Nucleophilic substitution at saturated carbon
Substitution Reactions

**Nucleophilic substitution**

\[
\begin{align*}
\text{H} & \quad \text{X} \\
\text{H} & \quad \text{Nuc} \\
\text{C} & \quad \text{C}
\end{align*}
\]

- The halogen atom on the alkyl halide is replaced with a nucleophile (Nuc\(^-\)).
- Since the halogen is more electronegative than carbon, the C—X bond breaks heterolytically and X\(^-\) leaves.

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Alkyl halides have relatively good leaving groups

How do alkyl halides react?

\[
\begin{align*}
\delta^+ & \quad \delta^- \\
RCH_2\text{X} & \quad X = \text{F, Cl, Br, I}
\end{align*}
\]

Alternatively …

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

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Because a nucleophile substitutes for the halogen, these reactions are known as nucleophilic substitution reactions.

The reaction mechanism which predominates depends on the following factors:

- the structure of the alkyl halide
- the reactivity of the nucleophile
- the concentration of the nucleophile
- the solvent of the reaction
S_N2 Mechanism

- Bimolecular nucleophilic substitution.
- Concerted reaction: new bond forming and old bond breaking at same time.
- Rate is first order in each reactant.
- Walden inversion.
The $S_N2$ reaction is a one-step reaction.
Transition state is highest in energy.
The Mechanism of an $S_{N2}$ Reaction

Consider the kinetic of the reaction:

$$\text{Rate} = k_2[\text{alkyl halide}][\text{nucleophile}]$$

a second-order reaction
Steric hindrance in nucleophilic substitution

In the approach to the $S_N^2$ transition state, the carbon atom under attack gathers in another ligand and becomes (briefly) **five-coordinate**.

In the starting material there are **four angles of about 109°**. In the transition state, there are **three angles of 120° and six angles of 90°**, a significant increase in crowding. The **larger the substituents R, the more serious this is**.
Reaction coordinate diagrams for (a) the $S_{N2}$ reaction of methyl bromide and (b) an $S_{N2}$ reaction of a sterically hindered alkyl bromide.
Steric Effects of the Substrate on $S_N2$ Reactions

- Nucleophile approaches from the back side.
- It must overlap the back lobe of the $C-X$ sp$^3$ orbital.
Table 10.1 Relative Rates of $S_N2$ Reactions for Several Alkyl Halides

<table>
<thead>
<tr>
<th>Alkyl halide</th>
<th>Class of alkyl halide</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{—Br}$</td>
<td>methyl</td>
<td>1200</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{—Br}$</td>
<td>primary</td>
<td>40</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{CH}_2\text{—Br}$</td>
<td>primary</td>
<td>16</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}\text{—Br}$</td>
<td>secondary</td>
<td>1</td>
</tr>
</tbody>
</table>
| $\begin{array}{l} \text{CH}_3 \\
                      \text{CH}_3 \\
                      \text{CH}_3 \\
\end{array}$ |                      |               |
| $\text{CH}_3\text{C—Br}$ | tertiary              | too slow to measure |
Structure of Substrate on $S_{N2}$ Reactions

- Relative rates for $S_{N2}$:
  \[
  CH_3X > 1^\circ > 2^\circ >> 3^\circ
  \]

- Tertiary halides do not react via the $S_{N2}$ mechanism, due to steric hindrance.
Stereochemistry and substitution

Inversion of configuration (Walden inversion) in an $S_N^2$ reaction is due to back side attack

three bonds are in the same plane
Stereochemistry of $S_{N2}$

$S_{N2}$ reactions will result in an inversion of configuration also called a Walden inversion.

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The products resulting from substitution of cyclic compounds

Only the trans product is obtained because the carbon bonded to the leaving group is attacked by the nucleophile only on its back side.
Nucleophilic attack **with inversion gives the trans product.** As the epoxide is up, attack has to come from underneath. Notice that the new C–N bond is down and that the H atom at the site of attack was down in the epoxide but is up in the product. Inversion has occurred.
Three Experimental Evidences Support an $S_{N2}$ Reaction Mechanism

1. The rate of the reaction is dependent on the concentration of the alkyl halides and the nucleophile

2. The rate of the reaction with a given nucleophile decreases with increasing size of the alkyl halides

3. The configuration of the substituted product is inverted compared to the configuration of the reacting chiral alkyl halide
It also depends, as do all reactions, on factors like temperature and solvent.
The $S_{N1}$ Reaction

- The $S_{N1}$ reaction is a unimolecular nucleophilic substitution.
- It is a two step reaction with a carbocation intermediate.
- Rate is first order in the alkyl halide, zero order in the nucleophile.
- Racemization occurs.
**S_N1 Mechanism: Step 1**

Formation of carbocation (rate determining step)

X is taking on a partial negative charge

Partial bonding in the transition state
$S_N1$ Mechanism: Step 2

- The nucleophile attacks the carbocation, forming the product.
- If the nucleophile was neutral, a third step (deprotonation) will be needed.
SN1 Energy Diagram

• Forming the carbocation is an endothermic step.
• Step 2 is fast with a low activation energy.
The opposite is true of the $S_N1$ reaction. The starting material is again tetrahedral (four angles of about 109°) and in the intermediate cation there are just three angles of 120°—fewer and less serious interactions.

