Atom and Group Transfer Reactions Involving High-valent Iron Complexes

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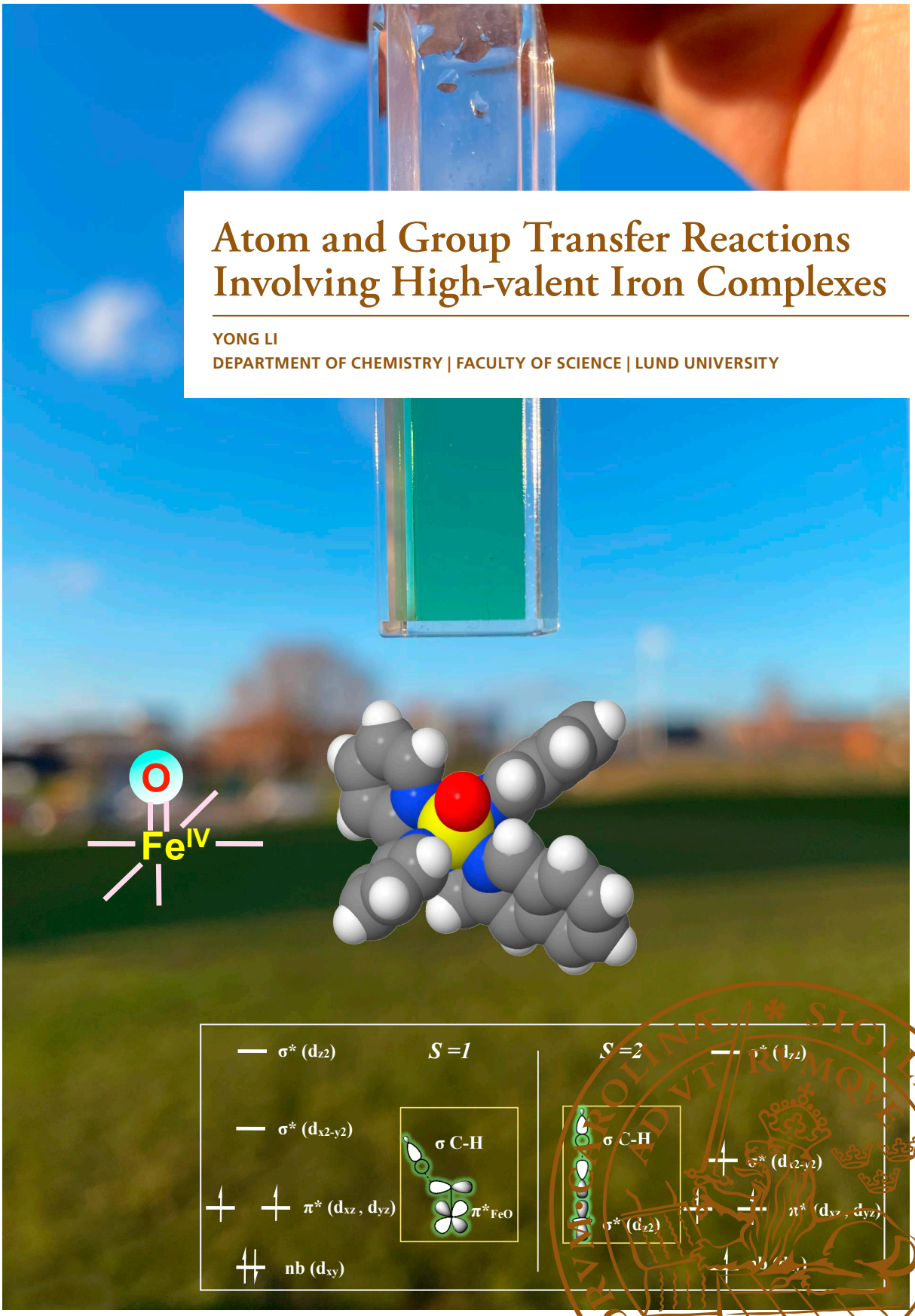

Atom and Group Transfer Reactions Involving High-valent Iron Complexes

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Yong Li

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

Iron enzymes play critical roles in biological oxidation reactions by utilizing highly reactive high-valent iron intermediates, such as Fe^{IV}=O, Fe^{V}(O)(OH), and Fe^{IV}=NR species, for catalytic reactions. These intermediates exhibit remarkable catalytic behavior with high reactivities and high regio- and stereospecificity in various biochemical reactions. Understanding these metal intermediates is crucial not only for replicating their activity but also for discovering new synthetic possibilities in chemical synthesis.

