Extension 17: Haemoglobin, the transport of oxygen in the blood and pH buffers in the blood

1. Prerequisites

The ideas which form the background to this case study are listed in the following table.

Topic	Book page
Oxidation State	104
Protein and polypeptide	356-357
pH	152, 298-303
Le Chatelier's Principle	274
Buffer	308, 310-311

2. Transport of oxygen to living cells and of carbon dioxide from living cells

Although it is a simplification, we can begin by thinking of blood as salty water with many 'extras' in it. The 'extras' include red and white cells, enzymes and hormones. It is the red cells that carry the protein haemoglobin (sometimes written as hemoglobin). Haemoglobin picks up O_2 from the tiny blood capillaries at the base of the lungs. The blood, rich in oxygen, is then pumped around the body and carried to cells. The blood also carries waste carbon dioxide (temporarily stored as hydrogen carbonate ions) away from those cells, to the blood capillaries at the base of the lungs (Fig. 17.1). CO_2 is then exhaled. We now look at these events in more detail.

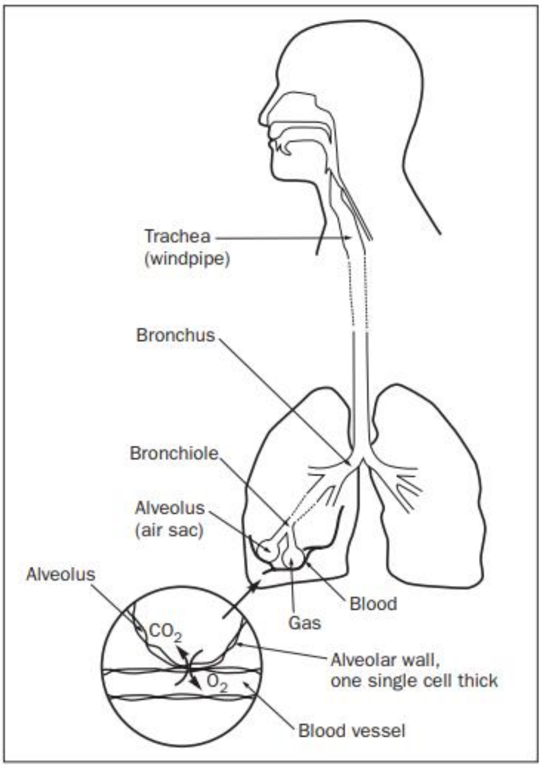

Fig. 17.1 The respiratory system. Air passes from the mouth and nose to the trachea (windpipe), bronchi (the larger tubes in the lungs), and bronchioles (the smaller tubes in the lungs), to the alveoli (the air sacs). Each alveolus has a wall one cell thick that is in contact with a blood vessel (a capillary). In this way gases, including O_2 and CO_2, can cross to and from the bloodstream.

3. The role of haemoglobin

Haemoglobin consists of a very large protein molecule with a molecular mass of 65 000 u. The molecule contains four polypeptide chains each of which encloses an iron containing molecular grouping called a haem group (Fig. 17.2). The haem groups each contain iron in an oxidation state of 2. Haemoglobin (Fig. 17.3) is given the symbol Hb. Haemoglobin attached to a H_3O^+ ion is symbolized H-Hb and is called **protonated haemoglobin**.

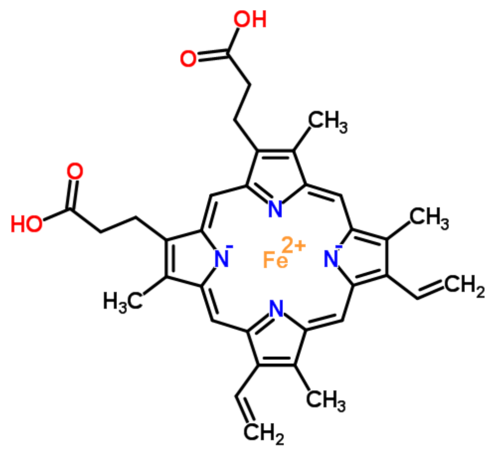

Fig. 17.2 A haem group. It consists of a iron(II) ion at the centre of a symmetrical arrangement of nitrogen-containing rings. Source: ChemSpider, www.chemspider.com/Chemical-Structure.4802.html, Accessed 29/05/2018.

