

Ester Derivatives of Salicylic Acid

Objective:

Esters are an important class of organic chemical compounds. In this experiment, two esters of salicylic acid with important medicinal properties will be prepared.

Introduction:

Two common esters, acetylsalicylic acid and methyl salicylate, are very important over-the-counter drugs. Since ancient times, it has been known that the barks of certain trees, when chewed or brewed as a tea, had *analgesic* (pain-killing) and *antipyretic* (Fever-reducing) properties. The active ingredient in such barks was determined to be salicylic acid. When pure salicylic acid was isolated by chemists, however, it proved to be much too harsh to the linings of the mouth, esophagus, and stomach for direct use as a drug in the pure state. Salicylic acid contains the phenolic (-OH) functional group in addition to the carboxyl (acid) group, and it is the combination of these two groups that leads to the harshness of salicylic acid on the digestive tract.

Because salicylic acid contains both the organic acid group (-COOH) as well as the phenolic group (-OH), salicylic acid is capable of undergoing two separate esterification reactions, depending on whether it is behaving as an acid (through the -COOH) or as an *alcohol* analog (through the -OH). Research was conducted in an attempt to modify the salicylic acid molecule in such a manner that its desirable analgesic and antipyretic properties would be preserved, but its harshness to the digestive system would be decreased. The Bayer Company of Germany, in the late 1800s, patented an ester of salicylic acid that had been produced by reaction of salicylic acid with acetic acid.

The ester, commonly called acetylsalicylic acid, or by its original trade name (aspirin), no longer has the phenolic functional group. The salicylic acid has acted as an alcohol when reacted with acetic acid. Acetylsalicylic acid is much less harsh to the digestive system. When acetylsalicylic acid reaches the intestinal tract, however, the basic environment of the small intestine causes hydrolysis of the ester (the reverse of the esterification reaction) to occur. Acetylsalicylic acid is converted back into salicylic acid in the small intestine and is then absorbed into the bloodstream in that form. Aspirin tablets sold commercially generally contain binders (such as starch) that help keep the tablets dry and prevent the acetylsalicylic acid in the tablets from decomposing into salicylic acid. Since the other component in the production of acetylsalicylic acid is acetic acid, one indication that aspirin tablets have decomposed is an odor of vinegar from the acetic acid released by the hydrolysis.

Insert illustration of salicylic acid + acetic anhydride → aspirin + acetic acid reaction.

The second common ester of salicylic acid that is used as a drug is methyl salicylate. When salicylic acid is heated with methyl alcohol, the carboxyl group of salicylic acid is esterified, producing a strong-smelling liquid ester (methyl salicylate).

Insert illustration of salicylic acid + methyl alcohol → methyl salicylate + water.

The minty odor of many common liniments sold for sore muscles and joints is due to this ester. Methyl salicylate is absorbed through the skin when applied topically and may permit the pain-killing properties of salicylic acid to be localized on the irritated area. Methyl salicylate is a skin irritant, however, and causes a sensation of warmth to the area of the skin where it is applied. This is usually considered to be a desirable property of the ester. Methyl salicylate is also used as a flavoring/aroma agent in various products and is referred to commercially as oil of wintergreen.

Safety Precautions:

- READ ALL INSTRUCTIONS (in the lab before beginning this lab)
- Safety eyewear approved by your institution must be worn at all times while you are in the laboratory, whether or no you are working on an experiment.

Apparatus/Reagents Required:

Hotplate, suction filtration apparatus, ice, melting point apparatus, salicylic acid, acetic anhydride, methyl alcohol (methanol), 50% sulfuric acid, sodium bicarbonate, 1 M iron(III) chloride

Procedure:

Record all data and observations directly on the report pages in ink.

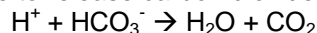
A. Preparation of Aspirin

- Set a 250-mL beaker about half full of water to warm on a hotplate in the exhaust hood. A water heating bath at approximately 70°C is desired, so use the lowest setting of the hotplate control. Check the temperature of the water before continuing.
- Weigh out approximately 1 g of salicylic acid and transfer to a clean, dry 125-mL Erlenmeyer flask. In the exhaust hood, add approximately 3 mL of acetic anhydride (*Caution!*) and 2-3 drops of 50% sulfuric acid (*Caution!*) to the alicylic acid. Stir until the mixture is homogeneous.
- Transfer the Erlenmeyer flask to the beaker of 70°C water (see Figure 31-1) and heat for 15-20 minutes, stirring occasionally. Monitor the temperature of the water bath during this time, and do not let the temperature rise above 70°C.
- *Insert Figure 31-1*
- At the end of the heating period, cool the Erlenmeyer flask in an ice bath until crystals begin to form. If crystallization does not take place, scratch the walls and bottom o the flask with a stirring rod to promote formation of crystals.
- To destroy any excess acetic anhydride that may be present, add 50 mL of cold water, stir, and allow the mixture to stand for a the last 15 minutes to permit the hydrolysis to take place.
- Remove the liquid from the crystals by filtering under suction in a Büchner funnel (see Figure 31-2). Wash the crystals with two 10-mL portions of cold water to remove any excess reagents. Continue suction through the crystals for several minutes to help dry them.
- *Insert Figure 31-2*
- You will perform some tests on this crude product today, and your instructor may ask you to save a small portion of you crystals for a melting point determination to be performed during the net laboratory period. If your instructor directs, set aside a small portion of your crystals in a beaker to dry until the next lab period.
- Dissolve the remaining portion of the aspirin product in 2-3 mL of 95% ethyl alcohol in a 50-mL Erlenmeyer flask. Stir and warm the mixture in the 70°C water bath on the hotplate until the crystals have dissolved completely.
- Add approximately 5-mL of distilled water to the Erlenmeyer flask, and heat to redissolve any crystals that may have formed.
- Remove the Erlenmeyer flask from the hot water bath, and allow it to cool slowly to room temperature. By allowing the solution to cool slowly, relatively large, needle-like crystals of aspirin should form.
- Filter the purified product by suction, allowing suction to continue for several minutes to dry the crystals as much as possible.
- If your instructor has indicated that you will be performing the meltin point determination for your aspirin inn the next lab period, set aside a small portion of the recrystallized product in a labeled test tube or beaker to dry until the next laboratory period.

