



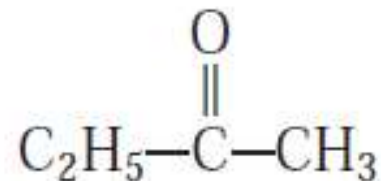
Physical Properties of Drug Molecules

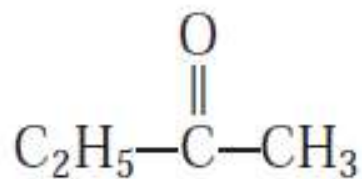


- study of the physical properties of drug molecules is a prerequisite for product formulation and leads to a better understanding of the relationship between a drug's molecular and physicochemical properties and its structure and action.
- These properties come from the molecular bonding order of the atoms in the molecule and may be thought of as either
 - ✓ **additive** (derived from the **sum of the properties of the individual atoms or functional groups** within the molecule) ..e.g. mass or
 - ✓ **constitutive** (dependent on **the structural arrangement** of the atoms within the molecule)e.g. optical rotation



- Many physical properties are constitutive and yet have some measure of additivity.
- The **molar refraction** of a compound, for example, is the sum of the refraction of the atoms and the array of functional groups making up the compound.
- Because the arrangements of atoms in each group are different, the refractive index of two molecules will also be different.
- The molar refractions of the two compounds which have exactly the same number of carbon, hydrogen, and oxygen atoms, are calculated using **Table:**





8H	$8 \times 1.100 =$	8.800
3C (single)	$3 \times 2.418 =$	7.254
1C (double)	$1 \times 1.733 =$	1.733
1O (C=O)	$1 \times 2.211 =$	<u>2.211</u>
		19.998 = 20.0

Windows 6.0.0.0

$\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_2-\text{OH}$		
8H	$8 \times 1.100 =$	8.800
2C (single)	$2 \times 2.418 =$	4.836
2C (double)	$2 \times 1.733 =$	3.466
1O (OH)	$1 \times 1.525 =$	<u>1.525</u>
		18.627 = 18.7

ATOMIC AND GROUP CONTRIBUTIONS TO MOLAR REFRACTION*

C— (single)	2.418
—C= (double)	1.733
—C≡ (triple)	2.398
Phenyl (C ₆ H ₅)	25.463
H	1.100
O (C=O)	2.211
O (O—H)	1.525
O (ether, ester, C—O)	1.643
Cl	5.967
Br	8.865
L	13.900

- ✓ The molar refractions of the atoms are additive, but the carbon and oxygen atoms are constitutive in refraction.



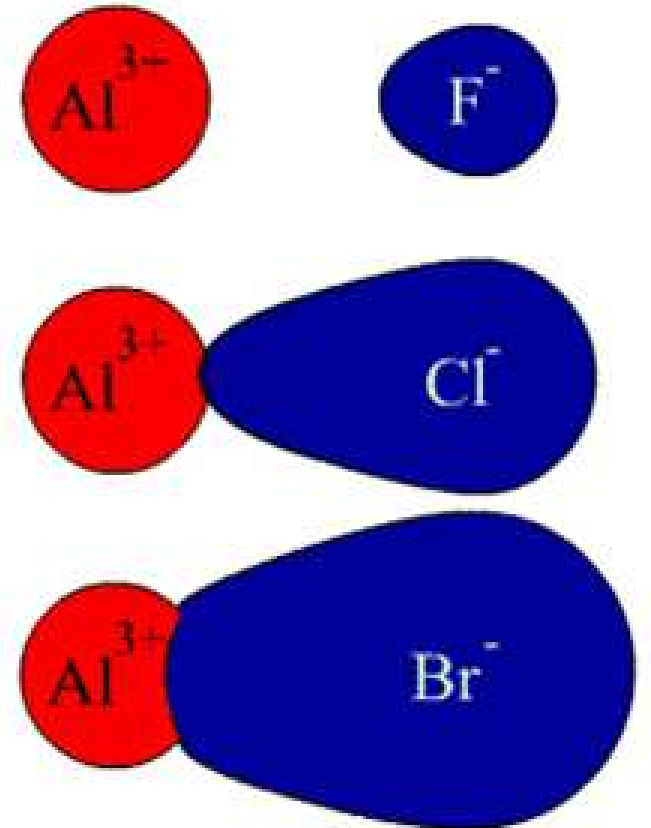
When one carefully associates specific physical properties with the chemical nature of closely related molecules, one can:

- (a) describe the spatial arrangement of atoms in drug molecules,
- (b) provide evidence for the relative chemical or physical behaviour of a molecule, and
- (c) suggest methods for the qualitative and quantitative analysis of a particular pharmaceutical agent.



POLARIZABILITY

- Polarizability is defined as the ease with which an ion or molecule can be polarized by any external force, whether it be an electric field or light energy or through interaction with another molecule.
- Large anions have large polarizabilities because of their loosely held outer electrons.

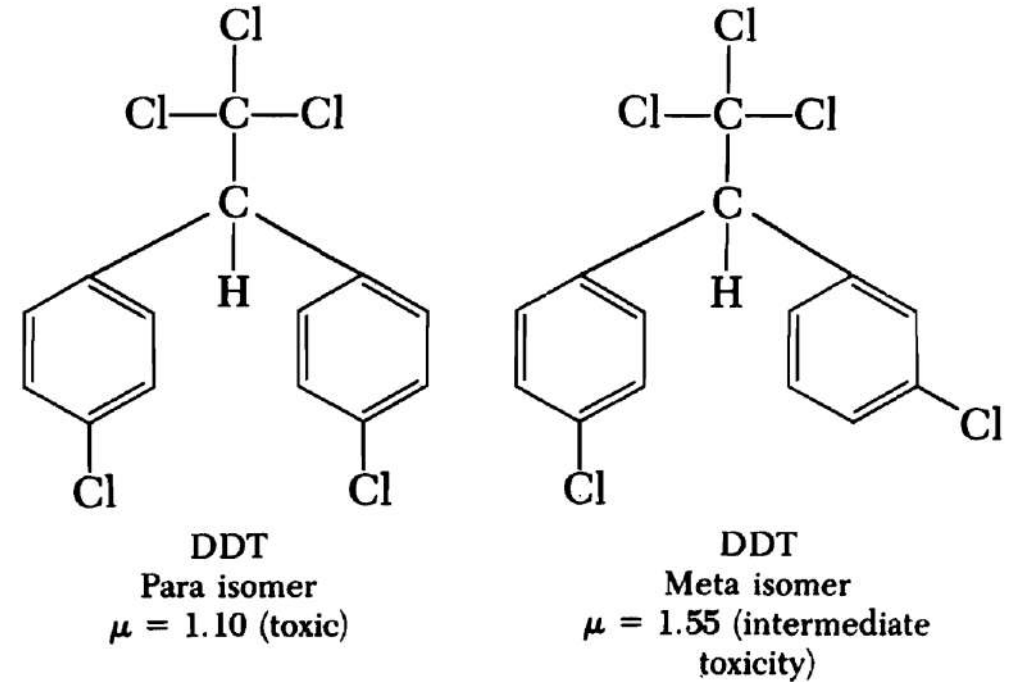


PERMANENT DIPOLE MOMENT OF POLAR MOLECULES

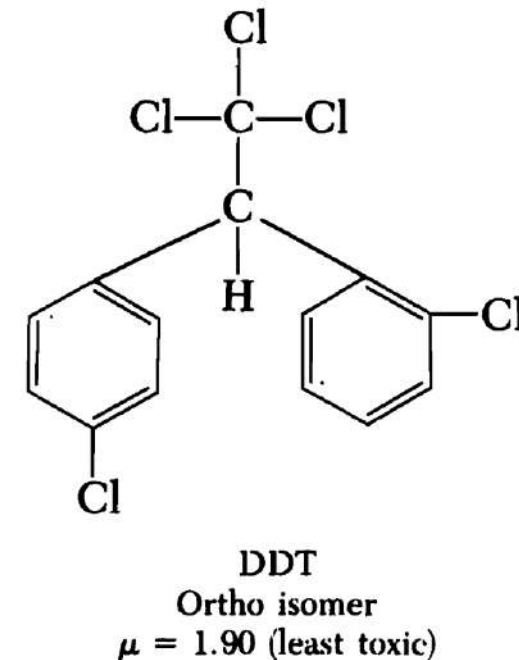
- In a polar molecule, the separation of positively and negatively charged regions can be permanent, and the molecule will possess a permanent dipole moment, μ . (H₂O)
- The magnitude of the permanent dipole moment, μ , is independent of any induced dipole from an electric field.
- It is defined as the vector sum of the individual charge moments within the molecule itself, including those from bonds and lone-pair electrons.
- The vectors depend on the distance of separation between the charges



- Permanent dipole moments can be correlated with biologic activities of certain molecules to obtain valuable information about the relationship of physical properties and charge separation in a class of compounds.

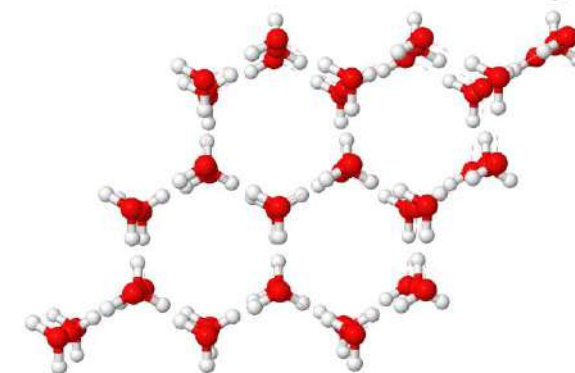
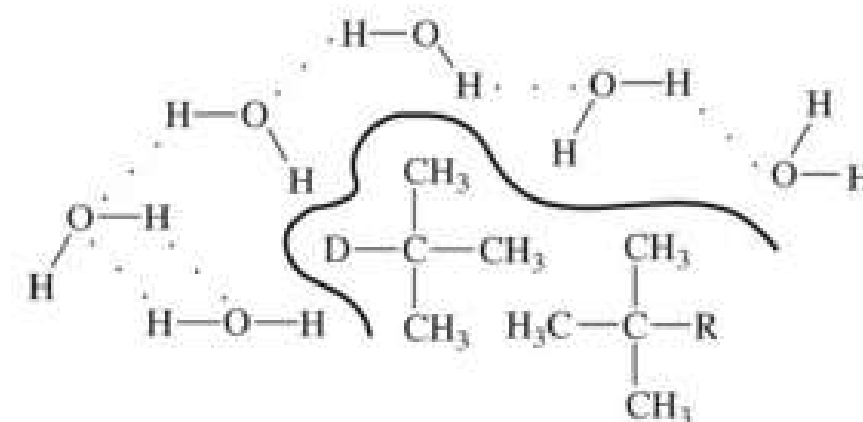
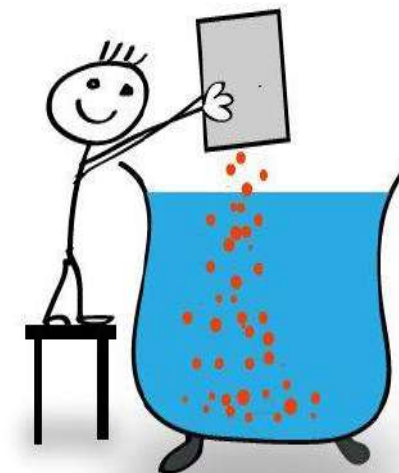


- For example, the insecticidal activity of the three isomers of DDT, shown in the following structures, can be associated with their permanent dipole moments.



