Chapter 7: Alkyl Halides and Nucleophilic Substitution

**SN2 Reaction**
Mechanism:

![SN2 Reaction Mechanism Diagram]

Notes:
- One step reaction
- Order of reactivity: **Methyl > Primary > Secondary > Tertiary**
- Stereochemistry: Inversion of configuration at stereogenic center (because of backside attack)
- Better leaving group = faster reaction
- Favors: Strong nucleophiles
- Favors: Not-sterically-hindered alkyl halides
- Favors: Polar aprotic solvents (cannot hydrogen bond)

**SN1 Reaction**
Mechanism:

![SN1 Reaction Mechanism Diagram]

Notes:
- Two step reaction
- Order of reactivity: **Tertiary > Secondary > Primary > Methyl**
- Stereochemistry: Racemization (because the carbocation is planar)
- Better leaving group = faster reaction
- Favors: Weak nucleophiles
- Favors: Sterically hindered alkyl halides
- Favors: Polar protic solvents (can hydrogen bond)
Chapter 8: Alkyl Halides and Elimination Reactions

**E2 Reaction**

Mechanism:

Notes:
- One step reaction
- Order of reactivity: **Tertiary > Secondary > Primary**
- Stereochemistry: antiperiplanar arrangement of H and X
- Better leaving group = faster reaction
- Favors: Polar aprotic solvents, **strong bases**
- Products follow Zaitsev rule (more substituted alkene is the major product)

**E1 Reaction**

Mechanism:
Notes:
- Two step reaction
- Order of reactivity: Tertiary > Secondary > Primary
- Stereochemistry: Trigonal planar carbocation intermediate
- Better leaving group = faster reaction
- Favors: Polar protic solvents, weak bases
- Products follow Zaitsev rule

Chapter 9: Alcohols, Ethers, and Epoxides

Preparation of Alcohols
Mechanism:

Notes:
- SN2 mechanism

Preparation of Alkoxides
Mechanism:

Preparation of Ethers (Williamson Ether Synthesis)
Mechanism:
Notes:
- SN2 mechanism

**Preparation of Epoxides**

Alcohol Dehydration: Secondary and Tertiary

Mechanism:
Notes:
- E1 mechanism
- Zaitzev rule applies (the most substituted product is the major product)
- Carbocation rearrangements are possible

**Alcohol Dehydration: Primary**

![Alcohol Dehydration Reaction](image)

Mechanism:

![Mechanism Diagram](image)

Notes:
- E2 mechanism
- Zaitzev rule applies

**Other Reagents to Form Alkenes: POCl3 and Pyridine**

![Other Reagents Reaction](image)

Notes:
- E2 mechanism
Alkyl Halides Formation from Alcohols: Secondary and Tertiary

\[
\text{OH} + \text{H-Cl} \rightarrow \text{Cl}
\]

Mechanism:

Notes:
- SN1 mechanism
- Carbocation rearrangements are possible

Alkyl Halides Formation from Alcohols: Primary

\[
\text{OH} + \text{H-Br} \rightarrow \text{Br}
\]

Mechanism:

Notes:
- SN2 mechanism (inversion of stereochemistry)

Other Reagents to Form Alkyl Halides: SOCl2 and PBr3

\[
\begin{align*}
\text{R-OH} + \text{SOCl}_2 & \rightarrow \text{R-Cl} \\
\text{pyridine} & \\
\text{R-OH} + \text{PBr}_3 & \rightarrow \text{R-Br}
\end{align*}
\]

Notes:
- SN2 reaction, both reagents will lead to inversion of stereochemistry

Reaction with Alkyl Tosylates
First step:
- Note: Stereochemistry is retained

Second step:
- Substitution is carried out with strong \( \text{Nu}^- \), so the mechanism is \( S_N2 \).
- Elimination is carried out with strong bases, so the mechanism is \( E2 \).

Ether Cleavage with Strong Acids: Secondary and Tertiary

Ether Cleavage with Strong Acids: Primary

Notes:
- SN1 mechanism
Mechanism:

\[
\text{Epoxide Reactions with Acids}
\]

Notes:
- SN2 mechanism

Epoxide Reactions with Strong Nucleophiles

Notes:
- SN1/SN2 mechanism
- Attacks at the more substituted carbon
- Backside attack = inversion of configuration
Mechanism:

Notes:
- SN2 mechanism
- Attacks the less substituted carbon
- Backside attack = inversion of configuration

Chapter 10: Alkenes

Hydrohalogenation

Mechanism:

Notes:
- Carbocation rearrangements are possible
- Markovnikov’s rule is followed (H bonds to less subbed carbon, X bonds to more subbed carbon)
- Stereochemistry: Syn (added to same sides) and anti (add to opposite sides) addition

