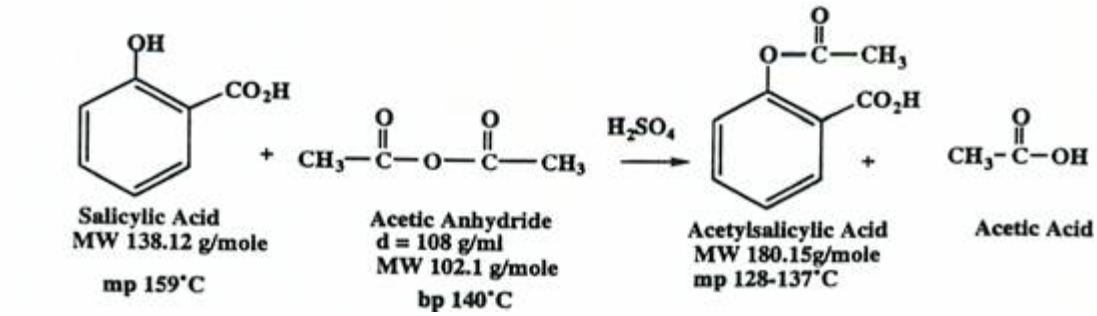
Experiment 11
Synthesis and Analysis of Aspirin

INTRODUCTION

Aspirin is most widely sold over-the-counter drug. It has the ability to reduce fever (an antipyretic), to reduce pain (an analgesic), and to reduce swelling, soreness, and redness (an anti-inflammatory agent). One of the first recorded accounts for the discovery of aspirin appeared in England, in 1763, crediting the bark of willow trees with a beneficial effect in alleviating distress due to fevers, aches, and pains. Later, the compound salicylic acid (named for the Latin word for willow, salix) was isolated from willow bark. It proved to be the active ingredient. By 1860, organic chemists were able to synthesize salicylic acid from basic starting materials, this furthered the therapeutic use of the substance, but there were problems. Salicylic acid proved to be irritating to the membranes of the throat, mouth, and stomach. These problems are directly associated with the high acidity of the compound, but a simple remedy was discovered, namely, replacement of the acidic phenolic hydrogen atom with an acetyl group.

When interpreting the structures of the above organic compounds, note the following characteristics of these molecules. Organic molecules are complex compounds of carbon. Carbon always shares four pairs of electrons in bonds with other molecular groups or atoms. When the structure of an organic molecule is drawn using the condensed method, carbon rings are represented with simple geometric shapes, such as a hexagon. Each corner of the hexagon represents a carbon atom and the number of hydrogen atoms required to share 4 pairs of electrons with the carbon. If the "corner" has no other marks, that means there is a carbon atom bonded to 2 other carbon atoms (in the ring) plus 2 hydrogen atoms. The hydrogen atoms are implied, not show. If a carbon to carbon double bond (C =C) is present and the carbons are attached in a ring, each of the two carbon atoms is bonded to two others with 6 pairs of electrons, and only one hydrogen is attached to each of these carbons give the full compliment of four bonds. If a triple bond is present then only one other atom may be attached. Check the structures below to see that each carbon has four and only four bonds. Oxygen, on the other hand, will bond covalently to only two atoms, and hydrogen bonds to only one.

A useful synthesis of acetylsalicylic acid was developed in 1893, patented in 1899, marketed under the trade name of "aspirin" by the Bayer Company in Germany. The name aspirin was invented by the chemist, Felix Hofmann, who originally synthesized acetylsalicylic acid for Bayer. More than 50 million 5-grain tablets of aspirin are consumed daily in the United States. In Part I of this experiment, you will prepare aspirin by reaction of salicylic acid with acetic anhydride, using concentrated sulfuric acid as a catalyst.



Aspirin still has its side effects. Note that the carboxylic acid functional group remains intact.

