Summary of Reaction Types, Ch. 4-6, Test 2

1. Radical Halogenation (Ch. 4)
   - **Recognition**: $X_2$, hv
   - **Predicting product**: Identify which carbon could give the most stable radical, and substitute a Br for an H on that carbon.
   - **Stereochemistry**: Leads to racemic, due to achiral radical intermediate.
   - **Mech**: Radical. Be able to draw propagation steps.

2. $S_N2$ Substitution
   - Any of a large variety of nucleophiles or electrophiles can work.
   - **Recognition**: A. Anionic Nucleophile, and B. 1º or 2º alkyl halide
   - (3º alkyl halides fail, will give E2 upon treatment with Anionic Nucleophile/Base. For 2º alkyl halides, $S_N2$ is often accompanied by variable amounts of E2.)
   - **Predicting product**: Replace the halide with the anion nucleophile
   - **Stereochemistry**: Leads to Inversion of Configuration
   - **Mech**: Be able to draw completely. Only one concerted step!

3. E2 Reactions.
   - **Recognition**: A. Anionic Nucleophile/Base, and B. 3º or 2º alkyl halide
   - (1º alkyl halides undergo $S_N2$ instead. For 2º alkyl halides, E2 is often accompanied by variable amounts of $S_N2$.)
   - **Orientation**: The most substituted alkene forms (unless a bulky base is used, ch. 7)
   - **Predicting product**: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans, however.
   - **Stereochemistry**: Anti/trans elimination. The hydrogen on the neighbor carbon must be trans/anti.
   - **Mech**: Concerted. Uses anion. Be able to draw completely. Only one concerted step!
4. **S_N1 Reactions.**

\[ \text{Br} \xrightarrow{\text{HOCH}_3} \text{OCH}_3 \text{+ H-Br} \]

**Recognition:**
- A. Neutral, weak nucleophile. No anionic nucleophile/base, and
- B. 3º or 2º alkyl halide. (Controlled by cation stability).

(1º alkyl halides undergo S_N2 instead. For 2º alkyl halides, S_N1 is often accompanied by variable amounts of E1.)

**Predicting product:** Remove halide and replace it with the nucleophile (minus an H atom!)

**Stereochemistry:** Racemization. The achiral cation intermediate forgets any stereochem.

**Mech:** Stepwise, 3 steps, via carbocation. Be able to draw completely.

5. **E1 Reactions. 3º > 2º > 1º (Controlled by cation stability)**

\[ \text{Br} \xrightarrow{\text{HOCH}_3 \ 	ext{slow step}} \text{+ OCH}_3 \text{+ H-Br} \]

**Recognition:**
- A. Neutral, weak nucleophile. No anionic nucleophile/base, and
- B. 3º or 2º alkyl halide. (Controlled by cation stability).

(For 2º alkyl halides, E1 is often accompanied by variable amounts of S_N1.)

**Orientation:** The most substituted alkene forms

**Predicting the major product:** Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.

**Stereochemistry:** Not an issue. The eliminating hydrogen can be cis or trans.

**Mech:** Stepwise, 2 steps, via carbocation. Be able to draw completely.

---

**Sorting among S_N2, S_N1, E2, E1: How do I predict?**

**Step 1:** **Check nucleophile/base.**
- If **neutral**, then \( S_N1/E1 \rightarrow \) mixture of both
- If **anionic**, then \( S_N2/E2. \)

**Step 2:** If **anionic**, and in the \( S_N2/E2 \), then **Check the substrate.**
- 1º \( \rightarrow S_N2 \)
- 2º \( \rightarrow S_N2/E2 \) **mixture.** Often more \( S_N2 \), but not reliable...
- 3º \( \rightarrow E2 \)
Ch. 6 Alkyl Halides: Nucleophilic Substitution and Elimination

6.1,2 Classification, Nomenclature

A. General Classification

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;alkyl halide&quot;</td>
<td>halide connected to an sp³ (alkyl) carbon</td>
<td>( \text{C}_3\text{H}_7\text{Cl} )</td>
</tr>
<tr>
<td>&quot;vinyl halide&quot;</td>
<td>( \text{sp}^2 ) vinyl (( \text{sp}^2 ) alkene)</td>
<td>( \text{C}_2\text{H}_4\text{Br} )</td>
</tr>
<tr>
<td>&quot;aryl halide&quot;</td>
<td>aromatic ( \text{sp}^2 )</td>
<td>( \text{C}_6\text{H}_5\text{Br} )</td>
</tr>
<tr>
<td>&quot;allylic halide&quot;</td>
<td></td>
<td>( \text{C}_2\text{H}_5\text{I} )</td>
</tr>
</tbody>
</table>

B. 1º, 2º, 3º Classification

C. Systematic Naming: \( x \)-Haloalkane (test responsible) (Include number!)

D. Common Naming: “alkyl halide” (not tested)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Formal Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}_3\text{H}_7\text{Cl} )</td>
<td>1-chloropropane</td>
<td>propyl chloride</td>
</tr>
<tr>
<td>( \text{C}_2\text{H}_4\text{Br} )</td>
<td>2-bromo pentane</td>
<td></td>
</tr>
<tr>
<td>( \text{C}_2\text{H}_5\text{I} )</td>
<td>2-ido propane</td>
<td>Isopropyl iodide</td>
</tr>
</tbody>
</table>

Systematic Nomenclature: \( x \)-Haloalkane (test responsible)
Common: “alkyl halide” (not tested)

Uses:
1. solvents
2. anesthetics
3. refrigerants
4. pesticides
5. reactants
6.4 Structure:

A. Polar

B. Weak Bonds, Breakable

<table>
<thead>
<tr>
<th>Stability</th>
<th>Bond</th>
<th>Bond Strength</th>
<th>Reactivity Toward Breakage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-Cl</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-Br</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-I</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

6.5 Physical Properties

- boiling point: controlled by molecular weight (London force)
- water solubility: low, no hydrogen-bonding
- density: greater than water, so they sink (unlike hydrocarbons, which float)

6.6 Preparation of Alkyl Halides

- Review: R-H + Br₂ → RBr + HBr (under photolysis, Ch. 4)
- We will learn other preparations in chapters 8 and 11
6.7 Basic Overview/Preview of Alkyl Halide Reactions: Substitution ($S_{N2}$ or $S_{N1}$) or Elimination ($E2$ or $E1$)

- Because $R-X$ bonds are weak, halides are good leaving groups.

