

Principles Of Acid-Base Balance

I. Introduction

- A. For normal body function the free H^+ concentration $[H^+]$ or pH must be kept within a narrow normal range. Some reasons why:
1. The proton "pump" within the mitochondria is essential for the oxidative phosphorylation process which produces ATP.
 2. Enzyme function depends upon $[H^+]$.
 3. Chemical reactions are influenced by $[H^+]$.
 4. The carrying power of hemoglobin for O_2 is influenced by $[H^+]$ (Bohr effect).
- B. Body fluids are slightly alkaline: pH = 7.40, or 40 nM H^+ . Remember that H_2O is neutral, with a pH of 7.00, and a H^+ of 100 nM.
- C. Cellular activity results in a constant addition of acid to the body fluids, yet for normal function, these fluids must remain slightly alkaline. **This is very important: We're not just talking about a system for fine-tuning the body pH, but rather, a system whose job it is to constantly excrete the acid which the body is making.**

II. Measurement of $[H^+]$. (More details on the chemistry are in the appendix)

- A. Concentration is expressed in mols/liter, abbreviated "M".
1. A nanomole = 10^{-9} mols, and "nM" means nanomols/liter.
 2. $pH = \text{negative log } [H^+]$ ("negative logarithm to the base 10 of the molar H^+ concentration")
 3. For pure water, the H^+ concentration = 10^{-7} M, so the log of this is -7, and the negative of the log is 7, i.e., pH = 7.00.
 4. The chart below shows some conversions between pH and $[H^+]$ in the physiological range.

pH	[H ⁺], nM
7.80	16
7.70	20
7.60	26
7.50	32
7.40	40
7.30	50
7.20	63
7.10	80
7.00	100
6.90	125
6.80	160

Figure 1 : Relationship between the pH and the H⁺ concentration in the physiological range

B. Normal [H⁺] within various body fluids:

Fluid	[H ⁺]	pH
Arterial plasma	40 nmol/L ± 3 nmol/L	pH = 7.4 ± .03
Venous plasma	45 nmol/L	pH = 7.35
Interstitial fluid	42 nM	pH = 7.38
Intracellular fluid	from 63 nM to 125 nM	pH = 7.2 to 6.9

C. Extremes of [H⁺] compatible with life: (abnormal)

from about 10 nM (pH 8.0) to about 150 nM (pH 6.8).

III. Difference between the total acidity and free H⁺ concentration or pH

A. Buffers allow a solution to carry a lot of acid without the free H⁺ concentration being very high. In other words, its not always the pH that's most important. This is very important in considering acid excretion by the kidney.

1. Example: Two solutions, each 1 liter:

a. Solution A: 0.001 M HCl, pH = 3

b. Solution B: 0.1 M acetic acid, (The pH would be 3.86).

2. Which solution would require more NaOH if we had to bring the pH of

both solutions to 7.00 ?

3. Even though the HCl solution has a lower pH (3) than the acetic acid solution (3.86), it would take much more NaOH to bring the pH of the acetic acid solution to 7 (almost 0.1 mol) than it would to bring the pH of the HCl solution to 7 (only about 0.001 mol). This is because the acetic acid solution is a buffer.
- B. The kidney uses this trick to allow us to excrete lots of acid in a relatively small volume of urine without having the pH get below about 4.40.

IV. Weak acids and weak bases can act as buffers

- A. When a strong acid like HCl dissolves in water, it ionizes completely to form H⁺ and Cl⁻ ions. When a weak acid, represented as HA, dissolves in water, only a portion of it ionizes to form H⁺ and A⁻; some of it remains in the non-dissociated form as HA.
- B. The A⁻ species is called the "conjugate base".
- C. The extent to which an acid dissociates is expressed by its equilibrium acid dissociation constant, K_a, or K_d.
- $$K_a = \frac{[H^+][A^-]}{[HA]}$$
- D. pK_a means the "negative of the log to the base 10 of K_a". The pK_a is a way of describing the acidity of an acid. The lower the pK_a, the stronger the acid.
- E. When the pH is equal to the pK_a, there are equal amounts of protonated and unprotonated species. In the case of acetic acid, there would be equal concentrations of CH₃COOH and CH₃COO⁻ when the pH equals the pK_a of 4.86.
- F. When a weak acid is added to water, it is possible to compute how much of the acid dissociates into H⁺ and A⁻, and therefore the pH, by using the pK_a, some assumptions, a calculator, and maybe even the quadratic equation.
- G. An example: when you add 0.2 mols acetic acid to 1 liter of water: x mols acetic acid dissociates to form x mols acetate anion and x mols H⁺. The equilibrium concentrations will be: Acetic acid (0.2 - x) mols/liter; Acetate anion, x mols/liter; H⁺, 10⁻⁷ + x mols/liter (the 10⁻⁷ is from water). Working this example out for acetic acid, with a K_a of 1.38 x 10⁻⁵ M, there will be 1.6 mM acetate anion, 1.6 mM H⁺ (pH 2.78), and 198.4 mM undissociated acetic acid.

