Unit 1

Introduction to Medicinal chemistry

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Content

INTRODUCTION TO MEDICINAL CHEMISTRY

- History and development of medicinal chemistry

Physicochemical properties in relation to biological action

- Ionization, Solubility, Partition Coefficient, Hydrogen bonding, Protein binding, Chelation,
- Bioisosterism, Optical and Geometrical isomerism.

Drug metabolism

- Drug metabolism principles- Phase I and Phase II.
- Factors affecting drug metabolism including stereo chemical aspects.

CHEMISTRY

What is Chemistry?

- Chemistry is known

as the **central of science.**

- **It is a branch of physical science that studies the composition, structure, properties and changes of matter.**
- MATTER = Solid / Liquid/ Gas.

BRANCHES OF CHEMISTRY

PHYSICAL CHEMISTRY

- the branch of chemistry concerned with the application of the techniques and theories of physics to the study of chemicalsystems.
- Branches : chemical Kinetics, Electrochemistry, spectroscopy, photochemistry.

INORGANIC CHEMISTRY

- deals with the synthesis and behaviour of **inorganic** and organometallic compounds
- Branches :Bioinorganic, Cluster, Material & Nuclear Chemistry

ORGANIC CHEMISTRY

- study of the structure, properties, and reactions of **organic** compounds and **organic** materials, i.e., matter in its various forms that contain carbon atoms.
- Branches : Biochemistry, biophysical, Biorganic, P'ceutical, Medicinal

WHAT IS MEDICINAL CHEMISTRY

- It is a discipline or intersection of chemistry especially synthetic organic chemistry & pharmacology.

OR

- Medicinal chemistry involves discovery, development, identification & interpretation of Mode of action of biologically active compounds at molecular level

- Medicinal chemistry is best to be defined as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery).
- In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

- Generally Medicinal Chemists can:
  - Make new compounds
  - Determine their effect on biological processes.
  - Alter the structure of the compound for optimum effect and minimum side effects.
  - Study uptake, distribution, metabolism and excretion of drugs

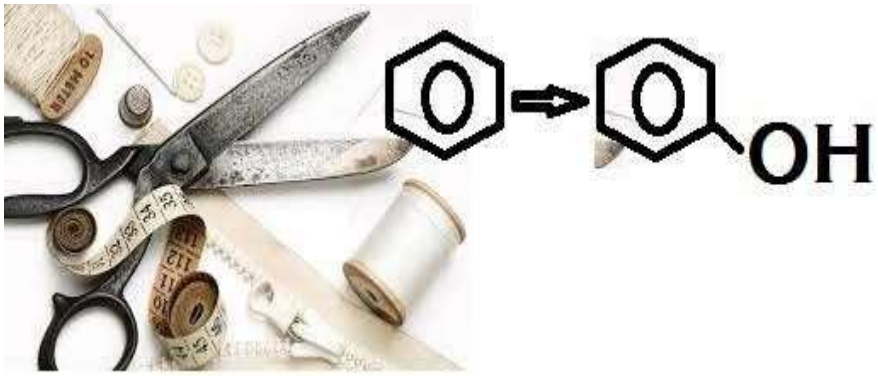
Finally medicinal chemistry ….

- Medicinal chemistry includes synthetic & computational aspects of the study of existing drugs and agents in development in relation to their bioactivities i.e., understandings a **SAR**s (Structure Activity Relationships).

OR

•It is a tailoring

of drugs



Origins of Medicinal Chemistry

3500 BC - Sumerians report use of opium

3000 BC - Chinese report use of ma huang (ephedra)

Greek culture:

Hippocrates- followed the teachings of Aristotle; focus is on the soul.

Galen- followed the teachings of Plato; focus is on experiment- believed the whole could be explained by the parts

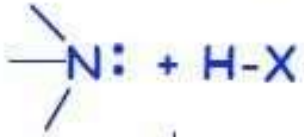
Renaissance period:

Doctors were humanists- followers of Hippocrates- treat the soul and the body will heal. Initially, there were no relationships with alchemy.

