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Drugs and acid dissociation constants

Ionisation of drug molecules

Most drugs ionise in aqueous solution.[1] They are weak acids or weak bases. Those that are weak acids ionise in water to give acidic solutions while those that are weak bases ionise to give basic solutions.

Drug molecules that are weak acids	Drug molecules that are weak bases
$HA + H_2O \leftrightarrow H_3O^+ + A^-$	$B + H_2O \leftrightarrow BH^+ + OH^-$
where, HA = acid (the drug molecule)	where, B = base (the drug molecule)
H_2O = base	H_2O = acid
A^- = conjugate base (the drug anion)	OH^- = conjugate base (the drug anion)
H_3O^+ = conjugate acid	BH^+ = conjugate acid

Acid dissociation constant, K_a

For a drug molecule that is a weak acid

$$HA + H_2O \leftrightarrow H_3O^+ + A^-$$

The equilibrium constant for this ionisation is given by the equation

$$equilibrium\ constant = \frac{[H_3O^+][A^-]}{[HA][H_2O]}$$

where $[H_3O^+]$, $[A^-]$, [HA] and $[H_2O]$ are the concentrations at equilibrium.

In a dilute solution the concentration of water is to all intents and purposes constant. So the equation is simplified to:

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

where K_a is the acid dissociation constant for the weak acid

Also, H_3O^+ is often written simply as H^+ and the equation for K_a is usually written as:

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

Values for K_a are extremely small and, therefore, pK_a values are given (similar to the reason pH is used rather than $[H^+]$.

$$pK_a = -log_{10}K_a$$

The relationship between pK_a and pH is given by the Henderson–Hasselbalch equation:

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

This relationship is important when determining pK_a values from pH measurements.

Base dissociation constant, K_b

For a drug molecule that is a weak base:

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[1] *Ionisation of drug molecules.*

$$B + H_2O \leftrightarrow BH^+ + OH^-$$

Following the same logic as for deriving K_a, base dissociation constant, K_b, is given by:

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

Ionisation of water

Water ionises very slightly.

$$H_2O \leftrightarrow H^+ + OH^-$$

The equilibrium constant for this ionisation is given by the equation:

$$equilibrium\ constant = \frac{[H^+][OH^-]}{[H_2O]}$$

where $[H^+]$, $[OH^-]$ and $[H_2O]$ are the concentrations at equilibrium.

The concentration of water is to all intents and purposes constant. So the equation is simplified to give the ionic product of water, K_w:

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

Its value is temperature dependent. At 25 °C,

$$K_w = 1 \times 10^{-14} mol^2\ dm^{-6}$$

$$pK_w = -log_{10}K_w$$

The relationship between the ionic product of water, the acid dissociation constant and the base dissociation constant is:

$$K_w = K_a \times K_b = 1 \times 10^{-14} mol^2\ dm^{-6}\ (at\ 25℃)$$

$$pK_w = pK_a + pK_b = 14$$

So, to convert pK_b to pK_a the equation to use is:

$$pK_a = 14 - pK_b$$

For convenience, pK_a values are usually quoted for all drugs, whether they are acidic or basic.

Some experimentally determined values[2]

Acidic drugs	K_a / mol dm^{-3}	pK_a	Basic drugs	K_a / mol dm^{-3}	pK_a
Penicillin G	2.0×10^{-3}	2.7	**Tetracycline**	5.0×10^{-4}	3.3
Aspirin	3.3×10^{-4}	3.5	**Adrenaline**	2.5×10^{-9}	8.6
Fenoprofen	3.2×10^{-5}	4.5	**Diphenhydramine**	1.0×10^{-9}	9.0
Phenobarbital	3.9×10^{-8}	7.4	**Ephedrine**	2.5×10^{-10}	9.6

Finding out

Show how the relationship $K_w = K_a \times K_b$ may be derived.

Hint: Consider these two equations:

$$HA + H_2O \leftrightarrow H_3O^+ + A^-$$

$$A^- + H_2O \leftrightarrow HA + OH^-$$

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[2] See *Ionisation of drug molecules* for structures.