Chapter 6
Ionic Reactions-Nucleophilic Substitution and Elimination Reactions of Alkyl Halides
Introduction

- The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge.
  - In alkyl halides this polarity causes the carbon to become activated to substitution reactions with nucleophiles.

<table>
<thead>
<tr>
<th>C—X Bond length (Å)</th>
<th>1.39</th>
<th>1.78</th>
<th>1.93</th>
<th>2.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>C—X Bond strength (kJ mol⁻¹)</td>
<td>472</td>
<td>350</td>
<td>293</td>
<td>239</td>
</tr>
</tbody>
</table>

- Carbon-halogen bonds get less polar, longer and weaker in going from fluorine to iodine.
Alkyl Halides and Nucleophilic Substitution

The Polar Carbon-Halogen Bond

- Alkyl halides undergo substitution reactions with nucleophiles.

\[ R-X + :Nu^- \rightarrow R-Nu + X^- \]

- Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

\[ \text{elimination of } HX \]
Alkyl Halides and Nucleophilic Substitution

General Features of Nucleophilic Substitution

- Three components are necessary in any substitution reaction.

\[
R-X + :Nu^- \rightarrow R-Nu + X^-
\]

- \( sp^3 \) hybridized C
- Nucleophile
- Leaving group

Examples

\[
\begin{align*}
[1] & \quad \text{CH}_3-\text{Cl} + \cdot\text{OH} \rightarrow \text{CH}_3-\cdot\text{OH} + \text{Cl}^- \\
[2] & \quad \text{CH}_3\text{CH}_2\text{CH}_2-\text{I} + \cdot\text{SH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2-\cdot\text{SH} + \text{I}^- \\
[3] & \quad \text{CH}_3\text{CH}_2-\text{Br} + \cdot\text{OCH}_3 \rightarrow \text{CH}_3\text{CH}_2-\cdot\text{OCH}_3 + \text{Br}^-
\end{align*}
\]

A new C–Nu bond forms.
The leaving group comes off.
Alkyl Halides and Nucleophilic Substitution

General Features of Nucleophilic Substitution

- Negatively charged nucleophiles like $\text{HO}^-$ and $\text{HS}^-$ are used as salts with $\text{Li}^+$, $\text{Na}^+$, or $\text{K}^+$ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{Na}^+\cdot\text{HO}^- \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\cdot\text{HO}^- + \text{Na}^+\text{Br}^-
\]

- When a neutral nucleophile is used, the substitution product bears a positive charge.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \cdot\text{N(CH}_3)_3 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\cdot\text{N(CH}_3)_3 + \text{Br}^-
\]
Alkyl Halides and Nucleophilic Substitution

General Features of Nucleophilic Substitution

• Furthermore, when the substitution product bears a positive charge and also contains a proton bonded to O or N, the initially formed substitution product readily loses a proton in a Brønsted-Lowry acid-base reaction, forming a neutral product.
The Nucleophile

A nucleophile may be any molecule with an unshared electron pair.

We’ll discuss later what makes a nucleophile strong or weak (good or bad).

Chapter 6
A leaving group is a substituent that can leave as a relatively stable entity. It can either leave as an anion or as a neutral molecule.

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

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

\[ \text{H}_3\text{N}^- + \text{CH}_3\text{--Br} \rightarrow \text{CH}_3\text{--NH}_3^+ + :\text{Br}^- \]

...or as a neutral molecule

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

\[ \text{CH}_3\text{--O}^- + \text{CH}_3\text{--O}^+\text{--H} \rightarrow \text{CH}_3\text{--O}^+\text{--CH}_3 + :\text{O}^-\text{--H} \]
Alkyl Halides and Nucleophilic Substitution

The Leaving Group

- In a nucleophilic substitution reaction of R—X, the C—X bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming \( X^- \). The more stable the leaving group \( X^- \), the better able it is to accept an electron pair.

