Outline

Nucleophilic Substitution

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REACTIONS
Introduction to $S_N$

$$R\overset{\text{X}}{-} + \bar{Y} \rightarrow R\overset{-}{-}Y + \bar{X}$$

- **Type I** $R\overset{-}{-}I + \text{OH}^- \rightarrow R\overset{-}{-}\text{OH} + \text{I}^-$
- **Type II** $R\overset{-}{-}I + \text{NMe}_3 \rightarrow R\overset{-}{-}\text{NMe}_3 + \text{I}^-$
- **Type III** $R\overset{-}{-}\text{NMe}_3 + \text{OH}^- \rightarrow R\overset{-}{-}\text{OH} + \text{NMe}_3$
- **Type IV** $R\overset{-}{-}\text{NMe}_3 + \text{H}_2\text{S} \rightarrow R\overset{-}{-}\text{SH}_2 + \text{NMe}_3$
Representative Nucleophilic Substitution Reactions

A. Neutral reactant + neutral nucleophile

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

1a. \( \text{CH}_2\text{CH}_2\text{I} + (\text{n-C}_4\text{H}_9)_3\text{P} \rightarrow (\text{n-C}_4\text{H}_9)_3\text{P}^+\text{C}_2\text{H}_5^- \)

acetone

2b. \( \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{Cl} \rightarrow \text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{OC}_2\text{H}_5 + \text{HCl} \)

3c. \( \text{CH}_2\text{CHCH}_2\text{CH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CHCH}_2\text{CH}_3 + \text{OH} \)

acetone

87% \( \rho\text{-HO}_2\text{SC}_6\text{H}_4\text{CH}_3 \)

77%

B. Neutral reactant + anionic nucleophile

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

4d. \( \text{CH}_3\text{C}==\text{N} + \text{NaI} \rightarrow \text{CH}_3\text{C}==\text{N} + \text{NaBr} \)

acetone

96%

5e. \( \text{C}_7\text{H}_9\text{OTs} + \text{LiBr} \rightarrow \text{CH}_2\text{Br} \)

acetone

94%

6f. \( \text{CH}_3\text{CH}(\text{CH}_2)_5\text{CH}_3 + \text{NaSC}_6\text{H}_5 \rightarrow \text{CH}_3\text{CH}(\text{CH}_2)_5\text{CH}_3 \)

ethanol

\( \text{SC}_6\text{H}_5 \)
The $S_N2$ Mechanism

\[ \text{Rate} = k[RX][Y] \]

Second-order kinetics

\[ \text{Rate} = -\frac{d[R-X]}{dt} = -\frac{d[Y^-]}{dt} = k[R-X][Y^-] \]
Walden examples

\[
\begin{align*}
\text{COOH} & \xrightarrow{(+)\text{CHCl}} \text{CHCl} & \text{COOH} & \xrightarrow{(+)\text{CHOH}} \text{CHOH} & \text{COOH} & \xrightarrow{(+)\text{CHCl}} \\
\text{CH}_2\text{COOH} & \quad & \text{CH}_2\text{COOH} & \quad & \text{CH}_2\text{COOH} & \\
\text{COOH} & \xrightarrow{(+)\text{CHCl}} \text{CHCl} & \text{COOH} & \xrightarrow{(+)\text{CHOH}} \text{CHOH} & \text{COOH} & \xrightarrow{(+)\text{CHCl}} \\
\text{CH}_2\text{COOH} & \quad & \text{CH}_2\text{COOH} & \quad & \text{CH}_2\text{COOH} & \\
\end{align*}
\]

Phillips, Kenyon, and co-workers.

\[
\begin{align*}
\text{CH}_2\text{Ph} & \xrightarrow{\text{Me} - \text{CH} - \text{OH}} \text{CH}_2\text{Ph} & \xrightarrow{\text{Me} - \text{CH} - \text{OTs}} \text{CH}_2\text{Ph} & \xrightarrow{\text{Me} - \text{CH} - \text{OEt}} \\
\alpha = +33.0^\circ & \quad & \alpha = +31.1^\circ & \quad & \alpha = -19.9^\circ \\
\text{K} & \quad & \text{K}_2\text{CO}_3 & \quad & \\
\text{CH}_2\text{Ph} & \xrightarrow{\text{Me} - \text{CH} - \text{OK}} \text{CH}_2\text{Ph} & \xrightarrow{\text{Me} - \text{CH} - \text{OEt}} \\
\alpha = +23.5^\circ & \quad & \\
\end{align*}
\]
$S_N^2$  

