

On the bonding of FeO₂ in hemoglobin and related dioxygen complexes

(chromium/superoxide/oxidation state formalism/porphyrin/redox potential)

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ABSTRACT The celebrated Fe(II)(O₂) versus Fe(III)(O₂⁻) debate over the formal representation of the FeO₂ moiety in hemoglobin can be resolved by consideration of the utility of each formalism. In the context of rationalizing the gross structural and electronic features of end-bound dioxygen, particularly in light of a new closely related chromium complex, the M(III)-(O₂⁻) formulation is both chemically reasonable and most useful. In conjunction with a qualitative molecular orbital overlap picture, the differing magnetic states of end-bound MO₂ complexes and their geometrical features can be rationalized or predicted.

In the four decades following Pauling and Coryell's determination (1) of the diamagnetism of oxyhemoglobin, HbO₂, there has been considerable debate over the structure and electronic configuration of the FeO₂ moiety (2-10). With the successful x-ray structure determination of the iron-"picket fence porphyrin"-dioxygen complex (11) there can be little doubt that an end-bound angular structure,



exists in HbO₂, but the challenge of securing very accurate bonding parameters remains. The diamagnetism and facile reversibility of oxygen binding have led many to favor the formal electronic description as Fe(II)(O₂) with spin paired dioxygen. On the other hand, a wealth of spectroscopic data (6, 12-17) indicates that the iron atom in HbO₂ is much more characteristic of the ferric oxidation state supporting the Weiss superoxide formulation, Fe(III)(O₂⁻), in which the low spin *d*⁵ ferric atom has its unpaired electron antiferromagnetically coupled to that on the coordinated superoxide ion (3). This debate, seemingly theological or even semantic at times, has arisen in part from a misunderstanding between experimenters who sought to gain a measure of the real electron density distribution and those who sought to assign chemically reasonable and useful formal oxidation states. Moreover, the uniqueness of HbO₂ has until now prevented its logical classification into the two recognized classes of mononuclear dioxygen complexes: (i) the superoxo type found in various



moieties and (ii) the peroxo type,



Abbreviations: TPP, dianion of *meso*-tetraphenylporphyrin; py, pyridine; MeIm, methylimidazole.

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known for a very wide variety of transition metals (18-21). Our synthetic efforts to expand the range of known dioxygen complexes (22, 23) have recently led to the discovery (24) of a molecular oxygen adduct of a chromium/pyridine/tetra-phenylporphyrin complex, Cr(O₂)(py)(TPP), whose paramagnetism has uncovered a clue to rationalizing the gross features of all known



complexes, including HbO₂, in terms of the M(III)(O₂⁻) formulation. We also suggest a qualitatively satisfying σ and π bonding overlap picture which rationalizes observed spin pairing and geometrical features. Many useful generalities emerge and some predictions ensue.

MATERIALS AND METHODS

Fe(TPP) (25) and Cr(TPP) (24) were prepared by literature methods and Co(TPP) was the generous gift of F. Ann Walker. Electrochemical measurements were made with a standard three electrode setup on Princeton Applied Research model 173, 175, and 179 equipment generously loaned by Martin D. Kamen and setup by Jean-Claude Marchon. All potentials were measured at Pt versus aqueous saturated calomel electrodes. Solutions were prepared under an argon atmosphere by dissolving the appropriate M(II) complex (*ca.* 0.5 mM) in dry, deoxygenated solvent containing 0.1 M tetra-1-butylammonium hexafluorophosphate as supporting electrolyte. Iron results were obtained by using *ca.* 1 mM 2-methylimidazole (2-MeIm) to attain five-coordinate hemes (26, 27); equilibrium Fe(II/III) potentials were obtained by potentiometric methods during controlled potential coulometry. For reasons of solubility (tetrahydrofuran) or stability (CH₂Cl₂), Cr(II/III) potentials were measured by cyclic voltammetry at 200 mV sec⁻¹; reversible waves were encountered and were virtually independent of axial ligand concentration. For Co(TPP)(1-MeIm) or Co(TPP)(2-MeIm) in tetrahydrofuran or CH₂Cl₂, a reversible cyclic voltammetry wave was not observed, possibly because of a five- to six-coordination number change upon oxidation (28). In these cases, the oxidation wave peak potential from cyclic voltammetry is quoted; it gives a lower limit (29) and is considered to be close to the true M^{II/III}(TPP)L potential. For all M(TPP) systems in dimethylsulfoxide, reversible cyclic voltammetry M(II/III) waves yielded half-wave potentials essentially identical to those obtained by potentiometric methods during controlled potential coulometry.