**In comparing two leaving groups, the better leaving group is the weaker base.**

![Nucleophilic substitution](image)
Alkyl Halides and Nucleophilic Substitution

The Leaving Group

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Leaving group</th>
<th>Conjugate acid</th>
<th>pKₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>R–Cl</td>
<td>Cl⁻</td>
<td>HCl</td>
<td>-7</td>
</tr>
<tr>
<td>R–Br</td>
<td>Br⁻</td>
<td>HBr</td>
<td>-9</td>
</tr>
<tr>
<td>R–I</td>
<td>I⁻</td>
<td>HI</td>
<td>-10</td>
</tr>
<tr>
<td>R–OH₂⁺</td>
<td>H₂O</td>
<td>H₃O⁺</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

These molecules undergo nucleophilic substitution. good leaving groups
Alkyl Halides and Nucleophilic Substitution

The Leaving Group

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Leaving group</th>
<th>Conjugate acid</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>R–F</td>
<td>F&lt;sup&gt;−&lt;/sup&gt;</td>
<td>HF</td>
<td>3.2</td>
</tr>
<tr>
<td>R–OH</td>
<td>O&lt;sup&gt;−&lt;/sup&gt;H</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>15.7</td>
</tr>
<tr>
<td>R–NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>38</td>
</tr>
<tr>
<td>R–H</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
</tr>
<tr>
<td>R–R</td>
<td>R&lt;sup&gt;−&lt;/sup&gt;</td>
<td>RH</td>
<td>50</td>
</tr>
</tbody>
</table>

These molecules do not undergo nucleophilic substitution. Poor leaving groups.
Neutral molecules as leaving groups

Poor leaving groups can be turned into good leaving groups by protonation.

CH₃-OH

Hydroxide ion is a poor leaving group because it is the anion of a weak acid, H₂O.

In the presence of a strong acid,

CH₃-OH + H₂SO₄ → CH₃OH + HSO₄⁻

a nucleophilic substitution reaction occurs:

CH₃OH (nucleophile) + CH₃OH (good leaving group) → CH₃OCH₃ (leaving group) + H₂O
The Leaving Group

- The best leaving groups are weak bases which are relatively stable.

★ Other very weak bases (besides halide ions) which are good leaving groups:

Alkylsulfonate

which is the conjugate acid of a sulfonic acid (a very strong acid)

Sulfonic acid

The most common alkylsulfonate is:

Tosylate
Kinetics of a Nucleophilic Substitution Reaction: An $S_{N2}$ Reaction

- The initial rate of the following reaction is measured

$$\text{CH}_3\text{Cl} + \text{OH}^- \xrightarrow{60^\circ\text{C}} \text{H}_2\text{O} \quad \text{CH} \quad \text{OH}^- + \text{Cl}^-$$

- The rate is directly proportional to the initial concentrations of both methyl chloride and hydroxide

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Initial [CH$_3$Cl]</th>
<th>Initial [OH$^-$]</th>
<th>Initial Rate (mol L$^{-1}$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0010</td>
<td>1.0</td>
<td>$4.9 \times 10^{-7}$</td>
</tr>
<tr>
<td>2</td>
<td>0.0020</td>
<td>1.0</td>
<td>$9.8 \times 10^{-7}$</td>
</tr>
<tr>
<td>3</td>
<td>0.0010</td>
<td>2.0</td>
<td>$9.8 \times 10^{-7}$</td>
</tr>
<tr>
<td>4</td>
<td>0.0020</td>
<td>2.0</td>
<td>$19.6 \times 10^{-7}$</td>
</tr>
</tbody>
</table>

- The rate equation reflects this dependence

$$\text{Rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]$$

- $S_{N2}$ reaction: substitution, nucleophilic, 2nd order (bimolecular)
A Mechanism for the $S_{N2}$ Reaction

A transition state is the high energy state of the reaction

★ It is an unstable entity with a very brief existence ($10^{-12}$ s)

In the transition state of this reaction bonds are partially formed and broken

★ Both chloromethane and hydroxide are involved in the transition state and this explains why the reaction is second order
The $S_N2$ Reaction

- The $S_N2$ reaction occurs when an electron pair on the nucleophile $\text{Nu}^-$ forces out the group $X^-$, which takes with it the electron pair from the former C-X bond.

- The transition state of an $S_N2$ reaction has a planar arrangement of the carbon atom and the remaining three groups.
An energy diagram of a typical $S_N2$ reaction

- An energy barrier is evident because a bond is being broken in going to the transition state (which is the top of the energy barrier).
- The difference in energy between starting material and the transition state is the free energy of activation ($\Delta G^\ddagger$).
- The difference in energy between starting molecules and products is the free energy change of the reaction, $\Delta G^\circ$.
In a highly endergonic reaction of the same type the energy barrier will be even higher ($\Delta G^\ddagger$ is very large)
There is a direct relationship between $\Delta G^\ddagger$ and the temperature of a reaction

- The higher the temperature, the faster the rate

$$k = k_0 e^{-\Delta G^\ddagger/RT}$$

- Near room temperature, a 10°C increase in temperature causes a doubling of rate
- Higher temperatures cause more molecules to collide with enough energy to reach the transition state and react
The Stereochemistry of $S_{N2}$ Reactions

