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Article

Reevaluation of the Kinetics of Polynuclear Mimics for Manganese Catalases

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Considerable effort has been expended in order to understand the mechanism of manganese catalases and to develop functional mimics for these enzymes. For many years, the most efficient reactivity mimic was $[Mn^{IV}salpn(\mu\text{-}O)]_2$ [H_2salpn = 1,3-bis(salicylideneiminato)propane], a compound that cycles between the $Mn^{IV}{}_2$ and $Mn^{III}{}_2$ oxidation levels instead of the $Mn^{II}{}_2$ and $Mn^{III}{}_2$ oxidation states used by the enzyme, with $k_{cat} = 250\ s^{-1}$ and $k_{cat}/K_M = 1000\ M^{-1}\ s^{-1}$. Recently, a truly exceptional high value of k_{cat} was reported for the complex $[Mn(bpia)(\mu\text{-}OAc)]_2{}^{2+}$ [bpia = bis(picolyl)(*N*-methylimidazol-2-yl)amine]. On the basis of a calculated k_{cat} value of 1100 s^{-1} and an efficiency k_{cat}/K_M of 34 000 $M^{-1}\ s^{-1}$, this complex has been suggested to represent a significant breakthrough in catalytic efficiencies of manganese catalase mimics. However, a plot of $r_i/[cat]_T$ vs $[H_2O_2]_0$, where the saturation value approaches 1.5 s^{-1}, is inconsistent with the 1100 s^{-1} value tabulated for k_{cat}. Similar discrepancies are observed for two other families of manganese complexes containing either a $Mn_2(\mu\text{-}OPh)_2{}^{2+}$ core and different substituted tripodal ligands or complexes of methyl and ethyl salicylimidate, with an $Mn_2(\mu\text{-}OPh)_2{}^{4+}$ core. Reevaluation of the kinetic parameters for these three systems reveals that the originally reported values were overestimated by a factor of ∼1000 for both k_{cat} and k_{cat}/K_M. We discuss the origin of the discrepancy between the previously published kinetic parameters and the newly derived values. Furthermore, we provide a short analysis of the existing manganese catalase mimics in an effort to provide sound directions for future investigations in this field.

Introduction

In recent years, the chemistry of manganese has been extensively studied because of the occurrence of this metal in the active site of several enzymes that participate in the chemistry of reactive dioxygen species, such as manganese catalases, manganese superoxide dismutase, ribonucleotide reductase, the photosynthetic oxygen-evolving system, manganese peroxidase, etc.[1] Many manganese complexes involving a variety of ligands have been fruitful in affording mechanistic insight into the enzymatic reactions and have made essential contributions to the understanding of the active-site structure and chemical reactivity of the above-mentioned enzymes.[2]

In the particular case of manganese catalase mimics, obtaining low molecular weight catalytic scavengers of H_2O_2 has been actively sought for the prevention of oxidative stress injuries. The active site of these enzymes possesses two Mn ions triply bridged through a $\mu_{1,3}$-carboxylato from a glutamate residue and two solvent-derived single atom bridges (the nature of which is dependent on the metal oxidation state and has yet to be fully ascertained).[3] This

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site disproportionates H_2O_2 by cycling between the Mn^{II}_2 and Mn^{III}_2 oxidation states during catalysis.[4] Given its recent structural resolution, a greater emphasis has been focused on the preparation of reactivity models of manganese catalases.[5−14,18−20] A comparison of the activity of structurally characterized complexes can help delineate the functional roles of the bridging ligands and structural motifs that play a key role in the mechanism of H_2O_2 disproportionation by these enzymes. For a number of model manganese complexes, the rate of the catalyzed reactions showed saturation kinetics upon H_2O_2 and first-order dependence on the catalyst, and the reactivity of the artificial mimics was compared to that of the enzyme based on the k_{cat}/K_M criterion,[5] where k_{cat} is the catalytic rate constant and K_M is a measure of the affinity for H_2O_2 (the lower the K_M value, the higher the affinity for H_2O_2). Complexes with $Mn^{II}_2(\mu\text{-OAc})(\mu\text{-OR})^{2+}$, $Mn^{II}_2(\mu\text{-OAc})(\mu\text{-OR})(\mu\text{-OH})^{+}$, $Mn^{III}_2(\mu\text{-OR})_2{}^{4+}$, $Mn^{III}_2(\mu\text{-O})(\mu\text{-OR})_2(OH)(OAc)^{+}$, $Mn^{III}_2(\mu\text{-OR})_2(\mu\text{-OAc})^{3+}$, $Mn^{III}Mn^{IV}(\mu\text{-O})_2{}^{3+}$, and $Mn^{III}Mn^{IV}_3(\mu\text{-O})_6{}^{3+}$ cores display saturation kinetics at a rate of 0.2−26 s^{-1} (vs $k_{cat} = 2.0 \times 10^5$ s^{-1} for the *Lactobacillus plantarum*[4] enzyme or $k_{cat} = 2.6 \times 10^5$ for *Thermus thermophilus*[15]) and k_{cat}/K_M = 14−990 M^{-1} s^{-1} (vs $k_{cat}/K_M = 6.0 \times 10^5$ for *L. plantarum*[4] or $k_{cat}/K_M = 3.1 \times 10^6$ for *T. thermophilus*[15]). In these studies, kinetic parameters were obtained by fitting the initial rates (r_i) vs $[H_2O_2]_0$ plots, at fixed $[\text{catalyst}]_0$, to eq 1, the well-known Michaelis−Menten equation.

