7.1 Introduction to Alkyl Halides

- **Alkyl halides** are organic molecules containing a halogen atom bonded to an \( sp^3 \) hybridized carbon atom.

- Alkyl halides are classified as primary (\( 1^\circ \)), secondary (\( 2^\circ \)), or tertiary (\( 3^\circ \)), depending on the number of carbons bonded to the carbon with the halogen atom.

- The halogen atom in halides is often denoted by the symbol “X”.

![Diagram of alkyl halides](image)
• There are other types of organic halides. These include vinyl halides, aryl halides, allylic halides and benzylic halides.

• Vinyl halides have a halogen atom (X) bonded to a C—C double bond.

• Aryl halides have a halogen atom bonded to a benzene ring.

• Allylic halides have X bonded to the carbon atom adjacent to a C—C double bond.

• Benzylic halides have X bonded to the carbon atom adjacent to a benzene ring.

Figure 7.1: Examples of 1°, 2°, and 3° alkyl halides

Figure 7.2: Four types of organic halides (RX) having X near a π bond
7.2 Nomenclature

**How To** Name an Alkyl Halide Using the IUPAC System

**Example**

Give the IUPAC name of the following alkyl halide:
\[
\begin{align*}
\text{CH}_3 & \quad \text{Cl} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} & \quad \text{CH}_3
\end{align*}
\]

**Step 1** Find the parent carbon chain containing the halogen.

- Name the parent chain as an alkane, with the halogen as a substituent bonded to the longest chain.
- 7 C's in the longest chain
- 7 C's → heptane

**Step 2** Apply all other rules of nomenclature.

a. Number the chain.

- Begin at the end nearest the first substituent, either alkyl or halogen.

b. Name and number the substituents.

- methyl at C5
- chloro at C2

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

- ANSWER: 2-chloro-5-methylheptane

7.2B Common Names

- Common names are often used for simple alkyl halides. To assign a common name:
  - Name all the carbon atoms of the molecule as a single alkyl group.
  - Name the halogen bonded to the alkyl group.
  - Combine the names of the alkyl group and halide, separating the words with a space.

**Common names**

<table>
<thead>
<tr>
<th>tert-butyl group</th>
<th>tert-butyl iodide</th>
<th>ethyl group</th>
<th>ethyl chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃C—I</td>
<td>CH₃CH₂—Cl</td>
<td>Cl⁻</td>
</tr>
<tr>
<td>iodine</td>
<td>iodide</td>
<td>chlorine</td>
<td>chloride</td>
</tr>
</tbody>
</table>

**Example**

- CH₃C—I → tert-butyl iodide
- CH₃CH₂—Cl → ethyl chloride
7.3 Physical Properties

- Alkyl halides are weak polar molecules. They exhibit dipole-dipole interactions because of their polar C—X bond, but because the rest of the molecule contains only C—C and C—H bonds, they are incapable of intermolecular hydrogen bonding.

![Dipole-dipole interactions](image)

Opposite ends of the dipoles interact.

---

### Table 7.1 Physical Properties of Alkyl Halides

<table>
<thead>
<tr>
<th>Property</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point and melting point</td>
<td>• Alkyl halides have higher bp’s and mp’s than alkanes having the same number of carbons.</td>
</tr>
<tr>
<td></td>
<td>CH₃CH₂Cl and CH₃CH₂Br</td>
</tr>
<tr>
<td></td>
<td>bp = 49 °C and bp = 39 °C</td>
</tr>
<tr>
<td></td>
<td>• Bp’s and mp’s increase as the size of R increases.</td>
</tr>
<tr>
<td></td>
<td>CH₃CH₂Cl and CH₃CH₂Cl</td>
</tr>
<tr>
<td></td>
<td>mp = 136 °C and mp = 135 °C</td>
</tr>
<tr>
<td></td>
<td>bp = 12 °C and bp = 47 °C</td>
</tr>
<tr>
<td></td>
<td>• Bp’s and mp’s increase as the size of X increases.</td>
</tr>
<tr>
<td></td>
<td>CH₃CH₂Cl and CH₃CH₂Br</td>
</tr>
<tr>
<td></td>
<td>mp = –19 °C and mp = –19 °C</td>
</tr>
<tr>
<td></td>
<td>bp = 12 °C and bp = 39 °C</td>
</tr>
<tr>
<td>Solubility</td>
<td>• RX is soluble in organic solvents.</td>
</tr>
<tr>
<td></td>
<td>• RX is insoluble in water.</td>
</tr>
</tbody>
</table>
7.4 Interesting Alkyl Halides

