

## A Synthetically Useful, Self-Assembling MMO Mimic System for Catalytic Alkene Epoxidation with Aqueous H<sub>2</sub>O<sub>2</sub>

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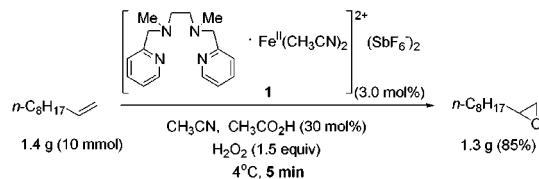
Received March 26, 2001

Revised Manuscript Received May 31, 2001

The discovery of efficient and practical epoxidation methods that utilize aqueous H<sub>2</sub>O<sub>2</sub> as terminal oxidant stands as an important objective in synthetic chemistry. While significant advances have been made in identifying catalysts for peroxide-based epoxidations,<sup>1</sup> important challenges remain; these include the development of highly reactive systems that effect rapid substrate conversion with high selectivity, and the use of inexpensive, environmentally friendly metals in coordination environments that can be adapted to sterically and electronically tunable chiral ligands.<sup>2</sup> Nature has evolved a variety of remarkable oxidative enzymes that may point to a solution. For example, in addition to its well-known biological role in the selective hydroxylation of small hydrocarbons, methane monooxygenase (MMO) is an efficient and selective catalyst for epoxidation of small terminal olefins (i.e. ethylene, propylene, 1-butene).<sup>3</sup> Moreover, oxidized MMO (diiron(III)) displays this oxidation activity with H<sub>2</sub>O<sub>2</sub>.<sup>4</sup> In this paper we describe a new protocol that employs low loadings of an inexpensive, easily prepared iron-tetradentate ligand complex and 50% aqueous H<sub>2</sub>O<sub>2</sub><sup>5</sup> to effect epoxidation of a wide variety of aliphatic olefins—including terminal olefins—within 5 min in 60–90% isolated yields (e.g. Scheme 1). On the basis of spectroscopic and crystallographic data, it is shown that this catalyst system self-assembles under the reaction conditions to form a  $\mu$ -oxo, carboxylate-bridged diiron(III) complex reminiscent of the  $\mu$ -hydroxo, carboxylate-bridged diiron(III) core found in the hydroxylase active site of oxidized methane monooxygenase (MMO).<sup>6</sup>

A variety of interesting synthetic non-heme iron complexes have been identified as functional mimics of MMO.<sup>7,8</sup> For example, both mononuclear<sup>8c</sup> and pre-assembled binuclear<sup>8d</sup> iron

### Scheme 1. Epoxidation of 1-Decene by the 1/Acetic Acid System



perchlorate complexes of the mep ligand (mep = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)-ethane, 1,2-diamine)<sup>9</sup> effect hydroxylation of cyclohexane in the presence of aqueous H<sub>2</sub>O<sub>2</sub> with modest catalytic activity (2–5 turnovers). Thus far, however, the application of functional MMO model systems to preparative oxidation chemistry has been prevented by low catalyst turnover numbers, poor selectivity for product formation (often attributed to generation of free hydroxyl radicals), and the requirement for large excesses of substrate relative to oxidant. Nonetheless, the (mep)iron system appeared to hold special promise for epoxidation catalysis because it was demonstrated to effect oxidation without the participation of free hydroxyl radicals.<sup>8c</sup> This feature, combined with the synthetically accessible and tunable nature of the mep ligand, prompted us to investigate its potential utility in epoxidation catalysis.

We evaluated mononuclear [Fe(II)(mep)(CH<sub>3</sub>CN)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub> complex (5 mol %) for epoxidation of 1-decene in the presence of varying amounts of H<sub>2</sub>O<sub>2</sub>. With 4 equiv of oxidant, complete conversion of alkene was achieved; however, epoxide was produced in only 40% yield and a variety of over-oxidized byproducts were detected. Use of the corresponding SbF<sub>6</sub> complex **1**<sup>10</sup> led to a substantially more efficient reaction, with only 1.5 equiv of H<sub>2</sub>O<sub>2</sub> required to achieve complete conversion of alkene, and with selectivity for formation of 1,2-epoxydecane improved to 71%. A screen of additives and solvents revealed that improvement to 82% selectivity for epoxide formation was possible with the addition of as little as 1 equiv of acetic acid with respect to catalyst. Moreover, the acetic acid-containing system was very well-behaved, with reductions in catalyst loading (S/C up to 100) and increases in H<sub>2</sub>O<sub>2</sub> addition rates (from dropwise to rapid addition) resulting in no change in selectivity for epoxide formation. In contrast, the system lacking acetic acid as additive displayed significant decreases in epoxide yield both at lower catalyst loadings and with increased addition rates of H<sub>2</sub>O<sub>2</sub>.

