INTRODUCTION

Aspirin is one of the most widely manufactured analgesics in the pharmaceutical industry. Acetylsalicylic acid (aspirin) may be synthesized in the laboratory by several different methods. But pharmaceutical companies are always looking for improved methods for their production.

A literature search suggests aspirin could be made from the reaction between salicylic acid and acetic anhydride, but the crude aspirin may be contaminated with unreacted salicylic acid. Because salicylic acid is more water-soluble than aspirin, 2-solvent recrystallization using ethanol/water may be used to purify the aspirin sample.

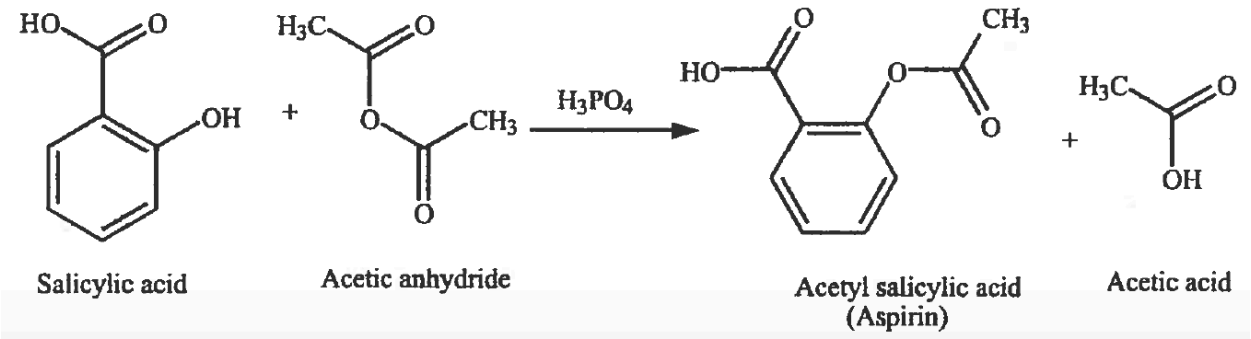
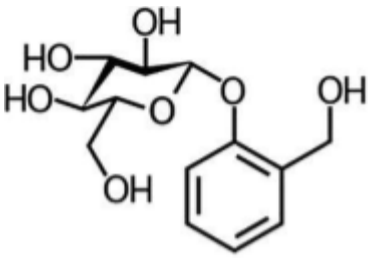


Figure 1 - Reaction Schema

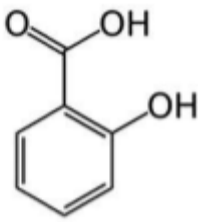
Suppose that you are asked to see if aspirin could indeed be prepared in reasonable yield and purity by this method and whether recrystallization by the two-solvent method is necessary to produce pure aspirin.

Look up, "**two solvent recrystallization**" and be prepared to explain what this term means.

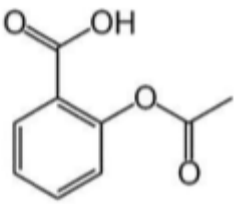
CHEMISTRY BACKGROUND



Salicin



Salicylic Acid



2-(acetyloxyl)-benzoic acid

Aspirin

Aspirin is the trade name for the compound acetylsalicylic acid. Aspirin was the first discovered member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are chemicals that are analgesic (pain-reducer), antipyretic (anti-fever) and anti-inflammatory. NSAIDs have become an important part of the pharmaceutical treatment of pain (at low doses) and inflammation (at higher doses). When used in long-term low doses, aspirin is also believed to be an anticoagulant and therefore may prevent heart attacks. The most commonly used NSAIDs are aspirin , ibuprofen and naproxen. Unlike Opioids, NSAIDs do not produce sedation, respiratory depression or addiction.

Despite their popularity as a pharmaceutical drug, it was not until the 1970's that the mechanism of action of aspirin and other NSAIDs was elucidated: In a piece of research for which he was awarded both a Nobel prize and a knighthood, John Vane showed in 1971 that aspirin suppresses the production of prostaglandins and thromboxanes. This happens because cyclooxygenase, an enzyme which participates in the production of prostaglandins and thromboxanes, is irreversibly inhibited when aspirin acetylates it. Prostaglandins are local hormones produced in the body and have diverse effects in the body, including but not limited to transmission of pain information to the brain, modulation of the hypothalamic thermostat and inflammation.

