Alkyl halides are easily converted to many other functional groups. The halogen atom can leave with its bonding pair of electrons to form a stable halide ion; we say that a halide is a good leaving group. When another atom replaces the halide ion, the reaction is a substitution. When the halide ion leaves with another atom or ion (often H\(^+\)), the reaction is an elimination. In many eliminations, a molecule of H\(\rightarrow\)X is lost from the alkyl halide to give an alkene. These eliminations are called dehydrohalogenations because a hydrogen halide has been removed from the alkyl halide. Substitution and elimination reactions often compete with each other.

In a nucleophilic substitution, a nucleophile (Nuc\(^-\)) replaces a leaving group (X\(^-\)) from a carbon atom, using its lone pair of electrons to form a new bond to the carbon atom.

\[
\text{Nucleophilic substitution} \\
\begin{array}{c}
\text{C} \quad \text{C} \\
\text{H} \quad \text{X}
\end{array} + \text{Nuc}^- \rightarrow \begin{array}{c}
\text{C} \quad \text{C} \\
\text{H} \quad \text{Nuc}
\end{array} + \text{X}^-
\]

In an elimination, both the halide ion and another substituent are lost. A new \(\pi\) bond is formed.

\[
\text{Elimination} \\
\begin{array}{c}
\text{C} \quad \text{C} \\
\text{H} \quad \text{X}
\end{array} + \text{B}^- \rightarrow \text{B} \cdots \text{H} + \begin{array}{c}
\text{C} \quad \text{C} \\
\end{array} + \text{X}^-
\]

In the elimination (a dehydrohalogenation), the reagent (B\(^-\)) reacts as a base, abstracting a proton from the alkyl halide. Most nucleophiles are also basic and can engage in either substitution or elimination, depending on the alkyl halide and the reaction conditions.

Besides alkyl halides, many other types of compounds undergo substitution and elimination reactions. Substitutions and eliminations are introduced in this chapter using the alkyl halides as examples. In later chapters, we encounter substitutions and eliminations of other types of compounds.

**Problem 6-11**

Classify each reaction as a substitution, elimination, or neither.

(a) \[\text{HBr} \xrightarrow{\text{Na}^+ \cdot \text{OCH}_3}\] \[\text{H} \quad \text{OCH}_3 + \text{NaBr}\]

(b) \[\text{H}_2\text{SO}_4\] \[\text{H} \quad \text{OH} + \text{H}_2\text{O}^+ + \text{HSO}_4^-\]

(c) \[\text{KI}\] \[\text{H} \quad \text{Br} + \text{IBr} + \text{KBr}\]
PROBLEM 6-12

Give the structures of the substitution products expected when 1-bromohexane reacts with:
(a) Na^+OCH_2CH_3
(b) NaCN
(c) NaOH

A nucleophilic substitution has the general form

\[
\text{Nuc}^+ + \text{C} - \text{X}^- \rightarrow \text{Nuc} - \text{C}^- + \text{X}^-
\]

where Nuc: is the nucleophile and X^- is the leaving halide ion. An example is the reaction of iodomethane (CH_3I) with hydroxide ion. The product is methanol.

\[
\begin{align*}
\text{H} - \text{O}^- &\quad + \quad \text{H} - \text{C} - \text{I}^- \\
\text{H} &\quad \text{H}
\end{align*}
\]

Hydroxide ion is a strong nucleophile (donor of an electron pair) because the oxygen atom has unshared pairs of electrons and a negative charge. Iodomethane is called the substrate, meaning the compound that is attacked by the reagent. The carbon atom of iodomethane is electrophilic because it is bonded to an electronegative iodine atom. Electron density is drawn away from carbon by the halogen atom, giving the carbon atom a partial positive charge. The negative charge of hydroxide ion is attracted to this partial positive charge.

\[
\begin{align*}
\text{H} &\quad \text{C}^- \\
\text{H} &\quad \text{H}
\end{align*}
\]

Hydroxide ion attacks the back side of the electrophilic carbon atom, donating a pair of electrons to form a new bond. (In general, nucleophiles are said to attack electrophiles, not the other way around.) Notice that arrows are used to show the movement of electron pairs, from the electron-rich nucleophile to the electron-poor carbon atom of the electrophile. Carbon can accommodate only eight electrons in its valence shell, so the carbon–iodine bond must begin to break as the carbon–oxygen bond begins to form. Iodide ion is the leaving group; it leaves with the pair of electrons that once bonded it to the carbon atom.

This one-step mechanism is supported by kinetic information. One can vary the concentrations of the reactants and observe the effects on the reaction rate (how much methanol is formed per second). The rate is found to double when the concentration of either reactant is doubled. The reaction is therefore first order in each of the reactants and second order overall. The rate equation has the following form:

\[
\text{rate} = k \lbrack \text{CH}_3\text{I} \rbrack \lbrack \text{OH} \rbrack
\]

This rate equation is consistent with a mechanism that requires a collision between a molecule of methyl iodide and a hydroxide ion. Both of these species are present in the
transition state, and the collision frequency is proportional to both concentrations. The rate constant $k_1$ depends on several factors, including the energy of the transition state and the temperature (Section 4-9).

This one-step nucleophilic substitution is an example of the $S_{N2}$ mechanism. The abbreviation $S_{N2}$ stands for Substitution, Nucleophilic, bimolecular. The term bimolecular means that the transition state of the rate-limiting step (the only step in this reaction) involves the collision of two molecules. Bimolecular reactions usually have rate equations that are second order overall.

The $S_{N2}$ reaction of methyl iodide (iodomethane) with hydroxide ion is a concerted reaction, taking place in a single step with bonds breaking and forming at the same time. The middle structure is a transition state, a point of maximum energy, rather than an intermediate. In this transition state, the bond to the nucleophile (hydroxide) is partially formed, and the bond to the leaving group (iodide) is partially broken. Remember that a transition state is not a discrete molecule that can be isolated; it exists for only an instant.

The reaction-energy diagram for this substitution (Figure 6-4) shows only one transition state and no intermediates between the reactants and the products. The reactants are shown slightly higher in energy than the products because this reaction is known to be exothermic. The transition state is much higher in energy because it involves a five-coordinate carbon atom with two partial bonds.

The following mechanism shows a general $S_{N2}$ reaction. A nucleophile attacks the substrate to give a transition state in which a bond to the nucleophile is forming at the same time as the bond to the leaving group is breaking.

**Problem-Solving Hint**

A transition state is unstable and cannot be isolated. It exists for only an instant.

**KEY MECHANISM 6-2 The $S_{N2}$ Reaction**

The $S_{N2}$ reaction takes place in a single (concerted) step. A strong nucleophile attacks the electrophilic carbon, forcing the leaving group to leave.

\[
\text{Nuc} \rightarrow \text{C} \rightarrow \text{Nuc} \quad \text{(electrophile)}
\]

The order of reactivity for substrates is $\text{CH}_3\text{X} > 1^\circ > 2^\circ$. (3° alkyl halides cannot react by this mechanism.)

(Continued)
EXAMPLE: Reaction of 1-bromobutane with sodium methoxide gives 1-methoxybutane.

PROBLEM 6-13: Under certain conditions, the reaction of 0.5 M 1-bromobutane with 1.0 M sodium methoxide forms 1-methoxybutane at a rate of 0.05 mol/L per second. What would be the rate if 0.1 M 1-bromobutane and 2.0 M NaOCH₃ were used?

6-9
Generality of the S_N2 Reaction

Many useful reactions take place by the S_N2 mechanism. The reaction of an alkyl halide, such as methyl iodide, with hydroxide ion gives an alcohol. Other nucleophiles convert alkyl halides to a wide variety of functional groups. The following table summarizes some of the types of compounds that can be formed by nucleophilic displacement of alkyl halides.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>Class of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—X + •I⁻</td>
<td>R—I⁻</td>
<td>alkyl halide</td>
</tr>
<tr>
<td>R—X + •OH</td>
<td>R—OH</td>
<td>alcohol</td>
</tr>
<tr>
<td>R—X + •OR’</td>
<td>R—OR’</td>
<td>ether</td>
</tr>
<tr>
<td>R—X + •SH</td>
<td>R—SH</td>
<td>thiol (mercaptan)</td>
</tr>
<tr>
<td>R—X + •SR’</td>
<td>R—SR’</td>
<td>thioether (sulfide)</td>
</tr>
<tr>
<td>R—X + •NH₃⁺</td>
<td>R—NH₃⁺</td>
<td>amine</td>
</tr>
<tr>
<td>R—X + •N≡N≡N⁻</td>
<td>R—N≡N≡N⁻</td>
<td>azide</td>
</tr>
<tr>
<td>R—X + •C≡C−R’</td>
<td>R—C≡C−R’</td>
<td>alkyne</td>
</tr>
<tr>
<td>R—X + •C≡N⁻</td>
<td>R—C≡N⁻</td>
<td>nitrile</td>
</tr>
<tr>
<td>R—X + R’−COO⁻</td>
<td>R’−COO−R</td>
<td>ester</td>
</tr>
<tr>
<td>R—X + •P(Ph)₃⁻</td>
<td>[R—P(Ph)₃]⁺−X</td>
<td>phosphonium salt</td>
</tr>
</tbody>
</table>
Halogen Exchange Reactions  The $S_N2$ reaction provides a useful method for synthesizing alkyl iodides and fluorides, which are more difficult to make than alkyl chlorides and bromides. Halides can be converted to other halides by halogen exchange reactions, in which one halide displaces another.

Iodide is a good nucleophile, and many alkyl chlorides react with sodium iodide to give alkyl iodides. Alkyl fluorides are difficult to synthesize directly, and they are often made by treating alkyl chlorides or bromides with KF under conditions that use a crown ether and an aprotic solvent to enhance the normally weak nucleophilicity of the fluoride ion (see Section 6-10).

\[
R - X + I^- \quad \rightarrow \quad R - I + X^- \\
R - X + KF \quad \xrightarrow{18\text{-crown-6}} \quad R - F + KX
\]

Examples

\[
H_2C\equiv CH - CH_2Cl \quad + \quad NaI \quad \rightarrow \quad H_2C\equiv CH - CH_2I \quad + \quad NaCl \\
\text{allyl chloride} \qquad \text{allyl iodide}
\]

\[
CH_3CH_2Cl \quad + \quad KF \quad \xrightarrow{18\text{-crown-6}} \quad CH_3CH_2F \quad + \quad KCl \\
\text{ethyl chloride} \quad \text{ethyl fluoride}
\]
PROBLEM 6-14
Predict the major products of the following substitutions.
(a) CH₃CH₂Br + (CH₃)₃CO⁻ + K⁺ →
(b) H₂C==C⁻Na⁺ + CH₃CH₂CH₂CH₂Cl →
(c) (CH₃)₂CHCH₂Br + excess NH₃ →
(d) CH₃CH₂I + NaCN →
(e) 1-chloropentane + NaI →
(f) 1-chloropentane + KF →¹⁸-crown-6 → CH₃CN

PROBLEM 6-15
Show how you would convert 1-chlorobutane into the following compounds.
(a) 1-butanol
(b) 1-fluorobutane
(c) 1-iodobutane
(d) CH₃(CH₂)₂CN
(e) CH₃(CH₂)₂C≡CH
(f) CH₃CH₂O(CH₂)₃CH₃
(g) CH₃(CH₂)₃NH₂

6-10
Factors Affecting S_n² Reactions: Strength of the Nucleophile

We will use the S_n² reaction as an example of how we study the properties of the species that participate in the reaction. Both the nucleophile and the substrate (the alkyl halide) are important, as well as the type of solvent used. We begin by considering what makes a good nucleophile.

The nature of the nucleophile strongly affects the rate of the S_n² reaction. A strong nucleophile is much more effective than a weak one in attacking an electrophilic carbon atom. For example, both methanol (CH₃OH) and methoxide ion (CH₃O⁻) have easily shared pairs of nonbonding electrons, but methoxide ion reacts with electrophiles in the S_n² reaction about 1 million times faster than methanol. It is generally true that a species with a negative charge is a stronger nucleophile than a similar, neutral species.

