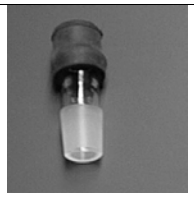
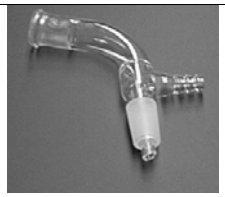
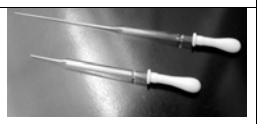
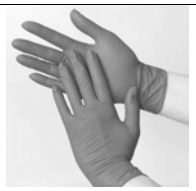
Lab Manual for Organic Chemistry 7A and 7B V. 4.1

 Keck clamp	 Thermometer adaptor	 Vacuum adaptor	 Stir Bar
 Büchner Funnel	 Separatory Funnel	 Distillation Head	 Pasteur Pipet with Bulbs
 Variable Autotransformer	 Heating mantle (Fiberglass type)	 Distillation or Reflux Condenser	 Round Bottomed Flask
	 Safety Goggles	 Latex Gloves	By Prof. S. Joiner, Ph.D. Prof. R. Keil, Ph.D

For Chem 7A and 7B courses in Spring 2014-Present

Safety

Working in an organic chemistry lab requires you to pay attention to what you are doing and to what your neighbors are doing. I take safety very seriously and you should be aware that I will remove you from lab if I feel you cannot conduct yourself in a safe manner. I've included a list of "common sense" warnings that you should be aware of.

1) General

   a) You will wear safety goggles **whenever anyone in the lab is working**. Once the lab starts, wear goggles. If you want to work on your notebook, go outside and take them off. You get three warnings. The first warning has no penalty. The second warning results in a zero for that lab. **The third warning will result in expulsion from the course!**

   NO GOGGLES! = NO LAB! = NO POINTS!

   We also require lab coats to be worn in lab. We have a few loaner pairs, but youmust purchase your own!

   b) Don't wear sandals in lab. There is often broken glass flying around! In addition, wear long pants if possible and tie back long hair.

   c) Don't leave your backpacks and texts on the lab bench. They get in the way and will be damaged by chemicals.

   d) Don't eat, drink or smoke in lab. Material on your hands will get transferred into your mouth. It is good practice to wash your hands often during the lab to keep them clean.

   e) Don't do any unauthorized procedures. Do only the assigned experiment.

   f) Wear latex gloves while handling chemicals whenever possible. Remember to remove the gloves when you are done handling the chemical, otherwise, you will spread that chemical from the glove to yourself. If you have a latex allergy, try nitrile gloves. Good gloves can be purchased at grocery/hardware stores. They're more comfortable than the ones the stockroom doles out.

2) Handling chemicals

a) Don't look directly down into a container. The contents could suddenly "bump" or boil over and splash you.

b) Don't smell a container directly. Always "waft" the vapors with your hand to see if it has a strong smell. Some chemicals (*e.g*. ammonia) cause great pain if you smell them deeply.

c) When you use a bottle, either close it *immediately* after you use it **or** hand it to someone who is using it. Don't leave bottle open or sitting with spatulas in them.

d) Only take what you need from a bottle. Don't take a beaker, fill it, take it back to your bench, use a bit and throw the rest away.

e) Most of the chemicals used in this lab are not very harmful, if you avoid ingesting them. By washing you hands and wearing gloves, you can minimize (but never eliminate) exposure to these chemicals. I have tried to use chemicals that occur in foods or in the house. If you have questions about chemical toxicity, please see me and I can tell you where to find more about any particular chemical.

3) Handling Apparatus

a) Always clamp the reaction flask securely by the neck. If you suddenly have to remove the heat or take the reaction to the hood, you will have a handle to grab it by.

b) Never heat any apparatus that does not have an outlet for gas (*i.e*. a closed system). The resulting pressure build-up can blow up in your face!

c) When handling separatory funnel or test tubes, point the openings *away* from your neighbors! Don't spray them and they won't spray you!

d) Don't use Bunsen burners without checking with your neighbors first. They may have flammable materials around. You probably will not need to use flames at all in this course.

e) Always secure glassware and your apparatus so that it cannot be knocked over by someone brushing against it or by a careless movement.

f) Never heat any piece of glass that does not have Pyrex™ or Kimax™ on it. These types of glass can be heated and cooled without cracking. Never use a piece of glassware that is cracked without checking with the instructor.

Safety Quiz

(adapted from CU Boulder)

1) If you spill an acid or a base on yourself, you should:

a) rinse with acetone or another suitable solvent or neutralizing solution
b) ask your TA what to do
c) immediately wash with soap and cool water and tell your TA
d) go immediately to the health center
e) do nothing unless you feel a burn or irritation

2) You may remove your goggles while in the lab room:

a) never
b) if no one is doing an experiment or washing glassware
c) if no one is doing an experiment
d) anytime

3) You can safely wear contact lenses while doing an organic chemistry lab:

a) if you are wearing goggles
b) if they are soft lenses
c) never

4) Broken glassware left around the lab is a hazard because:

a) if on the floor, might step on it and cut their foot
b) if on the lab bench, someone might lean on the bench and cut their arm
c) if in the sink, someone might try to pick it up to throw it away properly and cut themselves.
d) all of the above

5) You have looked up the hazards of the chemicals you will be using in a particular lab, and found out that they are mild health hazards, requiring you to avoid skin contact and vapor inhalation. Therefore, when in lab you should:

a) wear short shorts and sandals
b) wear long pants and closed toed shoes, and even a lab coat if possible
c) keep the chemicals in your safety hood as much as possible
d) wear gloves
e) b, c, and d
f) a, b, and c

6) Volatile solvents can cause irritation of the respiratory tract, intoxication, central nervous system depression, drowsiness, or nausea. How can you prevent accidental vapor inhalation?

a) work with volatile solvent in your student hood
b) cover containers of them if you have to carry them through the lab
c) a and b

7) If something on your lab benches catches fire, what is the best choice below?

a) always run for the fire extinguisher if you see a flame
b) if and only if it is possible to do so safely, cover the flames with a beaker or watchglass, remove solvents from the area, then get the fire extinguisher; if it is not possible to do this, leave the room and pull the fire alarm, and call 911 from a safe phone
c) get the safety wash and aim the water at the flames
d) the moment you see a hint of the flame, immediately leave the room and pull the fire alarm

8) If the fire alarm sounds, you should:

a) do nothing - it is probably a false alarm
b) shut down your experiment, get your stuff, then leave the building
c) leave the building immediately
d) grab a fire extinguisher and/or safety wash

9) Which of the following is the eye/face wash?

a.

b.

c.

d.

10) You get a chemical in your eye. What should you do?

a) nothing
b) rinse with water for a few minutes and tell your TA or the lab coordinator
c) immediately flush with water, continue washing for 15 minutes, tell your TA, then go to the health center if so advised
d) go to the restroom and rinse with water because the water is better there

Lab Notebooks

You may be keeping a laboratory notebook (check with your instructor) that records the results of the labs you will be performing. There are a few rules of lab notebooks.

- Please buy a simple English composition book. DO NOT use spiral bound notebooks (It's very inconvenient to stack those notebooks)
- Leave a blank page or two at the front for a table of contents.
- Please do not use pencil. Only pen! (and no red pens!)
- If you make a mistake or change something, just put a single line through your mistake. No white-out or liquid paper!
- Please use one side of the page only, as this makes grading easier. Also, leave at least a 3/4" margin on all sides.
- Record what you actually did, and don't just repeat the procedure. I've included a sample of a notebook to give you an idea of what to do.

  The basic format to follow is
  - Title
  - Purpose
  - Reagent Chart
  - Procedure
  - Data
  - Conclusion

Exp #1 – Physical Properties of Compounds: Melting Points

With some exceptions (*e.g.* carbon dioxide), most pure solids will melt in a well-defined, reproducible temperature range. Whenever a chemist creates or isolates a new compound, a melting point is recorded so that others may compare their compound to this reference value. Also, the range of temperatures in which a compound melts is quite dependent upon the purity of the compound. The melting point serves as a convenient benchmark of purity for solids.

Although you may be used to seeing melting points recorded as exact temperatures, melting points should be recorded as a range from when the compound begins to melt, to the point at which it is completely liquefied. When a compound is very pure, the melting point range will be less than 0.5 ºC. For a typical compound, the range can be from 1 to 3 ºC. Compounds with more impurities will have broader ranges. In addition, when a compound has impurities in it, the overall melting point is lower than for the pure compound. This phenomenon is the same as when salt lowers the melting point of ice.

The reason why impurities both lower the melting point and broaden the melting point range can be explained in a qualitative sense. It is very important to note that only *soluble* impurities can affect melting points. For example, sand (insoluble in water) mixed with ice will melt at the same temperature as plain ice, because the sand doesn't affect the hydrogen bonds of the water molecules. Salt (soluble in water) mixed with ice disturbs the symmetric crystal structure of the ice, which lowers the amount of heat needed to break apart that structure.

Although a sharp melting point is generally an indication of purity, there are the rare situations in a mixture of two different compounds give a sharp melting point. This is called a eutectic point and may (or may not) occur for any two compounds. Imagine that you have compound **A**, which melts at 150-150.5 ºC when pure. You then add a few percent of compound **B**, which also melts at 150-150.5 ºC . The melting point of **A** is lowered (even though **A** and **B** have the same melting point! Strange, isn't it?). As you mix in more and more **B**, the melting point of the mix goes down and the range gets larger, as discussed above. However, at the eutectic point, the melting point becomes sharp, although the melting point of the mix is lower than for the pure compound. As the proportion of **B** increases, the melting point returns toward the values for pure **B.** (Figure 1)

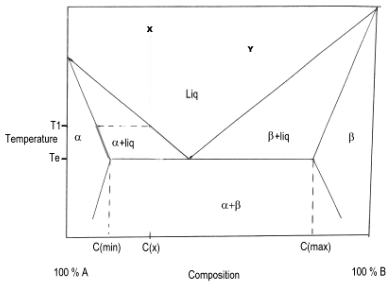


*Fig. 1 - Melting point of a mixture of **A** and **B.** Note Eutectic point and broadened range.*

Not every pair of compounds forms a eutectic point, and the eutectic ratio is not always 1:1. Whenever you record a sharp melting point, you should always consider the possibility that you have two compounds that happen to be at the right ratio for a eutectic point and is not a pure, single compound.

The melting point can tell you about a compound's purity but it can also be used to deduce a compounds identity. To do this, you compare the measured melting point to the value given in the chemical literature. If they are different, then the compounds cannot be the same. If they are the same, you *may* have the same compound. There are millions of solids in the world, and because most of them melt within a few hundred degrees of another, there is a good chance that you may be looking at the wrong molecule. How do you tell if you've got the right compound? The **mixed melting point** technique is used to verify the unknown's identity. The unknown compound is mixed (usually in a 1:1 ratio) with the compound you believe is the same and the melting point of the mixture is taken. If the melting point remains the same, then the unknown and the compound must be the same. If the melting point is lowered or the range increases, then the two compounds must be different. Very cautious workers will make two or three mixtures in varying proportions to check for eutectic points; however, a single mixed melting point is usually sufficient.

Melting Point Techniques

Measuring melting points is a simple procedure that requires patience to get good results. The sample is placed in a thin glass tube with a sealed end (this will be demonstrated in lab), the tube is placed in the Mel-Temp apparatus (with the closed end down!), and heat is gradually applied. The dial on the Mel-Temp controls the rate of heating of the block, however, it is not a linear control. Thus, a setting of "5" may heat the block quickly at lower temperatures, but very slowly at higher temps.

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Heat the solid slowly: about 2-3 ºC per minute. Heating faster than that will result in a low reading, as the heating will be uneven and the thermometer will read a different value than the actual temperature in the tube.

If you do not know the approximate range of your unknown, a useful technique is to prepare two or three sample tubes. Heat the first one quickly and record the point at which it melted. Let the Mel-Temp cool well below that value, then redo the measurement more slowly. Do not speed the cooling of the Mel-Temp with a wet rag, you will merely cause the block to have an uneven temperature gradient which will give you inaccurate reading.

Mel-Temps have channels for three tubes, so run more than one sample at a time.

Always record the melting point as a range, from the initial temperature when the crystals start or glistening to the final temperature when the solid turns completely liquid.

Today's Experiment (first part)

Practice measuring a melting point with one of the standards. Try and get a feeling for how fast to increase the heat source. Do not worry if your melting point is exact, this is a practice run. This also gives you a chance to calibrate your thermometer. If the melting point that you get for the practice run is ~ 5 °C high, then you know to lower all of your melting points by 5 °C.

After you feel confident with a standard, take a melting point of unknown #1 (green label). You may want to do several runs to get an accurate value. You'll earn points for how accurate your measurement is.

Unknown #2 (blue label) is either urea, *trans*-cinnamic acid or acetylsalicylic acid, all of which melt at about 135 ºC. Using the mixed melting point technique, decide which compound your unknown you have. You will need to mix a few small batches of your compound plus one of the standards.

Safety:

Mel-Temps are quite safe. Be careful when preparing the sample tubes, as they are made of glass and break easily. Also, the Mel-Temps get very hot (that's what they are designed to do!) and will burn you if you touch them.

I have read the paragraph above and understand it _____ .

I have read the paragraph above and have some questions. _____ .

Pre-Lab:

1) You've isolated a chemical from a plant. You test its melting point and find that it ranges from 185ºC to 186ºC. What does this tell you about the chemical?

2) You look up the melting point in a reference text, and find that éclairine has the same melting point. Do you believe that your compound is eclarine?

Exp #1 - Melting point Lab Write-Up Name _____

Identity of standard measured: _____

Melting point range of standard: _____

Suggested Adjustment to make to other melting points:

Green Unknown Number: _____

Measured Melting point range of (Green) Unknown_____

Adjusted Melting point range of (Green) Unknown _____

Blue Unknown Number: _____

Measured melting point range of unknown mixed with acetylsalicylic acid_____

Mixed with urea _____

Mixed with cinnamic acid _____

Identity of second (Blue) unknown _____

Exp #2 – Boiling Points and Density Measurements

Most liquids exhibit fairly sharply defined boiling points. By carefully identifying the boiling point of a liquid, you can determine whether a liquid is fairly pure, and whether it matches the literature value for that compound. In addition, the specific gravity of a liquid can be determined by using a container of fixed size and a balance.

The difficulty is measuring boiling points is mostly rooted in the scale of the experiment. Boiling large amounts of solvent can make the lab smell bad, give you a headache, and is a potential fire hazard. A microscale technique makes alleviates most of these problems.

Boiling Point Technique:

The first step that needs to be done is to construct a microscale boiling point apparatus. You will need to make a small closed tube, by first cutting and then closing a Pasteur pipette. The proper technique will be demonstrated in class. You will assemble an apparatus that will look like the figure below. Immerse the tubes in a oil bath that you will slowly heat.

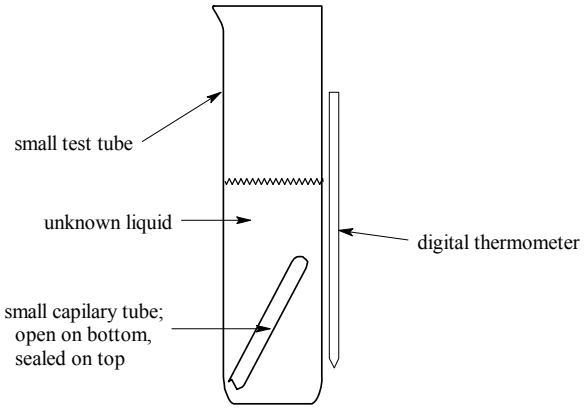


Fig 1. Boiling Point Apparatus

As the temperature increases, you will see bubbles coming out of the inner test tube. This is the result of the increasing vapor pressure of the liquid pushing out the trapped air. As the temperature rises, the bubbles will come out at first slowly and then very quickly and the inner tube will appear to be empty (but is actually filled with the solvent vapor, not air!). This is not the boiling point! At this point, turn off the temperature and let the system cool. As the solvent cools to the boiling point, the vapor bubbles will slow down and then briefly stop, and then start flowing back into the bell tube. When they stop, record that temperature as the boiling point. At this temperature, the vapor pressure of the solvent is just equals the air pressure.

Boiling Point Lab *Version 1* Write-Up: Name_____

Procedure:
Obtain an unknown and determine its boiling point. Then determine its density.

Unknown number _____

Boiling point measured _____

Measured density of water _____

Measured density of unknown _____

Calculated density of unknown _____

Boiling Point Lab *Version 2* Write-Up: Name_____

Procedure:
Obtain three unknowns and determine their boiling points and densities. In lab, you will be given a list of the possible unknowns. Using your understanding of intermolecular forces and your measured boiling points, match each unknown to the corresponding structure.

Unknown A

Measured boiling point: _____

Measured density: _____

Identity of unknown: _____

Unknown B

Measured boiling point: _____

Measured density: _____

Identity of unknown: _____

Unknown C

Measured boiling point: _____

Measured density: _____

Identity of unknown: _____

On the back of this page, respond to the following questions:

1) Describe the procedure that you used to measure the density of each unknown liquid. How did you minimize evaporation of the unknown during your measurement?

2) How did you use your understanding of chemical structure and intermolecular forces to identify each of the three unknown substances? Be specific and detailed.

Exp #3 – Recrystallization of Benzoic Acid

Recrystallization is one of the most important and oldest forms of lab procedures, having its origins with the alchemists. Even today, it is still the cheapest and fastest way of purifying large amounts of solids, and is used to prepare samples ranging from hundreds of grams of a reagent to milligrams of complex proteins for x-ray analysis. Many people have conducted recrystallizations at home, making rock candy from sugar or crystallized ginger, almost certainly without thinking about the chemistry involved!

Recrystallization depends on one simple physical property: most compounds are more soluble in a hot solvent than in a cool solvent. Thus, if you swirl a compound in just enough hot solvent to get it to dissolve and then slowly cool the solution, you will saturate the solution. Soon, crystals of the solid will form as the temperature drops. In the case of rock candy, the sugar that you start with is quite pure. Therefore, the main reason for that recrystallization is to grow larger, more regular crystals.

In order to characterize a compound with x-ray crystallography, recrystallization is used to prepare large enough crystals to shine radiation through. This is of critical importance when trying to determine the structure of proteins, such as enzymes, that occur in nature. Every time you see a picture of a biological macromolecule, it was prepared through painstaking crystallization and X-ray analysis.

Solubility data and removal of impurities – a theoretical example:

When there is an impurity that is soluble in the recrystallization solvent, recrystallization can be an effective way to remove that impurity, although there is always a loss of the desired material associated with doing so. The basic idea is simple. Imagine you have 10 g of compound **A** mixed with 0.5 g of compound **X** and you want pure **A**. You find (perhaps from the Merck Index) that **A** and **X** have the following solubilities:

	Solubility in water @ 100 ºC	Solubility in water @ 25 ºC
A	10g / 100mL	1.0g / 100mL
X	10g / 100mL	1.0g / 100mL

So if you take 100 mL of boiling water and swirl it with your mixture, you should be able to dissolve both **A** and **X**. (Note how the amount of **X** in the water doesn't affect the amount of **A** the water can dissolve, this may seem counter-intuitive, but it's true!) As you let the solution cool to room temperature, the solution will only dissolve 1.0 g of **A** and 1.0 g of **X**, which means that 9 g of **A** (*i.e.* 10 g – 1 g = 9 g) will precipitate out of the solution, while no **X** will become a solid. When you filter out the solid, you will have 9 g of pure **A**, with 1.5 g of **A** and **X** still dissolved in the solution. In exchange for higher purity, you lost 10% of your original material, which is not an unreasonable tradeoff.

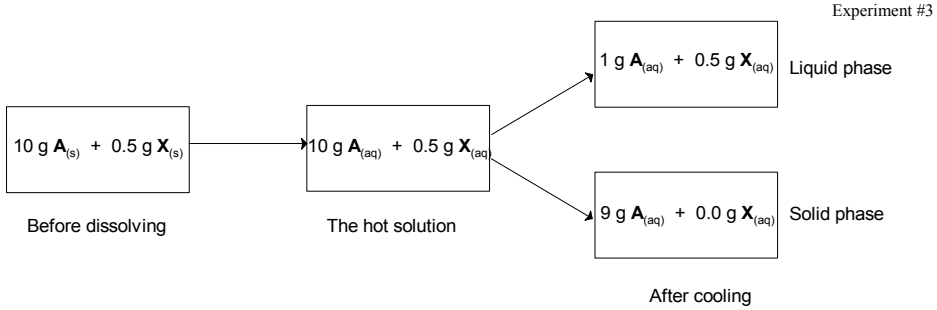


Fig. 1 - A simple recrystallization

In practice, you rarely know what the solubility of the compound, let alone the impurity, really is. You usually add just enough of a hot solvent for the compound to dissolve and hope for the best when it cools. How do you what solvent to try? Trial & error and patience are the watchwords for any chemist!

Techniques - General

As you might imagine, there are many fine points to recrystallization technique. It is often said that recrystallization is one part art and one part science. It is a skill that improves with practice, but the most important point is to remember to be patient.

When you start to dissolve your mixture, it is best to add the solvent a little at a time. You can always add more, but it's difficult to remove solvent once it's added. Also, it's best to heat your solution before you add more solvent. Otherwise, you will cool your solution every time you add fresh solvent.

When the solvent you are using is something like water or ethanol, the procedure is very forgiving. If you try recrystallizing from a very volatile solvent like ether or dichloromethane, you find that the warm solvent evaporates nearly as fast as you add it. Also, it cools very quickly. With experience, these solvents become easier to manage.

The solution that the solids precipitate out of is called the mother liquor. Often the mother liquor is saved in hopes of getting a second batch of crystals (often called a "crop") even though the purity is lower.

A common method of recrystallization involves the use of two solvents. The first is used to get the compound to dissolve. The second, usually less polar, solvent is added very slowly until the solution shows signs of turbidity (cloudiness) occur. The solution is left alone until crystals appear. This technique is very commonly used. Of course, it involves trying to figure out what the second solvent should be (and with the corresponding increase in effort!)

The exact physics and mechanics of crystal formation is very complicated and still poorly understood. However, it is known that most crystals seem to form around tiny impurities such as dust specks or scratches on the glass. Also, crystals grow at a certain rate. If the solution is cooled too quickly, the crystals won't be able to keep up with the molecules precipitating out of solution, and so new sites of crystallization (called "nucleation") will occur. Therefore, if you cool quickly, you will get smaller, more numerous crystals that contain more impurities within them. If cooling is very rapid, the compound will "oil out" and refuse to form any crystals at all. When this occurs, you will see oil at the bottom of your flask; a sad sight indeed. Try redissolving the compound and cooling slowly.

Techniques - Dealing With Insoluble Stuff

Often, when you try to dissolve the initial mixture, there is some material that will sit in the bottom of your flask no matter what you do. This stuff may be sand, hair or some insoluble tar. Whatever it is, you don't want it. So before you let your solution cool, you need to get rid of this junk. This is done with *hot filtration*. The best method is to use a warm filter funnel and a very porous filter paper. However, keeping the filter funnel hot can be quite and setting up the apparatus can be quite a chore, so often the hot solution is simply poured though a *short-stemmed* filter funnel lined with filter paper. Why a short-stemmed funnel? Sometimes, the solution will cool as it goes down the outlet and crystals will form and clog up the drain part of the funnel. This may sound unlikely, but it can happen!

Sometimes, the solution will have a dark color, even to the point of being blackish. One way of dealing with this is to add charcoal to the cool solution. Students often blanch at the idea of adding a black powder to add already dark mixture, but the charcoal often will adsorb colored impurities. That is, the polymers and "goo" stick to the charcoal. When you hot filter the solution, the charcoal and most of the "goo" stay in the filter. Remember to add the charcoal when the solution is cool. If you add a finely divided powder to a hot liquid, it may suddenly boil over.

Techniques - Getting Crystals

Now that you have a clear, hot solution, you wait. And wait. Often, you'll have the urge to plunge the flask in an ice bath before the solution is even at room temperature. Resist that urge! Let the flask cool at its own pace, preferably while its set upon an upside down beaker or piece of Styrofoam, which slows the loss of heat from the flask.

If no crystals form, immerse the flask in a ice-water bath and scratch the sides of the flask with a glass rod. Scratching the glass may seem like "hocus-pocus", but it seems to cause sites of nucleation to occur and give the crystals a place to start growing. Be careful not to push too hard, the glass rods and/or the flask can break!

If you are still bereft of crystals, you can try adding a seed crystal. Take a very small amount from of the desired compound and drop it in the flask. Do not swirl the solution to dissolve it! Often, more crystals will grow around this one. Of course, this only works if you have a sample of the pure compound to work with!

If none of the above tricks work, it's probably because you've added too much solvent at the initial step. The best bet is to boil off the excess solvent (*i.e.* reduce its volume) and let it recool. Repeat this until you get crystals.

Once you get crystals, you need to collect them. Set up a Buchner funnel, a vacuum flask and a piece of filter paper (remember to clamp the flask!). Before you filter the crystals, break them up with a spatula and give the solution a swirl. Turn the vacuum on, make sure the filter paper is covering the holes, and pre-moisten the paper. Now swirl the solution and pour it onto the Buchner flask quickly. Don't let the crystals settle to the bottom of the flask, you'll just have to rinse them out later. Once you have gotten the crystals on the paper, wash them with some cold solvent. Always use the same solvent you did the recrystallization from. If it looks like the solid is dissolving when you wash it, stop washing it! If you see crystals forming in your vacuum flask, you may want to refilter this solution to increase your recovery.

Depending on the solvent used, it can take a few days before the crystals dry enough to allow you to take a melting point.

Calculations

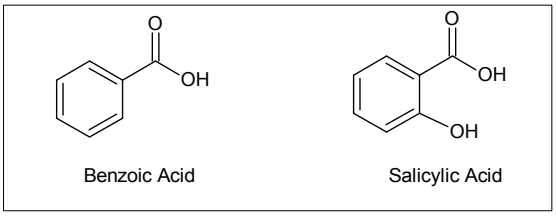
Whenever you report a recrystallization, you should report the percent recovery. This is a simple calculation, it is merely the amount (in grams) that you isolated, divided by the amount you started with (times 100%). Since there are no chemical changes going on, there is no need to convert reagents to moles. Because you don't know how much of you starting material consisted of impurities, the perfect percent recovery will be less than 100%. Please note the difference between the percent recovery and the percent yield.

% recovery = weight of material recovered / original weight of impure sample

Thus, even though you recovered all the possible **A**, you have no way of knowing how much of the original mixture was really **A** and how much was **X**. Also, percent recoveries will always be less than 100% for dried products.

Procedure

You will be given a jar of benzoic acid that is contaminated with some insoluble material (dirt) and some salicylic acid (<5%). Your task is to get a pure, dried sample of benzoic acid.



Part One

- Dissolve 1.0g of the sample in the minimum amount of hot water (which is the recrystallization solvent). Some of sample will not dissolve! In the past, around 40mL worked well.
- While the solution is hot, filter it through a short-stemmed funnel and a piece of fluted filter paper to remove any insoluble material present.
- Allow the solution to cool undisturbed, for at least 20 minutes, and crystals to form.
- Then, cool in ice for 15 minutes.
- Collect the crystals with vacuum filtration.
- Oven dry the crystals on a watch glass for 20 min. at 90°C.
- Record a melting point. (A pure sample should melt around 122°C)

Part Two: Perform the experiment again, but include one of the following variations. We'll use the whole classes' results to determine which variation is best.

Group a) Same as above. You're the control group!
Group b) Dissolve 1.0g of sample in 100mL of water.
Group c) Use only 25mL of water to dissolve the compound initially
Group d) Immediately after you gravity filter the solution, place it in the ice bath for 20min.

ENTER YOUR DATA ONLINE!

Safety:

- Wear your goggles! No flames!
- Boiling water will burn you!
- Benzoic acid and Salicylic acid are not very toxic, but the dust is very irritating.

I have read and understood the above safety statement and have no questions. _____

I have read and understood the above safety statement and do have some questions. _____

Pre-Lab

1) I did a recrystallization of an impure substance and found that my percent recovery was 100%. What does that mean?

2) I did a recrystallization of an impure substance and found that my percent recovery was 110%. What happened?

Benzoic Acid Recystallization Write-Up: Name _____

Part One:

Starting Mass _____
Mass of Purified product _____
MP range of Purified Product _____
_____

Describe the purified product (using one or more complete sentences!)

What was the percent recovery of benzoic acid (show calculation)?

Part Two:

Which group were you in? _____

What did you do differently on the second run?

Starting Mass _____
Mass of Purified product _____
MP range of Purified Product _____
_____

Describe the solid product (using one or more complete sentences!)

What was the percent recovery of solid product (show calculation)?

Write-up page 2

Calculate the average yields and melting ranges for each method from previous year's data:

	Group A	Group B	Group C	Group D
Average Yield:				
Avg Melting Range:				

Based on these umbers, which method gives the maximum yield?

Based on these umbers, which method gives the most pure product?

How did ***your second run*** compare (in yield and purity) to ***your first run***? Did you do better or worse?

How did ***your*** modification compare to the average of ***Group A*** (the "standard" method) from previous years? Is your modification a good one? [skip this if you did the A method twice]

Exp #4 – Stereochemistry Model-Building Lab

This lab will help you discover and learn about stereochemistry and the various terms associated with it. You will be provided with a model kit. Bring your textbook to help you with some of these concepts. As you go along, answer the questions on separate sheets of paper.

Stereocenters

Construct a model (called Structure **A**) in which a carbon atom (represented by a black ball) has four different colored balls attached to it – yellow, green, orange, and purple – representing four different substituents attached to the central carbon. The yellow ball represents hydrogen, the green ball represents chlorine, the orange ball represents bromine, and the purple ball represents iodine.

Q-1) Using wedges and dashes, draw this molecule on a separate sheet of paper in at least four different orientations. In each orientation that you draw, the same two atoms should NOT both be on wedges and dashes. Practice rotating the molecule in your hands and on paper, until you are comfortable with viewing molecules in three dimensions.

Q-2) Does this molecule have a plane of symmetry? The carbon of structure **A** is called a stereocenter.

Replace the orange ball with a green one.

