Interaction of Manganese with Dioxygen and Its Reduced Derivatives

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Contents

I. Introduction

Recognition of the involvement of manganese in biological redox chemistry began in 1970 with the discovery of manganese superoxide dismutase (SOD).[1] The importance of manganese in dioxygen metabolism was further confirmed with the discovery that the oxygen-evolving complex (OEC) in photosystem II, which provides the reducing equivalents for photosynthesis, requires manganese as part of the active site.[2] While Mn(II) had been established in structural roles and as a component of metal ATP complexes,[3,4] these findings of redox activity ushered in the modern era of bioinorganic manganese coordination chemistry. The discovery in the early 1980s that some bacterial catalases required Mn,[5-7] and the subsequent discovery of other Mn-containing redox enzymes such as manganese ribonucleotide reductase (RR),[8,9] have fueled interest in this field and accelerated the progress of understanding during the past 10 years. It is now recognized that manganese interacts with dioxygen and its reduced derivatives in biological systems in numerous ways, making use of a variety of different Mn structures. The nuclearity of Mn sites that interact with O_2^{n-} (n = 0, 1, 2) in biology range from mononuclear (Mn SOD) and binuclear (Mn catalase, Mn RR) to tetranuclear (OEC), making use of the Mn(II), Mn(III), Mn(IV), and possibly, Mn(V) oxidation states. (*In this review we use the term "dioxygen" to mean specifically molecular oxygen, O_2, while the term "Mn–dioxygen adduct" will refer to the general case of Mn bound to O_2^{n-} in any oxidation state.*)

The synthesis and characterization of manganese coordination complexes to model the structure, reactivity, and spectroscopy of manganese in its various oxidation states, with various ligand types and nuclearities, has contributed substantially to our understanding of the role and mechanism of manganese interaction in biological dioxygen chemistry. Initially, much of the work in this field involved the oxygenation of Mn–porphyrin complexes, building on studies of manganese-substituted hemoglobin.[10] Once it was understood that the Mn sites in Mn SOD and the OEC were "non-heme" sites, however, model studies expanded to use Schiff base and other N- and O-donor ligand sets. An extensive research effort has produced structural models for the higher oxidation state sites often by reaction of lower oxidation state precursors with dioxygen. The many Mn coordination complexes which resulted have allowed the effects of various geometric and electronic modifications to the metal coordination sphere to be probed in order to elucidate the rich spectroscopy of the biological Mn sites. Additionally, increased mechanistic understanding of the interaction of dioxygen and its reduced derivatives with the various oxidation states of Mn, primarily through functional models of the Mn catalase and Mn SOD, has proven to be seminal to understanding the enzymatic systems at a more chemical level.

In 1980, Taylor wrote an excellent review[11] on the chemistry of manganese with dioxygen primarily emphasizing the different ligand types that had been used to prepare manganese complexes capable of interaction with dioxygen. After the discovery of the Mn catalase, the field began to mature and this was reflected by another excellent review in 1989 by Wieghardt[12] in which the emphasis was on the structure of manganese sites with varying nuclearity. In this review we attempt to reflect a further maturation of the field through an emphasis on the reactivity of manganese complexes with dioxygen and its reduced derivatives. First we will discuss the structurally defined Mn–dioxygen adducts, of which four have so far been characterized by X-ray crystallography, and the well-established work on peroxide adducts of Mn–porphyrin complexes. We then discuss the reactivity of dioxygen with Mn(II) complexes, functional models of Mn SOD and Mn catalase, and reports of water oxidation to dioxygen by high-valent Mn complexes. Whenever possible, we discuss the proposed mechanisms for these various reactions of manganese with dioxygen and its reduced derivatives. This review will not specifically address the Mn-containing biological systems except to convey the relevance of the model systems, as the biological redox chemistry of manganese has been well covered in a number of recent reviews.[2,13-17] Furthermore, readers are encouraged to examine the Wieghardt review and other contemporaneous references[18-22] to gain a greater appreciation for the structural models of manganese active sites that have been prepared.

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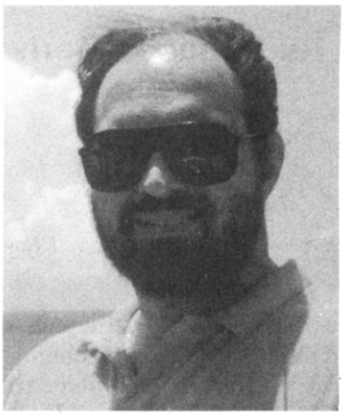

Vincent L. Pecoraro was born in Freeport, NY, in 1956 and received his B.S. degree in Biochemistry from the University of California, Los Angeles, in 1977. He received his Ph.D. in chemistry in 1981 working on microbial and mammalian iron metabolism under Professor Kenneth N. Raymond at the University of California, Berkeley. He then moved to the Biochemistry Department at the University of Wisconsin, Madison, where he was an NIH postdoctoral fellow with Professor W. W. Cleland. Here he used chiral metallonucleotides to probe the mechanism of phosphoryl group transfer in kinases and ATP synthases. In 1984 he joined the faculty at The University of Michigan, Ann Arbor, as an Assistant Professor and was promoted to Professor of Chemistry in 1992. He spent a term at the University of North Carolina, Chapel Hill, as Visiting Associate Professor of Chemistry in 1991. He was a G. D. Searle Biomedical Research Scholar from 1986 to 1989 and received an Alfred P. Sloan Fellowship in 1989. His research interests span a wide range of disciplines which include the biological chemistry of manganese and vanadium, the development and exploitation of metallacrowns for new materials, the molecular genetics of electron-transfer proteins and the *de novo* synthesis of metallopeptides. He has been involved in undergraduate curricular reform and was a recipient of the University of Michigan LS & A Award for Excellence in Undergraduate Instruction in 1991. He also received the University of Michigan Faculty Recognition Award in 1993 for his contributions in science, education, and professional service.

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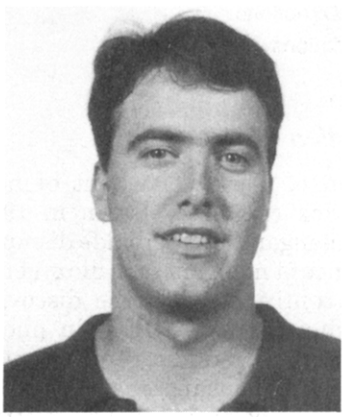


Andrew Gelasco was born in Newton, MA, in 1968. He received his B.S. in Chemistry from The University of Massachusetts while working with Professor Michael Maroney on nickel thiolate complexes. He is currently working toward his Ph.D. at The University of Michigan in the research group of Professor Vincent L. Pecoraro, exploring the reaction mechanisms of model compounds for manganese redox enzymes with oxygen and its redox partners.

II. Structurally Characterized Mn–Dioxygen Adducts

The first dioxygen adduct for a manganese-containing complex was prepared in 1975 by Basolo and co-workers[23] using synthetic manganese porphyrins. These complexes were prepared using *meso*-tetraphenylporphyrin(pyridine)manganese(II), Mn^{II}(TPP)(py), and reacting that species with dioxygen at −78 °C. The Mn–dioxygen adducts were characterized by the changes in the EPR spectrum at 77 K shown in Figure 1 and by observing the splitting of the Soret peak in the UV–vis spectrum. In that report, and studies that followed,[24,25] this reaction with dioxygen was found to be reversible by bubbling N_2 through the solution. This oxygenation–deoxygenation cycle could be repeated several times.

Basolo and co-workers determined the equilibrium constants for the binding of dioxygen to various para-substituted Mn(TPP)(O_2^{n-}) complexes at −78 °C.[26] The series of complexes Mn^{II}(T(*p*-X)PP), where X = H, CH_3, OCH_3, F, and Cl was prepared, and the equilibrium constants for eq 1 were determined, where L = pyridine.

$$Mn^{II}(T(p\text{-}X)PP)(L) + O_2 \rightleftharpoons Mn(T(p\text{-}X)PP)(O_2) + L \quad (1)$$

The log K for the reaction ranged from −5.75 for X = OCH_3 to −6.53 for the Cl derivative. Variable-temperature equilibrium constants were measured for the addition of 4-cyanopyridine to a four coordinate Mn^{II}(TPP). The equilibrium constant for eq 1 when L = various nitrogen donors at −78 °C was also measured and a value of $K_{O_2} = 10^{2.1}$ $Torr^{-1}$ was calculated for the dioxygenation of Mn^{II}(TPP).

The EPR studies of these complexes give insight into the formal oxidation state of the metal and the oxygen species bound to it. The Mn(TPP)(O_2^{n-}) complex is formed by the replacement of pyridine in Mn^{II}(TPP)(py) with dioxygen giving a five-coordinate complex that exhibits an $S = {}^3/_2$ ground state that indicates a Mn(IV) formal oxidation state. The EPR studies were interpreted as ruling out a Mn(II) ($^1O_2$) species or a low-spin Mn(III) superoxide species. Furthermore, the electronic spectrum indicated a large transfer of electron density from manganese to O_2 upon binding. The quartet ground state and an absence of spin density on

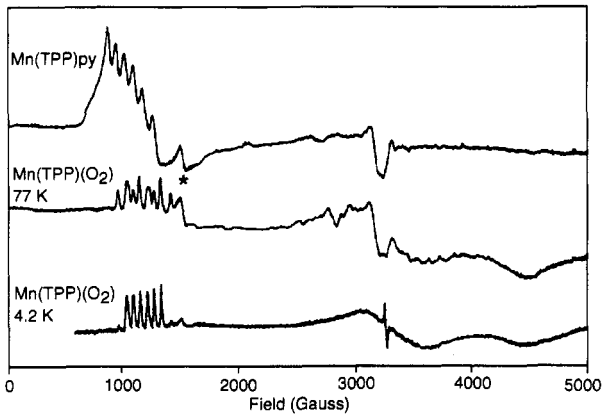


Figure 1. EPR spectra of Mn(TPP)py at 77 K (top), Mn(TPP)(O_2) at 77 K (center), and Mn(TPP)(O_2) at 4.2 K (bottom). (Adapted from ref 23. Copyright 1975 American Chemical Society.)

the O_2^{n-} moiety confirmed the Mn(IV) formulation. The binding mode was still unknown but a simple molecular orbital analysis of the system indicated that the O_2^{n-} was oriented symmetrically in a side-on fashion. These data taken together are consistent with a manganese peroxo formulation such as $Mn^{IV}(TPP)(O_2^{2-})$.

Valentine and Quinn had prepared a dioxygen adduct of $Mn^{III}TPP$ as early as 1976[27] by the reaction of superoxide with the $Mn^{II}TPP$ in dmso. However it was not until 1987 that a manganese–dioxygen adduct was crystallographically characterized. Valentine and co-workers prepared the [peroxotetraphenylporphinato]manganese(III) complex from the reaction of [chlorotetraphenylporphinato]manganese(II) with potassium superoxide in thf.[28] These complexes were both crystallized as monoanions with [K(K222)] (potassium 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8,8]hexacosane) as the cation. ORTEP plots of the Mn(II) precursor and the Mn(III)–peroxo product are shown in Figure 2. These crystal structures conclusively established that the O_2^{n-} moiety was bound in a side-on manner and in the peroxide oxidation level. This observation was in conflict with an earlier spectroscopic analysis of the complex[29] which indicated a manganese(II) species rather than the manganese(III) species was formed. Iterative extended Hückel calculations performed on this Mn(TPP)(O_2^{n-}) complex (like those applied to the $Mn^{IV}TPP(O_2^{2-})$ complexes by Hanson and Hoffman)[30] reconciled those apparent differences.

The second manganese–dioxygen adduct to be crystallographically characterized was a trinuclear μ_3-oxo–manganese(III) complex with a bound μ-peroxo group, $Mn_3(dien)_3(OAc)_2I_3O_3H_2O{\cdot}0.33CH_3OH$.[31] This complex was prepared by the addition of manganese(II) acetate to diethylenetriamine in methanol and precipitating a solid with sodium perchlorate. A crystal structure of this complex is presented in Figure 3, showing the unique μ_3-oxo core and the peroxo bridge. The binding of dioxygen as peroxide is apparently reversible since bubbling dry N_2 through a warmed solution of the complex gives the deoxygenated species and cooling of this solution in the presence of O_2 gives $Mn_3(dien)_3(OAc)_2I_3O_3H_2O{\cdot}0.33CH_3OH$. A binding constant for this process was not reported.

In 1990, Wieghardt and co-workers synthesized the first bis μ_2-O-μ-peroxo-manganese complex by the reaction of $Mn^{II}(ClO_4)_2$ and 1,4,7-trimethyl-1,4,7-triazacyclononane with O_2 in a basic methanol solution at −5 °C.[32] The dinuclear complex $[L_2Mn_2(\mu_2\text{-}O)_2(\mu\text{-}O_2)]^{2+}$ is shown in Figure 4. This complex has a Mn–Mn distance of 2.531 Å, and a peroxo O–O bond length of 1.46 Å that is typical of peroxide bridging transition metals. This complex loses 75% of the bound peroxide as dioxygen at ambient temperatures in aqueous solution, but is stable in CH_3CN for several hours. This release of dioxygen apparently goes through a Mn(III) intermediate that then disproportionates to give a $Mn^{II}L(OH)$ species and the dimeric $Mn^{IV}_2L_2(\mu_2\text{-}O)_3$ species that had been characterized previously.[33] When the complex was placed in solutions containing chloride ions, 100% of the dioxygen was released and a $Mn^{III}(L)Cl_3$ species[33] recovered. This chemistry has been proposed to mimic dioxygen release, the final step in dioxygen production, by a manganese dimer in the "dimer of dimers" model for the oxygen-evolving complex. Recently Wieghardt has examined the kinetics of the release of dioxygen from $[L_2Mn_2(\mu_2\text{-}O)_2(\mu\text{-}O_2)]^{2+}$ in the presence of acid and believes that the complex goes to a Mn(III) dimer, which in turn can bind dioxygen, and therefore shows reversible dioxygen binding.[34]

Recently, Kitajima and co-workers obtained the X-ray crystal structure of the Mn(III)–peroxo complex $\{Mn^{III}[HB(3,5\text{-}iPr_2pz)_3](3,5\text{-}iPr_2pzH)(\eta^2\text{-}O_2^{2-})\}$.[35] The peroxo is bound side-on (Figure 5), as in the Mn–porphyrin complexes, although the Mn is bound to a non-porphyrin ligand system containing four pyrazole donors. The O–O distance is 1.428 Å, consistent with its formulation as peroxide. The complex is thermally unstable and decomposes at room temperature to a $[Mn^{III}L(\mu\text{-}O)]_2$ complex, which has been structurally characterized (*vide infra*).[36] Otherwise, the peroxo complex does not appear to be very reactive, oxidizing $(CH_3)_2SO$ to $(CH_3)_2S(O)_2$ in low yield (5–10%), and oxidizing PPh_3 in about 20% yield.

In summarizing the crystallographically characterized Mn–dioxygen adducts one notes that the best description for each compound is a metal–peroxo complex. This observation is independent of formal manganese oxidation state [Mn(III) or Mn(IV)], nuclearity (monomer through trimer), or metal–metal separation (2.54 to 3.3 Å). Thus, while the complexation of dioxygen to manganese as superoxide or dioxygen is quite reasonable, these binding modes have yet to be identified by X-ray crystallography. The important structural parameters for the four crystallographically characterized dioxygen adducts are presented in Table 1.

