Acid/Conjugated Base and Base/Conjugated Acid Pairs

In biological systems, drug molecules face water everywhere and an acid-base reaction can occur. Water is an amphoteric molecule, can be either a weak base accepting a proton from acidic drugs to form the strongly acidic hydrated proton or hydronium ion (H_3O^+), or a weak acid donating a proton to a basic drug to form the strongly basic hydroxide anion (OH^-).

$$\text{Acid} + \text{Base} \rightleftharpoons \text{Conjuate Acid} + \text{Conjugate Base} \quad \text{-------- Eq.1}$$

$$\text{Acidic Drug} + \text{Water} \rightleftharpoons \text{Conjugate Base} + H_3O^+$$

$$\text{Basic Drug} + \text{Water} \rightleftharpoons \text{Conjuate Acid} + OH^-$$

Acid Strength

Two logical questions to ask at this point, these are:

- How one predicts in which direction an acid–base reaction lies? and
- To what extent the reaction goes to completion?

The common physicochemical measurement that contains this information is known as the pKa. The pKa is the negative logarithm of the modified equilibrium constant, Ka which can be calculated as follow (depending on Eq.1):

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

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

the Ka or pKa are modified equilibrium constants that indicate the extent to which the acid (proton donor) reacts with water to form conjugate acid and conjugate base. The equilibrium for a strong acid (low pKa) in water lies to the right, favoring the formation of products (conjugate acid and conjugate base). The equilibrium for a weak acid (high pKa) in water lies to the left, meaning that the conjugate acid is a better proton donor than the parent acid is or that the conjugate base is a good proton acceptor (table below).

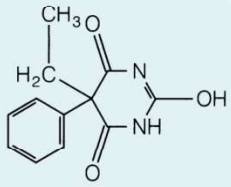
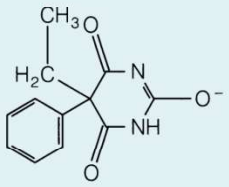
It is important to recognize that a pKa for a base (B) is in reality the pKa of the conjugate acid (acid donor or protonated form, BH^+) of the base, and the pKa for an acid (AH) is the pKa of its conjugate base (proton acceptor or deprotonated form, A^-).

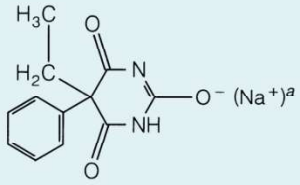
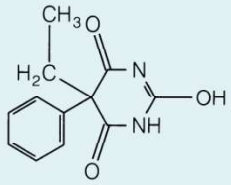
Examples of Acid–Base Reactions (with the Exception of Hydrochloric Acid, Whose Conjugate Base [Cl^-] Has No Basic Properties in Water, and Sodium Hydroxide, which Generates Hydroxide, the Reaction of the Conjugate Base in Water Is Shown for Each Acid)

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	+	$HPO_4^{2-}(2Na^+)^a$	⇌	$H_2PO_4^{2-}(Na^+)^a$	+	$OH^-(Na^+)^a$
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	+	$OH^-(Na^+)^a$

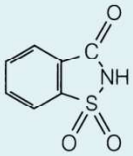
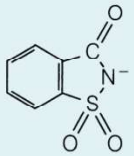
Indomethacin and its conjugate base, indomethacin sodium, show the identical acid–base chemistry as acetic acid and sodium acetate, respectively.

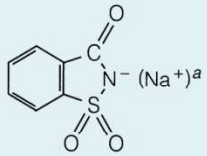
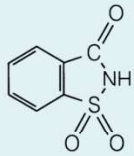
Phenobarbital and its conjugate base, phenobarbital sodium

(i)  + H_2O ⇌ H_3O^+ + 

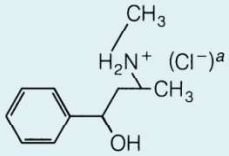
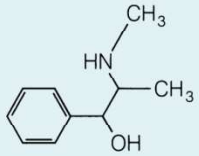
(j) H_2O +  ⇌  + $OH^-(Na^+)^a$

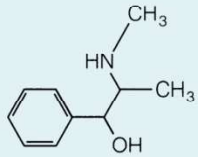
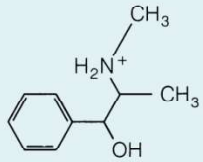
Saccharin and its conjugate base, saccharin sodium

(k)  + H_2O ⇌ H_3O^+ + 

(l) H_2O +  ⇌  + $OH^-(Na^+)^a$

Ephedrine HCl and its conjugate base, ephedrine

(m)  + H_2O ⇌ $H_3O^+(Cl^-)^a$ + 

(n) H_2O +  ⇌  + OH^-

[a]The chloride anion and sodium cation are present only to maintain charge balance. These anions play no other acid–base role.