E. Substitution

$$R-X + NaZ \text{ or } HZ \rightarrow R-Z + NaX \text{ or } HX$$

Anion or neutral

2 Variants

6. $S_{N2}$:
- Anionic nucleophile
- The $R-X$ bond breaking is simultaneous with $R-Z$ bond formation

7. $S_{N1}$:
- Neutral nucleophile
- The $R-X$ bond breaks first to give a carbocation in the rate determining step; formation of the $R-Z$ bond comes later

F. Elimination

$$HX + NaZ \text{ or } HZ \rightarrow C=C + NaX \text{ or } HX$$

alkene

2 Variants

1. $E2$:
- Anionic base
- The $R-X$ and $C-H$ bond breaking is simultaneous with $C=C$ bond formation

2. $E1$:
- Neutral base
- The $R-X$ bond breaks first to give a carbocation in the rate determining step. $C-H$ bond cleavage and $C=C$ bond formation comes later
6.8 The S<sub>N</sub>2 Reaction

General:

- "nucleophile"
- "electrophile"
- "leaving group"

Example, with test-level mechanism:

- double-barbed arrows (electron pairs move)
- Na<sup>+</sup> is a spectator

More Detailed Mechanism:

Notes:
1. Simple, concerted one-step mechanism. No intermediates.
2. The anion needs to be very reactive and thus not too stable. Normally ANIONIC NUCLEOPHILE.
3. Both nucleophile and electrophile are involved in the rate determining step.
   - Rate = k[anion][R-X]
4. 2<sup>nd</sup> order rate law is why it’s called S<sub>N</sub>2: Substitution<sub>NUCLEOPHILE</sub> 2<sup>nd</sup> order
5. The nucleophile attacks opposite side from the leaving group.
6. This “backside attack” (or opposite side attack) results in inversion of stereochemistry when a chiral, 2° R-X is involved

Inversion of Stereochemistry at Chiral Center

7. The transition state involves a 5-bonded, trigonal bipyramidal carbon that is more cluttered than either the original tetrahedral reactant or the final tetrahedral product
8. Steric crowding in the transition-state makes the reaction very, very, very sensitive to steric factors
   a. For the electrophile R-X: CH<sub>3</sub>-X > 1° R-X > 2° R-X > 3° R-X for steric reasons
   b. For the nucleophile it also helps to be smaller rather than larger
Mechanism
1. Crowded transition state (sterics are crucial)
2. 2nd order (SN2)
3. Opposite-side attack => inversion

Steric Factor: methyl > primary > secondary >>> tertiary (can't work)
6.9 Generality of $S_N2$ Reactions
-many kinds of nucleophiles, give many products

1. $R-X + NaOH \rightarrow R-OH$  
   Alcohols

2. $R-X + NaOR \rightarrow R-O-R$  
   Ethers

3. $R-X + NaO\rightarrow R-O\rightarrow R$  
   Esters

4. $R-X + KI \rightarrow R-I$  
   Iodides

5. $R-X + NaCN \rightarrow R-CN$  
   Nitriles

6. $R-X + \overset{\equiv}{\equiv}R \rightarrow R\rightarrow R$  
   Alkynes

Etc.

Notes
1. Most nucleophiles are **ANIONS**
2. Various oxygen anions are good to make alcohols, ethers, or esters
3. Halogen exchange useful route to iodides (more valuable and less accessible)

4. There are a few neutral nucleophiles (not for test): nitrogen family

---

Predicting Products for $S_N2$ Reactions

1. **Don’t change the structure for the carbon skeleton**

2. **Put the nucleophile in exactly the spot where the halide began…**

3. Unless the halide was attached to a **chiral** center; in that case invert the configuration for the product:
   - If the halide was “wedged”, the nucleophile should be “hashed”
   - If the halide was “hashed”, the nucleophile should be “wedged”

4. Don’t mess with any “spectator” portions: whatever was attached to the nucleophilic anion at the beginning should still be attached at the end
\[
\text{Nuc}^- + \text{R} - \text{X} \rightarrow \text{Nuc} - \text{R} + \text{X}^{-}
\]

