Biomimetic Oxidation Studies. 11. Alkane Functionalization in Aqueous Solution Utilizing in Situ Formed $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$, as an MMO Model Precatalyst, Embedded in Surface-Derivatized Silica and Contained in Micelles

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The biomimetic, methane monooxygenase enzyme (MMO) precatalyst, $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$ (TPA = tris[(2-pyridyl)methyl]amine), **1**, formed in situ at pH 4.2 from $[Fe_2O(\mu\text{-}OAc)(TPA)_2]^{3+}$, **2**, was embedded in an amorphous silicate surface modified by a combination of hydrophilic poly(ethylene oxide) and hydrophobic poly(propylene oxide). The resulting catalytic assembly was found to be a biomimetic model for the MMO active site within a hydrophobic macroenvironment, allowing alkane functionalization with *tert*-butyl hydroperoxide (TBHP)/O_2 in an aqueous reaction medium (pH 4.2). For example, cyclohexane was oxidized to a mixture of cyclohexanone, cyclohexanol, and cyclohexyl-*tert*-butyl peroxide, in a ratio of ∼3:1:2. The balance between poly(ethylene oxide) and poly(propylene oxide), tethered on the silica surface, was crucial for maximizing the catalytic activity. The silica-based catalytic assembly showed reactivity somewhat higher in comparison to an aqueous micelle system utilizing the surfactant, cetyltrimethylammonium hydrogen sulfate at its critical micelle concentration, in which functionalization of cyclohexane with TBHP/O_2 in the presence of **1** was also studied at pH 4.2 and was found to provide similar products: cyclohexanol, cyclohexanone, and cyclohexyl-*tert*-butyl peroxide, in a ratio of ∼2:3:1. Moreover, the mechanism for both the silica-based catalytic assembly and the aqueous micelle system was found to occur via the Haber−Weiss process, in which redox chemistry between **1** and TBHP provides both the *t*-BuO$^\bullet$ and *t*-BuOO$^\bullet$ radicals. The *t*-BuO$^\bullet$ radical initiates the C−H functionalization reaction to form the carbon radical, followed by O_2 trapping, to provide cyclohexyl hydroperoxide, which produces the cyclohexanol and cyclohexanone in the presence of **1**, whereas the coupling product emanates from *t*-BuOO$^\bullet$ and cyclohexyl radicals. A discussion concerning both approaches for alkane functionalization in water will be presented.

Introduction

Methane monooxygenase (MMO) and cytochrome P-450 enzymes, although active in aqueous media, have a structure wherein the diiron nonporphyrin and iron porphyrin active sites, respectively, are embedded within a hydrophobic pocket, which enables the uptake and subsequent functionalization (hydroxylation) of alkanes.[1,2] In the continuing search for biomimetic models for these metalloenzyme oxidation catalysts, the emphasis is usually placed on the structure of the active site and whether this biomimic can perform alkane functionalization chemistry. Generally, the macroenvironment and the efficacy of the oxidation process in aqueous media with the various monooxygenase model complexes has not been a focus of the bioinorganic catalysis community. Nevertheless, for metalloporphyrins, some significant research has been directed toward alkene epoxidation and alkane functionalization in aqueous media, by embedding the active site model compounds within lipid bilayers,[3−5] thermotropic liquid crystals,[6] and micelles.[7,8] However, in the more nascent field of MMO biomimetic catalysis, the question of the macroenvironment and the possibility of alkane functionalization in aqueous media has not been extensively studied.[9]

To study the functionalization of hydrophobic alkanes in aqueous media using a biomimetic MMO enzyme assembly, including the active site and a hydrophobic pocket, we have developed both a derivatized amorphous silica, which allows one to balance the hydrophilicity and the hydrophobicity of a silicate surface,[10,11] and a classically formed aqueous micelle

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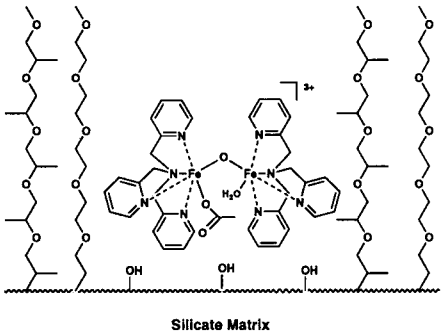
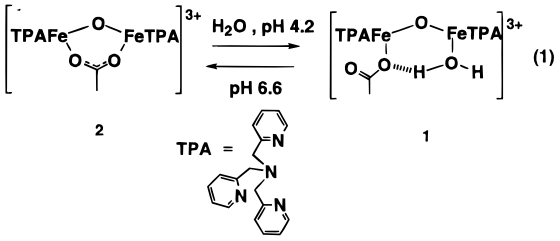


Figure 1. A schematic representation of in situ formed $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$, **1**, embedded in the PEO and PPO derivatized silica, for alkane functionalization in water at pH 4.2.

