Fall Organic Chemistry Experiment #3
Extractions

Suggested Reading:

"The Student's Lab Companion: Laboratory Techniques for Organic Chemistry", by John W. Lehman (on reserve in the Wilmot Library)

OP-18 pages 95-107 (extractions)
OP-24 pages 146-148 (washing liquids – contrast with the term “extraction”)
OP-25 pages 148-154 (drying agents)
OP-16 pages 88-93 (vacuum filtration)
OP-28 pages 161-178 (recrystallization – if you have not already read)

Extraction Theory:

Extraction is a process of purification involving the use of two solvents or solutions that are immiscible with one another. It helps to picture an oil and vinegar salad dressing mixture. When you prepare this salad dressing mixture, two independent layers are formed, one of which is an "organic" (oil) layer and the other is the "aqueous" (water) layer. The theory here is that any solute that is present will distribute itself between the two phases – the solute is in EQUILIBRIUM between the two layers. As a result, the concentration of the solute in each phase will determine if the solute will more likely exist in one layer or the other. In addition, it is also possible for the solute to be distributed equally between the two layers. This concentration is a constant value for each solute and is called the partition coefficient (K). It is defined by the following equation:

\[ K = \frac{C_2}{C_1} \]

where \( C_2 \) and \( C_1 \) are the concentrations of the solute in each solvent (aqueous and organic) in grams per liter. The process of extraction involves the use of this partitioning of the solute between the two phases in order to isolate components from a mixture. Hopefully, the solute will have a preference for one layer and, therefore, be easily isolated from the other compounds.

In general, we will be interested in the two primary applications of extraction in the organic chemistry laboratory. The first use is to employ extraction as a means of isolating chemicals that are present in plant or animal tissue (natural products). The second application is utilized by the synthetic organic chemist. In many cases, a synthetic chemist will utilize a single extraction or a series of extractions at the end of a reaction in order to isolate a product from a mixture. We say that the chemist is performing a reaction "work-up". Usually, the goal is to use a two-phase solvent system (e.g. water and ether) that forms two separate layers. In other words, the organic layer and the water layer remain distinct and separate (you can see this). Our objective in doing this is to have the desired product remain in one of the phases and the "garbage" to stay in the other phase. There are actually many variations on this theme. In some cases, we have the product in the aqueous phase and the junk goes into the organic phase. In other cases, the product goes into the organic phase and the junk goes into the aqueous phase. It is our job, therefore, to design an extraction system that will enable us to isolate our compound into its appropriate phase and to insure that most of what we do NOT want goes
into the other. We will be using specific extraction solvents or solutions to isolate a desired solute.

Extractions may be grouped into three main categories: neutral, acidic, and basic. Each method is specifically used depending upon the identity of the impurity to be removed or the compound to be isolated. In a neutral extraction, the organic phase is extracted with water. Water is useful in removing highly polar materials (e.g. inorganic salts) and low molecular polar organics (e.g. alcohols and carboxylic acids). In an acidic extraction, the organic phase is extracted with a dilute solution of acid, usually HCl. Acidic extractions are used to remove basic impurities (e.g. amines). In a basic extraction, the organic phase is extracted with a solution of dilute base, usually NaHCO₃. Basic extractions are used to remove acidic components (e.g. carboxylic acids and phenols). You'll definitely want to pay attention to the application of acid/base chemistry in this experiment.

**** CLICK here to see a video showing you how to perform an extraction. Be sure to select Video #5 “Reaction Work-Up I”

A conically shaped piece of glassware called the separatory funnel is the laboratory tool used for most types of extraction. Be careful when using them, they are not cheap!!! The general process involves adding the two immiscible solutions to the separatory and shaking with occasional opening of the stopcock. The proper use of the separatory funnel will be demonstrated during the prelab by your instructor. However, it never hurts to have a few helpful reminders:

(1) The basic process of extraction:

(a) First make sure that the stopcock is secured and CLOSED.
(b) Place a collection flask underneath the funnel.
(c) Use an iron ring to support the separatory funnel.
(d) Two heterogeneous liquids/solutions are added to the separatory funnel.
(e) The mixture of solutions is shaken with occasional venting to relieve any pressure buildup.
(f) The lower layer is drawn off through the stopcock.