DISCUSSION

The Superoxo Formalism. As a solid, Cr^{II}(py)₂(TPP) irreversibly adds molecular oxygen to yield Cr(O₂)(py)(TPP) that

Table 1. Summary of diagnostic features and trends in superoxo MO₂ complexes with Schiff base or porphyrin ligands^a

	CrO ₂	FeO ₂	CoO ₂	Free O ₂ ⁻	Present MO ₂ range
O—O Å	—	1.2 ^b	1.273(10)—1.302(3) ^c	1.28(2) ^d	1.2—1.3
M—O Å	—	1.75(2) ^b	1.873(7)—1.889(2) ^c		1.75—1.9
M—O—O angle °	—	135(4)—137(4) ^b	117—120 ^c		117—137
ν O—O cm ⁻¹	1142 ^e	1107 ^f , 1163 ^g	1120—1195 ^h	1145 ⁱ	1107—1195
E _M II/III _(Me/Im) (TPP) volts(CH ₂ Cl ₂) ^j	-1.00	-0.215	+0.16	-0.79 ^k	
E _M II/III _(Me/Im) (TPP) volts(tetrahydrofuran)	-0.80	-0.015	+0.28		
E _M II/III _(dimethylsulfoxide) ₂ (TPP) volts (dimethylsulfoxide)	-0.88	-0.080	+0.14		
Half-saturation O ₂ pressure ^l (torr)	Irrev.	0.3 ^m	100 ⁿ		

^a Superscripts are references. Numbers in parentheses are estimated standard deviations in the last digit.

^b See ref. 11. ^c See ref. 43. ^d See ref. 42. ^e See ref. 24. ^f See ref. 35. ^g See ref. 36. ^h See ref. 21. ⁱ See ref. 37. ^j All potentials versus standard calomel electrode. ^k See ref. 31. ^l For "picket fence" porphyrin systems. ^m See ref. 50. ⁿ J. P. Collman, personal communication.

can only be reasonably formulated as a chromium (III) superoxo complex (24). That a Cr(II)(O₂) formulation is entirely inappropriate follows from consideration of redox potentials, irreversibility, and other properties discussed below. In a pseudo-octahedral ligand field, chromium (III) complexes are invariably high spin with a $(d_{xy})^1(d_{xz})^1(d_{yz})^1$ configuration, and have measured magnetic moments consistent with three unpaired electrons. Because the magnetic moment ($\mu = 2.7$ BM) of Cr(O₂)(py)(TPP) is consistent with only two unpaired electrons, we must conclude that one of the three d_{π} electrons is coupled with the unpaired electron formally associated with the coordinated superoxide ion. In a similar manner, for Fe(III)(O₂⁻) the single unpaired d_{π} electron of the low spin d^5 ferric atom can be considered to couple with the unpaired electron of the superoxide ion leading to a diamagnetic FeO₂ moiety. In other words, oxyhemoglobin is diamagnetic, apparently for the same reason that Cr(O₂)(py)(TPP) has only two unpaired electrons. Cobalt dioxygen complexes, having CoO₂ moieties with one more electron than FeO₂, are formulated as Co(III)(O₂⁻) complexes following electron spin resonance indications that the unpaired electron is largely dioxygen localized (30). The bonding considerations that follow from these arguments are developed below following further justification of the superoxo formalism.

