Chapter 5

• Nucleophilic aliphatic substitution mechanism

by

G. DEEPA
• Introduction

• The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge
  – In alkyl halides the $\delta^+ \delta^-$ causes the carbon to become activated to substitution reactions with nucleophiles

<table>
<thead>
<tr>
<th>C—X Bond length (Å)</th>
<th>1.39</th>
<th>1.78</th>
<th>1.93</th>
<th>2.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>C—X Bond strength (kJ mol$^{-1}$)</td>
<td>472</td>
<td>350</td>
<td>293</td>
<td>239</td>
</tr>
</tbody>
</table>
**Nucleophilic Substitution Reactions**

- In this reaction a nucleophile is a species with an unshared electron pair which reacts with an electron deficient carbon.

**Leaving group**

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

**Heterolysis occurs here.**

- Examples of nucleophilic substitution:
  
  \[
  \text{HO}^- + \text{CH}_3\text{I} \rightarrow \text{CH}_3\text{OH} + \text{I}^-
  \]
  
  \[
  \text{CH}_3\text{O}^- + \text{CH}_3\text{CH}_2\text{Br} \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_3 + \text{Br}^-
  \]
  
  \[
  \text{I}^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{I} + \text{Cl}^-
  \]
• **Nucleophile**
  - The nucleophile reacts at the electron-deficient carbon.

![Chemical reaction diagram showing nucleophile, alkyl halide, and alkyl oxonium ion formation.](image)

This is the positive center that the nucleophile seeks.
The electronegative halogen polarizes the C—X bond.

\[
\ce{H-O: + R-X: + H2O -> H-O+R + :X:- + H3O+}
\]

Nucleophile  Alkyl halide  Alkyl oxonium ion
• Leaving Group

• A leaving group is a substituent that can leave as a relatively stable entity

• It can leave as an anion or a neutral species

\[
\text{Nu}^\cdot + R-L \rightarrow R-Nu + :L^- \]

\[
\begin{align*}
\text{HO}^- + \text{CH}_3-\text{Cl}^- & \rightarrow \text{CH}_3-\text{OH}^- + :\text{Cl}^- \\
\text{H}_3\text{N}^- + \text{CH}_3-\text{Br}^- & \rightarrow \text{CH}_3-\text{NH}_3^+ + :\text{Br}^- \\
\end{align*}
\]

\[
\text{Nu}^+ + R-L^+ \rightarrow R-Nu^+ + :L
\]

Specific Example

\[
\begin{align*}
\text{CH}_3-\text{O}^- + \text{CH}_3-\text{O}^+\text{H}^- & \rightarrow \text{CH}_3-\text{O}^+\text{CH}_3^- + :\text{O}^-\text{H}^- \\
\end{align*}
\]
• **Kinetics of a Nucleophilic Substitution Reaction: An $S_N2$ Reaction**
  
  • The initial rate of the following reaction is measured

  \[
  \begin{align*}
  \text{CH}_3\text{Cl} + \text{OH}^- & \xrightarrow{60^\circ\text{C}} \text{CH}_2\text{OH} + \text{Cl}^- \\
  \text{H}_2\text{O}
  \end{align*}
  \]

  • The rate is directly proportional to the initial concentrations of both methyl chloride and hydroxide

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Initial [CH$_3$Cl]</th>
<th>Initial [OH$^-$]</th>
<th>Initial Rate (mol L$^{-1}$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0010</td>
<td>1.0</td>
<td>$4.9 \times 10^{-7}$</td>
</tr>
<tr>
<td>2</td>
<td>0.0020</td>
<td>1.0</td>
<td>$9.8 \times 10^{-7}$</td>
</tr>
<tr>
<td>3</td>
<td>0.0010</td>
<td>2.0</td>
<td>$9.8 \times 10^{-7}$</td>
</tr>
<tr>
<td>4</td>
<td>0.0020</td>
<td>2.0</td>
<td>$19.6 \times 10^{-7}$</td>
</tr>
</tbody>
</table>

