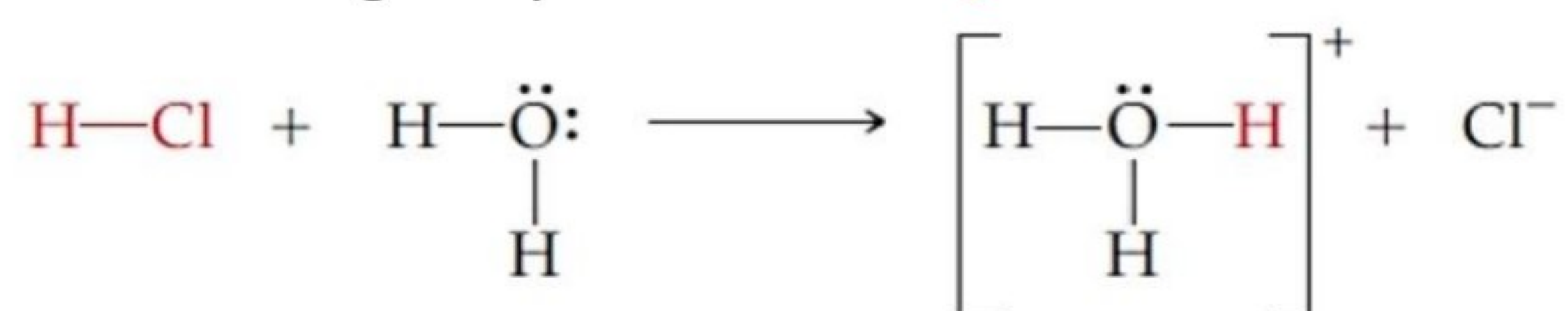# MED-HUB

BIOCHEMISTRY

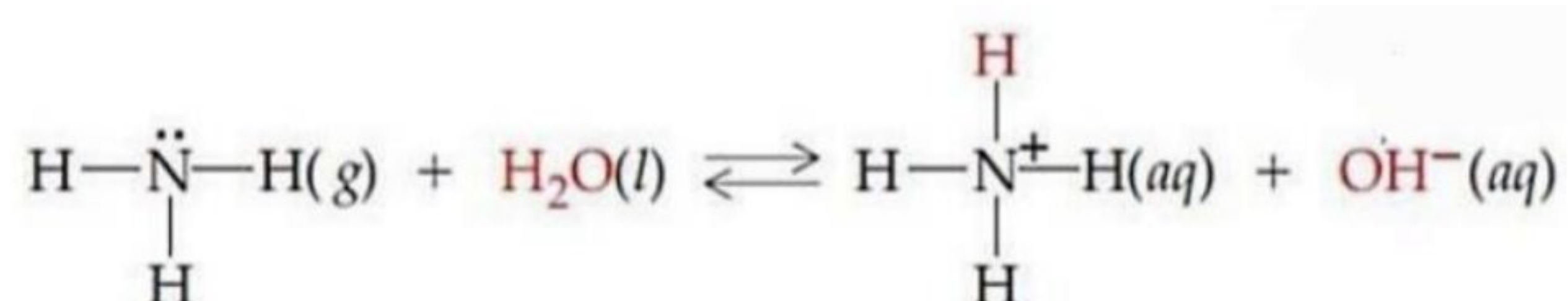## Acids & Bases

Acids and Bases 1

Acids and bases

We have three different definitions to acids and bases:

1) Arrhenius definition

● Acid: a substance that produces H^+ when dissolved in water, which then reacts with water to give hydronium ion H_3O^+.

● Base: a substance that produces OH^- hydroxyl ion when dissolved in water.

☆ Drawbacks of Arrhenius definition:

1. Reactions has to happen in an aqueous solution.
2. H_3O^+ is released but not H^+.

2) Bronsted-Lowry definition

● Acid (proton donor): a substance that gives a proton H^+ to another substance.

● Base (proton acceptor): a substance that accepts a proton H^+ from another substance.

☆ The acid HA donates its proton and gives a conjugate base A^- while the base B accepts the proton and becomes a conjugate acid BH^+.
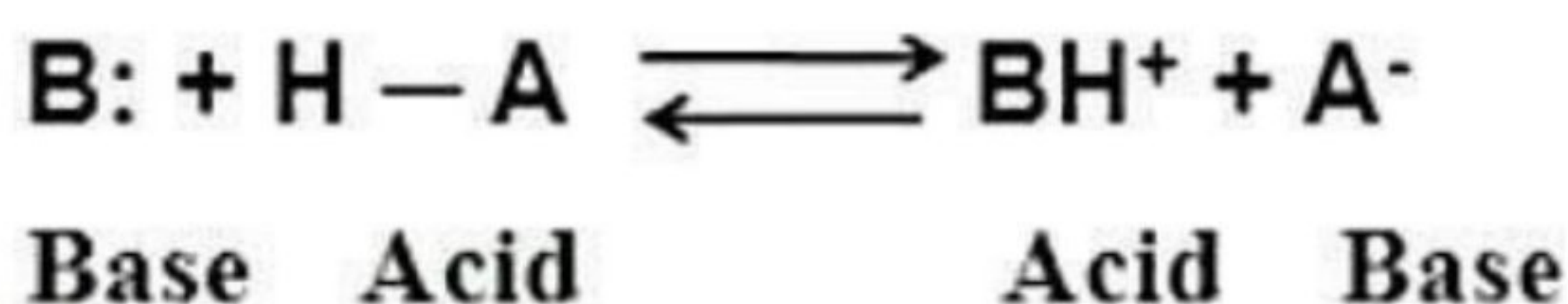
3) Lewis Definition

