CHAPTER 7

Further Reactions of Haloalkanes:
Unimolecular Substitution and Pathways of Elimination
The rate of $S_N2$ reactions decrease dramatically as the reaction center changes from primary to secondary to tertiary.

This is true only for bimolecular substitution.

Secondary and tertiary halides can be substituted, however, the mechanism is different.

Consider the reaction of 2-bromo-2-methylpropane and water.

When a substrate undergoes substitution by the solvent, the process is called solvolysis. If the solvent is water, the process is hydrolysis.

Water is the nucleophile, even though its nucleophilic capacity is low.
2-Bromopropane undergoes a similar reaction, but more slowly.

1-Bromopropane, bromoethane, and bromomethane do not react well under these conditions.

Solvolysis also occurs in alcohol solvents:
The following kinetic data demonstrates that the order of reactivity is reversed from that found under typical $S_{N2}$ conditions:

If the order of reactivity is different, a mechanism other than $S_{N2}$ must be involved.

**Table 7-1**

<table>
<thead>
<tr>
<th>Bromoalkane</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{Br}$</td>
<td>1</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{Br}$</td>
<td>1</td>
</tr>
<tr>
<td>$(\text{CH}_3)_2\text{CHBr}$</td>
<td>12</td>
</tr>
<tr>
<td>$(\text{CH}_3)_3\text{CB}$</td>
<td>$1.2 \times 10^6$</td>
</tr>
</tbody>
</table>
The rate law for the solvolysis of 2-bromo-2-methylpropane by water in formic acid (polar, low nucleophilicity) has been determined by varying the concentrations of the two reactants and measuring the rate of solvolysis.

The rate law consistent with the kinetic data depends only on the halide concentration, not the water concentration:

$$\text{Rate} = k[(\text{CH}_3)_3\text{CBr}] \text{ mol L}^{-1} \text{ s}^{-1}$$

To account for this kind of behavior, it is necessary to postulate a mechanism consisting of 2 or more steps having an initial rate-determining step, or slowest step which does not involve a water molecule.

The sum of all of the steps in the proposed mechanism must add up to the observed overall reaction as shown in the stoichiometric equation.
The mechanism of solvolysis includes carbocation formation.

The mechanism for the hydrolysis of 2-bromo-2-methylpropane occurs by a unimolecular nucleophilic substitution, or $S_{N}1$ reaction.

Only the haloalkane participates in the rate determining step.

The mechanism consists of three steps:

Step 1: Dissociation of the haloalkane to an alkyl cation and bromide:
Step 2: An immediate reaction of the 1,1-dimethylethyl cation (a powerful electrophile) with a water molecule (a nucleophilic attack on the electron deficient carbon).

The product is an alkyloxonium ion, which is the conjugate acid of the final product, 2-methyl-2-propanol.
Step 3: The alkyloxonium ion (a strong acid) is finally deprotonated by another water molecule to produce the final product.

![Deprotonation reaction](image)
Comparing the potential energy diagrams of an $S_{N}2$ reaction and an $S_{N}1$ reaction, one can see that the $S_{N}2$ reaction has only one transition state, whereas the $S_{N}1$ reaction has three:

Of the three transition states in the $S_{N}1$ reaction, the first has the highest energy because it represents a charge separation. The remaining steps have lower transition state energies and occur more rapidly than the rate-limiting first step.
Stereochemical Consequences of $S_N1$ Reactions

The transition state in a $S_N1$ substitution reaction contains an achiral, planar, $sp^2$ carbocation.

Optically active secondary or tertiary haloalkanes produce a racemic mixture of product molecules for many solvolyses.

The formation of a racemic mixture from optically active substrates is strong evidence that a symmetrical, achiral species exists as an intermediate in the reaction sequence.
Polar solvents accelerate the $S_N 1$ reaction.

The heterolytic cleavage of the C-X bond in an $S_N 1$ reaction involves a highly polarized transition state, whereas the transition state in an $S_N 2$ reaction the charges are dispersed rather than separated:

As the polarity of the solvent is increased, charge separation is stabilized, and the rates of $S_N 1$ reactions increase.
The stabilization of the transition state in a $S_{N}1$ reaction increases greatly when the polar solvent is changed from aprotic to protic.

This is illustrated by the hydrolysis of 2-bromo-2-methylpropane:

$$(\text{CH}_3)_3\text{CBr} \overset{100\% \text{ H}_2\text{O}}{\longrightarrow} (\text{CH}_3)_3\text{COH} + \text{HBr}$$

Relative rate: 400,000

$$(\text{CH}_3)_3\text{CBr} \overset{90\% \text{ propanone (acetone), 10\% H}_2\text{O}}{\longrightarrow} (\text{CH}_3)_3\text{COH} + \text{HBr}$$

Water stabilizes the transition state in this reaction by hydrogen bonding to the leaving group.