B. Tests on Aspirin

1. Test with Bicarbonate

Acetylsalicylic acid molecules still contain the organic acid group (carboxyl) and will react with sodium bicarbonate to release carbon dioxide gas:



Add a very small portion of your aspirin (crude or purified) to a test tube. Add also a small portion of sodium bicarbonate. Add a small amount of water and note the evolution of carbon dioxide. This test indicates only that aspirin is an acid; it is not a specific test for aspirin.

2. Test with Iron (III)

If the synthesis of aspirin has not been effective, or is aspirin has decomposed with time, then free salicylic acid will be present. This would be harmful if ingested. The standard United States Pharmacopoeia test for the presence of salicylic acid is to treat the sample in question with a solution of iron(III). If salicylic acid is present, the phenolic functional group (-OH) of salicylic acid present.

Set up four test tubes in a rack. To the first test tube, add a small quantity of pure salicylic acid as a control. To the second and third test tubes, add very small portions of your crude and purified aspirin, respectively. Add 5 mL of distilled water to each test tube, and stir to mix. Add 8-10 drops of iron(III) chloride (ferric chloride) solution. The appearance of a pink or purple color in your aspirin or the commercial table sample indicates the presence of salicylic acid.

3. Melting point determination

After the crude and purified aspirin samples have dried for a week, determine their melting points by the capillary method described in Experiment 4. Compare the observed melting points with the literature value.

C. Preparation of Methyl Salicylate

Place about 1 g (roughly measured) of salicylic acid in a small Erlenmeyer flask and add 5 mL of methyl alcohol. Stir thoroughly to dissolve the salicylic acid.

Add 3-4 drops of 50% sulfuric acid (*Caution!*) and heat the flask in the 70°C water bath on the hotplate in the exhaust hood for approximately 10 minutes.

Pour the contents of the test tube into approximately 50 mL of warm water in a beaker, and cautiously waft some of the vapors toward your nose. There should be a pronounced odor of wintergreen.

Safety Precautions:

- Safety eyewear approved by your institution must be worn at all times while you are in the laboratory, whether or no you are working on an experiment.
- Most of the organic compounds used or produced in this experiment are highly flammable. All heating will be done using a hotplate, and no flames will be permitted in the laboratory.
- Sulfuric acid is used as the catalyst for the esterification reactions. Sulfuric acid is dangerous and can burn skin, eyes, and clothing very badly. If it is spilled, wash immediately before the acid has a chance to cause a burn, and inform the instructor.
- Acetic anhydride is used in the synthesis of aspirin. Acetic anhydride can seriously burn the skin, and its vapors are harmful to the respiratory tract. If spilled, wash immediately and inform the instructor. Confine the pouring and use of acetic anhydride to the fume exhaust hood.

Pre-laboratory Questions

1. From the formulas of salicylic acid and acetylsalicylic acid given in the Introduction to this experiment, determine their molar masses.
2. Suppose 10.0 g of salicylic acid is heated with an excess amount of acetic acid. What is the expected yield of acetylsalicylic acid (aspirin)?
3. Suppose for the experiment outlined in Question 2, only 6.8 g of aspirin is isolated from the reaction mixture. Calculate the percent yield for the process.

Results/Observations

Observations on crude aspirin (appearance):

Observation of recrystallized aspirin (appearance):

Tests on aspirin:

Effect of bicarbonate:

Effect of iron(III) on crude aspirin:

Effect of iron(III) on salicylic acid:

Effect of iron(III) on aspirin tablet:

Melting Points:

Crude aspirin:

Literature value:

Purified Aspirin:

Reference:

Observations on methyl salicylate:

Odor?:

Questions:

1. What acid was used to catalyze the preparation of esters? Could some other acid be used?
2. Aspirin was for many years the major household painkiller, but more recently, other painkillers such as acetaminophen and ibuprofen have become popular. Find the structures of these substances in a chemical dictionary or handbook. Are these substances esters?
3. Arrange the various materials tested with iron(III) in order of increasing purity. How did your impure and recrystallized aspirin samples compare in purity with the commercial aspirin tablet?
4. Suppose instead of reacting salicylic acid with methyl alcohol (Part C), you had reacted it with ethyl alcohol, $\text{CH}_3\text{CH}_2\text{OH}$. Write the equation for the reaction indicating clearly the structure of the ester produced (ethyl salicylate).

[ADDITIONAL LAB for synthesis of ESTERS](#)