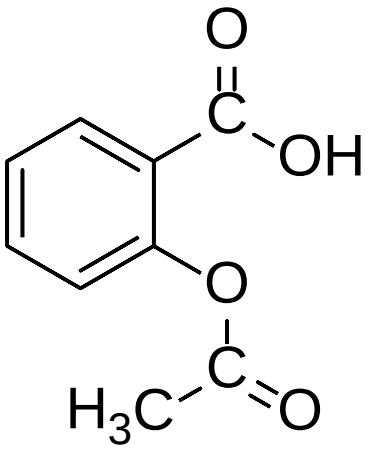
Synthesis of Aspirin

Aspirin (acetylsalicylic acid) is a synthetic organic derived from salicylic acid. Salicylic acid is a natural product found in the bark of the willow tree and was used by the ancient Greeks and Native Americans, among others, to counter fever and pain. However, salicylic acid is bitter and irritates the stomach.

In a Bayer laboratory in Wuppertal, Germany, Dr. Felix Hoffmann was the first to succeed in synthesizing a chemically pure and stable form of acetylsalicylic acid in 1897, which became the active ingredient in Aspirin.

Synthesis of Aspirin

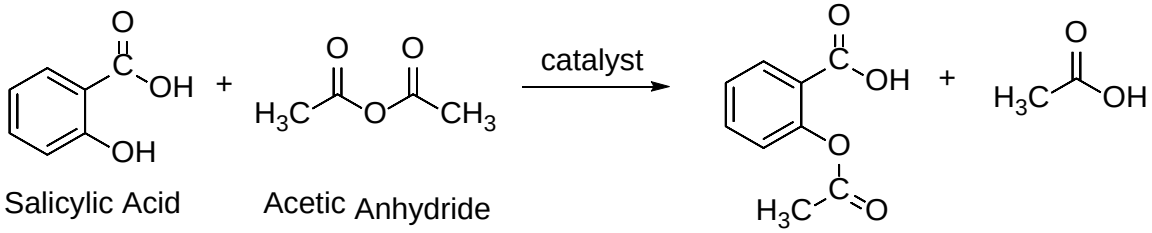
Aspirin is the most frequently sold pain reliever in the world, has been the subject of a Nobel prize (1982), and has been termed the ‘wonder drug’ of the century. It is singlehandedly responsible for the foundation and success of Bayer Pharmaceuticals (2019 revenue: 49 billion US Dollars).



Advertisement on a car in Netherlands 1929

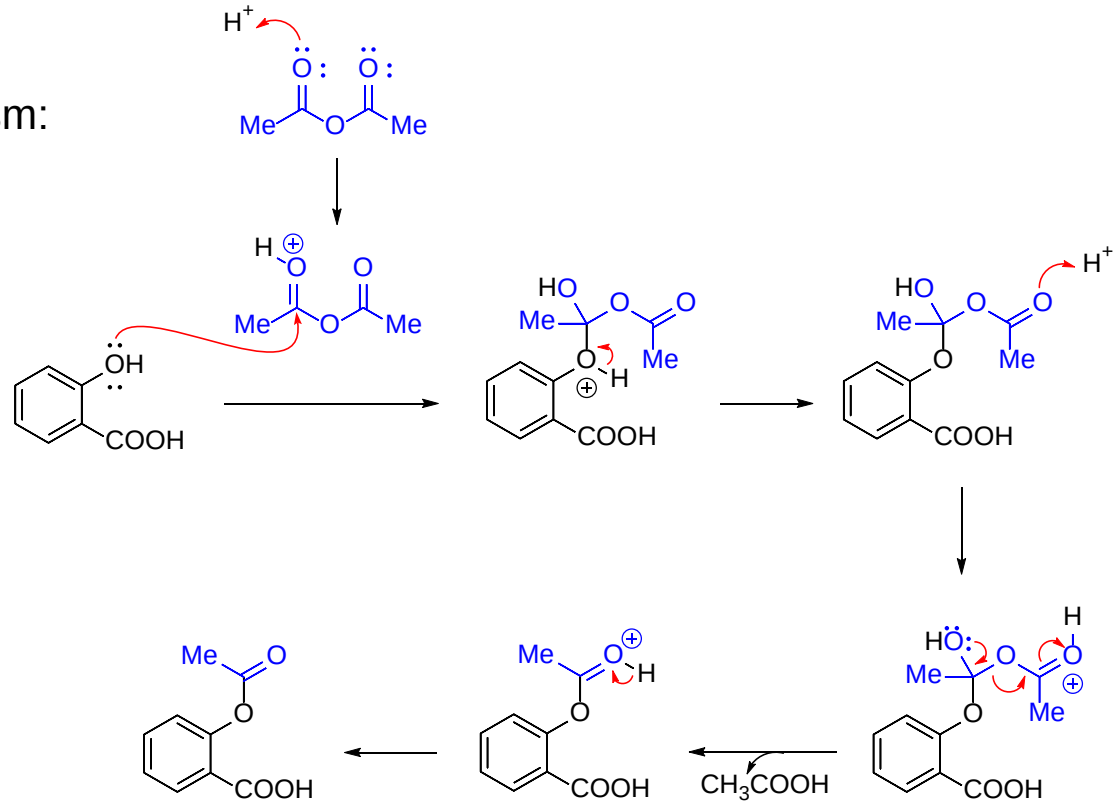
“No other drug in the world has had such a fascinating and record-breaking history – a development that has not yet come to an end.”
Sir John Vane (Nobel Prize Winner 1982)

