

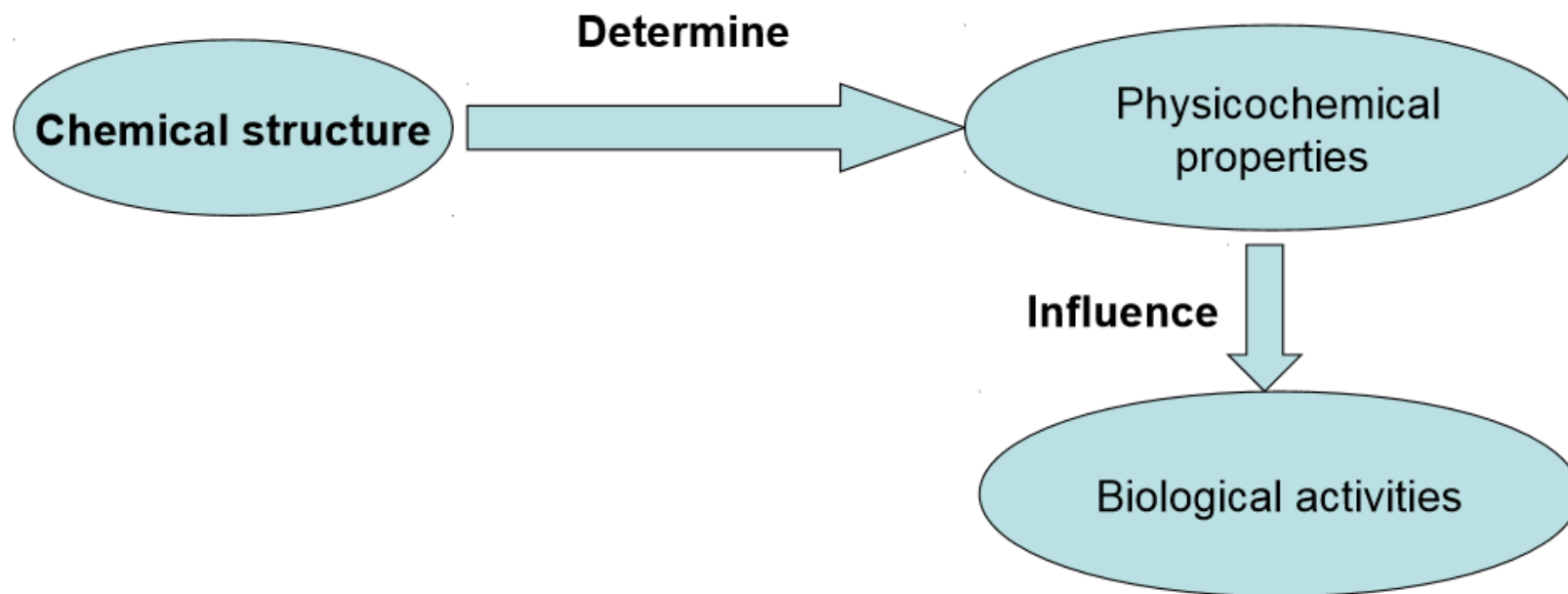
# **MEDICINAL CHEMISTRY**

## **Unit I**

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# Effects of Physicochemical properties on biological activities

Acid /base properties, partition= coefficient, stereochemistry



## DEFINITION:

□ The ability of a chemical compound to elicit a pharmacological/therapeutic effect is related to the influence of various physical and chemical (*physicochemical*) properties of the chemical substance on the bio molecule that it interacts with.

### 1) Physical Properties

Physical property of drug is responsible for its action

### 2) Chemical Properties

The drug react extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc

# Physico-chemical properties in relation to biological action

Drug action results from the interaction of drug molecules with either normal or abnormal physiological processes.

Drugs normally interact with targets (which they are proteins, enzymes, cell lipids, or pieces of DNA or RNA).

