Four mechanisms to learn: $S_N^2$ vs E2 and $S_N^1$ vs E1

$S_N^2$ competes with E2
$S_N^1$ competes with E1

These electrons always leave with X. R-X is the electrophile

Nu: / B: = is an electron pair donor to carbon (= nucleophile) or to hydrogen (= base). It can be strong ($S_N^2$/E2) or weak ($S_N^1$/E1).

R = methyl, primary, secondary, tertiary, allylic, benzylic
X = -Cl, -Br, -I, -OSO$_2$R (possible leaving groups in neutral, basic or acidic solutions)
X = -OH$^\ominus$ (only possible in acidic solutions)

Important details to be determined in deciding the correct mechanisms of a reaction.

1. Is the nucleophile/base considered to be strong or weak? We simplistically view strong electron pair donation as anions of all types and certain neutral nitrogen, sulfur and phosphorous atoms. Weak electron pair donors will be neutral solvent molecules, usually water (H$_2$O), alcohols (ROH), or simple, carboxylic acids (RCO$_2$H).

2. What is the substitution pattern of the R-X substrate at the C$\alpha$ carbon attached to the leaving group, X? Is it a methyl, primary, secondary, tertiary, allylic, or benzylic carbon? What about any C$\beta$ carbon atoms? How many additional carbon atoms are attached at a C$\beta$ position (none, one, two or three)?

Answers to these questions will determine $S_N^2$, E2, $S_N^1$ and E1 reactivities and alkene substitution patterns and relative stabilities in E2 and E1 reactions.

$S_N^2$ versus E2 overview (Essential features: strength of the nucleophile/base (as judged by its conjugate acid pK$_a$), and steric factors (size) of the nucleophile/base) These are competing reactions.

Nu: / B: = is an electron pair donor to carbon (= nucleophile) or to hydrogen (= base). It can be strong ($S_N^2$/E2) or weak ($S_N^1$/E1).

strong = anything with negative charge, and neutral sulfur, phosphorous or nitrogen in our course.

Nu: / B: = is an electron pair donor to carbon (= nucleophile) or to hydrogen (= base). It can be strong ($S_N^2$/E2) or weak ($S_N^1$/E1).

E2 > $S_N^2$ (when t-butoxide)
E2 always anti C$_\beta$-H, C$_\alpha$-X (in our course)
**S$_N$2 PE vs. POR Diagram** (= concerted energy picture that looks very similar to E2 reactions)

As carbon inverts configuration, its sp$^2$ transition state forms a high PE carbon with 10 electrons at carbon. This is a concerted, one-step reaction.

$E_a = -2.3RT \log(k_{SN2})$

$\Delta G = -2.3RT \log(K_{eq})$

$K_{SN2} = 10^{2.3RT}$

$\Delta G$ - this energy difference determines the extent of reaction, the ratio of products vs. reactants at equilibrium (when kinetics allows the reaction to proceed). Thermodynamics is determined by the strengths of the bonds and solvation energies of the reactant and product species.

Rate = $k_{SN2}[RX][Nu] = \text{bimolecular reaction}$

**E2 PE vs. POR Diagram** (= concerted energy picture that looks very similar to $S_N2$ reactions)

Transition state - requires parallel overlap of the two 2p orbitals forming the pi bond. This is easiest when C$_β$-H is anti to C$_α$-X.

Rate = $k_{E2}[RX][Nu] = \text{bimolecular reaction}$

If stereochemical priority is $R_1 > R_2$ and $R_3 > R_4$ then this would be Z configuration, which is fixed by the requirement for anti C$_β$-H / C$_α$-X elimination. If syn elimination occurred the stereochemistry would be E ("syn" is not typically observed).
SN₂ reactions are arguably the most important reactions in organic chemistry. They always occur by backside attack at Cα-X carbon. These are the common R-X patterns we encounter. Steric factors are very important.

\[
\begin{align*}
\text{methyl (Me)} & \quad \text{primary (1°)} \quad \text{secondary (2°)} \quad \text{tertiary (3°)} \\
methyl & \quad \text{primary} \quad \text{secondary} \quad \text{tertiary} \\
\end{align*}
\]

Relative rates of SN₂ reactions - Steric hindrance at the Cα carbon slows down the rate of SN₂ reactions.

Cα carbon patterns

As SN₂ slows down E₂ gets more competitive.

- **Methyl** [excellent]:
  - Primary RX
  - Tertiary RX

- **Primary** [good]:
  - Secondary RX

- **Tertiary** [very poor]:
  - Stabilized "allylic" transition state (benzylic too)

Tertiary substitution has no easy path of approach by the nucleophile. The Cα carbon is completely substituted, so the nucleophile cannot get close enough to make a bond with the Cα carbon. We do not propose any SN₂ reaction at tertiary RX centers. E₂ becomes the dominant mechanism here.

Negative charge is stabilized by delocalization into adjacent pi bond. Lowers T.S. energy, thus faster rate.
Relative rates of $S_{N2}$ reactions - Steric hindrance at the $C_\beta$ carbon slows down the rate of $S_{N2}$ reactions. All of these are primary R-X structures at $C_\alpha$, but substituted differently at $C_\beta$.

$C_\beta$ carbon patterns

<table>
<thead>
<tr>
<th>Structure</th>
<th>Rate Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl</td>
<td>$k \approx 1$</td>
</tr>
<tr>
<td>Propyl</td>
<td>$k \approx 0.4$</td>
</tr>
<tr>
<td>2-Methylpropyl</td>
<td>$k \approx 0.03$</td>
</tr>
<tr>
<td>2,2-Dimethylpropyl (1° neopentyl)</td>
<td>$k \approx 0.00001 \approx 0$</td>
</tr>
</tbody>
</table>

A completely substituted $C_\beta$ carbon atom also blocks the Nu: approach to the backside of the C-X bond. A large group is always in the way at the backside of the $C_\alpha$-X bond even when 1° RX. SN2 is not possible.

If even one bond at $C_\beta$ has a hydrogen then approach by Nu: to the backside of the $C_\alpha$-X bond is possible and an $S_{N2}$ reaction is possible.

Steric size of the nucleophile/base also affects the $S_{N2}$/E2 distribution of products.

