Experiment 11
Check-In; Aspirin

A. Check-in

Be sure that all of your glassware is present in your locker at check-in time. Once you have checked-in you will be held responsible for missing or damaged glassware items. Pay particular attention to the glassware that has ground glass joints. These joints have been ground by hand to fit in a secure manner so that no liquids or gases will escape. This glassware is very expensive. Treat it with respect.

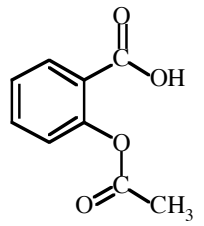
When you are checking–in it is a good idea to clean all of the glassware before putting it away the first time. Also, when you finish an experiment, always put away your glassware clean so that it will be **DRY** and ready for use the following week.

Store your safety glasses in your locker for the semester. No one else has access to your locker and your safety glasses will be safe and ready for you to use each week.

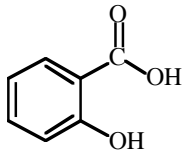
B. Preparation of Aspirin (Acetylsalicylic Acid)

You are going to synthesize aspirin from the naturally occurring salicylic acid or 2-hydroxybenzoic acid (Figure11.1). Salicylic acid occurs in nature in the form of esters in a variety

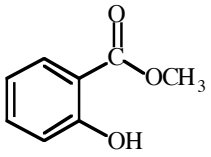
Figure 11.1 Derivatives of Salicylic Acid



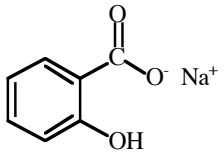
Acetylsaliclic acid
Aspirin



salicylic acid
2-hydroxybenzoic acid



methyl salicylate



sodium salicylate

of glycosides and essential oils. The methyl ester is present in oil of wintergreen and in many other fragrant oils from flowers, leaves and bark. It is used in flavoring candy and the oil is used as a pain-relieving ingredient in liniments such as Ben-Gay. In the human body, methyl salicylate is hydrolyzed to salicylic acid in the strongly acidic conditions of the stomach. Salicylic acid has analgesic (pain reliever) and antipyretic (fever reducer) effects similar to those of aspirin. It was first isolated from willow bark in 1860 and was used for therapeutic purposes for many years. As early as the time of ancient Greece (ca. 500 BC), willow bark extracts were used therapeutically (see the description of salicin in your text). Salicylic acid, however, has a sour taste and is irritating to swallow. The sodium salt, sodium salicylate, was used for several years. It is easier to swallow but is very irritating to the lining of the stomach. In an attempt to modify the structure of the molecule to remove the undesirable properties while retaining (and even improving) the desirable qualities, chemists at the German Bayer Company synthesized acetylsalicylic acid in 1899. It soon became the best selling drug in the world. Over 55 billion aspirin tablets are now consumed annually in North America.

Acetylsalicylic acid is made by treating salicylic acid with acetic anhydride in the presence of a catalytic amount of phosphoric acid (Figure 11.2). The OH of the salicylic acid simply acts as an alcohol in an acid catalyzed esterification reaction. The complete mechanism is given in Figure 11.3.

Acetic anhydride is an excellent electrophile. It is made even more electrophilic by treatment with phosphoric acid. This is a fairly strong acid (pK_a 2.12) and will protonate the oxygen of one of the carbonyls of acetic anhydride to make it even more reactive. The hydroxyl group of the salicylic acid then attacks the carbonyl carbon to form the tetrahedral intermediate that breaks down to lose the acetate anion. Final proton transfer gives acetylsalicylic acid. Notice that the phosphoric acid is regenerated so that it is needed in only catalytic amounts.

