Functional Models for Non-heme Mononuclear Iron Oxygenases

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Functional Models for Non-heme Mononuclear Iron Oxygenases

Mainak Mitra

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Functional Models for Non-heme Mononuclear Iron Oxygenases

Abstract
Non-heme mononuclear iron oxygenases catalyze a large number of oxidation reactions in biological systems. The reactions are often proposed to proceed via the intermediacy of high valent Fe(IV) oxo (ferryl) or, Fe(V) oxo (perferryl) intermediates. Therefore, in order to mimic the high valent Fe(IV) oxo chemistry as well as the catalytic processes exhibited by those enzymes, new functional model complexes have been prepared and their reactivities have been studied both experimentally and theoretically.

In order to prepare high valent Fe(IV) oxo complexes, two new pentadenate nitrogen donor-based ligands have been synthesized and their Fe(II) complexes have been synthesized and characterized. The Fe(II) complexes have been converted into the corresponding Fe(IV) oxo complexes using suitable oxidant. The Fe(IV) oxo complexes have been characterized by several spectroscopic techniques and their reactivities in C-H activation and the O-atom transfer reaction have been investigated. Theoretical studies have been carried out to investigate the H-atom transfer reaction. The Fe(II) complexes have also been employed in alkane oxidation catalysis using hydrogen peroxide and peracids.

To make functional models for Rieske oxygenases, three tetradentate nitrogen donor-based ligands have been prepared. The corresponding Fe(II) complexes have been prepared and characterized. The C-H hydroxylation and C=C oxidation reactions have been studied using these complexes as catalyst and hydrogen peroxide as oxidant. Isotope labeling studies and computational studies have been performed to investigate the reaction mechanisms.

A Fe(II) complex of a tetradentate chiral nitrogen donor based ligand has also been prepared to investigate the asymmetric epoxidation of olefins, using hydrogen peroxide as oxidant.

Key words: Bioinorganic chemistry, iron, oxygenases, mononuclear, high valent, catalysis, transition state, chiral.
Functional Models for Non-heme Mononuclear Iron Oxygenases

Mainak Mitra
Dedicated to my parents

‘Education is the manifestation of perfection already in man’ – Swami Vivekananda
List of papers

I. Non-heme Fe(IV)-oxo Complexes of Two New Pentadentate Ligands and Their Reactivities Towards Hydrogen- and Oxygen-Atom Transfer Reactions

Mainak Mitra, Hassan Nimir, Serhiy Demeshko, Matti Haukka, Julio Lloret-Fillol, Franc Meyer, Albert A. Shteinman, Wesley R. Browne, David A. Hrovat, Michael G. Richmond, Miquel Costas,* and Ebbe Nordlander*

To be submitted

II. Catalytic C-H oxidations by non-heme mononuclear Fe(II) complexes of pentadentate ligands: Evidence for Fe(IV) oxo intermediate

Mainak Mitra, Hassan Nimir, Albert A. Shteinman, David A. Hrovat, Michael G. Richmond, Miquel Costas,* and Ebbe Nordlander*

Manuscript

III. Evidence that steric factors modulate reactivity of tautomeric iron-oxo species in stereospecific alkane C-H hydroxylation

Mainak Mitra, Julio Lloret-Fillol, Matti Haukka, Miquel Costas,* and Ebbe Nordlander*


IV. An investigation of steric influence on the reactivity of Fe(V) oxo tautomers in stereospecific alkane C-H hydroxylation

Mainak Mitra, Alexander Brinkmeier, Julio Lloret-Fillol, Michael G. Richmond, Miquel Costas,* and Ebbe Nordlander*

Manuscript

V. Highly Enantioselective Epoxidation of Olefins by H₂O₂ Catalyzed by a Non-heme Fe(II) complex of a Chiral Tetradentate Ligand

Mainak Mitra, Mingzhe Sun, Olaf Cusso, Julio Lloret-Fillol, Miquel Costas,* and Ebbe Nordlander*

Manuscript

Publication not included in the thesis

VI. A Bis(μ-phenoxo)-Bridged Dizine Complex with Hydrolytic Activity

Mainak Mitra, Reena Singh, Monika Pyrkosz, Matti Haukka, Elzbieta Gumienna-Kontecka, and Ebbe Nordlander*

My contributions to the papers

**Paper I.** I have performed all syntheses, reactivity studies. I was involved in explaining the mechanistic conclusions. I wrote most part of the manuscript.

**Paper II.** I have performed the catalytic experiments. I was involved in explaining the mechanistic conclusions. I wrote most part of the manuscript.

**Paper III.** I have performed all syntheses, catalytic reactivity studies. I was involved in explaining the mechanistic conclusions. I wrote most part of the manuscript.

**Paper IV.** I have performed most of the syntheses, reactivity studies. I was involved in explaining the mechanistic conclusions. I wrote most part of the manuscript.

**Paper V.** I was involved in designing the project. I have performed part of the catalysis. I wrote most part of the manuscript.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>TauD</td>
<td>Taurine:α-ketoglutarate dioxygenase</td>
</tr>
<tr>
<td>P4H</td>
<td>Prolyl 4-hydrolase</td>
</tr>
<tr>
<td>TyrH</td>
<td>Tyrosine hydroxylase</td>
</tr>
<tr>
<td>PheH</td>
<td>Phenylalanine hydrolases</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Asp</td>
<td>Aspartate</td>
</tr>
<tr>
<td>His</td>
<td>Histidine</td>
</tr>
<tr>
<td>N4Py</td>
<td>$N,N$-bis(2-pyridylmethyl)-$N$-bis(2-pyridyl)methylamine</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>BDE</td>
<td>Bond dissociation energy</td>
</tr>
<tr>
<td>HAT</td>
<td>Hydrogen atom transfer</td>
</tr>
<tr>
<td>OAT</td>
<td>Oxygen atom transfer</td>
</tr>
<tr>
<td>KIE</td>
<td>Kinetic isotope effect</td>
</tr>
<tr>
<td>NDO</td>
<td>Naphthalene 1,2-dioxygenase</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>TACN</td>
<td>1,4,7-Triazacyclononane</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>BzIm</td>
<td>Benzimidazole</td>
</tr>
<tr>
<td>Im</td>
<td>Imidazole</td>
</tr>
<tr>
<td>Pyz</td>
<td>Pyrazole</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
</tbody>
</table>
Contents

List of papers........................................................................................................ 7
My contributions to the papers.............................................................................. 8
Abbreviations......................................................................................................... 9

Contents.................................................................................................................. 11

1. Introduction......................................................................................................... 13
  1.1 Bioinorganic chemistry.................................................................................. 13
  1.2 Metals in biology......................................................................................... 13
  1.3 Metalloenzymes............................................................................................ 14
  1.4 Active sites in metalloenzymes..................................................................... 15
  1.5 Iron in metalloenzymes................................................................................ 16
  1.6 Tools and methods for studying metalloenzymes......................................... 17
  1.7 Biomimetic chemistry: Modelling the active site of a metalloenzyme........ 18
  1.8 Scope of the thesis........................................................................................ 19
  1.9 References..................................................................................................... 20

2. High valent Fe(IV) oxo complex: Reactivities towards H- and O-atom transfer processes........................................................................................................ 21
  2.1 Introduction.................................................................................................... 21
  2.1.1 Fe(IV) oxo intermediate in non-heme mononuclear iron enzymes........ 21
  2.1.2 Synthetic non-heme mononuclear Fe(IV) oxo complexes....................... 24
  2.2 Motivation behind the work and design of ligands.................................... 25
  2.3 Fe(II) complexes: Synthesis and characterization....................................... 27
  2.4 Crystal and molecular structure................................................................. 28
  2.5 Synthesis and characterization of Fe(IV) oxo complexes.............................. 28
  2.6 Stabilities and half lives of Fe(IV) oxo complexes 3 and 4......................... 29
  2.7 Reactivities of Fe(IV) oxo complexes.......................................................... 30
    2.7.1 C-H bond activation: Hydrogen-atom transfer (HAT) reactions........... 30
    2.7.2 Oxygen-atom transfer (OAT) reactions............................................... 32
  2.8 Computational studies on the HAT reactivity by the Fe(IV) oxo complexes 32
  2.9 Catalytic oxidation reactions on alkanes by the Fe(II) complexes............ 33
  2.10 Summary and conclusion............................................................................ 35
  2.11 References................................................................................................... 35
3. Stereospecific and selective C-H hydroxylation and C=C oxidation by H₂O₂ mediated by Fe(II) complexes of tetradentate ligands: Steric and electronic influences on the reactivity ................................................................. 39
   3.1 Introduction: Oxidative transformation of a chemical bond ......................... 39
   3.1.1 C-H bond oxidation ........................................................................ 39
   3.1.2 C=C bond oxidation .................................................................... 40
   3.2 Oxidation reactions in Nature ................................................................. 40
   3.3 Rieske oxygenases: Structure and function ............................................. 40
   3.4 Model synthetic non-heme iron complexes: Background and motivation of the present study .......................................................... 42
   3.5 Ligands used in this study ................................................................. 44
   3.6 Synthesis and characterization of the Fe(II) complexes ......................... 44
   3.7 Crystal and molecular structures ......................................................... 45
   3.8 Catalytic oxidation studies ................................................................. 46
   3.8.1 C-H bond oxidation of alkanes ..................................................... 46
   3.8.2 Oxidation of olefin substrates ....................................................... 48
   3.9 Isotope labelling study .................................................................... 48
   3.10 Discussions .................................................................................. 50
   3.11 Summary and conclusion ................................................................. 52
   3.12 References .................................................................................. 52

4. Asymmetric epoxidation of olefins by hydrogen peroxide, catalysed by non-heme Fe(II) complexes of chiral tetradentate ligands ..................... 55
   4.1 Introduction .................................................................................. 55
   4.2 Asymmetric epoxidation ................................................................ 55
   4.3 Asymmetric epoxidation of olefins by synthetic non-heme Fe(II) complexes: Background and motivation of the present study .......................................................... 56
   4.4 Ligands used in this present study ..................................................... 57
   4.5 Synthesis and characterization of the Fe(II) complexes ....................... 58
   4.6 Crystal and molecular structure of complex 1OTf .................................. 59
   4.7 Catalytic asymmetric epoxidation study .......................................... 60
   4.8 Summary and conclusion ................................................................. 62
   4.9 References .................................................................................. 62

5. Concluding remarks .......................................................................... 65
   5.1 Summary of the present work .......................................................... 65
   5.2 Future perspective of the present work ............................................. 66

Populärvetenskaplig sammanfattning .......................................................... 67

Acknowledgment .................................................................................. 69
Chapter 1 Introduction

1.1 Bioinorganic chemistry

Bioinorganic chemistry is an important branch of inorganic chemistry and biochemistry. It is referred to as the inorganic chemistry of life. The introduction and gradual advancement of biochemistry during the 20th century led chemists to search for an understanding of the functions of metallobiomolecules on a molecular level, and hence the field of bioinorganic chemistry was born. This field deals with the application of the fundamental principles of chemistry in the biophysical processes of living organisms. It involves the study of all metallic and most non-metallic elements in biological systems.

The scope of bioinorganic chemistry is broad, ranging from chemical physics to clinical medicine. The area of this field has been expanded significantly during the past three decades. This is due to several reasons: (i) improved analytical techniques, (ii) the recognition of roles of essential elements in plant, animal and human nutrition, (iii) rapid preparative methods for metalloproteins, (iv) sophisticated spectroscopic/physical techniques (especially nuclear magnetic resonance (NMR) spectroscopy and protein crystallography) and diffraction techniques, (v) the improved and facile syntheses of small and simple inorganic complexes to mimic the various aspects of biomolecules, (vi) the use of metal complexes for therapeutic agents, and (vii) the growing concern about the environmental hazards caused by some metal ions and elements (e.g. Hg, As etc.).

1.2 Metals in biology

The importance of metals in biology, the environment and medicine has become increasingly evident over the last 30 years. This is why the study of the roles of metals and metal ions in biological systems has become so relevant in the interfaces of inorganic chemistry and biology.

There are 13 metals, namely, Na, K, Mg, Ca (belonging to the main group metals) and V, Cr, Mn, Fe, Co, Ni, Cu, Zn and Mo (belonging to the d-block transition
metals) that are considered to be essential for the biological functions of human and other living systems. Withdrawal or absence of one of these metals from the diet causes functional or structural abnormalities. The abnormalities are related to, or are a consequence of, specific biochemical changes that can be reversed by the presence of the essential metal. The human body requires different amounts of essential metals to survive, function and maintain its physical growth. For example, Ca is present as approximately 1.4 mass % and is the most abundant metal; therefore the recommended daily intake of calcium ranges from 1000 to 1300 mg for adults. Iron is also an important essential metal to the human body, which represents 0.0006 mass % of the body (i.e. 4-5 g of iron). Out of this, 2.5 g iron is bound to hemoglobin, an oxygen transport metalloprotein present in red blood cells (RBC), while most of the remaining part is contained in the ferritin iron storage protein present in all cells. The daily required intake for adults is 8 mg for men and 18 mg for women. Iron deficiency leads to many complications in the body, e.g. anaemia (a condition of decrease in the amount of hemoglobin in blood).

Figure 1. A periodic table of elements that are essential for human life (adapted from ref [2]).

1.3 Metalloenzymes

The overwhelming majority of metalloenzymes are proteins that contain metals that are tightly bound and always isolated with the protein. It has been estimated that one half of all known proteins contain metals, while approximately one third of the proteins are dependent on metals for their biological functions.³
Table 1. Lists of some essential metals and enzymes containing those metals in their active sites.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Examples of metalloenzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Catalase, Hydrogenase</td>
</tr>
<tr>
<td>Copper</td>
<td>Cytochrome c oxidase, Laccase</td>
</tr>
<tr>
<td>Zinc</td>
<td>Carboxypeptidase, Aminopeptidase</td>
</tr>
<tr>
<td>Nickel</td>
<td>Urease, Hydrogenase</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Glucose 6-phosphatase, Hexokinase</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Methionyl aminopeptidase, Nitrile hydratase</td>
</tr>
<tr>
<td>Manganese</td>
<td>Arginase</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Nitrate reductase, Sulfite oxidase</td>
</tr>
</tbody>
</table>

1.4 Active sites in metalloenzymes

The active site of a metalloenzyme is a three-dimensional pocket or groove where the substrate molecule binds and undergoes a chemical transformation. Generally, an enzyme has only one active site. This active site fits specifically with one particular substrate molecule. There are two proposed models describing how the active site of an enzyme fits with its specific substrate: (I) the lock and key model and (II) the induced fit model. According to the lock and key model⁴ (proposed by Emil Fischer), the active site is perfectly fit for a specific substrate and after binding the substrate no further modification occurs. According to the induced fit model⁵ (proposed by Daniel Koshland), the active site of the enzyme is flexible and it changes until the substrate binding is accomplished. Hence, the substrate is thought to induce changes in the shape of the active site.

![Enzyme-substrate binding](image-url)

The proteins consist of chains of amino acid residues that contain N (e.g. histidine, arginine), O (e.g. aspartate, glutamate, serine) and S (cysteine and methionine) donor
atoms that can coordinate to the metal ions. A protein-bound metal site consists of one or more metal ions that are coordinated to protein side chains and exogenous terminal and bridging ligands.\(^3\) This defines the first coordination sphere of each metal ion. Such metal sites can be classified into five categories on the basis of their functions:\(^3\)

(i) Structural: The metal sites hold the protein structure together and thus induces tertiary and/or quaternary structures of the protein. An example is the zinc finger proteins, where the protein motifs are folded via coordination to one or more zinc ions.

(ii) Storage: These metal sites are related to the uptake, binding and release of soluble metals. An example is the iron-oxo cluster core in ferritin, a globular protein responsible for the storage of iron inside the body.

(iii) Electron transfer: These metal sites function as relay stations in biological electron transfer, with the metals undergoing one-electron oxidations/reductions. Examples include the iron-sulfur sites in iron-sulfur proteins (e.g. ferredoxins).

(iv) Dioxygen-binding and transport: These metal sites effect the (reversible) binding of dioxygen from air. For example, hemoglobin and myoglobin are iron-containing oxygen-binding proteins. The oxygen binding process is often associated with simultaneous electron transfer.

(v) Catalytic: These metal sites are used for the binding of a substrate and the formation of a product via chemical transformation of the substrate, which often includes redox chemistry. This is the most diverse category in terms of function. The present thesis will highlight some examples of the catalytic metal sites in biology.

1.5 Iron in metalloenzymes

Iron is the fourth most common element (after oxygen, silicon and aluminium) in the Earth's crust, where it constitutes up to 5% of the total elements present. Biologically, iron plays vital roles in oxygen transport and storage as well as in electron transport.\(^6\) With only a few possible exceptions in the bacterial world, there would be no life without iron.\(^6\) There is a large number of metalloenzymes that contain iron in their active sites. Myoglobin and hemoglobin were among the first proteins to be structurally characterized and both of them contain iron-protoporphyrin IX (heme b) as an essential prosthetic center.
1.6 Tools and methods for studying metalloenzymes

It is very important to study the structures of metalloenzymes and their various functions. Therefore, scientists have over decades developed many techniques and equipment for such studies. These techniques and equipment have become more and more sophisticated and sensitive with the gradual advancement of technologies and facilities so that nowadays, there are many tools and methods that are available to study a metalloenzyme. Using small synthetic metal-ligand complexes, chemists have been able to model the active sites of various metalloenzymes and understand details of their functions.

Firstly, once isolated, a metalloenzyme is subjected to testing using different analytical methods, most of which are based on the use of spectroscopy. Table 2 lists different spectroscopy techniques and the information they can provide. Besides spectroscopy, X-ray crystallography (X-ray diffraction), neutron diffraction and electron diffraction are also very useful techniques to determine the structure of the protein/metalloenzyme accurately. Applying these tools, the identity of the metal (or, metals) present in the metalloenzyme is determined and the binding sites of the protein to the metal center as well as the primary structure are identified. Kinetic studies are used to elucidate the function of the metalloenzymes. On the basis of these results, plausible mechanistic hypotheses are derived, which may be further verified by means of modelling the active site of the metalloenzyme using metal-ligand complexes.

There are indirect methods that involve computational studies and they are widely used. The active sites of many enzymes have been modelled and detailed theoretical investigations have been made on the basis these models. These studies provide valuable information about possible transition state configurations, structures of various reactive intermediates and plausible catalytic cycles. Sometimes, a proposed mechanistic cycle can be verified by such studies.
### Table 2. Spectroscopic techniques and their applications to biological metal sites

<table>
<thead>
<tr>
<th>Spectroscopic method</th>
<th>Information obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vibrational (Raman and Infra Red)</td>
<td>Nature of bonds of ligands around metal centers</td>
</tr>
<tr>
<td>Electronic absorbance (UV/Visible)</td>
<td>Nature of ligand field and charge transfer transitions (ligand to metal/metal to ligand)</td>
</tr>
<tr>
<td>Nuclear Magnetic Resonance (NMR)</td>
<td>Structure and electronic properties of diamagnetic and paramagnetic systems</td>
</tr>
<tr>
<td>Electron Spin Resonance or, Electron Paramagnetic Resonance (ESR/EPR)</td>
<td>Detection and identification of free radicals and paramagnetic centers</td>
</tr>
<tr>
<td>Mössbauer</td>
<td>Oxidation state and spin state of, normally, $^{57}$Fe, sensitive to chemical environment around the metal</td>
</tr>
<tr>
<td>Magnetic Circular Dichronism (MCD)</td>
<td>Detection of electronic structures of both ground and excited states</td>
</tr>
<tr>
<td>Time-resolved spectroscopy</td>
<td>Deals on the study of the dynamic processes in chemical compounds or, materials.</td>
</tr>
<tr>
<td>X-ray photoelectron spectroscopy (XPS)</td>
<td>Measures chemical compositions, empirical formula, chemical and electronic state of the elements within the materials</td>
</tr>
</tbody>
</table>

### 1.7 Biomimetic chemistry: Modelling the active site of a metalloenzyme

It is often difficult to isolate and purify the real metalloenzyme, a fact that complicates studies of its structural and functional aspects of a metalloenzyme. In some cases, an isolated protein cannot be fully characterized by virtue of its complex structure and lack of crystallization. To overcome such difficulties, researchers have developed a strategy to synthesize metal complexes that can mimic the active site of a metalloenzyme of interest ('biomimetic' modelling). Such model complexes may make it possible to gain many insights into the intrinsic properties of a particular metal site in a metalloenzyme. However, due to the absence of the protein environment surrounding these model metal complexes, they cannot truly reflect the impact of the enzyme active site. Nevertheless, they may be used to understand/investigate the basic roles of the metals present in the active site as well as to develop a view on mechanistic pathways. Also, model complexes are relatively easy to modify by means of varying the surrounding ligand environment, and can
thus provide useful information about a particular donor atom/site. Some model complexes have also shown good catalytic properties that are similar to those of the enzymes and may therefore, in principle, be employed in industrial settings.

Model complexes can mimic the active site of an enzyme structurally, functionally, or they can serve both purposes. It is also possible to verify the influence of structural and functional changes by appropriate modifications. First, model metal complexes are synthesized and isolated, followed by identification by various spectroscopic techniques. Structural comparison is made between the model complex and the active site of enzyme (structural model). Then, the model complexes are explored as catalysts of the particular reaction that the enzyme catalyses (functional model). Often, a structural model complex does not show reactivity that is similar to, or as good as, that of the enzyme (i.e. it is not a functional model) and vice versa.

In recent years, a third aspect of synthetic modelling of metalloenzymes has become increasingly popular. This approach is often referred to as “bio-inspired modelling”, where the complexes that are prepared and studied are intended to serve as catalysts that reproduce enzymatic reactions, but bear little or no resemblance to the relevant metalloenzyme sites, neither in terms of metal(s) used nor coordination geometries or ligand environments. Such a “bio-inspired” approach is explored in many areas, e.g. artificial photosynthesis, where metal complexes that can function as light harvesters, and catalysts of, for example, water oxidation and proton reduction, are developed.

1.8 Scope of this thesis

The present thesis focuses on the functional mimicry of active sites of mononuclear non-heme iron oxygenase enzymes (cf. chapters 2 and 3 for more discussions about iron oxynenases). The studies include synthesis and spectroscopic characterization of mononuclear non-heme iron complexes of N-based polydentate ligands and catalytic oxidation reactions of some model organic substrates. High valent Fe oxo intermediates have also been generated and characterized. The reactivities of these intermediates have been explored in hydrogen atom transfer and oxygen atom transfer processes. Computational modelling studies have been performed to elucidate the structures and orientations of high valent Fe oxo intermediates and to propose plausible reaction mechanisms.

Paper I deals with the synthesis and characterization of two non-heme Fe(IV) oxo complexes of pentadentate ligands and detailed investigations on their reactivities towards hydrogen- and oxygen-atom transfer reactions. Paper II deals with the oxidation catalysis of alkanes and alkenes and studies of reaction mechanism mediated by the Fe(II) complexes of the above pentadentate ligands.
Papers III and IV deal with stereospecific C-H hydroxylation reactions by three Fe(II) complexes of tetrade ntate ligands and detailed investigations on the mechanisms of hydroxylation by isotope labelling and theoretical studies.

Paper V deals with the asymmetric epoxidation of olefins with hydrogen peroxide as oxidant catalysed by a Fe(II) complex of a tetrade ntate N4 chiral ligand.

1.9 References

Chapter 2.

High valent Fe(IV) oxo complexes: Reactivities towards H- and O-atom transfer processes

2.1 Introduction.

2.1.1 Fe(IV) oxo intermediates in non-heme mononuclear iron enzymes.

Non-heme mononuclear iron enzymes carry out essential metabolic transformations via activation of molecular oxygen inside living organisms.\(^1\)\(^-\)\(^2\) They catalyze oxidation of organic substrates, and the oxidation reactions include hydroxylation, halogenation, desaturation, epoxidation and cis-dihydroxylation.\(^3\)\(^-\)\(^7\) An example is proline 3-hydroxylase which catalyzes the conversion of L-proline into cis-3-hydroxy-L-proline in the presence of 2-oxoglutarate and molecular oxygen; 2-oxoglutarate functions as a “sacrificial” substrate (\textit{vide infra}).\(^7\)\(^-\)\(^8\) It is often postulated that the key oxidizing intermediate involved in the above-mentioned oxidation reactions is a high valent Fe(IV) oxo (ferryl-oxo or, simply ferryl) species.\(^6\)\(^,\)\(^9\)\(^-\)\(^11\) The presence of a reactive Fe(IV) oxo intermediate has been established in the catalytic cycles of \textit{E. coli} taurine-\(\alpha\)-ketoglutarate dioxygenase (TauD),\(^12\) prolyl 4-hydrolase (P4H),\(^13\) the halogenase CytC3,\(^14\) tyrosine hydroxylase (TyrH),\(^15\) pterin-dependent phenylalanine hydrolases (PheH),\(^16\) and the aliphatic halogenase SyrB2.\(^17\) In all cases, the Fe(IV) center is in a high spin (hs) \(d^4\) configuration. In many of these enzymes, the iron center is bound to a 2-His-1-carboxylate facial triad motif. Figure 1 depicts three proposed Fe(IV) oxo intermediate structures found in the non-heme mononuclear iron-enzyme active sites.
Figure 1. The proposed active site structures of taurine:α-ketoglutarate dioxygenase (TauD), the halogenase CytC3 (CytC3) and pterin-dependent phenylalanine hydroxylase (PheH), containing high valent Fe(IV) oxo centers (succ = succinate, glu = glutamate).

A powerful approach to study the mechanism and to establish a catalytic cycle by which an enzyme oxidizes substrate is to attempt the detection or trapping of reaction intermediates followed by detailed characterization of these intermediates using kinetics and spectroscopic techniques. The first direct detection of an intermediate in a reaction with dioxygen catalyzed by a mononuclear non-heme iron enzyme was reported for HPPD ((4-Hydroxyphenyl)pyruvate dioxygenase). Shortly after this, an Fe(IV) oxo intermediate was detected in the catalytic cycle of TauD by various spectroscopic techniques. On the basis of these novel findings, a general reaction mechanism has been proposed for this class of iron enzymes. Molecular oxygen initially coordinates to the Fe(II) center of the active site to form an Fe(III) superoxo species, Fe(III)-O2-. The superoxo species can itself act as an oxidant, as proposed for Fe-bleomycin. In a second scenario, the O-O bond is homolytically cleaved to generate the reactive FeIV(=O) intermediate (or even FeV(=O) intermediate in Rieske oxygenases). The FeIV(=O) intermediate then reacts with the substrate in a hydrogen atom transfer (HAT) reaction to form a substrate radical and a Fe(III)-OH species. The subsequent step is the so called “oxygen rebound”, which has been proposed and identified for heme enzymes; it involves the recombination of the substrate radical with a hydroxyl radical formed by homolytic cleavage of the metal oxygen bond, yielding the oxidized product (Scheme 1). In the whole process, one oxygen atom derived from atmospheric oxygen is inserted into the C-H bonds of the substrate.
Scheme 1. The oxygen rebound mechanism proposed for non-heme mononuclear iron enzymes, involving a Fe(IV) oxo intermediate.

So called \( \alpha \)-keto acid-dependent enzymes (e.g. prolyl 4-hydroxylases, lysyl hydroxylases, TauD, asparagine hydroxylase etc.) are found in microorganisms, plants, and animals and play key roles in vital transformations of environmental, pharmaceutical and biological importance.\(^6\) Figure 2 describes the common proposed mechanism for the \( \alpha \)-ketone acid-dependent iron oxygenases.\(^{11,22-24}\) In the resting state of the enzyme, the Fe(II) center is bound to a 2-His-1-carboxylate triad motif and three water molecules. Steady-state kinetics studies on some enzymes emphasise an ordered mechanism in which binding of an \( \alpha \)-keto carboxylate (e.g. \( \alpha \)-ketoglutarate) to the Fe(II) center occurs prior to dioxygen or substrate binding. The \( \alpha \)-keto carboxylate functions as a sacrificial substrate, accepting one of the two oxygens from the dioxygen molecule, while the second oxygen is incorporated into the enzymatic substrate.

Figure 2. The proposed catalytic cycle of \( \alpha \)-keto acid-dependent enzymes, SH = arbitrary substrate.
Trapping and characterization of high valent Fe(IV) oxo intermediates in non-heme iron enzymes have inspired synthetic chemists to design and construct suitable ligand systems for the synthesis of Fe(IV) oxo complexes and to study the reactivities of such complexes in small molecule transformation reactions that enable us to gain a solid understanding of and to interpret the molecular mechanisms of the real enzymes. This will be further discussed below.

2.1.2 Synthetic non-heme mononuclear Fe(IV) oxo complexes

Inspired by Nature, several non-heme mononuclear Fe(IV) oxo complexes have been synthesized and well characterized during the last two decades.25-28 Except a few complexes,29-34 most of them are found to contain low spin Fe(IV) centers. The Fe(IV) oxo complexes thus reported have different reactivity rates in hydrogen atom transfer (HAT) and oxygen atom transfer (OAT) reactions. The discrepancy in the observed reactivities of the various Fe(IV) oxo complexes is due to several factors including (I) the nature of the ligand, (II) denticity of the ligand (tetradentate vs pentadentate), and (III) the spin state (high spin vs low spin) of the Fe(IV) center. The ligand field strength plays an important role in tuning the reactivity of the Fe(IV) oxo complex; the field strength is associated with the electronic properties of the donor atoms/moieties of the ligand.

Significant contributions have been made by using Fe(IV) oxo complexes containing a labile coordination site occupied by a solvent molecule that is either cis or trans with respect to the oxo ligand.35-38 This permits exchange with other ligands. For example, Que, Shaik, Nam and coworkers37 have investigated the reactivities of mononuclear Fe(IV) oxo complexes, \([\text{Fe}^{IV}(\text{O})(\text{TMC})(\text{X})]^n^+\) (where TMC is 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclododecane and X is NCCH₃, CF₃SOO⁻, N₃⁻) and \([\text{Fe}^{IV}(\text{O})(\text{TMCS})]^+\) (where TMCS is 1-mercaptoethyl-4,8,11-trimethyl-1,4,8,11-tetraazacyclododecane) and have shown that the more electron donating the axial ligand is, the more reactive the Fe(IV) oxo complex becomes with respect to HAT reactions and the less reactive with respect to oxygen atom transfer to PPh₃.

The spin state of the Fe(IV) center is also an important aspect. It has been predicted that a high spin Fe(IV) oxo complex is more reactive than the corresponding low spin complex.39 However, the most reactive Fe(IV) oxo complex so far, \([\text{Fe}^{IV}(\text{O})(\text{Me}_3\text{NTB})]^2^+\) (where Me₃NTB = tris((N-methyl-benzimidazol-2-yl)methyl)amine)), reported by Nam and co-workers, contains a low spin \((S = 1)\) Fe(IV) center in the ground state.40 Density functional calculations revealed that the reactive state is likely to be \(S = 2\), which has a low energy barrier for the C-H abstraction reaction with respect to the triplet \((S = 1)\) ground state; this is the essential concept of the so-called “two state reactivity” (TSR) model – there is a crossover to a high spin reactive state upon formation of the transition state from the ground state.40 The geometry of the ligand sometimes dictates the spin state of the Fe(IV) center. The ligand field energy diagram for an octahedral Fe(IV) oxo complex
reveals that the energy gap between the $d_{xy}$ and $d_{x^2-y^2}$ orbitals determines the spin state on the iron.\textsuperscript{41} For most Fe(IV) oxo complexes having $S = 1$, this energy gap is larger than the spin pairing energy. If the ligand strength is weakened, then the energy gap becomes smaller than the spin pairing energy leading to $S = 2$ Fe(IV) oxo species as demonstrated in the case of $[\text{Fe}^{IV}(\text{O})(\text{H}_2\text{O})_3]^{2+}\textsuperscript{29,42}$ Attaining $S = 2$ spin states can be approached by adoption of trigonal bipyramidal geometry (TBP) around the Fe(IV)-center, which leads to degeneracy of the $d_{xy}$ and $d_{x^2-y^2}$ orbitals. This requires a tetradeutate ligand system with sufficient steric constraints. Examples of such cases are $[\text{Fe}^{IV}(\text{O})(\text{TMG}_{3}\text{tren})]^{2+}$ ($\text{TMG}_{3}\text{tren} = \text{tris(tetramethylguanidino)tren}$)\textsuperscript{30} and $[\text{Fe}^{IV}(\text{O})(\text{H}_3\text{buea})]^{-}$ ($\text{H}_3\text{buea} = \text{tris(tert-butylureaylethylen)aminato}$).\textsuperscript{32} Despite their high spin character, they do not possess superior reactivities when compared to the low spin Fe(IV) oxo complexes. This fact is explained by the steric inhibition by the bulky ligand, making it difficult for the substrate to approach the Fe(IV) oxo center. Recently, Que, Munck and co-workers reported an Fe(IV) oxo complex, $[\text{Fe}^{IV}(\text{O})(\text{Mecyclam-C}_2\text{C(O)NMe}_2)]^{+}$ with very high thermal stability (half life 5 d at room temperature).\textsuperscript{27} This complex, owing to its high stability, is a sluggish catalyst of HAT reactions. Addition of strong base to this complex resulted in the formation of a new oxo iron(IV) complex that is far less stable and can be converted back to the stable complex by treatment with acid. This represents the first example of a conjugate acid-base pair in Fe(IV) oxo chemistry. Goldberg and coworkers have reported a series of Fe(IV) oxo complexes that can mediate ring hydroxylation/halogenations of the ligand coordinating to the Fe-oxo unit.\textsuperscript{43} All these studies testify to the diverse nature of synthetic non-heme high valent Fe oxo complexes. This chapter will summarize my investigations within this challenging area of research.

