Organic Chemistry I

Lab Course Manual

Fall Semester 2016

JACOBS
UNIVERSITY

Experimental Part

Exp. 1   -   Separation of a two-component mixture

The desired compound from a reaction is frequently part of a mixture, and its isolation in pure form can be a significant experimental challenge. Two of the more common methods for separating and purifying organic liquids and solids are **extraction** and **distillation**. Two other important techniques available for these purposes are **recrystallization** and **chromatography**.

Extraction

Extraction involves selectively removing one or more components of a solid, liquid, or gaseous mixture into a separate phase. The substance being extracted will partition between the two phases that are in contact and the ratio of its distribution between the phases will depend on the relative solubility of the solute in each phase.

The two solvents must be immiscible and form two distinct layers, and in general one layer is aqueous and the other is an organic solvent such as diethyl ether, hexane, or dichloromethane. The two liquids in the mixture have different densities, making the heavier liquid settle at the base of the container. Separation of the two layers results in the separation of the two compounds.

Depending upon the amounts of material, the physical separation of the two immiscible phases will be performed in separatory funnels or conical vials. The volumes of solvent are too small to use separatory funnels for extractions when reactions are conducted on a microscale level. In these instances, conical vials may be employed for volumes up to about 4 mL, and screw-cap centrifuge tubes may be used for volumes up to approximately 10 mL
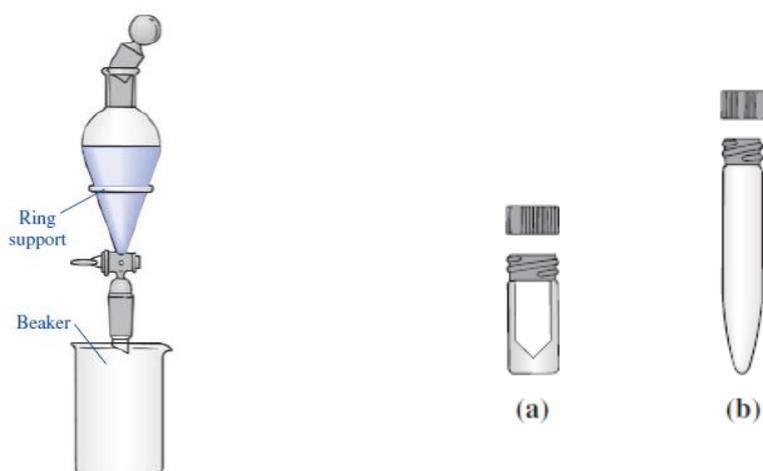

Figure 1: Separatory funnel positioned on iron ring with beaker located to catch liquid if funnel leaks

Figure 2: Apparatus for microscale extraction: (a) conical vial; (b) screw-cap centrifuge tube.

Depending upon the solvent used, the organic phase may be either the upper or lower layer, and a slightly different procedure is used for separating each. The more common situation is one in which the organic solvent is less dense than water, and it is this layer that is removed. For example, if you extract an aqueous solution with diethyl ether (ether), the organic layer is the upper one because ether is less dense than water. Alternatively, when a solvent that is heavier than water, such as dichloromethane, is used for the extraction, the lower layer is the organic layer, and it is the one removed.

It is important to ascertain which of the two layers in a separatory funnel is the aqueous layer and which is the organic. Because the layers should separate so that the denser solvent is on the bottom, knowledge of the densities of the liquids being separated provides an important clue as to the identity of each layer.

Because one of the layers is usually aqueous and the other is organic, there is a simple and foolproof method to identify the two layers. Withdraw a few drops of the upper layer with a pipet and add these drops to about 0.5 mL of water in a test tube. If the upper layer is aqueous, these drops will be miscible with the water in the test tube and will dissolve, but if the upper layer is organic, the droplets will not dissolve.

Distillation

Simple distillation allows separation of distillates from less-volatile substances that remain as pot residue at the completion of the distillation. It allows isolation of the various components of the mixture in acceptable purity if the difference between the boiling points of each pure substance is grater than 40 -50°C. For example, a mixture of diethyl ether, bp 35°C (760 torr) and toluene, bp 111°C (760 torr) could easily be separated by simple distillation, with the ether distilling first.

If this is not the case, the technique of fractional distillation is normally used to obtain each volatile component of a mixture in pure form. It should be noted that the boiling points of the ideal solution containing different components may be lower than the boiling point of any component of the mixture on its own.
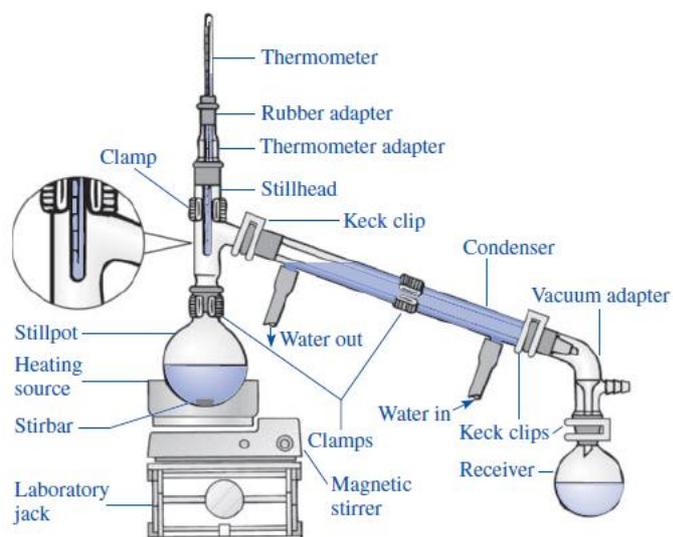
Figure 3: Typical apparatus for simple distillation at atmospheric pressure or under vacuum.

