Chapter 9

The Chemistry of Alkyl Halides

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Chapter 9 Overview

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• 9.3 Reaction Rates
• 9.4 The SN2 Reaction
• 9.5 The E2 Reaction
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• 9.7 Summary of Substitution and Elimination Reactions of Alkyl Halides
• 9.8 Carbenes and Carbenoids
Substitution and Elimination Reactions

- Alkyl halides provide simple models for these reactions
- Nucleophilic substitution reactions:

\[
\text{Na}^+ \text{CH}_3\text{CH}_2\text{O}^- + \cdot\text{Br} \rightarrow \text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{O}^- \text{CH}_2\text{CH}_3 + \text{Na}^+ \cdot\text{Br}^-
\]

sodium ethoxide \hspace{1cm} ethyl bromide \hspace{1cm} diethyl ether \hspace{1cm} sodium bromide

9.1 An Overview of Nucleophilic Substitution and β-Elimination Reactions
Substitution and Elimination Reactions

(X = halogen or other leaving group; R, R' = alkyl groups)

\[
\begin{array}{lll}
R\rightarrow\ddot{X}: & + \text{Nucleophile (name)} & \rightarrow \ddot{X}^- + \text{Product (name)} \\
R\rightarrow\ddot{X}: & + :\ddot{Y}^- \text{ (another halide)} & \rightarrow \ddot{X}^- + R\rightarrow\ddot{Y}: \text{ (another alkyl halide)} \\
& + \ddot{\text{C}}\equiv\ddot{\text{N}}: \text{ (cyanide)} & \rightarrow + R\rightarrow\ddot{\text{C}}\equiv\ddot{\text{N}}: \text{ (nitrile)} \\
& + \ddot{\text{OH}} \text{ (hydroxide)} & \rightarrow + R\rightarrow\ddot{\text{OH}} \text{ (alcohol)} \\
& + \ddot{\text{O}}R' \text{ (alkoxide)} & \rightarrow + R\rightarrow\ddot{\text{O}}R' \text{ (ether)} \\
& + \ddot{\text{N}}_3 \text{ (azide = :N} \equiv\ddot{\text{N}}=\ddot{\text{N}}: \rightarrow + R\rightarrow\ddot{\text{N}}_3 \text{ (alkyl azide)} \\
& + \ddot{\text{S}}R' \text{ (alkanethiolate)} & \rightarrow + R\rightarrow\ddot{\text{S}}R' \text{ (thioether or sulfide)} \\
& + :\ddot{\text{NR}}_3 \text{ (amine)} & \rightarrow R\rightarrow\ddot{\text{NR}}_3 :\ddot{X}^- \text{ (alkylammonium salt)} \\
& + :\ddot{\text{OH}}_2 \text{ (water)} & \rightarrow R\rightarrow\ddot{\text{O}}H :\ddot{X}^- \leftrightarrow R\rightarrow\ddot{\text{O}}H + H\ddot{X}: \text{ (alcohol)} \\
& + \ddot{\text{O}}R' \text{ (alcohol)} & \rightarrow R\rightarrow\ddot{\text{O}}R' :\ddot{X}^- \leftrightarrow R\rightarrow\ddot{\text{O}}R' + H\ddot{X}: \text{ (ether)}
\end{array}
\]

9.1 An Overview of Nucleophilic Substitution and β-Elimination Reactions
Substitution and Elimination Reactions

• *Intramolecular* reactions are also possible:
Substitution and Elimination Reactions

- β-Elimination reactions:

\[
\text{Na}^+ \text{C}_2\text{H}_5\text{O}^- + \text{H} - \text{CH}_2 - \text{C} - \text{CH}_3 \rightarrow \text{C}_2\text{H}_5\text{O} - \text{H} + \text{H}_2\text{C} = \text{C} - \text{CH}_3 + \text{Na}^+ \text{Br}^-
\]

- Sodium ethoxide
- tert-butyl bromide
- Ethanol
- 2-methylpropene (isobutylene)
- Sodium bromide
Substitution and Elimination Reactions

- The carbon bearing the halogen is often labeled as the $\alpha$-carbon
- Any adjacent carbons are labeled as $\beta$-carbons

- Loss of two groups from adjacent carbons is a $\beta$-elimination
Substitution vs Elimination