Q-3) Does the model have a plane of symmetry now? Find an orientation in which it is easy to draw this plane of symmetry, then draw the molecule using wedges and dashes. Also, draw a dotted line representing the plane of symmetry.

Chirality

A stereocenter is a center of chirality or of "handedness" in a molecule.

Reconstruct Structure **A**. Put the model on a flat surface so that the yellow ball points up. Now, construct a model (Structure **B**) which is a mirror image of Structure **A**. Place Structure **B** on a flat surface adjacent to Structure **A** with the yellow ball of both pointing at the ceiling.

*Q-4) Try superposing (aligning) all five atoms at the same time. Can you superpose Structure **B** and Structure **A**? How many atoms can you superpose at one time? Try to improve on this number until you think that you cannot get any more atoms to superpose at any one time.*

*Q-5) Are Structure **A** and Structure **B** identical?*

Q-6) How do the structures differ?

Enantiomers

The two structures **A** and **B** are chiral molecules. A chiral molecule does not have a plane of symmetry and has a non-superposable mirror image. The pair of structures that are non-superposable mirror images are called enantiomers. These two compounds differ only in the way they rotate plane-polarized light. Each enantiomer is said to be optically active.

On both structures **A** and **B** replace the orange ball with a green one and call the new structures **C** and **D**.

*Q-7) Are structures **C** and **D** still mirror images of each other?*

*Q-8) Do **C** and **D** have internal planes of symmetry?*

*Q-9) Can you superpose structures **C** and **D**? Are these molecules identical or different?*

Structures **C** and **D** represent achiral molecules. Achiral molecules have a superposable mirror image, a plane of symmetry, and do not rotate plane-polarized light. Achiral molecules are optically inactive. (Remember: the prefix a- means the same as non-)

The R/S Convention

The *R/S* convention is used to designate the configurations at stereocenters. The attached atoms to the stereocenter are arranged in order of increasing atomic number. Thus, higher atomic number means higher priority. If two atoms have the same priority, you move to the next atom out and compare those atoms. Continue this until you break the tie. Look at the molecule from the side opposite the group with the lowest priority. If you count the highest to lowest priority and you go in a clockwise direction, you have the *R* configuration. If you move counterclockwise, the stereocenter is *S*.

Rebuild structures **A** and **B**. Place both structures on flat surface with the yellow ball of both pointing at the ceiling.

*Q-10) Look straight down at the models, starting with the green ball and proceeding clockwise, record the order of the balls for both Structure **A** and **B**.*

In our model kits, the black balls represent carbon atoms, the yellow balls represent hydrogen atoms, the green balls represent chlorine atoms, the orange balls represent bromine atoms, and the purple balls represent iodine atoms.

*Q-11) Using wedges and dashes, draw molecules **A** and **B**. Give each molecule a proper IUPAC name, including the (R) and (S) designations. (Note: the halogen "groups" are named chloro, bromo, and iodo.)*

Working with structure **A**, interchange any two balls attached to the stereocenter. Call this molecule **E**.
*Q-12) What happened to the configuration at the stereocenter? How does molecule **E** compare to molecule **B**?*

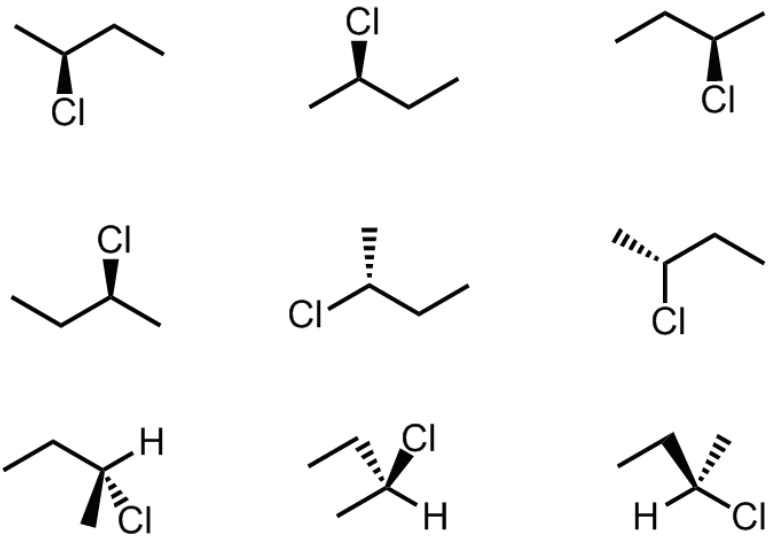
In your molecule **E**, interchange two ***different*** balls (not the same ones as you did in the previous step). Call this molecule **F**.
*Q-13) How does molecule **F** compare to molecule **B**? How does it compare to your original molecule **A** (refer to your question 4 answer as needed)?*

*Q-14) Repeat this process by swapping two groups at a time several more times. How many **different** stereoisomers do you find through this process?*

Converting Between Flat and 3-Dimensional Molecules

Build a model of *(R)*-2-chlorobutane and a model of *(S)*-2-chlorobutane

Q-15) Using your models, determine which of the structures, below, have the R configuration, and which of the structures have the S configuration. To verify your answer, rotate each model to align it with the structure that is drawn, below. Copy each structural drawing onto your paper and label the stereocenter as R or S.



Diastereomers and Meso Forms

Two compounds with the same molecular formula but a different arrangement in space are called stereoisomers. A stereoisomer that has a non-superposable mirror image is called an enantiomer. A stereoisomer with a non-superposable non-mirror image is called a diastereomer. Diastereomers usually have two or more stereocenters.

Working with a partner, build the following four molecules (you should each build two of the four):

(2R, 3R)-2,3-dichlorobutane = Molecule **G**
(2R, 3S)-2,3-dichlorobutane = Molecule **H**
(2S, 3R)-2,3-dichlorobutane = Molecule **I**
(2S, 3S)-2,3-dichlorobutane = Molecule **J**

Label each model with a piece of tape that has the molecule's letter (**G**, **H**, **I**, or **J**).

Q-16) Work with two molecules at a time and determine their relationship (for example: "Molecule **X** and Molecule **Y** are diastereomers"). *Repeat this process until you have examined each pair of molecules. You will make six total comparisons:* ***G*&*H*, *G*&*I*, *G*&*J*, *H*&*I*, *H*&*J*, *I*&*J*.**

A meso compound is an achiral compound that contains a stereocenter. In otherwords, a meso compound is a stereoisomer that is superposable with its own mirror image.

Q-17) Which of the 2,3-dichlorobutane isomers is (are) meso?

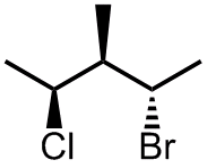
Q-18) Does each meso compound have an internal plane of symmetry? Rotate around bonds until you find the plane of symmetry, then sketch the molecule, using dashes and wedges, on your report sheet. Identify the plane of symmetry with a dotted line.

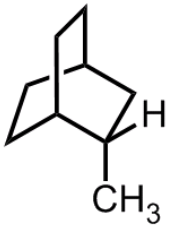
Q-19) Does each chiral compound have an internal plane of symmetry? If so, sketch them in your lab notebook.

Q-20) Removing any duplicate 2,3-dichlorobutane molecules, how many total isomers are there of 2,3-dichlorobutane? Sketch all of these in your lab notebook and label each with a proper full name. Under the full name, indicate whether the molecule would be ***optically active*** *or* ***optically inactive.***

Model kits are useful in determining stereochemistry – you are allowed to use a model kit on all exams in this class, provided that you have one! You may not, however, use any instruction booklet that comes with your model kit. A cheap model kit can be made from gum drops and toothpicks (although this kit can become VERY expensive if you have a sweet tooth).

Q-21) Practice assigning stereocenters by building models of these. Copy each molecule onto your paper and assign all stereocenters in the molecules as (R) or (S).





Please put your model kit away exactly the way that you found it. There is a sample model kit at the front of the room if you've forgotten where everything goes.

Exp #5 – Gas Chromatography

Chromatography (from Greek χρώμα:chroma, colour and γραφειν:"grafein" to write) is the collective term for a family of techniques to separate mixtures. It involves passing a mixture dissolved in a "mobile phase" through a stationary phase, separating the analyte from other molecules in the mixture.

Chromatography may be preparative or analytical. Preparative chromatography seeks to separate the components of a mixture for further use, while analytical chromatography operates with smaller amounts of material and measures the relative proportions of analytes in a mixture. The two are not mutually exclusive.

Suppose a mixture of bees and wasps passing over a flower bed. The bees would be more attracted to the flowers than the wasps, and would become separated from them. If one were to observe at a point past the flower bed, the wasps would pass first, followed by the bees. In this analogy, the bees and wasps represent the analytes to be separated, the flowers represent the stationary phase, and the mobile phase is the air. The key to the separation is the differing affinities of the analyte to the stationary and mobile phase. The observer represents the detector.

Gas chromatography (GC), sometimes called gas-liquid chromatography is a type of chromatography in which the mobile phase is a carrier gas, usually an inert gas such as helium or nitrogen, and the stationary phase is a microscopic layer of liquid or polymer on an inert solid support, inside glass or metal tubing, called a column.

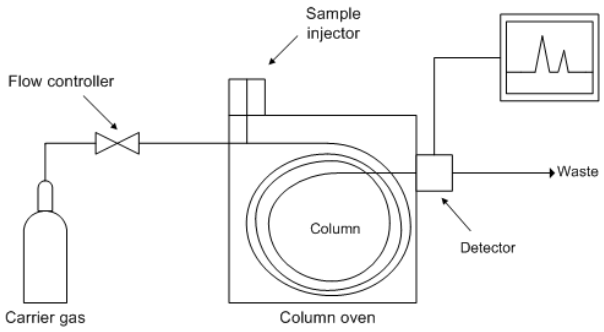


Fig. 1- Schematic diagram of a Gas Chromatograph

A typical GC (**Figure 1**) is operated by injecting a liquid sample into a gas stream, which then runs through a column with a high surface area-volume ratio. The column can be made by either filling a tube with a solid support (such as small glass beads), or by using a very narrow tube (a capillary). The temperature of the column is controlled by placing the column in an oven. As the injected liquid alternately evaporates and condenses through the column, it is drawn toward a detector at a speed that is related to its boiling point and to the temperature of the oven. Eventually, the compound escapes through a detector which examines the quantity of material present in the gas stream (usually by burning the material that escapes). The oven typically is programmed to slowly increase in temperature as the sample travels through to allow for good separation of both low- and high-boiling substances.

Why Does the Sample Separate?

Through the long column, compounds with a lower boiling point will be in the gas phase longer than compounds with a higher boiling point. This causes them to pass through the column faster than the higher boiling compounds.

Why is the Oven Temperature Increased?

If the oven starts off at a high temperature, then compounds whose boiling points are well below the temperature of the oven will all pass through the column at the same rate as the helium gas. Starting the oven at a low temperature allows these low-boiling compounds to separate. The temperature is then slowly increased so that compounds with higher boiling points will be able to evaporate (and therefore travel through the column to the detector).

How is the sample detected?

Typically, the compounds exit the column and land on hot wire. The wire is momentarily cooled, the resistance is changed and the current flow across the wire is measured.

What about My Sample?

Only a very, very small quantity of sample is used in the GC, but the sample is burned and therefore lost. One interesting technique, often used in forensic analysis, uses a mass spectrometer as a detectorgiving a characteristic "fingerprint" for each type of molecule. In this way, the combination gas chromatograph – mass spectrometer (GC-MS) not only identifies the quantities of material present in a sample, it also can identify which compound is represented by each peak. GC-MS could be used, for example, to analyze samples from a crime scene to identify which brand of cleaner was used to clean up after a crime, since each brand of cleaner will have different ingredients and different concentrations of each of these ingredients.

Today's Experiment

Part One: (Demonstration) A rudimentary GC can be constructed by filling a glass tube with laundry detergent. One end of this tube is connected to the gas line in the lab, and the other end is connected to a Bunsen burner fitted with a piece of copper wire. The laundry detergent acts as the stationary phase, while the methane gas acts as the mobile phase. A syringe is used to inject a small quantity of various chlorine-containing liquids into one end of the tube. The Bunsen burner acts as a detector – the chlorine containing liquid is burned as it exits the tube, and reacts with the copper wire in the flame. This causes the flame to change to a green color.

For this part of the experiment, you will record the time that it takes for dichloromethane (CH_2Cl_2) and for chloroform ($CHCl_3$) to travel through the gas chromatograph (this is called the retention time). Then, a sample containing both liquids will be injected into the GC.

On separate sheet(s) of paper, answer the following questions using complete sentence(s):

1) Which compound had a longer retention time?

2) Why did this compound have a longer retention time? (Explain your answer, considering the STRUCTURES of the two compounds!!!)

3) How well did the mixture separate? Could you tell the difference between the two compounds? Were they COMPLETELY separated, or did the second one start coming out of the column while the first one was still finishing? If so, suggest ways to improve the separation.

Part Two:

The Vernier Mini GC uses a metal column with the inside of the column coated with the stationary phase. A sample, consisting of one or more compounds, is injected into the column and is pushed through by air, which acts as the mobile phase. Organic compounds flowing out of the chromatography column are seen as a *peak* on a chromatograph, as seen in Figure 1. The amount of time it takes for a compound to exit the column after it is injected is called the *retention time*. With a GC, a compound can be identified from a mixture of chemicals by its retention time.

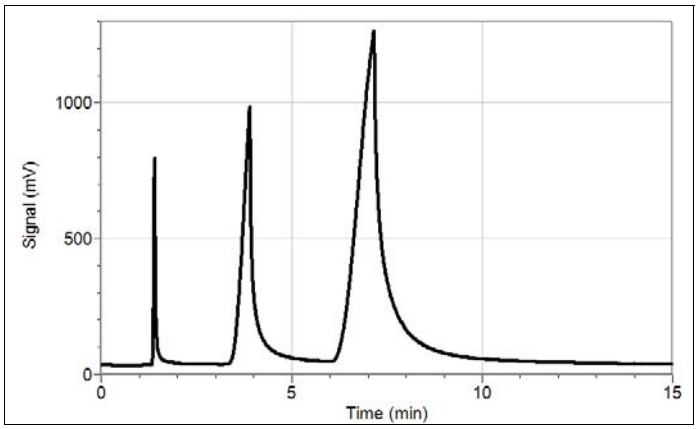


Figure 1: Sample gas chromatogram

Several factors can affect the interaction of a compound with the GC. More volatile compounds (i.e., compounds with a lower boiling point) tend to move through the column faster because they are flowing in the mobile phase and interacting very little with the stationary phase. The functional groups present on the compound are also a factor. For example, alcohols may interact with a polar stationary phase more than esters because alcohols can form strong hydrogen bonds. The molecular weight of a compound can also play a role, although it is not a simple matter of saying that the heavier the molecule the slower it will travel through a GC column.

In this experiment, you will gain experience with the Vernier Mini GC by running a known sample through the unit. The sample contains nine compounds that will separate under the proper conditions. You will test this one mixture of compounds repeatedly and vary the profile of the Mini GC operation to obtain the best possible separation of this mixture.

OBJECTIVES

In this experiment, you will

- Measure and analyze the chromatogram of a mixture of nine compounds as they pass through a Vernier Mini GC.
- Vary the temperature-pressure profile of the Mini GC and observe how the chromatogram is affected by changes in the profile.
- Determine the best temperature-pressure profile to obtain the best possible chromatographic separation of the mixture.

PRE-LAB EXERCISE

Complete the table below.

Compound	Boiling point (°C)	Molecular weight	Functional group
methanol			
acetone			
methyl ethyl ketone			
ethyl acetate			
2-hexanone			
propyl acetate			
butyl acetate			
2-pentanone			
4-methyl-2-pentanone			

PROCEDURE

1. Obtain and wear goggles.

2. Obtain a glass syringe, a vial of acetone, and a vial containing the mixture to be tested. The acetone will be used to clean the syringe.

Important: The glass syringe is fragile and can be easily damaged. Be careful not to bend the needle or bend the plunger. If the plunger is accidentally pulled out of the glass barrel, reinserting it is extremely difficult, sometimes impossible.

3. Prepare the Vernier Mini GC for data collection.
   a. Turn on the Mini GC.
   b. Connect the USB cable of the Mini GC to the USB port on your computer or LabQuest.
   c. Start the data-collection program, and then choose New from the File menu.
   d. Click Collect in Logger *Pro*, or tap ► in LabQuest, to bring up the Temperature-Pressure profile.
   e. Set the Temperature-Pressure values according to the settings listed for Run 1:

f.

	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
Start temperature	85°C	85°C	65°C	35°C	35°C	35°C
Hold time	10 min	10 min	10 min	3 min	3 min	3 min
Ramp rate	0°C/min	0°C/min	0°C/min	10°C/min	10°C/min	10°C/min
Final temperature	85°C	85°C	65°C	65°C	65°C	65°C
Hold time	0 min	0 min	0 min	7 min	1 min	4 min
Total length	10.0 min	10.0 min	10.0 min	10.0 min	10.0 min	10.0 min
Pressure	9.0 kPa	7.0 kPa	7.0 kPa	7.0 kPa	4.0 kPa	7.0 kPa

g. Select Done to initiate the Mini GC warm up. Note: A new message will appear, "Do not inject until GC is ready", and the LED on the Mini GC is red. The Mini GC will take a few minutes to warm up and stabilize. When the Mini GC is ready for injection in Step 7, the message will read, "Inject and select Collect simultaneously", and the LED will turn to green. Continue with Step 4 during warm up.

4. Follow the steps below to clean and flush the syringe with acetone. **Important**: The glass syringe is fragile. Be careful not to bend the needle or bend the plunger. Never pull the plunger back more than 50% of its total volume. Be careful not to bend the plunger as you press it down.
   a. Depress the plunger fully.
   b. Submerge the tip of the syringe needle into the vial of acetone.
   c. Pull back the plunger to fill the barrel about 1/3 full of acetone. Examine the barrel of the syringe and estimate the amount of acetone in the barrel.
   d. Expel the liquid onto a Kimwipe or a paper towel.
   e. Repeat Steps a–d at least two times, until you are comfortable pulling up a liquid into the syringe and measuring the volume in the syringe barrel. Use a Kimwipe or a paper towel to carefully pat around the tip of the syringe needle.
5. Follow the process in Step 4 to clean and flush the syringe with the mixture.
6. Collect a volume of the mixture for injection.
   a. Submerge the needle into the vial of mixture one last time.
   b. Draw up approximately 0.2 µL of liquid. It is not critical that the volume be exactly 0.2 µL; a tiny bit more or less volume is all right.
   c. After collecting your sample, gently wipe the needle from barrel to tip, with a Kimwipe.

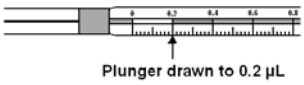


Figure 2

7. Prepare for injection and the start of data collection. It is important for you and your lab partner to divide the tasks in this step. One person will operate the syringe and the other person will operate the computer controls.
   a. When the Mini GC has reached the correct start temperature and pressure, the message reads, "Inject and select Collect simultaneously", and the LED on the Mini GC is green.
   b. To insert the needle of the syringe into the injection port of the Mini GC, hold the syringe with one hand and steady the needle with your other hand. Insert the needle into the injection port until the needle stop is fully seated, as shown in Figure 3. If the needle sticks, rotate it slightly while inserting. Do not move the plunger yet.
   c. Simultaneously, depress the syringe plunger and select Collect to begin data collection. Pull the needle out of the injection port immediately.

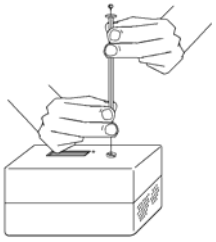


Figure 3

8. While the data collection proceeds, repeat Step 4 to thoroughly clean the syringe and needle. It may take more than three flushes to feel the syringe plunger move smoothly again, which is your indicator that the syringe and needle are both suitably clean.

9. Data collection will end after 10 minutes.

10. Analyze your chromatogram and write your comments in your data table. Consider these points when you make your comments.
    - How long does it take for all of the peaks to appear?
    - How well are the peaks separated from each other?
    - How sharp are the peaks?

11. To store the data, choose Store Latest Run from the Experiment menu in Logger *Pro* or tap the File Cabinet icon in LabQuest.

12. Change the temperature/pressure profile for the next run.
    a. Click Collect in Logger *Pro*, or tap ► in LabQuest, to bring up the Temperature-Pressure profile. Change the parameters to match the information for Run 2, given in Step 3. Click OK to initiate the Mini GC profile.
    b. While the Mini GC adjusts to its new Temperature-Pressure profile, repeat Steps 5 and 6.
    c. After the Mini GC is ready, repeat Steps 7–11 using your sample.

13. Repeat Step 12 until you have completed Run 6.

14. Devise your own operating conditions to optimize the performance of the Mini GC with your mixture. Write these new settings in your data table and get your instructor's OK before conducting your test. The chart below shows the available range for each setting.

Parameter	Range
Temperature	30–120°C
Ramp rate	0–10°C
Pressure	1–20 kPa

DATA TABLE

Run	Observations of the chromatogram
1	
2	
3	
4	
5	
6	

DATA ANALYSIS

1. In Run 3, what did you notice about the shape of the peaks?

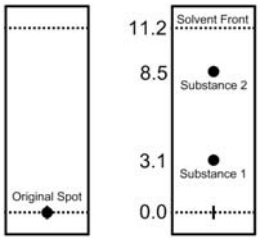
2. Of the six runs, which two showed the most significant differences? Explain.

3. What conditions of temperature and pressure worked best for the first three peaks, and for the last three peaks?

4. What parameter had the greatest effect on peak shape?

Part Three: For the third part of this experiment, we will use paper chromatography to examine the principles of chromatography. In paper chromatography, a sheet of paper is used as the stationary phase, and a liquid is used as the mobile phase. The sample is "spotted" onto the paper, and then the edge of the paper is placed into a container of liquid. As the liquid rises up the paper, the solubility of each compound in the liquid determines how quickly it rises up the paper. We report the "retention factor" (R_f) for each compound, which is defined as follows:

$$R_f = \frac{\text{Distance of the center of the solvent spots from the origin}}{\text{Distance of the solvent front from the origin}}$$

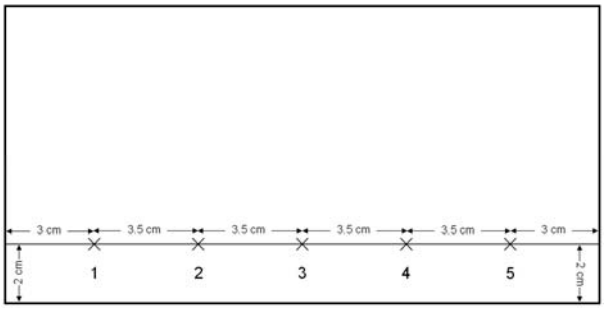


For example, in the figure, above, the R_f values for the two substances are as follows:

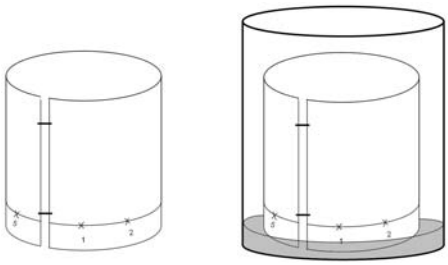
R_f (substance 1) = 3.1 cm / 11.2 cm = 0.28
R_f (substance 2) = 8.5 cm / 11.2 cm = 0.76

By comparing R_f values, you can try to identify the individual components present in a mixture, just as you did by comparing retention times with the GC. For this part of the experiment, we will examine the colored inks found in five different pens.

Obtain a rectangular filter paper and place it on a very clean surface, then use a ruler to draw lines and Xs, (lightly ***in pencil***) and number the lanes 1 through 5 as shown below:



On the center of the X in lane 1, quickly and lightly put a "dot" from a felt-tip pen. On lane 2, using your ruler, draw a horizontal line that is 1 cm in length directly on top of the line that you drew in pencil, centered on the X, in black ink, using a four-color Bic Pen. Repeat this process for lanes 3–5 using blue ink in lane 3, green ink in lane 4, and red ink in lane 5. Staple your filter paper so that it forms a "tube" as shown on the next page.



Obtain a 600 mL beaker and add 10 mL of ethanol and 10 mL of deionized water, then swirl to mix. Place the beaker on your bench and allow the liquid to stop moving before continuing on to the next step. When the liquid is motionless, insert your paper tube into the beaker, as shown above. The ink should be near the bottom of the beaker, but should not be covered by the solvent level. Without moving the beaker or disturbing the liquid, cover the beaker with aluminum foil and leave undisturbed until it is time to remove the filter paper.

The solvent will begin to "climb" up the paper tube. Leave the paper tube in the beaker until the liquid level is between 0.5 and 1 cm from the top. This will take between 15 minutes and 1 hour. Monitor the paper carefully. If the solvent gets to the top of the paper, you will have to start again! When the solvent is at the right height, remove the paper tube from the solvent and ***immediately mark the position of the solvent using a pencil***, then let the paper tube dry, standing on its edge in the fume hood. When it is dry, you can remove the staples.

On separate sheet(s) of paper, answer the following questions using complete sentence(s):

11) Tape your paper chromatogram onto a sheet of paper that you will turn in with your report. By clearly circling them in pencil on your chromatogram, identify as many different colors of inks as you can.

12) Which inks contained more than one colored compound? Which inks contained only one colored compound? How can you tell?

13) Calculate the R_f values for each ink color on your chromatogram. Write each R_f value in pencil directly on your chromatogram in the center of each circle that you drew for question 11. Show your calculations separately on the paper that you turn in for your report.

14) For lane #4, which color ink has a stronger attraction for the paper than for the solvent – blue or yellow? How can you tell?

15) Does it appear that any of the inks contain some of the same chemical compounds? Which ones? How can you tell?

Exp #6 – Synthesis of 2-Ethoxynaphthalene: An S_N2 Reaction

β-Ethyl naphtholate is used as an ingredient in perfumes. It is prepared by a simple one-pot reaction, and serves as a good example of an S_N2 reaction. In the first step, potassium hydroxide is added which removes the acidic proton from the naphthol. The potassium naphtholate acts as a nucleophile towards the ethyl iodide. When the reaction is cooled and diluted with water, the product precipitates out and the salts remain soluble.

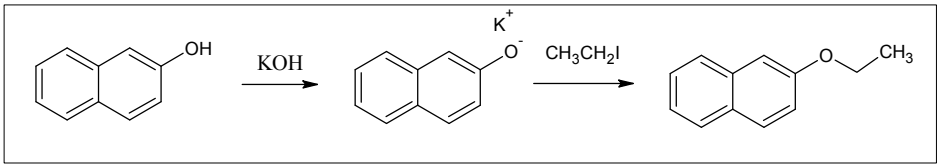


Fig. 1 - A two-step reaction done in one flask.

Techniques

In today's lab, you will *reflux* the solution. It's a simple idea, really. Because reactions occur more quickly at higher temperatures, chemists often heat up flasks filled with solvents. However, organic solvents will quickly boil away and the vapors from the flask can be a fire hazard. To solve this problem, you attach a reflux condenser to the pot. This cools the hot vapors and allows the condensed liquid to return to the pot.

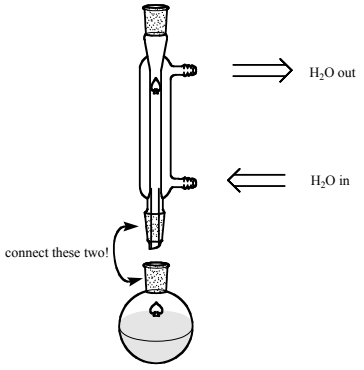


Fig 2 - The reflux apparatus

The Reaction

- Clamp a 100 mL round bottomed flask and equip it with a stir bar and a magnetic stirrer.
- To this flask, add 2.0 g of potassium hydroxide, 25 mL of anhydrous methanol and 2.5 g of 2-naphthol (or β-naphthol). Stir the solution until all the solids dissolve. **Caution: Potassium hydroxide is a caustic agent used to clean drains! If you get any on yourself, or you skin feels "soapy", immediately wash the affected area with large amounts of water.**
- To the solution, add 1.7 mL of iodoethane (or ethyl iodide) *via* a syringe. Take your flask to the hood to perform this operation. Avoid breathing the ethyl iodide fumes.
- Attach a reflux condenser and a heating unit. Warm the mixture to reflux, making sure all the water lines are connected properly and water is slowly flowing through the condenser.
- Reflux for 0.5 h. Time from when boiling starts!

Work-up

- Quickly, remove the condenser and pour the contents of the reaction flask into a 250 mL beaker with 40 mL of ice already in it. Stir the mixture and let the product precipitate. Don't use too much ice!
- Let the ice melt and collect the crystals in your Büchner funnel using vacuum filtration. Wash the crude crystals with 150 mL of ice cold water.
- In the fume hood! Dissolve the crude crystals in the smallest amount of hot 95 % ethanol that they will dissolve in. Let the solution slowly cool until crystals reappear. Collect these crystals again using vacuum filtration.
- Let the crystals air-dry in your drawer until the next lab period.
- Weigh the dried product and take its melting point.

Synthesis of 2-Ethoxynaphthalene write-up

Writing a good lab notebook is a valuable skill for a scientist.

The general format for a organic chemists lab notebook is:
1) Title (short and descriptive)
2) Purpose (one complete sentence - no more, no less)
3) Reagent chart (visual summary of the reaction, both qualitatively and quantitatively)
4) Procedure (detailed)
5) Data (copies of any data collected - from melting points to computer print-outs)
6) Conclusion (very short - the only section of your lab notebook with your "opinion")

A few stylistic rules for a good organic notebook:

1) Write only in blue or black ink. Never write in pencil (or red ink for this class). If you discover something amazing, your lab notebook is a legal record of your work and can be used to defend patent lawsuits, etc. If you make a mistake, simply cross out what you wrote with a single line making sure that your mistake is still legible. "White Out" or "Liquid Paper" should never be used.

2) Write on only one side of the page and leave 3/4 inch margins on all sides of the page. This way, if you realize that you left something out, you have plenty of space to go back and put it in! (In class, this space is also used for comments during grading).

3) A "real" lab notebook is always bound and begins with an up-to-date table of contents. We will be keeping "real" lab notebooks in Chem 7B. For now, you may simply staple together and turn in loose sheets of paper for your "notebook".

At the start of your experiment, you should include a title and a one sentence purpose. This is so that the reader can quickly take note of what it was that you were trying to do on a given page of your notebook.