III. Reactions of Mn with Dioxygen

A. Reversible O_2 Binding

In addition to the four structurally defined Mn–peroxide complexes and the other well-defined Mn(porphyrin)(O_2^{2-}) complexes described above, a number of other Mn–dioxygen adducts have been reported in the literature, although most lack definitive evidence for the proposed structures. A series of complexes related to the manganese porphyrins is the manganese phthalocyanines.[37-40] Manganese phthalocyanine was first observed to bind dioxygen in a pyridine solution in 1959 by Elvidge and Lever.[37] This work was revisited by Uchida et al. in 1978[38] and in more

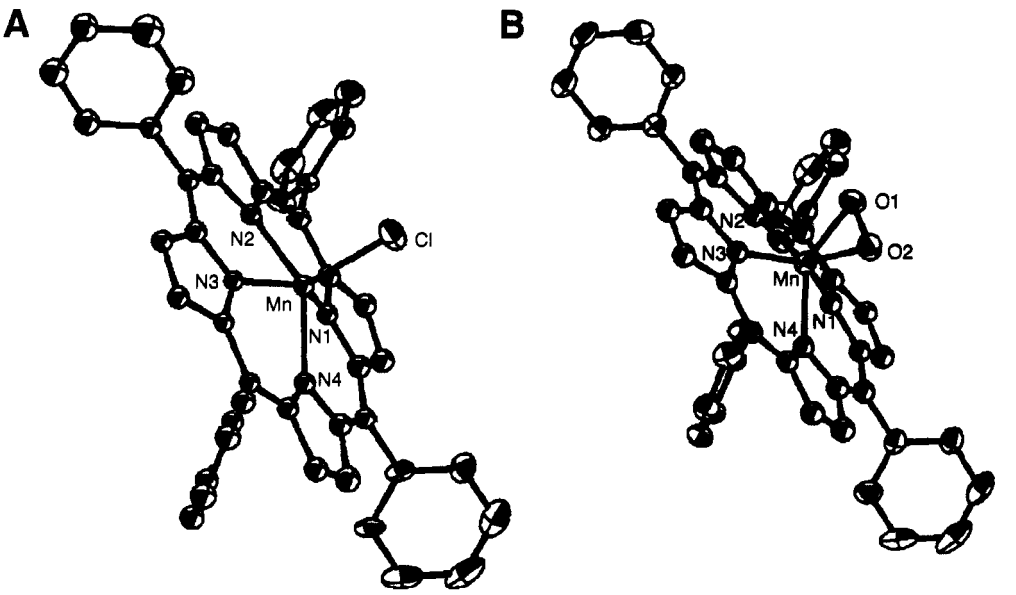


Figure 2. Molecular structures of (A) $Mn^{II}(TPP)Cl^-$ and (B) $Mn^{III}(TPP)(O_2)^-$ derived from X-ray crystallography. (Adapted from ref 28. Copyright 1987 American Chemical Society.)

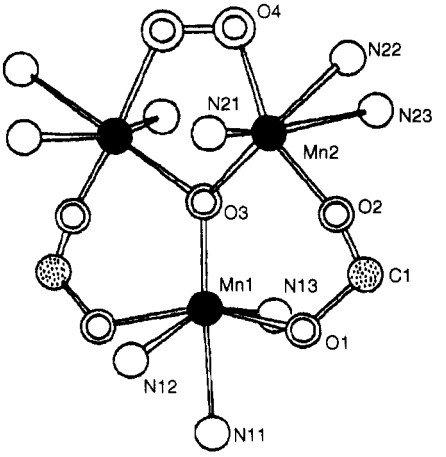


Figure 3. Molecular structure of $Mn^{III}_3(dien)_3(\mu\text{-}OAc)_2(\mu_3\text{-}O)(\mu\text{-}O_2)^{3+}$ derived from X-ray crystallography. (Adapted from ref 31. Copyright 1988 American Chemical Society.)

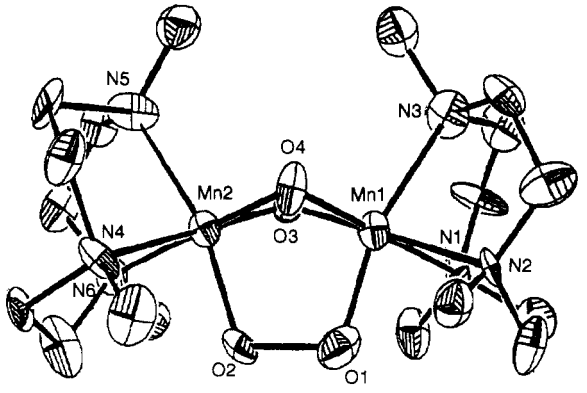


Figure 4. Molecular structure of $[Mn^{IV}_2L_2(\mu\text{-}O)_2(\mu\text{-}O_2)]^{2+}$ (L = 1,4,7-trimethyl-1,4,7-triazacyclononane) derived from X-ray crystallography. (Adapted from ref 32. Copyright 1990 American Chemical Society.)

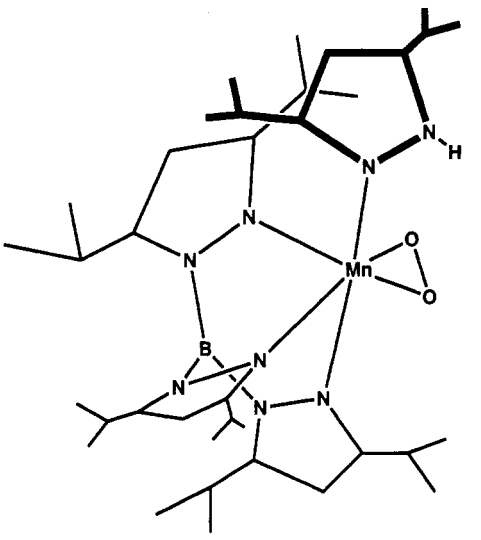


Figure 5. Drawing of the structure of $[Mn^{III}(HB(3,5\text{-}iPr_2pz)_3)(3,5\text{-}iPr_2pzH)(O_2)]$ based on the structure derived from X-ray crystallography. (Adapted with permission from Kitajima et al., ref 35).

detail by Lever and co-workers in 1979.[39] The latter examined the oxygenation of $Mn^{II}Pc$ in dma solutions and characterized the products by UV–visible, IR, and EPR spectroscopies, and using variable-temperature magnetic suceptibility. They proposed that the dioxygen binds end on as superoxide based on a weak band in the IR spectrum of the solid at 1154 cm^{-1} ($^{16}O_2$) and 1094 cm^{-1} ($^{18}O_2$). The complex was formulated as $PcMn^{III}(O_2^-)$ with some partial spin coupling between metal and superoxide. The manganese(III) phthalocyanine superoxo complex apparently also exhibited reversible dioxygen binding and oxygenase ability. Dioxygen is released and the Mn(II) complex is reformed when a suspension of the complex in dma was illuminated in vacuo with visible light. In this case, the dioxygen was measured by mass spectroscopy. However, when trace amounts of dimethyl amine or triethyl amine were present in solution the manganese(III) phthalocyanine superoxo complex converted back to $PcMn^{II}$ with no evolution of dioxygen, instead apparently oxygenating the amine.

The dioxygen adduct of the Mn complex of the tetrasulfonated Pc, $MnTsPc(O_2^{n-})$, has also been prepared,[40] and an apparent pH dependence for the mode of dioxygen binding was suggested. At pH 9, the O–O stretch in the vibrational spectrum was seen at 1702

Table 1. Structural Parameters for Crystallographically Characterized Mn–O_2 Adducts

Mn–O_2 adduct	Mn–Mn distance (Å)	Mn–O distance (Å)	O–O distance (Å)	Mn oxidation state	ref
$[Mn(TPP)(O_2)]^-$	n/a	1.901(4) 1.888(4)	1.421(5)	III	28
$Mn_3(dien)_2(OAc)_2I_3O_3H_2O\cdot 0.33CH_3OH$	3.32(3) Mn1–Mn2 3.14(4) Mn2–Mn2	2.0(1) Mn2–O4 1.8(1) Mn1–O3 1.9(1) Mn2–O3	1.6(1)	III	31
$[L_2Mn_2(\mu\text{-}O)_2(\mu\text{-}O_2)]^{2+}$ (L = 1,4,7-trimethyl-1,4,7-triazacyclononane)	2.531(7)	1.83(2) peroxo 1.81(2) oxo	1.46(3)	IV	32
$[Mn(HB(3,5\text{-}iPr_2pz)_3)(3,5\text{-}iPr_2pzH)(O_2)]$	n/a	1.851(5)	1.428(7)	III	35

cm^{-1} ($^{16}O_2$) and 1655 cm^{-1} ($^{18}O_2$), indicating a dioxygen formulation, while at higher pH and in the solid, these features are at 1135 cm^{-1} ($^{16}O_2$) and 1050 cm^{-1} ($^{18}O_2$), indicating a superoxide formulation. Nakamoto has observed[41] the IR spectrum of an Ar matrix of $Mn(Pc)(O_2^{n-})$, and identified a strong band corresponding to the O–O stretch at 992 cm^{-1} ($^{16}O_2$) or 935 cm^{-1} ($^{18}O_2$), similar to those he observed for the $Mn(TPP)(O_2^{2-})$ with a side-on bound peroxide (*vide supra*). He also observed these bands at 991 cm^{-1} ($^{16}O_2$) and 934 cm^{-1} ($^{18}O_2$) for $Mn(OEP)(O_2)$, indicating that it has a similar structure to $Mn(TPP)(O_2)$. The vibrational data on these isotopically substituted adducts definitively establishes an O_2^{n-} complex, but leaves unclear the question of the formal oxidation state for the bound O_2^{n-}.

Coleman and Taylor prepared a Mn(II) complex of the ligand 5-NO_2-salrdpt which readily reacts with O_2 in toluene to produce a Mn(III) complex which they formulated as $[Mn(5\text{-}NO_2\text{-salrdpt})]_2(O_2^{2-})$.[42] An IR band assigned as an Mn–O stretch was observed at 620 cm^{-1}; however, the corresponding band for an O–O stretch was not reported. Upon heating to 150 °C, the complex decomposed to a Mn(II) compound with the apparent loss of dioxygen. Hendrickson and co-workers observed[43] an EPR signal spread out over 5000 G in solutions of the product of dioxygen reaction with the Mn(II) complex of 5-NO_2-saldien, a ligand very similar to 5-NO_2-salrdpt, in dmf. On the basis of this EPR data, they assigned the resulting complex as a peroxide-bridged mixed-valent Mn(II,III) dimer. No quantitation of the EPR signal compared to the concentration of manganese in solution was described. Recently, Armstrong and co-workers reported the crystal structure for the Mn(III) complex $[Mn_2O(5\text{-}NO_2\text{-saldien})_2]$,[44] prepared by addition of O_2 to Mn^{II}(5-NO_2-saldien) in aceonitrile and obtained as crystalline material in 54% yield. The crystal structure in Figure 6 shows a Mn(III) dimer bridged by a single μ-oxo, not a μ-peroxo group. Like the Mn(III) complex of 5-NO_2-salrdpt and consistent with similar observations by Hendrickson, this complex decomposes to the Mn(II) precursor upon heating, although attempts to observe dioxygen evolution were unsuccessful. It is likely therefore that the complex formulated as $[Mn^{III}(5\text{-}NO_2\text{-salrdpt})]_2(\mu\text{-}O_2)$ has the μ-oxo structure as well.

Sawyer and co-workers have described the preparation of a dioxygen adduct of a Mn complex of 3,5-di-*tert*-butylcatecholate (dtbc).[45–47] However, some controversy has surrounded this chemistry.[48,49] Sawyer proposed that oxidation of some of the catecholate ligands to their semiquinones (dtbsq) occurs in the dioxygen adduct, initially formulated as $[Mn^{IV}(dtbc)_2(dtbsq)(O_2^-)]^{2-}$. However, Cooper suggested[48] that the

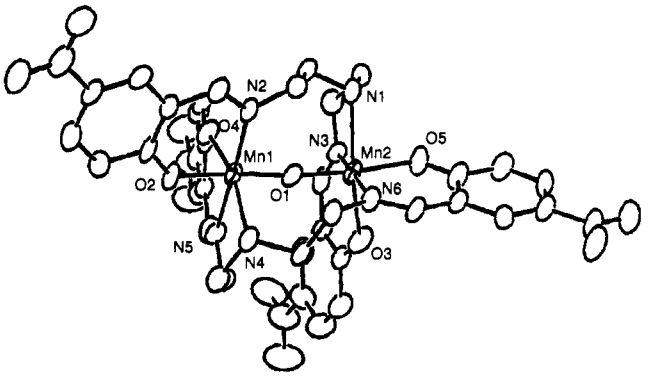


Figure 6. Molecular structure of $[Mn^{III}_2(\mu\text{-}O)(5\text{-}NO_2\text{-saldien})_2]$ derived from X-ray crystallography. (Adapted from ref 44. Copyright 1990 American Chemical Society.)

evidence for the reversible dioxygen adduct was more consistent with further oxidation of the free semiquinone, without formation of a dioxygen adduct. Upon repeating the absorption experiments, Sawyer maintained that the evidence does suggest a dioxygen adduct,[49] although he later reformulated this compound as $[Mn^{III}(dtbc)(dtbsq)_2(O_2^-)(OH)]^{3-}$.[47] It is clear that the chemistry of these complexes is very complicated and has not been well defined. The above two examples of proposed dioxygen adducts show that neither the apparent reversible uptake and release of dioxygen to regenerate the starting material nor reversible changes in the absorption spectra are sufficient to define a Mn–dioxygen adduct convincingly. More definitive evidence such as the X-ray crystal structures reported in section II or an isotopic shift of an O–O stretch in the vibrational (Raman or infrared) spectra discussed above are necessary for unambiguous assignment of Mn–dioxygen adducts.

Recently, Horwitz suggested $[Mn^{IV}(5\text{-}OCH_3\text{-salpn})(O_2^{2-})]$[50] was the product of the reaction of O_2 with Mn^{II}(5-OCH_3-salpn) in dmf at −30 °C. This assignment is based on the similarity of a six-line feature at around $g = 5$ in its EPR spectrum to the spectra of the well-characterized Mn(porphyrin)(O_2^{2-}) complexes.