• Nucleophilic substitution and β-elimination reactions often compete with one another

\[
\text{H}_3\text{C} \text{CH} - \text{CH}_3 + \text{C}_2\text{H}_5\text{O}^- \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \text{H}_3\text{C} \text{CH} - \text{CH}_3 + \text{H}_2\text{C} \equiv \text{CH} - \text{CH}_3
\]

isopropyl bromide

ethoxide

ethyl isopropyl ether
substitution product
(about 50%)

propene
elimination product
(about 50%)
Equilibria in Substitution Reactions

• Some substitution reactions proceed to completion, others may be unfavorable

\[
\text{-C≡N}^- + \text{H}_3\text{C}^-\text{I}^- \rightarrow \text{H}_3\text{C}^-\text{C≡N}^- + \text{I}^- \\
\text{acetonitrile}
\]

\[
\text{I}^- + \text{H}_3\text{C}^-\text{Br}^- \leftrightarrow \text{H}_3\text{C}^-\text{I}^- + \text{Br}^- \\
\]

\[
\text{I}^- + \text{H}_3\text{C}^-\text{OH} \leftrightarrow \text{H}_3\text{C}^-\text{I}^- + \text{OH}^- \\
\text{(does not proceed to the right)}
\]
Equilibria in Substitution Reactions

• Recognize that each nucleophilic substitution reaction is similar to a Brønsted-Lowry acid-base reaction

\[
\text{-OH} + \text{H}_3\text{C}\text{I} \rightarrow \text{H}_3\text{C}\text{OH} + \text{I}^- \quad (\text{substitution reaction})
\]

\[
\text{-OH} + \text{H-I} \rightarrow \text{H-OH} + \text{I}^- \quad (\text{acid–base reaction})
\]

• The equilibrium in a nucleophilic substitution reaction favors the release of the weaker base
Definition of Reaction Rates

• Knowledge of the equilibrium constant for a reaction says nothing about *how fast* it will take place.

• The quantities that changes with time in a chemical reaction are [reactants] & [products]

\[
\text{reaction rate} = \frac{\text{change in product concentration}}{\text{corresponding change in time}}
\]

\[
= -\frac{\text{change in reactant concentration}}{\text{corresponding change in time}}
\]
The Rate Law

• The rate law expresses how the reaction rate depends on the concentrations of reactants

• For example,

\[ \text{rate} = k[A][B] \]

• Overall kinetic order is second order
• First order in [A], first order in [B]
Rate Constant and $\Delta G^{\ddagger}$

- The rate constant is related to the standard free energy of activation, $\Delta G^{\ddagger}$

9.3 Reaction Rates
## Rate Constant and $\Delta G^{\circ\dagger}$

<table>
<thead>
<tr>
<th>Rate constant ($s^{-1}$) \ ($T = 298 \text{ K}$)</th>
<th>Time to completion*</th>
<th>$\Delta G^{\circ\dagger}$</th>
<th>(\text{kJ mol}^{-1})</th>
<th>(\text{kcal mol}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-8}$</td>
<td>22 years</td>
<td>119</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>$10^{-6}$</td>
<td>83 days</td>
<td>107</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>20 hours</td>
<td>96.0</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>$10^{-2}$</td>
<td>12 minutes</td>
<td>84.6</td>
<td>20.2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 seconds</td>
<td>73.2</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>$10^2$</td>
<td>70 milliseconds</td>
<td>61.7</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>$10^4$</td>
<td>700 microseconds</td>
<td>50.4</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>$10^6$</td>
<td>7 microseconds</td>
<td>38.9</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>$6.63 \times 10^{12}$</td>
<td>0.01 nanosecond</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Time required for 99% completion of reaction $\approx 7/k$

### 9.3 Reaction Rates
Rate Constant and $\Delta G^{\ddagger\ddagger}$

- Most often we are interested in the *relative rates* of two reactions.

\[
\text{relative rate} = \frac{\text{rate}_A}{\text{rate}_B} = 10^{\left(\frac{\Delta G_B^{\ddagger\ddagger} - \Delta G_A^{\ddagger\ddagger}}{2.3RT}\right)}
\]

\[
\log (\text{relative rate}) = \log \left(\frac{k_A}{k_B}\right) = \frac{\Delta G_B^{\ddagger\ddagger} - \Delta G_A^{\ddagger\ddagger}}{2.3RT}
\]
The $S_N2$ Reaction

$$C_2H_5O^- + H_3C—I \xrightleftharpoons{C_2H_5OH} C_2H_5O—CH_3 + I^-$$

• The rate law for this reaction was experimentally determined to be:

$$\text{rate} = k[H_3CI][C_2H_5O^-]$$

• Specifically, the concentration terms indicate which atoms are present in the transition state of the rate-limiting step.
The $S\text{N}_2$ Reaction

• The simplest possible mechanism is then:

$$
\begin{align*}
\ce{C2H5O^- &+ H3C^- &\rightarrow \ce{C2H5O^- &+ H3C^- \rightarrow C2H5O^-CH3 + I^-}}
\end{align*}
$$

transformation state

• This one-step, concerted mechanism is classified as an $S\text{N}_2$ reaction:

9.4 The $S\text{N}_2$ Reaction
The $S_{N}2$ Reaction

- The rate law tells us nothing about how the atoms are arranged.

