REATIONS OF ALKYL HALIDES: NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

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Klein (2nd ed.) sections 7.1, 7.3-7.9, 8.1, 8.6-8.14
Substitution and Elimination Reactions

- Reaction substrates
  - Alkyl halides
  - Alcohols

(Chapter 7)
(Chapter 8)
Alkyl Halides

- Contain F, Cl, Br, or I
- Widely used in:
  - Synthesis (electrophilic carbon and easy functional group transitions)
  - Solvents (CCl₄, CHCl₃, CH₂Cl₂)
  - Industrial applications

- Structure:
Properties of Alkyl Halides

• Bond strength
  • Measured by bond dissociation energy
  • Inversely proportional to bond length
  • Electronegativity and small size of F keep bonding electrons close

\[
\text{C-F} > \text{C-Cl} > \text{C-Br} > \text{C-I}
\]

short \quad \text{long}
strong \quad \text{weak}

• Which C-X bond is easier to break, C-Cl or C-Br?
Properties of Alkyl Halides

- **Polarity**
  - Alkyl halides have substantial dipole moments

- Dipole moments depend on:
  1. Electronegativity of X
     - F > Cl > Br > I
  2. C-X bond length
     - C-I > C-Br > C-Cl > C-F
  3. Polarizability of electrons (ease of distribution of electron density)
     - I > Br > Cl > F

- Since these trends oppose one another, the trend in molecular dipole moment is not periodic

\[ \text{C-Cl} > \text{C-F} > \text{C-Br} > \text{C-I} \]
# Summary of Alkyl Halide Properties

## Table 10.1 A Comparison of the Halomethanes

<table>
<thead>
<tr>
<th>Halomethane</th>
<th>Bond length (pm)</th>
<th>Bond strength (kJ/mol)</th>
<th>Bond strength (kcal/mol)</th>
<th>Dipole moment (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$F</td>
<td>139</td>
<td>460</td>
<td>110</td>
<td>1.85</td>
</tr>
<tr>
<td>CH$_3$Cl</td>
<td>178</td>
<td>350</td>
<td>84</td>
<td>1.87</td>
</tr>
<tr>
<td>CH$_3$Br</td>
<td>193</td>
<td>294</td>
<td>70</td>
<td>1.81</td>
</tr>
<tr>
<td>CH$_3$I</td>
<td>214</td>
<td>239</td>
<td>57</td>
<td>1.62</td>
</tr>
</tbody>
</table>
Reactions of Alkyl Halides

- Carbon bonded to X is electron-poor (electrophilic)
  - Will react with nucleophiles
- Nucleophiles are also bases! So, there are two competing reactions:
  1. Substitution
     - Nucleophile substitutes for X (the *leaving group*)
  2. Elimination
     - Nucleophile/base removes H, eliminates HX to yield an alkene

\[\text{Substitution: } \begin{array}{c}
\text{H} \\
\text{C} \quad \text{C} \\
\text{Br} \\
\end{array} + \text{OH}^- \rightarrow \begin{array}{c}
\text{H} \\
\text{C} \quad \text{C} \\
\text{OH} \\
\text{Br}^- \\
\end{array} \]

\[\text{Elimination: } \begin{array}{c}
\text{H} \\
\text{C} \quad \text{C} \\
\text{Br} \\
\end{array} + \text{OH}^- \rightarrow \begin{array}{c}
\text{C} \quad \text{C} \\
\text{H}_2\text{O} \\
\text{Br}^- \\
\end{array} \]
Substitution vs. Elimination

• How do we know which reaction will occur?