Figure 7.4 Some simple alkyl halides

- Chloromethane (CH$_3$Cl) is produced by giant kelp and algae and also found in emissions from volcanoes such as Hawaii's Kilauea. Almost all of the atmospheric chloromethane results from these natural sources.

- Dichloromethane (or methylene chloride, CH$_2$Cl$_2$) is an important solvent, once used to decaffeinate coffee. Coffee is now decaffeinated by using supercritical CO$_2$ due to concerns over the possible ill effects of trace amounts of residual CH$_2$Cl$_2$ in the coffee. Subsequent studies on rats have shown, however, that no cancers occurred when animals ingested the equivalent of over 100,000 cups of decaffeinated coffee per day.

- Halothane (CF$_3$CHClBr) is a safe general anesthetic that has now replaced other organic anesthetics such as CHCl$_3$, which causes liver and kidney damage, and CH$_3$CH$_2$OCH$_2$CH$_3$ (diethyl ether), which is very flammable.
7.5 The Polar Carbon-Halogen Bond

- The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient. Electrostatic potential maps of four simple alkyl halides illustrate this point.

Figure 7.5 Electrostatic potential maps of four halomethanes (CH₃X)

- Alkyl halides undergo substitution reactions with nucleophiles.

\[
R-X + :Nu^- \rightarrow R-Nu^- + X^-
\]

- Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

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

new \(\pi\) bond an alkene

elimination of HX
7.6 General Features of Nucleophilic Substitution

• Three components are necessary in any substitution reaction.

![General substitution reaction diagram]

**Examples**

<table>
<thead>
<tr>
<th>Alkyl group</th>
<th>Nucleophile</th>
<th>Leaving group</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] CH₃Cl</td>
<td>HO⁻</td>
<td>CH₃OH + Cl⁻</td>
</tr>
<tr>
<td>[2] CH₃CH₂CH₂I</td>
<td>HO⁻</td>
<td>CH₃CH₂CH₂OH + I⁻</td>
</tr>
<tr>
<td>[3] CH₃CH₂Br</td>
<td>HO⁻</td>
<td>CH₃CH₂CH₂OH + Br⁻</td>
</tr>
</tbody>
</table>

A new C–Nu bond forms. The leaving group comes off.

• Negatively charged nucleophiles like HO⁻ and HS⁻ are used as salts with Li⁺, Na⁺, or K⁺ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.

![Negatively charged nucleophile reaction diagram]

Na⁺ balances charge.

• When a neutral nucleophile is used, the substitution product bears a positive charge.

![Neutral nucleophile reaction diagram]

All CH₃ groups remain in the product.
• Furthermore, when the substitution product bears a positive charge and also contains a proton bonded to O or N, the initially formed substitution product readily loses a proton in a Brønsted-Lowry acid-base reaction, forming a neutral product.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{NH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3^+ + \text{Br}^- + \text{NH}_4^+
\]

• To draw any nucleophilic substitution product:
  ◆ Find the \(sp^3\) hybridized carbon with the leaving group.
  ◆ Identify the nucleophile, the species with a lone pair or \(\pi\) bond.
  ◆ Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

7.7 The Leaving Group

• In a nucleophilic substitution reaction of \(R—X\), the \(C—X\) bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming \(X:\bar{\text{\textdegree}}\). The more stable the leaving group \(X:\bar{\text{\textdegree}}\), the better able it is to accept an electron pair.

\[
\text{R—X} + \text{Nu}^- \rightarrow \text{R—Nu} + \text{X:\bar{\text{\textdegree}}}
\]

• In comparing two leaving groups, the better leaving group is the weaker base.

