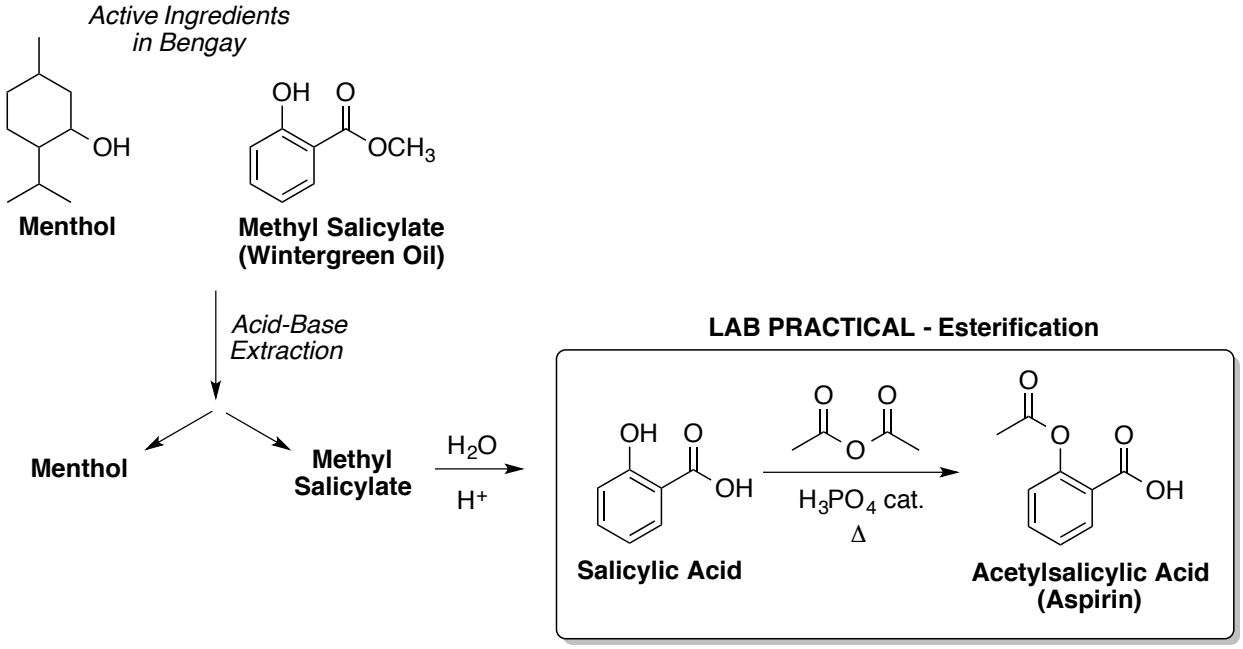
Experiment 6 – Synthesis of Aspirin, Lab Practical Exam

Preparation

- Students come to lab with a pen/pencil, calculator, and pre-lab questions (no notebook).
- Students will carry out the experiment individually; no consulting with lab-mates.
- TAs may not be able to answer procedure-related questions during the exam, but can help with safety-related issues. TAs CAN answer questions before the exam – plan ahead!
- **Keep your eyes on your own work (exam and wet lab work)**
- The exam packet will include the esterification reaction scheme below, reagent table, an abbreviated version of the procedure, spaces and/or tables to record data, IRs & NMRs (tables of values included), and cleanup and safety notes.
- The entire lab will be performed and turned in within the assigned exam period.
- **All wet lab work and cleanup must be completed within one hour and 15 minutes**.
- A minimum of 30 minutes remains for analysis. You may work on the in-lab questions, including analysis of provided IR & NMR spectra, at any time during your exam period.

In this experiment, students will perform the final step in the synthesis of aspirin. The pre-cursor starting material to be used in this experiment, methyl salicylate, could be isolated from the topical ointment Bengay using an acid-base extraction (**Scheme 1**). Students should review the extraction of methyl salicylate from menthol as part of the learning objectives of this course, as it is similar in theory to the isolation of the active ingredients in Excedrin (experiment 2). Hydrolysis of methyl salicylate yields salicylic acid, the starting material in the synthesis of aspirin.

Students will carry out the esterification of salicylic acid using acetic anhydride and isolate aspirin as a white solid (**Scheme 1**). This is not strictly a Fischer esterification since an acid anhydride is used in place of a carboxylic acid. However, the mechanisms are analogous and proceed *via* nucleophilic acyl substitution. Conversion to product will be confirmed using an iron (III) chloride chemical test in comparison to standards. IR spectra of starting material and product as well as ^{1}H and ^{13}C NMR spectra of aspirin will be analyzed from the literature.



