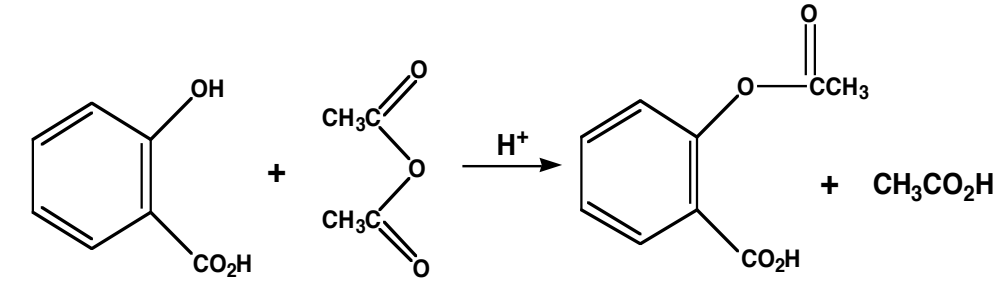
University of Pennsylvania Department of Chemistry

Pre-Lab Background & Write-up Instructions - Experiment # 9:
Preparation of Aspirin and Oil of Wintergreen

- **Refer also to the listing of this experiment in the Catalyst text from Chem 53.**

Introductory Remarks, Questions, & an Example:

In this experiment, you will have the opportunity to synthesize a compound that is probably the most frequently ingested and purchased over-the-counter pharmaceutical - aspirin - aka acetylsalicylic acid ($C_9H_8O_4$). As your lab text mentions , it is an antipyretic (reduces fever) as well as an analgesic (reduces pain). Aspirin is also an anti-inflammatory agent. The synthesis protocol that you will use is to combine salicylic acid ($C_7H_6O_3$) - the limiting reagent here - with an excess amount of acetic anhydride ($C_4H_6O_3$). The products from the stoichiometric reaction are aspirin as well as acetic acid ($C_2H_4O_2$). Hopefully, you remember acetic acid as the monoprotic acid that is the major ingredient in vinegar (do you recall ANAL-395 from Chem 53?). The overall synthesis reaction - showing the structural formulae of reactants and products - is shown in Figure 1 on the following page. Your text symbolizes the reaction in an "abbreviated" structural formula format:



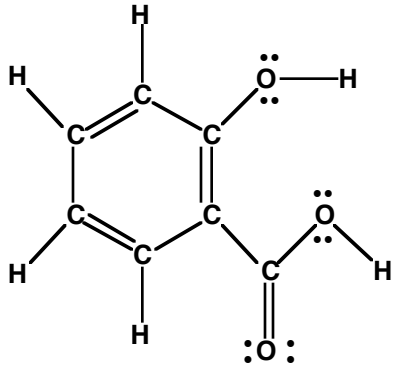
Salicylic Acid + **Acetic Anhydride** → **Acetylsalicylic Acid (Aspirin)** + **Acetic Acid**

Compare this version with Figure 1 so that you may become familiar with a common way to depict compounds and reactions that you will often see in organic chemistry texts - as well as biochemistry, physiology, and pharmacology texts. [Compounds depicted in this notation often do not show some or all of the carbon atoms. In that case, each unlabeled vertex of bonds implies a carbon atom. Also, each carbon atom is presumed to have four bonds (an octet) of electrons. Any carbon atom showing less than four bonds explicitly is presumed to be single bonded to enough hydrogen atoms to make up the difference. Any (non-carbon) "hetero"-atom is explicitly shown - along with all of its bonds; however, lone pair electrons are traditionally omitted. So, lone pair electrons must be inserted to allow each hetero-atom achieve its octet.] You should be able to easily switch between these two formats.