Methoxide ion has nonbonding electrons that are readily available for bonding. In the transition state, the negative charge is shared by the oxygen of methoxide ion and by the halide leaving group. Methanol, however, has no negative charge; the transition state has a partial negative charge on the halide but a partial positive charge on the methanol oxygen atom. We can generalize the case of methanol and the methoxide ion to say that a base is always a stronger nucleophile than its conjugate acid.

```
CH₃O⁻⁺CH₂⁺ → [CH₃O⁻⁺CH₂⁺]⁺ → CH₃O⁻⁺CH₂⁺ + H⁺
```

Conjugate base (stronger nucleophile)

```
CH₃O⁻⁺CH₂⁺ → [CH₃O⁻⁺CH₂⁺]⁺ → CH₃O⁻⁺CH₂⁺ + H⁺
```

Conjugate acid (weaker nucleophile)
### TABLE 6-3 Some Common Nucleophiles, Listed in Decreasing Order of Nucleophilicity in Hydroxylic Solvents Such as Water and Alcohols

<table>
<thead>
<tr>
<th>Strong nucleophiles</th>
<th>Moderate nucleophiles</th>
<th>Weak nucleophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₂CH₂)₂P⁺</td>
<td>Cl⁻</td>
<td>F⁻</td>
</tr>
<tr>
<td>+S⁻</td>
<td>NH₃</td>
<td>OH⁻</td>
</tr>
<tr>
<td>H⁻</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
</tr>
<tr>
<td>(CH₂CH₂)₂NH⁻</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
</tr>
<tr>
<td>+C≡N</td>
<td>N₂</td>
<td>Cl⁻</td>
</tr>
<tr>
<td>(CH₂CH₂)₂N⁺</td>
<td>CH₃⁻</td>
<td>N⁺</td>
</tr>
<tr>
<td>H⁻</td>
<td>CH₃⁻</td>
<td>CH₃⁻</td>
</tr>
<tr>
<td>CH₃⁻</td>
<td>OH⁻</td>
<td>OH⁻</td>
</tr>
</tbody>
</table>

We might be tempted to say that methoxide is a much better nucleophile because it is much more basic. This would be a mistake because basicity and nucleophilicity are different properties. Basicity is defined by the equilibrium constant for abstracting a proton. Nucleophilicity is defined by the rate of attack on an electrophilic carbon atom. In both cases, the nucleophile (or base) forms a new bond. If the new bond is to a proton, it has reacted as a base; if the new bond is to carbon, it has reacted as a nucleophile. Predicting which way a species will react may be difficult; most (but not all) good nucleophiles are also strong bases, and vice versa.

**Basicity**

\[ \text{B}^- + \text{H}^- \overset{K_B}{\leftrightarrow} \text{B}^- \text{H}^- + \text{A}^- \]

**Nucleophilicity**

\[ \text{B}^- + \text{C}^+ - \overset{k_n}{\rightarrow} \text{B}^- \text{C}^- + \text{X}^- \]

Table 6-3 lists some common nucleophiles in decreasing order of their nucleophilicity in common solvents such as water and alcohols. The strength of nucleophiles shows three major trends:

**SUMMARY  Trends in Nucleophilicity**

1. A species with a negative charge is a stronger nucleophile than a similar neutral species. In particular, a base is a stronger nucleophile than its conjugate acid.

\[ \cdot\cdot\cdot\overline{\text{O}}^- > \text{H}_2\overline{\text{O}}^-; \quad \cdot\overline{\text{S}}^- > \text{H}_2\overline{\text{S}}^-; \quad \cdot\overline{\text{NH}}_2^- > \cdot\overline{\text{NH}}_3^- \]

2. Nucleophilicity decreases from left to right in the periodic table, following the increase in electronegativity from left to right. The more electronegative elements have more tightly held nonbonding electrons that are less reactive toward forming new bonds.

\[ \cdot\overline{\text{O}}^- > \cdot\overline{\text{F}}^-; \quad \cdot\overline{\text{NH}}_2^- > \text{H}_2\overline{\text{O}}^-; \quad (\text{CH}_2\text{CH}_2)_3\text{P}^- > (\text{CH}_2\text{CH}_2)_3\text{S}^-; \]

3. Nucleophilicity increases down the periodic table, following the increase in size and polarizability.

\[ \cdot\overline{\text{I}}^- > \cdot\overline{\text{Br}}^- > \cdot\overline{\text{Cl}}^- > \cdot\overline{\text{F}}^-; \quad \cdot\overline{\text{Se}}^- > \cdot\overline{\text{H}}^- > \cdot\overline{\text{O}}^- \quad (\text{CH}_2\text{CH}_2)_3\text{P}^- > (\text{CH}_2\text{CH}_2)_3\text{N}^- \]
The third trend (size and polarizability) reflects an atom's ability to engage in partial bonding as it begins to attack an electrophilic carbon atom. As we go down a column in the periodic table, the atoms become larger, with more electrons at a greater distance from the nucleus. The electrons are more loosely held, and the atom is more polarizable: its electrons can move more freely toward a positive charge, resulting in stronger bonding in the transition state. The increased mobility of its electrons enhances the atom's ability to begin to form a bond at a relatively long distance.

Figure 6-5 illustrates this polarizability effect by comparing the attack of iodide ion and fluoride ion on a methyl halide. The outer shell of the fluoride ion is the second shell. These electrons are tightly held, close to the nucleus. Fluoride is a "hard" (low-polarizability) nucleophile, and its nucleus must approach the carbon nucleus quite closely before the electrons can begin to overlap and form a bond. In the transition state, there is little bonding between fluorine and carbon. In contrast, the outer shell of the iodide ion is the fifth shell. These electrons are loosely held, making the iodide ion a "soft" (high-polarizability) nucleophile. The outer electrons begin to shift and overlap with the carbon atom from farther away. There is a great deal of bonding between iodine and carbon in the transition state, which lowers the energy of the transition state.

6-10A Steric Effects on Nucleophilicity

To serve as a nucleophile, an ion or molecule must get in close to a carbon atom to attack it. Bulky groups on the nucleophile hinder this close approach, and they slow the reaction rate. For example, the t-butoxide ion is a stronger base (for abstracting protons) than ethoxide ion, but t-butoxide ion has three methyl groups that hinder any close approach to a carbon atom. Therefore, ethoxide ion is a stronger nucleophile than t-butoxide ion. When bulky groups interfere with a reaction by virtue of their size, we call the effect steric hindrance.
Steric hindrance has little effect on basicity because basicity involves attack on an unhindered proton. When a nucleophilic attack at a carbon atom is involved, however, a bulky base cannot approach the carbon atom so easily. Most bases are also nucleophiles, capable of attacking either a proton or an electrophilic carbon atom. If we want a species to act as a base, we use a bulky reagent like tri-n-butylamine. If we want it to react as a nucleophile, we use a less hindered reagent, like ethoxide.

**PROBLEM 6-16**

For each pair, predict the stronger nucleophile in the $S_{N}2$ reaction (using an alcohol as the solvent). Explain your prediction.

(a) (CH$_3$)$_2$NH or (CH$_3$)$_2$NH
(b) (CH$_3$)$_2$O or (CH$_3$)$_2$S
(c) NH$_3$ or PH$_3$
(d) CH$_3$S$^-$ or H$_2$S
(e) (CH$_3$)$_3$N or (CH$_3$)$_2$O
(f) CH$_3$S$^-$ or CH$_3$OH
(g) (CH$_3$)$_3$CHO$^-$ or CH$_3$CH$_2$CH$_2$O$^-$
(h) I$^-$ or Cl$^-$

**PROBLEM-SOLVING Hint**
Steric hindrance (bulkiness) hinders nucleophilicity ($S_{N}2$) more than it does basicity.

### 6-10B Solvent Effects on Nucleophilicity

Another factor in the nucleophilicity of these ions is their solvation, particularly in protic solvents. A protic solvent is one that has acidic protons, usually in the form of O—H or N—H groups. These groups form hydrogen bonds to negatively charged nucleophiles. Protic solvents, especially alcohols, are convenient solvents for nucleophilic substitutions because the reagents (alkyl halides, nucleophiles, etc.) tend to be quite soluble.

Small anions are solvated more strongly than large anions in a protic solvent because the solvent approaches a small anion more closely and forms stronger hydrogen bonds. When an anion reacts as a nucleophile, energy is required to “strip off” some of the solvent molecules, breaking some of the hydrogen bonds that stabilized the solvated anion. More energy is required to strip off solvent from a small, strongly solvated ion such as fluoride than from a large, diffuse, less strongly solvated ion like iodide.

The enhanced solvation of smaller anions in protic solvents, requiring more energy to strip off their solvent molecules, reduces their nucleophilicity. This trend reinforces the trend in polarizability: The polarizability increases with increasing atomic number, and the solvation energy (in protic solvents) decreases with increasing atomic number. Therefore, nucleophilicity (in protic solvents) generally increases down a column in the periodic table, as long as we compare similar species with similar charges.
In contrast with protic solvents, aprotic solvents (solvents without O—H or N—H groups) enhance the nucleophilicity of anions. An anion is more reactive in an aprotic solvent because it is not so strongly solvated. There are no hydrogen bonds to be broken when solvent must make way for the nucleophile to approach an electrophilic carbon atom. The relatively weak solvating ability of aprotic solvents is also a disadvantage: Most polar, ionic reagents are not soluble in simple aprotic solvents such as alkanes.

**Polar aprotic solvents** have strong dipole moments to enhance solubility, yet they have no O—H or N—H groups to form hydrogen bonds with anions. Examples of useful polar aprotic solvents are acetonitrile, dimethylformamide, and acetone. We can add specific solvating reagents to enhance solubility without affecting the reactivity of the nucleophile. For example, the “crown ether” 18-crown-6 solvates potassium ions. Using the potassium salt of a nucleophile and solvating the potassium ions causes the nucleophilic anion to be dragged along into solution.

![Chemical Structures]

The following example shows how fluoride ion, normally a poor nucleophile in hydroxylic (protic) solvents, can be a good nucleophile in an aprotic solvent. Although KF is not very soluble in acetonitrile, 18-crown-6 solvates the potassium ions, and the poorly solvated (and therefore nucleophilic) fluoride ion follows.

\[
\text{CH}_2\text{Cl} \quad \overset{\text{KF, 18-crown-6}}{\text{CH}_3\text{CN}} \quad \overset{+ \text{Cl}^-}{\text{CH}_3\text{F}}
\]

### 6-11
**Reactivity of the Substrate in S_N2 Reactions**

Just as the nucleophile is important in the S_N2 reaction, the structure of the alkyl halide is equally important. We will often refer to the alkyl halide as the substrate; literally, the compound that is being attacked by the reagent. Besides alkyl halides, a variety of other types of compounds serve as substrates in S_N2 reactions. To be a good substrate for S_N2 attack by a nucleophile, a molecule must have an electrophilic carbon atom with a good leaving group, and that carbon atom must not be too sterically hindered for a nucleophile to attack.

#### 6-11A  **Leaving-Group Effects on the Substrate**

A leaving group serves two purposes in the S_N2 reaction: It polarizes the C—X bond—making the carbon atom electrophilic—and it leaves with the pair of electrons that once bonded it to the electrophilic carbon atom. To fill these roles, a good leaving group should be

1. electron withdrawing, to polarize the carbon atom,
2. stable (not a strong base) once it has left,
3. polarizable, to stabilize the transition state.
1. The leaving group must be electron withdrawing to create a partial positive charge on the carbon atom, making the carbon electrophilic. An electron-withdrawing leaving group also stabilizes the negatively charged transition state. Halogen atoms are strong electronegative, so alkyl halides are common substrates for $S_{N2}$ reactions. Oxygen, nitrogen, and sulfur also form strongly polarized bonds with carbon; given the right substituents, they can form the basis for excellent leaving groups.

$$\text{Nuc}^- + \overset{\delta^+}{\underset{\delta^-}{\text{C-X}}} \rightarrow \overset{\delta^+}{\text{Nuc}} - \overset{\delta^-}{\text{C}} + \overset{\delta^-}{\text{X}}^-$$

2. The leaving group must be stable once it has left with the pair of electrons that bonded it to carbon. A stable leaving group is needed for favorable energetics. The leaving group is leaving in the transition state; a reactive leaving group would raise the energy of the transition state, slowing the reaction. Also, the energy of the leaving group is reflected in the energy of the products. A reactive leaving group would raise the energy of the products, driving the equilibrium toward the reactants.

Good leaving groups should be weak bases; therefore, they are the conjugate bases of strong acids. The hydrohalic acids HCl, HBr, and HI are strong, and their conjugates (Cl\(^-\), Br\(^-\), and I\(^-\)) are all weak bases. Other weak bases, such as sulfate ions, sulfonate ions, and phosphate ions, can also serve as good leaving groups. Table 6-4 lists examples of good leaving groups.

