STATES OF MATTER and INTERMOLECULAR FORCES

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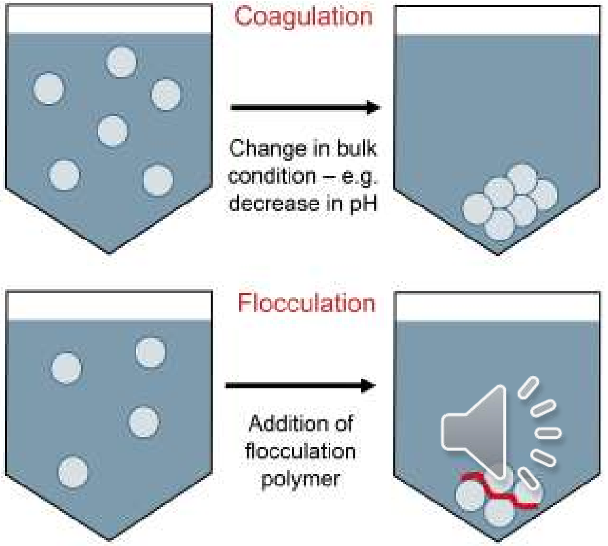
1st level

2020

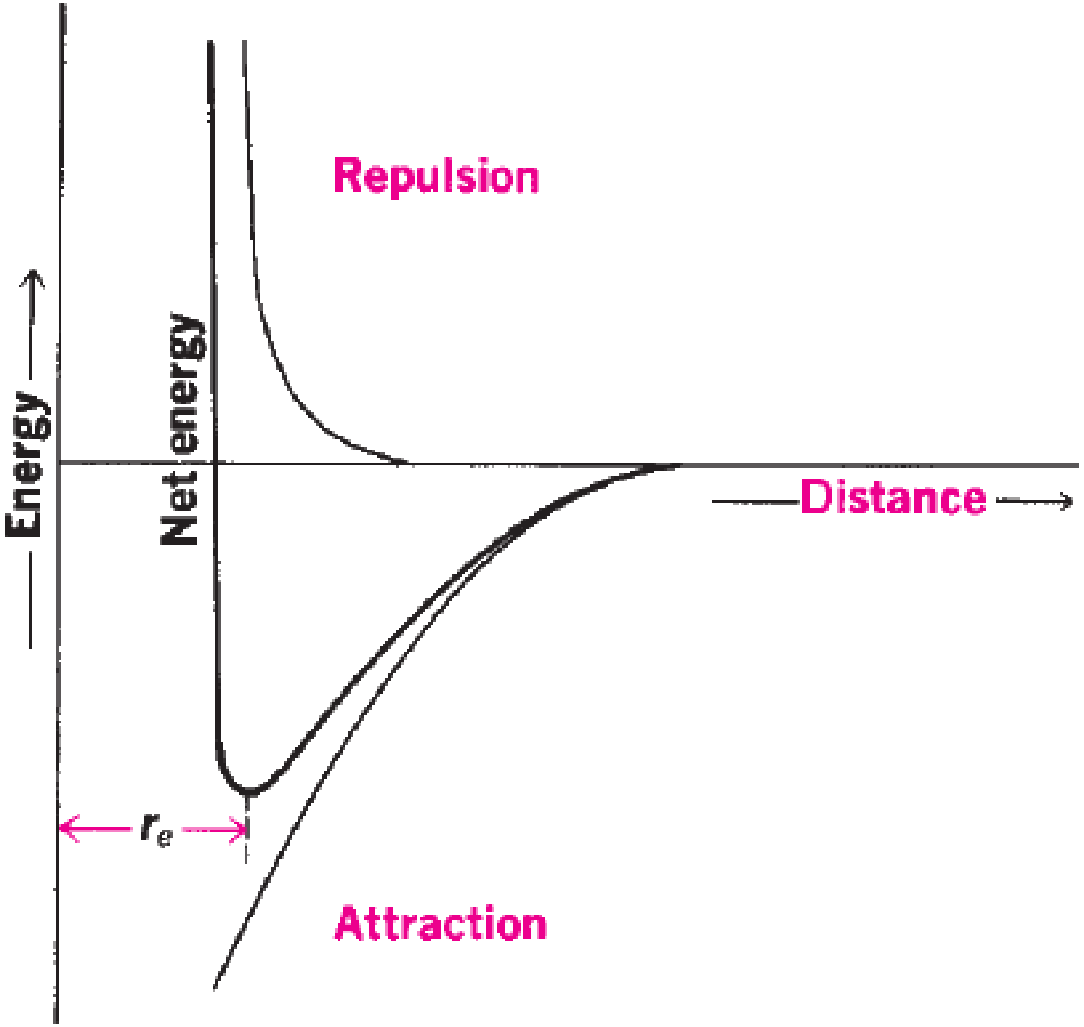
- In order for molecules to exist in aggregates in gases, liquids, and solids, intermolecular forces must exist.

- manifestations of intermolecular forces:
- Cohesion, or the attraction of like molecules
- adhesion, attraction of unlike molecules

- knowledge of these forces is important for an understanding not only of the properties of gases, liquids, and solids, but also :
    - flocculation in suspensions,
    - stabilization of emulsions,
    - compaction of powders in capsules,
    - compression of granules to form tablets.



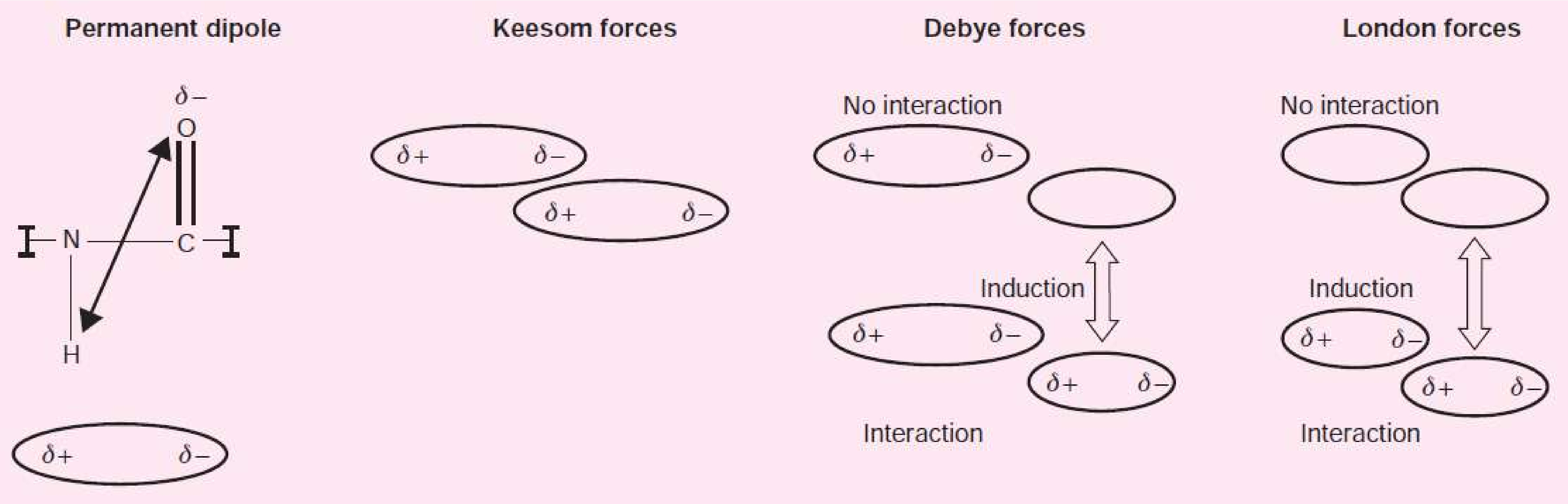
Repulsive and attractive forces



- $R \propto \frac{1}{r^{12}}$

Attractive intermolecular forces

1- VAN DER WAALS FORCES

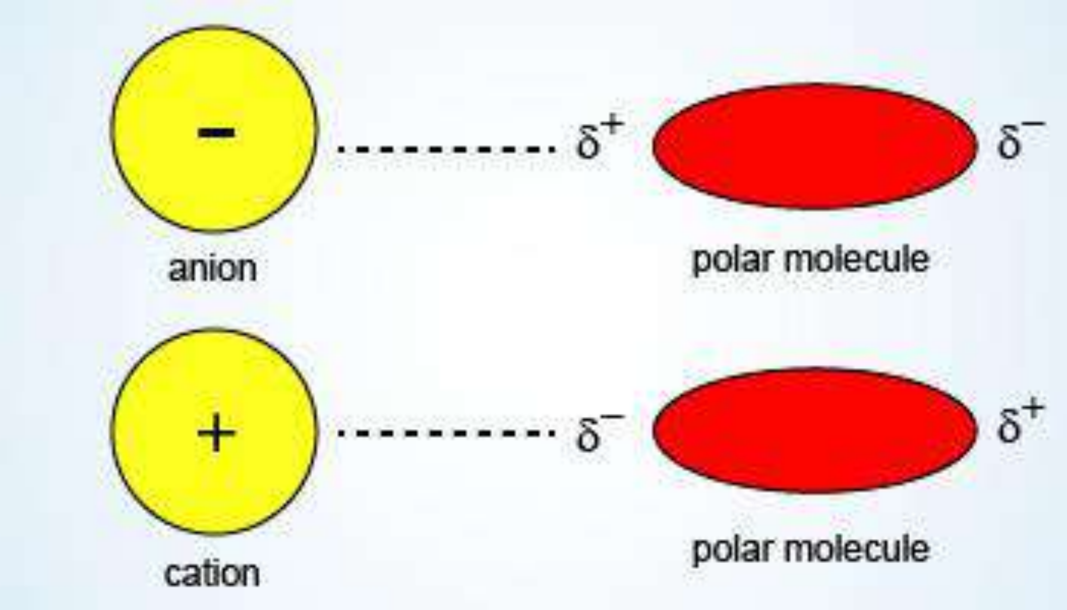


$$A \propto \frac{1}{r^6}$$

INTERMOLECULAR FORCES AND VALENCE BONDS

Bond Type		Bond Energy (approximately) (kcal/mole)
Van der Waals forces and other intermolecular attractions		
Dipole–dipole interaction, orientation effect, or Keesom force		1–10
Dipole-induced dipole interaction, induction effect, or Debye force		
Induced dipole–induced dipole interaction, dispersion effect, or London force		
Ion–dipole interaction		
Hydrogen bonds:	O—H · · · O	6
	C—H · · · O	2–3
	O—H · · · N	4–7
	N—H · · · O	2–3
	F—H · · · F	7
Primary valence bonds		
Electrovalent, ionic, heteropolar		100–200
Covalent, homopolar		50–150

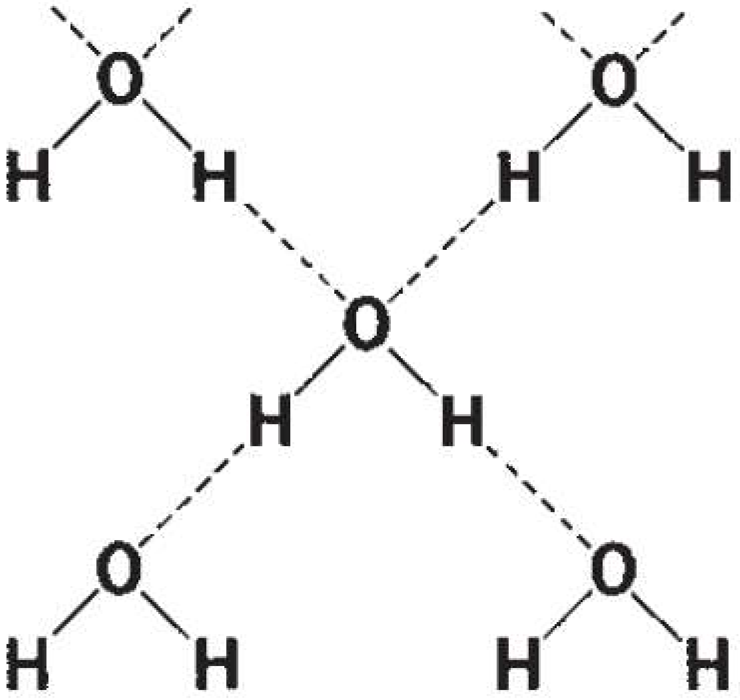
2- Ion–Dipole and Ion-Induced Dipole Forces



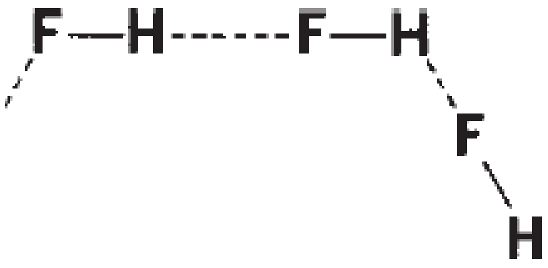
$$I_2 + K^+I^- = K^+I_3^-$$

3- Hydrogen Bonds

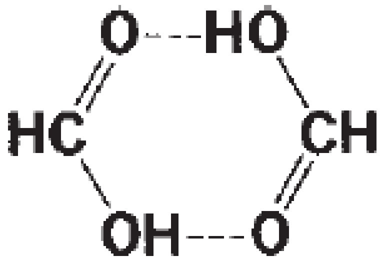
- The small size of the hydrogen atom and its large electrostatic field, it can move in close to an electronegative atom and form an electrostatic type of union known as a hydrogen bond or hydrogen bridge.
- The interaction between a molecule containing a hydrogen atom and a strongly electronegative atom such as fluorine, oxygen, or nitrogen
- an open but well ordered three-dimensional array of regular tetrahedra with oxygen in the center of each tetrahedron and hydrogen atoms at the four corners.



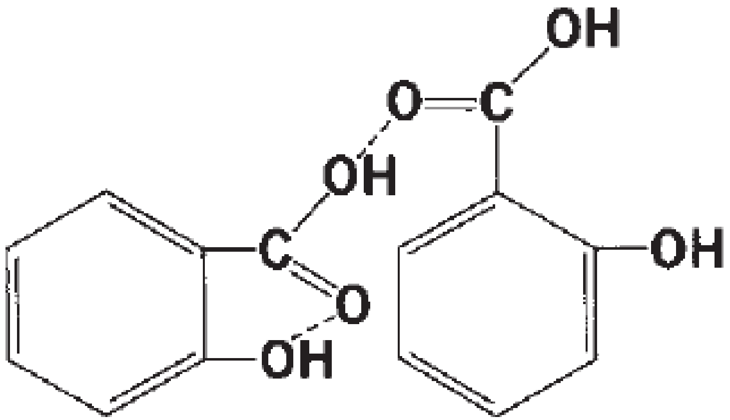
- Hydrogen bonding are tow types:
- Intermolecular
- Intramolecular



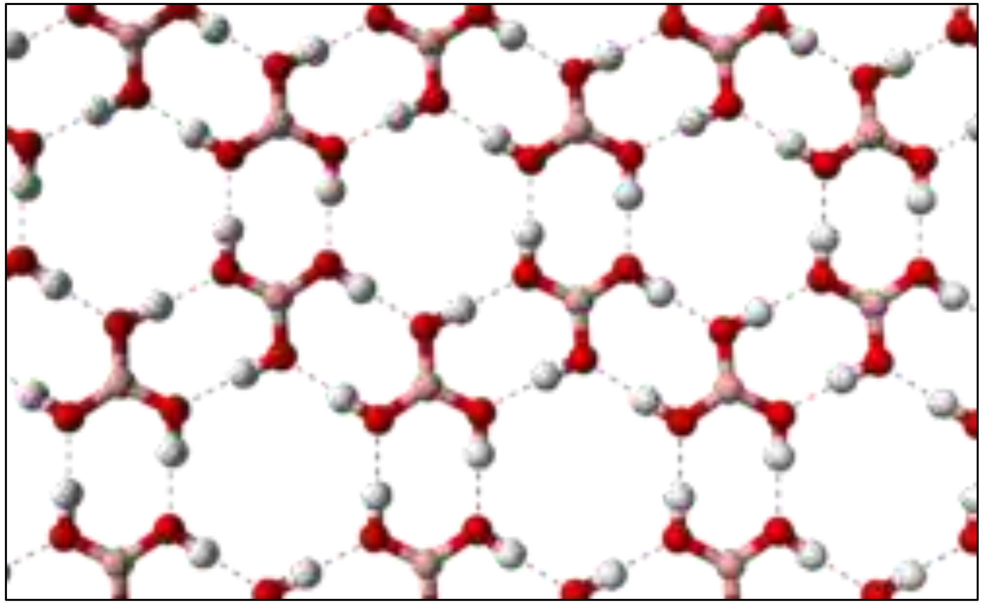
Hydrogen fluoride



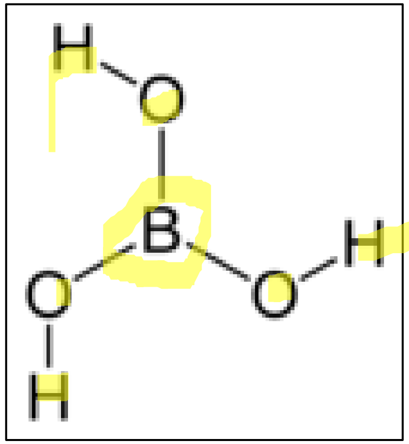
Formic acid dimer



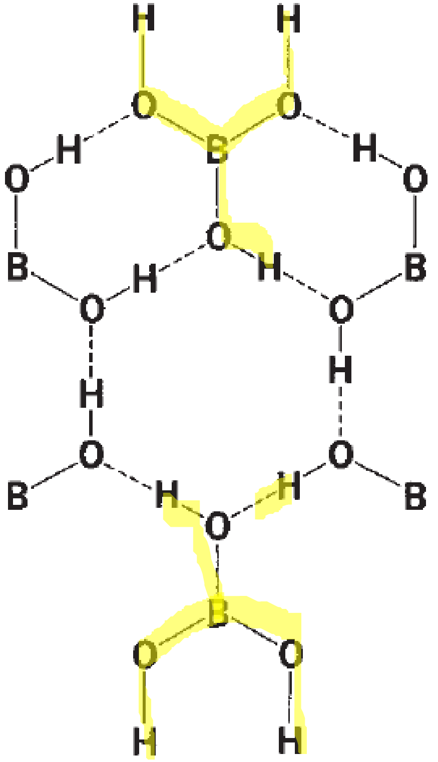
Salicylic acid showing intermolecular and intramolecular hydrogen bonding



Boric acid

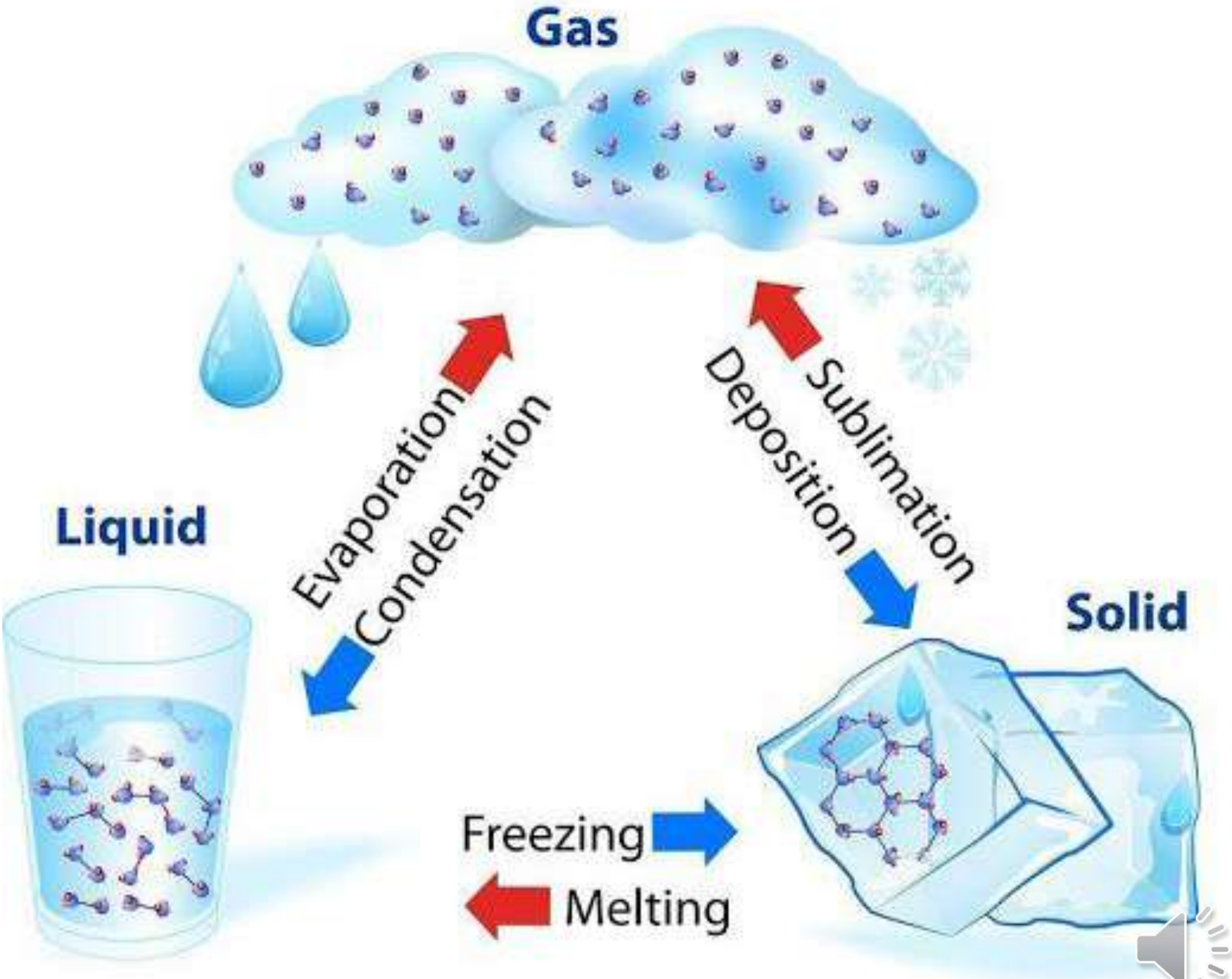


- ✓ Antibacterial and antifungal. Used chiefly in aqueous solutions or powders for external use.
- ✓ Boric acid has been used as mild antiseptics or bacteriostats in eyewashes, mouthwashes, burn dressing
- ✓ included in rectal suppositories for hemorrhoids
- ✓ intravaginal gelatin capsules/vaginal douche



Layer of boric acid molecules in a crystal
The molecules are linked by hydrogen bonds

STATES OF MATTER



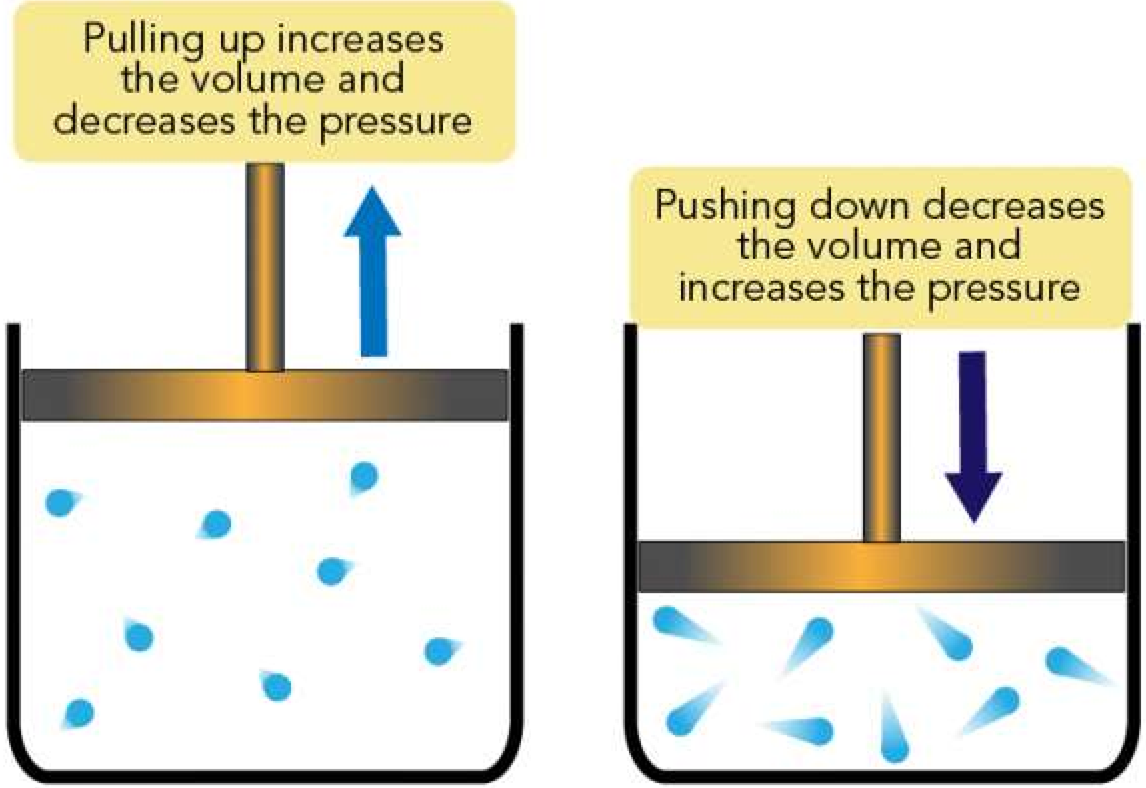
1- gaseous state

- vigorous and rapid motion, gas molecules travel in random paths, frequently colliding with one another and with the walls of the container in which they are confined

- they exert a *pressure-a* force per unit area
- volume, is usually expressed in liters or cubic centimeters
- The temperature involved in gas equations is given in absolute or Kelvin degrees (K).
- Zero degrees on the centigrade scale is equal to 273.15° K.

