11 Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations

Organic KNOWLEDGE TOOLS

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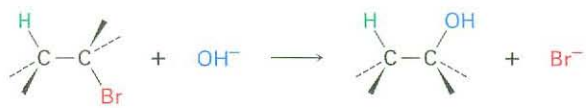
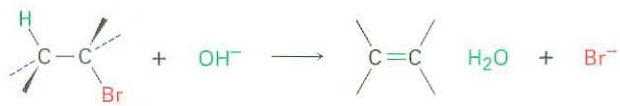
We saw in the preceding chapter that the carbon–halogen bond in an alkyl halide is polar and that the carbon atom is electron-poor. Thus, alkyl halides are electrophiles, and much of their chemistry involves polar reactions with nucleophiles and bases. Alkyl halides do one of two things when they react with a nucleophile/base, such as hydroxide ion: either they undergo *substitution* of the X group by the nucleophile, or they undergo *elimination* of HX to yield an alkene.

Substitution



Elimination



WHY THIS CHAPTER?

Nucleophilic substitution and base-induced elimination are two of the most widely occurring and versatile reaction types in organic chemistry, both in the laboratory and in biological pathways. We'll look at them closely in this chapter to see how they occur, what their characteristics are, and how they can be used.

11.1 The Discovery of Nucleophilic Substitution Reactions

In 1896, the German chemist Paul Walden made a remarkable discovery. He found that the pure enantiomeric (+)- and (−)-malic acids could be interconverted through a series of simple substitution reactions. When Walden treated (−)-malic acid with PCl_5, he isolated (+)-chlorosuccinic acid. This, on treatment with wet Ag_2O, gave (+)-malic acid. Similarly, reaction of (+)-malic acid with

Sean Duggan

Paul Walden

Paul Walden (1863–1957) was born in Cesis, Latvia, to German parents who died while he was still a child. He received his Ph.D. in Leipzig, Germany, and returned to Russia as professor of chemistry at Riga Polytechnic (1882–1919). Following the Russian Revolution, he went back to Germany as professor at the University of Rostock (1919–1934) and later at the University of Tübingen.

PCl_5 gave (−)-chlorosuccinic acid, which was converted into (−)-malic acid when treated with wet Ag_2O. The full cycle of reactions reported by Walden is shown in Figure 11.1.

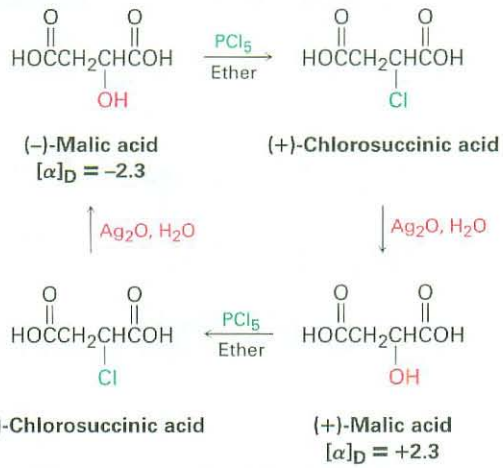


Figure 11.1 Walden's cycle of reactions interconverting (+)- and (−)-malic acids.

At the time, the results were astonishing. The eminent chemist Emil Fischer called Walden's discovery "the most remarkable observation made in the field of optical activity since the fundamental observations of Pasteur." Because (−)-malic acid was converted into (+)-malic acid, *some reactions in the cycle must have occurred with a change, or inversion, in configuration at the chirality center.* But which ones, and how? (Remember from Section 9.5 that the direction of light rotation and the configuration of a chirality center aren't directly related. You can't tell by looking at the sign of rotation whether a change in configuration has occurred during a reaction.)

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

Following the work of Walden, a further series of investigations was undertaken during the 1920s and 1930s to clarify the mechanism of nucleophilic substitution reactions and to find out how inversions of configuration occur. Among the first series studied was one that interconverted the two enantiomers of 1-phenyl-2-propanol (Figure 11.2).

Although this particular series of reactions involves nucleophilic substitution of an alkyl *p*-toluenesulfonate (called a *tosylate*) rather than an alkyl halide, exactly the same type of reaction is involved as that studied by Walden. For all practical purposes, the *entire* tosylate group acts as if it were simply a halogen substituent. In fact, when you see a tosylate substituent in a molecule, do a mental substitution and tell yourself that you're dealing with an alkyl halide.

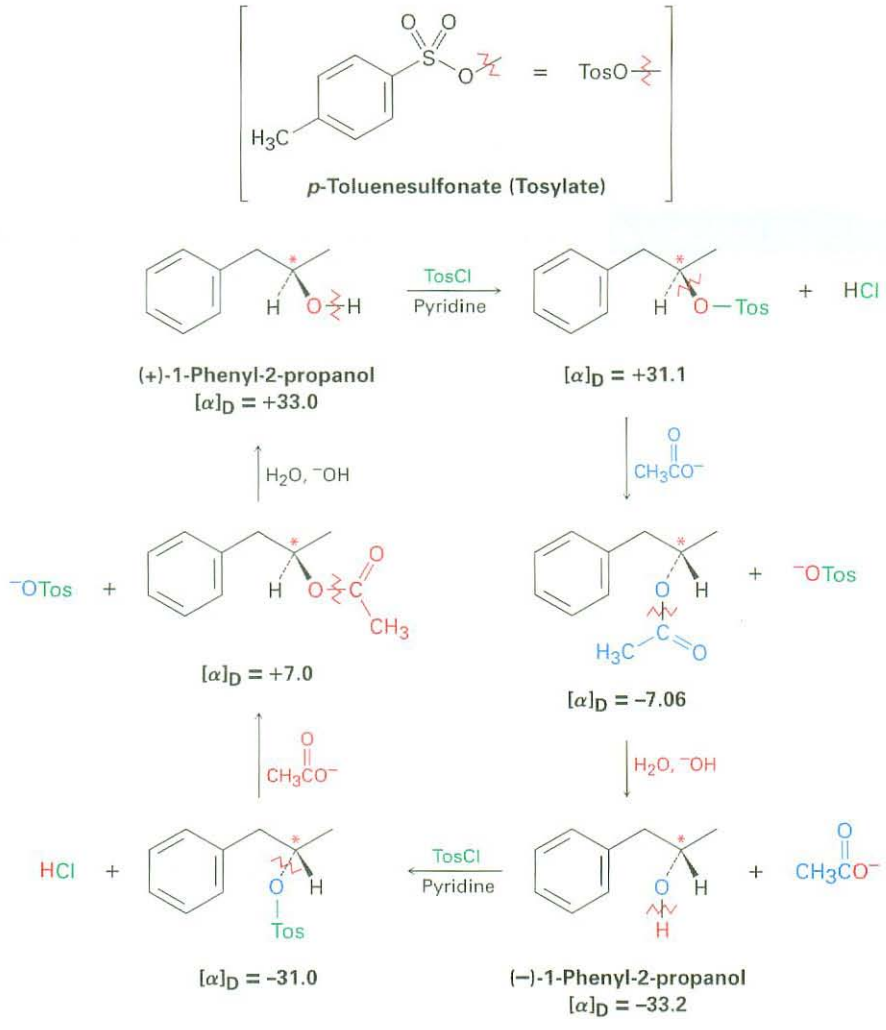
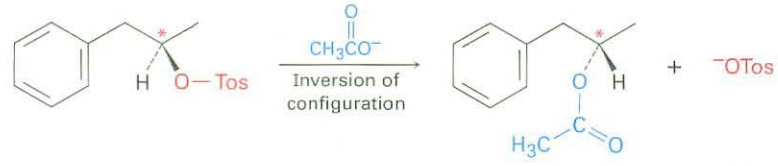


Figure 11.2 A Walden cycle interconverting (+) and (−) enantiomers of 1-phenyl-2-propanol. Chirality centers are marked by asterisks, and the bonds broken in each reaction are indicated by red wavy lines.

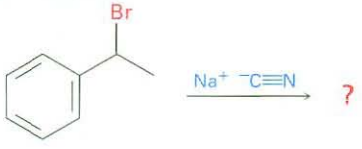
In the three-step reaction sequence shown in Figure 11.2, (+)-1-phenyl-2-propanol is interconverted with its (−) enantiomer, so at least one of the three steps must involve an inversion of configuration at the chirality center. The first step, formation of a toluenesulfonate, occurs by breaking the O−H bond of the alcohol rather than the C−O bond to the chiral carbon, so the configuration around carbon is unchanged. Similarly, the third step, hydroxide ion cleavage of the acetate, takes place without breaking the C−O bond at the chirality center. *The inversion of stereochemical configuration must therefore take place in the second step, the nucleophilic substitution of tosylate ion by acetate ion.*



From this and nearly a dozen other series of similar reactions, workers concluded that the nucleophilic substitution reaction of a primary or secondary alkyl halide or tosylate always proceeds with inversion of configuration. (Tertiary alkyl halides and tosylates, as we'll see shortly, give different stereochemical results and react by a different mechanism.)

WORKED EXAMPLE 11.1 ***Predicting the Stereochemistry of a Nucleophilic Substitution Reaction***

What product would you expect from a nucleophilic substitution reaction of (*R*)-1-bromo-1-phenylethane with cyanide ion, $^-C{\equiv}N$, as nucleophile? Show the stereochemistry of both reactant and product, assuming that inversion of configuration occurs.



Strategy Draw the *R* enantiomer of the reactant, and then change the configuration of the chirality center while replacing the ^-Br with a ^-CN.

Solution

(*R*)-1-Bromo-1-phenylethane (*S*)-2-Phenylpropanenitrile

Problem 11.1 What product would you expect to obtain from a nucleophilic substitution reaction of (*S*)-2-bromohexane with acetate ion, $CH_3CO_2^-$? Assume that inversion of configuration occurs, and show the stereochemistry of both reactant and product.

11.2 The S_N2 Reaction

In every chemical reaction, there is a direct relationship between the rate at which the reaction occurs and the concentrations of the reactants. When we measure this relationship, we measure the **kinetics** of the reaction. For example, let's look at the kinetics of a simple nucleophilic substitution—the reaction of CH_3Br with OH^- to yield CH_3OH plus Br^-—to see what can be learned.

ThomsonNOW Click *Organic Process* to **view an animation showing the stereochemistry of the S_N2 reaction.**

At a given temperature and concentration of reactants, the substitution occurs at a certain rate. If we double the concentration of OH^-, the frequency of encounter between the reaction partners doubles and we find that the reaction rate also doubles. Similarly, if we double the concentration of CH_3Br, the

reaction rate again doubles. We call such a reaction, in which the rate is linearly dependent on the concentrations of two species, a **second-order reaction**. Mathematically, we can express this second-order dependence of the nucleophilic substitution reaction by setting up a *rate equation*. As either [RX] or [$^-$OH] changes, the rate of the reaction changes proportionately.

$$\text{Reaction rate} = \text{Rate of disappearance of reactant}$$

$$= k \times [\text{RX}] \times [^-\text{OH}]$$

where [RX] = CH_3Br concentration in molarity

[$^-$OH] = $^-$OH concentration in molarity

k = A constant value (the rate constant)

Edward Davies Hughes

Edward Davies Hughes (1906–1963) was born in Criccieth, North Wales, and earned two doctoral degrees: a Ph.D. from Wales and a D.Sc. from the University of London, working with Christopher Ingold. From 1930 to 1963, he was professor of chemistry at University College, London.

A mechanism that accounts for both the inversion of configuration and the second-order kinetics that are observed with nucleophilic substitution reactions was suggested in 1937 by E. D. Hughes and Christopher Ingold, who formulated what they called the **S_N2 reaction**—short for *substitution, nucleophilic, bimolecular.* (*Bimolecular* means that two molecules, nucleophile and alkyl halide, take part in the step whose kinetics are measured.)

The essential feature of the S_N2 mechanism is that it takes place in a single step without intermediates when the incoming nucleophile reacts with the alkyl halide or tosylate (the *substrate*) from a direction opposite the group that is displaced (the *leaving group*). As the nucleophile comes in on one side of the substrate and bonds to the carbon, the halide or tosylate departs from the other side, thereby inverting the stereochemical configuration. The process is shown in Figure 11.3 for the reaction of (*S*)-2-bromobutane with HO^- to give (*R*)-2-butanol.

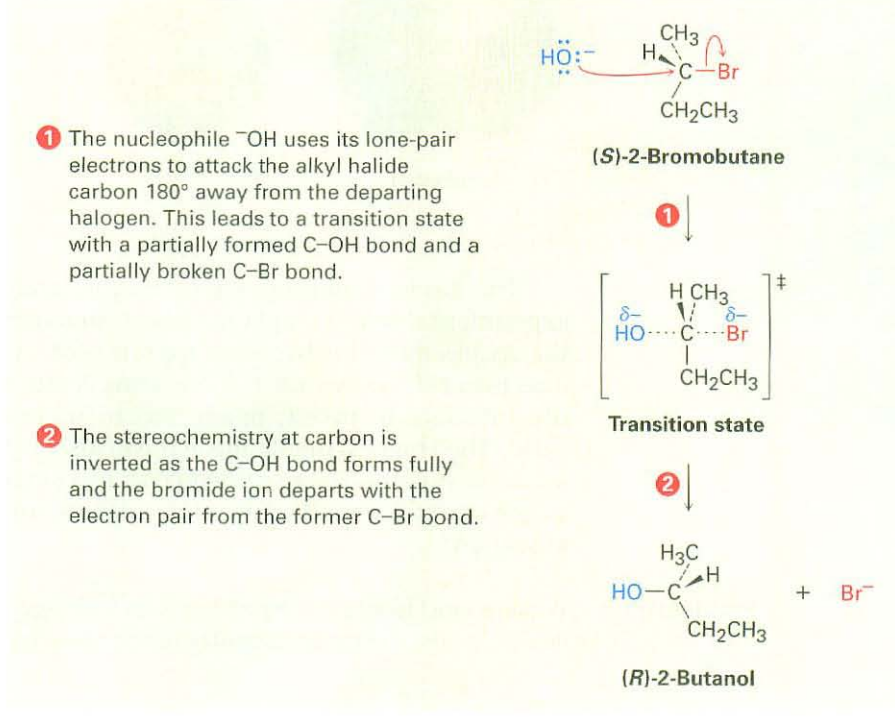


Figure 11.3 MECHANISM: The mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.

As shown in Figure 11.3, the S_N2 reaction occurs when an electron pair on the nucleophile Nu^- forces out the group $X:^-$, which takes with it the electron pair from the former C–X bond. This occurs through a transition state in which the new Nu–C bond is partially forming at the same time that the old C–X bond is partially breaking and in which the negative charge is shared by both the incoming nucleophile and the outgoing halide ion. The transition state for this inversion has the remaining three bonds to carbon in a planar arrangement (Figure 11.4).

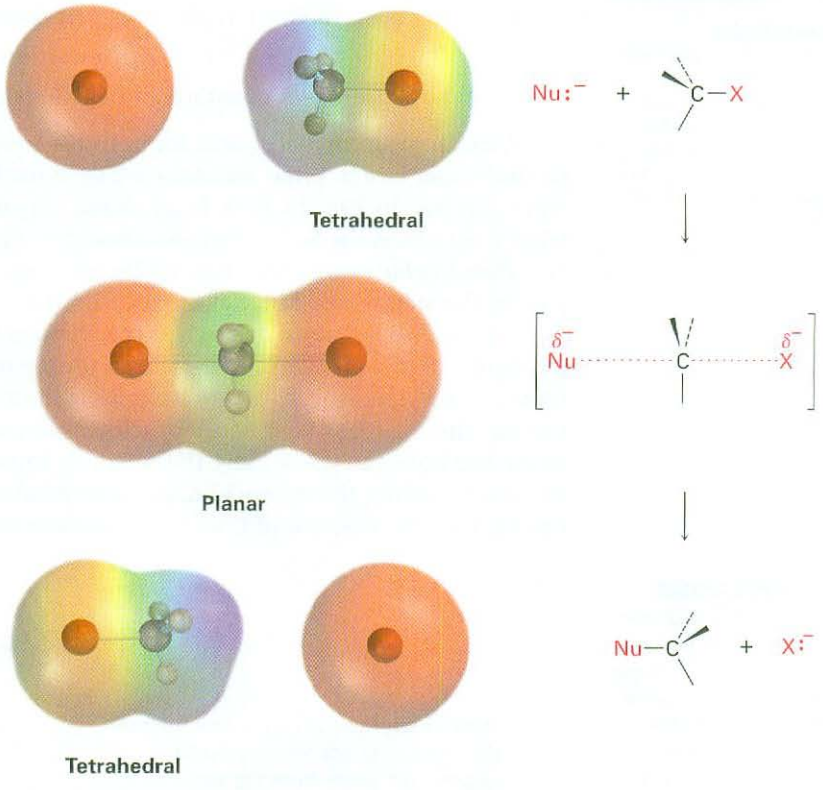
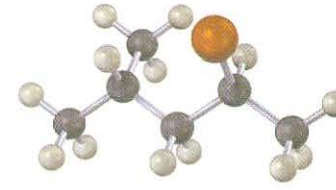


Figure 11.4 The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups. Electrostatic potential maps show that negative charge (red) is delocalized in the transition state.

The mechanism proposed by Hughes and Ingold is fully consistent with experimental results, explaining both stereochemical and kinetic data. Thus, the requirement for backside approach of the entering nucleophile from a direction 180° away from the departing X group causes the stereochemistry of the substrate to invert, much like an umbrella turning inside out in the wind. The Hughes–Ingold mechanism also explains why second-order kinetics are found: the S_N2 reaction occurs in a single step that involves both alkyl halide and nucleophile. Two molecules are involved in the step whose rate is measured.

Problem 11.2 What product would you expect to obtain from S_N2 reaction of OH^- with (*R*)-2-bromobutane? Show the stereochemistry of both reactant and product.

Problem 11.3 Assign configuration to the following substance, and draw the structure of the product that would result on nucleophilic substitution reaction with HS^- (reddish brown = Br):



11.3 Characteristics of the S_N2 Reaction

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

Now that we have a good picture of how S_N2 reactions occur, we need to see how they can be used and what variables affect them. Some S_N2 reactions are fast, and some are slow; some take place in high yield and others, in low yield. Understanding the factors involved can be of tremendous value. Let's begin by recalling a few things about reaction rates in general.

The rate of a chemical reaction is determined by $\Delta G^{\ddagger}$, the energy difference between reactant ground state and transition state. A change in reaction conditions can affect $\Delta G^{\ddagger}$ either by changing the reactant energy level or by changing the transition-state energy level. Lowering the reactant energy or raising the transition-state energy increases $\Delta G^{\ddagger}$ and decreases the reaction rate; raising the reactant energy or decreasing the transition-state energy decreases $\Delta G^{\ddagger}$ and increases the reaction rate (Figure 11.5). We'll see examples of all these effects as we look at S_N2 reaction variables.

