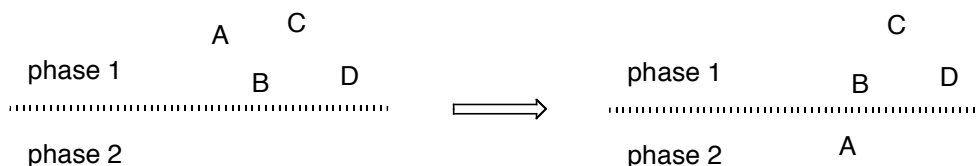


EXTRACTION

Extraction is a process in which a substance is transferred from one phase into another, distinct phase (or phases). At least two phases are required to conduct an extraction. Depending on the physical state of those phases, the following types of extraction can be envisioned: liquid-liquid, liquid-solid, vapor-liquid and vapor-solid. Multiphase extraction processes are possible, but become quite complicated to carry out and to rationalize.

Traditionally, and during this course, the term extraction would refer to a liquid-liquid extraction. In this case, a compound (sometimes referred to as a solute) is dissolved in one liquid substance (known as solvent) to form a solution of that particular compound. This solution is placed in contact with another immiscible solvent, and the compound is transferred from its original solvent (original or source phase) into the other solvent (extracting or receiving phase). An important characteristic of a solvent is that it has to be inert towards the solute. Additionally, the solvent should be volatile enough to be easily removed in order to recover the compound in its original state.

The extraction is one of the primary tools to separate mixtures of compounds. For example, a mixture of **A**, **B**, **C**, **D** is dissolved in *phase 1*, and placed in contact with an immiscible *phase 2* (Scheme 1). The transfer of compound **A** from *phase 1* into the *phase 2* will constitute an extraction of compound **A**. In case when only **A** is transferred into *phase 2*, and all other compounds stay in the original phase, the extraction is considered to be selective. In those cases, when more than one compound is transferred between the phases, *e.g.*, **B** would be extracted into *phase 2* along with **A**, a non-selective extraction is realized.



Scheme1.

The reason for compound **A** to be transferred into *phase 2* from *phase 1* (Scheme 1) is a higher affinity of **A** towards *phase 2*, than *phase 1*. This paradigm is known as “**like dissolves like**.” Polar compounds would tend to be more soluble/miscible with/in polar solvents, whereas non-polar compounds would have higher solubilities/miscibilities in/with non-polar solvents. A polar compound such as methanol, CH_3OH , is completely miscible with water or other alcohols (ROH , where R is an alkyl group); hexane, C_6H_{14} , which is a non-polar substance, will not be miscible in water. Following the same line of reasoning, a two-phase mixture of diethyl ether, $(\text{CH}_3\text{CH}_2)_2\text{O}$, and water can be turned into a one-phase (homogeneous) mixture by adding *iso*-propanol, $(\text{CH}_3)_2\text{CHOH}$, which has an affinity to both water (due to the hydrophilic, polar OH-group) and to diethyl ether (due to the presence of hydrophobic, non-polar *iso*-propyl group).

Fundamentally, there is no difference whether the receiving phase is at the top or at the bottom. Relative position of the original and receiving phases, *i.e.*, the top or the bottom, is determined by their respective densities. For liquid-liquid extraction, at low concentrations of the compound, the density of the solution is assumed to be the same as the density of the pure solvent. At higher concentrations, the solubilized species can significantly alter the density of the solvents in which they are dissolved.

The distribution of a compound between two distinct phases is based on the affinity of the compound towards those phases. At equilibrium and at a given temperature, the ratio of concentrations of a compound in two distinct phases is a constant:

$$K = [A]_{\text{phase2}} / [A]_{\text{phase1}}$$

where $[A]$ is the concentration of compound **A** in phase 1 and phase 2 in g/ml, and K is the partition coefficient. The above equation in a more descriptive version can be rewritten as follows:

$$K = \frac{\text{grams of A in phase 2 / ml of phase 2}}{\text{grams of A in phase 1 / ml of phase 1}}$$

The above equation is applicable only to dilute solution, *i.e.*, low concentrations of the compound. In addition, the degree of association of the compound should be similar in both phases. The compound can be effectively transferred from one phase onto the other, if $K \gg 100$. If $K < 100$, multiple extractions have to be carried out to transfer **A** from *phase 1* into *phase 2*. Unquestionably, the greater the number of extractions, and hence the larger the volume of the extracting phase, will result in a more efficient transfer of **A** from *phase 1* into *phase 2*. The practical limitation of such an approach is the amount of solvents that one can use for a given extraction process. With the limited volume of the extraction phase, the above equation can be used to establish whether a single extraction with a given amount of *phase 2* will be more (or less) efficient in transferring **A** from *phase 1* into *phase 2*, than multiple extractions with smaller volumes of the same total volume.