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>Class of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—X + \text{-I}^-</td>
<td>R—\text{I}^-</td>
<td>alkyl halide</td>
</tr>
<tr>
<td>R—X + \text{-OH}</td>
<td>R—\text{OH}</td>
<td>alcohol</td>
</tr>
<tr>
<td>R—X + \text{-OR}'</td>
<td>R—\text{OR}'</td>
<td>ether</td>
</tr>
<tr>
<td>R—X + \text{-SH}</td>
<td>R—\text{SH}</td>
<td>thiol (mercaptan)</td>
</tr>
<tr>
<td>R—X + \text{-SR}'</td>
<td>R—\text{SR}'</td>
<td>thioether (sulfide)</td>
</tr>
<tr>
<td>R—X + \text{NH}_3</td>
<td>R—\text{NH}_3^+\text{X}^-</td>
<td>amine</td>
</tr>
<tr>
<td>R—X + \text{N=\bar{N}=\bar{N}}^-</td>
<td>R—\text{N=\bar{N}=\bar{N}}^-</td>
<td>azide</td>
</tr>
<tr>
<td>R—X + \text{C\equiv C—R}'</td>
<td>R—\text{C\equiv C—R}'</td>
<td>alkyne</td>
</tr>
<tr>
<td>R—X + \text{C\equiv N}</td>
<td>R—\text{C\equiv N}</td>
<td>nitrile</td>
</tr>
<tr>
<td>R—X + \text{R'—COO}^-</td>
<td>R—\text{R'—COO}—R</td>
<td>ester</td>
</tr>
<tr>
<td>R—X + \text{P(Ph)}_3</td>
<td>[R—\text{PPh}_3]^+\text{X}^-</td>
<td>phosphonium salt</td>
</tr>
</tbody>
</table>
6.10, 6.11 Structural Factors that Impact $S_N^2$

A. Nucleophile

1. Anion versus Neutral: Should be **ANIONIC**

2. Anion Stability: Less Stable should be More Reactive (Reactant Stability-Reactivity Principle)
   - anion nucleophilicity **decreases** across a **horizontal row** (electronegativity factor)
   - CH$_2$Na $>$ NHNa $>$ ONa $>$ NaF
   - anion nucleophilicity **decreases** when an anion is stabilized by **resonance**
   - ONa $>$ COONa
   - anion nucleophilicity **increases** down a **vertical column**
     - NaSeH $>$ NaSH $>$ NaOH

3. Size: all else equal, smaller is better than bigger
   - ONa $>$ ONa

B. Electrophile

1. Substrate: **Allylic $>$ 1º $>$ 2º $>$ >> 3º, alkenyl, aryl**
   - 3º and alkenyl, aryl never do $S_N^2$
   - transition-state stability-reactivity principle
   - Steric clutter in the transition state explains the 1º $>$ 2º $>$ >> 3º pattern
   - Allylic benefits from a complex orbital resonance effect in the T-state
   - Alkenyl/aryl halides are bad for some molecular orbital reasons (backside attack doesn’t work, particularly for aryl halides)

2. Leaving Group: **R-I $>$ R-Br $>$ R-Cl**
   - reactant stability-reactivity principle
   - weaker bonds break faster
Various Leaving Groups.
1. Halides are good, but not the only leaving groups.
2. The more stable something is after it leaves, the better it is as a leaving group.
   - the halide anions are like what you'd get from HCl, HBr, HI (strong acids).
   - the sulfonates are like what you'd get from sulfuric acid (strong acid)
   - water is like what you'd get from hydronium (strong acid)
3. Notice that things were one charge unit more positive with one extra bond before they actually left.
   - to get H2O off, you'd have had charge ROH2 (cation) first.
   - From a neutral alcohol, the leaving group would be hydroxide (bad), not water.
Steric Factor: primary > secondary >>> tertiary

1. Crowded Transition-state. Sterically sensitive
2. Inversion of stereochemistry
6.12 Inversion of Stereochem in $S_{N2}$

In the mechanism, the nucleophile attacks from the “backside” or opposite side from the leaving group $\rightarrow$ inverts configuration

- Inversion occurs mechanistically in every $S_{N2}$ reaction
- But inversion is chemically relevant only when a chiral carbon is involved

<table>
<thead>
<tr>
<th>$\text{Br} \cdot \text{H}$</th>
<th>$+ \text{NaOCH}_3$</th>
<th>$\rightarrow \text{H} \cdot \text{OCH}_3$</th>
<th>$\text{Br} \cdot + \text{NaOCH}_3$</th>
<th>$\rightarrow \text{OCH}_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inversion matters, since product is chiral</td>
<td>Inversion doesn’t matter, for achiral product</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predicting products when chiral carbons undergo inversion:
1. Keep the carbon skeleton fixed
2. If leaving group is “hashed”, the nucleophile will end up “wedged” in the product
3. If leaving group is “wedged”, the nucleophile will end up “hashed” in the product

Two Standard Proofs for $S_{N2}$ mechanism:
- Inversion of configuration on a chiral carbon
- $2^{nd}$ order rate law

Predicting Products for $S_{N2}$ Reactions
1. Don’t change the structure for the carbon skeleton
2. **Put the nucleophile in exactly the spot where the halide began**…
3. Unless the halide was attached to a chiral center; in that case invert the configuration for the product
   a. If the halide was “wedged”, the nucleophile should be “hashed”
   b. If the halide was “hashed”, the nucleophile should be “wedged”
4. Don’t mess with any “spectator” portions: whatever was attached to the nucleophilic anion at the beginning should still be attached at the end
S_N2 Problems: For each of the following
  a. Identify whether or not an S_N2 reaction would take place?
  b. If not, why not?
  c. For those that could undergo S_N2 substitution, draw in the product.

1. Nucleophile: Anionic or neutral? Must be anion for SN2
2. Electrophile: Primary, secondary, or methyl required. Tertiary, vinyl, aryl no SN2.

