Biomimetic Oxidation Studies. 8. Structure of a New MMO Active Site Model, $[Fe_2O(H_2O)_2(tris((1\text{-methylimidazol-2-yl})methyl)amine)_2]^{4+}$, and Role of the Aqua Ligand in Alkane Functionalization Reactions

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Structural and alkane functionalization studies of plausible biomimetic models of methane monooxygenase enzymes (MMO) have been an active area of research.[1,2] Recent spectroscopic studies, including an X-ray crystallographic analysis, on methane monooxygenase enzymes (MMO) have shown that the active site has a diiron μ-hydroxo structure $[Fe_2(\mu\text{-OH})]$, with both terminal and μ-carboxylate anions and a terminal H_2O ligand, as well as terminal histidine ligands.[3]

We have previously reported on a pertinent biomimetic model of MMO, $[Fe_2O(OAc)(tmima)_2]^{3+}$, **1** (tmima = tris((1-methylimidazol-2-yl)methyl)amine), that incorporates many of the above-mentioned structural characteristics found for MMO and, more importantly, that catalytically functionalizes a wide variety of alkanes with hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP) in the presence of oxygen gas.[1e-g] Moreover, few reported biomimetic oxidation studies with LFeOFeL complexes as catalysts have clearly defined what important structural features or ancillary ligands are needed for optimum alkane functionalization activity.[1,2c,d]

In this communication, we report on an X-ray crystallographic study of a new MMO active site analogue, $[Fe_2O(H_2O)_2(tmima)_2](ClO_4)_4$, **2**, and on important mechanistic aspects of the C–H bond functionalization reaction of several hydrocarbons with **2** as the catalyst using anhydrous TBHP in the presence of oxygen gas (O_2) and acetonitrile (CH_3CN) as the solvent. We will demonstrate that, by removing the μ-OAc group and replacing it with terminal H_2O ligands, complex **2** enhances the number of turnovers/h for the alkane functionalization reaction, while UV–vis and ^1H NMR spectroscopic data suggest that **2** retains its integrity upon reaction with TBHP. In addition, we have further verified the previously found free radical mechanism for alkane functionalization[1e,g] with **2** by the use of a radical clock substrate, *trans*-2-phenylmethylcyclopropane, to show only ring-opened products that must emanate from a cyclopropylcarbinyl radical rearrangement.

Reaction of tmima with $Fe(ClO_4)_3 \cdot 9H_2O$ in ethanol containing triethylamine provided complex **2**, which, after recrystallization from acetonitrile/methanol (1:1), gave suitable crystals for X-ray analysis (Figure 1).[4] Complex **2** has a bent (μ-oxo)diiron(III) structure (Fe(1)–O–Fe(2) = 162.0(3)°) and an Fe- -Fe separation of 3.504(1) Å, with each iron center also containing a distorted octahedral coordination with three imidazole nitrogens, an amine nitrogen, and a water molecule. The Fe–O bond lengths (1.771(5), 1.777(5) Å) are similar to other reported oxo–iron complexes,[5] while the water ligands are shown to be weakly coordinated to the Fe centers with an average bond length of 2.157(4) Å.

Table 1 shows the results of alkane functionalization studies with **2** and compares turnovers/h with the μ-OAc complex, **1**, for several hydrocarbons. The turnovers/h for **2** are approximately twice those of the μ-acetate derivative, **1**, for cyclohexane, toluene, and adamantane, which suggests that the loss of the terminal H_2O or μ-OAc ligand by TBHP displacement must be rate limiting in the formation of the active Fe oxidant complex; i.e., the terminal aqua ligand is more easily displaced by TBHP compared to the μ-OAc ligand and, in fact, when excess H_2O is added to **1** and TBHP in CH_3CN, **2** is formed *in situ*, as shown by the increase in turnovers/h. This is an important result, since there have been few reported biomimetic oxidation studies that have demonstrated the role of ancillary ligands with LFeOFeL complexes on the turnovers/h for alkane functionalization activity[2c,d] and it may also have a future bearing on understanding the MMO enzyme mechanisms, since the recent X-ray study of *M. capsulatus* (Bath)[3d] shows a terminal H_2O ligand at the active enzyme site. It is pertinent to mention that the conversion of **1** to **2** was confirmed by ^1H NMR spectroscopy with excess H_2O in CH_3CN-d_3, which clearly shows the formation of AcOH.

