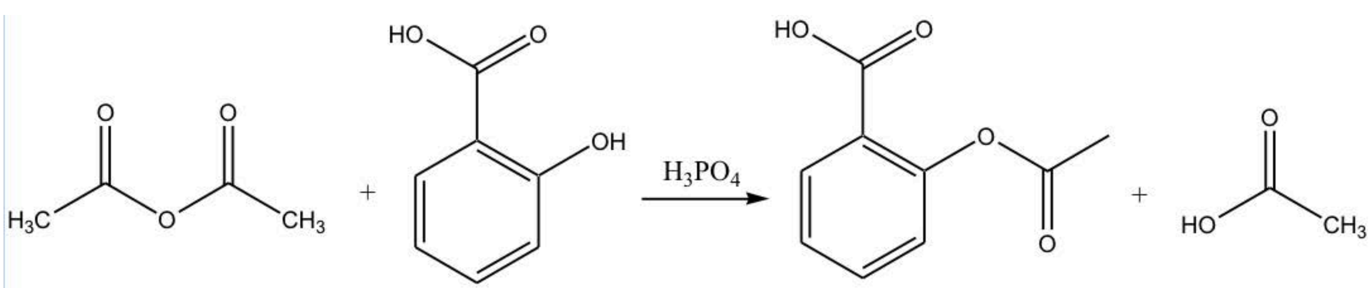
12BL Experiment 4: Aspirin Synthesis

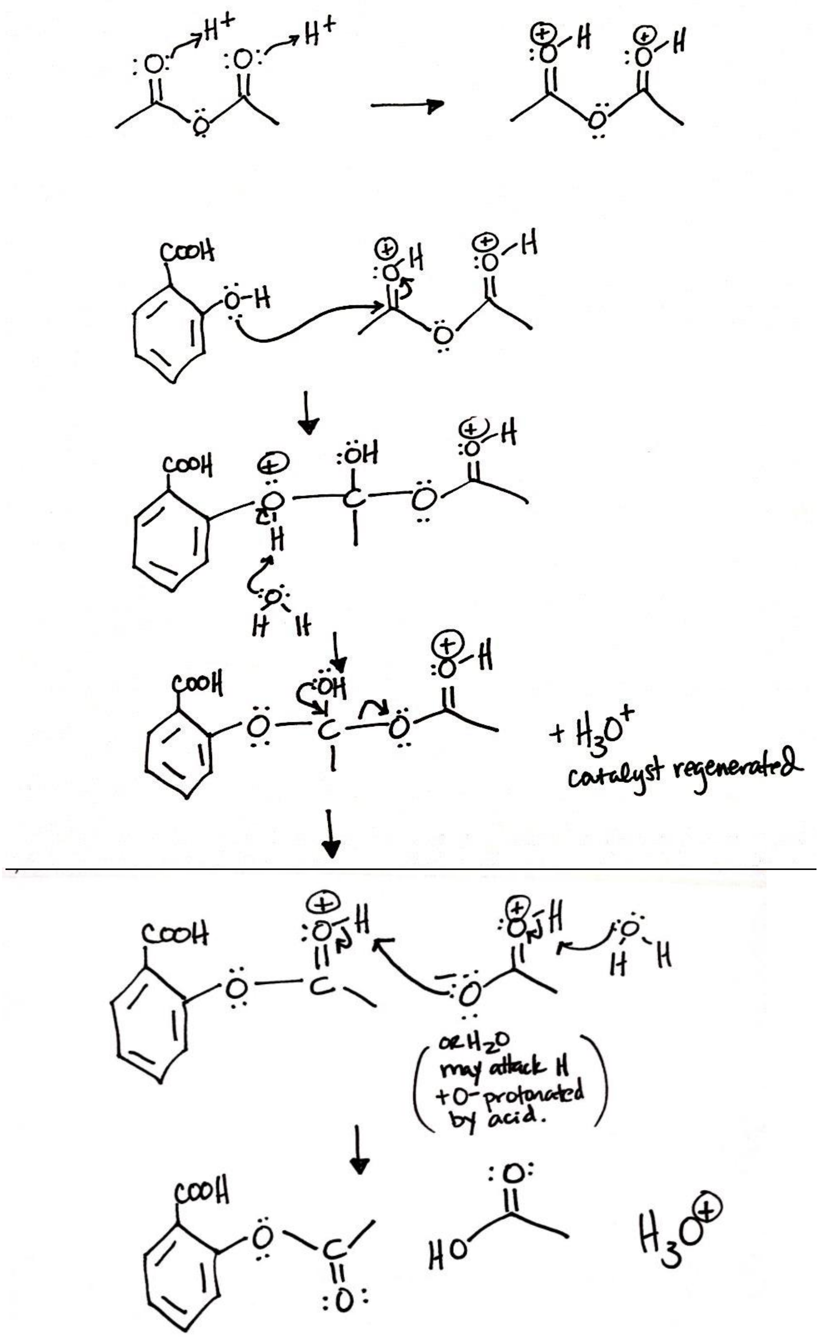
Safety: Proper lab goggles/glasses must be worn (even over prescription glasses). As always, ask where organic waste containers are located in the lab.

