Chapter 9 Outline: Nucleophilic Substitution Reactions

1. Nucleophilic Substitution Mechanisms
   
   A. **SN2**
   
   B. **SN1**
   
   C. Structure of the RX
   
   D. Choice of Solvent – polar protic vs. polar aprotic
   
   E. Structure of the Nu-

2. Evidence Possible Mechanisms

3. Practicing Problems

Of course I would want you to do ALL the problems at the end of the chapter, but your doing the following problems would be a good start: 9.12-9.15, 9.17, 9.18, 9.20, 9.22-9.26, 9.31, 9.32, 9.34, and 9.35.
1. Nucleophilic Substitution Reactions

Nucleophilic substitution reactions are extremely useful as they are the gateway to synthesizing a host of functional groups depending on your choice of nucleophile.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>Class of Compound Formed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{HO}^-$</td>
<td>$\text{CH}_3\text{OH}$</td>
<td>An alcohol</td>
</tr>
<tr>
<td>$\text{RO}^-$</td>
<td>$\text{CH}_3\text{OR}$</td>
<td>An ether</td>
</tr>
<tr>
<td>$\text{HS}^-$</td>
<td>$\text{CH}_3\text{SH}$</td>
<td>A thiol (a mercaptan)</td>
</tr>
<tr>
<td>$\text{RS}^-$</td>
<td>$\text{CH}_3\text{SR}$</td>
<td>A sulfide (a thioether)</td>
</tr>
<tr>
<td>$\text{HC}≡\text{C}^-$</td>
<td>$\text{CH}_3\text{C}≡\text{CH}$</td>
<td>An alkyne</td>
</tr>
<tr>
<td>$\text{N}≡\text{C}^-$</td>
<td>$\text{CH}_3\text{C}≡\text{N}^-$</td>
<td>A nitrile</td>
</tr>
<tr>
<td>$\text{I}^-$</td>
<td>$\text{CH}_3\text{I}$</td>
<td>An alkyl iodide</td>
</tr>
<tr>
<td>$\text{N}=\text{N}=\text{N}^-$</td>
<td>$\text{CH}_3\text{N}=\text{N}=\text{N}^-$</td>
<td>An alkyl azide</td>
</tr>
<tr>
<td>$\text{N}=\text{N}^-$</td>
<td>$\text{CH}_3\text{NH}_3^+$</td>
<td>An alkylammonium ion</td>
</tr>
<tr>
<td>$\text{OH}^-$</td>
<td>$\text{CH}_3\text{O}^+\text{H}$</td>
<td>An alcohol (after proton transfer)</td>
</tr>
<tr>
<td>$\text{O}^-$</td>
<td>$\text{CH}_3\text{O}^+\text{CH}_3$</td>
<td>An ether (after proton transfer)</td>
</tr>
</tbody>
</table>
Three components are necessary in any substitution reaction:

1. **R** – an alkyl group containing an **sp\(^3\)** hybridized carbon involved in a C—X bond.

2. **X** – a leaving group; the LG must be able to accept the electron density in the C—X bond (heterolytic bond cleavage occurs).

3. **Nu** – a nucleophile; the nucleophile must contain a lone pair or a pi bond, but it does not necessarily have to be negatively charged. Charged nucleophiles react more easily than neutral ones.

Examples:
Why do alkyl halides undergo a reaction with nucleophiles?

\[ \text{H}_3\text{C} \rightarrow \text{X} \]

Do all RX compounds undergo substitution?

- Yes, for alkyl or allylic halides (needs to be a 1°, 2° or 3° \( sp^3 \) C-X bond):

- No, for vinylic and aryl halides:

Do all RX react at the same rate?

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond length (pm)</th>
<th>Bond strength (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C—F</td>
<td>142</td>
<td>439</td>
</tr>
</tbody>
</table>

(responsible for Teflon™)

| C—H  | 109             | 377 – 418              |
| C—C  | 153             | 368                    |
| C—O  |                 | 358                    |
| C—N  |                 | 293                    |
| C—Cl | 178             | 328                    |
| C—Br | 193             | 272                    |
| C—I  | 214             | 209                    |

Which RX below would you expect to react the fastest via substitution? C—Cl, C—Br, or C—I bonds?
2. Evaluating Possible Mechanisms

How does this reaction occur?

