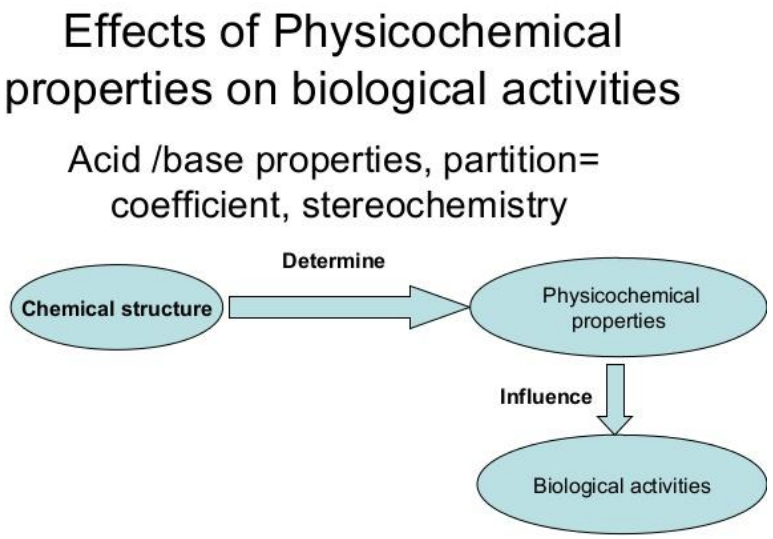
Physico-chemical properties



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Learning Outcomes

At the end of this lesson students will be able to

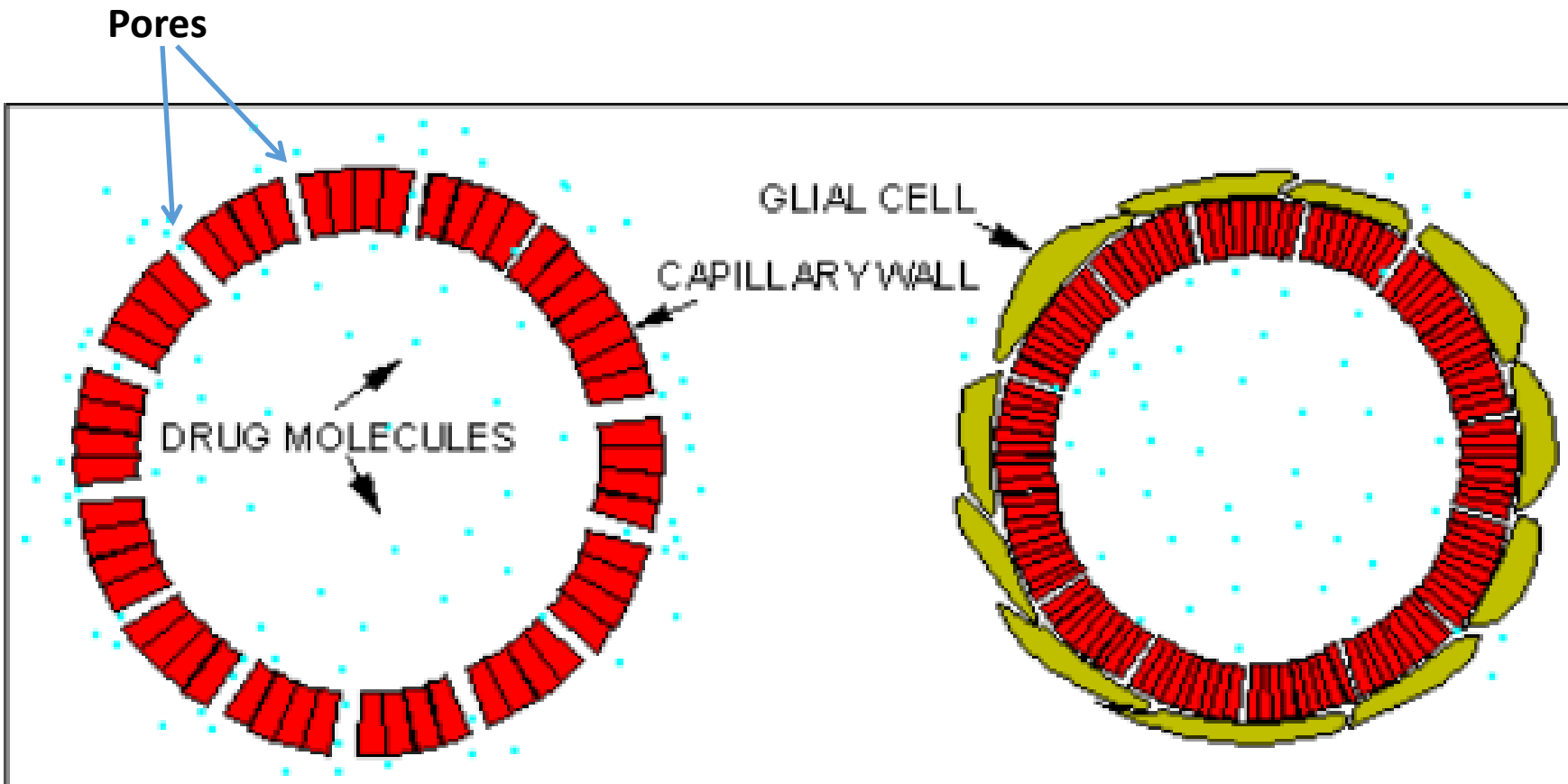
- Describe about various physicochemical properties affecting the drug action.
- Describe the effect of solubility, other properties like lipophilicity, partition co-efficient, acidity and basicity, and pH affecting the activity of drugs.
- Explain parameters such as ionization and dissociation constant.
- Describe the effect of acidity and basicity.

Molecular properties

- The molecular properties affect the pharmacodynamics and the pharmacokinetic aspects of drugs.
- Molecular properties essentially include the chemical properties, physical properties, and structural properties of molecules, including drugs.
- Molecular properties also determine the dosage form and the route of administration for the drug.
- Important molecular properties include
    1. Solubility.
    2. Lipophilicity and Partition coefficient.
    3. Dissociation constant (degree of ionization).
    4. Chemical stability.

Drug solubility

- Is drug soluble enough in the GIT content?
- Is it soluble enough in blood to be given parenterally?
- More water soluble drug in blood….large volume of distribution.
- More water soluble drugs…poor penetration into CNS through the lipophilic blood brain barrier.
- As a result, very limited number of drugs can act on CNS.



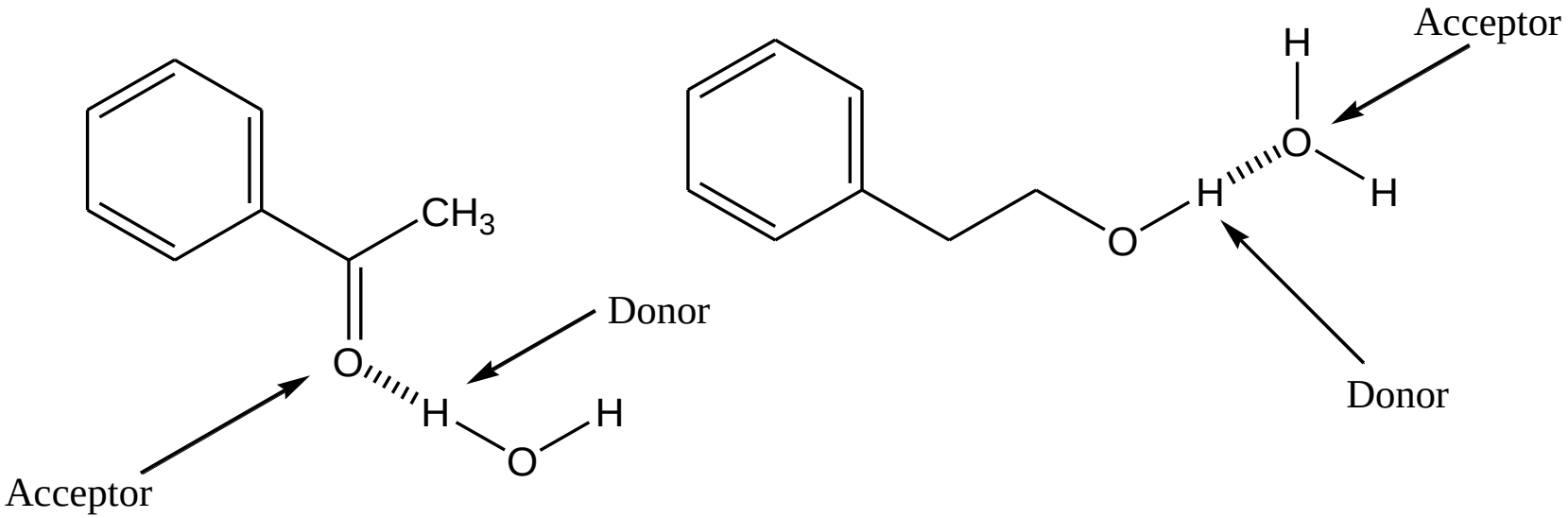
General body capillaries allowdrug molecules to pass freely into the surrounding tissue.

Brain capillaries have a dense-walled structure and are surrounded by glial cells (lipid). This prevents many drug molecules from entering the surrounding tissue.

