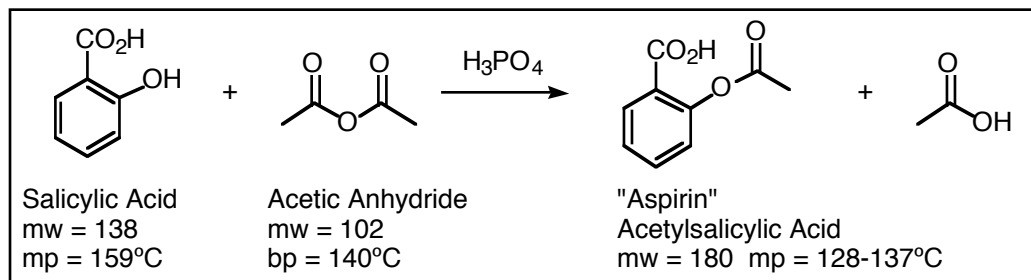


Alcohol Unknowns and Aspirin

Part 1: Microscale Synthesis of Aspirin



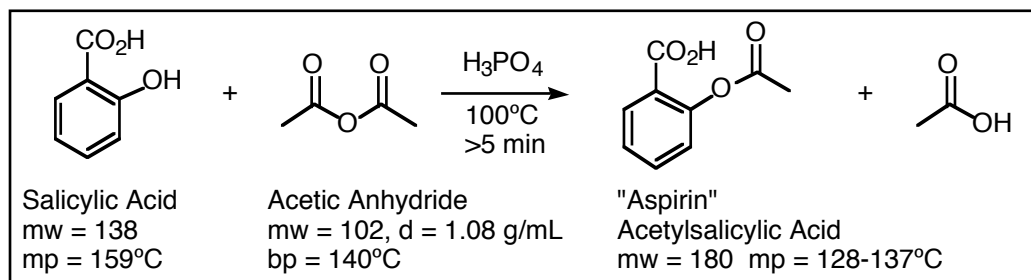
Intro Aspirin is among the most versatile drugs known to medicine, and is among the oldest (the first known use of an aspirin-like preparation can be traced to ancient Greece...). The starting material salicylic acid is cheap (\$15/kg), because it is available by carboxylation of phenol with carbon dioxide. 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 (Anacin, Excedrin, Alka-Seltzer, Coricidin, Midol, Vanquish, etc.) It is usually used for one of three reasons: as an analgesic (painkiller), as an antipyretic (fever reducer), or as an anti-inflammatory agent. It is the premier drug for reducing fever, a role for which it is uniquely suited. 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 (Bufferin, for example). 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 many 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, etc., 40%), ibuprofen (Advil, etc., 26%) and Naproxen (Aleve, 6%) are major players in the market formerly dominated by aspirin. (Although these percentages are based on sales, not quantity, and thus underestimate aspirin because it is so much cheaper.)

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, but yours is also "undiluted". By law all commercial aspirins contain 0.325 g of aspirin held together by a binder (which makes up most of the mass). The price difference between a generic aspirin and a commercial aspirin is simply a reflection of advertising budget for the company that sells it. 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 all aspirins are the same, for many others medicines the dosage of active ingredient varies (children's Tylenol versus adult...)



Procedure

1. Work with partner or individually, as you wish.
2. Weigh out 0.138 g of salicylic acid (1.0 mmol) and add it to a small test tube
3. Add one small drop of 85% phosphoric acid
4. 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.
5. Swirl the reactants thoroughly, then heat the mixture in a beaker of boiling water for ≥ 5 minutes.
6. Remove the test tube from the heat.
7. Add 5 drops of water to the mixture to decompose excess acetic anhydride. (One molecule of acetic anhydride plus one water reacts to give two molecules of acetic acid.)
8. Add about 1 mL (about half of a full pipet) of water 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 scratching, adding an ice chip, adding a second pipet of cold water, or adding a seed crystal.
11. Vacuum-filter using a small Hirsch 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.
15. Lab report on the aspirin: report the mass recovered, calculate the % yield, and report the melting range. (The melting range is typically rather broad for aspirin because of the carboxylic acid which hydrogen-bonds to the ester.)

Part 2: Analysis of an unknown alcohol.

- A list of alcohol candidates with their boiling points is listed on page 31
- Conduct the 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. Shake vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
 - Interpretation:
 - a. Alcohols with >6 carbons definitely won't be soluble.
 - b. Alcohols with <3 carbons definitely will be soluble.
 - c. Alcohols with 3-6 carbons may be borderline, and could go either way. (If you think you're borderline, then adding more water should enable full dissolving. Or adding more drops of alcohol should confirm incomplete solubility)
 - d. An insoluble alcohol that sinks is an alcohol that has an aromatic ring present
 - e. An insoluble alcohol that floats is probably an alkyl alcohol, although some aromatics are also floaters.