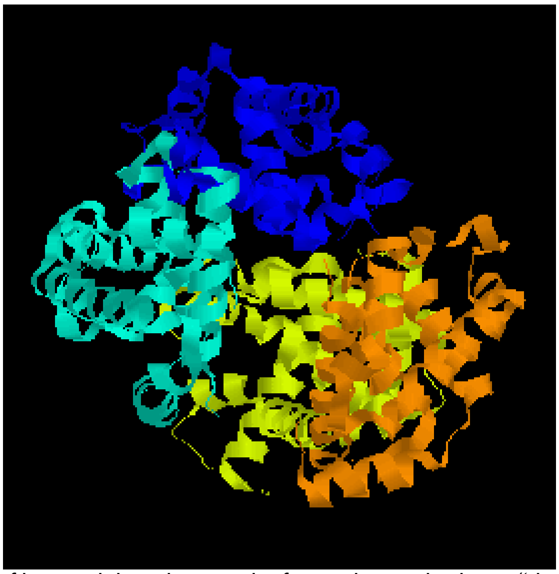

Fig. 17.3 Model of a molecule of haemoglobin, showing the four polypeptide chains ('the twists', coloured differently for clarity) and the four haem groups (by courtesy of Professor Paul May, Bristol University, http://www.chm.bris.ac.uk/motm/motm.htm).

Protonated haemoglobin cannot bind with O_2, but haemoglobin can. Each Fe(II) can bond to an oxygen molecule so that up to four O_2 molecules can be linked to a haemoglobin molecule at one time. The molecule formed between haemoglobin and oxygen is called **oxyhaemoglobin** and is symbolized $Hb–O_2^-$ (note the negative charge). Oxyhaemoglobin is red, and gives red cells (and blood) its characteristic colour.

Without haemoglobin, the amount of O_2 that could be carried by the blood would be tiny. If we think of blood as being similar to salty water for the purposes of oxygen dissolution, 1 dm^3 of blood would only dissolve about 4 mg (4 *milligrams*) of oxygen gas at 37 °C (blood temperature). But the presence of haemoglobin allows up to 300 mg of O_2 to be absorbed into the same volume of blood. The extra O_2 is not simply dissolved, it is chemically bound to the haemoglobin molecule and the reaction of haemoglobin and oxygen is one of the most important reactions in chemistry.

4. The transport of oxygen

The equilibrium between protonated haemoglobin, oxygen, oxyhaemoglobin and aqueous hydrogen ions in the presence of water,

$$\underset{\text{protonated haemoglobin}}{H{-}Hb} + O_2(g) \rightleftharpoons \underset{\text{oxyhaemoglobin}}{Hb{-}O_2^-} + H_3O^+(aq) \quad (1)$$

is the key to the transport of O_2 in the body (Fig. 17.4). Oxyhaemoglobin is formed in the *forward reaction*

$$\underset{\text{in blood from lungs}}{H{-}Hb + O_2(g)} \rightarrow \underset{\text{in blood}}{Hb{-}O_2^-} + H_3O^+(aq) \quad (2)$$

In Unit 15, under the heading of Le Chatelier's principle, it is shown that the presence of a reactant at high concentration increases the yield of products. Similarly, the relatively high partial pressure of O_2 (a reactant in equation (1)) in the tiny capillaries at the base of the lungs, encourages the formation of $Hb{-}O_2^-$ molecules. Not all of the oxygen transported in the blood is used by the cells of the body. If a person is resting only about 25% of the available O_2 is consumed, whereas in the case of an athlete running a race this can rise to 90%.

