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INORGANIC OXYGEN CARRIERS AS MODELS FOR BIOLOGICAL SYSTEMS

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CONTENTS

ABBREVIATIONS

acacen	acetylacetonatoethylenediimine
amben	bis(2-amino-1-benzaldehyde)ethylenediimine
amp	aminomethylpyridine
BAE (benacen)	benzoylacetoneethylenediimine
bipy	bipyridyl
CoHb	coboglobin - (cobalt substituted hemoglobin)
CoMb	cobalomyoglobin
cys	cysteine
cyt	cytochrome
dgenta	diglycylethylenediaminetetraacetic acid
dien	diethylenetriamine
dipsalen	3,3'diiminodipropylaminebissalicylaldehyde
dmg (D_2H_2)	dimethylglyoxime
sdtma	symmetric diethylenetriaminemonoacetic acid
dtda	N,N''-diethylenetriaminediacetic acid
udtma	diethylenetriaminemonoacetic acid
dmf	dimethylformamide
dmso	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
sedda	N,N'-ethylenediaminediacetic acid

uedda	N,N-ethylenediaminediacetic acid
en	ethylenediamine
F salen	fluorosalicylaldehydeethylenediimine
gg(glygly)	glycylglycine
glysarc	glycylsarcosine
his	histamine
hist	histidine
hedien	N(2-hydroxyethyl)diethylenetriamine
Hb	hemoglobin
im	imidazole
(CH_3Im)	1-methylimidazole
Mb	myoglobin
meacacen	N,N′-ethylenediaminebis(3-methylacetylacetone)
napsalen	bis(2-hydroxy-1-naphthaldehyde)ethylenediimine
oep (oeporphine)	octaethylporphine
orn	ornithine
P	protoporphyrin IX dimethyl ester
phen	1,10-phenanthroline
phacacen	N,N′-ethylenediaminebis(3-phenylacetylacetone)
pip	piperidine
pn	1,2-propylenediamine
pts	pthalocyaninetetrasulfonate
py	pyridine
salen	salicylaldehydeethylenediimine
sacsacen	N,N′-ethylenediaminebis(monothioacetylacetone)
saloph	bis(salicylaldehyde)-σ-phenylenediimine
tep	tetraethylenepentamine
tren	triaminotriethylamine (tris(2-aminoethyl)amine)
trien	triethylenetetramine
tpp	tetraphenylporphine
trpy	terpyridyl

A. INTRODUCTION

The utilization of molecular oxygen in biological systems is obviously of extreme importance. As the terminal electron acceptor in the electron transport chain, molecular oxygen is essential for the electron flow which produces most of the adenosinetriphosphate (ATP) for aerobic metabolism. In addition to this vital role (which accounts for approximately ninety percent of dioxygen utilization), oxygen is also activated and utilized in a number of biological reactions mediated by oxygenases [1,2] (which catalyze oxygen insertion reactions) and oxidases [1,2] (which catalyze the oxidation of organic substrates). A common feature of all these reactions of molecular oxygen, including transport to the site of utilization, is the involvement of metal atoms in complexing and activating oxygen (Table 1).

TABLE 1

Representative metalloproteins involved in oxygen metabolism

Protein	Metal	Reaction catalyzed or function
Hb	Fe	oxygen transport
Mb	Fe	oxygen transport
Cytochromes	Fe	electron transport
Peroxidase	Fe	$O_2^{2-} \rightarrow H_2O$
Superoxide dismutase	Cu, Zn	$2O_2^- \rightarrow O_2^{2-} + O_2$
Dioxygenases	Fe	O_2 insertion → diol derivative
Ex : pyrocatechase	Fe	catechol → *cis* muconate
Monooxygenase	Cu	O_2 insertion → mono OH derivative
Ex : monophenol oxidase		phenol → catechol
cyt P450	Fe(heme)	O_2 insertion, detoxification
Oxidases	Cu	oxidation of organic substrates

The transport proteins hemoglobin and myoglobin utilize iron, with one oxygen bound per iron atom in the fully saturated state, while the somewhat more primitive transport proteins hemerythrin [3] (found in sipunculids) and hemocyanin [4] (found in molluscs) utilize iron and copper respectively, with an apparent metal : dioxygen stoichiometry of 2 : 1. The oxidase and oxygenase enzymes generally contain copper, while the cytochromes involved in oxygen utilization in the electron transport systems use iron. Other metals believed to be involved in oxygen metabolism include manganese, implicated as a possible oxygen transport agent in photosynthesis [5,6], and cobalt, which is thought to utilize oxygen in free radical reactions of vitamin B_{12} [7].

Oxygen transport involving hemoglobin has been intensely studied, so that many of the details of its interaction with oxygen are now known [8]. However, the fundamental question of the nature of the metal dioxygen interaction remains a matter of controversy for hemoglobin, and all oxygen utilizing proteins. This problem has been fruitfully approached by the use of model systems in which simple compounds incorporating a metal dioxygen bond have been synthesized and studied by a number of physical techniques in order to gain insight into the bonding. Two basic classes of metal dioxygen complexes have been proposed as model systems; those incorporating a side-on π linkage (the "Vaska complexes") [9], and those involving a metal dioxygen σ bond, proposed by Pauling and others [10—12] (Fig. 1). The former class, discovered and intensively studied by Vaska [13] and others [14,15], while of intrinsic interest, is probably a poor model for biological systems for the following reasons.

First, these compounds incorporate metals in low or zero oxidation states, not found in biological systems, and generally incorporate rather arcane (from a biological standpoint) ligands (e.g. phosphines) and are generally unstable in aqueous media. From the rather naive standpoint of hard soft acid base theory,

Fig. 1. Diagramatic representation of the possible modes of O_2 binding to metal ions.

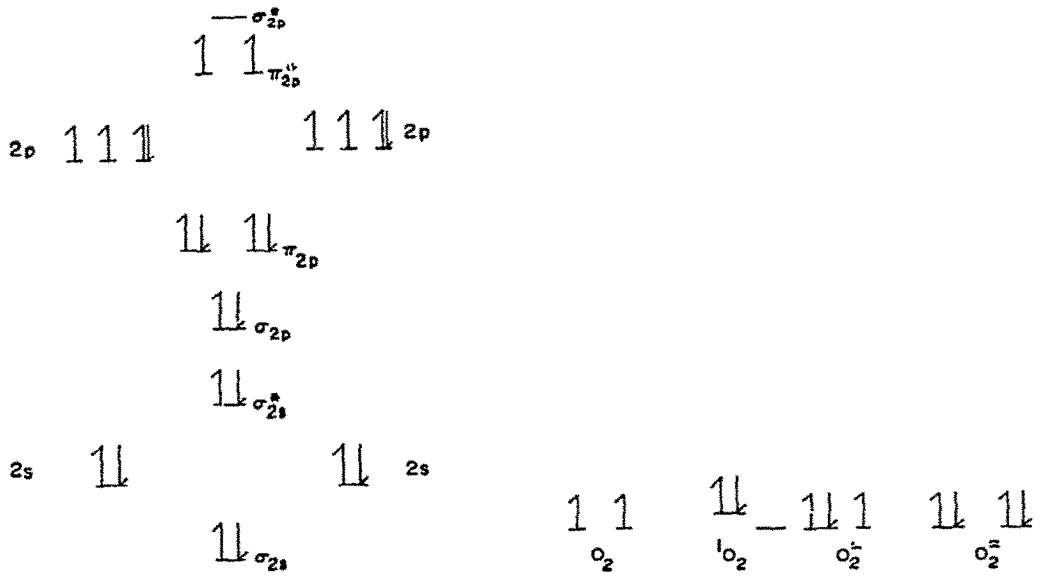


Fig. 2. (a) M.O. diagram of O_2
(b) π^* occupancy of dioxygen, singlet dioxygen, superoxide and peroxide.

these metal complexes would be considered very "soft" and thus would preferentially bind oxygen in a soft π linkage, whereas metals of biological interest (e.g. iron) in higher oxidation states, would favor a "harder" σ bonding mode. (It might be noted that such qualitative arguments are subject to exception, e.g. chromium(IV) is rather "hard" yet binds oxygen in a π linkage [16]).

Furthermore, as Mingos [16] has pointed out, even if π bonding is initially assumed, the operation of a second order Jahn Teller effect will lead to a bent bond for copper and iron. In a somewhat less qualitative vein, it has been noted by Valentine [14] that π bonding is favored by complexes susceptible to $2e^-$ oxidative addition (Rh^I, Ir^I), whereas one electron reductants might favor end-on binding resulting in a $1e^-$ reduction of oxygen to superoxide (Fig. 2). Having noted this distinction, and assuming the σ bonding model, a second criterion for oxygen complexation may be stated.

Among the first row transition metals, only those capable of undergoing a one electron oxidation interact with dioxygen. Thus Mn^{II}, Fe^{II}, Co^{II}, Cu^{I}, Cr^{II} all complex dioxygen, while Fe^{III}, Co^{III}, Cu^{II} as well as Ni^{II} and Zn^{II} which have no readily accessible higher oxidation states, do not. This, then, we take to be a basic tenet of dioxygen complexation under biologically relevant conditions: in the oxygenation reaction, the metal reversibly transfers an electron

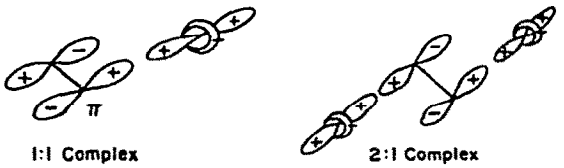
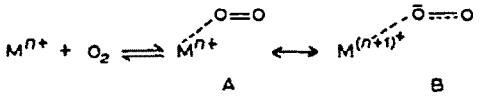


Fig. 3. Diagramatic representation of orbital overlap occurring in metal dioxygen complex formation.

to the dioxygen, conveniently represented as a formally oxidized metal bonded to the formally reduced oxygen. More succinctly, of the resonance forms below, form (B) makes the major contribution to the ground state.



This can be visualized [16—18] by considering a bonding scheme in which σ bonding occurs by transfer of metal d_{z^2} electron to the π^* oxygen orbital, with possible retrodative bonding from oxygen to metal $d\pi$ (Fig. 3).

If this description is valid, then by utilizing model systems based on one or more of the possible first row transition metals (Fe^{II}, Co^{II}, Cu^{I}, Cr^{II}) one should be able to accumulate physical evidence consistent with such a description. Such has been the case for all of the metals listed above. While the primary metals of biological interest are Fe^{II} and Cu^{I}, their chemistry is rather intractable (particularly in aqueous solution) as is the case for Mn^{II} and Cr^{II}. Cobalt, on the other hand, is quite easily studied in aqueous solution, and allows utilization of a number of physical probes unavailable in the other systems (e.g. ESR).

These considerations, coupled with the tremendous literature available on cobalt chemistry, have made cobalt chelates the primary target for model system studies. We will therefore deal first with the work on cobalt, focusing on physical studies of bonding, and dynamics of the cobalt—dioxygen interaction. As will be demonstrated, the cobalt model systems yield results consistent with the most recent discoveries in Fe^{II} and Cu^{I} dioxygen chemistry, and can lead to a clearer understanding of enzymic dioxygen interactions.

B. COBALT MODELS

The literature dealing with dioxygen cobalt complexes is vast, and has been reviewed several times in the past [19—22]. The earliest known synthetic dioxygen complex is probably $[(NH_3)_{10}Co_2O_2]^{4+}$ characterized by Werner and Myelius in 1898 [23]. This discovery in the formative years of coordination chemistry was not pursued further for almost forty years, until the discovery by Tsumaki [24] of the oxygen complexing properties of some cobalt Schiffs base complexes. This work was followed by that of Calvin et al. [25—30],

Diehl et al. [31] and others, and has been reviewed elsewhere [32,33].