![Frontside substitution](image1.png)

![Backside substitution](image2.png)

9.4 The $S_{N}2$ Reaction
S_N2 vs Brønsted-Lowry Reaction Rates

• Most ordinary acid-base reactions occur instantaneously

\[ \text{C}_2\text{H}_5\overset{\cdot}{\text{O}}^- + \text{H}^- + \overset{\cdot}{\text{I}}^- \rightarrow \text{C}_2\text{H}_5\overset{\cdot}{\text{O}}^-\text{H}^- + \overset{\cdot}{\text{I}}^- \]  
  (complete in $10^{-9}$ second)

• Most nucleophilic substitution reactions are much slower

\[ \text{C}_2\text{H}_5\overset{\cdot}{\text{O}}^- + \text{H}_3\text{C}^- + \overset{\cdot}{\text{I}}^- \rightarrow \text{C}_2\text{H}_5\overset{\cdot}{\text{O}}^-\text{CH}_3 + \overset{\cdot}{\text{I}}^- \]  
  (complete in about an hour)
Stereochemistry of the $S_N2$ Reaction

- How does the $S_N2$ reaction occur?
- Via retention of configuration:

- ...or via inversion of configuration?

9.4 The $S_N2$ Reaction
Stereochemistry of the $S_N2$ Reaction

- Experimental results have shown that $S_N2$ reactions proceed via **inversion**!
Stereochemistry of the $S_N2$ Reaction

9.4 The $S_N2$ Reaction
MO Analysis of the $S_{N2}$ Reaction

9.4 The $S_{N2}$ Reaction
Effect of Alkyl Halide Structure

- The reaction rate is *strongly influenced* by structure (a *steric effect*)

\[
R-\text{Br} + \text{I}^- \xrightarrow{25 \degree C \text{ acetone}} R-\text{I} + \text{Br}^-
\]

<table>
<thead>
<tr>
<th>R—</th>
<th>Name of R</th>
<th>Relative rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃—</td>
<td>methyl</td>
<td>145</td>
</tr>
<tr>
<td>(CH₃)₂CHCH₂—</td>
<td>propyl</td>
<td>0.82</td>
</tr>
<tr>
<td>(CH₃)₂CH—</td>
<td>isobutyl</td>
<td>0.036</td>
</tr>
<tr>
<td>(CH₃)₃CCH₂—</td>
<td>neopentyl</td>
<td>0.000012</td>
</tr>
</tbody>
</table>

*All rates are relative to that of ethyl bromide.

*Estimated from the rates of closely related reactions.

9.4 The $S_N2$ Reaction
Transition States for $S_N2$ Reactions

(a) $\text{Br}^- + \text{CH}_3\text{I}$

(b) $\text{Br}^- + (\text{CH}_3)_3\text{C} = \text{CH}_2\text{I}$

9.4 The $S_N2$ Reaction
Nucleophilicity in the $S_N^2$ Reaction

- A wide variety of nucleophiles may be used for the $S_N^2$ reaction
- This adds great versatility to the $S_N^2$ reaction
- There is a correlation between nucleophilicity and basicity (both are aspects of Lewis basicity)
Basicity of the Nucleophile and $S_N2$ Rates

9.4 The $S_N2$ Reaction
Basicity of the Nucleophile and $S_N2$ Rates

![Nuc$^{-}$ + H$_3$C$\rightarrow$I $\xrightarrow{25^\circ C \text{CH}_3\text{OH}}$ Nuc$\text{-CH}_3 + I^-$]

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>$pK_a$ of conjugate acid*</th>
<th>$k$ (second-order rate constant, $M^{-1}$ s$^{-1}$)</th>
<th>log $k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 6A Nucleophiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhS$^-$</td>
<td>6.52</td>
<td>1.1</td>
<td>+0.03</td>
</tr>
<tr>
<td>PhO$^-$</td>
<td>9.95</td>
<td>$7.9 \times 10^{-5}$</td>
<td>−4.1</td>
</tr>
<tr>
<td>Group 7A Nucleophiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I$^-$</td>
<td>−10</td>
<td>$3.4 \times 10^{-3}$</td>
<td>−2.5</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>−8</td>
<td>$8.0 \times 10^{-5}$</td>
<td>−4.1</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>−6</td>
<td>$3.0 \times 10^{-6}$</td>
<td>−5.5</td>
</tr>
<tr>
<td>F$^-$</td>
<td>3.2</td>
<td>$5.0 \times 10^{-8}$</td>
<td>−7.3</td>
</tr>
</tbody>
</table>