The Ideal Gas law

- **Boyle's law:** Relates the' volume and pressure of a given mass of gas at constant temperature.
- $P \alpha \frac{1}{V}$ T constant
- $P = \frac{K}{V}$ or P V = K



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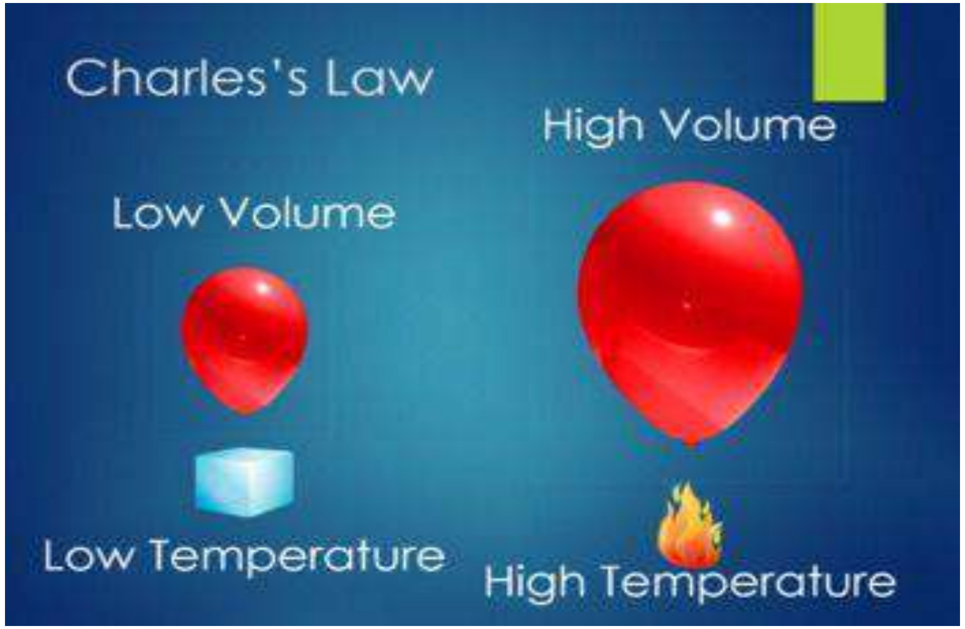
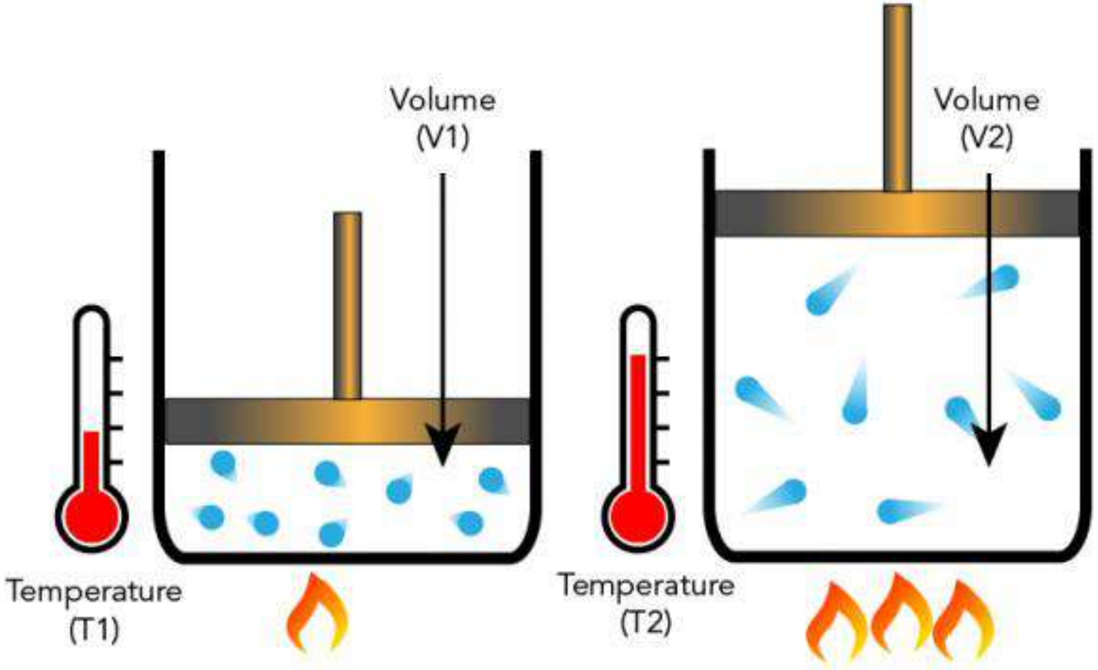
Gray Lussac and Charles Law

- heating a gas will cause it to expand by a certain fraction

$V \; \alpha \; T$ or **$V = kT$**





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- These equations can be combined to obtain the relationship:

at one conditions $$\boxed{\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2}}$$ another set of conditions

- although P, V, and T change, the ratio PV/T is constant and can be expressed mathematically as:

$$\boxed{\frac{PV}{T} = R}$$ molar gas constant

$$\boxed{PV = RT}$$

for one mole

$$\boxed{PV = nRT}$$

the general ideal gas law

- **Example**
- In the assay of ethyl nitrite spirit, the nitric oxide gas that is liberated from a definite quantity of spirit and collected in a gas burette occupies a volume of 30.0 mL at a temperature of,2O" C and a pressure of 74O mm of mercury. What is the volume at 0°C and 760 mmHg? (assume that the gas behaves ideally.)

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2} \qquad \frac{740 \times 30.0}{273 + 20} = \frac{760 \times V_2}{273}$$

$$V_2 = 27.2 \text{ mL}$$

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The molar gas constant (R)

- is highly important in physical chemical science;
- it appears in a number of equations in
    - electrochemistry
    - solution theory
    - Colloid chemistry
    - in the gas laws

- **To obtain a numerical value for R, let us proceed as follows:**
- If 1 mole of an ideal gas is chosen, its volume under standard conditions of temperature and pressure (STP) (i.e., at **0° C** and **760 mm Hg**) has been found by experiment to be **22.414 liters**

1 atm × 22.414 liters = 1 mole × R × 273 K

R = 0.08205 liter. atm/mole.deg

- **The molar gas constant can also be given in energy units:**
- by expressing the pressure in **dynes/cm2** (1 atm = 1.0133 × 106 dynes/cm2) and the volume in the corresponding units of **cm3** (22.414 liters = 22,414 cm3). Then:

$$R = \frac{PV}{T} = \frac{(1.0133 \times 10^{6}) \times 22{,}414}{273.16^{\circ}}$$

$$= 8.314 \times 10^{7} \text{ erg/mole deg}$$

- Because $1 \text{ joule} = 10^{7} \text{ ergs},$ **R = 8.314 joules/mole.deg**

- 1 cal = 4.184 joules ,,, $R = \dfrac{8.314 \text{ joules/mole deg}}{4.184 \text{ joules/cal}}$

R = 1.987 cal/mole deg

- What is the volume of 2 moles of an ideal gas at 25◦C and 780 mm Hg?

PV = nRT

780 mmHg x (1 atm/760 mmHg) x V = 2moles x 0.08205 (Liter.atm/mol.deg) x 298 K

V = 47.65 Liters

MolecularWeight

- The approximate molecular weight of a gas can be determined by use of the ideal gas law.
- The number of moles of gas **n** is replaced by its equivalent **g/M**, in which g is the number of grams of gas and M is the molecular weight:

$$PV = \frac{g}{M}RT \qquad M = \frac{gRT}{PV}$$

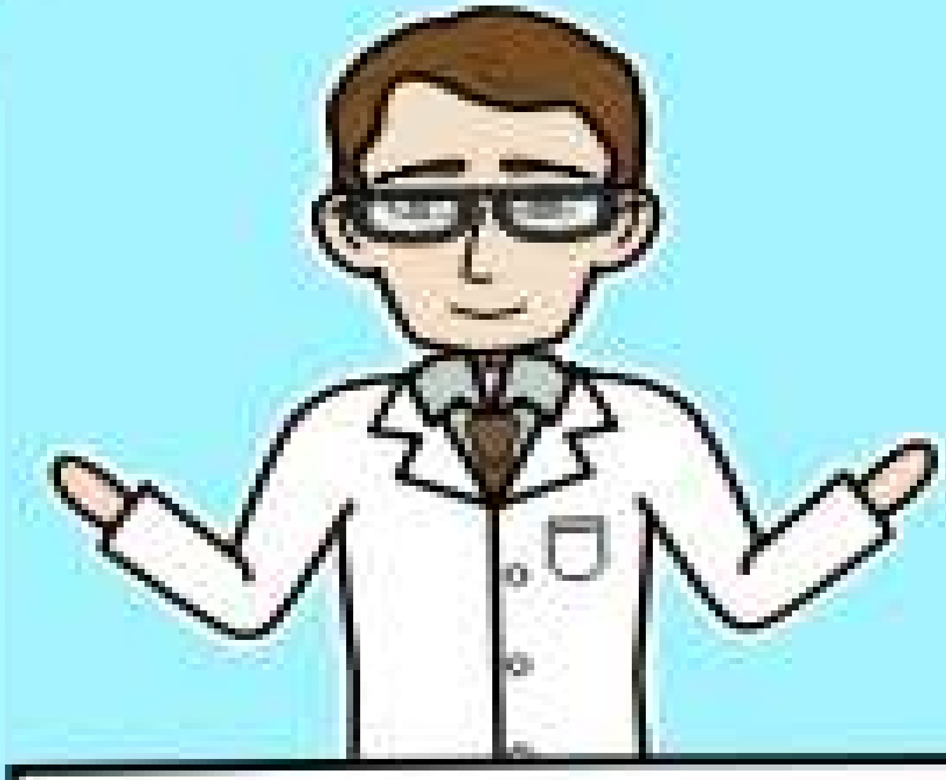
EXAMPLE

- If 0.30 g of ethyl alcohol in the vapor state occupies 200 mL at a pressure of 1 atm and a temperature of 100◦C, what is the molecular weight of ethyl alcohol? Assume that the vapor behaves as an ideal gas.

$$M = \frac{gRT}{PV}$$

$$M = \frac{0.30 \times 0.082 \times 373}{1 \times 0.2}$$

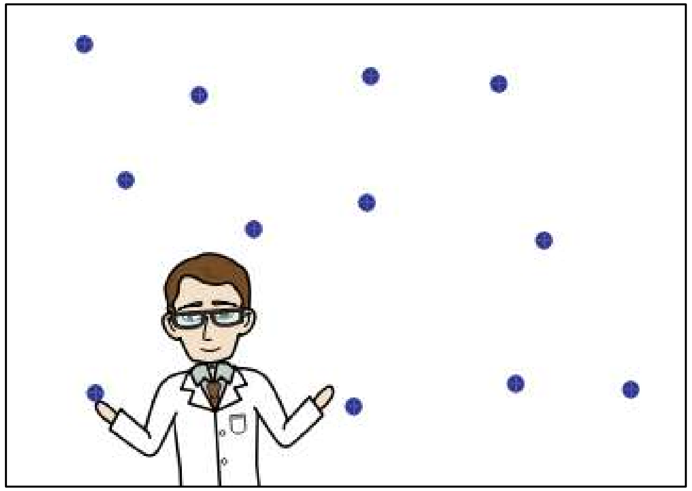
$$M = 46.0\ \mathrm{g/mole}$$



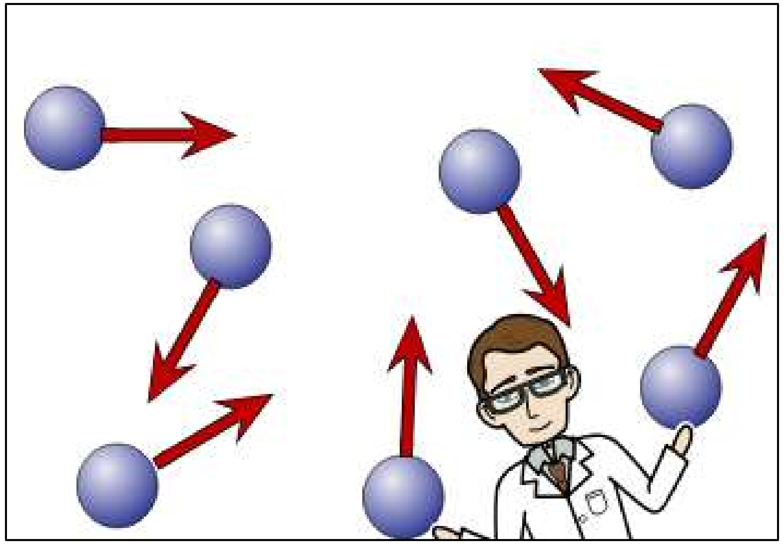
Kinetic Molecular Theory

The theory that was developed to explain the behavior of gases and to lend additional support to the validity of the gas laws is called the **kinetic molecular theory:**

1. Gases are composed of particles called atoms or *molecules*, the total **volume** of which is so small as to be negligible in relation to the volume of the space in which the molecules are confined. (only at low pressures and high temperatures, in which case the molecules of the gas are far apart).



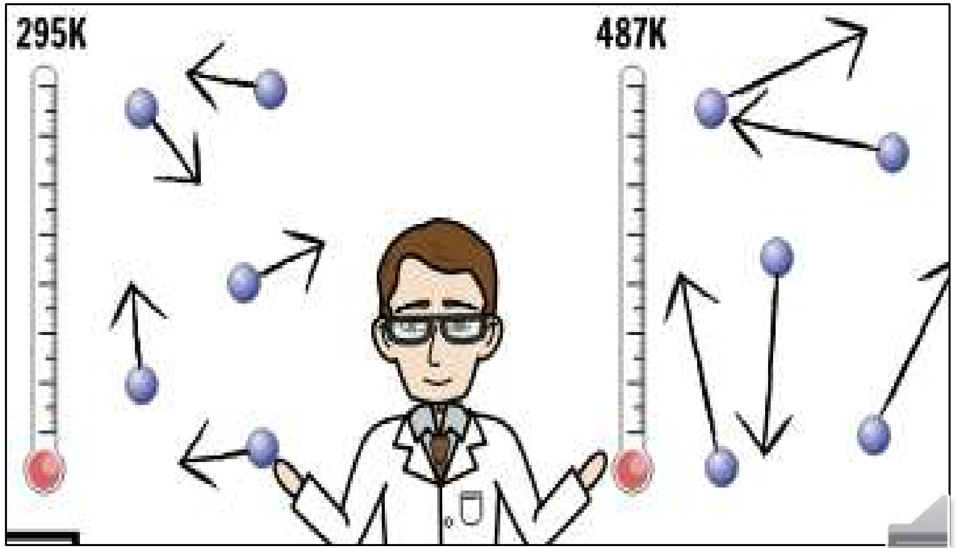
2. The particles of the gas do not attract one another, but instead move with complete **independence** (only at low pressures).



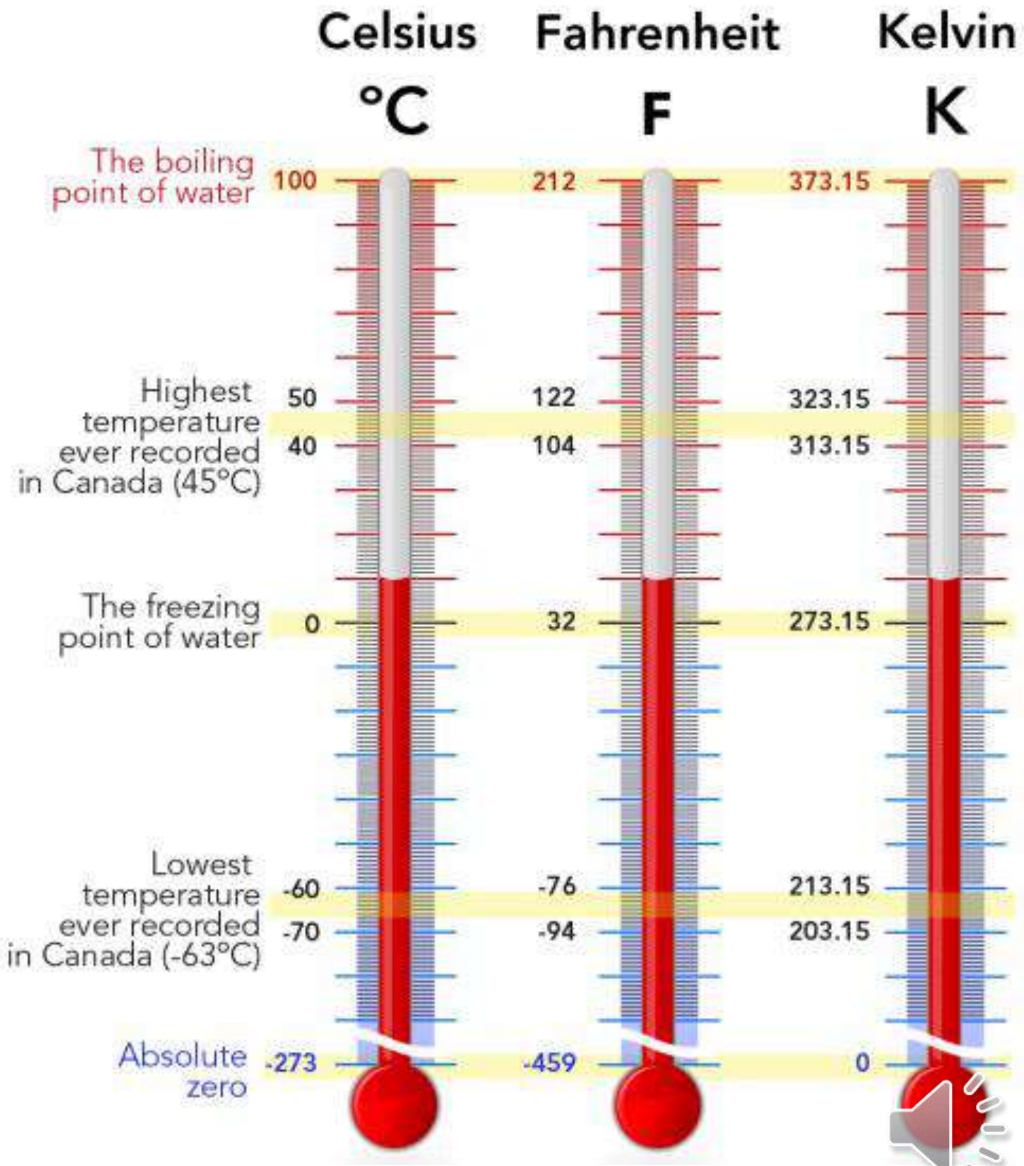
3. The particles exhibit continuous random motion owing to their **kinetic energy**. The average kinetic energy, E, is directly proportional to the absolute temperature of the gas, or $E = (3/2)RT$.

✓All of the energy of a gas is in the form of kinetic energy (energy from movement)

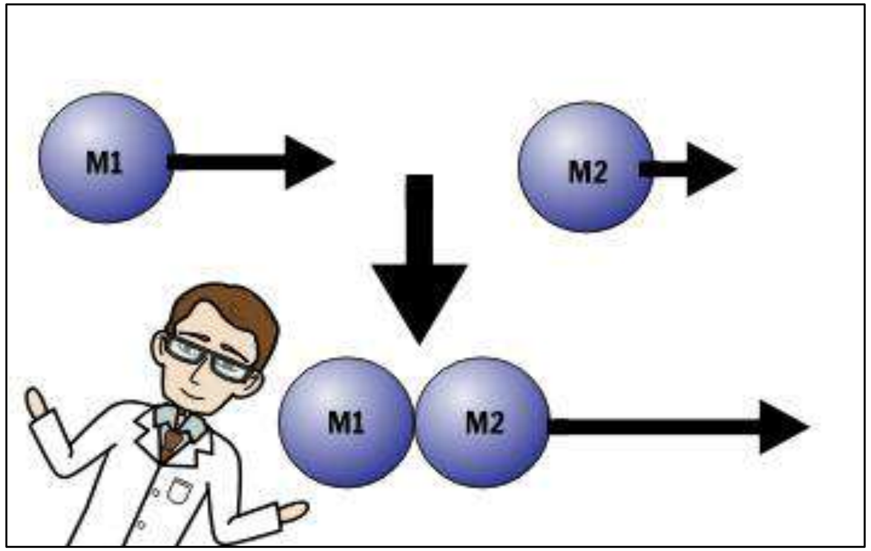
✓Any change in kinetic energy is accompanied by a change in temperature and vice versa



- **Why do the Celsius and Fahrenheit scales not work well for describing gases?**
- kinetic energy is related to temperature.
- A substance at a temperature of 0°C does not mean it has zero kinetic energy (the particles of a substance at 0°C still has a considerable amount of kinetic energy)
- It is needed for gases a temperature scale in which zero means the particles are not moving at all (i.e., have zero kinetic energy).
- absolute zero, or 0 K, is the lowest temperature



4. The molecules exhibit **perfect elasticity**; that is, there is no net loss of speed or transfer of energy after they collide with one another and with the molecules in the walls of the confining vessel, which latter effect accounts for the gas pressure.



- the net velocity can be an **average velocity** of many molecules; thus, a distribution of individual molecular velocities can be present in the system.

- From these and other postulates, the following fundamental kinetic equation is derived:

$$\boxed{PV = \frac{1}{3} nm\overline{c^2}}$$

- where P is the pressure and V the volume occupied by any number n of molecules of mass m having an average velocity c.

- **Rate of diffusion:**

- Because the term ***nm/V*** is equal to density:

$(\overline{c^2})^{1/2}$ (usually written μ)
the root mean square velocity

$$\boxed{\mu = \sqrt{\frac{3RV}{nm}}}$$

$$\boxed{\mu = \sqrt{\frac{3RT}{M}}}$$

$$\boxed{\mu = \sqrt{\frac{3P}{d}}}$$

$$\boxed{\mu = \sqrt{\frac{3P}{d}}}$$

- the rate of diffusion of a gas is inversely proportional to the square root of its density.
- a light gas diffused more rapidly through a porous membrane than did a heavier one

EXAMPLE

What is the root mean square velocity of oxygen (molecular weight, 32.0) at 25°C (298 K)?

$$\mu = \sqrt{\frac{3RT}{M}}$$

$$\mu = \sqrt{\frac{3 \times 8.314 \times 10^{7} \times 298}{32}} = 4.82 \times 10^{4}\,\text{cm/sec}$$

Problem:

Nitrous oxide ($N2O$) is used for the rapid induction of anesthesia (80% $N20$, 20% $O2$) and at lower percentages for maintenance anesthesia.

(a) Using the ideal gas equation, compute the molecular weight of this gas, given that 1 liter at 0' C and 760 mmHg pressure weight 1.97g.

(b) Compute the root mean square velocity, µ , of $N20$.

(c) Compute the density p of $N20$ at 1 atm and 0" C.

(a) $P.V = n.R.T$

$1 \times 1 = n \times 0.08205 \times 273$

$n = 0.0446$ mole

$n = wt / M \rightarrow M = wt / n = 44.17$ g/mol

(b) $\mu = \sqrt{3RT/M} = 3.9 \times 10^4$ cm/sec

(c) $d = wt / V = 1.97 / 1 = 1.97$ g/L

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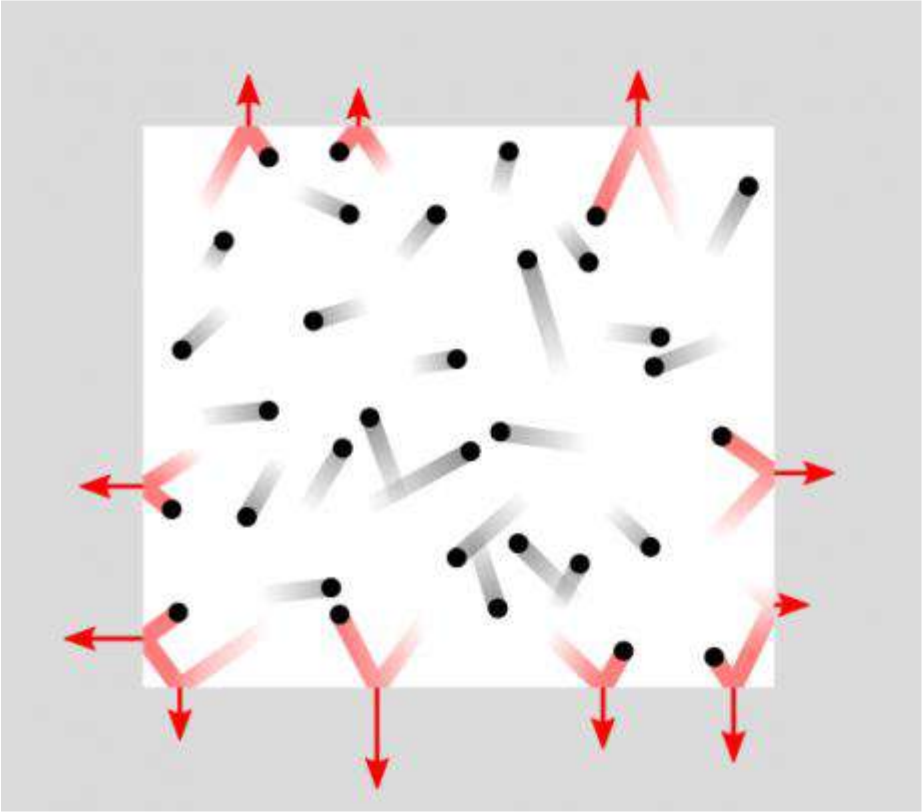
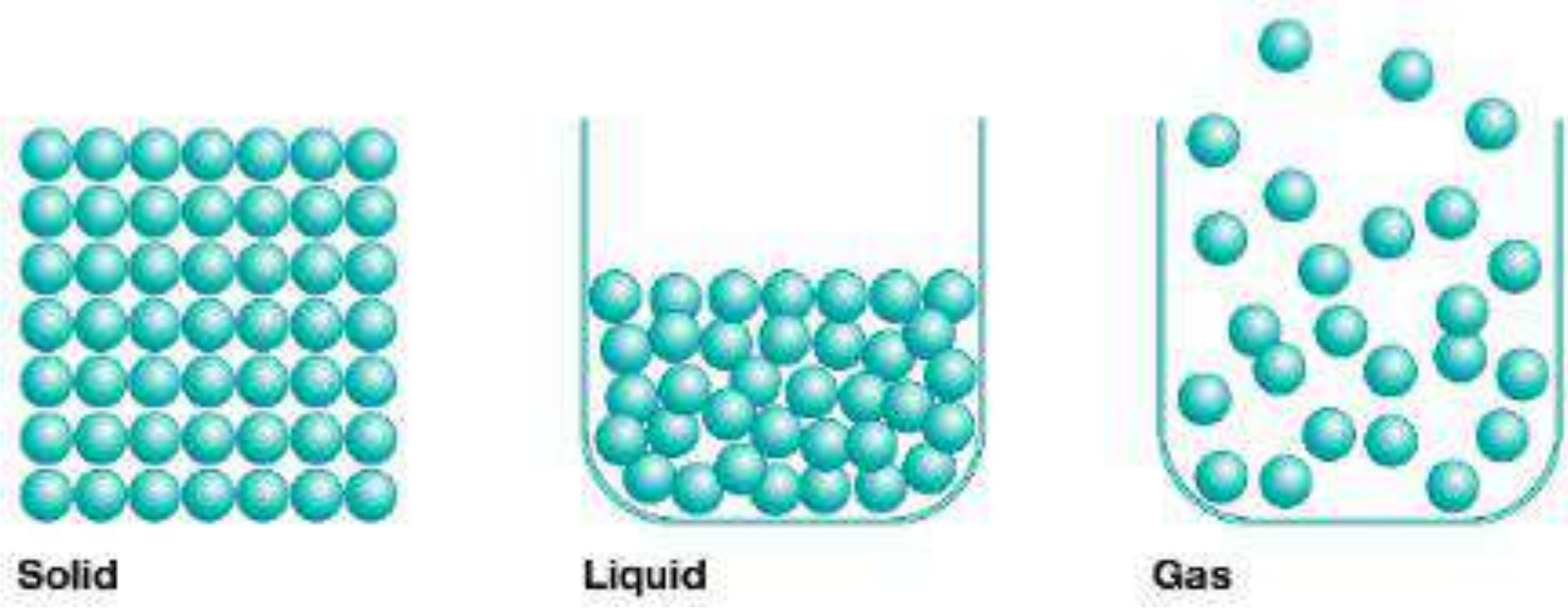
- the theory explains **the pressure**: The force of many collisions by many molecules against the walls of a container



Internal pressure

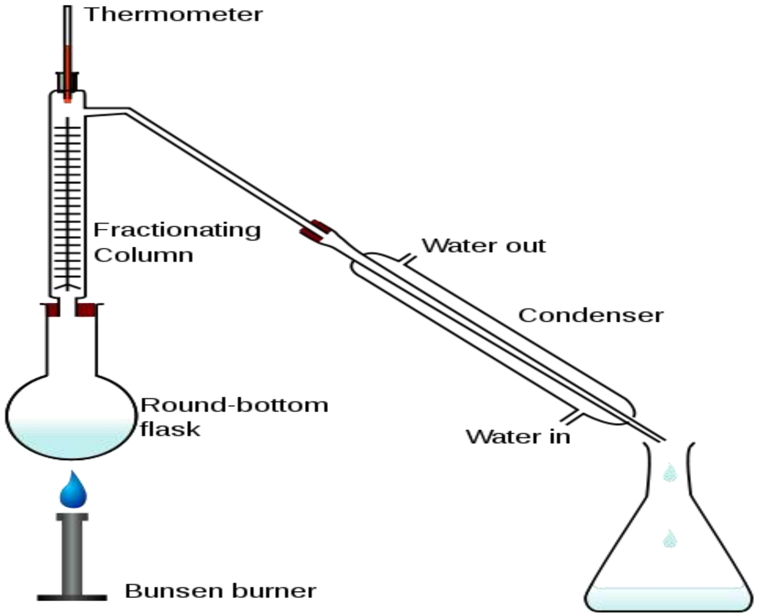
- resulting from the intermolecular forces of attraction between the molecules (cohesive forces)
- **Polar liquids** have high internal pressures and serve as solvents only for substances of similar internal pressures.
-
- **Nonpolar molecules** have low internal pressures and are not able to overcome the powerful cohesive forces of the -polar solvent molecules.
- Mineral oil is immiscible with water for this reason.

