DOI: 10.1002/ange.200701681

Oxidation Catalysis

Biomimetic High-Valent Non-Heme Iron Oxidants for the *cis*-Dihydroxylation and Epoxidation of Olefins**

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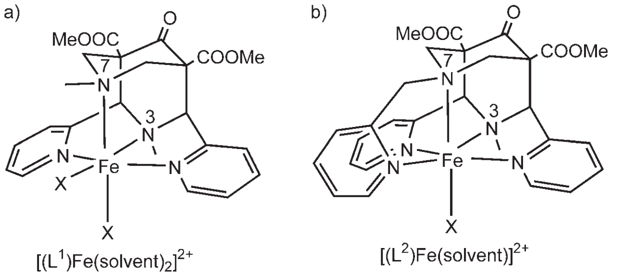
High-valent iron oxidants are known to be the catalytically active species in heme enzymes, and the last decade has seen similar developments in non-heme-iron biomimetics and biochemistry.[1,2] Extensive reactivity studies, structural, spectroscopic, and computational work have established $\{Fe^{III}OOH\}$ and $\{Fe^{IV}{=}O\}$ as relevant intermediates in catalytic oxygenation processes.[2,3] The species $\{Fe^{V}{=}O\}$ has also been trapped, characterized, and found to be active in oxygen transfer, and discrete $\{Fe^{VI}\}$ species have been spectroscopically characterized.[4,5] TauD, an α-ketogluterate-dependent enzyme, is a well-characterized non-heme iron enzyme and has a high-spin ($S=2$) center in its active form.[6] The aqua ion is the only other known high-spin ferryl complex.[7,8] All biomimetic ferryl complexes characterized to date have intermediate-spin ($S=1$) electronic configuration. Herein we present experimental data of the iron-catalyzed oxidation of cyclooctene by H_2O_2 with the tetradentate bispidine ligand L^1 (Scheme 1 a). The data indicate that unprecedented Fe^{IV} centers may be involved as the active oxidants, and these species are predicted by DFT calculations to be the novel intermediate-spin $\{Fe^{IV}(OH)_2\}$ ($S=1$) and the high-spin $\{Fe^{IV}{=}O\}$ ($S=2$) species, which have not been observed in model chemistry until now.[7]



Scheme 1. Iron complexes of a) L^1 and b) L^2. X denotes coordinated solvent.

With the pentadentate bispidine ligand L^2 (Scheme 1 b) the $\{(L^2)Fe^{II}\}/H_2O_2$ chemistry produced the low-spin $\{Fe^{III}OOH\}$, high-spin $\{Fe^{III}(O_2)\}$, and intermediate-spin ferryl $\{Fe^{IV}{=}O\}$ complexes, which have been fully characterized.[9,10] It was shown that there is a direct path from $\{(L^2)Fe^{II}\}$ to the $\{(L^2)Fe^{IV}\}$ ferryl complex, which was identified as the catalytically active species.[10–12] In sharp contrast, in the corresponding L^1-based system, no Fe^{III} species has been identified, with the exception of an $\{Fe^{III}OOR\}$ complex obtained by the oxidation of $\{(L^1)Fe^{II}\}$ with *t*BuOOH; this complex was shown to be close to the spin-crossover limit.[13] We have also been unable to trap and characterize the intermediate-spin ferryl complex. A DFT analysis indicated that this result is not unexpected, as the $\{(L^1)Fe^{II}\}$ system is predicted to be directly oxidized by H_2O_2 to the novel $\{Fe^{IV}(OH)_2\}$ complex with an intermediate-spin ($S=1$) electronic configuration, and which reacts through proton transfer to the corresponding and slightly more stable high-spin ($S=2$) ferryl oxidant.[14]