The above complexes contain ligands of potential biological relevance. A series of manganese systems with less biological relevance has been proposed by McAuliffe and co-workers to effectively and reversibly absorb and desorb dioxygen over 400 times without apparent sample decomposition.[51–54] These systems cover the series of complexes $[Mn^{II}X_2(PR_3)]$ [X = Cl, Br, I; R_3 = (alkyl)$_3$, Ph(alkyl)$_2$, and Ph_2(alkyl)] with the order of O_2 reactivity being (alkyl)$_3$ > Ph(alkyl)$_2$ > Ph_2(alkyl) and Cl > Br > I. The complexes of PPh_3 do not react with O_2. The reversible dioxygen binding appears to take place either for the solid or in nonprotic solvents such as thf or toluene with equilibrium binding con-

stants, K_{O_2}, of (5–50) × 10^{-3} $Torr^{-1}$ in toluene and (50–200) × 10^{-3} $Torr^{-1}$ in thf. They interpret the EPR spectra of the dioxygen adducts as having an $S = {}^5/_2$ spin state and thus a Mn(II) oxidation state, suggesting that the bound dioxygen is not reduced by the Mn(II). They proposed an octahedral $Mn^{II}X_2(PR_3)(thf)_2(O_2)$ structure in the coordinating solvent thf and a tetrahedral $Mn^{II}X_2(PR_3)(O_2)$ in toluene and the solid state, with the O_2 binding end-on in each case. As in the cases of the other complexes discussed in this section, there has been no direct, definitive evidence for the presence of a Mn–O_2 structure in this system. For some of the complexes with P(alkyl)$_3$, the reaction with dioxygen is not reversible. For example, the reaction of $MnI_2(PPr_3)$ with dioxygen results in the structurally characterized $Mn_4(\mu_4\text{-}O)(\mu_2\text{-}I)_6(PPr_3)_4$.[55]

B. Nonreversible Dioxygen Reactions

It has been shown that, in general, Mn(II) complexes of neutral nitrogen donor ligands tend to be less likely to react with dioxygen than complexes with anionic oxygen donor ligands.[11] Unfortunately, the oxygenation products of these oxygen donor complexes have seldom been well characterized. The most thoroughly studied system is the reaction of Mn^{II}salpn with dioxygen. Taylor proposed a Mn(III)–O_2^{2-}–Mn(III) complex, formed from an initial $Mn^{III}(O_2^-)$ intermediate, which eventually decomposes to a $[Mn^{IV}(salpn)O]_2$ complex, as described by eqs 2–4:[56]

$$Mn^{II}(salpn) + O_2 \rightarrow Mn^{III}(salpn)(O_2^-) \quad (2)$$

$$Mn^{III}(salpn)(O_2^-) + Mn^{II}(salpn) \rightarrow [Mn^{III}(salpn)(\mu\text{-}O_2^{2-})]_2 \quad (3)$$

$$[Mn^{III}(salpn)(\mu\text{-}O_2^{2-})]_2 \rightarrow [Mn^{IV}(salpn)(\mu_2\text{-}O)]_2 \quad (4)$$

Horwitz has done electrochemical studies on the reactions of the complexes $[Mn^{II}(salpn)]$ and $[Mn^{III}(salpn)]^+$ with dioxygen to form $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$.[50,57] Exposure of slurries of the Mn(II) complexes to O_2 causes oxidation to the $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ complex, while application of a reducing potential to the corresponding Mn(III) Schiff base complexes in the presence of O_2 causes rapid formation of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$. Horwitz proposed that a $[Mn^{IV}(salpn)(O_2^{2-})]$ species is initially generated in the reaction of $Mn^{II}(salpn)$ with O_2:[50]

$$Mn^{II}(salpn) + O_2 \rightarrow Mn^{IV}(salpn)(O_2^{2-}) \quad (5)$$

$$Mn^{IV}(salpn)(O_2^{2-}) + Mn^{II}(salpn) \rightarrow [Mn^{IV}(salpn)(\mu_2\text{-}O)]_2 \quad (6)$$

This dioxygen adduct then combines with 1 equiv of $Mn^{II}(salpn)$ to give the product dimer, as in eq 6. The first step of the electrochemically induced reaction of $Mn^{III}(salpn)^+$ with O_2 is proposed to be reduction of an equivalent of $Mn^{III}(salpn)^+$ to $Mn^{II}(salpn)$, eq 7, followed by reaction 5 above. A second reduction, of another

$$Mn^{III}(salpn)^+ + e^- \rightarrow Mn^{II}(salpn) \quad (7)$$

equivalent of $Mn^{III}(salpn)^+$ to $Mn^{II}(salpn)$, followed by reaction 6 to form the product dimer would then occur. Alternatively, the $Mn^{IV}(salpn)(O_2^{2-})$ intermediate may be reduced to a negatively charged $[Mn(salpn)(O_2^{n-})]^-$, which would react with 1 equiv of $Mn^{III}(salpn)^+$ to form the $[Mn^{III}(salpn)(\mu\text{-}O_2^{2-})]_2$ complex proposed by Taylor,[56] eqs 8 and 9:

$$Mn^{IV}(salpn)(O_2^{2-}) + e^- \rightarrow [Mn(salpn)(O_2^{n-})]^- \quad (8)$$

$$[Mn(salpn)(O_2^{n-})]^- + Mn^{III}(salpn)^+ \rightarrow [Mn^{III}(salpn)(\mu\text{-}O_2^{2-})]_2 \quad (9)$$

On the basis of their electrochemical results, Horwitz and co-workers[50] prefer the reaction scheme which includes exclusively eq 7 for the electrochemical reductions [that is, in the order (7) → (5), (7) → (6)] rather than including eqs 8 and 9.

Under reaction conditions in which the primary product of the reaction between $Mn^{II}(salpn)$ and O_2, $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$, is insoluble, the yield is 100%. However, under conditions in which it is soluble, side reactions with the Mn(II) starting material may occur and the reaction is not as clean. Under such conditions an additional tetrameric Mn(III) product has been proposed,[57] although the evidence for this formulation, particularly the nuclearity, is open to interpretation.

While reversible dioxygen binding to Mn porphyrins has been discussed in detail above, irreversible oxidation products result when Mn porphyrins are reacted with dioxygen or superoxide in nondonating solvents. In 1987, Dismukes showed that the primary product of the air oxidation of $Mn^{II}TPP$ in chlorobenzene was a monooxo-bridged mixed-valent Mn(II,III) complex.[58] Monitoring the reaction progress by EPR at 10 K he observed the transition from a $g = 6$ signal (typical for a $Mn^{II}TPP$ species[24]) through a narrow free-radical spectrum to a 16-line "multiline" spectrum with a field width of 1410 G. Simulation of the observed spectrum and a comparison to a mixed-valent Mn(III,IV) complex from the decomposition of $(Mn^{IV}(TPP)X)_2O$ (where X = N_3, OCN, or OI(Br)Ph$^-$)[59,60] indicated that the spectrum observed was due to a $[(TPP)Mn^{II}OMn^{III}(TPP)]$ or a $[(TPP)Mn^{II}OOMn^{III}(TPP)]^-$ species. Both $Mn^{II}TPP$ and O_2 are required for the formation of the mixed valent complex and a proposed mechanism for the reaction is shown through the following equations:

$$[Mn^{II}(TPP)] + O_2 \rightarrow [Mn^{III}(TPP)]^+ + O_2^- \quad (10)$$

$$[Mn^{II}(TPP)] + O_2^- \rightarrow [Mn^{III}(TPP)O_2]^- \quad (11)$$

$$[Mn^{II}(TPP)] + [Mn^{III}(TPP)O_2]^- \rightarrow [(TPP)Mn^{II}OOMn^{III}(TPP)]^- \quad (12)$$

$$[(TPP)Mn^{II}OOMn^{III}(TPP)]^- \rightarrow [Mn^{IV}(TPP)O] + [Mn^{III}(TPP)O]^- \quad (13)$$

$$[Mn^{II}(TPP)] + [Mn^{IV}(TPP)O] \rightarrow [(TPP)Mn^{III}OMn^{III}(TPP)] \quad (14)$$

$$[Mn^{II}(TPP)] + [Mn^{III}(TPP)O]^- \rightarrow [(TPP)Mn^{II}OMn^{III}(TPP)]^- \quad (15)$$

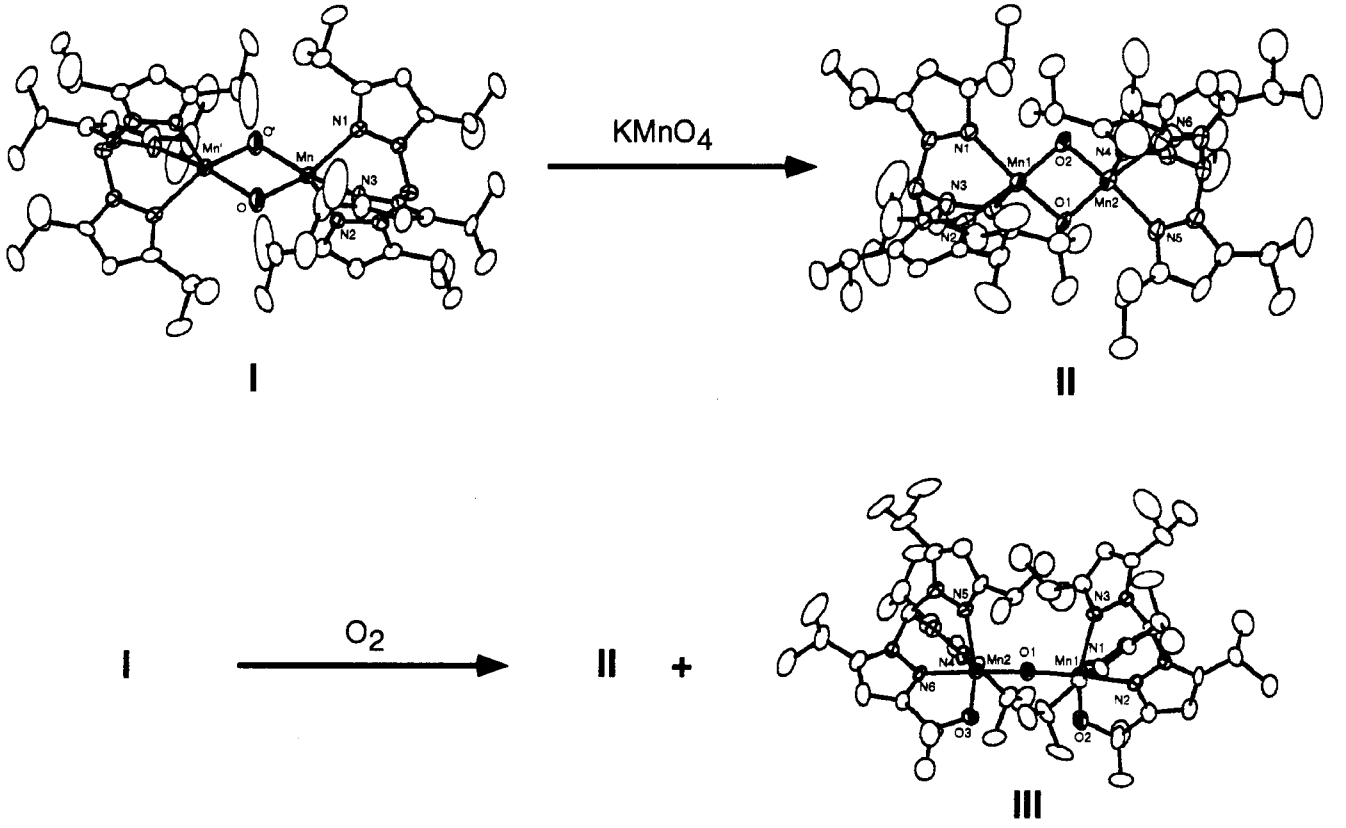


Figure 7. Reaction scheme for oxidation of $[Mn^{II}(HB(3,5\text{-}iPr_2pz)_3)(\mu\text{-}OH)]_2$ (I) with $KMnO_4$ (top) and O_2 (bottom). (Molecular structures of I, II ($[Mn^{II}(HB(3,5\text{-}iPr_2pz)_3)(\mu\text{-}O)]_2$), and III (dioxygenase product of I, described in text), derived from X-ray crystallography, are adapted from ref 36 and 62. Copyright 1991 American Chemical Society.)

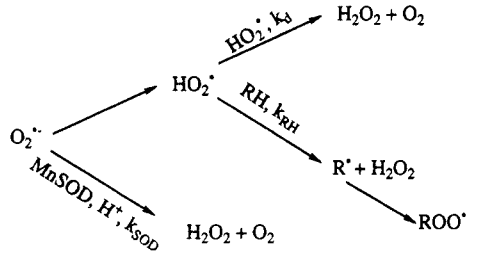
While the EPR experiments and simulations indicated a Mn(II,III) species the authors were unable to distinguish between the product of eq 12 or eq 15 as the source of the EPR multiline signal.

Perrée-Fauvet and co-workers have also done studies of $Mn^{II}(TPP)$ and $Mn^{III}(TPP)^+$ with superoxide.[61] They were able to show that two different species were formed dependent on the concentration of superoxide in solution. In these studies the two species were determined to be $[Mn^{III}(TPP)O_2]^-$ (EPR silent) formed by the reaction of 1 equiv of $O_2^{\bullet-}$ and $Mn^{II}(TPP)(py)$, and Mn(III,IV) dimeric species (16-line EPR signal) formed by the addition of 0.5 equiv of $O_2^{\bullet-}$ to $Mn^{II}(TPP)(py)$ or excess $O_2^{\bullet-}$ to $Mn^{III}(TPP)Cl$. In addition to the characterization of these complexes by EPR and visible spectroscopy, electrochemical measurements (linear voltametry and cyclic voltametry) showed the two species to have comparable thermodynamic stabilities. Both species have reduction potentials at approximately −1400 mV vs SCE in DMSO with the $[Mn^{III}(TPP)O_2]^-$ showing a one-electron reduction, and the Mn(III,IV) dimer having a two-electron reduction.

In addition to the reactions of superoxide with Mn porphyrins Perrée-Fauvet also reproduced the experiments of Dismukes and co-workers[58] (*vida supra*) reacting $Mn^{II}(TPP)$ with dioxygen in C_6H_5Cl. He found that the EPR signal observed for the product of this reaction, postulated as $[(TPP)Mn^{II}\text{-}O_x\text{-}Mn^{III}(TPP)]^-$, is not temperature dependant (giving the same spectrum at 110 K as observed at 10 K) and that it indeed is different from the dimer mixed-valent species formed upon reaction of $Mn^{III}(TPP)Cl$ with superoxide. Perrée-Fauvet and co-workers also observed that if this air oxidation of $Mn^{II}(TPP)$ is performed in toluene instead of chlorobenzene the only EPR-active product is a small amount of the Mn(III,IV) dimeric complex formed from the reaction of $Mn^{III}(TPP)Cl$ with superoxide. These results show the solvent dependence of these reactions. In addition to the solvent dependence observed, the type of reduced oxygen species used, the temperature of the reaction, and the presence or absence of an axial ligand have all been shown to influence the product formation from dioxygen with Mn porphyrins. It has also been shown that many of these species are of comparable thermodynamic stability and under varying conditions can interchange.[61]

Kitajima and co-workers have recently observed interesting Mn–dioxygen chemistry using the ligand $[HB(3,5\text{-}iPr_2pz)_3]$. They prepared the complex $[Mn^{II}(HB(3,5\text{-}iPr_2pz)_3)(\mu\text{-}OH)]_2$ (structure I in Figure 7) which can be oxidized by either $KMnO_4$ or O_2 to $[Mn^{III}(HB(3,5\text{-}iPr_2pz)_3)(\mu\text{-}O)]_2$ (structure II in Figure 7).[36] With $KMnO_4$, the reaction proceeds in about 90% yield. With O_2 as the oxidant, however, much lower yields (50%) are obtained with additional side products. The primary side product (38% yield) was structurally characterized by X-ray crystallography.[62] It was found to be a Mn(III) dimer bridged by a single oxo bridge, in which one iPr group of each ligand has been oxygenated and coordinates as an alkoxo group to Mn (structure III in Figure 7). Isotope labeling studies show that the bridging oxo group comes from one of the hydroxo bridges of the Mn(II) dimer, while both alkoxo oxygens originate from the same dioxygen molecule. The mechanism for the formation of this product is suggested to proceed through a (μ-peroxo)bis(μ-hydroxo)Mn^{III} dimer, then a (μ-peroxo)(μ-oxo)Mn^{III} dimer with loss of H_2O, followed by a (μ-oxo)Mn^{IV}=O dimer

Scheme 1



which oxygenates one alkyl group of each ligand to produce the (μ-oxo)Mn^{III} dimer with coordination by the newly formed alkoxides of the oxygenated ligands. The isotope labeling studies indicate that the dimer remains intact once the dioxygen binds to the Mn(II) dimer.