* $pK_a$ values in water

- Notice the *reversal* of the basicity vs nucleophilicity trend for these cases

9.4 *The $S_N2$ Reaction*
Basicity of the Nucleophile and $S_{N2}$ Rates

- The following apply to nucleophilic anions in polar, protic solvents (e.g., water, alcohols):
  - *For nucleophiles in the same period*, more basic nucleophiles are more nucleophilic
  - *For nucleophiles in the same group*, less basic nucleophiles are more nucleophilic
  - The *solvent* has the greatest influence on these relationships
Solvent Effects

• In protic solvents, H-bonding can occur with the nucleophilic (Lewis basic) anions

• Stronger bases form stronger H-bonds

9.4 The $S_{N}2$ Reaction
Solvent Effects

• Changing to a polar, aprotic solvent greatly enhances nucleophilicity

\[ \text{Nuc}^- + \text{H}_2\text{C} = \text{I} \xrightarrow{25 \degree \text{C}} \text{Nuc} - \text{CH}_3 + \text{I}^- \]

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>pK_a*</th>
<th>( k, M^{-1} s^{-1} )</th>
<th>Reaction is over in—‡</th>
<th>( k, M^{-1} s^{-1} )</th>
<th>Reaction is over in—‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>I^-</td>
<td>-10</td>
<td>( 3.4 \times 10^{-3} )</td>
<td>17 min</td>
<td>( 4.0 \times 10^{-1} )</td>
<td>8.7 s</td>
</tr>
<tr>
<td>Br^-</td>
<td>-8</td>
<td>( 8.0 \times 10^{-5} )</td>
<td>12 h</td>
<td>1.3</td>
<td>2.7 s</td>
</tr>
<tr>
<td>Cl^-</td>
<td>-6</td>
<td>( 3.0 \times 10^{-6} )</td>
<td>13 days</td>
<td>2.5</td>
<td>1.4 s</td>
</tr>
<tr>
<td>F^-</td>
<td>3.2</td>
<td>( 5.0 \times 10^{-8} )</td>
<td>2.2 years</td>
<td>&gt;3</td>
<td>&lt;1.2 s</td>
</tr>
<tr>
<td>-CN</td>
<td>9.4</td>
<td>( 6.3 \times 10^{-4} )</td>
<td>1.5 h</td>
<td>( 3.2 \times 10^{2} )</td>
<td>0.011 s</td>
</tr>
</tbody>
</table>

*pK_a* values of the conjugate acid in water
‡Time required for 97% completion of the reaction
‡DMF = N,N-dimethylformamide (see Table 8.2, p. 341)
Leaving-Group Effects in the $S_N2$ Reaction

- The best leaving groups are the ones that give the *weakest bases*

  Relative reactivities in $S_N2$ reactions:

  $R—F << R—Cl < R—Br < R—I$

- Leaving groups are not limited to halogens
- A variety of alcohol derivatives will soon be introduced
Rate Law and Mechanism of E2

\[
\text{rate} = k([(\text{CH}_3)_3\text{C} - \text{Br}][\text{C}_2\text{H}_5\text{O}^-])
\]

E2

elimination

bimolecular

9.5 The E2 Reaction
A Concerted Mechanism

• Removal of the β-H and loss of the leaving group occurs simultaneously
Leaving Group Effects

• The trend observed for the $S_N^2$ reaction is seen again for the E2 reaction.

Relative rates of E2 reactions:

$\text{R–Cl} < \text{R–Br} < \text{R–I}$
Deuterium Isotope Effects

• The C-D bond is somewhat stronger than the C-H bond
• This retards the E2 reaction rate

\[
\begin{align*}
\text{Ph—CH}_2—\text{CH}_2—\text{Br} + \text{C}_2\text{H}_5\text{O}^- & \quad \xrightarrow{\text{rate constant } k_H \over \text{C}_2\text{H}_5\text{OH}} \quad \text{Ph—CH==CH}_2 + \text{Br}^- + \text{C}_2\text{H}_5\text{OH} \\
\text{Ph—CD}_2—\text{CH}_2—\text{Br} + \text{C}_2\text{H}_5\text{O}^- & \quad \xrightarrow{\text{rate constant } k_D \over \text{C}_2\text{H}_5\text{OH}} \quad \text{Ph—CD==CH}_2 + \text{Br}^- + \text{C}_2\text{H}_5\text{OD}
\end{align*}
\]

• Typically \(k_H/k_D\) is in the range of 2.5 - 8
• Referred to as a primary isotope effect