The ability of a chemical compound to elicit a pharmacologic /therapeutic effect is related to the influence of its various physical and chemical (physicochemical) properties

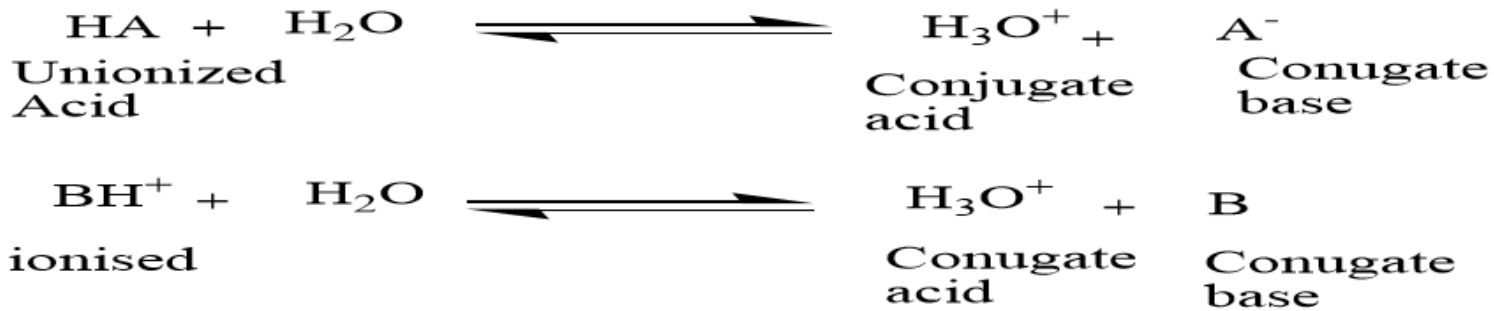
## Various Physico-Chemical Properties are,

- **Ionization of Drug**
- **Solubility**
- **Partition Coefficient**
- **Hydrogen Bonding**
- **Protein binding**
- **Chelation**
- **Bioisosterism**
- **Geometrical and optical isomerism**

# Ionization of drug

- Most of the drugs are either weak acids or base and can exist in either ionised or unionised state.
- Ionization = Protonation or deprotonation resulting in charged molecules.
- The ionization of the drug depends on its pKa & pH.
- The rate of drug absorption is directly proportional to the concentration of the drug at absorbable form but not the concentration of the drug at the absorption site.

- Ionization form imparts good water solubility to the drug which is required of binding of drug and receptor interaction
- Unionized form helps the drug to cross the cell membrane.
- Eg; Barbituric acid is inactive because it is strong acid. while, 5,5 disubstituted Barbituric acid has CNS depressant action because it is weak acid.



According to Henderson-Hasselbalch equation

for acids  $\text{pH} - \text{pKa} = \log [\text{ionized} / \text{unionised}]$

for base  $\text{pH} - \text{pKa} = \log [\text{unionized} / \text{ionised}]$

$$\% \text{ ionisation} = 100 \left[ \frac{1}{1 + 10^{(\text{pH} - \text{pKa})}} \right]$$

When an acid or base is 50% ionised:  $\text{pH} = \text{pKa}$

Eg: the solution of weak acid Aspirin in stomach (pH-1.0) will get readily absorbed because it is in the un-ionosed form(99%).



- Eg: Phenytoin injection must be adjusted to pH 12 with Sodium Hydroxide to obtain 99.98% of the drug in ionised form.
- Tropicamide eye drops an anti cholinergic drug has a  $pK_a$  of 5.2 and the drug has to be buffered to pH 4 to obtain more than 90% ionisation.

## ● Importance of Ionization of drug

- Weak acid at acid pH: more lipid soluble because it is uncharged, the uncharged form more readily passes through the biological membranes.



- Weak base at alkaline pH: more lipid soluble because it is uncharged, the uncharged form more readily passes through the biological membranes.



# SOLUBILITY OF ORGANIC MEDICINAL AGENTS

## Importance of solubility:

- (1) **Formulation** of the drug in an appropriate dosage form and
- (2) **Bio-disposition:** Disposition of drugs in the living system after administration (absorption, distribution, metabolism, and excretion).

**The solubility expression: in terms of its affinity/philicity or repulsion/phobicity for either an aqueous (hydro) or lipid (lipo) solvent.**

♣ hydrophilic..... water loving  
♣ lipophobic..... lipid hating  
~~♣ lipophilic..... lipid loving~~  
♣ hydrophobic..... water hating

# 1. Solubility:

- The solubility of a substance at a given temperature is defined as **the concentration of the dissolved solute, which is in equilibrium with the solid solute.**
- Solubility depends on the nature of solute and solvent as well as temperature , pH & pressure.
- The solubility of drug may be expressed in terms of its affinity/philicity or repulsion/phobicity for either an aqueous or organic solvent.
- The atoms and molecules of all organic substances are held together by various types of bonds (e.g. hydrogen bond, dipole –dipole, ionic bond etc.)
- These forces are involved in solubility because it is the solvent-solvent, solute-solute, solvent-solute interactions that governs solubility.