1. S + H_2O  \rightarrow \text{No Neutral}
2. Br + NaOH  \rightarrow \text{Yes}
3. Br + NaOCH_3  \rightarrow \text{No 3°}
4. HBr + NaOCH_3  \rightarrow \text{Inversion}
5. \text{Primary} + KOCH_2CH_3  \rightarrow \text{Condensed}
6. Br + NaOH  \rightarrow \text{Neutral}
7. \text{Polylic} + CH_3OH  \rightarrow \text{No Vinyl}
8. \text{Vinyl} + NaSCH_3  \rightarrow \text{No Vinyl}
9. Br + NaOCH_3  \rightarrow \text{Yes}
10. Br + NaOH  \rightarrow \text{No Aryl}
More S_N2 Problems
1. Rank the reactivity toward NaOCH_3 (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

Issues: 
1. primary > secondary >>> tertiary, vinyl, aryl
2. RI > RBr > RCl
3. Allylic > non-allylic
4. Steric tiebreaker, all else equal

2. Rank Reactivity toward Br (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

Issues: 
1. Charge: Anions > Neutral
2. Electronegativity/periodic table: N > O
3. Resonance stabilization reduces nucleophilic reactivity

3. What nucleophile should you use to accomplish the following transformations?

4. Draw the Products, Including Stereochemistry. (Stereochemistry will matter for S_N2 and S_N1 reactions anytime the haloalkane is 2º)

Issue: Inversion of stereochemistry at reacting carbon

5. Choose Reactants to make the following, from a haloalkane and some nucleophile.

Issues: but not because 3º RX

Electrophile RX needs to be methyl, primary, or secondary. But it can't be tertiary, vinyl, or aryl.
In the problem shown, the "boxed" answers involve a primary RX. The "bad" answer has a tertiary RX.
6.13 \( S_N1 = \text{Substitution}_{\text{Nucleophilic}} \) 1st Order = “Solvolysis”

- Dramatic difference in mechanism, rates, structure dependence, and stereochemical outcome (compared to \( S_N2 \))
  
  General: \( R-X + Z-H \rightarrow R-X + HX \) 
  
  neutral

**Neutral, non-anionic** nucleophiles do the substitution

1. Often this is just the solvent (\( H_2O, ROH, RCO_2H \) are common)
   - For this reasons, these reactions are often called “solvolysis” reactions
2. Heat is often required
3. Acid is sometimes used to accelerate \( S_N1 \) reactions

<table>
<thead>
<tr>
<th>Predicting Products for ( S_N1 ) Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Don’t change the structure for the carbon skeleton</td>
</tr>
<tr>
<td>2. Connect “R” and “Z”, while taking the halide off of the electrophile and H off of the nucleophile</td>
</tr>
<tr>
<td>3. Unless the halide was attached to a chiral center, a racemic mixture will result</td>
</tr>
<tr>
<td>4. Maintain the integrity of the spectator attachments</td>
</tr>
</tbody>
</table>

**Examples:**

\[
\begin{align*}
\text{Cl}^- + H_2O & \rightarrow \text{OH}^- + HCl \\
\text{CH}_3\text{CH}_2\text{I} + \text{CH}_3\text{OH} & \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_3 + H\text{I}
\end{align*}
\]

**3-Step Mechanism**

1. Step 1: Carbocation Formation. THIS IS THE SLOW STEP
   - **Therefore the rate is controlled by cation stability**!
2. Step 2: Carbocation capture by neutral molecule (usually a solvent molecule)
   - When cation and neutral combine, a cation is produced
3. Step 3: Deprotonation to get neutral

**Notes:**

1. Carbocation formation is key
2. Rate = \( k[R-X] \) \( \rightarrow \) First order
3. See cations, not anions. Neutral, not anionic nucleophile.
4. Charge and atoms must balance in step 2. Thus, the oxygen retains the hydrogen.
5. Oxygen eventually loses the H, but only in step 3.
6. Rate can be enhanced by \( \text{AgNO}_3 \). The Ag+ cation helps strip the halide off in step 1.
**Structural** Factors that Impact $S_N1$ Rates

**Nucleophile:** Should be **NEUTRAL**, but otherwise non-factor

**Electrophile**

1. **Substrate:** Allylic $> 3^\circ > 2^\circ >> 1^\circ$ > alkenyl, aryl
   - Resonance is huge
   - alkenyl, aryl never do $S_N2$, $1^\circ$ only with AgNO$_3$
   - product stability-reactivity principle: in the rate-determining step, the more stable the product cation, the faster it will form
   - In terms of $1^\circ$, $2^\circ$, $3^\circ$, $S_N1$ and $S_N2$ have exactly opposite patterns

2. **Leaving Group:** R-I $>$ R-Br $>$ R-Cl
   - reactant stability-reactivity principle: in the rate determining step, the weaker the C-X bond, the faster it will break
   - This pattern is the same as for $S_N2$

3. **AgNO$_3$ Helps**
   - Ag+ helps strip the halide off in step one

4. **Polar Solvent Helps**
   - A polar solvent helps to stabilize the ions that form in the rate-determining step

<table>
<thead>
<tr>
<th>Solvent Polarity:</th>
<th>H$_2$O</th>
<th>CH$_3$OH</th>
<th>O</th>
<th>O</th>
<th>CH$_3$OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Rate</td>
<td>8000</td>
<td>1000</td>
<td>0.001</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

6.14 $S_N1$ Stereo: Racemization

Original stereochemistry is forgotten at the carbocation stage, get racemic R/S mixture

Why? Carbocation forgets original stereo:

Ex.
**S_N1 Problems:** For the following, which are and aren’t S_N1 candidates? If not, why not? What would be the product if they are S_N1 candidates?

1. Check nucleophile. Neutral or Anion?
2. Check Electrophile RX. Tertiary or secondary (SN1 OK). Primary, vinyl, or aryl no SN1.

