Chapter 8 - Nucleophilic Substitution at \( sp^3 \) C

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

\[
\begin{align*}
\text{Nu:} & \quad \stackrel{\text{R}}{\text{X}} \quad \rightarrow \quad \text{Nu-R} \quad + \quad \text{X:}
\end{align*}
\]

8.1 Functional Group Transformation by \( S_{n2} \)

**Table 8.1 Examples of Nucleophilic Substitution**

**Alkoxide ion as the nucleophile**

\[
\begin{align*}
\text{Na} & \quad \text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \rightarrow \quad \text{OCH}_3 \quad (+ \quad \text{NaBr})
\end{align*}
\]

gives an ether

- Referred to as the Williamson ether synthesis
- Limited to primary alkyl halides
- Run in solvents such as diethyl ether and THF

**Carboxylate ion as the nucleophile**

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

\[
\begin{align*}
\rightarrow & \quad \text{O} \quad (+ \quad \text{Na} \text{Br})
\end{align*}
\]
gives an ester

- Not very useful – carboxylates are poor nucleophiles
- Limited to primary alkyl halides
- Run in solvents such as diethyl ether and THF
- Better ways of forming esters later in 3720
Cyanide as nucleophile

\[
\text{CN} \quad \overset{R-X}{\rightarrow} \quad R-CN
\]

Azide as nucleophile

\[
\text{N}_3 \quad \overset{R-X}{\rightarrow} \quad R-N_3
\]

Halides as Nucleophiles – Finkelstein Reaction

\[
\text{Br} \quad \overset{\text{Nal}}{\rightarrow} \quad \text{I}
\]

Nal is soluble in acetone, NaCl and NaBr are not

8.2 Relative reactivity of halide leaving groups

- I\(^-\) better than Br\(^-\) which is better than Cl\(^-\)
- F\(^-\) is not used as a leaving group

8.3 The \(S_2\) mechanism of Nucleophilic Substitution

Example:

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

inference: rate-determining step is bimolecular
8.4 Steric effects in substitution ($S_n2$) reactions

Figure 8.2

Table 8.3 - Relative rates of reaction of different primary alkyl bromides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl bromide</td>
<td>1.0</td>
</tr>
<tr>
<td>Propyl bromide</td>
<td>0.8</td>
</tr>
<tr>
<td>Isobutyl bromide</td>
<td>0.036</td>
</tr>
<tr>
<td>Neopentyl bromide</td>
<td>0.00002</td>
</tr>
</tbody>
</table>
8.5 - Nucleophiles and Nucleophilicity

Solvation of a chloride by ion-dipole
Figure 8.3

Choice of solvent is important for $S_n2$ - polar aprotic used often

8.6 The $S_n1$ reaction revisited

Tertiary system - favours $S_n1$ - carbocation possible
Carbocation will be the electrophile
Water will be the nucleophile
8.7 Relative rates of reaction by the SN1 pathway
Table 8.5

8.8 Stereochemical consequences in SN1 reactions
Figure 8.5
8.9 Carbocation rearrangements also possible in $S_N1$

\[
\text{Br} \quad \text{H}_2\text{O} \quad \text{OH}
\]

- Look for change in the product skeleton.
- Rearrangement (in this case hydride shift) to generate a more stable carbocation.

8.10 Choice of solvent important

More polar solvents (higher dielectric constant) will help stabilize the ionic intermediates.

8.10 Proper solvent can stabilize transition states
8.10 Choice of solvent important

8.11 Substitution vs. Elimination – $S_N$2 vs. E2

8.11 Substitution vs. Elimination - Figure 8.7
8.12 Sulfonate ester leaving groups