$$\text{NaOH} + \text{H}_3\text{C—Br} \rightarrow \text{CH}_3\text{OH} + \text{NaBr}$$

*Three possible reaction mechanisms exist:*

a. Bond-breaking come first followed by formation of the new bond?

\[ \begin{align*}
\text{Br} & \rightarrow \text{Br} \\
\text{H} & \text{H} & \text{O} & \text{H} & :\text{Br} \\
\text{H} & & & & \\
\end{align*} \]

b. Bond-forming comes first, followed by bond breaking?

\[ \begin{align*}
\text{H} & \text{H} & \text{O} & \text{Br} & & \text{Br} \\
& & & & & \\
\text{H} & \text{H} & \text{Br} & & & \\
\end{align*} \]

c. Bond-breaking and bond-forming are more or less simultaneous?

\[ \begin{align*}
\text{H} & \text{O} & \text{Br} & & \text{Br} \\
& & & & \\
\text{H} & \text{H} & \text{Br} & & & \\
\end{align*} \]
A. Mechanism for SN2 = “substitution nucleophilic bimolecular”
Steric effects in the $S_N2$ reaction:

Sterics plays a part at the reactive carbon ($\alpha$-carbon), but also at the $\beta$-carbon.

Which type of species will react fastest? Compare the $\alpha$-carbon first:

![Steric effects diagram]

What if you change the rest of the molecule’s sterics? Compare the $\beta$-carbon:

<table>
<thead>
<tr>
<th>Alkyl bromide</th>
<th>$\beta$-Branches</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>$4.1 \times 10^{-1}$</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>$1.2 \times 10^{-3}$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>$1.2 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

Put the following reactants in order of ease of reacting via an $S_N2$ reaction (1-4).

a. ![Reactant images]

b. ![Reactant images]
B. Mechanism for $S_N1$ = “substitution nucleophilic unimolecular”

Which is the rate determining step for $S_N1$?

*Mechanism*?
**S_N1 reactions are governed by the stability of the intermediate formed.**

“Intermediates” are the species formed on the way to products. They are less stable than the reactants and products; hence, they are short-lived and always proceed to products.

What is the geometry/hybridization around a carbocation?

Which carbocation intermediate is more stable and why?

**Stability of the intermediate helps to dictate the reaction pathway…**

\[
\text{methyl} < 1^\circ \text{ alkyl} < \begin{cases} 2^\circ \text{ alkyl} \\ 1^\circ \text{ allylic} \\ 1^\circ \text{ benzylic} \end{cases} < \begin{cases} 3^\circ \text{ alkyl} \\ 2^\circ \text{ allylic} \\ 2^\circ \text{ benzylic} \end{cases} < \begin{cases} 3^\circ \text{ allylic} \\ 3^\circ \text{ benzylic} \end{cases}
\]

Increasing stability of carbocations
C. Structure of the RX

- $S_N^2$ reactions are governed by the steric hindrance at the center of reactivity.
- $S_N^1$ reactions are governed by the stability of the carbocation intermediate.

Determine the TYPE of alkyl halide (e.g. 2º alkyl or 1º allylic) that reacts below, draw the products for the following substitution reactions, and name the new functional group you synthesized.

\[ \text{Br} \quad \rightarrow \quad \text{NaOH} \]

\[ \text{I} \quad \rightarrow \quad \text{NaOCH}_3 \]

\[ \text{Cl} \quad \rightarrow \quad \text{ONa} \]
D. Choice of Solvent

We will discuss two specific types of solvents:

- **Polar Protic** – contains an HBD
- **Polar Aprotic** – does NOT contain an HBD

**Common Protic Solvents:**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Structure</th>
<th>Dielectric Constant (25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>H₂O</td>
<td>79</td>
</tr>
<tr>
<td>Formic acid</td>
<td>HCOOH</td>
<td>59</td>
</tr>
<tr>
<td>Methanol</td>
<td>CH₃OH</td>
<td>33</td>
</tr>
<tr>
<td>Ethanol</td>
<td>CH₃CH₂OH</td>
<td>24</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>CH₃COOH</td>
<td>6</td>
</tr>
</tbody>
</table>

Polar protic solvents reduce nucleophilicity AND helps stabilize carbocations.
**Polar aprotic solvents** = are other solvents that exhibit dipole-dipole interactions **WITHOUT** containing O—H and N—H bonds (**no ABD**).