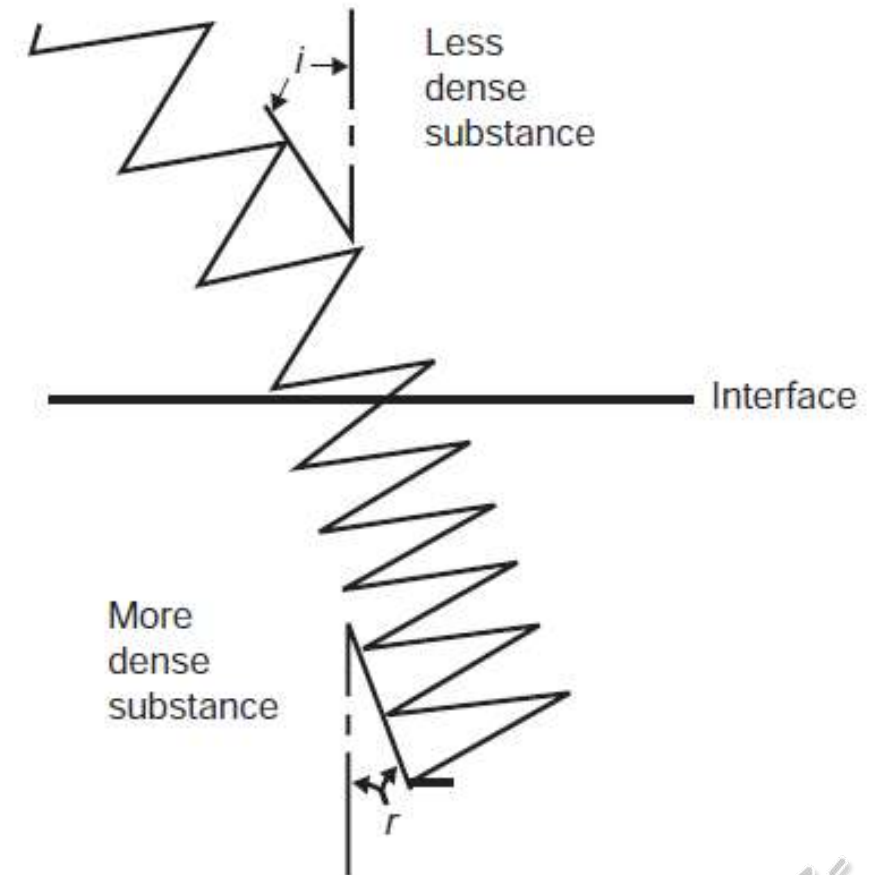
- **The importance of dipole interactions:**

- ✓ For ionic solutes and nonpolar solvents, ion-induced dipole interactions have an essential role in **solubility** phenomena
- ✓ For **drug-receptor binding**, dipole-dipole interactions are essential noncovalent forces that contribute to enhance the pharmacologic effect
- ✓ For solids composed of molecules with permanent dipole moments, the dipole interactions contribute to the **crystalline arrangement and overall structural nature of the solid.**

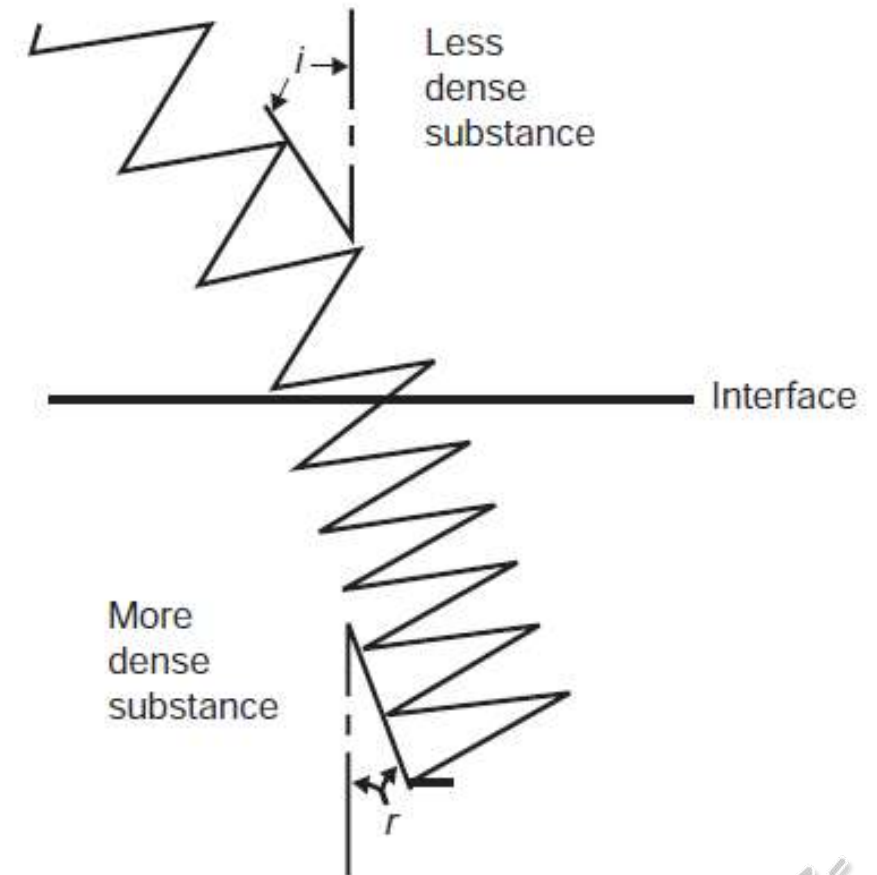


REFRACTIVE INDEX AND MOLAR REFRACTION

- Light passes more slowly through a substance than through a vacuum.
- As light enters a denser substance, the advancing waves interact with the atoms in the substance at the interface and throughout the thickness of the substance.
- These interactions modify the light waves by absorbing energy, resulting in the waves being closer together by reducing the speed and shortening the wavelength



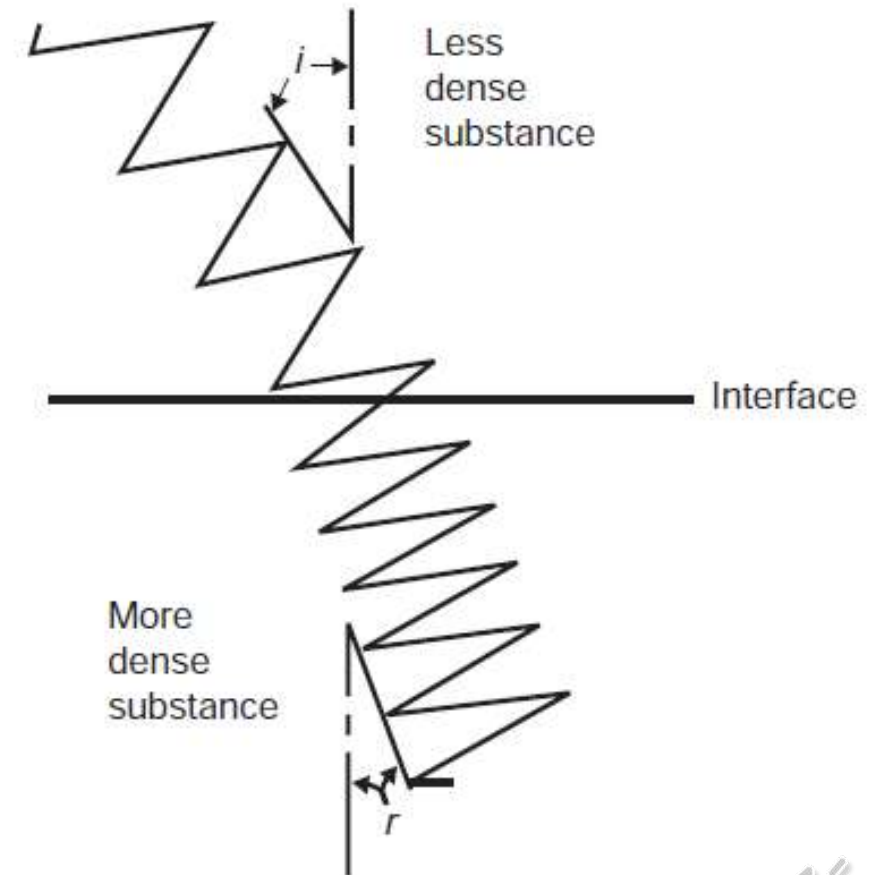
- If the light enters the denser substance at an angle, as shown, one part of the wave slows down more quickly as it passes the interface, and this produces a bending of the wave toward the interface.
- This phenomenon is called refraction.
- If light enters a less dense substance, it is refracted away from the interface rather than toward it.
- The relative value of the effect of refraction between two substances is given by the refractive index, n :



$$n = \frac{\sin i}{\sin r} = \frac{\text{Velocity of light in the first substance}}{\text{Velocity of light in the second substance}} = \frac{c_1}{c_2}$$



- If the light enters the denser substance at an angle, as shown, one part of the wave slows down more quickly as it passes the interface, and this produces a bending of the wave toward the interface.
- This phenomenon is called refraction.
- If light enters a less dense substance, it is refracted away from the interface rather than toward it.
- The relative value of the effect of refraction between two substances is given by the refractive index, n :



$$n = \frac{\sin i}{\sin r} = \frac{\text{Velocity of light in the first substance}}{\text{Velocity of light in the second substance}} = \frac{c_1}{c_2}$$



$$n = \frac{\sin i}{\sin r} = \frac{\text{Velocity of light in the first substance}}{\text{Velocity of light in the second substance}} = \frac{c_1}{c_2}$$

- Normally, the numerator is taken as the velocity of light in air, and the denominator is the material being investigated.
- The refractive index, by this convention, is greater than 1 for substances denser than air.
- Refractive index varies with the wavelength of light and the temperature.



- **Refractive index can be used to:**
 - a) identify a substance
 - b) measure its purity
 - c) determine the concentration of one substance dissolved in another.

- Typically, a **refractometer** is used to determine refractive index.



The molar refraction

- R_m , is related to both the refractive index and the molecular properties of a compound being tested.
- It is expressed as

$$R_m = \frac{n^2 - 1}{n^2 + 2} \left(\frac{M}{\rho} \right)$$





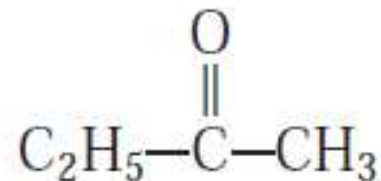
Physical Properties of Drug Molecules

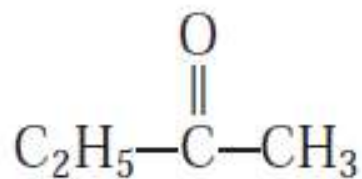


- study of the physical properties of drug molecules is a prerequisite for product formulation and leads to a better understanding of the relationship between a drug's molecular and physicochemical properties and its structure and action.
- These properties come from the molecular bonding order of the atoms in the molecule and may be thought of as either
 - ✓ **additive** (derived from the **sum of the properties of the individual atoms or functional groups** within the molecule) ..e.g. mass or
 - ✓ **constitutive** (dependent on **the structural arrangement** of the atoms within the molecule)e.g. optical rotation



- Many physical properties are constitutive and yet have some measure of additivity.
- The **molar refraction** of a compound, for example, is the sum of the refraction of the atoms and the array of functional groups making up the compound.
- Because the arrangements of atoms in each group are different, the refractive index of two molecules will also be different.
- The molar refractions of the two compounds which have exactly the same number of carbon, hydrogen, and oxygen atoms, are calculated using **Table:**





8H	$8 \times 1.100 =$	8.800
3C (single)	$3 \times 2.418 =$	7.254
1C (double)	$1 \times 1.733 =$	1.733
1O (C=O)	$1 \times 2.211 =$	<u>2.211</u>
		19.998 = 20.0

Windows 6.0.0.0

$\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_2-\text{OH}$		
8H	$8 \times 1.100 =$	8.800
2C (single)	$2 \times 2.418 =$	4.836
2C (double)	$2 \times 1.733 =$	3.466
1O (OH)	$1 \times 1.525 =$	<u>1.525</u>
		18.627 = 18.7

ATOMIC AND GROUP CONTRIBUTIONS TO MOLAR REFRACTION*

C— (single)	2.418
—C= (double)	1.733
—C≡ (triple)	2.398
Phenyl (C ₆ H ₅)	25.463
H	1.100
O (C=O)	2.211
O (O—H)	1.525
O (ether, ester, C—O)	1.643
Cl	5.967
Br	8.865
L	13.900

- ✓ The molar refractions of the atoms are additive, but the carbon and oxygen atoms are constitutive in refraction.



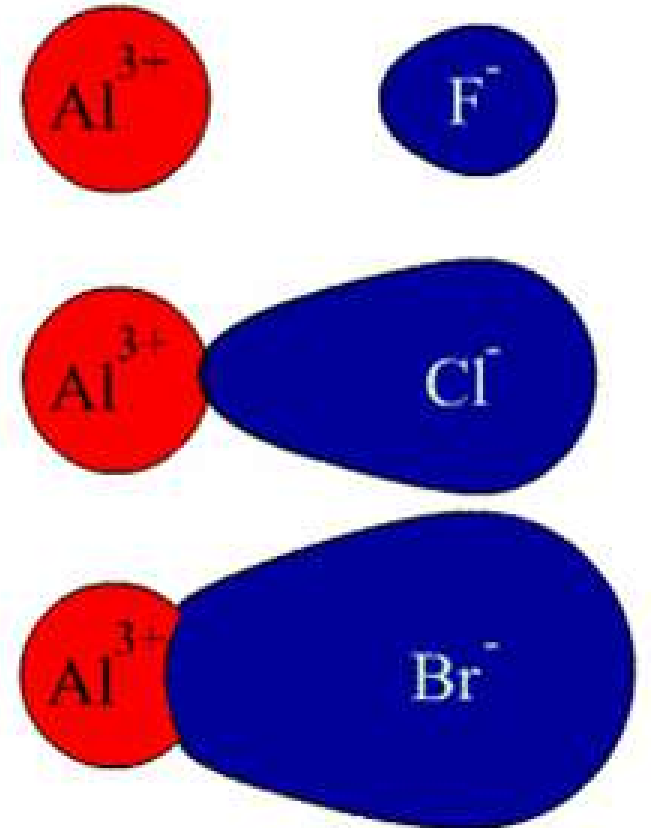
When one carefully associates specific physical properties with the chemical nature of closely related molecules, one can:

- (a) describe the spatial arrangement of atoms in drug molecules,
- (b) provide evidence for the relative chemical or physical behaviour of a molecule, and
- (c) suggest methods for the qualitative and quantitative analysis of a particular pharmaceutical agent.