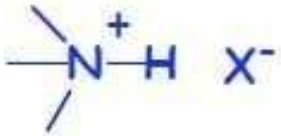
In 1793, Faureroy & Vauquehin split from the monarchy-controlled bodies and establish the Ecole Supurieure de Pharmacie- 1st to incorporate chemistry into the pharmacy curriculum. Develop research to find the active principles in plant-based drugs.

1803 - Derosome isolates a crystalline salt from opium

1817 - Sertürner publishes work demonstrating that the narcotic principle of opium is basic (alkaline) and, thus, it will form salts with acids- names the principle "morpheus"

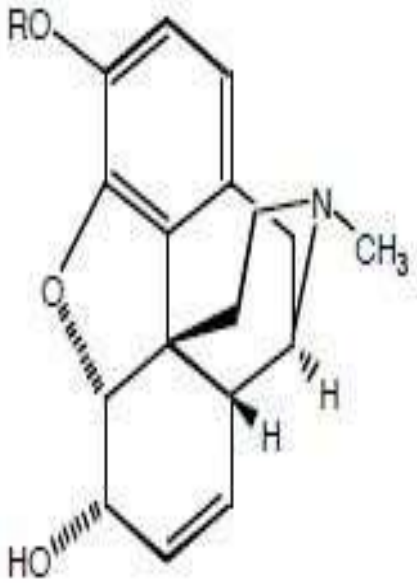


Gay-Lussac predicts that other alkaline plant extracts will have useful medical properties- changes name of morpheus to morphine

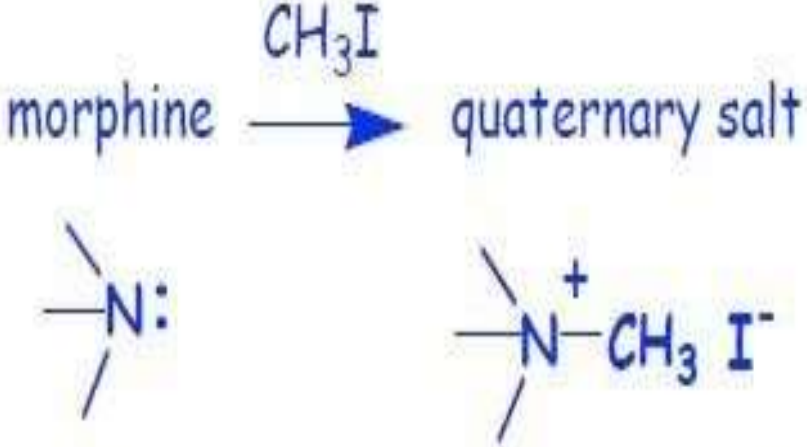


1818 - Meissner proposes the general term alkaloids

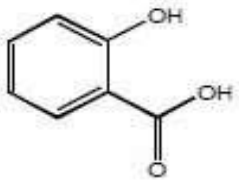
1853 - Henry How proposes that there are "functional groups" that can be chemically modified to alter reactivities….



morphine R = H
codeine R = CH_3

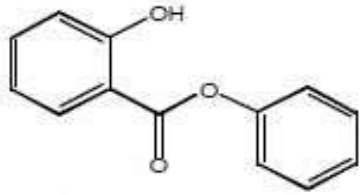


Fraser and Brown make quaternary salts of many different alkaloids (i.e, morphine, strychnine, nicotine) and find that all exhibit curare-paralyzing activities- propose that quaternary salts have curariform activity



salicylic acid

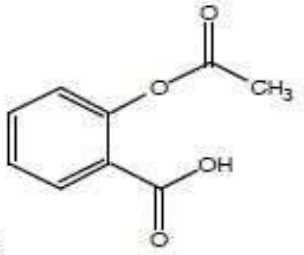
1875- Carl Buss isolates salicylic acid from *Spirea ulmaria* and shows that it is an effective antipyretic- however, it is unpalatable and causes gastric distress.