(2) The difference between extraction and washing:

Extraction is the removal of a desired compound from one phase (usually the aqueous phase) into another (usually the organic phase). Washing involves the removal of impurities by shaking the solution with an aqueous solvent that will dissolve only the impurities and leave the desired compound behind in the organic phase.

(3) Identifying the aqueous phase and the organic phase:

Keeping track of which layer is the organic layer and which is the aqueous layer can be frustrating. However, if you remember one simple rule, then you troubles will be few. The rule here is that the more dense liquid will be on the bottom. It will be helpful for you to consult a text (e.g. CRC handbook, Aldrich catalog) to find the densities of the solvents you'll be using. If you are in doubt, there are two things you should do:

1. Remove a drop of one layer and place it in a small test tube. Add a drop of water. If it dissolves, the layer is aqueous. If it doesn't, then the later is organic.
2. Save ALL of your discarded layers until the end of the experiment.

(4) The practical aspects of doing an extraction:

Most of the time, we simply want to rush through the procedure without thinking about the experimental design and the chemistry that is actually going on. However, that is a big mistake. We certainly want to avoid the "cookbook" approach. Therefore, you will need to think about the critical variables that are involved in the design of an extraction procedure. In the list below are the practical variables that need to be considered prior to carrying out an experiment.

1. Choice of solvent -- This list commonly includes the following: water, diethyl ether, dichloromethane, chloroform, carbon tetrachloride, petroleum ether, hexane, ligroin, benzene, ethanol, 1-butanol, etc.

2. Use of acidic/basic solutions -- This list commonly includes the following: solutions of 5% NaHCO₃, 1 M NaOH, 6 M HCl, 3 M HCl, etc. Remember basic solutions isolate acidic compounds and acidic solutions isolate basic compounds.

3. Emulsions -- Usually if you shake gently they can be avoided. If that doesn't work, then let the solution stand for a length of time, make the aqueous layer ionic (by adding salt), or perform a vacuum filtration may do the trick. The key is to avoid them altogether.

4. Pressure buildup -- This is avoided by venting (opening the stopcock while the separatory funnel is inverted).

5. Removal of water -- Accomplished by the use of chemical drying agents such as, magnesium sulfate, sodium sulfate, calcium chloride, Drierite, or molecular sieves. A final wash with a saturated solution of sodium chloride also helps.

(5) How much solvent/how many extractions?

The general rule of thumb here is to perform multiple extractions with smaller amounts of extracting solvent rather than one extraction with a large amount of solvent. Remember, we are dealing with the partitioning of a solute equally between two phases. By performing the extraction a number of times, we can effectively pull out more material than if doing it once with a large amount.

Situation

One of the primary responsibilities of the Federal Food and Drug Administration (FDA) is to insure that over-the-counter drugs are both effective and safe. Scientists at the FDA are responsible for the testing of drugs to verify that the manufacturer has accurately reported the composition of the product. Your assignment in today’s experiment is to separate the constituents of a simulated over-the-counter analgesic drug preparation and identify an unknown component of the three-component mixture. The three components are a carbohydrate, a common analgesic, and an unknown analgesic that is suspected to be unsafe for use even though it is chemically similar to the popular drug, acetaminophen (Tylenol). The unknown is either one of two possible compounds, acetanilide or phenacetin. Both compounds were previously marketed drugs, but have been subsequently found to be toxic (and removed from the market). Acetanilide was marketed as a popular analgesic/antipyretic drug called antifebrin. However, it was discovered that antifebrin causes a serious form of anemia called methemoglobinemia. Phenacetin was used in the preparation of APC tablets and other analgesics. By 1981, it had been
shown that phenacetin is not only toxic (causing hemolytic anemia and kidney damage), but is also listed as a carcinogen.

