ORGANIC CHEMISTRY LABORATORY EXPERIMENTS
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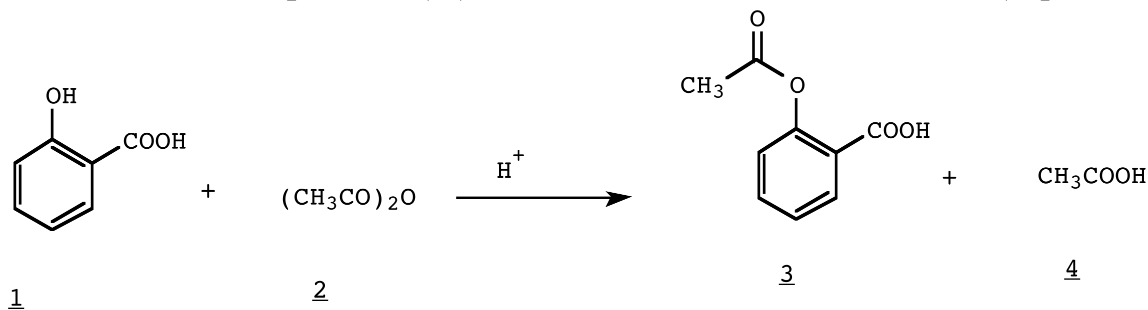
ORGANIC CHEMISTRY 121
EXPERIMENT 1
SYNTHESIS OF ASPIRIN FROM SALICYLIC ACID

Aspirin is one of the oldest and most common drugs in use today. It is both an analgesic (pain killer) and antipyretic (reduces fever). One method of preparation is to react salicylic acid (1) with acetic anhydride (2) and a trace amount of acid (equation 1).



The chemical name for aspirin is acetylsalicylic acid (3)

PROCEDURE
Place 3.00 g of salicylic acid in a 125 ml Erlenmeyer flask. Cautiously add 6 ml of acetic anhydride and then 5 drops of concentrated H_2SO_4. Mix the reagents and heat the flask in a beaker of water warmed to 80-90°C, for 10 minutes. Remove the Erlenmeyer flask and allow it to cool to room temperature. Add 40 ml of H_2O and let the sample crystallize in an ice-water bath.* Filter and wash the crystals with cold water. Allow them to air dry overnight and weigh the product. What is the percent yield?

One drawback to this synthetic procedure is that there is the possibility of some left over salicylic acid. To test for unreacted salicylic acid, add a few drops of 1% ferric chloride solution to a tube containing a few mg of salicylic acid dissolved in water. What do you observe? Do the same for a few mg of your sample dissolved in water. Is there any salicylic acid?

Write-Up: As soon as you are finished write this lab report in your notebook as a "normal" lab write-up and hand it in. You will also need to draw and label the chemical reaction using the software available on the CNS network. Staple or tape this in your write-up.

* A problem with this procedure is that very often crystals do not initially form. One gets a viscous oil that will eventually solidify. If you get an oil, stir it with a glass rod while it is in the ice bath. For the best results make sure that the glass rod is "scratching" the flask's surface.

MELTING POINTS AND SUBLIMATION

MELTING POINT

The temperature range at which a crystalline solid changes into a liquid is defined as the melting point. To obtain the melting point of a compound, a small sample is slowly heated. The sample is carefully observed (usually through a small tube) and the temperature at which liquid is first observed is noted. When all of the solid has liquified, this temperature is noted as well. In most instances a sample will melt over a small range of temperature. Thus the temperature at which the liquid is first observed and the solid is totally liquified is referred to as the **melting point range**. Most pure samples melt over a very small (<1°) temperature range while some samples may melt over a couple of degrees. In general, samples that melt over a broad range (>5°) probably have soluble impurities which depress the melting point. Consequently, the melting point range of a compound can be an indication of purity.

SUBLIMATION

Sublimation is a process by which a compound goes from a solid to a gas without going through a liquid phase. Most of you have observed this process when you have seen "dry ice" ($CO_{2(s)}$) or "freeze dried" a substance. Many organic compounds "sublime" at readily accessible temperatures and pressures which gives us a route to a simple and quick purification.

PROCEDURE

(Since we only have a limited number of melting point apparatuses, some of you should do the sublimation first and melting point second.)

1) Melting point

A) Obtain a small sample of **cinnamic acid** or **urea** and obtain its melting point range. Repeat the process with another sample. Compare the melting point you recorded to the melting point in the literature.

B) Take a "mixed melting point" of one of the cinnamic acid / urea mixtures provided. What do you observe?

2) Sublimation

Obtain a 50 mg sample of salicylic acid and place it into the side arm Erlenmeyer flask from your microscale kit. Assemble the apparatus as depicted on page 212 of Zubrick or shown in the lab demo. Fill the centrifuge tube with ice. Heat the flask gently on a heating mantel. You should observe the solid evaporating into "whiffs" of gas and condensing as a solid on the cold surface of the centrifuge tube. (This is often referred to as a "cold finger")

Carefully disassemble the apparatus so as not to dislodge any solid on the cold finger. Scrape the solid off the cold finger and weigh it. Calculate the % recovery.

Compound Purification: Recrystallization

Purification of compounds that are either synthesized in the lab or that have been isolated from sources in nature is a very important part of organic chemistry. A variety of methods may be used including distillation, sublimation, extraction, different kinds of chromatography and recrystallization. The basic process of recrystallization involves dissolving the substance in a solvent to remove insoluble impurities then letting the desired compound crystallize.

Products obtained from an organic reaction are seldom pure when isolated directly from the reaction mixture. If the product is solid, it may be purified by recrystallization from a suitable solvent. A good recrystallization solvent should dissolve a moderate quantity of the substance to be purified at elevated temperatures but only a small quantity of the substance at lower temperature. It should dissolve impurities readily at low temperatures or not at all. Finally, the solvent should be readily removed from the purified product. This usually means that it has a relatively low boiling point. A chemist can consult the literature for information regarding recrystallizing solvents for a particular substance, or if that information is not available, test several solvents. A small amount of the substance to be recrystallized is placed in several test tubes and a small amount of a different solvent is added to each. Solubility is then noted both at cold and elevated temperatures. The quality and quantity of crystals obtained when the solution is cooled are also noted. To get a good yield of purified material, the minimum amount of hot solvent to dissolve all the impure material is used. In practice 3-5% more solvent than necessary is used so the solution is not saturated. If the impure compound contains traces of colored material that are not native to the compound, they may be removed by adding a small amount of decolorizing charcoal to the hot solution, quickly filtering it and allowing it to crystallize. Usually crystallization spontaneously occurs upon cooling the solution. If it does not, crystallization may be induced by cooling the solution in an ice bath, scratching the vessel wall with a glass stirring rod or by adding a single crystal of pure material (a seed crystal). The crystals are then isolated using vacuum filtration. The collected crystals are then washed with ice cold solvent to further remove impurities.

Procedure

Solubility Tests

Place about 10 mg of anthracene into each of 4 reaction tubes or micro test tubes. Weigh out the 10 mg quantity until you are familiar with the appearance (size) of approximately 10 mg of sample. Once familiar with 10 mg as a small pile on the end of your spatula, you may estimate the amount and not weigh it out. Add 0.25 mL of ethanol to tube 1 and observe the mixture. Repeat with water (tube 2), toluene (tube 3), and ligroin (tube 4). The sample is considered dissolved when the solution is clear with no cloudiness or solid apparent. A solution of dissolved solute may have color; it is still considered dissolved if no solid is apparent. If you observe any solid on the bottom of the tube, floating on the top of the solvent, or dispersed in the solvent (cloudy), the sample is considered not to have dissolved.

If the samples dissolve in a solvent at room temperature, you do not need to heat the sample in the next step. If the sample readily dissolves in ethanol at room

temperature, add one or two drops of water to see if cloudiness (precipitate) forms. Continue adding one or two drops of water and checking for precipitation until you have added 10 drops total.

For those samples which did not dissolve in a solvent at room temperature, gently heat the mixture on the steam bath and observe if the sample dissolves in hot solvent. Pay particular attention to the ligroin mixtures. Ligroin has a low boiling point and can be easily boiled away completely. If you boil away a solvent, simply add the 0.25 mL again and continue.

Repeat the experiment with [4-amino-1-naphthalenesulfonic acid, sodium salt] and then again with benzoic acid.

Record your observations in your notebook. Did the sample dissolve in a solvent at room temperature? Did the sample dissolve in hot solvent? Did the sample precipitate (crystallize) upon cooling of the solvent? Recording this data in table form works best.

Microscale Recrystallization of acetylsalicylic acid from water.

Calculate the required minimum volume of hot water to dissolve 60 mg of acetylsalicylic acid. The solubility of acetylsalicylic acid in 25° C water is 1.0g/300 mL. The solubility of acetylsalicylic acid in 37° C water is 1.0g/100 mL. <u>Aspirin will hydrolyze in boiling water, so do not heat the recrystallization solution very long.</u> Heat until you just see thermal gradients (wavy heat lines) or bubbles begin to form. Use the aspirin solubility at 37° C for your hot solubility calculation and reduce the solvent volume by 1/3 to 1/2 (we are guessing at the higher solubility of aspirin in 100° C water).

Place the 60 mg of acetylsalicylic acid in a reaction tube and add the required minimum volume of water calculated above. Add a boiling stick and begin gently heating on the sand bath. As the solvent begins to boil (see above), add water dropwise until the sample just dissolves. Add 1 more drop of water. Record the total volume of water needed to dissolve the sample (21 drops = 1 mL) Remove the solution from the heat and place in the test tube holder to cool to room temperature undisturbed.

If crystals have not formed upon cooling, scratch the side of the reaction tube with a glass stir rod. If crystals still do not form, ask your instructor for help on the next steps to take.

Once crystals have formed, place the reaction tube in an ice bath and allow crystallization to complete. Once the reaction tube is ice cold and no further crystallization is occurring, proceed with the following isolation steps.

Place the tip of your Pasteur pipette firmly on the bottom of the reaction tube. Not so firmly as to break the pipette stem. Draw the solvent away from the crystals leaving as many crystals as possible. There should be very few crystals in your pipette stem. If too many crystals enter the pipette, use the vacuum filtration apparatus with the Hirsch funnel to isolate your crystals. The Hirsch funnel and vacuum is also a good way to pre-dry your crystals.

Complete the drying of the crystals by attaching the reaction tube containing the crystals to an aspirator apparatus set up gently heating over a steam bath while the crystals are under vacuum. All visible solvent must be removed before using the aspirator drying technique. Remove the crystals from the reaction tube by scraping with a

spatula and complete the drying in the lab drying oven if necessary. Weigh the dry crystals. Obtain a melting point of dry crystals and of the crude starting mixture.

Recrystallization of naphthalene from 80% methanol/water

Recrystallize naphthalene (40 mg) from the mixed solvent 80% methanol/water. You will not calculate the minimum volume of solvent needed for this experiment, therefore you will measure it as the experiment proceeds.

