Oxidation

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Distinct Reactivity Differences of Metal Oxo and Its Corresponding Hydroxo Moieties in Oxidations: Implications from a Manganese(IV) Complex Having Dihydroxide Ligand**

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Transition-metal ions play the critical roles in a series of enzymatic electron-transfer, hydrogen-abstraction, and oxygenation events in nature, and the active metal oxo functional groups (i.e., M^{n+}=O) have been long recognized as the key active moieties in these biological and chemical oxidation processes.[1,2] However, recent discoveries revealed significant exceptions. Green found that the compound II intermediate in chloroperoxidase is in an iron(IV) hydroxo form (i.e., (Porp)Fe^{IV}–OH; Porp = porphyrin ligand), rather than the generally expected iron(IV) oxo form, while the active forms of the corresponding compound II in other peroxidases are still controversial.[3,4] In xanthine oxidases, a molybdenum(VI) hydroxo group (i.e., Mo^{VI}–OH) was suggested to play the key role in hydroxylation of hypoxanthine even though an Mo^{VI}=O group exists in the same molybdenum(VI) center.[5] In lipoxygenases, iron(III) hydroxo or manganese(III) hydroxo, rather than their corresponding oxo groups, were also proposed to perform hydrogen abstraction from the unsaturated fatty acid, and a few inorganic models with the M^{n+}–OH moiety confirmed its hydrogen-abstraction ability.[6,7] Interestingly, using the method introduced by Bordwell et al. and Mayer,[8] it was found that the hydrogen-abstraction ability of a metal oxo moiety and the related metal hydroxo in those models are very similar.[7,9,10] The major difference between the M^{n+}=O and its corresponding M^{n+}–OH group is their protonation state. The immediate issue is "what are the reactivity relationships between the metal oxo and its corresponding hydroxo intermediate?" Clarifying their reactivity relationships would undoubtedly promote the understanding of the natural enzymes' selection of M^{n+}=O or M^{n+}–OH to serve as the key active intermediate in specific oxidative events, thus promoting the understanding of their mechanisms and the design of new medicines for many diseases. Also, these advances would benefit the rational design of synthetic oxidation catalysts.

During studies to distinguish their activity differences in hydrogen abstraction, a fundamental event in biological oxidations, we found that the Mn^{IV}=O moiety in the [Mn^{IV}(Me_2EBC)] complex (Me_2EBC = 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane) reacted more than 40 times faster than its protonated Mn^{IV}–OH counterpart, even though their oxidizing powers are very similar (84.3 kcal mol^{-1} vs. 83.0 kcal mol^{-1}).[11] Later Fiedler and Que observed a rate difference of more than 100 times between the Fe^{IV}=O and Fe^{IV}–OH group in their Fe^{IV}(β-BPMCN) complex.[12] Using Mn^{IV}(salen) complexes (salen = *N*,*N*′-bis(salicylidene)ethylenediamine anion), Fujii and co-workers also found that Mn^{IV}=O demonstrates much faster rate than its protonated Mn^{IV}–OH counterpart in hydrogen abstraction from substituted phenols, whereas Mn^{IV}=O and Mn^{IV}–OH demonstrate amazingly similar oxidizing power (84.2 kcal mol^{-1} vs. 83.1 kcal mol^{-1}) as well as these in [Mn^{IV}(Me_2EBC)] complexes.[13] Recently, some of us found that Mn^{IV}=O and Mn^{IV}–OH groups in the identical [Mn^{IV}(Me_2EBC)] complexes perform triphenylphosphine oxygenation through different mechanisms, one by concerted oxygen transfer, the other by electron transfer.[14] The present findings reveal that the oxidative differences of the Mn^{IV}=O and Mn^{IV}–OH groups in the [Mn^{IV}(Me_2EBC)] complex are not only in their activity, that is, rate difference, but distinctly in their reactivity, which reveals insights into the factors controlling the selectivity process at work when redox metalloenzymes choose a metal oxo or hydroxo functional group to serve specific oxidations.

