Experiment 22

Synthesis of Aspirin and Oil of Wintergreen

GOALS:
In this two-week experiment the important area of organic chemistry will be illustrated by the preparation and characterization of two compounds. The usefulness of functional groups will be illustrated as well as the use of NMR, IR, and melting point in characterizing a product. The analysis will be done next week in Experiment 23.

INTRODUCTION:
Synthesis and use of organic compounds is an extremely important area of modern chemistry. Approximately half of all chemists work with organic chemicals. In everyday life, many if not most of the chemicals you come in contact with are organic chemicals. Examples include drugs, synthetic fabrics, paints, plastics, etc.

Synthesis of Aspirin and Methyl Salicylate.
The two compounds we will be preparing, aspirin (acetylsalicylic acid) and oil of wintergreen (methyl salicylate), are both organic esters. An ester is a compound that is formed when an acid (containing the –COOH group) reacts with an alcohol (a compound containing an –OH group).

\[
\text{acid} + \text{alcohol} \rightarrow \text{ester} + \text{water}
\]

Eqn 1

Here \( R_1 \) and \( R_2 \) represent groups such as \( \text{CH}_3 \) or \( \text{CH}_3\text{CH}_2^- \). The reaction type shown above may be called a condensation reaction because the small molecule \( \text{H}_2\text{O} \) is eliminated from the reactants while the remaining bits of the reactants condense together to give the main product. This reaction may also be called an esterification, since the product of the reaction is an ester, a compound containing the \( \text{CO}_2\text{R} \) group (see chapter 20 for definitions of acids, esters, and alcohols). Esters usually have pleasant, fruit-like odors and are the chemicals responsible for the odors and flavors of many fruits (oranges, bananas, pineapples) and flowers. In most cases, such natural products get their properties from a mixture of organic compounds.

In this experiment you will prepare two esters of \( \alpha \)-hydroxybenzoic acid, more commonly known as salicylic acid. One of the esters, acetylsalicylic acid, is aspirin, the common analgesic. We will synthesize aspirin by mixing salicylic acid with acetic anhydride. The second ester product is oil of wintergreen, or methyl salicylate, which we prepare by allowing salicylic acid to react with methanol. This compound, which has a familiar odor is used as a flavoring agent and in rubbing ointments. Both of these reactions are shown below.

This experiment illustrates several properties of organic synthesis. While both product compounds in the experiment are esters of the same compound (salicylic acid), they are quite different in structure. Aspirin involves a reaction of the –OH group of salicylic acid, while methyl salicylate involves a reaction of the –COOH group of salicylic acid. Organic chemistry is the broad field of studying the tremendous variety of such reactions of organic functional groups.
Preparation of acetylsalicylic acid

\[
\text{salicylic acid} + \text{acetic anhydride} \xrightarrow{\text{H}^+} \text{acetylsalicylic acid (aspirin)} + \text{acetic acid}
\]

Preparation of methyl salicylate

\[
\text{salicylic acid} + \text{methanol} \xrightarrow{\text{H}^+} \text{methyl salicylate (oil of wintergreen)} + \text{water}
\]

Purification by Recrystallization.

After preparing the aspirin, we will purify it. Most solids can be purified by recrystallization, at a cost of lower percent yield. Recrystallization is usually done by dissolving the substance in a suitable solvent, which is hot. If insoluble particles are present, the hot solution is filtered to remove them (we will skip this hot filtration step). The solution is allowed to cool slowly, and is eventually cooled in ice. The crystals that form slowly are more pure than the original solid. We can also get a solute to re-precipitate by adding a second solvent in which it is less soluble.

HAZARDS:

Acetic anhydride is caustic and has a very strong odor. It must be dispensed in a hood. Keep your reaction in the hood as well. Both ethanol and methanol are flammable. No open flames are allowed in lab this week.

LABORATORY OBSERVATIONS AND DATA:

Be sure that you record what you do and make good qualitative observations, noting initial colors, odors, etc. in each step of the procedure. Clearly label all numerical data.
PROCEDURE FOR THE FIRST WEEK:

1. Weigh out approximately 1.0 g of salicylic acid (record exact mass), and transfer it to a clean, dry 6 inch test tube.

2. Use the dispenser to carefully add 1.5 mL of acetic anhydride to the salicylic acid. Then add 2 drops of concentrated sulfuric acid, $\text{H}_2\text{SO}_4$, to the reaction mixture (it acts as a catalyst and speeds up the reaction). Put the test tube in a beaker of boiling water in a hood. Stir the mixture with a glass rod to break up any lumps. Once all the solid dissolves, heat five minutes longer.

