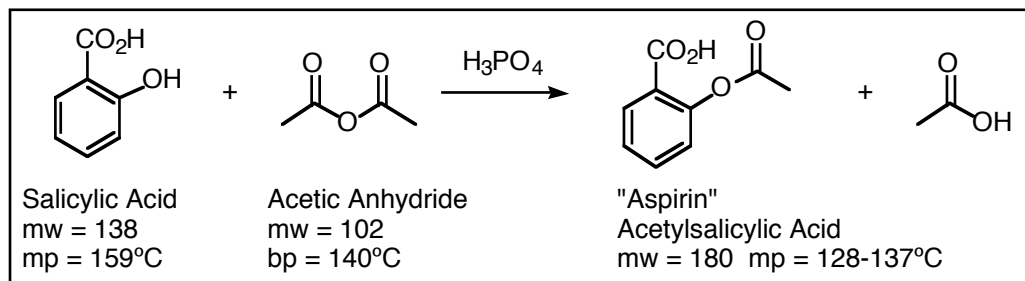


Alcohol Unknowns and Aspirin

Part 1: Microscale Synthesis of Aspirin



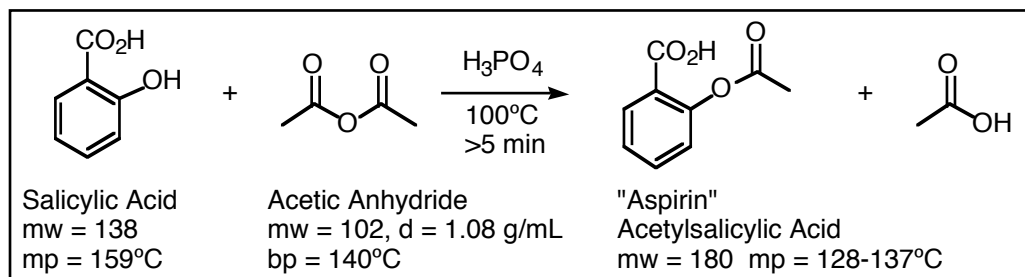
Intro Aspirin is among the most versatile drugs known to medicine, and is among the oldest (the first known use of an aspirin-like preparation can be traced to ancient Greece...). The starting material salicylic acid is cheap (~\$50/kg), because it is available by carboxylation of phenol with carbon dioxide. The esterification that we will do today is the same process that is used industrially for commercial aspirin synthesis.

Aspirin is found in more than 100 common medications. It is usually used for one of four reasons: as an analgesic (painkiller), as an antipyretic (fever reducer), as an anti-inflammatory agent, or as an anti-clotting agent. It is a premier drug for reducing fever. As an anti-inflammatory, it has become the most widely effective treatment for arthritis. Patients suffering from arthritis must take so much aspirin (sometimes several grams a day) that gastric problems may result. For this reason aspirin is often combined with a buffering agent. The ability of aspirin to diminish inflammation occurs because aspirin transfers its acetyl group onto an enzyme; conversion of the enzyme from its amine form to amide form inhibits the synthesis of certain prostaglandins that enhance inflammation.

If aspirin were a new invention, the FDA would place hurdles in the path of its approval. It has an effect on platelets, which play a vital role in blood clotting. In newborn babies and their mothers, this reduction in clotting can lead to bleeding problems. However, this same reduction in clotting has been turned to great advantage. Heart specialists urge potential stroke victims to take aspirin regularly to inhibit clotting in their arteries, and it has been shown that one-half tablet per day will help prevent heart attacks in healthy men. Adult diabetics are routinely advised to take regular aspirin as a preventative measure against heart attacks.

Although aspirin once made up >90% of the commercial pain-killer market, it now faces stiff competition from other analgesics (acetaminophen [Tylenol], ibuprofen [Advil], and naproxen [Aleve]...)