Physicochemical properties of drugs

Partition coefficient	Lipophilicity/hydrophilicity
Ionisation/ dissociation constant	Strong or weak acids/bases Salt formation
Solubility	Water-soluble salts Lipid soluble
Stability	Chemical degradation – oxidation, hydrolysis, light. Enzyme degradation (metabolism) esterases, amidases, cytochrome P_{450}

Lipophilicity/hydrophilicity of drugs



Partition coefficient

- The lipid solubility or the lipophilicity of the drug can be measured by partition coefficient ‘P’.
- Partitioning means that the drug will be divided in parts between two immiscible liquids [aqueous (water) and organic (lipophilic membrane)].

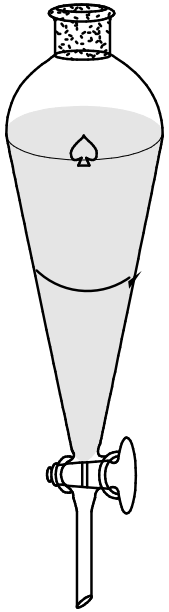
  - $P = [C_o]/[C_w]$; $LogP = Log[C_o]/[C_w]$.

- LogP > 2 lipophilic drug; LogP < 2 hydrophilic drug.
- Low logP….. Low penetration to CNS.
- High logP….. Low water solubility…. Not suitable for oral administration.

Partition coefficient

- ✓ **As a measure of lipophilicity, Hansch proposed 'partition coefficient, *P*' a measure of the solubility of compound in 1-octanol versus water.**

$$P = \frac{[\text{Compound}]_{\text{oct}}}{[\text{Compound}]_{\text{aq}}\,(1-\alpha)}$$



Where,

P **= partition coefficient**

α = degree of dissociation of the compound in water calculated from ionization constant.

oct = 1-Octanol; aq = aqueous buffer or water.

In general, ionization makes the compound more soluble in water. Experimentally, log *P* can be determined by 'shake flask method'. The orally administered drug must have moderate lipophilicity (logP = 2-5) in order to absorbed through the lipophilic mucus membrane or membrane solubility.

PARTITIONING OF ACIDS AND BASES

P_{app} is the apparent partition coefficient and varies with pH.

For acid substance

$$P_{app} = \frac{P}{1+10^{pH-pKa}}$$

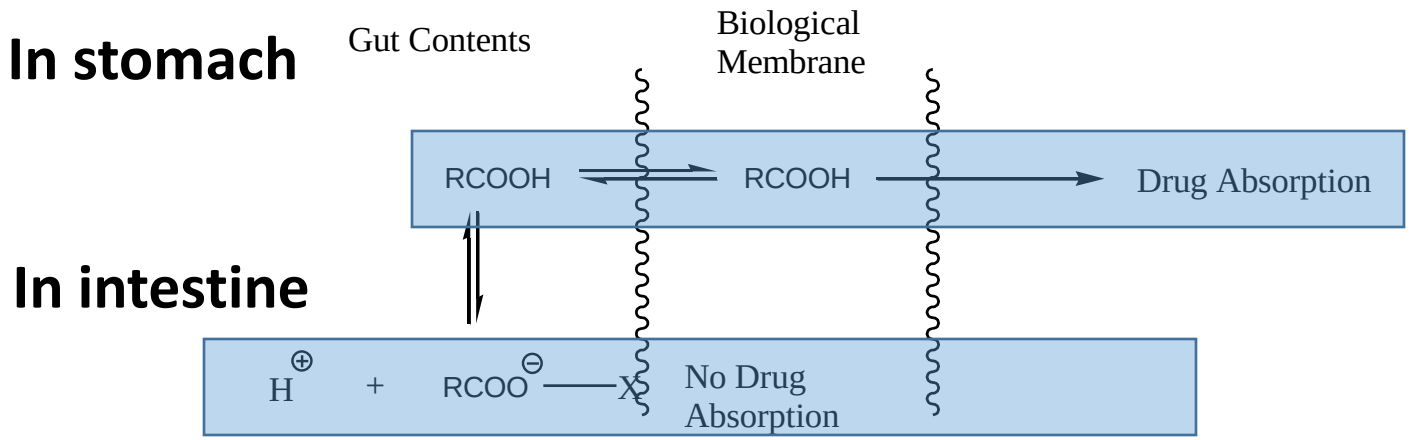
For base substance

$$P_{app} = \frac{P}{1+10^{pKa-pH}}$$

- For acids, at pH values below the pKa, ***P_{app}*** = P.
- At pH values above the pKa, the value of ***P_{app}*** decreases because the species is ionizing and moving into the aqueous layer.

PARTITIONING OF ACIDS AND BASES

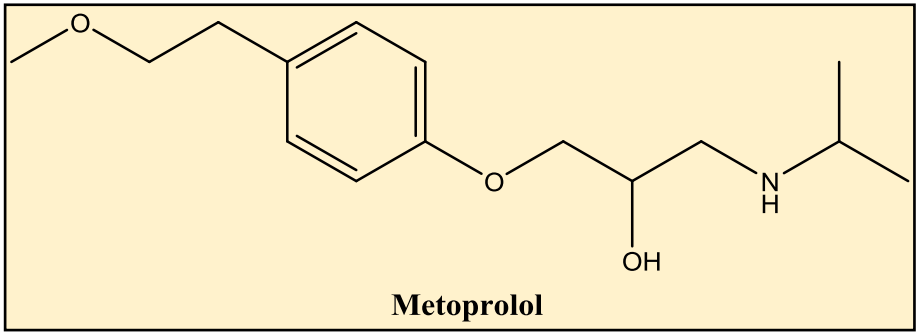
Consider drugs that are acids, for example RCOOH, which has a pKa of 4.0, and a partition coefficient of 200.



- P_{app} becomes 198 in the stomach suggesting that absorption will take place.
- pH 8.0 in the small intestine, the calculated P_{app} suggests no absorption.

- ✓ **Because of the problems associated with ionization of compounds, the term log *D* (the log of the distribution coefficient) is used to describe the lipophilicity of the ionizable compound.**
- ✓ **log *D* describes the log *P* of ionizable compound at a particular pH.**

Example: Metoproplol (change in log *D* as a function of pH)