• In this chapter:
  I. Mechanisms of substitution
  II. Mechanisms of elimination
  III. Substitution vs. elimination
I. Nucleophilic Substitution

- Nucleophile substitute for leaving group \((X)\)

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

- Example:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{NaOCH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 + \text{NaBr}
\]

  - Substrate =
  - Leaving group =
  - Nucleophile =
Products

R-LG

NaO → R-O

NaCN → R-CN

NaSH → R-SH

NaOH → R-OH

NaOR → R-OR

NaX → R-X

Ester

Nitrile

Thiol

Alcohol

Ether

Alkyl halide
Stereochemistry

• When the product has a stereocenter, we must consider stereochemistry
• Examples:

  •  

    \[
    \text{Br} \quad \xrightarrow{\text{NaCN}} \quad \text{CN} \quad + \quad \text{NaBr}
    \]
    
    (100% inversion)

  •  

    \[
    \text{Cl} \quad \text{CH}_3 \quad \xrightarrow{\text{NaOAc}} \quad \text{AcO} \quad \text{CH}_3 \quad + \quad \text{CH}_3 \quad \text{OAc} \quad + \quad \text{NaCl}
    \]
    
    (50% retention)  
    (50% inversion)

• How can we explain the observed stereochemistry?
Stereochemistry

• How can we explain the observed stereochemistry?
  • There is more than one possible mechanism
  • $S_N2$ and $S_N1$ (differ in timing of C-X breaking and C-Nu formation)
The $S_{N2}$ Reaction

- Bimolecular nucleophilic substitution
- Bimolecular = two species (RX and Nu) participate in RDS
- Rate = $k [RX] [Nu]$
- Mechanism:
  - Single step
  - No intermediates
  - Bonds broken and made simultaneously (concerted)
  - Same mechanism as acetylide ion and methyl/primary RX

$$R - \text{C} \equiv \text{C}^- + \text{CH}_3\text{Br} \xrightarrow{S_{N2} \text{ reaction}} R - \text{C} \equiv \text{C} - \text{CH}_3 + \text{Br}^-$$

An acetylde anion
Transition State of $S_N2$ Reaction

$Nu^{-} + C-X \rightarrow \delta^{-} Nu \equiv C \equiv \delta^{-} X \rightarrow Nu-C + X^{-}$
\[ \text{CH}_3\text{Br} + \text{NaOH} \rightarrow \]

- **Products:**
- **Mechanism:**
$S_{N2}$ Energy Diagram

- One step
- Exothermic

Reaction Coordinate
**S_N2 Stereochemistry**

- Nucleophile attacks reaction center (electrophilic carbon) from the direction opposite the leaving group
  - Backside attack

- Causes change (inversion) in configuration
  - Stereocenter: $S \leftrightarrow R$
  - Rings: cis $\leftrightarrow$ trans

- Ex: (S)-2-bromobutane + NaSH
$S_{N2}$ Characteristics

- Factors influencing the rate of $S_{N2}$ reaction:
  - Alkyl halide (substrate) structure
  - Nucleophile
  - Leaving group
  - Solvent
**S<sub>N</sub>2 Characteristics: RX Structure**

- **Steric effects**
  - Nucleophile must have access to reaction center
  - Access is hindered with bulky substituents
$S_N2$ Characteristics: RX Structure

- **Trends in RX reactivity:**
  - Methyl halide most reactive
  - Tertiary alkyl halide not likely to react
  - Branched $1^\circ$ and $2^\circ$ alkyl halides react slower than unbranched

- Allylic and benzylic halides can also react
- Vinyl and aryl halides will not react
$S_n2$ Characteristics: Nucleophile

- Nucleophile: contains lone pair
- Some nucleophile are better than others
- Better nucleophile = faster $S_n2$ reaction
- Some common nucleophiles:

<table>
<thead>
<tr>
<th>Poor</th>
<th>Good</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROH</td>
<td>$\text{RCO}_2^-$</td>
<td>$\text{I}^-$</td>
</tr>
<tr>
<td>$\text{RCO}_2\text{H}$</td>
<td>RSH</td>
<td>$\text{HS}^-$</td>
</tr>
<tr>
<td>$\text{H}_2\text{O}$</td>
<td>$\text{NH}_3/\text{NR}_3$</td>
<td>$\text{HO}^-$</td>
</tr>
<tr>
<td>$\text{F}^-$</td>
<td>$\text{Cl}^-$</td>
<td>$\text{RO}^-$</td>
</tr>
<tr>
<td></td>
<td>$\text{Br}^-$</td>
<td>$\text{CN}^-$</td>
</tr>
</tbody>
</table>

