Chapter 6: Nucleophilic Substitution and Elimination Reactions
Nucleophilic Substitution

A **nucleophilic substitution** reaction involves the replacement of a **leaving group** with a **nucleophile**, i.e.

\[
\text{Nu}^- \rightarrow \text{Nu} \quad \text{LG}^+ \rightarrow \text{LG}^-
\]

Note: this reaction is an equilibrium since the leaving group can, in principle, act as a nucleophile.
Nucleophiles

*Nucleophiles* (Nu) are electron rich (i.e. have lone pair(s) of electrons) and are attracted to the positive nuclear charge of an e⁻ poor species, the *electrophile* (E).

*Nucleophiliicity* refers to the ability of the nucleophile to react this way, i.e. how available are the e⁻ in the nucleophile. The more available the e⁻ the more reactive the Nu. These may be lone pair e⁻ but π bonding e⁻ are also “available”.
Nucleophiles

Common nucleophiles include:

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Neutral</th>
<th>Anionic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halide</td>
<td></td>
<td>I^-, Br^-, Cl^-</td>
</tr>
<tr>
<td>Oxygen</td>
<td>H₂O, ROH</td>
<td>OH^-, RO^-, RCO₂^-</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>NH₃, RNH₂, R₂NH, R₃N</td>
<td>N₃^-</td>
</tr>
<tr>
<td>Sulfur</td>
<td>RSH, R₂S</td>
<td>SH^-, RS^-</td>
</tr>
<tr>
<td>carbon</td>
<td></td>
<td>N≡C^-, R-C≡C^-</td>
</tr>
</tbody>
</table>
Nucleophiles

Nucleophilicity trends (compared with basicity):

1) Across a row in the periodic table nucleophilicity (lone pair donation) $C^- > N^- > O^- > F^-$ since increasing electronegativity decreases the lone pair availability. This is the same order as for basicity.

2) For the same central atom, higher electron density will increase the nucleophilicity, i.e. an anion will be a better Nu (lone pair donor) than a neutral atom (i.e. $\text{HO}^- > \text{H}_2\text{O}$). This is the same order as for basicity.

3) Within a group in the periodic table, increasing polarization of the nucleophile as you go down a group enhances the ability to form the new $\text{C-X}$ bond and increases the nucleophilicity, so $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$. The electron density of larger atoms is more readily distorted i.e. polarized, since the electrons are further from the nucleus.

Note: this is the opposite order to basicity (acidity increases down a group) where polarizability is much less important for bond formation to the very small proton.
Nucleophiles

The following tables ranks the strength of common nucleophiles (as compared in methanol CH$_3$OH):

<table>
<thead>
<tr>
<th>Strength</th>
<th>Nucleophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good</td>
<td>I$^-$, HS$^-$, RS$^-$</td>
</tr>
<tr>
<td>Good</td>
<td>Br$^-$, OH$^-$, RO$^-$, N≡C$^-$, N$_3^-$</td>
</tr>
<tr>
<td>Fair (moderate)</td>
<td>NH$_3$, Cl$^-$, RCO$_2^-$</td>
</tr>
<tr>
<td>Weak</td>
<td>H$_2$O, ROH</td>
</tr>
<tr>
<td>Very weak</td>
<td>RCO$_2$H</td>
</tr>
</tbody>
</table>
Leaving Groups

- A **leaving group**, LG, is an atom (or a group of atoms) that is displaced as a stable species taking with it the bonding electrons. Typically the LG is an anion (*i.e.* Cl⁻) or a neutral molecule (*i.e.* H₂O). The better the LG, the more likely it is to depart.

- A "good" LG can be recognized as being the **conjugate base of a strong acid**.

- What do we mean by this? First we should write the chemical equations for the two processes:
Leaving Groups

Note the similarity of the two equations: both show heterolytic cleavage of a σ bond to create an anion and a cation.

