pharmaceutical chemistry

3rd stage

lec. 3

Dr. Leaqaa

Acid —Base properties :

** greatly influence its biodistribution and partitioning characteristics.

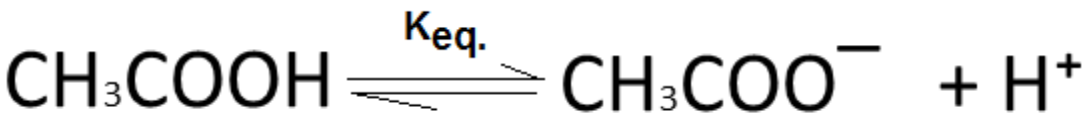
- Lowry and Brønsted.

* proton donor (acid) and
* proton acceptor (base) (charged or uncharged)

Acid-Conjugate Base

Table 2-1.

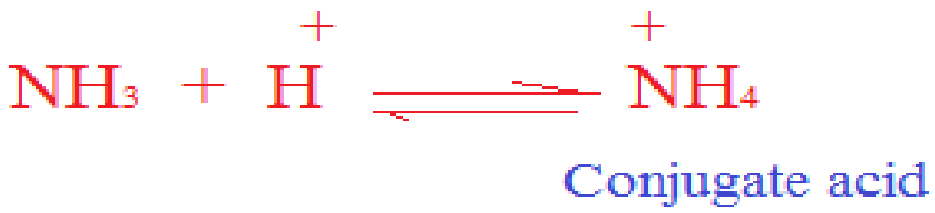
* Each acid, or proton donor, yields a conjugate base.



Base-conjugate acid:

table: 2.1

each base ,yield conjugate acid (product produced from the addition of a proton to the base)

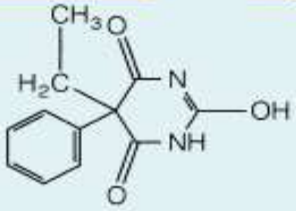
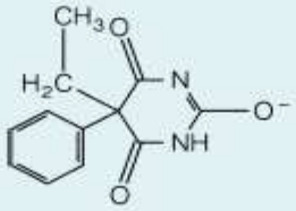


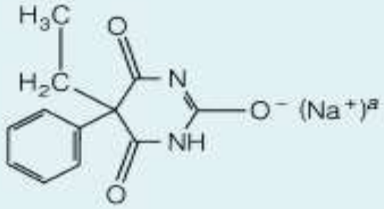
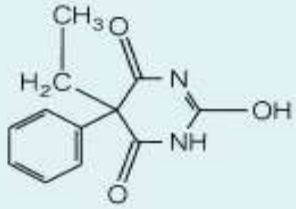
Representative examples of pharmaceutically important drugs

Acid		Base		Conjugate Acid		Conjugate Base
Hydrochloric acid						
(a) HCl	+	H_2O	⟶	H_3O^+	+	Cl^-
Sodium hydroxide						
(b) H_2O	+	NaOH	⟶	H_2O	+	$OH^-(Na^+)^a$
Sodium dihydrogen phosphate and its conjugate base, sodium monohydrogen phosphate						
(c) $H_2PO_4^-(Na^+)^a$	+	H_2O	⇌	H_3O^+	+	$HPO_4^{2-}(Na^+)^a$
(d) H_2O	+	$HPO_4^{2-}(2Na^+)^a$	⇌	$H_2PO_4^-(Na^+)^a$	+	$OH^-(Na^+)^a$
Ammonium chloride and its conjugate base, ammonia						
(e) $NH_4^+(Cl^-)^a$	+	H_2O	⇌	$H_3O^+(Cl^-)^a$	+	NH_3
(f) H_2O	+	NH_3	⇌	NH_4^+	+	OH^-
Acetic acid and its conjugate base, sodium acetate						
(g) CH_3COOH	+	H_2O	⇌	H_3O^+	+	CH_3COO^-
(h) H_2O	+	$CH_3COO^-(Na^+)^a$	⇌	CH_3COOH	+	$OH^-(Na^+)^a$

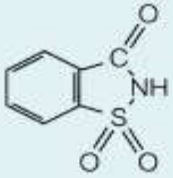
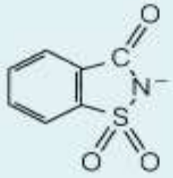
Indomethacin and its conjugate base, indomethacin sodium, show the identical acid–base chemistry as acetic acid and sodium acetate, respectively.

