



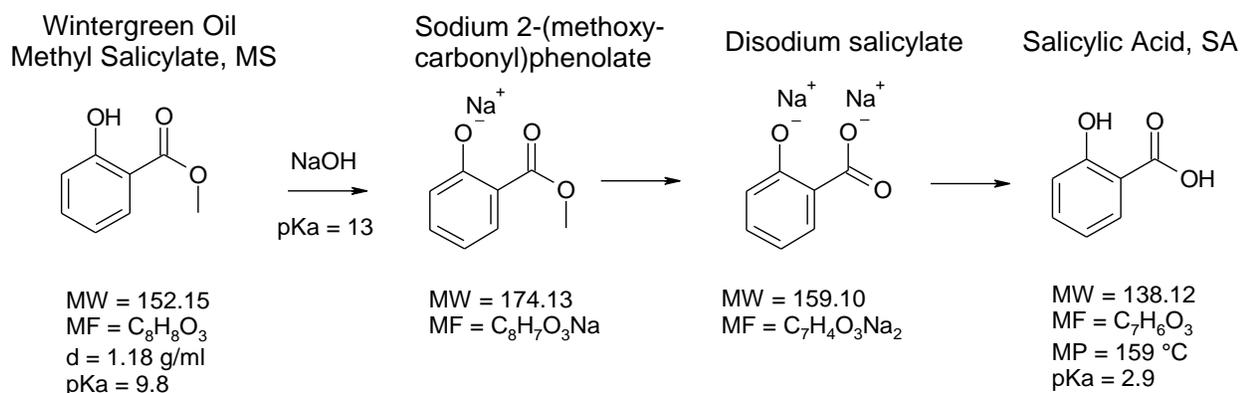
# The Synthesis of Salicylic Acid from Wintergreen Oil – Student Guide

## Background:

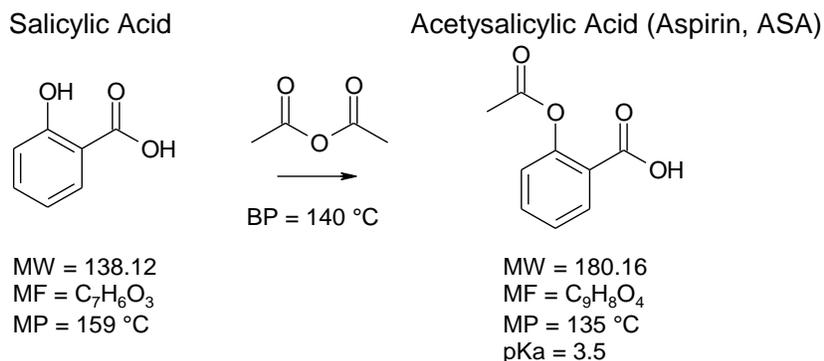
Our new company is preparing to manufacture aspirin by synthesis from wintergreen oil. The two step synthesis encompasses aqueous base hydrolysis of wintergreen oil (methyl salicylate, MS) to salicylic acid (SA) followed by acetylation to acetylsalicylic acid (aspirin, ASA).

## Scheme 1: Synthesis of Aspirin

### STEP 1: Hydrolysis of methyl salicylate



### STEP 2: Acetylation of Salicylic Acid



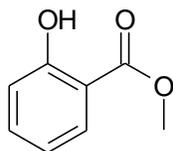
**You will be carrying out the first step, hydrolysis of methyl salicylate.**



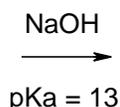
## Experimental Procedures

### STEP 1: Hydrolysis of methyl salicylate

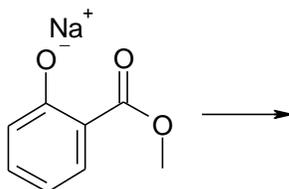
Wintergreen Oil  
Methyl Salicylate, MS



MW = 152.15  
MF = C<sub>8</sub>H<sub>8</sub>O<sub>3</sub>  
d = 1.18 g/ml  
pKa = 9.8