**MO description of $S_N^2$ TS**

The $S_N^2$ Transition state: (3-center, 4 electron)

- The $SN_2$ transition state approximates a case 2 situation with a central carbon p-orbital.
- The three orbitals in reactant molecules are:
  1. Nonbonding MO from Nucleophile (2 electrons)
  2. Bonding MO $\sigma$ C−Br (2 electrons)
  3. Antibonding MO $\sigma^*$ C−Br

**Energy Diagram**

- **sigma-orientation**
  - bonding
  - nonbonding
  - antibonding

**Case 2: 3 p-Orbitals**
Why do $S_n2$ Reactions proceed with backside displacement?

$\text{Nu}^- \quad R \quad C \quad X \quad H \quad H \quad H \quad H$

$\text{Nu} \quad C \quad R \quad X \quad H \quad H \quad H \quad H$

$\text{Nu} \quad C \quad H \quad X \quad : \quad -$

Given the fact that the LUMO on the electrophile is the C–X antibonding orbital, nucleophilic attack could occur with either inversion or retention.

**Inversion**

Constructive overlap between $\text{Nu} \& \sigma^* \text{C–X}$

**Retention**

Overlap from this geometry results in no net bonding interaction.

Expanded view of $\sigma^* \text{C–X}$

- **Stereoelectronic Effects**
- Geometrical constraints placed upon ground and transition states by orbital overlap considerations.

**Fukui Postulate for reactions:**

"During the course of chemical reactions, the interaction of the highest filled (HOMO) and lowest unfilled (antibonding) molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition structure."
The $S_N 1$ Mechanism

First-order kinetics

$$\begin{align*}
R-X & \xrightarrow{k_1} \text{slow} \quad R^+ + X^- \\
R^+ + Y^- & \xrightarrow{k_2} \text{fast} \quad R-Y
\end{align*}$$

rate = $k_1[R-X]$ 

$$\begin{align*}
RX & \xrightarrow{k_1/k_1} R^+ + X \\
R^+ + Y & \xrightarrow{k_2} RY
\end{align*}$$

Rate = $\frac{k_1k_2[RX][Y]}{k_{-1}[X] + k_2[Y]}$

Reaction energy profile for nucleophilic substitution by the ionization $S_N 1$ mechanism.
**Potential Energy Diagram**

**Hammond Postulate**

---

**Solvent effects**

Solid line: polar solvent.
Dashed line: nonpolar solvent

(a) $R\text{--}X \rightarrow R^+ + X^-$
Polar solvents increase the rate by stabilization of the $R^+\text{--}^-X^-\text{--}^-\text{TS}$. 

(b) $R\text{--}X^+ \rightarrow R^+ + X$
Polar solvents decrease the rate because stabilization of $R^-\text{--}^+X^-\text{--}^+\text{TS}$ is less than for the more polar
Ion pair

Detailed mechanism

\[ \text{R-X} \xrightarrow{\text{ionization}} \text{R}^+\text{X}^- \xrightarrow{\text{contact ion pair}} \text{R}^+||\text{X}^- \xrightarrow{\text{solvent-separated ion pair}} \text{R}^+ + \text{X}^- \]

Support to scheme

At 100 °C, \( k_{\text{ex}} / k_{\text{rac}} = 2.3 \)
ERG favors exchange

Isotopic scrambling with no racemization

Avoids a carbocation intermediate but requires a front-side displacement!
Schematic relationship between reactants, ion pairs, and products in substitution proceeding through ion pairs.

The gradation from $S_N^1$ to $S_N^2$ mechanisms can be summarized in terms of the shape of the potential energy diagrams for the reactions.
Jencks: reaction energy profiles showing decreasing carbocation stability in change from $S_N1$(lim) to $S_N2$(lim) mechanisms.

