

Bio-inspired iron-catalyzed olefin oxidation. Additive effects on the *cis*-diol/epoxide ratio

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Abstract

A landscape of mechanistic possibilities for the oxidation of olefins by bio-inspired non-heme iron catalysts has been explored in this work. The complexes studied consist of iron centers coordinated to the tetradentate N4 ligands tpa and bpmen, which provide two *cis*-labile sites to the iron center. These complexes catalyze conversion of olefin substrates into epoxide and/or *cis*-diol products. The diol-to-epoxide ratio is very sensitive to the nature of the tetradentate ligand and reaction conditions. With the aim of understanding how these systems can be modulated, the effects of additives such as water, acetone or acetic acid have been explored. These additives significantly alter the catalytic activity of Fe(bpmen) and Fe(tpa) complexes. Accordingly, the initial mechanistic proposals where the HO–Fe^V=O intermediate appeared as the unique active oxidizing species have been expanded and other key catalytic intermediates such as Fe^{III}(OOH) or Fe^{IV}=O are implicated as a consequence of the results reported in this work.

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1. Introduction

In the last few years, a family of bio-inspired non-heme iron catalysts for olefin oxidation has emerged that differs from previously reported iron catalysts [1]. Their main distinction is their ability to catalyze olefin *cis*-dihydroxylation, representing the first example of such catalytic activity by a non-biological iron center. This *cis*-dihydroxylation reactivity mimics the action of Rieske dioxygenases, which are non-heme iron enzymes that carry out the *cis*-dihydroxylation of arene double bonds in the first step of arene biodegradation by soil bacteria [2]. The active site of these enzymes consists of an iron center ligated to two histidines and a bidentate aspartate [3] (Scheme 1) in a variation of the emerging 2-His-1-carboxylate facial triad motif common to many mononuclear non-heme iron enzymes that activate dioxygen [4]. The reported catalysts consist of iron complexes with tetradentate N4 ligands that provide, like enzyme active sites, two *cis*-labile sites at which the H₂O₂ oxidant is efficiently activated. Scheme 2 illustrates the structures of the Fe(bpmen) and Fe(tpa) complexes that represent the bio-inspired catalysts investigated thus far in the most detail. Using these

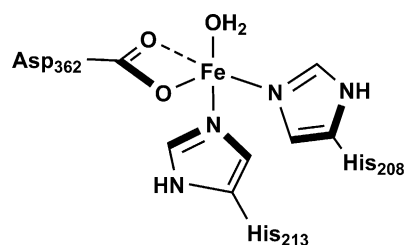
catalysts, olefin substrates are converted into epoxide and/or *cis*-diol products, depending on the tetradentate ligand and reaction conditions. Overall, the available data reveal a surprisingly complex reaction landscape and demonstrate for the first time that olefin epoxidation and *cis*-dihydroxylation are in fact closely related transformations that can be carried out by the common HO–Fe^V=O oxidant that like the Roman god Janus has two faces (Fig. 1) [5,6].

Scheme 3 shows the previously proposed general mechanistic scheme that has evolved from experimental and computational investigations on how these catalysts work to perform *cis*-dihydroxylation of olefins. Key features of this scheme are the presence of two *cis*-labile sites on the metal center that allow the activation of H₂O₂ to occur in the desired fashion and the involvement of an HO–Fe^V=O oxidant that can give rise to both epoxide and *cis*-diol. In this paper, we discuss the effects of additives on the catalytic activities of the two complexes in Scheme 2 and how the mechanistic landscape described in Scheme 3 is expanded by recent results.

