

**LIQUID/LIQUID SEPARATION: EXTRACTION OF ACIDS OR BASES FROM NEUTRAL ORGANICS.** Introduction.

**Background** Extraction is one of humankind's oldest chemical operations. The preparation of a cup of coffee or tea involves the extraction of flavor and odor components from dried vegetable matter with hot water. Many other substances, flavors and spices and perfumes and medicines, have been extracted from plants for centuries (quinine, morphine, menthol...). Many undesirable drugs are also isolated by extraction (cocaine from coca leaves). Extraction, like recrystallization, is based on solubility factors.

The most common and simple separation in organic chemistry involves the separation of neutral organics from ionic compounds, whether the ionic compound is an inorganic salt ( $\text{NaCl}$ ) or is an ionized version of the organic. The two most commonly ionized organic families are carboxylic acids, which are ionized by deprotonation to their carboxylate  $\text{RCO}_2^-$  form, or basic amines, which are ionized by protonation to their ammonium  $\text{RNH}_3^+$  form.

Neutrals and ionics are easily separated because ionics are preferably soluble in water rather than in organic solvents, whereas neutral organics are preferably soluble in organic solvents rather than in water. The following three separations are thus common:

1. A neutral/ionic mixture is shaken with ether and water.
  - The neutral goes into the ether layer.
  - The ionic goes into the water layer.
2. A neutral/carboxylic acid mixture is shaken with ether and  $\text{NaOH}/\text{water}$ . (Part 1)
  - The neutral goes into the ether layer.
  - The carboxylic acid is deprotonated by  $\text{NaOH}$  to its carboxylate form ( $\text{RCO}_2^-$ ), which goes into the water layer.
3. A neutral/amine mixture is shaken with ether and  $\text{HCl}/\text{water}$ . (Part 2)
  - The neutral goes into the ether layer.
  - The basic amine is protonated by  $\text{HCl}$  to its ammonium form ( $\text{RNH}_3^+$ ), which goes into the water layer.

Once a chemical is separated from its original mixture, it must still be isolated from solvent.

1. Isolating a neutral from ether solvent:
  - **Dry** The ether will contain not only the neutral solute, but also some water. The water is absorbed by a chemical drying agent (usually sodium sulfate or magnesium sulfate or calcium chloride).
  - **Filter (and rinse)** The drying agent is then usually removed by filtration. (Rinse!)
  - **Concentrate** The solvent is then removed by simple distillation, leaving the desired neutral as the residue. The simple distillation is usually done via a “rotary evaporator”.
2. Isolating a neutral carboxylic acid from the  $\text{NaOH}/\text{water}$  layer:
  - **Acidify/Neutralize**  $\text{HCl}$  is added to acidify the water. In the process the carboxylate anion  $\text{RCO}_2^-$  is protonated and reverts to its neutral form  $\text{RCO}_2\text{H}$ .
  - **Filter or Extract** Because the acid is now neutral, its solubility in water will be low. If it crystallizes, you can filter it. If it comes out of the water as an oil, you can extract it in ether!
3. Isolating a neutral amine from the  $\text{HCl}/\text{water}$  layer:
  - **Basify/Neutralize**  $\text{NaOH}$  is added to basify the water. In the process the ammonium cation  $\text{RNH}_3^+$  is deprotonated and converted back to its neutral form  $\text{RNH}_2$ .
  - **Filter or Extract** Because the amine is now neutral, its solubility in water will be low. If it crystallizes, you can filter it. If it comes out of the water as an oil, you can extract it in ether!

### **Partition Coefficients and Multiple Extractions**

In the presence of two solvents (ether and water in our case), each specific chemical has a characteristic “partition coefficient”, with the following formula:

$$\text{Partition coefficient} = \text{solubility in ether}/\text{solubility in water}.$$

The partition coefficient basically tells you what fraction of the material will partition into each solvent layer. If the value is 4:1, that means 80% will partition into the ether layer, and 20% will partition into the water layer.