H. The equation describing the equilibrium $K_a = \frac{[H^+][Ac^-]}{[HAc]}$

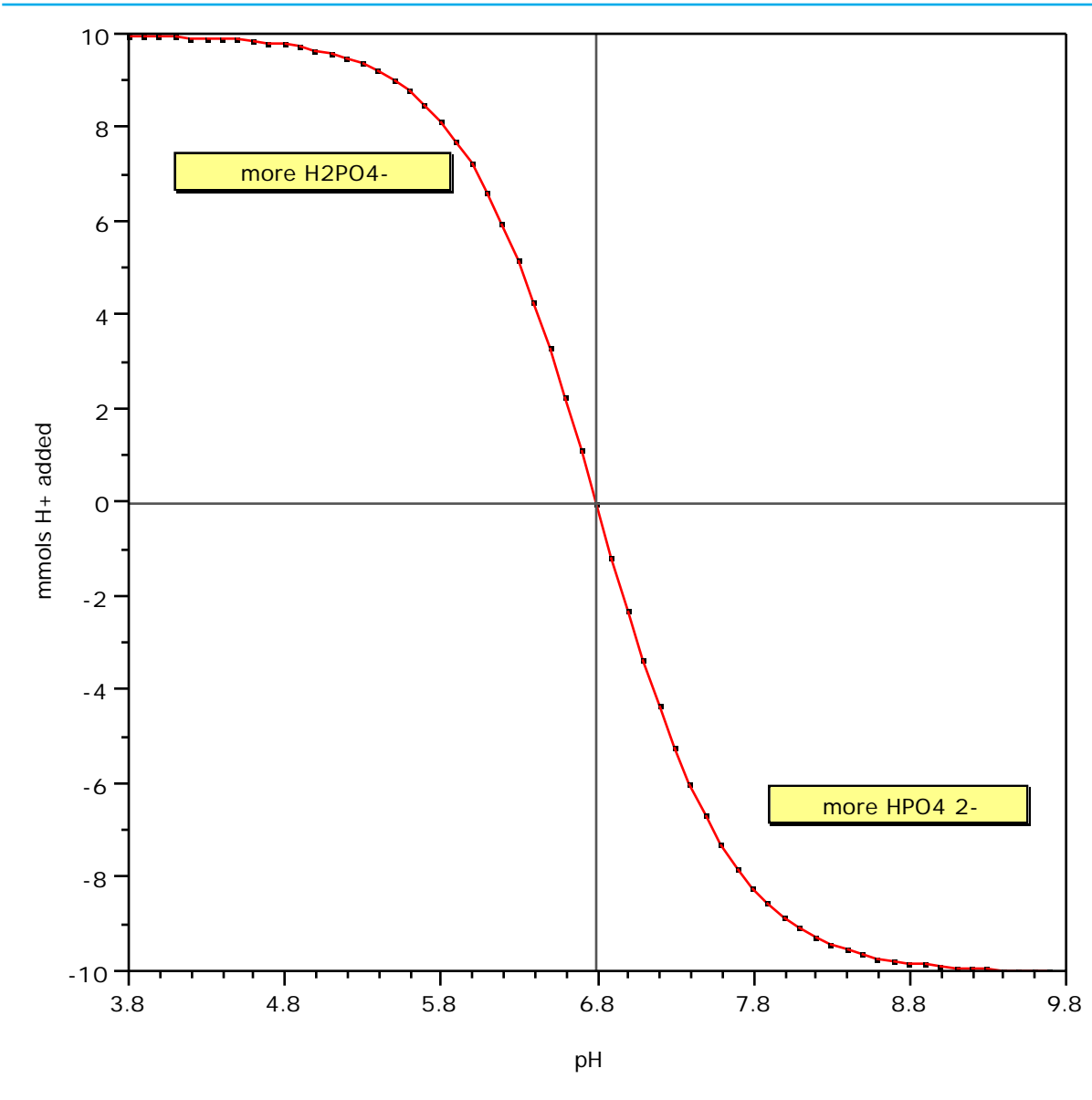
can be rearranged as below:

$$[H^+] = K_a \frac{[HAc]}{[Ac^-]} \quad \text{The Henderson Equation}$$

This is a general form of the Henderson equation using acetic acid as an example; you will see the Henderson equation more specifically in reference to bicarbonate buffers.

- I. When several acids are present in the same solution, they are in equilibrium with each other. This is known as the **isohydric principle**. Basically, it means that when you write the equilibrium equations for all the buffers, they all have $[H^+]$ in them. This means that if you know the pH and the pK_a 's of all the buffers, you know the status of all the buffers in the system.
- J. Finally, it is relatively easy to see that adding a weak acid will make a solution more acidic. What is not so obvious is that adding a salt of a weak acid and a strong base, like sodium acetate, will make a solution more alkaline. (Details in appendix.)

Titration of 20 mM sodium phosphate, pH 6.8



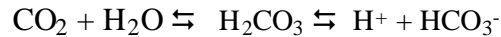
mmols H⁺ added

Start at the middle of the plot, pH 6.8, which is the pK of phosphate buffer. There are equal amounts of the HPO₄²⁻ and H₂PO₄⁻ forms at pH 6.8. The added H⁺ combines with HPO₄²⁻ to make H₂PO₄⁻ and moves the system to a lower pH.

Subtracting H⁺ is the same as adding NaOH and makes more HPO₄²⁻, moving the system to higher pH.

V. The free H⁺ concentration in body fluids is due to the dissociation (ionization) of the dissolved acids. Sources of H⁺ in the body:

A. The major source of H⁺ is CO₂, which reacts with water to produce the volatile acid, H₂CO₃.



1. CO₂ is formed within cells during the production of ATP by cellular respiration.
2. CO₂ diffuses through the interstitial fluid and the plasma into the red cell where it is hydrated and H₂CO₃ is formed.
3. The daily production of CO₂ is 13,000 to 24,000 m mol which yields 13,000 - 24,000 m mol H⁺/day.
4. H₂CO₃ is called a "volatile" acid because it can be excreted as CO₂ by the lungs.

B. All other chemical reactions in the body which produce acids, produce "fixed", or "non-volatile" acids. About 70-100 m mols H⁺ are produced per day from:

1. Protein catabolism: sulfur containing amino acids produce H₂SO₄.
2. Phospholipid catabolism produces H₃PO₄.
3. Lactic acid is produced during anaerobic metabolism.
4. Ketone acids are produced by the liver.
5. Vegetarians produce less fixed acids.

C. Also acids in diet.

D. Another source of acidity is the constant loss of alkalinity through the normal bicarbonate secretions in the colon. In diarrhea, the HCO₃⁻ loss increases.

VI. The body must maintain the alkalinity of the body fluids in spite of the daily acid load.

A. Despite the constant addition of acids to body fluids, the actual H⁺ concentration is maintained at 40 ± 5 nM.

B. Three mechanisms for maintaining pH:

1. Immediate buffering.
2. Quick adjustments of alveolar ventilation to remove CO₂. (seconds to minutes)

3. Slower activity of the kidney which excretes H^+ ion and maintains and restores bicarbonate. (days)

VII. Buffer pairs available in the body:

A. Extracellular:

1. Bicarbonate - carbonic acid: $HCO_3^- + H^+ \rightleftharpoons H_2CO_3$
 - a. most important of the buffers in the ECF.
 - b. 24 mM
 - c. $pK_a = 6.1$; You wouldn't expect this to be very useful at the plasma pH of 7.40, but bicarbonate works differently than other buffers because the $[CO_2]$ is controlled. Covered in detail in next lecture.