Of primary concern to present research was the demonstration that molecular oxygen could be reversibly bound by certain metal chelates, including those formed by acacen, salen, and salicylaldehyde.

At about the same time, Burk, Hearon and others [34—37] discovered that certain cobalt amino acid complexes [38,39] (particularly bis histidinato cobalt(II)) were capable of reversibly complexing dioxygen. Reviews of this early work have been published [19,20]. Interest in this work slackened, but underwent a renaissance in the mid to late 1960's and continues to elicit considerable interest.

Tables 2—5 contain a list of all characterized cobalt dioxygen complexes. As the tables show, cobalt complexes are capable of bonding oxygen in both 2 : 1 and 1 : 1 stoichiometries. The dimeric complex is generally more stable and will be formed unless inhibited sterically (as in B_{12}, coboglobin, and "picket fence"), or by combined use of low temperature, low concentration and nonaqueous solvents (to inhibit formation of a highly charged dimer).

TABLE 2

Mononuclear dioxygen complexes of cobalt(II) **

Ligand	Formula of Complex	Reference
1,7-Bis(salicylidineimine)-4-azaheptane, H_2L	$CoLO_2^{2+}$	25, 28, 40
Bis(acetylacetone)ethylenediimine, H_2L; L′ = pyridine, 4-aminopyridine, 4-methylpyridine, 4-cyanopyridine	$L'CoLO_2$	41—43
Bis(salicylaldehyde)ethylenediimine, H_2L; L′ = pyridine, DMF, DMSO	$L'CoLO_2$	43, 44—49
Bis(methoxysalicylaldehyde)ethylenediimine, H_2L; L′ = pyridine	$L'CoLO_2$	46, 47, 49
Bis(benzoylacetoneethylenediimine), H_2L; L′ = pyridine	$L'CoLO_2$	50, 52
Bis(salicylidine-γ-iminopropyl)methylamine, H_2L	$CoLO_2$	53
2,(2′-pyridyl)ethylethylenebis(salicylidimine), H_2L	$CoLO_2$	54
Dimethylglyoxime, H_2L; L′ = pyridine, dimethyl sulfide, triethylamine	$L'Co(H_2L_2)O_2^{2+}$	55
Cobalamine (vitamin B_{12}r), H_2L	$CoLO_2$	55, 56
Tetraphenylporphine, H_2L (also tetra(p-methoxyphenyl)porphine); L′ = pyridine, nitrogen bases	$L'CoLO_2$	57—59
Protoporphyrin IX dimethyl ester, H_2L	$LCoO_2$	57,60,61
Tetrasulfophthalocyanine, H_6L	$CoLO_2^{4-}$	62, 63
Mesotetra(α,α,α,α-o-pivalamidophenyl)porphine, H_2L	$CoLO_2$	64
Coboglobin, H_2L	$CoLO_2$	65—71
1,2-Bis(diphenylphosphino)ethylene, L	$CoL_2O_2^+$	72

* The mononuclear dioxygen complex $[Co(CN)_5O_2]^{3-}$ has recently been characterized in aprotic polar solvents (e.g. dmf) [230, 231].

* In an important work, Lever and co-workers have demonstrated mononuclear dioxygen complex formation by bis-s-N,N′-dimethethylenediaminedichlorocobalt(II) in nonaqueous solvents [232].

TABLE 3

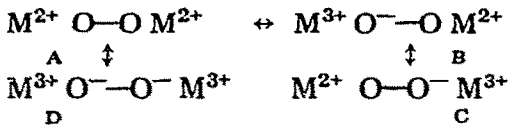
Binuclear oxygen complexes of cobalt

Ligand	Formula of Complex	References
Ammonia, L	$L_5CoO_2CoL_5^{4+}$	23, 73—77
Ethylenediamine, L; Ammonia, L′	$L'L_2CoO_2CoL_2L'^{4+}$	74
Diethylenetriamine, L	$L_2CoO_2CoL_2^{4+}$	78, 79
Diethylenetriamine, L Ethylenediamine, L′	$LL'CoO_2CoLL'^{4+}$	78, 79
Diethylenetriamine, L Trimethylenediamine, L′	$LL'CoO_2CoLL'^{4+}$	80
Diethylenetriamine, L; Ammonia, L′	$LL'CoO_2CoLL'^{4+}$	81
Dipropylenetriamine L Ethylenediamine, L′	$LL'CoO_2CoLL'^{4+}$	80
Dipropylenetriamine, L Trimethylenediamine, L′	$LL'CoO_2CoLL'^{4+}$	80
Triethylenetetramine, L; Ammonia, L′	$L'LCoO_2CoLL'^{4+}$	78
Terpyridyl, L; *o*-Phenanthroline L′	$LL'CoO_2CoLL'^{4+}$	82
Terpyridyl, L; Dipyridyl, L′	$LL'CoO_2CoLL'^{4+}$	82
Tetraethylenepentamine, L	$LCoO_2CoL^{4+}$	78, 83
Cyclam, L	$LCoO_2CoL^{4+}$	84, 85
Triaminotriethylamine, L Ammonia, L′	$LL'O_2LL'^{4+}$	86
Cyanide ion, L^-	$L_5CoO_2CoL_5^{6-}$	87—89
Histidine, HL	$L_2CoO_2CoL_2$	34—37, 90—94
2,3-Diaminopropionic Acid, HL	$L_2CoO_2CoL_2$	95a, 95b
2,4-Diaminobutyric Acid, HL	$L_2CoO_2CoL_2$	95a
Ornithine, HL	$L_2CoO_2CoL_2$	95a
Glycylglycine, HL	[a] $L_2CoO_2CoL_2$	38, 39, 96—100
Various dipeptides, HL = histidyl-histidine, glycylalanine, alanylglycine, alanylalanine	[a] $L_2CoO_2CoL_2$	99a, 99b, 100
Bissalicylaldehydeethylenediimine, H_2L and phenylsubstituted derivatives	$LCoO_2CoL$	25—33, 48, 101
Bissalicylaldehydeethylenediimine, H_2L L′ = DMF, DMSO, pyridine, thiocyanate, azide	$LL'O_2CoLL'$	45, 47, 62, 101
Dimethylglyoxime, H_2L; L′ = pyridine, triphenylphosphine, dimethyl sulfide	$L'(H_2L_2)CoO_2Co(H_2L_2)L'^{4+}$	55
N,N′-diglycylethylenediamine-tetraacetic acid, H_4L	$H_{-2}LCoO_2CoH_{-2}L^{8-}$	102
N,N′-diglycylbutylenediamine-tetraacetic acid, ML	$LCoO_2CoL^{8-}$	81

[a] Active complex involves deprotonated amide.

Quite recently stable 1 : 1 complexes of simple Co^{II} polyamines have been obtained in large zeolite cavities, where dimerization is sterically hindered [123—125].

Under the theoretical framework outlined, the 1 : 1 complexes can be visualized as superoxo cobaltic complexes, and the 2 : 1 complexes similarly as μ-peroxo bis cobaltic complexes, with resonance forms



where form D predominates. These μ-peroxo complexes can be oxidized by a variety of appropriate oxidizing agents (e.g. Cl_2, Ce^{IV}) to give corresponding μ-superoxo complexes (M^{3+}—O—O^-—M^{3+}) with the odd electron residing primarily on the oxygen bridge.

The tables show a preponderance of complexes based on nitrogen donors. This trend, noted by Fallab, led to the formulation of the widely quoted "3N rule" [21] which states that the presence of three nitrogen donors in the coordination sphere of cobalt is a necessary condition for dioxygen complexation. However, it is apparent that cobalt acacen violates this rule. Among simpler aliphatic ligands the complexation of molecular oxygen by Co(EDDA) has recently been demonstrated [115] thus invalidating the "3N concept". The trend, however, remains and might allow one to surmise that, in the absence of other factors, the presence of three donor nitrogens is sufficient but not necessary for oxygen complex formation. Results with NH_3 dispute even this

TABLE 4

Binuclear dioxygen complexes of cobalt(II) containing μ-hydroxo bridges

Ligand	Formula of Complex	References
Ethylenediamine, L	$L_2CoO_2OHCoL_2^{3+}$	74, 79, 103—106
Bipyridyl, L	$L_2CoO_2OHCoL_2^{3+}$	107, 108
o-phenanthroline, L	$L_2CoO_2OHCoL_2^{3+}$	108, 109
Histamine, L	$L_2CoO_2OHCoL_2^{3+}$	99, 106, 79
Diethylenetriamine. L	$LCoO_2OHCoL^{3+}$	79, 104
Triethylenetetramine, L	$LCoO_2OHCoL^{3+}$	103, 110—112
Triaminotriethylamine, L	$LCoO_2OHCoL^{3+}$	74, 85, 103, 113
N,N-Bis(aminoethyl)glycine, HL	$LCoO_2OHCoL^{+}$	114
N-diethylenetriamineacetic acid, HL	$LCoO_2OHCoL^{+}$	114
N,N'-ethylenediaminediacetic acid, H_2L	$LCoO_2OHCoL^{-}$	115
N,N-ethylenediaminediacetic acid, H_2L	$LCoO_2OHCoL^{-}$	115
Hydroxyethyldiethylenetriamine, L	$LCoO_2OHCoL^{3+}$	81
Glycylhistidine	$LCoO_2OHCoL^{-}$	99a, 100
Various amino acids, HL	$L_2CoO_2OHCoL_2^{-}$	100

claim [77], although the results are questionable. The role of the nitrogen donor can be easily visualized in terms of the complexation scheme previously discussed. As the electron donating power of the ligand increases, it should be easier for the metal to donate an electron to the electrophilic oxygen forming the "oxidized metal—reduced dioxygen" linkage postulated.

This concept has been subjected to quantitative evaluation, as discussed in the dynamics section. Similarly, while electron donors tend to promote oxygenation, electron withdrawing groups (e.g. carboxylates, aromatic rings) might tend to retard stable oxygen complex formation. Such is indeed the case. General methods for the preparation of solid dioxygen complexes have been given elsewhere [26—28,74,80] and vary for each complex.

A standard preparation used successfully in the authors' laboratory for μ-peroxo biscobalt polyamines involves preparing a concentrated (0.1 M) solution of cobalt and ligand in the proper stoichiometric ratio, and high pH (to insure complete formation), aerating, and precipitating the mixture at ice temperature with excess $NaClO_4$ or EtOH. These complexes may then be used to prepare μ-superoxo derivatives [74].

It may be noted that in cases where two *cis* sites are, or can be, made available on the metal, a second bridge may be formed. This will occur spontaneously in aqueous solution [103—115] in which case a μ-hydroxo bridge will be formed. Alternatively, using Vortmann's sulfate [116—122] as a starting material and substituting multidentate ligands for ammonia yields the corresponding μ-amido bridged complexes.

Methods for preparation of some solid 1 : 1 complexes can be found in the literature [44,45]. A useful high pressure method for obtaining crystalline monomeric complexes has been described [48,49].

