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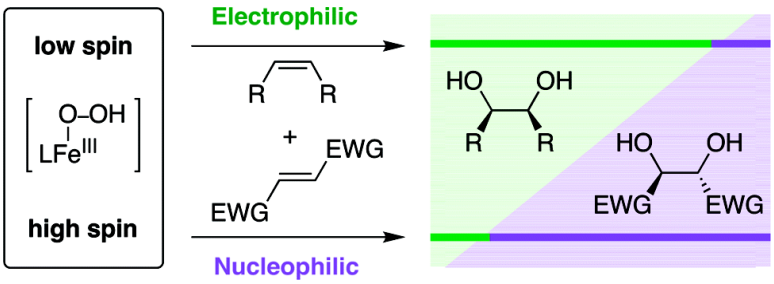

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Iron-Catalyzed Olefin *cis*-Dihydroxylation by H_2O_2: Electrophilic versus Nucleophilic Mechanisms

Megumi Fujita, Miquel Costas, and Lawrence Que, Jr.*

Department of Chemistry and Center for Metals in Biocatalysis, University of Minnesota, Minneapolis, Minnesota 55455

Received December 20, 2002; E-mail: que@chem.umn.edu

The first examples of nonheme iron complexes to catalyze olefin *cis*-dihydroxylation by H_2O_2 have recently been reported.[1] Olefin epoxidation is observed as well, and the *cis*-diol/epoxide ratio can be tuned by the nature of the metal coordination environment.[1a−c] In general, the catalysts have mononuclear iron(II) centers coordinated to tetradentate ligands that allow cis labile sites and convert to active Fe^{III} forms upon treatment with H_2O_2. On the basis of reaction behavior, these catalysts can be categorized into two classes. Class A catalysts form low-spin Fe^{III}−OOH intermediates and give rise to *cis*-diol products with one oxygen atom derived from H_2O_2 and the other from H_2O.[1a,b] On the other hand, Class B catalysts afford high-spin Fe^{III}−OOH intermediates and give rise to *cis*-diol products with both oxygen atoms coming from a single molecule of H_2O_2.[1a,2] On the basis of these observations, different spin-state-dependent mechanisms have been suggested for these two classes (Scheme 1). Compelling evidence has been obtained for the participation of an Fe^{V}(=O)OH oxidant for Class A catalysts, a notion supported by DFT calculations,[3] but the nature of the Class B oxidant is less understood. To gain further insight into the mechanistic differences between class A and B catalysts, we have investigated the oxidation of electron-deficient olefins and found that the active intermediate(s) responsible for olefin oxidation are, respectively, electrophilic and nucleophilic in character.

Complexes [(TPA)Fe(OTf)$_2$] (**1**) and [(6-Me$_3$-TPA)Fe(OTf)$_2$] (**2**)[4] have been selected as prototypical for classes A and B, respectively. In contrast to its oxidation of electron-rich olefins that affords both epoxide and *cis*-diol products, **1** catalyzes oxidation of electron-deficient olefins to afford only *cis*-diol products in good to excellent yield (turnover numbers of 6−9.5 from 10 equiv of H_2O_2) (Table 1). In fact, the oxidation of dimethyl fumarate to dimethyl *rac*-tartrate is essentially quantitative (entry 5), because 0.5 equiv/Fe of H_2O_2 is required to convert the iron(II) catalyst to its active iron(III) form.[1a] For **2** as well, electron-deficient olefins are converted only to diols, but turnover numbers range from 4 to 7, consistent with its observed lower efficiency in oxidations of electron-rich olefins (Table 1).