\subsection*{2.2 Motivation behind the work and design of ligands}

Figure 3. The Fe(IV) oxo complexes, $[\text{Fe}^{IV}(\text{O})(\text{N}_4\text{Py})]^{2+}$ (left), $[\text{Fe}^{IV}(\text{O})(\text{TPA})]^{2+}$ (middle) and $[\text{Fe}^{IV}(\text{O})(\text{Me}_3\text{NTB})]^{2+}$ (right).
The Fe(IV) oxo complex of the pyridine-based pentadentate N4Py ligand, i.e. [Fe\textsuperscript{IV}(O)(N4Py)]\textsuperscript{2+} (Figure 3), constitutes a unique example of the combination of good thermal stability with considerable reactivity.\textsuperscript{44} This complex has a half life (t\textsubscript{1/2}) of 60 h at room temperature, allowing it to be crystallographically characterized. At the same time, it possesses sufficient reactivity to oxidize C-H bonds as strong as those in cyclohexane (C-H bond dissociation energy 99.3 kcal/mol) at room temperature. While, the Fe(IV) oxo complex of the pyridine-based tetradsentate TPA ligand, [Fe\textsuperscript{IV}(O)(TPA)]\textsuperscript{2+} (Figure 3), is less stable (stable at -40 °C for several days) compared to [Fe\textsuperscript{IV}(O)(N4Py)]\textsuperscript{2+} and has moderate reactivities.\textsuperscript{45} In contrast, the complex [Fe\textsuperscript{IV}(O)(Me\textsubscript{3}NTB)]\textsuperscript{2+} (Figure 3) is the most reactive Fe(IV) oxo complex in HAT and OAT reactions that has thus far been published, but it decomposes very rapidly even at low temperature (t\textsubscript{1/2} is 2 min at -40 °C).\textsuperscript{40} These observations indicate that while the pyridine-containing pentadentate ligand (N4Py) stabilizes the high valent Fe(IV) oxo moiety, the (N-methyl)benzimidazolyl moiety (as in Me\textsubscript{3}NTB) destabilizes it, but enhances the reactivity. Considering these observations, we decided to investigate how the introduction of (N-methyl)benzimidazolyl moieties into the pentadentate N4Py ligand framework may affect the properties of the Fe(IV) oxo species.

Thus, two new pentadentate N5-donor ligands, L\textsubscript{1} and L\textsubscript{2} (Figure 4) were synthesized. These ligands are based on the N4Py ligand framework, with one (L\textsubscript{1}) or two (L\textsubscript{2}) ((2-pyridyl)methyl side arm(s) of N4Py being replaced by (N-methyl)benzimidazolyl)methyl arm(s). Introduction of the (N-methyl)benzimidazolyl moieties permits an assessment of potential electronic and/or steric effects of substituents on the reactivities of high valent Fe(IV) oxo complexes as well as the reactivities of analogous Fe(II) complexes in oxidation catalysis. In general, (N-methyl)benzimidazolyl moieties possess greater steric bulk than pyridyl moieties, and (N-methyl)benzimidazole is better σ-donor than pyridine\textsuperscript{46} but also a better π-acceptor. In Nature, the active sites of iron enzymes contain one or more coordinating imidazole rings from histidine residues of the protein chain. Imidazole is more basic but its electronic properties are similar to benzimidazole. Therefore, it was envisioned that (N-methyl)benzimidazole-containing ligands may provide useful information on the impact of basic donor groups on the C-H activation and other organic transformation reactions mediated by high valent Fe-oxo centers.
Figure 4. Structures of ligands L\textsuperscript{1} (left) and L\textsuperscript{2} (right) used for this study.

The ligands were synthesized and were characterized by mass spectra and NMR spectra (cf. paper I for detailed synthetic procedures).

2.3 Fe(II) complexes: Synthesis and characterization

The Fe(II) complexes of the two new ligands, namely [Fe\textsuperscript{II}(L\textsuperscript{1})(\text{CH}_3\text{CN})](\text{ClO}_4)\textsubscript{2} (\textit{1}(\text{ClO}_4)\textsubscript{2}) and [Fe\textsuperscript{II}(L\textsuperscript{2})(\text{CH}_3\text{CN})](\text{ClO}_4)\textsubscript{2} (\textit{2}(\text{ClO}_4)\textsubscript{2}; Figure 5) were synthesized (cf. paper I for detailed syntheses). Both complexes were obtained as air-stable solids.

The complexes were characterized by ESI-MS, elemental analysis, \textsuperscript{1}H-NMR spectroscopy, IR spectroscopy and UV/Visible spectroscopy (cf. paper I). The \textsuperscript{1}H-NMR spectra of the complexes establish the ls configuration of the Fe(II)-center. The UV/Vis spectra of the complexes have shown two distinct metal to ligand charge transfer (MLCT) transitions originating from the electron donation of t\textsubscript{2g} orbitals of Fe(II) to the $\pi^*$ orbitals of the ligand.

The zero field Mössbauer spectra recorded for naturally abundant solid samples of complexes \textit{1}(\text{ClO}_4)\textsubscript{2} and \textit{2}(\text{ClO}_4)\textsubscript{2} at 80 K further confirm the ls state of the Fe(II)-centers (cf. paper I for details).
2.4 Crystal and molecular structures

Figure 6. The crystal structures of the cations of 1(ClO\(_4\))\(_2\) (left) and 2(ClO\(_4\))\(_2\) (right) (Mercury plot); hydrogen atoms have been omitted for clarity.

The crystal structures of complexes 1(ClO\(_4\))\(_2\) and 2(ClO\(_4\))\(_2\) (Figure 6) reveal Fe-N bond distances that are consistent with the presence of low spin Fe(II) centers in both complexes. A structural comparison of 1(ClO\(_4\))\(_2\) and 2(ClO\(_4\))\(_2\) and the parent complex [Fe\(^{II}\)(N4Py)(CH\(_3\)CN)](ClO\(_4\))\(_2\) is discussed in paper I.

2.5 Synthesis and characterization of Fe(IV) oxo complexes

The Fe(IV) oxo complexes [Fe\(^{IV}\)(O)(L\(_1\))]\(^{2+}\) (3) and [Fe\(^{IV}\)(O)(L\(_2\))]\(^{2+}\) (4) were conveniently synthesized by reaction of the Fe(II) complexes/precursors (1(ClO\(_4\))\(_2\) and 2(ClO\(_4\))\(_2\), respectively) with excess solid PhIO in CH\(_3\)CN (Scheme 2).

Scheme 2. Generation of the Fe(IV)-oxo complexes 3 and 4 from their precursor Fe(II)-complexes, 1 and 2, respectively.

Both 3 and 4 exhibit a characteristic absorption in the near IR region with a maximum at \(\lambda_{\text{max}} = 708\) nm (\(\epsilon \approx 400\) M\(^{-1}\) cm\(^{-1}\)) and 725 nm (\(\epsilon \approx 380\) M\(^{-1}\) cm\(^{-1}\)), respectively.
respectively. This absorption is associated with a ligand field transition rather than a charge transfer transition. The parent complex $[\text{Fe}^\text{IV}(\text{O})(\text{N}4\text{Py})]^2+$, containing four equatorial pyridyl groups, has a corresponding $\lambda_{\text{max}} = 695$ nm and this value increases gradually as pyridyl groups are replaced by $(N$-methyl)benzimidazolyl groups and may therefore be directly related to and correlated with the donor strength of the pentadentate ligand. Furthermore, Mössbauer spectroscopy was used to confirm the oxidation and spin states of complexes 3 and 4 (Figure 7). The isomer shift values for the two complexes are very similar to those obtained for $[\text{Fe}^\text{IV}(\text{O})(\text{N}4\text{Py})]^2+$ and $[\text{Fe}^\text{IV}(\text{O})(\text{Bn-tpen})]^2+$, indicating that both 3 and 4 are low spin ($S = 1$) non-heme Fe(IV) oxo complexes.

![Graph 1](image1)

![Graph 2](image2)

Figure 7. (Left) The zero-field Mössbauer spectrum of $^{57}\text{Fe}$ enriched 3 (light gray) in acetonitrile solution (5 mM) measured at 80 K. The minor black subspectrum corresponds to ca. 14% unidentified Fe(III) impurity. (Right) The zero-field Mössbauer spectrum of $^{57}\text{Fe}$ enriched 4 (light gray) in acetonitrile solution (2 mM) measured at 80 K. The minor black subspectrum corresponds to ca. 20% unidentified Fe(III) impurity. Complex 3, isomer shift ($\delta$) = -0.03 mm s$^{-1}$ and quadrupole splitting value ($\Delta E_Q$) = 1.1 mm s$^{-1}$; Complex 4, $\delta$ = -0.02 mm s$^{-1}$ and $\Delta E_Q$ = 1.34 mm s$^{-1}$.

### 2.6 Stabilities and half-lives of the Fe(IV) oxo complexes 3 and 4

Complexes 3 and 4 are relatively stable at room temperature. Complex 3 has a half-life ($t_{1/2}$) of 40 h at ambient temperature and is more stable than complex 4, for which $t_{1/2}$ is 2.5 h at room temperature. These data may be compared to $t_{1/2}$ of 60 h at room temperature for the parent complex $[\text{Fe}^\text{IV}(\text{O})(\text{N}4\text{Py})]^2+$, which contains four equatorial pyridyl groups. The relative stabilities for the three complexes are directly related to the successive replacement of pyridylmethyl arms in the N4Py ligand with (N-methylbenzimidazolyl)methyl arms, $[\text{Fe}^\text{IV}(\text{O})(\text{N}4\text{Py})]^2+$ (most stable) > complex 3 > complex 4 (least stable). It may be concluded that the relative stabilities of the
Fe(IV) oxo complexes are also influenced by the relative donor strength of the pentadentate ligands.

Figure 8. Fe(IV) oxo complexes 3 (left) and 4 (right).

2.7 Reactivities of Fe(IV) oxo complexes

2.7.1 C-H bond activation: Hydrogen-atom transfer (HAT) reactions

The reactivities of complexes 3 and 4 were investigated towards hydrogen atom transfer (HAT) reactions using different alkanes with C-H bond dissociation energies (BDE's) ranging from 81 to 99.3 kcal/mol. It was found that both complexes are capable of oxidizing C-H bonds of the substrate to give moderate to good yields of oxidized products (cf. paper I). The reactions were run under pseudo-first-order conditions using excess substrate, and the observed rate constant ($k_{obs}$) was found to be linearly dependent on the concentration of the substrate. From this analysis, the second order rate constant ($k_2$) was determined. The products were analysed using gas chromatography. The reactivities of the two Fe(IV)=O complexes are summarized below.

Scheme 3. Hydroxylation of triphenylmethane into triphenylmethanol by complex 3 or 4.
Complexes 3 and 4 oxidized triphenylmethane, with a C-H BDE of 81 kcal/mol, to triphenyl methanol with 89-90% yields (Scheme 3). When cyclohexane (which has a relatively high C-H BDE of 99.3 kcal/mol) was employed as substrate, 3 and 4 oxidized the substrate to give both cyclohexanol and cyclohexanone in moderate yields (18% and 26%, respectively). The second order rate constants and details of the product analyses for complexes 3 and 4 are listed in paper I and the supplementary material. A plot of log $k_2^*$ ($k_2^*$ is obtained by dividing $k_2$ with the number of equivalent C-H bonds of the alkane substrate of interest) versus the C-H BDE for complexes 3 and 4 showed a linear dependency (Figure 9), which is characteristic of the HAT reaction. The second order rate constant ($k_2$) values obtained for the two complexes indicated that complex 4 is more reactive than complex 3 towards alkane substrates (C-H activation), in accordance with its lower stability.

![Figure 9. Comparison of log $k_2^*$ v/s bond dissociation energy (BDE) of different alkanes between complexes 3, 4 and [Fe$^{IV}$(O)(N4Py)]$^{2+}$.](image)

The log $k_2^*$ versus C-H BDE plot indicates that the reactivity rates towards HAT reactions are increased from [Fe$^{IV}$(O)(N4Py)]$^{2+}$ to complex 3 to complex 4 by approximately one order of magnitude, i.e. successive replacement of the pyridylmethyl arms of N4Py with (N-methylbenzimidazolyl)methyl arms leads to an increase in the reactivity rate of the corresponding Fe(IV) oxo complex. The introduction of N-methylbenzimidazole donor moieties did not appear to lead to any significant steric inhibition of substrate access to the Fe-oxo center, as evidenced by similar $k_2$ values for the reactions of 4 in separate reactions with sterically bulky...
9,10-dihydroanthracene and the smaller 1,4-cyclohexadiene. Therefore, the reactivity trends exhibited by complexes 3 and 4 could be attributed to the electronic influence of the ligand system (cf. paper I for detailed discussion).

2.7.2 Oxygen-atom transfer (OAT) reactions

![Scheme 4. Oxygen atom transfer (OAT) to thioanisole by complex 3 (or, 4) at 243 K.](image)

The oxo transfer reactivities of 3 and 4 were investigated using thioanisole (PhSCH$_3$) as a substrate (Scheme 4). Both complexes oxidized thioanisole to its sulfoxide at 243 K, in very good yields. Complex 4 reacted faster and gave slightly higher yield than 3 (88 vs 84%). During the course of the reaction, both complexes were converted into their corresponding Fe(II) precursors as identified by UV/Vis spectrophotometry (cf. paper I for details). In presence of excess substrate (5-20 equivalents w.r.t. complex 3 or 4) the reaction showed pseudo-first order behaviour and the observed rate constant ($k_{obs}$) was linearly dependent on substrate concentration. From this linear plot, a second order rate constant ($k_2$) with a value of $3.3 \times 10^{-2}$ M$^{-1}$ s$^{-1}$ was obtained for complex 3 and $3.1 \times 10^{-1}$ M$^{-1}$ s$^{-1}$ for complex 4. Comparing the reactivities between complexes 3, 4 and [Fe$^{IV}$(O)(N4Py)]$^{2+}$ in thioanisole oxidation, it can be concluded that the reactivity is increased ten-fold in the order [Fe$^{IV}$(O)(N4Py)]$^{2+}$ < 3 < 4. Clearly, the (N-methyl)benzimidazole substituent plays a positive role in enhancing the OAT reactivity in a systematic manner.

2.8 Computational studies on the HAT reactivity by the Fe(IV) oxo complexes

The excellent reactivities of the Fe(IV) oxo complexes 3 and 4 in HAT processes can be explained on the basis of the two-state reactivity model as proposed by Shaik.$^{39a,b,d,g,h}$ This involves the transition of reaction surfaces between a triplet
(S = 1) state and a quintet (S = 2) state (cf. Section 2.1.2). The lowest energy path for methane activation by complex 3 is shown in Figure 10 (cf. Paper I for more details). The ground spin state of complex 3 is a triplet (S = 1) (3A). The methane activation via the triplet Fe-oxo (3A) state leads a release of 7.5 kcal/mol energy (cf. Paper I for more details). On the other hand, the methane activation via a quintet Fe-oxo (5A) state leads to a release of 25.8 kcal/mol energy (cf. Paper I for more details). Thus, a reaction that proceeds via spin crossover from the 3A ground state to the 5A state will have significantly lower activation energy than the pure triplet pathway, in keeping with the two-state reactivity model, and the computational study indicates that both complexes 3 and 4 react with substrates via this pathway, as has previously been computed for alkane oxidation by [FeIV(O)(N4Py)]2+.39b

Figure 10. B3LYP potential energy surface for reaction of 3A/5A and methane (B) to give methanol-substituted complexes 3E and 5E. Energy values are in ΔG in kcal/mol relative to 3A+B.

2.9 Catalytic oxidation reactions on alkanes with Fe(II) complexes

The catalytic activities of the two Fe(II) complexes, 1(ClO4)2 and 2(ClO4)2, were also investigated in the oxidation of different alkanes, using hydrogen peroxide (H2O2), peracetic acid (PAA) or meta-chloroperoxybenzoic acid (mCPBA) as oxidant.

Complex 1(ClO4)2 or 2(ClO4)2 oxidizes cyclohexane to produce cyclohexanol and cyclohexanone in the presence of H2O2. The complexes gave similar turnover numbers for the formation of the two products, and the overall yields were also similar (39% for 1(ClO4)2 and 32% for 2(ClO4)2, based on oxidant). The alcohol/ketone (A/K) ratio was found to be low (1.2) in both cases, implicating the possible involvement of freely diffusing carbon centered radicals that are trapped by
molecular oxygen, followed by a Russell termination step. Furthermore, the kinetic isotope effect (KIE) was determined for the formation of cyclohexanol in competition experiments between cyclohexane and its d12 isotopomer. The KIE values obtained for 1(ClO₄)₂ and 2(ClO₄)₂ were 1.45 and 1.7 respectively, and are consistent with the involvement of a hydroxyl radical in the rate-determining step of hydrogen atom abstraction from a C-H bond.

The oxidation of adamantane by 1(ClO₄)₂/2(ClO₄)₂ was examined to probe the nature of the H-abstracting species, on the basis of the tertiary to secondary (C3/C2) C-H bond selectivity. The C3/C2 parameters in this reaction were small (the normalized C3/C2 ratio obtained was 3.6 for 1(ClO₄)₂ and 4.5 for 2(ClO₄)₂), and thus consistent with the implication of a highly reactive and poorly selective species. Finally, complex 1(ClO₄)₂/2(ClO₄)₂ together with H₂O₂ oxidized cis-1,2-dimethyleclohexane (cis-DMCH) to both cis- and trans-1,2-dimethylcyclohexanol. The reaction took place without retention of cis-configuration, again implicating a radical reaction rather than a metal-based reaction. Overall, the reactivity patterns that arise from the oxidation of these mechanistic probes are consistent with Fenton-type activation of H₂O₂ to generate hydroxyl radicals that then attack the substrate, generating freely diffusing carbon-centered radicals.

Analogous reactions were carried out using peracids. When PAA was used as an oxidant, both the conversion and turnover numbers diminished (cf. paper II) but mCPBA gave a catalytic efficiency analogous to H₂O₂. An overall yield of 30% was obtained for complex 1(ClO₄)₂ with a TON of 23 for A and 6.9 for K, and complex 2(ClO₄)₂ produced an overall yield 32.5% with a TON of 22.3 for A, 10.2 for K 10.2 (cf. paper II). The A/K ratios were slightly increased in favour of the alcohol product (for complex 1(ClO₄)₂, A/K ~ 3; for complex 2(ClO₄)₂, A/K ~ 2). Furthermore, the KIE values estimated in the competitive oxidation of cyclohexane and its perdeuterated analogue were found to be higher than with H₂O₂ for both complexes (4.2 for complex 1(ClO₄)₂ and 4.5 for complex 2(ClO₄)₂). On the basis of the improved A/K ratio and the comparatively higher KIE values, a significant participation of hydroxyl radicals in the peracid-based oxidations may be excluded.

Further, selectivity probes indicated that oxidation with peracids involve species more selective than those involved with H₂O₂. For example, in the oxidation of adamantane by 1 (ClO₄)₂/peracid, the C3/C2 parameters were found to be higher (the normalized C3/C2 ratio obtained for 1 was 15.8 with PAA and 11.4 with mCPBA, as opposed to 3.5 for H₂O₂). For complex 2, the normalized C3/C2 parameters were 15.0 (with PAA) and 12.3 (with mCPBA). More interestingly, the C3/C2 selectivity/ratio in the oxidation of cis-DMCH by 1 was around 1 with H₂O₂, but this selectivity was found be approximately 12 with PAA/mCPBA. Finally, the oxidation of cis-DMCH was found to occur without stereoretention, pointing towards the existence of long-lived carbon-centered radicals.
Overall, the reactivity patterns exhibited by the Fe(II) complexes in H₂O₂ or peracid media are comparable to those observed for [Fe²⁺(N₄Py)(CH₃CN)](ClO₄)₂⁵¹,⁵² suggesting that all these complexes follow the same mechanistic patterns under the conditions described above (cf. paper II for detailed discussion).

2.11 Summary and Conclusion

Two new pentadentate N₅-donor ligands have been synthesized, and their corresponding Fe(II) complexes have been prepared and fully characterized. High valent Fe(IV) oxo complexes have been synthesized by reaction of the Fe(II) complexes with the two electron oxidant PhIO in CH₃CN. The Fe(IV) oxo complexes have been characterized by UV/Vis spectroscopy, high resolution mass spectrometry and Mössbauer spectroscopy. The Mössbauer spectra of the Fe(IV) oxo complexes have established that they contain low spin (S = 1) Fe(IV) ions, and this assignment is further supported by DFT calculations indicating an S = 1 ground state. The reactivities of the Fe(IV) oxo complexes have been investigated in hydrogen atom transfer (HAT) and oxygen atom transfer (OAT) processes. The HAT reactivity of the Fe(IV) oxo complexes has been modelled by DFT calculations which indicate a two-state reactivity model involving a spin crossover from the triplet (S = 1) ground state to a quintet (S = 2) transition state. Catalytic oxidation of alkane substrates by the Fe(II) complexes in H₂O₂ and peracid media have also been investigated. Measurement of kinetic isotope effects and the use of specific substrates as mechanistic probes indicate the involvement of hydroxyl radicals in the H₂O₂-based catalytic system, while in the peracid-based catalytic systems any significant participation of hydroxyl radicals can be excluded.

2.12 References


Chapter 3.

Stereospecific and selective C-H hydroxylation and C=C oxidation by H₂O₂ mediated by Fe(II) complexes of tetradeutate ligands: steric and electronic influences on the reactivity

3.1 Introduction: Oxidative transformation of a chemical bond

For the purpose of this thesis, an oxidative transformation of a chemical bond can be defined as the addition/insertion of oxygen inside that bond. This chapter will focus on the oxidation of C-H and C=C bonds.

3.1.1 C-H bond oxidation

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.

\[
\begin{align*}
\text{CH}_4 + \text{H}_2\text{O} &\xrightarrow{700-850 ^\circ C, 40 \text{ Bar}, \text{Ni-catalyst}} \text{CO} + 3\text{H}_2 \\
\text{CO} + 2\text{H}_2 &\xrightarrow{200-4000 ^\circ C, 50-350 \text{ Bar}, \text{Cu-ZnO/Al}_2\text{O}_3} \text{CH}_3\text{OH}
\end{align*}
\]

Scheme 1. Schematic depiction of the catalytic reactions involved in industrial production of methanol from methane.²
3.1.2 C=C bond oxidation

Alkenes/olefins contain C=C bonds and oxidations of olefins lead to formation of epoxides, syn-diols, alcohols, aldehydes, ketones etc. that serve as precursors for useful fine chemicals.\(^3\) Selective oxidation of olefins is also a challenging field of synthetic research, and such oxidations will be discussed in Chapter 4.

3.2 Oxidation reactions in Nature

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.\(^4\)-\(^5\) 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.\(^6\)-\(^9\) The cytochrome P450 enzymes have been extensively studied and their catalytic cycles have been well interpreted/established.\(^5\) The C-H hydroxylation is carried out by an oxo-Fe(IV) porphyrin radical cation by ‘rebound mechanism’ as proposed by Groves et al.\(^10\) 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.\(^4\),\(^11\)-\(^13\). The next section will discuss this class of non-heme iron dependent enzymes in greater details.

3.3 Rieske oxygenases: Structure and function

Rieske oxygenases are multi-component non-heme iron enzymes found in bacteria.\(^4\) They have two components in their active sites:\(^4\) (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*.\(^14\)
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.\textsuperscript{4,15-17} Besides cis-dihydroxylation, these enzymes are also known to catalyze benzylic hydroxylation, sulfoxidation, desaturation and O- and N-dealkylation.\textsuperscript{15}

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.\textsuperscript{9} 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.\textsuperscript{18} 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\textsuperscript{5,19}) and a hydroxynaphthalene 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\textsuperscript{5,19,20}), which subsequently reacts with naphthalene to form the Fe(III) alkoxyhydroxynaphthalene species (Figure 2).\textsuperscript{4,11,21} 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.
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 O₂ or H₂O₂. An additional goal of this bioinspired approach has been to trap/isolate, identify and characterize high valent Fe(V) oxo intermediates analogous to those postulated in the catalytic cycles of Rieske oxygenases.

3.4 Model synthetic non-heme iron complexes: Background and motivation of the present study

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.²²-²⁶ 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.\textsuperscript{26-28} Mechanistic probes employed for these complexes implicate the involvement of an Fe(\text{V})(O)(OH) active oxidant during the catalytic process.\textsuperscript{26} The formation of such high valent Fe(V) oxo species has been further verified by variable-temperature mass spectroscopy (VT-MS),\textsuperscript{29} EPR spectroscopy,\textsuperscript{30} isotope labeling studies and DFT calculations.\textsuperscript{27} The involvement of an iron(V)-oxo species as an active oxidant has also been proposed in some other catalytic systems.\textsuperscript{31-33} In parallel, there are thus far three Fe(V) oxo complexes that have been fully characterized using spectroscopy.\textsuperscript{34}

The Fe(\text{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\textsubscript{A} and O\textsubscript{B}, which are connected through a prototopic oxo-hydroxo tautomerism (involving proton shift from the hydroxide to the terminal oxo ligand).\textsuperscript{27,29} 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 \textsuperscript{18}O incorporation provides indirect evidence for the relative reactivities of the two tautomers in C-H hydroxylation reactions.\textsuperscript{27} 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.\textsuperscript{23a,31a} 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,\textsuperscript{31a} 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.\textsuperscript{35}

The relative reactivities of O\textsubscript{A} and O\textsubscript{B} is influenced by the nature of the ligand. Introduction of different electron-donating and -withdrawing groups (e.g. Me\textsubscript{2}N, MeO, Me, NO\textsubscript{2}, Cl, F etc.) in the \(\alpha\)- and \(\gamma\)-positions of the pyridyl ring of PyTACN affects the relative reactivity of O\textsubscript{A} and O\textsubscript{B} both electronically and sterically.\textsuperscript{36} This unique feature found in the Fe(PyTACN) systems served as an inspiration for further

\[ \text{R} = \text{H, } [\text{Fe}^{\text{II}}(\text{Me}_{\text{2}}\text{N(PyTACN)(OTf)}_{\text{2}}] \]
\[ \text{R} = \text{Me, } [\text{Fe}^{\text{II}}(\text{Me}_{\text{2}}\text{MePyTACN)(OTf)}_{\text{2}}] \]

Figure 3. The oxo-hydroxo tautomerism observed in the Fe(PyTACN) family of complexes.
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.

3.5 Ligands used in this study

In the present study, three new tetradentate N4 ligands were developed (Figure 4). 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,MeBzImTACN ligand), an (N-methyl)imidazolylmethyl arm (the Me2,MeImTACN ligand), or a (3,5-dimethyl)pyrazolylethyl arm (the Me2,Me2PyzTACN 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. The basicity order for the different side arms is as follows: (N-methyl)imidazole (pKa of conjugate acid 7.06) > (N-methyl)benzimidazole (pKa of conjugate acid 5.41) ~ pyridine (pKa of conjugate acid 5.22) > (3,5-dimethyl)pyrazole (pKa of conjugate acid 4.12). At the same time, the different heterocyclic N-donor moieties possess different steric bulkiness.

The details of the syntheses of all three ligands are described in papers III and IV.

3.6 Synthesis and characterization of the Fe(II) complexes

The Fe(II) complexes of the three ligands were synthesized by reaction with [FeII(CH3CN)2(CF3SO3)2] (cf. paper II and III for detailed synthetic procedures). Figure 5 describes the structures of the three new Fe(II) complexes, [FeII(Me2,MeBzImTACN)(CF3SO3)2] (1OTf), [FeII(Me2,MeImTACN)(CF3SO3)2] (2OTf) and [FeII(Me2,Me2PyzTACN)(CF3SO3)2] (3OTf). The three complexes were characterized by mass spectroscopy, 1H-NMR spectroscopy, elemental analysis, IR-spectroscopy and UV/Vis spectroscopy (cf. papers III and IV for detailed characterizations). The 1H-NMR spectra are paramagnetically shifted; they contain
broad peaks with a spectral window range from -20 to 140 ppm, indicating that the complexes possess high spin Fe(II) ions (cf. Supplementary Materials for papers III and IV).

Figure 5. The structures of the Fe(II) complexes investigated in this study.

3.7 Crystal and molecular structures

Complexes $1^{OTf}$ and $3^{OTf}$ were also characterized by X-ray crystallography. The crystal structures (Figure 6) reveal that in both compounds, the Fe(II) center is in a distorted octahedral coordination environment with four sites occupied by the four nitrogen atoms of the tetradentate ligands, leaving two cis-sites available for binding with two triflate anions. The Fe-N and Fe-O bond distances lie in the ranges consistent with the presence of a high spin Fe(II) center, as reported for the Fe(PyTACN) family of complexes and other related Fe(II) complexes.$^{25a,36}$ The Fe-N(benzimidazole) bond distance is 2.134(7) Å in complex $1^{OTf}$ and the Fe-N(pyrazole) bond distance is 2.209(3) Å in complex $3^{OTf}$ (cf. papers III and IV for detailed crystallographic data, bond distances and bond angles) while the Fe-N(pyridine) bond distance is 2.165(4) Å in [Fe$^{II}$(Me$_2$PyzTACN)(CF$_3$SO$_3$)$_2$]$^{26a}$ and 2.246(2) Å in the more sterically hindered [Fe$^{II}$(Me$_2$MePyTACN)(CF$_3$SO$_3$)$_2$].$^{37}$
3.8 Catalytic oxidation studies

3.8.1 C-H bond oxidation of alkanes

The three Fe(II) complexes were investigated in the catalytic oxidation of various alkanes, using H₂O₂ 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) (cf. papers III and IV for detailed catalytic results). 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 1OTf; 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 7). 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 7. Time course for the oxidation of cyclohexane in presence of H₂O₂ catalyzed by 1OTf.

When the kinetic isotope effect (KIE) was determined in a competitive reaction between cyclohexane and its fully deuterated isotopomer, the values obtained for complexes 1OTf, 2OTf and 3OTf 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 (cf. papers III and IV for details) 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 (cf. papers III and IV for details). 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.
3.8.2 Oxidation of olefin substrates

Complexes $1^{\text{OTf}}$, $2^{\text{OTf}}$ and $3^{\text{OTf}}$ also catalyzed the oxidation of $\text{cis}$-cyclooctene to produce both $\text{cis}$-cyclooctene epoxide (E) and $\text{syn}$-cycloctane-1,2-diol (D) (Scheme 3) (cf. papers III and IV for detailed analysis). The complexes $1^{\text{OTf}}$ and $2^{\text{OTf}}$ were found to slightly favour the formation of $\text{syn}$-diol over epoxide. Formation of $\text{syn}$-cyclooctane-1,2-diol is indicative of the involvement of an Fe(V)(O) oxidant (vide supra, Section 3.3) as originally proposed for the Fe(TPA) and Fe(BPMEN) complexes and subsequently observed for the Fe(PyTACN) family of complexes. Isotope labeling studies were able to provide further information re the nature of the active metal-based oxidant, as discussed below.

3.9 Isotope labeling study.

Isotope labeling is a very useful technique to characterize the nature of a metal-based oxidant and also to derive mechanistic conclusions. Therefore, these studies have also been employed in the present research. Complexes $1^{\text{OTf}}$, $2^{\text{OTf}}$ and $3^{\text{OTf}}$ incorporated different amounts (percentages) of $^{18}$O into alcohol products in the oxidation of alkanes. In the presence of 10 eq of $H_2^{16}$O$_2$ and 1000 eq of $H_2^{18}$O, the levels of water incorporation into alcohol product in the oxidation of cyclohexane were 48, 39 and 3% for complexes $1^{\text{OTf}}$, $2^{\text{OTf}}$ and $3^{\text{OTf}}$, respectively (Scheme 4, cf. papers III and IV). Complementary experiments performed with 10 equiv of $H_2^{18}$O$_2$ and 1000 equiv of $H_2^{16}$O showed that peroxide was the source of the remaining oxygen incorporated into the alcohol product.