- What trends do you notice relating nucleophilicity and structure?
Trends in Nucleophile Structure

1. Anions are stronger nucleophiles than neutral molecules
   \[ \text{HO}^- > \text{H}_2\text{O} \]
   \[ \text{RO}^- > \text{ROH} \]
2. Less stable anions are stronger nucleophiles than more stable anions

\[ \text{RO}^- > \text{RCO}_2^- \]

3. Generally, nucleophilicity increases down a group

\[ I^- > Br^-, Cl^- > F^- \]

4. Bulky anions are more likely to act as a base, rather than a nucleophile

\[ (\text{CH}_3)_3\text{CO}^- \text{ vs. } \text{CH}_3\text{O}^- \]

- base
- nucleophile
Nucleophile Structure

• Some common good nucleophiles are also *strong* bases
  • HO⁻
  • RO⁻
  • H₂N⁻

• Some common good nucleophiles are *weak* bases
  • X⁻
  •-CN
  • RCO₂⁻

• This will be important later when comparing substitution and elimination
**SN2 Characteristics: Leaving Group**

- Better LG results in a faster reaction
- Better LGs are more stable anions
**$S_{N2}$ Characteristics: Solvent**

- Dissolves reactants, creates environment of reaction, can affect outcome of reaction
- Solvents are either protic or aprotic
- Polar protic
  - H-bond donor
  - Contain NH or OH
  - Alcohols, carboxylic acids, amines, water
- Polar aprotic
  - Cannot donate H-bond
  - Dimethyl sulfoxide (DMSO)
  - Acetone
  - Acetonitrile
  - $N,N$-Dimethylformamide (DMF)
$S_N2$ Characteristics: Solvent

- Polar aprotic solvents solvate cations, but not anions
- Anions shielded from $\delta^+$ by methyl groups
  - Less solvated
  - More available to react as nucleophiles
  - Good for $S_N2$!

The lone pairs on the oxygen atoms of DMSO stabilize the cation.

The anion is not stabilized by the solvent.
S_N2 Characteristics: Solvent

- Polar protic solvents solvate both cations AND anions
- Anion is well-solvated
  - Less available to react as nucleophiles
  - Not good for S_N2!

The lone pairs on the oxygen atoms of H_2O stabilize the cation.

Hydrogen-bonding interactions stabilize the anion.
# S\textsubscript{N}2 Summary

## Rates of Reaction (Kinetics):
- What is the rate-determining step for the S\textsubscript{N}2 reaction?
- Does the rate of reaction depend on the concentration of alkyl halide only OR both the alkyl halide and nucleophile?

## Stereochemistry:
- What happens to a stereocenter (chirality center) during the course of this reaction?

## Structure of the Alkyl Halide:
- List alkyl halide type (1°, 2°, 3°) in order of decreasing ability to undergo this type of substitution reaction. Are there any types of alkyl halides that do not undergo this type of reaction? Why?
- Given this order or reactivity, are electronic factors important for this reaction? Why or why not?
- Are steric factors important for this reaction? Why or why not?

## The Nucleophile:
- Is the nature of the nucleophile important for the S\textsubscript{N}2 reaction? Why or why not?

## The Leaving Group:
- Rank the leaving groups of alkyl halides (F\textsuperscript{-}, Cl\textsuperscript{-}, Br\textsuperscript{-}, I\textsuperscript{-}) in their ability to “leave.” Why is this trend observed?

## The Solvent:
- How do polar aprotic solvents and polar protic solvents affect substitution reactions?
- What are the best solvents for the S\textsubscript{N}2 reaction? Why?
The $S_N1$ Reaction

- Unimolecular nucleophilic substitution
- Unimolecular = one species (RX) participates in RDS
- Rate = $k [RX]$
- Mechanism:
  - Multiple steps
  - Carbocation intermediate
  - C-X bond broken before C-Nu bond formed
  - Which step is RDS?
Mechanism of $S_N_1$ Reaction

1. Spontaneous dissociation of the alkyl bromide occurs in a slow, rate-limiting step to generate a carbocation intermediate plus bromide ion.