The [Mn^{IV}(Me_2EBC)$(OH)_2$$(PF_6)_2$] complex was synthesized according to the literature method.[11a] Since two determined pK_a values, 6.86 and 10, represent the removal of the first and second proton from [Mn^{IV}(Me_2EBC)$(OH)_2$]$^{2+}$ to form [Mn^{IV}(Me_2EBC)(O)(OH)]$^{+}$ and [Mn^{IV}(Me_2EBC)$(O)_2$)], respectively, and an estimated pK_a of 2 represents the addition of one proton to form [Mn^{IV}(Me_2EBC)(OH)(H_2O)]$^{3+}$, the dominant species at pH 1.5, 4.0, and 13.4 are [Mn^{IV}(Me_2EBC)(OH)(H_2O)]$^{3+}$, [Mn^{IV}(Me_2EBC)$(OH)_2$]$^{2+}$, and [Mn^{IV}(Me_2EBC)$(O)_2$)], respectively (Figure 1).[11c] Thus, reactivity differences of the Mn^{IV}–OH moiety in [Mn^{IV}(Me_2EBC)(OH)(H_2O)]$^{3+}$ and [Mn^{IV}(Me_2EBC)$(OH)_2$]$^{2+}$, and of Mn^{IV}=O in [Mn^{IV}(Me_2EBC)$(O)_2$)] can be investigated under three different

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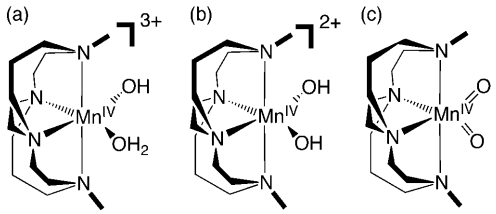


Figure 1. Manganese(IV) species under three pH conditions: a) pH 1.5, b) pH 4.0, and c) pH 13.4.

pH conditions. Hydrogen abstraction reactions from 9,10-dihydroanthracene substrate were performed in acetone/water (4:1) under nitrogen, and the product distributions are summarized in Table 1. It was found that the product distributions are different under these three pH conditions. At pH 4.0, hydrogen abstraction by Mn^{IV}–OH in $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$ provides anthracene as the dominant product (17.6%) with only a trace of anthraquinone (0.8%). In strong base at pH 13.4, where Mn^{IV}=O is in large excess in $[Mn^{IV}(Me_2EBC)(O)_2)]$, only 6.3% yield of anthracene was found with the 21.8% yield of anthraquinone being dominant. The Mn^{IV}–OH moiety in $[Mn^{IV}(Me_2EBC)(OH)(H_2O)]^{3+}$ at pH 1.5 gives a 3.0% yield of anthracene and an 8.3% yield of anthraquinone, a surprisingly similar product distribution to that for the Mn^{IV}=O moiety at pH 13.4. Although the product yields are relatively low because of the sluggish oxidizing power of the manganese(IV) species, the obtained mechanistic information is fruitful (see below).

Table 1: Hydrogen abstraction from 9,10-dihydroanthrancene by the manganese(IV) complex under different pH conditions.[a]

pH	Mn^{IV} moiety	Product distribution [%]			
		anthracene	anthraquinone	anthrone	monochlorinated anthracene
1.5	Mn^{IV}–OH	3.0	8.4	trace	trace
4.0	Mn^{IV}–OH	17.6	0.8	none	none
13.4	Mn^{IV}=O	6.3	21.8	trace	none

[a] Reaction conditions: acetone/water (4:1) 5 mL, manganese(IV) complex 5 mM, 9,10-dihydroanthrancene 2.5 mM, stirring under nitrogen at 298 K for a) 24 h at pH 1.5 and 4.0; or b) 6 h for pH 13.4.