IV. Dioxygen-Producing Systems

A. Reactions with Superoxide

Since the discovery in 1969 that superoxide ion (O_2^-) is a common intermediate of aerobic respiration,[63] compounds that disproportionate superoxide and that are stable under physiological conditions have been sought as therapeutic agents for oxygen reperfussion injury. In 1976, Sawyer and co-workers[64] found that tris(picolinato)Mn^{II} was a reasonable functional model for the Mn-containing SOD's of mitochondria. They carried out most of their reactivity studies in dmso, which can be considered a model matrix for the biomembranes in which superoxide is formed. In this case, the concentration of the ion O_2^-, not $HO_2^\bullet$, is controlled, which is a better model for the enzymatic activity. It is believed that $HO_2^\bullet$ can oxidize and peroxidate lipids (e.g. linoleic and arachidonic acid esters), which in biomembranes is probably the most harmful reaction of superoxide. In this view, controlling the concentration of the ion and preventing its protonation are the important enzymatic functions of SOD's. Yamaguchi et al. found that tris(picolinato)-Mn^{II} was effective at disproportionating O_2^- before it can extract a proton from an organic substrate, a reaction that is competitive with autodisproportionation of $HO_2^\bullet$. Their functional model for MnSOD was 2 orders of magnitude faster at scavenging O_2^- than the disproportionation of $HO_2^\bullet$. A scheme for the catalytic reactions is shown in Scheme 1.

Complexes formed by reaction of hydrated manganese dioxide [$Mn^{IV}(OH)_4$] with the linear trihydroxamic acid, desferrioxamine B (desferal) have been claimed by Fridovich and co-workers to decompose superoxide.[65-67] Two complexes have been prepared: a green complex prepared from $Mn^{IV}(OH)_4$ and desferal and a pink complex formed with addition of ascorbate to protect the ligand from oxidation. The green complex was formulated by Fridovich as a Mn(III) complex with one of the three hydroxamate groups of desferal oxidized and unbound. However Rush et al. have purified the complex by column chromatography and shown by UV–vis, EPR, electrochemistry, and magnetic susceptibility that the correct oxidation state is Mn(IV) and that the complex is oligomeric in solution, probably as oxo-bridged [Mn^{IV}(desferal)(μ-O)]$_n$.[68] The pink complex is even more poorly characterized, although a Mn(II) formulation seems likely. The catalytic rate constant of the green complex for superoxide dismutase activity is $1.7 \times 10^6\ M^{-1}\ s^{-1}$, about 1% of Mn(SOD) activity, and about 10% of the rate constant for manganese(II) nitrilotriacetate ($2.2 \times 10^7\ M^{-1}\ s^{-1}$).[68] The nitrilotriacetate complex requires excess ligand, however, to assure binding of all of the manganese, while 1 equiv of desferal completely binds the manganese. The activity of the pink complex is somewhat greater than that of the green complex.[66] Rush et al. propose a mechanism[68] for the superoxide dismutase activity of [Mn^{IV}(desferal)(O)]$_n$ whereby superoxide and water react with the oligomer to remove a Mn^{III}(desferal)-(OH) complex, leaving the broken oxo bridge on the oligomer protonated and releasing dioxygen. This is followed by a series of ligand displacement, disproportionation, and superoxide and dioxygen reaction steps to regenerate the $Mn^{IV}(OH)_4$ and desferal starting materials for further reaction.

The metal ion in both the Mn and Fe superoxide dismutases has a trigonal bipyramidal ligand array, with two histidines and a carboxylate in the equatorial positions and an additional histidine and a solvent-derived hydroxide or water in the axial positions.[69] A crystal structure of the azide-bound derivative of Fe-(SOD) shows that small molecules may bind to the active-site metal making it six coordinate.[70] This suggests direct binding of superoxide to the metal site during the catalytic disproportion cycle.

Recently, Kitajima and co-workers prepared two functional and structural mimics for the Mn-containing superoxide dismutase from the reactions of Mn(Cl)-[HB(3,5-$iPr_2pz)_3$] and Mn(Cl)(3,5-iPr_2pz)[HB(3,5-iPr_2-$pz)_3$] with sodium benzoate yielding the five coordinate Mn(II) complexes: Mn(OBz)[HB(3,5-$iPr_2pz)_3$] and Mn(OBz)(3,5-iPr_2pz)[HB(3,5-$iPr_2pz)_3$], respectively.[71] Mn(OBz)[HB(3,5-$iPr_2pz)_3$] has the benzoate group binding in a bidentate mode, whereas Mn(OBz)(3,5-iPr_2pz)[HB(3,5-$iPr_2pz)_3$] has only one of the oxygen atoms of the benzoate group bound and the other hydrogen bonded to a proton on the 3,5-iPr_2pz moiety. The latter complex has been crystallographically characterized and is represented in Figure 8. The SOD activity of the complexes was determined using the common xanthine–xanthine oxidase–nitro blue tetrazolium (NBT) method. These complexes are very efficient functional mimics, especially when compared to other manganese complexes previously reported as functional models.

B. Reactions Involving Hydrogen Peroxide

1. *$Mn^{IV}_2(\mu$-O)$_2$ Chemistry*

The chemistry of Mn with the Schiff base (SB) ligands H_2salen and H_2salpn has been studied extensively for nearly two decades. One of the earliest structural reports of high-valent materials was that of a dinuclear complex that was described by Maslen and Waters as [Mn^{III}(salpn)(μ-OH)]$_2$.[72] It was felt at the time that the lower valent formulation was more likely the true oxidation level since coordination complexes of manganese(IV) were relatively unknown. Boucher and Coe prepared similar Schiff base complexes which they initially formulated[73] as [Mn^{IV}(SB)(μ-O)]$_2$ and subsequently reformulated[74] as [Mn^{IV}(SB)(μ-O,μ-OH)(SB)-

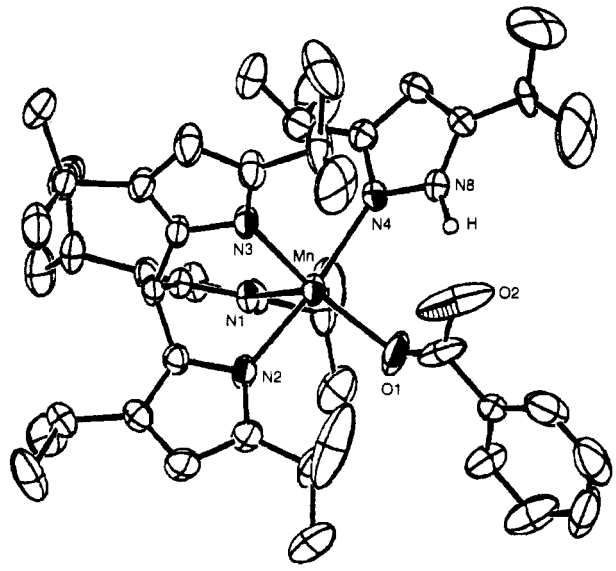


Figure 8. Molecular structure of Mn(OBz)(3,5-iPr_2pz)(HB(3,5-iPr_2pz)$_3$) derived from X-ray crystallography. (Adapted from ref 71. Copyright 1993, American Chemical Society.)

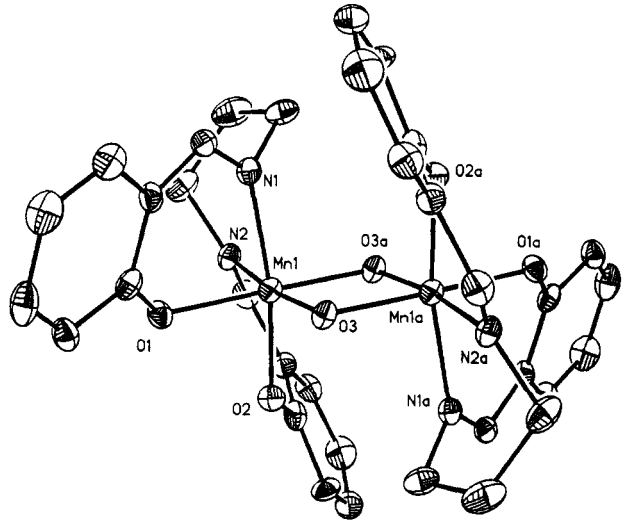


Figure 9. Molecular structure of $[Mn^{IV}(salpn)(\mu\text{-}O)]_2$ derived from X-ray crystallography. (Adapted from ref 75. Copyright 1991 American Chemical Society.)

Mn^{III}]. The similarities of these compounds to $Mn^{IV}_2(\mu_2\text{-}O)_2$ complexes (shown in Figure 9) studied in our group[75,76] and others,[57,77] however, demonstrates that the $[Mn^{IV}(SB)(\mu\text{-}O)]_2$ description is correct. Boucher and Coe suggested[74] the reactions in eqs 16–19 to explain the formation of the bis(μ-oxo) dimers from a Mn(III) precursor:

$$2\{[Mn^{III}(SB)(H_2O)]^+ + OH^- \rightleftharpoons Mn(SB)OH + H_2O\} \quad (16)$$

$$2Mn(SB)(OH) \rightleftharpoons [Mn^{III}(SB)(\mu\text{-}OH)]_2 \quad (17)$$

$$[Mn^{III}(SB)(\mu\text{-}OH)]_2 + 2OH^- \rightleftharpoons [Mn^{III}(SB)(\mu\text{-}O)]_2^{2-} + 2H_2O \quad (18)$$

$$[Mn^{III}(SB)(\mu\text{-}O)]_2^{2-} + {}^1/_2O_2 + H_2O \rightarrow [Mn^{IV}(SB)(\mu\text{-}O)]_2 + 2OH^- \quad (19)$$

Upon addition of 2 equiv of dilute $HClO_4$ to these complexes in acetone solutions at 0 °C, Boucher and Coe report the chemical detection of hydrogen peroxide and the isolation of 62% of the manganese in solution as the $[Mn^{III}(SB)H_2O]^+$ material from which the bis(μ-oxo) dimers were prepared. They formulated this reaction as indicated in eqs 20 and 21:

$$[Mn^{IV}(SB)(\mu\text{-}O)]_2 + 2H^+ \rightarrow [Mn^{IV}(SB)(\mu\text{-}OH)]_2^{2+} \quad (20)$$

$$[Mn^{IV}(SB)(\mu\text{-}OH)]_2^{2+} + 2H_2O \rightarrow 2\,[Mn^{III}(SB)(H_2O)]^+ + H_2O_2 \quad (21)$$

They point out that the total of eqs 16–21 gives:

$$2H^+ + 2OH^- + {}^1/_2O_2 \rightarrow H_2O_2 + H_2O \quad (22)$$

which when rearranged is essentially the reverse of the catalase (hydrogen peroxide disproportionation) reaction (eq 23), promoted by Mn(III):

$$H_2O + {}^1/_2O_2 \rightarrow H_2O_2 \quad (23)$$

In addition to the reaction of Mn^{II}salpn with O_2 described in section III.B, $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ can be prepared from Mn^{III}salpn precursors. The complex $[Mn^{III}(salpn)(CH_3OH)_2]ClO_4$ will react with dioxygen only if reduced, as described in section III.B, or in the presence of base. The latter method has been used by our group[76] and Armstrong's[77] to obtain $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$. The details of dioxygen binding to this Mn(III) complex have not been established although isotope labeling experiments using $^{16}O_2$ in the presence of $^{18}OH^-$ conclusively show that the dioxygen label scrambles in the process of forming bridging oxides in the product.[76] This would suggest that the air oxidation of the Mn(III) species is more complex than that observed for the Mn^{II}(salpn) chemistry.

Larson and Pecoraro[76] decided to explore the reactivity of Mn Schiff base complexes with hydrogen peroxide based on the observations of Boucher and Coe.[73] The $[Mn^{III}(salpn)(CH_3OH)_2]ClO_4$ will not react with hydrogen peroxide unless 2 equiv of base are present. In this case, rapid (seconds) and quantitative formation (~98% yield) of $[Mn^{IV}(salpn)(\mu_2\text{-}O)_2]$ is observed. The complex $[Mn^{III}(salpn)(CH_3OH)_2]ClO_4$ converts to $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$ if NaOMe is added to a degassed acetonitrile solution. Reaction of this Mn(III) dimer with peroxide in acetonitrile follows the same kinetics and gives the same yield of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ as when base is added to the monomer. Dioxygen will also react with $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$ to give $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$; however, the reaction is approximately 1000 times slower and gives ~70% product. The related molecule $[Mn^{III}(salpn)(AcAc)]$ will react with H_2O_2 in the absence of exogenous base but is unreactive in dry solvents with dioxygen. On the basis of these observations, it was suggested that base was needed to deprotonate hydrogen peroxide to initiate the reaction for binding to the manganese ions.

The incorporation of ^{18}O from labeled $H_2{}^{18}O_2$ in the presence of a large excess of $H_2{}^{16}O$ into $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ was monitored using negative ion FAB mass spectrometry of the dimer.[76] The doubly labeled [Mn^{IV}-

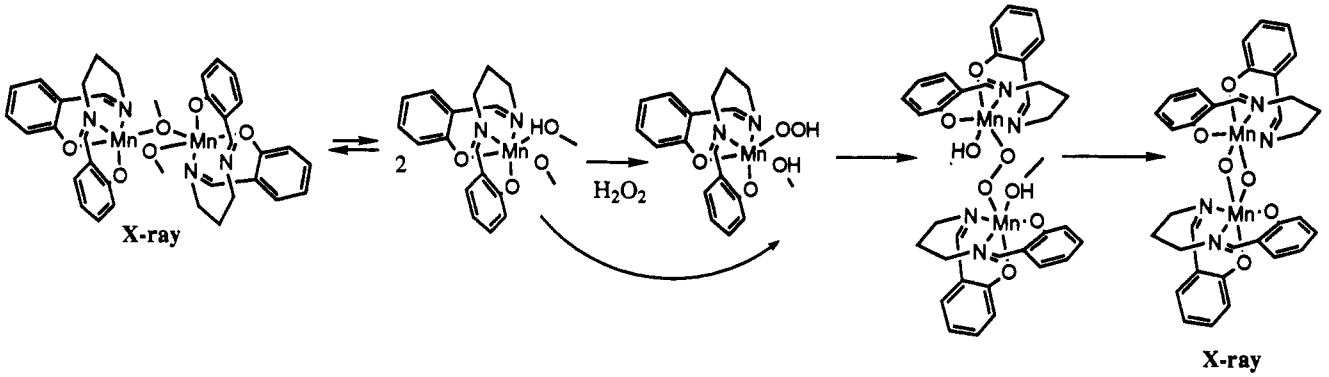


Figure 10. Proposed mechanism for the formation of $[Mn^{IV}(salpn)(\mu\text{-}O)]_2$ from the reaction of $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$ with hydrogen peroxide.

$(salpn)(\mu_2\text{-}^{18}O)]_2$ was exclusively recovered, demonstrating that the bridging oxide source was hydrogen peroxide. In addition, mixtures of $H_2{}^{16}O_2$ and $H_2{}^{18}O_2$ were reacted with $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$, with no observed increase in the mixed-labeled dimer $[Mn^{IV}{}_2(salpn)_2(\mu_2\text{-}^{16}O,\mu_2\text{-}^{18}O)]$. From these results, it was concluded that hydrogen peroxide is the source of the oxide oxygens in $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ and that both oxide bridging atoms originate from the same peroxide molecule. This isotopic distribution demonstrates that monomeric intermediates such as $LMn^{IV}O$ or $LMn^{V}O$ are not part of the reaction mechanism. Ligand labeling experiments showed scrambling of the LMn units upon reaction of the Mn(III) dimer with hydrogen peroxide, indicating that insertion of hydrogen peroxide requires the dissociation of the Mn(III) dimer prior to cleavage of the peroxide bond.