Scheme 1. Outline in the acid-base extraction of Bengay, hydrolysis to salicylic acid, and esterification to synthesize aspirin.

PROCEDURE - *Only the bold sentences will be given on the exam (students do not bring lab notebooks or this handout); the paragraphs below explain the bolded phrases in more detail.*

To a 15-mL round-bottom flask equipped with a small stir bar was added salicylic acid (200 mg), acetic anhydride (2 mL), and phosphoric acid (2 drops). A microscale water-jacketed condenser was attached and the system was heated in a boiling water bath for 5 minutes. After cooling, the reaction was quenched with water (1 mL)* and heated again in the water bath (5 min).

Fill a small crystallizing dish half way with water.[1] Place on a hotplate (medium setting) and bring to a gentle boil. You may do this when you enter the lab, before the TA's pre-lab talk. *The water bath must be pre-heating before obtaining reagents.* In the meantime, in a clean and **dry** 15-mL round-bottom flask add a small stir bar and approximately 200 mg of salicylic acid. Add 2 mL of acetic anhydride using the pluringe provided (keep this and all reagent bottles in the fume hood). Finally, add 2 drops of H_3PO_4 to catalyze the reaction.

Attach a microscale condenser using a small amount of grease and Keck clip. Place the apparatus half-way in the *boiling* water bath and let the system react for about 5 minutes. The reaction will not proceed if the water bath is not at a boil for the full 5 minutes. *Carefully* move the apparatus out of the water bath and allow the system to cool to room temperature. Add 1 mL of water through the top of the condenser to quench excess acetic anhydride. Place the system back in the water bath and allow this to react for an additional 5 minutes. There is no need to continue heating the water bath during this time - just the warm water bath is sufficient.

The reaction was cooled to room temperature and the crude reaction mixture was pipetted into a small beaker using water (2 mL) to aid in the transfer. Aspirin was precipitated from water (additional 3 mL) and isolated *via* vacuum filtration.

Carefully remove the water bath from the hot plate using a hot mitt and let the reaction apparatus cool to room temperature. Use a pipet to transfer the liquid to a labeled 50-mL beaker. Wash the walls of the RBF with 2 mL of water to facilitate transfer of any reaction mixture still in the flask. Add 3 mL of water and 2 small pieces of ice to the beaker then cool the system in an ice-water bath for a few minutes. Once the solution has cooled, raise your hand to obtain a seed crystal from your TA. Allow crystals to form undisturbed in the ice-water bath for an additional 5 minutes (Pro-tip: crystals tend to form when you're not watching them!). Set up the vacuum filtration apparatus while crystals continue form and pre-weigh the filter paper. Vacuum-filter the product using a Hirsch or Buchner funnel. Either funnel is adequate if the correct size filter paper is used or cut to the right size. Carefully collect a small amount of aspirin off the filter paper for the chemical test (microspatula tip). The effect on product yield is negligible. Let the solid dry on the filter paper with the vacuum on for 10 minutes while performing the chemical tests. Weigh the product and have your TA initial your exam to confirm you obtained product.

Salicylic acid and water standards and the product were tested for phenols using the ferric chloride test in three separate test tubes using 1 mL of 0.1% $FeCl_3$ in each.

Start early with the standards while the reaction is running, aspirin crystals are forming, or any other down time. Obtain reagents in the fume hood then bring the samples back to your workspace. Prepare 3 labeled test tubes each with 1 mL of a 0.1% aqueous ferric chloride solution in each. To one test tube, add a small amount of salicylic acid (microspatula tip). Add the aspirin product to another test tube. Add a drop of water to the third test tube. Observe any change in color. A red-purple color is a positive test for phenols; yellow is considered negative. Have your TA initial your exam to confirm that you have completed the chemical tests.

[1] A hot-plate, ring stand, clamp and holder, crystallizing dish, microscale condenser, Keck clip, and a vial of pre-weighed salicylic acid will be waiting for you at your station. You're welcome!