system utilizing a cationic surfactant, cetyltrimethylammonium hydrogensulfate.[9] In our derivatized amorphous silica technique, hydrophilic poly(ethylene oxide) (PEO) and/or hydrophobic poly(propylene oxide) (PPO) were covalently attached to siloxane monomers. The siloxane monomers were then polymerized using sol−gel synthesis that yields an amorphous silicate with PEO and/or PPO anchored to the silica surface. The PEO/PPO phases are to be considered comparable to anchored solvents, in which the anchoring of the solvent is somewhat analogous to the use of bonded phase columns in gas chromatography in place of simple, physically adsorbed phases. Therefore, active MMO biomimetic complexes, such as in situ-formed $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$, **1** (TPA = tris[(2-pyridyl)-methyl]amine)), from the $[Fe_2O(\mu\text{-}OAc)(TPA)_2]^{3+}$ analogue, **2**, at pH = 4.2,[12] can then be embedded into the PEO and PPO tethered silica (Figure 1). Thus, the placement of the precatalyst into the anchored solvents potentially allows one to functionalize alkanes in aqueous solution with *tert*-butyl hydroperoxide (TBHP) in the presence of oxygen gas (O_2); in this paper, we compare this former MMO model enzyme system to the latter-mentioned technique, in which the precatalyst, alkane, and oxidants were dissolved within the hydrophobic layers of the aqueous micelle dispersions (Figure 2).[9]

Results and Discussion

Synthesis of $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$, Complex 1. We had previously determined by UV−vis and ^{1}H NMR analysis that the $[Fe_2O(\mu\text{-}OAc)(TPA)_2]^{3+}$ complex, **2**, was converted to the $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$ complex, **1**, at pH 4.2 (eq 1), and that this η^1-H_2O ligand was thought to



be responsible for the dramatic increase in the oxidation of water-soluble alcohols to their aldehydes and ketones in the presence of TBHP/O_2.[12] For example, the UV−vis titration experiment, starting with complex **2**, shows (Figure 3) that as the pH is adjusted from 6.6 to 4.2, the absorbances at 496, 458, and 420 nm all decrease, while an isobestic point occurs at 310 nm; the UV−vis spectra are totally reversible depending on the pH (eq 1). Moreover, the UV−vis spectrum at pH 4.2 is intermediate between complex **2** (pH 6) and that of authentic $[Fe_2O(\eta^1\text{-}H_2O)_2(TPA)_2]^{4+}$, complex **3** (pH 4), further suggesting the formation of **1**. Also, the ^{1}H NMR experiments reflect the fact that the structure of compound **2** changes at ∼pH 4. The μ-OAc signal observed at 14.0 ppm for compound **2** in CD_3CN broadens at pH 6 and diminishes in intensity at pH ∼ 4.2 (80% D_2O, 20% CD_3CN), while a new signal appears at 9.6 ppm; we attribute this signal to a η^1-OAc ligand. In addition, no signal associated with free acetic acid was observed, further verifying that the OAc ligand remains bonded to an Fe center. These UV−vis and ^{1}H NMR experiments allowed us to propose that complex **1** has the η^1-H_2O, η^1-OAc structure as designated in eq 1 and is in equilibrium with complex **2**, as a function of pH.[12] Another analogue of **1**, $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(BPIA)_2]^{3+}$, **4**, (BPIA = bis[(2-pyridyl)-methyl][2-(1-methylimidazolyl)methyl]amine) also was found, via its μ-OAc precursor, to provide similar UV−vis/^{1}H NMR results.[12] It is worth noting that the stability of the Fe−μ-OAc bond at lower pH values seems to decrease with ligand modification (TPA∼BPIA>BIPA∼TMIMA, see Experimental Section).

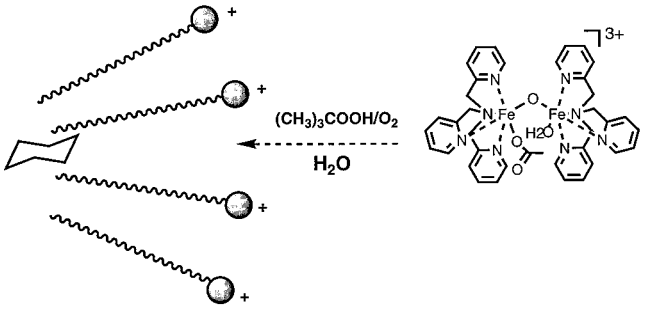


Figure 2. A schematic representation of in situ-formed **1** diffusing, along with the oxidants, TBHP/O_2, into aqueous micelles formed with the surfactant, cetyltrimethylammonium hydrogensulfate, for alkane functionalization in water at pH 4.2.

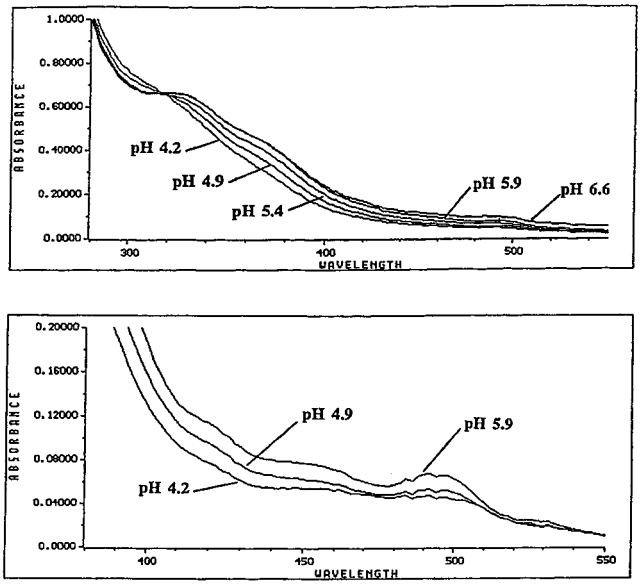


Figure 3. UV−vis spectra of complex **2** in water as a function of pH (adjusted by addition of dilute NaOH/$HClO_4$). (Top) Total UV−vis spectra; (Bottom) pH 4.2, 4.9, and 5.9 from 400 to 550 nm.