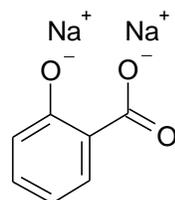


Sodium 2-(methoxy-  
carbonyl)phenolate



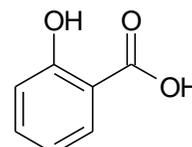
MW = 174.13  
MF = C<sub>8</sub>H<sub>7</sub>O<sub>3</sub>Na

Disodium salicylate



MW = 159.10  
MF = C<sub>7</sub>H<sub>4</sub>O<sub>3</sub>Na<sub>2</sub>

Salicylic Acid, SA



MW = 138.12  
MF = C<sub>7</sub>H<sub>6</sub>O<sub>3</sub>  
MP = 159 °C  
pKa = 2.9

**Important: Check off each step as you complete that step**

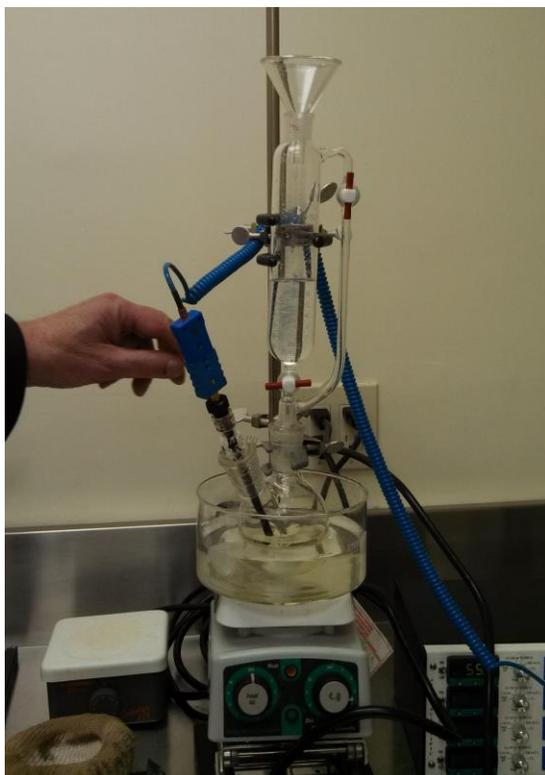
- Place a clean 250 mL 2-necked round bottom flask on a cork ring on a top load balance, zero the balance, add ~4.0 g of wintergreen oil with a pipette and record the weight to the nearest 0.01 g. Record the mass here: \_\_\_\_\_.
- Add water (25 mL) using the bottle top dispenser.
  - Is this a homogeneous or heterogeneous mixture? \_\_\_\_\_
- Gently add a stir bar by sliding down the side of the flask. **Do not drop** the stir bar directly into the flask.
- Securely clamp the reaction flask to a ring stand
- Place the heating mantle on top of the magnetic stirrer and raise the jack until it is snug to the flask.
- Turn on the stirrer to mix.
- Check that the bottom valve of the addition funnel is closed.**
- Measure out 15 mL of 6M aqueous NaOH into the addition funnel using the bottle top dispenser attached to the bottle labeled **6M NaOH** by pulling the pump up until it stops, then pushing down until it stops.
  - WARNING: sodium hydroxide (NaOH) is very caustic to the skin. If you get any on your skin, let the instructors know and immediately wash it off at the sink with cold water for 10 minutes.**



○ **Replace your gloves immediately if you get any of the hydroxide solution on them. Do not touch anything with contaminated gloves.**

- Place an equilibrating addition funnel to the top hole of the 250 mL flask.
- Place the thermocouple probe assembly into the side hole of the 250 mL round bottom flask.