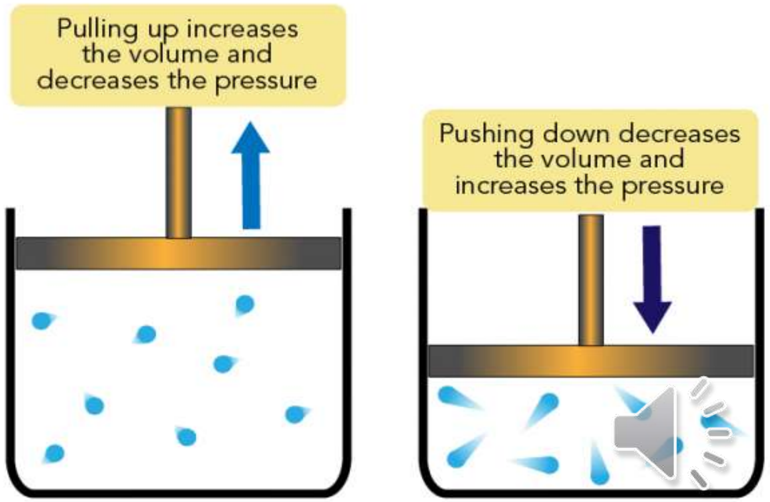
2- Liquid state



- **Liquefaction of Gases**
- When a gas is cooled→ it loses some of its kinetic energy in the form of heat → the velocity of the molecules decreases→ turned into the liquid state.

- If pressure is applied to the gas → the molecules are brought within van der Waals interaction forces → pass into the liquid state.





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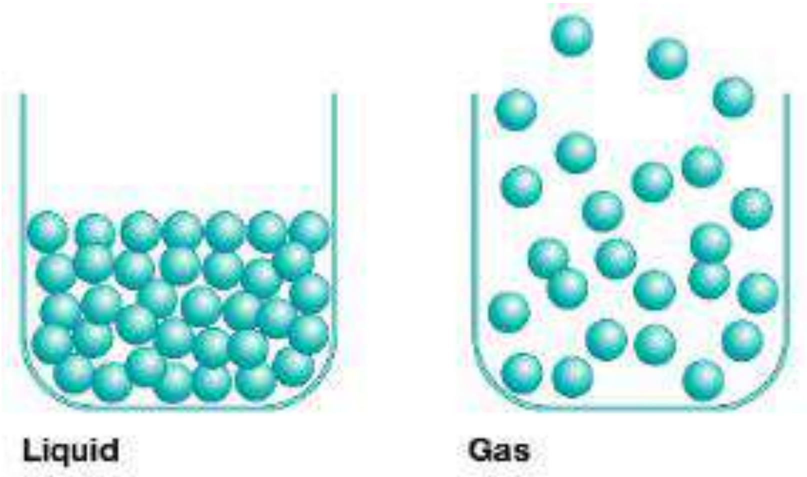
- ✓Because of these forces, liquids are considerably **denser** than gases and occupy a definite volume.

- ✓The transitions from a gas to a liquid and from a liquid to a solid depend not only on the temperature, but also on the pressure to which the substance is subjected.



- **Critical temperature**
- Temperature above which a liquid can no longer exist

- If the temperature is elevated sufficiently, a value is reached above which it is impossible to liquefy a gas, irrespective of the pressure applied.

- **Critical pressure**
- The pressure required to liquefy a gas at its critical temperature.
- Which is also the highest vapor pressure that the liquid can have.

- The further a gas is cooled below its critical temperature, the less pressure is required to liquefy it.

- Based on this principle, all known gases have been liquefied.

- The critical temperature of **water** is **374** C or **647** K, and its critical pressure is **218** atm (high critical values due to strong dipolar forces between the molecules and particularly the hydrogen bonding)

- while the corresponding values for **helium** are **5.2 K -267.8 C** and **2.26 atm** (molecules are attracted only by the weak London force) → consequently, this element must be cooled to the extremely low temperature of 5.2 K before it can be liquefied. Above this critical temperature, helium remains a gas no matter what the pressure.

- The critical temperature serves as a rough measure of the **attractive forces** between molecules: for at temperatures above the critical value, the molecules possess sufficient kinetic energy so that no amount of pressure can bring them within the range of attractive forces that cause the particles to "stick" together.

Aerosols

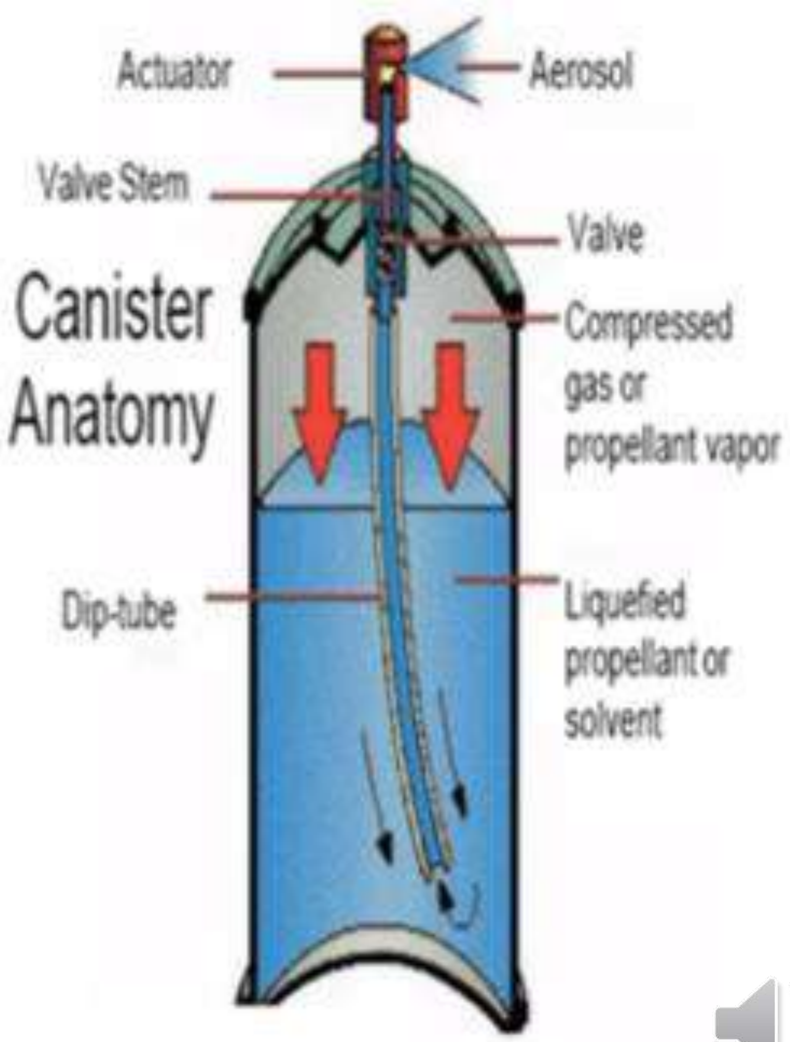
- An aerosol (abbreviation of "aero-solution") is a suspension of fine solid particles or liquid droplets in a gas

- Gases can be liquefied by increasing pressure, provided we work below the critical temperature.

- When the pressure is reduced, the molecules expand and the liquid reverts to a gas.

- This reversible change of state is the basic principle involved in the preparation of pharmaceutical aerosols.

- A drug is dissolved or suspended in a **propellant**, a material that is liquid under the pressure conditions existing inside the container but that forms a gas under normal atmospheric pressure
- The container is so designed that, by depressing a valve, some of the **drug–propellant mixture** is expelled owing to the excess pressure inside the container.



- The containers are filled either by:
    - ✓cooling the propellant and drug to a low temperature within the container, which is then sealed with the valve
    - ✓sealing the drug in the container at room temperature and then forcing the required amount of propellant into the container under pressure

- In both cases, when the product is at room temperature, part of the propellant is in the gaseous state and exerts the pressure necessary to extrude the drug, whereas the remainder is in the liquid state and provides a solution or suspension vehicle for the drug.

- The formulation of pharmaceuticals as aerosols is continually increasing because the method frequently offers distinct advantages over some of the more conventional methods of formulation.

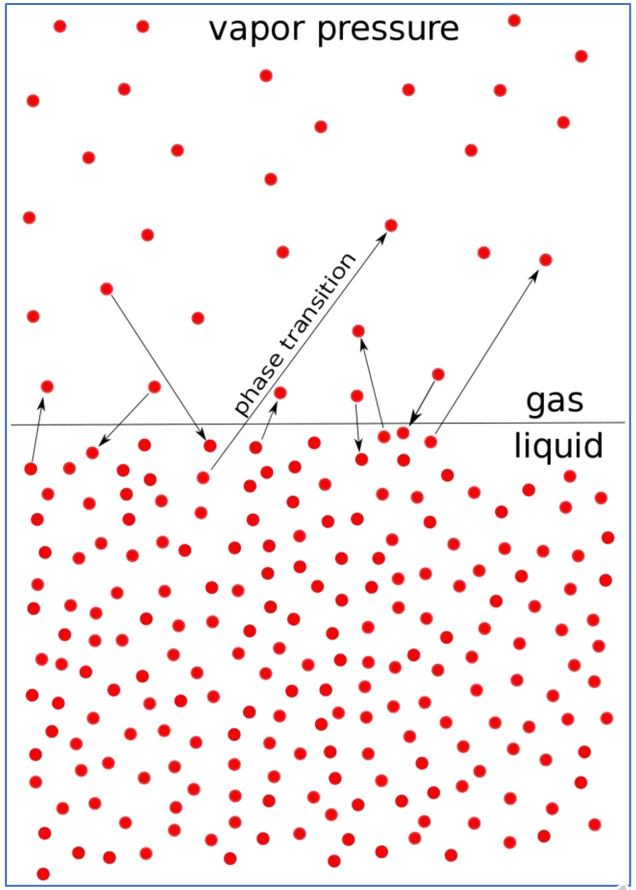
- ethyl chloride, local anesthesia.

- The identification of biotechnology-derived products has also dramatically increased the utilization of aerosolized formulations. Proteins, DNA, oligopeptides, and nucleotides all demonstrate poor oral bioavailability due to **the harsh environment** of the gastrointestinal tract and their relatively large size and rapid metabolism.

Vapor pressure of liquid

- some of the molecules have more energy and hence higher velocities than others at any moment.

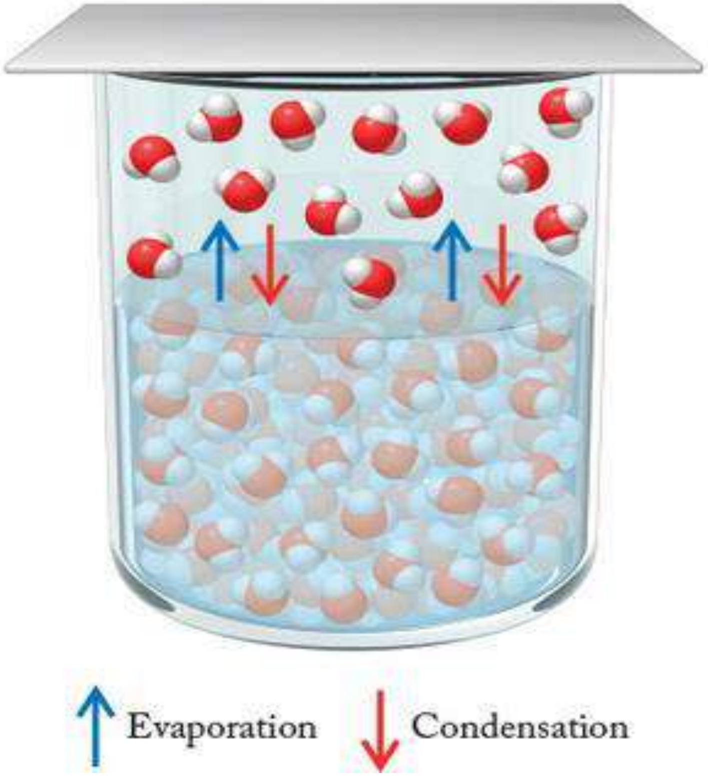
- When a liquid is placed in an evacuated container at a constant temperature → the molecules with the highest energies break away from the surface of the liquid and pass into the gaseous state ↔ some of the molecules subsequently return to the liquid state, or condense.



- When the rate of condensation equals the rate of vaporization at a definite temperature, the vapor becomes **saturated** and a dynamic equilibrium is established.

- **equilibrium vapor pressure:** The pressure of the saturated vapor above the liquid

- Can be measured by **manometer**



Open Ended Manometer

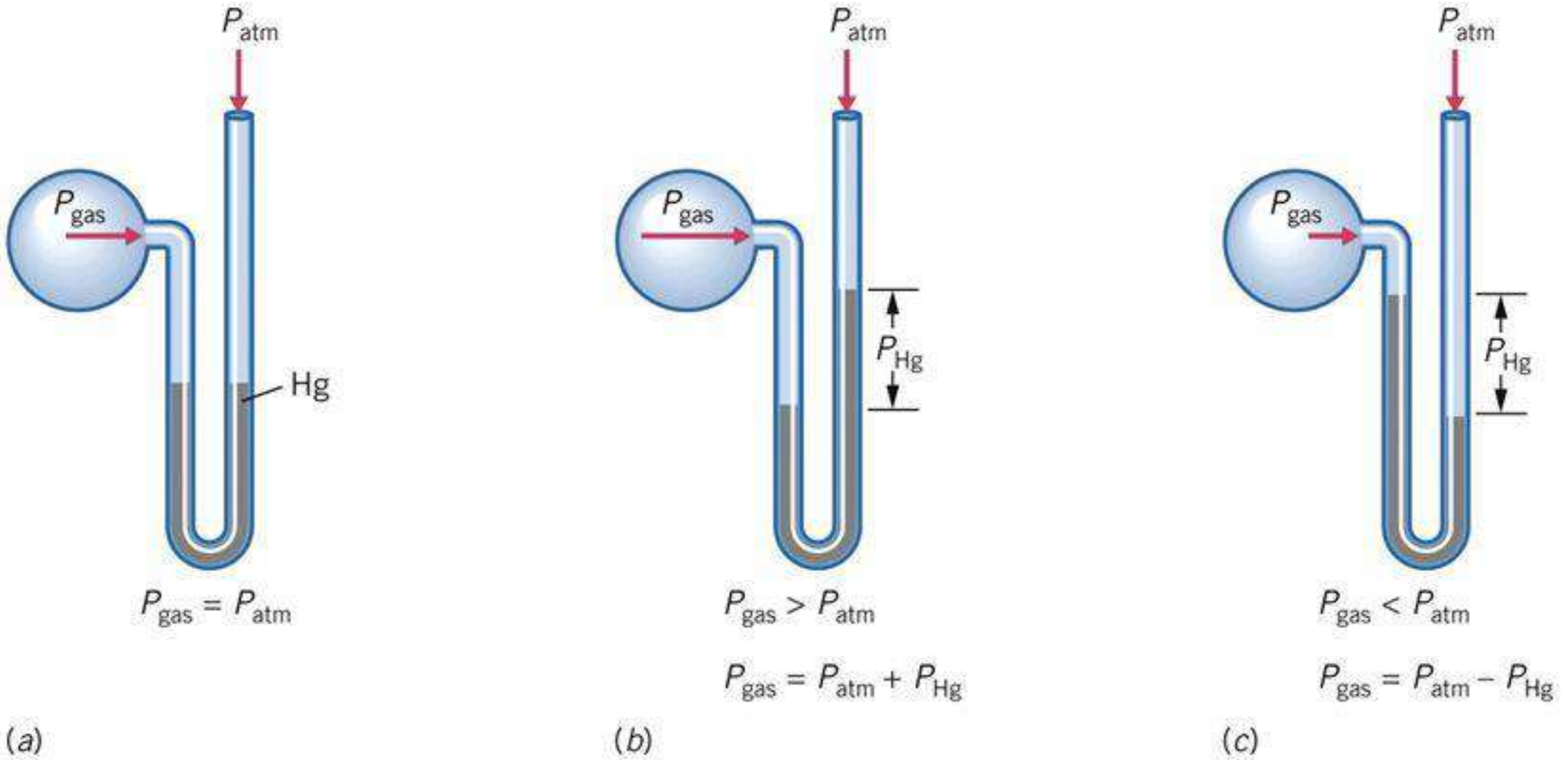
$P_{gas} = P_{atm}$

$P_{gas} > P_{atm}$

- Gas pushes Hg up tube

$P_{gas} < P_{atm}$

- Atm pushes Hg down tube



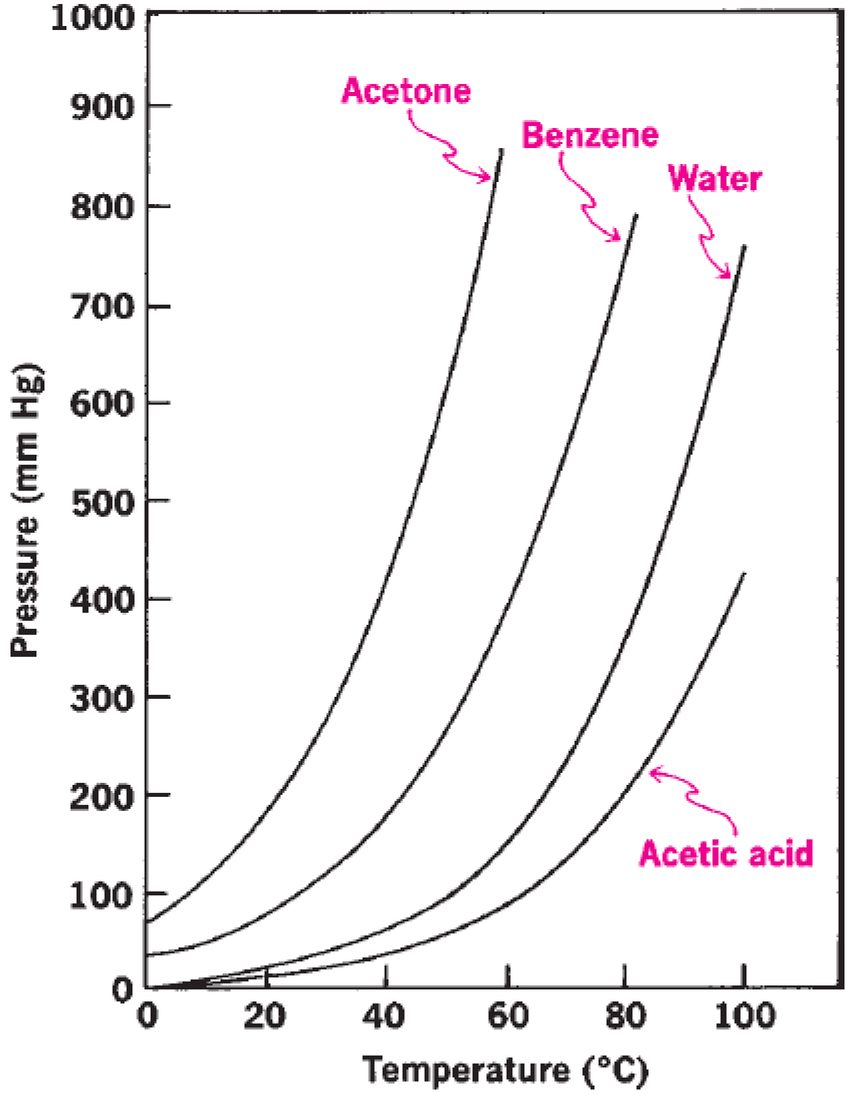
(a) $P_{gas} = P_{atm}$

(b) $P_{gas} > P_{atm}$ $\quad P_{gas} = P_{atm} + P_{Hg}$

(c) $P_{gas} < P_{atm}$ $\quad P_{gas} = P_{atm} - P_{Hg}$

- The presence of a gas, such as air, above the liquid decreases the rate of evaporation, but it does not affect the equilibrium pressure of the vapor.

- As the temperature of the liquid is elevated, more molecules approach the velocity necessary for escape and pass into the gaseous state. As a result, **the vapor pressure increases with rising temperature**



Clausius-Clapeyron Equation:
Heat of Vaporization

- Describe the relationship between the vapor pressure and the absolute temperature of a liquid

$$\boxed{\log \frac{p_2}{p_1} = \frac{\Delta H_v (T_2 - T_1)}{2.303\, R T_1 T_2}}$$

- where p1 and p2 are the vapor pressures at absolute temperatures T1 and T2, and **ΔHv** is the molar heat of vaporization, that is, the heat absorbed by 1 mole of liquid when it passes into the vapor state

EXAMPLE

- Compute the vapor pressure of water at 120◦C. The vapor pressure p1 of water at 100◦C is 1 atm, and ΔHv may be taken as 9720 cal/ mole for this temperature range.

$$\log \frac{p_2}{p_1} = \frac{\Delta H_v (T_2 - T_1)}{2.303\, R T_1 T_2}$$

$$\log \frac{p_2}{1.0} = \frac{9720 \times (393 - 373)}{2.303 \times 1.987 \times 393 \times 373}$$

$$p_2 = 1.95 \text{ atm}$$

- The Clausius–Clapeyron equation can be written in a more general form:

$$\log p = -\frac{\Delta H_v}{2.303R}\frac{1}{T} + \text{constant}$$

- or in natural logarithms

$$\ln p = -\frac{\Delta H_v}{R}\frac{1}{T} + \text{constant}$$

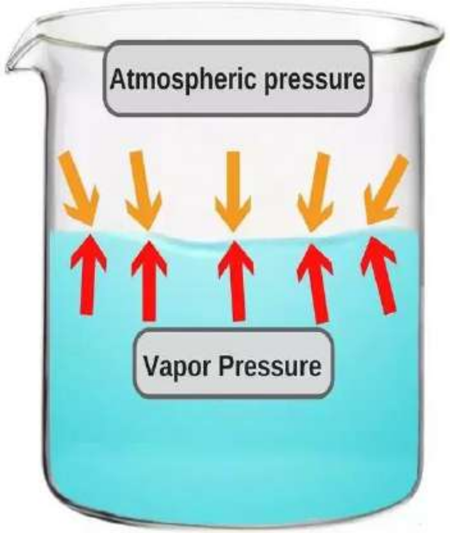
- from which it is observed that a plot of the logarithm of the vapor pressure against the reciprocal of the absolute temperature results in a straight line, enabling one to compute the heat of vaporization of the liquid from the slope of the line.

Boiling Point

- If a liquid is placed in an open container and heated until the vapor pressure equals the atmospheric pressure, the vapor will form bubbles that rise rapidly through the liquid and escape into the gaseous state.

- **Boiling point:** The temperature at which the vapor pressure of the liquid equals the external or atmospheric pressure

- All the absorbed heat is used to change the liquid to vapor, and the temperature does not rise until the liquid is completely vaporized.



- The atmospheric pressure at **sea level** is approximately 760 mm Hg; at higher elevations, the atmospheric pressure decreases and the boiling point is lowered.

- At a pressure of **700 mm Hg**, water boils at 97.7◦C; at 17.5 mm Hg, it boils at 20◦C.
- The change in boiling point with pressure can be computed by using the Clausius–Clapeyron equation.

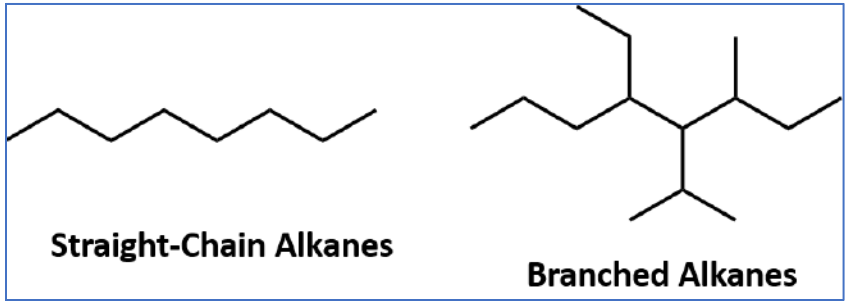
- The boiling point may be considered the temperature at which thermal agitation can overcome the attractive forces between the molecules of a liquid

- the boiling point of a compound and the vapor pressure at a definite temperature, provides a rough indication of the magnitude of the attractive forces.

Factors affecting the boiling point

1. The boiling points of normal hydrocarbons, simple alcohols, and carboxylic acids increase with **molecular weight** because the attractive van der Waals forces become greater with increasing numbers of atoms.

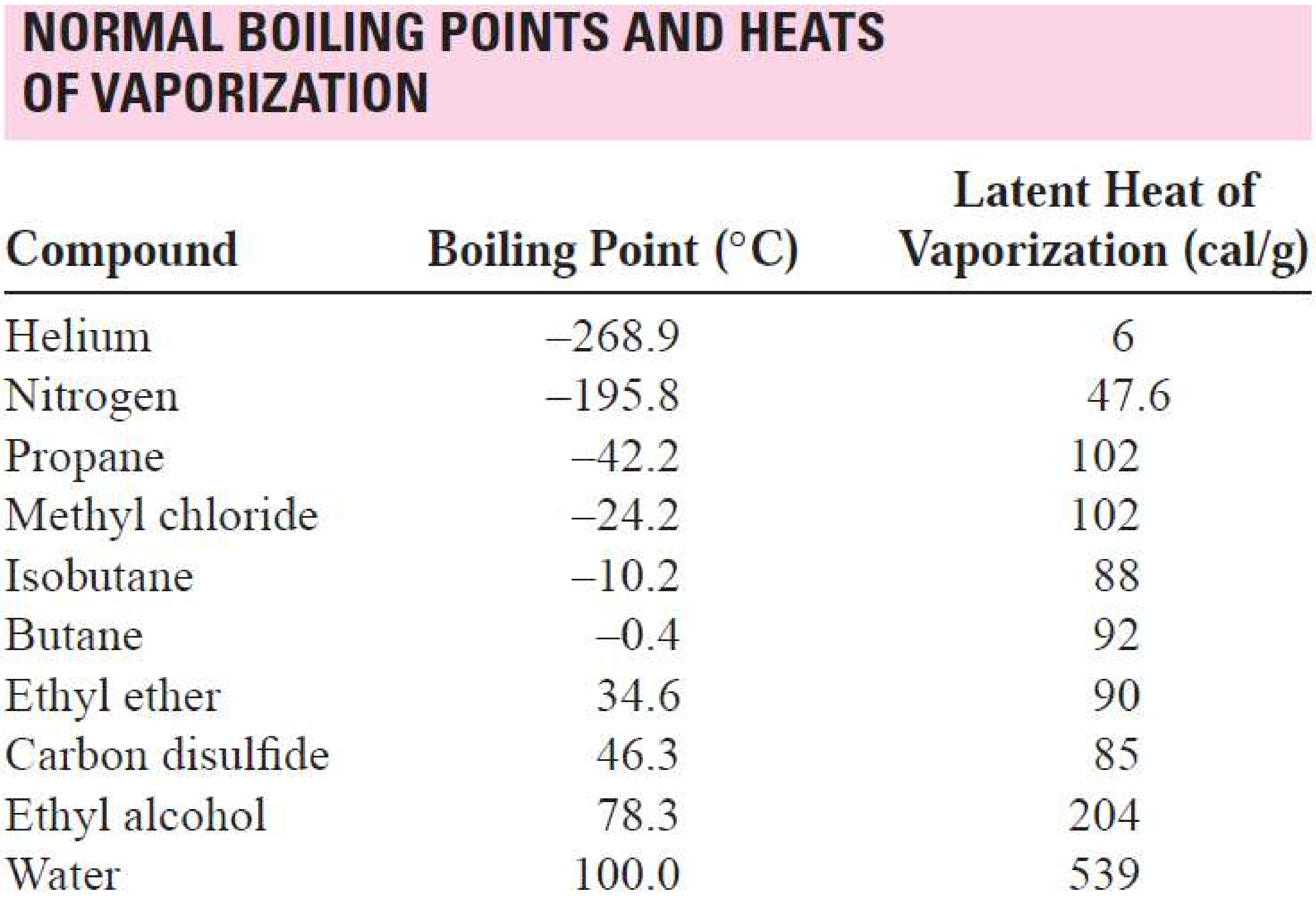
2. **Branching** of the chain produces a less compact molecule with reduced intermolecular attraction, and a decrease in the boiling point results.



3. **hydrogen bonding**: the alcohols boil at a much higher temperature than saturated hydrocarbons of the same molecular weight because of association of the alcohol molecules through hydrogen bonding.

- The boiling points of carboxylic acids are more abnormal still because the acids form dimers through hydrogen bonding that can persist even in the vapor state.
- The boiling points of straight-chain primary alcohols and carboxylic acids increase about 18◦C for each additional methylene group.

