Experiment F. Nucleophilic Substitution Reactions: $S_N1$ vs $S_N2$

1. **EXPERIMENTAL OBJECTIVES:** To review $S_N1$, $S_N2$, $E1$, $E1cB$ and $E2$ reactions and mechanisms and compare and contrast the effect of the leaving group and the structure of the substrate on nucleophilic substitution reactions of $1^o$, $2^o$, $3^o$ alkyl halides and aryl halides.

2. **SPECIAL INSTRUCTIONS:**

   a. Work in groups of 2/3 students. Each group will turn in one report for grade, but you should all complete a report for your own records. You will not complete the lab report in your lab notebook using the usual format. Instead, the entire report is provided in the procedures section of these lab materials. You will complete the report by providing the missing information. Report is due at the end of the lab period.

   b. While this lab is not done using your lab notebook, you should still look up the chemicals below and enter them into your UTORP.

   Chemicals and Solvents, Chemical Abstract Service [CAS]:
   
   (1) 1-chlorobutane, [109-69-3]  (2) 1-bromobutane, [109-65-9]  
   (3) 2-chlorobutane, [78-86-4]  (4) 2-bromobutane, [75-26-3]  
   (5) 2-chloro-2-methylpropane, [507-20-0]  (6) bromobenzene, [108-86-1]  
   (7) 2-bromo-2-methylpropane, [507-19-7]  (8) ethanol, [64-17-5]  
   (9) acetone, [67-64-1]

3. **PRE-LAB REPORT:**

   1. The structure of the substrate impacts on a nucleophilic substitution reaction; some substrates are better $S_N2$ reactants, others are more suitable as $S_N1$ reactants.

   (0.5) a. Which type(s) of halide will undergo an $S_N1$ reaction?

   (0.5) b. Which type(s) of halide will undergo an $S_N2$ reaction?

   (0.5) c. Predict the order of reactivity (1=least, 4=most) of primary, secondary, tertiary, and aryl halides toward nucleophilic displacement by an $S_N2$ reaction mechanism.

   (0.5) d. Predict the order of reactivity (1=least, 4=most) of primary, secondary, tertiary, and aryl halides toward nucleophilic displacement by an $S_N1$ reaction mechanism.
(1) e. Draw the skeletal structure of and categorize the following substrates which you will use in this experiment as a primary, secondary, tertiary, or aryl halide.

1-chlorobutane  1-bromobutane  2-chlorobutane  2-bromobutane

2-chloro-2-methylpropane  2-bromo-2-methylpropane  bromobenzene

(5) f. Draw the S_N2 mechanism of the reaction between (S)-2-bromobutane and iodide ion. Show lone pairs, electron pushing arrows, 3-D view to reflect appropriate stereochemistry, reactants, transition states, and products. Name the product. Draw and completely label a reaction energy diagram corresponding to the mechanism you have drawn.
(5) g. Draw the SN1 mechanism of the reaction between (R)-3-bromo-3-methylhexane and ethanol. Show lone pairs, electron pushing arrows, 3-D view to reflect appropriate stereochemistry, reactants, intermediates, and products. You do not have to show transition states. Name the product. Draw and completely label a reaction energy diagram corresponding to the mechanism you have drawn.
(5) h. Draw the E2 mechanism for the reaction of meso-1,2-dichloro-1,2-diphenylethane. Show lone pairs, electron pushing arrows, 3-D view to reflect appropriate stereochemistry, reactants, transition states, and products. Name the product. Draw and completely label a reaction energy diagram corresponding to the mechanism you have drawn.
(5) i. Draw the E1 mechanism for the reaction of (S)-3-chloro-3-methylhexane with 80% aqueous ethanol. Show lone pairs, electron pushing arrows, 3-D view to reflect appropriate stereochemistry, reactants, intermediates, and products. You do not have to show transition states. Name the product. Draw and completely label a reaction energy diagram corresponding to the mechanism you have drawn.
(5) j. Draw the E1cB mechanism for the reaction of 4-chloropentan-2-one with potassium hydroxide. Show lone pairs, electron pushing arrows, 3-D view to reflect appropriate stereochemistry, reactants, intermediates, resonance structures, and products. You do not have to show transition states. Name the product. Draw and completely label a reaction energy diagram corresponding to the mechanism you have drawn.
4. PROCEDURES:

1. SN₂ Reaction.

For the SN₂ reaction, the nucleophile is I⁻, introduced into the solution as sodium iodide dissolved in acetone. If the reaction occurs, sodium bromide or sodium chloride will form and precipitate in acetone. The general reaction is:

\[ R-X + NaI \rightarrow [I \cdots R \cdots X]^+ \rightarrow R-I + NaX(s) \]

a. Write the reactions (total of 5) for each of the primary, secondary, and aryl substrates listed in 1.e. above with sodium iodide in the table on the following page.

b. Obtain 5 clean, dry, new test tubes (10 x 75 mm size) and parafilm. Devise a scheme to enable you to keep track of each tube, reaction time, observations, etc. You are working in groups so you can keep track of many activities simultaneously. If you don’t have a good scheme, you will lose track of what you are doing and have to begin again.