A mechanistic pathway for the production of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ by reaction of H_2O_2 with $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$ is shown in Figure 10.[76] This scheme features H_2O_2 reacting via two successive deprotonation steps which utilize basic oxyanions associated with the Mn(III) precursors. The presence of some form of base has been shown to be an absolute requirement. It was concluded that it is the proton-accepting feature of these anions which allows oxidation at the metal center and that deprotonation must, therefore, occur before cleavage of the peroxide bond. Although H_2O_2 may transiently coordinate to $[Mn^{III}(salpn)(CH_3OH)_2]^+$, metal-centered oxidation probably does not occur prior to deprotonation. Hydroperoxide anion complexation to Mn(III) creates a ligand environment similar to that seen in $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$, a complex that is more easily oxidized than $[Mn^{III}(salpn)(CH_3OH)_2]ClO_4$, leading to stabilization of the Mn(IV) oxidation level. Concurrently, the replacement of $Mn(salpn)^+$ for H^+ on H_2O_2 [giving instead $Mn(salpn)(O_2H)$] may make the coordinated peroxide molecule more easily reduced. Both of these factors should lead to an increase in the driving force for internal oxidation of the intermediate. These and other observations argued for dissociation that was instigated by H_2O_2 rather than a predissociation step. The authors prefer the formulation of $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$ converting to $[Mn^{III}(salpn)(O_2H)]$ and then $[Mn^{III}(salpn)]_2(O_2{}^{2-})$ as intermediates in this process; however, on the basis of these data, a side-on bound peroxo monomer as seen in $[Mn(TPP)(O_2{}^{2-})]^-$ (*vide supra*) reacting with a monomeric $Mn^{III}(salpn)^+$ to form $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ is equally possible.

The formation of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ from $[Mn^{III}(salpn)(\mu\text{-}OCH_3)]_2$ using *tert*-butyl hydroperoxide as the oxidant was also investigated and appears to follow a pathway very different from that of reaction with H_2O_2.[76] The reaction requires a number of hours (at room temperature) and water must be present to initiate the process. Unlike the H_2O_2 oxidation, significant mixing of label from water into the product dimer was observed. Although numerous pathways could be envisioned which might fit this and other observations, the isotopic pattern is consistent with the initial formation of $Mn^{V}(salpn)O$ which then reacts with 1 equiv of $Mn^{III}salpn(OH)$ to give $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$.[76]

The reactions described above examined the oxidation of Mn(salpn) complexes by hydrogen peroxide and dioxygen. The observation that the oxygen-evolving complex could undergo a catalase reaction, apparently using $Mn^{IV}(\mu_2\text{-}O)$ cores,[78] inspired examination of the reactivity of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ with hydrogen peroxide.[79] Addition of a small aliquot of H_2O_2 to a dichloromethane solution containing $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ resulted in the turnover of hydrogen peroxide to yield dioxygen in a quantitative disproportionation reaction that was complete in less than 1 min. The catalyst was stable and could be recovered intact even after as much as 1000-fold molar excess H_2O_2 had been consumed. These observations clearly demonstrated that $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ was an effective "catalase". Isotope labeling of the hydrogen peroxide and of the oxo bridges demonstrated that the dioxygen is derived exclusively from hydrogen peroxide and not from the μ_2-oxo linkages of the dimer, and that both oxygen atoms of dioxygen must come from the *same* hydrogen peroxide molecule. Single turnover reactions completed under high dilution conditions using a 2:1 ratio of $H_2{}^{18}O_2$ and $[Mn^{IV}(salpn)(\mu_2\text{-}^{16}O)]_2$ demonstrated that the $\mu_2\text{-}O^{2-}$ ligands were stoichiometrically replaced during the course of the reaction. In addition, the catalase reaction was shown to result in both bridging oxo groups originating from the same peroxide molecule. Ligand labeling experiments showed scrambling of the MnL units, requiring that a monomeric intermediate must be formed during the "catalase" reaction.

Protonation of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ at the oxo bridge to form $[Mn^{IV}{}_2(salpn)_2(\mu_2\text{-}O)(\mu_2\text{-}OH)]^+$ can be achieved by weak acids in acetonitrile.[80] The electrochemistry of this species is less reversible than for $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ and occurs nearly 800 mV to more positive potential. In addition, $[Mn^{IV}{}_2(salpn)_2(\mu_2\text{-}O)(\mu_2\text{-}OH)]^+$

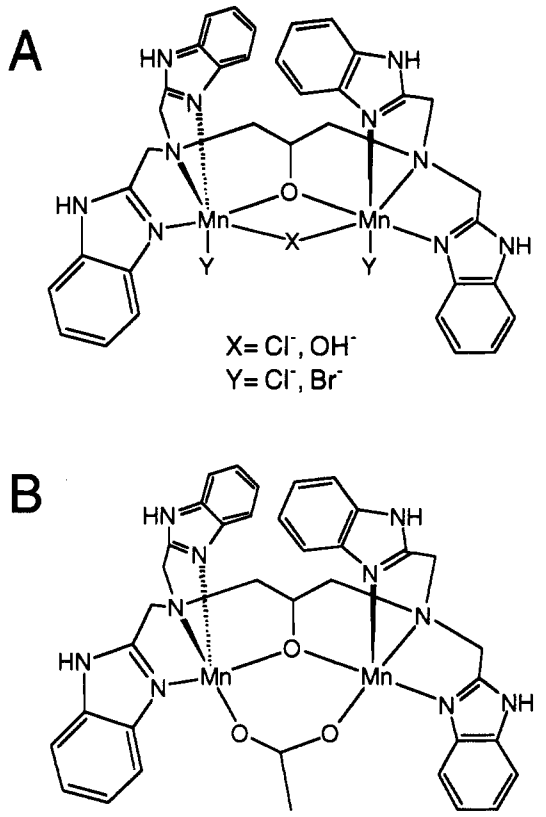
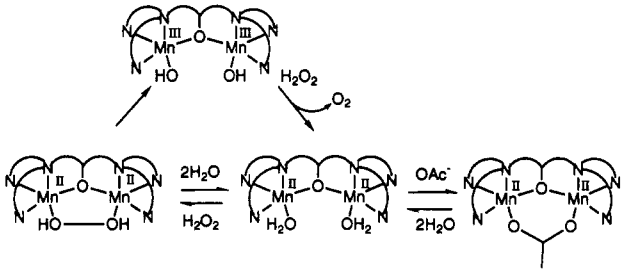


Figure 11. Proposed structures for (A) $[Mn^{II}_2(L)Y_2X]$ (L = *N,N,N',N'*-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol) (ref 89) and (B) $[Mn^{II}_2(L)CH_3COO]^{2-}$ (ref 90).

is not competent in the catalase reaction with H_2O_2 but will react with $NaHO_2$. Interestingly, Boucher and Coe claim to have generated hydrogen peroxide produced in solutions of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ upon addition of stoichiometric amounts of $HClO_4$,[73] which should occur by protonation of *both* oxo bridges, followed by decomposition to H_2O_2 and Mn(III) complexes. They used a pyrogallol solution to test for dioxygen evolution upon addition of acid, however none was detected. Otsuji et al. also reported[81] the observation of hydrogen peroxide as a product in the photochemical reduction of $[Mn^{IV}L_2O]_2$ and $[Mn^{III,IV}L_2O]_2$ dimers (L = 2,2'-bipyridyl or 1,10-phenanthroline) in acidic medium. However, they observed one-electron reductions and proposed hydroxyl radical as the oxidation product from water, from which the hydrogen peroxide is subsequently produced. Sawyer and co-workers prepared the complex $[Mn^{IV}(gluconate)_2(\mu\text{-}O)]_2$ which upon addition of acid in aqueous medium appears to evolve dioxygen.[82-84] The chemistry of this system appears to be analogous to that described above. These observations suggest that protons may be very important in the catalytic reactions of oxo manganese clusters.

While $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ is an efficient catalase mimic and can be protonated, previous $[Mn^{IV}L(\mu_2\text{-}O)]_2$ complexes, where L does not contain oxyanion donors, have not been reported to show similar chemistry. Recent electrochemical studies of compounds that contain neutral nitrogen donor ligands have shown pK_a values in aqueous solution of ~11 for $[Mn^{III}L(\mu_2\text{-}O)]_2$[85] and ~2.3 for $LMn^{III}(\mu_2\text{-}O)_2Mn^{IV}L$.[86] This compares with a pK_a in acetonitrile for $[Mn^{IV}_2(salpn)_2(\mu_2\text{-}O)(\mu_2\text{-}OH)]^+$ of 13.3, corresponding to an aqueous pK_a of about 6.[87] Substituting electron donors and acceptors (e.g., 5-OMe, 5-Cl, 3,5-dichloro, 5-NO_2) onto the phenolate rings markedly perturbs both the pK_a of the protonated species and the reduction potential of the unprotonated complex. In fact, the change in reduction potential correlates linearly with the pK_a of the protonated complex which has led Baldwin et al. to conclude that the $[Mn^{IV}O]_2$ core acts as a strongly electronically coupled unit.[87] The relative ease of protonation is a result of increased anionic charge and stronger donor ability of phenolates as compared to pyridine and related ligands that leads to more electron density on the metal centers. Therefore, the oxo bridges are not required to donate as much electron density to the metal center and can be involved in proton-acceptor chemistry. Carroll and Norton have shown that protonation rates of molecules such as $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ are slow compared to organic oxygens.[88] This appears to be due to π donation from the dioxygen lone pair to the high-valent metals.

Scheme 2



2. Other Catalase Mimics

The first dinuclear manganese complex to be reported that catalytically disproportionated H_2O_2 was that of Dismukes and co-workers, in 1987.[89] This functional model contained two Mn(II) ions bridged by two different functional groups. The first bridge was an alkoxide oxygen from the septadentate ligand, *N,N,N',N'*-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol. The other bridging site could be occupied by either a Cl^- or hydroxide ion. Furthermore, the complex is believed to have terminal Cl^- at each manganese ion. A representation of this compound, $[Mn_2(L)Cl_3]$ is shown in Figure 11a. Although not crystallographically characterized, the dinuclear structure was confirmed by EPR spectroscopy and a metal–metal distance of 3.3 Å was estimated from relaxation experiments. This complex was the first dinuclear manganese model to exhibit better than stoichiometric reactivity with hydrogen peroxide. Preliminary kinetic studies indicated that the complex cycled between the Mn(II,II) and Mn(III,III) oxidation states during the reaction with H_2O_2, reactivity observed for the manganese catalases.

Recently Dismukes has reported replacing the Cl^- or OH^- bridges with a carboxylate moiety, forming a dinuclear complex with five coordinate Mn(II) ions that is illustrated as Figure 11b.[90] These complexes cycle between Mn(II,II) and Mn(III,III) oxidation states during the catalase reaction as well. The original Cl^--bridged complexes underwent approximately 200 turnovers before decomposing. The loss of activity probably occurs through protonation of the ligand and then loss of dinuclear structure, releasing Mn(II) ion. The carboxylate bridged complexes are more soluble and

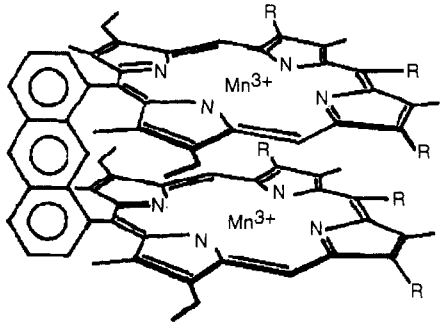


Figure 12. Drawing of the structure of the catalase-active $[Mn^{III}(porphyrin)]_2$ dimer complex with a rigid spacer linking the porphyrins as described in the text. (Adapted from ref 91. Copyright 1991 American Chemical Society.)

more stable than the OH^- or Cl^- species in acetonitrile and methanol leading to improvements in turnover number to greater than 1000 with very little activity loss. Some preliminary kinetic and spectroscopic data has revealed a second-order rate constant of 1.2 M^{-1} s^{-1} and indicates that the rate limiting step for these reactions is most likely the reduction of peroxide and regeneration of a Mn(III,III) complex, as shown in Scheme 2.[90] The rate constant for the Mn catalase is over 10^7 times faster than these complexes. Pessiki et al. have proposed that this is due to a difference in reduction potentials between the enzyme and the acetate-bridged complex given that the enzyme is more easily oxidized to the Mn(III,III) form by dioxygen.[90]

Another attempt at modeling catalase function using dinuclear manganese models incorporated synthetic Mn porphyrins linked together with spacer molecules (anthracene and biphenylene) to control both the metal–metal distance and to sterically hinder the reaction site.[91] These dinuclear complexes had various Mn–Mn distances ranging from 3.8 to 4.5 Å (Figure 12). These complexes are efficient catalysts for the disproportionation of hydrogen peroxide that are dependent on both complex and 1-methylimidazole concentration for activity. The authors propose that the linkers used in generating the dinuclear complexes prevent the formation of a six-coordinate bis(1-methylimidizole) complex. Instead, 1-methylimidizole occupies one axial position and the sixth coordination site is open to react with H_2O_2.

These complexes had rates that ranged from 10–325 mol O_2 (mol catalyst)$^{-1}$ min^{-1} and could survive more than 1000 turnovers. The isotopic studies using ^{18}O labeled hydrogen peroxide gave only $^{18}O_2$ and $^{16}O_2$, consistent with the isotope labeling seen in the native enzymes, and implying that the oxidation of hydrogen peroxide to O_2 is a unimolecular rate-determining step.

An earlier attempt at catalase modeling by Mn(III)–porphyrin complexes used a water-soluble complex: aquo[5,10,15,20-tetrakis(2,6-dimethyl-3-sulfonatophenyl)porphinato]manganese(III) which is sterically blocked to μ-oxo dimer formation.[92] Bruice and coworkers used the stable radical initiator abts as a partial trap for the high-valent intermediates to study reaction kinetics. They determined that the rate of the reaction is linearly dependent on the concentration of the Mn(III)–porphyrin complex and first order in the formation of the products O_2 and $abts^{\bullet-}$, but independent of the concentration of both hydrogen peroxide and abts. The rate-limiting step in the reaction was determined to be

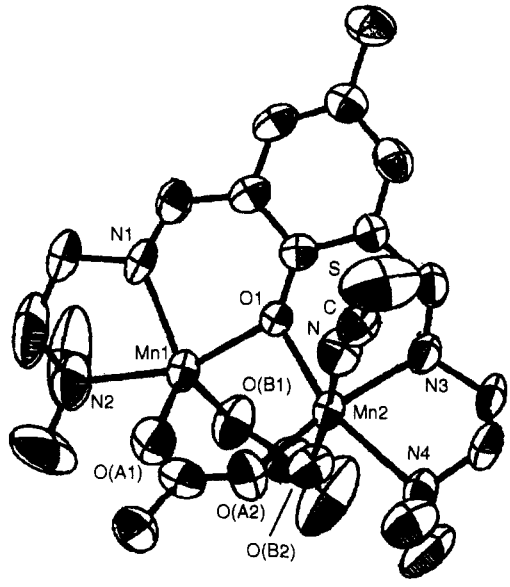
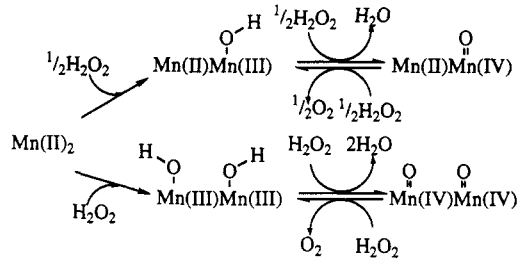


Figure 13. Molecular structure of $[Mn_2(L)(CH_3CO_2)_2(NCS)]$ [L = 2,6-bis[*N*-[2-(dimethylamino)ethyl]iminomethyl]-4-methylphenolate] derived from X-ray crystallography. (Adapted with permission from ref 94. Copyright 1993 The Royal Society of Chemistry.)

Scheme 3



the oxygen transfer from hydrogen peroxide to the manganese(III) porphyrin to form the manganese(IV)–oxoporphyrin π-cation radical or manganese(V)–oxoporphyrins.