Hydrochloric acid, a Ka of 1.26 x 10^6 means that the product of the molar concentrations of the conjugate acid, [H_3O^+], and the conjugate base, [Cl^-], is huge relative to the denominator term, [HCl]. In other words, there essentially is no unreacted HCl left in an aqueous solution of hydrochloric acid. At the other extreme is ephedrine HCl with a pKa of 9.6 or a Ka of 2.51 x 10^{10-}. Here, the denominator representing the concentration of ephedrine HCl greatly predominates over that of the products, which, in this example, is ephedrine (conjugate base) and H_3O^+ (conjugate acid). In other words, the protonated form of ephedrine is a very poor proton donor. Free ephedrine (the conjugate base in this reaction) is an excellent proton acceptor.

Representative K_a and pK_a Values

Hydrochloric acid	1.26×10^{6}	−6.1
Dihydrogen phosphate	6.31×10^{-8}	7.2
Ammonia (ammonium)	5.01×10^{-10}	9.3
Acetic acid	1.58×10^{-5}	4.8
Phenobarbital	3.16×10^{-8}	7.5
Saccharin	2.51×10^{-2}	1.6
Indomethacin	3.16×10^{-5}	4.5
Ephedrine (as the HCl salt)	2.51×10^{-10}	9.6

A general rule for determining whether a chemical is strong or weak acid or base is
- pKa < 2: strong acid; conjugate base has no meaningful basic properties in water
- pKa 4 to 6: weak acid; weak conjugate base
- pKa 8 to 10: very weak acid; conjugate base getting stronger
- pKa >12: essentially no acidic properties in water; strong conjugate base

Percent Ionization

Using the drug's pKa, we can adjust the pH to ensure maximum water solubility (ionic form of the drug) or maximum solubility in nonpolar media (un-ionic form). This is why understanding the drug's acid–base chemistry becomes important.

$$\underset{\text{Acid}}{HA_{(\text{un-ionized})}} + \underset{\text{Base}}{H_2O} \rightleftharpoons \underset{\text{Conj. Acid}}{H_3O^+} + \underset{\text{Conj. Base}}{A^-_{(\text{ionized})}}$$

$$\underset{\text{Acid}}{BH^+_{(\text{ionized})}} + \underset{\text{Base}}{H_2O} \rightleftharpoons \underset{\text{Conj. Acid}}{H_3O^+} + \underset{\text{Conj. Base}}{B_{(\text{un-ionized})}}$$

Acids can be divided into two types, HA and BH^+, on the basis of the ionic form of the acid (or conjugate base). HA acids go from un-ionized acids to ionized conjugate bases. In contrast, BH^+ acids go from ionized (polar) acids to un-ionized (nonpolar)

conjugate bases. In general, pharmaceutically important HA acids include the inorganic acids (e.g., HCl, H_2SO_4), enols (e.g., barbiturates, hydantoins), carboxylic acids, and amides and imides (e.g., sulfonamides and saccharin, respectively). The chemistry is simpler for the pharmaceutically important BH^+ acids: They are all protonated amines.

