

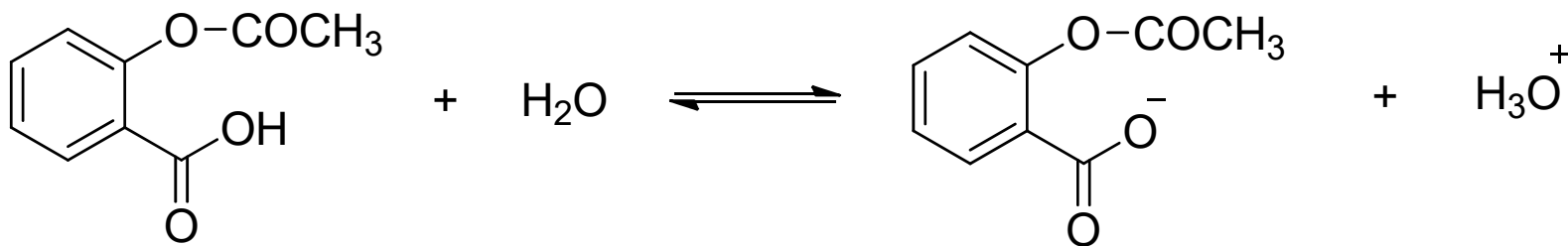
Physico-chemical Properties and Biological activity

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Effect of ionisation on biological activity

- ❖ The majority of the drugs are either **weak acid** (for example, acetylsalicylic acid [aspirin]) or **weak base** (for example, procaine).
- ❖ Acidic drugs can give proton and basic drug can accept a proton to ionise.
- ❖ **Amphoteric** drugs containing both acidic and basic drug can give and accept proton.
- ❖ The dissociation of acetylsalicylic acid, a weak acid, could be represented below. In this equilibrium, acetylsalicylic acid acts as an acid, because it donates a proton.



- ❖ As membranes are lipid in nature, hence it **permits only** unionised drug (**lipophilic**) to pass through.
- ❖ Therefore the extent of ionisation of a drug has an important effect on its absorption, distribution and elimination.
- ❖ The degree to which these drugs are ionised in solution are **dependent on the pH..**
- ❖ For example, the pH of urine may be adjusted by administration of ammonium chloride in cases of overdosing with amphetamines and narcotics. Similarly sodium bicarbonate is used in case of barbiturates and salicylic acid, to ensure that these drugs are completely ionised and hence readily excreted

Effect of solubility on biological activity

- ❖ Solubility is the important parameter to attain desired concentration of drugs in the systemic circulation that could show desired therapeutic response.
- ❖ A drug to be absorbed from the site of absorption **must be present in** the form of an **aqueous solution**. Since, water remains the solvent of choice many liquid dosage forms, poor water soluble drugs have slow absorption leading to inadequate bioavailability.
- ❖ Most of the drugs are either weakly acidic or weakly basic, having poor aqueous solubility, especially in BCS Class II drugs, the rate-limiting step is drug release from dosage form and its solubility in gastric pH than absorption.

❖ Various solubilization techniques, including **cosolvency**, **addition of surfactants**, **salt formation**, and solid dispersion are employed into solubilized poorly soluble drugs

❖ Aqueous solubility of a given molecule is the interplay of multiple factors, including solid-state properties (eg, **crystal packing**, **lattice energy**), **ionization** (pH, pK_a), and **solute/solvate interactions**.

❖ It is important to understand what limits solubility to design new formulation .

- ❖ The ionization state of a molecule can significantly impact its solubility.
- ❖ The **solubility** of an ionizable compound is strongly **dependent on the pH** of the media and the pK_a of the molecule.
- ❖ The solubility of an ionizable compound can be described by the pH-solubility relationship derived from the **Henderson–Hasselbalch equation**.

$$pH = pK_a + \log_{10} \left(\frac{[A^-]}{[A]} \right)$$

Effect of Partition coefficient on biological activity

- ❖ The partition coefficient of a drug is defined as the equilibrium constant of drug concentrations in two phase (namely oil and water phase).

$$P = \frac{[Drug]_{lipid}}{[Drug]_{water}}$$

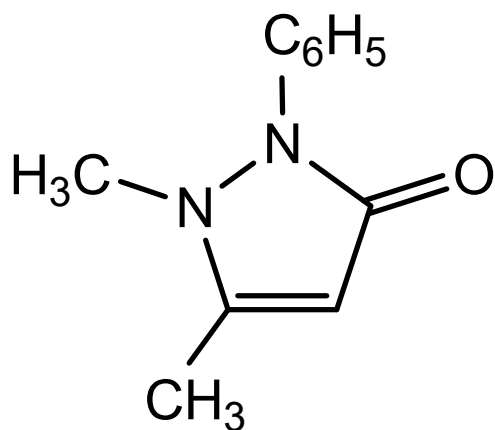
- ❖ Partition coefficient is important in explaining the mode of action of general anesthetics & hypnotics such as barbiturates.
- ❖ Meyer and Overton in 1899 observed that the **narcotic efficacy** of drugs was **directly related** to their **partition coefficients** between oil and water. i.e narcosis depends on its ability to attain a certain molar concentration specifically in cell lipids.

- ❖ Partition coefficient plays important role in transport and absorption of drug.
- ❖ Partition coefficient of certain unionized barbiturates and % absorption from rat colon is represented .