POLARIZABILITY

- Polarizability is defined as the ease with which an ion or molecule can be polarized by any external force, whether it be an electric field or light energy or through interaction with another molecule.
- Large anions have large polarizabilities because of their loosely held outer electrons.

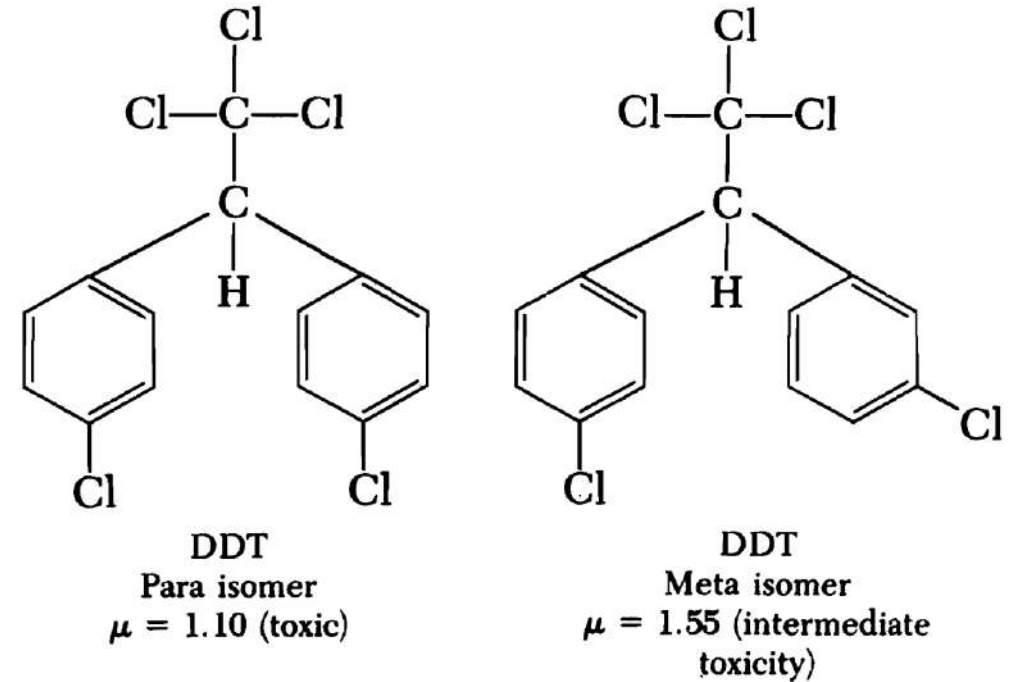


PERMANENT DIPOLE MOMENT OF POLAR MOLECULES

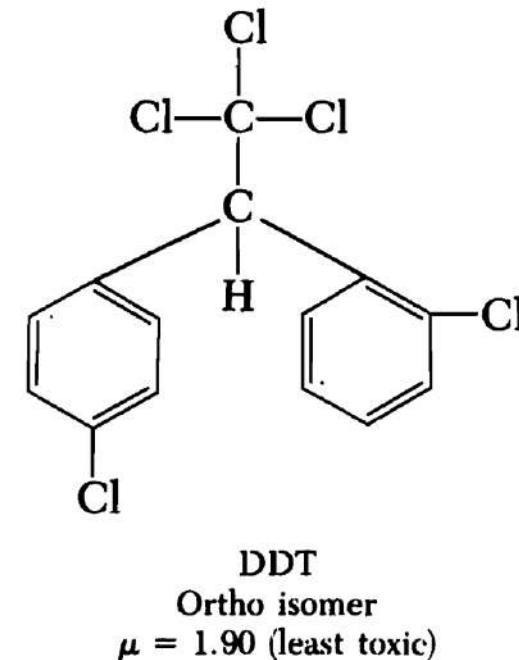
- In a polar molecule, the separation of positively and negatively charged regions can be permanent, and the molecule will possess a permanent dipole moment, μ . (H₂O)
- The magnitude of the permanent dipole moment, μ , is independent of any induced dipole from an electric field.
- It is defined as the vector sum of the individual charge moments within the molecule itself, including those from bonds and lone-pair electrons.
- The vectors depend on the distance of separation between the charges



- Permanent dipole moments can be correlated with biologic activities of certain molecules to obtain valuable information about the relationship of physical properties and charge separation in a class of compounds.

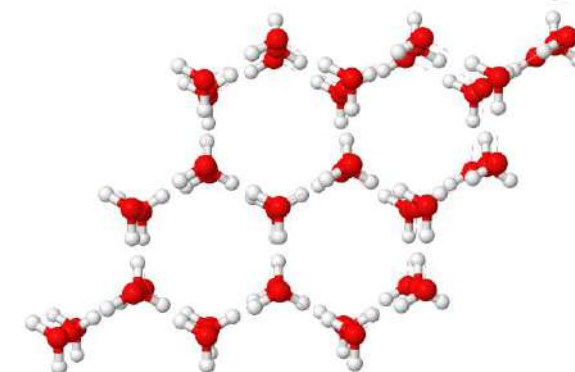
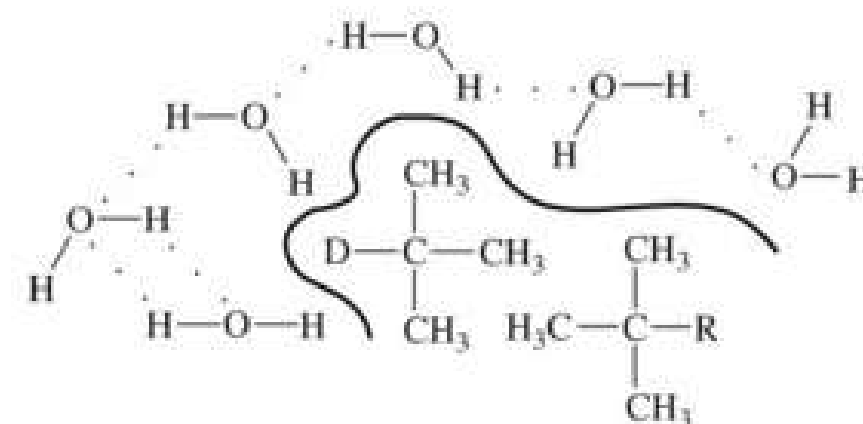
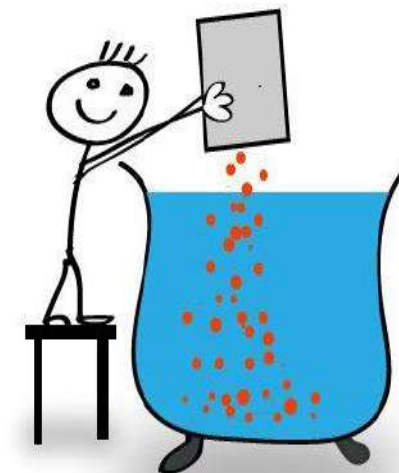


- For example, the insecticidal activity of the three isomers of DDT, shown in the following structures, can be associated with their permanent dipole moments.



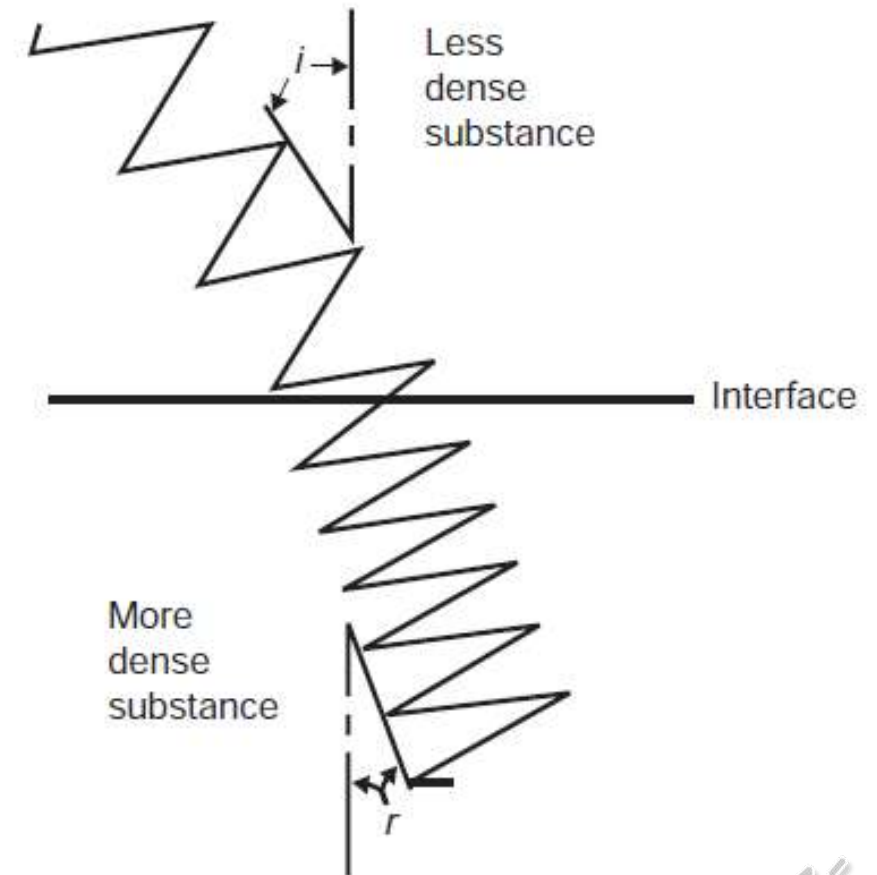
- **The importance of dipole interactions:**

- ✓ For ionic solutes and nonpolar solvents, ion-induced dipole interactions have an essential role in **solubility** phenomena
- ✓ For **drug-receptor binding**, dipole-dipole interactions are essential noncovalent forces that contribute to enhance the pharmacologic effect
- ✓ For solids composed of molecules with permanent dipole moments, the dipole interactions contribute to the **crystalline arrangement and overall structural nature of the solid.**

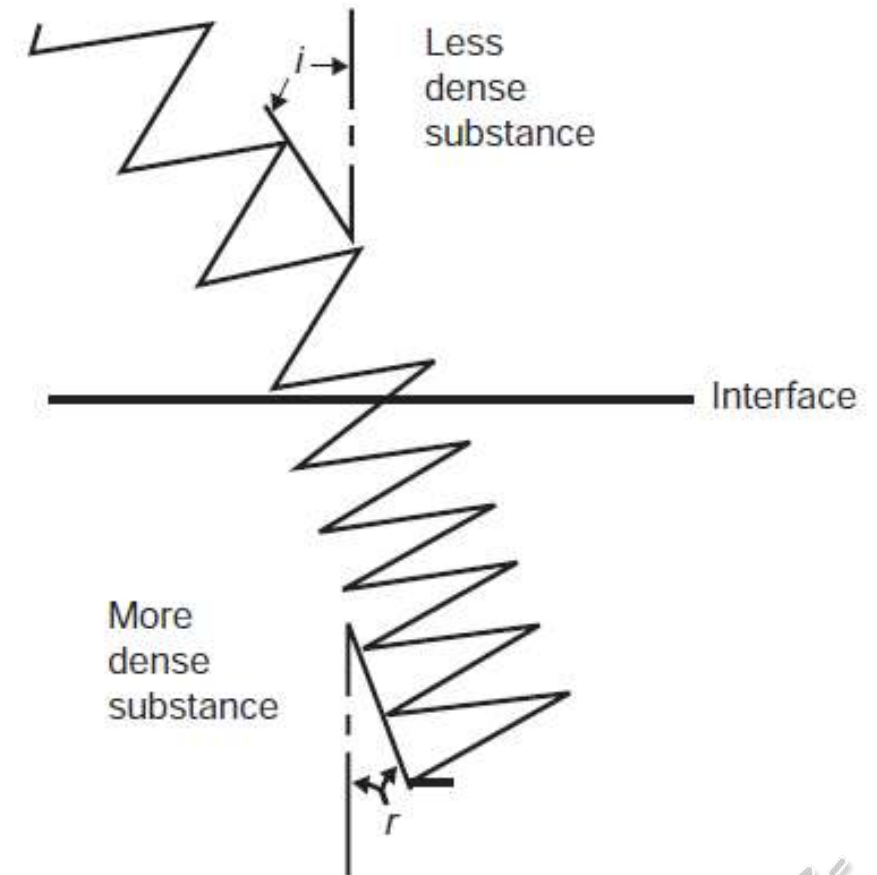


REFRACTIVE INDEX AND MOLAR REFRACTION

- Light passes more slowly through a substance than through a vacuum.
- As light enters a denser substance, the advancing waves interact with the atoms in the substance at the interface and throughout the thickness of the substance.
- These interactions modify the light waves by absorbing energy, resulting in the waves being closer together by reducing the speed and shortening the wavelength