The percent ionization of a drug is calculated by using equations below:

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

for HA acids

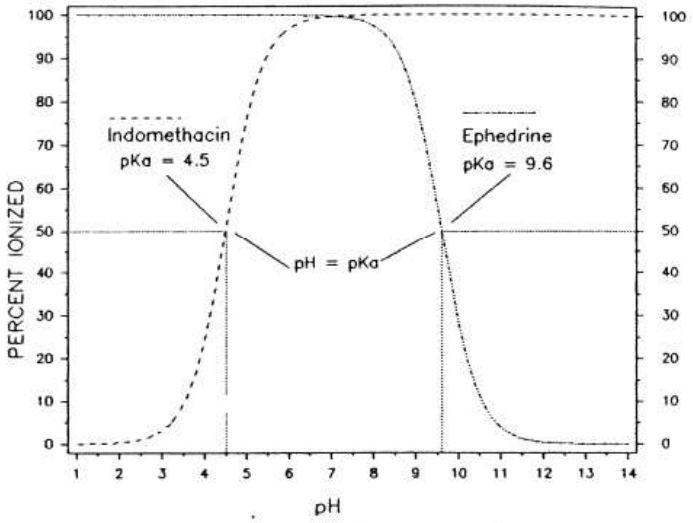
$$\% \text{ ionization} = \frac{100}{1 + 10^{(pH - pK_a)}}$$

for BH^+ acids

when pH = pKa, the compound is 50% ionized (or 50% un-ionized). In other words, when the pKa is equal to the pH, the molar concentration of the acid equals the molar concentration of its conjugate base. In the Henderson-Hasselbalch equation, pKa = pH when log [conjugate base]/[acid] = 1. An increase of 1 pH unit from the pKa (increase in alkalinity) causes an HA acid (ex. indomethacin) to become 90.9% in the ionized conjugate base form, but in a BH^+ acid (ex. ephedrine HCl) decreasing its percent ionization to only
9.1%. An increase of 2 pH units essentially shifts an HA acid to complete ionization (99%) and a BH^+ acid to the nonionic conjugate base form (0.99%).
Just the opposite is seen when the medium is made more acidic relative to the drug's pKa value. Increasing the hydrogen ion concentration (decreasing the pH) will shift the equilibrium to the left, thereby increasing the concentration of the acid and decreasing the concentration of conjugate base. Table below summarizes the relation of percent ionization and the pKa.

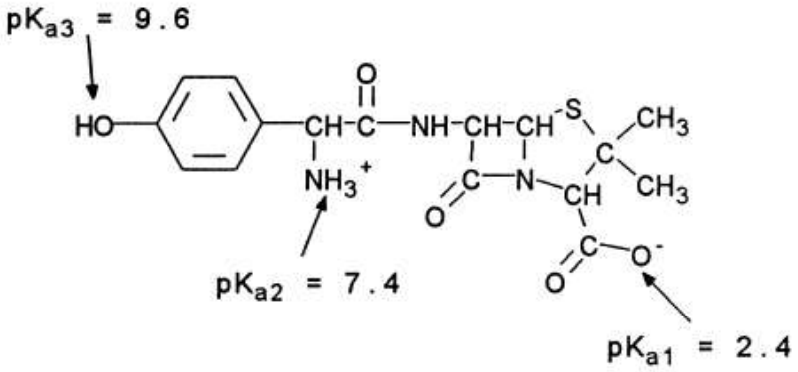
Percentage Ionization Relative to the pK_a

	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



Percent ionized versus pH for indomethacin (pK_a 4.5) and ephedrine (pK_a 9.6).

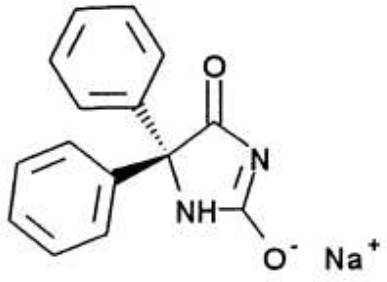
A polyfunctional drug can have several pKa's (e.g., amoxicillin). At physiological pH, the carboxylic acid (HA acid; pKa_1 2.4) will be in the ionized carboxylate form, the primary amine (BH^+ acid; pKa_2 7.4) will be 50% protonated and 50% in the free amine form, and the phenol (HA acid; pKa_3 9.6) will be in the un-ionized protonated form.



Amoxicillin

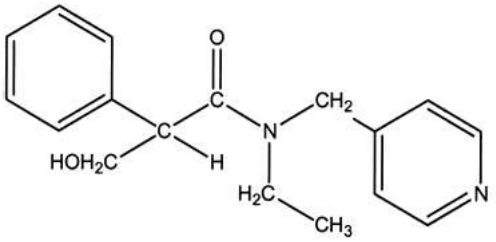
Knowledge of percent ionization makes it easier to explain and predict why the use of some preparations can cause problems and discomfort as a result of pH extremes.