Place 40 mg of naphthalene in a reaction tube and add 5-10 drops of the mixed solvent, just enough to cover the crystals. Add a boiling stick and begin gently heating over the steam bath. Add solvent dropwise as the mixture warms to boiling. The methanol is relatively low boiling, so it will be easy to boil off your solvent if you heat too strongly, pay attention and heat gently. Once all of the crystals have dissolved, add one more drop of solvent and remove from the heat. Record the total volume of solvent used (21 drops = 1 mL). Place the reaction tube in a test tube stand and allow to cool to room temp undisturbed. Follow the normal procedure if crystal growth does not occur.

Once crystals are observed, place the reaction tube in an ice bath and allow crystallization to complete. Remove the solvent by pipette as previously described. Scrape the crystals onto filter paper and allow them to air dry for 10-15 minutes. Do not heat the crystals as naphthalene will sublime. Do not dry the crystals in the drying oven for the same reason. Do not air dry naphthalene for prolonged periods (days) or you will lose your product to sublimation. If you need to store naphthalene, do so in a screw top vial to prevent product loss. Once the naphthalene is dry, weigh the crystals and determine the melting point.

Recrystallization of an Unknown

Dissolving the impure substance.

Measure the solubility properties of your unknown using 10 mg samples and water, ethanol, and methanol. Determine the appropriate solvent to recrystallize your unknown. Keep in mind that your unknown will have insoluble impurities. Not all material will dissolve. Look for differently colored material that does not dissolve. This is insoluble impurity and does not affect your decision of the appropriate solvent for recrystallization.

Accurately weigh out approximately 1.0 g of impure unknown. Place your unknown in a 50-125 mL Erlenmeyer flask and add your chosen solvent dropwise until the crystals are just covered with solvent. Begin heating using a hot plate until the solvent is boiling gently. Add solvent dropwise until the crystals dissolve. Insoluble impurties will not dissolve. These impurities may have a different color or different crystal type than your unknown which makes up the bulk of the crystals. Once the crystals have just dissolved, add 5% more solvent. Record the total volume of solvent used (21 drops = 1 mL).

Remove the insoluble impurities

Filter the hot solution by gravity filtration using fluted filter paper and the apparatus described in chapter 13 of your techniques. The plastic funnel should be heated on your steam bath until just before use. Hot solvent should be available at this time. The receiving Erlenmeyer flask should also be heated either on the steam bath or

hot plate (add a small amount of solvent to the flask if you use the hot plate). Place the fluted filter paper into the hot plastic funnel. Place the filter paper and funnel onto the heated receiving Erlenmeyer flask which should be setting on a ceramic disk just prior to use. Poor the hot recrystallization mixture as quickly as possible into the fluted filter paper. Use a clamp (burette or universal), paper towel ring, or other suitable means to avoid burning your fingers as you poor the hot solution. Allow the solution to drain through the paper. Poor a small volume (no more than 1-2 mLs) of hot solvent through the paper to dissolve any crystals that have precipitated in the paper or funnel.

Cooling the solution

Cool the solution to room temperature and then place the flask in ice water. Do not rush this process as the material may form very small crystals that are difficult to collect or form an oil in the recrystallizing solvent instead of crystals. Follow the normal procedure if crystal growth is not observed upon cooling.

Collect the crystals

When it doesn't appear that any more crystals are forming, wait 5 more minutes and then collect the crystals using a vacuum filter apparatus. Swirl the flask to suspend the crystals and then pour the slurry into the funnel (make sure that the vacuum is going!) Wash the crystals with a very small amount of ice cold solvent. The liquid that is in the vacuum flask is referred to as the mother liquor. Allow the crystals to dry with the vacuum on for several minutes. During this time, crystals may be observed forming in the mother liquor. These crystals are known as the second crop of crystals and are usually formed as the solvent in the vacuum flask evaporates and gets colder. Additional crops of crystals may form depending on the substance and solvent. We will not be collecting second crops of crystals. Estimate the amount. You will need to refer to this amount in your conclusion section when discussing potential points of loss in the experiment. Dry the crystals in the oven unless otherwise instructed by the lab staff. After the crystals are dry, determine the final weight.

Determine the melting point of your unknown and consult the charts on the bulletin board to identify your unknown. A mixed melting point would be appropriate at this time to confirm your identification, but we will not do this to save time and materials.

Pre-Lab Questions

1. What is the purpose of recrystallization?

2. What properties should a solvent have to be a good recrystallization solvent for a particular compound? Under what conditions is a mixed solvent appropriate?

3. Why is vacuum filtration preferred to gravity filtration for product isolation in a recrystallization? Why is gravity filtration, and not vacuum filtration, used to filter suspended (insoluble) impurities during hot filtration?

4. Assuming that sand and sodium chloride were the impurities in a sample of acetanilide, tell whether each was a soluble or insoluble impurity in the solvent system (water) and describe how each was removed from the acetanilide during recrystallization.

5. A sample of naphthalene (white when pure) was found to be grayish after a complete recrystallization (no steps omitted). What accounts for the gray color?

6. What is the purpose of fluting filter paper?

7. Why are stemless funnels preferred for hot filtrations?

Distillation Experiment

Distillation is the most common method used to separate and purify liquids. The process consists of heating a liquid to its boiling point and conducting the vapors to a cooling device where they are condensed. The condensate is then collected.

The vapor pressure of a liquid is defined as the pressure that is exerted by a liquid at a given temperature. This force is due to the molecules escaping from the liquid's surface into the gas phase. The vapor pressure of a liquid increases with increasing temperature. The boiling point of a liquid is that temperature at which the vapor pressure is equal to the pressure of the surroundings. If a flask is open to the air, the vapor pressure at the boiling point is equal to the atmospheric pressure. The boiling points of many liquids are listed in the literature referenced to 760 mm Hg (standard pressure). The boiling point of a liquid at a different pressure can then be determined by using a Pressure-Temperature Alignment Chart.

The boiling point of a liquid is determined by placing a thermometer in the vapor. The temperature of the vapor will remain constant throughout the distillation if the vapor is pure. The boiling point at a given pressure is a characteristic property of the pure compound just as the melting point of a pure crystalline compound.

If a mixture of two miscible liquids with different boiling points is heated to boiling, the vapor will not have the same composition as the liquid; it will be richer in the more volatile component. In order to obtain pure components, the now enriched mixture must be redistilled. Each successive distillation results in a purer distillate of the lower boiling component until the pure component is obtained. A fractionating column is a device for increasing the efficiency of the distillation process. It consists of a vertical column packed with inert materials or with indentations which increase the surface area of the column. As the hot vapors of the liquid rise, they condense on the greater surface area. As the condensate flows back down to the boiling flask, the liquid is revaporized as it comes in contact with the hotter portion of the lower column. This is repeated many times, until the final distillate is nearly pure. By using select columns, liquids with boiling points just 2° C apart can be separated.

Some liquid mixtures do not form nearly ideal solutions (as described in the preceding section), but instead form a constant boiling solution that is a constant mixture of components. This is known as an azeotrope. An example of an azeotrope is water and ethanol. A solution of 95.6% ethanol and 4.4% water will boil at 78.2° C and the distillate will have the same composition. The boiling point of the azeotrope is lower than ethanol (78.3° C) or water (100° C).

In this experiment you will separate a nearly ideal solution of cyclohexane (bp 81° C) and toluene (bp 111° C) using simple and fractional distillations. In addition you will do the experiments using the "traditional" glassware and using microscale glassware.

Caution!!! No Open Flames

Procedure

Set up the simple distillation apparatus shown in the figures, using a 100 ml round bottom flask if available (use a larger flask if necessary). Very lightly lubricating the ground glass joints with silicone grease is recommended. Pay particular attention to the

placement of clamps in the figures. Also pay attention to the placement of the thermometer in the figures. Proper thermometer placement is critical to accurate temperature readings. Remember, water goes in the lower end of the condensing column and out the higher end. Use rubber bands to secure all of the pieces together, also shown in the figures. The greased joints will tend to slide apart if not secured together. Have your instructor check the apparatus before starting. Be sure to add a boiling chip before heating the solvents. Add 30 mL of cyclohexane and 30 mL of toluene to your distillation flask. Heat the round bottom with the heating mantel until the distillate drops at a regular rate of approximately 1 drop per second. Collect distillate in a graduated cylinder. Record the temperature as the distillate starts to collect in the graduated cylinder. After 3 drops have distilled over, collect into a small vial three drops of the distillate. This is your GC sample "First Drops – Simple". Record the temperature every 2 ml as the distillation proceeds. Stop the distillation when there is still a small amount of liquid in the flask (approximately 50 ml collected in the graduated cylinder). Never distill to dryness! Collect three drops into a second small vial just before turning off the heat. This is your GC sample "Last Drops – Simple". Submit the GC samples for analysis.

Allow the apparatus to cool until it is comfortable to handle. Add the fractionating column to the simple distillation apparatus and adjust the clamping as shown in the fractional distillation apparatus figure. The fractionating column is a condenser column filled with stainless steel sponge. Reuse the cyclohexane and toluene from the simple distillation, simply pour it from your graduated cylinder back into the boiling flask. (Do not discard the pot residue.) Add fresh boiling chips. Repeat the distillation experiment as outlined above, recording temperatures every 2 mL of collected distillate. Collect First (after several drops have run through and the column has been "rinsed") and Last drops of the Fractional distillation experiment as described for the Simple experiment. (Be sure to allow 3 drops to pass through the column before collecting the first GC sample.) Submit the samples "First Drops – Frac" and "Last Drops – Frac" for analysis.

Graph your results. Volume of distillate on the x-axis and temperature recorded on the y-axis. Compare the curves in your conclusions.

Set up the microscale simple distillation apparatus as shown in the figure. Add two mL of cyclohexane and two mLs of toluene along with a boiling chip to the boiling flask. Heat with a sand bath (**do not elevate the sand bath**) until the distillate drops at a rate of 1 drop every 5 seconds. Heating using a sand bath is best controlled by moving sand toward (more heat) and away (less heat) from your boiling flask. Set the Powermite switch at approximately 5 and use a spatula to move sand for fine heating control. Monitoring the volume collected during the microscale fractional distillation is best done by counting drops. Record a temperature every two or three drops.

Repeat the process above using a microscale fractional distillation apparatus. For this experiment be sure to add fresh boiling ships and use new cyclohexane and toluene (2 mLs of each).

Graph your results. Volume of distillate on the x-axis and temperature recorded on the y-axis. Compare the curves in your conclusions.

Questions

1. What is the purpose of the boiling chips?

2. If ideal liquids x and y both have a boiling point of 110° C, what will be the boiling point of a mixture of x and y? Can you separate the two liquids by distillation? How does this limit the value of boiling points as a criteria for determining the purity of liquids?

