4.15: Role of the Protein in Effecting Biological Oxygen Transport

In our survey of the dioxygen chemistry of iron and copper species in earlier subsections, three general functions for the protein matrix became apparent: provision of ligand(s) in an appropriate stereochemistry; protection of the metal-dioxygen moiety from oxidation and competitive ligands; and modulation of dioxygen affinity through nonbonded interactions with distal groups.

Provision of Ligands to the Metal

In the hemoglobin family the heme group is anchored in a cleft in the globin chain by an imidazole ligand from a histidine residue (the proximal histidine). The other (distal) side of the heme plane is more or less open to accommodate a small sixth ligand (see Figure 4.2).

For hemerythrin and hemocyanin the requirements of the protein chain are more severe. In contrast to the hemoglobin family, all but two of the ligands are provided by the protein chain, and in addition the metal ions are encapsulated as a pair. The exogenous ligands for hemerythrin are a μ-(hydr)oxo moiety and dioxygen or anions (depending on oxidation state); for hemocyanin, the identity of the second exogenous ligand, if there is one at all, is still unclear. Although hemerythrin has a distinctive cofacial bioctahedral structure (Figure 4.10)[46-48] that would appear to be very difficult to assemble in the absence of the protein, it turns out that with a variety of tridentate ligands the (μ-oxo)bis(μ-carboxylato)diiron(III) core may be assembled rather easily.[82,156,157] Thus, this core appears to be a thermodynamically very stable structural motif. Such a synthesis has been termed "self-assembly" and appears to be a common phenomenon in biological systems.[158] The low-temperature assembly of bis-copper(II)-μ-peroxo complexes (models for oxyhemocyanin) from mononuclear copper(l) compounds provides other examples of this phenomenon.[103f,g]

Protection of the Metal-Dioxygen Moiety

The immobilization of the heme group inside the protein prevents (i) the bimolecular contact of an FeO_2 species with an Fe^{ll} species (Reaction 4.29b), the key step in the irreversible oxidation of Fe^{II} porphyrins; (ii) the facile access of nucleophiles that would cause autoxidation (Reactions 4.30 and 4.31); (iii) the oxygenase activity (Reaction 4.32) that is the normal function of other hemoproteins, such as cytochrome P-450, horseradish peroxidase, catalase, etc.; and (iv) the self-oxygenase activity that has been observed in some iron(II) systems that bind dioxygen, activating it for destruction of the ligand itself. Avoiding these last two fates also appears to be very important in the active site of hemocyanin. Finally (v), the globin chain serves to restrain the binding of the distal histidine to give a six-coordinate hemochrome (Reaction 4.33), at least at room temperature.[159] Thus, unoxygenated hemoglobin is held in a five-coordinate state, allowing a rapid rate of oxygen binding and greater oxygen affinity—hemochromes such as $Fe(TPP)(Py)_2$ are impervious to oxygenation and subsequent oxidation.

Modulation of Ligand-binding Properties

The protein chain in hemoglobin may place restraints on the iron-to-proximal histidine bond. On the other side of the heme, the distal histidine and occluded water molecules may hydrogen-bond to the coordinated dioxygen and force ligands to adopt geometries that are different from those observed in the absence of steric hindrances. The conformation of the porphyrin skeleton may also be perturbed by the protein chain. Clearly, it is the protein chain that bestows the property of cooperativity on oligomeric oxygen carriers.