Interestingly, salicylic acid is actually the compound of medicinal value. It is absorbed into the blood stream through the intestines. However, salicylic acid is rather acidic ($K_a \approx 10^{-3}$) and thus irritates the mouth and stomach linings. Acetylsalicylic acid is less acidic ($K_a \approx 10^{-4}$) by a factor of ten and so does not cause this irritation. In addition, this compound is readily converted (hydrolyzed) to salicylic acid in the aqueous alkaline environment of the intestines. A bit of history reveals that salicylic acid was used in folk medicine for relief of mild pain and fever for over two hundred years. The natural source of salicylic acid is the bark of the willow tree from the genus *Spirea*. In 1763, Reverend Edmund Stone described his success in treating fever with a powdered form of the bark from this willow tree - termed salicin. Hydrolysis of salicin yields the aforementioned salicylic acid. Acetylsalicylic acid was synthesized in 1853, but was not used on a regular basis until 1899. Note that acetylsalicylic acid (see Figure 1) differs from

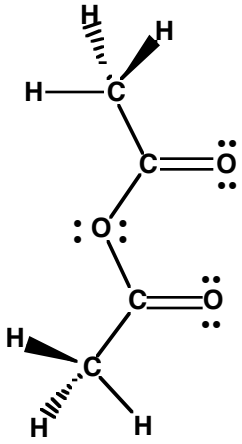
salicylic acid in that the H of the OH group attached to the benzene ring is replaced by an acetyl group ($-C(O)CH_3$). For any trivia fans, the name aspirin was coined from the German word for the compound - acetylspirsäure - the "spir" portion derives from the genus *Spirea* and the "säure " portion is the German word for acid. So, "aspirin" is the acetylated compound which derives from a plant of the genus *Spirea* that is an acid!! With this deeper appreciation of aspirin, let's look at the synthesis reaction and related compounds in some more detail.

Synthesis Reaction :