- Backside attack of nucleophile results in an inversion of configuration

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

An inversion of configuration

(R)-(−)-2-Bromooctane
\[ [\alpha]_D^{2} = -34.25^\circ \]
Enantiomeric purity = 100%

(S)-(+)2-Octanol
\[ [\alpha]_D^{2} = +9.90^\circ \]
Enantiomeric purity = 100%

- In cyclic systems a cis compound can react and become trans product

\[
\text{cis-1-Chloro-3-methylcyclopentane} \quad \text{trans-3-Methylcyclopentanol}
\]
Alkyl Halides and Nucleophilic Substitution

Mechanisms of Nucleophilic Substitution

• All $S_N^2$ reactions proceed with backside attack of the nucleophile, resulting in inversion of configuration at a stereogenic center.

Figure 7.9 Stereochemistry of the $S_N^2$ reaction

: $\text{Nu}^-$ and $\text{Br}^-$ are 180° away from each other, on either side of a plane containing R, H, and D.
Alkyl Halides and Nucleophilic Substitution

Mechanisms of Nucleophilic Substitution

Figure 7.10 Two examples of inversion of configuration in the $S_{N}2$ reaction

- The bond to the nucleophile in the product is always on the opposite side relative to the bond to the leaving group in the starting material.

![Diagram of inversion of configuration in $S_{N}2$ reaction with examples involving SH and OH nucleophiles.]
The Reaction of tert-Butyl Chloride with Hydroxide Ion: An $S_N1$ Reaction

- tert-Butyl chloride undergoes substitution with hydroxide
- The rate is independent of hydroxide concentration and depends only on concentration of tert-butyl chloride

\[
(CH_3)_3C\text{—Cl} + OH^- \xrightarrow{\text{acetone}} (CH_3)_3C\text{—OH} + Cl^- \\
\text{Rate } \propto [(CH_3)_3CCl] \\
\text{Rate } = k[(CH_3)_3CCl]
\]

$S_N1$ reaction: Substitution, nucleophilic, 1st order (unimolecular)

- The rate depends only on the concentration of the alkyl halide
- Only the alkyl halide (and not the nucleophile) is involved in the transition state of the step that controls the rate
Mechanism of the $S_{N}1$ Reaction (Stepwise)

**bond heterolysis:**

$$
\begin{align*}
\text{CH}_3\text{C-Cl} & \xrightarrow{\text{RDS slow step}} \text{CH}_3\text{C}^+ + \text{Cl}^- \\
\text{CH}_3 & \quad \text{t-butyl carbocation} \\
& \quad \text{a high energy intermediate}
\end{align*}
$$

**nucleophilic addition:**

$$
\begin{align*}
\text{CH}_3\text{C}^+ & + \text{H} :\text{O}^- \xrightarrow{\text{fast}} \text{CH}_3\text{C-O}^- + \text{H}_3\text{O}^+ \\
\text{CH}_3 & \quad \text{nucleophile} \\
& \quad \text{t-butyloxonium ion}
\end{align*}
$$

**proton exchange:**

$$
\begin{align*}
\text{CH}_3\text{C-O}^- & \xrightarrow{\text{fast}} \text{CH}_3\text{C-O}^- + \text{H}_3\text{O}^+ \\
\text{CH}_3 & \quad \text{base}
\end{align*}
$$
Multistep Reactions and the Rate-Determining Step

- In multistep reactions, the rate of the slowest step will be the rate of the entire reaction.
- This is called the rate-determining step.
- In the case below $k_1 \ll k_2$ or $k_3$ and the first step is rate determining.
Mechanism of the $S_{N1}$ Reaction

Key features of the $S_{N1}$ mechanism are that it has two steps and involves a carbocation intermediate.
Reaction Energy Diagram: $S_N^1$ Mechanism

- Since the $S_N^1$ mechanism has two steps, there are two energy barriers.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn with $\Delta H^\circ_{\text{overall}}$ as a negative value, since the products are lower in energy than the starting materials.
Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

• The effect of the type of alkyl halide on $S_N1$ reaction rates can be explained by considering carbocation stability.

• Carbocations are classified as primary ($1^0$), secondary ($2^0$), or tertiary ($3^0$), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.
Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

• The order of carbocation stability can be rationalized through inductive effects and hyperconjugation.

• Inductive effects are electronic effects that occur through σ bonds. Specifically, the inductive effect is the pull of electron density through σ bonds caused by electronegativity differences between atoms.

