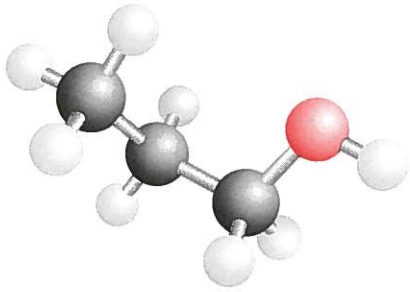
CHAPTER

41



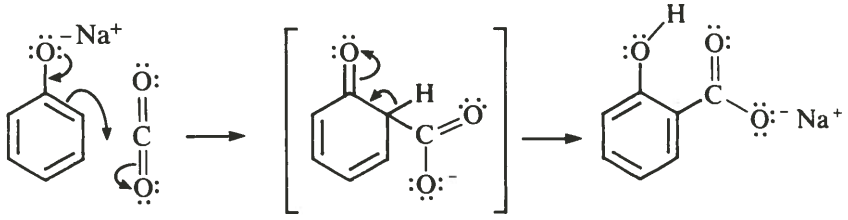
Acetylsalicylic Acid (Aspirin)

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This icon will direct you to techniques, equipment setups, and online resources at http://college.hmco.com/PIC/williamsonMMOE5e.

PRELAB EXERCISE: Write detailed mechanisms showing how pyridine and sulfuric acid catalyze the formation of acetylsalicylic acid.

Aspirin is among the most fascinating and versatile drugs known to medicine; it is also among the oldest. The first known use of an aspirin-like preparation can be traced to ancient Greece and Rome. Salicin, an extract obtained from the bark of willow and poplar trees, has been used as a pain reliever (analgesic) for centuries. In the middle of the 19th century, it was found that salicin is a glycoside formed from a molecule of salicylic acid and a sugar molecule. The sodium salt of salicylic acid, sodium salicylate, is easily synthesized on a large scale by heating sodium phenoxide with carbon dioxide at 150°C under slight pressure (the Kolbe synthesis):



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 intended 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 adding 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 its new product to reflect its acetyl nature and its natural occurrence

in the spirea plant. Over the years Bayer has allowed the term *aspirin* to fall into the public domain so it is no longer capitalized. The manufacturers of Coke (Coca-Cola) and Sanka are working hard to prevent a similar fate befalling their trademarks.

In 1904 Carl Duisberg, the head of Bayer, decided to emulate John D. Rockefeller's Standard Oil Company and formed an *interessen gemeinschaft* (I.G.) 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 its assets were seized and sold after World War I. Soon after, an American company, Sterling Drug, bought the rights to aspirin for $5.3 million. Sterling was bought by Eastman Kodak in 1988, which was then sold to Smith-Kline Beecham in 1995, which combined in 2000 with Glaxo Wellcome to become GlaxoSmithKline.

Because of their involvement at Auschwitz, the top management of I.G. Farbenindustrie was tried and convicted at the Nuremberg trials after World War II, and the cartel was broken into three large branches—Bayer, Hoechst, and BASF (*Badische Anilin und Sodafabrik*)—each of these companies does more business than DuPont, the largest American chemical company. In 1997 the American rights to the Bayer name and trademark were sold back to Bayer A.G. for $1 billion.

By law, all drugs sold in the United States must meet the purity standards set by the U.S. Food and Drug Administration (FDA), and so all aspirin is essentially the same. Each tablet contains 0.325 g (325 mg) 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. Bayer has 5% of the painkiller market; lower-priced generic aspirin has 18%.

The gross profit margin on Bayer aspirin is 80%. After advertising costs, the profit margin is 60%.