(i) Physical methods

A number of physical methods have been utilized in the study of these oxygen complexes in an attempt to define the nature of the bonding of oxygen

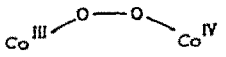
TABLE 5

Amido-bridged oxygen complexes of cobalt(II)

Ligand(s)	Formula of Complex	References
Ammonia, L	$L_4CoO_2(NH_2)CoL_4^{3+}$	23, 116
Ethylenediamine, L	$L_2CoO_2(NH_2)CoL_2^{3+}$	74, 117, 118—120
Bipyridyl, L	$L_2CoO_2(NH_2)CoL_2^{3+}$	121, 122
o-Phenanthroline, L	$L_2CoO_2(NH_2)CoL_2^{3+}$	121, 122
Triethylenetetramine, L	$LCoO_2(NH_2)CoL^{3+}$	78
Triaminotriethylamine, L	$LCoO_2(NH_2)CoL^{3+}$	86

and consequent effects on the complex reactivity. Perhaps the first and most widely employed tool has been magnetic susceptibility studies. The brown dimeric μ-dioxygen complexes as initially prepared are diamagnetic [118]. This diamagnetism is consistent with their formulation as μ-peroxo biscobalt-(III) complexes with all electrons paired in low spin Co^{III}, and the electrons of dioxygen pairing in the π^* orbital. (A somewhat more complex explanation involving loss of degeneracy of the oxygen π^* orbitals to give singlet oxygen, combined with super exchange of the unpaired electrons on Co^{II} through the oxygen bridge would also explain the observed diamagnetism.) The simplicity of the former explanation makes it the more attractive of the two.

The green complexes prepared by $1e^-$ oxidation of the μ-peroxo biscobalt species are paramagnetic ($\mu \cong 1.6$ BM), and may most easily be assigned as a μ-superoxo biscobalt(III) species with the unpaired electron residing principally in the oxygen π^* orbitals [127]. A more historical formulation proposed a mixed valence dimer [23] to account for the magnetic properties of the complex. Such a formulation postulates an unusual Co^{IV} state, indicated below:



This ambiguity has been resolved by a number of elegant ESR experiments [7,78,123–128]. Typical spectra are given below for 2 : 1 and 1 : 1 systems (Figs. 4, 5).

For the 2 : 1 μ-superoxo dicobalt complex, a well defined isotropic spectrum is obtained at room temperature in aqueous solution (0.2 M $HClO_4$), consisting of 15 lines (due to hyperfine splitting of the ^{59}Co nucleus) with a

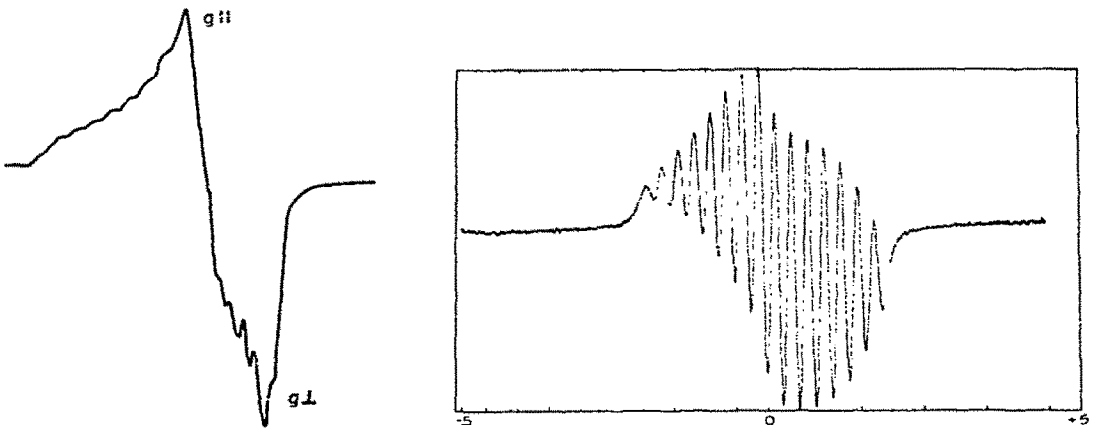


Fig. 4. ESR spectrum of the 1 : 1 Co : O_2 complex $[Co(NH_3)_5O_2]^{3+}$ at −196°C. (Data from Vansant and Lunsford [123]).

Fig. 5. ESR spectrum of $[Co_2tren_2O_2]^{5+}$ in 0.3 M $HClO_4$, 25.0°C.

peak separation $A_{iso} = 10$ gauss. Such a spectrum would be expected if the two cobalt nuclei were equivalent (number hyperfine lines = $2nI + 1$, n = number identical nuclei, I = nuclear spin magnetic moment = 7/2 for ^{59}Co). On this basis then the Co^{III}—Co^{IV} formalism may be discarded, as the cobalt nuclei are clearly magnetically equivalent. Furthermore, the very small hyperfine splitting observed is consistent with localization of >90% of the unpaired electron density onto the dioxygen bridge [127]. (By contrast, for simple Co^{II} complexes in the absence of oxygen, poorly resolved spectra with hyperfine splitting $A = 100$ gauss are obtained [127]). These results have been extended using ^{17}O labelled oxygen. The ^{17}O hyperfine structure is consistent with such a formalism.

Mononuclear species have been similarly characterized [43,44,52—54,123—125,129—131]. They are paramagnetic, as might be expected if assigned as Co^{III}—O_2^- superoxo complexes. ESR has served as an invaluable tool in their identification and characterization. The complexes exhibit a well defined 8 line ^{59}Co hyperfine spectrum (consistent with their mononuclear character) with peak separation of 10—12 gauss ($\sim$12 cm^{-1}), implying a bonding mode very similar to the μ-superoxo bridged dimers.

^{17}O labelling has shown the two atoms of bound dioxygen to be equivalent in solution [52,125], which is unexpected for binding of the metal to a terminal oxygen. The equivalence may be due to a rapid equilibrium between two bent conformations in solution. In frozen solution, or solid, non equivalence is restored, as expected [123]. The percent electron density on the dioxygen moiety is >90% but cannot be accurately calculated due to overlap of ^{59}Co—^{17}O lines. Recently, Tovrog and Drago [53] have challenged the Co^{III} formalism, based on studies of a carbomonoxy adduct of cobalt which appeared to exhibit a very similar spectrum to the dioxygen adduct. As no reasonable Co^{III}—CO^- form could be expected this result cast doubt on the validity of the charge separation. Further studies by Basolo and coworkers [129] have revealed Drago's spectra to be the result of residual O_2 contamination, as the cobalt porphine complex investigated has little affinity for carbon monoxide, but high oxygen affinity, in common with most five coordinate cobalt porphine complexes [130].

Relevant ESR data from a number of investigations is summarized in Table 6. It might be emphasized, however, that the formulation is primarily a convenient visualization of bonding in the complex, and all resonance forms previously given contribute to the observed properties. The particular amount of electron density transferred to the oxygen moiety will depend on the ligands complexed to the cobalt center. In this regard, recent investigations by Pratt and co-workers [131] of the "*cis* effect" in cobalt dioxygen complexes may be evaluated. The effect of varying equatorial Schiffs base ligands on cobalt hyperfine splitting (ACo) has been rationalized in terms of decreasing donation to the axial dioxygen through Co. An alternative but closely related explanation may be proposed in which the equatorial ligands which have significant π acceptor properties compete with dioxygen for the available electron densi-

TABLE 6

ESR data for some cobalt dioxygen complexes

Complex	g_{iso}	$g_{\parallel}$	$g_{\perp}$	A_{iso}	$A_{\parallel}$	$A_{\perp}$	Reference
Binuclear.							
$TrenCoO_2Cotren$	2.03			10.4			81
$SdtmaCoO_2Cosdtma$	2.03			11.0			81
$TrienCoO_2Cotrien$	2.03			11.0			81
$TepCoO_2Cotep$	2.03			10.9			81
$Py_2(D_2H_2)_2Co_2O_2$	2.03			12			7
$Dien(en)CoO_2Codien(en)$	2.03			11.0			78
$(CN)_5CoO_2Co(CN)_5$	2.02			8.0			83
$(NH_3)_5CoO_2Co(NH_3)_5$	2.03			11.4			127
Mononuclear.							
$Py(D_2H_2)CoO_2$	2.01	2.06	2.00	8.5	16	12	7
Vit $B_{12}(r)O_2$	2.02	2.07	2.00	12	16	13	7, 56
$BAECoO_2$	2.02	2.08	1.99	13.7	19.6	10.7	131
$SalenCoO_2$	2.02	2.08	1.99	13.0	17.5	10.8	131
$AmbenCoO_2$	2.02	2.08	1.99	12.9	18.2	10.3	131
$SalophCoO_2$	2.02	2.08	1.99	12.1	16.8	9.8	131
$OeporphineCoO_2$	2.02	2.08	1.99	12.1	19.6	8.4	131
$NapsalenCoO_2$	2.02	2.07	1.99	12.1	16.8	9.8	131
$AcacenCopyO_2$		2.08	1.99		19.6	10.7	43
$PzsCoO_2$		2.07	2.00		15.9	8.5	63
$TppCoO_2L$		2.07	2.00		18.3	14.2	59
L = 4-aminopyridine							
$Co(NH_3)_5O_2$		2.07	2.00		17.7	15.6	121

ty. A similar phenomenon has been found by Walker [132] in that strong π accepting solvents (e.g. trinitrobenzene) compete with oxygen for the sixth position in cobalt porphines. Similar solvent effects have been noted elsewhere [133]. This effect of ligands on electron transfer is underscored in crystallographic studies of the dioxygen complexes (Figs. 6 and 7). These results are summarized in Table 7.

It is worthy of note that the bulk of crystallographic data is consistent with a *trans* configuration of the cobalt nuclei about the dioxygen bridge, rather than the skewed arrangement suggested by Vleck [9b]. The early crystallographic investigations which suggested such an arrangement [134] have been shown to be erroneous [135]. The O—O bond distance for the diamagnetic μ dioxygen (μ peroxo) complexes is generally of the order of 1.47 Å, consistent with the peroxo formulation (O—O in Na_2O_2 = 1.49 Å) with a non planar arrangement of the Co—O—O—Co grouping as in H_2O_2. For the μ-superoxo complexes, the bond distances correlate well with the O_2^- structural assignment (O—O = 1.35 Å in $[(NH_3)_5Co—O—O—Co(NH_3)_5]^{5+}$, O—O = 1.33 Å in KO_2) and the coplanar arrangement of the Co—O—O—Co group is consistent with the

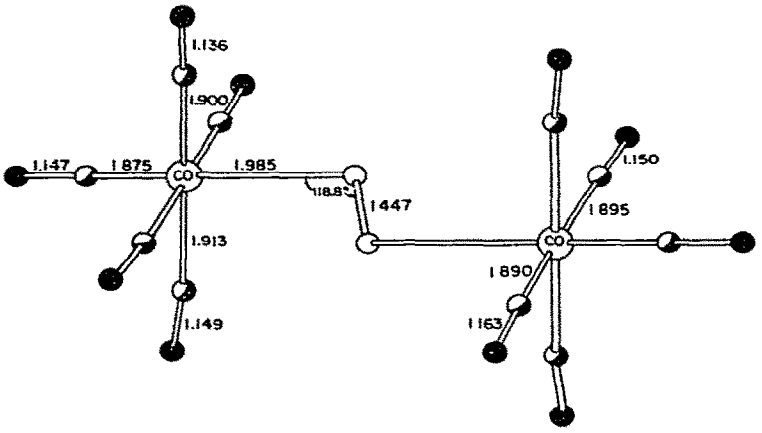


Fig. 6. Crystal structure of $[Co_2(CN)_{10}O_2]K_6$. (Data from Fronczek and Schaeffer [139].)

bonding requirements of O_2^- (partial sp^2 character). On the latter point of planarity vs. non planarity it has recently been found that the planarity of the Co—O—O—Co group depends strongly on packing forces, and thus must be interpreted carefully [140].