An example of a coupled displacement: the “exploded” $S_N2$ TS.

Second-order kinetics with a substantially $\rho^+$
### Stereochemistry of Nucleophilic Substitution Reactions

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Conditions</th>
<th>Product</th>
<th>Stereocchemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CH₃CH₂CH₂CH₂CHDOBs</td>
<td>HCO₂H, 99°C</td>
<td>CH₃CH₂CH₂CH₂CHDO₂CH</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆H₅CHDOTHs</td>
<td>CH₃CO₂H, 25°C</td>
<td>C₆H₅CHDOTH₂CCH₃</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH₃CH(CH₂)₃CH₃ OTs</td>
<td>Et₂N⁻·O₂CCH₃, acetone, 56°C</td>
<td>CH₃CH(CH₂)₃CH₃ O₂CCH₃</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CH₃CH(CH₂)₃CH₃ OTs</td>
<td>75% aq. dioxane, 65°C</td>
<td>CH₃CH(CH₂)₃CH₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75% aq. dioxane, 0.06 M NaN₃, 65°C</td>
<td>CH₃CH(CH₂)₃CH₃ OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CH₃CH(CH₂)₃CH₃ OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CH₃CH(CH₂)₃CH₃ N₃</td>
</tr>
</tbody>
</table>

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![Stereochemistry Diagram](attachment:image.png)

- CH₃OH, DTBP, 25°C: 78% inv.
- C₆H₅OH, DTBP, 40°C: 55% inv.
- HCO₂H, DTBP, 0°C: 42% inv.
- CF₃CH₂OH, 13% ret.
- DTBP, 25°C: 49% inv.
- t-BuOH, 20% H₂O, 25°C: 98% inv.
- Dioxane, 20% H₂O, 25°C: 98% inv.
Stereochemical, kinetic, and isotope effects on solvolysis reactions of 1-phenylethyl chloride in several solvent systems

\[
\begin{align*}
\text{Stereochemical, kinetic, and isotope effects on solvolysis reactions of 1-phenylethyl chloride in several solvent systems} \\
\text{6f} & \quad \text{C}_6\text{H}_5\text{CHCH}_3 \quad \text{K}^+\text{O}_2\text{CCH}_3 \quad \text{CH}_3\text{CO}_2\text{H, 50° C} \\
& \quad \text{Et}_4\text{N}^-\text{O}_2\text{CCH}_3 \quad \text{50% acetone} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} \quad \text{Cl} & \quad \overset{80}{\longrightarrow} \quad \text{R}^+ \quad \text{Cl}^- \quad \overset{13}{\underset{0}{\longrightarrow}} \quad \text{R}^+ \quad \text{Cl}^- \\
\text{Cl} \quad \text{R} & \quad \overset{6}{\underset{1}{\longrightarrow}} \quad \text{Cl}^- \quad \text{R}^+ \quad \overset{0}{\underset{1}{\longrightarrow}} \quad \text{Cl}^- \\
\end{align*}
\]

\[
\begin{align*}
\text{R} \quad \text{Cl} & \quad \overset{80}{\longrightarrow} \quad \text{R}^+ \quad \text{Cl}^- \quad \overset{13}{\underset{0}{\longrightarrow}} \quad \text{R}^+ \quad \text{Cl}^- \\
\text{Cl} \quad \text{R} & \quad \overset{6}{\underset{1}{\longrightarrow}} \quad \text{Cl}^- \quad \text{R}^+ \quad \overset{0}{\underset{1}{\longrightarrow}} \quad \text{Cl}^- \\
\end{align*}
\]

Structural and Solvation Effects on Reactivity Characteristics of Nucleophilicity

1. **Strong solvation lowers the energy of an anionic nucleophile relative to the TS**, in which the charge is more diffuse, and results in an increased \(E_a\).

2. Because the S$_{2}$ process is concerted, the strength of the partially formed new bond is reflected in the TS.

3. A more **electronegative** atom binds its electrons more tightly than a less electronegative one.

4. **Polarizability** describes the ease of distortion of the electron density of the nucleophile.