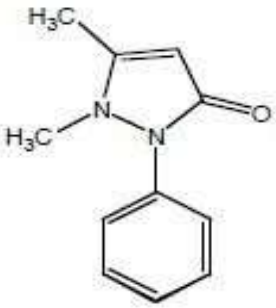
salol (phenyl salicylate)

1883- von Nencki makes a salicylate ester with phenol, salol- it has very poor solubility but it is better tolerated. It is hydrolyzed slowly in the small intestine to give salicylic acid- the first sustained release drug

1890s - Hoffman at Bayer tests acetyl salicylic acid and finds it to be better tolerated- names it aspirin as in "a" for acetyl and "spirin" for *Spirea*. It is rapidly hydrolyzed in the gut to give active salicylic acid- it is a "pro-drug"



acetyl salicylic acid



phenazone

Phenazone was synthesized in 1884 and was the most popular drug world-wide until it was taken over by aspirin in the early 1900s- in addition to being an antipyretic, it also cured headaches- a new market was born...

There is a long history of plants being used to treat various diseases.

The therapeutic properties of plants were described by the Ancient Greeks and by the Romans and are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus.

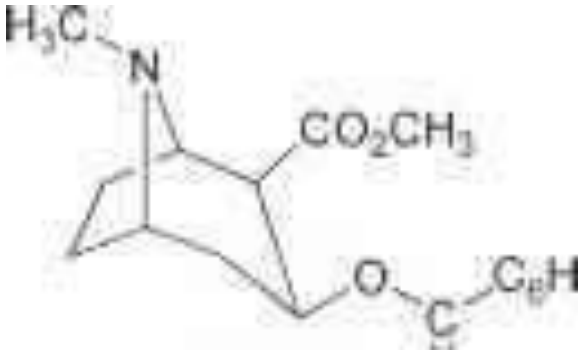
Some metals and metal salts were also used at this time.

In the Middle Ages various 'Materia Medica and pharmacopeas brought together traditional uses of plants.

- The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry.
- The isolation of a number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud.
- General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)). Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery. The hypnotic activity of chloral (trichloroethanal) (1869) was also reported.

- The use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin and of salicylic acid were developed in the 1860s and 1870s.
- p-Hydroxyacetanilide (paracetamol) and phenacetin (1886) were also recognized as pain-killers.
- Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899.

- The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time.
- Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) and procaine (1905). The barbiturates, veronal (1903) and phenobarbital (1911) were introduced as sleeping tablets.



- The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins.
- It was also a period in which there was exposure of many Europeans to tropical diseases. The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentary and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness.
- Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) and later chloroquine (1943) and paludrine (1946) were introduced as quinine replacements.

- In 1935 Domagk observed the anti-bacterial action of the sulfonamide dyestuff, prontosil red , from which the important family of sulfonamide anti-bacterial agents were developed.
- With the onset of the Second World War, there was a need for new antibiotics. In 1929 Fleming had observed that a strain of Penicillium notatum inhibited the growth of a Staphylococcus. In 1940-1941 Chain, Florey and Heaton isolated benzylpenicillin
- . After considerable chemical work, the b-lactam structure for the penicillins was established. The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including streptomycin (1944), chloramphenicol (1949) and the tetracyclines such as aureomycin (1949).

- A number of developments took place in the 1960s, which changed medicinal chemistry.
- It was found that a drug, thalidomide, which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children. The consequences of this teratogenic effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines.
- The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine (1976) and then ranitidine (1981). The reasoning behind this work had a major impact on the development of medicinal chemistry.

