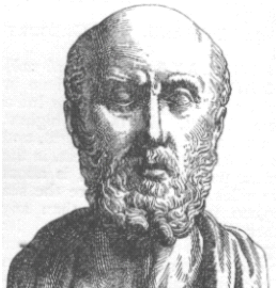
Experiment 6

Fig. 6-1



EXTRACTION: A SEPARATION AND PURIFICATION TECHNIQUE

(with a possibly unexpected result)

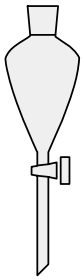
Hippocrates (460 - 377 BC). Used extract of willow bark and leaves for pain and fever (~400 BC). http://www2.sjsu.edu/depts/Museum/hippoc.html

New Techniques

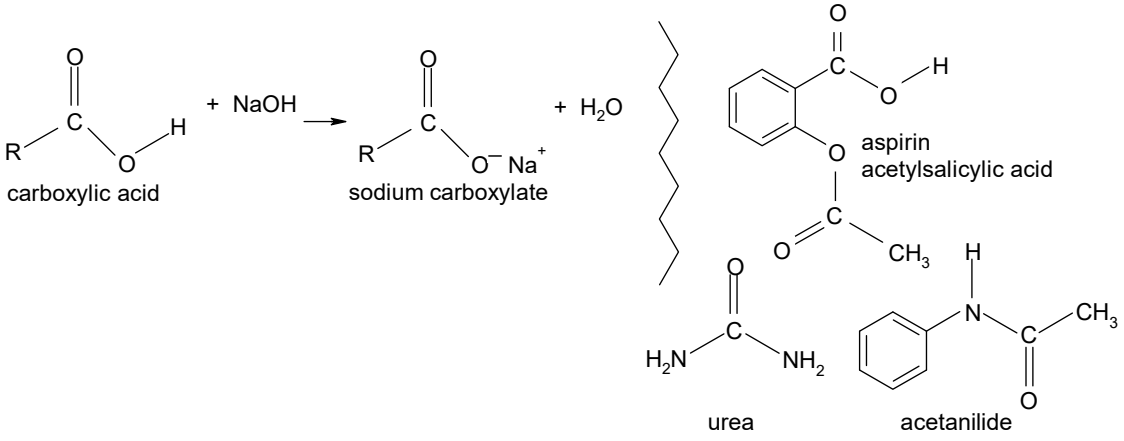
Extraction, use of a separatory funnel, use of drying agent, solvent evaporation.

Discussion

Today's experiment focuses on the separation technique called extraction. There are many extractions that lead to chemicals that are extremely important in our lives. Taxol is a very minor constituent of the bark of the Pacific yew but it has valuable chemotherapeutic properties for the treatment of ovarian and breast cancer. Starting with about 3000 trees, extraction is part of the process that produces 2 pounds of the drug. Coffee contains the chemical caffeine, a temporary stimulant. Some people drink the coffee for the stimulant but others like the taste and do not want the caffeine. Two of the common ways of removing the caffeine involve either extraction with dichloromethane or with supercritical carbon dioxide.



For most synthetic procedures, you will find that immediately after running the reaction, the next step is to transfer the reaction mixture to a separatory funnel. The separatory funnel has been designed to facilitate liquid - liquid extractions. Almost all liquid - liquid extractions use two immiscible liquids, usually including water and an organic solvent (typically diethyl ether, methylene chloride or hexanes). As an example, consider today's experiment. You will be given a mixture of acetanilide, urea and aspirin (acetylsalicylic acid). The sample will be mixed with dichloromethane (also called methylene chloride). The acetanilide and aspirin should dissolve. Urea has a very low solubility in dichloromethane. The mixture is filtered to collect the urea and the filtrate is transferred to a separatory funnel. Compounds such as aspirin with the general formula RCOOH are called carboxylic acids. Acids are neutralized by sodium hydroxide to yield a salt and water. The salt expected from aspirin is an ionic compound that should be at least somewhat soluble in water.

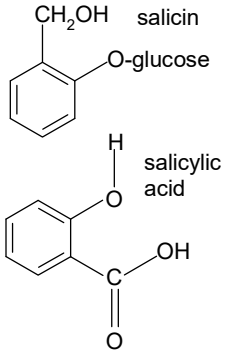


If a sodium hydroxide solution is added to the separatory funnel containing the acetanilide and aspirin solution in dichloromethane, the aspirin should undergo a neutralization reaction that yields a water soluble salt. The salt should partition itself between the two solvents. The polar salt should be much more soluble in the highly polar water than in the low polarity dichloromethane and most of the salt should end up in the water. (Please note, however, that you should recall the consequences of mixing methyl salicylate (oil of wintergreen with base in ***Experiment 4***. Like methyl salicylate, aspirin is also an ester and could be subject to a saponification reaction.) Because of the conical shape of the separatory funnel, it is now easy *(why the conical shape?)* to carefully separate the dichloromethane layer from the water layer. Acidification of the separated aqueous layer should lead to protonation of the salt and formation of aspirin. Since aspirin has a very low solubility in water, a precipitate should form which should be collectable by filtration. Evaporation of the dichloromethane layer should yield a residue of acetanilide. A separation of acetanilide and aspirin has been achieved by extracting the "aspirin" out of the dichloromethane layer into the water layer.