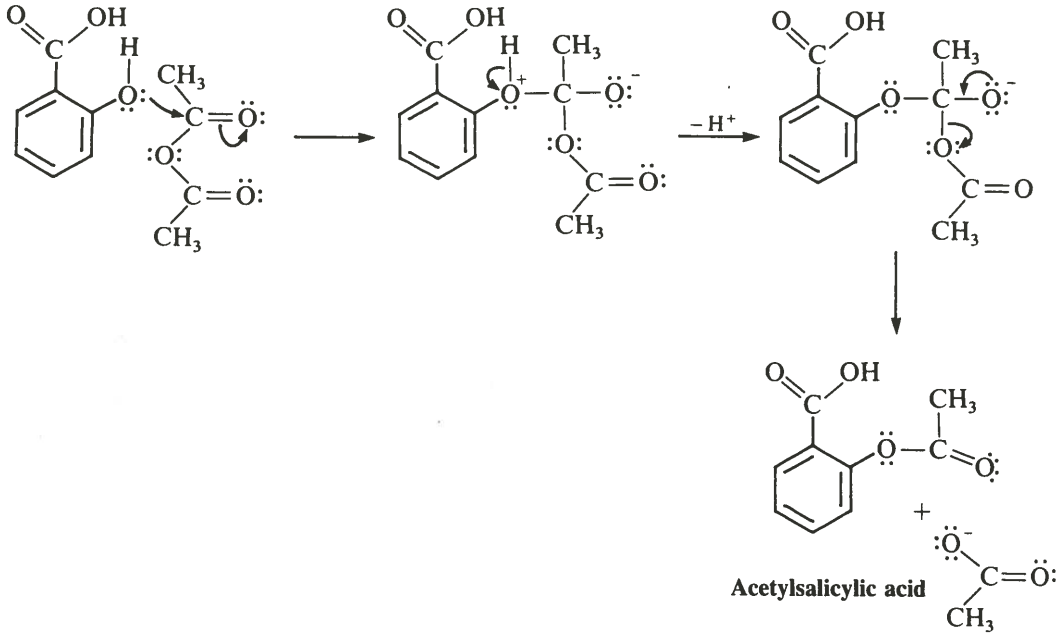
Aspirin is an analgesic, an antipyretic (fever reducer), and an anti-inflammatory agent. It is the premier drug for reducing fever, a role for which it is uniquely suited. As an anti-inflammatory, it has become the most widely effective treatment for arthritis. Unfortunately, people suffering from arthritis must take so much aspirin (several 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 exacerbate 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 FDA would place many hurdles in the path of its approval. It has been implicated, for example, in Reye's syndrome, a brain disorder that strikes children and young persons under age 18 who take aspirin after contracting flu or chickenpox. 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 circulation problems for the baby—even brain hemorrhages 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 been shown that taking aspirin will help prevent first heart attacks from occurring.

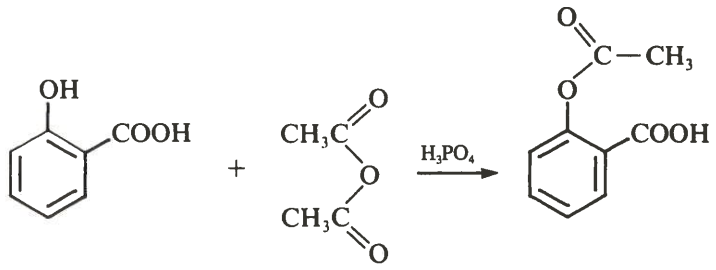
Over 100 common medications contain aspirin, including, for example, Alka-Seltzer, Anacin, Coricidin, Excedrin, Midol, and Vanquish. Despite its side effects, aspirin is one of the safest, cheapest, and efficacious nonprescription drugs, although acetaminophen (Tylenol, etc.) has 40% and ibuprofen (Advil, etc.) has 26% of the painkiller market in dollar volume ($2.47 billion in 1996). Naproxen (Aleve) has 6% of the market. Aspirin is made commercially employing the same synthesis presented in this chapter.

The mechanism for the acetylation of salicylic acid is as follows:



EXPERIMENT

Synthesis of Acetylsalicylic Acid (Aspirin)



Salicylic acid
MW 138.12, mp 159°C

Acetic anhydride
MW 102.09, bp 140°C

Acetylsalicylic acid
MW 180.15, mp 128–137°C

Microscale Procedure

IN THIS EXPERIMENT salicylic acid, acetic anhydride, and an acid catalyst are heated briefly. Water is added to convert excess acetic anhydride to acetic acid and also serves as the crystallization solvent. After the water is removed from the crystals, they are washed, collected, and dried to give pure aspirin.

⚠ Measure acetic anhydride in the hood, as it is very irritating to breathe.