- Ideally, the distribution will be either zero (all stays in water) or infinity (totally in ether).
- This is not often the case. Frequently some of the neutral organic material will be lost to the water layer, and sometimes some of the ionic material will go into the ether layer. In either case, either the yield and/or the purity will not be 100%.

To improve extraction efficiency, **often two (or more) extractions may be appropriate**.

- **Example 1: Suppose you are trying to get all of your organic material into the organic phase,** but the partition coefficient for your desired neutral organic is only 4:1. If you do one separation, you should have 80% of the material in the ether extract, and 20% of the material in the water phase. By extracting the water again with more ether, you should get 80% of the remaining 20% that was in the water, i.e. you should get another 16% out into the ether, and now only 4% of the neutral should remain in the water. A third ether extraction of the water should take out 80% of the remaining 4%, thus leaving less than 1% of your material left in the water layer. Combine all the ether extracts, dry/concentrate, and you should get 99% yield.
- **Example 2: Suppose you are trying to use aqueous base to extract a carboxylic acid from a neutral organic,** but only 90% of the acid goes into the NaOH/water and 10% stays in the ether. If you do only one separation, your neutral organic will still be contaminated by the residual 10% of acid. But if you do a second extraction with NaOH/water, 90% of that 10% will be extracted as well, and now only 1% of the acid will remain in the ether layer to contaminate your neutral.

The process of extracting from a particular phase, to either make sure you get all the target organic out (example 1) or to make sure you remove all of an undesired contaminant (example 2) is often referred to as “**washing**”. In example 2, the carboxylic acid was “washed out” of the ether layer by a couple of NaOH/water “washes”.

To determine how many “extractions” are required to achieve a target minimum of non-extracted material, use  $y^x$ , where “y” is the fraction that survives a particular extraction, and “x” is the number of extractions. (In example 1,  $y^x = 0.20^3 = 0.008 = 0.8\%$ .)

### **Choice of Organic Solvent**

1. **Low Boiling Point** Since you normally have to distill off your solvent at the end, a low-boiling solvent that can be simply distilled away quickly and rapidly is very desirable.
2. **Good Dissolving Ability for Organics** Obviously you'd like your organic solvent to have much better dissolving ability for organics than does water. Sometimes the nature of the solute dictates which solvents are acceptable.
3. **Low Miscibility with Water** You'd like relatively water to dissolve into the organic phase, and vice versa.
4. **Higher or Lower Density Than Water, Depending on Extraction Purpose** Typically when multiple extractions/washes are used, it is desirable to have the “extraction solvent” be denser than the solvent that is “being washed”.
  - **If you are going to “wash” the organic solvent several times with water** (example 2), it is technically convenient if the organic layer floats on the water layer. **This is true for ether.**
  - **If you are going to “wash” the water layer several times** to make sure you get all your organic material into the organic phase, it is more convenient to use a solvent that is more dense than water, so that the water will float on the organic solvent and you can pour the organic solvent out the bottom. This is not true for ether, so it isn't that convenient for multiple washes/extractions from water. **Dichloromethane, which is more dense than water, is frequently used** instead for doing multiple washes/extraction from a water layer.
5. **Safe, Cheap, Unreactive...**

**LIQUID/LIQUID SEPARATION: EXTRACTION OF ACIDS OR BASES FROM NEUTRAL ORGANICS. PROCEDURES.**

Carboxylic acid unknown options (Part 1): benzoic acid (mp 123) or 2-chlorobenzoic acid (mp 141)

Amine unknown options (Part 2): 4-chloroaniline (mp 68-71) or ethyl 4-aminobenzoate (mp 90)

Neutral options (same choices for both Part 1 and Part 2): 1,4-dimethoxybenzene (mp 57), naphthalene (mp 82), dibenzalacetone (mp 110-111), or benzoin (137). Note: You may have the same neutral in both parts.