Hydroxide ion, alkoxide ions, and other strong bases are poor leaving groups for $S_{N2}$ reactions. For example, the $-\text{OH}$ group of an alcohol is a poor leaving group because it would have to leave as hydroxide ion.

$$\overset{\delta^-}{\text{Br}}^- + \overset{\delta^-}{\text{CH}_3\text{OH}} \rightarrow \overset{\delta^-}{\text{Br}}^- + \overset{\delta^-}{\text{CH}_3} + \overset{\delta^-}{\text{OH}}^-$$ (strong base)

Ions that are strong bases and poor leaving groups:

- $\overset{\delta^-}{\text{OH}}$ hydroxide
- $\overset{\delta^-}{\text{OR}}$ alkoxide
- $\overset{\delta^-}{\text{NH}_2}$ amide

Table 6-4 also lists some neutral molecules that can be good leaving groups. A neutral molecule often serves as the leaving group from a positively charged species.

**TABLE 6-4 Weak Bases That Are Common Leaving Groups**

<table>
<thead>
<tr>
<th>Ions:</th>
<th>$\overset{\delta^-}{\text{Cl}}$</th>
<th>$\overset{\delta^-}{\text{Br}}$</th>
<th>$\overset{\delta^-}{\text{I}}$</th>
<th>$\overset{\delta^-}{\text{O}}$</th>
<th>$\overset{\delta^-}{\text{O}}$</th>
<th>$\overset{\delta^-}{\text{O}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>halides</td>
<td>sulfonate</td>
<td>sulfate</td>
<td>phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral molecules:</td>
<td>$\overset{\delta^-}{\text{O-H}}$</td>
<td>$\overset{\delta^-}{\text{O-R}}$</td>
<td>$\overset{\delta^-}{\text{N-R}}$</td>
<td>$\overset{\delta^-}{\text{P-R}}$</td>
<td>$\overset{\delta^-}{\text{R}}$</td>
<td>$\overset{\delta^-}{\text{R}}$</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>alcohols</td>
<td>amines</td>
<td>phosphines</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For example, if an alcohol is placed in an acidic solution, the hydroxyl group is protonated. Water then serves as the leaving group. Note that the need to protonate the alcohol (requiring acid) limits the choice of nucleophiles to those few that are weak bases, such as bromide and iodide. A strongly basic nucleophile would become protonated in acid.

\[
\text{CH}_3\text{-OH} + H^+ \rightleftharpoons \text{Br} \rightarrow \text{CH}_3\text{-O}^-\text{H} \rightarrow \text{Br} \rightarrow \text{CH}_3 + \text{O}^-\text{H} \text{ water}
\]

3. Finally, a good leaving group should be polarizable, to maintain partial bonding with the carbon atom in the transition state. This bonding helps stabilize the transition state and reduce the activation energy. The departure of a leaving group is much like the attack of a nucleophile, except that the bond is breaking rather than forming. Polarizable nucleophiles and polarizable leaving groups both stabilize the transition state by engaging in more bonding at a longer distance. Iodide ion, one of the more polarizable ions, is both a good nucleophile and a good leaving group. In contrast, fluoride ion is a small, “hard” ion. Fluoride is both a poor nucleophile (in protic solvents) and a poor leaving group in SN2 reactions.

**Problem 6-17**

When dimethyl ether (CH\(_3\)OCH\(_3\)) is treated with concentrated HBr, the initial products are CH\(_3\)Br and CH\(_3\)OH. Propose a mechanism to account for this reaction.

**6-11B Steric Effects on the Substrate**

Different alkyl halides undergo SN2 reactions at vastly different rates. The structure of the substrate is the most important factor in its reactivity toward SN2 displacement. The reaction goes rapidly with methyl halides and with most primary substrates. It is more sluggish with secondary halides. Tertiary halides fail to react at all by the SN2 mechanism. Table 6-5 shows the effect of alkyl substitution on the rate of SN2 displacements.

For simple alkyl halides, the relative rates for SN2 displacement are

Relative rates for SN2: \( \text{CH}_3\text{X} > 1^\circ > 2^\circ > 3^\circ \)

The physical explanation for this order of reactivity is suggested by the information in Table 6-5. All the slow-reacting compounds have one property in common: The backside of the electrophilic carbon atom is crowded by the presence of bulky groups. Tertiary halides are more hindered than secondary halides, which are more hindered than primary halides. Even a bulky primary halide (like neopentyl bromide) undergoes SN2 reaction at a rate similar to that of a tertiary halide. The relative rates show that

**Table 6-5 Effect of Substituents on the Rates of SN2 Reactions**

<table>
<thead>
<tr>
<th>Class of Halide</th>
<th>Example</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>CH(_3)Br</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>primary (1°)</td>
<td>CH(_3)CH(_2)Br</td>
<td>50</td>
</tr>
<tr>
<td>secondary (2°)</td>
<td>(CH(_3))(_2)CHBr</td>
<td>1</td>
</tr>
<tr>
<td>tertiary (3°)</td>
<td>(CH(_3))(_3)CBr</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n-butyl (1°)</td>
<td>CH(_3)CH(_2)CH(_2)Br</td>
<td>20</td>
</tr>
<tr>
<td>isobutyl (1°)</td>
<td>(CH(_3))(_2)CHCH(_2)Br</td>
<td>2</td>
</tr>
<tr>
<td>neopentyl (1°)</td>
<td>(CH(_3))(_2)CCH(_2)Br</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*Note: Two or three alkyl groups, or even a single bulky alkyl group, slow the reaction rate. The rates listed are compared to the secondary case (isopropyl bromide), assigned a relative rate of 1.*
is the bulk of the alkyl groups, rather than an electronic effect, that hinders the reactivity of bulky alkyl halides in the $S_N2$ displacement.

This effect on the rate is another example of steric hindrance. When the nucleophile approaches the back side of the electrophilic carbon atom, it must come within bonding distance of the back lobe of the $C-X\text{ }sp^3$ orbital. If there are two alkyl groups bonded to the carbon atom, this process is difficult. Three alkyl groups make it impossible. Just one alkyl group can produce a large amount of steric hindrance if it is unusually bulky, like the $t$-butyl group of neopentyl bromide.

Figure 6-6 shows the $S_N2$ reaction of hydroxide ion with ethyl bromide ($1^\circ$), isopropyl bromide ($2^\circ$), and $t$-butyl bromide ($3^\circ$). The nucleophile can easily approach the electrophilic carbon atom of ethyl bromide. In isopropyl bromide, the approach is hindered, but still possible. In contrast, $S_N2$ approach to the tertiary carbon of $t$-butyl bromide is impossible because of the steric hindrance of the three methyl groups. Make models of ethyl bromide, isopropyl bromide, and $t$-butyl bromide, and compare the ease of bringing in an atom for a back-side attack.

**Problem 6-18**

Rank the following compounds in decreasing order of their reactivity toward the $S_N2$ reaction with sodium ethoxide ($Na^+\text{ }\text{CH}_2\text{CH}_2\text{O}^-$) in ethanol.

- Methyl chloride
- $t$-butyl iodide
- Neopentyl bromide
- Isopropyl bromide
- Methyl iodide
- Ethyl chloride

**Problem 6-19**

For each pair of compounds, state which compound is the better $S_N2$ substrate.

(a) 2-methyl-1-iodopropane or $t$-butyl iodide
(b) Cyclohexyl bromide or 1-bromo-1-methylcyclohexane
(c) 2-bromobutane or isopropyl bromide
(d) 2,2-dimethyl-1-chlorobutane or 2-chlorobutane
(e) 1-iodo-2,2-dimethylpropane or isopropyl iodide
6-12
Stereochemistry of the $S_N2$ Reaction

As we have seen, the $S_N2$ reaction requires attack by a nucleophile on the back side of an electrophilic carbon atom (Figure 6-7). A carbon atom can have only four filled bonding orbitals (an octet), so the leaving group must leave as the nucleophile bonds to the carbon atom. The nucleophile’s electrons insert into the back lobe of carbon’s $sp^3$ hybrid orbital in its antibonding combination with the orbital of the leaving group (because the bonding MO is already filled). These electrons in the antibonding MO help to weaken the $C-Br$ bond as bromine leaves. The transition state shows partial bonding to both the nucleophile and the leaving group.

**Back-side attack** literally turns the tetrahedron of the carbon atom inside out, like an umbrella caught by the wind (Figure 6-7). In the product, the nucleophile assumes a stereochemical position opposite the position the leaving group originally occupied. We call this result an **inversion of configuration** at the carbon atom.

In the case of an asymmetric carbon atom, back-side attack gives the opposite configuration of the carbon atom. The $S_N2$ displacement is the most common example of a **Walden inversion**, a step (in a reaction sequence) where an asymmetric carbon undergoes inversion of configuration. In the 1890s, Paul Walden, of the University of Tübingen (Germany), was one of the first to study reactions giving inversion of configuration.

---

**MECHANISM 6-3**

**Inversion of Configuration in the $S_N2$ Reaction**

Back-side attack inverts the configuration of the carbon atom.

EXAMPLE:

```
    HO:  C  Br:
     CH_3  CH_2CH_3
(S)-2-bromobutane
```

```
    HO:  C  Br:
     CH_3  CH_2CH_3
(R)-2-butanol
```

```
    HO:  C  Br:
     CH_3  CH_2CH_3
(R)-2-butanol
```

---

▲ **Figure 6-7**

Back-side attack in the $S_N2$ reaction. The $S_N2$ reaction takes place through nucleophilic attack on the back lobe of carbon's $sp^3$ hybrid orbital. This back-side attack inverts the carbon atom's tetrahedron, like the wind inverts an umbrella.
In some cases, inversion of configuration is readily apparent. For example, when cis-1-bromo-3-methylcyclopentane undergoes S_N2 displacement by hydroxide ion, inversion of configuration gives trans-3-methylcyclopentanol.

The S_N2 displacement is a good example of a stereospecific reaction; one in which different stereoisomers react to give different stereoisomers of the product. To study the mechanism of a nucleophilic substitution, we often look at the product to see if the reaction is stereospecific, with inversion of configuration. If it is, the S_N2 mechanism is a good possibility, especially if the reaction kinetics are second order. In many cases (no asymmetric carbon or ring, for example), it is impossible to determine whether inversion has occurred. In these cases, we use kinetics and other evidence to help determine the reaction mechanism.

PROBLEM 6-20

Draw a perspective structure or a Fischer projection for the products of the following S_N2 reactions.

(a) trans-1-bromo-3-methylcyclopentane + KOH
(b) (R)-2-bromopentane + KCN
(c) Br
      H   + NaI
      CH_3CH_2
      H   acetone
      CH_3CH_2
(d) H
     Br  + NaSH
     C
     C
     H
     F
     CH_3
(e) H
     Br + NaOCH_3
     CH_3
     CH_2CH_3
     CH_3
(f) H
     C
     C
     D
     Cl
     + NH_3

PROBLEM 6-21

Under appropriate conditions, (S)-1-bromo-1-fluoroethane reacts with sodium methoxide to give pure (S)-1-fluoro-1-methoxyethane.

\[
\text{CH}_3\text{CHBrF} + \text{NaOCH}_3 \rightarrow \text{CH}_3\text{CHFOCH}_3 + \text{NaBr}
\]  

(a) Why is bromide rather than fluoride replaced?
(b) Draw perspective structures (as shown on the previous page for 2-bromobutane) for the starting material, the transition state, and the product.
(c) Does the product show retention or inversion of configuration?
(d) Is this result consistent with reaction by the S_N2 mechanism?
When t-buty1 bromide is placed in boiling methanol, methyl t-bu1yl ether can be isolated from the reaction mixture. Because this reaction takes place with the solvent acting as the nucleophile, it is called a solvolysis (solv for "solvent," plus lysis, meaning "cleavage").

$$\text{(CH}_3\text{)}_3\text{C} − \text{Br} \quad \text{CH}_3 \rightarrow \text{OH} \quad \text{boil} \quad \text{methanol} \quad \rightarrow \quad \text{(CH}_3\text{)}_3\text{C} \rightarrow \text{O} − \text{CH}_3 \quad + \quad \text{HBr}$$

This solvolysis is a substitution because methoxide has replaced bromide on the t-bu1yl group. It does not go through the $\text{SN}_2$ mechanism, however. The $\text{SN}_2$ requires a strong nucleophile and a substrate that is not too hindered. Methanol is a weak nucleophile, and t-bu1yl bromide is a hindered tertiary halide—a poor $\text{SN}_2$ substrate.

