4.11: Nature of the Metal-Dioxygen Linkage in Biological Systems

Many techniques have been used to probe the geometry and electronic structure of the metal-dioxygen moiety in biological systems and in synthetic models. The results form the basis of any understanding of the factors that determine and modulate oxygen affinity.

Oxyhemocyanin and Oxyhemerythrin

By resonance Raman techniques, the O—O stretch is observed at 744 cm^{-1} in oxyhemocyanin and at 844 cm^{-1} in oxyhemerythrin.[140-142] Dioxygen is therefore coordinated as peroxo species. By use of unsymmetrically labeled dioxygen, ^{18}O—^{16}O, it was established that dioxygen coordinates symmetrically:[141]

$$(4.43)$$

Carbon monoxide binds to only one of the Cu^I centers in deoxyhemocyanin, through the C atom,* apparently blocking the second Cu^I site.[15] Similar behavior is also seen for the nitrosyl adduct.

* A report[143] that CO binds to the copper center through the O atom, an unprecedented mode, has been challenged.[144]

On the other hand, in an experiment parallel to that just described for hemocyanin, dioxygen was found to bind asymmetrically in oxyhemerythrin:[142]
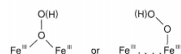

Figure 4.13).[45] This mode of dioxygen coordination remains unobserved to date in small-molecule synthetic systems. The O$_2$-binding process is formally very similar to the combinations of Reactions (4.29a) and (4.29b), except that dioxygen attaches to only one Fe center (bridging carboxylato groups omitted in Reaction 4.45):

$$(4.45)$$

The existence and location of the proton, which cannot be proven in the crystal structure of deoxyhemerythrin or of oxyhemerythrin, are inferred from a model system for the former that contains a hydroxo group bridging two high-spin, weakly antiferromagnetically coupled Fe^{ll} centers (J = -10 cm^{-1}).[88] For oxyhemerythrin (and for one conformation of methydroxohemerythrin), a small change in the position of the symmetric Fe—O—Fe mode is observed when H$_2$O is replaced by D$_2$O.[146] The strong antiferromagnetic coupling observed for methemerythrin and oxyhemerythrin (-J ~ 100 cm^{-1})[147] is uniquely consistent with a bridging oxo moiety between a pair of Fe^{III} centers.[80] Finally, a Bohr effect (release or uptake of protons) is absent in oxygen binding to hemerythrin.[16,18] These observations are consistent with a μ-oxo group slightly perturbed by hydrogen bonding to a coordinated hydroperoxo species. An important role for the protein in hemerythrin is to assemble an asymmetric diiron(II) species. Only a few of the myriad of known μ-oxodiiron(III) complexes are asymmetric,[81] and the synthesis of realistic asymmetric models remains a challenge.

Deoxyhemocyanin (Cu^I d^{10}) and deoxyhemerythrin (Fe^{ll} d^6) are colorless. In the oxygenated derivatives there is considerable charge transfer between the coordinated peroxo groups and the metal centers. This phenomenon makes the essentially d-d metal transitions more intense than those for the simple aquated Fe^{3+} or Cu^{2+} ions, and permits facile measurement of oxygen-binding curves. The spectral changes accompanying oxygenation are shown in Figures 4.20 and 4.21.[5]

Nitric oxide binds to deoxyhemocyanin, to deoxyhemerythrin, and to the mixed valence Fe^{III} • • • Fe^{ll} semimethemerythrin.[148] Carbon monoxide binds to neither form of hemerythrin: apparently the other ligands have insufficiently strong fields to stabilize the low-spin state for which electron density would be available for back donation into the CO π* orbitals.
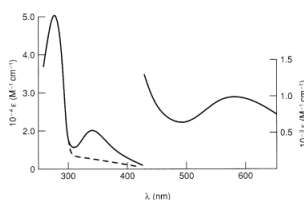

Figure 4.20 - Spectral changes accompanying oxygenation of hemocyanin: deoxyhemocyanin (- - -); oxyhemocyanin (——).[5] Reproduced with permission from A. G. Sykes, in A. G. Sykes, ed., Advances in Irorganic and Bioinorganic Mechanisms, Academic Press, **1** (1985), 121-178.

