School of Engineering
Institute of Materials
Laboratory of Macromolecular
and Organic Materials

Organic Chemistry (MSE 211)

Synthesis and Purification of Aspirin

1. Introduction

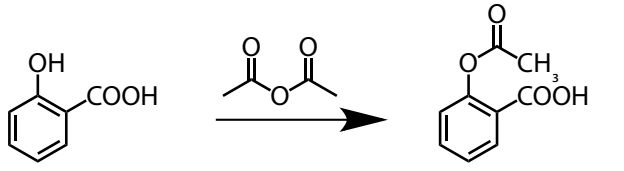
Aspirin, or acetylsalicylic acid, is one of the most widely used anti-inflammatory and analgesic drugs. Its therapeutic effect arises from the inhibition of cyclooxygenase enzymes, which catalyse the formation of prostaglandins, key mediators of pain, inflammation, and blood coagulation.

In this experiment, aspirin is synthesized through the acetylation of salicylic acid. The transformation proceeds via a nucleophilic substitution at a carbonyl center. While this reaction is carried out industrially on a tonne scale, the purpose of this laboratory experiment is to synthesize and purify aspirin on the gram scale.

See also: *Chapter 4.5* of the class.
Reading Recommendation: *McMurry,* 7th ed., chapters 21.2-21.5; *Clayden*, Chapter 12.

2. General Principle of the Synthesis

Acetylsalicylic acid is prepared by an esterification of salicylic acid with acetic anhydride in the presence of a catalytic amount of sulfuric acid. The reaction takes place without an additional solvent. The crude aspirin is separated from the catalyst and acetic acid by washing with water (in which aspirin is only poorly soluble) and then purified by recrystallization from ethanol/water.



salicylic acid — acetylsalicylic acid

3. Required Equipment

- A 100 mL three-necked round-bottom flask
- A DrySin©, heating plate, magnetic stirrer
- Thermometer
- Reflux condenser
- Büchner funnel
- Spatula

4. Experimental Procedure

Salicylic acid (72 mmol) is put into a 100 mL three-necked, round-bottom flask. Acetic anhydride (14 mL) is added under vigorous stirring. Five drops of concentrated sulfuric acid are added, and the mixture is stirred at 60 °C for 15 min. The mixture is cooled to room temperature and then, 70 mL of water is added. A colorless solid forms that is collected over a Büchner funnel. The solid is washed with 150 mL water.

5. Purification

The crude aspirin is recrystallized from ethanol/water (2:5). Use 10 mL of this solvent mixture. The crystals are collected over a Büchner funnel and dried in an oven. The dry crystals are weighed to determine the yield of the reaction.

6. Control of the Purity

The melting point (MP) of the dry sample is measured and compared with the literature-known value (135 °C).

Analyze the ^{1}H-NMR spectrum of the starting and target compound dissolved in $CDCl_3$ and compare them.

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Learning Objective: **Melting Point**

The melting point (MP) is the temperature at which a solid substance changes to the liquid state.

For a pure and crystalline substance, the melting point is a characteristic physical property of the substance. It is therefore used as a first check of the identity of a substance, but more importantly as a qualitative measure of purity, since all impurities reduce the melting point.

In the most common method for melting point determination, a small amount of the solid is collected in a glass capillary tube, which is slowly heated within a "melting point apparatus" until the solid melts.

In practice, two temperatures are observed: the temperature at which the liquid state begins to appear (starting temperature of melting) and the disappearance of the last solid trace (end temperature of melting). Both temperatures define the melting range.

In organic chemistry, the melting range is always reported, and not a single temperature, e.g. MP = 122-124 °C indicates that melting began at 122 °C and ended at 124 °C.

Recording the two temperatures is important

7. End of the Manipulation

1.) Aspirin is weighed in a glass vial labelled with compound name, student name, and date.

2.) All starting materials and chemicals are put back into the retention trays.

3.) The glassware is cleaned from any contaminant and put into the dishwasher. Remaining trances of chemical compounds are removed by rinsing the flask with a minimum of solvent (for example acetone), which is subsequently disposed as non-halogenated organic solvent waste. Clean glass ware from the dishwasher is placed pack into its original location.

4.) The fume hood is tidied up. All electrical appliances are unplugged. Ventilation and lighting of the hood are switched off.

5.) The sink (if used) is cleaned.

6.) All waste contaminated with chemicals (absorbent paper, etc.) is collected in specific recovery cans, according to the indications of the assistants.

8. To be Addressed in the Protocol

1.) Give a detailed reaction mechanism including the elementary steps.

2.) What is the reactivity of acetic anhydride compared to other carbonyl functions (carboxylic acids, acyl chlorides, esters, ketones, aldehydes).

3.) What is the purpose of the catalytic amount of sulfuric acid? Would it make sense to use a base for the activation of the nucleophile?

4.) Calculate the yield of the reaction. What is the relevance of this value?

5.) Why is acetylsalicylic acid less soluble in water than salicylic acid?

Be sure you have also completed the prelab protocol with the relevant safety information (**BEFORE** the lab course).

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