MEDICINAL CHEMISTRY

Physicochemical Properties of a drug molecule

Unit I

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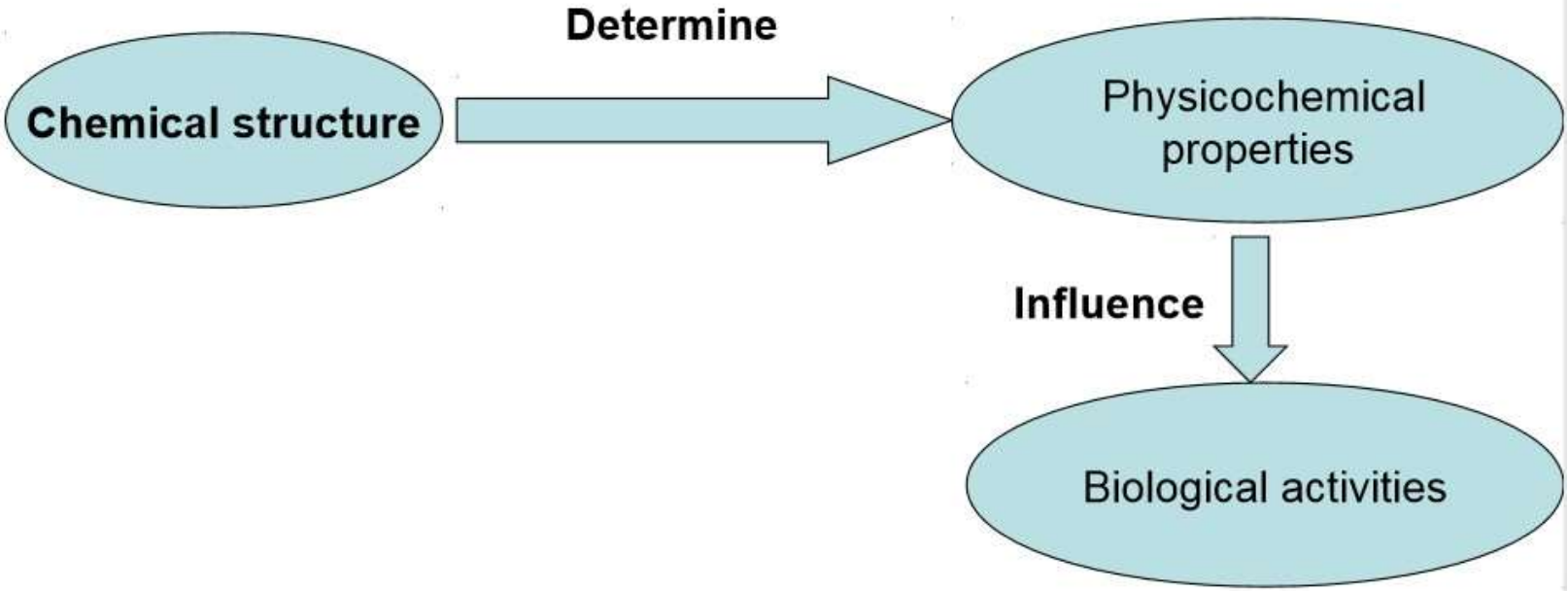
Effects of Physicochemical properties on biological activities

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)<u>Physical Properties</u>

Physical property of drug is responsible for its action

2)<u>Chemical Properties</u>

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

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

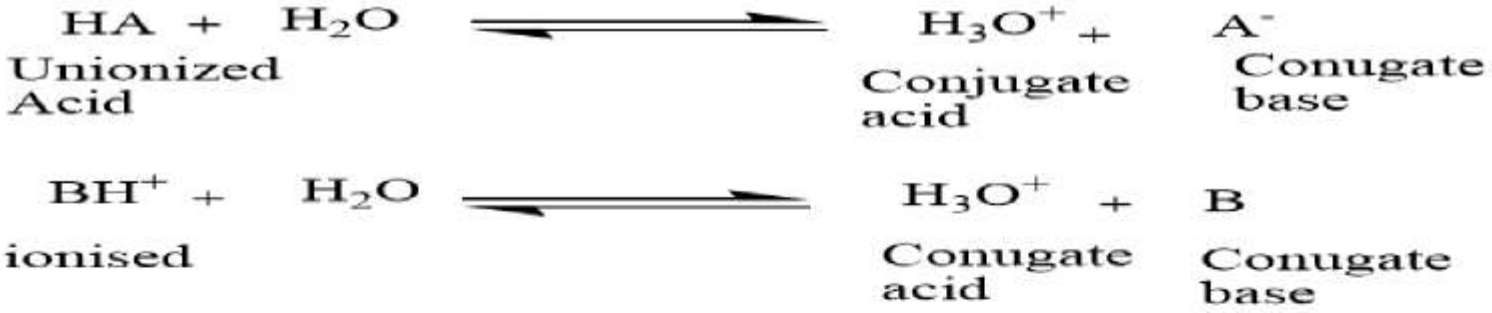
Various Physico-Chemical Properties are,

- 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 pH-pKa = log [ionized/unionised]

for base pH-pKa = log [unionized/ionised]

% ionisation = $100\backslash[\ 1+10^{(pH-pka)}\ ]$.