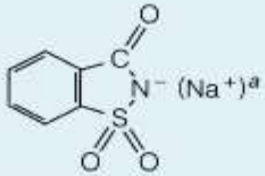
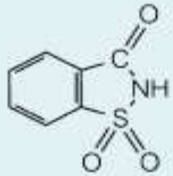
Phenobarbital and its conjugate base, phenobarbital sodium

(i)  + H_2O ⇌ H_3O^+ + 

(j) H_2O +  ⇌  + $OH^-(Na^+)^a$

Saccharin and its conjugate base, saccharin sodium

(k)  + H_2O ⇌ H_3O^+ + 

(l) H_2O +  ⇌  + $OH^-(Na^+)^a$

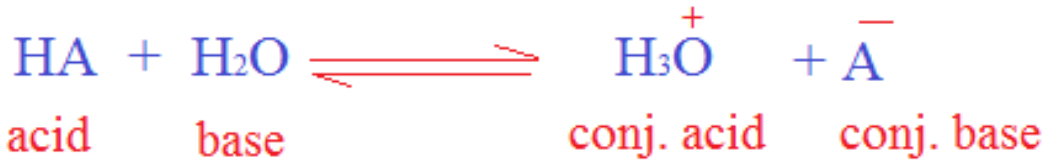
Ephedrine HCl and its conjugate base, ephedrine

Acid Strength

* ability of acid to give proton as table, to indicate which sequences are unidirectional or show only a small reversal.

*The information of acid strength is given by pka.

pKa = -log ka

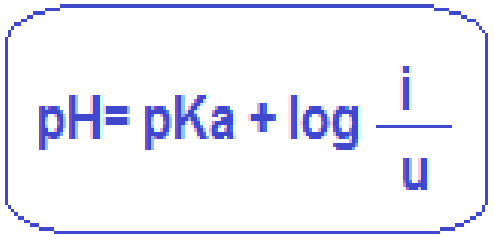


$$K_a = \frac{[\text{conj. acid}][\text{conj. base}]}{[\text{ acid}]}$$

$$\boxed{Ka = K_{eq} \times [H_2O]}$$

pH= pKa+ log [conj.base]/[acid]

*hinderson-Hasselbalch eq.



A very similar set of equations is obtained from the reaction of a protonated amine BH^+ in water.

$$K_a = \frac{[\text{conj. acid}][\text{conj.base}]}{[\text{acid}]}$$

$$K_a = K_{eq} \times [H_2O]$$

$$K_a = \frac{[H_3O^+]\,[B]}{[BH^+]}$$

$$pH = pKa + \log \frac{[\text{conj. base}]}{[\text{acid}]}$$

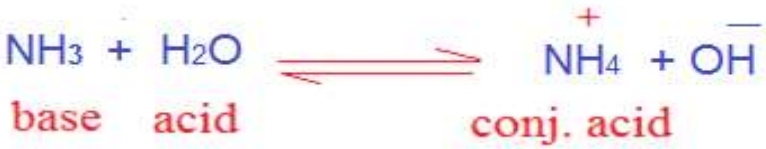
$$pH = pKa + \log \frac{u}{i}$$

What about weak bases & weak acids in aqueous solutions.

- using the relationship in Equation:

$$pK_a + pK_b = 14$$

It is now more common to express the basicity of a chemical in terms of pka .since pka for a base is in reality the of the conjugate acid of base (acid donor 9.3 or protonated form, BH^+), e.g. $NH_3 \rightarrow$pka=9.3



* A general rule for determining whether action is strong or weak acid or base:

- pKa < 2
- pka = (4-6)
- pka = (8-10)
- pka > 12

- the pka give indication of the acid property not represent anything else.e.g. potential toxicity

ex:

* Phenol (pKa = 9.9)

ephedrine HCl (pka=9.6).

- phenol → corrosive to the skin,
- ephedrine HCl → save when applied to the skin.

Why???

