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Mechanism of Selective C−H Hydroxylation Mediated by Manganese Aminopyridine Enzyme Models

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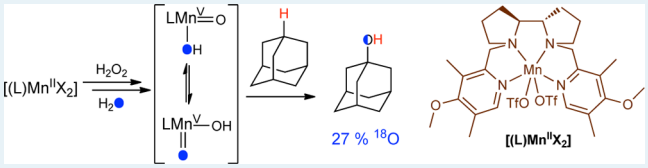
Supporting Information

ABSTRACT: The mechanism of selective oxidation of aliphatic C−H groups with H_2O_2 in the presence of aminopyridine Mn complexes, modeling the reactivities of natural oxygenases of the cytochrome P450 superfamily, has been examined. The oxygenation of C−H groups proceeds via hydrogen atom abstraction by the electrophilic metal site; the logarithm of C−H oxidation rates correlates linearly with bond dissociation energies for homolytic C−H bond cleavage. Hammett correlations and stereospecificity studies reflect the formation of a short-lived electron-deficient radical intermediate. Isotopic labeling studies confirm the incorporation of ^{18}O from added $H_2{}^{18}O$, thus providing so far lacking evidence for the oxomanganese(V)-mediated oxidation mechanism.



KEYWORDS: *C−H hydroxylation, biomimetic catalysis, enzyme models, hydrogen peroxide, manganese, mechanism*

INTRODUCTION

Iron-catalyzed oxidations of aliphatic C−H groups have been considered to be an area of paramount significance, in part owing to their relevance to the problem of modeling the catalytic cycle of monoiron enzymes of the cytochrome P450 superfamily[1−14] as well as giving credit to the potential impact of direct preparative C−H oxofunctionalization processes on synthetic chemistry.[15−25] In contrast, though various naturally manganese-containing enzymes are known,[26−28] Mn-based enzyme models have so far been much less extensively studied in the context of biomimetic selective C−H oxidations.[29−39] In particular, until a couple of years ago there have been only two reports on predictably selective C−H oxidations with H_2O_2 in the presence of mononuclear biomimetic manganese complexes;[40,41] in none of those cases did the turnover numbers exceed 10.

In 2012, we reported the first example of highly efficient, predictably regioselective, and stereospecific oxidation of unactivated aliphatic C−H groups with H_2O_2 in the presence of mononuclear manganese complexes **1**−**3** (Figure 1).[42] The turnover numbers approached 970; high sensitivity of the oxidation selectivity to electronic effects was documented. Notably, aminopyridine Mn complexes in some cases demonstrated better characteristics (i.e., activity, efficiency, and selectivity) than structurally related nonheme iron complexes,[42] thus representing an attractive platform for solving the two major challenges with the development of practical catalysts, i.e., generating sufficiently reactive metal complexes and controlling the oxidation selectivity.[24] Particularly promising is the ability of direct and selective oxofuntionalizing organic substrates of natural origin, which may be exploited for further derivatization. Two examples of this kind are presented in Figure 1.

Although the high selectivity (adamantane oxidation: 3°/2° = 40−49) and stereospecificity (*cis*-1,2-dimethylcyclohexane oxidation: >99% retention of cis configuration)[42] ruled out nonselective free-radical-driven reaction pathways, the nature of true active sites and the reaction mechanism remained unestablished, which essentially inspired this work. Herein, we report the experimental insight into the mechanism of regio- and stereoselective bioinspired C−H oxidations with H_2O_2, mediated by manganese aminopyridine synthetic enzyme models, achieved on the basis of combined Hammett, KIE, stereospecificity, and isotopic labeling studies.

RESULTS AND DISCUSSION

First, the oxidation of substrates with benzylic C−H moieties was explored with the aim of selecting proper substrates for further mechanistic studies. It was found that complex **1** did not demonstrate very high efficiencies in the benzylic oxidation of ethylbenzene, as well as cumene and its derivatives (Table 1). On the contrary, novel manganese catalysts **4** and **5** (Figure 1) with electrophilicities attenuated by the introduction of electron-donating substituents[43] were much more efficient, performing up to 760 turnovers (Table 1). Table 1 demonstrates the general trend rather explicitly: for benzylic oxidations, less-reactive catalysts appear to be more productive. As distinct from the oxidations of aliphatic C−H groups (yielding a mixture of the alcohol and ketone),[42,44−47] the resulting benzylic alcohols were partially converted to the corresponding acetate under the experimental conditions, owing to the presence of abundant acetic acid.