Interestingly, in the oxidation of substrates containing tertiary C-H bonds ($\text{cis}$-DMCH and adamantane), the extent of incorporation of $^{18}$O from water into products was dramatically affected by the specific catalyst used. For example, in the oxidation of $\text{cis}$-DMCH in the presence of 10 eq of $H_2^{16}$O$_2$ and 1000 eq of $H_2^{18}$O, complex $1^{\text{OTf}}$ incorporated 24% water into product while complex $2^{\text{OTf}}$ incorporated 31% water into product. However, under similar conditions, complex $3^{\text{OTf}}$ did not incorporate any significant amount of oxygen originating from water into the alcohol product.
Scheme 4. Incorporation of labeled oxygen from H$_2^{18}$O in C-H hydroxylation catalyzed by Fe(II) complexes.

All complexes incorporate > 90% of $^{18}$O into the syn-diol product in the oxidation of cis-cyclooctene. These results suggest that for all three complexes, an Fe(V)(O)(OH) species containing one oxygen from water and the other oxygen from peroxide is responsible for the observed isotopic pattern. On the other hand, the extent of $^{18}$O incorporation in the epoxide is different for each complex (Table 1).

**Table 1.** $^{18}$O incorporation from H$_2^{18}$O in C-H hydroxylation reactions mediated by different Fe(II)-complexes$^{(1)}$

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Complex $^{1}_{OTf}$</th>
<th>Complex $^{2}_{OTf}$</th>
<th>Complex $^{3}_{OTf}$</th>
<th>Complex $^{4}_{OTf}$</th>
<th>Complex $^{5}_{OTf}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexane</td>
<td>48</td>
<td>39</td>
<td>3</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>Cyclohexane-d$_{12}$</td>
<td>48</td>
<td>NA</td>
<td>3</td>
<td>40</td>
<td>NA</td>
</tr>
<tr>
<td>Cyclooctane</td>
<td>41</td>
<td>43</td>
<td>3</td>
<td>44</td>
<td>NA</td>
</tr>
<tr>
<td>Cis-DMCH</td>
<td>26</td>
<td>31</td>
<td>0</td>
<td>79</td>
<td>2</td>
</tr>
<tr>
<td>Adamantane</td>
<td>28</td>
<td>39</td>
<td>0</td>
<td>74</td>
<td>3</td>
</tr>
<tr>
<td>Cis-cyclooctene epoxide$^{(4)}$</td>
<td>24</td>
<td>36</td>
<td>2</td>
<td>77</td>
<td>5</td>
</tr>
<tr>
<td>Syn-cyclooctane-1,2-diol$^{(4)}$</td>
<td>98</td>
<td>92</td>
<td>97</td>
<td>97</td>
<td>78</td>
</tr>
</tbody>
</table>

$^{(1)}$ Reaction conditions: catalyst:H$_2$O$_2$:H$_2^{18}$O:substrate = 1:10:1000:1000, CH$_3$CN, RT, air; $^{(2)}$ [Fe$^{II}$($^{3}$H$_2$PyTACN)(CF$_3$SO$_3$)$_2$]; $^{(3)}$ [Fe$^{II}$($^{3}$H$_2$Me$_2$PyTACN)(CF$_3$SO$_3$)$_2$]; $^{(4)}$ cis-cyclooctene was employed as the substrate.
3.10 Discussion

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 5) can also be applied for the Fe(II) complexes 1OTf, 2OTf and 3OTf.

Scheme 5. The mechanism of C-H hydroxylation reaction catalyzed by Fe(II) complexes.

According to the proposed mechanism depicted in Scheme 5, a highly electrophilic [FeV(O)(OH)(LN4)]2+ oxidant (O), is formed via water-assisted cleavage of the hydroperoxide intermediate [FeIII(OOH)(OH2)(LN4)]2+ (see also Figs 2 and 3 above). Species O can exist in two tautomeric forms: OA and OB, which differ in the relative orientation of the side arm connected to TACN ring with respect to the Fe-V=O bond (cf. Fig 3 and Scheme 6). For example, in the case of [FeV(O)(OH)(Me2,MeBzImTACN)]2+, the tautomer OA refers to the orientation of the (N-methyl)benzimidazolyl ring parallel to the FeV=O bond and OB refers to the orientation of the (N-methyl)benzimidazolyl ring perpendicular to the FeV=O bond (Scheme 6). The relative reactivity of the OA and OB 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,MeBzImTACN, Me2,MeImTACN, Me2,Me2PyzTACN etc.), and the differences in the relative reactivities of the tautomers result in the different isotope labelling patterns exhibited by the corresponding Fe-complexes.
Scheme 6. The proposed structures of the two tautomers OA and OB of [FeV(O)(OH)(Me2,MeBzImTACN)]2+. It appears that the steric bulk of the side arm dictates the relative reactivities of the tautomers. It has been found that for the Fe(PyTACN) family of complexes, there are two distinct categories: for class I catalysts, the tautomers OA and OB are equally active, resulting in a large percentage of incorporation of oxygen from water into the cyclohexanol product (39-50%), while for class II catalysts, OB is more active than OA, resulting in lower percentages of incorporation of water-derived oxygen into cyclohexanol.27 For complexes 1OTf and 2OTf, both OA and OB are operative in the oxidation of secondary C-H bonds, giving 39-48% 18O-incorporated product from labelled water. However, when the substrate contains tertiary C-H bonds, OB reacts faster than OA in the case of complex 1OTf, resulting in lower 18O incorporation (Table 2). On the other hand, for complex 2OTf, the reactivities of OA and OB are more or less comparable. These results suggest that the (N-methyl)benzimidazolyl moiety exerts a greater steric influence than the (N-methyl)imidazolyl moiety in protecting the approach of (a bulky) substrate towards the Fe-oxo unit of the OA tautomer. This makes the tautomer OB intrinsically more reactive than OA, particularly for substrates containing tertiary C-H bonds. On the other hand, the very low level of incorporation of water-derived oxygen into hydroxylated products by 3OTf, regardless of secondary and tertiary C-H bonds, signifies that OB performs the hydroxylation reaction exclusively and that the orientation of the methyl group of the substituted pyrazole side arm induces large steric inhibition on the Fe-oxo unit of OA tautomer.
3.11 Summary and conclusion

Three new tetradentate N4 ligands have been prepared. The corresponding Fe(II) complexes have been synthesized and fully characterized. The catalytic C-H hydroxylation of alkanes and olefin oxidation reactions by the three Fe(II) complexes have been investigated using H₂O₂. 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. Isotope labelling experiments performed with these complexes indicate that the active oxidant is an Fe(V)(O)(OH) species which is formed via water assisted heterolytic O-O cleavage of an Fe(III)(HOOH)(OH₂) species. The Fe(V)(O)(OH) species can exist in two tautomeric forms. Isotope labelling studies have shown that the two tautomeric forms 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 labelling 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.

3.12 References


53


Chapter 4.

Asymmetric epoxidation of olefins by hydrogen peroxide, catalyzed by non-heme Fe(II) complexes of chiral tetradequate ligands

4.1 Introduction

Epoxidation reactions involve the formation of three membered cyclic ethers (epoxides) through oxidation of C=C bonds. Epoxides are used as versatile intermediates in organic syntheses owing to their inherent polarity and strained structure, making them susceptible to attack by nucleophiles, electrophiles, acids, bases etc. \(^1\) This chapter deals with asymmetric epoxidation of olefins.

4.2 Asymmetric epoxidation

Asymmetric epoxidation is one of the most synthetically important organic transformation reactions since it can produce optically active (chiral) epoxides with up to two stereogenic centers. \(^1\) Chiral epoxides are used as precursors to many biologically active chiral molecules that are useful in pharmacy and the chemical industry. \(^1\)

The cytochromes P450 constitute a very large and versatile family of thiolate-ligated heme-containing enzymes and are amongst the most well studied metalloenzymes. \(^1\) \(^f\) \(^,\) \(^2\) They catalyze a wide range of oxidation reactions of biological relevance, including olefin epoxidations, using molecular oxygen as terminal oxidant with excellent efficiency. \(^2\) These enzymes have thus inspired chemists to investigate the use of porphyrin-based iron catalysts in asymmetric epoxidation reactions. Groves and coworkers reported the first asymmetric epoxidation catalyzed by a chiral iron porphyrin complex. \(^3\) Thereafter, several other chiral metalloporphyrin-based catalysts have been reported for asymmetric epoxidation. \(^1\) \(^f\) \(^,\) \(^4\) \(^-\) \(^7\)

Other transition metal-based catalysts have been extensively employed for epoxidation reactions in the last three decades. In this area, the investigations by Katsuki and Sharpless on the epoxidation of allylic alcohols (Scheme 1) \(^8\) and the development of manganese salen complexes in the epoxidation of unfunctionalized alkenes by Katsuki et al \(^9\) and Jacobsen et al \(^10\) are particularly notable.
4.3 Asymmetric epoxidation of olefins using synthetic non-heme iron complexes: Background and motivation for the present study

Iron-based catalytic systems have often found potential interest because of the inexpensiveness, non-toxicity and ready availability of iron. Although iron porphyrin-based catalysts have been well studied for a long time (vide supra), non-heme iron-based catalysts have been much less explored. In 2007, Beller and co-workers reported a new library of ligands for the iron-catalyzed epoxidation of stilbene derivatives with high enantioselectivity, using H₂O₂ as the oxidant. These studies bore promise for future development of non-heme iron-based catalysts for such oxidations. Many other iron complexes have thereafter been prepared in order to improve the efficiency and enantioselectivity in asymmetric epoxidation reactions, and some of these complexes have been found to exhibit very promising catalytic properties. The use of novel chiral iron-based catalysts together with green oxidants such as dioxygen or H₂O₂ has become a growing research area in the field of asymmetric epoxidation.
The development of efficient iron catalysts for asymmetric epoxidation is a challenging task. The factors that determine/affect the efficiency (in terms of substrate conversion or product yield) and enantioselectivity are not understood and therefore need to be thoroughly investigated. It has been previously observed that the presence of a catalytic amount of carboxylic acid can enhance the yield as well as enantioselectivity in iron-based catalytic systems.\textsuperscript{13d,15} Costas and coworkers have investigated the electronic properties of the ligands on the catalytic properties of a series of Fe(II) complexes in asymmetric epoxidation reactions (Figure 1).\textsuperscript{15} It was found that complex \textsuperscript{Me2N1} (Fig 1) showed excellent catalytic efficiency with high enantioselectivity.\textsuperscript{15} Assuming the formation of a high-valent iron-oxo active oxidant, the high activity of \textsuperscript{Me2N1} might be explained by the electron-donating property of the ligand, which may enhance the electrophilicity of the iron-oxo moiety to give high conversion into products.\textsuperscript{15} However, proper mechanistic investigations that can explain the high catalytic efficiency of complex \textsuperscript{Me2N1} remain to be undertaken. The present study aimed to examine the possible effects on iron-based asymmetric epoxidation reactions of systematic replacement of the pyridyl moieties of the PDP framework (Figure 1) with (N-methyl)benzimidazolyl moieties.

### 4.4 Ligands used in this present study

The present work has been developed on the basis of two chiral tetradentate ligands \textsuperscript{L1} (1-methyl-2-\{((S)-2-[(S)-1-(1-methylbenzimidazol-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-yl} methyl)benzimidazole) and \textsuperscript{L2} (1-methyl-2-\{((S)-2-[(S)-1-(pyridin-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-yl} methyl)benzimidazole) (Figure 2). Ligand \textsuperscript{L1} has a symmetric structure with two (N-methyl)benzimidazolylmethyl moieties being attached to the two nitrogen atoms of the chiral bispyrrolidine backbone. On the other hand, ligand \textsuperscript{L2} has an asymmetric structure with one pyridylmethyl moiety and one (N-methyl)benzimidazolylmethyl moiety being attached to the two nitrogen atoms of the chiral bispyrrolidine backbone.

![Figure 2](image-url)
Ligand L\textsuperscript{1} was synthesized in one step by reaction of one equiv of \((S,S)-2,2'\)-bispyrrolidine D-tartrate with 2.3 equiv of 2-(chloromethyl)-1-methylbenzimidazole in the presence of excess base (1M NaOH solution) (Scheme 2). Ligand L\textsuperscript{2} was synthesized in two steps (Scheme 2). In the first step, one equiv of \((S,S)-2,2'\)-bispyrrolidine D-tartrate was reacted with one equiv of 2-(chloromethyl)pyridine hydrochloride in the presence of excess NaOH to form 2-\{(\textit{S})-2-[\textit{S})-pyrrolidin-2-yl]pyrrolidin-1-yl)methyl\}pyridine (it may be noted that there is only one unique chiral product because of the identical chiralities of the two stereogenic centers of the bispyrrolidine backbone). In the second step, one equiv. of 2-\{(\textit{S})-2-[(\textit{S})-pyrrolidin-2-yl]pyrrolidin-1-yl)methyl\}pyridine was reacted with one equiv of 2-(chloromethyl)-1-methylbenzimidazole in the presence of excess NaOH solution to give the desired ligand L\textsuperscript{2}.

Scheme 2. Schematic presentation of the synthetic routes to ligands L\textsuperscript{1} and L\textsuperscript{2}.

4.5 Synthesis and characterization of the Fe(II) complexes

The Fe(II) complexes of the two chiral ligands L\textsuperscript{1} and L\textsuperscript{2}, namely \([\text{Fe}^{\text{II}}(L^1)(\text{CF}_3\text{SO}_3)_2]\) (1\textsuperscript{OTf}) and \([\text{Fe}^{\text{II}}(L^2)(\text{CF}_3\text{SO}_3)_2]\) (2\textsuperscript{OTf}) (Figure 3), were synthesized by reaction of L\textsuperscript{1} or L\textsuperscript{2} with an equimolar amount of
[Fe\textsuperscript{II}(CH\textsubscript{3}CN)\textsubscript{2}(CF\textsubscript{3}SO\textsubscript{3})\textsubscript{2}] (\textit{cf.} paper V for experimental conditions). Both complexes were obtained as off-white solids. Complex 1\textsubscript{OTf} was characterized by high resolution mass spectroscopy, \textsuperscript{1}H-NMR spectroscopy and FT-IR spectroscopy (\textit{cf.} paper V). The characterization of complex 2\textsubscript{OTf} is underway.

**Figure 3.** The structures of the Fe(II) complexes, [Fe\textsuperscript{II}(L\textsubscript{1})(CF\textsubscript{3}SO\textsubscript{3})\textsubscript{2}] (top left) and [Fe\textsuperscript{II}(L\textsubscript{2})(CF\textsubscript{3}SO\textsubscript{3})\textsubscript{2}] (top right).

**4.6 Crystal and molecular structure of complex 1\textsubscript{OTf}.**

**Figure 4.** The crystal structure (Mercury plot) of complex 1\textsubscript{OTf}; H-atoms have been omitted for clarity. The crystal structure of complex 1\textsubscript{OTf} (Figure 4) reveals that the Fe(II) center is in a distorted octahedral coordination environment with four sites being occupied by the nitrogen atoms of the chiral ligand and the two cis-sites being occupied by two triflate anions. The Fe-N and Fe-O bond distances are in agreement with the presence of a high spin Fe(II) center. A detailed description of the molecular structure of this complex is found in paper V.
4.7 Catalytic asymmetric epoxidation study.

Scheme 3. Catalytic epoxidation of cis-β-methylstyrene with H$_2$O$_2$ by an Fe catalyst in the presence of acetic acid as an additive.

The complex $1^{OTf}$ catalyzed the epoxidation of cis-β-methylstyrene to form the two chiral epoxides with a total yield of 60% and an enantiomeric excess (ee) value of 41% (Scheme 3). The catalytic experiment was performed under conditions similar to those reported earlier in order to enable direct comparison between this catalyst and the series of related iron catalysts reported by Costas and coworkers$^{15}$ (Figure 1 and Table 1).

Table 1. Comparison of conversion of substrate (cis-β-methylstyrene), yield of epoxides and ee’s for different Fe catalysts (cf. Figure 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>AcOH (mol%)</th>
<th>Conversion in % (Yield of epoxides in %)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1^{OTf}$</td>
<td>3</td>
<td>84 (60)</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>$\text{Me}_{2}\text{N}1$</td>
<td>3</td>
<td>100 (87)</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>$\text{H}1$</td>
<td>3</td>
<td>49(26)</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>$\text{Cl}1$</td>
<td>3</td>
<td>32(15)</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>$\text{CO}_{2}\text{Et}1$</td>
<td>3</td>
<td>31(13)</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>$\text{Me}1$</td>
<td>3</td>
<td>31(17)</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>$\text{MeO}1$</td>
<td>3</td>
<td>38(26)</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>$\text{dMM}1$</td>
<td>3</td>
<td>82(67)</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>$\text{pin}1$</td>
<td>3</td>
<td>53(41)</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>$\text{iQuin}1$</td>
<td>3</td>
<td>34(15)</td>
<td>19</td>
</tr>
</tbody>
</table>

As seen in Table 1, complex $1^{OTf}$ is an efficient catalyst for the epoxidation of cis-β-methylstyrene by H$_2$O$_2$, and is surpassed only by $\text{Me}_{2}\text{N}1$ under the same reaction conditions.

The catalytic efficiency of this complex was also investigated for the oxidation of the cyclic enone substrate 2-cyclohex-1-one, which is relatively hard to oxidize. The detailed catalytic results are described in paper V. The collective results indicate that $1^{OTf}$ is able to epoxidize the alkene substrate with good enantioselectivity (> 80%); however, the yields of the epoxide products are low (< 20%) and the conversion of
substrate is moderate. The low yield and conversion may be due to deactivation of the catalyst being more rapid than substrate conversion, when the substrate is not itself rapidly oxidized.

The mechanism of acetic acid-assisted iron-catalyzed epoxidation of olefins was first proposed by Que and co-workers.\textsuperscript{16} It is proposed that an Fe(III)-carboxylate species reacts with \( \text{H}_2\text{O}_2 \) to form an iron(III)-acylperoxo intermediate. Such an intermediate has been trapped very recently by Que and co-workers.\textsuperscript{17} In the next step, acid-assisted heterolytic cleavage of the O-O bond of the iron(III)-acylperoxo intermediate results in the formation of the active oxidant, an oxoiron(V) carboxylate species that transfers the oxygen to the olefin substrate. Spectroscopic studies by Talsi and co-workers\textsuperscript{18} and computational studies by Rajaraman \textit{et al.}\textsuperscript{19} support the formation of an oxoiron(V) carboxylate intermediate. On the other hand, Que, Shaik \textit{et al.}\textsuperscript{20} have carried out computational modeling that suggests that the carboxylate has a redox non-innocent nature and therefore can donate an electron to the metal center to form an oxoiron(IV) carboxyl radical intermediate that serves as the oxygen donor to the substrate (a situation similar to the formation of compound I for Cytochrome P450, where the ferryl moiety is coupled with a porphyrin cation radical, \textit{cf.} Section 3.2). A similar catalytic cycle for complex \textit{1}\textit{OTf} can be inferred for the asymmetric epoxidation of olefins (Scheme 4).

![Scheme 4. The proposed catalytic cycle for olefin epoxidation by non-heme iron-complexes.](image-url)
4.8 Summary and conclusion

Two new chiral tetradentate N4 ligands, L¹ and L², have been synthesized and fully characterized. Ligand L¹ is symmetric and L² is an asymmetric ligand. The Fe(II) complex of ligand L¹ has been fully synthesized and characterized. The catalytic activity of this Fe complex in asymmetric epoxidation reactions of olefins, using H₂O₂ as the oxidant, has been investigated and the initial results indicate that the complex has the potential to initiate good enantioselective epoxidation, but the yields are relatively poor. Further investigations using various other olefin substrates as well as using other reaction conditions (e.g. catalyst loading, carboxylic acid loading) to optimize the yields are warranted. Furthermore, detailed characterization and investigation of the catalytic activity of the Fe(II) complex of the asymmetric ligand L² are in progress.

4.9 References


Chapter 5.

Concluding remarks

Nature uses specific enzymes to carry out specific reactions that are essential for the sustainability of living organisms. This remarkable feature is an underlying reason for most biomimetic research. The goals of such biomimetic studies are to (i) unravel and/or understand the structure and function of a certain enzyme of interest (ii) replicate the function of the enzyme.

5.1 Summary of the present work

The present work describes some functional models of non-heme mononuclear iron oxygenases. The focus of this work is based on two aspects of the enzymatic systems: (i) catalytic properties and (ii) formation (and isolation) of high valent ferryl (Fe(IV) oxo) species.

Two pentadentate nitrogen donor-based ligands have been developed for the purpose of generation and characterization of non-heme Fe(IV) oxo complexes. First, the Fe(II) complexes of these two ligands have been synthesized and fully characterized. Then, the corresponding Fe(IV) oxo complexes have been prepared and characterized by various spectroscopic techniques. The reactivities of these Fe(IV) oxo complexes have been examined towards hydrogen-atom transfer reactions, using a number of alkane substrates, and oxygen-atom transfer reactions using thioanisole. The rates of the reactivities have been measured and these values suggest that both complexes are efficient catalysts for both C-H activation and O-atom transfer. Computational modelling of the transition states of the H-atom transfer process have been performed and they have provided information on the mechanism(s) of C-H activation by the Fe(IV) oxo complexes.

The catalytic properties of Fe(II) complexes have also been investigated. The catalytic activities of the two Fe(II) complexes that are based on the above-mentioned pentadentate ligands have been found to be moderate, and similar to those of some related pentadentate ligand-based Fe(II) complexes. Theoretical studies have been performed to illustrate the catalytic reaction mechanism. In addition, three new tetradentate N4 ligands have been synthesized and their Fe(II) complexes have been fully characterized. These Fe(II) complexes have been found to perform efficient catalytic oxidation of alkanes and alkenes using hydrogen peroxide as co-oxidant. The mechanistic probes have been studied to elucidate the nature of the active oxidant and for the complexes based on tetradentate ligands, the reactions are proposed to proceed via the involvement of Fe(V) oxo-hydroxo species. Such an
active intermediate has been proposed in the catalytic cycle of Rieske oxygenases. Isotope labeling experiments have been performed to understand the origin of oxygen atom in the hydroxylated products. The steric and electronic properties of the ligands have been investigated to draw a dependency of the origin of the oxygen atom to the relative reactivities of the two taotomers of the Fe(V)(O)(OH) species.

Two chiral ligands and their Fe(II) complexes have been synthesized for the purpose of effecting asymmetric epoxidation reactions using the environmentally friendly oxidant hydrogen peroxide. Experiments performed on one of Fe(II) complexes have shown that it is capable of oxidizing olefins with high enantioselectivity. Further investigations of the two complexes are ongoing.

5.2 Future perspective of the present work

The present work has opened some new directions towards catalysis research and the modulation of the reactivity of synthetic high valent ferryl (or, perferryl) complexes by utilizing properly designed ligands. The study provides further understanding of the impact of electron rich/donating sites surrounding the metal center in non-heme mononuclear iron oxygenases (Chapter 2). As and extension, different and more electron-donating ligand moieties can be introduced to attempt modulation of the reactivity of ferryl species in oxidation reactions in a predictable way. The present work will also be useful to construct such ligands and to understand the basics of high valent Fe(IV) oxo chemistry. Furthermore, these studies also emphasise the role of ligands on the catalytic efficiencies mediated by non-heme Fe(II) complexes.

Developing efficient, low cost catalysts that can be utilized in industry remains a challenging task for the synthetic chemists. The studies summarized in Chapters 2-4 provide some useful understanding on how catalyst properties may be tuned by modification of the side arms of a ligand. The excellent catalytic properties of the Fe(II) complexes suggest that they can also be employed for oxidations of many other organic substrates of interest. The trapping and characterization of Fe(V) oxo species is another future aspect of this present work. The Fe(II) complexes of symmetric and asymmetric chiral ligands warrant thorough investigation as catalysts for asymmetric epoxidation reactions. It is likely that both the yields of epoxide products and the enantioselectivities of the reactions may be improved by optimizing the reaction conditions, including carboxylic acid loading and catalyst loading.
Populärvetenskaplig sammanfattning på svenska


Molekylärt syre är ett miljövänligt och därför önskvärt oxidationsmedel. Ett närbesläktat alternativ oxidationsmedel som är nästan lika miljövänligt är väteperioxid. Mycken katalysforskning har fokuserats på att använda syntetiska järnkomplex som katalysatorer med syre eller väteperioxid som ”gröna” oxidationsmedel.

Forskningen som beskrivs i denna avhandling syftar till att efterlikna den katalytiska aktiviteten hos icke-heminnehållande järn-oxygenaser och att bidra till karakterisering och reaktivitetsstudier av högvalenta Fe(IV)-oxo-intermediat. Två högvalenta Fe(IV)-oxo-komplex har karakteriserats och deras reaktivitetsmönster indikerar att ligander med goda elektrongivande egenskaper kan öka hastigheten på de reaktioner som utgör delsteg i oxidationen av kolväten. Dessa observationer hjälper oss att förstå varför vissa elektrondonerande sidokedjor vill aminosyror (imidazolringen i histidin, carboxylatenheterna i aspartat och glutamat) är vanligt förekommande i de aktiva sätena hos många metallenzym som fungerar som oxygenaser; dessa aminosyror hjälper till att stabilisera de högvalenta järn-oxo-intermediat som utför själva oxygeneringsprocessen.

Oxidation av alkaner och alkener som katalyseras av Fe(II)-komplex beskrivs i avhandlingen. Dessa komplex visade sig vara i stånd att utföra oxidation av kolväten med hög stereospecificitet, selektivitet och utmärkt effektivitet. Reaktionerna utfördes med hjälp av väteperoxid som oxidationsmedel, och i närvaro av vatten.

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Non-Heme Fe(IV) Oxo Complexes of Two New Pentadentate Ligands and Their Reactivities Towards Hydrogen- and Oxygen-Atom Transfer Reactions

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Supporting Information

ABSTRACT: Two new pentadentate N5-donor ligands based on the N4Py framework have been synthesized, viz. [N-(1-methyl-2-benzimidazolyl)methyl-N-(2-pyridyl)methyl-N-(bis-2-pyridylmethyl)amine] (L1) and [N-bis(1-methyl-2-benzimidazolyl)methyl-N-(bis-2-pyridylmethyl)amine] (L2), where one or two pyridyl arms of N4Py have been replaced by corresponding (N-methyl)benzimidazolyl-containing arms. The complexes [FeIV(O)(L1)(CH3CN)]2+ (L1 = L1, L2) and [FeIV(O)(L2)]2+ (L = L1, L2), which were characterized by UV/Vis spectroscopy, high resolution mass spectrometry and Mössbauer spectroscopy. The ferryl complexes are relatively stable with half lives at room temperature of 40 h (L = L1) and 2.5 h (L = L2). The redox potentials of the ferrous complexes, visible spectra, and half lives indicate that the ligand field weakens as ligand pyridyl substituents are progressively substituted by (N-methyl)benzimidazolyl moieties. The reactivities of the two ferryl complexes in hydrogen atom transfer (HAT) and oxygen atom transfer (OAT) reactions show that both complexes exhibit high reactivities when compared to the analogous N4Py complexes, and that the normalized HAT rates increase by approximately one order of magnitude for each replacement of a pyridyl moiety, i.e. [FeIV(O)(L1)]2+ exhibits the highest rates; C-H bond activation reactions and oxo transfer reactions, and the reactivities of these different non heme Fe(IV) oxo complexes have been found to vary widely. For example, non-heme high spin (S = 2) Fe(IV) oxo intermediates have been identified as active oxidizing species in the catalytic cycles of E. coli taurine-α-ketoglutarate dioxygenase (TauD),4b propyl-4-hydroxylase,6 halogenase CytC3,6 tyrosine hydroxylase,7 and the aliphatic halogenase SyrB28 by means of various spectroscopic techniques. These reactive intermediates activate C-H bonds in a wide number of substrates, transforming them into hydroxylated, unsaturated, or halogenated products.4b,6,7,9

Introduction.

The interesting chemistry that is exhibited by non-heme iron enzymes has inspired extensive efforts to mimic their high-valent intermediates and emulate their reactivities.2,10 Over the last decade, several non heme Fe(IV) oxo (ferryl) complexes supported by a wide range of pentadentate and tetradentate ligands have been prepared.2,10,11 These Fe(IV) oxo complexes have been investigated for, inter alia, C-H bond activation reactions, C=C bond activation reactions and oxo transfer reactions, and the reactivities of these different non heme Fe(IV) oxo complexes have been found to vary widely. For example, [FeIV(O)(TMC)(CH3CN)]2+ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) can only oxidize substrates with C-H bond dissociation energies (BDE’s) of <80 kcal/mol,12 while [FeIV(O)(N4Py)]2+, (N4Py = N,N-bis(2-pyridylmethyl)-N-bis(2-pyridylmethyl)amine) and [FeIV(O)(Bn-tpen)]2+, (Bn-tpen = N-benzyl-N,N'-tris(2-pyridylmethyl)-1,2-diaminoethane) (Fig.
1) have been shown to oxidize strong C-H bonds, e.g. those in cyclohexane (C-H BDE 99.3 kcal/mol) at room temperature.\textsuperscript{13}

Figure 1. Non heme Fe(IV)-oxo complexes, [Fe\textsuperscript{IV}(O)(N4Py)]\textsuperscript{2+} and [Fe\textsuperscript{IV}(O)(Bn-tpen)].

The spin state on the Fe(IV)-center of the Fe(IV) oxo unit plays a crucial role in terms of reactivity since high spin (S = 2) Fe(IV) oxo complexes have a crucial role in terms of reactivity since high spin (S = 2) Fe(IV) oxo complexes have been demonstrated to be more reactive than low spin (S = 1) Fe(IV) oxo complexes.\textsuperscript{14} A significant aspect of the observed reactivities and spin states of ferryl complexes is that they can be modulated by the various ligand environments supporting the Fe(IV) oxo unit. A high spin (S = 2) Fe(IV) oxo unit may be achieved by adopting a trigonal bipyramidal (TBP) geometry using tetradentate ligands with sufficient steric constraints, as observed in the case of [Fe\textsuperscript{IV}(O)(TMG\textsuperscript{2+}tren)] (TMG = tris(tetramethylguanidino)tren)\textsuperscript{15} and [Fe\textsuperscript{IV}(O)(H\textsubscript{3}buea)] (H\textsubscript{3}buea = tris(2-butylureaethyl)amine)\textsuperscript{16} leading to degeneracy of the second highest occupied molecular orbitals, which have significant d\textsubscript{xy} and d\textsubscript{x\textsuperscript{2}-y\textsuperscript{2}} character. A detailed investigation was recently made on five low spin Fe(IV)-oxo complexes comprising pentadentate pyridine- and amine-based ligands to examine the correlation of the rates of hydrogen atom transfer and oxygen atom transfer processes with their spectroscopic and electrochemical properties which are controlled by the ligand scaffold.\textsuperscript{17} The oxo transfer process to thiioanisole by these five Fe-oxo complexes has been correlated to the redox potential of Fe(IV)/Fe(III) couple which was influenced by the ligands bound to the Fe-oxo unit; however, such a direct correlation could not be concluded in the case of hydrogen abstraction processes.

We wish to investigate whether the reactivity of ferryl complexes can be tuned by modification of the steric and electronic properties of ligands, and whether the reactivity of such complexes can be improved while maintaining thermal stability. For this purpose, we chose to modify/derivatize the N4Py ligand framework.\textsuperscript{18} Among bio-inspired Fe\textsuperscript{IV}=O complexes, [Fe\textsuperscript{IV}(O)(N4Py)]\textsuperscript{2+} has been shown to exhibit the unique combination of powerful oxidative reactivity towards alkanes, enabling it to cleave strong C-H bonds, while at the same time possessing considerable thermal stability; indeed, the stability has been proven sufficient to permit its structure to be characterized by X-ray crystallography.\textsuperscript{19} A number of modifications of the N4Py ligand framework have been made,\textsuperscript{20,21} but they do not include the replacement of the pyridyl group. We were therefore interested in attempting to modify the stability and reactivity of N4Py by tuning the ligand coordination environment, and we chose to introduce (N-methylbenzimidazol-2-yl)methylamine, the (N-methylbenzimidazol-2-yl)methylamine ligand equivalent of the tripodal 2,6-dichlorophenylporphinato dianion (Scheme 1). Ligand L\textsubscript{1} was synthesized by reaction of 3-chloromethyl-1-methylbenzimidazole with one equivalent of 2-chloromethyl-1-methylbenzimidazole in refluxing dry acetone, in the presence of K\textsubscript{2}CO\textsubscript{3} and tetrabutylammonium bromide (Scheme 1). Ligand L\textsubscript{2} was synthesized by reaction of bis(2-pyridyl)methylamine with 2 equivalents of 2-
chloromethyl-1-methylbenzimidazole in the presence of aqueous NaOH solution (Scheme 2).