References:

Gilbert, John C. and Stephen F. Martin ; *Experimental Organic Chemistry*. Belmont, CA: Thomson Brooks/Cole, 2006.

Exp. 2   -   Nucleophilic Substitution

Nucleophilic substitution reactions are among the most fundamental types of organic reactions. In a nucleophilic substitution reaction a nucleophile (Nu) displaces a leaving group (LG) in the molecule that undergoes the substitution (the substrate).

The nucleophile is always a Lewis base, and it may be negatively charged or neutral. The leaving group is always a species that takes a pair of electrons with it when it departs.

Often the substrate is an alkyl halide and the leaving group is a halide anion. The following equation is a generic nucleophilic substitution reaction

$$Nu\overset{\ominus}{\colon} \;+\; R\!\!-\!\!LG \longrightarrow R\!\!-\!\!Nu \;+\; \overset{\ominus}{LG}\colon$$

In nucleophilic substitution reactions the bond between the substrate carbon and the leaving group undergoes heterolytic bond cleavage. The unshared electron pair of the nucleophile forms the new bond to the carbon atom.

A key question we shall want to address is this: when does the bond between the leaving group and the carbon break? Does it break at the same time that the new bond between the nucleophile and carbon forms? Or, does the bond to the leaving group break first?

When a nucleophile reacts with an alkyl halide, the carbon atom bearing the halogen atom is the positive center that attracts the nucleophile. This carbon carries a partial positive charge because the electronegative halogen pulls the electrons of the carbon–halogen bond in its direction.
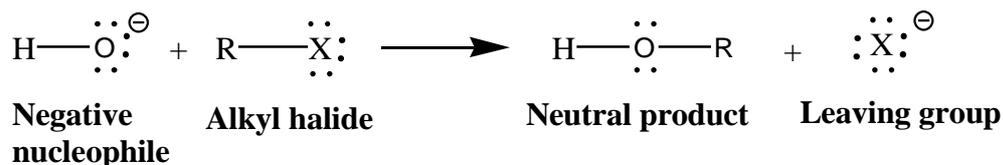
S$_N$2 reaction:

The S$_N$2 reaction is said to be a concerted reaction, because bond forming and bond breaking occur in concert (simultaneously) through a single transition state.

Use of a negatively charged nucleophile (hydroxide in this case) results in a neutral product (an alcohol in this case). Formation of the covalent bond between the negative nucleophile and the substrate neutralizes the formal charge of the nucleophile. Nucleophilic substitution by a negatively charged nucleophile results directly in a neutral product.

In the first step of the reaction, the negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The leaving group (X) begins to move away with the pair of electrons that bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and the leaving group is partially broken. The configuration of the carbon atom begins to invert. As the nucleophile forms a bond and the leaving group departs, the substrate carbon atom undergoes an inversion of its tetrahedral bonding configuration ; it is turned inside out.
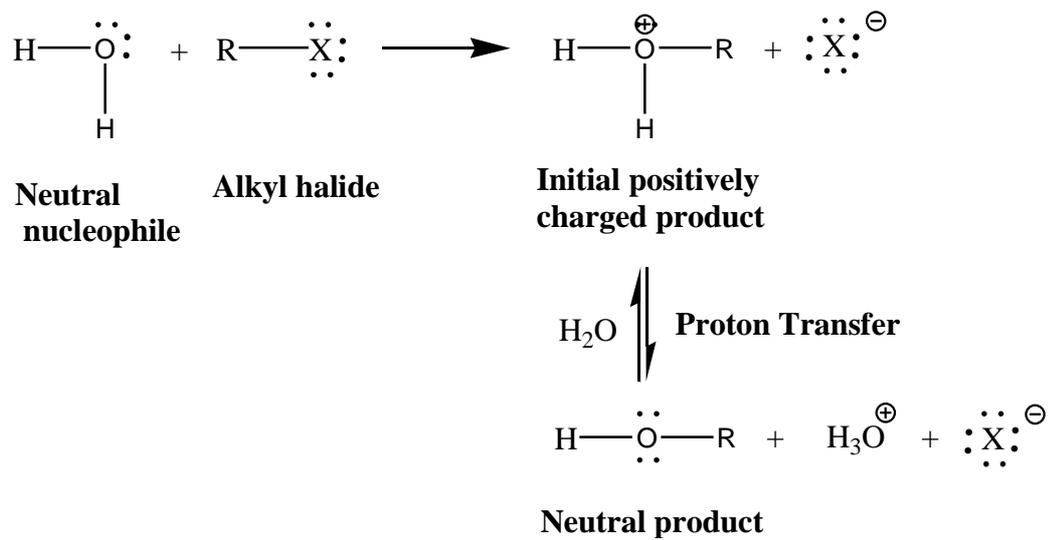
$$H—\overset{..}{\underset{..}{O}}{:}^{\ominus} \quad + \quad R—\overset{..}{\underset{..}{X}}{:} \quad \longrightarrow \quad H—\overset{..}{\underset{..}{O}}—R \quad + \quad {:}\overset{..}{\underset{..}{X}}{:}^{\ominus}$$

Negative   **Alkyl halide**   **Neutral product**   **Leaving group**
nucleophile

S$_N$1 reaction:

S$_N$1 reaction is a nucleophilic substitution reaction and it is said to be unimolecular (first-order) in the rate-determining step, thus, the rate equation is often shown as having first-order dependence on electrophile and zero-order dependence on nucleophile.

