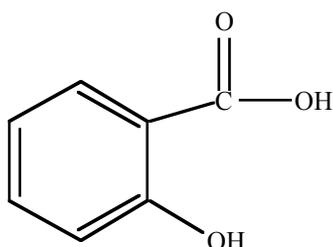
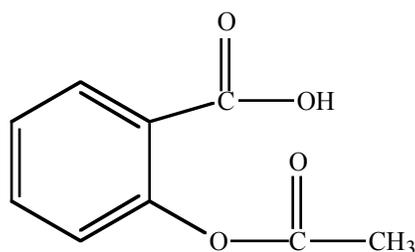


Experiment 8 – Synthesis of Aspirin

Aspirin is an effective analgesic (pain reliever), antipyretic (fever reducer) and anti-inflammatory agent and is one of the most widely used non-prescription drugs. The use of aspirin had its origin in the 18th century, when it was found that an extract from the bark of willow trees was useful in reducing pain and fever. The active ingredient in willow bark was later found to be salicylic acid. The structure of salicylic acid is shown below. Although salicylic acid was effective at reducing pain and fever, it also had some unpleasant side effects. It is irritating to the lining of the mouth, esophagus, and stomach, and can cause hemorrhaging of the stomach lining. In 1899, the Bayer Company in Germany patented a drug they called aspirin, which was a modification of salicylic acid.



Salicylic Acid
 $C_7H_6O_3$

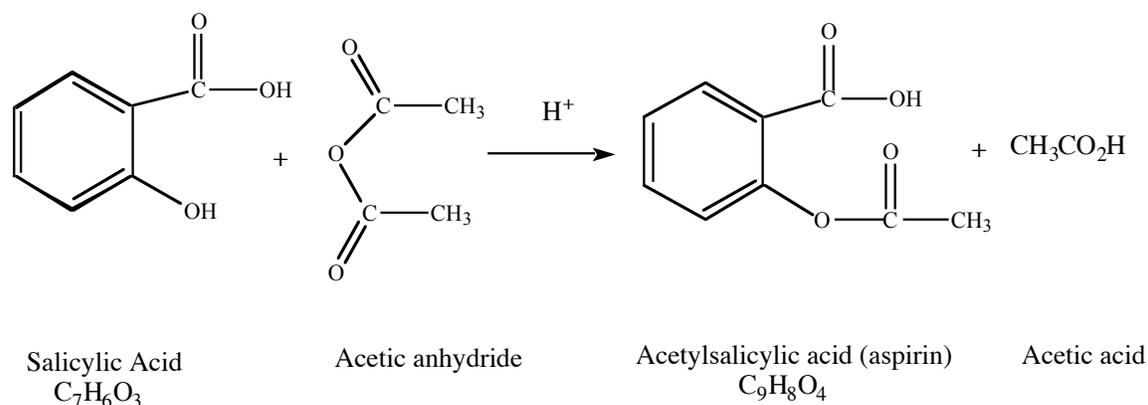


Acetylsalicylic acid (aspirin)
 $C_9H_8O_4$

Salicylic acid contains a phenol group, and phenols are known to be irritating. The Bayer Company replaced the phenol group with an ester group. This esterified compound (acetylsalicylic acid, also known as aspirin) was shown to be much less irritating than salicylic acid. Unfortunately, it is still irritating to the stomach and can cause hemorrhaging of the stomach walls.

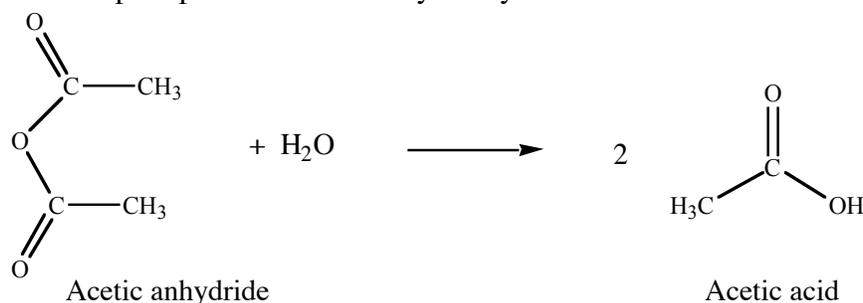
An aspirin tablet contains a small amount of aspirin (usually 300-400 mg) in a starch “binder” and sometimes contains other ingredients like caffeine and buffers. When aspirin is ingested, it is broken down to salicylic acid by the basic conditions in the small intestine. It is then absorbed into the bloodstream.

