



FORCES OF ATTRACTION

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- **Intramolecular Forces**

forces of attraction within the molecule

Types:

Ionic Bonds

- **Transfer of electrons between a non metal & a metal**
- **Observed in formation of salts , example NaCl**

Covalent Bond

- **Sharing of electrons between two non metals**
- **Observed in organic compounds , example CH₄**



- **Intermolecular Forces**

- **Forces of attraction between molecules**

- **Types**

- Binding & Attractive Forces

- **Binding Forces**

- Cohesion – similar molecules
- Adhesion – different molecules
- Repulsive – prevent molecules from annihilating each other

- **Attractive Forces**

- Van der Waals
- Hydrogen Bond
- Ion-Dipole
- Ion-induced Dipole



Binding Forces Between Molecules



Binding Forces Between Molecules

- For molecules to exist as aggregates in **gases**, **liquids**, and **solids**, intermolecular forces must exist.
- **Intermolecular forces**
- **Cohesion**, or the attraction of like molecules,
- **Adhesion**, or the attraction of unlike molecules,
- **Repulsion** is a reaction between two molecules that forces them apart.
- For molecules to interact, these forces must be balanced in an energetically favored arrangement.

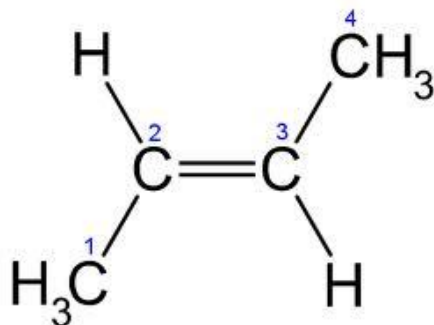


Repulsive and Attractive Forces

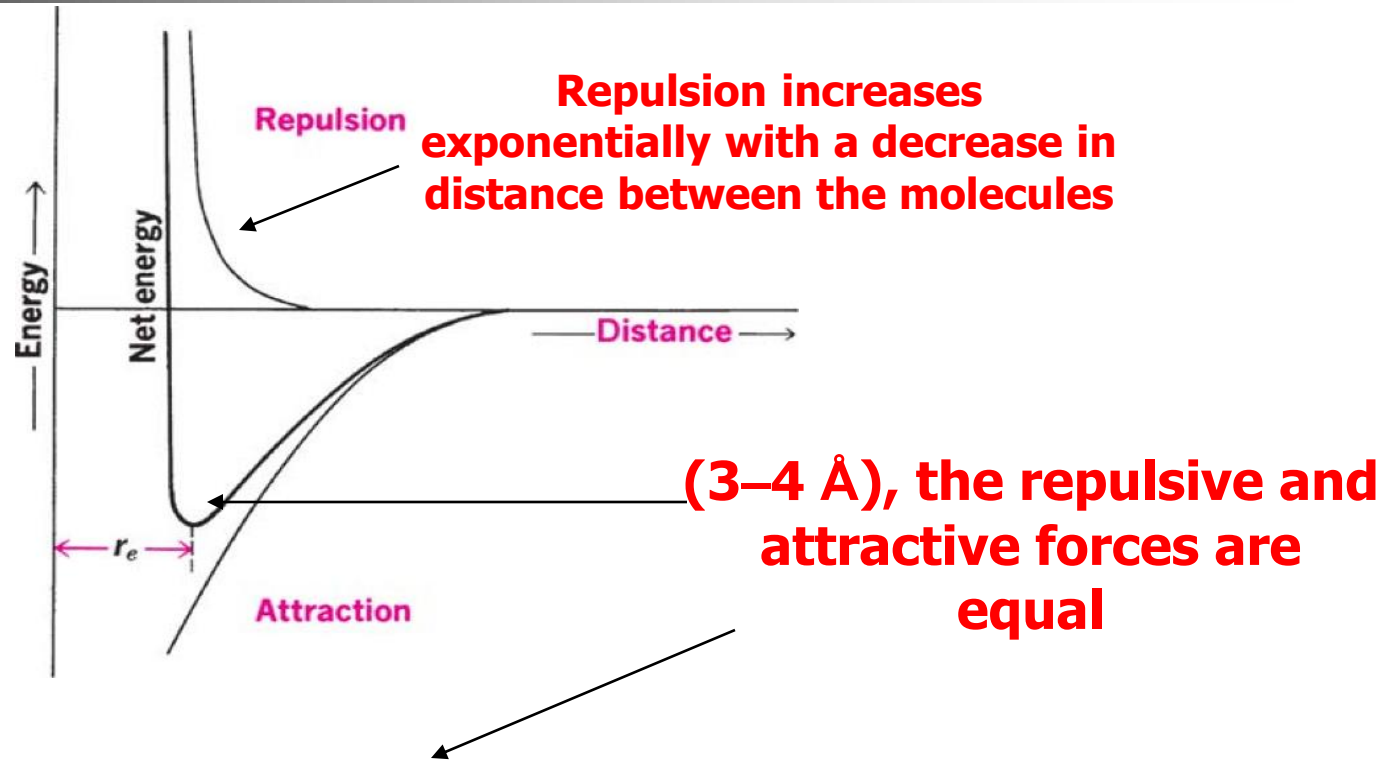
- When molecules interact, both repulsive and attractive forces operate.
- **When the molecules are brought so close that the outer charge clouds touch, they repel each.**
- **Thus, attractive forces are necessary for molecules to cohere, whereas repulsive forces act to prevent the molecules from interpenetrating and annihilating each other.**

Repulsive Forces

- Repulsion is due to the interpenetration of the electronic clouds of molecules and increases exponentially with a decrease in distance between the molecules.
- At a certain equilibrium distance, about $(3-4) \times 10^{-8}$ cm (3–4 Å), the repulsive and attractive forces are equal.
- At this position, the potential energy of the two molecules is a minimum and the system is most stable .
- The effect of repulsion on the intermolecular three-dimensional structure of a molecule is well illustrated in considering the conformation of the two terminal methyl groups in butene, where they are energetically favored in the trans - conformation because of a minimization of the repulsive forces.



Repulsive and attractive energies and net energy as a function of distance between molecules.



- a minimum occurs in the **net energy** (potential energy) because of the different character of the attraction and repulsion curves.



Attractive Forces

- ***Van der Waals Forces***
- ***Orbital Overlap***
- ***Ion–Dipole and Ion-Induced Dipole Forces***
- ***Ion–Ion Interactions***
- ***Hydrogen Bonds***



Attractive Forces :

1. Van der Waals Forces

- Van der Waals forces relate to **nonionic interactions** between molecules, yet they involve **charge – charge interactions**.
- **partial charges** can be permanent or be induced by neighboring groups

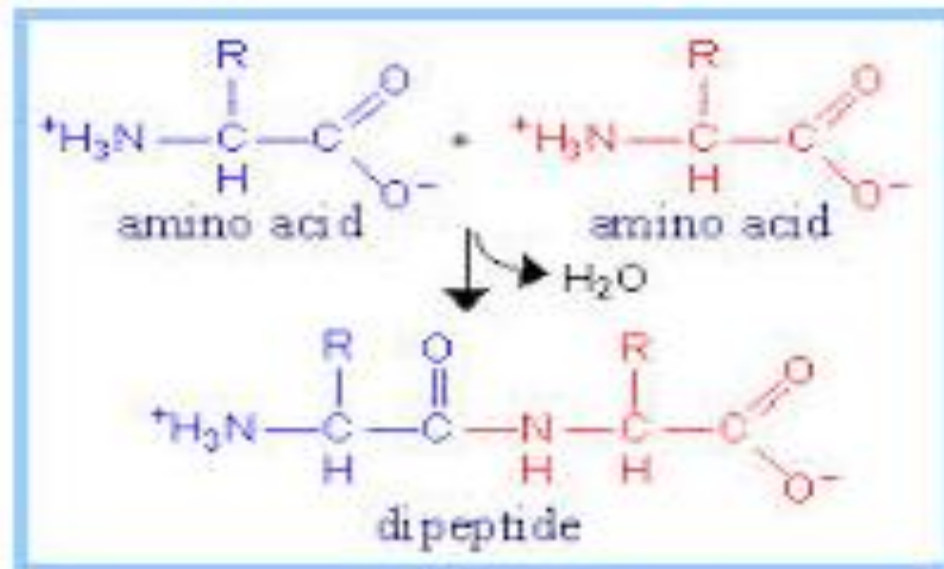
Types of Van der Waals Forces:

- Keesom forces
- Debye forces
- London forces

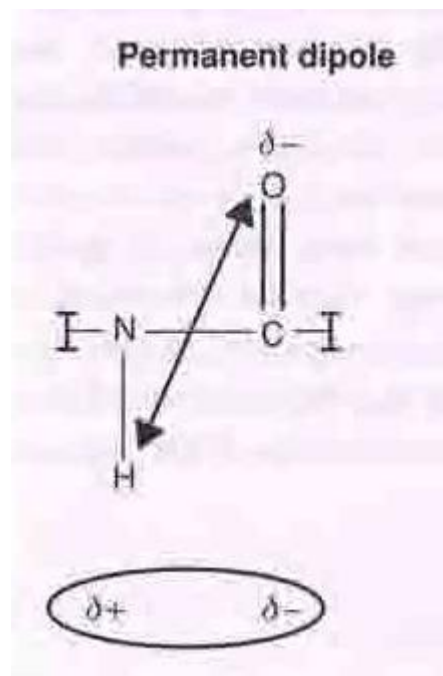
- Van der Waal interactions are **weak forces** that involve the dispersion of charge across a molecule called a **Permanent dipole**.

Permanent dipole

In a permanent dipole, as illustrated by the peptide bond, the electronegative oxygen draws the pair of electrons in the carbon–oxygen double bond closer to the oxygen nucleus.



- The bond then becomes polarized due to the fact that the oxygen atom is strongly pulling the nitrogen lone pair of electrons toward the carbon atom, thus creating a partial double bond.
- the nucleus of the nitrogen atom pulls the electron pair involved in the nitrogen–hydrogen bond closer to itself and creates a partial positive charge on the hydrogen.

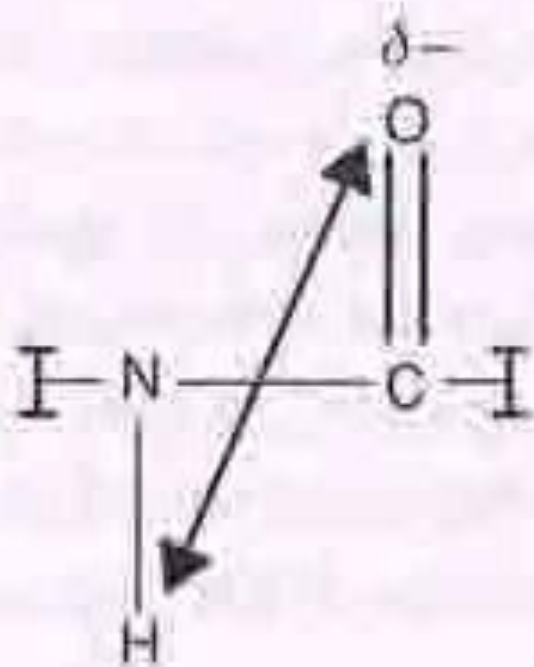




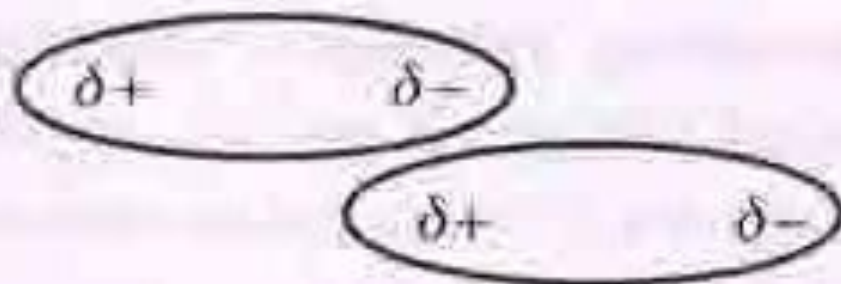
Keesom forces:

- *dipole–dipole* interaction.
- the permanent dipoles interact with one another in an **ion-like fashion**.
- the **negative pole** of one molecule points toward the **positive pole** of the next.
- because the charges are partial, the strength of bonding is much weaker.