Co—N bond lengths are very similar to those found in simple Co^{III} complexes. For Co(salen)dmf, the situation is not so simple, as might be expected from ESR results. Here the non planarity of the grouping is consistent with peroxo character (although packing forces might enter here) while the O—O bond length is quite short (1.37 Å) implying less than total delocalization of electron density on to the oxygen bridge. We feel these results might be easily explained by considering the electron withdrawing effects of the equatorial ligand, consistent with the earlier observation that σ donating groups increase peroxo character, and electron withdrawing groups decrease it.

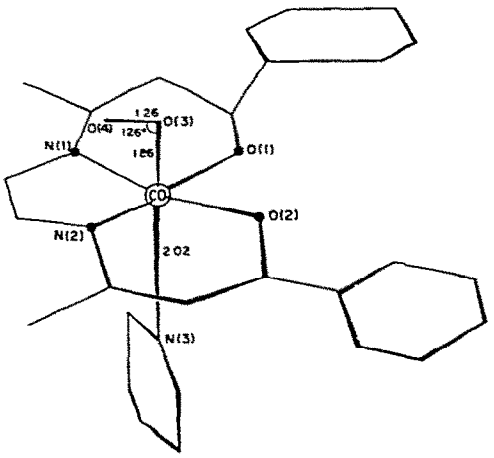


Fig. 7. Crystal structure of [Co(bzacen)(py)O_2]. (Data from Rodley and Robinson [50].)

TABLE 7

X-ray data for cobalt dioxygen complexes

Complex	O—O (Å)	Co—O—O	Co—O	Reference
Peroxo.				
$[(NH_3)_{10}Co_2O_2](SCN)_4$	1.65	112	1.83	134
$[(NH_3)_{10}Co_2O_2](SO_4)_2$	1.47	112 (non planar)	1.88	76, 135—138
$[(en)_4Co_2O_2NH_2](SCN)_3 \cdot H_2O$	1.46	110	1.87	117
$[(dipsalenCo)_2O_2]C_6H_5CH_3$	1.45	118	1.93	136
$[(salenCo)_2O_2]dmf_2$	1.34	120	1.91	101
$[Co_2(CN)_{10}O_2]K_6$	1.45		1.99	139
$[FsalenCoO_2CoFsalen\ (H_2O)]$	1.31	120	1.90	142
Hydroperoxo.				
$[(en)_4Co_2(O_2H)NH_2]\cdot(NO_3)_4 \cdot 2H_2O$	1.42	115	1.92	143
Superoxo.				
$[(NH_3)_8Co_2O_2NH_2](NO_3)_4$	1.32	120.8 (planar)	1.87	116
$[(en)_4Co_2O_2NH_2](NO_3)_4$	1.36	119 (planar)		143
$[(NH_3)_{10}Co_2O_2]SO_4(HSO_4)_3$	1.31	118 (planar)		137
$[Co_2(CN)_{10}O_2]K_5$	1.26		1.94	140
1 : 1 complex.				
[Co(bzacen)(py)O_2]	1.26	126	1.86	50
[Co(acacen)(py)O_2]			1.95	141
$[(C_2H_5)_4N]_3[Co(CN)_5O_2]$	1.24	153	1.91	230

Similarly, Schaeffer and others have recently investigated the structures of analogous μ dioxygen bis(pentacyanocobalt) complexes with interesting results [139,140]. For the μ superoxo complex an O—O bond length of 1.26 Å was found much shorter than that for the corresponding ammine (cf Table 7). This result may be rationalized by considering a competition of CN^- and O_2^- for the available electron density, as CN^- is a good π acceptor. Consistent with this interpretation are quite long Co—O bond distances (1.94 Å vs. 1.88 Å for the decaammine). In this light, the small A_{Co} in $[Co_2CN_{10}O_2]^{5+}$ should be reinterpreted not as high electron density on O_2^-, as originally thought [93] but as delocalization of electron density onto the CN^- ligands.

It is unfortunate that crystallographic results from a wide range of complexes are unavailable, particularly for the dibridged complexes. In the absence of such data a rather sensitive probe, which has only recently yielded valuable information on the nature of bonding in the complexes, is vibrational spectroscopy. The oxygen linkage is highly symmetric in these complexes, thus simple stretching modes might not result in an appreciable dipole moment change. In accord with this, oxygen stretching modes have not been reli-

TABLE 8

Vibrational spectra of dioxygen complexes

Complex	ν_{O_2} (cm^{-1})	ν_{Co-O} (cm^{-1})	Reference
μ-peroxo dicobalt single bridged.			
$[(NH_3)_5Co]_2O_2$ (soln.)	800		145
(solid)	808		145
$[(hist)_2Co]_2O_2$	805		145
$[(salen)_2Co]O_2$		565	144
Dibridged complexes.			
$[(his)_2Co]_2O_2OH$	790		145
$[(NH_3)_4Co]_2O_2NH_2$	793		145
μ-superoxo dicobalt complexes.			
$[(his)_2Co]_2O_2$	1120		145
$[(NH_3)_5Co]_2O_2$	1122		146
$[(CN)_5Co]_2O_2$	1104	493	146
Dimeric biological complexes.			
Oxyhemerythrin	844		147
Oxyhemocyanin	742		148
Mononuclear species.			
$[Co(bzacen)L]O_2$	1128		43
$[Co(acacen)L]O_2$	1140		43
$[Co(mesoalen)L]O_2$	1128		43
$[CoHb]O_2$	1105		43
$[FeHb]O_2$	1107		149
$[FeMb]O_2$	1103		150
Fe "picket fence" [a] [b]	1385		151
Representative data for oxygen.			
O_2	1556		152
$O_2(^1\Delta)$	1483		153
KO_2	1145		152
Na_2O_2	738		154
NH_4HO_2	830		152

[a] "picket fence" = meso tetra($\alpha,\alpha,\alpha,\alpha$-*o*-pivalamidephenyl) porphine. N-methylimidizole is incorporated as an axial ligand.

[b] This stretch has recently been shown to be an artifact arising from physisorbed oxygen and should thus be disregarded.

ably identified in the IR, although a Co—O_2 stretch has tentatively been assigned [144].

The use of Raman spectroscopy has alleviated this difficulty and O—O stretching modes have now been positively assigned for several μ-peroxo [145] and μ superoxo [146] complexes. The stretching frequency ($\nu \cong 900$ cm^{-1} for μ peroxo and ~1100 cm^{-1} for μ superoxo) fits quite well within the range expected for such groupings (cf. KO_2 $\nu_{O_2} = 1145$ cm^{-1} NH_4HO_2 $\nu O_2 = 830$ cm^{-1}).

The Co—N stretching frequencies are also consistent with appreciable Co^{III} character at the metal center (Table 8).

It is interesting to note that while little difference was found in the O—O distance for the monobridged (μ O_2) versus dibridged (μ O_2, NH_2) complexes (cf Table 7), solution Raman spectra show a clear distinction, with ν_{O_2} 10 cm^{-1} lower for the dibridged complexes, corresponding to greater peroxo character of the bridge. This interesting finding is consistent with the suggestion of Martell and co-workers [110,115] that dibridging of the complex tends to "lock in" the dioxygen moiety. This point is more fully discussed in the dynamics section.

The ν_{O_2} vibrational band is in resonance with an electronic transition at ~350 nm in the visible spectrum. This peak, which is highly allowed ($\epsilon > 10^3$) is generally assigned to a L → M charge transfer (which for the bonding scheme presented herein, may be visualized as transfer of an electron to the cobalt d_{z^2} from the π_g O_2 orbital). This transition is responsible for the ubiquitous yellow-brown color of the bis cobalt μ peroxo complexes and serves as a fingerprint in the UV for identifying μ peroxo complex formation [100,102]. Dependent on the nature of the ligand, the band maximum shifts slightly from ~360 nm in the case of simple polyamines and amino acid complexes to ~390 nm for pyridyl systems [82,108].

In this latter case, it is not entirely clear whether the 390 nm band represents the actual charge transfer band, or simply a d—d transition of proper symmetry to steal intensity from the CT band. Empirically, it has been noted that mono (μO_2^{2-}) bridged complexes generally exhibit two maxima at ~300, 330 nm * while dibridged ($\mu(O_2, NH_2,)$ and $\mu(O_2, NH)$) complexes exhibit a single maximum between 350—360 nm [92,81,99,155,156].

Of secondary interest are the Co^{III} like transitions at ~510 and 620 nm which are quite similar to those observed in simple Co^{III} chelates, supporting the ground state formalism. However, recent thorough spectral studies of the $Co_2(phen)_2O_2OH$ system show ligand bands intermediate to those observed for Co^{II} and Co^{III} systems [108]. On oxidation to the μ-superoxo species, a complex spectrum characterized by highly allowed bands at 670—700 nm, ~470 nm and ~300 nm are found, corresponding to the strong green color of the complex.

The spectra of the superoxo species have been shown to be highly dichroic [145]. Here, the 670 nm band is a "fingerprint" for these complexes, as few Co^{III} complexes absorb strongly in this region. Further d—d bands in the near IR have been reported for salen cobalt oxygen complexes [156].

Spectra of mononuclear Co—O_2 adducts are less well characterized, as d—d bands are generally obscured in these complexes by strong ligand bands. Reflectance spectra of $[Co(en)_2O_2]^{2+}$ should prove interesting in this regard. Several theoretical treatments of the spectra of cobalt dioxygen (primarily μ-

* The splitting may be explained as a splitting of the O_2 π and π^* levels into in-plane π_h and out-of-plane π_v components. For the dibridged complexes, with smaller allowed dihedral angles, this separation will be reduced and thus only one band is observed [229].

superoxo) complexes have appeared [156—165,16,17] often with contradictory results. A definitive treatment has yet to appear, particularly for the μ-peroxo and mononuclear complexes *.

In an attempt to define more closely spectral assignments, CD spectra have been obtained for several Schiffs base [156,162] and polyamine [121,163] oxygen carriers. These results suggest that the peak at ~1000 nm should not be assigned as a *d—d* transition. For the $(Lpn)_4Co_2O_2$ complex, an absolute configuration of $\Delta\Delta$ has been assigned [156]. Further studies in this area could be of value, particularly in the assignment of μ-peroxo and mononuclear complexes.

In order to quantify the "oxidized cobalt-reduced oxygen" formalism, these systems have been studied polarographically [143,166—171]. These studies have reinforced the ($Co^{III}—O_2^-$) concept. In particular Vleck [171] has found the μ-superoxo decammine cobalt(III) complex to be more stable than the corresponding μ-peroxo complex, in acid media. Such "stability" is questionable however, as it is a function of the medium. In acidic solution, the superoxo species is stable, whereas in basic solution it is rapidly reduced to the μ-peroxo complex, even in the absence of conventional reducing agents [166]. More interestingly, Basolo and co-workers have found an apparent correlation between redox potential of the dioxygen complex and oxygen complex stability [43], for a series of mononuclear complexes, as suggested by the "internal redox" model *.