● Acid: a substance that accepts electrons.
● Base: a substance that donates electrons.
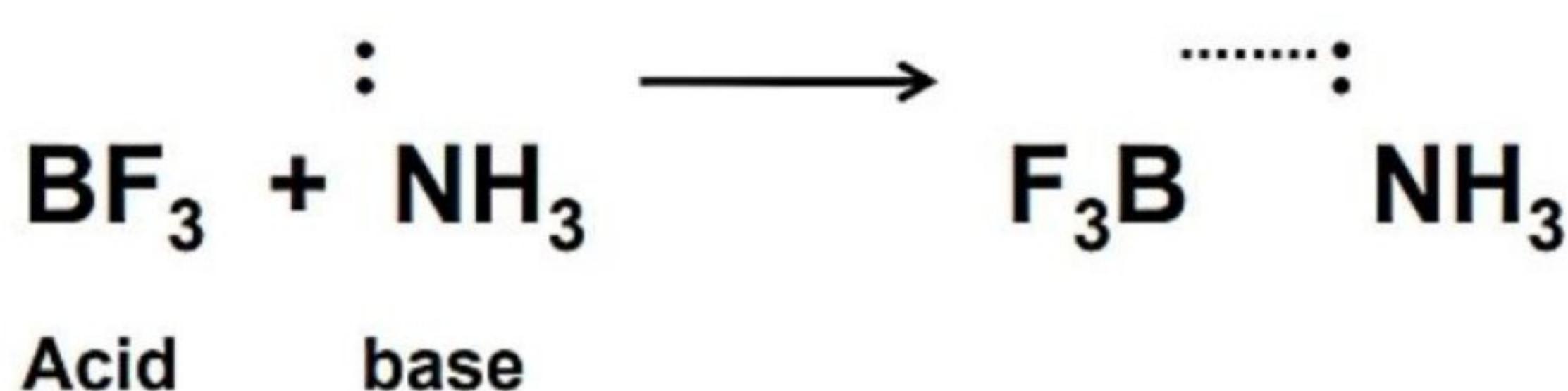
Types of acids

Acids can be divided depending on the number of protons they contain:
- Monoprotic acid, containing 1 proton: HCl, HNO_3, CH_3COOH.
- Polyprotic acids, containing more than 1 proton, they can be either diprotic (H_2SO_4) or triprotic (H_3PO_4).

Is water an acid or a base?

Water is neither considered an acid nor a base as it acts as an acid or a base depending on the other substance.

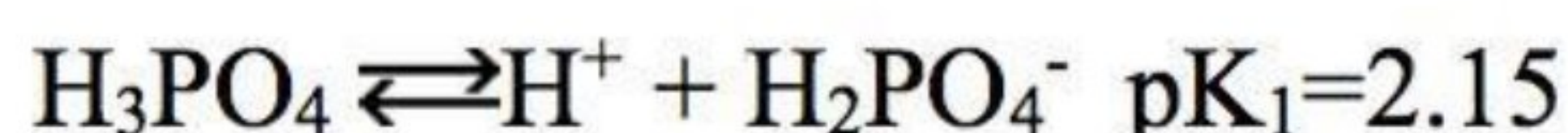Substances that can act as acids and bases (depending on the other substance) are called amphoteric (like water).

Here, water acts as an acid → $NH_3 + H_2O \leftrightarrow NH_4^+ + OH^-$

But here, it acts as a base → $HCl + H_2O \rightarrow H3O^+ + Cl^-$

Strength of acids and bases

- Acids differ in their ability to release protons, and bases differ in their ability to accept protons as well.
- Strong acids dissociate completely (all the molecules release their protons) in a one way reaction, whereas weak acids dissociate partially (release a very small number of protons) in a two ways reaction (indicated by two headed arrow).
- For polyprotic acids, they dissociate gradually (in steps) and give several protons (a proton in every step), becoming weaker after releasing each proton.
- The first step is the fastest and the easiest, because the acid in this step is stronger than the next steps.

(H_3PO_4 is stronger than $H_2PO_4^-$ which is stronger than HPO_4^{-2})

$$H_3PO_4 \rightleftharpoons H^+ + H_2PO_4^- \quad pK_1 = 2.15$$

$$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-} \quad pK_2 = 7.20$$

$$HPO_4^{-2} \rightleftharpoons H^+ + PO_4^{3-} \quad pK_3 = 12.40$$

- Generally, acids produce conjugate bases and bases produce conjugate acids.
- Strong acids produce weak conjugate bases and weak acids produce strong conjugate bases and the same principle applies to bases and their conjugate acids.

2

Equilibrium constant and Acid dissociation constant K_a

Equilibrium constant equals the concentrations of the products multiplied by each other, over the concentrations of the reactants multiplied by each other. When dealing with acids, we use K_a, which is the same as the equilibrium constant, but we multiply both sides with water concentration (because it is constant), so the final formula will equal to the concentration of the hydronium ion multiplied by the concentration of the conjugate base, over the concentration of the acid.

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

● Higher K_a values indicate higher proton concentrations and higher dissociation rate, which means a stronger acid.
● The value of the K_a indicates the direction of reaction as well.
● When K_a is greater than 1, the product side is favoured (the acid is a strong one).
● When K_a is less than 1, the reactants are favoured (the acid is a weak one).

What is pK_a?

Because the values of K_a (especially those of weaker acids) contain negative powers, they are difficult to deal with, so we converted those values into integers by taking the negative logarithm of these values and we end up with pK_a values.

$$pKa = -logKa$$

The values of K_a and pK_a are inversely proportional, the higher the K_a (the stronger the acid) the lower the pK_a and vice versa.

Base dissociation constant K_b

Similarly, K_b is equal to the concentration of the hydroxyl ion multiplied by the concentration of the conjugate acid, over the concentration of the base (we multiply both sides with water concentration since it is constant).
Weak bases have small K_b values, and strong bases have large K_b values.

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

3

Concentration measurement

Acids and bases can be expressed in terms of their molarity (M) or equivalence (Eq).

● Molarity is the number of moles over the volume of the solution, and we can calculate the moles of a solution by dividing the mass over its molecular weight (MW).

$$M = moles\ /\ volume \qquad moles = grams\ /\ MW$$

● Equivalents, which equals the number of H^+ moles an acid solution can give, or the number of OH^- moles a base solution can give, and for ions, it is the molar mass of the ion divided by the ionic charge.

Acids and Bases 2

Titration

It is the neutralization of an acid (whether it is strong or weak) by adding a strong base, or neutralization of a base (whether it is strong or weak) by adding a strong acid.

In titration, the number of moles for H^+ and OH^- must be the same, so we take into consideration the molarity and the volume of the acid and the base as follows:

$$M1 \times Vol1 = M2 \times Vol2$$

● Note: we use the previous formula when the acid contains one proton H^+ (monoprotic) and the base contains one hydroxyl OH^-, but if the acid is diprotic we multiply its side by 2, and by 3 if the acid is triprotic, and the same goes for the base, if it contains two OH^- groups, we multiply its side by 2, because we want the H^+ and OH^- moles to be the same, not necessarily the acid and the base moles will be equal.