Permanent dipole

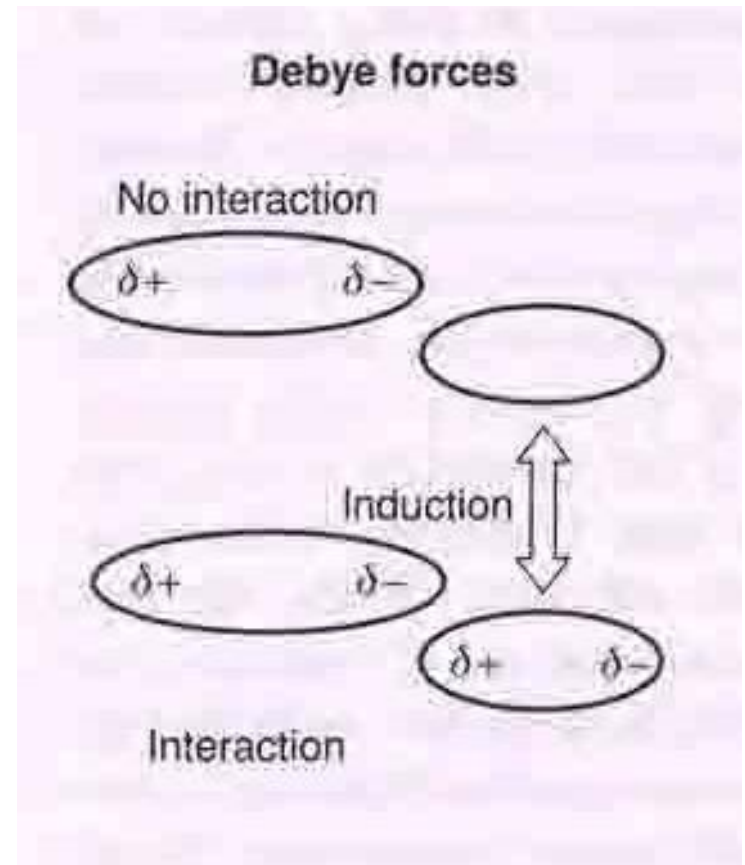


Keesom forces



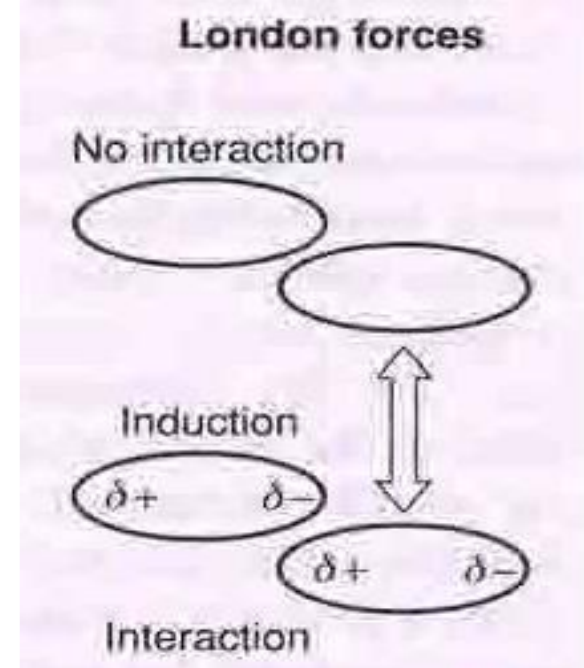
Debye forces:

- *dipole-induced dipole interactions*
- **show the ability of a permanent dipole to polarize charge in a neighboring nonpolar easily polarizable molecule.**



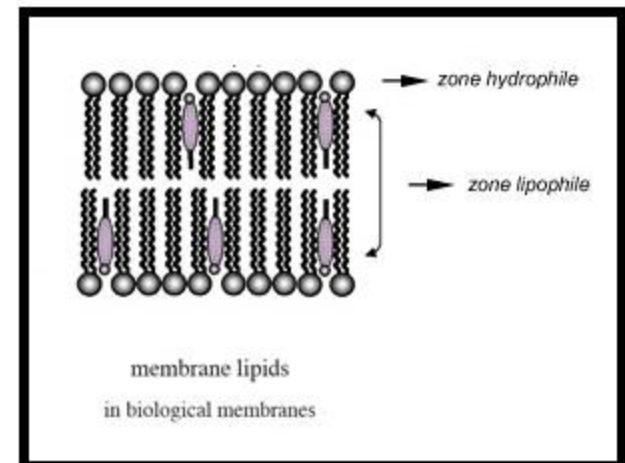
London forces:

- *induced dipole-induced dipole* interaction.



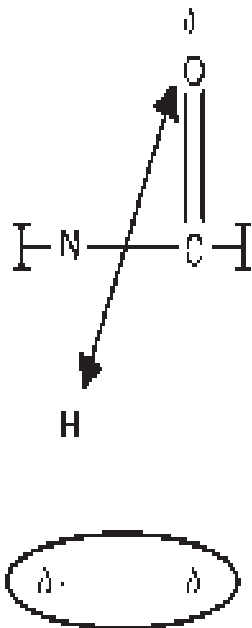
- Two neighboring nonpolar **molecules**, for example, Lipid core aliphatic hydrocarbons chains of a biological membrane , **interior neighboring chains** induce partial charge distributions (polarity) .

Helps to hold the interior interact give rise to the fluidity and cohesiveness of the membrane.



Types of van der Waals forces:

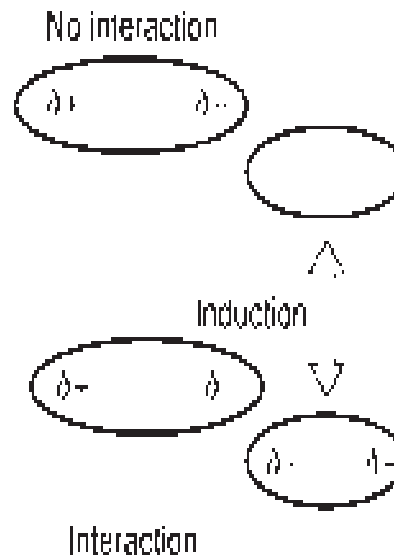
Permanent dipole



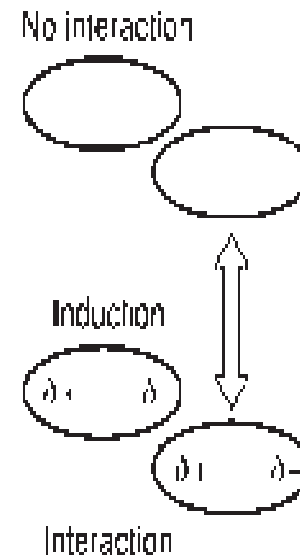
Keesom forces

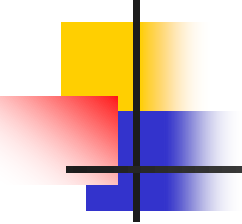


Debye forces



London forces

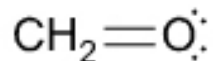
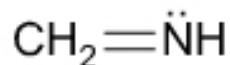
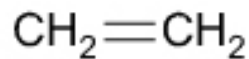
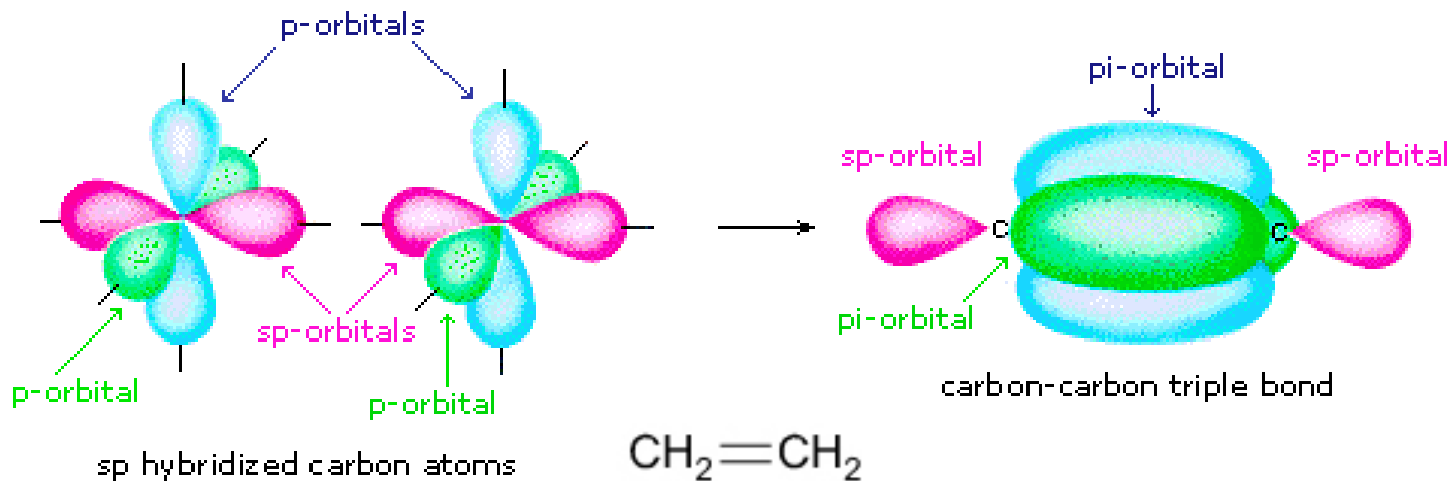


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- In all three types of van der Waals forces, the potential energy of attraction varies inversely with the distance of separation, r , raised to the sixth power, r^6 .
 - The potential energy of repulsion changes more rapidly with distance.
 - This accounts for the potential energy minimum and the resultant equilibrium distance of separation, r_e .

Attractive Forces :

2. Orbital overlap

- *dipole-dipole* force.
- the interaction between pi-electron orbitals in systems.
- For example, **aromatic-aromatic interactions** can occur when the **double-bonded pi-orbitals** from the two rings overlap





3. Ion–Dipole and Ion-Induced Dipole Forces

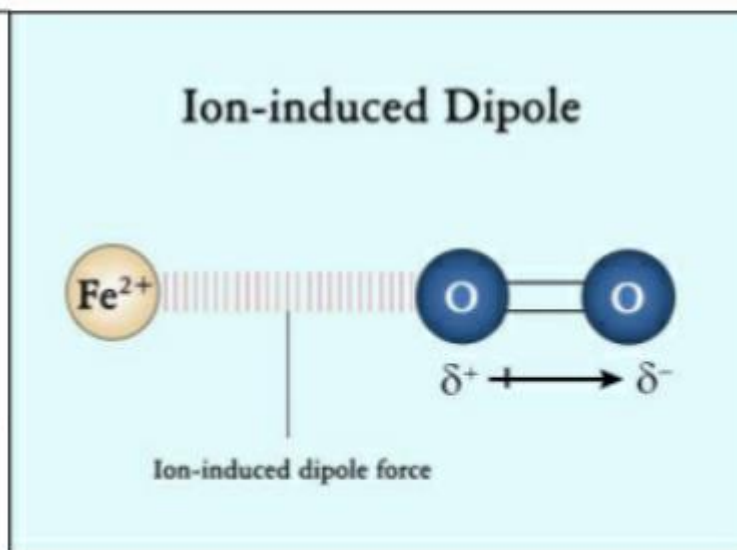
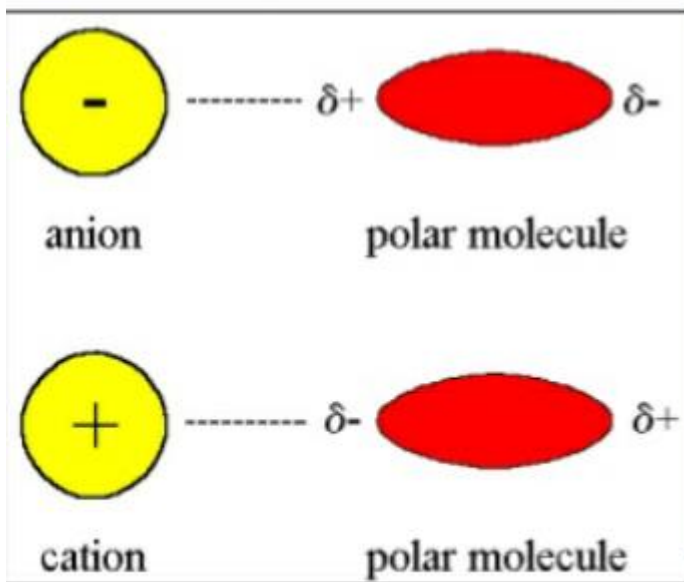
- occur between polar or nonpolar molecules and ions.
- **account in part for the solubility of ionic crystalline substances in water;** the cation, for example, attracts the relatively negative oxygen atom of water and the anion attracts the hydrogen atoms of the dipolar water molecules.
- Ion-induced dipole forces are involved in the formation of the iodide complex,



nonpolar

polar

Ion-dipole and ion-induced dipole forces





4. Ion –Ion Interactions

- An ionic, electrovalent bond between two counter ions is the strongest bonding interaction and can persist over the longest distance.
- **weaker ion–ion interactions, in salt formations, exist and influence pharmaceutical systems.**
- A cation on one compound will interact with an anion on another compound, giving rise to an *intermolecular* association.
- Ion–ion interactions can also be repulsive when two ions of like charge are brought closely together.

5. Hydrogen Bonds

- **The interaction between a molecule containing a hydrogen atom and a strongly electronegative atom such as fluorine, oxygen, or nitrogen.**
- **it accounts for many of the unusual properties of water including its high dielectric constant, abnormally low vapor pressure, and high boiling point.**
- **Roughly one sixth of the hydrogen bonds of ice are broken when water passes into the liquid state, and essentially all the bridges are destroyed when it vaporizes.**
- **Hydrogen bonds can also exist between alcohol molecules, carboxylic acids, aldehydes, esters, and polypeptides**

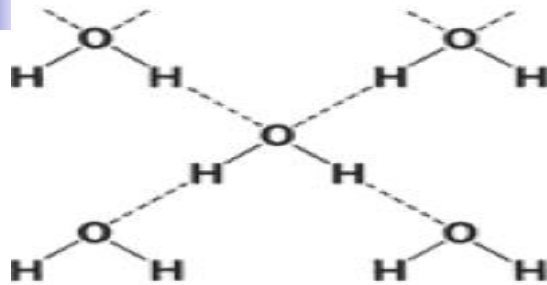
hydrogen-bonded structures



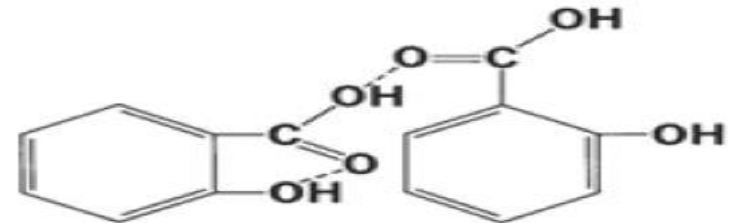
Hydrogen fluoride



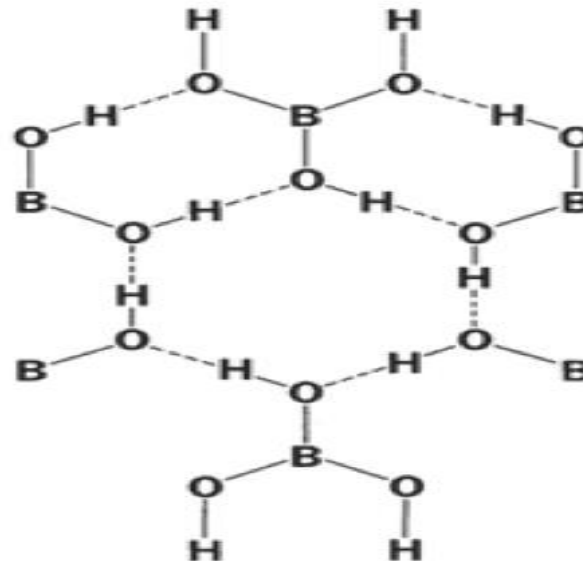
Formic acid dimer



Water



Salicylic acid showing intermolecular and intramolecular hydrogen bonding



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



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	
Dipole-induced dipole interaction, induction effect, or Debye force	1–10
Induced dipole–induced dipole interaction, dispersion effect, or London force	
Ion–dipole interaction	