To address the challenge of comprehending high-valent iron intermediates in biology, chemists have developed a number of bio-inspired functional models that exhibit a diverse range of catalytic properties. The main objective of this thesis is to examine the functional mimicry of mononuclear non-heme active sites in iron enzymes, specifically targeting Fe^{IV}=O, Fe^{V}(O)(OH) and Fe^{IV}=NR intermediates.

Chapter 1 provides an introduction to active sites of iron enzymes in biological systems and related bio-inspired models utilizing iron complexes. Chapter 2 relates to Papers I and IV. Paper I describes the syntheses and characterizations of four new Fe^{IV}=O complexes based on new ligands with minor steric restriction. The reactivity of these complexes in C-H activation and O-atom transfer reactions has been investigated in detail. As the ligands include negligible steric restrictions, the reactivity differences between these Fe^{IV}=O complexes are attributed to the electronic properties of the ligands. On the other hand, Paper IV provides an example of a ligand framework where the steric restrictions of the specific ligand dictate the substrate accessibility. Chapter 3 relates to Paper II and gives a comparative study on the structure and reactivity patterns of a new Fe^{IV}=NR complex versus its Fe^{IV}=O congener. Chapter 4 relates to Paper III and studies the epoxidation of alkenes by two mononuclear non-heme Fe^{IV}=O complexes based on ligands with different electron-donating properties. The catalysis and kinetics studies shed light on the influence of electron-donating properties on the reactivity and mechanism of alkene epoxidation.

This research provides insights into the influence exerted by ligand environments on the reactivities of Fe^{IV}=O, Fe^{V}(O)(OH) and Fe^{IV}=NR complexes. The study may contribute to the development of new, highly active catalysts for important oxidation reactions.

Keywords
Key words: Iron enzymes, high-valent iron intermediates, bio-inspired iron complexes, Fe^{IV}=O, Fe^{IV}=NR, catalytic reactions, electronic effects, steric restriction.

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To my family: my wife and my son

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Abstract

Iron enzymes play critical roles in biological oxidation reactions by utilizing highly reactive high-valent iron intermediates, such as Fe^{IV}=O, Fe^{V}(O)(OH), and Fe^{IV}=NR species, for catalytic reactions. These intermediates exhibit remarkable catalytic behavior with high reactivities and high regio- and stereospecificity in various biochemical reactions. Understanding these metal intermediates is crucial not only for replicating their activity but also for discovering new synthetic possibilities in chemical synthesis.

To address the challenge of comprehending high-valent iron intermediates in biology, chemists have developed a number of bio-inspired functional models that exhibit a diverse range of catalytic properties. The main objective of this thesis is to examine the functional mimicry of mononuclear non-heme active sites in iron enzymes, specifically targeting Fe^{IV}=O, Fe^{V}(O)(OH) and Fe^{IV}=NR intermediates.

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This research provides insights into the influence exerted by ligand environments on the reactivities of Fe^{IV}=O, Fe^{V}(O)(OH) and Fe^{IV}=NR complexes. The study may contribute to the development of new, highly active catalysts for important oxidation reactions.

Popular Science Summary

Catalysts are essential for enabling efficient and selective chemical reactions, leading to benefits in productivity, product quality, and waste reduction in various industries, including pharmaceutical and petrochemical industries. Despite their importance, designing effective catalysts can be a challenging task. Researchers have been inspired by biological catalysts – enzymes - that have evolved in Nature over millions of years to perform specific chemical transformations with high efficiency and selectivity.

However, mimicking the active sites of enzymes is challenging due to the complex interplay of various factors that contribute to their efficiency and selectivity, including their specific environment and reliance on metal cofactors and specific residues. While many bioinspired complexes have been synthesized by altering the design of ligands, it remains challenging to precisely determine the influence of different factors on the properties of these complexes due to compounding of several factors, such as steric and electronic effects.

This thesis addresses the influences of steric and electronic effects on the catalytic properties of high-valent iron complexes by examining these factors separately. Studies have focused on reactions involving the transfer of a hydrogen atom from a hydrocarbon to the iron catalyst/reactant, and/or the transfer of an oxygen atom from the catalyst to a hydrocarbon, or the analogous transfer of a nitrogen-based imido group (=N-R, R = hydrocarbon substituent). New multidentate ligands with only minor steric effects but varying electronic influence on the metal ion have been designed and synthesized. The influence of electronic effects exerted by these reactivities on the reactivities of the iron catalysts has been analyzed. Conversely, the preparation of ligands that have varying steric effects but seemingly little electronic influence on the reactivity of high-valent iron-oxido catalysts has also been undertaken.