Use of a neutral nucleophile (water in this case) results initially in a positively charged product. The neutral nucleophile gains a positive formal charge through formation of the covalent bond with the substrate. A neutral product results only after a proton is removed from the atom with the formal positive charge in the initial product.

Departure of the leaving group (assisted by hydrogen bonding with water) leads to the carbocation. The carbocation is an achiral intermediate. Because both faces of the carbocation are the same, the nucleophile can bond with either face to form a mixture of stereoisomers.

H—O: + R—X: → H—O⁺—R + :X:⁻
| H |
H

Neutral nucleophile   **Alkyl halide**   **Initial positively charged product**

H_2O ⇅ **Proton Transfer**

H—O—R + $H_3O^⊕$ + :X:⁻

Neutral product

References:

Solomons, T. W. Graham, Craig B Fryhle, and S. A Snyder. Organic Chemistry.

Exp. 3 - Elimination

Alkenes represent unsaturated hydrocarbons, possessing a polarizable carbon-carbon double bond, a σ- and a π-bond. Elimination reactions are among the most common ways to produce a carbon-carbon π-bond. For example, the elements of hydrogen halide, H–X, may be eliminated from an alkyl halide. The process by which the carbon-halogen bond and an adjacent carbon-hydrogen bond are converted into a carbon-carbon π-bond is called dehydrohalogenation. The same type of π-bond may also be formed by removing the elements of water from an alcohol; this reaction is called dehydration (Eq. 1).
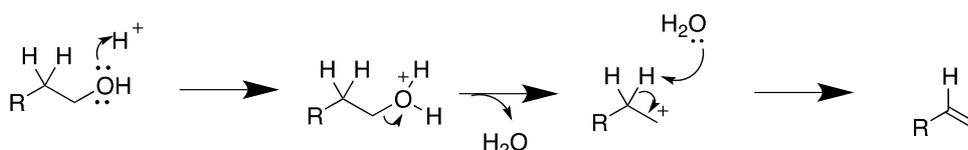
$$\text{(Eq. 1)}$$

Alcohols are amphoteric - they can act both as acid or base. The lone pair of electrons on oxygen atom makes the –OH group weakly basic. The electronegative oxygen atom of an alcohol polarizes the carbon-oxygen bond so the carbon atom bears a partial positive charge $^{(+)}$ and the oxygen atom a partial negative charge $^{(-)}$ in addition to a lone electron pair. This polarization may be transmitted through the π-bond network, a phenomenon referred to as an inductive effect, to enhance the acidity of hydrogen atoms on the adjacent π-carbon atom. Furthermore, oxygen can donate two electrons to an electron-deficient proton. Thus, in the presence of a strong acid, R—OH acts as a base and protonates into the very acidic alkyloxonium ion $^+OH_2$. This is a very good leaving group, as it produces water, allowing for a short living carbocation intermediate. An important characteristic of a good leaving group is that it should be a weak base. The water molecule formed, having this characteristic, may then attack the β-hydrogen leading to the formation of a double bond. The preferred dihedral angle between the β-hydrogen being removed and the leaving group is 180°, an angular relationship called anti-periplanar. This transformation of alkohols to form alkenes is called dehydration.

The reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures. The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

1° alcohols: 170° - 180°C

2° alcohols: 100° - 140°C

3° alcohols: 25° - 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers.

$$2 \text{ R—OH} \xrightarrow{\text{Acid, low } \Delta} \text{R—O—R}$$
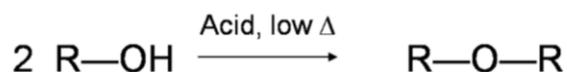
There are different mechanisms for the elimination reactions, the two main ones being E2 and E2. E1 describes an elimination reaction (E) in which the rate-determining step is unimolecular (1) and does not involve additional reagents (Eq. 2). The leaving group leaves in this step, and the proton is removed in a separate second step. The rate of the reaction can be represented by: R = k[alkyl halide]
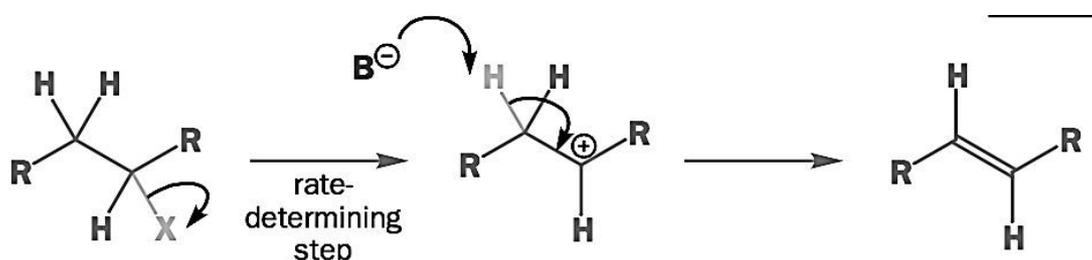
Eq.2