- For acidity, the more stable A⁻ is, then the more the equilibrium will favor dissociation, and release of protons meaning that HA is more acidic.
- For the leaving group, the more stable LG⁻ is, the more it favors "leaving".
- Hence factors that stabilize A⁻ also apply to the stabilization of a LG⁻.
# Leaving Groups

The following tables lists some of the common leaving groups.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Leaving Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>NH₃</td>
</tr>
<tr>
<td>Very Good</td>
<td>I⁻, H₂O</td>
</tr>
<tr>
<td>Good</td>
<td>Br⁻</td>
</tr>
<tr>
<td>Fair</td>
<td>Cl⁻</td>
</tr>
<tr>
<td>Poor</td>
<td>F⁻</td>
</tr>
<tr>
<td>Very poor</td>
<td>OH⁻, RO⁻, NH₂⁻</td>
</tr>
</tbody>
</table>
Mechanism of Substitution Reactions

Experimentally if you measure the rate of substitution for the following reactions you will find the following rate laws:

\[
\text{OH}^- + \text{CH}_3\text{CBr} \rightarrow \text{CH}_3\text{COH} + \text{Br}^- \quad \text{rate} = k[\text{CH}_3\text{Br}][\text{OH}^-]
\]

\[
\text{OH}^- + (\text{CH}_3)_3\text{CBr} \rightarrow (\text{CH}_3)_3\text{COH} + \text{Br}^- \quad \text{rate} = k[(\text{CH}_3)_3\text{CBr}]
\]

Why the difference?
Substitution Reactions: $S_{N2}$

The first reaction is dependent on the concentrations of both the substrate and nucleophile, i.e.

$$\text{rate} = k [\text{CH}_3\text{Br}] [\text{OH}^-]$$

This implies it is a bimolecular reaction that occurs in one step. There is a single TS in which the new bond to the Nu is forming while the old bond to the LG is breaking, i.e.

$$\text{OH}^- + \text{CH}_3\text{Br} \rightarrow \text{HO}^- + \text{CH}_3\text{O}^- $$
Substitution Reactions: $S_{N2}$

The reaction coordinate diagram right indicate this one step mechanism.

- Rate = [substrate] & [nu]
- $S_{N2}$ results in an inversion of configuration if it occurs at a chiral center. (Back-side attack of the Nu)
- Fastest for 1°, slowest for 3°
Substitution Reactions: $S_{N1}$

The second reaction is dependent only on the concentration of the substrate, i.e.

\[
\text{CH}_3\text{CBr} \rightarrow \text{CH}_3\text{COH} \quad \text{Br}^{-}
\]

This implies it is a unimolecular reaction that occurs in several steps. The reaction involves the loss of the LG to generate an intermediate carbocation, i.e.
$S_{N}1$ Mechanism

- $S_{N}1$ is illustrated by the solvolysis of *tert*-butyl bromide.
  - **Step 1:** Break a bond to form a stable ion or molecule. Ionization of the C-X bond gives a **carbocation**.

![Diagram showing the $S_{N}1$ mechanism with a reaction between tert-butyl bromide and forming a carbocation.](image)

A carbocation intermediate; carbon is trigonal planar
Step 2: Reaction of a nucleophile and an electrophile to form a new covalent bond.

- The locations of the two lobes of the empty $p$ orbital of the carbocation allow the nucleophile to attack from either face.

Step 3: Take a proton away. Proton transfer to methanol completes the reaction.
Substitution Reactions: $S_{N1}$

The reaction coordinate diagram right indicate this multi-step mechanism.

- Rate = [substrate]
- Generate intermediate carbocation
- $S_{N1}$ results in racemization of configuration if it occurs at a chiral center.
- Fastest for $3^\circ$, slowest for $1^\circ$ (parallels $C^+$ stability)
S$_{N}$2: Stereochemistry

Inversion of configuration for chiral atoms, i.e.

S-2-bromobutane

R-butan-2-ol
$S_{N1}$: Stereochemistry

Racemization of chiral atoms, i.e.
$S_N1$ vs. $S_N2$: Nature of Substrate

The substrate itself has an effect on the mechanism. $S_N1$ requires an intermediate carbocation, while $S_N2$ requires a backside attack of the nucleophile (steric effects), i.e.
$S_{N1}$ vs. $S_{N2}$: Nature of Substrate

Reactivity of Alkyl bromide to $S_{N1}$ mechanism:

1. 
2. 
43. 
100,000,000.