• For example, \(\text{H}_2\text{O}\) is a better leaving group than \(\text{HO}^-\) because \(\text{H}_2\text{O}\) is a weaker base.
• There are periodic trends in leaving group ability:

  - Left-to-right across a row of the periodic table, basicity decreases so leaving group ability increases.

  ![Increasing basicity](image)

  With second-row elements: \( \text{NH}_3 \rightarrow \text{H}_2\text{O}^+ \) better leaving group

  ![Increasing leaving group ability](image)

  - Down a column of the periodic table, basicity decreases so leaving group ability increases.

  ![Increasing basicity](image)

  \( \text{F}^- \rightarrow \text{I}^- \) weakest base best leaving group

  ![Increasing leaving group ability](image)

---

**Table 7.2 Good Leaving Groups for Nucleophilic Substitution**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Leaving group</th>
<th>Conjugate acid</th>
<th>( pK_a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-Cl</td>
<td>Cl(^-)</td>
<td>HCl</td>
<td>-7</td>
</tr>
<tr>
<td>R-Br</td>
<td>Br(^-)</td>
<td>HBr</td>
<td>-9</td>
</tr>
<tr>
<td>R-I</td>
<td>I(^-)</td>
<td>HI</td>
<td>-10</td>
</tr>
<tr>
<td>R-CH(_3)^+</td>
<td>H(_2)O</td>
<td>H(_2)O(^+)</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

These molecules undergo nucleophilic substitution. **good leaving groups**
7.8 The Nucleophile

- Nucleophiles and bases are structurally similar: both have a lone pair or a π bond. They differ in what they attack.

- Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).
• Although nucleophilicity and basicity are interrelated, they are fundamentally different.

Basicity is a measure of how readily an atom donates its electron pair to a proton. It is characterized by an equilibrium constant, $K_a$, in an acid-base reaction, making it a thermodynamic property.

Nucleophilicity is a measure of how readily an atom donates its electron pair to other atoms. It is characterized by a rate constant, $k$, making it a kinetic property.

• Nucleophilicity parallels basicity in three instances:

1. For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.

   The relative nucleophilicity of $\text{HO}^-$ and $\text{CH}_3\text{COO}^-$, two oxygen nucleophiles, is determined by comparing the $pK_a$ values of their conjugate acids ($\text{H}_2\text{O} = 15.7$, and $\text{CH}_3\text{COOH} = 4.8$). $\text{HO}^-$ is a stronger base and stronger nucleophile than $\text{CH}_3\text{COO}^-$.  

2. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.

   $\text{HO}^-$ is a stronger base and stronger nucleophile than $\text{H}_2\text{O}$.

3. Right-to-left—across a row of the periodic table, nucleophilicity increases as basicity increases:

   ![Increasing basicity, increasing nucleophilicity](image)

   For second-row elements with the same charge:
Nucleophilicity does not parallel basicity when steric hindrance becomes important.

Steric hindrance is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.

Steric hindrance decreases nucleophilicity but not basicity.

Sterically hindered bases that are poor nucleophiles are called nonnucleophilic bases.

If the salt NaBr is used as a source of the nucleophile Br\(^{-}\) in H\(_2\)O, the Na\(^+\) cations are solvated by ion-dipole interactions with H\(_2\)O molecules, and the Br\(^{-}\) anions are solvated by strong hydrogen bonding interactions.
• In polar protic solvents, nucleophilicity increases down a column of the periodic table as the size of the anion increases. This is the opposite of basicity.

![Diagram: Increasing nucleophilicity in polar protic solvents](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>CH$_2$CH$_2$OH</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>CH$_3$COOH</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>

Figure 7.6 Example of polar protic solvents

• Polar aprotic solvents also exhibit dipole–dipole interactions, but they have no O–H or N–H bonds. Thus, they are incapable of hydrogen bonding.

