

## EXPERIMENT 1: Preparation and Reactivity of Alkyl Halides

### Relevant Sections in the text (Wade, 7<sup>th</sup> ed.)

- 6.7 (p. 228) Reactions of alkyl halides
- 6.8 – 6.12 (p. 229 – 242) The S<sub>N</sub>2 reaction: generality, factors affecting S<sub>N</sub>2 reactions, substrate reactivity, mechanism
- 6.13 – 6.14 (p. 243 – 249) The S<sub>N</sub>1 reaction: mechanism, stereochemistry

### General Concepts

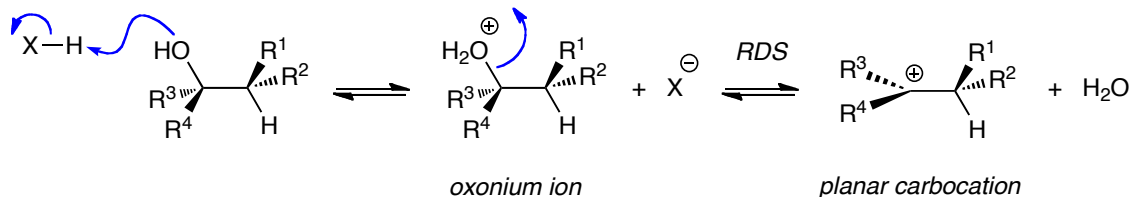
The most common of the variety of methods available for preparing alkyl halides is the replacement of the hydroxyl group of an alcohol. This type of reaction is representative of an important class of reactions in organic chemistry called *nucleophilic aliphatic substitution reactions*. There are numerous ways of doing this transformation, and we will discuss these in lecture. In this experiment you will convert an alcohol to an alkyl halide by reaction with a hydrohalic acid. The overall reaction is shown in equation 1; however the mechanism of the reaction depends on the structure of the alkyl group bearing the functional group being replaced.



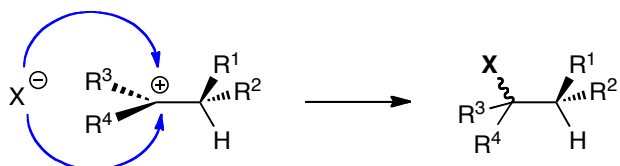
The reaction may occur by one of two mechanisms designated S<sub>N</sub>1 or S<sub>N</sub>2. Which mechanism operates depends on the structure of the R group and the reaction conditions. The first step in both mechanisms is the protonation of the alcohol to form an oxonium ion, converting the OH group into a good leaving group. What happens next depends on the nature of the alkyl group, R. If R is a group that readily forms a carbocation, then the slow, rate-determining step is the loss of a water molecule from the oxonium ion. Once formed, the carbocation then reacts rapidly with a halide ion to form the alkyl halide.

### S<sub>N</sub>1 Mechanism:

The first step is protonation of the alcohol, followed by the second step which is the formation of the carbocation *via* the oxonium ion. This second step is the slow step (*rate-determining*).

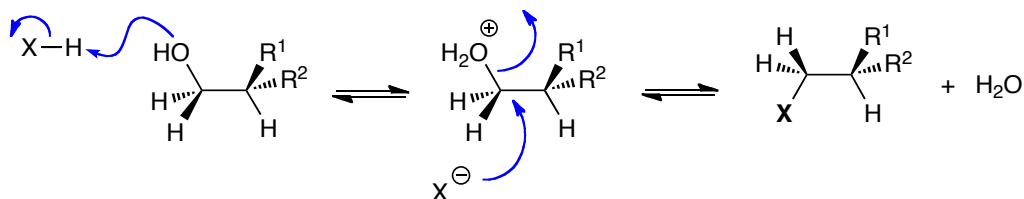


The third step is the attack of the planar carbocation by X<sup>-</sup> (in our case the halide ion).



