -\log [\text{H}_3\text{O}^{\oplus}] + \log \frac{[\text{HA}]}{[\text{A}^{\ominus}]}$$

By definition, $-\log K_a = \text{p}K_a$ and $-\log [\text{H}_3\text{O}^{\oplus}] = \text{pH}$; hence

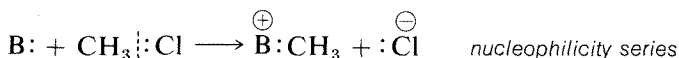
$$\text{p}K_a = \text{pH} + \log \frac{[\text{HA}]}{[\text{A}^{\ominus}]}$$

or

$$\text{p}K_a = \text{pH} + \log \frac{[\text{undissociated acid}]}{[\text{anion of the acid}]}$$

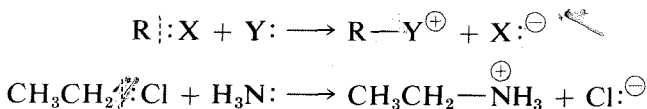
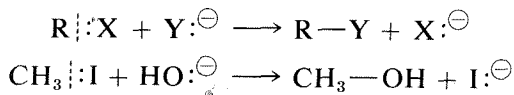
(This sometimes is referred to as the Henderson-Hasselbalch equation.)

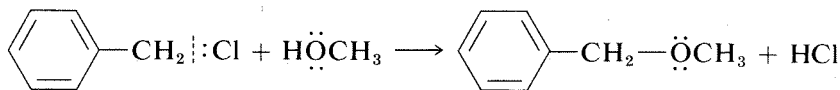
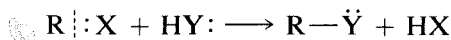
However, in referring to the strength of reagents as electrophiles or nucleophiles we usually are not referring to chemical equilibria but to *reaction rates*. A good nucleophile is a reagent that reacts rapidly with a particular electrophile. In contrast, a poor nucleophile reacts only slowly with the same electrophile. Consequently, it should not then be taken for granted that there is a parallel between the acidity or basicity of a reagent and its reactivity as an electrophile or nucleophile. For instance, it is incorrect to assume that the strengths of a series of bases, B:, in aqueous solution will *necessarily* parallel their nucleophilicities toward a carbon electrophile, such as methyl chloride:



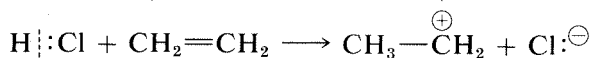
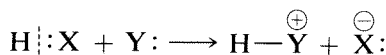
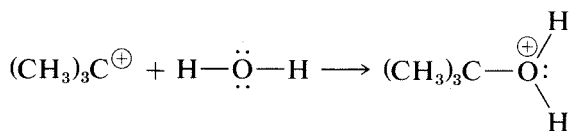
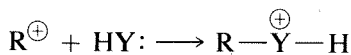
The important difference is that the *strength* of the base, B:, is determined in an *equilibrium* reaction, whereas its *nucleophilicity* is determined by its reactivity in slow substitution reactions. To put it another way, the base strength corresponds to the overall energy change of a reaction while the nucleophilicity corresponds to the activation energy of a reaction (see Figure 4-4). Even so, it turns out that most strong bases are good nucleophiles and that most strong proton acids are good electrophiles. We will see that the converse may not be true. Good nucleophiles are not always strong bases [examples are Cl^{\ominus} , Br^{\ominus} , I^{\ominus} , and $(\text{CH}_3)_2\text{S}$] and good electrophiles are not always strong acids by either the Brønsted-Lowry or Lewis definitions (examples are HOBr , Br_2 , Cl_2 , I_2).

In what follows we will be concerned with the rates of ionic reactions under *nonequilibrium* conditions. We shall use the term *nucleophile* repeatedly and we want you to understand that a nucleophile is any neutral or charged reagent that supplies a pair of electrons, either bonding or nonbonding, to form a new covalent bond. In substitution reactions the nucleophile usually is an anion, Y^{\ominus} , or a neutral molecule, Y: or HY: . The operation of each of these is illustrated in the following equations for reactions of the general compound RX and some specific examples:





An *electrophile* is any neutral or charged reagent that accepts an electron pair (from a nucleophile) to form a new bond. In the preceding substitution reactions, the electrophile is RX . The electrophile in other reactions may be a carbon cation or a proton donor, as in the following examples:



Exercise 8-1 Write Lewis structures for each of the following reagents and classify them as either electrophilic, nucleophilic, both, or neither by evaluating whether they will react appreciably with hydroxide ion, HO^{\ominus} , or hydronium ion, $\text{H}_3\text{O}^{\oplus}$. Write equations for each of the reactions involved.

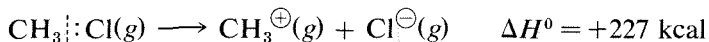
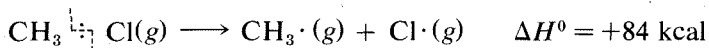
- | | | |
|----------------------------|--|--|
| a. NH_3 | f. CH_4 | k. HBr |
| b. NH_2^{\ominus} | g. CN^{\ominus} | l. $\text{HC}\equiv\text{C}^{\ominus}$ |
| c. Na^{\oplus} | h. CH_3OH | m. $:\text{CH}_2$ |
| d. Cl^{\ominus} | i. $\overset{\oplus}{\text{C}}\text{H}_3\text{OH}_2$ | n. FSO_3H |
| e. Cl_2 | j. BF_4^{\ominus} | o. SO_3 |

Exercise 8-2 Identify the electrophile and the nucleophile in each of the following reactions:

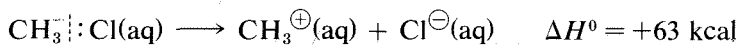
- $\text{CH}_3\text{I} + \overset{\ominus}{\text{O}}\text{CH}_3 \longrightarrow \text{CH}_3-\text{O}-\text{CH}_3 + \text{I}^{\ominus}$
- $\text{CH}_2=\text{CH}_2 + \text{Br}_2 \longrightarrow \overset{\oplus}{\text{C}}\text{H}_2-\text{CH}_2-\text{Br} + \text{Br}^{\ominus}$
- $\text{CH}_3\text{NH}_2 + \text{CH}_3\text{I} \longrightarrow (\text{CH}_3)_2\text{NH} + \text{HI}$
- $\text{Br}^{\ominus} + \overset{\oplus}{\text{C}}\text{H}_3-\text{OH}_2 \longrightarrow \text{CH}_3\text{Br} + \text{H}_2\text{O}$

8-2 THERMOCHEMISTRY OF SUBSTITUTION REACTIONS

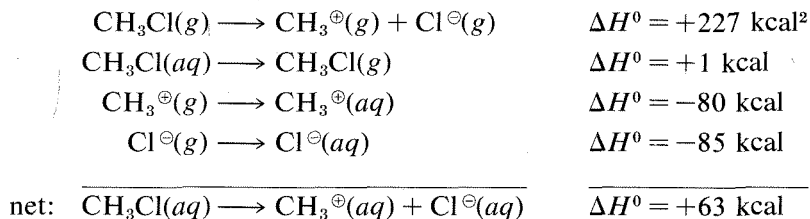
Ionic or polar reactions of alkyl halides rarely are observed in the vapor phase because the energy required to dissociate a carbon-halogen bond heterolytically is almost prohibitively high. For example, while the heat of dissociation of chloromethane to a methyl radical and a chlorine atom is $84 \text{ kcal mole}^{-1}$ (Table 4-6), dissociation to a methyl cation and a chloride ion requires about $227 \text{ kcal mole}^{-1}$:



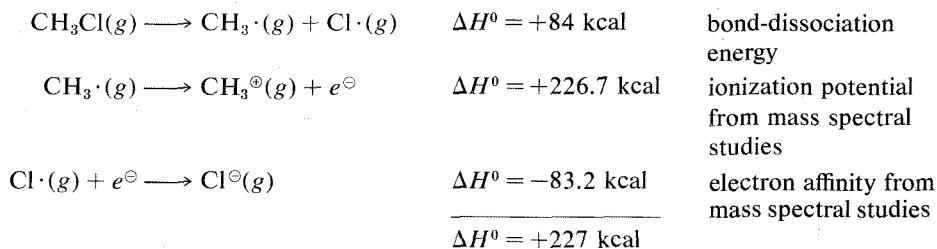
However, the heat of ionic dissociation of methyl chloride in aqueous solution is estimated to be 63 kcal , and while this reaction is still substantially endothermic, it requires about $227 - 63 = 164 \text{ kcal}$ *less* energy than in the gas phase:



The reason is that ions are much more stable in water than in the gas phase; for example, the transfer of a chloride ion from the gas to water is exothermic by -85 kcal . The ΔH^0 value for the corresponding transfer of a methyl cation, CH_3^{\oplus} , is not known with certainty, but is about -80 kcal . These ionic solvation energies are clearly large. In contrast, the ΔH^0 for solution of methyl chloride in water is small (about 1 kcal). We can use these data to calculate the heat of ionic dissociation of chloromethane in water:

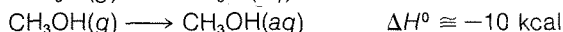
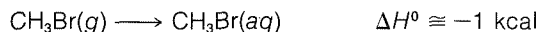
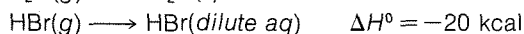


²Calculated from the following data:



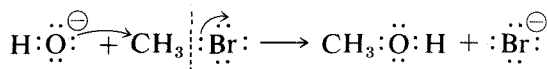
Thermochemical data for the solvation of ions as used in the preceding calculations are difficult to measure and even to estimate. Therefore this kind of calculation of ΔH^0 for ionic reactions involving organic molecules in solution usually cannot be made. As a result, we have considerably fewer possibilities to assess the thermodynamic feasibility of the individual steps of polar reactions in solution than we do of vapor-phase radical processes. Bond energies are not of much use in predicting or explaining reactivity in ionic reactions unless we have information that can be used to translate gas-phase ΔH^0 values to solution ΔH^0 values. Exercise 8-3 will give you a chance to see how this is done.

Exercise 8-3 Calculate ΔH^0 for the polar reaction of one mole of bromomethane with water in accord with the equation $\text{CH}_3\text{Br} + \text{H}_2\text{O} \longrightarrow \text{CH}_3\text{OH} + \text{HBr}$ (a) in the gas phase and (b) with all of the participants in dilute aqueous solution. For Part (a) you will need the bond energies of Table 4-3 and for Part (b) you will require the bond energies and the following ΔH^0 values:



8-3 GENERAL CONSIDERATIONS OF SUBSTITUTION REACTIONS

We now wish to discuss displacements by *nucleophilic* reagents (Y^-) on alkyl derivatives (RX). These are *ionic* or *polar* reactions involving attack by a nucleophile at *carbon*. A typical example is the reaction of hydroxide ion with bromomethane to displace bromide ion:



The electron pair of the C–O bond can be regarded as having been donated by the hydroxide ion, while the electron pair of the C–Br bond departs with the leaving bromide ion. The name for this type of reaction is abbreviated S_{N} , S for substitution and N for nucleophilic.

Reactions of this type are very useful. They can lead to compounds in which the new bond to carbon in the alkyl group, R, is to chlorine, bromine,

iodine, oxygen, sulfur, carbon, nitrogen, or phosphorus, depending on the nature of the nucleophile used.

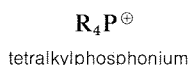
Nucleophilic substitutions are especially important for alkyl halides, but they should not be considered to be confined to alkyl halides. Many other alkyl derivatives such as alcohols, ethers, esters, and "onium ions"³ also can undergo S_N reactions if conditions are appropriate. The scope of S_N reactions is so broad that it is impossible to include all the various alkyl compounds and nucleophiles that react in this manner. Rather we shall approach the subject here through consideration of the mechanisms of S_N reactions, and then develop the scope of the reactions in later chapters.

The mechanism of an S_N reaction and the reactivity of a given alkyl compound RX toward a nucleophile Y depend upon the nature of R , X , and Y , and upon the nature of the solvent. For an S_N reaction to occur at a reasonable rate, it is very important to select a solvent that will dissolve both the alkyl compound and the nucleophilic reagent; considerable assistance may be required from both the solvent and the nucleophile to break what usually is a slightly polar $C-X$ bond. However, the solvents that best dissolve slightly polar organic compounds seldom will dissolve the common, rather highly polar, nucleophilic agents such as $NaBr$, $NaCN$, and H_2O . In practice, relatively polar solvents, or solvent mixtures, such as 2-propanone (acetone), aqueous 2-propanone, ethanol, aqueous 1,4-dioxacyclohexane (dioxane), and so on, provide the best compromise for reactions between alkyl compounds and saltlike nucleophilic reagents. The importance of the solvent in stabilizing ions can be evaluated from the estimated thermochemistry of ionic reactions discussed in Section 8-2.

8-4 MECHANISMS OF S_N REACTIONS

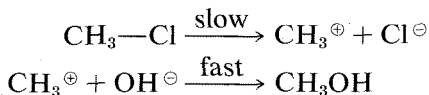
Two simple mechanisms can be written for the reaction of chloromethane with hydroxide ion in aqueous solution that differ in the *timing* of bond breaking relative to bond making. In the first mechanism, **A**, the overall reaction is the result of two steps, the first of which involves a *slow* dissociation of chloro-

³Examples of -onium cations are

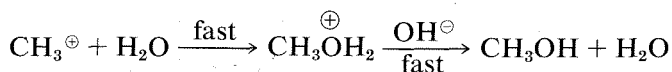


methane to solvated methyl carbocation⁴ and solvated chloride ion. The second step involves a *fast* reaction between the carbocation and hydroxide ion (or water) to yield methanol.

Mechanism A:

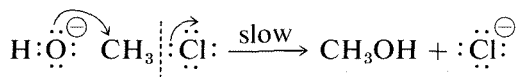


or



In the second mechanism, **B**, the reaction proceeds in a single step. Attack of hydroxide ion at carbon occurs simultaneously with the loss of chloride ion; that is, the carbon–oxygen bond is formed as the carbon–chlorine bond is broken.

Mechanism B:



Both of these mechanisms are important in the displacement reactions of alkyl compounds, although chloromethane appears to react *only* by Mechanism **B**. Now we will discuss the criteria for distinguishing between the concerted and stepwise mechanisms.