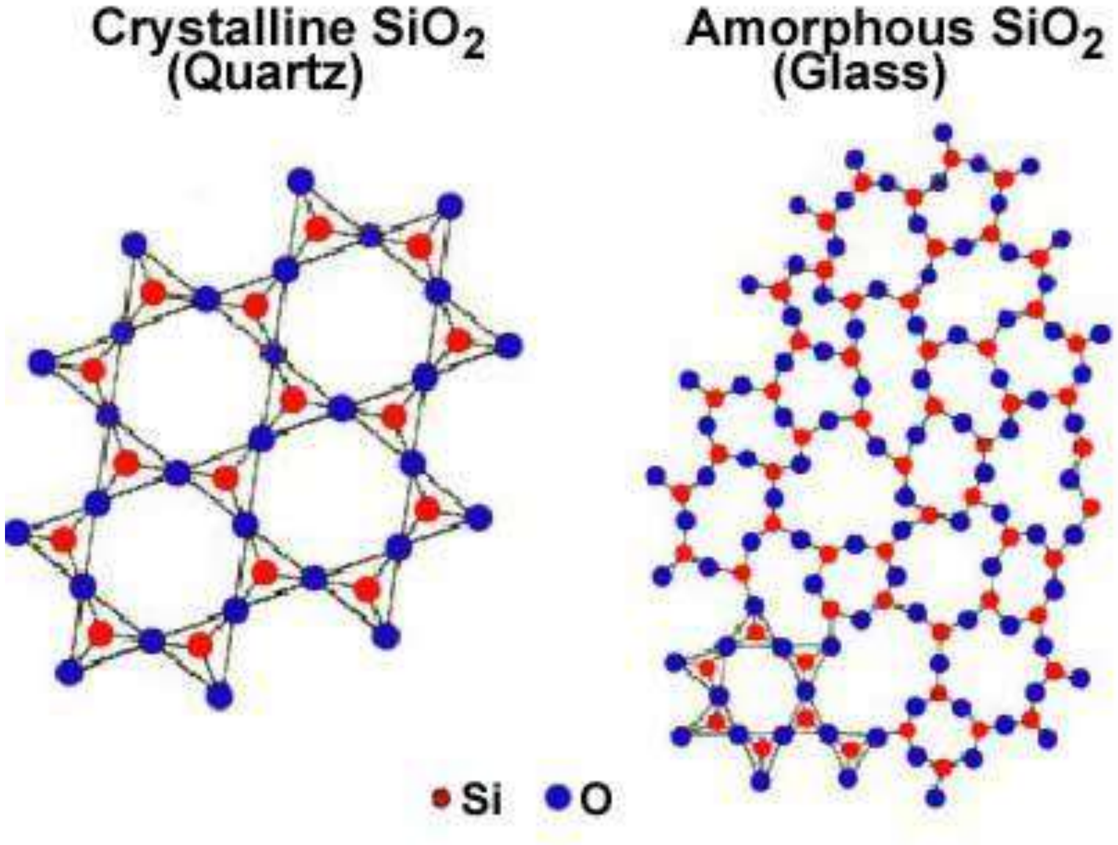
- The rough parallel between the intermolecular forces and the boiling points is illustrated in the table



NORMAL BOILING POINTS AND HEATS OF VAPORIZATION

Compound	Boiling Point (°C)	Latent Heat of Vaporization (cal/g)
Helium	–268.9	6
Nitrogen	–195.8	47.6
Propane	–42.2	102
Methyl chloride	–24.2	102
Isobutane	–10.2	88
Butane	–0.4	92
Ethyl ether	34.6	90
Carbon disulfide	46.3	85
Ethyl alcohol	78.3	204
Water	100.0	539

3- Solid and Crystalline state



- The molecules are arranged in a somewhat random manner as in the liquid state
- They tend to flow when subjected to sufficient pressure over a period of time, and they do not have definite melting points.
- Such as glass and many synthetic plastics

Crystalline solids

- The structural units of crystalline solids, such as ice, sodium chloride, and menthol, are arranged in fixed geometric patterns or lattices.
- Crystalline solids, unlike liquids and gases, have definite shapes and an orderly arrangement of units.
- Gases are easily compressed, whereas solids, like liquids, are practically incompressible.
- Crystalline solids show definite melting points.

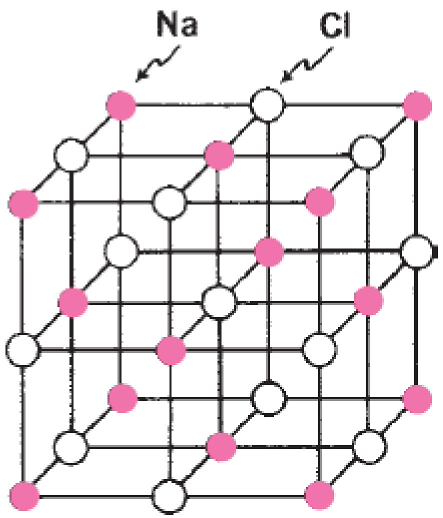
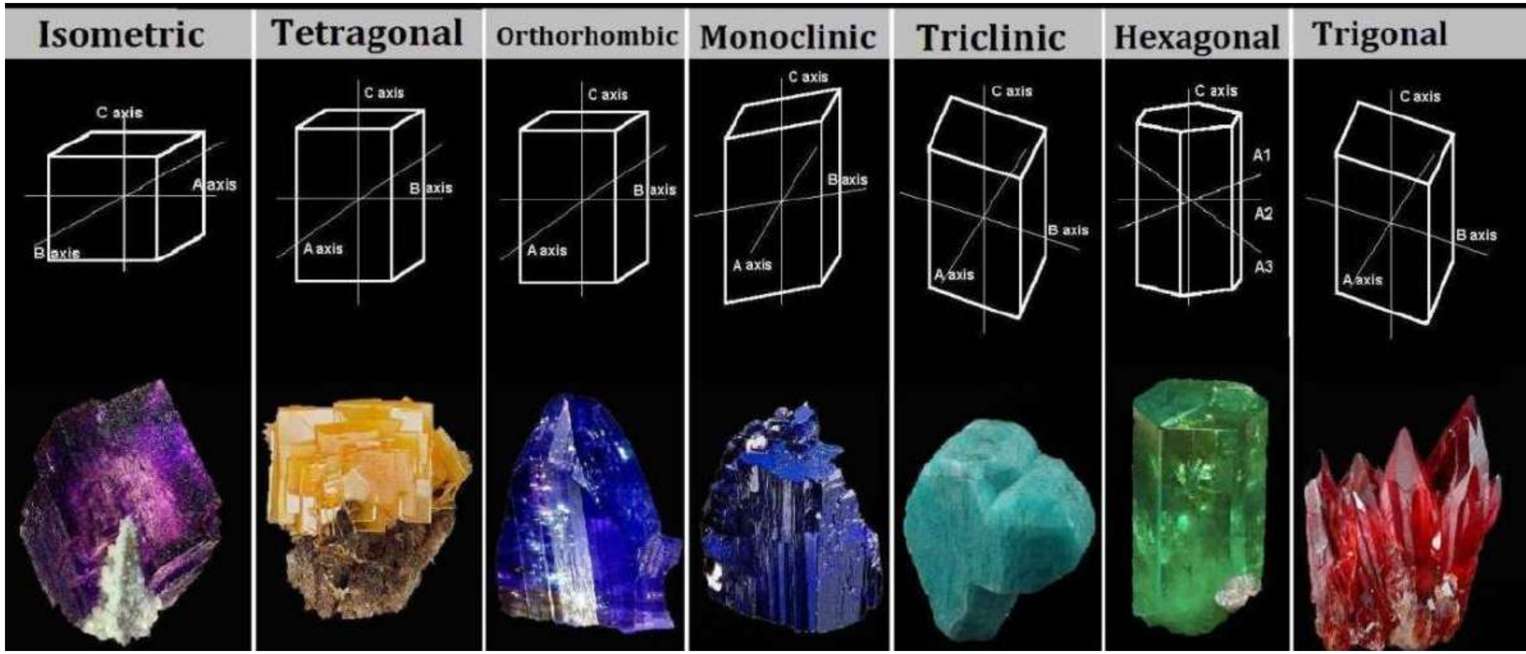


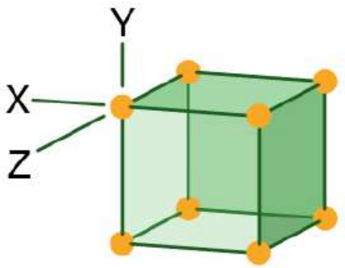
Fig. 2–6. The crystal lattice of sodium chloride.

- The various crystal forms are divided into six distinct crystal systems based on symmetry.
- They are, together with examples of each:

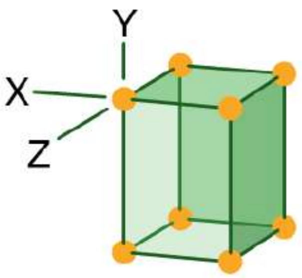
1) cubic (sodium chloride),
2) tetragonal (urea),
3) Hexagonal (iodoform),
4) rhombic (iodine),
5) monoclinic (sucrose),
6) triclinic (boric acid).



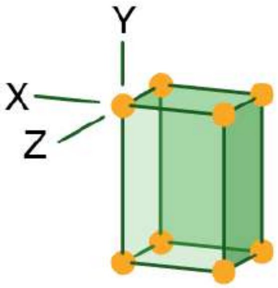
The seven primitive crystal systems



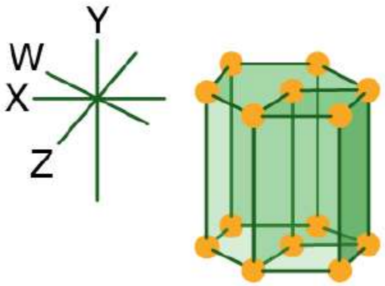
Isometric (or cubic)
All three axes are equal in length, and all are perpendicular to one another.



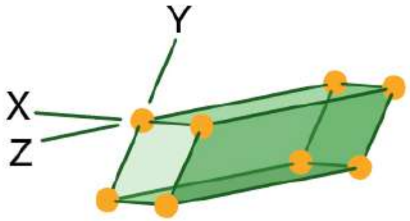
Tetragonal
Two of the three axes are equal in length, and all three axes are perpendicular to one another.



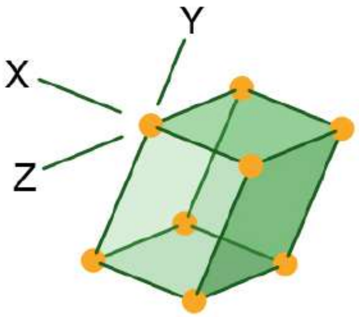
Orthorhombic
All three axes are unequal in length, and all are perpendicular to one another.



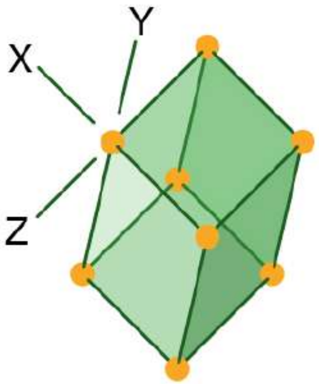
Hexagonal
Of four axes, three are of equal length, are separated by equal angles, and lie in the same plane. The fourth axis is perpendicular to the plane of the other three axes. Hexagonal cells have lattice points in each of the two six-sided faces.



Triclinic
All three axes are unequal in length, and none is perpendicular to another.



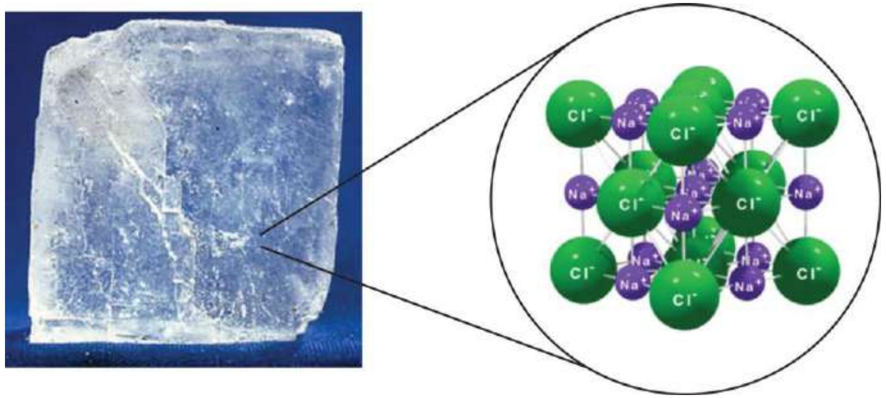
Monoclinic
All three axes are unequal in length, and two axes are perpendicular to each other.

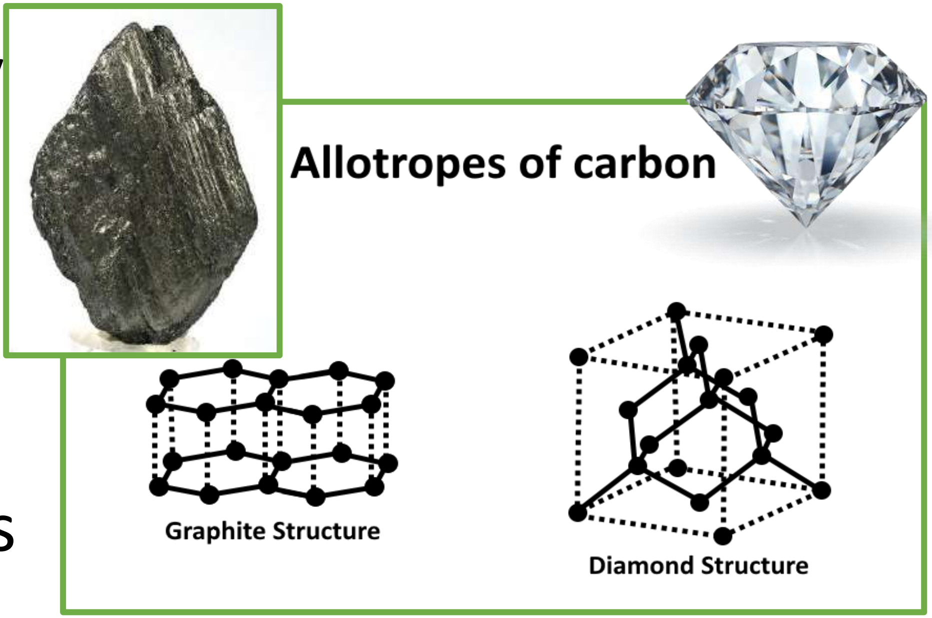


Rhombohedral (or trigonal)*
All three axes are of equal length, and none of the axes is perpendicular to another, but the crystal faces all have the same size and shape.

*Some sources do not separate the hexagonal and rhombohedral (trigonal) systems.

- The units that constitute the crystal structure can be atoms, molecules, or ions.
- The **sodium chloride** crystal consists of a cubic lattice of sodium ions interpenetrated by a lattice of chloride ions, the binding force of the crystal being the electrostatic attraction of the oppositely charged ions.
- In **diamond** and **graphite**, the lattice units consist of atoms held together by covalent bonds.
- **Solid carbon dioxide**, **hydrogen chloride**, and **naphthalene** form crystals composed of molecules as the building units.





Melting Point and Heat of Fusion

- **Freezing point:** The temperature at which a liquid passes into the solid state
- It is also the **melting point** of a pure crystalline compound.

- The freezing point or melting point of a **pure crystalline** solid is strictly defined as the temperature at which the pure liquid and solid exist in **equilibrium** (at 1 atm)

- **Latent heat of fusion:** The heat (energy) absorbed when 1 g of a solid melts or the heat liberated when it freezes

- Changes of the freezing or melting point with pressure can be obtained by using a form of the Clapeyron equation, written as

$$\boxed{\frac{\Delta T}{\Delta P} = T\frac{V_1 - V_s}{\Delta H_f}}$$

- **Hf** is the molar heat of fusion, that is, the amount of heat absorbed when **1 mole** of the solid changes → into **1 mole** of liquid,
- **ΔT** is the change of melting point brought about by a pressure change of ΔP.
- **Vl** and **Vs** are the molar volumes of the liquid and solid, respectively. Molar volume (volume in units of cm3/mole) is computed by dividing the gram molecular weight by the density of the compound.

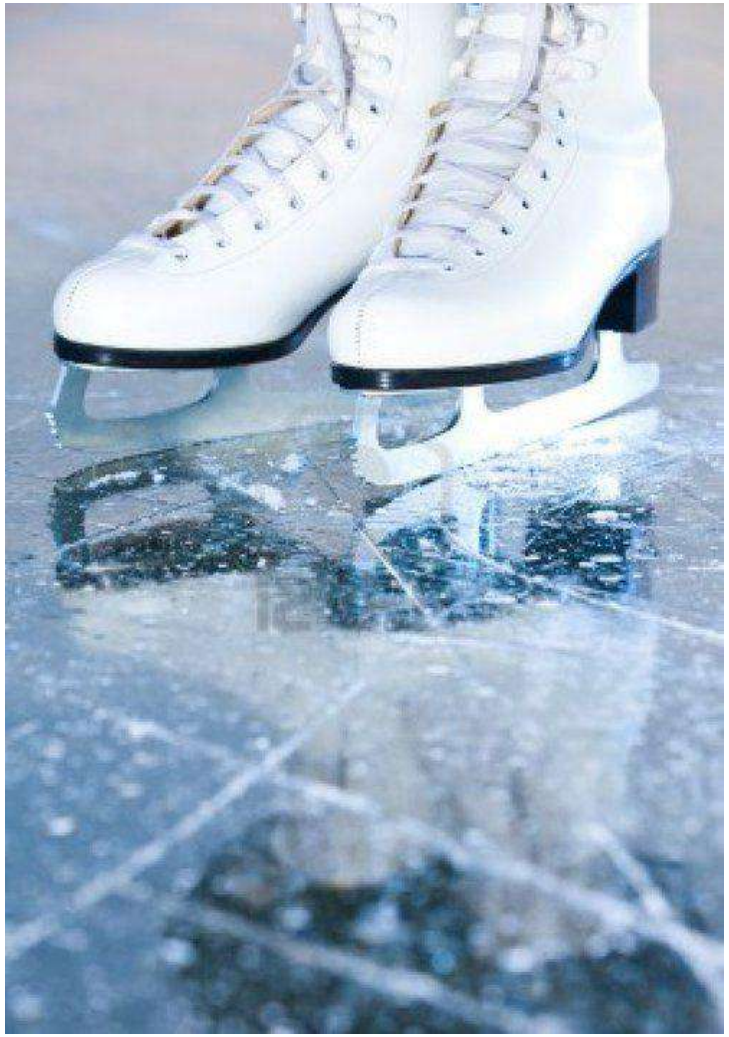
- **Water** is unusual in that it has a larger molar volume in the solid state than in the liquid state (Vs > Vl) at the melting point.

- Therefore, **T/P** is negative, signifying that the melting point is lowered by an increase in pressure.

- This phenomenon can be rationalized in terms of **Le Chatelier’s principle**, which states that a system at equilibrium readjusts so as to reduce the effect of an external stress (restore a new equilibrium state).

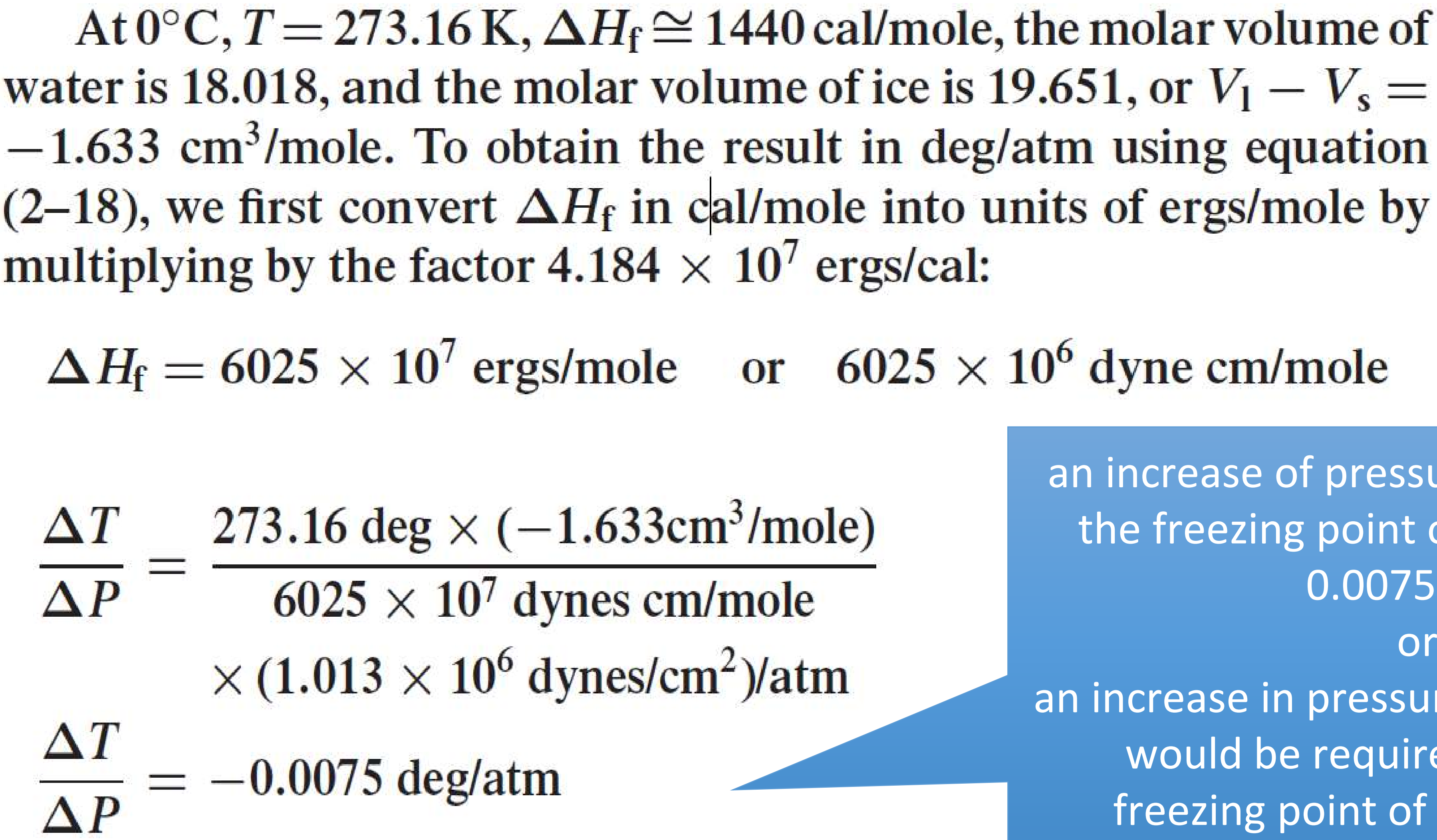
- Accordingly, if a pressure is applied to ice at 0°C, it will be transformed into liquid water, that is, into the state of lower volume, and the freezing point will be lowered.

- The large molar volume or low density of **ice** (0.9168 g/cm3 as compared with 0.9988 g/cm3 for water at 0◦C) accounts for the fact that the ice floats on **liquid water**.
- The lowering of the melting point with increasing pressure is taken advantage of in **ice-skating.**
- The pressure of the skate lowers the melting point and thus causes the ice to melt below the skate.
- This thin layer of liquid provides lubricating action and allows the skate to glide over the hard surface.
- Of course, the friction of the skate also contributes greatly to the melting and lubricating action.



Demonstration of Le Chatelier's Principle

- **What is the effect of an increase of pressure of 1 atm on the freezing point of water (melting point of ice)?**



At 0°C, $T = 273.16$ K, $\Delta H_f \cong 1440$ cal/mole, the molar volume of water is 18.018, and the molar volume of ice is 19.651, or $V_l - V_s = -1.633$ cm^3/mole. To obtain the result in deg/atm using equation (2–18), we first convert ΔH_f in cal/mole into units of ergs/mole by multiplying by the factor 4.184×10^7 ergs/cal:

$$\Delta H_f = 6025 \times 10^7 \text{ ergs/mole} \quad \text{or} \quad 6025 \times 10^6 \text{ dyne cm/mole}$$

$$\frac{\Delta T}{\Delta P} = \frac{273.16 \text{ deg} \times (-1.633 \text{cm}^3/\text{mole})}{6025 \times 10^7 \text{ dynes cm/mole}} \times (1.013 \times 10^6 \text{ dynes/cm}^2)/\text{atm}$$

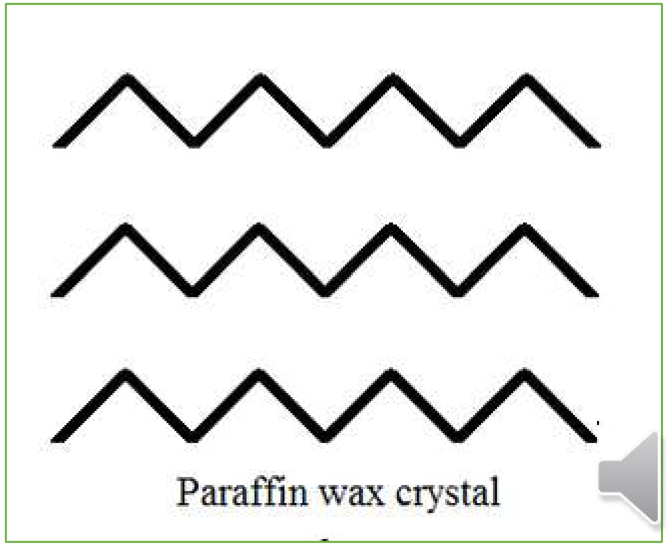
$$\frac{\Delta T}{\Delta P} = -0.0075 \text{ deg/atm}$$

an increase of pressure of 1 atm lowers the freezing point of water by about 0.0075 deg,
or
an increase in pressure of about 133 atm would be required to lower the freezing point of water by 1 deg.

Melting Point and Intermolecular Forces

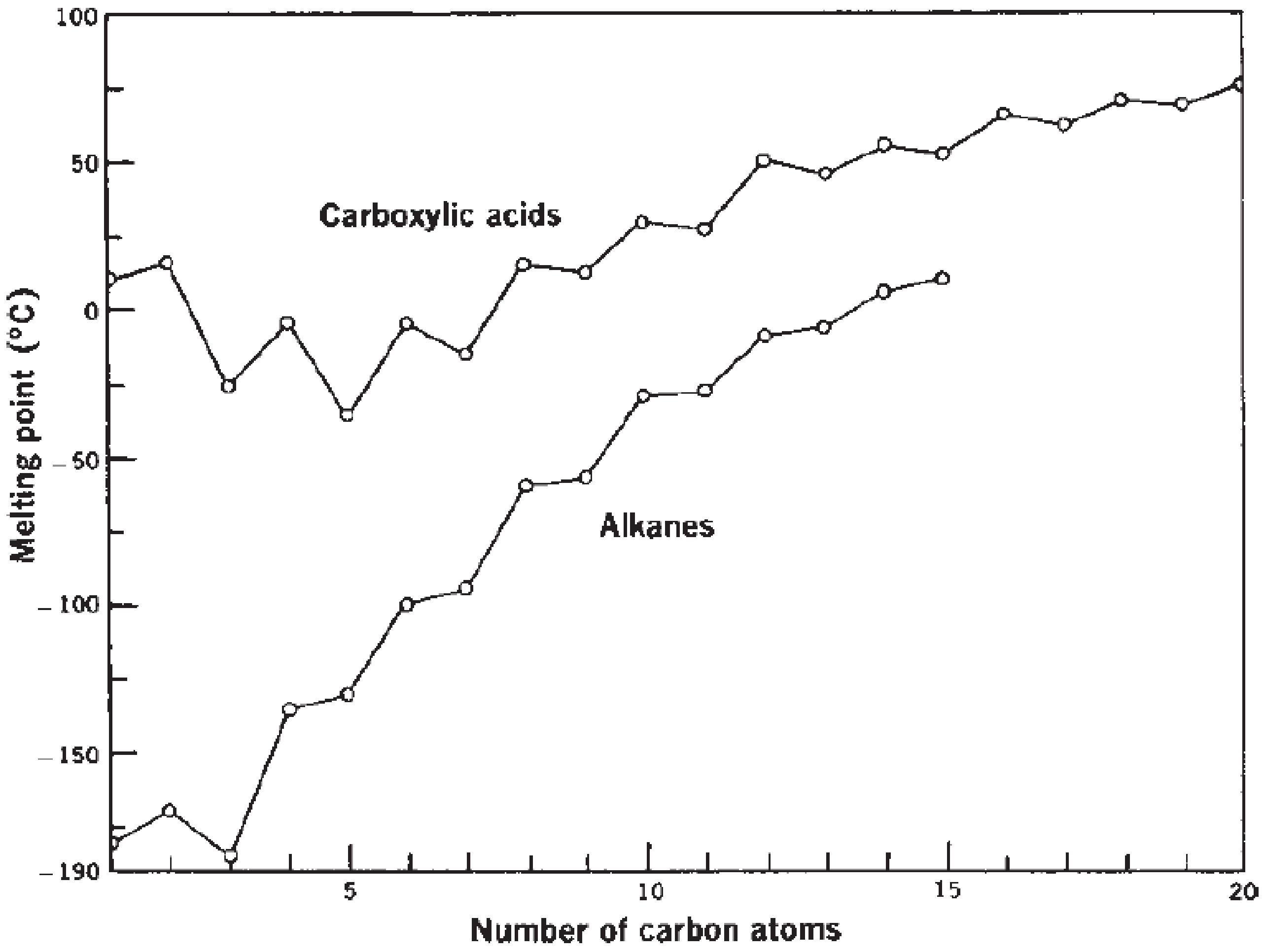
The heat of fusion

- the heat required to increase the interatomic or intermolecular distances in crystals, thus allowing melting (increased molecular motion) to occur.
- A crystal that is bound together by weak forces generally has a low heat of fusion and a low melting point, whereas one bound together by strong forces has a high heat of fusion and a high melting point.
- Paraffins crystallize as thin leaflets composed of zigzag chains packed in a parallel arrangement.