Olefin oxidation experiments similar to those with the pentadentate ligand L^2 were carried out ($\{(L^1)Fe^{II}\}/H_2O_2/\text{cyclooctene} = 1{:}10{:}1000$, 298 K, aerobic or argon atmosphere, MeCN as solvent, $TON_{max}=10$,[15] reaction time 0.5 h, standard work-up procedure, and GC-MS analysis; for details see the Supporting Information). Product distribution and labeling studies (^{18}O) indicate that, while the reactivities of the L^1- and L^2-based catalysts are similar ($TON_{total}=3.8$ and 5.0; Table 1), the reaction mechanisms must be different. With the L^2-based system, diol products are only produced under argon and are stereochemically scrambled (*cis*- and

Table 1: TON, product ratios, and ^{18}O labeling studies for the iron–bispidine-catalyzed oxidation of cyclooctene with H_2O_2.[a]

	$\{(L^1)Fe\}$		$\{(L^2)Fe\}$[10]	
	O_2	Ar	O_2	Ar
diol, epoxide TON	1.6, 2.2	1.5, 1.0	0.0, 5.0	1.0, 1.0
epoxide %^{18}O:				
$H_2{}^{18}O_2/H_2{}^{18}O/{}^{18}O_2$	45/0/55	100/–/–	15/0/85	82/18/–
cis diol %^{18}O from:				
$H_2{}^{18}O_2$[b]	0/5/95	0/4/96	–	0/23/77
$H_2{}^{18}O$[b]	92/8/0	93/7/0	–	0/30/0
trans diol %^{18}O from:				
$H_2{}^{18}O_2$[b]	–	–	–	0/56/44
$H_2{}^{18}O$[b]	–	–	–	0/50/0

[a] $TON_{max}=10$;[15] error limit is 5 %. [b] percentage of no/one/two ^{18}O atoms in the diol product.

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[**] Financial support by the German Science Foundation (DFG) and an Alexander von Humboldt fellowship to G.R. are gratefully acknowledged.

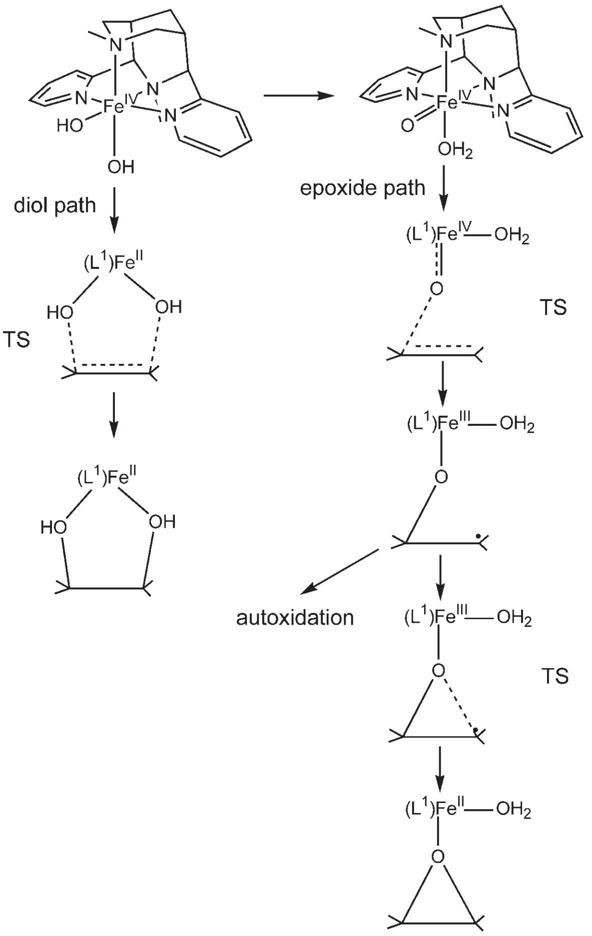
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

trans-diols). This result indicates a carbon-radical-based process.[10] In the L^1-based system, there is a constant amount of pure *cis*-diol product, irrespective of whether oxygen is present or not. This finding suggests that there is a different reaction channel for the diol production with L^1, which does not involve carbon radical intermediates.