8-4A Kinetics of Substitution Mechanisms

Of the two mechanisms, **A** requires that the reaction rate be determined solely by the rate of the first step (cf. earlier discussion in Section 4-4C). This means that the rate at which methanol is formed (measured in moles per unit volume per unit time) will depend on the chloromethane concentration, but *not* on the hydroxide ion concentration, because hydroxide ion is not utilized except in a

⁴Many organic chemists, and indeed the previous versions of this book, use the term “carbonium ion” for species of this kind. However, there is well-established usage of the *-onium* suffix, for ammonium, oxonium, chloronium, and so on, to denote positively charged atoms with *filled* valence shells. In the interest of greater uniformity of nomenclature we shall use “carbocation” for carbon positive ions that have *unfilled* valence shells (6 electrons).

fast secondary reaction. In contrast, Mechanism **B** requires the rate to depend on the concentrations of both reagents because the slow step involves collisions between hydroxide ions and chloromethane molecules. More precisely, the reaction rate (v) may be expressed in terms of Equation 8-1 for Mechanism **A** and Equation 8-2 for Mechanism **B**:

$$v = k[\text{CH}_3\text{Cl}] \quad (8-1)$$

$$v = k[\text{CH}_3\text{Cl}][\text{OH}^\ominus] \quad (8-2)$$

Customarily, v is expressed in moles of product formed per liter of solution per unit of time (most frequently in seconds). The concentration terms $[\text{CH}_3\text{Cl}]$ and $[\text{OH}^\ominus]$ are then in units of moles per liter, and the proportionality constant k (called the specific rate constant) has the units of sec^{-1} for Mechanism **A** and $\text{mole}^{-1} \times \text{liter} \times \text{sec}^{-1}$ for Mechanism **B**.

It is important to recognize the difference between *the order of a reaction with respect to a specific reactant* and *the overall order of a reaction*. The order of a reaction with respect to a *particular* reactant is the power to which the concentration of *that reactant* must be raised to have direct proportionality between concentration and reaction rate. According to Equation 8-2 the rate of the chloromethane–hydroxide ion reaction is *first order* with respect to chloromethane and *first order* with respect to hydroxide ion. In Equation 8-1 the rate is *first order* with respect to chloromethane and *zero order* with respect to hydroxide ion because $[\text{OH}^\ominus]^0 = 1$. The *overall order* of reaction is the *sum* of the orders of the respective reactants. Thus Equations 8-1 and 8-2 express the rates of overall *first-order* and *second-order* reactions, respectively.

We can use the overall reaction order to distinguish between the two possible mechanisms, **A** and **B**. Experimentally, the rate of formation of methanol is found to be proportional to the concentrations *both* of chloromethane and of hydroxide ion. Therefore the reaction rate is second order overall and is expressed correctly by Equation 8-2. This means that the mechanism of the reaction is the single-step process **B**. Such reactions generally are classified as **bimolecular nucleophilic substitutions**, often designated $\text{S}_{\text{N}}2$, S for substitution, N for nucleophilic, and 2 for bimolecular, because there are *two* reactant molecules in the transition state. To summarize: For an $\text{S}_{\text{N}}2$ reaction,

rate:

$$v = k[\text{RX}][\text{Y}]$$

mechanism:



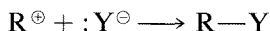
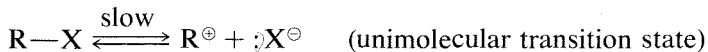
The stepwise Mechanism **A** is a **unimolecular nucleophilic substitution** and accordingly is designated $\text{S}_{\text{N}}1$. The numeral 1 (or 2) used in these designa-

tions does *not* refer to the kinetic order of the reaction, but refers to the number of molecules (not including solvent molecules) that make up the transition state. Thus for S_N1 ,

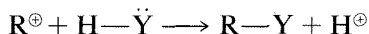
rate:

$$v = k[\text{RX}]$$

mechanism:



or

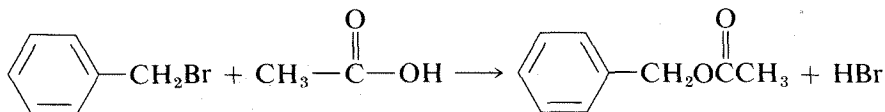
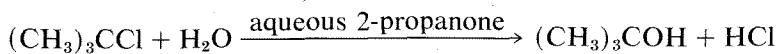


Exercise 8-4 Ethyl chloride (0.1M) reacts with potassium iodide (0.1M) in 2-propanone (acetone) solution at 60° to form ethyl iodide and potassium chloride at a rate (v) of 5.44×10^{-7} mole liter $^{-1}$ sec $^{-1}$.

- If the reaction proceeded by an S_N2 mechanism, what is the value of k (in proper units) and what would be the rate of the reaction in moles per liter per sec at 0.01M concentrations of both reactants? Show your method of calculation.
- Suppose the rate were proportional to the square of the potassium iodide concentration and the first power of the ethyl chloride concentration. What would be the rate with 0.01M reactants?
- If one starts with solutions initially 0.1M in both reactants, the rate of formation of ethyl iodide initially is 5.44×10^{-7} mole liter $^{-1}$ sec $^{-1}$, but falls as the reaction proceeds and the reactants are used up. Plot the rate of formation of ethyl iodide against the concentration of ethyl chloride as the reaction proceeds (remembering that one molecule of ethyl chloride consumes one molecule of potassium iodide). Assume that the rate of reaction is proportional to the first power of the ethyl chloride concentration; and to (1) the zeroth power, (2) the first power, and (3) the second power of the potassium iodide concentration.
- What kind of experimental data would one need to determine whether the rate of the reaction of ethyl chloride with potassium iodide is first order in each reactant or second order in ethyl chloride and zero order in potassium iodide?
- Suppose the reaction is first order in both ethyl chloride and potassium iodide. Plot the rate of formation of ethyl iodide against the concentration of ethyl chloride, assuming one starts with 0.01M ethyl chloride and 1M potassium iodide. Compare this plot with the zeroth- and first-order plots you made in Part c.

8-4B Solvolysis

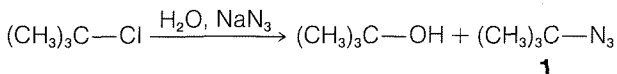
Many S_N reactions are carried out using the solvent as the nucleophilic agent. They are called solvolysis reactions and involve solvents such as water, ethanol, ethanoic acid, and methanoic acid. Two examples are



In these examples, solvolysis is necessarily a first-order reaction, because normally the solvent is in such great excess that its concentration does not change appreciably during reaction, and hence its contribution to the rate does not change. (This point will be much clearer if you work Exercise 8-4e.) However, that the *overall* rate is first order does not mean the reaction necessarily proceeds by an S_N1 mechanism, particularly in solvents such as water, alcohols, or amines, which are reasonably good nucleophilic agents. The solvent can act as the displacing agent in an S_N2 reaction.

To distinguish between S_N1 and S_N2 mechanisms of *solvolysis* requires other criteria, notably stereochemistry (Sections 8-5 and 8-6), and the effect of added nucleophiles on the rate and nature of the reaction products. For example, it often is possible to distinguish between S_N1 and S_N2 solvolysis by adding to the reaction mixture a relatively small concentration of a substance that is expected to be a more powerful nucleophile than the solvent. If the reaction is strictly S_N1 , the rate at which RX disappears should remain essentially unchanged because it reacts only as fast as R^\oplus forms, and the rate of this step is not changed by addition of the nucleophile, even if the nucleophile reacts with R^\oplus . However, if the reaction is S_N2 , the rate of disappearance of RX should *increase* because RX reacts with the nucleophile in an S_N2 reaction and now the rate depends on both the nature and the concentration of the nucleophile. (See Exercises 8-5 and 8-6.)

Exercise 8-5 The rate of solvolysis of *tert*-butyl chloride in aqueous solution is unaffected by having sodium azide, $\text{Na} \text{:}\overset{\oplus}{\text{N}}=\overset{\ominus}{\text{N}}=\overset{\oplus}{\text{N}}\text{:}$, in the solution, yet the products include both 2-azido-2-methylpropane, **1**, and *tert*-butyl alcohol:



Show how this information can be used to determine whether an S_N1 or an S_N2 mechanism occurs in the solvolysis of *tert*-butyl chloride in aqueous solution.

Exercise 8-6 What inference as to reaction mechanism might you make from the observation that the rate of hydrolysis of a certain alkyl chloride in aqueous 2-propanone is *retarded* by having a moderate concentration of lithium chloride in the solution?

8-5 STEREOCHEMISTRY OF S_N2 REACTIONS

There are two simple ways in which the S_N2 reaction of methyl chloride could occur with hydroxide ion. These differ in the direction of approach of the reagents (Figure 8-1). The hydroxide ion could attack chloromethane at the **front side** of the carbon where the chlorine is attached or, alternatively, the hydroxide ion could approach the carbon on the side opposite from the chlorine in what is called the **back-side** approach. In either case, the making of the C–O bond is essentially *simultaneous* with the breaking of the C–Cl bond. The difference is that for the back-side mechanism the carbon and the attached hydrogens become planar in the transition state.

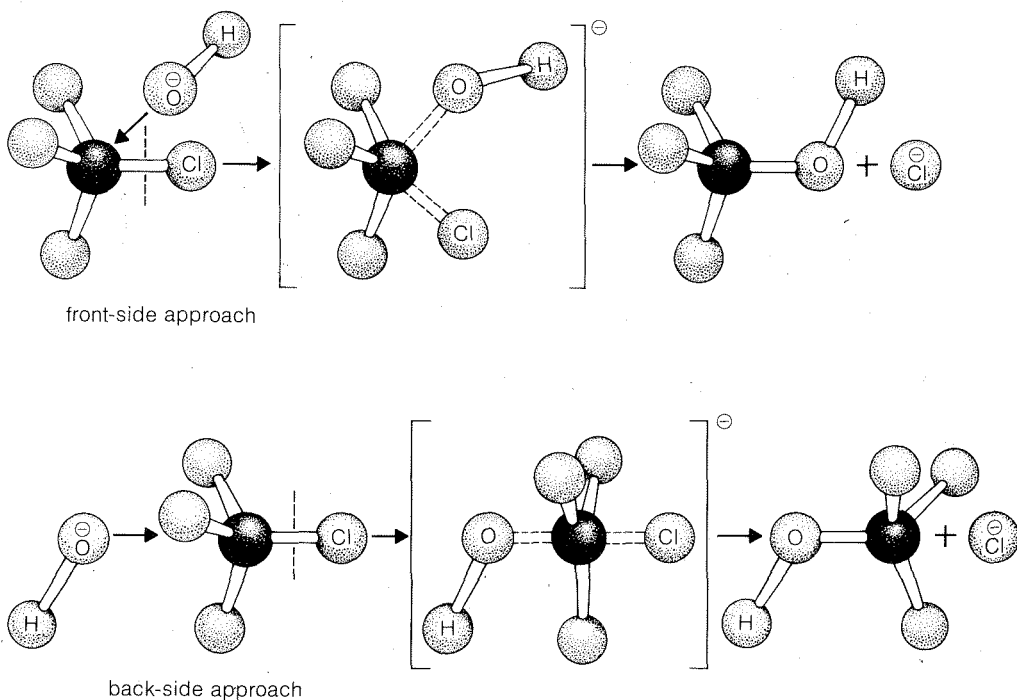
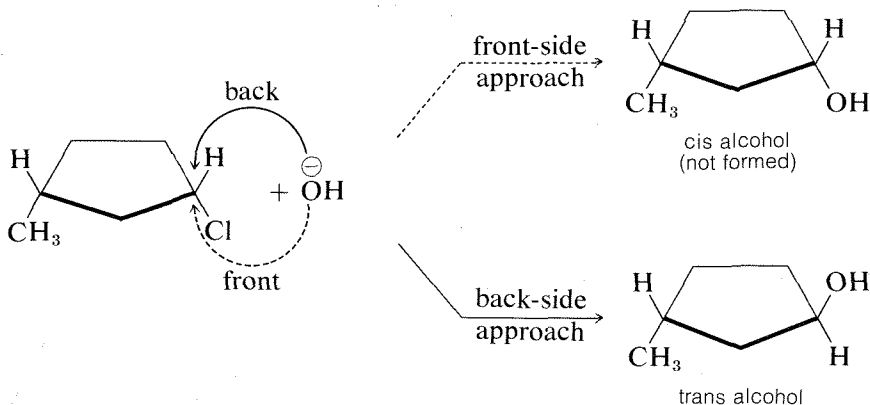


Figure 8-1 Back-side (inverting) and front-side (noninverting) approach of hydroxide ion on methyl chloride, as visualized with ball-and-stick models

The stereochemical consequences of front- and back-side displacements are different. With cyclic compounds, the two types of displacement lead to *different* products. For example, an S_N2 reaction between *cis*-3-methylcyclopentyl chloride and hydroxide ion would give the *cis* alcohol by front-side approach but the *trans* alcohol by back-side approach. The actual product is the *trans* alcohol, from which we know that reaction occurs by back-side displacement:



For open-chain compounds, back-side displacement has been established conclusively with the aid of stereoisomers, particularly those with chiral atoms. Inspection of the enantiomers of 2-chlorobutane, shown in Figure 8-2, demonstrates that *front-side* displacement of chloride by hydroxide ion will give an enantiomer of 2-butanol of the *same* configuration as the original chloride, whereas back-side displacement will give the alcohol of the *opposite*, or *inverted*, configuration. Experiments using either of the two enantiomers show that hydroxide ion attacks 2-chlorobutane exclusively by back-side

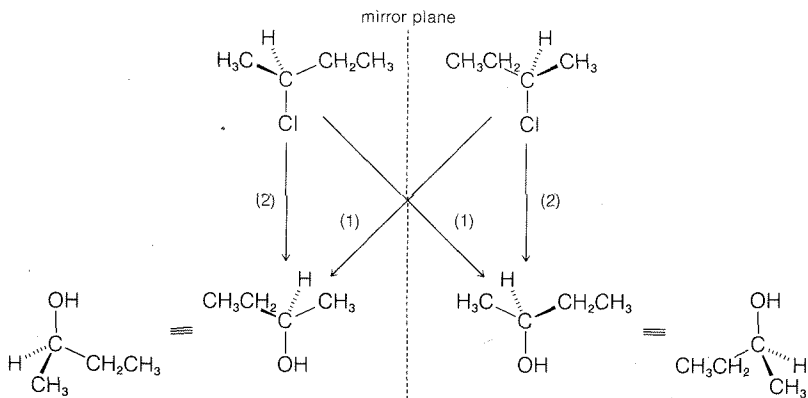
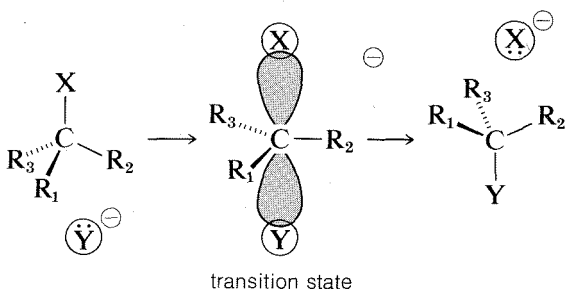
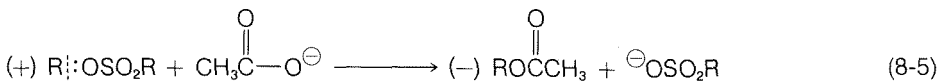
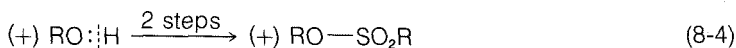
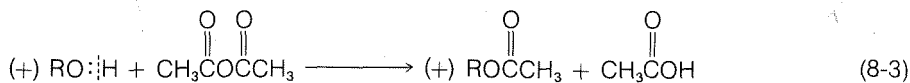


Figure 8-2 Stereochemistry of displacement of 2-chlorobutane with hydroxide by (1) front-side attack (not observed) and (2) back-side attack

displacement to give 2-butanol with the inverted configuration. Similar studies of a wide variety of displacements have established that S_N2 reactions invariably proceed with inversion of configuration via back-side attack. This stereochemical course commonly is known as the **Walden inversion**.⁵ An orbital picture of the transition state of an S_N2 reaction that leads to inversion of configuration follows:



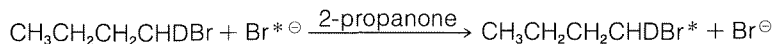
Exercise 8-7 Equations 8-3 through 8-5 show how Kenyon and Phillips established that inversion of configuration accompanies what we now recognize to be S_N2 substitutions. For each reaction, we indicate whether R—O or O—H is broken by an appropriately placed vertical line. Explain how the sequence of steps shows that inversion occurs in the S_N2 reaction of Equation 8-5. The symbols (+) or (–) designate for each compound the sign of the rotation α of the plane of polarized light that it produces.