More recently, Newcomb and Lippard and their co-workers reported studies on the mechanism of alkane functionalization with the MMO enzyme system from *M. capsulatus* (Bath) by utilization of a radical clock substrate, *trans*-2-phenylmethylcyclopropane.[6] They found that no (or trace) ring-opened products were observed, with only cyclopropylcarbinyl alcohol and a phenyl ring hydroxylation product being formed. Thus, Newcomb and Lippard et al.[6] argue that their diagnostic results tentatively show no carbon free radicals are being formed in this MMO-catalyzed C–H functionalization reaction.

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(4) Crystal data (296 K) for **2**: monoclinic, $P2_1/n$ (No. 14), a = 11.644(2) Å, b = 29.391(4) Å, c = 14.767(3) Å, β = 108.83(2)°, V = 4783.2(8) Å^3, Z = 4, λ = 0.710 373 Å, μ = 9.1 cm^{-1}. Final discrepancy indices are R = 6.2% and R_w = 6.6% for 4463 unique reflections with $I > 3\sigma(I)$ and 619 variable parameters. Anal. Calcd (found) for $C_{30}H_{46}Cl_4Fe_2N_{14}O_{19}$: C, 31.04 (31.28); H, 3.97 (3.98); N, 16.90 (16.67).

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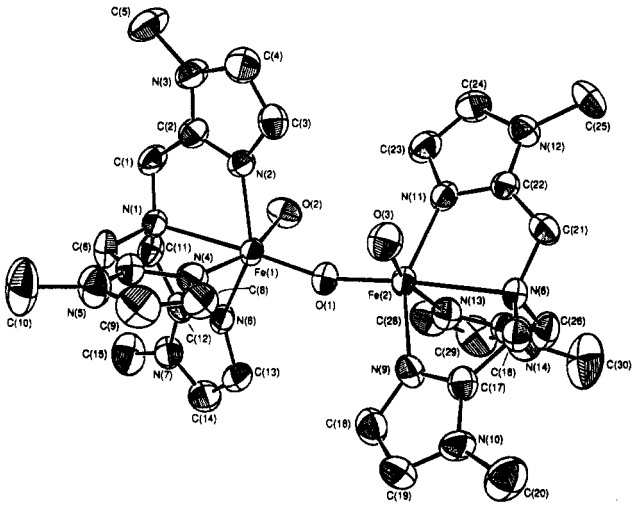


Figure 1. ORTEP view of **2** with selected bond distances (Å) and angles (deg): Fe(1)–O(1), 1.771(5); Fe(1)–O(2), 2.161(5); Fe(1)–N(1), 2.382(6); Fe(1)–N(2), 2.057(6); Fe(1)–N(4), 2.077(5); Fe(1)–N(6), 2.071(7); Fe(2)–O(1), 1.777(6); Fe(2)–O(3), 2.156(5); Fe(2)–N(8), 2.376(6); Fe(2)–N(9), 2.083(6); Fe(2)–N(11), 2.068(6); Fe(2)–N(13), 2.076(6); Fe(1)- -Fe(2), 3.504(1); Fe(1)–O(2)–Fe(2), 162.0(3); N(1)–Fe(1)–O(1), 176.1(2); N(8)–Fe(2)–O(1), 175.1(2).

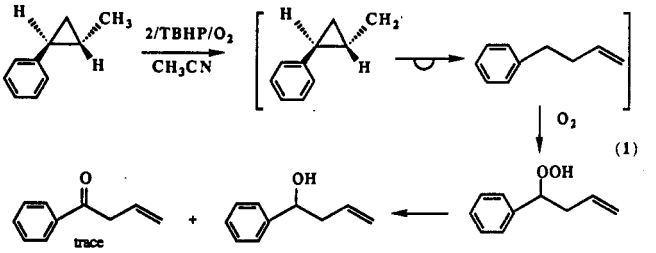
Table 1. Functionalization of Alkanes with $[Fe_2O(H_2O)_2(tmima)_2]^{4+}$ and TBHP in the Presence of Oxygen Gas[a]

substrate	products	(mmol of product/mmol of $[Fe_2O(H_2O)_2(tmima)_2]^{4+}$)/h (OAc)[b,c]
cyclohexane	cyclohexanol	3.7 (1.9)
	cyclohexanone	3.8 (1.8)
toluene	benzaldehyde	3.5 (1.2)
	benzoic acid	0.4
adamantane	1-adamantanol	1.6 (0.8)
	2-adamantanol	0.14
	2-adamantanone	0.33
propane	propionaldehyde	0.4
	acetone	4
	2-propanol	3
	1-propanol	0.19
	propionic acid	
ethane	ethanol	0.2
	acetaldehyde	0.12
	acetic acid	0.5

[a] Typical reaction conditions: $[Fe_2O(H_2O)_2(tmima)_2](ClO_4)_4$ (10^{-3} mmol) and substrate (0.9 mmol) were dissolved in 1 mL of CH_3CN, and the solution was stirred vigorously while anhydrous TBHP (0.15 mmol) was added at room temperature in the presence of oxygen gas (~1 atm). [b] $[Fe_2O(OAc)(tmima)_2](ClO_4)_3$ turnover/h comparison. [c] See supplementary material for additional data.