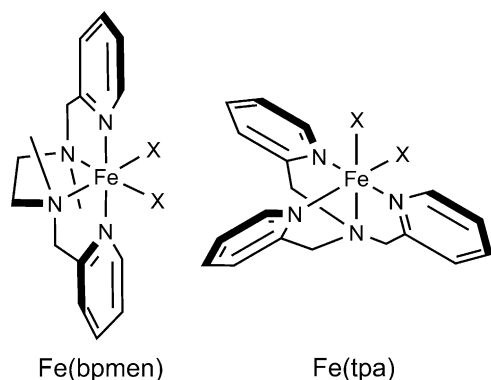
2. Experimental

Catalytic oxidations were carried out as previously reported [5]. About 0.3 mL of a 70 mM H₂O₂ solution (diluted from

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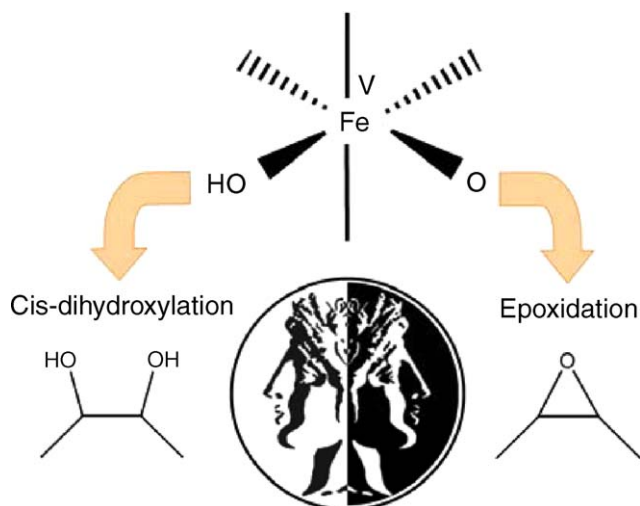
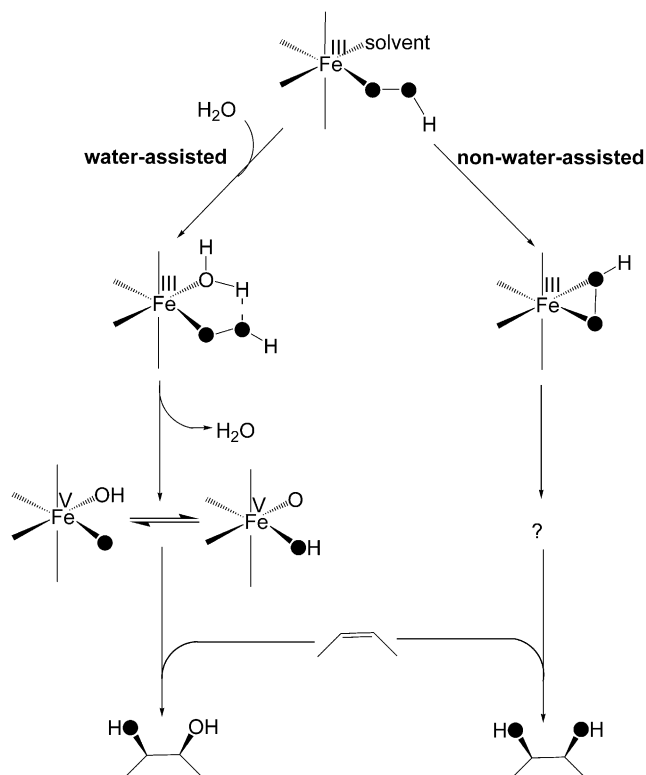


Scheme 1. Active site of a Rieske dioxygenase.



Scheme 2. Schematic structures of bio-inspired catalysts.

a 35% H_2O_2 solution) in CH_3CN was delivered by syringe pump over 25 min at 25°C in air to a CH_3CN solution (2.7 mL) containing iron catalyst and olefin substrate. The final concentrations were 0.7 mM mononuclear iron catalyst, 7.0 mM H_2O_2 , and 0.70 M olefin. The solution was stirred for another 5 min after syringe pump addition was complete. The resulting solutions were treated with 1 mL of acetic anhydride together with 0.1 mL of 1-methylimidazole in order to esterify the diol products. Naphthalene was added as an internal standard. Organic products were extracted with CHCl_3 . The solution was subjected to GC analysis and products were identified by comparison of their GC retention times. All experiments were run at least in duplicate, the reported data being the average of these reactions.