If this substitution cannot go by the $\text{SN}_2$ mechanism, what kind of mechanism might be involved? An important clue is kinetic: Its rate does not depend on the concentration of methanol, the nucleophile. The rate depends only on the concentration of the substrate, t-bu1yl bromide.

$$\text{rate} = k_{\text{f}}(\text{(CH}_3\text{)}_3\text{C} − \text{Br})$$

This rate equation is first order overall: first order in the concentration of the alkyl halide and zeroth order in the concentration of the nucleophile. Because the rate does not depend on the concentration of the nucleophile, we infer that the nucleophile is not present in the transition state of the rate-limiting step. The nucleophile must react after the slow step.

This type of substitution is called the $\text{SN}_1$ reaction, for Substitution, Nucleophilic, unimolecular. The term unimolecular means there is only one molecule involved in the transition state of the rate-limiting step. The mechanism of the $\text{SN}_1$ reaction of t-bu1yl bromide with methanol is shown here. Ionization of the alkyl halide (first step) is the rate-limiting step.

**Step 1: Formation of carbocation (rate limiting)**

$$\text{(CH}_3\text{)}_3\text{C} \rightarrow \text{Br}^− \quad \leftrightarrow \quad \text{(CH}_3\text{)}_3\text{C}^+ \quad + \quad \text{Br}^− \quad \text{(slow)}$$

**Step 2: Nucleophilic attack on the carbocation**

$$\text{(CH}_3\text{)}_3\text{C}^+ \quad \text{CH}_3 \quad \leftrightarrow \quad \text{(CH}_3\text{)}_3\text{C} \rightarrow \text{O} − \text{CH}_3 \quad \text{H} \quad \text{(fast)}$$

**Final Step: Loss of proton to solvent**

$$\text{(CH}_3\text{)}_3\text{C} \rightarrow \text{O} − \text{CH}_3 \quad + \quad \text{CH}_3 \rightarrow \text{OH} \quad \leftrightarrow \quad \text{(CH}_3\text{)}_3\text{C} \rightarrow \text{O} − \text{CH}_3 \quad + \quad \text{CH}_3 \rightarrow \text{O} \rightarrow \text{H} \quad \text{(fast)}$$

The $\text{SN}_1$ mechanism is a multistep process. The first step is a slow ionization to form a carbocation. The second step is a fast attack on the carbocation by a nucleophile. The carbocation is a strong electrophile; it reacts very fast with nucleophiles, including weak nucleophiles. The nucleophile is usually weak, because a strong nucleophile would be more likely to attack the substrate and force some kind of second-order reaction. If the nucleophile is an uncharged molecule like water or an...
The **S<sub>N</sub>1** reaction involves a two-step mechanism. A slow ionization gives a carbocation that reacts quickly with a (usually weak) nucleophile. Reactivity: 3° > 2° > 1°.

**Step 1.** Formation of the carbocation (rate-limiting).

\[
\text{R}^+ \xrightarrow{\ddag} \text{R}^+ + \ddag \text{X}^- 
\]

**Step 2.** Nucleophilic attack on the carbocation (fast).

\[
\text{R}^+ + \text{Nuc}^- \xrightarrow{\ddag} \text{R}^- \text{Nuc} 
\]

If the nucleophile is water or an alcohol, a third step is needed to deprotonate the product.

**EXAMPLE: Solvolysis of 1-iodo-1-methylcyclohexane in methanol.**

**Step 1:** Formation of a carbocation (rate-limiting).

**Step 2:** Nucleophilic attack by the solvent (methanol).

**Step 3:** Deprotonation to form the product.

**PROBLEM 6-22:** Propose an **S<sub>N</sub>1** mechanism for the solvolysis of 3-bromo-3-dimethylpentane in ethanol.

PROBLEM-SOLVING Hint
Never show a proton falling off into thin air. Show a possible base (often the solvent) abstracting the proton.
Figure 6-8

Reaction-energy diagrams of the $S_N1$ and $S_N2$ reactions. The $S_N1$ is a two-step mechanism with two transition states ($\ddagger$1 and $\ddagger$2) and a carbocation intermediate. The $S_N2$ has only one transition state and no intermediate.

The carbocation intermediate appears as a relative minimum (a low point) in the reaction-energy diagram. Reagents and conditions that favor formation of the carbocation (the slow step) accelerate the $S_N1$ reaction; reagents and conditions that hinder its formation retard the reaction.

6-13A Substituent Effects

The rate-limiting step of the $S_N1$ reaction is ionization to form a carbocation, a strongly endothermic process. The transition state resembles the carbocation (Hammond postulate, Section 4-14); consequently, rates of $S_N1$ reactions depend strongly on carbocation stability. In Section 4-16A, we saw that alkyl groups stabilize carbocations by donating electrons through sigma bonds (the inductive effect) and through overlap of filled orbitals with the empty $p$ orbital of the carbocation (hyperconjugation). Highly substituted carbocations are therefore more stable.

Carbocation stability:

$3^\circ > 2^\circ > 1^\circ > +\text{CH}_3$

- Inductive effect
- Hyperconjugation

Reactivity toward $S_N1$ substitution mechanisms follows the stability of carbocations:

$S_N1$ reactivity: $3^\circ > 2^\circ > 1^\circ > \text{CH}_3X$

This order is opposite that of the $S_N2$ reaction. Alkyl groups hinder the $S_N2$ by blocking attack of the strong nucleophile, but alkyl groups enhance the $S_N1$ by stabilizing the carbocation intermediate.

Resonance stabilization of the carbocation can also promote the $S_N1$ reaction. For example, allyl bromide is a primary halide, but it undergoes the $S_N1$ reaction...
about as fast as a secondary halide. The carbocation formed by ionization is resonance stabilized, with the positive charge spread equally over two carbon atoms.

![ Allyl bromide resonance-stabilized carbocation ]

Vinyl and aryl halides generally do not undergo $S_N1$ or $S_N2$ reactions. An $S_N1$ reaction would require ionization to form a vinyl or aryl cation, either of which is less stable than most alkyl carbocations. An $S_N2$ reaction would require back-side attack by the nucleophile, which is made impossible by the repulsion of the electrons in the double bond or aromatic ring.

6-13B Leaving-Group Effects

The leaving group is breaking its bond to carbon in the rate-limiting ionization step of the $S_N1$ mechanism. A highly polarizable leaving group helps stabilize the rate-limiting transition state through partial bonding as it leaves. The leaving group should be a weak base, very stable after it leaves with the pair of electrons that bonded it to carbon.

Figure 6-9 shows the transition state of the ionization step of the $S_N1$ reaction. Notice how the leaving group is taking on a negative charge while it stabilizes the new carbocation through partial bonding. The leaving group should be stable as it takes on this negative charge, and it should be polarizable to engage in effective partial bonding as it leaves. A good leaving group is just as necessary in the $S_N1$ reaction as it is in the $S_N2$, and similar leaving groups are effective for either reaction. Table 6-4 (page 235) lists some common leaving groups.

**Problem 6-23**

Choose the member of each pair that will react faster by the $S_N1$ mechanism.

(a) 1-bromopropane or 2-bromopropane
(b) 2-bromo-2-methylbutane or 2-bromo-3-methylbutane
(c) $n$-propyl bromide or allyl bromide
(d) 1-bromo-2,2-dimethylpropane or 2-bromopropane
(e) 2-iodo-2-methylbutane or tert-butyl chloride
(f) 2-bromo-2-methylbutane or ethyl iodide

**Problem-Solving Hint**

Primary cations are rarely formed in solution unless they are resonance-stabilized.

---

**Figure 6-9**

In the transition state of the $S_N1$ ionization, the leaving group is taking on a negative charge. The $C-X$ bond is breaking, and a polarizable leaving group can still maintain substantial overlap.
PROBLEM 6-24
3-Bromocyclohexene is a secondary halide, and benzyl bromide is a primary halide. Both halides undergo S_N1 substitution about as fast as most tertiary halides. Use resonance structures to explain this enhanced reactivity.

6-13C Solvent Effects
The S_N1 reaction goes much more readily in polar solvents that stabilize ions. The rate-limiting step forms two ions, and ionization is taking place in the transition state. Polar solvents solvate these ions by an interaction of the solvent’s dipole moment with the charge of the ion. Protonic solvents such as alcohols and water are even more effective solvents because anions form hydrogen bonds with the \( -\text{OH} \) hydrogen atom and cations complex with the nonbonding electrons of the \( -\text{OH} \) oxygen atom.

\[
R-\underset{X}{\text{X}} \rightarrow \underset{X^-}{R^+} \quad \text{ionization}
\]

Ionization of an alkyl halide requires formation and separation of positive and negative charges, similar to what happens when sodium chloride dissolves in water. Therefore, S_N1 reactions require highly polar solvents that strongly solvate ions. One measure of a solvent's ability to solvate ions is its dielectric constant \( (\epsilon) \), a measure of the solvent's polarity. Table 6-6 lists the dielectric constants of some common solvents and the relative ionization rates for t-buty1 chloride in these solvents. Note that ionization occurs much faster in highly polar solvents such as water and alcohols. Although most alkyl halides are not soluble in water, they often dissolve in highly polar mixtures of acetone and alcohols with water.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( \epsilon )</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>78</td>
<td>8000</td>
</tr>
<tr>
<td>methanol</td>
<td>33</td>
<td>1000</td>
</tr>
<tr>
<td>ethanol</td>
<td>24</td>
<td>200</td>
</tr>
<tr>
<td>acetone</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>diethyl ether</td>
<td>4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>hexane</td>
<td>2.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

6-14 Stereochemistry of the S_N1 Reaction
We saw (Section 6-12) that the S_N2 reaction is stereospecific: The nucleophile attacks from the back side of the electrophilic carbon atom, giving inversion of configuration. In contrast, the S_N1 reaction is not stereospecific. In the S_N1 mechanism, the carbocation intermediate is \( sp^2 \)-hybridized and planar. A nucleophile can attack the carbocation from either face. Figure 6-10 shows the S_N1 solvolysis of a chiral compound, (S)-3-bromo-2,3-dimethylpentane, in ethanol. The carbocation is planar and achiral; attack from both faces gives both enantiomers of the product. Such a process, giving both enantiomers of the product (whether or not the two enantiomers are produced in equal amounts), is called racemization. The product is either racemic or at least less optically pure than the starting material.

If a nucleophile attacks the carbocation in Figure 6-10 from the front side (the side the leaving group left), the product molecule shows retention of configuration. Attack from the back side gives a product molecule showing inversion of configuration. Racemization is simply a combination of retention and inversion. When racemization
Figure 6-10
Racemization. An asymmetric carbon atom undergoes racemization when it ionizes to a planar, achiral carbocation. A nucleophile can attack the carbocation from either face, giving either enantiomer of the product.

occurs, the product is rarely completely racemic, however; there is often more inversion than retention of configuration. As the leaving group leaves, it partially blocks the front side of the carbocation. The back side is unhindered, so attack is more likely there.

Figure 6-11 shows a cyclic case where one of the faces of a cyclopentane ring has been "labeled" by a deuterium atom. Deuterium has the same size and shape as hydrogen and it undergoes the same reactions. It distinguishes between the two faces of the ring: The bromine atom is cis to the deuterium in the reactant, so the nucleophile is cis to the deuterium in the retention product. The nucleophile is trans to the deuterium in the inversion product. The product mixture contains both cis and trans isomers, with the trans isomer slightly favored because the leaving group hinders approach of the nucleophilic solvent from the front side.

MECHANISM 6-5 Racemization in the S_N Reaction

The S_N reaction involves ionization to a flat carbocation, which can be attacked from either side.

Step 1: Ionization of a tetrahedral carbon gives a flat carbocation.

\[
\begin{align*}
\text{C}^+ & \rightleftharpoons \text{C}^+ \text{X}^- \\
\end{align*}
\]

Step 2: A nucleophile may attack either side of the carbocation.

These two products may be different if the carbon atom is stereogenic.
Step 1: Formation of the carbocation

Front-side attack is slightly hindered by leaving group.

Attack from the top.

Step 2: Nucleophilic attack

Nucleophilic attack with methanol.

40% retention of configuration.

60% inversion of configuration.

▲ Figure 6-11
In the $S_N1$ reaction of cis-1-bromo-3-deuteriocyclopentane with methanol, the carbocation can be attacked from either face. Because the leaving group (bromide) partially blocks the front side as it leaves, back-side attack (inversion of configuration) is slightly favored.

6-15
Rearrangements in $S_N1$ Reactions

Carbocations frequently undergo structural changes, called rearrangements, to form more stable ions. A rearrangement may occur after a carbocation has formed or it may occur as the leaving group is leaving. Rearrangements are not seen in $S_N2$ reactions where no carbocation is formed and the one-step mechanism allows no opportunity for rearrangement.