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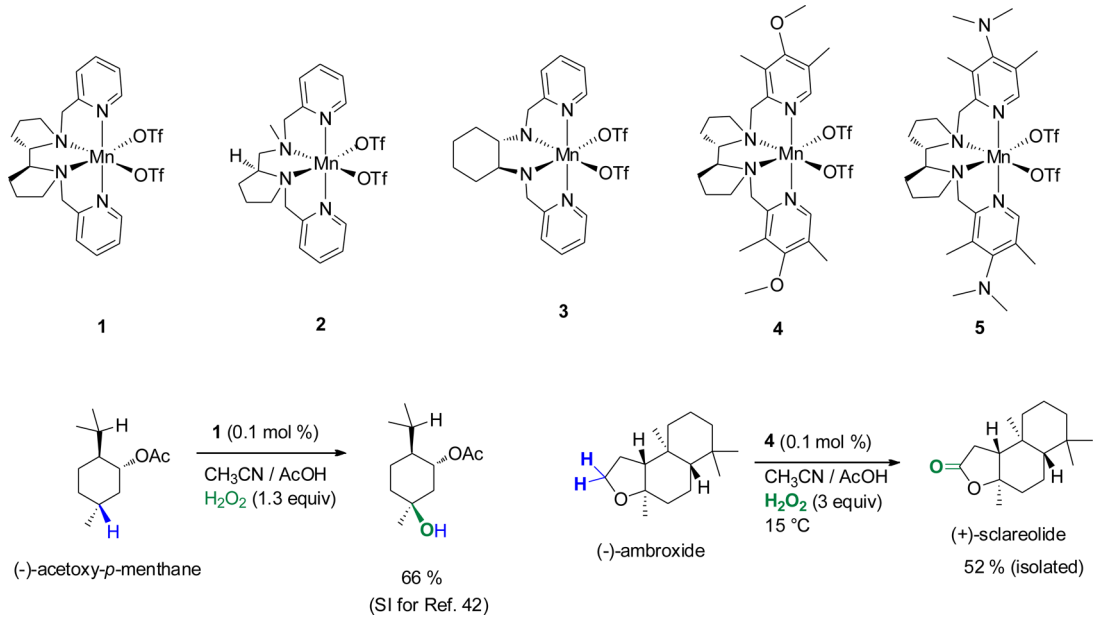
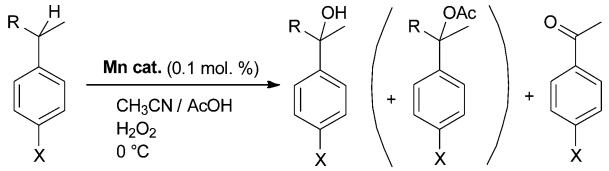


Figure 1. Examples of manganese aminopyridine catalysts for C−H oxidation with H_2O_2 (**1**−**3**)[42] and catalysts considered in this study (**4** and **5**). Examples of oxidations of substrates of natural origin.

Table 1. Oxidation of Cumenes with H_2O_2 on Complexes 1, 4, and 5[a]



entry	substrate	catalyst	conversion (%) (TN)	yield of alcohol/ ketone/acetate
1	ethylbenzene	**1**	19 (190)	11/8/−
2	ethylbenzene	**4**	47 (470)	5/41/−
3	ethylbenzene	**5**	25 (250)	1/24/−
4	cumene	**1**[b]	41 (41)	32/−/9
5	cumene	**4**	62 (620)	49/1/12
6	cumene	**5**	67 (670)	56/3/7.5
7	cumene	**5**	76 (760)[c]	62/2/12
8	*p*-NO_2-cumene	**5**	44 (440)	41/3/−
9	*p*-Br-cumene	**5**	64 (640)	47/10/7
10	*p*-Me-cumene	**5**	39 (390)	32/−/7
11	*p*-MeO-cumene	**5**	42 (420)	32/[d]

[a]At 0 °C, [substrate]/[H_2O_2]/[AcOH]/[Mn] = 0.100 mmol:0.13 mmol:0.600 mmol:0.1 μmol. Oxidant was added via syringe pump over 1 h, and the mixture was stirred for an additional 3 h and analyzed by GC. [b]Catalyst load: 1 mol %. [c]H_2O_2: 0.200 mmol. [d]Unidentified minor products (by GC): 10%.