Fig. 1. The $\text{HO-Fe}^{\text{V}}=\text{O}$ oxidant, like Janus, has two faces.Scheme 3. Common mechanistic scheme for bio-inspired *cis*-dihydroxylation.

For the reactions with added water, 42 μL of H_2O or H_2^{18}O (0.70 M, 1000 equivalents) were added to the catalyst solution prior to the injection of H_2O_2 . In experiments where labeled water was used the organic products were subjected to GC/CI-MS analyses.

For the reactions with added acetone, 50 μL of acetone were added to the catalyst solution prior to the injection of H_2O_2 .

For the reactions with added acetic acid, variable amounts of CH_3COOH were added to the catalyst solution prior to the injection of H_2O_2 . For the competition experiments, the final concentrations of 1-octene and *tert*-butyl acrylate were 0.35 M.

3. Effect of adding water

The evolution of the mechanistic paradigm for non-heme iron catalyzed olefin oxidation to include water-assisted (wa) and non-water-assisted (nwa) branches that afford a unique $\text{HO-Fe}^{\text{V}}=\text{O}$ oxidant stems from the observation of label incorporation from labeled water into the *cis*-diol product with some catalysts but not with others [1,5]. Indeed for $\text{Fe}(\text{tpa})$, one oxygen atom of the *cis*-diol product derives from H_2O_2 and the other from H_2O , while both atoms of diol derive from H_2O_2 in the case of $\text{Fe}(\text{6-Me}_3\text{-tpa})$. Since the labeled H_2O_2 experiments required the use of commercially available 2% $\text{H}_2^{18}\text{O}_2$ solution, with the consequent introduction of ~ 1000 equivalents of water, the question of whether the addition of this amount of water can change the chemistry of the catalyst needed to be addressed. In the case of $\text{Fe}(\text{bpmen})$, the addition of 1000 equivalents H_2O decreased the overall yield of olefin oxidation products by 35%

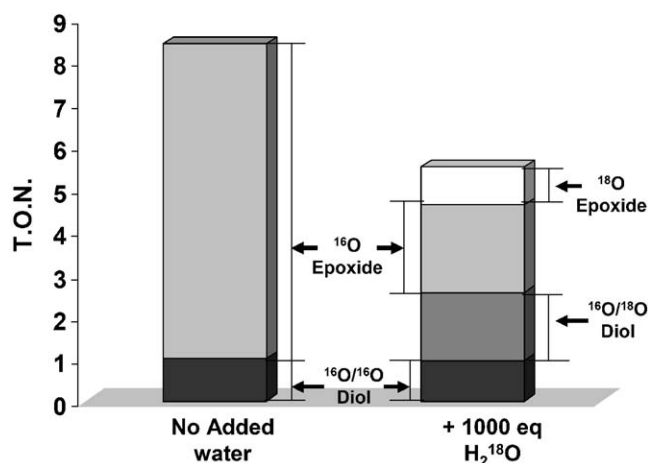
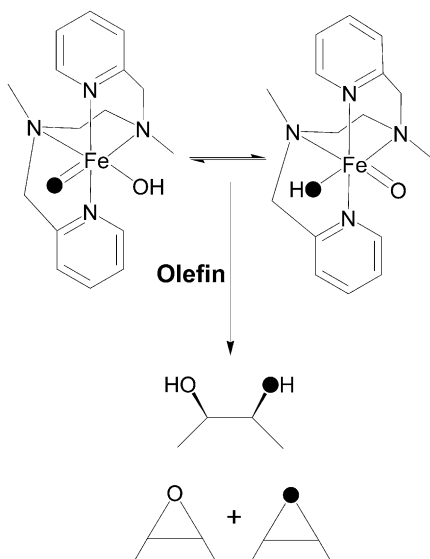


