INTRODUCTION

Aspirin is one of the milder and least expensive pain relievers available. Today, Americans spend about $2 billion a year for non-prescription pain relievers. This figure mainly reflects purchase of 16,000 tons of aspirin tablets or 80 million tablets a year. Unlike many other formulations, the production of hard aspirin tablets only requires four ingredients: the active ingredient (acetylsalicylic acid), a lubricant such as hydrogenated vegetable oil, corn starch, and water.

From the time of ancient Greeks to the present, acetylsalicylic acid or its parent - salicylic acid - has been used to relieve pain and symptoms of illness. In the early 1800s, salicin, a glycoside of salicylic acid, was found in the bark of a willow tree, Salix alba. Salicylic acid was found in the flowers of that tree. Although salicylic acid is a good pain reliever, its acidic properties cause irritation in the moist membranes of the mouth, throat, and stomach. In 1875, the sodium salt of salicylic acid was used because it is less sour to the taste. However, it still caused gastric discomfort problems.

In 1893, Felix Hoffman Jr., a chemist working for the Bayer Laboratories in Germany, discovered a practical route for synthesizing an ester derivative of salicylic acid, acetylsalicylic acid. Acetylsalicylic acid does not have the bad taste and stomach problems of salicylic acid. Once acetylsalicylic acid is absorbed from the intestine, it is converted back to salicylic acid. It enters the bloodstream where it interferes with the synthesis of prostaglandins and irreversibly binds to an enzyme called cyclooxygenase 2. Prostaglandins and cyclooxygenase 2 are involved in generating a pain signal and inflaming the painful area. Salicylic acid interferes with prostaglandins production and cyclooxygenase 2 activity, so there is less pain and inflammation. Bayer called its new product "aspirin," the name being derived from "a" for acetyl, and the root ",spir", from the Latin name Spiraea ulmaria, the meadow sweet flower, from which salicylic acid had been isolated.

In this experiment, Le Châtelier's principle and esterification of the phenolic hydroxyl group of salicylic acid will be used to synthesize aspirin. Unlike the original Bayer Laboratory synthesis, acetic anhydride is used instead of acetyl chloride. Acetic anhydride is preferred because it is less hazardous to use and less expensive than acetyl chloride. In industry, the acetic acid produced in this reaction can be recovered and converted back into acetic anhydride.

The reaction that is used for the synthesis is shown below. This reaction uses an excess of acetic anhydride, sulfuric acid as a catalyst, and heat to push the equilibrium toward the products.

\[
\text{C}_6\text{H}_5\text{CO}_2\text{H} + \text{O}_3\text{C}-\text{C}=\text{O} \xrightarrow{\Delta, \text{H}_2\text{SO}_4} \text{C}_6\text{H}_5\text{CO}_2\text{H} + \text{O}_3\text{C}-\text{C}=\text{O}
\]

Water is added to quench the reaction, destroy the excess acetic anhydride, and cause crude aspirin to crystallize. The isolation will be carried out based on the solubility of the starting materials,
product, and byproducts. In water, acetic anhydride slowly converts to acetic acid, and acetic acid, sulfuric acid, and water are infinitely miscible. Aspirin and salicylic acid are poorly soluble in cold water. After the hydrolysis of acetic anhydride is complete, the reaction is diluted with water and cooled. Filtration separates product and any unreacted salicylic acid from acetic and sulfuric acids. To further purify aspirin, one must know that both salicylic acid and aspirin are fairly soluble in warm water; however, salicylic acid is more soluble than aspirin in ethanol. Therefore, a mixed solvent recrystallization technique is used where ethanol is the primary solvent and water is the secondary solvent. Use of this system makes the bulk of salicylic acid remain in solution but permits aspirin to crystallize. The purity of the product will be confirmed by qualitative analysis using ferric chloride, melting point range, and an IR spectrum using an ATR accessory.