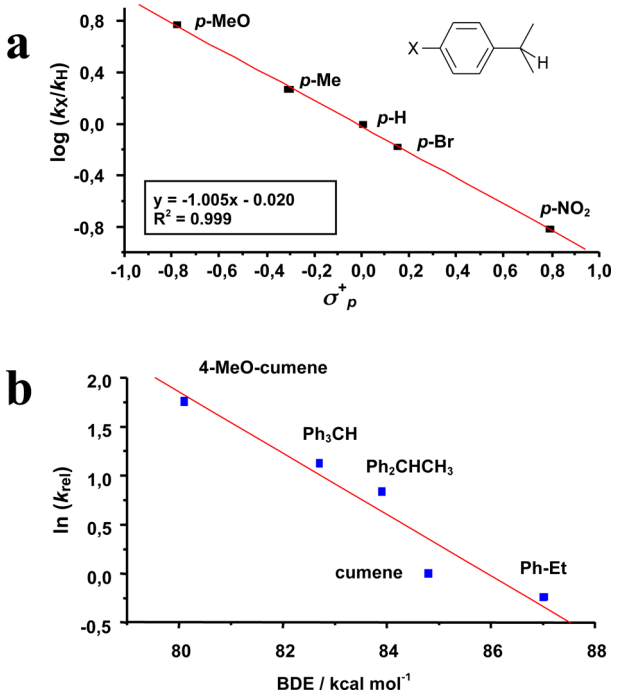


Figure 2. Hammett plot for the oxidation of para-substituted cumenes with H_2O_2 on complex **5** (a). Correlation between the relative rates for the oxidations of various hydrocarbons with H_2O_2 on complex **5** (b). Conditions: (0 °C), [substrate]/[H_2O_2]/[AcOH]/[Mn] = 0.100 mmol:0.13 mmol:0.600 mmol:0.1 μmol, oxidant added via syringe pump over 1 h and the mixture stirred for an additional 3 h (details in the SI).

The higher efficiency of complex **5** in benzylic oxidations was exploited for the competitive oxidations of *p*-substituted cumenes to evaluate the influence of electronic properties on the rates of C−H oxidations. A very linear Hammett correlation versus σ_p^+ was obtained (Figure 2a), giving a moderately negative slope (ρ^+) of −1.0. The negative sign of ρ^+ reflects an electron-demanding transition state. Its absolute value is somewhat higher than those documented for hydrogen abstraction by free radical species (−0.4 to −0.6) such as the cumyloxyl radical,[48] *t*BuO•,[49,50] *t*BuOO•,[51] and benzotriazole-*N*-oxyl[52] but is close to the range typical for hydroxylations by electron-deficient transition-metal complexes (−1.1 to −2.0),[53−58] including cytochrome P450 (−1.6).[48] Thus, the Hammett study points to a hydrogen-atom transfer mechanism

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Table 2. C−H Oxidation with H_2O_2 on Complexes 1, 4, and 5[d]

Complex	k_H/k_D[a] H/D	C_6H_{12}/C_6D_{12}	RC (%)[b] *cis*-1,2-DMCH 0 °C	20 °C	30 °C	^{18}O (%) from $H_2{}^{18}O$[a,c] *cis*-1,2-DMCH	adamantane
1	3.5	4.1	> 99	> 99	> 99	–	–
4	3.8	4.7	> 99	98.6	98.6	18 (2.3)	27 (9.1)
5	3.9	3.8	> 99	97.1	94.3	7 (1.5)	18 (21.8)

[a]At 0 °C. [b]For all isomers of 1,2-dimethylcyclohexan-1-ol: RC = 100% × [(1*R*, 2*R*) + (1*S*, 2*S*)) − ((1*R*, 2*S*) + (1*S*, 2*R*))]/[(1*R*, 2*R*) + (1*S*, 2*S*)) + ((1*R*, 2*S*) + (1*S*, 2*R*))]. [c]No AcOH; 20 equiv of $H_2{}^{18}O$ relative to alkane; yields of the corresponding alcohols are given in parentheses as turnover numbers. [d]For experimental details, see the Supporting Information. *cis*-1,2-DMCH = *cis*-1,2-dimethylcyclohexane.

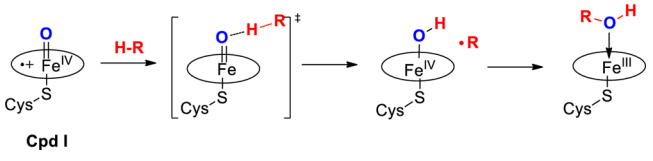
with the formation of an electron-deficient, possibly radical, intermediate.[56]

Furthermore, the logarithms of relative rate constants (SI) for the oxidations of a series of hydrocarbons correlated linearly with the homolytic C−H bond dissociation energies (BDEs) of the substrates (Figure 2b). This linear relationship suggests that the reaction occurs via a common mechanism.[59−62] The sensitivity of the relative rates to BDE(C−H)[63,64] represented by the slope of ca. −0.32 in Figure 2b is similar to those previously reported by Tanaka (−0.3),[65] Que (−0.35),[62] Goldberg (−0.39),[56] and Mayer (−0.4)[60] for H abstractions by high-valence oxometal species.