Ionization of water

● When alone, water dissociates into both hydronium ion H_3O^+ and hydroxyl ion OH^-, because two water molecules will interact with each other, one will act as an acid giving its proton and forming OH^-, while the other one will act as a base accepting the proton and forming H_3O^+.

● For simplicity, we refer to the hydronium ion as a hydrogen ion H^+, and write the equation as if one H_2O molecule dissociates as shown below:

$$H_2O(l) \rightleftharpoons H^+(aq) + HO^-(aq)$$
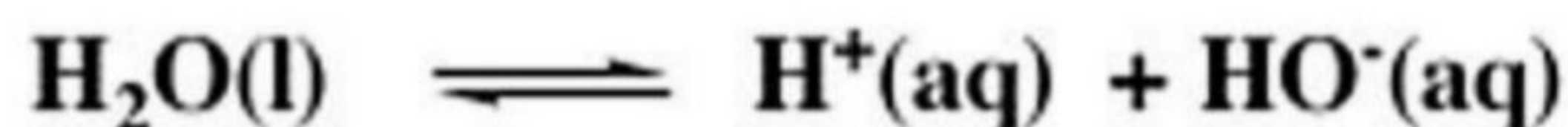
And we can write the equilibrium constant as: $\quad K_{eq} = \dfrac{[H+][OH-]}{[H2O]}$

And by multiplying both sides with water concentration (because it is constant as we said 55.5) and knowing that K_{eq} for water is 1.8×10^{-16} and it is constant (as its name implies), we can find a new constant (and we call it the ion product of water or K_w) for the concentrations of H^+ and OH^- multiplied.

$$K_{eq}(55.5\ M) = [H^{\oplus}][OH^{\ominus}] \rightarrow K_w = [H^{\oplus}][OH^{\ominus}] = 1.0 \times 10^{-14}\ M^2$$

● For neutral solutions as pure water, the concentrations of H^+ and OH^- are constant, each with a value of 1×10^{-7} M.

● Since K_w is a fixed value, the concentrations of H^+ and OH^- are inversely changing.

● If the concentration of H^+ is high, then the concentration of OH^- must be low, and vice versa.
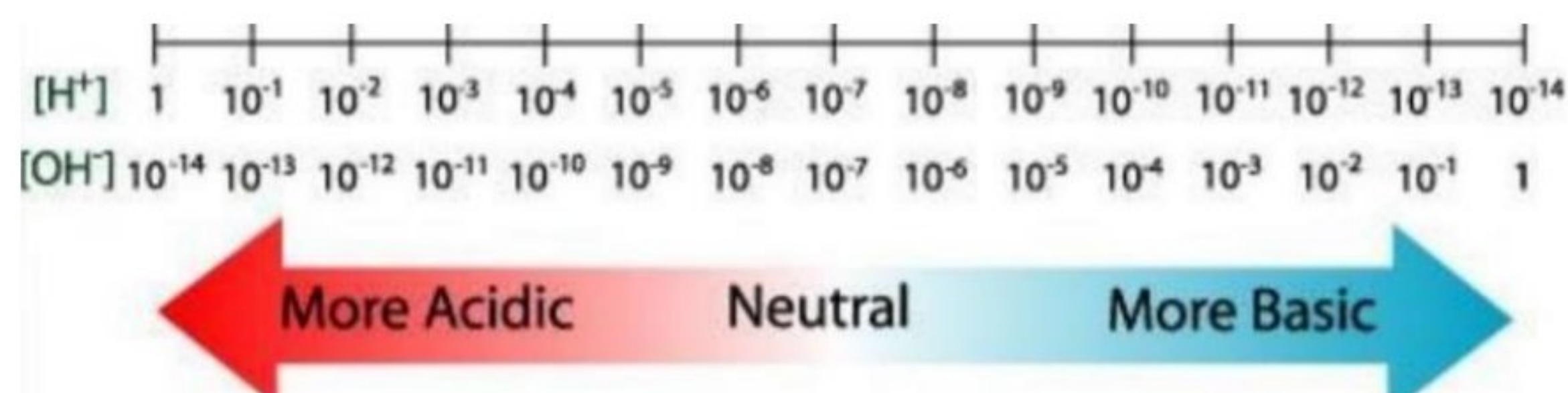
pH and buffers

☆ pH is a quantitative (numerical) measure of the acidity or basicity of a solution, it ranges from 0 to 14.

☆ It depends on the H^+ concentration, if the H^+ concentration is high, the pH will be low.

☆ The pH scale is a logarithmic scale, one unit difference in pH implies 10-fold difference in H^+ concentration, (a solution with pH of 3 has 100 times more H^+ than a solution with pH of 5).

☆ Solutions with higher OH^- concentration are considered basic, and those with higher H^+ concentration are considered acidic.

☆ We can calculate the pH using this formula:

$$pH = \log_{10}(1/[H^+]) = -\log_{10}[H^+]$$

Some pH values we need to remember:
● Blood plasma 7.4
● Gastric juice 1.2-3
● pancreatic fluid 7.8-8
● Saliva 6.6 (it can be affected by cleaning habits and becomes more acidic).
● Urine 5-8 (closer to 5 for females, and closer to 8 for males).

Determination of pH

There is two ways to determine the pH of a solution:

1) Acid-base indicators, (litmus paper for example), they have the least accuracy, they work by turning red when you add an acid, and turning blue when you add a base, they give you an idea whether the solution is acidic or basic, but they don't give the exact pH value.

2) Electronic pH meter, which is the most accurate, it gives a numerical reading of the pH for an unknown solution when you put its electrode in that solution.

Henderson-Hasselbalch Equation

If we rearrange the K_a formula, then take the logarithm for both sides, and by using some of the logarithm features, we will end up with this equation

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

It might help us in some questions (that ask about ratio) to know this form of the equation

$$10^{pH\text{-}pKa} = \frac{[A\text{-}]}{[HA]}$$

☆ If pH equals pK_a, then the acid and its conjugate base have the same concentrations.

☆ If pH is greater than pK_a, the conjugate base has greater concentration than the acid.