Synthesis of Derivatized Amorphous Silica and Impregnated Precatalyst. The general approach utilized to prepare

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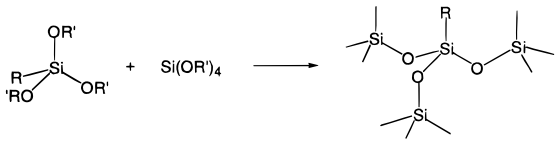
Table 1. Oxidation of Cyclooctane with Complex **1** Embedded in Surface-Derivatized Silica[a]

silica support	total TON (hr^{-1})	products[b]
10% PEO−SiO_2	19 (6.3)	43%, 55%, 1%, 1%
20% PEO−SiO_2	25 (8.3)	42%, 56%, 1%, 1%
10% PPO,10% PEO−SiO_2	142 (47.3)	26%, 35%, 13%, 25%
10% PPO−SiO_2	24 (8.0)	40%, 55%, 0%, 5%
20% PPO−SiO_2	21 (7.0)	37%, 49%, 0%, 4%
none	< 1	na

[a] Reactions were carried out by mixing 0.38 mmol cyclooctane, 3.8 mmol TBHP in 5 mL water at pH 4.2, and 0.38 μmol of in situ-formed **1** (as 1 wt % $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$ on derivatized silica) for 3 h at room temperature. [b] Mol % total products for cyclooctene, cyclooctanone, cyclooctanol, and cyclooctyl-*tert*-butyl peroxide, respectively. Yields based on TBHP were 80−90%.

derivatized silica with appropriate tethers has been the sol-gel synthesis process,[13] with alkoxy silanes as key reagents (eq 2).



(2)

R = (4-Si)-$PhCH_2(OCH_2CH_2)_nOCH_3$ or (4-Si)-$PhCH_2(OCH(CH_3)CH_2)_nOCH_3$ (n_{ave} = 7-8); R' = CH_3- or CH_3CH_2-

Moreover, the introduction of a nonhydrolytic substituent (R) led to the formation of the desired derivatized silica. In this example, a combination of two substituents were used: a) poly(ethylene oxide) (PEO), known as a hydrophilic polyether, and b) poly(propylene oxide) (PPO), known as a hydrophobic polyether. The hydrophobicity/hydrophilicity of surface tethered silica was estimated by measuring the wetting (contact) angles of films prepared from these sols. Thus, for 25 mol % PPO−SiO_2; 10 mol % PPO, 10 mol % PEO−SiO_2; and 25 mol % PEO−SiO_2, wetting angles of 79°, 54°, and 38°, respectively, were measured and were compared to the wetting angles of 90° for pure PPO and 20° for pure PEO, demonstrating that the critical hydrophobicity/hydrophilicity factors can be controlled in a systematic manner.

The tethered silicates were then wet impregnated with the precatalyst (complex **2**) dissolved in CH_2Cl_2 at a loading of 1wt %, and again dried under vacuum. In water at pH 4.2, we presume that impregnated complex **2** is converted to precatalyst **1**.

Alkane Functionalization Studies with Surface Derivatized Silicates. As an initial example of alkane functionalization using various surface derivatized silicates, the oxidation of cyclooctane was carried out with in situ-formed (pH = 4.2) $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$, **1**, as the precatalyst, in the presence of TBHP/O_2. From the results presented in Table 1, one can clearly observe that silicates with both hydrophobic PPO and hydrophilic PEO tethers provided a significantly improved reaction medium, compared to either PEO or PPO alone, with ∼140 turnovers (TON, mmol of product/mmol of catalyst) being observed with 10 mol % PPO and 10 mol % PEO−SiO_2, whereas approximately 25 TON were observed with PPO−SiO_2 or PEO−SiO_2. It is interesting to note that $Fe(ClO_4)_3$ showed no alkane functionalization activity when impregnated in 10 mol % PPO and 10 mol % PEO−SiO_2, which indicates that the TPA ligands might be necessary for solubilization in the anchored polyether solvents, and therefore, for catalysis to occur.