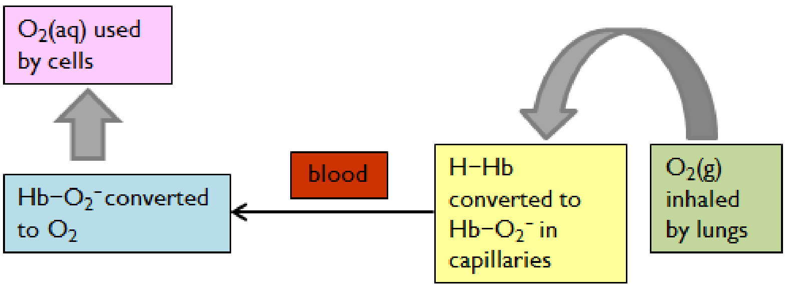

Fig. 17.4 Scheme for the transport of O_2 to cells.

5. Transport of carbon dioxide

Living cells produce CO_2 and $H_3O^+(aq)$ as waste products. Both are toxic in high concentrations and must be removed. When an oxyhaemoglobin molecule reaches a cell, it reacts with waste $H_3O^+(aq)$ and gives up its oxygen in the reverse of equilibrium (1):

$$\underset{\text{in blood}}{Hb{-}O_2^-} + \underset{\text{from cells}}{H_3O^+(aq)} \rightarrow \underset{\text{in cells}}{H{-}Hb} + \underset{\text{in cells}}{O_2(g)} \quad (3)$$

In this reaction, the haemoglobin is mopping up the $H_3O^+(aq)$ ions and in doing so is reducing the acidity of the blood.

What about CO_2? The ultimate fate of CO_2 is to be exhaled by the lungs. The blood carries the CO_2 from the cells to the lungs. The problem is that CO_2 is not very soluble in blood! It turns out that the ejection of $H_3O^+(aq)$ in equation (2) is crucial to the removal of cellular CO_2.

This is how the CO_2 is removed. In Unit 17 of the book the CO_2–HCO_3^- equilibrium is introduced.

$$CO_2(aq) + 2H_2O(l) \rightleftharpoons HCO_3^-(aq) + H_3O^+(aq) \qquad (4)$$

Applying Le Chatelier's principle to this equilibrium shows that if the concentration of $H_3O^+(aq)$ ion is reduced, more CO_2 reacts with water to form the hydrogencarbonate ion, $HCO_3^-(aq)$. In practice, an enzyme inside the red cells, carbonic anhydrase, is needed to make the reaction fast enough:

$$\underset{\text{from cells}}{CO_2(aq)} + 2H_2O(l) \rightarrow \underset{\text{in plasma or in red cells}}{HCO_3^-(aq)} + \underset{\text{in red cells}}{H_3O^+(aq)} \qquad (5)$$

The $H_3O^+(aq)$ ions are stored in a special compartment within the red blood cells. In effect, CO_2 is being temporarily converted to hydrogencarbonate ion so it can be transported. Some of the $HCO_3^-(aq)$ ions are *in* the blood plasma (the watery part of the blood): others are stored inside the red cells themselves and transported *through* the blood. Once the blood reaches the capillaries of the lungs the hydrogencarbonate ions react with the H_3O^+ stored in the red cells:

$$HCO_3^-(aq) + H_3O^+(aq) \rightarrow CO_2(aq) + 2H_2O(l) \qquad (6)$$

This converts the hydrogencarbonate ions back to CO_2 (Fig. 17.5). The CO_2 pressure is greater on the capillary side of the lungs than in the lungs themselves and so the CO_2 diffuses out of solution and is exhaled by the lungs into the outside air.

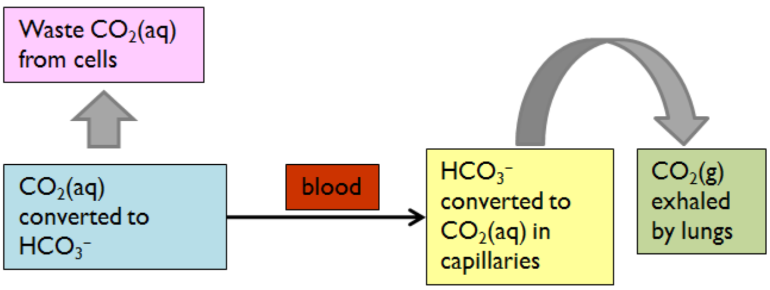

Fig. 17.5 Scheme for the removal of CO_2 from cells.

