

# PREPARATION OF ASPIRIN AND ACETAMINOPHEN

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## OBJECT

To synthesize some common pain relievers: aspirin and acetaminophen.

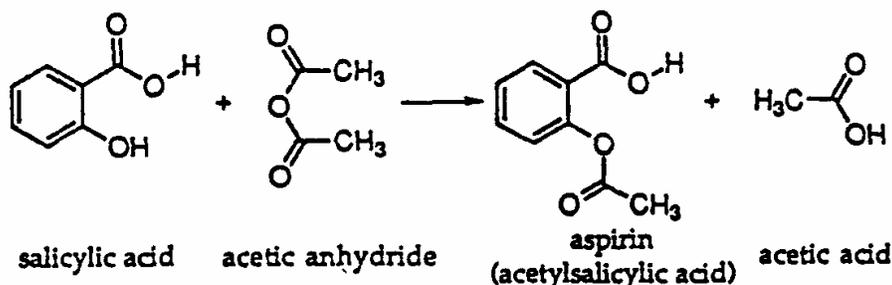
To determine the purity of the aspirin or acetaminophen.

## THEORY

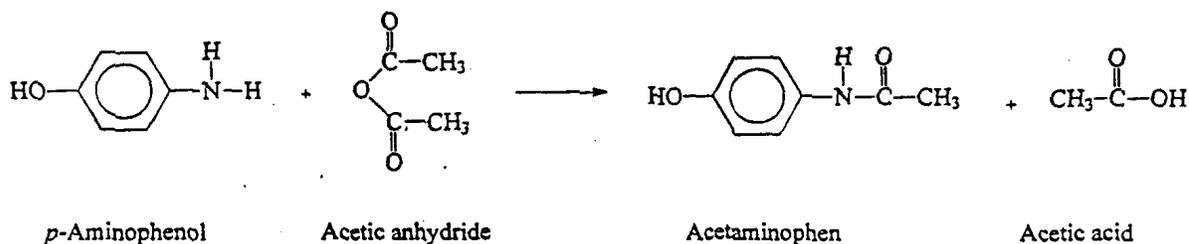
Aspirin, acetylsalicylic acid, was first synthesized in 1893 by Felix Hofmann, a chemist for the German firm of Bayer. This compound had the medicinal properties of salicylic acid, an extract of willow bark, without the unpleasant taste or the high degree of irritation of the mucous membranes lining the mouth, gullet, and stomach.

Aspirin is both an organic ester and an organic acid. It is used extensively in medicine as a pain killer (analgesic) and as a fever-reducing drug (antipyretic). When ingested, acetylsalicylic acid remains intact in the acidic stomach, but in the basic medium of the upper intestinal tract, it hydrolyzes forming the salicylate and acetate ions. However, its additional physiological effects and biochemical reactions are still not thoroughly understood.

Aspirin (molar mass of 180.2 g/mol) is prepared by reacting salicylic acid (molar mass of 138.1 g/mol) with acetic anhydride (molar mass of 102.1 g/mol). Aspirin is a weak monoprotic acid.



Acetaminophen is an amide, a compound that is a derivative of ammonia that has been reacted with an acidic substance, in this case, acetic acid. Acetaminophen acts as a fever reducer and pain reliever. It can be found in several analgesic preparations, such as Tylenol, some of which may contain other ingredients such as caffeine and buffers.



Qualitatively, the purity of an aspirin or acetaminophen sample can be determined from its melting point. The melting point of a substance is essentially independent of atmospheric pressure, but it is always lowered by the presence of impurities (a colligative property of pure substances). The degree of lowering of the melting point depends on the nature and the concentration of the impurities.

## SAFETY PRECAUTIONS

Wear safety glasses or goggles at all times in the laboratory.

Acetic anhydride is corrosive and its vapor is irritating to the respiratory system. Avoid skin contact and inhalation of the vapors. In the event of skin contact, rinse well with cold water. If the vapors are inhaled, move to an area where fresh air is available.

Sulfuric acid is corrosive. Avoid skin contact. In the event of skin contact, rinse well with cold water.

p-aminophenol is harmful by inhalation and by contact with the skin. In the event of skin contact, rinse well with cold water. If the vapors are inhaled, move to an area where fresh air is available.