Extraction is commonly used to separate water soluble chemicals from organic compounds. Even neutral organic compounds, organic acids and organic bases can be separated by appropriately adjusting the pH of the aqueous layer to increase or decrease solubility of organic compounds in water to distribute them as desired between the aqueous layer and an immiscible organic solvent.

There are several properties to consider when selecting the organic solvent. First, it must be essentially immiscible with water. The solvent should also have a relatively low boiling point as it will often have to be evaporated after the extraction procedure. Solvents like ether (b.p. = 35°C), dichloromethane (b.p. = 40°C) and pentane (b.p. = 35°C) are commonly used. The organic compound of interest must be soluble in the solvent. This limits the use of pentane as it is non-polar and is a good solvent only for non-polar compounds. The solvent should also have low toxicity and cost.

Extraction is often used to separate organic compounds from their original sources. Although Hippocrates apparently used a powder derived from the leaves and bark of the willow tree to treat pain and fever, it was not until 2200 years later in the nineteenth century that chemists extracted the chemicals from willow and found that salicin and salicylic acid were responsible for the analgesic properties. Unfortunately, salicylic acid causes severe stomach upset. In 1897 Felix Hoffman took advantage of some research published in 1853 by Charles Gerhardt on the possible synthesis of acetylsalicylic acid. Searching for a compound to relieve his father's suffering from arthritis, Hoffman synthesized acetylsalicylic acid and found it had excellent analgesic properties without significant stomach stress. Hoffman worked for the Bayer Company and convinced them to produce acetylsalicylic acid (they named it aspirin) and now you know the rest of the story.



Techniques

Use of a separatory funnel. Choose a separatory funnel that has a capacity about four times the volume of the solution to be extracted. Set up a ring stand with a ring that holds the funnel about ½ of the way up the funnel. Be especially careful when handling the funnel as the glass is thin. Transfer the solution to the separatory funnel. Add the extracting liquid. Insert the stopper and while holding it in, invert the funnel. Immediately open the stopcock to release any built up pressure. Close the stopcock and with the funnel up-side-down and the stopper held in, gently swirl the contents briefly and reopen the stopcock. In the inverted position, swirl more vigorously and again reopen the stopcock. Now vigorously swirl but be aware that with mixtures of some liquids, an emulsion can result that sometimes takes a very long time to separate. Return the funnel to its normal up-right position and insert it in the ring. Allow the two liquid phases to separate as much as possible. This could take several minutes or longer if an emulsion has formed.

Drain the bottom layer out the through the stopcock. The next step depends on whether the desired compound was in the bottom or top layer. Make sure you know which layer is which. When one phase is aqueous and the other is an organic solvent, the aqueous phase is usually denser and at the bottom unless the organic phase is a chlorine containing solvent. When the solvent is dichloromethane, be especially careful as water is usually the top layer. However, if the water contains sufficient dissolved salts, its density can be more than dichloromethane. To be sure which is which, draw off a few drops of the bottom layer into a test tube and determine if it is miscible with water.

If the bottom layer (more dense layer) is going to extracted again, pour the top layer out through the top of the funnel and save it in a flask. Do not drain it out through the stopcock *(why?)*. Add the bottom layer back into the funnel, add the other solvent and repeat the process. Add the new top layer to the flask with the previously collected top layer. Generally, three extractions should be performed and it is best not to throw away the original phase until you establish later that you extracted the desired compound.

If the top layer (less dense layer) is going to be extracted again, leave it in the funnel, add more extracting solvent and repeat the procedure. Add the bottom layer to the previously removed bottom layer.

Drying the solvent. Usually the desired compound is now dissolved in an organic solvent that has been used to extract it. The next step is often the evaporation of the solvent. However, before this is done, the solvent should be dried as the presence of water can cause problems. To remove the water, one of several possible anhydrous inorganic salts is added. The possible compounds all have a high affinity for water and readily form hydrates in the presence of water. After the hydrate is formed, the liquid is decanted or filtered to remove the remaining salt and hydrates and evaporation can then be carried out. A table of some commonly used drying agents is below along with some criteria that can be used to choose among them.

Drying agent	Speed	Capacity/unit mass of drying agent	Degree of dryness	Comments
calcium sulfate (Drierite)	very fast	low	high	
calcium chloride	medium	high	medium	do not use for acids, alcohols, amines, esters
magnesium sulfate	fast	medium	medium	inert
sodium sulfate	slow	high	low	inexpensive

Evaporating the solvent. A future experiment will focus on distillation, the technique most commonly used for separation and purification of liquids. Distillation can be used for removal of solvent but often a faster method for removing solvent called evaporation is used. Both distillation and evaporation involve vaporization of the solvent. The primary difference between distillation and evaporation is that simple evaporation generally does not include condensation and collection of the vaporized solvent. The method of choice for the evaporation of the solvent is to use a commercial rotary evaporator. If one is available, ask your instructor how to use it. If a rotary evaporator is not available, the solvent can be distilled off or a crude vacuum evaporator can be made. Transfer the solvent to an appropriately sized filter flask. Insert a magnetic stirring bar into the flask and put it on a heater - magnetic stirrer unit. Stopper the flask and connect the flask with thick walled rubber tubing to a trap which is in turn connected to an aspirator. With the vacuum established and the stirrer on a relatively high speed, **gently** heat the flask until evaporation is complete.