Metoprolol

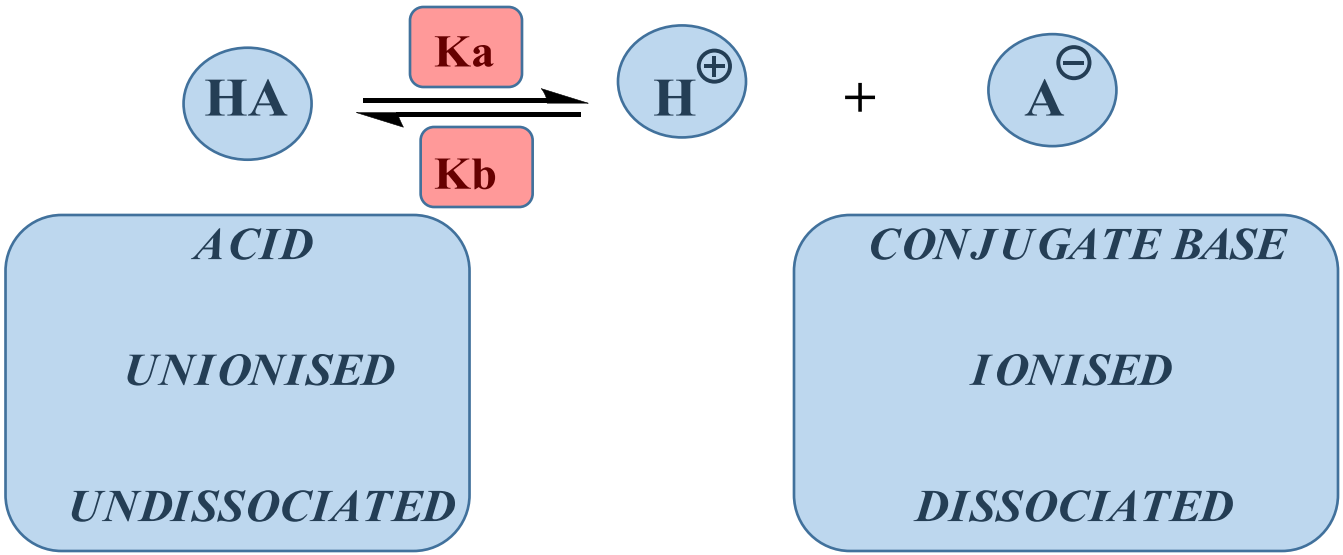
Log *D*	pH
-1.31	2.0
0.12	7.5
1.73	10.0

- ❑ **log *P* of unionizable compound is independent of pH.**

Ionisation and dissociation

ACIDS ARE PROTON DONORS

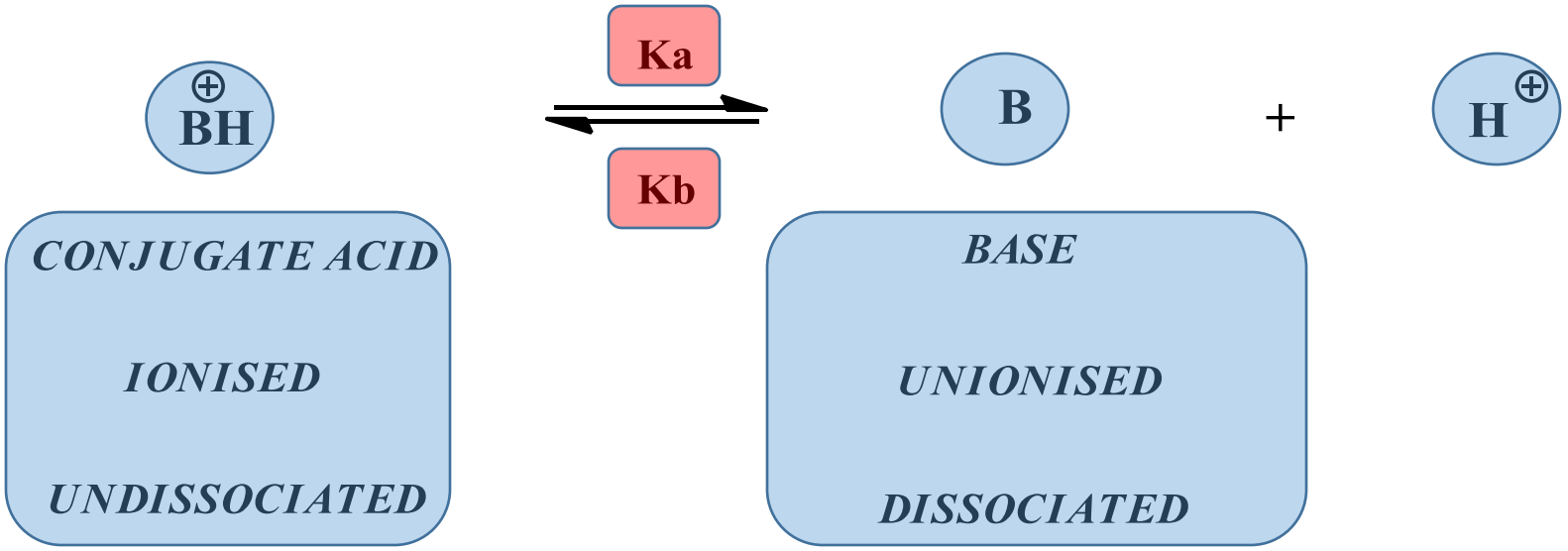
Acid is a substance that can dissociate to give H^+ and a negative ion (anion) which is called a conjugate base:



Ionisation and dissociation

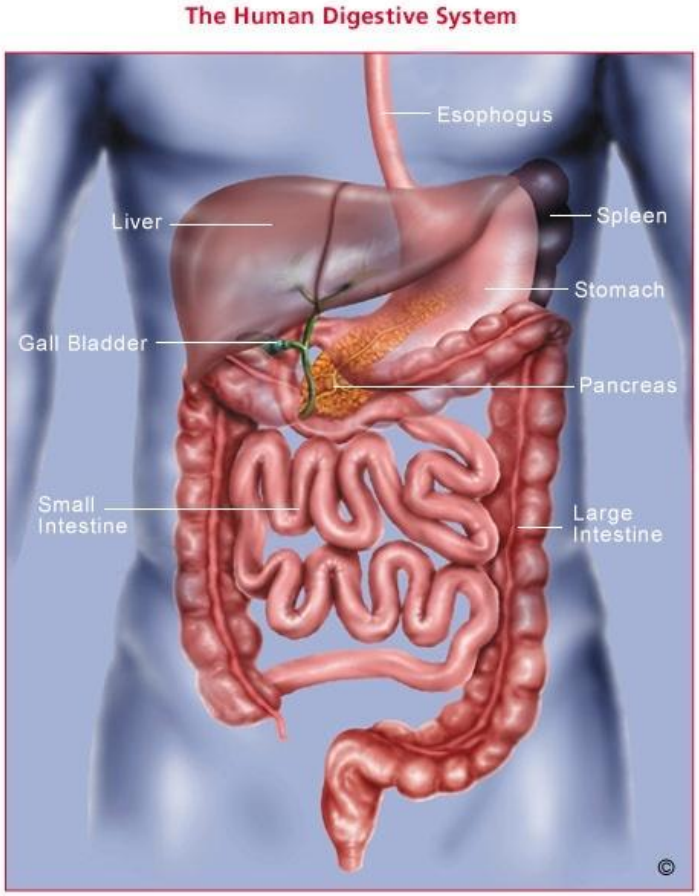
BASES ARE PROTON ACCEPTORS

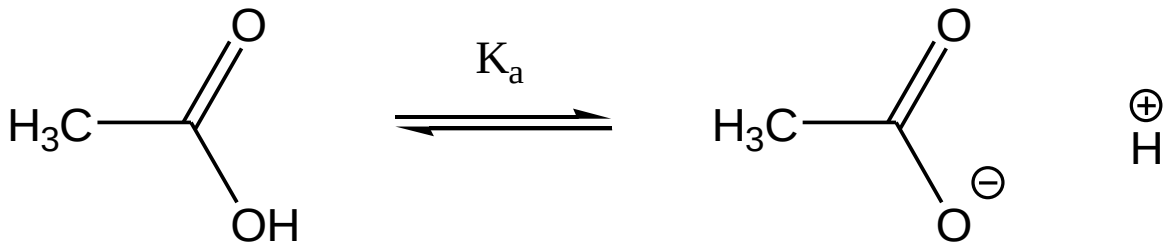
Bases can accept a proton to form the positively charged cation (conjugate acid of the base):



pH in different body compartments

Plasma	7.35 – 7.45
Buccal cavity	6.2 – 7.2
Stomach	1.0 – 3.0
Duodenum	4.8 – 8.2
Jejunum & ileum	7.5 – 8.0
Colon	7.0 – 7.5





$$K_a = \frac{[CH_3COO^-][H^+]}{[CH_3COOH]}$$

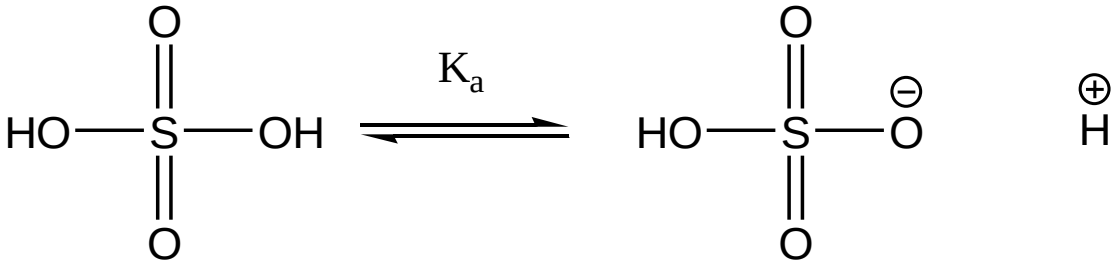
K_a for CH_3COOH is approximately 10^{-5}

i.e. only 1 molecule in 100,000 is DISSOCIATED (ionised).

$-\log_{10}K_a = pK_a$

So pKa for acetic acid is 5

$$K_a = \frac{1}{10^5}$$



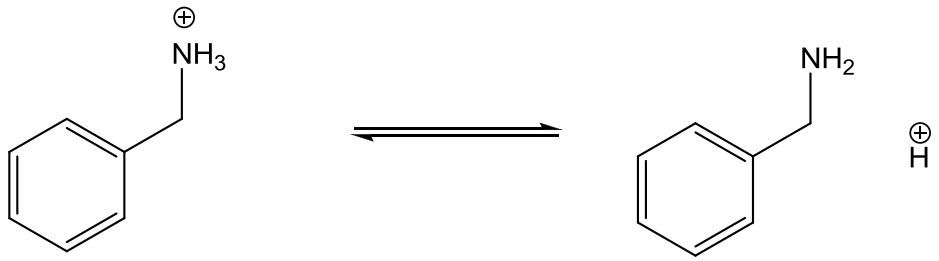
$$K_a = \frac{[HSO_4^-][H^+]}{[H_2SO_4]}$$

K_a for H_2SO_4 is approximately 10^5

i.e. 100,000 molecules are DISSOCIATED (ionised) for every one undissociated.

The pKa of H_2SO_4 is therefore -5

$$K_a = \frac{10^5}{1}$$



$$K_a = \frac{[PhCH_2NH_2][H^+]}{[PhCH_2NH_3^+]}$$

K_a for $PhCH_2NH_3^+$ is approximately 10^{-9} (pKa = 9)

i.e. only 1 molecule in 1,000,000,000 is DISSOCIATED (UNIONISED).