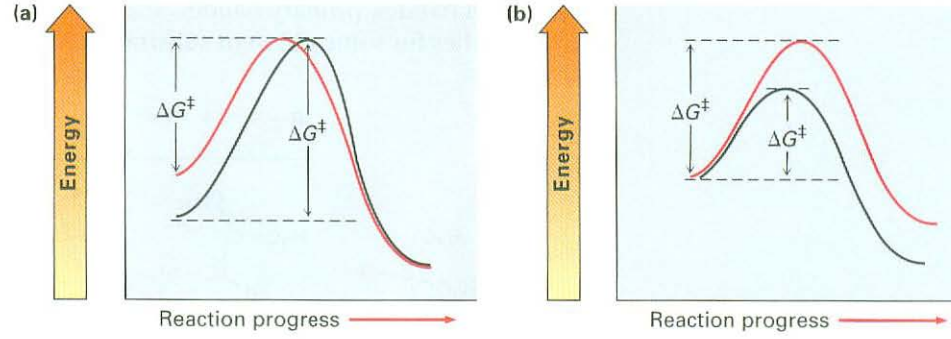


Figure 11.5 The effects of changes in reactant and transition-state energy levels on reaction rate. **(a)** A higher reactant energy level (red curve) corresponds to a faster reaction (smaller $\Delta G^{\ddagger}$). **(b)** A higher transition-state energy level (red curve) corresponds to a slower reaction (larger $\Delta G^{\ddagger}$).

The Substrate: Steric Effects in the S_N2 Reaction

The first S_N2 reaction variable to look at is the structure of the substrate. Because the S_N2 transition state involves partial bond formation between the incoming nucleophile and the alkyl halide carbon atom, it seems reasonable that a hindered, bulky substrate should prevent easy approach of the nucleophile, making bond formation difficult. In other words, the transition state for reaction of a sterically hindered alkyl halide, whose carbon atom is "shielded" from approach of the incoming nucleophile, is higher in energy

and forms more slowly than the corresponding transition state for a less hindered alkyl halide (Figure 11.6).

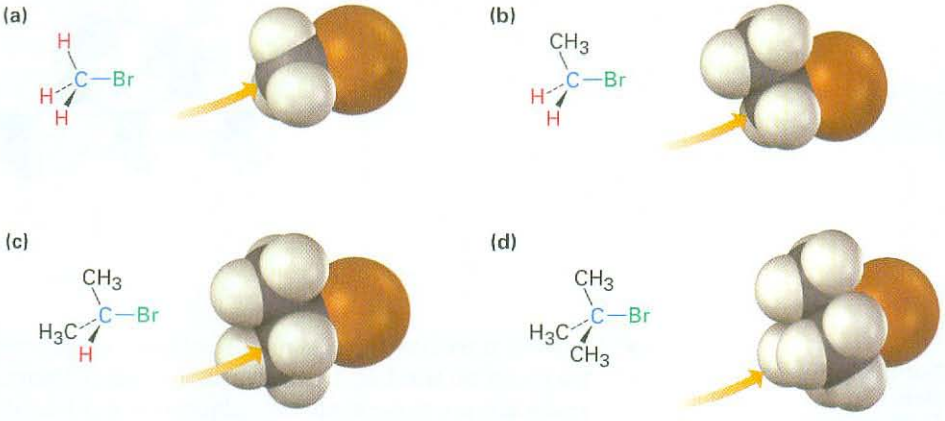
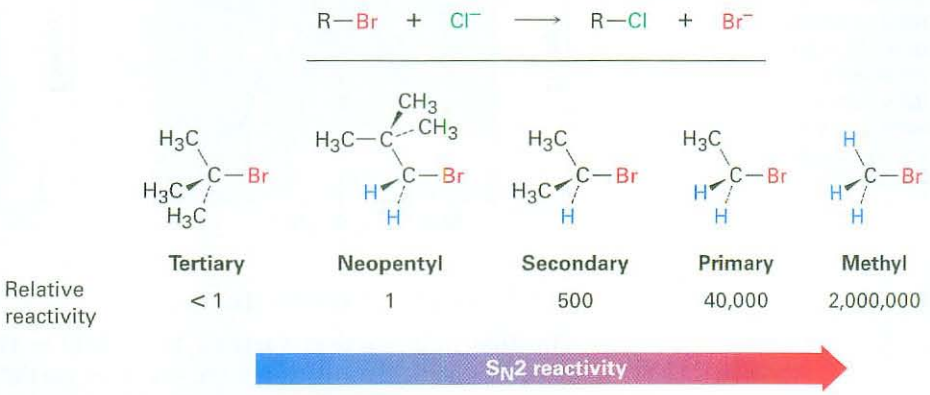


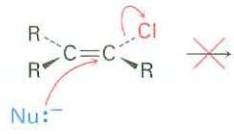
Figure 11.6 Steric hindrance to the S_N2 reaction. As the computer-generated models indicate, the carbon atom in **(a)** bromomethane is readily accessible, resulting in a fast S_N2 reaction. The carbon atoms in **(b)** bromoethane (primary), **(c)** 2-bromopropane (secondary), and **(d)** 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S_N2 reactions.

As Figure 11.6 shows, the difficulty of nucleophilic approach increases as the three substituents bonded to the halo-substituted carbon atom increase in size. Methyl halides are by far the most reactive substrates in S_N2 reactions, followed by primary alkyl halides such as ethyl and propyl. Alkyl branching at the reacting center, as in isopropyl halides (2°), slows the reaction greatly, and further branching, as in *tert*-butyl halides (3°), effectively halts the reaction. Even branching one carbon removed from the reacting center, as in 2,2-dimethylpropyl *(neopentyl)* halides, greatly slows nucleophilic displacement. As a result, *S_N2 reactions occur only at relatively unhindered sites* and are normally useful only with methyl halides, primary halides, and a few simple secondary halides. Relative reactivities for some different substrates are as follows:



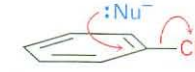
Although not shown in the preceding reactivity order, vinylic halides ($R_2C{=}CRX$) and aryl halides are unreactive toward S_N2 reaction. This lack of reactivity is probably due to steric factors, because the incoming nucleophile

would have to approach in the plane of the carbon–carbon double bond to carry out a backside displacement.



No reaction

Vinylic halide

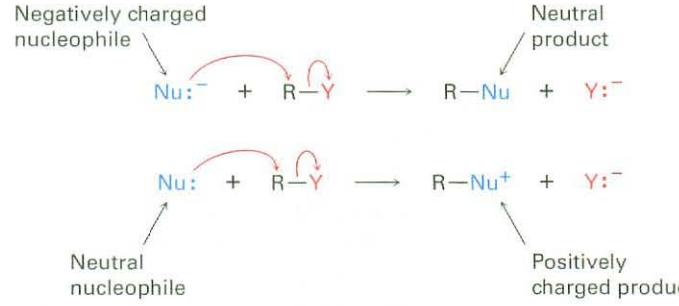


No reaction

Aryl halide

The Nucleophile

Another variable that has a major effect on the S_N2 reaction is the nature of the nucleophile. Any species, either neutral or negatively charged, can act as a nucleophile as long as it has an unshared pair of electrons, that is, as long as it is a Lewis base. If the nucleophile is negatively charged, the product is neutral; if the nucleophile is neutral, the product is positively charged.



A wide array of substances can be prepared using nucleophilic substitution reactions. In fact, we've already seen examples in previous chapters. The reaction of an acetylide anion with an alkyl halide (Section 8.8), for instance, is an S_N2 reaction in which the acetylide nucleophile replaces halide.

An acetylide anion

Table 11.1 lists some nucleophiles in the order of their reactivity, shows the products of their reactions with bromomethane, and gives the relative rates of their reactions. Clearly, there are large differences in the rates at which various nucleophiles react.

What are the reasons for the reactivity differences observed in Table 11.1? Why do some reactants appear to be much more "nucleophilic" than others? The answers to these questions aren't straightforward. Part of the problem is that the term *nucleophilicity* is imprecise. The term is usually taken to be a measure of the affinity of a nucleophile for a carbon atom in the S_N2 reaction, but the reactivity of a given nucleophile can change from one reaction to the next. The exact nucleophilicity of a species in a given reaction depends on the substrate, the solvent, and even the reactant concentrations. Detailed

Table 11.1 Some S_N2 Reactions with Bromomethane

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

Nucleophile		Product		Relative rate of reaction
Formula	Name	Formula	Name	
H_2O	Water	$CH_3OH_2^+$	Methylhydronium ion	1
$CH_3CO_2^-$	Acetate	$CH_3CO_2CH_3$	Methyl acetate	500
NH_3	Ammonia	$CH_3NH_3^+$	Methylammonium ion	700
Cl^-	Chloride	CH_3Cl	Chloromethane	1,000
HO^-	Hydroxide	CH_3OH	Methanol	10,000
CH_3O^-	Methoxide	CH_3OCH_3	Dimethyl ether	25,000
I^-	Iodide	CH_3I	Iodomethane	100,000
^-CN	Cyanide	CH_3CN	Acetonitrile	125,000
HS^-	Hydrosulfide	CH_3SH	Methanethiol	125,000

explanations for the observed nucleophilicities aren't always simple, but some trends can be detected in the data of Table 11.1.

- **Nucleophilicity roughly parallels basicity** when comparing nucleophiles that have the same reacting atom. For example, OH^- is both more basic and more nucleophilic than acetate ion, $CH_3CO_2^-$, which in turn is more basic and more nucleophilic than H_2O. Since "nucleophilicity" is usually taken as the affinity of a Lewis base for a carbon atom in the S_N2 reaction and "basicity" is the affinity of a base for a proton, it's easy to see why there might be a correlation between the two kinds of behavior.
- **Nucleophilicity usually increases going down a column of the periodic table.** Thus, HS^- is more nucleophilic than HO^-, and the halide reactivity order is $I^- > Br^- > Cl^-$. Going down the periodic table, elements have their valence electrons in successively larger shells where they are successively farther from the nucleus, less tightly held, and consequently more reactive. The matter is complex, though, and the nucleophilicity order can change depending on the solvent.
- **Negatively charged nucleophiles are usually more reactive than neutral ones.** As a result, S_N2 reactions are often carried out under basic conditions rather than neutral or acidic conditions.

Problem 11.4 What product would you expect from S_N2 reaction of 1-bromobutane with each of the following?

(a) NaI (b) KOH (c) $H-C\equiv C-Li$ (d) NH_3

Problem 11.5 Which substance in each of the following pairs is more reactive as a nucleophile? Explain.

(a) $(CH_3)_2N^-$ or $(CH_3)_2NH$ (b) $(CH_3)_3B$ or $(CH_3)_3N$ (c) H_2O or H_2S

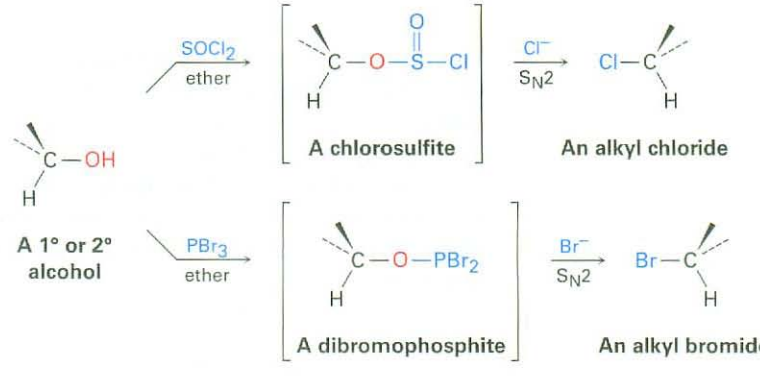
The Leaving Group

Still another variable that can affect the S_N2 reaction is the nature of the group displaced by the incoming nucleophile. Because the leaving group is expelled with a negative charge in most S_N2 reactions, the best leaving groups are those that best stabilize the negative charge in the transition state. The greater the extent of charge stabilization by the leaving group, the lower the energy of the transition state and the more rapid the reaction. But as we saw in Section 2.8, those groups that best stabilize a negative charge are also the weakest bases. Thus, weak bases such as Cl^-, Br^-, and tosylate ion make good leaving groups, while strong bases such as OH^- and NH_2^-make poor leaving groups.

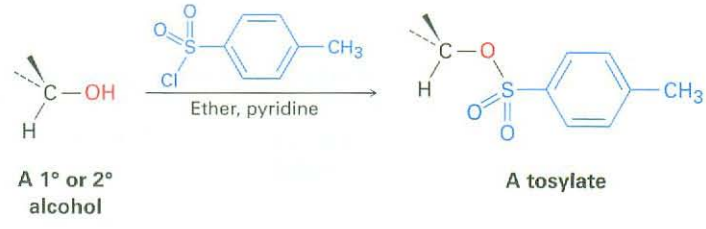
	OH^-, NH_2^-, OR^-	F^-	Cl^-	Br^-	I^-	$TosO^-$
Relative reactivity	<<1	1	200	10,000	30,000	60,000

Leaving group reactivity →

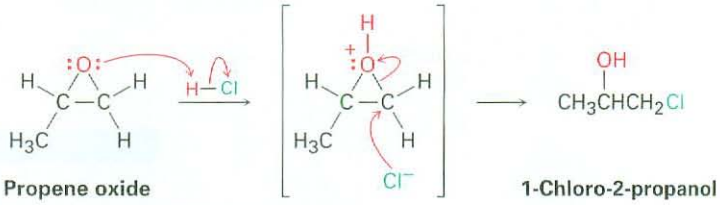
It's just as important to know which are poor leaving groups as to know which are good, and the preceding data clearly indicate that F^-, HO^-, RO^-, and H_2N^- are not displaced by nucleophiles. In other words, alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions. To carry out an S_N2 reaction with an alcohol, it's necessary to convert the ^-OH into a better leaving group. This, in fact, is just what happens when a primary or secondary alcohol is converted into either an alkyl chloride by reaction with $SOCl_2$ or an alkyl bromide by reaction with PBr_3 (Section 10.6).



Alternatively, an alcohol can be made more reactive toward nucleophilic substitution by treating it with *para*-toluenesulfonyl chloride to form a tosylate. As noted on several previous occasions, tosylates are even more reactive than halides in nucleophilic substitutions. Note that tosylate formation does not change the configuration of the oxygen-bearing carbon because the C–O bond is not broken.



The one general exception to the rule that ethers don't typically undergo S_N2 reactions occurs with epoxides, the three-membered cyclic ethers that we saw in Section 7.8. Epoxides, because of the angle strain in the three-membered ring, are much more reactive than other ethers. They react with aqueous acid to give 1,2-diols, as we saw in Section 7.8, and they react readily with many other nucleophiles as well. Propene oxide, for instance, reacts with HCl to give 1-chloro-2-propanol by S_N2 backside attack on the less hindered primary carbon atom. We'll look at the process in more detail in Section 18.6.



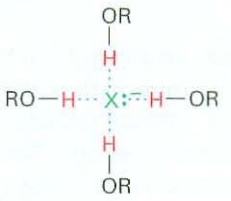
Problem 11.6 Rank the following compounds in order of their expected reactivity toward S_N2 reaction:

CH_3Br, CH_3OTos, $(CH_3)_3CCl$, $(CH_3)_2CHCl$

The Solvent

The rates of S_N2 reactions are strongly affected by the solvent. *Protic solvents*—those that contain an −OH or −NH group—are generally the worst for S_N2 reactions, while *polar aprotic solvents*, which are polar but don't have an −OH or −NH group, are the best.

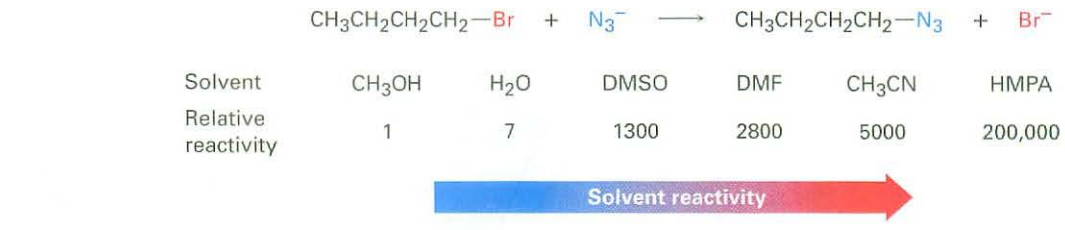
Protic solvents, such as methanol and ethanol, slow down S_N2 reactions by **solvation** of the reactant nucleophile. The solvent molecules hydrogen bond to the nucleophile and form a "cage" around it, thereby lowering its energy and reactivity.



A solvated anion (reduced nucleophilicity due to enhanced ground-state stability)

In contrast with protic solvents, which *decrease* the rates of S_N2 reactions by *lowering* the ground-state energy of the nucleophile, polar aprotic solvents *increase* the rates of S_N2 reactions by *raising* the ground-state energy of the nucleophile. Acetonitrile (CH_3CN), dimethylformamide [$(CH_3)_2NCHO$,

abbreviated DMF], dimethyl sulfoxide [$(CH_3)_2SO$, abbreviated DMSO], and hexamethylphosphoramide {$[(CH_3)_2N]_3PO$, abbreviated HMPA} are particularly useful. These solvents can dissolve many salts because of their high polarity, but they tend to solvate metal cations rather than nucleophilic anions. As a result, the bare unsolvated anions have a greater nucleophilicity, and S_N2 reactions take place at correspondingly faster rates. For instance, a rate increase of 200,000 has been observed on changing from methanol to HMPA for the reaction of azide ion with 1-bromobutane.



Problem 11.7 Organic solvents such as benzene, ether, and chloroform are neither protic nor strongly polar. What effect would you expect these solvents to have on the reactivity of a nucleophile in S_N2 reactions?

A Summary of S_N2 Reaction Characteristics

The effects on S_N2 reactions of the four variables—substrate structure, nucleophile, leaving group, and solvent—are summarized in the following statements and in the energy diagrams of Figure 11.7:

Substrate Steric hindrance raises the energy of the S_N2 transition state, increasing $\Delta G^{\ddagger}$ and decreasing the reaction rate (Figure 11.7a). As a result, S_N2 reactions are best for methyl and primary substrates. Secondary substrates react slowly, and tertiary substrates do not react by an S_N2 mechanism.

Nucleophile Basic, negatively charged nucleophiles are less stable and have a higher ground-state energy than neutral ones, decreasing $\Delta G^{\ddagger}$ and increasing the S_N2 reaction rate (Figure 11.7b).

Leaving group Good leaving groups (more stable anions) lower the energy of the transition state, decreasing $\Delta G^{\ddagger}$ and increasing the S_N2 reaction rate (Figure 11.7c).

Solvent Protic solvents solvate the nucleophile, thereby lowering its ground-state energy, increasing $\Delta G^{\ddagger}$, and decreasing the S_N2 reaction rate. Polar aprotic solvents surround the accompanying cation but not the nucleophilic anion, thereby raising the ground-state energy of the nucleophile, decreasing $\Delta G^{\ddagger}$, and increasing the reaction rate (Figure 11.7d).