When an acid or base is 50% ionised: pH = 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.

$$RCOO^- + H^+ = RCOOH$$

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

$$RNH^+ = RNH^2 + H^+$$

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..... waterloving**
- **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 equillibrium 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 govern 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:

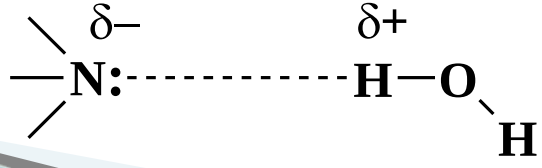
The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:

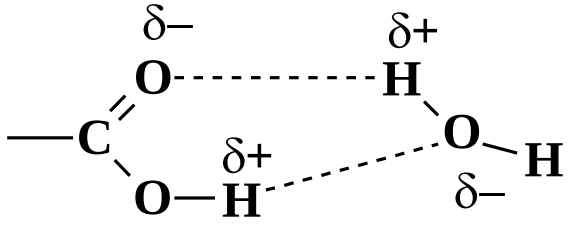
1. Van der Waals Attraction

- 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

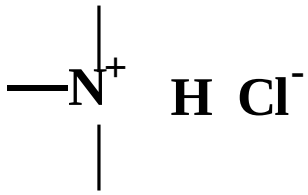
- stronger (1.0 to 10 kcal/mole)
- occurs electrostatically between electron deficient and electron excessive /rich atoms (dipoles)
- hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity

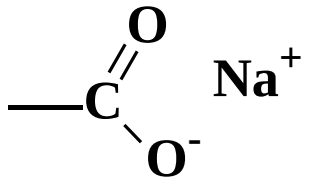




3. Ionic Bonding

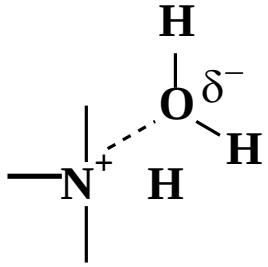
- electrostatic attraction between cations and anions
- common in inorganic compounds and salts of organic molecules
- relatively strong (5 kcal/mole)

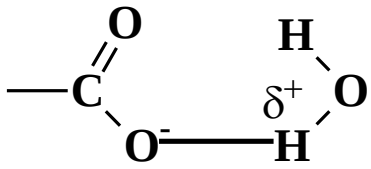




4. Ion-Dipole Bonding

- electrostatic between a cation/anion and a dipole
- relatively strong (1-5 kcal/mole)
- low temperature and distance dependence
- important attraction between OMAs and H2O





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=[Drug]lipid/ [Drug]aqueous). P is often expressed as a log value.**