A weak conjugate acid does not easily donate its proton (1 molecule in 1,000,000,000 donates a proton)

Therefore a strong base willingly accepts a proton (1,000,000,000 molecules accept a proton for every one)

$$K_a = \frac{1}{10^9}$$

pKa is a different term than pH

pH is simply a measure of the $[H^+]$ concentration in a given solution.

pH = 1 .....the environment is acidic

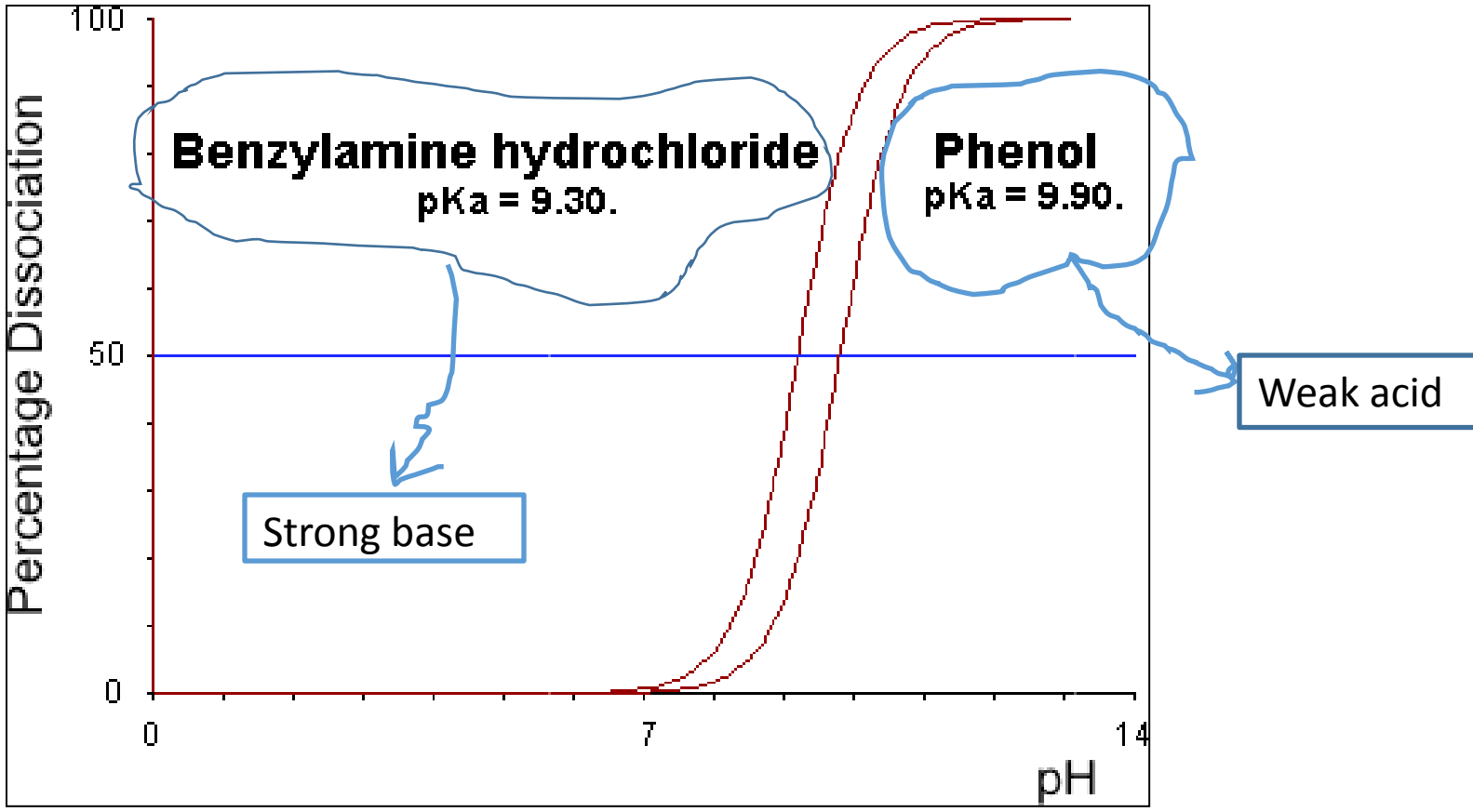
pKa = 1 DOES NOT mean an acidic molecule

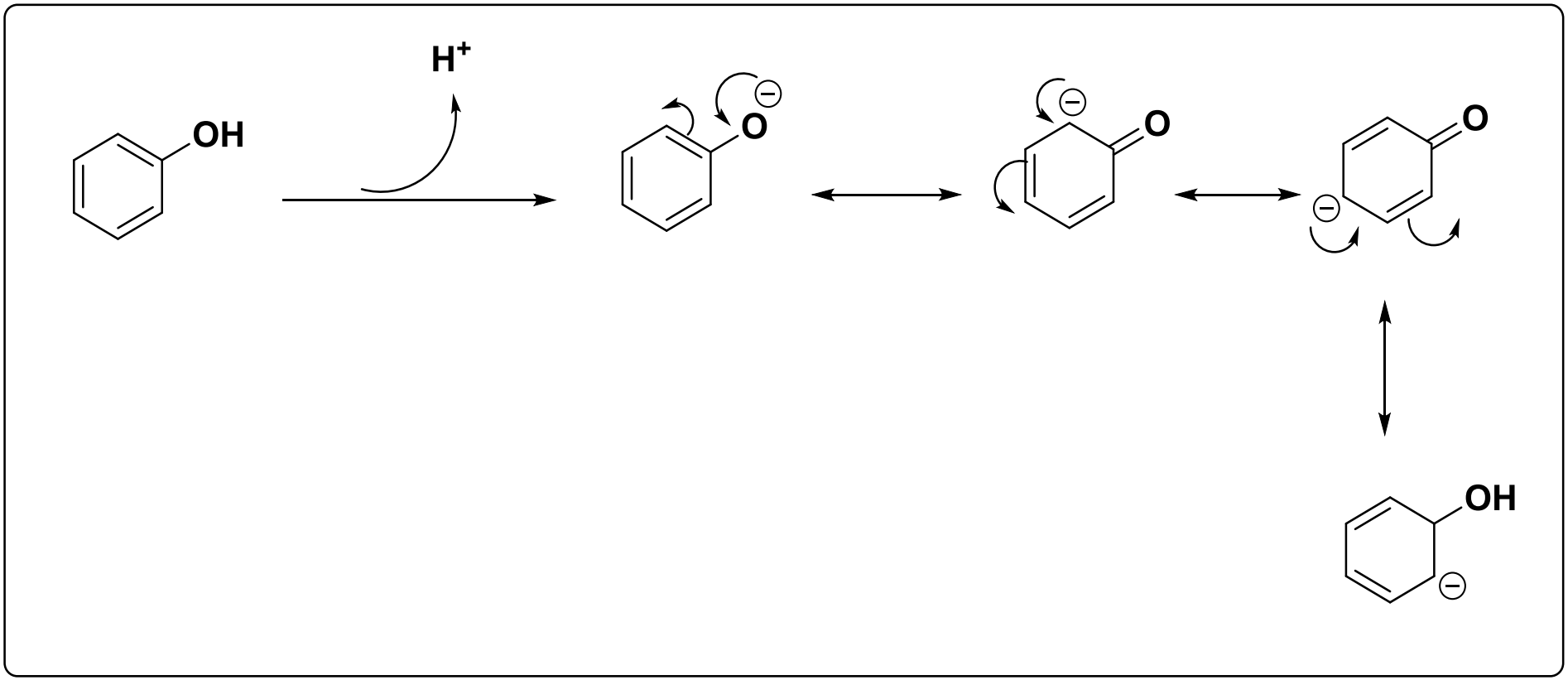
pH = 14 .....the environment is basic

pKa = 1 DOES NOT mean a basic molecule

Can pKa value tell the molecule is acidic or basic?

The answer is NO.





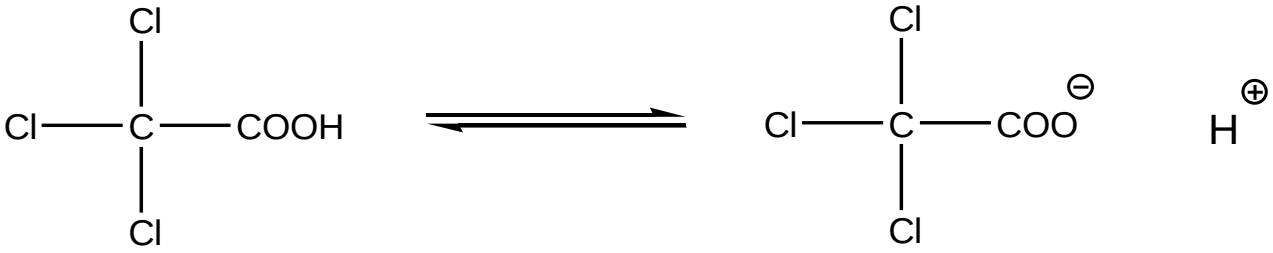
Phenoxide anion is stable by resonance that means phenol can give stable anion upon donating its proton. So phenol is acidic.

Factors affecting the strength of acid

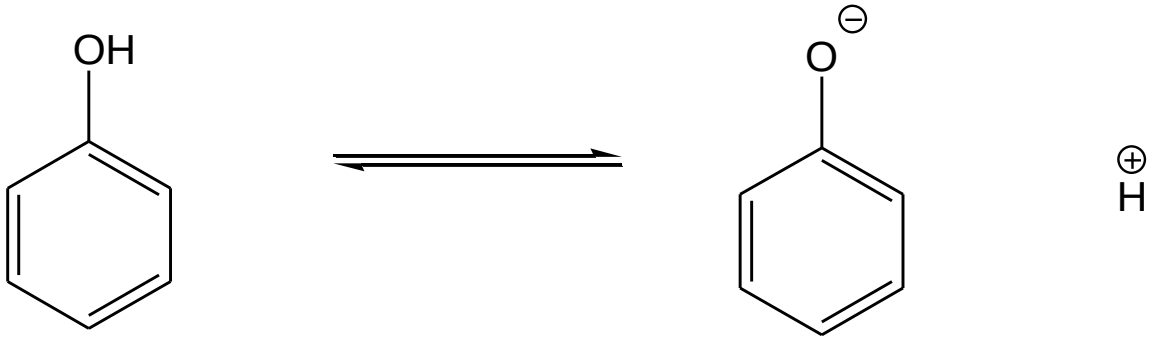
- The more stable conjugate base (anion) formed, the stronger the acid will be.