The first clue to recognize is strong nucleophile/bases (most anions, neutral sulfur and phosphorous, some nitrogen) vs. weak nucleophile/bases (neutral solvents = H$_2$O, ROH, RCO$_2$H)
Nucleophile / Bases: Strong electron pair donation (S_N2 / E2) or Weak electron pair donation (S_N1 / E1)

You can used any of these whenever you need (buy)

- Na⁺ : O⁻ H⁺ hydroxide
- Na⁺ : S⁻ H⁻ hydrogen sulfide (thiolate)
- Li⁺ : N⁻ N=N⁻ Na⁺ azide
- Na⁺ : O⁻ : N⁻ N⁻ O⁻ cyanide

You have to make these from given compounds (acid/base chem)

- Na⁺ : O⁻ R⁺ phthalimide
- Na⁺ : O⁻ R⁺ dithiane anion

Almost always a base in our course

- Sodium borohydride
- Sodium hydride (very strong base)
- Sodium amide (very strong base)
- Lithium aluminium hydride
- Lithium aluminium deuteride

Almost always a base in our course

- Sodium hydride (very strong base)
- Potassium hydride (very strong base)
- Sodium amide (very strong base)

Enolate chemistry

- Used to make LDA, which is the base used to make enolates of all types
- Used to make aldehydes and ketones

Dithiane chemistry

- Used to make aldehydes and ketones
- Used to make nitriles

Free radical chemistry

- Phthalimide
- Peroxydic peroxide

Oxidizing reagents at ROH and RCHO

- CrO₃ / H₂O pyridinium chlorochromate (PCC: oxidizing E2 reaction, makes carboxylic acids and ketones
- CrO₃ / pyridine cuprous bromide (makes cuprates)

Miscellaneous reagents

- Chlorine / Br₂: S⁻ Cl⁻ (tosyl chloride) makes ROH into tosylates
- Diphenyl sulfide, used with C=O to make epoxides
- Triphenylphosphine, used with C=O to make alkenes

Neutural functional group examples to make enolates (we can make our own nitriles)

- Propanone
- Methyl ethanoate
- N,N-dimethylethanamide
- Ethanoic acid

Strong nucleophile and/or base

- S_N2 / E2: concerted reactions (one step)
- S_N1 / E1: multistep reactions, carbocation formation requires 2°, 3°, allylic or benzylic RX and a polar hydrogen bonding solvent
- Rearrangements are likely to form similar or more stable carbocations

Weak nucleophile and/or base

- S_N1 / E1: multistep reactions, Carbocation formation requires 2°, 3°, allylic or benzylic RX and a polar hydrogen bonding solvent
- Rearrangements are likely to form similar or more stable carbocations
- Nucleophiles can add to both sides of R⁺ and beta protons can be lost from both faces of R⁺, generally not as useful due to many possibilities.
- Usually S_N1 > E1, except for dehydration of ROH using H₂SO₄ and heat (distills out the E1 alkene)

Weak nucleophiles (in our course) (usually S_N1 > E1)

- Water
- Alcohols
- Carboxylic acids

E1 exception: ROH + H₂SO₄ / Δ
Special requirements for cyclohexane rings (Sₙ₂ and E₂)

Sₙ₂ Inversion of Configuration in Cyclohexane Rings – Axial leaving group is preferred.

Backside approach is not possible when leaving group is equatorial.

Backside approach is possible when leaving group is equatorial.

An axial leaving group is also required for E₂ reactions because it is the only way to have the required anti Cβ-H / Cα-X orientation

More stable conformation, but less reactive.

Less stable conformation, but more reactive.

Predict products. Explain choices. In pairs, predict the faster reacting stereoisomer (why?).
Stability of pi bonds

Greater substitution of carbon groups in place of hydrogen atoms at alkene carbons translates into greater stability (lower potential energy). There are three types of disubstituted alkenes and their relative stabilities are usually as follows: geminal \( \approx \) cis \( < \) trans. This is also true in alkenes.

Relative stabilities of substituted alkenes.

1 = unsubstituted alkene (ethene is unique)
2 = monosubstituted alkene
3 = cis disubstituted alkene
4 = geminal disubstituted alkene
5 = trans disubstituted alkene
6 = trisubstituted alkene
7 = tetrasubstituted alkene

Saytzeff's rule: More stable alkenes tend to form faster (because of lower \( E_a \)) in dehydrohalogenation reactions (E2 and E1). They tend to be the major alkene product, though typically a little of every alkene product possible is obtained.

Possible explanations for greater stability with greater substitution of the pi bond

A fairly simple-minded explanation (the one we will use) for the relative alkene stabilities is provided by considering the greater electronegativity of an sp\(^2\) orbital over an sp\(^3\) orbital. An alkyl group (R\( \rightarrow \)) inductively donates electron density better than a simple hydrogen. The more R groups at the four sp\(^2\) positions of a double bond, the better. Hyperconjugation is also used to explain electron donation into the pi bond. However, be aware that other features, such as steric effects or resonance effects, can reverse expected orders of stability.

inductive donation to more electronegative sp\(^2\) orbital (than sp\(^3\) orbital)

hyperconjugation reason (MO argument) (sigma resonance?)
Summary chart of similar looking nucleophiles versus bases (2° RX centers are the most ambiguous)

<table>
<thead>
<tr>
<th>R-X patterns</th>
<th>carbon nucleophile / bases</th>
<th>nitrogen nucleophile / bases</th>
<th>less basic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>more basic</td>
<td>more basic &amp; sterics</td>
<td>Kₐ = 10⁻⁹</td>
</tr>
<tr>
<td></td>
<td>Kₐ = 10⁻²⁵</td>
<td>Kₐ = 10⁻¹⁶</td>
<td></td>
</tr>
<tr>
<td>methyl</td>
<td>only S_N₂</td>
<td>only S_N₂</td>
<td>NA</td>
</tr>
<tr>
<td>primary</td>
<td>S_N₂ &gt; E₂</td>
<td>S_N₂ &gt; E₂</td>
<td>E₂ &gt; S_N₂</td>
</tr>
<tr>
<td>secondary</td>
<td>E₂ &gt; S_N₂</td>
<td>S_N₂ &gt; E₂</td>
<td>only E₂</td>
</tr>
<tr>
<td>tertiary</td>
<td>only E₂</td>
<td>only E₂</td>
<td>only E₂</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>oxygen nucleophile / bases</th>
<th>hydrogen nucleophile / bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>more basic &amp; sterics</td>
<td>less basic</td>
</tr>
<tr>
<td>Kₐ = 10⁻¹⁹</td>
<td>Kₐ = 10⁻⁵</td>
</tr>
<tr>
<td>R-X patterns</td>
<td></td>
</tr>
<tr>
<td>methyl</td>
<td>only S_N₂</td>
</tr>
<tr>
<td>primary</td>
<td>E₂ &gt; S_N₂</td>
</tr>
<tr>
<td>secondary</td>
<td>only E₂</td>
</tr>
<tr>
<td>tertiary</td>
<td>only E₂</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>hydrogen nucleophile / bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;D&quot; shows rxn site (H)</td>
</tr>
<tr>
<td>Kₐ = 10⁻³⁷</td>
</tr>
<tr>
<td>R-X patterns</td>
</tr>
<tr>
<td>methyl</td>
</tr>
<tr>
<td>primary</td>
</tr>
<tr>
<td>secondary</td>
</tr>
<tr>
<td>tertiary</td>
</tr>
</tbody>
</table>
Simple reactions to practice on:

1. hydroxide nucleophile

2. alkoxide nucleophiles
3. carboxylate nucleophiles

4. t-butoxide base
5. imidate nucleophile

6. azide nucleophile
7. dialkylamide anion

8. hydrogen sulfide nucleophile
9. thiolate nucleophiles

10. cyanide nucleophile
11. terminal acetylide nucleophiles

12. ketone enolate nucleophiles
13. ester enolate nucleophiles

14. 3° amide nucleophiles
15. nitrile enolate nucleophiles

16. carboxylate dianion enolate nucleophiles
17. dithiane nucleophiles

18. aluminum hydride (Li AlH₄ or LiAlD₄) / borohydride nucleophiles (NaBH₄ or NaBD₄)
19. diphenylsulfide nucleophile (sulfonium salt is used to make epoxides with aldehydes and ketones)

20. triphenylphosphine nucleophile (phosphonium salt is used to make E or Z alkenes with aldehydes and ketones)
Other reactions we need to know.

'acyl substitution,' many carboxyl groups react this way, and it can occur in aqueous base or aqueous acid.

organic ambiguity
a. attack C=O
b. attack C-O
c. attack Cα-H

\[
\begin{array}{c}
\begin{array}{c}
\text{ester carboxylic acid alcohol} \\
\text{neutralization}
\end{array}
\end{array}
\]

The elements of water have been added to the ester to make a carboxylic acid and an alcohol. Hydrolysis means 'addition of water' (can also be called hydration) and is a very common reaction in organic chemistry and biochemistry. We will see similar reactions many times, as well as the opposite reactions (dehydration = removal of water).

Problem 7 – Show the acyl substitution mechanism for each functional group below with hydroxide.

Functional Groups to use - What is the leaving group?

- acid chloride
- anhydride
- ester
- 3° amide
Make imidate and use as nucleophile at Me-X, 1º RCH₂-X and 2º R₂CH-X in Sₙ2 RX centers to convert to primary amines.

Gabriel 1º amine synthesis = 1. Make alkyl imides by Sₙ2 2. Hydrolyze in base to make primary amines (acyl substitution) 3. Workup (neutralize base conditions) For an alternative approach see the azide primary amine synthesis, next: 1. Sₙ2 with NaN₃ 2. Sₙ2 with LiAlH₄ at nitrogen 3. workup)

```
imide (buy)  pKₐ ≈ 9
```

```
Ng
O
H
\text{acid/base rxn}
\text{K}_{eq} = \text{resonance stabilized makes imidate less basic and a better behaved nucleophile}
```

```
imide
\text{acid/base}
\text{K}_{eq} =
```

```
N
O
H
\text{acid/base rxn}
\text{K}_{eq} =
```

```
N
```

Look at similarities with ester hydrolysis, just above.

Alternative azide strategy to make primary amines (Sₙ2 and acid/base reactions) at methyl, 1º and 2º RBr.

step 1 - make alkyl azide

```
\text{SN}_2
```

step 2 - make primary amine

```
1º amine
```
Alkyne synthesis (via two E2 reactions with RBr₂ and NaNR₂, two times)

To make starting alkynes from our simple given alkanes requires substituting on two leaving groups (Br for H), followed by 3 equivalents of very basic R₂N⁻. The 3rd equivalent of R₂N⁻ is necessary because of the acidity of the sp C-H bond. This would have to be added back on in a final workup step.

Possible steps in mechanism (E2 twice then 2. acid/base or 2. RX electrophile)

Make terminal acetylides and use as nucleophiles only at Me-X and 1° RCH₂-X in S_N2 reactions.
The Zipper reaction moves a triple bond from an internal position along an unbranched chain to the end of linear chain to form the most stable anionic charge (sp carbanion). Further nucleophile chemistry is possible using the terminal acetylide carbanion. This reaction is similar to tautomers, without any heteroatoms (it just uses a much stronger base).
Synthesis of lithium diisopropyl amide, LDA, sterically bulky, very strong base used to remove Cα-H proton of carbonyl groups. (acid/base reaction) to make carbonyl enolates of ketones, esters, nitriles and others (next).

React ketone enolate (nucleophile) with R-Br electrophile (SN2 reaction at Me, 1o and 2o RX compounds)

React ester enolate (nucleophile) with R-Br electrophile (SN2 reaction at Me, 1o and 2o RX compounds)

React carboxylate dianion enolate (nucleophile) with R-Br electrophile (SN2 reaction at Me, 1o and 2o RX compounds)
React nitrile ‘enolate’ with R-Br electrophile (S_N2 reaction at Me, 1° and 2° RX compounds)

Make nitrile enolate (nitriles)

\[
\text{LDA} \quad \begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array}
\text{nitriles}
\]

\[
\text{pK}_a = 30
\]

\[
\begin{array}{c}
\text{H} \\
\text{C} \\
\text{N} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{Li} \\
\end{array}
\text{nitrile enolates}
\]

\[
\text{Keq} = \frac{\text{pK}_a}{37}
\]

React nitrile enolate with RX compounds (methyl, 1° and 2° RX)

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{Li} \\
\end{array} \\
\begin{array}{c}
\text{CH}_2 \\
\text{Li} \\
\end{array}
\text{nitrile enolates}
\]

\[
\text{CH}_2
\]

\[
\text{R} \quad \begin{array}{c}
\text{Br} \\
\text{S} \\
\end{array} \\
\begin{array}{c}
\text{S} \\
\text{C} \\
\text{H}_3
\end{array}
\text{Larger nitrile made from smaller ester.}
\]

Problem 11 – Predict the major product of each set of conditions below and write a plausible mechanism for how the reaction(s) work.

