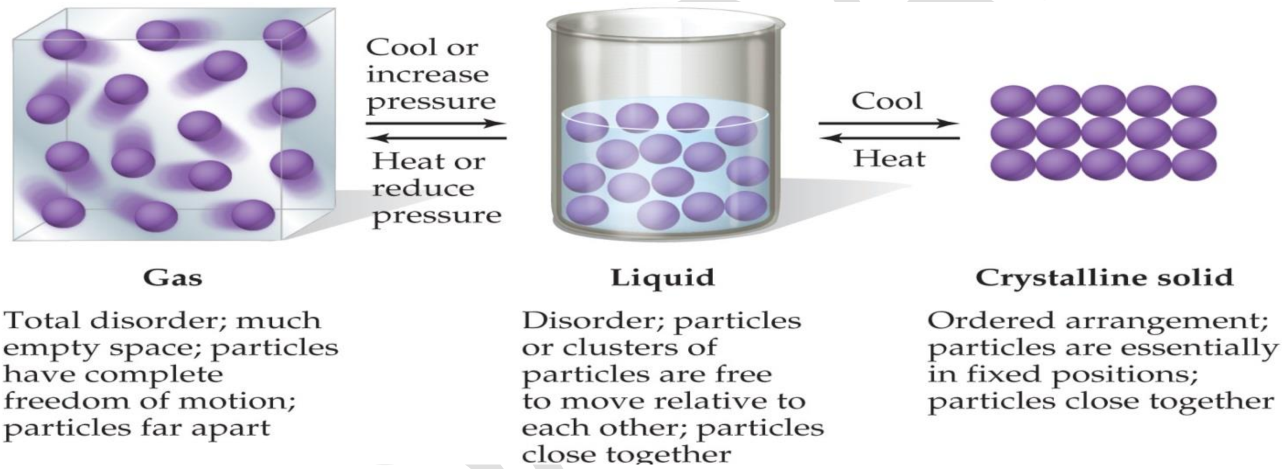
INTRODUCTION TO PHYSICAL PHARMACY

Physical pharmacy provides critical information on pharmaceutical formulations, such as physicochemical principles of dosage forms, principle of drug delivery of dosage forms, and principle of dosage form stability and drug degradation.

States of Matter

The Three States of Matter 1. Gas 2. Liquid 3. Solid

In order for molecules to exist as aggregates in gases, liquids and solids Intermolecular forces must exist

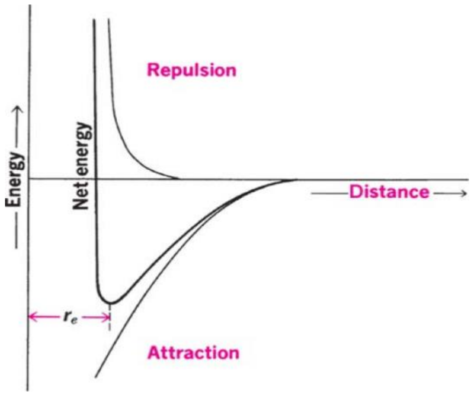


Binding forces between molecules

- **1) Attraction**
- **A) Intermolecular force divided to Adhesion and cohesion**
- **B) Intramolecular force**
- **2) Repulsion**

Repulsive and Attractive Forces

As two atoms or molecules are brought closer together, the opposite charges and binding forces in the two molecules are closer together than the similar charges and forces, *causing* the molecules to attract one another.The negatively charged electron clouds of molecules largely govern the balance (equilibrium) forces between the two moleculesWhen the molecules are brought so close that the outer charge clouds touch, they repel each other like rigid elastic bodies



Intermolecular forces may be attractive or repulsive.