Fig. 2. Yields of diol and epoxide (in turnovers) obtained from the oxidation of cyclooctene by 10 equivalents H_2O_2 in the presence of $[(\text{bpmen})\text{Fe}(\text{OTf})_2]$ in CH_3CN , with or without addition of O^{18} -labeled water.

and changed the diol/epoxide ratio from 1/8 to 1/1.2 (Fig. 2) [7]. The divergent results obtained depending on the amount of water present in solution suggest differences in the nature of the active oxidizing species generated through a wa or a nwa mechanism.

Strong support for the wa mechanism was obtained from H_2^{18}O labeling experiments, which showed the incorporation of ^{18}O into both epoxide and diol products (Fig. 2). The H_2^{18}O labeling results can be understood in the following manner. About 30% of the epoxide product has an ^{18}O label. Since the $(\text{bpmen})\text{Fe}^{\text{V}}(\text{O})(\text{OH})$ species has effective two-fold symmetry and should undergo facile oxo-hydroxo tautomerization (Scheme 4), 60% of this epoxide must derive from the oxidant. On the other hand, the oxidant reacts with substrate to transfer both oxygen atoms to produce the diol product. Consistent with the epoxide labeling results, 60% of the diol has one ^{18}O label incorporated. Thus, when $\text{Fe}(\text{bpmen})$ catalysis occurs in the presence of 1000 equivalents water, the oxidant shown in



Scheme 4. Representation of the putative $(\text{bpmen})\text{Fe}^{\text{V}}(\text{O})(\text{OH})$ intermediate generated via a wa mechanism in the presence of labeled water.

Scheme 4 generated via a wa mechanism, which contains one ^{18}O atom, appears to be responsible of the obtention of the 60% of the oxidation products of cyclooctene.

The remaining 40% must be formed by a different non-water-assisted mechanism. We note that the amount of diol that does not incorporate ^{18}O from H_2^{18}O is the same as that produced under standard conditions. Suitable candidates as active oxidizing species include: the initial $(\text{bpmen})\text{Fe}^{\text{III}}\text{-OOH}(\text{MeCN})$ itself (a), or its side-on bound isomer $(\text{bpmen})\text{Fe}(\eta^2\text{-OOH})$ (b) or an $\text{HO-Fe}^{\text{V}}=\text{O}$ oxidant (c) derived from O-O cleavage of (b). Unfortunately none of these species has been experimentally observed, although DFT calculations provide support for (a) as an effective epoxidating agent. The nwa pathway for *cis*-dihydroxylation however remains unclear, and requires further work.

Interestingly, addition of 1000 equivalents H_2O in the $\text{Fe}(\text{tpa})$ -catalyzed cyclooctene oxidation has no effect on the diol/epoxide product ratio of 1.2/1 in MeCN . Furthermore the diol product shows 100% incorporation of one label from H_2^{18}O , indicating sole operation of the wa pathway for *cis*-dihydroxylation. These results suggest that, unlike in the case of $\text{Fe}(\text{bpmen})$, the $\text{HO-Fe}^{\text{V}}=\text{O}$ species generated via the wa pathway is the unique active oxidant generated from $\text{Fe}(\text{tpa})$, even if the amount of water present in solution is relatively low. This difference may be a consequence of the different topology of the tpa ligand that favors the binding of water and results in inequivalent *cis*-labile sites. The different topologies may also give rise to spin state differences that affect the reactivity of the metal centers [1], but more effort has to be made to trap intermediates in the $\text{Fe}(\text{bpmen})$ reaction.