Percent Ionization

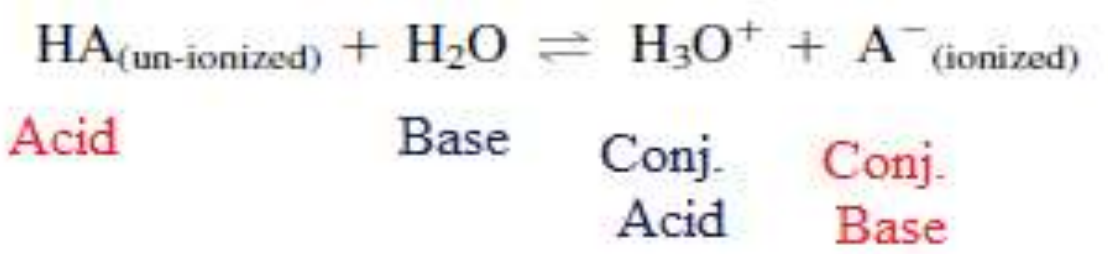
* pKa →important for formulation

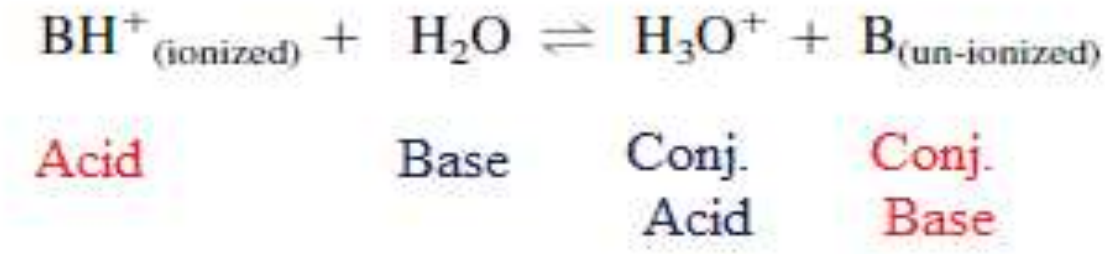
- acid can be divided into 2 types :

1. HA (un-ionized) ex: [inorganic acid (HCl, H_2SO_4),
   Enols
   COOH

amides and imides

2. BH^+ (ionized) : all protonated amine



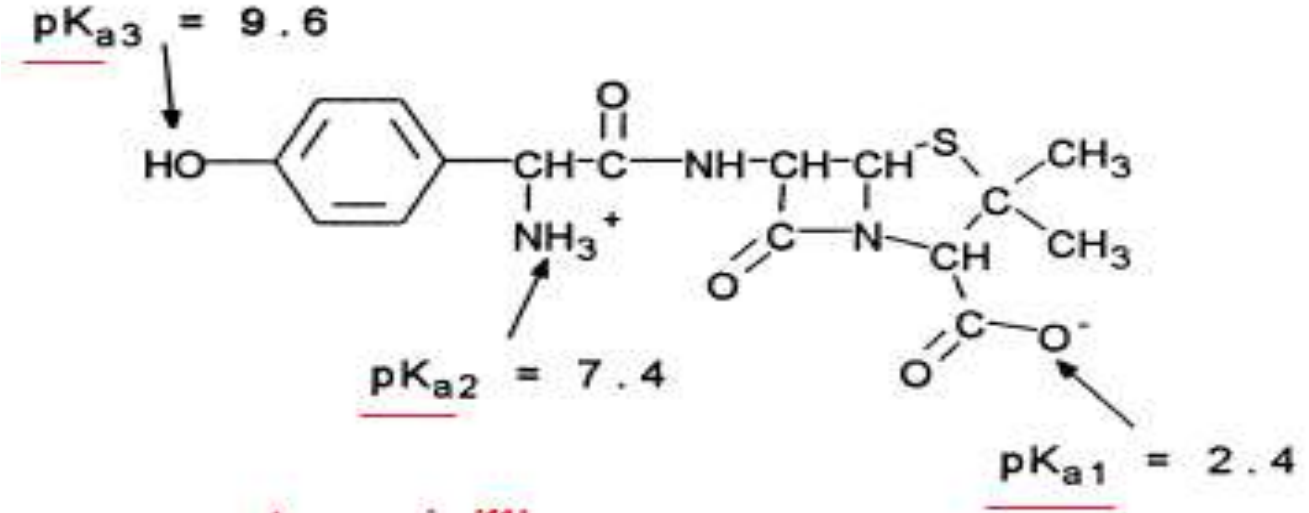


A polyfunctional drug can have several pKa's (e.g., amoxicillin).

at physiological pH 7.4.