• Alkyl groups are electron donating groups that stabilize a positive charge. Since an alkyl group has several σ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and more able to donate electron density.

• In general, the greater the number of alkyl groups attached to a carbon with a positive charge, the more stable will be the cation.
Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

Increasing number of electron-donating R groups
Increasing carbocation stability

Figure 7.17  Electrostatic potential maps for different carbocations

- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.
Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

- The order of carbocation stability is also a consequence of hyperconjugation.
- Hyperconjugation is the spreading out of charge by the overlap of an empty $p$ orbital with an adjacent $\sigma$ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a large volume, and this stabilizes the carbocation.

- Example: $\text{CH}_3^+$ cannot be stabilized by hyperconjugation, but $(\text{CH}_3)_2\text{CH}^+$ can.

\[
\begin{align*}
\text{CH}_3^+ & \quad \text{H} \quad \text{C} \quad \text{H} \\
\text{Overlap of the C-H }\sigma\text{ bond with the adjacent vacant }p\text{ orbital stabilizes the carbocation.}
\end{align*}
\]

This carbocation has no opportunity for orbital overlap with the vacant $p$ orbital.
Alkyl Halides and Nucleophilic Substitution

Stereochemistry of the $S_N1$ Reaction:

• Loss of the leaving group in Step [1] generates a planar carbocation that is achiral. Attack of the nucleophile in Step [2] can occur on either side to afford two products which are a pair of enantiomers.

• Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a racemic mixture. We say that racemization has occurred.
If an $S_N1$ reaction is carried out on one enantiomer of a chiral reactant and proceeds through an achiral carbocation intermediate, the product will be optically inactive.

The symmetrical intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic 50 : 50 mixture of enantiomers.
**Alkyl Halides and Nucleophilic Substitution**

**Mechanisms for Nucleophilic Substitution**

*Figure 7.16* Two examples of racemization in the $S_N1$ reaction

- Nucleophilic substitution of each starting material by an $S_N1$ mechanism forms a **racemic mixture** of two products.
- With $H_2O$, a neutral nucleophile, the initial product of nucleophilic substitution ($ROH_2^+$) loses a proton to form the final neutral product, $ROH$ (Section 7.6).
Factors Affecting the Rate of $S_N1$ and $S_N2$ Reactions

- The Effects of the Structure of the Substrate
- $S_N2$ Reactions
  
  In $S_N2$ reactions alkyl halides show the following general order of reactivity:
  
  Methyl > primary > secondary >> (tertiary — unreactive)

  Steric hinderance: the spatial arrangement of the atoms or groups at or near a reacting site hinders or retards a reaction
  
  * In tertiary and neopentyl halides, the reacting carbon is too sterically hindered to react.
• **$S_N1$ reactions**

  ➔ Generally only tertiary halides undergo $S_N1$ reactions because only they can form relatively stable carbocations.

  (Secondary substrates can be made to undergo $S_N1$ reactions by manipulating other factors which help stabilize the $2^\circ$ carbocation.)

• **The Hammond-Leffler Postulate**

  SKIP THIS SECTION
The Effect of the Concentration of the Nucleophile

- $S_N\text{1 Reaction}$
  - Rate does not depend on the identity or concentration of nucleophile

- $S_N\text{2 Reaction}$
  - Rate is directly proportional to the concentration of nucleophile
Characteristics of the $S_N2$ Reaction

- Nucleophilicity usually increases going down a column of the periodic table
  - $\text{HS}^- \text{ is more nucleophilic than HO}^-$
  - Halide reactivity order is $\text{I}^- > \text{Br}^- > \text{Cl}^-$
  - Going down the periodic table, elements have their valence electrons in successively larger shells, where they are successively farther from the nucleus, less tightly held, and consequently more reactive

- Negatively charged nucleophiles are usually more reactive than neutral ones
  - $S_N2$ reactions are often carried out under basic conditions rather than neutral or acidic conditions (in order to insure that the nucleophile has a charge)
The Leaving Group

- Best leaving groups are the most stable bases.
  - Weak bases such as Cl\(^-\) and tosylate ion make good leaving groups, while strong bases such as OH\(^-\) and NH\(_2\)\(^-\) make poor leaving groups

<table>
<thead>
<tr>
<th>Relative reactivity</th>
<th>OH(^-), NH(_2)(^-), OR(^-)</th>
<th>F(^-)</th>
<th>Cl(^-)</th>
<th>Br(^-)</th>
<th>I(^-)</th>
<th>TosO(^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;&lt;1</td>
<td>1</td>
<td>200</td>
<td>10,000</td>
<td>30,000</td>
<td>60,000</td>
<td></td>
</tr>
</tbody>
</table>

Leaving group reactivity
THE STRENGTH OF THE NUCLEOPHILE

However,

• **Nucleophilicity does not parallel basicity** when steric hindrance becomes a factor.
  