After the purpose, you should always create a reagent chart. This chart allows the reader to quickly scan a notebook and identify which reaction was attempted and how much of the product was obtained. ***Only include reagents that appear in the product or are otherwise consumed.*** Don't include solvents! The reaction product(s) that you isolate should always appear as the last column(s). Include as much quantitative information as you know about the reaction. At the **minimum**, *each column* must include:

1) amount of reactant or product, given in the units you measured
2) the number of moles of reactant or product that you started with or finished with
3) all constants that you used to convert from the units that you measured to "moles"

				→
grams				
mL				
density				
M.W.				
moles				

The procedure section should be a record of what you *actually did*, not what the recipe called for. If the recipe says "add between 1.5 and 2 g of salt", you would write "1.789 g of salt was added to the reaction" in your notebook. Small details can be important! Try to imagine that a future Chem 7A student will need to repeat your work based only on your notebook; could they do it? Remember: use pen and simply cross-out any mistakes. A lab notebook is a document that should be written ***as you perform the reaction, not after the fact***. It is not a "formal composition," so there is no need to go back and re-write anything to make it more "tidy."

After the procedure, create a section for the data obtained during your experiment, such as the melting point (and how it compares to the known value) and the weight and percent yield of the product. The data section of your notebook should not contain any commentary. If you believe that the product was impure based on the melting point data, give that information in the conclusion. By separating the facts from your opinions, a separate scientist who reviewed your results would not be pre-disposed to adopt the same conclusions that you did.

The conclusion should ***just be a few sentences long***: a summary of whether the reaction worked, what the percent yield was, and whether the product was pure. If any of your data needs interpretation, this is the place to do it. (Example: Due to the very broad melting range and the fact that it was 32° lower than the literature melting point, the product is probably not very pure.) If the yield was very poor, suggestions for improvement should be given.

Safety:

Define lachrymator:

Which chemical used today is a lachrymator:

Which chemical is caustic?

Exp #7 – Simple and Fractional Distillation

At first glance, there seem to be little difference between the two techniques used in today's experiment. However, the extra column used in today's experiment greatly contributes to the efficiency of the separation of the volatile liquids. Simple distillation involves an apparatus that heats a liquid and turns it into a vapor. The vapors travel a short distance and are re-cooled and condensed into a liquid, which is collected. In a simple distillation, there is little separation of liquids unless the boiling points are quite different (*i.e.* greater than 50 °C). Thus, simple distillations are useful for removing impurities with high boiling points, polymers, or salts.

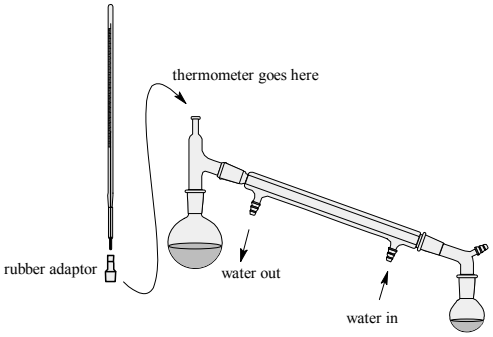


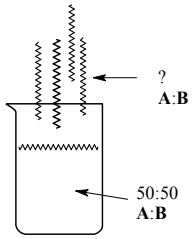
Fig. 1 - Simple Distillation Set-up

A fractional distillation is essentially the same as a simple distillation but here, the vapors of the hot mixture are forced to travel a longer distance. As the vapors go through the fractionation column, the compound cools, condenses, and drips back into the boiling liquid. The liquid and vapors have more time to equilibrate and come out of the fractionation column at different rates depending on their boiling points. Fractional distillation is used when the liquids have a boiling point difference of 10-30 °C

You can calculate the composition of the distillate if you know the vapor pressures.

Dalton's Law of partial pressures: $P_T = P_A + P_B$
Vapor pressure of a liquid: $P_A = X_A P_A^o$

Example: Consider a 50:50 solution of two liquids, **A** and **B**. **A** has a vapor pressure of 75 mmHg at 30°C, while **B** has one of 25 mmHg. If you were to condense the vapor above the solution, what would be the mole fraction of **A** and **B** in the vapor phase?



For a very efficient distillation, the temperature *vs.* volume distillate graph might look like the one shown below.

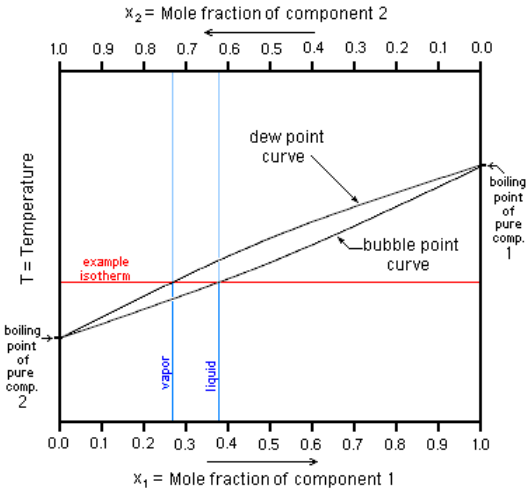


Fig 2 Temperature vs. volume distillate graph

At any given temperature for a distillation the lower boiling component of a mixture makes a larger contribution to the vapor composition than the higher boiling component. In the example below, A has a lower boiling point. The vapor is richer in A than the liquid from which it escaped. The two points ("y" and "x") give the two concentrations which are in equilibrium.

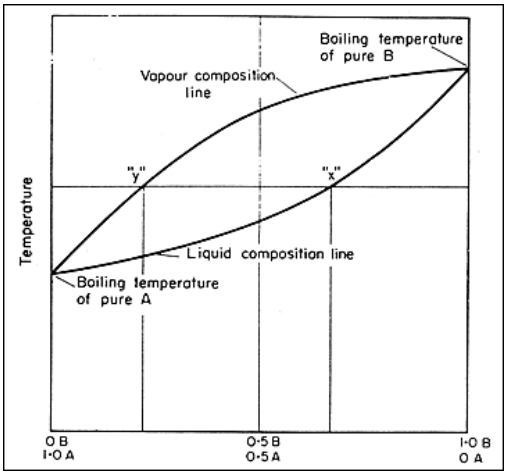


Fig 3 Boiling point diagram for a mixture of two liquids

When you're thinking about the temperature in a distillation, it's important to make a distinction between the pot temperature and the head temperature. The pot temperature is the temperature of the liquid in the flask with the stirbar (called the "pot"). The head temperature is the temperature of the vapor as it reaches the top of the column and condenses. If you are distilling at a steady rate (generally 1 drop/2-3 sec) the head temperature is identical to the boiling point of the liquid being distilled.

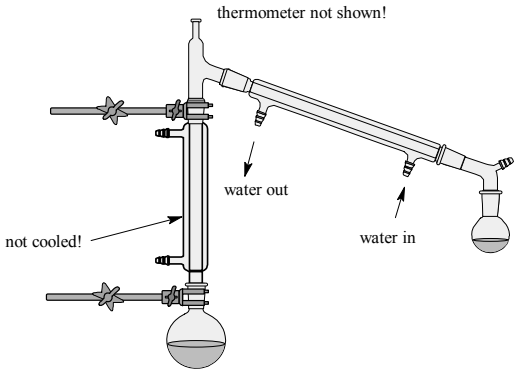


Fig. 2 - Fractional Distillation Set-up

How can you tell how pure your liquid is?

You will analyze the distillate using either a Gas Chromatograph or an Abbe refractomoter, which measures the refractive index of your mixture. Since the refractive index of any liquid is in direct proportion to the index of its components, you can determine a liquid's composition quantitatively.

Example: If your mixture is 50 % of a compound with a refractive index of 1.4216 and 50% of a compound with a refractive index of 1.3216, then the refractive index of the mixture would be:

0.50(1.4216) + 0.50(1.3216) = 1.3716

In today's lab, you will try one of four variants of the procedure in an attempt to see what effect each of these has on the separation.

Check-list for setting up distillation apparatus:

Do you have the pot tightly clamped securely by the neck?
Do you have the water in the bottom and out the top?
Have you used clamps to secure the condenser and adapters (slightly less tightly than the pot)?
Is the thermometer placed at the right height (just below the "hump" of the head)?
Do you have a stir bar/boiling chips?
Are all your joints secure?
Does your water flow into the sink?
Have you used Keck clamps/rubber bands to secure the adapters/condensers?
Don't turn the Variac to 100% power! It will burn out the heater and you will have to pay for it!

Procedure:

- Obtain 25 mL of one of three mixtures (whichever mixture you are assigned). Place it in a 50mL r.b. flask with a stir bar.
- Setup either a fractional or simple distillation apparatus (whichever apparatus you are assigned) and distill it.
- Collect 3 mL portions of the distillate in test tubes, record the boiling range of each sample. You should get six or seven tubes. Don't try to distill the very last bit of liquid.
- When you are finished, measure the refractive index of each sample
- When you are done, pour all liquids into the waste container.

Procedure for GC analysis:

1. Obtain a glass syringe and three vials containing: ethyl acetate, butyl acetate, and a mixture of ethyl acetate and butyl acetate. **CAUTION**: *Ethyl acetate and butyl acetate are both hazardous in case of ingestion or inhalation*.

Important: The glass syringe is fragile and can be easily damaged. Be careful not to bend the needle or bend the plunger. If the plunger is accidentally pulled out of the glass barrel, reinserting it is extremely difficult, sometimes impossible.

2. Prepare the Vernier Mini GC for data collection.

   a. Turn on the Mini GC.
   b Connect the USB cable of the Mini GC to the USB port on your computer or LabQuest.
   c Start the data-collection program, and then choose New from the File menu.
   d Click Collect in Logger *Pro*, or tap ► in LabQuest, to bring up the Temperature-Pressure profile.
   e Set the Temperature-Pressure values to:

Start temperature	35°C
Hold time	1 min
Ramp rate	10°C/min
Final temperature	65°C
Hold time	2 min
Total length	6.0 min
Pressure	7.0 kPa

   Select Done to initiate the Mini GC warm up. Note: A new message will appear, "Do not inject until GC is ready", and the LED on the Mini GC is red. The Mini GC will take a few minutes to warm up and stabilize. When the Mini GC is ready for injection in Step 13, the message will read, "Inject and select Collect simultaneously" and the LED will turn to green. Continue with Step 10 during warm up.

3 .Follow the steps below to clean and flush the syringe with acetone. **Important**: The glass syringe is fragile. Be careful not to bend the needle or bend the plunger. Never pull the plunger back more than 50% of its total volume. Be careful not to bend the plunger as you press it down.

   f. Depress the plunger fully.

g. Submerge the tip of the syringe needle into the vial of acetone.
h. Pull back the plunger to fill the barrel about 1/3 full of acetone. Examine the barrel of the syringe and estimate the amount of acetone in the barrel.
i. Expel the liquid onto a Kimwipe or a paper towel.
j. Repeat Steps a–d at least two times, until you are comfortable pulling up a liquid into the syringe and measuring the volume in the syringe barrel. Use a Kimwipe or a paper towel to carefully pat around the tip of the syringe needle.

4. Follow the process in Step 4 to clean and flush the syringe with ethyl acetate, the first sample to be injected into the Mini GC.

5. Collect a volume of ethyl acetate for injection.

d. Submerge the needle into the vial of ethyl acetate one last time.
e. Draw up approximately 0.2 µL of liquid. It is not critical that the volume be exactly 0.2 µL; a tiny bit more or less volume is all right.
f. After collecting your sample, gently wipe the needle from barrel to tip, with a Kimwipe.

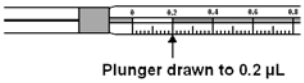


Figure 4

6. Prepare for injection and the start of data collection. It is important for you and your lab partner to divide the tasks in this step. One person will operate the syringe and the other person will operate the computer controls.

d. When the Mini GC has reached the correct start temperature and pressure, the message reads, "Ready to Inject," and the LED on the Mini GC is green.
e. To insert the needle of the syringe into the injection port of the Mini GC, hold the syringe with one hand and steady the needle with your other hand. Insert the needle into the injection port until the needle stop is fully seated, as shown in Figure 5. If the needle sticks, rotate it slightly while inserting. Do not move the plunger yet.
f. Simultaneously, depress the syringe plunger and select Collect to begin data collection. Pull the needle out of the injection port immediately.

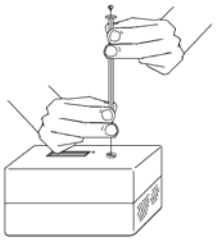


Figure 5

7. While the data collection proceeds, repeat Step 10 to thoroughly clean the syringe and needle. It may take more than three flushes to feel the syringe plunger move smoothly again, which is your indicator that the syringe and needle are both suitably clean.

8. Data collection will end after 6 minutes. Observe the graphed data that characterize an ethyl acetate chromatogram.

Analyze your chromatogram.

a. Choose Peak Integration from the Analyze menu.
b. Select and integrate the left-most peak. To do this, drag from a little before the peak to a point far enough to the right that includes all of the peak. Then choose Add.
c. Record the retention time and the peak area in your data table.
d. Enter the name of the compound, if known.

9. Complete one or both of the following as directed by your instructor.

a. Print your chromatogram.
b. You can choose to save this chromatogram and peak analysis for later use, with a unique file name, by choosing Save from the File menu.

10. Prepare the butyl acetate sample.

d. Click Collect in Logger *Pro*, or tap ► in LabQuest, to bring up the Temperature-Pressure profile. This profile will be the same as for your previous run. If you are satisfied with these values, click OK to initiate the Mini GC profile.
e. While the Mini GC adjusts to its Temperature-Pressure profile, repeat Steps 11 and 12 with the 1-butanol sample.
f. After the Mini GC is ready, repeat Steps 13–18.

11. Repeat Step 18 for the ethyl acetate/ butyl acetate mixture and the three fractions you collected from the fractional distillation in Part I. **Note:** Make sure to record the % ethyl acetate and % butyl acetate for the mixture and the three fractions you collected from the distillation.

12. When you have completed your final data-collection run, turn off the Mini GC.

Exp #7 - Simple and fractional distillation writeup **Name** _____
For GC analysis

Results

Compound	Retention time (min)	Peak area
ethyl acetate (EtOAc)		
butyl acetate (BuOAc)		
EtOAc/BuOAc Mixture		

Fraction	Temperature range	Volume collected
1		
2		
3		

Analysis of the Chromatograms

	Peak area EtOAc	%EtOAc	Peak area BuOAc	%BuOAc
EtOAc/BuOAc mixture				
1st fraction				
2nd fraction				
3rd fraction				

1. Based on the distillation and GC data, what percent of each substance was in your mixture? Explain.

2. How well did your column separate the chemicals? What could you change to achieve better separation?

3. Why does a rapid distillation that floods the column lead to poor separation of components?

4. What would happen to the separation of chemicals in the GC if the temperature was started out at 90ºC?

5. What is the mole fraction for each ester in your known mixture? The mixture was prepared using equal volumes of ethyl acetate and butyl acetate. The density of ethyl acetate is 0.879 g/mL and the density of butyl acetate is 0.800 g/mL.

Exp #7 - Simple and fractional distillation writeup Name _____
For Refractive Index Analysis

What were the refractive indices of your samples, and what was the mole fraction of methyl acetate in each sample?

tube	1	2	3	4	5	6	7
n_d							
$X_{m.a.}$							
Boil Range							

Show a sample calculation for determining $X_{m.a.}$:

Using a spreadsheet (like Microsoft Excel) and the previous class data, plot the ***average*** $X_{m.a.}$ *vs* test tube number for the simple distillation of the solvent mixture that you distilled.

On the same graph, make a plot of the ***average*** $X_{m.a.}$ *vs* test tube number for the fractional distillation of the solvent mixture that you distilled.

Based on these graphs, which method gave a better separation for your solvent?

Would it be worth doing the fractional distillation considering that it takes longer to perform?

Using a spreadsheet and the data sheet, plot $X_{m.a.}$ *vs* test tube number for *your* distillation.

For your distillation, if you collected the first four samples (assuming they are 3 mLs each) and combined them, how pure would your methyl acetate be?

	Measured	Lit
N_D of pure Methyl Acetate	_____	1.361
N_D of pure Ethyl Acetate	_____	1.372
N_D of pure Propyl Acetate	_____	1.384
N_D of pure Butyl Acetate	_____	1.394

Mole Fraction of Methyl Acetate in each fraction

Mixture type	fraction number						
methyl acetate / ethyl acetate	**1**	**2**	**3**	**4**	**5**	**6**	**7**
simple	0.736	0.636	0.636	0.636	0.636	0.473	0.491
	0.818	0.764	0.655	0.627	0.545	0.363	0.182
	0.773	0.727	0.682	0.636	0.573	0.500	0.355
	0.750	0.680	0.680	0.640	0.540	0.480	0.380
	0.772	0.723	0.681	0.654	0.581	0.472	0.393
fractional	0.909	0.764	0.727	0.682	0.636	0.500	0.336
	0.763	0.680	0.720	0.670	0.590	0.500	0.350
	0.820	0.820	0.750	0.730	0.640	0.500	0.300
	0.860	0.760	0.710	0.640	0.500	0.410	0.220
methyl acetate / propyl acetate	**1**	**2**	**3**	**4**	**5**	**6**	**7**
simple	0.833	0.781	0.714	0.595	0.433	0.333	0.024
	0.857	0.757	0.733	0.648	0.505	0.167	0.005
	0.857	0.810	0.729	0.671	0.505	0.281	0.038
	0.048	0.119	0.152	0.214	0.738	1.000	-0.240
	0.929	0.857	0.728	0.523	0.109	-0.023	-0.023
fractional	0.952	0.952	0.810	0.281	0.019	0.019	na
	0.976	0.914	0.881	0.857	0.019	0.000	na
	0.905	0.857	0.867	0.690	0.333	-0.014	-0.029
	1.000	0.952	0.691	0.914	0.410	0.024	0.033
	0.929	0.905	0.871	0.762	0.533	0.014	na
	0.876	0.876	0.833	0.805	0.171	0.048	0.048
	0.952	0.852	0.714	0.952	0.000	0.000	0.000
	0.957	0.910	0.852	0.548	0.710	0.240	0.240
methyl acetate / butyl acetate	**1**	**2**	**3**	**4**	**5**	**6**	**7**
simple	0.982	0.967	0.924	0.667	0.303	0.042	0.042
	0.970	0.936	0.906	0.833	0.470	0.045	0.039
	0.982	0.969	0.969	0.524	0.045	0.045	0.045
	0.939	0.891	0.861	0.797	0.470	0.061	0.033
	0.969	0.939	0.909	0.833	0.406	0.064	0.030
	0.969	0.921	0.921	0.879	0.367	0.054	0.036
fractional	1.000	1.000	0.955	0.955	0.109	0.045	0.030

Exp #8 – Steam Distillation of Cloves: Isolation of Eugenol

Along with recrystallization, distillation is a technique that would be familiar to an alchemist of the middle ages. Distillation is used to separate liquids of different boiling points. There are several types of distillation: simple, fractional and steam.

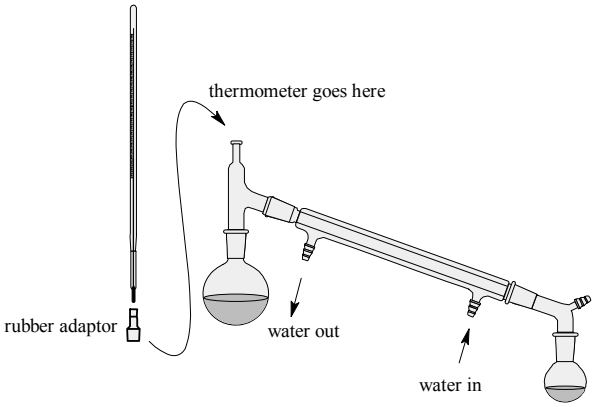
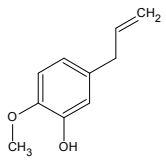


Fig. 1 - Simple Distillation Set-up

Steam distillation is an ancient method used to manufacture perfumes and food flavorings from plant products. This technique consists of placing the substance to be distilled in water, and then boiling the water. The steam generated carries the compound over to the receiving flask where it ends up as a two phase mix of water and the compound. This technique *does not* involve using steam to heat the main flask, which is a common misconception.

One early use of steam distillation was in the isolation of formic acid from ants. A large flask filled with ants and water was distilled. The solution that came over was named formic acid, from the Latin *formis* (ant). It should be noted that this technique is not strictly steam distillation by today's definition. In today's lab, we will be distilling a more pleasant compound: eugenol.



Eugenol

Eugenol comes from clove oil and is a topical analgesic that has been used as a remedy for tooth pain.

Steam distillation works best with compounds that have a fairly low vapor pressure and are insoluble in water. How does this process work? Because the compound is insoluble in the water, the composition of the vapor is proportional to the sum of the vapor pressures of both components. Therefore, even though the insoluble component has a low vapor pressure, the vapor coming over at the boiling point will consist of a small portion of the desired compound and mostly water.

Check-list for setting up distillation apparatus:

Do you have the pot tightly clamped securely by the neck?
Do you have the water in the bottom and out the top?
Have you used clamps to secure the condenser and adapters (slightly less tightly than the pot)?
Is the thermometer placed at the right height (just below the "hump" of the head)?
Do you have a stir bar/boiling chips?
Are all your joints secure?
Does your water flow into the sink?
Have you used Keck clamps/rubber bands to secure the adapters/condensers?

Procedure

- Grind 10 g of cloves into a coarse powder and place it in a 500mL (or the largest one in your kit) round bottomed flask.
- Equip the flask with a magnetic stir bar and clamp it by the neck. Fill the flask about half-way with water. Set-up a heating mantle, a stir plate, and a simple distillation apparatus.
- Make sure all connections are secure and that water is slowly flowing through the condenser. Heat the flask at a temperature sufficient to allow the water to distill continuously.
- During the distillation, you may start to run out of water. If this happens, use the squirt bottle to carefully add more water by removing the thermometer adapter and squirting it through the hole.
- Collect about 75mL total water, or stop when the distillate is clear and not cloudy.

Work-up

- Cool the distillate until it is ice-cold using an ice bath. You may see two layers at this point. Add about 15 mL diethyl ether, transfer the entire contents to a separatory funnel, swirl the funnel, and allow the layers to separate. (NOTES: If you extract when the water is warm, the heat will boil the ether, causing a mess! Do not vigorously shake the seperatory funnel – this will cause an emulsion to form, which means that your layers will not separate) Remove the ether layer. Add another portion of 15mL ether to the separatory funnel, swirl, let settle, then remove the ether and combine with the previous ether extract. Repeat one last time with 15mL ether and combine the ether layers into one flask.
- Dry the ether with anhydrous magnesium sulfate for 5 to 10 minutes. Then, gravity filter the solution through a piece of fluted filter paper into a pre-weighed 100-mL round bottomed flask.
- Distill off the ether using a simple distillation apparatus setup. Heat at no more than 30% power until the ether begins to distill.
- Collect the ether until the solution in round bottomed flask stops boiling. Recycle the ether in the "recycled ether" bottle provided
- Take an infrared spectrum of your product

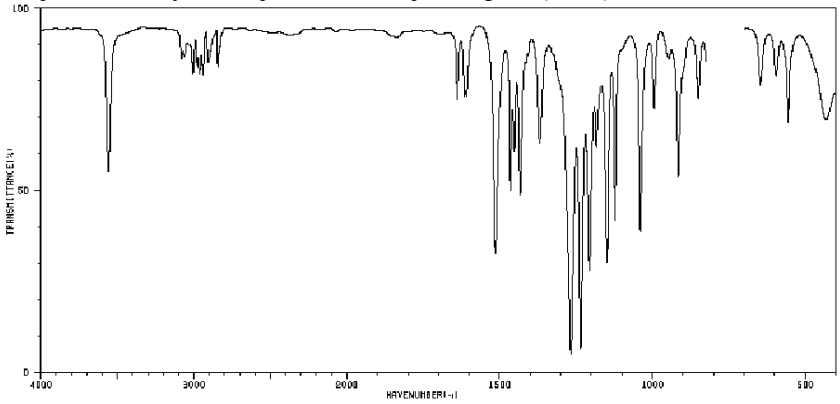
SAFETY:

- You'll be using a flammable solvent. No Flames!
- Cool your distillate before extracting wth ether
- Ether vapors can make you dizzy!

Exp #8 - Steam distillation writeup Name _____

Calculate a percent recovery for your compound. Base this on the weight of the plant material you started with. (This yield will be low!)

Compare the IR of your compound to that of pure Eugenol (below)



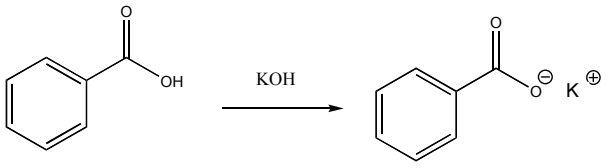
Based on your comparison, did you isolate eugenol and was it pure? If not, list the likely impurity(ies):

Attach your spectrum to this page and on the back of your spectrum, give a full analysis of the spectrum. Does it match with the structure of eugenol?

Exp #9 – Acid-Base Extraction of Benzophenone and Benzoic Acid

An extraction is a commonly used technique that separates components of a mixture based on their solubility. All extractions are based on the simple idea that "like dissolves like". That is, salts dissolve in water and most organic compounds prefer to stay in organic solvents. An extraction is performed after a reaction is completed in order to separate products from reactants, from leftover reagents, or from side-products with different solubilities.

Most extractions are performed with an aqueous phase and an organic phase in a separatory funnel, a device that allows you to remove the top or bottom phase. In the simplest case of extraction, you would have a compound that was soluble in an organic phase and one soluble in water. When you dissolve them in a mixture of organic solvent and water, the compounds would migrate to the layer they were most soluble in, and the extraction would be complete.



insoluble in water *soluble in water*

Fig. 1 - Reaction of acid and base affects solubility.

Often, you have two compounds that are both soluble in an organic solvent, but one of them can be converted into a water-soluble salt by treatment with an acid or base. For example, benzoic acid and benzophenone are both soluble in diethyl ether. However, when you treat benzoic acid with a base (say, sodium hydroxide), you obtain sodium benzoate, which is soluble in water and insoluble in ether.

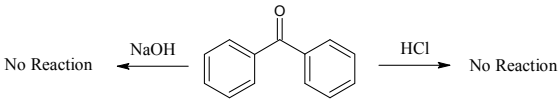


Fig. 2 - Hydrocarbons are generally unaffected by aqueous acid and bases

Therefore, in order to separate benzophenone and benzoic acid, you dissolve both in ether. You would then add aqueous sodium carbonate, resulting in a two phase system with benzophenone in the ether layer and sodium benzoate in the aqueous layer. The two phases are separated with the separatory funnel. The ether layer is then treated with a drying agent (typically sodium sulfate) which acts like a sponge and absorbs any water in the ether layer. The ether is evaporated, leaving behind benzophenone.

The sodium benzoate layer is a bit more complicated. You must convert the salt back into benzoic acid. This is accomplished by adding an acid (*e.g.* HCl) to the aqueous layer. The benzoic acid formed finds itself in a solvent that it is insoluble in, thus it precipitates out of the water. The solid benzoic acid is collected *via* vacuum filtration.

Some people like to visualize the procedure using a flow chart to keep track of all the various reagents and solvents added. You should learn how to make flowcharts for the various work-ups in this course; they are very useful!

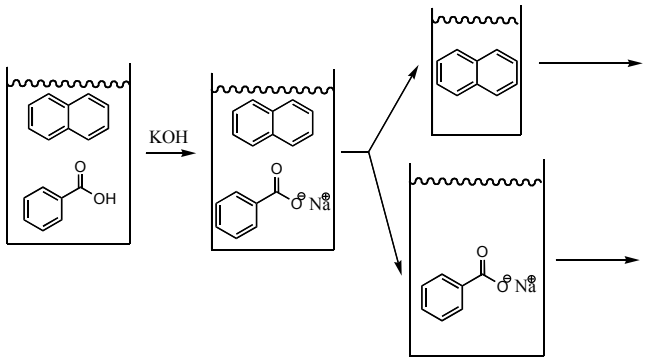


*Fig. 3 - Sample flow chart for separation of benzoic acid and naphthalene (**not** today's experiment)*

Techniques

There are many small details involved in extractions that it are important to remember. With practice, they become "second-nature" and you rarely think about them. Be organized and think about what you are doing!

When handling the separatory funnel, *never point the nozzle at your neighbor or yourself*. Often the gas evolved from an acid-base reaction, or the increased vapor pressure of a warmed solvent can cause the cap to pop off the top, spraying everyone around you! Also, keep the open end pointed up. Sometimes the stopper will not fit tight and the assembly will leak all over you!

Before you pour something into the funnel, check that the stopcock is closed! At one time or another, everyone has been intently staring at the open end while pouring, as the solution runs onto the bench top through the open nozzle!

Whenever you add an acid or base, **add it slowly** (especially a carbonate or bicarbonate, which release gases!), Sometimes, it'll be more exothermic or fizzy than you expected!

Before you start, collect and clean all your glassware that you'll need. Then, label beakers with what they are going to contain. Being organized will prevent you from suddenly looking around and realizing that you have no idea what's in the flask in front of you!

It is always more efficient to perform several extractions with smaller amounts of solvent rather than one big single extraction. An analogy is when you wash soap out of a glass: Three small rinses remove more soap than one large rinse. Unfortunately, it's more work!

As mentioned above, drying agents are used to remove the last traces of moisture from organic layers. Ether can absorb about 5% of its weight in water without any visible sign that it's there. If you attempt to evaporate an organic layer that is wet, you will end up with a product that has little drops of water in it, taking days and days to evaporate, and often not crystallizing properly. To prevent this, inorganic sulfates are added to the organic layer, which react with the excess water. The composition of the sulfate usually changes from a free-flowing powder to a chunky one as they absorb water. Keep adding the drying agent until it remains free-flowing! Remember, you'll be filtering it away anyway, so it's better to add too much than too little.

There are two ways to filter. *Vacuum* filtration is used to *collect a solid* that you want to save. Simple *gravity* filtration is used when you want to *strain out a solid*, usually a drying agent. If you try and vacuum filter an organic solution, it will often boil at the reduced pressure and cause a mess. If you gravity filter a product, it will often clog the pores of the paper and take a very long time.