A good example of E1 dehydration would be acid catalyzed removal of water, as the acid reappears in the very last step (Eq. 3):
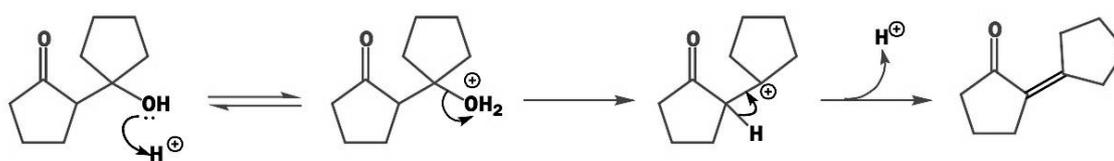
Eq. 3

E2 describes an elimination (E) that has a bimolecular (2) rate-determining step that must involve the base. Loss of the leaving group is triggered by an extra reagent. (Eq. 4) The rate of the reaction can be represented by: R = k[alkyl halide][B:¯]

(Eq. 4)

There are a number of factors that affect whether an elimination goes by an E1 or E2 mechanism. One is immediately obvious from the rate equations: only the E2 is affected by the concentration of base, so at high base concentration E2 is favored. The rate of an E1 reaction is not even affected by what base is present—so E1 is just as likely with weak as with strong bases, while E2 goes faster with strong bases than weak ones: strong bases at whatever concentration will favor E2 over E1. If you see a strong base being used for an elimination, it is certainly an E2 reaction.

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reaction is ranked as the following

methanol < primary < secondary < tertiary

The relative free energies of transition states of competing elimination reactions may be influenced by steric factors that increase the energies of some transition states relative to others. For instance, the less stable alkene may become the major product if steric factors raise the energy of the transition state leading to the more highly substituted alkene more than that for forming the less highly substituted. This may occur when sterically demanding substituents on the carbon atom from which the proton is being removed offer hindrance to the approaching base. Removal of a proton from a less substituted carbon to give a less substituted alkene then becomes more favorable. As more sterically demanding, bulky bases are used, abstraction of the more accessible proton will also be favored, thereby leading to the formation of even greater amounts of the less substituted alkene.
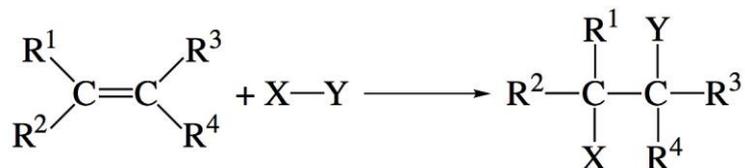
References:

John C. Gilbert, Stephen F. Martin. *Experimental Organic Chemistry_ A Miniscale and Microscale Approach*. 5th ed. N.p.: n.p., 2010. 364-67

Warren, Stuart, and Jonathan Clayden. *Organic Chemistry*. Oxford: Oxford UP, 2001.

Exp. 4 - Addition

Alkenes are useful starting materials for organic syntheses because they undergo a large variety of reactions involving their functional group, the carbon-carbon double or π-bond. One of the typical reactions of alkenes is the addition of a reagent X–Y across the π-bond (Eq. 1).

$$R^2\diagup\!\!\!\!\overset{R^1}{\underset{R^2}{C}}\!\!=\!\!\overset{R^3}{\underset{R^4}{C}} + X\!-\!Y \longrightarrow R^2\!-\!\overset{R^1}{\underset{X}{C}}\!-\!\overset{Y}{\underset{R^4}{C}}\!-\!R^3$$

Eq. 1

Such additions occur because of two principal factors. First, the strength of the carbon-carbon π-bond is 60–65 kcal/mol, a value substantially lower than the 80–100 kcal/mol that is typical for the σ-bond strengths of other atoms bound to carbon. Adding a reagent across the double bond is therefore usually entropically and enthalpically favored, and therefore exothermic, as instead of one π-bond, we observe the formation of two σ-bonds. Second, the π-electrons of the double bond are more loosely held than σ-electrons, so they are more polarizable. Consequently, the π-electron "cloud" is readily distorted through electrostatic interaction with an electron-deficient reagent (electrophile), and this polarization enhances the reactivity of the alkene towards attacks.

In order to understand the mechanism of electrophilic addition, it is helpful to consider this type of addition in terms of reactions in a sequence of Lewis acids and Lewis bases (Eq. 2).
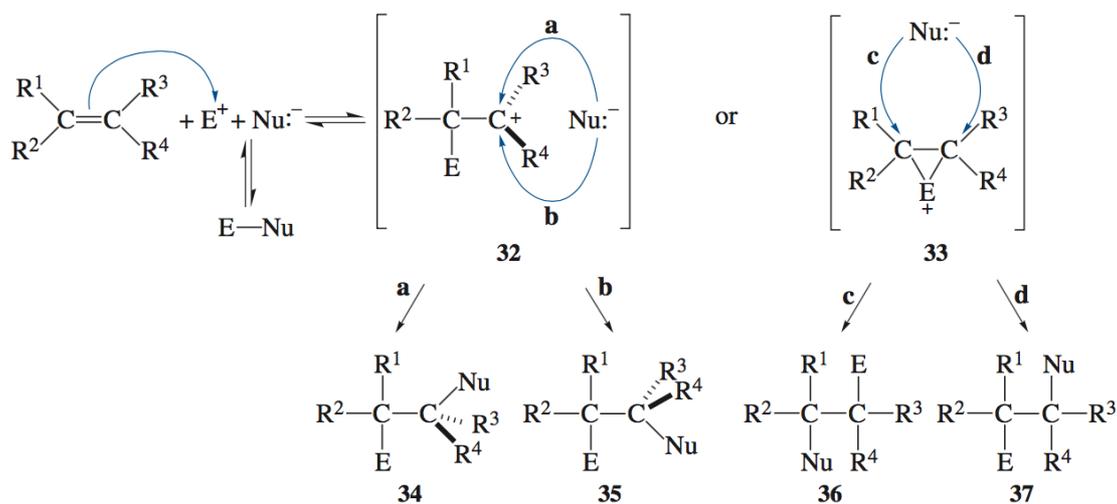
$$\text{Eq. 2}$$