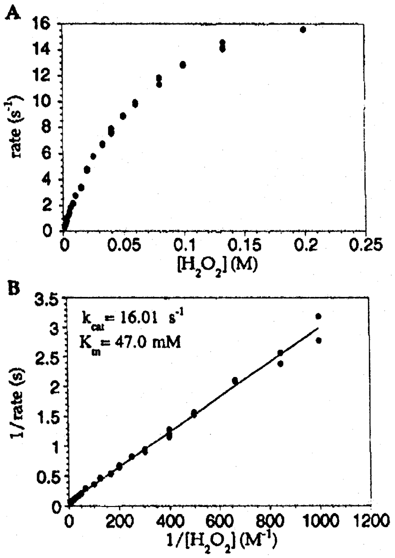

Figure 1. (A and B) = Figure 2(A and B) from: Gelasco, A. and Pecoraro, V. L. *J. Am. Chem. Soc.* **1993**, *115*, 7928−7929.

$$r_i\ (\text{concn} \times t^{-1}) = k_{cat}[\text{cat}]_T[H_2O_2]_0/(K_M + [H_2O_2]_0) = V_{max}[H_2O_2]_0/(K_M + [H_2O_2]_0) \quad (1)$$

According to this expression, the limiting rate at high $[H_2O_2]_0$ is designated as V_{max} ($=k_{cat}[\text{cat}]_T$). In some cases, the initial rates were expressed per mole of catalyst, or unit concentration of catalyst, and the resulting $r_i/[\text{cat}]_T$ vs $[H_2O_2]_0$ plots were fitted with eq 2.

$$r_i/[\text{cat}]_T\ (t^{-1}) = k_{cat}[H_2O_2]_0/(K_M + [H_2O_2]_0) \qquad (2)$$

where the limiting value at high $[H_2O_2]_0$ is now k_{cat}. A series of $\{r_i, [H_2O_2]_0\}$ or $\{[r_i/[\text{cat}]_T, [H_2O_2]_0\}$ data pairs can then be fitted with eq 1 or 2 by nonlinear least-squares methods to determine the values of V_{max} and K_M or k_{cat} and K_M, respectively, or alternately by linear least-squares fits of the double reciprocal of eqs 1 and 2 (Lineweaver−Burk plots). The values of the kinetic parameters obtained by any of the alternative treatments of data yield similar results.[16]

Although calculation of the kinetic parameters by fitting of the experimental rate data with the Michaelis−Menten equation is a basic topic, the paragraphs that follow intend to show how the kinetic data need to be handled with care and the units and consistency of the results carefully checked. The consistency of the kinetic results can be easily verified by comparing the values of k_{cat} or V_{max} with those expected from plotted experimental data. k_{cat} gives information under saturating substrate conditions, and k_{cat}/K_M, or more precisely V_{max}/K_M, pertains under low substrate concentrations.