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from simple S_N2 reactions.**

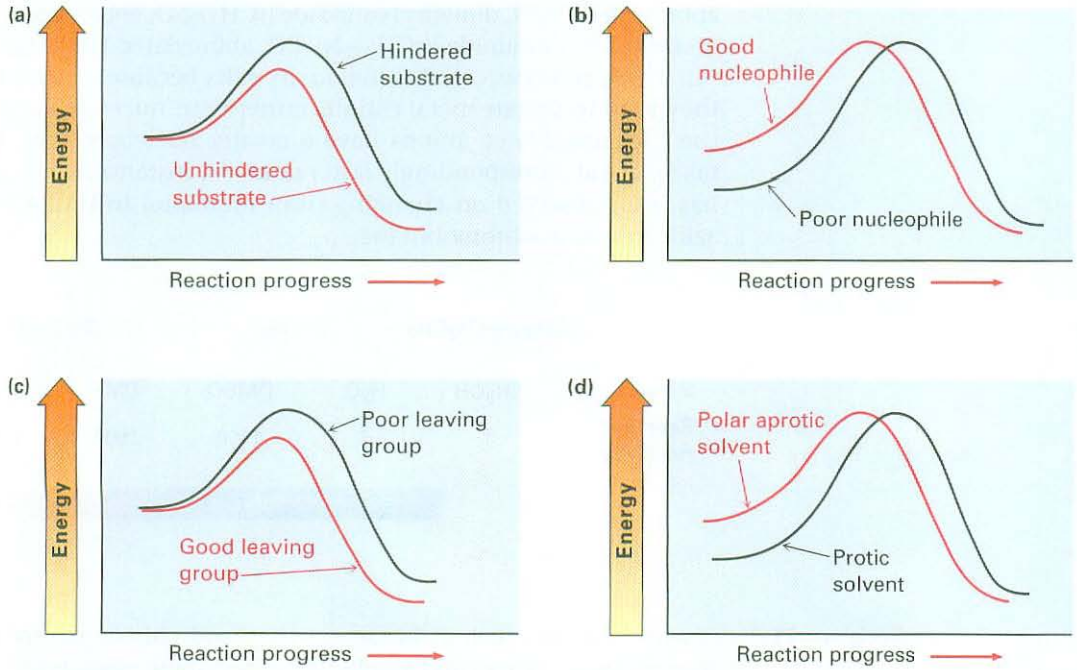
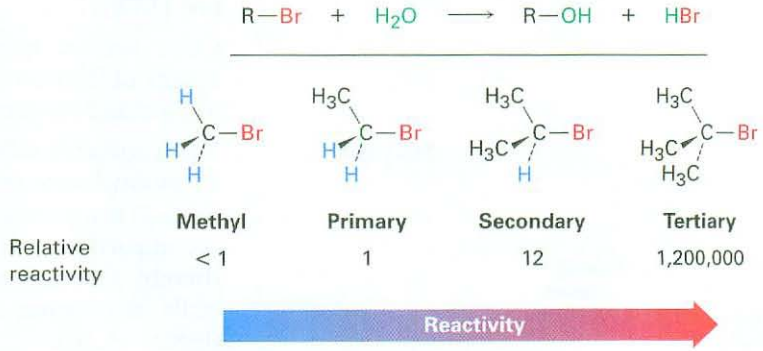


Figure 11.7 Energy diagrams showing the effects of **(a)** substrate, **(b)** nucleophile, **(c)** leaving group, and **(d)** solvent on S_N2 reaction rates. Substrate and leaving group effects are felt primarily in the transition state. Nucleophile and solvent effects are felt primarily in the reactant ground state.

11.4 The S_N1 Reaction

As we've seen, the S_N2 reaction is best when carried out with an unhindered substrate and a negatively charged nucleophile in a polar aprotic solvent, but it is worst when carried out with a hindered substrate and a neutral nucleophile in a protic solvent. You might therefore expect the reaction of a tertiary substrate (hindered) with water (neutral, protic) to be among the slowest of substitution reactions. Remarkably, however, the opposite is true. The reaction of the tertiary halide $(CH_3)_3CBr$ with H_2O to give the alcohol 2-methyl-2-propanol is more than *1 million times* as fast as the corresponding reaction of CH_3Br to give methanol.



What's going on here? Clearly, a nucleophilic substitution reaction is occurring, yet the reactivity order seems backward. These reactions can't be taking place

by the S_N2 mechanism we've been discussing, and we must therefore conclude that they are occurring by *an alternative substitution mechanism*. This alternative mechanism is called the **S_N1 reaction** (for *substitution, nucleophilic, unimolecular*).

In contrast to the S_N2 reaction of CH_3Br with OH^-, the S_N1 reaction of $(CH_3)_3CBr$ with H_2O has a rate that depends only on the alkyl halide concentration and is independent of the H_2O concentration. In other words, the reaction is a **first-order process**; the concentration of the nucleophile does not appear in the rate equation.

$$\text{Reaction rate} = \text{Rate of disappearance of alkyl halide}$$

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

To explain this result, we need to learn more about kinetics measurements. Many organic reactions occur in several steps, one of which is usually slower than the others. We call this slow step the *rate-limiting step*, or *rate-determining step*. No reaction can proceed faster than its rate-limiting step, which acts as a kind of traffic jam, or bottleneck. In the S_N1 reaction of $(CH_3)_3CBr$ with H_2O, the fact that the nucleophile does not appear in the first-order rate equation means that the alkyl halide is involved in a *unimolecular* rate-limiting step. But if the nucleophile is not involved in the rate-limiting step, then it must be involved in some other, non–rate-limiting step. The mechanism shown in Figure 11.8 accounts for these observations.

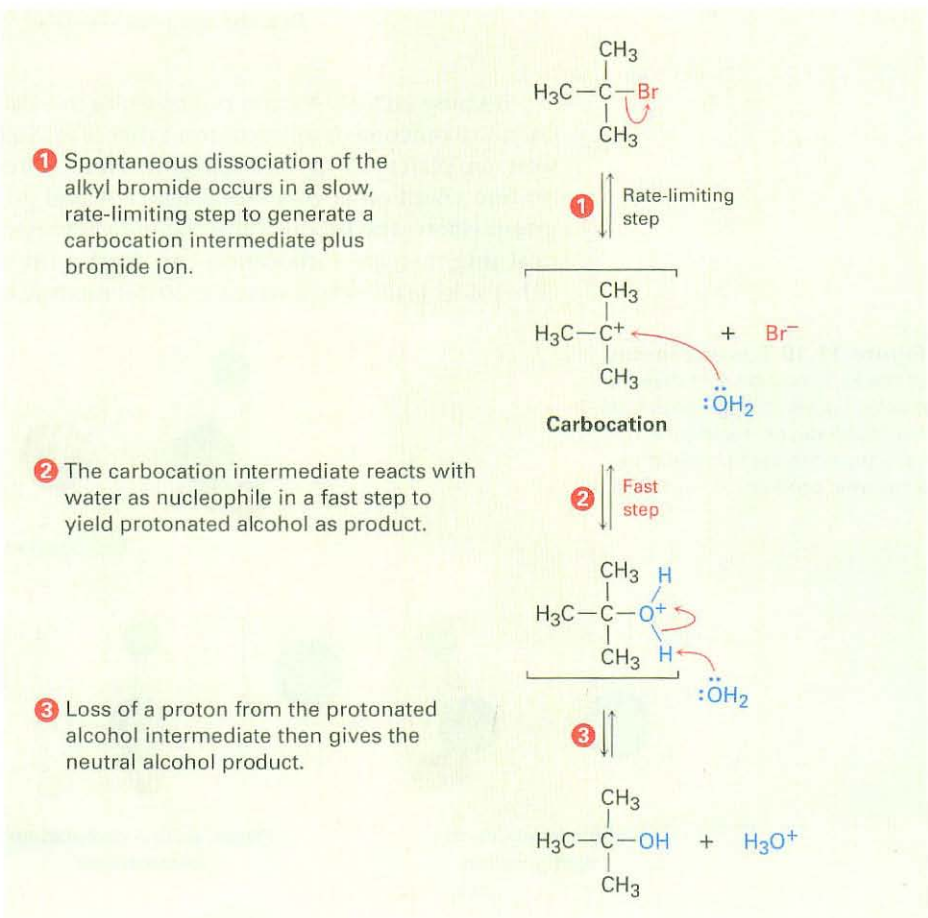


Figure 11.8 MECHANISM: The mechanism of the S_N1 reaction of 2-bromo-2-methylpropane with H_2O involves three steps. The first step—spontaneous, unimolecular dissociation of the alkyl bromide to yield a carbocation—is rate-limiting.

ThomsonNOW Click *Organic Process* to **view animations showing the S_N1 reaction of 2-methyl-2-propanol with HCl and the S_N1 solvolysis of 2-chloro-2-methylpropane.**

Unlike what happens in an S_N2 reaction, where the leaving group is displaced at the same time the incoming nucleophile approaches, an S_N1 reaction takes place by loss of the leaving group *before* the nucleophile approaches. 2-Bromo-2-methylpropane spontaneously dissociates to the *tert*-butyl carbocation plus Br^- in a slow, rate-limiting step, and the intermediate carbocation is then immediately trapped by the nucleophile water in a faster second step. *Water is not a reactant in the step whose rate is measured.* The energy diagram is shown in Figure 11.9.

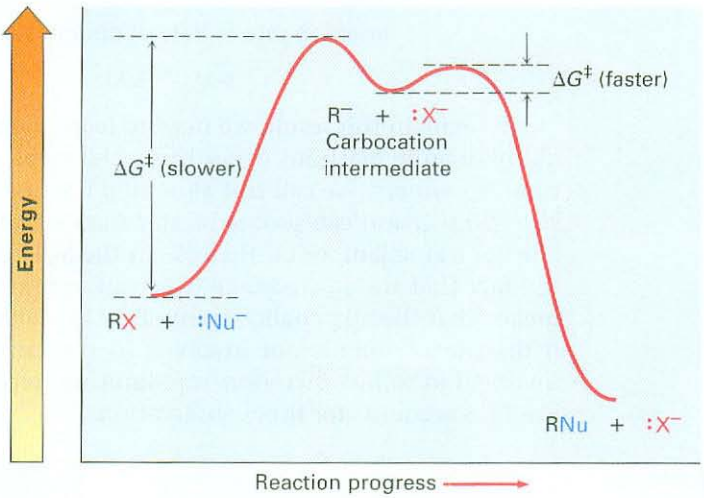


Figure 11.9 An energy diagram for an S_N1 reaction. The slower, rate-limiting step is the spontaneous dissociation of the alkyl halide to give a carbocation intermediate. Reaction of the carbocation with a nucleophile then occurs in a second, faster step.

Because an S_N1 reaction occurs through a carbocation intermediate, its stereochemical outcome is different from that of an S_N2 reaction. Carbocations, as we've seen, are planar, sp^2-hybridized, and achiral. Thus, if we carry out an S_N1 reaction on one enantiomer of a chiral reactant and go through an achiral carbocation intermediate, the product must be optically inactive (Section 9.10). The symmetrical intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic, 50:50 mixture of enantiomers (Figure 11.10).

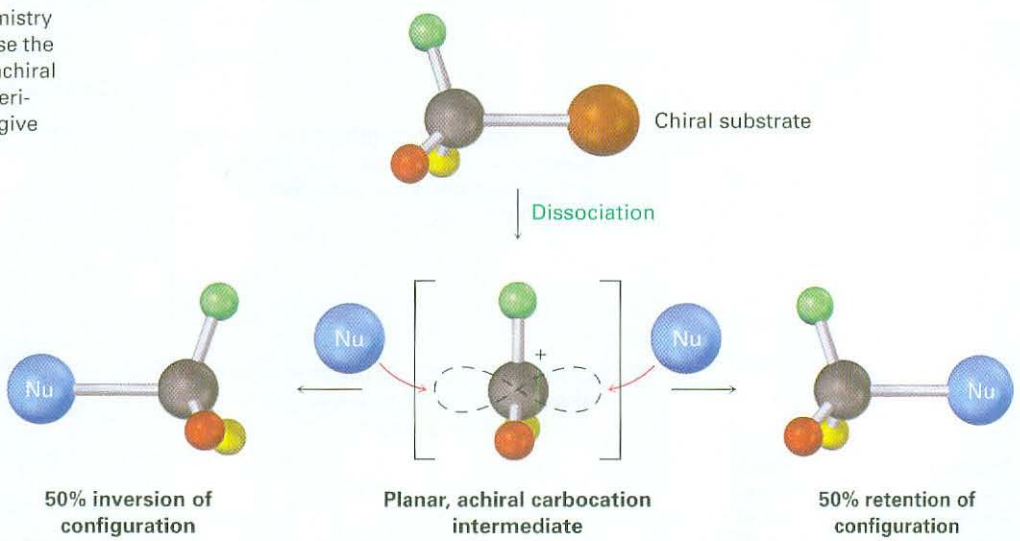
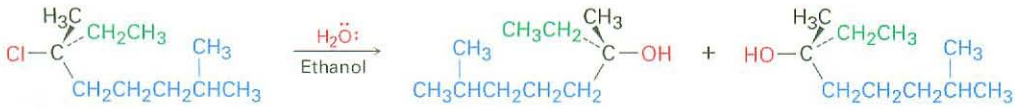


Figure 11.10 Stereochemistry of the S_N1 reaction. Because the reaction goes through an achiral intermediate, an enantiomerically pure reactant should give a racemic product.

The conclusion that S_N1 reactions on enantiomerically pure substrates should give racemic products is nearly, but not exactly, what is found. In fact, few S_N1 displacements occur with complete racemization. Most give a minor (0%–20%) excess of inversion. The reaction of (*R*)-6-chloro-2,6-dimethyloctane with H_2O, for example, leads to an alcohol product that is approximately 80% racemized and 20% inverted (80% *R*,*S* + 20% *S* is equivalent to 40% *R* + 60% *S*).



(*R*)-6-Chloro-2,6-dimethyloctane **60% *S* (inversion)** **40% *R* (retention)**

Saul Winstein

Saul Winstein (1912–1969) was born in Montreal, Canada, and received his Ph.D. in 1938 at the California Institute of Technology. From 1942 to 1969, he was professor of chemistry at the University of California, Los Angeles, where he devoted his scientific career to the study of organic reaction mechanisms, particularly those involving carbocations.

This lack of complete racemization in most S_N1 reactions is due to the fact that *ion pairs* are involved. According to this explanation, first proposed by Saul Winstein, dissociation of the substrate occurs to give a structure in which the two ions are still loosely associated and in which the carbocation is effectively shielded from reaction on one side by the departing anion. If a certain amount of substitution occurs before the two ions fully diffuse apart, then a net inversion of configuration will be observed (Figure 11.11).

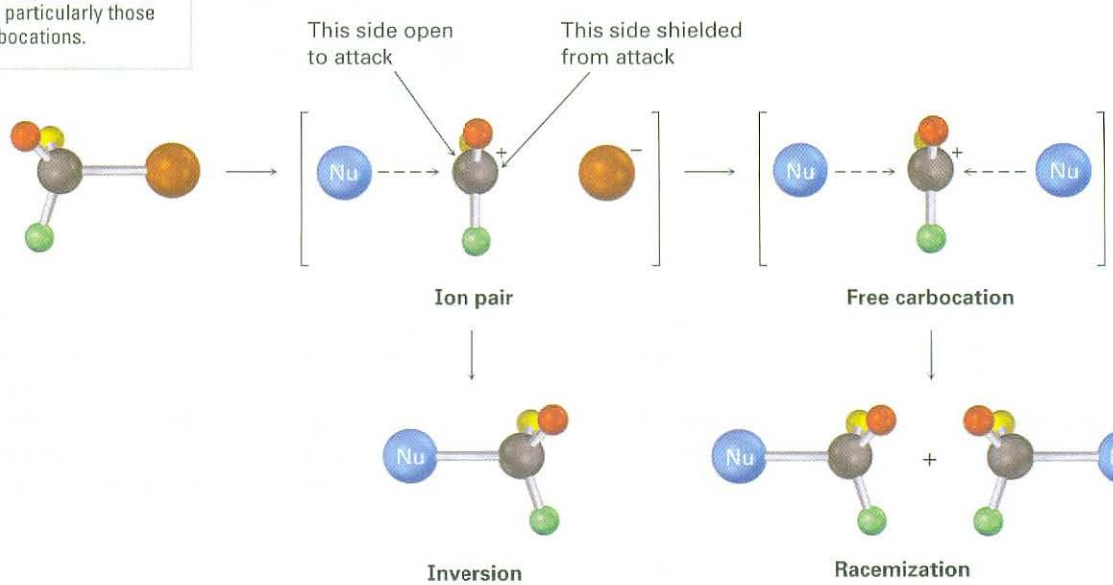
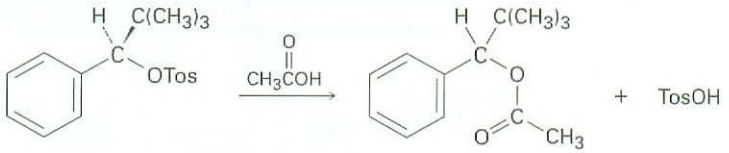


Figure 11.11 Ion pairs in an S_N1 reaction. The leaving group shields one side of the carbocation intermediate from reaction with the nucleophile, thereby leading to some inversion of configuration rather than complete racemization.

Problem 11.8 What product(s) would you expect from reaction of (*S*)-3-chloro-3-methyloctane with acetic acid? Show the stereochemistry of both reactant and product.

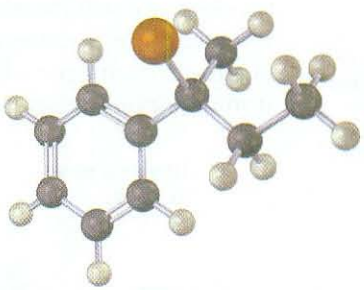
Problem 11.9 Among the numerous examples of S_N1 reactions that occur with incomplete racemization is one reported by Winstein in 1952. The optically pure tosylate of

2,2-dimethyl-1-phenyl-1-propanol ($[\alpha]_D = -30.3°$) was heated in acetic acid to yield the corresponding acetate ($[\alpha]_D = +5.3°$). If complete inversion had occurred, the optically pure acetate would have had $[\alpha]_D = +53.6°$. What percentage racemization and what percentage inversion occurred in this reaction?



$[\alpha]_D = -30.3$ **Observed $[\alpha]_D = +5.3$ (optically pure $[\alpha]_D = +53.6$)**

Problem 11.10 Assign configuration to the following substrate, and show the stereochemistry and identity of the product you would obtain by S_N1 reaction with water (reddish brown = Br):



11.5 Characteristics of the S_N1 Reaction

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

Just as the S_N2 reaction is strongly influenced by the structure of the substrate, the leaving group, the nucleophile, and the solvent, the S_N1 reaction is similarly influenced. Factors that lower $\Delta G^{\ddagger}$, either by lowering the energy level of the transition state or by raising the energy level of the ground state, favor faster S_N1 reactions. Conversely, factors that raise $\Delta G^{\ddagger}$, either by raising the energy level of the transition state or by lowering the energy level of the reactant, slow down the S_N1 reaction.

