Organic Reactions
Substitution – $S_N^2$

Dr. Sapna Gupta
Kinetics of Nucleophilic Reaction

• Rate law is order of reaction
• 0 order is when rate of reaction is unaffected by change in concentration of the reactants
• 1\textsuperscript{st} order is when rate of reaction doubles when one of the reactants is doubled
• 2\textsuperscript{nd} order is when rate of reaction quadruples when two of the reactants are doubled
• Order of reaction explains the reaction mechanism
Nucleophilic Substitution Reactions

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

• A leaving group is substituted by a nucleophile

• Examples of nucleophilic substitution

\[
\begin{align*}
\text{HO}^- + \text{CH}_3\text{I} & \rightarrow \text{CH}_3\text{OH} + \text{I}^- \\
\text{CH}_3\text{O}^- + \text{CH}_3\text{CH}_2\text{Br} & \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_3 + \text{Br}^- \\
\text{I}^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} & \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{I} + \text{Cl}^-
\end{align*}
\]
The $S_N^2$ Reaction

- $2^{\text{nd}}$ order substitution reaction
- $S =$ substitution
- $N$ (subscript) = nucleophilic
- $2 =$ (bimolecular) both nucleophile and substrate in characteristic step
- Inversion of stereochemistry occurs
An $S_N2$ Reaction

- The initial rate of the following reaction is measured

$$
\text{CH}_3\text{Cl} + \text{OH}^- \xrightarrow{60^\circ C} \text{H}_2\text{O} \quad \text{CH}_3\text{OH} + \text{Cl}^-
$$

- The rate is directly proportional to the initial concentrations of both methyl chloride (substrate) and hydroxide (nucleophile)

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Initial $[\text{CH}_3\text{Cl}]$</th>
<th>Initial $[\text{OH}^-]$</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>

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

- The rate equation reflects this dependence
- $S_N2$ reaction: substitution, nucleophilic, 2nd order (bimolecular)
A transition state is the high energy state of the reaction

- 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
**SN2 Energy Diagram**

- One-step reaction.
- Transition state is highest in energy.
Examples of Nucleophilic Substitution

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

- When a neutral nucleophile is used, the substitution product bears a positive charge.
# Uses for $S_N^2$ Reactions

- Synthesis of other classes of compounds.
- Halogen exchange reaction.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>Class of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—X + I⁻</td>
<td>R—I⁻</td>
<td>alkyl halide</td>
</tr>
<tr>
<td>R—X + OH⁻</td>
<td>R—OH</td>
<td>alcohol</td>
</tr>
<tr>
<td>R—X + OR’⁻</td>
<td>R—OR’</td>
<td>ether</td>
</tr>
<tr>
<td>R—X + SH⁻</td>
<td>R—SH</td>
<td>thiol (mercaptan)</td>
</tr>
<tr>
<td>R—X + SR’⁻</td>
<td>R—SR’</td>
<td>thioether (sulfide)</td>
</tr>
<tr>
<td>R—X + NH₃⁺</td>
<td>R—NH₃⁺X⁻</td>
<td>amine</td>
</tr>
<tr>
<td>R—X + N≡N⁻</td>
<td>R—N≡N⁻</td>
<td>azide</td>
</tr>
<tr>
<td>R—X + C≡C—R’</td>
<td>R—C≡C—R’</td>
<td>alkyne</td>
</tr>
<tr>
<td>R—X + C≡N⁻</td>
<td>R—C≡N⁻</td>
<td>nitrile</td>
</tr>
<tr>
<td>R—X + R’—COO⁻</td>
<td>R’—COO—R</td>
<td>ester</td>
</tr>
<tr>
<td>R—X + P(Ph)₃</td>
<td>[R—PPh₃]⁺⁻X⁻</td>
<td>phosphonium salt</td>
</tr>
</tbody>
</table>
Factors Affecting $S_{N2}$

1. Nucleophile Strength
2. Size of the nucleophile
3. Substrate (steric effect)
4. Leaving group
5. Effect of solvent
1) Nucleophilic Strength

• Stronger nucleophiles react faster.
• Strong bases are strong nucleophiles, but not all strong nucleophiles are basic*.
• Strength of Nu is based on:
  • **Charge**: In a conjugate acid-base pair, the base (anion) is stronger:
    \[ \text{OH}^- > \text{H}_2\text{O}, \ \text{NH}_2^- > \text{NH}_3 \]
  • **Periodicity**: Decreases left to right on the Periodic Table. More electronegative atoms less likely to form new bond:
    \[ \text{OH}^- > \text{F}^-, \ \text{NH}_3 > \text{H}_2\text{O} \]
  • **Size**: Increases down Periodic Table, as size and polarizability increase:
    \[ \text{I}^- > \text{Br}^- > \text{Cl}^- \]

* Bases are characterised by their ability to abstract a proton while nucleophiles reacts with electrophiles.
Nucleophiles

• Some examples

<table>
<thead>
<tr>
<th>strong nucleophiles</th>
<th>moderate nucleophiles</th>
<th>weak nucleophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃CH₂)₃P:</td>
<td>:Br⁻</td>
<td>:F⁻</td>
</tr>
<tr>
<td>−:S—H</td>
<td>:NH₃</td>
<td>H—O—H</td>
</tr>
<tr>
<td>:I⁻</td>
<td>CH₃—S—CH₃</td>
<td>CH₃—O—H</td>
</tr>
<tr>
<td>(CH₃CH₂)₂NH</td>
<td>:Cl⁻</td>
<td></td>
</tr>
<tr>
<td>−:C≡N</td>
<td>CH₃C—O⁻</td>
<td></td>
</tr>
<tr>
<td>(CH₃CH₂)₃N:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H—O⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃—O⁻</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2) Size of Nucleophile

- Larger nucleophiles are not good for $S_{N2}$ because they will not be able to access the electrophilic carbon.
- E.g. EtO$^-$ better than tBuO$^-$ even though tBuO$^-$ is a stronger base.