<table>
<thead>
<tr>
<th>a.</th>
<th>b.</th>
<th>c.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical structure" /></td>
<td><img src="image2.png" alt="Chemical structure" /></td>
<td><img src="image3.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td><img src="image4.png" alt="Chemical structure" /></td>
<td><img src="image5.png" alt="Chemical structure" /></td>
<td><img src="image6.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td><img src="image7.png" alt="Chemical structure" /></td>
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<tr>
<td><img src="image10.png" alt="Chemical structure" /></td>
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<tr>
<td><img src="image19.png" alt="Chemical structure" /></td>
<td><img src="image20.png" alt="Chemical structure" /></td>
<td><img src="image21.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td><img src="image22.png" alt="Chemical structure" /></td>
<td><img src="image23.png" alt="Chemical structure" /></td>
<td><img src="image24.png" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>
Special case of intramolecular **S\(_{N}\)2 reaction** - synthesis of **epoxides (oxiranes)** under base conditions

Problem 23 – Predict S\(_{N}\)2 products and propose mechanisms for the following reactions. What constitutes a ‘strong’ nucleophile in our course? How could this form under the reaction conditions? What is the necessary stereochemistry for an S\(_{N}\)2 reaction? What conformation in a cyclohexane ring allows this approach?

Example Mechanisms shown below.

<table>
<thead>
<tr>
<th>p.</th>
<th>q.</th>
<th>r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(_2) / hv</td>
<td>Br</td>
<td>2 eqs. Br(_2) / hv</td>
</tr>
<tr>
<td></td>
<td>t-butoxide</td>
<td></td>
</tr>
<tr>
<td>s.</td>
<td>t.</td>
<td>u.</td>
</tr>
<tr>
<td>Br, Br</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>1. excess NaNR(_2) 2. workup</td>
<td>1. LDA, -78(^\circ)C 2. CH(_3)Br 3. workup</td>
<td>1. LDA, -78(^\circ)C (2 eqs.) 2. CH(_3)Br 3. workup</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3R-bromo-2S-deuterohexane

One S\(_{N}\)2 product and four E2 products.  
1. strong Nu\(^+\) /B\(^-\)  
2. 2\(^{\circ}\) R-X

sigma bond rotations

(2S,3R) only one S\(_{N}\)2 product

(2E, with “D”) four possible E2 products

(3E, lost H\(_a\))

(3Z, lost H\(_b\))
**S<sub>N</sub>1 and E<sub>1</sub> Competition – Multistep Reactions Arising From Carbocation Chemistry**

**S<sub>N</sub>1 versus E<sub>1</sub> overview** (essential feature: stability of the carbocation) These are competing reactions.

Example: requires 2° or 3° RX and a weak nucleophile/base. S<sub>N</sub>1 generally out competes E<sub>1</sub>.

![Carbocation Chemistry Diagram](image-url)

**R-X Substitution Pattern and rates of S<sub>N</sub>1 reactions (backwards from S<sub>N</sub>2 reactions)**

S<sub>N</sub>1 (and E<sub>1</sub>) relative reactivities of R-X compounds:

\[
\text{R} - \text{X} \xrightarrow{\text{polar protic solvent}} \text{R}^+ \xrightarrow{\Theta^+} \text{X}^\ominus
\]

- **R<sup>⊕</sup>:** Carbocation intermediate
- **Θ: X leaving group**
- **R<sup>+</sup>:** Ion formation requires assistance from the polar solvent

Relative rates:

- Methyl (1°) \(10^{-5} \approx 0\)
- Primary (1°) \(10^{-4} \approx 0\)
- Secondary (2°)
- Tertiary (3°) \(10^6 = 1,000,000\)

1.0 reference compound

The order of stability at the electron deficient carbocation carbon is methyl \(<\) primary \(<\) secondary \(<\) tertiary. This is explained by either inductive effect or hyperconjugation or both. Hyperconjugation can be considered as sigma resonance.

**Sigma electrophilic substituent helps stabilize C<sup>⊕</sup>**

Sigma electrons are pulled toward the carbocation carbon. Part of the \(\delta^+\) is distributed on to the hydrogen atoms, but not typically shown with formal charge.

Additional sigma bonds of alkyl substituent(s) allow further polarizations of electrons from more bonds (inductive donating effect), which spreads out \(\delta^+\) charge through sigma bond polarizations and help stabilize the electron deficient carbocation carbon.

---

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Resonance effects also make carbocations more stable, from an adjacent pi bond or lone pair.

Resonance effects help stabilize carbocations (from pi bonds and from lone pairs).

Gas phase Stabilities as Indicated by Hydride Affinities

Hydride affinity is the energy released when a hydride is added to a carbocation (gas phase reaction). The energy of reaction, ΔH, is very negative (favorable). How much do inductive and resonance effects help a carbocation center? The following gas phase data below show the differences in carbocation stability are enormous. In fact, differences are so large that we will almost never propose methyl or primary carbocation possibilities as reaction pathways in solutions in our course. We will consider these two patterns (CH3-X and RCH2-X) as unreactive in SN1 and E1 chemistry, and that should make your life a little bit easier.

Problem 25 - Explain the differences in stability among the following carbocations (hydride affinities). All relative energy values in kcal/mole versus a primary carbocation. A positive value is less stable and a negative value is more stable relative to the reference primary carbocation.

A more negative Δ (compared to 1° R+) is a more stable carbocation.
Problem 27 – The bond energy depends on charge effects in the anions too. Can you explain the differences in bond energies below? (Hint: Where is the charge more delocalized?) We won’t emphasize these differences.

\[
\begin{array}{c|c}
X & \text{Gas Phase B.E.} \\
\hline
\text{Cl} & +157 \\
\text{Br} & +149 \\
\text{I} & +140 \\
\text{H} & +230 \\
\end{array}
\]

The activation energies for ionization in solvents are on the order of 20-30 kcal/mole (SN1 and E1 reactions). It is clear from the difference in the gas phase energies of ionization (> 200 kcal/mole) that the solvent is the most stabilizing factor in ion formation. Because solvent structure is so complex we ignore it, but we do so at our own peril.

Many small solvent / ion interactions make up for a single large covalent bond (heterolytic cleavage). A typical hydrogen bond is about 5-7 kcal/mole and typical covalent bonds are about 50-100 kcal/mole. In a sense the polar protic solvent helps to pull the \( \text{C}-X \) bond apart. The "polarized" protons tug on the "X" end and the lone pairs of the solvent molecules tug on the "\( \text{C}_\alpha \)" end. If the carbocation is stable enough, the bond will be broken.

**Weak Nucleophile/Bases are used in SN1/E1 Reactions**

R \(^+\) has to be secondary, tertiary or resonance stabilized carbon.