Exercise 8-8 Explain how, in the presence of bromide ion, either enantiomer of 2-bromobutane racemizes (Section 5-1B) in 2-propanone solution at a rate that is first order in Br^- and first order in 2-bromobutane.

⁵The first documented observation that optically active compounds could react to give products having the opposite configuration was made by P. Walden, in 1895. The implications were not understood, however, until the mechanisms of nucleophilic substitution were elucidated in the 1930's, largely through the work of E. D. Hughes and C. K. Ingold, who established that S_N2 substitutions give products of inverted configuration (see Exercise 8-7).

Exercise 8-9* When either of the enantiomers of 1-deuterio-1-bromobutane is heated with bromide ion in 2-propanone, it undergoes an S_N2 reaction that results in a slow loss of its optical activity. If radioactive bromide ion ($\text{Br}^{*\ominus}$) is present in the solution, radioactive 1-deuterio-1-bromobutane is formed by the same S_N2 mechanism in accord with the following equation:



Within experimental error, the time required to lose 10% of the optical activity is just equal to the time required to have 5% of the $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHDBr}$ molecules converted to $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHDBr}^*$ with radioactive bromide ion. Explain what we can conclude from these results as to the degree to which the S_N2 reaction produces inversion of configuration of the primary carbon of 1-deuterio-1-bromobutane.

8-6 STEREOCHEMISTRY OF S_N1 REACTIONS

When an S_N1 reaction is carried out starting with a single pure enantiomer, such as D-2-chlorobutane, the product usually is a mixture of the enantiomeric substitution products with a slight predominance of that isomer which corresponds to inversion. Theoretically, a carbocation is expected to be most stable in the planar configuration (Section 6-4E) and hence should lead to exactly equal amounts of the two enantiomers, regardless of the chiral configuration of the starting material (Figure 8-3). However, the extent of configuration change that actually results in an S_N1 reaction depends upon the degree of "shielding" of the front side of the reacting carbon by the leaving group and its associated solvent molecules. If the leaving group does not get away from the carbocation before the product-determining step takes place, there will be some preference for nucleophilic attack at the *back side* of the carbon, which results in a predominance of the product of *inverted* configuration.

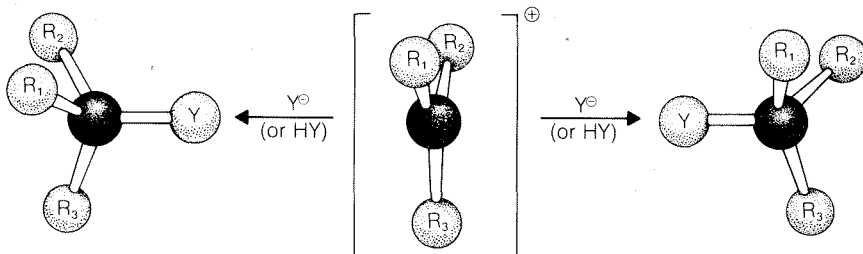
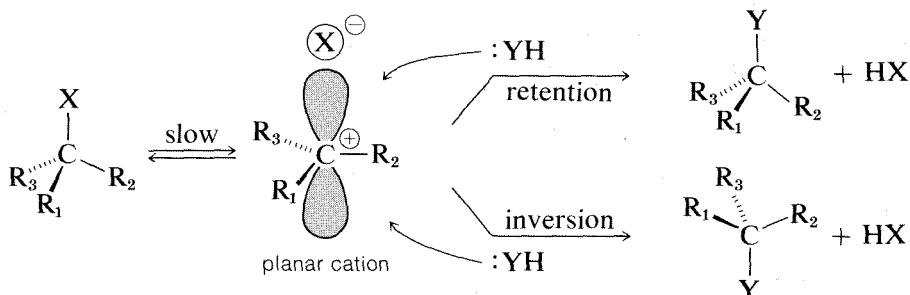


Figure 8-3 Representation of a planar carbocation (with no leaving group close-by) with a ball-and-stick model, having R_1 , R_2 , and R_3 as different alkyl groups, to show why the cation should react equally probably with Y^\ominus or HY to give the right- and left-handed substitution products

Other things being equal, the amount of inversion decreases as the stability of the carbocation intermediate increases, because the more stable the ion the longer is its lifetime, and the more chance it has of getting away from the leaving anion and becoming a relatively "free" ion. The solvent usually has a large influence on the stereochemical results of S_N1 reactions because the stability and lifetime of the carbocations depend upon the nature of the solvent (Section 8-7F).

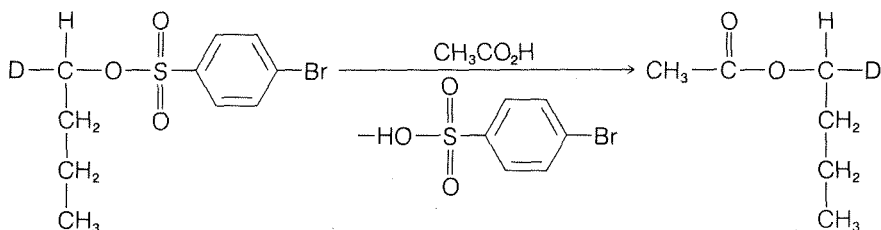
An orbital picture of S_N1 ionization leading to a racemic product may be drawn as follows:



It should be clear that *complete* racemization is unlikely to be observed if X^- stays in close proximity to the side of the positive carbon that it originally departed from. We can say that X^- "shields" the front side, thereby favoring a predominance of inversion. If X^- gets far away before $:YH$ comes in, then there should be no favoritism for one or the other of the possible substitutions.

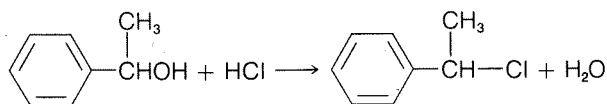
If X^- and the carbocation, R^+ , stay in close proximity, as is likely to be the case in a solvent that does not promote ionic dissociation, then a more or less "tight" ion pair is formed, $R^+ \cdots X^-$. Such ion pairs often play an important role in ionic reactions in solvents of low dielectric constant (Section 8-7F).

Exercise 8-10 What can be concluded about the mechanism of the solvolysis of 1-butyl derivatives in ethanoic acid from the projection formulas of the starting material and product of the following reaction?



Would you call this an S_N1 or S_N2 reaction?

Exercise 8-11 In the reaction of 1-phenylethanol with concentrated HCl, 1-phenylethyl chloride is formed:



If the alcohol originally has the D configuration, what configuration would the resulting chloride have if formed (a) by the S_N2 mechanism and (b) by the S_N1 mechanism?

8-7 STRUCTURAL AND SOLVENT EFFECTS IN S_N REACTIONS

We shall consider first the relationship between the structures of alkyl derivatives and their reaction rates toward a given nucleophile. This will be followed by a discussion of the relative reactivities of various nucleophiles toward a given alkyl derivative. Finally, we shall comment in more detail on the role of the solvent in S_N reactions.

8-7A Structure of the Alkyl Group, R, in S_N2 Reactions

The rates of S_N2 -displacement reactions of simple alkyl derivatives, RX, follow the order *primary R* > *secondary R* \gg *tertiary R*. In practical syntheses involving S_N2 reactions, the primary compounds generally work very well, secondary isomers are fair, and the tertiary isomers are almost completely impractical. Steric hindrance appears to be particularly important in determining S_N2 reaction rates, and the slowness of tertiary halides seems best accounted for by steric hindrance to the back-side approach of an attacking nucleophile by the alkyl groups on the reacting carbon. Pertinent data, which show how alkyl groups affect S_N2 reactivity toward iodide ion, are given in Table 8-1. Not only do alkyl groups suppress reactivity when on the same carbon as the leaving group X, as in *tert*-butyl bromide, but they also have retarding effects when located one carbon away from the leaving group. This is evident in the data of Table 8-1 for 1-bromo-2,2-dimethylpropane (neopentyl bromide), which is very unreactive in S_N2 reactions. Scale models indicate the retardation to be the result of steric hindrance by the methyl groups located on the adjacent β carbon to the approaching nucleophile:

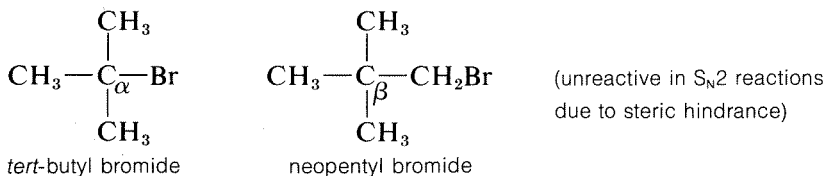


Table 8-1Rates of S_N2 Displacement of Alkyl Bromides with Iodide Ion in 2-Propanone (Acetone) Relative to Ethyl Bromide at 25°

R: (α substitution)	CH ₃ —	CH ₃ CH ₂ —	CH ₃ —CH— CH ₃	CH ₃ —C— CH ₃ CH ₃
relative rate:	145	(1)	0.0078	<0.00051
R: (β substitution)	CH ₃ CH ₂ —	CH ₃ —CH ₂ —CH ₂ —	CH ₃ —CH—CH ₂ — CH ₃	CH ₃ —C—CH ₂ — CH ₃ CH ₃
relative rate:	(1)	0.82	0.036	0.000012

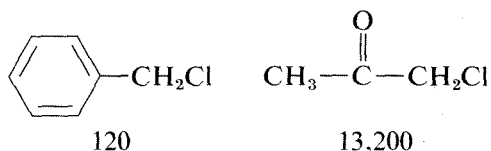
In addition to steric effects, other structural effects of R influence the S_N2 reactivity of RX. A double bond β to the halogen,⁶ as in 2-propenyl, phenylmethyl (benzyl), and 2-oxopropyl chlorides enhances the reactivity of the compounds toward nucleophiles. Thus the relative reactivities toward I[⊖] in 2-propanone are



(1)

0.4

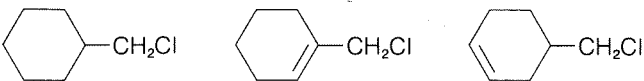
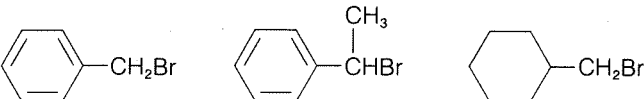
40



Possible reasons for these high reactivities will be discussed later (Section 14-3B).

⁶The Greek letters α, β, γ are used here not as nomenclature, but to designate the positions along a carbon chain from a functional group, X: C_w ··· C_δ—C_γ—C_β—C_α—X (also see Section 7-10).

Exercise 8-12 Predict which compound in each of the following groups reacts most rapidly with potassium iodide in 2-propanone as solvent by the S_N2 mechanism. Give your reasoning and name the substitution product by the IUPAC system.

- a. $(\text{CH}_3)_3\text{CCH}_2\text{Cl}$ $(\text{CH}_3)_3\text{CCl}$ $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$
- b. 
- c. 

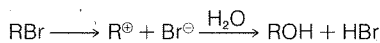
8-7B Structure of the Alkyl Group, R, in S_N1 Reactions

The rates of S_N1 reactions of simple alkyl derivatives follow the order *tertiary* $\text{R} \gg$ *secondary* $\text{R} \gg$ *primary* R , which is exactly opposite that of S_N2 reactions. This is evident from the data in Table 8-2, which lists the relative rates of hydrolysis of some alkyl bromides; only the secondary and tertiary bromides react at measurable rates, and the tertiary bromide reacts some 10^5 times faster than the secondary bromide.

Why do tertiary alkyl compounds ionize so much more rapidly than either secondary or primary compounds? The reason is that tertiary alkyl cations are more *stable* than either secondary or primary cations and therefore are formed more easily. You will appreciate this better by looking at the energy diagram of Figure 8-4, which shows the profile of energy changes for hydrolysis of an alkyl compound, RX , by the S_N1 mechanism. The *rate* of

Table 8-2

Rates of Hydrolysis of Alkyl Bromides in Water at 50° Relative to Ethyl Bromide



R:	CH_3-	CH_3CH_2-	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CH}- \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{C}- \\ \\ \text{CH}_3 \end{array}$
relative rate:	1.05 ^a	(1.00) ^a	11.6	1.2×10^6

^aThe reaction mechanism is almost surely S_N2 with solvent acting as the nucleophile because addition of hydroxide ion causes the reaction rate to increase markedly (see Section 8-4B). The relative rate given can be regarded only as an upper limit to the actual S_N1 value, which may be as much as 10^5 times slower.

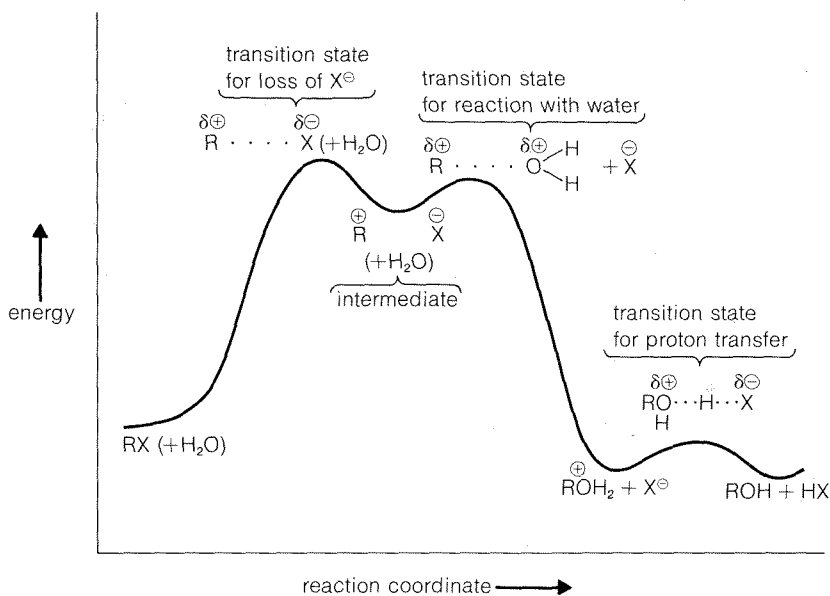
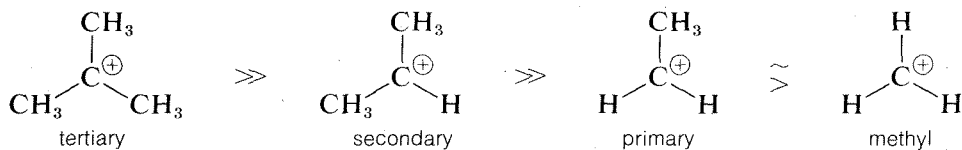


Figure 8-4 Profile of energy changes for hydrolysis of RX by the S_N1 mechanism in accord with the steps $RX \xrightarrow{\text{slow}} R^{\oplus}X^{\ominus} \xrightarrow[\text{fast}]{H_2O} ROH_2^{\oplus} + X^{\ominus} \rightarrow ROH + HX$. The last step is not part of the S_N1 process itself but is included for completeness. The water molecule shown in parentheses ($+ H_2O$) is necessary to balance the equations, but it should not be considered to be different from the other water molecules in the solvent until it is specifically involved in the second transition state.