![Scheme 2. Synthesis of ligand L2.](image1)

The corresponding Fe(II) complexes, [Fe\(^{III}\)(CH\(_3\)CN)(L\(^2\))](ClO\(_4\))\(^2-\) (1(ClO\(_4\))\(^2-\)) and [Fe\(^{III}\)(CH\(_3\)CN)(L\(^2\))](ClO\(_4\))\(^2-\) (2(ClO\(_4\))\(^2-\)), were prepared by reaction of one equivalent of L\(^2\)/L\(^1\) with one equivalent of hydrated Fe(ClO\(_4\))\(^2-\) in a minimum amount of dry acetonitrile solvent at room temperature (Scheme 3). Both complexes 1(ClO\(_4\))\(^2-\) and 2(ClO\(_4\))\(^2-\) were isolated and obtained as air-stable solids.

![Scheme 3. Synthesis of Fe(II)-complexes, [Fe\(^{III}\)(CH\(_3\)CN)(L\(^1\))](ClO\(_4\))\(^2-\) (1(ClO\(_4\))\(^2-\)) and [Fe\(^{III}\)(CH\(_3\)CN)(L\(^2\))](ClO\(_4\))\(^2-\) (2(ClO\(_4\))\(^2-\)).](image2)

The natural abundance \(^{57}\)Fe Mössbauer spectra of the solid samples of complexes 1(ClO\(_4\))\(^2-\) and 2(ClO\(_4\))\(^2-\) measured at 80 K confirm the presence of low spin Fe(II) in both complexes (Figure 4). The isomeric shift values (δ) and quadrupole splitting values (ΔE\(_Q\)) are listed in Table 1. Single-point DFT energy calculations on the S=0, S=1, and S=2 spin states of 1(ClO\(_4\))\(^2-\) and 2(ClO\(_4\))\(^2-\) using the structures obtained from the X-ray diffraction data, confirm the S=0 spin state as the ground-state of each complex.

![Figure 3. UV/Vis spectra of complexes 1(ClO\(_4\))\(^2-\) (gray) and 2(ClO\(_4\))\(^2-\) (black) (0.25 mM) in acetonitrile.](image3)

Electrochemistry of complexes 1(ClO\(_4\))\(^2-\) and 2(ClO\(_4\))\(^2-\):

The cyclic voltammograms of complexes 1(ClO\(_4\))\(^2-\) and 2(ClO\(_4\))\(^2-\) were measured in acetonitrile at 298 K using a glassy carbon electrode as the working electrode and SCE as the reference electrode. Complex 1(ClO\(_4\))\(^2-\) showed an irreversible oxidation wave at E\(_{pa}\) = 0.70 V and two reduction potential waves (E\(_{pc}\)) at ca. 0.41 and 0.23 V (Figure S, Supplementary Material). On the other hand, complex 2(ClO\(_4\))\(^2-\) showed an electrochemically reversible redox curve at E\(_{1/2}\) = 0.395 V for the Fe\(^{III}/Fe^{II}\) couple (Figure S, Supplementary Material). In general, strong ligand fields result in higher oxidation potential values for the Fe\(^{III}/Fe^{II}\) couple. [Fe\(^{III}\)(CH\(_3\)CN)(N4Py)](ClO\(_4\))\(^2-\) has a high redox potential value (1.01 V vs SCE, in acetonitrile). Clearly, successive replacement of the pyridyl moieties in N4Py by (N-methyl)benzimidazolyl transfer (MLCT) bands arising from electron transfer from low spin Fe(II) \(^{3d}\) orbitals to the \(\pi^*\) orbitals of the ligand.

![Figure 4. The zero field Mössbauer spectra of complexes 1(ClO\(_4\))\(^2-\) (left) and 2(ClO\(_4\))\(^2-\) (right) collected at Scheme 4.](image4)

Table 1. Mössbauer parameters for complexes 1(ClO\(_4\))\(^2-\) and 2(ClO\(_4\))\(^2-\):

<table>
<thead>
<tr>
<th>Complex</th>
<th>Isomeric shift value (δ) in mm s(^{-1})</th>
<th>Quadrupole splitting value (ΔE(_Q)) in mm s(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(ClO(_4))(^2-)</td>
<td>0.41</td>
<td>0.19</td>
</tr>
<tr>
<td>2(ClO(_4))(^2-)</td>
<td>0.44</td>
<td>0.21</td>
</tr>
</tbody>
</table>
moieties led to a lowering of the oxidation potential value of the corresponding Fe(II) complexes and it may thus be concluded that the ligand field strength of the ligand is concomitantly weakened.

In this specific case, the weak field indicates relatively poor π-acid properties (relative to the equatorial pyridyl substituents in N4Py) exerted by the (N-methyl)benzimidazolyl moieties in ligands L1 and L2.

Crystal and molecular structures of 1(CIO4)2 and 2(CIO4)2.

Single crystals suitable for X-ray diffraction were grown for both 1(CIO4)2 and 2(CIO4)2, and their crystal structures were determined in order to confirm the proposed molecular structures. The structures of the two cationic complexes are shown in Figure 5; relevant crystallographic data are summarized in Table 2 and selected bond distances and bond angles are collated in Table 7 in the experimental section. The crystal structures are similar to that of the "parent" complex [Fe(N4Py)(CH3CN)](ClO4)2 and show that the pentadentate ligands L1 and L2 coordinate as envisaged, with the sixth coordination site at the iron ion being occupied by a (solvent) acetonitrile molecule. The short Fe-N bond lengths (1.9-2.0 Å) observed for both complexes are in agreement with the presence of low spin Fe(II) centers in 1(CIO4)2 and 2(CIO4)2, as observed for Fe3+N4Py(CH3CN)](ClO4)2 and some previously reported related Fe(II) complexes.2,19,20 A comparison between different Fe-N bond distances in 1(CIO4)2, 2(CIO4)2, and [Fe3+(N4Py)(CH3CN)](ClO4)2 are shown in Table 3. It is not possible to discern clear structural trends, but the following observations may be made: The Fe-Npy bond distance (Py = pyridyl) bond distances that are trans with respect to each other in 1(CIO4)2 are non-equivalent (1.948(6) and 1.960(6) Å), while the corresponding distances in the parent complex are virtually equivalent, and the Fe-Npy bond distance that is trans to Fe-NHt {BzIm = (N-methyl)benzimidazolyl} bond is 1.957(6) Å for 1(CIO4)2. For each replacement of a pyridyl moiety by an (N-methyl)benzimidazolyl moiety (going from the parent complex to 1(CIO4)2 to 2(CIO4)2), the specific Fe-N bond that is subject to the change is lengthened. Replacement of a pyridyl moiety by a second (N-methyl)benzimidazolyl moiety in 2(CIO4)2 results in a lengthening of both equatorial Fe-Npy bond distances (1.964(3) and 1.983(3) Å) with respect to 1(CIO4)2. The acetonitrile molecule becomes more tightly bound to the Fe ion in 2(CIO4)2 (1.901(3) Å) than in 1(CIO4)2 (1.909(6) Å), and, consequently, the Fe-Namide bond distance, trans to the acetonitrile ligand, follows the reverse trend – it is lengthened by approximately 0.048 Å, going from 1(CIO4)2 to 2(CIO4)2.

Figure 5. The crystal structures of the cations of 1(CIO4)2 (left) and 2(CIO4)2 (right) (ORTEP plot). Thermal ellipsoids are plotted at 30% probability ellipsoids, hydrogen atoms have been omitted for clarity.

Table 2. Crystallographic data of complexes 1(CIO4)2 and 2(CIO4)2.

<table>
<thead>
<tr>
<th>Complex</th>
<th>1(CIO4)2</th>
<th>2(CIO4)2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C26H20Cl2FeN8O8</td>
<td>C26H20Cl2FeN9O8</td>
</tr>
<tr>
<td>Formula weight</td>
<td>757.37</td>
<td>830.96</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
<td>Triclinic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Space group</th>
<th>P 1</th>
<th>P 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit cell dimensions</td>
<td>a = 11.5569(11) Å</td>
<td>a = 11.8936(12) Å</td>
</tr>
<tr>
<td></td>
<td>b = 12.4532(20) Å</td>
<td>b = 12.8988(12) Å</td>
</tr>
<tr>
<td></td>
<td>c = 12.5679(11) Å</td>
<td>c = 13.1477(3) Å</td>
</tr>
<tr>
<td></td>
<td>α = 82.359(5)°</td>
<td>α = 89.788(4)°</td>
</tr>
<tr>
<td></td>
<td>β = 63.653(6)°</td>
<td>β = 67.173(4)°</td>
</tr>
<tr>
<td></td>
<td>γ = 87.358(6)°</td>
<td>γ = 73.470(4)°</td>
</tr>
<tr>
<td>Volume</td>
<td>1606.3(2) Å3</td>
<td>1768.8(3) Å3</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.566 Mg/m3</td>
<td>1.560 Mg/m3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.701 mm-1</td>
<td>0.645 mm-1</td>
</tr>
<tr>
<td>F(000)</td>
<td>780</td>
<td>858</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.37 x 0.20 x 0.11 mm3</td>
<td>0.22 x 0.08 x 0.08 mm3</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.82 to 25.00°</td>
<td>1.66 to 26.00°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13&lt;=h&lt;=12, -14&lt;=k&lt;=14, -14&lt;=l&lt;=13</td>
<td>-14&lt;=h&lt;=15, -15&lt;=k&lt;=15, -16&lt;=l&lt;=15</td>
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<tr>
<td>Reflections collected</td>
<td>10606</td>
<td>23734</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>5570 [R(int) = 0.0403]</td>
<td>6845 [R(int) = 0.0604]</td>
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<td>Completeness to theta = 25.00°</td>
<td>98.5 %</td>
<td>98.4 %</td>
</tr>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9288 and 0.7806</td>
<td>0.9520 and 0.8727</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F2</td>
<td>Full-matrix least-squares on F2</td>
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<tr>
<td>Data / restraints / parameters</td>
<td>5570 / 36 / 445</td>
<td>6845 / 0 / 510</td>
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<tr>
<td>Goodness-of-fit on F2</td>
<td>1.048</td>
<td>1.006</td>
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<td>Final R indices</td>
<td>R1 = 0.0924, wR2 = 0.2196</td>
<td>R1 = 0.0506, wR2 = 0.0882</td>
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<tr>
<td>[F&gt;2sigma(F)]</td>
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</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1257, wR2 = 0.2369</td>
<td>R1 = 0.0506, wR2 = 0.0882</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>7.160 and -0.771 eÅ-3</td>
<td>0.489 and -0.472 eÅ-3</td>
</tr>
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</table>

Table 3. Comparison of different Fe-N bond distances between 1(CIO4)2, 2(CIO4)2, and [Fe3+(N4Py)(CH3CN)](ClO4)2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Complex 1(CIO4)2</th>
<th>Complex 2(CIO4)2</th>
<th><a href="ClO4">Fe3+(N4Py)(CH3CN)</a>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-Npy (average)</td>
<td>1.953</td>
<td>1.974</td>
<td>1.972</td>
</tr>
<tr>
<td>Fe-Npy (average)</td>
<td>1.977</td>
<td>1.981</td>
<td>------</td>
</tr>
<tr>
<td>Fe-NHt (average)</td>
<td>1.909</td>
<td>1.901</td>
<td>1.915</td>
</tr>
<tr>
<td>Fe-Namide (average)</td>
<td>1.980</td>
<td>2.028</td>
<td>1.961</td>
</tr>
</tbody>
</table>
Generation and characterization of high valent Fe(IV)-oxo complexes.

The two Fe(II) complexes contain a relatively labile coordinated solvent (acetonitrile) molecule and they are easily converted into the corresponding Fe(IV) oxo species upon reaction with the strong O-atom donor agent iodosylbenzene (PhIO). Complex 1(ClO4): reacted with excess (10 equivalents) solid PhIO in acetonitrile at room temperature to form a pale green complex, [FeIV(O)(L1)]2+ (Scheme 4).

Figure 6. The absorbance spectra of complexes 3 (gray) and 4 (black) [0.5 mM] in acetonitrile (left); the corresponding molar extinction coefficient values (ε) of complexes 3 (gray) and 4 (black) (right).

Complexes 3 and 4 were also characterized by high resolution mass spectrometry (HRMS). The HRMS of an acetonitrile solution containing complex 3 showed major peaks at m/z = 246.0681, corresponding to the formulation [FeIV(O)(L3)]2+ (m/z calc. 246.0675) and at m/z = 591.0847, corresponding to the formulation [FeIV(O)(L1)(ClO4)]1+ (m/z calc. 591.0841) (Figure S9, Supplementary Material). Similarly, the HRMS of complex 4 (with trflate counter anion, derived from [FeIV(L3)(CH3CN)][CF3SO3]) showed major peaks at m/z = 272.5837, corresponding to the formulation [FeIV(O)(L2)]2+ (m/z calculated 272.5808) and at m/z = 694.1153, corresponding to the formulation [FeIV(O)(L1)(CF3SO3)]1+ (m/z calculated 694.1142) (Figure S12, Supplementary Material).

Mössbauer spectroscopy was also employed to confirm the oxidation state of the iron ions in complexes 3 and 4. The zero field Mössbauer spectrum of an acetonitrile solution containing 20% of 57Fe enriched sample of 3 showed an isomeric shift value, δ = -0.03 mm s⁻¹, and quadrupole splitting value, ΔEₐ = 1.1 mm s⁻¹ (Figure 7), indicating the presence of an Fe(IV) species. Approximately 86% of the Fe sample accounts for the presence of 3, the remaining absorption corresponds to Fe(III) contaminants. Similarly, the Mössbauer spectrum of 4 measured under the same conditions showed an isomeric shift value, δ = -0.02 mm s⁻¹, and quadrupole splitting value, ΔE₀ = 1.34 mm s⁻¹, indicating the presence of an Fe(IV) species, with ~80% of the Fe sample accounting for the presence of 4 (Figure 7). The isomeric shift values for 3 and 4 are very similar to those obtained for [FeIV(O)(N4Py)]2+ (δ = -0.04 mm s⁻¹; ΔE₀ = 0.93 mm s⁻¹) and [FeIV(O)(Bn-tpen)]2+ (δ = 0.01 mm s⁻¹; ΔE₀ = 0.87 mm s⁻¹), indicating that both 3 and 4 are low spin (S = 1) non-heme Fe(IV) oxo complexes. The structure of 3 (as the dication) was investigated by DFT and a triplet Fe(IV) oxo species 1A was computed to be the ground-state minimum in keeping with the available experimental data. The corresponding high spin quintet (S = 2) state lies 2.6 kcal/mol above the triplet species. Analysis of the unpaired spin density in 1A reveals significant unpaired spin population on the iron (1.15) and the oxygen (0.09) centers.

The half lives (t₁/₂) for complexes 3 and 4 were determined at room temperature. The t₁/₂ for complex 3 is 40 h while for complex 4 it is 2.5 h, demonstrating that complex 4 is thermally much more stable compared to complex 3. In Table 4, the half lives and the characteristic wavelengths of these two new Fe(IV)-oxo complexes are compared to some previously reported low spin Fe(IV) oxo complexes bearing pentadentate ligands; it may be noted that...
the thermal stability of complex 3 is very similar to that of the parent N4Py complex.

Table 4. Comparison of wave lengths and half lives of different low spin (S = 1) Fe(IV) oxo complexes bearing pentadentate ligands.

<table>
<thead>
<tr>
<th>Complex</th>
<th>λ_{max}, nm (¢ in M^{-1} cm^{-1})</th>
<th>t_{1/2} at RT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Fe^{IV}(O)(L1)]^{2+}</td>
<td>708 (400)</td>
<td>40 h</td>
<td>this work</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(L2)]^{2+}</td>
<td>725 (380)</td>
<td>2.5 h</td>
<td>this work</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(N4Py)]^{2+}</td>
<td>696 (400)</td>
<td>60 h</td>
<td>13</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(MePy2TACN)]^{2+}</td>
<td>739 (400)</td>
<td>6 h</td>
<td>13</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(MeTCN)]^{2+}</td>
<td>834 (260)</td>
<td>7 h</td>
<td>42</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(TMC-py)]^{2+}</td>
<td>810 (270)</td>
<td>5 d</td>
<td>41</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(BP2)]^{2+}</td>
<td>730 (400)</td>
<td>-----</td>
<td>43</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(BP)]^{2+}</td>
<td>730 (380)</td>
<td>-----</td>
<td>43</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(MgPcL2TACN)]^{2+}</td>
<td>736 (310)</td>
<td>-----</td>
<td>44</td>
</tr>
<tr>
<td>[Fe^{IV}(O)(TACPy2)]^{2+}</td>
<td>740 (340)</td>
<td>-----</td>
<td>17</td>
</tr>
</tbody>
</table>

Hydrogen atom transfer (HAT) reactions: Reactivities with alkanes.

The Fe(IV) oxo complexes 3 and 4 efficiently oxidize the C-H bonds of various alkanes at room temperature. A series of alkane substrates having different C-H bond dissociation energies (BDE’s) (range from 81-99.3 kcal/mol) were investigated and the relative reactivities between complexes 3 and 4 were evaluated.

Reactivity of [Fe^{IV}(O)(L1)]^{2+} 3. Addition of 20 equivalents of triphenyl methane (C-H BDE = 81 kcal/mol) to 3 resulted in rapid decay of 3 to its Fe(II)-precursor species as identified by UV/Vis spectroscopy (Figure S15, Supplementary Material) and formation of triphenyl methanol with ~ 89% yield. On the other hand, complex 3 reacted with the comparatively less reactive substrate cyclohexane (C-H BDE = 99.3 kcal/mol) at a slower rate to form cyclohexanol and cyclohexanone (total yield ~ 18%); details of product analyses are provided in the Supplementary Material. The decay of the Fe-oxo absorbance band of 3 monitored at 708 nm was monitored under pseudo-first-order conditions, i.e. in presence of excess substrate (50-400 equivalents) for a range of substrates. The second-order rate constants (k_2) for the different substrates were obtained from the slope of plots of the observed pseudo-first-order rate constant, k_{obs}, versus molar concentration, taken at three different substrate concentrations. The k_2 values thus obtained are listed in Table 5. A primary kinetic isotope effect (KIE) value of ~ 14 was obtained by determining the second-order rate constants corresponding to separate reactions of toluene and its deuterated isomer with 3 (Figure 8, right), using the same methodology described above.

A plot of logarithmic values of second-order rate constants (log k_2) (k_2 is the second-order rate constant divided by the number of equivalent C-H bonds in the substrate) for absorbance decay versus bond dissociation energies for various hydrocarbons shows a linear correlation (Figure 10). The linear correlation between log k_2 and C-H BDE’s of substrates, as well as the observed large KIE value constitute strong evidence of the reactions taking place via hydrogen atom transfer (HAT).

Reactivity of [Fe^{IV}(O)(L1)]^{2+} 4. Complex 4 also reacted rapidly with different alkane substrates and the decay of the Fe-oxo absorbance was monitored at 725 nm to determine the observed pseudo-first-order rate constants. Complex 4 reacted with triphenyl methane with faster rate producing triphenyl methanol with ~ 90% yield (Figure 9), while its reactivity slowed for substrates with higher C-H BDE. The same kinetic analysis was applied for complex 4 as for 3; the k_2 values for reactions of 4 with various alkane substrates are listed in Table 5. A linear correlation plot between log k_2 versus C-H BDE’s of alkanes was also observed for complex 4 (Figure 10) which also indicates that the reactions proceeded through hydrogen atom transfer in the rate determining step, and a primary KIE value of ~ 11 was obtained for separate reactions of toluene and its deuterated isomer with 4.

Figure 9. (Left) Kinetic decay of complex 4 (¢ 0.5 mM in acetonitrile) upon addition of 30 equivalents of triphenylmethane. (Right) Determination of second order rate constant for triphenylmethane from k_{obs}, versus concentration plot.

Scheme 5. The reactivity of Fe(IV)-oxo complex with 1,4-cyclohexadiene.

The reactivity of complex 4 with substrates like 9,10-dihydroanthracene (9,10-DHA) and 1,4-cyclohexadiene (1,4-CHD) was also investigated in order to examine any possible influence of the bulky methylbenzimidazole group on the access to the Fe(IV) oxo center by the substrate. Both substrates have similar C-H bond dissociation energies (C-H BDE ~ 77 kcal/mol for 9,10-DHA and 78 kcal/mol for 1,4-CHD), but 9,10-DHA is a sterically bulky substrate relative to 1,4-CHD. The second order rate constants obtained for complex 4 measured at 243 K were 1.4 M^{-1} s^{-1} with 9,10-DHA and 1.2 M^{-1} s^{-1} with 1,4-CHD. Similar values of k_2 for 4 indicated that access to the Fe(IV)-oxo center by the substrates were equally feasible and not influenced by the nearby methylbenzimidazole groups. It should be mentioned that 4 acted as a one electron oxidant in these cases, thereby requiring two equivalents of complex 4 to form benzene (identified by GC) from one equivalent of 1,4-CHD (Scheme 5). While the steric
hindrance in complex 4 has not been probed by an extensive range of substrates, the results above indicate that there is relatively little steric discrimination of substrates by 4 (and implicitly by 3).

The HAT curve clearly indicates that 4 reacted with faster rates of reactions with different alkane substrates with respect to 3. The nearly parallel slopes observed for the HAT curves of [FeIV(O)(N4Py)]2+,13 complex 3 and complex 4 (Figure 10) suggest that simple variation in the side arm of the ligand plays an important role in the reactivity of the Fe(IV) oxo unit in this family of complexes. Considering that there does not seem to be a significant steric discrimination of substrates for complex 4 (vide supra), the observed HAT reactivities suggest that the influence of the replacement of a pyridyl side arm by a (N-methyl)benzimidazolyl side arm is primarily electronic. Since the reaction of an Fe(IV)-oxo species with a substrate R-H involves the rate determining transfer of a hydrogen atom (one electron coupled with a proton), it may be concluded that the effective basicity of the ferryl unit is increased by the successive introduction of (N-methyl)benzimidazolyl moiety increases the rate constant by one order of magnitude (Figure 10).

Table 5. C-H bond dissociation energies of different alkane substrates and the second order rate constants ($k_2$) of 3 and 4 for HAT reactivities

<table>
<thead>
<tr>
<th>Substrate</th>
<th>BDE (kcal/mol)</th>
<th>$k_2$ for 3 (M⁻¹s⁻¹)</th>
<th>$k_2$ for 4 (M⁻¹s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triphenylmethane</td>
<td>81 0.031</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Cumene</td>
<td>84.5 0.008</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>87 0.0076</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>90 0.0013</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Cyclooctane</td>
<td>95.3 0.0015</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>2,3-Dimethylbutane</td>
<td>96.5 0.00032</td>
<td>0.0025</td>
<td></td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>99.3 0.0003</td>
<td>0.0029</td>
<td></td>
</tr>
</tbody>
</table>

O-atom transfer (OAT) reactions: Oxidation of sulfides.

Scheme 6. Oxygen atom transfer (OAT) to thioanisole by complex 3 at 243 K.

The oxo transfer reactivities of 3 and 4 were also investigated, using thioanisole (PhSCH₃) as a substrate. Complex 3 reacted with thioanisole at 243 K and transferred the oxygen to form methyl phenyl sulfoxide quantitatively (yield ~ 84%) (Scheme 6). During the course of the reaction, complex 3 was converted into its Fe(II)-precursor (complex 1) as identified by UV/Vis spectrophotometry (Figure 10). The reaction showed pseudo-first order behaviour under condition of excess substrate (5-20 equivalents w.r.t. complex 3 and the observed rate constant ($k_{obs}$) was linearly dependent on substrate concentration (Figure 11). From this linear plotting, a second order rate constant ($k_2$) with a value of 3.3 x 10⁻² M⁻¹ s⁻¹ was obtained in the oxidation of thioanisole by complex 3. Similarly, 4 was reacted with thioanisole under the same conditions, and a faster rate with respect to complex 3 and methyl phenyl sulfoxide was obtained with a yield of ~ 88% . The second order rate constant ($k_2$) for complex 4 in oxo transfer reaction was found to be 3.1 x 10⁻¹ M⁻¹ s⁻¹. Table 8 shows a comparison in the reaction rates of OAT processes between complex 3, 4 and previously reported Fe(IV)-oxo complexes. In parallel with the observed trend for HAT, the $k_2$ values suggest that complex 4 is more reactive (by one order of magnitude) than complex 3 in the OAT reaction (i.e. thioanisole oxidation).

Table 6. Comparison of rates of OAT process (thioanisole oxidation) between complex 3, complex 4 and some other relevant low spin Fe(IV)-oxo complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$k_2$ (in M⁻¹s⁻¹)</th>
<th>Temp. of measurement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[FeO(NTB)][L]⁺ (3)</td>
<td>3.3 x 10⁻²</td>
<td>243 K</td>
<td>this work</td>
</tr>
<tr>
<td>[FeO(L)][L]⁺ (4)</td>
<td>3.1 x 10⁻¹</td>
<td>243 K</td>
<td>this work</td>
</tr>
<tr>
<td>[FeO(N4Py)]⁻</td>
<td>1.4 x 10⁻¹</td>
<td>263 K</td>
<td>17</td>
</tr>
<tr>
<td>[FeO(N4Py)]⁻</td>
<td>2.8 x 10⁻⁴</td>
<td>233 K</td>
<td>22</td>
</tr>
<tr>
<td>[FeO(Bn-tpen)]⁻</td>
<td>3.3 x 10⁻⁴</td>
<td>263 K</td>
<td>17</td>
</tr>
<tr>
<td>[FeO(MeNTB)]⁺</td>
<td>1.8 x 10⁻²</td>
<td>233 K</td>
<td>22</td>
</tr>
</tbody>
</table>

Discussion. The excellent HAT and OAT reactivities of 3 and 4 may be rationalized using two popular approaches - either Shaik’s exchange-enhanced-reactivity (EER) model22 or the Bell-Evans-Polanyi principle (BEP) of Linear Free Energy Relations (LFER).31,32 which has been fruitfully developed by J. Mayer for HAT reactions.33 These approaches are not mutually exclusive but
rather complementary, as the EER approach applies to the kinetics and the BEP to the thermodynamics of the process.

According to the EER, or Two-State Reactivity (TSR) model, the HAT reactivity of FeIV=O (S = 1) complexes may be explained by a more reactive quintet (S = 2) transition state that is populated via spin-crossover during movement over the energy surface along the reaction coordinate. This principle shows that an increase of the number of unpaired and spin-identical electrons on the iron center will be favourable to the reactivity of the high spin state in comparison with the low-spin state. Therefore the proximity of the quintet excited state to the triplet (S = 1) ground state in the FeIV=O complex and correspondingly the easiness of triplet/quintet spin-crossover is significant for its reactivity. Oxygen atom transfer reactions are two-electron processes and hence should not exhibit EER.

In order to elucidate the HAT mechanism(s) for reaction of alkanes with 3 and 4, and establish the spin states of the active species on the potential energy surface, DFT calculations were carried out on the triplet and quintet states of 3 (3A and 5A), using methane (B) as the substrate. Figure 12 shows the lowest energy pathways that have been computed for methane activation, while Figure 13 shows the pertinent transition-state structures responsible for H-abstraction. The results are in concert with a two-state reactivity model, as popularized by Shaik, involving the triplet (S = 1) and quintet (S = 2) reaction surfaces.

The side-on approach of methane to the oxo moiety in 3A leads to 5TSAB’CD through a pi-directed manifold. This transition structure lies 33.9 kcal/mol above the triplet oxo 3A and affords the corresponding geminate radical pair [FeIV(OH)(L)3]2+ (C) and methyl radical D. Collapse of CD completes the formal hydroxylation and gives the MeOH-coordinated complex [FeIV(MeOH)(L)3]2+ (F). The overall process is exergonic by 7.5 kcal/mol.

Population of the thermodynamically favored quintet surface proceeds through a 3A → 5A spin crossover. The quintet oxo species (5A) undergoes HAT reaction through a linear, sigma-directed transition structure, 7TSAB’CD, which lies 12.6 kcal/mol lower than the energy of the triplet transition structure (5TSAB’CD). This energetic stabilization more than compensates for the ground-state exchange destabilization experienced by 5A. The collapse of the geminate radical pair, 7CD, affords the MeOH-coordinated complex [FeIV(MeOH)(L)3]2+ (F) with a net release of 25.8 kcal/mol.

The BEP/LFER principle establishes the linear correlation of the reaction barrier height (ΔΔG°) with the thermodynamic driving force of reaction determined by the free energy value (ΔG°).

Some deviations may be related to contributions by the second term of this equation (pKa) or the non-adiabaticity of the reaction (EER model). Such an “anti-electrophilic trend” was observed in a study of the axial ligand effect on the HAT reactivity of [FeIV(O)(TMC)(X)]n+ and the least electrophilic complex in the series appears the most reactive. It seems that such a trend is observed only for axial ligands. For equatorial donors an increase of the donor strength of the ligand will lower the redox potential of the FeIV=O moiety and increase the pKa of the FeIV-OH product formed upon hydrogen atom transfer. On the other hand, a better electron donor ligand will not only strengthen the Fe-OH bond and thus enhance the thermodynamic drive for hydrogen atom transfer, but will also simultaneously weaken the Fe=O bond and thus assist OAT reactivity. This applies to complexes 3 and 4.

It has been found that ligand donor moieties in cis-position to the oxo unit (equatorial donors) exert less influence on the reactivity of FeIV=O (S = 1) octahedral complexes than those ligated trans (axial) as “trans-ligands can interact with both σ- and π-orbitals involved in the Fe=O bond but cis ligands cannot.” However, in the present case, the effect of replacing equatorial pyridyl donors with (N-methyl)benzimidazole units is quite significant. The (number and positions of) equatorial donors in octahedral complexes can modulate the spin state and reactivity of the oxo unit by altering the energies, and thus the occupancies, of the iron dσ, dπ, and dπ-σ orbitals. In 3 and 4, one or two pyridine moieties in cis-position to the oxo ligand have been replaced by (N-methyl)benzimidazolyl units, and the electrochemical measurements on the precursors 1 and 2 indicate that this replacement leads to a weaker ligand field. However, the (N-methyl)benzimidazolyl units are sufficiently strong-field donors to support a dπσ/dπ-π gap in the FeIV=O complexes that leads to spin pairing to form the S = 1 ground states for 3 and 4. A weaker equatorial field should decrease the triplet/quintet gap relative to that of [FeIV(O)(N4Py)]2+. The decrease of field strength may thus, in principle, facilitate the spin crossover required for two-state reactivity (vide supra) and can thus explain the increase in...
HAT rates that are observed upon substitution of pyridyl moieties by (N-methyl)benzimidazolyl moieties in the ligand framework.

As mentioned above, it has previously been found that the activities of FeIV=O complexes with tetramethyleclaym (TMC) ligands in oxygen-atom transfer reactions correlate directly with the electrophilicity of the FeV=O moiety. One may thus expect complexes 3 and 4 to be less electrophilic and more poor OAT reagents than [FeV(O)(N4Py)]2; however, our results show that the trend is exactly opposite. Thus, the trends observed in the present study and some others do not follow those found in the TMC study with trans (axial) donors. The redox potentials of complexes 1 and 2 (vide supra) clearly indicate that the ligand fields exerted by ligands L1 and L2 are weaker than that of N4Py, suggesting that the σ-donor properties of the equatorial (N-methyl)benzimidazolyl moieties do indeed prevail over their π-acceptor properties (vide infra).

Summary and Conclusions.

The octahedral ferryl complexes 3 (t1/2 = 40 h, RT) and 4 (t1/2 = 2.5 h, RT) with pendentate Nσ-donor ligands (cf. Table 5) that have been prepared by us are significantly more stable than the previously studied [FeV(O)(Me3NTB)]2 complex, and have thus permitted detailed spectroscopic and reactivity investigations of ferryl complexes with (N-methyl)benzimidazolyl donor moieties. More importantly, 3 and 4 demonstrated excellent hydrogen atom transfer (HAT) and oxygen atom transfer (OAT) activities, surpassing the very active [FeV(O)(N4Py)]2 and [FeV(O)(Bnpen)]2 complexes by approximately one to two orders of magnitude (Tables 7 and 8, Figures 7-10). For example, in the oxidation of cyclohexane (which has the strongest C-H bonds among the alkanes studied here) the successive replacement of pyridyl moieties of the N4Py ligand by one and two (N-methyl)benzimidazolyl moieties led to increases in the corresponding values for the rate constants by one order of magnitude for each nitrogen donor replacement. Despite the increased steric bulk of the (N-methyl)benzimidazolyl groups relative to the pyridyl moieties, no influence of this replacement on the access to the Fe(IV)-oxo center by the substrate molecules could be detected.