![Diagram: Examples of polar aprotic solvents](image)

- acetone
- acetonitrile
- tetrahydrofuran (THF)
- dimethyl sulfoxide (DMSO)
- dimethylformamide (DMF)
- hexamethylphosphoramide (HMPA)

Figure 7.7 Examples of polar aprotic solvents
- Polar aprotic solvents solvate cations by ion—dipole interactions.
- Anions are not well solvated because the solvent cannot hydrogen bond to them. These anions are said to be “naked”.

\[(\text{CH}_3)_2\text{C}=\text{O} \text{ solvates } \text{Na}^+ \text{ well by ion—dipole interactions.}\]

\[\text{Br}^- \text{ anions are surrounded by solvent but not well solvated by the (CH}_3)_2\text{C}=\text{O molecules.}\]

- In polar aprotic solvents, nucleophilicity parallels basicity, and the stronger base is the stronger nucleophile.
- Because basicity decreases as size increases down a column, nucleophilicity decreases as well.

Down a column of the periodic table

Increasing nucleophilicity in polar aprotic solvents
In a nucleophilic substitution:

**Overall reaction**

\[
R_X + \text{Nu}^- \rightarrow R\text{Nu} + X^-
\]

This σ bond is broken. This σ bond is formed.

But what is the order of bond making and bond breaking? In theory, there are three possibilities.

**[1] Bond making and bond breaking occur at the same time.**

In this scenario, the mechanism is comprised of one step. In such a bimolecular reaction, the rate depends upon the concentration of both reactants, that is, the rate equation is second order.
In this scenario, the mechanism has two steps and a carbocation is formed as an intermediate. Because the first step is rate-determining, the rate depends on the concentration of RX only; that is, the rate equation is first order.

This mechanism has an inherent problem. The intermediate generated in the first step has 10 electrons around carbon, violating the octet rule. Because two other mechanistic possibilities do not violate a fundamental rule, this last possibility can be disregarded.
Consider reaction [1] below:

\[ \text{CH}_3\text{Br} + \text{CH}_3\text{COCH}_3 \rightarrow \text{CH}_3\text{COCH}_3 + \text{Br}^- \]

Both reactants appear in the rate equation.

Kinetic data show that the rate of reaction [1] depends on the concentration of both reactants, which suggests a bimolecular reaction with a one-step mechanism. This is an example of an $S_N2$ (substitution nucleophilic bimolecular) mechanism.

Consider reaction [2] below:

\[ (\text{CH}_3)_2\text{CBr} + \text{CH}_3\text{COCH}_3 \rightarrow (\text{CH}_3)_2\text{CBr} + \text{CH}_3\text{COCH}_3 \]

Only one reactant appears in the rate equation.

Kinetic data show that the rate of reaction [2] depends on the concentration of only the alkyl halide. This suggests a two-step mechanism in which the rate-determining step involves the alkyl halide only. This is an example of an $S_N1$ (substitution nucleophilic unimolecular) mechanism.
7.11 The SN2 Mechanisms

The mechanism of an SN2 reaction would be drawn as follows. Note the curved arrow notation that is used to show the flow of electrons.

**Mechanism 7.1 The SN2 Mechanism**

One step. The C–Br bond breaks as the C–O bond forms.

---

*Figure 7.8* An energy diagram for the SN2 reaction:

\[ \text{CH}_3\text{Br} + \text{CH}_3\text{COO}^- \rightarrow \text{CH}_3\text{COOCCH}_3 + \text{Br}^- \]

- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.
7.11C Stereochemistry of the $S_N2$ Reaction

- All $S_N2$ reactions proceed with backside attack of the nucleophile, resulting in inversion of configuration at a stereogenic center.

Figure 7.9 Stereochemistry of the $S_N2$ reaction

- The bond to the nucleophile in the product is always on the opposite side relative to the bond to the leaving group in the starting material.

Figure 7.10 Two examples of inversion of configuration in the $S_N2$ reaction

\[ \text{inversion of configuration} \]
7.11D The Identity of the R Group

- As the number of R groups on the carbon with the leaving group increases, the rate of an SN2 reaction decreases.