An example of a reaction with rearrangement is the $S_N1$ reaction of 2-bromo-3-methylbutane in boiling ethanol. The product is a mixture of 2-ethoxy-3-methylbutane (not rearranged) and 2-ethoxy-2-methylbutane (rearranged).

PROBLEM 6-25
Give the $S_N1$ mechanism for the formation of 2-ethoxy-3-methylbutane, the unrearranged product in this reaction.

The rearranged product, 2-ethoxy-2-methylbutane, results from a hydride shift, the movement of a hydrogen atom with its bonding pair of electrons. A hydride shift is represented by the symbol $\sim H$. In this case, the hydride shift converts the initially formed secondary carbocation to a more stable tertiary carbocation. Attack by the solvent gives the rearranged product.
Carbocations often rearrange to form more stable carbocations. This may occur when a hydrogen atom moves with its bonding pair of electrons. Formally, this is the movement of a hydride ion (H⁻), although no actual free hydride ion is involved.

**Step 1:** Unimolecular ionization gives a carbocation.

```
CH₃–C–C–CH₃  ↔  CH₃–C–C–CH₃
  H     CH₃

2° carbocation
```

**Step 2:** A hydride shift forms a more stable carbocation.

```
CH₃–C–C–CH₃
  H     CH₃

2° carbocation
```

```
CH₃–C–C–CH₃
  H     CH₃

3° carbocation
```

This rearrangement involves movement of a hydrogen atom with its bonding pair of electrons over to the empty p orbital of the carbocation. In three dimensions, the rearrangement looks like this:

```
H₃C

CH₃

2° carbocation
```

```
H₃C

CH₃

3° carbocation
```

**Step 3:** Solvent (a weak nucleophile) attacks the rearranged carbocation.

```
CH₃–C–C–CH₃  +  CH₂CH₂OH
  H     CH₃

tertiary carbocation
```

```
CH₃–C–C–CH₃
  H     CH₃
```

(Continued)
**Step 4:** Deprotonation gives the rearranged product.

When neopentyl bromide is boiled in ethanol, it gives only a rearranged substitution product. This product results from a methyl shift (represented by the symbol \(\sim\text{CH}_3\)), the migration of a methyl group together with its pair of electrons. Without rearrangement, ionization of neopentyl bromide would give a very unstable primary carbocation.

The methyl shift occurs while bromide ion is leaving, so that only the more stable tertiary carbocation is formed.

**PROBLEM-SOLVING Hint**

Primary halides and methyl halides rarely ionize to carbocations in solution. If a primary halide ionizes, it will likely ionize with rearrangement.

**MECHANISM 6-7** Methyl Shift in an \(S_{N}1\) Reaction

An alkyl group can rearrange to make a carbocation more stable.

**Step 1:** Ionization occurs with a methyl shift.

In three dimensions,

**Step 2:** Attack by ethanol gives a protonated version of the rearranged product.
ProBLEM 6-26

Propose a mechanism involving a hydride shift or an alkyl shift for each solvolysis reaction. Explain how each rearrangement forms a more stable intermediate.

(a) $\text{CH}_3\text{C} = \text{CH} = \text{CH}_2$ \(\xrightarrow{\text{CH}_3\text{OH}, \text{heat}}\) $\text{CH}_3\text{C} \text{CH} = \text{CH}_3 + \text{CH}_3\text{C} = \text{CH}_2$;

(b) $\text{CH}_3\text{CH}_2\text{Cl}$ \(\xrightarrow{\text{CH}_3\text{CH}_2\text{OH}, \text{heat}}\) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ + $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$;

(c) $\text{CH}_3\text{CH}_2\text{I}$ + $\text{CH}_3\text{C} = \text{CH}_2$ \(\xrightarrow{\text{heat}}\) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ + $\text{CH}_3\text{C} = \text{CH}_2$;

(d) $\text{CH}_3\text{CH}_2\text{I}$ \(\xrightarrow{\text{CH}_3\text{CH}_2\text{OH}, \text{heat}}\) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ + $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$.

The rearrangements of carbocations also play a role in the formation of terpene natural products. Menthol and camphor are examples of terpenes derived from plant oils. They are constructed using a common building block and undergo a series of rearrangements in the course of construction to generate the most stable carbocation.

PROBLEM-SOLVING HINT

Most rearrangements convert $2^v$ (or incipient $1^v$) carbocations to $3^v$ or resonance-stabilized carbocations.

6-16 Comparison of $S_N 1$ and $S_N 2$ Reactions

Let's compare what we know about the $S_N 1$ and $S_N 2$ reactions, then organize this material into a brief table.

Effect of the Nucleophile The nucleophile takes part in the slow step (the only step) of the $S_N 2$ reaction but not in the slow step of the $S_N 1$. Therefore, a strong nucleophile promotes the $S_N 2$ but not the $S_N 1$. Weak nucleophiles fail to promote the $S_N 2$ reaction; therefore, reactions with weak nucleophiles often go by the $S_N 1$ mechanism if the substrate is secondary or tertiary.

$S_N 1$: Nucleophile strength is unimportant (usually weak).

$S_N 2$: Strong nucleophiles are required.
Effect of the Substrate  The structure of the substrate (the alkyl halide) is an important factor in determining which of these substitution mechanisms might operate. Methyl halides and primary halides cannot easily ionize and undergo SN1 substitution because methyl and primary carbocations are high in energy. They are relatively unhindered, however, so they make good SN2 substrates.

Tertiary halides are too hindered to undergo SN2 displacement, but they can ionize to form tertiary carbocations. Tertiary halides undergo substitution exclusively through the SN1 mechanism. Secondary halides can undergo substitution by either mechanism, depending on the conditions.

\[
\begin{align*}
\text{SN1 substrates:} & \quad 3^\circ > 2^\circ \quad (1^\circ \text{ and } CH_3X \text{ are unlikely}) \\
\text{SN2 substrates:} & \quad CH_3X > 1^\circ > 2^\circ \quad (3^\circ \text{ is not suitable})
\end{align*}
\]

If silver nitrate (AgNO₃) is added to an alkyl halide in a good ionizing solvent, it removes the halide ion to give a carbocation. This technique can force some unlikely ionizations, often giving interesting rearrangements (see Problem 6-29.)

Effect of the Solvent  The slow step of the SN1 reaction involves formation of cations. Solvation of these ions is crucial to stabilizing them and lowering the activation energy for their formation. Very polar ionizing solvents such as water and alcohols are needed for the SN1. The solvent may be heated to reflux (boiling) to provide the energy needed for ionization.

Less charge separation is generated in the transition state of the SN2 reaction. Strong solvation may weaken the strength of the nucleophile because of the energy needed to strip off the solvent molecules. Thus, the SN2 reaction often goes faster in less polar solvents if the nucleophile will dissolve. Polar aprotic solvents may enhance the strength of weak nucleophiles.

\[
\begin{align*}
\text{SN1:} & \quad \text{Good ionizing solvent required.} \\
\text{SN2:} & \quad \text{May go faster in a less polar solvent.}
\end{align*}
\]

Kinetics  The rate of the SN1 reaction is proportional to the concentration of the alkyl halide but not the concentration of the nucleophile. It follows a first-order rate equation.

The rate of the SN2 reaction is proportional to the concentrations of both the alkyl halide [R−X] and the nucleophile [Nuc:−]. It follows a second-order rate equation.

\[
\begin{align*}
\text{SN1 rate} & = k_1[R−X] \\
\text{SN2 rate} & = k_2[R−X][Nuc:−]
\end{align*}
\]

Stereochemistry  The SN1 reaction involves a flat carbocation intermediate that can be attacked from either face. Therefore, the SN1 usually gives a mixture of inversion and retention of configuration.

The SN2 reaction takes place through a back-side attack, which inverts the stereochemistry of the carbon atom. Complete inversion of configuration is the result.

\[
\begin{align*}
\text{SN1 stereochemistry:} & \quad \text{Mixture of retention and inversion; racemization.} \\
\text{SN2 stereochemistry:} & \quad \text{Complete inversion.}
\end{align*}
\]

Rearrangements  The SN1 reaction involves a carbocation intermediate. This intermediate can rearrange, usually by a hydride shift or an alkyl shift, to give a more stable carbocation.
The $S_N2$ reaction takes place in one step with no intermediates. No rearrangement is possible in the $S_N2$ reaction.

**$S_{N1}$:** Rearrangements are common.

**$S_{N2}$:** Rearrangements are impossible.

### SUMMARY: Nucleophilic Substitutions

<table>
<thead>
<tr>
<th>Promoting factors</th>
<th>$S_{N1}$</th>
<th>$S_{N2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>nucleophile</td>
<td>weak nucleophiles are OK</td>
<td>strong nucleophile needed</td>
</tr>
<tr>
<td>substrate (RX)</td>
<td>$3^\circ &gt; 2^\circ$</td>
<td>$CH_3X &gt; 1^\circ &gt; 2^\circ$</td>
</tr>
<tr>
<td>solvent</td>
<td>good ionizing solvent needed</td>
<td>wide variety of solvents</td>
</tr>
<tr>
<td>leaving group</td>
<td>good one required</td>
<td>good one required</td>
</tr>
<tr>
<td>other</td>
<td>$AgNO_3$ favors ionization</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>$S_{N1}$</th>
<th>$S_{N2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>kinetics</td>
<td>first order, $k_{RX}$</td>
<td>second order, $k_{[RX][Nu^{-}]$</td>
</tr>
<tr>
<td>stereochemistry</td>
<td>mixture of inversion and retention</td>
<td>complete inversion</td>
</tr>
<tr>
<td>rearrangements</td>
<td>common</td>
<td>impossible</td>
</tr>
</tbody>
</table>

### PROBLEM 6-27

For each reaction, give the expected substitution product, and predict whether the mechanism will be predominantly first order or second order.

(a) $2$-chloro-$2$-methylbutane + $CH_3COOH$

(b) isobutyl bromide + sodium methoxide

(c) $1$-iodo-$1$-methylcyclohexane + ethanol

(d) cyclohexyl bromide + methanol

(e) cyclohexyl bromide + sodium ethoxide

### PROBLEM-SOLVING HINT

The strength of the nucleophile (or base) usually determines the order of the reaction. Strong nucleophiles encourage second-order reactions, and weak nucleophiles more commonly react by first-order reactions. Also, $S_{N2}$ is unlikely on $3^\circ$ halides, and $S_{N1}$ is unlikely on $1^\circ$ halides.

### PROBLEM 6-28

When (R)-2-bromobutane is heated with water, the $S_{N1}$ substitution proceeds twice as fast as the $S_{N2}$. Calculate the e.e. and the specific rotation expected for the product. The specific rotation of (R)-2 butanol is $-13.5^\circ$.

### PROBLEM 6-29

A reluctant first-order substrate can be forced to ionize by adding some silver nitrate (one of the few soluble silver salts) to the reaction. Silver ion reacts with the halogen to form a silver halide (a highly exothermic reaction), generating the cation of the alkyl group.

$$R - X + Ag^+ \rightarrow R^+ + AgX$$

Give mechanisms for the following silver-promoted rearrangements.

(a) $\text{CH}_3 - \text{C} - \text{CH}_3 - \text{I} \quad AgNO_3, H_2O \rightarrow \text{CH}_3 - \text{C} - \text{CH}_2 - \text{CH}_3$

(b) $\text{CH}_3\text{CH}_2\text{I} \quad AgNO_3, H_2O/CH_3CH_2OH \rightarrow$
An elimination involves the loss of two atoms or groups from the substrate, usually with the formation of a pi bond. Elimination reactions frequently accompany and compete with substitutions. By varying the reagents and conditions, we can often modify a reaction to favor substitution or to favor elimination. First we will discuss eliminations by themselves. Then we consider substitutions and eliminations together, trying to predict what products and what mechanisms are likely with a given set of reactants and conditions.

Depending on the reagents and conditions involved, an elimination might be a first-order (E1) or second-order (E2) process. The following examples illustrate the types of eliminations we cover in this chapter.

**E1:**

\[
\begin{align*}
&\text{H} \quad \text{CH}_3 \quad \text{Br}^- \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3 \quad \text{O}^- \\
&\text{H} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

**E2:**

\[
\begin{align*}
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
&\text{H} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

**6-17A Mechanism and Kinetics of the E1 Reaction**

The abbreviation E1 stands for Elimination, unimolecular. The mechanism is called unimolecular because the rate-limiting transition state involves a single molecule rather than a collision between two molecules. The slow step of an E1 reaction is the same as in the SN1 reaction: unimolecular ionization to form a carbocation. In a fast second step, a base abstracts a proton from the carbon atom adjacent to the C⁺. The electrons that once formed the carbon–hydrogen bond now form a pi bond between two carbon atoms. The general mechanism for the E1 reaction is shown in the following Key Mechanism box.

