NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

A STUDENT WHO HAS MASTERED THE MATERIAL IN THIS SECTION SHOULD BE ABLE TO:

1. Define, recognize, and give examples of each of the following terms:
   - Nucleophilic substitution, elimination, substrate, nucleophile, leaving group
   - $S_N^1$, $S_N^2$, E1, and E2 reactions; rate-determining step
   - Retention, inversion, racemization (reaction stereochemistry)
   - Polar and nonpolar, protic and aprotic solvents

2. Predict the product or products of nucleophilic substitution and elimination reactions, including the stereochemistry where appropriate. Note that the statement of the problem will usually not say which of the reaction types is occurring in any individual case.

   In the presence of a strong base/nucleophile, $S_N^2$ and E2 reactions are favored over $S_N^1$ and E1. When the base/nucleophile is strong, $S_N^2$ is favored over E2 when the substrate is methyl or 1°. The opposite is true when the substrate is 2° or 3°; in those cases E2 is favored (no $S_N^2$ reactions occur in 3° substrates). Exception: If the base/nucleophile is the very bulky tert-butoxide anion, E2 reactions occur even in 1° substrates.

   If the base/nucleophile is weak, substitution is favored. The substitution is $S_N^2$ in methyl and most 1° and 2° substrates, and is $S_N^1$ in most 3° substrates. E1 reactions are usually very minor pathways in real substitution and elimination reactions.

   High temperatures favor elimination, both E2 and E1, over substitution. Polar aprotic solvents such as dimethyl sulfoxide (DMSO or CH$_3$SOCH$_3$) strongly accelerate $S_N^2$ reactions.

3. From your knowledge of the mechanism, predict and interpret experimental results for the $S_N^1$, $S_N^2$, E1, and E2 reactions. Be prepared to draw mechanisms with arrows that show electron movement. For a summary of important factors that influence reaction rates, see the study guide on the next page.

4. Given a reaction coordinate diagram, identify transition states and reactive intermediates, and calculate activation energies and enthalpies of reaction.

5. Propose syntheses using these reactions and those learned earlier.

(For a summary of the factors that affect the rates of these reactions see the next page.)
Factors Affecting The Rates Of Reactions:

Alkyl group (in the substrate): $S_N^2$ reactions are fastest in CH$_3$ substrates; rates are: CH$_3$ > 1° > 2° >> 3° (this is a steric effect; larger groups interfere with the approaching nucleophile). $S_N^1$ and E1 reactions are faster in 3° substrates (because the more stable the carbocation, the faster the reaction; this means 3° > 2° >> 1° > CH$_3$). E2 reactions are also faster in 3° substrates. Vinylic (R$_2$C=CR—) and aromatic substrates are unreactive in all four reaction types.

Leaving groups: All of these reactions are faster when the leaving group is a weak base. For the alkyl halides as leaving groups, the resulting order is I– > Br– > Cl– >> F–.

Nucleophile: $S_N^2$ and E2 reactions are usually faster when a strong base/nucleophile is used (there are some solvent effects on this). Base/nucleophile identity and concentration has no effect on the rates of $S_N^1$ and E1 reactions.

Temperature: High temperatures increase the rates of all reaction types by increasing both the collision frequency and the energy factor.

Solvent: Polar protic solvents give faster $S_N^1$ and E1 reactions; polar aprotic solvents such as DMSO give faster $S_N^2$ reactions.

Reactant concentration: The reaction rate is directly proportional to substrate concentration for all reaction types. For $S_N^2$ and E2 reactions, the rate is also proportional to the nucleophile/base concentration. For $S_N^1$ and E1 reactions, base/nucleophile concentration has no effect on reaction rate at all.
A STUDENT WHO HAS MASTERED THE OBJECTIVES ON THE PREVIOUS PAGES SHOULD BE ABLE TO SOLVE THE FOLLOWING PROBLEMS AND RELATED ONES:

1.1 Identify the substrate, the nucleophile, and the leaving group in each of the following reactions.

   a) CH₃CH₂Br + CH₃S⁻ —→ CH₃CH₂SCH₃ + Br⁻

   b) (CH₃)₂CHCH₂OSO₂F + NH₃ —→ (CH₃)₂CHCH₂NH₃⁺ + FSO₃⁻

1.2 Characterize each of the following reactions as proceeding with retention, inversion, or racemization. What reaction type is each (Sₙ₁, Sₙ₂)?

   a) 
   
   b) 
   
   c) 