Solubility Prediction

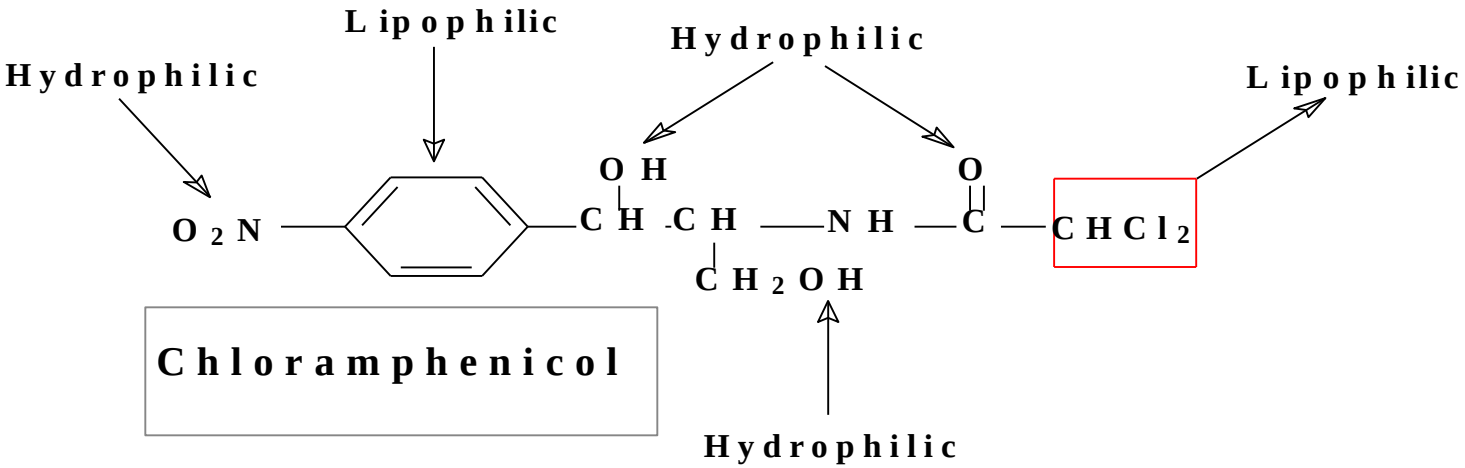
A mathematical procedures also have been developed to estimate the relative solubility of an organic molecule based upon differential contributions of various structural features to overall solubility.

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.

$$\text{Partition coefficient} = \frac{\text{Conc. of compunds in } C_8H_{16}OH}{\text{Conc. of compunds in } H_2O}$$

18

2. Partition Co-efficient

- $Drug_{(aqueous)} \xrightleftharpoons{PC} Drug_{(lipid)}$

- 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.
- $$P_{[\text{Unionized molecule}]} = \frac{[drug]_{lipid}}{[drug]_{water}}$$

For ionized (acids, bases and salts)

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

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
  - Po/w is easy to measure
  - Po/w often correlates with many biological properties
  - It can be predicted using computational mode

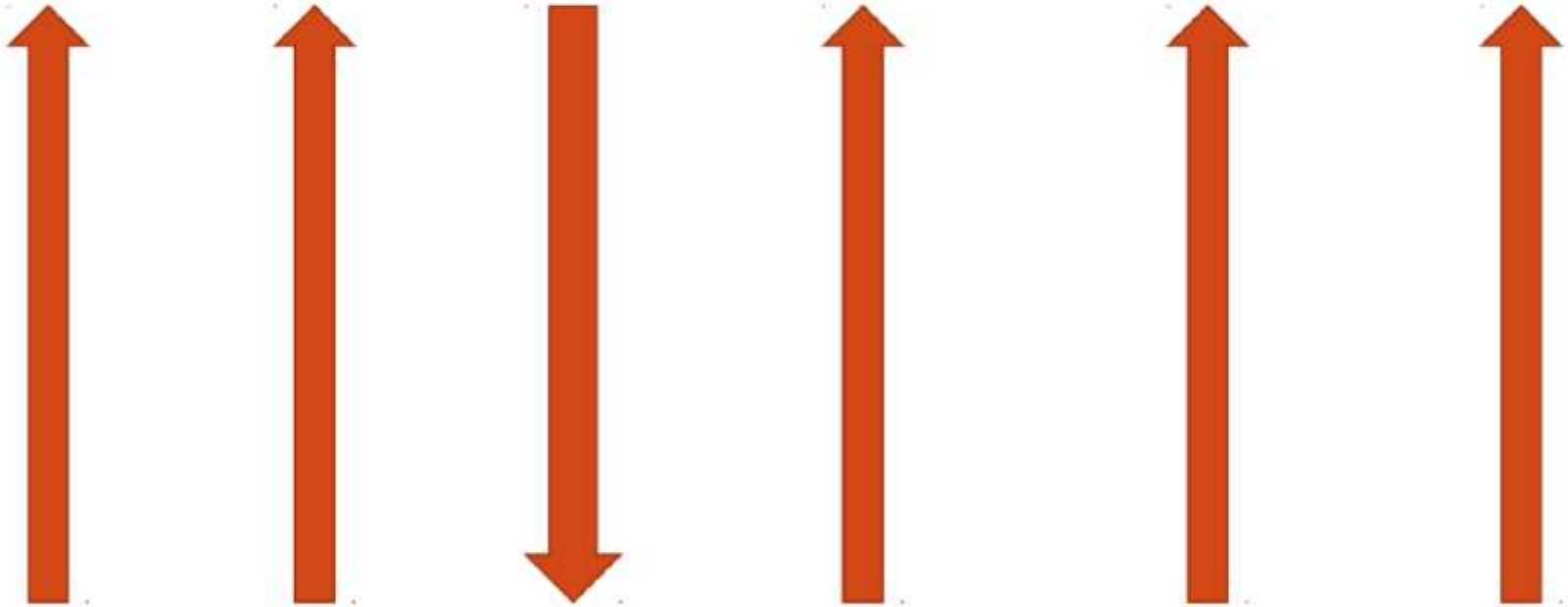
- The Partition co-efficient, P is dimensionless and its logarithm, log P is widely used as the measure of lipophilicity.