-COOH [HA] acid, pka=2.4), → ionized

- NH_2 [BH^+ acid;pka2=7.4]
- phenol[HA acid,pka3=9.6



Amoxicillin

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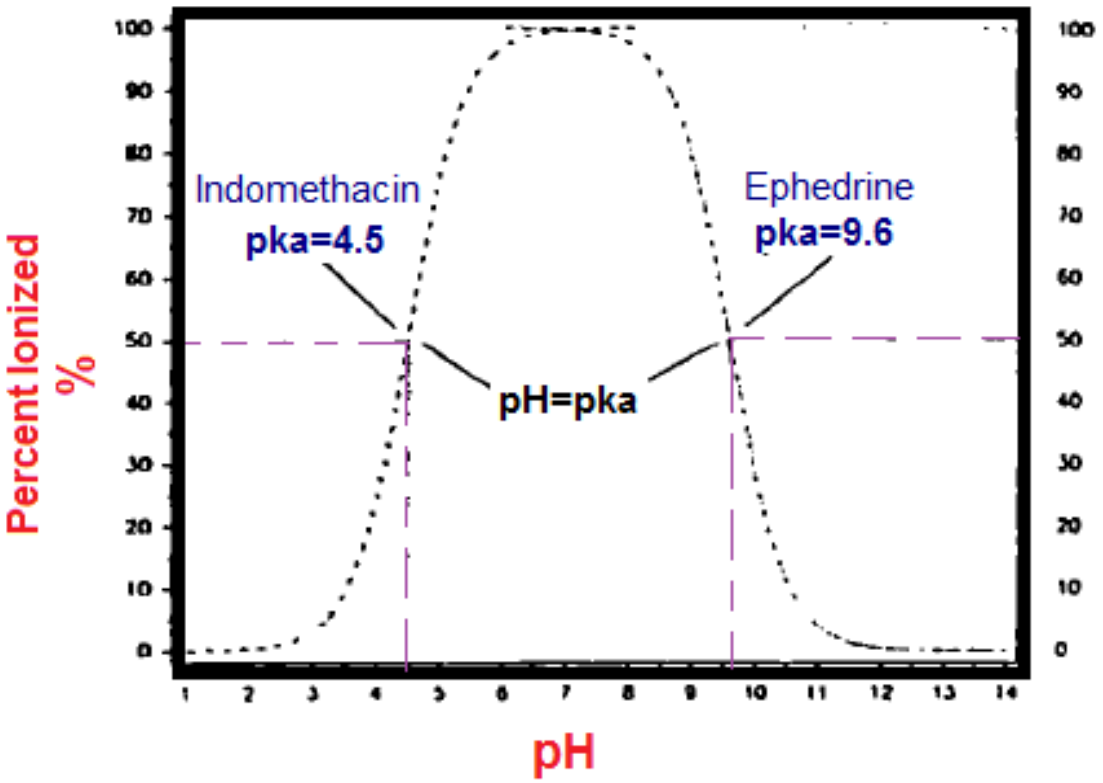
The % ionization of drug is calculated by using Equation for both HA acids and BH^+ acids. Respectively

* pH> pka = ionized
* PH< pka
* pH= pka

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pK_a - pH)}}$$

$$\% \text{ ionization} = \frac{100}{1 + 10^{(pH - pK_a)}}$$

A plot of p n can be
shifted sig omethacin
and BH' (p und is 50%
ionized (or



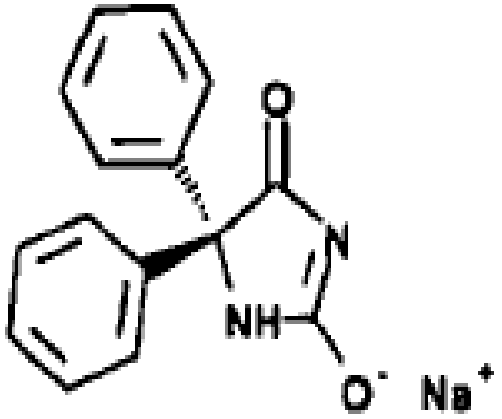
Percent Ionized versus pH for indomethacin & ephedrine

TABLE 2–6 Percentage Ionization Relative to the pK_a

	Ionization (%)	
	HA Acids	BH^+ Acids
pK_a – 2 pH units	0.99	99 0
pK_a – 1 pH unit	9.1	90 9
pK_a = pH	50 0	50.0
pK_a + 1 pH unit	90.9	9.1
pK_a + 2 pH units	99.0	0.99

-predict why the use of some preparations can cause problems and discomfort as a result of pH extremes. Phenytoin(HA acid: pKa= 8.3) injection must be adjusted to pH 12 with NaOH

In theory, a pH of 10.3 will result in 99.0% of anionic water-soluble conjugate base.



Phenytoin Sodium

This decrease in pH would result in the parent unionized phenytoin precipitating out of solution.

* To predict chemical stability problems

e.g. indomethacin (HA acid: pKa=4.5), which is unstable in alkaline media. So oral liquid dosage form (suspension) buffered at pH 4 – 5 .~ 50% be in the water-soluble form.so can not prepare as i.v.

Drug Distribution and pka

The pKa can have a pronounced effect on the pharmacokinetics of the drug, including the distribution

.

1-

* drugs in an ionized form will tend to distribute throughout the body more rapidly than will unionized (nonpolar) molecules.

