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Steric and Electronic Influences on Stereospecific C-H Hydroxylation by Fe(II) Complexes of N4 Tetradentate Ligands

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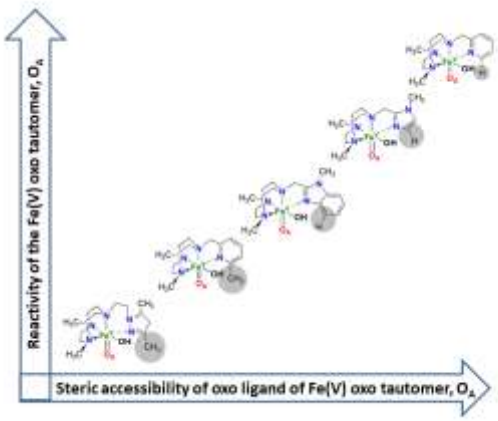
Abstract:

The catalytic C-H hydroxylation reactions of different alkane substrates are investigated employing three Fe(II) complexes containing TACN-derivatized tetradentate N4 ligands using H_2O_2 as a co-oxidant. The large normalized C3/C2 bond selectivity in adamantane oxidation, high degrees of stereoretention in the oxidation of *cis*-1,2-dimethylcyclohexane and the high kinetic isotope effect values for C-H bond activation indicates the involvement of metal-based oxidant in catalytic processes. The active oxidant is proposed to be an (L)Fe^{V}(O)(OH) species (L = ^{Me2,Me}BzImTACN, ^{Me2,Me2}PyzTACN, ^{Me2,Me}ImTACN) which may exist in two tautomeric forms related by a proton shift between the oxo and hydroxo ligands. Isotope labeling experiments are in agreement with the oxygen atom in the hydroxylated products originating from both water and hydrogen peroxide, and labeling experiments involving oxygen atom transfer to sterically bulky substrates provide indirect information on the steric influence exerted by the three ligands. These studies indicate that the ^{Me2,Me2}PyzTACN, exerts a greater steric influence compared to the ^{Me2,Me}ImTACN and ^{Me2,Me}BzImTACN ligands.

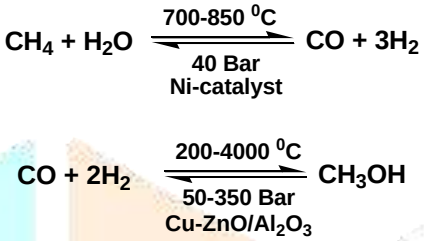
Graphical Abstract



Keywords: C-H bond functionalization, stereospecific, nonheme, iron, selective oxidation

INTRODUCTION

Carbon-hydrogen bonds are present in almost every organic substance including saturated hydrocarbons (alkanes). The high availability of hydrocarbons in Nature, e.g. in the form of natural gas or crude oil, makes them energy-rich and low-cost chemical feedstocks [1]. The activation/oxidation of C-H bonds to produce new feedstocks, e.g. alcohols, aldehydes, is of tremendous chemical and economic importance, and is therefore a major research subject for synthetic chemists. However, selective functionalization of C-H bonds is one of the most difficult transformations in organic synthesis. This is because C-H bonds are thermodynamically stable and relatively chemically inert, owing to their relative high bond dissociation energy (BDE) values. Industrial processes employ methodologies that require high temperature (endothermic reactions), and thus large energy consumption and high cost (see Scheme 1 for an example). The major drawback of these processes is the lack of chemoselectivity and regioselectivity, which is essential for the synthesis of valuable/desirable products.



Scheme 1. Schematic depiction of the catalytic reactions involved in industrial production of methanol from methane [2].

In Nature, enzymes that carry out the oxidation of substrates using molecular oxygen as oxidant are known as oxygenases. They are classified into two categories: (i) monooxygenases, which transfer one oxygen atom of O_2 into the substrate and convert the other oxygen atom into water and (ii) dioxygenases, which transfer both oxygen atoms of O_2 into the substrate.

Iron is found in the active sites of most of these mono- and dioxygenases. Amongst the various iron oxygenases, cytochrome P450, methane monooxygenases and Rieske oxygenases catalyze an array of extremely challenging oxidative transformations with a high degree of selectivity and catalytic efficiency [3-4]. Discovery and mechanistic investigations of these enzymes is thus a crucial starting point for contemporary catalysis research because they serve as the inspiration for the development of inexpensive, efficient, selective and green 'biomimetic' catalysts [5-8]. The cytochrome P450 enzymes have been extensively studied and their catalytic cycles have been well interpreted/established [4]. The C-H hydroxylation is carried out by an oxo-Fe(IV) porphyrin radical cation by 'rebound mechanism' as proposed by Groves *et al* [9]. Rieske oxygenases are considered to be the non-heme counterparts of cytochrome P450 enzymes and they catalyze a wide range of oxidative transformations that are more diverse than those associated with analogous heme enzymes [3,10-12]. The next section will discuss this class of non-heme iron dependent enzymes in greater details.

Rieske oxygenases: Structure and function

Rieske oxygenases are multi-component non-heme iron enzymes found in bacteria [3]. They have two components in their active sites [3]: (I) an oxygenase component where O_2 activation and dihydroxylation of arenes take place and (II) a reductase component that mediates the electron transfer between NAD(P)H and the oxygenase component. In the oxygenase component, the active site contains an Fe(II) center bound to a 2-histidine-1-carboxylate facial motif. Figure 1 describes the active site structure of the oxygenase component of naphthalene 1,2-dioxygenase (NDO) from *Pseudomonas putida* [13].