The reaction selectivity also differed as a function of the silicate support. For example, with PPO−SiO_2 or PEO−SiO_2, the major product was cyclooctanone and the minor product was cyclooctene, formed consistently in a ratio of ∼1.2:1. Furthermore, very minor amounts (<5%) of cyclooctanol and the mixed dialkylperoxide, cyclooctyl-*t*-butylperoxide, were also formed. For 10 mol % PPO and 10 mol % PEO−SiO_2, about 25% of the products formed was the dehydrogenated cyclooctene, while the remaining 75% of oxygenated products, cyclooctanol, cyclooctanone, and cyclooctyl-*t*butylperoxide, were formed in approximately a 1:3:2 ratio. The reaction was carried out at pH 4.2 and, as in previous studies, the solution turned colorless from its original yellow color with formation of the proposed $[(TPA)Fe^{2+}(\mu\text{-}OH)Fe^{3+}(TPA)]$ complex, which designates a Haber−Weiss process in the decomposition of TBHP.[9,12] This observation is further supportive of the Haber−Weiss process in that after the TBHP oxidant was completely decomposed, the yellow color returned.

It is clearly evident that alkane functionalization reactions with TBHP/O_2 as oxidants and in the presence of MMO biomimetic complexes, such as **1**, as well as other metal complexes, are initiated by formation of *t*-BuO$^\bullet$ and *t*-BuOO$^\bullet$ radicals.[9,12,14,15] In this case, by invoking the Haber−Weiss mechanism, the intermediate cyclooctyl radical can react with either dioxygen, leading to the formation of cyclooctanone and cyclooctanol via the proposed cyclooctyl hydroperoxide or with a *t*-BuOO$^\bullet$ radical to form the mixed dialkyl peroxide. Interestingly, and uniquely for cyclooctane, cyclooctene was formed as a significant product, plausibly by an intramolecular oxidative dehydrogenation pathway from the cyclooctyl radical.[16] Moreover, cyclooctene is *not* formed by dehydration of cyclooctanol, as its use as a substrate, under typical reaction conditions, yielded no cyclooctene but was converted to cyclooctanone.

The scope of the alkane functionalization reaction in aqueous solution with TBHP/O_2 and complex **1** in 10 mol % PPO and 10 mol % PEO−SiO_2 was extended to additional substrates (Table 2). For cycloalkanes, it was found that the activity sequence was: cyclohexane > cycloheptane ∼ cyclooctane. However, in contrast to the reaction with cyclooctane, no alkene dehydrogenation products were observed, but the product ratios, ketone:alcohol:dialkyl peroxide, were similar. Alkyl aromatic compounds were also oxidized to benzylic ketones and alcohols. Furthermore, a representative linear alkane, nonane, yielded ketones and secondary alcohols in a 2:1 ratio (Table 2).

Alkane Functionalization Studies with Aqueous Micelles. In our initial communication on the use of aqueous micelles for the functionalization of hydrophobic alkanes, in conjunction with MMO biomimetic complex **1** as well as an analog $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(BPIA)_2]^{3+}$, **4** (BPIA = bis[(2-pyridyl)methyl][2-(1-methylimidazolyl)methyl]amine)[12] including TBHP/O_2, we demonstrated that this model enzyme system, similar to the presently reported surface-derivatized silica system, proceeded by the Haber-Weiss process.[14,15] Thus, we fully describe details of our aqueous micelle studies using cyclohexane as a model hydrophobic alkane as well as other substrates.

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Table 2. Oxidation of Alkanes with 1 wt % Complex **1**, 10% PPO, 10% PEO−SiO_2[a]

substrate	total TON	products[b]	
cyclohexane	238	cyclohexanone	51%
		cyclohexanol	16%
		cyclohexyl-*tert*-butyl peroxide	33%
cycloheptane	146	cycloheptanone	55%
		cycloheptanol	19%
		cycloheptyl-*tert*-butyl peroxide	26%
tetrahydronaphthalene	141	α-tetralone	94%
		α-tetralol	6%
ethylbenzene	157	acetophenone	72%
		1-phenylethanol	28%
n-nonane	31	2-, 3-, 4-nonanone	68%
		2-, 3-, 4-nonanol	32%

[a] Reactions were carried out by mixing 0.38 mmol alkane, 3.8 mmol TBHP in 5 mL water at pH 4.2 with 0.38 μmol precatalyst (as 1 wt % **1** on 10% PPO, 10% PEO−SiO_2) for 3 h at room temeperature. [b] Products as mol % total products. Yields based on TBHP were 80−90%.

Our approach included the previously described in situ-formed MMO model, complexes **1** and **4** at pH 4.2[12] with the oxidants, TBHP/O_2, in combination with a surfactant. Initially, we demonstrated the need for a surfactant in our alkane functionalization reactions via a preliminary control experiment, which lacked the presence of a surfactant. This experiment with cyclohexane in water (pH 4.2) showed only *traces of functionalization products (cyclohexanol < 1 TON; cyclohexanone < 1 TON)* either in the biphasic system or in a microemulsion obtained by vigorous stirring. Because the cyclohexane substrate was not soluble in water, which contains both the precatalyst and the oxidant, the alkane functionalization reaction would occur at the interface of the two phases. These types of reactions at the interface tend to be limited not only by the concentration of the reactants but also by the interfacial area available, and hence by the stirring rate. Therefore, under our control reaction conditions, the TBHP decomposition reaction catalyzed by **1** in the aqueous phase was found to be much faster than the cyclohexane functionalization reaction occurring at the interface.