As expected, the introduction of equatorial (N-methyl)benzimidazolyl donors in the N4Py framework reduces the energy difference between the iron dσ and dπ2,2* orbitals, but the resulting dσ/dπ2,2* gap is not sufficiently small to make the high spin S = 2 state the ground state of 3 and 4. While this gap is small, computational modeling of the HAT/hydroxylation of substrates by 3 (vide supra) does not support spin crossover, as the preferred spin state for the transition state is the triplet (S = 1) state.

Following the principles of the BEP/LFER principle described above, the enhanced reactivities of complexes 3 and 4 relative to that of [FeV(O)(N4Py)]2 may be explained by the (N-methyl)benzimidazolyl moieties in ligand L1 and L2 being stronger σ-donors but weaker π-acceptors relative to the pyridyl substituents of the N4Py ligand, thus enabling increased electron donation in the equatorial plane but an overall weaker ligand field due to the relatively poor π-acceptor properties. The observed reactivities for the new ferryl complexes discussed here may be rationalized by both the BEP/LFER principle and the EER/TSR model.

Experimental Section

Materials:

The reagents and solvents were purchased from Sigma-Aldrich and Fisher chemicals. All solvents were of at least 99.5 % purity and used as received. Reagents were of at least 99 % purity and used without any further purification. N-[di(2-pyridinyl)methyl]-N-(2-pyridinyl)methyl]25 bis(2-pyridyl)methyamine,26 and 2-chloromethyl-1-methylbenzimidazole45 were prepared according to literature procedures.

Physical methods:

UV/Visible spectra and all kinetic experiments were performed on a 8453 UV/Vis Agilent Technologies equipped with a diode-array detector and a Unisoku which permits monitoring of the temperature of the experiments from -90 °C to 100 °C. All UV/Vis spectra were measured ins 1cm quartz cell. NMR spectra were collected on Bruker DPX 400 MHz and Varian Inova 500 MHz spectrometer in CDCl3 and CD3CN solvents and referenced to the residual signal of the solvent. Elemental analysis was performed using an Elementar Vario EL III instrument. The mass spectrometry (ESI) was performed with a Bruker HCT ultra mass spectrometer. The high resolution mass spectrum (HRMS) was performed using a Bruker FTICR APEX IV instrument. The electrochemical analyses were performed on a model a model CHI760B Electrochemical Workstation (CH Instrument). Tetrabutylammonium hexafluorophosphate [t-Bu4N]PF6 was used as a supporting electrolyte and the measurements were carried out using 3 mm diameter Teflon-shrouded glassy carbon working electrode, a Pt wire auxiliary electrode and a SCE reference electrode. Product analyses were performed on a Agilent technologies 7820A with 16 sample automatic liquid sampler and flame ionization detector. The products were identified by their GC retention times. Mössbauer spectra were recorded with a 57Co source in a Rh matrix using an alternating constant acceleration Wissel Mössbauer spectrometer operated in the transmission mode and equipped with a Janis closed-cycle helium cryostat. Isotherm shifts are given relative to iron metal at ambient temperature. Simulation of the experimental data was performed with the Mfit program (E. Bill, Max-Planck Institute for Chemical Energy Conversion, Mülheim/Ruhr, Germany).

Synthesis of ligand L1: [N-(1-methyl-2-benzimidazolyl)methyl]-N-(2-pyridinyl)methyl]N-(bis-2-pyridyl)methyamine

A two-necked round bottom flask was charged with N-[di(2-pyridinyl)methyl]-N-(2-pyridinyl)methyl]methyamine (1.00 g, 3.6 mmol), 2-chloromethyl-1-methylbenzimidazole (0.651 g, 3.6 mmol), K2CO3 (2.5 g, 18 mmol) and tetrabutylammonium hexafluorophosphate [t-Bu4N]PF6 was used as a supporting electrolyte and the measurements were carried out using 3 mm diameter Teflon-shrouded glassy carbon working electrode, a Pt wire auxiliary electrode and a SCE reference electrode. Product analyses were performed on a Agilent technologies 7820A with 16 sample automatic liquid sampler and flame ionization detector. The products were identified by their GC retention times. Mössbauer spectra were recorded with a 57Co source in a Rh matrix using an alternating constant acceleration Wissel Mössbauer spectrometer operated in the transmission mode and equipped with a Janis closed-cycle helium cryostat. Isotherm shifts are given relative to iron metal at ambient temperature. Simulation of the experimental data was performed with the Mfit program (E. Bill, Max-Planck Institute for Chemical Energy Conversion, Mülheim/Ruhr, Germany).
A total of 0.403 g 2-Chloromethyl-1-methylbenzimidazole (2.23 mmol) was dissolved in 2 ml of 5 (M) NaOH solution. Stirring for about 10 min, bis(2-pyridyl)methylamine (0.206 g, 1.115 mmol) in 2 ml 5 (M) NaOH was added. The stirring was continued for three days at room temperature. After stirring was finished, the sticky solid that was formed was collected and HFPs were added dropwise to precipitate a brick-red solid. The resultant solid was dissolved in hot water. After recrystallization from hot water, 5 (M) NaOH was added to basify the reaction mixture (pH > 12). The product was extracted with dichloromethane, dried over Na2SO4 and the dichloromethane extract was evaporated to give the desired ligand L2 as a pale brownish solid. Yield: 0.749 g (71%). ESI-MS: 474.2 [M+H]+; 1H-NMR (500 MHz, CDCl3) δ (ppm) 8.635 [d, 2H, J = 8 Hz], 7.714-7.645 [m, 6H], 7.62 [dt, 2H], 7.19 [m, 4H], 5.402 [s, 1H], 4.285 [s, 4H], 3.619 [s, 6H]; 13C-NMR (125 MHz, CDCl3) δ ppm 136.47 [s], 136.05 [s], 124.97 [s], 122.8 [s], 122.39 [d], 119.41 [s], 136.47 [s], 136.05 (s), 124.97 (s), 122.8 (s), 122.39 (d), 119.41 (s), 109.1 (s), 48.31 (s), 29.8 (s).

Synthesis of [FeII(CH3CN)(L1)(ClO4)]+ (1.(ClO4)2):
A total of 100 mg (0.23 mmol) of ligand L1 was taken in a vial and dissolved in a minimum amount of CH3CN. To this solution, 58.6 mg (0.23 mmol) of Fe(ClO4)2 in acetonitrile was dissolved in 2 ml of a 5 (M) NaOH solution. Stirring for about 10 min, bis(2-pyridyl)methylamine (0.206 g, 1.115 mmol) in 2 ml 5 (M) NaOH was added. The stirring was continued for three days at room temperature. After stirring was finished, the sticky solid that was formed was collected and HFPs were added dropwise to precipitate a brick-red solid. The resultant solid was dissolved in hot water. After recrystallization from hot water, 5 (M) NaOH was added to basify the reaction mixture (pH > 12). The product was extracted with dichloromethane, dried over Na2SO4 and the dichloromethane extract was evaporated to give the desired ligand L2 as a pale brownish solid. Yield: 0.749 g (71%). ESI-MS: 474.2 [M+H]+; 1H-NMR (500 MHz, CDCl3) δ (ppm) 8.635 [d, 2H, J = 8 Hz], 7.714-7.645 [m, 6H], 7.62 [dt, 2H], 7.19 [m, 4H], 5.402 [s, 1H], 4.285 [s, 4H], 3.619 [s, 6H]; 13C-NMR (125 MHz, CDCl3) δ ppm 136.47 [s], 136.05 [s], 124.97 [s], 122.8 [s], 122.39 [d], 119.41 [s], 109.1 (s), 48.31 (s), 29.8 (s).

Synthesis of [FeII(CH3CN)(L2)(ClO4)]+ (1.(ClO4)2):
A total of 71 mg (0.15 mmol) of ligand L2 was taken in a vial and dissolved in minimum amount of acetonitrile. To this solution, 65.4 mg (0.15 mmol) of [Fe(CH3CN)(CF3SO3)]n in acetonitrile was added under stirring at room temperature under nitrogen atmosphere. After stirring for about 30 min, the reaction mixture was placed into an ethyl acetate bath and stored overnight. The precipitate was collected by filtration, washed with ethyl acetate, dried under vacuum and obtained as red solid. Yield: 101 mg (78%). ESI-MS (in CH3CN): m/z 264.6 [Fe6(L2)2]+ (z = 2) calc. 264.6, 678.1 [Fe6(L2)2(CF3SO3)]+ (z = 1) calc. 678.1.

Crystal structure determinations.
The crystal of 1.(ClO4)2 and 2.(ClO4)2 were immersed in cryo-oil, mounted on a Nylon loop, and measured at a temperature of 100 K. The X-ray diffraction data were collected on a Bruker Kappa Apex II and Bruker Kappa Apex II Duo diffractometers using Mo Kα radiation (λ = 0.71073 Å). The APEX2® program package was used for cell refinements and data reductions. The structure was solved by charge flipping technique (SUPERFLIP®) or direct methods using the SIR2011® program with the Olex2® graphical user interface. A semi-empirical numerical absorption correction based on equivalent reflections (SADABS®) was applied to all data. Structural refinements were carried out using SHELXL-97. The crystal of 1.(ClO4)2 was diffracting only weakly and therefore atoms N2, C16, C17, C18, C19, and C20 were restrained to have the same Uij components within the standard uncertainty of 0.02. In 2.(ClO4)2 one molecule of the acetonitrile of crystallization was disordered over two sites with equal occupancies. Hydrogen atoms were positioned geometrically and were also constrained to ride on their parent atoms, with C-H = 0.95-1.00 Å, and Uiso = 1.2-1.5 Ueq(parent atom). The crystallographic details are summarized in Table 2.

Hydrogen atom transfer (HAT) reactions:
Fe(IV) oxo solutions (in the concentration ranges 0.5 mM – 1.0 mM) in CH3CN were prepared by using excess solid PhIO to optimize yield; after filtration of unreacted PhIO, the solutions represent a reaction system without any methanol or per-acid contaminants. On deaeration of the solutions and a temperature equilibration at 25 °C in the UV/Vis cuvette, substrates were added to the stirred solutions. The concentrations of substrates used were ranged from 25 mM to 800 mM and were adjusted to achieve convenient times for the reduction of Fe(IV) oxo species. The time course decay of the Fe(IV) oxo was then monitored at 25 °C by the UV-Vis spectrophotometer. Time courses were subjected to pseudo-first order fit and second order rate constants were evaluated from the concentration dependence data.

To isolate the organic products, the solutions after the end of the reaction was passed through a silica column, using ethyl acetate as the eluent, in order to remove the metal complex. The ethyl acetate solutions were then analyzed by GC using a known strength of biphenyl solution as the quantification standard. All the data obtained from these studies were collected in Table S3.

Oxygen atom transfer (OAT) reactions: The Fe(IV) oxo solutions were prepared as described before. The solutions were placed in cuvette and the temperature of the UV/Vis instrument was monitored to -30 °C. Then, appropriate amounts of thioanisole substrate were added to the Fe(IV) oxo solution and the subsequent decay was monitored. Time courses were subjected to pseudo-first order fit and second order rate constants were evaluated from the concentration dependence data.

The products were quantified following the procedure as described before. The chirality of the sulfoxide product was not determined.
Computational Details and Modeling

All DFT calculations were carried out with the Gaussian 09 package.22 using the B3LYP hybrid functional. This functional is comprised of Becke's three-parameter hybrid exchange functional (B3)23 and the correlation functional of Lee, Yang, and Parr (LYP).24 The iron atom was described with the Stuttgart-Dresden effective core potential and SDD basis set,25 and the 6-31G(d) basis set16 was employed for all remaining atoms.

All reported geometries were fully optimized, and analytical second derivatives were evaluated at each stationary point to determine whether the geometry was an energy minimum (no negative eigenvalues) or a transition structure (one negative eigenvalue). Unscaled vibrational frequencies were used to make zero-point energy corrections to the electronic energies. The resulting potential energies and enthalpies are reported in kcal/mol relative to the specified standard. Standard state corrections were applied to all species to convert concentrations from 1 atm to 1M according to the treatise of Cramer.25 Internal reaction coordinate (IRC) calculations were performed on $^{1}T_{1}$S$^{4}$A$^{6}$B$^{3}$C$^{2}$D and $^{1}T_{1}$S$^{4}$A$^{6}$B$^{3}$C$^{2}$D in order to establish the reactant and product species associated with these transition-state structures. The geometry-optimized structures have been drawn with the JIMP molecular visualization and manipulation program.18

Table 7. Selected bond distances (Å) and bond angles (º) of complexes 1(ClO$_{4}$)$_{2}$ and 2(ClO$_{4}$)$_{2}$:

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<tr>
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<th>Complex 2(ClO$<em>{4}$)$</em>{2}$</th>
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ASSOCIATED CONTENT

Supporting Information

ESI-MS, 1H-NMR and FT-IR spectra of complexes 1(ClO$_{4}$)$_{2}$ and 2(ClO$_{4}$)$_{2}$, the UV/Vis spectra of the ligands, the cyclic voltammetric diagrams of complexes 1(ClO$_{4}$)$_{2}$ and 2(ClO$_{4}$)$_{2}$, the kinetic absorbance spectra of formation of complexes 3 and 4, HRMS of complexes 3 and 4, detailed product analyses, figures of the optimized ground-state and transition-state structures for the toluene and methane oxidation cycles involving $^{1}E$, along with tables of atomic coordinates and electronic energies for all optimized structures are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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REFERENCES


Catalytic C-H oxidations by non-heme mononuclear Fe(II) complexes of pentadentate ligands: Evidence for Fe(IV)-oxo intermediate


Keywords: Oxidation/Catalysis/Mononuclear/Non-heme/Kinetic isotope effect/Reactive intermediates.

The oxidation reactions of alkanes with hydrogen peroxide and peracids (peracetic acid and m-chloroperoxybenzoic acid) catalysed by two Fe(II) complexes of pentadentate ligands have been investigated. Kinetic isotope effect experiments and the use of other mechanistic probes have also been performed. Catalytic reactions in H$_2$O$_2$ medium are consistent with the involvement of hydroxyl radicals in the rate-determining step, and resultant low kinetic isotope effect values. On the other hand, catalytic reactions performed using peracid media indicate the involvement of an oxidant different from the hydroxyl radical. For these reactions, the kinetic isotope effect values are relatively high (within a range of 4.2-5.1) and the C3/C2 selectivity parameters in adamantane oxidation are greater than 11, thereby excluding the presence of hydroxyl radicals in the rate-determining step. A low spin Fe(III)-OOH species has been detected in the H$_2$O$_2$-based catalytic system by UV/Vis, mass spectrometry and EPR spectroscopy, while an Fe(IV)-oxo species is postulated to be the active oxidant in peracid-based catalytic systems.

Introduction

The selective functionalization of organic substrate molecules remains a great challenge in catalysis research. For decades, considerable efforts have been made to develop robust and selective homogeneous oxidation catalysts based on transition metals. Nature employs a number of heme and non-heme iron enzymes to carry out analogous vital biological transformations, involving oxidation of substrates that use dioxygen as the ultimate oxidant. These metalloenzymes show high regio- and stereoselectivity and operate under mild conditions. Examples of such enzymes include soluble methane monooxygenases and Rieske oxygenases (Figure 1).

Inspired by Nature, a wide range of mononuclear non-heme iron complexes have been synthesized and investigated as catalysts for the oxidation of alkanes and alkenes, using hydrogen peroxide, peracids, or dioxygen as an external oxidant. Amongst these complexes, mononuclear Fe(II) catalysts bearing tetradentate N$_4$-donor ligands, such as TPA,[12] BPMEN,[13] BQEN,[10b] S,S-PDP,[14] Me$_2$Py/TACN,[15] Me$_3$Methyl/TACN,[16] deserve special mention (Figure 2). Such Fe(II) complexes exhibit excellent catalytic efficiencies in hydrocarbon oxidation reactions with high stereoretention and C-H bond selectivity. An important structural feature regarding the above-mentioned catalysts is that the Fe(II) ion has two cis-coordinated labile sites, which is considered to be a necessary prerequisite for efficient catalytic oxidation.
Figure 1. The structures of the ligands, TPA (1), BPMEN (2), BQEN (3), S5-PDP (4), \(\text{Me}_2\text{PyTACN} \) (5) and \(\text{Me}_2\text{MeBzImTACN} \) (6).

On the other hand, activated bleomycin, a biomolecule and potential antitumor drug that effects the oxidative cleavage of DNA and also the oxidation of hydrocarbons,\(^{17}\) contains a low spin Fe(III)-hydroperoxo unit surrounded by five nitrogen donors.\(^{18}\) Therefore, oxygen activation and hydrocarbon oxidation by mononuclear Fe(II) complexes containing pentadentate ligands with one labile coordination site have been studied extensively during the last two decades.\(^{19-27}\) Reactions with suitable oxidants, e.g. \(\text{O}_2\), \(\text{H}_2\text{O}_2\), \(\text{PhIO}\), give rise to Fe(III)-OOH or Fe(IV)=O intermediates that have been characterized by various spectroscopic techniques.\(^{28-30}\) In contrast to the ferrous complexes of tetradentate ligands that have been discussed above, Fe(II) complexes of pentadentate ligands can form high valent Fe(IV)=O intermediates that possess relatively high thermal stability, permitting thorough investigations of such high-valent intermediates in oxidative transformation reactions. In this context, the pentadentate ligand \(\text{N}_4\text{Py}\) and its Fe(II)-complex are noteworthy.\(^{19}\) Both \([\text{Fe}^{\text{II}}(\text{OOH})(\text{N}_4\text{Py})]^{2+}\)\(^{19b,28}\) and \([\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}\)\(^{29}\) have been synthesized from the Fe(II) precursor complex and characterized. The catalytic activities of the Fe(II) complex of \(\text{N}_4\text{Py}\) have been studied\(^{20}\) and the involvement of \([\text{Fe}^{\text{III}}(\text{OOH})(\text{N}_4\text{Py})]^{2+}\) and \([\text{Fe}^{\text{IV}}(\text{O})(\text{N}_4\text{Py})]^{2+}\)\(^{27}\) as possible active oxidants during catalysis has been established both experimentally and theoretically.\(^{20,27,30,31}\)

We have previously demonstrated that successive replacement of pyridyl substituents of the ligand \(\text{N}_4\text{Py}\) by (N-methyl)benzimidazolyl moieties results in an increase in the rates of hydrogen atom abstraction reactions and oxo-transfer reaction by the Fe(IV)-oxo complexes \([\text{Fe}^{\text{IV}}(\text{O})(\text{L})]^{2+}\) and \([\text{Fe}^{\text{IV}}(\text{O})(\text{L})]^{2+}\) (\(\text{L}^1 = [\text{N-(1-methyl-2-benzimidazolyl)methyl-N-(2-pyridyl)methyl-N-(bis-2-pyridylmethyl)amine}]\) and \(\text{L}^2 = [\text{N-(bis-1-methyl-2-benzimidazolyl)methyl-N-(bis-2-pyridylmethyl)amine}]; \) Fig. 2).\(^{32}\)

Here we report oxidation of various hydrocarbons by \(\text{H}_2\text{O}_2\) or peracids using these Fe(II) complexes as catalyst precursors. Spectroscopic studies of possible reactive intermediates operating during catalysis are also described.

**Results and Discussion**

The catalytic activities of the two Fe(II) complexes \([\text{Fe}^{\text{II}}(\text{L}^1)(\text{CH}_3\text{CN})](\text{ClO}_4)^2 \) (1) and \([\text{Fe}^{\text{II}}(\text{L}^2)(\text{CH}_3\text{CN})](\text{ClO}_4)^2 \) (2) were studied in oxidation of different alkanes, utilizing hydrogen peroxide, peracetic acid (PAA) or \(\text{m-}\)chloroperoxybenzoic acid (mCPBA) as co-oxidants. The oxidation reactions were carried out under standard catalytic conditions (1:100:1000 ratio for catalyst:oxidant:substrate) in acetonitrile at room temperature, and the results were compared to those for \([\text{Fe}^{\text{II}}(\text{N}_4\text{Py})(\text{CH}_3\text{CN})](\text{ClO}_4)^2 \). The oxidant was added using a syringe pump and a large excess of substrate was used to minimize over-oxidation of the products.

![Figure 2](image-url)

**Figure 2.** The structures of the Fe(II)-complexes, \([\text{Fe}(\text{L}^1)(\text{CH}_3\text{CN})]^{2+} \) (1\(^{2+}\)) (left) and \([\text{Fe}(\text{L}^2)(\text{CH}_3\text{CN})]^{2+} \) (2\(^{2+}\)) (right).

Complex 1 together with \(\text{H}_2\text{O}_2\) oxidizes cyclohexane and a turnover number (TON) of 21.1 for cyclohexanol and 18.0 for cyclohexanone was obtained with an overall yield of 39% (based on oxidant). Under similar conditions, for complex 2, a TON of 17.4 for cyclohexanol and 14.7 for cyclohexanone was obtained with an overall yield of 32% (Table 1). The alcohol/ketone (A/K) ratio was found to be low (1.2) in both cases, and may be explained by considering the possible involvement of freely diffusing carbon-centered radicals that are trapped by molecular oxygen, followed by a Russell termination step.\(^9\) Addition of 50 mol% (w.r.t. the oxidant, \(\text{H}_2\text{O}_2\)) of acetic acid does not lead to any significant improvement of the overall yield or A/K ratio in cyclohexane oxidation. The kinetic isotope effect (KIE) was determined for the formation of cyclohexanol in competition experiments between cyclohexane and its d\(_{12}\) isotopomer. The KIE values obtained for complexes 1 and 2 were 1.45 and 1.7, respectively. These low KIE values are consistent with the involvement of hydroxyl radicals in the rate-determining step of C-H bond cleavage. When cyclooctane was employed as the substrate, both cyclooctanol and
cyclooctanone were formed. Complex 1 together with H2O2 (50 eq.) produced cyclooctanol with a TON of 3.7 and cyclooctanone with a TON of 14 and an overall yield of 35.7%, while complex 2 together with H2O2 (100 eq.) produced cyclooctanol with a TON of 6.6 and cyclooctanone with a TON of 24.7 and an overall yield of 31.3%.

The oxidation of adamantane by 31.3%.

6.6 and cyclooctanone with a TON of 24.7 and an overall yield of
cyclohexene epoxide was formed.

Cyclohexene oxidation afforded the corresponding allylic alcohol only a small amount of styrene epoxide (yield 3%) was obtained. Styrene was converted mainly into benzaldehyde (yield 41%) and

peracetic acid (PAA), both the conversion and turnover numbers diminished. Complex 1 gave an overall conversion of 5% with a TON of 3.8 for cyclohexanol (A) and 1.3 for cyclohexanone (K) (A/K = 3), while complex 2 gave an overall conversion of 9% with a TON of 5.2 for cyclohexanol and 4.0 for cyclohexanone (A/K = 1.3) (Table 2). On the other hand, mCPBA exhibited a catalytic efficiency analogous to H2O2. Complex 1 produced an overall yield of 30%, TON for A = 23, TON for K = 6.9, and complex 2 produced an overall yield 32.5%, TON for A = 22.3, TON for K = 10.2 (Table 2). The A/K ratios were slightly increased in favour of the alcohol product (complex 1, A/K ~ 3; complex 2, A/K ~ 2). The KIE values estimated in the competitive oxidation of cyclohexane and its perdeuterated analogue were found to be higher than with H2O2 for both complexes (Table 2). On the basis of the improved A/K ratio and comparatively high(er) KIE values, significant participation of hydroxyl radicals in the peracid-based oxidation reactions may be excluded.

The behaviour of 1/H2O2 with olefins also supports the mechanistic conclusions derived from the alkane oxidation reactions by H2O2. Styrene was converted mainly into benzoaldehyde (yield 41%) and only a small amount of styrene epoxide (yield 3%) was obtained. Cyclohexene oxidation afforded the corresponding allylic alcohol and ketone as the major product and a minor amount of cyclohexene epoxide was formed.

The nature of the H-abstracting species, on the basis of the tertiary to secondary (C3/C2) C-H bond selectivity. The C3/C2 parameters in this reaction were small (the normalized C3/C2 ratio obtained was 3.6 for 1 and 4.5 for 2), and thus consistent with the formation of a highly reactive but poorly selective species. Finally, complexes 1/2 together with H2O2 oxidized cis-1,2-dimethylcyclohexane (cis-DMCH) to both cis- and trans-1,2-dimethylcyclohexanol. The reaction took place without retention of cis-configuration. Overall, the reactivity patterns that arise from the oxidation of these mechanistic probes are consistent with Fenton type activation of H2O2 to generate hydroxyl radicals that then attack the substrate, generating freely diffusing carbon centered radicals.

The catalytic efficiencies of complexes 1/complexes 1 and 2 with H2O2.[a]

<table>
<thead>
<tr>
<th>Complex</th>
<th>Oxidant</th>
<th>TON of A</th>
<th>TON of K</th>
<th>Yield (%)</th>
<th>A/K</th>
<th>KIE[d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PAA</td>
<td>3.8</td>
<td>1.3</td>
<td>5.1</td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>PAA</td>
<td>5.2</td>
<td>4.0</td>
<td>9.2</td>
<td>1.3</td>
<td>5.1</td>
</tr>
<tr>
<td>1</td>
<td>mCPBA</td>
<td>23</td>
<td>6.9</td>
<td>30</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>mCPBA</td>
<td>22.3</td>
<td>10.2</td>
<td>32.5</td>
<td>2.2</td>
<td>4.5</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: see Experimental section [b] Cyclohexanol [c] Cyclohexanone [d] Kinetic isotope effect was determined for the formation of cyclohexanol from a competitive reaction of a (1:1) mixture of cyclohexane and cyclohexane-d13.

Furthermore, selectivity probes indicated that oxidations with peracids involve species more selective than those involved with H2O2 (vide supra). For example, in the oxidation of adamantane by 1/peracid, the C3/C2 parameters were found to be significantly higher (the normalized C3/C2 ratio obtained for 1 was 15.8 with PAA and 11.4 with mCPBA). For complex 2, the normalized C3/C2 parameters were 15.0 (with PAA) and 12.3 (with mCPBA). More interestingly, the C3/C2 selectivity/ratio in the oxidation of cis-DMCH by 1 was around 1 with H2O2, but this selectivity was found to be approximately 12 with PAA/mCPBA. However, the oxidation of cis-DMCH occurs without stereoretention, implicating the presence of long-lived carbon centered radicals.

The catalytic efficiencies of complexes 1 and 2 are comparable to those of [FeII(N4Py)(CH3CN)](ClO4)2 in oxidations utilizing both H2O2 and peracids. For example, both complex 1 and complex 2 convert cyclohexane into cyclohexanol and cyclohexanone with overall yields of 39 and 32%, respectively (vide supra), while the value for [FeII(N4Py)(CH3CN)](ClO4)2 was 30% (Table 3). The A/K ratio lies in the range 1-2 for all three (pre-)catalysts. The low KIE values suggest significant participation of hydroxyl radicals in
the rate-determining step when H$_2$O$_2$ is used as oxidant. When mCPBA was employed as co-oxidant, the yields were found to be similar (30% for complex 1, 32.5% for complex 2 and 33% for [Fe$^{II}$($N_4$Py)(CH$_3$CN)](ClO$_4$)$_2$) to those obtained in the analogous H$_2$O$_2$ systems, but the A/K ratio slightly improved in the mCPBA system (Table 3). The KIE values for all three complexes were high (in the range 4-5, Table 3) excluding significant participants of hydroxyl radicals.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Oxidant</th>
<th>Total yield (%)$^b$</th>
<th>A/K$^c$</th>
<th>KIE$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$O$_2$$^e$</td>
<td>39</td>
<td>1.2</td>
<td>1.45</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$O$_2$$^e$</td>
<td>32</td>
<td>1.2</td>
<td>1.7</td>
</tr>
<tr>
<td>3$^f$</td>
<td>H$_2$O$_2$$^e$</td>
<td>30.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>1</td>
<td>mCPBA$^g$</td>
<td>30</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>mCPBA$^g$</td>
<td>32.5</td>
<td>2.2</td>
<td>4.5</td>
</tr>
<tr>
<td>3$^h$</td>
<td>mCPBA$^g$</td>
<td>33</td>
<td>5.6</td>
<td>4.5</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1:100:1000 for cat:oxidant:sub in CH$_3$CN at RT
[b] Total yield of cyclohexanol and cyclohexanone
[c] Mol of cyclohexanol/mol of cyclohexanone
[d] Kinetic isotope effect was determined for the formation of cyclohexanol from a competitive reaction of a (1:1) mixture of cyclohexane and cyclohexane-d$_{12}$
[e] Under air
[f] Ref.
[g] Under inert atm.
[h] Ref.

An EPR spectroscopy measurement of complex $^{10}$H$_2$O$_2$ in CH$_3$CN also indicated the formation of 3 as a low spin Fe$^{III}$ species, exhibiting g-values at 1.98, 2.12, 2.16 (Figure 4). These values are very similar to those obtained for a low spin [Fe$^{III}$OOH($N_4$Py)]$^{2+}$ species (g-values: 1.98, 2.12, 2.17).$^{19a}$

Figure 4. The X-band EPR spectrum (at 80 K) of a frozen solution of $^{10}$H$_2$O$_2$ in CH$_3$CN (after mixing at -20 °C).

Addition of excess H$_2$O$_2$ at room temperature to complex 2 in acetonitrile did not lead to purple colouration, rather a brownish yellow colour appeared (Figure 5), which could presumably be an Fe(III)-OH species. However, HRMS collected for a cooled (-20 °C) acetonitrile solution containing complex 2 with H$_2$O$_2$ showed mass peaks at m/z 281.0809 and 661.1125 corresponding to the formulations [Fe$^{IV}$OOH($L_2$)]$^{2+}$ (calc. 281.0822) and [Fe$^{IV}$OOH($L_2$)(ClO$_4$)]$^+$ (calc. 661.1134) (cf. Figure S4-S6, SI). A prominent mass peak at m/z 272.5826, corresponding to [Fe$^{IV}$O($L_2$)]$^{3+}$ (calc. 272.5808), appeared; this ferryl complex

The UV/Vis spectrum of 1$^{10}$H$_2$O$_2$ (red line), 3 (purple line) and decay product of 3 (orange line) in acetonitrile measured at room temperature.
might be formed by decomposition of the \([\text{Fe}^{II}(\text{OOH})(L^2)]^{2+}\) during the measurement.

Figure 5. The UV/Vis spectra of 2 (red line) and 2 + H_2O_2 (orange line) in acetonitrile measured at room temperature.

Formation of \([\text{Fe}^{III}(\text{OOH})(L^2)]^{2+}\) was further established by EPR spectroscopy. Complex 2 in CH_3CN together with H_2O_2 (at -20 °C) exhibited EPR signals with g-values 1.98, 2.12, 2.16 (Figure 6), which could be assigned to a low spin \([\text{Fe}^{III}(\text{OOH})(L^2)]^{2+}\) species (vide supra).

Figure 6. The X-band EPR spectrum (at 80 K) of a frozen solution of 2 + H_2O_2 in CH_3CN (after mixing at -20 °C).

On the other hand, reaction of 1^OTf with mCPBA resulted in formation of a transient Fe^{IV}(O) species, as indicated by UV/Vis spectroscopy and HRMS. The room temperature UV/Vis spectra of 1^OTf with excess mCPBA showed formation of a transient species with a broad absorbance maximum in the range 720-725 nm (cf. Figure S7, SI). This transient species decayed very rapidly at room temperature to form new species (Figure 7) which possibly could be an Fe(III) species.

The HRMS spectrum of 1^OTf together with mCPBA (mixed at -20 °C) showed formation of \([\text{Fe}^{IV}(O)(L^1)]^{2+}\) as well as \([\text{Fe}^{IV}(O)(L^1)(\text{CF}_3\text{SO}_3)]^{+}\) (cf. Figures S8-S10, SI). The isotopic distribution patterns were found to correspond to the formulations of dicaticionic \([\text{Fe}^{IV}(O)(L^1)]^{2+}\) and monocaticionic \([\text{Fe}^{IV}(O)(L^1)(\text{CF}_3\text{SO}_3)]^{+}\). Therefore, the transient species observed in the UV/Vis spectra is most likely \([\text{Fe}^{IV}(O)(L^1)]^{2+}\), which decays rapidly at room temperature under the reaction conditions.

Figure 7. The UV/Vis spectral change taking place upon addition of mCPBA to 1^OTf (red line) in CH_3CN at room temperature.