- So any factor will stabilize the anion will increase the acidity of the group, such as resonance and induction stabilization.

- Stable negative charge results from lowering the electron density on the atom.



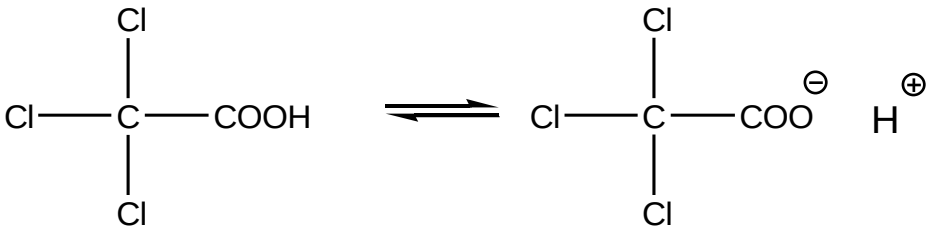
pKa = 0.9



pKa = 10.0

Which one is the stronger acid?

Considering Ka values relates ratio of products to reactants

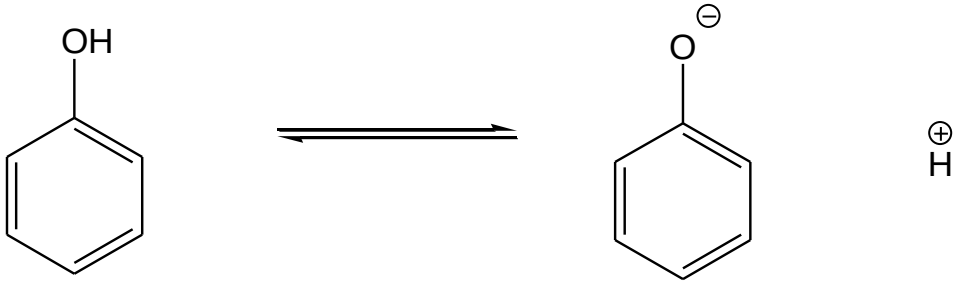


pKa = 0.9

Ka = $10^{-0.9}$

$$K_a = \frac{[Cl_3COO^-][H^+]}{[Cl_3COOH]}$$

$$K_a = \frac{1}{10^{0.9}}$$



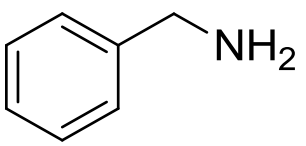
pKa = 10.0

Ka = 10^{-10}

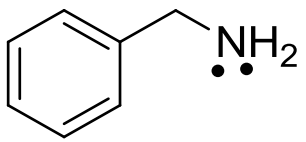
$$K_a = \frac{[PhO^-][H^+]}{[PhOH]}$$

$$K_a = \frac{1}{10^{10}}$$

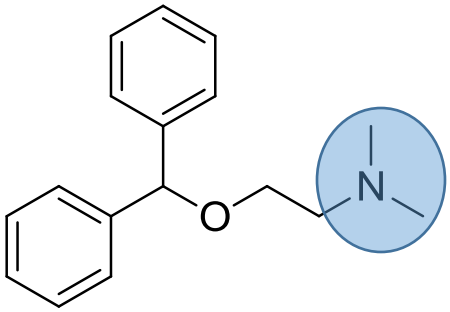
Phenols are weaker acids than acetates



Basicity means availability of electrons

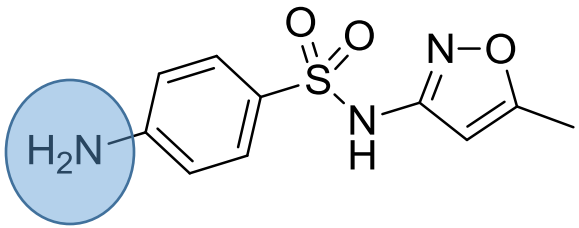


- If the atom has an available lone pair of electrons, it can act as a base…
- The availability of these electrons will determine the strength of the base.
- As a result of that, aromatic amino group is much weaker base than aliphatic one.



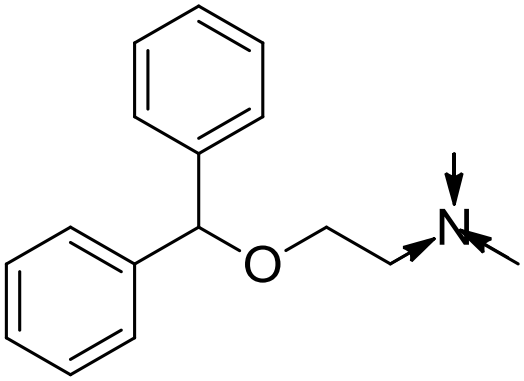
Diphenhydramine
Antihistaminic agent

Aliphatic amine.....strong base..... Pka of 10.6



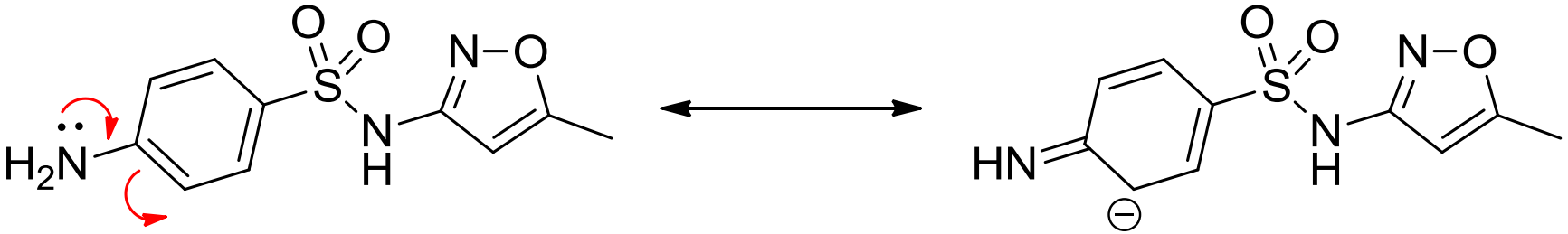
Sulfamethoxazole
Antibacterial agent

Aromatic amine..... weaker base..... Pka of 4.6



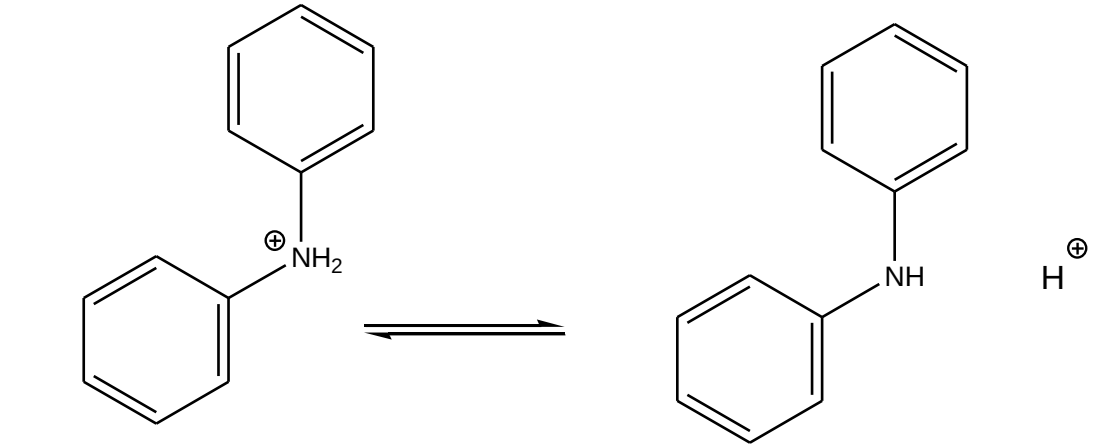
tertiary amine: methyl groups compared to phenyl group are better donating groups by induction **(more available lone pair of electrons)**

Diphenhydramine

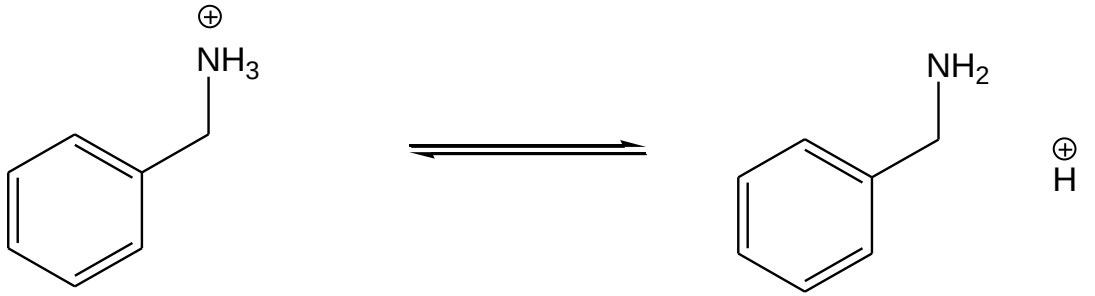


Sulfamethoxazole

the lone pair of electrons are not available....delocalized through the phenyl ring **(stabilized by resonance)**

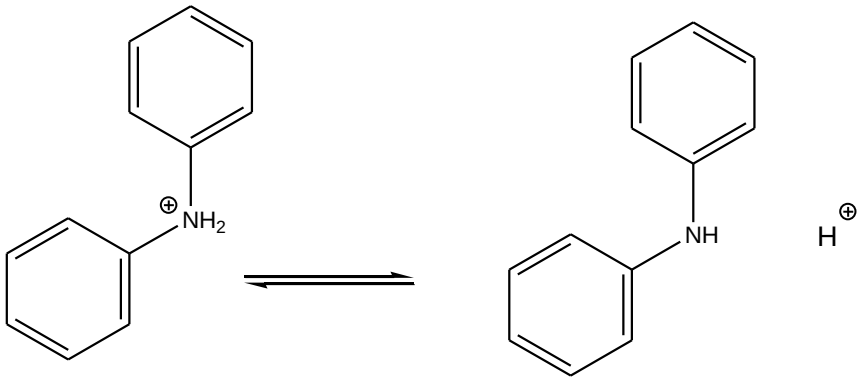


pKa = 0.5



pKa = 9.0

Which one is the stronger base?