2. The carbocation intermediate reacts with water as nucleophile in a fast step to yield protonated alcohol as product.

3. Loss of a proton from the protonated alcohol intermediate then gives the neutral alcohol product.
$S_N1$ Energy Diagram

$\Delta G^\ddagger$ (rate-limiting)

RX + :Nu$^-$

R$^+$ + :X$^-$

Carbocation intermediate

RNu + :X$^-$

Reaction progress
$S_N1$ Stereochemistry

- Racemic mixture
  - 50% inversion of configuration
  - 50% retention of configuration
- Why? Look at intermediate…

![Diagram showing racemic mixture and intermediate steps in $S_N1$ reaction](image)
$(R)$-3-chloro-3-methylhexane + NaOAc $\rightarrow$

- Products:
- Mechanism:
$t$-Butyl chloride + CH$_3$OH $\rightarrow$
**S_N1 Stereochemistry**

- Sometimes slightly more than one enantiomer is observed
  - 55-60% inversion
  - 40-45% retention

- Why?
  Association of leaving group with carbocation

\[(R)-6\text{-Chloro-2,6-dimethyloctane}\] →\[(CH_3CH_2CH_2CH_2CH_2CH_3)\] + \[\text{HO-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\]

- 60% **S** (inversion)
- 40% **R** (retention)
$S_{N1}$ Characteristics

- Factors influencing the rate of $S_{N1}$ reaction:
  - Alkyl halide structure
  - Nucleophile
  - Leaving group
  - Solvent
**S_N1 Characteristics: RX Structure**

- **Electronic effects**
  - More stable carbocation = faster reaction
  - Remember carbocation stability

![Chemical structure diagram](image)
**S\textsubscript{N}1 Characteristics: RX Structure**

- **Trends in RX reactivity:**
  - Tertiary alkyl halides most reactive
  - Primary alkyl halides will not form unless allylic or benzylic

- Vinylic and aryl still will not react
$S_N1$ Characteristics: Nucleophile

- Nucleophile is not important for $S_N1$ reactions
  - Not in the rate equation
- Even poor nucleophiles are OK for $S_N1$
  - $H_2O$, ROH, etc.
$S_N1$ Characteristics: Leaving Group

- Better LG = faster reaction

$\text{HO}^- \ < \ \text{Cl}^- \ < \ \text{Br}^- \ < \ \text{I}^- \ \approx \ \text{TosO}^- \ \text{H}_2\text{O}$

Leaving group reactivity
$S_N1$ Characteristics: Leaving Group

- $S_N1$ on alcohols
- Need strong acid to protonate $\text{–OH}$ and form a better LG

![Chemical reaction diagram](image)
$S_N 1$ Characteristics: Solvent

- Polar protic solvents = faster reaction
  - Solvate both cations AND anions

- Speed up RDS by solvating and separating carbocation intermediate and leaving group anion
- Good for $S_N 1$

- Commonly $S_N 1$ nucleophile = solvent
  - Solvolysis reaction
## $S_N1$ Summary

### Rates of Reaction (Kinetics):
- What is the rate-determining step for the $S_N1$ reaction?
- Does the rate of reaction depend on the concentration of alkyl halide only OR both the alkyl halide and nucleophile?

### Stereochemistry:
- What happens to a stereocenter (chirality center) during the course of this reaction?

### Structure of the Alkyl Halide:
- List alkyl halide type ($1^\circ$, $2^\circ$, $3^\circ$) in order of decreasing ability to undergo this type of substitution reaction. Are there any types of alkyl halides that do not undergo this type of reaction? Why?
- Given this order or reactivity, are *electronic* factors important for this reaction? Why or why not?
- Are *steric* factors important for this reaction? Why or why not?

