Synthesis of Acetylsalicylic Acid (Aspirin)

from K. L. Williamson, Macroscale and Microscale Organic Experiments, 2nd Ed. 1994, Houghton Mifflin, Boston. p379; revised 6/22/06

Prelab Exercise
Write a detailed mechanism of the following acid-catalyzed reaction, the formation of aspirin.

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\text{Salicylic acid} + \text{Acetic anhydride} \rightarrow \text{Acetylsalicylic acid (aspirin)} + \text{Acetic acid}
\]

Introduction
Aspirin is among the most fascinating and versatile drugs known to medicine, and it is among the oldest. The first known use of an aspirin-like preparation can be traced to ancient Greece and Rome. Salicigen, an extract of willow and poplar bark, has been used as a pain reliever (analgesic) for centuries. In the middle of the last century it was found that salicigen is a glycoside formed from a molecule of salicylic acid and a sugar molecule. Salicylic acid is easily synthesized on a large scale by heating sodium phenoxide with carbon dioxide at 150°C under slight pressure (the Kolbe synthesis):

\[
\text{Sodium salicylate}
\]

Unfortunately, however, salicylic acid attacks the mucous membranes of the mouth and esophagus and causes gastric pain that may be worse than the discomfort it was meant to cure. Felix Hoffmann, a chemist for Friedrich Bayer, a German dye company, reasoned that the corrosive nature of salicylic acid could be altered by addition of an acetyl group; and in 1893 the Bayer Company obtained a patent on acetylsalicylic acid, despite the fact that it had been synthesized some 40 years previously by Charles Gerhardt. Bayer coined the name Aspirin for their new product to reflect its acetyl nature and its natural occurrence in the Spiraea plant. Over the years the company has allowed the term aspirin to fall into the public domain so that it is no longer capitalized.

In 1904, the head of Bayer, Carl Duisberg, decided to emulate John D. Rockefeller’s Standard Oil Company and formed an interessen gemeinschaft (IG, a cartel) of the dye industry (Farbenindustrie). This cartel completely dominated the world dye industry before World War I, and it continued to prosper between the wars, even though some of their assets were seized and sold after World War I. After World War I, an American company, Sterling Drug, bought the
rights to aspirin. The company’s Glenbrook Laboratories division still is the major manufacturer of aspirin in the United States (Bayer Aspirin).

Because of their involvement at Auschwitz, the top management of IG Farbenindustrie was tried and convicted at the Nuremberg trials after World War II, and the cartel broken into three large branches, Bayer, Hoechst, and BASF (Badische Anilin and Sodafabrik), each of which now does more business than DuPont, the largest American chemical company.

By law, all drugs sold in the United States must meet purity standards set by the Food and Drug Administration, so all aspirin is essentially the same. Each 5 grain tablet contains 0.325 g of acetylsalicylic acid held together with a binder. The remarkable difference in price for aspirin is primarily a reflection of the advertising budget of the company that sells it.

Aspirin is an analgesic (painkiller), an antipyretic (fever reducer), and an anti-inflammatory agent. It is the premier drug for reducing fever, a role for which it is uniquely suited. As an anti-inflammatory, it has become the most widely effective treatment for arthritis. Patients suffering from arthritis must take so much aspirin (up to four grams per day) that gastric problems may result. For this reason, aspirin is often combined with a buffering agent. Bufferin is an example of such a preparation.

The ability of aspirin to diminish inflammation is apparently due to its inhibition of the synthesis of prostaglandins, a group of C-20 molecules that enhance inflammation. Aspirin alters the oxygenase activity of prostaglandin synthetase by moving the acetyl group to a terminal amine group of the enzyme.

If aspirin were a new invention, the U.S. Food and Drug Administration (FDA) would place many hurdles in the path of its approval. It has been implicated, for example, in Reyes syndrome, a brain disorder that strikes children and young people under 18. It has an effect on platelets, which play a vital role in blood clotting. In newborn babies and their mothers, aspirin can lead to uncontrolled bleeding and problems of circulation for the baby—even brain hemorrhage in extreme cases. This same effect can be turned into an advantage, however. Heart specialists urge potential stroke victims to take aspirin regularly to inhibit clotting in their arteries, and it has recently been shown that one-half tablet per day will help prevent heart attacks in healthy men.