Your reaction setup should look like PICTURE 1



**Picture 1**

- Add the first 5 mL of the 6M NaOH dropwise over 3-4 minutes by **carefully and slowly opening the bottom valve** of the addition funnel. You must do this carefully to avoid creating a gum ball in the reaction flask.
  - Does anything physically change during this addition?
  - What do you think is happening? (Hint: the pKa of methyl salicylate is 9.8, look at the reaction scheme above.)
  - Does the temperature of the reaction change? If so, how and why?
- Add the remaining hydroxide to the flask over 1 minute by opening the bottom valve of the addition funnel.
-

- After complete addition of the hydroxide, rinse the addition funnel with approximately 5 - 10 ml of di ionized water using a wash bottle. **Remember to be careful.**



Picture 2



Picture 3

- The power to the J-Kem Controller has been turned on and pre-set to 105 °C, do not flip the switch on the left side.
- Turn the power dial from “OFF” to “300 mL—2L” for your position number. Note the start time here: \_\_\_\_\_

While the reaction is heating, perform the following calculations in Table 1, but one team member must continue to monitor the reaction temperature. Lab awareness must be constantly maintained. Do not get distracted.

- Record the weight of methy salicylate used on line (1) of Table 1.
- Calculate the amount of moles of methyl salicylate and record on line (2) in the Table 1.  
 $\text{moles} = \text{g} / \text{Molar Mass}$
- Calculate the theoretical yield of salicylic acid and record on line (3) in Table 1.  
 $\text{g of salicylic acid} = \text{moles of methyl salicylate} \times \text{Molar Mass of salicylic acid}$
- When the reaction temperature reaches 96 °C. Note the time: \_\_\_\_\_
- Continue to heat the reaction for 20 minutes. Notice the droplets of water in lower part of the addition funnel. The water in the reaction is boiling and condensing, which is called refluxing.



After heating the reaction for 20 minutes, turn the power dial on the controller to “OFF.”  
Do not touch the switch on the left side of the controller. Note the time: \_\_\_\_\_

**Warning: the reaction vessel and heating mantle are HOT**

- Lower the lab jack and remove the heating mantle (**HOT**). Place a crystallizing dish beneath the reaction flask. Raise the lab jack so that the bottom of the crystallizing dish is just below the bottom of the reaction flask.
- Close the bottom stopcock of the addition funnel.
- Place the plastic funnel in the top opening of the addition funnel.
- To a clean 100-mL beaker add 36 mL of 3M aq HCl and transfer the acid to the addition funnel.
- Fill the crystallizing dish only half way with room temperature water and continue stirring.
- When the reaction temperature is  $\sim 60^{\circ}\text{C}$ , begin adding  $\sim 20$  mL of the acid dropwise to the reaction solution over 2-4 minutes.

**Warning: Acid addition to base is exothermic (produces heat).  
You may observe a temperature rise. Stop adding the acid if the  
temperature rises above  $60^{\circ}\text{C}$**

- Dropwise add the remaining acid solution over 5 minutes while maintaining a temperature of less than  $60^{\circ}\text{C}$ .
  - What happened during the initial addition of acid? \_\_\_\_\_
  - What happened during this final addition of acid? \_\_\_\_\_
- When the addition of acid is complete, check the pH of the reaction mixture and ensure that the pH is  $< 2$  using the pH paper supplied.
  - Remove the temperature probe from the reaction flask and dip the glass rod into the reaction mixture.
  - Touch the wet end of the glass rod to the pH paper.
  - If the pH is  $< 2$ , place the glass rod in the Hydrolysis Waste container and proceed to the next step
  - If the pH is  $> 2$ , dropwise add 3M HCl from the 3M HCl dropping bottle and retest the pH. Continue until the pH is  $< 2$  and proceed to the next step.
- Replace the temperature probe into the reaction flask.
- Add lots of ice to the water bath and cool the reaction mixture to  $10^{\circ}\text{C}$ .
- The instructor will help you with the following steps:
  - Using the lab jack, lower the stirrer and ice bath from the reaction flask.
  - Remove the additional funnel and carefully place it in the Hydrolysis Waste container.
  - Remove the thermocouple and lay it aside.