9.5 The E2 Reaction
Deuterium Isotope Effects

\[ \Delta G_{D}^{\ddagger} \text{ (larger)} \]

somewhat weaker bond

\[ \Delta G_{H}^{\ddagger} \text{ (smaller)} \]

somewhat stronger bond

reaction coordinate

9.5 The E2 Reaction
Stereochemistry of the E2 Reaction

- The E2 reaction can take place in two stereochemically distinct ways:

  - **Syn-elimination**: the dihedral angle is 0°

    \[
    \text{syn: base:} \quad \text{H} \quad \begin{array}{c} \text{R}_2 \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{R}_1 \end{array} \rightarrow \begin{array}{c} \text{R}_2 \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{R}_1 \end{array} + \text{base} \rightarrow \text{H} + \text{X}^{-}
    \]

  - **Anti-elimination**: the dihedral angle is 180°

    \[
    \text{anti: base:} \quad \text{H} \quad \begin{array}{c} \text{R}_2 \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{R}_1 \end{array} \rightarrow \begin{array}{c} \text{R}_2 \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{R}_1 \end{array} + \text{base} \rightarrow \text{H} + \text{X}^{-}
    \]
Stereochemistry of the E2 Reaction

• *Most* E2 eliminations are stereoselectively *anti*-eliminations

\[ \text{C}_2\text{H}_5\text{O}^- \quad \text{H} \quad \text{Ph} \quad \text{C} \quad \text{H} \quad \text{CH}_3 \quad \text{Br}^- \quad \rightarrow \quad \text{C}_2\text{H}_5\text{O}^- \quad \text{H} \quad \text{Ph} \quad \text{C} \quad \text{H} \quad \text{CH}_3 \quad \text{Br}^- \]

bonds to H and Br are anti

\[ \text{Ph} \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{H} \quad \text{Ph} \quad \text{H}_3\text{C} \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{Ph} \quad \text{Br}^- \]

(\text{Z})-\text{\(\alpha\)-methylstilbene} (only product observed)

\[ \text{C}_2\text{H}_5\text{O}^- \quad \text{H} \quad \text{Ph} \quad \text{C} \quad \text{H} \quad \text{CH}_3 \quad \text{Br}^- \quad \rightarrow \quad \text{C}_2\text{H}_5\text{O}^- \quad \text{H} \quad \text{Ph} \quad \text{C} \quad \text{H} \quad \text{CH}_3 \quad \text{Br}^- \]

bonds to H and Br are eclipsed

\[ \text{Ph} \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{H} \quad \text{Ph} \quad \text{H}_3\text{C} \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{Ph} \quad \text{Br}^- \]

(\text{E})-\text{\(\alpha\)-methylstilbene} (not observed)

9.5 The E2 Reaction
Stereochemistry of the E2 Reaction

• Some conformationally restricted cases may proceed via syn-elimination
Stereochemistry of the E2 Reaction

- Reasons why *anti*-elimination is preferred:

  - syn-elimination: molecule is in an eclipsed conformation
  - *anti*-elimination: molecule is in a staggered conformation

  - this electron pair enters backside to the C—X bond
  - this electron pair enters frontside to the C—X bond
Regioselectivity of the E2 Reaction

• When more than one type of β-H is available, more than one alkene product can be formed.

\[
\begin{align*}
\text{H}_3\text{C} - \text{C} - \text{CH} - \text{CH}_3 & \xrightarrow{\text{elimination of } \text{HBr}} \text{H}_3\text{C} = \text{C} - \text{CH}_3 + \text{H}_3\text{C} - \text{C} - \text{CH}_3 + \text{CH}_3\text{CH}_2\text{CH} = \text{CH}_2 \\
2\text{-bromobutane} & & \text{cis-2-butene} & & \text{trans-2-butene} & & 1\text{-butene}
\end{align*}
\]

• With simple alkoxide bases, the most stable alkene isomer usually dominates.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{C(CH}_3)_2 & \xrightarrow{\text{C}_2\text{H}_5\text{OH, K}^+} \text{CH}_3\text{CH} = \text{C(CH}_3)_2 + \text{CH}_3\text{CH}_2\text{C} - \text{CH}_3 \\
\text{Br} & & (70\%) & & (30\%)
\end{align*}
\]

9.5 The E2 Reaction
Regioselectivity of the E2 Reaction

- The predominance of the more stable alkene isomer *does not result from equilibration*
- The alkenes products are stable under the reaction conditions
- Hence, the product distribution reflects the relative rates of their formation
Regioselectivity and Transition States

9.5 The E2 Reaction
• $S_N2$ vs E2 is dependent on the structure of the alkyl halide and structure of the base
**S_N2 vs E2**

