**Student Experimental Procedure**

**Synthesizing Aspirin using an Iron (III) Chloride Catalyst**

**A Lewis Acid Approach**

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*Purpose of the Experiment*

Prepare acetylsalicylic acid (aspirin) using Iron (III) chloride.

*Background Information:*

Aspirin is found in medicine cabinets and pharmacy departments across the world. It is one of the least expensive yet most useful drugs. In 1827, salicin, an aspirin precursor, was identified from the willow bark as the compound responsible for its effectiveness as a pain reliever. Salicylic acid, a derivative of salicin, was later identified in 1853 and utilized as an analgesic (pain reliever), anti-inflammatory (swelling reducer) and antipyretic (fever reducer). However, the relatively high acidity (pKa of 2.97) of salicylic acid leads to unwanted side effects including irritation of the mouth, esophagus and stomach. In 1893, Felix Hoffman employed a condensation reaction of acetic acid and salicylic acid producing acetylsalicylic acid in an effort to reduce the painful side effects of the drug while retaining its therapeutic properties (e.g. fever reduction and pain relief). Bayer began marketing this new drug under the name aspirin in 1899 and made it commercially available in tablet form in 1915 (1,2).

 As aspirin is ingested by the human body, the drug passes straight through the acidic environment in the stomach and into the intestinal tract. Since, the intestines are alkaline; aspirin becomes neutralized forming the sodium salt forms known as sodium acetylsalicylate. The sodium acetylsalicylate is then absorbed by the bloodstream through the intestinal walls and is transported to the different parts of the body.

 A primary side effect of aspirin is stomach irritation. Due to this side effect, most aspirin is manufactured using buffers and other ingredients to reduce the side effects. Other side effects of aspirin include a runny nose and Reye’s syndrome in children.

Aspirin is prepared via an esterification reaction, which involves the creation of an ester using an alcohol or phenol (i.e. salicylic acid), and a carboxylic anhydride (i.e. acetic anhydride, Figure 1).



*Figure 1: Esterification of Acetylsalicylic Acid (Aspirin)*

Typically, this synthesis is conducted via a Brönsted-Lowry type acid, for example sulfuric acid. Brönsted-Lowry acids act as proton donors in a proton-transfer reaction. However, not all acids have protons to donate, as in the case of iron (III) chloride. Iron(III) chloride is an example of a Lewis acid. Lewis acids act as electron acceptors. In this synthesis of aspirin, iron (III) chloride acts as a Lewis acid and accepts electrons from salicylic acid to form a complex ion. The reaction then proceeds through a series of intermediates to synthesize aspirin.

An iron (III) chloride solution (FeCl3) reacts with phenols to produce a colored complex ranging from blue-green to red-brown depending on the substrate of the phenol (3, 4). Aliphatic alcohols, acids, and other functional groups do not respond to the addition of an FeCl3 solution. Salicylic acid has both a phenolic alcohol group and a carboxyl group. Salicylic acid will form a complex with the FeCl3 through the phenolic alcohol functional group; acetylsalicylic acid does not have this group. Hence, upon crystallization, aspirin will remain in the reaction flask and both the FeCl3 and any unreacted salicylic acid will be removed.

 In this experiment, you will add a measured volume of acetic anhydride and the iron (III) chloride catalyst to a measured mass of salicylic acid. You will then determine the yield and purity of the crystallized aspirin.

*Procedure:*

**Chemical Alert**

Acetic anhydride - strongly corrosive and lachrymator, CAS # 108-24-7

Iron (III) chloride - irritant, corrosive, CAS # 7705-08-0

Salicylic acid - toxic, irritant, harmful, CAS # 69-72-7

**Caution:** Wear departmentally approved eye protection while doing this experiment.

**Note:** If the balances you are using do not have a tare function, your laboratory instructor will describe the weighing procedure you should follow and how you should record your data.

 If weighing papers are not available in your laboratory, you will be given instructions for weighing and transferring the solid in this experiment.

 Unless your laboratory instructor tells you otherwise, record all masses to the nearest milligram (0.001 g).

1. Prepare a hot water bath by filling a 600 mL beaker with 350-450 mL of tap water, add a stir bar to beaker, stir and heat to a boil.
2. Stabilize the beaker on the hot plate with a ring stand and ring support.
3. Tare a piece of clean weigh paper. Weigh approximately 2.1 grams of salicylic acid. Record the exact mass on the Data Sheet. Transfer the solid to a clean 125 mL Erlenmeyer flask.

**Caution:** Acetic anhydride is strongly corrosive and a lachrymator. Use a fume hood when working with this reagent. Prevent eye, skin and clothing contact. Avoid inhaling vapors.

If you spill this reagent on yourself, ***immediately*** rinse with a large amount of running water. If you spill any on the laboratory bench, immediately notify your laboratory instructor.