Defining an adequate surfactant constituted the first step in our aqueous micelle studies, because the nature of the surfactant would have a direct influence on this type of phase-transfer-catalysis by its interaction with the biomimetic precatalyst, **1** or **4**. Therefore, we chose cetyltrimethylammonium hydrogensulfate (CTAHS) to create micelles for the oxidation of cyclohexane with TBHP/O_2 in aqueous solution.[17] Figure 4 clearly demonstrates that the addition of the surfactant, CTAHS, to the biphasic system provides an efficient oxidation system. This system (complexes **1** and **4**, TBHP/O_2) provided CyOH, CyONE, and CyOOBu-*t*; no other products were formed (as determined by GC−MS).

When the CTAHS concentration is increased, the total TON increased. At C_{CTAHS} > 10 mM, no significant increase in the TON of the products was observed. Moreover, the results at C_{CTAHS} > 10 mM are on the same order as those obtained in the homogeneous system using CH_3CN as the solvent (27 TON and 19 TON for the μ-OAc derivatives of **1** and **4**, respectively, in CH_3CN) and show the efficiency of this catalytic system due to the combined presence of the micelles (CTAHS) and the catalytic effects of complex **1** or **4**. The alcohol/ketone ratios are similar for both complexes **1** and **4** with values between 0.5 (C_{CTAHS} < 10 mM) and 0.7 (C_{CTAHS} > 10 mM). For comparison, a ratio of 0.8 was obtained in CH_3CN. The excess of cyclohexanone observed under the aqueous emulsion conditions is in agreement with the concentration of cyclohexane "solubilized" in the aqueous phase being low and with cyclohexanol, which is formed during the oxidation process and is further oxidized to cyclohexanone (confirmed with CyOH and catalyst **4**), becoming a competing substrate within the micelle.

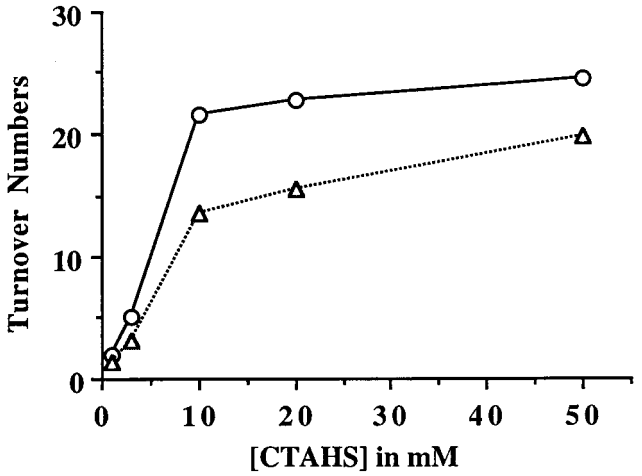

Figure 4. Turnover numbers (mmol of product/mmol of catalyst) of oxidation products (CyOH and CyONE) versus the CTAHS concentration. Reactions were carried out by mixing precatalysts [**1**, Δ] or [**4**, O] (1 mmol); TBHP (150 mmol); cyclohexane (500 mmol) in 1 mL of H_2O at pH 4.2 for 1h with **1**, and 5h with **4**; this represents the time period for complete consumption of TBHP.

The change in the curve shape in Figure 4 (found to be more important for complex **4**) at CTAHS concentrations of ∼10 mM corresponds to the critical micelle concentration (CMC) in the aqueous system.[9,17] As we increase the concentration of CTAHS below the CMC, the volume of the micelles, that is, the amount of cyclohexane "solubilized" in the micelles, is increased. Alternatively, increasing the concentration of CTAHS above the CMC provides an increase in the overall number of micelles.[18]

As observed in water, complex **1** provides faster oxidation reactions than complex **4**, whereas complex **4** gives rise to a larger TON of oxidation products. The catalytic system with complex **1** or **4** appears to be stable under these aqueous micelle conditions, because the addition of another 150 mM TBHP solution led to a doubling of the TON of the oxidation products, CyOH, CyONE, and CyOOBu-*t*; this procedure was repeated several times without loss of activity.

Table 3 shows that as the concentration of cyclohexane and TBHP were varied, a dependence of the TON of the products on each reactant was observed with catalyst **4**. We also observe that an increase in the cyclohexane concentration from 150 to 750 mmols concomitantly increases the amount of oxidation products from 11 TON to 32 TON and, more importantly, increases the CyOH/CyONE ratio from 0.47 to 0.82. By halving the amount of TBHP, we observe a decrease in the amount of oxidation products by a factor ∼1.8, whereas the CyOH/CyONE ratio does not change. *These overall results strongly suggest that the cyclohexane oxidation occurs within the micelles.* We also evaluated other substrates, such as toluene (500 mmol) and octanol (500 mmol), in our aqueous micelle system, under similar conditions as shown in Table 3. We found that toluene provided only benzyl alcohol and benzaldehyde in a ratio of 1.5 with a total TON of 7, while octanol provided only octanal

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Table 3. Influence of Cyclohexane and TBHP Concentrations on the Total TON of Cyclohexanol/Cyclohexanone/Cyclohexyl-*tert*-butyl Peroxide with Catalyst **4**[a,b]

amounts of reactant, mmol		products, TON			
CyH	TBHP	CyOH	CyONE	CyOO^{t}Bu	CyOH/CyONE
150	112	2.9	6.2	1.2	0.47
375	112	9.6	13.6	4.9	0.70
750	112	12.2	14.8	5.5	0.82
375	56	5.6	7.7	2.3	0.71