The Substrate

According to the Hammond postulate (Section 6.10), any factor that stabilizes a high-energy intermediate also stabilizes the transition state leading to that intermediate. Since the rate-limiting step in an S_N1 reaction is the spontaneous, unimolecular dissociation of the substrate to yield a carbocation, the reaction is favored whenever a stabilized carbocation intermediate is formed. The more stable the carbocation intermediate, the faster the S_N1 reaction.

We saw in Section 6.9 that the stability order of alkyl carbocations is $3° > 2° > 1° > -CH_3$. To this list we must also add the resonance-stabilized allyl and benzyl cations. Just as allylic *radicals* are unusually stable because the

unpaired electron can be delocalized over an extended π orbital system (Section 10.5), so allylic and benzylic *carbocations* are unusually stable. (The word **benzylic** means "next to an aromatic ring.") As Figure 11.12 indicates, an allylic cation has two resonance forms. In one form the double bond is on the "left"; in the other form it's on the "right." A benzylic cation has five resonance forms, all of which make substantial contributions to the overall resonance hybrid.

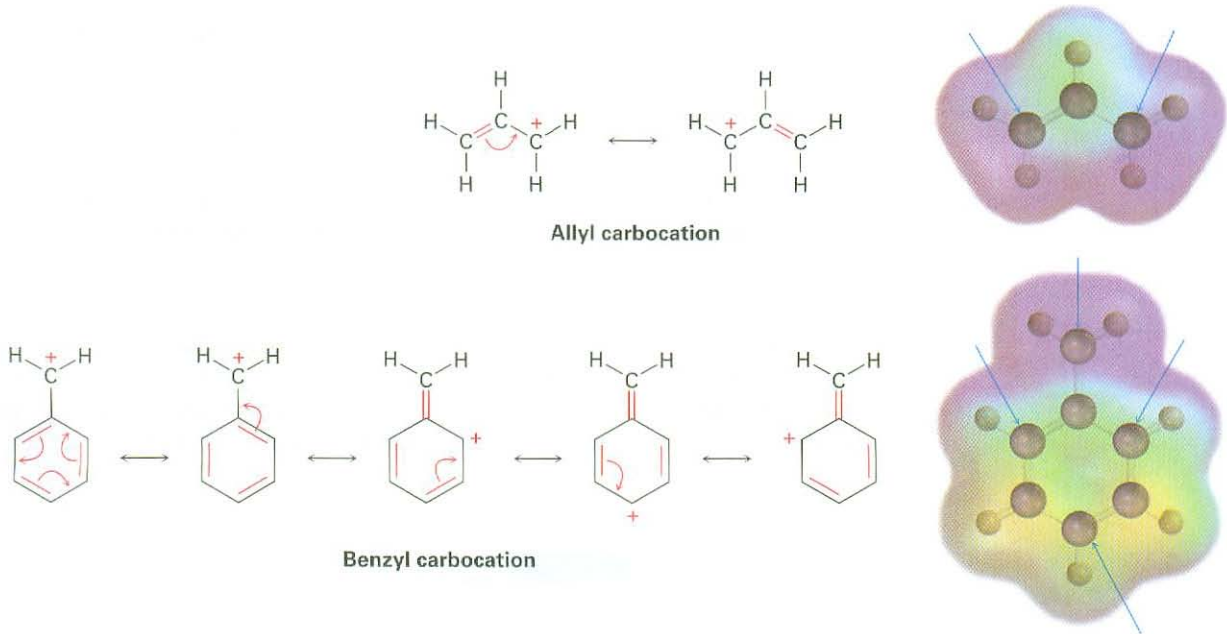
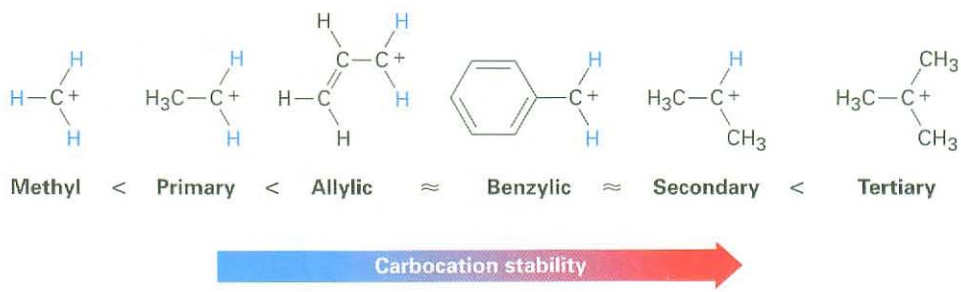


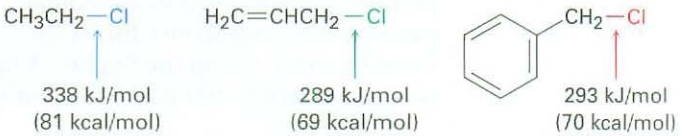
Figure 11.12 Resonance forms of the allyl and benzyl carbocations. Electrostatic potential maps show that the positive charge (blue) is delocalized over the π system in both. Electron-poor atoms are indicated by blue arrows.

Because of resonance stabilization, a *primary* allylic or benzylic carbocation is about as stable as a *secondary* alkyl carbocation and a *secondary* allylic or benzylic carbocation is about as stable as a *tertiary* alkyl carbocation. This stability order of carbocations is the same as the order of S_N1 reactivity for alkyl halides and tosylates.

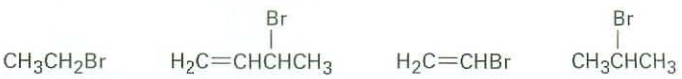


Parenthetically, we might also note that primary allylic and benzylic substrates are particularly reactive in S_N2 reactions as well as in S_N1 reactions.

Allylic and benzylic C–X bonds are about 50 kJ/mol (12 kcal/mol) weaker than the corresponding saturated bonds and are therefore more easily broken.



Problem 11.11 Rank the following substances in order of their expected S_N1 reactivity:



Problem 11.12 3-Bromo-1-butene and 1-bromo-2-butene undergo S_N1 reaction at nearly the same rate even though one is a secondary halide and the other is primary. Explain.

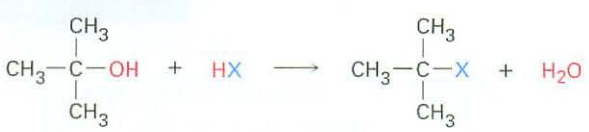
The Leaving Group

We said during the discussion of S_N2 reactivity that the best leaving groups are those that are most stable, that is, those that are the conjugate bases of strong acids. An identical reactivity order is found for the S_N1 reaction because the leaving group is directly involved in the rate-limiting step. Thus, the S_N1 reactivity order is

Note that in the S_N1 reaction, which is often carried out under acidic conditions, neutral water can act as a leaving group. This occurs, for example, when an alkyl halide is prepared from a tertiary alcohol by reaction with HBr or HCl (Section 10.6). The alcohol is first protonated and then spontaneously loses H_2O to generate a carbocation, which reacts with halide ion to give the alkyl halide (Figure 11.13). Knowing that an S_N1 reaction is involved in the conversion of alcohols to alkyl halides explains why the reaction works well only for tertiary alcohols. Tertiary alcohols react fastest because they give the most stable carbocation intermediates.

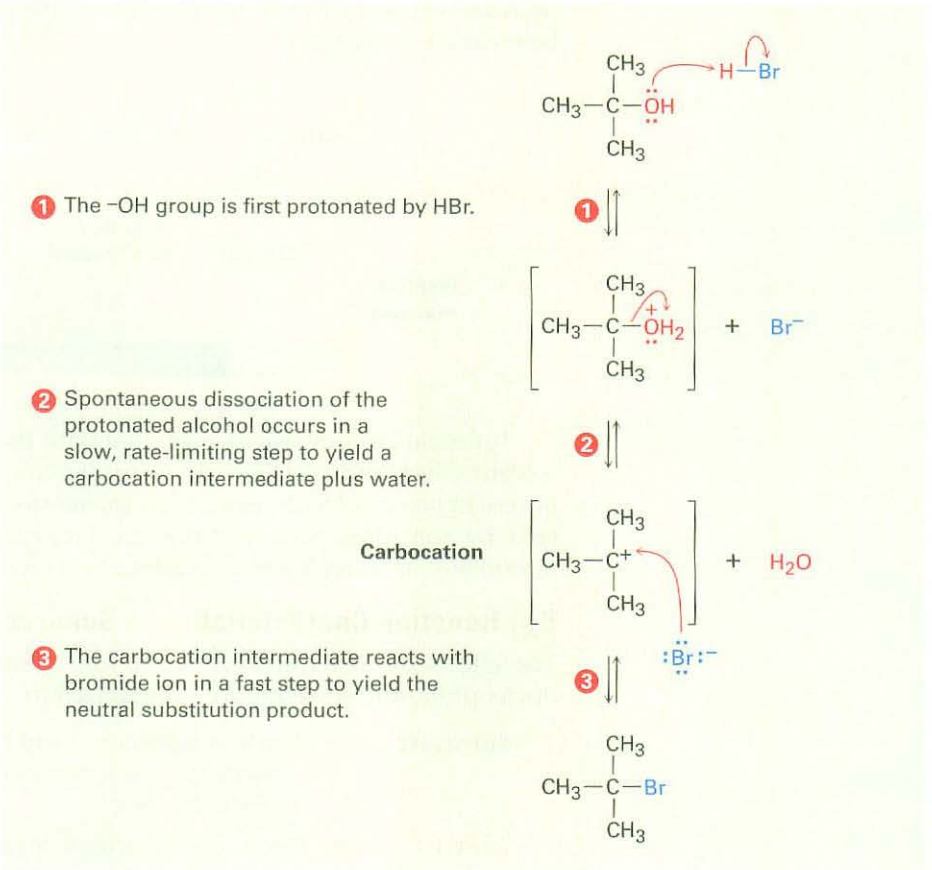
The Nucleophile

The nature of the nucleophile plays a major role in the S_N2 reaction but does not affect an S_N1 reaction. Because the S_N1 reaction occurs through a rate-limiting step in which the added nucleophile has no part, the nucleophile can't affect the reaction rate. The reaction of 2-methyl-2-propanol with HX, for instance, occurs at the same rate regardless of whether X is Cl, Br, or I. Furthermore, neutral nucleophiles are just as effective as negatively charged ones, so S_N1 reactions frequently occur under neutral or acidic conditions.



2-Methyl-2-propanol (Same rate for X = Cl, Br, I)

Figure 11.13 MECHANISM: The mechanism of the S_N1 reaction of a tertiary alcohol with HBr to yield an alkyl halide. Neutral water is the leaving group.



The Solvent

What about solvent? Do solvents have the same effect in S_N1 reactions that they have in S_N2 reactions? The answer is both yes and no. Yes, solvents have a large effect on S_N1 reactions, but no, the reasons for the effects on S_N1 and S_N2 reactions are not the same. Solvent effects in the S_N2 reaction are due largely to stabilization or destabilization of the nucleophile *reactant*. Solvent effects in the S_N1 reaction, however, are due largely to stabilization or destabilization of the *transition state*.

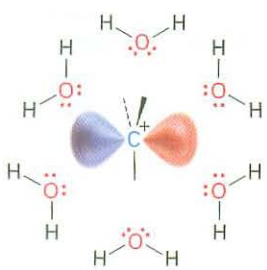
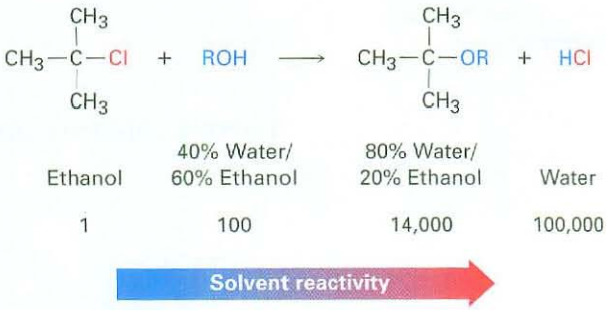


Figure 11.14 Solvation of a carbocation by water. The electron-rich oxygen atoms of solvent molecules orient around the positively charged carbocation and thereby stabilize it.

The Hammond postulate says that any factor stabilizing the intermediate carbocation should increase the rate of an S_N1 reaction. Solvation of the carbocation—the interaction of the ion with solvent molecules—has just such an effect. Solvent molecules orient around the carbocation so that the electron-rich ends of the solvent dipoles face the positive charge (Figure 11.14), thereby lowering the energy of the ion and favoring its formation.

The properties of a solvent that contribute to its ability to stabilize ions by solvation are related to the solvent's polarity. S_N1 reactions take place much more rapidly in strongly polar solvents, such as water and methanol, than in less polar solvents, such as ether and chloroform. In the reaction of 2-chloro-2-methylpropane, for example, a rate increase of 100,000 is observed on going from ethanol (less polar) to water (more polar). The rate

increases on going from a hydrocarbon solvent to water are so large they can't be measured accurately.



It should be emphasized again that both the S_N1 and the S_N2 reaction show solvent effects but that they do so for different reasons. S_N2 reactions are *disfavored* in protic solvents because the *ground-state energy* of the nucleophile is lowered by solvation. S_N1 reactions are *favored* in protic solvents because the *transition-state energy* leading to carbocation intermediate is lowered by solvation.

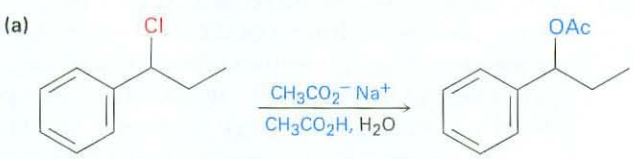
S_N1 Reaction Characteristics: A Summary

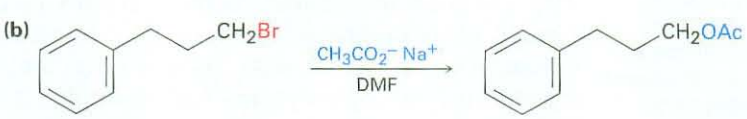
The effects on S_N1 reactions of the four variables—substrate, leaving group, nucleophile, and solvent—are summarized in the following statements:

Substrate	The best substrates yield the most stable carbocations. As a result, S_N1 reactions are best for tertiary, allylic, and benzylic halides.
Leaving group	Good leaving groups increase the reaction rate by lowering the energy level of the transition state for carbocation formation.
Nucleophile	The nucleophile must be nonbasic to prevent a competitive elimination of HX (Section 11.7), but otherwise does not affect the reaction rate. Neutral nucleophiles work well.
Solvent	Polar solvents stabilize the carbocation intermediate by solvation, thereby increasing the reaction rate.

WORKED EXAMPLE 11.2 ***Predicting the Mechanism of a Nucleophilic Substitution Reaction***

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:



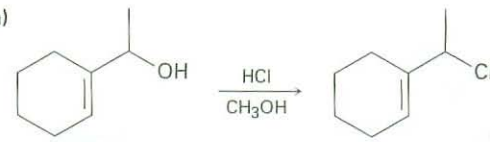


Strategy Look at the substrate, leaving group, nucleophile, and solvent. Then decide from the summaries at the ends of Sections 11.3 and 11.5 whether an S_N1 or an S_N2 reaction is favored. S_N1 reactions are favored by tertiary, allylic, or benzylic substrates, by good leaving groups, by nonbasic nucleophiles, and by protic solvents. S_N2 reactions are favored by primary substrates, by good leaving groups, by good nucleophiles, and by polar aprotic solvents.

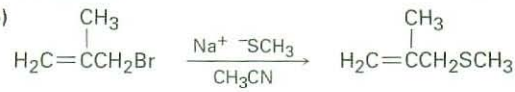
Solution (a) This is likely to be an S_N1 reaction because the substrate is secondary and benzylic, the nucleophile is weakly basic, and the solvent is protic.
(b) This is likely to be an S_N2 reaction because the substrate is primary, the nucleophile is a reasonably good one, and the solvent is polar aprotic.

Problem 11.13 Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:

(a)

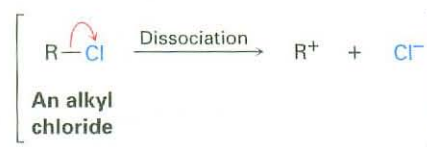


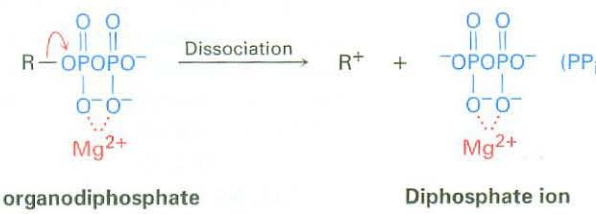
(b)



11.6 Biological Substitution Reactions

Both S_N1 and S_N2 reactions are well known in biological chemistry, particularly in the pathways for biosynthesis of the many thousands of terpenes (Chapter 6 *Focus On*). Unlike what typically happens in the laboratory, however, the substrate in a biological substitution reaction is often an organodiphosphate rather than an alkyl halide. Thus, the leaving group is the diphosphate ion, abbreviated PP_i, rather than a halide ion. In fact, it's useful to think of the diphosphate group as the "biological equivalent" of a halogen. The dissociation of an organodiphosphate in a biological reaction is typically assisted by complexation to a divalent metal cation such as Mg^{2+} to help neutralize charge.





Two S_N1 reactions occur during the biosynthesis of geraniol, a fragrant alcohol found in roses and used in perfumery. Geraniol biosynthesis begins with dissociation of dimethylallyl diphosphate to give an allylic carbocation, which reacts with isopentenyl diphosphate (Figure 11.15). From the viewpoint of isopentenyl diphosphate, the reaction is an electrophilic alkene addition, but from the viewpoint of dimethylallyl diphosphate, the process in an S_N1 reaction in which the carbocation intermediate reacts with a double bond as the nucleophile.

Following this initial S_N1 reaction, loss of the *pro-R* hydrogen gives geranyl diphosphate, itself an allylic diphosphate that dissociates a second time. Reaction of the geranyl carbocation with water in a second S_N1 reaction, followed by loss of a proton, then yields geraniol.