Johannes D van der Waals, Dutch, was the first to postulate intermolecular forces in developing a theory to account for properties of real gases

Intermolecular forces

Intermolecular forces are attractive forces **between** molecules

Intramolecular forces hold atoms together in a molecule

Intermolecular vs Intramolecular

- 41 kJ to vaporize 1 mole of water (**inter**)
- 930 kJ to break all O-H bonds in 1 mole of water (**intra**)

Measure of intermolecular force

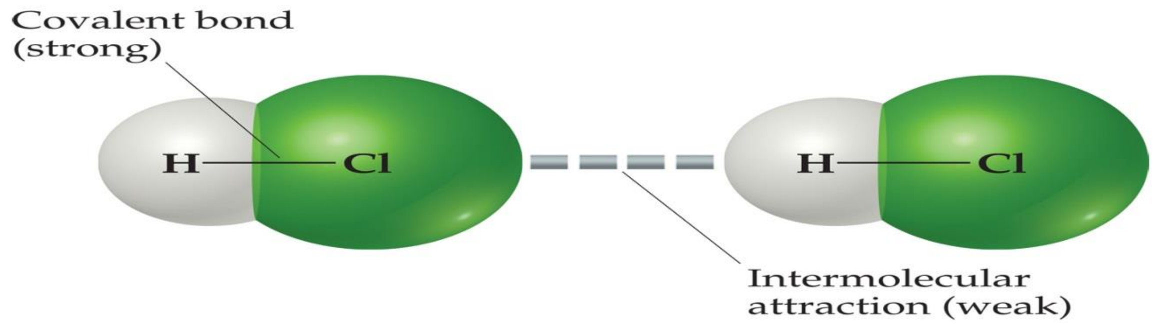
boiling point

melting point

ΔH_{vap}

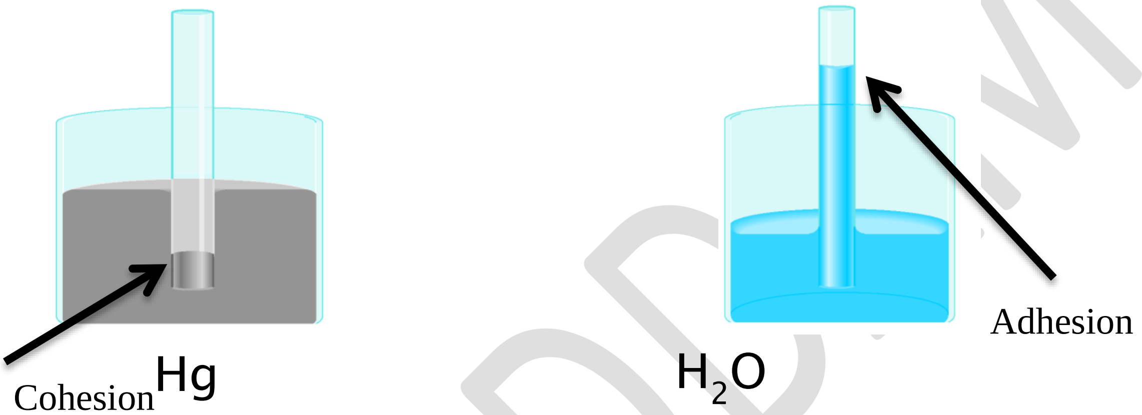
ΔH_{fus}

- Generally, **inter**molecular forces are much weaker than **intra**molecular forces.
    - **Repulsion forces:** is the reaction between two molecules that force them apart.
    - **Attractive forces:** are necessary for molecules to cohere, whereas repulsive forces act to prevent the molecules from interpenetrating and destroying each other.
    - The attractions between molecules are not nearly as strong as the intramolecular attractions that hold compounds together.



Cohesion: is the intermolecular attraction between **like** molecules (same type).

Adhesion: is an attraction between **unlike** molecules (different substances).