Hydration
**Mechanism:**

Addition of water to alkenes

**Notes:**
- Carbocation rearrangements are possible
- Markovnikov’s rule is followed
- Same mechanism if using alcohol instead of water to make ethers
- Stereochemistry: Syn and anti-addition occur

**Halogenation**

**Mechanism:**

**Step [1]** Addition of the electrophile (X⁺) to the π bond

- Four bonds are broken or formed in this step: the electron pair in the π bond and a lone pair on a halogen atom are used to form two new C–X bonds. The X–X bond is also cleaved heterolytically, forming X⁺. This step is rate-determining.
- The three-membered ring containing a positively charged halogen atom is called a **bridged halonium ion**. This strained three-membered ring is highly unstable, making it amenable to opening of the ring in the second step.

**Step [2]** Nucleophilic attack of X⁻

- **Nucleophilic attack of X⁻** opens the ring of the halonium ion, forming a new C–X bond and relieving the strain in the three-membered ring.
Halogen attacks most subbed carbon in halonium ion
- No carbocation rearrangements
- Stereochemistry: anti-addition

Halohydrin Formation

**Mechanism:**

Notes:
- H$_2$O attacks more subbed carbon (recall acid-catalyzed ring opening of an epoxide)
- No carbocation rearrangements
- Stereochemistry: Anti-addition
- Special reagent: NBS
Hydroboration-Oxidation

Mechanism:

Notes:
- You only need to know the hydroboration step, not the oxidation step
- Anti-markovnikov (OH is added to less subbed carbon)
- No carbocation rearrangements
- Syn-addition
- Retention of configuration
- Same mechanism as 9-BBN

Chapter 11: Alkynes

Preparation of Alkynes

Mechanism (2\textsuperscript{nd} step):
Hydrohalogenation

Mechanism:

Addition of first equivalent:

Addition of second equivalent:

Notes:

- Markovnikov’s rule is followed
- The carbocation will form on the more substituted or resonance-stabilized carbon

Halogenation

Mechanism:
Anti-addition

Halogens will attack the more substituted or resonance-stabilized side

**Hydration**

\[ \text{H}_2\text{C}≡\text{CH}_3 + \text{H}_2\text{O} → \text{H}_3\text{C}=-\text{OH} \]

**Mechanism:**

Notes:
- Markovnikov’s rule is followed
- Unstable enol
- End product is a ketone
- Acid-catalyzed
Hydroboration-Oxidation

Mechanism:

Notes:
- Anti-markovnikov
- Unstable enol
- End product is aldehyde (if it’s a terminal alkyne) or ketone

Formation of Acetylide Anions

Acetylide Anion Reactions with Alkyl Halides

Acetylide Anion Reactions with Epoxides

Chapter 12: Oxidation and Reduction
Reduction of Alkenes

\[ R-\text{CH}=\text{CH}-R \xrightarrow{\text{H}_2, \text{Pd/C}} R-\text{CH}_2-\text{CH}_2-R \]

- Syn addition occurs

Reduction of Aldehydes

\[ \text{PhCH}_2\text{CHO} \xrightarrow{\text{H}_2, \text{Pd/C}} \text{PhCH}_2\text{CH}_2\text{OH} \]

- Stereochemistry: Racemic mixture

Reduction of Ketones

\[ \text{PhCOCH}_3 \xrightarrow{\text{H}_2, \text{Pd/C}} \text{PhCH}_2\text{CH}_2\text{OH} \]

Reduction of Alkynes

\[ R-\text{C}≡\text{C}-R \xrightarrow{2\text{H}_2, \text{Pd/C}} R-\text{C}-\text{C}-R \]

- 2 equivalents of H2 are required
- 4 new C-H bonds are formed

\[ R-\text{C}≡\text{C}-R \xrightarrow{\text{H}_2, \text{Lindlar catalyst}} \text{HC}≡\text{C}-\text{H} \]

- Syn addition occurs = cis alkene product

\[ R-\text{C}≡\text{C}-R \xrightarrow{\text{Na}, \text{NH}_3} \text{HC}=\text{C}-\text{R} \]

- trans alkene
• Anti-addition occurs = trans alkene product

Reduction of Alkyl Halides

\[
\text{R-X} \xrightarrow{[1]} \text{LiAlH}_4 \xrightarrow{[2]} \text{H}_2\text{O} \rightarrow \text{R-H} \quad \text{alkane}
\]

• SN2 mechanism
• Attacks the less substituted carbon if attacking epoxides

Epoxidation

Mechanism:

Notes:
• One step reaction
• Syn addition
• Reaction is stereospecific (syn alkene = cis product, trans alkene = trans product)

Syn Dihydroxylation
- Cis products
- Stereochemistry: Racemic mixture (but for the example above the products are identical)