(7) For a review on MMO model systems, see: Hu, Z.; Gorun, S. M. In *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College Press: London, 2000; pp 269–307.

(8) Hydroxylations with MMO model systems: (a) Leising, R. A.; Kim, J.; Perez, M. A.; Que, L., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 9524–9530. (b) Nishida, Y.; Okuno, T.; Ito, S.; Harada, A.; Ohba, S.; Matsushima, H.; Tokii, T. *Chem. Lett.* **1995**, 885–886. (c) Ito, S.; Okuno, T.; Matsushima, H.; Tokii, T.; Nishida, Y. *J. Chem. Soc., Dalton Trans.* **1996**, 4479–4484. (d) Okuno, T.; Ito, S.; Ohba, S.; Nishida, Y. *J. Chem. Soc., Dalton Trans.* **1997**, 3547–3551. (e) Chen, K.; Que, L., Jr. *Chem. Commun.* **1999**, 1375–1376. Epoxidations with MMO model systems: (f) H<sub>2</sub>O<sub>2</sub> as oxidant: Duboc-Toia, C.; Menage, S.; Lambeaux, C.; Fontecave, M. *Tetrahedron Lett.* **1997**, *38*, 3727–3730. (g) TBHP as oxidant: Menage, S.; Vincent, J. M.; Lambeaux, C.; Chottard, G.; Grand, A.; Fontecave, M. *Inorg. Chem.* **1993**, *32*, 4766–4773. (h) PhIO as oxidant: Stassinopoulos, A.; Caradonna, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 7071–7073. (i) O<sub>2</sub> as oxidant: Kitajima, N.; Fukui, H.; Morooka, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 485–486. (j) Murch, B. P.; Bradley, F. C.; Que, L., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5027–5028.

(9) Toftlund, H.; Pedersen, E.; Yde-Andersen, S. *Acta Chem. Scand. A* **1984**, *38*, 693–697.

(10) Preparation of **1**: Complexation of mep with Fe(II)Cl<sub>2</sub>·xH<sub>2</sub>O was effected in CH<sub>3</sub>CN by stirring at room temperature over 24 h. The resulting yellow complex was precipitated by addition of ether and washed with ether. Addition of AgSbF<sub>6</sub> in CH<sub>3</sub>CN (2 equiv) followed by stirring for 24 h, filtration through Celite to remove silver salts, and solvent removal afforded [Fe(II)(mep)(CH<sub>3</sub>CN)<sub>2</sub>](SbF<sub>6</sub>)<sub>2</sub> (**1**) as a purple solid that can be stored indefinitely in the solid state (see Supporting Information).

(1) For examples of catalytic systems for alkene epoxidation employing aqueous H<sub>2</sub>O<sub>2</sub>: Methyl trioxorhenium: (a) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189–6190. (b) Herrmann, W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1638–1641. Heteropolyoxotungstates: (c) Zuwei, X.; Ning, Z.; Yu, S.; Kunlan, L. *Science* **2001**, *292*, 1139–1141. (d) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310–8311. (e) Venturello, C.; Alneri, E.; Ricci, M. *J. Org. Chem.* **1983**, *48*, 3831–3833. (TMTACN)Mn: (f) Berkessel, A.; Sklorz, C. A. *Tetrahedron Lett.* **1999**, *40*, 7965–7968. (g) De Vos, D.; Bein, T. *Chem. Commun.* **1996**, 917–918. MnSO<sub>4</sub>: (h) Lane, B. S.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 2933–2934.

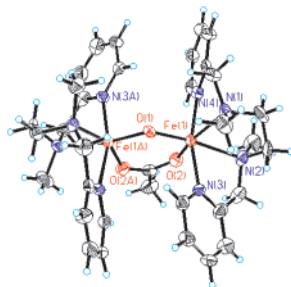
(2) To date, efforts directed toward the development of asymmetric catalytic systems for epoxidations with H<sub>2</sub>O<sub>2</sub> have met with limited success. See, for example: (a) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 937–941. (b) Pietikainen, P. *Tetrahedron* **1998**, *54*, 4319–4326. (c) Bolm, C.; Kadereit, D.; Valacchi, M. *Synlett* **1997**, *6*, 697–698.

(3) (a) Ono, M.; Okura, I. *J. Mol. Catal.* **1990**, *61*, 113–122. (b) Higgins, I. J.; Best, D. J.; Hammond, R. C. *Nature* **1980**, *286*, 561–564. (c) Colby, J.; Stirling, D. I.; Dalton, H. *Biochem. J.* **1977**, *165*, 395–402.