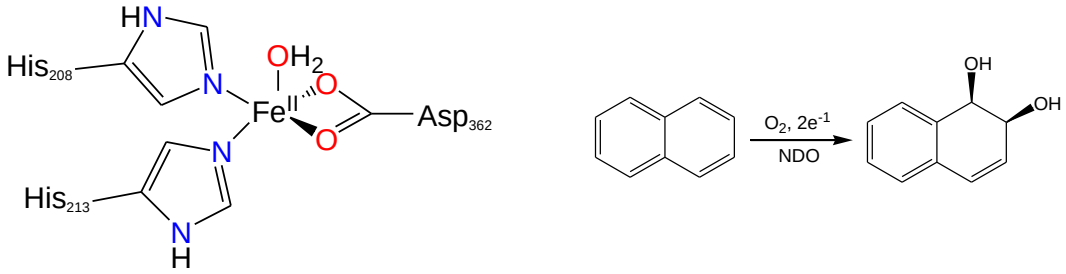


Figure 1. The active site structure (non-heme iron center) of naphthalene 1,2-dioxygenase (NDO), a class of Rieske dioxygenases (left); the *syn*-dihydroxylation of naphthalene catalyzed by NDO (right).

Rieske dioxygenases catalyze the regio- and stereospecific *cis*-dihydroxylation of arenes (Scheme 3), the first step in the biodegradation of pollutants, e.g. aromatic molecules by soil bacteria [3,14-16]. Besides *cis*-dihydroxylation, these enzymes are also known to catalyze benzylic hydroxylation, sulfoxidation, desaturation and O- and N-dealkylation [14].

Naphthalene 1,2-dioxygenase catalyzes the *syn*-1,2-dihydroxylation of naphthalene (Figure 1). This is the best-known enzyme amongst the Rieske oxygenases. The proposed mechanism for the reaction catalyzed by NDO is shown in Figure 2 [8]. The catalytic cycle starts with an Fe center in its reduced state (+2) (resting state of the enzyme) that binds the naphthalene substrate, resulting in a loss of water ligand. The Fe(II) center reacts with dioxygen in conjunction with the transfer of one electron from the reductase component (called the Rieske [2Fe-2S] cluster) to form a Fe(III)-hydroperoxo intermediate. This intermediate has been characterized by time-resolved X-ray crystallography [17]. The Fe(III)-OOH intermediate is proposed to react with the substrate by two routes: (i) simultaneous O-O bond cleavage and substrate oxidation generates an Fe(IV) oxo intermediate (analogous to compound II in Cytochrome P450 [4,18,19]) and a hydroxynapththalene radical species (Figure 2) or, (ii) O-O bond cleavage first forms an Fe(V)(O)(OH) intermediate (analogous to compound I in the catalytic cycle of Cytochrome P450), which subsequently reacts with naphthalene to form the Fe(III) alkoxyhydroxynaphthalene species (Figure 2) [3,10,20]. In the next step, a second electron is transferred from the reductase component to form a Fe(II) alkoxyhydroxynaphthalene species. Finally, protonation of the alkoxide leads to the release of the *syn*-diol product and the regeneration of the resting state of the enzyme.

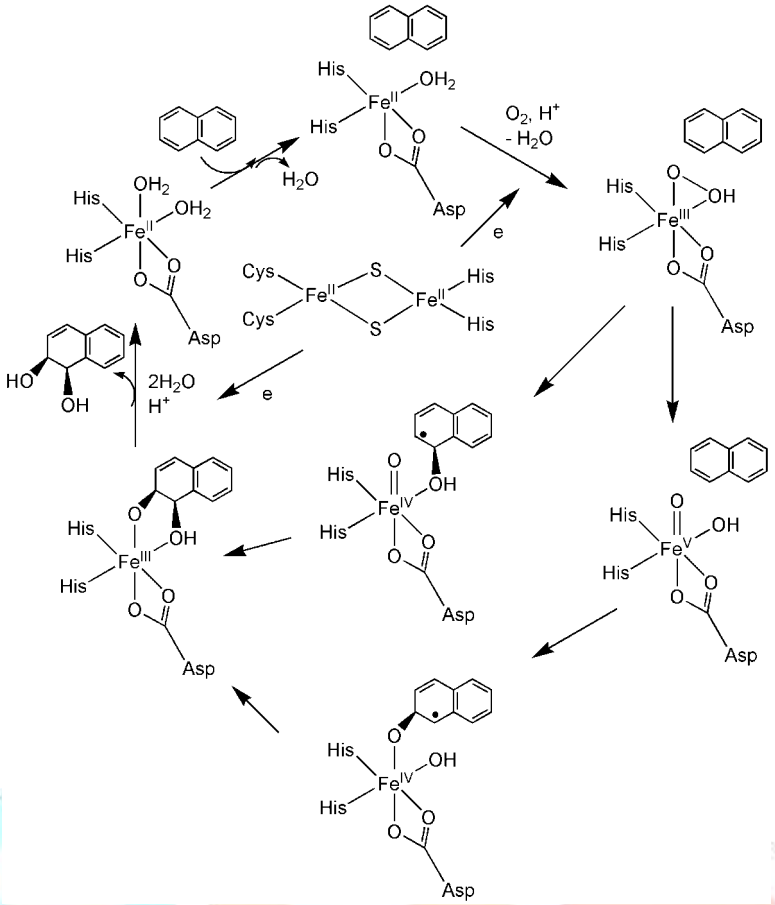


Figure 2. The proposed catalytic cycle for the dihydroxylation of naphthalene by naphthalene 1,2-dioxygenase (NDO) [8].

The fascinating chemistry exhibited by the non-heme iron-dependent oxygenases, in particular the Rieske oxygenases, has inspired synthetic chemists to attempt to achieve good catalytic efficiencies, as well as high degrees of stereospecificity and regio-selectivity with catalysts based on cheap and abundant iron, while using environmentally friendly oxidants such as O_2 or H_2O_2. Synthetically prepared Fe-complexes have been employed in wide range of oxidative catalytic transformation reactions [21-35]. H_2O_2 is often used a benign oxidant [36]. We have previously reported the catalytic properties of Pd(II) complex using redox active ligand [37]. Tetradentate N4 ligands also play important role in coordinating Fe-metal ion and exhibit remarkable catalytic properties [38].