Sakiyama and co-workers[93] have recently prepared a high-valent catalase model which is purported to go through a Mn(IV)=O intermediate. This intermediate has been detected by mass spectrometric measurements and by visible spectroscopy. The dinuclear manganese(II) complex $[Mn_2(L)(C_6H_5CO_2)_2(NCS)]$ [where L = 2,6-bis[*N*-[2-(dimethylamino)ethyl]iminomethyl]-4-methylphenolate] has been shown to catalyze H_2O_2 disproportionation.[93,94] The structure of this molecule is shown in Figure 13. The possible reaction mechanism is given in Scheme 3 and describes the products observed in the mass spectrum. There is a time dependence for the formation of the dimanganese(IV)–oxo complex as observed in the mass spectrum and this scheme is proposed for the two different formation reactions for monomanganese(IV)–oxo and dimanganese(IV)–oxo complexes. These interesting formulations for the manganese–oxygen interaction are based primarily on the fine structure observed in the visible spectrum of the reacting species (Figure 14), which has been proposed to be the Mn=O vibration coupled to a ligand-to-metal charge-transfer band [from $O^{2-} \rightarrow Mn(IV)$] through vibronic interaction.

A slight modification of the H_2salpn (*vide supra*) ligand led to dramatically different coordination chem-

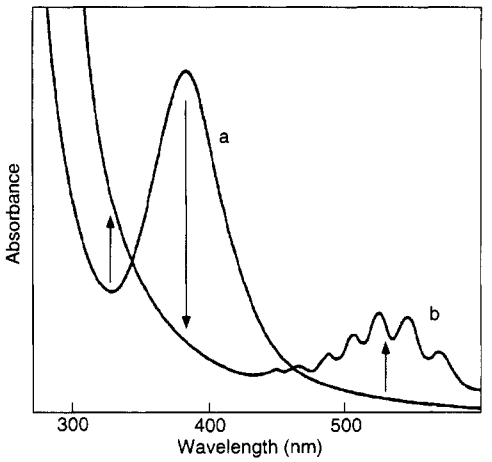


Figure 14. UV–vis absorption spectra of the charge-transfer transitions of (a) $[Mn_2(L)(C_6H_5CO_2)_2(NCS)]$ [L = 2,6-bis-[*N*-[2-(dimethylamino)ethyl]iminomethyl]-4-methylphenolate] after addition of excess H_2O_2, and (b) after 30 min. The arrows indicate changes in the absorption spectrum over time. (Adapted from ref 93 with permission. Copyright 1993 The Royal Society of Chemistry.)

istry that has provided significant insight into the manganese catalase reactions. Substitution of a hydroxide group at the 2 position of the propane backbone on H_2salpn gives the pentadentate ligand 2-OHsalpn that forms three distinct dinuclear structures. These are a di-μ-oxo-bridged core, analogous to $[Mn^{III,IV}(salpn)(\mu_2\text{-}O)]_2^-$, where the alcohol is not bound and two complexes where the 2-hydroxyl group is bound as an alkoxide. Both symmetric (e.g., $[Mn^{III}(2\text{-}OHsalpn)]_2$ with two, equivalent alkoxide donors bridging manganese ions)[95] and asymmetric (e.g., $[Mn^{III}_2(2\text{-}OHsalpn)_2\text{-}CH_3OH]$ with only one of the alkoxide dioxygen atoms participating in a bridge between the manganese ions)[96,97] complexes have been prepared and structurally characterized. Examples of each group are given as Figure 15.

The symmetric $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$ reacts with dioxygen to form $[Mn^{III}(2\text{-}OHsalpn)]_2$ in acetonitrile and $[Mn^{III}_2(2\text{-}OHsalpn)_2CH_3OH]$ in a coordinating donor solvent such as methanol. Available evidence, using a wide variety of phenyl ring substituted derivatives, suggests that this is an outer-sphere oxidation of the manganese ions by dioxygen proceeding through the symmetric intermediate $[Mn^{II,III}(2\text{-}OHsalpn)]_2^-$. For example, if the $[Mn^{II}(2\text{-}OH\text{-}(3,5\text{-}diCl\text{-}sal)pn)]_2^{2-}$ is air oxidized at −40 °C in ethanol, the intermediate $[Mn^{II,III}\text{-}(2\text{-}OH\text{-}(3,5\text{-}diCl\text{-}sal)pn)]_2^-$ can be isolated in high yield. The $[Mn^{III}(2\text{-}OHsalpn)]_2$ can be converted into the asymmetric complex, $[Mn^{III}_2(2\text{-}OHsalpn)_2CH_3OH]$, by dissolving in methanol. The desolvation of $[Mn^{III}_2(2\text{-}OHsalpn)_2CH_3OH]$ to give the symmetric dimer can be achieved by redissolving in acetonitrile.

Hydrogen peroxide reacts with $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$ or $[Mn^{III}(2\text{-}OHsalpn)]_2$ in acetonitrile. When 1 equiv of peroxide was added to $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$, the $[Mn^{III}(2\text{-}OHsalpn)]_2$ was quantitatively generated. Similarly, 1 equiv of peroxide added to $[Mn^{III}(2\text{-}OHsalpn)]_2$ quantitatively yielded $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$. The observation of an isosbestic point demonstrated a clean conversion from the $[Mn^{III}(2\text{-}OHsalpn)]_2$ to the $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$, without showing evidence for an intermediate. This suggested that evolution of dioxygen in a catalase reaction that cycled between the two

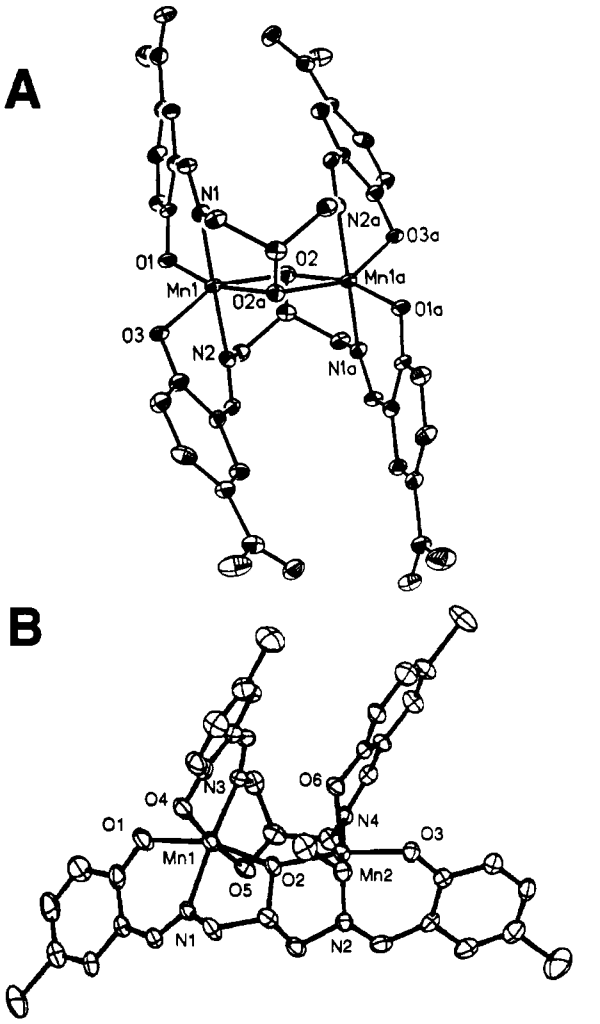


Figure 15. Molecular structures of (A) $[Mn^{III}(2\text{-}OH(5\text{-}NO_2\text{-}sal)pn)]$, an example of the symmetric Mn(III,III) systems (ref 95) and (B) $[Mn^{III}_2(2\text{-}OH(5\text{-}Clsal)pn)_2(CH_3OH)]$ an example of the asymmetric Mn(III,III) systems (ref 96).

molecules was achievable.[95] Oxygen evolution experiments indicated that these complexes complete the catalase reaction for at least 1000 turnovers without significant decomposition of the catalyst. Isolation of dioxygen after the addition of $H_2{}^{18}O_2$ yielded exclusively $^{18}O_2$. If $H_2{}^{18}O_2$ and $H_2{}^{16}O_2$ were added to either manganese complex, $^{18}O_2$ and $^{16}O_2$ were recovered but no $^{16,18}O_2$ was detected. The reaction of hydrogen peroxide with a 50:50 mixture of $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$ and $[Mn^{II}(2\text{-}OH(5\text{-}NO_2sal)pn)]_2^{2-}$ gave mass peaks for the recovered material only for $[Mn^{III}(2\text{-}OHsalpn)]_2$ and $[Mn^{III}(2\text{-}OH(5\text{-}NO_2sal)pn)]_2$, and no $[Mn^{III}_2(2\text{-}OH\text{-}(salpn)(2\text{-}OH(5\text{-}NO_2sal)pn)]$ providing strong evidence that the dimer did not dissociate into monomers during the catalytic process.

The initial rates of reaction for the derivatives of $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$ and $[Mn^{III}(2\text{-}OHsalpn)]_2$ with H_2O_2 were determined using a modified Clark-type O_2 electrode and were identical regardless of initial oxidation state and within a factor of 2 for ring-substituted derivatives. A detailed kinetic study of the $[Mn^{III}(2\text{-}OH(5\text{-}Clsal)pn)]_2$ demonstrated that this complex exhibited saturation kinetics with respect to hydrogen peroxide (Figure 16a). At saturating hydrogen peroxide concentrations, the reaction was first order in $[Mn^{III}\text{-}(2\text{-}OH(5\text{-}Clsal)pn)]_2$. The saturation type kinetics

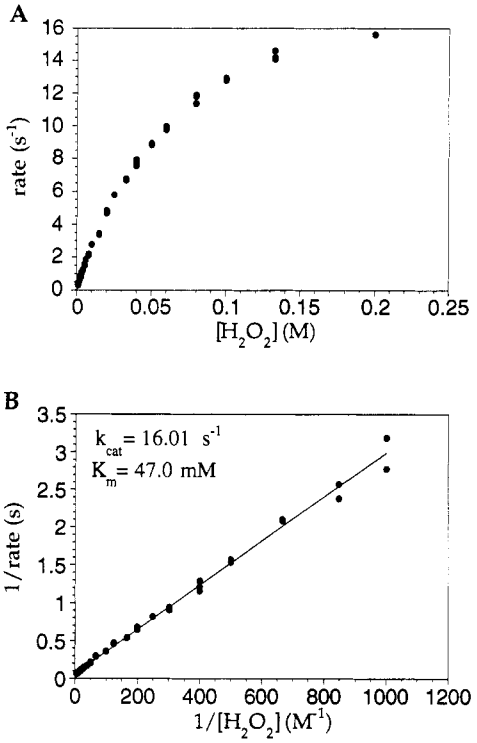


Figure 16. (A) Rate of H_2O_2 disproportionation vs H_2O_2 concentration in acetonitrile. The plot shows saturation kinetics for $Na_2[Mn_2(2\text{-}OH(5\text{-}Clsal)pn)]_2$. Part B shows a Lineweaver–Burke plot (double reciprocal plot) of the data in part A (ref 95).

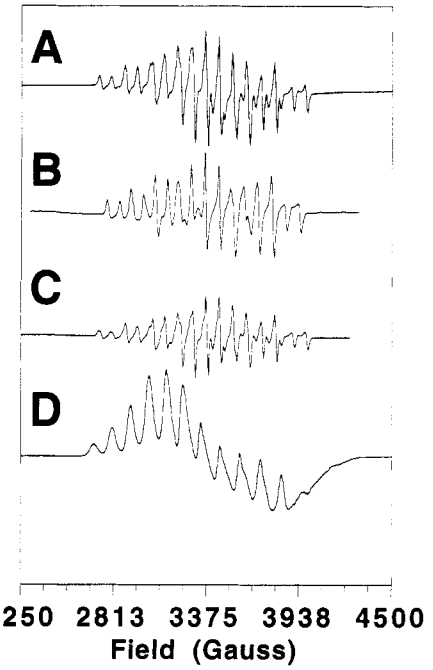


Figure 17. X-Band EPR spectra of various Mn(III,IV) dimers as models for the inactive state of the Mn catalases at 4.8 K: (A) A $[Mn^{III,IV}(2\text{-}OH(5\text{-}NO_2sal)pn)_2]^+$ complex; (B) the inactive form of the Mn catalase from *L. plantarum*; (C) The $[Mn^{III,IV}(salpn)_2(O)_2]^-$ complex, (D) The $Mn^{III}Mn^{IV}(2\text{-}OH\text{-}(3,5\text{-}Clsal)pn)_2(THF)]^+$ complex in dmf.

suggest that there is a reversibly formed "peroxy[Mn-(2-OH(5-Clsal)pn)]$_2$" intermediate in the turnover-limiting step; however, the UV–vis spectra show no evidence of this intermediate. A double reciprocal plot of the data revealed a linear relationship from which k_{cat} and K_m was calculated (Figure 16b). The $K_m(H_2O_2)$ = 37 ± 10 mM and k_{cat} = 13 ± 3 s^{-1}. In comparison, $[Mn^{II}(H_2O)_6](ClO_4)_2$ has $k_{cat} = 6.3 \times 10^{-3}$ s^{-1} while Penner-Hahn[98] has shown that the Mn catalase from *Lactobacillus plantarum* has a $K_m(H_2O_2)$ = 200 mM and $k_{cat} = 2 \times 10^5$ s^{-1}. Relative values for k_{cat}/K_m for the Mn catalase and $[Mn^{III}(2\text{-}OH(5\text{-}Clsal)pn)]_2$ are 1×10^6 M^{-1} s^{-1} and 3.5×10^2 M^{-1} s^{-1}, respectively, indicating that the enzyme is only 3000 times more efficient than this synthetic catalyst.

Azide and hydroxylamine are substrate analogues that have been studied extensively as inhibitors of a variety of dioxygen and peroxide utilizing enzymes. The $[Mn^{III}(2\text{-}OH(5\text{-}Clsal)pn)]_2$ was not inhibited in acetonitrile to saturating concentrations of azide (~50 mM). The $[Mn^{II}(2\text{-}OHsalpn)]_2^{2-}$ system can be driven to a catalytically inactive Mn(III,IV) form that has an EPR spectrum that is strikingly similar to the spectra of both the superoxidized Mn catalase and $[Mn^{III,IV}(salpn)(\mu_2\text{-}O)]_2^-$. It is important to note that the EPR spectrum of this complex is different from that of the asymmetric complex $[Mn^{III,IV}_2(2\text{-}OHsalpn)_2(thf)]^+$.[97] A comparison of the different Mn(III,IV) EPR spectra is shown in Figure 17.

The $[Mn^{III}(2\text{-}OHsalpn)]_2$ system is very exciting since it is the first crystallographically characterized dinuclear Mn model that begins to approach some of the structural, spectroscopic, and functional properties of the Mn catalases. The catalyst cycles between the Mn-(II,II) and Mn(III,III) oxidation levels and maintains its dinuclear integrity throughout the process, shows respectable turnover rates, has saturation kinetics with hydrogen peroxide, is reasonably stable showing greater than 1000 turnovers, can be reduced by hydroxylamine, is azide insensitive under conditions that the enzyme is not inhibited by azide, forms a catalytically inactive Mn(III,IV) form (with an almost identical EPR to the enzyme) that can be reduced to a catalytically active state by hydroxylamine, and has the same $^{18}O_2$ labeling as the enzyme.