Paraffin wax crystal

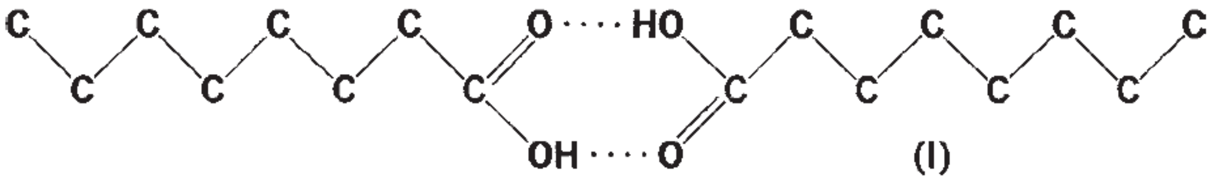
- The melting points of normal saturated hydrocarbons increase with molecular weight because the van der Waals forces between the molecules of the crystal become greater with an increasing number of carbon atoms.



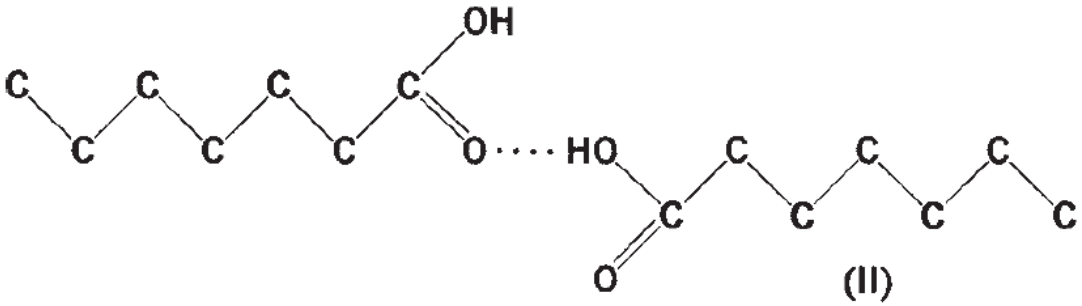
- The melting points of the alkanes with an even number of carbon atoms are higher than those of the hydrocarbons with an odd number of carbon atoms

  - The even numbered carbon acids are arranged in the crystal as seen in the more symmetric structure I, whereas the odd-numbered acids are arranged according to structure II.

  - The carboxyl groups are joined at two points in the even-carbon compound; hence, the crystal lattice is more stable and the melting point is higher.

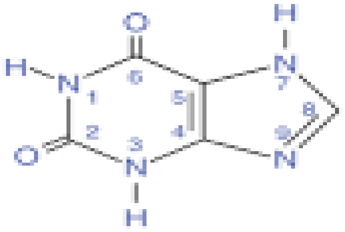


(I)

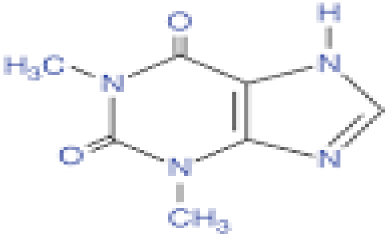


(II)

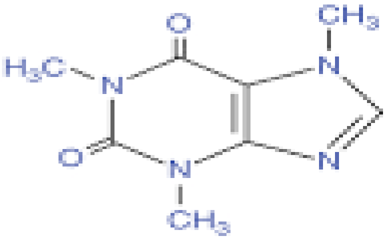
- The melting points and solubilities of the **xanthines** of pharmaceutical interest



Xanthine



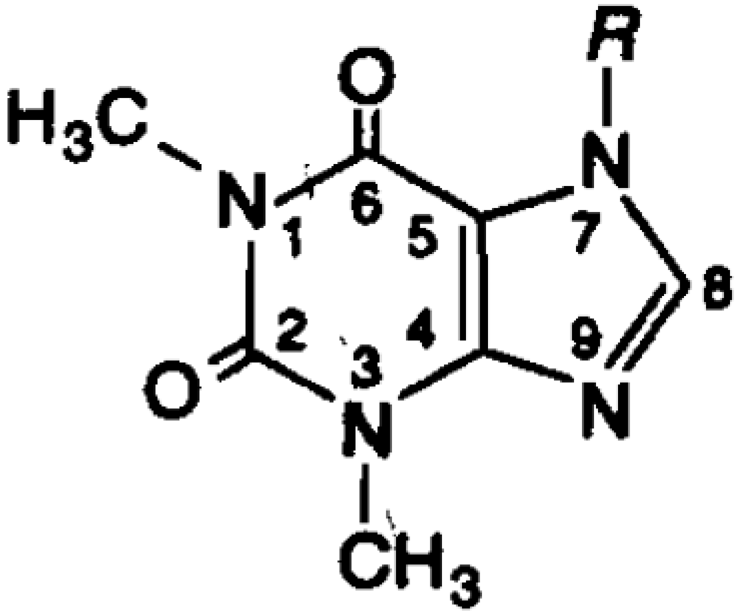
Theophylline



Caffeine

- Solubilities, like melting points, are strongly influenced by intermolecular forces

- methylation of theophylline to form caffeine and the lengthening of the side chain from methyl (caffeine) to propyl in the 7 position result in a decrease of the melting point and an increase in solubility

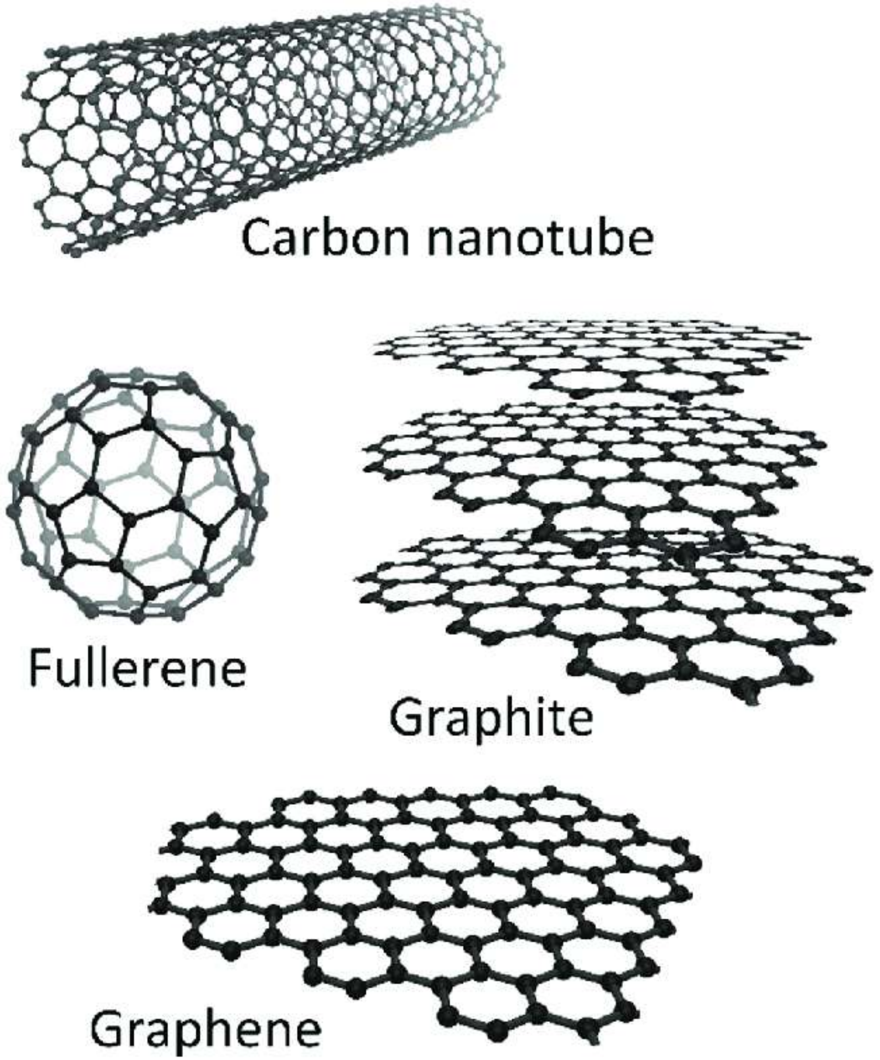


MELTING POINTS AND SOLUBILITIES OF SOME XANTHINES*

Compound	Melting Point (°C Uncorrected)	Solubility in Water at 30°C (mole/liter × 10^2)
Theophylline (R = H)	270–274	4.5
Caffeine (R = CH_3)	238	13.3
7-Ethyitheophylline (R = CH_2CH_3)	156–157	17.6
7-Propyltheophylline (R = $CH_2CH_2CH_3$	99–100	104.0

Polymorphism

- Some elemental substances, such as carbon and sulfur, may exist in **more than one crystalline form** and are said to be polymorphic



- Polymorphs have different **melting points** and **solubilities**, even though they are chemically identical.

- Solubility and melting points are very important in pharmaceutical processes, including **dissolution** and **formulation**, explaining the primary reason we are interested in polymorphs.

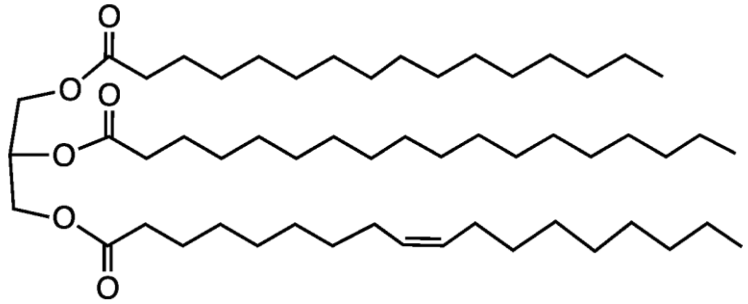
- **Examples:**

- Nearly all long-chain organic compounds exhibit polymorphism.

1) In fatty acids, this results from different types of attachment between the carboxyl groups of adjacent molecules

1) The triglyceride tristearin proceeds from the low-melting metastable alpha (α) form through the beta prime (β′) form and finally to the stable beta (β) form, having a high melting point

3) Theobroma oil, or cacao butter, is a polymorphous natural fat.



extracted from the cocoa bean. It is used to make chocolate, as well as some ointments, toiletries, and pharmaceuticals

Because it consists mainly of a single glyceride, it melts to a large degree over a narrow temperature range (34°C–36°C).

- Theobroma oil is capable of existing in four polymorphic forms:
  a) the unstable gamma form, melting at 18°C
  b) the alpha form, melting at 22°C
  c) the beta prime form, melting at 28°C
  d) the stable beta form, melting at 34.5°C

- There a relationship between polymorphism and the preparation of cacao butter suppositories.

- If theobroma oil is heated to the point at which it is **completely liquefied** (about 35°C) ➔ the nuclei of the stable beta crystals are destroyed and the mass does not crystallize until it is supercooled to about 15°C.

- The crystals that form are the metastable gamma, alpha, and beta prime forms, and the suppositories melt at 23°C to 24°C or at ordinary room temperature.

- The proper method of preparation involves melting cacao butter at the lowest possible temperature, about **33°C.**

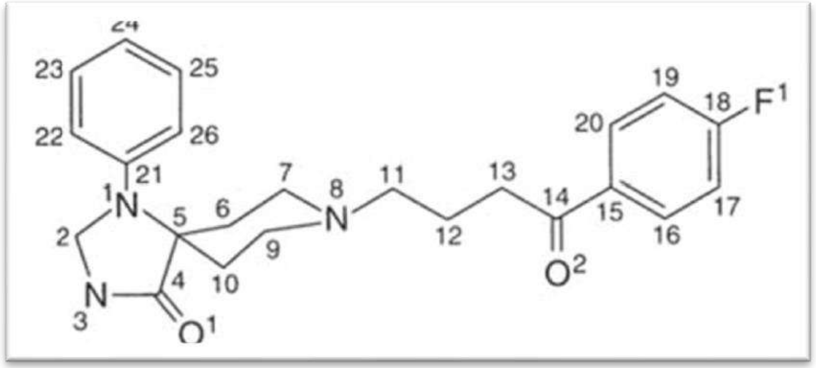
- The mass is sufficiently fluid to pour, yet the crystal nuclei of the stable beta form are not lost.
- When the mass is chilled in the mold, a stable suppository, consisting of beta crystals and melting at 34.5°C, is produced.

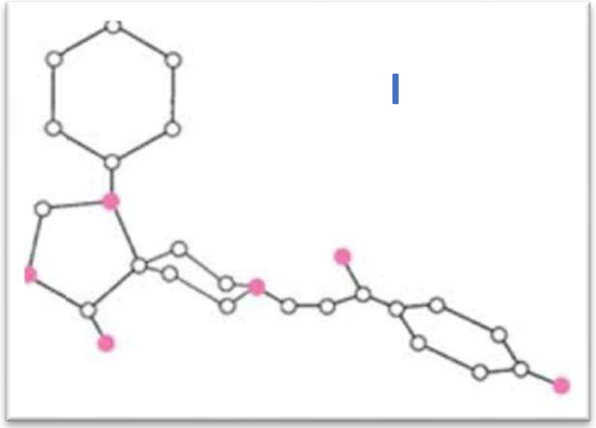
- Polymorphism has achieved significance in last decade because different polymorphs exhibit different solubilities.

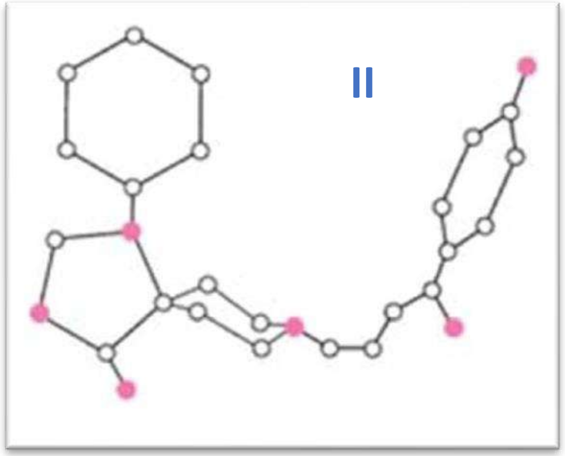
- In the case of slightly soluble drugs, this may affect the rate of dissolution. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug.

  ✓ the polymorphic state of **chloramphenicol palmitate** has a significant influence on the biologic availability of the drug. form II was more active orally in humans than form III

- Molecular conformation of Spiperone is responsible for polymorphism it has two forms the difference is the position of atoms in the side chain
- Polymorph II is a dimer, while polymorph I is non dimerized



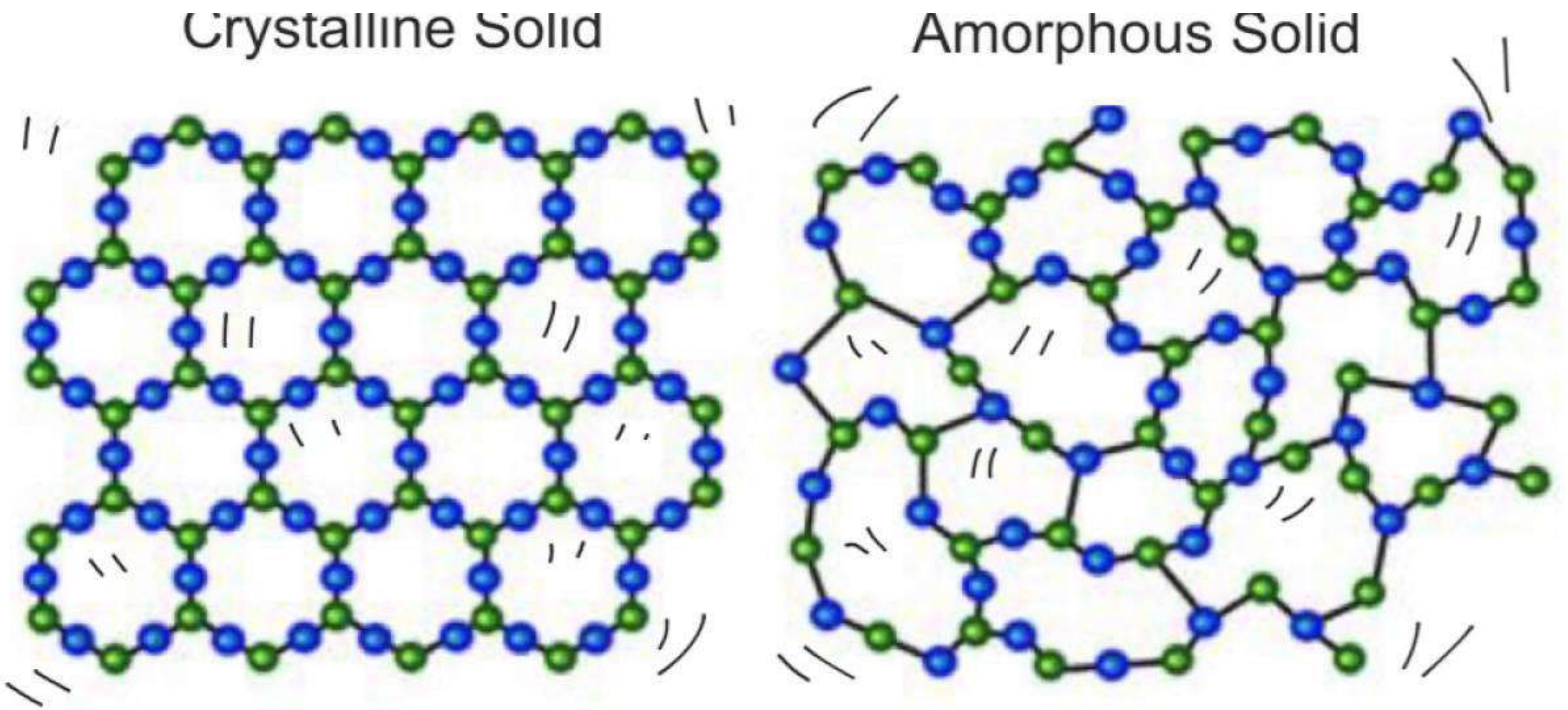




- When the change from one form to another is reversible, it is said to be **enantiotropic.**

- When the transition takes place in one direction only—for example, from a metastable to a stable form—the change is said to be **monotropic.**

Amorphous Solids



Crystalline Solid

Amorphous Solid

Atoms vibrate in place in a fixed pattern

Atoms vibrate in place in more random arrangements

- **Amorphous solids** as a first approximation may be considered supercooled liquids in which the molecules are arranged in a somewhat random manner as in the liquid state

- Amorphous substances, as well as cubic crystals, are usually **isotropic**, that is, they exhibit similar properties in all directions.

- Crystals other than cubic are **anisotropic**, showing different characteristics (electric conductance, refractive index, crystal growth, rate of solubility) in various directions along the crystal.

- It is not always possible to determine by casual observation whether a substance is crystalline or amorphous.

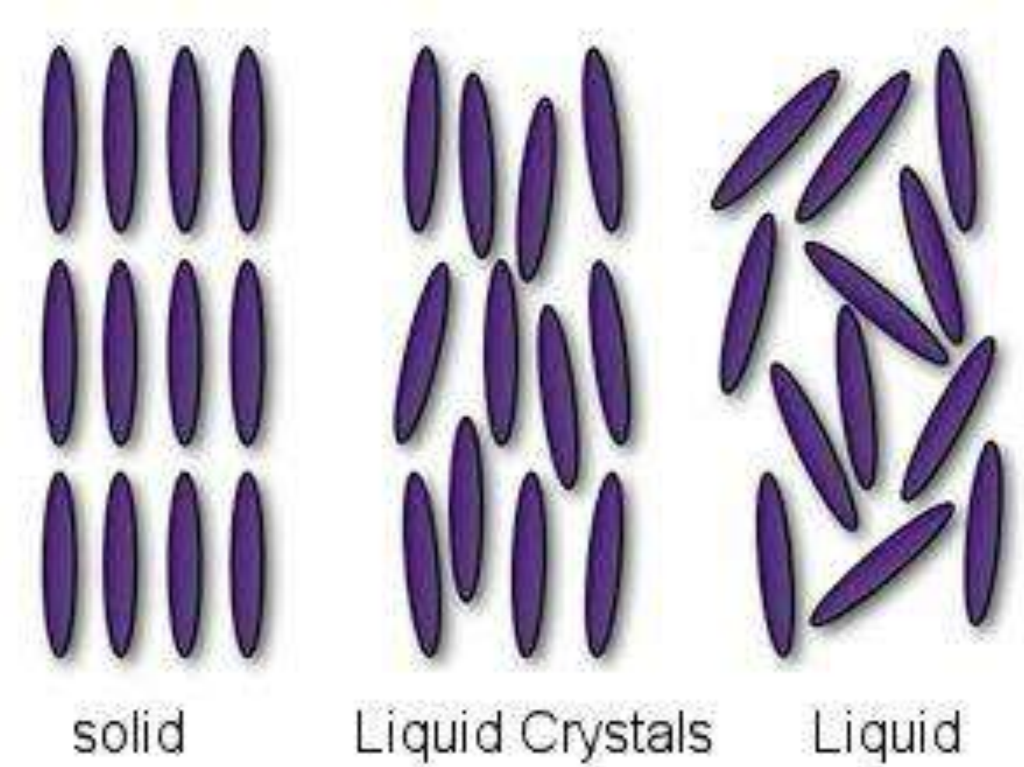
- Beeswax and paraffin, although they appear to be amorphous, assume crystalline arrangements when heated and then allowed to cool slowly.
- glass, may crystallize after long standing.

- Whether a drug is amorphous or crystalline has been shown to affect its therapeutic activity.

- Thus, the crystalline form of the antibiotic **novobiocin acid** is poorly absorbed and has no activity, whereas the amorphous form is readily absorbed and therapeutically active

The liquid crystalline state

- **= mesophase**
- A fourth state of matter ….. A phase between a solid and a liquid



Structure of Liquid Crystals

- **liquid state:** molecules are mobile in three directions and can also rotate about three axes 'perpendicular to one another.

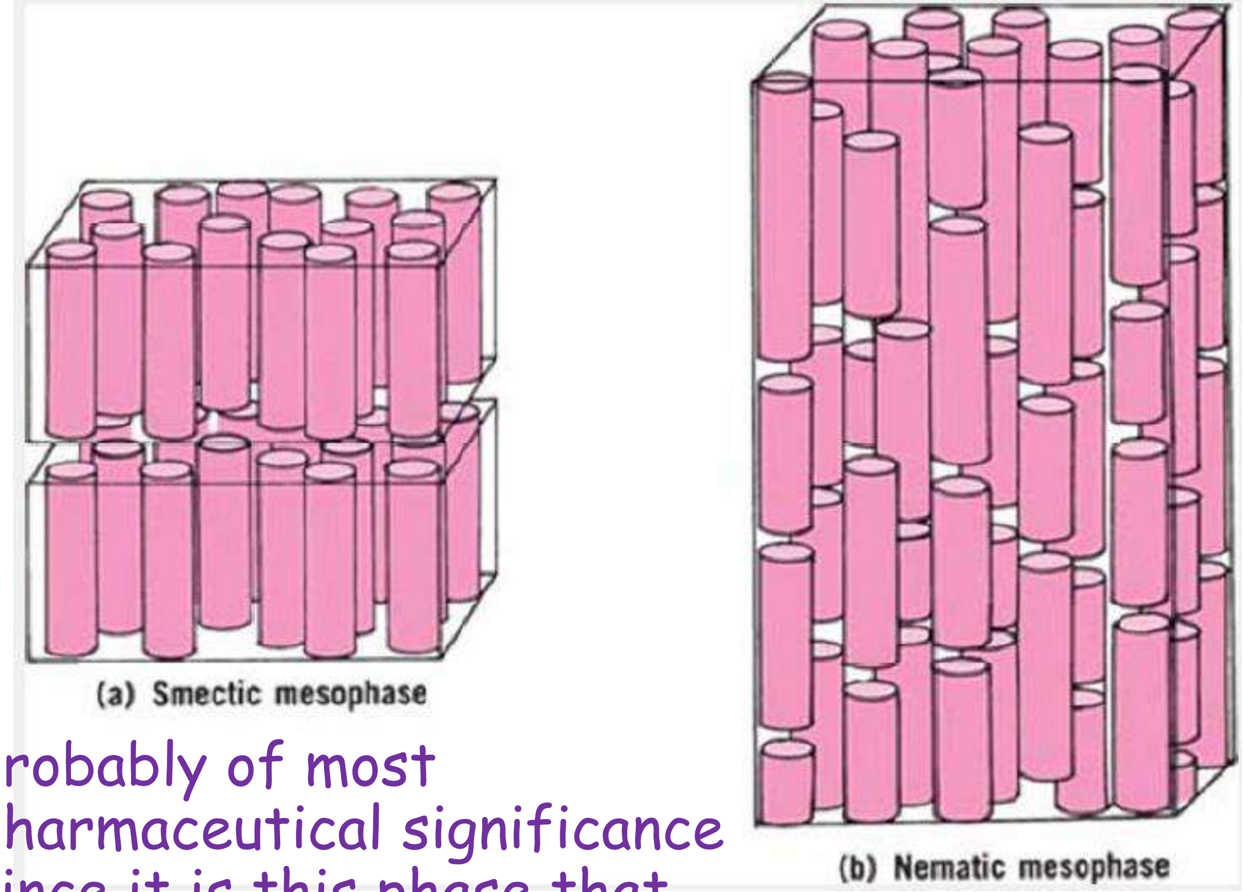
- **Solid state:** the molecules are immobile, and rotations are not possible.

- **Liquid Crystals:** intermediate states of mobility and rotation

- **The two main types of liquid crystals:**

- Smectic (soap- or grease-like): molecules are mobile in two directions and can rotate about one axis

- Nematic (thread-like): molecules again rotate only about one axis but are mobile in three dimensions


(a) Smectic mesophase
(b) Nematic mesophase

probably of most pharmaceutical significance since it is this phase that usually forms in ternary (or more complex) mixtures containing a surfactant, water, and a weakly amphiphilic or nonpolar additive

Properties of molecules that form mesophases:

(1) are organic,

(2) are elongated and rectilinear in shape,

(3) are rigid,

(4) possess strong dipoles and easily polarizable groups.

The liquid crystalline state may result from:

heating of solids (thermotropic liquid crystals)

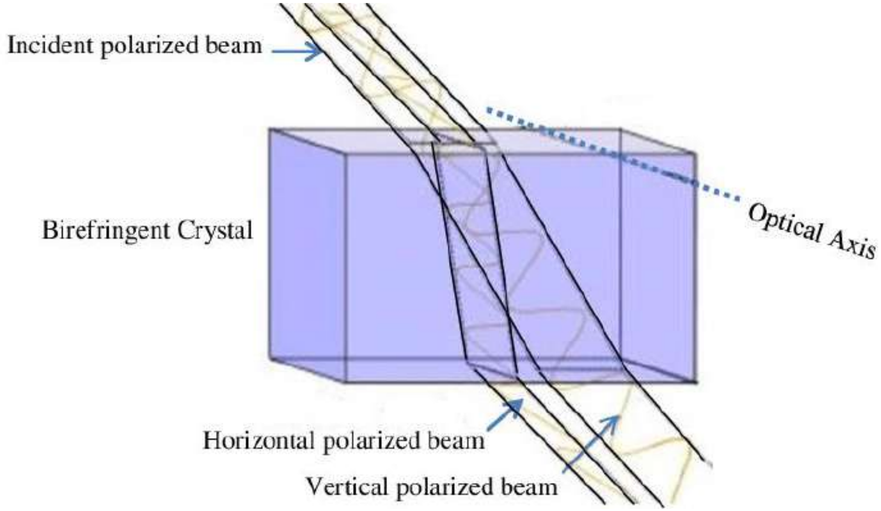
e.g. cholesteryl benzoate.

action of certain solvents on solids (lyotropic liquid crystals).