Methodology and Materials

Materials and reagents

Reagents and solvents were of at least 99% purity and used as received without any further purification. $H_2{}^{18}O_2$ (90% ^{18}O-enriched, 2% solution in $H_2{}^{18}O$) and $H_2{}^{18}O$ (95% ^{18}O-enriched) were purchased from ICON isotopes. All reagents and solvents were purchased from Sigma Aldrich or Fisher Scientific. Dichloromethane and acetonitrile were dried by distillation from CaH_2; diethyl ether was dried by distillation from Na/benzophenone.

Instrumentation

The product analyses after catalysis experiments were carried out on an Agilent Technology7820A gas chromatograph equipped with a 16-sample automatic liquid sampler, flame ionization detector and EzChrom Elite Compact software. GC-MS analyses were performed on an Agilent Technology 7890A GC system equipped with a 5975C inert XL EI/CI MSD with Triple-Axis Detector. The products were identified by comparison of their GC retention times and, in the case of GC/MS, with those of authentic compounds.

Syntheses

In the present study, three tetradentate N4 ligands were prepared (Figure 3) following the literature procedures [21,22]. These are based on the 'PyTACN' ligand framework where the pyridylmethyl arm of 'PyTACN' was replaced with either an (*N*-methyl)benzimidazolylmethyl arm (yielding the ^{Me2,Me}BzImTACN ligand), an (*N*-methyl)imidazolylmethyl arm (the ^{Me2,Me}ImTACN ligand), or a (3,5-dimethyl)pyrazolylethyl arm (the ^{Me2,Me2}PyzTACN ligand). The purpose of these modifications was to address the effects of steric and electronic properties of the side arms on the reactivity patterns of their Fe(II) complexes in the oxidative catalysis of alkanes and alkenes with hydrogen peroxide.

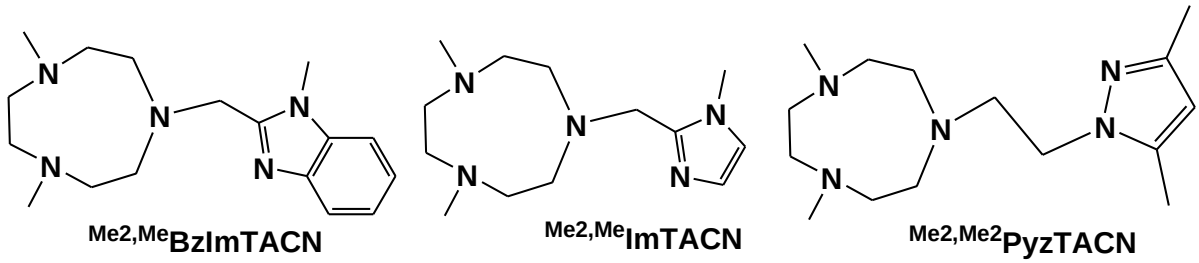


Figure 3. Structures of the tetradentate N4 ligands used in this study.

The Fe(II) complexes of the three ligands were synthesized by reaction with $[Fe^{II}(CH_3CN)_2(CF_3SO_3)_2]$ using previously reported literature procedures [21,22]. Figure 4 describes the structures of the three Fe(II) complexes, $[Fe^{II}(^{Me2,Me}BzImTACN)(CF_3SO_3)_2]$ (**1**^{OTf}), $[Fe^{II}(^{Me2,Me}ImTACN)(CF_3SO_3)_2]$ (**2**^{OTf}) and $[Fe^{II}(^{Me2,Me2}PyzTACN)(CF_3SO_3)_2]$ (**3**^{OTf}) used for this present report.

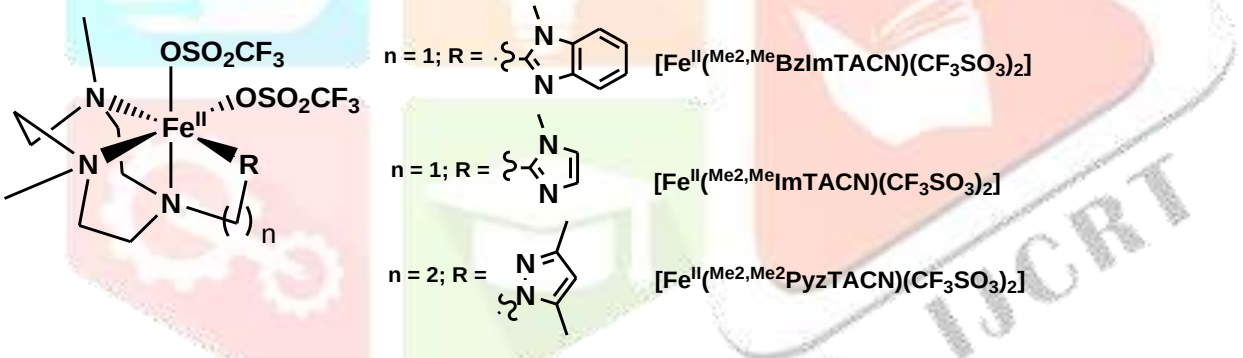


Figure 4. The structures of the Fe(II) complexes investigated in this study.