6. Saturation curve for take-up of O_2 by haemoglobin

Suppose that a blood sample (containing red blood cells) can hold *x* mg of O_2 in its haemoglobin. We might expect the take-up of oxygen to be constant wherever the haemoglobin comes into contact with oxygen gas in the body. However, it is found that the take-up increases with the partial pressure of oxygen to which the haemoglobin is exposed.

Fig 17.6 shows this graphically. The y-axis shows the take-up of O_2 by the haemoglobin, expressed as a % of the maximum O_2 that it is found can be taken up. The y-axis shows the partial pressure of O_2 (pO_2) in units of mm of mercury[1]. Above about 80 mm of O_2, the haemoglobin is virtually fully saturated. The exact shape of the curve depends upon the health of the individual and pH: a lower pH shifts the curve slightly to the right so that the haemoglobin holds slightly less O_2.

[1] See Box 10.2, p. 159 in the book. 80 mm of mercury (80 torr) is about one-tenth of a standard atmosphere.

This behaviour suggests that the haemoglobin molecule has different capacity for O_2 as pO_2 changes. We know that haemoglobin can take up a maximum of four oxygen molecules. It is believed that while the first O_2 molecule bounds with difficulty with one of the haem groups, the presence of a bound O_2 twists the haemoglobin molecule so that the Fe atom lies in a flatter position and this makes it easier for a second O_2 molecule to bind. Similarly, the second makes it easier for a third and the third easier for a fourth. The top flat part of the saturation curve corresponds to all four oxygen molecules being bound in the four haem sites. The effective of successive oxygen atoms on the binding of the next oxygen is an example of 'cooperative binding'.

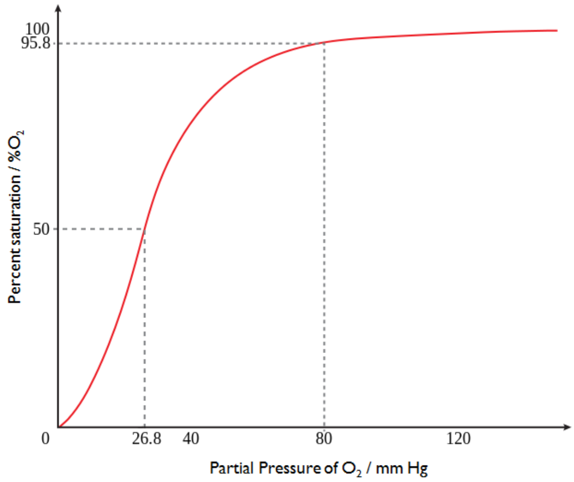

Fig. 17.6 Typical haemoglobin/O_2 saturation curve for a healthy person.

7. Transport of gases: a summary

There is a beautiful symmetry about the way that these reactions work:

- Just as an efficient house remover will never waste a trip and will use the return journey to dispose of unwanted furniture or carpets, so haemoglobin has been designed to act as a vehicle for the transport of O_2 to the cells and as a mechanism for the removal of CO_2 from the cells.
- At the capillaries close to the lungs, the formation of oxyhaemoglobin generates hydrogen ions (increasing pH), whereas the production of CO_2 as waste by the cells of the body absorbs hydrogen ions (so reducing pH). The CO_2 is eventually exhaled via the lungs. The net result is that the haemoglobin helps to maintain the pH of blood, via the CO_2–H_2O equilibrium.

There was a further twist to the story of haemoglobin in 1996, when scientists discovered that, in addition to oxygen and carbon dioxide, haemoglobin takes up and releases a third gas, nitric oxide (NO), which helps control blood pressure.