Reactivity of Alkyl bromide to $S_{N2}$ mechanism:

220,000. 
1350. 
1. 
too small to measure.
The solvent can effect the rate of formation and stability of charged species. In general two types of solvents are used:

- **Polar protic solvents**: a solvent that contains an –OH group, they are good for dissolving anions and cations. This increases the rate of $S_N1$ but decreases $S_N2$ by solvating the Nu. (water, alcohols, acids)

- **Polar aprotic solvents**: only solvate cations well therefore good for $S_N2$ as the Nu is very reactive in these conditions. (acetone, DMSO, DMF, acetonitrile)
S_N1 vs. S_N2: Solvent Effects

Effects of polar protic/aprotic solvent polarity on S_N2 mechanism

<table>
<thead>
<tr>
<th>Protic /aprotic Solvent</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_3OH</td>
<td>1</td>
</tr>
<tr>
<td>H_2O</td>
<td>7</td>
</tr>
<tr>
<td>(CH_3)_2SO (DMSO)</td>
<td>1,300</td>
</tr>
<tr>
<td>(CH_3)_2NCHO (DMF)</td>
<td>2,800</td>
</tr>
<tr>
<td>CH_3C≡N</td>
<td>5,000</td>
</tr>
</tbody>
</table>

Dimethyl sulfoxide  Dimethylformamide  Acetonitrile
$S_N1$ vs. $S_N2$: Nucleophile

1) Anions are stronger nucleophiles than neutral molecules, i.e. $\text{HO}^- \text{ vs. H}_2\text{O}$ (but more basic).

2) Nucleophilic strength increases down a column in the Periodic Table (polarizability).

3) Across a row in the periodic table nucleophilicity (lone pair donation) $\text{C}^- > \text{N}^- > \text{O}^- > \text{F}^-$ since increasing electronegativity decreases the lone pair availability.
# S<sub>N</sub>1 vs. S<sub>N</sub>2: Summary

Summary of S<sub>N</sub>1 & S<sub>N</sub>2 reactions:

<table>
<thead>
<tr>
<th>Variable</th>
<th>S&lt;sub&gt;N&lt;/sub&gt;1</th>
<th>S&lt;sub&gt;N&lt;/sub&gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halide: 1°</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>2°</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3°</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Stereochemistry</td>
<td>Racemization</td>
<td>Inversion</td>
</tr>
<tr>
<td>nucleophile</td>
<td>Neutral ok as rate doesn’t depend on [Nu]</td>
<td>Best when anionic</td>
</tr>
<tr>
<td>Solvent</td>
<td>Polar protic</td>
<td>Polar aprotic best, Polar protic slow</td>
</tr>
</tbody>
</table>
Summary of $S_N1$ & $S_N2$ reactions:

- 1° - react $S_N2$! Can’t make stable carbocation
- 3° - react $S_N1$! Too sterically crowded for $S_N2$
- 2° - reacts either $S_N1$ or $S_N2$, this is the one you have to use nucleophilic strength and solvent conditions to control the mechanism if needed.
<table>
<thead>
<tr>
<th>Nu</th>
<th>R—Nu</th>
<th>Formula</th>
<th>Name</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxygen nucleophiles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. HO⁻</td>
<td>R—OH</td>
<td>H₂O</td>
<td>hydroxide</td>
<td>alcohol</td>
</tr>
<tr>
<td>2. RO⁻</td>
<td>R—OR</td>
<td>ROH</td>
<td>alkoxide</td>
<td>ether</td>
</tr>
<tr>
<td>3. H₂O</td>
<td>R—O⁻</td>
<td>alkylxonium</td>
<td>water</td>
<td>ion lose a proton and the products are alcohols and ethers. (alcohol)</td>
</tr>
<tr>
<td>4. ROH</td>
<td>R—OR</td>
<td>RO₂⁻</td>
<td>alcohol</td>
<td>dialkylxonium ion</td>
</tr>
<tr>
<td>5. R—C=O</td>
<td>R—O⁻</td>
<td>carboxylate</td>
<td>ester</td>
<td></td>
</tr>
<tr>
<td><strong>Nitrogen nucleophiles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. NH₃</td>
<td>R—NH₃</td>
<td>NH₃</td>
<td>ammonia</td>
<td>alkylammonium ion</td>
</tr>
<tr>
<td>7. RNH₂</td>
<td>R—NH₂R</td>
<td>R₂NH</td>
<td>primary amine</td>
<td>dialkylammonium ion</td>
</tr>
<tr>
<td>8. R₂NH</td>
<td>R—NHR₂</td>
<td>R₃NH</td>
<td>secondary amine</td>
<td>trialkylamonium ion</td>
</tr>
<tr>
<td>9. R₃N</td>
<td>R—NR₃</td>
<td>R₄N</td>
<td>tertiary amine</td>
<td>tetraalkylamonium ion</td>
</tr>
<tr>
<td><strong>Sulfur nucleophiles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. HS⁻</td>
<td>R—SH</td>
<td>SH⁻</td>
<td>hydrosulfide</td>
<td>thiol</td>
</tr>
<tr>
<td>11. RS⁻</td>
<td>R—SR</td>
<td>SR⁻</td>
<td>mercaptide</td>
<td>thioether (sulfide)</td>
</tr>
<tr>
<td>12. R₂S⁻</td>
<td>R—SR₂</td>
<td>R₃S⁻</td>
<td>thioether</td>
<td>trialkylsulfonium ion</td>
</tr>
<tr>
<td><strong>Halogen nucleophiles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I⁻</td>
<td>R—I</td>
<td>I⁻</td>
<td>iodide</td>
<td>alkyl iodide</td>
</tr>
<tr>
<td><strong>Carbon nucleophiles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. C≡N⁻</td>
<td>R—C≡N</td>
<td>R_C≡N</td>
<td>cyanide</td>
<td>alkyl cyanide (nitrile)</td>
</tr>
<tr>
<td>15. C≡CR⁻</td>
<td>R—C≡CR</td>
<td>R_C≡CR⁻</td>
<td>acetylide</td>
<td>alkyne</td>
</tr>
</tbody>
</table>
**Elimination Reactions**