- Turn off the J-Chem Controller for your position.
  - Carefully remove the reaction flask from the apparatus.
  - One member of the team should hold the reaction flask upright so that it does not tip and spill your product.
- Place a 60-mL sintered glass filter funnel onto a cone rubber adapter set on a 500 - 1000 mL filter flask that is securely clamped on a ring stand. Attach the side arm of the flask to a vacuum source and turn on the vacuum.
- Gently swirl the reaction flask, and then pour the contents of the reaction flask into the filter funnel.
- Using the chilled DI water squeeze bottle, rinse the reaction product off the sides of the reaction flask, swirl gently, and transfer any remaining solids to the filter. Repeat twice.
- Using a magnetic retriever, remove the stir bar from the reaction mixture, Wash the magnetic stir bar and filtrate with water two times each with approximately 20 mL of cold DI water.
  - What is being washed from the product? \_\_\_\_\_
- When almost no solution is dripping from the filter funnel, turn off the vacuum source.
- Label a small crystallizing dish with your names. Weigh the labeled crystallizing dish and record its mass to the nearest 0.01 g. Tare mass: \_\_\_\_\_ g
- Using a spatula, carefully transfer all of the filtrate to the weighed crystallizing dish. Place a Kimwipe and rubber band on top of the crystallizing dish to prevent contamination.
- Place the covered crystallizing dish into the vacuum oven and dry at 90°C under vacuum for 30 minutes.
- Turn off the vacuum and carefully remove the crystallizing dish from the oven.

**Warning: the crystallizing dish will be very hot!**
- Allow the crystallizing dish to cool to room temperature. Remove the Kimwipe and rubber band, and weigh the crystallizing dish to the nearest 0.01 g. Gross mass: \_\_\_\_\_ g
- Calculate the amount of product in the crystallizing dish. Dried product mass: \_\_\_\_\_ g Record the Dried product mass in Table 1 on line (4).
- After the solids have dried for 30 minutes, one team member is to proceed to the IR station. Bring your sample of methyl salicylate with you for identity assays. When finished with the IR, perform a Melting Point Determination.
- The other team member is to proceed to the Spectrophotometer station for the Fe(III)-Salicylic Acid Assay.

## Analytical Procedures

### IR (identity)



The infrared spectrum of each organic compound is unique to the types and number of bonds in the molecule. Obtain an IR spectrum for methyl salicylate and salicylic acid. Compare to known identified spectra.

### **Method:**

Sample preparation:

**The instructor reviews the following steps before the students begin their work.**

#### **Running a Background IR Spectrum**

1. Place one salt plate in the sample holder and lay the holder flat on the bench top.
2. Place a second salt plate over the first.
3. Place the cover over the plates and insert the holder into the IR spectrophotometer.
4. Record the background spectrum.

#### **Preparing a Sample in Acetone**

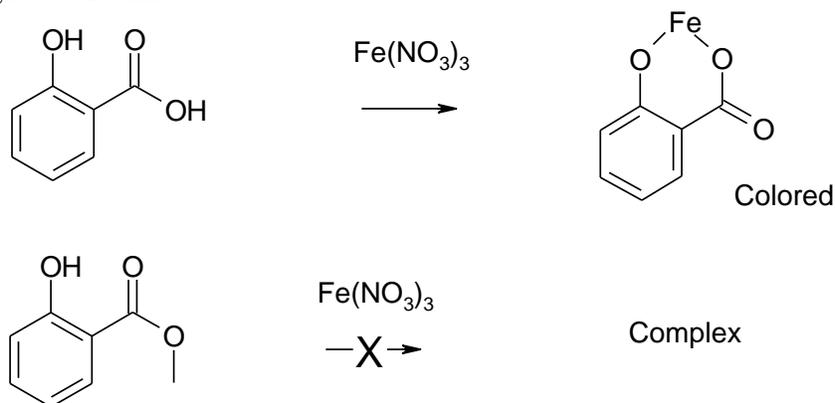
1. Using the spatula, transfer a very small amount of your sample to the agate mortar. Note each spatula is marked with line to provide guidance on the amount of sample required.
2. Grind the sample to a very fine powder using the agate pestle.
3. Add 4 drops of Acetone using micro pipette to dissolve the sample.
4. Place one salt plate flat on the bench top.
5. Place one drop of the Acetone / sample solution on the face of the salt plate.
6. Allow to evaporate and the sample to crystallize.
7. Carefully place the salt plate sandwich into the sample holder.
8. Carefully place the cover over the plates and insert the holder into the IR spectrophotometer.
9. Record the sample spectrum.
  - a. Select instrument from the menu
  - b. Select scan background or scan sample
  - c. Enter the sample ID: background, Acetone or unknown ID
  - d. Click OK to begin scan
  - e. Select View and Label Peaks from the menu
  - f. Print a copy of each spectrum