Summary and Conclusions

The complexes \([\text{Fe}^{III}(L^1)(\text{CH}_3\text{CN})](\text{ClO}_4)_2\) (1) and \([\text{Fe}^{III}(L^2)(\text{CH}_3\text{CN})](\text{ClO}_4)_2\) (2) are competent catalyst precursors for oxidation of alkanes by hydrogen peroxide and peracids (peracetic acid and m-chloroperoxybenzoic acid). Kinetic isotope effect measurements and alcohol/ketone ratios indicate that when H_2O_2 is used as an oxidant, a Fenton type mechanism takes place, where the metal complex serves to generate hydroxyl radicals that function as the effective oxidants. Formation of low spin Fe(III)-OOH species from both 1 and 2 have been detected in the H_2O_2-based catalytic system by UV/Vis, mass spectrometry and EPR spectroscopy, and such species may be immediate precursors to hydroxyl radicals, which would be generated by homolytic cleavage of the O-O bond. On the other hand, when the peracids are used as oxidants, relatively high kinetic isotope effects and high C3/C2 selectivity parameters in adamantane oxidation are detected, effectively ruling out a Fenton-type mechanism. For these oxidants, we postulate that the catalytic oxidation mechanism involves \([\text{Fe}^{IV}(O)(L)]^{2+}\) (L = L^1, L^2) species that react with the substrates via an oxygen rebound mechanism. These Fe(IV) oxo complexes have previously been isolated and characterized by reaction of 1 or 2 with iodosyl benzene. Overall, the catalytic reactivities of the
Fe(II) complexes follow similar trends (in terms of efficiencies and mechanistic scenarios) to that of \([\text{Fe}^2(\text{N4Py})(\text{CH}_3\text{CN})]^{\text{ClO}_3}\) and can be regarded amongst the most efficient non-heme mononuclear iron catalysts.

**Experimental Section**

**Materials and methods.** All solvents were of at least 99.5% purity and used as received. Reagents were of at least 99% purity and used without any further purification. The reagents and solvents were purchased from Sigma-Aldrich and Fisher chemicals.

UV/Visible spectra and all the kinetic experiments were performed on a VWR double-beam UV/Vis spectrophotometer. The reaction mixture in case of kinetic experiments and the complex solution in case of spectra scan were placed in 1 cm quartz cell. The mass spectrometry (ESI) was performed with a Bruker HCT ultra. The high resolution mass spectrum (HRMS) was performed using a Bruker FTICR APEX IV instrument. EPR spectra (X-band, 9.46 GHz) were recorded on a Bruker ECS 106 spectrometer at 80 K using liquid nitrogen. Product analyses were performed on an Agilent technologies 7820A gas chromatograph with a 16 sample automatic liquid sampler and flame ionization detector. The products were identified by their GC retention times.

**Syntheses.**

The Fe(II) complexes, \([\text{Fe}^2(\text{L}^1)(\text{CH}_3\text{CN})]^{\text{ClO}_3}\) (1) and \([\text{Fe}^2(\text{L}^2)(\text{CH}_3\text{CN})]^{\text{ClO}_3}\) (2) were prepared using literature procedure.\(^{32}\)

**Synthesis of \([\text{Fe}^2(\text{CH}_3\text{CN})(\text{L}^1)]^{\text{ClO}_3}\) (100\%).**

A total of 63 mg (0.15 mmol) of ligand \(\text{L}^1\) was taken in a vial and dissolved in minimum amount of acetonitrile. To this solution, 65.4 mg (0.15 mmol) of \([\text{Fe}(\text{CH}_3\text{CN})_2^{2-}(\text{CF}_3\text{SO}_3)_{3}]\) in acetonitrile was added under stirring at room temperature under nitrogen atmosphere. After stirring for about 30 min, the reaction mixture was placed into an ethyl acetate bath and stored overnight. The precipitate was collected by filtration, washed with ethyl acetate, dried under vacuum and obtained as red solid. Yield: 87 mg (71 %); ESI-MS (in CH₃CN): \(m/z \, 238.1 \, [\text{Fe}^2(\text{L}^1)]^{2+} \, (z = 2)\) calc. 238.1, 625.1 \([\text{Fe}^2(\text{L}^1)(\text{CF}_3\text{SO}_3)]^{3-} \, (z = 1)\) calc. 625.1.

**Reaction conditions for catalysis.** In a typical reaction, 2ml of 100 mM (200 μmol) \(\text{H}_2\text{O}_2\) (diluted from 35% \(\text{H}_2\text{O}_2\), aqueous solution) or 2ml of 100 mM (200 μmol) PAA/mCPBA solution in CH₃CN was delivered by syringe pump in air or under nitrogen to a stirred solution of catalyst, i.e. complex 1 (2 μmol), and the substrate (2000 μmol) inside a vial. The final concentrations of the reagents were ~0.7 mM iron catalyst, ~70 mM oxidant and ~700 mM substrate. After syringe pump addition, a known amount of biphenyl solution was added as an internal standard. The iron complex was removed by passing the reaction mixture through a small silica column followed by elution with ethyl acetate. Finally, the solutions were subjected to GC analysis. The organic products were identified and their yields were determined by comparison with authentic compounds. To determine the kinetic isotope effect, an equimolar mixture of cyclohexane and cyclohexane-d₆ was used as a substrate and the reactions were performed under nitrogen atmosphere.

**Supporting Information**

High resolution mass spectra of the reactive intermediates and the UV/Vis spectrum of \(\text{FeH}\) with mCPBA are available in the Supporting Information file.

**Acknowledgments**

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**References**


Evidence that steric factors modulate reactivity of tautomerically iron–oxo species in stereospecific alkane C–H hydroxylation†

Mainak Mitra,* Julio Lloret-Fillol,† Matti Haukka,‡ Miquel Costas*§ and Ebbe Nordlander*†

A new iron complex mediates stereospecific hydroxylation of alkyl C–H bonds with hydrogen peroxide, exhibiting excellent efficiency. Isotope labelling studies provide evidence that the relative reactivity of tautomERICally related oxo–iron species responsible for the C–H hydroxylation reaction is dominated by steric factors.

While the selective functionalization of hydrocarbons remains a significant challenge for chemists,1 several iron-dependent oxygenases are able to mediate the hydroxylation of C–H bonds under mild conditions, using dioxygen as the terminal oxidant.2 Examples include the cytochrome P450 enzymes,3 and the family of non-heme iron-dependent Rieske oxygenases.4 In both cases, C–H hydroxylation occurs with almost complete stereoretention, and is accomplished via the intermediacy of an electrophilic high valent iron–oxo species that attacks the C–H bond via the so-called oxygen-rebound mechanism (Scheme 1).5

A fundamental difference between heme and non-heme sites is that active sites in the latter contain lower coordination numbers, and a number of them form reactive intermediates containing a cis-Fe(O)(X) unit (X = HO(H), Cl, Br). This leads to a versatile reactivity that opens new mechanistic scenarios. Arene cis-dihydroxylation and aliphatic chlorination constitute unique examples of the reactivity exhibited by cis-Fe(O)(X) units (X = OH, Cl and Br).4,5,6

The reactivity of non-heme oxygenases has inspired the design of synthetic model complexes as selective C–H oxidation catalysts.7 Mechanistic studies have shown that in selected cases reactions are metal based, involving high-valent oxo–iron species, and are fundamentally distinct from radical pathway Fenton processes.8 The Fe(PyTACN) family of complexes (Scheme 2) belongs to the group of catalysts that mediate C–H hydroxylation with retention of configuration.9–11 We and others have proposed a mechanistic scenario resembling the “peroxide shunt”3 of cytochrome P450 and model systems. A highly electrophilic [FeV(O)(OH)(LN4)]2+ oxidant (O), formed via water-assisted cleavage of a hydroperoxide [FeIV(OOH)-(OH2)(LN4)]2+ (Pa) (Scheme 2), is ultimately responsible for C–H oxidation reactions.9,a,b,d–f Intermediate O can exist as two tautomerically related species, OA and OB, that differ in the relative positions of the oxo and hydroxide ligands, and are connected through prototopic oxo–hydroxo tautomerism. We have also previously studied C–H oxidation reactions using a set of catalysts where electronic properties of the PyTACN ligand were systematically tuned, and found that the relative reactivity of OA and OB in C–H oxidations remains basically the same, irrespective of the catalyst.10

In this work we turn our attention towards investigation of steric effects. Towards this end, C–H oxidation reactions catalyzed by a Rieske oxygenase enzyme.

Scheme 1 Schematic mechanism for C–H hydroxylation by a Rieske oxygenase enzyme.

† Electronic supplementary information (ESI) available: Ligand synthesis, complex synthesis, proton NMR spectra, ESI-MS and IR spectra of the complex, crystallographic data for complexes 10H and 10H+, catalysis experiments and results and details of isotope labelling experiments. CCDC 960138 and 960139. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47830k
using the new iron complex \([\text{Fe}^\text{III}(\text{CF}_3\text{SO}_3)\text{Me}_2(\text{BzImTACN})]\) (Fig. 1), \(1^\text{III}\), and \([\text{Fe}^\text{II}(\text{H}_2\text{O})\text{Me}_2(\text{BzImTACN})](\text{CF}_3\text{SO}_3)\), \(1^\text{II}\), were prepared and characterized following standard procedures (see ESI† for details). The X-ray structures of \(1^\text{II}\) and \(1^\text{III}\) are very similar to those of \(2^\text{II}\) and \(3^\text{II}\) and have an iron center in a distorted octahedral environment surrounded by the four N atoms of the ligand, with the TACN ring capping one face of the octahedron, and two oxygen atoms of triflate anions (\(1^\text{II}\)) or water molecules (\(1^\text{III}\)), cis to each other (cf. Fig. 1 and ESI†). The average Fe–NTACN and Fe–OH distances are 2.23 Å and 2.13 Å respectively, characteristic of a high spin ferrous center.12

Complex \(1^\text{III}\) was found to be an outstanding catalyst in C–H oxidation reactions with \(\text{H}_2\text{O}_2\). Catalytic oxidation of cyclohexane was chosen for appropriate comparison with literature precedents.8,11 Syringe pump addition of 10 equivalents (w.r.t. the complex) of \(\text{H}_2\text{O}_2\) together with 1000 equivalents of \(\text{H}_2\text{O}\) to a \(\text{CH}_2\text{CN}\) solution containing 1 and a substrate (1000 equivalents) over 30 min in air at room temperature resulted in the formation of cyclohexanol (A) with a turnover number (TON) of 8.5 and a small amount of cyclohexanone (K) with a TON of 0.8, giving an alcohol/ketone (A/K) ratio of 10.6. The efficiency w.r.t. consumption of the oxidant was around 99–100%, and remains unusually high (54%) when 100 equiv. of \(\text{H}_2\text{O}_2\) are employed. Interestingly, when followed over time, the A/K product ratio in oxidation of cyclohexane showed that the initial value of A/K was around 35, which gradually decreased to 10.6 (cf. Fig. S5, ESI†). This provides strong evidence that cyclohexanol is the almost exclusive primary product of the alkane oxidation reaction, and cyclohexanone is a result of further oxidation of the alcohol, thereby eliminating the significant implication of a Russell-type termination mechanism initiated by hydroxyl radicals and producing equal amounts of alcohol and ketone.

Several mechanistic probes further substantiate that the reactions are metal-based. The intermolecular kinetic isotope effect was determined for the formation of cyclohexanol from a mixture (1:3) of cyclohexane and its deuterated isotopomer cyclohexane-d12, and was found to be 5. Also, complex \(1^\text{III}\) oxidizes adamantane with a large \(\text{C}_3\text{H}_7\text{Cl}\) normalized selectivity (14) towards the tertiary C–H bond. The oxidation of cis-1,2-dimethylcyclohexane (DMCH) leads to the corresponding tertiary alcohol product with 97% retention of configuration. These data are consistent with the implication of selective oxidants whose relative reactivities against C–H bonds are modulated by their bond strengths and steric properties.7a The reactivity of \(1^\text{III}\) against these mechanistic probes is thus in good accordance with that described for iron catalysts that mediate steroselective C–H hydroxylation, including those of the \([\text{Fe}(\text{PyTACN})]\) family.8 Since these catalysts operate via a \([\text{Fe}^\text{IV}(\text{O})(\text{OH})(\text{L}^\text{III})](\text{OTf})_2\) oxidant,8,b,d,10,11 the same was tentatively inferred for \(1^\text{III}\). Strong experimental evidence in favor of this scenario arises from olefin cis-dihydroxylation reactions. The water assisted cleavage of the O–O bond (Scheme 2) determines the oxygen atom inventory in the \(\text{HO}--\text{Fe}^\text{III}--\text{O}\) oxidant (O). One of the oxygen atoms originates from the water molecule, while the second oxygen atom is derived from the peroxide. cis-Dihydroxylation reactions incorporate both oxygen atoms of O into the product and consequently syn-diols must contain one oxygen atom that originates from water and one from the peroxide.13 Indeed, \(1^\text{III}\) catalyzes the oxidation of cyclooctene (\(1^\text{III}\), \(\text{H}_2\text{O}_2\); \(\text{H}_2\text{O}^{18}\text{O}\)-cyclooctene, 1:10:1000:1000) affording cis-cyclooctene epoxide (TON = 2) and syn-cyclooctene-1,2-diol (TON = 7). The syn-diol is 98% \(^{18}\text{O}\) labeled, providing strong support in favor of O as the oxidant.

Having obtained positive evidence that \(1^\text{III}\) operates through the same mechanism as that of \(2^\text{II}\) and \(3^\text{II}\), we proceeded to investigate the relative reactivity of the \(\text{O}_2^-/\text{O}_2\) tautomers in C–H hydroxylation reactions. Since the origin of the oxygen atoms is determined in the peroxide precursor (\(\text{P}_\text{O}_\text{II}\)), the relative reactivity of \(\text{O}_2^-/\text{O}_2\) in C–H hydroxylation can be probed using isotopically labeled water and hydrogen peroxide (Scheme 2). The oxidation of cyclohexane by \(1^\text{III}\) in the presence of 10 equivalents of \(\text{H}_2\text{O}^{16}\text{O}\) and 1000 equivalents of \(\text{H}_2\text{O}\) afforded 45% \(^{18}\text{O}\)-labeled cyclohexanol. Complementary experiments with 10 equivalents of \(\text{H}_2\text{O}^{18}\text{O}\) and 1000 equivalents of \(\text{H}_2\text{O}\) afforded 48% \(^{18}\text{O}\)-labeled cyclohexanol (Table 1).

Similar levels of \(^{18}\text{O}\)-label incorporation from \(\text{H}_2\text{O}^{18}\text{O}\) were observed in the case of cyclooctene (41%) and cyclohexane-d12 (48%). These levels of water incorporation are unusually high, only bypassed in the literature by \(2^\text{II}\) and constitute strong evidence that \(\text{O}_2^+\) and \(\text{O}_2^\text{--}\) are roughly equally reactive against secondary C–H bonds. Most interestingly, when the substrates contain tertiary C–H bonds (e.g. DMCH and adamantane), the percentages of \(^{18}\text{O}\) incorporation from \(\text{H}_2\text{O}^{18}\text{O}\) were found to be in the range 25–29%, indicating a preferential oxidation via \(\text{O}_2^+\).

Interpretation of these values can be done by considering those obtained using \(2^\text{II}\) and \(3^\text{II}\) in analogous reactions. Table 1 shows that hydroxylation of tertiary C–H bonds mediated by \(2^\text{II}\) is predominantly performed by \(\text{O}_2^+\) as shown by the large extent of oxygen atoms originating from water in the alcohol.
because steric hindrance at position B induced by the C–C-sp$^2$
and 6-Me-pyridine arms (Fig. 2). Accordingly, when secondary C–H
imidazole ring introduces steric bulk in the proximity of position B
the $[\text{FeV(O)(OH)(LN4)}]^2+$ (Fig. 2) that systematic tuning of the steric properties of the two sites in
OB
C-sp$^3$ methyl substituent.

In conclusion, the present work adds to the growing evidence
that analogous product yields and A/K selectivity values were obtained
when H$_2$O (1000 equiv.) was not specifically added. Analogous product yields and A/K selectivity values were obtained
‡

Notes and references

" analogous product yields and A/K selectivity values were obtained when H$_2$O (1000 equiv.) was not specifically added.

\[\text{FeV(O)(OH)(LN4)}]^2+\]

Table 1
Comparison of percentage of $^{18}$O incorporation into alcohol
products by different Fe-catalysts using 1000 equivalents of H$_2$O

<table>
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<th>Substrate</th>
<th>1$^{\text{st}}$</th>
<th>2$^{\text{nd}}$</th>
<th>3$^{\text{rd}}$</th>
<th>Fe(TPA)$^b$</th>
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<tr>
<td>Cyclohexane</td>
<td>48</td>
<td>45</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Cyclohexane-d$_{12}$</td>
<td>48</td>
<td>40</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>Cyclooctane</td>
<td>41</td>
<td>44</td>
<td>—</td>
<td>23</td>
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<td>cis-DMCH</td>
<td>26</td>
<td>79</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Adamantane</td>
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<td>74</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>cis-Cyclooctene epoxide$^a$</td>
<td>24</td>
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<td>5</td>
<td>9</td>
</tr>
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<td>98</td>
<td>97</td>
<td>78</td>
<td>86</td>
</tr>
</tbody>
</table>

$^a$ Cyclooctene was employed as a substrate. $^b$ $[\text{Fe(TPA)}(\text{CH}_3\text{CN})]^2+$, Ref. 8a.

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An investigation of steric influence on the reactivity of Fe(V) oxo tautomers in stereospecific alkane C-H hydroxylation

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Abstract
Two new tetradebate N4 ligands, Me2,Me2PyzTACN (1-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)ethyl)-4,7-dimethyl-1,4,7-triazacyclononane) and Me2,MeImTACN (1-((1-Methyl-1H-imidazol-1-yl)methyl)-4,7-dimethyl-1,4,7-triazacyclononane) have been synthesized and their Fe(II) complexes have been prepared and characterized. The Fe(II) complexes have been found to be capable of hydroxylating C-H bonds of alkanes with excellent efficiencies, using hydrogen peroxide as oxidant. The high kinetic isotope effect values for C-H bond activation, large normalized C3/C2 bond selectivity in adamantane oxidation and high degrees of stereoretention in the oxidation of cis-1,2-dimethylcyclohexane are indicative of metal-based oxidation processes. The complexes are also able to oxidize cyclooctene to form its corresponding epoxide and syn-diol. For [FeII(Me2,Me2PyzTACN)(CF3SO3)2] the epoxide is the main product, while for the analogous [FeII(Me2,Me2PyzTACN)(CF3SO3)2] complex, the syn-diol predominates. The active oxidant is proposed to be an (L)Fe V(O)(OH) species (L = Me2,Me2PyzTACN, Me2,MeImTACN) 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 two ligands. These studies indicate that the Me2,Me2PyzTACN, exerts a greater steric influence than the Me2,MeImTACN ligand.

Introduction
Over the last two decades, a number of transition metal-based complexes have been developed as catalysts for selective oxidations of C-H and C=C bonds in unsaturated and saturated alkanes and alkenes.1 Iron is often a metal of choice for such catalytic transformations because it is inexpensive, non-toxic and highly abundant.2 In the course of this research, emphasis has also been made on the use of green oxidants, such as dioxygen or hydrogen peroxide, and improvement of selectivities and efficiencies in the oxidation reactions.1 In Nature, oxygenases carry out a wide range of oxidations of organic substrates, and many of them contain iron in their active sites.3,4,5 These iron oxygenases are usually highly selective towards specific C-H bonds, in the presence of several other C-H bonds in the substrate, and utilize atmospheric oxygen as the ultimate oxidant. An example is the Rieske oxygenase family of non-heme iron enzymes, which contain an Fe(II) center bound to two histidine residues and one aspartate in the active site.5,6a This enzyme family catalyzes the cis-dihydroxylation of arenes via activation of dioxygen (Scheme 1) as the first step in
biodegradation of pollutants. The proposed active species consists of a formally high valent Fe(V) center bound to an oxo and a hydroxo group that are *cis* to each other (Scheme 1). The mechanism of C-H hydroxylation is proposed to consist of two concerted steps that are directly related to the “oxygen rebound” mechanism, which has been identified for the cytochrome P450 family of heme oxygenases; this mechanism involves (i) abstraction of a hydrogen atom from a substrate C-H bond by the oxo group to form a transient substrate-based alkyl radical and an Fe(IV)(OH)$_2$ moiety, and (ii) interaction of the alkyl radical with one of the hydroxyl groups of the Fe(IV)(OH)$_2$ moiety to form the product (Scheme 1).

With the reactivities of non-heme iron oxygenases such as Rieske oxygenases serving as an inspiration, several mononuclear non-heme iron catalysts have been developed to address the challenging oxidations of poorly reactive C-H and C=C bonds. 

![Scheme 1. Proposed reaction mechanism for cis-dihydroxylation by Rieske dioxygenases.](image)

The Fe(PyTACN) family of complexes has been shown to mediate C-H hydroxylation via stereoretention of configuration and with excellent efficiencies. Isotope labeling studies and other mechanistic studies strongly indicate that the oxidations occur via the involvement of high valent Fe(V)-oxo intermediates. The reactive intermediate in C-H hydroxylation reactions has been identified as a highly electrophilic [Fe$^V$(O)(OH)(L$^N_4$)$^2+$ oxidant (L$^N_4$ corresponds to tetradeutate TACN-based ligands) which is formed via water-assisted O-O cleavage of the hydroperoxo precursor [Fe$^{III}$[OOH](OH)$_2$(L$^N_4$)]$^{2+}$. The [Fe$^V$(O)(OH)(L$^N_4$)]$^{2+}$ oxidant can exist in two tautomeric forms, corresponding to structures O$_A$ and O$_B$ in Scheme 2, because of the unsymmetric nature of the tetradeutate TACN-derivatives that serve as ligands. The two tautomers differ in the relative positions of the *cis*-coordinated oxo and hydroxo groups, and are connected through a prototopic oxo-hydroxo tautomerism (the barrier to this proton transfer is relatively high (*vide infra*). Investigations have been made on the influence on C-H hydroxylation reactions exerted by manipulation of the electronic as well as steric properties via introduction of different groups (e.g. Me, F, NO$_2$, NMe$_2$) in $\alpha$ and $\gamma$ positions of the pyridine ring of the PyTACN ligand. These studies indicated that electronic properties of the groups in $\gamma$ position on the pyridine ring have no direct effect on the relative reactivities between the two tautomers O$_A$ and O$_B$, while the steric properties of the groups in the $\alpha$ position of the pyridine ring do influence the relative reactivity between the tautomers. The discrimination between the relative reactivities of O$_A$ and O$_B$ was found to be more pronounced in cases of substrates containing tertiary C-H bonds.

Replacement of the pyridyl arm of the PyTACN ligand with a corresponding (N-methyl)benzimidazolyl arm led to the formation of the complex [Fe$^\text{II}$Me$_2$,Me$_2$BzImTACN](CF$_3$SO$_3$)$_2$. Reactivity (catalytic oxidation) studies on this complex were entirely in keeping with the proposed formation of an active Fe(V)(O)(OH) oxidant, and it was found that the (N-methyl)benzimidazolyl moiety exerted a steric influence in discriminating the relative reactivities of O$_A$ and O$_B$ that lies in between that of pyridyl and $\alpha$-
Me-pyridyl moieties, in full agreement with the crystal structures of the Fe(II) complexes of the three ligands. Importantly, $[\text{Fe}^{II}(\text{Me}_2,\text{Me}^2\text{BzImTACN})(\text{CF}_3\text{SO}_3)_2]$ was found to maintain high efficiencies and selectivities in the hydroxylation of alkanes and olefins.\textsuperscript{15}

Scheme 2. Oxidation of alkane and olefin by the two tautomers $O_A$ and $O_B$ observed in reactions catalyzed by Fe(PyTACN) family of complexes.

In this work, we describe the syntheses of two new tetradentate N4 ligands, $\text{Me}_2,\text{Me}^2\text{PyzTACN}$ and $\text{Me}_2,\text{Me}^2\text{ImTACN}$ (Fig. 1). These ligands are based on the PyTACN ligand scaffold, where the pyridyl side arm is replaced by $(N$-methyl)imidazolyl and 3,5-dimethylpyrazolyl arms, respectively. The ligand $\text{Me}_2,\text{Me}^2\text{PyzTACN}$ contains an ethylene spacer connecting one of the amines of the trisazacyclononane (TACN) ring and the N(2) atom of the 3,5-dimethylpyrazole, whereas the corresponding spacer is a methylene in $\text{Me}_2,\text{Me}^2\text{ImTACN}$, in direct correspondence to the ligand frameworks of BzImTACN and PyTACN. The $(N$-methyl)imidazolyl moiety (pK\textsubscript{a} of conjugate acid: 7.06) is more basic than $(N$-methyl)benzimidazolyl (pK\textsubscript{a} of conjugate acid: 5.41) and pyridine (pK\textsubscript{a} of conjugate acid: 5.22), while 3,5-dimethylpyrazole is less basic (pK\textsubscript{a} of conjugate acid: 4.12). Collectively, the different ligands discussed above are thus expected to span a range of steric and electronic demands, while yielding structurally similar Fe(II) complexes which in turn may give rise to analogous Fe(V)(O)(OH) complexes that will exist in tautomeric forms. Thus, the ligands are expected to exert not only electronic but also steric influence on the relative reactivities of the Fe(V)(O)(OH) $O_A$ and $O_B$ tautomers operating in the C-H hydroxylation reactions. Here, we describe the syntheses and characterization of two new Fe(II) complexes of the $\text{Me}_2,\text{Me}^2\text{PyzTACN}$ and $\text{Me}_2,\text{Me}^2\text{ImTACN}$ ligands, and an investigation of the catalytic hydroxylation reactions effected by these two iron complexes. Isotope labeling studies and computational methods have also been performed to elucidate the C-H hydroxylation reaction mechanism(s) and to assess the steric and electronic influence of the ligands on the reactivities of the iron catalysts.

Results and Discussion

The two new tetradentate N4 ligands $\text{Me}_2,\text{Me}^2\text{PyzTACN}$ and $\text{Me}_2,\text{Me}^2\text{ImTACN}$ were synthesized by reaction of TACN$3\text{HBr}$ [1,4-dimethyl-1,4,7-triazacyclononane trihydrobromide] with the corresponding chloromethylene/chloroethylene precursor complex of the five membered
heterocyclic ring (pyrazole and imidazole). In the case of the pyrazole ligand, 1.2 equiv of TACN·3HBr was reacted with 1-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole (one equiv) in refluxing dry MeCN for 5 d, in the presence of K$_2$CO$_3$ and NaI (Scheme 3, cf. Experimental Section for detailed synthesis). The ligand was purified by dissolving in hexane - the impurities remained undissolved. After filtration, the filtrate was evaporated to obtain the pure ligand. For the synthesis of Me$_2$MeImTACN, the TACN·3HBr salt was initially converted into the corresponding free base using NaOH and then extracted with CH$_2$Cl$_2$ to obtain free TACN. This TACN free base (one equiv) was reacted for 20 h with 2-chloromethyl-1-methylimidazole·HCl (one equiv) in refluxing dry MeCN under N$_2$ atmosphere, in the presence of K$_2$CO$_3$ to give the desired ligand Me$_2$MeImTACN (Scheme 3, cf. Experimental section for detailed synthesis). The ligand was obtained in pure form by extraction with hexane.

Scheme 3. Schematic synthetic routes to the ligands Me$_2$Me$_2$PyzTACN and Me$_2$MeImTACN.

The Fe(II) complexes of the two ligands were synthesized inside a dry atmosphere box. Reaction of one equivalent of [Fe$^{II}$(CH$_3$CN)$_2$(CF$_3$SO$_3$)$_2$] with one equivalent of Me$_2$Me$_2$PyzTACN in dry THF resulted in precipitation of the corresponding complex [Fe$^{II}$(Me$_2$Me$_2$PyzTACN)(CF$_3$SO$_3$)$_2$] ($^{1}$OTf), which was collected by filtration, washed with a small amount of THF and dried under vacuum (cf. Experimental section for a detailed description of the synthesis). The corresponding reaction with the Me$_2$MeImTACN ligand in dry THF led to the formation of a complex that mostly remained in solution. The reaction solution was evaporated under vacuum and a small amount of a CH$_2$Cl$_2$:CH$_3$CN (4:1) mixture was added to the resultant residue. Diffusion of diethyl ether into the resultant solution resulted in precipitation of the complex [Fe$^{II}$(Me$_2$MeImTACN)(CF$_3$SO$_3$)$_2$] ($^{2}$OTf).
Scheme 3. Synthesis of Fe(II) complexes \(1^{\text{OTf}}\) (top) and \(2^{\text{OTf}}\) (bottom).

The complexes \(1^{\text{OTf}}\) and \(2^{\text{OTf}}\) were characterized by mass spectrometry and \(^1\text{H}\) NMR spectroscopy. The high resolution mass spectrum (HRMS) of \(1^{\text{OTf}}\) in CH\(_3\)CN showed prominent mass peaks at \(m/z = 167.5903\) and 484.1303, corresponding to the formulations \([\text{Fe}^{\text{II}}(\text{Me}_2\text{,Me}_2\text{PyzTACN})]^2+\) (calc. 167.5881) and \([\text{Fe}^{\text{II}}(\text{Me}_2\text{,Me}_2\text{PyzTACN})(\text{CF}_3\text{SO}_3)]^+\) (calc. 484.1287), respectively (Figures S1-S3, Supplementary Material). The HRMS of complex \(2^{\text{OTf}}\) in CH\(_3\)CN showed prominent mass peaks at \(m/z = 153.5751\) and 456.0970, corresponding to the formulations \([\text{Fe}^{\text{II}}(\text{Me}_2\text{,Me}_2\text{ImTACN})]^2+\) (calc. 153.5724) and \([\text{Fe}^{\text{II}}(\text{Me}_2\text{,Me}_2\text{ImTACN})(\text{CF}_3\text{SO}_3)]^+\) (calc. 456.0974), respectively (Figures S4-S6). The \(^1\text{H}\) NMR spectra of the two complexes were measured in CD\(_3\)CN solvent (cf. Figures S7-S8). Both complexes gave broad paramagnetically shifted spectra in spectral windows ranging from -10 to 120 ppm, indicative of the presence of high spin ferrous ions.

**Crystal and molecular structure of \([\text{Fe}^{\text{II}}(\text{Me}_2\text{,Me}_2\text{PyzTACN})(\text{CF}_3\text{SO}_3)]_2\) (\(1^{\text{OTf}}\))**

Figure 2. The X-Ray crystal structure (ORTEP plot) of complex \(1^{\text{OTf}}\) with 50% probability ellipsoids; the hydrogens and the triflate anions, except the oxygen directly bound to the metal, have been omitted for clarity.
In order to confirm its identity, the solid-state structure of $^{1}$OTf was established by X-Ray crystallography. The details of the structure determination are collected in Table 1 and the selected bond distances and bond angles are listed in Table 2. The X-Ray structure (Figure 1) shows that the Fe(II) center is in a slightly distorted octahedral coordination geometry. The ligand $^{1}$Me$_2$Me$_2$PzTaCN is tetradentate with the three nitrogens of the triazacyclononane ring bound facially to the metal center and the pyrazole ring providing a fourth coordinated nitrogen. The two triflate anions are coordinated in cis positions on the Fe(II) ion. The Fe-N bond distances lie in the range 2.2-2.25 Å, which are typical distances observed for high spin Fe(II) complexes. The Fe-O$_{OTf}$ bond distances are 2.088(3) and 2.199(3) Å. In order to ensure that coordination of the pyrazole nitrogen would be geometrically possible, the $^{1}$Me$_2$Me$_2$PzTaCN ligand was designed to contain an ethylene spacer between the TACN ring and the pyrazole moiety, distinguishing this ligand from the related ligands discussed here, all of which contain methylene spacers in the corresponding positions. The Fe-N (pyrazole) bond distance is 2.209(3) Å while the Fe-N (pyridine) bond distance is 2.165(4) Å in $[^{3}$Fe^{II}(Me$_2$HPyTACN)(CF$_3$SO$_3$)$_2]$ ($^{3}$OTf)$_{11a}$ and 2.246(2) Å in $[^{4}$Fe^{II}(Me$_2$MePyTACN)(CF$_3$SO$_3$)$_2]$ ($^{4}$OTf)$_{17}$. The Fe-N (benzimidazole) bond distance is 2.134(7) Å in $[^{5}$Fe^{II}(Me$_2$MeBzImTACN)(CF$_3$SO$_3$)$_2]$ ($^{5}$OTf)$_{15}$. The differences in Fe-N bond distance may be attributed to the relative basicities of the heterocyclic N-donor moieties. The (N-methyl)benzimidazole and pyridine moieties are better Lewis bases than the pyrazole. The $^{1}$OTfFe-O$_{OTf}$ angle is much larger in $^{1}$OTf (93.6(1)°) than that of $^{3}$OTf (91.64(14)°)$_{11a}$ $^{4}$OTf (94.9(7)°)$_{17}$ and $^{5}$OTf (89.1(3)°)$_{15}$, which could be due to the presence of the longer bridging ethylene spacer and the resulting greater steric demand between the methyl group of the pyrazole side arm and the triflate anions. It should be noted that one of the methyl groups of the pyrazole moiety is parallel to the oxygen of the triflate anion and perpendicular to the oxygen of the second triflate anion (cf. Fig. 2).