From the data of the $\{(L^2)Fe\}$-based system in Table 1, it was concluded that, under an aerobic atmosphere, about 80 % of the epoxide results from autoxidation, which arises from a carbon-based radical intermediate (5 vs 1 TON epoxide, in agreement with the labeling data), and this radical is also assumed to be responsible for the formation of diol (no diol in presence of O_2).[10] For the $\{(L^1)Fe\}$-based system, there also is an increased amount of epoxide under aerobic conditions (TON 2.2 versus 1.0). This finding is in agreement with the fact that in air, 55 % of the epoxide oxygen results from O_2 (^{18}O labeling); the other 45 % is from H_2O_2. The hypothesis for the L^1-based system is that the epoxide product is produced, as in the L^2-based system, by direct attack of the ferryl oxygen at the double bond, and that this attack leads to a carbon-based radical intermediate. The fact that the diol production is not quenched by O_2 indicates that diol results from another reaction channel. This finding is supported by two observations, namely: a) there is only *cis*-diol product, and b) both oxygen atoms of the diol originate from the H_2O_2 oxidant. An appealing hypothesis is that the diol is produced by the new $[(L^1)Fe(OH)_2]^{2+}$ oxidant.[14] The experimentally determined mechanism of the L^2-based system[10] was confirmed by DFT calculations,[16] and a similar set of calculations was therefore done with the L^1-based system to more thoroughly understand the new reaction mechanism, and specifically to validate the above hypotheses.

From the decay of the $[(L^1)Fe^{II}(H_2O_2)(NCMe)_2]^{2+}$ precursor there are four possible high-valent iron complexes, $[(L^1)Fe^{V}{=}O(OH)]^{2+}$, $[(L^1)Fe^{IV}{=}O(OH)]^{+}$, $[(L^1)Fe^{IV}(OH)_2]^{2+}$, and $[(L^1)Fe^{IV}{=}O(OH_2)]^{2+}$; the latter is formed from the dihydroxo complex in a water-assisted proton-transfer reaction with an energy barrier of 34.7 $kJ\,mol^{-1}$.[14] The potential oxidant $[(L^1)Fe^{V}{=}O(OH)]^{2+}$ is not discussed in detail owing to unfavorable energetics.[14,17]

Oxo-hydroxo-iron(IV) complexes, such as $[(L^1)Fe^{IV}{=}O(OH)]^{+}$, are expected to perform both epoxidation and *cis*-dihydroxylation of olefins. This reactivity has been reported for the Fe–tpa-based system (tpa = tris-2-pyridylmethylamine).[18,19] Epoxidation and dihydroxylation based on the $[(L^1)Fe^{IV}{=}O(OH)]^{+}$ complex are exothermic but involve relatively high energy barriers (approx. 70 $kJ\,mol^{-1}$, see Supporting Information). Also, the direct formation of $[(L^1)Fe^{IV}{=}O(OH)]^{+}$ has been predicted to be significantly less probable than that of $[(L^1)Fe^{IV}(OH)_2]^{2+}$ and its tautomer $[(L^1)Fe^{IV}{=}O(OH_2)]^{2+}$.[14] Therefore, pathways arising from $[(L^1)Fe^{IV}{=}O(OH)]^{+}$ are not considered as major reaction channels. Consequently, the hypothesis is that $[(L^1)Fe^{IV}(OH)_2]^{2+}$, formed in a direct process from $[(L^1)Fe^{II}(H_2O_2)]^{2+}$ by O–O bond homolysis, is the key intermediate in the oxidation processes (Scheme 2).



Scheme 2. Diol pathway (left) and epoxide pathway (right) for the *cis*-dihydroxylation and epoxidation of olefins.