### The Nucleophile:
- Is the nature of the nucleophile important for the $S_N1$ reaction? Why or why not?

### The Leaving Group:
- Rank the leaving groups of alkyl halides ($F^-$, $Cl^-$, $Br^-$, $I^-$) in their ability to “leave.” Why is this trend observed?

### The Solvent:
- How do polar aprotic solvents and polar protic solvents affect substitution reactions?
- What are the best solvents for the $S_N1$ reaction? Why?
Summary of $S_{N2}$ vs. $S_{N1}$

<table>
<thead>
<tr>
<th>TABLE 7.1</th>
<th>A COMPARISON OF $S_{N2}$ AND $S_{N1}$ PROCESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_{N2}$</td>
<td>$S_{N1}$</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td><img src="image" alt="Diagrams" /></td>
</tr>
<tr>
<td><strong>Energy diagram</strong></td>
<td><img src="image" alt="Graphs" /></td>
</tr>
<tr>
<td>Potential energy</td>
<td>$E_a$</td>
</tr>
<tr>
<td>Reaction coordinate</td>
<td></td>
</tr>
<tr>
<td><strong>Rate equation</strong></td>
<td>Rate = $k$ [substrate] [nucleophile]</td>
</tr>
</tbody>
</table>
# Summary of $S_N2$ vs. $S_N1$

<table>
<thead>
<tr>
<th></th>
<th>$S_N2$</th>
<th>$S_N1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Driving force</strong></td>
<td>Steric factors</td>
<td>Electronic factors</td>
</tr>
<tr>
<td><strong>Alkyl halide</strong></td>
<td>Methyl 1°</td>
<td>3°</td>
</tr>
<tr>
<td></td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td></td>
<td>Allylic</td>
<td>Allylic</td>
</tr>
<tr>
<td></td>
<td>Benzylic</td>
<td>Benzylic</td>
</tr>
<tr>
<td><strong>Stereochemistry</strong></td>
<td>100% inversion</td>
<td>Racemic mixture</td>
</tr>
<tr>
<td><strong>Regiochemistry</strong></td>
<td>No rearrangements</td>
<td>Rearrangements possible</td>
</tr>
<tr>
<td><strong>Nucleophile</strong></td>
<td>Good</td>
<td>Good or poor</td>
</tr>
<tr>
<td><strong>Solvent</strong></td>
<td>Aprotic</td>
<td>Protic</td>
</tr>
</tbody>
</table>
Consider the reactions below…

- Classify the substrate in each reaction as 1°, 2°, or 3°.
- What is the solvent? Is it protic or aprotic?
- What is the nucleophile? Is it strong or weak?
- Which reaction is faster?
- Classify each mechanism as $S_N1$ or $S_N2$. 
Predict the substitution mechanism and products for the following reactions...
Carbocation Rearrangements

• Carbocation intermediates can rearrange to form a more stable carbocation structure

• Types of rearrangements:
  • Hydride shift
    \[
    \begin{align*}
    \text{CH}_3\text{CH}_2\text{C}^+\text{CH}\text{CH}_3 & \quad \text{hydride shift} \\
    & \quad \text{CH}_3\text{CH}_2\text{C}^+\text{CH}_2\text{CH}_3
    \end{align*}
    \]
  • Alkyl shift (methyl or phenyl)
    \[
    \begin{align*}
    \text{H}_3\text{C}\text{C}^+\text{C}^+\text{CH}_3 & \quad \text{Methyl shift} \\
    & \quad \text{H}_3\text{C}\text{C}^+\text{CH}_3
    \end{align*}
    \]

• Can $S_{N2}$ reactions undergo rearrangement?
Draw the Mechanism…
Outline

• In this chapter:
  I. Mechanisms of substitution
     • $S_{N2}$
     • $S_{N1}$
  II. Mechanisms of elimination
     • E2
     • E1
  III. Substitution vs. elimination
II. Elimination Reactions