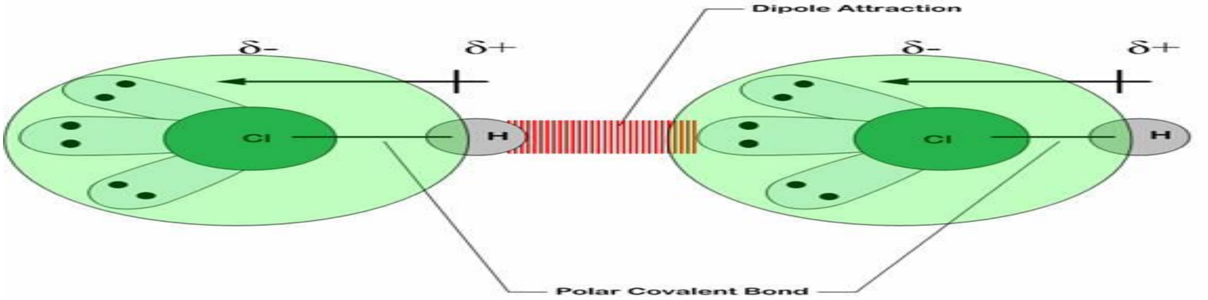
Types of attractive Intermolecular Forces

- Keesom forces (Dipole-dipole)
- Dipole-induced dipole
-
- Dispersion (London forces)

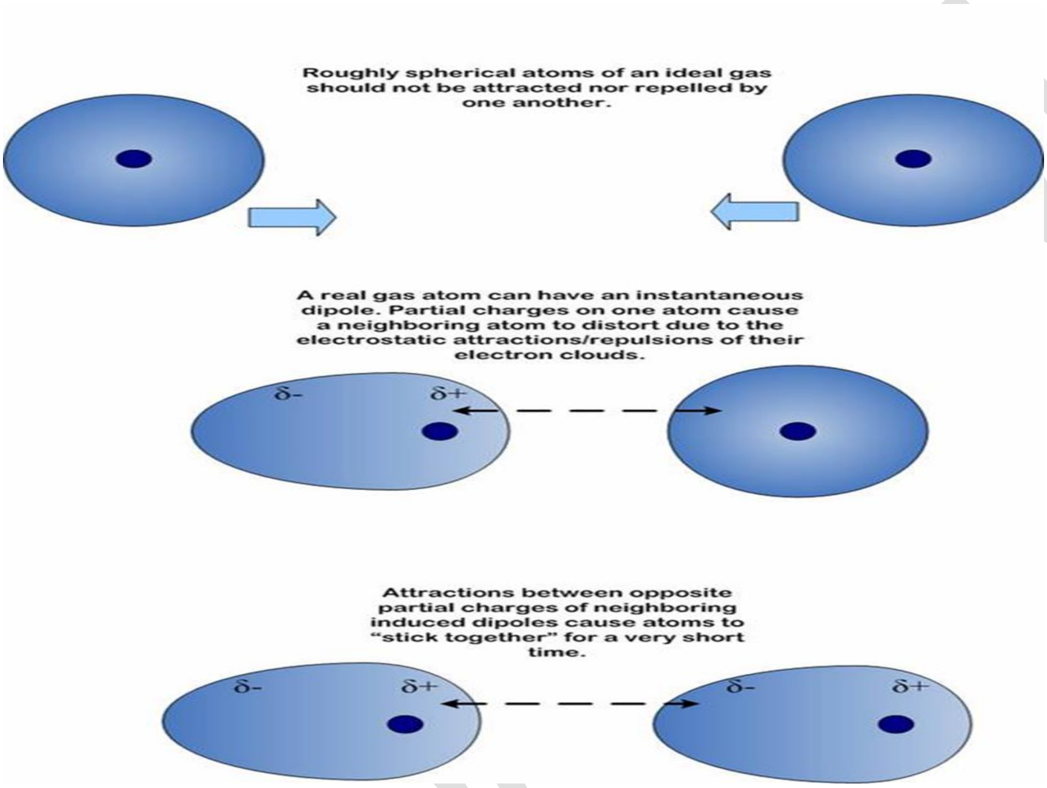
Van der Waals forces

- **Ion - induced dipole interaction**
- **Ion - dipole interactions**
- **Hydrogen bonding**

Depending on the phase of a substance, the nature of Chemical bonds, and the type of element present, more than one type of inter. can be present between the molecules

