Ionic equilibria

Introduction

Many drugs are:

- Weak acids such as acetylsalicylic acid and ibuprofen
- Weak bases such as procaine and lidocaine
- Salts such as sodium diclofenac and metformin hydrochloride

Ionization of drug is important in:

- Formulation: ionized drug is more soluble
- Absorption: unionized drugs easily diffuse across membrane.
- Distribution: unionized drugs have high volumes of distribution and protein binding
- Excretion: ionized drugs excreted more readily.

Arrhenius Theory

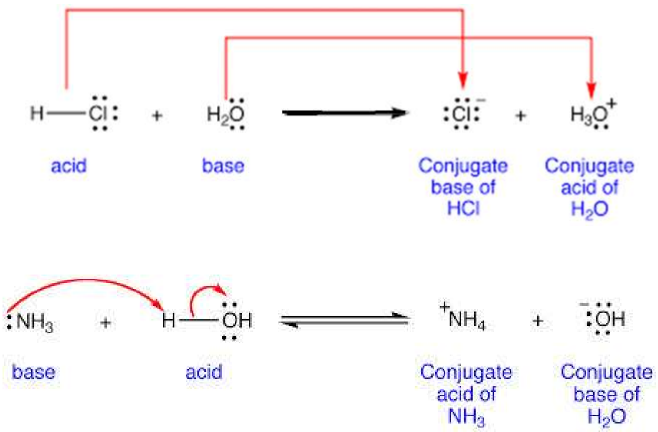
- Arrhenius defined an acid as a substance that liberates hydrogen ions, H^+ and a base as a substance that supplies hydroxyl ions, OH^- on dissociation.
- However; Arrhenius definition could not explain the basic behavior of many compounds that do not contain hydroxyl ions, OH^- (e.g.NH_3)

$$NH_3 + HCl \rightarrow NH_4^+ + Cl^-$$

- Therefore; the Brönsted–Lowry theory is more useful than the Arrhenius theory for the representation of ionization in both aqueous and non-aqueous systems.

Brönsted–Lowry Theory

- According to the Brönsted–Lowry theory, an acid is a substance that is capable of donating a proton, and a base is a substance that is capable of accepting a proton from an acid.



Brönsted–Lowry Theory

- The relative strengths of acids and bases are measured by the tendencies of these substances to give up and take on protons:
  - HCl is a strong acid in water because it gives up its proton readily
  - CH_3COOH is a weak acid because it gives up its proton only to a small extent.
- The strength of an acid or a base varies with the solvent:
  - HCl is a weak acid in glacial acetic acid
  - CH_3COOH is a strong acid in liquid ammonia.
- i.e. the strength of an acid depends not only on its ability to give up a proton but also on the ability of the solvent to accept the proton from the acid.

Brönsted–Lowry Theory

- Solvents can be classified as protophilic, protogenic, amphiprotic, and aprotic.

➢ **Protophilic** or basic solvent is one that is capable of accepting protons from the solute (e.g. liquid ammonia **NH_3).**

➢ **Protogenic** solvent is a proton donating compound (e.g. acetic acid **CH_3COOH)**

➢ **Amphiprotic** solvents act as both proton acceptors and proton donor (e.g.water **H_2O).**

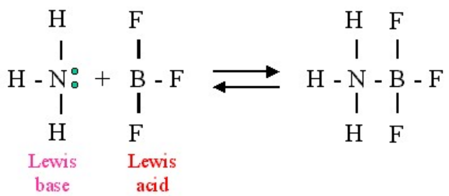
➢ **Aprotic** solvents neither accept nor donate protons (e.g. methane **CH_4).**

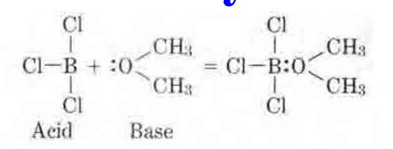
Lewis Electronic Theory

According to the Lewis theory:

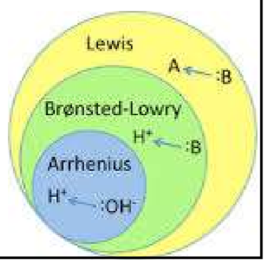
- An acid is a molecule or an ion that accepts an electron pair to form a covalent bond.
- A base is a substance that provides the pair of unshared electrons to coordinate with an acid.
- Certain compounds such as BF_3 are considered acids even when they are not proton donors (do not contain hydrogen).
- Other compounds such as ethers and NH_3 are considered bases even when they do not accept proton.