In addition to mimicking the function of the enzyme reasonably well, this system may provide some insight into the inactivation of the Mn catalase by the mixture of hydroxylamine and hydrogen peroxide. It is known that hydroxylamine functions as a hydrogen peroxide mimic as a reductant of the Mn catalase. However, unlike hydrogen peroxide, hydroxylamine reduces the enzyme by only one electron. If this is done in the Mn(III,III) oxidation level an intermediate Mn(II,III) enzyme is formed. If the next molecule to bind is hydroxylamine, then the enzyme will be reduced to Mn-(II,II) and the cycle can be continued; however, if hydrogen peroxide binds the enzyme will be oxidized by two electrons to the Mn(III,IV) form. Since reduction of the Mn(III,IV) enzyme is slow, this superoxidized level will accumulate and eventually be the primary species. A scheme for this process is shown in Figure 18. Similar chemistry is observed with $[Mn^{II,III}(2\text{-}OHsalpn)]_2^-$ as this molecule can be oxidized to a Mn-(III,IV) by hydrogen peroxide and can be reduced to $[Mn^{II,II}(2\text{-}OHsalpn)]_2^{2-}$ by hydroxylamine. This proposal is illustrated in Figure 19.

An example of a higher nuclearity manganese cluster that reacts catalytically with hydrogen peroxide is a tetranuclear complex prepared by Gorun and co-workers.[99] A crystal structure of the complex $(Ba,Ca)_2$-

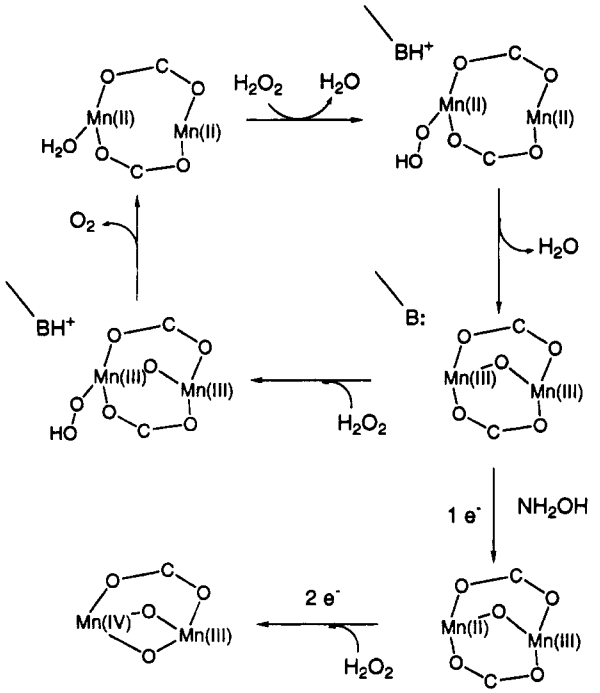


Figure 18. Proposed mechanism for the inactivation of the Mn catalase by reaction of NH_2OH and then H_2O_2. The mechanism for the reaction mechanism of Mn catalase with H_2O_2 is based on that proposed by Penner–Hahn. The scheme for the inactivation is based on model studies with $[Mn^{II}(2\text{-OHsalpn})]_2$.

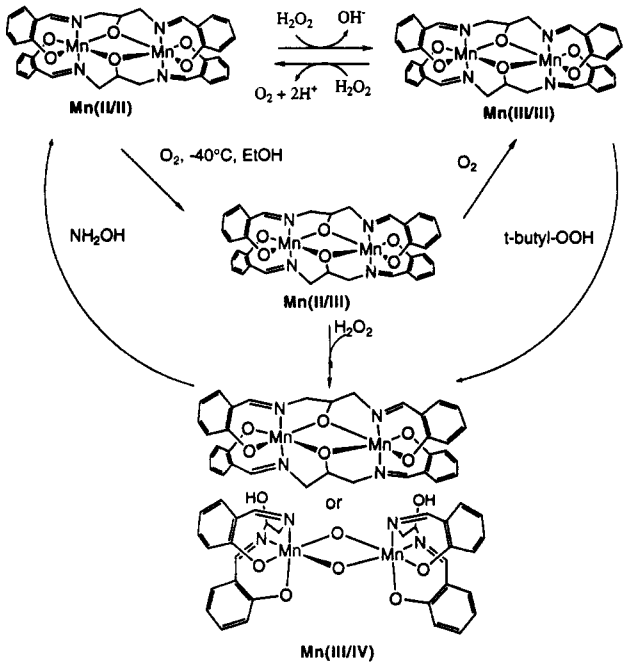


Figure 19. Reactions of the $[Mn^{II}(2\text{-OHsalpn})]_2$ system as a model for the reactions of the Mn catalases (refs 95 and 15).

$[Mn_4(\mu\text{-O})(\mu\text{-OH})(O_2CCH_3)_2L_2]$ (where L = 1,3-diamino-2-hydroxypropane-*N,N,N',N'*-tetraacetic acid) is shown in Figure 20. The Mn cluster is linked in the solid state by Ba(II) and Ca(II) ions. One of the interesting structural features of this Mn(II,III,III,III) tetramer is that it contains an $(O_2H)^{3-}$ core. When this complex is dissolved in H_2O, H_2O_2 is disproportionated at a rate that is more than 100 times faster than $Mn^{II}(H_2O)_6^{2+}$ ion in solution. This was interpreted as indicating that the multinuclear structure was responsible for this

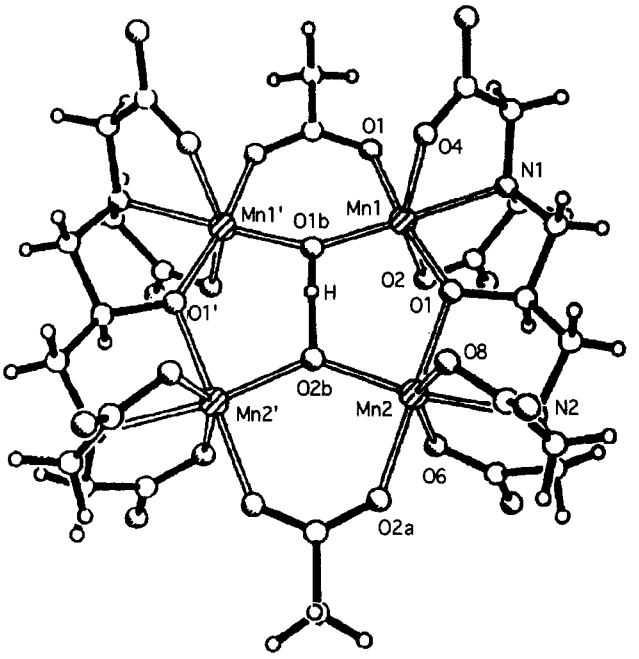


Figure 20. Molecular structure of $[Mn_4(\mu\text{-O})(\mu\text{-OH})(O_2CCH_3)_2L_2]$ (L is defined in the text) derived from X-ray crystallography. (Adapted with permission from ref 99. Copyright 1990 VCH Publishers.)

activity; however, there was no spectroscopic evidence presented that the molecule retained its structure in solution, nor was the possible influence of barium or calcium on this reaction described.

The above discussion has presented the various functional Mn catalase models that have been prepared. The reaction rates with hydrogen peroxide, turnover numbers, and structural parameters of these complexes are compiled in Table 2. These models include mononuclear, dinuclear, and tetranuclear Mn centers and involve both low-valent and high-valent catalase cycles. The dimeric complexes are the best characterized and most efficient catalase mimics. To date, the $[Mn^{IV}\text{-salpn(O)}]_2$ is the best model for the high valent (OEC type) system because it is the most active model known and has a bis μ-oxo core which is the proposed structural moiety present in the OEC. The $[Mn^{III}(2\text{-OHsalpn})]_2$ is the best functional model for the low-valent (Mn catalase type) system because it is crystallographically characterized, has the same oxygen isotope labeling as the enzyme, exhibits saturation kinetics, and has an inactive III/IV oxidation state that can be reactivated by hydroxylamine. However some less active functional models such as that prepared by Dismukes and coworkers[89,90] (*vide supra*) may be structurally more analogous to the dinuclear manganese site present in the Mn catalases and, therefore, provide important information about catalytic function.

C. Water Oxidation

1. O_2 Release from the Photolysis of $KMnO_4$

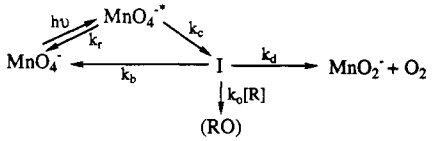
The photochemical decomposition of permanganate (MnO_4^-) has been known for many years[100] and has been shown to release dioxygen.[101] The quantum yield of dioxygen release is essentially pH independent in neutral and mildly acidic or mildly basic solutions; however, it is wavelength dependent with a small

Table 2. Comparison of Functional Models for Mn Catalases

catalyst for H_2O_2 disproportionation	rate (s^{-1})	k_{cat}/K_M (M^{-1} s^{-1})	Mn redox cycle	Mn–Mn distance (Å)	ref(s)
Mn catalase[a]	2.0×10^5	5.7×10^5	II,II ↔ III,III	≈3.6[b]	98
$[Mn^{IV}salpn(O)]_2$	~50	c	III,III ↔ IV,IV	2.73	76, 79
$[Mn^{III}(2\text{-}OHsalpn)]_2$	3.4–16.4	350–610	II,II ↔ III,III	3.33 $Mn(II)_2$ 3.232 $Mn(III)_2$	95, *i*
$[Mn^{III}_2(anthracenediporphyrin)]Cl_2$	5.4	c	III,III ↔ IV,IV	4.5	91
$[Mn^{II}_2L(CH_3COO)](ClO_4)_2$ (L = *N,N,N′,N′*-tetrakis-(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol)	1.2	c	II,II ↔ III,III	3.3	89, 90
$(Ba,Ca)_2[Mn_4(\mu\text{-}O)(\mu\text{-}OH)(OAc)_2L_2]$ (L = *N,N,N′,N′*-tetraacetato-1,3-diaminopropan-2-ol)	1.04[d]	c	unknown	3.379[e] 3.584[f] 3.718[g]	99
$[Mn_2(L)(C_6H_5COO)_2(NCS)]$ [L = 2,6-bis[*N*-[2-(dimethylamino)ethyl]iminomethyl]-4-methylphenolate]	7.9×10^{-1}	c	III,III ↔ IV,IV or III,III ↔ II,IV[h]	3.325	93, 94
$[Mn^{III}(TPP)]^+$	1.3×10^{-2}	c	III ↔ V	n/a	91, 99
$[Mn(H_2O)_6](ClO_4)_2$	6.3×10^{-3}	c	unknown	n/a	95

[a] Mn catalase from *Lactobacillus plantarum*. [b] Mn···Mn distance from 3.0-Å resolution crystal structure for the reduced enzyme from *Thermus thermophilus* from Barynin et al. (Barynin, V. V.; Vagin, A. A.; Melik-Adamyan, W. R.; Gebenko, A. I.; Khangulov, S. V.; Povov, A. N.; Andrianova, M. E.; Vainshtein, B. K. *Dolk. Akad. Nauk SSSR(Crystallogr.)* **1986**, *288*, 877–880). [c] These complexes have not been examined for saturation kinetics. [d] Rate based on normalization of $[Mn(TPP)]^-$ results in footnote 17 of ref 99 to that for Mn(TPP)Cl in ref 91. [e] Mn1···Mn1′ distance for complex shown in Figure 18 from ref 99. [f] Mn2···Mn2′ distance for complex shown in Figure 18 from ref 99. [g] Mn1···Mn2 distance for complex shown in Figure 18 from ref 99. [h] Two different catalase-type mechanisms have been proposed for this complex, these are compared in Scheme 3. [i] Gelasco, A.; Kampf, J. W.; Pecoraro, V. L. Manuscript in preparation.

Scheme 4



temperature dependence at lower energies.[101] Both the 311- and 546-nm ligand-to-metal charge transfer (LMCT) transitions promote the dioxygen-evolving decomposition, with the 311-nm transition being much more efficient.[102] Isotopic labeling studies[101] have been interpreted as indicating that both oxygen atoms in the evolved dioxygen come from MnO_4^- rather than water in solution. Addition of the oxidizable substrates acetone or *p*-alkylbenzenesulfonic acids, under conditions in which these substrates do not react appreciably with permanganate in the absence of photoactivation (acidic pH, 6 °C), accelerates permanganate decomposition while suppressing dioxygen evolution. This has been interpreted as indicating the production of an intermediate, proposed to be a Mn(V)–peroxide, which is a faster oxidant but with a longer inherent lifetime (microseconds vs nanoseconds) than the initially formed electronically excited MnO_4^{*-}. Lee et al.[102] have proposed the reaction series in Scheme 4 to account for these observations.

The photochemically catalyzed production of dioxygen by permanganate was used as a model for the reactions of the oxygen evolving complex of photosystem II in the early literature, particularly before it was appreciated that four manganese ions are involved in biological water oxidation. It is unlikely that the photochemical process associated with Scheme 4 can occur in photosystem II since the high concentration of photopigments which absorb in the wavelength range which activates the permanganate reaction would make the catalytic conversion highly unlikely due to an insufficient flux of photons. The only photochemistry that has been demonstrated for the OEC is photoxidation of P_{680} followed by reduction of this pigment by a redox active tyrosine Y_z.[2] The Y_z^+ is then reduced by the manganese core of the enzyme. Thus, photochemistry generates oxidizing equivalents but does not initiate reactions at the manganese cluster.

While the photochemical aspect of the permanganate reaction is clearly abiological, there are proposals that utilize terminal oxo groups, either from a single manganese center or two spatially constrained ions, to form dioxygen. The single center model condenses two terminal oxo groups to release dioxygen and give a four-electron reduced manganese ion. Since the highest oxidation level that any manganese ion attains in the OEC is +4 or +5 and there is strong evidence that all of the manganese ions have at least one close manganese nearest neighbor, it is unlikely that all of the chemistry occurs on a single, isolated metal center; however, it would be possible to have two terminal oxygens on the same manganese ion in a metal cluster while spreading the charge distribution throughout the cluster. An alternative proposal is that terminal oxo groups from two manganese ions can condense to form dioxygen leaving each manganese reduced by two electrons.

Model chemistry reveals some precedent for this type of reactivity. Groves and Hill have shown that oxomanganese(IV) and oxomanganese(V) porphyrins can be prepared and were efficient oxo transfer agents, although they apparently do not show catalase-like activity.[103,104] On the basis of these observations, Naruta prepared Mn(III)–porphyrin dimers linked by rigid spacers which performed the catalytic disproportionation of hydrogen peroxide, with oxomanganese(IV) intermediates proposed[91] (*vide supra*). This catalase chemistry was achieved with manganese porphyrins; however, it is well established that the OEC does not contain manganese porphyrin prosthetic groups. Despite this limitation one cannot rule out this mechanism since other non-porphyrin ligands have been prepared that form high valent Mn=O complexes. Among these are the Schiff bases such as Mn^VO(salen) first described by Kochi[105,106] and the crystallographically characterized

$Mn^{V}OL$ (where L is a tetradentate amide ligand) prepared by Collins.[107,108]

2. Water Photolysis in Mn(III) Complexes

McAuliffe and co-workers reported[109] that dioxygen can be evolved by the photolysis of Mn(III) Schiff base complexes of the type $\{[Mn^{III}L(H_2O)]_2(ClO_4)_2\}$. Illumination of solutions of the Mn(III) complex and a hydrogen-atom acceptor such as *p*-benzoquinone was found to result in an increased dioxygen concentration in solution, as monitored by using an O_2 electrode, and conversion of the quinone to an hydroquinone, on the basis of spectrophotometric monitoring of the reaction. The similarity of the rate of dioxygen evolution for aqueous and anhydrous ethanolic solutions was interpreted as indicating that the oxygen atoms in the evolved dioxygen come from the coordinated water in the Mn(III) complex rather than from the solvent. A dark precipitate that deposited during illumination was formulated as $[\{Mn^{III}L\}_2O]$. No EPR signal associated with any intermediate or product was observed during the course of the reaction. The reaction was proposed to be that shown in eq 24:

$$[\{Mn^{III}L(H_2O)\}_2][ClO_4]_2 + \text{quinone} + h\nu \rightarrow {}^1/_2O_2 + \text{hydroquinone} + 2H^+ + 2ClO_4 + [\{Mn^{III}L\}_2O] \quad (24)$$

Under constant illumination, the rate of dioxygen evolution was observed to be constant for 10–12 h followed by rapid decrease of the rate to zero, after evolution of approximately 0.25 mol O_2 per mole of Mn dimer. The maximum rate of dioxygen evolution appears to occur with illumination in resonance with an unassigned absorption band at 590 nm. The rate increases with increasing pH for $4.5 < pH < 6.9$. Above pH = 8 semiquinones are formed so the reaction was not studied in basic solutions. The temperature dependence of the reaction indicated an activation energy of ~80 kJ mol^{-1}, and the reaction was found to be first order in $[[Mn^{III}L(H_2O)]_2]$ and 0.5 order in quinone. Although this is an interesting photochemical water oxidation reaction, it is unlikely that it will provide mechanistic information useful for defining the photosynthetic water oxidation reaction since the photon flux to the manganese cluster of the OEC is not believed to be sufficiently high to support a manganese centered photochemically driven reaction (*vide supra*).