Figure 11.2 Formation of Aspirin

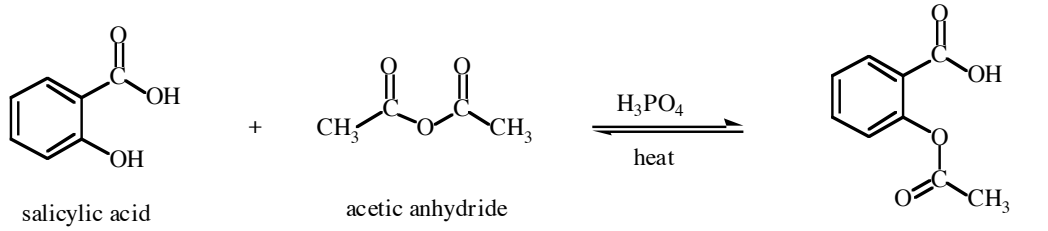
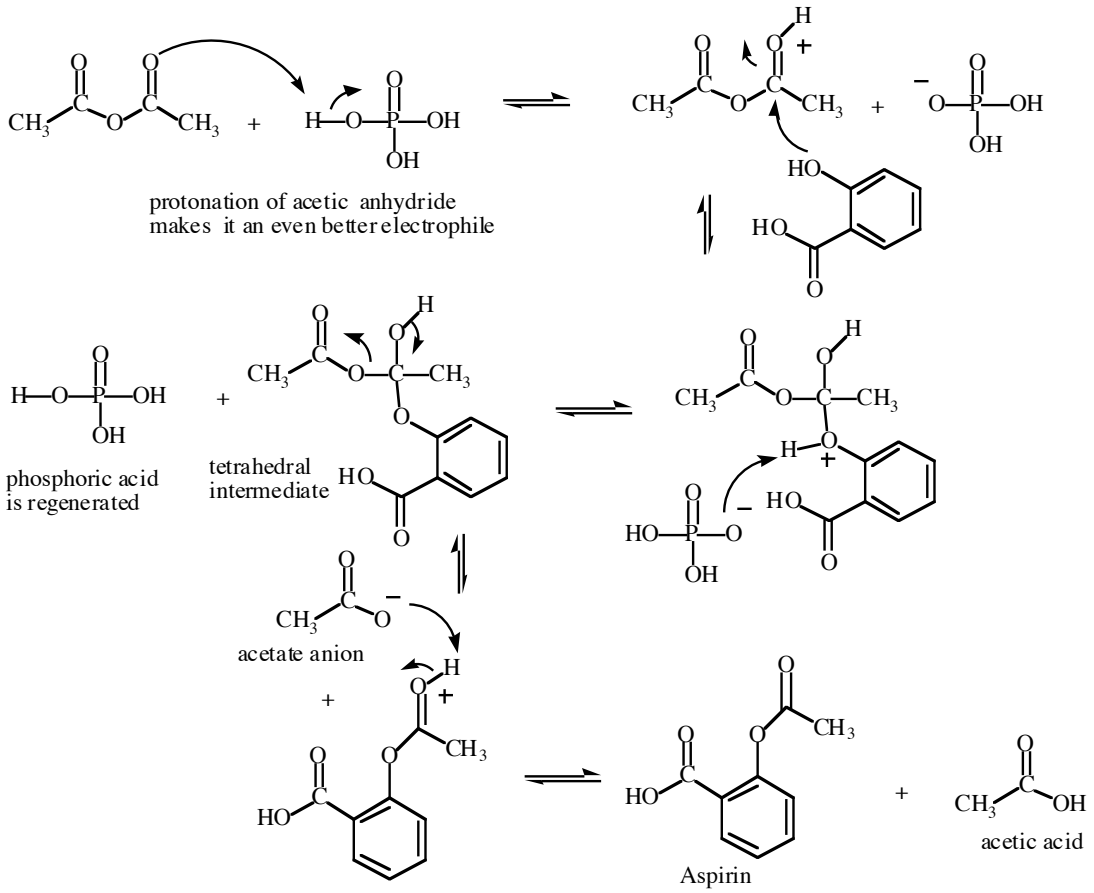


Figure 11.3 Mechanism of Acetylation Reaction



Physical Constants

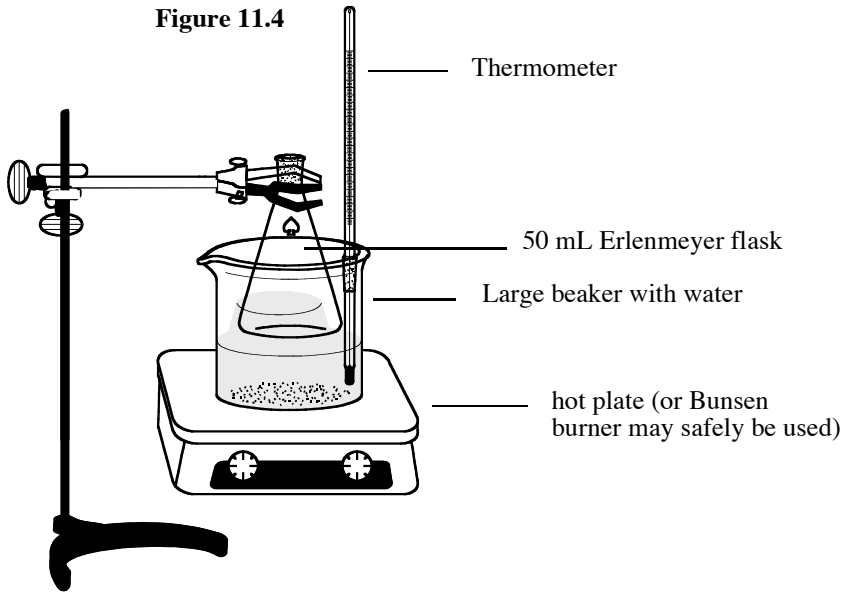
Compound	Mol. Wt (g/mol)	Density (g/mL)	B.p. (°C)	m.p. (°C)
Salicylic acid	138.12	solid	211/20 mm	158-161
Acetic anhydride	102.09	1.082	138-140	-73
Acetylsalicylic acid	180.16	solid	-	138-140
Ethyl acetate	88.11	0.902	76-77	-84
Hexane	86.18	0.659	69	-95