Hydrogen bonds: $\text{O}-\text{H}\cdots\text{O}$	6
$\text{C}-\text{H}\cdots\text{O}$	2-3
$\text{O}-\text{H}\cdots\text{N}$	4-7
$\text{N}-\text{H}\cdots\text{O}$	2-3
$\text{F}-\text{H}\cdots\text{F}$	7
Primary valence bonds	
Electrovalent, ionic, heteropolar	100-200
Covalent, homopolar	50-150





Ionic bond
Covalent bonds
Dipole - ion interaction
hydrogen bond
Dipole - Dipole interaction
Dipole - induced dipole interaction
London Force

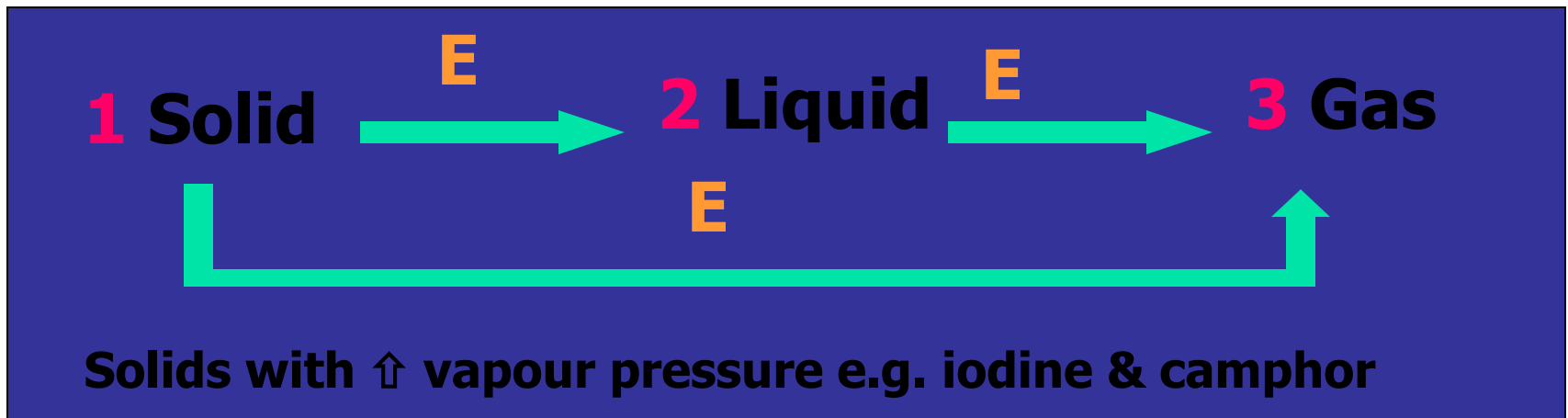


Home work

Give two Examples for the previously discussed intermolecular attraction forces

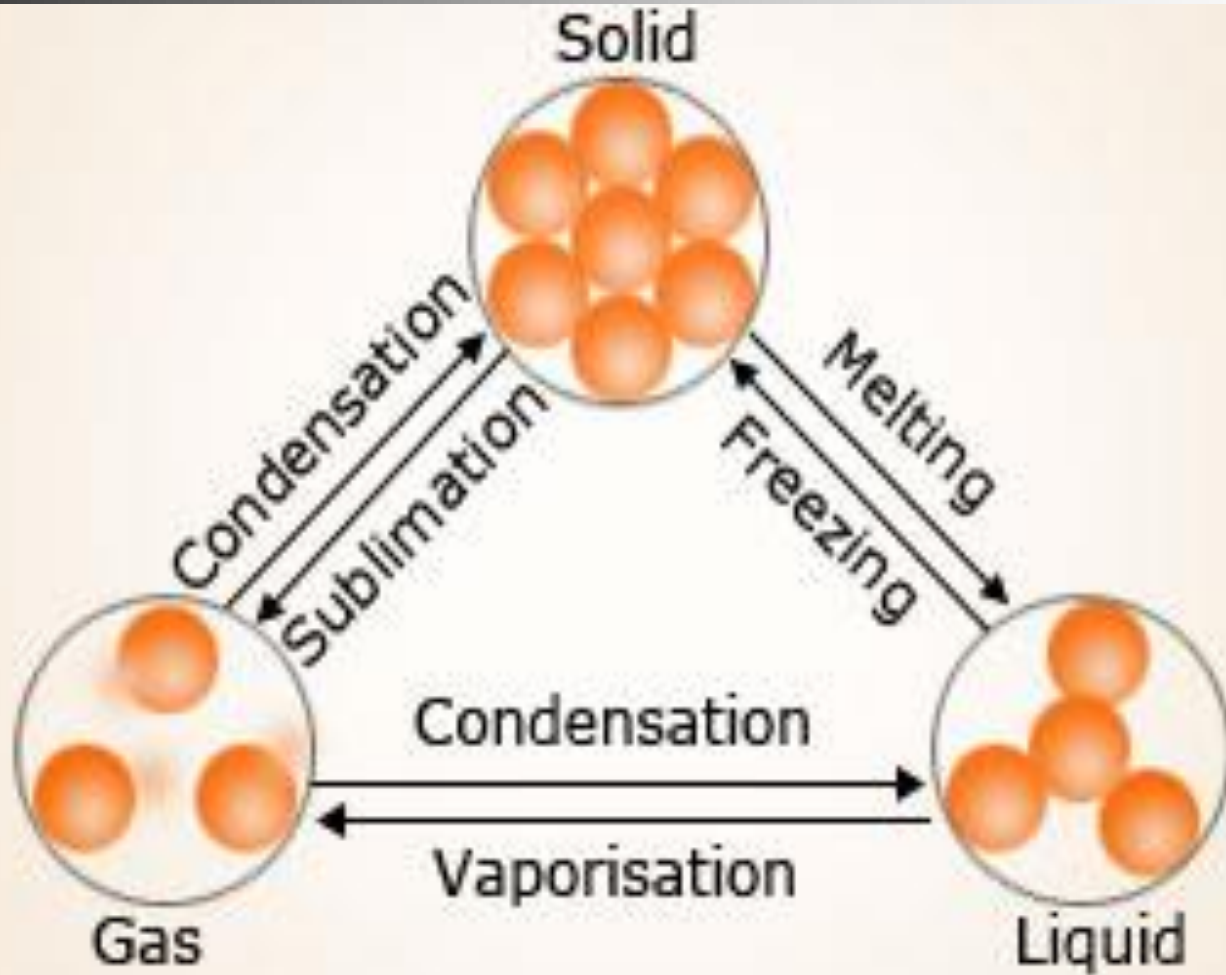
- *Van der Waals Forces*
- Keesom forces , Debye forces , London forces
- *Orbital Overlap*
- *Ion–Dipole and Ion-Induced Dipole Forces*
- *Ion–Ion Interactions*
- *Hydrogen Bonds*

State of Matter



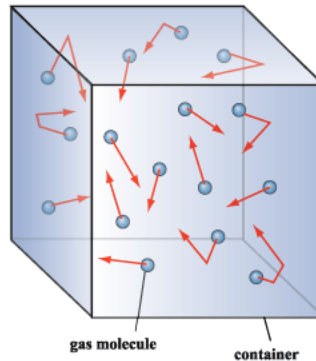
4 Liquid crystal

States of Matter



Gases

- The **intermolecular forces** of attraction in gases are virtually nonexistent at room temperature; gases display little or no ordering.
- Molecules in the gaseous state move in all directions, at high velocities until **collisions occur with other molecules and boundaries of the system** (e.g. the walls of a container holding the gas).



- This process is responsible for the **pressure** exhibited within the system.



Gases

- Hence, they **exert a *pressure*** —a force per unit area, expressed in dynes/cm² or in atmospheres or in millimeters of mercury (mmHg).
- Another important characteristic of a gas, its ***volume***, is usually expressed in liters or cubic centimeters (1 cm³ = 1 mL).
- The **temperature** involved in the gas equations is given according the **absolute or Kelvin scale**. Zero degrees on the centigrade scale is equal to 273.15 Kelvin (K).



Pharmaceutical gases include:

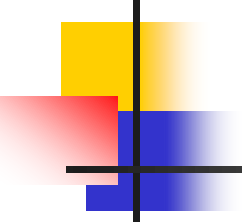
Anesthetic gases, such as nitrous oxide and halothane.

Compressed gases include oxygen for therapy; nitrogen, CO₂

Sterilization gases e.g. ethylene oxide

Aerosols:

The Ideal Gas Law:

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- **refers to an ideal situation where:**
 1. **no intermolecular interactions exist**
 2. **collisions are perfectly elastic, and thus**
 3. **no energy is exchanged upon collision.**

The Ideal Gas Law:

$$P \propto \frac{1}{V}$$

$$PV = k$$

$$V \propto T$$

$$V = kT$$

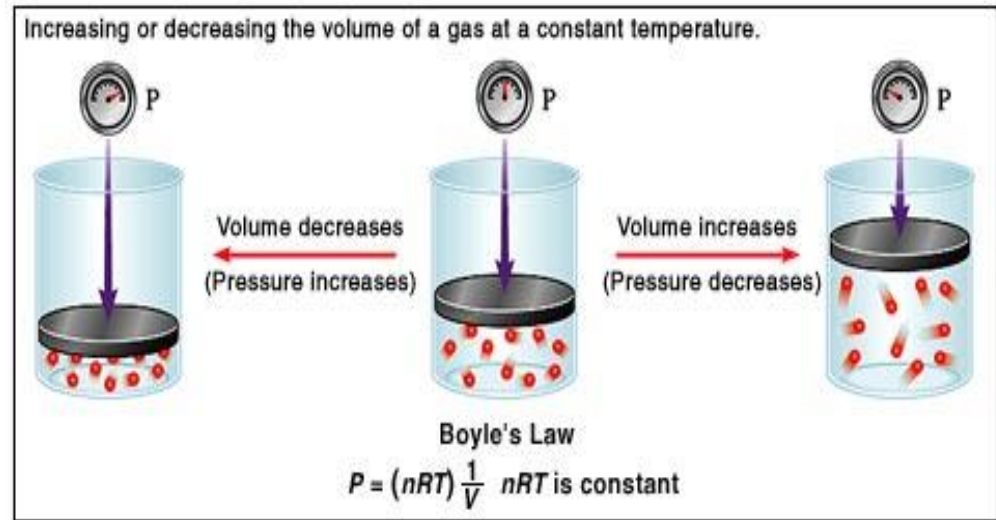
$$\frac{PV}{T} = k$$

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2}$$

(2-4)

PV/T under one set of conditions is equal to *PV/T* under another set

In equation (2-4), P_1 , V_1 , and T_1 are the values under one set of conditions and P_2 , V_2 , and T_2 the values under another set.





- 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 20°C** and a **pressure of 740 mm Hg**. **Assuming the gas is ideal**, what is the volume at 0°C and 760 mm Hg?

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2} \quad \longrightarrow \quad \frac{740 \times 30.0}{273 + 20} = \frac{760 \times V_2}{273}$$
$$V_2 = 27.2 \text{ mL}$$

- PV/T under one set of conditions is equal to PV/T under another set, and so on.
- the ratio PV/T is constant and can be expressed mathematically as

$$\frac{PV}{T} = R$$

$$PV = RT \quad (2-5)$$

- in which R is the constant value for the PV/T ratio of an ideal gas.
- This equation is correct only for 1 mole of gas.
- for n moles it becomes

$$PV = nRT \quad (2-6)$$

- known as the ***general ideal gas law***

The general Gas Law:

The volume (**V**), the pressure (**P**) and the absolute temperature (**T**) of a given gas are interrelated by the

general ideal gas law:

$$PV = n RT$$

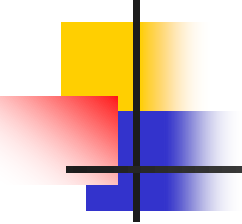
Where **n** is the number of moles of gas and **R** is the molar gas constant (0.082051 L . atm/mole. K)

- R is the molar gas constant
- If 1 mole of an ideal gas is chosen, its **volume** under standard conditions of temperature and pressure (i.e., at 0°C and 760 mm Hg) has been found by experiment to be 22.414 liters. Substituting this value in the equation

$$PV = nRT$$

$$1 \text{ atm} \times 22.414 \text{ liters} = 1 \text{ mole} \times R \times 273.16 \text{ K}$$

$$R = 0.08205 \text{ liter atm/mole K}$$



$$\begin{aligned}R &= 0.08205 \text{ liter atm/mole K} \\ &= 8.314 \times 10^6 \text{ erg/mole K} \\ &= 1.987 \text{ cal/mole deg}\end{aligned}$$

Example :

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

$$\begin{aligned} & (780 \text{ mm}/760 \text{ mm atm}^{-1}) \times V \\ &= 2 \text{ moles} \times (0.08205 \text{ liter atm/mole deg}) \times 298 \text{ K} \\ & V = 47.65 \text{ liters} \end{aligned}$$