4. Effect of adding acetone

We have also explored the effect of adding small amounts of acetone on the observed diol/epoxide ratio in the case of $\text{Fe}(\text{tpa})$ catalysis in MeCN . In re-examining the product analysis for cyclooctene and 1-octene oxidation, we noted the presence of small amounts of the corresponding α -hydroxyketone, which suggested some extent of diol over-oxidation under the reaction conditions. We then sought to protect the diol products from over-oxidation and added acetone as a means of protection via the formation of diol acetonides. As shown in Fig. 3 for a series of four olefins studied, we found that adding acetone (2% v/v) indeed effected a significant increase in the amounts of diol products observed while the epoxide obtained remained constant. For instance, in the cyclooctene case, adding acetone increased observed diol yield by 50% and all of the diol product appeared as the acetonide derivative. This raises the conversion efficiency of H_2O_2 into olefin oxidation products close to 90%. Improvements in diol yield were observed for other olefins as well. These results demonstrate that $\text{Fe}(\text{tpa})$ is in fact a more effective catalyst than we reported initially and exhibits a higher selectivity towards *cis*-dihydroxylation.

This acetone effect is different from that reported for $\text{Fe}(\text{tpa})$ catalysis in pure acetone as solvent [8]. In the latter case, the product distribution observed is not changed dramatically from that in MeCN , but the catalysis is less efficient. We have found

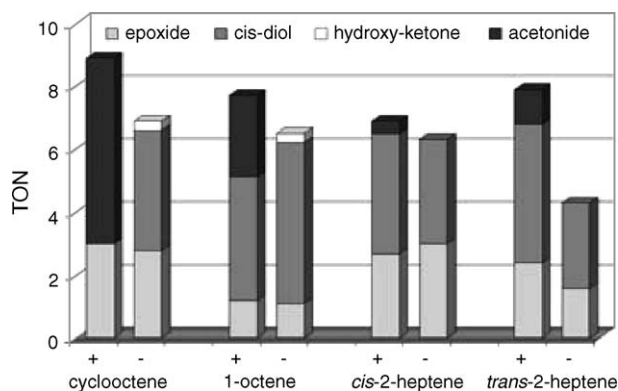


Fig. 3. Comparison of the yields of epoxide, *cis*-diol, α -hydroxyketone and diol acetonide (in turnovers) obtained from oxidation of different olefins by 10 equivalents H_2O_2 in the presence of $[(\text{tpa})\text{Fe}(\text{OTf})_2]$ in CH_3CN . + Denotes addition of acetone and – indicates that acetone has not been added to the reaction mixture.

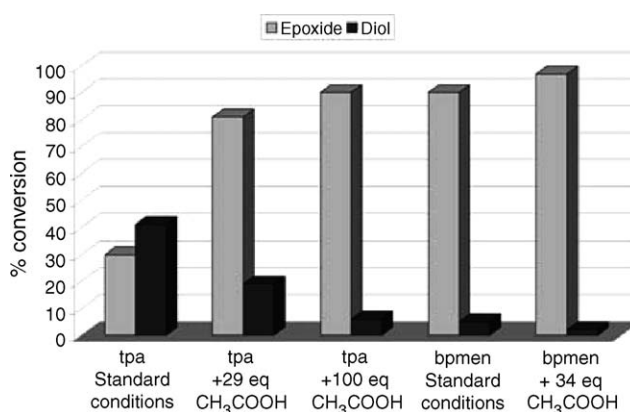
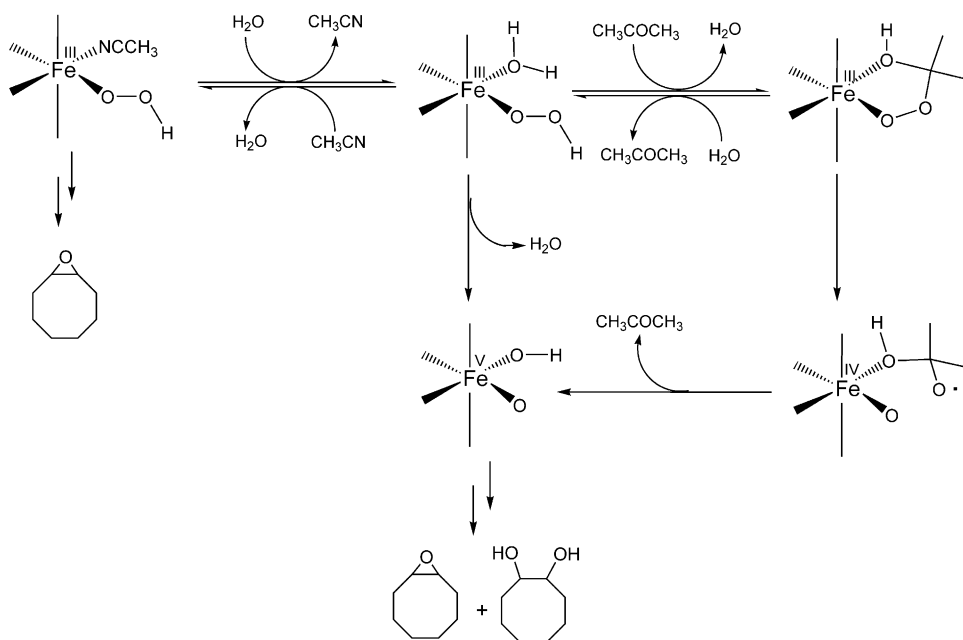