3. There is a 63° difference in boiling points between heptane and pentane. What is this difference attributed to?

4. What effect is produced on the boiling point of a solution by a soluble, non-volatile substance? What is the effect produced on the boiling point of a liquid by an insoluble substance? What is the vapor temperature above the surfaces of these to liquids?

5. Why doesn't a pure liquid distill all at once when the boiling point is reached?

6. Why is a packed column more efficient than an unpacked column for fractional distillation?

7. Why does slow distillation result in better separation of two liquids than fast distillation?

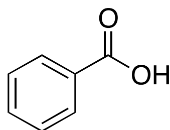
8. Why is it dangerous to attempt a distillation in a completely closed system?

Extraction

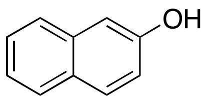
Separation of a Three Component Mixture Using Extraction Techniques

Extraction is a method often used by organic chemists for the rapid crude separation of mixtures containing acidic and/or basic compounds often in the presence of neutral materials. The separation uses acid-base chemistry and two mutually insoluble layers of solvent (water and t-butylmethylether).

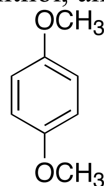
You will be separating 3 compounds: benzoic acid, 2-naphthol, and p-dimethoxybenzene.



benzoic acid



2-naphthol



p-dimethoxybenzene

Determination of a Partition Coefficient

In this experiment, you will extract a dichloromethane solution of benzoic acid with water. Subsequent evaporation of the CH_2Cl_2 layer, and recovery of the remaining benzoic acid will allow you to calculate the partition coefficient of benzoic acid in CH_2Cl_2/water.

Weigh out 100 mg of benzoic acid and dissolve it in a reaction tube containing 1.6 mL CH_2Cl_2. Add 1.6 mL distilled water and mix thoroughly. You may do this by drawing ~1/2 of your solution into your pipette and expelling it into the remaining solution in the reaction tube several times. Alternatively, you may shake the tube after sealing with a sleeve stopper. Set the tube aside and allow the layers to separate. Remove the aqueous layer without removing any organic layer. This requires careful pipette skills. Add anhydrous $CaCl_2$ to the CH_2Cl_2 layer until you do not observe any further clumping of the pellets. Water in the organic layer adsorbs to the pellets, partially dissolving the outer material and causing them to stick together, this is called clumping. You should flick the reaction tube to promote mixing. Do not shake so vigorously that you break the pellets. After 5 minutes of drying time, remove the organic layer by pipette and place in a clean, dry, pre-weighed 10 mL Erlenmeyer flask with a boiling chip. The flask and chip must be pre-weighed. Rinse the pellets twice with about 1 mL fresh CH_2Cl_2 and add these rinses to the Erlenmeyer flask. Evaporate the solvent on a steam bath in the hood to dryness. Weigh the flask with boiling chip and benzoic acid. Use this mass to determine the partition coefficient.

Macroscale Extraction of 3 Component System (Acidic and Neutral)

It is critical that you have prepared a flow chart of the extraction sequence before beginning the experiment. These extractions rely on acid/base chemistry that you have studied in Gen Chem and Org I. Find the pKa's of the compounds and determine the reactions that will occur with the bases used in this experiment. Complete the flow chart outline at the end of the this lab.

Obtain a pre-mixed sample of equal parts benzoic acid, 2-naphthol, and p-dimethoxybenzene. Weigh the sample. Dissolve the sample in a 100 mL beaker with 30 mL of t-butyl methyl ether. Transfer the ether solution to a 250 mL separatory funnel and rinse the beaker with about 10 mL ether to complete the transfer.
Add 10 mL of water to the separatory funnel and note which layer is organic and which is aqueous. Add 10 mL of saturated sodium bicarbonate solution to the separatory funnel. Shake the funnel as depicted on page 121 of Zubrick or the figure below. Be sure to vent several times during the shaking to relieve pressure. Place the separatory funnel back on the iron ring, with the stopcock closed, and remove the stopper. Allow the layers to separate. You want to remove the aqueous layer, which in this case is the lower layer. Drain the aqueous layer into the labeled flask (A). Repeat the sodium bicarbonate extraction with 10 mL fresh solution, draining the aqueous layer into flask A to combine the two aqueous extractions.
The separatory funnel should contain the organic layer at this point. The first, bicarbonate, extraction aqueous layer should be combined in flask A. Now repeat the extraction sequence as described above, using 10 mL of 1.5 M NaOH. As described for the first extraction, you will extract twice with NaOH, combining the aqueous layers in flask B. Add 5 mL of distilled water, shake, and add the aqueous layer to flask B. Add 15 mL of saturated NaCl solution and shake. Drain the lower, aqueous layer and discard. This is a coarse drying step for the organic layer.
Pour the organic layer from the separatory funnel to an Erlenmeyer flask (C), taking care to not transfer any water. Add anhydrous $CaCl_2$ (about 4 g) and set the mixture aside to dry.
Add concentrated HCl dropwise with caution to flask A until the solution is acidic by wide range pH paper test and set the flask into ice. Do the same with flask B. Precipitate should form almost immediately.
Check the contents of flask C. If the $CaCl_2$ pellets are not clumped, the organic layer is dry and you may proceed. If clumping is observed, add more drying agent and allow further drying time. Once dry, decant the organic layer from flask C, taking care to not transfer any pellets, into a pre-weighed Erlenmeyer flask. Wash the pellets with about 5 mL additional ether (twice for 10 mL total) and add the ether to the pre-weighed flask, taking care not to transfer any drying compound. If transfer is difficult, gravity filter the ether layer into the pre-weighed flask. Add a boiling stick to the flask and evaporate off the ether on a steambath in the hood. Once the organic layer has been evaporated to dryness, remove the boiling stick and weigh the contents.
Isolate the precipitate from flask A by vacuum filtration. Rinse the flask with a small amount of ice cold water. Draw air through the precipitate for several minutes to dry the solid and complete drying in the lab drying oven. Isolate the precipitate from flask B in the same way. Weigh the solids from flask A and B after drying.
Calculate the % recovery of each compound assuming equal masses of each in the original sample.

Calculate the % recovery of each component of the mixture.

Experiment 3: SEPARATING A NEUTRAL AND A BASIC COMPOUND (microscale)

Go to the prep room and get a sample that contains a neutral and basic compound. Write-out an extraction scheme and carry out the procedure. Recrystallize the compounds, take a melting point and give the recovered yield of the procedure. (you will be told what solvents to use for the recrystallization.

Pre-Lab Questions

1. Fill out a flow chart for the extraction of the three component system.

2. Sketch out how a sample containing aniline (a basic compound), benzoic acid and phenol could be separated.

3. What is the purpose of the saturated NaCl (sodium chloride) or brine solution?

4. What is the purpose of $CaCl_2$?

5. Why must you remove the stopper from the separatory funnel before draining?

6. Would you expect p-nitrophenol (pKa = 7.15) to dissolve in a sodium bicarbonate solution? Would you expect 2,5-dinitrophenol (pKa = 5.15) to dissolve in a sodium bicarbonate solution?

<u>Chromatography</u>

Background

All chromatography techniques have in common a mobile phase and stationary phase. The separation of compounds depends on a unique affinity of each compound for the combination of stationary and mobile phase. Several chromatographic techniques and the most common associated mobile and stationary phases are listed below.

Technique	mobile phase	stationary phase
Thin layer	polar and non-polar solvents	silica gel and alumina
Column	polar and non-polar solvents	silica gel and alumina
HPLC	polar and non-polar solvents	silica gel and alumina, organic
coated silica gel	Under high pressure	
Gas	hot gas, He, H2	polar and non-polar liquids coated on diatomaceous earth

The affinity of a compound for a mobile or stationary phase depends on the same forces as discussed with other physical properties such as solubility and boiling point. Non-polar compounds have a high affinity for non-polar mobile and stationary phases because the interaction between the compounds and the phases is strong. Polar compounds have a high affinity for polar mobile and stationary phases for the same reason. Hydrogen bonding and ionic interactions increase the affinity of compounds with phases that can bond through these types of interactions.

Just as with solubility, a non-polar compound will not interact strongly with a polar phase, and a polar compound will not interact strongly with a non-polar phase. The distance a compound travels through a column in a set time depends on an equilibrium between the compounds affinity (interaction) for the stationary phase and the mobile phase.

A non-polar compound spotted on a silica gel (polar) tlc plate will travel farther with any solvent than a more polar compound in the same amount of time because the more polar compound has a higher affinity and therefore stronger interactions with the polar stationary phase. As the polarity of the mobile phase increases, the affinity of polar compounds for the mobile phase increases, and the compounds travel farther along the column in the same time. The stronger interactions (higher affinity) with the polar mobile phase partially offsets the strong interactions with the stationary phase.

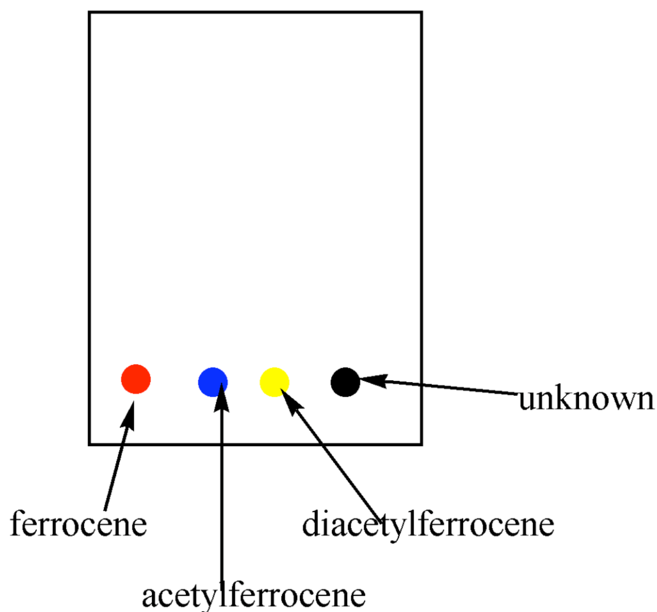
As the solubility and affinity of each compound for each stationary and mobile phase will be different, separation occurs as each compound travels a different distance along the column in a set time. The distance the compound travels along the column with time is noted as the Rf for tlc and the retention time or retention volume for column chromatography.

The Rf, used in tlc to identify compounds during a separation and analysis, is the distance the compound has traveled divided by the distance the solvent traveled during the tlc development.

The retention time, used to identify compounds in HPLC and GC, is the time required for the compound to elute off the column. The retention volume, used to identify compounds with column chromatography, is the volume of mobile phase

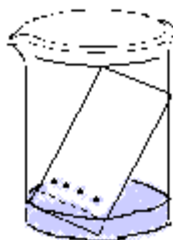
required to elute off the compound. The retention volume is often noted in column volumes, a column volume being the volume of mobile phase the packed column can contain.