## PROCEDURE

### OPTION 1: THE PREPARATION OF ASPIRIN

#### Materials Needed

- Salicylic acid
- Acetic anhydride
- Sulfuric acid, concentrated
- Ethanol
- Dropper
- Erlenmeyer flask, 125-mL
- Beakers, 2 400-mL, 100-mL, 10 or 20-mL
- Graduated cylinders, 10-mL, 25-mL
- Watch glass
- Stirring rod
- Vial to hold aspirin sample
- Ring stand
- Clamp (to hold 125-mL Erlenmeyer flask)
- Buchner funnel
- Filter paper to fit Buchner funnel
- Vacuum filtration flask
- Rubber tubing for vacuum flask
- Ice
- Thermometer, 110°C
- Melting point capillary tube
- Melting point apparatus
- dropper
- Disposable IR card
- Optional: rubber gloves

#### Procedure

Weigh out 2.0 g of salicylic acid. Place it in a 125-mL Erlenmeyer flask.

Add 5 mL of acetic anhydride. Swirl the flask to wet the salicylic acid crystals. Add 5 drops of concentrated sulfuric acid,  $\text{H}_2\text{SO}_4$ , to the mixture.

Gently heat the flask in a boiling water bath for about 10 minutes.

Remove the flask from the hot water bath and add 10 mL of deionized ice water to decompose any excess acetic anhydride. Chill the solution in an ice bath until crystals of aspirin no longer form, stirring occasionally to

decompose residual acetic anhydride. If an "oil" appears instead of a solid, reheat the flask in the hot water bath until the oil disappears and again cool.

Set up a vacuum filtration apparatus. Wet the filter paper in the Buchner funnel with 1-2 mL of distilled water. Turn on the water aspirator. Decant the liquid onto the filter paper, minimizing any transfer of the solid aspirin. If some aspirin is inadvertently transferred to the filter, that will not cause any difficulty.

Add 15 mL of cold water to the flask, swirl, and chill again. Pour the liquid and the crystals of aspirin onto the filter paper. Repeat until the transfer of the crystals to the vacuum filter is complete. Wash the aspirin crystals on the filter paper with 10 mL of ice water.

Maintain the vacuum to dry the crystals as best possible.

If aspirin forms in the filtrate in the vacuum flask, transfer the filtrate and aspirin to a beaker, chill in an ice bath, and vacuum filter as before, using a new piece of filter paper. Dispose of the filtrate in the sink.

Determine the mass of the crude aspirin crystals.

### **Recrystallization of the Aspirin.**

The major impurity in aspirin is salicylic acid. It can be removed by a recrystallization.

Place the aspirin crystals in a 100-mL beaker. Add 8 mL of ethanol and 25 mL of water.

Warm the mixture in a 60°C water bath (no flame, use a hot plate or a hot water bath). Warm the mixture until the aspirin dissolves. (If the solid does not dissolve after heating, consult with your instructor.)

Cover the beaker with a watch glass, remove it from the heat, and set it aside to cool slowly. Set the beaker in an ice bath. Beautiful needle-like crystals of acetylsalicylic acid form.

Collect the aspirin by vacuum filtration. Wash the crystals with two 10-mL volumes of ice water. Maintain the vacuum to air dry the aspirin. If time does not permit, place the filter paper and aspirin sample on a watch glass and allow them to air-dry. The time for air-drying the sample may require that it be left with your instructor until the next laboratory period.

Transfer the dry aspirin crystals to a pre-weighed sample container or vial. Determine the mass of the aspirin crystals.

### **Determine the Melting Point of the Aspirin Sample**

Fill a capillary melting point tube to a depth of 0.2 cm with the recrystallized aspirin.

Place the capillary tube in the melting point apparatus. Determine its melting point. (Your instructor will demonstrate the use of this apparatus.)

Pure aspirin melts at 135°C.

The aspirin sample should be labeled with your name, the mass of the aspirin, the percent yield, and its melting point.

**NOTE:** Don't use your aspirin for a headache! Its purity is not assured.

## Verification of Aspirin

Place a small amount of your aspirin sample (about 0.10 g) in a 10-mL or 20-mL beaker. Add approximately 2 mL of ethanol. Stir or swirl to dissolve. If necessary, warm the mixture slightly on a hot plate to assist in solution. CAUTION: Ethanol is flammable. Do not allow it to boil.

Place one or two drops of the acetaminophen solution on a disposable IR card. Allow the ethanol to evaporate.

Run an IR of your aspirin.

Compare your IR spectrogram with the standard IR spectra of salicylic acid and acetylsalicylic acid (aspirin). How do they agree?

## OPTION 2: THE PREPARATION OF ACETAMINOPHEN

### Materials Needed

- p*-aminophenol
- Acetic anhydride
- Phosphoric acid, concentrated
- Ethanol
- Dropper
- Erlenmeyer flask, 125-mL
- Beakers, 2 400-mL, 100-mL, 10 or 20-mL
- Graduated cylinders, 10-mL, 25-mL
- Watch glass
- Stirring rod
- Vial to hold aspirin sample
- Ring stand
- Clamp (to hold 125-mL Erlenmeyer flask)
- Buchner funnel
- Filter paper to fit Buchner funnel
- Vacuum filtration flask
- Rubber tubing for vacuum flask
- Ice
- Melting point capillary tube
- Melting point apparatus
- dropper
- Disposable IR card
- Optional: rubber gloves

### Procedure

Fill a 400-mL beaker about half full with water. Place the beaker and water on a hot plate and bring to a boil.