<table>
<thead>
<tr>
<th>R</th>
<th>Increasing rate of an SN2 reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>1°</td>
</tr>
<tr>
<td>R1CH2-X</td>
<td>2°</td>
</tr>
<tr>
<td>R2CH-X</td>
<td>3°</td>
</tr>
</tbody>
</table>

- Methyl and 1° alkyl halides undergo SN2 reactions with ease.
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides do not undergo SN2 reactions. This order of reactivity can be explained by steric effects. Steric hindrance caused by bulky R groups makes nucleophilic attack from the backside more difficult, slowing the reaction rate.

Electrostatic potential maps illustrate the effects of steric hindrance around the carbon bearing the leaving group in a series of alkyl halides.

Figure 7.11 Steric effects in the SN2 reaction
• The higher the $E_a$, the slower the reaction rate. Thus, any factor that increases $E_a$ decreases the reaction rate.

Figure 7.12 Two energy diagrams depicting the effect of steric hindrance in $S_{N2}$ reactions

- $CH_3Br$ is an unhindered alkyl halide. The transition state in the $S_{N2}$ reaction is lower in energy, making $E_a$ lower and increasing the reaction rate.
- $(CH_3)_2CHBr$ is a sterically hindered alkyl halide. The transition state in the $S_{N2}$ reaction is higher in energy, making $E_a$ higher and decreasing the reaction rate.

• Increasing the number of R groups on the carbon with the leaving group increases crowding in the transition state, thereby decreasing the reaction rate.
• The $S_{N2}$ reaction is fastest with unhindered halides.

\[
\begin{align*}
\text{less crowded transition state} &\quad \text{lower in energy} & \quad \text{more crowded transition state} \\
\text{faster } S_{N2} \text{ reaction} & & \text{slower } S_{N2} \text{ reaction}
\end{align*}
\]
**Table 7.5** Characteristics of the SN₂ Mechanism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetics</td>
<td>Second-order kinetics; rate = k[RX][Nu⁻]</td>
</tr>
<tr>
<td>Mechanism</td>
<td>One step</td>
</tr>
<tr>
<td>Stereochemistry</td>
<td>Backside attack of the nucleophile</td>
</tr>
<tr>
<td></td>
<td>Inversion of configuration at a stereogenic center</td>
</tr>
<tr>
<td>Identity of R</td>
<td>Unhindered halides react fastest.</td>
</tr>
<tr>
<td></td>
<td>Rate: CH₃X &gt; RCH₂X &gt; R₂CHX &gt; R₃CX</td>
</tr>
</tbody>
</table>

7.12 Application: Useful SN₂ Reactions

The SN₂ reaction is a key step in the laboratory synthesis of many important drugs.

*Figure 7.13* Nucleophilic substitution in the synthesis of two useful drugs

In both syntheses, the NH₂ group serves as a neutral nucleophile to displace halogen. The new bonds formed by nucleophilic substitution are drawn in red in the products.
Nucleophilic substitution reactions are important in biological systems as well.

This reaction is called methylation because a CH₃ group is transferred from one compound (SAM) to another (\(\text{Nu}^-\)).
7.13 The SN1 Mechanism

The mechanism of an SN1 reaction would be drawn as follows: Note the curved arrow formalism that is used to show the flow of electrons.

**Mechanism 7.2 The SN1 Mechanism**

**Step (1) The C-Br bond is broken.**

\[
\text{CH}_3\text{CH}_2\text{C}^+\text{-Br} \rightarrow \text{CH}_3\text{CH}_2\text{C}^+ + \text{Br}^-
\]

- **Heterolysis of the C-Br bond** forms an intermediate carboxation. This step is rate-determining because it involves only bond cleavage.

**Step (2) The C-O bond is formed.**

\[
\text{CH}_3\text{CH}_2\text{C}^+ + \text{CH}_3\text{CO}^- \rightarrow \text{CH}_3\text{CH}_2\text{C}^=\text{O} + \text{HBr}
\]

- **Nucleophilic attack of the acetalate** on the carboxation forms the new C-O bond in the product. This is a Lewis acid-base reaction; the nucleophile is the Lewis base and the carboxation is the Lewis acid. Step (2) is faster than Step (1) because no bonds are broken and one bond is formed.

