

CH 241 EXPERIMENT #6

WEEK OF NOVEMBER 12, 2001

NUCLEOPHILIC SUBSTITUTION REACTIONS (S_N1 and S_N2)

Background

By the time you do this experiment we should have covered nucleophilic substitution reactions in class. Please review your class notes and chapter six of your text before coming to lab. You should be able to answer the questions posed in this handout even before performing the experiments, and you should be able to predict the results of these experiments based on your knowledge of the concepts. Many laboratory manuals include experiments designed to illustrate nucleophilic substitution reactions. This series of experiments was taken primarily from *Introduction to Organic Laboratory Techniques*, 3rd edition, by Donald L. Pavia, Gary M. Lampman, and George S. Kriz.

This week you will be performing two kinds of experiments. In the first set of experiments you will determine the importance of the nucleophile under S_N1 and S_N2 conditions. You will allow an equimolar mixture of competing nucleophiles, Br^- and Cl^- , to react under S_N1 conditions with 2-methyl-2-propanol (*tert*-butyl alcohol) and under S_N2 conditions with 1-butanol. The alkyl halide products of each reaction will be analyzed by gas chromatography to determine the relative amounts of each formed.

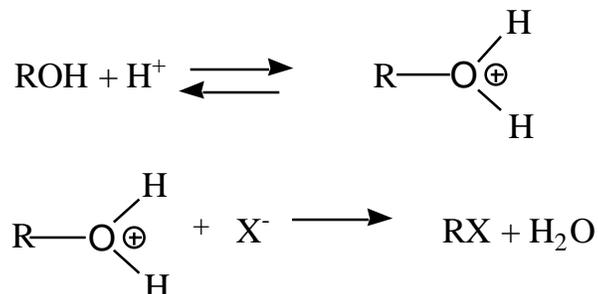
Which is the better nucleophile in aqueous solution, Br^- or Cl^- ? What products form in the S_N1 reaction? In what ratio do you predict they will be formed? What are the products of the S_N2 reaction? Do you expect the same ratio of products as in the S_N1 reaction? Explain why or why not. Look up the boiling points and densities of all of the reactants and products.

In the second experiment you will compare the structure of a substrate with its rate of reaction under S_N1 and S_N2 conditions. **Determine the structure of each of the substrates in Part B of this experiment, and predict which substrates will react rapidly under S_N1 conditions and which under S_N2 conditions. Which substrates would you anticipate reacting very slowly or not at all? What criterion did you use for your predictions?**

Experimental

Part A: Competing Nucleophiles under S_N1 and S_N2 Conditions

You will be running the following reaction, where X⁻ is either Br⁻ or Cl⁻:



You will need to prepare the equimolar mixture of Br⁻ and Cl⁻ in concentrated sulfuric acid, H₂SO₄. CAUTION: Sulfuric acid is a very strong, corrosive acid. Be very careful handling it. **Why is it necessary to perform this reaction under acidic conditions? Why does the reaction of the halide with the unprotonated alcohol not work?** Carefully add 38 mL of concentrated H₂SO₄ to 50 g of ice in a 250-mL Erlenmeyer flask. Set aside. Weigh 9.5 g of ammonium chloride and 17.5 g of ammonium bromide. **How many moles is this?** Crush any lumps, then transfer these salts to a 500-mL Erlenmeyer flask. Slowly add the sulfuric acid, a little at a time, and swirl to dissolve the salts. You may have to heat the mixture over a steam bath and add as much as 5 mL of water to get the salts into solution. Allow the solution to cool slightly as you prepare the apparatus for the S_N1 and S_N2 reactions.

S_N2: Assemble an apparatus for reflux using a 500-mL round-bottomed three-necked flask, a condenser, and a gas trap. A demonstration set up will be available for you to see. Sketch the apparatus in your notebook.

S_N1: You will just need to set up a 125-mL separatory funnel.

