

Reminder: These notes are meant to supplement, not replace, the laboratory manual.

Synthesis of Aspirin Notes

History and Application.

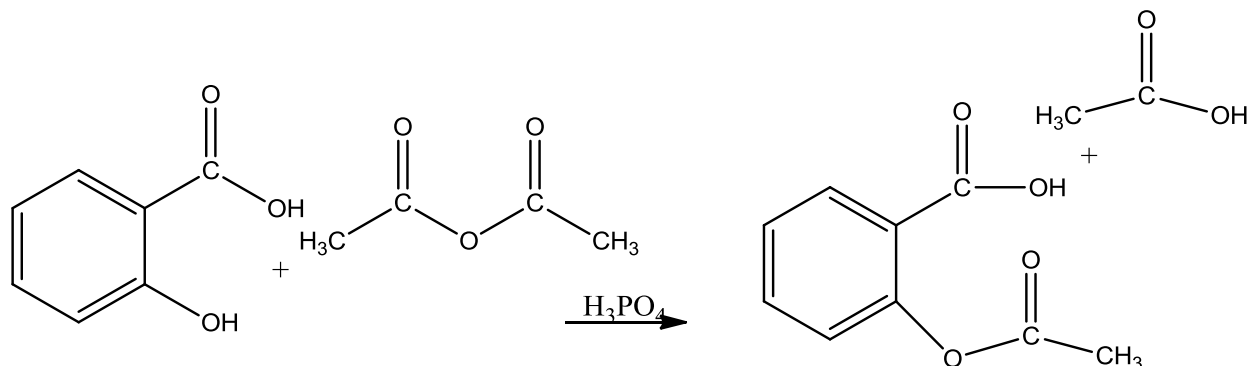
Aspirin is one of the most commonly used drugs in the world with approximately 100 billion tablets¹ being consumed annually. Salicylic acid is a precursor of aspirin. Salicylic acid is found naturally in willow tree bark. Hippocrates, the father of medicine, documented the use of willow tree bark as a medicine in the 4th century B.C.E². The first modern documentation of medicinal use of willow bark occurred in 1763³. The material within willow bark that was responsible for the analgesic effect was isolated in 1826. Salicylic acid is a purified version of this material. Salicylic acid was prescribed to patients by physicians starting around 1850. Salicylic acid is very harsh on stomach linings and many people could not tolerate its use⁴. Salicylic acid is no longer used for oral consumption but can be found in many skin creams, wart removal, and pimple creams⁵. When salicylic acid is acetylated (an acetyl group is added to the phenol group) it is much less irritating to the stomach. Aspirin is Acetylsalicylic acid. Bayer® company first manufactured and sold Aspirin in 1899^{2,6}. Aspirin has since been shown to prevent and reduce the severity of heart attacks. Many people with heart conditions are put on a daily aspirin regimen⁷. If you believe someone may be having a heart attack, it is recommended by that you give that person an aspirin immediately to reduce damage⁸.

Safety Precautions^{9,10}

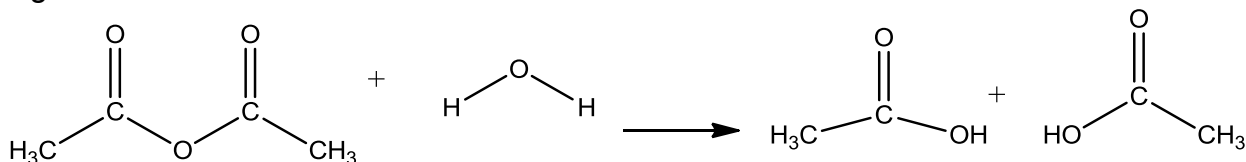
Acetic Anhydride is corrosive, reacts violently with water, is toxic by inhalation, harmful by ingestion and a lachrymator (makes eyes hurt and water severely). Keep reaction in the hood until quench water has been added.

Salicylic Acid causes mild skin irritation. Causes severe eye damage. Ethyl acetate and hexanes are flammable organic solvents. Phosphoric Acid is a strong acid. It will cause immediate destruction of tissue upon contact. Avoid all direct contact. Wash with copious amounts of water if accidental contact is made.

1. In this experiment salicylic acid will be acetylated by acetic anhydride and acetyl salicylic acid, aspirin, will be formed¹¹. Here is the balanced equation for the reaction:



2. Salicylic Acid is o-hydroxy benzoic acid. This compound has both a phenol functional group and a carboxylic acid. Acetic anhydride is an anhydride. Aspirin is a carboxylic acid and an ester. Acetic acid is a carboxylic acid. Phosphoric acid is added as a catalyst. After the reaction is complete, water is added to quench (destroy) any remaining acetic acid and turn it into acetic acid.



The water adds across the anhydride bridge, cleaving it, and releasing two acetic acid molecules. Acetic acid is much less reactive than acetic anhydride.

3. Solubility. Both salicylic Acid and aspirin are slightly soluble in water at room temperature (~0.2 g/100mL). A minimum of water needs to be used in order to induce the product aspirin to precipitate out of solution as a solid. The solution will be iced after crystals start to form to reduce solubility of the product in the water further and increase the percent yield.