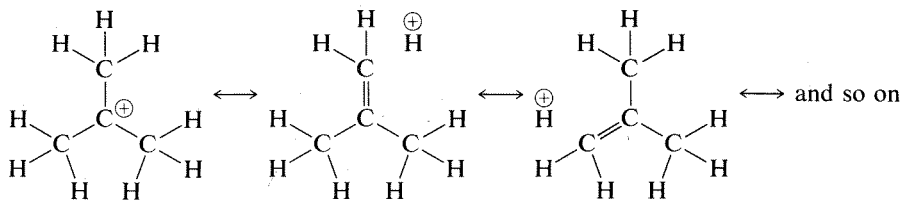
reaction is determined by the ionization step, or by the energy of the transition state relative to that of the reactants. Actually, the energy of the transition state is only slightly higher than the energy of the ionic intermediates $R^{\oplus}X^{\ominus}$. Thus to a first approximation, we can say that the rate of ionization of RX will depend on the energies of the ions formed. Now if we compare the rates for a series of compounds, RX , all having the same leaving group, X , but differing only in the structure of R , their relative rates of ionization will correspond to the relative stabilities of R^{\oplus} . The lower energy of R^{\oplus} , the faster will be the rate of ionization. Therefore the experimental results suggest that the sequence of carbocation stabilities is *tertiary* $R^{\oplus} \gg$ *secondary* $R^{\oplus} \gg$ *primary* R^{\oplus} .

Just why this sequence is observed is a more difficult question to answer. Notice in the following stability sequence that alkyl cations are more stable the more alkyl groups there are on the positive carbon:



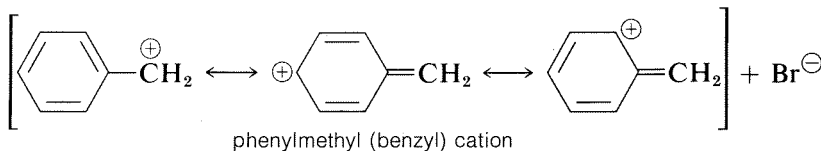
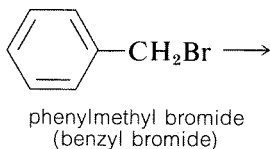
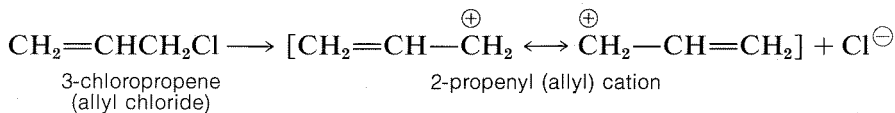
The simplest explanation for why this is so is that alkyl groups are more **polarizable** than hydrogens. In this case, more polarizable means the electrons of the alkyl groups tend to move more readily toward the positive carbon than do those of the hydrogens. Such movements of electrons transfer part of the charge on the cationic carbon to the alkyl groups, thereby spreading the charge over a greater volume. This constitutes *electron delocalization*, which results in enhanced stability (see Section 6-5A).

An alternative way of explaining how the cationic charge is spread over the alkyl groups of a tertiary cation, such as the *tert*-butyl cation, is to write the cation as a hybrid of the following structures:

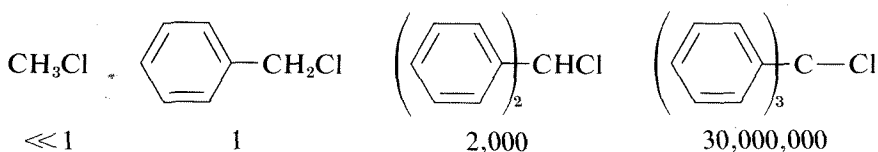


Here, the principal structure is the one on the far left, but a small contribution of the others is assumed to delocalize the C–H bonding electrons to the central carbon and thus stabilize the ion. Obviously, the number of such structures will decrease with decreasing number of alkyl groups attached to the cationic carbon and none can be written for CH_3^+ . This explanation is known as the **hyperconjugation** theory.

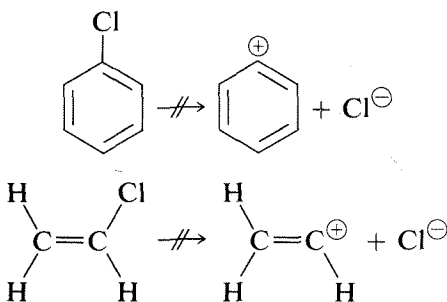
Other organohalogen compounds besides secondary and tertiary alkyl compounds can react by $\text{S}_{\text{N}}1$ mechanisms provided they have the ability to form reasonably stabilized carbon cations. Examples include 2-propenyl (allylic) and phenylmethyl (benzylic) compounds, which on ionization give cations that have delocalized electrons (see Section 6-6):



In general, the more stabilized the carbon cation derived from an alkyl halide, the more reactive the compound will be in S_N1-type reactions. This is especially apparent in the reactivities of compounds with phenyl groups on the reacting carbon. As the number of phenyl groups increases from zero to three, the S_N1 reactivity of the chlorides increases by more than 10⁷ because of increasing stabilization of the carbon cation by the phenyl groups:

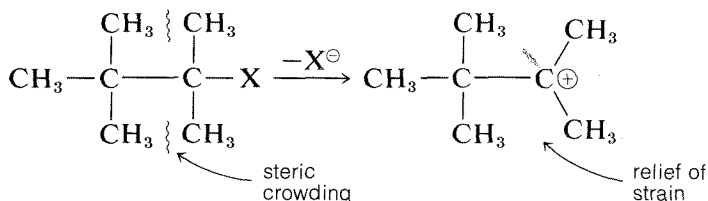


In contrast, compounds such as chlorobenzene and chloroethene, in which the halogen is attached directly to a multiply bonded carbon atom, do *not* exhibit S_N1-type reactions. Evidently then, unsaturated carbon cations such as phenyl or ethenyl are appreciably less stable (more difficult to form) than *tert*-alkyl cations:



Reasons for this will be considered in Section 14-4B.

Steric hindrance is relatively unimportant in S_N1 reactions because the rate is independent of the nucleophile. In fact, steric acceleration is possible in the solvolysis of highly branched alkyl halides through relief of steric compression between the alkyl groups in the halide by formation of a planar cation:



Along with the effect R has on the *rate* at which an alkyl compound RX reacts by an S_N1 mechanism, the group R also affects the nature of the products

obtained. The intermediate alkyl cations R^{\oplus} may react in various ways to give products of substitution, elimination, and rearrangement. Elimination pathways are discussed more fully starting in Section 8-8, and rearrangement of carbon cations in Section 8-9B.

Exercise 8-13 Which of the monobromine-substituted methylcyclohexanes would you judge to be the most reactive in (a) S_N2 -type displacement and (b) S_N1 -type displacement?

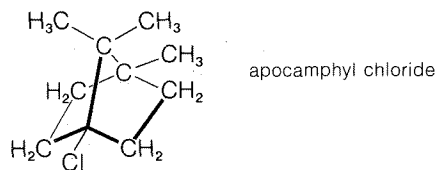
Exercise 8-14 Answer the question in the preceding exercise, but with the monobromine-substituted 1-methylcyclohexenes.

Exercise 8-15 Select the compounds from the following list that would be expected to hydrolyze *more rapidly* than phenylmethyl (benzyl) chloride by the S_N1 mechanism:

- | | |
|----------------------------|------------------------------|
| a. 2-phenylethyl chloride | d. (chloromethyl)cyclohexane |
| b. diphenylmethyl chloride | e. 1-chloro-4-methylbenzene |
| c. 1-phenylethyl chloride | |

Exercise 8-16 Explain the following observations:

- a. The tertiary chloride, apocamphyl chloride, is unreactive in either S_N1 or S_N2 reactions. For example, no reaction occurs when its solution in aqueous ethanol containing 30% potassium hydroxide is refluxed for 20 hours.



- b. Chloromethyl alkyl (or aryl) ethers, $ROCH_2Cl$, are very reactive in S_N1 solvolysis reactions. Compared to chloromethane, the rate of hydrolysis of chloromethyl phenyl ether is about 10^{14} . Also, the rate of hydrolysis is retarded significantly by lithium chloride.

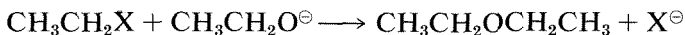
8-7C The Leaving Group

The reactivity of a given alkyl derivative, RX , in either S_N1 or S_N2 reactions, is influenced strongly by the leaving group, X . The choice of leaving group is therefore an important consideration in any synthesis involving S_N reactions.

From the foregoing discussion of structural effects in the R group on S_N reactivity, particularly in S_N1 reactions, we might expect the *stability* of $:X$

as an ion or neutral molecule to play a major role in determining how good or poor X is as a leaving group. The stability of :X is indeed important—the problem is that there are several factors that contribute to the stability and hence the lability of the leaving group.

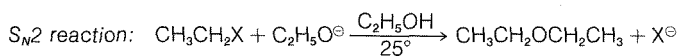
For the purpose of initially identifying good and poor leaving groups, consider development of a practical synthesis of diethyl ether. One route is by way of S_N2 displacement using an ethyl compound, CH₃CH₂X, and ethoxide ion:

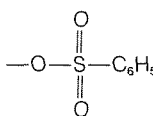


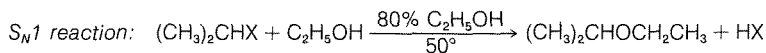
Many CH₃CH₂X compounds have X groups that are quite unsatisfactory in this reaction. They include compounds such as ethane, propane, ethanol, ethyl methyl ether, ethylamine, and ethyl ethanoate; the respective groups, H[⊖], CH₃[⊖], HO[⊖], CH₃O[⊖], NH₂[⊖], and CH₃CO₂[⊖] all can be classified as *very poor* leaving groups. The more reactive ethyl derivatives (see Table 8-3) include the halides, particularly ethyl iodide, and sulfonic acid derivatives; the corresponding anions Cl[⊖], Br[⊖], I[⊖], and RS(O₂)O[⊖] therefore are *moderate to good* leaving groups. Table 8-3 includes pertinent data for the rates of ether formation from various alkyl compounds and illustrates that the relative abilities of groups to leave are about the same in S_N1 reactions as they are in S_N2 reactions.

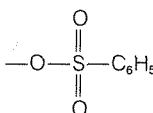
Table 8-3

Dependence of Rate of S_N Reactions on the Leaving Group, X



X:		—I	—Br	—Cl	—F
relative rate ^a :	5.8	1.9	(1.0)	0.024 ^b	—
C—X bond energy (kcal):	—	53	69	82	109



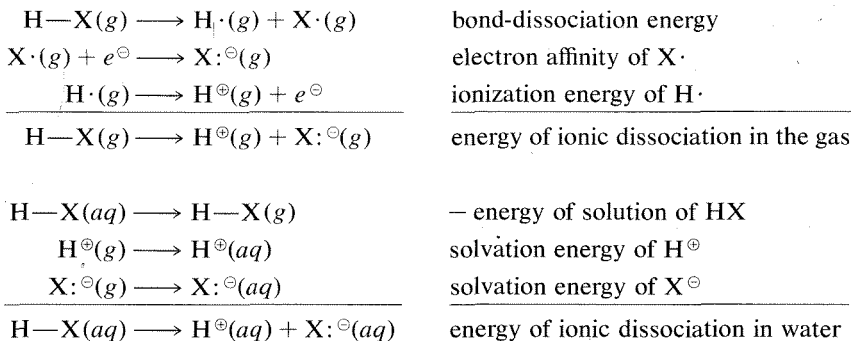
X		—I	—Br	—Cl
relative rate ^a	76.3	—	(1.0)	0.0131

^aThe rates are relative to the bromo compound as 1.0. ^bAt 40°.

Why are groups such as I^\ominus and RSO_3^\ominus good leaving groups, whereas others such as H^\ominus , HO^\ominus , and NH_2^\ominus are poor? The simplest correlation is with the strength of HX as an acid. This is very reasonable because the ease of loss of X^\ominus , as from $(\text{CH}_3)_3\text{C}-\text{X}$ in an $\text{S}_\text{N}1$ reaction, would be expected to be related, to some degree at least, to the ease of ionization of $\text{H}-\text{X}$ to H^\oplus and X^\ominus . Therefore the stronger HX is as an acid, the better X will be as a leaving group. Thus HF is a relatively weak acid and F^\ominus is not a very good leaving group; $\text{H}-\text{I}$ is a very strong acid and I^\ominus is a good leaving group. The usual order of reactivity of alkyl halides, $\text{R}-\text{I} > \text{R}-\text{Br} > \text{R}-\text{Cl} > \text{R}-\text{F}$ (when R is the same group throughout), is in accord with the acid strengths of the halogen acids. Similarly, CF_3CO_2- is a much better leaving group than CH_3CO_2- , and we find that trifluoroethanoic acid, $\text{CF}_3\text{CO}_2\text{H}$, is a several thousand times stronger acid than ethanoic acid, $\text{CH}_3\text{CO}_2\text{H}$. For the same reason, $\text{CF}_3\text{SO}_3^\ominus$ is a better leaving group than $\text{CH}_3\text{SO}_3^\ominus$.

This correlation can be extended easily to groups that leave as neutral $\text{X}:$. For example, $\text{ROH}_2^\oplus \longrightarrow \text{R}^\oplus + \text{H}_2\text{O}$ occurs far more readily than $\text{ROH} \longrightarrow \text{R}^\oplus + \text{OH}^\ominus$ and we know that $\text{H}_3\text{O}^\oplus$ is a stronger acid (or better proton donor) than H_2O .