In an $S_{N}2$ reaction, the solvent effect is on the nucleophile. Aprotic solvents accelerate these reactions.
The $S_{N\text{1}}$ reaction speeds up with better leaving groups.

Since the leaving group is involved in the rate determining step in an $S_{N\text{1}}$ reaction, the nature of the leaving group strongly affects the reaction rate. Sulfonates are particularly good leaving groups.

Relative Rate of Solvolysis of R-X (R = Tertiary Alkyl)

$$X = -\text{OSO}_2R' > -\text{I} > -\text{Br} > -\text{Cl}$$
The strength of the nucleophile affects the product distribution but not the reaction rate.

Since the rate determining step does not involve the nucleophile, changing the nucleophile does not affect the reaction rate of an S_N1 reaction.

However, if 2 or more nucleophiles are present, they may compete in attacking the carbocation intermediate and a product distribution may be obtained.

**Competing Nucleophiles in the S_N1 Reaction**

\[
\begin{align*}
(CH_3)_3CCl + H_2O & \xrightarrow{k_i \text{ Rate determining}} (CH_3)_3C^+ + Cl^- + \text{Calcium formate} \\
(CH_3)_2COH + HCl & \rightarrow (CH_3)_3COCH + (CH_3)_3CaCl_2 \text{ (1,1-Dimethylethyl formate)}
\end{align*}
\]
Effect of the Alkyl Group on the $S_N$1 Reaction: Carbocation Stability

In the reaction of haloalkanes with nucleophiles, only secondary and tertiary systems can form carbocations.

Tertiary halides transform only by the $S_N$1 mechanism.

Secondary halides transform by the $S_N$1 or $S_N$2 mechanism depending upon conditions.

Primary halides transform only by the $S_N$2 mechanism.
Carbocation stability increases from primary to secondary to tertiary.

The observed mechanism for nucleophilic substitution of haloalkanes depends upon two factors concerning the carbocation:

- Steric hindrance
- Stabilization

Both factors increase in going from primary to tertiary carbocations:

Tertiary  >  Secondary  >  Primary
(CH\textsubscript{3})\textsubscript{3}C\textsuperscript{+}  CH\textsubscript{3}CHCH\textsuperscript{+}HCH\textsubscript{3}  CH\textsubscript{3}CH\textsubscript{2}CH\textsubscript{2}C\textsuperscript{+}H\textsubscript{2}
Hyperconjugation stabilizes positive charge.

The positive charge on a carbocation is stabilized in the same manner as for radical stabilization, hyperconjugation.

Hyperconjugation involves overlap of a p orbital on the carbocation with a neighboring bonding molecular orbital, for instance, a C-H or C-C bond.
The tertiary butyl system is so highly stabilized that it can be isolated, crystallized and characterized by X-ray diffraction measurements.
Secondary systems undergo both $S_{N1}$ and $S_{N2}$ reactions.

In secondary haloalkane systems, either $S_{N1}$ or $S_{N2}$ substitution occurs depending upon:

- Solvent
- Leaving group
- Nucleophile

A very good leaving group, poor nucleophile, and a polar protic solvent favor $S_{N1}$.

A reasonable leaving group, high concentration of a good nucleophile, and a polar aprotic solvent favor $S_{N2}$. 
The reactivity of haloalkanes towards nucleophiles can be summarized:

**TABLE 7-2** Reactivity of R-X in Nucleophilic Substitutions: R-X + Nu\(^-\) → R-Nu + X\(^-\)

<table>
<thead>
<tr>
<th>R</th>
<th>(S^1)</th>
<th>(S^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)</td>
<td>Not observed in solution (methyl cation too high in energy)</td>
<td>Frequent; fast with good nucleophiles and good leaving groups</td>
</tr>
<tr>
<td>Primary</td>
<td>Not observed in solution (primary carbocations too high in energy(^a))</td>
<td>Frequent; fast with good nucleophiles and good leaving groups, slow when branching at C2 is present in R</td>
</tr>
<tr>
<td>Secondary</td>
<td>Relatively slow; best with good leaving groups in polar protic solvents</td>
<td>Relatively slow; best with high concentrations of good nucleophiles in polar aprotic solvents</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Frequent; particularly fast in polar, protic solvents and with good leaving groups</td>
<td>Extremely slow</td>
</tr>
</tbody>
</table>

\(^a\)Exceptions are resonance-stabilized carbocations; see Chapter 14.