[a] CyH = cyclohexane; CyOH = cyclohexanol; CyONE = cyclohexanone; CyOOBu-*t* = cyclohexyl-*tert*-butyl peroxide. [b] Precatalyst **4** (1 mmol) in 1 mL of H_2O; TBHP (150 mmol); cyclohexane (500 mmol); CTAHS (15 mmol) at pH 4.2 for 5 h. This represents the time period for complete consumption of TBHP. The conversion of CyH to products is ~5%, while selectivity is also based on CyH conversion. The efficiency to products from TBHP is ~26%; however, addition of another 112 μmol of TBHP doubles the TON. Reactions were conducted under atmospheric conditions, and purging with N_2 showed no significant difference in the product concentrations.

with a total TON of 3. It is intertesting to note, in the latter result, that in the absence of the surfactant (CTAHS), ~ 1 TON was observed.

The addition of a competitive substrate, or radical trap, in the cyclohexane oxidation reaction provided further insight into the mechanism of the catalyzed cyclohexane functionalization reaction. Therefore, the presence of CCl_4 (13 vol %) in the reaction of **4**/TBHP/CTAHS/cyclohexane afforded 3 TON for chlorocyclohexane formation (determined by GC−MS), which shows the presence of cyclohexyl radicals as intermediates that were then trapped by CCl_4. Several other experiments with complex **4** were performed that evaluated the TBHP decomposition product ratio (R) of $(CH_3)_2C{=}O$/*t*-BuOH in the presence and/or absence of cyclohexane or CTAHS, and these results were as follows: (1) $R = 3.5$ (in the absence of cyclohexane and CTAHS); (2) $R = 1.3$ (in the absence of cyclohexane and in the presence of CTAHS); and (3) $R = 0.5$ (in the presence of 15 mM CTAHS and 500 mM cyclohexane). The first experiment shows that *t*-BuO$^\bullet$ radicals are present from the $(CH_3)_2C{=}O$ decomposition product,[12] whereas the latter experiment further demonstrates the predominant formation of Cy$\bullet$ radicals.

More importantly, experiments using a 1:1 mixture of cyclohexane and cyclohexane-d_{12} (GC; GC−MS analysis) as substrates afforded substantial primary kinetic isotope effects for the products, CyOH, CyONE, and cyclohexyl-*tert*-butyl peroxide (CyOOBu-*t*), indicating that the C−H abstraction reaction was an important component in the mechanism of formation of CyOH, CyONE, and CyOOBu-*t*.[12] Complexes **1** and **4** provided the same k_H/k_D value, 7.8 ± 0.3, for CyOOBu-*t* formation; 6.4 ± 0.3 and 7 ± 0.3, respectively, for CyOH formation; and 11.0 ± 0.4 and 12.6 ± 0.2; respectively, for CyONE formation. For comparison, in CH_3CN, the μ-OAc derivatives of complexes **1** and **4** provided k_H/k_D values of 4.6 ± 0.3 and 4.8 ± 0.3, respectively, for CyOH formation, 11.35± 0.45 (μ-OAc of **4**) for CyONE formation, and 7.7 ± 0.5 (μ-OAc of **1**) for CyOOBu-*t* formation.

Comparative Alkane Functionalization Experiments. Finally, a comparative cyclohexane functionalization reaction with the derivatized silica system (0.5 μmol **1**, 1 wt %, in 10 mol % PPO, 10mol % PEO−SiO_2, 500 μmol cyclohexane, 150 μmol TBHP in 1 mL water) and the aqueous micelles (0.5 μmol **1**, 50 μmol CTAHS, 500 μmol cyclohexane, 150 μmol TBHP in 1 mL water) showed that the silicate system was slightly more active in this comparison, 38 versus 22 total TON, respectively. Thus, the generation of a biomimetic enzymatic macroenvironment either by a derivatized silica surface or by the classical aqueous micelle technique allows facile alkane functionalization in water.

Haber−Weiss Mechanism. To reiterate, the mechanism of CyOH oxidation in water with complexes **1** and **4** as precatalysts and TBHP/O_2 as the oxidants was a consequence of a facile redox process ($Fe^{3+}Fe^{3+} \rightarrow Fe^{2+}Fe^{3+}$) for the homolytic decomposition of TBHP at pH 4.2.[12] Furthermore, in the latter study, we also observed for catalysts **1** and **4**, in their UV−vis spectra, that the addition of TBHP was followed by a rapid change of color from yellow to colorless (the yellow color returns after ~20 min). Notably, the observation of a colorless solution was indicative of the presence of an $LFe^{2+}(\mu\text{-OH})Fe^{3+}L$ intermediate (Haber−Weiss process).[12] In fact, we see similar UV−vis color changes, yellow to colorless, as noted above for **1**, in the presence of TBHP and CTAHS, and this observation seems to further strengthen the argument for a homolytic decomposition mechanism for TBHP in the aqueous micelle system, as well as the derivatized silica system, to form *t*-BuO$^\bullet$ radicals (eqs 3−8).