Consider the following scenario:

10 g of compound **X**, which has $K=10$ for the given set of solvents, is dissolved in 500ml of *solvent 1*. 150 ml of *solvent 2* is to be used to transfer **X** from *solvent 1* into *solvent 2*. Which of the following procedures will allow a more efficient transfer of **X**: i) using a single extraction of 150 ml or ii) three extractions with 50 ml each?

To solve it, one can rewrite the above equation as follows:

$$K = \frac{g_{\text{extracted}} / \text{ml}_{\text{sol2}}}{g_{\text{remained}} / \text{ml}_{\text{sol1}}}$$

where $g_{\text{extracted}}$ is the number of grams of **X** that were extracted from *solvent 1* (sol1) into *solvent 2* (sol2); g_{remained} is the number of grams of **X** that were left in *solvent 1*; $g_{\text{extracted}} + g_{\text{remained}} = g_{\text{initial}} = 10 \text{ g}$.

The above equation can be solved either for $g_{\text{extracted}}$ or g_{remained} , and the fraction of **X** that is left, *i.e.*, $g_{\text{remained}}/g_{\text{initial}}$, or the fraction of **X** that is transferred, *i.e.*, $g_{\text{extracted}}/g_{\text{initial}}$, can be expressed as follows:

$$\frac{g_{\text{remained}}}{g_{\text{initial}}} = \frac{\text{ml}_{\text{sol1}}}{K\text{ml}_{\text{sol2}} + \text{ml}_{\text{sol1}}} ; \quad \frac{g_{\text{extracted}}}{g_{\text{initial}}} = \frac{K\text{ml}_{\text{sol2}}}{K\text{ml}_{\text{sol2}} + \text{ml}_{\text{sol1}}}$$

It is apparent that performing more extractions is more efficient than performing a single extraction even if the total volumes used in both cases are the same. For example, after the 1st extraction:

$$\frac{g_{\text{remained}}^{1\text{st}}}{g_{\text{initial}}^{1\text{st}}} = \frac{m_{\text{sol1}}}{K m_{\text{sol2}} + m_{\text{sol1}}}$$

After 2nd extraction:

$$\frac{g_{\text{remained}}^{2\text{nd}}}{g_{\text{initial}}^{2\text{nd}}} = \frac{m_{\text{sol1}}}{K m_{\text{sol2}} + m_{\text{sol1}}}$$

Since $g_{\text{initial}}^{2\text{nd}} = g_{\text{remained}}^{1\text{st}}$:

$$\frac{g_{\text{remained}}^{2\text{nd}}}{g_{\text{initial}}^{1\text{st}}} = \left(\frac{m_{\text{sol1}}}{K m_{\text{sol2}} + m_{\text{sol1}}} \right)^2$$

Applying the same rationale, it can be recognized that the amount of **X** remaining in the *solvent 1* will be decreasing with each subsequent extraction, as the fraction of the remained **X** after the 3rd, 4th ... nth extractions can be described as:

$$\frac{g_{\text{remained}}^n}{g_{\text{initial}}^{1\text{st}}} = \left(\frac{m_{\text{sol1}}}{K m_{\text{sol2}} + m_{\text{sol1}}} \right)^n$$

Furthermore, it is also evident that as *K* decreases, the number of extractions should be increased to assure an efficient extraction. It should be kept in mind, however, that the amount of solvent and the number of extractions, *i.e.*, the time of the extraction, must be justifiable with respect to the value of compound **X**. For the majority of cases in this course, two-three extractions should be sufficient to extract a particular compound from the original phase.

Another useful parameter is a separation factor, β , which is used to estimate whether two compounds (**A** and **B**, for example) can be separated using a simple extraction:

$$\beta = K_A / K_B.$$

For $\beta > 100$, both **A** and **B** can be separated using simple extraction; for $\beta < 100$, simple extraction will not work, and continuous extraction methods should be applied.

The mass transfer between the phases is realized only at the interface. Therefore, increasing the surface area of the two phases. In case of the liquid-liquid system, the biphasic mixture is shaken or stirred; in case of a solid-liquid or vapor-solid extractions, the solid has to be finely ground.