1. Plasma proteins: $Pr^- + H^+ \rightleftharpoons HPr$

- a. These form a series of buffer pairs with pK_a 's ranging from 5.3 to 8.5.
- b. This allows effective buffering over a wide range of pH's.
- c. Buffering is accomplished by the histidine residues in the proteins. Different microenvironments of the different histidines give them different pK_a 's.

2. Inorganic phosphates: $HPO_4^{2-} + H^+ \rightleftharpoons H_2PO_4^-$

- a. $pK = 6.80$, which is useful, but
- b. only present at about 1 mM in ECF.

B. Intracellular buffers:

1. Hemoglobin in the red cell: $Hb^- + H^+ \rightleftharpoons HHb$

- a. The pK ranges between 7-8.

2. Other intracellular protein: $Pr^- + H^+ \rightleftharpoons HPr$

3. Organic phosphates.

- a. pK_a 's about 7.
- b. ATP, ADP, G-6-P, etc.

4. Bicarbonate, the most important extracellular buffer, is also an intracellular buffer. Because CO_2 can diffuse across cell membranes easily, the HCO_3^- concentration at the intracellular pH of 7 and P_{CO_2} of 40 mmHg can be

calculated as about 10 mM.

C. The effectiveness of a buffer system depends upon:

1. Its pK_a . This should be close to the desired pH. Remember that bicarbonate is an exception, and in fact is an excellent buffer at pH 7.4 even though its pK_a is 6.1.
2. The concentration of the buffer. In ECF, there is so little inorganic phosphate (1 mmol/L) that it is an unimportant buffer, despite its pK of 6.80.

VIII. Cells must maintain their intracellular pH:

Most of acid-base physiology is focused on maintaining the extracellular fluid at the proper pH, 7.40. How do cells keep internal pH at about 7 ?

Cells have these problems:

1. H^+ can enter and exit cells.
2. Metabolism produces H^+ inside the cells.
3. Cells with large resting membrane potentials are electrically negative inside, which attracts H^+ into the cell.

Remember how chloride was passively distributed in axons? A similar thing happens with hydrogen ions. The resting membrane potential drives H^+ into the cell, and we could calculate equilibrium distributions in the same way, with the Nernst potential equation. Suffice it to say that if the membrane potential is -60 mV, the equilibrium $[H^+]$ in the cell would be 400 nM, 10 times greater than the extracellular fluid H^+ concentration of 40 nM. (The pH inside would be 6.4, 1 unit lower than outside pH of 7.4).

The fact that intracellular pH is usually about 7.0, not the equilibrium pH of 6.4, means that the cell must be transporting H^+ out to the extracellular fluid.

Several mechanisms have been described in a variety of cell types, but the most widely distributed and studied one seems to be the Na^+/H^+ exchanger, or anti-port, which can extrude H^+ from cells coupled to the entry of Na^+ .

Appendix: Review of Chemistry concepts.

- I. Definitions of acids and bases.
- A. An acid is a proton (H^+) donor.
 - B. A base is a proton (H^+) acceptor.
 - C. Thus, hydrochloric acid is an acid because when you add it to water, it adds protons (or Hydrogen ions, H^+), and ammonia is a base because it accepts protons from water to make ammonium ion, NH_4^+ .
 - D. Hydrogen ions do not exist as free protons in water. They are actually hydrated to form species such as hydronium ions, H_3O^+ . But for our purposes, we will just write H^+ .
- II. Measurement of $[H^+]$.
- A. Units of measurement:
 - 1. Concentration is expressed in mols/liter (molar, or M)
 - 2. The square brackets, $[]$ mean "concentration".
 - 3. The H^+ concentration in pure water is 10^{-7} M, or 0.0000001 M. Water dissociates :
$$H_2O \rightleftharpoons H^+ + OH^- \quad x \text{ mols/L dissociate, so } [H^+] = [OH^-] = x$$
 - 4. The prefix "nano" means 10^{-9} , so 1 Nanomol = 10^{-9} moles, and "nM" means nanomols/liter.
 - 5. Thus, the H^+ concentration of pure water can also be expressed as 100 nM.
 - 6. Expressing the H^+ concentration as a nanomolar concentration makes things much easier in Acid Base Physiology.
 - B. The pH scale:
 - 1. Useful for laboratory work, but more cumbersome for acid-base physiology.
 - 2. Definition: $pH = \text{negative log } [H^+]$ ("negative logarithm to the base 10 of the molar H^+ concentration")
 - 3. For pure water, the H^+ concentration = 10^{-7} M, so the log of this is -7, and the negative of the log is 7, i.e., $pH = 7.00$.