**Substitution of a Secondary Haloalkane Under \(S^2\) Conditions**

\[
\begin{align*}
\text{CH}_3\text{C-Br}^- + \text{CH}_3\text{Si}^- \xrightarrow{\text{Propanone (acetone)}} \text{CH}_3\text{Si-CH}_3 + \text{Br}^- \\
\end{align*}
\]

**Substitution of a Secondary Substrate Under \(S^1\) Conditions**

\[
\begin{align*}
\text{H}_3\text{C-C-O-SCF}_3 \xrightarrow{\text{H}_2\text{O}} \text{H}_3\text{C-C-OH} + \text{CF}_3\text{SO}_3\text{H}
\end{align*}
\]
An alternative reaction of nucleophiles towards haloalkanes is the abstraction of a proton and loss of halide, rather than the addition of the nucleophile.

The abstraction of a proton leads to the formation of a double bond. This process is called elimination.
When 2-bromo-2-methyl propane is dissolved in methanol, a solvolysis reaction occurs ($S\textsubscript{N}1$). However, a second minor reaction (20%) also occurs forming an alkene.

Kinetic analysis shows that the rate of alkene formation depends only upon the starting haloalkane concentration and is thus 1\textsuperscript{st} order.

This reaction is termed “E1” and has the same rate-determining step as the $S\textsubscript{N}1$ reaction: the formation of a carbocation.
The orbital picture of the proton abstraction looks like:

The complete mechanism is:

The E1 Reaction Mechanism

$$\text{CH}_3\text{C}^\text{Br} \overset{\text{CH}_3\text{OH}}{\rightleftharpoons} \text{Br}^- + \text{H}_3\text{C}^+\text{C}^\text{H}_3 \underset{\cdot\cdot\cdot}{\text{HOCH}_3} \rightarrow \text{H}_3\text{C}\text{C}^\text{C}^=\text{C}^\text{H}_3 + \text{H}^+\text{OCH}_3$$
There are 9 possible protons which could be abstracted by the methanol molecule, however, each would lead to the same product.

Other substrates may give more than one product:
The nature of the leaving group has no effect on the ratio of substitution to elimination.

<table>
<thead>
<tr>
<th>X in (CH₃)₃CX</th>
<th>Ratio S₉₁:E₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>95:5</td>
</tr>
<tr>
<td>Br</td>
<td>95:5</td>
</tr>
<tr>
<td>I</td>
<td>96:4</td>
</tr>
</tbody>
</table>

At low base concentration, addition of base only has a small effect on the product ratio, however at high concentrations of a strong base, the ratio of elimination to substitution rises greatly.
7-7  Bimolecular Elimination: E2

**Strong bases effect bimolecular elimination.**

At higher concentrations of strong base, the rate of alkene formation becomes proportional to both the starting halide and the base.

Under these conditions the second order kinetics are called bimolecular elimination or E2.

\[
(CH_3)_3 CCl + Na^+ OH^- \xrightarrow{k} \overset{\cdot}{CH_2} = C(CH_3)_2 + NaCl + H_2O
\]

rate = \( k[(CH_3)_3 CCl][\overset{\cdot}{OH}] \) mol L\(^{-1}\) s\(^{-1}\)

Strong bases (OH\(^-\), RO\(^-\)) can attack haloalkanes before carbocation formation.

The hydrogen extracted is on a carbon next to the leaving group.
\( S_N2 \) and E2 reactions compete when the substrate is a secondary or primary system.

\[
\text{Compition Between E2 and } S_N2 \text{ Reactions}
\]

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{CH}_3\text{O}^-\text{Na}^+, \text{CH}_3\text{OH}} \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 + \text{H}_3\text{C} \quad \begin{array}{c}
\text{C=CH} \\
\text{H} \\
\text{H}_3\text{C} \\
\text{H}
\end{array}
\]

92% 1-Methoxypropane

8% Propene
E2 reactions proceed in one step.

The E2 reaction proceeds in a single step:

Three changes take place in a single step:

• Deprotonation by base
• Departure of leaving group
• Rehybridization of carbon center
Experiments elucidate the detailed structure of the E2 transition state.

Evidence supporting the E2 transition state:

• Both the haloalkane and base must take part in the rate-determining step since it is a 2$^{nd}$ order reaction.

• Better leaving groups result in faster eliminations. (Implies that the bond to the leaving group is partially broken in the transition state).

• Stereochemistry – the C-H and C-X bonds must be in an anti relation for the reaction to be fast.

*Anti Elimination Occurs Readily for cis- but Not for trans-1-Bromo-4-(1,1-dimethylethyl)cyclohexane*
Weakly basic nucleophiles give substitution.