The discoveries of acetanilide and phenacetin are both intriguing stories. In 1886, Arnold Cahn and Paul Hepp were trying to find a drug that would rid a patient of intestinal worms. They systematically tested chemicals found in their stockroom until they found one that worked. On one occasion they used the contents of a bottle labeled “naphthalene” which is the major constituent of mothballs. Well, needless to say, the compound had no effect on the worms. However, it did effectively reduce the patient’s fever considerably. After consulting with Hepp’s cousin (a chemist), they discovered that the compound was not really naphthalene, but the potent antipyretic, acetanilide.

In the following year, Carl Duisberg, a research director at the Friedrich Bayer Company, found a unique way to get rid of 50 tons of a by-product of dye manufacturing (p-aminophenol). He decided to convert the p-aminophenol into something useful, possibly a drug. Duisberg came up with the synthesis of phenacetin by masking the aminophenol hydroxyl group with an ethyl group and then acetylating the amine functionality. The interesting thing is that his synthesis is very close to the way in which acetaminophen (a safer drug than phenacetin) is prepared. In fact, it is widely held that acetanilide and phenacetin are actually converted via an enzyme into an active form (acetaminophen) in the human body.

\[
\begin{align*}
\text{p-aminophenol} & \xrightarrow{\text{Williamson ether synth.}} \text{p-aminophenol} \\
\text{p-aminophenol} & \xrightarrow{\text{acetylation}} \text{acetaminophen} \\
\text{acetaminophen} & \xrightarrow{\text{enzyme}} \text{phenacetin} \\
\end{align*}
\]

In today’s experiment, you will be given a preparation containing the three components. Your job is to separate them in order to find out what they are.

**Procedure**

Accurately weigh about 3 grams of the preparation and transfer it to a 125 mL Erlenmeyer flask. Add 50 mL of methylene chloride (dichloromethane or DCM) and stir the mixture thoroughly to dissolve as much solid as possible. Using a pre-weighed piece of filter paper, gravity filter the mixture to isolate the carbohydrate. Set the filter paper aside and let it completely dry before weighing. Record the **mass** of the carbohydrate in your notebook.
Transfer the filtrate to a 125 mL separatory funnel and extract the **common analgesic** with two 25 mL portions of 1M sodium hydroxide solution. Two layers should result, an aqueous layer and an organic layer. Separate the layers each time and set aside the organic layer for the next part. Take the combined aqueous layers and slowly add 10 mL of 6M HCl. Test the pH of the solution and adjust accordingly so that the solution has a pH of 2 or lower. Cool the mixture in an ice bath and collect the recovered common analgesic by vacuum filtration. You may wash the solid with cold water. Let the material dry on the filter with the aspirator running for a few minutes to remove as much water as possible. Remove the product and let air dry to constant mass. Record the **mass** of the common analgesic in your notebook and obtain its **melting point**.

Take the remaining organic layer and evaporate the methylene chloride solution and transfer to a 100 mL round-bottom flask. Remove the solvent using the rotary evaporator (as demonstrated by your instructor). You should receive a solid material after removal of the solvent. Recrystallize the solid by dissolving it in the minimum amount of hot distilled water. **Be sure to perform a hot gravity filtration through a funnel in order to remove any undissolved impurities.** Let the filtrate cool to room temperature and induce crystallization by scratching the flask with a glass stirring rod. Cool further in an ice bath to maximize recovery of the unknown component. Dry the product to constant mass and record the **mass** in your notebook. Measure the **melting points** of: (a) the recrystallized unknown; (b) a 1:1 mixture of the unknown with pure acetanilide; and (c) a 1:1 mixture of the unknown with phenacetin.