5. A **sterically congested nucleophile** is less reactive than a less hindered one. The trigonal bipyramidal geometry of the S$_{2}$ transition state is sterically more demanding than the tetrahedral reactant so steric interactions increase as the TS is approached.
Effect of Solvation on Nucleophilicity

In protic hydrogen-bonding solvents, anions are subject to strong interactions with solvent.

Hard nucleophiles are more strongly solvated by protic solvents than soft nucleophiles, and this difference contributes to the greater nucleophilicity of soft anions in such solvents.

Nucleophilic substitution reactions of anionic nucleophiles usually occur more rapidly in polar aprotic solvents than they do in protic solvents, owing to the fact that anions are weakly solvated in such solvents.
Common polar aprotic solvents

But, in methanol, the relative reactivity order
$N_3^- > I^- > CN^- > Br^- > Cl^-$

Becomes, in DMSO
$CN^- > N_3^- > Cl^- > Br^- > I^-$

The nucleophilicity of the solvent.

The Weinstein-Grunwald equation

$$\log(k/k_0) = lN + mY$$

Standard reactant $l = 1.00$; Standard solvent $N = 0.00$, for solvolysis of $t$-butyl chloride. The scale has also been assigned for $2$-adamantyl tosylate. Ethanol-water in the ratio 80:20 is taken as the standard solvent.
Leaving group effects

Relative Solvolysis Rates of 1-Phenylethyl Esters and Halides

<table>
<thead>
<tr>
<th>Leaving group</th>
<th>(k_{rel})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF(_3)SO(_2)- (triflate)</td>
<td>(1.4 \times 10^8)</td>
</tr>
<tr>
<td>(p)-Nitrobenzensulfonate (nosylate)</td>
<td>(4.4 \times 10^5)</td>
</tr>
<tr>
<td>(p)-Toluenesulfonate (tosylate)</td>
<td>(3.7 \times 10^4)</td>
</tr>
<tr>
<td>CH(_3)SO(_3)- (mesylate)</td>
<td>(3.0 \times 10^4)</td>
</tr>
<tr>
<td>I(^-)</td>
<td>91</td>
</tr>
<tr>
<td>Br(^-)</td>
<td>14</td>
</tr>
<tr>
<td>CF(_3)CO(_2)-</td>
<td>2.1</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>1.0</td>
</tr>
<tr>
<td>F(^-)</td>
<td>(9 \times 10^{-6})</td>
</tr>
<tr>
<td>(p)-Nitrobenzoate</td>
<td>(5.5 \times 10^{-6})</td>
</tr>
<tr>
<td>CH(_3)CO(_2)-</td>
<td>(1.4 \times 10^{-6})</td>
</tr>
</tbody>
</table>

Relative rates of solvolysis of 1-phenylethyl esters and halides in 80% aqueous ethanol at 75 °C.

Ionization exhibits greater dependence on LG

<table>
<thead>
<tr>
<th>R</th>
<th>(k_{Tos}/k_{Br})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>11</td>
</tr>
<tr>
<td>Ethyl</td>
<td>10</td>
</tr>
<tr>
<td>Isopropyl</td>
<td>40</td>
</tr>
<tr>
<td>t-Butyl</td>
<td>4000</td>
</tr>
<tr>
<td>1-Adamantyl</td>
<td>9750</td>
</tr>
</tbody>
</table>

Tosylate/Bromide Rate Ratios for Solvolysis of RX in 80% Ethanol.
Relative Reactivity of Leaving Groups in $S_N^2$ Substitution Reactions

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>CH$_3$I</th>
<th>CH$_3$Br</th>
<th>CH$_3$OTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_2$</td>
<td>MeOH</td>
<td>8.0 x 10$^{-5}$</td>
<td>5.0 x 10$^{-5}$</td>
</tr>
<tr>
<td>NCS$^-$</td>
<td>MeOH</td>
<td>3.2</td>
<td>5.0 x 10$^{-1}$</td>
</tr>
<tr>
<td>NC$^-$</td>
<td>MeOH</td>
<td>5.0 x 10$^{-5}$</td>
<td>5.0 x 10$^{-4}$</td>
</tr>
<tr>
<td>ArS$^-$</td>
<td>DMF</td>
<td>3.2 x 10$^{-2}$</td>
<td>1.3 x 10$^{-2}$</td>
</tr>
</tbody>
</table>

A poor leaving group can be made more reactive by coordination to an electrophile.

