

## Iron-Catalyzed Olefin *cis*-Dihydroxylation by H<sub>2</sub>O<sub>2</sub>: Electrophilic versus Nucleophilic Mechanisms

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The first examples of nonheme iron complexes to catalyze olefin *cis*-dihydroxylation by H<sub>2</sub>O<sub>2</sub> have recently been reported.<sup>1</sup> Olefin epoxidation is observed as well, and the *cis*-diol/epoxide ratio can be tuned by the nature of the metal coordination environment.<sup>1a-c</sup> In general, the catalysts have mononuclear iron(II) centers coordinated to tetradentate ligands that allow *cis* labile sites and convert to active Fe<sup>III</sup> forms upon treatment with H<sub>2</sub>O<sub>2</sub>. On the basis of reaction behavior, these catalysts can be categorized into two classes. Class A catalysts form low-spin Fe<sup>III</sup>-OOH intermediates and give rise to *cis*-diol products with one oxygen atom derived from H<sub>2</sub>O<sub>2</sub> and the other from H<sub>2</sub>O.<sup>1a,b</sup> On the other hand, Class B catalysts afford high-spin Fe<sup>III</sup>-OOH intermediates and give rise to *cis*-diol products with both oxygen atoms coming from a single molecule of H<sub>2</sub>O<sub>2</sub>.<sup>1a,2</sup> 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<sup>V</sup>(=O)OH oxidant for Class A catalysts, a notion supported by DFT calculations,<sup>3</sup> 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)<sub>2</sub>] (**1**) and [(6-Me<sub>3</sub>-TPA)Fe(OTf)<sub>2</sub>] (**2**)<sup>4</sup> 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<sub>2</sub>O<sub>2</sub>) (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<sub>2</sub>O<sub>2</sub> is required to convert the iron(II) catalyst to its active iron(III) form.<sup>1a</sup> 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.<sup>1b</sup> In the conversion of dimethyl fumarate to dimethyl *rac*-tartrate, there is >99% retention of configuration for both catalysts. <sup>18</sup>O-Labeling studies (Table S1) show that the diol from **1** incorporates one oxygen atom each from H<sub>2</sub>O<sub>2</sub> and H<sub>2</sub>O, while that from **2** derives both oxygen atoms from H<sub>2</sub>O<sub>2</sub>, 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, <sup>18</sup>O-labeling experiments show the same oxygen incorporation pattern as for the other olefins (Scheme 1,

**Table 1.** Olefin Oxidation Products<sup>a</sup>

entry	olefin	1	2
		diol/epoxide <sup>b</sup> [%RC] <sup>c</sup>	diol/epoxide <sup>b</sup> [%RC] <sup>c</sup>
1	acrylonitrile	8.5(4)/–	7.3(7)/–
2	methacrylonitrile	7.0(12)/–	6.9(12)/–
3	<i>tert</i> -butyl acrylate	5.8(8)/–	6.2(6)/–
4	ethyl <i>trans</i> -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	<i>cis</i> -2-heptene <sup>1b</sup>	3.0(3)/1.9(1) [96]	4.1(4)/0.4(1) [93]
8	<i>cis</i> -cyclooctene <sup>1b</sup>	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)

<sup>a</sup> Reaction conditions: An H<sub>2</sub>O<sub>2</sub> solution (21  $\mu$ mol or 0.30 mL of a 70 mM solution in CH<sub>3</sub>CN with  $\geq 245$  mM H<sub>2</sub>O) was added via syringe pump over 22 min to a solution of olefin (1050  $\mu$ mol) and the catalyst (2.1  $\mu$ mol) in CH<sub>3</sub>CN (2.7 mL) at 22–25 °C under air. <sup>b</sup> Yield expressed as turnover numbers ( $\mu$ mol product/ $\mu$ mol catalyst) determined by GC analysis; average of 2–3 runs. <sup>c</sup> %RC:  $100 \times (A - B)/(A + B)$  where A = yield of *cis*-diol with retention of configuration and B = yield of epimer.

