4.14: Requirements for Effective Oxygen Carriers

In order for dioxygen transport to be more efficient than simple diffusion through cell membranes and fluids, it is not sufficient that a metalloprotein merely binds dioxygen. Not only is there an optimal affinity of the carrier for dioxygen, but also, and more importantly, the carrier must bind and release dioxygen at a rapid rate. These thermodynamic and kinetic aspects are illustrated in Figure 4.3, a general diagram of energy vs. reaction coordinate for the process

$$M + O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} MO_2 \tag{4.2}$$

where M is an oxygen carrier, for example hemocyanin or a simple nonbiological metal complex. Thermodynamic or equilibrium aspects are summarized by ΔG in Figure 4.3. As illustrated there, ΔG is negative, and thus the forward reaction, dioxygen binding, is spontaneous. The equilibrium constant (K) is given by

$$K = \frac{a(MO_2)}{a(M)a(O_2)}, \tag{4.3}$$

where a is the activity (i.e., effective concentration) of the component. The equilibrium constant is related to the change in free energy by

$$\Delta G^o = -RT \ln K. \tag{4.4}$$

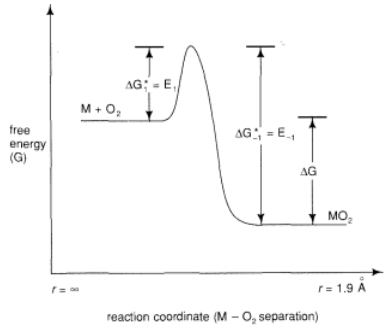

Figure 4.3: Schematic diagram of energy changes in dioxygen binding.

The rate of the forward reaction (k_1) is related to ΔG_1^*; the rate of the reverse reaction (k_{-1}) is related to ΔG_{-1}^*. Provided that oxygen binding is effectively a single-step process, then

$$K = \frac{k_1}{k_{-1}}. \tag{4.5}$$

Usually the rates of the forward and reverse reactions are related by the empirical Arrhenius expression to quantities termed the activation energies (E_1 and E_{-1}) of the reactions, where

$$k_1 = A_1^{\frac{-E_1}{RT}} \; and \; k_{-1} = A_{-1}^{\frac{-E_{-1}}{RT}}. \tag{4.6}$$

These quantities are experimentally accessible through the change in rate as a function of temperature.

Kinetic Factors

It is of little benefit to the organism if its dioxygen carrier, such as hemoglobin, binds and releases O_2 at such slow rates that O_2 is not delivered faster than it would be by simple diffusive processes. Thus, a binding rate within a couple of orders of magnitude of the rate of diffusion, together with the high carrying capacity of O_2 that high concentrations of oxygen carrier enable (noted earlier), and a pumping system ensure adequate O_2 supplies under all but the most physiologically stressful conditions.

Whereas measurements of equilibrium give little or no molecular information, rather more molecular information may be inferred from kinetic data. The processes of binding and release can be examined by a variety of techniques, with timescales down to the picosecond range. The temperature behavior of the rates gives information on the heights of energy barriers that are encountered as dioxygen molecules arrive at or depart from the binding site. The quantitative interpretation of kinetic data generally requires a

molecular model of some sort. It is because of this multibarrier pathway that the equilibrium constant measured as k_1/k_{-1} (Equation 4.5) may differ substantially from the thermodynamically measured value (Equation 4.3).

The simple Adair scheme outlined above is readily adapted to cater to kinetic data.

Dioxygen Reactions

Most biological conversions involving dioxygen require enzymatic catalysis. It is reasonable then that metals found in the proteins involved in the transport and storage of O_2 also frequently appear, with minor modification of ligands, in enzymes that incorporate oxygen from dioxygen into some substrate. Dioxygen, in this case, is not only coordinated, but also activated and made available to the substrate. In the family of proteins with heme groups, hemoglobin is a dioxygen carrier and cytochrome P-450 is an oxygenase. A similar differentiation in function is also found for hemocyanin and tyrosinase from the family of proteins with a dinuclear copper complex at the active site. Note that not all enzymes that mediate the incorporation of oxygen from O_2 into some substrate coordinate and activate dioxygen. For example, lipoxygenase probably catalyzes the conversion of a 1,4-diene to a 1,3-diene-4-hydroxyperoxy species by activation of the organic substrate. The active site does not resemble that of any known oxygen-carrier protein. This topic is discussed more fully in Chapter 5.