"Washing" and "Extracting" a Layer

Two terms are used constantly in organic chemistry procedures: "washing a layer" and "extracting a layer". For example, a procedure will say "wash the ether layer with saturated sodium chloride". What this means is that you take your ether layer and you add some "wash" layer, in this case salt water. You swirl the mixed layers around, then let them settle. You remove and *discard* the salt water layer, while *keeping* the ether layer. What you have done is to extract any inorganic compounds that you don't want. Washing is an extraction where you throw away one layer. Remember that often a wash will be carried out two or three times just to be thorough.

If the procedure says "extract the ether layer with 10% aqueous sodium hydroxide", it means you take the ether layer and add some aqueous base to it. You swirl the layers around, let them settle, and separate them. You now *keep* the aqueous base layer and *discard* the ether layer. (you have gotten all of the compound out of the ether, so why keep it around?) Remember, an extraction is usually carried out three times or so to ensure complete removal of the compound. When the procedure calls for multiple extractions, you take each layer that comes out of the separatory funnel and combine them into one big layer.

Just to be on the safe side, never discard layers until the end of the experiment! You never know when you will grab the wrong beaker by mistake. Nothing is more disheartening than realizing that you've just washed your product into a red, several gallon jug of organic waste!

Today's Most Commonly Asked Question

Sooner or later, you will be confronted with a separatory funnel that has two clear, immiscible liquids and you'll ask "Which layer is the organic layer?" People are surprised to find that water and organic solvents look pretty similar. If the solvent has a lower density that water (e.g. diethyl ether or hexane) then they will be on top. Some solvents, like chloroform, are heavier than water and are found on the bottom. To confuse the picture further, water saturated with salts is more dense than some chlorinated solvents! The solution to this mess is quite simple. When you have two layers in a separatory funnel and you know one of them is water, add a little bit of water with a squirt bottle. Watch where the drops go and watch to see which layer increases in size. The layer that gets bigger is the water layer.

Procedure

- In a 150mL beaker, dissolve about 2.0 g (record the exact mass on your report sheet) of a 1:1 mixture of benzophenone:benzoic acid in 30mL of 1:1 hexane:ethyl acetate solvent mixture.
- Pour the solution into a 125mL separatory funnel and extract it with 20mL of 10% sodium hydroxide.
- Drain the aqueous layer in a beaker. Label it.
- Pour the remaining organic solvent layer into another beaker. Label this.
- Extract the aqueous layer with 10 mL of the 1:1 hexane:ethyl acetate mix. Drain away the aqueous layer and save it in the aqueous layer beaker. Pour the organic layer into the beaker containing the other organic layer. (*i.e*. combine the organic layers)

Isolating Benzoic Acid From the Aqueous Layer:

- Cool the aqueous layer in an ice bath (to about 15 ^{o}C), then slowly add cold 10% aqueous hydrochloric acid until the pH is about 1. (NEVER put pH paper into your reaction. Transfer a drop from your aqueous layer using a glass stirring rod.) A precipitate should form. It might take quite a bit of acid to do the job. An excess of acid is not harmful.
- Collect the precipitate with vacuum filtration. Wash sparingly with cold water.
- Oven dry the crystals on a watch glass for 20 min. at 90 °C
- Take the mass and melting point of the Benzoic Acid that you recovered

Isolating Benzophenone From the Organic Layer:

- Briefly rinse out your separatory funnel with water. Pour the organic solution into the funnel and wash it with 20mL of water. Remove and discard the aqueous layer.
- Pour the organic layer into a 100mL Erlenmeyer flask, then add enough anhydrous sodium sulfate to cover the bottom of the flask. Let the solution stand for about 10 minutes.
- Gravity filter the solution into a 100mL beaker using a short stemmed funnel and piece of filter paper.
- Place a boiling stone in the flask and gently boil off the organic solvent (**in the fume hood**!) to reveal the benzophenone.
- Take the mass and melting point of the benzophenone that you recovered.

Exp #9 - Acid Base Extraction Name: _____

Initial mass of mixture:

Percent recovery of benzoic acid (show calculations and assume the original sample contained a 1:1 mixture)

Melting range of recovered benzoic acid:

Comment on the purity and yield of your benzoic acid. Be sure to compare the melting range to the literature value. Write no more than three complete sentences:

Percent recovery of benzophenone (show calculations and assume the original sample contained a 1:1 mixture)

Melting range of recovered benzophenone:

Comment on the purity and yield of your benzophenone. Be sure to compare the melting range to the literature value. Write no more than three complete sentences:

On the back of this page, draw a flowchart for today's extraction procedure (similar to figure 3). Draw the structure of each compound at each step of the procedure and include the name of each solvent along the way. Your flowchart should only show the extraction portion of the procedure. Start your flowchart with your dissolved 1:1 mixture and end your flowchart with both of the ***original*** substances in separate solvents in separate containers.

Exp #10 – A Grignard-like Organic Reaction in Water

The Grignard reaction is a useful reaction commonly employed in a wide variety of reactions. However, one difficulty that occurs with this reaction is that the Grignard reagent vigorously reacts with water. This becomes especially difficult when the reaction is performed on a small (less than 1 gram) scale, as just a little water can ruin the reaction.

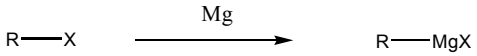


Fig. 1 - Grignard reagents convert a halide into a nucleophile

Other metals have been used to create Grignard-like reagents. For example, there are organolithiums, organocopper, and organozinc compounds. In the last two decades, these "unconventional" organometallic reagents have been found to have useful and unusual properties. For example, organozinc reagents will react with aldehydes faster than they will react with water! This enables a nucleophilic reaction to occur in water, rather than in the more commonly used ethyl ether.

The reactivity of an organo-metal compound can be judged by using the activity series (a.k.a. electromotive chart). Sodium and lithium, at the top of the list, produce very reactive organo-metals. They can react with air or many solvents. Copper and zinc produce moderately reactive compounds. Lead and mercury produce very stable compounds. For example, tetraethyl lead, used as a gasoline additive for many years, is quite stable to air and moisture (although it is poisonous)

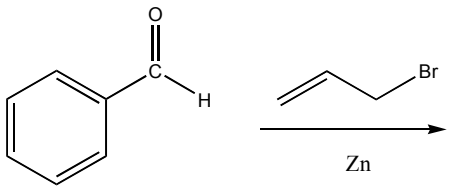


Fig. 2 - The pieces of today's reactions. Can you identify the product?

Procedure

Prepare a mixture of 320 mg of powdered Zinc and 4 mL of saturated aqueous ammonium chloride in a 25-mL round bottomed flask.

To this mixture, add a stir bar and a solution of 0.20 mL (2.00 mmol) of benzaldehyde in 2.0 mL of THF (prepare this solution first in a separate container in the fume hood).

Add a condenser and connect it to your flask with a Keck clamp. In the fume hood, remove the condenser for just long enough to add 0.40 mL (4.60 mmol) of allyl bromide. You should see evidence of a reaction. Let the mixture stir for another 0.5 h.

Add 2 or 3 mL of ether, and filter the resulting mixture through a plug of glass wool into a 50 mL Erlenmeyer flask. Wash the precipitate with another mL or two of ether.

Using a Pasteur pipette, separate the two phases and dry the combined organic layers with Na_2SO_4. Filter the organic layer through a small plug of glass wool in a Pasteur pipette into a 10 mL beaker, and gently boil off the organic layer (in the hood) to leave an oil behind

Take an IR of the product.

If your instructor asks you to submit a GCMS sample, wait until after you have taken your IR, then add 3 mL of acetone to the remaining oil in the 10 mL beaker. Stir this mixture with the tip of a Pasteur pipette. Using the pipette, fill a GCMS vial until it is half-full with this solution, then cap the vial. Submit the vial to your instructor and record the sample identification number that you are assigned in your mock lab notebook for future reference.

Write Up

You will report the results of this experiment as a "mock lab notebook" on separate sheets of paper that you have stapled together. Be sure to include a title, purpose, reagent table, procedure, data section, and your conclusions.

Your reagent table should include the structure of the product formed in the reaction.

In the procedure section, be sure to describe the procedure using language that a future Chem 7A student could understand.

In your data section, include your IR spectrum and give a full analysis of your IR spectrum. Be sure to mention which functional groups are present and absent.

If you obtained a GCMS, discuss how the GC trace allows you to determine product purity and how the mass spectrum allows you identify your product (and impurities in it).

For your conclusion, calculate your percent yield and comment on the purity of your product as determined by the IR and GCMS. Address the following questions as a part of your conclusion: Based on the IR, is there any benzaldehyde in the product that didn't react? How would you be able to tell? Based on the GCMS, is your product pure? How can you tell? If it is not pure, what impurities did you detect?

Exp #11 – Infrared Spectroscopy

"Infrared Light" (IR) is the wavelength of electromagnetic radiation that resonate with molecular vibrations, also known as heat.

Consider a guitar. When you pluck the string, the string vibrates at a certain frequency which produces a musical note of a specific pitch. If you hold a second guitar next to the vibrating guitar, the same string on the second guitar will vibrate as it absorbs the sound energy from the first. This is because both strings have the same "resonant frequency". That means that they produce waves that resonate (vibrate) at the same frequency and the same wavelength.

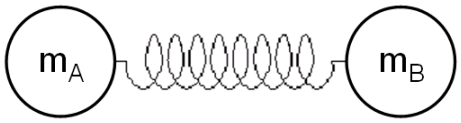
We can use this analogy for molecules. All molecules are vibrating at a frequency related to ***temperature***. Each molecule is vibrating at a frequency that is in the infrared region of the electromagnetic spectrum. That means that every molecule is releasing infrared light, and the more heat that the molecule is releasing, the more light can be seen. Night vision goggles work by measuring the amount of infrared light emitted by the surrounding area,

Many fast food restaurants store food underneath infrared-emitting light bulbs known as "heat lamps". These heat lamps work by bombarding food molecules (containing mostly water) with infrared light that has the same resonant frequency as water molecules. The water molecules in the food absorb this energy and this causes the food to heat up.

Infrared Energy Absorbed by a Bond Depends On…

...The Dipole Moment of the Bond. The larger the dipole moment between two atoms, the more infrared energy can be absorbed by the bond. Therefore, a bond between two atoms with a large difference in electronegativity will absorb a large amount of energy, while a bond with no difference in electronegativity in a highly symmetric molecule will absorb little or no energy. **(**Example: The C=O bond easily absorbs a *large amount of infrared energy*, while the Cl–Cl bond in Cl_2 absorbs *no infrared energy*. The C–C bond in $H_3C–CH_3$ absorbs a *very small amount* of infrared energy because the molecule is very symmetric, but at a given instant, each C–H bond might be a slightly different length, so the C–C bond is not always perfectly symmetric.)

…Hooke's Law. Assume that you have two masses connected by a spring, as shown below:



Hooke's law states that the resonant frequency for the vibration of this spring is given by the following equation:

$$\text{Frequency} = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$

Where k = spring constant (stiffness of spring). For a bond between two atoms, this is related to the strength of the bond.

For example: C–C is less stiff than C=C which is less stiff than C≡C. Therefore, the stretching frequency of C–C will be less than C=C which will be less than C≡C.

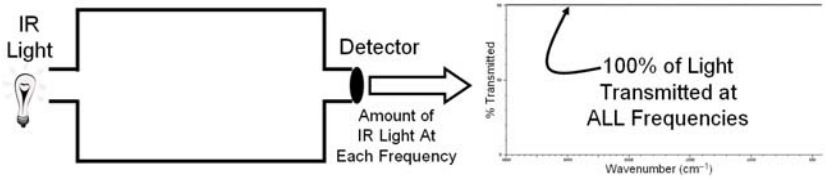
Also, this is related to the hybridization of the atoms, so the stretching frequency of C_{sp}–H is greater than $C_{sp}2$–H which is greater than $C_{sp}3$–H.

$$\text{Reduced Mass } (\mu) = \frac{m_A m_B}{m_A + m_B}$$

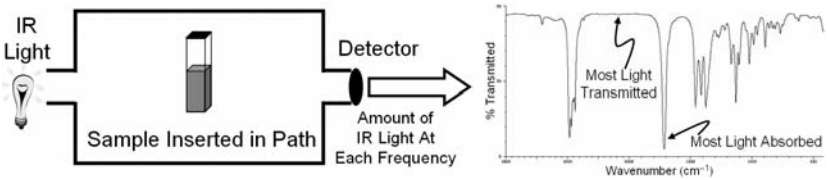
This is obviously related to the atomic mass of each atom in the bond. Notice that as the mass of an atom increases, the numerator gets larger faster than the denominator. Therefore, as the mass of the atoms in the bond increases, the stretching frequency decreases.

How Does an IR Spectrometer Work?

Step One: Determine how much IR light is absorbed by a detector at each frequency in IR spectrum. Frequency is measured in cm^{-1} and is called the "wavenumber":



Step Two: Insert sample and determine how much of original light is absorbed by sample and how much is still transmitted:



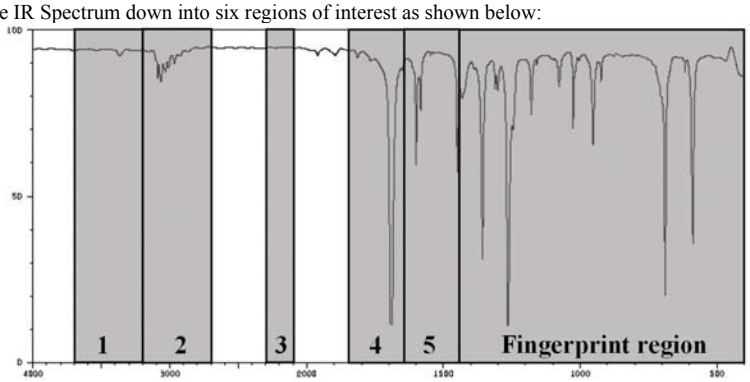
What do these "Peaks" tell us?

Recall: Absorption *frequency* depends on masses of atoms and strength of bond between them. Absorption *strength* depends on dipole moment of atoms and dipole moment of molecule as a whole.

The best way to analyze the spectrum is to think about bonds according to *functional groups* and determine where each functional group tends to show up.

Analyzing an IR Spectrum

We can break the IR Spectrum down into six regions of interest as shown below:



By analyzing a spectrum according to these regions of interest, we can determine which functional groups are present in a compound and which ones are absent. Each region contains specific peaks of interest.

Region 1 (3700 – 3200 cm^{-1})

Type of Bond	***Frequency Range***	***Shape / Intensity***
Alcohol O–H	3650–3200 cm^{-1}	Usually Broad / Strong
Alkyne ≡C–H	3340–3250 cm^{-1}	Sharp / Strong
Amine or Amide N–H	3500–3300 cm^{-1}	Usually Broad / Medium Intensity

Region 2 (3200 – 2700 cm^{-1})

Type of Bond	***Frequency Range***	***Shape / Intensity***
Aryl* or Vinyl** C–H	3100–3000 cm^{-1}	Varies
Alkyl sp^3 C–H	2960–2850 cm^{-1}	Varies
Aldehyde C–H	~2900; ~2700 cm^{-1}	Two Peaks / Medium Intensity
Carboxylic Acid O–H	3000–2500 cm^{-1}	Very Broad / Usually Strong

*Attached to Benzene Ring **Attached to Alkene

Region 3 (2300 – 2000 cm^{-1})

Type of Bond	***Frequency Range***	***Shape / Intensity***
Alkyne C≡C	2260–2000 cm^{-1}	Sharp / Intensity Varies
Nitrile C≡N	2260–2220 cm^{-1}	Sharp / Intensity Varies

Region 4 (1750 – 1650 cm^{-1})

Type of Bond	***Frequency Range***	***Shape / Intensity***
Carbonyl C=O***	1750–1650 cm^{-1}	Sharp / Strong

***The exact frequency can help to identify which carbonyl functional group. The more resonance, the lower the frequency! Some values are included on your IR table.

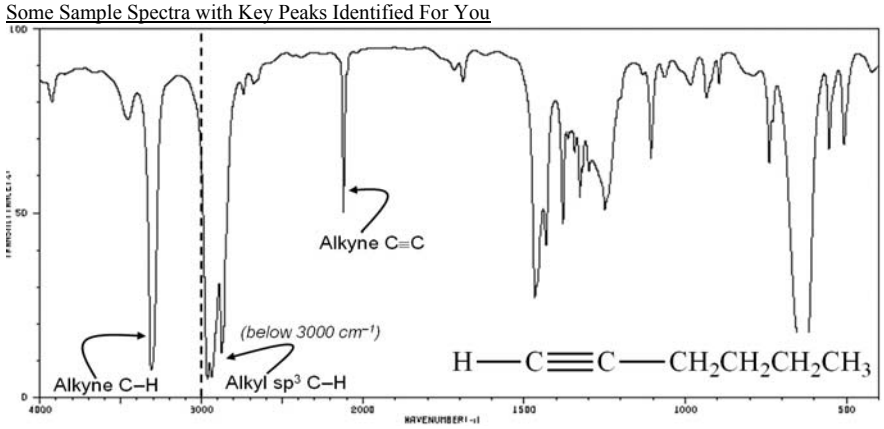
Region 5 (1680 – 1450 cm^{-1})

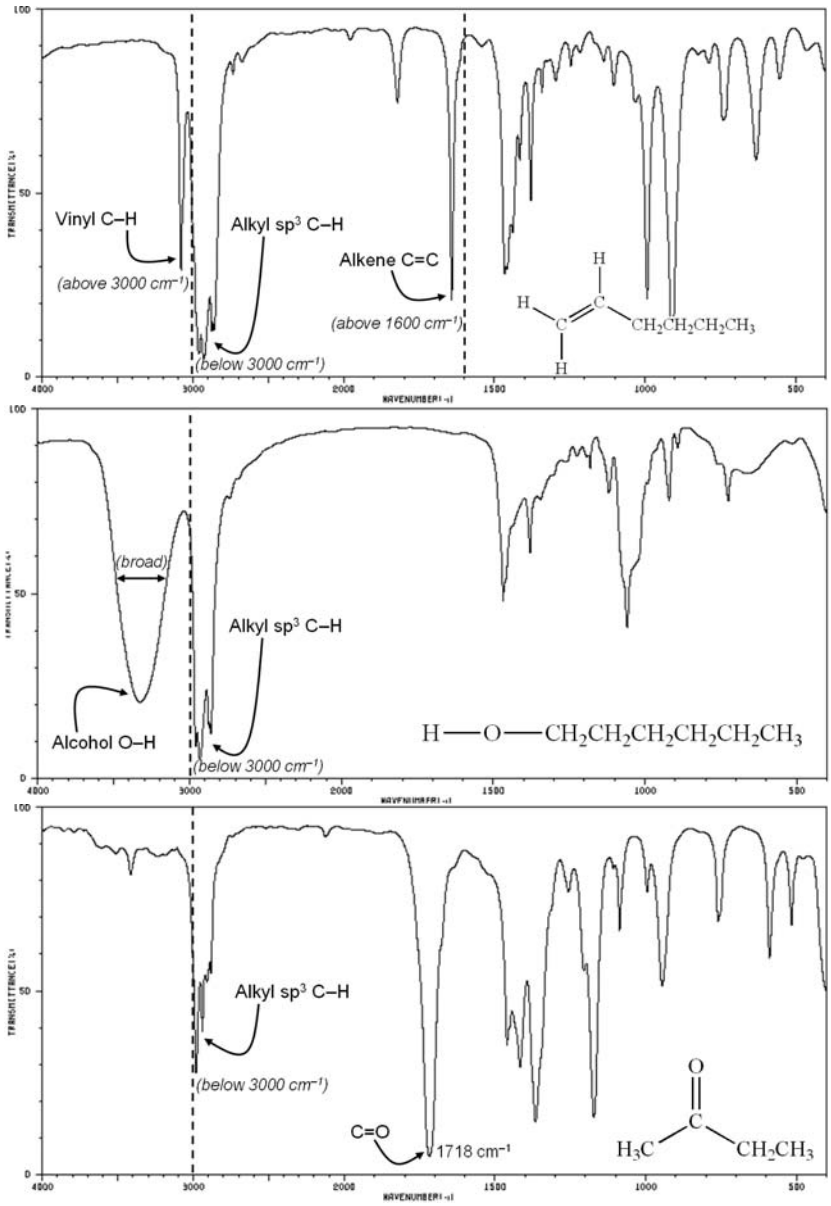
Type of Bond	***Frequency Range***	***Shape / Intensity***
Alkene C=C	1680–1620 cm^{-1}	Varies
Benzene C=C	1600, 1500 – 1450 cm^{-1}	Often 2 peaks (1 at 1600) / Varies

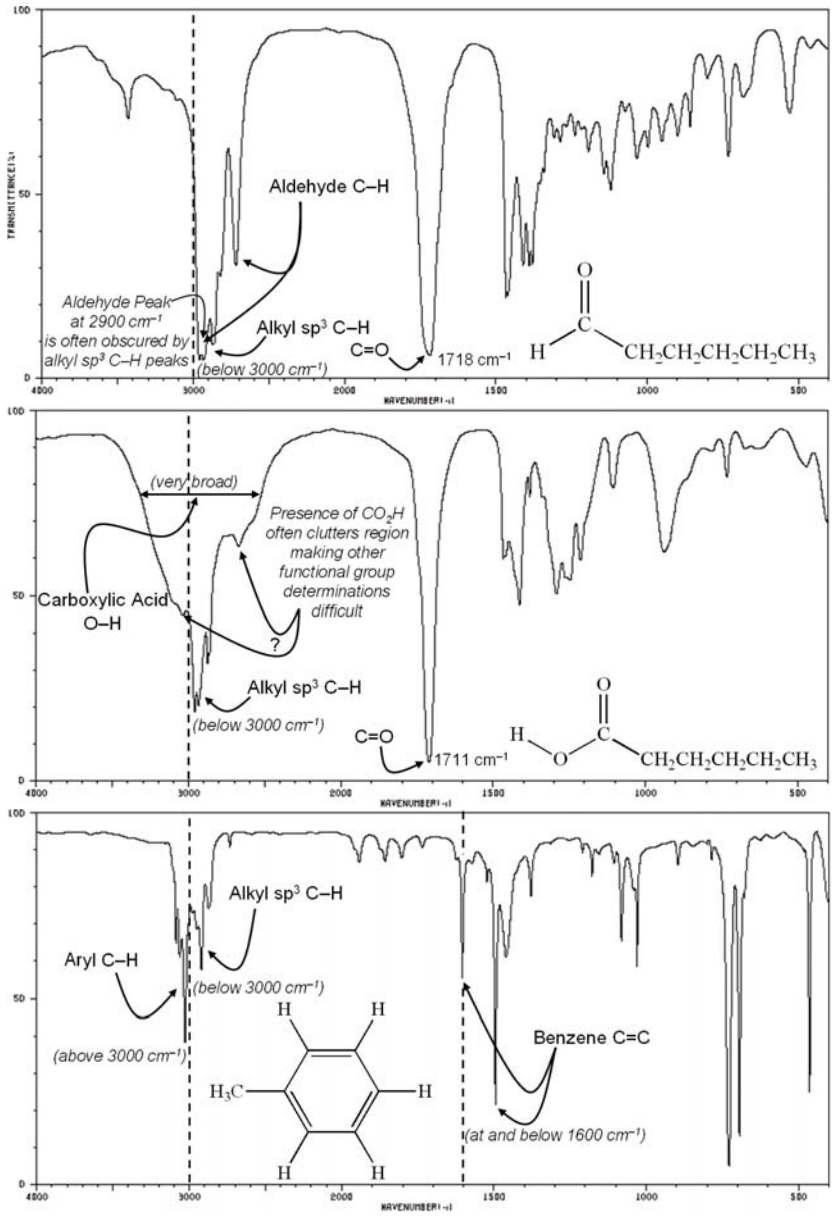
Finger Print Region (1450 –400 cm^{-1})
Many functional group absorptions occur here!!! They include C–C bonds, C–O bonds, C–H bonds, the NO_2 group, and carbon–halogen bonds. This region is often cluttered and accurate functional group identification is very difficult. However, if you have a spectrum of a molecule from another source, this region can be used like a fingerprint to see if your sample is the same or different from a previously produced sample.

What Do I Have To Memorize?
You need to memorize the methodology behind determining whether a functional group is present or absent, and it may be helpful to memorize the "regions" that groups commonly occur in. However, you do not need to memorize specific frequency ranges – an IR table (see later in this handout) will be given to you on the exam.

Some Sample Spectra with Key Peaks Identified For You




Vinyl C–H
(above 3000 cm⁻¹)
Alkyl sp³ C–H
(below 3000 cm⁻¹)
Alkene C=C
(above 1600 cm⁻¹)
(broad)
Alcohol O–H
Alkyl sp³ C–H
(below 3000 cm⁻¹)
Alkyl sp³ C–H
(below 3000 cm⁻¹)
C=O
1718 cm⁻¹


Aldehyde C–H
Aldehyde Peak at 2900 cm⁻¹ is often obscured by alkyl sp³ C–H peaks
Alkyl sp³ C–H
(below 3000 cm⁻¹)
C=O
1718 cm⁻¹
(very broad)
Presence of CO₂H often clutters region making other functional group determinations difficult
Carboxylic Acid O–H
?
Alkyl sp³ C–H
(below 3000 cm⁻¹)
C=O
1711 cm⁻¹
Alkyl sp³ C–H
Aryl C–H
(below 3000 cm⁻¹)
(above 3000 cm⁻¹)
Benzene C=C
(at and below 1600 cm⁻¹)

Procedure

You will work in groups of three, learning to use the IR spectrometer. Each group of three will be trained about the parts of the spectrometer, how to load a sample, and how to acquire a spectrum. You should plan to take notes during this time because you will need to be able to acquire spectra during labs throughout the rest of the course (and also in Chem 7B!!!).

After being trained on the use of the spectrometer, each member of the group will acquire an IR spectrum of a different substance.

Write-Up

Directly on the spectrum that you acquired, complete the following:

1) Write your name on the top right corner of your spectrum.

2) Across the top of the spectrum, write down the name of the substance that you took an IR spectrum of.

3) In the center of the spectrum (find an "empty space"), draw the skeletal structure of the substance that you took at IR spectrum of.

4) ***ON*** the spectrum, identify at least two peaks that are characteristic of your molecule. Label each of these peaks with the name of the characteristic bond stretch (*example:* "alkyne C≡C")

5) On the ***back*** of the spectrum, give a full analysis of your IR spectrum. Be sure to identify all groups that you can determine are present AND absent based on your spectrum.

6) Compare the spectrum that you acquired to a copy of the spectrum found in the literature. On the ***back*** of the spectrum that you acquired, note any similarities and differences between these spectra.

7) Based on your comparison of the two spectra (in question 6), do you believe that these are the same substances? Give your answer to this question as a complete sentence on the ***front*** of the spectrum that you acquired.

Turn in your annotated spectrum for credit at the end of the lab period.

On the next pages is a workshop on IR spectroscopy that can be completed while you wait for your group's turn on the instrument.

Exp #12 – The Blue Bottle Reaction Mechanism

The rate at which a homogeneous reaction takes place depends upon the following factors: inherent properties of the reacting materials, the temperature, the concentration of the reactants and catalysts. The order of reaction and mechanism can only be determined experimentally.

For example, an S_N2 reaction is second order, but an S_N1 reaction is first order. This knowledge has allowed us to deduce that the S_N1 mechanism involves a highly unstable carbocation because the nucleophile is not involved in the slow step.

The "Blue Bottle" reaction is a fairly common demonstration in general chemistry courses. In this lab, you will attempt to deduce the reaction mechanism based on simple qualitative experiments and tests. The key to this lab is to try to make accurate observations without trying to get the "right" answer. Your initial hypotheses will likely be proven wrong along the way!

Equipment: A stoppered flask containing the unknown solution, a clock, and some tubing connected to a one-hole stopper, to be used as a simple manometer in Step 8.

Procedure

You will be working in groups of 2 – 4 for this experiment. Be sure to discuss your hypotheses and results as you go along. You will be submitting one report for your entire group.

Answer the following numbered questions on separate sheets of paper. You do not need to copy the question. Simply give a complete, thorough answer. Use as many sheets of paper as necessary. Be sure that all group members names are on the report at the time that you submit it.

1. Shake the flask vigorously. What is observed?

2. After the flask has stood for a while what is observed?

3. Shake the flask again. What is observed now?

4. Does the coloration come from the rubber stopper? How did you show this?

5. What other possible sources of the coloration can you suggest? (Come up with at least two. There are at least three good answers to this question.) Suggest methods for verifying or disproving these possibilities:

INSTRUCTOR CHECK POINT
Defend your answer for question 5 before you move on. The instructor will ask you to rule out some of your hypotheses at this stage. You MUST get the instructor's initials on your paper before you can continue on to step 6.

6. Replace the air in the flask with natural gas and quickly stopper the flask again. Now shake the flask as was done previously. What is observed?

7. Replace the natural gas in the flask with air, stopper and shake as before. What is observed now?

8. Replace the rubber stopper with a simple manometer. Put water into the U-tube until it is about half full. (This may be a bit tricky. Ask the instructor or members of another group that have already completed this step to show you how to set up the manometer.) Use the manometer to observe any changes in pressure inside the flask during several coloration-decoloration cycles. What is observed?

9. What conclusions can be drawn from your observations in 6, 7, and 8?

INSTRUCTOR CHECK POINT
Defend your answer for question 9 before you move on. Be sure to explain how the experiments you performed in steps 6 – 8 helped you to reach your conclusions. If the instructor is not satisfied with your conclusions, you may be asked to repeat one or more of these steps in his or her presence. You MUST get the instructor's initials on your paper before you can continue on to step 10.

10. How does the rate of the coloration step compare with the rate of the decoloration step?

11. Is the initial reaction reversed when going from blue to colorless again? What led you to this conclusion?

12. Write a tentative reaction mechanism for the reaction taking place based on what has been observed thus far. (Use letters for the reactants and products since the experimenter does not know what substances are present in the reaction mixture.) Which step in your tentative reaction mechanism is the slow step?

INSTRUCTOR CHECK POINT
Defend your answer to question 12 before you move on. If the instructor is not satisfied with your mechanism in question 12, you may be asked to come up with alternatives. You MUST get the instructor's initials on your paper before you can continue on to step 13.