The key results of our DFT calculations related to the *cis*-diol production are illustrated in the energy diagram in Figure 1. $[(L^1)Fe^{IV}(OH)_2]^{2+}$ has a triplet (S = 1) ground state with a margin of 18.2 $kJ\,mol^{-1}$ to the quintet (S = 2) state. The transition state of the concerted reaction to the *cis*-diol has a relative energy of 36.1 $kJ\,mol^{-1}$ on the triplet surface. The spin

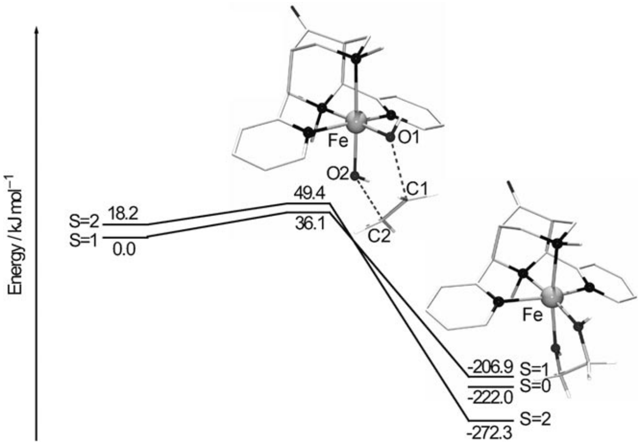


Figure 1. Computed pathway for the iron–bispidine-catalyzed *cis*-dihydroxylation of ethylene (see also Scheme 2, left). The initial energy levels (left) refer to the triplet ground state (S = 1, 0.0) and quintet exited state (S = 2, 18.2 $kJ\,mol^{-1}$) of $[(L^1)Fe^{IV}(OH)_2]^{2+}$. Spin densities and bond lengths are given in the Supporting Information.

density in the triplet transition state is distributed between the iron center (1.08), the two oxygen atoms (0.18, 0.19) and the partially oxidized olefinic carbon atoms (0.40, 0.27). The reaction is highly exothermic ($-272.3\,\text{kJ}\,\text{mol}^{-1}$) and the product has a quintet ground state. Therefore, the reaction involves a spin-crossover, which is expected to occur after the formation of the transition state (the optimized structure of the transition state on the quintet surface is given as Supporting Information).

The proton transfer from $[(L^1)Fe^{IV}(OH)_2]^{2+}$ to $[(L^1)Fe^{IV}{=}O(OH_2)]^{2+}$ has an energy barrier of $34.7\,\text{kJ}\,\text{mol}^{-1}$ and is exothermic ($-18.5\,\text{kJ}\,\text{mol}^{-1}$); this process also involves a spin-crossover from the $\{Fe^{IV}(OH)_2\}$ ($S=1$) to the $\{Fe^{IV}{=}O(OH_2)\}$ ($S=2$) tautomer.[14,20] Stepwise and concerted pathways have been considered for the epoxidation, and the results are presented in Figure 2. In the stepwise reaction on the quintet surface the energy barrier is $7.3\,\text{kJ}\,\text{mol}^{-1}$. Spin coupling between the two magnetic centers in the emerging Fe^{III} radical intermediate leads to several possible spin states, and a quintet state with high-spin Fe^{III} and spin-down on the radical center is found to be the ground state. We have also considered the possibility of a concerted transition state, which directly leads to the Fe^{II}–epoxide product. On the quintet surface we were not able to refine a true transition state. We have also tested for two-state reactivity by computation of the reaction on the triplet-state surface. Both concerted and stepwise transition states are close-lying with energy barriers of 56.2 and $55.2\,\text{kJ}\,\text{mol}^{-1}$, respectively, but these barriers are so high in energy that they can be neglected.

The ring closure from the radical intermediate to form the Fe^{II}–epoxide product has an energy barrier of $16.1\,\text{kJ}\,\text{mol}^{-1}$ on the quintet ($S=2$) surface, and the calculated energy barrier on the heptet ($S=3$) surface is prohibitively high ($233.1\,\text{kJ}\,\text{mol}^{-1}$). The final Fe^{II}–epoxide product also has a quintet ground state. In the final step the epoxide is cleaved, leading to the regeneration of the catalyst. This step has an energy barrier of $12.9\,\text{kJ}\,\text{mol}^{-1}$, and the overall reaction occurs in the quintet state. The reaction is exothermic in each step. From our previous DFT calculations with the iron complexes of the pentadentate ligand L^2 it emerges that the reaction of O_2 with the Fe^{III} radical intermediate has a lower barrier than the ring closure, and this is required for the formation of epoxide by an autoxidation process.[16] A similar behavior is expected in this case.