Key features of the SN1 mechanism are that it has two steps, and carbocations are formed as reactive intermediates.

---

**Figure 7.15 An energy diagram for the SN1 reaction:**

\[
\text{(CH}_3\text{)}_2\text{CBr} + \text{CH}_3\text{COO}^- \rightarrow \text{(CH}_3\text{)}_2\text{COCOCH}_3 + \text{Br}^-
\]

- Since the SN1 mechanism has two steps, there are two energy barriers.
- \( E_1 \) > \( E_2 \) since Step [1] involves bond breaking and Step [2] involves bond formation.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn with \( \Delta H_{\text{overall}} \) as a negative value, since the products are lower in energy than the starting materials.
7.13C Stereochemistry of the \( S_N1 \) Reaction

To understand the stereochemistry of the \( S_N1 \) reaction, we must examine the geometry of the carbocation intermediate.

- Loss of the leaving group in Step [1] generates a planar carbocation that is achiral. In Step [2], attack of the nucleophile can occur on either side to afford two products which are a pair of enantiomers. Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a racemic mixture. We say that racemization has occurred.
7.13C The Identity of the R Group

- The rate of an $S_N1$ reaction is affected by the type of alkyl halide involved.

- As the number of R groups on the carbon with the leaving group increases, the rate of an $S_N1$ reaction increases.

- $3^\circ$ Alkyl halides undergo $S_N1$ reactions rapidly.
- $2^\circ$ Alkyl halides react more slowly.
- Methyl and $1^\circ$ alkyl halides do not undergo $S_N1$ reactions.

- This trend is exactly opposite to that observed in $S_N2$ reactions.
7.14 Carbocation Stability

- The effect of the type of alkyl halide on $S_N1$ reaction rates can be explained by considering carbocation stability.
- Carbocations are classified as primary ($1^\circ$), secondary ($2^\circ$), or tertiary ($3^\circ$), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetics</td>
<td>First-order kinetics; rate $= k[RX]$</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Two steps</td>
</tr>
<tr>
<td>Stereochemistry</td>
<td>Trigonal planar carbocation intermediate</td>
</tr>
<tr>
<td></td>
<td>Racemization at a single stereogenic center</td>
</tr>
<tr>
<td>Identity of R</td>
<td>More substituted halides react fastest.</td>
</tr>
<tr>
<td></td>
<td>Rate: $R_3CX &gt; R_2CHX &gt; RCH_2X &gt; CH_3X$</td>
</tr>
</tbody>
</table>

Increasing carbocation stability
7.14A Inductive Effect

- The order of carbocation stability can be rationalized through inductive effects and hyperconjugation.
- **Inductive effects** are electronic effects that occur through $\sigma$ bonds. Specifically, the inductive effect is the pull of electron density through $\sigma$ bonds caused by electronegativity differences between atoms.
- Alkyl groups are **electron donating** groups that stabilize a positive charge. Since an alkyl group has several $\sigma$ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.
- In general, the greater the number of alkyl groups attached to a carbon with a positive charge, the more stable will be the cation.

**Figure 7.17** Electrostatic potential maps for different carbocations

- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.
7.14B Hyperconjugation

- The order of carbocation stability is also a consequence of hyperconjugation.
- Hyperconjugation is the spreading out of charge by the overlap of an empty $p$ orbital with an adjacent $\sigma$ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.
- Example: $\text{C}_2\text{H}_3^+$ cannot be stabilized by hyperconjugation, but $(\text{C}_2\text{H}_3)_2\text{C}_2\text{H}_3^+$ can.

\[ \text{CH}_3^+ = \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \end{array} \quad \text{and} \quad \text{CH}_3^+ = \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \end{array} \]

This carbocation has no opportunity for orbital overlap with the vacant $p$ orbital.

Overlap of the $\text{C} - \text{H} \sigma$ bond with the adjacent vacant $p$ orbital stabilizes the carbocation.