13. Does the length of time the flask remains blue depend on how long one shakes the flask? Does the intensity of the blue color depend on how long one shakes the flask?

    Complete the following experiments to assist in answering these questions.

Number of Shakes	Duration of Blue Color (sec)	Intensity Observation
2		
4		
6		
8		

    Draw simple graphs of 1) the duration of the blue color vs. the number of shakes and 2) the intensity of the blue color vs. time for two different numbers of shakes.

14. How can these observations be explained? In this explanation, consider how they relate to the mechanism proposed in 12, and determine what modifications are necessary in this mechanism.

INSTRUCTOR CHECK POINT
Defend your answer to question 14 before you move on. If the instructor is not satisfied with your explanation, you may be asked to come up with alternatives. You MUST get the instructor's initials on your paper before you can continue on to step 15.

15. Write a final mechanism for the reaction which is consistent with all observations. Indicate which step is the slow step and identify any catalyst that may be present.

    Write the net reaction.

16. Write the rate law for the reaction. It may be necessary to include in the rate law an intermediate instead of only reactants and products.

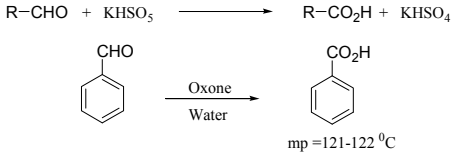
    What is the order of the reaction?

INSTRUCTOR CHECK POINT
Defend your answers to questions 15 and 16 before you turn in your paper.. If the instructor is not satisfied with your mechanism and rate law, you may be asked to come up with alternatives. You MUST get the instructor's final approval before you can turn in your report and leave the lab.

Exp #13 – Oxidation of Aromatic Aldehydes Using Oxone

Eliminating or reducing hazardous wastes safeguards our environment and health. Green chemistry is a new sub-discipline of chemistry that is aimed at designing chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Using environmentally benign solvents such as water and environmentally friendly reagents is one of the principle objectives of green chemistry.

In this experiment you will oxidize benzaldehyde to benzoic acid in water using Oxone® as the oxidizing agent. Oxone® is the trade name for a potassium triple salt containing potassium peroxymonosulfate ($KHSO_5$), potassium hydrogensulfate ($KHSO_4$), and potassium sulfate (K_2SO_4) in a 2:1:1 molar ratio. The formula weight of Oxone® is 614.8 g. Potassium peroxymonosulfate present in Oxone® is a powerful oxidant capable of effecting numerous transformations including oxidation of aldehydes to carboxylic acids. The use of Oxone® as a green oxidant is due in part to its non-toxic nature and nonpolluting byproducts.



Procedure

In a 50 mL round bottom flask, place 1.0 mL of benzaldehyde, 7.25 g of Oxone® and 25 mL of water. Add a stir bar and connect the flask to a reflux condenser using a Keck clip. Carefully lower the flask into a water bath (a beaker containing water) making sure that the neck of the flask is clamped to your ring stand and that the flask is not completely immersed in the water-bath. Heat the mixture at 60-70 °C (monitor the temperature of the water bath using a thermometer) for 75 min and subsequently cool the flask in an ice-bath for 15-20 min. Care should be taken to make sure that the reaction flask does not tip over and the contents flow into the ice bath. Collect the acid product by vacuum filtration using a Büchner funnel and remove the boiling stone with forceps. Transfer the acid product completely from the flask by rinsing with minimum amounts of ice cold water and finally wash the solid with 10 mL of ice cold water.

Recrystallize the crude product from hot water and collect the crystallized product by vacuum filtration in a Büchner funnel using a pre-weighed piece of filter paper. Transfer the filter paper to a watch glass and put into a ~90 °C oven for 20 minutes to dry. Determine the mass and the melting point of your product. Confirm the identity of your product by taking a mixed melting point with pure benzoic acid (provided).

Take an IR of your product and fully analyze the spectrum.

Moorpark College Chemistry Department Laboratory Report Rubric – Graded out of 24 Points

CATEGORY	4 – Accomplished	3 – Good	2 - Developing	1 - Beginning	0 – Substandard	Score
Abstract	Clear, concise (~½ page), and thorough summary of results with appropriate literature references.	Refers to most of the major results; some minor details are missing or not clearly stated.	Misses one or more major aspects of the results.	Missing several major aspects of the results and merely repeats information from the introduction.	None, unrelated, or plagiarized.	_____
Introduction *For this lab, write about "Green Chemistry"* *Hint: Think about Chromium reactions*	A cohesive, well-written summary (including relevant reaction chemistry) of the background material pertinent to the experiment with appropriate literature references (at least one scientific reference is required by your instructor) and a statement of purpose.	Introduction is nearly complete but does not provide context for minor points. Contains relevant information but fails to provide background for one aspect of the experiment, or certain information is not cohesive.	Certain major introductory points are missing (e.g., background, theory, reaction chemistry), or explanations are unclear and confusing. References are not scholarly.	Very little background information is provided, and information is incorrect. No references are provided.	None, unrelated, or plagiarized.	_____
Methods/ Materials *See sample methods / materials section at the end of this rubric.*	Contains a complete listing of safety information, a narrative of experimental procedures followed, and materials used. Omits information that can be assumed by peers. Includes observations when appropriate and only important experimental details.	Narrative includes most important experimental details. Missing one or more relevant pieces of safety information or experimental procedure.	Narrative is missing several experimental details and safety information or includes insignificant procedural details.	Several important experimental details and safety information are missing. Procedural steps are incorrect, illogical, or occasionally copied directly from the laboratory manual.	None, unrelated, or plagiarized (including completely copied from the laboratory manual).	_____X ½
Results/ Calculations	All figures, graphs, and tables are numbered with appropriate titles and captions. Sample calculations are shown and correctly solved. All data is explicitly mentioned in the text. % Yield is calculated and full analysis of IR spectrum is included.	All figures, graphs, and tables are correctly drawn, but some have minor problems or could still be improved. All data and sample calculations are mentioned in the text.	Most figures, graphs, and tables are included, but some important or required features are missing. Certain data and sample calculations are not explained in the text and/or solved incorrectly.	Figures, graphs, and tables are poorly constructed, have missing titles, captions or numbers. Certain data and sample calculations are not referenced in the text and solved incorrectly.	None, unrelated, or plagiarized.	_____

CATEGORY	4 - Accomplished	3 – Good	2 - Developing	1 - Beginning	0 – Substandard	Score
Discussion/ Conclusion	Demonstrates a logical, coherent working knowledge and understanding of important experimental concepts, forms appropriate conclusions based on interpretations of results and/or spectrum (spectra) analysis, includes applications of and improvements in the experiment, refers to the literature when appropriate, and demonstrates accountability by providing justification for any errors.	Demonstrates an understanding of the majority of important experimental concepts, forms conclusions based on results and/or spectrum (spectra) analysis but either lacks proper interpretation, does not answer post-lab questions in paragraph format, suggests inappropriate improvements in the experiment, refers to the literature insufficiently, or lacks overall justification of error.	While some of the results have been correctly interpreted and discussed, partial but incomplete understanding of results is still evident. Student fails to make one or two connections to underlying theory.	Does not demonstrate an understanding of the important experimental concepts, forms inaccurate conclusions, does not answer post-lab questions in paragraph format, suggests inappropriate improvements in the experiment, refers to the literature insufficiently, and lacks overall justification of error.	None, unrelated, insignificant error analysis and incorrect explanation, or plagiarized.	_____
References** (see sample on next page)	All sources (information and graphics) are accurately documented in ACS format. At least one reference is taken from scientific literature relevant to the report.	All sources are accurately documented, but a few are not in ACS format. Some sources are not accurately documented.	All sources are accurately documented, but many are not in ACS format. Most sources are not directly cited in the text.	All sources are accurately documented but not directly cited in the text.	Sources are not documented nor directly cited in the text.	_____X ½
Miscellaneous ☐ Mechanics, grammar, and appearance ☐ Appendix: Mock Lab Notebook	Grammar and spelling are correct. All required components are included, complete, and/or illustrated correctly. Paper is not written in first person. Mock Lab Notebook (completed during the lab period) is stapled to the back of the report.	Less than three grammatical and spelling errors are present or mock lab notebook contains one or two minor errors.	More than three grammatical and spelling errors are present or paper is written in first person. Features multiple errors with mock lab notebook.	Frequent grammatical and spelling errors, and writing style lacks cohesion and fluidity. Paper is written in first person. Mock lab notebook is not attached to report.	None, unrelated, or plagiarized.	_____

Sample Materials / Methods Section

Below is a sample materials / methods section. Many students assume that this section needs to be lengthy since this summarizes several hours of lab work, but this is not the case. It simply needs to be descriptive. This sample section describes the synthesis of 2-ethoxynaphthalene (an experiment that you completed earlier this semester):

2-Ethoxynaphthalene – Potassium hydroxide (2.065 g, 0.0368 mol) and 2-naphthol (2.539 g, 0.0176 mol) were added to 25 mL methanol in a 100 mL round bottom flask. The solution was stirred with a magnetic stirrer until all solids were dissolved (~ 3 minutes). To this solution, iodoethane (1.7 mL, 0.029 mol) was added via a syringe in the fume hood. The solution was heated under reflux for 30 minutes, and then was dumped into a 250 mL beaker containing 40 mL of ice, forming a white precipitate. The solid was collected in a Buchner funnel using vacuum filtration and was washed with 150 mL of ice cold water. The resulting solid was recrystallized from 95 % ethanol (~ 10 mL) to yield 0.408 g (0.00237 mol, 13.5 %) of the desired product as a white solid.

SAFETY NOTES: Potassium hydroxide is a strong base, so care should be used to avoid exposure to skin or eyes. Iodoethane is a volatile narcotic and a possible teratogen, so it should only be used in the fume hood and contact with the substance should be avoided.

Journal citations must include author or editor, *title (in italics)* followed by a period, **year (boldface), *volume (in italics)*, and page numbers. For example: Schrauzer, G.N.; Windgassen, R.J. *J. Am. Chem. Soc.* **1966**, *99*, 3738-3743. For additional examples, see the *ACS Style Guide* (summary can be found online).

Exp #14 – Preparation of 2-(2,4-dintitrobenzyl)pyridine: A Photochromic Compound

A photochromic compound is one that changes it's color when exposed to light. Today's product is interesting in that the change in conformation is reversible, that is, the compound changes from one form to another and then back again. The transformation from the brown form to blue is very fast, while the conversion back takes almost a day at room temperature. The conversion appears to be reversible any number of times. In addition, it is possible to create single crystals as large as 800mg in this experiment*; certainly an experimental challenge!

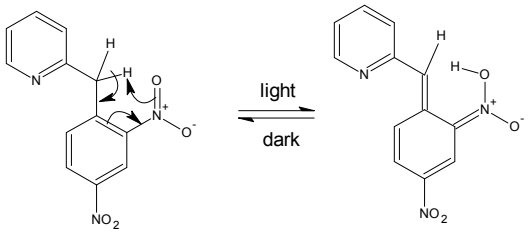


Fig. 1 - Light induced tautomerization of 2-(2,4-dintitrobenzyl)pyridine

2-(Benzyl)pyridine is nitrated smoothly by a mixture of sulfuric acid and concentrated nitric acid, without the use of fuming nitric acid. The nitration almost certainly proceeds by electrophilic aromatic substitution, which explains why the incoming nitro group ends up in the ortho position and para position. The refluxing nitric acid is strong enough to nitrate the activated benzene ring twice.

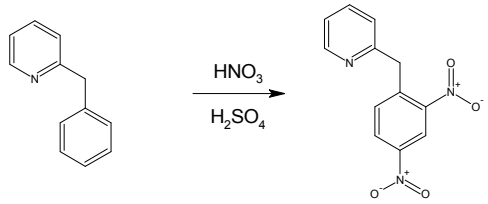


Fig. 2 - Today's nitration reaction.

Procedure

Caution: Concentrated sulfuric and nitric acids are very corrosive! Wash any spills with large amounts of water and neutralize with baking soda (or sodium carbonate). Wear goggles and gloves at all times!!

- Place 12 mL of concentrated sulfuric acid (0.22 mole) in a 100-mL round bottomed flask. Cool the flask to 5^{o}C or below with an ice bath, and place a stir bar in it.

- To the flask, slowly add 2.5mL of 2-(benzyl)pyridine (2.60g, 0.016 mole) with good mixing. To this well stirred mixture, add drop by drop through the condenser over a period of about 3 minutes, 2.25mL concentrated nitric acid. (0.036 mole; density 1.42 g/mL) The first few drops will cause the solution to become brown, but it should gradually lighten up as the acid is added. After the acid has been added, heat to 100^{o}C for 20 min. Use a hot water bath and an air-cooled condenser.

- After heating, pour the mixture onto about 200g of ice in a 1-L Erlenmeyer flask. Basify the solution to about pH 11 using a solution of 20 grams sodium hydroxide in 250 mL water**. Toward the end of the addition, the product should separate to give a milky, yellow solution. **Caution: Concentrated sodium hydroxide is very corrosive! Wash any spills with large amounts of water immediately! Wear goggles and gloves at all times!**

- Add about 200mL of ether and stir for about 10-15 min to extract the product into the organic layer. Cover the flask and make sure your hot plate is cool to the touch before you use it as a stir plate!

- Separate the ether layer using a large separatory funnel, dry the ether over magnesium sulfate, then transfer the ether to a simple distillation apparatus. Distill to reduce the volume until it is about 25mL. ***Do not allow the reaction to evaporate to dryness!!!*** Please save the distilled ether in a container provided! Don't turn the power on the transformer past 40%. *The ether is very flammable and volatile*!

- Crystallize the product by cooling in an ice bath. Collect the sandy crystals with suction filtration, and wash then with 95% cold ethanol. The product can be recrystallized from 95% ethanol with about 90% recovery using 10mL ethanol per gram of product.

Write-up

Calculate the percent yield of the reaction and comment on the purity of the product obtained.

Pre-Lab

Include the standard reagent chart.

* - Ault, A. *J. Chem. Ed.* Vol. 77, No. 11 p. 1386
**- to make this solution, add 26 mL of "50% NaOH" to 230 mL water.

Exp #15 – Nuclear Magnetic Resonance (NMR) - A Bare Bones Guide

NMR is an extremely powerful technique that allows the chemist to determine a compound's molecular structure. There are two main types of NMR that are used routinely in labs. The oldest and most common is ^{1}H NMR, or proton NMR. This technique allows you to look at the compound's protons. The second most common NMR spectra is the ^{13}C NMR.

Because ^{13}C is a bit more time-consuming to run, and was developed after ^{1}H. It is therefore often covered after ^{1}H NMR in most texts. However, ^{13}C is actually easier to interpret than ^{1}H, so we will start with it.

We'll start with determining what spectra a compound should have based on its structure. After we do that, you will try to find a compound's structure based on it's spectra, a more useful and challenging task.

The Basics: NMR spectra can tell you *four things* about a molecule.

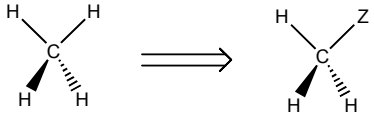
1) How many types of that nuclei (^{1}H or ^{13}C) you have.
2) What kind of environment each type of nuclei are in.
3) How many nuclei are in each type. (^{1}H only)
4) How many neighboring nuclei are next to that group. (^{1}H only)

You should always keep this list in mind. Whenever you look at a peak, ask yourself "what kind of nuclei is this", "how many nuclei made this peak", and "how many neighbors does this peak have".

We'll start with ^{13}C because you only have to ask/answer the first two questions. This makes it much simpler!

Equivalency: The first question, "how many types of nuclei you have", depends on the number on equivalent nuclei. That means the nuclei are all the "same". What does being the "same" mean? The easiest definition is that two nuclei are the same if replacing them with some group Z would give you identical compounds, then those nuclei are the same.

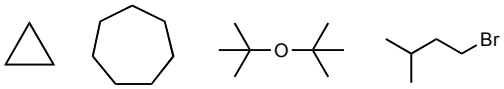
replace any of these H's,
rotate and manipulate single bonds,
and you get only one compound.
These Hydrogens are "magnetically equivalent"



Ex. replace any H in methane will give you the same compound. Thus, all the H's in CH_4 are identical.

The easiest way to spot equivalent C's (or H's) is to look for planes of symmetry. If you can bisect a molecule with a plane of symmetry, then the nuclei that lie on opposite sides of that plane are identical.

Practice! Decide how many types of carbons there are in each structure.

CH_4 CH_3CH_3 

total C's =

number of "types" of C's =

In a ^{13}C NMR spectra, the number of peaks that you see will be the same as the number of different types of carbons. However, sometimes the peaks will be so close together that they look like one peak (this is especially a problem with ^{1}H NMR, less so with ^{13}C NMR) In the ^{1}H NMR spectra, a peak will usually not be a single peak, but rather a more complicated pattern. Look at some spectra to get an idea.

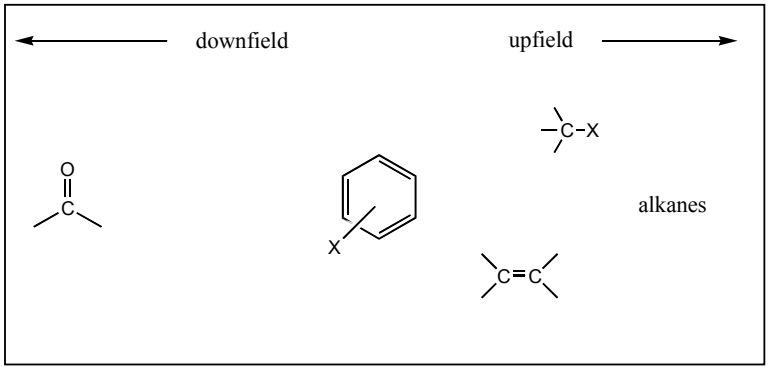
Chemical Shifts: In any spectra, the peaks will be spread out along the page. The positions will be given by a number called the chemical shift (δ). For ^{13}C NMR, this number goes from -10 to +200 ppm (parts per million). As might be expected, the chemical shift varies depending on what type of magnetic environment the nuclei is in.

How can you tell what kind of environment it is in? First off, the more negative charge the nuclei has, the further to the right it will be (i.e. lower value). This nuclei is said to be *shielded*. The peak at δ 0 ppm is from $(CH_3)_4Si$ (tetramethylsilane - TMS). Here, the C and H nuclei are more electronegative than the SI, so they have a slight negative charge. Therefore, they are shielded and occur to the right of most compounds. TMS is defined to be δ 0 ppm.

Over time, many spectra have been recorded and charts have been made of the chemical shift of every functional group you can think of. In theory, you should be able to look up any shift you want. In practice, it is not so simple. Since the charts are generally short, they can't include exactly what you want. You often have to guess which value to use…

There are several regions that certain groups always appear in. The order is pretty much the same as with ^{1}H NMR, so you only have to learn this once.

General regions of ^{13}C NMR shifts - memorize these!



Remember, the more positive the carbon, the more to the left (*i.e.* the more deshielded) it is. Me_3C^+ has a shift of δ 328 ppm! Carbons with a negative charge (like Me^-Li^+, come in a round -10 ppm) These are shielded (or electron rich) carbons…

What about the other questions? For simple carbon NMR, that is all the information you need (or get!) The height of each peak doesn't result entirely from the number of nuclei present, but also from the relaxation times of the different carbons. So don't try and interpret the peak heights of a ^{13}C spectra!

Coupled spectra: Recently, coupled spectra have become easy to obtain. With these types of NMR, you can tell how many H's are attached to each Carbon. This is a very powerful technique, and it is fairly easy to interpret. Above each peak in a ^{13}C, you will often see a letter. These letters, *s*, *d*, *t* or *q* stand for singlet, doublet, triplet or quartet. This letter indicates how many hydrogens are attached to the carbon that is causing that peak. In other words, a *s* indicates a methyl group, a *d* indicates two attached hydrogens (a methylene group), a *t* is a methine group, and a *q* results from a quaternary carbon (with no attached hydrogens). The computer power needed to do run these experiments only became affordable sometime in the mid-to late 1980's so many older spectra do not have this information.

Solving problems: Going from structure to spectra is fairly simple. There are a wide variety of computer programs that can simulate a spectra quite accurately. Unfortunately, if you already know the structure, you usually don't need a spectra. But its a good place to start.

The best way to start is to decide how many different types of nuclei you have. Since we've already done cyclohexane, let's start there. There is only one type of carbon for cyclohexane. (ring flipping makes them all the same, the NMR is a slow technique that only sees averages of positions at normal temperatures). So you would predict only one peak. Now you figure out what the chemical shift would be. Looking at chart, you see that a secondary carbon with no other functional groups has a shift of about 16 ppm. If you look at a

larger chart, or the actual spectra, you find that the shift is δ 27.7 ppm. Your prediction is a little off, but remember the scale is fairly large (0-200).

TYPICAL SHIFTS FOR ^{13}C SPECTRA

If there is more than one carbon, the shift is for the underlined carbon

Group		Shift (in ppm)
Primary Methyl group		6-15
2° and 3° Methyl		25-30
Cl-<u>C</u>		+20
Br-<u>C</u>		+10
CH_3OCH_3		59
$CH_3CO\underline{C}H_3$ (acetone)		29
$\underline{C}H_3$-C_6H_6		21
$\underline{C}H_3$-$N(CH_3)_3$		47.5
1-Pentanol	C1	62.2
	C2	33.1
	C3	26.1
	C4	32.3
	C5	14.5

CH_3 C_aH=C_bH_2	Ca	115.9
	Cb	136.2
C_6H_6		128.7
$CH_3\underline{C}OCH_3$		205.1
$CH_3\underline{C}OOCH_3$ (ester)		170.7
$CH_3\underline{C}OH$ (aldehyde)		201
$CH_3\underline{C}O_2H$		179
$C_2H_5C_aC_bH$	Ca	85.0
	Cb	67.3
$CH_3\underline{C}N$		117.8
$\underline{C}H_3CN$		0.5

Exp #16 – ^{1}H NMR Spectra

Although the ^{13}C NMR is a powerful tool, it is the proton NMR that is the primary analytical technique of organic chemistry. It requires only a small amount of sample, and can provide a wealth of information about a molecule. The principles behind the interpretation of ^{1}H NMR are the same as for carbon NMR, but there are additional pieces of information that you can glean from the ^{1}H spectra that you cannot from ^{13}C.

CHEMICAL SHIFTS: In general, the shifts for proton parallel the shifts for carbon. However, the range of shifts doesn't vary as much. So you scale runs from δ 0 to 10 ppm as opposed to δ 0 to 200 ppm. Peaks are more likely to overlap with ^{1}H NMR than with ^{13}C, so be careful!

Aromatic and alkene shifts: Before, I said that the more positive the charge on the nuclei, the farther downfield it was. But why do neutral compounds like benzene show chemical shifts at δ 7 ppm? The large shifts (in both ^{13}C and ^{1}H) are due to the effects of ring current upon the atoms.

INTEGRATION: In the ^{13}C NMR, the heights of the peaks did not tell you anything useful. The peaks from an aromatic ring could vary in height, even though each peak was caused by the same number of carbon atoms. (This is due to differences in *relaxation times*) In ^{1}H NMR, the areas of the peaks is very important.

The area of each peak is proportional to the number of hydrogens
that are causing that peak to occur.

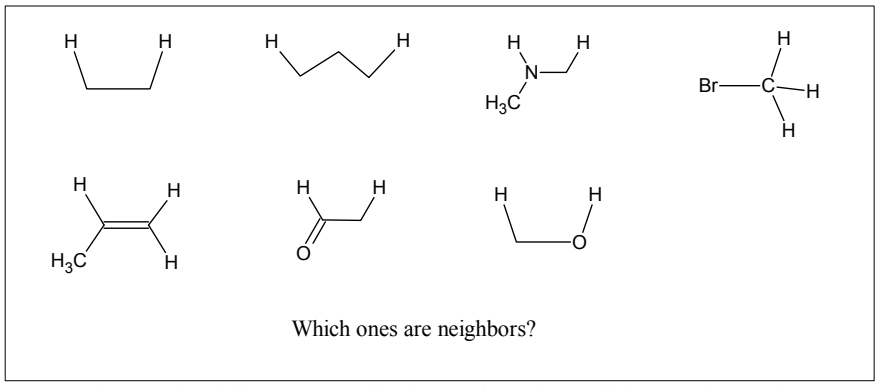
For example, if you have a NMR spectra of propane, you have two different types of H's and two different types of C's. The ^{13}C will show two peaks, and you can predict which peak comes from which carbon by examining a table of chemical shifts. But the heights of the peaks will tell you nothing. When you examine the ^{1}H NMR, you will see two peaks of different sizes. One peak will be three times the area of the other. The larger peak results from the methyl group; the smaller from the methylene. (note - 6 H's from CH_3 : 2 H's from CH_2 gives a 3 : 1 ratio)

When you look at ^{1}H NMR, the peaks often will be split into several smaller peaks (see below). It becomes difficult to compare a tall, thin peak with a short, stubby one. Therefore, integration lines are calculated by the computer and displayed above each peak. Other times, the area of each peak is simply given to you. Remember that the numbers given are ratios and not necessarily the number of protons in that molecule.

SPLITTING: The most striking feature of a ^{1}H NMR is the number of peaks that are split into sub-peaks. The most common patterns are labeled singlet (s), doublet (d), triplet (t), and quartet (q). You may see (dd) for a "doublet of doublets". There are many types of patterns!

This splitting is caused by the effect of the neighboring hydrogens on that type of hydrogen. What is a neighbor*? A neighbor is another hydrogen atom that is three bonds away from that nuclei*. Hydrogens on the same carbon (two bonds away) do not count, nor do hydrogens four bonds away.

One minor complication: If an Oxygen or Nitrogen atom is one of nuclei you go through while counting three bonds, don't count it as a neighbor. O and N usually prevent splitting from occuring.

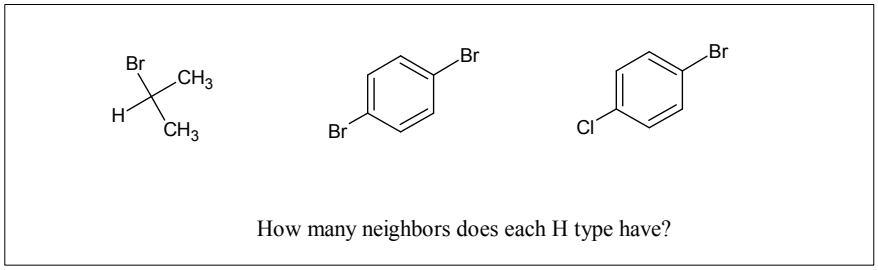


Which ones are neighbors?

*For each neighbor a group of hydrogens have (let's call that number N), *
you will generate N + 1 peaks.

This is called the N + 1 rule. So if you have a group of hydrogens with no neighbors (N = 0), you get a singlet. (*e.g*. *tert*-butyl bromide). If you have one neighbor, you get a doublet. (*e.g*. the methyl of isopropyl bromide). etc.

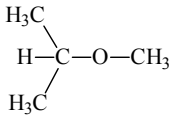
This can get confusing. Remember that the area of a peak and it's position depend upon the nuclei that cause that peak. The splitting pattern depends upon that peak's neighbors.



How many neighbors does each H type have?

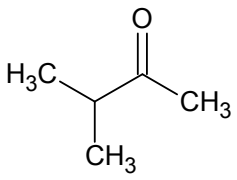
PREDICTING A SPECTRA:

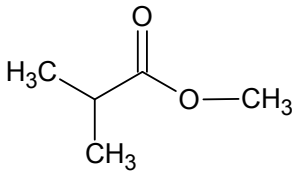
Let's draw the spectra of a compound, methyl isopropyl ether. To start, set up a chart with an entry for the number of hydrogens in each group, the expected chemical shift, the number of neighbors for each group, and for the final area ratio and peak type.

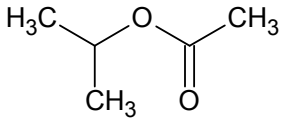


Group Type	# of H's	ratio	# of N	splitting	δ (in ppm)
-CH3					
CH					
OCH3					

Now, sketch the expected ^{1}H NMR spectra of the following compounds (on a separate sheet).





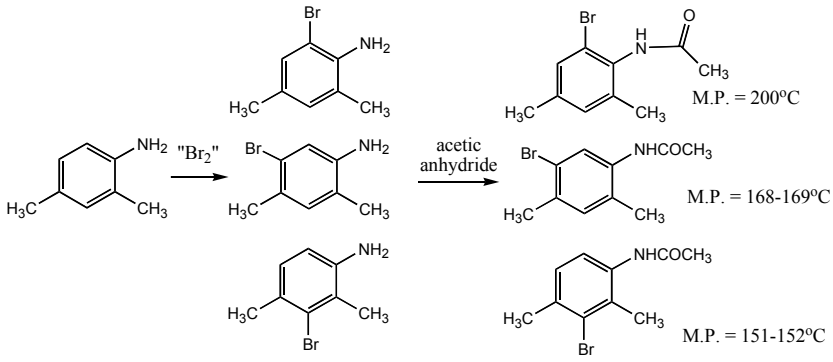


Exp #17 – Where Does the Bromine Go? Puzzles in Aromatic Electrophilic Substitution

Sometimes, even straight forward reactions can give surprising results. In today's lab, you'll perform one of three reactions and then identify what product you made. Before you try the reaction, predict what you think the product will be.

Puzzle One: Is the amino or are the methyls more powerful directors?

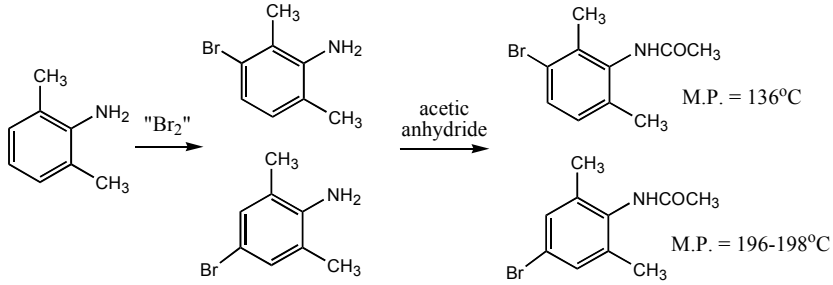
In this puzzle, you'll brominate 2,4-dimethylaniline and see what product you obtain. One complication is that the product of direct bromination is a waxy solid, which makes obtaining a good melting point quite difficult. Therefore, the amine will be converted into an acetanilide, which is much easier to characterize.