TLC plates are usually purchased as a silica or alumina coating adhered to a polyethylene or glass backing. Samples are introduced to the plate by spotting. A drawn capillary tube, a tube heated to near melting and pulled to draw the point very fine, is used to apply the compounds in solution to the plate in a very small spot. The solvent used to spot the plate should be volatile, so as to minimize solvent interactions during development. The amount of sample should be small so all the compound can interact with the stationary phase. If too much sample is spotted, some compound will not be



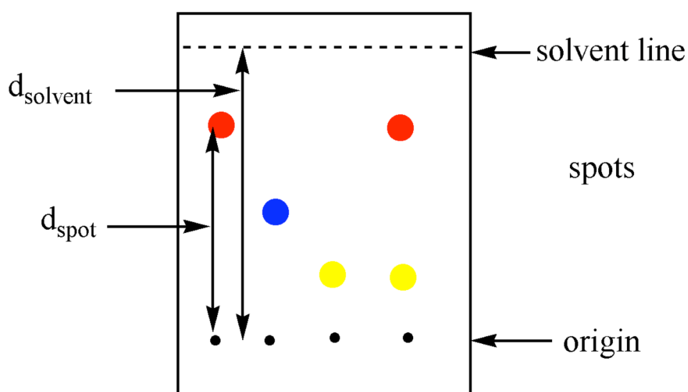
retained because it cannot interact with the stationary phase. This portion of the sample will move along the column too quickly and appear as a less polar compound.

The spotted plate is placed in a development chamber, a jar or beaker with a top or lid. The level of the mobile phase must be below the spot. As the mobile phase moves up the plate due to capillary action, it will interact with the sample, establish equilibrium and separate the compounds in the sample as discussed above. If the mobile phase level is above the spot, the solvent will extract the sample into the solvent reservoir.



When the mobile phase has reached a point near the top of the plate, the plate is removed from the chamber, a line quickly marked where the solvent last reached, and the plate allowed to evaporate.

The plate is then viewed and spots marked. Many tlc plates have a fluorescent marker incorporated into the stationary phase. This allows spots to be viewed by short wave (254 nm) blacklight. Illuminate the plate and mark the position of the spots with a pencil. Alternatively, iodine chambers, sulfuric acid chambers, and polymolybdic acid can be used to visualize spots.



$$Rf = \frac{d_{spot}}{d_{solvent}}$$

Once the spots are marked, a ruler is used to measure the distance moved by each compound (spot), and the distance moved by the solvent. The Rf is calculated for each compound (spot) by dividing the distance moved by the compound by the distance moved by the solvent.

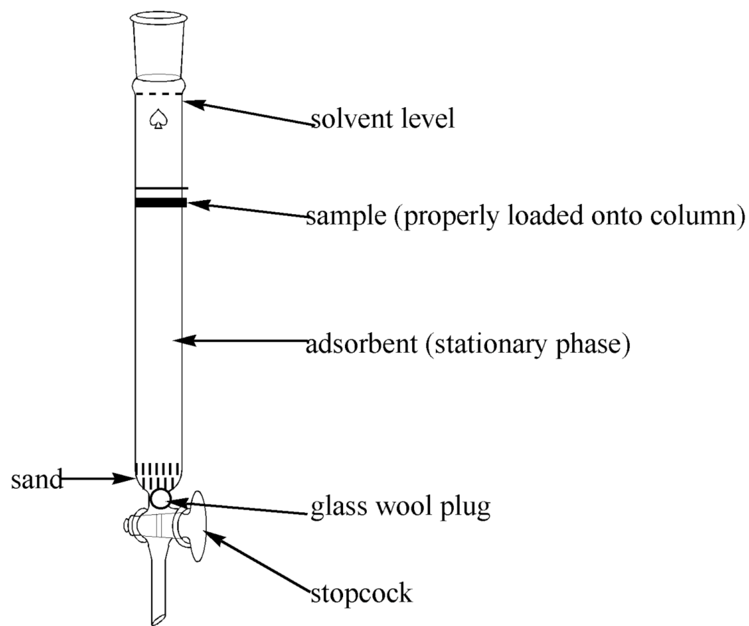
Column chromatography as practiced in this lab uses gravity to move the mobile phase through the column (elution). A suitable glass column or burette with a stopcock on the bottom has a glass wool plug inserted into the entry to the stopcock. A layer of washed sand is added next, approximately one cm.

The adsorbent is added next. The stationary phase can be dry packed or slurry packed. We will be using the dry pack technique. The stationary phase is carefully poured into the column, slowly. As the adsorbent is poured in, the column is gently but firmly tapped with a rubber stopper on the end of a pencil or stir rod. This tapping helps air trapped in the adsorbent escape as the adsorbent packs into the column. You will want to use approximately 50-100 g of adsorbent for every gram of sample to be separated. More adsorbent is used for difficult to separate compounds (compounds with similar polarity).

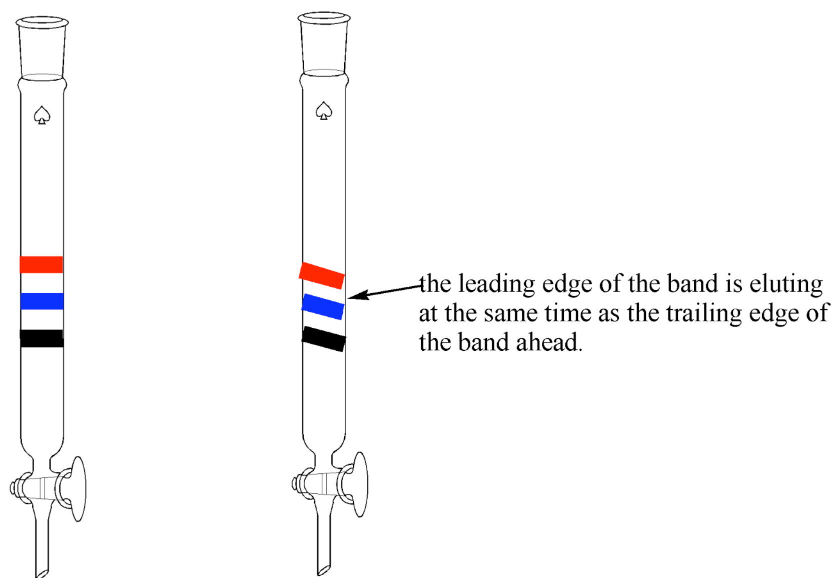
The slurry pack technique is fundamentally the same, except, the adsorbent is mixed with, or suspended in, a small amount of solvent, and this slurry is poured carefully into the column. More air can often be removed from the column by slurry packing.

The sample is introduced, or loaded, onto the column by dissolving the sample in the minimum amount of solvent. The column is drained until the solvent is right at the top of the stationary phase layer. The solution is then added dropwise to the top of the column. As the solution layer increases, the column is again drained until the mobile

phase layer (solvent) is again at the top of the stationary phase layer. This is repeated until all the sample is added to the top of the column. Solvent is then added dropwise to the top of the column, trying to add the solvent down the sides of the column walls so as not to disturb the top of the column. As the solvent layer builds to 1-2 cm, the column is drained until the solvent layer is again at the top of the column. This is repeated 5-10 times, or until it is clear the sample has moved a few mm down the column. The sample is now loaded. Add solvent carefully, dropwise at first, and then by careful pouring until the column is full. From now on, never let the solvent layer drain below the top of the stationary phase layer. As the solvent drains, add more to keep the column full.



Effect of disturbing the column after loading the sample or uneven loading of the sample, non-vertical bands.

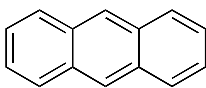


The solvent draining or eluting out the bottom of the column is collected in fractions of approximately equal volume. Each fraction is tested by spotting a tlc or some other technique to determine if sample is present. Rarely can you see the samples elute down the column. Fractions containing compounds other than solvent are analyzed by tlc to determine the identify of the compounds present.

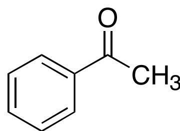
Separation of Colorless Compounds by Thin Layer Chromatography

In this experiment, you will find a solvent or mixed solvent that will separate a group of compounds by TLC with sufficiently different Rf's to enable the identification of the compounds.

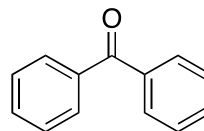
Anthracene, acetophenone, and benzophenone will be supplied as 1% solutions in dichloromethane. A mixture of the three in dichloromethane solution, to be used for solvent selection, will be supplied.



Anthracene



Acetophenone



Benzophenone

The unknown for this experiment can be any one or a mixture of these compounds.

The solvents to be used in this experiment are; hexane, toluene, cyclohexane, dichloromethane, ethyl acetate, and methanol.

Procedure

Choosing the solvent involves developing TLC plates spotted with each compound to be separated with each potential solvent. This can be done by developing a plate spotted with the three component mixture with each of the solvents (6 plates), or by a faster method using microTLC development. You will choose a solvent by the micro method.

Spot the three component mixture at three places on a precut TLC plate approximately equal distances apart. Draw solvent into a capillary spotter and touch the component spot, allowing the solvent to drain down and through the TLC plate. Use a different solvent for each spot. You will need two TLC plates to complete the experiment with all six solvents. Use the UV lamp to view the results. You are looking for a ring pattern that results from separation of the compounds as the plate develops.

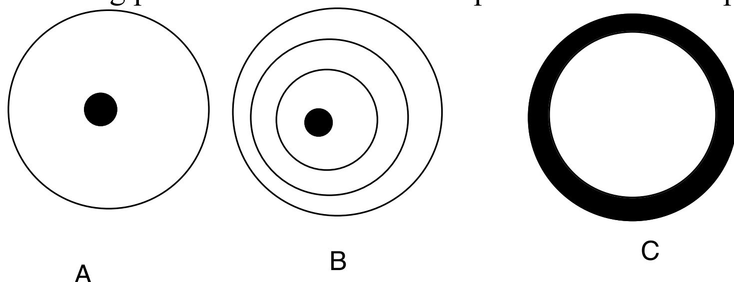


Figure A shows the results of no movement of any compound with a solvent system, all material is still at the origin. The darker color is due to solvent, either incomplete drying or minor impurities in the solvent quenching the fluorescent dye. Figure B shows a successful separation. Each component of the mixture is separated from the other components and shows up as rings. Figure C shows the result of all compounds moving with the solvent. All components are observed as a ring at the solvent front. Solvents used in A or C are not suitable for separations as they do not effectively separate the compounds. The solvent used in B is the solvent of Choice.

Obtain an unknown from the lab instructors. Pick up two precut TLC plates and spot two compounds and your unknown per plate. This will allow you to spot all three compounds and your unknown over two plates and have references to compare if the plates do not develop exactly the same. Develop the plates as described above using the solvent chosen in the microTLC experiment. Dry the developed plates and view under the UV lamp. Do not forget to mark the solvent front before drying. Use a pencil to outline the spots. Calculate the Rf's for each spot and use the Rf data as well as inspection to identify the compounds in your unknown.