To clarify whether the anthraquinone product at both high and low pH is due to a sequential oxidation of the anthracene produced during the reaction, anthracene was tested as the substrate under identical conditions to those used in the 9,10-dihydroanthracene oxidation. The yields of anthraquinone were 33.4% at pH 1.5, 2.5% at pH 4.0, and 2.9% at pH 13.4, indicating that the formation of anthraquinone from 9,10-dihydroanthracene substrate by the Mn^{IV}–OH center at pH 1.5 and by the Mn^{IV}=O center at pH 13.4 proceed through different pathways. In GC–MS analysis of the products from 9,10-dihydroanthracene oxidation, in addition to minor yields of anthrone, identified as the intermediate for anthraquinone formation at pH 1.5 and 13.4, a trace of monochlorinated anthracene was observed for the Mn^{IV}–OH at pH 1.5 (monochlorinated anthracene product was also observed for anthracene as the substrate at pH 1.5). However, no chlorinated product was detected for the Mn^{IV}=O system when keeping a similar concentration of chloride anion at pH 13.4 as at pH 1.5 (HCl and NaOH were used to adjust the pH as needed). Formation of monochlorinated anthracene is typical evidence for an electron-transfer process in which the anthracene cation intermediate has been generated. Accordingly, the anthraquinone formed by the Mn^{IV}–OH at pH 1.5 is most probably the product of sequential oxidation of anthracene by electron transfer, whereas anthracene is not an intermediate for anthraquinone formation by oxidation by the Mn^{IV}=O functional group at pH 13.4.

Electron-transfer ability of the Mn^{IV}–OH functional group at pH 1.5 was further supported by oxygenation of thianthrene. It was found that, while the Mn^{IV}=O group at pH 13.4 is incapable of oxygenating thianthrene, the Mn^{IV}–OH group at pH 1.5 provides 35.1% yield of thianthrene-*S*-oxide, and a yield of 12.1% at pH 4.0. The solvent kinetic isotope effect for this oxygenation in neutral acetone/water (ratio 4:1) revealed an inverse KIE value of 0.604 (in acetone/H_2O: $k_{obs} = 2.33 \times 10^{-5}\ s^{-1}$, in acetone/$D_2O$: $k_{obs} = 3.86 \times 10^{-5}\ s^{-1}$; see Figure S3 in the Supporting Infomration), implying that protonation of $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$ to generate $[Mn^{IV}(Me_2EBC)(OH)(H_2O)]^{3+}$ is essential for electron transfer as has previously been demonstrated for the oxygenation of triphenylphosphine.[14,15] Such an inverse KIE value also suggests that the formation of minor amounts of anthraquinone from 9,10-dihydroanthracene at pH 4.0 could be attributed to electron transfer by the Mn^{IV}–OH, present in trace amounts as $[Mn^{IV}(Me_2EBC)(OH)(H_2O)]^{3+}$. The redox potentials of the Mn^{IV}/Mn^{III} couple for the manganese(IV) species under the hydrogen-abstraction conditions are 0.54 V, 0.46 V, and 0.10 V (*vs* SCE) at pH 1.5, 4.0, and 13.4, respectively, which are also consistent with the different electron-transfer capabilities between Mn^{IV}–OH and Mn^{IV}=O (see Figure S10). Very interestingly, the sole difference between the Mn^{IV}–OH moiety in the species $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$ and in $[Mn^{IV}(Me_2EBC)(OH)(H_2O)]^{3+}$ species is one proton and one unit of net charge (2+ vs. 3+) because of the different protonation states of the manganese(IV) complex. This increase of one unit of positive charge has made it possible for the manganese(IV) in $[Mn^{IV}(Me_2EBC)(OH)(H_2O)]^{3+}$ to perform electron transfer in addition to hydrogen abstraction from 9,10-dihydroanthracene substrate, whereas the Mn^{IV}–OH center in $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$ can only perform hydrogen abstraction even though their redox potentials are very similar (0.54 V vs. 0.46 V). Thus, modulating the net charge has the power to significantly change the reactivity of the Mn^{IV}–OH moiety in the same manganese(IV) complex.