**KEY MECHANISM 6-8 The E1 Reaction**

The E1 reaction requires ionization to a carbocation intermediate like the SN1, so it follows the same order of reactivity: 3° > 2° > 1°. A base (usually weak) deprotonates the carbocation to give an alkene.

**Step 1:** Unimolecular ionization to give a carbocation (rate-limiting).

\[
\begin{align*}
&\text{H} \quad \text{C} \quad \text{C} \\
&\text{H} \quad \text{C} \quad \text{C} \\
&\text{H} \quad \text{C} \quad \text{C} \\
&\text{H} \quad \text{C} \quad \text{C}
\end{align*}
\]

**Step 2:** Deprotonation by a weak base (often the solvent) gives the alkene (fast).

\[
\begin{align*}
&\text{B}^- \\
&\text{H} \quad \text{C} \quad \text{C} \\
&\text{B}^- \quad \text{H} \\
&\text{B}^- \quad \text{H} \\
&\text{B}^- \quad \text{H}
\end{align*}
\]
EXAMPLE: E1 elimination of bromocyclohexane in methanol.

Step 1: Ionization gives a carbocation and bromide ion.

\[
\text{CH}_3\text{Br} + \text{CH}_3\text{OH} \xrightarrow{\text{heat}} \text{CH}_3\text{CH}_2^+ + \text{Br}^-
\]

Step 2: Methanol abstracts a proton to give cyclohexene.

\[
\text{CH}_3\text{OH} + \text{C}_6\text{H}_10 \rightarrow \text{CH}_2=\text{C}\text{H}_2 + \text{CH}_3\text{OH}_2
\]

PROBLEM: Show what happens in step 2 of the Example, (E1 elimination of bromocyclohexane in methanol) if the solvent acts as a nucleophile rather than as a base.

6.17B Competition with the S_N1 Reaction

The E1 reaction almost always occurs together with the S_N1. Whenever a carbocation is formed, it can undergo either substitution or elimination, and mixtures of products often result. The following reaction shows the formation of both elimination and substitution products in the reaction of t-butyl bromide with boiling ethanol.

\[
\text{CH}_3\text{CH}_2\text{Br} + \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{heat}} \text{CH}_3\text{CH}==\text{CCH}_3 + \text{CH}_3\text{CH}==\text{CCH}_2\text{CH}_3
\]

The 2-methylpropene product results from dehydrohalogenation, an elimination of hydrogen and a halogen atom. Under these first-order conditions (the absence of a strong base), dehydrohalogenation takes place by the E1 mechanism: Ionization of the alkyl halide gives a carbocation intermediate, which loses a proton to give the alkene. Substitution results from nucleophilic attack on the carbocation. Ethanol serves as a base in the elimination and as a nucleophile in the substitution.

Step 1: Ionization to form a carbocation.

\[
\text{CH}_3\text{CH}==\text{CCH}_3 + \text{Br}^-
\]

Step 2: (by the E1 mechanism): Basic attack by the solvent abstracts a proton to give an alkene.

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{H}^+ \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}==\text{CCH}_3 + \text{CH}_3\text{CH}_2\text{OH}^-
\]
or, (by the S_N1 mechanism): Nucleophilic attack by the solvent on the carbocation.

Under ideal conditions, one of these first-order reactions provides a good yield of one product or the other. Often, however, carbocation intermediates react in two or more ways to give mixtures of products. For this reason, S_N1 and E1 reactions of alkyl halides are not often used for organic synthesis. They have been studied in great detail to learn about the properties of carbocations, however.

**PROBLEM 6-30**

Some S_N1 substitution probably accompanies the E1 elimination of bromocyclohexane, shown in Key Mechanism Box 6-8.

(a) Show the mechanism and product of the corresponding S_N1 reaction.
(b) Compare the function of the solvent (methanol) in the E1 and S_N1 reactions.

### 6-17C Orbitals and Energetics

In the second step of the E1 mechanism, the carbon atom next to the C^+ must rehybridize to sp^2 as the base attacks the proton and electrons flow into the new pi bond.

The potential-energy diagram for the E1 reaction (Figure 6-12) is similar to that for the S_N1 reaction. The ionization step is strongly endothermic, with a rate-limiting transition state. The second step is a fast exothermic deprotonation by a base. The base...

**Figure 6-12**

Reaction-energy diagram of the E1 reaction. The first step is a rate-limiting ionization. Compare this energy profile with that of the S_N1 reaction, Figure 6-8.
is not involved in the reaction until after the rate-limiting step, so the rate depends only on the concentration of the alkyl halide. Weak bases are common in E1 reactions.

Like other carbocation reactions, the E1 may be accompanied by rearrangement. Compare the following E1 reaction (with rearrangement) with the S_N1 reaction of the same substrate, shown in Mechanism 6-6. Note that the solvent acts as a base in the E1 reaction and a nucleophile in the S_N1 reaction.

**MECHANISM 6-9**

Rearrangement in an E1 Reaction

Like other reactions involving carbocations, the E1 may be accompanied by rearrangement.

**Step 1:** Ionization to form a carbocation.

\[
\text{CH}_3\text{C}^-\text{C}^-\text{CH}_3 \leftrightarrow \text{CH}_3\text{C}^-\text{C}^-\text{CH}_3
\]

2-bromo-3-methylbutane

2° carbocation

**Step 2:** A hydride shift forms a more stable carbocation.

\[
\begin{align*}
\text{CH}_3\text{C}^-\text{C}^-\text{CH}_3 & \xrightarrow{\text{H}} \text{CH}_3\text{C}^-\text{C}^-\text{CH}_3 \\
2° \text{ carbocation} & \xrightarrow{\text{3° carbocation}}
\end{align*}
\]

**Step 3:** The weakly basic solvent removes either adjacent proton.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{OH} & \rightarrow \text{CH}_3\text{CH}_2\text{OH}_2 \\
\text{2-methyl-2-butene} & + \text{2-methyl-1-butene}
\end{align*}
\]

**PROBLEM 6-31**

The solvolysis of 2-bromo-3-methylbutane potentially can give several products, including both E1 and S_N1 products from both the unrearranged carbocation and the rearranged carbocation. Mechanism Boxes 6-6 (page 247) and 6-9 (above) show the products from the rearranged carbocation. Summarize all the possible products, showing which carbocation they come from and whether they are the products of E1 or S_N1 reactions.

**PROBLEM 6-1 (PARTIALLY SOLVED)**

When the following compound is heated in methanol, several different products are formed. Propose mechanisms to account for the four products shown.

\[
\begin{align*}
\text{CH}_2\text{Br} & \xrightarrow{\text{heat}} \text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{OCH}_3 + \text{cyclopentane} + \text{cyclohexane}
\end{align*}
\]

(Continued)
**Solution:** With no strong base and a good ionizing solvent, we would expect a first-order reaction. But this is a primary alkyl halide, so ionization is difficult unless it rearranges. It might rearrange as it forms, but we'll imagine the cation forming then rearranging.

\[
\begin{align*}
\text{H} & \text{C} \text{Br}^+ \text{H} \quad \xrightarrow{\text{heat}} \quad \begin{cases} 
\text{H}_2\text{C} - \text{C}^+ \text{H} & \quad \text{1° carbocation} \\
\text{H}_2\text{C} - \text{C}^+ \text{H} & \quad \text{3° carbocation}
\end{cases} \\
\text{or} & \\
\text{H}_2\text{C} - \text{C}^+ \text{H} \quad \xrightarrow{\text{CH}_3\text{OH}} \quad \begin{cases} 
\text{H}_2\text{C} - \text{C}^+ \text{H} & \quad \text{1° carbocation} \\
\text{H}_2\text{C} - \text{C}^+ \text{H} & \quad \text{2° carbocation}
\end{cases}
\end{align*}
\]

From these rearranged intermediates, either loss of a proton (E1) or attack by the solvent (S_N1) gives the observed products. Note that the actual reaction may give more than just these products, but the other products are not required for the problem.

**PROBLEM 6-32**

Finish Partially Solved Problem 6-1 by showing how the rearranged carbocations give the four products shown in the problem. Be careful when using curved arrows to show deprotonation and/or nucleophilic attack by the solvent. The curved arrows always show movement of electrons, not movement of protons or other species.

We can now summarize four ways that a carbocation can react to become more stable.

**SUMMARY - Carbocation Reactions**

A carbocation can:
1. React with its own leaving group to return to the reactant: \( R^+ + X^- \rightarrow R - X \)
2. React with a nucleophile to form a substitution product (S_N1): \( R^+ + \text{Nuc}^- \rightarrow R - \text{Nuc} \)
3. Lose a proton to form an elimination product (an alkene) (E1):
\[
\begin{align*}
\text{C} \text{H}_3 & + \text{RO}_2^+ \\
\text{H} & \rightarrow \text{C} = \text{C} + \text{ROH}
\end{align*}
\]
4. Rearrange to a more stable carbocation, then react further.

The order of stability of carbocations is: resonance-stabilized, 3° > 2° > 1°.

**PROBLEM 6-33**

Give the substitution and elimination products you would expect from the following reactions:
(a) 3-bromo-3-ethylpentane heated in methanol
(b) 1-iodo-1-methylcyclopentane heated in ethanol
(c) 3-bromo-2,2-dimethylbutane heated in ethanol
(d) iodocyclohexane + silver nitrate in water (see Problem 6-29)
Many compounds can eliminate in more than one way, to give mixtures of products. In many cases, we can predict which elimination product will predominate. In the example shown in Mechanism Box 6-9, the carbocation can lose a proton on either of two adjacent carbon atoms.

The first product has a *trisubstituted* double bond, with three substituents (circled) on the doubly bonded carbons. It has the general formula \( \text{R}_2\text{C} \equiv \text{CHR} \). The second product has a *disubstituted* double bond, with general formula \( \text{R}_2\text{C} \equiv \text{CH}_2 \) (or \( \text{R} \equiv \text{CH} \equiv \text{CH} \equiv \text{R} \)). In most E1 and E2 eliminations where there are two or more possible elimination products, the product with the most substituted double bond will predominate. This general principle is called Zaitsev’s rule,* and reactions that give the most substituted alkene are said to follow Zaitsev orientation.

**ZAITSEV’S RULE:** In elimination reactions, the most substituted alkene usually predominates.

\[
\begin{align*}
\text{R}_2\text{C} \equiv \text{CR}_2 & \quad > \quad \text{R}_2\text{C} \equiv \text{CHR} & \quad > & \quad \text{RHC} \equiv \text{CHR} \quad \text{and} \quad \text{R}_2\text{C} \equiv \text{CH}_2 & \quad > & \quad \text{RHC} \equiv \text{CH}_2 \\
\text{monosubstituted} & \quad \text{trisubstituted} & \quad \text{disubstituted} & \quad \text{monosubstituted}
\end{align*}
\]

This order of preference is the same as the order of stability of alkenes. We consider the stability of alkenes in more detail in Section 7-7, but for now, it is enough just to know that more substituted alkenes are more stable. In Chapter 7, we will study some unusual reactions where Zaitsev’s rule does not apply.

**PROBLEM 6-34**

When 1-bromo-1-methylecyclohexane is heated in ethanol for an extended period of time, three products result: one ether and two alkenes. Predict the products of this reaction, and propose a mechanism for their formation. Predict which of the two alkenes is the major elimination product.

**SOLVED PROBLEM 6-2**

When 3-iodo-2,2-dimethylbutane is treated with silver nitrate in ethanol, three elimination products are formed. Give their structures, and predict which ones are formed in larger amounts.

**SOLUTION**

Silver nitrate reacts with the alkyl iodide to give silver iodide and a cation.

\[
\text{CH}_3 \quad \text{C} \equiv \text{CH} \equiv \text{CH}_3 + \text{Ag}^+ \rightarrow \text{CH}_3 \quad \text{C} \equiv \text{CH} \equiv \text{CH}_3 + \text{AgI} \downarrow
\]

(Continued)

---

*Zaitsev is transliterated from the Russian, and may also be spelled Sayteff.*
This secondary carbocation can lose a proton to give an unrearranged alkene (A), or it can rearrange to a more stable tertiary cation.

**Loss of a proton**

This reaction occurs when a secondary carbocation interacts with an alcohol, such as CH₃CH₂OH. The loss of a proton results in the formation of an alkene and an ion:

- **Product (A)**: CH₃CH₂OH
- CH₃C=CH₂

**Rearrangement**

The tertiary cation can lose a proton in either of two positions. One of the products (B) is a tetrasubstituted alkene, and the other (C) is disubstituted.