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

It is endothermic by 16 kcal mol$^{-1}$

\[
\text{CH}_3(\text{CH}_2)\text{CH}_2\text{OH} + \text{NaBr} \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3(\text{CH}_2)\text{CH}_2\text{Br}
\]

N$_2$ best LG

\[
\text{RNH}_2 + \text{HONO} \rightarrow \text{R}^-\text{N}^-\text{N}⇌\text{O} + \text{H}_2\text{O}
\]

\[
\text{R}^-\text{N}^-\text{N}⇌\text{O} \xrightarrow{\text{H}^+} \text{RN}⇌\text{NOH} \xrightarrow{\text{H}^+} \text{R}^-\text{N}⇌\text{N} + \text{H}_2\text{O}
\]

\[
\text{R}^-\text{N}⇌\text{N}. \rightarrow \text{R}^+ + \text{N}_2
\]

\[
\text{R}^+ + \text{Nu}: \rightarrow \text{R}^-\text{Nu}
\]
Steric & strain effects

Rate Constants for Nucleophilic Substitution of Primary Alkyl Bromides and Tosylates

\[
\begin{array}{cccccc}
\text{RCH}_2X & \text{R} & \text{CH}_3 & \text{CH}_3\text{CH}_2 & (\text{CH}_3)_2\text{CH} & (\text{CH}_3)_3\text{C} \\
\hline
\text{RCH}_2\text{Br + LiCl, acetone, 25° C} & 600 & 9.9 & 6.4 & 1.5 & 2.6 \times 10^{-4} \\
\text{RCH}_2\text{I + n-Bu}_2\text{P, acetone, 35° C} & 26,000 & 154 & 64 & 4.9 & \\
\text{RCH}_2\text{Br + NaOCH}_3, \text{methanol} & 8140 & 906 & 335 & 67 & \\
\text{RCH}_2\text{OTs, acetic acid, 70° C} & 5.2 \times 10^{-2} & 4.4 \times 10^{-2} & 1.8 \times 10^{-2} & 4.2 \times 10^{-3} & \\
\end{array}
\]

In contrast to S\textsubscript{N}2 reactions, rates of reactions involving TSs with cationic character increase with substitution.

A high CH\textsubscript{3}/H rate ratio is expected if nucleophilic participation is weak and stabilization of the cationic nature of the TS is important.

Effects of conjugation

For example, allyl chloride is 33 times more reactive than ethyl chloride toward iodide ion in acetone!
α-Substituent Effect

Substituent Effects of α-EWG Substituents

<table>
<thead>
<tr>
<th>Z</th>
<th>Relative rate</th>
<th>Z</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂CH₂</td>
<td>1</td>
<td>PhC=O</td>
<td>3.2×10⁴</td>
</tr>
<tr>
<td>PhSO₂</td>
<td>0.25</td>
<td>N≡C</td>
<td>3×10³</td>
</tr>
<tr>
<td>CH₃C=O</td>
<td>3.5×10⁴</td>
<td>C₆H₅OC≡O</td>
<td>1.7×10³</td>
</tr>
</tbody>
</table>

Steric effects may be responsible for part of the observed acceleration.

Stabilizing π orbital TS

![Diagram showing stabilization of π orbital through resonance and MO interaction with carbonyl group](image)
Neighboring-Group Participation

The rates of solvolysis of the cis and trans isomers of 2-acetoxy-cyclohexyl p-toluenesulfonate differ by a factor of about 655!
The $\pi$ electrons of C=C can also become involved in $S_N$

![Chemical diagram with $\pi$ electrons of C=C involved in $S_N$ reaction](image)

It is more reactive by a factor of about $10^{11}$ than the saturated analog toward acetolysis.

![Chemical diagram with reaction rates comparison](image)

It reacts $10^7$ times slower than the anti isomer.