8. Removal of other acids by the kidneys

One of the reasons that the CO_2–HCO_3^- equilibrium is so successful in maintaining the pH of blood is that the H_3O^+ ions (the acidity) of the blood are ultimately converted to a gas, CO_2, which can be removed by the lungs. But there are also acids produced by the breakdown of proteins, sulfur-containing amino acids and fatty acids, which are not gaseous. Such acids are removed by the kidneys and excreted in the urine. The removal is mainly by neutralization of the acids with ammonia (itself produced in the kidney) so that urine usually contains a relatively high concentration of ammonium salts (particularly ammonium sulfate). In an adult, about one-third of the excess (unwanted) H_3O^+ ions of the body are removed this way.

9. Buffers: worked examples using the theory of Unit 17

EXAMPLE 1

The phosphate ion equilibrium helps maintain the pH of blood and urine:

$$H_2PO_4^-(aq) + H_2O(l) \rightleftharpoons HPO_4^{2-}(aq) + H_3O^+(aq) \qquad (7)$$

dihydrogen phosphate ion — monohydrogen phosphate ion

In this equilibrium, the $H_2PO_4^-(aq)$ ion is acting as an acid (compare equation (16.4) in the book). The pK_a of $H_2PO_4^-(aq)$ is 7.2.

(i) Calculate the pH of a solution containing 0.0250 mol of $H_2PO_4^-(aq)$, i.e. the acid, and 0.05 mol of $HPO_4^{2-}(aq)$, i.e. the salt.

(ii) Write equations showing the response of the phosphate ion equilibrium in the presence of (a) excess H_3O^+ and (b) excess hydroxide ion, $OH^-(aq)$.

Answer

(i) pH = pK_a + log (C_S/C_A) = 7.2 + log(0.050/0.025)
= 7.2 + 0.30 = 7.5

(ii) **(a)** In excess acid, the reverse of equation (7) occurs and the reaction is:
$HPO_4^{2-}(aq) + H_3O^+(aq) \rightarrow H_2PO_4^-(aq) + H_2O(l)$

EXAMPLE 2

The $CO_2(aq)$–$HCO_3^-(aq)$ equilibrium controls the pH of blood. In normal blood, the mole ratio of $CO_2(aq)$ to $HCO_3^-(aq)$ is about 1:10.

(i) Given that p$K_a(CO_2(aq))$ = 6.4, calculate the pH of normal blood.

(ii) The concentration of $HCO_3^-(aq)$ in the normal blood is approximately 20 millimoles per dm^{-3}. Estimate the concentration of dissolved CO_2.

(iii) The pH of human arterial blood cannot change by much or the human dies. The extremes of pH that are just tolerable are pH = 7.40 ± 0.40. Calculate $[H_3O^+]$ at the extremes of this range.

Answer

(i) pH = 6.4 + log ($[HCO_3^-(aq)]/[CO_2(aq)]$)
= 6.4 + log(10/1) = 7.4.

(ii) Since ($[HCO_3^-(aq)]/[CO_2(aq)]$ is about 10 in normal blood, $[CO_2(aq)]$ is approximately 2 mmol per dm^{-3} (i.e. 2×10^{-3} mol dm^{-3}).

EXAMPLE **2** *(continued)*

(iii) pH of 7.0 corresponds to $[H_3O^+(aq)] = 10^{-7.00} = 1.0 \times 10^{-7}$ mol dm^{-3}.
pH of 7.4 = $10^{-7.40}$ corresponds to $[H_3O^+(aq)] = 3.9(8) \times 10^{-8}$ mol dm^{-3}.
pH of 7.8 = $10^{-7.80}$ corresponds to $[H_3O^+(aq)] = 1.5(8) \times 10^{-8}$ mol dm^{-3}.
In specifying that arterial blood must be in the pH range 7.0–7.8, we are really specifying the permissible range of hydrogen ion concentration as being 1.58–10.0 $\times 10^{-8}$ mol dm^{-3}.

Reference

There are a number of freely available videos on this and related chemistry. An entertaining one is ‘A Breathtaking Journey: one oxygen atom's journey through the body’ at
https://www.youtube.com/watch?v=3ZsvIDBoRns