In the transition state, the angles are increasing towards 120° and all interactions with the leaving group are diminishing as it moves away. There is steric acceleration in the $S_N1$ reaction rather than steric hindrance. This, as well as the stability of t-alkyl cations, is why t-alkyl compounds react by the $S_N1$ mechanism.
### Table 10.4 Relative Rates of $S_N1$ Reactions for Several Alkyl Bromides (solvent is $H_2O$, nucleophile is $H_2O$)

<table>
<thead>
<tr>
<th>Alkyl bromide</th>
<th>Class of alkyl bromide</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{C}—\text{Br}$</td>
<td>tertiary</td>
<td>1,200,000</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}—\text{Br}$</td>
<td>secondary</td>
<td>11.6</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2—\text{Br}$</td>
<td>primary</td>
<td>1.00*</td>
</tr>
<tr>
<td>$\text{CH}_3—\text{Br}$</td>
<td>methyl</td>
<td>1.05*</td>
</tr>
</tbody>
</table>

*Although the rate of the $S_N1$ reaction of this compound with water is 0, a small rate is observed as a result of an $S_N2$ reaction.*
• Order of reactivity follows stability of carbocations (opposite to S_N2)
  – 3° > 2° > 1° >> CH₃X
  – More stable carbocation requires less energy to form.
• A better leaving group will increase the rate of the reaction.
Stereochemistry of $S_N 1$

The $S_N 1$ reaction produces mixtures of enantiomers. There is usually more inversion than retention of configuration.
The products resulting from substitution of cyclic compounds are obtained in the $S_N$ reaction because the nucleophile can approach the carbocation intermediate from either side.

Both the cis- and trans-4-methylcyclohexanol are obtained in the $S_{N1}$ reaction because the nucleophile can approach the carbocation intermediate from either side.
Sometimes extra inverted product is formed in an $S_N_1$ reaction because …
Experimental Evidence for an $S_{N1}$ Reaction

1. The rate of the reaction depends only on the concentration of the alkyl halide

2. The rate of the reaction is favored by the bulkiness of the alkyl substituent

3. In the substitution of a chiral alkyl halide, a racemic mixture of product is obtained
The leaving group

$S_N2$ Reactions Are Affected by the Leaving Group

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Relative Rates of Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{HO}^- + \text{RCH}_2\text{I} \rightarrow \text{RCH}_2\text{OH} + \text{I}^-$</td>
<td>30,000</td>
</tr>
<tr>
<td>$\text{HO}^- + \text{RCH}_2\text{Br} \rightarrow \text{RCH}_2\text{OH} + \text{Br}^-$</td>
<td>10,000</td>
</tr>
<tr>
<td>$\text{HO}^- + \text{RCH}_2\text{Cl} \rightarrow \text{RCH}_2\text{OH} + \text{Cl}^-$</td>
<td>200</td>
</tr>
<tr>
<td>$\text{HO}^- + \text{RCH}_2\text{F} \rightarrow \text{RCH}_2\text{OH} + \text{F}^-$</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 17.4 Halide leaving groups in the $S_N2$ reaction

<table>
<thead>
<tr>
<th>Halide X in MeX</th>
<th>$pK_a$ of conjugate acid HX</th>
<th>Rate of reaction with NaOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>+3</td>
<td>very slow indeed</td>
</tr>
<tr>
<td>Cl</td>
<td>−7</td>
<td>moderate</td>
</tr>
<tr>
<td>Br</td>
<td>−9</td>
<td>fast</td>
</tr>
<tr>
<td>I</td>
<td>−10</td>
<td>very fast</td>
</tr>
</tbody>
</table>
The weaker the base, the better it is as a leaving group

relative basicities of the halide ions

$I^- < Br^- < Cl^- < F^-$

weakest base, most stable base

strongest base, least stable base

relative leaving abilities of the halide ions

$I^- > Br^- > Cl^- > F^-$

best leaving group

worst leaving group

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The Effect of the Leaving Group on an $S_{N1}$ Reaction

The nucleophile has no effect on the rate of an $S_{N1}$ reaction

**relative reactivities of alkyl halides in an $S_{N1}$ reaction**

- most reactive: $RI > RBr > RCl > RF$ (least reactive)

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Nucleophilic substitutions on alcohols

Hydroxide ion is very basic, very reactive, and a bad leaving group. But we want to use alcohols in nucleophilic substitution reactions because they are easily made.