(ii) Dynamics of the oxygenation reaction

In summary, the physical methods outlined have provided a framework for understanding the interaction of dioxygen with cobalt. A quantitative understanding of how these factors are reflected in the formation and reactivity of the dioxygen species has been obtained from recent studies of solution dynamics. Wilkins and co-workers have provided definitive kinetic support for the mechanism of oxygen complexation in the μ-peroxo systems [19,79,85,90, 91,109,112] as outlined below.

$$CoL + O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CoLO_2$$

$$CoLO_2 + CoL \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} CoLO_2CoL$$

Since as already discussed, the μ-dioxygen complexes have characteristic $L \rightarrow M$ CT bands in the 360—390 nm range, the reaction can conveniently be followed by monitoring this band. As these reactions are generally quite rapid

* Assignments for μ-peroxo complexes have recently been made by Miskowski et al. [229] and by Bogucki et al. [108] with essentially identical results. Recent studies of the 1 : 1 dioxygen complex of pentacyanocobaltate(II) show the spectra to be essentially the same as those of the binuclear "superoxo-bridged" dioxygen complex of pentacyanocobaltate(II), implying a minimal perturbation by the second cobalt. The spectra may be assigned [231] with some modification following the assignments of Gray and co-workers [229—231] for the binuclear complex.

* An excellent review of this type of dioxygen complex has recently appeared [233].

($t_{1/2} << 10$ s) a stopped flow system is required for the measurement.

For the mechanism given, assuming a steady state in $CoLO_2$ and following initial rates so that the term k_{-2} [$CoLO_2CoL$] is small, we have

$$\frac{d[CoLO_2CoL]}{dt} = \frac{k_1k_2[CoL]^2[O_2]}{k_{-1} + k_2[CoL]} = k_{obs}[O_2]$$

under conditions generally chosen, [CoL] >> O_2 (pseudo first order) and k_2[CoL] >> k_{-1} so that the expression reduces to a first order dependence on [CoL]

$$\frac{d\ complex}{dt} = k_1[CoL][O_2]$$

and k_1 is obtained directly. If [CoL] is small so that k_2[CoL] is not dominant, the rate terms may be obtained graphically [85,90,91] by plotting [CoL]/k_{obs} vs. 1/[CoL] giving k_1 and k_1k_2/k_{-1}. If k_{-2} can be determined independently

TABLE 9

Kinetic parameters for the oxygenation reaction at 25°

Complex	k_1(M^{-1} sec^{-1})	k_{-2} (sec^{-1})	ΔH [d]	ΔS [d] (eu)	Reference
Co(trien)	2.5×10^4	0.45	7	−15	112
Co(trien)(OH)	2.8×10^5	0.46			112
Co(tep)	$\sim 10^5$		18	+9	112
$Co(histamine)_2$	1.8×10^4				79
$Co(en)_2$	4.7×10^5	0.015	15	+19	79
$Co(Lhist)_2$	3.5×10^3	0.47	5	−25	90
$Co(LhistH)_2$ [a]	2.6×10^4				91
$Co(glygly)_2$	1.0×10^4				90, 98
Co(glygly)	$>10^4$				98
$Co(Lcys)_3$	2×10^5				19
$Co(DLhist)_2$	7.6×10^3	0.04			90
Co(tren)[b]	2.8×10^3	0.4			113
Co(sdtma)[b]	3×10^3	0.6			114
Co(udtma)[b]	1.4×10^4	0.3			114
Co(dien)	<100				79
$Co(dien)_2$	1.2×10^3	0.016	10	−12	79
$Co(amp)_2$	720		6	−25	79
$Co(amp)_3$	47				79
Co(sedda)[b]	25				115
Co(uedda)[b]	22				115
$Co(NH_3)_5$	2.5×10^4	56	4	−25	77
Co(pts)	<100				
Co(trpy)(bipy)[b,c]	1×10^{6}[b]	~0.5			82
Co(trpy)(ophen)[b,c]	8.5×10^{5}[b]	0.5			82

[a] Tetrahedral species.
[b] I = 0.1 M.
[c] M^{-2} sec^{-1}.
[d] I = 1—2 M except where noted.

(by decomposition of the fully formed complex with dithionite, EDTA or H^+) a measure of the overall equilibrium constant $K_{O_2} = k_1k_2/k_{-1}k_{-2}$ can be obtained. Values obtained in this way are in good agreement with other methods. These results have been extended to a number of different complexes in our own laboratory [98,113,115,108]. The kinetic results of all workers are summarized in Table 9.

Recently, Huchital and Martell [82] have described the kinetics of dioxygen complexation by the trpy-bipy and trpy-phen cobalt mixed ligand systems. Here, a second order dependence of CoL is observed implying $k_{-1} >> k_2[CoL]$ i.e. a rapid pre-equilibrium is obtained. Activation parameters for the reaction have been obtained for a number of systems.

As can be seen, rate constants and activation parameters are generally similar in magnitude, implying a common process of H_2O replacement by oxygen, dominated by H_2O exchange, but are smaller than the rates of ligand replacement for simple Co^{II} systems (e.g., $Co(NH_3)_5H_2O + NH_3 \overset{k_1}{\rightarrow} Co(NH_3)_6$, $k_1 = 10^6$) [172] implying stricter orientation requirements. Interpretation of the rate constant k_{-2} is somewhat less straightforward, particularly for complexes in which secondary bridging may be involved [12,79,113,115].

An exhaustive study of one such dibridged complex ($CotrienO_2OHCotrien$) has been reported [112]. Here the mechanism supported by pH dependence of the rate is

$$CoL^{2+} + O_2 \rightleftharpoons CoLO_2^{2+}$$

$$CoLO_2^{2+} + CoL^{2+} \rightleftharpoons H_2OCoLO_2CoLH_2O^{4+} \rightleftharpoons HOCoLO_2CoLH_2O^{3+} \rightleftharpoons HOCoLO_2CoLOH^{2+}$$

$$\rightleftharpoons CoLO_2OHCoL^{3+}$$

in which the secondary bridging is a slow, first order, intramolecular process subsequent to the initial oxygenation and dimerization [112,113], so that the initial oxygenation rate (k_1) may be observed independently. Here, however, decomposition experiments performed by plunging the formed solution into a low pH buffer [79,112] are complicated by the presence of the hydroxo bridge as the observed rate probably incorporates breakup of the hydroxide bridge. Thus the k_{-2} values obtained in this way must be cautiously interpreted.

In conjunction with the kinetic studies, a number of equilibrium studies have been carried out to define the salient factors contributing to dioxygen complex formation and stability. A number of methods have been utilized in these studies including oxygen pressure measurements (both Warburg [36] and polarographic [79,115]), spectral measurements [115,106] and potentiometric equilibrium methods [82,98,102,104,108,100,113—115].

Of these, the most powerful technique, where applicable, has been the potentiometric equilibrium method. In this method, competition is set up between proton and metal for the basic ligand groups (e.g. amines). From the

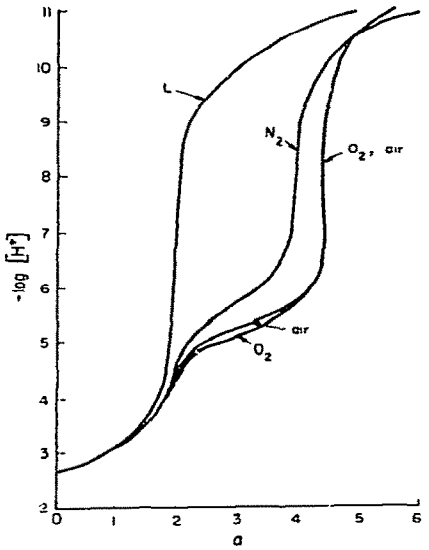


Fig. 8. Potentiometric equilibrium curves for the cobalt system at 25°C, μ = 0.1 M (KNO_3). L = ligand alone; N_2 = 1 : 1 molar ratio of ligand to cobalt under an inert atmosphere; air, O_2 = 1 : 1 molar ratio of ligand to cobalt under air, and pure O_2 respectively; a = moles base added per mole ligand.

observed $[H^+]$ concentration, the amount of metal—ligand species in solution may be calculated, if the ligand acid dissociation constants are accurately known, simply by setting up and solving the appropriate charge and mass balance equations. By performing these studies in the presence and absence of oxygen, the relevant equilibrium constants may be obtained.

Typical resultant equilibrium curves are given in Figure 8 for the Co(sdtma) system *. Two points of particular interest are demonstrated in the curves. First of all, the stoichiometry of the complex can be assigned by noting the break that occurs at 4.5 equivalents of metal complex, one extra equivalent of base for every two equivalents of metal complex, over and above that required to neutralize the ligand. This result is highly suggestive of formation of a dibridged μ-peroxo—μ-hydroxo bis cobalt system as the final stable product in solution. Such complexes have been isolated and characterized by analysis and spectral techniques [86,113—115]. Although no structural determination is available, they are analogous to the well known μ-peroxo—μ-amido complexes [116—122]. μ-Hydroxo bridge formation has been shown to occur whenever two *cis* sites are available on the metal—ligand complex.

This point has often been overlooked in assignment of structures [107,79] and interpretation of kinetic [79] and thermodynamic data [106]. For example the slow decomposition processes observed by Miller et al. [79] for the $Co(en)_2$ and $Co(histamine)_2$ system and ascribed to ligand bridging are more probably due to hydroxo bridging. Similarly, while Nancollas recognized μ-hy-

* Fallab and co-workers have recently described dioxygen complexation by Co(dtda) in which a secondary μ-hydroxo bridge is formed at high pH [235].

droxo bridging in the $Co(en)_2$ dioxygen complex, it was ignored for the Co(histamine)/dioxygen system [106]. Similar examples may be found in the "non stoichiometric reactions" of Co + en [173], and studies of $Co(bipy)_2$ [107], and others. Even the well characterized $Co(histidine)_2$ system has been suggested to undergo olation at high pH [92].

Thus, such dibridging must always be considered wherever two *cis* sites can be made available at the metal center. The effect of dibridging seems to be to "lock in" the dioxygen bridge more tightly, perhaps by restricting rotation. Thus oxygenation of some cobalt polyamines (e.g. Co(tren)) is reversible within the buffer region, where significant amounts of the monobridged species exists in the equilibrium

$$H_2O + CoLO_2CoL \rightleftharpoons CoLO_2OHCoL^- + H^+$$

but not at high pH, where the olated species is present almost exclusively. Physical evidence for the "locking in" process has been found in vibrational spectra, as previously discussed.

A second important qualitative observation is the displacement of the equilibrium curve obtained under oxygen below that obtained under nitrogen, implying much stronger competition by the metal for the ligand in the metal dioxygen complex than in the simple metal—ligand complex. This observation is most easily explained by considering the effect of partial transfer of an electron from cobalt to dioxygen. The increased effective charge (Co^{III} character) of the metal would enable it to compete more effectively with protons for the nucleophilic ligand; thus complexation would occur at a lower pH.

This qualitative observation is amenable to quantitative testing. If this mechanism is operative, as the cobalt center becomes more strongly electron donating to the electrophilic oxygen, the stability of the complex should increase. Such an effect might be expected on increasing the σ donating ability of the coordinated ligand (as measured by the ligand pK's) for a group of ligands without significant π donor or acceptor properties, so that σ donation can be evaluated independently. The results of such an analysis [174] are given in both tabular (Table 10) and graphical form (Fig. 9) for a series of dibridged complexes.

$$K_{O_2} = \frac{[MLO_2OHML][H^+]}{[ML]^2[O_2]}$$

Considering the crudeness of the approximation, the observed fit is quite remarkable and offers substantive, quantitative support for the chemical relevance of the $Co^{III}—O_2^{2-}—Co^{III}$ description. It is unfortunate that limited data for non hydroxo bridged μ-peroxo complexes are available, so that the oxygenation reaction cannot be evaluated in the absence of the olation reaction over a wide range of compounds.