In the first step, the electrons of the polarizable σ-bond, a Lewis base attacks the electrophile E^+, an electron-deficient species, formed during the heterolytic fission (Lewis acid) via S_N1. This results in either an acyclic planar carbocation 32 or a cyclic cation 33.

If carbocation 32 is formed as an intermediate in the electrophilic addition to an unsymmetrically substituted alkene, the electrophile E^+ generally adds to the terminus of the double bond that produces the more stable carbocation 32 according to Markovnikov's rule. Subsequent reaction of this carbocation, a Lewis acid, with the nucleophile $Nu:^-$, a Lewis base, gives the addition product. When the positively charged carbon of 32 is substituted with three different groups, the nucleophile may attack from both faces of the planar ion by paths a and b to give a mixture of 34 and 35, which are stereoisomers. The ionic addition of hydrogen bromide and the acid-catalyzed addition of water to an alkene proceed via planar carbocations (32) the formation of products derived from rearranged carbocations is relatively common.

Some electrophilic reagents add to a carbon- carbon double bond to form a cyclic cation 33; such cations tend not to rearrange. The nucleophile $Nu:^-$ may then attack 33 from both sides by paths c and d to give mixtures of isomers 36 and 37 (S_N2).

The halogenation of alkenes, which is illustrated by the addition of bromine to cyclopentene (Eq. 3), occurs via a cyclic halonium ion (chloronium, bromonium 38, iodonium) related to 33, so skeletal rearrangements of such cations are not generally observed.

Cyclopentene	Bromine	A cyclic bromonium ion	trans-1,2-
(colorless)	(red-brown)		Dibromocyclopentene
			(colorless)
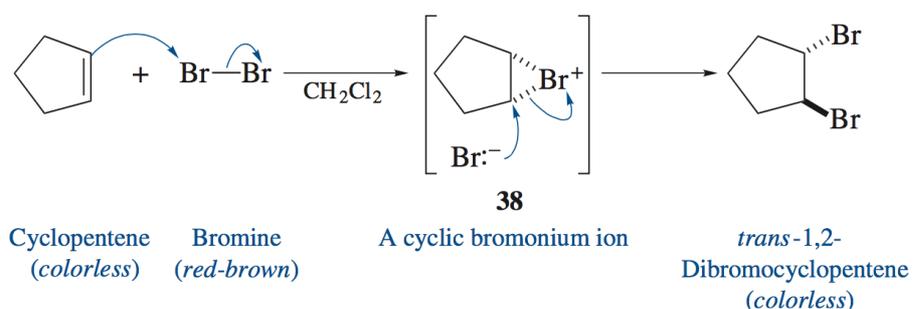
Eq. 3

Moreover, the intervention of this cyclic ion dictates that the stereochemistry of the addition is completely in the anti sense, as shown.

The reddish color of bromine is discharged upon addition to an alkene, making this reaction a useful qualitative test for unsaturation. The more unsaturated an unknown is, the more bromine it reacts with, and the less colored the solution will appear. The iodine value (iodometry) is a way to determine the presence of unsaturation quantitatively. When a yellow/brown iodine solution is added to an unsaturated hydrocarbon solution the strength or magnitude of the color drastically changes. Thus the amount of iodine required to make a solution retain the characteristic yellow/brown color can effectively be used to determine the amount of iodine sensitive groups present in the solution.

References:

Firestone D. *Journal of Aoac International* "Determination of the Iodine Value of Oils and Fats: Summary of Collaborative Study". 77 (3) 674-76.

John C. Gilbert, Stephen F. Martin. *Experimental Organic Chemistry_ A Miniscale and Microscale Approach*. 5th ed. N.p.: n.p., 2010. 364-67

Exp. 5   -   Electrophilic aromatic substitution

Electrophilic aromatic substitution is an important reaction that allows the introduction of many different functional groups onto an aromatic ring. A general form of the reaction is given by the following equation:

$$Ar-H + E^{\oplus} \longrightarrow Ar-E + H^{\oplus}$$

Where Ar–H is an aromatic compound, an arene, and E+ represents an electrophile that replaces a H on the ring. The electrophile is usually produced by the reaction between a catalyst and a compound containing a potential electrophile.