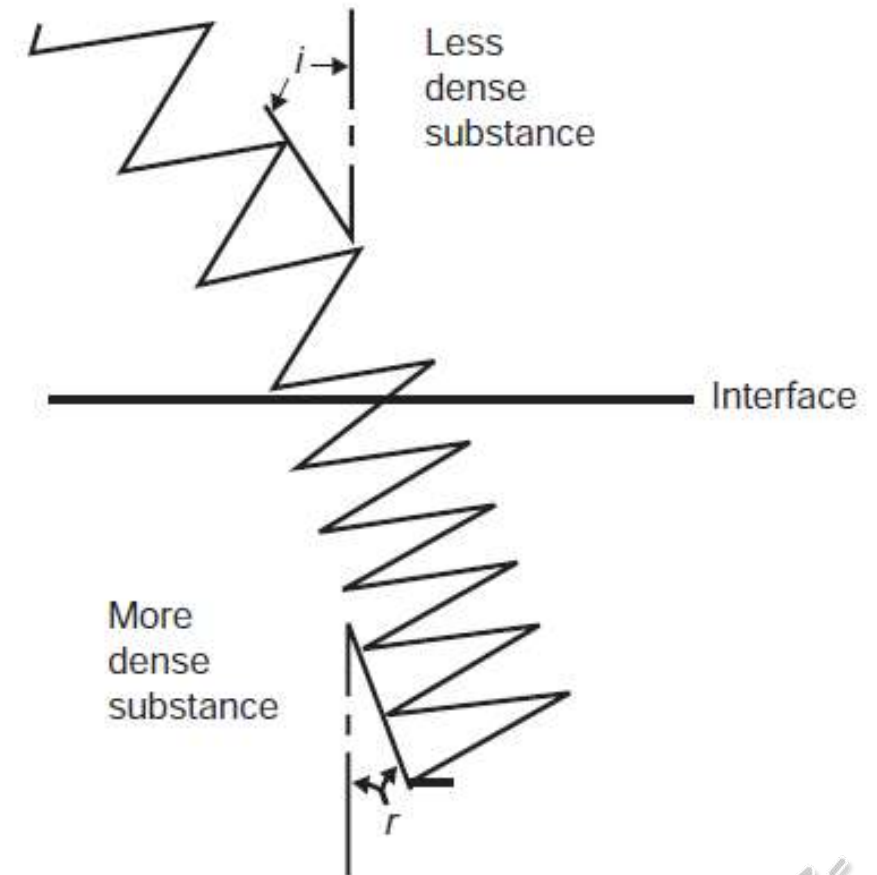
- If the light enters the denser substance at an angle, as shown, one part of the wave slows down more quickly as it passes the interface, and this produces a bending of the wave toward the interface.
- This phenomenon is called refraction.
- If light enters a less dense substance, it is refracted away from the interface rather than toward it.
- The relative value of the effect of refraction between two substances is given by the refractive index, n :



$$n = \frac{\sin i}{\sin r} = \frac{\text{Velocity of light in the first substance}}{\text{Velocity of light in the second substance}} = \frac{c_1}{c_2}$$



- If the light enters the denser substance at an angle, as shown, one part of the wave slows down more quickly as it passes the interface, and this produces a bending of the wave toward the interface.
- This phenomenon is called refraction.
- If light enters a less dense substance, it is refracted away from the interface rather than toward it.
- The relative value of the effect of refraction between two substances is given by the refractive index, n :



$$n = \frac{\sin i}{\sin r} = \frac{\text{Velocity of light in the first substance}}{\text{Velocity of light in the second substance}} = \frac{c_1}{c_2}$$



$$n = \frac{\sin i}{\sin r} = \frac{\text{Velocity of light in the first substance}}{\text{Velocity of light in the second substance}} = \frac{c_1}{c_2}$$

- Normally, the numerator is taken as the velocity of light in air, and the denominator is the material being investigated.
- The refractive index, by this convention, is greater than 1 for substances denser than air.
- Refractive index varies with the wavelength of light and the temperature.



- **Refractive index can be used to:**
 - a) identify a substance
 - b) measure its purity
 - c) determine the concentration of one substance dissolved in another.

- Typically, a **refractometer** is used to determine refractive index.



The molar refraction

- R_m , is related to both the refractive index and the molecular properties of a compound being tested.
- It is expressed as

$$R_m = \frac{n^2 - 1}{n^2 + 2} \left(\frac{M}{\rho} \right)$$

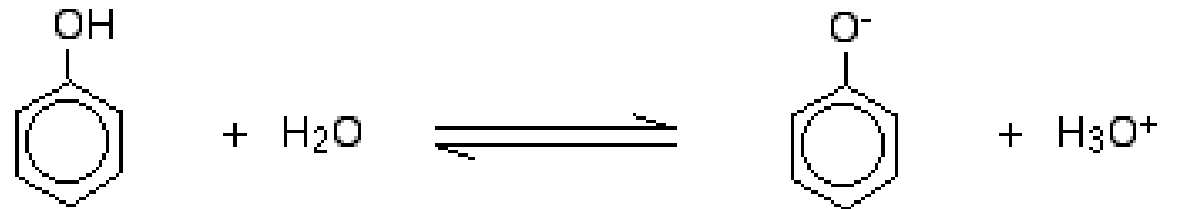


Two component systems containing liquid phases

- **ethyl alcohol and water** are miscible in all proportions,
- whereas **water and mercury** are, for all practical purposes, completely immiscible regardless of the relative amounts of each present.
- Between these two extremes lies a whole range of systems that exhibit partial miscibility
- One such system is **phenol and water**

✓ Also known as carbolic acid, hydroxybenzene and phenyl alcohol

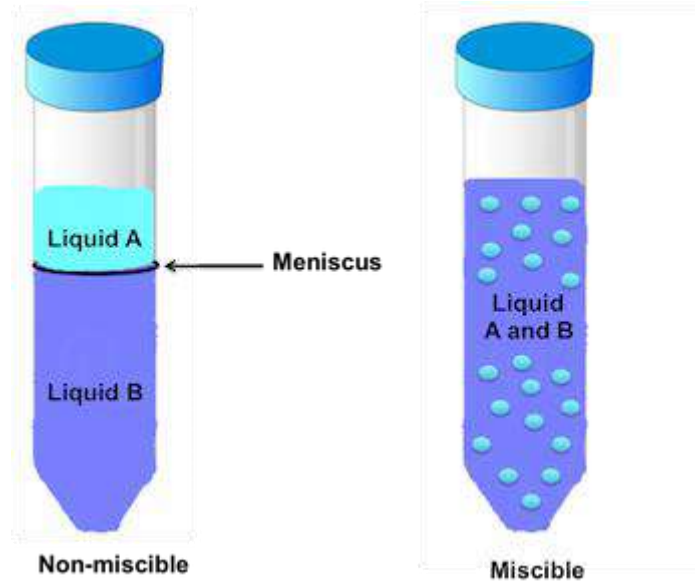
✓ It is a starting material in the manufacture of plastics and drugs



a phenoxide ion



- Under certain temperature and concentration of phenol and water, the phenol and water maybe in 1 phase condition or maybe being separated into 2 different phases.



PROCEDURES

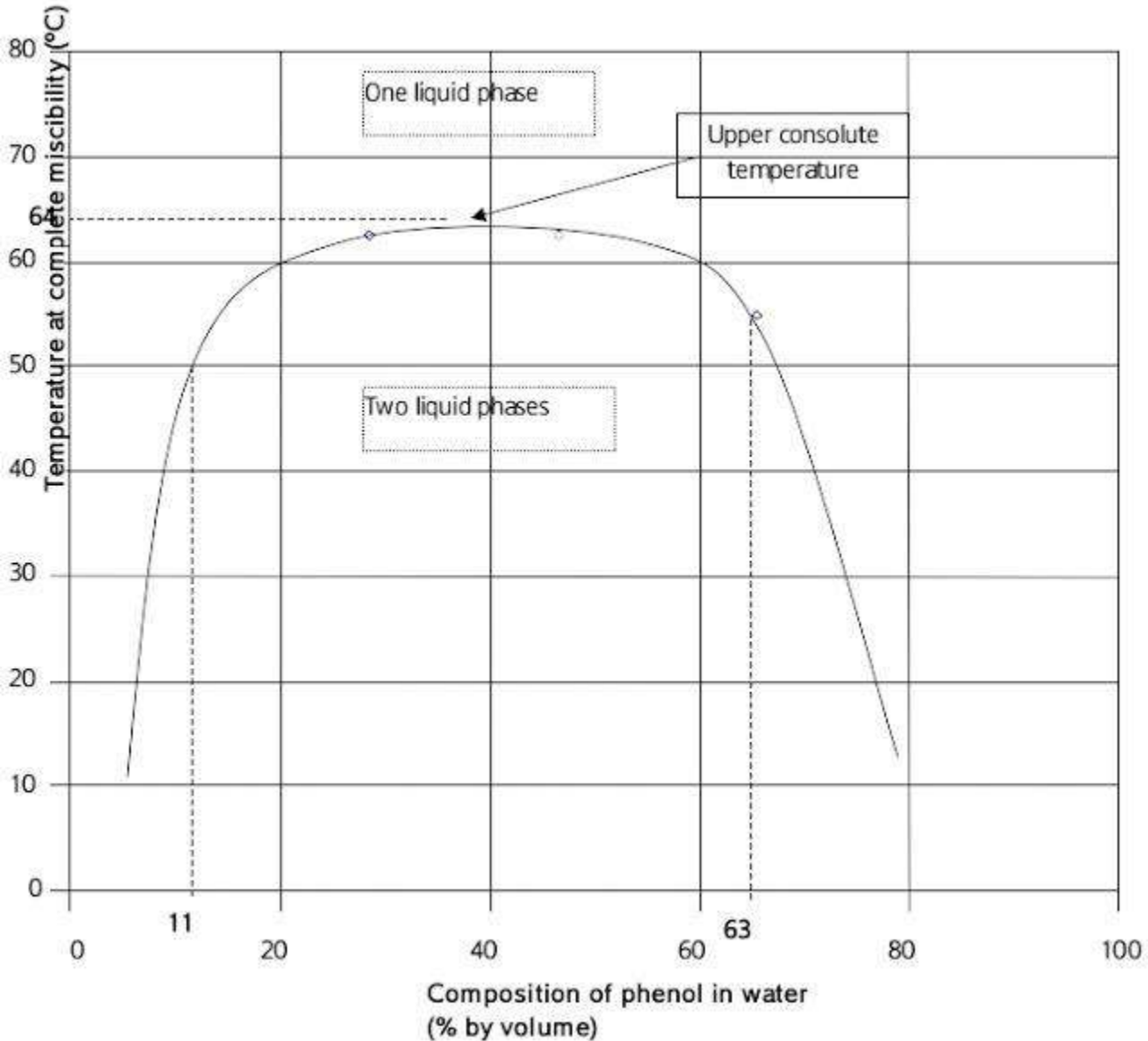
1. Mixture of phenol and water in boiling tubes was prepared in the way that phenol was added in water in various percentages from 8%, 11%, 20%, 50%, 60%, 63% and 80%.
2. The total amount of 2 liquids in the boiling tubes was fixed to be 30ml and the boiling tubes were labeled accordingly from A to G.
3. Then, the boiling tube A was heated in hot water and the mixture was stirred.
4. The temperature at which the turbid liquid became clear was recorded.
5. Finally, repeated for tubes B to G.
6. A graph of temperature at complete miscibility against phenol composition in the different mixtures was plotted.