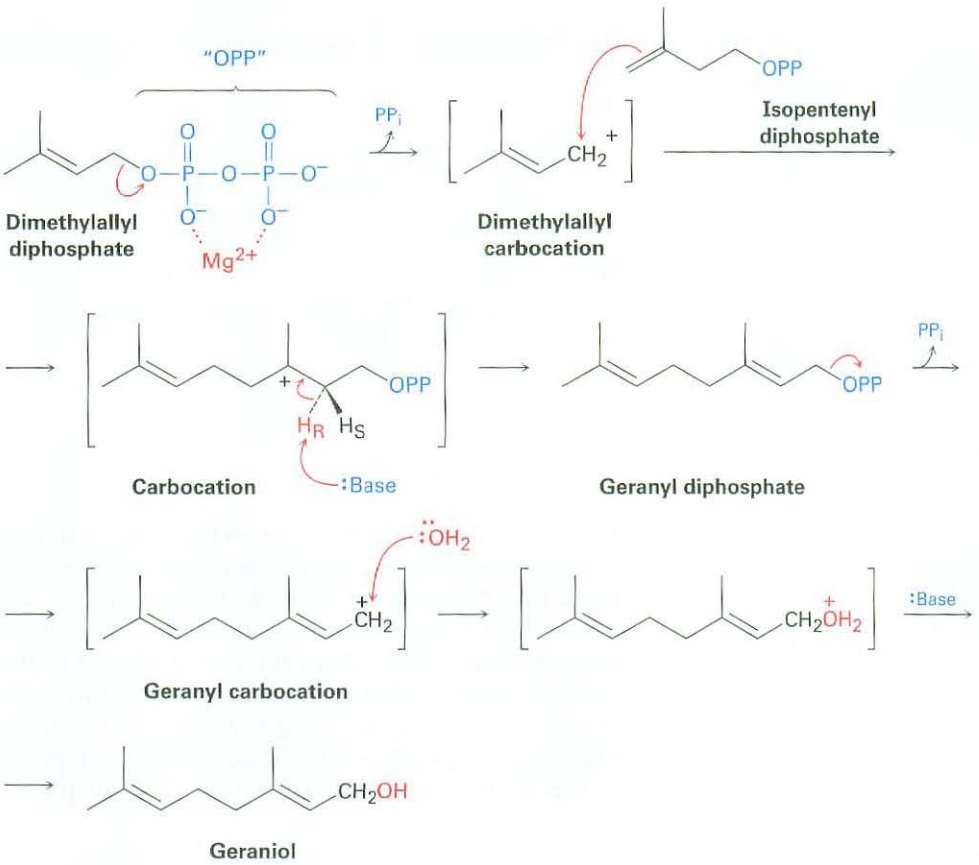


Figure 11.15 Biosynthesis of geraniol from dimethylallyl diphosphate. Two S_N1 reactions occur, both with diphosphate ion as the leaving group.

S_N2 reactions are involved in almost all biological methylations, which transfer a $-CH_3$ group from an electrophilic donor to a nucleophile. The donor is *S*-adenosylmethionine (abbreviated SAM), which contains a positively charged sulfur (a sulfonium ion; Section 9.12), and the leaving group is the neutral *S*-adenosylhomocysteine molecule. In the biosynthesis of epinephrine (adrenaline) from norepinephrine, for instance, the nucleophilic nitrogen atom of norepinephrine attacks the electrophilic methyl carbon atom of *S*-adenosylmethionine in an S_N2 reaction, displacing *S*-adenosylhomocysteine (Figure 11.16). In effect, *S*-adenosylmethionine is simply a biological equivalent of CH_3Cl.

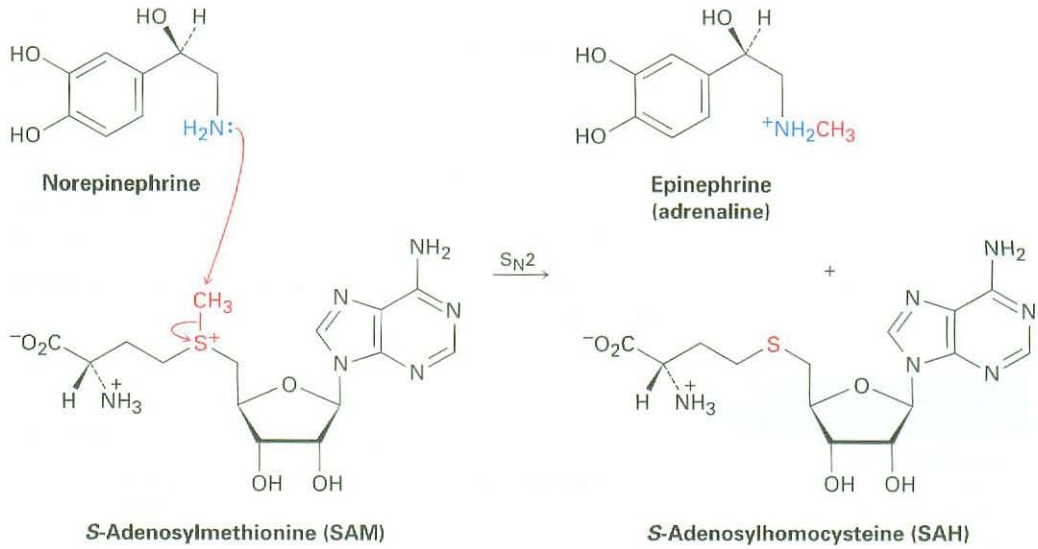
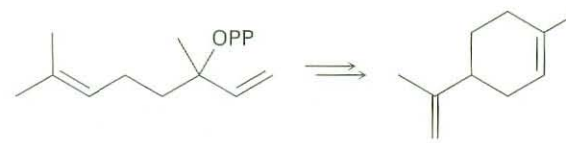


Figure 11.16 The biosynthesis of epinephrine from norepinephrine occurs by an S_N2 reaction with *S*-adenosylmethionine.

Problem 11.14 Review the mechanism of geraniol biosynthesis shown in Figure 11.15, and then propose a mechanism for the biosynthesis of limonene from linalyl diphosphate.



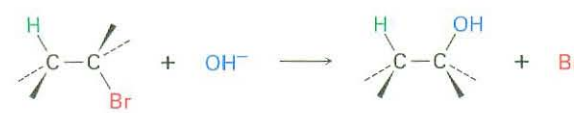
11.7 Elimination Reactions of Alkyl Halides: Zaitsev's Rule

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

We said at the beginning of this chapter that two kinds of reactions can happen when a nucleophile/Lewis base reacts with an alkyl halide. The nucleophile can either substitute for the halide by reaction at carbon or cause elimination of HX by reaction at a neighboring hydrogen:

Substitution



Elimination

Elimination reactions are more complex than substitution reactions for several reasons. There is, for example, the problem of regiochemistry. What

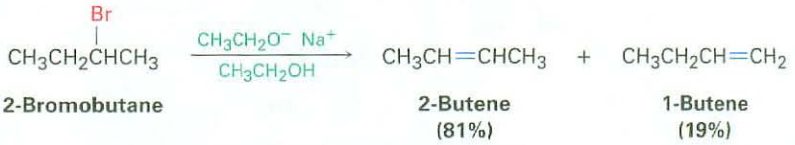
products result by loss of HX from an unsymmetrical halide? In fact, elimination reactions almost always give mixtures of alkene products, and the best we can usually do is to predict which will be the major product.

According to **Zaitsev's rule**, formulated in 1875 by the Russian chemist Alexander Zaitsev, base-induced elimination reactions generally (although not always) give the more stable alkene product—that is, the alkene with more alkyl substituents on the double-bond carbons. In the following two cases, for example, the more highly substituted alkene product predominates.

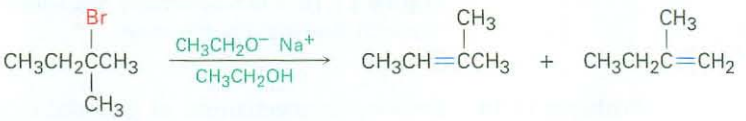
Zaitsev's rule In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.

Alexander M. Zaitsev

Alexander M. Zaitsev (1841–1910) was born in Kazan, Russia, and received his Ph.D. from the University of Leipzig in 1866. He was professor at the University of Kazan (1870–1903) and at Kiev University, and many of his students went on to assume faculty positions throughout Russia.



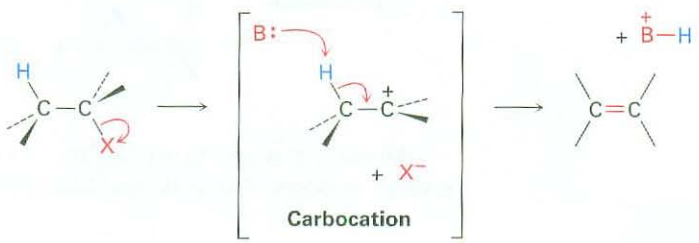
2-Bromobutane **2-Butene (81%)** **1-Butene (19%)**



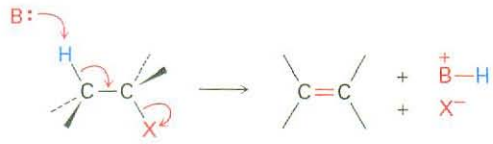
2-Bromo-2-methylbutane **2-Methyl-2-butene (70%)** **2-Methyl-1-butene (30%)**

A second factor that complicates a study of elimination reactions is that they can take place by different mechanisms, just as substitutions can. We'll consider three of the most common mechanisms—the E1, E2, and E1cB reactions—which differ in the timing of C–H and C–X bond-breaking. In the E1 reaction, the C–X bond breaks first to give a carbocation intermediate that undergoes subsequent base abstraction of H^+ to yield the alkene. In the E2 reaction, base-induced C–H bond cleavage is simultaneous with C–X bond cleavage, giving the alkene in a single step. In the E1cB reaction (cB for "conjugate base"), base abstraction of the proton occurs first, giving a carbon anion, or *carbanion* intermediate. This anion, the conjugate base of the reactant "acid," then undergoes loss of X^- in a subsequent step to give the alkene. All three mechanisms occur frequently in the laboratory, but the E1cB mechanism predominates in biological pathways.

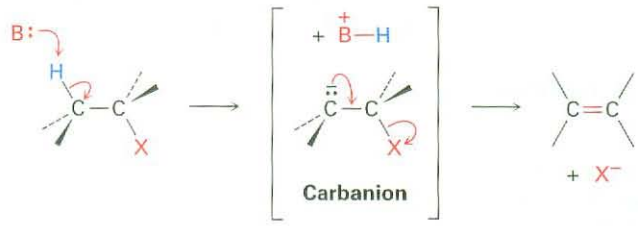
E1 Reaction: C–X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.



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

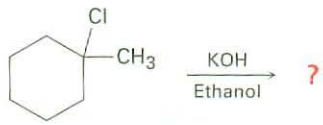


E1cB Reaction: C–H bond breaks first, giving a carbanion intermediate that loses X^- to form the alkene.



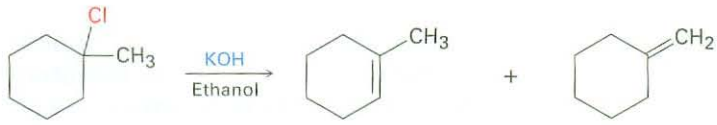
WORKED EXAMPLE 11.3 ***Predicting the Product of an Elimination Reaction***

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



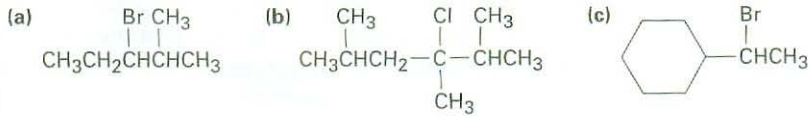
Strategy Treatment of an alkyl halide with a strong base such as KOH yields an alkene. To find the products in a specific case, locate the hydrogen atoms on each carbon next to the leaving group. Then generate the potential alkene products by removing HX in as many ways as possible. The major product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

Solution



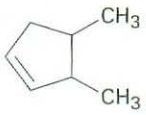
1-Chloro-1-methylcyclohexane | **1-Methylcyclohexene (major)** | **Methylenecyclohexane (minor)**

Problem 11.15 Ignoring double-bond stereochemistry, what products would you expect from elimination reactions of the following alkyl halides? Which will be the major product in each case?



Problem 11.16 What alkyl halides might the following alkenes have been made from?

(a) $CH_3CHCH_2CH_2CHCH{=}CH_2$ (with CH_3 groups on the two CH carbons)

(b) 

11.8 The E2 Reaction and the Deuterium Isotope Effect

The **E2 reaction** (for *elimination, bimolecular*) occurs when an alkyl halide is treated with a strong base, such as hydroxide ion or alkoxide ion (RO^-). It is the most commonly occurring pathway for elimination and can be formulated as shown in Figure 11.17.

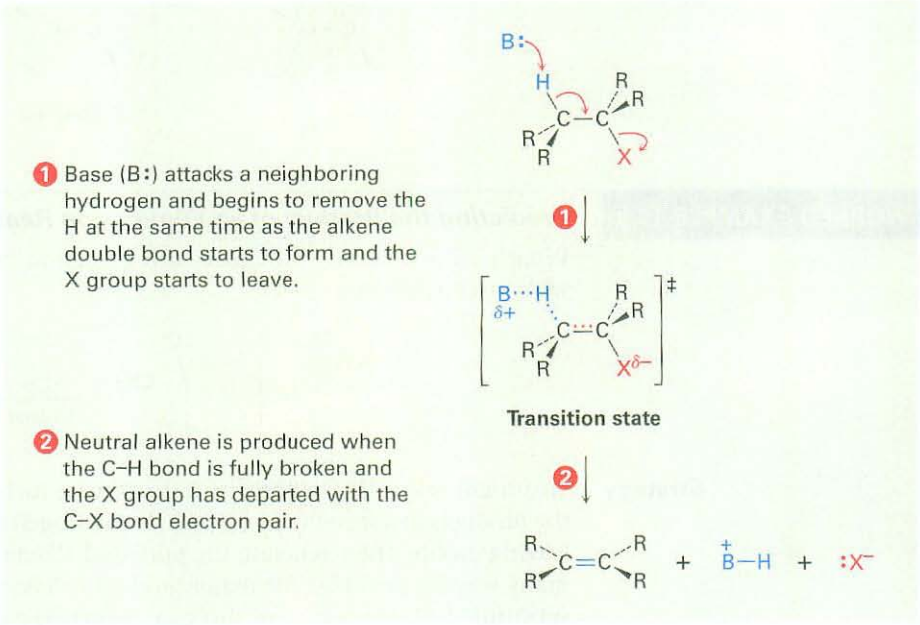


Figure 11.17 MECHANISM: Mechanism of the E2 reaction of an alkyl halide. The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving.

1. Base (B:) attacks a neighboring hydrogen and begins to remove the H at the same time as the alkene double bond starts to form and the X group starts to leave.
2. Neutral alkene is produced when the C–H bond is fully broken and the X group has departed with the C–X bond electron pair.

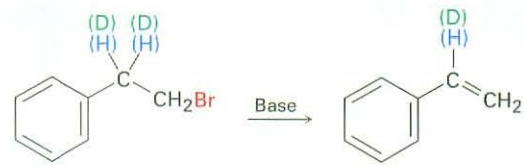
ThomsonNOW Click *Organic Process* to **view an animation showing the mechanism of an E2 elimination reaction.**

Like the S_N2 reaction, the E2 reaction takes place in one step without intermediates. As the base begins to abstract H^+ from a carbon next to the leaving group, the C–H bond begins to break, a C=C bond begins to form, and the leaving group begins to depart, taking with it the electron pair from the C–X bond. Among the pieces of evidence supporting this mechanism is that E2 reactions show second-order kinetics and follow the rate law: rate = $k \times$ [RX] $\times$ [Base]. That is, both base and alkyl halide take part in the rate-limiting step.

A second piece of evidence in support of the E2 mechanism is provided by a phenomenon known as the **deuterium isotope effect.** For reasons that we won't go into, a carbon–*hydrogen* bond is weaker by about 5 kJ/mol (1.2 kcal/mol) than the corresponding carbon–*deuterium* bond. Thus, a C–H bond is more easily broken than an equivalent C–D bond, and the rate of C–H bond cleavage is faster. For instance, the base-induced elimination of HBr from 1-bromo-2-phenylethane proceeds 7.11 times as fast as the corresponding

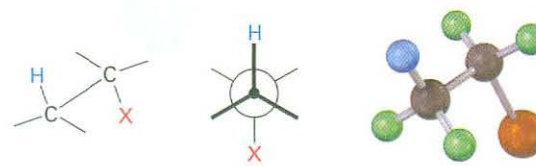
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from simple elimination reactions.**

elimination of DBr from 1-bromo-2,2-dideuterio-2-phenylethane. This result tells us that the C–H (or C–D) bond is broken *in the rate-limiting step,* consistent with our picture of the E2 reaction as a one-step process. If it were otherwise, we couldn't measure a rate difference.

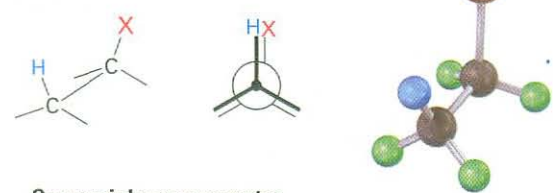


(H)—Faster reaction
(D)—Slower reaction

Yet a third piece of mechanistic evidence involves the stereochemistry of E2 eliminations. As shown by a large number of experiments, E2 reactions occur with *periplanar* geometry, meaning that all four reacting atoms—the hydrogen, the two carbons, and the leaving group—lie in the same plane. Two such geometries are possible: **syn periplanar** geometry, in which the H and the X are on the same side of the molecule, and **anti periplanar** geometry, in which the H and the X are on opposite sides of the molecule. Of the two, anti periplanar geometry is energetically preferred because it allows the substituents on the two carbons to adopt a staggered relationship, whereas syn geometry requires that the substituents be eclipsed.



Anti periplanar geometry
(staggered, lower energy)



Syn periplanar geometry
(eclipsed, higher energy)

What's so special about periplanar geometry? Because the sp^3 σ orbitals in the reactant C–H and C–X bonds must overlap and become p π orbitals in the alkene product, there must also be some overlap in the transition state. This can occur most easily if all the orbitals are in the same plane to begin with—that is, if they're periplanar (Figure 11.18).