- The approximate **molecular weight of a gas** can be determined by use of the ideal gas law

$$PV = nRT \quad (2-6)$$

$$PV = \frac{g}{M}RT \quad (2-7)$$

$$M = \frac{gRT}{PV} \quad (2-8)$$

- ***g* is the number of grams of gas and *M* is the molecular weight.**

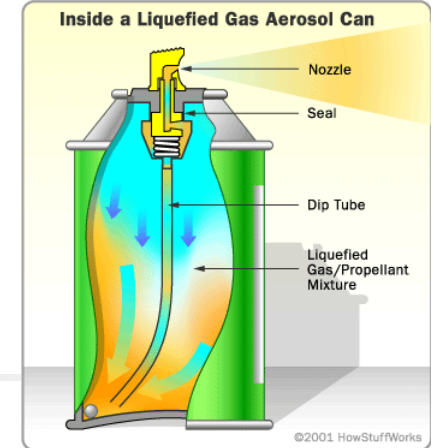


■ Example :

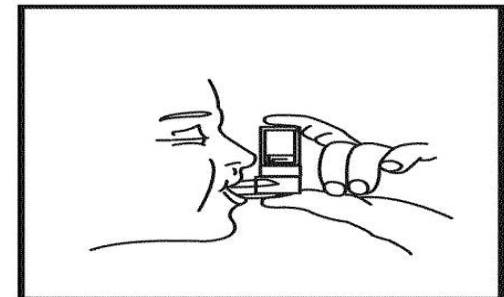
- If 0.30 g of ethyl alcohol in the vapor state occupies 200 mL at a pressure of 1 atm and a temperature of 100°C, what is the molecular weight of ethyl alcohol? Assume that the vapor behaves as an ideal gas.

$$M = \frac{gRT}{PV} \longrightarrow M = \frac{0.30 \times 0.082 \times 373}{1 \times 0.2}$$
$$M = 46.0 \text{ g/mole}$$

Aerosols:




- **Gases can be liquefied under high pressures** in a closed chamber as long as the chamber is maintained below the critical temperature.
- **When the pressure is reduced, the molecules expand and the liquid reverts to a gas.**
- **In 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 conditions.**
- **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.**



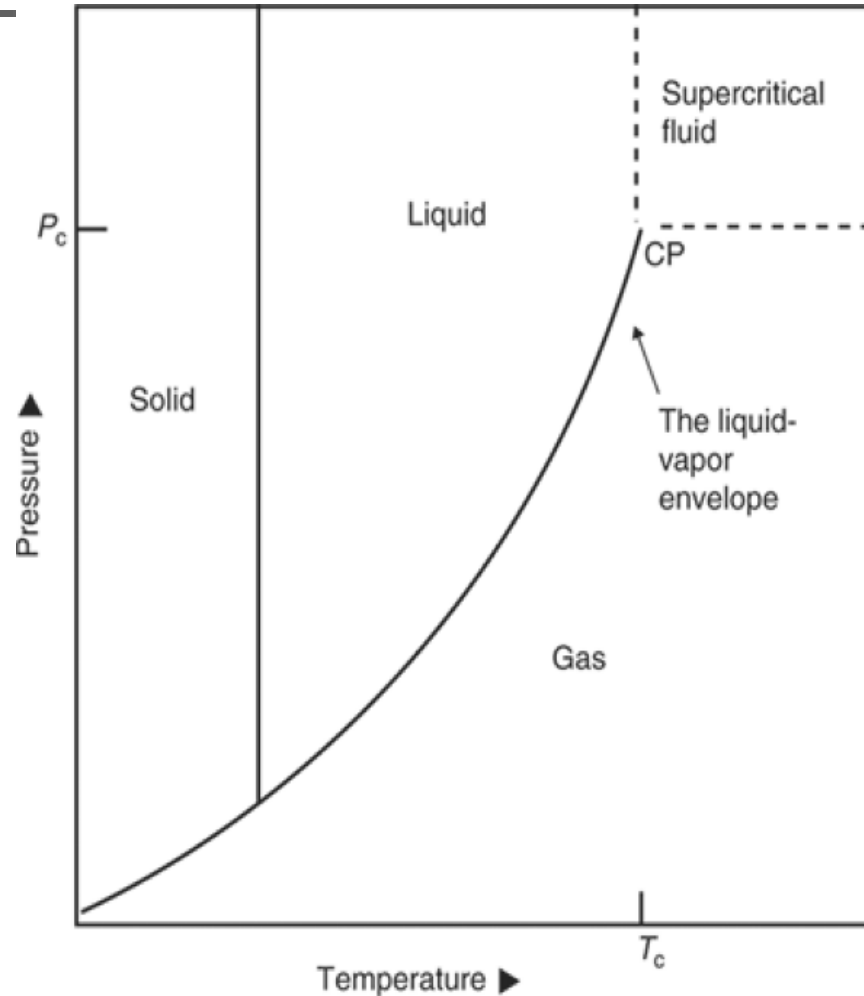


Liquefaction of Gases:

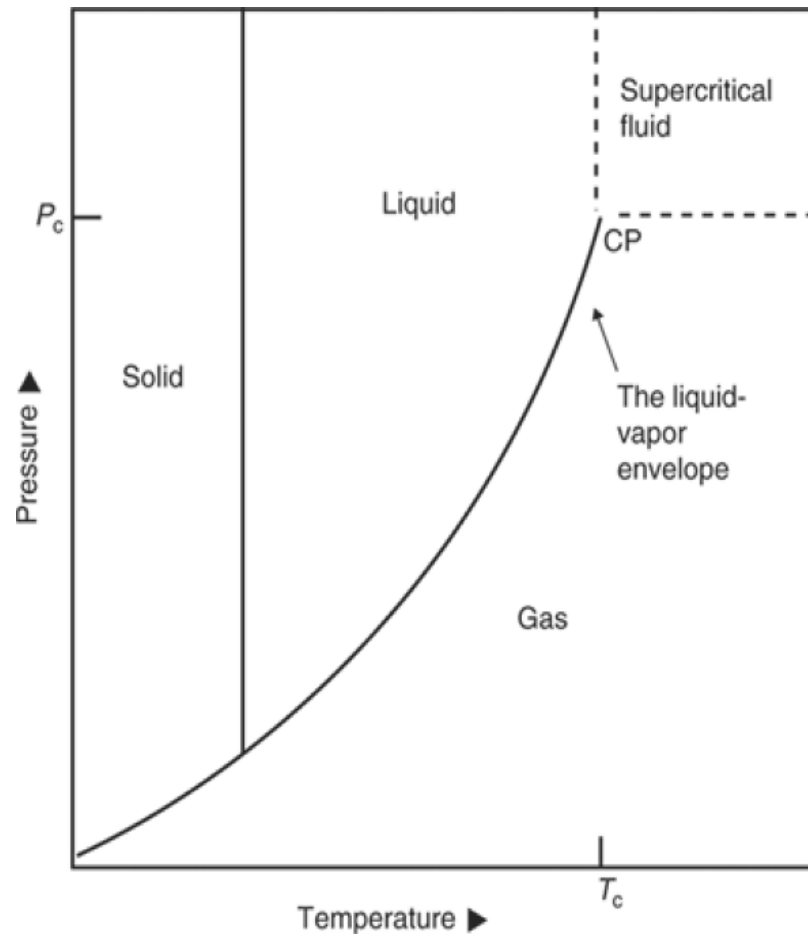
- When a **gas is cooled**, it loses some of its kinetic energy in the form of heat, and the velocity of the molecules decreases.
- If **pressure is applied to the gas**, the molecules are brought within the sphere of the van der Waals interaction forces and pass into the liquid state.
- Because of these 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.

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- **If the temperature is elevated sufficiently, a value is reached above which it is impossible to liquefy a gas irrespective of the pressure applied.**
 - **This temperature, above which a liquid can no longer exist, is known as the *critical temperature*.**
 - **The pressure required to liquefy a gas at its critical temperature is the *critical pressure*.**
 - **The critical temperature of water is 374°C, or 647 K, and its critical pressure is 218 atm.**

The Critical temperature of water is 374°C, or 647 K, and its critical pressure is 218 atm.

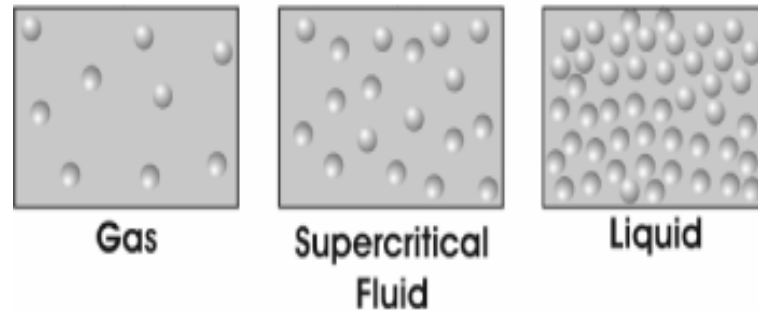


The Supercritical Fluid State



The Supercritical Fluid State

- A *supercritical fluid* is a **mesophase** from of the gaseous state where the gas is held under a combination of temperatures and pressures that **exceed** the *critical point* of a substance



- Supercritical fluids can be formed by many normal gases such as carbon dioxide.
- Supercritical fluids have **properties** that are intermediate between those of liquids and gases, **having better ability to permeate solid substances (gas like)** and **having high densities that can be regulated by pressure (liquid like)**.

ability to dissolve compounds





The Supercritical Fluid State

- Briefly, a gas that is brought above its *critical temperature* T_c will **still behave as a gas irrespective of the applied pressure**;
- **As the pressure is raised higher, the density of the gas can increase without a significant increase in the viscosity while the ability of the supercritical fluid to dissolve compounds also increases.**
- **A gas that may have little to no ability to dissolve a compound under ambient conditions can completely dissolve the compound under high pressure in the supercritical range.**

Common uses for supercritical fluids

- Extraction.
- Crystallization.
- Preparation of formulations (polymer mixtures, the formation of **micro- and nanoparticles**).
- Decaffeination of coffee.

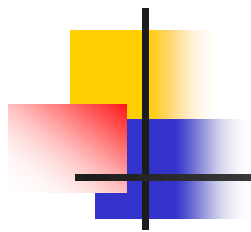


Crystallization



Carbon dioxide Super critical fluid

- The critical temperature of CO₂ is 31.1°C, and its critical pressure is 73.8 atm.
- Used in decaffeination and crystallization to give totally pure crystals without solvent residue



Liquids

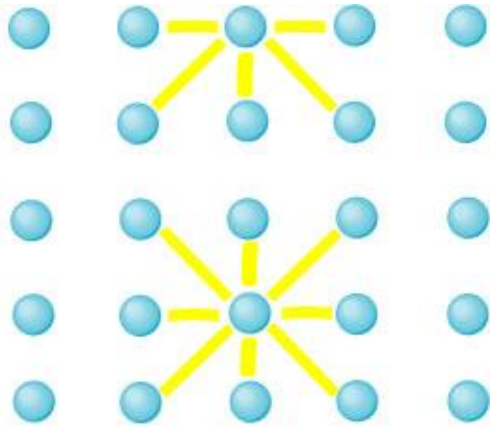


Liquids

The intermolecular force of attraction in liquids (Van der Waals forces) are sufficient to impose some ordering or regular arrangement among the molecules.

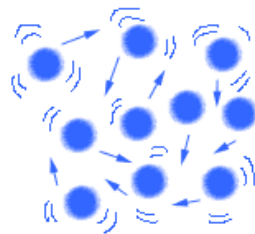
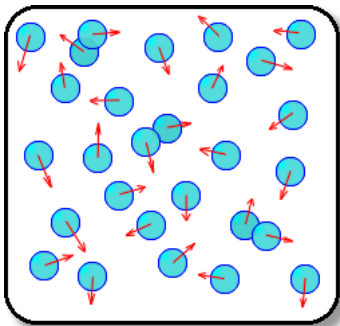
- Hydrogen bonding, when it occurs, increases the cohesion in liquids and further affects their physico-chemical behavior.
- However, these forces are much weaker than covalent or ionic forces (Solids). Thus, liquids, in general, tend to display short-range rather than long-range order.

- Although molecules of a liquid would tend to aggregate in localized clusters, **no defined structuring** would be evident.



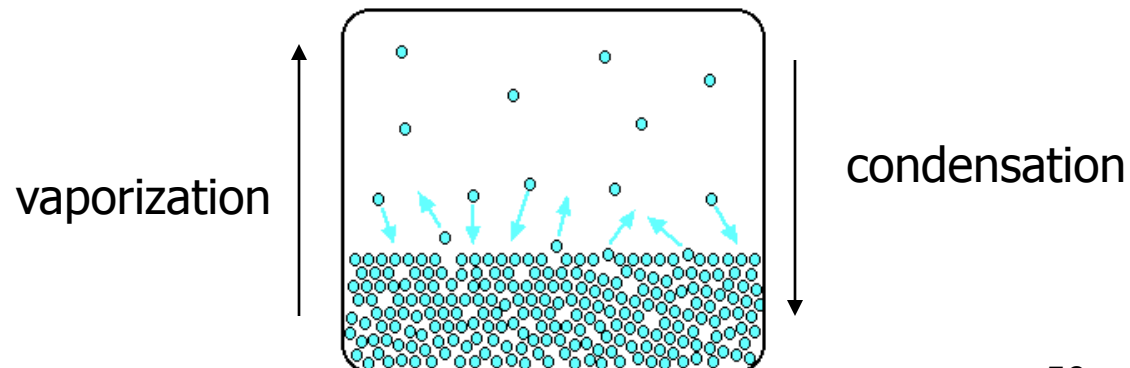
**Forces of attraction
between liquid molecules**

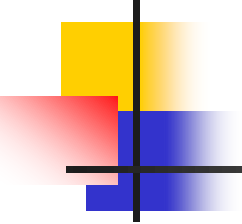
Movement of liquid molecules



Vapor Pressure of Liquids

- **Translational energy of motion (kinetic energy)** is not distributed evenly among liquid molecules; 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**, and some of the **molecules subsequently return to the liquid state, or condense**.