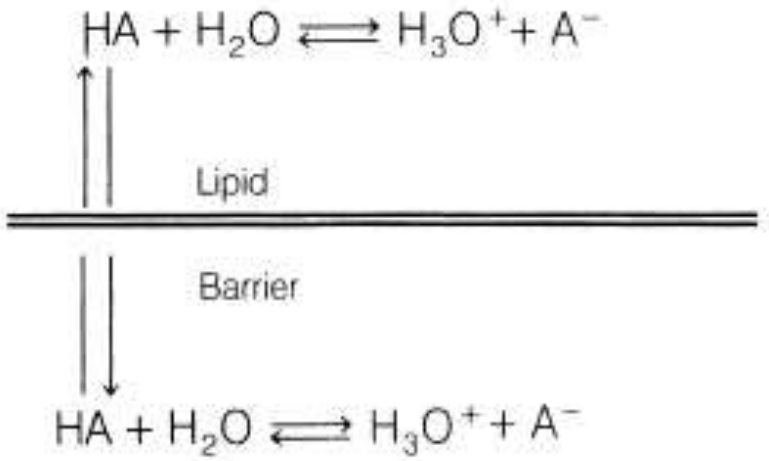
*the drug must leave the polar environment of the plasma to reach the site of action.

2-

* In general,

non polar membranes of capillary walls ,cell membrane & BBB in in unionized (non polar) form

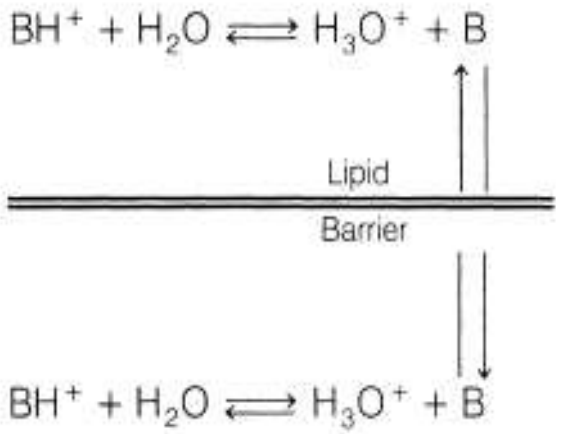
= for HA acid.



Passage of HA acids through lipid barriers

* BH^+ acids:

The un-ionized conjugate base (Free amine) is the species most readily crossing the nonpolar membranes



+ passage of BH acids through lipid barriers

So

* ionized form of drug will be mainly distribute
* un ionized form will be passage through the membrane.

3-

* Changing the pH Enviroment:

For orally ,administered drug:

acidic stomach, pH range 2 - 6 depending ???

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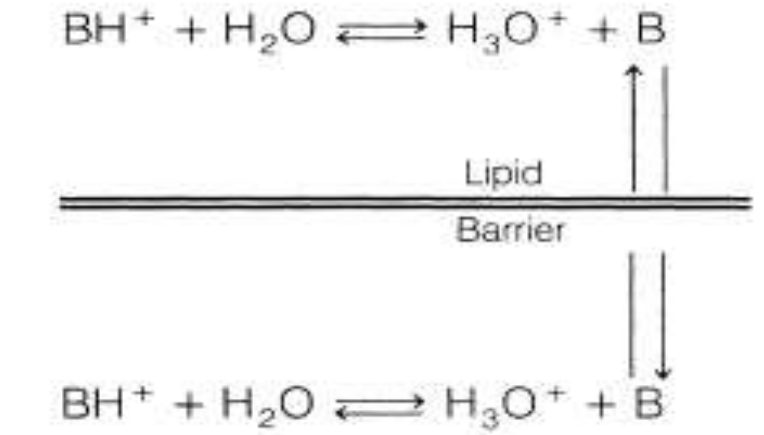
A) HA acids with pKa s of 4 - 5 will tend to be nonionic and be absorbed partially through the gastric mucosa.

why most acidic drugs are absorbed from the intestinal tract rather than the stomach ??

amines (pKa= 9 - 10) will be protonated (BH^+ acids) in the acidic stomach and usually will not be absorbed until reaching the mildly alkaline intestinal tract pH — 8).



+ passage of BH acids through lipid barriers

* plasma pH = 7.4

determinants of whether the drug will tend to remain in the aqueous environment of the blood or partition across lipid membranes into :

* hepatic tissue →metabolized,
* kidney → excretion,
* tissue depots,
* the receptor tissue.

-depending on the ratio [conj.base]/[acid] according on henderson-hasselblach eq. or % ionization