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STUDY ON THE BINDING AND ACTIVATION OF DIOXYGEN BY METALLOPORPHYRINOID

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ABSTRACT
Heme-containing proteins play an essential part in the physiological transport of dioxygen, and in the oxidative metabolism of both endogenous and exogenous substrates. These latter processes occur through a series of highly reactive heme–oxygen intermediates. The development of synthetic analogues of these proteins and metal–oxygen intermediates has helped to elucidate the molecular mechanisms of these proteins and to establish the fundamental criteria for metal binding and activation of O_2. This chapter outlines the basic chemical principles that govern the binding and activation of dioxygen by metalloporphyrinoid centers.

INTRODUCTION
An overview of the structures and mechanisms of heme mono- and dioxygenases is provided, with an emphasis on the factors that stabilize or activate the heme/O_2 interactions. Focus is given to iron and manganese porphyrinoid complexes, which include porphyrins, corroles, corrolazines, porphyrazines, and phthalocyanines. Recent examples of metal/O_2 species are discussed, together with catalytic, O_2-dependent oxidations of different substrates mediated by Mn/Fe porphyrinoid complexes. The dioxygen molecule, O_2, is a primary component of the atmosphere and is essential for sustaining aerobic life. This diatomic molecule reacts with a number of heme proteins that are involved in the physiological transport of dioxygen, and in the oxidative metabolism and hydroxylation of a wide range of metabolites. The latter processes typically involve a series of highly reactive heme–oxygen intermediates. The preparation of synthetic analogues of these heme sites and metal/oxygen intermediates not only provides spectroscopic benchmarks for comparison with enzymatic data, but also affords structurally well-characterized species through which detailed structure–function relationships can be investigated. While metallo-enzymes can perform a range of substrate hydroxylations with relative ease, the development of a synthetic catalyst that can utilize O_2 as the sole oxidant in the oxidation of commodity or specialty chemicals has remained the ultimate challenge for the inorganic chemist. Synthetic metalloporphyrinoid compounds have been prepared as model systems for addressing fundamental questions regarding the structural and electronic requirements for binding and activating O_2, as well as for catalyzing the oxidation of organic substrates with O_2 as the oxidant and/or oxygen source.

The aim of this paper is to outline the basic chemical principles of O_2 binding and activation by heme proteins, and their synthetic analogues constructed from porphyrin-related, or porphyrinoid, systems. Examples of O_2-binding proteins and O_2-activating heme enzymes, particularly mono- and dioxygenases, will be described to gain insight into the biological requirements for O_2 reactivity. Recent examples of Fe and Mn porphyrinoid models for O_2 binding and activation, together with organic catalytic applications will be discussed.

Due to the low solubility of molecular O_2 in blood plasma, O_2-binders are required for proper transport, storage, and subsequent incorporation of oxygen into substrates. The binding of dioxygen is typically facilitated by first-row transition metals, in part because of their fast substitution kinetics.[1] A vacant site on the metal center is a requirement, as well as access to multiple metal oxidation states. The stoichiometry of O_2 binding can differ depending on the steric requirements of the coordination environment. Transition metals allow binding of dioxygen in different redox states , which can be distinguished experimentally using various spectroscopic techniques, including those that measure O–O bond distances, vibrational stretching frequencies, oxidation states, and spin states.[2]Dioxygen has a triplet ground state, $^3\Sigma_g^-$, with a molecular configuration of $(1s\sigma_g)^2\ (1s\sigma_u^*)^2\ (2s\sigma_g)^2\ (2s\sigma_u^*)^2\ (2p_z\sigma_g)^2\ (2p_x\pi_u)^2\ (2p_y\pi_u)^2\ (2p_x\pi_g^*)^1\ (2p_y\pi_g^*)^1\ (2p_z\sigma_u^*)^0$.