Background: Using your salicylic acid from experiment 2, you will perform an acid-catalyzed alcoholysis of an anhydride reaction, which converts the alcohol functional group of salicylic acid to an ester.   This is a “type” of an esterification reaction – you have seen the classic Fischer Esterification in the past semester synthesizing banana oil, isopentyl acetate. Recall, a Fischer Esterification converts a carboxylic acid, R-CO-**OH**, to an ester, R-CO-**OR**, using alcohol as the weak nucleophile/ base, H-**OR**. Notice the bold-fonts in the previous sentence: The OR functional group of the alcohol becomes bonded to the carbonyl bond of the carboxylic acid, eliminating the -OH group of the carboxylic acid as H_2O in the mechanism.

In today's Alcoholysis, the alcohol is still the attacking nucleophile/base as in the Fischer Esterification. However, the alcohol is now attacking the carbonyl of an anhydride. Due to the lower nucleophilicity/basicity of the alcohol, the anhydride is mixed with an acid catalyst. This makes the anhydride carbonyl bonds super polarized (extremely electrophilic/acidic) so the alcohol has no problem bonding to the now super e-deficient carbon of the carbonyl bond. Unlike the synthesis of salicylic acid that required heating at reflux, the synthesis of aspirin occurs rapidly even at room temperature due to the extreme reactivity of the anhydride; even though the anhydride is extremely reactive due to it's extreme electronegativity and good leaving group, we will ensure reaction by using as acid-catalyst as well.



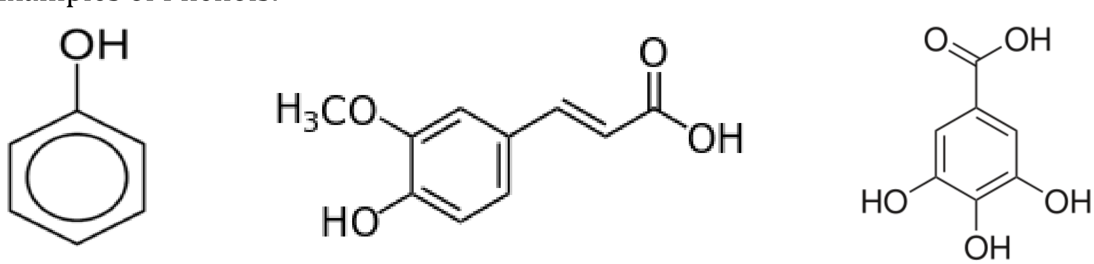
acetic anhydride **salicylic acid** **acetylsalicylic acid** **acetic acid**



$FeCl_3$ Test for Phenols

To test the purity of your aspirin, you will perform the Iron (III) Chloride Test for the presence of a phenol. A phenol consists of an aromatic ring bonded to –OH group. How would you classify salicylic acid? Aspirin? Upon addition of a few drops of $FeCl_3$, a clear yellow liquid, to your solid sample, the appearance of any purple color indicates the presence of a phenol. What color will salicylic acid show? What color will aspirin show?

Examples of Phenols:



The "Pain"ful Facts…

No one completely understands how pain works. Actually, a lot is known about pain, but the more we find out the more questions arise. So let's take a simplified view.

Pain is really something you feel in your brain. For example, let's say you hit your finger with a hammer (please don't try this at home). The part of your finger that is damaged has **nerve endings** in it -- these are little detectors in your joints and your skin that feel things like heat, vibration, light touch from things like the mouse you're holding, and, of course, big crushing shocks like being hit with a hammer. There are different receptors for each of these types of sensations. The damaged tissue in your finger also releases some chemicals that make those nerve endings register the crushing shock even stronger -- like turning up the volume on your stereo so you can hear it better. Some of these chemicals are prostaglandins, and working cells in the damaged tissues make these chemicals using an enzyme called cyclooxygenase 2 (COX-2).

Because of the **prostaglandins**, the nerve endings that are involved now send a strong signal through nerves in your hand, then through your arm, up your neck and into your brain, where your mind decides this signal means, "HEY! PAIN!" The prostaglandins seem to contribute just a portion of the total signal that means pain, but this portion is an important one. In addition, prostaglandins not only help you to feel the pain of the damaged finger, but they also cause the finger to swell up (this is called **inflammation**) to bathe the tissues in fluid from your blood that will protect it and help it to heal. Remember this is a simplified version of the pain story; lots of chemicals seem to be involved in this process, not just prostaglandins.

This pathway works very well as far as telling you your finger is hurt. The pain serves a purpose here: It reminds you that your finger is damaged and that you need to be careful with it and not use it until it's healed. The problem is that, sometimes, things hurt without the hammer or for any other good reason. For example, sometimes you get a headache, probably because your scalp and neck muscles are contracted from stress or because a blood vessel in your brain has a spasm. Many people have arthritis, which is swelling and pain in the joints such as the knuckles or knees, and this problem can not only make people uncomfortable, it can damage the joints permanently. And many women have pain in their abdomens during their periods, usually known as cramps, for no known useful reason. These processes appear to involve prostaglandins as well.