A problem arises in nucleophilic substitution reactions in that nucleophiles are also bases. This is especially true for anionic nucleophiles, i.e.

\[
\text{Nu}^- + \text{H}^+ \rightarrow \text{Nu}:\text{H} \ (\text{Nu-H})
\]

This can occur by the Nu abstracting a proton (i.e. acting as a base) from the substrate giving an elimination reaction.
Dehydrohalogenation Reactions

A dehydrohalogenation is an elimination reaction of alkyl halides. It will compete with a substitution to some degree, i.e.

It is used to produce alkenes from alkyl halides
E Mechanisms

Like substitution there are several possible mechanisms for elimination reactions. We will examine two of them: E1 and E2
E2 Mechanism

- Rate = $k[\text{alkyl halide}][\text{base}]$ (bimolecular)
- Stereochemical requirement: anti-periplanar arrangement of the H atom and LG is required
  - This results from an orbital interaction that allows the $\pi$ bond to form.
E2 Mechanism

Regioselectivity: where does the double bond form: **Zaitsev’s rule**: most highly substituted alkene (watch for sterically hindered bases)

Stereoisomers: trans $>$ cis

\[ \text{Br} \xrightarrow{\text{CH}_3\text{CH}_2\text{OH}} \text{CH}_3\text{CH}_2\text{O}^- \]

20% 60% 20%
E1 Mechanism

- Rate = $k[\text{alkyl halide}]$ (unimolecular)
E1 Mechanism

Base strength and competing mechanisms:

\[ \text{Br} \quad \xrightarrow{\text{CH}_3\text{CH}_2\text{OH}} \quad \text{Br} \quad \xrightarrow{\text{CH}_3\text{CH}_2\text{O}^-} \]

\[ \text{S}_\text{N}1 \ 64\% \quad \text{S}_\text{N}1 \ 7\% \]

30%

6%

93%

E1

E2
Substitution vs. Elimination

3° alkyl halides: only $S_N 1$ but either (E1 or E2)
– Weak Nu and polar solvent: $S_N 1$ and E1 compete

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{O} & \quad \text{OH} & \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CH} = \text{CH}_2 \\
\text{Cl} & \quad \text{OH}^- & \quad \text{OH} & \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CH} = \text{CH}_2 \\
\end{align*}
\]

~80%  
~20%  
~0%   
~100%
Substitution vs. Elimination

2° alkyl halides: $S_N^1, S_N^2, E1$ or $E2$ are all possible.

- Weak Nu $\Rightarrow$ substitution
- Strong base $\Rightarrow$ elimination
- Can use solvent to control $S_N^1$ vs. $S_N^2$
Substitution vs. Elimination

2° alkyl halides: i.e.