The relationship between X^\ominus as a leaving group and HX as an acid is very useful because much information is available on acid strengths. However, it is not a very fundamental explanation unless we can explain why some acids are strong acids and others are weak acids. One factor is the strength of the $\text{H}-\text{X}$ bond, but here we need to remember that the usual bond strengths are for dissociation to radicals or atoms, not ions, and for the gas, not for solutions. If we write the steps relating the bond-dissociation energy to the energy of ionic dissociation in solution, we see that for variations in X , in addition to the bond energy, the electron affinity of X^\cdot , the solvation energy of X^\ominus , and the solvation energy of HX , also will be contributing factors.



Pauling has shown for the halogen acids that the bond dissociation energy, which is highest for $\text{H}-\text{F}$ and lowest for $\text{H}-\text{I}$, can be regarded as the most important factor in determining the energy of dissociation in solution. The above energy equations can be written in the same way with RX in place of HX , and we would expect to reach the same conclusion about the ease of X leaving carbon, because $\text{C}-\text{X}$ bond energies are reasonably closely proportional to $\text{H}-\text{X}$ bond energies (see Figure 8-5 and Table 8-3).

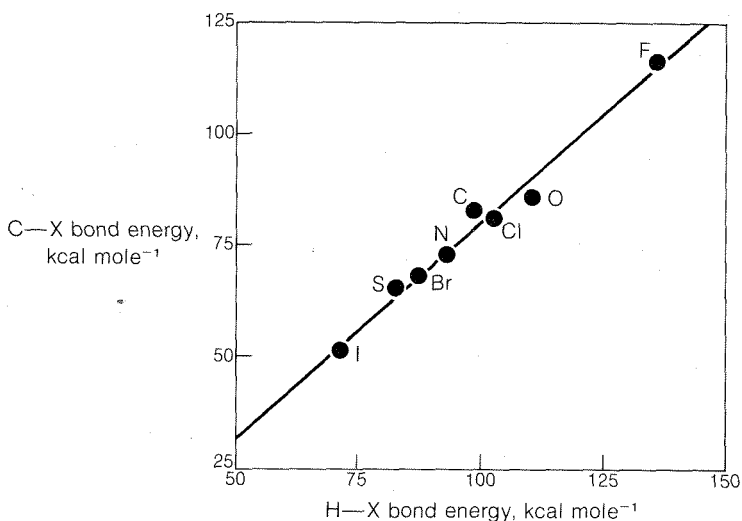


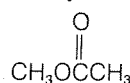
Figure 8-5 Plot of C-X bond energies against H-X bond energies, using the data of Table 4-3

Exercise 8-17 Methyl sulfides are prepared conveniently by the S_N2 reaction of a CH_3X derivative with a sulfur nucleophile: $\text{RS}^\ominus + \text{CH}_3\text{X} \longrightarrow \text{RSCH}_3 + \text{X}^\ominus$. The rate of the reaction with a given RS^\ominus will depend on the quality of X^\ominus as a leaving group. Indicate for the following CH_3X compounds which will react readily, slowly, or essentially not at all with RS^\ominus . If you are uncertain of the pK_a of the acids HX , look them up in an appropriate reference, such as the *CRC Handbook of Physics and Chemistry*.

a. dimethyl sulfate, $(\text{CH}_3\text{O})_2\text{SO}_2$

g. methyl acetate (ethanoate),

b. methyl nitrate, CH_3ONO_2



c. methyl cyanide (ethanenitrile), CH_3CN

d. methyl fluoride, CH_3F

e. methyl iodide, CH_3I

h. methanol, CH_3OH

f. methyl fluorosulfonate, $\text{CH}_3\text{—O—S—F}$

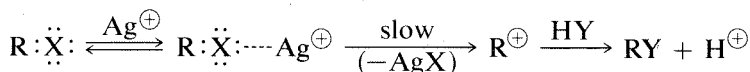
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{—O—S—F} \\ \parallel \\ \text{O} \end{array}$$

8-7D Enhancement of Leaving Group Abilities by Electrophilic Catalysis

In general, a leaving group that leaves as a neutral molecule is a much better leaving group than one that leaves as an anion. Alcohols, ROH , are particularly *unreactive* in S_N reactions because OH^\ominus is a very poor leaving group.

However, if a strong acid is present, the reactivity of the alcohol is enhanced greatly. The acid functions by donating a proton to the oxygen of the alcohol, thereby transforming the hydroxyl function into ROH_2^+ , which has a much better leaving group, H_2O in place of OH^- . The S_N reactions of ethers and esters are acid-catalyzed for the same reason.

Heavy-metal salts, particularly those of silver, mercury, and copper, catalyze $\text{S}_\text{N}1$ reactions of alkyl halides in much the same way that acids catalyze the S_N reactions of alcohols. A heavy-metal ion functions by complexing with the unshared electrons of the halide, thereby making the leaving group a metal halide rather than a halide ion. This acceleration of the rates of halide reactions is the basis for a qualitative test for alkyl halides with silver nitrate in ethanol solution:

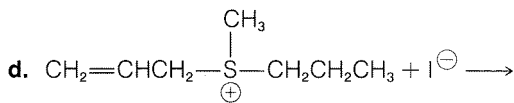
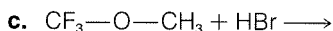
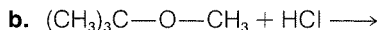
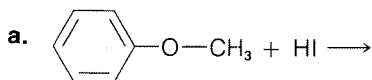


Silver halide precipitates at a rate that depends upon the structure of the alkyl group, *tertiary* > *secondary* > *primary*. Tertiary halides usually react immediately at room temperature, whereas primary halides require heating. That complexes actually are formed between organic halides and silver ion is indicated by an increase in water solubility in the presence of silver ion for those halides that are slow in forming carbocations.

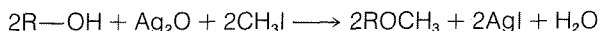
Exercise 8-18 Account for the following observations:

- tert*-Alkyl fluorides are unreactive in $\text{S}_\text{N}1$ solvolysis reactions *unless* a strong acid is present.
- D-1-Phenylethyl chloride dissolved in *aqueous* 2-propanone containing mercuric chloride loses much of its optical activity before undergoing hydrolysis to give racemic 1-phenylethanol.
- 1-Bromobutane can be prepared by heating 1-butanol with a mixture of sodium bromide and sulfuric acid. The reaction fails, however, if the sulfuric acid is omitted.
- Benzenoxide (phenoxide) ion, $\text{C}_6\text{H}_5\text{O}^-$, is a better leaving group than ethoxide, $\text{C}_2\text{H}_5\text{O}^-$.

Exercise 8-19 Using the discussion in Section 8-7 of how the structure of R and X influence the S_N reactivity of RX, predict the favored course of each of the following reactions. Give your reasoning.



Exercise 8-20 Methyl ethers of the type $R-O-CH_3$ cannot be prepared by the reaction of the alcohol ROH with CH_3I , but if Ag_2O is present the following reaction occurs under mild conditions:



Explain how Ag_2O promotes this reaction.

8-7E The Nucleophilic Reagent

The nucleophilicity of a particular reagent ($:Y$, $:Y^\ominus$, or HY) can be defined as its ability to donate an electron pair to another atom (see Section 8-1). In fact, the S_N2 reactivity of a reagent toward a methyl derivative can be taken to measure its nucleophilicity toward carbon. The relative reaction rates of some nucleophiles toward methyl bromide are listed in order of increasing nucleophilicity in Table 8-4, together with their basicities as measured by K_b . Important generalizations can be made from these data provided that one recognizes that they may apply only to hydroxylic solvents.

1. For the atoms representing any one group (column) of the periodic table, nucleophilicity *increases* with increasing atomic number: $I^\ominus > Br^\ominus >$

Table 8-4
Reactivities of Various Nucleophiles toward Methyl Bromide in Water at 50°

Nucleophile	Approximate reaction half-time, hr ^a	Rate relative to water	K_b
H_2O	1,100 ^b	(1)	10^{-16}
$CH_3CO_2^\ominus$	2.1	5.2×10^2	10^{-11}
Cl^\ominus	1	1.1×10^3	$\sim 10^{-20}$
Br^\ominus	0.17	7.8×10^3	$< 10^{-20}$
N_3^\ominus	0.11	1.0×10^4	10^{-11}
HO^\ominus	0.07	1.6×10^4	55
$C_6H_5NH_2$	0.04	3.1×10^4	10^{-10}
SCN^\ominus	0.02	5.9×10^4	10^{-14}
I^\ominus	0.01	1.1×10^5	$< 10^{-22}$

^aTime in hours required for half of methyl bromide to react at constant (1M) concentration of nucleophile.

^bCalculated from data for pure water, assuming water to be 55M.

^cDefined as the equilibrium constant for $X^\ominus + H_2O \rightleftharpoons HX + OH^\ominus$ or $X + H_2O \rightleftharpoons HX^\oplus + OH^\ominus$.

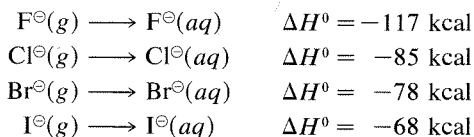
$\text{Cl}^\ominus > \text{F}^\ominus$; $\text{HS}^\ominus > \text{HO}^\ominus$; $\text{PH}_3 > \text{NH}_3$. Thus, other things being equal, larger atoms are better nucleophiles.

2. For nucleophiles having the same atomic number of the entering atom (e.g., oxygen nucleophiles), there is usually a good correlation between the basicity of the reagent and its nucleophilicity. Thus a weak base such as $\text{CH}_3\text{CO}_2^\ominus$ is a poorer nucleophile than a strong base such as $^\ominus\text{OH}$. The poorer X^\ominus is as a leaving group, the better it is as an entering group.

3. For nucleophiles of different atomic numbers, nucleophilicity usually does *not* parallel basicity. For example, for the halogens the reactivity sequence $\text{I}^\ominus > \text{Br}^\ominus > \text{Cl}^\ominus$ is opposite to the sequence of basicity $\text{Cl}^\ominus > \text{Br}^\ominus > \text{I}^\ominus$. Similarly, sulfur anions such as HS^\ominus are better nucleophiles but *weaker* bases than corresponding oxyanions such as HO^\ominus .

4. A number of nucleophilic agents, which are very reactive in $\text{S}_\text{N}2$ reactions, are of the type $\text{X}-\text{Y}$, where both atoms have unshared electron pairs. Examples include HOO^\ominus , $\text{H}_2\text{NO}^\ominus$, ClO^\ominus , and H_2NNH_2 , all of which are more reactive than the closely related nucleophiles HO^\ominus and NH_3 .

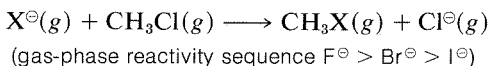
Why is the correlation between basicity and nucleophilicity so poor for atoms of different atomic number? It is now clear from much research that the dominant effect is associated with differences in the solvation energies of the ions, as defined for halide ions by the following equations:



The solvation energies of small ions with concentrated charge always are greater than those of large ions with diffuse charge.

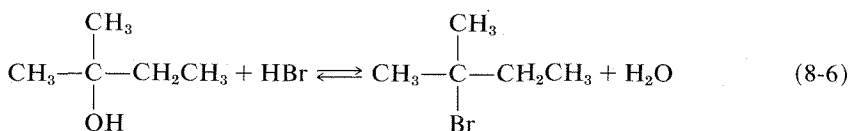
When an ion participates in a nucleophilic attack on carbon, it must slough off some of the solvent molecules that stabilize it in solution. Otherwise, the ion cannot get close enough to the carbon, to which it will become attached, to begin forming a bond. Sloughing off solvent molecules will be less favorable for a small ion than a large ion. Consequently, we expect Cl^\ominus to be less reactive than I^\ominus .

Strong evidence for solvation effects on reactivity is provided by the fact that chloride ion is *more* reactive than iodide ion in solvents that have low solvation energies for anions (see Section 8-7F). Furthermore, in the gas phase where solvation effects are absent, F^\ominus is more reactive than any of the other halide ions toward chloromethane:



It should be recognized that S_N reactions may be reversible when both the leaving group X and the entering group Y are good entering and leaving groups, respectively. In such circumstances, the position of the equilibrium often can

be changed by suitably adjusting the reaction conditions. Thus 48% aqueous hydrogen bromide can convert alcohols to alkyl bromides (Equation 8-6, forward direction), whereas the reverse reaction (hydrolysis) is achieved by high water concentration:



Exercise 8-21 Explain each of the following observations:

a. Methyl sulfide $(\text{CH}_3)_2\text{S}$ reacts with $\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$ in benzene to give the sulfonium

salt, $\text{C}_6\text{H}_5\text{COCH}_2\overset{\oplus}{\text{S}}(\text{CH}_3)_2\text{Cl}^\ominus$, which precipitates as it is formed. Attempts to recrystallize the product from ethanol result in formation of methyl sulfide and $\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$.

b. $\text{S}_{\text{N}}2$ displacements of alkyl chlorides by OH^\ominus often are catalyzed by iodide ion,



and may result in a product with less than 100% of inverted configuration at the carbon carrying the chlorine.

c.* Tris(trifluoromethyl)amine, $(\text{CF}_3)_3\text{N}$, is completely nonnucleophilic, whereas trimethylamine is a good nucleophile.

8-7F The Nature of the Solvent

The rates of S_{N} reactions are sensitive to the nature and composition of the solvent. This is easy to understand for $\text{S}_{\text{N}}1$ reactions because the ionizing

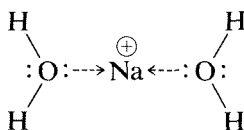
power of a solvent is crucial to the ease of formation of ions $\overset{\oplus}{\text{R}}$ and $\overset{\ominus}{\text{X}}$ from RX .