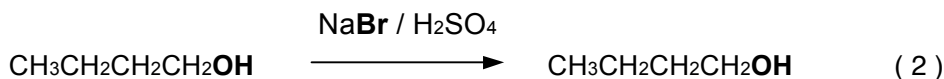
This mechanism is followed when R is a tertiary alkyl group and is called  $S_N1$  (substitution, nucleophilic, unimolecular in the rate-determining step). An  $S_N1$  mechanism may also be involved when R is a secondary group or when R can form a resonance-stabilized carbocation, such as an allyl or benzyl cation (*the more stable the carbocation, the more likely the  $S_N1$  mechanism*). If R is a primary alkyl group, then substitution occurs generally without formation of the carbocation by an  $S_N2$  mechanism (*why no carbocation? Because  $1^\circ$  carbocations are generally unstable*). In this case a halide ion attacks the primary carbon atom of the oxonium ion in the rate-determining step, and the alkyl halide forms directly (*why is this mechanism not favorable when  $R = \text{tertiary}$ ?*). Because two species, the nucleophile ( $X^-$ ) and the substrate (the protonated alcohol), are involved in the rate-determining step, the mechanism is designated  $S_N2$ . When R is a secondary group, an  $S_N1$  or an  $S_N2$  mechanism may be involved, depending on the reaction conditions.

### $S_N2$ Mechanism:



### Experiment: Preparation and Reactivity of Alkyl Halides

In this experiment you will prepare 1-bromobutane (1-butyl bromide) from 1-butanol shown in equation 2 (*by what mechanism do you expect this substitution reaction to occur?*). Compound 1-butanol is a primary alcohol and thus one might expect that the reaction would proceed by an  $S_N2$  reaction. However, when a strong, non-nucleophilic, acid is used as a solvent the conditions are very polar and the reaction can proceed via an  $S_N1$  reaction. You will use the NMR spectrum of your product and gas chromatography results to make decisions about which mechanism is operating.



The purity of the product (and any possible side products) will be assessed by gas chromatography and the identity of the product will be determined by IR,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectroscopy. You will also evaluate the reactivity of your product and other substrates using a number of qualitative tests in Part B.

**PART A: Preparation of 1-Bromobutane**

- Place 20.0 g of sodium bromide (NaBr) in a 250 mL round-bottom flask. Add 15 mL of water and 15 mL of 1-butanol. Mix thoroughly and cool the flask in an ice bath.
- **Slowly** add 15 mL of concentrated sulfuric acid (conc.  $\text{H}_2\text{SO}_4$ ) to the solution. Remove the flask from the ice bath, add a couple of boiling chips, and attach a reflux condenser (Figure 1). Your TA will discuss assembly of the apparatus.
- Heat the flask with a heating mantle until most of the salts have dissolved and the solution is at a gentle reflux (*what does “reflux” mean?*). Note the appearance of two layers (*lower layer is the alkyl bromide*). Continue the reflux for 45 min.
- Equip the flask for simple distillation with a heating mantle (Figure 2). Your TA will discuss assembly of the apparatus.
- Distil the mixture rapidly into an ice-cooled flask until the head temperature reaches 120 °C. (*Codistillation of 1-bromobutane and water occurs, and the increased boiling point is due to the codistillation of sulfuric acid and hydrobromic acid with water*).

**Figure 1.** Reflux setup**Figure 2.** Distillation setup

- Transfer the distillate to a separatory funnel **with a closed stopcock!** and perform an extraction. Add 25 mL of water to the organic layer in the funnel. Invert the funnel and point into the fume hood and away from any other people. Remember to shake the funnel gently **with venting!** Separate and label each layer carefully.
- Wash the organic layer with 15 mL of saturated sodium bicarbonate ( $\text{NaHCO}_3$ ) solution and then again with 15 mL of saturated sodium chloride solution. Collect the organic layers and discard the aqueous layers.

- Transfer the cloudy 1-bromobutane layer to a small Erlenmeyer flask, and dry it with anhydrous magnesium sulfate ( $\text{MgSO}_4$ ). After allowing drying for about 10 minutes, gravity filter the mixture into a clean, dry and **tared** (i.e. preweighed) 50 mL round-bottomed flask.
- Determine the yield of crude product.
- After adding a couple of new boiling chips, equip the flask for simple distillation again with a heating mantle. Collect the product that comes off when boiling at 90-103 °C into a clean and dry **tared flask**. Calculate the yield of the purified product.
- Analyze your product by gas chromatography on a nonpolar column (SF-96 or SE-30 is satisfactory). Obtain the retention times of standard samples of 1- and of 2-bromobutane.

Obtain an IR spectrum of your product and of 1-butanol and discuss the differences observed (you will likely have to add some drying reagent to remove traces of water). Prepare a sample of your product for NMR analysis (as you did in Chem 2273a experiment 3). You will be provided with the relevant spectra of 1-butanol and the authentic NMR spectra of the two possible products. Assign the signals as completely as possible and discuss the differences between the two spectra. In your report discuss the relative percentages of 1- and 2-bromobutanes in your product in terms of the mechanism(s) of the reaction. You will get this information by analyzing your GC trace and your NMR spectrum of your product.