Procedure:

Place 1.4 g salicylic acid in a 50 mL Erlenmeyer flask. Add 3.0 mL of acetic anhydride. Use a pipette to wash down all of the salicylic acid from the sides of the flask so that all of the solid material is in contact with the liquid. Add 5 drops of 85% phosphoric acid.

Set up a water bath using your iron tripod, Bunsen burner, the wire gauze and a 400 mL beaker as shown in Figure 11.4. Fill the beaker with enough water that the contents of the 50 mL Erlenmeyer are submerged in the water. Heat with the Bunsen burner. Clamp the 50 mL Erlenmeyer flask in place in the water bath at 85-90 °C (just below boiling) for 5 minutes.

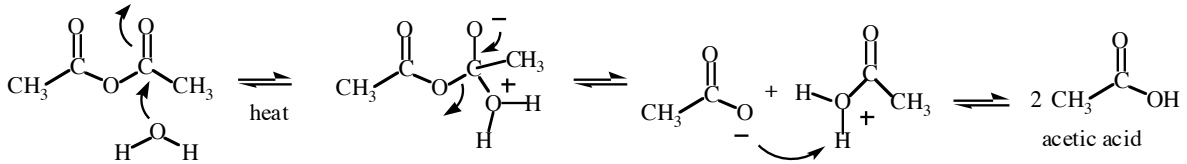
Figure 11.4



Work-up

After five minutes of heating, remove the Erlenmeyer from the water bath and while it is still hot, add 2 mL of tap water all at once. The reason we add the water is that we want to hydrolyze any excess acetic anhydride that is remaining after the acetylation reaction. The hydrolysis reaction is shown in figure 11.5. **Be careful. Vapors of acetic acid are released.**

Figure 11.5 Hydrolysis of Acetic Anhydride



When the temperature of the flask starts dropping (this should not take more than about 5 minutes), add 20 mL H_2O. Allow the flask to cool slowly to room temperature. Do not shake the flask. Crystals should form. It is important when doing crystallizations that the crystals are allowed to form slowly without disturbing the container by stirring or shaking. Otherwise impurities can begin to crystallize along with the desired compound.

If no crystals are visible, scratch the side of the flask with your glass stirring rod. This provides a sharp edge on the glass surface where crystal nucleation can initiate. Be patient. Sometimes this can take time.

When crystals begin to form, place the flask in an ice bath. Cool to 4-5 °C.

Collect the crystals on your Buchner funnel using the set-up at shown in Figure 2.3. Place the filter paper on the Buchner funnel and then wet the filter paper with a few mL of the reaction or recrystallization solvent; in this case use a few mL water. This keeps the paper pressed flat against the bottom of the Buchner funnel. Press the solid filter cake with your spatula to force out excess water so as to hasten the drying process.

When the solid filter cake is fairly dry (no more drops visibly coming off from the filter), recrystallize your product from a 50:50 mixture of hexane and ethyl acetate using the procedure described below.

Recrystallization

Background: The idea behind recrystallization is to dissolve your compound in a minimum of hot solvent and then to allow the solution to cool slowly to room temperature and then in an ice bath. Most compounds will dissolve more readily when the temperature of the solvent is raised and will be less soluble when the temperature is lowered. Ideally the compound will not be soluble in the given volume of cold solvent and will crystallize from the cooled solution and all impurities will remain dissolved in the recrystallization solvent (called the supernatant liquid). The product is then filtered through a Buchner funnel to remove the solvent and to provide pure product while the impurities remain behind in the supernatant liquid.