☆ If the pH is lesser than pK_a, the acid has greater concentration than the conjugate base.
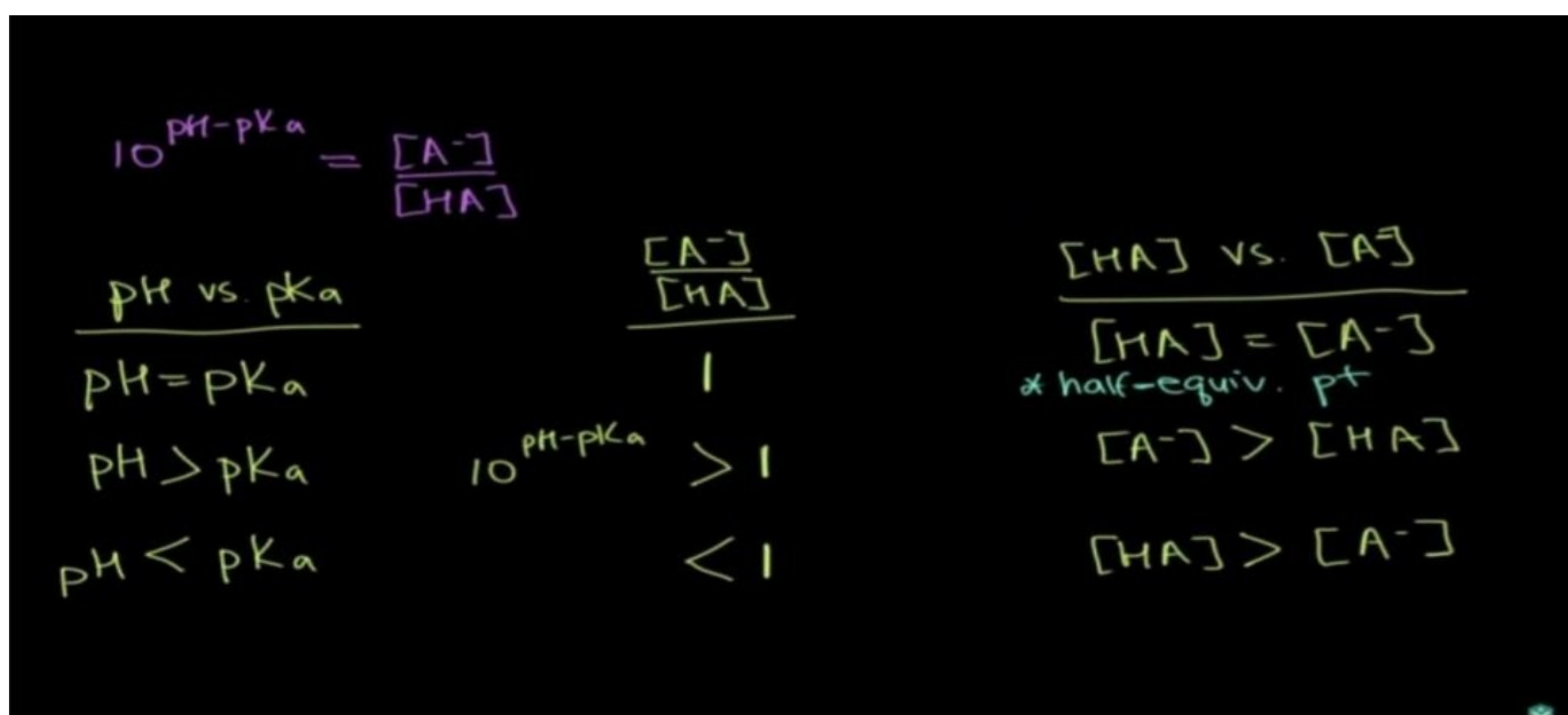
Acids and Bases 3

Le Châtelier's principle

If you leave any reaction for enough time, it will reach equilibrium, where the rate of forming the reactants equals the rate of forming the products, (pay attention, rates not concentrations), and after reaching equilibrium, if you add any substance from the reactants, the reaction will move forward forming more products, and if you add any substance from the products, the reverse reaction will form more reactants. Those changes happen in order to allow the reaction to reach the equilibrium state again.

when more reactants, A and/or B is added, the equilibrium shifts to reduce A and B by producing more C and D

$$A + 2B \rightleftharpoons C + D$$
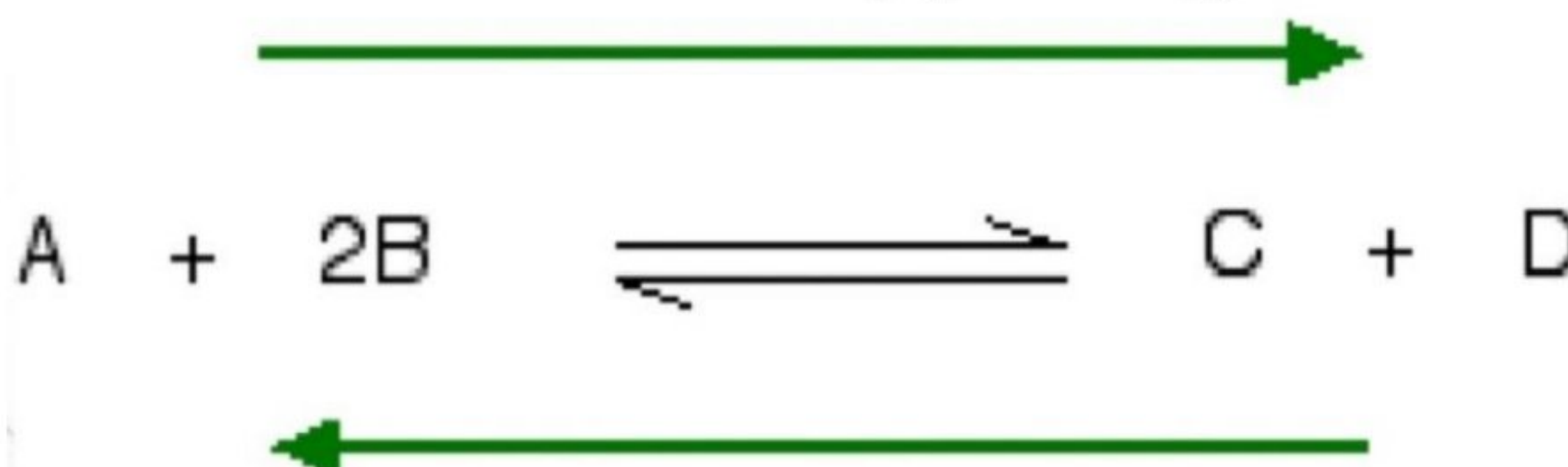
when more products, C and/or D is added, the equilibrium shifts to reduce C and D by producing more A and B

Buffers

Buffers are solutions that resist changes in pH by changing reaction equilibrium, they are made of a mixture of weak acid and roughly equal concentration of its conjugate base.

