

# Synthetic Oxygen Carriers Related to Biological Systems

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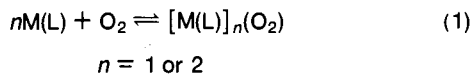
Received September 29, 1978

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## I. Introduction

Certain metal complexes provide the delicate balance required to form adducts with dioxygen without the metal (M) or the ligands (L) being irreversibly oxidized. Such systems, known as oxygen carriers, are biologically utilized in the transport and storage of molecular oxygen. The equation for adduct formation (eq 1) is written as an equilibrium process. To be classified as an oxygen carrier, it is necessary that the reverse reaction, i.e., the dissociation of the dioxygen complex to give M(L) and O<sub>2</sub>, be observable. In practice this process can be observed by lowering the partial pressure of O<sub>2</sub>, by heating the complex, or by the addition of a ligand capable of replacing the bound O<sub>2</sub>.



The study of compounds capable of reversibly binding molecular oxygen has received a great deal of attention for several years. Several of these compounds, like the Vaska<sup>1</sup> complex, Ir(PPh<sub>3</sub>)<sub>2</sub>(CO)(Cl), involve the addition of O<sub>2</sub> to group 8 metals. Although the chemistry of these compounds embraces a fascinating and worthwhile area of investigation, this review is limited to a discussion of those synthetic dioxygen complexes that are of specific interest as models of natural oxygen carriers. *Per force*, this review deals largely, but not exclusively, with complexes containing the elements iron, cobalt, and manganese.

In writing this paper, which reviews the literature through the

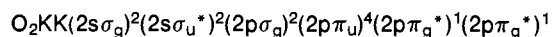
early part of 1978, no attempt has been made to totally cover all aspects of the problem. Rather we have tried to approach the subject in such a way as to complement the other reviews already available.<sup>2-18</sup> Specifically we have largely restricted our attention to the synthetic approaches that have been made to observe metastable metal-dioxygen complexes of biological importance.

## II. Nomenclature

The terminology used in this review, referring to oxygen in its various forms, is similar to that used by Vaska<sup>15</sup> in his recent review. The term *molecular oxygen* as used here refers only to the free uncombined O<sub>2</sub> molecule. Unless otherwise specified, it will be used to mean the ground (<sup>3</sup>Σ<sub>g</sub><sup>-</sup>) state of the molecule. The term *dioxygen* has been used as a generic designation for the O<sub>2</sub> moiety in any of its several forms, and can refer to O<sub>2</sub> in either a free or combined state. The only criterion for use of this term is the presence of a covalent bond between the oxygen atoms. Thus a metal-dioxygen complex refers to a metal containing the O<sub>2</sub> group ligated to the metal center. In using this term, no distinction is made between neutral dioxygen or dioxygen in any of its reduced forms. A *metal-superoxide* or *metal-peroxide* complex is one in which the coordinated dioxygen resembles a superoxide (O<sub>2</sub><sup>-</sup>) or peroxide (O<sub>2</sub><sup>2-</sup>) anion, respectively. The incorporation of O<sub>2</sub> into a metal complex to form a metal-dioxygen compound is called *oxygenation* (eq 1). Deoxygenation is the reverse of this process.

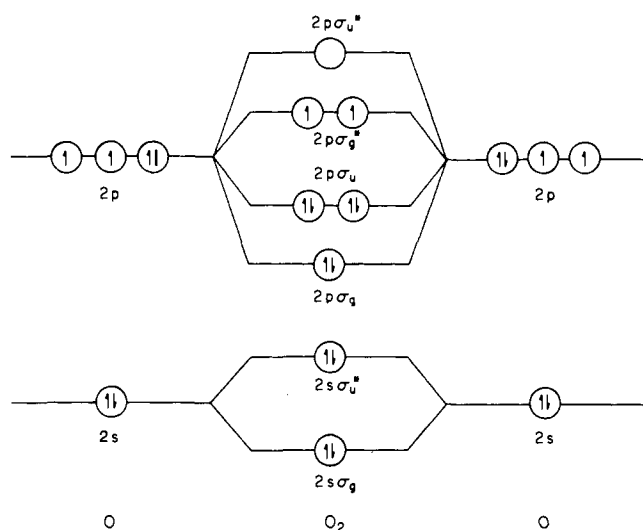
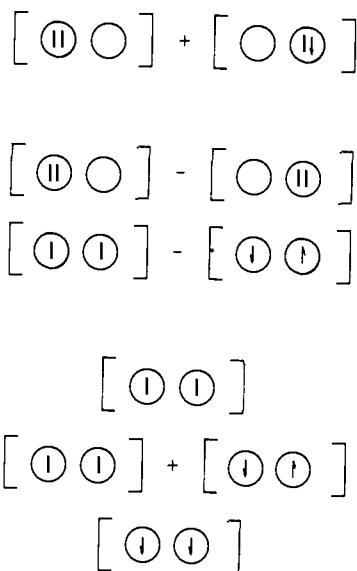
## III. Nature of O<sub>2</sub>

Molecular oxygen is a paramagnetic molecule, having a triplet, <sup>3</sup>Σ<sub>g</sub><sup>-</sup> ground state. The two lowest lying electronic excited states are the singlet state, <sup>1</sup>Δ<sub>g</sub> and <sup>1</sup>Δ<sub>g</sub><sup>+</sup>, lying 22.53 and 37.51 kcal/mol above the ground state, respectively. A molecular orbital description of the ground state, <sup>3</sup>Σ<sub>g</sub><sup>-</sup> level is

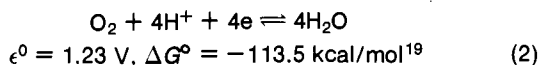


where the KK term indicates that the K shells of the two oxygen atoms are filled. The two unpaired electrons in the <sup>3</sup>Σ<sub>g</sub><sup>-</sup> ground state are found in the two degenerate antibonding 2pπ<sub>g</sub><sup>\*</sup> orbitals (Figure 1), leaving O<sub>2</sub> with a formal bond order of two. The electronic configurations for O<sub>2</sub> in its three lowest lying states is shown in Figure 2.

The MO description for molecular oxygen shows a vacancy for the addition of a single electron in both of the antibonding 2pπ<sub>g</sub><sup>\*</sup> orbitals. The addition of one or two electrons to a neutral dioxygen molecule results in formation of the superoxide (O<sub>2</sub><sup>-</sup>) and peroxide (O<sub>2</sub><sup>2-</sup>) anions, respectively, leaving superoxide with a bond order of 1.5, and the peroxide O-O link with a normal bond order of one. Consistent with this assignment of bond orders, both the O-O bond lengths and O-O bond energies fall in the order O<sub>2</sub> > O<sub>2</sub><sup>-</sup> > O<sub>2</sub><sup>2-</sup>. Some of the salient physical data for O<sub>2</sub>, both in its neutral and ionic forms, are summarized in Table I.

Figure 1. The molecular orbital energy-level description for O<sub>2</sub>.Figure 2. The electronic configurations for the unpaired electrons in the 2π<sub>g</sub> orbitals of O<sub>2</sub> in its three lowest lying states. The lower configuration represents O<sub>2</sub> in its <sup>3</sup>Σ<sub>g</sub><sup>-</sup> state, the middle <sup>1</sup>Δ<sub>g</sub>, and the upper the <sup>1</sup>Σ<sub>g</sub><sup>+</sup> state.

The primary fate of molecular oxygen in the higher biological organisms is its reduction to form water. This process, which occurs with the overall transfer of four electrons (eq 2),



is highly exothermic, both under standard conditions ([H<sup>+</sup>] = 1.0 M) and at biological concentrations of H<sup>+</sup> (pH 7.4,<sup>20</sup> ε = 0.79 V, ΔG = -72.9 kcal/mol), making molecular oxygen a powerful oxidizing agent.

The reduction of O<sub>2</sub> to H<sub>2</sub>O proceeds, in general, via a series of one- or two-electron transfer processes. The monodynamic nature of these processes can be seen by examining a Frost diagram<sup>21</sup> (Figure 3) for the O<sub>2</sub> to H<sub>2</sub>O reduction in acidic media. From this diagram it can be seen that although the overall reduction is highly exothermic, the one-electron reduction process



is quite endothermic, owing primarily to the large reduction in O-O bond strength on going from O<sub>2</sub> to HO<sub>2</sub>·. The highly favorable reduction of the hydroperoxyl radical (HO<sub>2</sub>·) to H<sub>2</sub>O<sub>2</sub> (eq 4) can

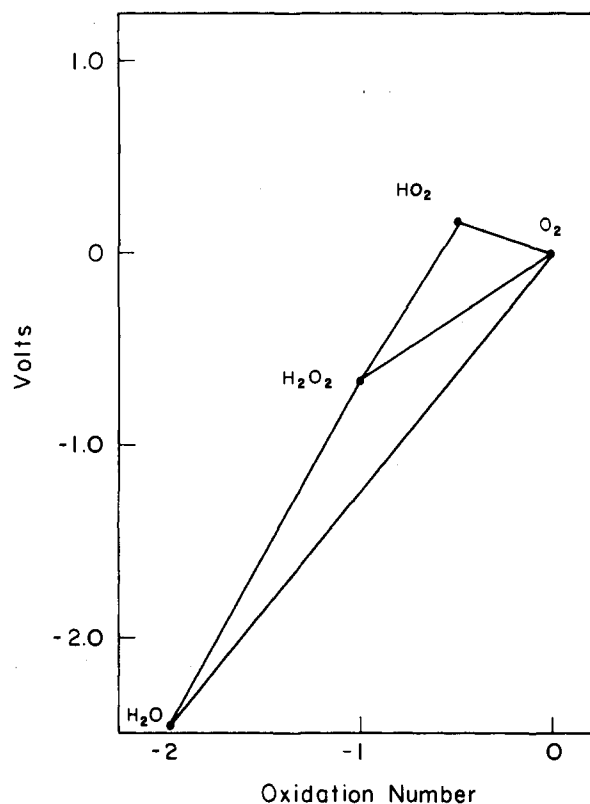
Figure 3. Frost diagram for the reduction of O<sub>2</sub> to H<sub>2</sub>O<sub>2</sub>.

TABLE I. Some Properties of the Dioxygen Moiety

	bond order	compd <sup>a</sup>	O-O distance, Å	bond energy, kcal/mol	ν <sub>O-O</sub> , cm <sup>-1</sup>
O <sub>2</sub> <sup>+</sup>	2.5	O <sub>2</sub> AsF <sub>6</sub>	1.123 <sup>a</sup>	149.4 <sup>b</sup>	1858 <sup>c</sup>
O <sub>2</sub>	2	O <sub>2</sub>	1.207 <sup>a</sup>	117.2	1554.7 <sup>d</sup>
O <sub>2</sub> ( <sup>1</sup> Δ)	2	O <sub>2</sub>	1.216 <sup>e</sup>	94.7 <sup>f</sup>	1483.5 <sup>g</sup>
O <sub>2</sub> <sup>-</sup>	1.5	KO <sub>2</sub>	1.28		1145 <sup>h</sup>
O <sub>2</sub> <sup>2-</sup>	1	Na <sub>2</sub> O <sub>2</sub>	1.49 <sup>i</sup>	48.8	842 <sup>j</sup>

<sup>a</sup> J. C. Abrahams, *Q. Rev., Chem. Soc.*, **10**, 407 (1956). <sup>b</sup> Reference 23. <sup>c</sup> J. Shamir, J. Beneboym, and H. H. Classen, *J. Am. Chem. Soc.*, **90**, 6223 (1968). <sup>d</sup> Reference 23. <sup>e</sup> M. Kasha and A. U. Khan, *Ann. N.Y. Acad. Sci.*, **171**, 5 (1970). <sup>f</sup> Calculated from the data in footnote d. <sup>g</sup> L. Herzberg and G. Herzberg, *Astrophys. J.*, **105**, 353 (1947). <sup>h</sup> J. A. Creighton and E. R. Lippencott, *J. Chem. Phys.*, **40**, 1779 (1964). <sup>i</sup> S. N. Foner and R. L. Hudson, *J. Chem. Phys.*, **36**, 2676 (1962). <sup>j</sup> J. C. Evans, *J. Chem. Soc. D*, 682 (1969).

be attributed to the rather small difference in bond energies between HO<sub>2</sub>· and H<sub>2</sub>O<sub>2</sub>



compared with the energetically favorable formation of the O-H bond, as can be seen by a comparison of the O-O bond energies (kcal/mol):

O <sub>2</sub> <sup>23</sup>	117.2
HO <sub>2</sub> · <sup>22</sup>	55.5
H <sub>2</sub> O <sub>2</sub> <sup>22</sup>	34.3

#### IV. Nature of Bound Dioxygen

In 1936, Pauling and Coryell<sup>24</sup> published their now classic paper on the magnetic properties of oxyhemoglobin. In this paper they noted that "the oxygen molecule undergoes a profound change in electronic structure on combination with hemoglobin". Since that time, the manner in which dioxygen is bound in metal complexes has proven a matter of considerable interest and controversy.

TABLE II. Properties of Some Metal-Dioxygen Complexes<sup>a</sup>

type of complex	M:O	structure	example	$\nu_{O-O}$ , $\text{cm}^{-1}$
superOxide-like	1:1		Co(bzacen)(py)(O <sub>2</sub> ) Fe(TpivPP)(1-Melm)(O <sub>2</sub> ) Cr(TPP)(py)(O <sub>2</sub> )	1128 <sup>b</sup> 1159 <sup>c</sup> 1142 <sup>d</sup> range 1130-1195
la				
lb			[Co <sub>2</sub> (NH <sub>3</sub> ) <sub>10</sub> (O <sub>2</sub> )] <sup>5+</sup> [Co <sub>2</sub> (CN) <sub>10</sub> (O <sub>2</sub> )] <sup>5-</sup>	1122 <sup>e</sup> 1104 <sup>e</sup> range 1075-1122
peroxide-like				
IIa	1:1		Ir(CO)(PPh <sub>3</sub> ) <sub>2</sub> (Cl)(O <sub>2</sub> ) Ti(OEP)(O <sub>2</sub> ) [Co <sub>2</sub> (CN) <sub>4</sub> (PMe <sub>2</sub> Ph) <sub>5</sub> (O <sub>2</sub> )]	875 <sup>f</sup> 898 <sup>g</sup> 881 <sup>h</sup> range 800-932
IIb	2:1		[Co(NH <sub>3</sub> ) <sub>10</sub> (O <sub>2</sub> )] <sup>+</sup> [Co <sub>2</sub> (CN) <sub>10</sub> (O <sub>2</sub> )] <sup>6-</sup>	808 <sup>i</sup> ... range 790-884
ionic dioxygen complexes			K <sup>+</sup> O <sub>2</sub> <sup>-</sup> 2Na <sup>+</sup> , O <sub>2</sub> <sup>2-</sup>	1145 <sup>j</sup> 842 <sup>k</sup>

<sup>a</sup> The values  $\nu_{O-O}$  are for the compounds listed and values for the range of  $\nu_{O-O}$  were taken in part from the values given in Table III in ref 15. In addition, the classification scheme used is identical with that given by Vaska. <sup>b</sup> Reference 35. <sup>c</sup> Reference 145. <sup>d</sup> K. Dey, *Z. Anorg. Allg. Chem.*, **366**, 209 (1970). <sup>e</sup> Reference 257. <sup>f</sup> Reference 1. <sup>g</sup> Reference 396. <sup>h</sup> J. Halpern, B. L. Goodall, G. P. Khare, H. S. Lim, and J. U. Pluth, *J. Am. Chem. Soc.*, **97**, 2301 ff (1975). <sup>i</sup> Reference 225. <sup>j</sup> J. L. Hoard in "Structural Chemistry and Molecular Biology", A. Rich and N. Davidson, Eds., Freeman and Co., San Francisco, 1968, p 573. <sup>k</sup> F. J. Blunt, P. J. Hendra, and J. R. Machkenzie, *J. Chem. Soc., Chem. Commun.*, 278 (1969).

This problem arises because the ligation of dioxygen to a metal complex differs from the ligation of a simple neutral or anionic species, such as ammonia or the chloride anion, to a metal center. The addition of molecular oxygen to a metal complex (eq 1) could involve a formal oxidation of the metal center with a concomitant reduction of the coordinated dioxygen. This arises from two factors: (1) that adduct formation between molecular oxygen and metal complexes is only observed for complexes containing metals in a reduced oxidation state; and (2) that there are readily accessible reduced oxidation states for the dioxygen species, i.e., O<sub>2</sub><sup>-</sup> and O<sub>2</sub><sup>2-</sup>. Thus, depending on the stoichiometry of the oxygenation reaction and the nature of the metal, it is possible to envision the transfer of none, one, or two electrons from the metal to the coordinated dioxygen moiety.

A comparison of the O-O stretching frequencies, obtained from metal-dioxygen complexes (Table II), with those observed for the compounds containing ionic superoxide or peroxide (Table I), shows that the metal-dioxygen complexes have O-O stretching frequencies similar to those obtained from compounds containing ionic superoxide or peroxide, suggesting a substantial transfer of electron density from the metal center to the coordinated dioxygen. That such a transfer of electron density is required becomes apparent if one considers, for example, the thermodynamics involved in the bonding of O<sub>2</sub> to deoxymyoglobin. To be consistent with the observed diamagnetism of oxymyoglobin and oxyhemoglobin,<sup>24</sup> formation of a strictly neutral Fe(II)-(O<sub>2</sub>) bond would have to involve O<sub>2</sub> coordinated in a singlet form. Since the lowest lying singlet state of O<sub>2</sub> has an energy of 22.53 kcal/mol above the ground state, and since  $\Delta H$  for dioxygen bonding to myoglobin has been measured as  $\sim$  15 kcal/mol,<sup>25</sup> this would require an unrealistic value for the Fe(II)-(O<sub>2</sub>) bond energy of approximately 38 kcal/mol. Thus the coordination of dioxygen to a metal center involves some electron delocalization from the metal to the dioxygen and, on the basis of collective experimental evidence, the coordinated dioxygen can be viewed as resembling either a coordinated superoxide or peroxide anion.

Before continuing further, we hasten to inject a word of caution. Although there exists a delocalization of electron density from the metal onto the dioxygen, and although it is often both useful and convenient to view the coordinated dioxygen as being either *superoxo-like* or *peroxo-like*, there may not be 1:1 correspondence between the formal valency of the coordinated

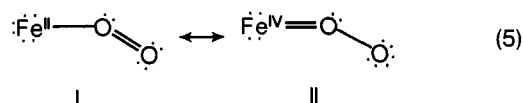
dioxygen, as assigned from a classical definition of oxidation states,<sup>26</sup> and the oxidation state that would be inferred from the O-O stretching frequency. The problem of assigning numerical oxidation states to metal-dioxygen complexes has been discussed in a recent publication.<sup>27</sup>

Although a more complete description of the bonding of dioxygen to specific metal complexes will be covered in the appropriate section, a brief discussion of dioxygen bonding for the classes of compounds listed in Table II will be presented here.

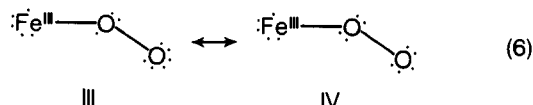
### 1. Type Ia

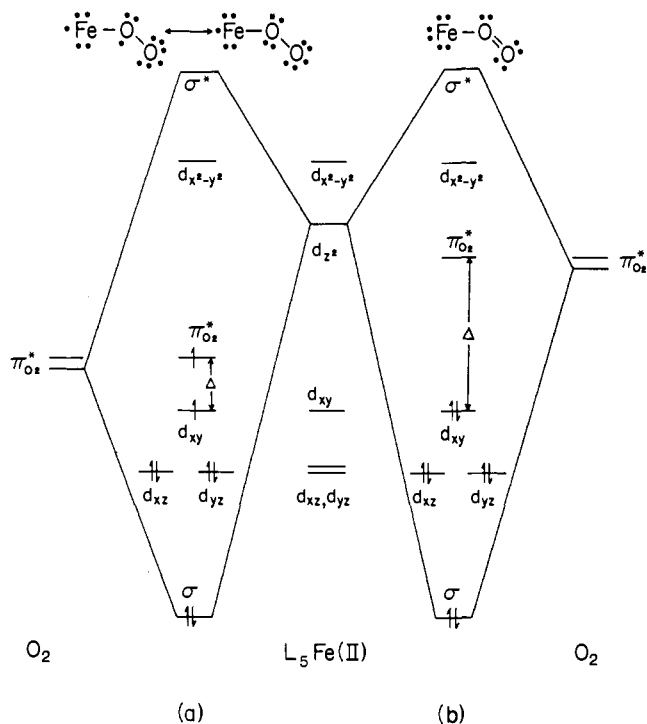
It has long been believed that the bonding of dioxygen in oxyhemoglobin and oxymyoglobin is of type Ia, and recently reported values for  $\nu_{O-O}$  (1103  $\text{cm}^{-1}$  for MbO<sub>2</sub><sup>28</sup> and 1107  $\text{cm}^{-1}$  for HbO<sub>2</sub><sup>29</sup>) as well as single-crystal X-ray structural studies of model compounds<sup>30</sup> make this almost a certainty. Synthetic type Ia complexes have been prepared from the reaction of molecular oxygen with metal complexes containing Cr(II), Fe(II), and Co(II).

In terms of simple valence bond theory, bonding in these complexes has been described in two ways. (1) The first approach, first proposed by Pauling<sup>24,31</sup> to explain the diamagnetism of HbO<sub>2</sub>, assumes an even number of electrons on the coordinated dioxygen and is represented as a resonance hybrid of the structures I and II:



It should be noted that, following the conventional method of assigning oxidation states, the canonical forms I and II have valencies corresponding to M<sup>II</sup>(O<sub>2</sub>) and M<sup>IV</sup>(O<sub>2</sub><sup>2-</sup>) respectively. (2) The second approach, proposed by Weiss<sup>32</sup> for the bonding of O<sub>2</sub> in HbO<sub>2</sub>, assumes an odd number of electrons on the coordinated dioxygen and is represented by the structures III and IV. For either of these two structures, the metal is in a +III oxidation state with the coordinated O<sub>2</sub> being formally O<sub>2</sub><sup>-</sup>. For this





**Figure 4.** A qualitative MO scheme for the bonding in iron-dioxygen complexes, showing both  $\sigma$  and  $\pi$  interactions between iron and coordinated  $O_2$ . This scheme is analogous to the  $Fe^I(O_2)-Fe^V(O_2^{2-})$  valence bond resonance hybrid when  $\Delta >$  pairing energy.

bonding model, the unpaired spins on  $Fe(III)$  and  $O_2^-$  are reputedly coupled, thus allowing for the observed diamagnetism of the  $FeO_2$  system.

Other bonding approaches are, of course, possible. For example, Figure 4 shows a simplified molecular orbital scheme for the  $Fe-O_2$  bond. From this scheme, two possible ground-state electronic configurations are possible: when the energy separation,  $\Delta$ , is greater than the electron-pairing energy, the spin-paired electronic configuration  $(\sigma)^2(yz)^2(d_{xz})^2(d_{yz})^2$  which is equivalent to the  $Fe^{II}(O_2) \leftrightarrow Fe^V(O_2^{2-})$  resonance pair suggested by Pauling, is obtained, whereas for  $\Delta$  smaller than the pairing energy, the electronic configuration  $(\sigma)^2(yz)^2d_{xz}^2(d_{yz})^1(\pi^*)^1$ , having two unpaired electrons, is obtained. This configuration can be considered similar to, but not equivalent to, the  $Fe^{III}(O_2^-)$  valence bond pair III and IV.<sup>33</sup>

Although further, and more sophisticated,<sup>33b</sup> bonding treatments can be proposed, and indeed may be required for the fullest understanding of a  $1a$   $M-O_2$  linkage, the fundamental question of whether or not the ground-state electronic configuration contains an unpaired electron located on the coordinated dioxygen moiety still persists. As we will discuss below, whereas this question has been answered for the cobalt case, the nature of the iron and chromium dioxygen bond remains in question.

In contrast to the  $Fe-O_2$  and  $Cr-O_2$  cases, the bonding picture for dioxygen adducts of  $Co(II)$  complexes is relative clear. Oxygen has been observed to form  $1a$  dioxygen adducts with a large number of  $Co(II)$  complexes, with the most common examples being the five-coordinate Schiff base complexes,  $Co^{II}(SB)(B)$ , where  $B$  represents a neutral donor ligand, and porphyrinocobalt(II) complexes,  $Co^{II}(Por)(B)$ . Magnetic susceptibility measurements on the cobalt-dioxygen adducts formed from these low-spin  $d^7$   $Co(II)$  complexes show<sup>34</sup> the presence of only one unpaired electron. On the basis of frozen solution EPR spectra,<sup>35</sup> it has been concluded that the majority of the unpaired electron spin density ( $>80\%$ ) resides on the dioxygen. Further EPR studies<sup>36</sup> employing  $^{17}O$ -labeled  $O_2$  have confirmed this conclusion, finding the electron spin density on the coordinated  $O_2$  to be close to  $100\%$ . On this basis, the unpaired electron clearly resides on the dioxygen moiety and the complex

is properly represented as  $Co^{III}(O_2^-)$ . These experimental results agree with recent molecular orbital calculations<sup>37</sup> that have been carried out on some cobalt Schiff base dioxygen complexes. These calculations show (1) bonding between  $Co$  and  $O_2$  arises primarily from the overlap of a dioxygen  $\pi_{O_2}^*$  orbital with the  $d_{z^2}$  orbital of cobalt; (2) there is negligible  $Co-O_2$   $\pi$ -overlap; and (3) the unpaired electron resides in the  $\pi_{O_2}^*$  orbital.

Unfortunately, the situation is not as clear for chromium- and iron- $O_2$  complexes. Experimental evidence has been collected on iron-dioxygen systems that has been interpreted in terms of an iron-dioxygen bond in which there appears to be a transfer of an electron from the  $Fe(II)$  center to the dioxygen to form an  $Fe-O_2$  bond that can be approximated by the  $Fe^{III}(O_2^-)$  formalism. This evidence includes (1) the infrared stretching frequencies of the coordinated dioxygen;<sup>28,29</sup> (2) the similarity between the optical spectra of oxyhemoglobin and alkaline methemoglobin;<sup>32,38</sup> (3) the position of certain peaks in the resonance Raman spectrum of oxyhemoglobin that are characteristic of an iron(III) heme;<sup>39</sup> (4) the large quadrupole splittings observed in the  $^{57}Fe$  Mössbauer resonance spectrum of oxyhemoglobin;<sup>40</sup> (5) the tendency of certain tetraphenylporphyrinatoiron(II) model systems to undergo oxygenation only in polar solvents;<sup>41</sup> (6) the release of free superoxide ( $O_2^-$ ) from the interaction of oxyhemoglobin with certain anions (e.g.,  $N_3^-$ );<sup>42</sup> and (7) the recent measurements of the magnetic susceptibility of oxyhemoglobin that have discovered a residual paramagnetism at low temperature indicative of a singlet-triplet equilibrium.<sup>43</sup>

Despite the apparent strength of the evidence in favor of describing the system as a superoxide adduct, in which an unpaired electron resides on both the iron(III) and coordinated superoxide moieties, several workers<sup>44,45</sup> have recently pointed out that most of the experimental data can also be explained in terms of bonding models in which the electrons are totally paired. This interpretation, which is based on theoretical calculations, accounts for the experimental results in terms of a delocalization of paired electron density from the iron to the coordinated dioxygen and suggests a bonding scheme which is thus similar to, but not identical with, the  $Fe(II) \leftrightarrow Fe(IV)$  formalism proposed by Pauling. The only data that are not consistent with this description, and which provide ineluctable evidence for an  $Fe^{III}(O_2^-)$  formalism, are the magnetic susceptibility measurements on oxyhemoglobin of Cerdonio et al.<sup>43</sup> These workers have observed a temperature-dependent magnetic susceptibility between 25 and 250 K indicative of two antiferromagnetically coupled  $S = 1/2$  systems having a singlet-triplet energy separation of  $|2J| = 146$   $cm^{-1}$ . This work has, however, been challenged recently by Pauling<sup>46</sup> who feels that the magnetic susceptibility measured by Cerdonio et al. may have arisen owing to experimental artifacts. At the moment the matter awaits further investigation.

The addition of  $O_2$  to low-spin,  $d^4$   $Cr(II)$  porphyrin complexes<sup>47</sup> of the type  $Cr^{II}(Por)(B)$ , where  $B$  represents a donor ligand such as pyridine, represents another example of type  $1a$  complexes ( $O-O$  stretching frequency for  $Cr(TPP)(py)(O_2)$  is found at  $1142$   $cm^{-1}$ ). The resulting dioxygen complexes, which have been shown to have two unpaired electrons, can be treated in a manner similar to that given for the dioxygen adducts with  $Fe(II)$ . Thus the dioxygen complexes can be written in terms of either a  $Cr(II) \leftrightarrow Cr(IV)$  or a  $Cr(III)$  valency depending on whether we have an even or odd-oxygen electronic configuration.<sup>48</sup> As with the iron-dioxygen complexes the matter has yet to be resolved.

## 2. Type $1a$

A large number of type  $1a$  metal complexes have been prepared, and a review of type  $1a$  complexes containing group 8 metals is available.<sup>8</sup> Although complexes of this type arising from the addition of  $O_2$  to low-valent, coordinately unsaturated

organometallic complexes have recently undergone a great deal of investigation, numerous examples of Ia complexes containing the early transition metals, e.g.,  $\text{Cr}(\text{O}_2)_4^{3-}$ , have been recognized for many years.<sup>3</sup> Among the salient differences between this type of bonding and the bonding observed in Ia complexes are the coordination geometry, with the dioxygen being bound to the metal center in a symmetric, triangular fashion, similar to that proposed by Griffith<sup>49</sup> for the bonding of  $\text{O}_2$  in oxyhemoglobin, and the  $\nu_{\text{O-O}}$  values, which are similar to those observed for free peroxide ion.

The only synthetic oxygen carriers of biological interest in which this type of bonding has been implicated are the porphyrinatomanganese-dioxygen complexes,  $\text{Mn}(\text{Por})(\text{O}_2)$ , which arise from the reaction of  $\text{O}_2$  with  $\text{Mn}^{\text{II}}(\text{Por})(\text{B})$ , in noncoordinating organic solvents at low temperature (see section IX). Although neither the O-O stretching frequencies nor single crystal X-ray structures have been determined for these complexes, the bonding of  $\text{O}_2$  is believed to occur in a Griffith geometry on the basis of EPR evidence and the chemical behavior of the complexes.

There exist four other metalloporphyrin complexes which have the dioxygen bond in a symmetrically triangular fashion. These are the complexes  $\text{Ti}(\text{MOEP})(\text{O}_2)$ ,<sup>50</sup>  $\text{Ti}(\text{TPP})(\text{O}_2)$ ,<sup>50</sup>  $\text{Ti}(\text{OEP})(\text{O}_2)$ ,<sup>50,51</sup> and  $\text{Mo}(\text{T}(\text{p-CH}_3)\text{PP})(\text{O}_2)_2$ .<sup>52</sup> The complexes are synthesized by the reactions of their corresponding titanyl and molybdenyl porphyrin complexes with organic peroxides. The titanium-porphyrin complex,  $\text{Ti}(\text{OEP})(\text{O}_2)$ , has in the solid state the two oxygen atoms eclipsing two of the nitrogens of the porphyrin moiety with an O-O bond length of 1.47 (3) Å. In solution there is rapid equilibration between the two eclipsing positions for all three of the titanium-porphyrin-dioxygen complexes. The complexes all exhibit strong infrared O-O stretches. The values obtained were 898, 895, and 855  $\text{cm}^{-1}$  for  $\text{Ti}(\text{OEP})(\text{O}_2)$ ,  $\text{Ti}(\text{TPP})(\text{O}_2)$ , and  $\text{Ti}(\text{MOEP})(\text{O}_2)$ , respectively. The molybdenum-porphyrin complex,  $\text{Mo}(\text{T}(\text{p-CH}_3)\text{PP})(\text{O}_2)_2$ , also has the dioxygens eclipsing the porphyrin nitrogens, with a bond length of 1.399(6) Å. The IR spectrum of the complex displays an intense band at 964  $\text{cm}^{-1}$ .

### 3. Type Ib

At the present time the only complexes of type Ib characterized are those that contain cobalt. These green complexes are readily prepared by the one-electron oxidation of the  $\mu$ -peroxo species. The chemistry of these complexes have been extensively reviewed.<sup>2,5-7,16,17</sup>

The cobalt complexes are paramagnetic with  $\mu \approx 1.6$  BM. Their room-temperature EPR spectra are well-defined isotropic spectra consisting of 15 lines, with  $A_{\text{iso}} \approx 10$  G. This is the expected spectrum if the two cobalt nuclei were magnetically equivalent with the majority (>90%)<sup>54</sup> of the unpaired spin density residing on the dioxygen bridge. Experiments employing  $^{17}\text{O}$  are consistent with these EPR results.

The Ib complexes of cobalt can be looked at as having two low-spin Co(III) metal centers containing a bridging  $\text{O}_2^-$ . Bond lengths for these complexes range between 1.24 and 1.35 Å, with an average value of 1.31 Å. In agreement with these bond lengths are the  $\nu_{\text{O-O}}$  values of 1075–1195  $\text{cm}^{-1}$ , with an average of 1125  $\text{cm}^{-1}$ . Both values support the formalism of  $\text{Co}(\text{III})-\text{O}_2^--\text{Co}(\text{III})$ .

### 4. Type IIb

The bonding of dioxygen in IIb complexes is believed to be similar to that of the natural systems of hemerythrin and hemocyanin. Bonding of dioxygen in these natural systems involves two metal centers with the bound dioxygen being in a reduced "peroxide-like" state with a concomitant one-electron oxidation of both metal centers.

With the exceptions of some rhodium<sup>55</sup> and molybdenum<sup>56</sup>

complexes, which are not strictly type IIb complexes since there is multiple  $\text{M}-(\text{O}_2)-\text{M}$  bridging and the coordination number of oxygen is higher than two, the predominance of synthetic type IIb complexes contain cobalt metal centers.

The literature dealing with dimeric (IIb) cobalt complexes is vast and has been reviewed several times.<sup>2,5-7,16,17</sup> The earliest known synthetic dioxygen complex is probably  $[(\text{NH}_3)_5-\text{Co}-\text{O}_2-\text{Co}(\text{NH}_3)_5]^{4+}$ , characterized by Werner and Mylius.<sup>57</sup> The dimeric peroxo complex is often more stable than the monomeric complex and will generally form unless its formation is inhibited. This inhibition can be accomplished sterically by having bulky ligands and/or kinetically by the use of low temperatures.

The cobalt dimers are readily formed by the addition of oxygen to solutions of the parent cobalt compounds. In the case of some cobalt-Schiff base complexes, the dimeric species can be formed in the solid state. These complexes are diamagnetic with the oxygen being viewed as "peroxide like" with a concomitant oxidation of the metal centers to low-spin  $d^6$  Co(III). The parent cobalt compounds vary from classical Werner-type complexes,  $[\text{Co}^{\text{II}}(\text{CN})_5]^{3-}$ , to Schiff base,  $\text{Co}^{\text{II}}(\text{salen})(\text{py})$ , to cobalt-porphyrin complexes,  $\text{Co}^{\text{II}}(\text{PPIXDME})(\text{py})$ .

The X-ray and infrared data on the O-O bond lengths and  $\nu_{\text{O-O}}$  of IIb complexes are consistent with the bound dioxygen being regarded as "peroxo-like". The O-O bond lengths vary between 1.31 and 1.49 with the average being 1.44 Å. The  $\nu_{\text{O-O}}$  span a range of 790–844  $\text{cm}^{-1}$  with an average value of 810  $\text{cm}^{-1}$ .

Recently La Mar<sup>53</sup> has reported on the existence of a  $\mu$ -peroxo iron porphyrin. From NMR and magnetic data La Mar postulates that the intermediate observed is dimeric with a bridging dioxygen. From the magnetic data he believes the best formalism is  $\text{PorFe}^{\text{III}}-\text{O}_2-\text{Fe}^{\text{III}}\text{Por}$  (where Por is  $\text{T}(\text{m-CH}_3)\text{PP}$  or OEP) with the dioxygen being peroxo-like.

## V. Natural Oxygen Carriers

Biological oxygen carriers are of three main types: the heme-containing proteins such as myoglobin (Mb) and hemoglobin (Hb); the hemerythrin; and the hemocyanins.<sup>58</sup> These complexes utilize either iron or copper to bind the dioxygen group. A vanadium-containing protein, haemovanadin, capable of reversibly binding dioxygen, has been found in the 1.5 to 2 N  $\text{H}_2\text{SO}_4$  solution found in the vacuoles of the blood cells of certain ascidians (tunicates). It is felt that the protein may be involved in oxygen transport. Little is known, however, about the nature of the vanadium complex. The partial pressure necessary to oxygenate one-half of the available sites, the  $P_{1/2}\text{O}_2$ , for the cells has been found to be about 2 Torr.<sup>59</sup> A summary of some of the characteristics of these biological oxygen carriers is given in Table III.

### A. Heme-Containing Proteins, Hb and Mb

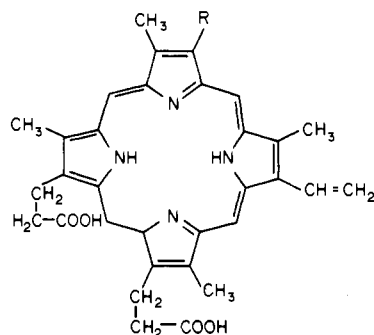
Hemoglobin and myoglobin<sup>60</sup> combine reversibly with dioxygen in the blood and tissues of numerous vertebrates and invertebrates by virtue of a heme (iron<sup>II</sup> porphyrin) prosthetic group. The proteins bind one  $\text{O}_2$  for each ferrous ion. For this class of respiratory pigments, the iron(II) is chelated to the four core nitrogen atoms of the protoporphyrin IX dianion (see Figure 5). The only exceptions are the oxygen-carrying hemoproteins, the chlorocruorins, found in some species of polychete worms of the phylum Annelida. Rather than having a vinyl group at position 2 on the porphyrin ring, as found for protoporphyrin IX, chlorocruoroporphyrin or Spirographis porphyrin has a formyl group (Figure 5).