  • The rate equation reflects this dependence

  \[
  \text{Rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]
  \]

  • $S_N2$ reaction: substitution, nucleophilic, 2nd order (bimolecular)
• A Mechanism for the $S_N2$ Reaction

The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

- It is an unstable entity with a very brief existence ($10^{-12}$ s)
- In the transition state of this reaction bonds are partially formed and broken
  - Both chloromethane and hydroxide are involved in the transition state and this explains why the reaction is second order
• Transition State Theory: Free-Energy Diagrams
  
  • Exergonic reaction: negative $\Delta G^\circ$ (products favored)
    
    \[
    \text{CH}_3\text{Cl} + \text{OH}^- \rightarrow \text{CH}_3\text{OH} + \text{Cl}^- \quad \Delta G^\circ = -100 \text{ kJ mol}^{-1}
    \]
    
  • Endergonic reaction: positive $\Delta G^\circ$ (products not favored)
    
  • The reaction of chloromethane with hydroxide is highly exergonic
    
    \[
    \Delta G^\circ = -RT \ln K_{eq}
    \]
    
    \[
    \ln K_{eq} = \frac{-\Delta G^\circ}{RT}
    \]
    
    \[
    \ln K_{eq} = \frac{-(-100 \text{ kJ mol}^{-1})}{0.00831 \text{ kJ K}^{-1} \text{ mol}^{-1} \times 333 \text{ K}} = 36.1
    \]
    
    \[
    K_{eq} = 5.0 \times 10^{15}
    \]
• An energy diagram of a typical $S_{N2}$ reaction
  – An energy barrier is evident because a bond is being broken in going to the transition state (which is the top of the energy barrier)
  – The difference in energy between starting material and transition state is the free energy of activation ($\Delta G^\ddagger$)
  – The difference in energy between starting molecules and products is the free energy change of the reaction, $\Delta G^\circ$
• In a highly endergonic reaction of the same type the energy barrier will be even higher ($\Delta G^\ddagger$ is very large)
• There is a direct relationship between $\Delta G^\ddagger$ and the temperature of a reaction
  
  – The higher the temperature, the faster the rate

  \[ k = k_0 e^{-\Delta G^\ddagger/RT} \]

  – Near room temperature, a 10°C increase in temperature causes a doubling of rate
  – Higher temperatures cause more molecules to collide with enough energy to reach the transition state and react
• The energy diagram for the reaction of chloromethane with hydroxide:

- A reaction with $\Delta G^\ddagger$ above 84 kJ mol$^{-1}$ will require heating to proceed at a reasonable rate
- This reaction has $\Delta G^\ddagger = 103$ kJ mol$^{-1}$ so it will require heating
• The Stereochemistry of $S_N 2$ Reactions
  • Backside attack of nucleophile results in an inversion of configuration.

\[
\text{(R)-(−)-2-Bromooctane} \quad \text{[α]}_D^{\text{o}} = -34.25^\circ \\
\text{(S)-(−)-2-Octanol} \quad \text{[α]}_D^{\text{o}} = +9.90^\circ
\]

Enantiomeric purity = 100%

• In cyclic systems, a cis compound can react and become a trans product.

\[
\text{cis-1-Chloro-3-methylcyclopentane} \quad \text{trans-3-Methylcyclopentanol}
\]

An inversion of configuration
The Reaction of \( \text{tert}-\text{Butyl Chloride} \) with \( \text{Hydroxide Ion: An} \) \( S_N1 \) Reaction

- \( \text{tert}-\text{Butyl chloride} \) undergoes substitution with hydroxide.
- The rate is independent of hydroxide concentration and depends only on concentration of \( \text{tert}-\text{butyl chloride} \).

\[
\text{(CH}_3\text{)}_3\text{C}-\text{Cl} + \text{OH}^- \xrightarrow{\text{acetone, } \text{H}_2\text{O}} \text{(CH}_3\text{)}_3\text{C}-\text{OH} + \text{Cl}^-
\]

\[
\text{Rate} \propto [(\text{CH}_3\text{)}_3\text{CCl}]
\]

\[
\text{Rate} = k[(\text{CH}_3\text{)}_3\text{CCl}]
\]