3. Pour the contents of the test tube into a 50 mL Erlenmeyer flask containing 15 mL of water. Swirl the flask for a few minutes to mix the solutions and get rid of any unreacted acetic anhydride. (The acetic anhydride reacts with water to produce acetic acid.) Be sure that you are writing in your lab notebook.

4. Place the flask in an ice bath until a white solid crystallizes out. Occasionally a reaction will yield an oily product that resists crystallization. If that happens, scratch the bottom and sides of the flask with a glass stir rod to help start crystal formation, or warm the mixture just until the oil dissolves, and then re-cool.

5. Allow 10 minutes for crystallization to occur. Meanwhile prepare a Buchner funnel and then filter the solid, being sure to use a trap flask between the Buchner funnel flask and the aspirator. Wash the solid with a small amount of cold distilled water.

6. Pour the liquid filtrate from the filter flask into a beaker. Add a scoop of NaHCO$_3$(s). After the bubbling subsides, discard this mixture down the sink with excess water.

7. Put a few crystals of your crude aspirin in a clean beaker. Label it as “crude aspirin.” Let this air-dry until next week when you will take its melting point. Label the beaker, but do not cover it.

8. Scrape the rest of your aspirin product off the filter paper and dissolve it in about 3 mL of 95% ethanol in a 50 mL Erlenmeyer flask. If not all of your aspirin dissolves, take your flask to one of the hot water baths set up in the hood. Use tongs to hold your flask in the hot water. After a few moments, remove, and swirl. Repeat until all the solid dissolves.

9. When the aspirin has dissolved, add 10 mL of warm distilled water (about 50 °C). If any crystals form at this point, reheat the mixture in the water bath to re-dissolve them. Let the solution cool slowly with the mouth of the flask covered by a watch glass. When it is at room temperature, place it into the ice bath and leave it there a full ten minutes. Be sure that you are recording what you do and what you observe.

10. After crystallization is complete, filter the crystals in a Buchner funnel, wash them with a little ice cold distilled water (put your squeeze bottle in the ice), and suction for several minutes. Discard the liquid filtrate down the drain with excess water. Scrape the solid onto a pre-weighed watch glass and put it in your drawer. Do not cover it because we want your product to finish drying by the next lab period.
Part 2: Synthesis of Methyl Salicylate.

1. Place 0.5 g of salicylic acid and 3 mL of methanol in a large test tube. Add 2 drops of concentrated sulfuric acid.

2. Place the test tube in the hood in a water bath at 70 °C for 15 minutes. The boiling point of methanol is 64.6 °C, so point the mouth of the tube away from others and avoid overheating, to minimize "bumping". Note the odor before and after heating.

3. Have your instructor check your product and initial your notebook. Discard your methyl salicylate in the designated waste container.

LAB REPORT FOR THE FIRST WEEK:

Results:
Give the balanced equation for the synthesis of aspirin, drawing the structures by hand. Calculate the theoretical yield for aspirin. You will need to add up molar masses by counting the atoms shown in the structures. Be sure to determine the limiting reagent, either salicylic acid or acetic anhydride. You will need to use the density of acetic anhydride. You can find it in reference books such as the CRC or Merck Index. Show this work clearly in your report. Record which source you use to find the density of acetic anhydride in your report. Watch significant figures and units.

Give the balanced equation for the synthesis of methyl salicylate, drawing the structures by hand. Calculate the theoretical yield for methyl salicylate, checking for limiting reagent first. You will need to look up the density of methanol. You can find this in reference books such as the CRC or Merck Index. Again, record with source you use in your report.

Note that in Eqn 1 on Page 1, the reacting groups are circled. Once these reacting groups are removed, the remaining bits of the two reactants are brought together to give the structure of the resulting ester. Following this format, in each of your balanced equations circle the reacting groups. You should be able to convince yourself that the remaining bits come together to give the product structures. Note that salicylic acid appears in both equations, reacting one time through its acid group and one time through its alcohol group. In each of your two equations, label the reacting part of salicylic acid as either acid or alcohol.

Discussion:
In a well-organized paragraph, discuss potential contaminants to your aspirin product. Begin by listing all the compounds that could be mixed in with your aspirin product, i.e. all reactants, solvents, and other products. You should have six compounds besides aspirin. Briefly describe the source of each compound. Considering factors such as limiting reagent (which you just calculated), and procedural steps which may have removed some of these compounds, discuss which compound(s) you think are most likely to contaminate your aspirin product, and the reasons for your conclusions.