Extraction of solids (liquid-solid extraction):

A solid which contains a compound **A** is heated in a given solvent (**A** should be completely soluble in that solvent), followed by filtration or decantation. In those instances, when incomplete extraction is realized, the extraction is repeated.

A more efficient extraction of organic compounds from solid mixtures is realized by using Soxhlet extraction (Figure 1). The solid material, which contains the compound of interest, is placed into a thimble (a tube open at the top, which is made of a thick filter paper). The thimble is placed into the main chamber of the Soxhlet extractor. The solvent is placed into a round bottom flask, and the set-up is connected to the condenser. The vapor of the solvent from the heated flask will be traveling through the distillation arm, and it will be condensing into the main chamber, where the contact with the solid will be made, and the extraction process will take place. The excess of the solvent (which contains the compound) will be removed from the main chamber into the flask *via* a side arm (siphon) once the main chamber is filled with solvent. The compound will be concentrated in the flask. This process can be allowed to proceed over hours or even days to achieve an efficient extraction. The Soxhlet extraction is used extensively for isolation of various natural products from natural extracts.



Figure 1

Extraction from liquids: liquid-liquid extraction

Extraction of compounds from solutions constitutes one of the main separation procedures in organic chemistry. Usually, the mixture of compounds is dissolved in a particular solvent and placed into a separatory funnel (Figure 2). An immiscible solvent is added to form a two-phase system. It is important not to overfill the separatory funnel: as a rule of thumb, no more than 2/3 of the funnel's volume should be occupied by both liquids. The funnel is topped with a stopper, and at first the mixture should be carefully and gently shaken, while tightly holding the stopper and the stopcock (Figure 3, A). The built-up pressure has to be released by slowly opening the stopcock to vent (Figure 3, B). After repeating this process several times, or until the pressure built-up has ceased, the mixture can be vigorously shaken for a few minutes to assure the maximum contact of the two phases. The phases should be allowed to separate to achieve a clear interface, followed by the phase separation.



Figure 2.

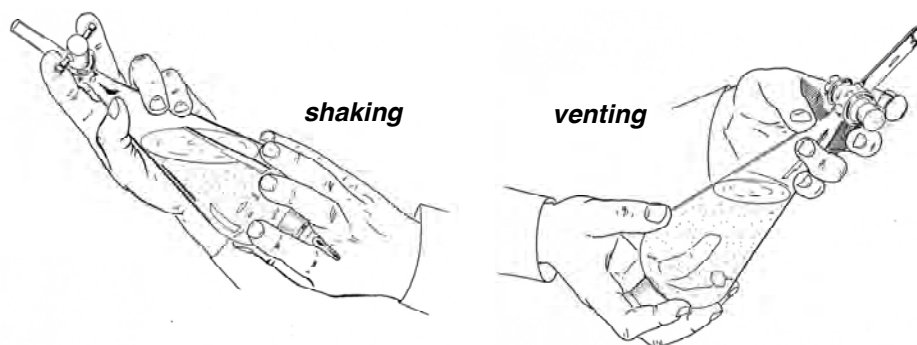


Figure 3.

Salting out

Altering one of solvents (*solvent 1* or *solvent 2*) of a biphasic system will alter the partition coefficient of compounds dissolved in the system. In a biphasic, organic/aqueous system an organic material with a low solubility in water will have even a lower solubility in water which is saturated with NaCl. Water will be involved in stabilizing Na^+ and Cl^- ions rather than the organic material. Thus, the solubility of the organic material in the aqueous phase will decrease. This process will afford a more efficient transfer of a organic species, which have some solubility in water, into an organic phase.

The same rationale is applied when a brine solution (saturated aqueous solution of NaCl) is added to break up the emulsions, which result from the dissolution/suspension of organic species in aqueous phase, and aqueous species in the organic phase. In aqueous-organic solvent systems, a formation of an emulsion is often observed upon shaking of the two phases.