Before you begin the reaction, what product would you predict will form?

Puzzle Two: Is the amino group a more powerful director than the methyls?

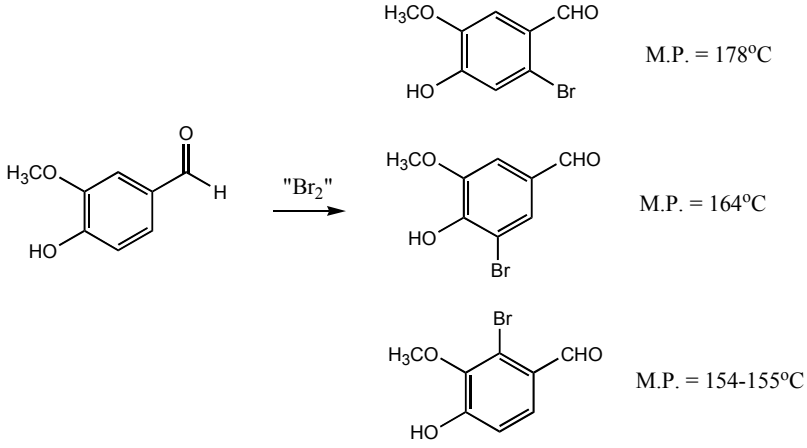
This reaction is similar to the one above. You'll brominate 2,6-dimethylaniline and see what product you obtain. One complication is that the product of direct bromination is a waxy solid, which makes obtaining a good melting point quite difficult. Therefore, the amine will be converted into an acetanilide, which is much easier to characterize.



Before you begin the reaction, what product would you predict will form?

Puzzle Three: Is the methoxy more powerful than a hydroxy and an aldehyde?

In this reaction, you will brominate vanillin and measure the melting point of the product obtained. Unlike the other two puzzles, you can get a good m.p. without making a derivative.



How can we brominate a benzene ring?

Because the rings in today's reactions are all activated, you won't need to resort to using strong catalysts such as $FeBr_3$. However, handling liquid bromine can be somewhat dangerous. So, you'll use a combination of $KBrO_3$, HBr in acetic acid to generate Br_2 *in situ*. (Latin: in solution)

$$CH_3CO_2H + BrO_3^- + 5\ HBr \longrightarrow 3\ Br_2 + 3\ H_2O + CH_3CO_2^-$$

Procedures

Puzzle One:

2,4-dimethylaniline (0.18g, 0.0015 mol) and 2mL of acetic acid were placed in a 25-mL Erlenmeyer flask. The mixture was stirred in an ice bath while first powdered potassium bromate (0.09g, 0.00054 mol) and then hydrobromic acid (48% or 8.7 M, 0.30 mL, 0.0026 mol) was added. The initial orange color caused by the bromine faded in 1 min. The mixture was stirred for an additional 4 min, and 10 mL of water was added. This resulted in a clear, faintly purple solution containing some solid (presumable the anilinium bromide).

The mixture was transferred to a 50-mL beaker and stirred and room temperature. 2 mL of 4M NaOH was added, followed by 5.0 mL (0.053 mol) of acetic anhydride. The mixture was stirred for 30 min; during this time the original precipitate dissolved and a new one appeared. The product was isolated by vacuum filtration, washed with water, and air-dried.

Puzzle Two:

The above procedure was carried out using 2,6-dimethylaniline. The resulting clear solution was stirred in a 50-mL Erlenmeyer beaker while 0.7 mL of 4 M NaOH and 2.0 mL of acetic anhydride were added. A precipitate soon formed. After 30 min, solid sodium carbonate was added, a little at a time, until effervescence stopped and the pH was 8. Vacuum filtration, washing with water, air-drying and vacuum drying gave faintly pink crystals.

Puzzle Three:

A solution of 0.23 g (0.0015 mol) of vanillin in 3.0 mL of acetic acid was stirred at room temperature, and 0.09 g of potassium bromate, followed by 0.30 mL of 48% hydrobromic acid, was added. The mixture was stirred for 50 min and poured into 25 mL of water. The resulting mixture was stirred for 20 min and filtered by vacuum. The solid was washed with water and dried to give an off-white solid.

Safety:

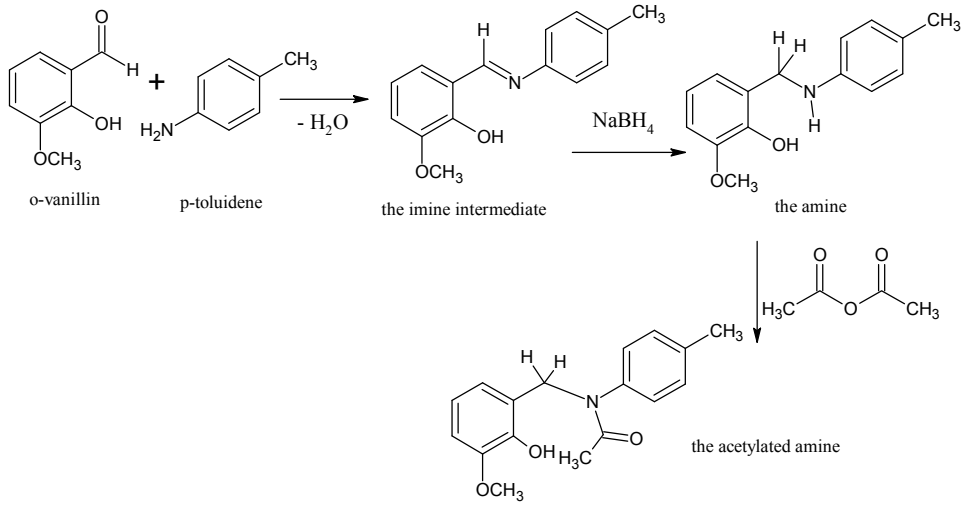
Hydrobromic acid is toxic and corrosive! Handle in the fume hood!

Potassium bromate is a cancer suspect agent and a strong oxidizer! Do not spill it on the balances. Clean up all spills immediately!

Acetic anhydride is corrosive and lachrymatory! It will make your eyes sting!

Exp #18 – Reductive Amination: Three Easy Pieces

Reductive amination is usually described as a one-pot procedure in which an aldehyde or ketone reacts with ammonia or an amine to form an imine, which is selectively reduced *as it is formed*. Hydrogen over nickel or a weakened hydride donor ($NaBH_3CN$, $NaBH(OAc)_3$)) is commonly used to reduce the imine as these reagents are slow to reduce the carbonyl compound. In this experiment we will react *ortho*-vanillin with *para*-toluidine to generate an imine.*



The reaction occurs between the two solids in a solvent free reaction. The imine is subsequently reduced with sodium borohydride to the amine, followed by acetylation to afford a solid amide derivative. The entire reaction sequence is performed in an open beaker.[rk1]

Procedure

Synthesis of 2-methoxy-6-(*p*-tolyliminomethyl)-phenol: Imine formation

Caution: Organic amines are considered potential carcinogens.

Weigh a 250 mL beaker and then add 0.76 grams (5 mmol.) of *ortho*-vanillin. Record the total mass of the beaker plus the *ortho*-vanillin. Using weighing paper, accurately weigh an equivalent amount of *para*-toluidine (0.535 grams, 5 mmol.) and add this to the beaker. Observe this mixture for a few minutes and record what is happening. Using a heavy glass-stirring rod, mix and grind the solids until they become a homogeneous dry powder. Weigh the beaker and record the mass. Determine the percent yield. Remove a small sample of this material for an IR or NMR and melting point analysis. Compare the features of your spectrum with those of the starting materials. The product may be recrystallized from hexanes if it looks impure.

Synthesis of N-(2-hydroxy-3-methoxybenzyl)-*p*-methylaniline: Reduction of the Imine

Add about 15 mL of 95% ethanol to the beaker containing your imine product and stir the mixture to partially dissolve the imine. Weigh out approximately 0.1 grams of sodium borohydride and slowly add this to the beaker in small increments with continued stirring. Record all observations and explain what is occurring in the reaction.

Synthesis of N-(2-hydroxy-3-methoxybenzyl)-N-*p*-tolylacetamide: Acetylation of the Amine

Add 2 mL of acetic acid to the amine to destroy the excess borohydride and to neutralize the phenoxide ion. Add 2 mL of acetic anhydride and a boiling chip and warm the solution on a hot steam bath for 5-10 minutes. Move this beaker to a stir plate, and stir the solution fairly rapidly while **slowly** adding 75 mL of water. Continued stirring should leach out the alcohol and acetic acid causing the amide product to precipitate. Cool the mixture in an ice bath and collect the solid. Allow it to air-dry overnight and then analyze your product by IR or NMR spectroscopy and melting point. A small sample may be recrystallized from hexanes.

Report

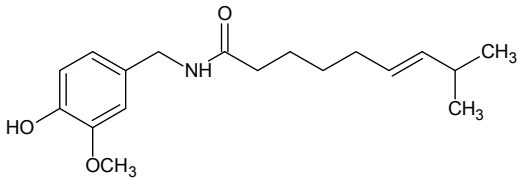
1. Complete two reagent charts: one for the formation of the imine and one for the synthesis of the amide from the imine.

2. The amine was not isolated in this reaction sequence. Briefly describe a procedure that would allow you to isolate the amine as a solid product. Predict how the IR spectrum of the amine would differ from the IR spectrum of the amide.

3. In the reduction of the imine to the amine, the imine appears to slowly dissolve in the solution, explain what is happening. Explain why the amide product precipitates out of solution as water is added to the ethanolic solution.

4. Identify the IR absorption peak for the C=N stretch for the imine product and suggest a reason why the frequency is so low.

5. The structure of capsaicin, the pungent ingredient in red pepper or *capsicum annuum*, is shown below. Suggest a multi-step synthetic scheme analogous to the sequence used in this experiment to prepare capsaicin.



Notes to Instructors:

1. All reagents were purchased from Aldrich Chemical Company and used without further purification. Reagents used: acetic acid [64-19-7], acetic anhydride [108-24-7], ethanol [64-17-5], hexanes [73513-42-5], sodium borohydride [16940-66-2], *para*-toluidine [106-49-0], *ortho*vanillin [148-53-8], vanillin [121-33-5].

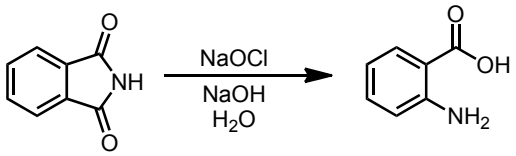
2. The imine, 2-methoxy –6-(*p*- (tolyliminomethyl)-phenol, is a bright orange solid, (around 100 ^{o}C) for the recrystallized material.

3. Isolation of the amine, N-(2-hydroxy-3-methoxybenzyl)-*p*-methylaniline, was accomplished by the addition of ~2mL of acetic acid to destroy the excess sodium borohydride and neutralize the solution. The reaction mixture was transferred to a separatory funnel, diluted with water, extracted with ether and dried over sodium sulfate. Recrystallization from hexanes afforded a white solid, (mp between 50 and 100^{o}C.)

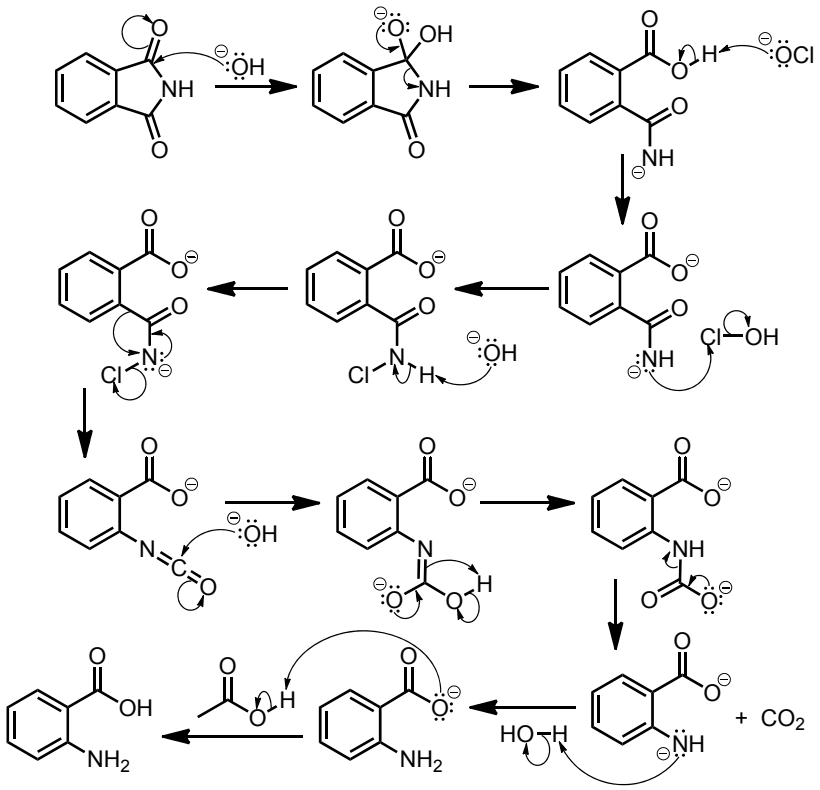
4. The amide, N-(2-hydroxy-3-methoxybenzyl)-N-*p*-tolylacetamide, is a white crystalline solid, (mp between 100 and 150^{o}C.)

Exp #19 – Synthesis of Anthranilic Acid from Phthalimide *via* a Hoffmann Rearrangement

Today's Reaction Scheme:



Mechanism of the Hoffmann Rearrangement:



Procedure:

Dissolve 3.88 g of solid sodium hydroxide (NaOH) in 13.0 mL of deionized water in a 125 mL Erlenmeyer flask. Cool this solution in an ice-water bath until the outside of the flask feels cold to the touch and then add 25 mL of bleach (NaOCl *(aq)*). Allow the reaction mixture to continue to cool in the ice-water bath. In the meantime, using a mortar and pestle, grind the phthalimide into a fine powder and measure 2.4 g of this powder into a weighing boat. Finally, fill a 400 mL beaker about ½ full of water and heat on a hot plate until the temperature is steady at 80 °C, monitoring the temperature with a digital "lollipop" thermometer (you may need to adjust the hot plate settings up or down – the important part here is a steady 80 °C water bath!)

Working quickly: Remove the Erlenmeyer flask (containing your bleach mixture) from the ice-water bath and immediately dump in the solid phthalimide all at once. As soon as the solid is added, swirl the flask vigorously to mix, then insert an alcohol thermometer and let your flask sit on the benchtop.

As the temperature rises slowly to room temperature, the solid should slowly dissolve. The temperature should then rise rapidly. As soon as the temperature stops rising on its own, remove the alcohol thermometer from the reaction mixture and allow the flask to "float" in the 80 °C water bath for about 3-5 minutes.

Wear gloves for this step: Cool the reaction mixture in an ice-water bath until the mixture is below 10 °C (check the temperature with your alcohol thermometer) and then add concentrated HCl drop-by-drop until the mixture has a pH of about 8 – this will require about 6.0 mL of HCl. Monitor the pH with pH paper and don't start checking the pH until you have added around 5 mL of HCl. Be sure to mix thoroughly before checking the pH.

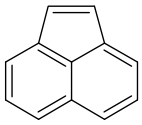
Wear gloves for this step: Once the correct pH has been reached and while your mixture is still in the ice-water bath, add 2.5 mL of glacial acetic acid drop-by-drop. The product should precipitate from the reaction mixture. (**WARNING:** The reaction will foam at this point. Be sure to add the acetic acid slowly to prevent overflow and make sure your solution is well mixed!)

Vacuum filter your crude product, then recrystallize from boiling water. Allow to dry in your drawer for one week. Alternatively, the product can be dried in an oven set to 100 °C for about 20 minutes. Take the mass of your final product and calculate a percent yield. Then, take an IR and melting point of your product.

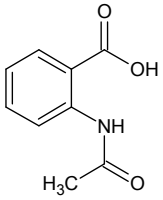
Exp #20 – Acetylation of Anthranilic Acid: Triboluminescent Crystals from the Microwave Oven

By Bruce W. Baldwin, Chemistry Department, Spring Arbor University, Spring Arbor, MI

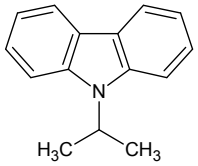
There are many examples of crystals that spark when they are crushed. This characteristic is called *triboluminescence*. The word *luminescence* means to glow, and *tribo* comes from the Greek word *tribien*, which means to rub. Many people have observed that wintergreen lifesavers exhibit this effect while crunching the candies in a darkened room. It is thought that the lifesaver sparking is due to triboluminescence of the sugar and wintergreen flavoring in the candy. There are some other compounds that give even brighter sparks when crushed. One of these is the subject of this laboratory synthesis. You will be able to check your crystals for the effect after they dry a little.



Acenaphthacene
poorly triboluminescent



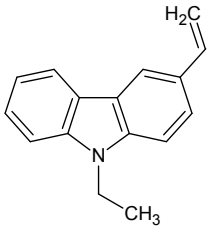
N-Acetyl anthranilic acid
very triboluminescent



N-Isopropyl carbazole
very triboluminescent

Although the triboluminesent effect was first observed by Francis Bacon in the early 1600's, the cause of the effect is still debated. Many ways of causing the sparks have been observed including quickly lowering the temperature of crystals, running mercury across the crystal surface, quickly forming the crystals by immersion in liquid nitrogen (brhhh!), or grinding them. Triboluminescent crystals have been studied by shining X-rays on them to determine the arrangement of atoms and molecules within the crystal. The results have not yet indicated specific, common molecular orientations that predispose a crystal to triboluminesce. An interesting consequence of making sparks with crystals is that if these crystals are ground in an atmosphere of neon, the sparks produced cause the neon to electrically discharge so that a red-orange glow is observed!

The most recent theory suggests that when triboluminescent crystals are crushed, the freshly prepared surfaces of the fractured crystals are highly charged. This causes many electrical potentials to exist inside the crystal. When the electrons suddenly rearrange to neutralize these potentials, sparks are formed. However, this has not been directly observed, so there are many questions about the cause of the sparks that remain unanswered. The question asked by many is "What can triboluminescence be used for?" A 1981 article in the Japanese journal, *Chemistry Letters*, provides a speculative application. What if a molecule could be made that would spark when crushed and polymerize because of the sparks? The Japanese researchers combined these characteristics in a single molecule.



N-ethyl-3-vinyl carbazole
triboluminescent and polymerizable

When crystals of this compound were crushed, a portion of them polymerized into molecules similar to high strength plastics. One application of this could be to include these compounds in lubricants for bearings. As the bearings moved, the crystals would be ground and sparks would initiate the polymerization, producing a tough plastic film on the grinding surfaces. Thus the lubricant would form hard coatings on the bearing surfaces, prolonging the life of moving parts!

This laboratory will provide another type of molecule that sparks when crushed. The microwave oven provides a little used, though very convenient, heating source for this process. The heating is a result of the oven's electrical fields oscillating at a different rate from the molecules in the reaction. When the difference is fairly small, as is the case for water and certain other polar molecules, heat is absorbed into the mixture. This allows the use of simple glassware, pyrex beakers and funnels, and fast reaction times, on the order of seconds rather than minutes. Thus, this laboratory will use an unconventional heating method, the microwave oven, to produce a compound with an unconventional crystal fracture energy release mechanism, triboluminescence

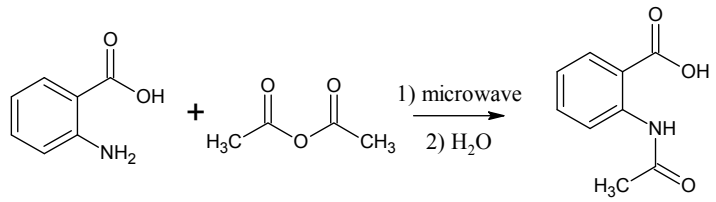
Safety

Acetic anhydride is corrosive and a lachrymator.

Methanol is a toxic, flammable chemical and will cause blindness if ingested. The students should be instructed to avoid contact with methanol.

Microwave Ovens - A comment about microwave oven safety is in order. Avoid placing thin or pointed metal objects like forks, spatulas, or aluminum foil in the oven because the arcing could pose a fire hazard inside the oven. Interestingly, magnetic stir bars do not cause arcing because they have no sharp places to act as an arc point. However, it's probably best to avoid metals in the microwave as a general rule. The microwave ovens should be placed in a fume hood. This way, if any vapors from the reaction come out, they're swept away from the experimenter.

Procedure



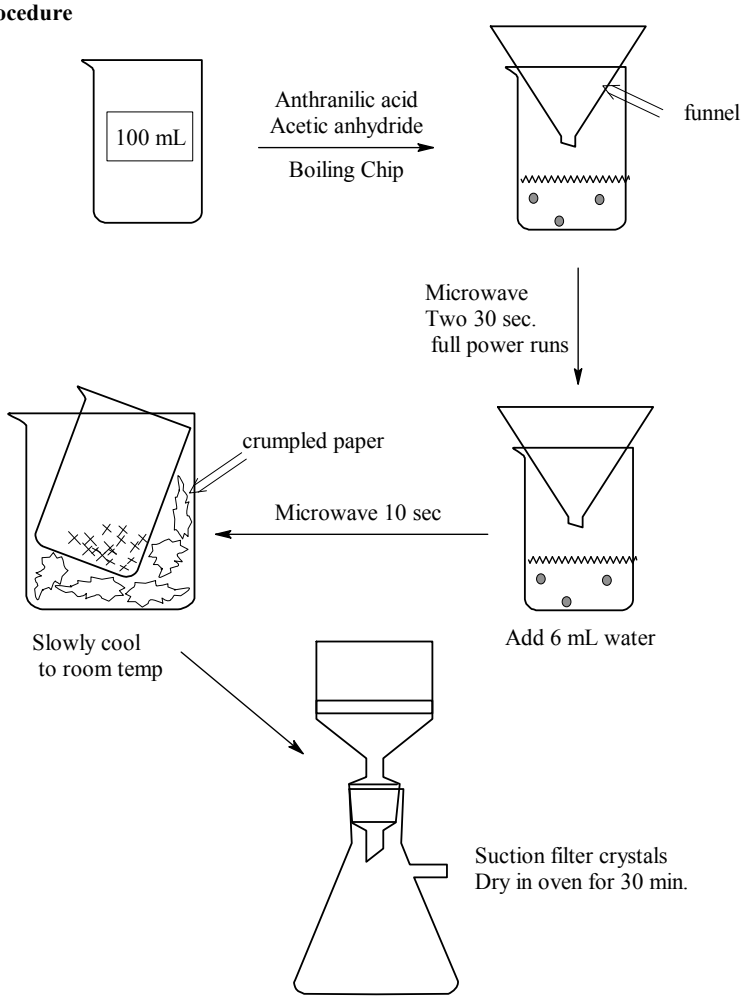
Anthranilic acid Acetic anhydride N-Acetyl anthranilic acid

1.37 g of anthranilic acid, 4.2 mL of acetic anhydride and 2 boiling stones were mixed in a 100 mL beaker, then placed in the middle of the turntable in a microwave oven (1,000 watts) and irradiated at full power for about 1 minute. The microwave oven should be turned off as soon as the crystals dissolve and the mixture boils about 1 second.

Before the next step, a paper towel insulated 250 mL beaker was prepared for cooling the reaction beaker after irradiation according to the graphical procedure on the next page. After cooling to room temperature, 6 mL of distilled water was added to the mixture. After ten seconds heating at full power in the microwave oven, all particles must dissolve and the mixture should boil again for about one second. This mixture was cooled in the insulated flask. (It is critical to avoid disturbing the mixture while it is cooling because the crystals could fall out of solution prematurely.)

The platelike crystals were suction filtered in a Büchner funnel and washed with 1.) ice cold water, 2.) ice cold methanol and air dried overnight to completely remove all solvent. High quality crystals gave yellow fluorescence when irradiated with a 360 nm mineral lamp. If your crystals fluoresce purple or only a little yellow, recrystallize them from 90% methanol/water using 0.5 milliliters solution for every 100 milligrams of crystals. The crystals should now glow yellow or yellow-green using the 360 nm mineral lamp. Crushing the crystals between two petri dishes in a darkened room demonstrates the triboluminescent effect by emitting bright blue sparks.

Illustrated Procedure



Write-up

Calculate the percentage yield of your crystals by dividing the mass of your crystals by the expected amount of product taken from the table. Report this as a percentage.

Another part of the discussion should include a description of the crystal appearance under long wave UV light (365 nm) and the triboluminescence effect when the crystals were ground between two watch glasses.

Include a reagent chart that clearly shows which reagents were present and how many moles of each were used. Clearly indicate the limting reactant.

Procedure – Include a detailed step-by-step description of how to conduct the experiment. It's written well if another student could perform the experiment using only your notes from the procedure.

Observations - Everything that happens during the laboratory: color changes, appearance of crystals, actual weights and measurements that you used in the lab (probably slightly different from what you intended), crude weights, weight of the flask you're measuring in, melting points, and boiling points

Data - This section is where the data of percent yield and melting point are presented. They should be clearly marked and easy to find. This is where you show your calculation of the theoretical and percentage yield.

Discussion - Please don't write a summary of the procedure! Instead, discuss the reaction. Answer any questions posed at the end of the procedures in the write-up section. This should allow for a good explanation of interesting points about the reaction, chemicals used, or application of the products in the real world.

Exp #21 – Thin layer chromatography (TLC)

Theory

One of the most common sights in an organic chemistry lab is that of upright glass tubes, filled with a white powder and slowly dripping solvent. In biochemical labs, electrophoresis plates identifying proteins and DNA are often seen. Both of these are forms of *chromatography*. The word "chromatography" describes any method that purifies a compound by passing it through some sort of stationary container. There are now many varieties of chromatography, and they collectively represent the most widely used means of purification. Thin Layer Chromatography (TLC) is a convenient and quick technique which demonstrates principles that apply to many types of chromatography.

In most chromatographic separations, compounds are dissolved in a solvent (called the *mobile phase*) and are then passed through a material (called the *stationary phase*). Some compounds pass through the stationary phase faster than others, and thus the compounds become separated. This simple idea is the basis of all chromatography.

Polarity

In TLC, the stationary phase is thin layer of silica coated on a plate of glass, aluminum or plastic. The silica (SiO_2) is Lewis acidic and interacts with the functional groups of the compound, therefore the compounds are separated according to functional groups. Groups that are *polar* slow the molecule down as it passes through the silica; molecules without polar groups (termed "greasy") travel through with little resistance.

What makes a group polar? Having a Lewis basic group increases polarity. The polarity can be related to the dipole moment, which can be measured. We are only interested in which groups are more polar that another, not in exact measurements. Also, the type of mobile phase and the nature of the stationary phase can modify or even reverse the positions of groups on a polarity list. So it is best to remember the rough order of functional groups, but to realize that they are only a guide

Functional Group Polarity

most polar	acids	travels slowest
	amides	
	amines	
	alcohols	
	halide	
	alkenes	
least polar ("greasy")	alkanes	travels fastest

The nature of the solvent is also very important. The more polar the solvent mixture is, the more it will "push" all the compounds through the stationary phase. A less polar mobile phase results is the compounds traveling more slowly. The proverb "a rising tide lifts all boats" is a perfect description of the effect of the mobile phase's polarity. Remember that each time you perform a TLC, you should consider the polarity of the solvent (which affects all the compounds) and the polarity of each component (which affects only that component' mobility).

Solvent Polarity		
Most polar	water	"pushes" compounds most
	methanol	
	acetonitrile	
	acetone	
	ethyl acetate	
	chloroform	
	dichloromethane	
	diethyl ether	
Least polar	hexanes	"pushes" compounds least

Obviously, in order to allow people to compare the results of their TLC's, you need a more exact scale than "the compound came out pretty fast". Therefore, the **R_f scale** was developed. In this simple scale, if a compound was not move at all by the mobile phase, the R_f is called 0.0. If a compound moves as fast as the solvent and travels the length of the plate, the R_f is 1.0. If a compound travels halfway through the stationary phase, the R_f is 0.5. Why not just use a percentage scale (*i.e*. 0%, 100% or 50%)? No reason at all! It's just an arbitrary convention.

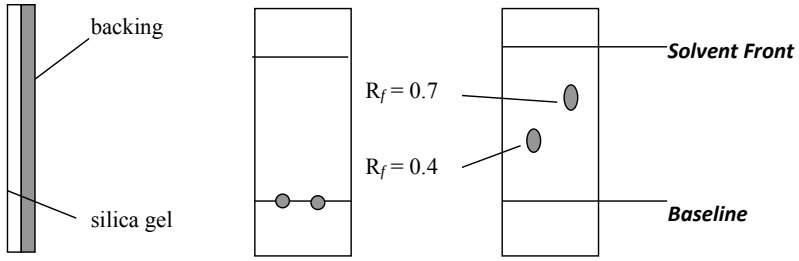


Fig. 1 - Views of a TLC Plate

Using TLC

A TLC is usually run to check to see if a reaction is done, or to check the purity of a sample. Usually, the TLC plate is about 3-4 cm wide and about 10-15 cm tall. A plate this size can accommodate about 3 to 4 *spots* (a spot is a bit of the compound on the plate). After the plate is *eluted,* (*i.e*. when the solvent goes up the plate) the spots are compared. If two spots are not side-by-side and therefore have a different R_f value, then they are different compounds. If they have the same R_f value, then they may be the same compound. (the idea is the same as with melting points)

Placing a known and an unknown compound in the same spot is called *co-spotting*, and is similar to doing a mixed melting point. However, even if the two compounds have the same R_f 's, it is still possible that they are different, so be careful!