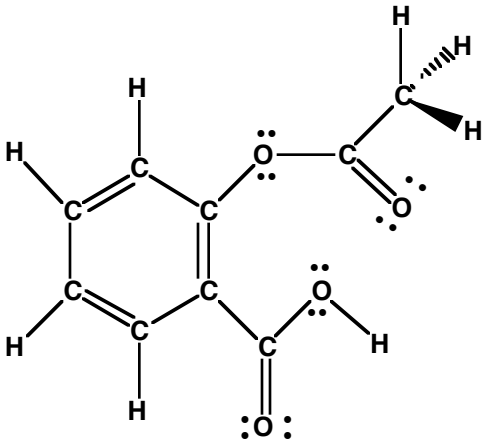
Salicylic Acid
$C_7H_6O_3$

+



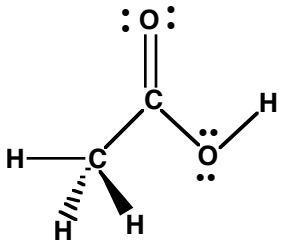
Acetic Anhydride
$C_4H_6O_3$

Δ | **Conc. (18 M) H_2SO_4 (catalyst)**



Acetylsalicylic Acid (Aspirin)
$C_9H_8O_4$

+

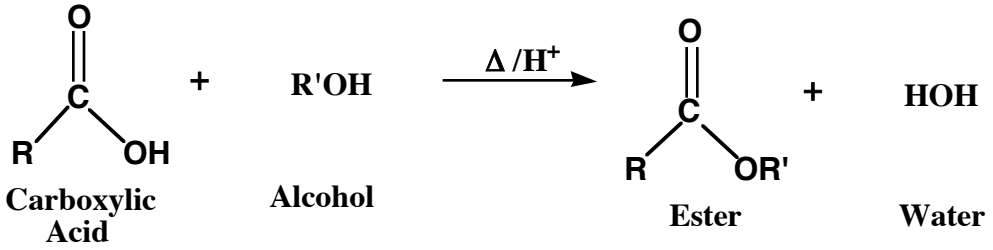


Acetic Acid
$C_2H_4O_2$

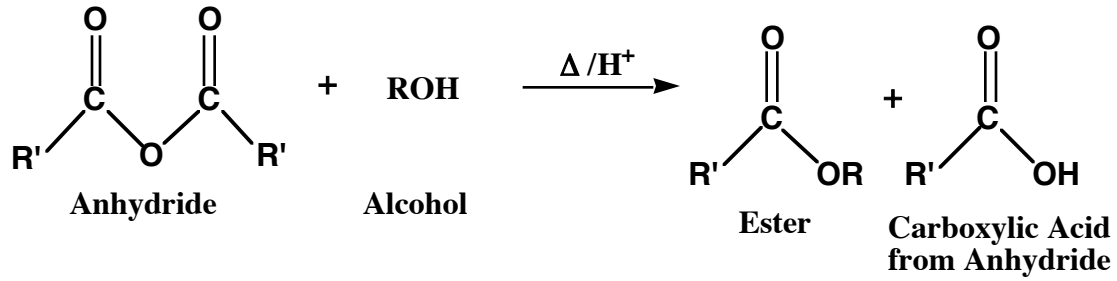
FIGURE 1

First, we list some of the types of compounds encountered in this experiment in Figure 2 on an upcoming page. Note that some of the compounds involved in this experiment may fit into more than one of the classifications listed in Figure 2. For example, acetic acid, salicylic acid, and aspirin can be classified as carboxylic acids, i.e., they each contain carboxylic acid functional groups. Aspirin can also be classified as an ester, i.e., it contains an ester functional group. Finally, salicylic acid can be classified as a phenol, whereas neither acetic acid nor aspirin can be classified as such. Verify these statements for yourself.

As noted above, aspirin can be classified as an ester (RC(O)OR'). There are some common methods to prepare an ester. One method involves the combination of a carboxylic acid and an alcohol and heat for a while to produce the ester and water. In addition, often a catalytic amount of an acid (such as sulfuric (H_2SO_4) or phosphoric (H_3PO_4)) is added. This reduces the time of reaction considerably. The generic reaction can be depicted as:



If salicylic acid and acetic acid are used as the reactants, which of the two "acids" - salicylic or acetic - would serve as the carboxylic acid and which would serve as the alcohol? Finally, the method that we will use in this experiment is the acid catalyzed combination of salicylic acid and acetic anhydride with heating. Note the structure of acetic anhydride and its relationship to acetic acid in Figure 1. Acetic anhydride results when two (2) molecules of acetic acid combine - eliminating a water (HOH) molecule in the process; hence, the name anhydride. You should be able to write down this reaction and determine - by looking at the structure of each molecule - how the combination generates water as the by-product. It turns out that the acetic anhydride is more reactive than acetic acid and - along with the catalytic amount of acid and heating - accomplishes the esterification more quickly. This reaction is listed in detail in Figure 1 and in abbreviated form on the initial page of this discussion. The generic reaction between an anhydride and an alcohol can be depicted as follows:



SOME COMMENTS ON EXPERIMENTAL PROCEDURE & PURIFICATION

The procedure (A) is listed on pages 104 and 105 of your lab text. Please read through it carefully. Some comments, clarifications, modifications, and elaborations are listed below. Be sure you incorporate this into the listed procedure so that you can achieve optimum results along with a careful understanding of what is happening and why.

Filtrations will be done in a Büchner filtration set-up. [Recall the synthesis of H_xWO_3 in Experiment # 299 from Chem 53.] Your T.A. will go through the procedure to remind you. Follow the listed procedure A (pages 104-105) in your lab text . The product collected at this stage in the procedure will be referred to as the "crude product" below. We will modify an optional recrystallization procedure that is listed on pages 104-105. This will hopefully yield an aspirin product that is less contaminated with impurities although the amount of recovered product may be attenuated.

Before you attempt the recrystallization procedure, thoroughly dry your aspirin product and weigh it. Use the analytical balance and be sure to subtract the weight of the pre-weighed filter paper (also weighed on the analytical balance). Then, test a small portion of this collected dried aspirin for purity. Follow the procedure in your lab text involving $FeCl_3$(aq) solution. To enhance the "degree" of purity, carry out the recrystallization procedure described below - <u>modified</u> from your lab text.