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- When the rate of condensation equals the rate of vaporization at a definite temperature, the vapor becomes saturated and a dynamic equilibrium is established.
 - The pressure of the saturated vapor above the liquid is known as the *equilibrium vapor pressure*.

- 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.

- if the temperature of the liquid is increased while the pressure is held constant,  vaporization

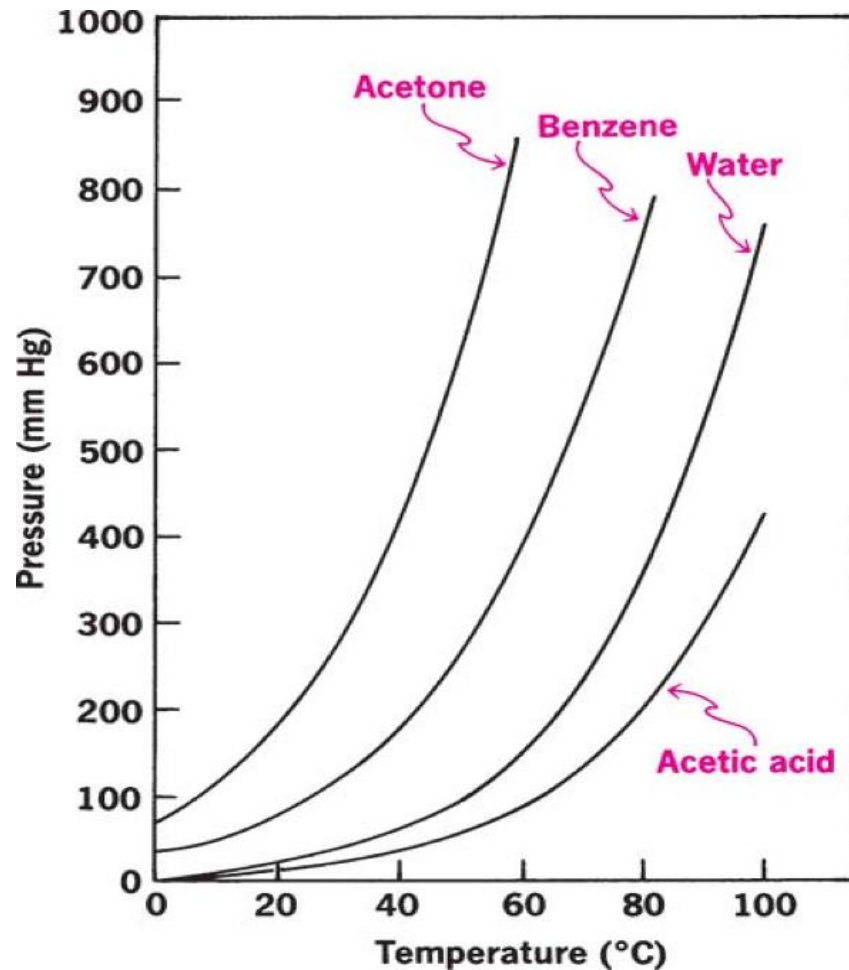
- or if the pressure is decreased while the temperature is held constant,  condensation

all the liquid will pass into the vapor state.



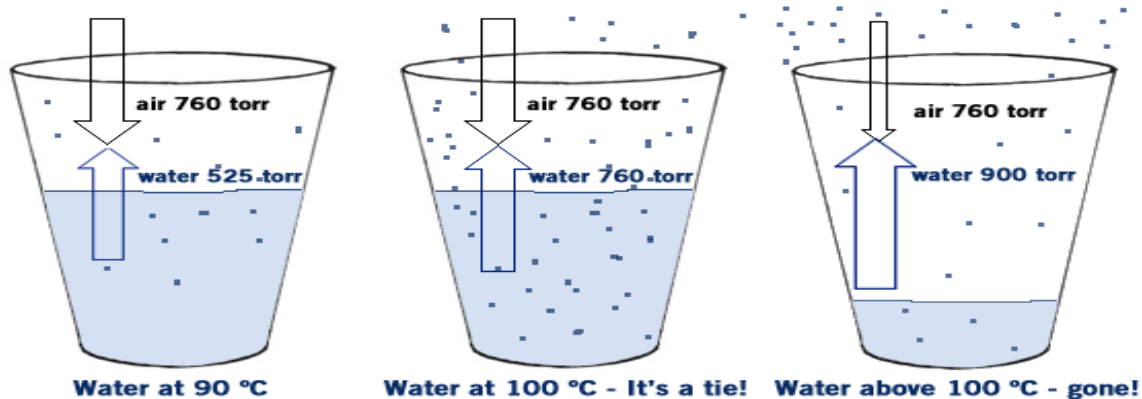
vapor pressure increases

The variation of the vapor pressure of some liquids with temperature.



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.
- The temperature at which the vapor pressure of the liquid equals the external or atmospheric pressure is known as the *boiling point*.





Boiling Point

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

Steam have temperatures higher than boiling water

- 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.




Latent Heats of Vaporization:

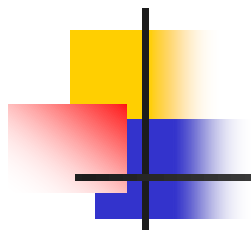
- the heat that is absorbed when water vaporizes at the normal boiling point
- the heat of vaporization for water at 100°C is 539 cal/g or about 9720 cal/mole.
- For benzene, the heat of vaporization is 91.4 cal/g at the normal boiling point of 80.2°C.

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

- **Nonpolar substances, have low boiling points and low heats of vaporization (the molecules are held together predominantly by the London force) .**
- **Polar molecules, such as ethyl alcohol and water, which are associated through hydrogen bonds, exhibit high boiling points and high heats of vaporization.**
- **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.**
- **Branching of the chain produces a less compact molecule with reduced intermolecular attraction, and a decrease in the boiling point results.**
- **The boiling points of straight-chain primary alcohols and carboxylic acids increase about 18°C for each additional methylene group.**



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
<u>Isobutane</u>	-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



Crystalline Solids

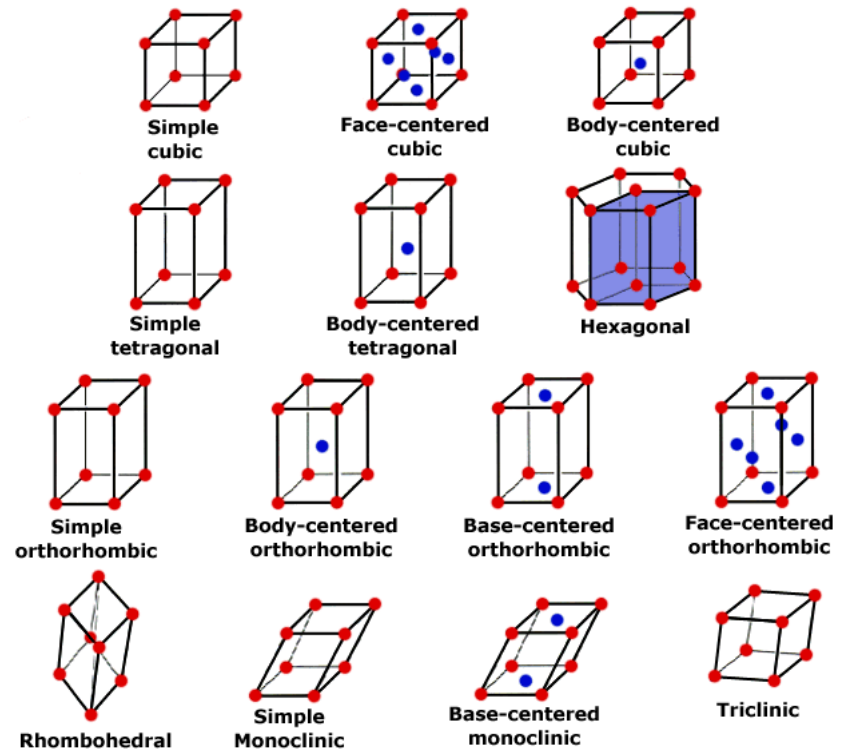


Solids and the Crystalline State

- The structural units of crystalline solids, such as ice, sodium chloride, and menthol, are arranged in fixed geometric patterns or lattices.
- Crystalline solids have definite shapes and an orderly arrangement of units.
- Crystalline solids show definite melting points, passing from the solid to the liquid state

The various crystal forms are divided into six distinct crystal systems based on symmetry:

- cubic (sodium chloride),
- tetragonal (urea),
- hexagonal (iodoform),
- rhombic (iodine),
- monoclinic (sucrose),
- triclinic (boric acid).

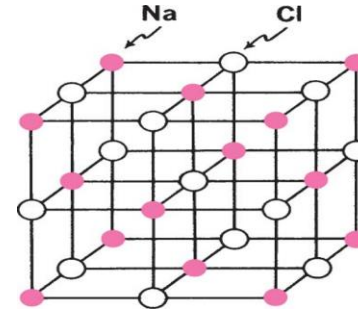


- 
- The units that constitute the crystal structure can be atoms, molecules, or ions
-

- The morphology of a crystalline form is often referred to as its *habit*,

- the crystal habit is defined as having the same structure but different outward appearance (or alternately, the collection of faces and their area ratios comprising the crystal).

- 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.**



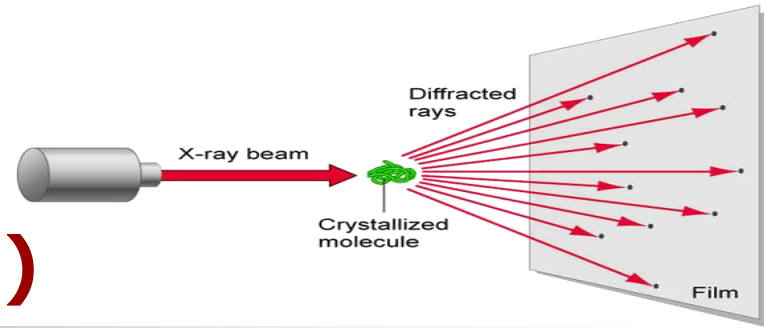
- In **diamond and graphite**, the lattice units consist of **atoms** held together by **covalent bonds**.
- Solid carbon dioxide, hydrogen chloride, and naphthalene form crystals composed of **molecules** as the building units.
- **ionic and atomic crystals** in general are **hard and non brittle** and **have high melting points**
- **molecular crystals** are **soft and have relatively low melting points.**



Characterization of Crystalline Materials:

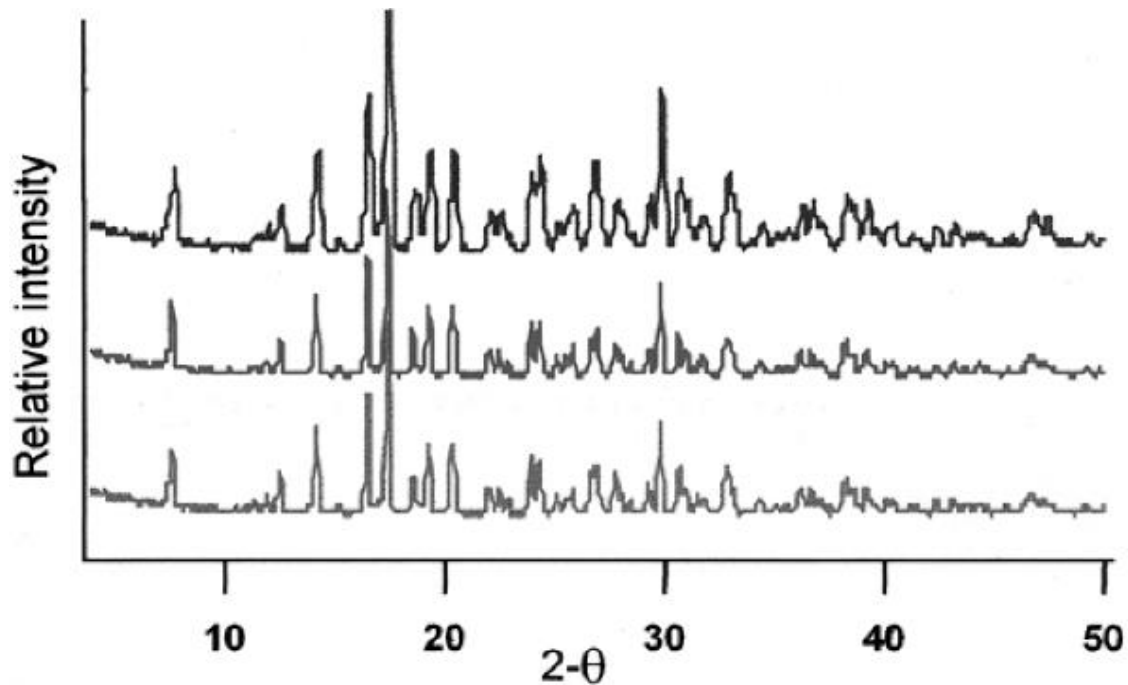
- a. X-Ray Diffraction (birefringent property)**
- b. Melting Point and Heat of Fusion**
- c. Polymorphism**

X-Ray Diffraction (birefringent property)



- X-rays are diffracted by the electrons surrounding the individual atoms in the molecules of the crystals.
- By such a method the structure of a crystal may be investigated.
- Two polymorphs will provide two distinct powder x-ray diffraction patterns.
- The presence of a solvate will also influence the powder x-ray diffraction pattern because the solvate will have its own unique crystal structure.

Powder x-ray diffraction patterns for spirapril hydrochloride



b. Melting Point and Heat of Fusion

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.**

In practice, it is taken as the temperature of the equilibrium mixture at an **external pressure of 1 atm.**

heat of fusion

- The heat absorbed when a gram of a solid melts or the heat liberated when it freezes is known as **the latent heat of fusion.**
- The **heat of fusion may be considered as** the heat required in increasing the interatomic or intermolecular distances in crystals, thus allowing melting to occur.
- A crystal that is bound together by weak forces has a low heat of fusion and a low melting point and vice versa.