In the heme proteins of vertebrates the porphyrin is embedded in a polypeptide chain having a molecular weight of 16 000 to 18 000. Myoglobins are monomeric, being composed of only one of these protein chains, while most vertebrate hemoglobins are tetrameric containing four such polypeptide subunits held

TABLE III. Properties of Naturally Occurring Oxygen Carriers

	hemoproteins			
	Hb	Mb	hemerythrin	hemocyanin
metal	Fe	Fe	Fe	Cu
oxidation state of deoxygenated form	II	II	II	I
metal:dioxygen ratio	1Fe:1O <sub>2</sub>	1Fe:1O <sub>2</sub>	2Fe:1O <sub>2</sub>	2Cu:1O <sub>2</sub>
magnetic-electronic properties				
deoxy	h.s., S = 2	h.s., S = 2	h.s., S = 2	d <sup>10</sup> , S = 0
oxy	diamagnetic	diamagnetic	$\mu_{\text{eff}}$ T-dependent diamagnetic ground state	diamagnetic
$p_{1/2}^{20^\circ}$ , Torr	2.5 <sup>a</sup>	0.65 <sup>b</sup>	4 <sup>c</sup>	4.3 <sup>d</sup>
subunit-subunit interaction	yes	no	slight	yes
major function	transport	storage	storage	transport
no. of subunits	4	1	8	variable

<sup>a</sup>  $p_{1/2}$  is the partial pressure of O<sub>2</sub> in Torr at which 50% of the sites are oxygenated. Data for human Hb, pH 8.0, in 0.15 M phosphate buffer taken from Figure 7 of E. Antonini, J. Wyman, M. Brunori, C. Fronticelli, E. Bucci, and A. Rossi-Fanelli, *J. Biol. Chem.*, **240**, 1096 (1965). <sup>b</sup> For human Mb, pH 8.0: A. Rossi-Fanelli and E. Antonini, *Arch. Biochem. Biophys.*, **77**, 478 (1958). <sup>c</sup> Taken from data on hemerythrin from spinunculid *S. nudus*, pH 7.0, 0.15 potassium phosphate buffer: G. Bates, M. Brunori, G. Amiconi, E. Antonini, and J. Wyman, *Biochemistry*, **7**, 3016 (1968). <sup>d</sup> At 20.6 °C, pH 8.2 for hemocyanin from *Levantini hiersolima*; Z. Er-el, N. Shaklai, and E. Daniel, *J. Mol. Biol.*, **64**, 341 (1972).



R = -CH = CH<sub>2</sub> : Protoporphyrin IX

R = -CHO : Chlorocruoroporphyrin

Figure 5. Structures of natural and synthetic porphyrins.

together in a tetrahedral array. Each molecule of normal adult human hemoglobin contains two subunits known as the  $\alpha$  chains and two subunits called the  $\beta$  chains. Although the primary structures of the various myoglobins and hemoglobin subunits show distinct variations, the tertiary structures are in general quite similar. The structure of the  $\beta$  subunit of Hb as deduced from X-ray data is shown in Figure 6.<sup>61</sup> The protoheme prosthetic group lies in a crevice between the E and F helices of the polypeptide, being held in place by nonbinding interactions with the protein. The single covalent attachment of the heme to the protein occurs by coordination of the heme iron to the imidazole nitrogen of the F8, or so-called "proximal" histidine residue.

TABLE IV. O<sub>2</sub> Affinities for Monomeric Hemoproteins

protein	source	$P_{1/2}^{O_2}$ , Torr <sup>a</sup>
Hb, $\alpha$ chain	human	0.46 <sup>b</sup>
Hb, $\beta$ chain	human	0.40 <sup>b</sup>
Mb	whale	0.51 <sup>c</sup>
	horse	0.70, <sup>b</sup> 0.65 <sup>d</sup>
	human Mb I, II	0.65 <sup>e,f</sup>
	human reconst.	0.72 <sup>e</sup>
	<i>Aplysia</i>	2.7 <sup>b</sup>

<sup>a</sup> At 20 °C and pH 7–7.4, unless otherwise noted. <sup>b</sup> M. Brunori, R. W. Noble, E. Antonini, and J. Wyman, *J. Biol. Chem.*, **241**, 5328 (1966). <sup>c</sup> From Table 9.1, ref 60a, p 221. <sup>d</sup> H. Theorell, *Biochem. Z.*, **268**, 46 (1934). <sup>e</sup> A. Rossi-Fanelli and E. Antonini, *Arch. Biochem. Biophys.*, **77**, 478 (1958). <sup>f</sup> Found at pH 8.

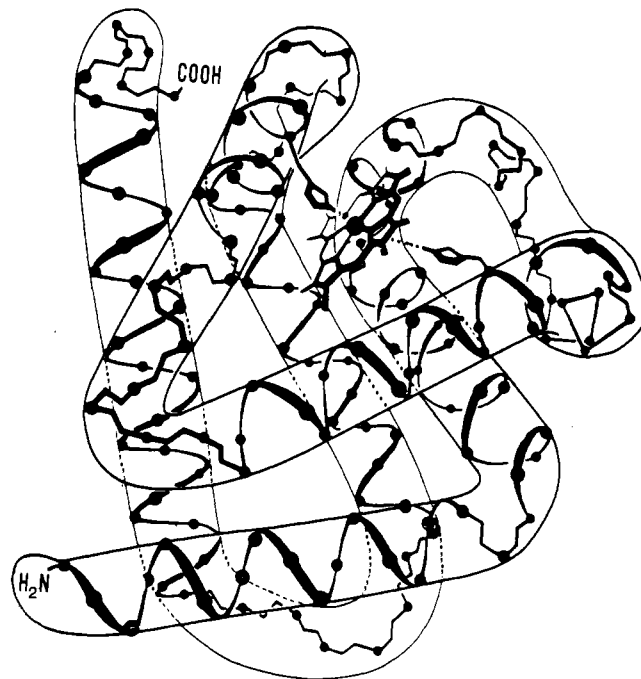


Figure 6. The structure of the  $\beta$  chain of Hb as determined from X-ray data. The helical regions are denoted A to H, beginning from the amino end. The nm-helical region bridging the helical regions are labeled AB, BC, . . . , etc. The heme prosthetic group can be seen lying between the E and F helices. Both the prosthetic group can be seen lying between the E and F helices. Both the proximal (F8) and distal (E7) histidine residues are clearly shown (from ref 61).

In the deoxygenated state the ferrous ion is found to be five-coordinate; four of the coordination sites of the Fe(II) are satisfied by the porphyrin moiety while the fifth, axial position is occupied by the imidazole group. The remaining axial position is vacant in the deoxygenated protein. In this conformation the iron has been shown to be in the high-spin,  $S = 2$ , configuration, and X-ray analysis indicates that the metal lies out of the plane of the porphyrin, toward the coordinated imidazole by several tenths of an angstrom.<sup>62,63</sup> On oxygenation, the sixth coordination sites is occupied by O<sub>2</sub> and the iron is situated in a pseudooctahedral environment. The effects of this new environment are sufficient to both stabilize a low-spin, diamagnetic ground state<sup>64</sup> for the iron-dioxygen complex and to place the iron in the mean plane of the porphyrin ring.<sup>65</sup>

The binding of O<sub>2</sub> to Mb or isolated monomeric subunits of Hb shows the behavior expected for simple 1:1 association between dioxygen and protein. The affinities of various myoglobins for O<sub>2</sub> lie within a fairly narrow range.



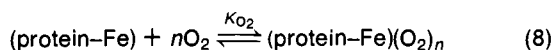
Table IV indicates  $P_{1/2}^{O_2}$  values (equal to  $1/K_{O_2}$  from eq 7) for several Mb's as well as data for oxygen binding to isolated Hb

subunits. The monomeric heme proteins obtained from mammalian sources generally yield  $P_{1/2}^{O_2}$  values in the range 0.4 to 0.7 Torr.

The equilibrium uptake of  $O_2$  by tetrameric hemoglobin turns out to be more complex than for the case of the heme-protein monomers. The affinity of a subunit in Hb to add a single molecule of  $O_2$  is apparently dependent upon the number of other subunits oxygenated in the tetramer. Typical plots of equilibrium  $O_2$  uptake data for normal human Hb and the isolated  $\alpha$  chain are shown in Figure 7.

Analysis of such data reveals a number of salient features.<sup>60</sup>

(1) The data for  $O_2$  uptake by either the isolated Hb subunits or Mb show behavior typical of a straightforward 1:1 association between the heme and  $O_2$ :



Such behavior is precisely described by the Hill equation<sup>66</sup> (eq 9) with  $n = 1$ .

$$Y = \frac{K_{O_2} P_{O_2}}{1 + K_{O_2} P_{O_2}} \quad \text{or} \quad \frac{Y}{1 - Y} = K_{O_2} P_{O_2} \quad (9)$$

$Y$  = fraction of sites oxygenated

$P_{O_2}$  = pressure of  $O_2$

Thus the total oxygen curve in Figure 7 can be reconstructed for the simple monomeric heme proteins from the  $K_{O_2}$  which is equal to  $(P_{1/2}^{O_2})^{-1}$ .

(2) In contrast to the hyperbolic curve obtained from the data for the monomeric hemes, the data obtained for Hb shows "sigmoidal" behavior, indicative of interaction between the subunits. While of no physical significance, the data obtained from Hb between ca. 10 and 90% oxygenation can be adequately, albeit empirically, fitted to the Hill equation to give values of  $n \sim 3$  for normal human Hb.

A careful analysis of the binding curve (Figure 7) for Hb at low partial pressure of  $O_2$ , where substantially less than one-fourth of the sites are oxygenated, shows that the equilibrium constant for binding the first  $O_2$  to the fully deoxygenated complex is about a factor of 100 less than the equilibrium constant for binding  $O_2$  to an isolated subunit. Thus the association of the monomeric units to form the Hb tetramer results in a large decrease in the affinity of the protein toward dioxygen, without changing the nature of the axial imidazole ligand bound to the heme.

(3) Although fully deoxy-Hb has a markedly reduced affinity for  $O_2$ , addition of  $O_2$  to a Hb sample which is largely (>90%) oxygenated proceeds with an affinity that is approximately equal to the affinity observed for the isolated subunits. Thus the effect of adding successive molecules of  $O_2$  to Hb relaxes the inhibition toward  $O_2$  binding that arises from the aggregation of the subunits to form the tetramer.

The dependence of the  $O_2$  affinity of Hb on the degree of oxygenation is known as the homotropic<sup>67</sup> or heme-heme interaction. From X-ray data and molecular models, Perutz<sup>68</sup> has proposed a stereochemical mechanism for the cooperative, heme-heme interaction based on the earlier two-state allosteric model of Monod<sup>69</sup> and Rubin and Changeux.<sup>70</sup> (For recent reviews of the heme-heme interaction, see ref 60e-g.)

The basis of this model is as follows. Association of the  $\alpha$  and  $\beta$  subunits to form deoxy-Hb occurs with the formation of one of two possible quaternary structures: (1) a low-energy, or tense (T) state and (2) a high-energy, or relaxed (R) state. The two forms are present as an equilibrium mixture. With no  $O_2$  present, the T state is more stable than the R state and the Hb is thus found to be almost exclusively in the T form. The  $O_2$  affinity of Hb in the T state is much less than the  $O_2$  affinity of Hb in the R state. Thus, the initial  $O_2$  affinity of Hb is significantly lower than that observed for the individual subunits. Addition of  $O_2$  to deoxy-Hb

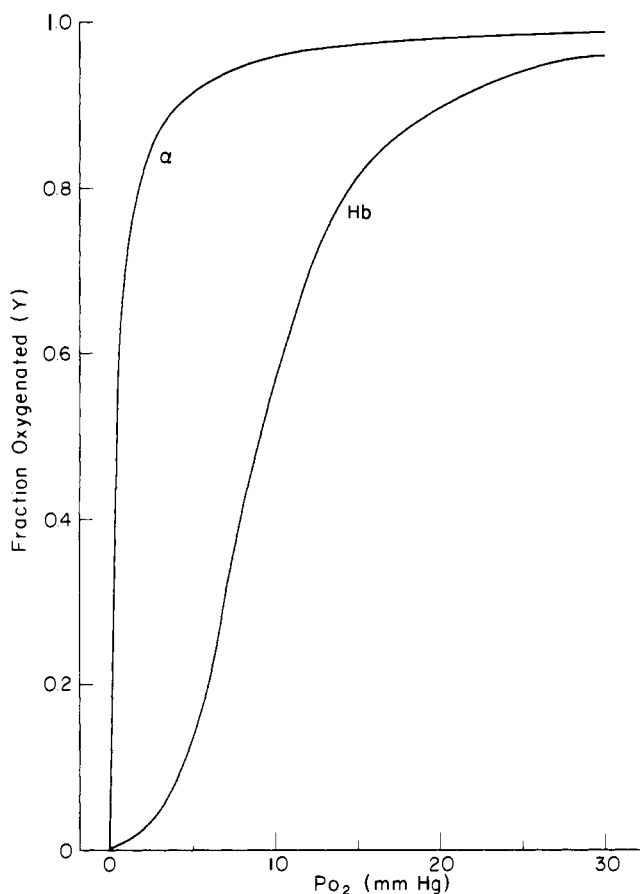
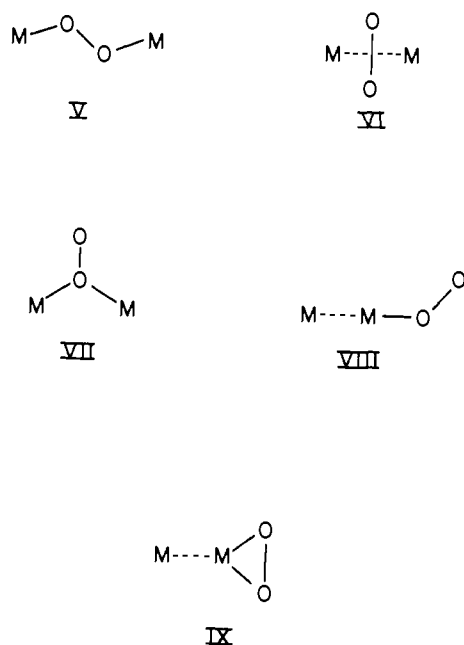


Figure 7. L. F. Ten Eyck, *Cold Spring Harbor Symp. Biol.*, **36**, 295 (1975). Fraction of sites oxygenated ( $Y$ ) vs. the partial pressure of  $O_2$  for human Hb and the isolated  $\alpha$  chain at  $\sim 20^\circ C$ . Data for Hb taken from ref 50a, pp 162.

changes the equilibrium between the T and R states. As Hb picks up oxygen, the equilibrium shifts toward the R state. Thus the more  $O_2$  molecules bound to Hb, the higher the probability that Hb will be in the R state. As the oxygen affinity of the R state is approximately the same as that of an isolated subunit, the  $O_2$  affinity of almost completely oxygenated Hb should be approximately equal to that of the isolated chains.

The intimate mechanism through which the heme-heme interaction occurs is still a matter of some controversy. Perutz (following the suggestions of Hoard<sup>71a</sup> and Williams<sup>71b,c</sup>), using both experimental results from studies on hemoglobin combined with studies on model heme systems, has postulated a "trigger" mechanism for the cooperative interaction. On oxygenation, the heme iron that is originally above the porphyrin plane undergoes a spin change and moves into the mean plane of the porphyrin ring. This is accompanied by the movement of the covalently linked proximal F8 histidine residue of the globin. The movement of this residue causes a change in the structure of the protein. It is this structural change which occurs in the binding of the dioxygen to the heme that results in the decrease in the stability of the T conformation relative to the R form and causes the observed cooperativity. However, it should be noted that other investigators<sup>72</sup> have concluded there are some shortcomings, or unresolved difficulties, with the trigger mechanism.

In addition to the effect that the bonding of a molecule of dioxygen to a heme site has on the oxygen affinity of the hemoglobin molecule it has also been observed that bonding of protons to a hemoglobin molecule affects the oxygen affinity. This heterotropic interaction,<sup>67</sup> known as the Bohr effect, can be viewed either as a change of pH in bonding a ligand to the heme site or as the change in the affinity of the heme site toward binding the ligand as a function of pH. For a discussion of the



**Figure 8.** Possible structures for the  $M_2O_2$  unit in hemerythrins and hemocyanins.  $M = Fe(III)$  for oxyhemerythrin and  $M = Cu(II)$  for oxyhemocyanin.

nature of the Bohr effect and the manner in which it is transmitted, see ref 60 and 68.

## B. Hemerythrin

Hemerythrins<sup>73,74</sup> are iron-containing, oxygen-carrying proteins found in certain species of four invertebrate phyla: sipunculids, polychaetes, priapulids, and brachiopods. Like hemocyanin (vide infra) the prosthetic group of hemerythrins does not contain a porphyrin moiety; rather the iron is bound directly to the protein side chains. In general, hemerythrin occurs as an octamer of molecular weight about 108 000; each subunit contains two iron atoms and binds one molecule of  $O_2$  per subunit.

Magnetic measurements and Mössbauer spectra show deoxyhemerythrin to contain high-spin ( $S = 2$ )  $Fe(II)$ .<sup>74</sup> Mössbauer spectra of deoxyhemerythrin from *Golfingia gouldii* indicate that the two iron(II) atoms in the subunits are in identical environments.<sup>74,75</sup> Consistent with the pale yellow color, the electronic absorption spectrum of the deoxy complex is relatively clear down to 300 nm.

The electronic spectrum of the red oxy form is quite similar to that observed for the met [ $Fe(III)$ ] species. This has led to the suggestion that the two iron centers in the oxy form are in the  $Fe(III)$  state with the  $O_2$  moiety being of the peroxide-like  $O_2^{2-}$  type. As indicated below, this interpretation is also consistent with Mössbauer data.

Mössbauer spectroscopy of oxyhemerythrin from *G. gouldii* shows the presence of two quadrupole doublets, indicating that the environments of the two iron nuclei differ.<sup>73a,74,75</sup> The isomer shifts of both doublets, which can be related to the oxidation state of the iron and the degree of covalency of the complex, are similar to the met derivatives of hemerythrin. This again suggests a formalism for the iron of  $Fe(III)$ . The manner in which dioxygen binds to the iron sites has still not been resolved. Several structures that have been suggested are shown in Figure 8.

Resonance Raman spectroscopy has been used to reinforce the assignment of a peroxide-like,  $O_2^{2-}$ , electronic state to the bound  $O_2$ .<sup>76</sup> A peak at  $844\text{ cm}^{-1}$  observed in the resonance Raman spectrum of oxyhemerythrin has been assigned to the symmetric O—O stretch and is similar to the value obtained for  $\nu_{O-O}$  for other peroxide-containing compounds. Further studies using resonance Raman spectroscopy on oxyhemerythrin made

with  $^{16}O$  labeled dioxygen have shown the two atoms of the bound  $O_2$  to be in different environments.<sup>77</sup> This would be consistent with structures VII and VIII shown in Figure 8.

Magnetic susceptibility measurements on both oxy- and methemerythrin have shown the two  $Fe(III)$  ions to be antiferromagnetically coupled.<sup>78</sup> While this is believed to occur through the  $O_2^{2-}$  for oxyhemerythrin, the coupling between the two iron centers in methemerythrin may occur through a bridging oxo anion. The magnetic, Mössbauer, and electronic absorption data obtained for methemerythrin have been interpreted as being consistent with a  $\mu$ -oxo bridge arrangement.<sup>74</sup>

Despite the large number of studies that have been performed, the manner in which the iron is bound to the protein in hemerythrin in its deoxy, oxy, and met forms remains uncertain. Several recent low-resolution X-ray crystallographic studies on the protein still leave the matter unresolved.<sup>79</sup>

As it is generally found in the main body cavity of the organism the physiological significance of hemerythrin appears to be oxygen storage. While it is in oxygen transport that the physiological significance of the homotropic interaction and Bohr effects become important, one might expect both of these effects to be absent in hemerythrin. These interactions have been observed to occur in hemerythrins to variable degrees. Hence, hemerythrin from the brachiopod *Lingula* exhibits both homotropic and heterotropic interactions; both effects are absent in hemerythrin from the sipunculid *P. agassizii*. Hemerythrin from the sipunculid *S. nudus* shows only a slight site-site interaction and no Bohr effect. The manner in which these subunit interactions are transmitted is still in the speculative stage.

## C. Hemocyanin

Hemocyanins<sup>80</sup> are nonheme copper containing proteins found only in some species of the phyla Arthropoda and Mollusca. Like hemoglobin and hemerythrin, the hemocyanin proteins consist of a number of subunits. The size of these subunits are phylum dependent: hemocyanins from arthropods have a molecular weight of about 36 700 per copper atom, while the ratio for molluscs is about 25 100. As for hemerythrins, the manner in which the metal centers are bound to the protein is not well understood, nor has the structure of the metal-dioxygen complex been well established.

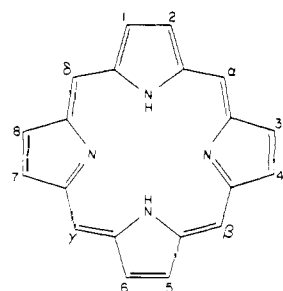
The copper in deoxyhemocyanin is present as  $Cu(I)$ . Reconstitution of the apoprotein with cuprous salts leads to regeneration of the activity of the protein. The color of the deoxygenated protein is almost colorless in keeping with the  $d^{10}$   $Cu(I)$  center. Upon oxygenation, hemocyanin has a deep blue color, having absorption maxima in the visible at  $\sim 345\text{ nm}$  ( $\epsilon/Cu \sim 500$ ). The similarity between these bands and those of known cupric proteins supports a  $Cu(II)$  center in oxyhemocyanin. These absorptions have been attributed to d-d transitions of  $Cu(II)$  in a distorted tetragonal ligand field.<sup>81</sup>

Hemocyanins absorb one  $O_2$  for every two copper atoms in the molecule. Several geometries have been proposed for the copper-dioxygen center in hemocyanins (Figure 8), which are analogous to those proposed for hemerythrin.

Resonance Raman spectroscopy of hemocyanins from both arthropods (*C. magister*) and molluscs (*B. canaliculatum*) has found the O—O vibration at  $744\text{ cm}^{-1}$  (*C. magister*) and  $749\text{ cm}^{-1}$  (*B. canaliculatum*). These frequencies suggest a description of the  $O_2$  as a peroxide-type, or  $O_2^{2-}$ , species.<sup>45</sup> This is consistent with a formal description of the copper as being in the (+II) oxidation state. The weakly paramagnetic nature of the oxyhemocyanin complex is apparently due to an exchange interaction between the two  $d^9$  centers; magnetic susceptibility measurements place a lower limit on the exchange coupling parameter ( $J$ ) of  $625\text{ cm}^{-1}$  for the antiferromagnetically coupled  $Cu(II)$  dimers.<sup>83</sup>

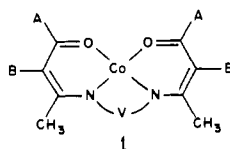
From a recent resonance Raman study on oxyhemocyanin



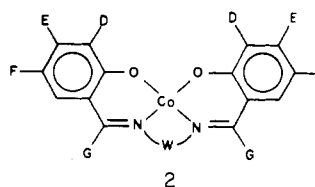


Porphyrin <sup>a</sup>	1	2	3	4	5	6	7	8	meso <sup>b</sup>
Protoporphyrin IX	Me	V	Me	V	Me	P	P	Me	H
Mesoporphyrin IX	Me	Et	Me	Et	Mz	P	P	Me	H
Deuteroporphyrin IX	Me	H	Mz	H	Me	P	P	Mz	H
Pyrroporphyrin XV	Me	Et	Me	Et	Me	H	P	Mz	H
meso-Tetraphenylporphyrin	H	H	H	H	H	H	H	H	Ph
Octaethylporphyrin	Et	Et	Et	Et	Et	Et	Et	Et	H
2,4-Diacetyldetero-porphyrin IX	Me	COCH <sub>3</sub>	Mz	COCH <sub>3</sub>	Mz	P	P	Me	H

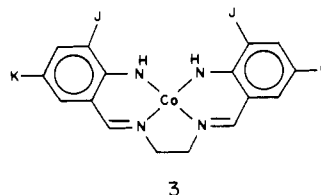
<sup>a</sup>Abbreviations: Me, methyl; V, vinyl; P, propionic acid; Et, ethyl; Ph, phenyl.  
<sup>b</sup>The  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  positions have the same substituent.



Compound	V	A	B
Co(acacen)	-(CH <sub>2</sub> ) <sub>6</sub> -	CH <sub>3</sub>	H
Co(Meacacen)	-(CH <sub>2</sub> ) <sub>2</sub> -	CH <sub>3</sub>	CH <sub>3</sub>
Co(Phacacen)	-(CH <sub>2</sub> ) <sub>2</sub> -	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
Co(benacen)	-(CH) <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub>	H
Co(Clbenacen)	-(CH <sub>2</sub> ) <sub>2</sub> -	p-ClC <sub>6</sub> H <sub>4</sub>	H
Co(Brbenacen)	-(CH <sub>2</sub> ) <sub>2</sub> -	p-BrC <sub>6</sub> H <sub>4</sub>	H
Co(Mebenacen)	-(CH <sub>2</sub> ) <sub>2</sub> -	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H
Co(Meobenacen)	-(CH <sub>2</sub> ) <sub>2</sub> -	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H
Co(bensacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub>	H
Co(Clbensacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	p-ClC <sub>6</sub> H <sub>4</sub>	H
Co(Brbensacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	p-BrC <sub>6</sub> H <sub>4</sub>	H
Co(Mebensacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H
Co(Meobensacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H
Co(sacacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	CH <sub>3</sub>	H
Co(sacacen) <sup>a</sup>	-(CH <sub>2</sub> ) <sub>2</sub> -	CH <sub>3</sub>	H
Co(sacsacpn) <sup>a</sup>	-CH <sub>2</sub> -CH-	CH <sub>3</sub>	H
Co(sacsactn)	-(CH <sub>2</sub> ) <sub>3</sub> -	CH <sub>3</sub>	H
Co(sacsacchxn)	-CH <sub>2</sub> -CH <sub>2</sub> -	CH <sub>3</sub>	H
	(CH <sub>2</sub> ) <sub>4</sub>		



Compound	W	D	E	F	G
Co(salen)	-(CH <sub>2</sub> ) <sub>2</sub> -	H	H	H	H
Co(3-MeOsalen)	-(CH <sub>2</sub> ) <sub>2</sub> -	CH <sub>3</sub> O	H	H	H
Co(4,6-Me <sub>2</sub> salen)	-(CH <sub>2</sub> ) <sub>2</sub> -	H	CH <sub>3</sub>	H	CH <sub>3</sub>
Co(Fsalen)	-(CH <sub>2</sub> ) <sub>2</sub> -	F	H	H	H
Co(napsalen)	-(CH <sub>2</sub> ) <sub>2</sub> -	H	b	H	H
Co(saloph)	-C <sub>6</sub> H <sub>4</sub> -	H	H	H	H
Co(sal(±) or (m)bn)	-CH-CH-	H	H	H	H
	CH <sub>3</sub> CH <sub>3</sub>				
Co(sal(±) or (m)dpn)	-CH-CH-	H	H	H	H
	C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>5</sub>				
Co(sal(±) or (m)chxn)	-CH-CH-	H	H	H	H
	(CH <sub>2</sub> ) <sub>4</sub>				
Co(saldpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NH-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
Co(3-MeOsaldpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NH-(CH <sub>2</sub> ) <sub>3</sub> -	CH <sub>3</sub> O	H	H	H
Co(5-MeOsaldpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NH-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	CH <sub>3</sub> O	H
Co(5-NO <sub>2</sub> saldpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NH-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	NO <sub>2</sub>	H
Co(-Mesaldpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NH-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	CH <sub>3</sub>
Co(salMedpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NCH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
Co(3-MzOsaldMedpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NCH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	CH <sub>3</sub> O	H	H	H
Co(5-MzOsaldMedpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NCH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	H	H	CH <sub>3</sub> O	H
Co(-MesalMedpt)	-(CH <sub>2</sub> ) <sub>3</sub> -NCH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	CH <sub>3</sub>
Co(sal-n-Prdpt)	-(CH <sub>2</sub> ) <sub>3</sub> -N(n-C <sub>3</sub> H <sub>7</sub> )-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
Co(sal-i-Prdpt)	-(CH <sub>2</sub> ) <sub>3</sub> -N(i-C <sub>3</sub> H <sub>7</sub> )-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
Co(salBydpt)	-(CH <sub>2</sub> ) <sub>3</sub> -N(CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> )-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
	(CH <sub>2</sub> ) <sub>3</sub> -				
Co(salPhdpt)	-(CH <sub>2</sub> ) <sub>3</sub> -N(C <sub>6</sub> H <sub>5</sub> )-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
Co(sal-p-MzOPhdpt)	-(CH <sub>2</sub> ) <sub>3</sub> -N(p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> )-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	H	H
	(CH <sub>2</sub> ) <sub>3</sub> -				
Co(5-BrsalMedapp)	-(CH <sub>2</sub> ) <sub>3</sub> -PCH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	H	H	Br	H
Co(3-MeosalMedapp)	-(CH <sub>2</sub> ) <sub>3</sub> -PCH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	CH <sub>3</sub> O	H	H	H
Co(5-Brsaldape)	-(CH <sub>2</sub> ) <sub>3</sub> -O-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	Br	H
Co(5-Claldape)	-(CH <sub>2</sub> ) <sub>3</sub> -O-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	Cl	H
Co(saltman)	-C-C-	H	H	H	H
	(CH <sub>2</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub>				
Co(salpy)	-CH <sub>2</sub> -CH(CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> N)-	H	H	H	H

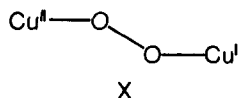


Compound	J	K
Co(amben)	H	H
Co(NO <sub>2</sub> amben)	H	NO <sub>2</sub>
Co(MeOamben)	MeO	H
Co(cyen) <sup>c</sup>	H	H

<sup>a</sup>The oxygen atoms are replaced by sulfurs. <sup>b</sup>The benzene rings are replaced by naphthalenes. <sup>c</sup>There is an ethylene bridge replacing the two protons on the nitrogens.

Figure 9. Names and structures of the porphyrins and cobalt Schiff base complexes.

using unsymmetrically labeled <sup>16</sup>O-<sup>18</sup>O, it has been suggested that the Cu<sub>2</sub>O<sub>2</sub> moiety adopts a nonplanar,  $\mu$ -dioxygen confirmation.<sup>84</sup>



VI. Synthetic O<sub>2</sub> Carriers

A. Porphyrins

Porphyrins are macrocyclic compounds that contain four pyrrole or substituted pyrrole rings joined by sp<sup>2</sup>-hybridized carbon atoms. As such, they can be viewed as being formally derived from the parent compound, porphine (Figure 5), by substitution of the hydrogen atoms at the peripheral positions of the macrocyclic ring. Although other forms of nomenclature can be used to label the positions on the porphyrin ring, the system of nomenclature used here is the same as that utilized by both Falk<sup>85</sup> and Smith<sup>86</sup> in their books on porphyrin chemistry. That is, the eight "β-pyrrole" positions are labeled 1 to 8 with the four "meso" positions labeled α, β, γ, and δ. In Figure 9 the

substitution patterns and trivial names of the porphyrin compounds discussed in this review are listed.

The porphyrins can be divided into two classes, the first class being the "natural" porphyrins that are derived either directly from, or by modification of, metalloporphyrin complexes obtained from nature, and the second class being those porphyrins which are obtained entirely via a synthetic route. Of the porphyrins listed in Figure 5, protoporphyrin IX, mesoporphyrin IX, and deuteroporphyrin IX are "natural" porphyrins being prepared from chloroporphyriniron(III), known as hemin, which is obtained from blood hemoglobin. These propionic acid chains which are common in these three porphyrins at positions 6 and 7 are often esterified to obtain the dimethyl or diethyl esters. Pyrroporphyrin XV is also a "natural" porphyrin, being obtained by chemical modification of the chlorin ring of chlorophyll.

Of the synthetic porphyrins the two most commonly studied are meso-tetraphenylporphyrin, TPPH<sub>2</sub>, and octaethylporphyrin, OEPH<sub>2</sub>. Compared with the natural porphyrins these synthetic porphyrins both have rather chemically inactive side chains and provide a symmetric square-planar environment for a metal coordinated in the porphyrin core.

For use in model studies of natural systems, octaethylpor-

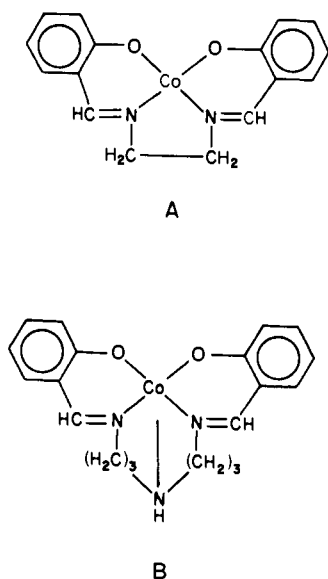
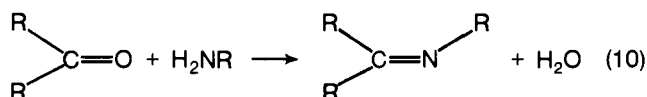


Figure 10. Type A and B Schiff base complexes studied in the solid state.

phyrinato-metal complexes represent in general a better choice than tetraphenylporphyrinato-metal complexes. Because of the ethyl substituents at positions 1–8 on OEPH<sub>2</sub>, the electronic properties of octaethylporphyrin are closer to those of the "natural" porphyrins than are those of tetraphenylporphyrin. Further, metalloporphyrin complexes of OEP are, in general, more soluble than those of TPP. However, the ease of synthesis of TPPH<sub>2</sub><sup>87</sup> compared with that of OEPH<sub>2</sub><sup>88</sup> has resulted in many more studies being conducted with TPPH<sub>2</sub>. One advantage of TPPH<sub>2</sub> over both the natural type porphyrin and OEPH<sub>2</sub> in studying the properties of metalloporphyrin systems is that the electron density on the metal can be varied by substitution of the phenyl rings of tetraphenylporphyrin. A number of phenyl-substituted tetraphenylporphyrins have been prepared and the effects of this substitution on the reactivity and electronic properties of the metal center in tetraphenylporphyrinato-metal complexes studied.<sup>89</sup>

## B. Schiff Bases

Schiff bases are macrocyclic compounds that are formed by the Schiff base condensation reaction (eq 10), often, but not



necessarily, employing a metal ion as a template. A number of reviews on Schiff base syntheses are available.<sup>90–92</sup> The Schiff bases used in these studies are generally tetradentate ligands, but some are pentadentate ligands. At least two of the ligating atoms are nitrogen atoms, with the others being nitrogen, oxygen, sulfur, or a combination of the three. Schiff base compounds are commonly referred to by their mnemonic abbreviations. The abbreviations are a combination of the ketone and amine precursors. For example, bis(acetylacetonate)ethylenediamine becomes acacen, and *N,N'*-bis(salicylidene)ethylenediamine becomes salen. If there are substituents on the Schiff base compound the mnemonic simply adds the group to the front; e.g., *N,N'*-bis(3-methoxysalicylidene)ethylenediamine is 3-MeOsalen (Figure 9).

The tetradentate ligands enforce a high degree of planarity to the metal chelates. Although chelating ligands such as acacen (Figure 9) allow for some distortion away from planarity, the inclusion of an aromatic ring as an integral part of the chelate, as in amben, or salen, stiffens the ligand and increases its pro-

pensity for planarity.

The pentadentate chelates have a fifth axial ligand atom present in the amine or ketonic precursor. If the chain is flexible enough, the fifth ligating atom can coordinate to the metal center. The pentadentate chelates can adopt two different geometries around the metal center depending on the flexibility of the chelate and length of the chain between two of the coordinated atoms containing the fifth ligand atom. If the chain is small or the chelate rigid, the metal–chelate complex will have a square-pyramidal-type structure. If the chelate is flexible enough, the resulting geometry will be trigonal bipyramidal. In all cases the tetra- and pentadentate chelates carry a –2 charge when ligated, so that the resulting M<sup>2+</sup> complexes are neutral overall.

Various substituents can be introduced on the periphery of the ligand by appropriate use of different aldehyde or ketone precursors. The substitutions alter the electronic properties of the metal chelates and their solubilities. In general, the Schiff base complexes are less aromatic than the natural and synthetic porphyrins. Unlike the porphyrins, the Schiff base compounds do not have extensive conjugated  $\pi$  systems available for  $\pi$  bonding to the central metal ion. This effect is noted, for instance, in that the classically inert Co(III) and Cr(III) metal ions in the complexes Cr<sup>III</sup>(TPP)(Cl)<sup>93–95</sup> and Co<sup>III</sup>(TPP)(Cl)<sup>96,97</sup> display anomalous lability. This increase in lability is said to be the presence of the extensive conjugated  $\pi$  system causing a loss of d<sup>3</sup> or d<sup>6</sup> character.

## VII. Cobalt–Dioxygen Carriers

### A. Early Work

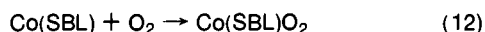
The first report of a synthetic reversible cobalt–oxygen carrier was made by Tsumaki in 1938.<sup>98</sup> He showed that the darkening that had been observed by Pfeiffer and co-workers in 1933,<sup>99</sup> when red-brown crystals of the cobalt(II) Schiff base complex Co(salen) were exposed to the atmosphere, was due to the reversible absorption of molecular oxygen. While this represents the first report of a synthetic reversible oxygen carrier, cobalt compounds containing bound dioxygen have been known for a much longer period. In 1852, Fremy<sup>100</sup> reported that the exposure of ammoniacal solutions of Co(II) salt to the atmosphere resulted in the formation of brown salts which he called oxocobaltates. They were later characterized by Werner and Mylius<sup>57</sup> in 1898 as containing the diamagnetic cation [(H<sub>3</sub>N)<sub>5</sub>-Co(O<sub>2</sub>)Co(NH<sub>3</sub>)<sub>5</sub>]<sup>4+</sup>. These complexes, which are mainly ionic and water soluble, are discussed in section VII.C.

Since the initial discovery by Tsumaki<sup>98</sup> that SB chelates of Co(II) are oxygen carriers, there has been a continued interest in this property of these complexes. The binding of dioxygen to cobalt(II) chelate complexes of Schiff bases has been studied both for heuristic interest and as a practical means of isolating pure dioxygen from the atmosphere. For a short period during World War II, the U.S. Navy used these complexes<sup>101</sup> in the production of pure dioxygen aboard a destroyer tender for use in welding and cutting. More recently, a cobalt Schiff base complex<sup>102</sup> was to be used in the B-1 bomber to provide oxygen when needed to the aircraft crew.

Complexes of both type A and type B (Figure 10) can be isolated as solids in active and inactive forms.<sup>103</sup> The oxygen binding characteristics of these complexes are very dependent upon the preparation and pretreatment of the sample, as well as the purity of the starting materials. Complexes of type A absorb up to 1 mol of O<sub>2</sub>/mol of cobalt, whereas those of type B can absorb up to 0.5 mol of O<sub>2</sub>/mol of Co.

Type A chelates are square planar, while type B chelates are trigonal bipyramidal. In the unoxxygenated states both type A and B complexes are paramagnetic,<sup>104</sup> with type A having a single unpaired electron and type B having three unpaired electrons. In the solid state, upon oxygenation type A complexes become diamagnetic, while type B reduce their paramagnetism to one

unpaired electron. This magnetic behavior is consistent with type A complexes forming  $\mu$ -peroxo dimeric species (eq 11), with the dioxygen being "peroxo-like". The oxygenated type B complexes are monomeric with the unpaired electron on the dioxygen fragment (eq 12). The dioxygen moiety is superoxo-like.



The cobalt chelates (types A and B) exist in several crystalline forms, some of which are active, whereas others are totally devoid of oxygen-carrying ability. Depending on the method of preparation and pretreatment, different crystalline modifications are obtained. Interconversion among crystalline forms is affected by heating in vacuo or grinding. In addition, oxygen uptake rates were dependent on these conditions.