The different electron-transfer capabilities of the Mn^{IV}–OH and Mn^{IV}=O functional groups were definitively distinguished through the tests with 2,2′-azino-di-(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS), a relatively facile electron-transfer reagent.[16] At pH 4.0 and 13.4, ABTS is in the same protonation state ($pK_a = 2.2$) with identical electrochemical properties,[16c] and the UV/Vis spectra of ABTS are also identical in the pH range 3–13.4 (see Figure S11). In aqueous solution, electron transfer from ABTS to the manganese(IV) species can be completed in minutes to form $ABTS^{+\bullet}$ with the

Mn^{IV}–OH center at pH 4.0, whereas, in contrast, the Mn^{IV}=O center at pH 13.4 is incapable of electron transfer from ABTS (Figure 2). These observations are important for understanding the role of the protein environment in peroxidases, which perform electron transfer rather than oxygen transfer. Those peroxidases generally have a polar protein environment surrounding the active site in which the hydrogen-bond network could readily modulate the surface charge (i.e., net charge) of the reaction center to facilitate its electron-transfer reactions.[1b,17] Although the protonation state of compound II in most peroxidases remains controversial, the reactivity difference of the Mn^{IV}–OH and Mn^{IV}=O groups in electron transfer demonstrated herein provides a strong implication that the protonated form of compound II in peroxidases, that is, Fe^{IV}–OH, is highly preferred during electron transfer.

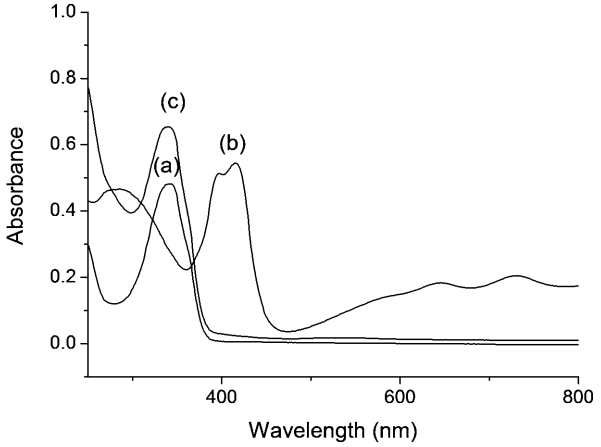
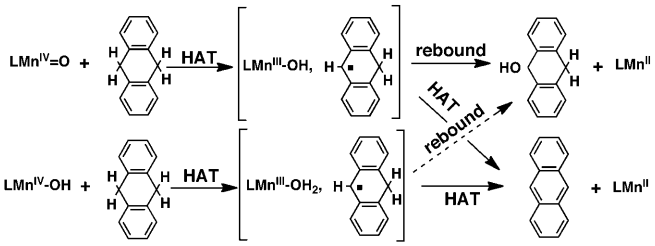


Figure 2. UV/Vis spectra of electron-transfer tests from ABTS by Mn^{IV}–OH at pH 4.0 and Mn^{IV}=O at pH 13.4 in aqueous solution. a) ABTS, b) ABTS + Mn^{IV} at pH 4.0, c) ABTS + Mn^{IV} at pH 13.4.