- Methods to improve solubility of drugs

- 1) Structural modification (alter the structure of molecules)
- 2) Use of Cosolvents (Ethanol, sorbitol, PPG, PEG)
- 3) Employing surfactants
- 4) Complexation

- Importance of solubility

1. Solubility concept is important to pharmacist because it governs the preparation of liquid dosage form and the drug must be in solution before it is absorbed by the body to produce the biological activity.
2. Drug must be in solution form to interact with receptors.

# SOLUBILITY OF ORGANIC MEDICINAL AGENTS

**In order for a chemical compound to dissolve in a particular solvent/medium the compound must establish attractive forces between itself and molecules of the solvent.**

**It is possible to estimate the solubility properties of an OMA (hydrophilic vs. lipophilic) by examining the structure of the drugs and noting whether its structural features promote affinity for aqueous or lipid media.**

**The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:**

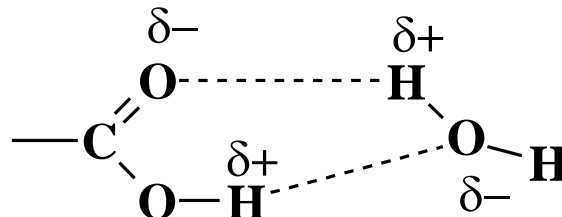
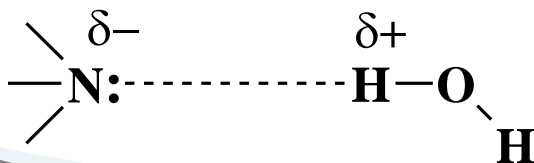
# The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are

## 1. Van der Waals Attraction

- weakest intermolecular force (0.5-1.0 kcal/mole)
- electrostatic
- occurs between nonpolar groups (e.g. hydrocarbons)
- highly distance and temperature dependent

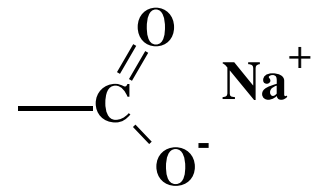
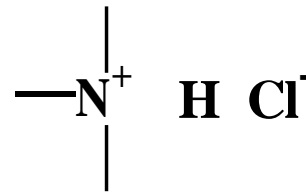
## 2. Dipole-Dipole Bonding

- stronger (1.0 to 10 kcal/mole)
- occurs electrostatically between electron deficient and electron excessive /rich atoms (dipoles)
- hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity



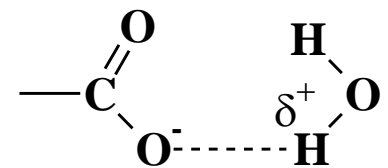
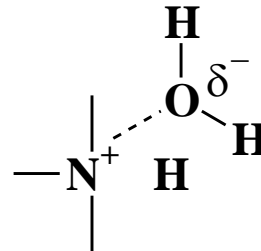
### 3. Ionic Bonding

- electrostatic attraction between cations and anions
- common in inorganic compounds and salts of organic molecules
- relatively strong (5 kcal/mole)



### 4. Ion-Dipole Bonding

- electrostatic between a cation/anion and a dipole
- relatively strong (1-5 kcal/mole)
- low temperature and distance dependence
- important attraction between OMAs and H<sub>2</sub>O





# Solubility Prediction

- **The relative solubility of a drug is a function of the presence of both lipophilic and hydrophilic features within its structure, which serve to determine the extent of interaction of the OMA with lipid and/or aqueous phases.**
- **The relative solubility of a drug can be determined in the laboratory, i.e. the partition coefficient [P; the ratio of the solubility of the compound in an organic solvent to the solubility of the same compound in an aqueous environment (i.e.,  $P = \frac{[\text{Drug}]_{\text{lipid}}}{[\text{Drug}]_{\text{aqueous}}}$ ). P is often expressed as a log value.**

