The Synthesis of a Medicinal Agent- Aspirin

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Introduction

Salicylic-acid-containing compounds derived from willow bark have been in use for hundreds of years as antipyretic (fever-reducing), analgesic (pain killing), and anti-inflammatory agents. It was eventually discovered that salicylic acid is the portion of these molecules responsible for the therapeutic effect. Two ester derivatives of this acid, synthesized as shown, are currently in common medicinal use: methylsalicylate (oil of wintergreen) for external applications and acetylsalicylic acid (aspirin) for internal consumption. The particular derivatives are chosen for their effectiveness in penetrating the physiological environment in the respective application-the skin or the intestines. Once within the body tissue, both compounds are hydrolyzed to a salicylic acid, the active agent. This experiment will demonstrate the preparation of aspirin.

Aspirin is superior to salicylic acid for oral dosage in that the latter is very bitter, and causes stomach upset. The aspirin possesses these properties to a markedly lesser degree and passes through the stomach largely unchanged, undergoing hydrolysis only in the small intestine and after absorption in the blood stream. This temporarily masking of a physiologically active compound, to facilitate oral ingestion or prevent decomposition during transport to the site of activity within the body, is a very common strategy in drug design.
The esterification reactants written above do not proceed fully to completion. A convenient way to obtain complete reaction in the preparation of an acetate ester is to use acetic anhydride.

![Chemical reaction diagram]

The reaction is catalyzed by concentrated phosphoric acid. Excess acetic hydride may be used in this reaction as the un-reacted portion is hydrolyzed after reaction is complete with water.

The acetic acid is produced is removed by filtration of the acetic acid-water solution to yield aspirin crystals. Trace amounts of salicylic remaining are removed by recrystallization from an ethanol/water solvent pair.

Purification of a solid by crystallization from a solvent-pair

Occasionally a mixture of two solvents (solvent-pair) is more satisfactory than a single solvent for recrystallization. Such solvent-pairs are made up of two miscible liquids, one of which dissolves the substance readily and another which dissolves it very sparingly. Examples of solvent-pairs are: ethanol and water, glacial (pure) acetic acid and water, diethyl ether and petroleum ether, and benzene and ethyl acetate. A typical procedure in using a solvent pair such as ethanol and water, is to dissolve the substance in ethanol at the boiling-point and add water dropwise, with shaking or stirring, until a faint turbidity persists in the hot solution. A few drops of ethanol are then added until the solution clears. The hot solvent mixture is then not quite saturated with the solute and is treated subsequently in the usual way (decolorized with charcoal (if necessary), filtered hot (if treated with charcoal), cooled, filtered, and washed.).
Experimental procedure

CAUTION: WEAR SAFETY GLASSES  Do experiment with your lab partner

Preparation of Aspirin

In a 125 ml Erlenmeyer flask place 4 g of pure salicylic acid. Add 10 ml of acetic anhydride in such a way as to wash down any material adhering to the walls of the flask, and then 10 drops of syrupy (85 percent) phosphoric acid. (CAUTION- concentrated phosphoric acid can cause chemical burns, handle with care!). Run the synthesis reaction by heating the flask for ten minutes in a boiling hot water bath (set up the bath in the hood). After heating is completed, remove the flask from the bath, tilt the mouth of the flask away from you, and add 4 ml of cold water to the flask. This process decomposes the excess acidic anhydride and should be carried out in the fume hood. After decomposition of the acetic anhydride, add 40 ml of water and let the flask cool to room temperature. Aspirin crystals will form as the flask cools. If no crystals form, cool the flask further in an ice bath. When crystallization is complete, cool the flask below room temperature with an ice bath and vacuum filter Set up the filtering apparatus while waiting for the flask to cool.) Wash the collected product with cold water and dry as much as possible on the Buchner funnel. Weigh the aspirin obtained by putting the aspirin in a clean, weighed beaker. You may want to test the aspirin for trace amounts of salicylic acid (see next paragraph) before weighing the aspirin.

Testing aspirin for trace salicylic acid

Using a scupula, place a few crystals of aspirin in the bottom of a test tube and then dissolve the aspirin in about 1 ml (an eye dropper full) of methanol. Add three or four drops of iron(III) chloride (FeC1₃) solution to the aspirin solution and record the color. Perform the same test on salicylic acid. If your aspirin tests positive for salicylic acid, recrystallize the impure aspirin using the procedure in the following section.

Recrystallization of salicylic acid contaminated aspirin

Dissolve the impure aspirin in 15 ml of ethyl alcohol, in a 150 ml beaker, then warm on a hot plate and pour into the solution 25 ml of warm water. If a solid separates at this point, continue warming until solution is transparent, then cover the beaker with a watch glass and set aside to cool slowly. Note, if warming the water/alcohol/aspirin mixture does not form a solution, add more alcohol in 5 ml increments until the mixture is transparent. After crystals form, collect the crystals using vacuum filtering. Wash the collected crystals with ice water and then test for salicylic acid. Weigh and determine the melting point of the pure aspirin.
Report Sheet

Name ____________________ Date __________ lab sheet __________ desk #_________

a. Preparation of aspirin

Equation for formation of aspirin : _____________________________

Weight of salicylic acid used _________g

Weight of aspirin obtained (crude) _________g

Weight of aspirin obtained (recrystallized) _________g

Weight of aspirin theoretically obtainable* _________g

Percentage of theoretical yield obtained _________g

B. Melting point of aspirin

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<tr>
<th></th>
<th>Crude</th>
<th>Recrystallized</th>
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<tr>
<td>Observed melting point of aspirin</td>
<td>_________°C</td>
<td>_________°C</td>
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<tr>
<td>Literature value</td>
<td>_________°C</td>
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*The chemical equation corresponding to the synthesis reaction is:

\[ \text{C}_7\text{H}_6\text{O}_3 + (\text{CH}_3\text{CO})_2\text{O} \rightarrow \text{C}_9\text{H}_8\text{O}_4 + \text{CH}_3\text{COOH}. \]

Salicylic acid  Acetic anhydride  Aspirin  Acetic acid

Please use this balanced equation and the weight of salicylic acid used to calculate the theoretical yield.
Questions

1. What is acetylation? Into what general class of reactions does acetylation fall?

2. How does the structure of salicylic acid differ from that of benzoic acid?

3. What is buffered aspirin? Why is buffered aspirin used?

4a. Compare the structural formulas of salicylic acid and aspirin and determine which functional group in organic chemistry gives a positive test with FeCl₃?

4b. How might the FeCl₃ test be useful in the preparation of a large-scale batch of aspirin?

4. On a long standing, an opened bottle of aspirin will develop an odor of vinegar. What causes this to happen?

6. A regular dose aspirin contains 325 mg of aspirin. How many aspirin tablets could be made from the aspirin prepared?