Pour 35 mL of your acidic nucleophile mixture into the separatory funnel and replace the stopper. Pour the rest of the mixture into the 500-mL round-bottomed flask, add a boiling stone, and replace its stopper. Begin the S_N2 reaction first. You should be able to complete the S_N1 reaction and **Part B** of this experiment during the reflux time necessary for the S_N2 reaction.

S_N2 reaction

Add 5 mL of 1-butanol (n-butyl alcohol) to the reflux apparatus by pouring it down the condenser. Replace the gas trap and reflux gently for 75 minutes, making sure that the reflux ring does not rise more than a quarter of the way up the condenser. At the end of the reflux period, discontinue heating and drop the heating mantle down to allow the flask to cool undisturbed (at this point, shaking the reaction flask may cause violent boiling and loss of product). Allow the flask to cool about 5 minutes in the air before

putting it into an ice water bath. Cool in an ice-water bath for a few minutes, and then begin to swirl the mixture to facilitate more rapid cooling. Transfer the cooled solution to a 125-mL separatory funnel, leaving any solid material behind, and separate the layers. Be sure you know which is the organic layer and which is the aqueous layer. Wash the organic layer with 10 mL of water and then with 10 mL of saturated sodium bicarbonate solution. Again, make sure you know which layer is which, and remember to release the pressure build up in the separatory funnel. Dry the organic layer with anhydrous Na_2SO_4 and decant the clear solution into a small, dry, ground-glass stoppered flask. Analyze your products by gas chromatography.

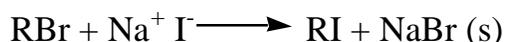
$\text{S}_{\text{N}}1$ reaction

Add 5 mL of 2-methyl-2-propanol to the separatory funnel containing the nucleophile mixture. Since the melting point of 2-methyl-2-propanol is 25°C , use a warm graduated cylinder for measuring. Swirl the mixture gently, then release the pressure build up. Keep swirling and “burping” the funnel until the pressures are equalized, then shake the funnel vigorously, with occasional venting, for 2 minutes. Allow the layers to separate for about a minute, then drain the lower layer. Wait 10-15 seconds longer, then drain another small portion, this time including a bit of the upper, organic layer, just to be sure that the remaining organic layer is not contaminated with water. Pour the organic layer out of the top of the separatory funnel into a beaker containing 1 g of solid sodium bicarbonate. Stir, and as soon as the bubbling stops, decant the clear solution into a clean, dry, ground-glass stoppered flask. Analyze your products by gas chromatography.

Part B: The Effect of Substrate Structure on Reactivity under $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ Conditions

$\text{S}_{\text{N}}2$ Conditions

Sodium iodide in acetone provides reaction conditions favorable to $\text{S}_{\text{N}}2$ reactions. Iodide is an excellent nucleophile, and acetone is a polar, aprotic solvent. In this series of reactions with various chloride and bromide substrates, you will rely on the fact that NaCl and NaBr are not soluble in acetone, and if they are products of a reaction, they will precipitate out of solution. You will time how long it takes to see a precipitate form in solution. Reactive halides usually give a precipitate within 3 minutes, moderately reactive halides give a precipitate upon heating, and unreactive halides do not give a precipitate at all.



Label a series of eight test tubes (10 x 75 mm). In each test tube place 0.2 mL of one of the following halides:

1. 2-chlorobutane
2. 2-bromobutane
3. 2-chloro-2-methylpropane (*tert*-butyl chloride)
4. 1-chlorobutane (*n*-butyl chloride)
5. 1-bromobutane (*n*-butyl bromide)
6. bromobenzene
7. bromocyclohexane
8. bromocyclopentane

Add 2 mL of the 15% NaI/acetone to each tube, mixing well and noting the time of each addition. Record the time it takes for precipitates to form. After about 5 minutes, place any tubes without precipitates into a 50^o C water bath (any hotter will boil off the acetone). Note when any precipitate forms. After 10 minutes in the water bath, cool the test tubes to room temperature to see if a reaction has occurred.