Phenytoin (HA acid; pKa 8.3) injection must be adjusted to pH 12 with sodium hydroxide to ensure complete ionization and maximize water solubility. In theory, a pH of 10.3 will result in 99.0% of the drug being an anionic water-soluble conjugate base. To lower the concentration of phenytoin in the insoluble acid form even further and maintain excess alkalinity, the pH is raised to 12 to obtain 99.98% of the drug in the ionized form. This highly alkaline solution is irritating to the patient and generally cannot be administered as an admixture with other intravenous fluids that are buffered more closely at physiological pH 7.4. This decrease in pH would result in the parent unionized phenytoin precipitating out of solution.



Phenytoin Sodium

Tropicamide is an anticholinergic drug administered as eye drops for its mydriatic response during eye examinations. With a pKa of 5.2, the drug has to be buffered near pH 4 to obtain more than 90% ionization. The acidic eye drops can sting. Some ophthalmologists use local anesthetic eye drops to minimize the patient's discomfort.



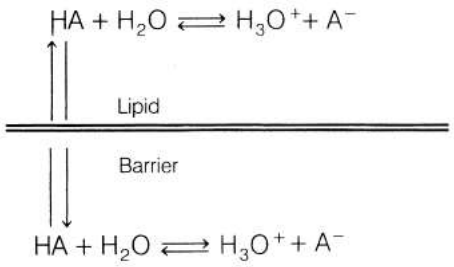
Tropicamide

The only atom with a meaningful pKa is the pyridine nitrogen. The amide nitrogen has no acid–base properties in aqueous media.

Adjustments in pH to maintain water solubility can sometimes lead to chemical stability problems. An example is indomethacin (HA acid; pKa 4.5), which is unstable in alkaline media. Therefore, the preferred oral liquid dosage form is a suspension buffered at pH 4 to 5. Because this is near the drug's pKa, only 50% will be in the water-soluble form. There is a medical indication requiring intravenous administration of indomethacin to premature infants. The intravenous dosage form is the sodium salt, which is reconstituted just prior to use.

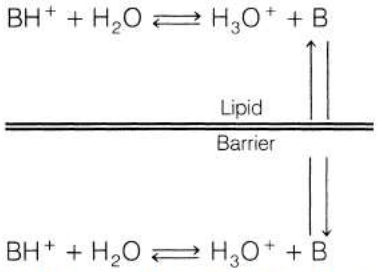
Drug Distribution and pKa

The pKa can have a pronounced effect on the pharmacokinetics of the drug. Drugs are transported in the aqueous environment of the blood. Those drugs in an ionized form will tend to distribute throughout the body more rapidly than will un-ionized (nonpolar) molecules. then, the drug must leave the polar environment of the plasma to reach the site of action by passing through the nonpolar membranes of capillary walls, cell membranes, and the blood-brain barrier in the un-ionized (nonpolar) form. For HA acids, it is the parent acid that will readily cross these membranes.



Passage of HA acids through lipid barriers

The situation is just the opposite for the BH^+ acids. The unionized conjugate base (B, free amine) is the species most readily crossing the nonpolar membranes.



Passage of BH^+ acids through lipid barriers

For drug molecules orally administered. The drug first encounters the acidic stomach, where the pH can range from 2 to 6 depending on the presence of food. HA acids with pKa's of 4 to 5 will tend to be nonionic and be absorbed partially through the gastric mucosa. (The main reason most acidic drugs are absorbed from the intestinal tract rather than the stomach is that the microvilli of the intestinal mucosa provide a large surface area relative to that found in the gastric mucosa of the stomach.) In contrast, 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).

Once in systemic circulation, the plasma pH of 7.4 will be one of the determinants of whether the drug will tend to remain in the aqueous environment of the blood or partition across lipid membranes into hepatic tissue to be metabolized, into the kidney for excretion, into tissue depots, or to the receptor tissue.

Of course, the effect of protein binding, discussed previously, can greatly alter any prediction of biodistribution based solely on pKa.