Actually, two factors are relevant in regard to the ionizing ability of solvents. First, a high dielectric constant increases ionizing power by making it easier to separate ions. This is because the force between charged particles varies inversely with the dielectric constant of the medium.⁷ Thus water, with a dielectric constant of 80, is 40 times more effective than a hydrocarbon with a dielectric constant of 2. Second, and usually more important, is the ability of the solvent to solvate the separated ions. Cations are solvated most effectively

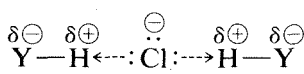
⁷Specifically, electrostatic force = $q_1q_2/r_{12}^2\epsilon$ in which q_1 and q_2 are the charges, r_{12} is the distance between the charges, and ϵ is the dielectric constant of the medium; $\epsilon = 1$ for a vacuum.

by compounds of elements in the first row of the periodic table that have unshared electron pairs. Examples are ammonia, water, alcohols, carboxylic acids, sulfur dioxide, and methylsulfinylmethane [dimethyl sulfoxide, $(\text{CH}_3)_2\text{SO}$]. Anions are solvated most efficiently by solvents having hydrogen attached to a strongly electronegative element Y so the H—Y bond is strongly

polarized as $\overset{\delta\oplus}{\text{H}} \cdots \overset{\delta\ominus}{\text{Y}}$. Such solvents usually are called **protic solvents**. Protic solvents form hydrogen bonds to the leaving group, which assist ionization in much the same way that silver ion catalyzes ionization of alkyl halides (Section 8-7D). We can represent solvation by the following structural formulas, but it must be recognized that the number of solvent molecules involved in close interactions can be as large as four or six, or as small as one:



solvation of a cation by a solvent with unshared electron pairs



solvation of an anion by a hydrogen-bonding or protic solvent

The most effective ionizing solvents are those that effectively solvate both anions and cations. Water strikes an excellent compromise with regard to the structural features that make up ionizing power, that is, dielectric constant *and* solvating ability. From this, we expect *tert*-butyl chloride to ionize much more readily in water than in ether, because ethers can solvate only cations effectively, whereas water can solvate both anions and cations. The fact is that $\text{S}_{\text{N}}1$ ionizations usually are so difficult that $\text{S}_{\text{N}}1$ reactions seldom occur in solvents that cannot effectively solvate *both* anions and cations, even if the dielectric constant of the solvent is high. Solvation by hydrogen bonding is especially helpful in assisting ionization. Solvents that cannot provide such hydrogen bonding [e.g., CH_3OCH_3 , $(\text{CH}_3)_3\text{N}$, CH_3NO_2 , CH_3CN , $(\text{CH}_3)_2\text{SO}$] generally are poor for $\text{S}_{\text{N}}1$ reactions. These solvents are called **aprotic solvents**. An important exception is liquid sulfur dioxide, SO_2 , which promotes $\text{S}_{\text{N}}1$ ionization by having a high dielectric constant and being able to solvate both anions and cations.

A list of protic and aprotic solvents, their dielectric constants, boiling points, and melting points is given in Table 8-5. This table will be useful in selecting solvents for nucleophilic substitution reactions.

With regard to $\text{S}_{\text{N}}2$ reactions, the solvent can affect profoundly the reactivity of a given nucleophile. Thus anions such as Cl^\ominus and CN^\ominus , which are weakly nucleophilic in hydroxylic solvents and in poor ionizing solvents such as 2-propanone (acetone), become very significantly nucleophilic in polar aprotic solvents such as $(\text{CH}_3)_2\text{SO}$. The reason is that for salts such as NaCl and NaCN the aprotic solvent preferentially solvates the cation, leaving the anion relatively bare. This dissociation of the anion from the cation together with its poor solvation makes the anion abnormally reactive as a nucleophile.

Table 8-5
Solvent Properties

Compound	Formula	Dielectric constant, ϵ^{20}	bp, °C	mp, °C	Solubility in water
hydrogen cyanide	HCN	115	26	-14	+
methanamide (formamide)	HCONH ₂	84	210.5	2.5	+
hydrogen fluoride	HF	84 ^a	19.7	-83.7	+
water	H ₂ O	80	100	0	+
methanoic (formic) acid	HCO ₂ H	58	100	8.5	+
methylsulfinylmethane (dimethyl sulfoxide)	(CH ₃) ₂ SO	45	189	18	+
1,2,3-propanetriol (glycerol)	HOCH ₂ CHOHCH ₂ OH	42.5	290 (dec)	17.8	+
ethanenitrile (acetonitrile)	CH ₃ CN	38.8	81.6	-45	+
<i>N,N</i> -dimethylmethanamide (dimethylformamide)	HCON(CH ₃) ₂	—	153	-61	+
nitromethane	CH ₃ NO ₂	38	101.2	-29	+ ^b
methanol	CH ₃ OH	32.6	64.7	-97.8	+
ethanol	CH ₃ CH ₂ OH	24	78.5	-118	+
2-propanone (acetone)	CH ₃ COCH ₃	21	56.5	-94	+
ammonia	NH ₃	17	-33	-78	+
sulfur dioxide	SO ₂	17.6 ^c	-10	-72	^a
azabenzene (pyridine)	C ₅ H ₅ N	12.3	115	-42	+
dichloromethane	CH ₂ Cl ₂	9.1	40	-95	—
ethanoic (acetic) acid	CH ₃ CO ₂ H	6.2	118	16.7	+
trichloromethane (chloroform)	CHCl ₃	4.8	61	-64	—
diethyl ether	(C ₂ H ₅) ₂ O	4.3	35	-116	—
carbon disulfide	CS ₂	2.6	46.5	-111.6	—
1,4-dioxacyclohexane (dioxane)	O[(CH ₂) ₂] ₂ O	2.2	101	11.8	+
tetrachloromethane (carbon tetrachloride)	CCl ₄	2.2	76.7	-23	—
benzene	C ₆ H ₆	2.3	80.1	5.5	—
cyclohexane	C ₆ H ₁₂	2.0	80.7	6.5	—

^aAt 0°. ^bSlightly soluble. ^cAt -20°. ^dReacts with water.

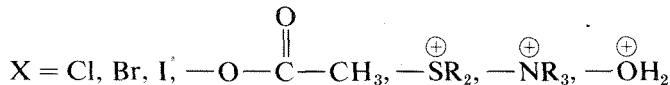
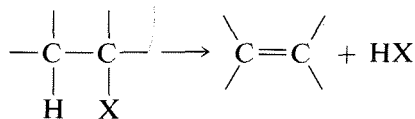
Exercise 8-22 Classify the following solvents according to effectiveness for solvation of (i) cations and (ii) anions:

- a. 2-propanone, CH_3COCH_3 d. trichloromethane, CHCl_3
 b. tetrachloromethane, CCl_4 e. trimethylamine, $(\text{CH}_3)_3\text{N}$
 c. anhydrous hydrogen fluoride, HF f. trimethylamine oxide, $(\text{CH}_3)_3\text{N}^+\text{O}^-$

Exercise 8-23* Would you expect the $\text{S}_{\text{N}}2$ reaction of sodium cyanide with methyl bromide to be faster, slower, or about the same with $(\text{CH}_3)_2\text{S}=\text{O}$ or ethanol as solvent? Explain.

Elimination Reactions

Generally, an alkyl derivative, under appropriate conditions, will eliminate HX , where X is commonly a halide, ester, or -onium function, provided that there is a hydrogen located on the carbon adjacent to that bearing the X function:

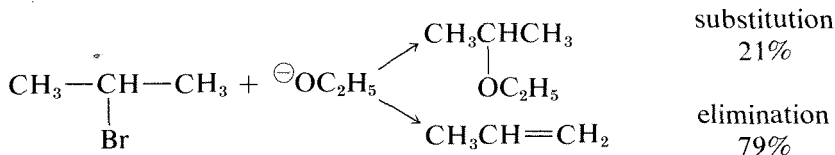


An important feature of many elimination reactions is that they occur with the same combinations of reagents that cause nucleophilic substitution. In fact, elimination and substitution often are competitive reactions. Therefore it should be no surprise that substitution and elimination have closely related mechanisms.

8-8 THE E2 REACTION

8-8A Kinetics and Mechanism

The conditions used for substitution reactions by the S_N2 mechanism very often lead to elimination. The reaction of 2-bromopropane with sodium ethoxide in ethanol provides a good example:

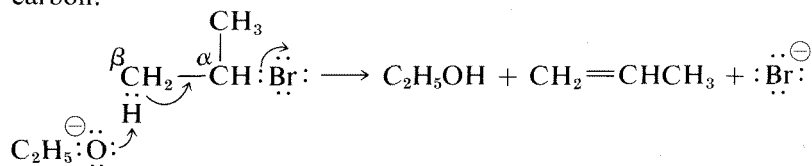


Elimination to give propene competes with substitution to give ethyl isopropyl ether. Furthermore, the rate of elimination, like the rate of substitution, is proportional to the concentrations of 2-bromopropane and ethoxide ion. Thus elimination here is a second-order reaction (it may be helpful to review Section 8-4 at this point):

$$\text{rate of substitution} = k_S[\text{RBr}][\text{OC}_2\text{H}_5\ominus]$$

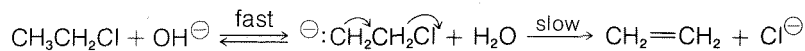
$$\text{rate of elimination} = k_E[\text{RBr}][\text{OC}_2\text{H}_5\ominus]$$

As to the *mechanism* of this kind of elimination, the attacking base, $\ominus\text{OC}_2\text{H}_5$, removes a proton from the β carbon more or less simultaneously with the formation of the double bond and the loss of bromide ion from the neighboring carbon:



The abbreviation for this mechanism is **E2**, E for elimination and 2 for bimolecular, there being two reactants involved in the transition state.

Exercise 8-24 An alternative mechanism for E2 elimination is the following:



a. Would this mechanism lead to overall second-order kinetics with respect to the concentrations of OH^\ominus and ethyl chloride? Explain.

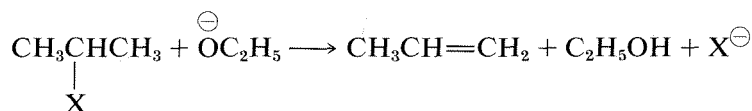
b. This mechanism as written has been excluded for several halides by carrying out the reaction in deuterated solvents such as D_2O and C_2H_5OD . Explain how such experiments could be relevant to the reaction mechanism.

c. Does the test in Part b also rule out $CH_3CH_2Cl + OH^- \xrightarrow{\text{slow}} :CH_2CH_2Cl + H_2O \xrightarrow{\text{fast}} CH_2=CH_2 + Cl^-$? Explain.

8-8B Structural Effects

Structural influences on E2 reactions have been studied in some detail. Like the competing S_N2 process, a good leaving group is necessary and of these, the most commonly used are the halides, Cl, Br, and I; sulfonate esters,

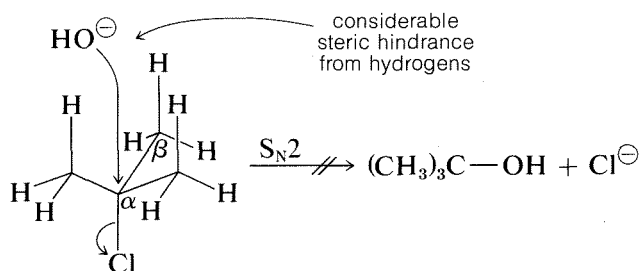
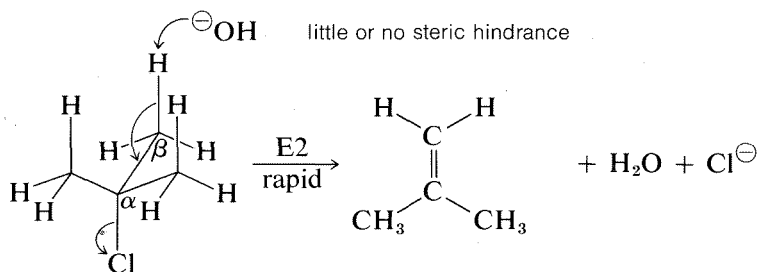
$RS(O_2)O-$; and -onium ions such as ammonium, $-\overset{\oplus}{N}-$, and sulfonium,



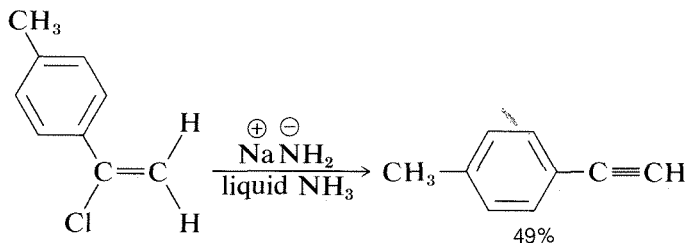
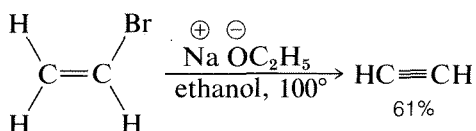
Rather strong bases generally are required to bring about the E2 reaction. The effectiveness of a series of bases generally parallels their base strengths, and the order $NH_2^- > OC_2H_5^- > OH^- > O_2CCH_3^-$ is observed for E2 reactions. This fact is important in planning practical syntheses, because the E2 reaction tends to predominate with strongly basic, slightly polarizable reagents such as amide ion, NH_2^- , or ethoxide ion, $OC_2H_5^-$. In contrast, S_N2 reactions tend to be favored with weakly basic nucleophiles such as iodide ion or ethanoate ion (unless dipolar aprotic solvents are used, which may markedly change the reactivity of anionic nucleophiles).

As for the alkyl group, there are two important structural effects to notice. First, at least one C-H bond adjacent (β) to the leaving group is required. Second, the ease of E2 elimination follows the order *tertiary* R > *secondary* R > *primary* R. Unlike S_N2 reactions, which are *not* observed for tertiary alkyl compounds because of steric hindrance to the approach of the nucleophile to carbon, the related E2 reaction usually occurs readily with tertiary RX compounds. The reason is that little or no steric hindrance is likely

for the approach of a base to a hydrogen unless the base is exceptionally bulky:

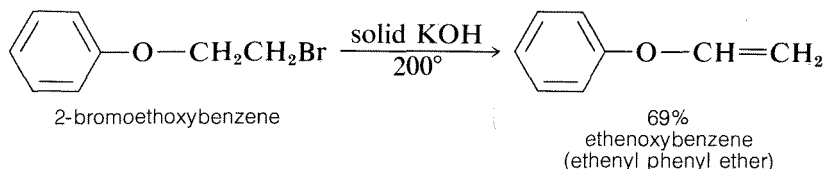


The reactivity order also appears to correlate with the C-X bond energy, inasmuch as the tertiary alkyl halides both are more reactive and have weaker carbon-halogen bonds than either primary or secondary halides (see Table 4-6). In fact, elimination of HX from haloalkenes or haloarenes with relatively strong C-X bonds, such as chloroethene or chlorobenzene, is much less facile than for haloalkanes. Nonetheless, elimination does occur under the right conditions and constitutes one of the most useful general methods for the synthesis of alkynes. For example,



The conditions and reagents used for E2 and S_N2 reactions are similar enough that it is difficult to have one occur without the other. However, E2

elimination is favored over S_N2 substitution by (a) strongly basic nucleophiles, (b) bulky nucleophiles, and (c) increasing alkyl substitution at the α carbon. It also is observed that increasing the reaction temperature generally leads to an increase in elimination at the expense of substitution. In fact, surprisingly good yields of alkene or alkyne can be obtained by adding a halogen compound directly to molten or very hot KOH with no solvent present, whereupon the product is formed rapidly and distills immediately from the hot reaction mixture:

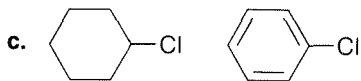
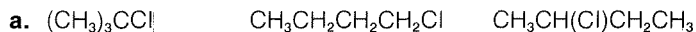


Exercise 8-25 Write equations and mechanisms for all the products that might reasonably be expected from the reaction of 2-chlorobutane with a solution of potassium hydroxide in ethanol.