Aspirin can be made by reacting salicylic acid with acetic acid in the presence of an acid catalyst. The phenol group on the salicylic acid forms an ester with the carboxyl group on the acetic acid. However, this reaction is slow and has a relatively low yield. If acetic anhydride is used instead of acetic acid, the reaction is much faster and has a higher yield (since acetic anhydride is much more reactive than acetic acid). The reaction is shown on the following page.



In this experiment, the salicylic acid is the limiting reactant and the acetic anhydride is in excess. After the reaction heating period is over, the excess unreacted acetic anhydride will be destroyed by the addition of water to the mixture: water reacts with acetic anhydride to form 2 molecules of acetic acid, according to the reaction shown below.

When the esterification reaction is complete, water will be added to the mixture. This will cause the precipitation of the acetylsalicylic acid and will react with any



remaining acetic anhydride. The solid aspirin will be collected using vacuum filtration. Any other reaction ingredients that are soluble (this includes acetic acid, phosphoric acid, and water) will pass through the filter paper.

The collected aspirin will be tested for its purity using $FeCl_3(aq)$. Iron (III) ion reacts with phenols to form a purple complex. Salicylic acid contains a phenol group, but acetylsalicylic acid does not. Therefore, if you add $FeCl_3$ to an aspirin sample and you see a purple color, it means that there is still some salicylic acid present and the sample is impure.

The aspirin collected will then be purified by recrystallization. In this purification method, the crude aspirin will be dissolved in a small amount of warm ethanol. Water will then be added and the solution will be cooled slowly and then chilled. The acetylsalicylic acid will recrystallize, and the solid impurities (unreacted salicylic acid) should remain dissolved in the solution. The solid aspirin will again be collected using vacuum filtration and tested for purity. This aspirin should be more pure than the original aspirin.

The final product will be dried and weighed and the theoretical and percent yields will be calculated.

Safety Precautions:

- Acetic anhydride is irritating to the nose and sinuses. Keep this compound under the hood at all times, and avoid breathing the vapors.

- The aspirin that you make in this lab is NOT pure enough to be taken internally! **Do not ingest the aspirin!**
- Avoid touching the chemicals.
- Wear your safety goggles.

Waste Disposal:

- All waste must be placed in the **organic** waste containers (which have a pink label) in one of the fume hoods.

Procedure

Part 1: Preparation of Aspirin

1. Weigh out about 1 gram of salicylic acid on a piece of weighing paper. To do this, first weigh a piece of weighing paper. Place some salicylic acid on the weighing paper and weigh again. Add or remove solid until you have about 1 gram of it on the paper. Record the mass of the weighing paper plus the solid. Subtract to determine the mass of the salicylic acid. Place this solid into a 50-mL Erlenmeyer flask.
2. **In the hood**, measure out 3.0 mL of acetic anhydride in a small graduated cylinder and add it to the flask. From this point on, keep your flask under the hood, because it now contains acetic anhydride (the vapors of acetic anhydride are very irritating).
3. Add 3 drops of concentrated (85%) phosphoric acid. This will be the catalyst for the reaction. Add a magnetic stirring bar to the flask.
4. In the hood, set up a ring stand and set a hot plate/magnetic stirrer on the base of the ring stand. Put some water in a glass crystallization dish and set this on the hot plate – this will be your hot water bath. Put your reaction flask in the water bath, and secure it in place with a utility clamp attached to the ring stand. (See the picture below.)



Reaction mixture setup

5. Start heating the reaction, and turn on the magnetic stirrer. Once the water bath starts boiling, start timing the reaction. When the mixture has been allowed to react at 100°C (the temperature of boiling water) for 15 minutes, you can consider the reaction to be complete. During the heating time, put 3 mL of water in each of two test tubes and chill these two test tubes in an ice bath. (These tubes of cold water will be used to rinse the solid aspirin after you collect it on the filter paper.)