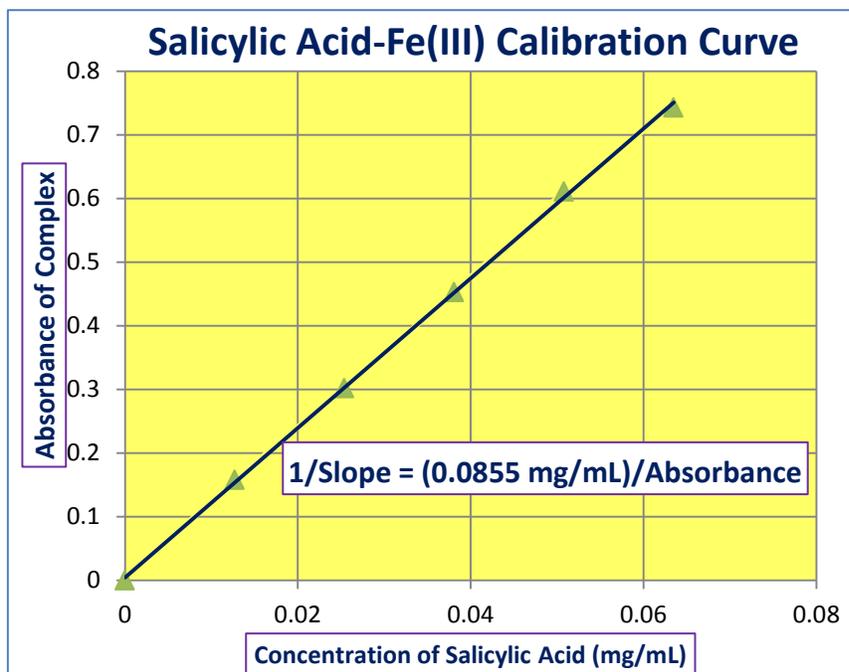
10. After obtaining the spectrum, disassemble the holder and wipe both plates clean with a Kimwipe.
11. Place a few drops of isopropanol on each plate and wipe clean with a new Kimwipe.

### Spectrophotometric Fe<sup>+3</sup> Assays

Salicylic Acid is an *ortho*-substituted carboxylic acid phenolic aromatic ring system. These ring systems can uniquely bind to iron(III) salts which are purplish in color and absorb visible light in a range with a maximum at 520 nm. Methyl salicylate does not bind with Fe(III), remains colorless, and does not absorb light at 520 nm.



This allows a quantitative measurement to be made of solutions of salicylic acid in water. Known samples of the iron complex were prepared at various concentrations and the amount of light absorption was measured at each concentration. A graph was prepared of absorbance (y-axis) vs. concentration (x-axis). If a sample of salicylic acid is weighed and the absorbance measured, then the difference between the expected absorbance and the observed absorbance can be used to determine the amount, or purity, in the sample.