  • **Steric hindrance** causes a decrease in nucleophile reactivity due to the presence of bulky groups as the site of a reaction.
  
  • Steric hindrance decreases nucleophilicity but not basicity.
  
  • Sterically hindered bases that are poor nucleophiles are called **nonnucleophilic bases**.

\[ \text{ethoxide} \quad \text{stronger nucleophile} \]

\[ \text{tert-butoxide} \quad \text{stronger base} \]

Three CH₃ groups sterically hinder the O atom, making it a **weaker nucleophile**.
THE STRENGTH OF THE NUCLEOPHILE

Also, remember that nucleophilicity **does not** parallel basicity in **polar protic solvents** (defined later):

That is, nucleophilicity increases down a column of the periodic table as the size of the anion increases. **This opposite to basicity.**
Solvent Effects on $S_{N2}$ Reactions:

Polar Protic and Aprotic Solvents

**Polar Protic Solvents**

- Polar protic solvents have a hydrogen atom attached to strongly electronegative atoms. That is, they contain an –OH or –NH group.
- They solvate nucleophiles and therefore they slow down $S_{N2}$ reactions by forming a “cage” around the nucleophile.

Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents:

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

Relative nucleophilicity in polar protic solvents:

$SH^- > CN^- > I^- > OH^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O$
Effects of Polar Protic and Polar Aprotic Solvents

- **Polar aprotic solvents** have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding. However, they are still very polar. They solvate the metal cations but not the nucleophilic anions.

![Figure 7.7 Examples of polar aprotic solvents](image)
Nucleophiles in Polar Protic Solvents

Polar aprotic solvents solvate cations by ion–dipole interactions, BUT anions are not well solvated because the solvent cannot hydrogen bond to them. These anions are said to be “naked”. These bare, unsolvated anions have greater nucleophilicity and \( S_N^2 \) reactions occur at a faster rate.
Effects of Polar Protic and Polar Aprotic Solvents

The result is that -

• in polar aprotic solvents, nucleophilicity does parallel basicity, and the stronger base is indeed the stronger nucleophile.
• Because basicity decreases with size down a column, nucleophilicity decreases as well.
Solvent Effects on $S_{N1}$ Reactions:

The Ionizing Ability of the Solvent

- Polar protic solvents are excellent solvents for $S_{N1}$ reactions.
- Polar protic solvents stabilize the carbocation-like transition state leading to the carbocation thus lowering the activation energy.
- Water-ethanol and water-methanol mixtures are most common.

\[
\begin{align*}
(CH_3)_3C\text{--Cl} & \rightarrow \left[(CH_3)_3C\text{--Cl}^{\delta+}\right]^{\ddagger} & \rightarrow (CH_3)_3C^+ \quad + \quad Cl^- \\
\text{Reactant} & \quad \text{Transition state} & \quad \text{Products} \\
\text{Separated charges are developing.}
\end{align*}
\]
### Summary $S_N 1$ vs. $S_N 2$

In both types of reaction alkyl iodides react the fastest because of superior leaving group ability.

$$\text{R—I} > \text{R—Br} > \text{R—Cl} \quad S_N 1 \quad \text{or} \quad S_N 2$$

<table>
<thead>
<tr>
<th>Factor</th>
<th>$S_N 1$</th>
<th>$S_N 2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>$3^\circ$ (requires formation of a relatively stable carbocation)</td>
<td>Methyl $&gt; 1^\circ &gt; 2^\circ$ (requires unhindered substrate)</td>
</tr>
<tr>
<td>Nucleophile</td>
<td>Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)</td>
<td>Strong Lewis base, rate favored by high concentration of nucleophile</td>
</tr>
<tr>
<td>Solvent</td>
<td>Polar protic (e.g., alcohols, water)</td>
<td>Polar aprotic (e.g., DMF, DMSO)</td>
</tr>
<tr>
<td>Leaving group</td>
<td>$I &gt; Br &gt; Cl &gt; F$ for both $S_N 1$ and $S_N 2$ (the weaker the base after the group departs, the better the leaving group)</td>
<td></td>
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Alkyl Halides and Nucleophilic Substitution

Predicting the Likely Mechanism of a Substitution Reaction.