When you add an acid H^+ to the buffer, the conjugate base will react and accept H^+ before the pH of the solution becomes lower, similarly, when you add a base OH^-, the weak acid will react and donate a proton H^+ to the base, resisting any increase in the pH.

Steps to form a buffer

1) We start with a 100% just weak acid, CH_3COOH for example (a monoprotic acid).
2) We gradually start adding a strong base OH^- to neutralize it.
3) Since the acid in our example is monoprotic, we would except that if we had 1 equivalent of the acid, we would need 1 equivalent of OH^- to completely neutralize it.
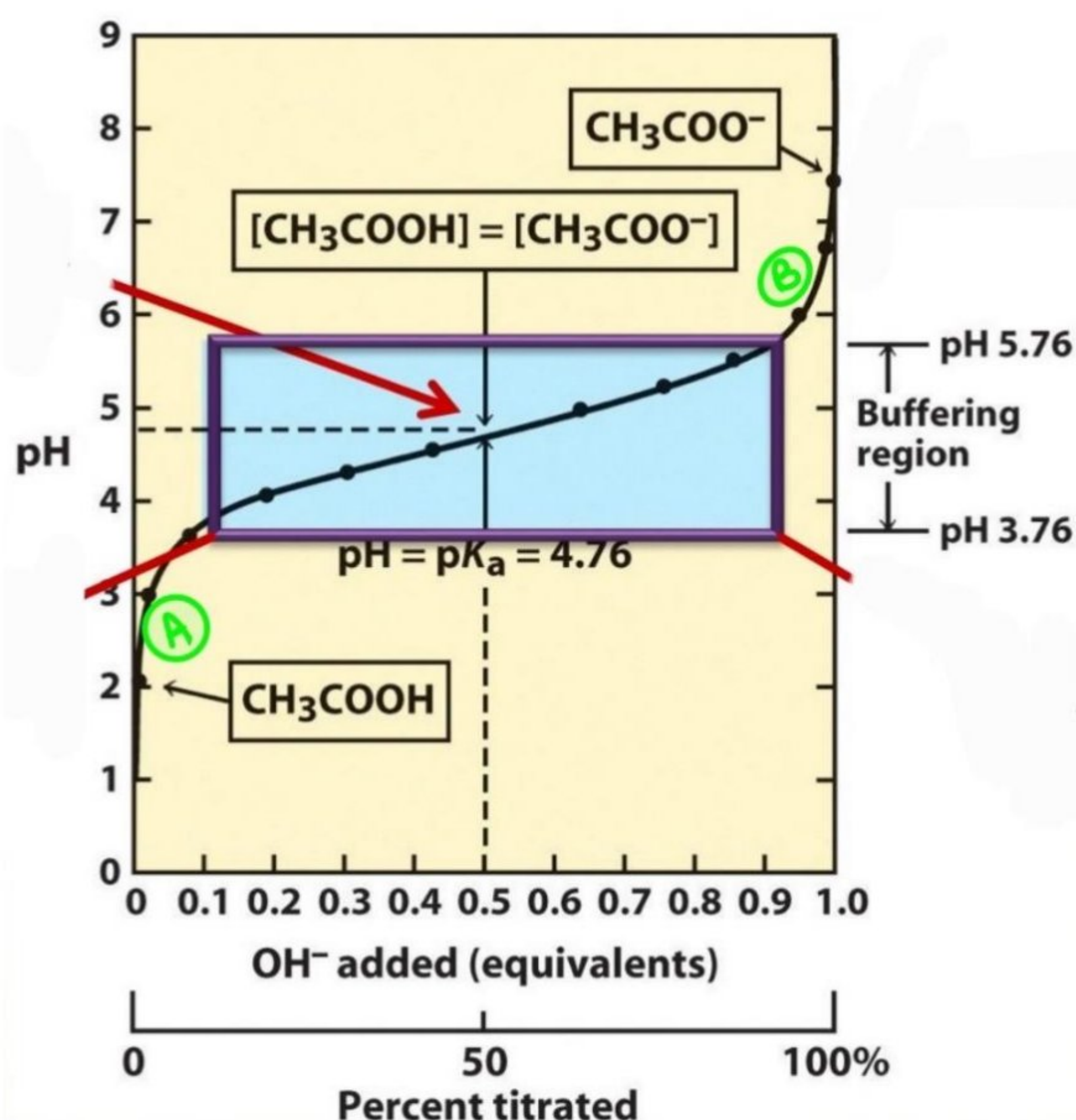
● At the beginning (A), there would be a sudden increase in the pH, because we only have acid molecules (not a buffer solution yet).

● Then the pH value starts to increase slowly, because the conjugate base is being formed, so the acid and the conjugate base will roughly have equal concentrations (forming a buffer solution).

● Until it reaches a certain point (B) where it would go fast again, because we have consumed all the acid molecules and the only remaining molecules are the conjugate base (not a buffer solution anymore).

● When 50% of titration is done, we have added 50% of OH^- at this point, the direction of the curve changes, and we call it the inflection point where $pH=pK_a$.

● The end of titration is called the equivalence point, at this point, pH doesn't have to be 7, because it is a matter of finishing the acid rather than having equal amounts of H^+ and OH^-.

● The buffering range is around the inflection point (or the pK_a value), 1 unit above and 1 unit below.

The ability of a buffer to function depends on:
1) Buffer concentration, high buffer concentration means high number of molecules and more resistance to pH changes.
2) pK_a of the buffer, which determines the buffering range.
3) The desired pH, we must make sure that the desired pH is within the buffering range.