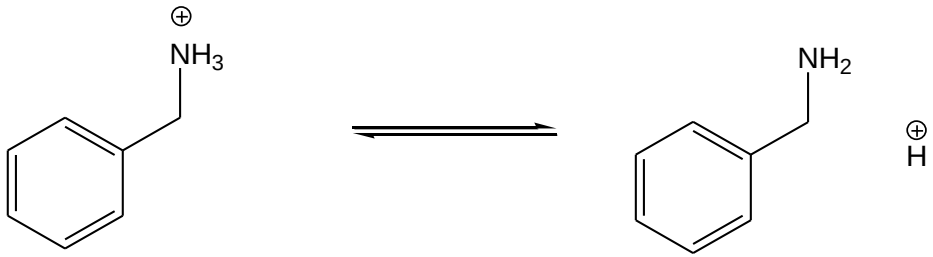


pKa = 0.5

Ka = $10^{-0.5}$

$$K_a = \frac{[Ph_2NH][H^+]}{[Ph_2NH_2^+]}$$

$$K_a = \frac{1}{10^{0.5}}$$



pKa = 9.0

Ka = 10^{-9}

$$K_a = \frac{[PhCH_2NH_2][H^+]}{[PhCH_2NH_3^+]}$$

$$K_a = \frac{1}{10^{9}}$$

Aromatic amines are weaker bases than aliphatic amines

We can quantify how pH changes the ratio of dissociated to undissociated species as follows:

$$pH - pK_a = \log_{10} \frac{[Dissociated]}{[Undissociated]}$$

$10^{(pH-pKa)} = \frac{[Dissociated]}{[Undissociated]}$	$anti\log(pH - pK_a) = \frac{[Dissociated]}{[Undissociated]}$

- For acidic drugs, this ratio describes the % ionization.
- For basic drugs, this ratio describes the % unionized form to the ionized form.

Effect of ionization on pharmacokinetic and pharmacodynamic profile

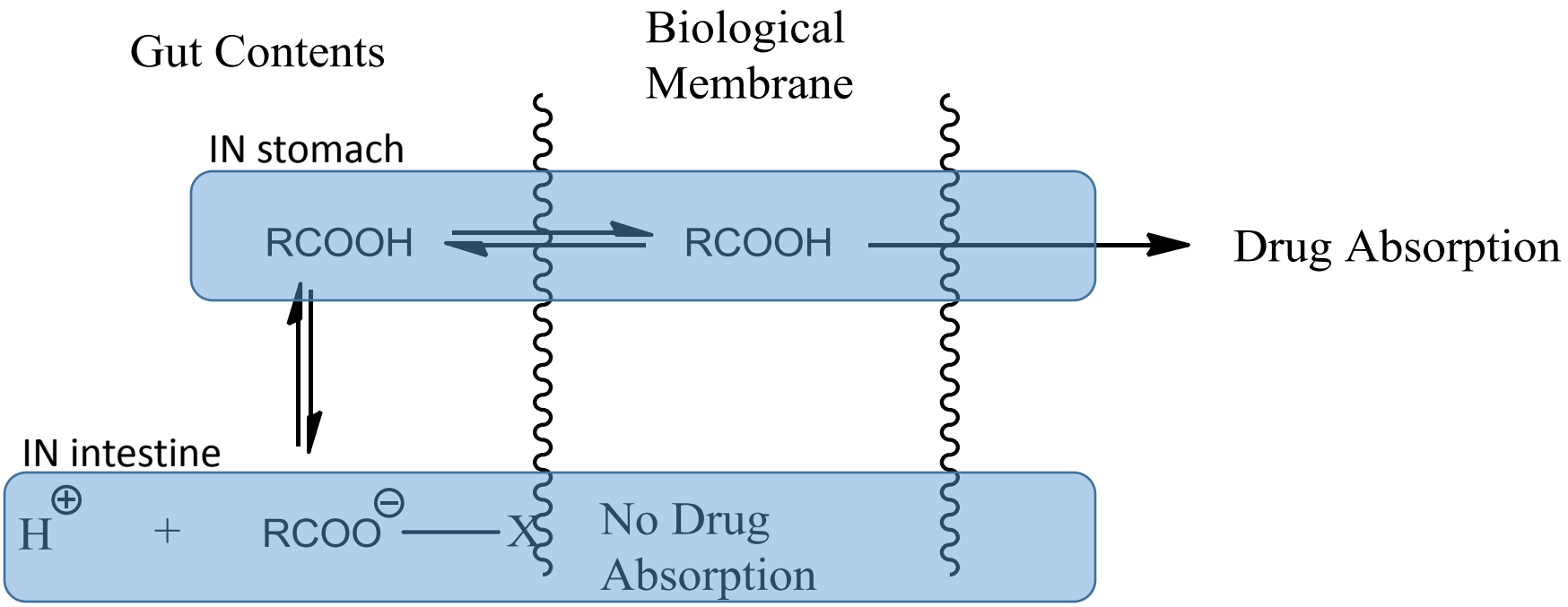
Importance of pKa values for acidic and basic drugs

- Only the unionised form of a drug can partition across biological membranes (providing the unionized form is lipophilic).

- The ionised form tends to be more water soluble [required for drug administration and distribution in plasma].