1. ![Reagent](image1) + H_2O → NO_1 →
2. ![Reagent](image2) + NaOCH_3 → NO → Anion
3. ![Reagent](image3) + HOCH_3 → Yes → S_N1 → Anion (E2, not S_N1)
4. ![Reagent](image4) + NaO → NO → Anion (E2, not S_N1)
5. ![Reagent](image5) + HO → Yes → S_N1
6. ![Reagent](image6) + CH_3OH → Yes → S_N1 → 2 isomers
7. ![Reagent](image7) + CH_3OH → No → Vinyl
8. ![Reagent](image8) + H_2O → Yes → S_N1
9. ![Reagent](image9) + H_2O → No → Aryl

10. Rank Reactivity towards HO (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

**Issues:**

1. Tertiary > secondary >>>>>>> primary, vinyl, aryl
2. RI > RBr > RCl
3. Allylic > non-allylic
### 6.16 Comparing $S_N^2$ vs $S_N^1$

<table>
<thead>
<tr>
<th></th>
<th>$S_N^1$</th>
<th>$S_N^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Nucleophile</td>
<td>Neutral, weak</td>
<td>Anionic, strong</td>
</tr>
<tr>
<td><strong>2</strong> Substrate</td>
<td>$3^\text{o}$ R-X $&gt; 2^\text{o}$ R-X</td>
<td>$1^\text{o}$ R-X $&gt; 2^\text{o}$ R-X</td>
</tr>
<tr>
<td>Allylic effect…</td>
<td>Allylic Helps</td>
<td>Allylic helps</td>
</tr>
<tr>
<td><strong>3</strong> Leaving Group</td>
<td>I $&gt; \text{Br} &gt; \text{Cl}$</td>
<td>I $&gt; \text{Br} &gt; \text{Cl}$</td>
</tr>
<tr>
<td><strong>4</strong> Solvent</td>
<td>Polar needed</td>
<td>Non-factor</td>
</tr>
<tr>
<td><strong>5</strong> Rate Law</td>
<td>$K[RX]$</td>
<td>$k[RX][\text{Anion}]$</td>
</tr>
<tr>
<td><strong>6</strong> Stereoechemistry (on chiral, normally $2^\text{o}$ R-X)</td>
<td>Racemization</td>
<td>Inversion</td>
</tr>
<tr>
<td><strong>7</strong> Ions</td>
<td>Cationic</td>
<td>Anionic</td>
</tr>
<tr>
<td><strong>8</strong> Rearrangements</td>
<td>Problem at times</td>
<td>Never</td>
</tr>
</tbody>
</table>

**Identify as $S_N^1$ or $S_N^2$ or No Reaction. Draw the Product(s), if a reaction occurs.**

1. ![SN1 Reaction](image1)

2. ![No Reaction](image2)

3. ![SN1 Reaction](image3)

4. ![SN2 Reactions](image4)

5. ![SN1 Reaction](image5)

**Which fit $S_N^1$, which fit $S_N^2$?**

1. Faster in presence of silver nitrate? $S_N^1$

2. Faster in water than in hexane? $S_N^1$

3. When the moles of reactant is kept the same, but the volume of solvent is cut in half, the reaction rate increases by 2-fold? $S_N^1$

4. By 4-fold? $S_N^2$

5. 2-bromobutane reacts faster than 1-bromobutane? $S_N^1$

6. 2-bromobutane reacts slower than 1-bromobutane? $S_N^2$
6-17 E1 Elimination Reactions

Examples:

\[
\begin{align*}
\text{Br} & \quad \text{H}_3\text{C} \quad \text{H} \\
\text{OH} & \quad \text{H} \quad \text{H} \\
\text{Sn}^1 & \quad \text{E}_1 \quad \text{H}_3\text{C} \quad \text{H} \\
\text{Sn}^1 & \quad \text{E}_1 \quad \text{H}_3\text{C} \quad \text{H} \\
\text{HOCH}_3 & \quad \text{H}_3\text{C} \quad \text{OCH}_3 \\
\text{E}_1 \quad \text{E}_1 & \quad \text{H}_3\text{C} \quad \text{H} \\
+ & \quad \text{HBr} \quad + \quad \text{HBr}
\end{align*}
\]

Notes:

- Under Sn1 conditions, some elimination product(s) form as well.
- E1 and Sn1 normally compete, resulting in mixtures.
  - This is not good from a synthetic perspective.
- Structurally Isomeric Alkenes can form
  - The double bond must involve the original halogenated carbon and any neighbor carbon (that had a hydrogen to begin with that can be eliminated).
  - Normally the alkene with fewer alkene H’s is formed more extensively over alkenes with more alkene H’s. (More C-substituted alkene is major).
- Neutral/acidic (the formula starts neutral, but acid is produced).
- 1^\text{st} order rate law \[ r = k[RX]^1 \]

E1 Mechanism: 2 Steps

1. Step 1: Carbocation Formation. THIS IS THE SLOW STEP
   - Therefore the rate is controlled by cation stability! Just like Sn1!
   - Benefits from exactly the same factors that speed up Sn1 (3^o > 2^o, RI > RBr, polar solvent, etc.)
2. Step 2: Deprotonation from a carbon that neighbors the cation/original halogenated carbon
   - Can draw bromide as base for simplicity
   - But often it’s actually water or alcohol solvent that picks up the proton

E1 Summary

**Recognition:** A. Neutral, weak nucleophile. No anionic nucleophile/base, and B. 3^o or 2^o alkyl halide. (Controlled by cation stability).

(For 2^o alkyl halides, E1 is often accompanied by variable amounts of Sn1.)