7.15 The Hammond Postulate

- The rate of an $S_n1$ reaction increases as the number of $R$ groups on the carbon with the leaving group increases.
- The stability of a carbocation increases as the number of $R$ groups on the positively charged carbon increases.
The Hammond postulate relates reaction rate to stability. It provides a quantitative estimate of the energy of a transition state. The Hammond postulate states that the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy.

7.15A The General Features of the Hammond Postulate

- In endothermic reactions, the transition state is closer in energy to the products.
- In exothermic reactions, the transition state is closer in energy to the reactants.

[1] An endothermic reaction

[2] An exothermic reaction

- Transition states in endothermic reactions resemble the products.
- Transition states in exothermic reactions resemble the reactants.
• In an endothermic reaction, the transition state resembles the products more than the reactants, so anything that stabilizes the product stabilizes the transition state also. Thus, lowering the energy of the transition state decreases $E_{\text{at}}$, which increases the reaction rate.

• If there are two possible products in an endothermic reaction, but one is more stable than the other, the transition state that leads to the formation of the more stable product is lower in energy, so this reaction should occur faster.

Figure 7.18 An endothermic reaction—How the energy of the transition state and products are related
- In the case of an exothermic reaction, the transition state resembles the reactants more than the products. Thus, lowering the energy of the products has little or no effect on the energy of the transition state.

- Since $E_a$ is unaffected, the reaction rate is unaffected.
- The conclusion is that in an exothermic reaction, the more stable product may or may not form faster, since $E_a$ is similar for both products.

**Figure 7.19** An exothermic reaction—How the energy of the transition state and products are related
7.15B The Hammond Postulate and the $S_n1$ Reaction

- The Hammond postulate estimates the relative energy of transition states, and thus it can be used to predict the relative rates of two reactions.
- According to the Hammond postulate, the stability of the carbocation determines the rate of its formation.

![Energy diagram for carbocation formation in two different $S_n1$ reactions](image)


7.16 Application: $S_n1$ Reactions, Nitrosamines and Cancer

- $S_n1$ reactions are thought to play a role in how nitrosamines, compounds having the general structure $R_2\text{NN}=\text{O}$, act as toxins and carcinogens.
7.17A The Alkyl Halide-The Most Important Factor

- Four factors are relevant in predicting whether a given reaction is likely to proceed by an $S_N1$ or an $S_N2$ reaction—The most important is the identity of the alkyl halide.
  - Increasing alkyl substitution favors $S_N1$.
  - Decreasing alkyl substitution favors $S_N2$.

![Diagram showing the rate of $S_N1$ and $S_N2$ reactions with different alkyl halides and nucleophiles.]

7.17B The Nucleophile

- The nature of the nucleophile is another factor.
- Strong nucleophiles (which usually bear a negative charge) present in high concentrations favor $S_N2$ reactions.
- Weak nucleophiles, such as $H_2O$ and ROH favor $S_N1$ reactions by decreasing the rate of any competing $S_N2$ reaction.
- Let us compare the substitution products formed when the $2^\circ$ alkyl halide A is treated with either the strong nucleophile $HO^-$ or the weak nucleophile $H_2O$. Because a $2^\circ$ alkyl halide can react by either mechanism, the strength of the nucleophile determines which mechanism takes place.

![Diagram showing the reaction of $cis-1$-bromo-4-methylcyclohexane A with $HO^-$ and $H_2O$.]
• The strong nucleophile favors an S<sub>N</sub>2 mechanism.

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

\[\text{S}_\text{N}2\]

trans-4-methylcyclohexanol

• The weak nucleophile favors an S<sub>N</sub>1 mechanism.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{H} + \text{Br}^-
\]

\[\text{A}\]

Planar carbocation + Br\(^-\)

\[\text{C}\]

\[\text{cis isomer E} + \text{HBr}\]

\[\text{B}\]

The nucleophile attacks from above and below.

Two products are formed.

7.17C The Leaving Group

• A better leaving group increases the rate of both S<sub>N</sub>1 and S<sub>N</sub>2 reactions.