What is recrystallization? It is a very valuable technique used often in chemistry - especially in organic chemistry. Generally, the technique involves complete dissolution of the crude product in a suitable solvent and - ideally - regrowth of the crystals of the desired product (aspirin) with all impurities left behind. Specifically, we will carry out <u>solution recrystallization</u> which takes advantage of the fact that almost all solids are more soluble in hot versus cold solvent. So, if the crude product is dissolved in a volume of hot solvent that is insufficient to dissolve it when cold, then the desired pure product (aspirin) should form when the hot solution is allowed to cool gradually to room temperature and lower. Note - one modification of the listed procedure is to place your entire amount of crude product (probably less than 6 g) in **35 - 45 mL (no more) of deionized water <u>instead</u> of 20 mL of absolute ethanol**. Then, heat this mixture in a hot water bath **maintained at 80^{o}C - 90^{o}C until dissolution occurs**. **This temperature range is crucial and should be carefully maintained.** In this range - depending on sample size - the dissolution process should take about about 5 - 10 minutes. However, in this situation - due to the fact that the aspirin is more soluble than the impurities - the solution should be gravity filtered while hot (as described on page 105), allowing the still-dissolved aspirin to remain in the filtrate. Therefore, the collection vessel should be carefully cleaned and rinsed with distilled water before it is used to collect the hot solution in the recrystallization procedure. Thus, the <u>filtrate</u> should be saved here. The hot filtrate should then be allowed to cool gradually to room temperature. Then, this vessel containing the room temperature filtrate should be placed into an ice bath and allowed to cool further. Note that rapid cooling as well as agitation should be assiduously avoided - as this will lead to small crystals. Smaller crystals will create a larger overall surface area - which facilitates adsorption of impurities from the solution. [Ironically, formation of crystals that are "too large" may cause <u>occlusion</u> - the trapping of solution (along with any impurities) <u>within</u> the crystals.] In any event, gradual cooling without agitation is the best course of action. Once the purified aspirin has settled out, isolate the aspirin via Büchner filtration. Be sure that the set-up has been cleaned first. As specified in the lab text, wash the aspirin crystals in the Büchner funnel with a few milliliters of ice-cold distilled water after complete recrystallization. After the recovered recrystallized aspirin has thoroughly dried, obtain and record its mass. Finally, before you transfer the bulk of the recovered aspirin to a clean labeled vial, separate a small portion to check for purity.

(Continued - following <u>Figure 2</u>)

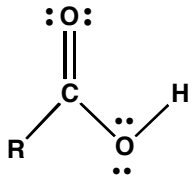
FIGURE 2

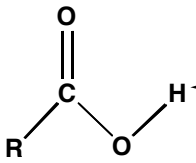
Classification of Some Compounds in Experiment 9:

In the structures below, R, R', R'', ... = unspecified hydrocarbon chains

Structural Formula **"Abbreviated" form**

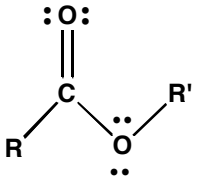
• Carboxylic acid:

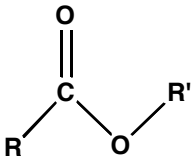




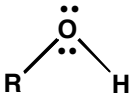
H attached to O is acidic.

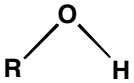
• Ester:



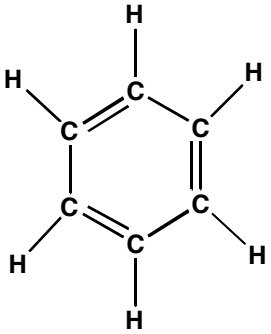


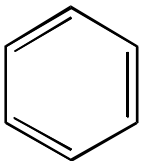
• Alcohol:



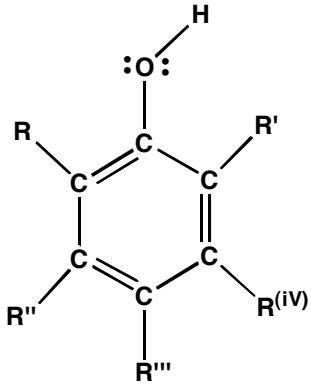


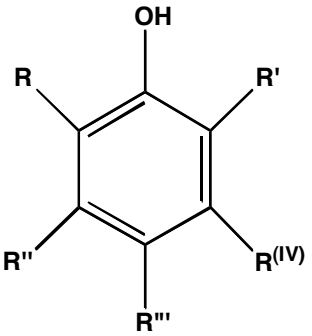
• Benzene (aromatic):



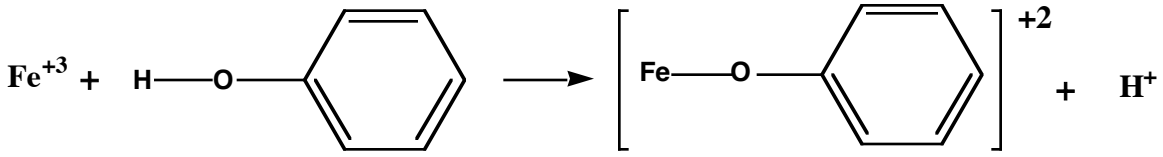


• Phenol - (aromatic) benzene ring with -OH group attached:





How can we determine the relative purity of the recovered (crude or recrystallized) aspirin? First, what do we mean by purity? We will assume that "foreign" impurities such as hair, dirt, and other chemicals not involved in the synthesis have been prevented (by you) from entering the recovered aspirin crystals. On the other hand, impurities involved in the synthetic procedure include: unreacted salicylic acid and/or acetic anhydride, as well as the acetic acid by-product. Much - if not all - of any unreacted acetic anhydride was probably hastened to decompose upon the addition of water early in the procedure. What is the reaction that takes place? You can detect any acetic acid present by carefully detecting the odor of the recovered aspirin. Recall that acetic acid is the major component of vinegar. Finally, how can we detect the presence of any unreacted salicylic acid (the "limiting reagent")? As your lab text states, salicylic acid contains an -OH group directly attached to the (aromatic) benzene ring. Such a species is termed a phenol (see Figure 2). Many compounds that contain this phenolic group will form colored complexes - ranging from green through blue and red through violet - when reacted with the ferric (Fe^{+3}) cation. Using the simplest possible phenol as an example, i.e., C_6H_5OH, the reaction can be depicted (in abbreviated form) as follows:



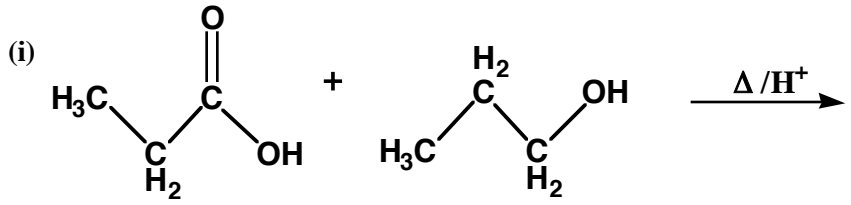
Phenol **"Purple" complex**

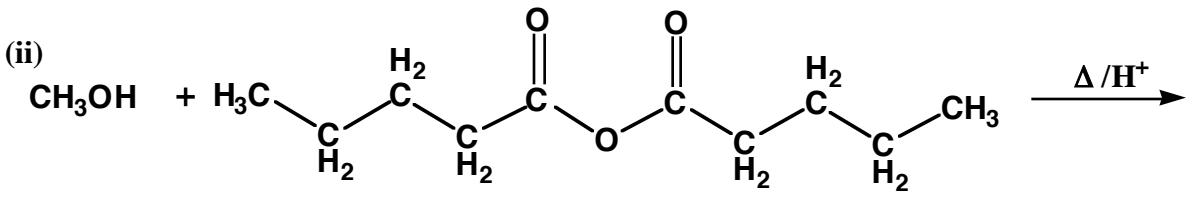
Note that aspirin does not contain the phenolic group.

Finally, in addition to submitting the bulk of the recrystallized aspirin in a clean labeled vial to your TA, determine the percent yield of the aspirin. Recall:

$$\textbf{\% yield of aspirin} = \frac{\textbf{actual yield}}{\textbf{theoretical yield}} \bullet \textbf{100 \% .}$$

Example:
(a) Predict the products of the following two reactions - (i) and (ii) - and balance them.





(b) 8.500 g of each reactant in (ii) are combined and 3.446 g of the product ester is isolated and purified. Determine the limiting reagent, theoretical yield of the ester (in g), and the percent yield of the ester.

Solution to Example:

(a) In condensed form, the two balanced reactions are as follows. In each case, the ester is listed in **bold**. Draw the full Lewis structures of all products in each reaction for yourself.

(i) $CH_3CH_2CO_2H + CH_3CH_2CH_2OH \longrightarrow \mathbf{CH_3CH_2C(O)OCH_2CH_2CH_3} + H_2O$

