

## Drugs and acid dissociation constants

### Ionisation of drug molecules

Most drugs ionise in aqueous solution.<sup>1</sup> 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) H <sub>2</sub> O = base	where, B = base (the drug molecule) H <sub>2</sub> O = acid
A <sup>-</sup> = conjugate base (the drug anion) H <sub>3</sub> O <sup>+</sup> = conjugate acid	OH <sup>-</sup> = conjugate base (the drug anion) BH <sup>+</sup> = conjugate acid

### Acid dissociation constant, $K_a$

For a drug molecule that is a weak acid



The equilibrium constant for this ionisation is given by the equation

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

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:

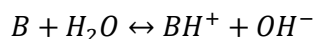
$$pH = pK_a - \log \frac{[HA]}{[A^-]} \quad \text{or} \quad pH = pK_a + \log \frac{[A^-]}{[HA]}$$

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:

<sup>1</sup> Ionisation of drug molecules.

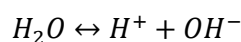


Following the same logic as for deriving  $K_a$ , base dissociation constant,  $K_b$ , is given by:

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

### Ionisation of water

Water ionises very slightly.



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

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

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,  $K_w$ :

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

Its value is temperature dependent. At 25 °C,

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

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

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

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

$$pK_w = pK_a + pK_b = 14$$

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.

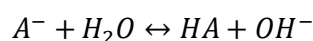
### Some experimentally determined values<sup>2</sup>

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

### Finding out

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

Hint: Consider these two equations:



<sup>2</sup> See *Ionisation of drug molecules* for structures.