(a) The simplest answer is to protonate the OH group with strong acid.

(b) Convert the OH group into a better leaving group.
The better leaving groups (such as the halogens) need no acid catalyst but the less good ones (N, O, S) usually need acid. Here is a summary diagram and a specific example.

\[ \text{S}_N1 \text{ mechanism} \]
With α-bromo carbonyl compounds, substitution leads to **two electrophilic groups** on neighbouring carbon atoms. **Each group has become more electrophilic because of the presence of the other**— the C=O group makes the C–Br bond more reactive and the Br makes the C=O group more reactive.

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**$S_N_2$ mechanism**
If a tertiary cation cannot become planar, it is not formed. A classic case is the cage halide below, which does not react with nucleophiles either by $S_N^1$ or by $S_N^2$. It does not react by $S_N^1$ because the cation cannot become planar nor by $S_N^2$ because the nucleophile cannot approach the carbon atom from the right direction (see below).
<table>
<thead>
<tr>
<th>Reactions</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl and 1° alkyl halides</td>
<td>$S_N^2$ only</td>
</tr>
<tr>
<td>Vinylic and aryl halides</td>
<td>Neither $S_N^1$ nor $S_N^2$</td>
</tr>
<tr>
<td>2° alkyl halides</td>
<td>$S_N^1$ and $S_N^2$</td>
</tr>
<tr>
<td>1° and 2° benzylic and 1° and 2° allylic halides</td>
<td>$S_N^1$ and $S_N^2$</td>
</tr>
<tr>
<td>3° alkyl halides</td>
<td>$S_N^1$ only</td>
</tr>
<tr>
<td>3° benzylic and 3° allylic halides</td>
<td>$S_N^1$ only</td>
</tr>
</tbody>
</table>
Write the mechanisms for each of the following reactions and specify whether it is $S_N1$ or $S_N2$:

$$\text{CH}_3\text{CH}═\text{CHCH}_2\text{Br} + \text{HO}^- \quad \rightarrow \quad \text{CH}_3\text{CH}═\text{CHCH}_2\text{OH} + \text{Br}^-$$

1-bromo-2-butene  
2-butene-1-ol

an allylic halide

$$\text{CH}_3\text{CH}═\text{CHCH}_2\text{Br} + \text{H}_2\text{O} \quad \rightarrow \quad \text{CH}_3\text{CH}═\text{CHCH}_2\text{OH} + \text{CH}_3\text{CHCH}═\text{CH}_2$$

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Write the mechanisms for each of the following reactions and specify whether it is $S_{N1}$ or $S_{N2}$:

Arrange these compounds in order of decreasing $S_{N2}$ reaction rate:
Explain which compound has a faster rate of $S_{N}^1$ reaction.
Basicity versus Nucleophilicity

**Basicity**

\[ B^- + H\text{--A} \rightleftharpoons K_{eq} B\text{--H} + A^- \]

**Nucleophilicity**

\[ B^- + C\text{--X} \rightarrow k_r B\text{--C} + X^- \]

- Basicity is defined by the equilibrium constant for abstracting a proton.
- Nucleophilicity is defined by the rate of attack on the electrophilic carbon atom.
When comparing molecules with the same attacking atom

<table>
<thead>
<tr>
<th>stronger base, better nucleophile</th>
<th>weaker base, poorer nucleophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH⁻</td>
<td>H₂O</td>
</tr>
<tr>
<td>CH₃O⁻</td>
<td>CH₃OH</td>
</tr>
<tr>
<td>-NH₂</td>
<td>NH₃</td>
</tr>
<tr>
<td>CH₃CH₂NH⁻</td>
<td>CH₃CH₂NH₂</td>
</tr>
</tbody>
</table>
When comparing molecules with attacking atoms of approximately the same size,

**relative acid strengths**

\[
\text{NH}_3 \ < \ \text{H}_2\text{O} \ < \ \text{HF}
\]

**relative base strengths and relative nucleophilicities**

\[
\text{NH}_2^- \ > \ \text{HO}^- \ > \ F^-
\]
When comparing molecules with attacking groups that are very different in size, another factor comes into play—the polarizability of the atom.

more bonding

little bonding
When comparing molecules with attacking groups that are very different in size, another factor comes into play—the polarizability of the atom. Because the electrons are farther away in the larger atom, they are not held as tightly and can, therefore, move more freely toward a positive charge. As a result, the electrons are able to overlap from farther away with the orbital of carbon, as shown in Figure 10.5. This results in a greater degree of bonding in the transition state, making it more stable.
Figure 10.5 An iodide ion is larger and more polarizable than a fluoride ion. Therefore, the relatively loosely held electrons of the iodide ion can overlap from farther away with the orbital of carbon undergoing nucleophilic attack. The tightly bound electrons of the fluoride ion cannot start to overlap until the atoms are closer together.