Lewis Electronic Theory





- The Lewis systems is probably too broad for convenient application to ordinary acid-base reactions.
- These reactions can be described as a form of electron sharing rather than as acid-base reactions.



Ionization of Weak Electrolytes

Weak Acids

The ionization of an uncharged weak acid, HA, in water:

HA	+	H_2O	$\leftrightarrow$	H_3O^+	+	A^-
Acid 1		Base 1		Acid 2		Base 2

The *acidity constant* K_a is expressed as:

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

Note: An acid and a base in equilibrium is termed a conjugate acid-base pair. E.g. A^- is the conjugate base of the weak acid HA

For a charged acid, BH^+, the reaction is written as:

BH^+	+	H_2O	$\leftrightarrow$	H_3O^+	+	B
Acid 1		Base 1		Acid 2		Base 2

The acidity constant K_a is expressed as :

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

Ionization of Weak Electrolytes

Weak Bases

The ionization of an uncharged weak base, B, in water can be written as:

B	+	H_2O	$\leftrightarrow$	OH^-	+	BH^+
Base 1		Acid 1		Base 2		Acid 2

The *basicity constant* K_b is expressed as :

$$K_b = \frac{[OH^-][BH^+]}{[B]}$$

For anionic base, A^-, the reaction is written as:

A^-	+	H_2O	$\leftrightarrow$	OH^-	+	HA
Base 1		Acid 1		Base 2		Acid 2

The basicity constant K_b is expressed as :

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

Ionization of salts

- Salts are the non-water product of an acid base neutralization.
- Drug salts are often used due to their complete ionization, and thus better aqueous solubility than weak acids and bases.
- Depending on the strength of the acid and base that form the salt, there are four possible types:

1.Salt of strong acid and a strong base (e.g. NaCl)

- This salt dissociates to give ions that practically do not consume or release protons.
- E.g. NaCl $\rightarrow$ $Na^+ + Cl^-$

  Salt (Practically neither Acid or Base)

Ionization of salts

2. Salt of weak acid and strong base (e.g. NaOAc)

This salt dissociates into ions; from which one acts as a base and consumes a proton to give its conjugate weak acid:

E.g. NaOAc $\rightarrow$ Na^+ + OAc^-

Salt Base1

OAc^- + H_2O $\leftrightarrow$ HOAc + OH^-

Base1 Acid1 Acid2 Base2

3. Salt of weak base and strong acid (e.g. NH_4Cl)

This salt dissociates into ions; from which one acts as a n acid and releases a proton to give its conjugate weak base:

E.g. NH_4Cl $\rightarrow$ $NH4^+$ + Cl^-

Salt Acid1

$NH4^+$ + H_2O $\leftrightarrow$ NH_3 + $H3O^+$

Acid1 Base1 Base2 Acid2

Ionization of salts

4. Salt of weak acid and weak base (e.g. NH_4OAc)

This salt dissociates into ions; from which one acts as an acid and the other as a base.

E.g. $NH_4OAc \rightarrow NH_4^+ + OAc^-$

Salt, Acid 1, Base 1

NH_4^+	+	H_2O	$\leftrightarrow$	NH_3	+	H_3O^+
Acid 1		Base 1		Base 2		Acid 2
AcO^-	+	H_2O	$\leftrightarrow$	$AcOH$	+	OH^-
Base 1		Acid 1		Acid 2		Base 2

Ionization of Polyprotic Electrolytes

Polyprotic acids can lose more than one H^+ ion.

E.g. *Diprotic acids*, such as H_2SO_4 and H_2CO_3, which release 2 protons, and *Triprotic acids*, such as H_3PO_4 which releases 3 protons.

Consider the ionization of the weak diprotic acid, H_2CO_3 that dissociates in two steps:

$$H_2CO_3 + H_2O \leftrightarrow H_3O^+ + HCO_3^-$$

$$HCO_3^- + H_2O \leftrightarrow H_3O^+ + CO_3^{2-}$$

Two acidity constants is used to describe the two equilibrium:

$$K_{a1} = \frac{[H_3O^+][HCO_3^-]}{[H_2CO_3]}, \qquad K_{a2} = \frac{[H_3O^+][CO_3^{2-}]}{[HCO_3^-]}$$

K_{a1} is larger than K_{a2} because the polyprotic acid lose its first proton more easily than the second (and third) proton.