Theoretical Background



Acetylation of salicylic acid leads to the product. Acid is used as a catalyst for this reaction.

Plausible Mechanism:

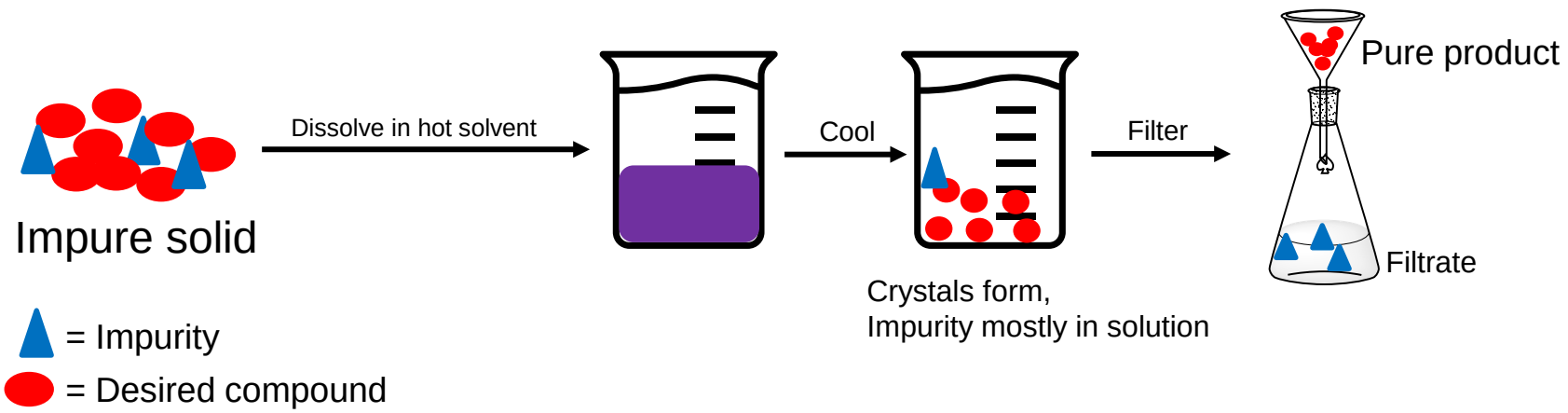


Recrystallisation

Solid organic compounds when isolated from organic reactions are seldom pure: they are usually contaminated with small amounts of other compounds (impurities) which are produced along with the desired product. The purification of impure crystalline compounds is usually effected by crystallization from a suitable solvent or mixture of solvents.

The purification of solids by crystallization is based upon differences in their solubility in a given solvent or mixture of solvents. In its simplest from, the crystallization process consists of:

(i) dissolving the impure substance in some suitable solvent at or near the boiling point
(ii) filtering the hot solution from particles of insoluble material and dust
(iii) allowing the hot solution to cool thus causing the dissolved substance to crystallize out
(iv) separating the crystals from the supernatant solution (or mother-liquor).

