Another important buffer system is the carbonic acid (H$_2$CO$_3$) bicarbonate (HCO$_3^-$) buffer, which is a major buffering component of blood plasma. This system is more complex than the phosphate buffer, because carbonic acid is formed by the reversible reaction of carbon dioxide in water:

$$
\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \quad \text{and} \quad \text{H}_2\text{CO}_3 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}_3\text{O}^+
$$

These are two reactions linked (or coupled) by a common intermediate. By examining these reactions more closely, we see how some systems exist under non-equilibrium conditions and how some reactions occur despite the fact that they have a positive free energy change and appear to contravene the second law of thermodynamics.

As we have seen previously, simple chemical reactions are characterized by how fast they occur (their rate) and how far they proceed toward equilibrium. While you will learn much more about reactions if you continue on in chemistry, that is not something we will pursue here - rather we will consider the behavior of systems of reactions and their behavior, particularly when they have not reached equilibrium. This is a situation common in open systems, systems in which energy and matter are flowing in and out. In Chapter 8, we considered single reactions and what happens when we perturb them, either by adding or taking away matter (reactants or products) or energy (heating or cooling the reaction.) Now it is time to look at what happens when reactions are coupled: when the products of one reaction are the starting materials for other reactions occurring in the same system.

Take for example the coupled system introduced above - the pair of reactions that are linked by the formation and reaction of carbonic acid.

$$
\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \quad \text{and} \quad \text{H}_2\text{CO}_3 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}_3\text{O}^+
$$

These coupled reactions are important for a number of reasons: they are responsible for the transport of excess carbon dioxide to the lungs and for buffering the pH of blood. Carbon dioxide enters the blood stream by dissolving in the plasma. However, it can also react with water in a reaction where the water acts as a nucleophile and the carbon dioxide acts an electrophile.

The formation of carbonic acid is thermodynamically unfavorable. The equilibrium constant for hydration of carbon dioxide is $1.7 \times 10^{-3}$ and the standard free energy change $\Delta G^0$ for the reaction $^{183}$ is 16.4 kJ. This means that the amount of carbonic acid in blood plasma is quite low; most carbon dioxide is just dissolved in the plasma (rather than reacted with the water). However, as soon as carbonic acid is formed, it can react with water:

$$
\text{H}_2\text{CO}_3 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}_3\text{O}^+
$$

to produce bicarbonate (HCO$_3^-$). Note that we now have the components of a buffer system (a weak acid, carbonic acid,
and its conjugate base bicarbonate). The rate of this reaction is increased by the enzymatic catalyst carbonic anhydrase. In this buffer system the carbonic acid can react with any base that enters the bloodstream, and the bicarbonate with any acid. This buffering system is more complex than the isolated ones we considered earlier, because one of the components (carbonic acid) is also part of another equilibrium reaction. In essence, this means that the pH of the blood is dependent on the amount of carbon dioxide in the bloodstream:

\[ \text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}_3\text{O}^+ \]

If we remove water from the equations (for the sake of clarity) we can see the connection better:

\[ \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}_3\text{O}^+ \]

The pKₐ of carbonic acid is 6.37 and the pH of blood is typically 7.2–7.4, which does fall just within the buffering range. Under normal circumstances, this buffer system can handle most changes. However, for larger changes, other systems are called into play to help regulate the pH. For example, if you exert yourself, one of the products generated is lactic acid, (which we denote as LacOH). When lactic acid finds its way into the bloodstream, it lowers the pH (increasing the amount of H₃O⁺) through the reaction:

\[ \text{LacOH} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{LacO}^- \]

lactic acid

If we use Le Chatelier’s principle, you can see that increasing the H₃O⁺ shifts the equilibrium toward the production of carbon dioxide in the buffer system. As the concentration of CO₂ increases, a process known as chemoreception activates nervous systems, which in turn regulate (increase) heart and respiratory rates, which in turn lead to an increase in the rate of CO₂ and oxygen exchange in the lungs. As you breathe in O₂, you breathe out CO₂ (removing it from your blood). In essence, Le Chatelier’s principle explains why we pant when we exercise! Conversely, when some people get excited, they breathe too fast (hyperventilate); too much CO₂ is removed from the blood, which reduces the H₃O⁺ concentration and increases the pH. This can lead to fainting (which slows down the breathing), a rather drastic way to return your blood to its correct pH. An alternative, non-fainting approach is to breathe into a closed container. By breathing expelled CO₂ (and a lower level of O₂), you increase your blood pH.

While we can use Le Chatelier’s principle to explain the effect of rapid or slow breathing, this response is one based on what are known as adaptive and homeostatic systems. Biological systems are characterized by many such interconnected regulatory mechanisms. They maintain a stable, internal chemical environment essential for life. Coupled
regulatory systems lie at the heart of immune and nervous system function. Understanding the behavior of coupled regulatory systems is at the forefront of many research areas, such as: measuring the physiological response to levels of various chemicals (chemoreception); recognizing and responding to foreign molecules in the immune system; and measuring the response to both external stimuli (light, sound, smell, touch) and internal factors (such as the nervous system). Downstream of the sensory systems examined by such efforts are networks of genes, proteins, and other molecules whose interactions are determined by the thermodynamics of the chemical system. Although they were formed by evolutionary processes, and are often baroque in their details, they are understandable in terms of molecular interactions, chemical reactions, and their accompanying energy changes.

**Questions to Answer**

- If the pK_{a} of carbonic acid is 6.35 and the pH of blood is over 7, what do you think the relative amounts of carbonic acid and bicarbonate are? Why?

- Draw out the series of reactions that occur when lactic acid is introduced into the blood stream and explain why this affects the concentration of carbon dioxide in the blood stream.

- If the amount of carbon dioxide in the atmosphere increases, what effect does it have on oceans and lakes?

- If carbon dioxide dissolves in water to give carbonic acid, what do you think nitrogen dioxide (NO_{2}) gives when dissolved in water? How about sulfur dioxide? What effect does this have on the pH of the water it dissolves in?

**References**

183 calculated from ΔG_{o}^{0} = –RTlnK at physiological temperature 37°C

184 This occurs primarily because O_{2} is in short supply and the aerobic respiration reaction cannot proceed to completion.


186 Although it does not explain why we would want to exercise in the first place.