- 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 lopP affects?



log P

Binding to enzymes /receptor

Aqueous solubility

Binding to P_{450} metabolising enzymes

Absorbance through membrane

Binging to blood/tissue proteins

Importance of partician coefficient

- It is generally used in combination with the Pka 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.

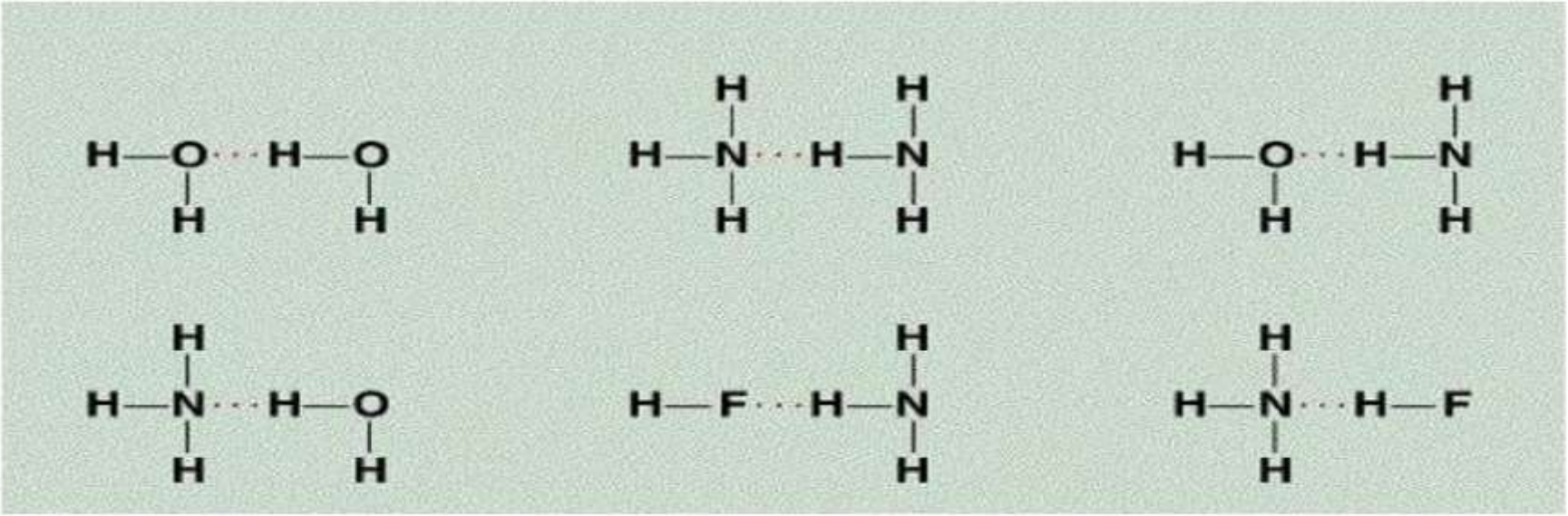
These are weak bonds and denoted as dotted lines.

