Chapter 8
Nucleophilic Substitution (in depth)
& Competing Elimination

8.1
Functional Group
Transformation By Nucleophilic Substitution

Nucleophilic Substitution

\[ \text{nucleophile} \rightarrow \text{substrate} \]

- Nucleophile is a Lewis base (electron-pair donor)
- Often negatively charged and used as Na\(^+\) or K\(^+\) salt
- Substrate is usually an alkyl halide

Substrate cannot be an allylic halide or an aryl halide, except under certain conditions to be discussed in Chapter 23.

Table 8.1 Examples of Nucleophilic Substitution

Alkoxide ion as the nucleophile

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

gives an ether

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

Example

\( (\text{CH}_3\text{CHCH}_2\text{CH}_2)\text{Na} + \text{CH}_2\text{CH}_3\text{Br} \)

\[ \text{Isobutyl alcohol} \]

\( (\text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_3) + \text{NaBr} \)

Ethyl isobutyl ether (66%)
Table 8.1 Examples of Nucleophilic Substitution

Carboxylate ion as the nucleophile
\[
\text{RCOO}^- \overset{\text{S}^2}\longrightarrow + \text{RX}
\]
gives an ester
\[
\text{RCO}^- \overset{\text{S}^2}\phantom{\text{RX}} \longrightarrow \text{R} + :X^-
\]
Example
\[
\text{CH}_3\text{(CH}_2\text{)}_{16}\text{C} = \text{O}^- + \text{CH}_2\text{CH}_3
\]
acetone, water
\[
\text{CH}_3\text{(CH}_2\text{)}_{16}\text{C} = \text{O}^- \text{CH}_2\text{CH}_3 + \text{K}^+
\]
Ethyl octadecanoate (95%)

Table 8.1 Examples of Nucleophilic Substitution

Hydrogen sulfide ion as the nucleophile
\[
\text{H}^+ \overset{\text{S}^2}\longrightarrow + \text{RX}
\]
gives a thiol
\[
\text{H}^+ \overset{\text{S}^2}\phantom{\text{RX}} \longrightarrow \text{R} + :X^-
\]
Example
\[
\text{K}^+\text{H} + \text{CH}_3\text{CH}(\text{CH}_2\text{)}_{16}\text{CH}_3
\]
ethanol, water
\[
\text{CH}_3\text{CH}(\text{CH}_2\text{)}_{16}\text{CH}_3 + \text{KBr}
\]
2-Nonanethiol (74%)

Table 8.1 Examples of Nucleophilic Substitution

Cyanide ion as the nucleophile
\[
:\text{N} \equiv \text{C}^- \overset{\text{S}^2}\longrightarrow + \text{RX}
\]
gives a nitrile
\[
:\text{N} \equiv \text{C} \phantom{\text{RX}} \longrightarrow \text{R} + :X^-
\]
Example
\[
\text{NaCN} + \text{Br} \phantom{\text{DMSO}}
\]
DMSO
\[
\text{CN} + \text{NaBr}
\]
Cyclopentyl cyanide (70%)
Azide ion as the nucleophile

\[
\text{N}_3^- + CH_3CH_2CH_2CH_2CH_3 \xrightarrow{\text{2-Propanol-water}} CH_3CH_2CH_2CH_2CH_3^-N_3 + \text{Na}^+
\]

Pentyl azide (52%)

Iodide ion as the nucleophile

\[
\text{Br}^- + CH_3CH_2CH_2CH_3^-N_3 \xrightarrow{\text{acetone}} CH_3CH_2CH_2CH_3^- + \text{NaBr}
\]

63%

NaI is soluble in acetone; NaCl and NaBr are not soluble in acetone.

8.2 Relative Reactivity of Halide Leaving Groups

Reactivity of halide leaving groups in nucleophilic substitution is the same as for elimination:

RI most reactive

RBr

RCl

RF least reactive
A single organic product was obtained when 1-bromo-3-chloropropane was allowed to react with one molar equivalent of sodium cyanide in aqueous ethanol. What was this product?

Br\(\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{NaCN}\)

\(\text{Br} \) is a better leaving group than \(\text{Cl}\).

**Problem 8.2**

**Improved Leaving Groups: Alkyl Sulfonates**

We have seen numerous examples of nucleophilic substitution in which \(X\) in \(R\text{X}\) is a halogen.

Halogen is not the only possible leaving group, though.

**Other RX Compounds**

Alkyl methanesulfonate (mesylate)

Alkyl \(p\)-toluenesulfonate (tosylate)

These undergo same kinds of reactions as alkyl halides.

**Preparation**

Tosylates are prepared by the reaction of alcohols with \(p\)-toluenesulfonyl chloride (usually in the presence of pyridine).