Let us illustrate this with an example: in a typical kinetic study of catalytic H_2O_2 disproportionation,[17] the authors show plots of $r_i/[\text{cat}]_T$ vs $[H_2O_2]_0$ (Figure 1A) and $[\text{cat}]_T/r_i$ vs $1/[H_2O_2]_0$ (Figure 1B) and *correctly* calculate the 16.01 s^{-1} value of k_{cat} from the double-reciprocal plot.[17]

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An interesting point regarding the data in Figure 1A is that this plot gives us an idea of the k_{cat} value by simple inspection of the curve because $r_i/[cat]_T$ values at high $[H_2O_2]_0$ approach the k_{cat} value. Therefore, from inspection of the plot in Figure 1A, we expect that k_{cat} should be around 16 s^{-1}, and actually the calculated k_{cat} value of 16.01 s^{-1} agrees[17] with the value expected from the plot. The same applies to the r_i vs $[H_2O_2]_0$ plots, which give us an idea of V_{max} at high $[H_2O_2]_0$.

For many years, the most efficient reactivity mimic was $[Mn^{IV}salpn(\mu\text{-}O)]_2$ [H_2salpn = 1,3-bis(salicylideneiminato)-propane], a compound that cycles between the Mn^{IV}_2 and Mn^{III}_2 oxidation levels instead of the Mn^{II}_2 and Mn^{III}_2 oxidation states used by the enzyme, with $k_{cat} = 250$ s^{-1} and $k_{cat}/K_M = 1000$ M^{-1} s^{-1}.[21] In 2002, a truly exceptional high value of k_{cat} was reported for the complex $[Mn(bpia)(\mu\text{-}OAc)]_2^{2+}$ [bpia = bis(picolyl)(*N*-methylimidazol-2-yl)-amine].[22] On the basis of a reported k_{cat} value of 1100 s^{-1} and an efficiency k_{cat}/K_M of 34 000 M^{-1} s^{-1}, this complex has been suggested to represent a significant breakthrough in the catalytic efficiencies of manganese catalase mimics. However, in the same paper where these kinetic parameters are tabulated, a plot of $r_i/[cat]_T$ vs $[H_2O_2]_0$ (Figure 8 in ref 22) has been provided, which cannot agree with the value of 1100 s^{-1} tabulated for k_{cat}. Similar high values are reported for another family of manganese complexes with a $Mn_2(\mu\text{-}OPh)_2^{2+}$ core and different substituted tripodal ligands, published in 2004.[9] Plots of $r_i/[cat]_T$ vs $[H_2O_2]_0$ show maximal values of ≈0.012−0.055 s^{-1} (see Figure 6 of ref 9), while k_{cat} values in the 88−283 s^{-1} range were reported for these complexes (see Table 4 of ref 9). A third example of such type of disagreement is observed in the kinetic study of H_2O_2 disproportionation by complexes of methyl and ethyl salicylimidate, with the $Mn_2(\mu\text{-}OPh)_2^{4+}$ core, in the presence of 5 equiv of NaOH.[10] While plots of $r_i/[cat]_T$ vs $[H_2O_2]_0$ show saturation kinetics with maximal values approaching ≈0.14 and 0.033 s^{-1} (see Figure 8 of ref 10), k_{cat} values, calculated from the double-reciprocal plot, of 807 and 190 s^{-1} (see the summary, p 305, and the first paragraph of the Discussion section, p 311, of ref 10) were reported. In the three cases mentioned here, the calculated efficiency values placed the complexes among the most efficient compounds yet developed, but these calculated values are not supported by the experimental data shown as figures in the respective papers. Therefore, reevaluation of the kinetics for the reported data has been performed.

On the basis of a recalculation of the kinetic parameters using the original data, we conclude that Figure 8 in ref 22 is not correct and must be replaced with the one in Figure 2, which now belongs to the H_2O_2 disproportionation catalyzed by $[Mn(bpia)(\mu\text{-}OAc)]_2^{2+}$.

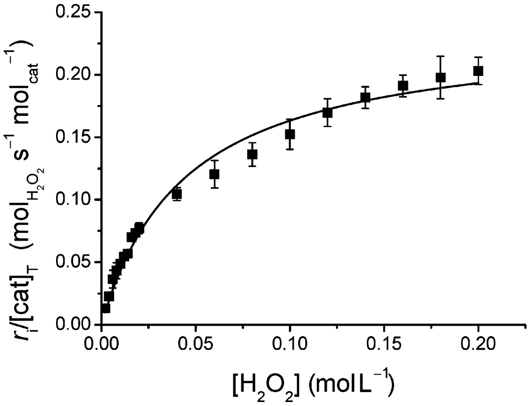

Figure 2. Initial rate of substrate consumption vs substrate concentration at a constant concentration of $[Mn(bpia)(\mu\text{-}OAc)]_2^{2+}$. New Figure 8 for *Inorg. Chem.* **2002**, *41*, 5544−5564.