One system for which it has been possible to separate the olation and oxygenation reactions is $Co(bipy)_2$ [108]. The chelate forms completely at low pH

TABLE 10

Correlation of stabilities of dioxygen complexes of cobalt with basicities of ligands [a] [174]

Ligand	ΣpK_a [b]	Log $K^{c}_{ML_X}$	Log K_{O_2}
Dibridged (monohydroxo) species.			
Sedda	16.2	11.2	−4.1
Uedda	16.7	11.6	−5.4
Sdtma	25.3	12.3	2.3
Udtma	24.6	12.1	2.4
Dien	23.2	8.2	1.1
Trien	28.7	10.4	6.1
Tren	30.5	12.3	4.4
En [c]	35	10.7	10.8
Histamine [c]	32	9.0	8.5
Hedien [c]	22.5	7.9	1.5
Monobridged species.			
Tep	34.5	13.2	15
Dgenta	44	8.5 [e]	14.5
Trpy(phen)	~13	6.53 [e]	6.3
Trpy(bipy)	~12	5.38 [e]	5.4
Histidine [c]	30.4	13.9	6.6

[a] All measurements made at 25 ± 0.1°C and ionic strength of 0.10 adjusted with KNO_3.
[b] ΣpK_a is summation of pK's of all donor groups of ligands coordinated to cobalt(II) ion.
[c] Data given are for 2 : 1 complexes.
[d] Recalculated from Ref. 14 for $K_{O_2} = [MLH_{-2}O_2MLH_{-2}]/[MLH_{-2}]^2[O_2]$ assuming stepwise amide deprotonation, $pK_1 = 12$, $pK_2 = 14$.
[e] For reaction for $Co(trpy)^{2+}$ with second ligand.

and in this buffer region complexes a small constant amount of oxygen in a pH independent reaction (measured polarographically).

$$2ML_2 + O_2 \rightleftharpoons (ML_2)_2O_2$$

After neutralization of the original ligand protons however, a new buffer region emerges, with concomittant formation of a deep brown oxygenated complex. Within this region oxygen uptake is markedly pH dependent, suggesting formation of a μ-hydroxo bridge, which, as discussed, pushes the equilibrium toward greater dioxygen complex formation.

The relevant equilibrium constants

$$K_{O_2} = \frac{[MLO_2ML]}{[ML]^2[O_2]} \text{ and } K_{O_2} = \frac{[MLO_2OHML][H^+]}{[ML]^2[O_2]}$$

may be combined to give the equilibrium constant for the olation reaction

$$K_{OH} = \frac{[MLO_2OHML][H^+]}{[MLO_2ML]}$$

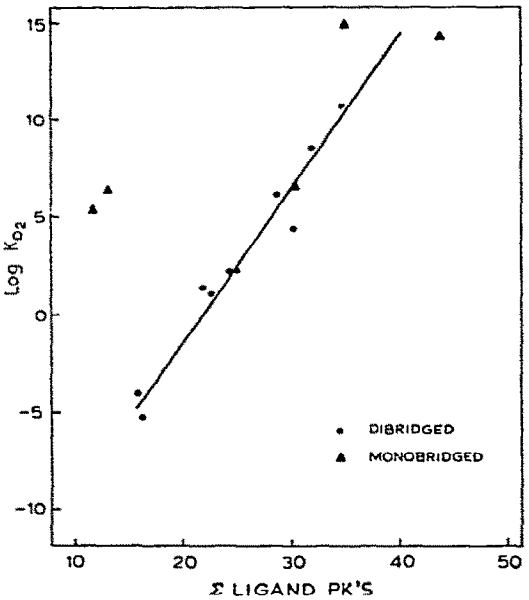


Fig. 9. Correlation between basicities of the auxiliary ligands (measured by Σ pK's) and the stabilities of the dioxygen complexes formed by cobaltous chelates of these ligands; t = 25.0°C, μ = 0.1 M (KNO_3).

For the $Co(bipy)_2$ system log K_{OH} = 6.7. Such a low hydrolysis constant is consistent with considerable, but not total, Co^{III} character.

Similar analyses of basicity vs. oxygen affinity based on somewhat more limited data have been undertaken for some mononuclear oxygen complexes, in which the equatorial ligands are held constant and the axial ligands varied [43,58,60], and vice versa. Although these results have been the subject of controversy [175,176] they are probably valid. These results are compiled in Table 11.

Using the Gibbs—Helmholtz treatment, equilibrium data obtained at various temperatures have been used to derive thermodynamic parameters ΔH and ΔS [113,79]. Recently calorimetric techniques have also been applied [106, 33]. These data are summarized in Table 12. The most striking feature of the results is the highly negative values of ΔH and ΔS. The negative entropy term probably arises from the loss of translational and rotational freedom of oxygen on binding, whereas the highly exothermic ΔH value can be accommodated by consideration of the simple energy cycle [106]. For the mononuclear systems, ΔH essentially parallels the basicity of the ligand, whereas ΔS (and thus K_{O_2}) exhibits marked variations dependent on a number of factors, including steric effects [43]. Increasing ligand π-donor ability also increases oxygen complexation markedly [233], as noted in the interpretation of X-ray and ESR data herein.

One limitation suffered by the potentiometric method, and to a lesser extent in all equilibrium techniques, is that a long term stable equilibrium is re-

TABLE 11

Equilibrium data for mononuclear cobalt—dioxygen complex formation at 293 K

Complex	Log K_{O_2} [a]	Log K'_{O_2} [b]	Reference
Co(acacen)py	−3.0	2.0	43
Co(phacacen)py	−3.7	1.3	43
Co(meacacen)py	−3.5	1.5	43
Co(sacsacen)py	−4.1	0.9	43
Co(benacen)py	−4.0	1.0	43
Co(benacen)nBuNH$_2$	−2.8	2.2	43
Co(benacen)iBuNH$_2$	−4.0	1.0	32
Co(benacen)secBuNH$_2$	−3.3	1.7	43
Co(benacen)NMeIm	−3.0	2.0	43
Co(benacen)5ClNMeIm	−3.1	1.9	43
Co(benacen)pip	−3.2	1.8	43
Co(benacen)3,4Lutidine	−3.6	1.4	43
CoPDMF	−4.7	0.3	60
CoPpy	−4.7	0.3	60
CoP4tBupy	−4.9	0.1	60
CoPIm	−4.2	0.8	60
CoPNMeIm	−4.1	0.9	60
CoP4NH$_2$py	−4.2	0.8	60
CoPpip	−4.2	0.8	60
Cobaltomyoglobin (whale)	−1.7 [c]	4.3	69
(ferro)myoglobin(whale)	+0.1 [c]	6.1	69

[a] $K_{O_2} = [CoLO_2]/[CoL]PO_2$;
[b] $K'_{O_2} = [CoL]/[CoL][O_2]$;
[c] pH = 7.0, phosphate buffer. Standard state for PO_2 = 1 torr; toluene solution except where specified. Solubility of O_2 from International Critical Tables.

quired for accurate measurements, whereas all the cobalt dioxygen complexes are subject to irreversible decomposition to mononuclear Co^{III} products. For a number of cobalt polyamine dioxygen complexes (e.g. $Co(en)_2$, Co(trien), Co(tren)) the intermediate dioxygen complex is stable enough to be readily examined by potentiometric methods. For other complexes, including most peptide and amino acid complexes, the irreversible reaction is quite rapid (e.g. $t_{1/2} < 5$ min for Co(glygly) at pH 9) precluding the use of potentiometric methods. In these cases, a polarographic oxygen sensor with a fast response time (>90% in 10 s) can be utilized to obtain useful, although less accurate, data. The precise mechanism of the conversion of binuclear oxygen complexes to mononuclear products is still unclear (Table 13).

For a series of dipeptide complexes the rate appears to be first order in both complex and H^+ [100] whereas cobalt polyamines are more stable at intermediate pH but decompose rapidly above pH 12 [103] and appear to follow complex kinetic schemes [81,84,94,103,177]. The overall oxidation products have not been fully characterized. One possible scheme involves proton-

TABLE 12

Thermodynamic parameters for the oxygenation reaction of cobalt complexes

Complex	ΔH kcal/m	ΔS (eu)	Method [b]	Reference
2 : 1 Complexes.				
$Co(hist)_2$	−30.1	−70	calorimetric	106
$Co(histamine)_2$ [a]	−29.4	−49	oxygen uptake	106
$Co(en)_2$	−29	−65	calorimetric	106
Co(tren)	−32	−100	potentiometric	113
1 : 1 Complexes.				
Co(salen)DMSO [c]	−16	−41	spectral	43
Co(acacen)py	−17.3	−73	"	43
Co(phacacen)py	−16.3	−72	"	43
Co(meacacen)py	−15.6	−69	"	43
Co(sacsacen)py	−13.3	−64	"	43
Co(benacen)py	−16.6	−75	"	43
Co(benacen)$nBuNH_2$	−17.4	−72	"	43
Co(benacen)$iBuNH_2$	−18.0	−80	"	43
Co(benacen)$secBuNH_2$	−17.8	−76	"	43
Co(benacen)NMeIm	−17.5	−73	"	43
Co(benacen)5ClNMeIm	−17.5	−74	"	43
Co(benacen)pip	−16.7	−72	"	43
Co(benacen)3,4Lutidine	−16.8	−74	"	43
CoPDMF	−11.0	−59	"	60
CoPpy	−9.2	−53	"	60
CoP4tBupy	−9.8	−56	"	60
CoPIm	−11.3	−58	"	60
CoPNMeIm	−11.8	−59	"	60
$CoP4NH_2py$	−9.9	−53	"	60
CoPpip	−9.0	−50	"	60
Cobaltomyoglobin (whale) [d]	−13.3	−53	"	69
(ferro)myoglobin (whale) [d]	−17.5	−59	"	69

[a] OH^- bridging not considered.
[b] All ΔH values calculated from temperature coefficient of ΔG, except for those labelled calorimetric.
[c] DMSO solution.
[d] pH 7.0 phosphate buffer. Standard state for PO_2 = 1 torr; toluene solution except where specified.

ation of the dioxygen bridge to give H_2O_2 and $2Co^{III}L$.

$$CoLO_2CoL + 2H^+ \rightarrow 2CoL + H_2O_2$$

For the $Co_2(CN)_{10}O_2$ system quantitative production of H_2O_2 has been observed [87]. Such an observation in other systems may be hampered by further reactions of H_2O_2 including oxidation of the ligand [84].