- \( S_N1 \) reaction: Substitution, nucleophilic, 1st order (unimolecular)
  - The rate depends only on the concentration of the alkyl halide.
  - Only the alkyl halide (and not the nucleophile) is involved in the transition state of the step that controls the rate.
• Multistep Reactions and the Rate-Determining Step

• In multistep reactions, the rate of the slowest step will be the rate of the entire reaction.

• This is called the rate-determining step.

• In the case below $k_1 << k_2$ or $k_3$ and the first step is rate determining.
• A Mechanism for the $S_{N1}$ Reaction (next slide)

• Step 1 is rate determining (slow) because it requires the formation of unstable ionic products
• In step 1 water molecules help stabilize the ionic products
Reaction:

$$\text{(CH}_3\text{)}_3\text{CCl} + 2 \text{H}_2\text{O} \rightarrow \text{(CH}_3\text{)}_3\text{COH} + \text{H}_3\text{O}^+ + \text{Cl}^-$$

Mechanism:

**Step 1**

Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon. This slow step produces the relatively stable $\text{3}^+\text{t}$ carbocation and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.

**Step 2**

A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons. The product is a tert-butyloxonium ion (or protonated tert-butyl alcohol).

**Step 3**

A water molecule acting as a Brønsted base accepts a proton from the tert-butyloxonium ion. The products are tert-butyl alcohol and a hydronium ion.

$\Delta G^{1(3)}$ is much larger than $\Delta G^{1(2)}$ or $\Delta G^{1(3)}$, hence this is the slowest step.
- Carbocations
  - A carbocation has only 6 electrons, is \( sp^2 \) hybridized and has an empty p orbital.

- The more highly substituted a carbocation is, the more stable it is.
  - The more stable a carbocation is, the easier it is to form.
Hyperconjugation stabilizes the carbocation by donation of electrons from an adjacent carbon-hydrogen or carbon-carbon σ bond into the empty p orbital.

- More substitution provides more opportunity for hyperconjugation.
The Stereochemistry of $S_N1$ Reactions

- When the leaving group leaves from a stereogenic center of an optically active compound in an $S_N1$ reaction, racemization will occur
  - This is because an achiral carbocation intermediate is formed

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{C}^-\text{Br} & \xrightleftharpoons[acetone]{\text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{C}^-\text{OH} + \text{HO}^-\text{C}^+\text{CH}_2\text{CH}_2\text{CH}_3 + \text{HBr} \\
\text{(S)-3-Bromo-3-methylhexane} & \quad \text{(S)-3-Methyl-3-hexanol} \\
\text{(optically active)} & \quad \text{(optically inactive, a racemic form)}
\end{align*}
\]
The carbocation has a trigonal planar structure and is achiral.

Front- and back-side attacks take place at equal rates, and the product is formed as a racemic mixture.
• **Solvolysis**

• A molecule of the solvent is the nucleophile in a substitution reaction

  - If the solvent is water, the reaction is a hydrolysis

\[
\begin{align*}
(CH_3)_3C-Br + H_2O & \rightarrow (CH_3)_3C-OH + HBr \\
(CH_3)_3C-Cl + CH_3OH & \rightarrow (CH_3)_3C-OCH_3 + HCl \\
(CH_3)_3C-Cl + HCOH & \rightarrow (CH_3)_3C-OCH + HCl
\end{align*}
\]
• Factors Affecting the Rate of $S_N1$ and $S_N2$ Reactions
  – The Effects of the Structure of the Substrate
  – $S_N2$ Reactions
    - Methyl > primary > secondary >> (ternary — unreactive)
    - In $S_N2$ reactions alkyl halides show the following general order of reactivity