Separation of Analgesics

Obtain an unknown number from the lab instructors. You will follow the same general procedure to spot your plates and develop your TLC's as described for the colorless compounds experiment. You will not choose a solvent, one has been designated for you and will be located on the solvent bench. Spot the 4 standards and your unknown and develop the plate(s) in the designated solvent. You may need to use two plates. Spot 2 standards and your unknown on each plate if all 5 do not fit on one plate. Use the Rf's and inspection to identify the compounds in your unknown sample.

Use the chart on the bulletin board to identify the analgesic product comprised of these compounds.

Column Chromatography

Obtain a column (25 ml buret), glass wool, sand, and stationary phase. The amount of stationary phase will be announced by your TA. Dry pack the column as described above. Be sure to tap the column to allow as much air as possible to escape. Fill the column with pet ether by carefully pouring pet ether down the sides of the column. Drain the column until the pet ether level is just at the top of the silica gel level. Obtain a pre-mixed sample of ferrocene derivatives. Dissolve the sample in a minimum amount of methylene chloride and load the column as previously described. Add pet ether dropwise (pipette) down the sides of the column until the level is 1-2 cm. Drain to the silica gel level and repeat the process 5-10 times. Do not disturb the column bed or separation will be affected. When the sample is properly loaded on the column, carefully fill the column with pet ether. We will be conducting a flash chromatography experiment. This means we will be pushing the solvent through with air pressure. Do not turn the air on too high and do not push the stopper into the burette, simply hold the stopper to the top of the burette. This will be demonstrated in kickoff.

Begin the elution and collection of fractions. Collect 20-40 ml fractions in beakers or Erlenmeyer flasks. You will be able to visually monitor the progress of the bands as they elute down the column. This is somewhat unusual, as most organic compounds are colorless and cannot be visually observed in the column. Always keep the solvent level above the silica gel, never allow the silica gel to dry.

When the first band has eluted off the column, change the mobile phase to a 80:20 pet ether:ethylacetate mixture. Drain the pet ether from the column to approximately 1 cm from the top of the silica gel and carefully add the 80:20 pet ether:ethylacetate mixture. Continue eluting the column, adding the 80:20 pet ether:ethylacetate mixture as the solvent level drops.

When the second band has eluted, drain the 80:20 pet ether:ethylacetate mixture to approximately 1 cm above the silica gel and carefully add a mixture of 50:50 pet ether:ethylacetate mixture. Continue eluting and add 50:50 pet ether:ethylacetate mixture as the solvent level drops to keep the level near the top. Stop the elution when the third band has completely eluted off the column.

Add all fractions with band 1 into a common beaker, all fractions with band 2 into a second beaker, and all fractions with band three into a third beaker. Use tlc (as described above) if required to identify the compounds in a fraction.

Evaporate the collected solutions of each band on a steam bath under the hood to remove solvent. Use a gentle stream of air or nitrogen, or better, use a rotary evaporator if available. You should have three samples when you are finished (more if separation was poor).

Dissolve the material from each band in the minimum amount of methylene chloride and spot a tlc plate with each of the three solutions. Spot a plate with individual samples all three ferrocene derivatives. Develop the plates with 80:20 pet ether: ethylacetate. Visualize the plate using the UV light and identify the compounds in each band.

Column Chromatography Separation of Ferrocene, Acetylferrocene, and Diacetylferrocene:Further Notes and Details

25 mL buret was used as the column.
Column was dry packed using 70-270 mesh, 60Å silica gel (Aldrich 28,861-6)
1:1:1 mixture of ferrocene, acetylferrocene, and diacetylferrocene (total sample ~45 mg) was dissolved in several drops of CH_2Cl_2 and loaded on the column.
Eluting solvent system consisted of

petroleum ether, b.p. range 37-53ºC
pet ether: ethyl acetate, 80:20
pet ether: ethyl acetate, 50:50

Approximate volumes to elute sample bands:

Band A – ferrocene	25 mL
Band B – acetylferrocene	25 mL
Band C – diacetylferrocene	20 mL

Some air pressure was applied to elute the last band.
Bands were eluted into preweighed beakers and the solvent was evaporated under the hood with air. A few crystals of each isolated solid were dissolved in 2-3 drops of CH_2Cl_2 and spotted on a TLC plate. The developing solvent used was the 80:20 pet ether: ethylacetate mixture. Solutions of 1% standards were also spotted.
A brown band at the top of the column just below the sand remained after the three other bands were eluted. This apparently is some type of impurity according to the websites of other colleges doing this same separation, even when different solvent systems were used to elute the colored bands.

Pre-Lab Questions

1. Why is it important to keep the solvent level below the spot line on a tlc?

2. Why is it important to keep the sample band level and even when performing a column chromatographic separation? Describe what can happen if the sample band is very uneven.

3. If you have a very polar compound on a silica gel column, what type of solvent should you use to rapidly elute the compound?

4. Paper chromatography is another thin layer technique. Paper is composed primarily of cellulose, a polysaccharide. Saccharides have a large number of hydroxyl groups.

Predict the polarity of paper, and the polarity of solvent needed to elute a very polar compound.

5. Make a sketch of each tlc plate you have run below. Mark the position of the spot origin, solvent line, and spots. Below each sketch, identify each spot by name and Rf.

6. Which compound eluted first from the column? What does this say about this compounds polarity compared to the other compounds?

7. Which compound eluted second?

Isolation of Limonene and other Terpenes from Citrus Rinds[1]

You will work in pairs in the lab. One person will do the procedure below (i.e. Liquid CO_2 extractions of some citrus rind.). Your "partner" will do a steam distillation of the same citrus and you will compare your results.

Preparing the sample:
Take a piece of citrus fruit and grate the colored part of the peel. You will need 2.5-3.0 grams of material.

Extraction Procedure (Liquid CO_2)
Obtain a 15 mL centrifuge tube and cap and get the tare weight. Take a piece of copper wire and make a small loop at one end that is small enough to fit in the tube but large enough to hold the sample. The remaining length of copper wire can be used as a "handle" so the sample can be removed from the tube after the extraction. Make sure it is below the top of the centrifuge tube so the cap and be placed on the tube.

Flute a small piece of filter paper and insert it in the loop of the copper wire and add the sample. Insert the copper wire and filter paper (containing the sample) in the tube.

Get a plastic beaker (or a plastic graduated cylinder) of water that is large enough to submerge the entire centrifuge tube. The water should be at 45°C +/- 5°C. Go to the dry ice box and quickly fill the tube with crushed dry ice. Immediately tighten the cap on the tube and place the sample in the water bath. If the conditions are correct, liquid CO_2 should appear in the tube within a minute and remain for about three minutes. (If you have not gotten liquid CO_2 after 2 minutes. Dump out the dry ice and try it again.)

After all the liquid has evaporated out of the tube, carefully repeat the process with fresh dry ice.

When the liquid CO_2 has evaporated away after the second extraction, carefully remove the sample. Weigh the tube and determine the amount of extract that remains in the tube. You should also weigh the citrus rind that remains. Hopefully the weights should "match up".

Steam Distillation procedure
Take a couple of grams of rind and place them in a microscale distillation flask with a boiling stone. Add 3 ml of water and distill about 1 mL of water into a vial. (There is no need to take the temperature.) Add a second mL of water to the boiling flask and distill a second mL into the same vial. Extract the two mL's of water with two 1 mL portions of CH_2Cl_2. Dry the sample with $CaCl_2$, Transfer it to a tared vial and evaporate the solvent off with a stream of air in the hood.

Analysis:
Submit the sample for GC analysis (both the liquid CO_2 and the steam). You may also take an infrared spectrum of your extract as well. Depending on the citrus fruit you used we may also obtain a mass spectrum as well.
Determine the percent limonene that was extracted from your sample.

[1] Green Chemical Processing in the Teaching Laboratory: A Convenient Liquid CO_2 Extraction of Natural Products, L. C. McKenzie, J. E. Thompson, R. Sullivan and J. E. Hutchison, *Green Chem.* 2004, 355-358.

FREE RADICAL CHLORINATION OF 1-CHLOROBUTANE[1]

If one were to look at the chapter on free radical halogenation in an organic chemistry text book you would find a section dealing with “relative reactivity”. The current theory is that the reactivity of an alkane to free radical halogenation is directly related to the energy required to homolytically cleave a carbon hydrogen bond. (98 kcal for a methyl group; 94.5 for a methylene and 93 for a methine.) It is also related to the “exothermicity” of the reaction. That is, radical reactions that are highly exothermic are not as selective as reactions that are less exothermic. Hence fluorination is not selective at all, chlorination somewhat selective and bromination highly selective. (You may look at chapter 4 of our current text to get the details.) The current literature “values” for selectivity in chlorination are 1:4:5 (methyl : methylene : methine). How does one arrive at these values? One way is to simply look at the product distribution in a chlorination reaction. In this experiment we will look at the product distribution that results from the free radical chlorination of 1-chorobutane.

GENERATION OF CHLORINE RADICALS

Since we do not want to have to use a bottle of chlorine gas in the lab (it could be dangerous) we will generate chlorine radicals via the route depicted in Figure 1.

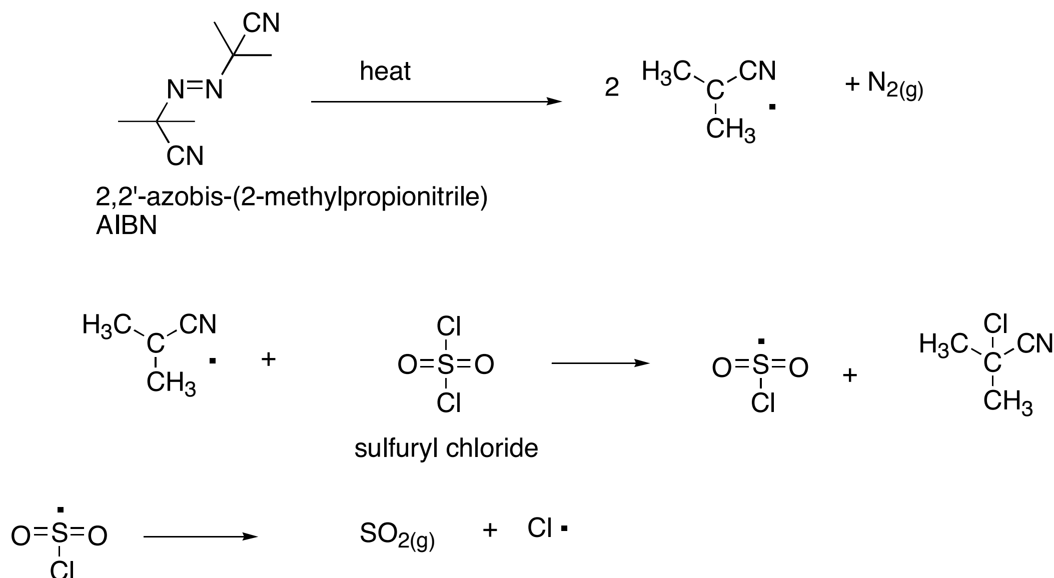


Figure 1. A convenient method for generating chlorine free radicals in the sophomore organic chemistry lab.