PARTITIONING OF ACIDS AND BASES

For acidic drugs, with a pKa of 4.0, the ionization state will be as follows:-

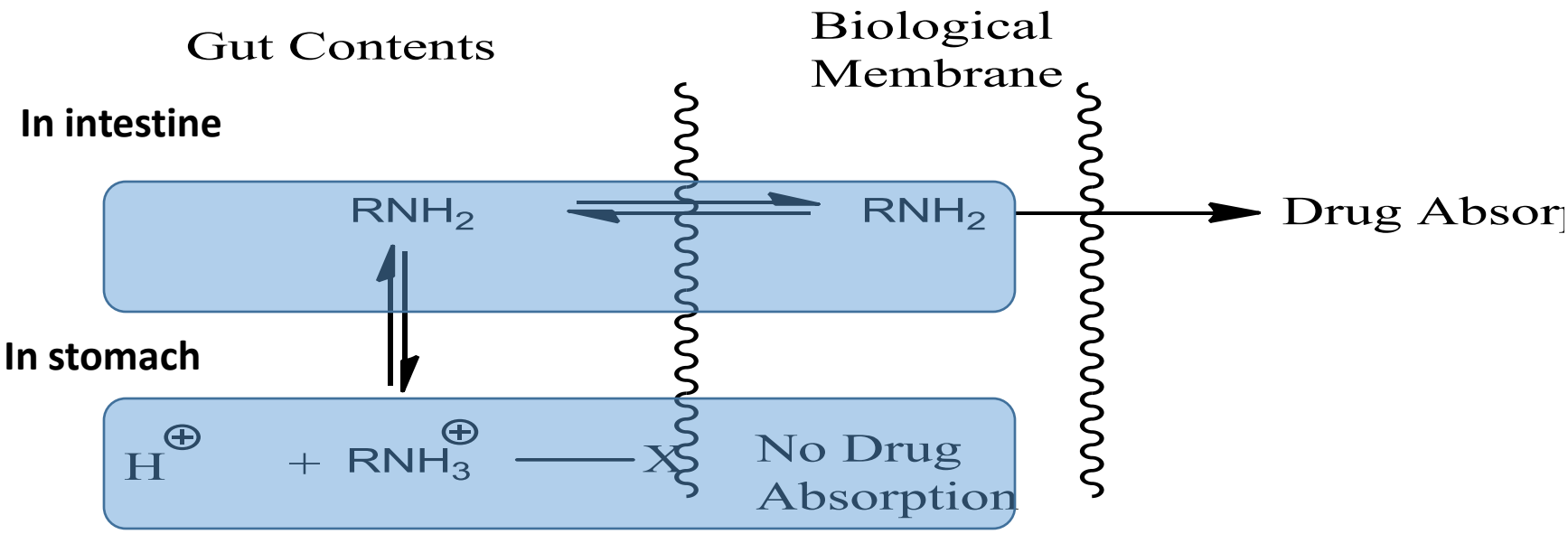


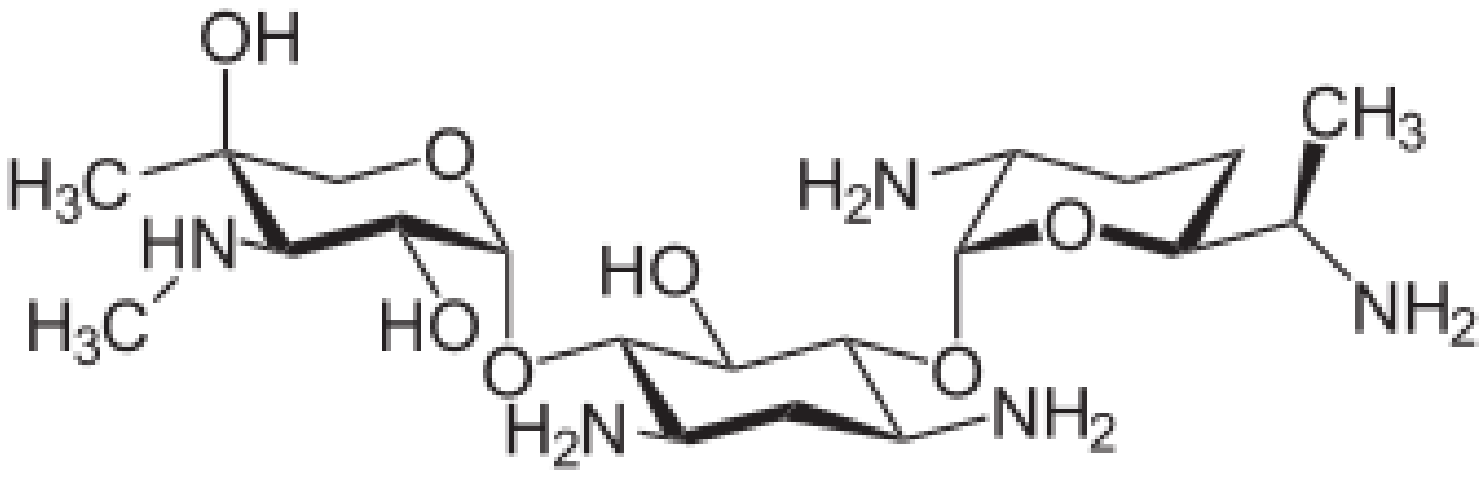
PARTITIONING OF ACIDS AND BASES

- If the pH shifts the balance towards the unionized form, the drug would be absorbed.
- If the pH shifts the balance towards the ionized form, the drug would not be absorbed.
- Assume the pH of the stomach is 2.0 and the pH of the small intestine is 8.0. Where would you expect absorption to take place from?

PARTITIONING OF ACIDS AND BASES

For basic drugs, the ionization will be as follows:-



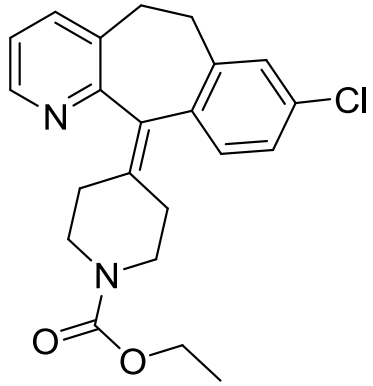


Gentamicin

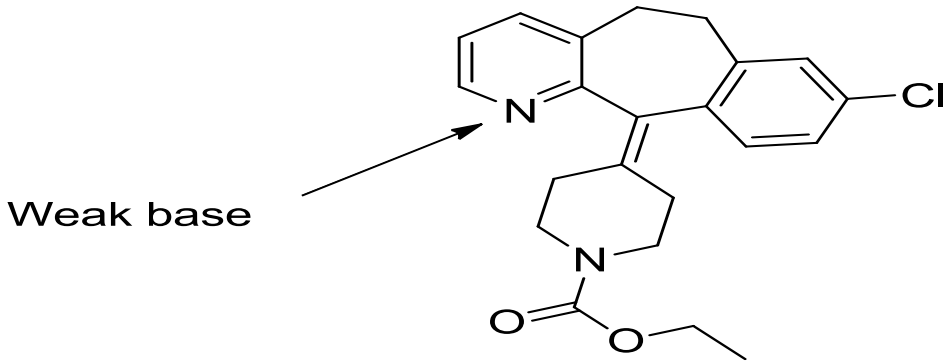
So we should expect that this compound will not be readily absorbed though the lipophilic membranes although it is in the unionized form.

Practice question

- **Loratadine is an orally available drug, it has a pKa of 5, answer the followings according to its structure:**
  - **Is it basic, acidic or neutral compound?**
  - **Calculate the % ionization:**
    - **In stomach (pH = 2):**
    - **In intestine (pH = 8):**



  - **Based on your calculation, from where do you think loratadine will be absorbed?**



$$pH - pK_a = \log_{10} \frac{[Dissociated]}{[Undissociated]} \qquad \frac{[Unionized]}{[Ionized]}$$

(for basic compounds)

Under acidic pH (stomach)	Under basic pH (intestine):
$\frac{[Unionized]}{[Ionized]}$	$\frac{[Unionized]}{[Ionized]}$
% ionization = 10^{-3} So 99.9% (under stomach pH)	% ionization =0.1%
So loratadine will be mainly in unionized form in intestine only. so main site of absorption is intestine and not stomach.	

Effect of Ionization on Drug Lipophilicity

- When the drug become ionized, this will increase its water solubility because there will be a better solvation by ionic-dipole interaction between ionized drug and water molecule.

- So, once the drug get ionized it will have lower logP than the unionized from (more polar).

- Because most drugs are ionizable at different body pH ranges, the % ionization must be taken into consideration when we are about to synthesize or develop certain drug.

- Lipophilicity will determine from where the drug will be absorbed and what target tissue will reach.

Oral administration and absorption

- If a drug is to be absorbed through the mucosal membranes that line the gut, then it must be in its lipophilic unionised form to partition out of the aqueous medium.
- The partition co-efficient of the unionised form will also determine how much is absorbed.
- The absorption phase of the dose-response curve is therefore heavily influenced by the pKa and log P of a drug.

Oral administration and absorption

Orally administered drugs must have:

- ❑ logP < 5.
- ❑ Not more than 10 hydrogen bond acceptors.
- ❑ Not more than 5 hydrogen bond donors.
- ❑ A molecular weight less than 500 Dalton.

These points are called ‘’ Lipinski’s rule of five’’

- Not more than 7 rotatable bonds.

Applications of Drug Ionization

For acids:

1. ***high pka*** **means the species is predominantly unionised, is a bad proton donor, and a weak acid**
2. ***low pka*** **means the species is predominantly ionised, is a good proton donor, and a strong acid**

pH < pKa by 2 units, 99% unionised

pH > pKa by 2 units, 99% ionised

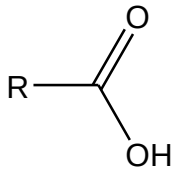
For bases:

1. ***high pka*** **means the species is predominantly ionised, is a good proton acceptor, and a strong base**
2. ***a low pka*** **means the species is predominantly unionised, is a bad proton acceptor, and a weak base**

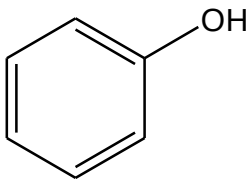
pH < pKa by 2 units, 99% ionised

pH > pKa by 2 units, 99% unionised

Common acidic functional groups and their pKa values



4-5



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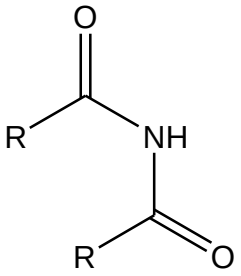

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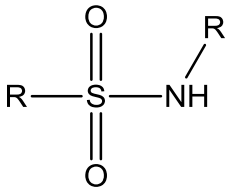

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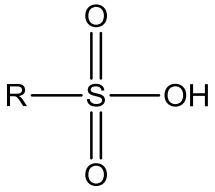
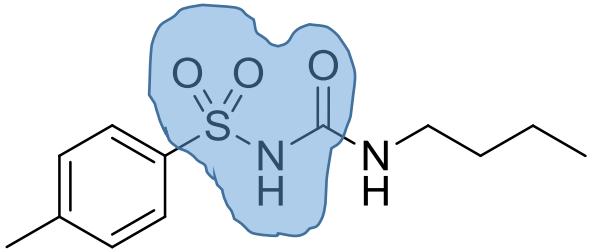
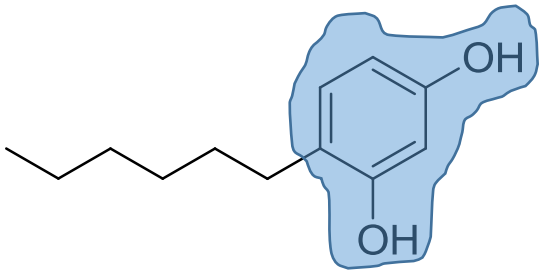