The new $\{r_i/[cat]_T, [H_2O_2]_0\}$ set of data was fitted to eq 2 by a nonlinear least-squares method, and the recalculated values of k_{cat} and K_M are listed in Table 1. Lineweaver−Burk plots for $[Mn(bpia)(\mu\text{-}OAc)]_2^{2+}$, $\{1/r_i, 1/[H_2O_2]_0\}$ (Figure 3), and $\{[cat]_T/r_i, 1/[H_2O_2]_0\}$ (Figure 4) yield straight lines and, therefore, confirm that the data follow the Michaelis−Menten mechanism. These double-reciprocal plots have a *y* intercept given by $1/V_{max}$ or $1/k_{cat}$ and a slope of K_M/V_{max} or K_M/k_{cat}, respectively. Values of $k_{cat} = 0.215 \pm 0.009$ s^{-1} and $K_M = 32 \pm 4$ mM obtained from these plots are similar to those calculated from Figure 2. Inasmuch as eq 2 is statistically better than Lineweaver−Burk plots for data fitting, recalculated kinetic parameters listed in Table 1 are those obtained from eq 2.

In the 2002 *Inorg. Chem.* paper[22] and two subsequent publications,[9,10] a Lineweaver−Burk plot was used to determine the K_M and k_{cat} values. In the three papers, the second option of plotting and presenting the data ($[cat]_T/r_i$ vs $1/[H_2O_2]_0$) was chosen; however, the K_M and k_{cat} parameters were extracted as if the first plot option ($1/r_i$ vs $1/[H_2O_2]_0$) were chosen. Consequently, the K_M numbers reported in the three papers are correct, but the k_{cat} numbers are wrong. We have reevaluated the K_M and k_{cat} values by fitting the data to the Michaelis−Menten equation with a nonlinear least-squares method, which is the method of choice to determine the values of k_{cat} and K_M when there are enough data near the saturation value. Table 1 summarizes the recalculated k_{cat} and K_M values for catalase mimics of these papers[9,10,22] as well as the catalysts that disproportionate H_2O_2 with the highest maximal rates or efficiencies (k_{cat}/K_M). The equation used to determine k_{cat} and K_M is mentioned, if reported.

Given these new values for the bpia and related manganese complexes, we must reconsider the best strategies for making functional manganese-based hydrogen peroxide disproportionation catalysts. At present, if the intent is to destroy hydrogen peroxide, the well-described $[Mn^{IV}_2(salpn)(\mu\text{-}O)]_2$ and its ring-substituted derivatives best serve the purpose. While possibly commercially significant in this purpose, $[Mn^{IV}_2(salpn)(\mu\text{-}O)]_2$ does not model well the manganese catalases because it is well-established that these enzymes cycle between the Mn^{II} and Mn^{III} oxidation levels and become inactive when a high-valent di-μ_2-oxo core is formed. Among the compounds assigned a Mn^{II}_2/Mn^{III}_2 redox cycle,

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Table 1. k_{cat} and K_M Values for Manganese Model Compounds