## Solubility Prediction

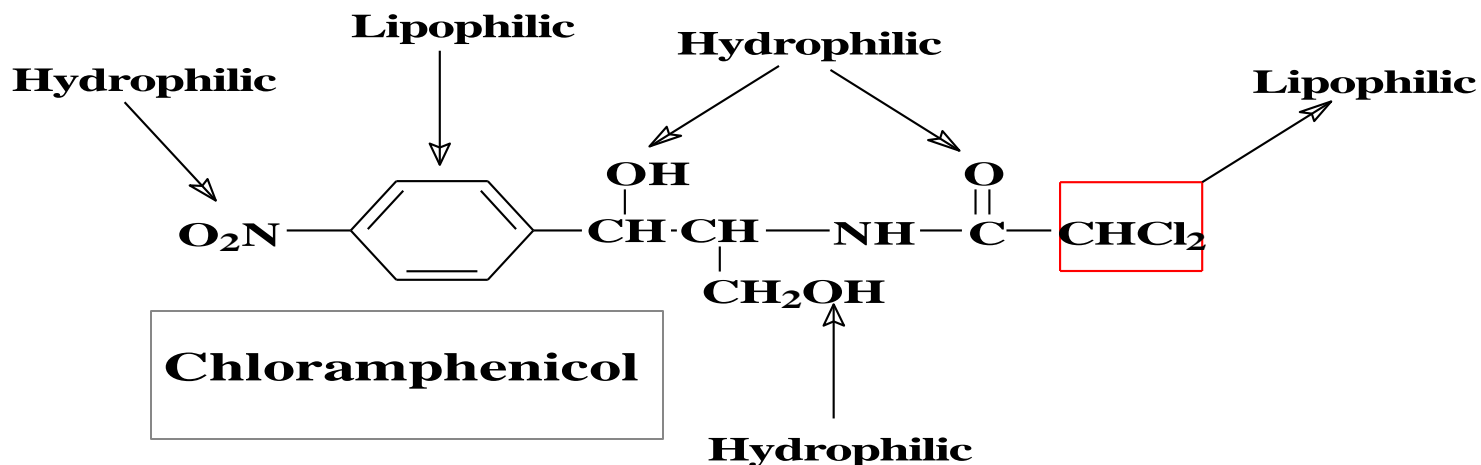
**A mathematical procedures also have been developed to estimate the relative solubility of an organic molecule based upon differential contributions of various structural features to overall solubility.**

**For example, the relative solubility of a drug is the sum of the contributions of each group and substituent to overall solubility.**

### Example:

**Examination of the structure of chloramphenicol (indicates the presence of both lipophilic (nonpolar) and hydrophilic (polar) groups and substituents.**

# Solubility Prediction



*The presence of oxygen and nitrogen containing functional groups usually enhances water solubility. While lipid solubility is enhanced by nonionizable hydrocarbon chains and ring systems.*

# Solubility Prediction

## 1. Laboratory Estimation of Relative Solubility

**The relative solubility of an organic compound is measured by determining the extent of its distribution into an aqueous solvent (usually pH 7.4 buffer) and a lipid solvent (usually n-octanol). These experiments generate a value, P, the partition coefficient for that particular compound.**

$$\text{Partition coefficient} = \frac{\text{Conc. of compounds in } \text{C}_8\text{H}_{16}\text{OH}}{\text{Conc. of compounds in } \text{H}_2\text{O}}$$

## 2. Partition Co-efficient

- Drug<sub>(aqueous)</sub>  $\xrightarrow{PC}$  Drug<sub>(lipid)</sub>
- Partition co-efficient is one of the Physicochemical parameter which influencing the drug transport & drug distribution., the way in which the drug reaches the site of action from the site of application.
- Partition co-efficient is defined as equilibrium constant of drug concentration for unionized molecule in two phases.
- $$P_{\text{[Unionized molecule]}} = \frac{[\text{drug}]_{\text{lipid}}}{[\text{drug}]_{\text{water}}}$$

For ionized (acids, bases and salts)

$$P_{\text{[ionized molecule]}} = \frac{[\text{drug}]_{\text{lipid}}}{[1-a][\text{drug}]_{\text{water}}}$$

a = degree of ionization in aqueous solution.

- Partition coefficient affects the drug transfer characteristics.
- The contribution of each functional group & structural arrangement help to determine the lipophilic or hydrophilic character of drug molecules.
- It is widely used in QSAR.