A second piece of evidence for an H-atom abstraction mechanism for the oxygenated products comes from the analysis of kinetic isotope effects. Competitive oxidations of cumene/α-D-cumene reveal a primary k_H/k_D of 3.5−3.9 (Table 2); the KIE values for the oxidation of cyclohexane/d_{12}-cyclohexane fall in the range of 3.8−4.7, thus clearly indicating that the hydrogen atom lies on the reaction coordinate and participates in a C−H bond-breaking step during oxygenated product formation. The observed k_H/k_D values are substantially higher than those documented for H abstraction from various C−H donors by the $^{\bullet}$OH radical (1−2),[66−68] comparable to KIE for H abstraction by the *t*BuO$^{\bullet}$ radical (ca. 4)[69] but lower than that by the benzotriazole-*N*-oxyl radical (11−27).[52] In fact, those moderate values are most consistent with the reported k_H/k_D values for the oxidations of various C−H donors by electron-deficient metal complexes such as iron (KIE = 3.2−4.3),[70−73] ruthenium (KIE = 4.2−6.5),[55,74] and manganese (KIE = 2.2−4.3).[75−77]

The obtained data may in principle point to a reaction mechanism similar to the classical rebound mechanism postulated for the cytochrome P450 reaction cycle, which assumes an aliphatic hydrogen abstraction by a ferryl intermediate (Cpd I) followed by an oxygen rebound to form the alcohol coordinated to the iron center (Scheme 1).[78−83]

Scheme 1. Part of the Proposed Catalytic Cycle for Hydrocarbon Oxidation by Cytochrome P450



Independent experimental evidence for the formation of carbon-centered radicals could provide additional arguments in favor of the viability of such a mechanism in the case of aminopyridine manganese complexes. Indirect information of this kind has been relatively abundant for nonheme-iron-based systems, such as either (1) partial erosion of stereochemistry upon the hydroxylation of alkane substrates containing 3° C−H bonds, such as cis or trans stereoisomers of 1,2-dimethylcyclohexane or decalin (intrinsically coupled to the trapping of dissolved O_2)[70,71] or (2) the documented existence of alternative reaction pathways, such as desaturations or secondary transformations ascribed to intramolecular rearrangements of the initially formed C-centered radicals.[17,18] As for secondary pathways, in manganese aminopyridine- mediated oxidations we have not obtained any experimental evidence for those; the reactions proceeded with high selectivity to alcohols (for 3° C−H bonds) or alcohol/ketone mixtures (for 2° C−H bonds).

The most straightforward evidence in favor of the formation of radical intermediates is derived from the partial erosion of stereochemistry in the course of oxidizing *cis*- or *trans*-1,2-dimethylcyclohexane because of the epimerization of intermediate tertiary alkyl radicals.[70,71] Mn-based catalysts of types **1**−**3** appear to be highly stereoretentive, leading to a >99% retention of stereoconfiguration (RC) in the oxidation of *cis*-1,2-dimethylcyclohexane at 0 °C (cf. also ref 42), which is characteristic of very short lived alkyl radicals with lifetimes of less than 10^{-10} s.[70] One could expect, however, that the attenuation of the electrophilicity of the Mn active site might slow the rebound step whereas increased temperature might accelerate the inversion of tertiary alkyl radicals, thus eventually leading to a lower RC. In full agreement with this prediction, electron-rich catalysts **4** and **5** at +30 °C showed only 98.6 and 94.3% RC, respectively (Table2), thus providing the first experimental evidence for the involvement of short-lived alkyl radicals and hence for the viability of the rebound oxidation mechanism.

Unraveling the nature of the reactive high-valent metal−oxo species in biomimetic systems is a particular challenge. By analogy to the aminopyridine iron-based catalyst systems, oxometal(V) complexes were recently proposed as the most likely active species of aminopyridine manganese-catalyzed epoxidations.[43,84] For oxidations promoted by structurally similar aminopyridine iron complexes, the so-called "water-assisted" mechanism[71,78] (Scheme 2) had been accepted, which recently found further experimental support in VT-MS