**Formation of a tetrasubstituted alkene**

- CH₃C=CH₂ → CH₃CH₂OH → CH₃C=CH₂ + CH₃CH₂OH

**Formation of a disubstituted alkene**

- CH₃C=CH₂ → CH₃CH₂OH → CH₃C=CH₂ + CH₃CH₂OH

Product B predominates over product C because the double bond in B is more substituted. Whether product A is a major product will depend on the specific reaction conditions and whether proton loss or rearrangement occurs faster.

**Problem 6-35**

Each of the two carbocations in Solved Problem 6-2 can also react with ethanol to give a substitution product. Give the structures of the two substitution products formed in this reaction.

**6-19 Second-Order Elimination: The E2 Reaction**

Eliminations can also take place under second-order conditions with a strong base present. As an example, consider the reaction of t-buty1 bromide with methoxide ion in methanol.

This is a second-order reaction because methoxide ion is a strong base as well as a strong nucleophile. It attacks the alkyl halide faster than the halide can ionize to give a first-order reaction. No substitution product (methyl t-buty1 ether) is observed, however. The SN2 mechanism is blocked because the tertiary alkyl halide is too hindered.
The observed product is 2-methylpropene, resulting from elimination of HBr and formation of a double bond.

The rate of this elimination is proportional to the concentrations of both the alkyl halide and the base, giving a second-order rate equation. This is a bimolecular process, with both the base and the alkyl halide participating in the transition state, so this mechanism is abbreviated E2 for Elimination, bimolecular.

In the E2 reaction just shown, methoxide reacts as a base rather than as a nucleophile. Most strong nucleophiles are also strong bases, and elimination commonly results when a strong base/nucleophile is used with a poor SN2 substrate such as a 3° or hindered 2° alkyl halide. Instead of attacking the back side of the hindered electrophilic carbon, methoxide abstracts a proton from one of the methyl groups. This reaction takes place in one step, with bromide leaving as the base is abstracting a proton.

In the general mechanism of the E2 reaction, a strong base abstracts a proton on a carbon atom adjacent to the one with the leaving group. As the base abstracts a proton, a double bond forms and the leaving group leaves. Like the SN2 reaction, the E2 is a concerted reaction in which bonds break and new bonds form at the same time, in a single step.

### KEY MECHANISM 6-10 The E2 Reaction

The concerted E2 reaction takes place in a single step. A strong base abstracts a proton on a carbon next to the leaving group, and the leaving group leaves. The product is an alkene.

\[
\text{B}^- + \text{H}^+ \text{C} - \text{C}^\delta^+ \text{X}^{-} \rightarrow \text{C} - \text{C}^\delta^- + \text{B}^- \text{H}^+ + \text{X}^- \]

**EXAMPLE:** E2 elimination of 3-bromopentane with sodium ethoxide.

\[
\text{Na}^+ \text{O}^- \text{CH}_2\text{CH}_3 \quad \text{H}^- \text{O}^- \text{CH}_2\text{CH}_3
\]

The order of reactivity for alkyl halides in E2 reactions is 3° > 2° > 1°.

**PROBLEM 6-36:** Under second-order conditions (strong base/nucleophile), SN2 and E2 reactions may occur simultaneously and compete with each other. Show what products might be expected from the reaction of 2-bromo-3-methylbutane (a moderately hindered 2° alkyl halide) with sodium ethoxide.
Reactivity of the Substrate in the E2  The order of reactivity of alkyl halides in the E2 reaction towards dehydrohalogenation is found to be:

\[ 3^° > 2^° > 1^° \]

This reactivity order reflects the greater stability of highly substituted double bonds. Elimination of a tertiary halide gives a more substituted alkene than elimination of a secondary halide, which gives a more substituted alkene than a primary halide. The stabilities of the alkene products are reflected in the transition states, giving lower activation energies and higher rates for elimination of alkyl halides that lead to highly substituted alkenes.

Mixtures of Products in the E2  The E2 reaction requires abstraction of a proton on a carbon atom next to the carbon bearing the halogen. If there are two or more possibilities, mixtures of products may result. In most cases, Zaitsev's rule predicts which of the possible products will be the major product: the most substituted alkene. For example, the E2 reaction of 2-bromobutane with potassium hydroxide gives a mixture of two products, 1-butene (a monosubstituted alkene) and 2-butene (a disubstituted alkene). As predicted by Zaitsev's rule, the disubstituted isomer 2-butene is the major product.

\[
\begin{align*}
\text{2-bromobutane} & \xrightarrow{\text{KOH, H}_2\text{O}} \text{1-butene} + \text{2-butene} \\
\end{align*}
\]

Similarly, the reaction of 1-bromo-1-methylcyclohexane with sodium ethoxide gives a mixture of a disubstituted alkene and a trisubstituted alkene. The trisubstituted alkene is the major product.

\[
\begin{align*}
\text{1-bromo-1-methylcyclohexane} & \xrightarrow{\text{NaOCH}_2\text{CH}_3, \text{CH}_2\text{CH}_3\text{OH}} \text{1-methylcyclohexene} + \text{1-methylcyclohexane} \\
\end{align*}
\]

PROBLEM 6-37

1. Predict the elimination products of the following reactions. When two alkenes are possible, predict which one will be the major product. Explain your answers, showing the degree of substitution of each double bond in the products.
2. Which of these reactions are likely to produce both elimination and substitution products?

(a) 2-bromopentane + NaOCH₃
(b) 3-bromo-3-methylpentane + NaOMe (Me = methyl, CH₃)
(c) 2-bromo-3-ethylpentane + NaOH
(d) cis-1-bromo-2-methylcyclohexane + NaOEt (Et = ethyl, CH₂CH₃)
Like the $S_N2$ reaction, the E2 follows a concerted mechanism: Bond breaking and bond formation take place at the same time, and the partial formation of new bonds lowers the energy of the transition state. Concerted mechanisms require specific geometric arrangements so that the orbitals of the bonds being broken can overlap with those being formed and the electrons can flow smoothly from one bond to another. The geometric arrangement required by the $S_N2$ reaction is a back-side attack; with the E2 reaction, a coplanar arrangement of orbitals is needed.

E2 elimination requires partial formation of a new pi bond, with its parallel $p$ orbitals, in the transition state. The electrons that once formed a $C-H$ bond must begin to overlap with the orbital that the leaving group is vacant. Formation of this new pi bond implies that these two $sp^3$ orbitals must be parallel so that pi overlap is possible as the hydrogen and halogen leave and the orbitals rehybridize to the $p$ orbitals of the new pi bond.

Figure 6-13 shows two conformations that provide the necessary coplanar alignment of the leaving group, the departing hydrogen, and the two carbon atoms. When the hydrogen and the halogen are anti to each other ($\theta = 180^\circ$), their orbitals are aligned. This is called the anti-coplanar conformation. When the hydrogen and the halogen eclipse each other ($\theta = 0^\circ$), their orbitals are once again aligned. This is called the syn-coplanar conformation. Make a model corresponding to Figure 6-13, and use it to follow along with this discussion.

Of these possible conformations, the anti-coplanar arrangement is most commonly seen in E2 reactions. The transition state for the anti-coplanar arrangement is a staggered conformation, with the base far away from the leaving group. In most cases, this transition state is lower in energy than that for the syn-coplanar elimination.

The transition state for syn-coplanar elimination is an eclipsed conformation. In addition to the higher energy resulting from eclipsing interactions, the transition state suffers from interference between the attacking base and the leaving group. To abstract the proton, the base must approach quite close to the leaving group. In most cases, the leaving group is bulky and negatively charged, and the repulsion between the base and the leaving group raises the energy of the syn-coplanar transition state.

**Enzyme-catalyzed eliminations generally proceed by E2 mechanisms and produce only one stereoisomer. Two catalytic groups are involved: One abstracts the hydrogen, and the other assists in the departure of the leaving group. The groups are positioned appropriately to allow an anti-coplanar elimination.**

*Figure 6-13*
Concerted transition states of the E2 reaction. The orbitals of the hydrogen atom and the halide must be aligned so they can begin to form a pi bond in the transition state.
Some molecules are rigidly held in eclipsed (or nearly eclipsed) conformations with a hydrogen atom and a leaving group in a syn-coplanar arrangement. Such compounds are likely to undergo E2 elimination by a concerted syn-coplanar mechanism. Deuterium labeling (using D, the hydrogen isotope with mass number 2) is used in the following reaction to show which atom is abstracted by the base. Only the hydrogen atom is abstracted, because it is held in a syn-coplanar position with the bromine atom. Remember that syn-coplanar eliminations are unusual, however, anti-coplanar eliminations are more common.

The E2 is a stereospecific reaction, because different stereoisomers of the starting material react to give different stereoisomers of the product. This stereospecificity results from the anti-coplanar transition state that is usually involved in the E2. We consider more of the implications of the anti-coplanar transition state in Chapter 7. For now, Problem 6-38 will give you an opportunity to build models and see how the stereochemistry of an E2 elimination converts different stereoisomers into different stereoisomers of the product.

PROBLEM-SOLVING Hint
Models are helpful whenever complex stereochemistry is involved.

PROBLEM 6-38
When the first compound shown here is treated with sodium methoxide, the only elimination product is the trans isomer. The second diastereomer (blue) gives only the cis product. Use your models and careful drawings of the transition states to explain these results.

Let's summarize the major points to remember about the E1 and E2 reactions, focusing on the factors that help us predict which of these mechanisms will operate under a given set of experimental conditions. Then we will organize these factors into a short table.

Effect of the Base The nature of the base is the single most important factor in determining whether an elimination will go by the E1 or E2 mechanism. If a strong base is present, the rate of the bimolecular reaction will be greater than the rate of ionization, and the E2 reaction will predominate (perhaps accompanied by the S_N2).

If no strong base is present, with a good solvent a unimolecular ionization is likely, followed by loss of a proton to a weak base such as the solvent. Under these conditions, the E1 reaction usually predominates (always accompanied by the S_N1).

E1: Base strength is unimportant (usually weak).
E2: Strong bases are required.

6-21
Comparison of E1 and E2 Elimination Mechanisms
Effect of the Solvent  The slow step of the E1 reaction is the formation of two ions. Like the $S_N1$, the E1 reaction critically depends on polar ionizing solvents such as water and the alcohols.

In the E2 reaction, the transition state spreads out the negative charge of the base over the entire molecule. There is no more need for solvation in the E2 transition state than in the reactants. The E2 is therefore less sensitive to the solvent; in fact, some reagents are stronger bases in less polar solvents.

E1: Good ionizing solvent required.
E2: Solvent polarity is not so important.

Effect of the Substrate  For both the E1 and the E2 reactions, the order of reactivity is

$$E1, E2: \quad 3^\circ > 2^\circ > 1^\circ \quad (1^\circ \text{ usually will not go E1})$$

In the E1 reaction, the rate-limiting step is formation of a carbocation, and the reactivity order reflects the stability of carbocations. In the E2 reaction, the more substituted halides generally form more substituted, more stable alkenes.

Kinetics  The rate of the E1 reaction is proportional to the concentration of the alkyl halide [RX] but not to the concentration of the base. It follows a first-order rate equation.

The rate of the E2 reaction is proportional to the concentrations of both the alkyl halide [RX] and the base [B$^-$]. It follows a second-order rate equation.

$$E1 \text{ rate} = k_1[RX]$$
$$E2 \text{ rate} = k_3[RX][B^-]$$

Orientation of Elimination  In most E1 and E2 eliminations with two or more possible products, the product with the most substituted double bond (the most stable product) predominates. This principle is called Zaitsev's rule, and the most highly substituted product is called the Zaitsev product.

$$\text{E1, E2: Usually Zaitsev orientation.}$$

Stereochemistry  The E1 reaction begins with an ionization to give a flat carbocation. No particular geometry is required.

The E2 reaction takes place through a concerted mechanism that requires a coplanar arrangement of the bonds to the atoms being eliminated. The transition state is usually anti-coplanar, although it may be syn-coplanar in rigid systems.

E1: No particular geometry required for the slow step.
E2: Coplanar arrangement (usually anti) required for the transition state.

Rearrangements  The E1 reaction involves a carbocation intermediate. This intermediate can rearrange, usually by the shift of a hydride or an alkyl group, to give a more stable carbocation.

The E2 reaction takes place in one step with no intermediates. No rearrangement is possible in the E2 reaction.