- Alkyl halide + base $\rightarrow$ alkene
  - X eliminated from one carbon
  - H eliminated from adjacent carbon
- Compete with substitution reactions
1-Bromobutane + t-BuOK →
Elimination Regiochemistry

- Multiple products can be formed if there is more than one adjacent H

- How do we know the major product?
Zaitsev’s Rule

• In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates
  • This alkene is more stable
  • There are some exceptions, but this rule is generally true

• Example:

- Which product is major?
The E2 Reaction

- Bimolecular elimination
- Rate = $k [RX] [Base]$
- Mechanism:
  - Single step
  - Concerted
  - No intermediates
  - Needs a strong base (NaOH, NaOR, NaNH$_2$)
E2 Stereochemistry

- The alkyl halide must have anti-periplanar geometry

  ![E2 Stereochemistry Diagram](image)

- Anti = H and X on opposite sides of molecule
  - Less steric strain between base and leaving group
- Periplanar = all 4 reacting atoms (H, C, C, X) are in the same plane
  - Maximizes molecular orbital overlap in transition state
What is the major product of E2 reaction of \((2S,3R)-2\text{-bromo-3\text{-methylpentane}}\)?
E2 Regiochemistry

- Usually Zaitsev
- Formation of non-Zaitsev (Hofmann) product:
  1. When the base is a bulky base

<table>
<thead>
<tr>
<th>TABLE 8.1 PRODUCT DISTRIBUTION OF AN E2 REACTION AS A FUNCTION OF BASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Reaction Scheme" /></td>
</tr>
<tr>
<td>Br → Base</td>
</tr>
<tr>
<td>EtO⁻</td>
</tr>
<tr>
<td>ZAITSEV: 71%</td>
</tr>
<tr>
<td>HOFMANN: 29%</td>
</tr>
<tr>
<td>t-BuO⁻</td>
</tr>
<tr>
<td>ZAITSEV: 28%</td>
</tr>
<tr>
<td>HOFMANN: 72%</td>
</tr>
</tbody>
</table>

- t-BuO⁻ is sterically hindered, does not remove more crowded H
E2 Regiochemistry

• Formation of non-Zaitsev product:
  2. When anti-periplanar geometry cannot be achieved (substituted cyclohexanes)

• Anti-periplanar = *trans* diaxial

When Cl is axial, it can be *anti*-periplanar with a neighboring hydrogen atom

When Cl is equatorial, it cannot be *anti*-periplanar with any of its neighboring hydrogen atoms
cis-1-Chloro-2-isopropylcyclohexane
trans-1-Chloro-2-isopropylcyclohexane
The E1 Reaction

- Unimolecular elimination
- Rate = $k \ [RX]$
- Mechanism:
  - Multiple steps
  - Carbocation intermediate
  - Weak base is OK due to reactive $R^+$ intermediate
  - Stereochemistry of RX not a factor due to $R^+$ planarity
  - Regiochemistry is Zaitsev
2-Methyl-2-chloropropane + CH$_3$OH →

- Products:

- Mechanism:
E1 Reaction of Alcohols

- Dehydration of an alcohol to form an alkene is also E1 mechanism
- Reaction is reversible
  - Remove alkene as formed (distillation) to push to the right
- Acid catalyst is needed (H₃PO₄ or H₂SO₄)
  - Protonates –OH to make a better leaving group (H₂O)
- Example:
E1 Carbocation Rearrangements

Proton transfer

Loss of LG

Rearrangement

Carbocation

Carbocation

Products from rearrangement

64%

33%

3%

Product from no rearrangement
## Summary of E2 vs. E1

<table>
<thead>
<tr>
<th></th>
<th>E2</th>
<th>E1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkyl halide</strong></td>
<td>1°</td>
<td>3°</td>
</tr>
<tr>
<td></td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td></td>
<td>3°</td>
<td></td>
</tr>
<tr>
<td><strong>Base</strong></td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Stereochemistry</strong></td>
<td>Anti-periplanar</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Regiochemistry</strong></td>
<td>Zaitsev, unless bulky base or no anti-</td>
<td>Zaitsev</td>
</tr>
<tr>
<td></td>
<td>periplanar conformation</td>
<td></td>
</tr>
</tbody>
</table>
Predict the elimination mechanism and products for the following reactions…
Outline