The *latent heat of fusion*

- The heat (energy) absorbed when 1 g of a solid melts or the heat liberated when it freezes is known as the *latent heat of fusion*, and for **water** at 0°C it is about 80 cal/g (1436 cal/mole).



Why The Water Latent heat of vaporization (539 cal/g) greater than Its Latent heat of fusion (80 cal/g)

different intermolecular forces are involved in holding the crystalline solid together and that the addition of heat to melt the crystal is actually the addition of energy.

Substance	Melting Point (K)	Molar Heat of Fusion, ΔH_f (cal/mole)
H ₂ O	273.15	1440
H ₂ S	187.61	568
NH ₃	195.3	1424
PH ₃	139.4	268
CH ₄	90.5	226
C ₂ H ₆	90	683
<i>n</i> -C ₃ H ₈	85.5	842
C ₆ H ₆	278.5	2348
C ₁₀ H ₈	353.2	4550

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


$$\frac{\Delta T}{\Delta P} = T \frac{V_l - V_s}{\Delta H_f} \quad (2-18)$$

- V_l and V_s are the molar volumes of the liquid and solid, respectively.
- Molar volume (volume in units of cm^3/mole) is computed by dividing the gram molecular weight by the density of the compound.
- ΔH_f is the molar heat of fusion: 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

- **Example:**
- **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**
- **The density of ice is 0.9167 g/cm³**
- **ΔH_f For water (6025x10⁷ dynes cm/mole)**
- **V_L = the molar volume of water is 18.018 cm³/mole**
- **V_s = the molar volume of ice is 19.651 cm³/mole**

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

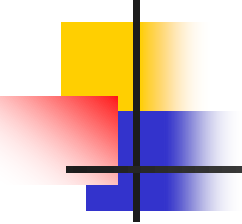
$$\frac{\Delta T}{\Delta P} = -0.0075 \text{ deg/atm}$$



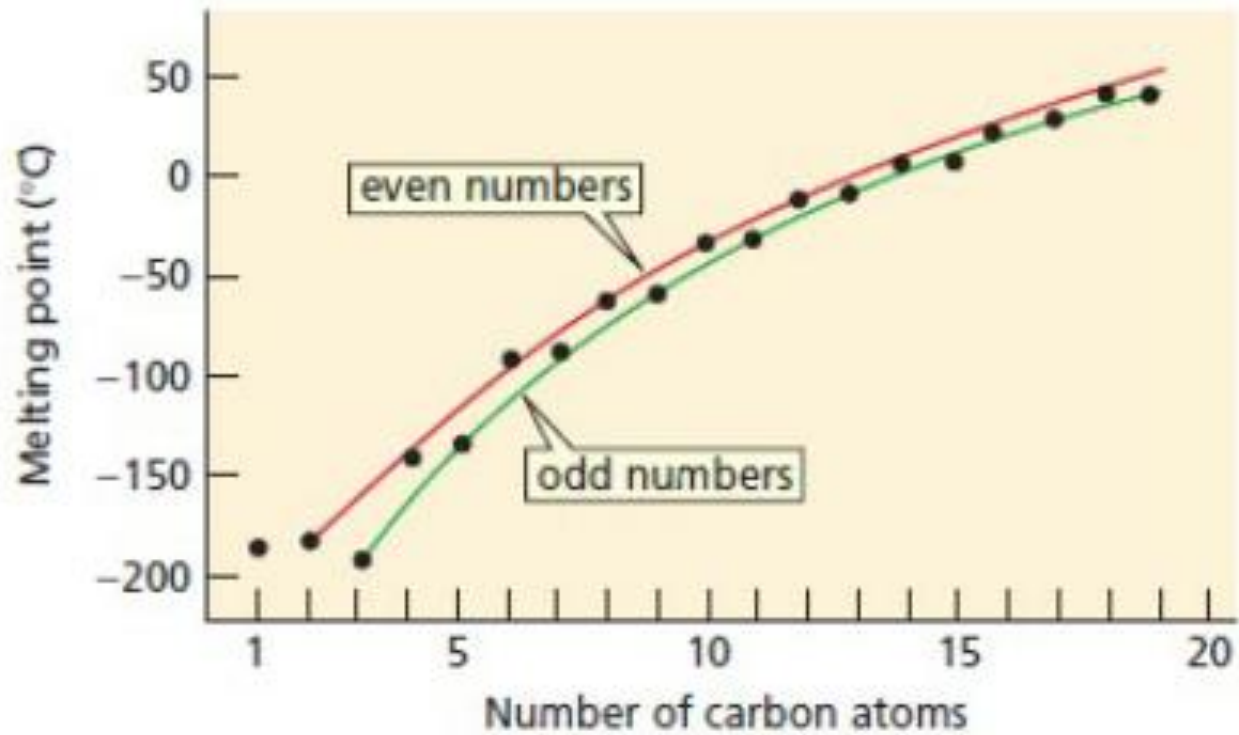


Melting Point and Intermolecular Forces

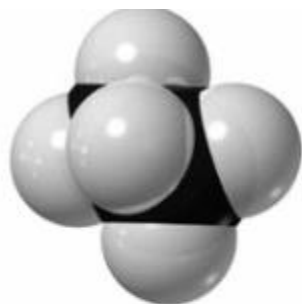
- A crystal that is bound together by **weak forces** generally has a **low heat of fusion** and a **low melting point**, whereas one bound together by **strong forces** has a **high heat of fusion** and a **high melting point**.
- Because **polymorphic forms represent different molecular arrangements** leading to different crystalline forms of the same compound, it is obvious that different intermolecular forces will account for these different forms.

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- Then consider polymorph A, which is held together by higher attractive forces than is polymorph B.
 - It is obvious that more heat will be required to break down the attractive forces in polymorph A, and thus its melting temperature will be higher than that of polymorph B.

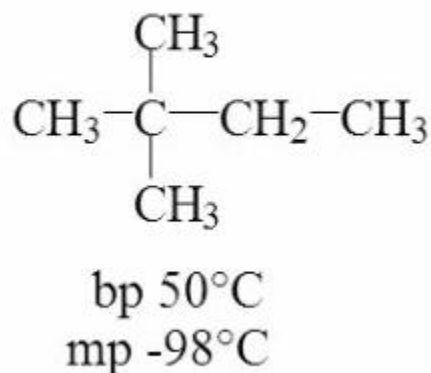
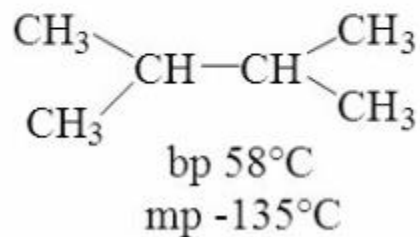
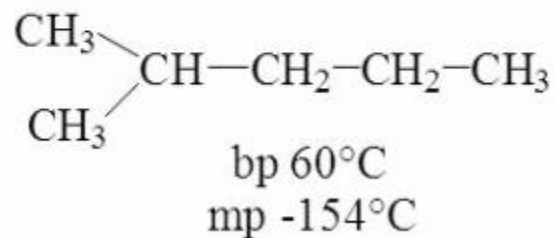
- The melting points of normal saturated hydrocarbons increase with molecular weight because the van der Waals forces between the molecules of the crystal become greater with an increasing number of carbon atoms.
- The melting points of the alkanes with an even number of carbon atoms are higher than those of the hydrocarbons with an odd number of carbon atoms, because alkanes with an odd number of carbon atoms are packed in the crystal less efficiently.

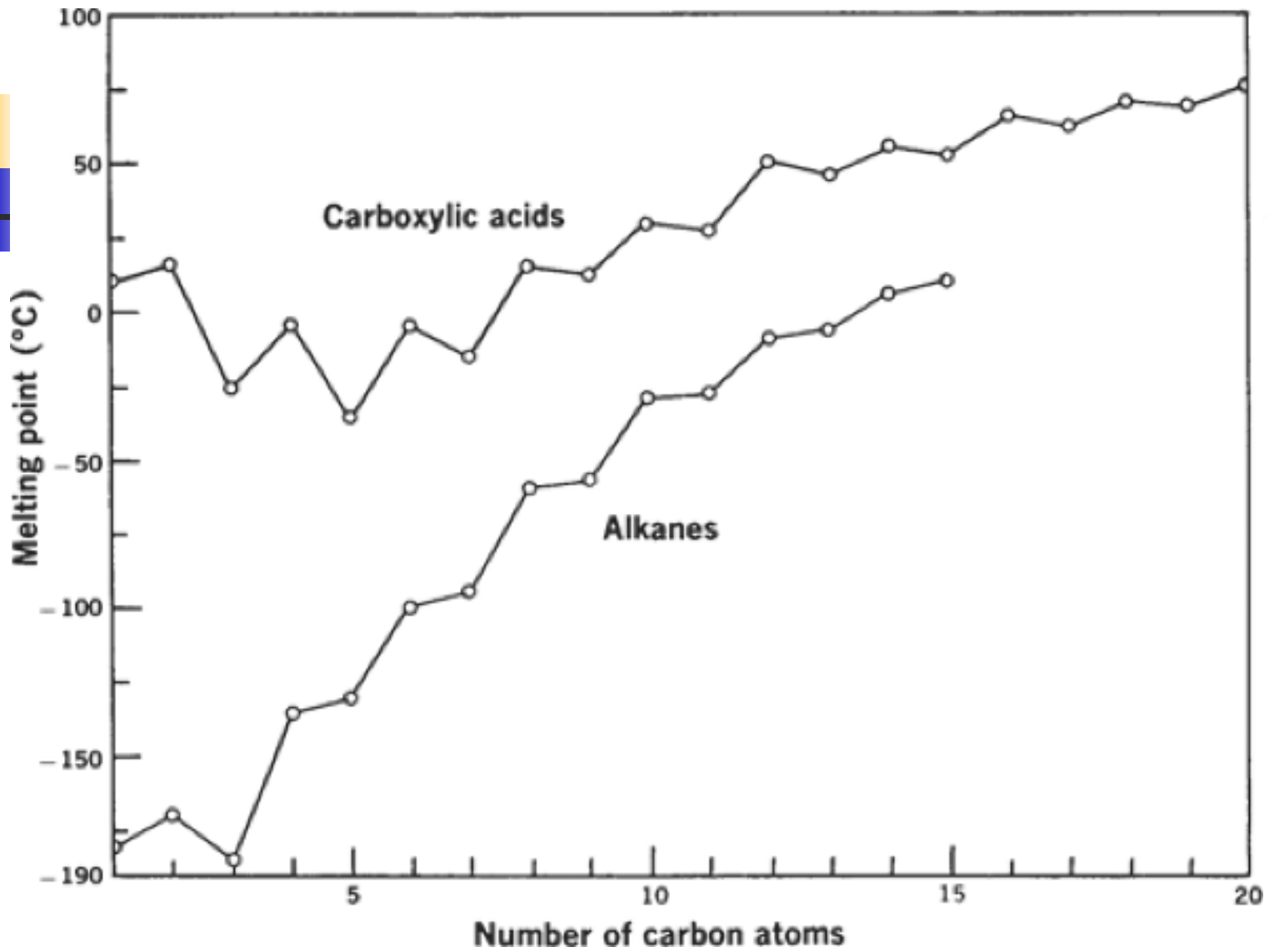


Branched Alkanes



- Lower b.p. with increased branching
- Higher m.p. with increased branching
- Examples:







Polymorphism

- Some substances, such as **carbon or sulfur**, may exist in more than one crystalline form (polymorphs) .
- Polymorphs are chemically identical.
- Polymorphs have different:
 1. **stabilities** and may spontaneously convert from the **metastable form** (unstable weak Polymorph) at a temperature to the stable form.
 2. **melting points**.
 3. **x-ray crystal and diffraction patterns**
 4. **solubility**



Polymorphism

- The formation of polymorphs of a compound may **depend upon several variables** pertaining to the crystallization process, including:
 1. **solvent differences** (the packing of a crystal might be different from a **polar** versus a **nonpolar** solvent).
 2. **impurities** that may favor a **metastable polymorph** because of specific inhibition of growth patterns;



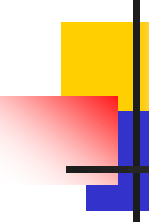
Polymorphism

3. the level of supersaturation from which the material is crystallized (generally the higher the concentration above the solubility, the more chance a metastable form is seen).
4. the temperature at which the crystallization is carried out.



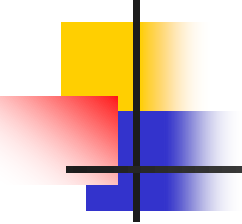
Examples of polymorphism

- Diamond (*metastable*) and graphite.
- all long-chain organic compounds exhibit polymorphism as fatty acids.
- Spiperone.
- haloperidol.
- sulfonamides
- Theobroma oil, or cacao butter, is a polymorphous natural fat.



Nearly all long-chain organic compounds exhibit polymorphism. In fatty acids, this results from different types of attachment between the carboxyl groups of adjacent molecules.

- Theobroma oil, or cacao butter, is a polymorphous natural fat. it consists mainly of a single glyceride.
- Theobroma oil is capable of existing in four polymorphic forms:
 - 1.the unstable gamma form, melting at 18°C.
 - 2.the alpha form, melting at 22°C.
 - 3.the beta prime form, melting at 28°C.
 - 4.the stable beta form, melting at 34.5°C.

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- 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.