## ● Factors affecting Partition Co-efficient

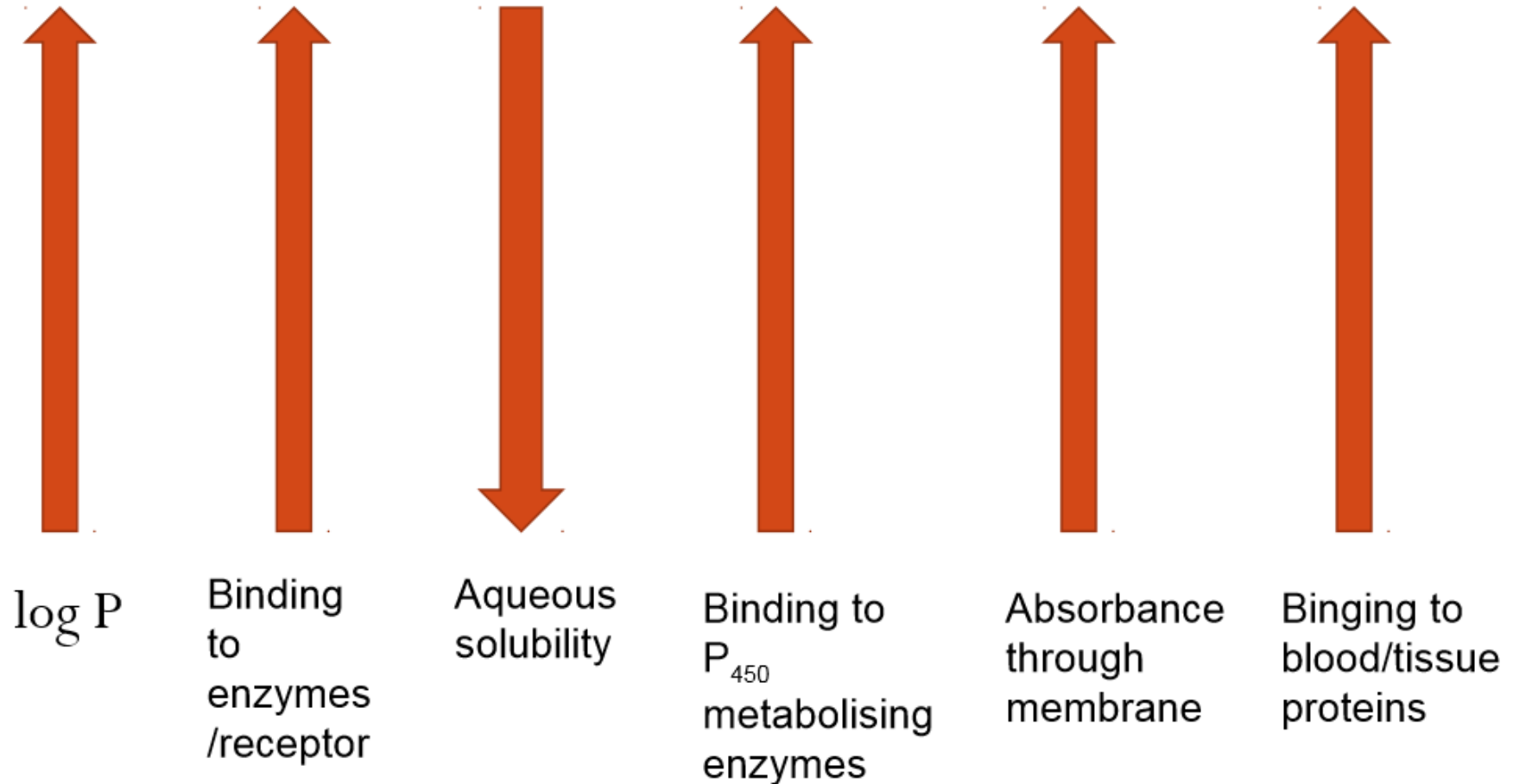
- pH
- Co solvents
- Surfactant
- Complexation

- Partition Co-efficient are difficult to measure in living system.
- They are usually determined in vitro 1-octanol as a lipid phase and phosphate buffer of pH 7.4 as the aqueous phase.
- 1-octanol as a lipid phase because,
  - It has polar and nonpolar region
  - $P_o/w$  is easy to measure
  - $P_o/w$  often correlates with many biological properties
  - It can be predicted using computational mode

- The Partition co-efficient,  $P$  is dimensionless and its logarithm,  $\log P$  is widely used as the measure of lipophilicity.
- The  $\log P$  is measured by the following methods.
  - 1) Shake flask method
  - 2) Chromatographic method (HPLC)
- Phenobarbitone has a high lipid/water partition coefficient of 5.9. Thiopentone sodium has a chloroform/water partition coefficient of about 100, so it is highly soluble in lipid.
- Hence, thiopentone sodium is used as ultra-short acting barbiturates.