Table 1. Crystal data for $^{1}$OTf

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<tr>
<th>Empirical formula</th>
<th>C$<em>{17}$H$</em>{29}$F$<em>{6}$FeN$</em>{5}$O$<em>{6}$S$</em>{2}$C$<em>{4}$H$</em>{10}$O</th>
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<tr>
<td>Empirical formula</td>
<td>$^{1}$OTf</td>
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<td>$\gamma$</td>
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Table 2. Selected bond distances (Å) and bond angles (°) in 1\textsuperscript{OTf}

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<th>Bond</th>
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<td>N(1)-Fe(1)-N(4)</td>
<td>97.1(1)</td>
</tr>
<tr>
<td>N(1)-Fe(1)-N(5)</td>
<td>171.0(1)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-N(3)</td>
<td>89.1(1)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-O(4)</td>
<td>93.6(1)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-N(4)</td>
<td>166.7(1)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-N(5)</td>
<td>90.4(1)</td>
</tr>
</tbody>
</table>
Catalytic C-H bond oxidation studies

The catalytic properties of 1OTf and 2OTf were tested in the hydroxylation of several alkanes employing H2O2 as the oxidant. In a typical catalytic experiment, 10 equiv of H2O2 (from a stock solution of 70 mM H2O2 in CH3CN) was delivered by a syringe pump to a CH3CN solution containing the Fe(II) complex (1 mM), alkane substrate (1 M) and H2O (1 M) over a period of 30 min. The catalysis experiments were performed under air at room temperature. Under these conditions, both complexes oxidized cyclohexane into cyclohexanol (1OTf: TON 6.5; 2OTf: TON 7.7) as the main product with high alcohol/ketone (A/K) ratios (1OTf: A/K 9.4; 2OTf: 12) and high conversions of the oxidant (H2O2) into products (1OTf: 72%; 2OTf: 83.4%). Such high conversion and high A/K ratios are comparable to those obtained with related iron complexes under analogous experimental conditions. 7a,10d,11,15,16d,18 The catalytic efficiencies of these two complexes with different alkane substrates are summarized in Table 3.

Table 3. Catalytic C-H bond oxidation of various alkanes by Fe-complexes using H2O2

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Substrate</th>
<th>TN (A)</th>
<th>TN (K)</th>
<th>A/K</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1OTf</td>
<td>Cyclohexane</td>
<td>6.5</td>
<td>0.7</td>
<td>9.4</td>
<td>72</td>
</tr>
<tr>
<td>2OTf</td>
<td>Cyclohexane</td>
<td>7.7</td>
<td>0.64</td>
<td>12</td>
<td>83.4</td>
</tr>
<tr>
<td>1OTf</td>
<td>Cyclohexane-d12</td>
<td>4</td>
<td>0.5</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>2OTf</td>
<td>Cyclohexane-d12</td>
<td>5</td>
<td>0.5</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>1OTf</td>
<td>Cyclooctane</td>
<td>6</td>
<td>0.6</td>
<td>10</td>
<td>66</td>
</tr>
<tr>
<td>2OTf</td>
<td>Cyclooctane</td>
<td>6.2</td>
<td>0.6</td>
<td>9.8</td>
<td>69</td>
</tr>
<tr>
<td>1OTf</td>
<td>n-hexane</td>
<td>3</td>
<td>0.8</td>
<td>3.8</td>
<td>38</td>
</tr>
<tr>
<td>2OTf</td>
<td>n-hexane</td>
<td>3.6</td>
<td>0.64</td>
<td>5.6</td>
<td>43</td>
</tr>
<tr>
<td>1OTf</td>
<td>2,3-dimethylbutane</td>
<td>2.6</td>
<td>-----</td>
<td>-----</td>
<td>26</td>
</tr>
<tr>
<td>2OTf</td>
<td>2,3-dimethylbutane</td>
<td>3.5</td>
<td>-----</td>
<td>-----</td>
<td>35.2</td>
</tr>
</tbody>
</table>

The remarkably high A/K ratios observed for these complexes suggests the involvement of a metal-based oxidant, as proposed previously. 19 Several other mechanistic substrate probes were used to verify the involvement of a metal-based active oxidant. The kinetic isotope effect (KIE) values obtained in the oxidation of a mixture of cyclohexane and its deuterated topoisomer (1:3 molar ratio) were 4.0 for 1OTf and 4.6 for 2OTf. Both of the complexes showed a preference for selective oxidation of tertiary C-H bonds over secondary C-H bonds in the oxidation of adamantane (normalized 3º/2º ratios were 12 for 1OTf and 26 for complex 2OTf). Finally, in the oxidation of cis-1,2-dimethylcyclohexane (cis-DMCH), the complexes showed a high degree of stereoretention, excluding any significant involvement of long-lived carbon-centered radicals or cations in the C-H oxidation reactions.
Isotope labeling studies

Isotope labeling experiments were performed using H$_2^{18}$O$_2$ and H$_2^{18}$O in order to gain insight into the hydroxylation mechanism as well as the origin of the oxygen atom incorporation into the (alcohol) products. In the oxidation of cyclohexane, 1$^{OTf}$ (1 equiv) was found to introduce only 2.6% labelled oxygen into the alcohol product in the presence of 10 equiv H$_2$O$_2$ and 1000 equiv of H$_2^{18}$O (Scheme 4). The complementary experiment performed with reverse labelling, i.e. 10 equiv H$_2^{18}$O$_2$ and 1000 equiv H$_2$O resulted in an $^{18}$O-label incorporation of 86% into the alcohol. It may thus be concluded that peroxide is the main source of oxygen in the alcohol product and only 11% of oxygen atoms are incorporated from air/water (mass balance) for this specific hydroxylation reaction. In the oxidation of other alkane substrates containing secondary C-H bonds, complex 1$^{OTf}$ with 10 equiv H$_2$O$_2$ and 1000 equiv of H$_2^{18}$O gave rise to similar low percentages of incorporated labeled oxygen (from water) into the alcohol (3% for cyclohexane-d$_{12}$ and cyclooctane).

On the other hand, 2$^{OTf}$ gave rise to considerably greater incorporation of oxygen from water into the products. In the presence of 10 equiv H$_2$O$_2$ and 1000 equiv of H$_2^{18}$O, complex 2$^{OTf}$ (1 eq.) gave 39 and 43% labeled alcohols in the oxidation of cyclohexane and cyclooctane, respectively (Scheme 4). The complementary experiment with 10 equiv H$_2^{18}$O$_2$ and 1000 equiv H$_2$O resulted in the formation of 55% labeled cyclohexanol in oxidation of cyclohexane. Thus, for this complex, both peroxide and H$_2$O are the sources of oxygen in the alcohol products.

In the oxidation of tertiary C-H bonds (cis-DMCH and adamantane), 1$^{OTf}$ did not incorporate any oxygen from water into the products ($\sim$ 0% $^{18}$O incorporation) (cf. Table 4). On the other hand, the equivalent experiments with 2$^{OTf}$ led to the incorporation of 39% and 31% oxygen incorporations from water into product(s) in the oxidation of adamantane and cis-DMCH, respectively (cf. Table 4).

**cis-Dihydroxylation vs epoxidation in the oxidation of alkenes**

Complexes 1$^{OTf}$ and 2$^{OTf}$ catalyzed the oxidation of alkenes in the presence of H$_2$O$_2$ and H$_2$O to give both epoxide and cis-dihydroxylated products. Under catalytic conditions (1:10:1000 for catalyst:oxidant:substrate), 1$^{OTf}$ oxidized cis-cyclooctene to give cis-cyclooctene epoxide (TON 8.2) as a major product with the concomitant formation of a minor amount of syn-cyclooctane-1,2-diol (TON 0.5), i.e. an epoxide:dilol (E/D) ratio of 16.5. Addition of H$_2$O (1000 equiv) slightly increased the formation of syn-diol (TON 1.1), but has almost no influence in the yield of epoxide (TON 8.2). When 100 equiv of H$_2$O$_2$ was employed, the yield of both epoxide (TON 53) and cis-diol (TON 4.8) was increased. In oxidation of 1-
octene, complex $1^{\text{OTf}}$ in the presence of 100 equiv H$_2$O$_2$ yielded 1-octene epoxide (TON 16.5) as the major product together with a minor amount of syn-dihydroxylated product (TON 2.5). Complex $2^{\text{OTf}}$, on the other hand, preferred formation of syn-diol over epoxide in the oxidation of cis-cyclooctene; in this reaction, complex $2^{\text{OTf}}$ (1 equiv) together with H$_2$O$_2$ (10 equiv) produced syn-cyclooctane-1,2-diol with a TON of 5.9 and cis-cyclooctene epoxide with a TON of 3.9 (E/D = 0.6) and an overall conversion of 96% (w.r.t the oxidant). In the oxidation of the terminal alkene 1-octene, complex $2^{\text{OTf}}$ (1 equiv) together with H$_2$O$_2$ (10 equiv) produced cis-diol with a TON of 4.4 and epoxide with a TON of 1.5 (E/D = 3) and a conversion of approximately 36%.

In order to investigate the identity of the active oxidant, isotope labeling studies were made for both complexes, employing cis-cyclooctene as substrate. Such studies on the Fe(PyTACN) family of complexes and the related complex $5^{\text{OTf}}$ have established that the oxygen atom in the cis-dihydroxylated product is originating from the oxygen coordinated to the iron metal center in cis-binding mode. In the presence of 10 equiv H$_2$O$_2$ and 1000 equiv H$_2$H$_{18}$O, $1^{\text{OTf}}$ (1 equiv) introduced 92% $^{18}$O into the product syn-cyclooctane-1,2-diol during the oxidation of cis-cyclooctene, while complex $2^{\text{OTf}}$ gave 97% label incorporation under the same conditions. These results are in full agreement with previous isotope labelling results which indicate that a high valent Fe$^V$(O)(OH) species is formed via water assisted O-O cleavage of Fe$^{III}$(OOH)(OH$_2$)$_{13}$ and acts as the active oxidant in the hydroxylation reactions. In accordance with this assumption and the expected reactivity pattern, the labelling studies confirm that one of the two oxygen atoms in the syn-diol product originates from water and the other from hydrogen peroxide.

Table 4. $^{18}$O incorporation from H$_2$H$_{18}$O in C-H hydroxylation reactions mediated by different Fe(II)-complexes$^1$

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Complex $1^{\text{OTf}}$</th>
<th>Complex $2^{\text{OTf}}$</th>
<th>Complex $3^{\text{OTf}}$</th>
<th>Complex $4^{\text{OTf}}$</th>
<th>Complex $5^{\text{OTf}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexane</td>
<td>3</td>
<td>39</td>
<td>45</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>Cyclohexane-$d_{12}$</td>
<td>3</td>
<td>NA</td>
<td>40</td>
<td>NA</td>
<td>48</td>
</tr>
<tr>
<td>Cyclooctane</td>
<td>3</td>
<td>43</td>
<td>44</td>
<td>NA</td>
<td>41</td>
</tr>
<tr>
<td>Cis-DMCH</td>
<td>0</td>
<td>31</td>
<td>79</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Adamantane</td>
<td>0</td>
<td>39</td>
<td>74</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>Cis-cyclooctene$^2$ epoxide</td>
<td>2</td>
<td>36</td>
<td>77</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>Syn-cyclooctane-1,2-diol$^2$</td>
<td>97</td>
<td>92</td>
<td>97</td>
<td>78</td>
<td>98</td>
</tr>
</tbody>
</table>

$^1$ Reaction conditions: catalyst:H$_2$O$_2$:H$_2$H$_{18}$O:substrate = 1:10:1000:1000, CH$_3$CN, RT, air; $^2$ cis-cyclooctene was employed as the substrate.

When the incorporation of water into the other oxidation product, cis-cyclooctene epoxide, was analyzed, complex $1^{\text{OTf}}$ behaved drastically different from complex $2^{\text{OTf}}$. The incorporation of $^{18}$O using labeled water was 36% for complex $2^{\text{OTf}}$, while that for complex $1^{\text{OTf}}$ was only ~ 2%. For the related complexes $5^{\text{OTf}}$ and $3^{\text{OTf}}$, the amount of $^{18}$O-labeled epoxide formed were 24 and 77%, respectively. On basis of these labelling studies, we may assign $3^{\text{OTf}}$ as belonging to what has been designated the class I category complexes,$^1$ where the oxygen in the epoxide originates mainly from water, and complex $1^{\text{OTf}}$ belongs to the
class II complexes where the oxygen comes exclusively from peroxide. The complexes $2^{\text{OTf}}$ and $5^{\text{OTf}}$ may be placed in intermediate positions between these two categories.

**Computational Modelling**

In order to gain an understanding of the relative energies of the postulated Fe$^V$(O)(OH) tautomers, computational modelling of the two tautomers generated from $[\text{Fe}^{\text{II}}(\text{Me}_2,\text{MeBzImTACN})(\text{CF}_3\text{SO}_3)_2]^-$ ($5^{\text{OTf}}$). The ground-state stability ordering of the two $\text{Me}_2,\text{MeBzIm}$ compounds was computationally investigated by Density Functional Theory (DFT), and here the tautomeric species that contains an oxo moiety coplanar with the benzimidazole ligand is labeled as A (*note*: corresponding to O$_B$). Species B represents the isomer whose oxo moiety is perpendicular to the heterocyclic ligand (*note*: corresponding to O$_A$). The DFT analyses confirm the quartet state ($S = 3/2$) as the thermodynamically favoured spin state for both isomers, with $4^A$ found to lie 2.4 kcal/mol lower in energy than $4^B$. Figure 3 shows the geometry-optimized structure for the two tautomers. The corresponding doublet spin states of $2^A$ and $2^B$ ($S = 1/2$) lie 11.5 and 9.1 kcal/mol higher in energy than their respective quartet counterparts. Having established the ground-state stability ordering and spin-state preference for the two isomeric oxo-hydroxyl compounds, the lability of proton transfer between these tautomers was next explored. Proton transfer between the different oxygen centers in $4^A$ and $4^B$ occurs through transition structure $4^\text{TS}^A4^B$, as depicted in Figure 3, and basically involves the synchronous transfer of the hydrogen between the two oxygen centers. The free-energy barrier is high and in excess of 30 kcal/mol, and these data are in keeping with the reported configurational stability of the related pyridyl-derivatives prepared by Company and Costas. The absence of facile proton transfer between the two oxygen centers in $4^A$ and $4^B$ suggests that the oxo-based C-H abstractions observed in these studies must originate from structurally different oxidants that do not allow equilibration of the oxo moiety on the time scale of the chemical reactions, a feature supported by the isotopic labeling studies.

![Figure 3. B3LYP-optimized structures and potential energy surface for the isomerization of $^4A$ to $^4B$. Energy values are in $\Delta G$ in kcal/mol relative to $^4A$.](image)
In order to elucidate the mechanism of the hydrogen-atom transfer (HAT) of alkanes by $^4A$ and $^4B$, DFT calculations were carried out using methane ($C$) as the substrate. This particular substrate was chosen in order to simplify the calculations and reduce the computational time. Figure 4 shows the geometry-optimized transition-state structures involved in the H-abstraction and the resulting MeOH-substituted compounds, while Figure 5 shows the potential energy surface for these reactions. H-abstraction is site selective and is mediated by the oxo moiety in $^4A$ and $^4B$, leading to the respective transition-state structures $^4TS^4AC^6D$ and $^4TS^4BC^6E$, each of which exhibits a similar activation barrier on the order of 25 kcal/mol. The expected geminate radical pairs that follow each H-abstraction could not be found by IRC calculations, presumably a manifestation of the flat nature of the reaction surface en route to the alcohol product. Collapse of the geminate radical pair in each reaction via a rebound process, coupled with a spin crossover to the thermodynamically favored high-spin sextet species ($S = 5/2$), completes the hydroxylation sequence and affords the MeOH-substituted products $^6D$ and $^6E$. Both hydroxylation routes are exergonic in nature, and the MeOH-substituted product having the alcohol ligand disposed perpendicular to the heterocyclic ligand is 3.1 kcal/mol more stable due to reduced interactions between the coordinated alcohol and ligand scaffold.

Figure 4. B3LYP-optimized transition structures $^4TS^4AC^6D$ and $^4TS^4BC^6E$ and the MeOH-substituted products $^6D$ and $^6E$ from the methane ($C$) hydroxylation reaction using $^4A$ and $^4B$. 
Summary and Conclusions

We have previously demonstrated the steric influence exerted by ligands on the reactivities of iron(V) oxo-hydroxo tautomers operating in C-H hydroxylation reactions.\textsuperscript{15} This study further addresses and strengthens the fact that the ligand exerts a profound influence on the oxygen atom transfer reactivity, with the steric bulk of the donor moiety of the pendant arm attached to the TACN ligand deciding the relative ease of approach of a substrate with a sterically hindered tertiary C-H bond to the oxo ligand of the O\textsubscript{B} tautomer (as opposed to the O\textsubscript{A} tautomer, where the oxo ligand is more accessible) of the proposed active Fe(V)(O)(OH) oxidant. As there is evidence that this specific oxo ligand originates from water,\textsuperscript{12,13} the relative incorporation of oxygen from H\textsubscript{2}\textsuperscript{18}O into a (sterically bulky) alkane substrate (especially those containing tertiary C-H bonds) may be used as a guide to the steric influence of the ligand on substrate access to the O\textsubscript{B} oxo ligand – low incorporation of labelled oxygen into the oxidation product indicates steric hindrance by the ligand. The levels of incorporation of \textsuperscript{18}O from water into the substrates (cyclohexane, cyclooctane, adamantane, cis-DMCH, cis-cyclooctene) are listed in Table 3. For complex 1\textsuperscript{OTf}, the very low percentage of \textsuperscript{18}O incorporation (< 3%) from H\textsubscript{2}\textsuperscript{18}O in the products suggests that the tautomer O\textsubscript{A} predominates over O\textsubscript{B} (irrespective of substrates containing secondary or tertiary C-H bonds) in the C-H hydroxylation reaction. On the other hand, the levels of \textsuperscript{18}O incorporation (within the range 30-45%) from H\textsubscript{2}\textsuperscript{18}O into products for complex 2\textsuperscript{OTf} indicate that both O\textsubscript{A} and O\textsubscript{B} are equally reactive towards substrates with little preference of O\textsubscript{A} over O\textsubscript{B} for substrates containing tertiary C-H bonds.

While the high percentage (above 90%) \textsuperscript{18}O incorporation in the syn-diol product in oxidation of cis-cyclooctene by complexes 1\textsuperscript{OTf} and 2\textsuperscript{OTf} (cf. Table 4) demonstrates the involvement of Fe(V)(O)(OH) oxidant as observed for Fe(PyTACN) complexes, the different range of \textsuperscript{18}O
incorporation into the epoxide product also discriminate the relative reactivity between O_A and O_B. The amounts of labeled epoxide were 2% and 36% for complexes 1^{OTf} and 2^{OTf} respectively, clearly implying that epoxidation reaction catalyzed by complex 1^{OTf} is performed exclusively by O_A and in complex 2^{OTf}, O_A and O_B are roughly equally active.

On the basis of these measurements, the order of steric interference of the ligand with the O_B oxo ligand (i.e. tautomer O_B) is 1^{OTf} > 4^{OTf} > 5^{OTf} > 2^{OTf} > 3^{OTf}. The crystal structures of the Fe(II) catalysts, which are direct precursors to the active perferryl (Fe^V(O)) oxidants, provide a structural basis for the steric influence of the ligands. In Figure 6, space filling plots of the crystal structures of the above-mentioned complexes are plotted and correlated to the steric influence exerted by the ligands.

As shown above, the computational modelling of the HAT reactions effected by the postulated tautomeric Fe^V(O)(OH) oxidants derived from 5^{OTf} do support that the ligand does influence the HAT reactivity in the manner discussed above. It should be noted that different basicities or, donor properties possessed by the side arms ((N-methyl)imidazole, (N-methyl)benzimidazole and 3,5-dimethylpyrazole) of the tetradeptate ligands might have some influence on the reactivity of Fe(V)(O)(OH) oxidant in general, and the relative reactivities of the two tautomers in particular. However, this is not as apparent or conclusive as the steric properties of the side arms from the present investigation. Thus, the possible effects of electronic properties of the ligands on the reactivities need to be clarified and further studies are undertaken towards this direction.

**Experimental section**

**Reagents and Materials**

Reagents and solvents were of at least 99% purity and used as received without any further purification. H_2^{18}O_2 (90% ^18O-enriched, 2% solution in H_2^{18}O) and H_2^{16}O (95% ^16O-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 CaH₂; diethyl ether was dried by distillation from Na/benzophenone. The starting materials 1-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole,²⁰ 1-(2-chloromethyl)-2-methylimidazole hydrochloride²¹ and 4,7-dimethyl-1,4,7-triazacyclononane trihydrobromide (TACN·3HBr)²² were synthesized according to a literature procedure.

**Instrumentation**

Infrared spectra were collected on a Nicolet Avatar 360 FTIR spectrometer. UV-Visible spectroscopy was performed in a 1 cm quartz cell using an Agilent Technology 8453 UV-Vis spectrophotometer equipped with a diode-array detector. NMR spectra were recorded on a Bruker DPX 400 MHz and Varian Inova 500 MHz spectrometers in CDCl₃ or CD₃CN solvent using standard conditions, and were referenced to the residual proton signal of the solvent. Elemental analysis was performed on a 4.1 Vario EL 3 elemental analyzer from Elementar. The ESI-MS experiments were performed with a Bruker Esquire 6000 LC/MS chromatograph, using acetonitrile as a mobile phase. The product analyses after catalysis experiments were carried out on an Agilent Technology 7820A 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.

**Synthesis**

**Synthesis of Me₂Me₂PyzTACN [1-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)ethyl)-4,7-dimethyl-1,4,7-triazacyclononane]**

A mixture of 1-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole (243 mg, 1.53 mmol, 1.0 equiv), 1,4-dimethyl-1,4,7-triazacyclononane (289 mg, 1.84 mmol, 1.2 equiv), K₂CO₃ (1.27 g, 9.18 mmol, 6.0 equiv), NaI (229 mg, 1.53 mmol, 1.0 equiv) and Na₂SO₄ (435 mg, 3.06 mmol, 2.0 equiv) in CH₃CN were stirred for 5 days at 90 ºC under N₂ atmosphere. After cooling down to room temperature, the resultant mixture was filtered through a celite pad, after which the celite pad was washed with CH₂Cl₂. The filtrate was washed with 1 M NaOH (2 × 50 ml) and saturated brine solution (50 ml). The organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. Then 50 ml hexane was added to the resulting residue and stirred overnight at room temperature. The solution was filtered through a celite pad. Removal of the solvent under reduced pressure gave the desired ligand as a yellow oil. Yield: 201 mg (47%). ESI-MS: m/z 280 [M+H]⁺; 302 [M+Na]⁺. ¹H-NMR (500 MHz, CDCl₃) δ (ppm): 5.74 (s, 1H), 4.01 (t, 2H), 2.91 (t, 2H), 2.76-2.74 (m, 4H), 2.65 (s, 4H), 2.64-2.62 (m, 4H), 2.34 (s, 6H), 2.22 (s, 3H), 2.19 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm): 147.2, 138.6, 104.8, 58.2, 57.5, 56.9, 56.2, 47.0, 46.7, 13.4, 11.7.

**Synthesis of Me₂MeImTACN [1-((1-Methyl-1H-imidazol-1-yl)methyl)-4,7-dimethyl-1,4,7-triazacyclononane]**

A mixture of 1-(2-chloromethyl)-2-methylimidazole hydrochloride (166 mg, 1.0 mmol, 1.0 equiv), 1,4-dimethyl-1,4,7-triazacyclononane (157.2 mg, 1.0 mmol, 1.0 equiv) and K₂CO₃ (268 mg, 2.0 mmol, 2.0 equiv) in extra dry CH₃CN were refluxed for about 20 h under N₂ atmosphere. The resulting yellow solution was then filtered through a celite pad and the celite pad was washed with CHCl₃. The filtrate was evaporated under reduced pressure and the resulting residue was stirred overnight with hexane (30 ml) and a small amount of CH₂Cl₂ (5 ml) at room temperature. The solution was filtered through a celite pad and removal of the solvent gave the ligand as yellow oil. Yield: 138 mg (55%). ESI-MS: m/z 252.1 [M+H]⁺. ¹H-NMR (500 MHz, CDCl₃) δ (ppm): 6.87 (s, 1H), 6.8 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.75-2.73 (m, 4H), 2.67 (s, 4H), 2.59-2.57 (m, 4H), 2.29 (s, 6H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm): 146.1, 127.0, 121.3, 57.0, 56.7, 55.7, 55.0, 46.5, 33.0.

**Synthesis of [FeII(Me₂Me₂PyzTACN)(CF₃SO₃)₂] (1OTf)**

A solution of Me₂Me₂PyzTACN (190 mg, 0.68 mmol, 1.0 equiv) in THF (1.0 ml) was added to a solution of [FeII(CH₃CN)₂(CF₃SO₃)₂] (296 mg, 0.68 mmol, 1.0 equiv) in THF (2.0 ml) and stirred overnight at room temperature inside a glove box. A white solid was precipitated which was filtered off and washed with THF (2 × 2 ml). After this, it was dissolved in CH₂Cl₂/CH₃CN (3.0 ml/three drops) and filtered through celite. Removal of
the solvent under reduced pressure gave the desired complex as a white solid. Yield: 199 mg (41%). X-ray quality crystals were grown by slow diffusion of ether into a solution of the metal complex in CH₂Cl₂ with few drops of CH₃CN. HRMS (m/z): 167.5903 [Fe(II)(Me₂,Me₂PyzTACN)]²⁺ (z = 2); 484.1303 [Fe(II)(Me₂,Me₂PyzTACN)(CF₃SO₃)]⁺ (z = 1); Elemental analysis C₁₇H₂₉F₆N₅O₆S₂Fe (MW = 633.406 g/mol) Calc. (%) C 32.24, H 4.61, N 11.06; Found (%) C 33.09, H 4.92, N 10.83; 1H-NMR (400 MHz, CD₃CN) 130.4, 98.4, 66.5, 52.5, 34.6, 34.0, 13.5, -3.41; UV/Vis λ (nm) 194 (ε = 8327 M⁻¹cm⁻¹), 220 (ε = 9622 M⁻¹cm⁻¹); FTIR (KBr) ν (cm⁻¹) 2963-2863, 1672, 1558, 1501, 1474, 1430, 1371, 1355, 1324, 1293, 1233, 1163, 1133, 1090, 1070, 1063, 974, 839, 788, 776, 759, 751, 638, 576, 516.

Synthesis of [Fe(II)(Me₂,MeImTACN)(CF₃SO₃)₂] (2OTf)

A solution of Me₂,MeImTACN (125.6 mg, 0.5 mmol, 1.0 equiv) in THF (1.0 ml) was added to a solution of [Fe(II)(CH₃CN)₂(CF₃SO₃)₂] (217.6 mg, 0.5 mmol, 1.0 equiv) in THF (1.5 ml) and stirred overnight at room temperature inside a glove box. The colour of the solution changed to pale yellow. The reaction solution was evaporated under vacuum and the residue was dissolved in CH₂Cl₂/CH₃CN (4:1 mixture) and filtered through celite. Diffusion of ether into the resultant solution resulted the complex as light yellowish white solid. Yield: 137 mg (45%). HRMS (m/z): 153.5751 [Fe(II)(Me₂,MeImTACN)]²⁺ (z = 2); 456.0970 [Fe(II)(Me₂,MeImTACN)(CF₃SO₃)]⁺ (z = 1); Elemental analysis C₁₅H₂₅F₆N₅O₆S₂Fe (MW = 605.353 g/mol) Calc. (%) C 29.76, H 4.16, N 11.57; Found (%) C 30.55, H 4.28, N 11.08; 1H-NMR (500 MHz, CD₃CN) 99.43, 82.93, 69.52, 64.56, 55.36, 50.00, 33.54, 21.24, 6.72, 4.06, 3.65, 3.59, 3.05-3.02, 2.88-2.82, 2.77-2.74, 2.66, 2.59, 2.51-2.48, 2.21, 1.94, 1.81, 1.56, 1.32, 1.24, 1.21, 0.05; UV/Vis λ (nm) 365 (ε = 3100 M⁻¹cm⁻¹), 512 (ε = 60 M⁻¹cm⁻¹); FTIR (KBr) ν (cm⁻¹) 2921, 1634, 1458, 1259, 1176, 1032, 756, 548, 519.

Crystal structure determination for complex 1OTf

Colourless crystals of 1OTf were grown from slow diffusion of ethyl ether in a CH₂Cl₂ solution of the compound, and used for low temperature (100(2) K) X-ray structure determination. The measurement was carried out on a BRUKER SMART APEX CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) from an X-ray Tube. The measurements were made in the range 1.636 to 28.083° for θ. Hemi-sphere data collection was carried out with ω and φ scans. A total of 16414 reflections were collected of which 6388 [R(int) = 0.0502] were unique. Programs used: data collection, Smart 23; data reduction, Saint+ 24; absorption correction, SADABS 25. Structure solution and refinement was done using SHELXTL 26. The structure was solved by direct methods and refined by full-matrix least-squares methods on F². The non-hydrogen atoms were refined anisotropically. The H-atoms were placed in geometrically optimized positions and forced to ride on the atom to which they are attached. A considerable amount of electron density attributable to a disordered Ethyl Ether solvent molecule per asymmetric unit was removed with the SQUEEZE option of PLATON 27. Those solvent molecules are, however, included in the reported chemical formula and derived values (e.g. formula weight, F(000), etc.).

Reaction Conditions for Catalysis Experiments

In a typical reaction, 360 μL of H₂O₂ (25 μmol), taken from a 70 mM H₂O₂ stock solution in CH₃CN 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 CH₃CN 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 H₂O and 1000 mM for substrate (1:10:1000:1000 for cat:ox:H₂O: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-d₁₂ in a ratio of 1:3 was used to improve the accuracy of the obtained KIE value.
Isotope labeling studies

Catalytic reaction conditions using H\textsubscript{2}\textsuperscript{18}O: In a typical reaction, 290 \(\mu\)L of H\textsubscript{2}O\textsubscript{2} (20 \(\mu\)mol), taken from a 70 mM H\textsubscript{2}O\textsubscript{2} stock solution in CH\textsubscript{3}CN, was delivered by syringe pump over 30 min at room temperature under air to a vigorously stirred CH\textsubscript{3}CN solution (1.71 ml) containing the Fe-catalyst (2.0 \(\mu\)mol), substrate (2000 \(\mu\)mol) and H\textsubscript{2}\textsuperscript{18}O (2000 \(\mu\)mol). The final concentrations were 1 mM for catalyst, 10 mM of the oxidant, 1000 mM for H\textsubscript{2}\textsuperscript{18}O and 1000 mM for substrate (1:10:1000:1000 for cat:H\textsubscript{2}O\textsubscript{2}:H\textsubscript{2}\textsuperscript{18}O:sub). For adamantane, due to the low solubility, only 50 \(\mu\)mol of the substrate was used and so the final concentration was 20 mM.

Catalytic reaction conditions using H\textsubscript{2}\textsuperscript{18}O\textsubscript{2}: In a typical reaction, 34 \(\mu\)L of H\textsubscript{2}\textsuperscript{18}O\textsubscript{2} (20 \(\mu\)mol) taken from a 2\% (wt/wt) H\textsubscript{2}\textsuperscript{18}O\textsubscript{2} solution in H\textsubscript{2}\textsuperscript{18}O was delivered by syringe pump over 30 min at room temperature under air to a vigorously stirred CH\textsubscript{3}CN solution (2 ml) containing the Fe-catalyst (2.0 \(\mu\)mol), substrate (2000 \(\mu\)mol) and 45 \(\mu\)L of H\textsubscript{2}O. The final concentrations were 1 mM for catalyst, 10 mM for the oxidant, 1000 mM for H\textsubscript{2}O and 1000 mM for substrate (1:10:1000:1000 for cat:H\textsubscript{2}O\textsubscript{2}\textsuperscript{18}:H\textsubscript{2}O:sub).

In the oxidation of adamantane and \textit{cis}-1,2-dimethylcyclohexane, the solution (after syringe pump addition) was passed through a small silica column to remove the Fe-catalyst, followed by elution with 2 ml ethyl acetate. For other substrates, the reaction solution was treated with 1 ml acetic anhydride and 0.1 ml of 1-methylimidazole to esterify the alcohol products for GC-MS analyses (tertiary alcohols are not esterified under these conditions). Samples were concentrated by removing part of the solvent under vacuum and subjected to GC-MS analyses.