1.3 Which of the following is a protic solvent?

   a) CH₃CH₂CH₂CH₂CH₃  b) CH₃SOCH₃  c) CH₃CH₂OH  d) HC-N(CH₃)₂

2. Predict the major organic product of each of the following reactions.

   a) CH₃CH₂CH₂Br + CH₃NH₂ —→

   b) CH₃I + (C₆H₅)₃P —→
2. Predict the product (continued)

   c) \((\text{CH}_3)_3\text{CBr} + (\text{CH}_3)_3\text{COK} \rightarrow (\text{CH}_3)_3\text{COH}\)

   d) \(\begin{array}{c}
   \text{Br} + \text{KOH} \\
   \text{alcohol, heat}
   \end{array} \rightarrow \)

3.1 Provide curved mechanism arrows for each of the following reactions.

   a) \(\begin{array}{c}
   \text{CH}_3
   \end{array} + \text{OH} \rightarrow \begin{array}{c}
   \text{OH}
   \end{array}
   \)

   b) \(\begin{array}{c}
   \text{CH}_3\text{CH}_2
   \end{array} + \text{CH}_3\text{OH} \rightarrow \begin{array}{c}
   \text{CH}_3\text{OH}_2
   \end{array}
   \)

   c) \(\begin{array}{c}
   \text{CH}_3
   \end{array} + \text{CH}_3\text{OH} \rightarrow \begin{array}{c}
   \text{CH}_3\text{O}_2\text{H}
   \end{array}
   \)
3.2 Consider the reaction \( \text{CH}_3\text{CHBrCH}_3 + \text{NH}_3 \rightarrow \text{CH}_3\text{CHOHCH}_3 + \text{Br}^- \).

What is the effect on the rate of the reaction if each of the following changes is made? Possible answers: increases, decreases, remains the same.

<table>
<thead>
<tr>
<th>CHANGE</th>
<th>IF THE RXN. IS SN1</th>
<th>IF THE RXN. IS SN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use CH(_3)CH(_2)Br instead of CH(_3)CHBrCH(_3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use CH(_3)CHICH(_3) instead of CH(_3)CHBrCH(_3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use NH(_2^-) instead of NH(_3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase the concentration of CH(_3)CHBrCH(_3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease the concentration of NH(_3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.1 In the reaction coordinate diagram shown: (a) What point(s) represent(s) transition states? (b) What point(s) is(are) reactive intermediates?
4.2 Answer the following questions using the reaction coordinate diagram shown.

a) What is $E_{act}$ of A ---> B?

b) What is $E_{act}$ for B ---> A?

c) What is $\Delta H$ for A ---> B?

d) What is $\Delta H$ for B ---> A?

5 Propose syntheses of each of the compounds shown, from the given starting materials and any other needed reagents.

a) CH$_3$CH$_2$NH$_2$ from CH$_3$CH$_2$Br

b) OCH$_2$CH$_3$ from CH$_3$CH$_2$Br

c) CH$_3$CH$_2$NH$_2$ from CH$_3$CH$_3$
ANSWERS TO THE PROBLEMS:

1.1  
\[ \text{a) } \text{CH}_3\text{CH}_2\text{Br is the substrate, CH}_3\text{S}^- \text{ is the nucleophile, Br}^- \text{ is the leaving group} \]
\[ \text{b) } (\text{CH}_3)_2\text{CHCH}_2\text{OSO}_2\text{F is the substrate, NH}_3 \text{ is the nucleophile, FSO}_3^- \text{ is the leaving group.} \]

1.2  
\[ \text{a) Inversion (at the reacting C, retention at the other stereocenter); } \text{S}_\text{N}2 \]
\[ \text{b) Racemization, } \text{S}_\text{N}1 \]
\[ \text{c) Retention (at the stereocenters, reacting carbon inverts); } \text{S}_\text{N}2 \]

1.3  
\[ \text{Compound (c) is a protic solvent.} \]

2.  
\[ \text{a) } \text{CH}_3\text{CH}_2\text{CH}_2\text{Br } + \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3 + \text{Br}^- \text{ (S}_\text{N}2\text{)} \]
\[ \text{b) } \text{CH}_3\text{I } + (\text{C}_6\text{H}_5)_3\text{P } \rightarrow (\text{C}_6\text{H}_5)_3\text{PCH}_3 + \text{I}^- \text{ (S}_\text{N}2\text{)} \]
\[ (\text{CH}_3)_3\text{COH} \]
\[ \text{c) } (\text{CH}_3)_3\text{CBr } + (\text{CH}_3)_3\text{COK } \rightarrow (\text{CH}_3)_2\text{C} = \text{CH}_2 + (\text{CH}_3)_3\text{COH} + \text{KBr} \text{ (E}2\text{)} \]
\[ \text{d) } \begin{array}{c} \text{Br} + \text{KOH} \rightarrow \text{alcohol, heat} \end{array} \]
\[ \rightarrow \begin{array}{c} \text{+ KBr + H}_2\text{O} \end{array} \text{ (E}2\text{)} \]