\( \text{SN1/E1 reactions - form carbocation (R\(^+\)) in first step,} \)

\( \text{R}^+ \text{ has three common choices} \)

1. rearrange to similar or more stable R \(^+\)
2. add nucleophile to top/bottom (R/S)
3. lose any beta proton from top/bottom (E/Z)

(forms pi bonds)

these are our weak nucleophile / bases

- water
- alcohols
- carboxylic acids
We will view the attack on an sp² carbocation as equally accessible from either face (top or bottom). In reality, the leaving group often shields (blocks) the face it is leaving from, giving a preference for inversion over retention.

If all 3 attached groups at a carbocation carbon are different from one another and the attacking nucleophile, then a racemic mixture of enantiomers will form. If R₂ = R₃, then the Cα carbon is achiral.

There is, perhaps, a slower rate of attack from the face where the methyl is positioned, but remember, it rotates through a full 360°.

The new stereogenic center forms both R and S absolute configurations. If another chiral center is present, that does not change in the reaction then diastereomers will form (RR) vs. (RS). These would likely form in different amounts.
**Rearrangements of Carbocations – searching for a more stable carbocation (a common complication)**

Consider the migration of every group on a Cβ position, whether H or C. To keep our choices simpler (than they really are) we will only consider rearrangements of 2o to 3o and 3o to 3o carbocations. What are the likely SN1 and E1 products of the initial carbocation and the rearranged carbocations from “a”, “b” and “c”?

![Diagram showing the migration of groups and the formation of carbocations](image)

The RX compound must be 2o, 3o, allylic or benzylic to form the initial carbocation.

**Transition state of a carbocation rearrangement**

![Diagram showing the transition state](image)

The migrating group is always attached to the carbon skeleton; it is never a free anion.
The three fates of carbocations are to add a nucleophile (from either face), to lose any $C_\beta$-H from either face and to rearrange. Rearrangements are a temporary solution for an unstable carbocation. Rearrangements transfer the unstable carbocation site to a new position having a similar energy or, better yet, to a site where the positive charge is more stable. If such possibilities exist, this will very likely be one of the observed reaction pathways. However, even with a rearrangement a carbocation will not gain the two needed electrons. The electron deficiency is merely moved to a new position. This process can occur a number of times before a carbocation encounters its ultimate fates, discussed above, $S_N1$ and $E1$. Usually $S_N1$ will outcompete $E1$.

Strain energy is another factor that must be considered in carbocation rearrangements (in addition to the relative stabilities of $1o$, $2o$ and $3o$ carbocations). Consider the possible rearrangement choices available to the following tertiary carbocation in a polar ionizing solvent.

a. A hydride migration makes a primary carbocation from a tertiary carbocation. This reaction would increase the potential energy by about 35 kcal/mole and is not a realistic option.

b. At first this option (hydride shift) seems very reasonable (tertiary carbocation to tertiary carbocation), but there would be much additional ring strain energy because of bond angle changes in the small cyclobutane ring ($109^\circ = sp^3$ to $120^\circ = sp^2$), while geometric shape in the ring is trying to be $90^\circ$. This would, therefore, not be a favorable option.

c. At first this looks like a very poor reaction (tertiary carbocation to secondary carbocation via alkyl migration of a ring carbon) and would be uphill by about 15 kcal/mole based on carbocation stabilities. However, the reduction in ring strain would be downhill by about 20 kcal/mole (26 kcal/mole $\rightarrow$ 6 kcal/mole), resulting in an overall potential energy change of -5 kcal/mole.
Example $S_N1$ / E1 Mechanisms with rearrangement (2° $R^+$ to 3° $R^+$ rearrangement)

1. weak H-Nu/H-B:
2. 2° $R$-X

1. The first 2° $R^+$ forms two $S_N1$ products and three E1 products
2. The rearranged 3° $R^+$ forms two $S_N1$ products and five E1 products (next page)

1. add H-Nu: ($S_N1$)
2. lose $C-\beta$-H (E1)
3. rearrange (start over)

---

2R-bromo-3R-methylhexane

E1 product after loss of beta proton from methyl (CH$_3$)

E1 product after loss of beta proton from methine (CH) from either face

carboxcation continued with rearrangement)
Reaction Templates - sideways and vertical perspectives (either one will work)

$S_N2/E2$ (Nu: B: ) always backside for $S_N2$ and usually anti $C_\alpha$-H/$C_\beta$-X attack for E2

$S_N1/E1$ (H-Nu: / H-B:) - form $R^+$, attack from either face for both reactions (usually $S_N1 > E1$)

**Examples of Strong base / nucleophiles that can be used below = $S_N2$ / E2 (many others are possible)**

- **B: = Nu:**

  - $\text{H-O}^-$
  - $\text{conjugate acid pK}_a = 16$

  - $\text{O}^-$
  - $\text{conjugate acid pK}_a = 16$

  - $\text{O}^-$
  - $\text{conjugate acid pK}_a = 5$

  - $\text{O}^-$
  - $\text{conjugate acid pK}_a = 19$

**Examples of Weak base / nucleophiles that can be used below = $S_N1$ / E1 (most common for us)**

- **water**
- **liquid alcohols**
- **liquid carboxylic acids**

**methyl (Me)**

**side views**

- **Nu:**
  - **strong**

- **vertical views**

- **Nu:**
  - **strong**

- **simplistic views**

- **Nu:**

  - H$_3$C\(\text{Br}\)
**primary (1°)**

side views

\[ \begin{align*}
\text{Nu} & : \quad H - C_\beta - C_\alpha - X \\
\end{align*} \]

vertical views

\[ \begin{align*}
\text{Nu} & : \quad H - C_\beta - C_\alpha - X \\
\end{align*} \]

**secondary (1°)**

priorities: R₁ > R₂

side views

\[ \begin{align*}
\text{Nu} & : \quad H - C_\beta - C_\alpha - X \\
\end{align*} \]

vertical views

\[ \begin{align*}
\text{Nu} & : \quad H - C_\beta - C_\alpha - X \\
\end{align*} \]
simplistic views

\[ \begin{align*}
\text{Nu} : & \\
\text{B} : & \\
\end{align*} \]

tertiary (1°) priority \( R_1 > R_2 > R_3 \)

side views

\[ \begin{align*}
\text{Nu} : & \\
\text{B} : & \\
\end{align*} \]

vertical views

\[ \begin{align*}
\text{Nu} : & \\
\text{B} : & \\
\end{align*} \]

simplistic views

\[ \begin{align*}
\text{Nu} : & \\
\text{B} : & \\
\end{align*} \]
**methyl (Me)**