The DFT calculations demonstrate that $[(L^1)Fe^{IV}(OH)_2]^{2+}$ ($S=1$) may be responsible for both *cis*-dihydroxylation and epoxidation. Formation of *cis*-diol from intermediate-spin $[(L^1)Fe^{IV}(OH)_2]^{2+}$ is relatively sluggish compared to the formation of epoxide from its high-spin tautomer (36.1 vs

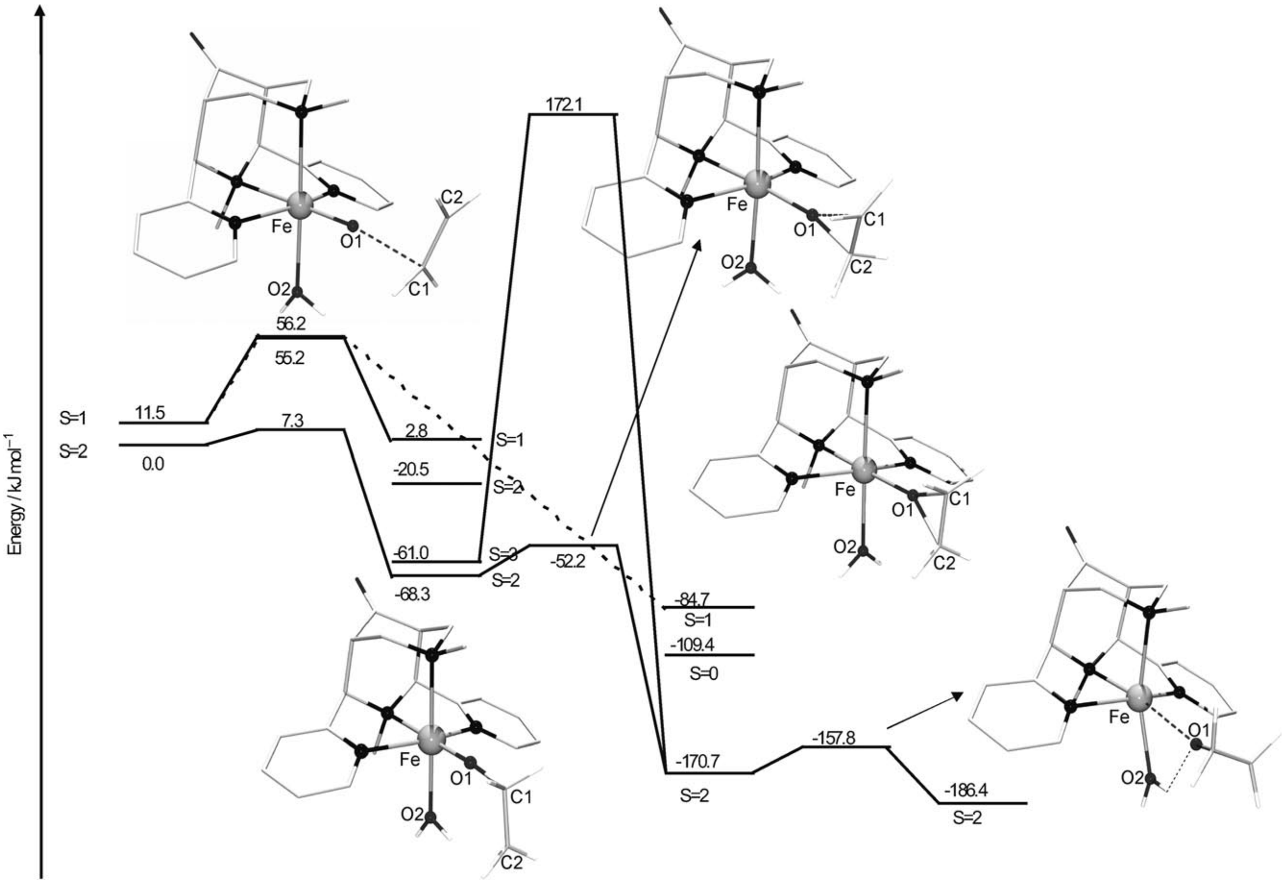


Figure 2. Computed pathways (stepwise and concerted) for the iron–bispidine-catalyzed epoxidation of ethylene. The dashed line indicates a concerted transition state. See also Scheme 2, right. The initial energy levels (left) refer to the quintet ground state ($S=2$, 0.0) and triplet exited state ($S=1$, $11.5\,\text{kJ}\,\text{mol}^{-1}$) of $[(L^1)Fe^{IV}{=}O(OH_2)]^{2+}$. Spin densities and bond lengths are given in the Supporting Information.

23.4 kJ mol^{-1}, sum of energy barriers for each process). However, the generation of $[(L^1)Fe^{IV}{=}O(OH_2)]^{2+}$ from $[(L^1)Fe^{IV}(OH)_2]^{2+}$ by proton transfer also has a significant energy barrier (34.7 kJ mol^{-1}). Starting from $[(L^1)Fe^{IV}(OH)_2]^{2+}$, the sum of the computed energy barriers reveals that *cis*-dihydroxylation is favored by 22 kJ mol^{-1} over olefin epoxidation. Under anaerobic atmosphere this finding leads to the prediction of a diol/epoxide ratio of 1.6:1, in excellent agreement with the experimentally determined ratio of 1.5:1 (Table 1). Under aerobic conditions, the ratio cannot be directly compared because of the autoxidation process in the epoxidation path.