Calvin<sup>105</sup> interpreted the differing uptake rates as being due to the exposure of differing lattice faces in the crystallite caused by different activation processes. In line with this interpretation are the results of crystallographic studies. Type A cobalt Schiff base chelates in the solid state crystallize in layers.<sup>106</sup> All the atoms of the basic Schiff base ligand lie in the same plane. Substituents and the ethylenic hydrogens usually lie outside of this plane. The holes between layers are large enough to allow for the passage of oxygen; the holes between chelates are slightly smaller yet still allow for the passage of oxygen. These "holes" are passages through the lattice shown by X-ray analysis to be present in all active compounds and absent in at least the inactive form of the parent compound. Calvin<sup>103b,105</sup> found that the binding of dioxygen at measurably fast rates of cobalt Schiff base complexes in the solid state were indirectly correlated with the existence of holes in the crystal lattice. He believed that such holes allowed for the rapid diffusion of oxygen throughout the crystal and that the arrangement of the holes allowed the bridging of two cobalt atoms by an oxygen molecule without extensive rearrangement of the structure.

The oxygenation process can be reversed by either heating or evacuation. After continued cycling Calvin<sup>107</sup> et al. found that for Co(salen) and Co(3-Fsalen) the amount of oxygen desorbed on each cycle slowly decreased with time, indicating a slow concurrent decomposition of the chelate. Calvin attributed irreversible oxidation as the most important cause of deterioration. They actually observed the fracturing of a Co(salen)<sup>103b</sup> crystal during cyclization, though they did not ascribe the loss of oxygen carrying ability to this process. It has been reported that fine-grained material is the most efficient oxygen carrier.<sup>101</sup>

Berkeley and Calvin<sup>105</sup> studied the kinetics of oxygen uptake for the type A complexes Co(salen), Co(3-Fsalen), and Co(3-EtOsalen). For all three compounds the oxygenation reaction was first order with respect to oxygen pressure. The complexes Co(salen) and Co(3-EtOsalen) were first order in complex, but Co(3-Fsalen) displayed second-order dependence on complex. The first step is the formation (eq 13) of activated oxygen molecules (this condition exists when the oxygen is bonded to only one cobalt atom) followed by the formation of the dimeric species (eq 14). For first-order behavior, reaction 13 is rate



determining; for second order behavior, reaction 13 is a rapid equilibrium and reaction 14 is the rate-determining step. The  $P_{1/2}\text{O}_2$  values for type A chelates were on the order of 5 Torr at 25 °C, whereas type B chelates exhibited  $P_{1/2}\text{O}_2$  values greater than 1 atm; in addition, type B chelates reach equilibrium very slowly. For the type A complexes studied, thermodynamic values of  $\Delta H \sim -20 \text{ kcal mol}^{-1}$  and  $\Delta S \sim -50 \text{ cal deg mol}^{-1}$  for the oxygenation reaction were obtained.

Earlier solution work by Harle and Calvin<sup>108</sup> involved mainly the type B cobalt chelates. They found at 0 °C that the oxygen uptake by types A and B complexes was reversible to some extent. For the complex used in the studies, Co(3-Clsalen) in quinoline and ethyl benzoate, greater than 97% of activity remained after cycling once. Above 0 °C there was present in the experimental runs a slow irreversible uptake of oxygen. The slow uptake may be due to oxidation of the chelate. The type A compound Co(salen) at 0 °C, when exposed to an oxygen pressure sufficient to cause oxygenation in the solid state, does not oxygenate in solution. If the pressure is increased sixfold approximately one-fourth of the sample oxygenates.

## B. Recent Studies on Cobalt-Dioxygen Complexes in Nonaqueous Solutions

Research on simple iron complexes in solution to mimic the naturally occurring systems of hemoglobin and myoglobin was, for many years, unsuccessful. Because of this and of the success Calvin and co-workers<sup>103b</sup> had with their studies of the interactions of solid cobalt chelates with gaseous dioxygen, there began a renewed interest in the solution studies of cobalt(II) Schiff base compounds. Recent interest in the reversible oxygenation of cobalt complexes received a pronounced impetus from the work of Floriani and Calderazzo<sup>34</sup> and Basolo and Crumbliss<sup>109,110</sup> who discovered that, under the proper conditions in nonaqueous solutions, certain Schiff base cobalt(II) complexes would reversibly bind one molecule of  $\text{O}_2$  per molecule of cobalt. Floriani and Calderazzo<sup>34,111</sup> studied the behavior of derivatives of Co<sup>II</sup>salen in nonaqueous media and found in general an  $\text{O}_2$  uptake of 1  $\text{O}_2$  per 2 Co. However, when pyridine solutions of (3-methoxysalen)cobalt(II) were exposed to  $\text{O}_2$  at 10.4 °C, an uptake corresponding to 1 molecule of  $\text{O}_2$  per molecule of cobalt was observed. The starting material was regenerated by heating the dioxygen adduct in vacuo.

Independent experiments by Basolo and Crumbliss<sup>109,110</sup> made use of *N,N'*-ethylenebis(acetylacetonato)(cobalt(II)) (Co(acacen)). At room temperature, in either a coordinating solvent (e.g., DMF) or in a noncoordinating solvent (e.g., toluene) in the presence of a coordinating ligand (e.g., pyridine), a solution of Co(acacen) shows a slow nonstoichiometric uptake of  $\text{O}_2$  over a period of days (Figure 11). Under these conditions, it appears that some oxidation of the organic ligand is occurring. At temperatures of 0 °C or below, however, there is a rapid and reversible uptake of  $\text{O}_2$  corresponding to the formation of a 1:1 Co: $\text{O}_2$  complex.

With the discovery of the 1:1 dioxygen adducts of cobalt-Schiff base complexes, it was apparent that parallel studies on cobalt-porphyrin compounds were in order, since metalloporphyrins are utilized in natural proteins. At this time the significant result of Perutz<sup>112</sup> that the dioxygen molecule travels through a hydrophobic pocket to reach the coordination site on the iron atom in hemoglobin was well known. It followed that one might simulate the hydrophobic environment on the protein by the use of nonaqueous aprotic solvents, known to work for cobalt(II)-Schiff base chelates. For this reason cobalt(II)-porphyrin model systems were studied using solvents such as toluene or  $\text{CH}_2\text{Cl}_2$ . The generality of the ability of cobalt(II) chelates to reversibly bind dioxygen under such conditions was soon extended to complexes synthesized by the research groups of Busch,<sup>92</sup> Cummings,<sup>113</sup> and McLendon.<sup>114</sup>

Four-coordinate Schiff base,<sup>92,115-120</sup> porphyrin,<sup>118,121-125</sup> and macrocyclic<sup>92,114,126</sup> complexes of cobalt(II) in the presence of a slight excess of a coordinating base normally form low-spin, five-coordinate base adducts. However, there are exceptions among certain Schiff base and macrocyclic complexes. Complexes<sup>115</sup> such as Co<sup>II</sup>(amben), Co<sup>II</sup>(cyen), and Co<sup>II</sup>(MeOamben) do not form base adducts. This is believed to be due to the fact that in these low-spin complexes the odd electron resides in the

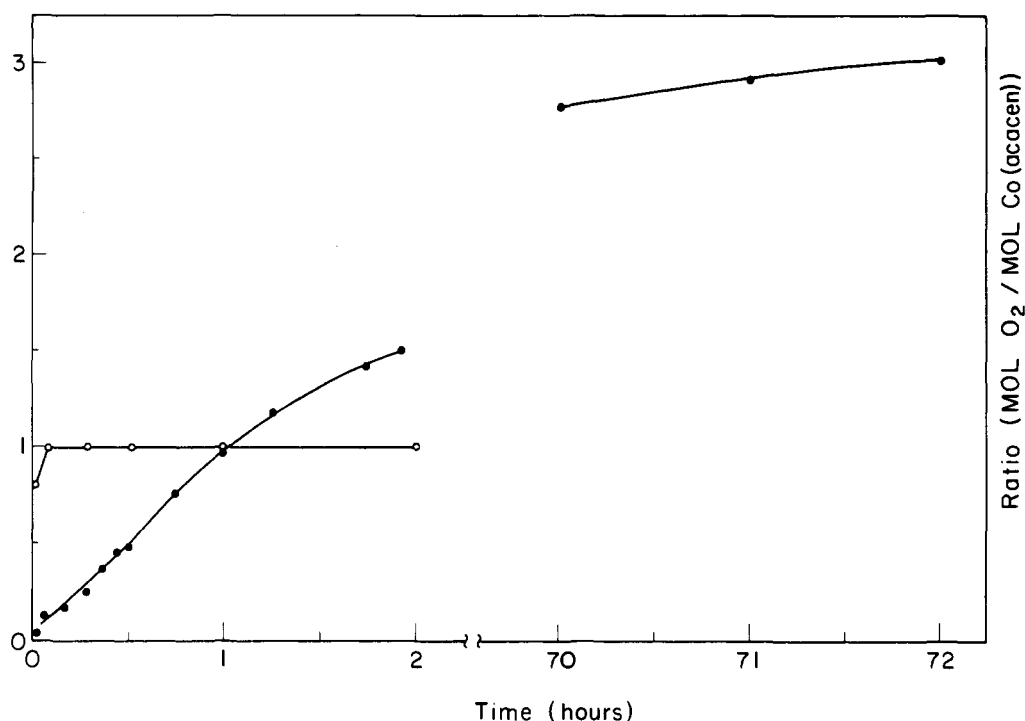


Figure 11. Oxygen absorption by DMF solutions of Co(acacen), data collected at 6 °C and 760 Torr of O<sub>2</sub> pressure denoted by open circles; filled circles are data collected at 25 °C and 480 Torr of O<sub>2</sub>. Data from refs 109 and 110.

TABLE V. Equilibrium Constants for the Binding of an Axial Ligand to Cobalt(II) Chelates:  $\text{Co}(\text{L}_4) + \text{B} \xrightleftharpoons{K_B} \text{Co}(\text{L}_4)\text{B}$

compound <sup>a</sup>	base	T, °C	log K <sub>B</sub> , M <sup>-1</sup>	ref	compound <sup>a</sup>	base	T, °C	log K <sub>B</sub> , M <sup>-1</sup>	ref
Co(salen)	quin	25	-0.52 <sup>b</sup>	c	Co(T( <i>p</i> -OCH <sub>3</sub> )PP)	3,5-Cl <sub>2</sub> py	25	2.28	127
	PPh <sub>3</sub>	25	-0.82	c		4-MeO <sub>2</sub> Cpy	25	2.70	127
	2-Mepy	25	0	c		2,4,6-Me <sub>3</sub> py	25	1.83	127
	2,6-Me <sub>2</sub> py	25	0.45	c		IsoQ	25	2.81	127
	OPPh <sub>3</sub>	25	.38	c		quin	25	1.20	127
	3-Mepy	25	0.57	c		acr	25	<-1	127
	4-Mepy	25	0.85	c		lm	25	3.15	127
	4-EtCOOpy <sup>d</sup>	25	0.45	c		Melm	25	3.37	127
	3-EtNCOpy <sup>e</sup>	25	0.57	c		5-ClMelm	25	3.09	127
	py	25	0.57	c		N-aclm	25	2.89	127
	py	20	1.1 <sup>f,g</sup>	h		1,2-Me <sub>2</sub> lm	25	2.79	127
Co(sal(±)dpen)	py	20	0.53 <sup>f</sup>	h	Bzlm	25	2.44	127	
Co(sal( <i>m</i> )dpen)	py	20	0.57 <sup>f</sup>	h	1-SiMe <sub>3</sub> lm	25	3.14	127	
Co(sal(±)chxn)	py	20	1.02 <sup>f</sup>	h	pip	25	3.39	127	
Co(sal( <i>m</i> )chxn)	py	20	0.75 <sup>f</sup>	h	Mor	25	3.20	127	
Co(acacen)	py	23	1.8	115	quinuc	25	3.19	127	
Co(Phacacen)	py	23	1.9	115	Co(T( <i>p</i> -CH <sub>3</sub> )PP)	pip	25	3.386	124
Co(Meacacen)	py	23	1.9	115	py	25	2.685	124	
Co(benacen)	py	23	2.3	115	Co(T( <i>p</i> -Cl)PP)	pip	25	3.517	124
Co(benacen)	2,4,6-Me <sub>3</sub> py	23	1.8	115	py	25	2.742	124	
Co(sacacen)	py	23	2.5	115	Co(TPP)	pip	25	3.616	124
Co(PPIXDME)	DMF	23	1.18	129	py	25	2.880	124	
Co(PPIXDME)	4-CNpy	23	3.24	129	Co(T( <i>p</i> -F)PP)	py	25	2.972	124
	py	23	3.78	129	Co(T( <i>p</i> -Cl)PP)	pip	25	3.698	124
	4- <i>t</i> -Bupy	23	3.85	129	py	25	3.004	124	
	lm	23	3.64	129	Co(T( <i>p</i> -CN)PP)	pip	25	3.937	124
	Melm	23	3.70	129	py	25	3.268	124	
Co(T( <i>p</i> -MeO)PP)	4-NH <sub>2</sub> py	23	4.00	129	Co(T( <i>p</i> -NO <sub>2</sub> )PP)	pip	25	4.036	124
	py	23	3.83	129	py	25	3.386	124	
	Bzlm	23	3.5	122	Co(MPIXDME)	PPh <sub>3</sub>	26	1.48	125
	py	25	2.69	127	P( <i>n</i> -Bu) <sub>3</sub>	20.5	4.08	125	
	4-Mepy	25	2.90	127	P(OMe) <sub>3</sub>	25.4	1.65	125	
Co(T( <i>p</i> -MeO)PP)	3,4-Mepy	25	3.03	127	SMe <sub>2</sub>	26.0	1.35	125	
	4-Me <sub>2</sub> Npy	25	3.62	127	AsPh <sub>3</sub>	24.9	1.40	125	

<sup>a</sup> Solvent is toluene unless otherwise noted. <sup>b</sup> Solvent is DMA. <sup>c</sup> A. V. Savitski and N. K. Zheltukhin, *Izv. Akad. Nauk SSSR*, 222, 348 (1973). <sup>d</sup> Ethyl isonicotinate. <sup>e</sup> Nicotinic acid diethylamide. <sup>f</sup> Solvent is CHCl<sub>3</sub>. <sup>g</sup> Approximate value. <sup>h</sup> E. Cesarotti, M. Gullotti, A. Pasini, and R. Ugo, *J. Chem. Soc., Dalton Trans.*, 757 (1977).

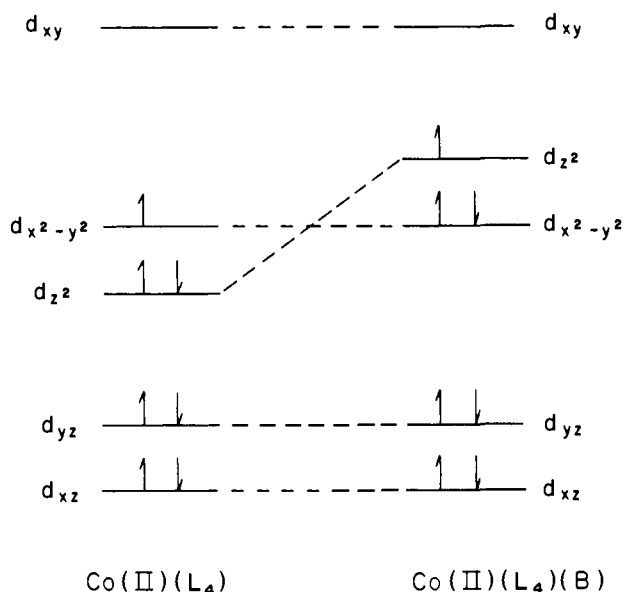


Figure 12. Energy level diagrams denoting the changes in energy levels for the axial ligation of  $\text{Co}(\text{SB}_4)$ . The diagram on the left is for  $\text{Co}(\text{SB}_4)$ ; that on the right is for  $\text{Co}(\text{SB}_4)(\text{B})$ .

$d_{xy}$  orbital. Thus in order to bind an axial ligand it would be necessary to promote the  $d_{z^2}$  orbital above the  $d_{xy}$ . However, the energy gained from binding an axial ligand is not enough to compensate for the energy of rearrangement, and hence the complexes remain four-coordinate.

Toluene solutions of cobalt(II) porphyrins<sup>118,121-125,127-129</sup> in the presence of base rapidly form the five-coordinate complexes  $\text{Co}^{\text{II}}(\text{Por})(\text{B})$ . In the presence of a large excess of base the bis-base complexes,  $\text{Co}^{\text{II}}(\text{Por})(\text{B})_2$ , are formed. For example, in toluene solutions containing piperidine (>1 M)  $\text{Co}^{\text{II}}(\text{PPIXDME})(\text{pip})_2$  is formed. Stynes<sup>129</sup> et al. found that at room temperature the weaker coordinating bases such as pyridine and 4-*tert*-butylpyridine do not form bis-base complexes with  $\text{Co}^{\text{II}}(\text{PPIXDME})$ . However, at  $-40^\circ\text{C}$ , formation of the bis-base adduct was observed for 4-*tert*-butylpyridine. Walker<sup>127</sup> noted that only strong  $\sigma$ -donor bases such as quinuclidine, piperidine, or *n*-hexylamine readily form 2:1 complexes with  $\text{Co}^{\text{II}}(\text{T}(p\text{-MeO})\text{PP})$ . Weaker binding ligands such as pyridine formed 2:1 complexes only at high ligand concentrations and bases such as pyrrole and quinoline did not under any conditions form bis-base adducts. Thermodynamic values for the addition of a base (eq 15) as a fifth ligand are given in Table V.



There appears to be no direct correlation between  $\log K_B$  and the  $\text{p}K_a$  of the ligand, although Walker<sup>127</sup> did note that for structurally similar bases (substituted pyridines and imidazoles) there was a linear correlation between  $\text{p}K_a$  and  $\log K_B$ .

### 1. EPR

Analyses of the EPR spectra of five-coordinate cobalt(II) Schiff base, porphyrin, and macrocyclic complexes<sup>35,130</sup> show that the complexes are low-spin  $d^7$ , with the unpaired electron in the  $d_{z^2}$  orbital. This is inferred from the presence of superhyperfine splittings from the axial nitrogen. Certain five-coordinate  $\text{Co}(\text{II})$  Schiff base and macrocyclic complexes remain high spin. The complexes<sup>92,114,130d,131</sup>  $[\text{Co}^{\text{II}}(\text{cyclam})(\text{Br})]^+$ ,  $\text{Co}^{\text{II}}(\text{SalMeDPT})$ , and  $\text{Co}^{\text{II}}(\text{salHDPT})$  are high spin as evidenced by magnetic moments of  $\mu_{\text{eff}} \approx 3.3$  BM and the analysis of their EPR spectra.

Four-coordinate cobalt(II) chelates are very poor oxygen binders,<sup>115</sup> whereas their corresponding mono(base adducts) and five-coordinate chelates readily bind dioxygen at ambient pressures of oxygen. The binding of an axial fifth ligand leads

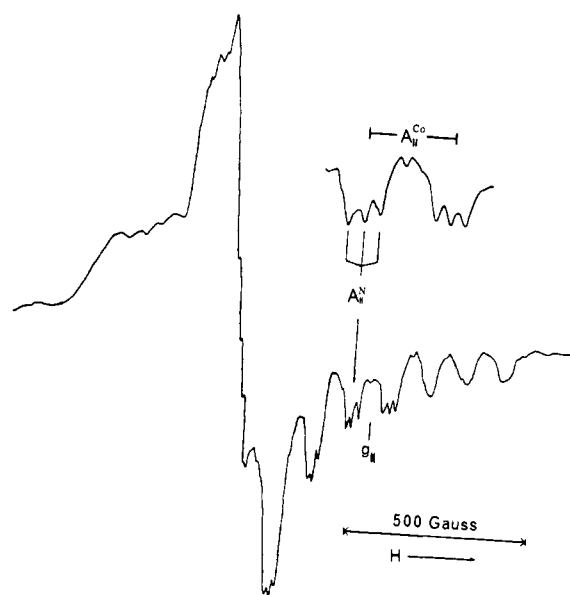
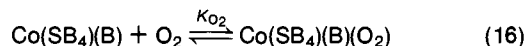


Figure 13. EPR spectrum of  $\text{Co}(\text{acacen})(\text{py})$  in frozen toluene solution at 77 K (from ref 35).

to a square-pyramidal arrangement, raising the  $d_{z^2}$  orbital above the  $d_{xy}$  (Figure 12), thus resulting in the configuration  $(d_{xz})^2(d_{yz})^2(d_{xy})^2(d_{z^2})^1$ . This latter configuration appears to be a necessary prerequisite of oxygenation. Basolo<sup>132</sup> and co-workers have reported that five-coordinate complexes of the cobalt(II) Schiff base  $\text{Co}^{\text{II}}(\text{benacen})(\text{B})$ , where B represents an N-donor ligand, readily bind dioxygen in toluene solutions at  $0^\circ\text{C}$  (eq 16). For example,  $\log K_{\text{O}_2} = -2.0$  at  $0^\circ\text{C}$  for B equals (1-Melm) and the electronic configuration of the complex is  $(d_{xz})^2(d_{yz})^2(d_{xy})^2(d_{z^2})^1$ .



However, only a small amount of the four-coordinate  $\text{Co}^{\text{II}}(\text{benacen})$  (electronic configuration of  $(d_{xz})^2(d_{yz})^2(d_{z^2})^2(d_{xy})^1$ ) complex is oxygenated under 1 atm of  $\text{O}_2$  in toluene at  $-83^\circ\text{C}$ .

The EPR spectra of  $\text{Co}^{\text{II}}(\text{L}_4)(\text{B})$  and  $\text{Co}^{\text{II}}(\text{L}_5)$ <sup>35,130</sup> complexes typically have an eight-line hyperfine splitting (Figure 13) due to the  $^{59}\text{Co}(I = 7/2)$  nucleus in the high field, "parallel", direction. Several of these are seen to be split into equal intensity triplets by the presence of the single nitrogen ( $I = 1$ ) nucleus of a N-donor base. EPR values for  $\text{Co}^{\text{II}}(\text{L}_4)(\text{B})$  and  $\text{Co}^{\text{II}}(\text{L}_5)$  complexes are given in Table VI. The  $\text{Co}^{\text{II}}(\text{SB}_4)(\text{B})$  complexes typically have EPR values for  $g_{\perp}$  of 2.30–2.45 and  $g_{\parallel}$  of 2.01, 2.02, while  $\text{Co}(\text{Por})(\text{B})$  complexes have  $g_{\perp}$  values of  $\sim 2.33$  and  $g_{\parallel}$  of 2.03.

Upon oxygenation the EPR spectra of low-spin  $\text{Co}(\text{Por})(\text{B})$  complexes undergo dramatic changes.<sup>36,92,130a-d,g,h,k,131-143</sup> The signal at  $g \sim 2.3$  disappears, with a new symmetrical signal replacing it at  $g \sim 2$ . The original superhyperfine (shf) splitting of  $\sim 80$  G are replaced (Figure 14) with a much smaller shf splitting due to  $^{59}\text{Co}$  of 10–12 G (values are in Table VII). This change can be reversed by removing the oxygen. The small shf splittings have been interpreted as meaning that the unpaired spin density no longer resides on the cobalt metal center, but instead resides on the dioxygen moiety. The results<sup>36,141</sup> of using  $^{17}\text{O}$  and magnetic data indicate that in the  $\text{Co}(\text{L}_4)(\text{B})(\text{O}_2)$  complexes there is present only one unpaired electron, and that greater than 90% of the residual electron spin resides on the dioxygen. Upon coordination the symmetry of the oxygen molecule is sufficiently reduced to split the otherwise degenerate antibonding  $1\Pi_g$  orbitals of the oxygen and constrains the two antibonding electrons to be paired in the more stable of the two orbitals. Because of this loss of this symmetry restriction, the

TABLE VI. EPR Parameters for Five-Coordinate Cobalt(II) Complexes<sup>a</sup>

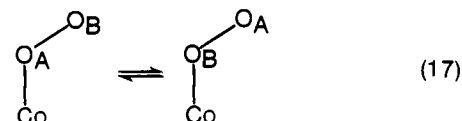
compound	solvent	$g_x$	$g_y$	$g_z$	$A_x$ , gauss	$A_y$ , gauss	$A_z$ , gauss	ref
Co(salen)(THF)	THF	2.409		2.013	50.7		126.7	130c
Co(salen)(NCS)	NCS <sup>-</sup> , DMA	2.54	2.31	2.011	≤59 <sup>b</sup>	≤37 <sup>b</sup>	104.4	130c
Co(salen)(DMSO)	DMSO	2.50	2.30	2.013	≤53 <sup>b</sup>	≤28 <sup>b</sup>	126.6	130c
Co(salen)(py)	c	2.380	2.180	2.014			101.0	115
Co(salen)(py)	py	2.354	2.27	2.028	≤18 <sup>b</sup>	≤19 <sup>b</sup>	81.3	130c
Co(3-MeOsalen)(py)	d	2.406	2.23	2.015	50 <sup>b</sup>	10	95.0	e
Co(acacen)(py)	1% py/toluene	2.449	2.73g	2.013	47.3		100	115, 132
Co(acacen)(py)	toluene	2.44 <sup>b</sup>	2.225	2.011	43.5	11.6 <sup>b</sup>	97.5	35, 130c
Co(acacen)(4-CNpy)	toluene	2.45	2.23	2.013	5.2	11	101.2	e, 35
Co(acacen)(4-Mepy)	toluene	2.445	2.22	2.012	51.3	11	98.7	e, 35
Co(acacen)(4- <i>t</i> -Bupy)	toluene	2.452	2.23	2.013	49	11	99.9	e
Co(acacen)(PPh <sub>3</sub> )	toluene-CH <sub>2</sub> Cl <sub>2</sub>	2.4 <sup>b</sup>	2.2 <sup>b</sup>	1.958			91.8	e
Co(acacen)(DMF)	toluene	2.461	2.23	2.011	57.2	15	100.4	e
Co(Meacacen)(py)	py	2.470	2.230	2.009	59	13	104.6	e, 115, 132
Co(Meacacen)(PPh <sub>3</sub> )	toluene	2.4 <sup>b</sup>	2.2 <sup>b</sup>	1.961			90.0	e
Co(Phacacen)(py)	1% py/toluene	2.446	2.237	2.014	52.5		103.0	115, 132
Co(sacacen)(py)	1% py/toluene	2.443	2.169	2.003			77.6	115, 132
Co(benacen)(py)	c	2.428	2.22	2.012	48.7	13	98.0	e
Co(benacen)(py)	1% py/toluene	2.444	2.231	2.014	45.0		98.0	115, 132
Co(benacen)( <i>n</i> -BuNH <sub>2</sub> )	f	2.428	2.237	2.009	40		96.3	132
Co(benacen)( <i>i</i> -BuNH <sub>2</sub> )	f	2.441	2.244	2.012	45		96.0	132
Co(benacen)( <i>sec</i> -BuNH <sub>2</sub> )	f	2.456	2.249	2.007	55		96.0	132
Co(benacen)(MeIm)	f	2.442	2.257	2.013	44		98	115, 132
Co(benacen)(5-ClMeIm)	f	2.451	2.267	2.013	50		101	115, 132
Co(benacen)(pip)	f	2.442	2.244	2.013	44		93.5	115, 132
Co(benacen)(3,4-Me <sub>2</sub> py)	f	2.441	2.248	2.009	45		98	115, 132
Co(benacen)(4-Mepy)	f	2.442	2.251	2.012	47.5		99	115, 132
Co(benacen)(4-CNpy)	f	2.470	2.267	2.013	47		103	115, 132
Co(benacen)(PPh <sub>3</sub> )	f	2.319	2.250	1.958			89	115, 132
Co(NO <sub>2</sub> amben)(py)	50% py/DMF	2.295	2.216	2.003			107	115
Co(salpy)	20% DMF/toluene	2.451	2.226	2.011	43.3		105.4	115
Co(saloph)(PPh <sub>3</sub> )	CH <sub>2</sub> Cl <sub>2</sub>	2.4 <sup>b</sup>	2.2 <sup>b</sup>	1.998			87.8	e
Co(saloph)(P( <i>n</i> -Bu) <sub>3</sub> )	toluene	2.4 <sup>b</sup>	2.2 <sup>b</sup>	1.950			78.0	e
Co(ptsm)(py)	py	2.37	2.21	2.001	37	17	76.5	e
Co(tetane)(py)	10% py/MeOH	2.626	2.364	2.019		34	116	115
Co(diene)(py)	10% py/MeOH	2.360	2.290	2.010			110	115
Co(tetene)(py)	10% py/MeOH	2.354	2.354	2.023			91.7	115
Co(T( <i>p</i> -MeO)PP)(py)	1% py/tol	2.312	2.312	2.022			83.3	115, 132
Co(T( <i>p</i> -MeO)PP)(py)	toluene	2.327	2.327	3.025	<11 <sup>b</sup>	<11 <sup>b</sup>	84.4	130c
Co(T( <i>p</i> -MeO)PP)(py)	toluene	≥2.327 <sup>g</sup>		2.025 <sup>h</sup>	≤11 <sup>i</sup>		84.4 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(2-Mepy)	toluene	≥2.324 <sup>g</sup>		2.027 <sup>h</sup>	≤10 <sup>i</sup>		82.4 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(3-Mepy)	toluene	≥2.326 <sup>g</sup>		2.028 <sup>h</sup>	≤10 <sup>i</sup>		83.1 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(4-Mepy)	toluene	≥2.323 <sup>g</sup>		2.028 <sup>h</sup>	≤10 <sup>i</sup>		83.3 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(3,4-Me <sub>2</sub> py)	toluene	≥2.318 <sup>g</sup>		2.027 <sup>h</sup>	≤10 <sup>i</sup>		81.8 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(3,5-Me <sub>2</sub> py)	toluene	≥2.316 <sup>g</sup>		2.029 <sup>h</sup>	≤10 <sup>i</sup>		80.7 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(2,4,6-Me <sub>3</sub> py)	toluene	≥2.324 <sup>g</sup>		2.027 <sup>h</sup>	≤10 <sup>i</sup>		83.2 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(quin) <sup>k</sup>	toluene	≥2.325 <sup>g</sup>		2.032 <sup>h</sup>	≤9 <sup>i</sup>		82.5 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(MeIm)	toluene	≥2.314 <sup>g</sup>		2.033 <sup>h</sup>	≤11 <sup>i</sup>		80.0 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(MeIm)	toluene	2.314	2.314	2.033	11.1	11.1	80.0	130c
Co(T( <i>p</i> -MeO)PP)(pyrrole)	toluene	≥2.323 <sup>g</sup>		2.028 <sup>h</sup>	≤10 <sup>i</sup>		81.7 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(pip)	toluene	≥2.318		2.026 <sup>h</sup>	≤12 <sup>i</sup>		81.8 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(quine) <sup>k</sup>	toluene	≥2.322		2.032 <sup>h</sup>	≤10 <sup>i</sup>		85.6 <sup>j</sup>	128
Co(T( <i>p</i> -MeO)PP)(1- <i>n</i> -hexylamine)	toluene	≥2.311 <sup>g</sup>		2.022 <sup>h</sup>	≤9 <sup>i</sup>		82.8 <sup>j</sup>	128
Co(TPP)(CO)	toluene	2.217 <sup>g</sup>		2.017 <sup>h</sup>	33 <sup>i</sup>		77.6 <sup>j</sup>	140
Co(TPP)(CNCH <sub>3</sub> )	toluene	2.247 <sup>g</sup>		2.025 <sup>h</sup>	35.6 <sup>i</sup>		70.9 <sup>j</sup>	140
Co(TPP)(P(OCH <sub>3</sub> ) <sub>3</sub> )	toluene	2.244 <sup>g</sup>		2.024 <sup>h</sup>	26.6 <sup>i</sup>		73 <sup>j</sup>	140
Co(TPP)(py)	toluene	2.324 <sup>g</sup>		2.027 <sup>h</sup>	12.0 <sup>i</sup>		83.4 <sup>j</sup>	140
Co(PPIXDME)(Im)	toluene	2.32 <sup>g</sup>		2.033 <sup>h</sup>			77 <sup>j</sup>	122
Co(PPIXDME)(MeIm)	toluene	2.32 <sup>g</sup>		2.033 <sup>h</sup>			76.5 <sup>j</sup>	122

<sup>a</sup> Measured as frozen solution at 77 K, unless otherwise noted. <sup>b</sup> Approximate value. <sup>c</sup> 1% py-10% DMF/toluene. <sup>d</sup> *N*-(4'-Methoxybenzylidene)-4-butylaniline. <sup>e</sup> D. L. Diemente, Ph.D. Thesis, Northwestern University, Evanston, Ill., 1971. <sup>f</sup> Solvent is 10% base/20% DMF/70% toluene, v/v/v, ~1 M in base. <sup>g</sup> Value given is  $g_{\perp}$ . <sup>h</sup> Value given in  $g_{\parallel}$ . <sup>i</sup> Value given as  $A_{\perp}$ . <sup>j</sup> Value given is  $A_{\parallel}$ . <sup>k</sup> quin = quinoline; quine = 1,4-ethylenepiperidine.

dioxygen moiety must be bound unsymmetrically.

The EPR spectra of the oxygenated complexes indicate that the unpaired electron has only a small spin density at the cobalt nucleus ( $a_{Co} \approx 10-12$  G as compared with 80-100 G for the nonoxygenated parent compounds (Table VII)). Labeling<sup>141</sup> experiments using <sup>17</sup>O have shown that the two atoms of oxygen are equivalent in solution. In frozen solution or solid spectra, there is nonequivalence of the oxygen atoms. The equivalence

in solution may be due to a rapid equilibrium between two bent conformations (eq 17). The percent of unpaired electron density on the dioxygen moiety from <sup>17</sup>O data is >90% but cannot be



accurately calculated because of the overlap of the  $^{59}\text{Co}$  and  $^{17}\text{O}$  hyperfine splittings. On the basis of magnetic resonance $^{36,92,130b-e,g-k,131a,132-141}$  and magnetic moment $^{34}$  data, the  $\text{Co}(\text{L}_4)(\text{B})(\text{O}_2)$  complexes are best described formally as  $\text{Co}^{\text{III}}(\text{L}_4)(\text{B})(\text{O}_2^-)$ . This description is borne out by structural studies. For example, in the compound  $\text{Co}(\text{benacen})(\text{py})(\text{O}_2)$ , $^{144}$  the dioxygen moiety is bound in an end-on configuration with a  $\text{Co}-\text{O}-\text{O}$  angle of  $126^\circ$ , and with a  $\text{O}-\text{O}$  bond distance of 1.26 Å. This bond distance corresponds approximately to that found for superoxide anions (Table I).

## 2. Nature of Bound $\text{O}_2$

One of the most useful "fingerprint" properties of coordinated dioxygen is the  $\text{O}-\text{O}$  stretching frequency ( $\nu_{\text{O}-\text{O}}$ ). In all cases reported, the monomeric dioxygen complexes of cobalt have values of  $\nu_{\text{O}_2}$  that fall in a narrow range $^{34,109,110,145,146}$  ( $\sim 50 \text{ cm}^{-1}$ ) near that of free superoxide anion,  $1145 \text{ cm}^{-1}$ . Similar values, which have been reported for a variety of cobalt-dioxygen complexes, show that  $\nu_{\text{O}_2}$  is rather insensitive to the nature of the ligands present (Table VIII). For example, the diverse series of compounds  $\text{Co}(\text{acacen})(\text{py})(\text{O}_2)$ , $^{109,110}$   $\text{Co}(\text{TpivPP})(\text{MeIm})(\text{O}_2)$ , $^{145}$  and  $((\text{C}_2\text{H}_5)_4\text{N})_3[\text{Co}(\text{CN})_5(\text{O}_2)]$  $^{147}$  have similar values of  $\nu_{\text{O}_2}$  of 1123, 1150, and  $1138 \text{ cm}^{-1}$ , respectively. These infrared  $\text{O}-\text{O}$  stretches reinforce the formalism that the bound dioxygen is superoxide-like.

Recently Gray et al. $^{148,149}$  have proposed that analyses of the optical spectra of dioxygen complexes allow one to determine the oxidation state of the bound dioxygen and metal center, as well as give information regarding the geometries of the complexes. This was accomplished by interpreting spectra on the basis of d-d and charge-transfer bands. The basis of band assignments in the metal-dioxygen complexes draws heavily from the related protonated derivatives,  $\text{HO}_2$  and  $\text{H}_2\text{O}_2$ .

The  $\text{Co}(\text{III})-(\text{O}_2^-)$  formalism has been challenged, $^{131b}$  based on studies of a presumed carbon monoxide adduct of cobalt which appeared to exhibit a very similar EPR spectrum to that of the corresponding dioxygen adduct. They argued that since no reasonable  $\text{Co}^{\text{III}}(\text{CO}^-)$  formalism is to be expected, this result casts doubt on the validity of a charge separation of  $\text{Co}^{\text{III}}(\text{O}_2^-)$  for the dioxygen-cobalt compounds. Further studies $^{138}$  revealed that the spectrum believed to be that of the carbon monoxide adduct was, in fact, the dioxygen adduct resulting from residual oxygen contamination. Such an experimental difficulty can readily occur, because the cobalt-Schiff base complex investigated has little affinity for carbon monoxide, while it has a high affinity for oxygen.

Recently, it has been proposed $^{131c}$  that although the dioxygen-cobalt complexes have an unpaired electron residing essentially in a dioxygen  $\pi^*$  orbital and can be considered formally as  $\text{Co}^{\text{III}}(\text{O}_2^-)$ , there is not necessarily a transfer of an electron from the cobalt metal center to the dioxygen moiety upon binding. It was suggested that, for a series of cobalt(II)-Schiff base compounds, there is a transfer of only 0.1 to 0.8 electron to the coordinated dioxygen fragment depending upon the ligand environment around the cobalt center. The point is made that earlier analyses of EPR spectra of cobalt-dioxygen complexes favoring the superoxide like formalism was incorrectly based on the greatly reduced anisotropy ( $A - A_{\text{iso}}$ ) in cobalt hyperfine coupling constants when compared with the parent five-coordinate cobalt(II) complexes. It is suggested that the reduced anisotropy results from a spin polarization mechanism with the unpaired electron residing mainly on  $\text{O}_2$ , which does not require a formal electron transfer to form  $\text{O}_2^-$ . Both research groups agree with the premise that the unpaired electron does reside in an oxygen  $\pi^*$  orbital, and it appears that the discrepancy arises from differing definitions of oxidation states. If one bases the oxidation states of cobalt and oxygen upon classical concepts (Pauling) where the shared electron pair is assigned to the more electronegative element, one arrives at a  $\text{Co}^{\text{II}}(\text{O}_2^-)$  for-

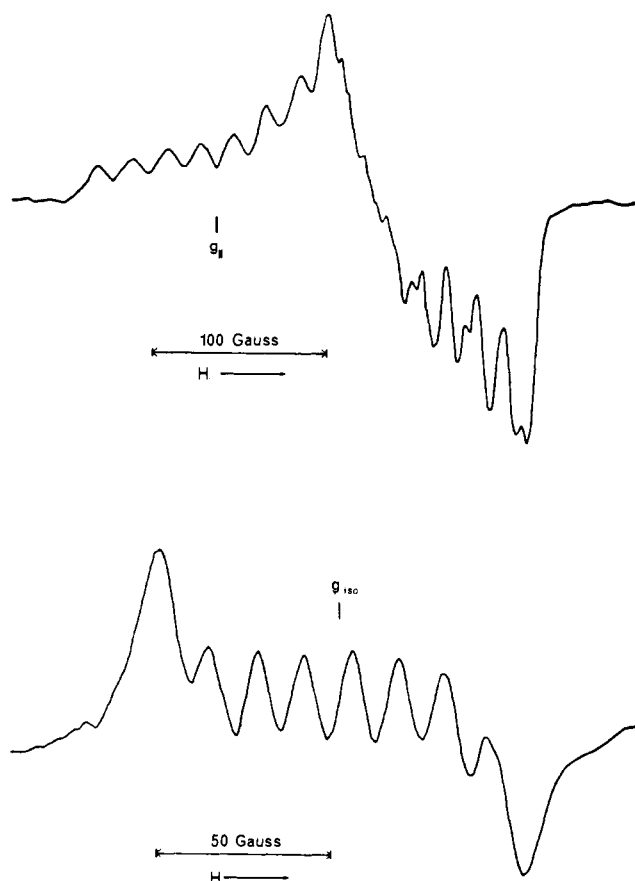


Figure 14. EPR spectra of  $\text{Co}(\text{acacen})(\text{py})\text{O}_2$ . Upper spectrum is a frozen toluene solution at 77 K; lower is of fluid toluene solution at  $-58^\circ\text{C}$  (data from ref 35).

malism. This formalism makes no attempt to define the amount of electron transferred. This formalism is just a simple construct designed to give useful first principle information.