2

Buffers made from polyprotic acids have more than one curve, because polyprotic acids gets neutralized at different steps, each step forming a new acid (and a new buffer solution).
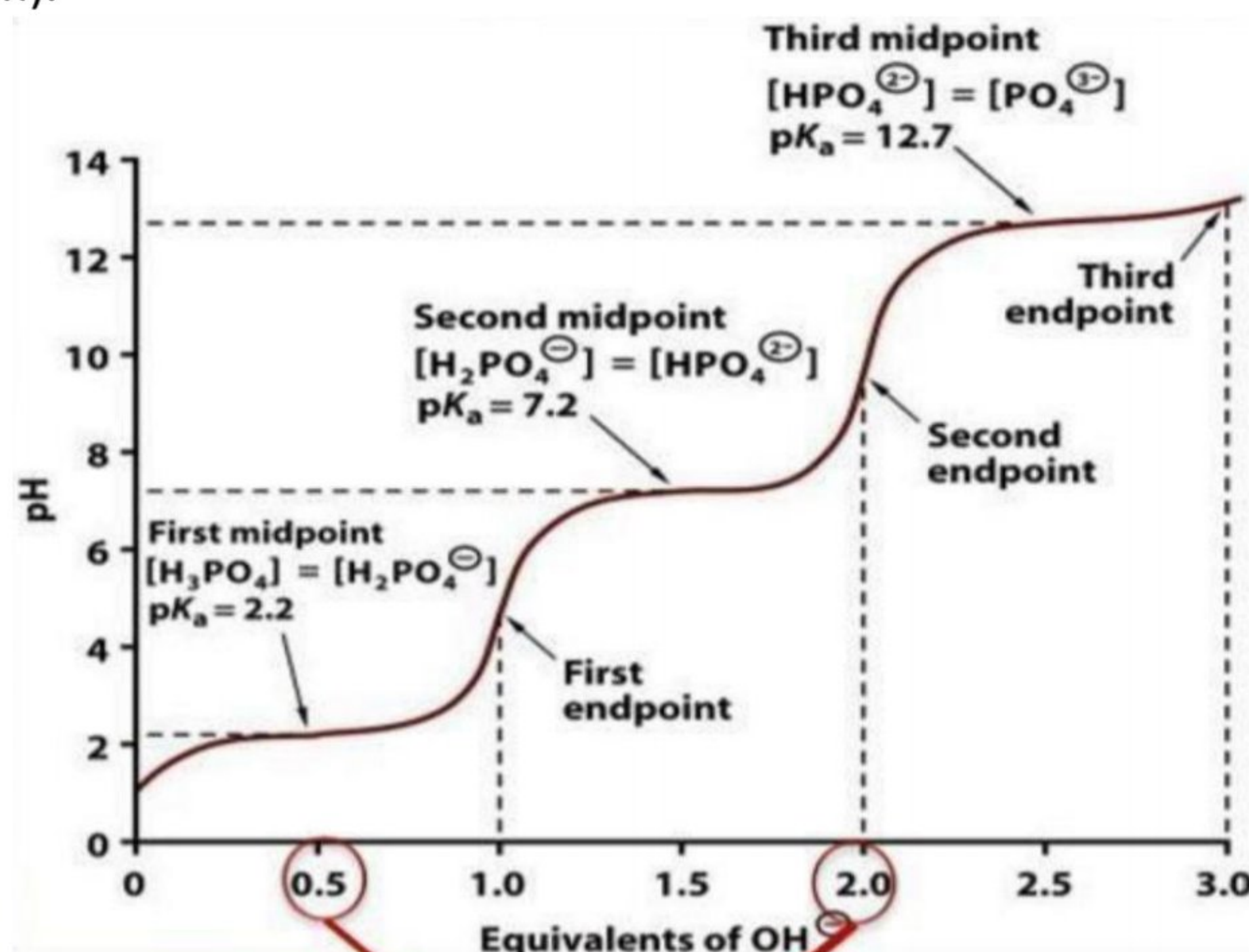
☆ We have 3 curves for H_3PO_4, each curve represents a step of titration (and a buffer solution), each has a product going to the next step as a reactant, the first curve represents the titration of H_3PO_4 (occur at the lowest pH, which means it is the strongest acid), giving its proton and becoming $H_2PO_4^-$, which will be titrated in the second curve and becomes HPO_4^{-2}, that will be titrated in the last curve (occur at the highest pH, which means it is the weakest acid) to end up with PO_4^{-3}.

☆ H_3PO_4 contains 3 protons, thus 3 equivalents of OH^- are needed, first equivalent will be used in the first titration, the second equivalent will be used in the second step, and the third equivalent will be used in the last titration.

☆ The inflection point for each curve can be calculated by finding the Pk_a value for each one of them, using H_3PO_4 pK_a for the first step, $H_2PO_4^-$ pK_a for the second step, and HPO_4^{-2} pK_a for the third curve.

● At the first endpoint, no more H_3PO_4 is left over, as all the molecules have converted to $H_2PO_4^-$.
● At the second end point, no more $H_2PO_4^-$ is left as all the molecules have converted to HPO_4^{-2}.
● At the last endpoint, no more HPO_4^{-2} is left as all the molecules have converted to PO_4^{-3}.

3

Biological buffers

There are three main buffer systems in our body that maintain the pH within normal range:

1) Carbonic acid-bicarbonate system in the blood.

2) Dihydrogen phosphate-monohydrogen phosphate system inside the cells (intracellular) which consists of molecules like ATP, glucose-6-phosphate and bisphosphoglycerate.

3) Proteins outside and inside the cells (extracellular and intracellular), like hemoglobin in the blood.

Carbonic acid- bicarbonate system

● It is the main buffer system in our body, located extracellularly in the blood.

● The way for forming this buffer → O_2 is inhaled into the lungs, transported to the cells, then used to generate energy and produce CO_2 in the combustion reactions, after that, CO_2 will be transported to the lungs to exit our bodies.

● While CO_2 is being transported in the blood to reach the lungs, part of it will enter the red blood cells (RBC), and because RBC have the enzyme carbonic anhydrase, CO_2 will react with water forming H_2CO_3, part of it will dissociate into HCO_3^- and H^+, and by this we have formed the buffer (H_2CO_3 and HCO_3^-).

● Carbonic acid-bicarbonate system is the first working buffer system to maintain pH in our bodies (specifically the blood), but it needs other systems to complete and finish the job, such as the respiratory system (2nd line of defence because it is faster than the 3rd, it affects CO_2 concentration) and the renal system (3rd line of defence because it is slower than the 2nd, it affects HCO_3^- concentration).