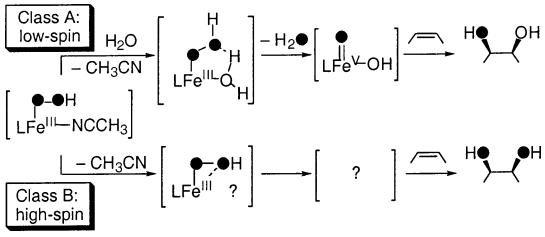
Further experiments show that the respective oxidations of electron-deficient olefins by **1** and **2** follow the patterns previously established with electron-rich olefins.[1b] In the conversion of dimethyl fumarate to dimethyl *rac*-tartrate, there is >99% retention of configuration for both catalysts. ^{18}O-Labeling studies (Table S1) show that the diol from **1** incorporates one oxygen atom each from H_2O_2 and H_2O, while that from **2** derives both oxygen atoms from H_2O_2, strongly suggesting that the same oxidizing intermediate is involved in oxidation of both electron-rich and electron-deficient olefins for each catalyst (Scheme 1). In contrast, the *cis*-dihydroxylation of dimethyl maleate results in some epimerization, with RC values of 79% for **1** and 10% for **2** (entry 6, Table 1). Despite the loss in stereochemistry, ^{18}O-labeling experiments show the same oxygen incorporation pattern as for the other olefins (Scheme 1, Table S1), indicating that O_2 does not play a role in these reactions. The observed loss of stereochemistry requires that the two C−O bonds of the diol product form in a stepwise mechanism for both catalysts.

Table 1. Olefin Oxidation Products[a]

		1	2
entry	olefin	diol/epoxide[b] [%RC][c]	diol/epoxide[b] [%RC][c]
1	acrylonitrile	8.5(4)/−	7.3(7)/−
2	methacrylonitrile	7.0(12)/−	6.9(12) /−
3	*tert*-butyl acrylate	5.8(8)/−	6.2(6) /−
4	ethyl *trans*-crotonate	6.9(5)/− [>99]	4.5(1)/− [>99]
5	dimethyl fumarate	9.5(3)/− [>99]	5.2(4)/− [>99]
6	dimethyl maleate	7.8(4)/− [79]	4.2(3)/− [10]
7	*cis*-2-heptene[1b]	3.0(3)/1.9(1) [96]	4.1(4)/0.4(1) [93]
8	*cis*-cyclooctene[1b]	4.2(2)/3.4(1)	4.9(6)/0.7(2)
9	1-octene	6.1(3)/1.1(2)	4.7(9)/0.1(1)

[a] Reaction conditions: An H_2O_2 solution (21 μmol or 0.30 mL of a 70 mM solution in CH_3CN with ≥245 mM H_2O) was added via syringe pump over 22 min to a solution of olefin (1050 μmol) and the catalyst (2.1 μmol) in CH_3CN (2.7 mL) at 22−25 °C under air. [b] Yield expressed as turnover numbers (μmol product/μmol catalyst) determined by GC analysis; average of 2−3 runs. [c] %RC: $100 \times (A - B)/(A + B)$ where A = yield of *cis*-diol with retention of configuration and B = yield of epimer.

Scheme 1



Competition experiments reveal the most significant difference in the nature of the oxidants generated by **1** and **2**. Figure 1 shows the results of pairwise oxidations among four olefins: cyclooctene (two alkyl substituents), 1-octene (one alkyl substituent), *tert*-butyl acrylate (one electron-withdrawing group or EWG), and dimethyl fumarate (2 EWGs). These results demonstrate that **1** clearly prefers to oxidize the more electron-rich olefin, while **2** has the opposite preference. For example, between cyclooctene and *tert*-butyl acrylate, **1** favors cyclooctene oxidation by a factor of 4, while **2** favors *tert*-butyl acrylate oxidation by a factor of 4. The opposite preferences exhibited by **1** and **2** imply the formation of distinct oxidants. The reactivity of **1** is consistent with an electrophilic oxidant, presumably the Fe^{V}(=O)OH species implicated by earlier ^{18}O-labeling results (Scheme 1). The contrasting behavior of **2**, on the other hand, suggests formation of a nucleophilic oxidant.

Thus far, there are two literature examples of nucleophilic substrate oxidations by high-spin iron(III) peroxo species. In case

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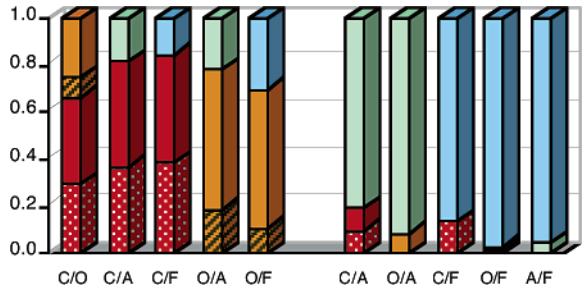
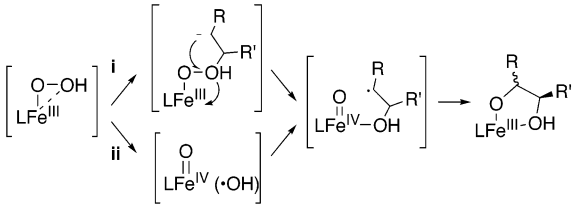