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**Mechanism of Rearrangements of Carbocations**

![Chemical mechanisms for alkyl and hydride shift](image)

- Alkyl shift: $R_2CC^+HR' \rightarrow R_2C^+CHR'$
- Hydride shift: $R_2CC^+HR' \rightarrow R_2C^+CH_2R'$

Types of Carbocations:

- Hydride-bridged carbocation
- Alkyl-bridged carbocation
- Corner-protonated cyclopropane
- Edge-protonated cyclopropane
The 2-butyl cation

The methyl-bridged ion is only slightly less stable.
The 2-butyl to t-butyl rearrangement gives the following energy surface:

A: H-bridged; B: methyl-bridged; C: Edge protonated methycyclopropane; D: classical secondary; E: classical primary; F: tertiary.

mechanism for C(3) - C(4) scrambling

mechanism for isomerization to t-butyl cation
The Norbornyl Cation
Nonclassical Carbocations

Racemic!
The exo-brosylate is more reactive than the endo isomer by a factor of 350.

The plane of symmetry: intermediate explains racemic product
Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

Step 1: \[ R-\overset{\text{Y}}{\overset{\text{X}}{\overset{\text{I}}{\overset{\text{O}}{C}}}} + \overset{\text{Y}}{\overset{\text{O}}{\overset{\text{X}}{\overset{\text{I}}{\overset{\text{O}}{C}}}}} \rightarrow R-\overset{\text{Y}}{\overset{\text{I}}{\overset{\text{O}}{\overset{\text{X}}{\overset{\text{I}}{\overset{\text{O}}{C}}}}}} \]

Step 2: \[ R-\overset{\text{I}}{\overset{\text{O}}{\overset{\text{X}}{\overset{\text{I}}{\overset{\text{O}}{C}}}}} \rightarrow R-\overset{\text{C}}{\overset{\text{I}}{\overset{\text{O}}{\overset{\text{X}}{\overset{\text{I}}{\overset{\text{O}}{C}}}}}} + \overset{\text{X}}{\overset{\text{O}}{\overset{\text{I}}{\overset{\text{O}}{C}}}}} \]
Phase-Transfer Catalysis

1. Quaternary Ammonium or Phosphonium Salts.

$$\text{Organic phase: } \quad Q^{+} \text{CN}^{-} + RC\text{I} \rightarrow 4 \quad \text{RCN} + Q^{+} \text{Cl}^{-}$$

$$\text{Aqueous phase: } \quad ^{+}Q \text{CN}^{-} + Na^{+} \text{Cl}^{-} \rightarrow 2 \quad Na^{+} \text{CN}^{-} + ^{+}Q \text{Cl}^{-}$$

$$Q^{+} = R_4N^{+} \quad \text{or} \quad R_4P^{+}$$

2. Crown Ethers and Other Cryptands (no water needed)

Ambident Nucleophiles: Regioselectivity

1. Ions of the Type. —CO—C:R—CO—

$$\begin{align*}
\text{—C—CR—C—} & \quad \leftrightarrow \quad \text{—C=CR—C—} & \quad \leftrightarrow \quad \text{—C—CR=C—} \\
\text{IQ} & \quad \text{IQ} & \quad \text{IQ} & \quad \text{IQ} \\
\end{align*}$$

$$\begin{align*}
\text{—C—CR=C—} & \quad \text{OR'} \\
\text{IQ} & \quad \text{IQ} \\
\end{align*}$$

$$\begin{align*}
\text{—C—CR=C—} & \quad \text{R'} \\
\text{IQ} & \quad \text{IQ} \\
\end{align*}$$
Ambident Substrates

\[
\text{R-CH-CH}_2\text{O}^- \quad \overset{\gamma^-}{\longrightarrow} \quad \text{O} \quad \overset{\gamma^-}{\longrightarrow} \quad \text{R-CH-CH}_2\text{Y} \quad \text{O}^- \\
\]

\[
\text{Nu} = H^+ \quad \text{N}_3^- \quad \text{RO}^- \quad \text{RS}^- \quad \text{RNH}_2 \quad \text{R}_2\text{NH} \quad \text{NH}_3 \quad \text{R}^+ \\
\text{R} = \text{various alkyl, aryl, or vinyl substituents}
\]

\[
\text{S}_\text{N}2 \text{ Transition-State}
\]
REGIOSELECTIVITY OF EPOXIDE RING OPENING