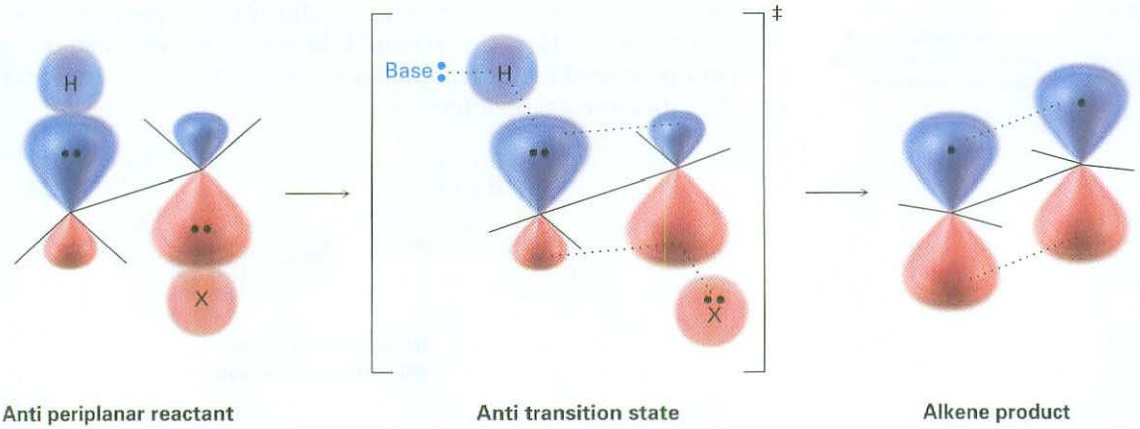
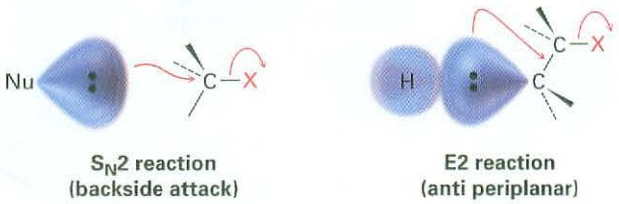
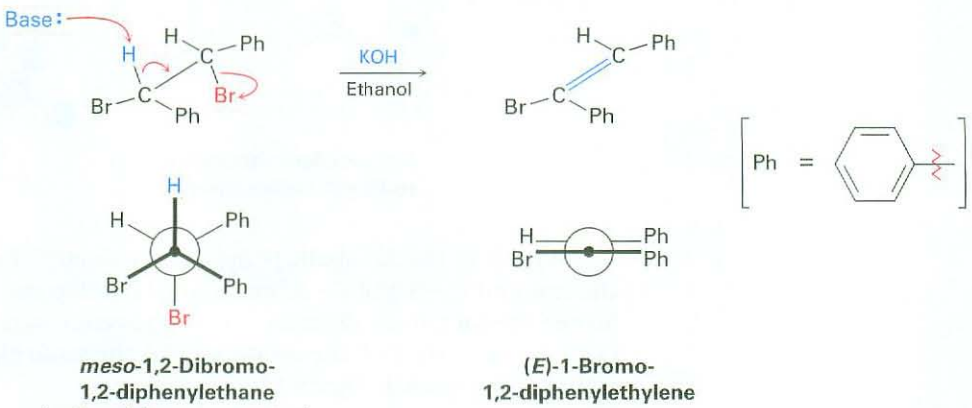


Figure 11.18 The transition state for the E2 reaction of an alkyl halide with base. Overlap of the developing *p* orbitals in the transition state requires periplanar geometry of the reactant.

It might help to think of E2 elimination reactions with periplanar geometry as being similar to S_N2 reactions with 180° geometry. In an S_N2 reaction, an electron pair from the incoming nucleophile pushes out the leaving group on the opposite side of the molecule. In an E2 reaction, an electron pair from a neighboring C–H bond pushes out the leaving group on the opposite side of the molecule.



Anti periplanar geometry for E2 eliminations has specific stereochemical consequences that provide strong evidence for the proposed mechanism. To take just one example, *meso*-1,2-dibromo-1,2-diphenylethane undergoes E2 elimination on treatment with base to give only the *E* alkene. None of the isomeric *Z* alkene is formed because the transition state leading to the *Z* alkene would have to have syn periplanar geometry and would thus be higher in energy.



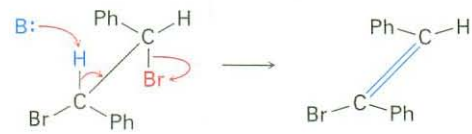
WORKED EXAMPLE 11.4

Predicting the Double-Bond Stereochemistry of the Product in an E2 Reaction

What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane?

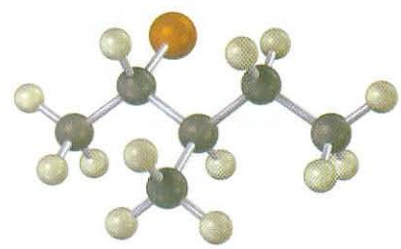
Strategy Draw (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane so that you can see its stereochemistry and so that the −H and −Br groups to be eliminated are anti periplanar. Then carry out the elimination while keeping all substituents in approximately their same positions, and see what alkene results.

Solution Anti periplanar elimination of HBr gives (*Z*)-1-bromo-1,2-diphenylethylene.



Problem 11.17 What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane? Draw a Newman projection of the reacting conformation.

Problem 11.18 What stereochemistry do you expect for the trisubstituted alkene obtained by E2 elimination of the following alkyl halide on treatment with KOH? (Reddish brown = Br.)



11.9 The E2 Reaction and Cyclohexane Conformation

Derek H. R. Barton

Derek H. R. Barton (1918–1998) was born in Gravesend, England, and received both Ph.D. and D.Sc. degrees from Imperial College, London. Among his numerous positions were those as professor at Imperial College, the University of London, Glasgow, Institut de Chimie des Substances Naturelles, and Texas A&M University. Barton received the Nobel Prize in chemistry in 1969 and was knighted by Queen Elizabeth in 1972.

Anti periplanar geometry for E2 reactions is particularly important in cyclohexane rings, where chair geometry forces a rigid relationship between the substituents on neighboring carbon atoms (Section 4.8). As pointed out by Derek Barton in a landmark 1950 paper, much of the chemical reactivity of substituted cyclohexanes is controlled by their conformation. Let's look at the E2 dehydrohalogenation of chlorocyclohexanes to see an example.

The anti periplanar requirement for E2 reactions overrides Zaitsev's rule and can be met in cyclohexanes only if the hydrogen and the leaving group are trans diaxial (Figure 11.19). If either the leaving group or the hydrogen is equatorial, E2 elimination can't occur.

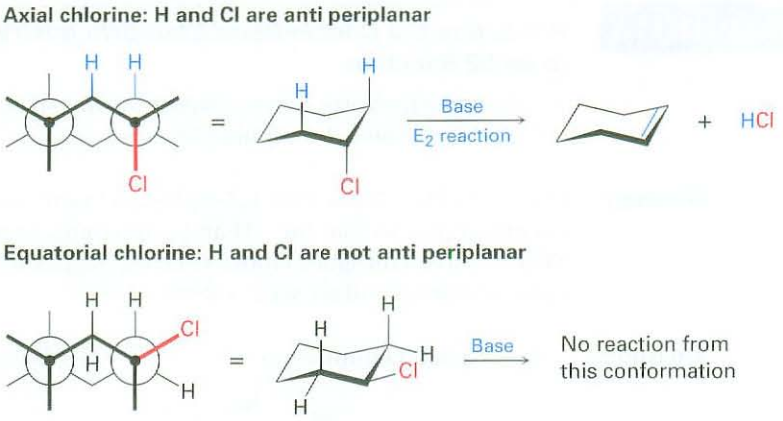
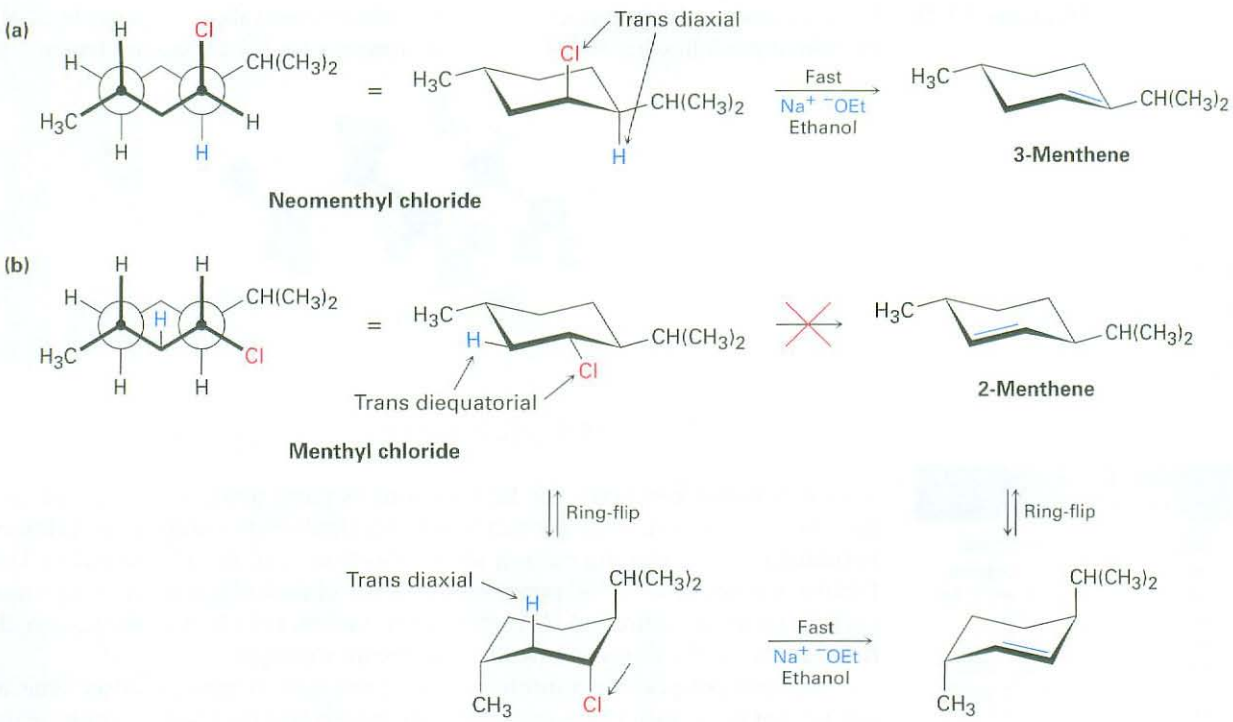


Figure 11.19 The geometric requirement for E2 reaction in a substituted cyclohexane. The leaving group and the hydrogen must both be axial for anti periplanar elimination to occur.

The elimination of HCl from the isomeric menthyl and neomenthyl chlorides shown in Figure 11.20 gives a good illustration of this trans-diaxial requirement. Neomenthyl chloride undergoes elimination of HCl on reaction with ethoxide ion 200 times as fast as menthyl chloride. Furthermore, neomenthyl chloride yields 3-menthene as the major alkene product, whereas menthyl chloride yields 2-menthene.



Active Figure 11.20 Dehydrochlorination of menthyl and neomenthyl chlorides. **(a)** Neomenthyl chloride loses HCl directly from its more stable conformation, but **(b)** menthyl chloride must first ring-flip before HCl loss can occur. The abbreviation "Et" represents an ethyl group. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

The difference in reactivity between the isomeric menthyl chlorides is due to the difference in their conformations. Neomenthyl chloride has the conformation shown in Figure 11.20a, with the methyl and isopropyl groups equatorial and the chlorine axial—a perfect geometry for E2 elimination. Loss of the hydrogen atom at C4 occurs easily to yield the more substituted alkene product, 3-menthene, as predicted by Zaitsev's rule.

Menthyl chloride, by contrast, has a conformation in which all three substituents are equatorial (Figure 11.20b). To achieve the necessary geometry for elimination, menthyl chloride must first ring-flip to a higher-energy chair conformation, in which all three substituents are axial. E2 elimination then occurs with loss of the only trans-diaxial hydrogen available, leading to the non-Zaitsev product 2-menthene. The net effect of the simple change in chlorine stereochemistry is a 200-fold change in reaction rate and a complete change of product. The chemistry of the molecule is controlled by its conformation.

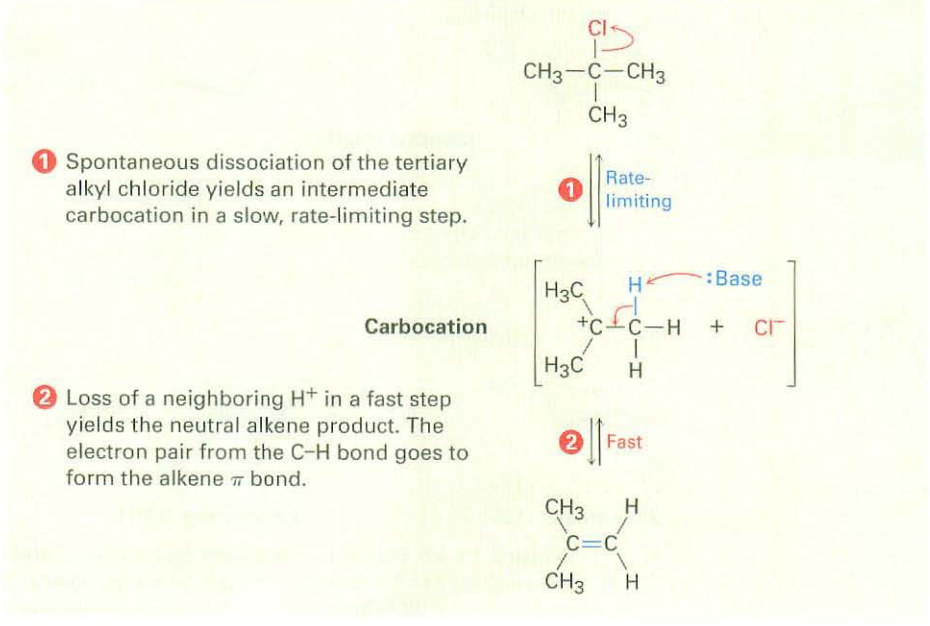
Problem 11.19 Which isomer would you expect to undergo E2 elimination faster, *trans*-1-bromo-4-*tert*-butylcyclohexane or *cis*-1-bromo-4-*tert*-butylcyclohexane? Draw each molecule in its more stable chair conformation, and explain your answer.

11.10 The E1 and E1cB Reactions

The E1 Reaction

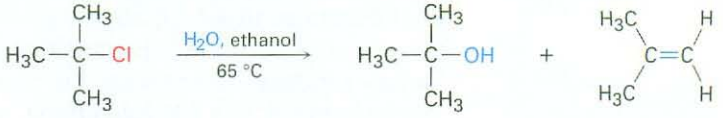
Just as the E2 reaction is analogous to the S_N2 reaction, the S_N1 reaction has a close analog called the **E1 reaction** (for *elimination, unimolecular*). The E1 reaction can be formulated as shown in Figure 11.21 for the elimination of HCl from 2-chloro-2-methylpropane.

Figure 11.21 MECHANISM: Mechanism of the E1 reaction. Two steps are involved, the first of which is rate-limiting, and a carbocation intermediate is present.



ThomsonNOW Click *Organic Process* to **view an animation showing the mechanism of an E1 elimination reaction.**

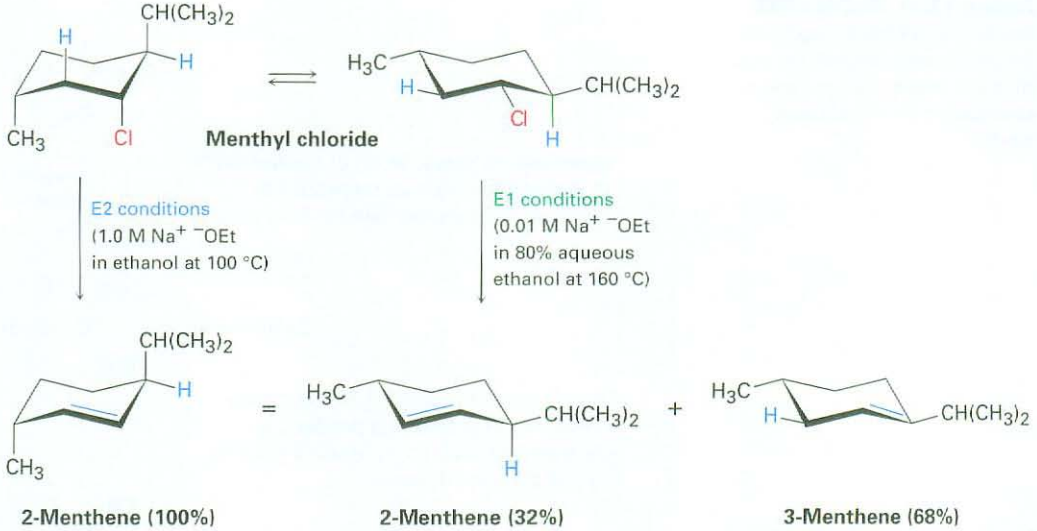
E1 eliminations begin with the same unimolecular dissociation we saw in the S_N1 reaction, but the dissociation is followed by loss of H^+ from the adjacent carbon rather than by substitution. In fact, the E1 and S_N1 reactions normally occur together whenever an alkyl halide is treated in a protic solvent with a non-basic nucleophile. Thus, the best E1 substrates are also the best S_N1 substrates, and mixtures of substitution and elimination products are usually obtained. For example, when 2-chloro-2-methylpropane is warmed to 65 °C in 80% aqueous ethanol, a 64:36 mixture of 2-methyl-2-propanol (S_N1) and 2-methylpropene (E1) results.



2-Chloro-2-methylpropane **2-Methyl-2-propanol (64%)** **2-Methylpropene (36%)**

Much evidence has been obtained in support of the E1 mechanism. For example, E1 reactions show first-order kinetics, consistent with a rate-limiting spontaneous dissociation process. Furthermore, E1 reactions show no deuterium isotope effect because rupture of the C–H (or C–D) bond occurs *after* the rate-limiting step rather than during it. Thus, we can't measure a rate difference between a deuterated and nondeuterated substrate.

A final piece of evidence involves the stereochemistry of elimination. Unlike the E2 reaction, where anti periplanar geometry is required, there is no geometric requirement on the E1 reaction because the halide and the hydrogen are lost in separate steps. We might therefore expect to obtain the more stable (Zaitsev's rule) product from E1 reaction, which is just what we find. To return to a familiar example, menthyl chloride loses HCl under E1 conditions in a polar solvent to give a mixture of alkenes in which the Zaitsev product, 3-menthene, predominates (Figure 11.22).

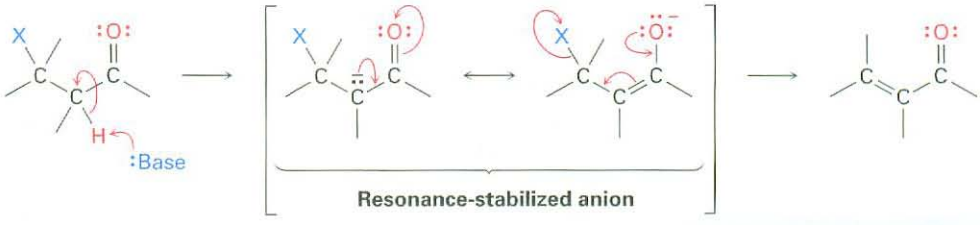


2-Menthene (100%) **2-Menthene (32%)** **3-Menthene (68%)**

Figure 11.22 Elimination reactions of menthyl chloride. E2 conditions (strong base in 100% ethanol) lead to 2-menthene through an anti periplanar elimination, whereas E1 conditions (dilute base in 80% aqueous ethanol) lead to a mixture of 2-menthene and 3-menthene.