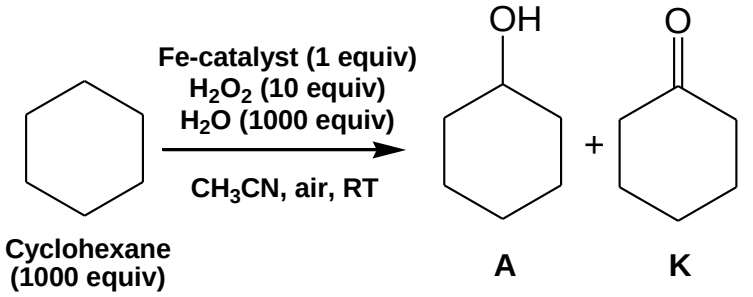
Reaction conditions for catalysis experiments

In a typical reaction, 360 µL of H_2O_2 (25 µmol), taken from a 70 mM H_2O_2 stock solution in CH_3CN together with 45 µL of water (2500 µmol), was delivered by syringe pump over 30 min at room temperature under air to a vigorously stirred CH_3CN solution (2.14 ml) containing the Fe-catalyst (2.5 µmol) and the alkane substrate (2500 µmol). The final concentrations were 1 mM for catalyst, 10 mM for the oxidant, 1000 mM for H_2O and 1000 mM for substrate (1:10:1000:1000 for cat:ox:H_2O:sub). For adamantane, due to the low solubility, only 50 µmol of the substrate was used and so the final concentration was 20 mM. At the conclusion of the syringe pump addition, 500 µL of a biphenyl solution of a known concentration (~25 mM) was added to the reaction mixture as an internal standard. The reaction mixture was then passed through a small silica column (to remove the iron complex), followed by elusion with 2 ml ethyl acetate. Finally, the solution was subjected to GC analysis. The organic products were identified, and their yields were calculated by using authentic compounds as quantitative standards.

For the measurement of kinetic isotope effects (KIE), a substrate mixture of cyclohexane:cyclohexane-d_{12} in a ratio of 1:3 was used to improve the accuracy of the obtained KIE value.

RESULTS AND DISCUSSIONS

C-H bond oxidation of alkanes



catalyst	TON(A)	TON(K)	A/K
1^{OTf}	8.5	0.8	10.6
2^{OTf}	7.7	0.6	12
3^{OTf}	6.5	0.7	9.4

Scheme 2. The catalytic oxidation of cyclohexane by H_2O_2 effected by the three new Fe(II) catalysts.

The three Fe(II) complexes were investigated in the catalytic oxidation of various alkanes, using H_2O_2 as a co-oxidant. Cyclohexane was employed first as a model substrate. All complexes oxidized cyclohexane efficiently to form cyclohexanol (A) as the major product with a very small amount of formation of cyclohexanone (K) (Scheme 2). The A/K ratio was found to be high in all cases (in the range 9-12 for the three complexes, Scheme 2). The time-dependent formation of cyclohexanol from cyclohexane was monitored for complex $\mathbf{1}^{OTf}$; this experiment showed that the initial product was almost exclusively cyclohexanol (the A/K ratio was around 35) and cyclohexanone was formed by the subsequent overoxidation of cyclohexanol (Figure 5). This suggests that for all three complexes, the active oxidant is metal-based and that any participation of a Russell-type termination mechanism initiated by hydroxyl radicals (leading to an A/K ratio ~ 1) may be ignored.

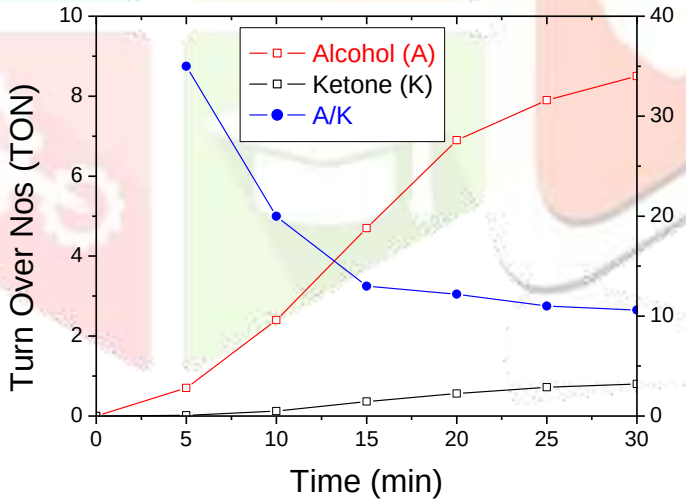


Figure 5. Time course for the oxidation of cyclohexane in presence of H_2O_2 catalyzed by $\mathbf{1}^{OTf}$.

When the kinetic isotope effect (KIE) was determined in a competitive reaction between cyclohexane and its fully deuterated isotopomer, the values obtained for complexes $\mathbf{1}^{OTf}$, $\mathbf{2}^{OTf}$ and $\mathbf{3}^{OTf}$ were 5.0, 4.6 and 4.0, respectively, supporting the assumption of the involvement of a metal based oxidant in the catalytic oxidation.

Several other mechanistic probes confirmed that the oxidation reactions were metal-based. For example, in the oxidation of adamantane, the normalized C3/C2 selectivity was found to be in the range 12-26 suggesting a preference for tertiary C-H bonds over secondary C-H bonds. The oxidation of *cis*-DMCH was exclusively performed via the *cis*-retention of configuration of the product. All these results are consistent with the implication of a selective oxidant (i.e. metal-based oxidant) in the C-H hydroxylation reactions as observed in the Fe(PyTACN) family of complexes.

There are several non-heme mononuclear iron catalysts that have been reported in the last decade that can perform enzyme-like metal based C-H oxidation without the involvement of free diffusing radicals [23-27]. Amongst these catalyst, the Fe(PyTACN) family of complexes deserve particular attention owing to their ability to not only catalyze stereo- and regio-selective alkane hydroxylation, but also the epoxidation and *syn*-dihydroxylation reactions of olefins [27-29]. Mechanistic probes employed for these complexes implicate the involvement of an Fe(V)(O)(OH) active oxidant during the catalytic process [27]. The formation of such high valent Fe(V) oxo species has been further verified by variable-temperature mass spectroscopy (VT-MS) [30], EPR spectroscopy [31], isotope labeling studies and DFT calculations [29]. The involvement of an iron(V)-oxo species as an active oxidant has also been proposed in some other catalytic systems [32-34]. In parallel, there are thus far three Fe(V) oxo complexes that have been fully characterized using spectroscopy [35].