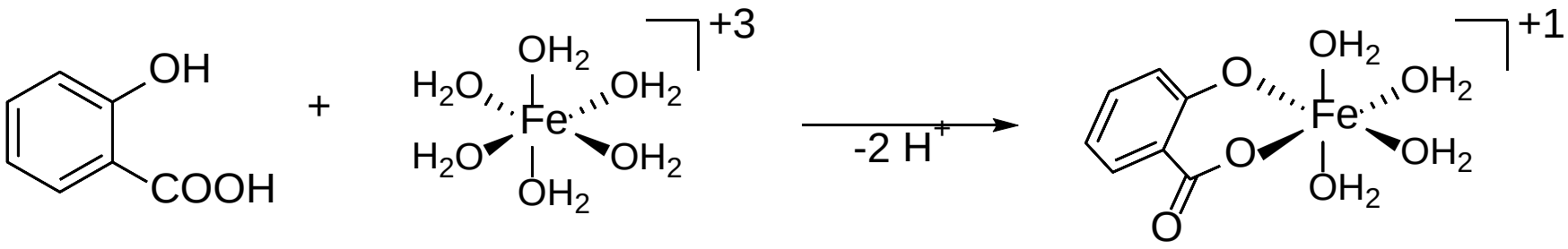


Test with Ferric Chloride

We can verify whether salicylic acid has been transformed to acetyl salicylic acid
By a performing a test with ferric chloride ($FeCl_3$)

$FeCl_3$ reacts with the phenolic group and forms a chelate complex of purple colour

Thus, a test reaction of salicylic acid with $FeCl_3$ should result in purple colour whereas aspirin should not result in such a colour change



Purple colour

Depending on the concentration of the reagent, mono to trichelate rings may be formed

Experimental Protocol

Synthesis

1.Take X g of salicylic acid (Mol. Wt. 138.12 g/mol) and transfer it to a dry 150 mL conical flask.
2. Add 2.7 equivalents of acetic anhydride (Mol. Wt. 102.08 g/mol; Density 1.08 g/mL) using a measuring cylinder to the salicylic acid. Now add 5-6 drops of concentrated sulfuric acid and stir until all salicylic acid is dissolved.
3. Leave the reaction mixture undisturbed for 15-20 minutes.
4. Add 50 mL of water to the flask and swirl for two minutes and filter using a (Buchner) funnel.
5. Collect the solid from the filter paper.

Recrystallization

1. Dissolve the crude product in 7 mL of ethanol in a beaker and add 15 mL of distilled water. Heat on water bath till you get a clear solution.
2. Allow the solution to cool in an ice bath without disturbing. Pure acetylsalicylic acid crystallizes.
3. Filter the pure product and dry it by placing in between sheets of filter paper. Report the percentage yield.
4. Dissolve a few crystals of the dry compound in 0.5 mL methanol and add 2 drops of $FeCl_3$ solution. Note the color change. Repeat the above test with similar amount of salicylic acid and note the color change.
5. Determine the melting point of acetylsalicylic acid.

Observations and Calculations

To calculate the amount of acetic anhydride needed for X grams of salicylic acid

We have been asked to add 2.7 equivalents of acetic anhydride with respect to salicylic acid

Salicylic acid : Mol. Wt. 138.12 g/mol
Acetic anhydride : Mol. Wt. 102.08 g/mol; Density 1.08 g/mL

Moles of salicylic acid = X grams / 138.12
Suppose X = 2.0 grams; moles of salicylic acid = 2.0 / 138.12 = 0.0144 moles

Hence moles of acetic anhydride = 0.0144 x 2.7= 0.0388 moles
Grams of acetic anhydride = 0.0388 moles x 102.08 g/mol = 3.96 grams

Acetic anhydride is a liquid, and we can calculate the volume using the given density

Volume of acetic anhydride = 3.96 / 1.08 = 3.67 mL

Observations and Calculations

To calculate percentage yield

Percentage yield = (Actual Yield / Theoretical Yield) x 100

From the chemical equation we know that one mole of salicylic acid will give one mole of acetyl salicylic acid

Again, assuming we started with 2.0 grams of salicylic acid
Moles of salicylic acid = 0.0144 moles
Hence, we should get 0.0144 moles of acetyl salicylic acid
Molecular weight of acetyl salicylic acid = 180.158 g/mol

0.0144 moles = 2.594 grams of acetyl salicylic acid – This is our theoretical yield

Actual Yield = Grams of product obtained by performing the reaction
Let us assume that we obtained 1.34 g of aspirin from our synthesis

Percentage Yield = (1.34/2.594) x 100 = 51.66 %

Results

- Acetylsalicylic acid was synthesized from salicylic acid
- Actual Yield : 1.34 g
- Percentage Yield: 51.66%
- Melting Point of acetyl salicylic acid : 134-136 °C
- Ferric chloride test confirms the absence of phenolic group in acetyl salicylic acid