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Photo: Filtration Using a Pasteur Pipette; Videos: Filtration of Crystals Using the Pasteur Pipette, Microscale Filtration on the Hirsch Funnel

To a reaction tube, add 138 mg of salicylic acid, a boiling chip, and one small drop of 85% phosphoric acid followed by 0.3 mL of acetic anhydride (the acetic anhydride serves to wash the reactants to the bottom of the tube). Mix the reactants thoroughly; then heat the reaction tube on a steam bath or in a beaker of 90°C water for 5 min. Cautiously add 0.2 mL of water to the reaction mixture to decompose excess acetic anhydride. This will be an exothermic reaction. When the reaction is over, add an additional 0.3 mL of water and allow the tube to cool slowly to room temperature. 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 10 min) and then remove the solvent with a Pasteur pipette. If the crystals are too fine for this procedure, collect the product by vacuum filtration on a Hirsch funnel. Complete the transfer of the product to the funnel using a very small quantity of ice water. In either case, turn the product out onto a piece of filter paper and squeeze the crystals between sheets of filter paper to absorb excess water. Allow the product to air-dry thoroughly before determining the weight and calculating the percent yield. Determine the melting point and the infrared (IR) spectrum in chloroform solution. Figure 41.1 shows the IR spectrum of acetylsalicylic acid. Aspirin is hydrolyzed by boiling water, but the reaction is not rapid; if desired, the product may be recrystallized from a small quantity of very hot water.

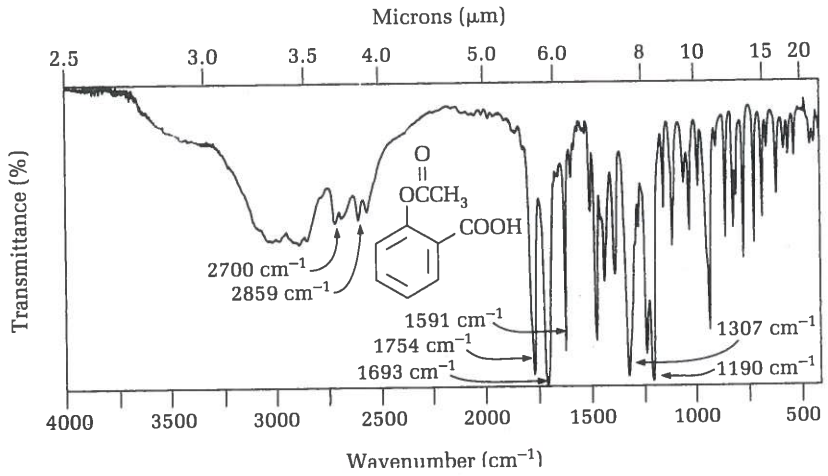


FIG. 41.1
The IR spectrum of acetylsalicylic acid in chloroform.

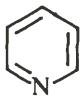
Compare a tablet of commercial aspirin with your sample. Test the solubility of the commercial tablet in water and in toluene and observe if it dissolves completely. Compare its behavior when heated in a melting-point capillary to the behavior of your sample. If an impurity is found, it is probably a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

Cleaning Up. Dilute the filtrate with water and flush it down the drain.

Macroscale Procedure

Measure acetic anhydride in the hood, as it is very irritating to breathe.

Acetylation catalysts:

1. $CH_3COO^- Na^+$
2. 
3. $BF_3 \cdot (C_2H_5)_2O$
4. H_2SO_4

Pyridine has a bad odor, and boron trifluoride etherate and sulfuric acid are corrosive; work in the hood. Handle with care.

Online Study Center
Video: Macroscale Crystallization

t-Butyl methyl ether and petroleum ether are very flammable.

Propose mechanisms to interpret your results.

Place 1 g of salicylic acid in each of four 13 × 100-mm test tubes and add to each tube 2 mL of acetic anhydride. To the first tube add 0.2 g of anhydrous sodium acetate, note the time, stir the mixture with a glass stirring rod, replace the rod with a thermometer, and record the time required for a 4°C rise in temperature. Continue to stir occasionally while starting the next acetylation. Obtain a clean thermometer, put it in the second tube, add 5 drops of pyridine, stir, observe as before, and compare it to the first results. To the third and fourth tubes add 5 drops of boron trifluoride etherate[1] and 5 drops of concentrated sulfuric acid, respectively. What is the order of activity of the four catalysts as judged by the rates of the reactions?

Put all of the tubes in a beaker of hot water for 5 min to dissolve solid material and complete the reactions; then pour all of the solutions into a 125-mL Erlenmeyer flask containing 50 mL of water and rinse the tubes with water. Swirl to aid hydrolysis of the excess acetic anhydride; then cool thoroughly in ice, scratch the side of the flask with a stirring rod to induce crystallization, and collect the crystalline solid; the yield is about 4 g.

