

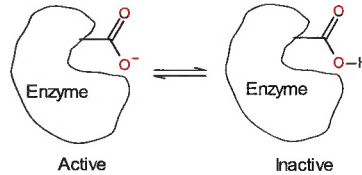
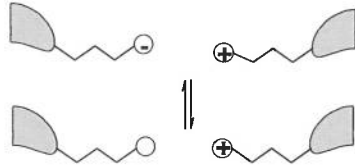
**Lecture 3: Acid-Base Chemistry.**

**Learning Goals:**

- Compare relative acid strength based on pKa values of weak acids.
- Predict protonation state given pH of the solution and the pKa of the acid.

**Why pH is important in Biochemistry.**

- i) Molecular interactions can be sensitive to pH. ii) Biological activity can be sensitive to pH.  
 Changing the pH can change the charge on molecules. e.g. ionized groups required for function.

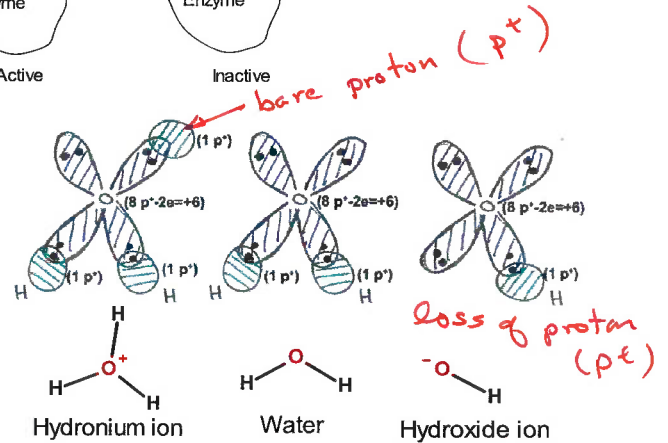


**Ionization Properties of Water:**

Water can gain a proton on one of its lone pair orbitals to become a hydronium ion (H<sub>3</sub>O<sup>+</sup>, often abbreviated H<sup>+</sup>) or it can lose a proton to become a hydroxide ion (OH<sup>-</sup>)

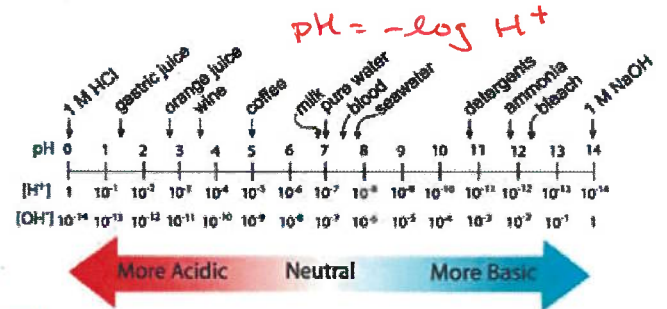
**pH:** pH is measured as the -log[H<sup>+</sup>], smaller pH, more acidic the solution, higher [H<sup>+</sup>]. Neutral pH is 7.0. At this pH there are an equal number of H<sup>+</sup> and OH<sup>-</sup> ions in solution. [H<sup>+</sup>]=10<sup>-7</sup> M.

**pH is a property of the solution, and can be changed by the addition of a strong acid (HCl) or base (NaOH)**

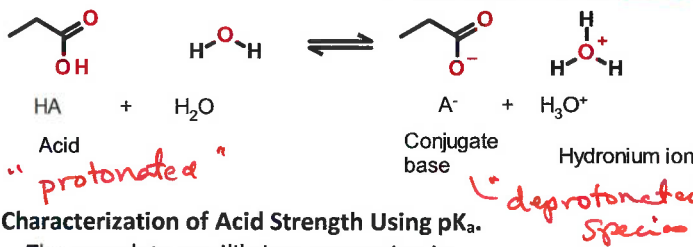


**Acids and Bases:**

- Acid: can donate protons to water, forming its conjugate base and a hydronium ion.
- Strong acid – always completely deprotonated (pKa <= 2).
- Base: can accept protons



The following describes ionization or *dissociation* of the proton from the acid.