Ionization of Polyprotic Electrolytes

Polyprotic bases can accept more than one H^+ ion.

E.g. *Diprotic bases*, such as CO_3^{2-} which accepts 2 protons, and *Triprotic bases*, such as PO_4^{3-} accepts 3 protons.

Consider the ionization of the weak diprotic base, CO_3^{2} that consumes protons in two steps:

$$\mathbf{CO_3^{2-} + H_2O \leftrightarrow OH^- + HCO_3^{1-}}$$

$$\mathbf{HCO_3^{1-} + H_2O \leftrightarrow OH^- + H_2CO_3}$$

Two basicity constants is used to describe the two equilibrium:

$$K_{b1} = \frac{[OH^-][HCO_3^-]}{[CO_3^{2-}]}, \qquad K_{b2} = \frac{[OH^-][H_2CO_3]}{[HCO_3^-]}$$

$\mathbf{K_{b1}}$ is larger than $\mathbf{K_{b2}}$ because the polyprotic base consumes its first proton more easily than the second (and third) proton.

Ionization of Water

Water ionizes slightly to yield hydrogen and hydroxyl ions by reacting with another molecule of water (*autoprotolytic* reaction):

$$\mathbf{H_2O + H_2O \leftrightarrow OH^- + H_3O^+}$$

The equilibrium constant is expressed as:

$$K = \frac{[OH^-][H_3O^+]}{[H_2O]^2} \quad \Rightarrow \quad K[H_2O]^2 = [OH^-][H_3O^+]$$

$[H2O]^2$ is considered as a constant and is combined with K to give a new constant, K_w, known as the *autoprotolysis constant*, or the *ion product* of water:

$$K_w = [OH^-][H_3O^+]$$

Ionization of Water

In *pure* water: $[OH^-] = [H_3O^+] = 1 \times 10^{-7}$ M at 25°C.

$K_w = [OH^-][H_3O^+] = (1 \times 10^{-7}) \times (1 \times 10^{-7}) = 1 \times 10^{-14}$ M

When an acid is added to pure water, the increase in hydrogen ions is offset by a decrease in the hydroxyl ions so that K_w remains constant at about 1×10^{-14} M at 25°C.

A simple relationship exists between K_a of a weak acid (**HB**) and K_b of its conjugate base (**B−**), and between K_a of **BH⁺** and K_b of **B** when the solvent is amphiprotic (e.g. water).

$$K_a K_b = K_w$$

pH

- $[H_3O]^+$ varies from 1 (in a 1 M solution of a strong acid) to 1×10^{-14} (in a 1 M solution of a strong base).
- Sorensen suggested a simplified method of expressing $[H_3O]^+$ via the term pH.
- pH is defined as the negative logarithm of $[H_3O]^+$

$pH = -\log [H_3O]^+$

- The pH of a solution is a numeric scale from 0 to 14, which expresses the degree of acidity (7-0) and alkalinity (7 - 14).
- The value 7 at which **$[H_3O]^+ = [OH]^-$** at room temperature is referred to as the neutral point

Mathematical revision

Exponential Laws	Logarithm Laws
$x^a \cdot x^b = x^{a+b}$	$\log(ab) = \log(a) + \log(b)$
$\frac{x^a}{x^b} = x^{a-b}$	$\log\left(\frac{a}{b}\right) = \log(a) - \log(b)$
$(x^a)^b = x^{ab}$	$\log(a^b) = b \cdot \log(a)$
$x^{-a} = \frac{1}{x^a}$	$\log_x\left(\frac{1}{x^a}\right) = -a$
$x^0 = 1$	$\log_x 1 = 0$

pK and pOH

- The term "p" is also used to express the negative logarithm of each of $[OH^-]$, K_a, K_b, K_w as pOH, pK_a, pK_b, and pK_w

$$\mathbf{pK_w = pH + pOH}$$

$$\mathbf{pK_w = pK_a + pK_b}$$

- pk_a and pK_b values provide a means of comparing the strengths of weak acid and weak bases:
- Lower pk_a values correspond to stronger acids
- Lower pK_b values correspond to stronger Bases