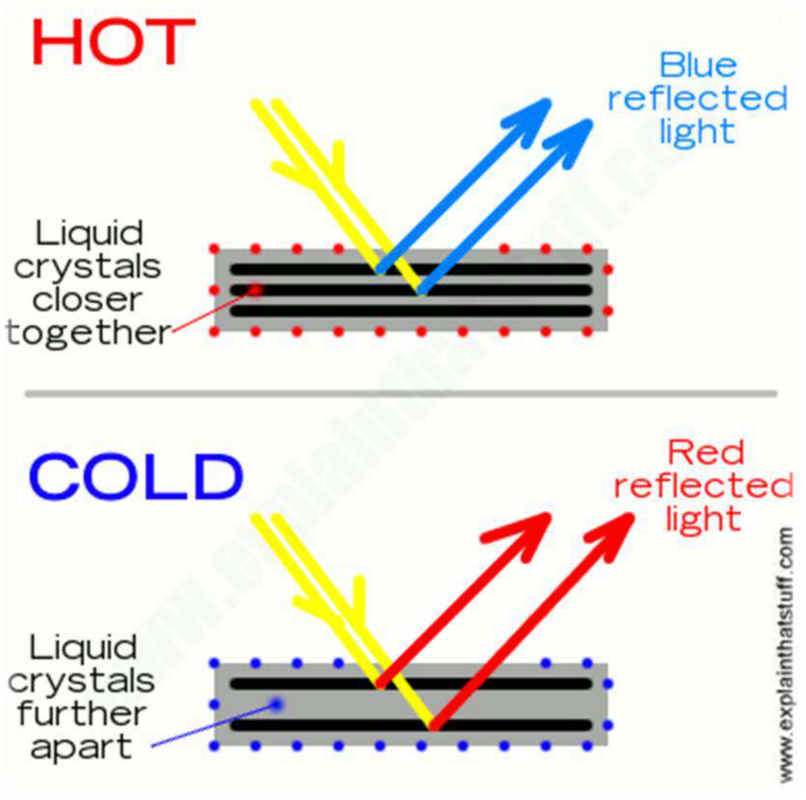
- **Properties and Significance of Liquid Crystals:**
- Because of their intermediate nature, liquid crystals have some of the properties of liquids and some of solids.

1) liquid crystals are mobile and thus can be considered to have the flow properties of liquids.

2) Be a birefringent, a property associated with crystals. In bireftingence, the light passing through a material is divided into two components with different velocities and hence different refractive indices.



- Some liquid crystals show consistent color changes with temperature, and this characteristic has resulted in their being used to detect areas of elevated temperature under the skin that may be due to a disease process.



- The smectic mesophase has application in the solubilization of water-insoluble materials.

- frequently present in emulsions and may be responsible for enhanced physical stability owing to their highly viscous nature.

- The liquid crystalline state is widespread in nature, with lipoidal forms found in nerves, brain tissue, and blood vessels. Atherosclerosis may be related to the laying down of lipid in the liquid crystalline state on the walls of blood vessels.

- have structures that are believed to be similar to those in cell membranes. As such, liquid crystals may function as useful biophysical models for the structure and functionality of cell membranes.

PHASE EQUILIBRIA AND THE PHASE RULE

- The amount of ice in the glass depends on several variables
  - ✓Amount of ice in the glass
  - ✓Temperature of water in which it was placed
  - ✓Temperature of the surrounding air

- The longer the drink is exposed to the warm air ➔ the more the amount of ice in the drink will decrease + the more water from the melting ice will produce + evaporation of the water into vapour that released into the large volume of air will decrease the amount of liquid volume

- For this system: there is no establishment of equilibrium because the volume of vapour is infinite in contrast to the ice and liquid volumes
- If the ice water is sealed in a bottle, evaporation effects are limited to the available headspace, the ice melts to liquid, and evaporation becomes **time** and **temperature** dependent

- This one component example can be extended to the **two-component system** of a drug **suspension** where solid drug is suspended and dissolved in solution and evaporation may take place in the headspace of the container.
- The suspended system will sit at equilibrium until the container is opened for administration of the drug, and then equilibrium would have to be re-established for the new system.
- A **new equilibrium or nonequilibrium state** is established because dispensing of the suspension will decrease the volume of the liquid and solid in the container.
- Therefore, a new system is created after each opening, dispensing of the dose, and then resealing.
- This will be discussed in more detail later…..

- Before we get into detail about the individual phases, it is important to understand **how the phases coexist**, **the rules that govern their coexistence**, and **the number of variables required to define the state(s) of matter present under defined conditions.**

The Phase Rule

- **J. Willard Gibbs** is credited with formulating the Phase Rule
- a useful device for relating the effect of the least number of independent variables (e.g., temperature, pressure, and concentration) upon the various phases (solid, liquid, and gaseous) that can exist in an equilibrium system containing a given number of components.

- The phase rule is expressed as follows:

$$F = C - P + 2$$

F is the number of degrees of freedom in the system,

C the number of components

P the number of phases present

$F = C - P + 2$

- a **phase** as a homogeneous, physically distinct Portion of a system that is separated from other portions of the system by bounding surfaces.
  - ✓Thus, a system containing water and its vapor' is a two-phase system.
  - ✓An equilibrium mixture of ice, liquid water, and water vapor is a three-phase system.

- The number of **components** is the smallest number of constituents by which the composition of each phase in the system at equilibrium can be expressed in the form of a chemical formula or equation.
  - ✓The number of components in the equilibrium mixture of ice, liquid water, and water vapor is one, since the composition of all three phases is described by the chemical formula H20.

- The number of degrees of **freedom** is the least number of intensive variables (temperature, pressure, refractive index, density, viscosity, ete.) that must be **fixed** → to describe the system completely.

- **Example:**

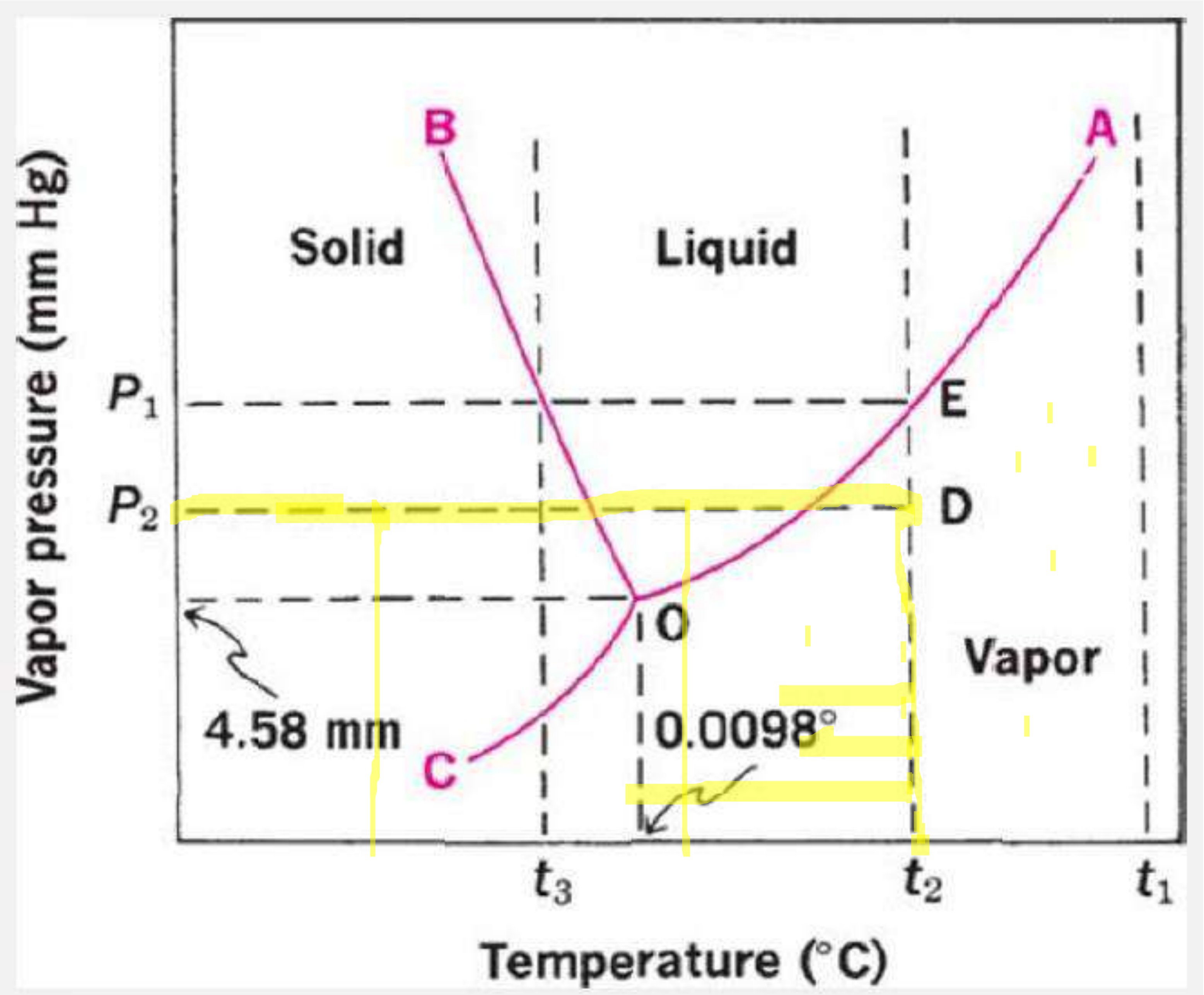
1) a system comprising a liquid, say water, in equilibrium with its vapor

- F = 1-2+2=1
- By stating the temperature, the system is completely defined.

2) A system composes of the three-phase ice - water- vapor system is completely defined

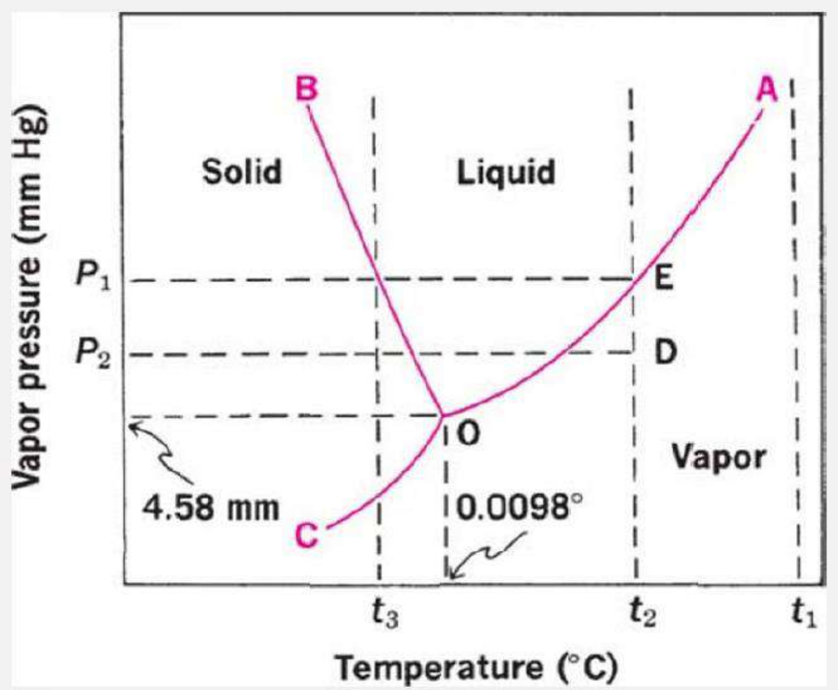
- F = 1 - 3 + 2 = 0
- in other words, there are no degrees of freedom.

Systems containing one component



Phase diagram for water at moderate temperature

- The curve **OA** is known as the vapor pressure curve.
- Its upper limit is at the critical temperature, 3740 C for water, and its lower end terminates at 0.00980 C, called the triple point

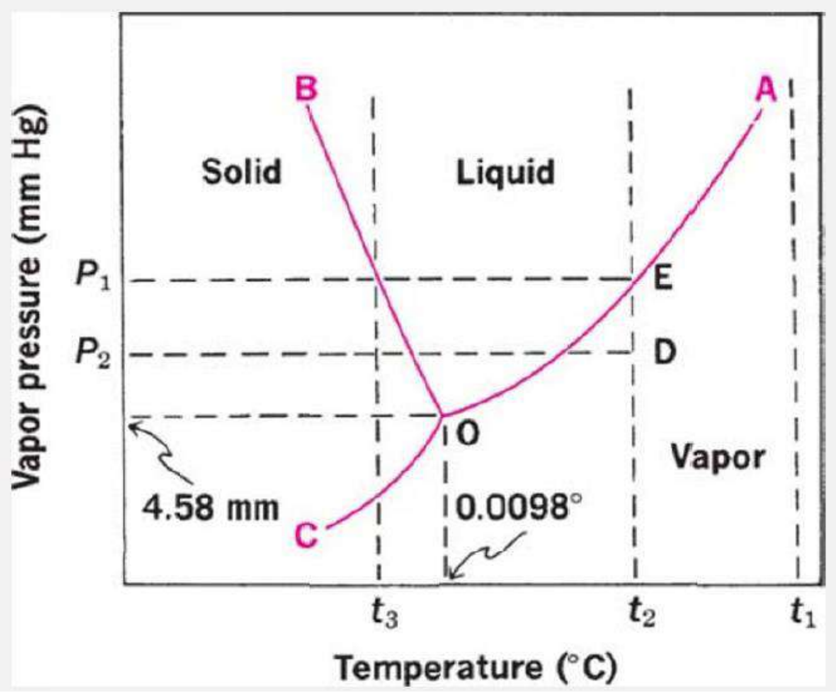


✓ Along the vapor pressure curve, vapor and liquid coexist in equilibrium.

✓ Curve **OC** is known as the sublimation curve, and here vapor and solid exist together in equilibrium.

✓ Curve **OB** is the melting point curve, at which liquid and solid are in equilibrium. The negative slope of **OB** shows that the freezing point of water decreases with increasing external pressure

- The result of changes in pressure (at fixed temperature) or changes in temperature (at fixed pressure) becomes evident by referring to the phase diagram

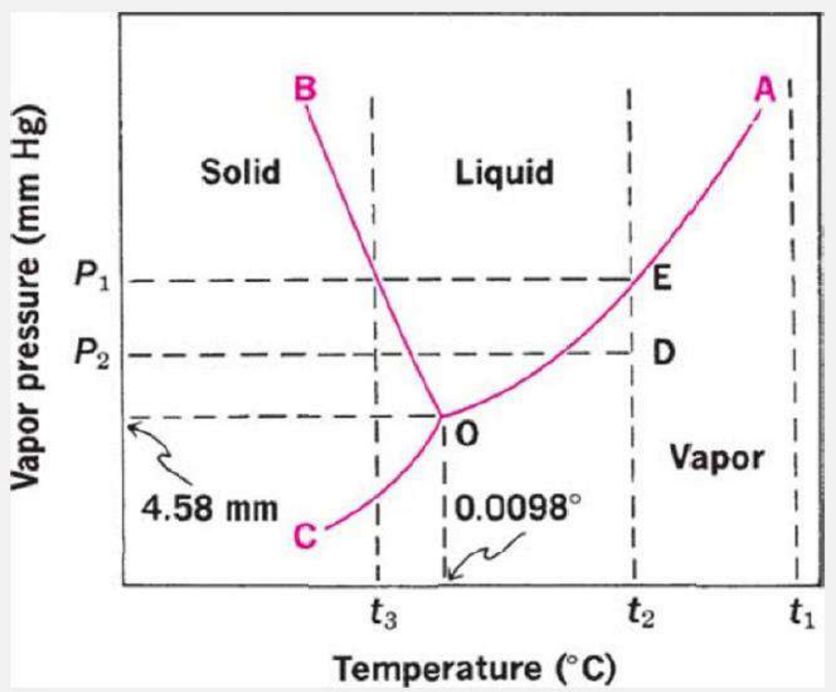


A. If the temperature is held constant at tit where water is in the gaseous state above the critical temperature, no matter how much the pressure is raised (vertically along the dotted line), the system remains as a gas.

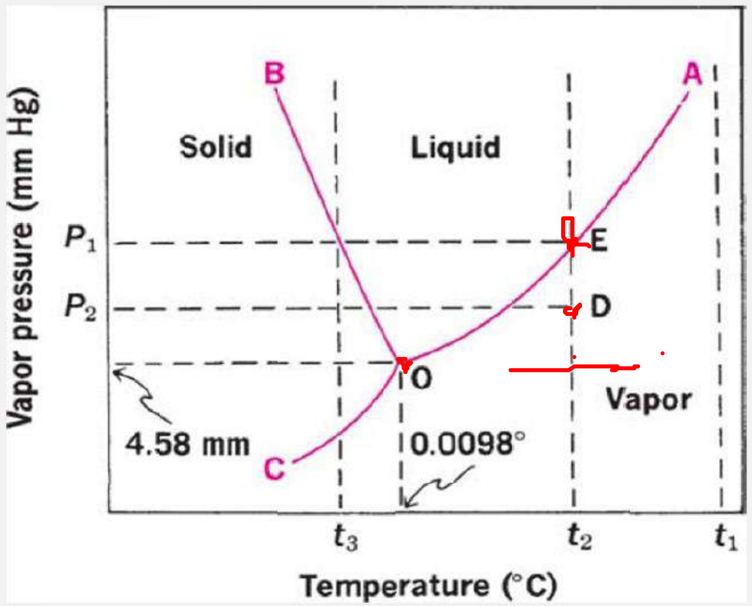
B. At a temperature below the 'Critical temperature, water vapor is converted into liquid water by an increase of pressure, since the compression brings the molecules within the range of the attractive van der Waals forces

C. at a temperature below the triple point, say t3, an increase of pressure on water in the vapor state converts the vapor first to ice and then at higher pressure into liquid water.

D. At the triple point, all three phases are in equilibrium



System	Number of Phases	Degrees of Freedom	Comments
Gas, liquid, or solid	1	$\mathbf{F} = C - P + 2 = \mathbf{1} - 1 + 2 = 2$	System is *bivariant* (**F** = 2) and lies anywhere within the area marked vapor, liquid, or solid in Figure 2-2 We must fix two variables, e.g., P_2 and t_2, to define system D.
Gas–liquid, liquid–solid, or gas–solid	2	$\mathbf{F} = C - P + 2 = \mathbf{1} - 2 + 2 = 1$	System is *univariant* (**F** = 1) and lies anywhere along a *line* between two-phase regions, i.e., AO, BO, or CO in Figure 2-22. We must fix one variable, e.g., either P_1 or t_2, to define system E.
Gas–liquid–solid	3	$\mathbf{F} = C - P + 2 = \mathbf{1} - 3 + 2 = 0$	System is *invariant* (**F** = 0) and can lie only at the *point* of intersection of the lines bounding the three-phase regions, i.e., point O in Figure 2-22.

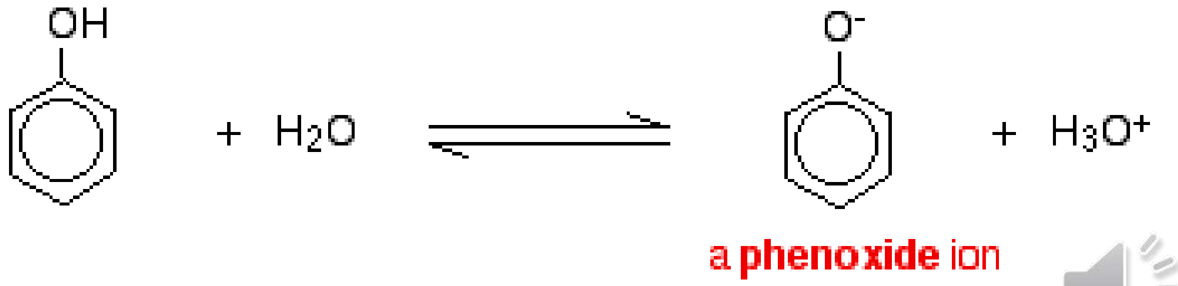


Tow component systems containing liquid phases

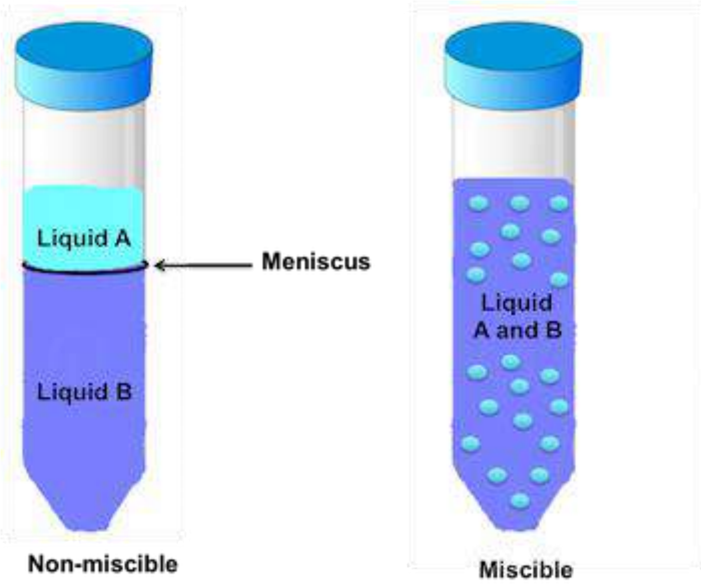
- **ethyl alcohol and water** are miscible in all proportions,
- whereas **water and mercury** are, for all practical purposes, completely immiscible regardless of the relative amounts of each present.
- Between these two extremes lies a whole range of systems that exhibit partial miscibility
- One such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



- 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%.

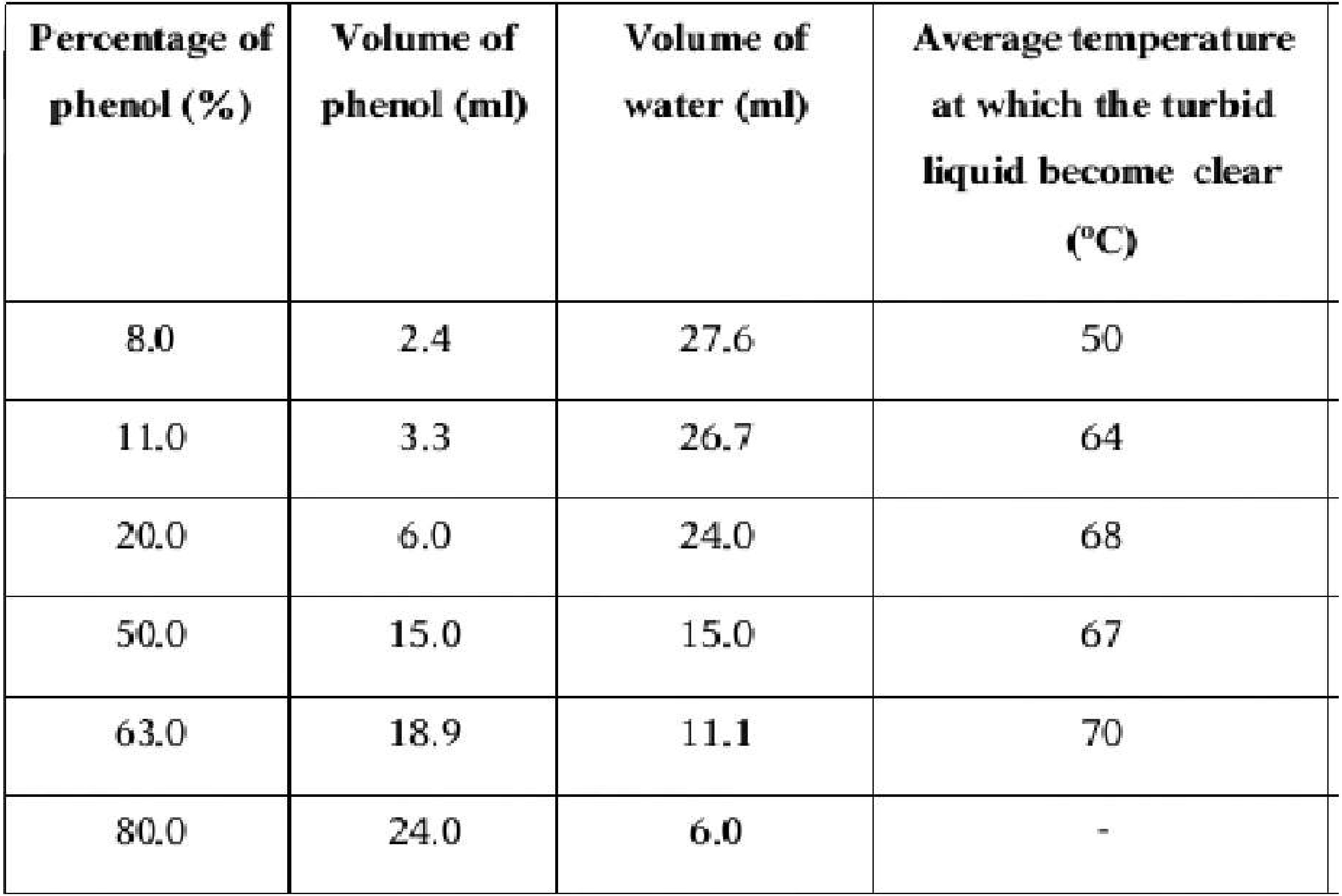
2. The total amount of 2 liquids in the boiling tubes was fixed to be 30ml and the boiling tubes were labeled accordingly from A to G.

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.

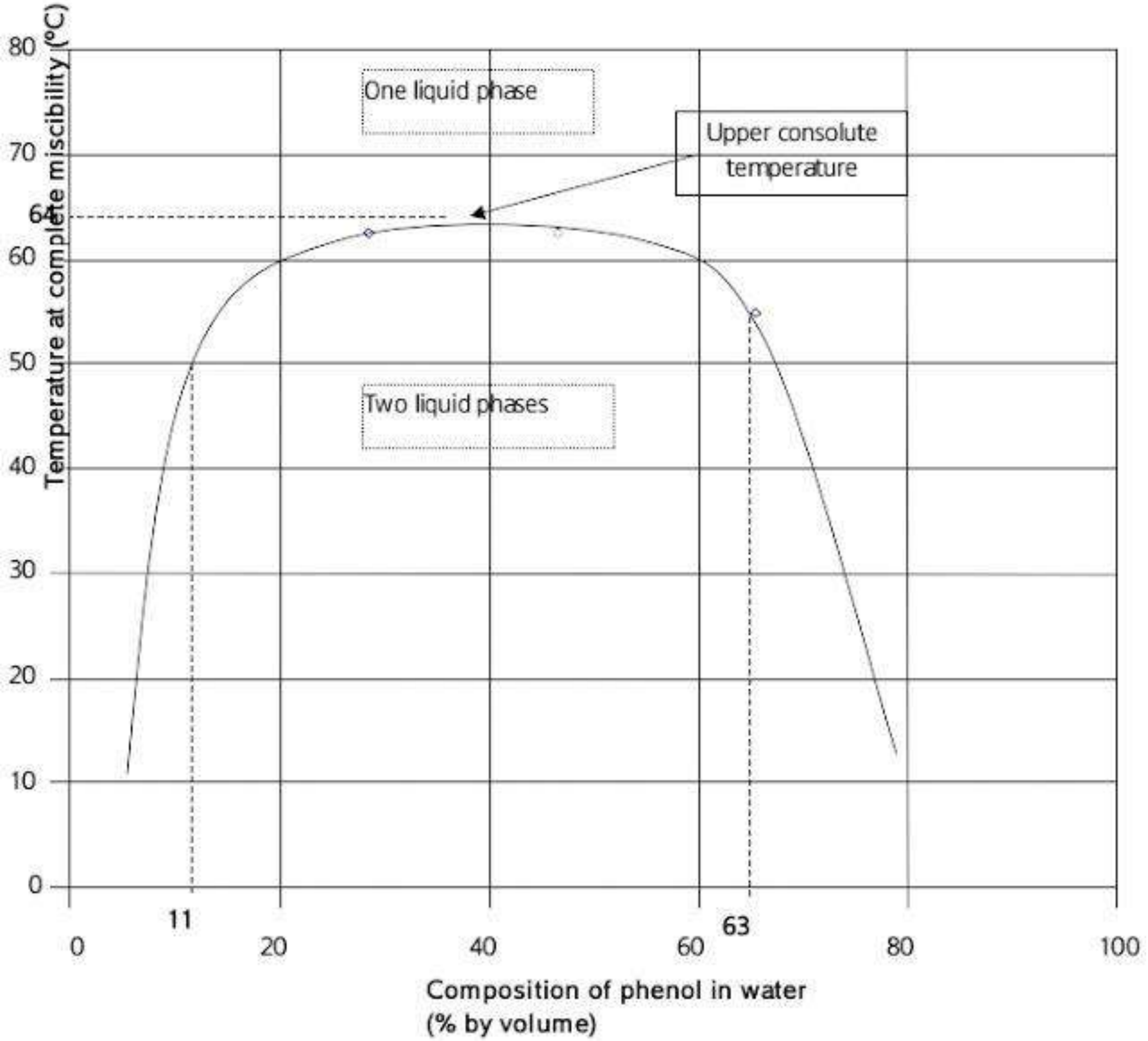
5. Finally, repeated for tubes B to G.