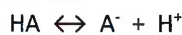


**Characterization of Acid Strength Using pKa.**

The complete equilibrium expression is:



Since the concentration of water is essentially constant, it can be ignored and we can write a modified equilibrium reaction that just focuses on the species of interest:



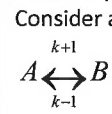
and write the equilibrium constant for that dissociation:

$$K_{EQ} = K_a = \frac{[\text{A}^-][\text{H}^+]}{[\text{HA}]}$$

"acidity"

**Equilibrium Constants: Why is the ratio of products to reactants a constant when a system is at equilibrium?**

Consider a simple reaction:



Equations that describe the rate of change of [A] and [B] are:

$$\frac{d[\text{A}]}{dt} = -k_{+1}[\text{A}] + k_{-1}[\text{B}]$$

$$\frac{d[\text{B}]}{dt} = +k_{+1}[\text{A}] - k_{-1}[\text{B}]$$

at equilibrium d[A]/dt=0, d[B]/dt=0

$$0 = \frac{d[\text{A}]}{dt} = -k_{+1}[\text{A}] + k_{-1}[\text{B}]$$

$$0 = -k_{+1}[\text{A}] + k_{-1}[\text{B}]$$

$$\frac{[\text{B}]}{[\text{A}]} = \frac{k_{+1}}{k_{-1}} = K_{EQ}$$

The equilibrium constant for acid dissociation is given a special name, the 'k-a', or 'k-acidity'. The acidity constant,  $K_a$  is a *fundamental* property of the acid, it does **not** depend on the pH of the solution. However, it does depend on the chemical structure **and** the environment of the acidic group.

When the  $[H^+] = K_a$ , then exactly  $\frac{1}{2}$  of the acid is protonated.

$$K_a = \frac{[A^-][H^+]}{[HA]}$$

$[H^+] = K_a$   
 $K_a = \frac{[A^-]}{[HA]} K_a \implies 1 = \frac{[A^-]}{[HA]}$

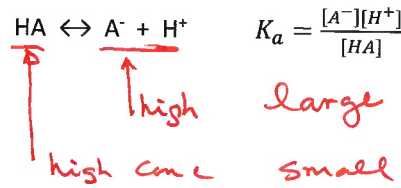
$pK_a$ : Since the pH scale is used to characterize  $[H^+]$ , it is useful to express the acidity constant in the same way, by taking its negative log, giving the "p-K-a":

$$pK_a = -\log K_a$$

When the  $pH = pK_a$ , then exactly  $\frac{1}{2}$  of the acid is protonated.

**Acid Strength and  $pK_a$**

How do the  $K_a$  &  $pK_a$  vary as the acid strength increases?



Strong acid:

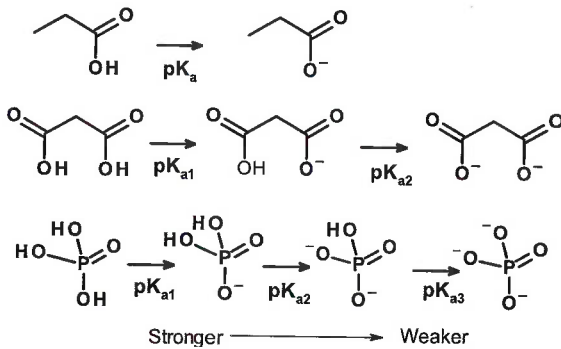
Weak acid:

$pH = -\log H^+$   
 $pK_a = -\log K_a$

$pK_a = -\log K_a$   
 small  
 large

When  $pH = pK_a$   
 $[HA] = [A^-]$   
 stronger  
 weaker

Multi-Protic Acids have more than one  $pK_a$ :



**Monoprotic acid:** releases one proton (e.g. Acetic acid)

**Diprotic acid:** releases two protons (e.g. Malonic acid)

**Triprotic acid:** releases three protons (e.g. Phosphoric acid)

**Prediction of Protonation State at any pH:**

In many cases only one of the two species (protonated or deprotonated) may be biologically active.

Given the  $pK_a$  of the ionizable group, and the pH of the solution, we would like to calculate the following:

- The fraction that is protonated:  $f_{HA}$ .
- The fraction that is deprotonated:  $f_{A^-}$ .

We need to know R in terms of pH and  $pK_a$ .

Beginning with the equilibrium constant for ionization:

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

Take  $-\log$  of both sides:

$$-\log K_a = -\log \left\{ \frac{[H^+][A^-]}{[HA]} \right\}$$

$$-\log K_a = -\log[H^+] - \log \left\{ \frac{[A^-]}{[HA]} \right\}$$

$$pK_a = pH - \log \left\{ \frac{[A^-]}{[HA]} \right\}$$

$$f_{HA} = \frac{[HA]}{[HA] + [A^-]}$$

$$= \frac{1}{1 + \frac{[A^-]}{[HA]}}$$

$$R = \frac{[A^-]}{[HA]}$$

$$f_{HA} = \frac{1}{(1 + R)}$$

$$f_{A^-} = \frac{[A^-]}{[HA] + [A^-]}$$

$$= \frac{[A^-]/[HA]}{1 + [A^-]/[HA]}$$

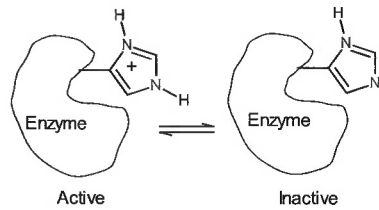
$$f_{A^-} = \frac{R}{(1 + R)}$$

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

$$pH = pK_a + \log(R)$$

$$pH - pK_a = \log(R)$$

$$10^{(pH - pK_a)} = R$$



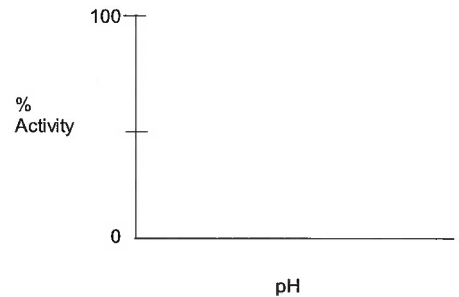
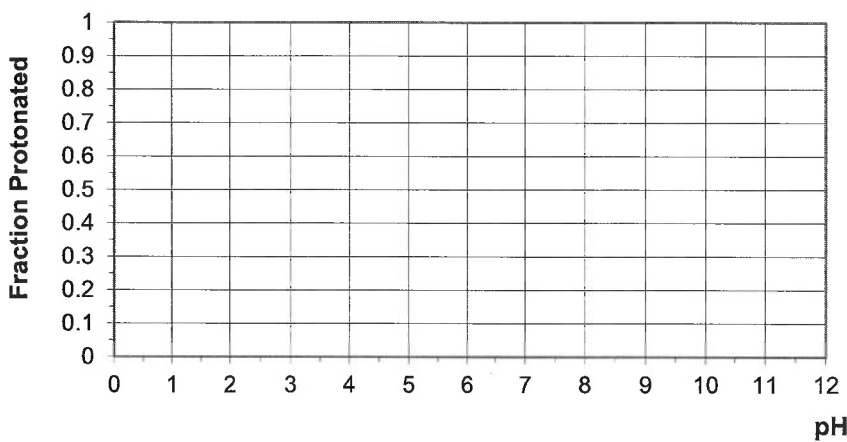
**Example:** Plot the % activity as a function of pH, assuming “HA” form is active.

- a) Calculate the fraction protonated of the side chain of Histidine, an amino acid found in proteins.  $pK_a = 6.0$ .  
 b) activity =  $100 \times f_{HA}$ .

**Important general features to note:**

- i) when  $pH = pK_a - 2$ ,  $f_{HA} = 0.99$
- ii) when  $pH = pK_a - 1$ ,  $f_{HA} = 0.91$
- iii) when  $pH = pK_a$ ,  $f_{HA} = f_A = 0.5$
- iv) when  $pH = pK_a + 1$ ,  $f_{HA} = 0.09$
- v) when  $pH = pK_a + 2$ ,  $f_{HA} = 0.01$

pH	$R = 10^{(pH - pK_a)}$	$F_{HA} = 1/(1+R)$	$\Delta = pH - pK_a$
4	$R = 10^{(4 - 6)} = 10^{-2}$	$F_{HA} = 1/(1 + 0.01) = 0.99$	-2
5	$R = 10^{(5 - 6)} = 10^{-1}$	$F_{HA} = 1/(1 + 0.10) = 0.91$	-1
6	$R = 10^{(6 - 6)} = 10^0$	$F_{HA} = 1/(1 + 1) = 0.5$	0
7	$R = 10^{(7 - 6)} = 10^{+1}$	$F_{HA} = 1/(1 + 10) = 0.091$	+1
8	$R = 10^{(8 - 6)} = 10^{+2}$	$F_{HA} = 1/(1 + 100) = 0.01$	+2



**Chemical Structure and Acidity:**

Key Concepts:

- The strength of an acid depends on the ability to break the A-H bond, e.g. NH versus OH.
- The strength depends on the relative stability of (HA) versus ( $A^-$ ), which can be affected by the chemical groups on the same molecule *and* the environment of the molecule (see next lecture).

Chemical bonding and effects on  $pK_a$ :

	Amine $pK_a \sim 10$ (Lys sidechain)	Easier to break an N-H bond versus an O-H bond, therefore an amine is a stronger acid than an alcohol, the $[H^+]$ is interacting with the lone pair of N – not a “real” covalent bond.
	Ethanol $pK_a \sim 14$ (Ser, Thr sidechain)	Alcohol is a weak acid because of highly localized negative charge on the oxygen, deprotonated species is high energy.
	Acetic Acid $pK_a \sim 4.0$ (Glu, Asp sidechain)	Negative charge delocalized over C=O, lower in energy, therefore a carboxylate is a stronger acid than an alcohol.
	Carboxy $pK_a \sim 2.0$ group on an amino acid.	Electronegative nitrogen can withdraw some charge from the negatively charged carboxylate, giving a stronger acid than just a COOH group.