TA Check-ins

1. Reaction set up
2. Vacuum filtration apparatus
3. Crystallized product
4. Chemical tests

Table 1. Clean up and safety instructions (provided in the exam packet)

<table>
<tr><th>Clean-up</th><th>Safety</th></tr>
<tr><td rowspan="2">Keep all reagents in the fume hood and clean up spills with spill mats, NOT the sponges from the sink.</td><td>Label all glassware (except for reflux setup).</td></tr>
<tr><td>Phosphoric acid is corrosive – change gloves after use</td></tr>
<tr><td>Return all shared glassware, cleaned, to its original location.</td><td>Acetic anhydride is a lachrymator (induces tears) – wear goggles</td></tr>
<tr><td>Unplug hotplates. Disassemble the reflux and filtration apparatus – leave materials as you found them.</td><td>Wear gloves, goggles, and lab coat at all times.</td></tr>
<tr><td>Solid waste: Used pipets, filter paper, product</td><td rowspan="2">* Allow reaction to cool (raise out of water bath) before quenching with water.</td></tr>
<tr><td>Liquid waste: filtrates</td></tr>
</table>

Introduction: Pre-Lab Questions, *20 points each*
Bring the typed responses to lab and staple to the back of the exam packet.

1. Classify methyl salicylate and menthol as acidic, basic, or neutral. Identify the functional groups present in each molecule and indicate which functional group dictates its acid-base properties.

2. Draw the arrow-pushing mechanism for the synthesis of aspirin from salicylic acid. You may abbreviate the aromatic ring (“Ar”) in the intermediates.

3. Calculate the mmol of salicylic acid and acetic anhydride used in the reaction. Calculate the theoretical yield for the esterification reaction (synthesis of aspirin from salicylic acid). Show your work.

4. What would happen if the glassware were not dry during the esterification reaction? How is water used to quench the reaction after it is complete? Support your explanation with a chemical reaction for the quenching of the water-sensitive reagent.

5. What differences would you expect to see in the ^{1}H NMR spectra of salicylic acid and aspirin?

Results: In-Lab Questions

These questions will be provided in the exam packet. Blank tables are provided for reporting chemical test results and interpretation of IR and NMR. Tables of values will be provided for assigning IR stretches and NMR chemical shifts.

1. (*8 points*) Report **raw data** (masses and volumes) with proper **sig figs** and **uncertainties (ILE).**

2. (*12 points*) Calculate the **% yield** of aspirin from salicylic acid.

3. (*20 points*) Report the observations in the **ferric chloride tests**. Was the reaction successful? Briefly explain.

4. (*20 points*) Interpret the **IR** spectra of starting material and product in table format. How could these IR spectra be used to tell whether the reaction is complete?

5. (*25 points*) Interpret the **^{1}H NMR** of aspirin. Report integration, chemical shift (expected and observed), and splitting patterns for each signal in table format. Clearly assign each signal to the structure. You may list a range of expected chemical shifts where appropriate but you are graded on proper assignments of all signals to observed shifts.

6. (*15 points*) Interpret the **^{13}C NMR** of aspirin. Assign as many signals as possible on the spectrum to the structure (you're not expected to definitively assign each carbon, but you can get close!). Report the appropriate expected chemical shift range of each carbon using the NMR table of values.

Adapted from Palleros, D. R. "Transforming Bengay into Aspirin" in *Experimental Organic Chemistry.* Wiley: New York, **2000**.

****The exam packet will include the grading rubric below.**

Exp 6 - Synthesis of Aspirin Name _____
Due at the end of the assigned 1 hour, 45 minute lab period

Section Day _____ Time _____ TA Name _____

CHEM 8M GRADING RUBRIC

SECTION	INSTRUCTOR COMMENTS	POINTS ASSIGNED
RESULTS Data reported and in-lab questions addressed on the exam report sheet.		/ **100**
INTRODUCTION Original responses to pre-lab questions stapled to the back of the exam.		/ **100**
LAB TECHNIQUE Includes neatness as well as observation of lab technique.		**/ 50**
	LAB EXAM TOTAL	**/ 250**

LAB TECHNIQUE
The following will be the basis for your lab technique grade; not provided in the exam packet.

Safety & Clean up
- Wear lab coat, goggles, & gloves during the entire experiment.
- Take off gloves while washing glassware.
- Bench tops and isles are free of clutter (non-lab-related belongings, ex. Cell phones)
- All glassware thoroughly washed and put away in drawer in an organized manner
- Student workspace is clean – wipe down counters, leave drawer closed but *unlocked*
- Community workspaces are clean – fume hoods, side counter-tops – all students responsible!

Technique
- Proper use of pluringe, pipets, reflux apparatus, and vacuum filtration apparatus
- Fume hood usage – work 6 inches into hood, no heads in the hood, no kneeling on the ground
- Proper waste procedures followed
- Careful not to spill chemicals or break glassware

General
- Independence – keep your eyes on your own work
- Proficiency - apparent preparation and understanding of the procedure
- All glassware labeled with contents and student name
- Ten points deducted if you re-start the experiment for any reason.

Revisit the syllabus for a full list of safety rules and regulations.