Data obtained from X-ray PES (photoelectron spectroscopy) experiments by Burness et al., $^{116}$  who studied the binding energies of the cobalt 2p electrons in the parent cobalt(II) complexes and the cobalt 2p and oxygen  $1s_{1/2}$  binding energies in the dioxygen adducts, support the formulation of the dioxygen adducts as  $\text{Co}^{\text{III}}(\text{O}_2^-)$ . They found that the oxygenation could be described as an oxidative addition type interaction between dioxygen and cobalt. For the complex  $\text{Co}(\text{3-CH}_3\text{Osalen})(\text{py})(\text{O}_2)$ , they calculated a value of 86% for the extent of electron transfer between cobalt and oxygen. This effect was also noted by Lauher and Lester $^{150}$  and others. $^{151}$

## 3. Coboglobins

The successful preparation of monomeric  $\text{Co}-\text{O}_2$  complexes suggested the possibility of introducing a functional paramagnetic probe into hemoglobin (Hb) and myoglobin (Mb) by removing the heme group and reconstituting the protein with a cobalt(II)-porphyrin to form an oxygen-carrying cobalt-metalloprotein. The study of such metal-substituted proteins would permit one to observe directly the influence of the protein environment upon the metalloporphyrin by comparing the oxygen-binding and spectroscopic properties with those of  $\text{Co}(\text{PPIXDME})$  in solution. Also, variation of the stereochemical properties of the functioning metal-atom binding site of hemoglobin would allow an examination of the involvement of the heme in the conformational changes which constitute hemoglobin allosteric, or cooperative, ligand binding (vide infra). Therefore, globins from hemoglobin and myoglobin were prepared and reconstituted with cobalt(II) protoporphyrin IX ( $\text{Co}(\text{PPIX})$ ). $^{152-158}$  These coboglobins, the cobalt analogs of hemoglobin (CoHb) and myoglobin (CoMb),

TABLE VII. EPR Parameters for Reversible Cobalt-Dioxygen Complexes<sup>a</sup>

compound	solvent	$g_{\perp}$	$g_{\parallel}$	$g_{\text{iso}}$	$A_{\perp}^{\text{Co}}, \text{G}$	$A_{\parallel}^{\text{Co}}, \text{G}$	$A_{\text{iso}}, \text{G}$	ref
Co(salen)	CH <sub>2</sub> Cl <sub>2</sub>	1.998	2.089	2.025	18.1	25.1		130c
Co(salen)(DMA)	DMA	1.998	2.086		20.0			130c
Co(salen)(THF)	THF	1.996	2.082	2.024	19.5	26.0		130c
Co(salen)(DMSO)	DMSO	1.998	2.091	2.024	17.8	23.8		130c
Co(salen)(py)	py	1.999	2.079	2.028	14.0	17.5		130c
Co(salen)(py)	py	1.997 <sup>b</sup>	2.079	2.024 <sup>c</sup>	10.4 <sup>b</sup>	18.0	12.9	<i>d</i>
Co(salen)(py)	toluene	1.999	2.072	2.023 <sup>e</sup>	14.3	16.8	13	115
Co(salen)(py)	50% py/50% CHCl <sub>3</sub>	2.007	2.08		12.7	16.8		139
Co(salen)(py) <sup>f,g</sup>	pyridine			2.022			13	179
Co(salen)(py)	50% py/50% CH <sub>2</sub> Cl <sub>2</sub>	1.995 <sup>b</sup>	2.082	2.024 <sup>h</sup>	10.5 <sup>b</sup>	17.4	12.3	133
Co(3-MeOsalen)(py)	toluene	1.998	2.079	2.024 <sup>i</sup>	14.6	16.8	12.6	115
Co(3-MeOsalen)(py)	py	1.997	2.079	2.024 <sup>i</sup>	10.2	17.3	12.6	<i>d</i>
Co(3-MeOsalen)(py) <sup>j</sup>	py			2.023			12.8	179
Co(3-MeOsalen)(4-Mepy) <sup>g,i</sup>	4-Mepy			2.022			13	179
Co(3-MeOsalen)(4-Etpy) <sup>k</sup>	4-Etpy			2.022			12.8	179
Co(3-MeOsalen)(DMF)	DMF			2.028			17.0	179
Co(3-MeOsalen)(DMSO) <sup>f</sup>	DMSO			2.028			17.3	179
Co(4,6-Me <sub>2</sub> salen)(py)	50% py/50% CH <sub>2</sub> Cl <sub>2</sub>	1.996	2.074	2.022 <sup>h</sup>	9.2	17.0	11.9	133
Co(Fsalen)(py)	toluene	1.999	2.078	2.028 <sup>m</sup>	13.0	17.0	14	115
Co(napsalen)(py) <sup>n</sup>	50% py/50% CH <sub>2</sub> Cl <sub>2</sub>		2.078			16.8		133
Co(acacen)(py)	toluene	1.998	2.080	2.027 <sup>n</sup>	16	19.3	13.7	115, 132
Co(acacen)(py)	toluene	1.999	2.082	2.027 <sup>n</sup>	10.7	19.7	13.7	<i>d</i> , 35, 130c
Co(acacen)(py)	50% py/50% CHCl <sub>3</sub>	2.008	2.08		15.1	18.7		139
Co(acacen)(H <sub>2</sub> O)	toluene	1.997	2.088	2.027 <sup>n</sup>	13.7	28.9	18.8	<i>d</i> , 35
Co(acacen)(DMF)	toluene	1.9962	2.0859	2.026 <sup>o</sup>	10.0	20.2		<i>d</i> , 35, 130c
Co(acacen)(4-CNpy)	toluene	1.997	2.080	2.024 <sup>o</sup>	10.3	20.1	13.6	<i>d</i> , 35
Co(acacen)(4-Mepy)	toluene	1.997	2.082	2.026 <sup>o</sup>	10.0	19.6	13.2	<i>d</i> , 35
Co(acacen)(4- <i>t</i> -Bupy)	toluene		2.084			19.9		<i>d</i>
Co(Meacacen)(py)	py	1.996	2.091	2.027 <sup>p</sup>	11.0	21.7	14.5	<i>d</i>
Co(Meacacen)(py)	toluene	2.007	2.082	2.019 <sup>q</sup>	17.0	20.3	14	115, 132
Co(Phacacen)(py)	toluene	1.999	2.084	2.023 <sup>q</sup>	15.7	19.3	12.8	115, 132
Co(sacacen)(py)	toluene	1.997	2.085	2.023 <sup>r</sup>	13.3	21.3	14	115, 132
Co(benacen)(MeIm)	<i>s</i>	2.000	2.008	2.024 <sup>h</sup>	15	18.6	13.1	115, 132
Co(benacen)(5-ClMeIm)	<i>s</i>	2.000	2.089	2.025 <sup>h</sup>	15.5	19.4	13.6	115, 132
Co(benacen)(pip)	<i>s</i>	2.000	2.088	2.025 <sup>h</sup>	17.5	19	13.0	115, 132
Co(benacen)(3,4-Me <sub>2</sub> py)	<i>s</i>	1.999	2.085	2.024 <sup>h</sup>	14	19	13.0	115, 132
Co(benacen)(4-Mepy)	<i>s</i>	1.999	2.085	2.024 <sup>h</sup>	18	19	13.1	115, 132
Co(benacen)(py)	<i>s</i>	2.000	2.085	2.024 <sup>h</sup>	18	19.2	13.2	115, 132
Co(benzcen)(py)	py	1.999	2.084	2.026 <sup>i</sup>	10.3	19.4	13.3	<i>d</i>
Co(benacen)(2,4,6-Me <sub>3</sub> py)	<i>s</i>	1.999	2.084	2.023 <sup>h</sup>	17.5	19.2	13.0	115
Co(benacen)(4-CNpy)	<i>s</i>	1.999	2.085	2.022 <sup>h</sup>	16	19.2	13.8	115, 132
Co(benacen)( <i>n</i> -BuNH <sub>2</sub> )	<i>s</i>	1.999	2.089	2.021 <sup>q</sup>	10.7	17.7	13	132
Co(benacen)( <i>i</i> -BuNH <sub>2</sub> )	<i>s</i>	1.992	2.087	2.026 <sup>q</sup>	10.7	18.6	13.3	132
Co(benacen)( <i>sec</i> -BuNH <sub>2</sub> )	<i>s</i>	2.000	2.088	2.025 <sup>n</sup>	10.2	19.4	13.3	132
Co(benacen)(DMF)	<i>s</i>	1.999	2.093	2.025 <sup>n</sup>	14.4	29.4	14.8	132
Co(benacen)(PPh <sub>3</sub> )	<i>s</i>	1.996	2.082	2.024 <sup>n</sup>	14	15.5	13.5	115, 132
Co(benacen)(EtSMe)	<i>s</i>	1.999	2.096	2.022 <sup>n</sup>	13	25.8	15.5	115, 132
Co(benacen)	<i>s</i>	1.999	2.093	2.025 <sup>n</sup>	14.5	29.4	14.8	115
Co(amben)(py)	toluene	2.007	2.083	2.018 <sup>r</sup>	16.5	20.0	15	115
Co(amben)(py)	50% py/CH <sub>2</sub> Cl <sub>2</sub>	1.995	2.079	2.023 <sup>i</sup>	10.2	18.2	12.9	133
Co(NO <sub>2</sub> amben)(py)	10% py/toluene	2.000	2.082	2.027 <sup>k</sup>	13.0	17.6	14.5	115
Co(MeOamben)(py)	toluene	1.996	2.083	2.005 <sup>t</sup>	15.5	20.0		115
Co(cyen)(py)	50% py/DMF	1.996	2.082	2.015 <sup>r</sup>	15.5	18.3	15.5	115
Co(salpy)	20% DMF/toluene	1.998	2.078	2.025	15.5	19.0	14	115
Co(saloph)(py)	50% py/CHCl <sub>3</sub>	2.007	2.08		13.2	16.9		139
Co(saloph)(py)	50% py/CH <sub>2</sub> Cl <sub>2</sub>	1.994	2.081	2.023 <sup>h</sup>	9.6	16.8	12.2	133
Co(saloph)(py)	py	1.995	2.082	2.024 <sup>j</sup>	10.0	17.6	12.5	<i>d</i>
Co(ptam)(py)	py		2.076			18.2		<i>d</i>
Co(tetane)(py)	10% py/MeOH	1.992	2.102	2.029 <sup>r</sup>	17.5	21.6	15.5	115
Co(diene)(py)	10% py/MeOH	1.987	2.075	2.034 <sup>q</sup>	18.7	27.3	15	115
Co(tetene)(py)	10% py/MeOH	1.995	2.054	2.008 <sup>q</sup>	10.0	12.4		115
Co(Me <sub>6</sub> [14]4,11-dieneN <sub>4</sub> (Im) <sup>2+</sup> )	DMF	2.007, 1.999	2.0843		13.3, 13.3	20.8		92
Co(T( <i>p</i> -MeO)PP)(py)	toluene	2.002	2.077	2.013 <sup>q</sup>	12.0	16.3	10.4	115
Co(T( <i>p</i> -MeO)PP)(py)	toluene	2.002	2.077		10.7	16.6		130c
Co(T( <i>p</i> -MeO)PP)(py)	toluene	2.002	2.077		11.4	17.1		128
Co(T( <i>p</i> -MeO)PP)(2-Mepy)	toluene	2.000	2.076		11.5	16.8		128



Table VII. (Continued)

compound	solvent	$g_{\perp}$	$g_{\parallel}$	$g_{iso}$	$A_{\perp}^{Co}, G$	$A_{\parallel}^{Co}, G$	$A_{iso}, G$	ref
Co(T( <i>p</i> -MeO)PP)(3-Mepy)	toluene	2.000	2.073		10.6	16.6		128
Co(T( <i>p</i> -MeO)PP)(4-Mepy)	toluene	2.001	2.024		11.0	16.9		128
Co(T( <i>p</i> -MeO)PP)(3,4-Me <sub>2</sub> py)	toluene	2.001	2.074		10.3	16.4		128
Co(T( <i>p</i> -MeO)PP)(3,5-Me <sub>2</sub> py)	toluene	2.001	2.073		10.5	16.3		128
Co(T( <i>p</i> -MeO)PP)(2,4,6-Me <sub>3</sub> py)	toluene	1.998	2.076		10.6	16.8		128
Co(T( <i>p</i> -MeO)PP)(quin)	toluene	2.002	2.074		11.0	16.8		128
Co(T( <i>p</i> -MeO)PP)(Melm)	toluene	2.002	2.086		10.5	16.7		128, 130c
Co(T( <i>p</i> -MeO)PP)(pyrrole)	toluene	2.004	2.081		11.4	18.9		128
Co(T( <i>p</i> -MeO)PP)(pip)	toluene	2.002	2.076		11.1	16.9		128
Co(T( <i>p</i> -MeO)PP)(quine)	toluene	1.998	2.074		13.0	16.7		128
Co(T( <i>p</i> -MeO)PP)( <i>n</i> -hexylamine)	toluene	2.002	2.077		10.7	16.4		128
	toluene	~1.998, 1.993	~2.05		~29.1, 30.1	~12.5		140
Co(TPP)(CH <sub>3</sub> CN)	toluene	2.004, 1.995	2.076		17.7, 17.8	15.6		140
Co(TPP)(CO)	toluene	~2.014	~2.07		~9.6	~12.4		140
Co(PPIXDME)(DMF) <sup>f</sup>	DMF			2.0197			11.47	168b
Co(PPIXDME)(py) <sup>f</sup>	CH <sub>3</sub> CN			2.0207			11.88	168b
Co(PPIXDME)(py) <sup>n</sup>	toluene			2.02			11.8	168b
Co(PPIXDME)(Im)	toluene	1.99	2.08			16.4		122
Co(PPIXDME)(Melm)	toluene	1.99	2.083			16.7		122
Co(PPIXDME)(BzIm)	toluene	1.99	2.08					122
Co(TpivPP)(Melm)	toluene	2.01	2.09			~20		164
Co(MPHDME)(py)	50% py/CHCl <sub>3</sub>	2.003	2.08		11.1	17.4		139
Co(saldpt)	<i>u</i>	2.007, * 2.000	*2.085 *	2.030 $\nu$	13.3, * 13.5 *	22.7 *	13.6 $\nu$	130d
Co(3-MeOsaldpt)	<i>u</i>	2.007, * 2.000	*2.091 *	2.030 $\nu$	13.1, * 13.6 *	20.7 *	13.7 $\nu$	130d
Co(5-MeOsaldpt)	<i>u</i>	2.008, * 2.003	*2.089 *	2.031 $\nu$	13.3, * 13.5 *	22.7 *	13.6 $\nu$	130d
Co(5-NO <sub>2</sub> saldpt)	<i>u</i>	2.002, * 1.999	*2.082 *	2.028 $\nu$	12.9, $\nu$ 14.2 *	21.6 *	13.3 $\nu$	130d
Co( $\alpha$ -Mesaldpt)	<i>u</i>	2.006, * 2.001	*2.091 $\nu$	2.003 $\nu$	12.7, * 14.7 *	21.3 *	13.9 $\nu$	130d
Co(salMedpt)	<i>u</i>	2.005, * 1.999	*2.086 $\nu$	2.030 $\nu$	12.0 *, 13.6 *	18.7 *	12.4 $\nu$	130d
Co(3-MeOsalmMedpt)	<i>u</i>	2.009, * 1.988	*2.090 *	2.033 $\nu$	12.1 *, 14.3 *	18.6 *	12.4 $\nu$	130d
Co(5-MeOsalmMedpt)	<i>u</i>	2.011, * 2.003	*2.091 $\nu$	2.035 $\nu$	12.3, * 14.1 *	19.6 *	12.6 $\nu$	130d
Co( $\alpha$ -MesalmMedpt)	<i>u</i>	2.004, * 1.998	*2.089 *	2.024 $\nu$	13.0, * 14.9 *	19.7 *	13.4 $\nu$	130d
Co(sal- <i>n</i> -Prdpt)	<i>u</i>	2.006, * 1.997	*2.084 $\nu$	2.022 $\nu$	12.1, * 13.9 *	19.0 *	13.5 $\nu$	130d
Co(sal- <i>i</i> -Budpt)	<i>u</i>	2.004, * 1.997	*2.087 *	2.025 $\nu$	12.1, * 14.3 *	19.3 *	13.4 $\nu$	130d
Co(salBzdpt)	<i>u</i>	2.004, * 1.998	*2.086 *	2.022 $\nu$	13.1, * 14.6 *	19.6 *	13.9 $\nu$	130d
Co(salPhdpt)	<i>u</i>	2.004, * 1.997	*2.088 *		16.0, * 17.0 *	22.6 *		130d
Co(salMeOPhdpt)	<i>u</i>	2.002, * 1.995	*2.084 *		14.6, * 16.9 *	22.1 *		130d
Co(5-Brsaldape)	<i>u</i>	2.004, * 1.996	*2.091 *		17.6, * 18.7 *	28.8 *		130d
Co(5-Claldape)	<i>u</i>	2.003, * 1.995	*2.090 *		16.4, * 19.1 *	27.6 *		130d
Co(5-BrsalmMedapp)	<i>u</i>	2.010, * 2.000	2.009 *		14.3, * 18.6 *	23.7 *		130d
Co(3-MeOsalmMedapp)	<i>u</i>	2.009, * 2.000	*2.097 *	2.034 $\nu$	14.3, * 19.1 *	23.6 *	14.3 $\nu$	130d

<sup>a</sup> Measured at 77 K, unless otherwise noted. <sup>b</sup>  $g_{\perp}$  and  $A_{\perp}^{Co}$  calculated from  $g_{\perp} = \frac{1}{2}(3g_{iso} - g)$  and  $A_{\perp} \cong \frac{1}{2}(3A_{iso} - A)$ . <sup>c</sup> Measured at  $-48^{\circ}C$ . <sup>d</sup> D. L. Diemente, Ph.D. Thesis, Northwestern University, Evanston, Ill., 1971. <sup>e</sup> Measured at  $-66^{\circ}C$ . <sup>f</sup> Measured at  $20^{\circ}C$ . <sup>g</sup> Spectrum not well resolved. <sup>h</sup> Measured at  $-70^{\circ}C$ . <sup>i</sup> Measured at  $-44^{\circ}C$ . <sup>j</sup> Measured at  $-35^{\circ}C$ . <sup>k</sup> Measured at  $-10^{\circ}C$ . <sup>l</sup> Measured at  $-15^{\circ}C$ . <sup>m</sup> Measured at  $-77^{\circ}C$ . <sup>n</sup> Measured at  $-74^{\circ}C$ . <sup>o</sup> Measured at  $-61^{\circ}C$ . <sup>p</sup> Measured at  $-25^{\circ}C$ . <sup>q</sup> Measured at  $-52^{\circ}C$ . <sup>r</sup> Measured at  $-80^{\circ}C$ . <sup>s</sup> Solvent was 70% toluene-20% DMF-10% base ( $\sim 1 M$ ). <sup>t</sup> Measured at  $-95^{\circ}C$ . <sup>u</sup> Measured in toluene/dichloromethane. <sup>v</sup> Measured at  $24^{\circ}C$ . <sup>w</sup> Measured at  $\sim 150^{\circ}C$ .

indeed function as oxygen-carrying proteins. Studies involving EPR showed that the cobalt atom in deoxy-CoMb and CoHb is five-coordinate and, as is true for the iron in natural proteins, is coordinated to the imine nitrogen of the proximal histidine residue.<sup>152</sup> Further, Co(PPIX) has the same orientation within the protein as does the heme.<sup>153,154</sup> Comparison with the spectrum of the monoimidazole complex of Co(PPIXDME) in organic solvents shows that the five-coordinate Co(II) of CoHb exhibits no significant perturbations which are caused by its incorporation into the protein environment.<sup>152</sup> Exposing CoHb (CoMb) to oxygen gives oxy-CoHb (oxy-CoMb).<sup>152-158</sup> EPR studies again show that the Co-O<sub>2</sub> linkage within the protein is not significantly different from that of an oxygenated cobalt porphyrin in solution ( $g_{\perp} = 2.08$ ,  $g_{iso} = 2.02$ ,  $A_{iso}^{Co} = 118 G$ ,  $A_{\perp}^{Co} \approx 9 G$ ).

Comparisons of the properties of the naturally occurring heme group both in and out of a protein environment were previously impossible, since heme cannot ordinarily be prepared in a five-coordinate state and heme in solution is oxidized to hemin upon exposure to oxygen. Hoffman and co-workers<sup>159</sup> reported the first such comparison when Mössbauer parameters of the daughter compound of <sup>57</sup>Co(PPIX)(py)(O<sub>2</sub>) agree well with the values for oxy-myoglobin,<sup>160</sup> suggesting that the electronic structure of the heme iron in oxy-Hb is not measurably influenced by the protein. This parallels the conclusions from EPR studies

TABLE VIII. Values of  $\nu_{O-O}$  for Cobalt-Dioxygen Complexes

compound	$\nu_{O_2}, cm^{-1}$ <sup>a</sup>	ref
Co(3-MeOsalen)(py)(O <sub>2</sub> )	1140	34
Co(acacen)(B)(O <sub>2</sub> ) <sup>b</sup>	~1130	110
Co(benacen)(py)(O <sub>2</sub> )	1128	c
Co(cyen)(py)(O <sub>2</sub> ) <sup>d,e</sup>	1137, 1078 <sup>f</sup>	g
Co(cyen)(Melm)(O <sub>2</sub> ) <sup>e,h</sup>	1137	g
[Co(CN) <sub>5</sub> (O <sub>2</sub> )] <sup>3-</sup>	1138 <sup>i</sup>	147
Co(TpivPP)(NTrIm)(O <sub>2</sub> ) <sup>k</sup>	1153, <sup>j</sup> 1077, <sup>f</sup> 1125 <sup>k</sup>	145
Co(TpivPP)(Melm)(O <sub>2</sub> )	1150, 1077 <sup>f</sup>	145
Hb(Co(deut))(O <sub>2</sub> ) <sup>l</sup>	1105, 1065 <sup>f</sup>	m

<sup>a</sup> Spectra obtained as a Nujol mull unless otherwise noted. <sup>b</sup> Values for  $\nu_{O-O}$  for B equal to py, CH<sub>3</sub>-py, NH<sub>2</sub>-py, and 4-CN-py. <sup>c</sup> J. D. Landels and G. A. Rodley, *Synth. Inorg. Met.-Org. Chem.*, **2**, 55 (1972). <sup>d</sup> Spectrum taken in 10% py in DMF. <sup>e</sup> Resonance Raman used to obtain  $\nu_{O-O}$ . <sup>f</sup> Value is for  $\nu_{18O_2}$ . <sup>g</sup> T. Szymanski, T. W. Cape, F. Basolo, and R. P. Van Duyne, *J. Chem. Soc., Chem. Commun.*, **5** (1979). <sup>h</sup> Spectrum taken in 10% Melm in DMF. <sup>i</sup> Spectrum taken in benzene. <sup>j</sup> Doublet, with  $\nu_{18O_2} = 1155, 1150 cm^{-1}$ , due perhaps to two different conformers of O<sub>2</sub> and NTrIm. <sup>k</sup> Value is for  $\nu_{18O-18O}$ . <sup>l</sup> Spectrum taken in buffered aqueous solution. <sup>m</sup> J. C. Maxwell and W. S. Caughey, *Biochem. Biophys. Res. Commun.*, **60**, 1309 (1974).

of oxy-CoHb.<sup>152</sup> Thus, the stabilization of the heme group in hemoglobin is probably not ascribable to protein-induced

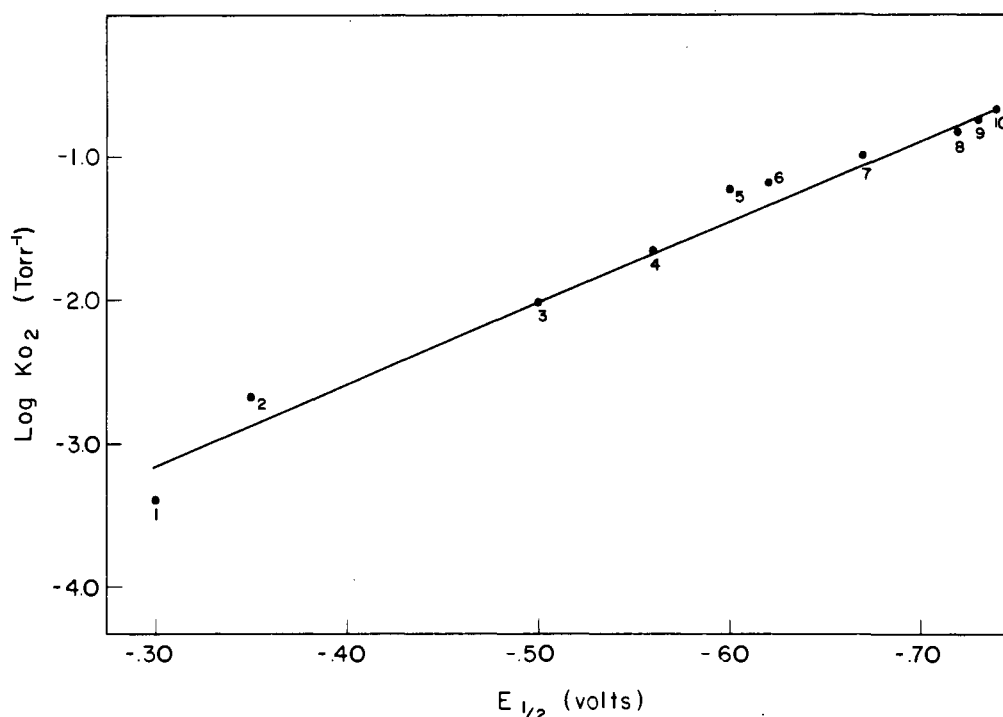


Figure 15. Comparison of oxygen uptake ( $\log K_{O_2}$ ,  $-21^\circ\text{C}$ ) with  $E_{1/2}$  values for  $\text{Co(II)} \rightarrow \text{Co(III)}$  of  $\text{Co}(\text{benacen})$  (B): (1)  $\text{PPh}_3$ ; (2) 4-CNpy; (3) py; (4) 3,4-Me<sub>2</sub>py; (5) pip; (6) *sec*-BuNH<sub>2</sub>; (10) *n*-BuNH<sub>2</sub> (data from refs 132 and 165).

changes at the electronic state of the iron in oxyheme.

A chief source of the ongoing interest in ligand binding to hemoglobin rests in the following allosteric properties which result from its tetrameric nature.<sup>60a</sup> The dioxygen binding curve is "cooperative" (autocatalytic), not hyperbolic (Figure 7). The degree of cooperative binding can be expressed by the Hill's constant,  $n$ , which has the value  $n \approx 2.8$ .<sup>161</sup> For comparison, independent O<sub>2</sub> binding by the four hemes of Hb would require  $n = 1.0$ , whereas all-or-none binding to the four hemes would require  $n = 4$ . The degree of cooperativity, as measured by the  $n$  value, appears to reflect the details of the ligation process and thus the nature and type of intermediates which occur as the four hemes of Hb react.

It was found that, for CoHb, the binding of oxygen is cooperative.<sup>152,155</sup> Hill's constant  $n$  (a measure of cooperativity) is at least 2.3 and probably as large as 2.5 when the prosthetic group is Co(PPIX).<sup>152</sup> When the prosthetic group is Co(MesP) or Co(DePP), values<sup>155</sup> for  $n$  are 1.2 and 1.5, respectively, compared with the Hb values of 2.8.<sup>161</sup> Thus in accord with Perutz's<sup>68a</sup> arguments, CoHb undergoes a quaternary structural change upon oxygenation, implying that the stereochemical changes that occur as the five-coordinate, low-spin  $\text{Co}^{\text{II}}(\text{PPIX})$  moiety of CoHb binds dioxygen are compatible with the mechanism that triggers the quaternary structural transition in Hb.

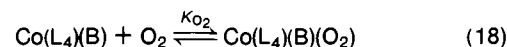
This cooperativity in CoHb has been used either to question or support Perutz's mechanism of cooperativity. Two different approaches have been used in attempts to mimic the T state of Hb. In one the cobalt has been restrained by the coordination to an axial base which is covalently attached to the porphyrin and the other uses the sterically hindered axial base 1,2-Me<sub>2</sub>Im. By varying the length of the chain<sup>162</sup> on which the axial base is attached, it was possible to enforce various amounts of steric constraint on the metal center. The greater strain resulted in a weaker cobalt-ligand bond destabilizing the dioxygen adduct. The use of a sterically hindered base<sup>163,164</sup> also destabilizes the dioxygen adduct. Both methods cause the cobalt metal center to be drawn out of the porphyrin plane toward the axial base, thus weakening the metal dioxygen bond.

#### 4. Equilibria

Since it has been found that cobalt is capable of serving as

an oxygen carrier in a natural environment, the question arises as to what properties of a metal are necessary to create an oxygen carrier. It had been suggested by Vogt et al.<sup>2</sup> in a review that in order to synthesize reversible oxygen carriers it was necessary to have metal ions that have oxidation potentials lying in a certain range so that there is some donation of electrons to the oxygen molecules but not enough to cause irreversible oxidation of the metal. This implies that metals that are readily oxidized (e.g., Cr(II)) react with oxygen irreversibly, and metals difficult to oxidize (e.g., Ni(II)) do not react with oxygen. However, metals between the two limiting redox potentials (e.g., Co(II)) should react reversibly with oxygen. They further stated that the oxidation potentials of the metal ions could be modified to fall within the range of reversible carriers by chelation with the proper ligands. Such qualitative suggestions have recently been given quantitative significance.<sup>132</sup>

Equilibrium constants,  $K_{O_2}$ , have been determined for the reaction of dioxygen with cobalt(II) in many different ligand environments (eq 18).



For a given cobalt(II)-Schiff base chelate  $\text{Co}(\text{SB}_4)$  and different axial base B, a linear correlation was found to show that as the ease of oxidation ( $E_{1/2}$  for  $\text{Co(II)} \rightarrow \text{Co(III)}$ ) of the complex increases, the dioxygen affinity ( $K_{O_2}$ ) of the complex increases (Figure 15).<sup>115,132,165,166</sup> There are enough data to show that the protonic base strength of the axial base does not correlate with oxygen uptake. For example, the values of  $K_{O_2}$  for changes in axial base decrease in the order *n*-butylamine > 1-methylimidazole > piperidine, although the  $\text{p}K_a$ 's of these protonated bases are 10.6, 7.25, and 11.3, respectively. That 1-methylimidazole is much more effective in promoting complex formation than is expected from its protonic basicity may arise from its good  $\pi$ -electron-donating property. This same type of behavior has been observed<sup>122,129,167</sup> for cobalt porphyrins. Figure 16 shows a plot of  $\log K_{O_2}$  vs.  $\text{p}K_a$  for different axial bases on Co-(PPIXDME) in toluene solution. Neither for these equilibrium constants nor for the derived thermodynamic quantities,  $\Delta H$ ,  $\Delta G$ , or  $\Delta S$ , is there a simple, general relationship that is related to the  $\text{p}K_a$ 's.

However, direct correlations between the  $pK_a$  of structurally related axial bases and  $O_2$  uptake have been observed. As the dashed line indicates (Figure 16) there is a reasonably linear correlation of the equilibrium constants with the  $pK_a$ 's of the substituted pyridine  $pK_a$ 's of the substituted pyridines. Tetraphenylporphyrin and other synthetic porphyrins yield approximately the same results. Also for the series of P-donor ligands  $P(C_6H_5)_3$ ,  $P(OC_6H_5)_3$ , and  $P(C_4H_9)_3$  with  $Co(MPIXDME)$ , Takayanagi<sup>125</sup> et al. noted a correlation between  $pK_a$  and  $\log K_B$ , and  $\log K_{O_2}$ . For uptake of an axial ligand, the  $\rho$  (slope of the line for  $pK_a$  vs.  $\log K$  and a measurement of the sensitivity of the equilibrium to  $\sigma$  donation) is much greater (0.4 vs. 0.1) for the phosphorus ligands than for nitrogen ligands. However, the  $\rho$  values for the oxygenation equilibria (eq 18) is very similar for both the phosphorus and the axial amine systems. The fact that a linear relationship is observed between the proton acidities of a series of ligands containing the same donor atom, i.e., N or P, and the equilibrium constants observed for the bonding to the cobalt(II) metal center implies either that the ligand metal  $\pi$ -bonding plays a relatively constant role or that there exists an intimate balance between  $\sigma$ - and  $\pi$ -bonding effects. Both  $\sigma$ - and  $\pi$ -bonding have been implicated in the bonding of pyridine and P-donor ligands to metals. The variation in bonding of the neutral ligand to the cobalt observed for the N- and P-donor series may therefore reflect differences in  $\pi$ -bonding between the cobalt(II) center and the nitrogen- and phosphorus-donor ligands.

Such differences can be attributed to the  $\pi$  donor properties of the ligands. In the Pauling<sup>31</sup> model the bonding of an oxygen atom to a metal complex may be explained in terms of the  $\sigma$  donation from a nonbonding  $sp^2$  lone pair on oxygen to the  $d_{z^2}$  orbital on the metal, accompanied presumably by synergistic  $\pi$ -back-bonding from the filled  $d_{xz}$  (or  $d_{yz}$ ) orbitals into the empty  $\pi^*$  orbitals of oxygen. Since ligands coordinated trans to oxygen will compete for  $\pi$ -electron density on the metal, the binding of  $O_2$  to  $Co(Por)(B)$  will be sensitive to the  $\pi$ -donating ability or  $\pi$ -accepting ability of the axial ligand B. Good  $\pi$ -acceptors will decrease  $\pi$ -electron density on the metal, resulting in a poorer oxygen carrier, whereas good  $\pi$  donors will promote oxygenation by increasing the electron density available for back-bonding. Imidazoles are much better  $\pi$  donors than pyridines; the strong  $\pi$ -donor properties of DMF have also been demonstrated. On the other hand, the  $\log K_{O_2}$  for piperidine is much less than that expected from basicity arguments. It is possible here that steric effects play a role through the interactions of the ring protons with parts of the porphyrin core, preventing close approach of the base to the metal.

The observed correlation between  $E_{1/2}$  values and  $\log K_{O_2}$  for base variation also holds for the variation of the equatorial ligand.<sup>109,132</sup> The greater the amount of electron density on the cobalt metal center, the greater the oxygen affinity. In varying the para substituents of the phenyl groups of  $Co(T(p-X)PP)(py)$ , Walker et al.<sup>124</sup> found a Hammett relationship between  $4\sigma$  and  $\log K_{O_2}$ ; again this is related to the amount of electron density at the cobalt center. Recently Cummings<sup>113</sup> and co-workers using  $Co(sacsacen)(Melm)$  found that the  $N_2S_2$  type ligands show less oxygen affinity than those of the ketoiminato counterparts ( $N_2O_2$  type). This is due to the poorer  $\sigma$  donor properties of the sulfur donor atoms. In addition the sulfur donors can drain electron density from the cobalt ion via a  $\pi$ -back-bonding interaction between filled  $d_{xz}$  and  $d_{yz}$  orbitals on the metal and empty d orbitals on the sulfurs. In addition the para substituents of  $Co(p-Xbenacen)$  and  $Co(p-Xbenacen)$  were varied and their effects on  $\log K_{O_2}$  were studied. It was found that the variation of para substituents resulted in a non-Hammett behavior of  $\log K_{O_2}$ . The trends observed,  $\log K_{O_2}$  for  $p-Cl$  greater than  $\log K_{O_2}$  for  $p-OCH_3$ , cannot be explained simply on the basis of inductive effects and Hammett-Taft parameters. Since the rings of these systems are expected to be coplanar with the  $Co-N_2O_2$  and  $Co-N_2S_2$ , the author explains his results in part to the domi-

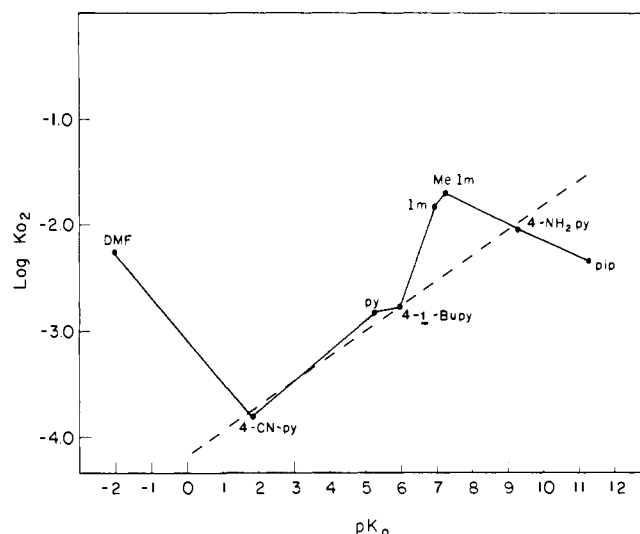


Figure 16. Comparison of  $\log K_{O_2}$  (toluene,  $-45^\circ C$ ) for  $Co(PPIXDME)(B)$  as a function of the  $pK_a$  of the axial base (B) (data from ref 129).

nance of  $\pi$  effects (resonance interactions) over  $\sigma$  effects (inductive contributions). Also solvent effects may contribute to this anomalous behavior. Furthermore, it has been noted<sup>168b</sup> that a change from a nonpolar solvent such as toluene to the polar solvent DMF has a pronounced effect<sup>132</sup> on the equilibrium (eq 18). In toluene ( $\epsilon = 2.4$ ) at  $-23^\circ C$   $Co(PPIXDME)(1-Melm)$  has a  $\log K_{O_2}$  of  $-2.62$ , while in DMF ( $\epsilon = 36.1$ ) at the same temperature  $\log K$  is  $-1.10$ . This large solvent effect can be ascribed to the stabilization of the polar  $Co(III)-(O_2^-)$  species in the more polar solvents.

