4.1: Biological Dioxygen Transport Systems

Most organisms require molecular oxygen in order to survive. The dioxygen is used in a host of biochemical transformations, although most is consumed in the reaction

$$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O \tag{4.1}$$

that is the terminal (or primary) step of oxidative phosphorylation (Chapters 5 and 6). For some small animals and for plants, where the surface-to-volume ratio is large, an adequate supply of dioxygen can be obtained from simple diffusion across cell membranes. The dioxygen may be extracted from air or water; for plants that produce dioxygen in photosynthesis, it is also available endogenously. For other organisms, particularly those with non-passive lifestyles, from scorpions to whales, diffusion does not supply sufficient dioxygen for respiration.

An elegant three-component system has evolved to transport dioxygen from regions of high abundance—water (at least if free of pollutant reductants) and air—to regions of relatively low abundance and high demand—the interior cells of the organism. This process is illustrated in Figure 4.1.[1-3]

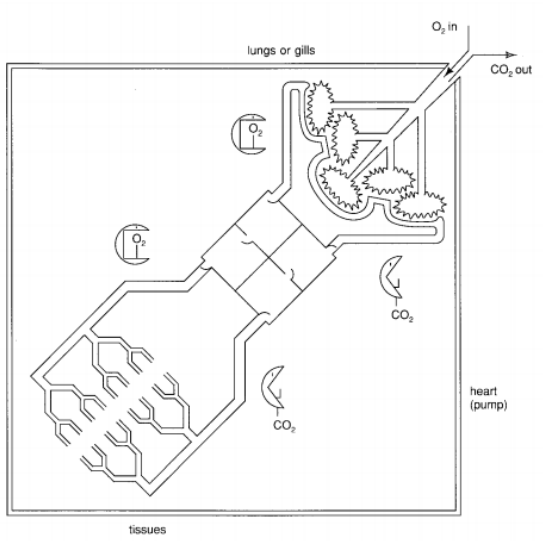

Figure 4.1: Oxygen sequestration and transport in the generalized organism Squarus squorur. The surface area of lungs or gills is typically 1-2 orders of magnitude greater than the external surface area of the organism.

The central component is a dioxygen-carrier protein. In the three chemically distinct carriers that have evolved and are found today, the dioxygen-binding site in the protein, that is, the so-called "active site," is a complex either of copper or of iron.[4-6] For hemoglobins, the most widely distributed family of dioxygen carriers, the active site has long been known to consist of an iron porphyrin (heme) group embedded in the protein. Almost all hemoglobins share the basic structure illustrated in Figure 4.2.[7-12] Hemocyanin[13-15] and hemerythrin,[16-18] the other two biological dioxygen carriers, feature pairs of copper atoms and iron atoms, respectively, at the active sites.* Some basic properties of these metalloproteins are summarized in Table 4.1.[4-6]

(A) Fe^{II} protoporphyrin IX (heme b) [hemoglobins and erythrocruorins]

(B) Chloroheme [chlorocruorin]

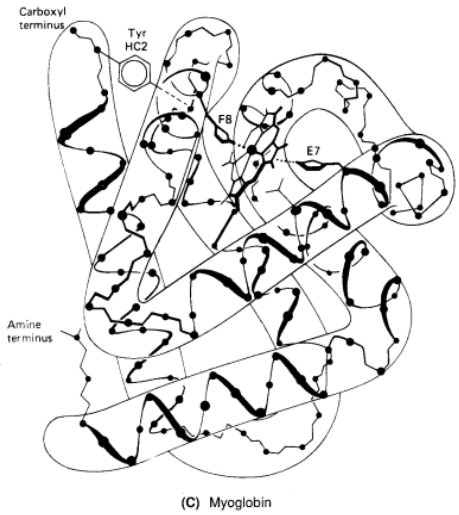

Figure 4.2: Heme groups used in hemoglobin: (A) Protoporphyrin IX (heme b), (hemoglobins and erythrocruorins); (B) Chloroheme (chlorocruorin); (C) The encapsulation of the heme molecule in myoglobin.[11a] Reproduced with permission from M. F. Perutz, Nature **228** (1970), 726-737.