Although the argument is not thermodynamically rigorous, M(II/III) redox potentials for closely similar M(L)(porphyrin) systems can be expected to give a reasonable indication of the relative tendency of the metal to transfer an electron to O₂ upon coordination. Our redox potential measurements under various conditions (Table 1) reveal M(II) oxidation tendencies with Cr > Fe > Co. Because Fe(II) has a greater tendency than Co(II) to become oxidized, in terms of electron transfer, the well-accepted Co(III)(O₂⁻) formulation ought to be even more acceptable for FeO₂. For Cr(O₂)(py)(TPP), a comparison of the Cr(II/III) potential (-1.00 V) to that of O₂/O₂⁻ (-0.79 V) (31) suggests that the Cr(III)(O₂⁻) formulation may actually approximate the real electron population. We note also that the same comparison rationalizes the irreversibility of dioxygen binding to chromium. It is apparent that dioxygen binding constants vary inversely with redox potential (Table 1) (32, 33).

A useful prediction which arises from the superoxo formulation is that end-on MO₂ bonding will result from dioxygen coordination to complexes having both a readily accessible single coordination site and one-electron oxidation available. This is in contrast to the formation of peroxy-type mononuclear dioxygen complexes where two adjacent coordination sites and a formal two-electron oxidation are apparently necessary (18).

Recently, \cdot Mn(CO)₅ has been shown to bind O₂ in a matrix (34). The readily accessible one electron oxidation, the single vacant site, and the electron spin resonance data all suggest this complex should be formulated as Mn(I)(O₂⁻) and, therefore, be named "superoxo" rather than "peroxy."

Finally, as recently highlighted by Barlow *et al.* (35) and Collman *et al.* (36), the formal reduction of coordinated dioxygen to superoxide is best demonstrated by the narrow range of ν O—O stretching frequencies (1107—1195 cm⁻¹) close to that of free superoxide (1145 cm⁻¹ in KO₂) (37) and distinct from free dioxygen (1556 cm⁻¹) or peroxidic type complexes (800—900 cm⁻¹).

Bonding Scheme for M(III)(O₂⁻). The coupling of an M(III) d_{π} electron with the unpaired electron formally associated with the superoxide ion is envisaged as overlap of the half-filled d_{xz} atomic orbital with a singly occupied π^* molecular orbital of O₂⁻ (Fig. 1A). The feasibility of this type of interaction has been investigated by calculation (10, 38).[†] Whereas the Weiss proposal viewed this interaction as an antiferromagnetic coupling, we believe it is preferable to invoke "significant bonding."[‡] The predominant bonding interaction, however, is almost certainly a σ interaction envisaged in Fig. 1B as lone pair donation from an sp^2 rehybridized superoxide ion into an empty metal σ orbital (d_{z^2}).

A qualitative molecular orbital energy level diagram consistent with this bonding picture is displayed in Fig. 2. For CrO₂, a $(\sigma^b)^2(\pi^b)^2(d_{yz})^1(d_{xy})^1$ configuration leads to two unpaired electrons whereas FeO₂, with two additional electrons, is diamagnetic (Fig. 2). A further electron in CoO₂ is located in the π^* orbital that has predominantly antibonding superoxide character. Such a diagram is part of a more general scheme for the coordination of diatomics discussed in detail by Wayland *et al.* (40). It should also be pointed out that although our molecular orbital diagram is conceptually convenient for the superoxo formalism it can be equally well generated from M(II) and O₂ atomic orbitals because symmetry is the only criterion

[†] As first pointed out by Rodley *et al.* (39) and as used in ref. 10, better overlap of the π^*O_2 orbital with d_{π} orbitals is achieved if both the d_{xz} and d_{yz} orbitals share this overlap. Our arbitrary assignment of the overlap to only the d_{xz} orbital is therefore a simplification. Despite this, we find that the qualitative theory developed from this assumption is entirely adequate to rationalize all experimental data.

[‡] The term "antiferromagnetic coupling" is logically reserved for situations where spin coupling is incomplete and is manifest in distinctly temperature-dependent paramagnetism. "Significant bonding" on the other hand implies orbital overlap sufficient to maintain spin pairing regardless of temperature and such bonding should be manifest in significant bond shortening.