For changes in the equatorial ligand,<sup>115,132</sup> keeping the same axial base, there is a linear correlation between  $\log K_{O_2}$  and the  $E_{1/2}$  value for the various cobalt(II) complexes. Basolo<sup>132</sup> et al. suggested that this correlation exists because the redox potential of the cobalt chelate provides a measure of the electron density on the cobalt metal center, which appears to be the major factor in determining  $O_2$  affinity. Increasing electron donor properties of the equatorial tetradentate ligand or the axial base results in an increase in the equilibrium constant  $K_{O_2}$ . The lower oxygen affinity<sup>117</sup> exhibited by  $Co^I(benacen)(py)$  ( $\log K = -0.28$  at  $31^\circ C$ ) results from the electron-withdrawing effect of the aromatic rings in the former.

It also follows that the fact that cobalt(II)-porphyrin complexes have a smaller tendency to form dioxygen complexes than do cobalt(II) Schiff base complexes may result from the porphyrin ligand having a greater tendency to delocalize  $\pi$  electron density away from the cobalt atom than do the less aromatic Schiff base ligands.

In addition to electronic effects, steric factors can greatly influence oxygen affinity. Ugo and others<sup>167</sup> have shown that the ethylene-bridge-substituted compounds of  $Co(salen)$  exhibit differing behavior toward oxygen in  $\sigma$ -donor solvents, mainly due to the effects of the substituent on the coordination sphere around the cobalt center. For example, in the complex  $Co(salpn)(py)$  the coordination of  $Co(salpn(+))$  can be viewed as a distorted square pyramid, where  $Co(salpn(meso))$  is intermediate between a square pyramid and a trigonal bipyramid. These differences in the coordination polyhedra are thought to account for the differences in oxygen affinity with  $Co(salpn(+))$  being much more reactive.

## 5. Thermodynamics

Thermodynamic data for ligand and dioxygen uptake by cobalt(II) complexes of Schiff bases and of porphyrins are given in Tables IX and X. A comparison of  $\log K_B$ ,  $\Delta H$ , and  $\Delta S$  for ligand uptake demonstrates that no simple correlation exists

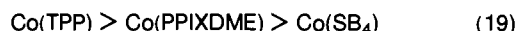
TABLE IX. Thermodynamic Values for the Binding of Axial Bases <sup>a</sup> to Cobalt(II) Complexes

Co(L <sub>4</sub> ) + B ⇌ Co(L <sub>4</sub> )(B)					
compound	base	ΔH, kcal/mol	ΔS, (eu/mol)	ref	
Co(T( <i>p</i> -OCH <sub>3</sub> )PP)	py	-8.5	-16	127	
	4-Mepy	-7.3	-11	127	
	3,4-Lut	-9.0	-16	127	
	Quin <sup>b</sup>	~0	-6	127	
	Melm	-11.4	-23	127	
	<i>N</i> -acIm <sup>c</sup>	-10.1	-20	127	
Co(PPIXDME)	pip	-6.8	-7	127	
	DMF	-7.9	-21	129	
	4-CNpy	-10.0	-19	129	
	py	-6.9	-6	129	
	py	-9.7	-18	171	
	Im	-7.9	-10	129	
	Melm	-10.7	-19	129	
	4-NH <sub>2</sub> py	-8.1	-9	129	
Co(MPIXDME)	pip	-10.4	-17	129	
	4- <i>t</i> -Bupy	-9.0	-13	129	
	py	-9.2	-17	125	
	P( <i>n</i> -Bu) <sub>3</sub>	-13.3	-27	171	
	P(OCH <sub>3</sub> ) <sub>3</sub>	-6.9	-15	125	
	PPh <sub>3</sub>	-7.0	-17	125	
Co(salen) <sup>d</sup>	AsPh <sub>3</sub>	-5.2	-15	125	
	S(CH <sub>3</sub> ) <sub>2</sub>	-4.5	-9	125	
	py	-7.8	-21	e	
	Co(sal(±)dpn) <sup>d</sup>	py	-8.8	-28.0	e
	Co(sal(m)dpn) <sup>d</sup>	py	-8.6	-27.0	e
	Co(sal(±)chpn) <sup>d</sup>	py	-6.5	-17.0	e
Co(sal(m)chpn) <sup>d</sup>	py	-7.4	-21.0	e	

<sup>a</sup> Solvent is toluene, unless otherwise noted. <sup>b</sup> Quinoline. <sup>c</sup> *N*-Acetyl-imidazole. <sup>d</sup> Values obtained with CHCl<sub>3</sub> as the solvent. <sup>e</sup> E. Cesarotti, M. Gullotti, A. Pasini, and R. Ugo, *J. Chem. Soc., Dalton Trans.*, 757 (1977).

between any of these parameters and the p*K*<sub>a</sub> of the protonated ligands. If one examines the data for a structurally similar series of bases, e.g., substituted pyridines, there does exist a correlation<sup>115,127,129,132</sup> between the thermodynamic data and p*K*<sub>a</sub> of the protonated ligand. A similar correlation also exists between the uptake of dioxygen and the p*K*<sub>a</sub> of the axial ligand. The values of Δ*S* for oxygenation are in the neighborhood of -60 eu. The main contribution to this value comes from the loss of degrees of freedom of dissolved dioxygen on coordination.

In the series of cobalt(II) chelates with the same axial base the following order is noted for Δ*H* and Δ*S* of oxygenation, with Co(SB<sub>4</sub>) being the most exothermic:



It is also interesting to note that the more negative Δ*H* values are associated with the more negative values of Δ*S*.

The thermodynamic values for oxygen uptake by Co<sup>II</sup>(PPIXDME)(B) complexes reported by Ibers and co-workers<sup>129,168</sup> were reanalyzed by Guidry and Drago.<sup>169</sup> They were unable to use the published data to obtain reliable values for thermodynamic properties of the system. Reanalyzing their own data, Ibers and co-workers<sup>169</sup> reaffirmed their method of analysis and values. They concluded again that there was no direct relationship between p*K*<sub>a</sub> of the axial base and log *K*<sub>O<sub>2</sub></sub>. Drago et al.<sup>170</sup> repeating the work of Ibers and co-workers found a Δ*H* of -7.80 kcal mol<sup>-1</sup> for the addition of O<sub>2</sub> to Co<sup>II</sup>(PPIXDME)(py) in toluene as compared to Ibers and co-workers<sup>129,168</sup> of -9.2 kcal mol<sup>-1</sup>. Recently Yamamoto<sup>171</sup> et al. investigating the same system reported Δ*H* for the same reaction as -10.3 kcal mol<sup>-1</sup>. These discrepancies may be largely due to the difficulties in obtaining good thermodynamic values on such systems.

Also shown in Table IX for comparison are the corresponding data for CoMb and Mb. The influence of the globin (apoprotein) can be directly observed by comparing the oxygen binding of the five-coordinate Co(PPIXDME)(Melm) complex with that of

CoMb. Although producing no major effect on the electronic structure of the oxygen adduct, the globin does produce a large effect on its oxygen affinity. At 25 °C, the incorporation of Co(PPIX) into globins of whale or horse myoglobins increases the value of *K*<sub>O<sub>2</sub></sub> by a factor of ~300.<sup>129,156</sup> It is found for horse myoglobins that the protein provides a significantly favorable<sup>63</sup> (positive) entropic contribution to O<sub>2</sub> binding whereas the enthalpic term is experimentally the same as that for the free metalloporphyrin in toluene solution. For whale CoMb there is a balance between a more favorable entropic (positive) and enthalpic (negative) contributions to O<sub>2</sub> binding.

The basis of the more favorable entropy of dioxygen binding in the protein environment is related at least in part to the solvation effects on the binding of dioxygen. Formation of the strongly dipolar Co(III)-O<sub>2</sub><sup>-</sup> linkage from a neutral cobalt(II) porphyrin and a neutral oxygen molecule causes solvent reorganization which accommodates the charge separation and thus stabilizes the metal-dioxygen bond. This reorganization would appear thermodynamically as a negative contribution to the entropy of oxygen binding to the complex in solution. If the hydrophobic protein crevice is already organized to accommodate a polar metal-oxygen group, the negative entropy associated with the formation of the crevice would appear as part of the entropy of formation of the metalloprotein itself, not as a contribution to the entropy change upon oxygen binding.

Anomalous oxygen affinity has been noted by Collman<sup>163,164,172</sup> for his cobalt "picket-fence" porphyrin. Although Co(T(*p*-OCH<sub>3</sub>)PP)(1-Melm) has *P*<sub>1/2</sub><sup>O<sub>2</sub></sup> of 15 500 Torr<sup>164</sup> (25 °C, toluene), Co(PFP)(1-Melm) has a *P*<sub>1/2</sub><sup>O<sub>2</sub></sup> of 140 Torr<sup>163</sup> (25 °C, toluene). The value for *P*<sub>1/2</sub><sup>O<sub>2</sub></sup> of Co(PFP)(1-Melm) is similar to that of CoHb and CoMb (*P*<sub>1/2</sub><sup>O<sub>2</sub></sup> at 25 °C ~55 Torr).<sup>152,156</sup> The anomalous behavior of Co(PFP)(1-Melm) when compared to other model systems, and similarity to CoHb and CoMb, is apparently due to a control of solvation factors which otherwise disfavor oxygenation.

## 6. Reactions

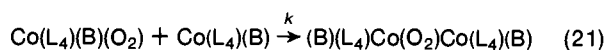
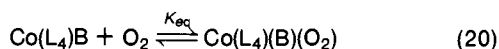
For the nonaqueous solvent system of Co(PPIXDME) in toluene qualitative EPR and visible spectroscopy observations are consistent with a rapid formation of the 1:1 complex followed by a slow reaction to yield the 1:2 species. James<sup>122</sup> et al. found that the rate-determining step appeared to be the formation of the dioxygen adduct. Since this is in direct contradiction with the bulk of qualitative measurements, they invoked a rate-determining step in which there is some slow rearrangement or distortion of the 1:1 oxygen complex. In addition, they found that when the axial base was imidazole or benzimidazole 1:1 oxygen complexes were formed, but upon warming to room temperature these complexes rapidly dimerized to the μ-peroxo compounds. This behavior is contrary to that observed when the base is 1-Melm or pyridine. This is believed due to the ability of imidazole to hydrogen bond, thus lowering the activation energy of dimerization.

This observation of possible hydrogen bonding agrees with Ochiai's<sup>130c</sup> proposed mechanism of dimerization. The cobalt-dioxygen complex has its odd electron in one of the π<sub>g</sub>\* orbitals of the oxygen. This unpaired electron may then pair with an unpaired electron in the d<sub>22</sub> orbital of another cobalt complex. This interaction is similar to the interaction between Co(II) and O<sub>2</sub> in forming the 1:1 oxygen adduct. The transition state is represented in Figure 17 and it can be seen that in the presence of bulky equatorial ligands (e.g., porphyrins) there would be considerable steric interactions. This barrier could be overcome by raising the temperature or by deforming or rotating the π<sub>g</sub>\* orbital in some way. The fact that dimerization is accelerated by imidazole and not by 1-Melm in the case of Co<sup>II</sup>(PPIXDME) may be understood in terms of its hydrogen bond forming capacity. The hydrogen bond may force rotation of the π<sub>g</sub>\* orbital, enhancing dimerization.

TABLE X. Thermodynamic Values for the Binding of Dioxygen<sup>a</sup> to Cobalt(II) Complexes:  $\text{Co(L}_4\text{)(B)} + \text{O}_2 \rightleftharpoons \text{Co(L}_4\text{)(B)(O}_2\text{)}$ 

compound	base	$\Delta H_f^b$ kcal/mol	$\Delta S_f^b$ eu/mol	ref	compound	base	$\Delta H_f^b$ kcal/mol	$\Delta S_f^b$ eu/mol	ref
Co(acacen) <sup>c</sup>	py	-15.03	-42.2	d	5-CIMelm		-8.6	-54	121
Co(acacen)	py	-17.3	-72.7	132	Melm		-8.9	-49	121
Co(Phacacen)	py	-16.3	-72.5	132	pip		-8.2	-49	121
Co(Meacacen)	py	-15.6	-69.5	132	3,4-Lut <sup>h</sup>		-8.5	-51	121
Co(benacen)	<i>n</i> -BuNH <sub>2</sub>	-17.4	-72.3	132	py <sup>h</sup>		-9.0	-53	121
	<i>i</i> -BuNH <sub>2</sub>	-18.0	-80.0	132	Co(T( <i>p</i> -CH <sub>3</sub> )PP) <sup>i</sup>	py	-9.30	-55	124
	Melm	-17.5	-73.5	132	Co(TPP) <sup>i</sup>	py	-9.54	-57	124
	5-CIMelm	-17.5	-74.5	132	Co(T( <i>p</i> -F)PP) <sup>i</sup>	py	-9.34	-56	124
	<i>sec</i> -BuNH <sub>2</sub>	-17.8	-76.1	132	Co(T( <i>p</i> -Cl)PP) <sup>i</sup>	py	-9.22	-56	124
	pip	-16.7	-71.9	132	Co(T( <i>p</i> -CN)PP) <sup>i</sup>	py	-8.39	-52	124
	3,4-Lut	-16.8	-73.9	132	Co(TPP)	3-Mepy	-8.1	-46	162
	4-CNpy	-16.9	-77.2	132	Co(2) <sup>i,k</sup>		-7.2	-40	162
	py	-13.3	-64.5	132	Co(2) <sup>k</sup>		-5.0	-34	162
	py	-16.2	-69.6	113	Co(3) <sup>i,k</sup>		-8.5	-49	162
Co(CH <sub>3</sub> Obenacen)	py	-16.5	-70.6	113	Co(PPIXDME)	<i>t</i> -Bupy	-10.0	-57	122
Co(CH <sub>3</sub> benacen)	py	-16.3	-69.8	113	Melm		-11.5	-58	122
Co(Brbenacen)	py	-17.1	-72.4	113	Im		-11.2	-58	122
Co(Clbenacen)	py	-17.3	-72.8	113	BzIm		-9.6	-56	122
Co(bensacen)	py	-8.05	-46.5	113	py		-9.2	-53	122
Co(CH <sub>3</sub> Obensacen)	py	-10.8	-57.6	113	py		-7.80	-48.7	170
Co(CH <sub>3</sub> bensacen)	py	-11.2	-57.8	113	py		-10.3	-57	171
Co(Brbensacen)	py	-12.1	-61.1	113	py <sup>e</sup>		-14.5	-66	171
Co(Clbensacen)	py	-13.3	-66.3	113	2-Melm <sup>e</sup>		-14.6	-66	171
Co(sacacen)	py	-16.6	-75.1	132	Co(MPIXDME)	P(OCH <sub>3</sub> ) <sub>3</sub>	-10.3	-57	125
	py	-12.0	-61.5	113		P( <i>n</i> -Bu) <sub>3</sub>	-11.8	-59	125
	DMF	-14.1	-71.3	113		S(CH <sub>3</sub> ) <sub>2</sub>	-8.1	-52	125
	Melm	-15.4	-75.0	113		py	-9.01	-50	171
	Melm <sup>e</sup>	-16.1	-75.6	113		py <sup>e</sup>	-12.0	-57	171
	Melm <sup>f</sup>	-18.5	-80.9	113		2-Melm <sup>e</sup>	-12.9	-59	171
Co(sal(±)dpen) <sup>c</sup>	py	-10.3	-42.1	g	Co(DPIXDME)	py	-9.9	-55	171
Co(sal(m)dpen) <sup>c</sup>	py	-17.2	-58.1	g		py	-13.7	-60	171
Co(sal(±)chxm) <sup>c</sup>	py	-12.9	-46.2	g		2-Melm	-13.1	-60	171
Co(sal(m)chxm) <sup>c</sup>	py	-14.1	-53.3	g	Co(TpivPP)	Melm <sup>f</sup>	-13.3	-53.2	163, 164
Co(T( <i>p</i> -OCH <sub>3</sub> )PP)	py	-9.3	-55	121		Melm	-12.2	-51.2	163, 164
	4-Pic	-8.8	-52	121		1,2-Me <sub>2</sub> Im	-11.8	-53.2	163, 164
	3,4-Lut	-9.2	-54	121	CoMb		-11.9	-47.6	197b
	4-Me <sub>2</sub> Npy	-8.5	-48	121	CoHb		-7.5	-35.1	197b
	γ-CoI	-9.5	-58	121					

<sup>a</sup> Solvent used is toluene unless otherwise noted. <sup>b</sup> Standard state 1 Torr unless otherwise noted. <sup>c</sup> Values obtained with piperidine as the solvent. Standard state 1 atm. <sup>d</sup> G. Amiconi, M. Brunori, E. Antonini, G. Taugher and G. Costa, *Nature (London)*, 228, 549 (1970). <sup>e</sup> Values obtained with DMF as the solvent. <sup>f</sup> Values obtained with CH<sub>3</sub>CN as the solvent. <sup>g</sup> E. Cesarotti, M. Gullotti, A. Pasini and R. Ugo, *J. Chem. Soc., Dalton Trans.*, 757 (1977). <sup>h</sup> Values obtained with CS<sub>2</sub> as the solvent. <sup>i</sup> Values calculated from data in ref 124. <sup>j</sup> Values obtained with CH<sub>2</sub>Cl<sub>2</sub> as the solvent. <sup>k</sup> Number in parentheses represents porphyrin: (2) 5-[2-(4-(3-pyridylcarbamide)-*n*-butoxy)phenyl]-10,15,20-tritylporphyrin; (3) 5-[2-(3-pyridyl)propoxy]phenyl-10,15,20-tritylporphyrin. <sup>l</sup> Values are for solid state.



Whether the 1:1 or 1:2 complex is observed depends on  $K_{\text{eq}}$  (eq 20) and  $k$  (eq 21). Kinetically the 1:1 adducts can be stabilized by use of low temperatures. At these temperatures the reaction to form the dimeric  $\mu$ -peroxo complex is virtually stopped. For example  $\text{Co(salen)(py)}^{34}$  reacts at room temperature with oxygen to form  $\mu$ -peroxo dimer,<sup>2</sup> whereas at  $-70^\circ\text{C}$ , only the formation of the 1:1 complex is observed.<sup>139</sup> The presence of bulky equatorial ligands, such as porphyrins, also hinder dimerization.

James et al.<sup>122</sup> noted in their studies on  $\text{Co}^{\text{II}}(\text{PPIXDME})$  complexes that if  $K_{\text{eq}}$  (eq 20) is small, only the reaction to give the 1:1 complex is detected. If  $K_{\text{eq}}$  is large the rapid reaction to give the 1:1 oxygen complex and the subsequent reactions can be observed. The equilibria between 1:1 and 1:2 are very solvent dependent. Since a charge separation is present in the 1:1 oxygen complexes, the use of polar solvent stabilizes the 1:1 adducts, as mentioned earlier. The less polar solvents afford

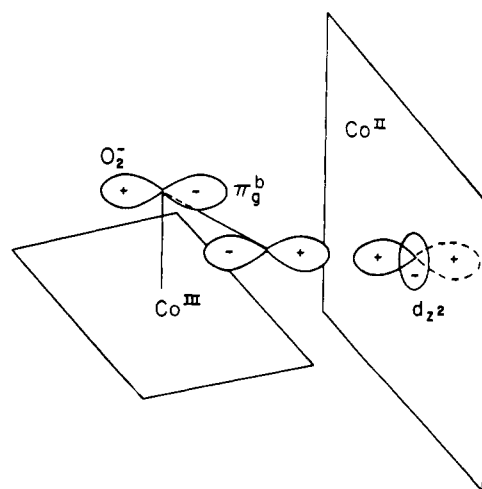


Figure 17. Arrangement in the transition state of  $\pi_g^b$  ( $\text{Co}^{\text{III}}\text{O}_2^-$ ) and  $d_z^2$  ( $\text{Co}^{\text{II}}$ ) in the formation of the 2:1 complex.

greater stability to the dimer over the monomer. Thus the choice of solvent greatly influences the system as to whether the 1:1 or 1:2 adducts will be observed.

It is interesting to note that the "stoichiometry switch" from binuclear to mononuclear complexation occurs with relatively little change in electronic structure. The EPR spectra of the parent compounds of the 1:1 and 1:2 dioxygen complexes show very little differences. McLendon and Mason<sup>114</sup> studied the binding of O<sub>2</sub> by cobalt(II) complexes of 14-member macrocycles. With increased oxidation of the macrocycle ligand, they found that the oxygen affinity of the complex drops dramatically, and a change to 1:1 stoichiometry occurs. This behavior correlates well with the observed behavior of cobalt-Schiff base and -porphyrin complexes. The more oxidized cobalt-porphyrin complexes are poorer oxygen binders and are less likely to form 1:2 complexes.

Theoretical calculations on the nature and geometry of the coordinated dioxygen in Co(acacen)(B)(O<sub>2</sub>) have been performed by Veillard et al.<sup>37</sup> Using ab initio SCF calculations with a minimal basis set, the calculated configuration is a Co(III)-(O<sub>2</sub><sup>-</sup>) with an end-on bent structure. Furthermore the calculations showed a direct relationship between the ease of oxygenation, the  $\sigma$ -donor ability of the fifth ligand, and the ease of oxidation of cobalt(II) to cobalt(III). The calculations support a formal description of Co(III)-(O<sub>2</sub><sup>-</sup>), where a bond is formed between the unpaired electron in the cobalt d<sub>22</sub> orbital and an electron in a  $\pi_g^*$  orbital of the dioxygen. This leaves one unpaired electron in an orbital of most oxygen  $\pi_g^*$  character. Though formally Co(III)-(O<sub>2</sub><sup>-</sup>), population analysis indicates that a negative charge of 0.44 to 0.64 is present on the dioxygen moiety, concomitantly there is a decrease of 0.48 of an electron from the d<sub>22</sub> orbital. The variation in electron population on the oxygen is due to the variation of the axial base.

If the coordinated dioxygen is superoxide-like it should be possible to add superoxide to cobalt(III) and obtain the same complex as if one had added O<sub>2</sub> to a cobalt(II) complex. This was done by Ellis and co-workers<sup>173</sup> when they added electrochemically generated free superoxide in DMF to the cobalt(III) complex aquocobalamin (vitamin B<sub>12a</sub>). Since aquocobalamin undergoes rapid ligand substitution in the axial positions, it was possible to coordinate the free superoxide. The EPR spectra at -170 °C ( $g = 1.999$ ,  $A_{Co} = 11.8$  G) were identical with those of the cobalt(II) aquocobalamin complex (reduced by NaBH<sub>4</sub>) product when reacted with oxygen ( $g = 1.998$ ,  $A_{Co} = 11.7$  G), providing support for the formalism of Co(III)-(O<sub>2</sub><sup>-</sup>).

Simic and Hoffman<sup>174</sup> reacted O<sub>2</sub><sup>-</sup> with Co(I), Co(II), and Co(III) chelate complexes in aqueous systems. They found that superoxide did not bind to their Co(III) chelate, [Co<sup>III</sup>(1,3,8,10-tetraeneN<sub>4</sub>)]<sup>3+</sup>. They did note that superoxide did bind to the cobalt(II) species, [Co<sup>II</sup>(1,3,8,10-tetraeneN<sub>4</sub>)]<sup>2+</sup> and [Co<sup>II</sup>(4,11-dieneN<sub>4</sub>)]<sup>2+</sup>. The resulting spectra of the adducts were not those of the corresponding Co(I) or Co(II) complexes, ruling out O<sub>2</sub><sup>-</sup> as a simple electron transfer agent. It was believed that the O<sub>2</sub><sup>-</sup> added to the metal center at a labile axial site. The resulting complexes display intense charge-transfer bands.

Since the addition of O<sub>2</sub><sup>-</sup> to Co(III) complexes generates the dioxygen adduct, the logical extension would be the generation of O<sub>2</sub><sup>-</sup> from the dioxygen complex. This has indeed been done, with the generation of LiO<sub>2</sub> from a cobalt(II) complex and O<sub>2</sub>.<sup>175</sup> Costa et al. using Co(salen) in pyridine solution, with added lithium perchlorate and oxygen present, electrocatalytically generated LiO<sub>2</sub>. A coordinated superoxide ion is postulated as the intermediate which transfers the superoxide moiety to a lithium ion forming LiO<sub>2</sub>.

## 7. Catalysis

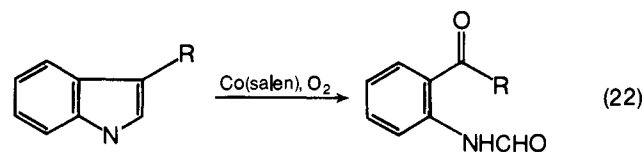
There is currently interest in the development of metal porphyrin catalysts. Approaches to the problem include the synthesis of "face to face"<sup>176</sup> or "cofacial"<sup>177</sup> diporphyrins, and also attachment of a metalloporphyrin to a rigid support. The cobalt "face to face" systems of Collman<sup>176</sup> show some

metal-metal interactions as evidenced from EPR and visible spectra. No attempt was made to study the interaction of the system with oxygen. However, Chang,<sup>177</sup> using a similar "cofacial" system, found that his system rapidly formed a type IIb complex when it reacted with oxygen in a toluene-dichloromethane mixture at room temperature.

Earlier less elaborate experiments involved the attachment of the porphinatocobalt(II) complex either covalently or coordinately to a support. Misono and co-workers<sup>178-180</sup> showed that when cobalt-Schiff base complexes were coordinately attached to poly(4-vinylpyridine) they reversibly bound dioxygen from 40 to 140 °C. This behavior was also noted for some cobalt porphyrins coordinately bound to copolymers<sup>178,181</sup> derived from styrene and 1-vinylimidazoles.

Numerous cobalt porphyrin and phthalocyanine systems have been used as catalysts for the oxidation of organic substrates. Hara and co-workers<sup>182-184</sup> have used phthalocyanatocobalt as a catalyst for the oxidation of organic substrates such as cumene and acrolein. In these systems a metal-dioxygen complex is formed which in turn initiates the oxidation process by abstracting a hydrogen atom from the substrate. This is followed by a series of radical reactions leading to the insertion of oxygen in the substrate. Similar to this is the oxidation of aldehydes by the same systems,<sup>185</sup> the initial step again being the formation of a radical by the abstracting of a hydrogen atom by a cobalt-dioxygen complex. Ohkatsu<sup>186,187</sup> and Tezuka<sup>188</sup> noted the same behavior of Co(T(*p*-CH<sub>3</sub>)PP) and Co(TPP).

A better model for natural systems is the insertion of dioxygen in the catalytic oxidation of indoles (eq 22).<sup>189,190</sup> The catalyst



can be either Co(salen)<sup>188,189</sup> or Co(TPP).<sup>190</sup> The oxidation products are the same as those observed for the oxidation of tryptophan by 2,3-dioxygenase. In the natural system<sup>191</sup> it has been demonstrated that the reaction intermediate is a transient superoxo complex.

Electrogenerated superoxide ion reacts with hydrocarbons having labile hydrogens. It was found that the addition of cobalt-phthalocyanine complexes to these systems<sup>192,193</sup> accelerated the reactions. The acceleration was believed due to the complexation of the generated superoxide ion to the metal center. The coordinated peroxo group would then facilitate the oxidation of the substrate.

## C. Cobalt-Dioxygen Complexes in Aqueous Solutions

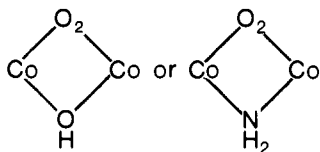
Much of the research on synthetic oxygen carriers has been done with metal complexes in aprotic solvents. Such solvents are believed to create an environment at the metal site similar to that provided by the hydrophobic pocket of the natural oxygen carriers. The use of protonic solvents often results in the irreversible dioxygen oxidation of the metal complex. However, it has long been known that certain cobalt(II) complexes reversibly react with dioxygen in aqueous solution. In fact the first dioxygen complex, [(NH<sub>3</sub>)<sub>5</sub>Co-O<sub>2</sub>-Co(NH<sub>3</sub>)<sub>5</sub>]<sup>4+</sup>, was isolated from aqueous solution in 1898 by Werner and Mylius.<sup>57</sup> The complex is readily prepared by the air oxidation of an ammoniacal solution of a cobalt salt. The complex has been extensively investigated with a variety of modern physical techniques, and it is known to be correctly formulated as a  $\mu$ -peroxo low-spin cobalt(III) complex (see type IIb, Table II). The complex reacts with oxidizing agents such as ceric ion to yield the corresponding  $\mu$ -superoxo cobalt(III) complex (type Ib, Table II).

Similar  $\mu$ -peroxo cobalt(III) complexes are formed by the

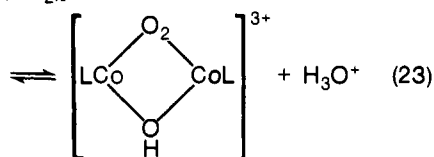
reaction of dioxygen with a variety of cobalt(II) chelates. These include amino acids, polyamines, and saturated macrocyclics as ligands. The dioxygen adducts of these cobalt complexes are listed and referenced in Table XI. Reviews which devote considerable attention to the aqueous solution chemistry of cobalt oxygen carriers include the excellent articles by Fallab,<sup>5</sup> Wilkins,<sup>7</sup> and McLendon and Martell.<sup>16</sup>

Most of the water-soluble dioxygen cobalt complexes given in Table XI are binuclear. One of the exceptions reported<sup>196</sup> recently is the mononuclear compound *cis*-[Co(*s*-Me<sub>2</sub>en)<sub>2</sub>(Cl)(O<sub>2</sub>)]Cl which was prepared by the room temperature reaction of an ethanol solution of [Co(*s*-Me<sub>2</sub>en)<sub>2</sub>Cl<sub>2</sub>] with dioxygen. The optical and EPR spectra of the dioxygen complex are in accord with its being a monomeric species of the superoxo type, Co<sup>III</sup>(O<sub>2</sub><sup>-</sup>). That this system yields the monomer, instead of the usual bridged dimer, is believed to be due to the steric hindrance afforded by the *N,N'*-dimethyl substitution on ethylenediamine. However, models show that it should still be possible to form the  $\mu$ -peroxo complex. Whatever the reason, this does show that there is a delicate energy and/or kinetic balance between the formation of the mononuclear and binuclear oxygen complexes.

Also worthy of note (Table XI) is the fact that although many of the complexes are of the monobridged ( $\mu$ ) type Co-O<sub>2</sub>-Co, several of the complexes are reinforced by forming dibridged ( $\mu, \mu$ )



species. It appears that dibridging tends to occur whenever two *cis* coordination sites are available on the metal center. For example, the tetraethylenepentamine complex [Co(tetraen)-H<sub>2</sub>O]<sup>2+</sup> forms the  $\mu$ -peroxo complex, whereas the triethylenetetramine complex [Co(trien)(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup> with two available (two water ligands) coordination sites forms the  $\mu$ -peroxo- $\mu$ -hydroxo complex. The effect of dibridging is said<sup>16</sup> to "lock in" more tightly the dioxygen bridge. This explains why the oxygenation of some cobalt complexes is reversible within the buffer region where significant amounts of the monobridged complex exists at equilibrium (eq 23). However, at higher pH where the [H<sub>2</sub>O]LCo-O<sub>2</sub>-CoL(OH<sub>2</sub>)<sup>4+</sup>



dibridged species is largely present, the dioxygen moiety may be locked in so firmly as to make the oxygenation irreversible.

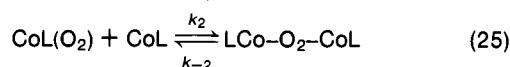
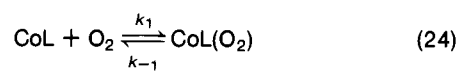
### 1. Kinetics and Mechanism of Reversible Oxygenation Reactions

The original dioxygen-cobalt complex, [(NH<sub>3</sub>)<sub>5</sub>Co-O<sub>2</sub>-Co(NH<sub>3</sub>)<sub>5</sub>]<sup>4+</sup>, was for many years not regarded as an oxygen carrier. The first synthetic oxygen carrier in water solution was discovered in 1946 by Burk and co-workers.<sup>206</sup> They observed that an aqueous solution of bis(histaminato)cobalt(II) reacts readily at room temperature with dioxygen to yield an amber-colored species, which in turn releases dioxygen upon the addition of acid or by flushing the solution with nitrogen. Early studies<sup>206</sup> characterized the amber compound as (hist)Co-O<sub>2</sub>-Co(hist). Some years later Simplicio and Wilkins<sup>207</sup> employed a stopped-flow apparatus to investigate the formation and decomposition of the dioxygen-cobalt complex. Wilkins and co-workers<sup>7</sup> have investigated the kinetics of the reversible

TABLE XI. Water-Soluble Dioxygen Complexes of Cobalt

complex	ref
A. Mononuclear Complexes	
[Co(CN) <sub>5</sub> (O <sub>2</sub> )] <sup>3-</sup>	147, 194, 195
[Co( <i>s</i> -Me <sub>2</sub> en) <sub>2</sub> (O <sub>2</sub> )X] <sup>n+</sup>	196
vitamin B <sub>12</sub> (O <sub>2</sub> )	130]
Co(HB)(O <sub>2</sub> ) and Co(Mb)(O <sub>2</sub> )	152, 154, 157, 197
B. Dinuclear Monobridged Complexes	
[(NH <sub>3</sub> ) <sub>5</sub> Co(O <sub>2</sub> )Co(NH <sub>3</sub> ) <sub>5</sub> ] <sup>4+</sup>	6, 7, 57, 198
[(tetraen)Co(O <sub>2</sub> )Co(tetraen)] <sup>4+</sup>	199
[NH <sub>3</sub> (en) <sub>2</sub> Co(O <sub>2</sub> )Co(en) <sub>2</sub> NH <sub>3</sub> ] <sup>4+</sup>	200
[(en)(dien)Co(O <sub>2</sub> )Co(dien)(en)] <sup>4+</sup>	199, 201
[(tn)(dien)Co(O <sub>2</sub> )Co(dien)(tn)] <sup>4+</sup>	202
[(pn)(dien)Co(O <sub>2</sub> )(dien)(pn)] <sup>4+</sup>	202
[(NH <sub>3</sub> )(trien)Co(O <sub>2</sub> )Co(trien)NH <sub>3</sub> ] <sup>4+</sup>	199
[(NH <sub>3</sub> )(tren)Co(O <sub>2</sub> )Co(tren)(NH <sub>3</sub> )] <sup>4+</sup>	203
[X(cyclam)Co(O <sub>2</sub> )Co(cyclam)X] <sup>n+</sup>	204
[(phen)(terpy)Co(O <sub>2</sub> )(terpy)(phen)] <sup>4+</sup>	205
[(bpy)(terpy)Co(O <sub>2</sub> )Co(terpy)(bipy)] <sup>4+</sup>	205
[(hist)Co(O <sub>2</sub> )Co(hist)]	206, 207
[(glygly)Co(O <sub>2</sub> )Co(glygly)]	208, 209
[(dipep)Co(O <sub>2</sub> )Co(dipep)]	209, 210
[(diapr)Co(O <sub>2</sub> )Co(diapr)]	211
[(CN) <sub>5</sub> Co(O <sub>2</sub> )Co(CN) <sub>5</sub> ] <sup>6-</sup>	212, 213
[(dgenta)Co(O <sub>2</sub> )Co(dgenta)] <sup>8-</sup>	214
C. Dinuclear Dibridged Complexes	
[(en) <sub>2</sub> Co(O <sub>2</sub> )(OH)Co(en) <sub>2</sub> ] <sup>3+</sup>	200, 201, 215, 216
[(trien)Co(O <sub>2</sub> )(OH)Co(trien)] <sup>3+</sup>	217-219
[(tren)Co(O <sub>2</sub> )(OH)Co(tren)] <sup>3+</sup>	200, 217, 220
[(phen) <sub>2</sub> Co(O <sub>2</sub> )(OH)Co(phen)] <sup>3+</sup>	221
[(bpy) <sub>2</sub> Co(O <sub>2</sub> )(OH)Co(bpy) <sub>2</sub> ] <sup>3+</sup>	221, 222
[(hista)Co(O <sub>2</sub> )(OH)Co(hista)] <sup>3+</sup>	201, 210, 215
[(sedda)Co(O <sub>2</sub> )(OH)Co(sedda)] <sup>-</sup>	223
[(uedda)Co(O <sub>2</sub> )(OH)Co(uedda)] <sup>-</sup>	223
[(sdtma)Co(O <sub>2</sub> )(OH)Co(sdtma)] <sup>+</sup>	224
[(udtma)Co(O <sub>2</sub> )(OH)Co(udtma)] <sup>+</sup>	224
[(glyhist)Co(O <sub>2</sub> )(OH)Co(glyhist)] <sup>-</sup>	209, 210
[(amacs)Co(O <sub>2</sub> )(OH)Co(amocs)] <sup>-</sup>	209
[(NH <sub>3</sub> ) <sub>4</sub> Co(O <sub>2</sub> )(NH <sub>2</sub> )Co(NH <sub>3</sub> ) <sub>4</sub> ] <sup>3+</sup>	57, 225
[(en) <sub>2</sub> Co(O <sub>2</sub> )(NH <sub>2</sub> )Co(en) <sub>2</sub> ] <sup>3+</sup>	200, 226-228
[(trien)Co(O <sub>2</sub> )(NH <sub>2</sub> )Co(trien)] <sup>3+</sup>	200
[(tren)Co(O <sub>2</sub> )(NH <sub>2</sub> )Co(tren)] <sup>3+</sup>	203
[(phen)Co(O <sub>2</sub> )(NH <sub>2</sub> )Co(phen)] <sup>3+</sup>	229, 230
[(bpy)Co(O <sub>2</sub> )(NH <sub>2</sub> )Co(bpy)] <sup>3+</sup>	229, 230

oxygenation of several different cobalt chelates and have explained their results in terms of the mechanism represented by eq 24 and 25.



This mechanism agrees with the recent studies by Martell and co-workers<sup>16</sup> on other cobalt complexes of polyamines, amino acids, and polypeptides. The kinetic data reported are collected in Table XII.