Acetylsalicylic acid melts with decomposition at temperatures reported between 128°C to 137°C. It can be crystallized by dissolving it in *t*-butyl methyl ether, adding an equal volume of petroleum ether, and letting the solution stand undisturbed in an ice bath.

Test the solubility of your sample in toluene and in hot water and note the peculiar character of the aqueous solution when it is cooled and when it is then rubbed against the tube with a stirring rod. Note also that the substance dissolves in cold sodium bicarbonate solution and is precipitated by adding concentrated hydrochloric acid.

Compare a tablet of commercial aspirin to your sample. Test the solubility of the commercial tablet in water and in toluene and observe if it dissolves completely. Compare its behavior when heated in a melting-point capillary to the behavior of your sample. If an impurity is found, it is probably a substance used as binder for the tablets. Is the binder organic or inorganic? To interpret your results, consider the mechanism whereby salicylic acid is acetylated.

Note that acetic acid is eliminated during the reaction. What effect would sodium acetate have? How might boron trifluoride etherate or sulfuric acid affect the nucleophilic attack of the phenolic oxygen on acetic anhydride? With what might the pyridine, a base, associate?

1. *To the instructor*: Commercial reagent, if dark, should be redistilled (bp 126°C, water-white).

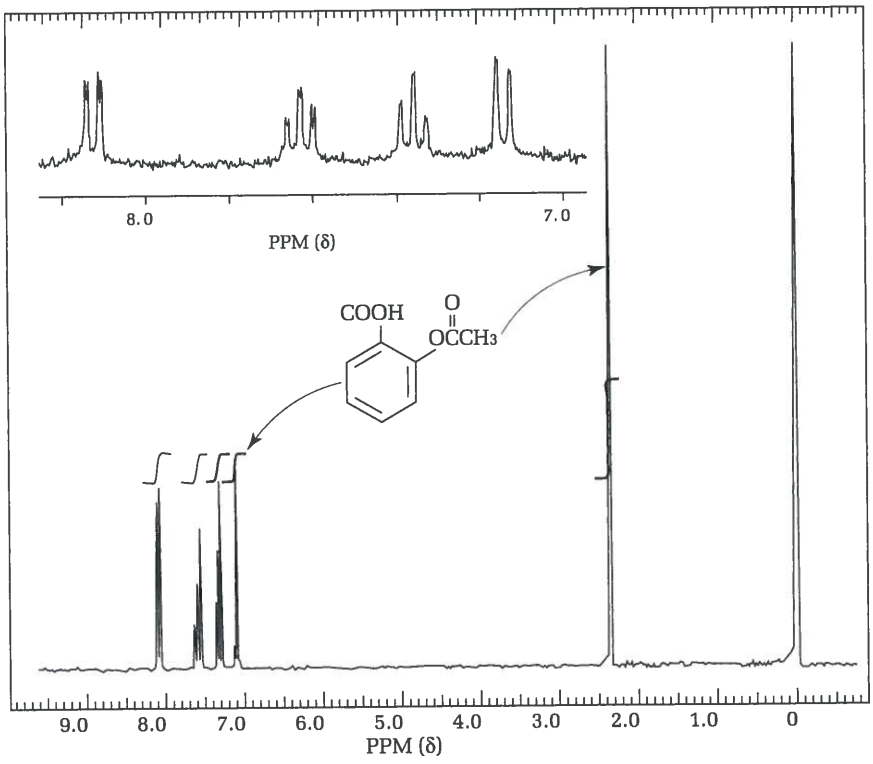


FIG. 41.2
The ^{1}H NMR spectrum of acetylsalicylic acid (250 MHz). The COOH proton does not appear on this spectrum.

The IR and ^{1}H NMR (nuclear magnetic resonance) spectra of acetylsalicylic acid are presented in Figure 41.1 (on page 572) and Figure 41.2.

Cleaning Up. Combine the aqueous filtrates, dilute with water, and flush the solution down the drain.

QUESTIONS

1. Hydrochloric acid is about as strong a mineral acid as sulfuric acid is. Why would HCl not be a satisfactory catalyst in this reaction?
2. How do you account for the smell of vinegar when an old bottle of aspirin is opened?

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