### Scheme 1

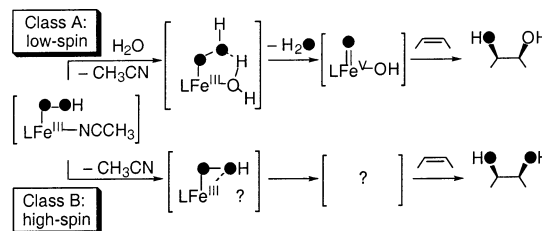
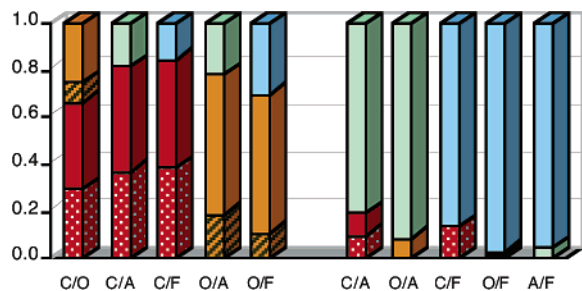


Table S1), indicating that O<sub>2</sub> does not play a role in these reactions. The observed loss of stereochemistry requires that the two C–O bonds of the diol product form in a stepwise mechanism for both catalysts.

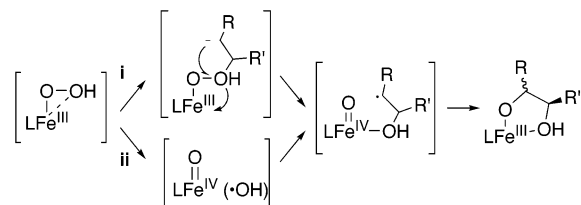
Competition experiments reveal the most significant difference in the nature of the oxidants generated by **1** and **2**. Figure 1 shows the results of pairwise oxidations among four olefins: cyclooctene (two alkyl substituents), 1-octene (one alkyl substituent), *tert*-butyl acrylate (one electron-withdrawing 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<sup>V</sup>(=O)OH species implicated by earlier <sup>18</sup>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) peroxy species. In case



**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  $\mu\text{mol}$  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**/ $\text{H}_2\text{O}_2$



I, epoxidation of  $\alpha,\beta$ -unsaturated ketones is initiated by nucleophilic attack of an ( $\eta^2$ -peroxo)iron(III) porphyrin complex,<sup>5</sup> followed by O–O bond heterolysis, analogous to the action of basic  $\text{H}_2\text{O}_2$ . In case II, a high-spin  $\text{Fe}^{\text{III}}-\eta^1\text{-OOH}$  intermediate is proposed to undergo O–O bond homolysis to generate a species that preferentially oxidizes dimethyl sulfoxide over dimethyl sulfide.<sup>6</sup> 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  $\text{Fe}^{\text{IV}}=\text{O}/\text{HO}\cdot$  pair, followed by nucleophilic attack of  $\text{HO}\cdot$  on the substrate. (The nucleophilicity of  $\text{HO}\cdot$  has been documented by Walling and El-Taliawi, who showed that  $\text{HO}\cdot$  readily adds to  $\alpha,\beta$ -unsaturated acids to form water addition products (but not diols).<sup>7</sup>) In both mechanisms, the available *cis* site on the iron center is recruited to facilitate formation of an  $\text{Fe}^{\text{IV}}-2\text{-hydroxyalkyl}$  radical species. This species is the key to diol formation, as iron complexes of related pentadentate ligands do not catalyze *cis*-dihydroxylation.<sup>1,8</sup> The subsequent collapse of this  $\text{Fe}^{\text{IV}}$ -radical species to diol is akin to the oxygen rebound step in iron-catalyzed alkane hydroxylations.<sup>9</sup> 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  $-\text{COOMe}$  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  $\text{H}_2\text{O}_2$ . This difference is likely related to the spin state of the  $\text{Fe}^{\text{III}}-\text{OOH}$  intermediate generated in the course of catalysis. The electrophilicity of the oxidant derived from **1**/ $\text{H}_2\text{O}_2$  is consistent with the reactivity expected for the previously proposed high-valent  $\text{Fe}^{\text{V}}(=\text{O})\text{OH}$  species derived from a low-spin  $\text{Fe}^{\text{III}}-\text{OOH}$  intermediate.<sup>1a,b</sup> Such a species may be viewed as related to the high-valent dioxometal species well known to carry out olefin *cis*-hydroxylation.<sup>10</sup> The observed nucleophilicity of the oxidant generated from **2**/ $\text{H}_2\text{O}_2$ , 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  $\text{Fe}^{\text{III}}-\text{OOH}$  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,<sup>11</sup> enzymes involved in biodegradation that catalyze *cis*-dihydroxylation of arenes and olefins.

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

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