Good nucleophiles that are weaker bases than $\text{OH}^-$:

$I^-, \text{Br}^-, \text{RS}^-, \text{N}_3^-, \text{RCOO}^-, \text{PR}_3$

- $S_N^2$ products with primary and secondary halides
- $S_N^1$ products with tertiary substrates
Weak nucleophiles react at appreciable rates only with secondary and tertiary halides (capable of $S_N1$ reactions). Unimolecular elimination is usually minor.
Strongly basic nucleophiles give more elimination as steric bulk increases.

Consider the reaction of sodium ethoxide (strong base) with several halides:

Primary halides with strongly basic nucleophiles give mostly $S_N2$ products.

Branched halides with strongly basic nucleophiles give about 50/50 $S_N2$ and E2 products.

Tertiary halides with strongly basic nucleophiles give exclusive E2 products. With neutral or weakly basic nucleophiles $S_N1$ and E1 pathways compete.
Sterically hindered basic nucleophiles favor elimination.

When the bulk of a substituted nucleophile hinders attack at the electrophilic carbon, elimination may predominate even with primary systems.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{(\text{CH}_3)_3\text{CO}^-\text{K}^+, (\text{CH}_3)_3\text{COH}} -\text{HBr} \rightarrow \text{CH}_3\text{CH}_2\text{CH}==\text{CH}_2 + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OC(\text{CH}_3)_3}
\]

85% 15%

Two examples of often used sterically hindered bases are:

When used in elimination reactions they are often dissolved in their conjugate acids.
In summary, three factors affect the competition between substitution and elimination:

Factor 1. Base strength of the nucleophile

- Weak bases: substitution more likely
  - H₂O, ROH, PR₃, halides, RS⁻, N₃⁻, NC⁻, RCOO⁻
  - (H₂O and ROH do not react with simple primary halides)
- Strong bases: likelihood of elimination increased
  - HO⁻, RO⁻, H₂N⁻, R₂N⁻

Factor 2. Steric hindrance around the reacting carbon

- Sterically unhindered: substitution more likely
  - primary haloalkanes
- Sterically hindered: likelihood of elimination increased
  - branched primary, secondary, tertiary haloalkanes
Factor 3. Steric hindrance in the nucleophile (strong base)

- Sterically unhindered: substitution may occur
  \[ \text{HO}^-, \text{CH}_3\text{O}^-, \text{CH}_3\text{CH}_2\text{O}^-, \text{H}_2\text{N}^- \]
- Sterically hindered: elimination strongly favored
  \[ \text{(CH}_3\text{)}_3\text{CO}^-, [(\text{CH}_3\text{)}_2\text{CH}]_2\text{N}^- \]

For predictive purposes, treat the 3 factors as having equal importance and let the “majority rule.”
Summary of Reactivity of Haloalkanes

• Primary haloalkanes
  • Unhindered: always bimolecular and almost always $S_N^2$. Sterically hindered strong bases may result in E2 reactions.
  • If branching is introduced, good nucleophiles still react predominately by $S_N^2$. Strong bases tend to react by $E_2$.
  • Primary haloalkanes react very slowly with poor nucleophiles.

• Secondary haloalkanes
  • Depending upon conditions, secondary alkanes may react by any of the 4 mechanisms: $S_N^1$, $E_1$, $S_N^2$, $E_2$.
    • Good nucleophiles favor $S_N^2$
    • Strong bases result in $E_2$
    • Weakly nucleophilic polar media give $S_N^1$ and $E_1$
• Tertiary haloalkanes
  • Concentrated strong base yields E2 products.
  • Non-basic media yields $S_N1$ products, accompanied by E1 products.
  • $S_N2$ is not observed.
7  Important Concepts

1. **Unimolecular Substitution in Polar Media** –
   - Secondary haloalkanes: slow
   - Tertiary haloalkanes: fast
   - When the solvent is the nucleophile, the process is called solvolysis.

2. **Rate-Determining Step in Unimolecular Substitution** –
   - Dissociation of the C-X bond to form a carbocation intermediate
   - Added strong nucleophile changes the product, but not the reaction rate

3. **Carbocation Stabilization by Hyperconjugation** –
   - Tertiary > Secondary
   - Primary and methyl unstable
7 Important Concepts

4. **Racemization** – Often occurs upon unimolecular substitution at a chiral carbon.

5. **Unimolecular Elimination** – Alkene formation accompanies substitution in secondary and tertiary system.

6. **Bimolecular Elimination** – May result from high concentrations of strong base. The elimination involves the *anti* conformational arrangement of the leaving group and the extracted hydrogen.

7. **Substitution Favored** – By unhindered substrates and small, less basic nucleophiles

8. **Elimination Favored** – By hindered substrates and bulky, more basic nucleophiles