Percentage of phenol (%)	Volume of phenol (ml)	Volume of water (ml)	Average temperature at which the turbid liquid become clear (°C)
8.0	2.4	27.6	50
11.0	3.3	26.7	64
20.0	6.0	24.0	68
50.0	15.0	15.0	67
63.0	18.9	11.1	70
80.0	24.0	6.0	-



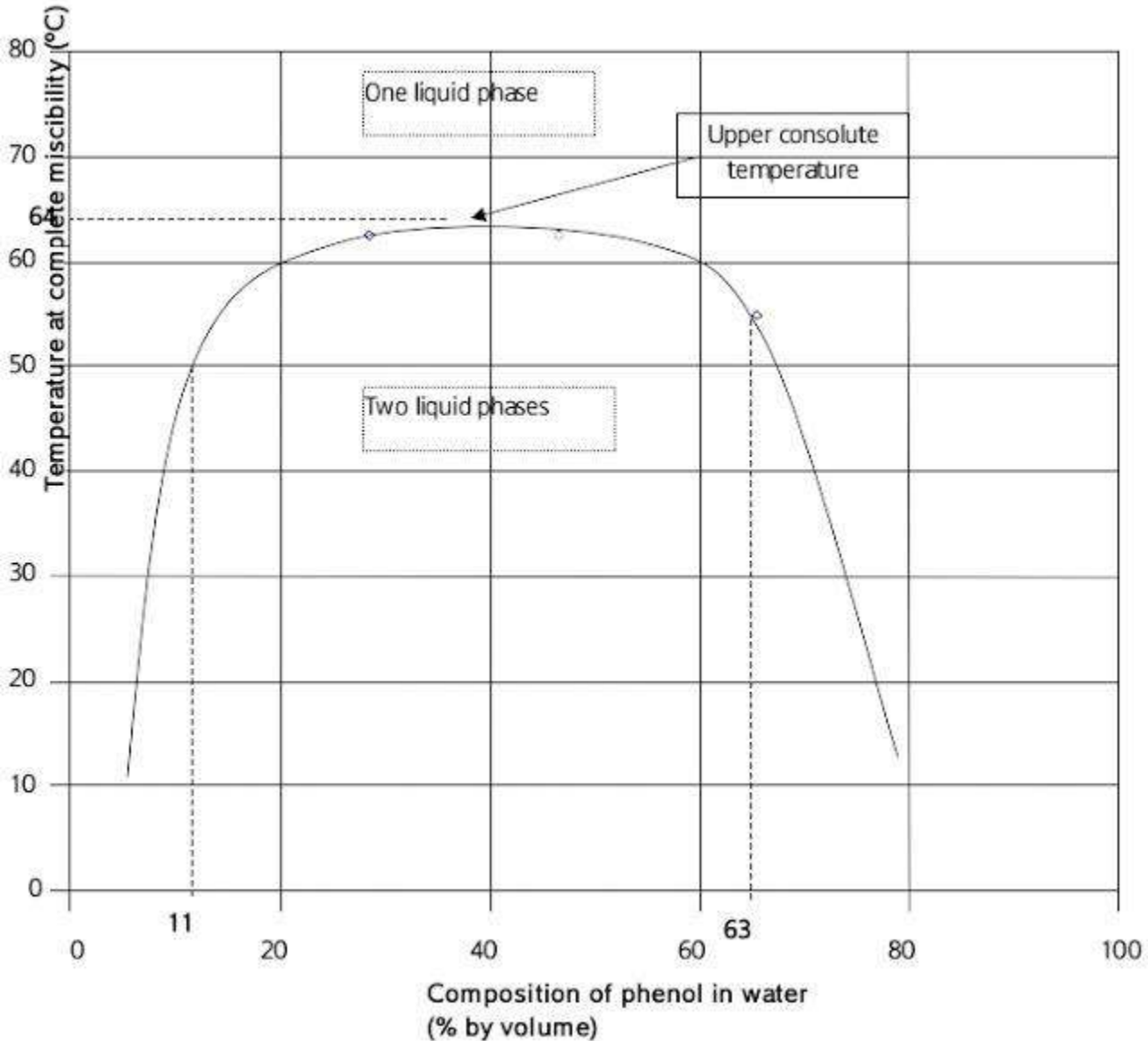
Temperature-composition diagram for the system consisting of water and phenol



- At any temperature below the critical solution temperature, the composition for the 2 layers of liquids in equilibrium state is constant and does not depend on the relative amount of these 2 phases.



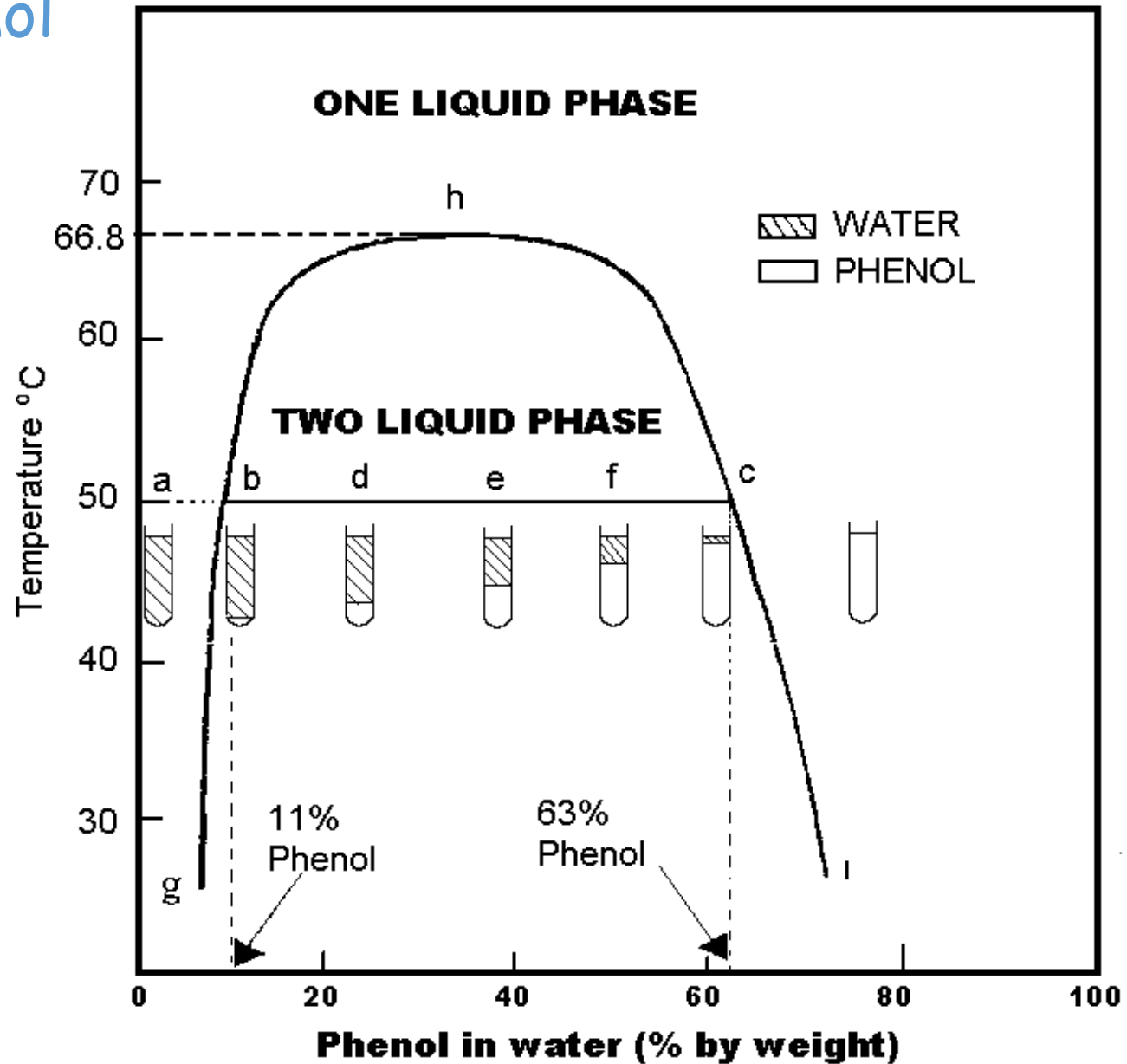
Temperature-composition diagram for the system consisting of water and phenol



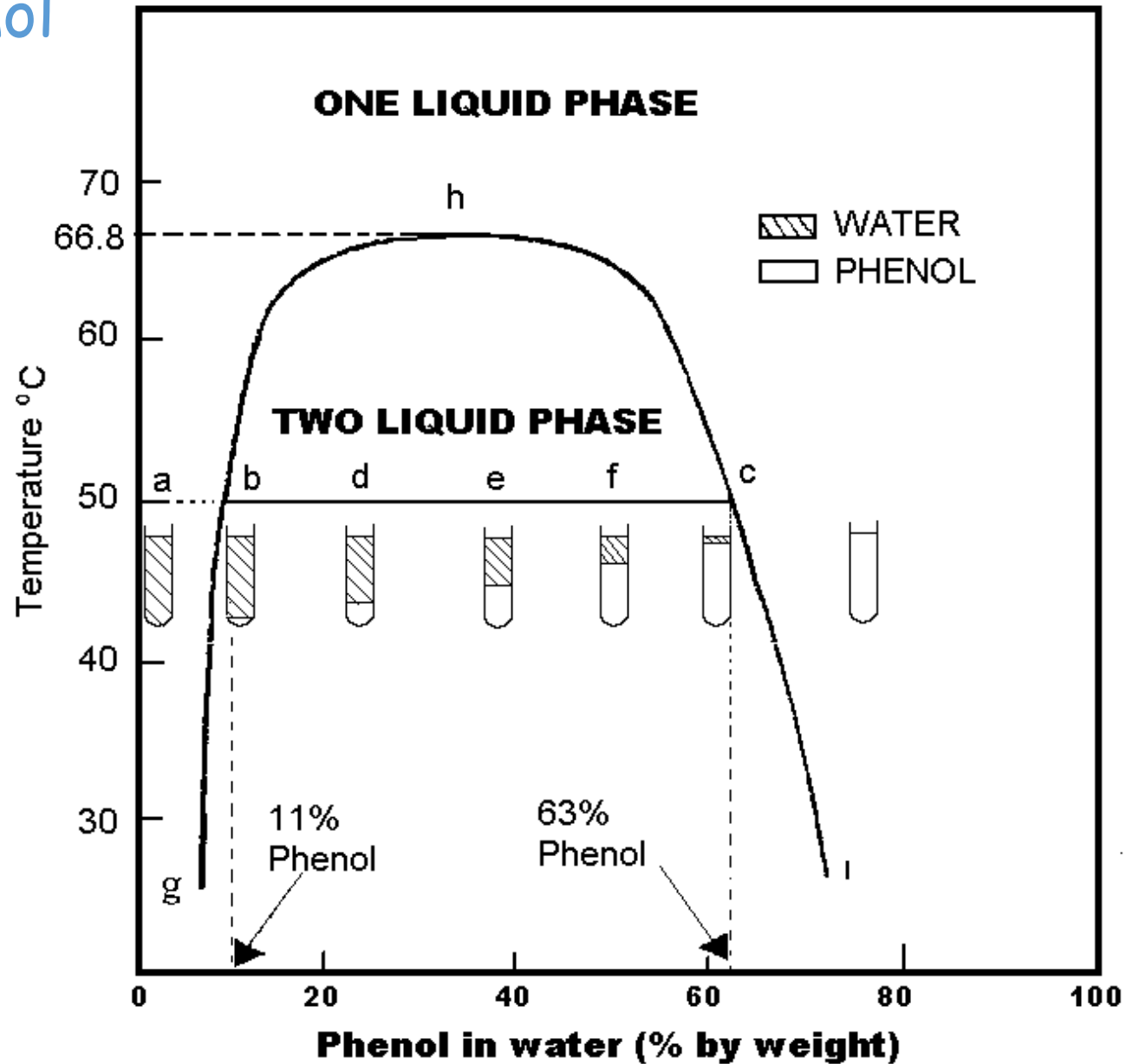
- At any temperature below the critical solution temperature, the composition for the 2 layers of liquids in equilibrium state is constant and does not depend on the relative amount of these 2 phases.