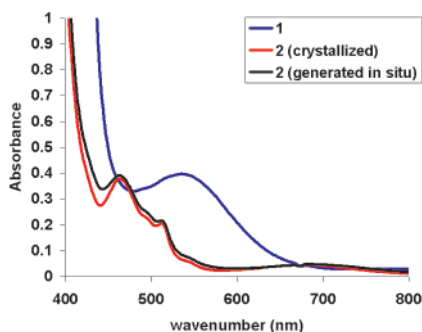
(4) Anderson, K. K.; Froland, W. A.; Lee, S.-K.; Lipscomb, J. D. *New J. Chem.* **1991**, *15*, 411–415.

(5) CAUTION: Hydrogen peroxide solutions are strongly oxidizing and should be handled with appropriate precautions. Use of commercial 30% and 50% solutions could be used interchangeably providing similar results in all cases examined.

(6) (a) Waller, B. J.; Lipscomb, J. D. *Chem. Rev.* **1996**, *96*, 2625–2657. (b) Elango, N.; Radhakrishna, R.; Froland, W. A.; Waller, B. J.; Earhart, C. A.; Lipscomb, J. D.; Ohlendorf, D. H. *Protein Sci.* **1997**, *6*, 556–568. (c) Rosenzweig, A. C.; Norlund, P.; Takahara, P. M.; Frederick, C. A.; Lippard, S. J. *Chem. Biol.* **1995**, *2*, 409–418. (d) Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J.; Norlund, P. *Nature* **1993**, *366*, 537–543.



**Figure 1.** ORTEP diagram of  $[\text{Fe}_2(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)(\text{mep})_2]$  (cation of **2**).



**Figure 2.** Electronic spectra of  $\text{CH}_3\text{CN}$  solutions of monomer **1** (6.5 mM), dimer **2** (0.81 mM) obtained by crystallization of **1**/acetic acid under air, and dimer **2** (0.81 mM) generated in situ by addition of 0.5 equiv. of  $\text{H}_2\text{O}_2$  to a solution of **1**/acetic acid.

Closer examination of the effect of acetic acid on the epoxidation system revealed dramatic effects on catalyst structure. X-ray crystallographic analyses were carried out on single-crystals grown by slow diffusion of ether into concentrated  $\text{CH}_3\text{CN}$  solutions of **1** both in the presence and absence of added acetic acid. In the latter case, an octahedral, mononuclear  $(\text{mep})\text{Fe}(\text{CH}_3\text{CN})_2(\text{SbF}_6)_2$  complex was identified, whereas in the presence of acetic acid a  $\mu$ -oxo, carboxylate bridged diiron(III) complex **2** was generated (Figure 1). The presence of characteristic absorbances in the UV–vis spectrum of **2** suggests that the binuclear structure is maintained in solution.<sup>11</sup> Complex **2** exhibited the same selectivity in the epoxidation of 1-decene as displayed by monomeric complex **1** in the presence of added acetic acid.

Formation of the carboxylate-bridged ( $\mu$ -oxo) diiron(III) dimer from **1** and acetic acid could be monitored readily by UV–vis spectroscopy. Under aerobic conditions, oxidation was found to require several days, indicating that generation of **2** under the conditions of epoxidation (<5 min) cannot be attributed to air oxidation. Addition of  $\text{H}_2\text{O}_2$  (0.5 equiv with respect to **1**) to a  $\text{CH}_3\text{CN}$  solution of **1** and acetic acid resulted in immediate conversion to a species with an electronic spectrum that was identical to that of complex **2** (Figure 2).<sup>12</sup> Addition of 1-decene to this complex followed by  $\text{H}_2\text{O}_2$  (1.4 equiv with respect to olefin) led to formation of 1,2-epoxydecane in the same yield as observed with isolated complex **2** and with **1**/acetic acid. This appears to be the first example of a catalytically active  $\mu$ -oxo, carboxylate-bridged diiron(III) complex **2** that is generated by self-assembly under the conditions of epoxidation. As in the case

(11) The following spectroscopic features are characteristic of bent ( $\mu$ -oxo) diiron(III) compounds: (1) strong absorbance near 330 nm (see Supporting Information), (2) three features from 400 to 500 nm, (3) shoulder near 525 nm, and (4) broad band near 700 nm: (a) Norman, R. E.; Yan, S.; Que, L. Jr.; Backes, G.; Ling, J.; Sanders-Loehr, J.; Zhang, J. H.; O'Connor, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 1554–1562. (b) Reem, R. C.; McCormick, J. M.; Richardson, D. E.; Devlin, F. J.; Stephens, P. J.; Musselman, R. L.; Solomon, E. I. *J. Am. Chem. Soc.* **1989**, *111*, 4688–4704. (c) Reference 8d.