## Spectrophotometric purity and quantitative analysis

### Method:

Sample preparation:

- Weigh 25-35 mg (to 3 significant figures [e.g., 33.2 mg]) of the isolated salicylic acid into a 200 mL volumetric flask. Record the mass of salicylic acid \_\_\_\_\_.
- Fill the volumetric flask to the 200 mL mark with DI water and shake to dissolve the salicylic acid.
- Using a bottle top dispenser, measure 5.0 mL of the 0.02M Fe(NO<sub>3</sub>)<sub>3</sub> solution into a 10 mL volumetric flask.
- Dilute the solution to the 10 mL line with salicylic acid solution. The clear solution will turn purple when the yellow Fe(III) solution is added.
- Calculate the theoretical concentration = mass of salicylic acid (mg) / (2 × 200 mL) (Why is the factor “2” in the denominator?)
- Record the theoretical concentration \_\_\_\_\_.
- Run the spectrometer blank using the Fe(III) solution in both cells.
- Measure the absorbance (peak height) at the absorbance maximum (~520 nm) and calculate the actual concentration of salicylic acid and the product purity.



Actual concentration =  $0.0855 \text{ (mg/mL)} \times \text{Absorbance}$  \_\_\_\_\_

Purity (%) ( $\text{Fe}^{+3}$  assay) =  $\text{actual concentration} / \text{theoretical concentration} \times 100\%$

Record the Purity (%) ( $\text{Fe}^{+3}$  assay) (**5**) in Table 1.

### MP (identity and purity)

Each crystalline organic compound has a unique melting point related to the stability of its crystal lattice energy. Measure the melting point of each dried crystalline solid that was obtained and record on line (**9**) in Table 1. Compare to the Theoretical melting point for pure salicylic acid listed in line (**10**) in Table 1

### Method:

- Dip the open end of a melting point capillary into the pile of crystals.
- Invert and tap the tube on the desk to collect the crystals at the bottom.
  
- Place the capillary into the melting point apparatus.
- Turn the unit on and watch the sample through the sight glass.
- Record the temperature when the sample begins to melt and when fully melted
- Record melting point range on line (**9**) in Table 1. Compare to the Theoretical melting point for pure salicylic acid listed in line (**10**) in Table 1

### Calculations:

Upon completion of assays, complete Table 1.

- Actual Yield (**6**) =  $\text{Dried product mass (4)} \times \text{Purity \% (Fe}^{+3} \text{ assay) (5)} / 100\%$
- Amount of salicylic acid (**7**) =  $\text{Actual Yield (6)} / \text{Molar Mass (0)}$
- Hydrolysis % Yield (**8**) =  $\text{Actual Yield (6)} / \text{Theoretical Yield (3)} \times 100\%$

### Conclusions and Evaluation

1. Summarize the results in the tables.
2. Pool your results on the hydrolysis and acetylation steps and prepare a short presentation on your evaluation of the hydrolysis of methyl salicylate to salicylic acid.
3. How might you evaluate the success of the hydrolysis of methyl salicylate to salicylic acid?



4. What was the reproducibility of the reaction yields?
5. What other assays might be of value in determining the quality of the products?
6. What recommendations does the synthesis team have to make?

**Table 1**

	Starting Material/ Product:	Methyl Salicylate	Salicylic Acid
	Molar Mass (g/mole)	152.15	138.12
1	Mass of methyl salicylate (g)		
2	Amount of methyl salicylate (moles)		
3	Theoretical yield of salicylic acid (g)		
4	Dried product mass (g)		
5	Purity % (Fe <sup>+3</sup> assay)		
6	Actual Yield of salicylic acid (g)		
7	Amount of salicylic acid (moles)		
8	Hydrolysis % Yield		
9	Melting Point observed (°C)		
10	Theoretical Melting Point (°C)		159°C

## S2S Team Report

### Step 1. Hydrolysis

#### Methyl salicylate identification ( yes or no)

Tests	Team 1	Team 2	Team 3	Team 4
IR conformity				

#### Step 1 Salicylic Acid Analyses

Tests	Team 1	Team 2	Team 3	Team 4
MP (135 lit)				
Spectrophotometric Weight % Assay				
Yield				