Computational Details and Modeling

All DFT calculations were carried out with the Gaussian 09 package of programs\textsuperscript{28} using the B3LYP hybrid functional. This functional is comprised of Becke’s three-parameter hybrid exchange functional (B3)\textsuperscript{29} and the correlation functional of Lee, Yang, and Parr (LYP).\textsuperscript{30} The iron atom was described with the Stuttgart-Dresden effective core potential and SDD basis set,\textsuperscript{31} and the 6-31G(d’) basis set\textsuperscript{32} was employed for all remaining atoms.

All reported geometries were fully optimized, and analytical second derivatives were evaluated at each stationary point to determine whether the geometry was an energy minimum (no negative eigenvalues) or a transition structure (one negative eigenvalue). Unscaled vibrational frequencies were used to make zero-point and thermal corrections to the electronic energies. The resulting potential energies and enthalpies are reported in kcal/mol relative to the specified standard. Standard state corrections were applied to all species to convert concentrations from 1 atm to 1M according to the treatise of Cramer.\textsuperscript{33} The geometry-optimized structures have been drawn with the \textit{JIMP2} molecular visualization and manipulation program.\textsuperscript{34}

Supporting information

ESI-MS, \textsuperscript{1}H-NMR, UV/Vis and FT-IR spectra of complexes \textit{1OTf} and \textit{2OTf} are available.

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Highly Enantioselective Epoxidation of Olefins by H$_2$O$_2$ Catalyzed by a Non-heme Fe(II) complex of a Chiral Tetradeutate Ligand

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Supporting Information

ABSTRACT: The new chiral tetradeutate N4-donor ligand 1-methyl-2-(1S)-2-(1-methylbenzimidazol-2-yl) methyl)pyrrolidin-2-yl]pyrrolidin-1-yl)methyl benzimidazole (S,S-PDZL), based on a chiral dipyrrolidene backbone, has been synthesized and its corresponding Fe(II) complex has been prepared and fully characterized. The X-ray structure of the complex reveals that the Fe(II) ion is in a distorted octahedral coordination environment with two cis-oriented coordination sites occupied by (labile) triflate anions. The ability of the iron complex to catalyze asymmetric epoxidation reactions of olefins with H$_2$O$_2$ was investigated, using 2-cyclohexen-1-one, 2-cyclopenten-1-one and cis-β-methylstyrene as substrate. Different carboxylic acids were used as additives to enhance yields and enantioselectivities. The catalysis results indicate that the Fe(II) complex is capable of effecting comparatively high enantioselectivities (> 80%) in the epoxidation reactions albeit with low product yields.

Introduction:

Optically active (chiral) epoxides are widely used in organic synthesis and industry as intermediates and building blocks for synthesis of drugs and agrochemicals. Amongst various methods developed over years to synthesize chiral epoxides, the catalytic asymmetric epoxidation of olefins has proven to be a very useful techniques that is employed both in fine chemical and industrial syntheses. Since the pioneering work by Sharpless and coworkers in the 1980s, there have been numerous efforts to develop efficient catalytic systems, including chiral metal complexes and organocatalysts, for such transformations. Development of environmentally benign and cheap catalysts and oxidants with wide ranges of applications remain great challenges to synthetic chemists. With the growing demand for green and sustainable chemistry, use of iron-based catalysts employing H$_2$O$_2$ as an oxidant has been an attractive research area because of the low cost, low toxicity and high abundance of iron in nature. Collman et al. reported the first enantioselective epoxidation of styrene derivatives catalyzed by iron-porphyrin complexes with iodosobenzene as an oxidant in 1999. Beller and co-workers have reported a methodology for the asymmetric epoxidation of stilbene derivatives using an in situ iron-based catalyst, giving up to 97% ee. Several non-heme iron-catalyzed asymmetric epoxidation reactions are reported with various olefin substrates giving moderate to good yield and enantioselectivity. The factors that indirectly control the yield and enantioselectivity in iron-catalysed asymmetric epoxidation need to be thoroughly investigated. The presence of catalytic amounts of a carboxylic acid has been found to enhance both the yield and enantioselectivity in epoxide formation. A mechanism scenario that has been proposed by Que and co-workers for the iron-catalysed epoxidation of alkenes with H$_2$O$_2$/acetic acid involves the formation of a carboxylate-Fe(V) species as the active oxidant via acetic acid-assisted heterolytic O-O bond cleavage of the hydroperoxide ligand in an Fe(II)(OOH)/(HOOCH$_3$)$_2$ precursor (Scheme 1). A recent computational study suggests that the carboxylic acid, owing to its non-innocent redox nature, can be oxidized by one electron and reduce the Fe ion to form a Fe(IV)-carboxyl radical intermediate, similar to the Cytochrome P450 compound I. Electronic factors imposed by the ligand on the iron ion play an important role in the activation of H$_2$O$_2$ and O-atom transfer, as observed in the epoxidation of different olefin substrates catalyzed by a series of [Fe$^{II}$(PDP)(CF$_3$SO$_3$)$_2$] complexes (PDP = 2-[(S)-2-(1-pyridyl-2-ylmethyl)pyrrolidin-2-yl] pyrrolidin-1-yl)methyl)pyridine), where the pyridine rings are substituted with electron withdrawing or donating moieties (Me$_3$N, MeO, Me, H, Cl, CO$_2$Et) at the meta and para-positions, Figure 1, giving up to 99% yield and 99% enantioselectivity. Electron-rich ligands decrease the electrophilicity of the Fe-oxo entity, favouring the transition state to be shifted towards a more product-like complex, while electron-deficient ligands increase the electrophilicity of the Fe-oxo unit, making it more indiscriminate and less stereoselective.

![Scheme 1. Proposed mechanism for olefin epoxidation catalyzed by a non-heme Fe(II) complex.](image-url)
In the present work, we have developed a new tetradentate ligand, \( S,S_{-}\text{PDBzL} \) (1-methyl-2-((S)-1-(4-methylbenzimidazol-2-ylmethyl)pyrrolidin-2-yl)pyrrolidin-1-yl)benzimidazole) (Figure 1), where we have introduced two \((N\text{-methyl})\)benzimidazolymethyl arms attached to the two nitrogen atoms of the chiral 2,2'-bispyrrolidine backbone. We have previously observed that an (N-methyl)benzimidazol-containing ligand can enhance the catalytic reactivity of an Fe(II) complex in stereospecific C-H hydroxylation reactions, and were therefore interested in investigating the influence of a chiral ligand containing \((N\text{-methyl})\)benzimidazolyl donor moieties on Fe(II)-catalyzed asymmetric epoxidation. Herein we report the synthesis and characterization of a non-heme Fe(II)-complex based on the ligand \( S,S_{-}\text{PDBzL} \) and results obtained on alkene epoxidation catalyzed by this complex.

![Figure 1. Structures of tetradeionate ligands (R1=R2,R3)PDP and S,S_{-}\text{PDBzL}.

Results and discussions.

Synthesis and characterization of ligand and metal complex.

The chiral ligand \( S,S_{-}\text{PDBzL} \) was synthesized by reaction of one eq. of \((S,S)-2,2'\)-bispyrrolidine tartrate with two eq. of 2-(chloromethyl)-1-methylbenzimidazole in the presence of base (NaOH) (Scheme 2; cf. Experimental Section for a detailed description of the synthesis). The \(^1H\) NMR spectrum established the formation of the ligand which has characteristic peaks at 2.32 ppm for the hydrogens at the tertiary carbons of the bispyrrolidine unit and two doublets at 4.23 and 3.63 ppm for the hydrogens of the bridging methylene groups. The ESI mass spectrum also confirmed the formation of the ligand.

![Scheme 2. Synthesis of the ligand S,S_{-}\text{PDBzL}.

Reaction of equimolar amounts of \( S,S_{-}\text{PDBzL} \) and \([\text{Fe}^{II}(\text{CH}_3\text{CN})_2(\text{CF}_3\text{SO}_3)_2]\) in THF under inert atmosphere gave the metal complex \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})(\text{CF}_3\text{SO}_3)_2]\) (1\(^{\text{OTf}}\)) as a light yellow solid (Scheme 3, cf. Experimental Section). The analogous acetonitrile derivative \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})(\text{CH}_3\text{CN})_2](\text{SbF}_6)_2\) (1\(^{\text{SbF}_6}\)) was prepared in two steps: initial reaction of one eq. \( S,S_{-}\text{PDBzL} \) with one equivalent of FeCl\(_2\) in MeCN to afford \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})(\text{CH}_3\text{CN})_2]\), followed by reaction two eq. AgSbF\(_6\) with one eq. of \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})(\text{Cl})_2]\) in CH\(_3\)CN to form the desired complex, 1\(^{\text{SbF}_6}\), as a red microcrystalline solid.

![Scheme 3. Synthesis of the metal complex [Fe^{II}(S,S_{-}\text{PDBzL})(CF_3SO_3)_2] (1^{\text{OTf}}).]

Complexes 1\(^{\text{OTf}}\) and 1\(^{\text{SbF}_6}\) were characterized by high resolution mass spectroscopy (HRMS). The HRMS of 1\(^{\text{OTf}}\) in CH\(_3\)CN showed a prominent mass peak at \( m/z \) 242.1042 corresponding to the formulation \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})]^{2+} \) (i.e. \( z = 2 \), calc. 242.1014) and at \( m/z \) 633.1517 corresponding to the formulation of \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})(\text{CF}_3\text{SO}_3)_2]\) (calc. 633.1558) (Figures S1-S3, Supplementary Material). The HRMS of complex 1\(^{\text{SbF}_6}\) in MeCN also showed prominent mass peaks at \( m/z \) 242.1022 and 719.0956 corresponding to the formulations of \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})]^{2+}\) (calc. 242.1014) and \([\text{Fe}^{II}(S,S_{-}\text{PDBzL})(\text{SbF}_6)_2]\) (calc. 719.0980), respectively (Figures S4-S5, Supplementary Material).

The \(^1H\) NMR spectra of 1\(^{\text{OTf}}\) and 1\(^{\text{SbF}_6}\) were measured in CD\(_3\)CN. The spectral window exhibited by both complexes range from -20 to 140 ppm, which is indicative of a high spin Fe(II) complex (Figures S6-S7, Supplementary Material).

Amongst the different absorption peaks in the IR spectrum of 1\(^{\text{OTf}}\) (Figure S8, Supplementary Material) the peak at 725 cm\(^{-1}\) corresponds to the aromatic =C-H out-of-plane bending vibration and 513 cm\(^{-1}\) corresponds to the Fe-O stretching frequency. The IR spectrum of complex 1\(^{\text{SbF}_6}\) (Fig. S9, Supplementary Material) reveals peaks at 2275 cm\(^{-1}\), corresponds to the C≡N stretches of the coordinated acetonitrile molecules, and the aromatic =C-H out-of-plane bending vibration appears at 748 cm\(^{-1}\). The UV/Vis spectrum of 1\(^{\text{OTf}}\) in MeCN showed an absorption maximum at \( \lambda_{\text{max}} = 198 \text{ nm (} c = 1.76 \times 10^5 \text{ M}^{-1}\text{ cm}^{-1}\) while 1\(^{\text{SbF}_6}\) in CH\(_3\)CN showed an absorption maximum at \( \lambda_{\text{max}} = 197 \text{ nm (} c = 1.47 \times 10^5 \text{ M}^{-1}\text{ cm}^{-1}\). These bands are assigned to identical high energy intra-ligand charge transfer transitions.
Crystal and molecular structure of complex 1OTf.

The solid state structure of complex 1OTf was confirmed by X-ray crystallography. The details of the structure determination are listed in Table 2 and selected bond distances and bond angles are listed in Table 3. The molecular structure (Fig. 2) shows that the iron ion adopts a distorted octahedral coordination geometry. Four coordination sites are occupied by the nitrogen atoms of the tetradentate $S,S$-PDP ligand while the remaining two cis-sites are occupied by the oxygen atoms of the triflate anions. The two (N-methyl)benzimidazole rings remain above and below the plane containing the iron, the two nitrogens of the $S,S$-bis-pyrrolidine backbone and the two oxygen atoms of the triflate anions, and are almost perpendicular with respect to each other. The Fe-N bond distances range from 2.15 to 2.25 Å and the Fe-O bond distances range from 2.12 to 2.17 Å, which are in agreement with a high spin Fe(II) ion. The bulky (N-methyl)benzimidazolyl moieties introduce steric strain making the O-Fe-O angle smaller (96.7(2)°) relative to the corresponding angle in $[\text{Fe}^{II}\text{(PDP)}(\text{CF}_3\text{SO}_3)_2]$ (108.47(5)°). Therefore, the study of epoxidation of 2-cyclohexene-1-one was performed using 2-eha.

Catalytic asymmetric epoxidation.

Relatively simple cyclic enones have been generally less explored as substrates for asymmetric epoxidation than $\alpha,\beta$-unsaturated aromatic ketones. In this study, focus has therefore been made on using the challenging substrate 2-cyclohexene-1-one for asymmetric epoxidation. The yields of the two chiral epoxide products have been determined by gas chromatography, using a chiral column. In a typical catalytic experiment, H$_2$O$_2$ was delivered using a syringe pump to a stirred solution of CH$_3$CN containing the Fe catalyst, 1OTf, and the substrate (Scheme 4) (cf. Experimental Section for detailed catalytic conditions). The catalytic reactions were carried out in air and at low temperature (-30 °C). As mentioned above, previous studies have shown that the presence of a carboxylic acid enhances the efficiency of the catalyst, and the choice of carboxylic acid plays an important role in tuning the efficiency and selectivity of the asymmetric epoxidation reactions. In a recent study reported by Costas and coworkers, it was found that the presence of racemic 2-ethylhexanoic acid (2-eha) resulted in high enantiomeric excess (ee) and relative good yields in iron-catalyzed asymmetric epoxidation reactions. Therefore, the study of epoxidation of 2-cyclohexene-1-one by 1OTf with 2-ethylhexanoic acid as an additive

The complex 1OTf (4 mol%) oxidized 2-cyclohexene-1-one to form the two epoxides with low yield (16%) in the presence of H$_2$O$_2$ (2 equiv w.r.t. substrate) and 2-eha (3 equiv w.r.t. substrate; Scheme 4), although the conversion of the substrate into oxidized products was 43% (based on oxidant). Furthermore, the ee value obtained was 89%. An increase of the carboxylic acid loading did not lead to any significant change in the epoxide yield or the ee value (with 5 equiv acids the yield of epoxides was 10% and ee was 86% and with 10 equiv acids the yield of epoxides was 13% and ee was 87%; entries 1-3, Table 1). The effect of different amount of catalyst loading on the substrate conversion, yield of epoxides and ee value was examined. In all cases, the amounts of H$_2$O$_2$ (2 equiv w.r.t. substrate) and carboxylic acid (10 equiv w.r.t. substrate) were kept fixed. Changing the catalyst loading from 4 mol% to 2 mol% resulted in a decrease in conversion of substrate into oxidized products (30%) and the yield of epoxides (10%), while maintaining high ee value (87%; entry 4, Table 1). Increasing the catalyst loading from 4 mol% to 8 mol% (or 10 mol%) increased the conversion of substrate into products (66 and 67% for 8 and 10 mol% catalyst loading, respectively), but the epoxide yield was more or, less similar (entry 5, Table 1). Finally, the amount of H$_2$O$_2$ was varied while the amounts of catalyst (4 mol%) and carboxylic acid (10 equiv w.r.t. substrate) were kept fixed. Addition of 1.3 equiv of H$_2$O$_2$ resulted in a conversion of 55% with a yield of epoxides of 11% and ee value of 84%, while addition of 3 equiv of H$_2$O$_2$ resulted in conversion of 68% but poor yield of epoxides (7%) and lowering of the ee value (74%; entries 6-8, Table 1).

As expected, complex 1SbF$_6$ exhibited the same behaviour as 1OTf (entries 3 and 9, Table 1). On changing the carboxylic acid, both the yields and enantioselectivities were diminished (2% yield and 60% ee for trimethylacetic acid and 1% yield and 58% ee for S-ibuprofen; entries 9-11, Table 1).
Complex $1^{OTf}$ was further investigated in the oxidation of 2-cyclopenten-1-one where it provided low conversion of the substrate (52%) with very low yield of epoxide (4%) and moderate enantiomeric excess (ee 76%).

Cis-$\beta$-methylstyrene was also employed as a substrate and the conditions for catalysis were used as reported earlier, in order to enable direct comparison of $1^{OTf}$ with related Fe(II) complexes. Under catalytic conditions (cf. Experimental Section for details), complex $1^{OTf}$ oxidized cis-$\beta$-methylstyrene to form epoxides with 60% yield and an ee of 41% (Scheme 5). Under the same conditions, the catalyst [Fe$^{III}$(dpdp)(CF$_3$SO$_3$)$_2$] ($P^1$) ([dpdp] = 2-((S)-2-((S)-1-(pyridyl-2-ylmethyl)pyrrolidin-2-yl)pyrrolidin-1-yl)methyl)pyrrole) and [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] ($Me_2$PDP) ([Me$_2$PDP] = methylbenzimidazol-2-ylmethyl)pyrrolidin-2-yl)pyrrole) were synthesized and fully characterized. The complex $1^{OTf}$ exhibited highly enantioselective epoxidations (ee > 80%) in the oxidation of cyclic olefin 2-cyclohexen-1-one, albeit with low yields of the chiral epoxides (10-15%). It has previously been shown that while the complex [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] provided poor yield (12%) and moderate enantiomeric excess (ee 76%) in the epoxidation of 2-cyclohexen-1-one, the complex [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] (Figure 1) showed excellent yield (99%) and high enantioselectivity (ee 84%) under similar conditions. This difference was attributed to the rapid deactivation of the former catalyst during the course of oxidation of the substrate, while the substrate oxidizes slowly under the reaction conditions. The similar reactivities of $1^{OTf}$ and [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] towards the substrate 2-cyclohexen-1-one might therefore be due to similar fast deactivation of the Fe-catalyst. With cis-$\beta$-methylstyrene, $1^{OTf}$ provided moderate yield (60%) and lower enantioselectivity (ee 41%). The relative orientation of the bulky (N/methyl)benzimidazole groups may also provide excessive steric constraints on the approach of the incoming substrate to interact with the active metal-oxo species, causing poor yield of the epoxides and unwanted side products. Further studies of the catalytic properties of $1^{OTf}$ and $1^{SbF_6}$ are needed to optimize reaction conditions and explore a wider range of substrates.

### Experimental Section

#### Reagents and Materials:

Reagents and solvents were of at least 99% purity and used as received without any further purification. 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/benzophene. The starting material 2-(chloromethyl)-1-methylbenzimidazole was synthesized according to a literature procedure.

#### Instrumentation:

Infrared spectra were collected on a Nicolet Avatar 360 FTIR spectrometer. UV-Visible spectroscopy was performed in a 1 cm quartz cell using an Agilent Technology 8453 UV-Visible spectrophotometer equipped with a diode-array detector. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in CDCl$_3$ or CD$_3$CN solvent using standard conditions and were referenced to the residual proton signal of the solvent. Elemental analysis was performed on a 4.1 Vario EL 3 elemental analyzer from Elementar. The ESI-MS experiments were performed on a Bruker Esquire 6000 LC/MS chromatograph, using acetoniitrile as a mobile phase. The product analyses after catalysis experiments were carried out on an Agilent Technology 7820A gas chromatograph equipped with a 16-sample automatic liquid sampler, flame ionization detector and EzChrom Elite Compact software.

### Conclusion

The new tetradeinate N$_4$ ligand S,S-$p$DPL$_4$, with an S,S-bispyrrolidine chiral backbone, has been synthesized. The corresponding Fe(II) complexes, [Fe$^{III}$(S,S-$p$DPL$_4$)(CF$_3$SO$_3$)$_2$] ($1^{OTf}$) and [Fe$^{III}$(S,S-$p$DPL$_4$)(CH$_3$CN)]$[SbF_6]_2$ ($1^{SbF_6}$) were synthesized and fully characterized. The complex $1^{OTf}$ exhibited highly enantioselective epoxidations (ee > 80%) in the oxidation of cyclic olefin 2-cyclohexen-1-one, albeit with low yields of the chiral epoxides (10-15%). It has previously been shown that while the complex [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] provided poor yield (12%) and moderate enantiomeric excess (ee 76%) in the epoxidation of 2-cyclohexen-1-one, the complex [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] (Figure 1) showed excellent yield (99%) and high enantioselectivity (ee 84%) under similar conditions. This difference was attributed to the rapid deactivation of the former catalyst during the course of oxidation of the substrate, while the substrate oxidizes slowly under the reaction conditions. The similar reactivities of $1^{OTf}$ and [Fe$^{III}$([Me$_2$PDP](CF$_3$SO$_3$)$_2$)] towards the substrate 2-cyclohexen-1-one might therefore be due to similar fast deactivation of the Fe-catalyst. With cis-$\beta$-methylstyrene, $1^{OTf}$ provided moderate yield (60%) and lower enantioselectivity (ee 41%). The relative orientation of the bulky (N/methyl)benzimidazole groups may also provide excessive steric constraints on the approach of the incoming substrate to interact with the active metal-oxo species, causing poor yield of the epoxides and unwanted side products. Further studies of the catalytic properties of $1^{OTf}$ and $1^{SbF_6}$ are needed to optimize reaction conditions and explore a wider range of substrates.

#### Table 1. Catalytic epoxidation of 2-cyclohexen-1-one by complex $1^{OTf}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>CA$^2$ (equiv)</th>
<th>Equiv of Conversion</th>
<th>H$_2$O$_2$</th>
<th>Yield of epoxides</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1^{OTf}$ (4)</td>
<td>2-eha (3)</td>
<td>2</td>
<td>45</td>
<td>16</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>$1^{OTf}$ (4)</td>
<td>2-eha (5)</td>
<td>2</td>
<td>52</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>$1^{OTf}$ (2)</td>
<td>2-eha (10)</td>
<td>2</td>
<td>64</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>$1^{OTf}$ (2)</td>
<td>2-eha (10)</td>
<td>2</td>
<td>30</td>
<td>10</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>$1^{OTf}$ (8)</td>
<td>2-eha (10)</td>
<td>2</td>
<td>66</td>
<td>11</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>$1^{OTf}$ (2)</td>
<td>2-eha (10)</td>
<td>1.3</td>
<td>55</td>
<td>11</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>$1^{OTf}$ (4)</td>
<td>2-eha (10)</td>
<td>1.6</td>
<td>59</td>
<td>12</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>$1^{OTf}$ (4)</td>
<td>2-eha (10)</td>
<td>3</td>
<td>68</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>$1^{SbF_6}$ (4)</td>
<td>2-eha (10)</td>
<td>2</td>
<td>64</td>
<td>13</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>$1^{SbF_6}$ (4)</td>
<td>(CH$_3$)$_2$CO</td>
<td>2</td>
<td>72</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>$1^{SbF_6}$ (4)</td>
<td>S-Ibuprofen</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>58</td>
</tr>
</tbody>
</table>

$^1$Reaction conditions: experimental section; $^2$carboxylic acids; $^3$enantioselectivity.

![Scheme 5. Epoxidation of cis-$\beta$-methylstyrene with H$_2$O$_2$ in presence of acetic acid catalyzed by Fe(II) complexes.](image-url)

- **Catalyst** ($1^{OTf}$ mol %)
- **H$_2$O$_2$ (1.8 equiv.)
- **AcOH (5 mol %)

- **Entry 1**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 2**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 3**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 4**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 5**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 6**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 7**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 8**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 9**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 10**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)
- **Entry 11**: Catalyst (1 mol %), H$_2$O$_2$ (1.8 equiv.), AcOH (5 mol %)

For more details, please refer to the Experimental Section.
was added. Then, 5.0 ml of a 1 M NaOH solution was added. After 72 h of stirring at room temperature, the reaction mixture was diluted with 30 ml 1 M NaOH solution. The aqueous layer was extracted with 3 x 15 ml CH2Cl2 and the organic part was collected, dried over Na2SO4 and concentrated under vacuum to obtain the crude product. The crude ligand was then passed through a column packed with silica gel and eluted with 5% CH2OH: 2% NaOH: 82% CH2Cl2: 11% petroleum ether. The collected fractions were combined, washed with 1 M NaOH solution, dried over Na2SO4 and concentrated under vacuum to obtain the ligand as a pale orange solid. Yield: 0.366 g (63.2%).

HRMS: 429.2760 [M+H]+, calc. 429.2761. 1H-NMR (400 MHz, CDCl3) δ (ppm): 7.72 (m, 2H), 7.33-7.21 (m, 6H), 4.23 (d, 2H), 3.80 (s, 6H), 3.66 (d, 2H), 2.80 (dt, 4H), 2.32 (m, 2H), 1.79 (m, 4H), 1.68 (m, 4H). 13C-NMR (100 MHz, CDCl3) δ (ppm): 152.4, 142.2, 136.1, 122.4, 121.8, 119.6, 109.0, 65.2, 55.6, 52.5, 29.9, 26.2, 24.0.

Synthesis of [FeII(S,S-PDBzL)(CF3SO3)2] (1OTf):
This reaction was performed inside a dry atmosphere box. [FeII(CH3CN)(CF3SO3)2] (166.8 mg, 0.38 mmol) was dissolved in 1 ml THF and added drop-wise to a stirring solution of S,S-PDBzL (163.2 mg, 0.38 mmol) in THF (1 ml). A yellow precipitate appeared upon addition of the Fe salt to the ligand solution. After stirring for about 1 h, the yellow precipitate was filtered off and dried under vacuum. The resultant solid was dissolved in 1.5 ml CH3CN. A total of 32 mg FeCl2 (32.3 mg, 0.22 mmol) was added. Then, 5.0 ml of a 1 M NaOH solution was added. After 72 h of stirring at room temperature, the reaction mixture was diluted with 30 ml 1 M NaOH solution. The aqueous layer was extracted with 3 x 15 ml CH2Cl2 and the organic part was collected, washed with CH3CN and ether, and dried under an N2 flow to afford a light yellow microcrystal. Yield: 157.7 mg (95%). HRMS: (m/z) 342.1022 [Fe II(S,S-PDBzL)(CF3SO3)2]2+ (z = 1), calc. 342.1042 [FeII(S,S-PDBzL)(CF3SO3)2]2+ (z = 2), calc. 242.1014.

Synthesis of [FeII(S,S-PDBzL)(CH3CN)2](SbF6)2 (1SbF6):
The ligand S,S-PDBzL (108.9 mg, 0.254 mmol) was dissolved in 1.5 ml CH3CN. A total of 32 mg FeCl2 (32.3 mg, 0.254 mmol) was added into the stirring solution. A yellow precipitate appeared within a few seconds of stirring. After 4h of stirring, the solvent of the reaction mixture was removed under vacuum and the resultant solid was washed with CH3CN and ether, and dried under an N2 flow to afford [FeII(S,S-PDBzL)(CH3CN)2] (88.6 mg, yield 63%). This complex (88.6 mg, 0.16 mmol) was suspended in 5 ml CH2CN. A total of 110 mg of AgSbF6 (109.7 mg, 0.32 mmol) was added into the stirred suspension, whereupon a white precipitate immediately appeared. The colour of the solution gradually changed from light yellow to orange. After 4h of stirring, the mixture was filtered through a celite column in the dark. The solvent was removed under vacuum to provide [FeII(S,S-PDBzL)(CH3CN)2][SbF6]2 as a red solid. Yield: 157.7 mg (95%). HRMS: (m/z) 242.1022 [FeII(S,S-PDBzL)(CH3CN)2]2+ (z = 2), calc. 242.1014; 719.0956 [FeII(S,S-PDBzL)(SbF6)2]2+ (z = 1), calc. 719.0980; Elemental analysis C30H38N8F12Sb2Fe (MW = 1038.021 g/mol) calc. (%) C 43.16, H 4.01, N 10.29; FT-IR (ATR) ν (cm-1) 3011, 2956, 1456, 1304, 121.4, 1157, 1034, 753, 634, 513, 429.

Crystal structure determination.
Orange crystals of 1OTf were grown by slow diffusion of diethyl ether into a CH2Cl2 solution of the compound. Collection of diffraction data was carried out at (100(2) K) on a BRUKER SMART APEX CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The measurements were made in the θ range 2.172 to 27.744°. A full-sphere data collection was carried out with ω and φ scans. A total of 82922 reflections were collected of which 8370 were unique. Programs used: data collection, Smart22; data reduction, SAINT+23; absorption correction, SADABS24. Structure solution and refinement was done using SHELXTL25.

The structure was solved by direct methods and refined by full-matrix least-squares methods on F2. The non-hydrogen atoms were refined anisotropically. The H-atoms were placed in geometrically optimized positions and forced to ride on the atom to which they are attached. The structure crystallized in the chiral space group P61.

Table 2. Crystal data for complex 1OTf.

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>CacH2:FeFeNoOsSz:Ch:Ch:</th>
<th>1OTf</th>
</tr>
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<tbody>
<tr>
<td>Formula weight</td>
<td>867.49</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
<td></td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
<td></td>
</tr>
<tr>
<td>Crystal system</td>
<td>Hexagonal</td>
<td></td>
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<tr>
<td>Space group</td>
<td>P61</td>
<td></td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.8264(3) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b = 10.8264(3) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c = 52.532(2) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α = 90°</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β = 120°</td>
<td></td>
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<tr>
<td></td>
<td>γ = 120°</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
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<td></td>
</tr>
<tr>
<td>Z</td>
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<td></td>
</tr>
<tr>
<td>Density (calculated)</td>
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<tr>
<td>Absorption coefficient</td>
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<tr>
<td>F(000)</td>
<td>2664</td>
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<tr>
<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<tr>
<td>Independent reflections</td>
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<td>Completeness</td>
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<tr>
<td>Absorption correction</td>
<td>Empirical</td>
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</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.0 and 0.900775</td>
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</tr>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data/restraints/parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indices</td>
<td>[1-2sigma(I)]</td>
<td>R1 = 0.0592, wR2 = 0.1622</td>
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<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0632, wR2 = 0.1668</td>
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</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>2.223 and -1.601 e.Å⁻³</td>
<td></td>
</tr>
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</table>
Table 3. Selected bond distances (Å) and bond angles (°) in complex $^{1}\text{OTf}$.

<table>
<thead>
<tr>
<th>Bond or Angle</th>
<th>Distance or Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe(1)-N(3)</td>
<td>2.148(4)</td>
</tr>
<tr>
<td>Fe(1)-O(1)</td>
<td>2.115(6)</td>
</tr>
<tr>
<td>Fe(1)-N(1)</td>
<td>2.249(6)</td>
</tr>
<tr>
<td>Fe(1)-N(4)</td>
<td>2.237(6)</td>
</tr>
<tr>
<td>Fe(1)-N(5)</td>
<td>2.168(6)</td>
</tr>
<tr>
<td>N(1)-Fe(1)-O(1)</td>
<td>96.8(2)</td>
</tr>
<tr>
<td>N(1)-Fe(1)-N(3)</td>
<td>76.5(2)</td>
</tr>
<tr>
<td>N(1)-Fe(1)-N(4)</td>
<td>98.1(2)</td>
</tr>
<tr>
<td>N(1)-Fe(1)-N(5)</td>
<td>90.0(2)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-N(3)</td>
<td>170.8(2)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-N(4)</td>
<td>91.1(3)</td>
</tr>
<tr>
<td>O(1)-Fe(1)-N(5)</td>
<td>160.6(2)</td>
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<td>N(4)-Fe(1)-N(5)</td>
<td>76.1(2)</td>
</tr>
<tr>
<td>O(4)-Fe(1)-N(5)</td>
<td>97.6(2)</td>
</tr>
</tbody>
</table>

**Reaction conditions for catalysis.**

**Conditions for epoxidation of 2-cyclohexen-1-one and 2-cyclopenten-1-one.**

An acetonitrile solution (750 μL) of the alkene substrate (0.0825 mmol, final concentration 0.11 M) and $^{1}\text{OTf}$ or $^{1}\text{SmBF}_6$ (3.32 μmol, 4 mol%, final concentration 4.4 mM) was prepared in a 10 ml vial equipped with a stir bar, and cooled in an acetonitrile freeze bath (temp -30 °C). A total of 12 μL of the carboxylic acid in CH$_3$CN was directly added to the reaction solution. Then 37.7 μL of 1:1 (v:v) H$_2$O$_2$ in CH$_3$CN was delivered to the reaction solution over a period of 30 min, using a syringe pump. Then the reaction solution was further stirred at 30 °C for 30 min. At this point, a known amount of biphenyl solution was added as internal standard. The solution was passed through a small alumina column and the column was rinsed with 2 × 1 ml ethyl acetate, and the resultant elute was subjected to GC analysis. The racemic products were identified by their GC retention times and the yields were determined from the integration area of the GC spectrum.

**Conditions for epoxidation of cis-β-methyl styrene.**