● The pK_a for this system is 6.1, so the buffer system will act in the range 5.1-7.1, this means that the blood pH (7.4) is not included in the buffering range, but this system can work as a buffer in the normal blood because it is an open system that interacts with the outer environment, and its components are under physiological control to make sure that the conjugate base HCO_3^- always have higher concentration than the acid H_2CO_3 (according to Henderson-Hasselbalch equation, HCO_3^-:H_2CO_3 ratio must be 20:1 in order to work as a buffer in physiological pH, and this what really happens).

Important notes

☆ We must understand that the main source for the carbonic acid is CO_2, so when we have high CO_2 concentration, it means high acid concentration.

☆ We deal with H_2CO_3 and its precursor CO_2 as an acid regarding their effect on the blood pH (they lower the pH), and we deal with HCO_3^- as a base regarding its effect on the blood pH (it increases the pH).

How does it work if we add an acid?

● When high concentrations of an acid are added to the blood, they will release many molecules of H^+, H^+ will then react with the conjugate base HCO_3^- forming H_2CO_3, that will get broken to H_2O and CO_2.

● The respiratory system will continue from here, exhaling CO_2 outside the body, preventing it from being in high concentration and being converted back to carbonic acid.

● The renal system is also involved in regulating the pH, by reabsorbing HCO_3^- from the urine back to the blood, to replace the molecules that reacted with the added acid.

How does it work if we add a base?

● When high concentrations of a base are added to the blood, they will release many molecules of OH^-, OH^- will then interact with the acid H_2CO_3 producing HCO_3^- and water.

● The renal system will continue from here, excreting HCO_3^- molecules outside the body, preventing it from accumulating.

● The respiratory system will increase CO_2 concentration in the blood, which will get converted back to carbonic acid to replace the molecules that reacted with the added base.

Dihydrogen phosphate ($H_2PO_4^-$) monohydrogen phosphate (HPO_4^{-2}) system

This system contains the molecules that have HPO_4^{-2} or $H_2PO_4^-$ like, ATP, glucose-6-phosphate and bisphosphoglycerate, it acts intracellularly and as a buffer by converting the phosphate group from one form to another by accepting or losing a proton ($H_2PO_4^-$ acting as an acid giving its proton, and HPO_4^{-2} as the conjugate base accepting the proton).

Protein buffer system

There is only one amino acid (from the 20 that form our proteins) that can act as a buffer under physiological conditions, and it is histidine, this amino acid has an imidazole group as a side chain, this group has a pK_a of (7.1) that is very close to the pH of the blood (7.4), so this group can be protonated or deprotonated according to the surrounding environment, the more histidines we have in the protein structure, the better it acts as a buffer.

Hemoglobin for example contains 38 histidines, so it can act as a buffer system, other proteins found inside and outside the cell can act as buffers depending on the number of histidines they contain.

The whole story (numbers in the paragraph below refer to the numbers in this picture)

Hepatic cell   Blood   Red blood cell
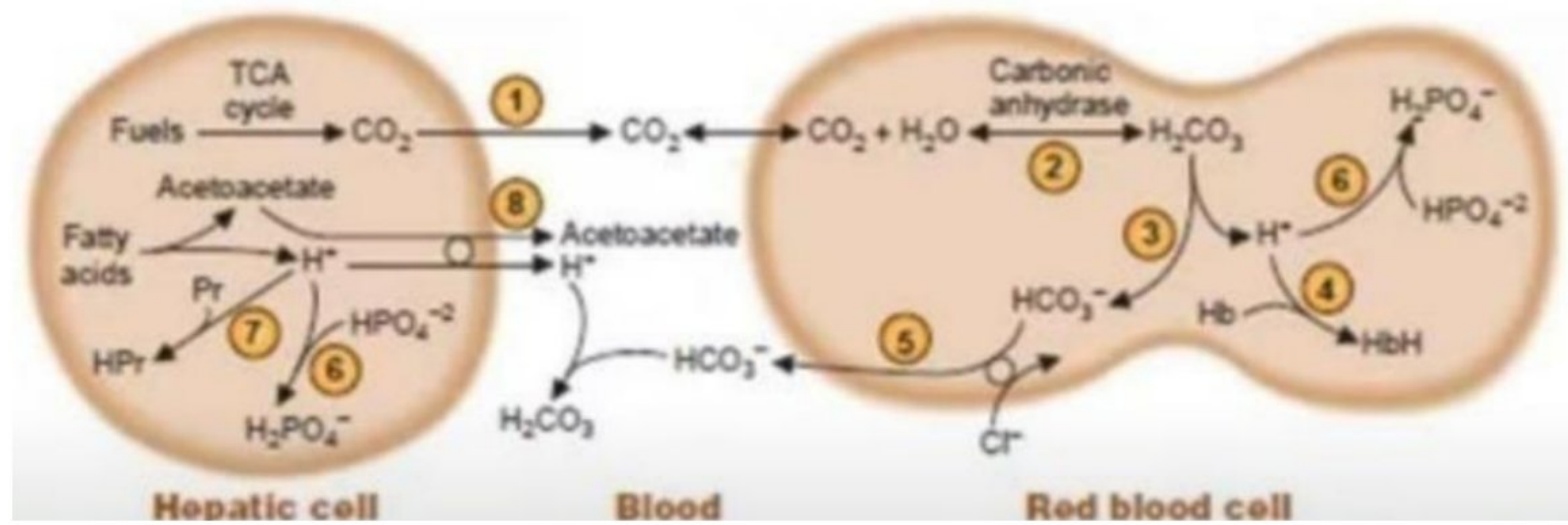
☆ Any cell in our body (a hepatic cell for example) will use the O_2 and nutrients (fuel) to produce energy and wastes (CO_2), then CO_2 will be transported out of the cell (1), and enter RBC, where it combines with H_2O by the enzyme carbonic anhydrase to produce H_2CO_3 (2), which will dissociate into H^+ and HCO_3^- (3), this H^+ will change the pH inside the cell, so to maintain the normal pH inside the cell we use the protein buffer system hemoglobin (Hb) (4) and dihydrogen phosphate $H_2PO_4^-$ monohydrogen phosphate HPO_4^{-2} system (6), and this is enough to restore the normal pH intracellularly, on the other side we have HCO_3^-, it will dissociate outside the RBC (5) and stay in the blood waiting for H^+.