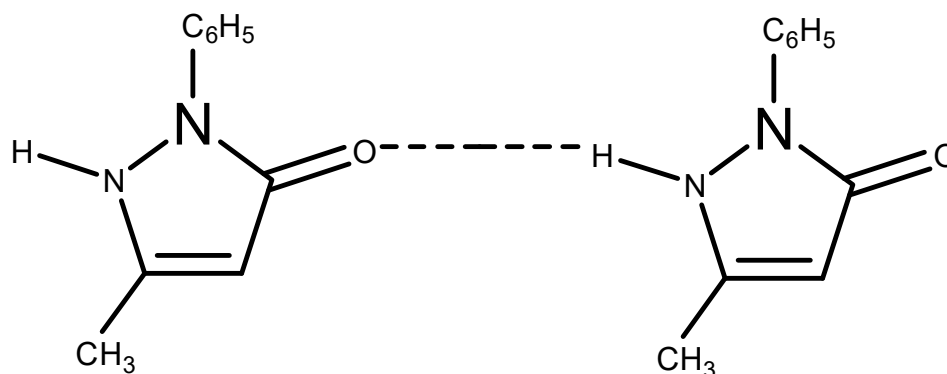
barbiturates	Partition coefficient	% absorption
Barbital	0.7	12
Cyclobarbital	13.9	24
Secobarbital	50.7	40

Effect of Hydrogen bonding on biological activity

- ❖ hydrogen bond is formed between hydrogen and electronegative atom.
- ❖ A bond in which a hydrogen atom serves to hold two other atoms together.
- ❖ **Antipyrin (1-Phenyl-2, 3-Dimethyl-5-Pyrazolone)** has analgesic activity but **1-phenyl-3-methyl-5-pyrazolone** is inactive.

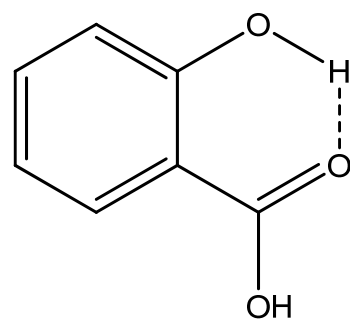


Antipyrin

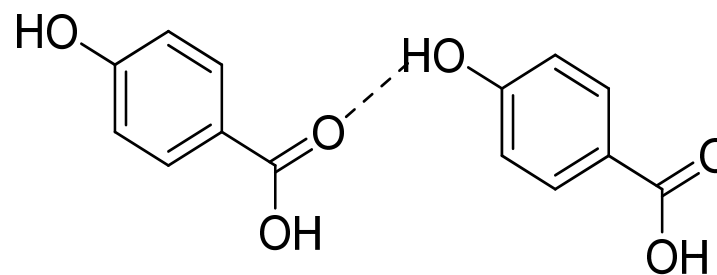


1-phenyl-3-methyl-5-pyrazolone forms intermolecular hydrogen bonding. Hence insoluble in water and devoid of activity.

- ❖ **Salicylic acid** (*o*-hydroxy benzoic acid) has **antibacterial activity** but ***p* and *m*-hydroxy benzoic acids** are **inactive**.
- ❖ Salicylic acid forms intramolecular hydrogen bonding.
- ❖ *m*- and *p*- hydroxy benzoic acids can form intermolecular hydrogen bonding resulting in dimer, which cannot pass through biological membrane and hence inactive.



Salicylic acid



***p*-hydroxy benzoic acid**

Effect of protein binding on biological activity

❖ The phenomenon of complex formation with protein is called **protein binding of drugs**. Binding of drug to protein is generally reversible.

Systemic solubility of drugs:

Water insoluble drugs such as heparin, several steroid and oil soluble vitamins are circulated and distributed by binding especially to lipoproteins which act as a vehicle for them.

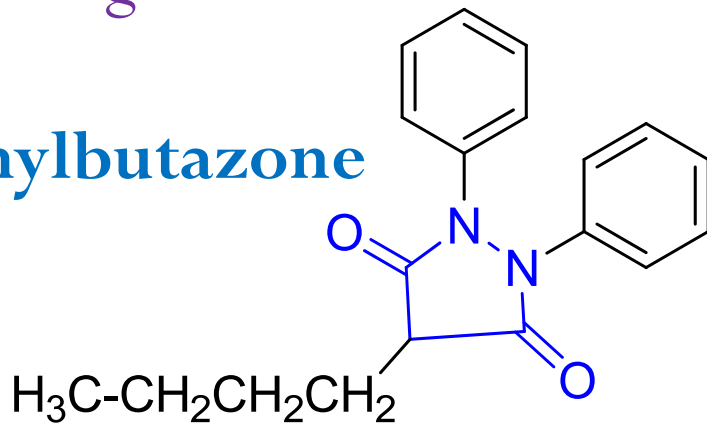
Distribution:

- Plasma protein binding favors uniform distribution of drug throughout the body by its buffer function.
- Prevents accumulation of large fraction of drug in specific tissue, thus prevent toxic reaction.

Displacement interactions and toxicity:

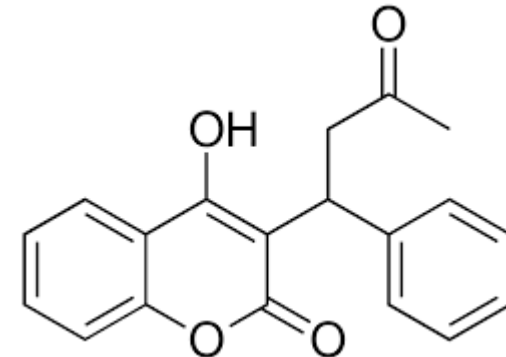
❖ displacement is significant in case of drugs which are more than 95% bound. e.g. Administration of phenylbutazone to a patient on warfarin therapy results in displacement of latter from its binding site. The free warfarin can cause adverse hemorrhagic reactions.

Phenylbutazone



Therapy and drug targeting:

- ❖ The binding of drugs to lipoproteins can be used for site specific delivery of hydrophilic moieties.
- ❖ This is particularly useful in cancer therapies since certain cells have greater affinity for LDL than normal tissues.



Warfarin