Fig. 4. Yields of epoxide and *cis*-diol (in % conversion) obtained from oxidation of cyclooctene by 14.5 equivalents H_2O_2 in the presence of $[(\text{tpa})\text{Fe}(\text{OTf})_2]$ or $[(\text{bpmen})\text{Fe}(\text{OTf})_2]$ in CH_3CN with or without added CH_3COOH .

5. Effect of adding acetic acid

that the nature of the intermediates produced in the reaction changes somewhat. Studies at -80°C showed that the initial peroxyiron(III) species formed is a peroxyacetone adduct that then undergoes subsequent O–O bond homolysis to form an oxoiron(IV) intermediate. The trapping of the oxoiron(IV) intermediate in the catalytic cycle may lead one to think that epoxide formation would be favored [9]; however, no significant change on the diol/epoxide ratio is observed when the reaction is carried out in acetone or in acetonitrile. This fact seems to indicate that the intermediate species detected at low temperature may not be directly related to the catalytic reaction at room temperature. One probable explanation to this observation is the further evolution of the initial intermediate generated in acetone, under standard catalytic conditions, to the $\text{HO-Fe}^{\text{V}}=\text{O}$ oxidizing species (Scheme 5) [8].

Lastly, another way to modulate the catalytic behavior of non-heme iron complexes in CH_3CN is by adding CH_3COOH . This effect was originally observed for $\text{Fe}(\text{bpmen})$ by Jacobsen and co-workers where addition of acetic acid to olefin oxidation reactions resulted in an increase in both catalytic activity and selectivity towards epoxidation [10]. More dramatic results were obtained upon extension to $\text{Fe}(\text{tpa})$, where the diol/epoxide ratio decreased appreciably, by nearly an order of magnitude from 1.2 to 0.15 for cyclooctene oxidation (Fig. 4). Similar results were found for 1-octene oxidation by the $\text{Fe}(\text{tpa})$ catalyst where the diol/epoxide ratio goes from 4.3 under standard conditions to 0.28 when an excess of acetic acid was added. The completely different diol/epoxide ratios with or without addition of acetic acid suggest that the presence of CH_3COOH changes the nature of the active oxidizing species. The different nature of the



Scheme 5. Expanded mechanistic landscape for bio-inspired iron catalysts.