(ii) $CH_3OH + CH_3CH_2CH_2CH_2C(O)OC(O)CH_2CH_2CH_2CH_3 \longrightarrow$

$\mathbf{CH_3CH_2CH_2CH_2C(O)OCH_3} + CH_3CH_2CH_2CH_2CO_2H$

(b) The molecular weight of the two reactants in (ii) are 32.05 g/mole for the alcohol (CH_3OH) and 186.28 g/mole for the anhydride ($C_{10}H_{18}O_3$). Given that 8.500 g of each reactant are combined, the moles of the alcohol and the anhydride are 0.2652 mol and 0.04563 mol, respectively. Since each reactant in (ii) reacts 1 : 1, the anhydride is the limiting reagent (LR) here and the alcohol is in stoichiometric excess. [Note - this is the reverse of what will be the case in Experiment 39.] Since 1 mole of the ester is produced for each 1 mole of the LR, 0.04563 mol is the theoretical yield of the ester ($C_6H_{12}O_2$). Since the molecular weight of the ester is 116.18 g/mole, **5.301 g** is the theoretical yield of the ester in grams. Thus, the percent yield of the ester is:

$$\textbf{\% yield of ester} = \frac{\textbf{3.446 g}}{\textbf{5.301 g}} \bullet \textbf{100 \%} = \textbf{65.0 \%}$$

Questions that you should be able to answer before beginning this experiment (as a result of the background reading and some careful thinking) are below. **Prepare the solutions to these questions and be prepared to submit them AT THE BEGINNING OF THE LABORATORY PERIOD.**

1. Consider two of the compounds in this synthesis: **salicylic acid** (one of the starting materials), the product **acetylsalicylic acid** (i.e., aspirin). Refer to Figure 2 and to your background reading as needed, to answer the following. Of the four functional group classifications: an **alcohol (A),** a **carboxylic acid (CA),** an **ester** (**E**), a **phenol (P);** one of the two compounds can be classified in two of the above categories and the other can be classified in three of the above categories. Using the choices: **A, CA, E, P** - **which classifications apply to acetylsalicylic acid and which apply to salicylic acid? Explain.**
2. If we were to synthesize aspirin via the combination of acetic acid and salicylic acid, which compound would serve as the carboxylic acid and which would serve as the alcohol? Explain. In the actual synthesis - involving salicylic acid and acetic anhydride - does salicylic acid fulfill the same role? Explain.
3. In the discussion on purity of the recrystallized aspirin, it was stated that probably most - if not all - of the unreacted acetic anhydride decomposed in the aqueous environment. Write down the balanced reaction that describes this decomposition.
4. A typical Bayer™ aspirin tablet - reputed to be 100 % aspirin - contains 5 grains of aspirin. There are 15 grains in one gram. Assuming excess acetic anhydride, how many grams of salicylic acid would minimally be required to produce all of the aspirin in two Bayer™ aspirin tablets? Show all work and reasoning.

(NEXT PAGE - FOR WRITE-UP INSTRUCTIONS & POST-LAB QUESTIONS)

Experiment # 9 : Preparation of Aspirin and Oil of Wintergreen
Laboratory Procedure Reminders & Report Write-up Directions

- **BE SURE TO READS THE "EXPERIMENT NOTES" for Exp. #9 in the EXPERIMENT NOTES folder within Course Documents on Blackboard.**

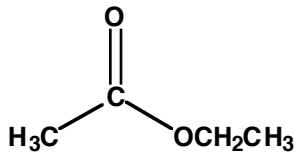
- **REMEMBER: FILL IN YOUR MEASURED DATA ON THE <u>POSTED</u> "RAW DATA" SHEET <u>BEFORE</u> YOU LEAVE LAB TODAY.**

- **REMEMBER: THE WRITE-UP FOR EXP. # 9 IS DUE AT THE <u>BEGINNING</u> OF THE <u>NEXT</u> LABORATORY PERIOD IN WHICH YOU MEET.**

- **YOU MAY RESERVE HANDING IN THE PRE-LAB ASSIGNMENT UNTIL YOU SUBMIT THE WRITE-UP. THE DISPENSATION IS FOR <u>THIS</u> LAB ONLY.**

- The write-up for Experiment # 9 will consist of the following items - in the order indicated:

1. **The answers to the Pre-lab Questions 1-4 for Experiment # 9. NOTE: YOU MAY HAND THIS IN WITH YOUR WRITE-UP**, as stated above.
2. **Page 107 (Section A - Synthesis of Aspirin). Be sure to show all work.**
3. The carefully worked out answers to questions **1, 2(a), 3, 4(a), & 5** on **pages 107-108**. If you don't have room to clearly write out the answers in the space provided, you may write out these answers on notebook paper. **Note: In question 4(a), on page 108 of the lab text, <u>ethyl acetate</u> has the structure**