3.1  
\[ \text{Curved mechanism arrows:} \]
\[ \text{a) } \begin{array}{c} \text{CH}_3 \end{array} \]
\[ \begin{array}{c} \text{C} \text{H} \end{array} \]
\[ \begin{array}{c} \text{Br} \end{array} \]
\[ \begin{array}{c} \text{OH} \end{array} \]
\[ \begin{array}{c} \text{OH} \end{array} \]
\[ \text{+ Br}^- \text{ (S}_\text{N}2\text{)} \]

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b) \[ \text{CH}_3\text{CH}_2\text{Br} + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{OH} + \text{Br}^- \]

\[ \text{CH}_3\text{CH}_2\text{Br} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_3 \]

\[ \text{CH}_3\text{CH}_2\text{CH}_3 + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_3\text{OH} \]

\[ \text{CH}_3\text{CH}_2\text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_3 + \text{H}_2\text{O} \]

c) \[ \text{CH}_3\text{CH}_2\text{Br} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CH}_2\text{OH} + \text{Br}^- \]

\[ \text{CH}_3\text{CH}_2\text{Br} \rightarrow \text{CH}_3\text{CH}_2\text{OH} \]

\[ \text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_3 + \text{H}_2\text{O} \]

d) \[ \text{CH}_3\text{CH}_2\text{Br} + \text{OC(CH}_3\text{)}_3 \rightarrow \text{CH}_3\text{CH}_2\text{HOC(CH}_3\text{)}_3 + \text{Br}^- \]

3.2 CHANGE

<table>
<thead>
<tr>
<th>CHANGE</th>
<th>IF THE RXN. IS SN1</th>
<th>IF THE RXN. IS SN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use (\text{CH}_3\text{CH}_2\text{Br}) instead of (\text{CH}_3\text{CHBrCH}_3)</td>
<td>decreases</td>
<td>increases</td>
</tr>
<tr>
<td>Use (\text{CH}_3\text{CHICH}_3) instead of (\text{CH}_3\text{CHBrCH}_3)</td>
<td>increases</td>
<td>increases</td>
</tr>
<tr>
<td>Use (\text{NH}_2^-) instead of (\text{NH}_3)</td>
<td>remains the same</td>
<td>increases</td>
</tr>
<tr>
<td>Increase the concentration of (\text{CH}_3\text{CHBrCH}_3)</td>
<td>increases</td>
<td>increases</td>
</tr>
<tr>
<td>Decrease the concentration of (\text{NH}_3)</td>
<td>remains the same</td>
<td>decreases</td>
</tr>
</tbody>
</table>
4.1  
   a) B and D are transition states.
   b) C is a reactive intermediate.

4.2  
   a) $E_{\text{act}}$ for A ---> B = 20 kJ/mole
   b) $E_{\text{act}}$ for B ---> A = 30 kJ/mole
   c) $\Delta H$ for A ---> B = -10 kJ/mole
   d) $\Delta H$ for B ---> A = +10 kJ/mole

5.  
   a) CH$_3$CH$_2$NH$_2$ from CH$_3$CH$_2$Br
      
      Simple way, on paper:  CH$_3$CH$_2$Br  +  NH$_2^-$  --->  CH$_3$CH$_2$NH$_2$  +  Br$^-$ (S$_N$2)
      
      Better way in the lab:  CH$_3$CH$_2$Br  +  NH$_3$  --->  CH$_3$CH$_2$NH$_3^+$  +  Br$^-$ (S$_N$2)
      then:  CH$_3$CH$_2$NH$_3^+$  +  OH$^-$  --->  CH$_3$CH$_2$NH$_2$  +  H$_2$O (acid-base)

   b) OCH$_2$CH$_3$ from CH$_3$CH$_2$Br
      
      CH$_3$CH$_2$Br  +  O$^-$  ---->  OCH$_2$CH$_3$  +  Br$^-$

   c) CH$_3$CH$_2$NH$_2$ from CH$_3$CH$_3$
      
      CH$_3$CH$_3$  +  Br$_2$/light  --->  CH$_3$CH$_2$Br  +  HBr
      then CH$_3$CH$_2$Br  +  NH$_2^-$  --->  CH$_3$CH$_2$NH$_2$  +  Br$^-$
      (see problem 5a above)
1) Consider the reaction $(\text{CH}_3\text{CH}_2)_2\text{CHCl} + \text{CH}_3\text{OH} \rightarrow (\text{CH}_3\text{CH}_2)_2\text{CHOCH}_3 + \text{Cl}^-$. What is the effect of each of the given changes on the rate of the reaction? Possible answers: increases, decreases, remains the same.