The aspirin you make today is exactly the same chemically as a commercial aspirin except for two things: yours has not met FDA purity standards, and yours is also "undiluted". Commercial aspirin is held together by a binder which makes up most of the mass. Medicines are never the pure chemical. When you take a tablet or a capsule or a liquid dose or an injection of a medicine, the active ingredient usually comprises only a small fraction of the mass. Most of the "stuff" is binder (for a tablet) or solvent. While most aspirins are the same (other than "baby aspirin", for many others medicines the dosage of active ingredient varies (children's Tylenol versus adult...))



Procedure

1. Work with partner if you want.
2. Fill a 50-mL beaker with hot water, and begin heating on a hot plate. (Hot plate setting of ~5?). The goal is to get the water hot enough to approach a gentle boil.
3. Weigh out 0.138 g of salicylic acid (1.0 mmol) and add it to a small test tube
4. Add one small drop of 85% phosphoric acid
5. Add 0.30 mL of acetic anhydride by syringe. This is present in excess, and can be used in part to rinse down any salicylic acid that was stuck on the walls of the tube.
6. Swirl the reactants thoroughly; then heat the mixture in a beaker of boiling water for ≥ 5 minutes.
7. Remove the test tube from the heat.
8. Add about 1 pipet of water, carefully (a few drops) at first then faster, and allow the tube to cool slowly to room temperature.
9. Cool in ice-water bath.
10. If crystallization of the product does not occur during the cooling process, try swirling and poking with a boiling stick, and/or add an ice chip and poke some more with the boiling stick. If this still doesn't promote crystal formation, add a second pipet of cold water and poke some more with the boiling stick.
11. Vacuum-filter using a small Hirsch funnel, into which is molded a water-dampened (to make it limp and flexible) filter paper. (The size that is fitted and would lay perfectly flat on your smaller Buchner funnel).
12. Rinse the tube and the funnel with a pipet of ice-cold water.
13. Rinse with a second pipet of ice-cold water.
14. Let the crystals dry before getting the yield and taking a melting point. (Water doesn't evaporate/dry very fast, so you'd probably like it to be vacuuming for at least 15 minutes, or longer if you're busy with other work anyway.)

15. Lab report on the aspirin. Report the:

- mass recovered,
- calculate the % yield, and
- report the melting range.
 - Note: The melting range is typically rather broad for aspirin because of the carboxylic acid which hydrogen-bonds to the ester.
 - No procedure writeup required.
 - The data can be reported either on the bottom or on the back-side of your alcohol-unknown sheet.

Part 2: Analysis of an unknown alcohol.

- A list of alcohol candidates with their boiling points is listed two pages after this.
- Conduct classification tests shown below to try to determine the following:
 - Is alcohol “big” or “little”? (solubility test)
 - Is alcohol “dense” (aromatic) or “non-dense” (alkyl alcohol)? (solubility test)
 - Is alcohol 1°, 2°, or 3°? (NMR, Chromic Acid test, Lucas test)
- Use NMR to identify your specific alcohol
- Use micro-boiling point (hard!) to try to shorten your list of candidates

Classification Tests

1. Water Solubility Test (Helpful, but not always decisive or clear-cut. Useful, but don't depend on it too much?!)
 - Add 15 drops of water to a small test tube, and then add 2 drops of alcohol. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
 - Interpretation:
 - a. **Big alcohols:** Alcohols with >6 carbons definitely **won't be soluble**.
 - b. **Small alcohols:** Alcohols with <3 carbons definitely **will be soluble**.
 - c. **Borderline:** Alcohols with 3-6 carbons may be borderline, and **could go either way**.
 - d. An insoluble alcohol that **sinks** is an alcohol that has an aromatic ring present
 - e. An insoluble alcohols that **floats** is probably an alkyl alcohol, although some aromatics are also floaters.

Practical Interpretation: Insoluble doesn't prove ≥ 6 carbons; it only proves ≥ 3 carbons. And soluble doesn't prove ≤ 3 carbons; it only proves ≤ 6 carbons.

