21. Synthesis of an Analgesic: Aspirin

A. Background

Aspirin (acetylsalicylic acid) belongs to a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs), which work by blocking the synthesis of prostaglandins in the body. Before exploring the chemistry of aspirin, one should understand the biological process of inflammation.

Inflammation in the body occurs in response to the presence of harmful stimuli including: the presence of a foreign organism, nerve damage, and tissue irritation. Symptoms of inflammation include: redness, swelling, pain, and loss of mobility at the affected site. The experience of pain in the body begins with the stimulus invoking an immune response. To combat the stimulus, the brain signals the body to begin a number of biological cascade reactions that include the synthesis of histamine, bradykinin, and prostaglandins, all of which contribute to the experience of inflammation and pain. During an inflammation response, prostaglandins are synthesized from the ω-6 fatty acid, arachidonic acid, which comes from our diet and can be synthesized in the body from linoleic acid. An important enzyme in the conversion of arachidonic acid to a prostaglandin is cyclooxygenase-1 (COX-1) which abstracts a hydrogen atom from arachidonic acid to produce a radical intermediate. This reactive intermediate then undergoes a number of subsequent steps, eventually leading to the production of prostaglandins (PGE_2 is shown). Most anti-inflammatory drugs work by inhibiting the prostaglandin synthesis pathway in some manner. In the case of Aspirin, the COX-1 enzyme is deactivated by transfer of the aspirin acetyl group to an important –OH moiety of the COX enzyme. Once the COX enzyme is deactivated, prostaglandin synthesis is inhibited and the pain signal is suppressed.

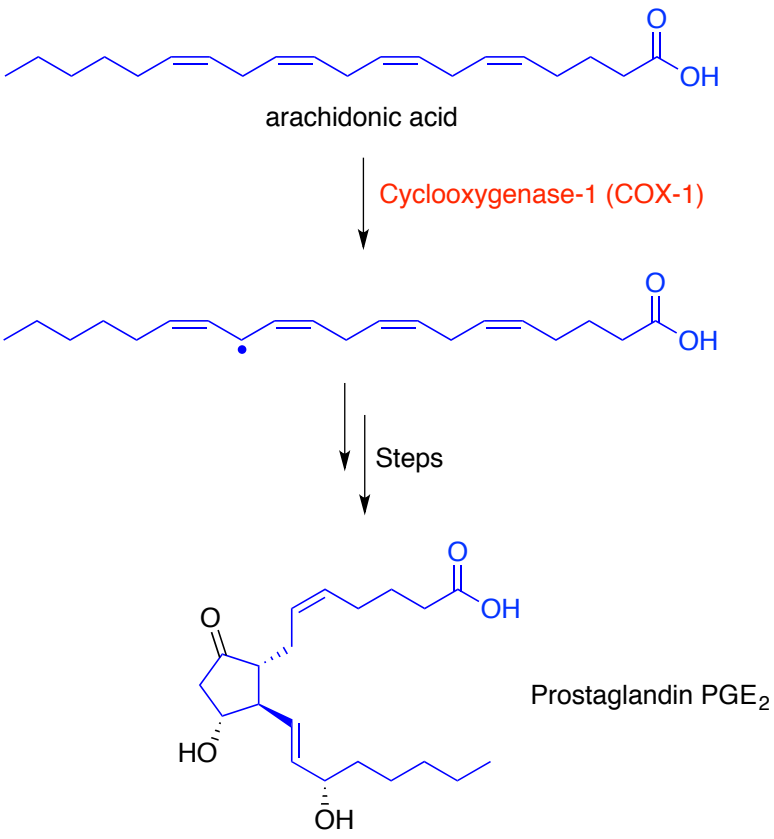

Figure 1. Synthesis of a Prostaglandin from Arachidonic Acid

The Discovery of Aspirin

The history of aspirin dates back to around 1500 B.C. when salicylic acid, the precursor to aspirin, was used medicinally. Salicylic acid is present in the bark of the willow tree and there is