SAFETY

- **Acetic Anhydride**: Corrosive, Flammable, and Lachrymator (makes you cry)
- **Concentrated Sulfuric Acid**: Very Corrosive
- **Ferric Chloride Solution**: Corrosive
- **Salicylic Acid and Aspirin**: Pulmonary Irritants- Don’t inhale dust
- **Ethanol**: Toxic and Flammable

EXPERIMENTAL SECTION

Thoroughly clean and flame dry a 50 mL beaker, a 10 mL graduated cylinder, and a 50 mL Erlenmeyer flask. Be careful not to burn yourself. Once the flask is slightly cooled, obtain its mass to the nearest 0.01 g. Do not let the flask cool back down to room temperature. Weigh out approximately 2.0 g of salicylic acid (to the nearest 0.01 g) directly into the 50 mL Erlenmeyer flask. Place a cork on the 50 mL Erlenmeyer flask. In the dried 10 mL graduated cylinder under a fume hood, measure out 4 mL of acetic anhydride. Add the acetic anhydride to the pre-weighed salicylic acid so that any salicylic acid clinging to the inside of the flask is rinsed down into the bottom. Using a Pasteur Pipette, add 5-8 drops of concentrated sulfuric acid to the Erlenmeyer flask and gently swirl the mixture. *What is the purpose of the sulfuric acid?*

Place a loose cork (not rubber) in the Erlenmeyer flask. Put the flask in a hot water bath located at the back of the room and make sure it is set to 85 °C – 90 °C. Cover the hot water bath with plastic wrap and make sure Erlenmeyer flask is loosely corked. Swirl the reaction mixture until all the salicylic acid has dissolved. Let the flask stand in the bath (propped up with something heavy) for approximately 15 minutes. While the reaction is going, chill on ice 4 - 5 mL of DI water that you will need to wash the crude aspirin. *Note: If the solution turns red, it overheated; start over.*

While the reaction mixture is still hot, pour the reaction mixture into the dry, clean 50 mL beaker, and cover with a watch glass. Let the beaker stand until a very small amount of precipitate forms or the reaction mixture gets close to room temperature. Put the beaker in an ice water bath. Add 2 mL of DI water, 3-5 drops at a time (swirl or stir between each addition), to hydrolyze the unreacted acetic anhydride. *Note: the decomposition of acetic anhydride is very exothermic. Thus, an ice water bath is used to prevent hot liquid from spattering. In addition, cold conditions minimize unwanted hydrolysis of the ester group in aspirin, which would re-form salicylic acid. Add an additional 10 mL of DI water, and swirl the beaker to achieve thorough mixing. If crystals do not appear, scratch the walls of the beaker with a stirring rod to induce crystallization. Continue to chill
the beaker in an ice water bath until the reaction mixture reaches about 5 °C (until no more crystals form). If lumping of the product should occur, break up the lumps with a stirring rod. Vacuum filter and wash the crude product three times with approx. equal portions of cold water (prepped earlier).

Transfer the entire crude product into a small beaker, and add a minimal amount of 95% ethanol to begin to dissolve the crystals. Cover the beaker with a watch glass, and keep the beaker covered at all times unless you need to access its contents! Heat and gently swirl the mixture on the hot plate until all the solid dissolves (add a little more ethanol if the entire solid is not in solution just as the solution begins to gently boil). While the solution is still on the hot plate, add 0.5 mL - 2 mL of DI water dropwise with good mixing, until the solution becomes cloudy. Then, add a few drops of 95% ethanol, swirl, and warm briefly to redissolve everything. Cool the mixture slowly to room temperature. After the mixture reaches approx. room temperature, cool to approx. 5 °C (or until not more crystals form) and vacuum filter on a Hirsch funnel. Break up any clumps, and let the solid dry for a day. Perform a qualitative test using ferric chloride (see below for theory and protocol). Measure yield, melting range, and obtain an IR spectrum (using the ATR accessory) of the product.