This latter result conflicts with recent MMO studies reported by Floss and Lipscomb and co-workers on optically active (*S*)- or (*R*)-[1-$^2H_1$,1-$^3H_1$]ethanes as substrates in their conversion to the corresponding partially racemized ethanols (~34%);[7] this study clearly defines the MMO alkane functionalization as a free radical process. Therefore, a more plausible explanation of the MMO radical clock experiment[6] might entail the faster kinetics of the rebound reaction ($k \sim 10^{12}$) to product (R• HO–Fe → ROH + Fe) in comparison to the radical rearrangement reaction.

In lieu of the above-mentioned MMO radical clock results, we also studied *trans*-2-phenylmethylcyclopropane with **2**, and our results show that only ring-opened products, 1-phenyl-but-3-en-1-ol and a trace of its ketone product, 1-phenyl-but-3-en-1-one (GC-MS analysis provided a 99:1 ratio of alcohol to ketone), are formed under similar conditions as described in Table 1. Thus, the initially formed cyclopropylcarbinyl radical rapidly rearranges to the phenyl-but-3-enyl radical ($k \sim 10^{11}$), before O_2 trapping ($k \sim 10^9$), to ultimately form the corresponding 1-phenyl-but-3-en-1-yl hydroperoxide. This hydroperoxide then catalytically decomposes to alcohol and ketone (trace) in the presence of **2**[18] (when O_2 is continually flushed from the catalytic reaction, no products are formed), further supporting a free radical mechanism for the C–H functionalization reaction (eq 1).



In order to ascertain the fate of **2** upon reaction with TBHP, we first studied this process by UV–vis spectroscopy (supplementary material). The intense and broad oxo → Fe^{3+} charge-transfer (CT) band at 276 nm decreases in intensity with increasing concentrations of TBHP, while, concomitantly, the shoulders at 315 and 480 nm increase in intensity. The isosbestic behavior observed, over a 1–65-fold concentration ratio of TBHP/**2**, is indicative of two species being present in solution and further suggests that TBHP is bonding to one or possibly both Fe centers, causing a decrease in the Fe–O–Fe bridging angle; i.e., more acute FeOFe angles lead to greater intensities of CT bands near 400 nm.[8]

In addition, the ^1H NMR spectrum of **2** shows three signals associated with the tmima ligand at 5.3, 13.4, and 15.8 ppm, which broaden significantly in the presence of an excess of TBHP (~65-fold). It is also interesting to note that the T_1 values for the proton signals for **2** are consistent with those reported for other paramagnetic $Fe^{III}_2(\mu\text{-O})$ complexes.[5] The UV–vis and NMR data suggest that when **2** reacts with TBHP, the putative intermediate LFeOFe(L)O(H)OBu-*t* complex decomposes to another putative high-valent oxo complex, LFeOFe(L)=O, and *t*-BuOH.[9]

In conclusion, we show that a terminal H_2O ligand of a structurally characterized LFeOFeL complex, **2**, enhances alkane functionalization activity in the presence of TBHP/O_2. The UV–vis and NMR experiments are indicative of **2** maintaining its integrity in the presence of a large excess of TBHP, while a radical clock substrate experiment clearly shows free radical rearrangement of the cyclopropylcarbinyl to phenyl-but-3-enyl radical to be faster than O_2 trapping. These important results allow a better understanding of alkane functionalization chemistry including the role of terminal aqua ligands, rates of formation of a putative Fe=O complex, and the now well-defined free radical pathways to oxidation products.[1e-g,10]

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Supplementary Material Available: Tables listing experimental details of the X-ray structure determination of **2**, atomic coordinates, isotropic and anisotropic thermal parameters, and bond distances and angles, additional footnotes for Table 1, and a figure showing the UV–vis experiment on TBHP/**2** isosbestic behavior (16 pages). Ordering information is given on any current masthead page.

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