- If you think you're **borderline**, then adding more water should enable full dissolving. Or adding more drops of alcohol should confirm incomplete solubility
2. Chromic Acid test (Jones Oxidation): positive for 1° or 2° alcohols (or amines)
 - Add 15 drops of acetone, 1 drop of alcohol, and then 1 drop of Jones reagent
 - A positive test is color change from orange → green/brown/ugly within 5 seconds. The reaction is normally accompanied by formation of a precipitate
 - Interpretation: indicates the presence of a 1° or 2° alcohol (or an amine)
 - Note: The test involves oxidation to a carbonyl product. If the alcohol doesn't have a hydrogen on the hydroxyl-bearing carbon, no oxidation is possible. Thus tertiary alcohols don't react, but both primary and secondary do.
 3. Lucas Test (ZnCl₂/conc. HCl): positive for 3° or 2° alcohols, or for allylic/benzylic 1°
 - Add 30 drops of Lucas reagent to small test tube, then add 3-4 drops of alcohol, stir really vigorously with a boiling stick, and let settle.
 - **Tertiary alcohols or allylic/benzylic alcohols** react pretty **quickly** to give **two layers**
 - **Secondary alcohols** react within **<5 minutes** to give a **cloudy solution or two layers**
 - **Primary alcohols that are neither benzylic or allylic dissolve**. Primary alcohols that are allylic/benzylic react, because they can make carbocations very well.
 - **Interpretation: if the mixture remains homogeneous** after several minutes, you know you have a non-allylic/non-benzylic **primary** alcohol.
 - Note: The test involves the S_N1 conversion of alcohols (acid-water soluble) to alkyl chlorides, which are insoluble.

NMR Run proton; decoupled carbon; and 2D H-C NMR.

- Add sample by drawing up about 1 inch of your unknown into the skinny part of a long-stemmed pipet, then place the pipet into an NMR tube.
- Add 0.8-mL of CDCl_3 solvent (volumes not critical) **directly through the same pipet into the NMR tube** to rinse the sample into the NMR tube.
- Cap and shake the sample and take it to the NMR room (SL 305), get it loaded, and submit into the queue. (This will involve both correctly placing it into the autosample, and entering/submitting info on the computer.) The experiment is probably called “H_C_HC” and is under the “355-365” folder. The instructor will presumably have this all ready and queued up.
- Upon completion, do expansions as appropriate to both H-NMR (to clarify splitting) and the 2D HC-NMR. Manual integrations on the H-NMR may often help. Zooming and adjusting the scaling on the 2D H-C NMR could also help. If available, consulting from instructor may help.
- The 2D H-C NMR is invaluable for identifying each carbon. Consult with instructor.
- Several challenges may complicate interpretation of the H-NMR:
 1. In **longish alkyl** groups, several alkyl CH_2 groups will often overlap. In 1-octanol, for example, CH_2 's 3-7 will probably all make a big superimposed lump that integrates for around 10H.
 2. For secondary alcohols, CH_2 groups adjacent to the OH-bearing-carbon often show the 2 H's as non-equivalent; one H is cis, the other H is trans to the OH. Due to this cis/trans nonequivalence, the two H's may end up with possibly different chemical shifts and much-complicated splittings.
 3. The OH hydrogen can come almost anywhere, and may superimposes on other alkyl H's.
 4. The OH hydrogen is often/usually (but not always) a lumpy shape.
 5. Often the OH doesn't split at all with the C-H hydrogens, but sometimes it does to variable extent.
 6. On the carbon to which the OH is attached, the hydrogens are sometimes broadened or deformed by the OH hydrogen. So splitting can be complex. Consult with instructor.
 7. Aromatic H's commonly overlap into one big 5H lump.

Micro-Boiling Points in the Melting Point Apparatus

A microscale boiling point can be taken in a melting point tube that has an inverted "bell" in it. A “bell” is a narrow piece of glass tubing, narrow enough to fit inside a melting point tube. A bell must have its upper end closed off, and should be at least the length of a fingernail.

Make six “bells” by glass melting/stretching/sealing/breaking (we'll make extras for later.) Bring a 50-mL Erlenmeyer with 6 regular empty melting-point tubes (into which the bells will be placed) to the bell-making station. The instructor will train you how to make the bells. (Scary and fun!)