Note: Insoluble doesn't prove ≥ 6 carbons; it only proves ≥ 4 carbons. And soluble doesn't prove ≤ 3 carbons; it only proves ≤ 5 carbons.

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 \rightarrow green/brown within 5 s. 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 hydroxy-bearing carbon, no oxidation is possible. Thus tertiary alcohols don't react, but both primary and secondary do.
3. Lucas Test ($\text{ZnCl}_2/\text{conc. HCl}$): 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, shake vigorously, and let settle.
 - Tertiary alcohols or allylic/benzylic alcohols react immediately to give two layers
 - Secondary alcohols react within 2-5 minutes to give a cloudy solution or two layers
 - Primary alcohols that are not benzylic or allylic dissolve
 - 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 $\text{S}_{\text{N}}1$ conversion of alcohols (acid-water soluble) to alkyl chlorides, which are insoluble.

NMR Run proton; decoupled carbon; coupled carbon; and 2-Dimensional proton-carbon NMR.

- Put about 0.12-mL of sample into an NMR tube, using syringe.
- Then add 0.8-mL of CDCl_3 solvent. The volumes are not critical.
- Put a cap on the sample.
- Carry over to the NMR room (SL 305) and get it loaded and entered into the queue. The experiment that will be run will be called “H-C-HH-HC” and is under the UserStudies folder.
- Note: The amount of sample is a little much for an H-NMR, so it may smear the H-NMR somewhat, but that will enable fast C^{13} NMR's.
- Do expansions as appropriate, to figure out splitting. Manual integrations may also help a lot.
- Depending on your sample, H-NMR alone may tell you almost everything, but in many cases the family of NMR experiments will help a lot.
- Several challenges may complicate things in the H-NMR:
 1. It will be entirely common in longish alkyl groups that several alkyl H groups will 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. The OH hydrogen can come almost anywhere, between 1-5, but most commonly comes around 1.5. As such it frequently superimposes on other alkyl H's.
 3. The OH hydrogen is often a lumpy shape. Sometimes it doesn't split at all with the C-H hydrogens, but sometimes it does.
 4. On the carbon to which the OH is attached, the hydrogens are sometimes broadened or deformed by the OH hydrogen. So the splitting can be complex. See instructor for consulting.
 5. For secondary alcohols, the hydrogens of adjacent CH_2 groups end up being non-equivalent; one is cis and one is trans to the OH, so they are different, and end up with possibly different chemical shifts and complicated splittings.
 6. For phenyl groups, even though o, m, p H's aren't strictly equal, they are often similar, so commonly come in one big 5H lump.
- Hints: A useful thing is to identify the O-bearing CH/CH_2 signal in the 3's. You can often use that, or a distinct OH signal, as an integration reference marker. You can also often easily use the integration of the O-bearing CH/CH_2 to establish/confirm whether your unknown is a 1° or 2° alcohol, and if you have a 3° alcohol, you won't get any H's in the 3's!

Micro-Boiling Points in the Melting Point Apparatus

A microscale boiling point can be taken by adding liquid (about 5 μL) to a melting point tube, and then adding an inverted "bell"; a narrow piece of tubing with the upper end closed off (about 15-20 mm long). This will require some glass-blowing. When the sample is heated in the melting point apparatus, bubbling will occur slowly from the bell as the air inside heats and the gas expands. When the boiling point is reached, then rapid bubbling from the bell will take place, as organic vapor is created. Mark down this temperature, then immediately turn off the melting point power and keep watching. As the temperature drops, at the point that the boiling point is reached again, now on the way down, the bell will fill because the organic vapor inside the bell will liquify. The boiling point will not be very accurate, especially for an inexperienced user. For you the beginner, don't trust it to be accurate better than about 10 degrees. While the observed boiling points are imprecise, they still greatly shorten the list of candidates.

- You will find it useful to run a sample of 1-propanol (bp 97°C) side-by-side with your real sample for practice.

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 No.

Name

Structure and Compound Name

Date

Data Summary

1. Physical Examination

a) Physical State _____ b) Color _____ c) Odor _____

2. Physical Constants measured bp _____ literature bp _____

3. Chemical Tests	Known	Known	Unknown
Test	Positive, Result	Negative, Result	Result

a. Water solubility

If insoluble, did it sink or float?

b. Jones Reagent (Chromic Acid)

c. Lucas Reagent

Comments:

4. Attach copies of all four of your NMR spectra. On the proton spectrum, draw the structure of your molecule, and make a standard summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings. On your structure, write in identifiers by each carbon (give them numbers or letters), and then on your standard summary table add a column in which you explain which hydrogens (CH₂-A. or CH₃-B...) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.

5. Confirmed Compound (Structure and Name and unknown Letter)

6. Comments (if any).