E1: Rearrangements are common.
E2: No rearrangements.
Chapter 6: Alkyl Halides: Nucleophilic Substitution and Elimination

**SUMMARY**  
Elimination Reactions

<table>
<thead>
<tr>
<th>Promoting factors</th>
<th>E1</th>
<th>E2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>base</strong></td>
<td>weak bases work</td>
<td>strong base required</td>
</tr>
<tr>
<td><strong>solvent</strong></td>
<td>good ionizing solvent</td>
<td>wide variety of solvents</td>
</tr>
<tr>
<td><strong>substrate</strong></td>
<td>3° &gt; 2°</td>
<td>3° &gt; 2° &gt; 1°</td>
</tr>
<tr>
<td><strong>leaving group</strong></td>
<td>good one required</td>
<td>good one required</td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
<td><strong>kinetics</strong></td>
<td><strong>kinetics</strong></td>
</tr>
<tr>
<td></td>
<td>first order, ( k_c[RX] )</td>
<td>second order, ( k_c[RX][B^-] )</td>
</tr>
<tr>
<td></td>
<td><strong>orientation</strong></td>
<td><strong>orientation</strong></td>
</tr>
<tr>
<td></td>
<td>most substituted alkene</td>
<td>most substituted alkene</td>
</tr>
<tr>
<td></td>
<td><strong>stereochemistry</strong></td>
<td><strong>stereochemistry</strong></td>
</tr>
<tr>
<td></td>
<td>no special geometry</td>
<td>coplanar transition state required</td>
</tr>
<tr>
<td></td>
<td><strong>rearrangements</strong></td>
<td>impossible</td>
</tr>
</tbody>
</table>

**PROBLEM-SOLVING STRATEGY**  
Predicting Substitutions and Eliminations

\[ S_{N1} \quad R\text{−}X^- \quad \overset{\text{slow}}{\rightleftharpoons} \quad R^+ \quad + \quad :X^- \]

\[ R^- \quad + \quad \text{Nuc}^- \quad \rightarrow \quad R\text{−}\text{Nuc} \quad \quad \text{(fast)} \]

\[ S_{N2} \quad \text{Nuc}^- \quad + \quad C\text{−}X^- \quad \rightarrow \quad \text{Nuc} \text{−} C \quad + \quad :X^- \]

\[ E1 \quad \overset{\text{slow}}{\overline{\text{C−C−}}} \quad \quad \overset{\text{slow}}{\leftarrow} \quad \overset{\text{C−C}}{\downarrow} \quad + \quad \overset{\text{−X}}{\downarrow} \quad \quad \text{(fast)} \]

\[ E2 \quad \overset{\text{B}^-}{\overline{\text{C−C−}}} \quad \quad \overset{\text{fast}}{\leftarrow} \quad \overset{\text{C=−C∞}}{\downarrow} \quad + \quad \overset{\text{B−H}}{\downarrow} \quad + \quad \overset{\text{−X}}{\downarrow} \]

Given a set of reagents and solvents, how can we predict what products will result and which mechanisms will be involved? Should you memorize all this theory about substitutions and eliminations? Students sometimes feel overwhelmed at this point.

Memorizing is not the best way to approach this material because it is too much and there are too many factors. Besides, the real world with its real reagents and solvents is not as clean as our equations on paper. Most nucleophiles are also basic, and most bases are also nucleophilic. Most solvents can solvate ions or react as nucleophiles, or both. We will review the most important factors that determine the reaction pathway, organized in a sequence that allows you to predict as much as can be predicted.

The first principle you must understand is that we cannot always predict one unique product or one unique mechanism. Often, the best we can do is to eliminate some of the possibilities and make some good predictions. Remembering this limitation, here are some general guidelines:
1. The strength of the base or nucleophile determines the order of the reaction.
   If a strong nucleophile (or base) is present, it will force second-order kinetics, either S_N2 or E2. A strong nucleophile attacks the electrophilic carbon atom or abstracts a proton faster than the molecule can ionize for first-order reactions.
   If no strong base or nucleophile is present, the fastest reaction will probably be a first-order reaction, either S_N1 or E1. Addition of silver salts to the reaction can force some kind of ionization.
   This is the most important of these guidelines. Consider the following examples:

   \[
   \begin{align*}
   \text{Br} \quad & \xrightarrow{\text{CH}_3\text{OH, heat}} \quad \text{S}_N1 \text{ and E1} \quad \text{Br} \quad & \xrightarrow{\text{NaOCH}_3, \text{CH}_3\text{OH}} \quad \text{S}_N2 \text{ and E2} \\
   (\text{CH}_3)_2\text{C} \quad & \xrightarrow{\text{Br, NaOCH}_3, \text{CH}_3\text{OH}} \quad \text{E2} \quad (\text{no S}_N2 \text{ on 3° carbon})
   \end{align*}
   \]

2. Primary halides usually undergo the S_N2 reaction, occasionally the E2 reaction.
   Primary halides rarely undergo first-order reactions, since primary carbocations are rarely formed. With good nucleophiles, S_N2 substitution is usually observed. With a strong base, E2 elimination may also be observed.
   Sometimes silver salts or high temperatures are used to force a primary halide to ionize, usually with rearrangement to give a more stable carbocation. In such a case, the rearranged S_N1 and E1 products may be observed.

   \[
   \begin{align*}
   \text{Br} \quad & \xrightarrow{\text{NaOCH}_3, \text{CH}_3\text{OH}} \quad \text{S}_N2 \quad (\text{and possibly E2}) \\
   \text{Br} \quad & \xrightarrow{\text{AgNO}_3, \text{heat, CH}_3\text{OH}} \quad \text{S}_N1 \text{ and E1} \quad (\text{both with rearrangement})
   \end{align*}
   \]

3. Tertiary halides usually undergo the E2 reaction (strong base) or a mixture of S_N1 and E1 (weak base).
   Tertiary halides cannot undergo the S_N2 reaction. A strong base forces second-order kinetics, resulting in elimination by the E2 mechanism. In the absence of a strong base, tertiary halides react by first-order processes, usually a mixture of S_N1 and E1. The specific reaction conditions determine the ratio of substitution to elimination.

   \[
   \begin{align*}
   (\text{CH}_3)_2\text{C} \quad & \xrightarrow{\text{Br, NaOCH}_3, \text{CH}_3\text{OH}} \quad \text{E2} \quad (\text{no S}_N2 \text{ on 3° carbon}) \\
   (\text{CH}_3)_2\text{C} \quad & \xrightarrow{\text{Br, CH}_3\text{OH, heat}} \quad \text{S}_N1 \text{ and E1}
   \end{align*}
   \]

4. The reactions of secondary halides are the most difficult to predict.
   With a strong base, either the S_N2 or the E2 reaction is possible. With a weak base and a good ionizing solvent, either the S_N1 or the E1 reaction is possible. Mixtures of products are common. Figure 6-14 shows these possibilities with a secondary halide under second-order and first-order conditions.

   \[
   \begin{align*}
   \text{Br} \quad & \xrightarrow{\text{NaOCH}_3, \text{CH}_3\text{OH}} \quad \text{S}_N2 \text{ and E2} \\
   \text{Br} \quad & \xrightarrow{\text{CH}_3\text{OH, heat}} \quad \text{S}_N1 \text{ and E1}
   \end{align*}
   \]

5. Some nucleophiles and bases favor substitution or elimination.
   To promote elimination, the base should readily abstract a proton but not readily attack a carbon atom. A bulky strong base, such as t-butoxide \(\text{[OCH(CH}_3)_3]\), enhances elimination.

   \(\text{(Continued)}\)
Figure 6-14
Under second-order conditions (strong base/nucleophile), a secondary alkyl halide might undergo either substitution (S_N2) or elimination (E2). Under first-order conditions (weak base/nucleophile), S_N1 and E1 are possible.

To promote substitution, we need a good nucleophile with limited basicity: a highly polarizable species that is the conjugate base of a strong acid. Bromide (Br^-) and iodide (I^-) are examples of good nucleophiles that are weak bases and favor substitution.

\[
\begin{align*}
\text{Br} &\rightarrow \text{NaI} \rightarrow \text{mostly } S_N2 \\
\text{Br} &\rightarrow \text{NaOC(CH}_3)_3 \rightarrow \text{mostly } E2
\end{align*}
\]

PROBLEM 6-39: Give the structures of the products expected from the indicated mechanisms in the preceding examples.

SOLVED PROBLEM 6-3
Predict the mechanisms and products of the following reactions.

(a) \[\text{Br} \quad \text{CH}_3\text{OH} \quad \text{heat} \]
1-bromo-1-methycyclohexane

(b) \[\text{CH}_3\text{CH} \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \quad \text{NaOCH}_3 \quad \text{CH}_3\text{OH} \]
2-bromohexane

SOLUTION
(a) There is no strong base or nucleophile present, so this reaction must be first order, with an ionization of the alkyl halide as the slow step. Deprotonation of the carbocation gives either of two elimination products, and nucleophilic attack gives a substitution product.

\[
\begin{align*}
\text{CH}_3\text{Br} &\rightarrow \text{Br}^- \quad \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 \\
\text{carbocation} &\rightarrow \text{major} \quad \text{minor} \quad \text{substitution product} \quad \text{E1 elimination products} \quad \text{(S_N1)}
\end{align*}
\]
(b) This reaction takes place with a strong base, so it is second order. This secondary halide can undergo both SN2 substitution and E2 elimination. Both products will be formed, with the relative proportions of substitution and elimination depending on the reaction conditions.

\[
\begin{align*}
\text{CH}_3\text{-CH=CH-CH}_2\text{CH}_3 & \quad \text{major} \\
\text{CH}_2\text{=CH-CH}_2\text{CH}_2\text{CH}_3 & \quad \text{minor}
\end{align*}
\]

E2 products

\[
\begin{align*}
\text{OCH}_3 \\
\text{CH}_3\text{-CH=CH-CH}_2\text{CH}_2\text{CH}_3
\end{align*}
\]

Sn2 product

**PROBLEM 6-40**

Predict the products and mechanisms of the following reactions. When more than one product or mechanism is possible, explain which are most likely.

(a) 1-bromohexane + sodium ethoxide in ethanol

(b) 2-chlorohexane + NaOCH3 in methanol

(c) t-buty1 bromide + NaOCH3CH3 in ethanol

(d) t-buty1 bromide heated in ethanol

(e) isobutyl iodide + KOH in ethanol/water

(f) isobutyl chloride + AgNO3 in ethanol/water

(g) neopentyl bromide + AgNO3 in ethanol/water

(h) 1-bromo-1-methylcyclopentane heated in methanol

(i) 1-bromo-1-methylcyclopentane + NaOEt in ethanol

**PROBLEM-SOLVING Hint**

The strength of the base/nucleophile usually determines the order of the reaction.

**PROBLEM-SOLVING Hint**

Don't try to memorize your way through this chapter. Try to understand what happens in the different reactions. Some memorizing is necessary, but simply memorizing everything won't allow you to predict new reactions.

**SUMMARY Reactions of Alkyl Halides**

Some of these reactions have not yet been covered, but they are included here for completeness and for later reference. Notice the section numbers, indicating where each reaction is covered.

1. **Nucleophilic substitutions** (Section 6-9)

   a. **Alcohol formation**

   \[
   \text{R-}X + \cdot \cdot \cdot \text{O} \rightarrow \text{R-OH} + \cdot \cdot \cdot X^-
   \]

   **Example**

   \[
   \text{CH}_3\text{CH}_2\text{-Br} + \text{NaOH} \rightarrow \text{CH}_3\text{CH}_2\text{-OH} + \text{NaBr}
   \]

   ethyl bromide

   ethyl alcohol

   b. **Halide exchange**

   \[
   \text{R-}X + \cdot \cdot \cdot \text{I}^- \rightarrow \text{R-I} + \cdot \cdot \cdot X^-
   \]

   \[
   \text{R-Cl} + \text{KF} \xrightarrow{\text{18-crown-6}} \text{CH}_3\text{CN} \rightarrow \text{R-F} + \text{KCl}
   \]

   **Example**

   \[
   \text{H}_2\text{C=CH-CH}_2\text{Cl} + \text{NaI} \rightarrow \text{H}_2\text{C=CH-CH}_2\text{I} + \text{NaCl}
   \]

   allyl chloride

   allyl iodide

   c. **Williamson ether synthesis**

   \[
   \text{R-}X + R'\cdot \cdot \cdot \rightarrow \text{R-}\cdot \cdot \cdot X^- + \cdot \cdot \cdot R'
   \]

   ether synthesis

   \[
   \text{R-}X + R'\cdot \cdot \cdot \rightarrow \text{R-}\cdot \cdot \cdot X^- + \cdot \cdot \cdot R'
   \]

   thioether synthesis