ACIDIC CONDITIONS: BORDERLINE $S_{N2}$ TO $S_{N1}$

$S_{N1}$

\[ \begin{align*}
R - O & \quad \xrightarrow{S_{N1}} \quad R^+ - OH \\
& \quad \xrightarrow{Nu} \quad R^+ - OH
\end{align*} \]

"BORDERLINE" $S_{N2}$

\[ \begin{align*}
R - O & \quad \xrightarrow{Nu} \quad R^+ - OH \\
& \quad \xrightarrow{A} \quad R^+ - OH
\end{align*} \]

Favored electronically
DisFavored sterically

R = alkyl

\[ \begin{align*}
R - O & \quad \xrightarrow{Nu} \quad OH - Nu \\
& \quad \xrightarrow{B} \quad OH - Nu
\end{align*} \]

DisFavored electronically
Favored sterically

"Abnormal Product"

"Normal Product"

Major product usually

REGIOSELECTIVITY OF EPOXIDE RING OPENING

ACIDIC CONDITIONS: BORDERLINE $S_{N2}$ TO $S_{N1}$

\[ \begin{align*}
\text{MeO} - O & \quad \xrightarrow{HX, H_2O, 70-85\degree C} \quad \text{MeO} - OH \\
& \quad \xrightarrow{X} \quad \text{MeO} - X
\end{align*} \]

<table>
<thead>
<tr>
<th>HX</th>
<th>Normal Prod</th>
<th>Abnormal Prod</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td>HBr</td>
<td>71</td>
<td>29</td>
</tr>
<tr>
<td>HI</td>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>HCl, Et_2O, $\Delta$</td>
<td>74</td>
<td>26</td>
</tr>
</tbody>
</table>

\[ \begin{align*}
\text{MeO} - O & \quad \xrightarrow{HCl, H_2O} \quad \text{MeO} - OH \\
& \quad \xrightarrow{Cl} \quad \text{MeO} - Cl
\end{align*} \]

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Exercício do dia

Keywords:
- Intramolecular interactions
- Frontier molecular orbitals relationships
- Marcus theory
- Nucleophilic substitution
- Regioselectivity

Ambient Reactivity

Hard and Soft Acids and Bases

Charge vs. Orbital Control

Marcus Theory

Regioselectivity

Thermodynamic Control

Kinetic Control

Diffusion Control

Activation Control

REGIOSELECTIVITY OF EPOXIDE RING OPENINGS

EFFECT OF CONJUGATING SUBSTITUENTS

\[
\begin{align*}
\text{Nu}^- & \rightarrow \text{Nu} \quad \text{Nu} \quad \text{Nu}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄</td>
<td>100:00</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>74:26</td>
</tr>
<tr>
<td>PhLi</td>
<td>100:00</td>
</tr>
<tr>
<td>MeONa</td>
<td>70:30</td>
</tr>
<tr>
<td>MeOH, H₂SO₄</td>
<td>10:90</td>
</tr>
<tr>
<td>NaN₃</td>
<td>00:100</td>
</tr>
<tr>
<td>NaOPh</td>
<td>24:76</td>
</tr>
<tr>
<td>HOPh</td>
<td>12:88</td>
</tr>
<tr>
<td>HOPh, TsOH</td>
<td>06:94</td>
</tr>
</tbody>
</table>
REGIOSELECTIVITY OF EPOXIDE RING OPENINGS

EFFECT OF CONJUGATING SUBSTITUENTS

\[
\begin{align*}
\text{Nu} & \quad \text{substituent (X)} & \text{Ratio} \\
\text{NO}_2 & \quad \text{-NO}_2 & 36.64 \\
\text{NaOPh} & \quad \text{-H} & 76:24 \\
\text{NaOPh} & \quad \text{-OMe} & 100:0 \\
\text{NaOMe} & \quad \text{-H} & 30:70
\end{align*}
\]

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