compound[a]	k_{cat} (s^{-1})	K_M (M)	k_{cat}/K_M (s^{-1} M^{-1})	equation used for data fitting	ref
$[Mn^{IV}_2(salpn)(\mu\text{-}O)]_2$	250	0.250	1000		21
$[Mn^{II}(2\text{-}OHpicpn)]_4^{4+}$	150	2.6	58	eq 2	24
$[Mn^{III}(2\text{-}OHsalpn)]_2$	10.1	0.0102	990	eq 2	20
$[Mn^{III}_2(\mu\text{-}O)(OH_2)(OAc)benzimpn]^+$ + 5 equiv of OH^-	2.1	0.003	700	Lineweaver−Burk plot	25
$[Mn^{III}_2(\mu\text{-}O)(OH_2)(OAc)benzimpn]^+$	2.7	0.006	450	Lineweaver−Burk plot	25
$[Mn^{III}(2\text{-}OH(5\text{-}Xsal)pn)]_2$	4.2−21.9	0.011−0.072	382−304	eq 2	20
$[Mn^{III}_2(\mu\text{-}MeO)(\mu\text{-}AcO)naphpentO]^+$	0.79	0.0035	226	eq 2	12
$[Mn(bpia)(OAc)]_2^{2+}$	0.237 ± 0.008	0.045 ± 0.004	5.2 ± 0.5	eq 2	22, this work
$[Mn_2L_1Cl_2]$	0.075 ± 0.004	0.066 ± 0.008	1.1 ± 0.15	eq 2	9, this work
$[Mn_2L_2Cl_2]$	0.048 ± 0.002	0.151 ± 0.014	0.3 ± 0.032		
$[Mn_2L_3Cl_2]$	0.060 ± 0.002	0.072 ± 0.007	0.8 ± 0.086		
$[Mn_2L_4Cl_2]$	0.017 ± 0.001	0.020 ± 0.003	0.8 ± 0.137		
$[Mn_2L_5Cl_2]$	0.056 ± 0.005	0.103 ± 0.019	0.5 ± 0.111		
$[Mn_2(etsalim)_4(Hetsalim)_2]^{2+}$ + 5 equiv of OH^-	0.221 ± 0.011	0.142 ± 0.014	1.6 ± 0.174	eq 2	10, this work
$[Mn(mesalim)_2(OAc)(MeOH)]$ + 5 equiv of OH^-	0.038 ± 0.001	0.021 ± 0.001	1.8 ± 0.098		

[a] Ligands: H_2salpn = 1,3-bis(salicylideneiminato)propane; 2-OHpicpn = *N*,*N*′-bis-1,3-(picolinimine)propan-2-ol; 2-$OHsalpnH_2$ = 1,3-bis(salicylideneamino)propan-2-ol; benzimpn = *N*,*N*,*N*′,*N*′-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol; 2-OH(5-Xsal)pnH_2 = 1,3-bis(5-Xsalicylideneamino)propan-2-ol; X = MeO, Cl; naphpentOH = bis(2-OH-naphtylidenamino)pentan-3-ol; bpia = bis(picolyl)(*N*-methylimidazol-2-yl)amine; HL_1 = 2-({bis[(pyridin-2-yl)methyl]amino}methyl)phenol, HL_2 = 2-({bis[(pyridin-2-yl)methyl]amino}methyl)4-nitrophenol; HL_3 = 2-[[((6-methylpyridin-2-yl)methyl)(pyridin-2-ylmethyl)amino]methyl]phenol; HL_4 = 2-[[((6-methylpyridin-2-yl)methyl)(pyridin-2-ylmethyl)amino]methyl]-4-nitrophenol; HL_5 = 2-[(bis(pyridin-2-ylmethyl)amino)methyl]-6-methoxyphenol; Hetsalim = ethyl salicylimidate; Hmesalim = methyl salicylimidate.

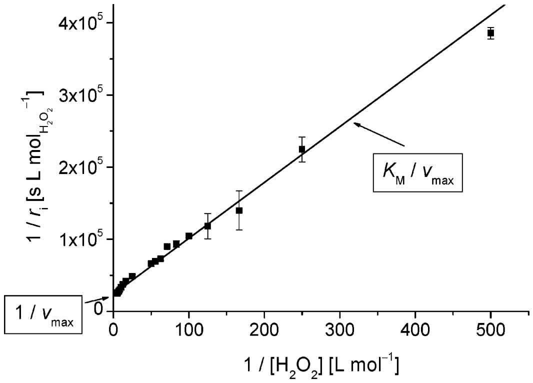

Figure 3. Lineweaver−Burk plot (double reciprocal of eq 1) for $[Mn(bpia)(\mu\text{-}OAc)]_2^{2+}$.

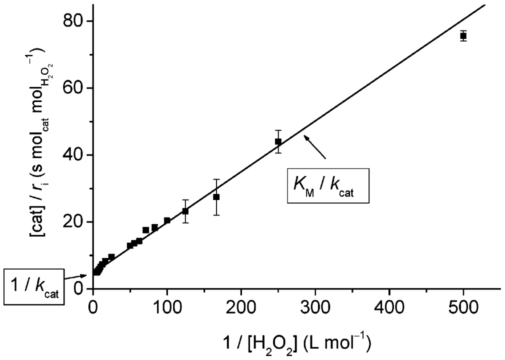

Figure 4. Lineweaver−Burk plot (double reciprocal of eq 2) for $[Mn(bpia)(\mu\text{-}OAc)]_2^{2+}$ obtained from the data in Figure 2.