Aspirin helps these problems by stopping cells from making prostaglandins. Remember the enzyme, COX-2? It is a protein made by your body's cells whose job is to take chemicals floating around in your tissues and turn them into prostaglandins.

COX-2 can be found in lots of normal tissues, but much more of it is made in tissue that has been damaged in some way. Aspirin, it turns out, sticks to COX-2 and won't let it do its job; it's like a lock you put on your bicycle. The bicycle won't move with the lock on, and COX-2 can't work with aspirin stuck in it. So by taking aspirin, you don't stop the problem that's causing the pain, like the tight muscles in your scalp, or the cramping in your abdomen, or the hammer-damaged finger. But it does
"lower the volume" on the pain signals getting through your nerves to your brain. http://health.howstuffworks.com/medicine/medication/aspirin2.htm

Objective: 1. To successfully convert your salicylic acid from experiment 2 to pure acetyl salicylic acid. 2. To learn about the Iron (III) Chloride test for the presence of phenols.

Procedure:

1. Before obtaining all of your chemicals, check out a micro stir bar from your instructor, put it in a 10mL flask, and check to make sure it spins/vibrates when placed upon the hot/stir plate - just turn the stir knob to 1 to 2.

2. Set up a 45-50˚C water bath in a 50-100mL beaker - the water level should not be too high - clamp the 10mL flask in the water bath AND check to make sure the stir bar can still SPIN/vibrate. If it does not, then adjust the height of your flask as needed.

3. After set-up, unclamp the 10mL flask so that you can now slowly combine 2.0mL of acetic anhydride with 0.500 grams of your salicylic acid from the previous experiment in the 10mL flask. Swirl the flask to thoroughly mix. If you have less than 0.500 grams, see your instructor to obtain additional salicyclic acid to complement yours.

4. Add 2 drops of 18M sulfuric acid and then reclamp in your warm water bath. Maintain the temperature of the water bath at 45-50˚C .

5. Heat until all the salicylic acid has been dissolved *PLUS an additional 10 minutes!*

6. Remove the flask from the water bath and add 5.0mL of ICE-COLD DI WATER to decompose the excess anhydride into a water soluble carboxylic acid AND induce crystallization of aspirin.

7. Put your flask in your own personal ice water bath – it may take a very long time to crystallize. Be patient! Help precipitation by "scratching" of the inside of your flask with a glass stirring rod - SCRATCH don't stir.

8. Filter your crystals using a micro filtration set-up. Rinse the flask and your crystals with ice-cold water.

9. (Most likely the second day).... Recrystallize your crude aspirin from 95% ethanol. Filter and collect your pure aspirin.

10. Bring a small amount of your aspirin in a small test tube or beaker to your Instructor. Perform the $FeCl_3$ test with your instructor to test for purity. Good luck!

12BL Prelab Experiment 4: Aspirin Synthesis

1. Who is the limiting reactant in the experiment?

2. Who is the excess reactant in the experiment?

3. Calculate the theoretical yield of aspirin. All calculations should be shown using dimensional analysis including chemical names and units.

4. Why is reflux of the reaction not necessary in this experiment?

5. Why is water added after the reaction between salicylic acid and acetic anhydride is complete?

6. Write a balanced <u>equation</u> for the reaction between water and acetic anhydride. (Show organic molecules in Lewis structure form, inorganic molecules in molecular form.)

12BL Postlab Experiment 4: Aspirin Synthesis

$FeCl_3$ Test- bring your final product to instructor to test purity: Color __________

Instructor Initials ______________

All work for your postlab questions must be shown NEATLY AND ALL NUMBERS MUST BE ACCOMPANIED BY UNITS & CHEMICAL NAMES in Calcs.

1. Show the complete esterification mechanism between isopropanol and propanoic anhydride using an acid-catalyst.

2. Using the structures of salicylic acid and aspirin, clearly explain which chemical is the stronger acid.

4. A small bottle of aspirin holds about 120 tablets. Each tablet contains about 0.33 grams of aspirin. *Current small-scale prices* are as follows: Salicylic acid = $18.57 for 50 grams. Acetic Anhydride = $16.02 for 5mL.

a. Calculate the cost of salicylic acid needed to prepare the aspirin contained in this bottle.

b. Calculate the cost of acetic anhydride needed to prepare the aspirin contained in this bottle. (Gen Chem Review: convert mass aspirin to moles of aspirin to moles of anhydride to grams of anhydride to mL of anhydride.... what do you need to look up for each of these steps?)

c. Based on your answers, explain how it is possible that a bottle of aspirin can be purchased for just a few dollars?

5. Old aspirin should be thrown away! Aspirin slowly decomposes in the presence of atmospheric moisture to form salicylic acid and acetic acid – much too acidic for your body to metabolize.
ON YOUR OWN: You need to show a **plausible mechanism** for the degradation of aspirin in the presence of moisture (water) into salicylic acid and acetic acid. Your only two reactants are water (your attacking base) and aspirin! You should be confident in knowing that bases attack acids; that “negatives attack positives”. Effort please! USE BACKSIDE.