<table>
<thead>
<tr>
<th>Change</th>
<th>Effect if rxn.</th>
<th>Effect if rxn.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use $\text{CH}_3\text{O}^-$, not $\text{CH}_3\text{OH}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use $(\text{CH}_3\text{CH}_2)_2\text{CHOH}$, not $(\text{CH}_3\text{CH}_2)_2\text{CHCl}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase the concentration of $\text{CH}_3\text{OH}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use $(\text{CH}_3\text{CH}_2)_3\text{CCl}$, not $(\text{CH}_3\text{CH}_2)_2\text{CHCl}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) Consider the reaction shown.

What is the mechanism of this reaction? Use the data at right.

- $\text{Br} + \text{KOH} \rightarrow \text{KBr} + \text{H}_2\text{O} + \text{E}$

<table>
<thead>
<tr>
<th>$[\text{RBr}]$</th>
<th>$[\text{KOH}]$</th>
<th>relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>0.02</td>
<td>0.01</td>
<td>2</td>
</tr>
<tr>
<td>0.01</td>
<td>0.02</td>
<td>2</td>
</tr>
</tbody>
</table>

- E1 □ E2 □ SN1 □ SN2

3) What are the values of a) $\Delta H$ and b) $E_{\text{ACT}}$ for the reaction $\text{A} \rightarrow \text{B}$? Use the reaction diagram shown.

- a) 
- b)

4) Predict the major organic product or products of each of the following reactions.

- a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CBrCH}_3 + \text{H}_2\text{O} \rightarrow \text{SN2}$
- b) $\text{Br} + \text{KOH} \rightarrow \text{heat}$

5) Propose a synthesis of $(\text{CH}_3)_2\text{CHOCH}_2\text{CH}_3$ from $\text{CH}_3\text{CH}_2\text{Br}$ and any other needed reagents.
1. Draw the structure of the product or products of each of the following reactions. You must show the three-dimensional structure where appropriate.

   a) \[
   \begin{align*}
   &\text{CH}_3 \quad \text{NH}_3 \\
   &\text{H} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
   \end{align*}
   \]

   b) \[
   \begin{align*}
   &\text{(CH}_3\text{)}_3\text{C} \quad \text{(CH}_3\text{)}_2\text{CHOH} \\
   &\text{Cl} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
   \end{align*}
   \]

   c) \[
   \begin{align*}
   &\text{CH}_3\text{CH}_2\text{CH}_2\text{I} \\
   \end{align*}
   \]

2. For each of the following sets, predict which reaction will be faster.

   Set 1 _____
   a) \[
   \text{(CH}_3\text{CH}_2\text{CH}_2\text{)}_3\text{CCl} + \text{OH}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{)}_3\text{COH} + \text{Cl}^- \\
   \]
   b) \[
   \text{(CH}_3\text{CH}_2\text{CH}_2\text{)}_3\text{CBr} + \text{OH}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{)}_3\text{COH} + \text{Br}^- \\
   \]

   Set 2 _____
   a) \[
   \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{H}_2\text{S} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{SH} + \text{HBr} \\
   \]
   b) \[
   \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{HS}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{SH} + \text{Br}^- \\
   \]

   Set 3 _____
   a) \[
   \text{CH}_3\text{CH}_2\text{CH}_2\text{F} + \text{OH}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{F}^- \\
   \]
   b) \[
   \text{CH}_3\text{CH}_2\text{CH}_2\text{F} + \text{OH}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{F}^- \\
   \]

   Set 4 _____
   a) \[
   \text{(CH}_3\text{CH}_2\text{CH}_2\text{)}_3\text{CCl} + \text{OH}^- \longrightarrow \text{(CH}_3\text{CH}_2\text{CH}_2\text{)}_3\text{COH} + \text{Cl}^- \\
   \]
   b) \[
   \text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + \text{OH}^- \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{Cl}^- \\
   \]
3. The reaction shown below was run several times using different concentrations of reagents and the rate of the reaction was determined each time. The results are shown. From this information, deduce the mechanism of the reaction. Note: OTs is shorthand for the $p$-toluenesulfonate or tosylate group, a leaving group.

$$(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHOTs} + \text{Br}^- \rightarrow (\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHBr} + \text{TsO}^-$$

<table>
<thead>
<tr>
<th>[ROTs]</th>
<th>[Br$^-$]</th>
<th>Relative Rate</th>
<th>Circle the correct mechanism</th>
</tr>
</thead>
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<td>E1  E2  SN1  SN2</td>
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<tr>
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<td>0.04</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

4. Sketch a reaction coordinate diagram for an E2 reaction. Label the positions for the reactants, the products, and the transition state, and indicate where the energy of activation would be measured.

5. Which of the following is a polar aprotic solvent?

A. CCl$_4$    A. HOCH$_2$CH$_2$OH    C. H-C-N(CH$_3$)$_2$    D. H$_2$O

6. Characterize both the stereochemistry and the mechanism of the following reaction.

Stereochemistry at stereocenters:
- inversion
- retention
- racemization

Mechanism:
- SN1
- SN2
- E1
- E2