- **Secondary alkyl halides:**

  \[
  \text{H}_3\text{C} \text{CH} - \text{Br} + \text{C}_2\text{H}_5\text{O}^- \rightarrow \text{H}_2\text{C} \text{CH} - \text{CH}_3 + \text{H}_3\text{C} \text{CH} - \text{OC}_2\text{H}_5
  \]
  (about 55% elimination)

  \[
  \text{H}_3\text{C} \text{CH}_2 \text{CH} - \text{Br} + \text{C}_2\text{H}_5\text{O}^- \rightarrow \text{H}_3\text{C} \text{CH} = \text{CH}_3 + \text{CH}_3 \text{CH} = \text{CH}_2 + \text{H}_3\text{C} \text{CH}_2 \text{CH} - \text{OC}_2\text{H}_5
  \]
  (82% elimination)

  \[
  \text{H}_3\text{C} \text{CH} = \text{CH} - \text{CH}_3 + \text{CH}_3 \text{CH} = \text{CH}_2 \rightarrow (18\% \text{ substitution})
  \]

9.5 *The E2 Reaction*
$S_N 2$ vs E2

- Primary alkyl halides:

\[
\text{H}_3\text{C} - \text{CH}_2 - \text{CH}_2 - \text{Br} + \text{C}_2\text{H}_5\text{O}^- \rightarrow \text{H}_3\text{C} - \text{CH} = \text{CH}_2 + \text{H}_3\text{C} - \text{CH}_2 - \text{OC}_2\text{H}_5
\]

(10% elimination) (90% substitution)

\[
\text{H}_3\text{C} - \text{CH} = \text{CH}_2 + \text{H}_3\text{C} - \text{CH}_2 - \text{CH}_2 - \text{OC}_2\text{H}_5
\]

(99% substitution)

9.5 The E2 Reaction
SN2 vs E2

- Base structure:

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{Br} + \text{OCH}_2\text{CH}_3 & \rightarrow \text{(CH}_3\text{)}_2\text{C} = \text{CH}_2 + \text{(CH}_3\text{)}_2\text{CHCH}_2\text{OCH}_2\text{CH}_3 \\
\text{ethoxide} & \text{ (a primary, unbranched alkoxide base)} \\
\text{C}_2\text{H}_5\text{OH} & \rightarrow \\
\text{(CH}_3\text{)}_2\text{C} = \text{CH}_2 & \text{ (62% elimination)} \\
\text{(CH}_3\text{)}_2\text{OCH}_2\text{CH}_3 & \text{ (38% substitution)}
\end{align*}
\]

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{Br} + \text{O} - \text{C} - \text{CH}_3 & \rightarrow \text{(CH}_3\text{)}_2\text{C} = \text{CH}_2 + \text{(CH}_3\text{)}_2\text{CHCH}_2\text{O} - \text{C} - \text{CH}_3 \\
\text{tert-butoxide} & \text{ (a tertiary, branched alkoxide base)} \\
\text{(CH}_3\text{)}_3\text{COH} & \rightarrow \\
\text{(CH}_3\text{)}_2\text{C} = \text{CH}_2 & \text{ (92% elimination)} \\
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{O} - \text{C} - \text{CH}_3 & \text{ (8% substitution)}
\end{align*}
\]

9.5 The E2 Reaction
Rate Law and Mechanism of $S_{N1}$ and E1

The reaction of an alkyl halide with a solvent (and no other base or nucleophile) is called a **solvolyis** reaction.

\[
\text{rate} = k[(\text{CH}_3)_3\text{CBr}]
\]

9.6 The $S_{N1}$ and E1 Reaction
Rate Law and Mechanism of $S_{N1}$ and E1

- The *rate-determining first step* is common to both reactions:

  $\text{(CH}_3\text{)}_3\text{C} \xrightarrow{\text{Br}^-} \text{(CH}_3\text{)}_3\text{C}^+ \xrightleftharpoons{\text{Br}^-} \text{ (rate-limiting step)}$

  carbocation intermediate

- For elimination:

  $\text{H} \xrightarrow{\text{CH}_2 \xrightarrow{\text{C}}^+ \text{C} \xrightarrow{\text{Br}^{-}} \text{H}_2\text{C} = \text{C} \xrightarrow{\text{CH}_3} + \text{H} \xrightarrow{\text{O} \xrightarrow{\text{C}_2\text{H}_5} \text{Br}^-}$

  (ionized form of HBr in ethanol)

  elimination  \quad E1  \quad unimolecular
Rate Law and Mechanism of $S_{N1}$ and $E1$

- For substitution:

\[
\begin{align*}
(CH_3)_3C^+ & \xrightleftharpoons{} HOC_2H_5 \\
:Br^- & \xrightleftharpoons{} (CH_3)_3C-O\overset{+}{C}_2H_5 :Br^- \\
(CH_3)_3C & \xrightleftharpoons{} HOC_2H_5 + HOC_2H_5 Br^- \\
& \text{(ionized form of HBr in ethanol)}
\end{align*}
\]