**Orientation:** The most substituted alkene forms

**Predicting the major product:** Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.

**Stereochemistry:** Not an issue. The eliminating hydrogen can be cis or trans.

**Mech:** Stepwise, 2 steps, via carbocation. Be able to draw completely.
6-19 E2 Reaction (2\textsuperscript{nd} Order, Under Anionic/Basic S\textsubscript{N}2 type Conditions)

**Examples**

\[
\begin{array}{c}
\text{Br} \\
H
\end{array}
\xrightleftharpoons{\text{NaOCH}_3} \begin{array}{c}
\text{E2 (major)} \\
\text{E2 (minor E2)}
\end{array}
+ \begin{array}{c}
\text{HOCH}_3 + \text{HBr}
\end{array}
\]

E2 only

**Notes**

- **E2 happens with anionic nucleophiles/bases**, when S\textsubscript{N}2 is hindered
- Structurally Isomeric Alkenes can form
  - The double bond must involve the original halogenated carbon and any neighbor carbon (that had a hydrogen to begin with that can be eliminated)
  - Normally the alkene with fewer alkene H’s is formed more extensively over alkenes with more alkene H’s. (More C-substituted alkene is major).

**Mech**

- anionic. Anion base gets things started.
- 2\textsuperscript{nd} order rate law. \[ \text{Rate} = k[R-X][\text{anion base}] \]
- It all happens in one concerted step, but there are three arrow to show all the bond making and breaking

<table>
<thead>
<tr>
<th>Bonds Made</th>
<th>Bonds Broken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base to hydrogen</td>
<td>C-X bond</td>
</tr>
<tr>
<td>C=C pi bond</td>
<td>C-H bond</td>
</tr>
</tbody>
</table>

---

Anionic 3\textsuperscript{o} R-X

E2 only

S\textsubscript{N}2 and E2

1\textsuperscript{st} S\textsubscript{N}2 only
E2 Summary

Recognition:
A. Anionic Nucleophile/Base and
B. 3º or 2º alkyl halide

(1º alkyl halides undergo SN2 instead. For 2º alkyl halides, E2 is often accompanied by variable amounts of SN2.)

Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7)

Predicting product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans. However.

Stereochemistry: Anti elimination. The hydrogen on the neighbor carbon must be trans/anti.

Mech: Concerted. Uses anion. Be able to draw completely. Only one concerted step!

$S^2N1$ vs $E1$

- Both satisfy the carbocation. They just meet it’s bonding need with different electrons.

$S^2N2$ vs $E2$

1. Both provide an electron pair to displace the C-Br bond pair. They just use different electrons.
2. Both involve the anion. It’s called the nucleophile in the SN2, the base in the E2.
3. The SN2 involves a crowded transition state, and thus is strongly impacted by steric factors. The E2 does not have any steric problems (and in fact alleviates them).
4. The difference in steric profile explains why for SN2, $1^o > 2^o > 3^o$, but that for E2, the reactivity of $3^o$ is just fine.
Zaitsev’s Rule: When E1 or E2 elimination can give more than 1 structurally isomeric alkene, the more highly Carbon-substituted alkene form will predominate over a less highly carbon-substituted alkene.

a. The fewer H’s on the product alkene the better.
   - Every Alkene has four attachments. The fewer of these that are H’s, the better.
   - When pictures are drawn in which the H’s are not shown, the more highly substituted alkenes turn out to be the best.

b. Why? Product Stability-Reactivity Rule. Alkenes with more C’s and fewer H’s attached are more stable.

c. Alkene Stability is shown below: tetra- > tri- > di- > mono- > unsubstituted
   - Why?
     - Alkene carbons are somewhat electron poor due to the inferior overlap of pi bonds. (One carbon doesn’t really “get” as much of the other carbon’s electron as is the case in a nice sigma bond).
     - Since alkyl groups are electron donors, they stabilize electron-deficient alkene carbons.
     - Analogous to why electron-donating alkyls give the 3º > 2º > 1º stability pattern for cations and radicals.

Examples

- **3º R-X**
  - \[ 
  \text{Br} \quad \text{H} \quad \text{H} \quad \text{OH} \quad \text{H} \quad \text{S}_2 \text{N} \text{O} \text{H} \text{H} \]  
  - **H₂O**
  - **E₁** (major E₁)
  - **HBr**

- **2º R-X**
  - \[ 
  \text{Br} \quad \text{H} \quad \text{OH} \quad \text{S}_2 \text{N} \text{O} \text{H} \text{H} \]  
  - **NaOH**
  - **E₂** (of the E₂'s)
  - **H₂O**
  - **HBr**

No Competing S₂ for 3º R-X

S₂ and E₂ Compete for 2º R-X
Normally there is more S₂ than E₂
Stereochemistry of E2 Eliminations (6.20)

1. For E2 (not for E1) C-H and C-X bonds must be in the same plane (coplanar)
2. The halogen and the hydrogen being removed must be trans to each other
3. Why?
   a. Due to orbital overlap requirements.
   b. In the concerted E2 mechanism, the electrons from the hydrogen must essentially come in backside to the leaving halide (opposite)
   o just as in backside-attack SN2 mechanism