$$LFe^{3+}(\mu\text{-O})Fe^{3+}L + t\text{-BuOO-H} \rightarrow LFe^{2+}(\mu\text{-OH})Fe^{3+}L + t\text{-BuOO}^\bullet \quad (3)$$

$$t\text{-BuOO}^\bullet \rightarrow t\text{-BuO}^\bullet + {}^1/_2O_2 \quad (4)$$

$$t\text{-BuO}^\bullet \rightarrow (CH_3)_2C{=}O + CH_3^\bullet \xrightarrow{O_2,\ \text{fast}} CH_3OO^\bullet \quad (5)$$

$$t\text{-BuO}^\bullet + t\text{-BuOO-H} \rightarrow t\text{-BuOH} + t\text{-BuOO}^\bullet \quad (6)$$

$$t\text{-BuOO}^\bullet + CH_3^\bullet \rightarrow t\text{-BuOOCH}_3 \quad (7)$$

$$LFe^{2+}(\mu\text{-OH})Fe^{3+}L + t\text{-BuO-OH} \rightarrow LFe^{3+}(\mu\text{-O})Fe^{3+}L + t\text{-BuO}^\bullet + H_2O \quad (8)$$

Conclusions

In conclusion, we have demonstrated the first example of the functionalization of hydrocarbon substrates with MMO biomimetic complexes embedded in a derivatized surface silica system and compared this synthesized macroenvironment with an aqueous micelle system using TBHP/O_2 as the oxidants. These free radical, alkane functionalization reactions were presumably initiated by the favorable redox chemistry of complexes **1** and **4** in both of the above-mentioned macroenvironments that provided *t*-BuO$^\bullet$ and *t*-BuOO$^\bullet$ radicals (Haber−Weiss process). The *t*-BuO$^\bullet$ radicals, we speculate, initiate alkyl radical formation, which was then trapped by O_2 to provide alcohol and ketone products via proposed alkyl hydroperoxide intermediates.[9,12,14,15] Finally, for alkane functionalization in water, using complex **1** as the precatalyst, it would appear that an amorphous silicate surface, derivatized with both hydrophobic PPO and hydrophilic PEO groups, can be an effective biomimetic model for the macroenvironment of the MMO enzyme system and seems to be more efficient in balancing the critical hydrophilic and hydrophobic parameters than the comparable aqueous micelle system; in micelles, this control is more limited, and the TON are slightly lower. Thus, we feel we have presented a new paradigm for conducting alkane functionalization reactions in water, with a concept for modeling the overall MMO enzyme system that contains the proverbial biomimetic active site and the hydrophobic pocket for alkane solubilization/functionaliza-

tion. We intend to further our knowledge using this approach in future studies.

Experimental Section

Materials and Instrumentation. Doubly distilled water was used as the solvent for all of the alkane functionalization reactions. The oxidant, *tert*-butyl hydroperoxide (70% TBHP); the surfactant for micelle formation, cetyltrimethylammonium hydrogensulfate (CTAHS); the reagents for the formation of the derivatized (tethered) silica; and alkane substrates were commercial products from Aldrich Chemical Co. and were used without further purification. The ^{1}H NMR spectra were obtained on a 500 MHz Brucker NMR spectrometer, and GC and GC−MS analyses were performed on HP instruments. The UV−vis spectra were recorded on an HP diode array instrument with accompanying software.

Synthesis of Complexes 1 and 4. The tris[(2-pyridyl)methyl]amine (TPA) ligand,[19] and subsequently, complex **2**, were synthesized according to reported literature procedures.[12,20] The tripodal ligand bis-[(2-pyridyl)methyl][2-(1-methylimidazolyl)methyl]amine (BPIA) was prepared by methods previously reported, and ligand purities were checked by ^{1}H and ^{13}C NMR spectroscopy.[12,21] Complexes **1** and **4** were formed in situ at pH 4.2, using the $[Fe_2O(\mu\text{-OAc})(L)_2](ClO_4)_3$ complexes as starting material (impregnated into the modified silicates). The stability of the μ-OAc group in aqueous solution depends on the ligand (L) and the pH of the solution. The ^{1}H NMR spectra obtained on a sample of **2** dissolved in 80% D_2O/20% CD_3CN at ∼pH 4 (adjusted with HBF_4) clearly show that the μ-OAc ligand is not lost at this pH (no resonance was observed for free acetic acid), but the μ-OAc signal shifts upfield to 9.6 ppm and is now assigned to an η^1-OAc ligand. The μ-OAc signal at 14 ppm does not disappear completely, and the intensity of the signal appears to vary with solution preparation, suggesting that an equilibrium likely exists in solution between bridged and monodentate forms, presumably as a function of the pH. This result implies that the μ-OAc ligand is no longer bridging to the two Fe metal centers but is apparently bonded η^1 to a single Fe center. The UV−vis spectrum obtained on a sample of **2** dissolved in H_2O at pH 4 was found to be intermediate between the spectrum of an aqueous solution (pH 4) of $[Fe_2O(\eta^1\text{-}H_2O)_2(TPA)_2](ClO_4)_4$[14] and the spectrum of **2** at pH 6. The BPIA complex appears to be slightly less stable in solution compared to the TPA complex. After a period of several hours at pH ∼4, signals attributed to the BPIA ligand are observed in the spectrum. If the pH is lowered further, these signals grow in intensity. The related BIPA (BPIA= [(2-pyridyl)methyl]bis[2-(1 methylimidazolyl)methyl]-amine) and TMIMA (TMIMA= tris[2-(1-methylimidazolyl) methyl]-amine) complexes are even less stable in aqueous solution, and the μ-OAc ligand is very labile at pH 6.