The Fe(V)(O)(OH) active oxidant (denoted as O in Figure 3) derived from the Fe(PyTACN) family of complexes can exist in two tautomeric forms, O_A and O_B, which are connected through a prototopic oxo-hydroxo tautomerism (involving proton shift from the hydroxide to the terminal oxo ligand) [28,30]. Isotope labelling studies have shown that these complexes can incorporate a large percentage range (2-79%) of labelled oxygen from water into hydroxylated products; the level of ^{18}O incorporation provides indirect evidence for the relative reactivities of the two tautomers in C-H hydroxylation reactions [28]. The existence of this kind of tautomerism has also been postulated for [Fe(bpmen)] and [Fe(tpa)] families of the non-heme mononuclear iron complexes [24a,32]. However, in the latter cases, the percentage of incorporation of labelled water incorporation is always less than 50% and this percentage is inversely related to the strength of the oxidized C-H bond [32], leading to a mechanistic scenario involving a competition between substrate attack (substrate with weaker C-H bonds reacts faster) and tautomerism, similar to that described for porphyrin-based systems [33].

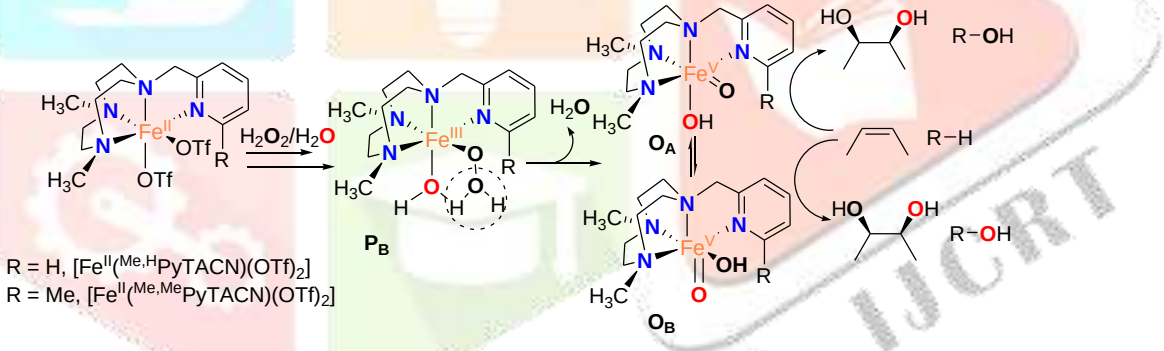


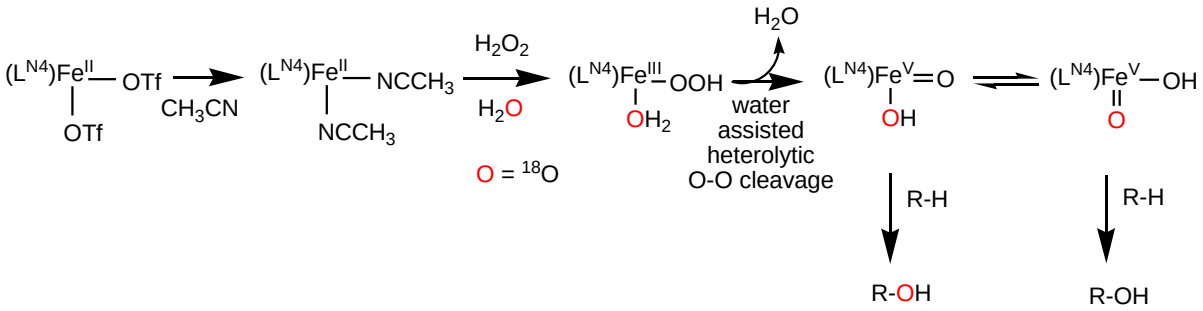
Figure 6. The oxo-hydroxo tautomerism observed in the Fe(PyTACN) family of complexes.

The relative reactivities of O_A and O_B is influenced by the nature of the ligand. Introduction of different electron-donating and -withdrawing groups (e.g. Me_2N, MeO, Me, NO_2, Cl, F etc.) in the α- and γ-positions of the pyridyl ring of PyTACN effects the relative reactivity of O_A and O_B both electronically and sterically [34]. This unique feature found in the Fe(PyTACN) systems served as an inspiration for further exploration of ligand influence by replacing the pyridylmethyl arm of the PyTACN ligand with other moieties with different steric bulk and electron donating properties. This chapter describes a detailed investigation on the effects of different side arms connected to the TACN ring on the overall catalytic efficiency (in terms of regio- and stereoselectivity) of the new Fe(II) complexes and the discrepancy of the relative reactivities between the iron-oxo tautomers.

Mechanistic pathways

The three Fe(II) complexes are capable of catalyzing the hydroxylation of C-H bonds of alkanes with high efficiencies, selectivities and A/K ratios. These results are comparable to the Fe(PyTACN) family of complexes and therefore implicate similar mechanistic interpretations. The stereoretention in the oxidation of *cis*-DMCH, high selectivity in the oxidation of adamantane, and the KIE values strongly indicate that the reactions proceed by metal-based oxidation.

The isotope labeling study explains the origin of the oxygen atom in the alcohol products and the nature of the metal-based oxidant. The isotope labeling experiments performed on the complexes indicate that the oxygen atom(s) in the alcohol product (or, epoxide and *syn*-diol products) originates from the water and the peroxide (*vide supra*). On the basis of these observations, the mechanism that has already been established for the Fe(PyTACN) family of complexes (Scheme 3) can also be applied for the Fe(II) complexes $\mathbf{1}^{\mathbf{OTf}}$, $\mathbf{2}^{\mathbf{OTf}}$ and $\mathbf{3}^{\mathbf{OTf}}$.



Scheme 3. The mechanism of C-H hydroxylation reaction catalyzed by Fe(II) complexes.