4. Sometimes, a molecule will need to single-bond spin into a “trans” conformation to enable a trans-elimination.

5. Eliminations in Cyclic Compounds are Often impacted by the Trans Requirement

Comparing E2 vs E1

<table>
<thead>
<tr>
<th></th>
<th>E1</th>
<th>E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Nucleophile/Base</td>
<td>Neutral, weak, acidic</td>
<td>Anionic, strong, basic</td>
</tr>
<tr>
<td>2 Substrate</td>
<td>3º RX not allowed</td>
<td>3º RX not allowed</td>
</tr>
<tr>
<td>Allylic effect…</td>
<td>Allylic Helps</td>
<td>Non-factor</td>
</tr>
<tr>
<td>3 Leaving Group</td>
<td>I &gt; Br &gt; Cl</td>
<td>I &gt; Br &gt; Cl</td>
</tr>
<tr>
<td>4 Solvent</td>
<td>Polar needed</td>
<td>Non-factor</td>
</tr>
<tr>
<td>5 Rate Law</td>
<td>k[RX]</td>
<td>k[RX][Anion]</td>
</tr>
<tr>
<td>6 Stereochemistry</td>
<td>Non-selective</td>
<td>Trans requirement</td>
</tr>
<tr>
<td>7 Ions</td>
<td>Cationic</td>
<td>Anionic</td>
</tr>
<tr>
<td>8 Rearrangements</td>
<td>Problem at times</td>
<td>Never</td>
</tr>
<tr>
<td>9 Orientation</td>
<td>Zaitsev’s Rule: Prefer more substituted alkene</td>
<td>Zaitsev’s Rule: Prefer more Substituted alkene (assuming trans requirement permits)</td>
</tr>
</tbody>
</table>
Elimination Problems: Draw the major elimination product for the following reactions. Classify as E1 or E2. (There may be accompanying S_N2 or S_N1 material, but to whatever degree elimination occurs, draw the major product.)

1. 

2. 

3. 

4. 

5. 

6. 

7. 

8. 

Diff. product from same reactant, due to E1 vs E2 stereo
diff. diastereomers reactants give diff. products

Note: The images contain chemical structures and reactions, along with annotations for classification as E1 or E2.
Comparing $S_N2$ vs $S_N1$ vs $E2$ vs $E1$: How Do I Predict Which Happens When?

Step 1: **Check nucleophile/base**
- If neutral, then $S_N1/E1 \rightarrow$ mixture of both
- If anionic, then $S_N2/E2$.

Step 2: If anionic and in the $S_N2/E2$ pool, then **Check the substrate**.
- $1^\circ \rightarrow S_N2$
- $2^\circ \rightarrow S_N2/E2$ mixture. (Often more $S_N2$, but not reliable…)
- $3^\circ \rightarrow E2$

Notes:

| 1° R-X | $S_N2$ only | No $E2$ or $S_N1/E1$ (cation too lousy for $S_N1/E1$; $S_N2$ too fast for $E2$ to compete) |
| 3° R-X | $E2$ (anionic) or $S_N1/E1$ (neutral/acidic) | No $S_N2$ (sterics too lousy) |
| 2° R-X | mixtures common |

Q1: **Anion or Neutral Nucleophile/Base?**
- Neutral
- $S_N1/E1$ Mix
- $S_N2/E2$ -

Q2: Is substrate $1^\circ$, $2^\circ$ or $3^\circ$ R-X?
- $1^\circ$ R-X
- $2^\circ$ R-X
- $3^\circ$ R-X
- $E2$ Only
- $S_N2$ Only
- $S_N2/E2$ Mix (normally favoring $S_N2$)

- Note: Aryl and Vinyl Halides will not undergo any of these types of reactions.
- If you see $Br_2/hv$ type recipe, then you’re back in the chapter 4 world of radical halogenation.
For each mixture,
a. Classify the Type of Reaction (or “no reaction”)
b. Draw the major product. (Or both a substitution and elim product.)

1. \[
\text{Br} + \text{NaO} + \text{acet} \rightarrow \text{OCH}_3
\]
   - \text{Sul/E2}

2. \[
\text{Br} + \text{NaOH} \rightarrow
\]
   - \text{Sul/E2}

3. \[
\text{I} + \text{NaOCH}_3 \rightarrow \text{OCH}_3
\]
   - \text{Sul/E2}

4. \[
\text{Br} + \text{OH} \rightarrow
\]
   - \text{Sul/E1}

5. \[
\text{Br} + \text{H}_2\text{O} \rightarrow \text{OH}
\]
   - \text{Sul}

6. \[
\text{Br} + \text{KOH} \rightarrow \text{No Rxn}
\]

7. \[
\text{I} + \text{H}_2\text{O} \rightarrow \text{No Rxn}
\]

8. \[
\text{Br} + \text{PhSH} \rightarrow \text{Sul}
\]
   - \text{Sul/E1}

9. \[
\text{Br} + \text{H}_2\text{O} \rightarrow \text{No Rxn}
\]
   - \text{Sul/E1}

10. \[
\text{Br} + \text{Br}_2 \rightarrow
\]
    - \text{Br}
**Design Synthetic Plans for converting the starting materials into the target molecules:**

1. In each case, more than one chemical operation will be required.
2. Strategy: $R-H \rightarrow R-Br$ (via bromination) $\Rightarrow$ Substitution product (via SN2) or alkene (via E2)

**Keys:**

1. These can't be done directly, in a single recipe. At least two laboratory operations are required.
2. Each sequence shown above requires an increase in functional groups. An $S_{N2}/S_{N1}$ or E2/E1 changes functionality but does not create functionality. But radical bromination does create a functional group.
3. Thus the key reaction for creating the functionality: $R-H \rightarrow R-Br$
4. Once you've converted the starting alkane to alkyl bromide, you can interconvert that bromide group into something else by $S_{N2}/S_{N1}$ or E2/E1
**Practice: Mechanism Practice**

Draw the **mechanism** for formation of the major product in each of the following reactions. In some cases where both elimination and substitution might compete, the problem specifies whether to draw the substitution or elimination mechanism.