**side views**

\[ \text{H} \rightarrow \text{Nu} : \quad \text{C}_\alpha \quad \text{X} \]

weak

**vertical views**

\[ \text{H} \rightarrow \text{Nu} : \quad \text{C}_\alpha \quad \text{D} \]

weak

**simplistic views**

\[ \text{H} \rightarrow \text{Nu} : \quad \text{H}_3\text{C} \quad \text{Br} \]

weak

---

**primary (1°)**

**side views**

\[ \text{H} \rightarrow \text{B} : \quad \text{C}_\beta \quad \text{D} \]

\[ \text{H} \rightarrow \text{Nu} : \]

**vertical views**

\[ \text{H} \rightarrow \text{B} : \quad \text{C}_\beta \quad \text{H} \]

: Nu → H

**simplistic views**

\[ \text{H} \rightarrow \text{B} : \quad \text{H}_3\text{C} \quad \text{CH} \quad \text{CH}_2 \quad \text{Br} \]

: Nu → H
**secondary (1°)**  priorities: \( R_1 > R_2 \)

side views

H—B:

H—Nu:

vertical views

H—B:

H—Nu:

simplistic views

H—B:

H—Nu:

**tertiary (1°)**  priority \( R_1 > R_2 > R_3 \)

side views

H—B:

H—Nu:
vertical views

Example: 3-bromo-4-deuterio-2-methoxyhexane (RRR), (SSS), (RRS), (RSR), (SRS), (SRR), (RSS)? It might help to draw a 2D structure first.
Alcohols in strong acid = Protonated Alcohols - Water as a Good Leaving Group

a. methyl, 1°, 2° and 3° ROH reacted with HX acids (HCl, HBr, HI) - usually SN₂ or SN₁ chemistry
b. 1°, 2° and 3° ROH reacted with H₂SO₄ and high temperature (Δ = heat) = E1 chemistry

Using strongly acidic sulfuric acid, H₂SO₄, at elevated temperatures favors E1 reactions because lower boiling alkenes distill out and continually shift the equilibrium to make more alkene, which continues to distill out, until there is no more alcohol left in the reaction pot. We will assume that an E1 mechanism is operating in all of the reactions below (even the primary alcohol). Rearrangements are possible and observed.

- **Primary Alcohol**
  - bp = +82°C
  - pHₐ = -5
  - Water is a good leaving group
  - ΔTbp = 129°C

- **Secondary Alcohol**
  - bp = +161°C
  - pHₐ = -5
  - Water is a good leaving group
  - ΔTbp = 78°C

- **Tertiary Alcohol**
  - bp = +102°C
  - pHₐ = -5
  - Alcohol → alkene
  - ΔTbp ≈ 63°C
  - 90% < alkene

- **Minor Alkene**
  - Less substituted
  - bp = +33°C
  - Distills out

- **Major Alkene**
  - More substituted
  - bp = +39°C
  - Distills out

Very difficult (high temperature)
Sulfonated Alcohols as Good Leaving Groups

Both Sulfuric acid and Sulfonic Acids are very strong acids, (they have very stable conjugate bases)

\[
\text{sulfuric acid} \quad \text{H} - \text{SO}_3^- \quad \text{bisulfate} \quad (\text{very stable anion})
\]

\[
\text{toluenesulfonic acid} \quad \text{H} - \text{SO}_3^- \quad \text{Sulfonates are stable anions, which make excellent leaving groups when bonded to carbon.}
\]

**Formation of an inorganic sulfonate ester (mechanism = acyl-like substitution)**

\[
\text{toluenesulfonyl chloride} \quad \text{sulfur valency = 4} \quad \text{alcohol} \quad \text{sulfur valency = 5}
\]

\[
\text{pyridine} \quad \text{acid/base}
\]

The pyridinium ion is a stable form of the otherwise very acidic proton.

Sulfonates esters have an excellent leaving groups and are useful in \( S_N2 \) chemistry.

**Formation of an analogous organic alkanoate ester (mechanism = acyl substitution)**

\[
\text{acid chloride} \quad \text{carbon valency = 3} \quad \text{alcohol} \quad \text{tetrahedral intermediate} \quad \text{carbon valency = 4}
\]

Problem 34 – Write a detailed arrow-pushing mechanism for each of the following transformations.
SN₂ at 2° RBr without rearrangement. 1. make tosylates from ROH + TsCl (toluenesulfonyl chloride = tosyl chloride) and 2. NaBr, S₅/E chemistry is possible without rearrangements (SN₂).
Other acyl-like transformations include thionyl chloride ($\text{SOCl}_2$) or thionyl bromide ($\text{SOBr}_2$) with alcohols (makes $\text{R-Cl}$ and $\text{R-Br}$) or carboxylic acids (makes acid chlorides, $\text{RCOCl}$). Acid chlorides formed can make esters, thioesters, amides and anhydrides.

Thionyl chloride with methyl, $1^\circ \text{ROH}$ = acyl-like substitution at $\text{SOCl}_2$, then $\text{S_N}_2$ at methyl and primary RX.

Thionyl chloride with $2^\circ$ and $3^\circ \text{ROH}$ = acyl substitution, then $\text{S_N}_1$ (there are various ways you can write this mechanism)

Synthesis of acid chlorides from acids + thionyl chloride ($\text{SOCl}_2$), use the carbonyl oxygen instead of the $\text{OH}$.
Formation of esters from ROH + acid chlorides, amides from RNH₂ or R₂NH + acid chlorides and anhydrides from RCO₂H + acid chlorides

**ester synthesis from acid chloride and alcohols**

There are many variations of ROH and RCO₂H joined together by oxygen.

**amide synthesis from acid chloride and amines**

There are many variations of RNH₂ or R₂NH and RCO₂H joined together by nitrogen.