Drying agents

Even though the terms immiscible and insoluble are used, it should be kept in mind that everything is soluble/miscible in everything, the only question is – to which extent? For example, dichloromethane (CH_2Cl_2), a commonly used organic solvent, is not miscible with water: a two-phase system is obtained when water is added to dichloromethane. However, the CH_2Cl_2 layer is saturated with water, and the water layer is saturated with CH_2Cl_2 . In order to remove small amounts of water from the organic solution, drying agents have to be used. The commonly used drying agents are inorganic materials that can adsorb water. Generally, one adds enough drying agent in portions until the appearance of the solid does not change, *i.e.*, it stays as a powder or in its original form, instead of “clumping”. Here is the list of commonly used drying agents:

Na_2SO_4 : one of the most common, inexpensive drying agent. Anhydrous Na_2SO_4 slowly forms a hexahydrate ($\text{Na}_2\text{SO}_4 \cdot 6\text{H}_2\text{O}$), which is responsible for the removal of the water. However, at elevated temperatures drying capacity of Na_2SO_4 is reduced, due to decreased concentration of the hexahydrate.

MgSO_4 : a very common drying agent. It possesses a very high surface area, and it is capable of quickly drying (much faster than Na_2SO_4) various solvents and liquid substances. Although it is generally believed to be a neutral drying agent, MgSO_4 is slightly acidic, and sometimes is used as a catalyst for organic transformations. In addition, milky solutions with methanol and acetonitrile, which are difficult to remove.

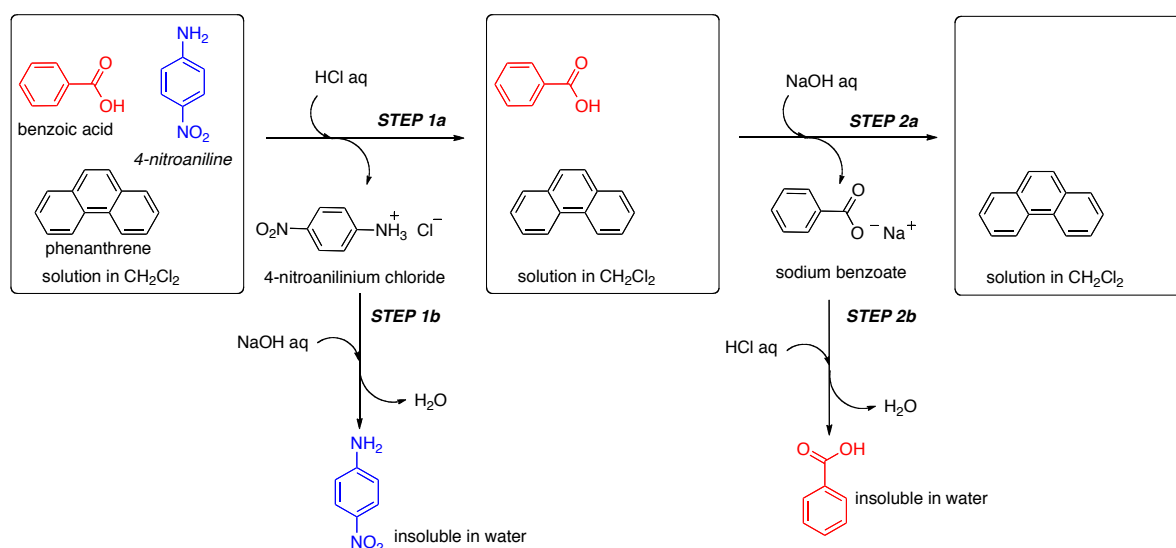
CaCl_2 : one of the common, very efficient and inexpensive drying agents. It is very reactive towards acidic hydrogens. Therefore, CaCl_2 should be used for drying such compounds as hydrocarbons and alkyl/aryl halides; drying of amines and alcohols with CaCl_2 should be avoided.

K_2CO_3 : is an inexpensive, and very efficient drying agent. However, it cannot be used to dry acidic substances or solvents, since K_2CO_3 is a base.

Molecular sieves (MS): aluminum silicates (known as zeolites) are porous materials, which can encapsulate various compounds within their framework. The compounds diffuse into the pores of the MS and they are being trapped. MS is an excellent drying agent for removing small amounts of water from various liquids that have a molecular size greater than water. The drying capacity of MS could be restored by extensive heating for prolonged periods of time.

Acid-base extractions:

In a variety of extraction processes, a chemical reaction (usually an acid-base reaction) is used to facilitate the extraction process. Charged species, such as organic salts are more polar than neutral species and therefore much more soluble in water. For example, a solid mixture containing phenanthrene, benzoic acid and 4-nitroaniline has to be separated into the individual components using simple extraction. All of the above organic compounds are completely soluble in an organic solvent, such as dichloromethane (following the principle – like dissolves like). The partition coefficients of all three compounds in a dichloromethane – water mixture are fairly similar. Hence, the efficient extraction cannot be realized. However, the chemical nature of all of these organic compounds is different: benzoic acid contains an acidic hydrogen, which can easily react with a base, leading to a formation of the salt; 4-nitroaniline has an unshared pair of electrons on the nitrogen of the amino-group, which can be easily protonated by an acid; phenanthrene, does not have any acid no basic groups, and therefore should not engage into any of the acid-base interactions. This process is illustrated in Scheme 2:



Scheme 2.