☆ Now back to the hepatic cell, there is so much reactions happening inside this cell producing H^+, this H^+ will change the pH inside the cell, and dissociate outside the cell and change the pH there, inside the hepatic cell we have two buffer systems acting together to maintain normal pH, dihydrogen phosphate $H_2PO_4^-$ monohydrogen phosphate HPO_4^{-2} system (6) and intracellular proteins (Pr) (7), and the part of H^+ that dissociate outside the cell will combine with HCO_3^- formed from the beginning, forming H_2CO_3 (8).

6

Acidosis and Alkalosis

Acidosis and alkalosis

● Both are pathological conditions that are dangerous and can cause death, they happen when the blood pH becomes higher or lower than the normal range (7.35-7.45), we will talk about the definition of each of them, some metabolic and respiratory causes, and the respond of the body.

● Respiratory causes are associated with problems in CO_2 concentration, and metabolic causes are associated with problems in H^+ and HCO_3^- concentrations.

Acidosis

When the blood pH becomes lower than the normal range (lower than 7.35).

》 Metabolic causes:

● Starvation: it reduces the main source of glucose, so cells start degrading stored glycogen (which will supply the body with glucose for 10-18 hours), after that, your body will start breaking lipids which will release larger amounts of acetyl CoA, some acetyl CoA will be used in Krebs cycle to produce energy, however, excess acetyl CoA will activate the production of ketone bodies (ketoacids), increasing H^+ concentration because they are acids.

● Uncontrolled diabetes: it has the same mechanism, the absence of insulin (which is what happens in diabetes) will inhibit the cells from absorbing glucose, causing the cells to start to degrade glycogen and then lipids after it, producing large amounts of acetyl CoA, that will have two fates, to produce energy from Krebs cycle, and to produce ketone bodies (ketoacids).

》 Respiratory causes:

● Asthma and emphysema: in those respiratory problems, CO_2 won't be exhaled outside the body, so it will accumulate inside and react with H_2O producing the acid H_2CO_3, that will dissociate into H^+ and HCO_3^-, increasing H^+ concentration which means increasing blood acidity.

Alkalosis

When the blood pH becomes higher than the normal range (higher than 7.45).

》 Metabolic causes:

● Administration of bases, or salts that will dissociate to a base, it is a straight forward cause, increasing the blood pH directly.

》 Respiratory causes:

● Hyperventilation that is associated with anxiety: in this case, people will breathe quickly, getting all CO_2 molecules outside the body, and as we said before CO_2 is the precursor for the acid H_2CO_3, so less CO_2 means less acid and higher pH.
● Going to high altitudes: these places have lower O_2 concentration in the atmosphere, so the person will breathe less O_2, producing less CO_2, and therefore less acid will be formed, raising the blood pH.

Important notes:

☆ Respiratory acidosis have high CO_2 concentration that leads to a low blood pH.

☆ Respiratory alkalosis have low CO_2 concentration that leads to a high blood pH.

☆ Metabolic acidosis have high concentration of H^+ and low concentration of HCO_3^-, leading to a low blood pH.

☆ Metabolic alkalosis have low concentration of H^+ and high concentration of HCO_3^-, leading to a high blood pH.

Other causes for
● Respiratory acidosis:

- choking.
- bronchopneumonia.
- chronic obstructive airways diseases (COAD) also known as chronic obstructive pulmonary diseases (COPD).

☆ In all three of them, CO_2 will accumulate and get converted to H_2CO_3 causing acidosis.

● **Respiratory alkalosis:**

- hysterical over breathing
- mechanical over-ventilation
- raised intracranial pressure

☆ In the first two, more CO_2 is getting outside the body, leading to less acid formation which means alkalosis.

☆ The last one has a different story, in this case, the body have increased pressure inside the skull, so it gets CO_2 outside the body in an attempt to decrease the pressure, less CO_2 means less acid formation, which means alkalosis.

● **Metabolic acidosis**

- impaired H^+ excretion
- impaired H^+ production or ingestion
- loss of HCO_3^-

☆ The first two cause acidosis by increasing H^+ concentration, either by increasing production and ingestion, or decreasing excretion.

☆ The last one causes acidosis by decreasing the base, so the acid will have a high concentration relatively.

● **Metabolic alkalosis**

- loss of H^+ in vomit
- alkali ingestion
- potassium deficiency

☆ The first one causes alkalosis be decreasing the acid.

☆ The second one causes alkalosis by increasing the base.

☆ The third one causes alkalosis because the body will try to restore the K^+ balance, by moving it from the cells to the blood, and to maintain the charges balance, H^+ will move in the opposite way, from the blood to the cells, decreasing its concentration in the blood and causing alkalosis.

Compensation

● It is the process of trying to reach the normal blood pH when having acidosis or alkalosis.

● As we said before, there is always a cooperation between renal system and respiratory system in maintaining the blood pH around its normal range, the renal system controls the concentration of HCO_3^-, while the respiratory system controls the CO_2 concentration.

● When we have a problem in one system, the other one will compensate for it, so if the problem is respiratory (in CO_2 concentration), the renal system will compensate, and if the problem is metabolic (in H^+ and HCO_3^- concentrations), the respiratory system will compensate.

Acid-Base Disorder	Primary Change	Compensatory Change
Respiratory acidosis	pCO_2 up	HCO_3^- up
Respiratory alkalosis	pCO_2 down	HCO_3^- down
Metabolic acidosis	HCO_3^- down	PCO_2 down
Metabolic alkalosis	HCO_3^- up	PCO_2 up

Complete and partial compensation

☆ Complete compensation: the two systems collaborate and succeed in getting the pH back to the normal range (7.35-7.45), in acidosis a little bit lower than 7.4, and in alkalosis a little bit higher than 7.4, but still within normal range.

	pH	pCO_2	HCO_3^-
Resp. acidosis	Normal But<7.40	↑	↑
Resp. alkalosis	Normal but>7.40	↓	↓
Met. Acidosis	Normal but<7.40	↓	↓
Met. alkalosis	Normal but>7.40	↑	↑

☆ Partial compensation: the two systems collaborate in getting the pH back to the normal range (7.35-7.45), but they can't, so in acidosis it will be lower than the normal range, and in alkalosis it will be higher than the normal range (outside the normal range).

	pH	pCO_2	HCO_3^-
Res.Acidosis	↓	↑	↑
Res.Alkalosis	↑	↓	↓
Met. Acidosis	↓	↓	↓
Met.Alkalosis	↑	↑	↑