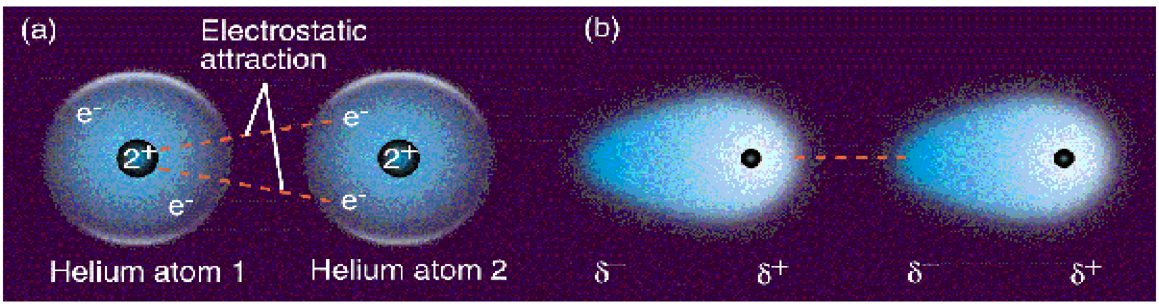


Induced dipole-induced dipole (London)



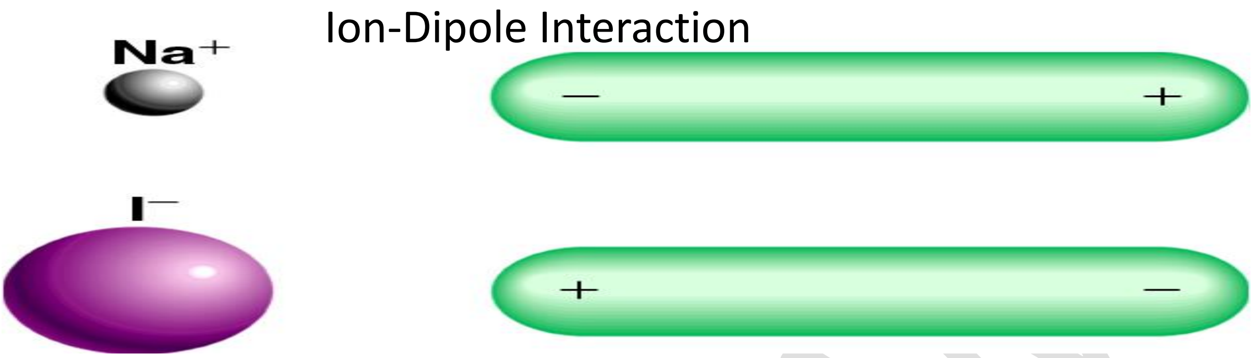
London Forces (Dispersion Forces)

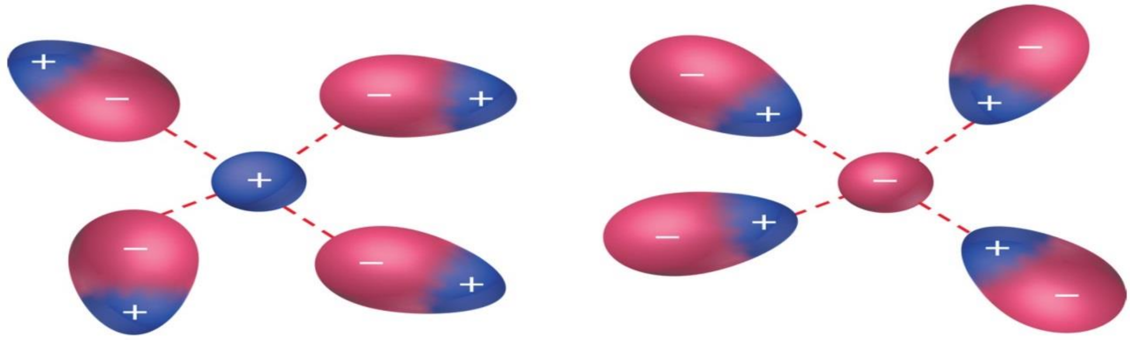
These arise from temporary variations in electron density in atoms and molecules. At any instant , the electron distribution may be unsymmetrical and hence produce an instantaneous dipole. This can cause an induced transient dipole in the neighboring molecule and cause the molecules to be attracted.