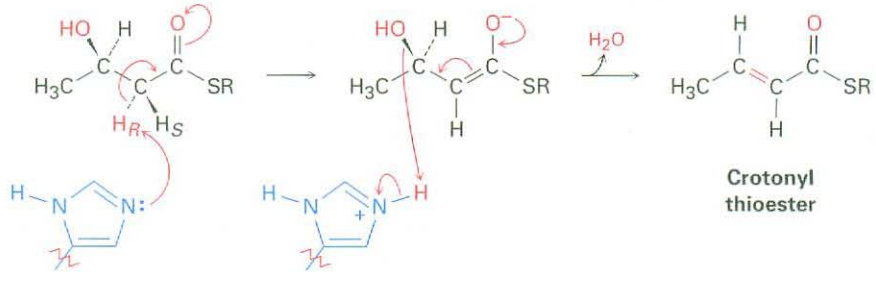
The E1cB Reaction

In contrast to the E1 reaction, which involves a carbocation intermediate, the **E1cB reaction** takes place through a *carbanion* intermediate. Base-induced abstraction of a proton in a slow, rate-limiting step gives an anion, which expels a leaving group on the adjacent carbon. The reaction is particularly common in substrates that have a poor leaving group, such as ^-OH, two carbons removed from a carbonyl group, HO—C—CH—C=O. The poor leaving group disfavors the alternative E1 and E2 possibilities, and the carbonyl group makes the adjacent hydrogen unusually acidic by resonance stabilization of the anion intermediate. We'll look at this acidifying effect of a carbonyl group in Section 22.5



11.11 Biological Elimination Reactions

All three elimination reactions—E2, E1, and E1cB—occur in biological pathways, but the E1cB mechanism is particularly common. The substrate is usually an alcohol, and the H atom removed is usually adjacent to a carbonyl group, just as in laboratory reactions. Thus, 3-hydroxy carbonyl compounds are frequently converted to unsaturated carbonyl compounds by elimination reactions. A typical example occurs during the biosynthesis of fats when a 3-hydroxybutyryl thioester is dehydrated to the corresponding unsaturated (crotonyl) thioester. The base in this reaction is a histidine amino acid in the enzyme, and loss of the ^-OH group is assisted by simultaneous protonation.



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

S_N1, S_N2, E1, E1cB, E2—how can you keep it all straight and predict what will happen in any given case? Will substitution or elimination occur? Will the reaction be bimolecular or unimolecular? There are no rigid answers to

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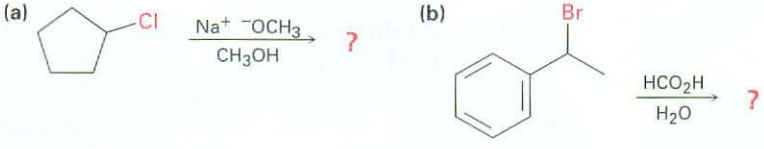
these questions, but it's possible to recognize some trends and make some generalizations.

- **Primary alkyl halides** S_N2 substitution occurs if a good nucleophile is used, E2 elimination occurs if a strong base is used, and E1cB elimination occurs if the leaving group is two carbons away from a carbonyl group.
- **Secondary alkyl halides** S_N2 substitution occurs if a weakly basic nucleophile is used in a polar aprotic solvent, E2 elimination predominates if a strong base is used, and E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group. Secondary allylic and benzylic alkyl halides can also undergo S_N1 and E1 reactions if a weakly basic nucleophile is used in a protic solvent.
- **Tertiary alkyl halides** E2 elimination occurs when a base is used, but S_N1 substitution and E1 elimination occur together under neutral conditions, such as in pure ethanol or water. E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group.

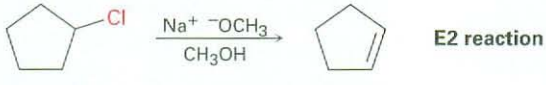
WORKED EXAMPLE 11.5 *Predicting the Product and Mechanism of Reactions*

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



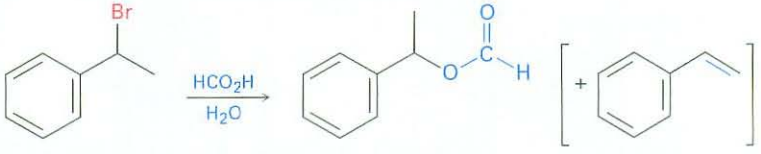
Strategy Look carefully in each reaction at the structure of the substrate, the leaving group, the nucleophile, and the solvent. Then decide from the preceding summary which kind of reaction is likely to be favored.

Solution (a) A secondary, nonallylic substrate can undergo an S_N2 reaction with a good nucleophile in a polar aprotic solvent but will undergo an E2 reaction on treatment with a strong base in a protic solvent. In this case, E2 reaction is likely to predominate.



E2 reaction

(b) A secondary benzylic substrate can undergo an S_N2 reaction on treatment with a nonbasic nucleophile in a polar aprotic solvent and will undergo an E2 reaction on treatment with a base. Under protic conditions, such as aqueous formic acid (HCO_2H), an S_N1 reaction is likely, along with some E1 reaction.



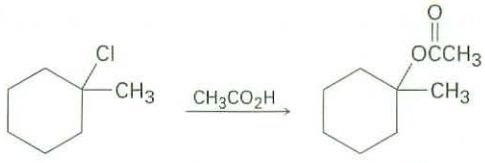
S_N1 **E1**

Problem 11.20 Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2:

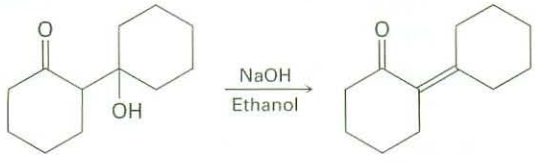
(a) $CH_3CH_2CH_2CH_2Br \xrightarrow[THF]{NaN_3} CH_3CH_2CH_2CH_2N{=}N{=}N$

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

(c)



(d)



Focus On . . .

Green Chemistry

© Rachel Dulson

Let's hope disasters like this are never repeated.

Organic chemistry in the 20th century changed the world, giving us new medicines, insecticides, adhesives, textiles, dyes, building materials, composites, and all manner of polymers. But these advances did not come without a cost: every chemical process produces wastes that must be dealt with, including reaction solvents and toxic by-products that might evaporate into the air or be leached into ground water if not disposed of properly. Even apparently harmless by-products must be safely buried or otherwise sequestered. As always, there's no such thing as a free lunch; with the good also comes the bad.

It may never be possible to make organic chemistry completely benign, but awareness of the environmental problems caused by many chemical processes has grown dramatically in recent years, giving rise to a movement called *green chemistry*. Green chemistry is the design and implementation of chemical products and processes that reduce waste and attempt to eliminate the generation of hazardous substances. There are 12 principles of green chemistry:

(continued)

Prevent waste. Waste should be prevented rather than treated or cleaned up after it has been created.

Maximize atom economy. Synthetic methods should maximize the incorporation of all materials used in a process into the final product so that waste is minimized.

Use less hazardous processes. Synthetic methods should use reactants and generate wastes with minimal toxicity to health and the environment.

Design safer chemicals. Chemical products should be designed to have minimal toxicity.

Use safer solvents. Minimal use should be made of solvents, separation agents, and other auxiliary substances in a reaction.

Design for energy efficiency. Energy requirements for chemical processes should be minimized, with reactions carried out at room temperature if possible.

Use renewable feedstocks. Raw materials should come from renewable sources when feasible.

Minimize derivatives. Syntheses should be designed with minimal use of protecting groups to avoid extra steps and reduce waste.

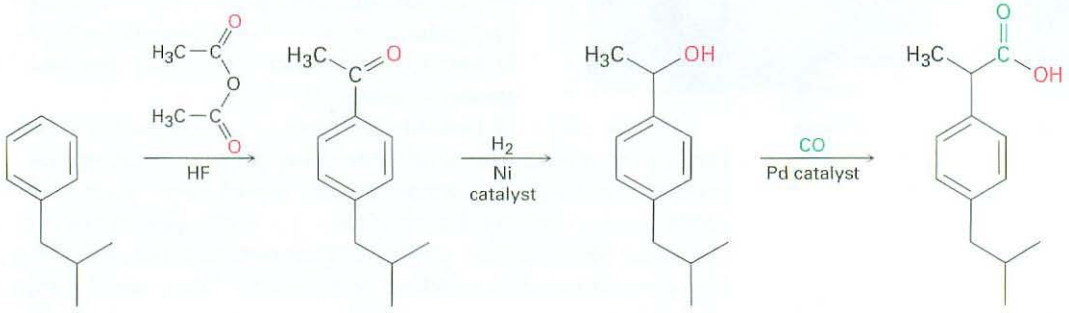
Use catalysis. Reactions should be catalytic rather than stoichiometric.

Design for degradation. Products should be designed to be biodegradable at the end of their useful lifetimes.

Monitor pollution in real time. Processes should be monitored in real time for the formation of hazardous substances.

Prevent accidents. Chemical substances and processes should minimize the potential for fires, explosions, or other accidents.

The 12 principles won't all be met in most real-world applications, but they provide a worthy goal to aim for and they can make chemists think more carefully about the environmental implications of their work. Success stories are already occurring, and more are in progress. Approximately 7 million pounds per year of ibuprofen (6 billion tablets!) is now made by a "green" process that produces approximately 99% less waste than the process it replaces. Only three steps are needed, the anhydrous HF solvent used in the first step is recovered and reused, and the second and third steps are catalytic.



Isobutylbenzene **Ibuprofen**

SUMMARY AND KEY WORDS

The reaction of an alkyl halide or tosylate with a nucleophile/base results eithe in *substitution* or in *elimination*. Nucleophilic substitutions are of two types **S_N2 reactions** and **S_N1 reactions**. In the S_N2 reaction, the entering nucleophil approaches the halide from a direction 180° away from the leaving group, result ing in an umbrella-like inversion of configuration at the carbon atom. The reac tion is kinetically **second-order** and is strongly inhibited by increasing steri bulk of the reactants. Thus, S_N2 reactions are favored for primary and secondary substrates.

The S_N1 reaction occurs when the substrate spontaneously dissociates to a carbocation in a slow rate-limiting step, followed by a rapid reaction with the nucleophile. As a result, S_N1 reactions are kinetically **first-order** and take place with racemization of configuration at the carbon atom. They are most favored for tertiary substrates. Both S_N1 and S_N2 reactions occur in biological pathways, although the leaving group is typically a diphosphate ion rather than a halide.

Eliminations of alkyl halides to yield alkenes occur by three mechanisms: **E2 reactions**, **E1 reactions**, and **E1cB reactions**, which differ in the timing of C–H and C–X bond-breaking. In the E2 reaction, C–H and C–X bond-breaking occur simultaneously when a base abstracts H^+ from one carbon at the same time the leaving group departs from the neighboring carbon. The reaction takes place preferentially through an **anti periplanar** transition state in which the four reacting atoms—hydrogen, two carbons, and leaving group—are in the same plane. The reaction shows second-order kinetics and a **deuterium isotope effect**, and it occurs when a secondary or tertiary substrate is treated with a strong base. These elimination reactions usually give a mixture of alkene products in which the more highly substituted alkene predominates (**Zaitsev's rule**).

In the E1 reaction, C–X bond-breaking occurs first. The substrate dissociates to yield a carbocation in the slow rate-limiting step before losing H^+ from an adjacent carbon in a second step. The reaction shows first-order kinetics and no deuterium isotope effect and occurs when a tertiary substrate reacts in polar, nonbasic solution.

In the E1cB reaction, C–H bond-breaking occurs first. A base abstracts a proton to give an anion, followed by loss of the leaving group from the adjacent carbon in a second step. The reaction is favored when the leaving group is two carbons removed from a carbonyl, which stabilizes the intermediate anion by resonance. Biological elimination reactions typically occur by this E1cB mechanism.

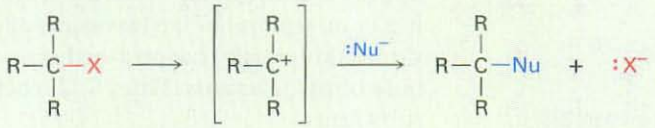
In general, substrates react in the following way:

RCH_2X (primary)	⟶	Mostly S_N2 substitution
R_2CHX (secondary)	⟶	S_N2 substitution with nonbasic nucleophiles E2 elimination with strong bases
R_3CX (tertiary)	⟶	Mostly E2 elimination (S_N1 substitution and E1 elimination in nonbasic solvents)

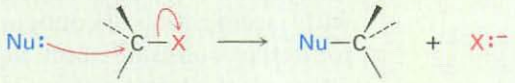
SUMMARY OF REACTIONS

1. Nucleophilic substitutions

(a) S_N1 reaction of 3°, allylic, and benzylic halides (Sections 11.4 and 11.5)

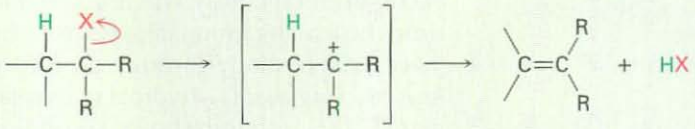


(b) S_N2 reaction of 1° and simple 2° halides (Sections 11.2 and 11.3)

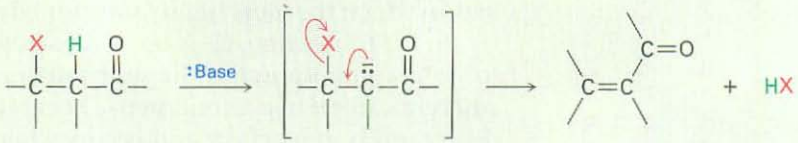


2. Eliminations

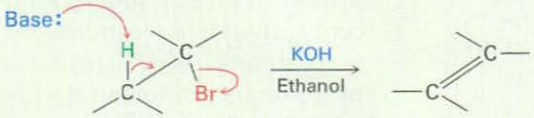
(a) E1 reaction (Section 11.10)



(b) E1cB reaction (Section 11.10)



(c) E2 reaction (Section 11.8)



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

▲ denotes problems linked to Key Ideas of this chapter and testable in ThomsonNOW.

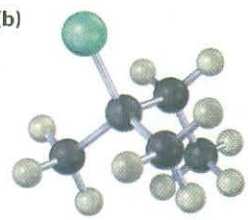
VISUALIZING CHEMISTRY

(Problems 11.1–11.20 appear within the chapter.)

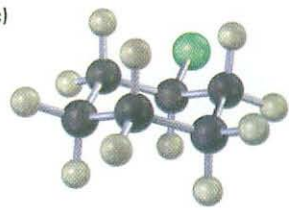
11.21 ■ Write the product you would expect from reaction of each of the following alkyl halides with (i) $Na^+ {}^-SCH_3$ and (ii) $Na^+ {}^-OH$ (yellow-green = Cl):

(a)

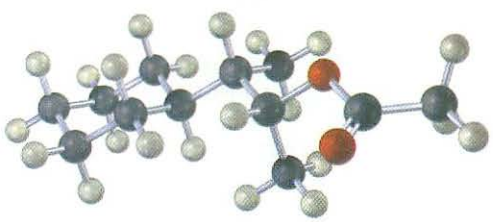
(b)



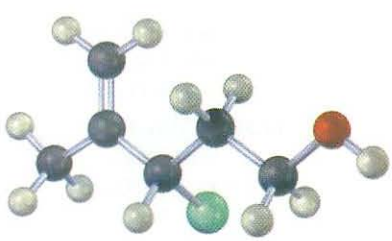
(c)



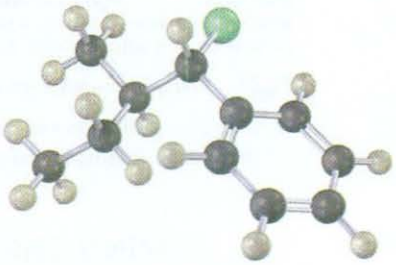
11.22 ■ From what alkyl bromide was the following alkyl acetate made by S_N2 reaction? Write the reaction, showing all stereochemistry.



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



11.24 ■ Draw the structure and assign *Z* or *E* stereochemistry to the product you expect from E2 reaction of the following molecule with NaOH (yellow-green = Cl):



ADDITIONAL PROBLEMS

11.25 ■ Which compound in each of the following pairs will react faster in an S_N2 reaction with OH^-?

(a) CH_3Br or CH_3I
(b) CH_3CH_2I in ethanol or in dimethyl sulfoxide
(c) $(CH_3)_3CCl$ or CH_3Cl
(d) $H_2C{=}CHBr$ or $H_2C{=}CHCH_2Br$

11.26 ■ What effect would you expect the following changes to have on the rate of the S_N2 reaction of 1-iodo-2-methylbutane with cyanide ion?

(a) The CN^- concentration is halved, and the 1-iodo-2-methylbutane concentration is doubled.
(b) Both the CN^- and the 1-iodo-2-methylbutane concentrations are tripled.

11.27 ■ What effect would you expect the following changes to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane?

(a) The concentration of the halide is tripled.
(b) The concentration of the ethanol is halved by adding diethyl ether as an inert solvent.

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

(a) $CH_3C{\equiv}CCH(CH_3)CH_3$ (b) $CH_3{-}O{-}C(CH_3)_2CH_3$ (c) $CH_3CH_2CH_2CH_2CN$ (d) $CH_3CH_2CH_2NH_2$

11.29 ■ ▲ Which reaction in each of the following pairs would you expect to be faster?

(a) The SN2 displacement by I^- on CH_3Cl or on CH_3OTos
(b) The S_N2 displacement by $CH_3CO_2^-$ on bromoethane or on bromocyclohexane
(c) The S_N2 displacement on 2-bromopropane by $CH_3CH_2O^-$ or by CN^-
(d) The S_N2 displacement by $HC{\equiv}C^-$ on bromomethane in benzene or in acetonitrile

11.30 ■ What products would you expect from the reaction of 1-bromopropane with each of the following?

(a) $NaNH_2$
(b) $KOC(CH_3)_3$
(c) NaI
(d) NaCN
(e) $NaC{\equiv}CH$
(f) Mg, then H_2O

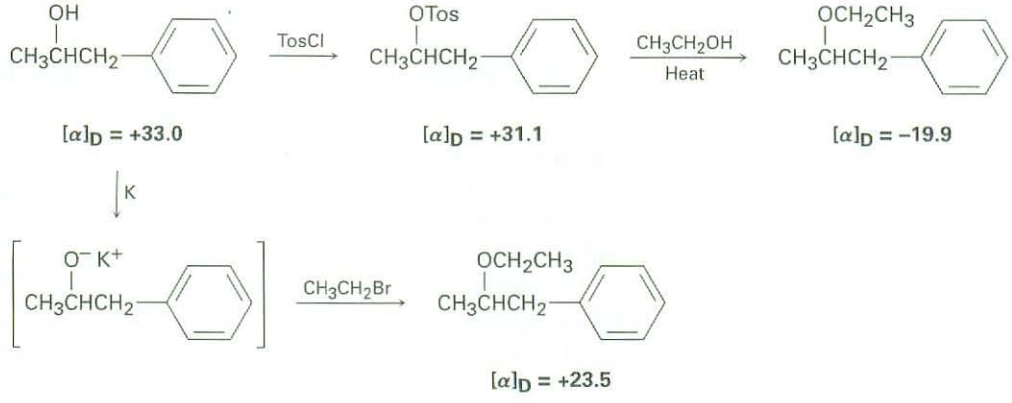
11.31 ■ Which reactant in each of the following pairs is more nucleophilic? Explain.