Trans Dihydroxylation

- Trans products
- Stereochemistry: Racemic mixture
- Step 2 can also use KOH instead of sulfuric acid and water

Oxidative Cleavage of Alkenes

Oxidative Cleavage of Alkynes

Oxidation of Alcohols
Chapter 15 Radical Reactions
Halogenation of Alkanes

Mechanism:

Initiation
Step [1] Bond cleavage forms two radicals.

\[ \text{CH}_3\text{CH}_3 \xrightarrow{h\nu \text{ or } \Delta} \text{CH}_3\text{CH}_2^* + \text{H}^* \]

- Homolysis of the weakest bond in the starting materials requires energy from light or heat.
- Thus, the Cl-Cl bond (\( \Delta H^\circ = 242 \text{ kJ/mol} \)), which is weaker than either the C-C or C-H bond in ethane (\( \Delta H^\circ = 388 \text{ and } 410 \text{ kJ/mol} \), respectively), is broken to form two chlorine radicals.

Propagation

\[ \text{CH}_3\text{CH}_2^* + \text{Cl}^* \rightarrow \text{CH}_3\text{CH}_2\text{Cl}^* + \text{Cl}^* \]

- The Cl- radicals abstract a hydrogen atom from ethane (Step [2]). This forms H-Cl and leaves one unpaired electron on carbon, generating the ethyl radical (CH\(_3\)CH\(_2^*\)).
- CH\(_3\)CH\(_2^*\) abstracts a chlorine atom from Cl\(_2\) (Step [3]), forming CH\(_3\)CH\(_2\)Cl and a new chlorine radical (Cl\(^*\)).
- The Cl\(^*\) radical formed in Step [3] is a reactant in Step [2], so Steps [2] and [3] can occur repeatedly without an additional initiation reaction (Step [1]).
- In each propagation step, one radical is consumed and one radical is formed. The two products—CH\(_3\)CH\(_2\)Cl and HCl—are formed during propagation.

Termination
Step [4] Two radicals react to form a \( \sigma \) bond.

\[ \text{CH}_3\text{CH}_2^* + \text{Cl}^* \rightarrow \text{CH}_3\text{CH}_2\text{Cl}^* + \text{Cl}^* \]

- To terminate the chain, two radicals react with each other in one of three ways (Steps [4a, b, and c]) to form stable bonds.
Notes:
- Must be Br₂ or Cl₂
- Chlorination is faster and less selective than bromination = 2+ products
- Bromination = 1 product (most substituted carbon is chosen)
- Stereochemistry: Racemic mixture

Radical Addition of HBr to an Alkene

Mechanism:

Step 1: Initiation

Step 2: Addition of bromine radical to alkene

Abstraction of hydrogen from H-Br to give addition product

Step 3: Termination

Notes:
- Bromine gets added to the less substituted side (vs adding to the most substituted side with only H-Br)

Chapter 16: Conjugation, Resonance, and Dienes

1,3 Diene Electrophilic Addition
Mechanism:

Notes:
- Markovnikov’s rule is followed
- Kinetic product: 1,2 product. More formed at lower temperatures
- Thermodynamic product: 1,4 product. More formed at higher temperatures

Diels-Alder Reaction

Mechanism:

Notes:
- Reaction is one-step (concerted)
- Diene must be in s-cis conformation
- Trans diene = no reaction
- Stereochemistry is retained
• (ie. If the dienophile was trans, product will be trans)

Chapter 17: Benzene and Aromatic Compounds

Huckel’s Rule

**Aromatic compound**
- A cyclic, planar, completely conjugated compound that contains $4n + 2\ \pi$ electrons ($n = 0, 1, 2, 3$, and so forth).
- An aromatic compound is more stable than a similar acyclic compound having the same number of $\pi$ electrons.

**Antiaromatic compound**
- A cyclic, planar, completely conjugated compound that contains $4n\ \pi$ electrons ($n = 0, 1, 2, 3$, and so forth).
- An antiaromatic compound is less stable than a similar acyclic compound having the same number of $\pi$ electrons.

**A compound that is not aromatic**
- A compound that lacks one (or more) of the requirements to be aromatic or antiaromatic.

<table>
<thead>
<tr>
<th>Examples of aromatic compounds with 6 $\pi$ electrons (17.8)</th>
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<tbody>
<tr>
<td><img src="image" alt="benzene" /> <img src="image" alt="pyridine" /> <img src="image" alt="pyrrole" /> <img src="image" alt="cyclopentadienyl anion" /> <img src="image" alt="tropylium cation" /></td>
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</tr>
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<tr>
<td><img src="image" alt="not cyclic" /> <img src="image" alt="not planar" /> <img src="image" alt="not completely conjugated" /></td>
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