- $S_{N1}$ substitution

- Nucleophilic

- Unimolecular
Rate-Limiting and Product-Determining Steps

- The rates of the product-forming steps have nothing to do with the rate at which the alkyl halide reacts.
Rate-Limiting and Product-Determining Steps

9.6 The S<sub>N</sub>1 and E1 Reaction
Reactivity and Product Distribution

Reactivity of alkyl halides in $S_N1$ or $E1$ reactions:

tertiary $>>$ secondary $>>$ primary

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{C} & \quad \text{Br} \\
\text{CH}_3 & \\
\end{align*}
\quad \xrightarrow{25^\circ C} \quad \xrightarrow{\text{C}_2\text{H}_5\text{OH}}
\begin{align*}
\text{H}_3\text{C} & \quad \text{C} = \text{CH}_2 \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{CH}_3 & \\
\end{align*}
\text{C} = \text{CH}_2 + \begin{align*}
\text{H}_3\text{C} & \quad \text{C} = \text{OC}_2\text{H}_5 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\text{C}_2\text{H}_5\text{OH}^+ \quad \text{Br}^-

(19\% \text{ elimination product}) \quad (81\% \text{ substitution product})

9.6 The $S_N1$ and $E1$ Reaction
Reactivity and Product Distribution

$\text{H}_3\text{C} - \text{CH} - \text{CH} - \text{Br}$\text{H}_3\text{C} - \text{CH} - \text{CH} - \text{C} = \text{C} +$

$\text{H}_3\text{C} - \text{CH} - \text{C} = \text{C} +$\text{H}_3\text{C} - \text{CH} - \text{C} = \text{C} +$

major isomer formed; has four alkyl substituents on the double bond

$\{62\% \text{ elimination products}\}$

$\text{H}_3\text{C} - \text{CH} - \text{C} - \text{OH}$ + $\text{H}_3\text{C} - \text{CH} - \text{C} - \text{OC}_2\text{H}_5$ + $\text{C}_2\text{H}_5\text{OH}_2$ $\text{Br}^- + \text{H}_3\text{O}^+ \text{ Br}^-$

$\{38\% \text{ substitution products}\}$
Rearrangements

- Rearrangements are a telltale sign of *carbocation intermediates*

\[ \text{H}_3\text{C} \cdots \text{C} \cdots \text{CH} \cdots \text{Cl} \xrightarrow{80 \, ^\circ \text{C}, \text{C}_2\text{H}_5\text{OH}} \text{H}_3\text{C} \cdots \text{C} \cdots \text{CH} \cdots \text{CH}_3 + \text{C}_2\text{H}_5\text{OH}_2^+ \text{Cl}^- + \text{other products} \]
Stereochemistry of the $S_N1$ Reaction

- Racemization is expected
Stereochemistry of the $S_{N}1$ Reaction

• …but, experimentally:

\[
\begin{array}{c}
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} + \text{H}_2\text{O} \quad \text{60°} \quad 80\% \text{ aqueous acetone} \\
\text{elimination products} + \text{H}_3\text{O}^+ \text{ Cl}^- + \\
\text{(R)-6-chloro-2,6-dimethyloctane} \\
\end{array}
\]

\[
\begin{array}{c}
\text{(CH}_3\text{)}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{OH} + \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH(CH}_3\text{)}_2 \\
\text{(R)-product (39.5%)} \quad \text{(S)-product (60.5%)}
\end{array}
\]

• Partial racemization is observed; net inversion is also observed
Stereochemistry of the $S_N1$ Reaction

$R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$ → $R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$

2$p$ orbital

$R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$ → $R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$

ion pair; carbocation is solvated at back side only

fully solvated, achiral carbocation

reaction with $H_2\overbrace{\text{O}}^{-}$:

$R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$ → $R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$

inversion

reaction with $H_2\overbrace{\text{O}}^{-}$:

$R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$ → $R^1\overbrace{\text{C}}^{\text{Cl}^-}$ + $R^2\overbrace{\text{Cl}^-}$

racemization

9.6 The $S_N1$ and E1 Reaction
Summary of Substitution and Elimination

- Key questions for evaluation:
  1. Is the alkyl halide primary, secondary, tertiary? If primary or secondary, is there significant $\beta$-substitution?
  2. Is a Lewis base present? Is it a good nucleophile, strong Brønsted base, or both?
  3. What is the solvent? Polar protic or polar aprotic?
# Summary of Substitution and Elimination