evidence that Hippocrates suggested chewing the tree bark to treat fever and to relieve pain. In somewhat more recent history (1753), Reverend Edward Stone of England used the willow tree bark for the successful treatment of malaria. Stone later reported his findings to the Royal Society. The modern synthesis and application of aspirin came in the late 1800s at the Bayer laboratory in Germany. Bayer's pharmaceutical division at the time was under the direction of Arthur Eichengrün. Working in Eichengrün's lab was a chemist named Felix Hoffmann. Hoffmann's father suffered from arthritis and took salicylic acid to relieve his symptoms. Unfortunately, the salicylic acid upset his stomach to such a degree that he had to discontinue using it. Hoffmann set out to find an alternative and began preparing salicylic acid derivatives in his laboratory. One such derivative that he crafted was acetylsalicylic acid (aspirin). Hoffmann gave the aspirin to his father who found the medication to successfully treat his arthritis without the negative effects on his stomach. Interestingly, the head of Bayer at that time was reluctant to pursue aspirin for fear that it caused heart problems. After continued persistence by Eichengrün, Bayer began to market aspirin, which yielded the company phenomenon success. Following World War I, Bayer lost their trademark of the aspirin name as part of the terms imposed in the 1919 Treaty of Versailles.

Acetylation of Salicylic Acid

One method for the preparation of acetylsalicylic acid involves the acylation of salicylic acid as shown in figure 2. The acylating agent is acetic anhydride, which in the presence of an acid catalyst reacts with salicylic acid to provide acetylsalicylic acid in an excellent yield. First, acetic anhydride is protonated by the acid to form an activated carbonyl species. Next, a lone pair from the salicylic acid OH attacks the carbonyl carbon of the activated electrophile. A proton is then transferred from the phenol oxygen to the ester carbonyl oxygen. Next, acetic acid (CH_3COOH) is dispelled. The resulting protonated ester loses its proton upon reaction with a weak base to provide acetylsalicylic acid. Only a catalytic amount of acid is required to carry out the acylation.