This may result in hemorrhaging of the stomach walls even with normal dosages. The acidic irritation can be reduced through the use of buffering agents, like antacids, in the form of magnesium hydroxide, magnesium carbonate, and aluminum glycinate when mixed with aspirin (Bufferin). While the ester can be formed from acetic acid and salicylic acid, a better preparative method uses acetic anhydrides in the reaction instead of acetic acid. An acid catalyst, like sulfuric acid or phosphoric acid, is used to speed up the process.

Part I: Synthesis of Aspirin

Caution! The preparation of aspirin involves the use of two very hazardous materials - concentrated sulfuric acid and acetic anhydride. Proceed only if you have a fume hood to work in, and after you have listened carefully to the instructor's safety directions. As usual, goggles must be worn at all times.

PROCEDURE

1. Weigh 4.0 g (0.030 mol) of salicylic acid in a 125 mL Erlenmeyer flask. Using this quantity of salicylic acid to calculate the theoretical yield of aspirin. Record the weigh on the report sheet.
2. Carefully add 6 mL (0.051 mol) of acetic anhydride to the flask. (**CAREFUL!** Acetic anhydride is irritating to the skin and eyes.)
3. Using extreme caution, add 5 drops of concentrated sulfuric acid to the flask, swirl gently, and place the flask in a beaker of boiling water. Clamp the flask to a ring stand and heat for 20 minutes. Constantly stir with a glass rod; the entire solid must completely dissolve.
4. Remove the flask from the boiling water bath and allow to cool to room temperature. Crystallization should occur during cooling. If crystals begin to grow, let the flask sit undisturbed until crystals stop growing then add the 40 mL of ice water. If crystals do not grow, slowly pour the solution into a 250-mL beaker containing 40 mL of ice water, mix thoroughly, and place the beaker in ice water and let sit undisturbed until crystals have grown. The water destroys any unreacted acetic anhydride and will cause the insoluble aspirin to precipitate out of solution.
5. Collect the crystals by vacuum filtration (using a Buchner funnel, if available).
6. Wash the crystals with two 10-mL portions of cold water followed by one 10 mL portion of cold ethanol. Allow the crude product to dry, then weigh it on the rough balance.

7. Weigh a watch glass. Add the crystals and re-weigh. Calculate the weight of crude aspirin. Determine the percent yield. Test a small amount of this crude product for its melting point as described in Part II. Test the freshly made product for purity. Aspirin naturally decomposes into acetic acid over time so the purity test should be done the day the aspirin is prepared. Save some of your aspirin for testing.

   Recrystalization: The crude aspirin needs to be further purified. The crude products obtained from most preparations of organic compounds are contaminated with unreacted starting materials and substances from side-reactions. These can often be eliminated by a simple process known as RECRYSTALLIZATION. The next phase of this experiment involves the recrystallization, and thus, purification, of your crude aspirin sample.

8. Dissolve about 2-4 g of your crude product in about 20 mL ethyl alcohol in a 125 mL Erlenmeyer flask, warming the alcohol in a water bath to speed up dissolution. Caution: Do not use a flame to heat ethyl alcohol as it is a flammable compound. If you obtained less than 6 g of crude product, use proportionately less alcohol.

9. If any solid material remains undissolved, filter the solution.

10. Add 50 mL of warm water (about 50 °C) to the clear alcohol solution. If any crystals appear at this point, heat the contents of the flask until they dissolve.

11. Set the flask aside to cool, observing it carefully.

12. When crystals start to form, cool the flask by surrounding it with cold water. The crystallization process will then go to completion.

13. Collect the crystals by vacuum filtration.

14. Allow the crystals to dry.

15. Save your sample of the aspirin for a melting point determination and further analysis.

Part II: Analysis of Aspirin

A. Determination of the Melting Point

Most organic compounds have a sharp melting point, which can be measured accurately to within 1 °C or better, using the method below. Furthermore, the measurement is easily made with a small quantity of material (a few small crystals) using a simple apparatus. Melting point determinations are routinely made on solid organic compounds, and extensive compilations of melting points are available in reference books. One use of the melting point is to establish that a preparative or isolation procedure has led to an expected product. (The prepared substance should have the documented melting point for that substance.)