For flow chart, use "N" for neutral, " $\text{RCO}_2\text{H}$ " for protonated carboxylic acid, " $\text{RCO}_2^-$ " for ionic carboxylate salt, " $\text{RNH}_2$ " for neutral amine, and " $\text{RNH}_3^+$ " for ionic ammonium salt.

**Part 1: Separation of a Neutral from a Carboxylic Acid.**

Setup:

1. Attach your small metal ring to one of the vertical rods on your rack
2. Get your separatory funnel and a glass stopper out of your organic kit. Rest the separatory funnel into the ring.
3. Make sure the stopcock is closed (and screwed tight)!

Procedure:

**Phase 1: Separating the two Chemicals into Two Liquid Phases. Extracting the Acid.**

1. Weight out about 2 g (record exact weight) of a 50/50 mixture (by weight) of N/ $\text{RCO}_2\text{H}$ . (In other words, the mixture consists of 1 gram of neutral and one gram of acid). Pour the solid mix into your separatory funnel.
2. Add 20 mL of diethyl ether ("ether"). If the mixture doesn't dissolve, add enough ether to fully dissolve it.
3. Add 10 mL of 3M NaOH to the separatory funnel, stop it, shake vigorously, vent, and allow the layers to separate. (Purpose: to convert the neutral acid into carboxylate anion, which should then go into the aqueous layer rather than staying in the ether layer).
4. Label a 50-mL Erlenmeyer flask as "Flask 1" with your Sharpie pen, and a 150 mL beaker as "waste".
5. Get a couple of pieces of pH paper or litmus paper.
6. Drain off the aqueous layer into Flask 1 (use a funnel). Pass a stick of pH paper into the draining stream to confirm that it is basic. (Be sure you have removed the stopper from your separatory funnel first.) (Note: it is better to have a little water stay in the ether layer than to have some of the ether layer go into the aqueous.)
7. Add an additional 5 mL of 3M NaOH to the separatory funnel, shake the mixture as before, let it settle, and again drain the aqueous layer into Flask 1.
8. Save Flask 1, the contents of which you will process a little later.

**Phase 2: Isolating the Neutral Organic from the Ether Phase.**

9. Add 15 mL of "brine" (saturated aqueous solution of sodium chloride) to the separatory funnel, shake the mixture thoroughly, allow the layers to separate, and drain off the aqueous layer into the "waste" beaker. The contents can be poured down the drain. (Purpose: the brine reduces the solubility of water in the ether, so the ether will be less wet.)
10. Carefully pour the ether layer into a 125-mL Erlenmeyer flask (labeled "Flask 2") from the top of the separatory funnel, taking care to minimize transfer of water droplets.
11. Rinse the separatory funnel with an additional 5-mL of ether, and add that rinse to Flask 2.
12. Add sodium sulfate to Flask 2 and swirl. The amount required depends on how much water is in the mixture. Typically one full scoopula of sodium sulfate should suffice, but frequently additional drying agent is required. If the solution is dry, the liquid should look very clear and not cloudy, and at least some of the granules should not clump together. If all of the moisture has been absorbed, there should be at least some fine granular "non-clumpy" sodium sulfate granules left, and the solution should be clear. (Purpose: the sodium sulfate is intended to absorb any water that is in the ether solution.)
13. Pre-weigh a 50-mL round-bottomed flask, and then clamp it onto a vertical rod.
14. Take your long stem funnel and push a little glass wool into the neck. A little bit will suffice. A pipet is often helpful for pushing it in a little bit.