The earliest known use of aspirin has been traced back to the fifth century B.C. The Greek physician Hippocrates described an extract of willow tree bark, a bitter powder that could be used to reduce fevers. In 1829, Salicin was isolated from willow bark and used as a pain reliever. Unfortunately Salicin was not very popular since it was found to be very acidic and a stomach irritant. In 1897 a German chemist named Felix Hoffman was working for the Bayer chemical company. Hoffman was looking for a less acidic pain reliever that his father could take for his arthritis. His research led to the synthesis of acetylsalicylic acid (ASA) or aspirin. Bayer patented the name and commenced to market the product in 1899. It was a huge success and sales grew rapidly. In fact, the company set up by Friedrich Bayer & Company is generally reckoned to have been the first pharmaceutical company, and the production of aspirin is generally accepted to have laid the foundation of the modern pharmaceutical industry.

EXPERIMENTAL AND LEARNING OBJECTIVES

In addition to reviewing and further practicing laboratory operations from earlier experiments, including solid and liquid transfer, vacuum filtration, recrystallization, and melting point determination, this experiment also introduces the common stages of organic synthesis: reaction, isolation, purification, and characterization. Characterization of a synthesis product means obtaining data to prove you have indeed synthesized aspirin and proven its purity. In this case, you will determine m.pt and obtain an infrared (IR) spectrum of your sample. These results will then be compared to reference databases to establish whether you have indeed synthesized aspirin and determine the purity of both the crude and purified aspirin samples.

PHYSICAL DATA:

	Molar Mass	Melting Pt.	Density
	(g/mole)	(℃)	(g/mL)
Salicylic acid	138.1	159	-
Acetic Anhydride	102.1	-	1.08
Acetylsalicylic Acid	180.2	135	-

Disposal & Cleaning

- Rinse all used glassware with acetone in your fume hood before washing in hot soapy water.
- Rinse in cold water and, if needed and in the fume hood, rinse the glassware with a small amount of acetone.
- Transfer waste acetone washes to the organic waste station.
- Wipe fume hood with damp paper towels.

Report

- Your working notes should have your name and date the work was done, a title indicating scenario and/or experimental objective(s).
- Include any relevant data and information such as chemical structures or reaction equations.
- Report and interpret relevant evidence – including observations, data and measurements, and calculations. Calculations of yields must be clearly laid out.
- State your conclusion, and explain how your evidence supports your conclusion.

SAFETY:

All chemicals are toxic and/or corrosive. Wear gloves and goggles.

PROCEDURE

A) Reaction

1. (Optional) A helpful deck to explain this lab may be presented.

2. (Optional) One student (or instructor) should make a COPY of the spreadsheet to enter all data. This COPY must then be shared out to the rest of the class. Again, this is optional.[1]

3. Place ~0.400 g of salicylic acid in a dry, pre-weighed, 5 mL conical vial. Record exact mass you used.
4. Use a graduated pipet to add **950 µL** of acetic anhydride to the salicylic acid.
   NOTE: The instructor *may* assist with this step.
5. Place the conical vial in an aluminum heating block.
6. Carefully add 3 drops of concentrated phosphoric acid to the mixture; take care that the acid goes into the mixture rather than the side of the conical vial.
7. Add a magnetic spin **vane** to the conical vial and attach an air condenser. Secure the setup with a small clamp. Set the heater set on medium heat.
8. Note the temperature of the alum block when the mixture dissolves.
9. The alum block temperature should be approximately 90 degrees C. Heat for another 20 minutes.
10. Meanwhile, set up an ice bath in anticipation of later steps, also chill approximately. 5 mL of deionized water in a test tube in an ice bath.
11. Remove the vial from the aluminum block. Allow mixture to cool to room temperature before placing in an ice bath.
12. Detach the air condenser. Remove the magnet with the magnet retriever. Rinse the magnet with a small amount of water.

[1] Video on how to make a copy to edit a google file.

B) Isolation

1. During the cooling cycle, crystals of acetylsalicylic acid (aspirin) form. If not, ask the lab instructor for assistance. A few drops of ice water directly in the vial ***may*** help; be sure to have your vial in an ice bath, though as it will generate heat.
2. After crystallization is complete, add approx. 2 mL ice-cold DI water and stir thoroughly using a spatula, loosening any crude product from the side of the vial.
3. Set up a Hirsch funnel for vacuum filtration. Moisten the filter paper with a few drops of water and turn on the vacuum fully. Vacuum-filter reaction mixture. Rinse out any solid remaining using 1 mL of pre-chilled water. Repeat if necessary.
4. Rinse crystals in a Hirsch funnel with three (3) x 1 mL portions of ice-cold water. Make sure you wash all the crystals evenly.
5. Continue to draw air through the crystals for a few minutes to remove the bulk of the water – this will help dry the crystals.
6. Remove crystals for air-drying on a pre-weighed small container, and determine and record crude wet mass.
7. Next lab prepare a melting point tube sample of your crude aspirin material and measure the melting point of the crude material.