- $\text{CH}_3\text{S}^-\text{Na}^+$
  - strong Nu
  - major
  - minor

- $\text{CH}_3\text{O}^-$
  - strong base
  - minor
  - major

- $\text{CH}_3\text{OH}$
  - weak Nu
  - major
  - minor
Substitution vs. Elimination

1° alkyl halides:

- Only $S_N 2$ and $E2$ are possible (no carbocations)
- Substitution dominates unless you use a sterically hindered base like $(CH_3)_3CO^-K^+$

\[
\begin{array}{c}
\text{Cl} \quad \text{EtO} \cdot \text{Na}^+ \\
\text{EtOH}
\end{array}
\Rightarrow
\begin{array}{c}
\text{O} \\
\text{90%}
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{10%}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \quad \text{t-BuO} \cdot \text{K}^+ \\
\text{t-BuOH}
\end{array}
\Rightarrow
\begin{array}{c}
\text{O} \\
\text{15%}
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{85%}
\end{array}
\]
Summary of $S_N$ versus E for Haloalkanes
– For Methyl and Primary Haloalkanes

<table>
<thead>
<tr>
<th>Halide</th>
<th>Reaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>$S_N2$</td>
<td>The only substitution reactions observed.</td>
</tr>
<tr>
<td>CH$_3$X</td>
<td>$S_N1$</td>
<td>$S_N1$ reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.</td>
</tr>
<tr>
<td>Primary</td>
<td>$S_N2$</td>
<td>The main reaction with strong bases such as OH$^-$ and EtO$^-$. Also, the main reaction with good nucleophiles/weak bases, such as I$^-$ and CH$_3$COO$^-$.</td>
</tr>
<tr>
<td>RCH$_2$X</td>
<td>E2</td>
<td>The main reaction with strong, bulky bases, such as potassium tert-butoxide.</td>
</tr>
<tr>
<td></td>
<td>$S_N1/E1$</td>
<td>Primary cations are never formed in solution; therefore, $S_N1$ and E1 reactions of primary halides are never observed.</td>
</tr>
</tbody>
</table>
### Summary of $S_N$ versus E for Haloalkanes

– For Secondary and Tertiary Haloalkanes

**TABLE 7.7** Summary of Substitution versus Elimination Reactions of Haloalkanes

<table>
<thead>
<tr>
<th>Halide</th>
<th>Reaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary $R_2CHX$</td>
<td>$S_N2$</td>
<td>The main reaction with weak bases/good nucleophiles, such as $I^-$ and $CH_3COO^-$.</td>
</tr>
<tr>
<td></td>
<td>E2</td>
<td>The main reaction with strong bases/good nucleophiles, such as $OH^-$ and $CH_3CH_2O^-$.</td>
</tr>
<tr>
<td></td>
<td>$S_N1/E1$</td>
<td>Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.</td>
</tr>
<tr>
<td>Tertiary $R_3CX$</td>
<td>$S_N2$</td>
<td>$S_N2$ reactions of tertiary halides are never observed because of the extreme crowding around the $3^\circ$ carbon.</td>
</tr>
<tr>
<td></td>
<td>E2</td>
<td>Main reaction with strong bases, such as $HO^-$ and $RO^-$.</td>
</tr>
<tr>
<td></td>
<td>$S_N1/E1$</td>
<td>Main reactions with poor nucleophiles/weak bases.</td>
</tr>
</tbody>
</table>

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\[
\text{Cl} \quad \xrightarrow{\text{KCN} \atop \text{DMSO}} \quad \text{H}_2\text{O} \quad \xrightarrow{\text{CH}_3\text{CH}_2\text{O} \cdot \text{Na}^\text{+} \atop \text{ethanol}} \quad \text{CH}_3\text{OH} / \text{H}_2\text{O}
\]
Cl-\text{C}_2\text{Cl}\xrightarrow{\text{NaI (1 equiv.)}}\xrightarrow{\text{acetone}}\
H-\text{C}_2\text{H}-\text{I}\xrightarrow{\text{NaSH}}\xrightarrow{\text{DMSO}}
Summary of $S_N$ versus E for Haloalkanes

**Examples**: Predict the major product and the mechanism for each reaction.

1. $\text{Cl} + \text{Na}^+\text{OH}^- \xrightarrow{80 \, ^\circ \text{C}, \text{H}_2\text{O}}$ 

2. $\text{Br} + (\text{C}_2\text{H}_5)_3\text{N} \xrightarrow{30 \, ^\circ \text{C}, \text{CH}_2\text{Cl}_2}$ 

3. $\text{Br} + \text{CH}_3\text{O}^- \text{Na}^+ \xrightarrow{\text{methanol}}$ 

4. $\text{Cl} + \text{Na}^+\text{OH}^- \xrightarrow{\text{acetone}}$

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