4. The $[H^+]$ of plasma = 40×10^{-9} moles/liter, or 40 nM.
5. The pH of plasma :
- $$\log (40 \times 10^{-9}) = \log 40 + \log 10^{-9} = 1.6 + (-9) = -7.40$$
- Of course pH is the negative of the log, or 7.40.

III. Strong acids and strong bases: pH and concentration

- A. For strong acids added to pure water, the H^+ concentration of the solution is approximately the same as predicted from the amount of strong acid added. For example, if you add 0.01 mol HCl to a liter of water, the $[H^+]$ is 0.01 M (pH = 2); if you added only 0.001 mol, the concentration would be 0.001 M (pH = 3).
- B. For strong bases, it's not quite so easy to calculate because of the following.
- C. The dissociation constant of water, K_w , is 1×10^{-14} . This means that **the product of the molar concentrations of $[H^+]$ and $[OH^-]$ is 1×10^{-14}** . This also means that the $pH + pOH = 14$. Thus, in pure water, the pH and the pOH are both 7. In an acid solution, when the pH is 2, the pOH = 12. The table gives some examples.
- D. To figure the pH when a strong base is added to pure water, first determine the OH^- concentration. The OH^- concentration is approximately the same as the amount added, so adding 0.01 mol NaOH to a liter of water gives a $[OH^-]$ of 0.01 or a pOH of 2. If you only added 0.001 mol NaOH, the $[OH^-]$ would be 0.001, or a pOH of 3.

$[H^+]$	pH	pOH	$[OH^-]$
1	0	14	1×10^{-14}
.1	1	13	1×10^{-13}
.01	2	12	1×10^{-12}
.001	3	11	1×10^{-11}
.0001	4	10	1×10^{-10}
1×10^{-5}	5	9	1×10^{-9}
1×10^{-7}	7	7	1×10^{-7}
1×10^{-9}	9	5	1×10^{-5}
1×10^{-11}	11	3	0.001

Relationship between pH, pOH, and molar H^+ and OH^- concentrations

- a) Then use the fact that $pH + pOH = 14$ to calculate the pH of the resulting solution. (You could also make the calculation using the fact that the product of the molar $[H^+]$ and $[OH^-]$ concentrations must equal 1×10^{-14} .)

IV. Weak Acids and Weak Bases

- A. When a strong acid like HCl dissolves in water, it ionizes completely to form H⁺ and Cl⁻ ions. When a weak acid, represented as HA, dissolves in water, only a portion of it ionizes to form H⁺ and A⁻; some of it remains in the non-dissociated form as HA.
- B. Nomenclature: In this system, the A⁻ species is called the "conjugate base".
- C. The extent to which an acid dissociates is expressed by its equilibrium acid dissociation constant, K_a, or K_d.

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

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- H. What happens if we instead add 0.2 mols sodium acetate (abbreviation: NaAc) to a liter of water? The reaction is Ac⁻ + H⁺ ⇌ HAc. The acetate anion, Ac⁻, combines with, and binds most of the H⁺ present in pure water, forming acetic acid, HAc, and depleting the H⁺ concentration.
1. To compute the concentrations above, x mols of Ac⁻ react with H⁺ to form x mols HAc. Since x works out to be between 99 and 100 nM, the equilibrium concentrations will be 99 nM HAc, (0.2 - x) M Ac⁻, which is essentially unchanged, and (100 nM - 99 nM) H⁺. (The H⁺ concentration works out to be about 6.8 x 10⁻¹² M, for a pH of 11.16.

2. The point of the above example is that the pH of a solution can be increased by adding a salt of a weak acid and a strong base, like sodium acetate.

I. The equation describing the equilibrium can be rearranged as below:

$$K_a = \frac{[H^+][Ac^-]}{[HAc]}$$

$$[H^+] = K_a \frac{[HAc]}{[Ac^-]} \quad \text{The Henderson Equation}$$

Please note that this is a general form of the Henderson equation using acetic acid as an example; you will see the Henderson equation more specifically in reference to bicarbonate buffers.

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