Ion-Dipole Forces

Attractive forces between an ion and a polar molecule, this type of interaction account in part for the solubility of ionic crystalline substances in water (like sodium chloride.



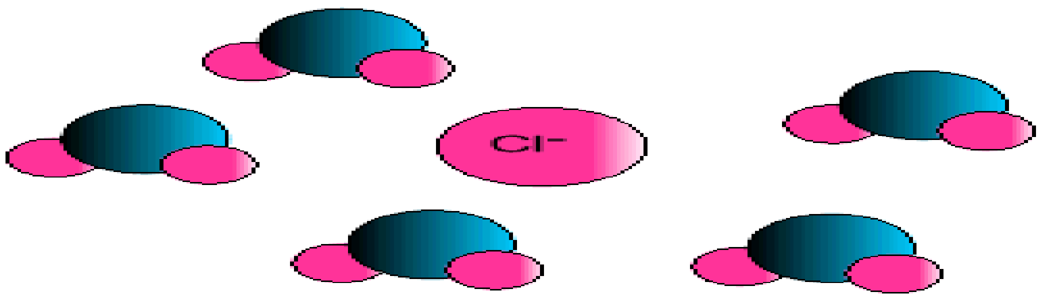


Cation-dipole attractions   Anion-dipole attractions

Ion –dipole Interactions

These interactions depend on

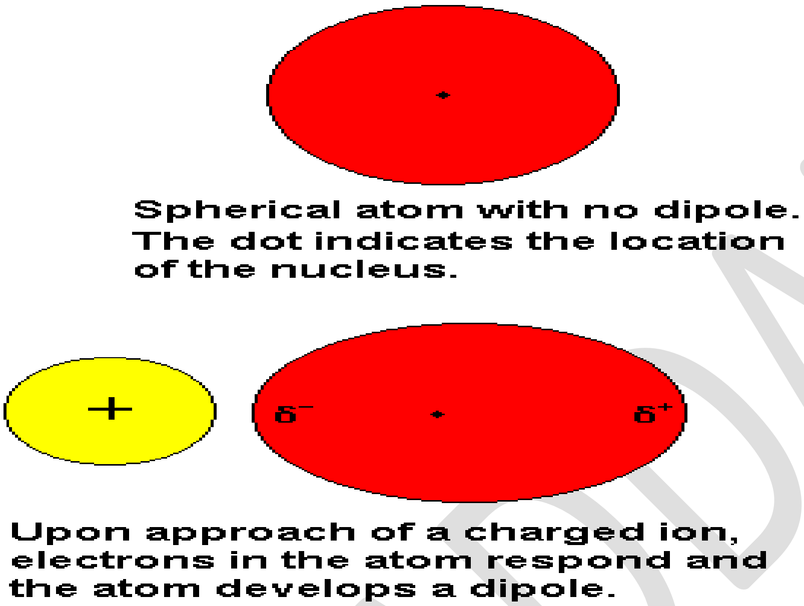
- Charge and size of ion
- Magnitude of dipole moment of polar molecule
- Size of polar molecule



Ion-Induced dipole Forces

Attractive forces between an ion and a polar molecule. Ion-induced dipole forces are involved in the formation of Iodide complexes (preparation of aqueous solution)

$I_2 + K^+I^- \rightleftharpoons KI^-_3$



Hydrogen bond

The interaction between a molecule containing a hydrogen atom and a strongly electronegative atom such as fluorine, oxygen, or nitrogen. Because of 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.

- Hydrogen bonding arises in part from the high electronegativity of nitrogen, oxygen, and fluorine.
- Also, when hydrogen is bonded to one of those very electronegative elements, the hydrogen nucleus is exposed. It is an electrostatic force of attraction that exists between covalently bonded hydrogen atom of one molecule and the electronegative atom of another molecule.