Oxidation reactions mediated by O_2 are unusual processes; even though oxidation by O_2 is thermodynamically favorable in many cases, dioxygen is relatively kinetically unreactive. The low kinetic reactivity and triplet ground state of O_2 seems counterintuitive, given the inherent reactivity of diradicals in other molecules.[3] This lack of kinetic reactivity can be traced to the very large resonance stabilization energy of O_2 (*ca.* −100 kcal mol^{-1}), arising from the *four* O_2 resonance structures that arise from assigning six electrons, four α-spin and two β-spin, to the four $2p_x$ and $2p_y$ π atomic orbitals in the triplet ground state of the O_2 molecule.[4] The triplet ground state of O_2 also makes its reaction with most biological molecules, which have singlet ground states, a spin-forbidden process, adding to the kinetic barrier. On the other hand, the weak O–O σ bond makes reactions with O_2 very favorable thermodynamically. Nature overcomes the large kinetic barrier inherent to reactions of triplet O_2 by utilizing transition metals that also exist in open-shell spin ground states. The function of metal ions here is two-fold: they serve as O_2 binding sites for transport, and as reaction centers, where they can perform multi-electron redox chemistry that ultimately leads to the incorporation of oxygen atoms in organic substrates. There are three general classes of metalloproteins that have evolved to bind and transport dioxygen in multicellular organisms: hemoglobins, hemerythrins, and hemocyanins Hemoglobins (Hb), including myoglobins (Mb), are generally found in vertebrates and in all mammals. Their active site consists of an Fe^{II} center chelated by a protoporphyrin IX ligand and an axial imidazole ligand from a histidine residue, all enclosed in a hydrophobic protein pocket. Dioxygen binding to the Fe^{II} center occurs in an η^1 fashion, and typically involves one electron transfer from Fe^{II} to O_2 to form an Fe^{III}–superoxo complex. In most cases, hydrogen-bonding interactions between the O_2 molecule and the amino acid residues in the distal side can be observed by X-ray crystallography and resonance Raman spectroscopy, and are a key structural element for O_2 binding. Mimicking the structural properties of hemoglobins in a synthetic system has been the subject of several studies, and significant efforts have focused on incorporating the necessary secondary coordination sphere elements that promote binding of O_2 and discourage side reactions that inhibit reversible oxygen binding. However, the secondary coordination sphere can also be exploited to tune the properties of the complex away from reversible O_2 binding, and toward O_2 activation and cleavage of the O–O bond. This subtle interplay between O_2 binding and activation will be discussed further in detail in Section 1.4. The other two metalloproteins, hemerythrin and hemocyanin, have dinuclear metal centers directly ligated to protein side chains, obviating the need for the production of a complex protein cofactor such as protoporphyrin IX. Hemerythrin (Hr), found in several marine invertebrates, possesses an unsymmetrical (5-coordinate/6-coordinate) diiron active site linked by carboxylate groups and a μ-hydroxo bridge, and ligated to the protein backbone through the imidazole groups of His side-chains. Dioxygen binds to the reduced Fe^{II} center with a vacant site as an η^1-hydroperoxide ligand. Two electrons are transferred from the diiron $(Fe^{II})_2$ core to O_2, yielding an oxidized diferric $(Fe^{III})_2$ core and a peroxo (O_2^{2-}) species, which is protonated by transfer of H^+ from the μ-hydroxide ligand proximal to the coordinated oxygen. Hemocyanins (Hc), found in arthropods and molluscs, have several features in common with Hr. They bind dioxygen at a reduced dinuclear Cu^I active site coordinated to the protein scaffold through His groups. Reaction with O_2 leads to an oxidized dicopper(II) center and the transfer of two electrons to O_2 to give a $\mu\text{-}\eta^2:\eta^2$ peroxo ligand that bridges the oxidized cupric ions. Several reviews have outlined examples of synthetic models of hemocyanin and hemerythrin, and these will not be discussed here. Cytochrome P450

Examples of monooxygenation reactions catalyzed by cytochrome P450 (CYP) include alkane and aromatic hydroxylations, olefin epoxidations, as well as N-, S- or O-dealkylations. While CYP can perform oxygenation reactions with a variety of organic substrates through diverse mechanisms, these reactions share common mechanistic intermediates. A consensus mechanism for the catalytic hydroxylation of C–H bonds by CYP is shown in Electronic tuning, substrate orientation, and control over electron and proton transfer all combine to form an efficient and well-choreographed sequence that delivers a reaction utilizing molecular oxygen. The resting ferric heme state is a 6-coordinate, low-spin species, and substrate binding to the active site pocket displaces the aqua ligand and turns the heme into a high-spin 5-coordinate iron complex with an increased redox potential. Reduction of the high-spin ferric heme, usually by nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NADH/NADPH) reducing equivalents, generates a high-spin Fe^{II} heme, which is activated for O_2 binding. Addition of O_2 gives a ferric superoxo complex. A second reduction event occurs to give a ferric peroxo complex, which is then protonated to form

a ferric hydroperoxo intermediate labeled "Compound 0" (Cpd 0). Heterolytic cleavage of the O–O bond of Cpd 0 generates a high-valent iron–oxo porphyrin species, $Fe^{IV}(O)(porphyrin^{\cdot+})(Cys)$, labeled Compound I (Cpd I). The generally accepted mechanism for substrate hydroxylation is the radical rebound mechanism, where Cpd I abstracts an H-atom from the C–H substrate to form $Fe^{IV}(OH)(porphyrin)(Cys)$ or protonated Compound II (Cpd II). The newly generated carbon-centered radical then rapidly recombines with protonated Cpd II to give an alcohol product and the ferric heme resting state. Nitric Oxide Synthase

Nitric oxide (NO) synthase is a heme monooxygenase that catalyzes the oxidation of L-arginine to L-citrulline and nitric oxide. Similar to CYP, NO synthase heme is axially ligated by a cys thiolate donor. The enzyme architecture, however, is very different from that of CYP, and a tetrahydrobiopterin (BH4) cofactor is also found in the active site pocket. The first step of the reaction, the hydroxylation of L-arginine to *N*-hydroxy-L-arginine, is generally described to proceed *via* a classic CYP hydroxylation mechanism with the BH4 serving as an electron source. The second step of the reaction, the conversion of *N*-hydroxy-L-arginine to L-citrulline and NO, has been more challenging to assess, and a proposed mechanism is shown in . The requirement of only one exogenous electron for this reaction has ruled out the involvement of Cpd I (which typically requires two exogenous electrons to assist with O–O bond cleavage on the way to Cpd I). Current proposals have focused instead on a superoxo/peroxo–iron intermediate as the key species needed to initiate attack of the substrate. The substrate may or may not serve as a direct electron donor to the Fe/O_2 intermediate, depending on whether the BH4 cofactor is oxidized.Following $NO^{\cdot}$ production, the ferric heme can then be reduced by NADPH to regenerate the ferrous form for another round of O_2 activation and *N*-hydroxylation. It is interesting to note that NO synthase demonstrates the versatility of the heme–thiolate center in activating O_2 for different purposes within the overall transformation of L-arginine to NO.

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