Procedure

This procedure has been designed to separate acetanilide, aspirin and urea from a mixture of all three. As indicated in earlier experiments, it is very important to verify the identity of a compound no matter what its source and how much confidence you have the compound is what it is supposed to be. For this experiment, melting range measurements of each product should be sufficient for identification. **If a melting range leads to some doubt abut the identification, be sure to investigate further to find the source of the problem.**

A bottle containing a mixture of approximately equal amounts of acetanilide, aspirin and urea will be available in the laboratory. Weigh 3.0 grams of the mixture into a 125 mL Erlenmeyer flask. Add 50 mL of dichloromethane to the mixture and thoroughly mix to give any soluble solid the opportunity to dissolve. Be sure to break up any solid chunks with a stirring rod. Vacuum filter the mixture to collect the undissolved solid. Be sure to wash the flask and the funnel contents with a small amount of dichloromethane a couple of times. Weigh the collected solid and take its melting point. If necessary, take a mixed melting point to help determine the identity of the solid.

Transfer the filtrate to a separatory funnel. Rinse the filter flask with a small amount of dichloromethane and add the wash to the separatory funnel. Extract it twice with 25 mL portions of 1 M NaOH and combine the two aqueous layers. Be sure you determine which layer is which and that you save both the aqueous and organic layers. Add some magnesium sulfate to the dichloromethane layer. Usually, a gram or two is sufficient but add it slowly until it appears to stop caking as it is added with stirring. Decant the dichloromethane layer into a flask to be used for evaporation. Rinse the residue with a small amount of dichloromethane, add it to the flask and begin the evaporation process.

Meanwhile, add 10 mL of 6 M HCl to the combined aqueous layers. Test the pH with 0-13 pH Hydrion paper. If the pH is above 2, add more HCl until the pH is 2 or lower. Cool the mixture in an ice bath and vacuum filter to collect the product. Wash the solid with a small amount of ice cold water. Allow the sample to dry before weighing and determining the melting range. This may require waiting overnight or until the next laboratory period. If necessary, take a mixed melting point to help determine the identity of the solid.

After the evaporation of the dichloromethane layer is complete, determine the mass of the product and its melting range. If appropriate, recrystallize the product from water. After it is dry, determine the melting range and mass.

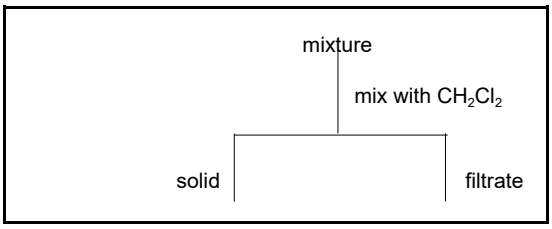
Note: although the original 3 g of product contained approximately equal amounts of each compound, mixing of solids is difficult and the amounts were probably not equal. Because of this, the best way to express percent recovery is probably the total amount of solid recovered divided by the original mass of starting material. Even this percent is not completely meaningful because of the unexpected result.

Reference

Lehman, J. W., *Operational Organic chemistry: A Laboratory Course*, Prentice Hall, 2nd. ed., **1988**, pp. 28-35.
A recently published extraction experiment is available at: Raydo, M. L.; Church, M. S.; Taylor, Z. W.; Taylor, C. E. Danowitz, A. M. *J. Chem. Educ.*, **2015**, *92*, 139-142.
A guided-inquiry extraction was recently published at: Mistry, N.; Fitzpatrick, C.; Groman, S. *J. Chem. Educ.*, **2016**, *93*, 1091-1095.

Prelaboratory Preparation - *Experiment 6*

First, be sure to list all the goals of the experiment. You should prepare a table that will contain the masses, percent recoveries (assume the mixture contained equal amounts of each substance) and melting ranges obtained at each step of the process. Most importantly, **prepare a flow diagram for the separation procedure that will help guide you through the procedure.** A start to the diagram is given to the right. Make sure you know the meaning of the term "analgesic" and you should review the term "saponification" in ***Experiment 5***.



Observations

Report all relevant observations including, masses and melting ranges. Do not overlook any unexpected results. If there are any unexpected results, attempt to figure out what happened.

Conclusions

This section should include the following:

1. Were the goals of the experiment achieved? Explain your answer.
2. Why was the percent recovery less than 100% and how could it be improved?
3. Did you obtain acetanilide, aspirin and urea? State your evidence in each case.
4. When is extraction an appropriate technique for separation (e.g., is there an ideal sample size range, is there a minium starting purity, what final purity should be expected, etc.)?
5. Explain anything unexpected that occurred.
6. Suggest a modification to the procedure that should avoid the unexpected result and lead to separation of the three compounds.