<table>
<thead>
<tr>
<th>Alkyl halide</th>
<th>Mechanism</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃X</td>
<td>Sₙ₂</td>
<td>Favored by</td>
</tr>
<tr>
<td>RCH₂X (1°)</td>
<td></td>
<td>• strong nucleophiles (usually a net negative charge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• polar aprotic solvents</td>
</tr>
<tr>
<td>R₃CX (3°)</td>
<td>Sₙ₁</td>
<td>Favored by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• weak nucleophiles (usually neutral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• polar protic solvents</td>
</tr>
<tr>
<td>R₂CHX (2°)</td>
<td>Sₙ₁ or Sₙ₂</td>
<td>The mechanism depends on the conditions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Strong nucleophiles favor the Sₙ₂ mechanism over the Sₙ₁ mechanism. For example, RO⁻ is a stronger nucleophile than ROH, so RO⁻ favors the Sₙ₂ reaction and ROH favors the Sₙ₁ reaction.</td>
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</tbody>
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Predicting the Mechanism of a Nucleophilic Substitution Reaction

\[ \text{SN}_1 \text{ reactions} \] are favored by tertiary substrates, by good leaving groups, by nonbasic (i.e., weak) nucleophiles, and by polar protic solvents.

\[ \text{SN}_2 \text{ reactions} \] are favored by primary substrates, by good leaving groups, by good nucleophiles, and by polar aprotic solvents.
Organic Synthesis: Functional Group Transformations Using $S_N2$ Reactions

- $\text{OH}^- \rightarrow R\text{OH}$, Alcohol
- $\text{R'O}^- \rightarrow R\text{OR}'$, Ether
- $\text{SH}^- \rightarrow R\text{SH}$, Thiol
- $\text{R'S}^- \rightarrow R\text{SR}'$, Thioether
- $\text{CN}^- \rightarrow R\text{C}=\text{N}$, Nitrile
- $\text{R'=C\equiv C}^- \rightarrow R\text{C}=\text{C}=\text{R}'$, Alkyne
- $\text{O} \quad \text{O} \rightarrow R\text{OCR}'$, Ester
- $\text{R}_2\text{N} \rightarrow R\text{NR}_3$, Quaternary ammonium halide
- $\text{N}_3^- \rightarrow R\text{N}_3$, Alkyl azide

$\text{R-X} \xrightarrow{(-\text{X}^-)}$ (R = Me, 1°, or 2°) (X = Cl, Br, or I)
Elimination Reactions

Remember, another major class of organic reactions is elimination reactions.

In an elimination reaction, groups X and Y are lost from a larger molecule

When X and Y are on adjacent C’s, this is called 1,2-elimination or beta-elimination.

For example, loss of HX from an alkyl halide produces an alkene. This elimination reaction is called DEHYDROHALOGENATION.

\[
\begin{align*}
\text{A base} & \quad \xrightarrow{\text{HX}} \quad \text{C} = \text{C} \\
\text{C}_\alpha & - \text{C}_\beta \ X \\
\text{C}^- \quad & + \quad \text{B}^- \\
& \quad \xrightarrow{\text{HX}} \\
& \quad \text{C} = \text{C} \quad + \quad 	ext{H} \cdot \text{B} \quad + \quad \text{X}^-
\end{align*}
\]
Elimination Reactions of Alkyl Halides

Useful for the synthesis of alkenes

Strong bases such as alkoxides favor this elimination reaction

\[
\begin{align*}
\text{CH}_3\text{CHCH}_3 & \xrightarrow{\text{C}_2\text{H}_5\text{ONa}, 55^\circ\text{C}} \text{CH}_2=\text{CH}-\text{CH}_3 + \text{NaBr} + \text{C}_2\text{H}_5\text{OH} \\
\text{CH}_3\text{CH}_3\text{CH}_3 & \xrightarrow{\text{C}_2\text{H}_5\text{ONa}, 55^\circ\text{C}} \text{CH}_3=\text{CH}-\text{CH}_3 + \text{NaBr} + \text{C}_2\text{H}_5\text{OH}
\end{align*}
\]
Alkoxide bases are made from the corresponding alcohols

By adding metallic Na or K to carefully dried alcohol

\[
2 \text{CH}_3\text{CH}_2\text{OH} + 2 \text{Na} \rightarrow 2 \text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ + \text{H}_2
\]

Ethanol (excess)

\[
\text{Sodium ethoxide dissolved in excess ethanol}
\]

\[
2 \text{CH}_3\text{C}\text{CH}_3\text{OH} + 2 \text{K} \rightarrow 2 \text{CH}_3\text{C}\text{CH}_3\text{O}^-\text{K}^+ + \text{H}_2
\]

\[
\text{tert-Butyl alcohol (excess)}
\]

\[
\text{Potassium \text{tert-}butoxide}
\]