S_N1 Conditions

A 1% solution of silver nitrate in ethanol is used to test the reactivity of halide-containing substrates under S_N1 conditions. Nitrate is a poor nucleophile, so you don't have to worry about any competing S_N2 reactions, and ethanol is a polar, protic solvent that stabilizes ions in solution. Since the rate-determining step in an S_N1 reaction is the ionization of the substrate, if chloride or bromide ions are formed, they will react with silver ions to form insoluble AgCl or AgBr, respectively. If X⁻ is either Br⁻ or Cl⁻, the reaction you will be observing is the formation of the insoluble silver salt:



You will therefore be looking for the formation of precipitates, just like you did with the S_N2 reactions, above.

Repeat the procedure you used for observing the reactivity of halides under S_N2 conditions, but add 2 mL of 1% ethanolic AgNO₃ instead of the NaI/acetone. Note the time it takes for precipitates to form. After 5 minutes, heat the test tubes that do not contain precipitates to boiling in a steam bath and observe.

Prelab

All students: Bring a watch to lab!

In the body of your handout there are several questions posed in bold. The answers to those questions, repeated below, constitute your prelab assignment.

Part A

1. Which is a better nucleophile in aqueous solution, Br⁻ or Cl⁻? Why?
2. What products form in the S_N1 reaction?
3. In what ratio do you predict they will be formed?
4. What are the products of the S_N2 reaction?
5. Do you expect the same ratio of products as in the S_N1 reaction? Explain why or why not.
6. Look up the boiling points and densities of all of the organic reactants and products. Densities will help you to determine which layer is the organic layer and which is the aqueous layer in your separatory funnel, and boiling points will help you to determine the order of elution of the products (and any unreacted starting material) from the gas chromatographic column.
7. Why is it necessary to perform the competing nucleophiles reactions under acidic conditions (Why doesn't the reaction work with the halide and the unprotonated alcohol?)?
8. How many moles of Br⁻ and Cl⁻ are you weighing out for this part of the experiment?

Part B

9. Draw the structure of each of the substrates in Part B of this experiment and predict which substrates will react rapidly under S_N1 conditions and which under S_N2 conditions. Which substrates would you anticipate reacting very slowly or not at all? What criterion did you use for your predictions?

Report

Part A

Write the mechanism for the S_N1 reaction. Be sure to use arrows to show the movement of electrons. Discuss the results of your experiment run under S_N1 conditions. What was the molar ratio of your products? Explain how your results agree or disagree with your predictions. What byproduct might you expect in your S_N1 product mixture?

Write the mechanism for the S_N2 reaction. Be sure to use arrows to show the movement of electrons. Discuss the results of your experiment run under S_N2 conditions.

What was the molar ratio of your products? Explain how your results agree or disagree with your predictions. What byproduct might you expect in your S_N2 product mixture?

Part B

Tabulate the results of your rate experiments. Explain how your results agree or disagree with your predictions. Address the differences seen based on substrate structure, leaving groups, etc. Be sure to give a complete analysis for both your S_N1 and S_N2 data.

Questions based on Part A

1. A student completed the reactions, but left the products in an open Erlenmeyer flask until almost the end of the lab period before they were analyzed by gas chromatography. Would this affect the accuracy of the analysis? Why or why not?
2. If you had analyzed your products of the S_N2 reaction by NMR rather than by GC, which product would have peaks further downfield? Why?
3. What is the purpose of refluxing the S_N1 reaction mixture for 75 minutes? Why not simply boil the mixture in an Erlenmeyer flask?
4. Write a reaction mechanism showing how 1-butene is formed.
5. Write a reaction mechanism showing how di-*n*-butyl ether might be formed.

Questions based on Part B

1. If you had used benzyl chloride as one of the substrates treated with NaI/acetone, you would have found that it reacted faster than 1-chlorobutane. Explain this observation.
2. How do you predict that chlorocyclopropane would react under each set of reaction conditions?
3. What would be the effect of carrying out the sodium iodide in acetone reaction with the alkyl halides using an iodide solution half as concentrated?

General Question

Predict the product(s) of the following reaction, including the correct stereochemistry. What is the function of $AgNO_3$ in this reaction?