- It is represented by a dotted line - - - - - -
- Hydrogen bond is a electrostatic force of attraction existing between polar hydrogen (δ+) and electronegative atom(δ-) of dipoles.
- The hydrogen bond is weaker than the covalent bond, but relatively strong compared to van der Waals' force.
- Hydrogen bonding is a unique type of intermolecular molecular attraction. There are two requirements.

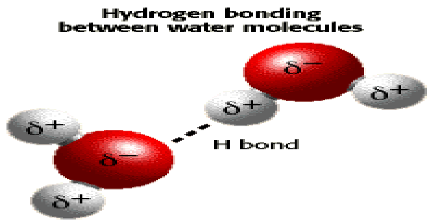
  1. The first is a covalent bond between a H atom and either F, O, or N (These are the three most electronegative elements.)
  2. The second is an interaction of the H atom in this kind of polar bond with a lone pair of electrons on a nearby atom of F, O, or N.

- **Hydrogen Bonding in an Ice Crystal**

Ice has a lower density than water as ice has an open structure. In ice, each molecule is tetrahedral bonded to other molecules by hydrogen bond.

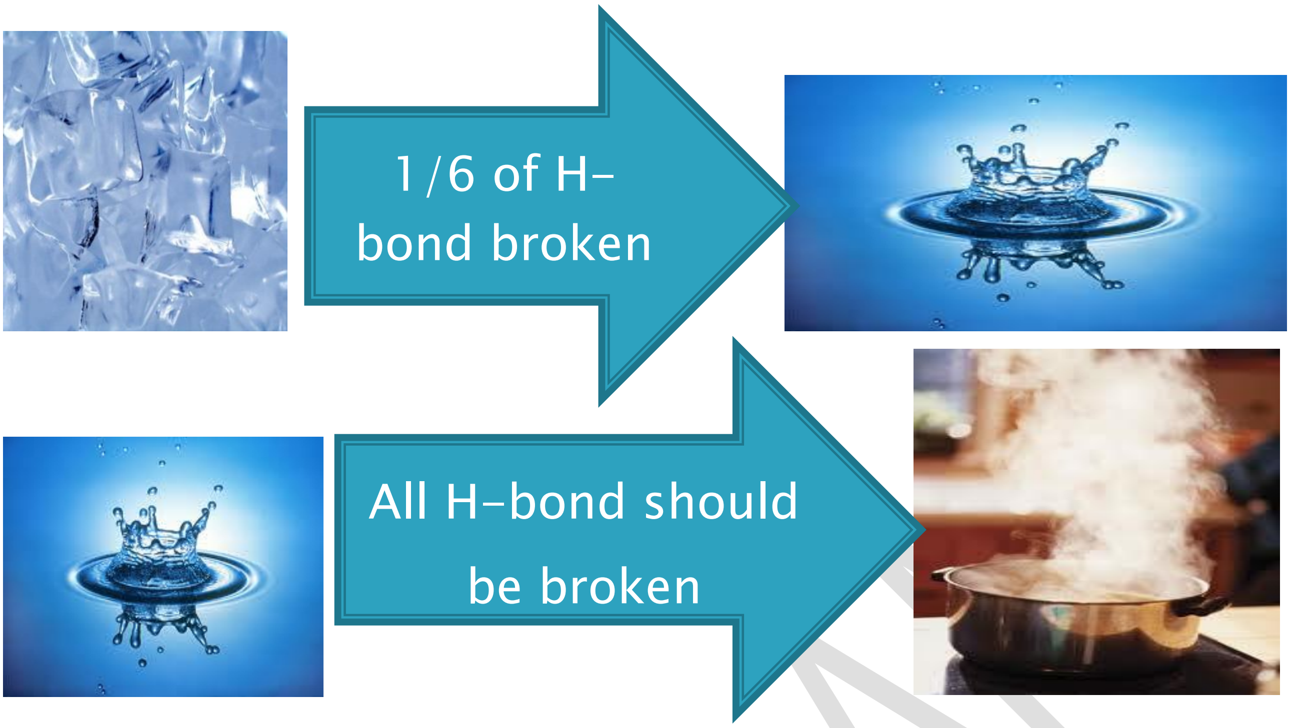
Hydrogen Bond in Water