Or by using a stronger base like sodium hydride (NaH)

\[
\text{R--O--H + Na}^+\text{H}^- \rightarrow \text{R--O}^-\text{Na}^+ + \text{H--H}
\]

\[
pK_a = 16
\]

Chapter 6

\[
pK_a = 35
\]
The reaction of isopropyl bromide with sodium ethoxide shows second order kinetics

\[
\text{C}_2\text{H}_5\text{O}^- + \text{CH}_3\text{CHBrCH}_3 \rightarrow \text{CH}_2=\text{CHCH}_3 + \text{C}_2\text{H}_5\text{OH} + \text{Br}^-
\]

Rate \propto [\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]

Rate = k[\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]

Mechanism:

Chapter 6
Energy diagram of the E2 reaction

$$C_2H_5O^- + CH_3CHBrCH_3 \rightarrow CH_2=CHCH_3 + C_2H_5OH + Br^-$$

Concerted means a single step, with no intermediates – like $S_{N2}$
Substitution versus Elimination

Every time an $S_N2$ reaction takes place, there will also be some E2 occurring as well.

Why? **Because nucleophiles are also bases.**

\[
\begin{align*}
\text{E2:} & \quad \text{Nu:} \\
\text{S}_N2: & \quad \text{Nu:}
\end{align*}
\]

\[
\text{Rate} = k_{\text{elim}} [RX][\text{Nu}^-] \quad \text{Rate} = k_{\text{sub}}[RX][\text{Nu}^-]
\]

However, this competition depends on the structure of RX and choice of base.
Substitution versus Elimination

**S<sub>N</sub>2 VERSUS E2**

★ If the base is small, S<sub>N</sub>2 is favored because approach at carbon is unhindered

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{CH}_3\text{CH}_2\text{ONa} \rightarrow \text{ethanol} \rightarrow \text{CH}_3\text{CH}==\text{CH}_2 + \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3
\]

(9%) (91%)

★ If the base is bulky, E2 is favored because approach at carbon is hindered

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{CH}_3\text{COK} \rightarrow \text{t-butyl alcohol} \rightarrow \text{CH}_3\text{CH}==\text{CH}_2 + \text{CH}_3\text{CH}_2\text{CH}_2\text{OC(CH}_3\text{)}_3
\]

(85%) (15%)

Chapter 6
**SECONDARY SUBSTRATE**

★ Approach to carbon is sterically hindered and **E2 ELIMINATION IS FAVORED**, especially if the base is strong.

\[
\text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ + \text{CH}_3\text{CHCH}_3 \underset{\text{C}_2\text{H}_5\text{OH}}{\xrightarrow{55^\circ\text{C}}} \text{CH}_3\text{CHCH}_3 + \text{CH}_2\equiv\text{CHCH}_3
\]

\[\text{Br} \quad \text{OCH}_2\text{CH}_3\]

\[\text{SN}_2 \quad (21\%) \quad \text{E2} \quad (79\%)
\]

**TERTIARY SUBSTRATE**

★ Approach to carbon is extremely hindered and **ELIMINATION PREDOMINATES**.

\[
\text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ + \text{CH}_3\text{CCH}_3 \underset{\text{C}_2\text{H}_5\text{OH}}{\xrightarrow{55^\circ\text{C}}} \text{CH}_3\text{CCH}_3 + \text{CH}_2\equiv\text{CCH}_3
\]

\[\text{Br} \quad \text{OCH}_2\text{CH}_3\]

\[\text{SN}_1 \quad (9\%) \quad \text{Mainly E2} \quad (91\%)
\]
★ EFFECT OF TEMPERATURE

★ Increasing temperature favors elimination over substitution

★ EFFECT OF THE SIZE OF THE BASE/NUCLEOPHILE

★ Large, sterically hindered bases favor elimination because they cannot directly approach the carbon closely enough to react in a substitution

★ Potassium tert-butoxide is an extremely bulky base and is routinely used to favor E2 reaction

\[
\text{CH}_3\text{C}^\text{−}\text{O}^− + \text{CH}_3\text{(CH}_2\text{)}_{15}\text{CH}_2\text{CH}_2\text{−Br} \xrightarrow{(\text{CH}_3)\text{COH} \ 40^\circ\text{C}} \text{H}_3\text{(CH}_2\text{)}_{15}\text{CH=CH}_2 + \text{CH}_3\text{(CH}_2\text{)}_{15}\text{CH}_2\text{CH}_2\text{−O−C−CH}_3
\]

E2 (85%)  S\text{N}_2 (15%)
The E1 reaction competes with the $S_{N1}$ reaction and likewise goes through a carbocation intermediate.