A mixture containing equal amounts of phenanthrene, benzoic acid and 4-nitroaniline is dissolved in dichloromethane (Scheme 2). When an aqueous solution of HCl is added to the dichloromethane solution, only 4-nitroaniline can participate in an acid-base reaction to produce the corresponding salt, *i.e.*, 4-nitroanilinium chloride (*STEP 1a*). This salt has a much higher solubility in aqueous medium than the corresponding 4-nitroaniline and therefore, it is selectively transferred into the aqueous layer. Two other components of the mixture will not react with HCl, and therefore, they will stay in the dichloromethane phase. Once the two phases are separated, a solution of NaOH is added to the aqueous phase to regenerate 4-nitroaniline *via* another acid-base reaction (*STEP 1b*). 4-Nitroaniline is not soluble in water, and therefore, it can be easily recovered by simple filtration (or it could also be extracted with dichloromethane). Next, the separation of benzoic from phenanthrene is conducted. Again, the reaction between benzoic acid and NaOH will be the only viable acid-base reaction under these conditions (*STEP 2a*). The produced sodium benzoate will have a higher solubility in water than the corresponding acid, and therefore, it will partition into the aqueous phase leaving phenanthrene as the only organic

species in the dichloromethane phase. Once the organic and aqueous phases are separated, the benzoic acid will precipitate upon an acidification of the aqueous phase (*STEP 2b*) (or it could also be extracted with dichloromethane). Simple filtration can be used to isolate the benzoic acid.

Since dichloromethane has been in contact with aqueous phases through *STEP 1a* and *STEP 2a*, it does contain some amounts of water. Therefore, the application of a drying agent, such as MgSO_4 is required to remove water. As an inorganic salt, MgSO_4 is not soluble in organic solvents (which again follows the principle “like dissolves like”), and therefore, it can be easily separated from the dichloromethane by simple filtration. Distilling out dichloromethane will yield phenanthrene.

Overall, the separation of three organic compounds has been achieved by using two extraction steps, which rely on simple acid-base reactions. The efficiency of this procedure is established by measuring the amount of the recovered materials. The purity of the recovered products is established by measuring the melting points. It should be kept in mind that there is no fundamental difference, for this particular system, as to whether *STEP 1a* is followed by *STEP 2a* or *vice versa* (Scheme 2).

pKa information for extraction

HCl/Cl^- pKa: -7

p-nitroaniline/ RNH_3^+ pKa ~1

Benzoic acid/ PhCOO^- pKa: 4.18

$\text{H}_2\text{O}/\text{HO}^-$ pKa ~16

Anthracene (or phenanthrene)

RH/R^- pKa >35

RH/RH_2^+ pKa <<-3

PROBLEMS

1. Sodium bicarbonate (NaHCO_3) is often used to neutralize acids during acid-base extractions. However, it also causes foaming and/or pressure buildup. Provide a chemical explanation for this phenomenon.
2. Which of the following organic solvents could be used for extracting an organic compound from the aqueous solution:
 - a. Acetone
 - b. Dichloromethane
 - c. Ethyl acetate
 - d. Ethanol
 - e. Toluene
 - f. Acetic acid
 - g. Cyclohexane
3. If you need to extract a 50ml aqueous solution with 50ml of dichloromethane, what is the minimum size of a separatory funnel you will have to use to safely carry out this procedure. Briefly explain your answer.
4. How many moles of potassium carbonate (K_2CO_3) are contained in 2ml of 1M aqueous solution?
5. Assuming that 50% of the compound can be separated using 1 extraction, how many extractions should be done to separate 75% of the compound.
6. Calcium hydride (CaH_2) is commonly used to dry hydrocarbons, halogen-containing hydrocarbons and ethers. However, this hydride reacts violently with carboxylic acids as well as methanol and ethanol. Provide a chemical reaction that explains the drying ability of CaH_2 .
7. An organic compound distributes between ethyl acetate and water with a partition coefficient 5. Suggest a simple method to increase this partition coefficient.