What are some of the polar aprotic solvents you have been asked to learn?

Polar aprotic solvents solubilize only CATIONS well but they do NOT solubilize anions well, hence nucleophilicity increases (i.e. promoting an S\textsubscript{N}2 reaction). The more polar the solvent, the faster the reaction for SN2.
E. Nature of the Nucleophile

“Strong” or “weak” nucleophiles dictate different reactions
What are some general trends about Nu- you can make using the pKa table?

<table>
<thead>
<tr>
<th>Acids</th>
<th>CB</th>
<th>51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-9</td>
</tr>
</tbody>
</table>

Indicate if the following will provide substitution (S), elimination (E) or both (B).

- NaOH
- NaH
- CH₃CH₂CH₂Li
- NaO
- NaNH₂
- NaBr
Are Nucleophilicity (substitution) & Basicity (elimination) the same thing?

Although nucleophilicity and basicity are interrelated, they are fundamentally different concepts.

- **Basicity** is a measure of how readily an atom donates its electron pair to a proton. It is characterized by an equilibrium constant, $K_a$ in an acid-base reaction, making it a thermodynamic property.

- **Nucleophilicity** is a measure of how readily an atom donates its electron pair to all other atoms. It is characterized by a rate constant, $k$, making it a kinetic property.

• Nucleophilicity increases down a column while basicity does not; why?

\[
\text{HS}^- > \text{HO}^- \\
\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-
\]

• Compare the **SIZE** of the nucleophile (molecule) as a whole:

\[
\text{\begin{align*}
\text{H}_3\text{C}^- \\
\text{H}_2\text{C}^- \\
\text{H}_2\text{O}^-
\end{align*}}
\]
### Table 9.8 Relative Nucleophilicities of Halide Ions in Polar Aprotic and Protic Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Increasing nucleophilicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polar aprotic</td>
<td>I⁻ &lt; Br⁻ &lt; Cl⁻ &lt; F⁻</td>
</tr>
<tr>
<td>Polar protic</td>
<td>F⁻ &lt; Cl⁻ &lt; Br⁻ &lt; I⁻</td>
</tr>
</tbody>
</table>

![Hydrogen bonding](image)
3. Gathering evidence for $S_N1$ vs. $S_N2$ mechanisms

What evidence exists that these two limiting mechanisms, $S_N1$ and $S_N2$, actually occur?

Chemists consider the following questions:

- Does the structure of the nucleophile affect the rate of reaction? (Employing kinetic measurements helps here.)

- What is the stereochemical outcome in the products? Did the products provide inversion of configuration or did a racemic mixture result?

- Does the identity of the solvent affect the rate? Protic versus aprotic matters.

- Under what conditions are skeletal rearrangements observed? (What the heck are these again? Are we really going to discuss cadavers?)
a. **Kinetics measurements**

A reaction mechanism can be studied by varying the amounts of the reagents and looking for a dependence of concentration on the rate of reaction.

**$S_N2$ – bimolecular reaction**

Based on the RDS, what is the expected reaction expression?

**$S_N1$ – unimolecular reaction**

Based on the RDS, what is the expected reaction expression?
b. Stereochemistry of the product

**S_N1**

- Nucleophilic attack can come from either side of a carbocation! (carbocation is planar…more later on this)

- **Racemization** occurs with an S_N1 mechanisms if the starting material is chiral.

![SN1 Reaction Diagram](image)

**S_N2**

- Since the reaction does a “back-side” attack, there is **inversion of configuration** if the starting material is chiral.

![SN2 Reaction Diagram](image)
c. Changing the solvent

Compare with $S_N2$ reactions:

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{NaOH solvent?}} \quad \text{OH} \\
\text{Solvent Type} & \quad \text{Solvent} & \quad \frac{k_{\text{(solvent)}}}{k_{\text{(methanol)}}} \\
\text{Polar aprotic} & \quad \begin{cases} 
\text{CH}_3\text{C}≡\text{N} \\
(\text{CH}_3)_2\text{NCHO} \\
(\text{CH}_3)_2\text{S}≡\text{O}
\end{cases} & \quad 5000 \\
\text{Polar protic} & \quad \begin{cases} 
\text{H}_2\text{O} \\
\text{CH}_3\text{OH}
\end{cases} & \quad 1300 \\
& & \quad 7 \\
& & \quad 1
\end{align*}
\]