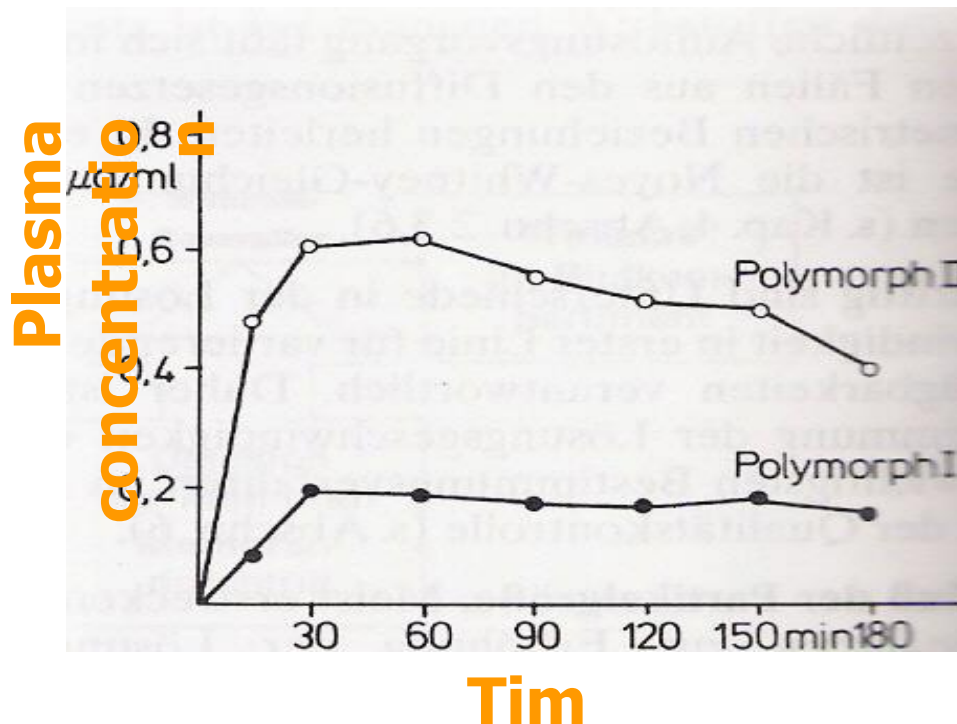
Polymorphism and solubility


- 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.

Polymorphism has achieved significance in recent years due to fact that different polymorphs exhibit different solubilities. As result, one polymorph may be more active therapeutically than another polymorph of the same drug.

EXAMPLE

The plasma concentration of 2 polymorphic forms of tetracyclin



- 
- Polymorphism can also be a factor in suspension technology.
 - Cortisone acetate exists in at least five different forms, four of which are unstable in the presence of water and change to a stable form.
 - Because this transformation is usually accompanied by appreciable caking of the crystals, these should all be in the form of the stable polymorph before the suspension is prepared.



Solvates

- Because many pharmaceutical solids are often synthesized by standard organic chemical methods, purified, and then crystallized out of different solvents, residual solvents can be trapped in the crystalline lattice.
- This creates a co-crystal termed a *solvate*.

Pseudopolymorphism (solvates)

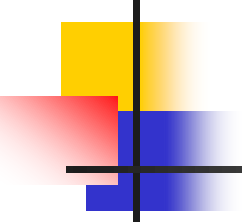


Amorphous Solids

- Amorphous (without shape) solid may be considered as supercooled liquid in which the **molecules are arranged in a random manner** somewhat as in the liquid state. Substances, such as glass and many synthetic plastics, are **amorphous solids**.

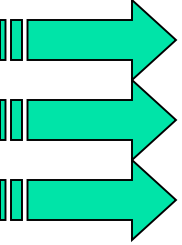
They differ from crystalline solid in that:

- ★ they flow when subjected to sufficient pressure for some time
- ★ they do not have definite melting points.

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- 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 usual observation whether a substance is crystalline or amorphous.

- **Beeswax and paraffin**, although they appear to be amorphous, assume crystalline arrangements when heated then cooled slowly.
- **Petrolatum** contains both crystalline and amorphous constituents.
- Some amorphous materials, such as **glass**, may crystallize after long standing.

- 
- Being amorphous or crystalline has been shown to affect the therapeutic activity of the drug. Thus, the crystalline form of the antibiotic **novobiocin acid** is poorly absorbed and had no activity, whereas the amorphous form is readily absorbed and therapeutically active.



The Liquid Crystalline State

A fourth state of matter is the liquid crystalline state or **mesophase**. Materials in this state are in many ways intermediate between the liquid and solid states.

- Materials in *liquid crystalline* state are intermediate between the liquid and solid states.


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

- 1. *Smectic* state** (soap like or grease like):

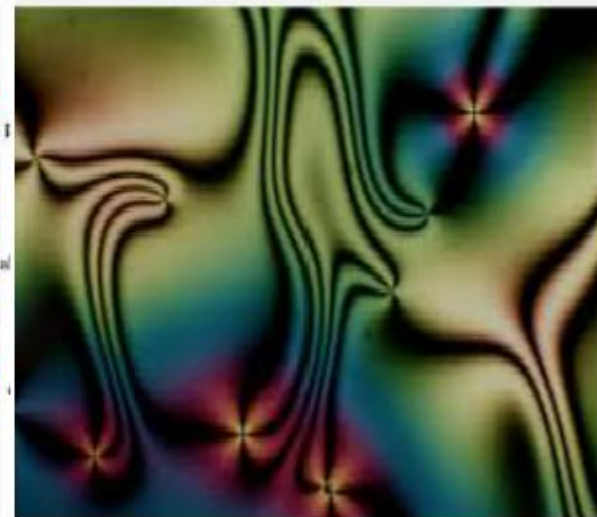
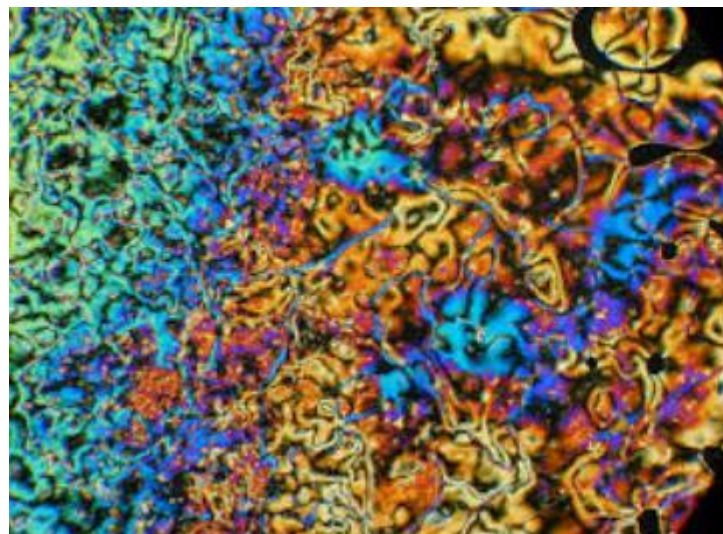
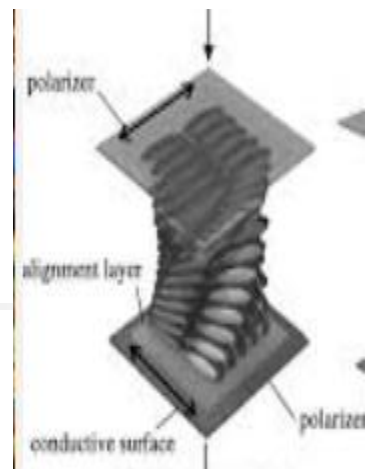
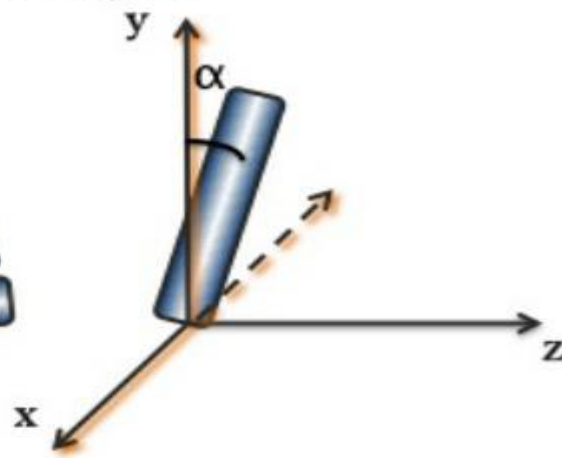
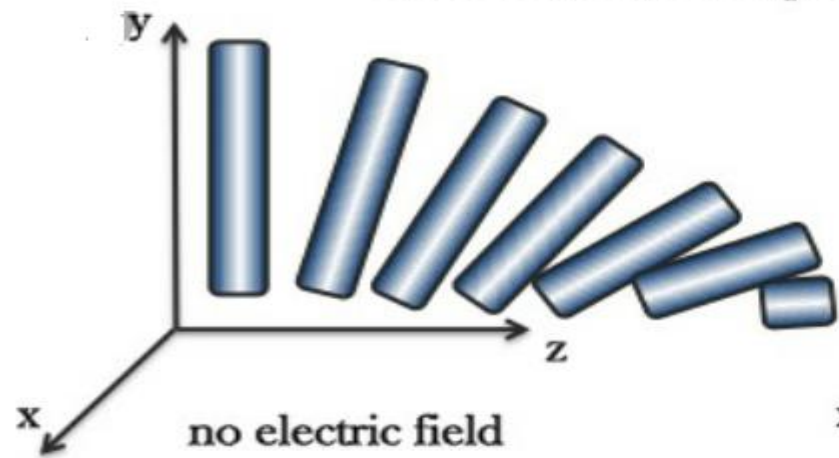
- molecules are mobile in two directions and can rotate about one axis

- 2. *Nematic* state** (threadlike):

- the molecules rotate only about one axis but are mobile in three dimensions

- 
- The smectic mesophase is of most pharmaceutical significance because it is this phase that **usually forms in ternary mixtures** containing a surfactant, water, and a weakly amphiphilic or nonpolar additive.
 - In general, molecules that form mesophases:
 1. are **organic**,
 2. are **elongated and rectilinear** in shape,
 3. are **rigid**, and
 4. possess **strong dipoles** and **easily polarizable groups**.

Twisted Nematic Liquid Crystal





The liquid crystalline state may result either from:

1. The heating of solids (thermotropic liquid crystals)
2. The action of certain solvents on solids (lyotropic liquid crystals).



Properties and Significance of Liquid Crystals

Properties and Significance of Liquid Crystals

Liquid crystals have some of the properties of liquids and some of solids.

⇒ Liquid crystals are mobile and thus can be considered to have the **flow properties of liquids**.

⇒ At the same time they possess the property of being **birefringent, a property associated with crystals**.

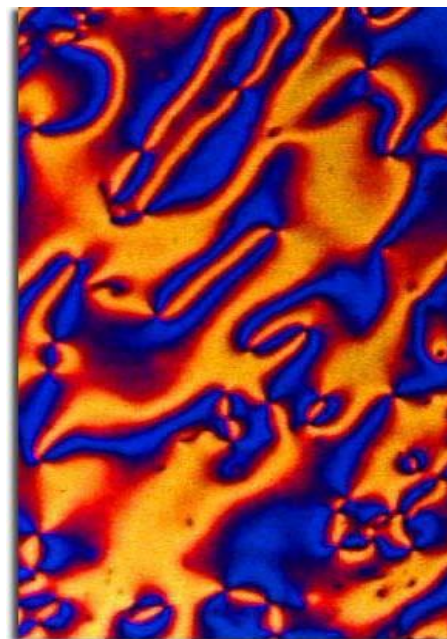
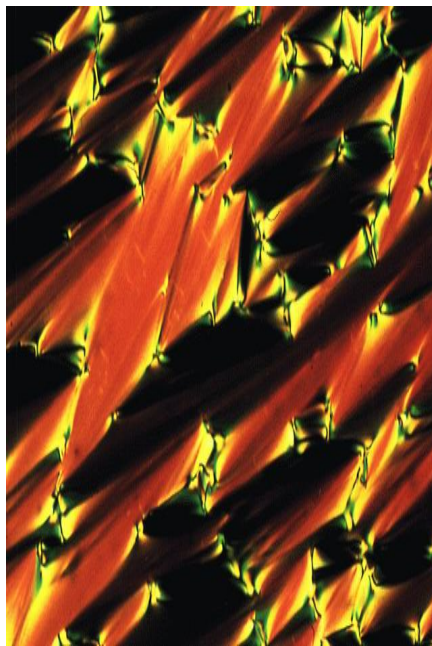
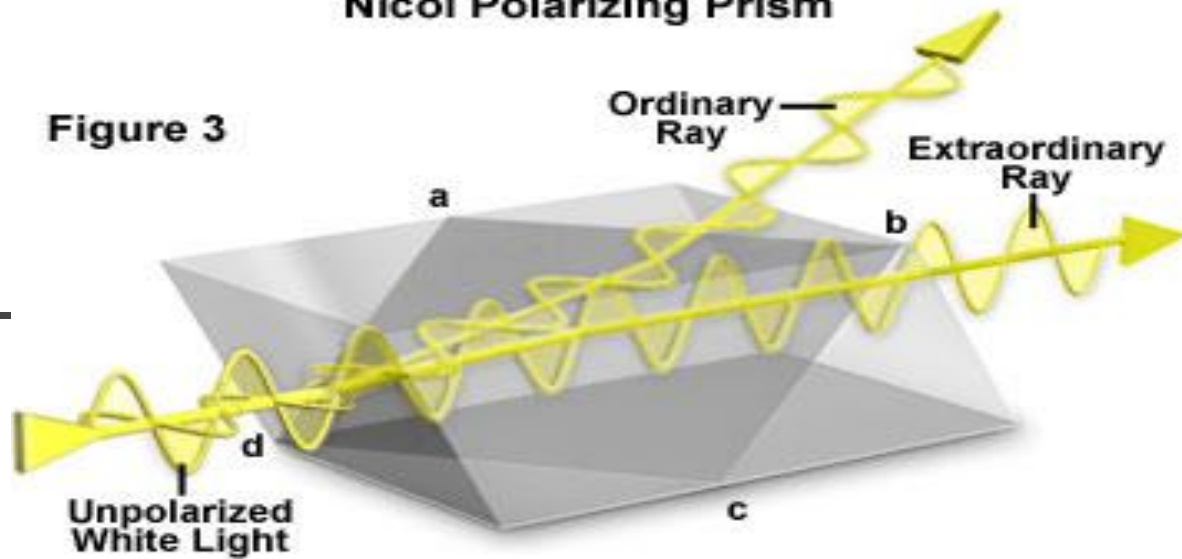


Significance of Liquid Crystals

- **Some liquid crystals show consistent color changes with temperature**
- **Some liquid crystals may be sensitive to electric fields, a property used in developing display systems.**
- **The smectic mesophase has application in the Solublization of water-insoluble materials.**
- **It also appears that liquid crystalline phases of this type are frequently present in emulsions and may be responsible for enhanced physical stability owing to their highly viscous nature.**

Nicol Polarizing Prism

Figure 3







Thermal Analysis

- Methods for characterizing physical and chemical changes alterations upon heating or cooling a sample of the material.