C) Purification using 2-solvent recrystallization method

1. Set a hot plate on a medium setting. In a small Erlenmeyer flask, warm about 10 mL of 95% ethanol (add a boiling chip to ensure smooth heating).
2. Place approximately 5 ml of DI water in a test tube and put it in an ice bath to chill.
3. Place crude aspirin in a 10 mL (or 25 mL if you do not have a 10 mL) Erlenmeyer flask, add the minimum amount (½ ~ 1mL) of hot 95% ethanol, and continue warming until all solids have dissolved. You can add more 95% ethanol if necessary, though minimize total solvent used.
4. Remove the aspirin solution flask from the hotplate and add dropwise approximately 1 mL chilled water to the solution - **DROPWISE**. Continue adding chilled water dropwise until the white cloudiness is persistent. At this point, add one drop of warm ethanol, warm the solution until the solid redissolves.
5. Remove solution from hotplate and allow it to cool to room temperature.
6. Once at room temperature, place in ice bath. Crystals should slowly begin to form. After crystals form, collect the crystals using vacuum filtration. Wash the collected crystals with ice –cold DI water. Continue to draw air through filter flask for about 15 seconds.
7. Transfer crystals to a preweighed small container. Determine and record mass of crystals (the product is still wet at this stage so the mass you record now is not the true mass. You will need to reweigh again after crystals have air-dried next session to obtain its true mass and yield).
8. Write your name, date and name of compound on the container and allow it to dry until next session.
9. Next session: reweigh your dry, pure sample. Record mass and determine yield of product.

D) Characterization

1. Obtain an FT-IR of your product and compare it with the reference IR spectrum of the starting material, salicylic acid and the end product, acetyl salicylic acid:
    a. salicylic acid
    b. acetyl salicylate (Aspirin)
2. Determine melting point ranges of both your crude and pure aspirin samples.

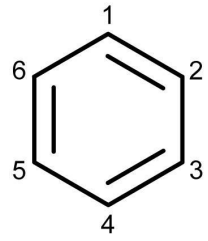
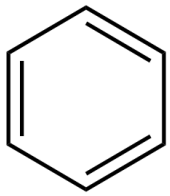
Prelab:

1. What are key properties of **NSAIDs**?

(1 Point)

2. Draw structure of **salicylic acid** and **acetylsalicylic acid** and compare their structure. Circle the acetyl group in acetyl salicylic acid (look at what is different in the product compared to the reactant salicylic acid).

(1 Point)

Salicylic Acid:	**Acetylsalicylic Acid:**
	
Use the template given, and place the most oxidized Carbon at position 1.	

3. What are the **stages** of an organic synthesis?

(1 Point)

-
-
-
-

4. What laboratory procedure is used in a) the isolation stage, b) the purification stage and c) characterization stage?

(1 Point)

A. Isolation: _____

B. Purification: _____

C. Characterization: _____

5. Assume you used **0.200 g of salicylic acid** and **0.480 mL of acetic anhydride**, and you obtain **0.152 g of pure, recrystallized, dry aspirin**.

Calculate your percent yield, clearly showing your calculations.

(1 Point)

Postlab:

1. Calculate the % yield of the aspirin. Show all working clearly, indicating the limiting reagent.

(1 Point)

Salicylic Acid (SA):

Acetic Anhydride (AA):

$$Percent\ Yield\ =$$

2. Quote your melting point of your pure sample and compare it to the literature value. Comment on the purity of the sample.

(2 Point)

Experimental Range: (Start - End)	-	°C
Experimental Range: (ΔT)		°C
Literature Melting Point:		°C
Experimental Melting Mid-Point:		°C
Percent Error:		%
Comments: (HINT: **ΔT** speaks to **purity**; whereas, **Percent error** helps us to understand if we got what we were making?)		

3. Have a fully labeled FTIR of your final product and comment on whether it agrees with a reference FTIR.

(1 Point)

4. During the recrystallization procedure you used a 2-solvent system.

What is a 2-solvent system and why is it sometimes used in recrystallization?

(1 Point)

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