According to the proposed mechanism depicted in Scheme 3, a highly electrophilic $[Fe^{V}(O)(OH)(L^{N4})]^{2+}$ oxidant (O), is formed via water-assisted cleavage of the hydroperoxide intermediate $[Fe^{III}(OOH)(OH_2)(L^{N4})]^{2+}$ (see Figure 6 above). Species O can exist in two tautomeric forms: O_A and O_B, which differ in the relative orientation of the side arm connected to TACN ring with respect to the Fe-oxo bond (Figure 6). For example, in the case of $[Fe^{V}(O)(OH)(^{Me2,Me}BzImTACN)]^{2+}$, the tautomer O_A refers to the orientation of the (*N*-methyl)benzimidazolyl ring parallel to the Fe^{V}=O bond and O_B refers to the orientation of the (*N*-methyl)benzimidazolyl ring perpendicular to the Fe^{V}=O bond (Scheme 3). The relative reactivity of the O_A and O_B tautomers is influenced by the nature of the ligand, in particular the nature of the side arms of the TACN derivatized ligands (e.g. PyTACN, ^{Me2,Me}BzImTACN, ^{Me2,Me}ImTACN, ^{Me2,Me2}PyzTACN etc.), and the differences in the relative reactivities of the tautomers result in the different isotope labelling patterns exhibited by the corresponding Fe-complexes.

As discussed above, it should be noted that the pyrazole, (*N*-methyl)imidazole and (*N*-methyl)benzimidazole groups have different basicities. Pyrazole group is particularly important for its rich medicinal properties [40]. Electronic influence on the overall reactivity of the Fe(V)(O)(OH) oxidant can therefore not be excluded, but the possible influence of electronic factors remains to be investigated.

CONCLUSIONS

The catalytic C-H hydroxylation of alkanes by the three Fe(II) complexes containing TACN derivatized tetradentate N4 ligands have been investigated using H_2O_2. All complexes exhibit high efficiencies with large A/K ratios, suggesting the reactions to be metal-based oxidation. The large KIE values together with high C3/C2 selectivity in adamantane oxidation and high stereoretention in oxidation of *cis*-DMCH further support the involvement of metal-based oxidants. The Fe(V)(O)(OH) species can exist in two tautomeric forms and they have distinct reactivity with a particular substrate and that reactivity is dependent on the nature of the ligand and the substrate. On basis of the isotope labeling studies, the relative reactivities of the two tautomers are attributed to the steric effects exhibited by the different side arm(s) of the tetradentate ligands.

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REFERENCES

[1] S. Friedle, E. Reisner, S. J. Lippard, Current challenges of modeling diironenzyme active sites for dioxygenactivation by biomimetic synthetic complexes, *Chem. Soc. Rev.*, **2010**, 39, 2768-2779.

[2] J. H. Lunsford, Catalytic conversion of methane to more useful chemicals and fuels: a challenge for the 21st century, *Catal. Today*, **2000**, 63, 165-174.

[3] M. Costas, M. P. Mehn, M. P. Jensen, L. Que Jr., Dioxygen activation at mononuclear nonheme iron active sites: enzymes, models, and intermediates, *Chem. Rev.*, **2004**, 104, 939-986.

[4] P. R. Ortiz de Montellano, J. J. De Voss, Eds.; *Cytochrome P450: Structure, Mechanism and Biochemistry*, 3rd ed.; Springer-Verlag: New York, **2008**.

[5] N. J. Turner, Enantioselective Oxidation of C–O and C–N Bonds Using Oxidases, *Chem. Rev.*, **2011**, 111, 4073-4087.

[6] L. Que Jr., W. B. Tolman, Biologically inspired oxidation catalysis, *Nature*, **2008**, 455, 333-340.

[7] R. E. Parales, S. M. Resnick, In Applications of Aromatic Hydrocarbons Dioxygenases in Biocatalysis in the Pharmaceutical and Biotechnology Industries, R. N. Patel, Ed.; CRC Press: Boca Raton, Fl, **2006**.

[8] S. M. Barry, G. L. Challis, Mechanism and catalytic diversity of rieske non-heme iron-dependent oxygenases, *ACS Catal.*, **2013**, 3, 2362-2370.

[9] J. T. Groves, G. A. McClusky, R. E. White, M. J. Coon, Aliphatic hydroxylation by highly purified liver microsomal cytochrome P-450. Evidence for a carbon radical intermediate, *Biochem. Biophys. Res. Commun.*, **1978**, 81, 154-160.

[10] E. G. Kovaleva, J. D. Lipscomb, Versatility of biological non-heme Fe(II) centers in oxygen activation reactions, *Nat. Chem. Biol.*, **2008**, 4, 186-193.

[11] M. M. Abu-Omar, A. Loiza, N. Hontzeas, Reaction Mechanisms of Mononuclear Non-Heme Iron Oxygenases, *Chem. Rev.*, **2005**, 105, 2227-2252.

[12] P. C. A. Bruijnincx, G. V. Koten, R. J. M. Klein Gebbink, Mononuclear non-heme iron enzymes with the 2-His-1-carboxylate facial triad: recent developments in enzymology and modeling studies, *Chem. Soc. Rev.*, **2008**, 37, 2716-2744.

[13] B. Kauppi, K. Lee, E. Carredano, R. E. Parales, D. T. Gibson, H. Eklund, S. Ramaswamy, Structure of an aromatic-ring-hydroxylating dioxygenase-naphthalene 1,2-dioxygenase, *Structure*, **1998**, 6, 571-586.

[14] D. T. Gibson, S. M. Resnick, K. Lee, J. M. Brand, D. S. Torok, L. P. Wackett, M. J. Schocken, B. E. Haigler, Desaturation, dioxygenation, and monooxygenation reactions catalyzed by naphthalene dioxygenase from Pseudomonas sp. strain 9816-4, *J. Bacteriol*., **1995**, 177, 2615-2621.

[15] D. M. Jerina, J. W. Daly, A. M. Jeffrey, D. T. Gibson, Cis-1,2-dihydroxy-1,2-dihydronaphthalene: a bacterial metabolite from naphthalene, *Arch. Biochem. Biophys.*, **1971**, 142, 394-396.