Table 4.1: General Features of Dioxygen-carrier Proteins

Metalloprotein	Active Site of deoxy
Hemoglobins	
Vertebrate	

Human A	heme Fe^{II}	purified
Invertebrate		
Erythrocruroin (*Lumbricus terrestris*, earthworm)	heme Fe^{II}	upon oxidation
Chlorocruorn *(Eudistylia vancouveri)*	chloroheme Fe^{II}	purple green
Hemocyanins		
Mollusc (*Helix pomatia-α*, edible snail)	Cu^{1} . . . Cu1	colorless blue

Arthropod *(Cancer magister*, crab)	Cu^{1} . . . Cu1	colorless
Hemerythrins *(Phascolopsis* syn. *golfingia gouldii)*	Fe^{II} . . . Fe^{II}	colorless

* The use of the prefix *hem-* is confusing. In this context *hem* connotes blood. Thus, since hemocyanin and hemerythrin lack a heme group [an iron(II) porphyrin], they are nonheme metalloproteins.

The second component of the dioxygen-transport system facilitates the sequestration of dioxygen by the dioxygen-carrier protein. Specialized organs, such as lungs in air-breathing creatures or gills in fish, offer a very large surface area to the outside environment in order to facilitate diffusion. The third component is the delivery system. The oxygen carrier is dissolved or suspended in a fluid, called blood plasma or hemolymph, that is pumped throughout the animal by another specialized organ, the heart, through a network of tubes, the blood vessels. In many organisms an additional dioxygen-binding protein, which stores dioxygen, is located in tissues that are subject to sudden and high dioxygen demand, such as muscles. These dioxygen-storage proteins are prefixed *myo-* (from the Greek root *mys* for muscle). Thus for the dioxygen-transport protein hemerythrin there exists a chemically similar dioxygen-storage protein myohemerythrin. For the hemoglobin family the corresponding storage protein is called myoglobin. Interestingly, some organisms that use hemocyanin as the dioxygen-*transport* protein use myoglobin as the dioxygen-*storage* protein.

At the center of biological dioxygen transport are transition-metal complexes of iron or copper. To model such systems, chemists have prepared several synthetic oxygen carriers, especially of iron and cobalt porphyrins. In this chapter the structures and properties of biological and nonbiological oxygen carriers are described, with particular attention to the hemoglobin family. This family has been studied in more detail than any other group of proteins, and as a result a deeper understanding of the relationships among structure, properties, and biological function (i.e., physiology) exists. The central focus of this chapter is to delineate chemical features that determine the affinity of an active site, especially an iron porphyrin, for molecular oxygen. In order to develop this theme, macroscopic (thermodynamic and kinetic) factors associated with dioxygen binding and release are summarized first. The

nonbiological chemistry of iron and copper in the presence of dioxygen is described briefly to elucidate the key role that the protein plays in supporting oxygen transport by preventing irreversible oxidation of the binding site or of its ligands. The macroscopic behavior of the biological systems is related to the microscopic picture that has been developed over the last 30 years from x-ray crystallographic studies and a miscellany of spectroscopic probes of the oxygen-binding site. Relationships between the geometry and charge distribution in the metal-dioxygen moiety and the nature of the interactions between this moiety and its surroundings are examined. Nonbiological dioxygen carriers have proved particularly useful in providing precise and accurate structural information as well as thermodynamic and kinetic data against which the corresponding data from biological oxygen carriers can be contrasted.

The bioinorganic chemistry of the hemoglobin family of oxygen binders is particularly amenable to study by means of small-molecule model systems: four of the five ligands that make up the active site are provided by a square-planar tetradentate ligand, the protoporphyrin IX dianion (Figure 4.2). One axial ligand in hemoglobin, imidazole from a histidine residue, is provided by the protein, and the remaining sixth coordination site is available for the exogenous ligand, e.g., dioxygen or carbon monoxide. Thus a model system that approximates the stereochemistry of the active site in hemoglobin may be assembled from an iron(II) porphyrin and a ligand, such as imidazole or pyridine. On the other hand, in hemocyanin and hemerythrin most of the ligands are supplied by the protein. Thus the assembly of a model system that provides appropriate ligands correctly disposed around the pair of metal atoms poses a major synthetic challenge, especially for hemocyanin, where details on the number, type, and arrangement of ligands have been difficult to establish. Many aspects of the physical, inorganic, and structural chemistry underlying biological oxygen transport and utilization (Chapter 5) have been clarified through model systems.