Elimination can also follow first order kinetics: the E1 REACTION.
Mechanism for E1

**Step 1**

\[
\text{H}_3\text{C}-\overset{\beta \alpha}{\text{C}}-\overset{\text{Cl}:}{\text{Cl}} \xrightarrow{\text{slow} \ \text{H}_2\text{O}} \text{H}_3\text{C}-\overset{\beta \alpha}{\text{C}}^+ + \overset{\text{Cl}:}{\text{Cl}}^- 
\]

Slow step is ionization of C-Cl bond, aided by solvent

**Step 2**

\[
\text{H-O} : + \overset{\beta \alpha}{\text{H-C}}^+ \rightarrow \text{H-O}^+ + \overset{\beta \alpha}{\text{H-C}} 
\]

Water can act as nucleophile (S\text{N}1)

**OR** as base (E1)
Mechanism for E1

In other words, there are two competing pathways that a carbocation can take:

1. The nucleophile bonds to the carbocation carbon giving the $S_{N1}$ product.
   OR

2. The nucleophile acts as a base and removes the $\beta$ proton giving the $E1$ product.

Chapter 6 62
Free Energy Diagram for competing pathways

Once the carbocation forms, it can go two different ways to give the $S_{N1}$ product and the $E1$ product.
## Overall Summary

<table>
<thead>
<tr>
<th>Factor</th>
<th>( S_{N1} )</th>
<th>( S )</th>
<th>( S_{N2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>3° (requires formation of a relatively stable carbocation)</td>
<td>Methyl &gt; 1° &gt; 2° (requires unhindered substrate)</td>
<td></td>
</tr>
<tr>
<td>Nucleophile</td>
<td>Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolyisys)</td>
<td>Strong Lewis base, rate favored by high concentration of nucleophile</td>
<td></td>
</tr>
<tr>
<td>Solvent</td>
<td>Polar protic (e.g., alcohols, water)</td>
<td>Polar aprotic (e.g., DMF, DMSO)</td>
<td></td>
</tr>
<tr>
<td>Leaving group</td>
<td>I &gt; Br &gt; Cl &gt; F for both ( S_{N1} ) and ( S_{N2} ) (the weaker the base after the group departs, the better the leaving group)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Overall Summary of Substitution/Elimination

#### Effect of Substrate Structure

<table>
<thead>
<tr>
<th></th>
<th>$S_{N1}$</th>
<th>$S_{N2}$</th>
<th>$E1$</th>
<th>$E2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CH_3X$</td>
<td></td>
<td>yes, very fast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$RCH_2X$</td>
<td></td>
<td>mostly</td>
<td></td>
<td>but hindered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bases give</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mostly alkenes</td>
</tr>
<tr>
<td>$R'\ \ \ \ \ \ \ \ RCHX$</td>
<td>very little</td>
<td>mostly $S_{N2}$ with weak bases</td>
<td>very little</td>
<td>strong bases promote E2</td>
</tr>
<tr>
<td>$R'\ \ \ \ \ \ \ \ \ R'X$</td>
<td>very favorable</td>
<td>none</td>
<td>always competes with $S_{N1}$</td>
<td>strong bases promote E2 path</td>
</tr>
<tr>
<td>$R''X$</td>
<td></td>
<td></td>
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Alkyl Halides and Nucleophilic Substitution

Predicting the Likely Mechanism of a Substitution Reaction.

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<th>Alkyl halide</th>
<th>Mechanism</th>
<th>Other factors</th>
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<tbody>
<tr>
<td>CH₃X</td>
<td>Sₙ2</td>
<td>Favored by</td>
</tr>
<tr>
<td>RCH₂X (1°)</td>
<td></td>
<td>• <strong>strong nucleophiles</strong> (usually a net negative charge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• polar aprotic solvents</td>
</tr>
<tr>
<td>R₃CX (3°)</td>
<td>Sₙ1</td>
<td>Favored by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>weak nucleophiles</strong> (usually neutral)</td>
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<td></td>
<td></td>
<td>• polar protic solvents</td>
</tr>
<tr>
<td>R₂CHX (2°)</td>
<td>Sₙ1 or Sₙ2</td>
<td>The mechanism depends on the conditions.</td>
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