c. Place six (6) drops of starting material halide, delivered by the disposable plastic pipet, into the correctly labeled test tube and immediately “stopper” with a square of parafilm.

d. To the test tube containing the alkyl halide, add 1.0 mL of the sodium iodide in acetone solution with a disposable plastic pipet and record the exact time of addition in the table in 2.a. Swirl the test tube to ensure complete mixing, and observe the test tube for the formation of a precipitate (which may appear only as cloudiness in the solution, i.e., turbidity). Record how long it takes for a precipitate to appear; some reactions occur quickly while others take considerable time. After 5 minutes at room temperature, if no precipitate (cloudiness or turbidity) forms, place the test tube in the 50 °C water bath and heat for another 10 minutes while noting the time at which any precipitate occurs. Do not let the reaction run longer than a total of 15 minutes. Record all your observations in the table.

e. Repeat the procedure for the remaining halides. Have your instructor review your results before you analyze the data.

f. Dispose of all chemicals from the test tubes into the liquid organic waste bottle; rinse the test tubes with a small squeeze of acetone, add the rinse to the waste bottle, and throw the test tubes into the broken glass containers.
(5) $S_N2$ Reaction: Data and Observations

<table>
<thead>
<tr>
<th>Substrate + Reactant</th>
<th>Expected Product</th>
<th>Time (Room Temp and Hotbath)</th>
<th>Observations</th>
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Professor’s initials________
2. S\textsubscript{N}1 Reaction.

For the S\textsubscript{N}1 reaction, the nucleophile is ethanol, introduced into the solution as the solvent in a silver nitrate-ethanol solution. If the reaction occurs, silver chloride or silver bromide will form a precipitate in ethanol. The general reaction is:

\[
R-X + AgNO_3 \rightarrow [R]^+ + HOCH_2CH_3 \rightarrow R-OCH_2CH_3 + AgX(s) + HNO_3
\]

a. Write the reactions (total of 5) for each of the secondary, tertiary, and aryl substrates listed in 1.e. above with ethanol and silver nitrate in the table on the next page.

b. Obtain 5 clean, dry, new test tubes (10 x 75 mm size) and parafilm. Devise a scheme to enable you to keep track of each tube, reaction time, observations, etc. You are working in groups so you can keep track of many activities simultaneously. If you don’t have a good scheme, you will lose track of what you are doing and have to begin again.

c. Place three (3) drops of starting material halide, delivered by the disposable plastic pipet, into the correctly labeled test tube and immediately “stopper” with a square of parafilm.

d. Do each of the kinetic measurements one at a time. To the test tube containing the first alkyl halide, add 1.0 mL of the silver nitrate-ethanol solution with a disposable plastic pipet and record the exact time of addition in the table in 3.a. Swirl the test tube to ensure complete mixing, and observe the test tube for the formation of a precipitate (which may appear only as cloudiness in the solution, i.e., turbidity). Record how long it takes for a precipitate to appear; some reactions occur quickly while others take considerable time. After 5 minutes at room temperature, if no precipitate (cloudiness or turbidity) forms, place the test tube in the 50 °C water bath and heat for another 10 minutes while noting the time at which any precipitate occurs. Do not let the reaction run longer than a total of 15 minutes. Record all your observations in the table.

e. Repeat the procedure for the remaining halide starting materials. Record times of addition, appearance of precipitate, and overall observations as above. Have your instructor review your results before you analyze the data.

f. Dispose of all chemicals from the test tubes into the liquid organic waste bottle; rinse the test tubes with a small squeeze of acetone, add the rinse to the waste bottle, and throw the test tubes into the broken glass containers.
(5) \( S_N1 \) Reaction: Data and Observations

<table>
<thead>
<tr>
<th>Substrate + Reactant</th>
<th>Expected Product</th>
<th>Time (Room Temp and Hot Bath)</th>
<th>Observations</th>
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Professor’s initials
3. Interpretation of Data.

(3) a. Based on your experimental results, list the alkyl/aryl halides in order of **decreasing** reactivity toward S_N2 reaction conditions. Why is this order of reactivity observed? Frame your answer on the basis of what the substrate is and what the leaving group is. Is there a difference between your experimental results and theoretical results you predicted in question 1? Discuss.

(3) b. Based on your experimental results, list the alkyl/aryl halides in order of **decreasing** reactivity toward S_N1 reaction conditions. Why is this order of reactivity observed? Frame your answer on the basis of what the substrate is and what the leaving group is. Is there a difference between your experimental results and theoretical results you predicted in question 1? Discuss.
(3) c. You subjected the secondary alkyl halides to both S_N2 and S_N1 reaction conditions. By which mechanism did each alkyl halide react faster, S_N2 or S_N1? On the basis of your comparison, what can you conclude about the likelihood of a secondary alkyl halide reacting by one or the other mechanism? Why?

(3) d. What do you conclude about an aryl halide's reactivity by S_N1 and S_N2 mechanisms?