Weigh out 1.5 g of *p*-aminophenol and transfer it into a 125-mL Erlenmeyer flask. (Avoid contact with skin. You may wish to wear gloves.)

Add 25 mL of water. Add 20 drops of concentrated phosphoric acid,  $\text{H}_3\text{PO}_4$ , and swirl the flask until all of the amine dissolves. If not, add a few more drops of phosphoric acid.

Turn off the hot plate. Place the flask in the hot water. Carefully add 2 mL of acetic anhydride to the flask. Leave the flask in the warm water for 10 minutes.

Remove the flask and place it in an ice-water bath. Stir the mixture to crystallize the acetaminophen. You may need to scratch the walls of the flask to start the crystallization. If no crystals appear, add a small seed of acetaminophen to start the crystal formation. Allow the flask to stay in the ice-water bath for 30 minutes.

Collect the crystals in a Buchner funnel using vacuum filtration.

Wash the crystals with 10 mL of cold water. Allow the crystals to dry.

Determine the mass of the crude acetaminophen.

### **Recrystallization of the Acetaminophen**

Place the crude acetaminophen in a 100-mL beaker. Add 20 mL of water and heat on a hot plate until the crystals dissolve. If the solution boils and crystals remain, add another 10 mL of water.

Remove the beaker and allow the solution to cool. When crystals begin to appear, place the beaker in an ice bath for 20 minutes. If no crystals appear, scratch the inside walls of the beaker.

Collect the crystals using the Buchner filtration apparatus. Wash with 10 mL of cold water.

Transfer the filter paper and crystals to a watch glass and let dry.

Determine the mass of the purified acetaminophen.

### **Determine the Melting Point of the Acetaminophen Sample**

Fill a capillary melting point tube to a depth of 0.2 cm with the recrystallized acetaminophen.

Place the capillary tube in the melting point apparatus. Determine its melting point. (Your instructor will demonstrate the use of this apparatus.)

The melting point of acetaminophen is 169-171°C. p-aminophenol melts at 189-190°C.

The acetaminophen sample should be labeled with your name, the mass of the acetaminophen, the percent yield, and its melting point.

**NOTE:** Don't use your acetaminophen for a headache! Its purity is not assured.

### **Verification of Acetaminophen**

Place a small amount of your acetaminophen sample (about 0.10 g) in a 10-mL or 20-mL beaker. Add approximately 2 mL of ethanol. Stir or swirl to dissolve. If necessary, warm the mixture slightly on a hot plate to assist in solution. **CAUTION:** Ethanol is flammable. Do not allow it to boil.

Place one or two drops of the acetaminophen solution on a disposable IR card. Allow the ethanol to evaporate.

Run an IR of your acetaminophen.

Compare your IR spectrogram with the standard IR spectra of p-aminophenol and acetaminophen. How do they agree?

# Report Sheet

## PREPARATION OF ASPIRIN AND ACETAMINOPHEN

Name \_\_\_\_\_

Course/Section \_\_\_\_\_

Partner (If applicable) \_\_\_\_\_

Date \_\_\_\_\_

### DATA

#### A. Preparation of Aspirin

Mass of salicylic acid \_\_\_\_\_ g

Mass of crude aspirin \_\_\_\_\_ g

Mass of purified aspirin \_\_\_\_\_ g

Theoretical yield of aspirin (show calculation below) \_\_\_\_\_ g

Percent yield of aspirin (show calculation below) \_\_\_\_\_ %

Melting point of aspirin \_\_\_\_\_ °C

Does the infrared spectrum of your aspirin sample confirm the identity of your product? (Attach the IR spectrograph to your report sheet.)

Based on your melting point and infrared data, the aspirin sample is (check one)  
 crude    purified

## B. Preparation of Acetaminophen

Mass of p-aminophenol \_\_\_\_\_ g

Mass of crude acetaminophen \_\_\_\_\_ g

Mass of purified acetaminophen \_\_\_\_\_ g

Theoretical yield of acetaminophen (show calculation below) \_\_\_\_\_ g

Percent yield of acetaminophen (show calculation below) \_\_\_\_\_ %

Melting point of acetaminophen \_\_\_\_\_ °C

Does the infrared spectrum of your acetaminophen sample confirm the identity of your product?  
(Attach the IR spectrograph to your report sheet.)

Based on your melting point and infrared data, the acetaminophen sample is (check one)  
 crude  purified