Figure 4.21 - Spectral ehanges accompanying oxygenation of hemerythrin.[5] Reprodueed with permission from A. G. Sykes, in A. G. Sykes, ed., Advances in Inorganic and Bioinorganic Mechanisms, Academic Press, **1** (1985), 121-178.
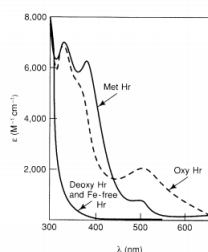
Oxyhemoglobin

The O—O stretch that is observed by difference infrared techniques at around 1105 cm^{-1} for oxyhemoglobin and oxymyoglobin[149] clearly categorizes the dioxygen moiety as a superoxo species; that is, the order of the O—O bond is about 1.5. Considerable ink has been spilled about the nature of the Fe—O$_2$ fragment since Pauling's original suggestion[150] in 1948 that dioxygen binds to iron in an end-on bent fashion:

$$(4.46)$$

He subsequently reaffirmed this geometry, and proposed that hydrogen bonding between the coordinated dioxygen and the distal imidazole H—N group was important in stabilizing the Fe—O$_2$ species.[137] In an alternative model Weiss proposed that a low-spin Fe^{III} center (S = $\frac{1}{2}$) was very strongly antiferromagnetically coupled to a superoxide anion radical (S = $\frac{1}{2}$).[151] A triangular peroxo mode has also been advanced.[152,153] The problem has been how to resolve the observed diamagnetism of oxyhemoglobin[92,98] with UV-visible, x-ray absorption, and resonance Raman spectroscopic characteristics[154] that are distinctly different from those of Fe^{ll} systems (such as carbonmonoxyhemoglobin and low-spin six-coordinated hemochromes, such as Fe(Porph)(Py)$_2$) and from unambiguously Fe^{III} systems (such as chloromethemoglobin or cyanomethemoglobin).

Any adequate theoretical treatment must also explain how iron-porphyrin systems can bind not only O_2, but also CO, NO, alkyl isocyanides, and alkyl-nitroso moieties. A simple qualitative model presented by Wayland and coworkers[129,155] conveniently summarizes ligand-binding geometries of cobalt and iron porphyrins. Although a reasonable quantitative theoretical consensus exists for 1:1 cobalt-dioxygen species, the same cannot be said yet for irondioxygen systems.

A Simple Model for the Electronic Structure of Liganded Hemoglobins

Why does dioxygen bind to iron and cobalt porphyrins in an end-on bentbond fashion as in (4.37) and (4.46)? Why does carbon monoxide bind in a linear manner (Equation 4.40)? Why are six-coordinate dioxygen and carbonmonoxide adducts more stable than five-coordinate ones? A unified picture of ligand binding that addresses these questions is important in understanding properly the specific case of dioxygen binding to hemoglobin and related systems.

The splitting of the metal d orbitals for a four-coordinate metalloporphyrin is shown in the center of Figure 4.22. These orbitals contain some porphyrin character and are antibonding with respect to metal-porphyrin bonds. As shown in Figure 4.16, the primary effect of a single σ-donor axial ligand, such as pyridine or 1-methylimidazole, is to elevate the energy of the antibonding d_{z^2} and lower the energy of the $d_{x^2-y^2}$ orbital and hence lead to a high-spin species in place of the intermediate-spin four-coordinate one. Thus, for simplicity in highlighting interaction of the metal center with the diatomic σ-donor: π-acid ligands CO, NO, and O_2, the perturbations wrought by primarily σ-donor ligands, such as 1-methylimidazole, are omitted. For the corresponding cobalt(II) compound, there is an additional electron. The diatomic ligands of interest share a qualitatively similar molecular orbital scheme. The filling of orbitals for CO is shown on the left-hand side. Dioxygen, which is shown on the right-hand side, has two more electrons than CO; these occupy the doubly degenerate π^* orbitals. Quantitative calculations show that the energy of the π^* orbitals decreases monotonically from CO to NO to O_2, indicating increasing ease of reduction of the coordinated molecule, a feature that has not been included in the diagram. Only those interactions of molecular orbitals that have appropriate symmetry and energy to interact significantly with the metal d orbitals are shown.