1. $\text{Br}^- + \text{H}_2\text{O}$ (Subst.)
2. $\text{H}_2\text{O}$ (elim.)
3. $\text{Cl}^-$ + Br$_2$ (trans)

### Mechs:
- Radical halogenation
- $\text{SN}_2$
- $\text{E}_2$
- $\text{SN}_1$
- $\text{E}_1$

### Deprot (in an $\text{SN}_1$ or an $\text{E}_1$)
- 1. No base shown
- 2. Bromide anion as base
- 3. Solvent molecule as base
Practice: Ranking Practice

Rank the Reactivity of the chemicals shown toward the thing in the box.

- Identify the type of reaction that would be involved
- Think about the rate-determining step and how reactant or product or transition-state stability would influence the rate.

1. OH
2. Br₂, hv
3. H₂C–CH₃
4. CH₃OH
5. NaOH
6. Solvent: Pentane

Stability: 1 neat 2 res 3
Reactivity: 3 2 1

SN1 (S₅N₆) Anion

I° > Br°
I > Br
**Practice: Predict-the-Product Practice**

Give the Major Product(s) for each of the following. If it’s likely to give a mixture of both substitution and elimination, just draw the substitution product. Designate stereochemical outcomes when stereochemistry is relevant (2° substrates).

Key: Try to recognize what type of reaction will happen first.

1. \( \text{Br} + \text{NaOCH}_3 \rightarrow \text{OCH}_3 \)

2. \( \text{Br} + \text{hv} \rightarrow \text{br} \)

3. \( \text{Br} + \text{CH}_3\text{SNa} \rightarrow \text{SCH}_3 \)

4. \( \text{I} + \text{CH}_3\text{OH} \rightarrow \text{OCH}_3 \)

5. \( \text{Br} + \text{NaOH} \rightarrow \text{OH} \)

6. \( \text{Br} + \text{NaOCH}_3 \rightarrow \) single isomer

7. \( \text{OH} + \text{H}_2\text{O} \rightarrow \text{OH} \) + \text{OH} \)

8. \( \text{Br} + \text{NaOCH}_3 \rightarrow \text{cis} + \text{trans} \)

---

**Key:**
- **S** S - **S** S - **S** S - **S** S - **S** S - **S** S - **S** S - **S** S
- **T** T - **T** T - **T** T - **T** T - **T** T - **T** T - **T** T - **T** T
- **E2** E2 - **E2** E2 - **E2** E2 - **E2** E2 - **E2** E2 - **E2** E2 - **E2** E2 - **E2** E2
- **Su2** Su2 - **Su2** Su2 - **Su2** Su2 - **Su2** Su2 - **Su2** Su2 - **Su2** Su2 - **Su2** Su2 - **Su2** Su2
- **radical** radical - **radical** radical - **radical** radical - **radical** radical - **radical** radical - **radical** radical - **radical** radical - **radical** radical
Provide Reactants for the Following (One of the Starting Chemicals must be an \( \text{R-Br} \))

1. 

2. 

3. 

4. 

5. 

Draw the Major Alkene Isomer, Following Elimination

6. 

7. 

\( \text{CN} \cdot \text{H} \cdot \text{C} \cdot \text{OCH}_3 \) (trans only) 

\( \text{CH}_3 \cdot \text{H} \) 

\( \text{Cl} + \text{NaOCH}_3 \) show elim only 

\( \text{CN} \cdot \text{Cl} \) 

\( \text{CN} \cdot \text{H} \cdot \text{Cl} \) 

\( \text{OH} \) 

\( \text{E} \) 

\( \text{E} \) 

\( \text{E} \) 

\( \text{E} \)
6-15 Carbocation Rearrangements (and their impact in S_N1 and E1 reactions)

1. Carbocations are very unstable, and sometimes rearrange to other more stable carbocations.
2. A rearrangement requires that a superior cation will result. Four cases:
   a. 2º \( \rightarrow \) 3º
   b. non-allylic \( \rightarrow \) allylic
   c. strained ring \( \rightarrow \) unstrained or less strained ring
   d. 1º cation \( \rightarrow \) 2º or 3º cation (rare, since 1º cations are hard to make and pretty rare)

<table>
<thead>
<tr>
<th>Hydride Shifts</th>
<th>Alkyl Shifts</th>
</tr>
</thead>
</table>
| \( \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array} \rightarrow \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array} \) |
| 2º \( \rightarrow \) 3º |
| \( \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H}
\end{array} \rightarrow \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H}
\end{array} \) |
| 2º \( \rightarrow \) 2º allylic |

3. Two processes for cation rearrangement:
   a. Hydride shift (an H jumps over)
   b. Alkyl shift (a carbon jumps over)
      - The resulting cation must always be on a carbon adjacent to the original
      - Rearrangement does not occur if you start with a good cation.
4. Most cation mechanisms that start with 2º or 3º cations don’t undergo rearrangement
   because rearrangement does not lead to improved cation stability

<table>
<thead>
<tr>
<th>Why Bother?</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No Stability Gain,</td>
<td>3º ( \rightarrow ) 2º</td>
<td>2º ( \rightarrow ) 2º</td>
</tr>
<tr>
<td>No Motive,</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Won’t Happen</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Examples in SN1

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{H}_2\text{O}} \text{OH} \\
\implies & \text{OH} + \text{OH} + \text{some E1 alkenes}
\end{align*}
\]

- Product mixture results from competition between Path A and Path B.

\[
\begin{align*}
\text{I} & \xrightarrow{\text{HOC}_3} \text{OCH}_3 \\
& \text{via} \text{H} + \text{via} \\
& \text{via} \text{H} + \text{via} 
\end{align*}
\]