15. Pour the ether solution from Flask 2 through the glass-wool plugged funnel into the round-bottomed flask. The wool should be sufficient to filter off the solid sodium sulfate, and only allow the solution to get into the flask.
16. Rinse Flask 2 and the sodium sulfate pad with 10 mL of ether, and pour the rinse through the funnel into the round-bottomed flask.
  - At this point, there should be only ether and neutral in the flask. The acid should have been removed by the NaOH; the water should have been removed by the sodium sulfate; and the sodium sulfate should have been removed by the filtration.
17. Concentrate the ether solution in the round-bottomed flask by rotary evaporation. Be sure the aspirator power is on; that the top air valve is closed; and that you have an adapter for a good glass seal. Make sure that the spinner is also turned on. Get help the first time you use this!
  - Note: This is a standard simple distillation to remove the volatile ether while leaving the higher boiling, less volatile organic material behind. The vacuum further lowers the boiling point for the ether so that it comes off very quickly.
18. Once the sample has concentrated to dryness, weight the flask and calculate your mass yield.
19. Take a melting point, perhaps after waiting for 15 hours or more.
  - You have now completed isolation of sample from Flask 2.
  - Note: the melting points are likely to be somewhat depressed, because the products will have some impurities. The products could be further purified by recrystallization, but time does not permit!

Phase 3: Isolating the Neutral Carboxylic Acid from the Aqueous Phase.

20. Acidify the contents of Flask 1 by adding concentrated hydrochloric acid pipet-by-pipet, while testing with pH or litmus paper until the solution is decidedly acidic ( $\text{pH} < 4$ ). There is little harm in adding extra acid. (Be sure you use concentrated hydrochloric acid. Otherwise it will take too long to neutralize the water, and your yield will go down because of so much solvent.)
21. Cool flask 1 in ice, then filter (Buchner funnel), rinsing with a little cold water. Let the product dry, weigh it, and test its melting point. (Give it  $> 15$  hours of drying before taking melting point.)
  - Note: the melting points are likely to be somewhat depressed, because the products will have some impurities. The products could be further purified by recrystallization, but time does not permit!

**Part 2: Separation of a Neutral from a Basic Amine.**

(See introduction above Part 1 for list of unknown candidates.)

The procedure should be largely analogous to that used for extracting an acid, with one huge difference: now you want to extract a basic amine instead of an acid. (When you extracted the acid, you used dilute basic water; to extract the basic amine instead, should you again use dilute basic water, or will you want to use dilute acidic water instead?)

Create a flow chart analogous to that used for the acid, and show it to instructor before going ahead.

Keys to consider: since an amine is basic rather than acidic, should you use HCl or NaOH to ionize it and make it water soluble in the first separation? And once you have ionized it, will you use HCl or NaOH to neutralize it and make it water insoluble? In other words, what changes in your flow chart and procedure result from the fact that you are extracting an amine rather than an acid?

Once you have established and checked your separation/purification plan, proceed to isolate the second neutral and the amine. Record their masses, and record their melting points.

**Extraction/Acid-Base/Separatory Funnel Lab Report**

Name:

1. Yields, Melting Ranges, and Identification: (see p 37 for candidates)

**Part 1: Starting Mass:**

Neutral: isolated yield (in grams) melting range: Identity:

Carboxylic Acid: isolated yield (in grams) melting range: Identity:

**Part 2: Starting Mass:**

Neutral: isolated yield (in grams) melting range: Identity:

Amine: isolated yield (in grams) melting range: Identity:

2. Complete the flow chart for Part 1 (opposite side). Use "N" for the neutral, "RCO<sub>2</sub>H" for the acid in its neutral form, and "RCO<sub>2</sub><sup>-</sup>" for the carboxylate anion form.

3. Include an analogous flow chart for Part 2 (opposite side), with any adjustments required due to starting with a basic amine rather than an acid. Use "N" for the neutral, "RNH<sub>2</sub>" for neutral amine, and "RNH<sub>3</sub><sup>+</sup>" for ionic ammonium salt.
4. Why is it necessary to remove the stopper from a separatory funnel when draining the liquid through the stopcock?

5. The pK<sub>a</sub>s of chemicals HX and HY are 5 and 7 respectively. The pK<sub>a</sub> of carbonic acid H<sub>2</sub>CO<sub>3</sub> is 6. If you made up an ether solution of chemicals HX and HY in a separatory funnel, and then added an aqueous solution of sodium bicarbonate NaHCO<sub>3</sub> to that separatory funnel, would both HX and HY stay in the ether layer? Or would either or both of them transfer into the aqueous layer? If one goes into the water layer, will it be in its neutral HX/HY form, or in its deprotonated anionic form?