One molecule each of arene and electrophile react to give a cationic intermediate. Experimental evidence indicates that electrophiles attack the p system of benzene to form a *nonaromatic cyclohexadienyl carbocation* known as an arenium ion (a, b and c in Figue1 below). The electrophile takes two electrons of the six-electron p system to form a σ bond to one carbon atom of the benzene ring. Formation of this bond interrupts the cyclic system of p electrons. There is firm experimental evidence that the arenium ion is a true intermediate in electrophilic substitution reactions.
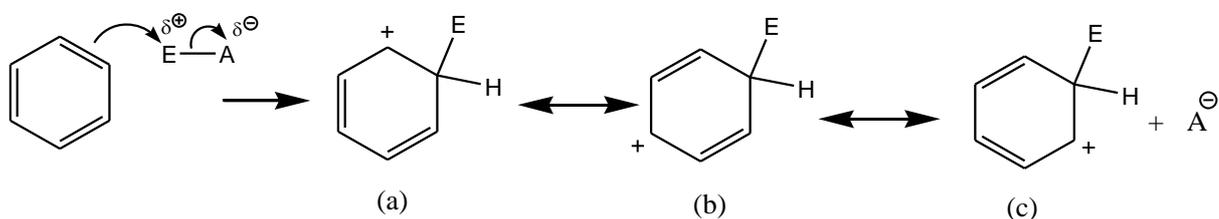

Figure 1: nucleophilic attack of the π-electrons of the benzene ring on the electrophile (E) and the resonance structures of the arenium ion (a), (b) and (c).

The formation of the cation is the rate-determining step (rds) in the overall reaction; the subsequent deprotonation of the cation (Figure 2 below) is fast. The two electrons that bonded the proton to the ring become a part of the p system. The proton is removed from the carbon atom of the arenium ion that bears the electrophile, restoring aromaticity to the ring. The proton is removed by any of the bases present, for example, by the anion derived from the electrophile.
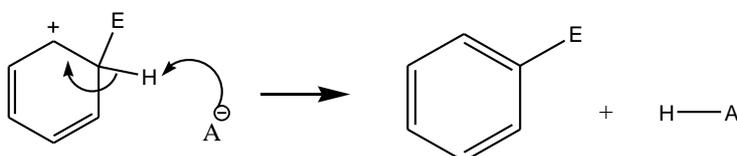
Figure 2: deprotonation of the cation.

The bimolecular nature of the transition state for the rate-limiting step and the fact that an electrophile is involved in attacking the aromatic substrate classifies the reaction as S_E2 (substitution electrophilic bimolecular)

Reaction of an aromatic compound such as bromobenzene with a mixture of concentrated sulfuric and nitric acids introduces a nitro group on the ring by way of electrophilic aromatic substitution. Concentrated sulfuric acid increases the rate of the reaction by increasing the concentration of the electrophile, the nitronium ion (NO_2^+). The nitronium-ion then reacts with benzene to form a resonance-stabilized arenium ion.

Substituents on the benzene ring:

A substituent group already present on a benzene ring can affect both the reactivity of the ring toward electrophilic substitution and the orientation that the incoming group takes on the ring.

If a substituent that is already present on the ring makes the ring more electron rich by donating electrons to it (thus an activating group), then the ring will be more nucleophilic, more reactive toward the electrophile, and the reaction will take place faster. On the other hand, if the substituent on the ring withdraws electrons (a deactivating group), the ring will be electron poor and an electrophile will react with the ring more slowly. Chlorobenzene and bromobenzene, for example, undergo nitration at a rate approximately 30 times slower than benzene.

A substituent on the ring can also affect the orientation that the incoming group takes when it replaces a hydrogen atom on the ring. Substituents fall into two general classes: ortho–para directors (all electron-donating groups) and meta directors (all electron-withdrawing groups with the exception of halogens).
The halogens are all more electronegative than carbon and exert an electron-withdrawing inductive effect.

The inductive effect of a substituent on the benzene ring arises from the electrostatic interaction of the polarized bond to the substituent with the developing positive charge in the ring as it is attacked by an electrophile. If, for example when the substituent on the ring is a more electronegative atom (or group) than carbon, then the ring will be at the positive end of the dipole:

X= F, Cl or Br

Attack by an electrophile will be slowed because this will lead to an additional full positive charge on the ring.

A resonance effect of a sbstituent, on the other hand, refers to the possibility that the presence of that substituent may increase or decrease the resonance stabilization of the intermediate arenium ion. Amino groups are highly activating, hydroxyl and alkoxyl groups are somewhat less activating, and halogen substituents are weakly deactivating. The more electronegative the substituent atom is, the less able it is to accept the positive charge (fluorine is the most electronegative, nitrogen the least). If Cl, Br, or I are the substituents (are all larger than carbon), the orbitals that contain the nonbonding pairs are further from the nucleus and do not overlap well with the 2p orbital of carbon. This is a general phenomenon: resonance effects are not transmitted well between atoms of different rows in the periodic table.

References:

Gilbert, John C, and Stephen F Martin. *Experimental Organic Chemistry*. Belmont, CA: Thomson Brooks/Cole, 2006.

Solomons, T. W. Graham, Craig B Fryhle, and S. A Snyder. *Organic Chemistry*.