Assuming a steady state of CoL(O<sub>2</sub>), and using the initial rate data where the term  $k_{-2}[\text{LCo-O}_2\text{-CoL}]$  is small, the mechanism proposed is consistent with the experimental rate expression given by

$$\frac{d[\text{LCo-O}_2\text{-CoL}]}{dt} = \frac{k_1 k_2 [\text{CoL}]^2 [\text{O}_2]}{k_{-1} + k_2 [\text{CoL}]} \quad (26)$$

If  $k_2 [\text{CoL}] \gg k_{-1}$ , then eq 26 reduces to

$$d[\text{LCo-O}_2\text{-CoL}]/dt = k_1 [\text{CoL}] [\text{O}_2] \quad (27)$$

which is what is generally found. However, Huchital and Martell<sup>205</sup> have reported that the reaction of [Co(terpy)(bpy)(H<sub>2</sub>O)]<sup>2+</sup> and of [Co(terpy)(phen)(H<sub>2</sub>O)]<sup>2+</sup> with dioxygen is second order in CoL. This implies that for these systems  $k_{-1} >> k_2 [\text{CoL}]$ ,

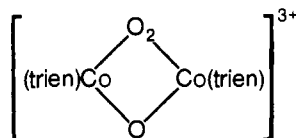
TABLE XII. Kinetic Data for the Reactions of Cobalt(II) Complexes with Dioxygen in Water Solution at 25 °C

complexes	$k_1$ , $M^{-1} s^{-1}$	$k_{-2}$ , $s^{-1}$	$\Delta H_1^\ddagger$ , kcal/mol	$\Delta S_1^\ddagger$ , eu	ref
[Co(NH <sub>3</sub> ) <sub>5</sub> H <sub>2</sub> O] <sup>2+</sup>	$2.5 \times 10^4$	56	4	-25	231
[Co(tetraen)H <sub>2</sub> O] <sup>2+</sup>	$\sim 10^5$		18	+9	218
[Co(en) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	$4.7 \times 10^5$	0.015	15	+19	201
[Co(dien) <sub>2</sub> ] <sup>2+</sup>	$1.2 \times 10^3$	0.016	10	-12	201
[Co(trien)(H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	$2.5 \times 10^4$	0.45	7	-15	218
[Co(trien)(H <sub>2</sub> O)(OH)] <sup>+</sup>	$2.8 \times 10^5$	0.46			218
[Co(tren)(H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	$2.8 \times 10^3$	0.4			220
[Co(amp) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	$7.2 \times 10^2$		6	-25	201
[Co(hista) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	$1.8 \times 10^4$				201
[Co(L-hist) <sub>2</sub> ]	$3.5 \times 10^3$	0.47	5	-25	207
[Co(D-hist)(L-hist)]	$2.6 \times 10^3$	0.043	6	-23	207
[Co(L-hist-H) <sub>2</sub> ] <sup>2-</sup>	$2.6 \times 10^4$				207
[Co(glygly)] <sup>2-</sup>	$1.0 \times 10^4$				232
[Co(L-cys) <sub>3</sub> ] <sup>-</sup>	$2.0 \times 10^5$				7
[Co(sdtma)(H <sub>2</sub> O) <sub>2</sub> ] <sup>+</sup>	$3 \times 10^3$	0.6			224
[Co(udtma)(H <sub>2</sub> O) <sub>2</sub> ] <sup>+</sup>	$1.4 \times 10^4$	0.3			224
[Co(sedda)(H <sub>2</sub> O) <sub>2</sub> ]	25				223
[Co(uedda)(H <sub>2</sub> O) <sub>2</sub> ]	22				223
[Co(TSPc)(H <sub>2</sub> O) <sub>2</sub> ] <sup>4-</sup>	<100				233
[Co(terpy)(phen)H <sub>2</sub> O] <sup>2+</sup>	$8.5 \times 10^5$	0.5			205
[Co(terpy)(bpy)H <sub>2</sub> O] <sup>2+</sup>	$1.0 \times 10^6$	$\sim 0.5$			205

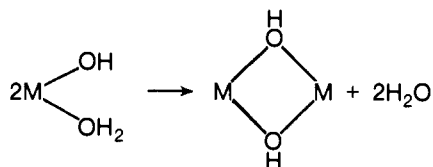
resulting in a rapid preequilibrium (eq 24) followed by the rate-determining dimerization (eq 25).

Data in Table XII show that values of rate constants ( $k_1$ ) and activation parameters are generally similar in magnitude, which seems remarkable for such a variety of complexes. This constancy is said<sup>7</sup> to be due to all of these reactions involving the same process of coordinated water replacement by dioxygen, which is dominated by water exchange. Yet the rates of oxygenation are roughly two to three orders of magnitude slower than that of water exchange. This may be caused by some strict orientation requirements of the O<sub>2</sub> moiety with respect to the complex in the transition state.

Values of rate constants  $k_{-2}$  are more difficult to interpret, especially in systems which involve secondary bridging. For example, the formation of the dibridged complex



was investigated in considerable detail. The initial rapid oxygenation to give the monobridged complex [(H<sub>2</sub>O)(trien)Co-O<sub>2</sub>-Co(trien)OH]<sup>3+</sup> is followed by the slower formation of the dibridged complex. Kinetic studies at different pH values suggest that the  $\mu$ -hydroxo bridge is formed by the usual olation process, e.g.,



represented by eq 28. Thus, for such systems  $k_{-2}$  is no longer simply the rate constant for the deoxygenation of a monobridged species, LCo-O<sub>2</sub>-CoL, but it must also include the breakup of the hydroxo bridge.

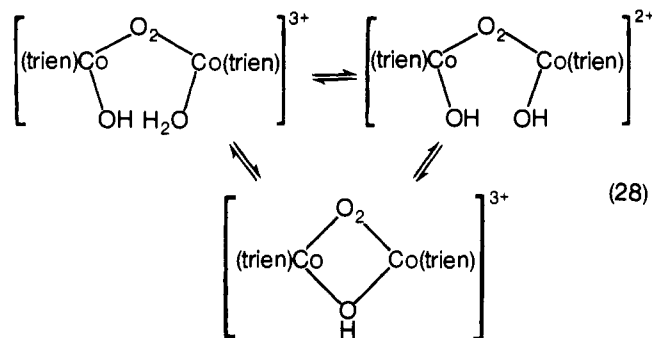
## 2. Thermodynamics of Reversible Oxygenation Reactions

There has been a continued interest in collecting thermodynamic data on the dioxygen uptake by oxygen carriers, in order

TABLE XIII. Equilibrium Constants for the Oxygenation of Cobalt(II) Complexes in Water Solution at 25 °C

complex	$\Sigma pK_a$	$\log K_{O_2}$	ref
Monobridged Species <sup>a</sup>			
[Co(tetraen)(H <sub>2</sub> O)] <sup>2+</sup>	34.6	15	235
[Co(dgenta)] <sup>2-</sup>	44	14.5	214
[Co(hist) <sub>2</sub> ]	30.4	6.6	215, 234
[Co(terpy)(phen)H <sub>2</sub> O] <sup>2+</sup>	$\sim 13$	6.3	205
[Co(terpy)(bpy)H <sub>2</sub> O] <sup>2+</sup>	$\sim 12$	5.4	205
Dibridged ( $\mu$ -Hydroxo) Species <sup>b</sup>			
[Co(en) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	35	10.8	215, 235
[Co(dien)(H <sub>2</sub> O) <sub>3</sub> ] <sup>2+</sup>	23.3	1.1	201
[Co(trien)(H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	28.7	6.1	219
[Co(tren)(H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	30.5	4.4	236
[Co(hedien) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	22.5	1.5	236
[Co(hista) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] <sup>2+</sup>	32	8.5	201, 215
[Co(sdtma)(H <sub>2</sub> O) <sub>2</sub> ] <sup>+</sup>	25.3	2.3	224
[Co(udtma)(H <sub>2</sub> O) <sub>2</sub> ] <sup>+</sup>	24.6	2.4	224
[Co(sedda)(H <sub>2</sub> O) <sub>2</sub> ]	16.2	-4.1	223
[Co(uedda)(H <sub>2</sub> O) <sub>2</sub> ]	16.7	-5.3	223

<sup>a</sup> Monobridged:  $K_{O_2} = [LMO_2]/[ML]^2[O_2]$ . <sup>b</sup> Dibridged:  $K_{O_2} = [LM(O_2)(OH)ML]/[H^+][ML]^2[O_2]$ .



to delineate the factors that have an important effect on the formation and stability of dioxygen metal complexes. Considerable data have recently been reported on synthetic oxygen carriers in aprotic solvents (Tables IX and X), but data for cobalt complexes in water solution remains rather limited. Again the first such system examined was [Co(hist)<sub>2</sub>]. Hearon<sup>234</sup> used the Warburg gas technique to obtain values of  $K_{O_2} = 3.6 \times 10^6$  and  $\Delta H = -38.2$  kcal/mol for the equilibrium represented by



Other investigators have obtained such equilibria data by using spectroscopic,<sup>223</sup> polarographic,<sup>201</sup> and potentiometric methods.<sup>224</sup> The recently reported data were largely obtained by Martell and co-workers,<sup>16</sup> using the potentiometric equilibrium method. The available data are collected in Table XIII.

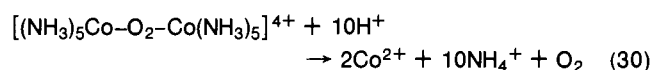
It should be noted that except for three ligands (bpy, phen, terpy), all of the ligands used are saturated. This is important because it restricts these ligands to  $\sigma$ -bonding, and avoids any effect due to  $\pi$ -bonding. With this restriction, it is important that McLendon and Martell<sup>236</sup> find a good linear free energy relation between the dioxygen uptake constants of the complexes and the protonic basicity of the ligands. The stronger the base strength of the ligand, the more stable the dioxygen complex. This is in accord with the concept that these systems involve a charge transfer of electron flow from cobalt to coordinated dioxygen. Thus the stronger the base strength of the ligand, the greater the electron density on cobalt, the greater the electron transfer from cobalt to dioxygen, the more stable the dioxygen complex. This result suggests that the  $K_{O_2}$  values should increase with increasing ease of oxidation ( $E_{1/2}$  for Co(II)  $\rightarrow$  Co(III)) of the cobalt complexes, as is true for corresponding systems in aprotic solvents.<sup>132</sup> Also these results show that it is the total basicities of the ligands that are important in determining whether a cobalt complex will form a dioxygen adduct. However, the



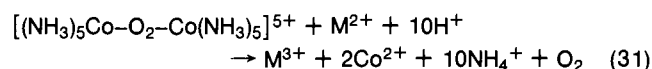
previous suggestion that for cobalt complexes containing only N and O ligand atoms, at least three N's are required to stabilize a dioxygen adduct, is not valid. For example, the symmetrical and unsymmetrical ethylenediamineacetato complexes (containing 2 N's and 4 O's) form stable dioxygen complexes in an appropriate pH range.

### 3. Reactions of Dioxygen-Cobalt Complexes

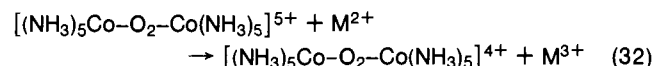
Numerous studies have been made of reactions of dioxygen-cobalt complexes in aqueous solution, but there remains a need for the discovery of catalytic dioxygen activation reactions which more closely mimic biological reactions. Using the classical complex  $[(\text{NH}_3)_5\text{Co}-\text{O}_2-\text{Co}(\text{NH}_3)_5]^{4+}$  as an example, it has long been known that the complex is stable in ammoniacal solution but that it readily decomposes with the stoichiometry given in eq 30.



Also, as stated earlier, the  $\mu$ -peroxo complex is readily oxidized to the  $\mu$ -superoxo complex. Complexes of both types can be reduced to give, for example, the overall reaction represented by the equation

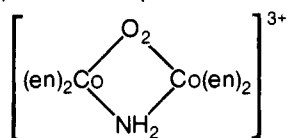


Sykes and co-workers<sup>228,237</sup> and others,<sup>238,239</sup> have investigated the kinetics and mechanism of this redox reaction using  $\text{M}^{2+} = \text{Cr}^{2+}, \text{V}^{2+}, \text{Fe}^{2+},$  and  $\text{Eu}^{2+}$ . The results show that there is an initial rapid reaction of the  $\mu$ -superoxo complex, followed by a slower much more complicated reduction of the  $\mu$ -peroxo complex. The rapid reaction

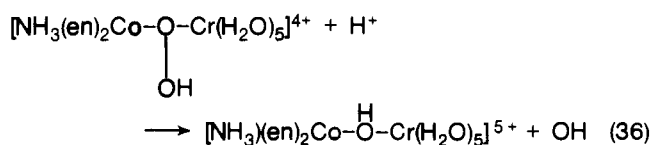
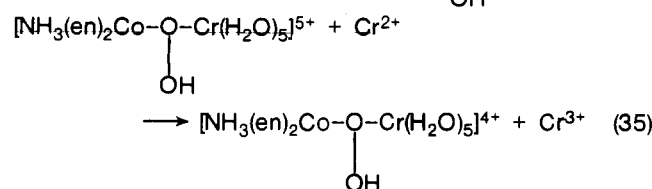
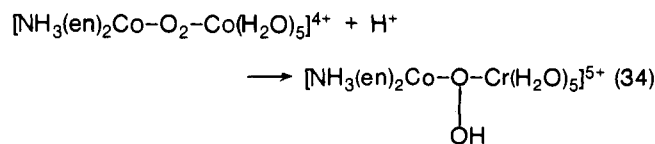
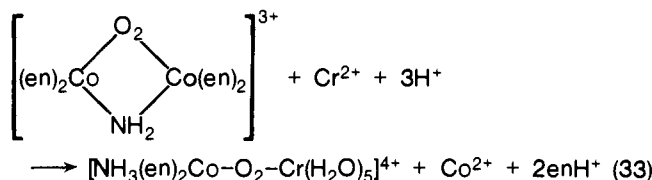


proceeds by an outer-sphere mechanism.

Hyde and Sykes<sup>228,237</sup> investigated in detail the  $\text{Cr}^{2+}$  reduction of the  $\mu$ -peroxo- $\mu$ -amido complex

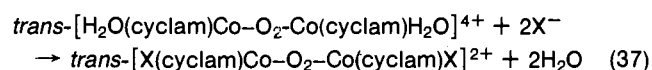


and they conclude that the mechanism is of the inner-sphere type and that it involves four steps (eq 33-36). The OH radical (eq 36) then rapidly reacts with  $\text{Cr}^{2+}$  to yield  $\text{OH}^- + \text{Cr}^{3+}$ . It is suggested that the inner-sphere process occurs with peroxo complexes, because peroxo groups are better donors than are superoxo



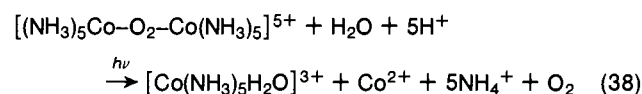
analogues. Also there is precedence<sup>240</sup> for the structure of the protonated species shown in eq 34. However, it should be noted that a recent study<sup>239</sup> suggests that such protonated species are not necessarily involved in the redox process.

Little work has been done on ligand substitution reactions of dioxygen cobalt complexes. One such study<sup>241</sup> involves the replacement of  $\text{NH}_3$  in  $[\text{NH}_3(\text{en})_2\text{Co}-\text{O}_2-\text{Co}(\text{en})_2\text{NH}_3]^{4+}$  by either  $\text{NO}_2^-$  or  $\text{NCS}^-$ . This reaction takes place with ease at room temperature, without cleavage of the  $\mu$ -peroxo bonds. That substitution at  $\text{Co(III)}-\text{NH}_3$  takes place this readily is most unusual when compared with the very firmly coordinated  $\text{NH}_3$ 's in other  $\text{Co(III)}$  complexes such as  $[\text{Co}(\text{NH}_3)_5\text{Cl}]^{2+}$ . At present it is a curious fact that the peroxo ligand has a marked stabilizing influence on the  $\text{Co}-\text{NH}_3$  bond, and speculation on why this is the case is premature. Another example<sup>204</sup> of a substitution reaction of a  $\mu$ -peroxo complex is given by eq 37



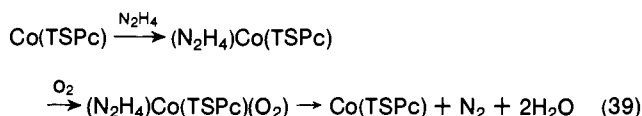
where  $\text{X}^- = \text{Cl}^-, \text{NO}_2^-, \text{NCS}^-,$  and  $\text{N}_3^-$ . The ready replacement of the aquo group qualitatively corresponds with the behavior of other aquoamminecobalt(III) complexes. There is a need for quantitative kinetic studies of substitution reactions of dioxygen-cobalt complexes.

Some studies have been reported on the photochemistry of  $\mu$ -superoxo complexes, but little has been done on the  $\mu$ -peroxo compounds. Valentine<sup>242</sup> reports the photochemical reaction represented by




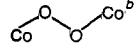
The reaction goes in good yield with irradiation at 365 and 313 nm, and similar reactions were observed for two other corresponding dioxygen compounds. In the presence of anions the product is  $[\text{Co}(\text{NH}_3)_5\text{X}]^{2+}$ , in accord with other experiments<sup>243</sup> designed to trap the intermediate  $[\text{Co}(\text{NH}_3)_5]^{3+}$ . The photochemical reaction was also tested for the formation of singlet state dioxygen by adding 1,3-cyclohexadiene to the reaction mixture. Some endo peroxide was formed, indicating singlet dioxygen, but other products also formed and the results remain inconclusive.

Other types of water-soluble cobalt oxygen carriers include the sulfonated porphyrin and phthalocyanine complexes. Less work has been done with these systems, but in general they behave similar to the polyamine and amino acid cobalt complexes discussed in this section. For example, a kinetic study<sup>233</sup> of the reaction of a water solution of tetrasulfophthalocyaninatocobalt(II), with dioxygen shows that the same mechanism (eq 39) is involved in the reversible formation of  $(\text{TSPc})\text{Co}-\text{O}_2-\text{Co}(\text{TSPc})$ . The complex  $\text{Co}(\text{TSPc})$  also behaves as a catalyst for the dioxygen oxidation of hydrazine and of hydroxylamine in aqueous solution.<sup>244</sup> Kinetic studies support a process shown by eq 39.



In contrast to this, the  $\text{Co}(\text{TSPc})$  catalyzed dioxygen oxidation of cysteine to cystine is believed<sup>245</sup> to involve the intermediate formation of  $\text{Co(I)}$  and RS. The free radical then dimerizes to give

TABLE XIV. Structural Parameters of Cobalt-O<sub>2</sub> Complexes

complex <sup>a</sup>	O-O, Å	deg		Co-O, (Å)	comments <sup>c</sup>	ref	
							
la monomeric, superoxo Co(bzacen)(py)(O <sub>2</sub> )	1.26(4)	126		1.86	reversible <sup>d</sup>	144	
	Co(acacen)(py)(O <sub>2</sub> )			1.95(5)	reversible <sup>e</sup>	167b	
	[Et <sub>4</sub> N] <sub>3</sub> [Co(CN) <sub>5</sub> (O <sub>2</sub> )]·5H <sub>2</sub> O	1.240(17)	153.4		1.904(14)	irreversible <sup>f</sup>	195, 251
	Co( <i>t</i> -Bu-saltmen)(BzIm)(O <sub>2</sub> )·1.5 Me <sub>2</sub> CO	1.273(10)	117.5		1.974(8)	reversible	252
	Co(3-F-saltmen)(Melm)(O <sub>2</sub> )·2Me <sub>2</sub> CO	1.257(10)	118.5		1.974(8)		
	Co(saltmen)(BzIm)(O <sub>2</sub> )·THF	1.302(3)	117.4		1.881(2)	reversible	253
	Co(salen-C <sub>2</sub> H <sub>4</sub> -py)(O <sub>2</sub> ) range	1.277(3) 1.1 1.1-1.302	120.0 136		1.889(2)	reversible irreversible <sup>f</sup>	254 195, 251
lb dimeric, superoxo K <sub>5</sub> [Co <sub>2</sub> (CN) <sub>10</sub> (O <sub>2</sub> )]·H <sub>2</sub> O	1.243(13) <sup>g</sup>	121.2	166	1.944		265	
	1.289(20)	120.7	180	1.919			
	[Co <sub>2</sub> (NH <sub>3</sub> ) <sub>10</sub> (O <sub>2</sub> )](NO <sub>3</sub> ) <sub>5</sub> <sup>h</sup>	1.317(20)	117.3	180	1.895		257
	[Co <sub>2</sub> (NH <sub>3</sub> ) <sub>10</sub> (O <sub>2</sub> )](SO <sub>4</sub> )(HSO <sub>4</sub> ) <sub>3</sub>	1.312(20)	117.7	175.3	1.894		258
	[Co <sub>2</sub> (en) <sub>4</sub> (NH <sub>2</sub> )(O <sub>2</sub> )](NO <sub>3</sub> ) <sub>4</sub> ·H <sub>2</sub> O <sup>i</sup>	1.353	119.2	23.4	1.878		240, 261
	[Co <sub>2</sub> (NH <sub>3</sub> ) <sub>8</sub> (NH <sub>2</sub> )(O <sub>2</sub> )](NO <sub>3</sub> ) <sub>4</sub> <sup>j</sup> range	1.320(5) 1.243-1.353	120.9	0.0	1.867		262
lla monomeric [Co(2=phos)(O <sub>2</sub> )](BF <sub>4</sub> )·2C <sub>6</sub> H <sub>6</sub>	1.420(10)			1.871(7) 1.902(7)	irreversible <sup>l</sup>	246	
	[Co <sub>2</sub> (CN) <sub>4</sub> (PMe <sub>2</sub> Ph) <sub>5</sub> (O <sub>2</sub> )] <sup>k</sup>	1.441(11)		1.888(9) 1.910(9)		247	
llb dimeric, peroxy K <sub>8</sub> [Co <sub>2</sub> (CN) <sub>10</sub> (O <sub>2</sub> )](NO <sub>3</sub> ) <sub>2</sub> ·4H <sub>2</sub> O	1.447(4)	118.8	180	1.985	irreversible	260	
	[Co <sub>2</sub> (NH <sub>3</sub> ) <sub>10</sub> (O <sub>2</sub> )](SO <sub>4</sub> ) <sub>2</sub> ·4H <sub>2</sub> O	1.473(10)	113	145.8	1.883	irreversible	198
	[Co <sub>2</sub> (NH <sub>3</sub> ) <sub>10</sub> (O <sub>2</sub> )](SCN) <sub>4</sub> <sup>l</sup>	1.469(6)	110.8	180	1.879	irreversible	259
	[Co <sub>2</sub> (en) <sub>2</sub> (dien) <sub>2</sub> (O <sub>2</sub> )](ClO <sub>4</sub> ) <sub>4</sub>	1.488(6)	110.0	180	1.896	irreversible	263
	[Co <sub>2</sub> (en) <sub>2</sub> (NO <sub>2</sub> ) <sub>2</sub> (O <sub>2</sub> )](NO <sub>3</sub> ) <sub>2</sub> ·4H <sub>2</sub> O	1.53	110	180	1.89	irreversible <sup>m</sup>	264
	[Co <sub>2</sub> (en) <sub>4</sub> (NH <sub>2</sub> )(O <sub>2</sub> H)](NO <sub>3</sub> ) <sub>4</sub> ·2H <sub>2</sub> O <sup>n</sup>	1.42	115		1.92	irreversible <sup>o</sup>	240, 261
	[Co <sub>2</sub> (F-salen) <sub>2</sub> (H <sub>2</sub> O)(O <sub>2</sub> )] <sub>2</sub> ·pip·2CHCl <sub>3</sub>	1.308(28)	118	122	1.931	reversible	265
	Co <sub>2</sub> (salen) <sub>2</sub> (DMF) <sub>2</sub> (O <sub>2</sub> )	1.339(6)	120.3	110.1	2.000 1.910	reversible <sup>p</sup>	266
	Co <sub>2</sub> (salprtr) <sub>2</sub> (O <sub>2</sub> )·toluene	1.45(2)	118.5	149.3	1.93	irreversible	267
	Co <sub>2</sub> (salen) <sub>2</sub> (pip) <sub>2</sub> (O <sub>2</sub> )· <sup>2</sup> / <sub>3</sub> Me <sub>2</sub> CO· <sup>1</sup> / <sub>3</sub> pip range	1.383(7) 1.308-1.488	120.0	121.9	1.911	reversible	268

<sup>a</sup> For abbreviations see section XI. <sup>b</sup> Torsion angle. <sup>c</sup> Reversible implies that some reversibility has been noted for these compounds *in solution*. <sup>d</sup> Reference 132. <sup>e</sup> Reference 110. <sup>f</sup> Reference 147. <sup>g</sup> Two crystallographically independent molecules occupy a unit cell. <sup>h</sup> This structure replaces an earlier study<sup>255</sup> that showed the O-O bond lying perpendicular to the Co-Co axis. <sup>i</sup> This compound contains a bridging NH<sub>2</sub><sup>-</sup> group as well as a bridging O<sub>2</sub><sup>-</sup>. <sup>j</sup> Reference 270. <sup>k</sup> The dioxygen is bound to only one of the Co centers. <sup>l</sup> This structure determination replaces an earlier one<sup>271</sup> that indicated a longer O-O bond length (1.65 Å). <sup>m</sup> Reference 241. <sup>n</sup> This compound has a bridging NH<sub>2</sub><sup>-</sup> group, and a bridging hydroperoxy, O<sub>2</sub>H<sup>-</sup>, group. Only one of the oxygen atoms is bound to both cobalt atoms. <sup>o</sup> Reference 272. <sup>p</sup> Reference 34.

the product RSSR, and Co(II) is restored by the reaction of Co(I) with dioxygen. Clearly more effort is needed in the direction of catalytic dioxygen activation by metal complexes.

## D. Solid-State Structures

### 1. Monomeric Cobalt-Dioxygen Complexes

The structures of several 1:1 cobalt-dioxygen adducts have now been reported (Table XIV). With the exception of the complexes [Co(2=phos)<sub>2</sub>(O<sub>2</sub>)]BF<sub>4</sub><sup>246</sup> and Co<sub>2</sub>(CN)<sub>4</sub>(PMe<sub>2</sub>Ph)<sub>5</sub>(O<sub>2</sub>)<sup>247</sup> the adducts reported have all been type Ia complexes (see Table XIV). Both [Co(2=phos)<sub>2</sub>(O<sub>2</sub>)]BF<sub>4</sub> and Co<sub>2</sub>(CN)<sub>4</sub>(PMe<sub>2</sub>Ph)<sub>5</sub>(O<sub>2</sub>) are type IIa complexes. Although the latter complex contains two metal centers, the compound is still considered a type IIa since the dioxygen moiety is bound to only one of the cobalt metal centers. Thus, it is a very special kind of "monomeric" cobalt-dioxygen complex.

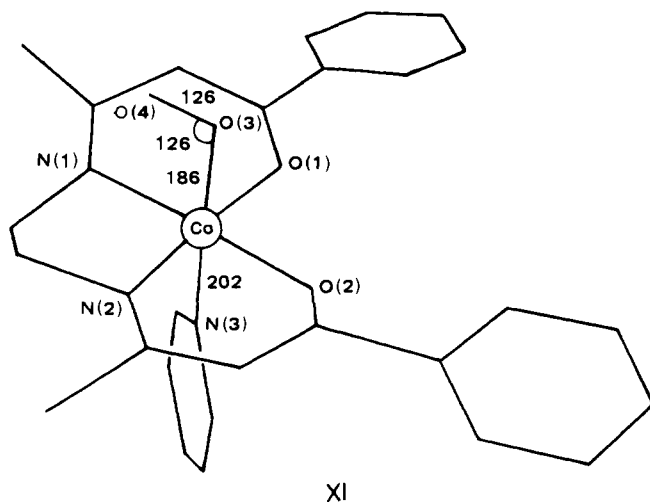
The compound [Co(2=phos)<sub>2</sub>(O<sub>2</sub>)]BF<sub>4</sub> was formed by exposing either crystals or a solution of the cobalt(I) chelate [Co(2=phos)<sub>2</sub>]BF<sub>4</sub> to atmospheric oxygen. Oxidative addition of the dioxygen to the cobalt(I) complex produced the cobalt(III)-peroxy

complex. This behavior is similar to that observed by Bosnich et al.<sup>249</sup> for the oxygenation of complexes of cobalt(I) containing a quadridentate arsine ligand, and it is also characteristic of the oxidative addition of molecular oxygen to low-valent complexes of second- and third-row group 8 transition metals. This generally occurs when the metal can readily increase its oxidation state by two. A unique exception is Co<sub>2</sub>(CN)<sub>4</sub>(PMe<sub>2</sub>Ph)<sub>5</sub>(O<sub>2</sub>), formed by the oxygenation of a benzene solution of the five-coordinate cobalt(II) complex Co<sup>II</sup>(CN)<sub>2</sub>(PMe<sub>2</sub>Ph)<sub>3</sub>.<sup>247</sup> The resulting dioxygen complex is a cyano-bridged dimer of the form (Me<sub>2</sub>PPh)<sub>3</sub>(NC)<sub>2</sub>-Co<sup>III</sup>-(NC)Co<sup>III</sup>(CN)(PMe<sub>2</sub>Ph)<sub>2</sub>(O<sub>2</sub><sup>2-</sup>). The dimer is apparently formed because the CN bridge allows electron transfer between the two cobalts, such that a total of two electrons are available to generate a peroxy group. It is not understood why peroxy is not the bridging group, as it is in all other known bridged reaction products of the reactions of Co(II) complexes with O<sub>2</sub> (including [Co(CN)<sub>5</sub>]<sup>3-</sup>).<sup>248</sup> Thus, the complex Co<sub>2</sub>(CN)<sub>4</sub>(PMe<sub>2</sub>Ph)<sub>5</sub>O<sub>2</sub> appears to be the only example of a π-bonded dioxygen complex formed from the reaction of a Co(II) complex with molecular oxygen.

The O-O bond lengths and Co-O bond lengths are similar for

both  $[\text{Co}(2=\text{phos})_2(\text{O}_2)]\text{BF}_4$  and  $\text{Co}_2(\text{CN})_4(\text{PMe}_2\text{Ph})_5(\text{O}_2)$  (Table XIV). These values (and also values of the O–O stretching frequencies) are comparable with O–O and M–O distances found for complexes of second- and third-row group 8 transition elements.<sup>15,250</sup>

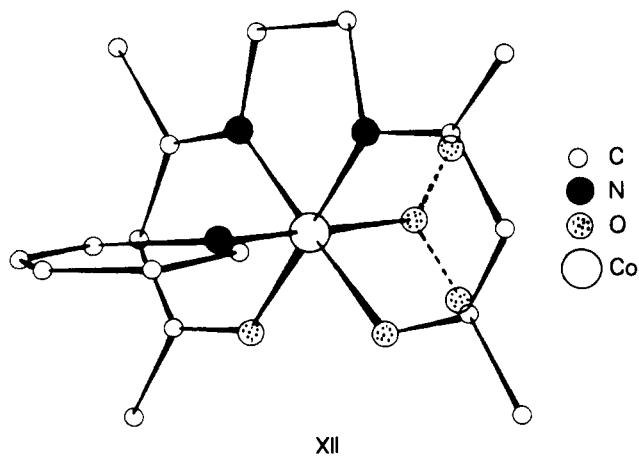
Despite difficulties in obtaining single crystals of adequate quality for X-ray analysis, including problems of disorder and those due to large anisotropic thermal vibration, the structures of several type Ia cobalt–dioxygen complexes have been reported. The first structurally characterized 1:1 Co–O<sub>2</sub> type adduct was the six-coordinate Schiff base complex  $\text{Co}(\text{benacen})(\text{py})(\text{O}_2)$  (XI).<sup>144</sup> The O–O bond length (1.26 Å) is in reasonable agreement



with that expected for a coordinated superoxide moiety. As indicated in XI, the cobalt lies essentially in the plane defined by the Schiff base ligand. The plane containing the cobalt center and the two dioxygen atoms bisects the N–Co–N angle of the Schiff base while the orientation of the plane of the pyridine ring is approximately normal to the Co–O–O plane. The two phenyl substituents are approximately coplanar with the plane of the Schiff base.

The orientation of the Co–O<sub>2</sub> unit permits maximum overlap of the  $\pi^*$  orbitals of the O<sub>2</sub> with a  $d\pi$  orbital of the cobalt. It has been suggested<sup>144</sup> that the coplanarity of the phenyl substituents may facilitate delocalization of the electron within the cobalt Schiff base, thus enhancing the  $\pi$  interaction of the cobalt with the O<sub>2</sub> moiety. It is interesting to note that although the orientation of the pyridine ring apparently minimizes interaction with adjacent atoms on the Schiff base, the  $\pi$  orbitals of the pyridine are not available for interaction with a delocalized  $\pi$  system of the Co–O<sub>2</sub> group.

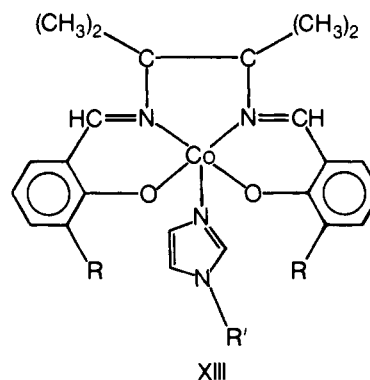
Structure XII of a similar Schiff base,  $\text{Co}(\text{acacen})(\text{py})(\text{O}_2)$ , has also been determined.<sup>167b</sup> The overall gross structural features of the molecule are quite similar to those of the corresponding



benacen derivative with the exception that the dioxygen atom shows a twofold disorder. Thus the O–O vector bisects both the O–Co–O and N–Co–N angles of the chelate ring. The large uncertainty in the structure determination ( $R = 0.19$ ) resulted in neither an O–O bond length nor a Co–O–O bond angle being reported.

Brown and Raymond<sup>195,251</sup> have reported the crystal structure of  $[\text{Et}_4\text{N}]_3[\text{Co}(\text{CN})_5(\text{O}_2)] \cdot 5\text{H}_2\text{O}$ . This 1:1 cobalt–dioxygen complex, which has been postulated as being an intermediate in the formation of the  $[(\text{CN})_5\text{Co}-\text{O}_2-\text{Co}(\text{CN})_5]^{6-}$  anion,<sup>248</sup> was formed by exposing a DMF solution of  $[\text{Et}_4\text{N}]_3[\text{Co}(\text{CN})_5]$  to atmospheric oxygen. The O–O distance of 1.240 (17) Å is somewhat less than that expected for an ideal superoxide anion. The most unusual aspect of the structure, however, is the large Co–O–O bond angle of  $153^\circ$  as compared with the bond angle observed for the Schiff base adducts. This may arise from the repulsive interaction of the negative charge on the terminal oxygen atom of the dioxygen species with the four adjacent cyanide anions in the  $[\text{Co}(\text{CN})_5(\text{O}_2)]^{3-}$  complex. The terminal oxygen atom in the Schiff base adducts have adjacent ligand atoms which are essentially neutral.

Recently, Schaefer and co-workers<sup>252–254</sup> have published structures for three 1:1 dioxygen–cobalt Schiff base complexes of the form XIII. It is interesting to note that the workers were able



to isolate a 1:1 adduct of the sterically unhindered Co(saltmen) complex. Similar complexes generally yield only the 2:1 adducts. These complexes have proven particularly suitable for X-ray analysis for two reasons: (1) the ligand apparently stabilizes the formation of the 1:1 adducts relative to the 2:1 adducts sufficiently to allow the isolation of good quality single crystals, and (2) the dioxygen adducts exhibit neither the solid-state disorder nor the large anisotropic thermal vibration observed for other 1:1 adducts.

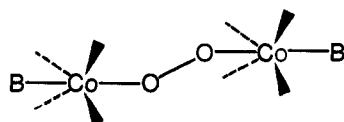
The gross structural features of the three dioxygen adducts are similar. In all cases the plane defined by the cobalt center and the dioxygen atoms essentially bisects the inplane O–Co–N bond angle. In all cases the Co–O<sub>2</sub> group lies almost in the plane of the substituted imidazole group. In this orientation, the substituted imidazole group, which has been shown to be capable of  $\pi$ -donation, is able to delocalize electron density by back-bonding to the cobalt  $d\pi$ -dioxygen  $\pi^*$  system. It must be pointed out, however, that the orientation of both the substituted imidazole groups and the dioxygen moiety in these complexes is largely dominated by steric effects. The O–O bond lengths and the Co–O–O bond angles observed for the three complexes (Table XIV) are all consistent with a formal representation of these cobalt–dioxygen adducts as superoxide–cobalt(III) complexes. The variation in the bond angles are within the range attributable to packing forces.

## 2. Dimeric Cobalt–Dioxygen Complexes

The single-crystal X-ray structure has been determined for a number of 2:1 cobalt–dioxygen complexes of the types Ib and IIb. The structural parameters obtained for these complexes are

summarized in Table XIV.

The classic example of these 2:1 cobalt-dioxygen adducts is the diamagnetic complex  $[(\text{NH}_3)_5\text{Co}^{\text{III}}-\text{O}_2-\text{Co}^{\text{III}}(\text{NH}_3)_5]^{4+}$  originally observed by Fremy<sup>100</sup> and later characterized by Werner and Mylius.<sup>57</sup> Oxidation of this complex gives the paramagnetic species  $[(\text{H}_3\text{N})_5\text{CoO}_2\text{Co}(\text{NH}_3)_5]^{5+}$  indicating that the  $\text{O}_2$  was  $\pi$ -bonded to the two cobalt orbitals with the O-O bond axis lying perpendicular to the Co-Co axis. This was in agreement with a suggestion made by Vlcek<sup>256</sup> on the basis of theoretical considerations. However, a recent reinvestigation of the structure for this complex,<sup>257</sup> as well as for the similar compound  $[(\text{NH}_3)_5(\text{Co}-\text{O}_2-\text{Co})(\text{NH}_3)_5](\text{SO}_4)(\text{HSO}_4)_3$ ,<sup>258</sup> has shown this initial structure to be incorrect. The  $\text{O}_2$  on the decamine structure adopts a skewed configuration (XIV).



XIV

The structural parameters for the  $\text{Co}_2\text{O}_2$  unit obtained from  $[(\text{NH}_3)_5\text{CoO}_2\text{Co}(\text{NH}_3)_5](\text{NO}_3)_5$ <sup>257</sup> and  $[(\text{NH}_3)_5\text{CoO}_2\text{Co}(\text{NH}_3)_5](\text{SO}_4)(\text{HSO}_4)_3$ <sup>258</sup> are quite similar. The O-O bond lengths, 1.317 (20) and 1.312 (10) Å, agree within experimental error and are in accord with the value expected for superoxide groups. The Co-O-O bond angles (117.3 and 117.7°) and the Co-O-O-Co torsion angles (180 and 175.3°) are close to what would be anticipated for an  $\text{sp}^2$ -hybridized superoxide bridge. Comparing these values with those obtained from the type Ib, peroxo-bridged species  $[(\text{NH}_3)_5\text{CoO}_2\text{Co}(\text{NH}_3)_5](\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$  and  $[(\text{NH}_3)_5\text{CoO}_2\text{Co}(\text{NH}_3)_5](\text{SCN})_4$ <sup>259</sup> shows that the O-O bond length in the peroxo-bridged species (1.473 (10) and 1.468 (6) Å) are significantly different for the  $\text{SO}_4^{2-}$  and  $\text{SCN}^-$  salts. This difference has been attributed to<sup>248,259</sup> hydrogen-bonding effects.

The  $\mu$ -peroxo- and  $\mu$ -superoxo-decacyanobiscobalt(III) complexes have also been studied by X-ray analysis.<sup>248,260</sup> The dimeric, type Ib,  $\mu$ -superoxo complex  $\text{K}_8[\text{Co}_2(\text{CN})_{10}(\text{O}_2)]$ <sup>260</sup> contains two structural independent molecules. A comparison of the two O-O bond lengths shows a difference between the two conformational types of 0.046 Å. Upon considering the differences involved in the structure determination, it is felt that while this difference may be real, it is of marginal significance. It was pointed out<sup>259</sup> that a single MO approach would predict  $\pi$ -bonding character and a planar conformation for the Co-O-O-Co linkage, allowing maximum overlap of the Co  $d\pi$  orbitals. The presence of both a planar (Co-O-O-Co = 180°) and a nonplanar (Co-O-O-Co = 166°) complex in the same crystal indicates that packing forces may play a dominant role in determining the O-O torsion angle. The  $\mu$ -peroxo complex  $\text{K}_8[\text{Co}_2(\text{CN})_{10}(\text{O}_2)](\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ <sup>260</sup> shows a significant increase in the O-O bond length compared with the  $\mu$ -peroxo criteria. The planar configuration of Co-O-O-Co has been explained as arising from the Coulombic repulsion between the two highly charged Co(III) centers.