[16] M. D. Wolfe, J. V. Parales, D. T. Gibson, J. D. Lipscomb, Benzoate 1,2-dioxygenase from Pseudomonas putida: single turnover kinetics and regulation of a two-component Rieske dioxygenase, *J. Biol. Chem.*, **2001**, 276, 1945-1953.

[17] A. Karlsson, J. V. Parales, R. E. Parales, D. T. Gibson, H. Eklund, S. Ramaswamy, Crystal structure of naphthalene dioxygenase: side-on binding of dioxygen to iron, *Science*, **2003**, 299, 1039-1042.

[18] I. G. Denisov, T. M. Makris, S. G. Sligar, I. Schlichting, Structure and Chemistry of Cytochrome P450, *Chem. Rev.*, **2005**, 105, 2253-2277.

[19] J. Rittle, M. T. Green, Cytochrome P450 compound I: capture, characterization, and C-H bond activation kinetics, *Science*, **2010**, 330, 933-937.

[20] L. B. Poole, K. J. Nelson, Discovering mechanisms of signaling-mediated cysteine oxidation, *Curr. Opin. Chem. Biol.*, **2008**, 12, 134-140.

[21] M. Mitra, J. Lloret-Fillol, M. Haukka, M. Costas, E. Nordlander, Evidence that steric factors modulate reactivity of tautomeric iron–oxo species in stereospecific alkane C–H hydroxylation, *Chem. Commun.*, **2014**, 50, 1408-1410.

[22] M. Mitra, A. Brinkmeier, Y. Li, M. Borrell, A. Call, J. Lloret-Fillol, M. G. Richmond, M. Costas, E. Nordlander, An investigation of steric influence on the reactivity of FeV(O)(OH) tautomers in stereospecific C–H hydroxylation, *Dalton Trans.*, **2023**, 52, 3596-3609.

[23] M. Costas, K. Chen, L. Que Jr., Biomimetic nonheme iron catalysts for alkane hydroxylation, *Coord. Chem. Rev.*, **2000**, 200-202, 517-544.

[24] (a) K. Chen, L. Que Jr., Stereospecific Alkane Hydroxylation by Non-Heme Iron Catalysts: Mechanistic Evidence for an Fe(V)=O Active Species, *J. Am. Chem. Soc.*, **2001**, 123, 6327-6337; (b) C. Kim, K. Chen, J. Kim, L. Que Jr., Stereospecific Alkane Hydroxylation with H2O2 Catalyzed by an Iron(II)−Tris(2-pyridylmethyl)amine Complex, *J. Am. Chem. Soc.*, **1997**, 110, 5964-5965.

[25] (a) M. S. Chen, M. C. White, A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis, *Science*, **2007**, 318, 783-787; (b) N. A. Vermeulen, M. Sc Chen, M. C. White, The Fe(PDP)-catalyzed aliphatic C–H oxidation: a slow addition protocol, *Tetrahedron*, **2009**, 65, 3078-3084; (c) M. S. Chen, M. C. White, Combined effects on selectivity in Fe-catalyzed methylene oxidation, *Science*, **2010**, 327, 566-571; (d) M. A. Bigi, S. A. Reed, M. C. White, Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations, *Nat. Chem.*, **2011**, 3, 218-222; (e) L. Gomez, I. Garcia-Bosch, A. Company, J. Benet-Buchholz, A. Polo, X. Sala, X. Ribas, M. Costas, Stereospecific C□H Oxidation with H2O2 Catalyzed by a Chemically Robust Site-Isolated Iron Catalyst, *Angew. Chem. Int. Ed.*, **2009**, 48, 5720-5723; (f) P. Liu, Y. Liu, E. L.-M. Wong, S. Xiang, C.-M. Che, Iron oligopyridine complexes as efficient catalysts for practical oxidation of arenes, alkanes, tertiary amines and N-acyl cyclic amines with Oxone, *Chem. Sci.*, **2011**, 2, 2187-2195; (g) Y. Hitomi, K. Arakawa, T. funabiki, M. Kodera, An Iron(III)–Monoamidate Complex Catalyst for Selective Hydroxylation of Alkane C-H Bonds with Hydrogen Peroxide, *Angew. Chem. Int. Ed.*, **2012**, 51, 3448-3452; (h) M. C. White, Chemistry. Adding aliphatic C-H bond oxidations to synthesis, *Science*, **2012**, 335, 807-809.

[26] (a) J. England, G. J. P. Britovsek, A. J. P. White, Non-heme Iron(II) Complexes Containing Tripodal Tetradentate Nitrogen Ligands and Their Application in Alkane Oxidation Catalysis, *Inorg. Chem.*, **2005**, 44, 8125-8134; (b) J. England, G. J. P. Britovsek, N. Rabadia, A. J. P. White, Ligand Topology Variations and the Importance of Ligand Field Strength in Non-Heme Iron Catalyzed Oxidations of Alkanes, *Inorg. Chem.*, **2007**, 46, 3752-3767; (c) J. England, C. R. Davies, M. Banaru, A. J. P. White, G. J. P. Britovsek, Catalyst Stability Determines the Catalytic Activity of Non-Heme Iron Catalysts in the Oxidation of Alkanes, *Adv. Synth. Catal.*, **2008**, 350, 883-897; (d) J. England, R. Gondhia, L. Bigorra-Lopez, A. R. Petersen, A. J. P. White, G. J. P. Britovsek, Towards robust alkane oxidation catalysts: electronic variations in non-heme iron(ii) complexes and their effect in catalytic alkane oxidation, *Dalton Trans.*, **2009**, 5319-5334.