A very pure substance has a very sharp melting point. Further purification will not change the melting point. Less pure substances melt over a range of temperatures that is below the actual melting point of pure material. Thus the sharpness of a melting point is a useful criterion of purity. When a melting point is determined, it is therefore important that the melting range be recorded. The bottom of the melting range is the temperature at which the first signs of liquid can be seen. The top of the melting range is the temperature at which the last of the solid fuses, *i.e.* turns into liquid. The compound is generally regarded as pure enough for most purposes if the melting range is no greater than 2 °C. A wide melting range signals the need for further purification.

PROCEDURE

1. Obtain a capillary tube from your instructor, and gently press the open end into the pile of aspirin crystals on the paper so that a few crystals of aspirin enter the capillary tube.

2. Tap the closed end of the capillary onto the bench top, so that the aspirin crystals work their way to the bottom. The aspirin crystals should be firmly packed, and fill the capillary tube to a depth of no more than 1-2 mm. Insert the capillary tube containing the sample into the melting point apparatus. Record the temperature where the melting point is first observed and when it becomes a liquid completely. This is your melting point range. Melting point of purified aspirin is 135-136 °C.

B. Determination of Purity

Phenols form a colored complex with the ferric ion. If phenol is present in a sample, the resulting color means the product is impure. The purple color indicates the presence of a phenol group. The intensity of the color qualitatively tells how much impurity is present.

PROCEDURE

1. Label three test tubes; place a few crystals of salicylic acid into test tube #1, a small sample of your aspirin into test tube #2, and a small sample of crushed commercial aspirin into #3. Add 5 mL of deionized water to each test tube and swirl to dissolve the crystals.

2. Add 10 drops of 1% ferric chloride to each test tube.

3. Compare and record your observations.

Experiment 10
ACID/BASE TITRATION

Scientist _____

Partner(s) _____

REPORT SHEET

Part I

1. Theoretical yield:

_____ g salicylic acid $\left(\frac{1\text{ mol salicylic acid}}{138\text{ g salicylic acid}}\right)\left(\frac{1\text{ mol salicylic acid}}{1\text{ mol aspirin}}\right)\left(\frac{180\text{ g aspirin}}{1\text{ mol aspirin}}\right)$ = _____ g of aspirin

(Theoretical yield of aspirin)

2. Experimental yield:

Weight of aspirin & watch glass _____ g

Weight of watch glass _____ g

Mass of crude product obtained after suction filtration _____ g

Percent Yield of crude product $\left(\frac{\text{experimental yield}}{\text{theoretical yield}}100\%\right)$ _____ %

Mass of re-crystallized product (optional) _____ g

Percent Yield of re-crystallized product $\left(\frac{\text{experimental yield}}{\text{theoretical yield}}100\%\right)$ _____ %

Part II

Melting Point of crude product (1st trial) _____ °C (2nd trial) _____ °C

Melting Point of re-crystallized product (1st trial) _____ °C (2nd trial) _____ °C

Ferric Chloride Test (Purity test)

SAMPLE	COLOR	INTENSITY
Salicylic acid		
Your aspirin		
Commercial aspirin		

QUESTIONS

1. What is the purpose of the 18 *M* sulfuric acid in the preparation of aspirin?

2. Explain why the percent of your aspirin was different from the results obtained from the commercial aspirin.

3. Old aspirin exposed to moisture often smells like acetic acid (vinegar). When aspirin is heated in boiling water, it decomposes and gives off a vinegar smell. The resulting solution gives a positive FeCl3 test. Why is this test positive? Write the chemical equation for the reaction of aspirin and water at high temperatures.

4. You have spent about 12 weeks learning about chemistry and its respective laboratory techniques. The typical street-drug producer usually doesn't have any chemistry background but instead simply mimics the synthesis learned from another person or, in some cases, a book. If you take this into consideration along with your success at producing aspirin, how well do you trust the producers of street drugs to make drugs safe for consumer use?