Preparation of Siloxane Monomers. The $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH_2CH_2)_nOCH_3$ (n_{av} = 7−8) was prepared by reacting 25 mmol $[4\text{-}(CH_3O)_3Si]PhCH_2Cl$ from ABCR GmbH with 25 mmol $CH_3(OCH_2CH_2)_nOH$ (MW = 350) in 100 mL acetone in the presence of 125 mmol solid K_2CO_3 at reflux for 18 h. The solid salts (KCl, K_2CO_3) were filtered off by centrifugation, and the solvent was evaporated. No further purification was made at this point. ^{1}H NMR ($CDCl_3$ (δ, ppm)): 7.66 (d, 2H), 7.44 (d, 2H), 3.5−3.8 (m, 39H), 3.31 (s, 3H), no free $[4\text{-}(CH_3O)_3Si]PhCH_2Cl$ was evident. Similarly, $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH(CH_3)CH_2)_nOCH_3$ (n_{av} = 3−4) was prepared by reacting 25 mmol $[4\text{-}(CH_3O)_3Si]PhCH_2Cl$ with 25 mmol $CH_3(OCH(CH_3)CH_2)OH$ (M_rw = 200) in 100 mL acetone in the presence of 125 mmol solid K_2CO_3 at reflux for 18 h. The solid salts were filtered off by centrifugation and the solvent evaporated, and again no further purification was made. ^{1}H NMR ($CDCl_3$ (δ, ppm)): 7.66 (d, 2H), 7.44 (d, 2H), 3.25−3.6 (m, 29H), 3.1 (t, 2H), 1.50 (m, 2H), 1.32 (m, 2H), 1.15 (s, 20H), 0.88 (t, 3H), no free $[4\text{-}(CH_3O)_3Si]PhCH_2Cl$ was evident.

Preparation of Derivatized Silicates and the Impregnated Precatalyst. In general, the derivatized silicates were prepared by dissolving the desired and appropriate amounts (total 20 mmol) of $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH_2CH_2)_nOCH_3$, $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH(CH_3)CH_2)_nOCH_3$ and $Si(OEt)_4$ in 200 mL acetone. Then, water (200 mmol) and dibutyltin dilaurate (0.2 mmol) were added to initiate the polymerization. The mixture was held at 60 °C for 6 h and left to slowly evaporate for 2 days at room temperature; then, the powder was thoroughly washed with CH_2Cl_2 and dried under vacuum. More specifically, for example, 10 mol % PEO, 10 mol % PPO−SiO_2 was prepared using 16 mmol $Si(OEt)_4$ and 2 mmol each of $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH_2CH_2)_nOCH_3$ and $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH(CH_3)CH_2)_nOCH_3$. The tethered silicates were finally wet impregnated with the precatalyst (complex **2**) dissolved in CH_2Cl_2 at a loading of 1wt % and again dried under vacuum.

Alkane Functionalization with Surface Derivatized Silicates. The alkane functionalization reactions were carried out in 10 mL magnetically stirred vials. Typically, reactions were carried out by mixing 0.38 mmol alkane, 3.8 mmol TBHP, and 0.38 μmol precatalyst (as 1wt % complex **1** on derivatized silica) for 3 h at room temperature. Analysis of the reaction mixtures was by GC using a HP 5890 instrument with a 15 m, 0.32 mm ID, 0.25 μm 5% phenylmethylsilicone coated (RTX-5) column. Products were identified using reference standards and GC-MS (HP-GCD) with the same column.

Wetting Angles. Wetting angles were measured using a goniometer (Rame-Hart) by forming a film on a clean glass substrate from the sol formed from a solution of $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH_2CH_2)_nOCH_3$, $[4\text{-}(CH_3O)_3Si]PhCH_2(OCH(CH_3)CH_2)_nOCH_3$, and $Si(OEt)_4$ (total 5 mmol), 50 mmol water, 0.05 mmol dibutyltin dilaurate in 20 mL acetone after 3 h at 60 °C.

Alkane Functionalization with Aqueous Micelles. The alkane functionalization reactions were carried out in 10 mL magnetically stirred vials. Typically, reactions were carried out by mixing precatalysts **1** or **4** (1 mmol); TBHP (150 mmol); cyclohexane (500 mmol); 10 mmol CTAHS in 1 mL of H_2O at pH 4.2 for 1h with **1** and 5h with **4**; this represents the time period for complete consumption of TBHP. Analysis of the reaction mixtures was by GC analysis using an HP 5890 instrument with a 30 m, 0.25 mm ID, 0.25 μm DBwax (J&W) column with cyclopentanone as the internal standard. Products were identified using reference standards and GC-MS analysis with the same column.

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