Exp. 6 - Isolation of a natural product

Extraction

Extraction is a technique commonly used in organic chemistry to separate a material you want from those you do not. While the term extraction may be unfamiliar to you, the process is actually something you commonly perform. For example, many of you probably start the day, especially after a long night of studying, with an extraction when you brew a pot of coffee or tea. By heating coffee grounds or tea leaves with hot water, you extract the caffeine, together with other water-soluble compounds such as dark-colored tannins, from the solid material. You can then drink the liquid, which is certainly more enjoyable than eating coffee grounds or tea leaves, to ingest the caffeine and benefit from its stimulating effect. Similarly, when you make a soup, the largely aqueous liquid portion contains numerous organic and inorganic compounds that have been extracted from spices, vegetables, fish, or meat, and these give your culinary creation its distinctive flavor. In the procedures found in this chapter, you will have an opportunity to develop your existing experimental skills further by isolating organic compounds using different types of extractions.

The desired compound from a reaction is frequently part of a mixture, and its isolation in pure form can be a significant experimental challenge. Two of the more common methods for separating and purifying organic liquids and solids are **recrystallization** and **distillation**. Two other important techniques available for these purposes are **extraction** and **chromatography**.

Distribution of solutes between phases is the result of partitioning or adsorption phenomena. Partitioning involves the difference in solubilities of a substance in two immiscible solvents—in other words, selective dissolution. Adsorption, on the other hand, is based on the selective attraction of a substance in a liquid or gaseous mixture to the surface of a solid phase. The various chromatographic techniques depend on both of these processes, whereas the process of extraction relies only on partitioning.

Extraction involves selectively removing one or more components of a solid, liquid, or gaseous mixture into a separate phase. The substance being extracted will partition between the two immiscible phases that are in contact, and the ratio of its distribution between the phases will depend on the relative solubility of the solute in each phase.

Liquid-liquid extraction is one of the most common methods for removing an organic compound from a mixture. This process is used by chemists not only in the isolation of natural products but also in the isolation and purification of products from most chemical reactions.
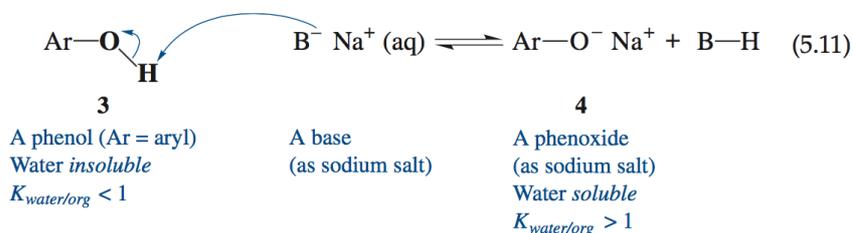
The technique involves distributing a solute, A, between two immiscible liquids, S_x, the extracting phase, and S_o, the original phase. The immiscible liquids normally encountered in the organic laboratory are water and some organic solvent, such as diethyl ether, $(C_2H_5)_2O$, or dichloromethane, CH_2Cl_2. At a given temperature, the amount of A,

in g/ml, in each phase is expressed quantitatively in terms of a constant, K, commonly called the partition coefficient.

Strictly speaking, the volumes of solution should be used in the definition of [A], but if the solutions are dilute, only slight errors result if volumes of solvent are used. Furthermore, a close approximation of the partition coefficient K may be obtained by simply dividing the solubility of A in the extracting solvent S_x by the solubility of A in the original solvent S_o.

Consider what happens if a mixture of two or more compounds is present in a given volume of solvent S_o and an extraction using a solvent S_x is performed. If the partition coefficient K of one component, A, is significantly greater than 1.0 and if those of other components are significantly less than 1.0, the majority of A will be in S_x, whereas most of the other compounds will remain in S_0. Physical separation of the two solvents will give a partial separation, and thus purification, of the solute A from the other components of the mixture.
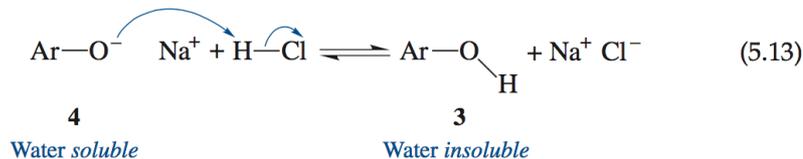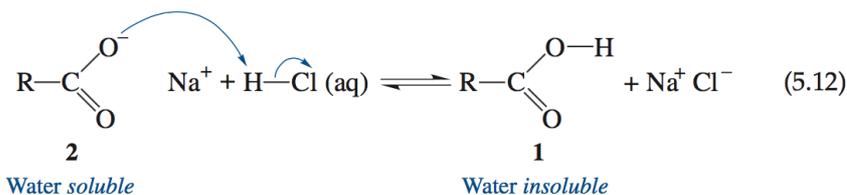
Solutes differing significantly in polarity should have very different coefficients K for partitioning between nonpolar and polar solvents. For example, consider the distribution of two organic compounds, the first neutral and nonpolar, and the second ionic and polar, between a nonpolar solvent and a polar solvent. If a solution of these compounds in the nonpolar solvent is shaken with the polar solvent, the neutral compound will preferentially partition into the nonpolar phase, whereas the polar partially charged constituent will interact more with the polar phase. Separating the two phases effects a separation of the two solutes.

$$\text{Ar—O} \overset{\curvearrowright}{\underset{\textbf{H}}{}} \quad \text{B}^- \text{Na}^+ \text{(aq)} \rightleftharpoons \text{Ar—O}^- \text{Na}^+ + \text{B—H} \quad (5.11)$$

3

A phenol (Ar = aryl)
Water *insoluble*
$K_{water/org} < 1$

A base
(as sodium salt)