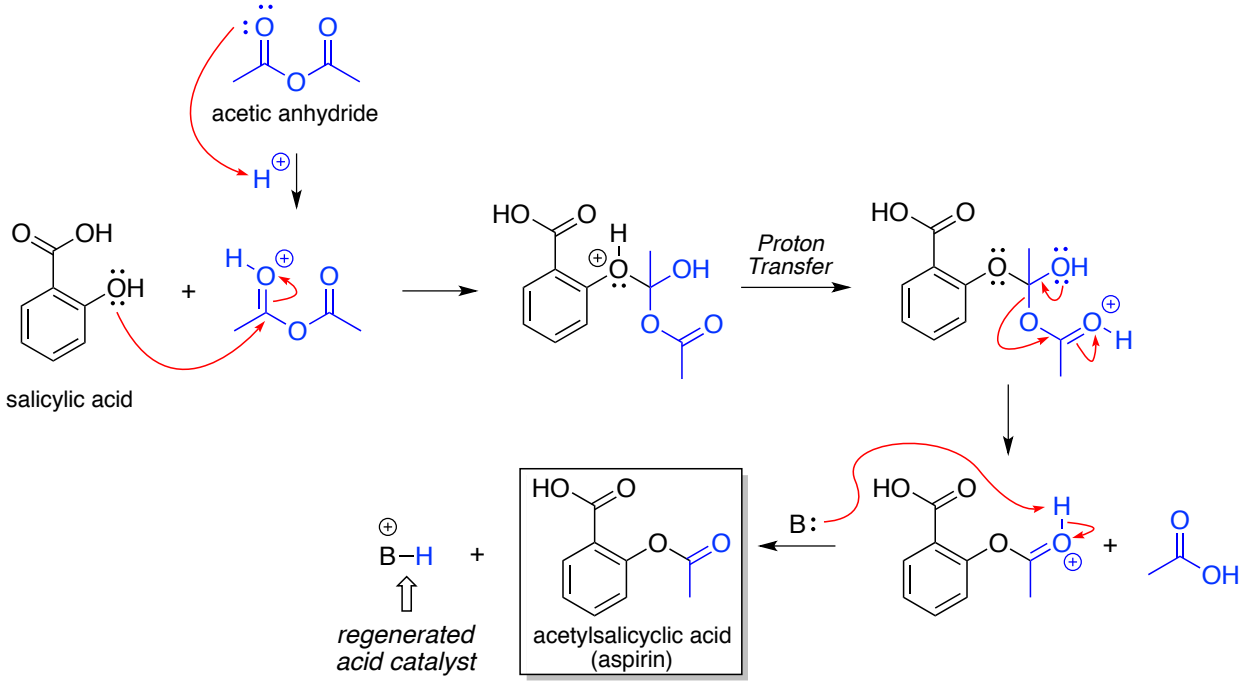

Figure 2. Mechanism for the Acylation of Salicylic Acid

B. Experimental Procedure

Reagent	Mol. Wt.	Density	Mass	Mmol	Equiv.
Salicylic Acid	138	-	175 mg	1.27	1
Acetic Anhydride	102	1.08 g/mL	389 mg	3.81	3
H_3PO_4 (85%)	98	-	3 drops	-	catalyst

Prepare a boiling water bath by filling a 100-mL beaker half full with water and placing it on the hot plate. Heat the water to boiling while you are measuring out the reactants.

Measure out 175 mg of salicylic acid and add this solid to a 5-mL conical reaction vial containing a spin vane. Add 389 mg (0.360 mL) of acetic anhydride and three drops of 85% phosphoric acid to the vial. Attach an air condenser using a lock nut and place the vial into the boiling water bath. You should use a clamp to secure the condenser/vial assembly. Commence stirring and heat the mixture for 5 min. Remove the vial from the boiling water bath and slowly add 10 drops of water. You may observe some fizzing during the water addition. Next, add 2 mL of water and cool the solution in an ice bath for at least 5 min. If crystals don't form, you may need to initiate crystallization by scratching the wall of the vial. Collect the solid via Hirsch filtration and allow the solid to air dry on the Hirsch funnel with the vacuum applied for ~10 min.

The solid can be recrystallized from a mixed toluene-hexane solvent system. In a 5-mL vial, dissolve the solid in ~1.5 mL of toluene. You will need to heat the vial to aid in dissolving the solid. To the solution, add hexane dropwise until you just start to see crystal formation. Cool the solution in an ice bath and collect the crystals via Hirsch filtration. Calculate the yield, determine the melting point, and record an IR spectrum of your product.

Chemical Tests

Test the solubility of salicylic acid and acetylsalicylic acid in:

- Water
- $NaHCO_3$ solution ($NaHCO_3$ is a base)

Test both salicylic acid and acetylsalicylic acid with $FeCl_3$ and observe any color changes. *Refer to experiment 18 to refresh yourself on the $FeCl_3$ test.*

C. Prelab Questions

1) Do you expect salicylic acid to be soluble in $NaHCO_3$? What happens when a benzoic acid derivatives is reacted with a base such as $NaHCO_3$? It may be beneficial to know that the pKa of benzoic acid is 4.2 and the pKa of H_2CO_3 is 10.3.

2) Using the reactions discussed in both lecture and lab, how could salicylic acid be synthesized from benzene?

3) Acetic anhydride is hydrolyzed by water to provide two molecules of acetic acid. Propose a mechanism for this reaction.

D. Postlab Questions

1) What important IR signals lead you to the conclusion that the reaction was successful?

2) Explain why the phenol –OH rather than the carboxylic acid –OH of salicylic acid is acetylated by acetic anhydride. *Hint: Think about the reactivity of these two groups.*

3) Which compounds gave a positive $FeCl_3$ test? Explain your results.