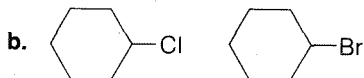
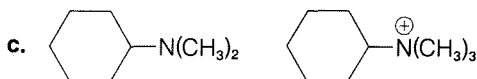
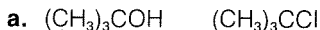
Exercise 8-26 a. Why is potassium *tert*-butoxide, $\text{KOC}(\text{CH}_3)_3$, an excellent base for promoting elimination reactions of alkyl halides, whereas ethylamine, $\text{CH}_3\text{CH}_2\text{NH}_2$, is relatively poor for the same purpose?

b. Potassium *tert*-butoxide is many powers of ten more effective a reagent for achieving E2 eliminations in methylsulfinylmethane (dimethyl sulfoxide) than in *tert*-butyl alcohol. Explain.

Exercise 8-27 Which one of the following groups of compounds would eliminate HCl most readily on reaction with potassium hydroxide? Draw the structure of the product and name it.



Exercise 8-28 Which one of each of the following pairs of compounds would react most rapidly with potassium hydroxide in an E2-type elimination? Draw the structure of the product and name it.



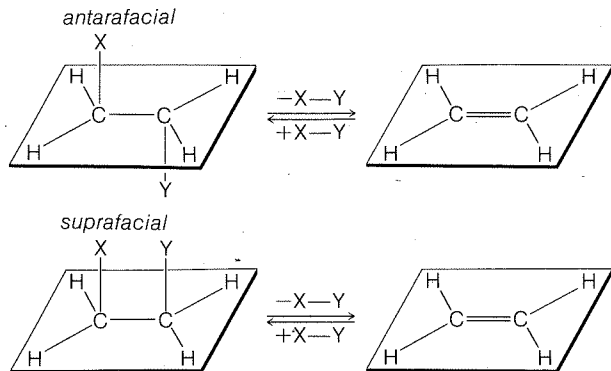
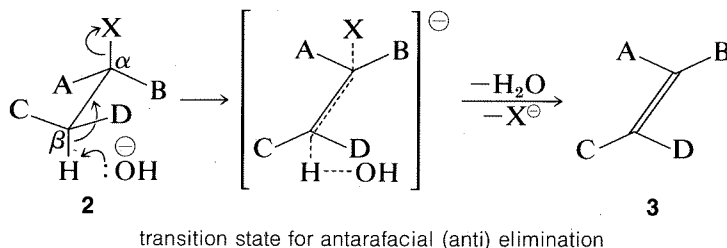


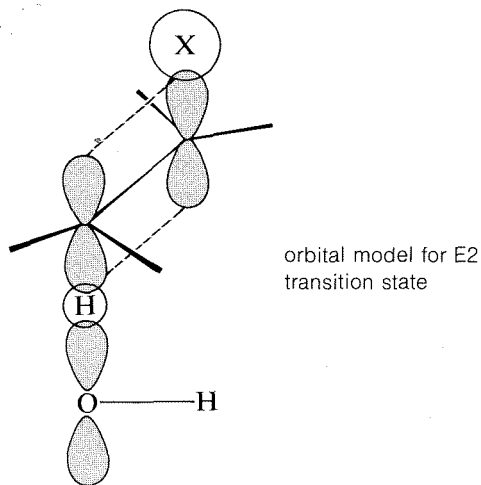
Figure 8-6 Schematic representation of antarafacial (literally “opposite-face”) and suprafacial (literally “above-face”) elimination or addition of a reagent X—Y to ethene

it from another possible mode of elimination that is called **suprafacial**. (See Figure 8-6).⁸

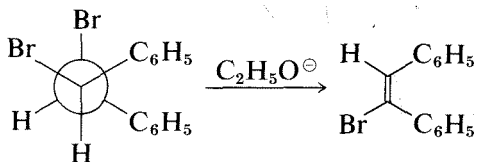


⁸Endless confusion is caused by the very prevalent use of the term “cis elimination” (or “cis addition”) and “trans elimination” (or “trans addition”) to denote the processes shown in Figure 8-6. At the risk of annoying those who often rightly dislike complicated names for simple processes, we have chosen to adopt the proposal of R. B. Woodward and R. Hoffmann, that elimination (or addition) which involves a *same-side* cleavage (or formation) of bonds be called **suprafacial** and the *opposite-side* cleavage (or formation) of bonds be called **antarafacial**. The alternative of using *syn* for suprafacial and *anti* for antarafacial would be simpler and easier to remember, but the terms *syn* and *anti* already are used for configurations, which is exactly what we want to avoid. The problem with the terms *cis* elimination (or addition) and *trans* elimination (or addition) is that they do not necessarily lead to products that, by other conventions, are understood to be *cis* and *trans* products, respectively. For example, to say that “*trans* elimination leads to *cis* product” is a needless confusion. It is much clearer to say that “*antarafacial* elimination gives the *cis* product”—and now there is no confusion of the mode of elimination with whatever stereochemical convention identifies the product.

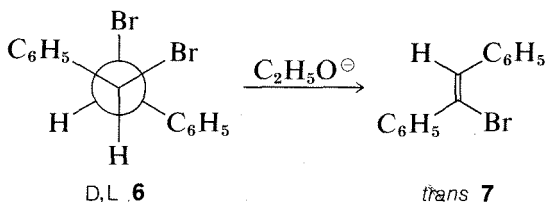
The transition state for conversion of **2** to **3** is particularly reasonable because it combines some of the geometry of both the reactants and the products and therefore gives the best overlap of the reacting orbitals necessary for the formation of the π bond. This is shown more explicitly below.⁹



As an illustration of the stereospecificity of eliminations, the meso compound **4** gives the *cis*-alkene **5**, whereas the D,L isomers **6** give the *trans*-alkene **7** with ethoxide. Both reactions clearly proceed by antarafacial elimination:



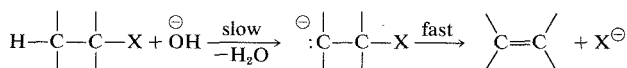
meso-1,2-dibromo-1,2-diphenylethane **4** *cis*-1-bromo-1,2-diphenylethene **5**



D,L **6**

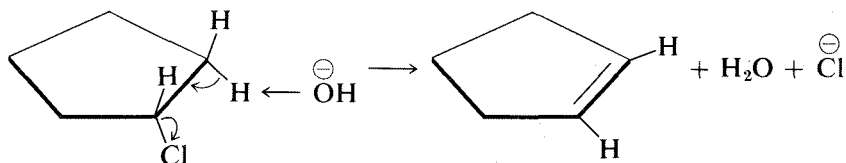
trans **7**

⁹Persuasive arguments have been made that many E2 reactions proceed by the sequence

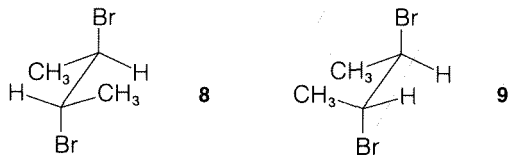


If this is so, antarafacial elimination still is predicted to be favored.

When antarafacial elimination is rendered difficult by the inability of the reacting groups to acquire the desired trans arrangement, then suprafacial elimination can occur, although less readily. An example is chlorocyclopentane, in which H and X cannot assume a trans configuration without very considerable strain but which does undergo suprafacial elimination at a reasonable rate:



Exercise 8-29 Write all the possible staggered conformations for each of the isomers of 2,3-dibromobutane, **8** and **9**:

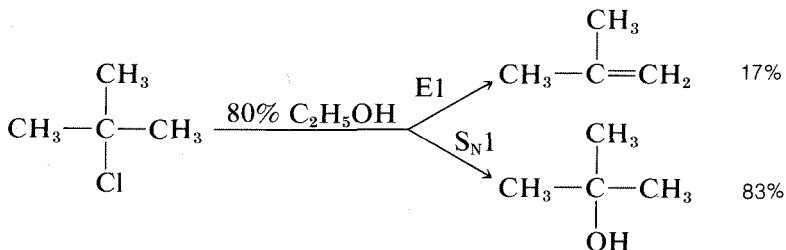


Show the structures of the alkenes that could be formed from each by antarafacial E2 elimination of one mole of hydrogen bromide with hydroxide ion. Which alkene should more readily eliminate further to form 2-butyne? Explain.

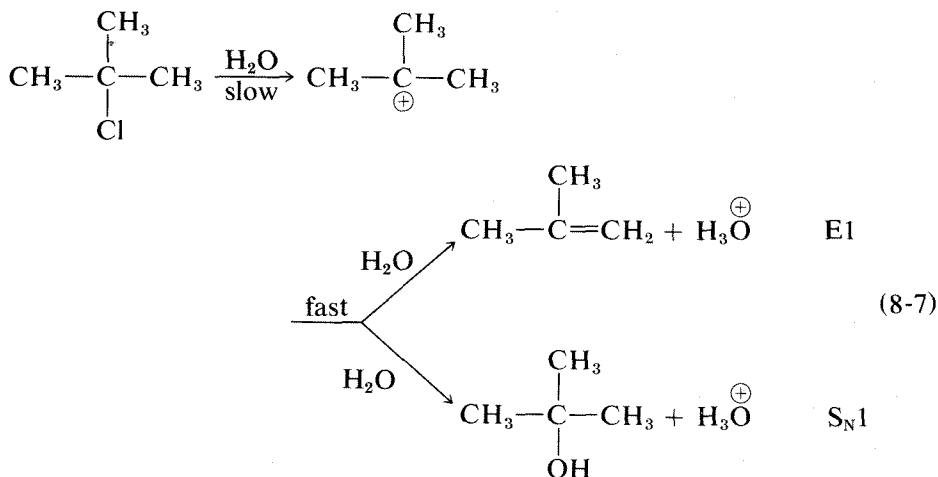
8-9 THE E1 REACTION

8-9A Scope and Mechanism

Many secondary and tertiary halides undergo E1 elimination in competition with the S_N1 reaction in neutral or acidic solutions. For example, when *tert*-butyl chloride solvolyzes in 80% aqueous ethanol at 25°, it gives 83% *tert*-butyl alcohol by substitution and 17% 2-methylpropene by elimination:

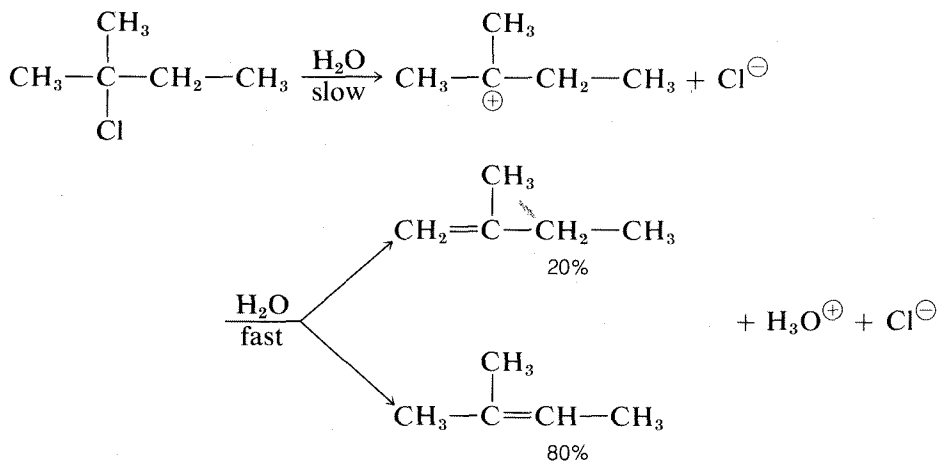


The ratio of substitution and elimination remains constant throughout the reaction, which means that each process has the same kinetic order with respect to the concentration of *tert*-butyl halide. The S_N1 and E1 reactions have a common rate-determining step, namely, slow ionization of the halide. The solvent then has the choice of attacking the intermediate carbocation at the positive carbon to effect substitution, or at a β hydrogen to effect elimination:



Factors influencing the E1 reactions are expected to be similar to those for the S_N1 reactions. An ionizing solvent is necessary, and for easy reaction the RX compound must have a good leaving group and form a relatively stable R^{\oplus} cation. Therefore the E1 orders of reaction rates are $X = \text{I} > \text{Br} > \text{Cl} > \text{F}$ and *tertiary* R > *secondary* R > *primary* R.

With halides such as 2-chloro-2-methylbutane, which can give different alkenes depending on the direction of elimination, the E1 reaction is like the E2 reaction in tending to favor the most stable or highly substituted alkene:



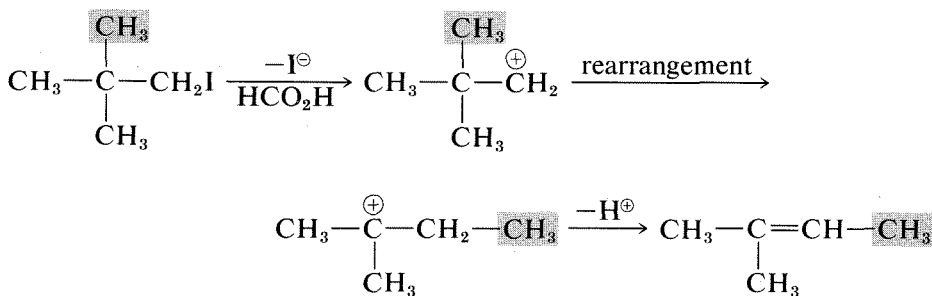
Exercise 8-30 For the reaction of Equation 8-7, would you expect the ratio of *tert*-butyl alcohol to 2-methylpropene to change significantly with changes in the nature of the leaving group [i.e., Cl, Br, I, or S(CH₃)₂][⊕]? Give your reasoning.

Would you expect the same or different behavior as X is changed, if elimination were occurring by an *E2 mechanism* with the solvent acting as the base? Explain.

Exercise 8-31 The reaction of *tert*-butyl chloride with water is accelerated strongly by sodium hydroxide. How would the ratio of elimination to substitution products be affected thereby? Explain.

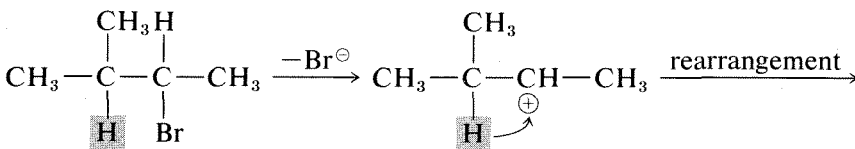
8-9B Rearrangement of Carbon Cations

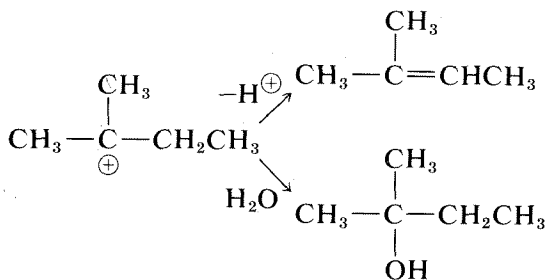
Another feature of *E1* reactions (and also of *S_N1* reactions) is the tendency of the initially formed carbocation to rearrange, especially if a more stable carbocation is formed thereby. For example, the very slow *S_N1* solvolysis of neopentyl iodide in methanoic acid leads predominantly to 2-methyl-2-butene:



In this reaction, ionization results in migration of a methyl group with its bonding pair of electrons from the β to the α carbon, thereby transforming an unstable primary carbocation to a relatively stable tertiary carbocation. Elimination of a proton completes the reaction.