[27] (a) A. Company, L. Gomez, M. Guell, X. Ribas, J. M. Luis, L. Que Jr., M. Costas, Alkane Hydroxylation by a Nonheme Iron Catalyst that Challenges the Heme Paradigm for Oxygenase Action, *J. Am. Chem. Soc.*, **2007**, 129, 15766-15767; (b) A. Company, L. Gomez, X. Fontrodona, X. Ribas, M. Costas, A Novel Platform for Modeling Oxidative Catalysis in Non-Heme Iron Oxygenases with Unprecedented Efficiency, *Chem. Eur. J.*, **2008**, 14, 5727-5731.

[28] I. Prat, A. Company, V. Postils, X. Rivas, L. Que Jr., J. M. Luis, M. Costas, The Mechanism of Stereospecific C-H Oxidation by Fe(Pytacn) Complexes: Bioinspired Non-Heme Iron Catalysts Containing cis-Labile Exchangeable Sites, *Chem. Eur. J.*, **2013**, 19, 6724-6738.

[29] I. Prat, D. Font, A. Company, K. Junge, X. Ribas, M. Beller, M. Costas, Fe(PyTACN)-Catalyzed cis-Dihydroxylation of Olefins with Hydrogen Peroxide, *Adv. Synth. Catal.*, **2013**, 355, 947-956.

[30] I. Prat, J. S. Mathienson, M. Guell, X. Ribas, J. M. Luis, M. Cronin, M. Costas, Observation of Fe(V)=O using variable-temperature mass spectrometry and its enzyme-like C–H and C=C oxidation reactions, *Nat. Chem.*, **2011**, 3, 788-793.

[31] O. Y. Lyakin, I. Prat, K. P. Bryliakov, M. Costas, E. P. Talsi, EPR detection of Fe(V)=O active species in nonheme iron-catalyzed oxidations, *Catal. Commun.*, **2012**, 29, 105-108.

[32] (a) K. Chen, L. Que Jr., Evidence for the participation of a high-valent iron–oxo species in stereospecific alkane hydroxylation by a non-heme iron catalyst, *Chem. Commun.*, **1999**, 1375-1376; (b) M. Costas, L. Que Jr., Ligand Topology Tuning of Iron-Catalyzed Hydrocarbon Oxidations, *Angew. Chem.*, **2002**, 114, 2283-2285; (c) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que Jr., Olefin Cis-Dihydroxylation versus Epoxidation by Non-Heme Iron Catalysts: Two Faces of an Fe^{III}–OOH Coin, *J. Am. Chem. Soc.*, **2002**, 124, 3026-3035; (d) S. H. Lee, J. H. Han, H. Kwak, S. J. Lee, E. Y. Lee, H. J. Kim, J. H. Lee, C. Bae, S. N. Lee, Y. Kim, C. Kim, Biomimetic Hydrocarbon Oxidation Catalyzed by Nonheme Iron(III) Complexes with Peracids: Evidence for an Fe^{V}=O Species, *Chem. Eur. J.*, **2007**, 13, 9393-9398; (e) J. Yoon, S. A. Wilson, Y. K. Jang, M. S. Seo, K. Nehru, B. Hedman, K. O. Hodgson, E. Bill, E. I. Solomon, W. Nam, Reactive Intermediates in Oxygenation Reactions with Mononuclear Nonheme Iron Catalysts, *Angew. Chem. Int. Ed.*, **2009**, 121, 1283-1286; (f) P. Das, L. Que Jr., Iron Catalyzed Competitive Olefin Oxidation and ipso-Hydroxylation of Benzoic Acids: Further Evidence for an Fe^{V}═O Oxidant, *Inorg. Chem.*, **2010**, 49, 9479-9485.

[33] (a) F. T. De Oliveira, A. Chanda, D. Banarjee, X. Shan, S. Mondal, L. Que Jr., E. L. Bominaar, E. Munck, T. J. Collins, Chemical and Spectroscopic Evidence for an Fe^{V}-Oxo Complex, *Science*, 2007, 315, 835-838; (b) K. M. Van Heuvelen, A. T. Fiedler, X. Shan, R. F. De Font, K. K. Meier, E. L. Bominaar, E. Munck, L. Que Jr., One-electron oxidation of an oxoiron(IV) complex to form an $[O{=}FeV{=}NR]^{+}$ center, *Proc. Natl. Acad. Sci. USA*, **2012**, 109, 11933-11938; (c) M. Ghosh, K. K. Singh, C. Panda, A. Weitz, M. P. Hendrich, T. J. Collins, B. B. Dhar, S. Sen Gupta, Formation of a Room Temperature Stable Fe^{V}(O) Complex: Reactivity Toward Unactivated C–H Bonds, *J. Am. Chem. Soc.*, **2014**, 136, 9524-9527.

[34] I. Prat, A. Company, T. Corona, T. Parella, X. Ribas, M. Costas, Assessing the Impact of Electronic and Steric Tuning of the Ligand in the Spin State and Catalytic Oxidation Ability of the Fe^{II}(Pytacn) Family of Complexes, *Inorg. Chem.*, **2013**, 52, 9229-9244.

[35] M. Mitra, A. A. Shteinman, Nonheme mono-and dinuclear iron complexes in bio-inspired C–H and C=C bond hydroxylation reactions: Mechanistic insight, *Inorg. Chim. Acta*, **2021**, 523, 120388.

[36] K. Bijudas, Selective Oxidation of Benzyl Alcohols by Hydrogen Peroxide under Phase Transfer Catalysis, *J. Applicable. Chem.*, **2019**, 8, 1887-1892.

[37] M. Mitra, A. A. Shteinman, Synthesis and Characterization of a New Ortho Palladed Complex Via C-H Activation of Redox Non-Innocent 2-(Arylazo)-N-Phenyl Aniline, *J. Applicable. Chem.*, **2018**, 7, 417-425.

[38] S. J. Swamy, S. Jyothi, P. Someshwar, K. Shashank, G. R. Rao, Synthesis and Structural analysis of N4-donar ligands and their complexes with some bivalent transition metal ions, *J. Applicable Chem.*, **2012**, 1, 218-232.