$[Mn^{II}(2\text{-}OHpicpn)]_4^{4+}$ [2-OHpicpn = *N*,*N*′-bis-1,3-(picolinimine)propan-2-ol] exhibits the maximal rates, being somewhat similar to that of $[Mn^{IV}_2(salpn)(\mu\text{-}O)]_2$. Unfortunately, this tetrameric complex possesses a very low affinity for the substrate, resulting in a low efficiency, and does not match the two manganese ion stoichiometries of the Mn catalases.

Thus, if one combines the restrictions of the proper metal ion stoichiometry and the proper Mn^{II}_2/Mn^{III}_2 redox cycle, there are two structure types with efficiencies slightly lower than that of $[Mn^{IV}_2(salpn)(\mu\text{-}O)]_2$ that stand out. These are $[Mn^{III}(2\text{-}OH\text{-}salpn)]_2$ (and its ring-substituted derivatives)[20] and $[Mn^{III}_2(\mu\text{-}O)(OH_2)(OAc)benzimpn]^+$ [benzimpn = *N*,*N*,*N*′,*N*′-tetrakis(2-methylenebenzimidazolyl)-1,3-diaminopropan-2-ol],[25] with approximately equivalent efficiencies. The former series of compounds, which likely remain dimers during their cycle, shows a rich chemistry with kinetic parameters that vary as a result of redox potential changes and other factors too lengthy to redescribe at this point. In general, the Mn−Mn distance of ∼3.25 Å reported for these compounds, the relatively small change in the metal−metal separation upon $Mn^{II}_2 \leftrightarrow Mn^{III}_2$ conversion, and the retention of catalyst integrity all contribute to the success of this molecular class. These distances are only slightly longer than the 3.18 Å found in the reduced form of *T. thermophilus*.[23] $[Mn^{III}_2(\mu\text{-}MeO)(\mu\text{-}AcO)naphpentO]^+$ [naphpentOH = bis(2-OH-naphthylideneamino)pentan-3-ol] and related compounds[12,13] also exhibit significant efficiencies; however, their redox cycle involves the Mn^{III}_2 and Mn^{IV}_2 oxidation levels.

It is also worth noticing that Table 1 is limited to the complexes for which kinetic studies report the k_{cat} and K_M values. Among other series of dinuclear manganese complexes relevant as manganese catalase models but not included in Table 1, we shall mention those by Wieghardt et al.[26] for which only k_{cat} is reported, the series by Sakiyama

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et al.[27] with complexes characterized by second-order kinetics, and the series by Latour et al.,[28] which have no saturation kinetics and for which the k_{cat} values are not reported [in a recent paper[29] in which kinetic studies are reported, activation parameters are calculated from $\ln(r_i)$ vs $1/T$, with $r_i = V(O_2)\ t^{-1}$ in mL min^{-1}, but the catalyst ratio is not given].

In conclusion, we have reexamined the reported kinetic parameters for a series of manganese compounds originally thought to be highly active hydrogen peroxide disproportionation catalysts and have found that while the original determination for K_M was correct, the calculation of the maximal rates was off significantly. This error was due to the inappropriate use of Lineweaver−Burk plots and could be realized by a careful examination of the plot of rate versus substrate concentration. Given the new values reported in Table 1, we conclude that investigators interested in utilizing a rapid hydrogen peroxide disproportionation catalyst should employ $[\mathrm{Mn^{IV}}_2(\mathrm{salpn})(\mu\text{-O})]_2$. Those workers seeking to develop new mimics for the manganese catalase enzyme that contain the proper metal stoichiometries and oxidation states for the enzymatic reaction are probably best served by designing dinuclear complexes or dimeric models that do not dissociate during the catalytic cycle, having Mn−Mn distances around 3.2 Å, and employing a ligand set that allows for both oxidation and reduction of the metals at appropriate potentials, as has been seen for $[\mathrm{Mn^{III}}(2\text{-OH-salpn})]_2$ and $[\mathrm{Mn^{III}}_2(\mu\text{-O})(\mathrm{OH_2})(\mathrm{OAc})\mathrm{benzimpn}]^+$.

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