# What else does $\log P$ affects?



## ● Importance of partition coefficient

- It is generally used in combination with the  $pK_a$  to predict the distribution of drug in biological system.
- The factor such as absorption, excretion & penetration of the CNS may be related to the  $\log P$  value of drug.
- The drug should be designed with the lowest possible
- $\log P$ , to reduce toxicity, nonspecific binding & bioavailability.

# Hydrogen Bond

- The *hydrogen bond* is a special dipole-dipole interaction between the hydrogen atom in a polar bond such as N-H, O-H or F-H & electronegative atom O, N, F atom.
- Dipoles result from unequal sharing of electrons between atoms within a covalent bond.

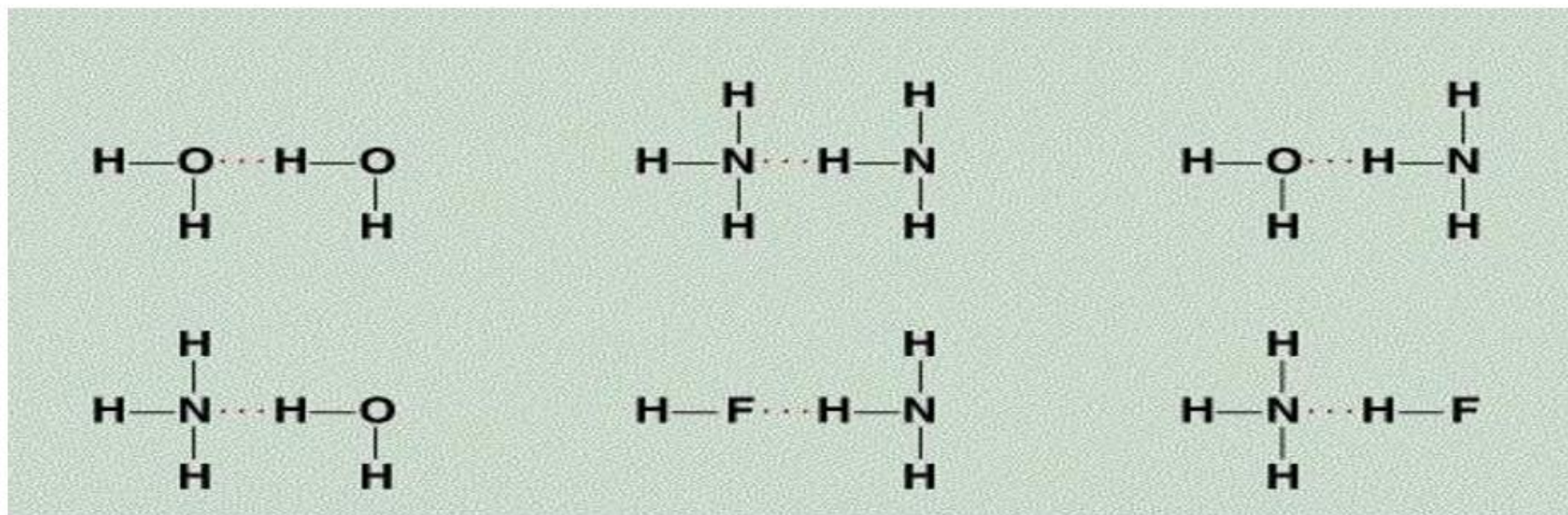
These are weak bonds and denoted as dotted lines.

O-H.....O, HN-H.....O,

- The compounds that are capable, of forming hydrogen bonding is only soluble in water.
- hydrogen bonding is classified into 2 types:
  1. Intermolecular
  2. Intramolecular

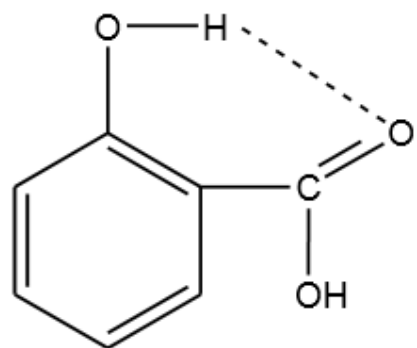
# 1) Intermolecular hydrogen bonding

- It occurs between two or more than two molecules of the same or different compound.
- Due to this increase the boiling point of the compound & increase the molecular weight of compound hence more energy is required to dissociate the molecular for vaporization.