\(\text{ROH} + \text{CH}_3\text{SO}_2\text{Cl} \xrightarrow{\text{pyridine}} \text{ROSO}_2\text{CH}_3\) (abbreviated as \(\text{OTs}\)).
Tosylates Undergo Typical Nucleophilic Substitution Reactions

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \overset{\text{KCN}}{\underset{\text{ethanol-water}}{\rightarrow}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \]

(86%)

The best leaving groups are weakly basic.

Table 8.8
Approximate Relative Reactivity of Leaving Groups

<table>
<thead>
<tr>
<th>Leaving Group</th>
<th>Relative Rate</th>
<th>Conjugate Acid of Leaving Group</th>
<th>pK_a of Conjugate Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>F^-</td>
<td>10^3</td>
<td>HF</td>
<td>3.5</td>
</tr>
<tr>
<td>Cl^-</td>
<td>1</td>
<td>HCl</td>
<td>-7</td>
</tr>
<tr>
<td>Br^-</td>
<td>10</td>
<td>HBr</td>
<td>-9</td>
</tr>
<tr>
<td>I^-</td>
<td>10^6</td>
<td>HI</td>
<td>1</td>
</tr>
<tr>
<td>RSO₂⁻</td>
<td>10^-3</td>
<td>CF₃SO₂OH</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Sulfonate esters are extremely good leaving groups; sulfonate ions are very weak bases.

Tosylates can be Converted to Alkyl Halides

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \overset{\text{NaOH}}{\underset{\text{DMSO}}{\rightarrow}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \]

(82%)

Tosylate is a better leaving group than bromide.

Tosylates Allow Control of Stereochemistry

Preparation of tosylate does not affect any of the bonds to the chirality center, so configuration and optical purity of tosylate is the same as the alcohol from which it was formed.

\[ \text{CH}_2\text{CH}_2\text{OH} \overset{\text{TeCl}}{\underset{\text{pyridine}}{\rightarrow}} \text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{CH}_2\text{OTs} \]
Having a tosylate of known optical purity and absolute configuration then allows the preparation of other compounds of known configuration by S_N_2 processes.

**Tosylates Allow Control of Stereochemistry**

\[ \text{CH}_3\text{(CH}_2\text{)}_3\text{H} \rightarrow \text{HO}^- + \text{CH}_3\text{OH} + \text{Br}^- \]

rate = \( k[\text{CH}_3\text{Br}][\text{HO}^-] \)

Inference: rate-determining step is bimolecular.

**Kinetics**

Many nucleophilic substitutions follow a second-order rate law.

**Bimolecular Mechanism**

\[ \Delta \]

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

\[ \Delta \]

HO\_\rightarrow\_CH\_3\_Br \rightarrow HOCH\_3\_ + \_Br\_}

One step

Three-dimensional arrangement of bonds in product is opposite to that of reactant.

**Stereochemistry**

Nucleophilic substitutions that exhibit second-order kinetic behavior are stereospecific and proceed with inversion of configuration.

**Inversion of Configuration**

Nucleophile attacks carbon from side opposite bond to the leaving group.
A stereospecific reaction is one in which stereoisomeric starting materials give stereoisomeric products.

The reaction of 2-bromooctane with NaOH (in ethanol-water) is stereospecific.

\[
\begin{align*}
(+)-2\text{-Bromooctane} & \rightarrow (-)-2\text{-Octanol} \\
(-)-2\text{-Bromooctane} & \rightarrow (+)-2\text{-Octanol}
\end{align*}
\]

The Fischer projection formula for (+)-2-bromooctane is shown. Write the Fischer projection of the (-)-2-octanol formed from it by nucleophilic substitution with inversion of configuration.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} & \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\end{align*}
\]

The rate of nucleophilic substitution by the $S_N2$ mechanism is governed by steric effects.

Crowding at the carbon that bears the leaving group slows the rate of bimolecular nucleophilic substitution.
Table 8.2: Reactivity Toward Substitution by the $S_N2$ Mechanism

<table>
<thead>
<tr>
<th>Alkyl</th>
<th>Class</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$Br</td>
<td>Methyl</td>
<td>221,000</td>
</tr>
<tr>
<td>CH$_2$CH$_3$Br</td>
<td>Primary</td>
<td>1,350</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CHBr</td>
<td>Secondary</td>
<td>1</td>
</tr>
<tr>
<td>(CH$_3$)$_3$CBr</td>
<td>Tertiary</td>
<td>too small to measure</td>
</tr>
</tbody>
</table>

The rate of nucleophilic substitution by the $S_N2$ mechanism is governed by steric effects. Crowding at the carbon adjacent to the one that bears the leaving group also slows the rate of bimolecular nucleophilic substitution, but the effect is smaller.