<2

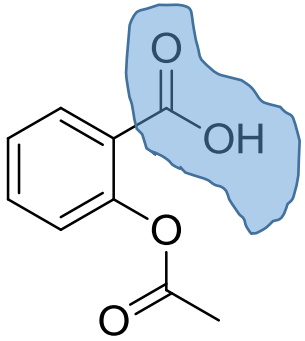
Examples of acidic drugs



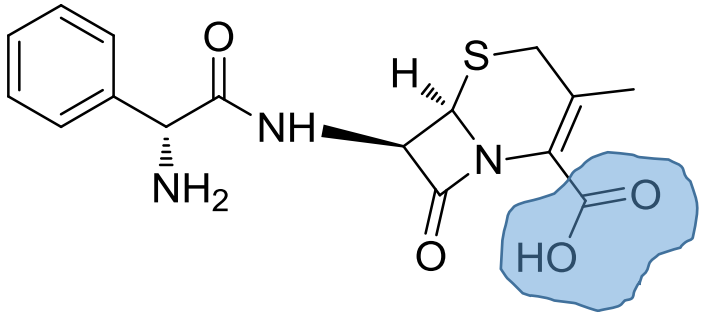
Tolbutamide
hypoglycemic agent



4-hexylresorcinol
topical anesthetic

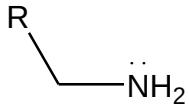


Aspirin
NSAID



Cephalexin
Antibacterial agent

Common basic functional groups and their pKa values



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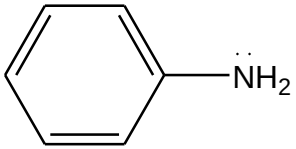

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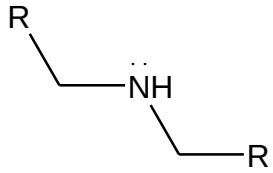
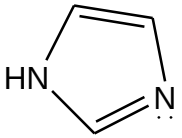


10.6-11.0



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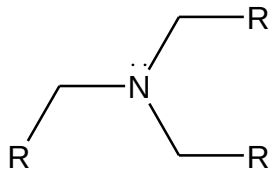
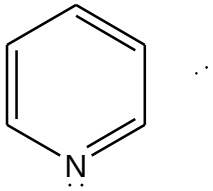
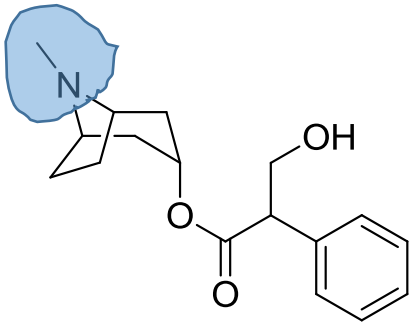


9.8-10.8

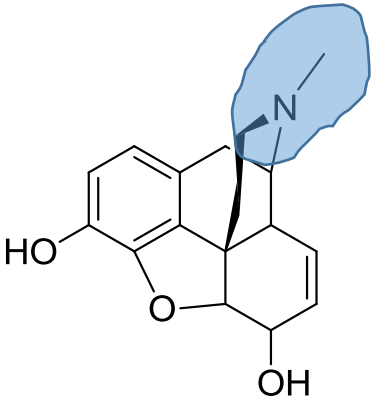


5.2

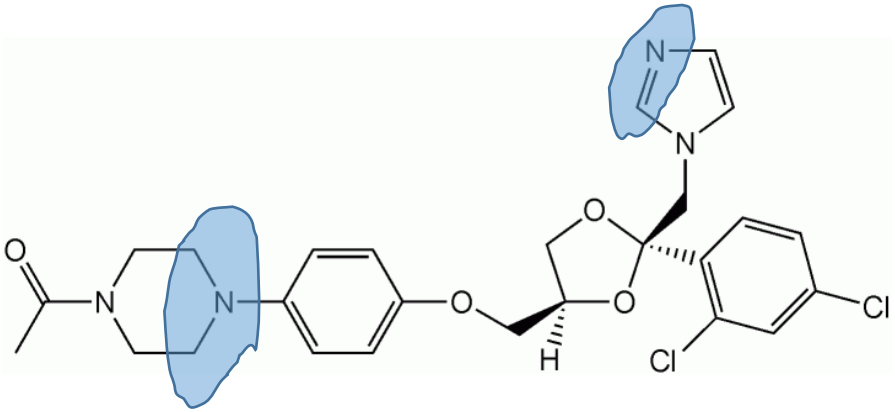
Examples of basic drugs



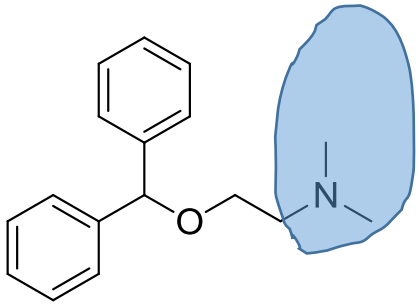
Atropine
Anticholinergic agent



Morphine
opioid analgesic

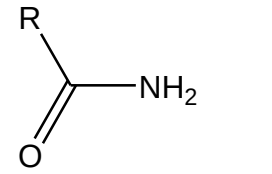


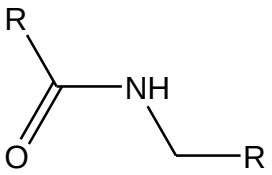
Ketoconazole
Antifungal agent

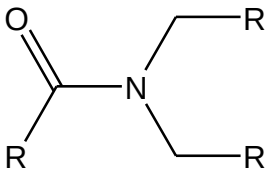


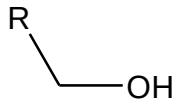
Diphenhydramine
Antihistaminic agent

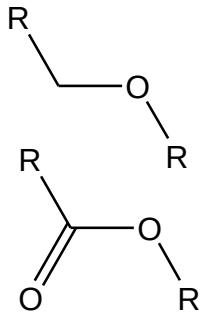
Common neutral functional groups

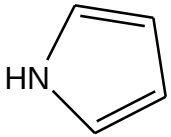


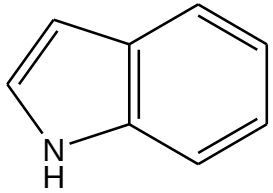






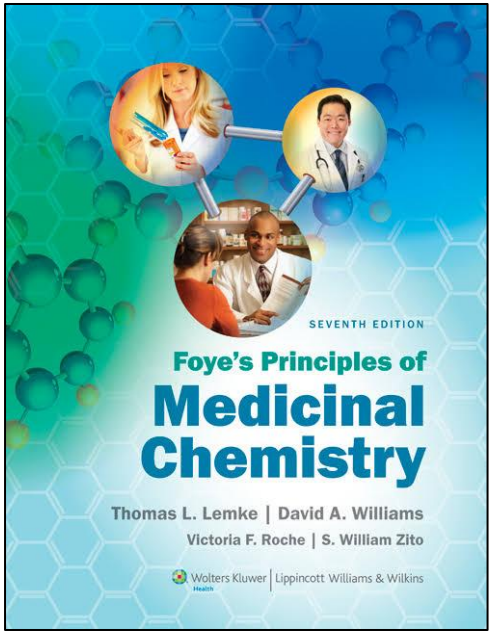


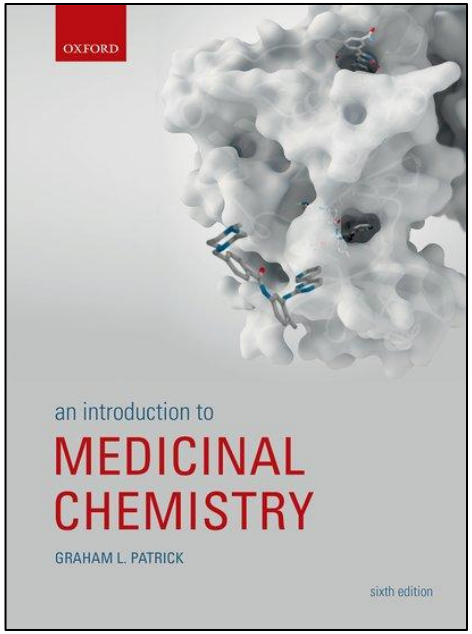


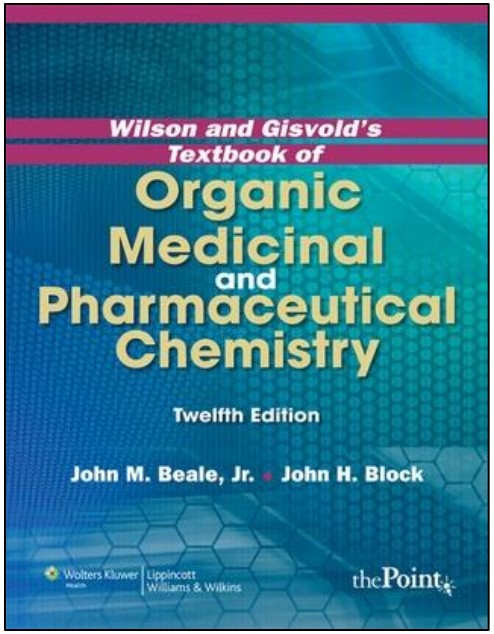


Factors to be considered while selecting a suitable route of drug administration

- Molecular properties of the drug
- Physiological nature of the route
- Patient compliance
- Onset of action
- Disease condition
- Systemic or local effect (side effects)
- Metabolism







1. **An introduction to Medicinal Chemistry by Graham L. Patrick. 4th edition, Oxford, 2009**
2. **Wilson and Gisvolds text book of organic medicinal and pharmaceutical chemistry by John H. Black and John M. Beale, jr. 12th edition, Lippincott Williams and Wilkings 2011.**
3. **Foyes principle of medicinal chemistry by David H. Williams, Thomas L. Leuke, Williams O. Foye. Lippincott William and Wilkins. 7th edition, 2013.**


Thank
You