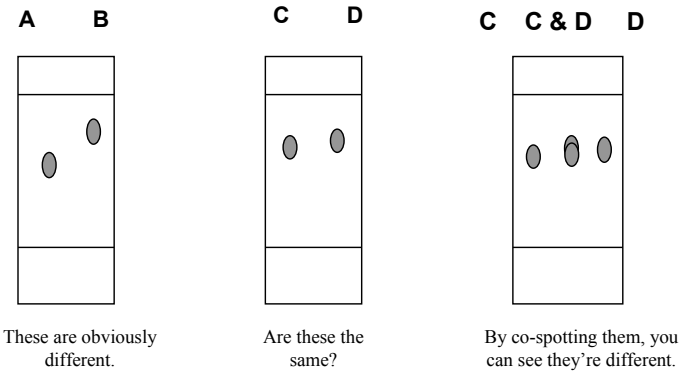


Fig. 2 - Co-Spotting with a TLC

Why can't you just have a standard for a TLC, in the same way you have a list of melting points? Unfortunately, the R_f 's can vary depending on factors such as the humidity, the thickness of the silica layer, small variations in the solvent composition, the amount of compound on the plate, and the age an composition of the silica. Because of these factors, one should never compare spots done of two different plates without realizing that they can be quite different.

Techniques

To run a TLC plate, you first need to set up a TLC chamber. This is simply a covered beaker with a little solvent in the bottom. It is important to only use about 1cm of solvent in the beaker. If you use more, the solvent will splash above the start line, ruining the plate. You should also include a piece of filter paper around the inside of the beaker in order to help saturate the atmosphere of the chamber with solvent.

Spotting or applying the compound is a tricky matter. It is better to put less on than more; the instructor will demonstrate the proper technique. Before you run the plate, check with the UV lamp to see if you can see your compound.

Visualizing Spots

Most organic compounds are invisible. After you run the plate, you will end up with a plate that looks blank! In order to see them, chemists use many visualization techniques. The most common is looking at the plate with a UV lamp, since many compounds absorb UV light and therefore look like dark spots. Another technique is the use of iodine. The plate is placed in a chamber with iodine crystals, which react with the compounds to make brownish spots. The last general technique is the use of stains, that is, reagent mixtures that react with the compounds to give various colors. There are literally hundreds of different stains for every type of functional groups.

Procedure

You will be given a solution of an over-the-counter medicine. Your goal is to identify the active ingredients present using TLC, and determine whether it contained any aspirin.

Prepare a TLC chamber

Prepare a TLC plate with the aspirin standard. That is, lightly spot the standard onto a "lane" on the plate. Then spot your unknown. Before you develop your plate, look at it under the UV lamp (make sure the solvent has dried!). If you don't see a dark spot on the baseline, spot the light compounds again until they are dark. Try to make short, small applications rather than a single big soak. The goal is to put a very small dot with enough compound to see, but not so much that is overwhelms the plate.

Elute the plate with ethyl acetate-ethanol-acetic acid (25:1:1) as the developing solvvent

Visualize the plate with UV light and an iodine chamber.

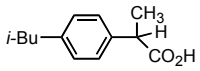
Write-up

Sketch the TLC plate.

Report the Rf's of the compounds present. <u>There may be more than one!</u>

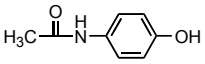
Did your medicine contain any aspirin?

Table of active ingredients, structures and R_f's



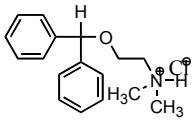
$R_f = 1.00$ Ibuprofen

2-(4-isobutyl)-propanoic acid



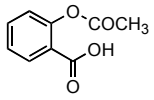
$R_f = 0.82$ Acetaminophen

4'-hydroxyacetanilide



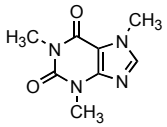
$R_f = 0.028$ Diphenhydramine hydrochloride

2-(benzhydryloxy)-N,N-dimethylethylamine hydrochloride



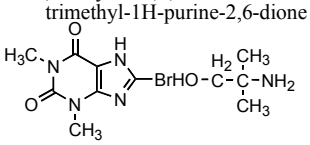
$R_f = 0.92$ Aspirin

acetylsalicylic acid



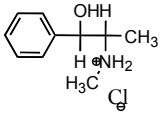
$R_f = 0.40$ Caffeine

3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione



$R_f = 0.47$ parabrom 1:1 complex

Note: Fluoresces under long wave UV all others visible with short wave only!



$R_f = 0.042$ Pseudoephedrine

threo-2-(methylamino)-1-phenylpropan-1-ol hydrochloride

Exp #22 – Synthesis of the sweetener Dulcin from the analgesic Acetaminophen

Dulcin is an "artificial" sweetener that can be prepared from acetaminophen, the active ingredient in Tylenol. Dulcin was in use for several years, but removed from the market due to concerns over it's possible toxicity. In today's lab, you will perform a series of reactions, isolate the product, and then analyze the purity of the product using TLC.

In the first step, the phenol is alkylated using ethyl iodide and sodium hydroxide, an example of the Williamson ether synthesis. Although you might expect to see sodium hydride used here (*i.e*. NaH), the phenol is acidic enough (about pH = 10) that sodium hydroxide is sufficient to deprotonate it

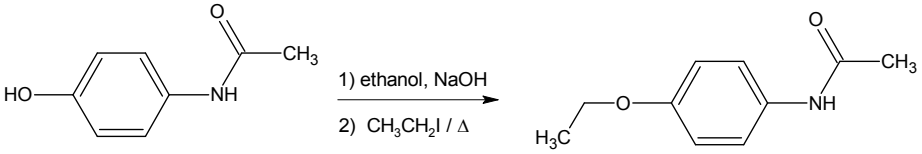


Fig. 1 - Alkylation of Tylenol

In the second step, the acetyl group is hydrolyzed under acidic conditions to give the *p*-ethoxyaniline hydrochloride salt. The mechanism of this reaction is similar to that of the Fisher esterification. It is driven to completion by the large excess of water present.

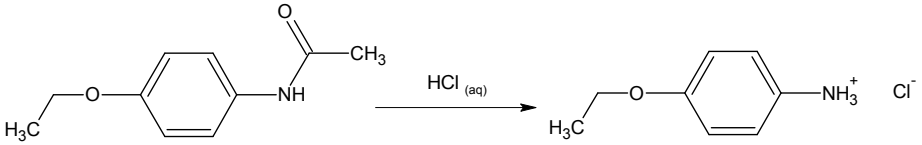


Fig. 2 - Hydrolysis of Phenacetin

In the final step, the carbamate is formed under carefully controlled pH conditions. The sodium bicarbonate reacts with the amine salt to "freebase" it. The aromatic amine can then attack urea, which expels ammonia in an addition-elimination mechanism.

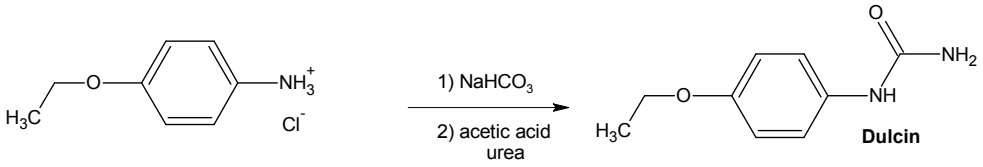


Fig. 3 - Synthesis of Dulcin

Safety:

Safety glasses are to be worn at all times and all chemicals should be considered hazardous. If possible, perform all experiments and chemical manipulations in the hood. Avoid direct physical contact with chemical substances. You should be aware of the following health hazards:

Iodoethane is a *lachrymator* (causes severe eye irritation) and skin irritant. **If exposed, flush affected area with water for at least 15 minutes** while removing contaminated clothing.

Hydrochloric acid, sodium hydroxide and glacial acetic acid are corrosive and can cause severe damage to eyes and skin. **In case of contact, immediately flush skin with plenty of water** for at least 15 minutes while removing contaminated clothing.

Phenacetin and dulcin are both considered toxic and should not be ingested or tasted.

Procedure

Step One - Preparation of Phenacetin:

Grind 4 tablets of Tylenol (500mg of acetaminophen per tablet or about 2.0 g total) using a mortar and pestle and place the powder in a 50-mL round bottom flask with a magnetic stir bar. To the powdered tablets add 15.5-mL of a 1M ethanolic NaOH solution. Fit the round bottom flask with a water-cooled condenser and bring to a vigorous reflux.[3] Maintain reflux for 15 minutes and then remove the flask from its heat source.

To the hot solution, add 2.0mL of ethyl iodide (iodoethane) using a syringe and return to reflux for an additional 15 minutes. Filter the **hot** solution under vacuum through a Buchner funnel and into a 200 to 300-mL side arm Erlenmeyer flask containing a 40-mL mixture of ice and water.[4] Collect the insoluble starches on the filter paper (if any) and dispose them. The phenacetin, upon contact with the cold water, precipitates from the filtrate as a white solid.

While still cold, the solid phenacetin is collected by vacuum filtration using a Buchner funnel and washed with cold water. Residual water can be removed by oven drying at 100°C for 5 to 10 minutes. The phenacetin prepared in this manner is generally quite pure and can be used directly in the preparation of dulcin.

Obtain the weight of the dry phenacetin for use in yield determinations. Set aside a portion of the product (~0.1 to 0.2 g is usually sufficient) for analysis by melting point. Weigh and save the remaining product for use in the preparation of dulcin.

Step Two - The Preparation of Dulcin from Phenacetin[7] *:*

To a 50-mL round bottom flask add a magnetic stir bar and the previously synthesized phenacetin. Calculate the moles of phenacetin present and using a 6M HCl solution, add 5 molar equivalents HCl relative to moles of phenacetin.[8] Bring the mixture to a boil and maintain a vigorous reflux for 15 minutes during which time the phenacetin should dissolve and the solution should become clear. This hydrolysis produces the *p*-ethoxyaniline hydrochloride salt (see Fig. 2)

While stirring, remove the flask from its heat source (or lower the heat setting) just enough to stop the reflux yet maintain a hot solution. **Slowly and with occasional swirlin**g, use a micro spatula to add small portions of solid $NaHCO_3$ until the solution is slightly acidic (pH 6 to 6.5).[9] The approximate amount of $NaHCO_3$ to be added can be calculated using the following formula: moles of $NaHCO_3$ to be added = (moles of HCl) – (moles of phenacetin X 1.1). Indicating pH paper can be used to verify that the pH has been appropriately adjusted.[10]

Once a pH of 6 to 6.5 has been achieved, add 4 molar equivalents of urea relative to phenacetin long with 3 drops of glacial acetic acid. Return the mixture to reflux for about one hour or until the dulcin sets into a solid mass of white crystals. Chill the mixture in an ice bath and collect the dulcin by acuum filtration using a Buchner funnel and wash with cold water.

Although it is usually not necessary, the dulcin can be recrystallized from hot water. Residual water can be removed by storing for one week at room temperature or by use of a microwave oven.

Obtain the weight of the dry dulcin for use in yield determinations. Confirm the melting point of the compound. **Do not** taste the sweetener dulcin!!

Instructor (and Student!) Notes

1. The experiment has been successfully performed in our laboratories with a single Tylenol tablet (350 mg of acetaminophen). However, in our laboratories this experiment is typically carried out towards the end of the second semester by students who have had considerable experience with the techniques employed. Since the procedure works well with any number of Tylenol tablets, the experiment can be performed on a scale suitable to the experience of a particular student body. Although the micro and macro procedures are essentially the same, a full description of each has been provided so that the student instructions can be used directly from this document.

2. The 1M ethanolic NaOH solution must be prepared in advance since it takes a while for the NaOH to dissolve in the ethanol.

3. If time is limited, you may recommend to your students that they bring their heat sources to an appropriate temperature while they are preparing the reaction mixture.

4. The precipitation of the phenacetin works best if solid portions of ice are visible during the filtration.

5. Alternatively, the samples can dry between laboratory periods although active drying allows for yield determinations and analysis within a single period.

7. It is useful to have a reserve of phenacetin in order to supplement product yields of those students who obtain an insufficient amount of phenacetin to proceed with the dulcin synthesis. Phenacetin is commercially available from the *Aldrich Chemical Company* at an approximate cost of $11.00 for 100 g.

8. Since the second experiment requires longer heating periods than the first, it is recommended that these calculations be performed either during the first period or prior to the beginning of the second.

9. The sodium bicarbonate must be added slowly and in small portions with a micro spatula to prevent excessive frothing and loss upon release of carbon dioxide. Also, the reaction should be kept hot since if it cools too much phenetidine hydrochloride salt may precipitate making it difficult to stir the reaction during the addition of the sodium bicarbonate. It is very important that the pH is adjusted correctly at this time or the reaction will fail. If too much sodium bicarbonate is added small portions of hydrochloric acid solution can be used to achieve the proper pH. Make sure that the mixture is well stirred between each assessment of the pH. Finally, solid NaHCO3 is used instead of an aqueous solution so as to avoid excessive dilution of the final reaction mixture and the reduction in the amount of dulcin precipitated that would result.

10. Remember that the important point is to adjust the pH. If you need to add more sodium icarbonate, then do so. But stir the mixture to ensure that the base you're adding gets mixed with the acid!

Physical Constants

Acetaminophen $C_8H_9NO_2$ FW = 151.17 MP = 170
Iodoethane C_2H_5I FW = 155.97 BP = 72.5 0 C d = 1.94g/ml
Phenacetin $C_{10}H_{13}NO_2$ FW = 179.22 MP = 137.5 ºC
Phenetidine $C_8H_{11}NO$ FW = 137.18 MP = 1.2ºC
Urea CH_4N_2O FW = 60.06 MP = 132.7ºC
Dulcin $C_9H_{12}N_2O_2$ FW = 180.21 MP = 173.5ºC
Sodium bicarbonate $CHNaO_3$ FW = 84.01

thumbnail sketches

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A Tale of Two Sweeteners

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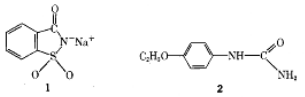
Today's synthetic sweeteners are widely advertised and extensively used. The present status of the industry is built upon the breakthroughs that occurred during the 1879–1910 period. An examination and comparison of two of these compounds, saccharin, **1**, and dulcin, **2**, discovered within six years of each other, reveals important scientific discoveries and considerations. It also points out common characteristics such as the lack of any particular structure–activity approach in the history of synthetic sweetener development.



1 **2**

The discovery of the first synthetic sweetener, saccharin, has been extensively discussed (*1*). The discovery has been attributed to the combined efforts of Ira Remsen and Constantine Fahlberg. Remsen established a laboratory to continue research on derivatives of toluenesulfonic acids and related materials when he joined the faculty of The Johns Hopkins University. In early 1878, Constantine Fahlberg joined the group and commenced a study on the oxidation of various ortho compounds in the toluene series during which he came into contact with a sweet-tasting *o*-toluenesulfonamide. While it may seem unusual to taste a compound today, it was quite common for chemists a hundred years ago to taste their compounds. Chemists would routinely taste their newly prepared compounds since they viewed taste as one of its noteworthy properties. This discovery, made in June 1878, was reported in a joint article by Fahlberg and Remsen in 1879 (*2*). Following Fahlberg's return to Europe he carried out tests of potential toxicity, applied for patents on preparing the compound in 1894 and soon thereafter began to manufacture it. Saccharin was widely adopted, held in high regard, and publicized over the next few decades. Intermittent concerns about its safety did surface at the beginning of its production and at the time of the 1906 Pure Food and Drug Act. Yet this compound became the dominant synthetic sweetener of the 20th century.

The history of the second sweetener which was discovered in 1884 has only recently been described by R. Goldsmith (*3*). Joseph Berlinerblau was involved in organic synthesis research under the direction of Schmitt, a professor at the University of Bern. His personal research involved products formed by the reaction of chlorine cyanide (ClCN) with various aromatic amines. In the course of his studies he carried out a reaction between chlorine cyanide and *p*-phenetidine (p-C_2H_5O–C_6H_4–NH_2), treated the intermediate product with water, and isolated a new compound he described as *p*-ethoxyphenylurea, **2**, which currently would be called (4-ethoxyphenyl)urea (CAS Registry No. 150-69-6) (*4*). In addition, he was able to prepare this compound by another route. His thorough investigation of the physical properties of each compound synthesized in his work was published as part of his overall study. His paper clearly reported that *p*-ethoxyphenylurea had a very sweet taste (*5*). Berlinerblau took out a patent seven years later describing his new synthetic approach using the action of phosgene upon *p*-phenetidine followed by the addition of water to prepare this sweetener. Other synthetic routes to this material were uncovered by several chemists over the next few years.

Because of its remarkably sweet taste, the term dulcin (meaning "sweet") was introduced by A. Kossell in 1893 when describing an early toxicity study in which the drug was screened on dogs and rabbits (*6*). In a series of tests performed on several species, including humans, mixed results were obtained. Some researchers claimed the drug would be safe in normal usage while others maintained the compound could prove toxic. The majority opinion seemed to have been that the drug's benefits outweighed any potential risks, and it was placed on the market. One important characteristic of dulcin affirmed in early testing in humans was the lack of a bitter aftertaste.

An examination of numerous medical texts as well as drug and pharmaceutical references revealed that, while there were many detailed descriptions of saccharin, dulcin was mentioned only in a small number of these publications and then only in a very limited manner. Both drugs, however, had their supporters and both were advocated for use by diabetics and by obese patients as an adjunct in weight loss. The initial publicity associated with saccharin and the ability of Fahlberg to produce, market, and promote saccharin gave it a clear and decided advantage over dulcin at the start. Saccharin would be viewed generally as safe while dulcin would never achieve much success. It would eventually be removed from the market after it was declared to be unsafe as a result of an FDA study published in 1951 describing the results of chronic toxicity testing on several new and older sweeteners (*7*). It should be noted that this removal occurred about 60 years after its discovery and early toxicity testing. Drugs on the market for a long time generally will stay on the market unless something serious happens to force them off. People get used to them and they become established. The proof of the chronic toxicity of dulcin was sufficient to remove it, especially as there were other safer sweeteners available.

We can learn much from our experience with these two sweeteners. First, it is evident that our current concern with toxicity was not as evident in the early period. Toxicity studies were carried out in a very elementary manner and not in the systematic or standardized fashion required today. These early studies were not regulated but improvised. They involved proving to others that the compound was not significantly toxic. Large numbers of animals were not used, nor were the tests designed to pick up long-term toxicity by carrying them out for long periods of time. There was no concern with cancer or other debilitative diseases. Human testing was not required. In contrast, today's studies are highly regulated, defined, and governed by a fixed and operational methodology. A chemical must be proved to be both safe and effective. Studies are carried out with large numbers of animals selected from several species. Studies are carried out for several years or designed to get the equivalent responses. Human testing is required and is highly regulat-

ed. Control groups are used to ensure drug effectiveness. A wide variety of toxic signs are looked for, and records are kept very carefully. This approach is reflective of a high public concern with toxicity that was not generally present a century ago.

Secondly, the discoveries of both dulcin and saccharin were accidental events in the course of organic synthesis. These two discoveries of synthetic sweeteners were a real surprise since prior to these events it was assumed that only natural chemicals could be sweet. No one had been looking for a synthetic sweetener. These accidental discoveries established a pattern that would be repeated for other sweeteners including the cyclamates and the dipeptide sweeteners such as aspartame.

Thirdly, these first two sweeteners were chemically quite distinct from each other. As new synthetic sweeteners were discovered, it became evident that they also had distinctive chemical structures. While some have begun to try to design sweetener molecules from theoretical considerations, a new sweetener can appear from very surprising sources or combinations. For example, the discovery of a sweet taste in dipeptides led to the recent and successful introduction of aspartame.

One final observation from a comparison of these two compounds is that the presence of a bitter aftertaste does not have to be associated with a sweetener. Investigators were aware of saccharin, which was the only synthetic sweetener in their experience, and it had that bitter aftertaste. They did not know whether other synthetic sweeteners would have this property or not. It was found that the bitter aftertaste of saccharin was not shared by dulcin. Future chemists would be aware of this observation, and it would be an important consideration in the search for new sweeteners.

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5. Berlinerblau, J. *J. Prakt. Chemie* **1884**, *30*, 103.
6. Kossell, A. *Archiv Anatomie Physiol.* **1893**, 389.
7. Fitzhugh, O.; Nelson, A. A.; Frawley, J. P. A. *J. Am. Pharm. Assoc.* **1951**, *40*, 583.

Mohr's Salt as a Wide-Coverage Testing Material for Analytical Chemistry Courses

Mohr's salt (ammonium iron(II) sulfate hexahydrate, $Fe(NH_4)_2(SO_4)_2{\cdot}6H_2O$) is recommended as a testing material for the lab curriculum of the analytical chemistry class in college. We have students individually prepare Mohr's salt as a common testing material. Using the Mohr's salt they have prepared, the students are able to perform a wide range of lab experiments in analytical chemistry; that is, they learn volumetric, gravimetric, and instrumental analyses through the determinations of iron and sulfate in Mohr's salt.

Syllabus for a Lab Class Using Mohr's Salt

Inorganic Chemistry	
Preparation and Purification of Mohr's salt	$(NH_4)_2SO_4 + FeSO_4 + H_2O \xrightarrow[\text{heat}]{\text{Fe wire}} Fe(NH_4)_2(SO_4)_2{\cdot}6H_2O$ Recrystallize twice from water, air-dry on filter paper at room temp. or in oven below 50 °C.
Volumetric Analysis	
Redox Titration	Standardization of $KMnO_4$ soln. against standard sodium oxalate soln. Determination of Fe(II) in student-prepared Mohr's salt by permaganometry.
Chelatometric Titration	Oxidation pretreatment of student-prepared Mohr's salt with hydrogen peroxide (Fe(II)→Fe(III)) Titration of Fe(III) with standard EDTA soln. by using of variamine blue B as an indicator.[a]
Gravimetric Analysis	Preparing, ignition, and weighing of $BaSO_4$.
Instrumental Analysis	
Colorimetry	Measurement of visible absorption spectrum of Fe(II)–phenanthroline with standard Mohr's salt. Making a calibration curve against standard Fe(II)–phenanthroline. Determination of Fe(II) content in the student-prepared Mohr's salt.
Potentiometry	Standardization of ammonium cerium(IV) sulfate soln. with standard Mohr's salt soln. Potentiometric titration of the student-prepared Mohr's salt soln. with the standardized ammonium cerium(IV) sulfate soln. using Pt electrode.[b]

[a] Erdey, L.; Rady, G. *Z. Anal. Chem.* **1956**, *149*, 250.
[b] Laitinen H. A. *Chemical Analysis*; McGraw-Hill: New York, 1960.

This lab class may be used as a combination curriculum of inorganic and analytical chemistry by consideration of preparation and purification of Mohr's salt. This curriculum is suitable for a one-credit half-semester course of two three-hour lab classes in a week or for a one-credit one-semester course consisting of one three-hour lab class a week. An example is shown in the table.

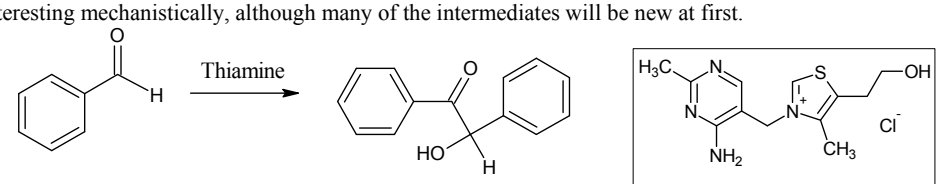
Presented at the 8th International Conference on Chemical Education, Tokyo, August 24, 1985.

Yoshiki Moriguchi
Fukuoka University of Education
Munakata Fukuoka, 811-41, Japan

from Williams, Brian D., *J Chem. Ed,* 2000, p. 357, v77 no. 3;

Exp #23 – Synthesis of Benzoin from Benzaldehyde

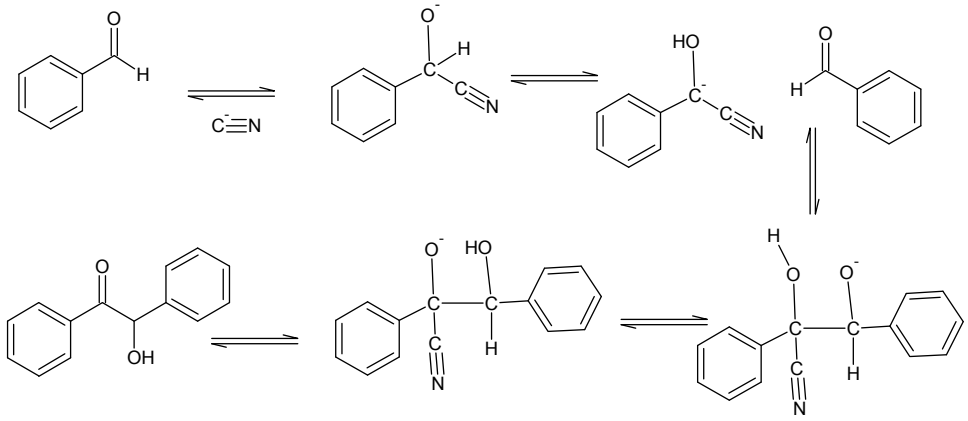
In the first step, you will use thiamine as a catalyst to prepare benzoin from benzaldehyde. This reaction is interesting mechanistically, although many of the intermediates will be new at first.



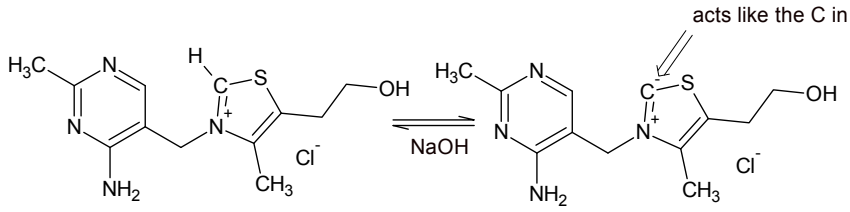
Benzaldehyde Benzoin Thiamine

Mechanism

This reaction is easier to follow if cyanide is used as a catalyst. In order for this reaction to work, the catalyst must be nucleophilic enough to attack a carbonyl, good enough of a leaving group that it can leave after the condensation has occurred, and be able to increase the acidity of the α-hydrogen after the initial attack.



Thiamine performs an analogous role in today's reaction and in biochemistry. The enzyme Thiamine pyrophosphate (TPP) is used to make α-hydroxy ketones *in vivo*.



Procedure

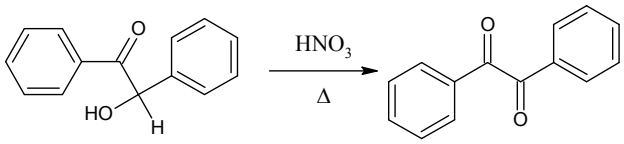
Dissolve 1.00 g of thiamine hydrochloride in about 2 mL of DI water in a 25-mL round bottom flask. Add 8.0 mL of 95% ethanol, and stir until the solution is homogeneous. Add 3.0 mL of 2 M NaOH dropwise to the solution over a 2 minute period. Note any color change.

When the solution is pale yellow, add 4.0 mL of benzaldehyde and stir until the mixture is homogeneous. Stopper the flask with a rubber stopper (not glass) and store it in your locker until next week.

Cool the reaction in an ice-bath to crystallize the product, scratching the inside of the flask if necessary. Let the solution crystallize for at least 5 min. Collect the crystals with vacuum filtration, washing them with some cold water. Let the product dry and record mass and melting point

To recrystallize the crude product, use 8 mL of 95% ethanol for each gram of product. Gently heat the mixture until the product just dissolves, remove it from the heat and let slowly cool. Collect the crystals with vacuum filtration. Let the product air dry, record the mass and melting point and record an IR spectrum.

Exp #24 – Synthesis of Benzil from Benzoin



Benzoin Benzil

Procedure

Place the benzoin from the previous step into a 100 mL round bottomed flask. For each 2.0 g of benzoin you have, add 7 mL of concentrated nitric acid. Don't use more than 20 mL of nitric acid.

Caution! HNO_3 is very corrosive! Wash any spills immediately with baking soda and water!

Warning! Add no more than 5 mL of nitric acid at a time! Place the condenser on top of the flask, the reaction may foam and ooze out of the flask!! Don't heat the flask until all of the nitric acid has been added and 5 minutes has elapsed!!

Heat this mixture to 100 ºC (or a gentle reflux) for 15 minutes. Use a magnetic stir bar. The reaction is probably done when all of the benzoin dissolves into the brown solution.

Caution: Lots of brown NO_2 fumes will be generated! You must do this whole process in the hood

Because you'll only be heating this reaction for a short time and because water is not terribly volatile, you can simply fill the reflux condenser with water (closing it with a piece of tubing) and set it on the flask. Do this if the hood is too crowded to allow everyone to use the water lines.

When heating is complete, pour the solution into a beaker with 75mL of water. Let the product (which may separate as an oil) cool and crystallize. You may need a seed crystal. Don't chill the solution until you see crystals form!

Collect the yellow solid with vacuum filtration and wash thoroughly with water to remove the nitric acid. Stop here for the day.

Exp #25 – Tetraphenylcyclopentadiene From Benzil and 1,3-Diphenylacetone

In this reaction, you will perform a double aldol condensation using potassium hydroxide as a base. The product formed should be a dark purple, almost black, color which results from the extended conjugation of the π system.

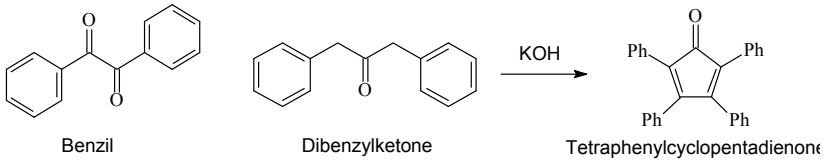


Fig. 1 - The overall reaction

The mechanism of the reaction is a classic example of the chemistry of enolizable protons. In the first step, the base deprotonates the ketone, resulting in a doubly resonance stabilized anion.

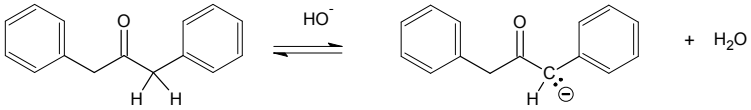


Fig. 2 - The first step of the mechanism

The anion then attacks one of the destabilized α–keto carbonyl group of the benzil. The resulting hydroxy group is removed by base is an example of a hydroxide acting as a leaving group!