- Types of thermal analysis :
 1. Differential Scanning Calorimetry (DSC)
 2. Differential thermal analysis (DTA).
 3. Thermogravimetric analysis (TGA).
 4. Thermomechanical analysis (TMA).

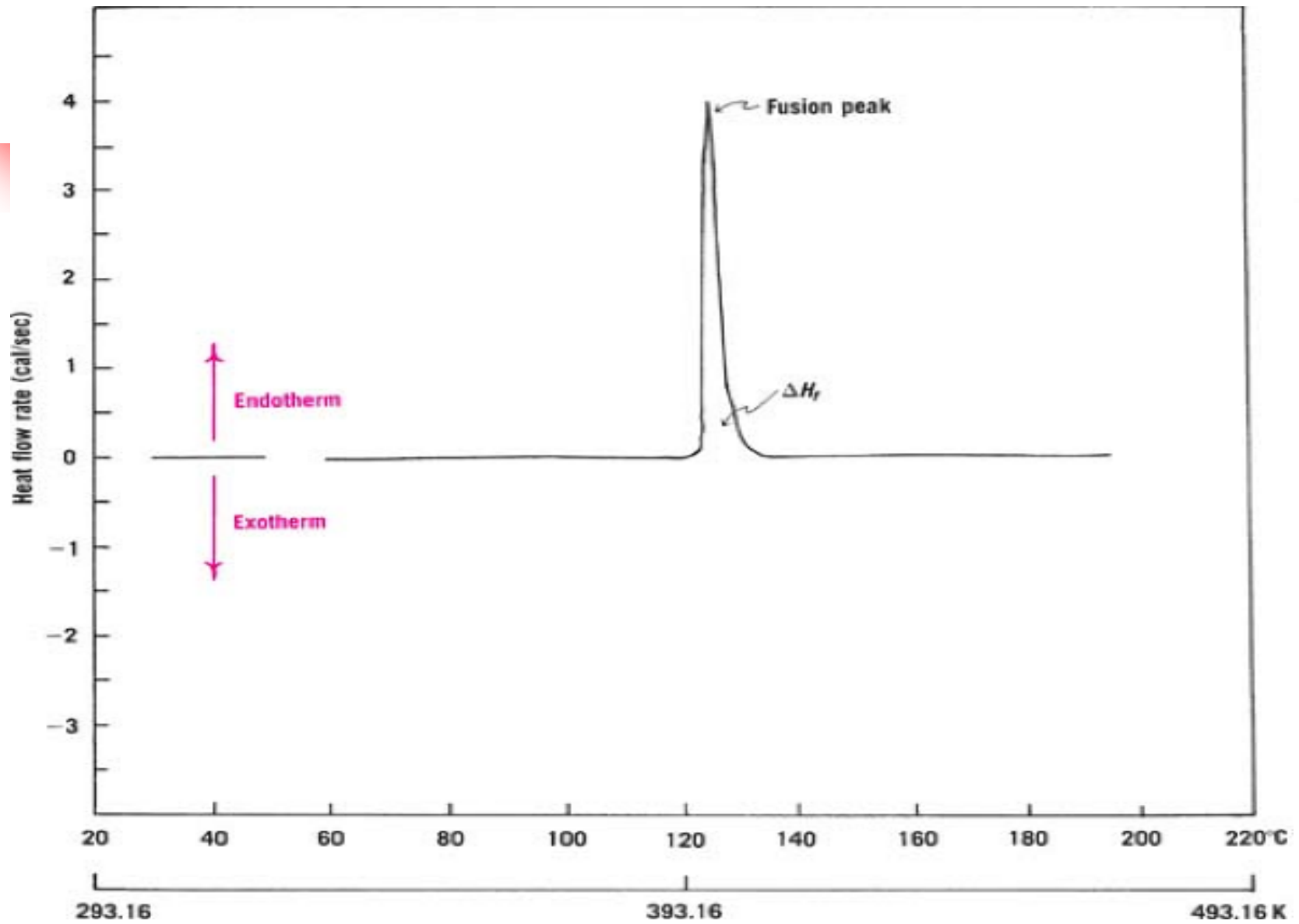
Differential Scanning Calorimetry

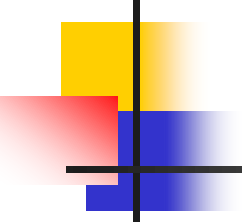




Differential Scanning Calorimetry

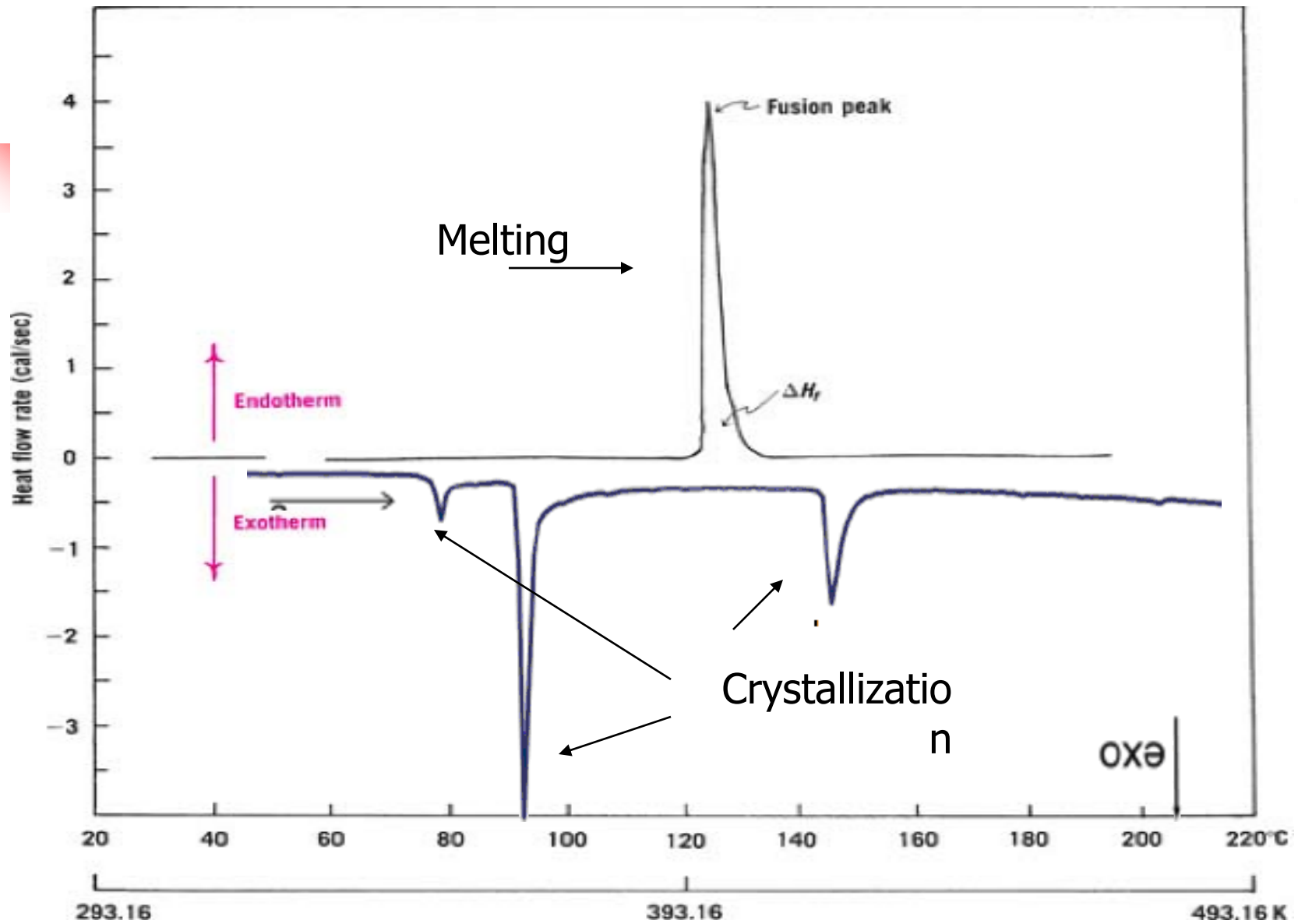
- **heat flows and temperatures are measured that relate to thermal transitions in materials.**
- **a sample and a reference material are placed in separate pans and the temperature of each pan is increased or decreased at a predetermined rate.**
- **When the sample, for example, benzoic acid, reaches its melting point, in this case 122.4°C, it remains at this temperature until all the material has passed into the liquid state because of the endothermic process of melting.**

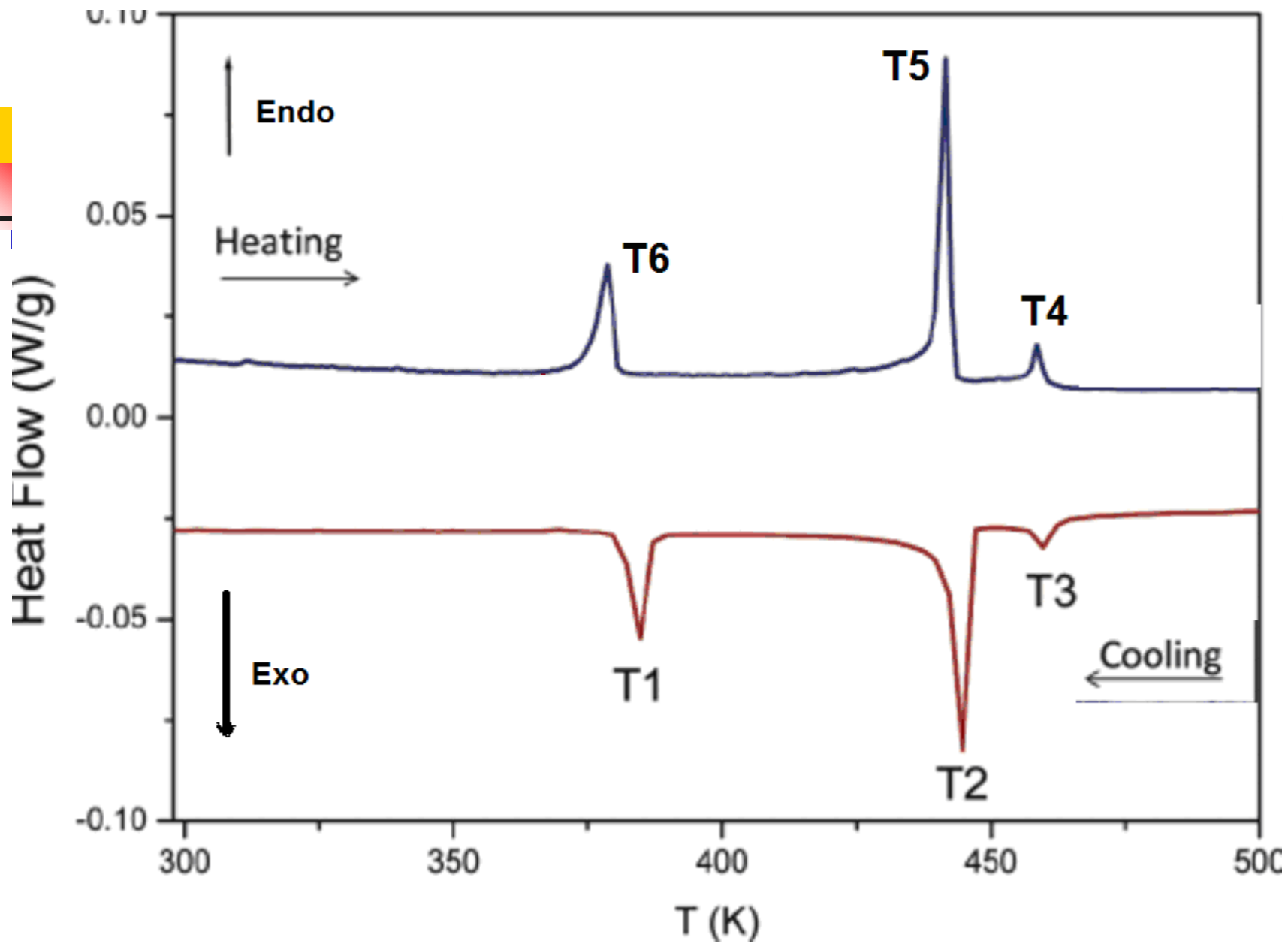


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- endothermic reaction on a DSC arises from:
 1. Desolvations.
 2. Melting.
 3. Glass transitions.

Glass transitions = The transition of amorphous materials from a hard state into a molten or rubber-like state

- exothermic reaction measured by DSC:
 1. Decomposition.
 2. Crystallization.







Differential scanning calorimetry is used in:

1. **standardization of the lyophilization process.**
2. **Crystal changes and eutectic formation in the frozen state.**
3. **Detection of amorphous character.**
4. **establish identity and purity.**
5. **obtain heat capacities and heats of fusion and capacities.**
6. **constructing phase diagrams to study the polymorphs**