Prepare two boiling point samples, one a control containing **1-propanol** with a known boiling point of $\sim 90\text{-}95^\circ\text{C}$; the **second** with your **actual unknown** alcohol. Bring your unknown alcohol and your tubes-with-bells to the loading area (on center table). For each tube, use a syringe to add about 5 μL of either the propanol or unknown sample; try to tap or drop such that the liquid settles to the bottom.

Run the two samples side-by-side (propanol in one tube, unknown in the other.) **Carefully note the original liquid levels at the start.** (Noticing that it drops later is key clue that boiling has occurred.)

When a liquid is heated, **pre-boiling bubbling** will usually occur as the air inside the bell heats and expands and gets displaced by sample evaporation. When the **real boiling point** is reached, more **rapid bubbling often takes place, but not always; in many cases, though, you won't see nice bubbles. What will always reliably happen**, though, is that at or somewhat beyond the boiling point, the **liquid level will drop, as liquid vaporizes and goes up the tube. This liquid-level-drop is a more reliable indicator, since it happens whether or not bubbling occurs.** Keep heating somewhat beyond the point where you think boiling has occurred, because you may not be experienced enough to distinguish “pre-boiling” bubbles from real boiling bubbles.

These **boiling points** will **not** be **very accurate**, especially for an inexperienced user. Don't trust them to be accurate better than to **about 10 degrees**. While the observed boiling points are imprecise, they still greatly shorten the list of candidates. The instructor will have a list of boiling points; **check with instructor** to confirm whether you're boiling point is within 10° and is close enough, or whether you need to re-run the micro-boiling point.

Alcohol Candidates

<u>bp</u>	<u>Alcohol</u>
65	Methanol
78	Ethanol (anhydrous)
82	2-propanol (isopropanol)
83	t-butyl alcohol (2-methyl-2-propanol)
97	1-propanol (propyl alcohol)
98	2-butanol (sec-butyl alcohol)
102	2-methyl-2-butanol
108	2-methyl-1-propanol (isobutyl alcohol)
115	3-pentanol
118	1-butanol
119	2-pentanol
129	3-methyl-1-butanol
132	4-methyl-2-pentanol
137	1-pentanol
140	cyclopentanol
140	2-hexanol
157	1-hexanol
160	cyclohexanol
176	1-heptanol
178	2-octanol
185	2-ethyl-1-hexanol
195	1-octanol
204	benzyl alcohol (phenyl methanol)
204	1-phenylethanol (sec-phenethyl alcohol)

Unknown Report Sheet

Unknown Number or Letter:

Your Name

Draw your unknown's Structure:

Data Summary

1. Boiling points: measured bp _____ listed bp _____

2. Chemical Tests _____ Result and probable meaning _____

a. Water solubility

If insoluble, did it sink or float?

b. Jones Reagent (Chromic Acid)

c. Lucas Reagent

3. Attach copies of all three of your NMR spectra, with interpretation details (see below).

4. **On the H-NMR spectrum, create a 4-column STANDARD SUMMARY REPORT of your ACTUAL H-NMR data, detailing chemical shifts, integrations, and splittings, and source.** Chemical shifts need to be specified to at least the nearest 0.1 ppm. Draw the structure of your molecule, with **identifiers** by each carbon (typically a, b, c... or 1, 2, 3...). Then on your standard summary table include a "source" column in which you show which hydrogens (CH₂-1 or CH₂-b, or CH₃-6 or CH₃-a, or whatever) are responsible for each signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic. The OH may also induce weird splitting, as may cis/trans issues in 2° alcohols. In many cases, some overlapping may occur. Consult with instructor if you have questions!

5. **On the carbon spectrum, draw the structure of your molecule, again with identifiers by each carbon (typically a, b, c... or 1,2,3).** Then **next to each line in the carbon spectrum, write the letter a, b, or c etc. which is responsible.** Using your H-C 2-dimensional NMR will be very helpful for figuring out which carbon is which in the 0-50 zone.

6. Comments (if any).

7. **Remember to attach your aspirin data, (including showing calculations), or write on this sheet somewhere (or on the backside).**