The procedure above will allow us to produce a controllable number of free radicals such that chlorination will only occur once on our substrate. The substrate of this reaction will be 1-chlorobutane (1):

1-chlorobutane is chosen because it is a liquid at room temperature and the resultant dichlorinated products can be easily separated using GC. (Figure 2.)

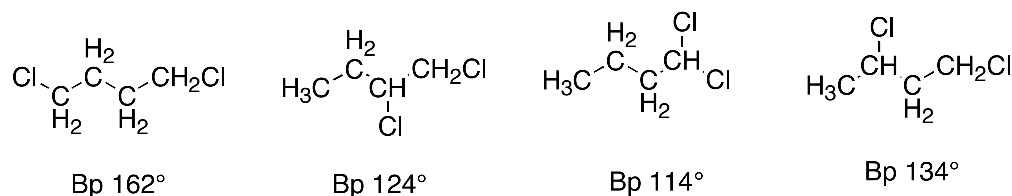


Figure 2. Dichloro isomers from the mono chlorination of 1-chlorobutane

Note that the substrate has one methyl group and three different sets of 2° hydrogens. Our intuition would tell us that the least reactive hydrogen will be on C-4. C-3, C-2, and C-1 are all 2° hydrogens and we would expect them to have similar reactivity. However, the chlorine on C-1 should have some type of an effect.

Procedure:

Set up the glassware for free radical generation as shown to you in the pre-lab. (We have also set up a “demo” setup in the lab for you to look at.) A crude drawing is given below in Figure 3.

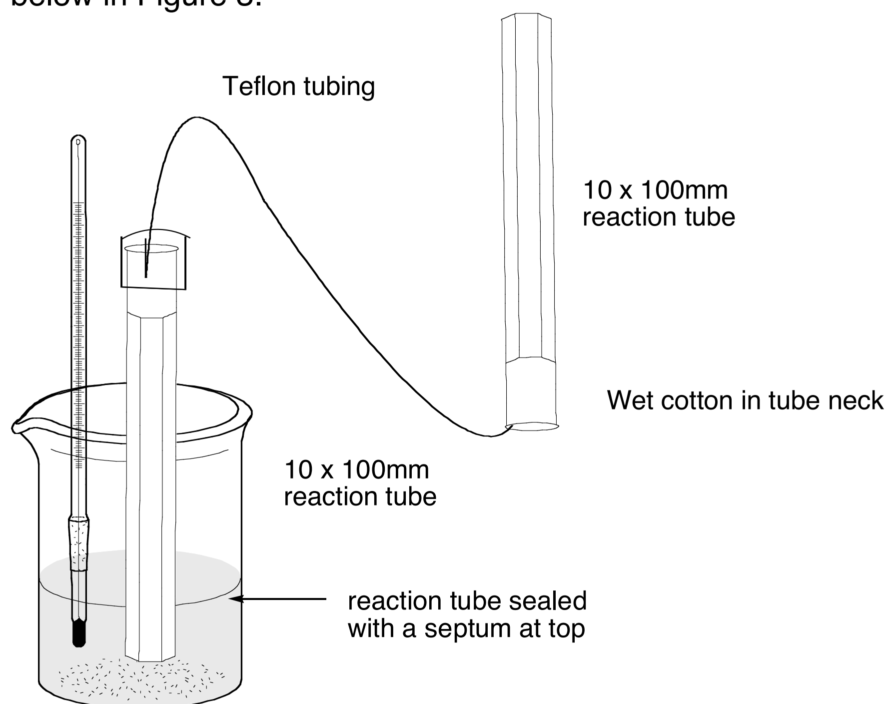


Figure 3. Set up for free radical generation.

1) Add 4.5 mmol of 1-chlorobutane(d=0.886; MW=92.57; Bp 77-78°C) and 0.0225 mmol of AIBN and a boiling chip to the reaction tube and cover the tube with a septum.

2) Go to the hood where you will be given 2.0 mmol of sulfuryl chloride.

3) Place the tube in a water bath at approximately 80°C and connect the septum with the teflon tubing to your reaction tube and the other end to a tube containing wet cotton

as shown in lecture. Let the sample heat for approximately 1/2 hour. You should see small bubbles which is the evolution of N_2 and SO_2 (around 80°) from the reaction.

3) After 1/2 hour cool the sample to room temperature and add 0.5 mL of water to the reaction tube (drop wise). Shake the contents and discard the aqueous layer. Wash the organic phase with 0.5 mL of 5% sodium bicarbonate. Discard the aqueous phase and wash with another 0.5 mL of water. Remove and discard the H_2O layer.

4) Add a few pellets of $CaCl_2$ to the organic layer. After it has cleared, transfer the organic layer (without the wet $CaCl_2$) to a tared vial, get the mass of product and submit it for GC analysis.

CLEAN UP

Rinse the cotton with water, combine that rinse with the washes from the work-up, and place them in the bottle labeled "chlorination waste". The wet cotton can be placed in the garbage can.

Write-up

This lab will be written-up as a formal report. Consult my WEB site for details on how to write a formal report.

Include:

1) A calculation on the limiting reagent in the reaction. Do the calculation in your notebook and give me the answer in the report.

2) Make a table that shows the relative reactivity of each hydrogen.

3) How do your results compare to what most text books say about free radical chlorination?

4) Clearly the presence of a chlorine has a big effect on the relative reactivity. Comment on why the chlorine affects the reaction the way it does.

5) Note that you have just completed a lab in the library on searching the chemical literature. Use that knowledge to search any research into how chlorine effects free radical stability. Include your results in the write-up.

[1]Modified from Williamson, K. E. *Macroscale and Microscale Organic Chemistry Experiments* , 4th ed., Houghton Mifflin, boston, 2003.

Nucleophilic Substitution Reactions: S_N1 and S_N2

Note: All the reactions need to be run in clean, dried test tubes that have been rinsed with distilled water.

Experiment 1: Reaction rate of S_N2 reactions as a function of substrate structure.

Procedure

Take three semi micro test tubes and add 2 mL of 15% NaI (acetone). Add two drops of 1-bromobutane to the first tube, 2 drops of 2-bromobutane to the second tube and 2 drops of 2-bromo-2-methylpropane to the third. Shake the tubes and wait 15-20 minutes and record your observations. The appearance of a precipitate indicates a substitution reaction. Note the time it takes for the appearance of the precipitate.

Experiment 2: Reaction rate of S_N1 reactions as a function of substrate structure.

Procedure

Take another three tubes and place 2 mL of 0.1 M $AgNO_3$ (ethanol) in each tube. Add one drop of 1-bromobutane to one tube, one drop of 2-bromobutane to another and one drop of 2-bromo-2-methylpropane to the third tube. Shake the tubes and wait 15-20 minutes and record your observations. The appearance of a precipitate indicates a substitution reaction. Note the time it takes for the appearance of the precipitate.

Make a table of the rate of S_N1 reactions as a function of substrate. Do your results agree with what you have had in lecture? Do the same for the S_N2 reactions.

Experiment 3: Secondary steric effects on S_N2 reactions.

Procedure

Take two semi micro test tubes and add 2 mL of 15% NaI (acetone). Add two drops of 1-bromobutane to one of the tubes and two drops of 1-bromo-2-methylpropane to the other test tube. Shake the samples and observe what happens.

Note that both of the substrates are 1° but 1-bromo-2-methylpropane is "1°, hindered". Is there a difference in reaction rate?

Experiment 4: Effect of leaving group on an S_N2 reaction.

Procedure

Take two clean semi micro test tubes and add 1 mL of 15% NaI (acetone) to each. Add two drops of 1-bromobutane to one of the tubes and two drops of 1-chlorobutane to the other tube. Shake and observe what happens.

Experiment 5: Effect of leaving group on an S_N1 reaction.

Procedure

Take two clean semi micro test tubes and add 2 mL of 0.1 M $AgNO_3$ (ethanol). Add 1 drop of 2-bromo-2-methylpropane to one of the tubes and one drop of 2-chloro-2-methylbutane to the other tube. Shake and observe what happens.

Experiment 6: Concentration effect on an S_N2 reaction

Part A. Changing Substrate Concentration

Procedure

Add 1 mL of 15% NaI (acetone) to two semi micro test tubes. Add 0.1 mL of 1M 1-bromobutane two one of the tubes and 0.1 mL of 2M 1-bromobutane to the second tube. Try to do this at the same time and observe if there is a difference in rate.

Part B. Changing Nucleophile Concentration
Add 1 mL of 1 bromobutane to two semi micro test tubes. Add 0.1 mL of 7.5% NaI (acetone) to one tube and 0.1 mL of 15% NaI in acetone to the other. Try to do this at the same time and observe if there is a difference in rate.

Experiment 7: Concentration effect on an S_N1 reaction

Part A. Changing Substrate Concentration

Procedure

Add 0.5 mL of 0.1M 2-chloro-2-methylpropane to a semi micro test tube. Add 0.5 mL of 0.2 M 2-chloro-2-methylpropane to a second semi micro test tube. Add 1 mL of of 0.1 M $AgNO_3$ (ethanol) to both tubes and record your observations. Try to do the addition at the same time.

Part B. Changing Nucleophile Concentration
Add 1 mL of 0.1 M $AgNO_3$ (ethanol) to a semi micro test tube and 0.5 mL of 0.1 M $AgNO_3$ (ethanol) and 0.5 mL of absolute ethanol to a second semi micro test tube. Add 1 mL of 0.1 M 2-chloro-2-methylpropane to each tube and record your observations.

Write-up
Describe the results from the above experiments in terms of what you have learned about S_N1 and S_N2 reactions.

All spent reactions should be placed in the bottles labeled (NaI and $AgNO_3$ test waste) in the hood.

FACTORS THAT AFFECT S_N1 RATES:
Leaving Group
Substrate Structure
Solvent Polarity

Experimental Design

To test the effect of leaving group, substrate structure and solvent polarity on an S_N1 reaction you will conduct a series of three experiments in which one of the above mentioned variables will be changed. The reaction you will be running is referred to as a **solvolysis reaction**. A solvolysis reaction is simply a nucleophilic substitution reaction where the nucleophile and the solvent are the same (**1**).

(1)

To measure the rate of the reaction we will exploit the fact that the by product is a strong acid and measure the pH change as a function of time.

Experiment 1:The effect of leaving group

Prepare 50 mL of a 1:1 mixture of 2-propanol and water (water will be the nucleophile). Add 200 ul of 0.5 M NaOH (be exact) and 5 drops of phenolpht halein solution.Take 25 mL of this solution and put it in a 50 mL Erlenmyer flask. Add 50 uL of 2-chloro-2-methylpropane and swirl the flask noting the time between the addition of the substrate and the disappearance of the pink color.