Many unique properties of water are due to the hydrogen bonds. For example, ice floats because hydrogen bonds hold water molecules further apart in a solid than in a liquid, where there is one less hydrogen bond per molecule. The unique physical properties, including a high heat of vaporization, strong surface tension, high specific heat, and nearly universal solvent properties of water are also due to hydrogen bonding.

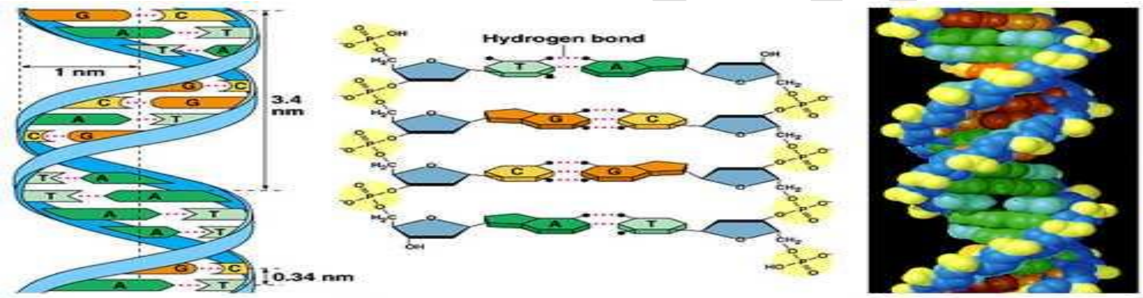


. **H_2O** **H_2S**

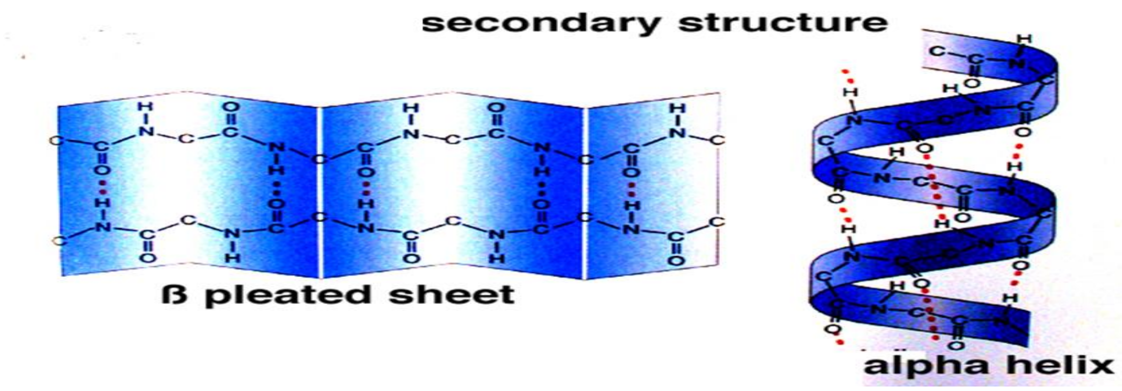
B.P $100C^0$ **B.P $-60C^0$**



Hydrogen Bonding in DNA



Secondary structure of Proteins-Hydrogen Bonding



<u>Hydrogen Bond</u>

The average strength of a hydrogen bond is quite large ~ 40kj/mol

Hydrogen bond have powerful effect on the structure and

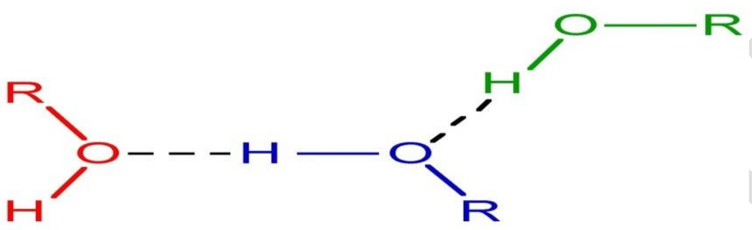
Properties of many compounds The strength of a hydrogen bond is determined by the **coulomb.**Interaction between the **lone-pair** of the electronegative atom and

the **hydrogen nucleus**.