Rearrangements involving shifts of hydrogen (as H:[⊖]) occur with comparable ease if a more stable carbocation can be formed thereby:

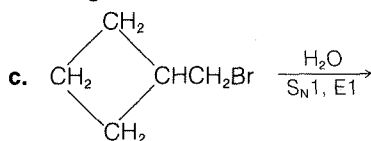
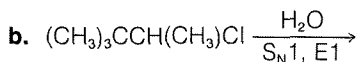
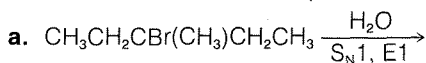




Rearrangements of carbocations are among the fastest organic reactions known and must be reckoned with as a possibility whenever carbocation intermediates are involved.

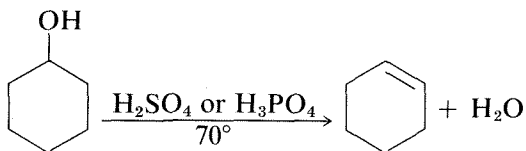
Exercise 8-32 Explain how $(\text{CH}_3)_2\text{CDCHBrCH}_3$ (where D is the hydrogen isotope of mass 2) might be used to determine whether 2-methyl-2-butene is formed directly from the bromide in an E1 reaction, or by rearrangement and elimination as shown in the preceding equations.

Exercise 8-33 Predict the products of the following reactions:



8-9C Acid-Catalyzed Elimination Reactions

Alcohols and ethers rarely undergo substitution or elimination unless strong acid is present. As we noted in Section 8-7D the acid is necessary to convert a relatively poor leaving group (HO^\ominus , $\text{CH}_3\text{O}^\ominus$) into a relatively good one (H_2O , CH_3OH). Thus the dehydration of alcohols to alkenes is an acid-catalyzed reaction requiring strong acids such as sulfuric or phosphoric acid:



These are synthetically useful reactions for the preparation of alkenes when the alkene is less available than the alcohol. They can occur by either the E1 or E2 mechanism depending on the alcohol, the acid catalyst, the solvent, and the temperature.

Additional Reading

J. Sicher, "The *syn* and *anti* Course in Bimolecular Olefin-Forming Eliminations," *Angew. Chem., Intl. Ed.*, **11**, 201 (1972).

F. G. Bordwell, "How Common are Base-Initiated, Concerted 1,2-Eliminations?," *Accts. of Chemical Research* **5**, 374 (1972).

A. Streitwieser, "Solvolytic Displacement Reactions at Saturated Carbon Atoms," *Chem. Rev.* **56**, 571 (1956).

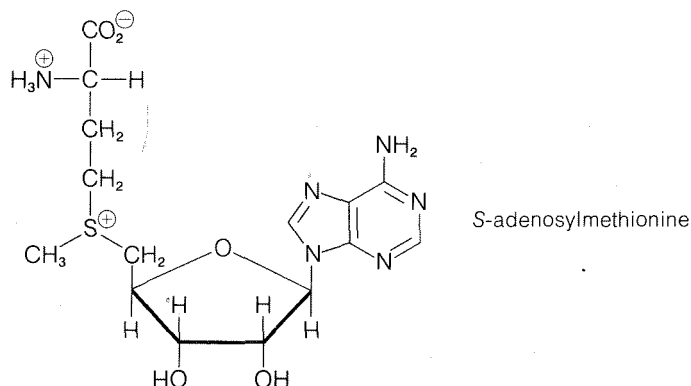
C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, N.Y., 1969.

Supplementary Exercises

8-34 Write reaction sequences, using specific and appropriate compounds, that illustrate the following conversions:

- a. alcohol \longrightarrow ether
 b. alcohol \longrightarrow alkene
 c. alcohol \longrightarrow alkyl chloride
 d. alcohol \longrightarrow nitrile (ROH \longrightarrow RCN)
 e. alkyl chloride \longrightarrow sulfonium salt \longrightarrow alkene

8-35 S-Adenosylmethionine is a biologically important compound that reacts in the S_N2 manner with the *amino group* of phosphorylated 2-aminoethanol, $\text{NH}_2\text{CH}_2\text{CH}_2\text{OPO}_3\text{H}_2$. Which carbon of S-adenosylmethionine would be most likely to undergo an S_N2 reaction with an RNH_2 compound? Give your reasoning and write the structures of the expected products.



8-36 Nitriles, RCN, can be prepared by S_N2 displacement of alkyl derivatives, RX, by using sodium or potassium cyanide:

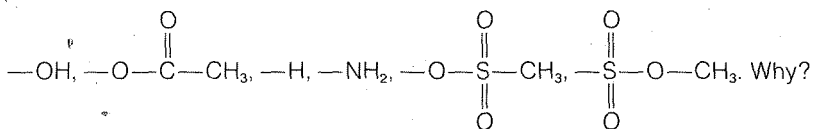


- a. Which of the following solvents would be most suitable for this reaction: water,

2-propanone, ethanol, benzene, $(\text{CH}_3)_2\text{S}=\text{O}$, or pentane? Give reasons for your choice.

b. Which of the six isomeric monobromoderivatives of 1-methylcyclohexene would you expect to react most rapidly with sodium cyanide? Why?

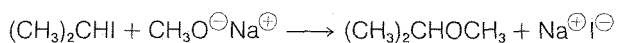
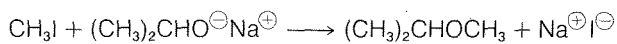
c. If you wished to make 2-phenylethanenitrile, $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$, which of the following phenylmethyl compounds, RCH_2X , would you select to convert to the nitrile? $\text{X} = -\text{F}$,



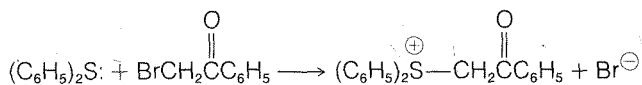
8-37 Give a plausible explanation for each of the following observations:

a. Aqueous sodium chloride will *not* convert *tert*-butyl alcohol to *tert*-butyl chloride but concentrated hydrochloric acid will.

b. Better yields are obtained in the synthesis of isopropyl methyl ether starting with methyl iodide rather than sodium methoxide:



c. The following reaction proceeds only if an equivalent amount of silver fluoborate, Ag^+BF_4^- , is added to the reaction mixture:



d. 1-Bromo-2-butene reacts with water to give a mixture of 2-buten-1-ol, 3-buten-2-ol, and some 1,3-butadiene.

8-38 Which compound in the following pairs would react faster under the reaction conditions? Draw the structures of the major products expected.

a. $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{Br}$ or $\text{C}_6\text{H}_5\text{—}\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}\text{—Br}$ in ethanol–water solution.

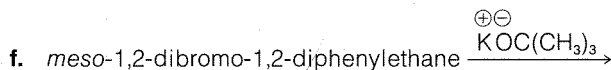
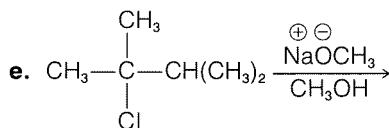
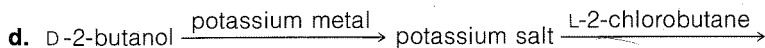
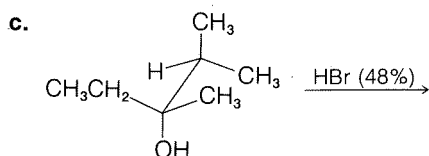
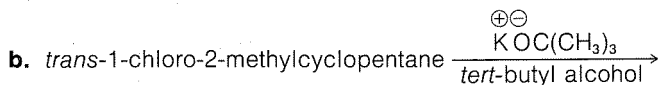
b. Same as in Part **a**, but with potassium iodide in acetone.

c. Same as in Part **a**, but with potassium hydroxide in ethanol.

d. $\text{CH}_3\text{CH}_2\text{N}^+(\text{CH}_3)_3 \text{BF}_4^-$ or $\text{CH}_3\text{CH}_2\text{N}^+(\text{CH}_3)_3 \text{OCH}_3^-$ on heating in methanol solution.

8-39 Show the products of the following reactions and indicate the stereochemistry where important.

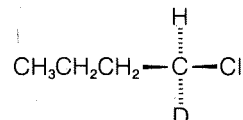
a. *trans*-1-bromo-3-methylcyclopentane $\xrightarrow[\text{acetone}]{\text{KI}}$



8-40 The S_N1 reactions of many RX derivatives that form moderately stable carbocations are substantially retarded by adding X^\ominus ions. However, such retardation is diminished, at given X^\ominus concentrations, by adding another nucleophile such as N_3^\ominus . Explain.

8-41 The reaction of 1-chlorobutane with sodium hydroxide to give 1-butanol is catalyzed by sodium iodide.

a. Work out the stereochemistry to be expected for both the catalyzed and the un-

catalyzed reactions if  (optically active) were used as the

starting material. Show your reasoning.

b. Does retention of configuration, as the overall result of an S_N2 reaction, automatically preclude operation of the usual inversion mechanism? Explain.

8-42* Suppose a water solution was made up initially to be 0.01M in methyl bromide and 1.0M in sodium ethanoate at 50°. In water, the S_N2 rate constant for reaction of hydroxide ion with methyl bromide at 50° is 30×10^{-4} liter mole $^{-1}$ sec $^{-1}$, whereas that of ethanoate ion at 50° is 1.0×10^{-4} liter mole $^{-1}$ sec $^{-1}$. The ionization constant of ethanoic acid at 50° is 1.8×10^{-5} . In the following, neglect the rates of the reactions of methyl bromide with water or ethanoic acid and any further reactions of ethanoate:

a. Calculate the hydroxide-ion concentration in the initial solution.

b. Calculate the initial rates of formation of methyl ethanoate and methanol.

c. Compute the concentrations of the organic products when the reaction is complete. Show your reasoning and justify any assumptions.

d. What kind of information would be needed to predict what products would be expected from a solution of methyl bromide and sodium hydroxide in methanol? Explain.

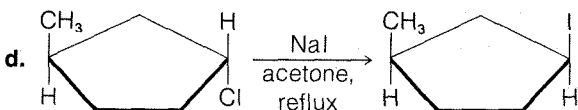
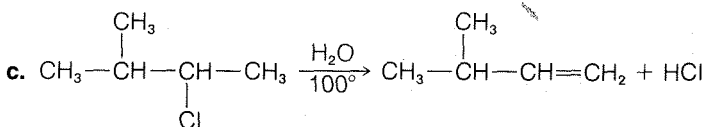
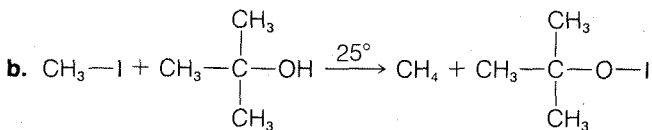
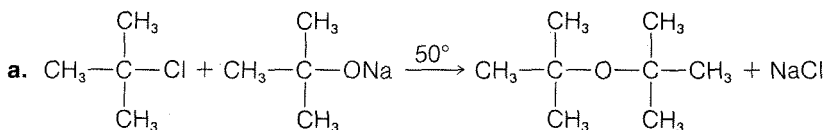
8-43 Indicate how you would synthesize each of the following substances from the given organic starting materials and any other necessary organic or inorganic reagents. Specify reagents and conditions. (You may have to use reactions discussed in Chapter 4.)

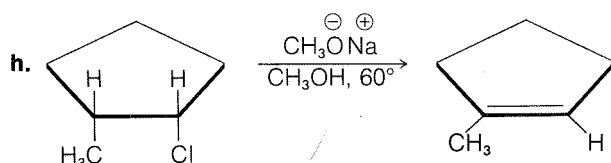
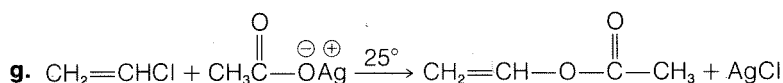
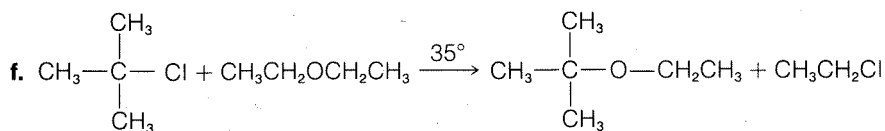
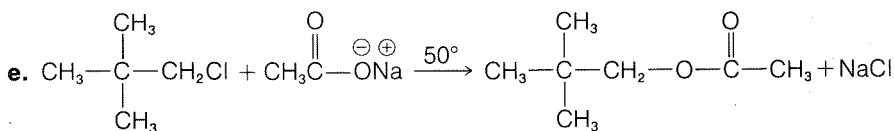
- a. $\text{CH}_2=\overset{\ominus}{\text{C}}\text{H}-\text{CH}_2-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$ from propene
 b. $\text{CH}_3-\text{O}-\text{CH}_2\text{CH}_3$ from ethanol
 c. $\text{CH}_3-\text{O}-\text{C}(\text{CH}_3)_3$ from *tert*-butyl alcohol
 d. cyclohexene from cyclohexane

8-44 Which compound in each of the following pairs would you expect to react more readily with (A) potassium iodide in 2-propanone, (B) concentrated sodium hydroxide in ethanol, and (C) silver nitrate in aqueous ethanol? Write equations for all the reactions involved and give your reasoning with respect to the predicted orders of reactivity.

- a. methyl chloride and isobutyl chloride with A, B, and C
 b. methyl chloride and *tert*-butyl chloride with A, B, and C
 c. *tert*-butyl chloride and 1-fluoro-2-chloro-2-methylpropane with B and C
 d. 1-chloro-2-butene and 4-chloro-1-butene with A, B, and C

8-45 Classify each of the following reactions from the standpoint of yield, side reactions, and reaction rate as good, fair, or bad synthetic procedures for preparation of the indicated products under the given conditions. Show your reasoning and designate any important side reactions.





8-46 Consider each of the following compounds to be in unlabeled bottles in pairs as indicated. For each pair give a chemical test (preferably a test-tube reaction) that will distinguish between the two substances. Write equations for the reactions involved.

<i>Bottle A</i>	<i>Bottle B</i>
a. $(\text{CH}_3)_3\text{CCH}_2\text{Cl}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$
b. $\text{BrCH}=\text{CHCH}_2\text{Cl}$	$\text{ClCH}=\text{CHCH}_2\text{Br}$
c. $(\text{CH}_3)_3\text{CCl}$	$(\text{CH}_3)_2\text{CHCH}_2\text{Cl}$
d. $\text{CH}_3\text{CH}=\text{CHCl}$	$\text{CH}_2=\text{CHCH}_2\text{Cl}$
e. $(\text{CH}_3)_2\text{C}=\text{CHCl}$	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCl}$
f. $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCl}$	$\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{Cl}$

8-47 Why does the following E1 reaction give more of the least substituted alkene? (Use models.)