3. $Mn^{IV}L_2Cl_2$ Complexes

While the addition of a weak acid with a noncoordinating anion such as pyridinium perchlorate to $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ leads to the singly protonated $[Mn^{IV}(salpn)_2(\mu_2\text{-}O),(\mu_2\text{-}OH)]ClO_4$,[80] strong acids give drastically different products. Boucher and Coe found that the addition of 2 equiv of a strong acid with a noncoordinating anion, such as perchloric acid, to a $[Mn^{IV}(\mu_2\text{-}O)]_2$ complex results in reduction of the Mn ions.[73] In contrast, addition of a strong acid in the presence of a coordinating anion such as chloride results in different chemistry. The monomeric $[Mn^{IV}(salpn)Cl_2]$ can be prepared by the addition of 4 equiv of HCl to a dichloromethane solution of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$.[15,110] This deep green complex has trans chloride ligation and exhibits a highly axial EPR spectrum. The details of this conversion have not been thoroughly elaborated, although the monoprotonated $[Mn^{IV}(salpn)_2(\mu_2\text{-}O)(\mu_2\text{-}OH)]^+$ and diprotonated $[Mn^{IV}(salpn)(\mu_2\text{-}OH)]_2^{2+}$ complexes appear to be intermediates.[111]

The $Mn^{IV}(salpn)Cl_2$ is a good oxidant, showing a reduction potential at +890 mV vs SCE, and will chlorinate a variety of substrates including cyclohexene, 1-methylcyclohexene and norbornene.[110] Cyclohexene can be converted to *trans*-dichlorocyclohexane in 58% yield after 36 h by $Mn^{IV}(salpn)Cl_2$ in CH_2Cl_2. The Mn compound recovered from this reaction is $Mn^{III}(salpn)Cl$. An important competing side reaction that lowers the chlorination yield is that of water with $Mn^{IV}(salpn)Cl_2$, giving a Mn(III) product. While this decomposition of the catalyst is an annoyance in the chlorination reactions, it may be of considerable interest as a process to generate dioxygen from water.

A series of $Mn^{IV}L_2Cl_2$ complexes (L = Schiff base of 3-nitrosalicylaldehyde and various monoamines) were prepared by the reaction of $Mn^{III}L_2Cl$ with HCl in air.[112,113] The Mn(IV) species is generated in a 25–40% isolated yield through a process that is believed to be a disproportionation of the Mn(III) complex. These $Mn^{IV}L_2Cl_2$ complexes were observed to generate O_2 upon reaction with water by the reaction in eq 25:

$$2Mn^{IV}L_2Cl_2 + 2H_2O \rightarrow 2Mn^{II}L_2 + O_2 + 4H^+ + 4Cl^- \quad (25)$$

The greatest quantity of liberated dioxygen (about 50% of that predicted by eq 25) was generated at neutral pH. Titration of the product solution with $AgNO_3$ indicates a stoichiometric amount of Cl^- is generated, and the change in pH of unbuffered solutions indicates generation of stoichiometric H^+. Dioxygen evolution using a 20% $H_2{}^{18}O$ enriched water sample led to low, but detectable, levels of $^{16,18}O_2$ and $^{18}O_2$ which indicated that the evolved dioxygen comes from the water in solution. Elemental analysis and UV–vis experiments indicate that the product Mn species is $Mn^{III}L_2(H_2O)_2$. The potential for the Mn(IV)/Mn(III) couple is around +1.0 V vs SCE, about 0.2 V more positive than the H_2O/O_2 couple at neutral pH. Although details of the water oxidation mechanism are unavailable, it is likely that one could generate an intermediate HOCl which could go on, under acid conditions in a second step, to form dioxygen. This is reminiscent of the Ru-based water oxidation system of Meyer where both O_2 and Cl_2 were detected.[114,115]

D. Recap of Biologically Relevant Mn–O_2 Redox Pathways

Recognizing the relevance of both the Boucher and Coe ($[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2 + HClO_4 \rightarrow H_2O_2$)[73] and Matsushita et al. ($Mn^{IV}(N\text{-Pr-3-}NO_2sal)_2Cl_2 + 2H_2O \rightarrow O_2 + 4H^+ + 4Cl^-$)[112,113] reactions, one can deduce two distinct mechanisms for producing dioxygen from water in a $[Mn^{IV}(\mu_2\text{-}O)]_2$ core. In addition, the catalase activity of $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ described by Larson and Pecoraro[79] provides an explanation for the alternative catalase activity observed for the OEC. These three processes are shown in Figure 21.

The OEC catalase activity is summarized in Figure 21a assuming a dimer of dimer formulation for the

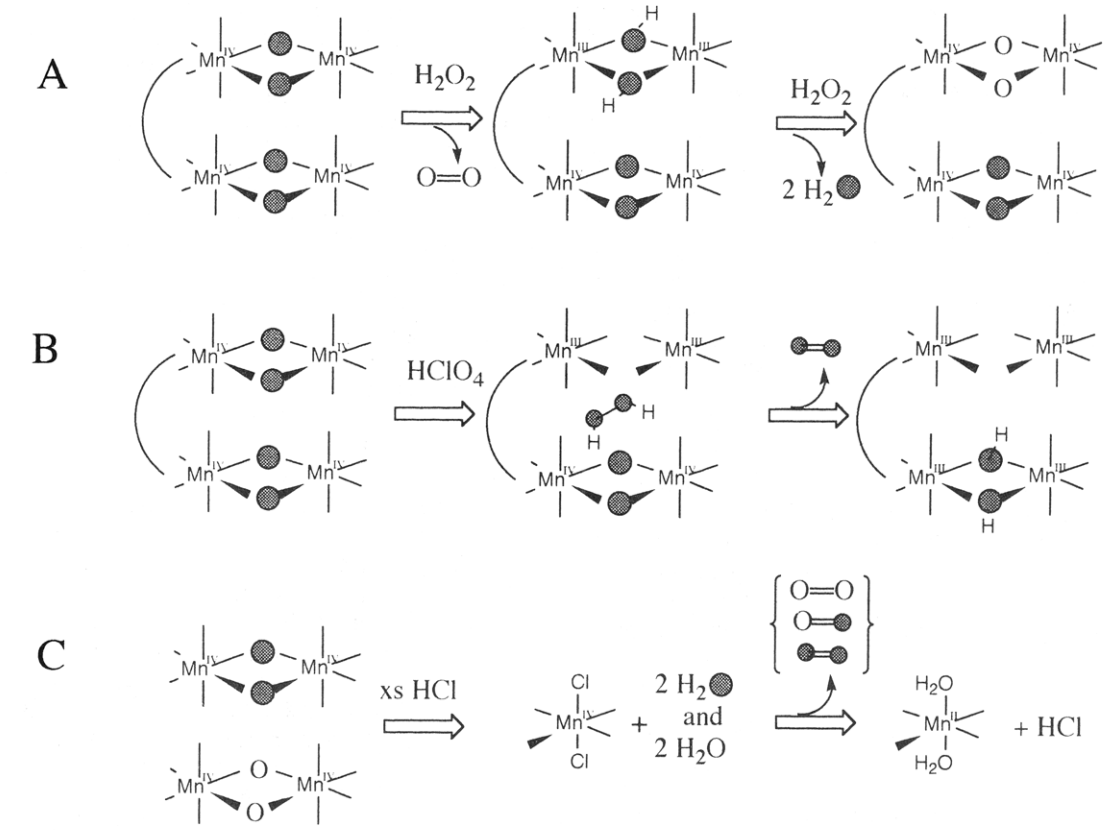


Figure 21. The potential relevance of the $[Mn^{IV}(O)]_2$ core to the reactions of the oxygen-evolving complex: (A) an explanation for the alternate catalase activity ($S_0 \rightarrow S_2$ cycle) of the oxygen-evolving complex; (B) a mechanism for water oxidation to dioxygen using a combination of the Boucher and Coe (ref 73) hydrogen peroxide producing reaction and the oxidation of peroxide by $[Mn^{IV}(salpn)(O)]_2$; and (C) a mechanism for water oxidation to dioxygen using the $Mn^{IV}(salpn)Cl_2$ formation reaction and the oxidative chemistry of Matsushita et al. (refs 112 and 113). The isotope labeling pattern for the resulting dioxygen differs significantly between mechanisms B and C. The filled oxygens represent ^{18}O and the open oxygens represent ^{16}O.

manganese cluster. Since the cycle is between S_2 and S_0, the relevant enzyme oxidation levels are (III,IV,IV,-IV) and Mn(III,III,III,IV), respectively. The catalase chemistry is illustrated at the Mn(IV,IV) dimer. The first equivalent of hydrogen peroxide is oxidized, giving dioxygen and the reduced cluster. A subsequent molecule of H_2O_2 reoxidizes the center to regenerate S_2. In this cycle dioxygen retains the label found in peroxide as has been shown both for the $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ and OEC reactions.[79,116]

The second process illustrated in Figure 21b combines the Boucher and Coe[73] acidification chemistry with the $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$ catalase chemistry to generate dioxygen. It relies on a two-step reaction sequence in which a $[Mn^{IV}(\mu_2\text{-}O)]_2$ core reacts with acid to generate 2Mn(III) and H_2O_2. Although Boucher and Coe did not follow the reaction using labeled $[Mn^{IV}(salpn)(\mu_2\text{-}O)]_2$, it is likely that this is simply the back reaction of the $[Mn^{IV}(salpn)(\mu_2\text{-}O]_2$ formation with hydrogen peroxide (i.e., $2Mn^{III} + H_2O_2 \rightarrow Mn^{IV}(\mu_2\text{-}O) + 2H^+$). In this case, both oxygens in the resultant hydrogen peroxide would originate from the same $[Mn^{IV}(\mu_2\text{-}O)]_2$ molecule. Subsequent oxidative chemistry of hydrogen peroxide with a second $[Mn^{IV}(\mu_2\text{-}O)]_2$ would give $O_2 + 2Mn^{III}$ along the lines reported by Larson and Pecorano.[79] Functionally, this corresponds to conversion of O^{2-} (as in water) to dioxygen at the expense of four manganese oxidizing equivalents. Furthermore, if the initial core was labeled as $[Mn^{IV}(\mu_2\text{-}^{18}O)]_2$, the liberated dioxygen should be exclusively $^{18}O_2$.

The dioxygen-producing reaction that proceeds through a monomeric $Mn^{IV}Cl_2$, shown in Figure 21c, is mechanistically dissimilar to the peroxide pathway described above and should lead to mixed labeled O_2. In the first step, acid and halide attack the $[Mn^{IV}(\mu_2\text{-}O)]_2$ core as we have described above; however, rather than liberating H_2O_2 in a redox reaction, the $Mn^{IV}Cl_2$ intermediate is formed and water is released. This H_2O can then back react with the $Mn^{IV}Cl_2$ to give dioxygen according to the chemistry of Matsushita et al. An oxygen label would scramble in this reaction since all of the oxygen atoms are released prior to reoxidation. Another important distinction between the Boucher/Coe and Matsushita intermediates is that in the first case two sequential two-electron oxidations at manganese dimers lead to product, while in latter acid/base chemistry precedes oxidation which occurs exclusively at mononuclear centers.

V. Future Directions

During the 1980s we witnessed an explosive expansion in the effort expended to characterize the active sites of manganese biomolecules. In particular, inorganic modeling chemists have provided a firm foundation for the categorization of the properties of manganese in its various attainable oxidation states and in a wide variety of structures that are accessible to multinuclear aggregates of the transition metals. The significant achievement of the past decade was to prepare struc-

tural analogues of enzyme active sites such as dimers, dimers of dimers, trimers, butterflies, adamantanes, and cubanes. This work provided a framework for the "possible" in a structural sense. The watchword for the 1990s is reactivity and, in particular, a mechanistic understanding of this reactivity. While oxo group transfer from manganese porphyrins and Schiff base molecules has been well studied for many years, the general state of understanding of manganese reactivity has lagged far behind that of other bioelements such as iron or copper.

The obvious targets for synthetic bioinorganic chemists include the elucidation of the mechanism of dioxygen production by the oxygen-evolving complex, a full chemical description of the chemistry of the manganese catalases and superoxide dismutases and functional mimics for the manganese ribonucleotide reductase. In most of these cases dioxygen or one of its reduced forms is an active participant in the chemical reaction. Surprisingly then, we have seen that only four authentic "dioxygen adducts" have been structurally characterized and that these are all reminiscent of peroxo ligation to a high-valent metal. Direct effort to prepare and characterize more such molecules which may serve to further our understanding of reactive intermediates is highly desirable. In addition, functional models for any of these enzyme activities are scarce. The ones which have been discovered need to be more fully understood and new reactions with complexes that more closely resemble the structure of the enzyme active sites need to be discovered. It might be said that the childhood of the field of manganese chemistry was in the 1970s when the wondrous reactions of this element were just beginning to be revealed. The adolescence of manganese chemistry was the 1980s when structure and rules were learned and great possibilities defined. As our understanding of manganese chemistry moves into young adulthood, we hope that the first inklings of the complex interplay between these structures so diligently discovered in adolescence can be weaved into a cohesive fabric that will provide this field a healthy and well-developed life.

VI. Abbreviations

2-OHsalpn	*N,N'*-disalicylidene-1,3-diaminopropan-2-ol
3,5-iPr$_2$pz	3,5-diisopropylpyrazole
5-NO$_2$-salrdpt	*N,N'*-bis(5-nitrosalicylidene)-1,7-diamino-4-azaheptane
5-NO$_2$-saldien	*N,N'*-bis(5-nitrosalicylidene)-1,5-diamino-3-azapentane
abts	2,2'-azinobis(3-ethylbenzothiazoline-sulfonic acid)
dien	diethylenediamine
dma	dimethylacetamide
dmf	dimethylformamide
dmso	dimethyl sulfoxide
dtbc	3,5-di-*tert*-butylcatecholate
dtbsq	3,5-di-*tert*-butylsemiquinone
EPR	electron paramagnetic resonance
FAB	fast-atom bombardment
H$_2$salen	*N,N'*-disalicylidene-1,2-diaminoethane
H$_2$salpn	*N,N'*-disalicylidene-1,3-diaminopropane
HB(3,5-iPr$_2$pz)	tris[(3,5-diisopropyl)pyrazolyl]borate
LMCT	ligand-to-metal charge transfer
MnRR	manganese ribonucleotide reductase
N-Pr-3-NO$_2$-sal	*N*-(3-nitrosalicylidene)-1-aminopropane
OEC	oxygen evolving complex
OEP	octaethylporphyrin
PA	picolinate
PAH	picolinic acid
Pc	phthalocyanine
py	pyridine
SCE	saturated calomel electrode
SOD	superoxide dismutase
thf	tetrahydrofuran
TPP	tetraphenylporphyrin

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