Transition state of the S<sub>N</sub>2 mechanism

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

Transition state of the rate-determining step of the S<sub>N</sub>1 mechanism

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

A better leaving group is more able to accept the negative charge.

Increasing leaving group ability

Increasing rate of S<sub>N</sub>1 and S<sub>N</sub>2 reactions
7.17D The Solvent

- The nature of the solvent is a fourth factor.
- Polar protic solvents like H₂O and ROH favor S₅¹ reactions because the ionic intermediates (both cations and anions) are stabilized by solvation.
- Polar aprotic solvents favor S₅² reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.

---

<table>
<thead>
<tr>
<th>Alkyl halide</th>
<th>Mechanism</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂X</td>
<td>S₅¹ or S₅²</td>
<td>The mechanism depends on the conditions.</td>
</tr>
<tr>
<td>RCH₂X (I°)</td>
<td>S₅¹</td>
<td>Favored by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- strong nucleophiles (usually a net negative charge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- polar aprotic solvents</td>
</tr>
<tr>
<td>R₂CX (I°)</td>
<td>S₅¹</td>
<td>Favored by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- weak nucleophiles (usually neutral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- polar aprotic solvents</td>
</tr>
<tr>
<td>R₂CHX (I°)</td>
<td>S₅¹ or S₅²</td>
<td>The mechanism depends on the conditions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- strong nucleophiles favor the S₅² mechanism over the S₅¹ mechanism. For example, RO⁻ is a stronger nucleophile than ROH, so RO⁻ favors the S₅² reaction and ROH favors the S₅¹ reaction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Proton solvents favor the S₅¹ mechanism and aprotic solvents favor the S₅² mechanism. For example, H₂O and CH₃OH are polar protic solvents that favor the S₅¹ mechanism, whereas acetone [(CH₃)₂C=O] and DMSO [(CH₃)₂S=O] are polar aprotic solvents that favor the S₅² mechanism.</td>
</tr>
</tbody>
</table>
7.18 Vinyl Halides and Aryl Halides.

- Vinyl and aryl halides do not undergo $S_{N}1$ or $S_{N}2$ reactions, because heterolysis of the $C$–$X$ bond would form a highly unstable vinyl or aryl cation.

Figure 7.22 Vinyl halides and nucleophilic substitution mechanisms

### Table 7.8: Molecules Synthesized from $R$–$X$ by the $S_{N}2$ Reaction

<table>
<thead>
<tr>
<th>Nucleophile ($\text{Nu}^-$)</th>
<th>Product</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen compounds</td>
<td>$\text{OH}$</td>
<td>alcohol</td>
</tr>
<tr>
<td></td>
<td>$\text{OR}^-$</td>
<td>ether</td>
</tr>
<tr>
<td></td>
<td>$\text{O}^-$</td>
<td>ester</td>
</tr>
<tr>
<td>Carbon compounds</td>
<td>$\text{CN}$</td>
<td>nitrile</td>
</tr>
<tr>
<td></td>
<td>$\text{C}=$</td>
<td>alkyn</td>
</tr>
<tr>
<td>Nitrogen compounds</td>
<td>$\text{N}_2$</td>
<td>azide</td>
</tr>
<tr>
<td></td>
<td>$\text{NH}_3$</td>
<td>amine</td>
</tr>
<tr>
<td>Sulfur compounds</td>
<td>$\text{SH}$</td>
<td>thiol</td>
</tr>
<tr>
<td></td>
<td>$\text{SR}$</td>
<td>sulfide</td>
</tr>
</tbody>
</table>

products of nucleophilic substitution
7.19 Organic Synthesis.

- To carry out the synthesis of a particular compound, we must think backwards, and ask ourselves the question: What starting material and reagents are needed to make it?
- If we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product.

To determine the two components needed for synthesis, remember that the carbon atoms come from the organic starting material, in this case, a 1° alkyl halide. The functional group comes from the nucleophile, HO⁻ in this case. With these two components, we can “fill in the boxes” to complete the synthesis.

The nucleophile provides the functional group.

The alkyl halide provides the carbon framework.