Table 8.3: Effect of Chain Branching on Rate of $S_N2$ Substitution

<table>
<thead>
<tr>
<th>Alkyl</th>
<th>Structure</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl</td>
<td>CH$_3$CH$_2$Br</td>
<td>1.0</td>
</tr>
<tr>
<td>Propyl</td>
<td>CH$_3$CH$_2$CH$_2$Br</td>
<td>0.8</td>
</tr>
<tr>
<td>Isobutyl</td>
<td>(CH$_3$)$_2$CHCH$_2$Br</td>
<td>0.036</td>
</tr>
<tr>
<td>Neopentyl</td>
<td>(CH$_3$)$_3$CCH$_2$Br</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

8.5 Nucleophiles and Nucleophilicity
**Nucleophiles**

The nucleophiles described in Sections 8.1-8.6 have been anions.

\[ \text{HO}^-, \text{HS}^-, \text{CH}_3\text{O}^- : \text{N} \equiv \text{C}^- \] etc.

Not all nucleophiles are anions. Many are neutral.

\[ \text{H} \text{OH}, \text{CH}_3\text{OH}, : \text{NH}_2 \] for example

All nucleophiles, however, are Lewis bases.

**Solvolysis**

The term solvolysis refers to a nucleophilic substitution in which the nucleophile is the solvent.

**Example: Methanolysis**

Methanolysis is a nucleophilic substitution in which methanol acts as both the solvent and the nucleophile.

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

\[ \text{R}^-\text{X} + :\text{Nu}-\text{H} \rightarrow \text{R}^-\text{Nu}-\text{H} + :\text{X}^- \] step in which nucleophilic substitution occurs

products of overall reaction \[ \rightarrow \text{R}^-\text{Nu} + \text{HX} \]

\[ \text{R}^-\text{X} + \text{CH}_3\text{OH} \rightarrow \text{R}^-\text{Nu} + \text{CH}_3\text{OH} \]

The product is a methyl ether.
Typical solvents in solvolysis

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Product from RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>water (HOH)</td>
<td>ROH</td>
</tr>
<tr>
<td>methanol (CH₃OH)</td>
<td>ROCH₃</td>
</tr>
<tr>
<td>ethanol (CH₂CH₂OH)</td>
<td>ROCH₂CH₂</td>
</tr>
<tr>
<td>formic acid (HCOH)</td>
<td>ROCH</td>
</tr>
<tr>
<td>acetic acid (CH₃COH)</td>
<td>ROCCH₂</td>
</tr>
</tbody>
</table>

Nucleophilicity is a measure of the reactivity of a nucleophile

Table 8.4 compares the relative rates of nucleophilic substitution of a variety of nucleophiles toward methyl iodide as the substrate. The standard of comparison is methanol, which is assigned a relative rate of 1.0.

Table 8.4 Nucleophilicity

<table>
<thead>
<tr>
<th>Rank</th>
<th>Nucleophile</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>strong</td>
<td>I⁻, HS⁻, NR⁻</td>
<td>10⁶</td>
</tr>
<tr>
<td>good</td>
<td>Br⁻, HO⁻</td>
<td>10⁴</td>
</tr>
<tr>
<td></td>
<td>RO⁻, CN⁻, N₂⁻</td>
<td></td>
</tr>
<tr>
<td>fair</td>
<td>NH₃, Cl⁻, F⁻, RCO₂⁻</td>
<td>10³</td>
</tr>
<tr>
<td>weak</td>
<td>H₂O, ROH</td>
<td>1</td>
</tr>
<tr>
<td>very weak</td>
<td>RCO₂H</td>
<td>10⁻²</td>
</tr>
</tbody>
</table>

Major factors that control nucleophilicity

- Basicity
- Solvation
  - Small negative ions are highly solvated in protic solvents.
  - Large negative ions are less solvated.

When the attacking atom is the same (oxygen in this case), nucleophilicity increases with increasing basicity.
Solvation of a chloride ion by ion-dipole attractive forces with water. The negatively charged chloride ion interacts with the positively polarized hydrogens of water.

Figure 8.3

Table 8.4 Nucleophilicity

<table>
<thead>
<tr>
<th>Rank</th>
<th>Nucleophile</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>strong</td>
<td>I-</td>
<td>$&lt;10^5$</td>
</tr>
<tr>
<td>good</td>
<td>Br-</td>
<td>$10^7$</td>
</tr>
<tr>
<td>fair</td>
<td>Cl-, F-</td>
<td>$10^3$</td>
</tr>
</tbody>
</table>

A tight solvent shell around an ion makes it less reactive. Larger ions are less solvated than smaller ones and are more nucleophilic.