Figure 1. Competition experiments for the oxidation of olefin pairs by catalysts **1** (left) and **2** (right): C = cyclooctene (red), O = 1-octene (orange), A = *tert*-butyl acrylate (green), F = dimethyl fumarate (blue). Conditions as described under Table 1 except that 1050 μmol each of two olefins was used. Solid blocks represent the fraction of diol formed, while patterned blocks represent the fraction of epoxide formed.

Scheme 2. Proposed Mechanisms of *cis*-Dihydroxylation by a Nucleophilic Oxidant Generated from **2**/H_2O_2



I, epoxidation of α,β-unsaturated ketones is initiated by nucleophilic attack of an (η^2-peroxo)iron(III) porphyrin complex,[5] followed by O−O bond heterolysis, analogous to the action of basic H_2O_2. In case II, a high-spin $Fe^{III}-\eta^1$-OOH intermediate is proposed to undergo O−O bond homolysis to generate a species that preferentially oxidizes dimethyl sulfoxide over dimethyl sulfide.[6] To apply to **2**, these mechanisms must be adapted to account for the unprecedented formation of *cis*-diol and its high yield.

Scheme 2 shows two proposed mechanisms for *cis*-dihydroxylation by **2**. Mechanism **i** entails a nucleophilic attack by the coordinated peroxide on the olefin, like case I, but followed by reductive O−O bond homolysis. Mechanism **ii** involves initial O−O bond homolysis, like case II, to form a tightly associated Fe^{IV}═O/HO• pair, followed by nucleophilic attack of HO• on the substrate. (The nucleophilicity of HO• has been documented by Walling and El-Taliawi, who showed that HO• readily adds to α,β-unsaturated acids to form water addition products (but not diols).[7]) In both mechanisms, the available cis site on the iron center is recruited to facilitate formation of an Fe^{IV}−2-hydroxyalkyl radical species. This species is the key to diol formation, as iron complexes of related pentadentate ligands do not catalyze *cis*-dihydroxylation.[1,8] The subsequent collapse of this Fe^{IV}-radical species to diol is akin to the oxygen rebound step in iron-catalyzed alkane hydroxylations.[9] The rate of oxygen rebound depends on the stability of the transient alkyl radical, thus affording a high RC value for *cis*-2-heptene and a lower value for dimethyl maleate due to the radical-stabilizing effect of the adjacent −COOMe group.

In summary, we have found that **1** and **2**, respectively, generate oxidants with electrophilic and nucleophilic character in the catalysis of olefin *cis*-dihydroxylation by H_2O_2. This difference is likely related to the spin state of the Fe^{III}−OOH intermediate generated in the course of catalysis. The electrophilicity of the oxidant derived from **1**/H_2O_2 is consistent with the reactivity expected for the previously proposed high-valent Fe^{V}(═O)OH species derived from a low-spin Fe^{III}−OOH intermediate.[1a,b] Such a species may be viewed as related to the high-valent dioxometal species well known to carry out olefin *cis*-hydroxylation.[10] The observed nucleophilicity of the oxidant generated from **2**/H_2O_2, on the other hand, has fewer precedents and requires the consideration of new mechanisms to rationalize the high conversion efficiency and stereoselectivity associated with the putative high-spin Fe^{III}−OOH intermediate. This study thus establishes the mechanistic versatility of iron-peroxo species in olefin oxidation; it also lays the foundation for understanding the mechanism of Rieske dioxygenases,[11] enzymes involved in biodegradation that catalyze *cis*-dihydroxylation of arenes and olefins.

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Supporting Information Available: Table S1 listing results of ^{18}O-labeling experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) TPA = tris(2-pyridylmethyl)amine; 6-Me_3-TPA = tris(6-methyl-2-pyridylmethyl)amine.

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