**Note: Alkoxides as Nucleophiles.**

- $\text{CH}_3\text{O}^-\text{Na}^+$, $\text{CH}_3\text{CH}_2\text{O}^-\text{K}^+$ - alkoxides are synthesized as salts – potassium or sodium. They are synthesized by dissolving solid sodium or potassium in the respective alcohol in a moisture and oxygen free environment.

  $$\text{CH}_3\text{OH} + \text{Na} \rightarrow \text{CH}_3\text{O}^-\text{Na}^+ + \text{H}_2$$

- Nomenclature: $\text{CH}_3\text{O}^-\text{Na}^+$, sodium methoxide, $\text{CH}_3\text{CH}_2\text{O}^-\text{K}^+$ potassium ethoxide, $(\text{CH}_3)_3\text{CO}^-\text{Na}^+$ sodium t-butoxide
3) Substrate: Steric Hindrance - 1

- Nucleophile approaches from the back side hence the electrophilic carbon should not be hindered.
- Best substrates for $S_N2$ are primary halides. 
  \[ 1^\circ > 2^\circ > 3^\circ \]

![Diagram showing ethyl bromide (1°), isopropyl bromide (2°), and t-butyl bromide (3°) with attack possibilities marked.](image-url)
• The more alkyl groups connected to the reacting carbon, the slower the reaction
4) Leaving Group

• Should be electron-withdrawing to provide an electrophilic carbon
• Stable once it has left (not a strong base)
• Usually halides are good LG.
• Weaker bases make best LG.
• NOTE: weaker base cannot displace stronger base in a $S_{N2}$ reaction

<table>
<thead>
<tr>
<th>Relative reactivity</th>
<th>$\text{OH}^-$, $\text{NH}_2^-$, $\text{OR}^-$</th>
<th>$\text{F}^-$</th>
<th>$\text{Cl}^-$</th>
<th>$\text{Br}^-$</th>
<th>$\text{I}^-$</th>
<th>$\text{TosO}^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;=1</td>
<td>1</td>
<td>200</td>
<td>10,000</td>
<td>30,000</td>
<td>60,000</td>
</tr>
</tbody>
</table>

Leaving group reactivity

Examples of leaving groups:

- Halides
- Sulfonate
- Sulfate
- Phosphate

- Water
- Alcohols
- Amines
- Phosphines
5) Solvents

3 kinds of solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Polar protic</th>
<th>polar aprotic</th>
<th>non polar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples</td>
<td>H₂O, CH₃OH, CH₃CH₂OH</td>
<td>DMF (dimethyl formamide), DMSO (dimethyl sulfoxide) <em>Shown below.</em></td>
<td>Hexane, Toluene, Diethyl ether, Dichloromethane</td>
</tr>
</tbody>
</table>

**Comments**

- Will form H-bonds with Nu and therefore need more energy to form transition state
- Does not form H-bond with Nu but still helps to solvate ions hence the best kind for $S_{N2}$
- Not good for $S_{N2}$ since they will not stabilize the ions formed.

*Shown below.*

![Solvent Diagram](image)
The Stereochemistry of $S_{N2}$ Reactions

- Backside attack of nucleophile results in an inversion of configuration

\[
\begin{align*}
\text{HO}^- & \quad \text{CH}_3 \quad \text{Br} & \quad \text{CH}_3 \quad \text{Br}^- \\
\text{H} & \quad \text{C}_6\text{H}_{13} & \quad \text{H} \quad \text{C}_6\text{H}_{13}
\end{align*}
\]

An inversion of configuration

\[
\begin{align*}
(R)-(\text{--})-2-\text{Bromooctane} & \quad [\alpha]_D^{25} = -34.25^\circ \\
\text{Enantiomeric purity} & = 100\% \\
(S)-(\text{+})-2-\text{Octanol} & \quad [\alpha]_D^{25} = +9.90^\circ \\
\text{Enantiomeric purity} & = 100\%
\end{align*}
\]

- In cyclic systems a cis compound can react and become trans product

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Cl}^- \quad \text{H} \quad \text{H} & \quad \text{H}_3\text{C} \quad \text{OH}^- \\
\text{H} & \quad \text{H} & \quad \text{H} \quad \text{Cl}^- \quad \text{OH}^-
\end{align*}
\]

cis-1-Chloro-3-methylcyclopentane  \quad trans-3-Methylcyclopentanol

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Solved Problems

• Predict mechanism and stereochemistry of each product

\[
\text{(R)-2-Chlorobutane} \\
\text{Cl} + \text{CH}_3\text{OH/H}_2\text{O} \rightarrow \text{OH} + \text{OCH}_3 + \text{HCl}
\]

• Predict mechanism of the following reaction

\[
\text{Br} + \text{Na}^+\text{CN}^- \xrightarrow{\text{DMSO}} \text{CN} + \text{Na}^+\text{Br}^-
\]

• Predict mechanism and stereochemistry of each product

\[
\text{(R)-2- Bromobutane} \\
\text{Br} + \text{CH}_3\text{S}^-\text{Na}^+ \xrightarrow{\text{acetone}} \text{SCH}_3 + \text{Na}^+\text{Br}^-
\]
Key Words/Concepts

• Substitution Reaction
• Substrate
• Nucleophile
• Leaving group
• 2nd order reaction (bimolecular)
• Transition state
• Rate determining step

• Solvents
  • Polar protic solvent
  • Polar aprotic solvent
  • Non polar solvent