Aspirin is found in more than 100 common medications, including AlkaSeltzer, Anacin ("contains the pain reliever doctors recommend most"), APC, Coricidin, Excedrin, Midol, and Vanquish. Despite its side effects, aspirin remains the safest, cheapest, and most effective nonprescription drug. It is made commercially employing the same synthesis used here.

**Procedure:** Microscale Synthesis of Acetylsalicylic Acid (Aspirin)

![Chemical diagram]

Prepare a hot water bath; in a beaker, heat water to ~ 90° C.
To a reaction tube, add 138 mg of salicylic acid, a boiling chip, and one small drop of 85% phosphoric acid. Then add 0.3 mL of acetic anhydride, which should be used to wash the reactants to the bottom of the tube. Mix the reactants thoroughly with a glass stirring rod, and then heat the reaction tube in the beaker of hot water at ~90°C for 5 min. **Cautiously** add 0.2 mL of water very slowly dropwise to the reaction mixture to decompose excess acetic anhydride. This will be an exothermic reaction.

When the reaction is over, take a very small portion of the reaction mixture out of the tube with a TLC capillary (use forceps to hold capillary); use this for the TLC analysis. The TLC should have three spots (or lanes) on the origin: one for the main organic starting material that is being transformed, one for a copspot (starting material and the reaction mixture), and one for the reaction mixture. You will need to find a mobile phase; start with 30% EtOAc in hexanes.

Add 0.3 mL more water and allow the tube to cool slowly to room temperature. You should let it sit for 10 minutes and if crystallization of the product does not occur during the cooling process, add a seed crystal, or scratch the inside of the tube with a glass stirring rod.

Cool the tube in ice until crystallization is complete (at least 20 min), and then remove the solvent with a square-tipped Pasteur pipette, pushing the pipette to the bottom and sucking out all the liquid. If the crystals are too fine for this procedure, collect the product by vacuum filtration on the Hirsch funnel. Complete the transfer of the product to the funnel using a very small quantity of ice water. This is done by adding a small amount of ice water to the tube then drawing up the water and crystals into a pipet for transfer to the Hirsch funnel.

In either case, place and spread the product out onto a piece of filter paper and squeeze the crystals between sheets of filter paper to absorb excess water and let it dry thoroughly in air for at least 24 hours. Determine the weight and calculate the percentage yield.

Compare a tablet of commercial aspirin with your sample. Test the solubility of the tablet in water and in toluene, and observe if it dissolves completely. Determine the melting point of your sample in a melting point capillary. Compare its behavior with the behavior of the crushed tablet when heated in a melting point capillary. If an impurity is found, it is probably some substance used as binder for the tablets. Can you tell if it is organic or inorganic?

Acetylsalicylic acid melts with decomposition at temperatures reported from 128 to 137°C. If necessary it may be recrystallized from either water or a ether/hexanes mixture. Aspirin is hydrolyzed by boiling water, but the reaction is not rapid; therefore, the product may be quickly recrystallized from a small quantity of very hot water. It can also be recrystallized from diethyl ether (use the wet ether found in a supply bottle in each hood) and hexanes. Keep adding diethyl ether until you do not see any more particles. Then you will want to add an equal volume of hexanes. Then you should let the solution stand undisturbed in an ice bath.

**Analyses**

In addition to TLC analysis, you may be instructed to analyze your final product by IR or NMR. Analyze your sample according to your Assignment sheet and prepare it as per the instructions on Sample Preparation in Lab Guide.

**Cleaning Up**

Combine the aqueous filtrates, dilute the filtrate with water and flush it down the drain.
Post Lab Questions

1. (a) Determine the bonds that correspond to the following stretches in the IR spectrum of aspirin shown below: ~3000 \(^{-1}\) (not labeled on spectrum), 1754, 1693, and 1190 cm\(^{-1}\).

(b) Explain the signals seen in the NMR spectrum found below for acetysalicylic acid in terms of chemical shift, integration, multiplicity/splitting.

2. Predict 4 peaks (molecular ion and three fragment ions) that would likely be observed in the mass spectrum of aspirin; show ions’ structures and give corresponding masses.