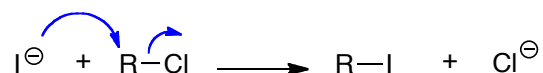
### Gas Chromatography

Gas chromatography is a versatile and widely used method for the examination of volatile mixtures by distributing each component in the mixture between a gas phase and either a liquid or solid phase. The method can be used to follow the course of a reaction both qualitatively and quantitatively, to separate and isolate components of a mixture, to examine purity, and to assist in the identification of compounds.

The compound mixture is passed through a heated column (glass capillary tubing) as a vapour, surrounded by an inert carrier gas. The column is coated with a stationary phase that varies in type and structure depending on the type of separation required. The separation process is readily understood in qualitative terms. Consider a two-component mixture entering the column. Each component will be partitioned between the gas phase and the stationary liquid phase depending on the volatility of the component and its affinity for the stationary phase. Since each component will have a different distribution between the two phases, the most volatile/least soluble in the stationary phase will be sent through the column more rapidly than the other, where separation is achieved.

**PART B: S<sub>N</sub>1 and S<sub>N</sub>2 Reactivity****(i) Reactivity of Alkyl Halides Towards Sodium Iodide: Test for S<sub>N</sub>2**

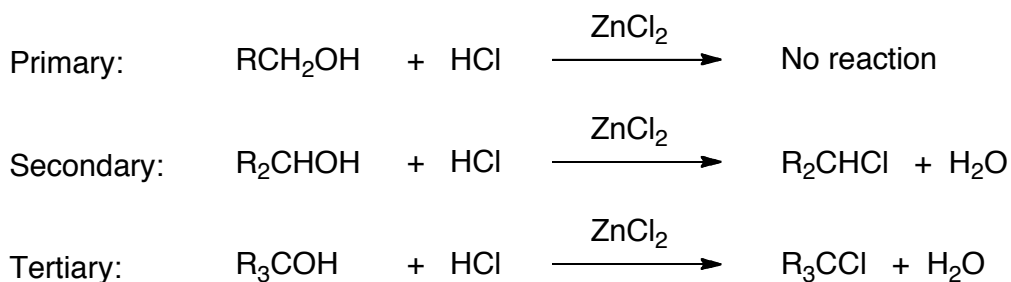
In this part of the experiment, you will test the reactivity of several alkyl halides in an S<sub>N</sub>2 reaction. Iodide ion (I<sup>-</sup>) is an effective nucleophile in S<sub>N</sub>2 displacements. In acetone solution, other alkyl halides (alkyl chlorides or bromides) can be converted to alkyl iodides easily by this method.



Although one might expect such a reaction to be reversible, it can be driven to formation of R-I by using anhydrous acetone as the solvent. Sodium iodide (NaI) is soluble in this solvent, but sodium chloride and sodium bromide are not. If a reaction occurs, a precipitate of sodium chloride or sodium bromide forms and thus the ion is not available in solution for the reverse reaction. The displacement mechanism involves a one-step, concerted, S<sub>N</sub>2 reaction. Therefore, the reaction occurs most quickly when attack at the carbon that bears the halogen (X) is least hindered sterically. For alkyl halides, the order of reactivity is *primary* > *secondary* > *tertiary*.

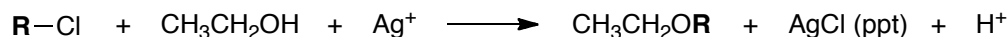
**(ii) Lucas Test: Test for S<sub>N</sub>1**

The reactivity of the product will be evaluated using the Silver Nitrate Test. The Lucas Test will also be used to distinguish the reactivity between various alcohols. The Lucas Test utilizes a reagent containing hydrochloric acid and zinc chloride, which converts alcohols to alkyl chlorides. Primary alcohols do not react, secondary alcohols react fairly quickly, and tertiary alcohols react very rapidly. A positive test depends on the fact that the alcohol is soluble in the reagent, whereas the alkyl chloride is not; thus the formation of a second layer or an emulsion constitutes a positive test. This is a good test for the feasibility of a particular alcohol to undergo an S<sub>N</sub>1 reaction. The overall reactions are as follows:

**(iii) Silver Nitrate Test: Test for S<sub>N</sub>1**

The Silver Nitrate Test allows for the identification of alkyl halides by observing them in an alcoholic silver nitrate environment. The rate at which the silver halide salt precipitate forms is characteristic of different types of alkyl halides. You will test the reactivity of several alkyl halides in a S<sub>N</sub>1 reaction. Organic halides may react with ethanol to form ethyl ethers. When the ethanol contains silver ion, the rate of reaction

increases because the silver ion acts as an electrophile toward the halogen and helps to break the carbon-halogen bond. Alkyl chlorides yield an observable silver chloride precipitate, which is insoluble in ethanol and thus provides a indicator that a reaction has occurred.