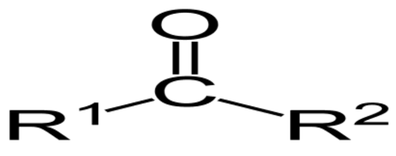
Fluorine is more electronegative than oxygen

$HF_{(l)}$ have stronger hydrogen bond than $H_2O_{(l)}$

- H-bond found in Alcohol and Aldehyde

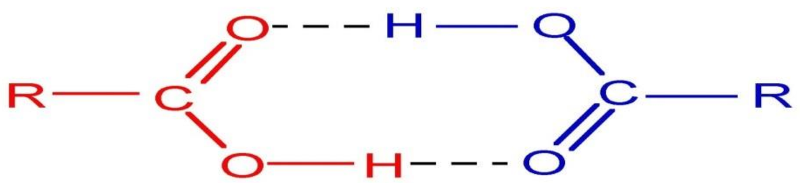


But not found in Keton



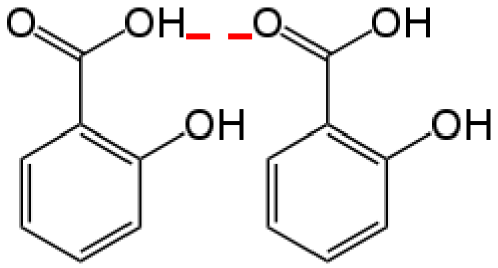
Aldehyde have boiling point higher than Ketone

The hydrogen bonds of formic acid and acetic acid (carboxylic acids) are sufficiently strong to yield *dimers* (two molecules attached together), which can exist even in the vapor state



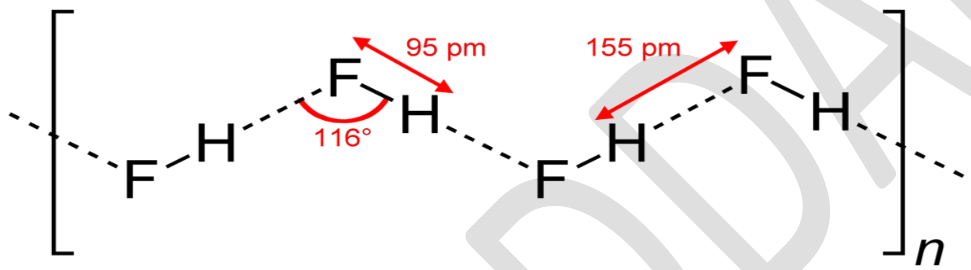
Hydrogen Bond can be classified to:

1. **Intermolecular forces**
2. **Intramolecular forces**



Salicylic acid

Hydrogen fluoride HF, polymer



Which of the following can form hydrogen bonds with water?

CH_3OCH_3, CH_4, F^- , HCOOH, Na^+

No electronegative elements (F, O or N) in either CH_4 an Na^+

CH_4 **can not** form hydrogen bond

Na^+ **can not** form hydrogen bond

CH_3OCH_3, F^-, and HCOOH **can form** hydrogen bond

Which of the following species are capable of hydrogen bonding among themselves?
(a) H_2S (b) C_6H_6 (c) CH_3OH

CH_3OH only

Bond Energies

- Bond energies serve as a measure of the strength of bonds

Interaction type	Energy
van der Waals force	1–10 Kcal/mole
Ion Dipole	1–7 Kcal/mole
Ion induced dipole	≃6 Kcal/mole
Hydrogen bond	2–7 Kcal/mole
Covalent bond	50–150 Kcal/mole
Ionic bond	100–200 Kcal/mole

Reference text: Physical Pharmacy by Alfred Martin et al.