(12) Moist air or  $\text{H}_2\text{O}_2$  have been shown to effect oxidation of iron(II) complexes of salen or porphyrin to the corresponding  $\mu$ -oxo diiron(III) compounds: (a) Murray, K. S. *Coord. Chem. Rev.* **1974**, *12*, 1–35. (b) Sadasivan, N.; Eberspaecher, H. I.; Fushman, W. H.; Caughey, W. S. *Biochemistry* **1969**, *8*, 534–541.

**Table 1.** Epoxidations Catalyzed by the **1**/Acetic Acid System (**2**)<sup>a</sup>

Entry	Substrate	Isolated Yields <sup>b</sup> (GC yield) <sup>c</sup>
1	$n\text{-C}_8\text{H}_{17}$	85%
2	$n\text{-C}_{10}\text{H}_{21}$	90% <sup>d</sup>
3	cyclo-C <sub>8</sub> H <sub>11</sub>	76% <sup>e</sup>
4	$\text{EtO}_2\text{C}$	63% <sup>f</sup>
5	TBSO	61% <sup>g</sup>
6		77%
7	cyclooctene	86%
8		87%
9		80% (90%)
10		85% (90%)

<sup>a</sup> Reaction conditions (see ref 12 and Supporting Information): olefin (2.0 mmol, 0.16 M in  $\text{CH}_3\text{CN}$ ), **1** (3.0 mol %),  $\text{CH}_3\text{CO}_2\text{H}$  (10 equiv relative to **1**),  $\text{H}_2\text{O}_2$  (aqueous 50 wt %, 3.0 mmol, 1.5 M in  $\text{CH}_3\text{CN}$ , added dropwise over 2 min), 4 °C, 5 min. <sup>b</sup> Isolated yields based on an average of 3 runs. <sup>c</sup> GC yields were determined using nitrobenzene as an internal standard for especially volatile substrates. <sup>d</sup> Reaction carried out at  $[\text{olefin}]_0 = 0.13$  M due to poor solubility in  $\text{CH}_3\text{CN}$ . <sup>e</sup> 5 mol % **1**. <sup>f</sup> 1.5 mol % **1**/1.5 mol %  $\text{CH}_3\text{CO}_2\text{H}$ . <sup>g</sup> 6 mol %  $\text{CH}_3\text{CO}_2\text{H}$ .

of MMO, it is likely that a “carboxylate shift” is responsible for generating the coordination site required for catalysis.<sup>13</sup>

Further optimization of reaction conditions and a preliminary investigation of substrate scope led to the results shown in Table 1.<sup>14</sup> A wide range of aliphatically substituted alkenes proved to be excellent substrates for epoxidation with catalyst **2**.<sup>15</sup> Terminal olefins (entries 1–5), which are normally least reactive to electrophilic oxidants and typically require long reaction times with any of the known epoxidation methods (e.g. 12 h to several days with peracid reagents), were found to undergo epoxidation within 5 min and in 60–90% isolated yields. The reaction is operationally simple in that it is insensitive to air and moisture and product isolation is effected simply by distillation or filtration through a short plug of silica. To our knowledge, this is the first example of an MMO model system that is useful for preparative oxidation chemistry. The mep ligand framework is modular in nature and promises to be a very useful template for chiral ligand design. Experiments aimed toward developing enantioselective variants of this epoxidation catalyst are underway.

**Acknowledgment.** This work was supported by the NIH (GM-43214) and a postdoctoral fellowship to M.C.W. from the NIH (1 F32 GM20077-01). The crystal structure analysis was performed by Dr. Richard Staples (Harvard University).

**Supporting Information Available:** Complete experimental details of catalyst synthesis, epoxidation reactions, crystallization, UV–Vis studies (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA015884G

(13) Whittington, D. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 827–838.

(14) General procedure: A  $\text{CH}_3\text{CN}$  solution of olefin (0.24 mmol, 0.16 M), **1** (0.007 mmol, 3 mol %, S/C = 33), and  $\text{CH}_3\text{CO}_2\text{H}$  (30 mol %) was cooled to 4 °C with rapid stirring in a screw cap glass vial. Nitrobenzene (40 mol %, 0.097 mmol) was added as internal standard. A  $\text{CH}_3\text{CN}$  solution of 50 wt %  $\text{H}_2\text{O}_2$  (1.5 equiv, 0.36 mmol, 0.36–5.0 M depending on scale) was precooled to 4 °C and added dropwise over <2 min. Reaction progress was monitored by GC, and in all cases complete conversion of olefin was observed within 5 min with epoxide as the only detectable product. However, small amounts of polar, carboxylic acid-containing byproducts were detected by NMR and IR analysis. Epoxide was isolated by extraction of the crude reaction mixture into pentane and purification through a short plug of silica.

(15) In contrast, substrates bearing aromatic substituents underwent decomposition to unidentified products.