• In this chapter:
  I. Mechanisms of substitution
     • $S_{N2}$
     • $S_{N1}$
  II. Mechanisms of elimination
     • E2
     • E1
  III. Substitution vs. elimination
     • $S_{N2}$ or $S_{N1}$ or E2 or E1
III. Substitution vs. Elimination

- Given starting material and reagents
- Predict mechanism and draw products
- Remember regiochemistry and stereochemistry

Where do we start?

- First, look at possible mechanisms for each RX structure
- Then, compare reaction conditions for each mechanism
## Possible Mechanisms

<table>
<thead>
<tr>
<th>RX Structure</th>
<th>$S_{N2}$</th>
<th>$S_{N1}$</th>
<th>E2</th>
<th>E1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
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Reaction Conditions

- $S_N^2$ vs. $S_N^1$
  - Good nucleophile and aprotic solvent favor $S_N^2$
  - Poor nucleophile and protic solvent favor $S_N^1$

- E2 vs. E1
  - Strong base favors E2
  - Weak base favors E1

- $S_N^2$ vs. E2
  - Good nucleophiles/weak bases favor $S_N^2$
  - Good nucleophiles/strong bases and $1^\circ$ RX result in $S_N^2$ and E2
  - Good nucleophiles/strong bases and $2^\circ$ RX result in E2
  - Bulky bases or branched RX favor E2

- $S_N^1$ vs. E1
  - $S_N^1$ and E1 are both favored with weak nucleophiles/bases
  - Mixture of products from both $S_N^1$ vs. E1 will result anytime a unimolecular mechanism is predicted
### The Magic Chart…

<table>
<thead>
<tr>
<th>Alkyl Halide</th>
<th>Mechanism</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>$S_N^2$</td>
<td>• Only option</td>
</tr>
</tbody>
</table>
| $1^\circ$    | $S_N^2$   | • Weak base/good nucleophile  
|              |           | • Strong base, non-bulky (competes with $E_2$)  
|              | $E_2$     | • Strong base, non-bulky (competes with $S_N^2$)  
|              |           | • Bulky base  
|              |           | • Branched RX substrate |
| $2^\circ$    | $S_N^2$   | • Weak base/good nucleophile |
|              | $E_2$     | • Strong base |
|              | $S_N^1/E_1$ | • Weak base/weak nucleophile |
| $3^\circ$    | $E_2$     | • Strong base |
|              | $S_N^1/E_1$ | • Weak base (good or weak nucleophile) |

- **Strong bases (non-bulky):** $\text{HO}^-$, $\text{RO}^-$, $\text{H}_2\text{N}^-$
- **Bulky base:** $\text{t-BuO}^-$
- **Weak base/good nucleophile:** $\text{X}^-$, $\text{CN}^-$, $\text{CH}_3\text{CO}_2^-$
- **Weak base/weak nucleophile:** $\text{ROH}$, $\text{H}_2\text{O}$, $\text{CH}_3\text{CO}_2\text{H}$ (anything neutral)
Predict the substitution and/or elimination mechanism and draw products for the following reactions…
Provide reagents (including special conditions, such as heat or light) and structures in the empty boxes to complete the following reaction schemes.

a) \[ \text{Br} \quad \text{[structure]} \quad \text{CH}_2=\text{CH} \]

b) \[ \text{Br}_2 \quad \Delta \quad \text{[structure]} \quad \text{NaOCH}_2\text{CH}_3 \quad \text{CH}_3\text{CH}_2\text{OH} \]

c) \[ \text{Br} \quad \text{NaOCH}_3 \quad \text{methanol} \quad \text{[structure]} \quad \text{HBr} \quad \text{[structure]} \quad \text{CH}_3\text{OH} \]