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

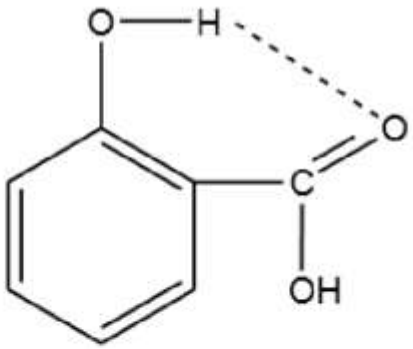
1) Intermolecular hydrogen bonding

- It is occur 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.

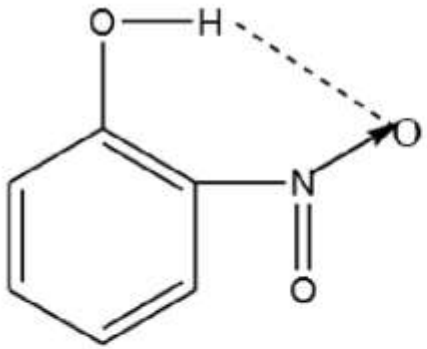


2) Intramolecular Hydrogen bonding

- 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



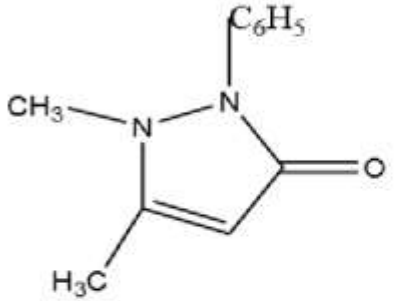
salicylic acid



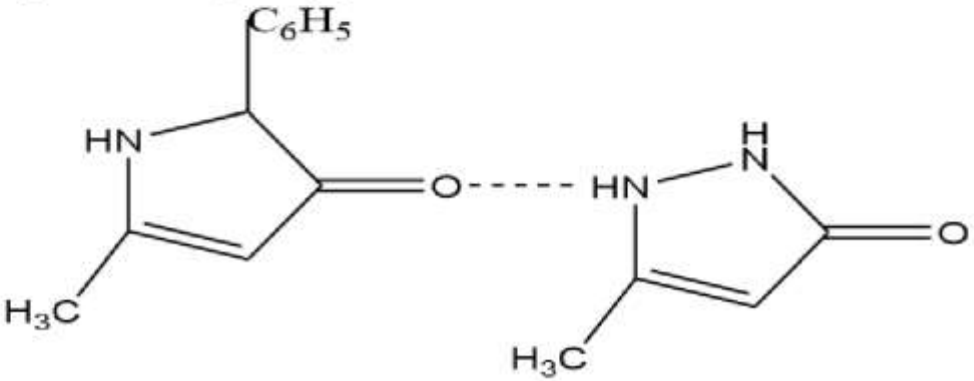
o-nitrophenol

Hydrogen Bonding and biological action

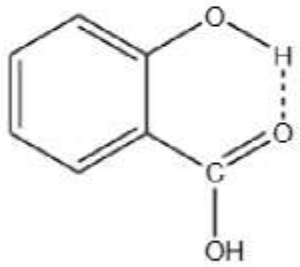
Eg. 1) Antipyrin i.e. 1- phenyl 2,3- dimethyl 5- pyrazolone has analgesic activity.



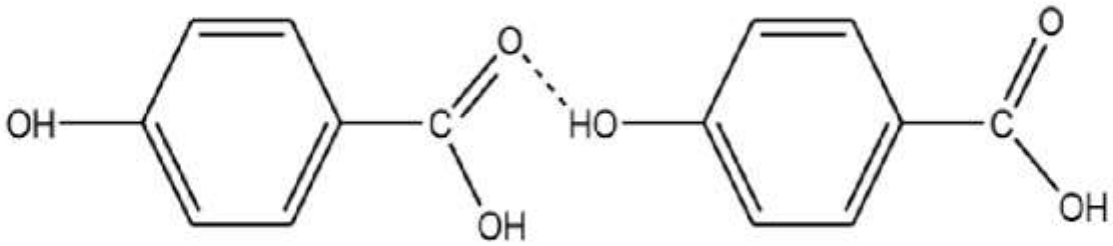
1-phenyl-3-methyl-5-pyrazolone is inactive.



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