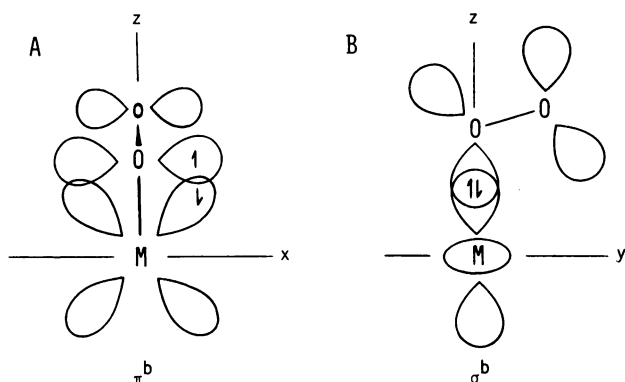


FIG. 1. Diagrammatic representation of the π (A) and σ (B) overlap which rationalizes gross geometric and electronic features of MO_2 bonding.

for overlap. At present, we are using the diagram only to rationalize magnetic states but we do note that actual electronic transition assignments have recently been advanced by Miskowski *et al.* (41) using a closely related scheme for dicobalt superoxo complexes.

The overlap scheme leads to the expectation that O—O bond lengths should approach that of the superoxide ion ($1.28 \pm 0.02 \text{ \AA}$) (42) or be somewhat shorter in situations where significant π^* antibonding electron density from the O—O region can be transferred back into the M—O bonding region. This should lead to M—O bond lengths for the first row transition metals of a pure σ bond or slightly less ($\leq 1.9 \text{ \AA}$). Such expectations are borne out in reliable estimates for cobalt derivatives (43) (Table 1). We expect rather trivial π bonding from O_2^- back to Co(III) in view of the filled d_{π^6} configuration and hence rather little variation in bond lengths and angles among various CoO_2 complexes whose other ligands cannot withdraw significant d_{π} electron density (44). However, for Fe(III) the half-filled d_{xz} orbital is expected to accept considerable π electron density back from O_2^- especially since the Fe(II/III) redox potential is only weakly negative. Indeed, the resonance Raman location of $\nu_{\text{Fe—O}}$ in HbO_2 at high frequency (567 cm^{-1}) (45) is good evidence of multiple $\text{M}^{\text{III}}\text{—O}$ bonding as originally suggested by Pauling (4). Extensive accurate data from disorder-free crystals is presently unavailable for FeO_2 complexes and although the

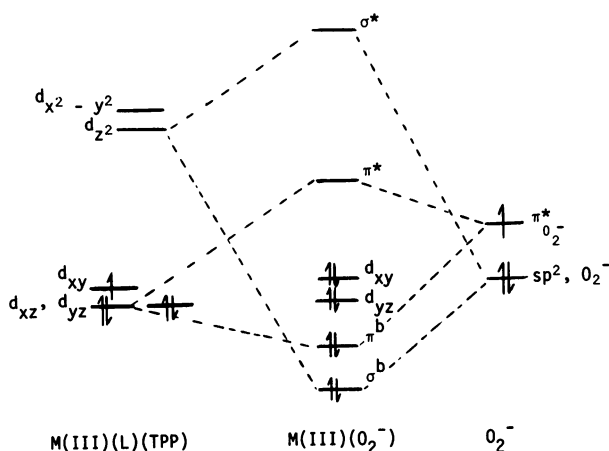


FIG. 2. Qualitative energy level diagram for molecular orbitals in the $\text{M(III)(O}_2^-)$ system (Center). Shown is the electron occupation for the FeO_2 moiety.

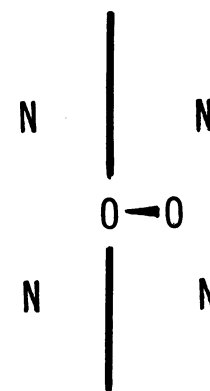


FIG. 3. Graphic representation of the ideal orientation of the MO_2 plane with respect to a π bonding axial base (heavy line) viewed down the z axis. The four N atoms represent an equatorial porphyrin or Schiff base ligand.

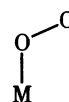
reported Fe—O [$1.75(2) \text{ \AA}$] and O—O [$1.23(8)$ and $1.26(8) \text{ \AA}$] distances for the picket fence complex (11) are short, agreement with our predictions should be taken *con granulo salis*. For $\text{Cr(III)(O}_2^-)$, the observed magnetism requires some π overlap but excessive π bonding is unlikely since it would be working against a strongly adverse redox potential. This should lead to bond lengths rather similar to cobalt complexes.