6. A graph of temperature at complete miscibility against phenol composition in the different mixtures was plotted.



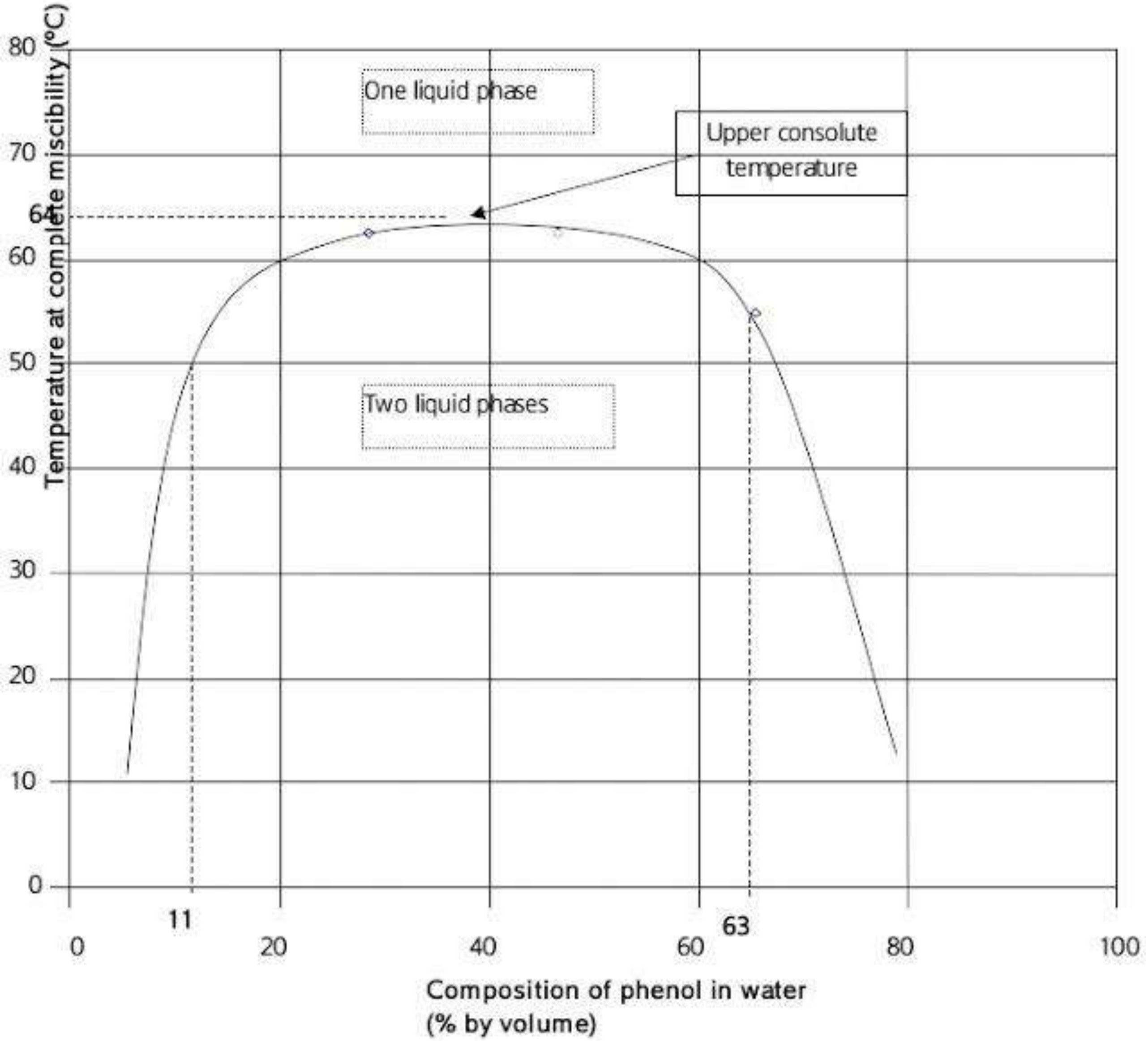
Percentage of phenol (%)	**Volume of phenol (ml)**	**Volume of water (ml)**	**Average temperature at which the turbid liquid become clear (°C)**
8.0	2.4	27.6	50
11.0	3.3	26.7	64
20.0	6.0	24.0	68
50.0	15.0	15.0	67
63.0	18.9	11.1	70
80.0	24.0	6.0	-

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



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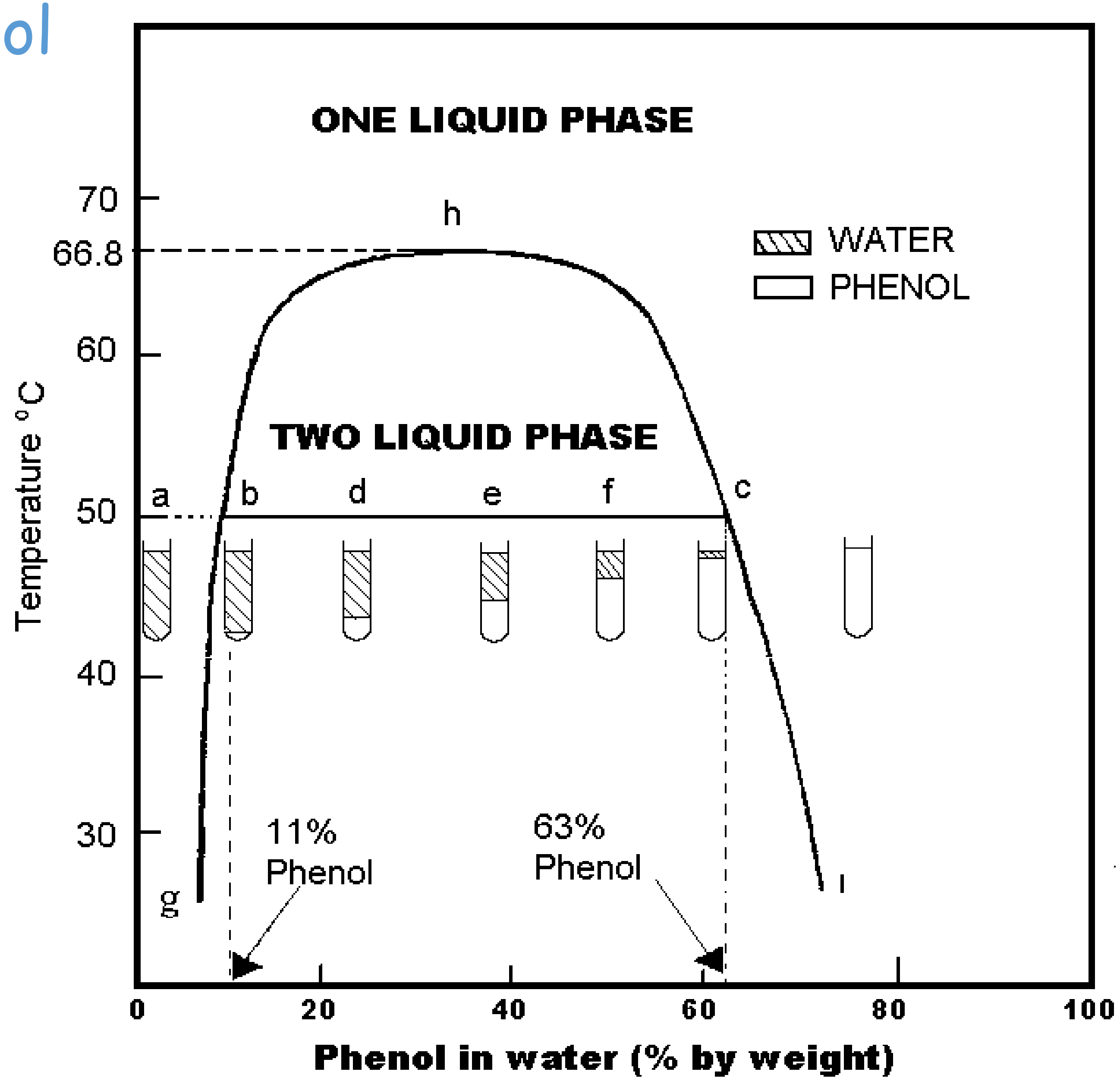
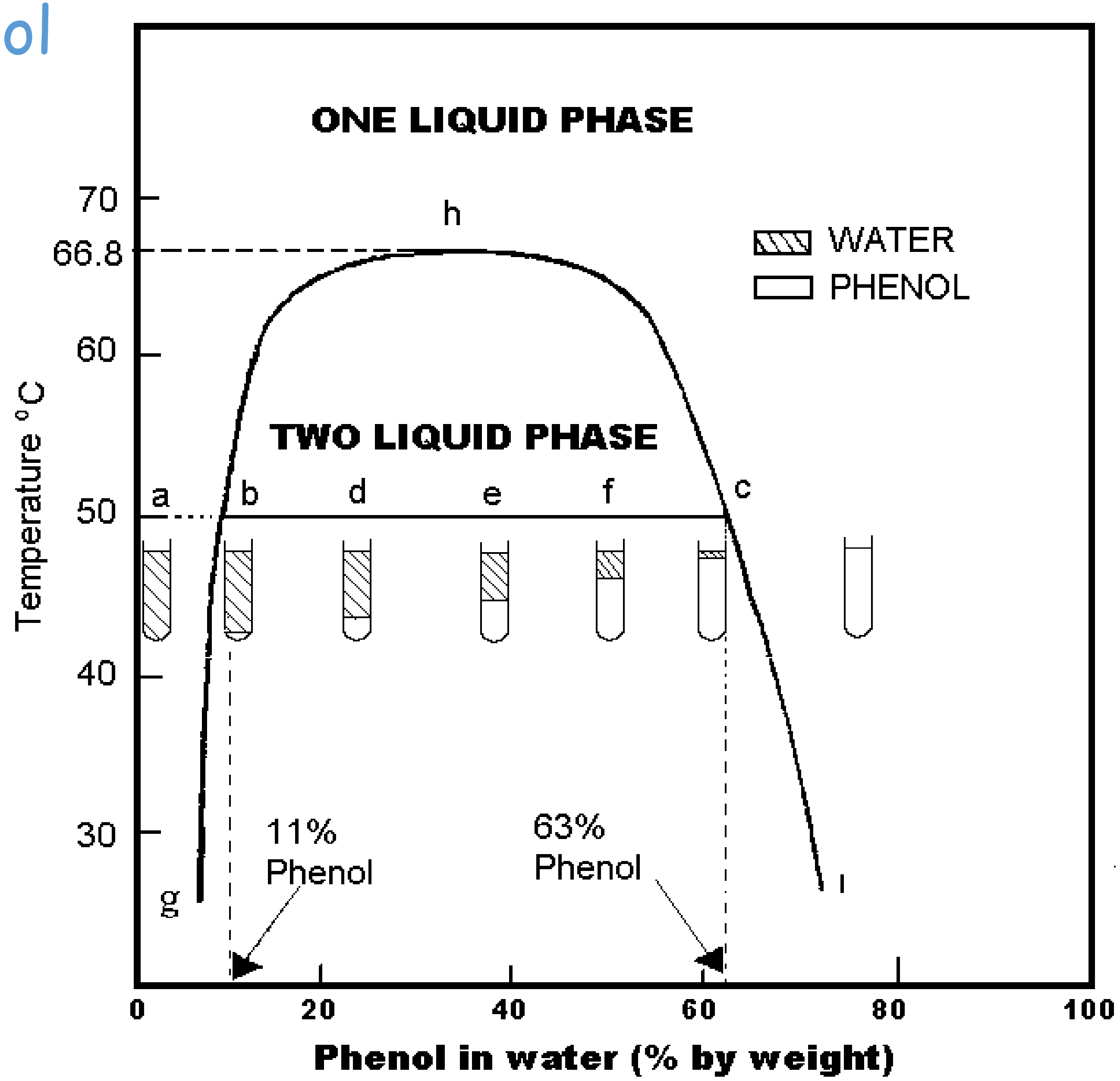
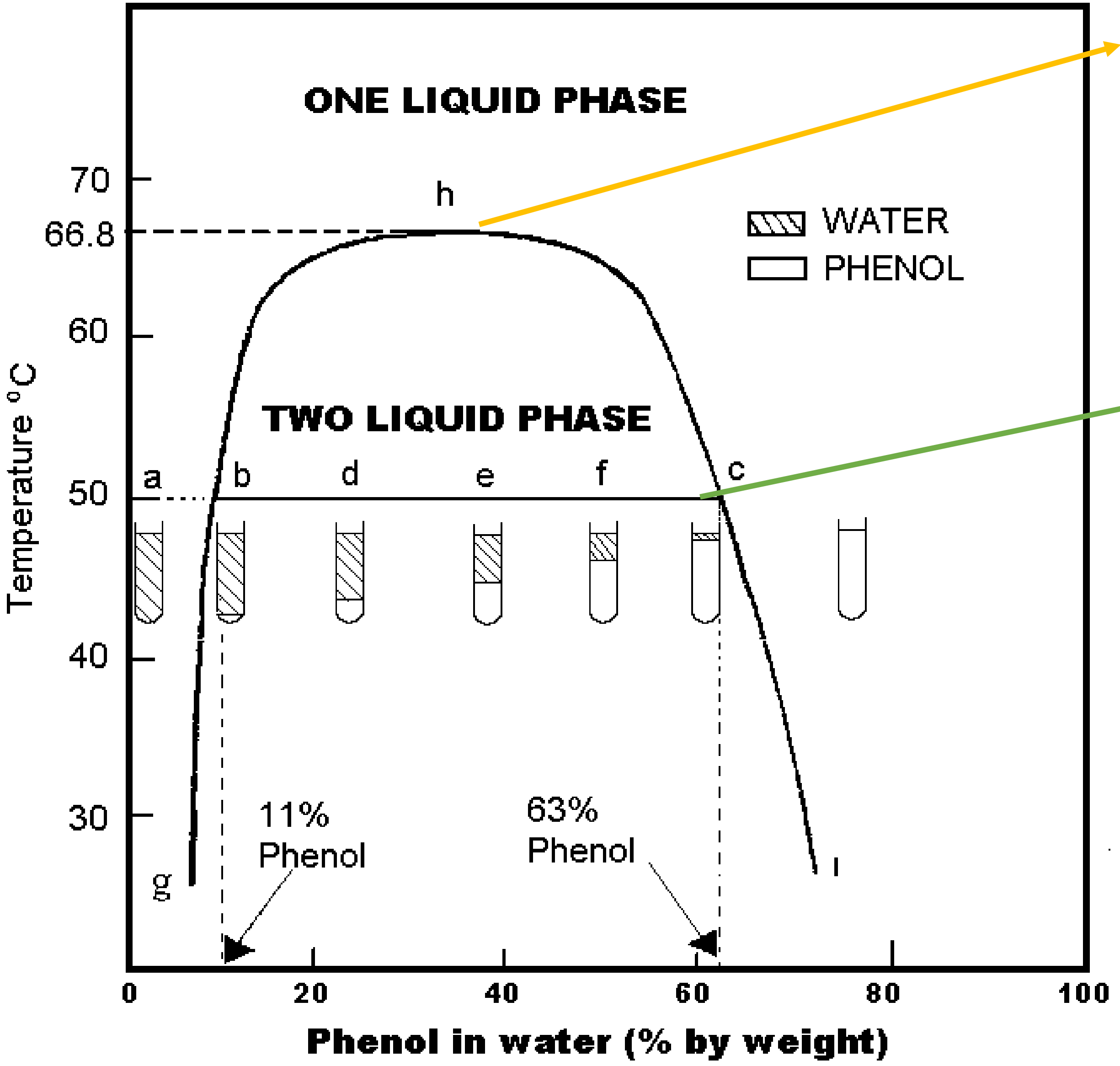
Temperature-composition diagram for the system consisting of water and phenol



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



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

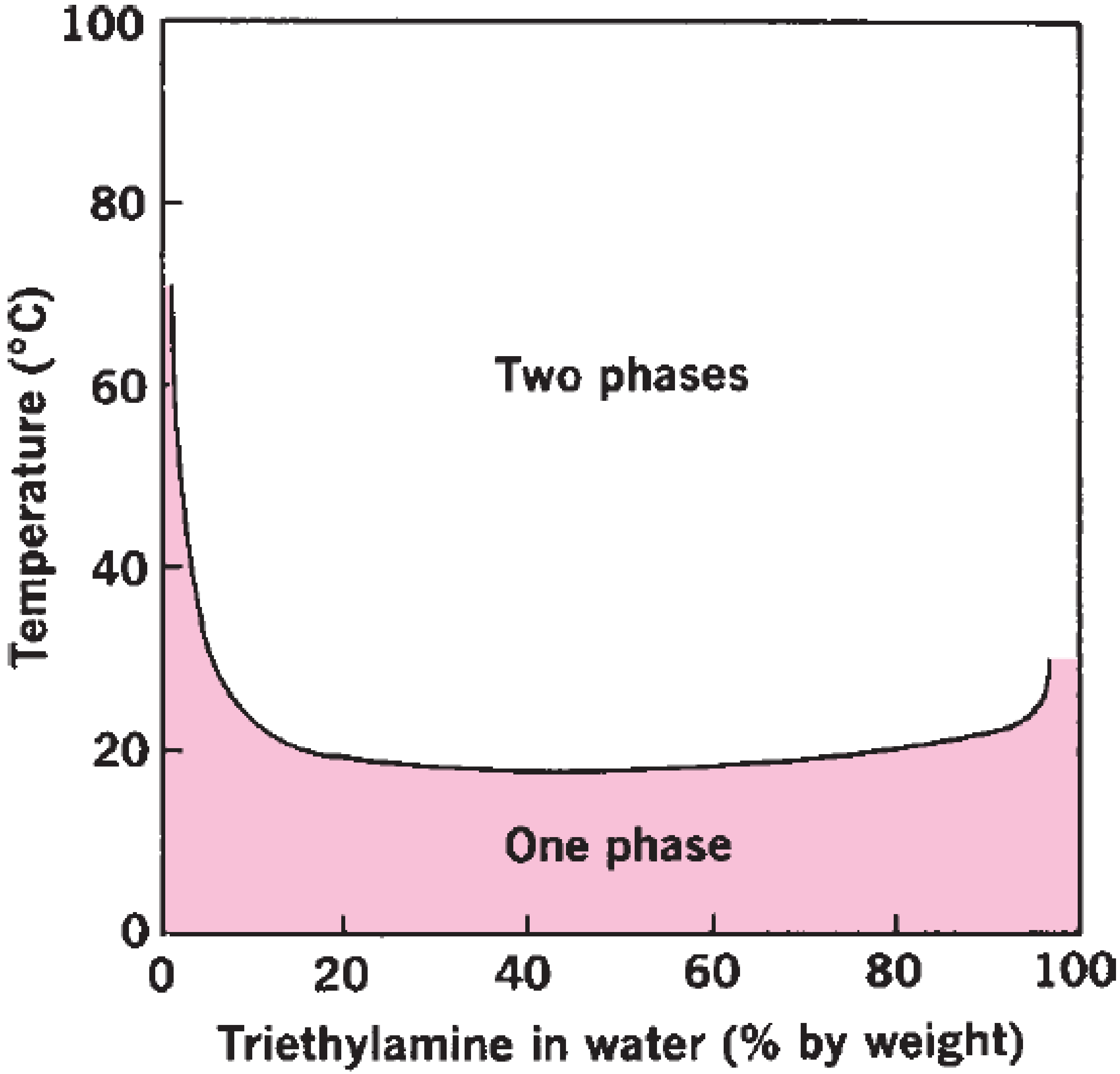


critical solution, or upper consolute, temperature.

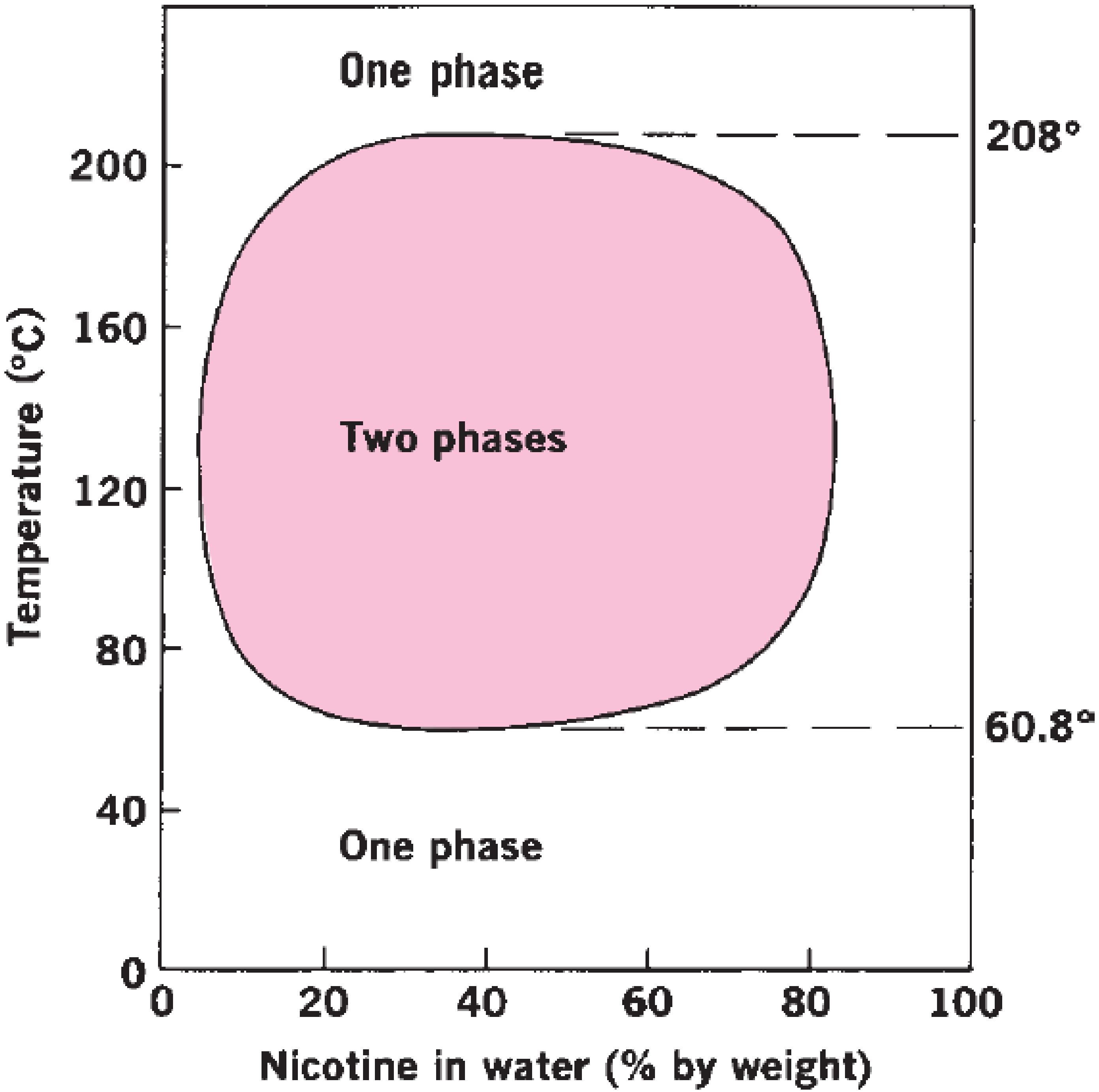
All combinations of phenol and water above this temperature are completely miscible and yield one-phase liquid systems.

tie line

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



Phase diagram for the system triethylamine–water showing lower consolute temperature

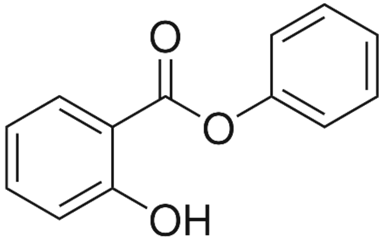


Nicotine–water system showing upper and lower consolute temperatures.