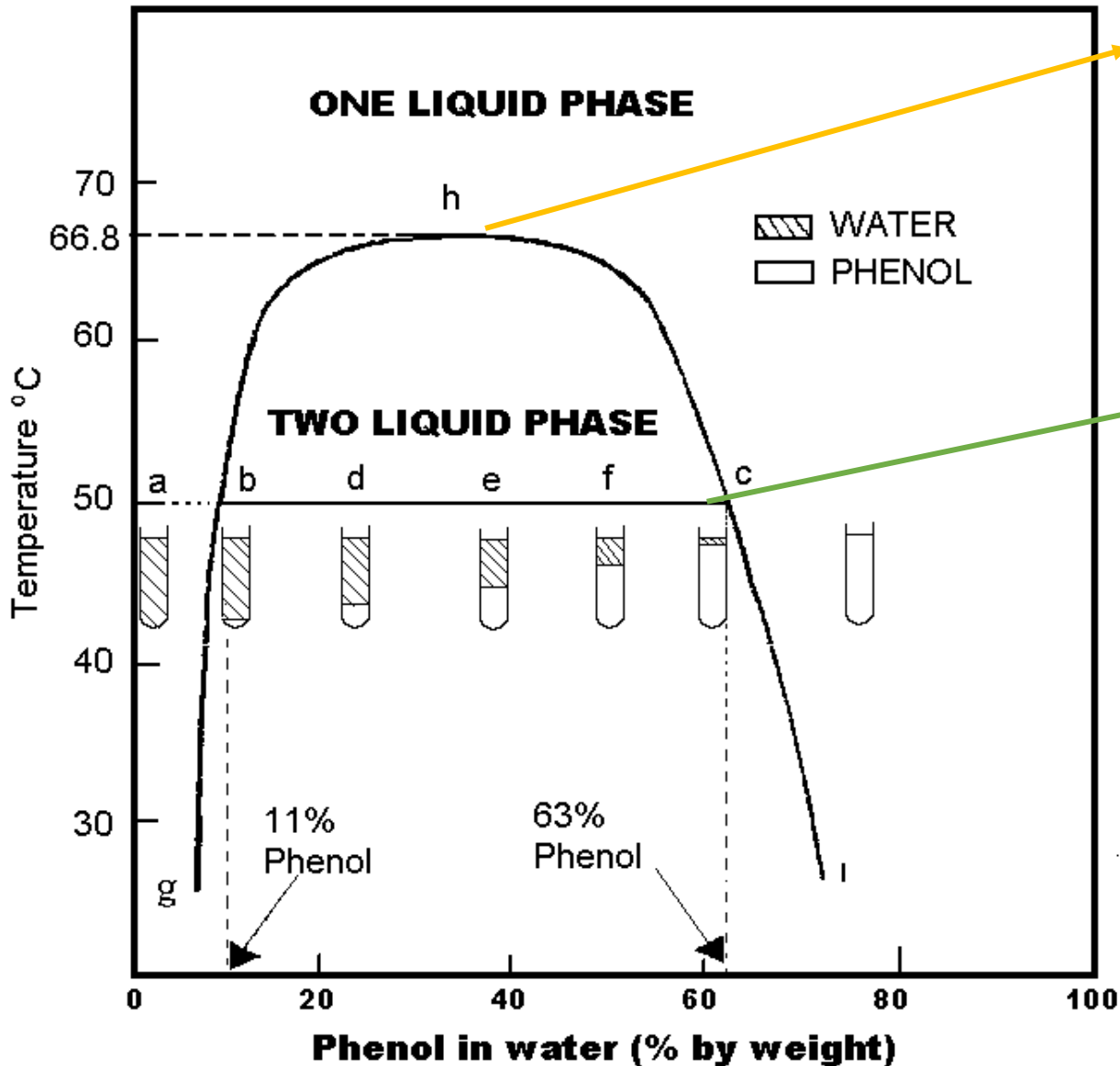
Temperature-composition diagram for the system consisting of water and phenol



Temperature-composition diagram for the system consisting of water and phenol



Temperature-composition diagram for the system consisting of water and phenol



critical solution, or upper consolute, temperature.

All combinations of phenol and water above this temperature are completely miscible and yield one-phase liquid systems.

tie line

at equilibrium, will separate into phases of constant composition. These phases are termed **conjugate phases**.

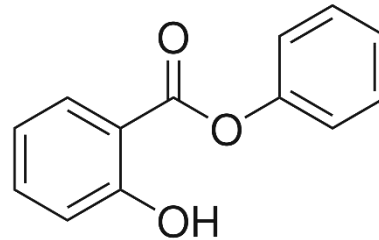


Two-Component Systems Containing Solid and Liquid Phases



- We restrict our discussion, in the main, to those solid–liquid mixtures in which the two components are completely miscible in the liquid state and completely immiscible as solids

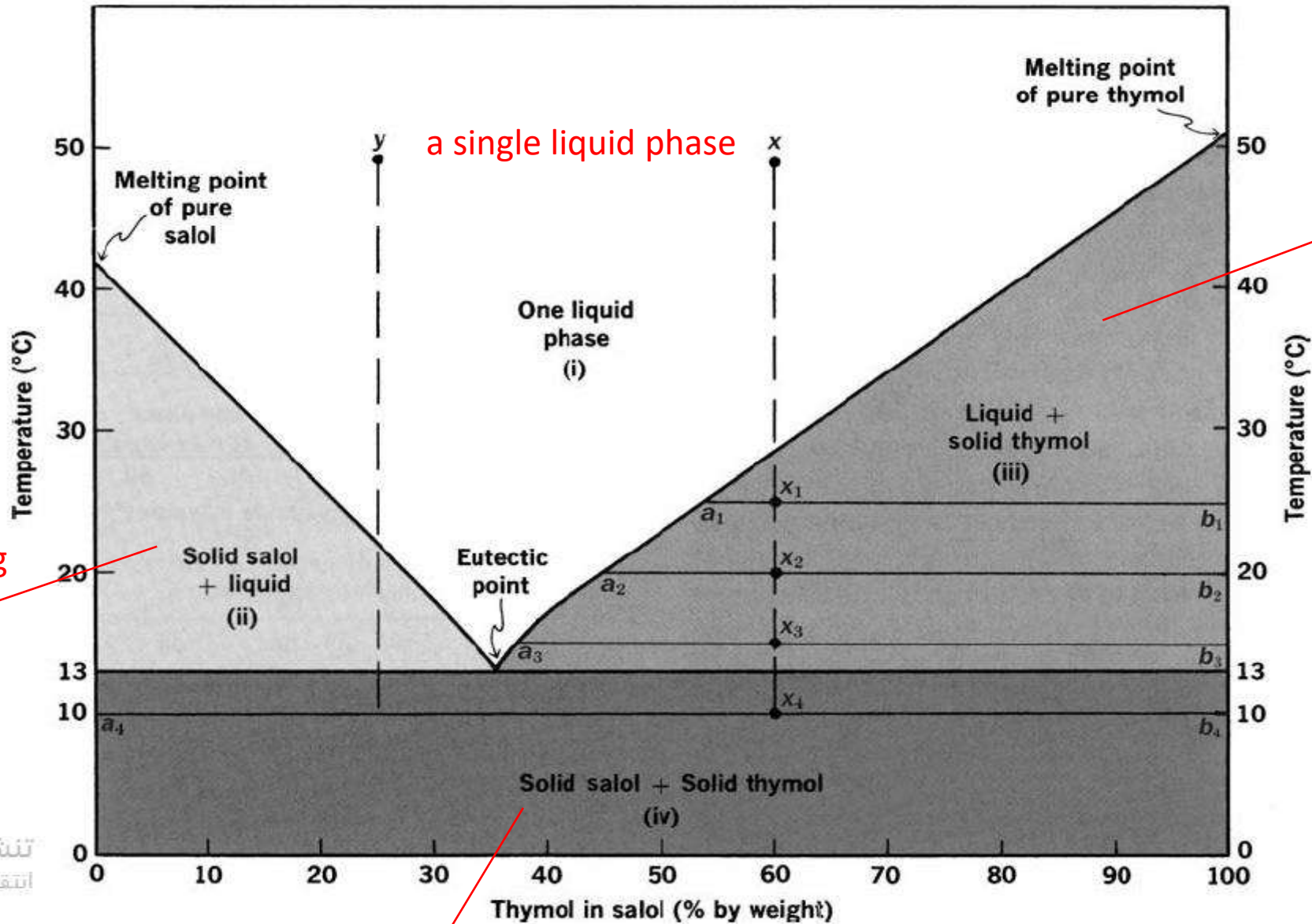
- Examples of such systems:
 - ✓ salol–thymol
 - ✓ salol–camphor



Phenyl salicylate, or salol, is a chemical substance, used in the manufacture of some polymers, lacquers, adhesives, waxes, and polishes



The phase diagram for the salol–thymol system showed four regions:



a region containing solid salol and a conjugate liquid phase

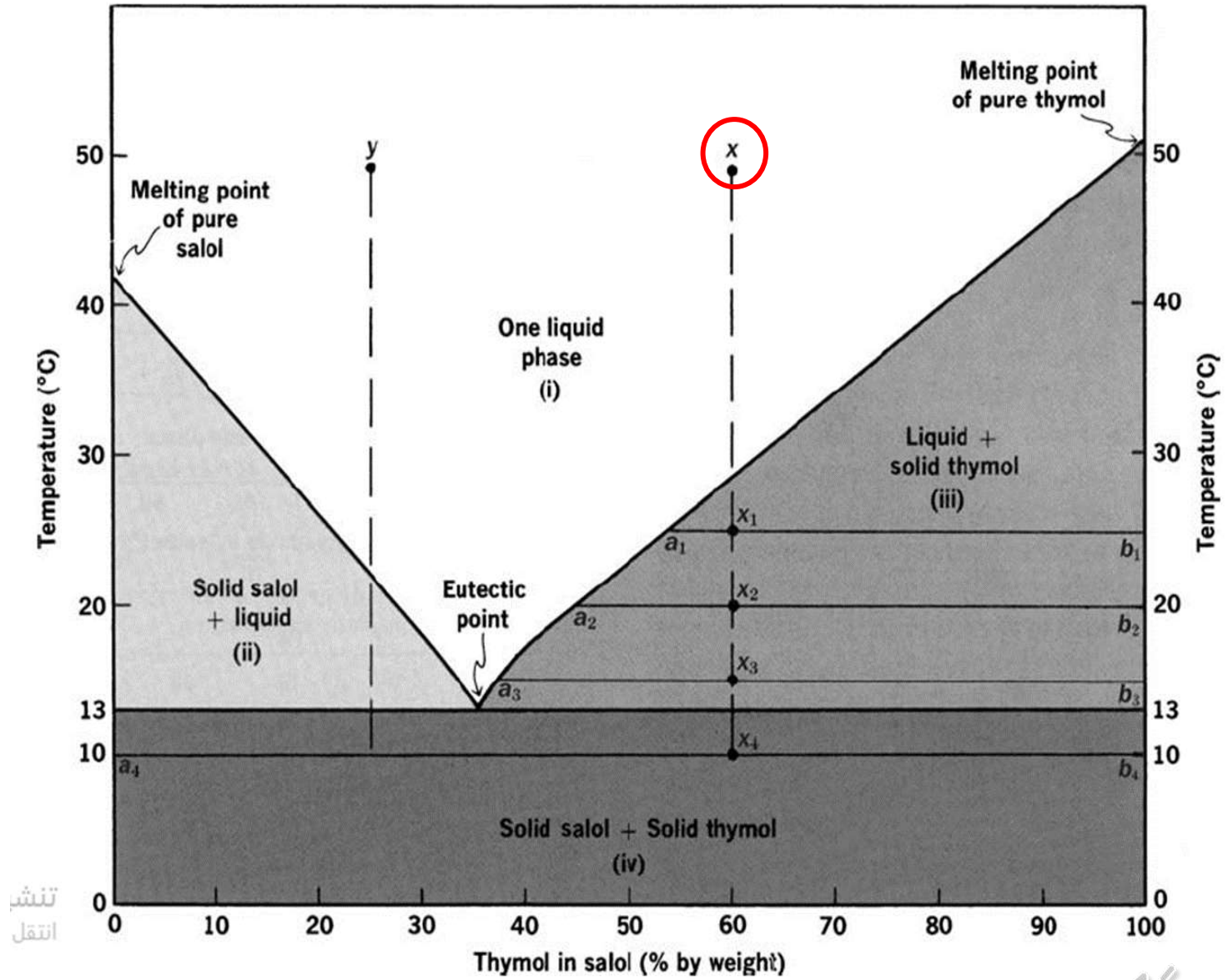
a single liquid phase

a region in which solid thymol is in equilibrium with a conjugate liquid phase

A region in which both components are present as pure solid phases.