For M—O—O angles, the predominant σ donation from an sp^2 hybridized oxygen atom of the superoxide ion rationalizes bond angles approaching 120° . In situations where significant π bonding occurs, however, we predict an increase in this angle owing to better $d_{xz} - \pi_{\text{O}_2}^*$ overlap as the angle increases. (This is a result of the $\pi_{\text{O}_2}^*$ orbital lobes being directed at an angle somewhat greater than 90° away from the O—O bond.) A considerable synthetic challenge remains in the isolation of disorder-free single crystals of superoxo type dioxygen complexes for x-ray analysis in order to test the various predictions.

The π bonding description for MO_2 correlates simply with previous conclusions (11, 39) regarding the orientation of axial ligand planes at right angles to each other. It is apparent that for steric reasons axial pyridine ligands and, to a lesser extent, imidazoles prefer to bind with their planes approximately bisecting the metal ligand bonds of equatorially coordinated porphyrins or Schiff bases. The orthogonality of the d_{yz} and d_{xz} orbitals quite naturally leads to a situation where M— O_2 π bonding is enhanced if any M-axial base π bonding occurs at right angles to it (Fig. 3) However, whereas these may represent the most favorable orientations, it is apparent (46) that steric factors are often more important at least in crystal structures. Histidine E7 and valine E11 are apparently sterically operative in directing the FeO_2 orientation in oxyhemoglobin (47).

CONCLUDING REMARKS

In conclusion, it is important to stress both the utility of the superoxo formulation and its limitations. While the present theory nicely rationalizes the gross features of all presently known



complexes (Table 1), it cannot, however, predict actual electron populations. Indeed, in situations of positive or weakly negative

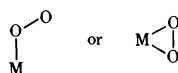
M(II/III) redox potentials, it is likely that charge transfer from M(II) to O₂ is but a fraction of unity. However, the correct bond polarity is implied and, as is often the case in inorganic chemistry, a formal valence classification based on unit oxidation states is the only coherent and useful framework on which to support a large weight of chemistry. The stage now appears set for the acceptance of this generality⁸ and while detailed structural, electronic, and theoretical studies should eventually lead to a more quantitatively satisfying bonding picture, we suggest that formalizing the charge population in an MO₂ moiety as M(II)(O₂) represents a simplification of limited utility, except in the context of discussing net charge populations. Here fractional, rather than integral, oxidation states might prove to be more useful because whereas calculated estimates of the net negative charge transfer from iron to dioxygen vary from close to zero (10) to 0.1 (8) to 0.52 (9), it seems likely that values from close to zero up to about unity will exist according to the ligands and the metal. Indeed estimates of 0.1 to 0.8 have recently been made for a series of cobalt dioxygen complexes (48). Consistent with the formalism all available *experimental* data indicate that *some* metal to dioxygen charge transfer occurs in all known dioxygen complexes. It is heartening to find that the interpretation of our results further cements the close analogy of certain CoO₂ complexes to HbO₂, a persuasion long championed by the Northwestern school (49).

In coordination chemists' terms we believe dioxygen in mononuclear complexes should be considered as an innocent ligand, bonding in either of two quite distinct ways—superoxo and peroxy. Structure, ν O—O, redox potentials, and coordination site availability are all properties apparently diagnostic of the classification and can be usefully predictive.

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⁸ The acceptance of the superoxo formalism requires some consideration of nomenclature. As suggested by Vaska (21), we believe that when the structure of a dioxygen complex has been determined as:



it should be named superoxo- or peroxy-, respectively. In contrast to his suggestion, however, we believe the generic term "dioxygen ligand" can usefully be reserved to imply origin from free dioxygen regardless of bonding or structure in the MO₂ complex. Thus, the trivially named oxyhemoglobin might properly be named (dioxygen)hemoglobin or superoxoFe(III)hemoglobin, although it is unlikely that the name oxyhemoglobin will fall from common usage. Cr(O₂)(py)(TPP) is named either (dioxygen) (pyridine)($\alpha,\beta,\gamma,\delta$ -tetraphenylporphinato)chromium or superoxopyridine ($\alpha,\beta,\gamma,\delta$ -tetraphenylporphinato)chromium(III), preferably the latter.

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