Repeat the above procedure using 2-bromo-2-methylpropane.

Experiment 2: The effect of alkyl structure

Prepare the same solvent system as you did above and add the same amount of phenolphthalein and 0.5 M NaOH as you did above. Take 25 mL of this solution and add 50 uL of 2-bromopropane, swirl the solution and note the time it takes for the pink color to disappear.

Repeat the above process using 2-bromo-2-methylpropane.

Experiment 3: The effect of solvent polarity

Prepare 50 mL of a 40% 2-propanol - 60% water solution (V/V). Add the same amount of phenolphthalein and NaOH as you did above. Add 50 uL of 2-bromo-2-methylpropane with swirling and note the time it takes for the pink color to disappear.

Repeat the process by changing the solvent to 60% 2-propanol-40% water.

Write-Up

Make a table of the rates that you observed. Comment on how each one of the experiments relates to the rate of S_N1 reactions.

Dehydration of Cyclohexanol

Procedure

Gather the apparatus for a microscale fractional distillation. The stainless steel sponge (packing) will be placed in the neck of your long neck 5mL flask. Place all reagents in the flask before placing the packing as the concentrated acid makes removal and replacement of the packing messy and potentially dangerous. Use your syringe to add 0.3 mL of distilled water to the long neck flask. Using the buret in the hood, slowly add 0.4 mL of concentrated sulfuric acid to the flask. From the buret provided add 2.0 g (2.08 mL) cyclohexanol to the flask. Finally, add an acid resistant boiling chip and place the stainless steel sponge into the neck of the flask. Clamp a beaker under the distillation head. Place a collection vial in the beaker and pack ice around the vial. This is needed to keep the product cold. Heat the flask gently on your sand bath. A heating mantle containing sand must always be placed on the benchtop; never raise it above bench level. Hot sand is a very dangerous burn hazard. Control the heat by using your spatula to move sand toward or away from your flask. Distill product until 0.5-1.0 mL are left in the flask. This will be very difficult to determine as the reaction typically turns black as the sulfuric acid chars the hydrocarbons. Count drops or otherwise estimate the amount of product distilled and thereby estimate when 0.5-1.0 mL are left in the flask. Remove the apparatus from the heat (and turn off the heating mantle) and allow it to cool somewhat. Keep the product on ice to avoid evaporation. Once the apparatus is cool, add 2.0 mL decalin using your Pasteur pipette. Introduce it into the top of the long neck flask and allow it to pour through the packing. Re-assemble the apparatus and begin heating again. Distill over an additional 0.5-1.5 mL.

Remove the apparatus from the heat (and turn off the heating mantle). Transfer the contents of the vial to a reaction tube. Rinse the vial with a little decalin and add the rinse to the reaction tube. Extract the product mixture with an equal volume of saturated NaCl. Discard the aqueous layer. Dry the organic layer with $CaCl_2$, adding enough pellets so no further clumping is observed. Dry the organic layer for 5 minutes. Clean your distillation apparatus. If the char cannot be removed, see Mrs. Paar for help or a new flask. Finish cleaning the glassware with an acetone wash. Gently blow air through the glassware to complete the drying. Transfer the dry cyclohexene to the clean and dry long neck flask. Add a boiling chip and a small amount of packing to the neck of the flask. Distill the product into a clean, dry, and pre-weighed vial. Stop distilling when the temperature recorded rises above 83° C. Weigh your product. Submit your product for GC analysis.

Analyze your product using non-aqueous bromine and permanganate tests. Take your product to the appropriate hood and obtain a 9-well plate. Add two drops of the bromine test solution to two wells. Add a drop or two of your product to the first well and note your observations. Add a drop or two of ligroin to the second well and note your observations. Repeat this procedure with the permanganate test solution.

Dehydration of 2-methyl-2-butanol

In this experiment, you will follow a similar procedure as the cyclohexanol dehydration. The butenes produced in this reaction are very volatile, so even greater care must be taken to keep the product cool, or you will lose it all. Add 1 mL water to your

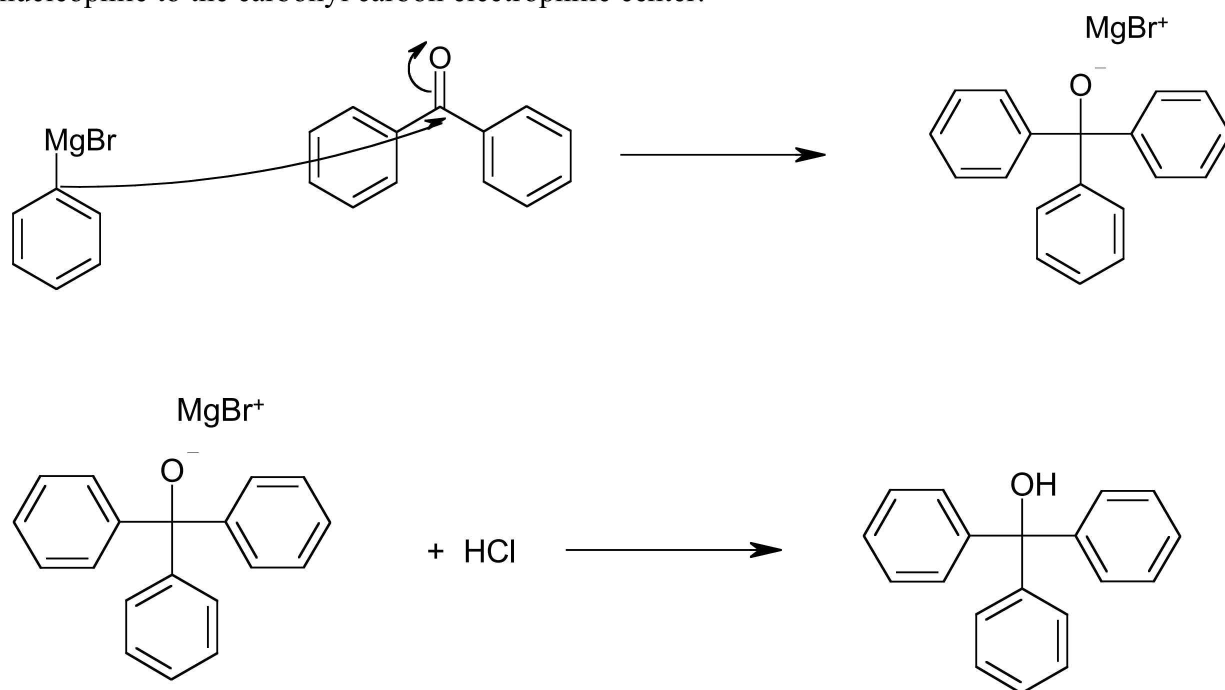
long neck flask. Add dropwise 0.5 mL concentrated sulfuric acid to the long neck flask. Cool the flask in ice. After cooling, add 1.00 mL 2-methyl-2-butanol. Mix thoroughly, add a boiling chip, and set up the apparatus for simple distillation. Be very careful to avoid spills of the concentrated acid as you assemble the apparatus. Clamp a beaker under the condenser. Place a vial in the beaker and pack ice around the vial. Gently warm the flask with your sand bath (placed on the benchtop). Distill the product over the temperature range of 30-45° C. Distillation should slow as the product comes over, but cease distillation if the temperature rises above 45° C. Transfer the contents of the vial to a reaction tube. Add 0.3 mL cold 3M NaOH solution to your product vial and mix. Draw off the aqueous layer and discard. Dry the organic layer with $CaCl_2$ pellets as usual. Keep the product cold and capped during the drying process. Clean and dry your distillation apparatus. Transfer the product into the boiling flask and complete the apparatus assembly. Distill the product into a clean, dry and pre-weighed vial. As before, the vial must be kept cold and capped to avoid loss of product. Collect distillate up to 43° C. Weigh your product and submit for GC analysis.

Grignard

Background

The Grignard reaction is a very versatile carbon-carbon bond forming reaction. Most hydrocarbon groups are compatible with the reaction. An alkyl, alkenyl, or aryl halide is reacted with magnesium metal to form the Grignard reagent. Alternatively, Grignard reagents of commonly used hydrocarbons can be purchased pre-made. The Grignard reagent is usually depicted as R-Mg-X, but experimental evidence suggests that dialkyl magnesium, coordinated complexes, and aggregates may be important intermediates in this reaction. Because the Grignard reagent is a strong base as well as a strong nucleophile, Grignard reactions are incompatible with acidic side chains or solvents. For this reason, you will take great care to remove all water from the reaction.

The mechanism of the Grignard reaction is the nucleophilic addition of the carbon nucleophile to the carbonyl carbon electrophilic center.



Procedure

Dry glassware is critical. If you have not washed your glassware the lab period before this lab, use the glassware as is. You will not have time to wash and dry the glassware and complete the portion of the lab required in this lab period.

Check out the following equipment for this lab: stir rod/septum assembly, micro stir bar, large test tube with septum cap, one vent needle.

Obtain an approximately 50 mg piece of magnesium ribbon. It will be precut for you into approximately 50 mg pieces. Polish the magnesium ribbon with steel wool or emery paper until shiny. Cut the piece into three or four smaller pieces and flare or fringe each piece by cutting the long side of the ribbon just short of one end. Curl the ribbon pieces into a loose roll, weigh the pieces and place them in a reaction tube. Cap the reaction tube with a stir rod/septum assembly. The laboratory instructors will dispense 0.5 mL anhydrous diethylether for you at the hoods. Calculate the volume of bromobenzene needed for your reaction given the mass of your magnesium. Calculate the bromobenzene to be a 5% excess so that the magnesium is the limiting reagent.

Calculations in case you forgot:
Moles Mg= mass Mg/MW Mg (MW=AW=24.3 g/mole)
Moles Mg x 1.05 = moles bromobenzene (5% excess)
Moles bromobenzene x MW bromobenzene = mass bromobenzene
Mass bromobenzene (g) / density bromobenzene (g/mL)= volume bromobenzene (mL)

Take a preweighed vial to the hood and your laboratory instructors will dispense the volume of bromobenzene you have calculated. Weigh the vial and bromobenzene to be sure the mass is close to the amount you calculated you need. Next, take the vial to the hood where 0.7 mL anhydrous diethylether will be dispensed. Insert one needle into the septum for pressure relief. Draw up all of the bromobenzene/ether solution into a syringe and place the syringe needle into the septum. Hold the bottom of the reaction tube in your hand to warm the tube. Add 0.1 mL of the bromobenzene solution to the magnesium and use the stir rod to grind the magnesium. Be firm but do not break the stir rod. Use a twisting motion as you press into the magnesium. The grinding provides mixing as well as clean surface on the magnesium for the reaction. The reaction is usually slow to start. Continue to slowly add bromobenzene solution 0.1 mL at a time as you grind the magnesium. You will observe bubbling and cloudiness as the reaction starts. Try to control the reaction by adding bromobenzene and stirring. You do not want the bubbling too vigorous. Do not let the ether bubble out of the reaction tube. Slowing the addition of bromobenzene or less stirring usually is enough to control the reaction. As the reaction continues, you will

observe a tan color. Ether will evaporate and you will need to have more added. Check with the lab instructors if you have lost much of your ether. Continue until all of the bromobenzene solution has been added. You may remove the syringe after the bromobenzene has been added, but leave the pressure relief needle in place. After the reaction seems to have slowed, quickly remove the stir rod, push the stir bar through the hole in the septum, and replace the stir rod. Keep the stir rod out of the solution and put the reaction tube assembly on a magnetic stirrer. Use an Erlenmeyer flask to hold the assembly. Stir for 10 minutes.