HX: ether layer or water layer?

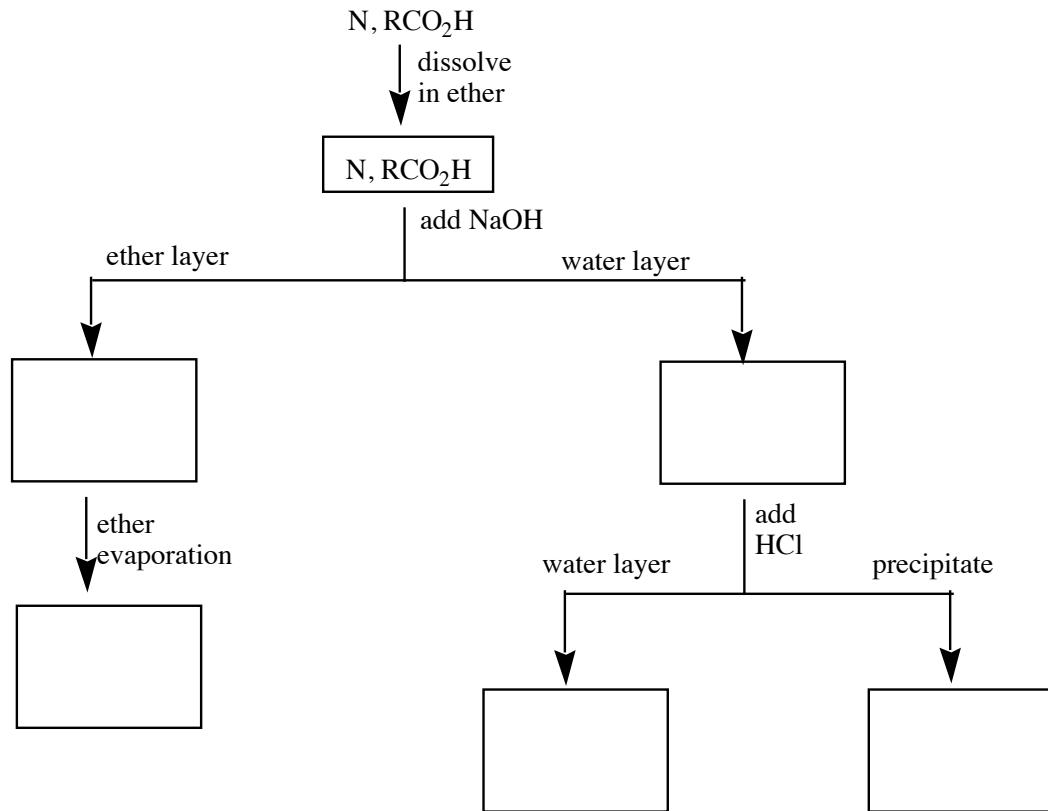
If in the water layer, in HX or X<sup>-</sup> form?

HY: ether layer or water layer?

If in water layer, in HY or Y<sup>-</sup> form?

6. Suppose you have an organic sample **X** that is somewhat soluble in water, even though it is somewhat more soluble in dichloromethane or ether solvents. But if you do a single extraction, you get only 60% of your material to transfer from the water to the organic layer.

- How many "washes" would it take to extract over 90% of your organic material extracted from the water layer?
  - In this case, would it be better to extract with dichloromethane or with ether?
7. Suppose you have an organic sample **X** that is contaminated with an impurity. When you wash with an aqueous phase, **X** stays exclusively in the organic phase, and most (about 80%) but not all of the impurity washes out into the water phase. How many aqueous extracts should you do so that less than 1% of your impurity remains in the organic layer? Will it be more convenient to use ether or dichloromethane as your organic solvent?

**Flow Chart for the Separation of Neutral from Carboxylic Acid**

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Create Your Own Flow Chart for the Separation of a Neutral from a Basic Amine