4

A phenoxide
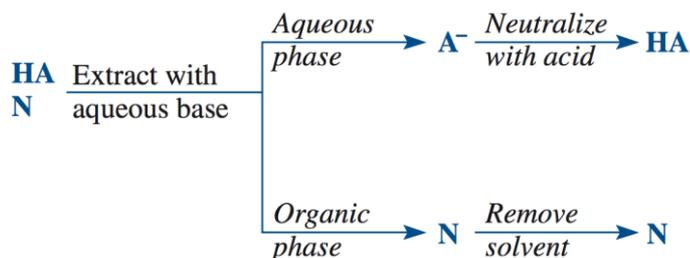(as sodium salt)
Water *soluble*
$K_{water/org} > 1$

Carboxylic acids and phenols (1 and 3, Eqs. 5.10 and 5.11, respectively) are two classes of organic compounds containing functional groups that are polar and hydrophilic (water-loving). Unless they contain fewer than about six carbon atoms, such compounds are generally either insoluble or only slightly soluble in water because of the hydrophobic (water-avoiding) properties of the carbon – containing portion, R or Ar, of the molecule. They are soluble in common organic solvents like dichloromethane or diethyl ether that have at least modest polarity. Consequently, carboxylic acids or phenols dissolved in diethyl ether, for example, will largely remain in that phase when the solution is extracted with water.

Now consider what happens if the organic solution is extracted with a basic aqueous solution. If the base, B^-, is strong enough, the organic acid 1 or 3 will be converted into the corresponding conjugate base 2 or 4 (Eqs. 5.10 and 5.11). Because it is a salt, the conjugate base is highly polar, and $K_{water/org} > 1$. Thus the conjugate bases of organic acids may be selectively extracted from an organic phase into an aqueous phase. If the basic extract is then neutralized by an acid such as hydrochloric acid, the conjugate base 2 or 4 will be protonated to regenerate the organic acid 1 or 3 (Eqs. 5.12 and 5.13). Because the

acid is water-insoluble, it will appear as either a precipitate or a second layer, if it is a liquid. The desired organic acid may then be recovered by filtration or separation of the layers.

$$R-C\overset{\overset{O^-}{|}}{\underset{O}{\|}} \quad Na^+ + H-Cl\ (aq) \rightleftharpoons R-C\overset{\overset{O-H}{|}}{\underset{O}{\|}} \quad + Na^+ Cl^- \qquad (5.12)$$

2
Water *soluble*   **1**
Water *insoluble*

$$Ar-O^- \quad Na^+ + H-Cl \rightleftharpoons Ar-O\underset{H}{\diagdown} \quad + Na^+ Cl^- \qquad (5.13)$$

4   **3**
Water *soluble*   Water *insoluble*

Thus, two water-insoluble organic compounds, HA, which is acidic, and N, which is neutral, that are dissolved in an organic solvent may be separated by selectively extracting the acidic compound into a basic aqueous phase. After the aqueous and organic phases are separated, HA is recovered from the aqueous phase upon neutralization, and N is obtained by removing the organic solvent. The choice of the base is determined by the acidity of the organic acid HA. This is defined in aqueous solution by K_a.

HA   Extract with   *Aqueous phase* → A^- *Neutralize with acid* → **HA**

N   aqueous base   *Organic phase* → **N**   *Remove solvent* → **N**

Recrystallization of solids is a valuable technique to master. The process of recrystallization involves dissolving the solid in an appropriate solvent at an elevated temperature and allowing the crystals to re-form on cooling, so that any impurities remain in solution due to osmotic effects. If the impurities present in the original solid mixture have dissolved and remain dissolved after the solution is cooled, isolation of the crystals that have formed should ideally provide pure material. Alternatively, the impurities may not dissolve at all in the hot solution and may be removed by filtration before the solution is cooled. The crystals that subsequently form should be purer than the original solid mixture.

Even after a solid has been recrystallized, it may still not be pure. Thus, it is important to determine the purity of the sample, and one of the easiest methods to do this is by determining the melting point of the solid.

The third most commonly used purification technique is distillation. Simple distillation allows separation of distillates from less-volatile substances that remain as pot residue at the completion of the distillation. It allows isolation of the various components of the

mixture in acceptable purity if the difference between the boiling points of each pure substance is greater than 40–50 °C. For example, a mixture of diethyl ether, bp 35 °C (760 torr), and toluene, bp 111 °C (760 torr), could easily be separated by simple distillation, with the ether distilling first. If this is not the case, the technique of fractional distillation is normally used to obtain each volatile component of a mixture in pure form. It should be noted that the boiling points of the ideal solutions containing different components may be lower or greater then the bp of any component of the mixture on its own. Thus, care should be taken with this method.

Chromatography is the last common technique used for separation. All of the various methods of chromatography operate on the principle that the components of a mixture will distribute unequally between two immiscible phases. The mobile phase is generally a liquid or a gas that flows continuously over the fixed stationary phase, which may be a solid or a liquid. The individual components of the mixture have different affinities for the mobile and stationary phases, so a dynamic equilibrium is established in which each component is selectively, but temporarily, removed from the mobile phase by binding to the stationary phase. When the equilibrium concentration of that substance in the mobile phase decreases, it is released from the stationary phase and the process continues.

This was a very brief introduction to the extraction and purification techniques you will encounter in organic synthesis on every-day basis.