4. The solids recovered after the reaction has been carried out will be analyzed by TLC. The solvent that will be used will be 50 % ethyl acetate 50 % hexanes¹². If you have forgotten how to set up, develop, calculate R_f, or interpret TLC, then re-read the on-line notes relating to TLC from 2230L.

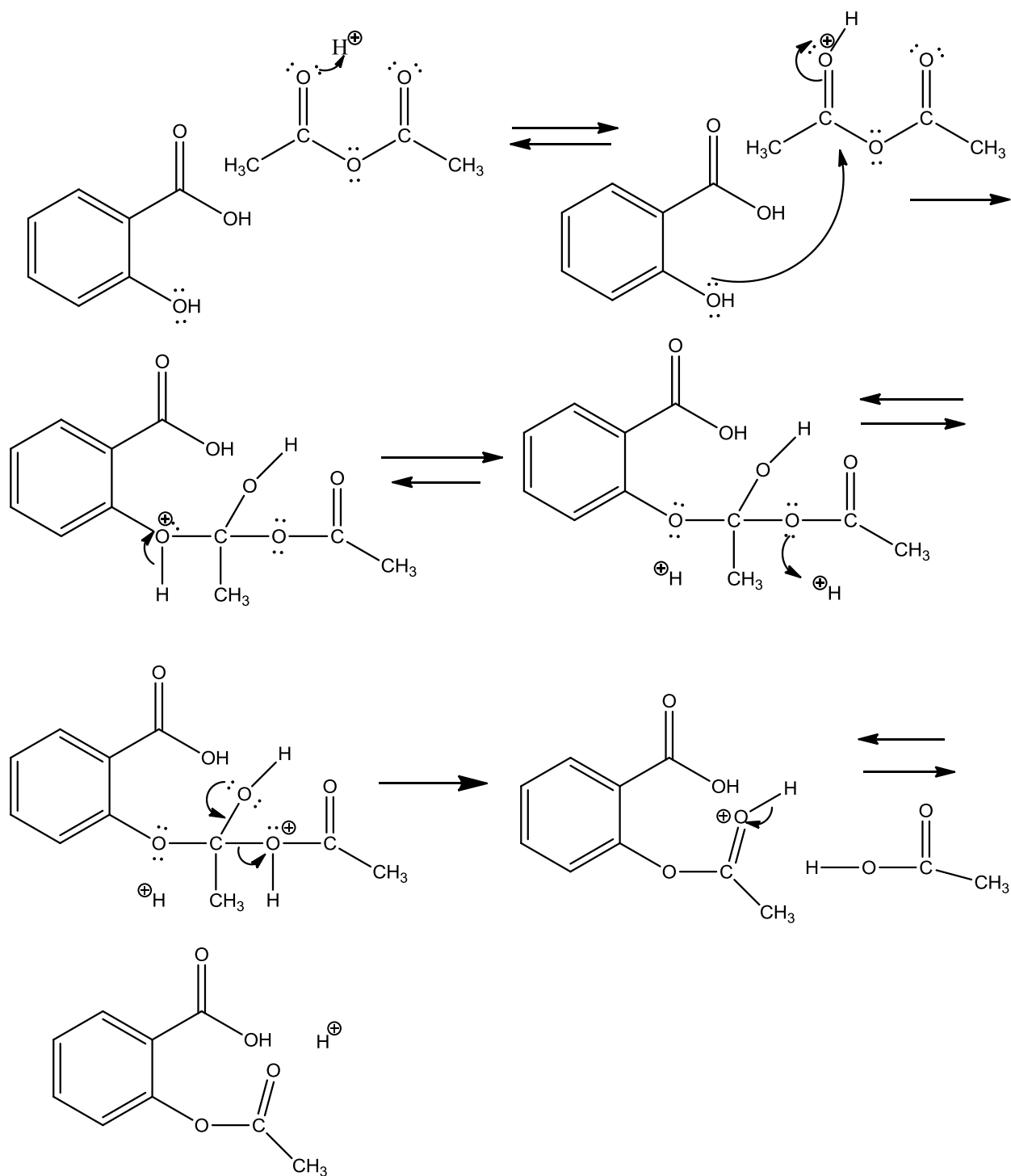
5. Mechanism¹³:

Phosphoric acid is added as a catalyst. It is a strong acid (pK_a ~2.1) so there are many available protons. Concentrated phosphoric acid is 85% wt H₃PO₄ in water.



The synthesis is acid catalyzed.

First there is a reversible reaction in which the oxygen of the carbonyl of the acetic anhydride is protonated. This increases the electrophilicity of the carbon of that carbonyl. The oxygen of the phenol in salicylic acid acts as a nucleophile and attacks the carbon of the carbonyl within acetic anhydride and simultaneously breaks the π bond to oxygen. This forms a tetrahedral intermediate. A series of proton transfers occur. The electrons on the oxygen of the hydroxyl group on the tetrahedral intermediate, ultimately come down and reform a carbonyl group, this simultaneously induces an acetic acid to leave. After one additional proton transfer, the final aspirin is formed.



6.Purity. The chemical structure of the acetylsalicylic acid we produce in the lab is identical to the structure of the acetylsalicylic acid found in commercial aspirin

tablets. What is the difference between the solid we produce in lab and aspirin tablets? It is highly ill advised to eat the solid formed from this experiment. Why?

References:

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