Calculation of pH

Strong Acids and Bases

- A strong acid, HA, ionizes completely to H_3O^+ and A^-. Therefore $[H_3O^+]$ =[HA] and pH is calculated as:

pH = -log [HA]

- While a strong base, B ionizes completely to BH+ and OH-. Therefore [OH-] = [B] and pOH is calculated as:

pOH = - log [B]

Since pH = pKw – pOH

Then: pH = pKw – (- log [B]) or:

pH = pKw + log [B]

Calculation of pH

Weak Acids and Bases

A weak acid, HA, ionizes partially H_3O^+ and A^-:

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \quad \text{Since } [A^-] = [H_3O^+]$$

$$\text{Then} \quad K_a = \frac{[H_3O^+]^2}{[HA]}$$

$$[H_3O^+]^2 = K_a\,[HA] \quad \Rightarrow \quad [H_3O^+] = (K_a\,[HA])^{1/2}$$

$$pH = \frac{1}{2}(pK_a - \log[HA])$$

Calculation of pH

Weak Acids and Bases

Example

Calculate the pH of a 50 mg mL^{-1} solution of ascorbic acid (MW 176.1, pK_a 4.17)

Convert concentration to M (or mol/L)

C = 50 mg/mL = 50 g/L

M = 50 / 176.1 = 0.284 mol/L

$$pH = \frac{1}{2}(pKa - \log[HA])$$

$$pH = \frac{1}{2}(4.17 - \log 0.284)$$

$$pH = \frac{1}{2}(4.17 + 0.574) = 2.36$$

Calculation of pH

Weak Acids and Bases

A weak base, B, ionizes partially to BH^+ and OH^-:

$$K_b = \frac{[BH^+][OH^-]}{[B]} \quad \text{Since} \quad [BH^+] = [OH^-]$$

Then $K_b = \frac{[OH^-]^2}{[B]}$

$$[OH^-]^2 = K_b\,[B] \quad \Rightarrow \quad [OH^-] = (K_b\,[B])^{1/2}$$

$$pOH = \frac{1}{2}pK_b - \frac{1}{2}\log[B]$$

Since $pOH = pKw - pH$ and $pK_b = pKw - pK_a$

Then $$pH = \frac{1}{2}(pK_w + pK_a + \log[B])$$

Calculation of pH

Weak Acids and Bases

Example

Calculate the pH of a saturated solution of codeine monohydrate (MW 317.4, pKa 8.2, solubility at room temperature is 1 g in 120 mL

Convert concentration to mol/L

C = 1 g / 120 mL = 8.33 g/L

M = 8.33/317.4 = 0.0263 mol/L

$$pH = \frac{1}{2}(pK_w + pKa + \log[B])$$

$$pH = \frac{1}{2}(14 + 8.2 + \log 0.0263)$$

$$pH = \frac{1}{2}(14 + 8.2 - 1.58) = 10.31$$

Calculation of pH

Salts of Strong Acid and Strong Base

- The salt of strong acid and strong base (e.g. NaCl) dissociates in water into Na^+ and Cl^-.

$$\mathbf{NaCl \rightarrow Na^+ + Cl^-}$$

- Neither Na^+ nor Cl^- ions are capable of consuming or releasing protons from /to water (they are neither acids nor bases)
- Therefore these ions have no effect on pH. The pH of the solution remains the same as that of pure water, 7.

Calculation of pH

Salts of Weak Acid and Strong Base

The salt of weak acid and strong base (e.g. Sodium acetate, AcONa (designated as S)) dissociates into Na^+ and AcO^-.

$AcONa \rightarrow AcO^- + Na^+$

AcO^- acts as a base and consumes one proton to form AcOH

$AcO^- + H_2O \leftrightarrow AcOH + OH^-$

The pH is calculated in the same way as in weak base:

$$pH = \frac{1}{2}(pK_w + pKa + \log[AcO^-])$$

Since $[AcO^-] = [S]$

Then $$pH = \frac{1}{2}(pK_w + pKa + \log[S])$$

Note: the pH is always > 7

Calculation of pH

Salts of Weak Base and Strong Acid

The salt of weak base and strong acid (e.g. ammonium chloride, NH_4Cl (designated as S)) dissociates into NH_4^+ and Cl^-.