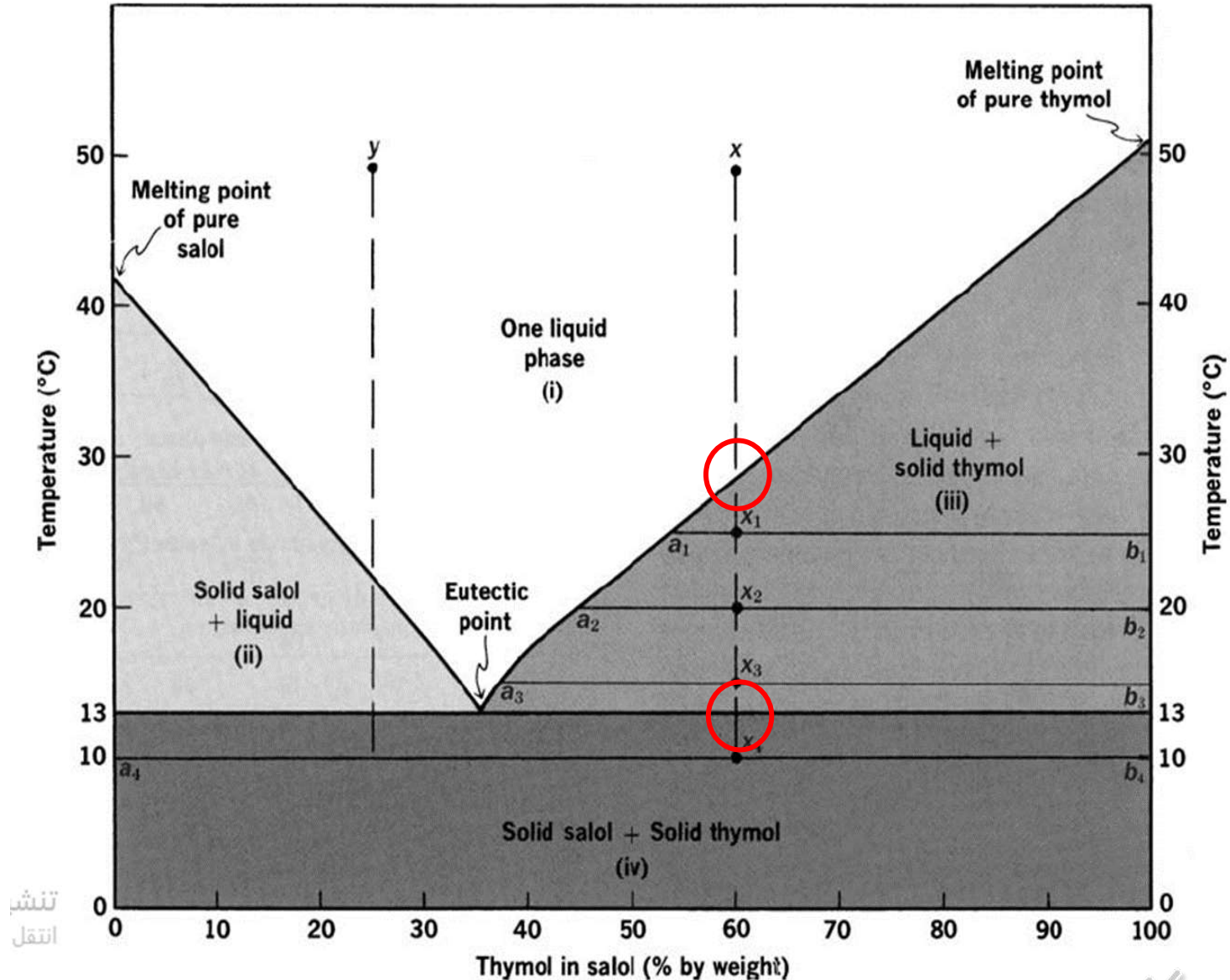
- Suppose we prepare a system containing 60% by weight of thymol in salol and raise the temperature of the mixture to 50°C. Such a system is represented by point **x** in the figure



تنشيط
انتقل



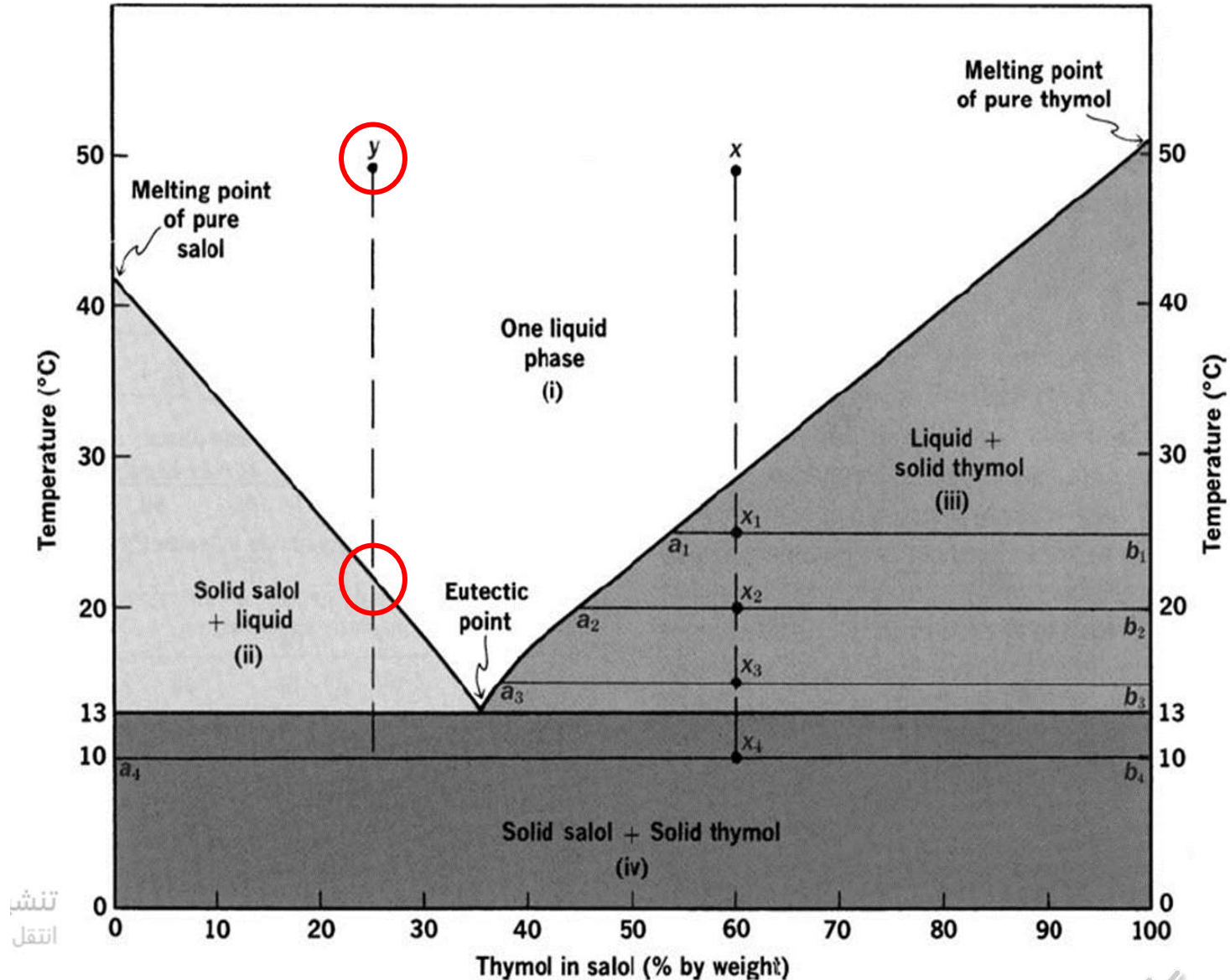
- On cooling the system, we observe the following sequence of phase changes:
 - ✓ The system remains as a single liquid until the temperature falls to 29°C, at which point a minute amount of solid thymol separates out to form a two-phase solid–liquid system.
 - ✓ Below 13°C, the liquid phase disappears altogether and the system contains two solid phases of pure salol and pure thymol.



تنشيط
انتقل



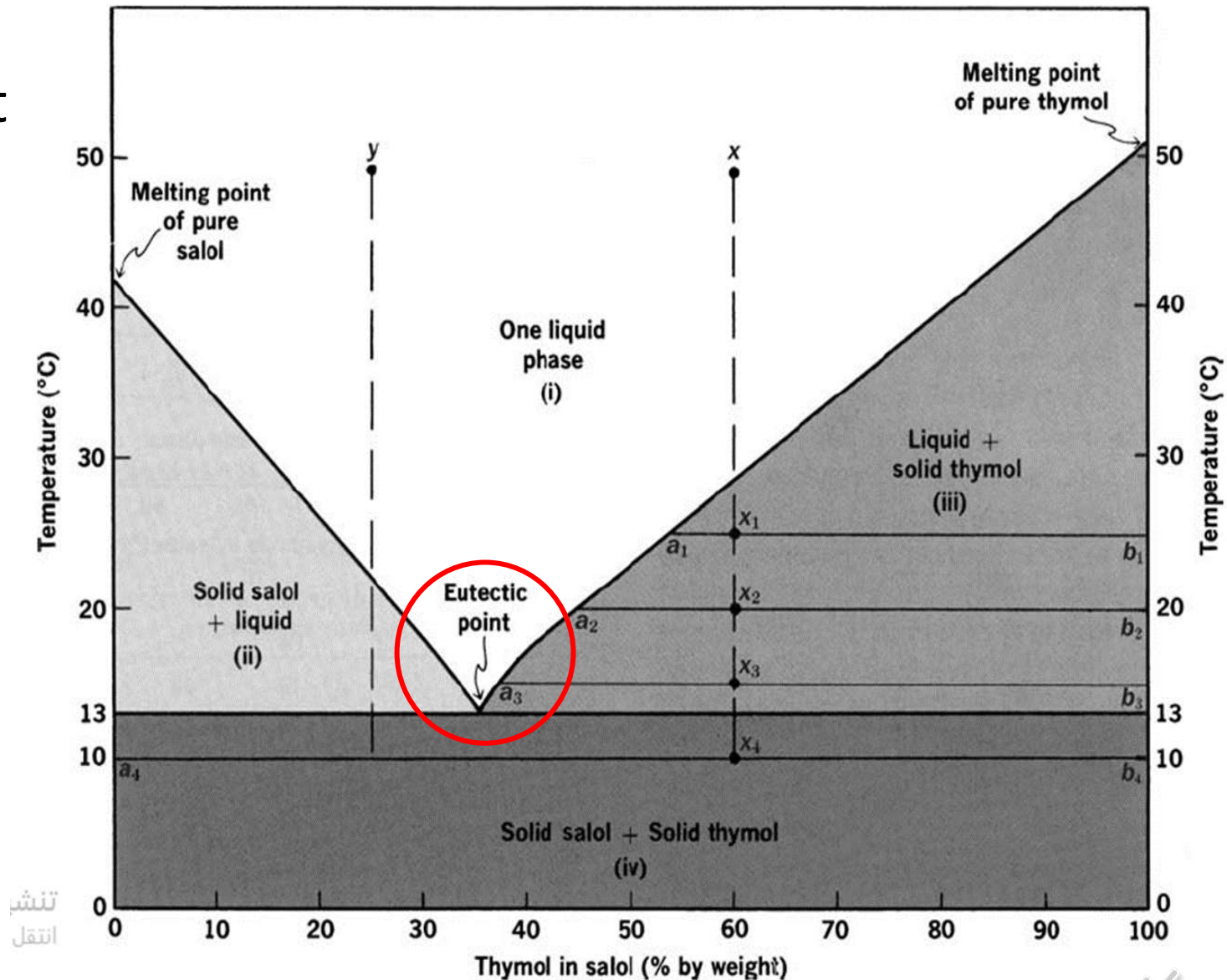
- ✓ As system x is progressively cooled, the results indicate that more and more of the thymol separates as solid.
- ✓ A similar sequence of phase changes is observed if system y is cooled in a like manner.
- ✓ In this case, however, the solid phase that separates at 22°C is pure salol.