In this case we will use a mixture of hexane and ethyl acetate. Since both of these solvents are flammable we must be very careful when using open flames. We will use a water bath, heated with a hot plate, and medium test tubes.

Acetylsalicylic acid is fairly polar and not soluble in pure hexane. Ethyl acetate ($CH_3CO_2CH_2CH_3$) is much more polar and acetyl salicylic acid is very soluble in pure ethyl acetate. In fact, if you dissolve your compound in pure ethyl acetate at say room temperature and then cool the solution to 4-5 °C in an ice bath, you would see no precipitate so you would not be able to recover your compound. We therefore use a mixture of the polar ethyl acetate and the non-polar hexane. If you use too much total solvent then you will not get crystals forming when you cool the solution in the ice bath.

But note that if you use too much recrystallization solvent and you do not get crystals forming when you cool down the mixture, you can always recover from your mistake by boiling off some of the excess solvent in a water bath (reduce the total volume) and then cooling again slowly, first to room temperature and then in the ice bath.

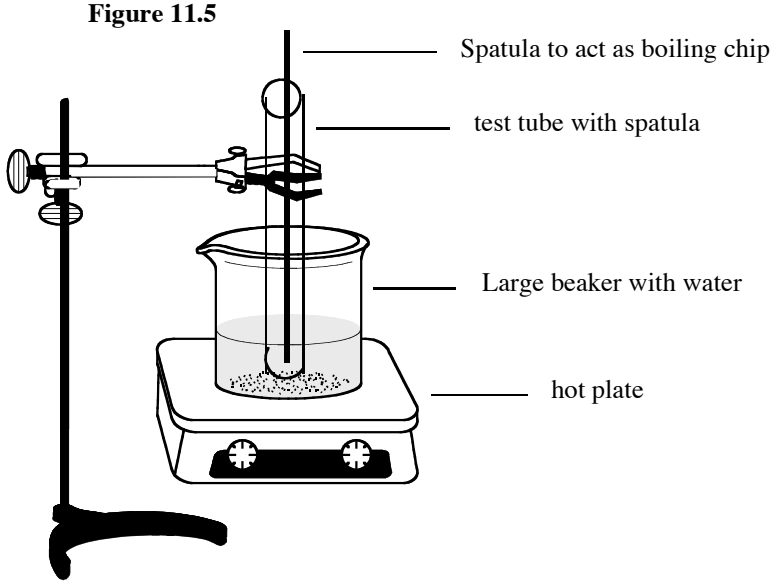
Procedure for Recrystallization of Acetylsalicylic Acid (see Fig. 11.5)

Place all of your solid acetylsalicylic acid inside a medium (or large) test tube. Use your spatula to scrape as much of it as possible from the damp filter paper. Add about 5-10 mL of the 50:50 hexane/ethyl acetate mixture and heat to boiling in the water bath. Hold the test tube using your wire test tube holder. The boiling point of hexane is 69 °C and the boiling point of ethyl acetate is 76-77 °C so the water bath does not need to be boiling.

Add 1-2 mL of the hexane/ethyl acetate using a pipette or medicine dropper and then heat the solution to boiling again. Stir with your spatula until the mixture boils and **ALWAYS LEAVE THE SPATULA IN THE TEST TUBE AT ALL TIMES.** The spatula will act like a boiling chip, preventing the mixture from boiling over violently` and spilling your product on the bench top.

Continue adding solvent and reheating to boiling each time until all of the material dissolves. Be sure to keep stirring with the spatula. It is important to work quickly as the solvent will boil away if you leave the test tube in the bath too long.

Figure 11.5



When all the solid material has dissolved (the solution should now be clear) remove it from the water bath and place it in your test tube rack. Allow it to cool slowly to room temperature and then in the ice bath. Filter your product using the Buchner funnel using a few mL of cold hexane to aid in the transfer of the solid from the test tube.

If you do not see a precipitate forming, then this means that you have used too much solvent. You will have to reduce the total volume by evaporative boiling in the water bath and then re-cooling slowly to room temperature again. Filter to collect the product

After the crystals dry, weigh your compound, determine the melting point range and calculate the percent yield. Turn in your sample and Yield Report to your teaching assistant.

Before you leave the laboratory make sure the glassware that you need for the following week for the Grignard experiment is <u>clean and dry</u>. You will need the following: 100 mL 3-necked round bottom flask, condensing column, and separatory funnel.