In this case, the reaction mechanism is  $\text{S}_{\text{N}}1$ , the slow step being the breaking of the carbon-halogen bond. The carbocation then reacts rapidly with alcohol to form the ether.

Organic halide reactivity parallels the stability of the corresponding carbocations. For saturated alkyl groups, this order is tertiary > secondary > primary. Tertiary, allylic, and benzylic alcohols react very quickly, while secondary alkyl halides react fairly quickly. Primary as well as aryl, alkenyl (vinyl), and alkynyl halides do not react at all. In addition, alkyl iodides and bromides react faster than chlorides, which sometimes require heating.

### Experimental Procedures Part B:

**IMPORTANT! Clean dry test tubes from oven must be used for these tests. Tests are to be performed in the fume hood; whenever transporting your test tube ensure they are safely stoppered with a cork.**

#### (i) Sodium Iodide Test: $\text{S}_{\text{N}}2$ Reactivity

- Test each of the following organic bromides:
  - 1-bromobutane
  - 2-bromobutane
  - bromobenzene
  - allyl bromide (3-bromopropene)
  - 2-bromo-2-methylpropene (*tert*-butylbromide)
  - your product from Part A
- Dry test tubes must be used for this experiment. Use the disposable small test tubes.
- Add 2 drops of the liquid to be tested to 1 mL of a 15% solution of sodium iodide in dry acetone. Mix the contents and note the order of reactivity by looking at how long it takes for a precipitate to form. The solution may turn slightly yellow – this is NOT due to the  $\text{S}_{\text{N}}2$  reaction. (Hint:  $\text{S}_{\text{N}}2$  reactions are slower than  $\text{S}_{\text{N}}1$  reactions. Save your test-tubes for 45-60 minutes and check occasionally for any changes before discarding).
- Tabulate the results of your qualitative tests including detailed observations. Discuss the results in terms of the reaction mechanism.

**(ii) Lucas Test: Reactivity of Alcohols**

- Conduct the test on each of the following alcohols:
  - methanol
  - 1-butanol
  - benzyl alcohol
  - ethanol
  - 2-butanol
  - 2-methylpropan-2-ol (*tert*-butanol)
- Add ~1 mL of the hydrochloric acid-zinc chloride reagent (Lucas reagent) to 4-5 drops of the alcohol compound in a small clean and dry test tube.
- Stopper the tube, shake, and note any change observed. Also record the time required for the formation (if any) of an alkyl chloride (second layer or an emulsion). If no reaction is observed after 5-10 min at room temperature, heat gently using a steam bath for 2-3 min.
- Tabulate the results of your qualitative tests including detailed observations. Discuss the results in terms of the reaction mechanism.

**(ii) Silver Nitrate Test: Reactivity of Alkyl Halides**

***CAUTION: Avoid skin contact with the silver nitrate solution. It will form a dark, hard-to- remove stain where it comes into contact with skin.***

- Conduct the test on each of the following alkyl halides:
  - 1-bromobutane
  - 1-bromo-2-methylpropane (*iso*-propylbromide)
  - your product
  - 2-bromo-2-methylpropane (*tert*-butylbromide)
  - bromobenzene
  - benzyl bromide
- Add 1 drop of the alkyl halide to 2 mL of a 0.1 M solution of silver nitrate in 95% ethanol in a small test tube. Stopper, shake, and note any change (and time required). If no reaction is observed within 5 min at room temperature, warm the mixture in a steam bath and observe any change.
- When noting the color of any precipitate, keep in mind that silver chloride is white, silver bromide is pale yellow, and silver iodide is yellow.
- Add several drops of 1 M nitric acid solution to any precipitate, and note any changes.
- If the precipitate remains, it is a silver halide. Silver halides are insoluble in acid, while the silver salts of organic acids are soluble. Also, silver hydroxide (oxide) is insoluble but dissolves in dilute acid. Tabulate the results of your qualitative tests including detailed observations. Discuss the results in terms of the reaction mechanism.

***At the end of the laboratory please be sure your clean test tubes are placed in the oven for your colleagues!***