(a) $^-NH_2$ or NH_3
(b) H_2O or $CH_3CO_2^-$
(c) BF_3 or F^-
(d) $(CH_3)_3P$ or $(CH_3)_3N$
(e) I^- or Cl^-
(f) $^-C{\equiv}N$ or $^-OCH_3$

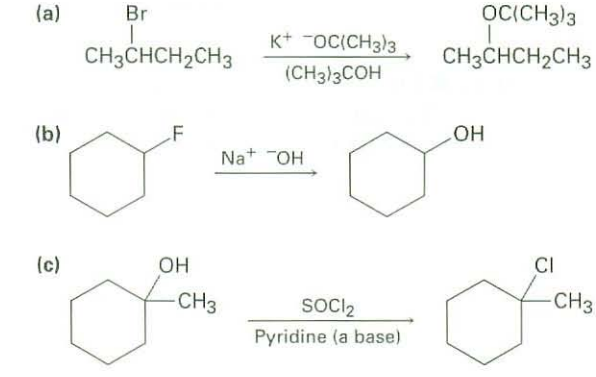
11.32 Propose structures for compounds that fit the following descriptions:
(a) An alkyl halide that gives a mixture of three alkenes on E2 reaction
(b) An organohalide that will not undergo nucleophilic substitution
(c) An alkyl halide that gives the non-Zaitsev product on E2 reaction
(d) An alcohol that reacts rapidly with HCl at 0 °C

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

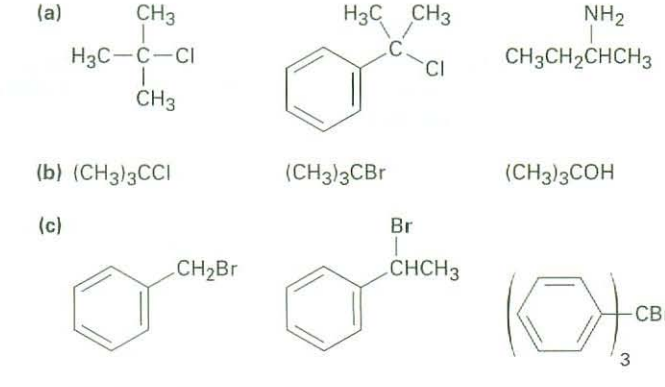
11.34 The following Walden cycle has been carried out. Explain the results, and indicate where Walden inversion is occurring.



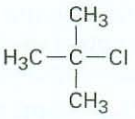
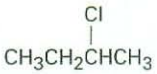
11.35 ■ The reactions shown below are unlikely to occur as written. Tell what is wrong with each, and predict the actual product.

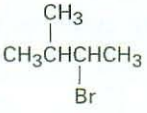
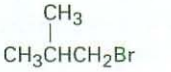
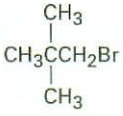


11.36 ■ Order each of the following sets of compounds with respect to S_N1 reactivity:



11.37 ■ Order each of the following sets of compounds with respect to S_N2 reactivity:

(a)  

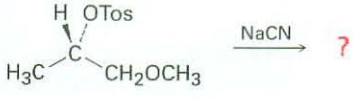
(b)   

(c) $CH_3CH_2CH_2OCH_3$ $CH_3CH_2CH_2OTos$ $CH_3CH_2CH_2Br$

11.38 ■ Predict the product and give the stereochemistry resulting from reaction of each of the following nucleophiles with (*R*)-2-bromooctane:
(a) ^-CN (b) $CH_3CO_2^-$ (c) CH_3S^-

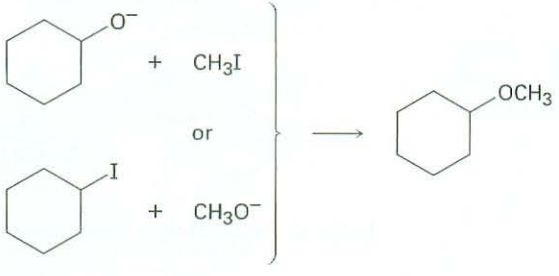
11.39 (*R*)-2-Bromooctane undergoes racemization to give (±)-2-bromooctane when treated with NaBr in dimethyl sulfoxide. Explain.

11.40 Reaction of the following *S* tosylate with cyanide ion yields a nitrile product that also has *S* stereochemistry. Explain.

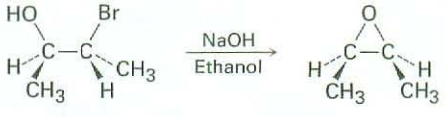


(***S* stereochemistry)**

11.41 ■ Ethers can often be prepared by S_N2 reaction of alkoxide ions, RO^-, with alkyl halides. Suppose you wanted to prepare cyclohexyl methyl ether. Which of the two possible routes shown below would you choose? Explain.



11.42 We saw in Section 7.8 that bromohydrins are converted into epoxides when treated with base. Propose a mechanism, using curved arrows to show the electron flow.

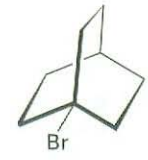


11.43 Show the stereochemistry of the epoxide (see Problem 11.42) you would obtain by formation of a bromohydrin from *trans*-2-butene, followed by treatment with base.

11.44 In light of your answer to Problem 11.42, what product might you expect from treatment of 4-bromo-1-butanol with base?

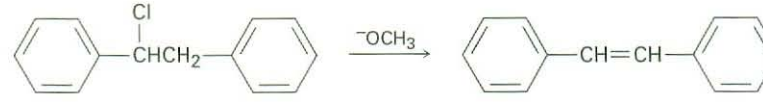
$$BrCH_2CH_2CH_2CH_2OH \xrightarrow{\text{Base}} \ ?$$

11.45 ▲ The following tertiary alkyl bromide does not undergo a nucleophilic substitution reaction by either S_N1 or S_N2 mechanisms. Explain.



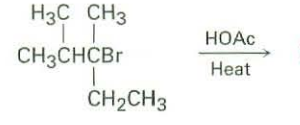
11.46 In addition to not undergoing substitution reactions, the alkyl bromide shown in Problem 11.45 also fails to undergo an elimination reaction when treated with base. Explain.

11.47 1-Chloro-1,2-diphenylethane can undergo E2 elimination to give either *cis*- or *trans*-1,2-diphenylethylene (stilbene). Draw Newman projections of the reactive conformations leading to both possible products, and suggest a reason why the trans alkene is the major product.

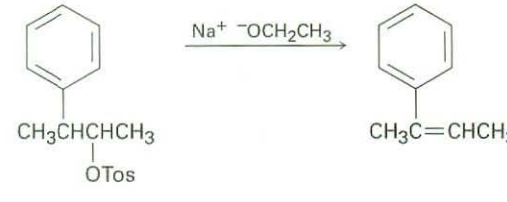


1-Chloro-1,2-diphenylethane **trans-1,2-Diphenylethylene**

11.48 ■ Predict the major alkene product of the following E1 reaction:



11.49 The tosylate of (2*R*,3*S*)-3-phenyl-2-butanol undergoes E2 elimination on treatment with sodium ethoxide to yield (*Z*)-2-phenyl-2-butene. Explain, using Newman projections.

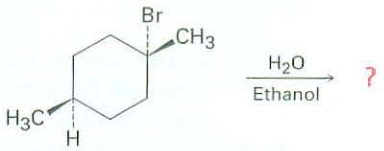


11.50 In light of your answer to Problem 11.49, which alkene, *E* or *Z*, would you expect from an E2 reaction on the tosylate of (2*R*,3*R*)-3-phenyl-2-butanol? Which alkene would result from E2 reaction on the (2*S*,3*R*) and (2*S*,3*S*) tosylates? Explain.

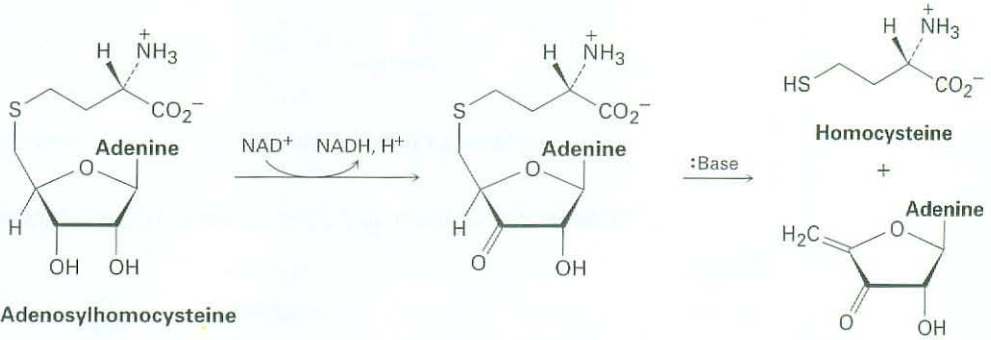
11.51 How can you explain the fact that *trans*-1-bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with base?

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

11.52 ■ Predict the product(s) of the following reaction, indicating stereochemistry where necessary:



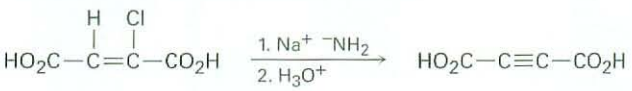
11.53 Metabolism of *S*-Adenosylhomocysteine (Section 11.6) involves the following sequence. Propose a mechanism for the second step.



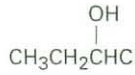
***S*-Adenosylhomocysteine**

11.54 Reaction of iodoethane with CN^- yields a small amount of *isonitrile*, $CH_3CH_2N{\equiv}C$, along with the nitrile $CH_3CH_2C{\equiv}N$ as the major product. Write electron-dot structures for both products, assign formal charges as necessary, and propose mechanisms to account for their formation.

11.55 ▲ Alkynes can be made by dehydrohalogenation of vinylic halides in a reaction that is essentially an E2 process. In studying the stereochemistry of this elimination, it was found that (*Z*)-2-chloro-2-butenedioic acid reacts 50 times as fast as the corresponding *E* isomer. What conclusion can you draw about the stereochemistry of eliminations in vinylic halides? How does this result compare with eliminations of alkyl halides?

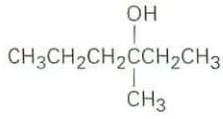


11.56 (*S*)-2-Butanol slowly racemizes on standing in dilute sulfuric acid. Explain.



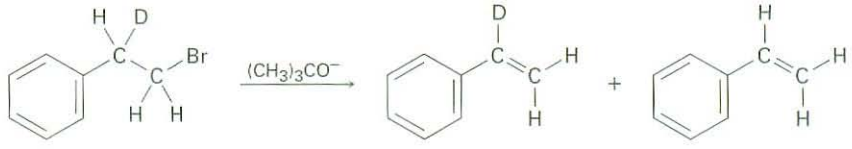
2-Butanol

11.57 Reaction of HBr with (*R*)-3-methyl-3-hexanol leads to racemic 3-bromo-3-methylhexane. Explain.



3-Methyl-3-hexanol

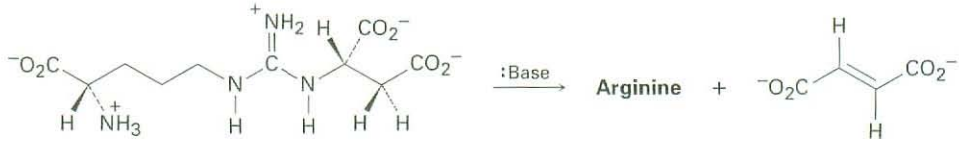
11.58 Treatment of 1-bromo-2-deuterio-2-phenylethane with strong base leads to a mixture of deuterated and nondeuterated phenylethylenes in an approximately 7:1 ratio. Explain.



7 : 1 ratio

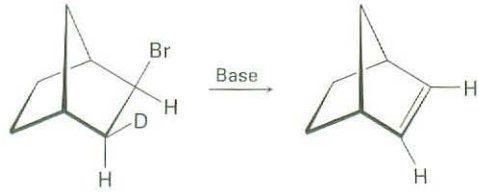
11.59 ▲ Propose a structure for an alkyl halide that gives only (*E*)-3-methyl-2-phenyl-2-pentene on E2 elimination. Make sure you indicate the stereochemistry.

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

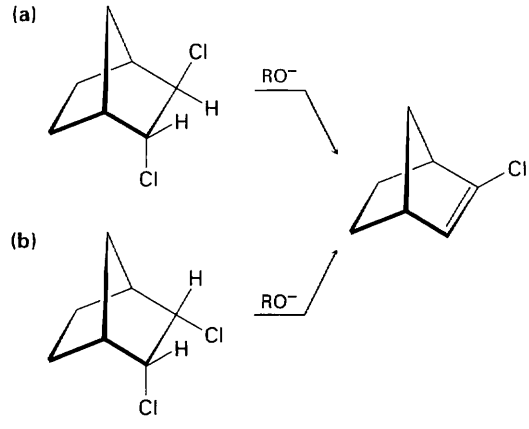


Argininosuccinate **Fumarate**

11.61 Although anti periplanar geometry is preferred for E2 reactions, it isn't absolutely necessary. The deuterated bromo compound shown here reacts with strong base to yield an undeuterated alkene. Clearly, a syn elimination has occurred. Make a molecular model of the reactant, and explain the result.

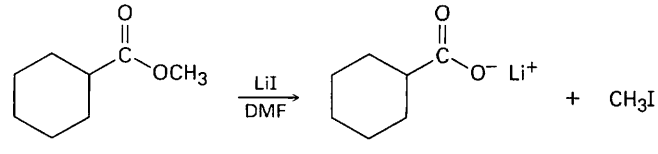


11.62 In light of your answer to Problem 11.61, explain why one of the following isomers undergoes E2 reaction approximately 100 times as fast as the other. Which isomer is more reactive, and why?



11.63 There are eight diastereomers of 1,2,3,4,5,6-hexachlorocyclohexane. Draw each in its more stable chair conformation. One isomer loses HCl in an E2 reaction nearly 1000 times more slowly than the others. Which isomer reacts so slowly, and why?

11.64 Methyl esters (RCO_2CH_3) undergo a cleavage reaction to yield carboxylate ions plus iodomethane on heating with LiI in dimethylformamide:

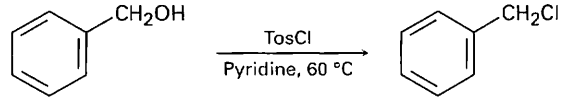


The following evidence has been obtained: (1) The reaction occurs much faster in DMF than in ethanol. (2) The corresponding ethyl ester ($RCO_2CH_2CH_3$) cleaves approximately 10 times more slowly than the methyl ester. Propose a mechanism for the reaction. What other kinds of experimental evidence could you gather to support your hypothesis?

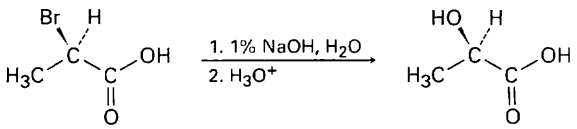
11.65 The reaction of 1-chlorooctane with $CH_3CO_2^-$ to give octyl acetate is greatly accelerated by adding a small quantity of iodide ion. Explain.

11.66 Compound X is optically inactive and has the formula $C_{16}H_{16}Br_2$. On treatment with strong base, X gives hydrocarbon Y, $C_{16}H_{14}$. Compound Y absorbs 2 equivalents of hydrogen when reduced over a palladium catalyst and reacts with ozone to give two fragments. One fragment, Z, is an aldehyde with formula C_7H_6O. The other fragment is glyoxal, $(CHO)_2$. Write the reactions involved, and suggest structures for X, Y, and Z. What is the stereochemistry of X?

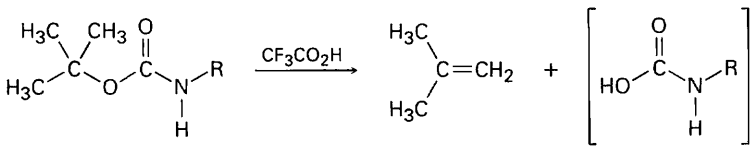
11.67 When a primary alcohol is treated with *p*-toluenesulfonyl chloride at room temperature in the presence of an organic base such as pyridine, a tosylate is formed. When the same reaction is carried out at higher temperature, an alkyl chloride is often formed. Explain.



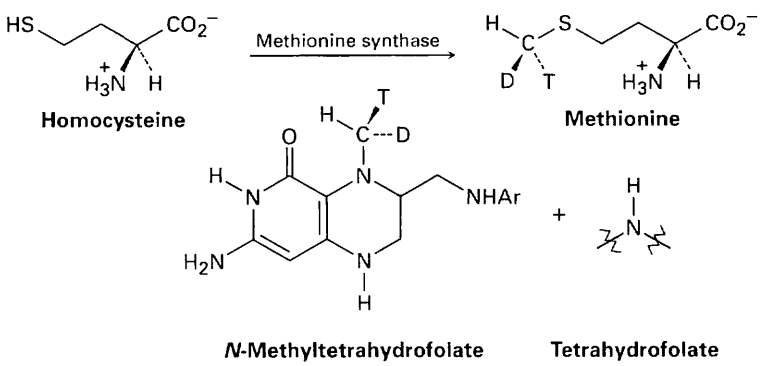
11.68 S_N2 reactions take place with inversion of configuration, and S_N1 reaction take place with racemization. The following substitution reaction, howeve occurs with complete *retention* of configuration. Propose a mechanism.



11.69 Propose a mechanism for the following reaction, an important step in the lab oratory synthesis of proteins:



11.70 The amino acid methionine is formed by a methylation reaction of homo cysteine with *N*-methyltetrahydrofolate. The stereochemistry of the reaction has been probed by carrying out the transformation using a donor with a "chiral methyl group" that contains protium (H), deuterium (D), and tritium (T) isotopes of hydrogen. Does the methylation reaction occur with inversion or retention of configuration?



11.71 Amines are converted into alkenes by a two-step process called the *Hofmann elimination*. S_N2 reaction of the amine with an excess of CH_3I in the first step yields an intermediate that undergoes E2 reaction when treated with silver oxide as base. Pentylamine, for example, yields 1-pentene. Propose a structure for the intermediate, and explain why it undergoes ready elimination.