- ![Diagram of $S_N2$ reactions with relative rates](image)
– *S<sub>N</sub>1* reactions
  - Generally only tertiary halides undergo *S<sub>N</sub>1* reactions because only they can form relatively stabilized carbocations

– The Hammond-Leffler Postulate
  - The transition state for an exergonic reaction looks very much like starting material
  - The transition state for an endergonic reaction looks very much like product
  - Generally the transition state looks most like the species it is closest to in energy
• In the first step of the $S_{N1}$ reaction the transition state looks very much like carbocation.
• The carbocation-like transition state is stabilized by all the factors that stabilize carbocations.
• The transition state leading to tertiary carbocations is much more stable and lower in energy than...
– The Effects of the Concentration and Strength of Nucleophile

– $S_{N1}$ Reaction
  - Rate does not depend on the identity or concentration of nucleophile

– $S_{N2}$ Reaction
  - Rate is directly proportional to the concentration of nucleophile
  - Stronger nucleophiles also react faster
    - A negatively charged nucleophile is always more reactive than its neutral conjugate acid
    - When comparing nucleophiles with the same nucleophilic atom, nucleophilicities parallel basicities
      - $RO^- > HO^- \gg RCO_2^- > ROH > H_2O$
  - Methoxide is a much better nucleophile than methanol
Solvent Effects on $S_N2$ Reactions: Polar Protic and Aprotic Solvents

- Polar Protic Solvents
  - Polar solvents have a hydrogen atom attached to strongly electronegative atoms
  - These solvents solvate nucleophiles and make them less reactive
  - Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents

\[
I^- > Br^- > Cl^- > F^- 
\]

- Larger nucleophiles are also more polarizable and can donate more electron density
- Relative nucleophilicity in polar solvents:

\[
SH^- > CN^- > I^- > OH^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O 
\]
• Polar Aprotic Solvents
  - Polar aprotic solvents do not have a hydrogen attached to an electronegative atom

  - They solvate cations well but leave anions unsolvated because positive centers in the solvent are sterically hindered

  - Polar protic solvents lead to generation of “naked” and very reactive nucleophiles
  - Trends for nucleophilicity are the same as for basicity
  - They are excellent solvents for $S_N2$ reactions

\[
F^- > Cl^- > Br^- > I^-
\]
Solvent Effects on $S_{N1}$ Reactions: The Ionizing Ability of the Solvent

- Polar protic solvents are excellent solvents for $S_{N1}$ reactions.
- Polar protic solvents stabilize the carbocation-like transition state leading to the carbocation, thus lowering $\Delta G^\ddagger$.

\[
(CH_3)_3C-Cl \rightarrow [(CH_3)_3C\underset{\delta^+}{\overset{\delta^-}{\cdots}}Cl]^\ddagger \rightarrow (CH_3)_3C^+ + Cl^- \]

- Water-ethanol and water-methanol mixtures are most common.
The Nature of the Leaving Group

- The best leaving groups are weak bases which are relatively stable
  - The leaving group can be an anion or a neutral molecule
  
- Leaving group ability of halides:
  \[ I^- > Br^- > Cl^- > F^- \]

- This trend is opposite to basicity:
  \[ F^- >> Cl^- > Br^- > I^- \]

- Other very weak bases which are good leaving groups:
  - The poor leaving group hydroxide can be changed into the good leaving group water by protonation
Summary $S_{N1}$ vs. $S_{N2}$

- In both types of reaction alkyl iodides react the fastest because of superior leaving group ability.