**anhydride synthesis from acid chloride and carboxylic acids**

There are many variations of R₁CO₂H and R₂CO₂H joined together by oxygen.
Phosphorous trichloride (PCl₃) = SN₂ of alcohol at phosphorous, then SN₂ (at methyl and primary R(OH)PCl₂⁺)

Phosphorous tribromide (PBr₃) = SN₂ of ROH at phosphorous, then SN₁ (at secondary, tertiary, allylic and benzylic R(OH)PBr₂⁺)
## Chart of $S_N$ and $E$ Chemistry (note exceptions)

<table>
<thead>
<tr>
<th>Strong Base Nucleophiles</th>
<th>Weak Base Nucleophiles</th>
<th>Alcohol Reactions in Strong Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_3\text{C}$ $\text{X}$ methyl</td>
<td>$\text{H}_3\text{C}$ $\text{OH}$ methyl</td>
<td>$\text{H}_2\text{SO}_4$ $\Delta$</td>
</tr>
<tr>
<td>$\text{R}_2\text{C}$ $\text{X}$ primary</td>
<td>$\text{R}_2\text{C}$ $\text{OH}$ primary</td>
<td>$\text{SOCl}_2$ $\text{SOBr}_2$ $\text{PCl}_3$ $\text{PBr}_3$</td>
</tr>
<tr>
<td>$\text{R}_2\text{CH}$ $\text{X}$ secondary</td>
<td>$\text{R}_2\text{CH}$ $\text{OH}$ secondary</td>
<td>$\text{NaBr}$ $\text{TsCl/py}$</td>
</tr>
<tr>
<td>$\text{R}_3\text{C}$ $\text{X}$ tertiary</td>
<td>$\text{R}_3\text{C}$ $\text{OH}$ tertiary</td>
<td>$\text{H}_2\text{SO}_4$ $\Delta$</td>
</tr>
</tbody>
</table>

### Typical Strong Base Nucleophiles

- $\text{H}_3\text{C}$ $\text{O}^-$
- $\text{R}_2\text{O}^-$
- $\text{R}_3\text{O}^-$

### Typical Weak Base Nucleophiles

- $\text{H}_3\text{C}$ $\text{O}^-$
- $\text{R}_2\text{O}^-$
- $\text{R}_3\text{O}^-$

### Alcohol Reactions in Strong Acid

- $\text{H}_3\text{C}$ $\text{OH}$ $\text{X}$ $\text{(X = Cl, Br or I)}$ $\text{H}_2\text{SO}_4$ $\Delta$
- $\text{R}_2\text{CH}$ $\text{OH}$ $\Delta$
- $\text{R}_3\text{C}$ $\text{OH}$ $\Delta$
Oxidation of alcohols – E2 elimination reactions can form carbonyl functional groups (C=O), including aldehydes, ketones and carboxylic acids.

Recall that in freshman oxidation/reduction electron counting rules, all electron credit in bonds goes to the more electronegative atom. Oxygen almost always is –2. Hydrogen atoms are usually +1. Formal charge on the other hand, views all bonded electrons as shared evenly between bonded atoms (single, double or triple bonds).

Problem 38 – What are the oxidation states of each carbon atom below? All of the atoms in these examples have a formal charge of zero.

\[
\begin{array}{cccc}
\text{CH}_4 & \rightarrow & \text{H}_3\text{C}–\text{OH} & \rightarrow & \text{H} \quad \text{C} \quad \text{=} \quad \text{O} \\
\text{oxidation state of carbon} = ? & & \text{oxidation state of carbon} = ? & & \text{oxidation state of carbon} = ? \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{H}_3\text{C}–\text{CH}_3 & \rightarrow & \text{H}_3\text{C}–\text{C}–\text{OH} & \rightarrow & \text{H} \quad \text{C} \quad \text{=} \quad \text{O} \\
\text{oxidation state of carbon} = ? & & \text{oxidation state of carbon} = ? & & \text{oxidation state of carbon} = ? \\
\end{array}
\]

Problem 39 – What are the oxidation states below on the carbon atom and the chromium atom as the reaction proceeds? Which step does the oxidation/reduction occur? (PCC, B: = pyridine and Jones, B: = water)

\[
\begin{array}{c}
\text{R}–\text{C}–\text{O} \quad \text{Cr} \quad \text{O} \quad \text{R} \\
\text{oxidation state of C} = ? \quad \text{oxidation state of Cr} = ? \\
\end{array}
\]

\[
\begin{array}{c}
\text{R}–\text{C}–\text{O} \quad \text{Cr} \quad \text{O} \quad \text{R} \\
\text{oxidation state of C} = ? \quad \text{oxidation state of Cr} = ? \\
\end{array}
\]

\[
\begin{array}{c}
\text{R}–\text{C}–\text{O} \quad \text{Cr} \quad \text{O} \quad \text{R} \\
\text{oxidation state of C} = ? \quad \text{oxidation state of Cr} = ? \\
\end{array}
\]

\[
\begin{array}{c}
\text{R}–\text{C}–\text{O} \quad \text{Cr} \quad \text{O} \quad \text{R} \\
\text{oxidation state of C} = ? \quad \text{oxidation state of Cr} = ? \\
\end{array}
\]
PCC = pyridinium chlorochromate, (CrO₃/pyridine), CrO₃ oxidations of alcohols (methyl, 1° and 2° ROH) without water. Steps are: 1. Cr=O addition, 2. acid/base and 3. E2 to form C=O (aldehydes and ketones).

CrO₃ oxidations of alcohols (methyl, 1° and 2° ROH) without water = PCC, Cr=O addition, acid/base and E2 to form C=O (aldehydes and ketones)
Problem 40 – Supply all of the mechanistic details in the sequences below showing 1. the oxidation of a primary alcohol, 2. hydration of the carbonyl group and 3. oxidation of the carbonyl hydrate (Jones conditions).

Under aqueous conditions, a hydrate of a carbonyl group has two OH groups which allow a second oxidation, if another C-H bond is present. This is only possible if the starting carbonyl group was an aldehyde (true when starting with methyl and primary alcohols).

Your next step is to write out the above mechanism completely on your own, using the following equation.
Typical oxidation possibilities are shown below for common alcohol patterns. Currently we can make the alcohols from RBr compounds using SN chemistry, and that’s a lot of alcohols. The alcohol carbon with oxygen is the key. Does it have any hydrogen atoms (is it methyl, primary or secondary)? How many hydrogen atoms does it have? Potentially all of the hydrogen atoms can be oxidized off, or only one of them, depending on the conditions you choose (Jones or PCC).

1. Primary alcohols (or methanol), without any water in the reaction mixture (PCC), oxidize only to aldehydes. No carbonyl hydrates can form without water, so there is no way to oxidize a second time. Pyridine is the base.

\[
\begin{align*}
&\text{methanol} \\
&\text{PCC} \text{ CrO}_3/\text{pyridine} \\
&\text{methanal}
\end{align*}
\]

2. Primary alcohols (or methanol) with water in the reaction mixture can oxidize twice (Jones). Once the aldehyde is formed, it can hydrate (add H}_2\text{O}) and form a chromium ester a second time, which oxidizes off a second hydrogen atom. Water is the base.

\[
\begin{align*}
&\text{primary alcohols} \\
&\text{CrO}_3\text{H}_2\text{SO}_4\text{H}_2\text{O} \text{Jones conditions} \\
&\text{aldehydes, carbonyl hydrates, carboxylic acid again}
\end{align*}
\]

3. Secondary alcohols can only oxidize once in either aqueous or nonaqueous conditions. Either reagent produces a ketone product.

\[
\begin{align*}
&\text{secondary alcohols} \\
&\text{either method (Jones or PCC)} \\
&\text{ketones}
\end{align*}
\]

There are no additional C-H bonds at the original alcohol carbon, so there is no additional oxidation possible at the ketone carbon.