1. In the fume hood, add 4.00 mL of acetic anhydride to the Erlenmeyer flask using a Mohr pipet. Carefully swirl the contents of the flask to dissolve the solid salicylic acid. Record the color of this solution on your Data Sheet.
2. The hot water bath should now be boiling. Add 5 drops 1.00 M FeCl3 (*aq*)to the Erlenmeyer flask. Again, swirl the contents carefully. Record the color of the solution.
3. Place this flask carefully into the hot water bath **immediately**. **DO NOT let the unheated solution sit on the bench for an extended period of time.** Secure the flask to the ring stand with a clamp. Make sure the lower half of the Erlenmeyer flask is below the water level. Heat the reaction flask for 10 minutes. Record all color changes.
4. While the reaction flask is heating, prepare an ice bath in a 600-mL beaker. Chill 60 mL of deioinzed water in a 150 mL beaker.
5. Carefully remove the Erlenmeyer flask from the boiling water bath using tongs or hot mitts. **Slowly add the 10 mL of the chilled deioinzed water in 1-2 mL portions**, carefully swirling the contents between additions of chilled water until all10 mL of the chilled water have been added. Record any color changes after the addition of the deioinzed water.
6. Chill the flask in the ice bath for 10-15 minutes. While the flask cools, assemble the filtering apparatus. To do so, clamp a 500 mL filter flask to a ring stand. Place a Büchner funnel in the filtration flask.
7. Add 25 mL chilled deioinzed water to the reaction flask. Carefully break the large clumps of solid with a glass stirring rod.
8. Weigh a piece of filter paper and a watch glass. Record the exact mass of each on your Data Sheet. Place the filter paper inside the Büchner funnel. Moisten the filter paper with 1-2 mL of deioinzed water. Attach rubber tubing to the side arm of the filtration flask. Attach the opposite end of the rubber tubing to a water aspirator. Turn on the aspirator to seal the filter paper to the funnel.
9. Transfer the solid from the reaction flask using a rubber policeman. Use deioinzed water to rinse out the reaction flask and rubber policeman. Wash the crystals collected on the filter paper with deioinzed water until the crystals are white.
10. Repeat the washing process again. Leave aspirator on for 5-10 minutes to dry the product. Turn off the aspirator and disconnect the rubber tubing.
11. Remove the filter paper carefully from the Büchner funnel and transfer it to the pre-massed watchglass. Place the watchglass in a secure area to dry until the next class meeting.
12. Weigh the watchglass, filter paper and crystals. Record the mass on your Data Sheet. Calculate the final mass of the crystals and the percent yield of your aspirin.

**Caution:** Wash your hands thoroughly with soap or detergent before leaving the laboratory.

**Data Sheet** (to be included on separate sheet)

DATA

Mass of salicylic acid (g) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Volume of acetic anhydride (mL) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Record the color of the acetic anhydride and salicylic acid solution. *(Step 4)*

Record the color after the addition of 5 drops iron (III) chloride (FeCl3 *(aq)*). (*Step 5)*

Record the color changes that occur during the 10 minutes of heating. *(Step 6)*

Record the color of the solution after the addition of the deionized water. *(Step 8)*

Mass of filter paper (g) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Mass of watch glass (g) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Mass of filter paper and watch glass (g) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Record the final color of the aspirin crystals \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Mass of crystals, filter paper and watch glass (g) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Mass of the aspirin crystals (g) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

CALCULATIONS

Calculate the mass of acetic anhydride using the volume of acetic anhydride

(Density = 1.08g/mL).

Calculate the number of moles of salicylic acid using the recorded mass of salicylic acid

(MM = 138 g/mol).

Calculate the number of moles of acetic anhydride using the calculated mass of acetic anhydride (MM = 102 g/mol).

Write a Balanced Reaction.

Determine the limiting reagent of the reaction.

Determine the theoretical yield of aspirin (MM = 180 g/mol).

What is the amount of excess material left over at the end of the reaction (in ml)?

Determine the percent yield of aspirin.

Briefly explain why the color of the solution is the same at the beginning and end of the reaction.

SUPPLEMENTARY QUESTIONS

*General Chemistry*

1. Briefly compare and contrast Bronsted-Lowry acids and Lewis Acids.
2. Identify the Lewis acid and base in this reaction.

*Organic Chemistry*

1. Draw the mechanism for the esterification of salicylic acid with acetic anhydride.
2. How does water affect the esterification reaction? Drawing a mechanism may be helpful for your explanation.
3. Compare the NMR and IR spectra of the starting material versus the product.

*Inorganic Chemistry*

1. Why does salicylic acid bind to iron (III) chloride, while acetylsalicylic acid does not? Draw basic structures to explain.
2. Draw an alternative possible mechanism for the synthesis of aspirin using Iron (III) Chloride as the catalyst.

**References Cited**

(1) Glogovsky, Robert L. *Synthesizing Aspirin*, in General Chemistry; Brooks Cole: Pacific Grove, CA, 2001; 33-40.

(2) Elwood, P. C. *Clinical Medicine* JRCPL **2001,** pp.132-37. <http://www.westhertshospitals.nhs.uk/whc/archive/evidence/01%20prevention/Aspirin-ClinMed%202001.pdf>

#### (3) Park, M. V.; *J. Chem. Soc. (A).*, 1966, 816-820.

(*4*) Gill, Maria J.; Martinez-Merino, Victor. Exercise I. 11: Determination of the Free Salicylic acid Concentration in Aspirin by Forming Fe+3 Complexes. In *Practical Studies for Medicinal Chemistry* [Online] ; Monge, Antonio and C. Robin Ganellin, eds.; 2006, Chapter 1, <http://old.iupac.org/publications/cd/medicinal_chemistry/Practica-I-11.pdf> (accessed July 24, 2007).