**FERRIC CHLORIDE TEST FOR PHENOLIC GROUPS**

In solution, ferric chloride becomes the Fe(H₂O)₆³⁺ ion. This ion can bind to salicylic acid because water is exchangeable in iron complexes. One water can be replaced by the negative carboxylic acid oxygen ion in salicylic acid. Because of the chelate effect and the formation of a new six membered ring, the phenolic oxygen of salicylic acid can also replace one of the waters in the iron complex (see figure below). This new iron complex has an intense violet color due to the quantum mechanics of iron orbitals and the ligand to metal charge transfer, which moves the absorption maximum from the ultraviolet to the visible region. In aspirin, the –OH group of salicylic acid has been replaced by an ester group which prevents the formation of the second bond to the phenolic oxygen. The resulting complex with aspirin shows only a slight yellow color, not very different from that of Fe(H₂O)₆³⁺ itself.

![Diagram of ferric chloride test](image)

**Ferric Chloride Test Protocol:**

Clean and dry four small test tubes. Add 1 mL of ethanol or methanol and 1 drop of 1% aqueous ferric chloride solution to each. Record initial observations. Into one test tube, add a crystal of salicylic acid. Into another test tube, add the same amount of your synthesized product. Into another test tube, add a small amount of authentic aspirin. The final test tube should be a blank and have nothing but the alcohol and ferric chloride in it. Shake the mixture in each test tube and record the results. Keeping in mind what sort of claim this test allows you to make, what do these results say about the purity of your product?
Clean Up:

Upon completion of all characterization tests, any remaining product should be thrown away.

References:


Schneider, R.F. Synthesis of Aspirin

Synthesis of Aspirin.


WEEKS 5 & 6 ASSIGNMENT: Staple and turn in the following results stapled to your notebook pages.

1. Reaction for esterification of salicylic acid to form acetylsalicylic acid
2. Reaction for the ferric chloride test using salicylic acid
3. Reaction for the ferric chloride test using acetylsalicylic acid
4. Table of results for the ferric chloride test including title, all 4 samples, and initial and final observations
5. Hard copy of IR spectrum, properly labeled
6. Melting range, listed
7. Mass of product, listed
8. Calculations for:
   a. Determination of limiting reagent (consider salicylic acid and acetic anhydride)
   b. Theoretical yield (in grams) based on limiting reagent
   c. % yield

STUDY QUESTIONS for Discussion Quizz # 5 or #6 on either 3/15/2016 or 3/29/2016

1. Review the theory of esterification:
   a. Specific reaction used in this experiment, and the general reaction / transformation that occurs
b. Identify the functional group in the final product’s structure compared with starting materials
c. Equilibrium reaction effects and how product formation was driven in this specific experiment

2. For the “side reaction” that could occur hydrolyzing the ester group in the product back to a phenol:
   a. Why would it occur and what step was taken in the procedure to avoid this?
   b. If it did occur, would the resulting re-formed salicylic acid be likely to be in the final crystal product?
   c. If “no” to 2B, what step would have removed it and why did this work?
   d. If “yes” to 2B, would its presence be heavier or lighter than the major product that could have formed and not re-formed salicylic acid?

3. What is the order and purpose of major procedural steps in the aspirin synthesis experiment?
   a. What was the purpose of H2SO4?
   b. What was the purpose of the ice water bath?
   c. Why did you have to use mixed-solvent recrystallization instead of single solvent recrystallization?

4. For the Ferric Chloride chemical characterization test:
   a. What functional group(s) does it test for the presence of?
   b. What is the reaction that occurs if that functional group is present?
   c. What are strong choices for positive and negative controls?
   d. What does a positive/negative test result look like?
   e. Keeping in mind what sort of claim this test allows you to make, what do your results say about the purity of your product?

5. Aside from glassware transfers / spills / etc., during what steps may product have been lost due to chemistry reasons? Explain the chemistry of each.

6. Why would the presence of trace contamination in the final solid product cause melting point depression to occur?

7. What compounds would make strong IR comparisons with your experimental product, and what notable peak changes (presence/absence) would indicate the correct product had formed?

PRE-LAB QUESTIONS: (complete these in your notebook before coming to lab)

1. What is the name of your experiment?
2. What are some important safety considerations for this experiment?
3. How will this experiment help you practice / prepare for the Single and Double Unknown Analyses at the end of the semester?
4. What theory / concept from class will be demonstrated in this experiment?