4. Tertiary alcohols can form chromium esters, but there is no hydrogen atom to eliminate at the alcohol carbon. Tertiary alcohols are unreactive with either reagent. At higher temperatures C-C bonds can be cleaved (usually making a mess).

\[
\begin{align*}
&\text{tertiary alcohols} \\
&\text{either method (no removable C-H at the alcohol carbon in tertiary alcohols)} \\
&\text{No productive reaction}
\end{align*}
\]
Allowed starting structures – our main sources of carbon – 1. Free radical substitution of sp³ C-H bonds to form sp³ C-Br bonds at the weakest C-H position and 2. Anti-Markovnikov addition to alkenes makes 1° R-Br.

1. Mechanism for free radical substitution of alkane sp³ C-H bonds to form sp³ C-Br bonds at weakest C-H position (faster at 3° > 2° > 1° C-H positions)

overall reaction

\[
\begin{align*}
\text{initiation} & : \text{Br} \quad \text{Br} : \xrightarrow{hv} : \text{Br} - \cdot : \text{Br} - \cdot : \\
\text{2a propagation} & : \text{Br} \quad \text{Br} : \quad \text{BE} = +95 \text{ kcal/mole} \\
& \quad \text{BE} = -88 \text{ kcal/mole} \\
\text{2b propagation} & : \text{Br} \quad \text{Br} : \quad \text{BE} = +46 \text{ kcal/mole} \\
& \quad \text{BE} = -68 \text{ kcal/mole} \\
\end{align*}
\]

\[\Delta H = 46 \text{ kcal/mole}\]

\[\Delta H = -15 \text{ kcal/mole (overall)}\]

3. termination = combination of two free radicals - relatively rare because free radicals are at low concentrations

2. Free radical addition mechanism of H-Br to alkene pi bonds (alkenes can be made from E2 or E1 reactions at this point in course) (anti-Markovnikov addition to alkenes)

overall reaction

\[
\begin{align*}
\text{initiation (two steps)} & : \text{R} \quad \text{O} - \text{O} \quad \text{R} : \xrightarrow{hv} : \text{R} - \cdot : \text{O} - \cdot : \\
\text{2a propagation} & : \text{R} \quad \text{O} - \text{O} \quad \text{R} : \quad \text{BE} = +95 \text{ kcal/mole} \\
& \quad \text{BE} = -88 \text{ kcal/mole} \\
\text{2b propagation} & : \text{R} \quad \text{O} - \text{O} \quad \text{R} : \quad \text{BE} = +46 \text{ kcal/mole} \\
& \quad \text{BE} = -68 \text{ kcal/mole} \\
\end{align*}
\]

\[\Delta H = -23 \text{ kcal/mole}\]

\[\Delta H = -15 \text{ kcal/mole (overall)}\]

3 termination = combination of two free radicals
For now, the structures below represent your hydrocarbon starting points to synthesize target molecules (TM) that are specified. We will only use the two free radical reactions, above, in our course, but they are very important reactions because they make versatile functionalized starting molecules for synthesis of all the other functional groups studied in this course. From these two free radical reactions and E2 reactions with potassium t-butoxide (to make alkenes) we can make 13 R-Br molecules below. We can use double E2 reactions with sodium dialkylamides to make 3 terminal alkynes.

We need to make these 1° RBr from anti-Markovnikov free radical addition of H-Br (ROOR) to alkenes (next reaction).

Examples of allylic RBr compounds: This is just free radical substitution at allylic sp³ C-H position of an alkene.

bromobenzene is given until aromatic chemistry is covered in 316
RBr, RBr₂, alkene and alkyne compounds we can currently make.

benzylic RBr,

allylic RBr

Alkenes

Alkynes

Dibromohydrocarbons

Additional organic compounds that are available as examples until we can make them

Simple examples of functional groups we can currently make.

Carboxylic acid (ethanoic acid)

Anhydride (ethanoic anhydride)

Ester (ethyl ethanoate)

Acid chloride (ethanoyl chloride)

2° Amide (ethanamide)

Nitrile (ethanenitrile)

Aldehyde (ethanal)

Ketone (propanone)

Alcohol (ethanol)

Thiol (ethanethiol)

Amine (ethanamine)

Ether (ethoxyethane)

Sulfide (ethylothioethane)

Azide (azidoethane)

Bromoalkane (bromoethane)

Alkene (propene)

Alkyne (propyne)
Problem 41 – We can now make the following molecules. Propose a synthesis for each from our starting materials.

starting sources of carbon

Possible RBr compounds from these starting hydrocarbons.

Possible alkenes and alkynes from these starting hydrocarbons.

aldydes

carboxylic acids

acid chlorides

(amides (not stable)

esters

conjugated aldehydes, carboxylic acids and esters

ketones

anhydrides

nitriles
R-Br examples $C_1 \rightarrow C_7$ (For now, these are given. Soon, we will have to make them.) You need to recognize reactive substitution patterns as: methyl (Me), primary ($1^o$), secondary ($2^o$), tertiary ($3^o$), allylic, benzylic and unreactive substitution patterns as: primary neopentyl, vinyl and phenyl.

**Categories of RX compounds:**

- **1° = primary RX**
- **2° = secondary RX**
- **3° = tertiary RX**
- **1° = primary neopentyl RX**
- **2° = secondary neopentyl RX**
- **3° = tertiary neopentyl RX**
- **allyl RX**
- **benzyl RX**
- **vinyl RX**
- **phenyl RX**

* = chiral centers

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<table>
<thead>
<tr>
<th>1°</th>
<th>2°</th>
<th>3°</th>
<th>4°</th>
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<tbody>
<tr>
<td><img src="image1" alt="Methyl RX" /></td>
<td><img src="image2" alt="Primary RX" /></td>
<td><img src="image3" alt="Secondary RX" /></td>
<td><img src="image4" alt="Tertiary RX" /></td>
</tr>
</tbody>
</table>

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Extra patterns to know (allylic and benzylic RX are very fast S_N2 patterns) (1° neopentyl, vinyl and phenyl RX patterns are unreactive).