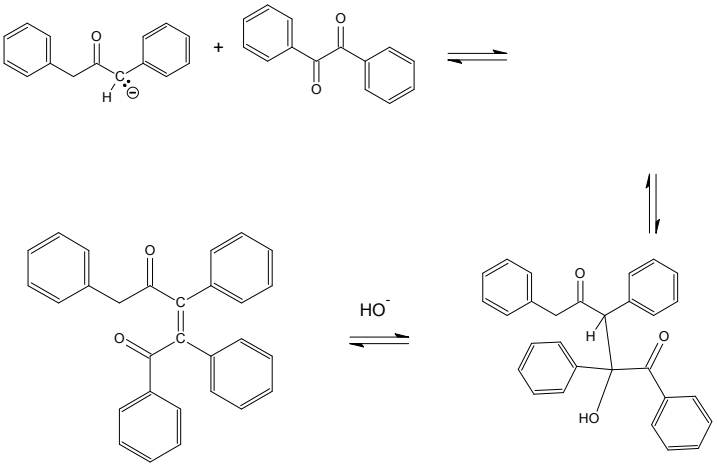


Fig. 3 - Forming one side of the ring

The process is repeated on the other side to close the ring. The last step, the elimination of the final hydroxy group, requires heat to drive the reaction eliminate water and form the fully conjugated ring (**B**). If the reaction is performed without heat, the intermediate alcohol (**A**) can be isolated.

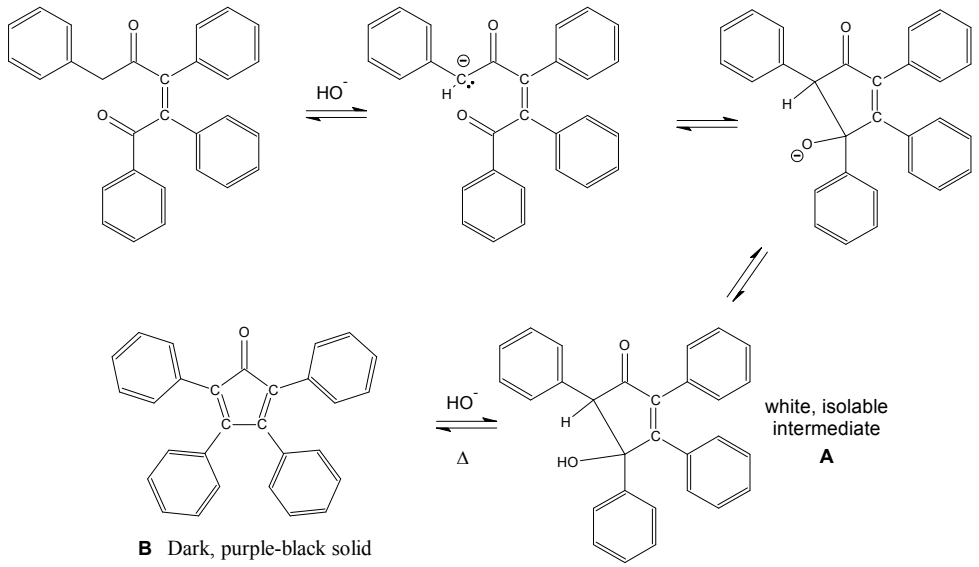


Fig. 4 - Closing the ring using base and heat.

Procedure

Potassium hydroxide (0.10 g) and anhydrous ethanol* (10 mL) were placed in a 50-mL Erlenmeyer flask, and the mixture was stirred mechanically until solution was achieved. To the vigorously stirred alkaline solution was then added benzil (2.0 g) and, before all the benzil had completely dissolved, 1,3-diphenylacetone (2.0 g). Stirring was then continued for an additional 20 min during which time the product precipitated as a white solid. The mixture was cooled (ice bath), suction-filtered, and the white solid so obtained washed with cold ethanol (4 x 5 mL) and sucked dry.

Save some of this product for an IR and melting point.

Notes: *use anhydrous ethanol for the reaction mixture, use 95% ("wet") ethanol for washing the product. Wet ethanol is less expensive.

Synthesis of Tetraphenylcyclopentadienone

A 25-mL rb flask is charged with 1.0 g benzyl, 1.0 g of 1,3-diphenylacetone, and 5 mL of anhydrous ethanol. The flask is heated with stirring on a hot water bath to about 80°C. As soon as the mixture begins to reflux, 2 mL of 30% ethanolic potassium hydroxide were added slowly (drop-by-drop) through the top of the condenser. The solution was refluxed for an additional 10-15 minutes and was then cooled to room temperature. The resulting solution was crystallized in an ice-water bath, filtered and washed three times using cold 95% ethanol.

Write-up

* Record weights of **B**.

* Calculate percent yields based on the limiting reactant present. Also calculate the percent yield based on the amount of benzaldehyde you started with.

* Record the melting point of the product.

* Include a short conclusion detailing the result of the experiment.

Exp #26 – Preparation of Hexaphenylbenzene *via* a Diels-Alder Reaction

Today's reaction consists of a simple Diels-Alder reaction, which is followed by a sigmatropic* rearrangement to form hexaphenyl benzene. The dienophile used today will be diphenyl benzene, while the diene will be tetraphenylcyclopentadienone.

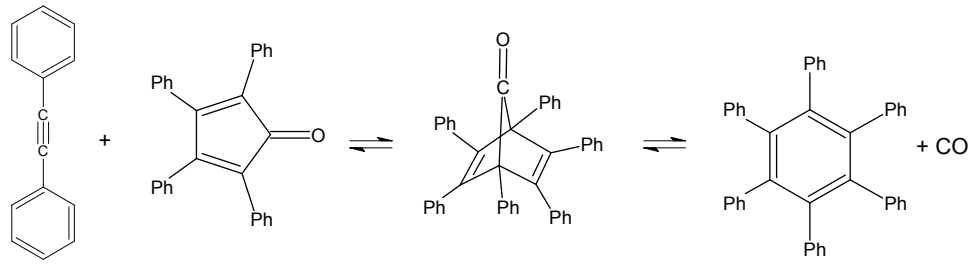


Fig. 1: today's reaction

The product of today's experiment has the highest melting point of any non-ionic organic molecular compound listed in the CRC handbook (1991 Ed.) The melting point is reported at 465°C, at which points it melts without decomposition.

* - sigmatropic: a rearranging of sigma bonds. (tropic is from the word *tropos* Gk. Shape)

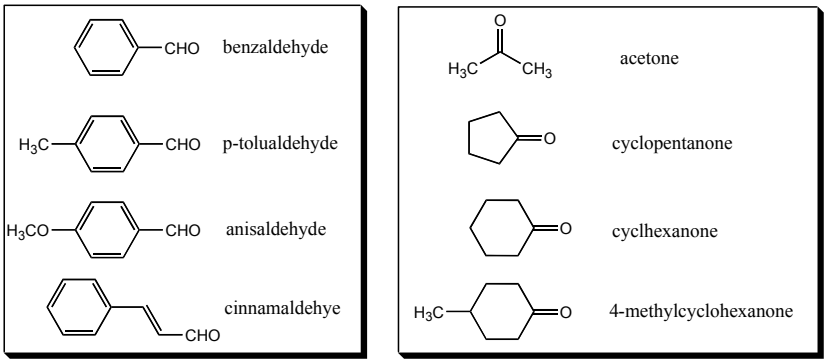
Procedure

- In a 13 x 100mm Pyrex tube, place 200mg of tetraphenylcyclopentadienone and 100mg of diphenylacetylene. To this tube, add about 1mL of silicone oil.
- Clamp the test tube at a 45° angle, with the open end pointing away from your face and any neighbors. You must wear safety goggles at all times today!
- Bring the mixture to a boil over a 3-5min period, the heating with micro-burner flame. On melting, the reagents dissolve in the hot oil to yield a dark purple-red solution. Continue to heat the mixture gently for another 10min. During this time, the product will begin to separate from the solution as a tan solid.
- Let the test tube cool to room temperature on it's own. (do **not** cool it with a wet towel!) Add 4mL of hexane, with stirring, to dilute the oil and dissolve any unreacted starting material.
- Collect the solid with a Buchner or Hirsch funnel and suction filtration. Wash the product with a few mL's of hexane.
- Record the weight and calculate a percent yield.

Exp #27 – Aldol Condensations

The aldol reaction is an extremely useful and general reaction that is fairly easy to perform. In today's lab, every student will perform a different aldol reaction and obtain a different product.

Crude yields for these reactions are often in the 30-80% range, with crude products of fairly good purity.



Mix them up! Pick one aldehyde and one ketone. Make sure you draw the structure of *your* product. Remember that there are 16 possibilities!

Generic Procedure

In a 125-mL Erlenmeyer flask are placed the ketone (1.0 mL), the aldehyde (3.2 molar equivalents), 95% ethanol (20 mL), and 2M aqueous sodium hydroxide (15 mL). The flask is stirred or gently shaken at room temperature for 15 min or until no more precipitate is formed. In some cases, no precipitate may have formed. These can be allowed to stand with occasional stirring or shaking (2-3 h may be needed for completion) or heated on a steam bath [ed. note: 100ºC] for 15 min, then cooled in ice and the product collected by suction filtration. The product is washed consecutively with ice-cold, 10 mL portions of (1) 95% ethanol, (2) 4% acetic acid in 95% ethanol, and in (3) 95% ethanol. If the product is no to be recrystallized, it is allowed to dry, then it is weighed and a melting point taken. If some or all of the product is to be recrystallized, then solubilities in 95% ethanol and toluene should be checked and the better solvent used.

Sign up sheet ! Please select one "box"…
Don't double up until every box is taken once!

	Acetone	Cyclopentanone	Cyclohexanone	4-methylcyclohexanone
Benzaldehyde				
Tolualdehyde				
Anisaldehyde				
Cinnamaldehyde				

Exp #28 – The Synthesis of NMP, a Fluoxetine (Prozac®) Precursor

By Daniel M. Perrine, Nathan R. Sabanayagam, and Kristy J. Reynolds

CAUTION! 3-Dimethlyaminopropiophenone (**1**) is a toxic irritant. Sodium borohydride is a flammable solid and corrosive. Ethyl alcohol and 4-chlorobenzotrifloride (**3**) are flammable liquids and irritants. Sodium hydroxide, hydrochloric acid, and oxalic acid are corrosive and toxic. Potassium *tert*-butoxide is corrosive. *N*,*N*-Dimethlyacetamide is an irritant. Ether is a flammable liquid and toxic. Oxalic acid is toxic. The toxicity of **2, 4,** and **4ox** are unknown (**Ins 1**).

Introduction

Fluoxetine, **5**, is the international nonproprietary, or generic name for Eli Lilly's Prozac, an antidepressant drug which was introduced in 1986 as the first in the class of selective serotonin reuptake inhibitors (SSRIs). Other more recent drugs in this class include Zoloft and Paxil. SSRIs are notable for having a much wider margin of safety and lower incidence of side effects than earlier antidepressants like the tricyclics (Tofranil, Anafranil). Fluoxetine (Prozac) is one of the most widely used (and most profitable) drugs of all time. In the original patent of Molloy et al. (1982), Prozac was synthesized by removing a methyl group from **4** (**Ins 2**) [**Fig. 1**]

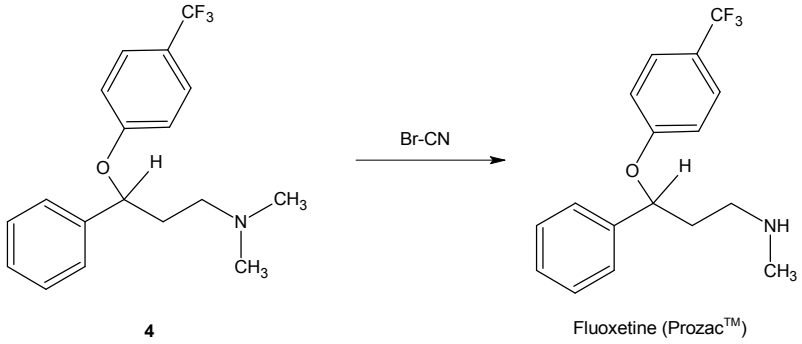


*Fig. 1 - Demethylation of **4** forms Fluoxetine (This step is not done in this lab!)*

We will synthesize **4**, which is *N*-methyl-Prozac (NMP)—i.e., Prozac with an extra methyl group on the amine nitrogen. NMP is of interest in itself, since it is nearly as active an SSRI as fluoxetine and is probably a prodrug for fluoxetine—i.e., it is metabolized in vivo to fluoxetine by *N*-demethylation. In our experimental procedure we will synthesize **2** the first week using sodium borohydride to reduce 3-N,N-dimethylaminopropiophenone. **[Fig. 2]**

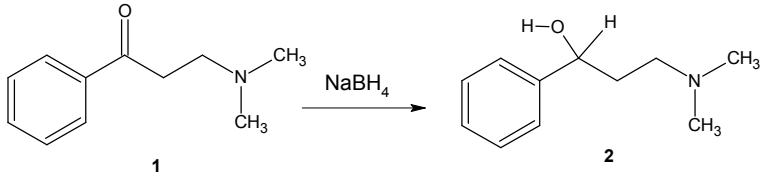


Fig. 2 - Reduction of an aryl ketone with sodium borohydride

In the second week to synthesize NMP, which we will isolate as the oxalate salt, **4ox**. **[Fig. 3]**

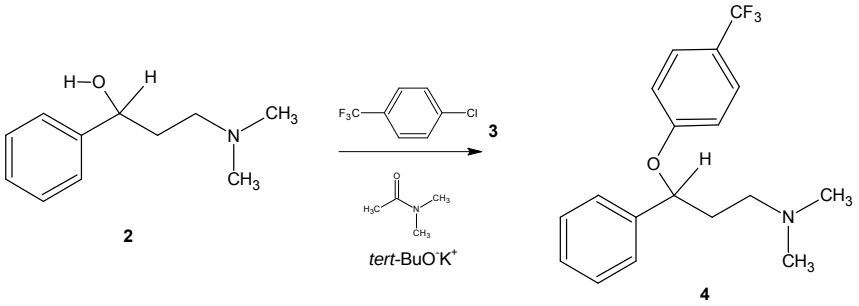


*Fig. 3 - Nucleophilic aromatic substitution of a substituted benzene with the alkoxide of **2**.*

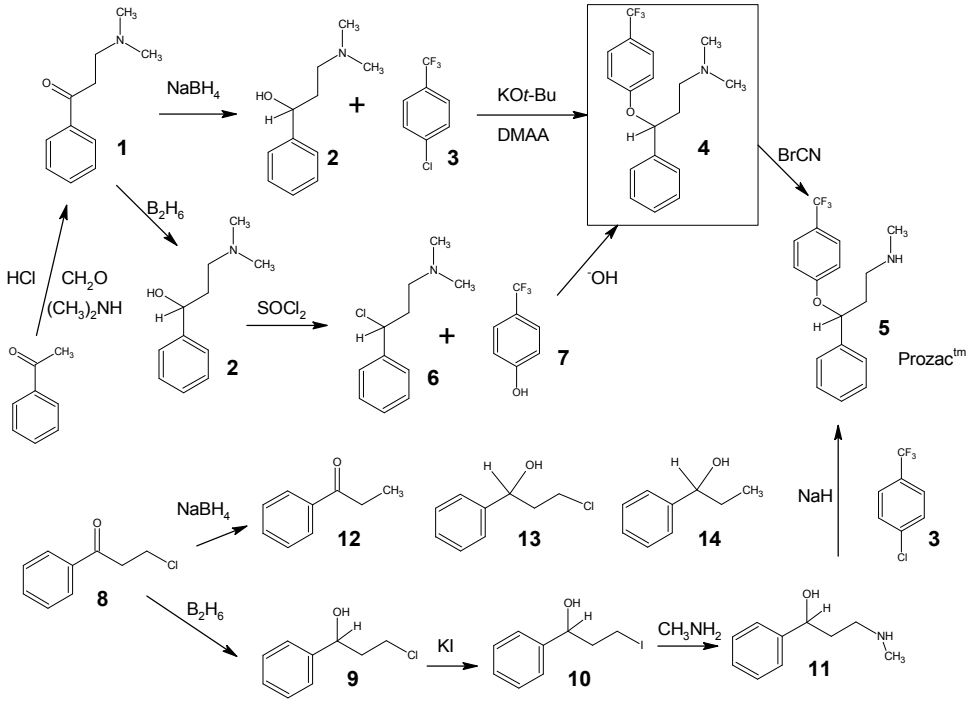


Fig. 4 - Various synthetic routes to Prozac[tm].

WEEK ONE

Synthesis of 2: (±)-3-(dimethylamino)-1-phenylpropanol. Weigh 2.00 g of 3-dimethylaminopropiophenone hydrochloride (the amine salt of the free base **1**) into a 100 mL beaker. Place the beaker on a magnetic stirrer, add a 1/2-in magnetic stir bar and 10 mL of water to the beaker, and stir to dissolve. Then add (with stirring) sufficient 10% NaOH (about 5-6 mL) to bring the solution to pH > 10. The free base of **1** will form and come out of solution as a milky oil. With continued stirring, add enough 95% EtOH (about 9-10 mL) to dissolve the free base of **1** and to form a clear solution again. In a vial or small beaker make 10 mL of water basic with 3 drops of 10% NaOH; add 0.40 g of $NaBH_4$ and stir to dissolve (Student Note 1). Add this $NaBH_4$ solution with stirring to the beaker containing **1**. Allow the reaction to stir for 15 min to ensure a complete reaction (**Ins 3**).

Cautiously *(vigorous evolution of hydrogen gas!),* with continued stirring, make the mixture acidic by dropwise addition of 6.0 *M* hydrochloric acid. (This destroys the excess $NaBH_4$. About 5 mL will be needed; add the acid until the "fizzing" stops.)

You now have an aqueous solution of the hydrochloride salt of **2**. We will need **2** in its free base form in order to couple it with **3**; to form the free base, make the solution basic again to pH > 10 with 10% NaOH. (About 15 mL will be needed to make the solution neutral, and a further 5-7 mL will be needed to bring the pH to >10.) Stir in a few chips of ice to cool the mixture to room temperature, and transfer the solution to a separatory funnel. Add 20 mL of diethyl ether, shake well *(pressure can develop!)* allow the layers to settle, and separate them. Reserve the upper ether layer in a beaker and extract the lower aqueous layer with an additional 10 mL portion of ether; add the second ether extract to the beaker containing the first ether extract. Discard the aqueous layer and dry the combined ether extracts over anhydrous $MgSO_4$ and (to ensure no $MgSO_4$ is transferred) filter the ether solution through a loose cotton plug in a funnel into a 250 mL RB flask containing a 1/2-inch stirbar.

Use a simple distillation apparatus (Claisen adaptor, thermometer, condenser; *flammable vapors!*) with magnetic stirring to remove the ether (**Ins 4**). Most of the ether will distill over near its bp of 36ºC; continue the distillation until the temperature of the distilling solvent is about 55-60ºC, at which point about 30 mL of ether should have been collected. The colorless oil which remains behind in the RB is ***(±)-3-(dimethylamino)-1-phenylpropanol,* 2**, along with some residual ether. Leave the stirbar in the flask, stopper it with a ground-glass stopper, and keep it in your drawer for use in the next lab. Depending on the amount of residual ether, on standing for a few days at cool temperatures, **2** may solidify to a waxy white solid with a mp slightly above room temperature, but whether this occurs or not will not affect the next step in your synthesis of NMP (**Ins 5**).

WEEK TWO

Synthesis of 4 (NMP): (±)-N,N-dimethyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine

(Student Note 2) To the 100 mL RB containing **2** and a 1/2-in stir bar, add 4 mL of 4-chlorobenzotrifluoride, **3**, and 30 mL of dimethylacetamide (Student Note 3). With stirring, add to this mixture 30 mL of 1.0 *M* potassium *tert*-butoxide *(caustic alkali!)* in *tert*-butyl alcohol (Student Note 4). Using a simple distillation apparatus, distill the mixture slowly, with stirring, over a 15-20 min period, until the temperature of the refluxing solvent mixture reaches 150ºC (**Ins 6**). Remove the heating mantle and disconnect the RB (*hot! use a towel!*) from the distillation apparatus. Cool the RB by briefly immersing it in a cold water bath or a stream of running water. Add 40 mL water and 30 mL ether to the RB, swirl to dissolve, remove the stirbar, and pour the contents of the RB into a 250-mL separatory funnel.

Shake well, allow the layers to separate, and drain the lower, aqueous layer into a 100 mL beaker. Transfer the upper, ether layer into a separate 100 mL beaker. Return the water layer to the separatory funnel, add 10 mL fresh ether, shake and separate, again reserving the lower layer but combining the ether layer with the previous 30 mL extract. Return the water layer to the separatory funnel and extract it a third time with 10 mL fresh ether. Discard the aqueous layer. Pour the ether extracts back into the separatory funnel and add 25 mL water. Shake well, allow the layers to settle, and discard the lower, aqueous layer. Add a final 25 mL water to the separatory funnel, and again shake well, allow the layers to settle, and discard the lower, aqueous layer. (If the aqueous washings are still cloudy at this point, add another 25 mL water to the ether solution in the separatory funnel, and once again shake well, allow the layers to settle, and discard the lower, aqueous layer. Repeat this process until the lower, aqueous layer is completely clear.) Dry the ether solution with anhydrous $MgSO_4$, and filter it through a funnel containing a cotton plug (to exclude any residual $MgSO_4$) into a dry dropping funnel (**Ins 7**).

Synthesis of 4ox, the oxalate salt of NMP

Dissolve 0.85 g of anhydrous oxalic acid (**Ins 8**) in 15 mL absolute ethanol in a 100-mL beaker. Place a magnetic stirbar in the solution and put the beaker on a stirring apparatus beneath the dropping funnel. With good stirring, allow the ether solution of NMP to drop into the acid solution in the beaker until the first permanent insoluble precipitate forms (Student Note 5). Usually this is a flocculent white material. Stop the addition of NMP at this point and stir the contents of the beaker for a few minutes. The precipitate will slowly grow in bulk; when formation of new precipitate has stopped, continue adding the NMP-ether solution from the dropping funnel with stirring. If necessary to maintain stirring, add additional 5-mL aliquots of absolute alcohol to the beaker. When all the NMP solution has been added, remove the stir bar from the beaker and allow the product to digest for 5 minutes in an ice bath.

Collect the crystals of **4ox** by vacuum filtration using a Büchner funnel. Wash them with ether and allow them to air dry in your drawer overnight (**Ins 9**). Report the mass and the melting point. This material *sinters* (softens) a few degrees before its actual melting point, which is between 120 and 150ºC (**Ins 10**).

Notes for the Student

Note 1. If the water is neutral or acidic, the sodium borohydride will rapidly react with it forming hydrogen gas. Note that the product of this borohydride reduction is the ± or racemic form (hydride is delivered to the ketone randomly from either side), and consequently the final NMP (and Prozac® itself) are likewise racemates.

Note 2. This coupling reaction of **2** with **3** is an example of a *nucleophilic aromatic substitution* (also known as the S_NAr mechanism). The alkoxide ion of **2**, formed by deprotonation of **2** by the strong (and strongly hindered) base K *t*-butoxide, can displace the Cl from the benzene ring only because of the presence of the electron withdrawing CF_3 group. (The trifluoromethyl group functions like the nitro group in this reaction)

Note 3. The dimethylacetamide (DMAA) has a bp of 165ºC. Ether boils at 34.6ºC, *t*-butyl alcohol at 83.0ºC , and 4-chlorobenzotrifluoride (**3**) at 137ºC. The coupling reaction of **2** with **3** probably occurs in DMAA as solvent at a temperature > 100ºC. The purpose of the distillation to 155ºC is twofold: to ensure that a high enough temperature is achieved for (rapid) coupling and to remove as much ether, *t*-butyl alcohol, and excess **3** as possible, simplifying the workup.

Note 4. The potassium *t*-butoxide is in about 2.5 molar excess to ensure complete deprotonation of alcohol **2**. Try to make the addition of this base as rapid as possible, avoiding exposure to moisture or air; if too much water is present, the coupling of **2** and **3** will not take place. On the other hand, a s*lower* distillation of the reaction mixture, particularly in the range from 100-150ºC, seems to favor a more complete reaction and a purer product.

Note 5. The free base of **4** and oxalic acid are both soluble in ethanol and in ether; the oxalate salt **4ox** is soluble in alcohol but very insoluble in ether. Without addition of the alcohol, the crystallization will occur too rapidly, and very fine crystals are formed which clog the filter paper.

Notes for the Instructor

These Notes are keyed to (**Ins #**) *within the "Instructions to the Student" document.*

Ins 1 The toxicity of **2** and **4** is not known, but is likely to be quite low. While oxalic acid is poisonous in large quantities, it occurs in the leaves of many edible plants, particularly rhubarb. It is probably a good idea (in order to disabuse any student adventurers who might imagine that consuming their product would give them some sort of a "high") to emphasize that antidepressants are *not* euphorigenic, i.e., they will not make you "feel good" if you are not already depressed any more than aspirin will make you feel better if you don't have a headache. (Even if a person is psychologically depressed, antidepressant drugs begin to help only after they have been taken daily at their regular dosage—which for fluoxetine is about 20-60 mg—for a minimum of two weeks; a one-time dose has no effect.)

Ins 2 The patent uses the von Braun reaction to remove the methyl group. This procedure involves reacting **4** with cyanogen bromide, CNBr, to eliminate MeBr and replace the *N*-methyl group with an *N*-cyano group (a cyanamide) which can then be easily hydrolyzed to the carbamate and eliminated. (See March, J. *Advanced Organic Chemistry*, 4 ed.; Wiley: New York, 1992; pp 436-437.) Other, less hazardous reagents for removing one of the methyl groups, such as ethyl chloroformate, could be used in an advanced laboratory for the synthesis of Prozac from NMP.

Ins 3 It is easy to monitor the course of this reaction by noting the disappearance of the ketone stretch in the IR at 1676 cm . We found it was invariably over in 10 minutes.

Ins 4 If students have access to a rotary evaporator, the ether can be removed from a tared flask and the yield for this stage of the reaction calculated.

Ins 5 A sample recrystallized once from MeOH/HOH had a melting point of 40-42ºC; the one reference we were able to find to the *racemic* material, like ours, was recrystallized from pentane, mp 46-47ºC (*12*). For the purpose of this experiment, using the crude oil for the next step is perfectly satisfactory.

Ins 6 The purest product by mp and GC-MS seemed to come from the students who distilled the reaction mixture fairly slowly, perhaps allowing time for the reaction. (Better results might be obtained by stopping the distillation when the distillate is above 100ºC and refluxing 5-10 minutes.)

Ins 7 The desired product is usually contaminated by unreacted **2**, as well as the excess of **3**. (All the literature methods upon which we modeled this step used an excess of **3**. When we attempted to run the reaction with a molar equivalent, the reaction failed to reach completion.) The presence of **3** is not a great problem, since it will not form an oxalate salt in the final step and is thus easily separated from the product **4ox**. However, **2** can form an oxalate salt which will make purification and isolation of **4ox** much more difficult. Fortunately, **2**, which is both an alcohol and an amine, is much more soluble in water than is **4**, an ether and an amine. We found that adequate washing of an ether solution of **4** contaminated with **2** resulted in complete elimination of **2** with no significant loss of **4**.

Ins 8 0.85 g of anhydrous oxalic acid is a rounded equivalent of the amount calculated on the basis of a 100% conversion of the 2.0 g of starting 3-dimethylaminopropiophenone hydrochloride into NMP free base (a most unlikely event). The anhydrous acid is preferable to the dihydrate. Isopropyl alcohol would probably be an acceptable substitute for absolute ethanol. Methanol is not a good choice, since the product is too soluble in it. Generally, amine salts are best formed under anhydrous conditions, hence the use of the anhydrous oxalic acid and the absolute ethanol. It is better to add the ether solution to the acid rather than the other way around: on reverse addition it forms a material which filters very poorly.
This may be because a mixture of the dibasic and the monobasic salt is formed when excess base is present or because the product is so insoluble in ether that a microcrystalline solid is formed which clogs the filter paper.

Ins 9 The oxalate salt takes some time to dry to constant mass. It appears very bulky and copious when first collected, but shrinks considerably on drying. The highest yield our students obtained by this procedure was about xx g (xx% based on the initial Mannich base hydrochloride).

Ins 10 The actual melting point is 1xx-1xxºC, but most student samples will melt from 115-130ºC. A sample which was twice recrystallized from an EtOH/EtOEt solvent mixture melted at the 1xx-1xxºC (with no decomposition noted up to 1xxºC), and was sent to Quantitative Technologies Inc for analysis. *Calc:* C 58.11, H 5.36, N 3.39, F 13.79 %. *Found:* C 58.02, H 5.41, N 3.46, F 13.52%. The only literature data on this compound are the mp and % elemental analysis which appear in the Eli Lilly patents, and both (mp "117-119ºC with decomposition," "calc. ... H 3.36. . . Found . . . H 3.49") seem to contain errors or typos (*2*). I (DMP) called Eli Lilly and spoke to Dr. Bryan Molloy as we were developing this laboratory exercise, which he found to be pedagogically interesting. But when the issue of this melting point and percent composition came up, he apologized, saying he had to discontinue the conversation because he was under orders from the company's lawyers not to discuss the matter due to pending litigation. A subsequent search of the Web disclosed that Barr Laboratories is challenging Lilly's Prozac patents http://www.barrlabs.com/prozac.htm); I had not been aware of this. The recrystallized material with melting point noted above was transformed to the free base and had the following spectral data: FTIR: 1616, 1510, 1460, 1330, 1110, 1060, 836 cm ; HNMR (60 MHz, CDCl) * 1.9-2.2 [10H, m, N-(C*H*) , N-C*H* -C*H*], 5.2 (1H, t, *J* = .5 Hz), 6.8-7.4 (9H, m, Ar*H*). MS *m/e* 324 (M + 1 , 1.2%), 323 (M , 6.5%), 58 (Me NCH , 100%). A sample was sent to Spectral Data Services for C DEPT NMR analysis: C NMR (91 MHz, CDCl) * 160.5 (C), 141.0 (C), 128.6 (CH), 127.6 (CH), 126.5 (CH), 125.7 (CH), 122.8 (C), 124.3 (q, *C*F , *J* = 267 Hz), 122.5 (q, *C*-CF , *J* = 30 Hz), 115.7 (CH), 78.5 (CH), 55.7 (CH), 45.5 (CH), 36.8 (CH).

Literature references

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