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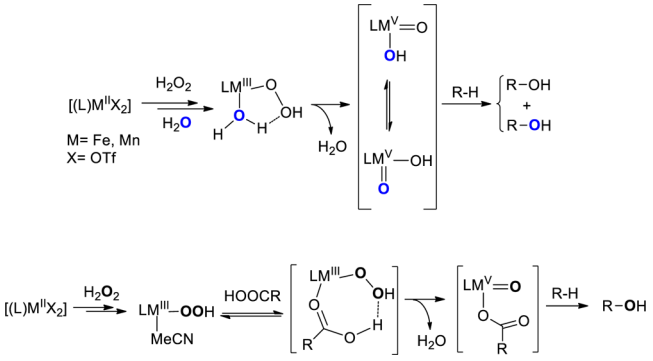
Scheme 2. Water-Assisted Mechanism (Top) and Carboxylic Acid-Assisted Mechanism for the Formation of Oxometal(V) Active Species[a]



[a]^{18}O-labeled oxygen atoms are colored blue.

studies.[85] Furthermore, the reactivities of the elusive oxoiron(V) species were monitored by EPR.[86,87] (We notice that Oloo et al. have recently challenged[88] the oxidation-state assignment for the iron centers responsible for the observed $S = {}^1/_2$ signal.[89]) Apparently, those approaches can hardly be directly transferred to Mn-based systems of types **1**−**5** because of the EPR invisibility of the expected oxomanganese(V) (d^2) species and their higher reactivity (and lower stability) as compared to iron prototypes. However, some useful evidence can be derived from isotopic labeling studies.

A characteristic feature of the water-assisted mechanism is the incorporation of the ^{18}O isotope from ^{18}O-labeled water added to the resulting alcohols, which becomes possible because of the participation of water in the heterolysis of the O−O bond of the hydroperoxoiron(III) intermediate[90] and the oxo−hydroxo tautomerism[70−72,91,92] in the oxoiron(V) species (Scheme 2, top). Previously, we noticed the apparent similarities in epoxidation mechanisms operated by aminopyridine manganese complexes and their iron counterparts.[43,84] However, the incorporation of ^{18}O into hydroxylated hydrocarbons on Mn complexes has never been achieved. The evident reason for that was the need for the presence of the abundant additive−carboxylic acid−which blocked $H_2{}^{18}O$ coordination to the Mn site, thus suppressing the isotopic scrambling.[43] We are pleased to report that this restriction can be overcome by the use of catalysts **4** and **5**, which turned out to be capable of hydroxylating C−H bonds even without added carboxylic acid. In particular, a 7−27% ^{18}O enrichment was documented for the oxidation of adamantane and *cis*-1,2-dimethylcyclohexane (Table 2), thus providing evidence lacking in favor of the water-assisted mechanism in manganese-catalyzed oxidations. It should be noted that in the absence of AcOH, complexes **4** and **5** demonstrate lower reactivity, which becomes insufficient for activating stronger 2° C−H bonds.[93]

In the presence of acetic acid, the mechanism of formation of oxometal(V) is diverted to the carboxylic-acid-assisted pathway (Scheme 2, bottom) that has been previously invoked in studies of nonheme Fe- and Mn-catalyzed oxidations to explain the cocatalytic effects of carboxylic acid additives.[5,13,14,43,84] The accelerating effects of carboxylic acids in biomimetic systems was also previously reported in refs 30−34 and 37−39.

CONCLUSIONS

Insight into the mechanism of direct oxofunctionalization of C−H groups performed by highly efficient and selective manganese-based synthetic enzyme models has been achieved. Hammett analysis, the correlation of oxidation rates with C−H BDEs, and KIE data show that oxygenated product formation proceeds via hydrogen atom abstraction from the C−H bond by the electrophilic metal center. At the same time, Hammett data and analysis of the stereospecificity of 3° C−H bond hydroxylations reflect the formation of an electron-deficient radical intermediate, which is consistent with the rebound mechanism postulated for oxidations by cytochrome P450 enzymes. Isotopic-labeling studies confirm the incorporation of ^{18}O from added $H_2{}^{18}O$, thus providing evidence for the viability of the water-assisted oxidation mechanism mediated by the high-valence aminopyridine manganese oxo complexes. We foresee further studies aimed at developing methods for the direct in situ detection of the elusive oxometal active species by spectroscopic techniques.

ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5013206.

Materials and methods, synthesis procedures, general procedures for C−H oxidations, KIE experiments, supplementary catalytic results, NMR data, examples of MS spectra, and GC−MS chromatograms (PDF).

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Notes

The authors declare no competing financial interest.

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(93) Indeed, although the attempted oxidation of cyclohexane under the conditions in the footnotes for Table 2 has yielded small amounts of cyclohexanol and cyclohexanone (total yield 43 TN), the alcohol/ketone ratio (1.0) and level of ^{18}O incorporation into the alcohol (0%) point to a different (apparently radical) oxidation pathway dominating in this case.