Weigh 2.0 mmol (0.364 g) benzophenone and place it in a vial. Go to the hood and have the lab instructors dispense 1 mL anhydrous diethylether to the vial. Mix to dissolve. Using the same syringe as before, add the benzophenone solution slowly to the Grignard reagent with stirring. You may leave the Grignard reagent reaction tube on the magnetic stirrer as you add benzophenone solution. The solution should turn pink and then thicken. Continue stirring until the pink color disappears and you are left with a white solid. You may stop at this point and store your materials until the next lab period as the need for anhydrous conditions is over.

Transfer the white solid (magnesium bromide alkoxide of triphenylmethanol) to the large test tube. Add 3M HCl dropwise and slowly to the large test tube. Add a total of 2 mL. Use the resulting solution and a pipette to rinse out the reaction tube of any white solid not transferred initially. Add diethylether, not anhydrous, to the test tube and shake until the oily triphenylmethanol dissolves. If solid is still observed, add more 3 M HCl dropwise. Note how much is added. After the solids and oils have dissolved and the layers separated, remove the aqueous layer and discard. Dry the organic layer with $CaCl_2$ pellets. Add pellets until no further clumping is observed and let set for at least 10 minutes. Decant the organic layer into a pre-weighed 10 mL Erlenmeyer flask. Wash the pellets with additional ether and add to the flask. Add a boiling stick to the flask and evaporate the ether in the hood by warming in your hand and gently blowing house air over the surface of the solution. Weigh the crude product. Set aside a very small sample of crude product for TLC analysis.

Triturate, a type of reverse re-crystallization, by grinding the crystals with low boiling pet ether. Add approximately 0.5 mL pet ether and grind the solvent through the crystals with a stir rod

while the flask is in an ice bath. Remove the pet ether with a pipette (pages 61-62 of Zubrick). Recrystallize the product from isopropanol. Determine the melting point of the product. Analyze the recrystallized product, the sample of crude product, and an authentic sample of triphenylmethanol by TLC (5:1 dichloromethane:pet ether). The samples must be dissolved in CH_2Cl_2 in order to spot on the TLC plate. Dissolve a very small amount (10 mg) in several drops of CH_2Cl_2.

Calculate the % yield for this synthesis. Draw conclusions about the purity of your sample from the melting point and TLC data.

Computational Lab
860-121-02
Lab # 11
Using SPARTAN

1) Log onto a PC in the chemistry computer lab and open the program PC SPARTAN Pro which is located in the chemistry programs window.

2) To draw a molecule go to "file" and select "new". On the right hand side of the window there will be an icon to draw a cyclohexane ring. Select this icon and click on the main window. A cyclohexane molecule should appear. Move the molecule around by experimenting with the following mouse operations:

Keyboard	left mouse button	right mouse button
none	Select molecule, atom, bond X,Y rotate	XY translate
shift key	Z rotate	scaling
Alt key	bond rotation	bond stretching

3) To put substituents on the cyclohexane ring you simply go to the menu on the right, choose what you want and then click on an open valence. An open valence will be the yellow part of the line extending off a carbon atom. To make a carbon - oxygen double bond go to the oxygen in the menu with two open valences (It is the oxygen with two lines coming off it.). The oxygen should appear on the carbon. To make the double bond go to the Make Bond icon and click. After you have done this it will ask you to click on two open valences. Click on the oxygen open valence and the open valence on the carbon to which it is attached. A double bond should appear if it is done correctly. In the same window where you got the building tools click on the "minimize E" button. The molecule should change conformation and a value (heat of formation) should appear in the lower right hand corner. You can now put a methyl group in either an axial or equatorial position.

4) R-2-methylcyclohexanone can exist in two conformations. Draw both of the conformations and determine which has the lowest ΔH_f. This is accomplished by first drawing the methyl cyclohexanone (either equatorial or axial) and doing an energy minimization. Once the structure has been completed go to the "SETUP" menu and select Calculations. Do "zero point energy", Semi-empirical/AM1. Close the window and submit. The job should take just a few seconds. When it is done go to the DISPLAY menu and open "output". The ΔH_f will be given there. Write down this value. Repeat the calculation with the other conformer.

Estimate the K_e by using the equation:

$$\ln K = \Delta H_{rxn}/-RT$$

$$\Delta H_{rxn} = \Delta H_{form\ prod.} - \Delta H_{form\ react}$$

$$T = 298K$$

$$R = 0.001987\ kcal/molK$$

Estimate the relative concentrations by using:

$K_{eq} = (100-X)/X$

If you calculated the $\Delta H_{rxn.}$ such that the more stable form was the product then 100-X is the concentration of the more stable isomer.

5) Take the most stable isomer and go to “surfaces” under the calculation window and add, LUMO under property, density under property, and ILUMOI under surface. Submit the job. When it is completed you will be instructed on how to view the molecule. The goal is to determine which face of the carbonyl carbon is most accessible for attack by a nucleophile. Once you have determined this, draw the structure of the major isomer expected from the $NaBH_4$ reduction of R-2-methylcyclohexanone.

6) Draw the two possible conformations of *cis*-2-methylcyclohexanol. Draw the two possible conformational isomers of *trans*-2-methylcyclohexanol. Submit all for of the compounds into SPARTAN and determine the ΔH_f of all of them. Which is the most stable *cis* conformation? Which is the most stable *trans* conformation?

Next week we will do the reduction of R-2-methylcyclohexanone with $NaBH_4$ and see how the “theory” compares with the experiment.

Multistep Synthesis

Reduction of 2-methylcyclohexanone

Procedure

In a reaction tube, weigh out 300 mg 2-methylcyclohexanone. Add to the reaction tube 1.25 mL methanol. Cool the reaction tube in ice. While keeping the reaction tube in the ice bath, carefully add 50 mg sodium borohydride. The reaction may be quite vigorous with a lot of bubbling. Leave the reaction tube in ice for approximately 30 minutes and then remove the reaction tube from the ice bath and let the reaction stand at room temperature for 10 minutes. Decompose the borate ester by adding 1.25 mL of 3 M NaOH solution. Add 1 mL water and allow the layers to separate. Your product is a small, layer on top of the aqueous layer. Remove as much of the organic layer as possible with a Pasteur pipette and place it in a reaction tube. Extract the aqueous layer twice with 0.5 mL dichloromethane each time. Add the organic layers to the product in the reaction tube. Dry the organic layer with sodium sulfate. Transfer the dry dichloromethane solution to a clean, dry and pre-weighed vial with a boiling chip. Evaporate the solvent in the hood. Weigh the product. Determine the proton NMR spectrum and the IR spectrum of the product. Submit a 1:600 dilution sample for capillary GC analysis. Use CH_2Cl_2 as the dilution solvent. Calculate the % yield for the reaction. Fully characterize the product from the data collected.

Oxidation of 2-Methylcyclohexanol to 2-Methylcyclohexanone

Procedure

Weigh and place 1.0 mmole of 2-methylcyclohexanol in a 5 mL round bottom flask. Add a microscale stirring bar to the flask and place the flask in ice in a small beaker. Add 0.25 mL of glacial acetic acid to the flask using the disposable transfer pipette that is out with the holster bottle of acetic acid. Set the beaker and flask on a stir plate (NO HEAT!) and adjust the stirring rate so the flask contents are stirring rapidly.

Using a Pasteur pipette, add dropwise 1.0 mL of household bleach (Clorox, 5.25 % sodium hypochlorite) to the flask. After the first mL is added, check the pH of the reaction solution with litmus paper. If it is not acidic, add additional acetic acid (~5 drops, NO MORE) until it is acidic. Continue to add an additional 1.3 mL of bleach to the reaction solution. When the bleach addition is complete, check the reaction solution for the presence of excess hypochlorite. Do this by testing a drop of the reaction mixture with potassium iodide-starch paper. A positive (+) test is indicated when the white KI-starch paper turns blue-black. This shows that there is an excess of hypochlorite present. If a positive test is not obtained, add additional bleach (1-3 drops) and retest with the KI-starch paper.

Remove the flask from the ice bath, set it in an empty beaker and continue to vigorously stir the reaction on the stir plate for a minimum of 15 minutes. Monitor the reaction solution every 5 minutes using KI-starch paper and add bleach to maintain a positive KI- starch test.

At the end of 15 minutes add saturated aqueous sodium bisulfite solution dropwise until the solution gives a negative KI-starch test.

Add a drop or two of thymol blue indicator to the reaction solution and then neutralize the solution with 6 M sodium hydroxide (~0.3-0.4 mL). [The solution should turn from yellow to blue] Add a boiling chip to the flask, attach the flask to a simple distillation set-up and distill. Collect between 0.5-1.0 mL of distillate, which consists of a mixture of water and 2-methylcyclohexanone. *(This is a steam distillation where steam is generated in situ.*) Transfer the distillate to a reaction tube, rinse the vial with ~0.5 mL of water and add the rinse to the reaction tube as well.

To salt out the 2-methylcyclohexanone, add approximately 100 mg of sodium chloride to the distillate. Stir and shake the tube until most of the salt dissolves. Extract the solution with 3 x 0.4 mL portions of methyl-t-butyl ether (MTBE). Dry the MTBE solution by passing it through a column of alumina and drying agent. The column is prepared by adding a small plug of glass wool to a clean Pasteur pipette. Use a boiling stick to push the glass wool down to where the pipette narrows. Make a small funnel from a sheet of weighing paper. Using the funnel, add about one inch of alumina to the pipette and top that with about one inch of anhydrous sodium sulfate.

Transfer the ether solution of 2-methylcyclohexanone to the column and collect the dry ether solution in a preweighed 5 mL round bottom flask containing a boiling chip. Wash out the column with an additional 2 mL of MTBE and collect this wash in the same preweighed flask.

Fit the flask for simple distillation and distill off all of the ether (bp 55°C). Tilt the distillation apparatus toward the collection vial to optimize the collection of the MTBE. The clear residue in the **round bottom flask** is the product. Determine the weight of the product, calculate the percentage yield, and run an IR of the product.

References:

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