It should be noted that several possible schemes are available for decomposition, as evidenced by the wide range of pH dependence of the rate. Whatever

TABLE 13

Rates of the reaction $CoLO_2CoL \rightarrow Co^{III}L$ [a]

Complex	$t_{1/2}$	Reference
$(Co(orn)_2)_2O_2$	800 min	95
$(Cosedda)_2O_2OH$	7 hr	77
$(Couedda)_2O_2OH$	~24 hr	77
$(Cosdtma)_2O_2OH$	>6 months	77
$(Coudtma)_2O_2OH$	>6 months	77
$(Cotren)_2O_2OH$	~4 months	77
$(Co(glygly)_2)_2O_2$	40 min	99
	~5 min	100
$(Co(histgly)_2)_2O_2$	7 hrs	99
	40 min	100
$(Co(dien)_2)_2O_2$	18 min	99
$(Co(histinamide)_2)_2O_2$	6 hr	99
$(Co(glycinamide)_3)_2O_2$	4 hr	99
$(Coglyhist)_2O_2OH$	7 hr	99
	3 hr	100
$(Co(dap)_2)_2O_2$	24 hr	95
$(Co(en)_2)_2O_2OH$	8 days	99
$(Co(his)_2)_2O_2OH$	12 days	99
$(Co(glyala)_2)_2O_2$	10 hr	99
	10 min	100
$(Co(glyval)_2)_2O_2$	3 months	99

[a] Approximate conditions, 1×10^{-3} M, pH 9—11, 25°, for reactions from ref. 99 only. Original papers should be consulted since rates are strongly pH and concentration dependent. The apparent inconsistency in the rates may be explained by sequential reactions: a fast oxidation followed by a slower substitution reaction of the cobalt(III) product [100].

the precise mechanism, the dioxygen complex is believed to be an obligatory intermediate in the standard preparation of Co^{III} complexes by air oxidation [19,99]. Those cobalt chelates which do not complex oxygen (e.g. glycylsarcosine [99,100]) appear to be totally inert to air oxidation to $cobalt^{III}$ species.

In some cases, however, (e.g. $Co(EDTA)^{2-}$) evidence for the dioxygen intermediate is minimal [178].

(iii) Reactions of dioxygen complexes

In order to understand the reactivity of oxygen complexes in biological systems, their reactivity to simple substitution and redox reactions must be defined, preferably first in well characterized model systems. Some progress has been made in this area, as outlined below.

The obvious suggestion has been made [17,114] that the stability of cobalt dioxygen complexes relative to the iron and copper species is a kinetic phenomenon, reflecting the inertness of the Co^{III} like metal center on dioxygen coordination. While such an explanation may be partially correct, it does not account for the fact that dioxygen complexes of formally Cr^{III} and Fe^{III} should

also be quite inert from a simple crystal field viewpoint, whereas dioxygen complexes of these metals are in fact quite unstable.

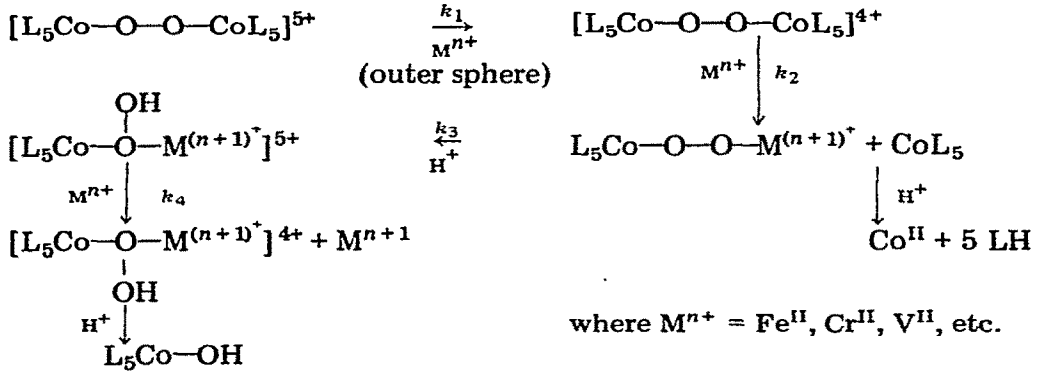
More importantly, the limited data available on substitution chemistry of cobalt dioxygen adducts shows them to be much more reactive than classic cobalt(III) complexes. For instance, acid hydrolysis of μ-peroxo dicobalt decaamine is extremely fast, requiring a stopped flow apparatus for measurement [179]. Similarly, data available for the deoxygenation reaction show it to be quite rapid ($t_{1/2} < 10$ s for most complexes). This apparently contradictory behavior may be rationalized by considering that the stable "cobalt(III)" dioxygen complex is in fact simply a resonance form of a labile cobalt(II) species so that reaction through the cobalt(II) species can rapidly occur. Thus the chemical lability of the complex may be ascribed to a rapid intramolecular redox reaction.

Shibahara and Mori [180] have studied the reactions of μ-peroxo bis cobalt decammine with a variety of substrates (NCS^-, NO_2^-, CN^-). The reaction pathway was found to be strongly pH dependent. Although reaction products were characterized, no kinetic data were obtained. A more thorough investigation of the reactivity of these complexes toward substitution is warranted.

The redox chemistry of μ dioxygen complexes has been more extensively investigated by Sykes [120,122,181—183], and others [179,184]. A review of earlier work is available [22] so that we will concentrate on more recent developments.

The μ-superoxo species have been shown to undergo rapid one electron reduction to the μ-peroxo species, which in several characterized cases undergoes further multi-step reduction [181] ultimately reducing oxygen to H_2O.

While the μ-superoxo species reacts by an outer sphere mechanism [179, 183], an inner sphere process has been postulated for the reduction of the μ-peroxo complex, as suggested by the relative rates for several μ-peroxo μ-hydroxo systems [184]. The scheme suggested by Sykes is reproduced below.



While the scheme given is that best supported by experimental evidence [184], it must be regarded as tentative beyond the second reduction step, although protonation rearrangement reactions of the type shown are well known. Rate

TABLE 14

Redox chemistry of some cobalt dioxygen complexes

Complex	Reductant	k_1 M^{-1} sec^{-1}	Reference
μ-peroxo complexes.			
$(Co(en)_2)_2O_2OH^{3+}$	Fe^{2+}	630	184
$(Codien)_2O_2OH^{3+}$	Fe^{2+}	230	184
$(Cotrien)_2O_2OH^{3+}$	Fe^{2+}	35	184
$(Cotep)_2O_2^{4+}$	Fe^{2+}	~2	184
$(Co(en)_2)_2O_2NH_2^{3+}$	Cr^{2+}	2000	181
μ-superoxo complexes.			
$(Co(en)_2)_2O_2NH_2^{4+}$	Cr^{2+}	$>10^5$	181
$(Co(en)_2)_2O_2^{5+}$	Fe^{2+}	>8000	184
$(Cotrien)_2O_2^{5+}$	Fe^{2+}	430	184
$(Cotep)_2O_2^{5+}$	Fe^{2+}	380	184
$(Co(NH_3)_5)_2O_2^{5+}$	Fe^{2+}	0.03	183
$(Co(NH_3)_4)_2O_2NH_2^{4+}$	Fe^{2+}	25.2	183
$(Co(bipy)_2)_2O_2NH_2^{4+}$	Fe^{2+}	7000	122
$(Co(phen)_2)_2O_2NH_2^{4+}$	Fe^{2+}	10,000	122

constants k_1 and k_2 for some complexes are listed in Table 14.

The inner sphere complex is formed in the initial one electron reduction of the μ-peroxo complexes, and the $\mu(OH, O_2)$ and $\mu(O_2, NH_2)$ complexes. Here, the effect of dibridging seems to be to increase the reactivity of the dioxygen moiety [181] by exposing the bridge to more direct attack. While the μ-amido bridge would be expected to be more basic than the μ-hydroxo, and thus less stable in strong acid, the reverse is actually found. This apparent anomaly may be understood in terms of metal proton competition for the bridging group. Thus the very strong bonding of $Co—NH_2^-$ more than compensates for the high basicity of NH_2^- so that the equilibrium strongly favors cobalt binding even in the presence of large H^+ excess.

In addition to these standard aqueous reactions, photochemically activated redox reactions have been intensively studied for the μ-superoxo species by Valentine [185—187] and others [188,189]. Irradiation of the CT band at 300 nm or of the *d—d* at 540 nm, which is mixed with the CT band, gives the following reaction.

$$(NH_3)_5CoO_2Co(NH_3)_5 \xrightarrow[H_2O,\ H^+]{k_2} Co(NH_3)_5H_2O^{3+} + Co^{2+} + O_2 + 5NH_4^+$$

The presence of anions leads to products of the type $[Co(NH_3)_5X]^{2+}$, suggesting formation of a penta coordinate intermediate [22,187]. Similar results have been obtained for two series of mono and dibridged μ-superoxo complexes [187].

Photochemistry of the corresponding μ-peroxo complexes is less well investigated.

One important area of dioxygen complex chemistry which has generated particular interest is the oxygenase and oxidase activity exhibited by these complexes. Although simple metal complexes exhibiting such activity have previously been studied [16] the mechanisms involved were unclear, as the role of oxygen can only be inferred kinetically [189]. Recently, however, several well characterized $Co—O_2$ complexes have been shown to exhibit oxidase [188, 190] and oxygenase [191] activity. A particularly interesting example is provided by the reaction $Co_2(glytrp)_4O_2 \rightarrow$ Co(III)glykyneurinine, a model for the kyneurinase reaction [234]. Both ternary complexes of the type $L—Co—O_2$ [194] (reaction 1) and $Co—O—O—L$ [191,193] (reaction 2) have been proposed as intermediate (where L is the reducing substrate).

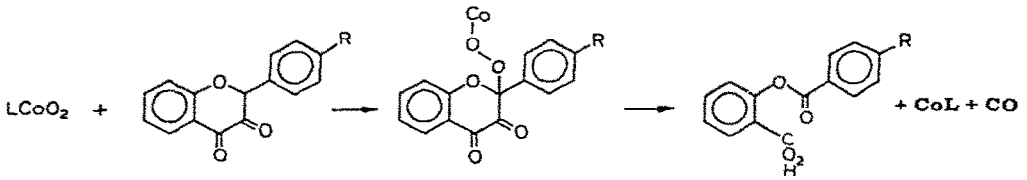
A third intermediate type, in which no ternary complex is involved, has been postulated [192] but these results are equally explicable by reaction scheme 2. By utilizing this process, the unfavorable one electron reduction of oxygen can be converted into a $2e^-$ process.

In the face of the wealth of data available for cobalt dioxygen complexes an attempt should be made to extend the understanding gained in these systems to the more complex enzymic systems utilizing iron and copper. In order that reasonable comparisons might be made, it is necessary first to examine the recent data obtained for similar model systems utilizing Fe, so that one might not be misled into neglecting differences between the metals themselves.

Reaction 1

$$CoTSP + NH_2OH \rightarrow HOH_2N—CoTSP \xrightarrow{O_2} HO—\overset{H_2}{\underset{|}{N}}—Co(TSP)—O_2$$
$$\rightarrow N_2 + H_2O + CoTSP$$

Reaction 2



C. IRON MODELS

Until quite recently, little work has appeared on iron-containing model systems. Early work by Corwin and Reyes with protoheme [195] has been controversial, as with the Fe—DMG [196] system. In the early 1960's, Wang [197] incorporated ferrous porphines into a polystyrene matrix, resulting in a system which could reversibly complex oxygen. This work demonstrated that iron model systems for hemoglobin could be synthesized in a properly constrained environment. Quite recently, the field of iron dioxygen complexes has gained appreciable attention.

The work described above with cobalt had suggested that mononuclear oxygen complexes are stabilized in aprotic, hydrophobic environments in which dimerization is inhibited sterically, or by use of low temperature. These same conditions have been utilized as a means to prepare monomeric Fe—O_2 complexes with conspicuous success. A summary of this work to date is contained in Table 15.

The success of this synthetic method has led to the understandable suggestions that stable Fe—O_2 complexes require a hydrophobic environment, and strict protection from dimerization, which might offer a pathway for irreversible oxidation. This latter requirement is questionable in view of hemerythrin, a biological oxygen carrier found in certain invertebrates, which is almost certainly dimeric [201]. Furthermore, the Fe—pts system appears to form a dimeric oxygen complex [217,218] which is stable in aqueous solution. If valid, this complex also violates the "hydrophobic rule". This system is presently being re-investigated by the authors.