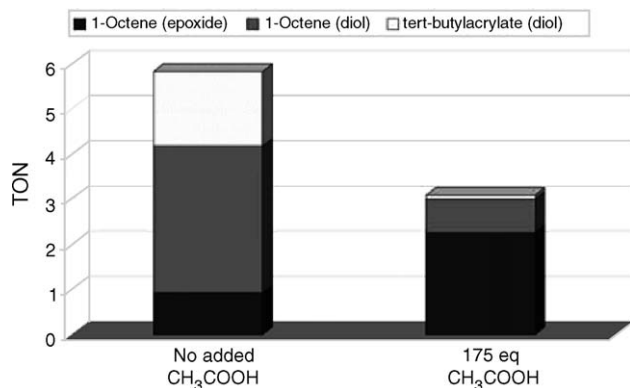


Fig. 5. Yields of epoxide and *cis*-diol (in turnovers) obtained from oxidation of an equimolar mixture of 1-octene and *tert*-butylacrylate by 10 equivalents H₂O₂ in the presence of [(tpa)Fe(OTf)₂] in CH₃CN with or without added CH₃COOH.

key catalytic species is also illustrated by the results of experiments where two different olefins compete as the substrate to be oxidized. Fig. 5 presents the results of oxidation of equimolar mixtures of 1-octene and *tert*-butyl acrylate by the Fe(tpa) catalyst with or without addition of acetic acid. While the oxidation product of *tert*-butyl acrylate is in both cases exclusively diol, oxidation of 1-octene results in formation of both diol and epoxide. Addition of CH₃COOH results in an increase of epoxide derived from 1-octene together with a decrease in yield of diol from 1-octene or *tert*-butyl acrylate. Interestingly, the ratio diol(octene)/diol(acrylate) drops from 0.5 (standard conditions) to 0.1 (after addition of acetic acid). This observation suggests that the *cis*-dihydroxylating agent becomes less electrophilic upon adding acetic acid.

The effect of acetic acid has been interpreted in several different ways. Jacobsen and co-workers proposed that the active form of the Fe(bpmen) catalyst was a (μ-oxo)(μ-carboxylato)diiron(III) complex, [(bpmen)Fe^{III}(μ-O)(μ-κ²-OAc)Fe^{III}(bpmen)]³⁺, that was isolated from the reaction mixture and structurally characterized [10]. However, its role as a catalytically active species has been questioned, as there are several reports that this diiron(III) complex and the related tpa complex are catalytically inactive [11–13]. Thus, its isolation from the reaction mixture seems to reflect the fact that complexes with such (μ-oxo)(μ-carboxylato)diiron(III) cores serve as the thermodynamic sink for oxidized non-heme iron compounds.

Alternatively, Fujita et al. proposed that the Fe(L)/H₂O₂/CH₃COOH combination may react to form a different oxidant in situ, namely peracetic acid, that is then activated for olefin oxidation by the iron complex [14]. This postulate derived from the observations that nearly identical product distributions were obtained for olefin oxidations catalyzed by Fe(bpmen) and Fe(tpa) with CH₃CO₃H as oxidant. Formation of the peracid from H₂O₂ and CH₃COOH catalyzed by the iron center can be proposed as a nucleophilic attack of a coordinated hydroperoxo group to a coordinated molecule of CH₃COOH to obtain

an acylperoxo intermediate species that could serve as the oxidant or its precursor. This species is essentially the same as the initial intermediate proposed for the reaction of [LFe^{II}] with peracetic acid, which is an efficient route to the formation of an Fe^{IV}=O intermediate. The high yield of epoxidation observed under these conditions makes the participation of an Fe^{IV}=O oxidant a very attractive postulate. Work in progress is aimed at establishing whether such an intermediate can be trapped under these reaction conditions.

6. Conclusions

The set of data reported in this work demonstrates the wide mechanistic landscape derived from reaction of non-heme iron complexes with H₂O₂. New features of this landscape have been added in order to explain the results recently obtained with Fe(tpa) and Fe(bpmen) with additives such as water, acetone or acetic acid. Thus, the initial proposals where the HO–Fe^V=O intermediate appeared as the unique active oxidizing species have been extended by these new experiments to include the participation of Fe^{III}(OOH) and Fe^{IV}=O oxidants.

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