Compare to $S_N1$ reactions:

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{H}_2\text{O or ROH}} \quad \text{OH (OR)} \\
\text{Solvent} & \quad \frac{k_{\text{(solvent)}}}{k_{\text{(ethanol)}}} \\
\text{Water} & \quad 100,000 \\
80\% \text{ water: } 20\% \text{ ethanol} & \quad 14,000 \\
40\% \text{ water: } 60\% \text{ ethanol} & \quad 100 \\
\text{Ethanol} & \quad 1
\end{align*}
\]
When solving problems, 3 factors must be examined to propose a mechanism:

1. **The alkyl halide reactant** – can it make a stable carbocation? Are rearrangements possible? If so, what mechanism does this support?

2. **The nucleophile** – strong or weak? Is it charged or neutral?

3. **The solvent** – is it protic or aprotic?

**Overview:**

<table>
<thead>
<tr>
<th>Type of Alkyl Halide</th>
<th>( \text{S}_\text{N}2 )</th>
<th>( \text{S}_\text{N}1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl ( \text{CH}_3\text{X} )</td>
<td>( \text{S}_\text{N}2 \text{ is favored.} )</td>
<td>( \text{S}_\text{N}1 \text{ does not occur.} ) The methyl cation is so unstable that it is never observed in solution.</td>
</tr>
<tr>
<td>Primary ( \text{RCH}_2\text{X} )</td>
<td>( \text{S}_\text{N}2 \text{ is favored.} )</td>
<td>( \text{S}_\text{N}1 \text{ rarely occurs.} ) Primary cations are so unstable that they are rarely observed in solution (allylic and benzylic cations can be exceptions).</td>
</tr>
<tr>
<td>Secondary ( \text{R}_2\text{CHX} )</td>
<td>( \text{S}_\text{N}2 \text{ is favored in aprotic solvents with good nucleophiles.} )</td>
<td>( \text{S}_\text{N}1 \text{ is favored in protic solvents with poor nucleophiles. Carbocation rearrangements may occur.} )</td>
</tr>
<tr>
<td>Tertiary ( \text{R}_3\text{CX} )</td>
<td>( \text{S}_\text{N}2 \text{ does not occur because of steric hindrance around the reaction center.} )</td>
<td>( \text{S}_\text{N}1 \text{ is favored because of the ease of formation of tertiary carbocations.} )</td>
</tr>
<tr>
<td>Substitution at a chiral center</td>
<td><strong>Inversion of configuration.</strong> The nucleophile attacks the chiral center from the side opposite the leaving group.</td>
<td><strong>Racemization is favored.</strong> The carbocation intermediate is planar, and attack of the nucleophile occurs with equal probability from either side. There is often some net inversion of configuration.</td>
</tr>
</tbody>
</table>
3. Practicing Problems

For the following reaction, indicate which reaction mechanism (i.e. write SN1 and/or SN2 in the blank below) the following observations would support.

\[
\begin{align*}
\text{Br} &+ \text{NaOCH}_3 \rightarrow ? \\
\end{align*}
\]

A. the reaction rate increased when the [Nu] was increased
B. the reaction rate decreased when the [RX] was decreased
C. the reaction rate increased in the presence of a polar protic solvent
D. the reaction showed a rearranged product
E. the reaction showed more than one product
F. the reaction rate decreased when the LG was changed to Cl
G. the product was an ether

Circle which of the following is a stronger nucleophile and provide a valid argument for your reasoning.

\[ \text{H}_2\text{O} \quad \text{NH}_3 \]

Circle which of the following is a better leaving group and provide a valid argument for your reasoning.

\[ \text{NH}_2 \quad \text{NH} \]
Provide substitution mechanisms and major product(s) for the following reactions.

\[
\begin{align*}
\text{Br} & \quad \rightarrow \quad \text{NaOCH}_3 \\
\text{acetone} & \\
\end{align*}
\]

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

\[
\begin{align*}
\text{CH}_3\text{I} & \quad \rightarrow \quad \text{ONa} \\
\text{DMF} & \\
\end{align*}
\]
Provide a viable step-by-step mechanism using mechanistic arrows to clearly demonstrate the following reaction outcome.

Through what substitution mechanism **MUST** this reaction have proceeded? _____
Mechanisms: Determine the anticipated mechanisms for the reactions below and provide correct products.