$NH_4Cl \rightarrow Cl^- + NH_4^+$

NH_4^+ acts as an acid and releases one proton to form NH_3

$NH_4^+ + H_2O \leftrightarrow NH_3 + H_3O^+$

The pH is calculated in the same way as in weak acid:

$$pH = \frac{1}{2}(pK_a - \log[NH_4^+])$$

Since $[NH_4^+] = [S]$

Then $$pH = \frac{1}{2}(pKa - log[S])$$

Note: the pH is always < 7

Calculation of pH

Salts of Weak Acid and Weak Base

The salt of weak acid and weak base (e.g. ammonium acetate, $AcONH_4$) dissociates into NH_4^+ and AcO^-.

$AcONH_4 \rightarrow AcO^- + NH_4^+$

NH_4^+ acts as an acid and releases one proton to form NH_3, while AcO^- acts as a base and consumes one proton to form AcOH

$NH_4^+ + H_2O \leftrightarrow NH_3 + H_3O^+$

$AcO^- + H_2O \leftrightarrow AcOH + OH^-$

The pH can be calculated by:

$$pH = \frac{1}{2}(pK_w + pKa - pK_b)$$

Note: the pH does not depend on the concentration of the salt, but rather depends on the strength of the weak acid and weak base

Calculation of pH

Weak Acids and their Salts

When a weak acid and a salt of that acid exist in solution (e.g., acetic acid and sodium acetate), both compound dissociate to give the conjugate base of that acid (in this case OAc^-).

$HOAc + H_2O \leftrightarrow H_3O^+ + OAc^-$

$NaOAc \rightarrow Na^+ + OAc^-$

OAc^- in this case is called a *common ion*.

Most OAc^- will come from the salt NaOAc, therefore;

$[OAc^-] = [NaOAc]$ (designated as [S])

The pH is calculated by the following equation:

$$pH = pKa + log\frac{[S]}{[HA]}$$

The solution above is considered a *buffer* solution, and the equation above is named *Henderson-Hasselbalch* equation for buffers of weak acids.

Calculation of pH

Weak Acids and their Salts

Example

What is the pH of a solution containing acetic acid 0.3 M and sodium acetate 0.05 M? (Ka for acetic acid = 1.75×10^{-5})

$$pK_a = -\log K_a$$

$$pK_a = -\log 1.75 \times 10^{-5} = 4.76$$

$$pH = pKa + \log \frac{[S]}{[HA]}$$

$$pH = 4.76 + \log \frac{0.05}{0.3} = 3.98$$

Calculation of pH

Weak Bases and their Salts

When a weak base and a salt of that base exist in solution (e.g., NH_3 and NH_4Cl), both compound dissociate to give the conjugate acid of that base (in this case NH_4^+).

$NH_3 + H_2O \leftrightarrow NH_4^+ + OH^-$

$NH_4Cl \rightarrow NH_4^+ + Cl^-$

NH_4^+ in this case is called a *common ion.*

Most NH_4^+ will come from the salt NH_4Cl, therefore;

$[NH_4^+] = [NH_4Cl]$ (designated as [S])

The pH is calculated by the following equation:

$$pH = pKa + \log \frac{[B]}{[S]}$$

The solution above is considered a *buffer* solution, and the equation above is named *Henderson-Hasselbalch* equation for buffers of weak bases.

Calculation of pH

Weak Bases and their Salts

Example

What is the pH of a solution containing ephedrine 0.1 M and ephedrine HCl 0.01 M? (K_b for ephedrine = 2.3×10^{-5})

$$pK_b = -\log K_a$$

$$pK_b = -\log 2.3 \times 10^{-5} = 4.64$$

$$pK_a = pKw - pKb$$

$$pK_a = 14 - 4.64 = 9.36$$

$$pH = pKa + \log\frac{[B]}{[S]}$$

$$pH = 9.36 + \log\frac{0.1}{0.01} = 10.36$$

Calculation of pH

Diprotic Acids and Bases

For weak diprotic acid, the $[H_3O^+]$ mostly comes from the first step of dissociation. Therefore; The second step is ignored during calculation of pH:

$$pH = \frac{1}{2}(pKa - \log[HA])$$

pH is calculated the same way as with monoprotic weak acid

For weak diprotic base, the $[OH^-]$ mostly comes from the first step of reaction. Therefore; The second step is ignored during calculation of pH:

$$pH = \frac{1}{2}(pK_w + pKa + \log[B])$$

pH is calculated the same way as with monoprotic weak base