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Alkyl halide structure</th>
<th>Good nucleophile?</th>
<th>Strong Brønsted base?</th>
<th>Type of solvent?*</th>
<th>Major reaction(s) expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methyl</td>
<td>Yes</td>
<td>Yes or No</td>
<td>PP or PA</td>
<td>$S_{N2}$</td>
</tr>
<tr>
<td>2</td>
<td>Primary, unbranched</td>
<td>Yes</td>
<td>No</td>
<td>PP or PA</td>
<td>$S_{N2}$</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Yes</td>
<td>Yes, unbranched</td>
<td>PP or PA</td>
<td>$S_{N2}$</td>
</tr>
<tr>
<td>4</td>
<td>Primary with $\beta$-substitution</td>
<td>Yes</td>
<td>Yes, unbranched</td>
<td>PP or PA</td>
<td>$E2 + S_{N2}$</td>
</tr>
<tr>
<td>5</td>
<td>Any primary</td>
<td>Yes</td>
<td>Yes, branched</td>
<td>PP or PA</td>
<td>$E2 + S_{N2}$</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>No</td>
<td>No</td>
<td>PP or PA</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Secondary</td>
<td>Yes</td>
<td>Yes</td>
<td>PP or PA</td>
<td>$E2$; some $S_{N2}$ with isopropyl halides; only E2 with a branched base</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>PA</td>
<td>$S_{N2}$</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>No</td>
<td>No</td>
<td>PP</td>
<td>$S_{N1-E1}$</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>No</td>
<td>No</td>
<td>PA</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

**9.7 Summary of Substitution and Elimination Reactions of Alkyl Halides**
## Summary of Substitution and Elimination

### Reactions of Alkyl Halides

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Alkyl halide structure</th>
<th>Good nucleophile?</th>
<th>Strong Brønsted base?</th>
<th>Type of solvent?*</th>
<th>Major reaction(s) expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Tertiary</td>
<td>Yes</td>
<td>Yes</td>
<td>PP or PA</td>
<td>E2</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>PP</td>
<td>$S_N^1$–$E_1$</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>PA</td>
<td>no reaction, or very slow $S_N^2$</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>No</td>
<td>No</td>
<td>PP</td>
<td>$S_N^1$–$E_1$</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>No</td>
<td>No</td>
<td>PA</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

### 9.7 Summary of Substitution and Elimination Reactions of Alkyl Halides
\(\alpha\)-Elimination Reactions

- Alkyl halides with no \(\beta\)-H’s, but an \(\alpha\)-H undergo a different elimination process

\[
(CH_3)_3C\overset{\bullet}{-}\overset{\bullet}{H}\overset{\bullet}{\longrightarrow}^{C}CCl_3 \quad \overset{\bullet}{(CH_3)_3C-OH} + \overset{\bullet}{-}CCl_3
\]

- This is an example of a carbene, a species with a divalent carbon atom

9.8 Carbenes and Carbenoids
Carbenes

• Carbon lacks an octet = electron deficient
• The lone pair can act as a nucleophile
• Hence, carbenes are simultaneously nucleophilic and electrophilic
Cyclopropane Formation from Carbenes

\[
\text{HCCl}_3 + (\text{CH}_3)_3\text{C} = \text{O}^- \text{K}^+ + (\text{CH}_3)_2\text{C} = \text{CH}_2 \rightarrow \text{Cl} \quad \text{Cl} \\
\text{chloroform} \quad \text{potassium} \quad \text{2-methylpropene} \\
\text{tert-butoxide} \quad \text{1,1-dichloro-} \quad 2,2\text{-dimethylcyclopropane}
\]

9.8 Carbenes and Carbenoids
Cyclopropane Formation from Carbenes

- Due to the concerted mechanism the stereochemistry of the starting alkene is preserved
The Simmons-Smith Reaction

• Cyclopropanes without halogens can also be prepared

\[
\text{cyclohexene} + \text{methylene iodide} \xrightarrow{\text{Zn–Cu couple}} \text{bicyclo[4.1.0]heptane (norcarane) (59\% yield)} + \text{ZnI}_2
\]

• A carbenoid is a reagent that is not a free carbene but has carbene-like reactivity

9.8 Carbenes and Carbenoids
The Simmons-Smith Reaction

• Similarly, the stereochemistry of the starting alkene is preserved

\[
\begin{align*}
\text{cis-3-hexene} & \quad + \quad \text{CH}_2\text{I}_2 & \quad \xrightarrow{\text{Zn-Cu}} & \quad \text{cis-1,2-diethylcyclopropane} \\
\text{trans-3-hexene} & \quad + \quad \text{CH}_2\text{I}_2 & \quad \xrightarrow{\text{Zn-Cu}} & \quad \text{trans-1,2-diethylcyclopropane}
\end{align*}
\]

9.8 Carbenes and Carbenoids