Our interpretation of the bispidine–iron-catalyzed olefin oxidation with H_2O_2 is at variance with the suggestion that the mechanism with the comparable tetradentate tpa- and bpmen-based catalysts (bpmen = *N*,*N'*-dimethyl-*N*,*N'*-bis(2-pyridylmethyl)-1,2-diaminoethane) involves a catalytically active $\{Fe^V{=}O\}$ intermediate.[21–25] Our proposal is based on $\{Fe^{IV}(OH)_2\}$ (S = 1) and its tautomer $\{Fe^{IV}{=}O(OH_2)\}$ (S = 2), which have not been considered and are derived from experiment and a DFT analysis. We suggest that the $\{Fe^V{=}O(OH)\}$ pathway is less probable but cannot be excluded with our L^1-based system.[14,17,26] There is no indication that our results and interpretation may be generalized, that is, it is quite possible that other systems follow different mechanistic pathways. An interesting recent observation, however, is that $[(tpa)Fe^{IV}{=}O]^{2+}$, derived from $[(tpa)Fe^{III}\text{-}OO\mathit{t}Bu]^{2+}$, is able to oxidize olefins.[27]

Received: April 17, 2007
Revised: June 12, 2007

Keywords: dihydroxylation · epoxidation · iron · oxidation · reaction mechanisms

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[17] Formation of $[(L^1)Fe^V{=}O(OH)]$ is thermodynamically and kinetically unfavorable with respect to the formation of $[(L^1)Fe^{IV}(OH)_2]$ and $[(L^1)Fe^{IV}{=}O(OH_2)]$, (all possible spin states and water-assisted as well as non-water-assisted pathways have been considered).[13] Moreover, the first transition state of the reaction of $[(L^1)Fe^V{=}O(OH)]$ with ethylene has a relative energy of 12 kJ mol^{-1}, which is slightly higher than the corresponding transition state of the $[(L^{1)}Fe^{IV}{=}O(OH_2)]$-based reaction (see Supporting Information).

[18] The catalytically active species in the $[Fe^{II}(tpa)(NCCH_3)_2]^{2+}/H_2O_2$ system leading to epoxide and diols has been proposed to be $[(tpa)Fe^VO(OH)]^{2+}$.[19]

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