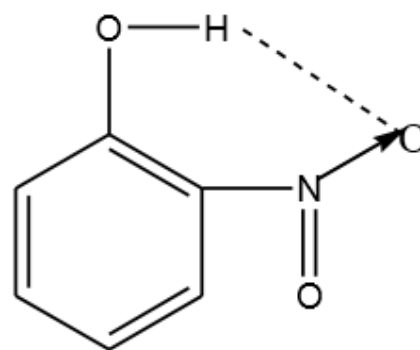


## 2) Intramolecular Hydrogen bonding

- H- bonding occurs within two atoms of the same molecules.
- This type of bonding is known as chelation and frequently occurs in organic compounds.
- Sometimes h-bond develop six or five member rings
- Due to decrease the boiling point



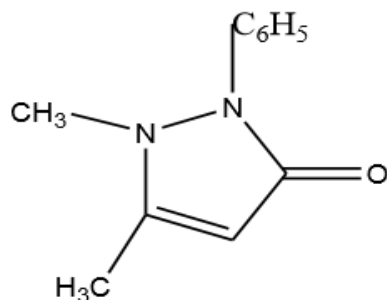
salicylic acid



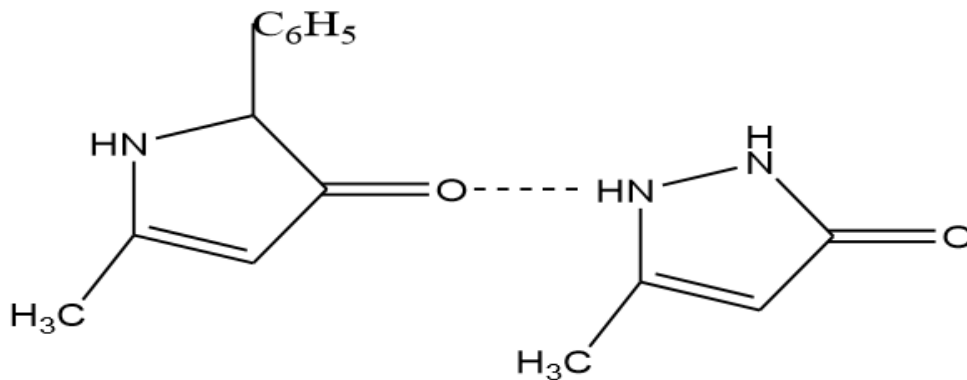
o-nitrophenol

## Hydrogen Bonding and biological action

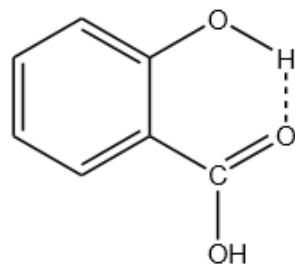
Eg. 1) Antipyrin i.e. 1-phenyl 2,3- dimethyl 5- pyrazolone has analgesic activity.



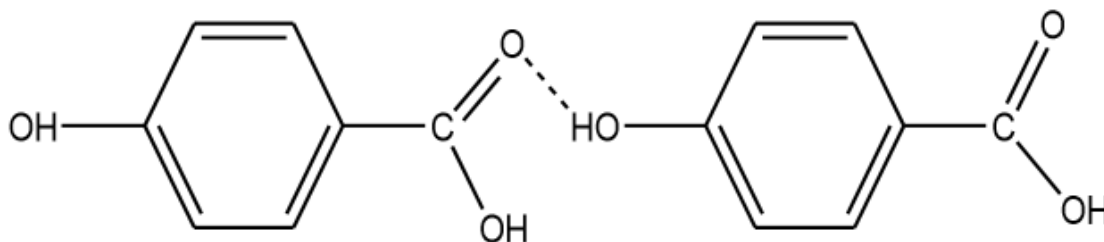
1-phenyl-3-methyl-5-pyrazolone is inactive.



Salicylic acid (O-Hydroxy Benzoic acid) has antebacterial activity



Para and meta Hydroxy Benzoic acids are inactive.



## Effect of H-bonding

All physical properties affected by H-bonding,

1. Boiling and Melting point
2. Water solubility
3. Strength of acids
4. Spectroscopic properties
5. On surface tension and viscosity
6. Biological products
7. Drug-receptor interaction



**NEXT 4 PHYSICOCHEMICAL PROPERTIES  
WILL BE DISCUSSED TOMORROW IN NEXT  
PPT**