6. After the reaction has gone on for 15 minutes at 100°C, add 1 mL of deionized water to the flask. This water will react with any excess acetic anhydride, converting it to acetic acid. Keep the mixture under the hood for a few more minutes – some of the acetic acid that is produced at this step will vaporize, and the vapor is irritating.
7. Turn off the hot plate and carefully remove the reaction flask from the water bath. At this point, the flask no longer needs to be under the hood, since the acetic anhydride is now gone. Add 9-10 mL of deionized water to the flask and swirl it around to mix it. As the flask cools, crystals of aspirin will start to form. When you see crystals, put the flask in an ice bath for 10 minutes. (Aspirin, like many other substances, is more soluble in hot water than in cold water. Therefore, to maximize the amount of crystals, it is best to cool the mixture as much as possible.) If no crystals appear, gently scratch the inside of the flask with a stirring rod.
8. Collect the aspirin crystals by vacuum filtration. To do this, set up a ring stand with a clamp. Clamp a side-arm flask to the ring stand, and connect a piece of rubber tubing to the side-arm. Connect the other end of the rubber tubing to an aspirator in the lab. Put a Büchner funnel with a rubber stopper in the flask. Get a piece of filter paper that fits in the funnel, and place it flat in the funnel. It must be flat and covering all of the holes in the funnel – if it is too large to lie flat, find a smaller piece of filter paper! (See the setup below.)



Vacuum Filtration Setup

9. Turn on the aspirator water full blast and wet the filter paper with a small amount of deionized water. Make sure your setup has a good seal – the water should quickly go through the funnel. Swirl the reaction flask containing the aspirin, and dump it on the filter paper. Scrape out the excess solid in the flask with a rubber policeman (ask for one at the stockroom) and place it on the filter paper. After the liquid has gone through the funnel, pour one of the 3-mL portions of chilled rinse water over the sample to rinse it. When this water has gone through the funnel, rinse the solid with the second chilled portion of water. Leave the setup in place with the aspirator on for several minutes – this will draw air through the sample and will help dry the aspirin.

Part 2: Recrystallization of Aspirin

10. Set aside a small amount of the crude aspirin you obtained in step 9 – you will test its purity later. (You will need enough to test its melting point and to test its reactivity with FeCl_3 .)
11. Transfer the rest of the crude aspirin to a 50-mL Erlenmeyer flask. Add 4 mL of ethanol and warm the flask on a hot plate until all of the solid dissolves. Immediately remove the flask from the heat and slowly add 13 mL of cold water. Crystals should form. Chill this solution in an ice-water bath, and collect the crystals using vacuum filtration as you did in steps 8 and 9.
12. Carefully lift the filter paper with the crystals on it and place it on a clean watch glass. Leave this aspirin in your drawer to dry until the next laboratory period.
13. At the following laboratory period (when your aspirin is dry), weigh the aspirin on a piece of weighing paper or a weighing boat. (You will need to scrape it off of the filter paper.)

Part 3: Purity of Aspirin

14. Using a melting point apparatus, determine the melting point of your crude aspirin and your recrystallized aspirin. (In order to get a meaningful result for the melting point determination, the solids must be **dry**.) The melting point should be recorded as a range – the first reading is the temperature at which the sample starts to liquefy, and the second reading is taken when the sample is completely melted. The melting point of pure aspirin is 135°C , and the melting point of salicylic acid is 158°C . Comment on the purity of your aspirin based on its melting point.
15. For the FeCl_3 test, the samples do not have to be dry. To do the test, get 4 test tubes. Place 1 mL of ethanol and 2 drops of FeCl_3 solution in each tube. Add a few crystals of salicylic acid to one test tube. Add a few crystals of your crude aspirin product to the second tube. In the third tube, place a few crystals of the recrystallized aspirin. Don't add anything else to the fourth tube – it will be your "blank". Shake each of the tubes and record your observations.

Questions

1. Write out the balanced equation for the reaction between salicylic acid and acetic anhydride.
2. Calculate the percent yield for the above reaction if the amount of aspirin obtained was 2.301 g.
3. Calculate the theoretical yield of aspirin if you start with 2.687 g of salicylic acid and an excess of acetic anhydride.
4. If you were to start with 1.00 g of salicylic acid, what volume of acetic anhydride would be needed to completely react with it? The density of acetic anhydride is 1.082 g/mL.
5. According to your results from part 3 of this experiment, what can you say about the purity of your aspirin? Be as specific as possible.
6. Explain why acetic acid is unlikely to be a contaminant in your solid aspirin.
7. Look up and record the boiling point of acetic acid, and explain why only some of it evaporates from the reaction mixture.
8. If you measured the melting point of the solid product from this experiment and obtained a melting range of $122\text{-}128^\circ\text{C}$, what does this tell you?
9. Aspirin that has been stored for a long time may give a vinegar-like odor and give a purple color with FeCl_3 . What reaction would cause this to happen?