Two-Component Systems Containing Solid and Liquid Phases

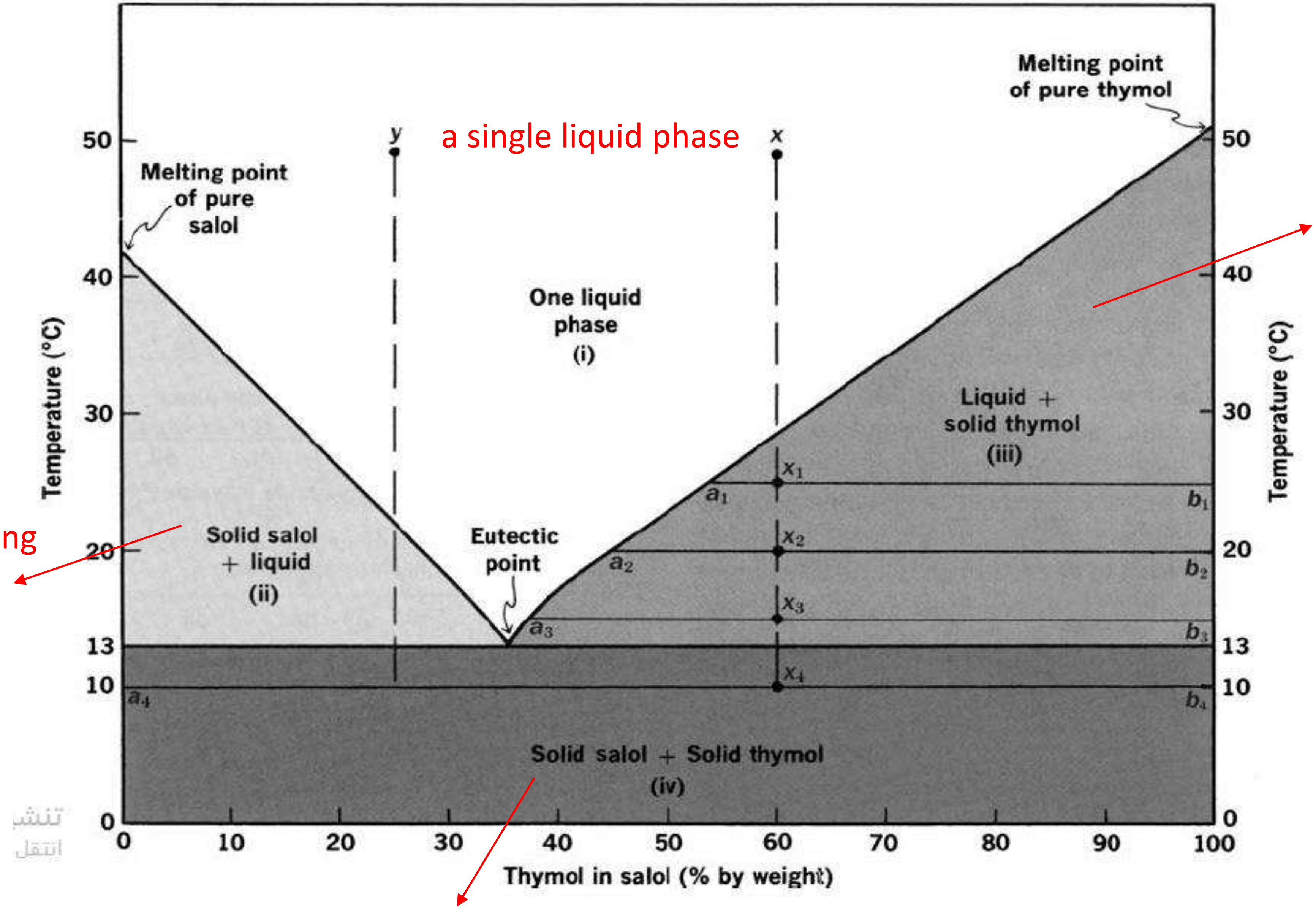
- We restrict our discussion, in the main, to those solid–liquid mixtures in which the two components are completely miscible in the liquid state and completely immiscible as solids

- 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:



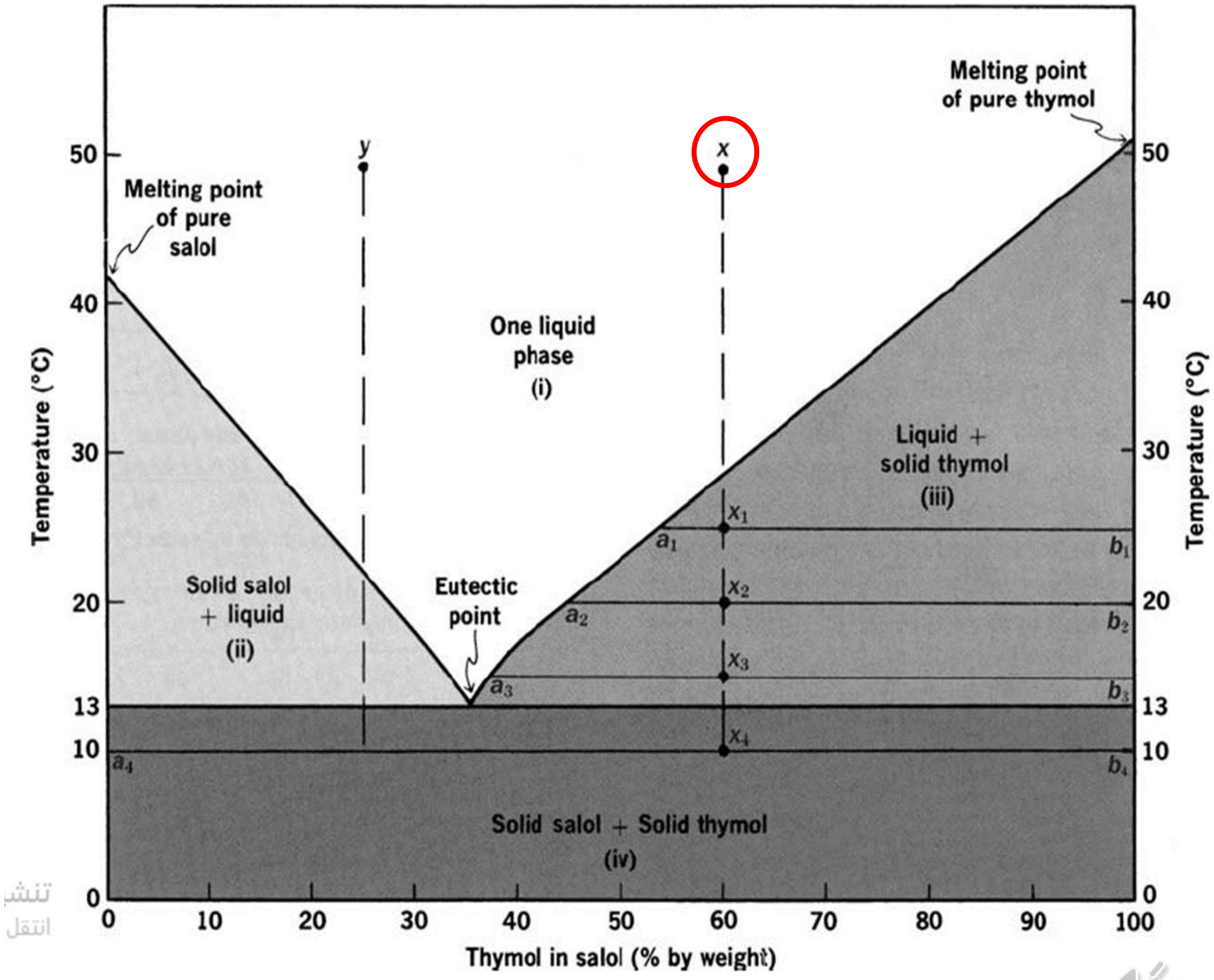
a single liquid phase

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

a region containing solid salol and a conjugate liquid phase

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

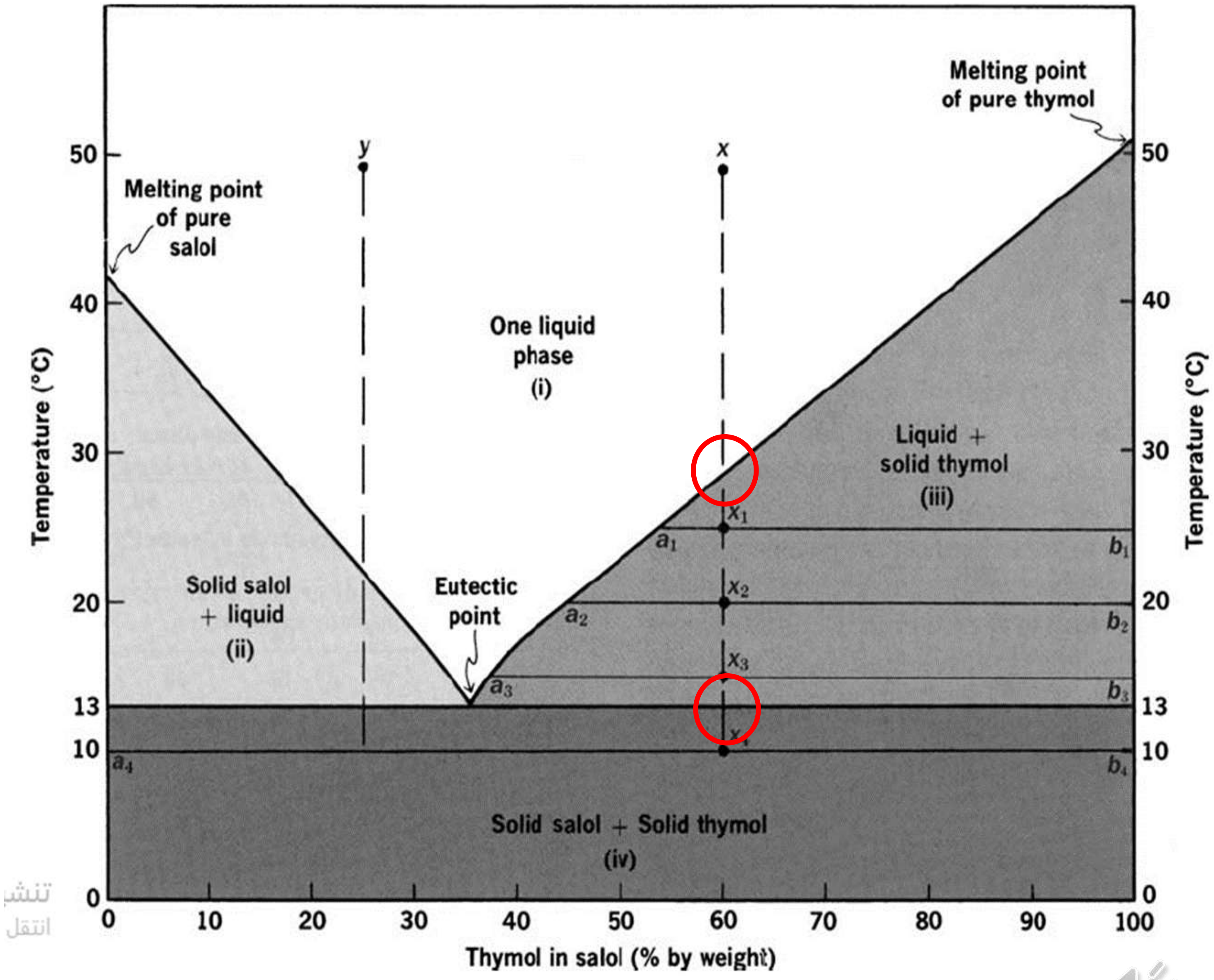
- Suppose we prepare a system containing 60% by weight of thymol in salol and raise the temperature of the mixture to 50◦C. Such a system is represented by point x in the figure



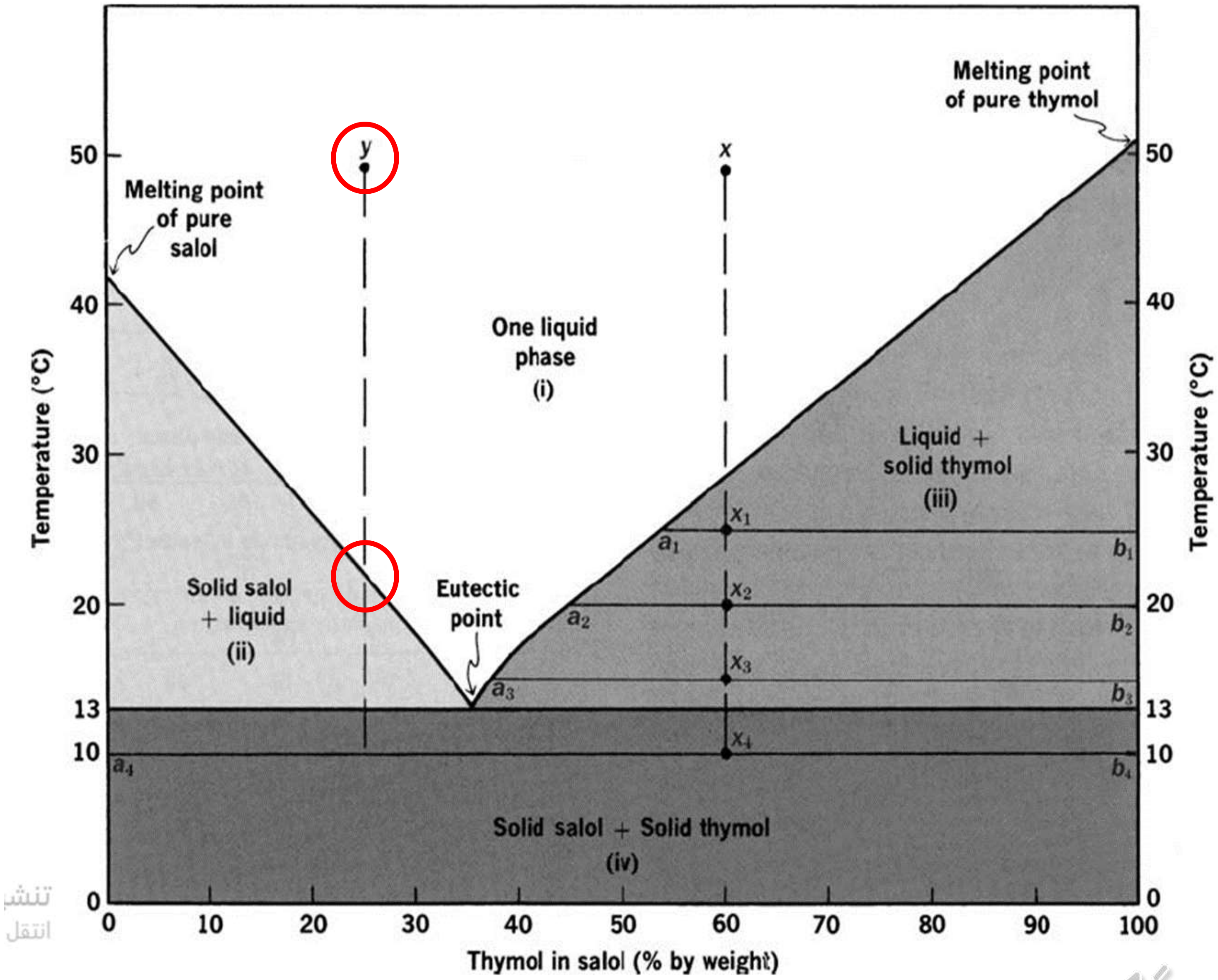
- On cooling the system, we observe the following sequence of phase changes:

✓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.

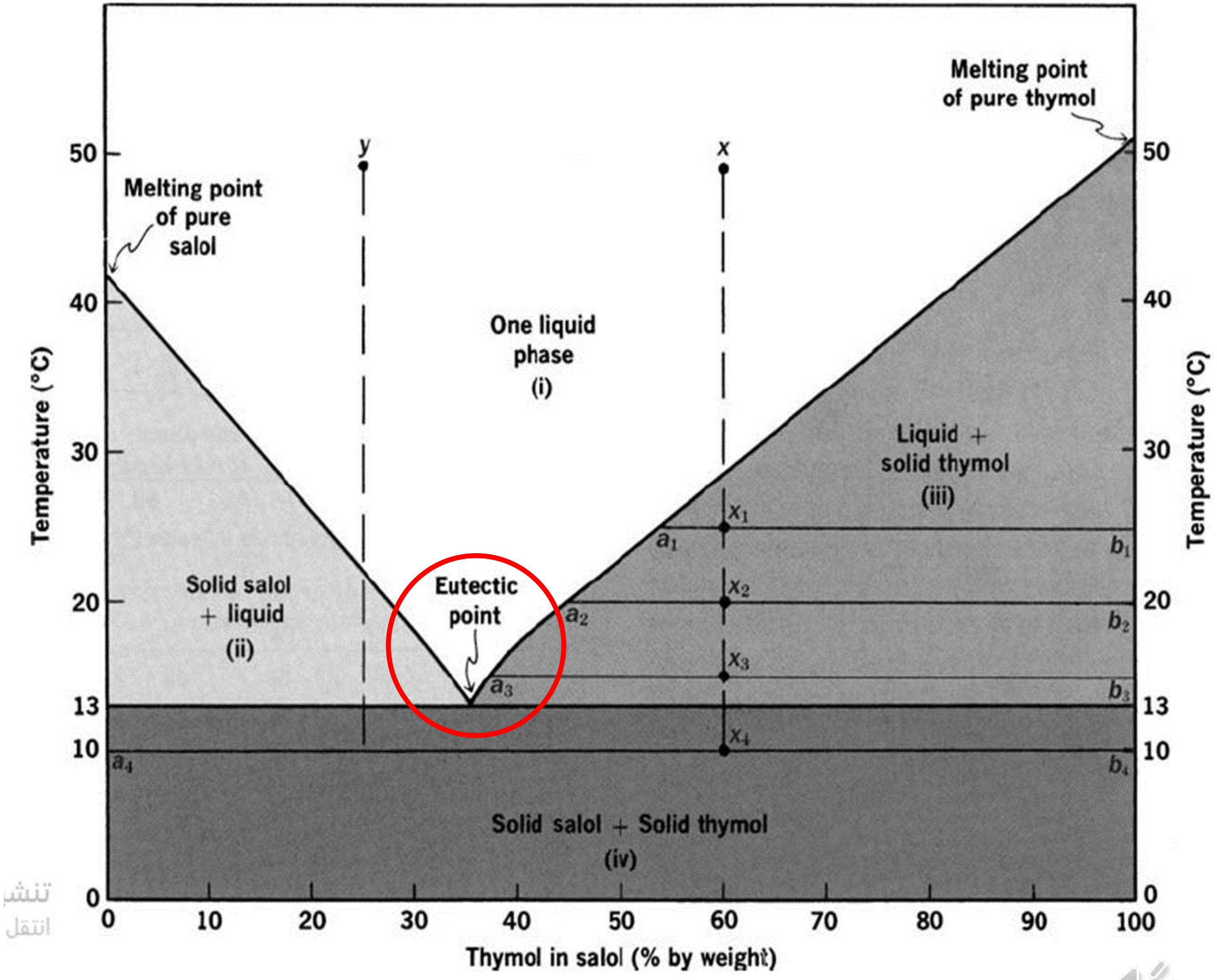
✓Below 13◦C, the liquid phase disappears altogether and the system contains two solid phases of pure salol and pure thymol.



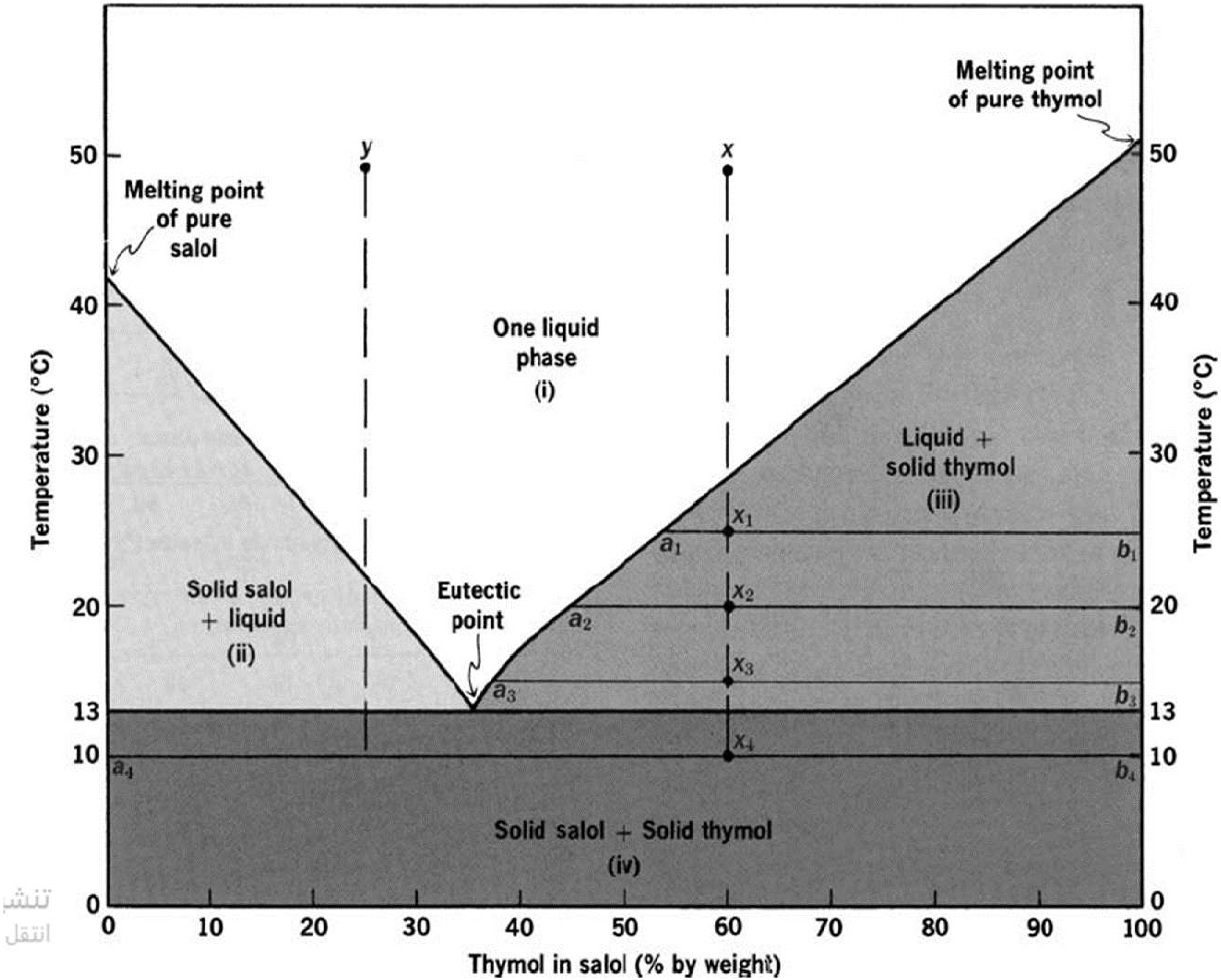
- ✓As system x is progressively cooled, the results indicate that more and more of the thymol separates as solid.
- ✓A similar sequence of phase changes is observed if system y is cooled in a like manner.
- ✓In this case, however, the solid phase that separates at 22◦C is pure salol.



- 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 solidb 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.

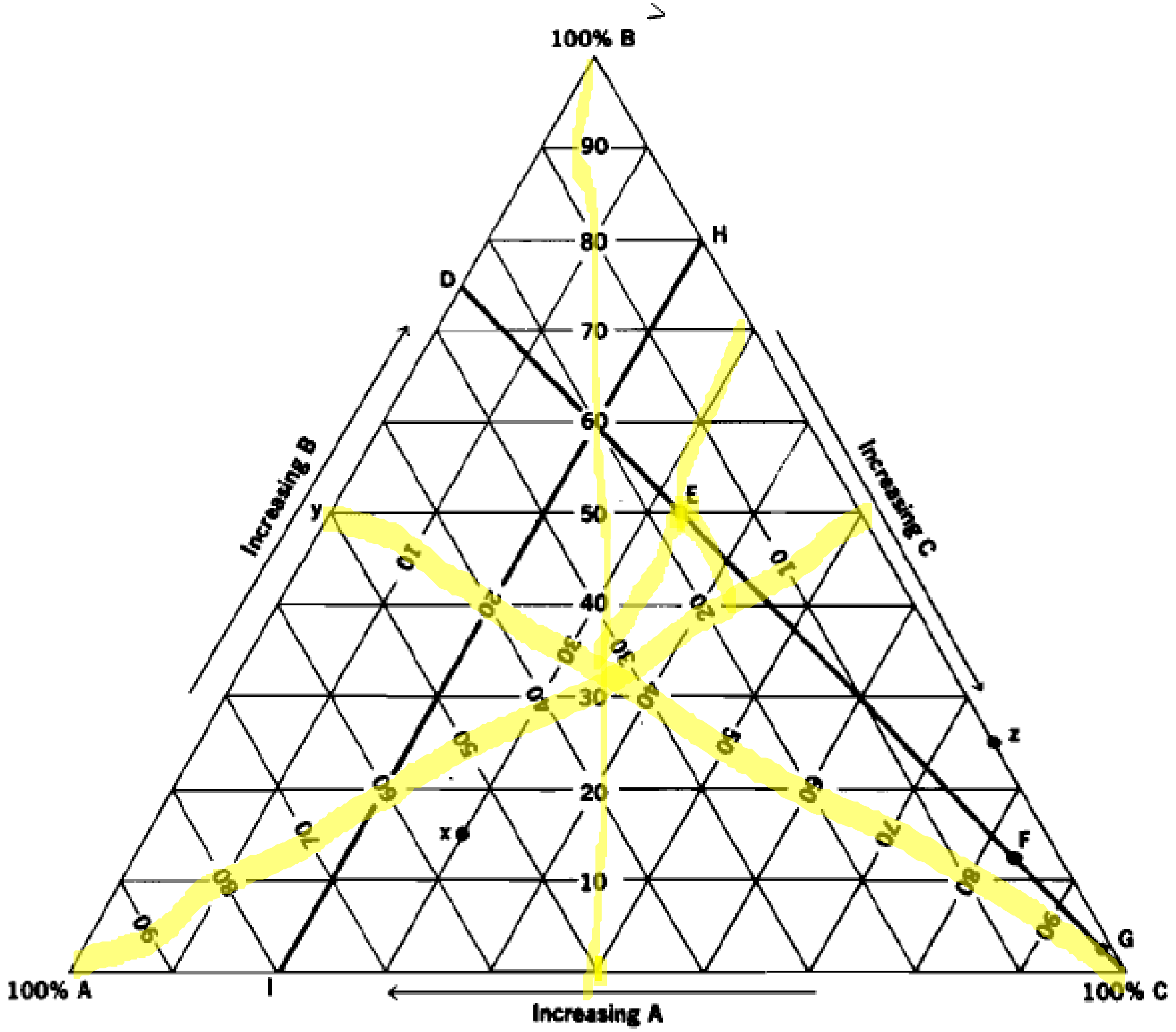

Melting point of pure thymol
Melting point of pure salol
y
x
One liquid phase (i)
Liquid + solid thymol (iii)
Solid salol + liquid (ii)
Eutectic point
Solid salol + Solid thymol (iv)
x_1
x_2
x_3
x_4
a_1
a_2
a_3
a_4
b_1
b_2
b_3
b_4
Temperature (°C)
Temperature (°C)
0
10
13
20
30
40
50
0
10
20
30
40
50
60
70
80
90
100
Thymol in salol (% by weight)

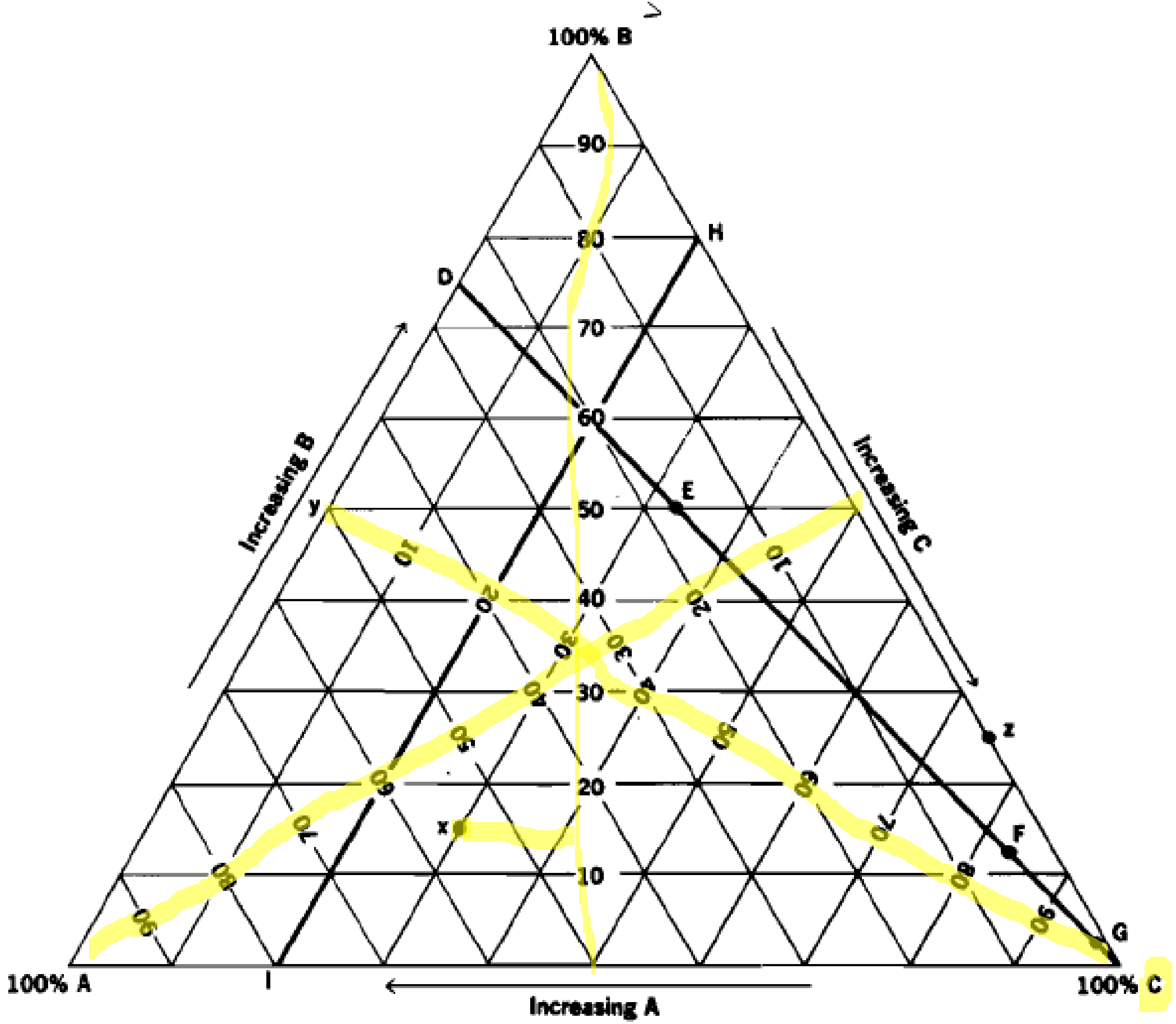
- **Lidocaine and prilocaine**, two local anesthetic agents, form a 1:1 mixture having a eutectic temperature of 18◦C.

- 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:




100% B
90
80
70
60
50
40
30
20
10
D
H
E
Increasing B
Increasing C
y
z
x
F
G
10
20
30
40
50
60
70
80
90
100% A
I
Increasing A
100% C

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