$R-I > R-Br > R-Cl$  \( S_{N1} \) or \( S_{N2} \)

<table>
<thead>
<tr>
<th>Factor</th>
<th>$S_{N1}$</th>
<th>$S_{N2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>$3^\circ$ (requires formation of a relatively stable carbocation)</td>
<td>Methyl $&gt; 1^\circ &gt; 2^\circ$ (requires unhindered substrate)</td>
</tr>
<tr>
<td>Nucleophile</td>
<td>Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolyis)</td>
<td>Strong Lewis base, rate favored by high concentration of nucleophile</td>
</tr>
<tr>
<td>Solvent</td>
<td>Polar protic (e.g., alcohols, water)</td>
<td>Polar aprotic (e.g., DMF, DMSO)</td>
</tr>
<tr>
<td>Leaving group</td>
<td>I $&gt; Br &gt; Cl &gt; F$ for both $S_{N1}$ and $S_{N2}$</td>
<td>(the weaker the base after the group departs, the better the leaving group)</td>
</tr>
</tbody>
</table>
• Organic Synthesis: Functional Group Transformations Using $S_N2$ Reactions

\[
\begin{align*}
\text{OH}^- & \rightarrow R\text{--OH} & \text{Alcohol} \\
R'O^- & \rightarrow R\text{--OR}' & \text{Ether} \\
SH^- & \rightarrow R\text{--SH} & \text{Thiol} \\
R'S^- & \rightarrow R\text{--SR}' & \text{Thioether} \\
CN^- & \rightarrow R\text{--C=NN} & \text{Nitrile} \\
R'\text{--C=CC}^- & \rightarrow R\text{--C=C--R}' & \text{Alkyne} \\
\text{O} & \rightarrow R\text{--OCCR}' & \text{Ester} \\
R'\text{CO}^- & \rightarrow R\text{--OCCR}' & \text{Ester} \\
R_3\text{N} & \rightarrow R\text{--NR}_3 \text{X}^- & \text{Quaternary ammonium halide} \\
N_3^- & \rightarrow R\text{--N}_3 & \text{Alkyl azide}
\end{align*}
\]

(R = Me, 1°, or 2°) (X = Cl, Br, or I)

• Stereochemistry can be controlled in $S_N2$ reactions

\[
\begin{align*}
\text{N}=\text{C}^- + \text{CH}_3\text{CH}_2\text{CH}_3\text{Br} & \xrightarrow{S_N2} \text{N}=\text{C}^- \text{CH}_3 + \text{Br}^- \\
(\text{R})\text{-2-Bromobutane} & \rightarrow (\text{S})\text{-2-Methylbutanenitrile}
\end{align*}
\]
• Substitution versus Elimination
  – $S_N2$ versus $E2$

  ![Chemical reaction diagram]

  • Primary substrate
    – If the base is small, $S_N2$ competes strongly because approach at carbon is unhindered

  \[
  \text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ + \text{CH}_3\text{CH}_2\text{Br} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3 + \text{CH}_2=\text{CH}_2
  \]

<table>
<thead>
<tr>
<th></th>
<th>$S_N2$</th>
<th>$E2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction</td>
<td>90%</td>
<td>10%</td>
</tr>
</tbody>
</table>

  • Secondary substrate
    – $E2$ elimination

  \[
  \text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ + \text{CH}_3\text{CHCH}_3 \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{CHCH}_3 + \text{CH}_2=\text{CHCH}_3
  \]

<table>
<thead>
<tr>
<th></th>
<th>$S_N2$</th>
<th>$E2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction</td>
<td>21%</td>
<td>79%</td>
</tr>
</tbody>
</table>
## Overall Summary

<table>
<thead>
<tr>
<th>Factor</th>
<th>$S_N1$</th>
<th>$S_N2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>3° (requires formation of a relatively stable carbocation)</td>
<td>Methyl &gt; 1° &gt; 2° (requires unhindered substrate)</td>
</tr>
<tr>
<td>Nucleophile</td>
<td>Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolyis)</td>
<td>Strong Lewis base, rate favored by high concentration of nucleophile</td>
</tr>
<tr>
<td>Solvent</td>
<td>Polar protic (e.g., alcohols, water)</td>
<td>Polar aprotic (e.g., DMF, DMSO)</td>
</tr>
<tr>
<td>Leaving group</td>
<td>I &gt; Br &gt; Cl &gt; F for both $S_N1$ and $S_N2$ (the weaker the base after the group departs, the better the leaving group)</td>
<td></td>
</tr>
</tbody>
</table>
THANK YOU