Two extremes are shown in Figure 4.22 for the interaction of a diatomic molecule A-B with the metal center: a linear geometry on the left and a bent geometry on the right. A side-on geometry is omitted for the binding of O_2 to a Co^{II} or Fe^{II} porphyrin, since this would lead to either an M^{III} side-on superoxo or an M^{IV} peroxo species; both these modes of coordination to these metals are currently without precedent.
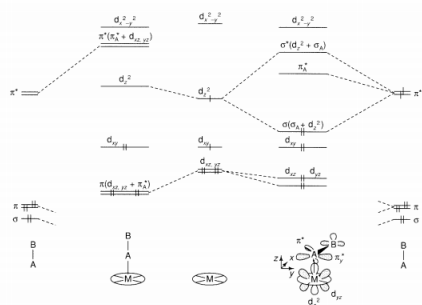

Figure 4.22 - A simple general model for ligand binding to metalloporphyrins:[129] AB = CO(π^{*0}), NO (π^{*1}), $O_2(\pi^{*2}$); M=Co ^{II}(d^7), Fe^{II}(d^6).

Linear diatomic metal bonding maximizes the metal-d_π to ligand-p_{π^*} bonding. When a ligand coordinates in a bent manner, axial symmetry is destroyed, and the degeneracy of the ligand p_{π^*} orbitals is lifted. One p_{π^*} orbital is now oriented to combine with the metal d_{z^2} orbital to form a σ bond, and the other is oriented to combine with d_{xz} and d_{yz} orbitals to form a π bond. A bent geometry for the diatomic molecule will result when either or both of the metal d_{z^2} or the ligand p_{π^*} orbitals are occupied, since this geometry stabilizes the occupied d_{z^2} orbital in the five-coordinate complex. Thus O_2 binds in a strongly bent manner to Co^{II} and Fe^{II} porphyrins; NO binds in a strongly bent manner to Co^{II} porphyrins; CO binds in a linear fashion to Fe^{II} porphyrins.

The interaction of NO with Fe^{II} porphyrins and CO with Co^{II} porphyrins—the resultant species are formally isoelectronic—is more complicated. The degree of bending seen in Fe^{II}(TPP)(NO) is midway between the two extremes.[111]For CO the higher-energy p_{π^*} orbitals lead to a greater mismatch in energy between the d_{z^2} and p_{π^*} orbitals, and less effective σ bonding. In EPR experiments the odd electron is found to be localized in a molecular orbital with about 0.87 metal d_{z^2} character for the five-coordinate Co—CO adduct, as expected for a nearly linear geometry.[129] On the other hand, for the Fe—NO adduct the metal d_{z^2} character of the odd electron is about 0.4 to 0.5;[155] a somewhat bent geometry (140°) is observed in the crystal structure of Fe(TPP)(NO). Because the CO ligand is a very weak σ donor, the Co—CO species exists only at low temperatures.

Only qualitative deductions can be made from this model about the extent of electron transfer, if any, from the metal onto the diatomic ligand, especially for dioxygen. The higher in energy the metal d_{z^2} orbital is with respect to the dioxygen p_{π^*} orbitals, the closer the superoxo ligand comes to being effectively a coordinated superoxide anion. With an additional electron, the dioxygen ligand in Co—O_2 complexes can acquire greater electron density than it can in Fe—O_2 complexes.

From the diagram it may be inferred that a ligand with very strong π-acceptor properties will lower the energy of the d_{xz} and d_{yz} orbitals through strong (d_{xz}, d_{yz})-π^* interaction. The resultant energy gap between these two orbitals and the other three metal d orbitals may be sufficient to overcome the energy involved in spin-pairing, and hence lead to five-coordinate low-spin species, as happens for complexes containing phosphines and carbon monosulfide.[99,132]

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