Although hydrogen abstraction is intrinsic to the mechanisms for both Mn^{IV}–OH at pH 4.0 and Mn^{IV}=O at pH 13.4 as reported earlier,[11c] their product distributions are distinctly different. At pH 4.0, hydrogen abstraction by the Mn^{IV}–OH moiety provides anthracene as, almost, the sole product, whereas the Mn^{IV}=O moiety at pH 13.4 provides anthraquinone (21.8%) as the major product with anthracene as a substantial but minor product (6.3%). Direct formation of anthraquinone by the Mn^{IV}=O oxidant, not via anthracene, can be explained by the well accepted oxygen-rebound mechanism.[18] Hydrogen abstraction from 9,10-dihydroanthracene by the Mn^{IV}=O generates an Mn^{III}–OH intermediate with a monohydroanthracene radical intermediate, and in next step the Mn^{III}–OH intermediate can rebind the OH group back to the monohydroanthracene radical to form 9-hydroxy-9,10-dihydroanthracene, which can be smoothly oxidized to anthrone, then to anthraquinone (formation of anthrone was identified by GC–MS analysis), or one more hydrogen atom can be abstracted from the monohydroanthracene radical by the Mn^{III}–OH intermediate (in this case, reorientation of the monohydroanthracene radical is essential for hydrogen abstraction) or by another Mn=O functional group (either neighboring Mn^{III}=O or exogenous Mn^{IV}=O) to generate anthracene. In addition, the high ratio of anthraquinone to anthracene product at pH 13.4 leads to the suggestion that in situ rebound of the OH group is more energetically favorable than further hydrogen abstraction after substrate reorientation. It is noteworthy that the hydrogen abstraction by the manganese oxio functional group and further rebound or hydrogen abstraction by the reduced manganese hydroxo moiety have been supported by recent DFT calculations.[19] In the case of the Mn^{IV}–OH at pH 4.0, formation of the almost exclusive anthracene product supports the conclusion that in situ rebound of the OH group to form 9-hydroxy-9,10-dihydroanthracene is not accessible after the first hydrogen abstraction to generate the reduced Mn^{III}–OH_2 intermediate, which leads to further hydrogen abstraction to generate anthracene (Scheme 1). Further, the formation of the almost exclusive anthracene product at pH 4.0 indicates that the rebound of the OH group from the neighboring Mn^{III}–OH_2 functional group (after substrate reorientation) or the exogenous Mn^{IV}–OH to form 9-hydroxy-9,10-dihydroanthracene is also highly unfavorable compared with further hydrogen abstraction to form anthracene product even though the system still needs substrate reorientation.



Scheme 1

Scheme 1. Mechanisms of oxidation of 9,10-dihydroanthracene by Mn^{IV}=O and Mn^{IV}–OH moieties. HAT = hydrogen abstraction.

The distinct reactivity differences of the active metal oxo and hydroxo moieties in hydrogen abstraction revealed by the Mn^{IV}=O and Mn^{IV}–OH are critical for understanding the origins of the abilities of redox metalloenzymes to choose an active transition-metal oxo or hydroxo moiety to serve as the key intermediate in a specific oxidation event. For example, in P450 enzymes, the iron(IV) oxo form of compound I is critical for substrate hydroxylation by the oxygen-rebound mechanism, whereas, in lipoxygenases, a metal hydroxo form of the active intermediate is in the same sense critical for hydrogen abstraction from the methylene group of the unsaturated fatty acid. For example, if a metal oxo moiety served hydrogen abstraction, rebound of the OH group to form hydroxylated fatty acid might occur as well as those in P450 enzymes, which would block the trapping of the substrate radical by dioxygen to generate the peroxide product.

In summary, we have demonstrated that, in hydrogen abstraction by Mn^{IV}=O, the generated Mn^{III}–OH moiety can rebind the OH group back to the substrate radical to form the hydroxylated product, whereas, in the case of the Mn^{IV}–OH moiety, the generated Mn^{III}–OH_2 moiety is incapable of

rebound. Whereas Mn^{IV}=O does not facilitate electron transfer, the Mn^{IV}–OH moiety demonstrates efficient electron-transfer capability, which can be further enhanced by increasing the net charge. These findings revealed by the Mn^{IV}=O and Mn^{IV}–OH centers herein have provided new clues to understand the origins of the redox metalloenzymes to select an active metal oxo or hydroxo function group to serve a specific oxidation event.

Experimental Section

Quantitative hydrogen abstraction from 9,10-dihydroanthracene by the manganese(IV) complex at pH 1.5, pH 4.0, and pH 13.4: In 5 mL acetone/water (4:1) solvent containing 5 mM manganese(IV) complex at selected pH values, including pH 1.5, pH 4.0, and pH 13.4 (HCl and NaOH were used to adjust pH value), 9,10-dihydroanthracene (0.0125 mmol) was added, and the resulting reaction mixture was stirred under nitrogen at room temperature. For pH 1.5 and 4.0, the reaction mixture was stirred for 24 h; for pH 13.4, it was stirred for 6 h. The product was analyzed by GC with an internal standard, and further identified by GC–MS analysis.

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