تنشيط
انتقل

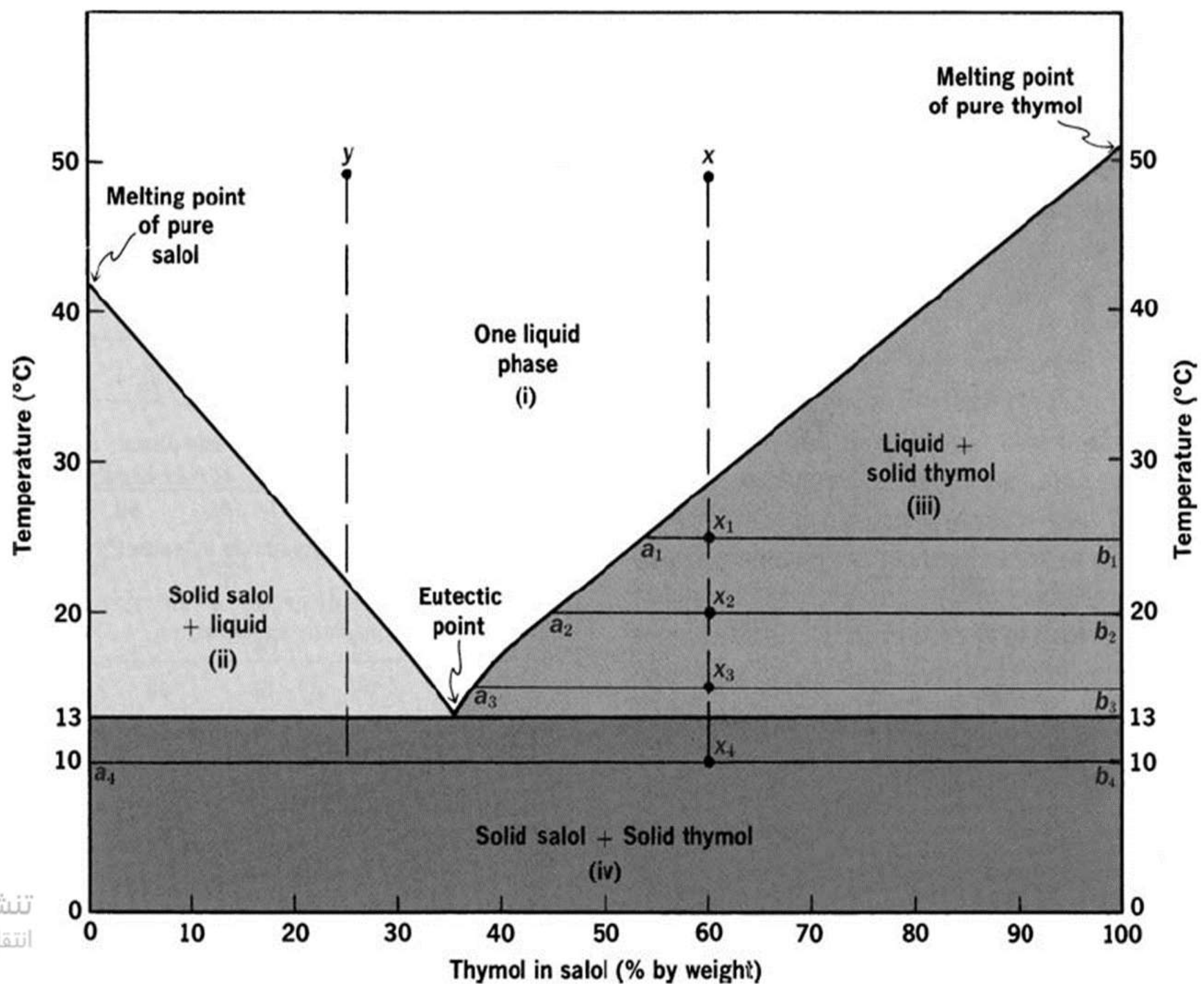


- The lowest temperature at which a liquid phase can exist in the salol–thymol system is 13°C , and this occurs in a mixture containing 34% thymol in salol.
- This point on the phase diagram is known as the **eutectic point**.
- The eutectic point is the point at which the liquid and solid phases have the same composition (*the eutectic composition*).



- **A eutectic mixture** is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components
- Eutectic point is the component ratio that exhibits the lowest observed melting point.





تنشیر
انتقل



- **Lidocaine and prilocaine**, two local anesthetic agents, form a 1:1 mixture having a eutectic temperature of 18°C.



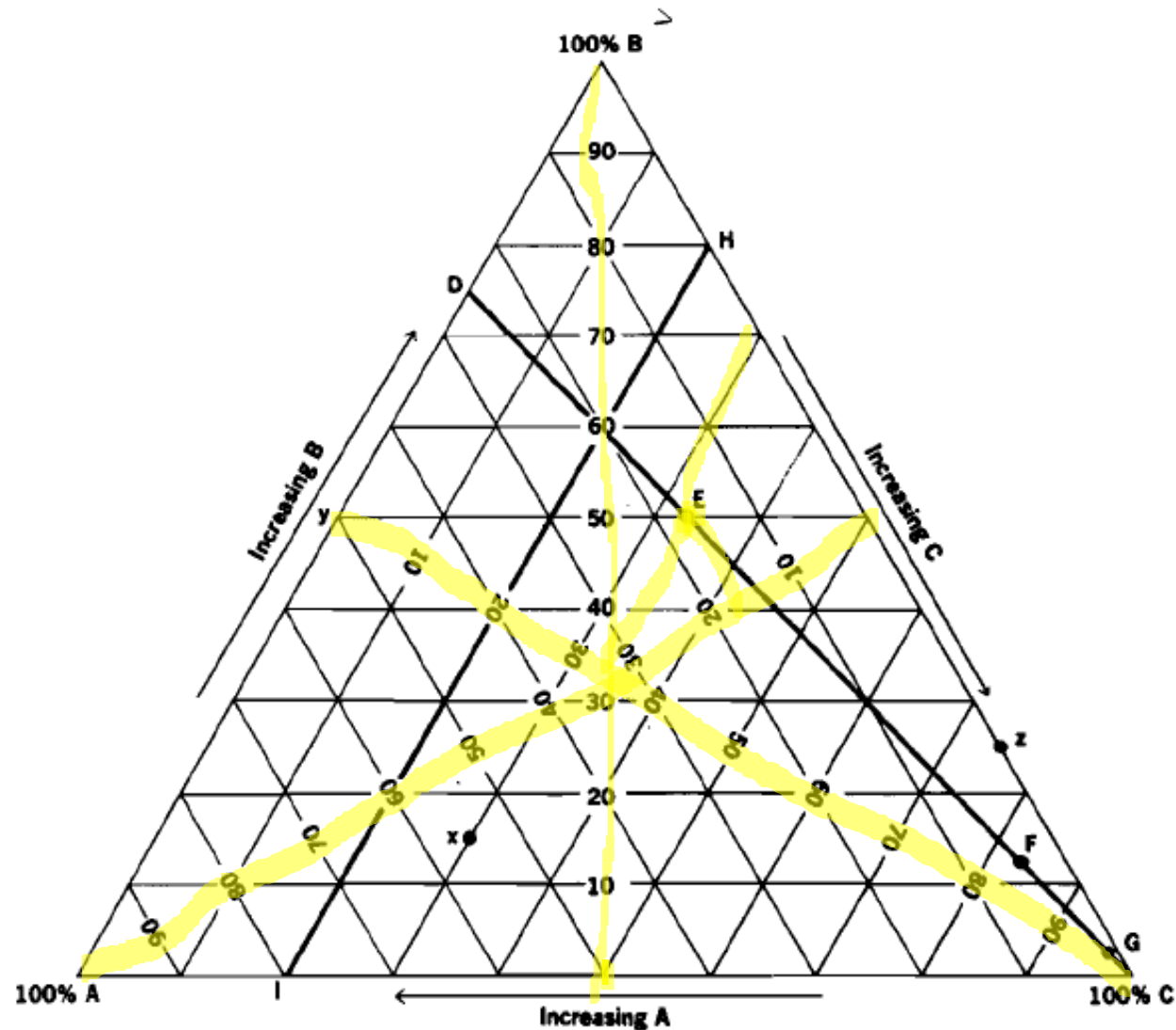
- The mixture is therefore liquid at room temperature and forms a mixed local anesthetic that may be used for topical application.
- Separately, lidocaine and prilocaine are solid bases. When mixed in equal quantities by weight, however, they form a eutectic mixture – that is the melting point of the mixture is lower than the melting points of the individual components.

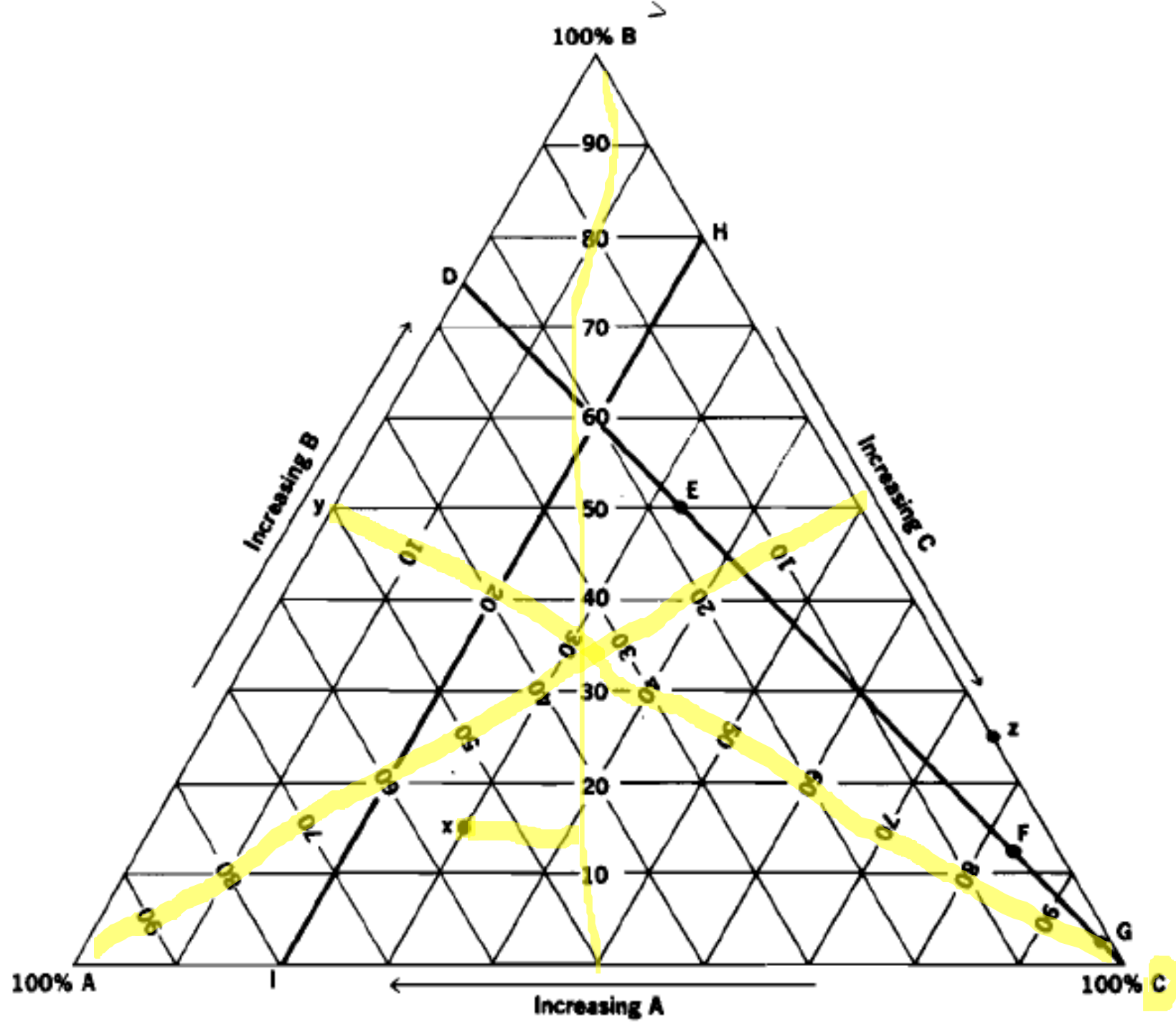


Phase Equilibria in Three-Component Systems



- Because we are dealing with a three-component system, it is more convenient to use triangular coordinate graphs
- Rules Relating to Triangular Diagrams:





Ternary Systems with One Pair of Partially Miscible Liquids

- Water and benzene are miscible only to a slight extent, and so a mixture of the two usually produces a two-phase system.
- On the other hand, alcohol is completely miscible with both benzene and water. It is to be expected, therefore, that the addition of sufficient alcohol to a two-phase system of benzene and water would produce a single liquid phase in which all three components are miscible
- It might be helpful to consider the alcohol as acting in a manner comparable to that of temperature in the binary phenol–water system considered earlier.
- Raising the temperature of the phenol–water system led to complete miscibility of the two conjugate phases and the formation of one liquid phase.



The addition of alcohol to the benzene–water system achieves the same end but by different means, namely, a solvent effect