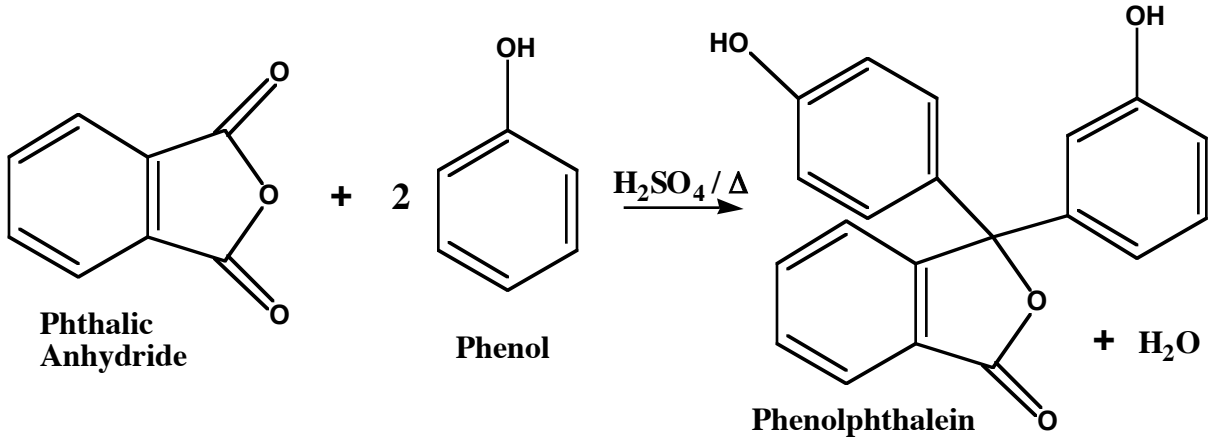


4. The carefully worked out and explained answer to the following problem - labeled "Problem" on the following page. Submit the explained solution to this problem on notebook paper.

- The **completed laboratory report** is considered to be items 1-4 above. **However, you may have already handed in the pre-lab questions. Thus, you must hand in** items **2-4 above** - in the order listed - **<u>stapled togethe</u>**r with your **NAME (Printed), CHEM COURSE # (54), & LAB SECTION #** clearly displayed at the top of the first page of the report.

(Next Page - for the Problem)

Problem:
Phenolphthalein - the often-used acid-base indicator as well as a non-prescription laxative - can be classified as an ester, but also contains other functional groups. It can be synthesized via a reaction similar to the one carried out in this experiment. Phthalic anhydride is combined with two moles of phenol to yield one mole of phenolphthalein and one mole of water. The reaction (in abbreviated form) is shown below:



Phthalic Anhydride **Phenol** **Phenolphthalein**

(a) Write down the molecular formula ($C_xH_yO_z$) for each reactant and product, specifying the numerical subscripts.
[Refer to Figure 2. Remember, in this notation each unlabeled vertex of bonds implies a carbon atom. Also, each carbon atom is presumed to have four bonds (an octet) of electrons. Any carbon atom showing less than four bonds explicitly is presumed to be single bonded to enough hydrogen atoms to make up the difference. Any (non-carbon) "hetero"-atom is explicitly shown - along with all of its bonds; however, lone pair electrons are traditionally omitted.]

(b) Besides being classified as an ester, give the possible other classification(s) of phenolphthalein according to its functional group(s).

(c) 9.000 g of phthalic anhydride is combined with 9.500 g of phenol - some H_2SO_4 is added and the reaction mixture is heated. When no more phenolphthalein is produced, it is isolated, purified and weighed. The mass of the purified phenolphthalein product is 11.650 g. Based upon this data, determine the **limiting reagent** as well as the **theoretical yield and percent yield of phenolphthalein**. Show all work and reasoning clearly and carefully.

- The total possible points for **Experiment # 9** are **60 points**. The points will be awarded in the following manner.

• **Pre-lab assignment - assigned questions from this lab document:**	12 points (4, 2, 2, & 4 points, respectively.)
• **Section A, on page 104-105 of the Catalyst text:**	12 points
• **Quality versus Quantity of synthesized aspirin:**	6 points
• **Solutions to Questions 1, 2(a), 3, 4(a), & 5 from pages 107-108 of the Catalyst text:**	19 points (1, 2, 6, 8, & 2 points, respectively.)
• **Solution to "Problem":**	11 points
TOTAL =	**60 points**