Unfortunately, the mononuclear systems so far investigated utilize extremely similar equatorial ligands, involving substitution of the basic porphine ring. Variations in axial ligand, however, as with cobalt systems, have yielded useful data. Traylor and co-workers have shown that increasing the basicity of the

TABLE 15

Dioxygen complexes of iron(II)

Ligand	Formula	References
Biological complexes.		
Hemoglobin, FeL	$FeLO_2$	8
Myoglobin, FeL	$FeLO_2$	8
Cytochrome P450, FeL	$FeLO_2$	198
Cytochrome *a*, FeL	$FeLO_2$	199
Cytochrome *o*, FeL	$FeLO_2$	200
Hemerythrin, FeL	$FeLO_2FeL$	201
Synthetic mononuclear complexes.		
Protoporphyrin IX, H_2L; L′ = imidazole, 1-methylimidazole	$L'FeLO_2$	202, 203
Protoporphyrin dimethyl ester, H_2L; L′ = 1-butylimidazole	$L'FeLO_2$	204
Mesoporphyrinbis[3-(1-methylimidazoyl)propyl]amide H_2L	$FeLO_2$	204—207
Mesoporphyrin-3-(3-pyridyl)propyl ester, H_2L	$FeLO_2$	208
Pyrroporphyrin-3-(3-pyridyl)propyl ester, H_2L	$FeLO_2$	209
Pyrroporphyrinbis[3-(1-methylimidazoyl)propyl]amide, H_2L	$FeLO_2$	208
Tetraphenylporphine, H_2L; L′ = pyridine, piperidine, 1-methylpyridine and in silica gel matrix	$L'FeLO_2$	210 210a
Meso-tetra(α,α,α,α,*o*-pivalamidophenyl)porphine, H_2L	$FeLO_2$	211—214
"Capped" porphyrin, $C_{62}H_{44}N_4O_{12}$	$FeLO_2$	215, 216
Synthetic binuclear complexes.		
Tetrasulfophthalocyanine, H_2L	$LFeO_2FeL$	217, 218

axial group results in net stabilization of the oxygen complex (indicated by $P_{1/2}O_2$, the partial pressure for half saturation) [204,208], as does increasing solvent polarity, consistent with a dipolar $Fe^{III}—O_2^-$ formulation [203].

In addition to π donating ligands, good σ donors (e.g. t-butylamine) also promote oxygen complexation when bound in an axial site, in accord with analogous cobalt chemistry [202]. Although elaborate ligands which protect the iron atom from dimerization [211—216] have been synthesized, much less hindered [215] models appear to possess comparable stability [203, 210]. However, use of a covalently bound axial ligand has allowed an unequivocal investigation of kinetic phenomena of oxygen complexation and dissociation, using flash photolysis techniques [209] *.

Further studies of thermodynamics and kinetics of dioxygen binding by ferrous model compounds would be very valuable, and will certainly be forthcoming. These results do confirm, however, that oxygenation of ferrous complexes proceeds independently of the protein, and that a major function of the protein is to inhibit irreversible oxidation. Limited physical data are available for $Fe—O_2$ systems, and are somewhat contradictory.

Vibrational spectral data, previously summarized in Table 8, have given a value of ν_{O_2} of 1105 cm^{-1} in oxyhemoglobin but 1380 cm^{-1} in the oxygenated Fe "picket fence", the former suggestive of O^-, the latter of $^1\Delta$ singlet oxygen. As this latter value is now known to arise from an artifact [228] the former bonding mode, more consistent with our arguments, should be assumed.

Mossbauer spectra for simple porphine $Fe—O_2$ complexes have been obtained [203,212] which are very similar to those found in oxymyoglobin. A crystal structure of the FeO_2 "picket fence" compound has been undertaken, which clearly demonstrated bent bonding, as predicted from cobalt models, but disorder in the oxygen moiety prevented the obtention of a good O—O bond length [212]. While changes in the Soret bands at approximately 450 nm have been used to characterize oxygenation, the spectra cannot easily be interpreted in a more quantitative manner. For the dimeric $Fe_2pts_2O_2$ system, however, it is obvious that spectra of the oxygenated complex much more closely resemble the ferric form than the ferrous [77,218].

The majority of $Fe—O_2$ complexes are diamagnetic consistent with low spin Fe^{II} and $\Delta' O_2$, or $Fe^{III}—O_2^-$ with spin pairing of the odd electrons (either through a super exchange-like process or accidental orbital degeneracy). As previously emphasized, the true situation probably lies between these extremes, more closely approximating to the latter.

A paramagnetic dioxygen derivative of "Fe picket fence" has been prepared [213] but ^{17}O ESR spectra which might yield information on the degree of O_2^- character are not available. It is obvious that further studies are necessary with the iron systems to clear up precisely the effects of ligand σ and π donation (and retrodonation) on oxygen complex stability, culminating hopefully in a

* Basolo and co-workers have examined the reaction $O_2 + Fe(tpp)L_2 \rightarrow Fe(tpp)LO_2$ and found a 5-coordinate species to be the oxygen-active form (233).

precise knowledge of electron distribution in such complexes. The role of solvent environment in stabilization of dioxygen complexation, and of dimerization in complex decomposition also remain to be elucidated fully. Far less has been accomplished in studies of other relevant metal dioxogen systems.

D. COMMENTS AND CONCLUSIONS

Recent reports have appeared of oxygen complexation by Cr^{2+} in zeolites [219] and Cu^{I} in a polymer matrix [220], but simple solution studies are nonexistent, although dioxygen intermediates have been implicated in autooxidation reactions [15]. As before, these results suggest that stable monomeric adducts might be obtained by utilizing dilute low temperature reactions in aprotic solvents, or simply by sterically inhibiting dimerization. Recently Mn^{II}—TPP has been shown to interact with oxygen, presumably in an oxidative addition to yield $Mn^{IV}—O_2^{2-}$ analogous to the Vaska complexes [221]. This mass of data may be rationalized by application of a few simple principles.

First, the metal dioxygen reaction is best viewed as a considerable transfer of electron density from the metal to the dioxygen, with some retrodative π bonding, i.e., the bulk of evidence indicates formal reduction of oxygen. Secondly, the precise extent of this transfer will be determined primarily by the ligands attached to the metal, and secondarily by the solvent environment. Sigma donating ligands (e.g. polyamines, imidazole) will tend to increase the transfer, while π acceptors will compete with oxygen for the available electron density, thus decreasing the degree of bond formation.

This straightforward principle explains a great variety of otherwise diverse data e.g. basicity stability trends [43,174—176], *cis* effects observed in ESR [131] and crystallographic [139—141] studies, as previously discussed in detail. Furthermore it emphasizes a qualitatively simple but important distinction in enzymic systems. By varying the amount of σ donor and π donor and acceptor characteristics of the ligands at the active site, the extent of charge transfer from the central metal to the dioxygen and thus the extent of oxygen activation will vary in a corresponding fashion. This redistribution of electron density may be accomplished not only by changing ligands, but more subtly by changing their orientation with respect to the central metal [222]. For instance, conformational changes which result in different metal—ligand bond distances will change the effective ligand field (and its donor acceptor capabilities) and thus the degree of oxygen activation. Such a distinction easily explains the drastically altered properties of mutant hemoglobins (e.g. HbM Milwaukee), in which the distal histidine is replaced by TYR, as well as offering a qualitative understanding of the activation of dioxygen in oxygenase and oxidase enzymes.

Considering the $Fe^{III}—O_2^-$ model, tyrosine (tyr), which can act as a one electron donor, offers a low energy pathway for iron oxidation:

$$Fe^{III}—O_2^- + tyr^- \rightarrow Fe^{III} + O_2^{2-} + tyr^{\cdot}$$

whereas simple superoxide dissociation

$$Fe^{III}—O_2^- \rightarrow Fe^{III} + O_2^-$$

would be less favorable. Oxidation of hemoglobin in this way by phenols, nitrite, and other one electron donors has recently been examined by Wallace and Caughey [223].

As yet the precise influence of solvent effects on oxygen complexation is unclear, although it appears (with the reservations already noted) that oxygen complexation is stabilized in hydrophobic environments. Thus, changes in residue polarity at or near the active site could markedly affect the degree of oxygen activation [223]. Quantifying these concepts awaits elucidation of the active site of oxidase and oxygenase enzymes, coupled with synthesis and study of better model compounds.

Recent studies by Chang and Traylor [225,226] offer promise of resolving solvent effects using flash photolysis. By this technique, oxygenation rates for simple heme complexes in water have been observed ($k_{on} = 1 \times 10^7$; $k_{off} = 400$), independently of slower oxidation processes. Solvent variation [224] with simple heme systems has shown the "off rate" to be decreased in more polar solvents (as would be expected for a highly polar $Fe^{III}—O_2^-$ bond). Thus the predominant effect of hydrophobicity is probably to decrease the tendency for oxidation, rather than increasing oxygenation, which is favored by polar environments.

One final point to be considered is the relation of mononuclear and binuclear oxygen adducts in biological systems. One interesting hypothesis in this area might be offered. Binuclear dioxygen complexes are found in hemocyanin and hemerythrin, while mononuclear complexation predominates elsewhere.

As has been shown for cobalt, binuclear complexation results in a kinetically relatively stable complex, as $2e^-$ transfer is required to regenerate molecular oxygen. This results in a net shift of the equilibrium constant toward oxygen complexation, much to the favor of the sedentary organisms utilizing these rather primitive systems, where the primary physiological problem is obtaining oxygen rather than its rapid utilization in the tissues. The high equilibrium constant (due to the relatively slow reverse reaction) also allows for slow constant release of oxygen during hibernation of these species.

For less sedentary organisms a mononuclear carrier would seem to be indicated, as a particular problem here is not complexation of oxygen, but its release to the site of utilization at a rate consistent with physiological demand. The faster deoxygenation rate found in these globin proteins fulfills this role (at the expense of requiring more complex respiratory systems). As indicated, this deoxygenation rate is further modified by the presence of the porphine ligand which, by participating in an extended π system, would tend to decrease the extent of the formal redox reaction.

After completion of this review, a preprint describing a detailed study of the electronic spectra of μ-superoxo dicobalt(III) complexes was kindly supplied by H.B. Gray [229]. By analogy to well known $[Co(NH_3)_5X]^{2+}$ complexes, bands in $[Co(NH_3)_5O_2Co(NH_3)_5]^{5+}$ were assigned as follows:

λ_{max}	ϵ	Assignment
800	110	$\pi_h^*(O_2^-) \rightarrow \pi_v^*(O_2^-)$
672	927	$d\pi \rightarrow \pi_v^*(O_2^-)$
480	309	"$^1A_{1g}$" $\rightarrow$ "$^1T_{1g}$"
345	3,450	"$^1A_{1g}$" $\rightarrow$ "$^1T_{2g}$"
302	20,160	$\pi_h^*(O_2^-) \rightarrow dz^2$
225	21,000	$\pi_v(O_2^-) \rightarrow \pi_v^*(O_2^-)$

Thus the suggested ligand field strength for O_2^- is (N bonded) $^-SCN \leqslant O_2^- < NH_3$, which is considerably higher than that found for O_2^{2-} [108] ($H_2O \cong O_2^{2-}$). This conclusion is consistent with the π-acceptor character of O_2^-, which is necessarily absent in O_2^{2-}, in which the π^* orbitals are filled.

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