### VIII. Iron-Dioxygen Carriers

Research on synthetic iron-containing oxygen carriers as models for the natural occurring heme containing oxygen-carrying proteins hemoglobin and myoglobin has undergone significant theoretical and experimental developments with the recent observation that, under the proper conditions, iron(II) porphyrin complexes react reversibly with molecular oxygen to form 1:1 dioxygen adducts:



Historically, the major difficulty that has been encountered in obtaining porphyrinatoiron-dioxygen complexes is the ten-

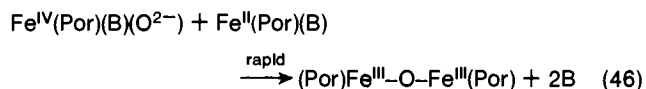
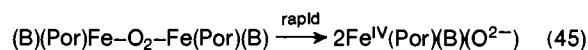
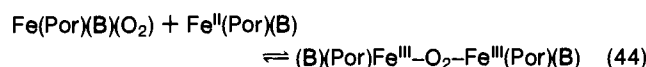
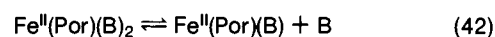
dency of the iron(II) porphyrin complexes, in the absence of large excesses of a strongly coordinating neutral ligand such as pyridine, to undergo rapid irreversible oxidation without detectable formation of an iron-dioxygen complex.<sup>272</sup> (In the presence of large excesses of a strongly coordinating neutral ligand it has long been realized<sup>273,274</sup> that the porphyrinatoiron(II) complexes are inert both toward irreversible oxidation and formation of dioxygen complexes.)

In contrast to the oxygen-carrying ability of hemoglobin and myoglobin, in the absence of special precautions, simple ferrous porphyrins are rapidly and irreversibly oxidized by molecular oxygen. Although it had been previously thought that the irreversible oxidation product was the heme hydroxide complex,<sup>275</sup>  $\text{Fe}^{\text{III}}(\text{Por})(\text{OH})$ , it is now known<sup>276-278</sup> that the autoxidation product is the  $\mu$ -oxo dimer:



Prior to confirmation that the presumed heme hydroxides were in reality  $\mu$ -oxo dimers, the dimeric nature of the autoxidation product had been postulated by one group of workers<sup>279</sup> on the basis of elemental analysis of the solid product obtained when benzene solutions of the dimethyl ester of dipyrindine 2,4-diacyldeuteroporphyrinatoiron(II) were exposed to  $\text{O}_2$ , and by analogy with the phthalocyanatomanganese(III)  $\mu$ -oxo dimer<sup>280</sup>  $(\text{py})(\text{Pc})\text{Mn}^{\text{III}}-\text{O}-\text{Mn}^{\text{III}}(\text{Pc})(\text{py})$ , obtained when pyridine solutions of  $\text{Mn}^{\text{II}}(\text{Pc})$  were exposed to  $\text{O}_2$ .<sup>281,282</sup>

On the basis of kinetic data<sup>283,284</sup> on the autoxidation of six-coordinate bis(base)iron(II) porphyrin complexes,  $\text{Fe}^{\text{II}}(\text{Por})(\text{B})_2$ , and on the basis of recent studies<sup>285</sup> of oxygen binding to these complexes at low temperatures, it is now generally believed that the autoxidation proceeds via formation of the monomeric iron-dioxygen adduct,  $\text{Fe}(\text{Por})(\text{B})(\text{O}_2)$ , to a dioxygen-bridged diiron complex<sup>278,279</sup> of the form  $(\text{B})(\text{Por})\text{Fe}-\text{O}_2-\text{Fe}(\text{Por})(\text{B})$ . This bridged species then rapidly decomposes via the formation of a presumably ferryl,  $\text{Fe}(\text{IV})-\text{O}^{2-}$ , intermediate, as first proposed by Caughey<sup>279</sup> and Hammond,<sup>286</sup> to give the  $\mu$ -oxo dimer:



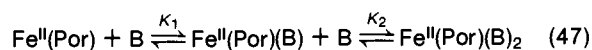
That the autoxidation reaction involves the formation of a dioxygen-bridged diiron intermediate is supported by a recent report<sup>53</sup> that exposure of toluene solutions of  $\text{Fe}^{\text{II}}(\text{T}(\rho\text{-CH}_3)\text{PP})$  at  $-50^\circ$  to  $\text{O}_2$  results in the formation of the  $\mu$ -peroxo dimer  $[\text{Fe}^{\text{III}}(\text{T}(\rho\text{-CH}_3)\text{PP})_2\text{O}_2]^{2-}$ , which upon warming gives the expected  $\mu$ -oxo dimer. The  $\mu$ -peroxo diiron(III) complex is analogous with the  $\mu$ -peroxo dicobalt(III) complexes formed by the reaction of  $\text{O}_2$  with the cobalt(II) Schiff base complexes. That the O-O bond in  $\mu$ -peroxo diiron(III) complex should cleave more rapidly than the O-O bond in the corresponding cobalt(III) complexes has been explained<sup>287</sup> on the basis of the relative stabilities of the Co-O and Fe-O species formed from direct cleavage of the O-O bond. It should be noted that a kinetic study on the autoxidation of the ferrous hemes, suggesting the formation of free superoxide, has been reported.<sup>288</sup> These data have been reinterpreted<sup>283,284</sup> in terms of the formation of a Fe-O<sub>2</sub>-Fe intermediate.

Three recent synthetic approaches<sup>13</sup> have led to the formation of 1:1 iron-dioxygen complexes by suppressing the formation of the  $\mu$ -peroxo diiron complex. These are (1) *steric*—in such

a fashion that dimerization is inhibited, (2) *low temperature*—in order that reactions leading to dimerization are very slow, and (3) *rigid surfaces*—attachment of the iron complex on the surface in a manner that dimerization is prevented. In addition to suppressing the irreversible oxidation of the iron(II)–heme complexes, two additional features are desirable in constructing a model for the natural heme oxygen carriers. These are (1) a five-coordinate geometry,  $\text{Fe}^{\text{II}}(\text{Por})(\text{B})$ , for the deoxyheme; and (2) a nonpolar, hydrophobic environment for the heme.

In the natural oxygen-carrying heme proteins, the protoporphyrinatoiron(II) active site lies within a "cleft" in the protein principally through noncovalent apolar interactions. The only covalent linkage between the iron(II) porphyrin and the protein arises from a coordinate bond between the iron(II) center and the imidazole portion of the proximal histidine residue. Thus in the deoxy form, the iron(II) center is five-coordinate with the high-spin ( $S = 2$ )  $\text{Fe}(\text{II})$  projecting out of the mean plane of the four porphyrin nitrogen atoms toward the coordinated imidazole moiety.

The problem encountered when attempting to model the natural heme oxygen carrier, using simple ferrous porphyrins in solution in the presence of strongly coordinating N-donor ligands, is the strong preference of the iron for six-coordination:



The difficulty in forming the five-coordinate complexes,  $\text{Fe}^{\text{II}}(\text{Por})(\text{B})$ , in solution results from the fact that, unlike the situation found for normal consecutive equilibria,  $K_n < K_{n-1}$ ,<sup>289</sup> for the consecutive equilibria  $K_2$  and  $K_1$ ,<sup>290</sup>  $K_2 > K_1$ , making the dominant species in solution  $\text{Fe}^{\text{II}}(\text{Por})(\text{B})_2$ . For example, in benzene at 25 °C, the bonding constants of pyridine to  $\text{Fe}^{\text{II}}(\text{TPP})$  have been estimated as  $K_1 \sim 1.5 \times 10^3$  and  $K_2 \sim 1.9 \times 10^4 \text{ M}^{-1}$ . The relative magnitudes of  $K_1$  and  $K_2$  undoubtedly result from a spin-state change in going from five- to six-coordination. The five-coordinate hemes have been shown to exist in the high-spin,  $S = 2$ , form,<sup>292,293</sup> whereas the six-coordinate hemes are well known to be diamagnetic low-spin complexes,<sup>294</sup> the simple four-coordinate ferrous hemes assume an intermediate,  $S = 1$ , spin state.<sup>292,293,295,296</sup>

Several of the synthetic strategies used to prevent autoxidation of the ferrous heme complexes have also led to the synthesis of five-coordinate heme containing oxygen carriers. These include (1) the use of sterically hindered systems, such as the Baldwin "capped" porphyrin (Figure 18),<sup>297</sup> in which steric hindrance inhibits not only irreversible oxidation but also the bonding of an axial ligand to one side of the porphyrin ring; and (2) the attachment of the heme to a rigid or semirigid support containing covalently attached donor ligands. In this case, the juxtaposition of heme and donor ligands attached to the surface can be such that formation of a six-coordinate adduct is not possible. In addition to these two approaches, five-coordination of the deoxy heme has been achieved by covalently attaching a donor ligand to the porphyrin moiety in such a way that it is capable of axial coordination with the iron(II) center,<sup>163,352,353</sup> and by the use of sterically hindered ligands such as 2-methylimidazole and 1,2-dimethylimidazole, in which case it has been shown that these sterically hindered bases form only the five-coordinate adducts with ferrous hemes at room temperature.<sup>292,299</sup> It should be noted that at low temperatures, evidence of six-coordination with the hindered ligands has been obtained.<sup>300</sup> That the five-coordinate hemes containing a sterically hindered axial N-donor ligand are capable of bonding dioxygen to form the six-coordinate complexes  $\text{Fe}(\text{Por})(\text{B})(\text{O}_2)$ , has recently been observed.<sup>163</sup>

In addition to preventing irreversible oxidation of the heme centers by keeping them spatially apart, the heme proteins Hb and Mb provide a hydrophobic environment for the heme centers. It is well recognized<sup>301-303</sup> that such an environment is important

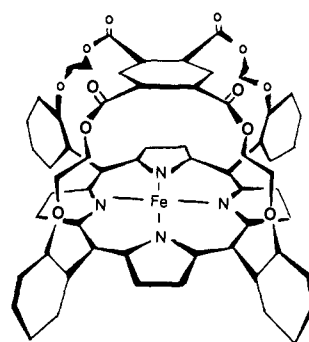
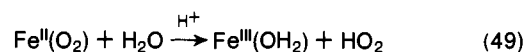
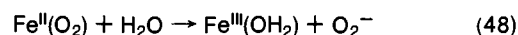


Figure 18. Structure of the ferrous "capped" porphyrin. Double bonds are deleted for clarity.

in preventing autoxidation of the heme–dioxygen complex by a reaction path that does not involve a second iron(II) center.<sup>304</sup> Even in the presence of the protein matrix,  $\text{HbO}_2$  and  $\text{MbO}_2$  are known to undergo a slow oxidation to the met species. In the normal human erythrocyte, HbA undergoes autoxidation at a rate large enough to necessitate the presence of enzyme systems to effect reconversion to functional Hb. Thus, a steady state concentration of  $\text{Fe}(\text{III})$  of about 1% of the total Hb present is maintained.<sup>305</sup>

The mechanistic pathways for this autoxidation reaction are not well understood. The formation of superoxide ion (or the hydroperoxyl radical,  $\text{HO}_2$ ) has been implicated in this oxidation reaction,<sup>306,307</sup> suggesting that the autoxidation proceeds via either of two pathways:



Such steps have also been suggested for the autoxidation of simple ferrous complexes in aqueous solutions.<sup>308-311</sup> On the basis of the redox potentials involved in the above processes, the production of a hydroperoxyl radical seems a more likely mechanism.<sup>312</sup> This is consistent with the recent report by Caughey and coworkers<sup>42</sup> that human Hb in the presence of excess nucleophile cleanly undergoes an acid-catalyzed oxidation which apparently involves the nucleophilic displacement of a superoxide ion (or hydroperoxyl radical) from a protonated intermediate. Although the precise mechanism by which ferrous hemes are oxidized in an aqueous environment has not been worked out, experiments with model systems of heme oxygen carriers are generally conducted in nonaqueous media.<sup>313</sup>

Although the investigation of iron-containing oxygen carriers has burgeoned in the past few years, a number of early claims of iron(II) oxygen carriers should be noted. In 1927, Kunz and Kress<sup>314</sup> reported the reversible absorption of  $\text{O}_2$  in pyridine by a ferrous indigo complex. More careful investigations,<sup>315,316</sup> however, have shown that  $\text{O}_2$  does not bind reversibly in this system. Later reports<sup>317,318</sup> that bis(dimethylglyoximate)iron(II),  $\text{Fe}^{\text{II}}(\text{DMG})_2$ , in aqueous dioxane solution in the presence of ligands such as pyridine, ammonia, histidine, or imidazole reversibly formed the dioxygen adducts,  $\text{Fe}(\text{DMG})_2(\text{B})(\text{O}_2)$ , have not been confirmed by a more recent study.<sup>319</sup> Other reports of iron(II) oxygen-carrying complexes that have appeared include the reversible combination with oxygen in the solid state by bis(imidazole) and bis(pyridine) complexes of proto- and mesoporphyrin.<sup>274,320</sup>

The synthesis of iron(II)-containing molecules having appended bulky substituents which prevent formation of a  $\mu$ -peroxo diiron(III) intermediate have led to a number of  $\text{Fe}(\text{II})$  reversible oxygen carriers. The first oxygen carrier that utilized steric encumbrance to inhibit irreversible oxidation was reported by Baldwin and Huff<sup>321</sup> in 1973. At  $-85$  °C, a pyridine–toluene solution of an iron(II) macrocycle containing 9,10-bridged

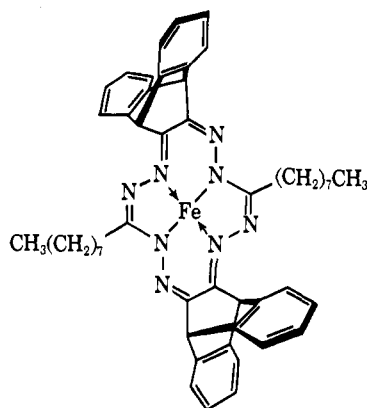


Figure 19. Structure of an iron(II) macrocycle containing 9,10-bridged 9,10-dihydroanthracenes.

9,10-dihydroanthracene<sup>322</sup> (Figure 19) reacted reversibly with 1 mol equiv of O<sub>2</sub>. Above -50 °C however, irreversible degradation of the oxygenated complex to yield an uncharacterized substance was observed. That the suppression of the irreversible oxidation process was due to steric hindrance and *not* a function of the low temperature, a similar unhindered ferrous macrocycle irreversibly absorbed 0.5 mol equiv of O<sub>2</sub> at -78 °C. Shortly after this report, Collman and co-workers<sup>323</sup> published the first example of the synthesis and room-temperature oxygen-carrying ability of an iron(II) porphyrin, Fe<sup>II</sup>(TpivPP) (Figure 20). This "picket-fence" porphyrin has all four of the pivaloylamide groups above one face of the porphyrin ring.<sup>324</sup> A number of picket-fence porphyrins containing different pendant groups have now been reported.<sup>325</sup> Suppression of irreversible oxidation was so successful with this complex that a benzene solution of Fe<sup>II</sup>(TpivPP) in the presence of an excess of Melm was observed to reversibly add O<sub>2</sub> at room temperature.

Despite the steric bulk of the pivaloyl groups, they do not block coordination of a sixth axial ligand, and solid complexes of the form Fe<sup>II</sup>(TpivPP)(B)<sub>2</sub> have been isolated.<sup>323,325</sup> However, it is believed that the binding constant for 1-Melm on the "picket-fence" side of the porphyrin is significantly less than on the unhindered side, and thus O<sub>2</sub> binding occurs inside the protective enclosure of the pivalamido groups. Were this not the case, significant amounts of the Fe(TpivPP)(1-Melm)(O<sub>2</sub>) complex with the O<sub>2</sub> bound to the unhindered side would be found in solution, with subsequent formation of the  $\mu$ -oxo dimer complex having the two unhindered sides of the porphyrin rings facing one another.

Although Fe<sup>II</sup>(TpivPP) is capable of binding two Melm ligands in solution, the five-coordinate complex Fe<sup>II</sup>(TpivPP)(Melm) has been isolated<sup>326</sup> as a solid and as such has been shown to react reversibly with O<sub>2</sub>. Thermodynamic data obtained from this solid-gas equilibrium gave values for the enthalpy and entropy of O<sub>2</sub> binding similar to those obtained from natural myoglobin. No cooperative binding of O<sub>2</sub> was noted for this complex. More recently, Collman and co-workers<sup>327</sup> have examined the solid-gas equilibria between dioxygen and the solid five-coordinate iron(II) picket-fence complexes containing the sterically hindered imidazole, 2-methylimidazole and 1,2-dimethylimidazole, in the axial position, and have shown the binding of O<sub>2</sub> to be cooperative. The binding of O<sub>2</sub> to solid Fe<sup>II</sup>(TpivPP)(2-Melm) is quantitatively similar to that found in human HbA; upon fitting the data to the Hill equation one observed limiting values for P<sub>1/2</sub>O<sub>2</sub> at low and high partial pressures of O<sub>2</sub> of 0.7 and 14 Torr for the model complex which compares with 0.3 and 9 Torr for HbA.<sup>328,329</sup> In addition, Hill coefficients of 2.6 were observed for Fe(TpivPP)(1,2-Me<sub>2</sub>Im), which is similar to the value of 2.5 observed for HbA.

Two other reports of the cooperative binding of O<sub>2</sub> to synthetic iron(II) porphyrin oxygen carriers have appeared. Tsuchida<sup>330,331</sup> and co-workers have observed sigmoidal behavior (Hill slope,

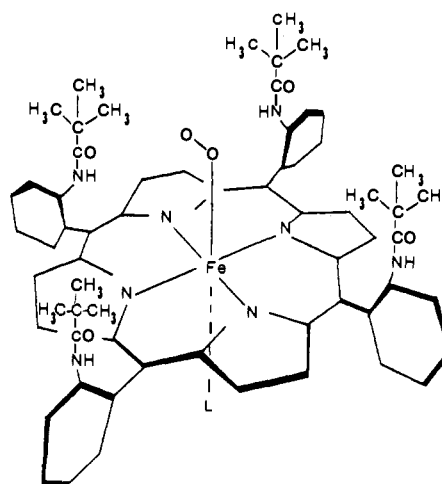
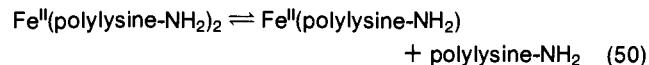


Figure 20. Structure of Fe(TpivPP)(L)(O<sub>2</sub>), the oxygen adduct of the "picket-fence" porphyrin. Double bonds are deleted for clarity.

$n = 2.4$ ) for the bonding of O<sub>2</sub> to a poly-L-lysine-protoporphyrinatoiron(II) polymer. The origin of the cooperativity appears to have been demonstrated by the authors. In the absence of the heme group, poly-L-lysine adopts a regular  $\alpha$ -helix conformation. Upon formation of the polymer-heme complex, in which two of the polylysine amine moieties are coordinated to the iron(II) center, the helical nature of the polymer is disturbed. When O<sub>2</sub> (or CO) is bound to the iron(II) center, the helix content of the polymer increases. Thus, bonding a dioxygen molecule to a heme center, and thereby displacing one of the coordinated lysine-NH<sub>2</sub> groups from the iron center, increases the helical nature of the polymer. This conformational change in the polymer results in a weakening of other (lysine-NH<sub>2</sub>)<sub>2</sub>-Fe(II) interactions, making the lysine dissociation



more favorable, thus increasing the overall equilibrium constants of the remaining deoxy iron(II) centers for O<sub>2</sub>. Since Tsuchida's models involve cooperativity in the formation of the O<sub>2</sub> complex from a six-coordinate complex, it does not represent a model for the cooperativity observed in Hb. A brief account of cooperative dioxygen bonding in a polymeric heme system has also been reported by Bayer.<sup>332</sup> However, it has been pointed out<sup>327</sup> that the Bayer isotherm, when displayed as a Hill plot, is not well behaved, and that the visible spectrum of the oxy complex does not correspond to that of known dioxygen complexes. It appears that the cooperativity found in solids and in polymeric solutions do not relate to that for Hb.

The dioxygen adduct, Fe(TpivPP)(1-Melm)(O<sub>2</sub>), has been isolated as a solid<sup>323</sup> and has been characterized by magnetic susceptibility measurements<sup>325</sup> as well as by Mössbauer<sup>333</sup> and infrared spectroscopy.<sup>334</sup> In addition, a single-crystal X-ray structure determination has been made.<sup>30,335</sup> In general these measurements indicate that the picket-fence dioxygen complex bears a close resemblance to the natural systems.

Magnetic susceptibility measurements<sup>327</sup> on Fe(TpivPP)(1-Melm)(O<sub>2</sub>) show the complex to be diamagnetic, the same as was found for oxyhemoglobin by Pauling and Coryell<sup>24</sup> in 1936. In contrast to this behavior, however, Cerdonio and co-workers<sup>43</sup> have recently observed that human oxyhemoglobin shows a magnetic susceptibility consistent with a thermal equilibrium between a ground-state singlet and an excited-state triplet, with the singlet-triplet energy separation,  $2J$ , being 146 cm<sup>-1</sup>. This work has been recently challenged by Pauling.<sup>46</sup> Mössbauer measurements<sup>333</sup> of the oxygenated picket-fence complexes indicate a close similarity to oxyhemoglobin with respect to both isomer shift and quadrupole splitting. In addition, the O-O infrared

stretching frequencies obtained for  $\text{Fe}(\text{TpivPP})(\text{Melm})(\text{O}_2)$ ,  $1159 \text{ cm}^{-1}$ ,<sup>334</sup> is similar to the values obtained for  $\text{HbO}_2$  ( $1107 \text{ cm}^{-1}$ )<sup>29</sup> and  $\text{MbO}_2$  ( $1103 \text{ cm}^{-1}$ ).<sup>28</sup>

In agreement with the structure predicted from the O–O stretching frequencies observed for the picket-fence iron-dioxygen complexes,<sup>334</sup> X-ray crystallographic results<sup>30</sup> on  $\text{Fe}(\text{TpivPP})(1\text{-Melm})(\text{O}_2)$  show the dioxygen bonding in an end-on, Pauling-type conformation with Fe–O–O bond angles for the crystallographically independent  $\text{O}_2$  groups present in the crystal being  $133(2)$  and  $129(2)^\circ$ . Problems with disorder and high thermal motion in many parts of the structure resulted in difficulties in obtaining a precise structure analysis. Thus, the O–O bond lengths of 1.15 and 1.14 Å, which are unrealistic when compared with the value of 1.21 Å found in  $\text{O}_2$ ,<sup>336</sup> may be underestimated by as much as 0.15 Å. As expected, the iron center lies virtually within the plane of the porphyrin ring, being displaced 0.015(3) Å from the porphyrinato ring toward the coordinated  $\text{O}_2$ . The Fe–O–O plane bisects an N–Fe–N right angle of the equatorial porphyrin plane and is, consequently, fourfold disordered.

In addition to the complex  $\text{Fe}^{\text{II}}(\text{TpivPP})(\text{Melm})$ , other picket-fence porphyrins have been shown to reversibly bind  $\text{O}_2$ . Reduction of  $\text{Fe}^{\text{III}}(\text{TpivPP})(\text{Br})$  in THF yields crystals<sup>337a</sup> of high-spin  $\text{Fe}^{\text{II}}(\text{TpivPP})(\text{THF})_2$ ,  $\mu_{\text{eff}} = 4.9 \text{ BM}$  at 25 °C, in which only one THF is presumed to coordinate to the iron(II) center. This assumption is in agreement with the behavior of simple ferrous complexes in THF solution.<sup>290</sup> In the solid state,  $\text{Fe}(\text{TpivPP})(\text{THF})_2$  reversibly absorbs 1 mol equiv of  $\text{O}_2$  to form a reported paramagnetic ( $\mu_{\text{eff}} = 2.4 \text{ BM}$ ) dioxygen adduct. The complex was later shown by Mössbauer spectroscopy to be diamagnetic.<sup>325,337</sup>

In addition to the picket-fence complex,  $\text{Fe}^{\text{II}}(\text{TpivPP})$ , in which the four pickets (pivalamido group) lie on one side of the porphyrin ring, Collman and co-workers<sup>163</sup> have synthesized "tail-base" iron(II) porphyrins,  $\text{Fe}^{\text{II}}(\text{triPiv}(4\text{C Im})\text{PP})$  and  $\text{Fe}^{\text{II}}(\text{triPiv}(5\text{C Im})\text{PP})$ , which have three pivalamido pickets lying on one side of the porphyrin and an appended imidazole moiety which is capable of coordinating to the iron(II) center. Solutions of these tail-base porphyrins reversibly oxygenate at 25 °C, having  $P_{1/2}^{\text{O}_2}$  values (0.60 and 0.58 Torr, respectively) comparable both with the  $P_{1/2}^{\text{O}_2}$  obtained from  $\text{Fe}^{\text{II}}(\text{TpivPP})(1\text{-Melm})$  (0.49 Torr) in the solid state and with those of Mb (0.7 Torr) and the isolated  $\alpha$  (0.63 Torr) and  $\beta$  (0.25 Torr) chains of Hb.

In a synthetic tour d'force Baldwin and co-workers synthesized the "capped" porphyrin-iron(II) complex<sup>292,338</sup> and have shown it to be an oxygen carrier in pyridine solution at 25 °C. Reversible oxygen binding has also been observed in a benzene solution containing 5% 1-methylimidazole; however, in this medium the stability of the oxygenated heme toward autoxidation has been shown to be considerably less than in neat pyridine. In 5% pyridine–benzene, autoxidation was rapid, consistent with the observed<sup>339</sup> stronger affinity of iron(II) heme for imidazole than for pyridine in benzene. The oxygen-carrying ability of the capped heme is due to two effects: (1) the small "pocket" inside the cap preventing the coordination of a donor ligand inside the cap (this permits high concentrations of an N-donor ligand to be present to prevent oxygen bonding to the open-side of the porphyrin with subsequent autoxidation while maintaining the iron(II) as five-coordinate); and (2) the steric influence of the cap preventing  $\mu$ -peroxo dimer formation.

At this point it is interesting to note that although the iron(II)-capped porphyrin reversibly binds  $\text{O}_2$  in 5% 1-methylimidazole–benzene, in 5% pyridine–benzene instantaneous autoxidation was noted. The autoxidation of iron(II) porphyrins coordinated by imidazole has been noted by other workers.<sup>340–342</sup> Although the nature of the reaction has not been investigated, a recent study<sup>343</sup> has shown that in the presence of acids iron(II) hemes are oxidized by an apparent outer-sphere acid-catalyzed process, and that the proton on imidazole is acidic enough to carry out the reaction.

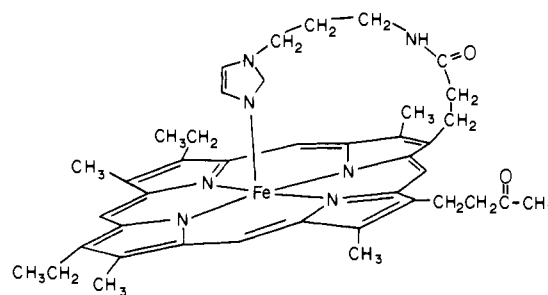


Figure 21. Structure of pyrroheme-*N*-(3-(1-imidazolyl)propyl)amide.

The synthesis of the capped porphyrins represents the first model for the natural oxygen-carrying heme proteins in which a five-coordinate iron(II) porphyrin is observed to bind oxygen reversibly in solution at room temperature. That such severe steric hindrance as is found in the capped porphyrin is necessary to prevent coordination of a sixth axial ligand is demonstrated both by the six-coordination of  $\text{Fe}^{\text{II}}(\text{TpivPP})(\text{B})_2$  in small excesses of a coordinating ligand and the recent synthesis<sup>344,345</sup> of iron(II) porphyrins containing a single bridge constructed across the porphyrin macrocycle that irreversibly oxidizes in solution at room temperature.<sup>346</sup>

In contrast with the picket-fence and capped porphyrins,<sup>347,348</sup> which are sterically hindered on only one face of the porphyrin, Vaska and coworkers<sup>349,350</sup> have synthesized meso-tetrakis(2,4,6-trimethoxyphenyl)porphyratoiron(II),  $\text{Fe}^{\text{II}}(\text{T}(\text{OMe})_3\text{PP})$ , and the ethoxy analog,  $\text{Fe}^{\text{II}}(\text{T}(\text{OEt})_3\text{PP})$ ,<sup>351</sup> which have protecting groups above and below the porphyrin plane. Exposure of these complexes to dioxygen as solids or in benzene solution at 25 °C involves uptake of  $\text{O}_2$ , which is at least partially reversible.

### 1. Low Temperature

One of the first synthetic iron(II) oxygen carriers was reported by Chang and Traylor<sup>352</sup> in 1973. By reacting 1-(3-aminopropyl)imidazole with the acid chloride of pyrroporphyrin XV these workers were able to prepare a pyrroporphyrin complex that had the imidazolyl propyl side chain covalently attached by an amide linkage to the porphyrin ring. After insertion of iron into the porphyrin, subsequent reduction gave the five-coordinate, iron(II) complex (Figure 21), which was observed to bind  $\text{O}_2$  reversibly both in the solid state and when dissolved in a polystyrene film. When the five-coordinate pyrroheme-*N*-[3-(1-imidazolyl)propyl]amide was dissolved in  $\text{CH}_2\text{Cl}_2$  at  $-45^\circ\text{C}$ , the complex was observed<sup>353</sup> to bind  $\text{O}_2$  reversibly. When the solution was warmed to room temperature, an irreversible oxidized product was obtained. These workers attributed the reversible oxygen binding of the heme complex to two factors: (1) the neighboring group effect of the covalently attached imidazole group; and (2) the fact that at low temperature the rate of irreversible oxidation was significantly inhibited. The fact that the pyrroheme complex used by Chang and Traylor was sterically capable of forming a  $\mu$ -oxo dimer led several groups<sup>354–358</sup> to examine the binding of dioxygen to six-coordinate iron(II) complexes having the form  $\text{Fe}^{\text{II}}(\text{porphyrin})(\text{B})_2$ . These workers discovered that exposing solutions of the six-coordinate heme to dioxygen at low temperature resulted in the reversible binding of  $\text{O}_2$  and were thus able to conclude that the oxygen-carrying ability of the Traylor complex was due to the effect of reduced temperature on the rate of irreversible oxidation and was not a function of a "neighboring group effect". That the effect of the pendant imidazole leads to an increased oxygen affinity of the ferrous heme when compared to the affinity of the heme in the presence of a free 1-alkyl-imidazole has been reported.<sup>355</sup> However, a recent investigation<sup>162</sup> using cobalt(II)–porphyrinato complexes with attached N-donor ligands has failed to see any enhancement of the oxygen affinity due to the attached axial base.

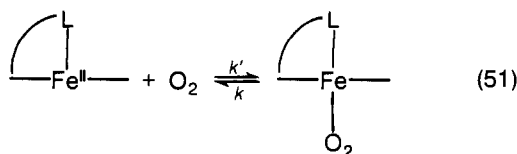
**TABLE XV. Comparison of Kinetics of Oxygenation of Heme Proteins and Model Systems<sup>a</sup>**

heme	$k^1$ , $M^{-1} s^{-1} \times 10^{-7}$	$k$ , $s^{-1}$	$k^1/k$ , $M^{-1} \times 10^{-6}$
1 (H <sub>2</sub> O, pH 7.3) <sup>b</sup>	6	35	1.7
1 (DMF) <sup>b</sup>	80	160	0.5
1 (CH <sub>2</sub> Cl <sub>2</sub> ) <sup>b</sup>	100	600	0.15
isolated $\alpha$ chains <sup>c</sup>	5.5	31	1.8
Mb (sperm whale) <sup>c</sup>	1.9	10	1.9
Mb (Aplysia) <sup>d</sup>	1.5	70	0.22
Hb <sup>e</sup>	0.2	1080	0.009
Hb(O <sub>2</sub> )	0.4	244	0.017
Hb(O <sub>2</sub> ) <sub>2</sub>	0.35	28	0.12
Hb(O <sub>2</sub> ) <sub>3</sub>	4.0	48	0.8

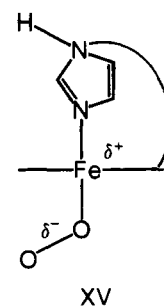
<sup>a</sup> Kinetic data at 20 or 22 °C. <sup>b</sup> Compound 1 refers to pyrrheme-*N*-[3-(1-imidazolyl)propyl]amide. Data for this compound come from ref 361. <sup>c</sup> M. Brunori and T. M. Schuster, *J. Biol. Chem.*, **244**, 4046 (1969). <sup>d</sup> B. A. Whittenberg, M. Brunori, E. Antonini, J. B. Wittenberg, and J. Wyman, *Arch. Biochem. Biophys.*, **111**, 576 (1965). <sup>e</sup> G. Ilgenfritz and T. M. Schuster, *J. Biol. Chem.*, **249**, 2959 (1974).

Despite the fact that the "tail-base" porphyrins do not inhibit irreversible oxidation, they do provide five-coordination for the iron(II) and a variety of tail-base porphyrins have now been prepared. A study<sup>359</sup> on a tail-base porphyrin containing a pendant pyridine coordinated to the iron(II) center has shown that, compared with the analogous imidazole complex, the affinity of the five-coordinate heme for O<sub>2</sub> is quite small. Comparative  $P_{1/2}O_2$  values (at -45 ° in CH<sub>2</sub>Cl<sub>2</sub>) are 0.2 and >760 Torr for the imidazole and pyridine complexes, respectively. It has been proposed<sup>359</sup> that this large difference is due to the ability of the *N*-alkylimidazole to donate  $\pi$ -electrons to the coordinated O<sub>2</sub>, thus stabilizing the Fe-O<sub>2</sub> bond. However, a systematic study of the O<sub>2</sub> affinities of five-coordinated hemes with different axial substituents has not been undertaken.

Several other studies on the kinetics and thermodynamics of O<sub>2</sub> and CO binding to tail-base hemes have appeared,<sup>360-363</sup> the results of which carry interesting implications both as to the nature of the environment about the heme prosthetic group in Hb and Mb, and as to possible modes for protein control of heme binding. Chang and Traylor<sup>361</sup> have measured the kinetics for the oxygenation of the tail-base heme complex, pyrrheme-*N*-[3-(1-imidazolyl)propyl]amide (Figure 21). In nonpolar solvents or in aqueous solution at approximately neutral pH, the tail-base heme exists almost entirely in the five-coordinate form and the kinetics for O<sub>2</sub> addition are consistent with the mechanism given by eq 51.

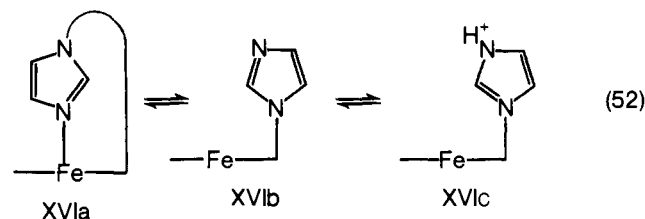


A comparison of the kinetic results obtained from the model compound with those from natural heme systems (Table XV) shows (1) the effect of going from a relatively nonpolar solvent to the polar solvent water is to significantly decrease the O<sub>2</sub> off-rate,  $k$ , while having a small effect on the O<sub>2</sub> on-rate,  $k'$ . This effect is consistent with the aqueous environment stabilizing an iron-dioxygen dipole relative to the less polar solvents CH<sub>2</sub>Cl<sub>2</sub> and DMF. However, the fact that the kinetics observed in water more closely resemble those obtained from the natural monomeric heme protein systems than do those obtained in the less polar solvents is somewhat surprising and may imply the presence of some polar interaction between the coordinate dioxygen and the protein. (2) The similarity between the kinetic data obtained for the model system and the addition of O<sub>2</sub> to Hb(O<sub>2</sub>)<sub>3</sub>, (where Hb(O<sub>2</sub>)<sub>3</sub> represents the Hb molecule with three of the four



heme sites oxygenated) may indicate that the tail-base heme represents a reasonable model for the bonding of O<sub>2</sub> to the R state of hemoglobin.

In addition to having shown that for nonaqueous solvents, as in water at approximately neutral pH, the addition reactions of CO and O<sub>2</sub> to the tail-base hemes proceed via the simple association process in eq 51, Traylor and co-workers<sup>364</sup> have recently shown that at low pH a different mechanism for CO addition is observed. At low pH, the equilibrium lies strongly to the right, and formation of the six-coordinate, carbon monoxide complex, XVla-CO, proceeds via coordination of CO to the



four-coordinate porphyrins, XVlb, followed by coordination of the appended imidazole to the iron center. The data obtained for CO addition to mesoheme dimethyl ester in aqueous solution in the presence of 2-Melm, a ligand which, owing to steric interference forces only five-coordinate complexes with hemes, is also consistent with the reaction proceeding via the so-called "base-elimination" pathway. Although such a mechanism has yet to be shown to occur for O<sub>2</sub> bonding, it may represent a mechanism by which the heme proteins can regulate oxygen affinity.

With the introduction of proximal base strain in the tail-base heme complexes Traylor<sup>364</sup> has created models for the R and T states of hemoglobin. The presence of strain decreases the oxygen affinity. This steric effect also changes the mechanism of binding carbon monoxide (but not that of oxygen), implying that such mechanism changes also occur in natural systems. This behavior supports the proposal that such strain could contribute to the differences in affinity of R- and T-state hemoglobin.

A detailed kinetic and thermodynamic study of oxygen and carbon monoxide binding to six-coordinate ferrous porphyrins, Fe<sup>II</sup>(TPP)(B)<sub>2</sub>, has been made.<sup>285,365</sup> These simple ferrous porphyrins, Fe(TPP)(B)<sub>2</sub>, in methylene chloride solution at -79 °C are excellent oxygen carriers. The spectral changes show that Fe(TPP)(py)<sub>2</sub> is oxygenated in the presence of dioxygen, and deoxygenated when the solution is purged with dinitrogen. Several oxygenation-deoxygenation cycles are possible at -79 °C with a minimum of irreversible oxidation occurring, and at this temperature a solution of the complex in 1 atm of oxygen is stable for at least 1 day. The stoichiometry of the reaction corresponds to 1 mole of dioxygen per mole of iron:



Under 1 atm of oxygen, complete complex formation occurs in methylene chloride; only a small amount of complex is formed in toluene, whereas the degree of complex formation in ethyl ether lies between these extremes. Similarly, dioxygen com-



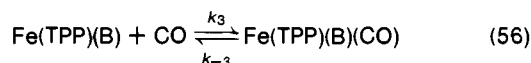
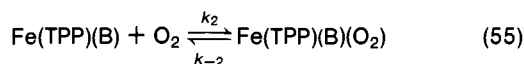
TABLE XVI. Comparisons between Kinetic and Thermodynamic Parameters for Reactions of O<sub>2</sub> and CO with a Simple Ferrous Porphyrin and with Heme Proteins

ferrous system <sup>a</sup>	$k_3/k_2$	$k_{-3}/k_{-2}$	$K_{CO}/K_{O_2}$
Fe(TPP)(Melm)	0.031	$<1.1 \times 10^{-3}$	$>30$
myoglobin <sup>b</sup> (horse)	0.016	$1.08 \times 10^{-3}$	14.4
myoglobin <sup>c</sup> (aplysia)	0.033	$0.29 \times 10^{-3}$	114
isolated $\alpha$ chains <sup>d,e</sup>	0.071	$0.52 \times 10^{-3}$	133
isolated $\beta$ chains <sup>d,e</sup>	0.030	$0.17 \times 10^{-3}$	180

<sup>a</sup> The values for the heme proteins are at 20 °C in aqueous solution (pH 7.0–7.4), whereas for Fe(TPP)(Melm) the conditions are –79 °C and methylene chloride solution (from ref 285 and 365). <sup>b</sup> G. A. Millikan, *Proc. R. Soc. London, Ser. B*, **120**, 366 (1936). <sup>c</sup> B. A. Wittenberg, M. Brunori, E. Antonini, J. B. Wittenberg, and J. Wyman, *Arch. Biochem. Biophys.*, **111**, 576 (1965). <sup>d</sup> M. Brunori, R. W. Noble, E. Antonini, and J. Wyman, *J. Biol. Chem.*, **241**, 5238 (1966). <sup>e</sup> R. W. Noble, Q. H. Gibson, M. Brunori, E. Antonini, and J. Wyman, *ibid.*, **244**, 3905 (1969).

plexes of cobalt are stabilized by polar solvents. The behavior in polar solvents supports formulation of the iron complex as Fe<sup>III</sup>(O<sub>2</sub><sup>-</sup>). This formulation is in accord with the IR spectra of HbO<sub>2</sub><sup>29</sup> and MbO<sub>2</sub><sup>28</sup>

Kinetic and equilibrium studies have been made on the reactions of Fe(TPP)(B)<sub>2</sub> with oxygen and with carbon monoxide in methylene chloride at –79 °C. The results of this investigation<sup>285,365</sup> are in accord with a rate-determining dissociation process (eq 54), followed by the rapid reaction of the five-coordinated intermediate, Fe(TPP)(B), with either oxygen (eq 55) or carbon monoxide (eq 56).



Some of the data obtained are given in Table XVI, along with corresponding data for Mb and for the isolated  $\alpha$  and  $\beta$  chains of Hb. The simple five-coordinate ferrous porphyrin Fe(TPP)(Melm) displays the same trends in reacting with dioxygen and carbon monoxide as do the more complicated heme proteins. This suggests that the simple system is a satisfactory model for the active site of heme proteins. Although the carbon monoxide complex is more stable than the corresponding oxygen complex, dioxygen reacts more rapidly than does carbon monoxide with the five-coordinate iron species.

The ratio  $k_2/k_{-1}$  (see eq 55 and 56) is approximately equal to 1 for different axial bases, which shows that there is no large kinetic preference of iron porphyrin for oxygen compared with nitrogenous bases. This illustrates the subtlety of the heme environment in the oxygen-carrying proteins. The distal imidazole can stabilize the oxygen complex through hydrogen bonding, but geometric constraints fortunately prevent its coordination to the iron center. The values of  $k_2/k_{-1}$  show that if the distal imidazole could bind to heme, it would seriously compete with oxygen for the available site, and the protein would cease to function as an effective oxygen carrier.

The synthesis of a porphyrinatoiron–dioxygen complex by reacting protoporphyrinatoiron(III) and superoxide, O<sub>2</sub><sup>-</sup>, has also been reported.<sup>378</sup> In DMF solution at –50 °C, [Fe<sup>III</sup>(PPDE)]<sup>+</sup>ClO<sub>4</sub><sup>-</sup> will react with 1 mol equiv of [Et<sub>4</sub>N]<sup>+</sup>O<sub>2</sub><sup>-</sup> to produce a species having an optical spectrum comparable with that of oxymyoglobin.

## 2. Solid

The third successful method of obtaining an oxygen-carrying iron complex is to attach it to the surface of a solid or polymer

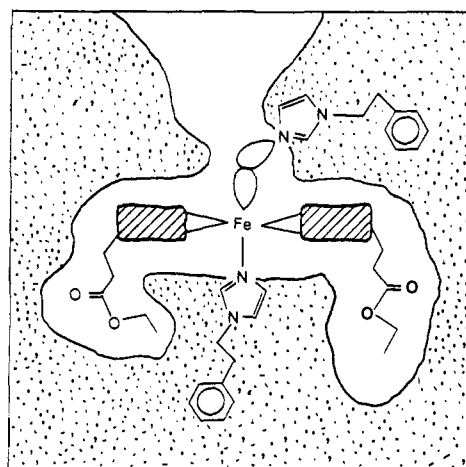
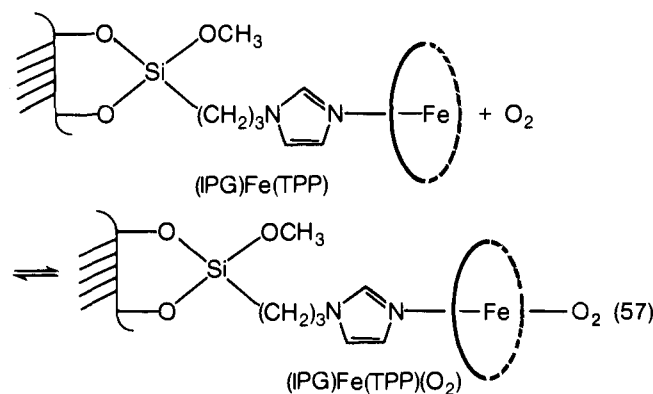


Figure 22. Structure of 1-(2-phenylethyl)imidazoleheme diethyl ester in a matrix of polystyrene and 1-(2-phenylethyl)imidazole.

support so that two iron atoms cannot approach each other to form a dimer. In a classic experiment Wang<sup>366</sup> reported the first synthetic Fe(II) oxygen carrier. Proceeding on the basis of a previous suggestion<sup>367</sup> that the stability of oxyhemoglobin and oxymyoglobin to autoxidation could be due to the low dielectric constant of the globin surroundings of the bound oxygen, Wang showed that oxygen binds reversibly to 1-(2-phenylethyl)imidazole heme diethyl ester embedded in a matrix of an amorphous mixture of polystyrene and 1-(2-phenylethyl)imidazole. Although reversible absorption of O<sub>2</sub> by bis(imidazole)protoporphyrinatoiron(II) had been previously described,<sup>272</sup> Wang's model (Figure 22) represents the first synthetic heme-containing oxygen carrier in which evidence was adduced that the O<sub>2</sub> is bound directly to the Fe(II) center. More recently Collman and Reed<sup>292</sup> reported that cross-linked polystyrene containing appended imidazole ligands coordinated to Fe<sup>II</sup>(TPP) was not a rigid enough support to prevent dimerization since treatment with O<sub>2</sub> in benzene caused linking of the oxidized product, [Fe<sup>III</sup>(TPP)]<sub>2</sub>O. It should be noted that on the basis of the diamagnetism of the complex as well as optical spectroscopy, the Fe(II) center appeared six-coordinate. Although the authors report that the irreversible oxidation was due to the mobility of the cross-linked polystyrene matrix, the possibility that the Fe(TPP) was first leached off the polymer and then underwent oxidation was not discussed by the authors.

Attachment of Fe<sup>II</sup>(TPP) to a rigid modified silica gel support has been shown to inhibit autoxidation and produces an efficient oxygen carrier.<sup>368</sup> The modified silica gel employed contains 3-imidazolylpropyl (IPG) groups bonded to surface atoms of silicon. This then reacts with Fe(TPP)(B)<sub>2</sub> to coordinate the iron(II) porphyrin to imidazole groups attached to the silica surface. Heating (IPG)Fe(TPP)(B) in flowing helium removes the axial base (pyridine or piperidine) and generates the active coordination site, (IPG)Fe(TPP) (see eq 57) resembling that of the five-coor-



minated iron(II) porphyrin in hemoglobin and myoglobin. The open coordination site can then reversibly bind dioxygen.

The reported chemisorption of oxygen is weak. It is irreversible at  $-127^{\circ}\text{C}$ ; it has a  $P_{1/2}\text{O}_2$  of 0.4 Torr at  $-78^{\circ}\text{C}$  and a  $P_{1/2}\text{O}_2$  of 230 Torr at  $0^{\circ}\text{C}$ . Data for human myoglobin<sup>60a</sup> extrapolated to  $0^{\circ}\text{C}$  give  $P_{1/2}\text{O}_2$  of 0.14 Torr. Successful  $\text{O}_2$  binding on the modified silica gel, however, confirms the utility of the rigid-surface approach. Recently it was suggested<sup>369</sup> that the low affinity for  $\text{O}_2$  found for the (Fe)(TPP)(IPG) system was due to physisorption of  $\text{O}_2$ . The system is being reinvestigated and seems to show evidence of iron centers having different activities.<sup>370</sup>

Protoporphyriniron(II) has been attached via a coordinate linking to several poly(4-vinylpyridine) and poly-L-lysine polymers.<sup>330,331,371-378</sup> These polymers have been shown to reversibly add dioxygen in a ratio of 1Fe:1 $\text{O}_2$  in the solid state and their behavior in solution has been studied. Bayer and Holzbach<sup>332</sup> have covalently attached protoporphyrinatoiron(II) to water-soluble polymers which also contain appended imidazole groups that are capable of bonding to the iron(II) center. Polymer complexes were prepared in which the heme had either one or two imidazole moieties bound to the heme. In aqueous solution at room temperature the complexes were shown to be oxygen carriers and the  $P_{1/2}\text{O}_2$  values observed are similar to those reported for myoglobin. In addition, cooperativity in  $\text{O}_2$  bonding between the heme sites was reported. Although it was previously reported<sup>379</sup> that iron(II) porphyrins attached to a polyphosphazene polymer reversibly bound oxygen in aqueous solution, later results<sup>380</sup> indicate that in aqueous solution or as solid films the presence of the polymeric ligands did not prevent the irreversible oxidation of heme on contact with oxygen.

Several binuclear metal complexes have been prepared in an attempt to model natural systems which have two metal ions in their active sites, such as hemerythrin or hemocyanin. There exist several ligands with the capabilities, such as Kagan's<sup>381</sup> *strati*-bisporphyrins, the picket-fence-like porphyrin (P-N<sub>4</sub>) of Elliot<sup>382</sup> and Buckingham<sup>383</sup> where the pivalamido pickets are replaced by nicotinoyl groups allowing for the coordination of a metal by four pyridines, or Chang's<sup>384</sup> crowned porphyrin. It has been possible to insert only one Fe(II) into the P-N<sub>4</sub> porphyrin, with the Fe(II) coordinated to the porphyrin. Its reactivity to oxygen is very similar to Collman's iron picket-fence complexes. At present there is no reported incorporation of any metals in the *strati*-bisporphyrin systems.

Chang's crowned porphyrin<sup>384</sup> has a crown ether covalently attached to the porphyrin and occupies a position directly above the porphyrin plane. This crown porphyrin allows for the coordination of a transition metal ion in the porphyrin plane with the simultaneous ligation of a metal ion in the crown ether portion. An interesting sidelight is that the crown can act in a similar manner as Baldwin's cap, with the addition of a bulky nitrogen donor, such as 1-triphenylmethylimidazole; the iron(II) complex is a stable ( $t_{1/2} > 1$  h) room-temperature ( $25^{\circ}\text{C}$ ) oxygen carrier.

## IX. Manganese-Dioxygen Carriers

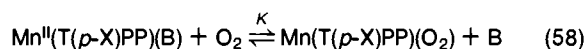
The interaction between dioxygen and tetradentate chelates of manganese(II) in solution usually results in the irreversible oxidation of the metal to a Mn(III) or Mn(IV) species.<sup>385</sup> The early report<sup>281</sup> that manganese phthalocyanine, Mn(II)(Pc), in pyridine solution at room temperature acts as a reversible oxygen carrier has been shown to be in error, and the end product of the auto-oxidation has been identified<sup>280,386</sup> as the  $\mu$ -oxo dimer, (py)-(Pc)Mn<sup>III</sup>O-Mn<sup>III</sup>(Pc)(py). Calvin and co-workers<sup>387-389</sup> have determined that the formation of the  $\mu$ -oxo dimer from MnPc proceeds via a manganese(III) intermediate. They have suggested that this intermediate is phthalocyanatohydroxomanganese(III), while Elvidge and Lever<sup>281</sup> have speculated that the

oxidation might proceed through a peroxy-bridged species. The possibility that this intermediate might be phthalocyanatosuperoxomanganese(III) has recently been suggested.<sup>390</sup>

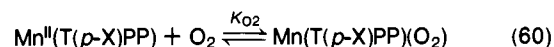
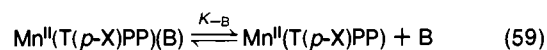
The first example of a synthetic reversible oxygen carrying compound of manganese(II) appears to be the report of the dioxygen adduct formed with *meso*-tetraphenylporphyrinatopyridinemanganese(II), Mn(TPP)(py), in toluene at  $-79^{\circ}\text{C}$ .<sup>391-393</sup> This reversible oxygenation was also observed independently<sup>394</sup> by using Mn(TPP) in a toluene-THF solution at  $-90^{\circ}\text{C}$ . As in the case of the synthetic iron(II) oxygen-carrying chelates, the aprotic solvent and low temperature inhibit the irreversible oxidation and stabilize the dioxygen adduct. At  $-79^{\circ}\text{C}$ , decomposition of the oxygenated complex to give unidentified irreversibly oxidized products is slow; 70% of the initial manganese(II)-porphyrin complex can be regenerated by flushing the solution with dinitrogen after exposure of the system to 1 atm of  $\text{O}_2$  for 14 h.<sup>391</sup>

On the basis of the optical and EPR spectra,<sup>391,392</sup> charge transfer from the manganese(II) to dioxygen appears to occur upon formation of the manganese-dioxygen complexes. Exposure of porphyrinatomanganese(II) to oxygen in toluene at  $-79^{\circ}\text{C}$  results in dramatic changes in the visible spectrum. The optical densities of the visible, Q bands,<sup>395</sup> decrease markedly, and the Soret band splits to give spectra similar to those observed for Mn<sup>III</sup>(TPP) species. Despite the appearance of a Mn(III)-type optical spectrum, a detailed analysis of the EPR spectra of Mn(TPP)( $\text{O}_2$ ) at 77 and 4.2 K has been interpreted as arising from a quartet ground state for a  $^4(t_2^3)$  manganese ion. These results and the absence of spin density on the dioxygen as determined by  $^{17}\text{O}$ -labeling experiments suggest a formal valence state for the complex as Mn<sup>IV</sup>(TPP)( $\text{O}_2^{2-}$ ). While the authors<sup>391,392</sup> have tentatively favored a symmetric, Griffith-type structure similar to that observed for a titanium porphyrin peroxide complex,<sup>396</sup> it is not possible to rule out a Pauling-type structure similar to that found for cobalt-dioxygen complexes with only one of the oxygen atoms of the dioxygen moiety bound to the manganese.

The reaction of molecular oxygen in toluene, with a series of para-substituted *meso*-tetraphenylporphyrinatomanganese(II) complexes, Mn<sup>II</sup>(T( $p$ -X)PP)(B), containing an axial ligand, B, has recently been studied.<sup>397</sup> Spectrophotometric titrations of toluene solutions of these complexes at  $-78^{\circ}\text{C}$  with molecular oxygen confirm the previous interpretation<sup>391,392</sup> that at low temperatures an equilibrium between the five-coordinate monoligated species, Mn<sup>II</sup>(T( $p$ -X)PP)(B), and the dioxygen complex, Mn(T( $p$ -X)PP)( $\text{O}_2$ ), is established



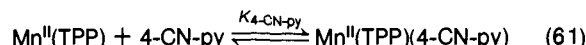
which can also be written in terms of the two equilibria:



Equilibrium constants for eq 58, where X = Cl, F, H, CH<sub>3</sub>, and OCH<sub>3</sub>, and B = pyridine, have been determined and a fit of the observed values for the equilibrium constants to the Hammett equation<sup>398</sup> ( $-\log K$  vs.  $4\sigma$ ) gave a Hammett  $\rho$  value of  $-0.41 \pm 0.08$ . By subtracting a calculated value for the Hammett  $\rho$  value for eq 59, the authors<sup>397</sup> obtained an estimated<sup>399</sup> value of  $-0.08$  at  $-78^{\circ}\text{C}$  for the oxygenation of the four-coordinate base-free Mn<sup>II</sup>(T( $p$ -X)PP) complexes. Thus, at low temperatures, para substitution of the peripheral phenyl rings of tetraphenylporphyrinatomanganese(II) has a relatively small effect on the oxygen affinity. A small Hammett  $\rho$  value was similarly observed<sup>124</sup> for the  $\text{O}_2$  affinities of Co<sup>II</sup>(T( $p$ -X)PP)(py) complexes.

The equilibrium constant for the oxygenation of Mn<sup>II</sup>(TPP)-

(4-CN-py) was determined, in toluene at  $-78\text{ }^\circ\text{C}$ , as  $K = 10^{-5.57}$ . In addition, equilibrium constants for the reaction:



were determined at several temperatures, and an extrapolated value for  $K_{4\text{-CN-py}}$  at  $-78\text{ }^\circ\text{C}$  of  $10^{7.63}$  was obtained. From these values of  $K$  and  $K_{4\text{-CN-py}}$  an estimate of the equilibrium constant for the oxygenation of four-coordinate  $\text{Mn}^{\text{II}}(\text{TPP})$  of  $K_{\text{O}_2} \sim 10^{2.1}$  Torr $^{-1}$  was obtained.

A comparison of the equilibrium constants for oxygenation for a series of porphyrinatometal(II) complexes at  $-78\text{ }^\circ\text{C}$  with the  $\text{M}^{\text{II/III}}$  half-wave reduction potentials (Table XVII) shows that, with the exceptions of  $\text{Mn}^{\text{II}}(\text{TPP})$ , there is a direct relationship between the affinity of the complex for dioxygen and the ease of oxidation of the metal(II) center. Thus,  $K_{\text{O}_2}$  observed for  $\text{Mn}^{\text{II}}(\text{TPP})$  is several orders of magnitude less than would be predicted on the basis of the half-wave reduction potential. This apparent anomaly in the binding of  $\text{O}_2$  to  $\text{Mn}(\text{TPP})$  compared with the porphyrinatometal(II) complexes of cobalt, iron, and chromium may indicate that the nature of the bond between manganese and dioxygen differs significantly from the  $\text{M}-\text{O}_2$  bonding with these other metals.

With the exception of manganese for which an O-O stretching frequency has not yet been reported, the porphyrinatometal-dioxygen complexes of cobalt, iron, and chromium have been shown to be *superoxide-like*, having O-O stretching frequencies at  $1120 \pm 50\text{ cm}^{-1}$ . If the bonding of  $\text{O}_2$  in manganese-dioxygen complexes were also *superoxide-like*, a  $K_{\text{O}_2}$  larger than that observed would be expected. The anomalous value observed for  $K_{\text{O}_2}$  of the manganese complex is an indication that the bonding may differ from that of the cobalt, iron, and chromium systems. Thus this result supports the assignment  $\text{Mn}^{\text{IV}}(\text{TPP})(\text{O}_2^{2-})$ .<sup>392</sup> There is, however, another interpretation for the anomalous manganese value for  $K_{\text{O}_2}$ . Basolo and co-workers<sup>132</sup> have reported that although five-coordinate complexes of the cobalt(II) Schiff base  $\text{Co}^{\text{II}}(\text{benacen})(\text{B})$  readily bind  $\text{O}_2$  in toluene solution at  $0\text{ }^\circ\text{C}$ , only a small amount of the four-coordinated  $\text{Co}^{\text{II}}(\text{benacen})$  complex is oxygenated under 1 atm of  $\text{O}_2$  in toluene at  $0\text{ }^\circ\text{C}$ . Thus if the dioxygen moiety in  $\text{Mn}(\text{TPP})(\text{O}_2)$  adopts the Pauling conformation, the seemingly low value of  $K_{\text{O}_2}$  is consistent with the absence of a sixth axial ligand.

A comparison can be made of the properties observed for the  $\text{O}_2$  adducts of tetraphenylporphyrinatomanganese(II) complexes with those expected on the basis of an assigned  $d^3\text{-Mn(IV)}$  ground state. A recent study<sup>400</sup> on the chemical and spectroscopic properties of  $\text{Cr}^{\text{III}}(\text{TPP})(\text{Cl})$ , which contains a  $d^3$  metal center, has shown that five-coordinate  $\text{Cr}^{\text{III}}(\text{TPP})(\text{Cl})$  has an exceptionally large affinity toward binding a sixth N-donor axial ligand. In contrast with this behavior, no tendency for the presumed  $d^3\text{-Mn(IV)}$  center in  $\text{Mn}(\text{TPP})(\text{O}_2)$  to bind an axial ligand at  $-78\text{ }^\circ\text{C}$  has been observed.<sup>397</sup> This large difference in the affinities of the  $d^3$  metalloporphyrin complexes  $\text{Cr}^{\text{III}}(\text{TPP})(\text{Cl})$  and  $\text{Mn}(\text{TPP})(\text{O}_2)$  for an axial ligand can be interpreted as arising from either of two factors: (1) repulsive steric interaction between the coordinated dioxygen and the porphyrinato ring in  $\text{Mn}(\text{TPP})(\text{O}_2)$  that results in the manganese center lying out of the plane of the porphyrin toward the coordinated dioxygen, and (2) differences in the ground-state electronic configurations of the chromium and manganese centers that favor the  $\text{Mn}(\text{TPP})(\text{O}_2)$  structure.

Two geometric conformations have been suggested for the bonding of dioxygen to the manganese-porphyrins (XVII and XVIII). On the basis of the formal  $\text{Mn}^{\text{IV}}(\text{O}_2^{2-})$  ground-state con-

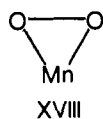
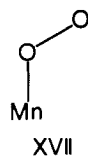


TABLE XVII. Equilibrium Constants for the Oxygenation of Metalloporphyrin Complexes at  $-78\text{ }^\circ\text{C}$ <sup>a</sup>

complex	conditions	log $K_{\text{O}_2}$	$E_{1/2}$ , $\text{M}^{\text{III}}$ <sup>b</sup>
$\text{Co}^{\text{II}}(\text{TPP})(\text{py})$	toluene soln	$-1.7^c$	$+0.13^c$
$\text{Co}^{\text{II}}(\text{T}(p\text{-OMe})\text{PP})(\text{Melm})$	toluene soln	$-0.8^d$	$+0.11^c$
$\text{Fe}^{\text{II}}(\text{TpivPP})(\text{Melm})$	solid	$6.4^e$	$-0.11^f$
$\text{Mn}^{\text{II}}(\text{TPP})$	toluene soln	$\sim 2.1^g$	$-0.27^h$
$\text{Cr}^{\text{II}}(\text{TPP})(\text{py})$	solid	large	$-0.86^i$

<sup>a</sup> The equilibrium constants reported in this table are for the addition of  $\text{O}_2$  to a vacant axial coordination site on the metal(II) center. Values for log  $K_{\text{O}_2}$  at  $-78\text{ }^\circ\text{C}$  are calculated from thermodynamic data given in references cited. Units of  $K_{\text{O}_2}$  are Torr. <sup>b</sup> In DMSO. Values reported in volts vs. SCE. <sup>c</sup> For  $\text{Co}(\text{TPP})$  and  $\text{Co}(\text{T}(p\text{-OMe})\text{PP})$ , ref 124. <sup>d</sup> Reference 121. <sup>e</sup> TpivPP represents the dianion of the "picket-fence" porphyrin. <sup>f</sup> K. M. Kadish, M. M. Morrison, L. A. Constant, L. Dickens, and D. G. Davis, *J. Am. Chem. Soc.*, **98**, 8387 (1976). <sup>g</sup> Reference 397. <sup>h</sup> T. W. Cape, Ph.D. Thesis, Northwestern University, 1979. K. M. Kadish and M. M. Morrison, *Bioelectrochem. Bioenerget.*, **3**, 480 (1976). <sup>i</sup> The dioxygen adduct forms irreversibly.

figuration, it has been suggested<sup>392</sup> that the Griffith conformation (XVII) is to be preferred, in agreement with the geometry favored for other metal-peroxo systems. This structural assignment is also consistent with the observation that the porphyrinatomanganese-dioxygen complexes do not bind an axial ligand. The binding of an axial ligand on the dioxygen complex would tend to draw the manganese center into the plane of the porphyrin. This would be expected to result in severe repulsive interaction between the coordinated dioxygen ligand and the porphyrinato ring. For the Pauling geometry (XVIII), however, this repulsive interaction would not occur, and the dioxygen complex of such a structure would be expected to bind an axial ligand readily.

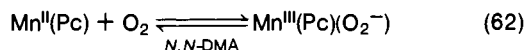
The differences in affinities of  $\text{Cr}^{\text{III}}(\text{TPP})(\text{Cl})$  and  $\text{Mn}(\text{TPP})(\text{O}_2)$  toward binding a sixth axial ligand can also be interpreted as arising from differences in the electronic ground-state configuration of the manganese(IV) and chromium(III) centers. For the porphyrinatochromium(III) complexes, the electrons adopt the expected  $(d_{xy})^1(d_{xz})^1(d_{yz})^1$  configuration. For the porphyrinatomanganese-dioxygen complexes, however, the ground-state electronic configuration has not yet been unambiguously determined. If the electronic ground-state configuration of the  $d^3$  manganese center has an unpaired electron in the  $d_{z^2}$  orbital, by analogy with the  $\text{Co}(\text{II})$  and  $\text{Mn}(\text{III})$  metalloporphyrin complexes which bind a sixth axial ligand only weakly,<sup>127</sup> the complexes would not be expected to strongly bind an axial ligand regardless of the geometry of the  $\text{MnO}_2$  bond. Although, in general, one would not predict an unpaired electron in a  $d_{z^2}$  orbital in a  $d^3$  complex, several configurations including  $d_{z^2}$  occupancy have been investigated<sup>401</sup> in some MO calculations. A recent reinvestigation<sup>402</sup> of the EPR spectra of some  $\text{Mn}(\text{Por})(\text{O}_2)$  complexes are consistent with the previous interpretation that the ground state electronic configurations of these manganese-dioxygen complexes do not include an unpaired electron in the  $d_{z^2}$  orbital and are better represented in terms of the  $\text{Mn}^{\text{IV}}(\text{O}_2^{2-})$  formalism.

The  $\text{O}_2$  binding of simple manganous porphyrins<sup>397</sup> is consistent with the observed<sup>403</sup> inability of manganese(II) hemoglobin to carry  $\text{O}_2$ . The proximal histidine of the protein provides an adjacent imidazole which coordinates with the  $\text{Mn}(\text{II})$  in  $\text{MnHb}$ . With this high effective local concentration of coordinating base, the equilibrium lies heavily toward the five-coordinate  $\text{Mn}^{\text{II}}(\text{Por})(\text{imidazole})$  complex rather than the dioxygen adduct.

Valentine<sup>404</sup> has investigated the reaction between  $\text{Mn}^{\text{III}}(\text{TPP})\text{Cl}$  and  $\text{KO}_2$  in DMSO solution. Addition of 1 equiv of superoxide to the complex in DMSO resulted in the rapid reduction of the metalloporphyrin to  $\text{Mn}^{\text{II}}(\text{TPP})$ . Further addition of  $\text{O}_2^-$  to the above solution or addition of  $\text{O}_2^-$  to a fresh  $\text{Mn}^{\text{II}}(\text{TPP})$  solution resulted in changes in the visible spectrum; however, the product has not been characterized. It is interesting to note that addition of  $\text{O}_2^-$  to a solution containing  $\text{Zn}^{\text{II}}(\text{TPP})$  results<sup>405</sup>

in the formation of the superoxo complex  $[\text{Zn}^{\text{II}}(\text{TPP})\text{O}_2]^-$ .

Recently, Lever and Wilshire<sup>390</sup> have reported that in rigorously purified pyridine, phthalocyanatomanganese(II) does not react with molecular oxygen. In the presence of a source of protons, i.e., water or imidazole, they observed the formation of a 1:1 adduct between dioxygen and MnPc:



The adduct is reported to be stable to further reaction under conditions of the experiment, and it was isolated as a solid. Reconversion to MnPc and  $\text{O}_2$  was accomplished by flushing the solution with dinitrogen or by freeze-thaw degassing. The reaction is reported to have a  $P_{1/2}^{\text{O}_2}$  of 1 Torr at 25 °C. It appears that this is the first example of a synthetic manganese(II) oxygen carrier at room temperature. On the basis of both the optical and infrared spectra, the authors tentatively suggest that the complex should be formally considered as the superoxo complex  $\text{Mn}^{\text{III}}(\text{Pc})(\text{O}_2^-)$ . A recent report<sup>406</sup> that exposure of a DMF solution of  $\text{Mn}^{\text{II}}(\text{Pc})$  at room temperature results in a complex having an EPR spectrum that is consistent with the presence of a superoxide moiety has appeared. No further characterization of the complex nor comments on the reversibility of complex formation were noted.

Although not of direct biological interest in terms of the biological oxygen carriers, a recent report<sup>407</sup> on the reversible bonding of  $\text{O}_2$  by an oxidation product of tris(3,5-di-*tert*-butylcatecholato)manganese(II) in DMSO may prove of interest as a model for the manganese-catalyzed oxygen evolution reaction of green plant biosynthesis. Upon exposure of a DMSO solution of tris(3,5-di-*tert*-butylcatecholato)manganese(III) to  $\text{O}_2$ , the first step appears to be oxidation of one of the bonded catechol ligands to the semiquinone resulting in a mixed catechol-semiquinone complex, which is then capable of reversibly binding  $\text{O}_2$ .

### X. Dioxygen Carriers of Other Metals

The reversible binding of dioxygen at room temperature to tetraphenylporphinato- and octaethylporphinatoruthenium(II) complexes has been reported.<sup>408</sup> Solutions of  $\text{Ru}(\text{OEP})(\text{CH}_3\text{CN})_2$  in DMA, DMF, or pyrrole, the exact nature of the axial ligation of the ruthenium(II) center in these solutions being uncertain, are observed to absorb 1.0 mol of oxygen for each ruthenium metal center at room temperature and 1 atm of  $\text{O}_2$ . At constant  $\text{O}_2$  pressures, the reactions follow pseudo-first-order behavior with the value for  $t_{1/2}$  being reported as  $\sim 1$  min (DMA),  $\sim 7$  min (pyrrole), and  $\sim 30$  min (DMF). However, solutions of  $\text{Ru}^{\text{II}}(\text{OEP})(\text{B})_2$ , where B = pyridine or 1-methylimidazole in the presence of oxygen, result only in irreversible oxidation of the ruthenium center to a Ru(III) species.

The synthesis of the chromium-dioxygen adduct,  $\text{Cr}(\text{TPP})(\text{py})(\text{O}_2)$ ,<sup>47</sup> from solid five-coordinate  $\text{Cr}^{\text{II}}(\text{TPP})(\text{py})$  represents a logical extension of metalloporphyrin complexes containing bivalent first-row transition metal ions. Previous to the preparation of the complex, on the basis of the  $\text{M}^{\text{II/III}}$  redox potentials, it had been predicted that the chromous porphyrins should bind  $\text{O}_2$  more strongly than do the Fe, Mn, and Co metalloporphyrin complexes. In agreement with this prediction  $\text{Cr}(\text{TPP})(\text{py})(\text{O}_2)$  is observed to form the dioxygen complex irreversibly. On the basis of the 1:1  $\text{O}_2/\text{Cr}$  uptake and an  $\nu_{\text{O-O}}$  of  $1142 \text{ cm}^{-1}$ ,  $\text{Cr}(\text{TPP})(\text{py})(\text{O}_2)$  appears to be a normal monomeric type Ia complex. The coordinated oxygen can therefore be described as superoxide-like. In solution, a stable dioxygen species does not appear to be formed.

Interest in model systems of hemocyanins has resulted in the appearance of two copper complexes capable of reversibly binding dioxygen. The copper(I)<sup>409</sup> complex of the pentadentate ligand derived from 2,6-diacetylpyridine and histamine reversibly binds dioxygen at room temperature in DMSO or acetonitrile solution. The reaction is readily reversed by gentle warming and

by purging with nitrogen. One mole of  $\text{O}_2$  is bound for two moles of Cu, suggesting the formation of a peroxo bridged species ( $\text{Cu}(\text{II})-\text{O}_2-\text{Cu}(\text{II})$ ). The complex does not bind CO, whereas a bimetallic complex of copper<sup>410</sup> in the solid state reversibly binds oxygen and CO. Using the ligand, 1,4-bis(1-oxo-4,10-dithio-7-azacyclododecan-7-ylmethyl)benzene, with two copper(I) atoms ligated the complex binds CO in the solid state or in nitromethane solution ( $\nu_{\text{CO}} \sim 2070 \text{ cm}^{-1}$ ). Purging the solution with argon at 80 °C removed the CO ligand. At 25 °C (slowly) or 80 °C the solid complex reacts with oxygen to give a compound with an EPR spectrum having values of  $g_{\perp} = 2.05$ ,  $g_{\parallel} = 2.22$ , and  $A_{\parallel} \sim 75 \text{ g}$ . Heating in vacuo at 110 °C regenerates the starting complex. Reversibility was not observed in solution. Because of the presumed structure of the complex it was referred to as an "earmuff" compound.

### XI. Addendum

Since the submission of this article two recent reports on the structural determinations of two oxy-heme proteins have appeared. Huber et al.<sup>411</sup> have studied the oxy-erythrocyruorin system. The oxygen molecule was found to be bound in an end-on fashion ( $\angle \text{Fe}-\text{O}-\text{O} \approx 170^\circ$ ) and hydrogen bonded to a water molecule. The large Fe-O-O angle, as compared to other natural and model complexes, may be due to the bonded water. Upon oxygenation, unlike most other natural systems, it was observed that the iron shifts only slightly toward the porphyrin plane with accompanying minimal changes in porphyrin conformation. This behavior of the erythrocyruorin system is consistent with the small changes observed for all of its other ligated states.

Diffraction data were collected to a resolution of 2.0 Å on the oxygen adduct of sperm whale myoglobin.<sup>412</sup> In the oxy form the oxygen is also bound in an end-on bent manner, with an Fe-O-O angle of  $121^\circ$ . However, Phillips found that the iron moves from 0.55 Å (deoxy state) to a position 0.33 Å (oxy state) above the mean porphyrin plane upon oxygenation. These results show the expected shift of iron toward the heme plane upon oxygenation, but the magnitude of this movement is smaller than that reported earlier.<sup>60e-g</sup> It now appears that current cooperativity theories may have to be somewhat modified.

### XII. Abbreviations

N-Aclm	N-acetylimidazole
acr	acridine
amaco	various amino acids
B	various neutral donor ligands
BM	Bohr magneton
bpy	2,2'-bipyridine
BzIm	benzimidazole
5-ClMelm	5-chloro-1-methylimidazole
3,5-Cl <sub>2</sub> py	3,5-dichloropyridine
4-CNpy	4-cyanopyridine
cyclam	1,4,8,11-tetraazacyclotetradecane
DePP	dianion of deuteroporphyrin IX
deut	dianion of deuteroporphyrin IX
dgenta	diglycylethylenediaminetetraacetic acid
diapr	2,3-diaminopropionic acid
dien	diethylenetriamine
dipep	various dipeptides
DMA	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
en	ethylenediamine
4-EtCOOp	ethyl isonicotinate
4-Et <sub>2</sub> NCOpy	nicotinic acid diethylamide
4-Etpy	4-ethylpyridine
gly	glycine
glygly	glycylglycine
glyhist	glycylhistidine
Hb	hemoglobin

HbA	hemoglobin A
hedien	<i>N</i> -2-(hydroxyethyl)ethylenediamine
hist	histidine
hista	histamine
Im	imidazole
IsoQ	isoquinoline
L	coordination sphere of a metal
L <sub>4</sub>	quadridentate ligand
L <sub>5</sub>	quinquedentate ligand
Mb	myoglobin
<i>s</i> -Me <sub>2</sub> en	<i>N,N'</i> -dimethylethylenediamine
Melm or 1-Melm	<i>N</i> -methylimidazole
2-Melm	2-methylimidazole
1,2-Me <sub>2</sub> Im	1,2-dimethylimidazole
4-Mepy	4-methylpyridine
3,4-Me <sub>2</sub> py	3,4-dimethylpyridine
3,5-Me <sub>2</sub> py	3,5-dimethylpyridine
2,4,6-Me <sub>3</sub> py	2,4,6-trimethylpyridine
MesP	dianion of mesoporphyrin
MOEP	dianion of <i>meso</i> -phenyloctaethylporphyrin
4-NH <sub>2</sub> py	4-aminopyridine
NtrIm	<i>N</i> -triphenylmethylimidazole
OEP	dianion of octaethylporphyrin
OEPH <sub>2</sub>	octaethylporphyrin
<i>P</i> <sub>1/2</sub> O <sub>2</sub>	pressure of oxygen necessary to oxygenate 1/2 of the available sites
Pc	phthalocyanine
PFP	dianion of "picket-fence porphyrin"
phen	1,10-phenanthroline
2 = phos	1,2-bis(diphenylphosphino)ethylene
pip	piperidine
pn	1,2-propylenediamine
Por	dianion of a natural or synthetic porphyrin
PPDE	dianion of protoporphyrin IX dimethyl ester
PPh <sub>3</sub>	triphenylphosphine
PPIX	dianion of protoporphyrin IX
PPIXDME	dianion of protoporphyrin IX dimethyl ester
py	pyridine
quin	quinoline
quinuc	quinuclidine
SB	any Schiff base
SB <sub>4</sub>	quadridentate Schiff base
SB <sub>5</sub>	quinquedentate Schiff base
sdtma	<i>N,N</i> -bis(2-aminoethyl)glycine
sedda	ethylenediamine- <i>N,N'</i> -diacetic acid
1-SiMe <sub>3</sub> Im	<i>N</i> -trimethylsilylimidazole
terpy	2,2',2''-terpyridine
tetraen	tetraethylenepentamine
THF	tetrahydrofuran
tn	trimethylenediamine
TpivPP	dianion of "picket-fence porphyrin", <i>meso</i> - tetra(α,α,α,α- <i>o</i> -pivalamidophenyl)por- phyrin
TPP	dianion of <i>meso</i> -tetraphenylporphyrin
TPPH <sub>2</sub>	<i>meso</i> -tetraphenylporphyrin
T( <i>p</i> -X)PP	dianion of a <i>para</i> -substituted <i>meso</i> -tetraphen- ylporphyrin
tren	tris(2-aminoethyl) amine
trien	triethylenetriamine
triPiv(4C Im)PP	<i>meso</i> -tri(α,α,α- <i>o</i> -pivalamidophenyl)-β- <i>o</i> -3- ( <i>N</i> -imidazolylpropylamidophenyl) porphyrin
triPiv(5C Im)PP	<i>meso</i> -tri(α,α,α- <i>o</i> -pivalamidophenyl)β- <i>o</i> -4- ( <i>N</i> -imidazolylbutylamidophenyl)porphyrin
TSPc	phthalocyaninetetrasulfonate ion
udtma	diethylenetriamine- <i>N</i> -acetic acid
uedda	ethylenediamine- <i>N,N</i> -diacetic acid

*Acknowledgments.* The authors thank Janice M. Summerville and Jan Goranson for the help and patience in the preparation

of this work. The authors also thank the National Institutes of Health and the National Science Foundation for their support.

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