Overall, the findings in this thesis can contribute to the optimization of ligand design for catalysts. By understanding the influence of steric and electronic effects on the catalytic properties of iron complexes, researchers can develop more efficient and effective biomimetic catalysts.

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Wow, it's amazing how time flies! Four and a half years have passed since I first arrived in Lund on October 5th, 2018. I still remember the beautiful autumn colors that impressed me as I looked out the window of Ebbe's old-school car. Ebbe kindly picked me up from Malmö airport and drove me to Lund, making me feel welcomed from the very start. Looking back at the pictures on my phone, I realize those memories will always be special to me and will continue to inspire me in the future.

As I reach the end of my PhD journey, I can't help but acknowledge that without the help and guidance of so many people, completing my PhD would have been impossible. Their amazing support has truly played a significant role in my academic success and personal growth.

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I also want to thank my co-authors: Reena Singh, Arup Sinha, George C. Lisensky, Matti Haukka, Justin Nilsson, Solomon Yiga, Serhiy Demeshko, Sophie Jana Groß, Sebastian Dechert, Ana Gonzalez, Giliandro Farias, Ola F. Wendt, for their hard work and support throughout our collaboration. I couldn't have done it without you!

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To my colleagues in Chemical Physics, thank you for your friendly support and helpful advice. The professors in our department have also been instrumental in my academic and personal growth.

I also want to thank the China Scholarship Council and the Royal Physiographic Society of Lund for their financial support. Their help made it possible for me to concentrate on my research. I'm truly grateful for their belief in me and their investment in my future.

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Lastly, but certainly not least, I want to express my deepest appreciation to my family, including my wife, son, parents, and sisters. You have been my rock, my support, and my inspiration throughout this journey. I know that I couldn't have made it this far without your unconditional love, encouragement, and unwavering faith in me. I'm proud to be your son, brother, your father, and husband, and I promise to make you proud in the future.

List of Publications

This thesis is based on the following publications, which will be referred to in the text by roman numbers. All publications have been attached in their current state by the end of this thesis.

I. Yong Li, Reena Singh, Arup Sinha, George C. Lisensky, Matti Haukka, Justin Nilsson, Solomon Yiga, Serhiy Demeshko, Sophie Jana Groß, Sebastian Dechert, Ana Gonzalez, Giliandro Farias, Ola F. Wendt, Franc Meyer, Ebbe Nordlander. "Non-heme Fe^{IV}=O complexes supported by four new pentadentate ligands: reactivity towards H- and O-atom transfer processes". (*Inorg. Chem.*, submitted).

II. Yong Li, Simindokht Gol Kar, Lintang Hizbullah, Serhiy Demeshko, Franc Meyer, Ebbe Nordlander. "A stable, yet reactive, Fe^{IV} imido complex" (Manuscript).

III. **Yong Li**, Jacop Rydén, Ebbe Nordlander. "Reactivity and chemoselectivity in the oxidation of alkenes by two nonheme Fe^{IV}=O Complexes" (Manuscript).

IV. Mainak Mitra, Alexander Brinkmeier, **Yong Li**, Margarida Borrell, Arnau Call, Julio Lloret Fillol, Michael G. Richmond, Miquel Costas, Ebbe Nordlander. "An investigation of steric influence on the reactivity of Fe^{V}(O)(OH) tautomers in stereospecific C–H hydroxylation", *Dalton Trans. 2023. 52. 3596-3609.*

My Contribution to the Publications

Paper I. I synthesized all ligands and iron complexes, and performed all reactivity studies, catalysis measurements and most of the spectroscopic experiments. I participated in explaining the mechanistic conclusions, drafted the manuscript, and participated at all stages in the writing of the manuscript.

Paper II. I synthesized all ligands and iron complexes, and performed all reactivity studies, catalysis measurements and the major part of the spectroscopic experiments. I participated in explaining the mechanistic conclusions and drafted the manuscript.

Paper III. I synthesized all ligands and iron complexes, and performed all reactivity studies and catalysis measurements. I participated in explaining the mechanistic conclusions and drafted the manuscript.

Paper IV. I performed the synthesis of one ligand and its iron complexes. I wrote part of the manuscript.

Chapter 1: Introduction

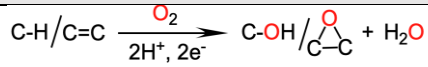
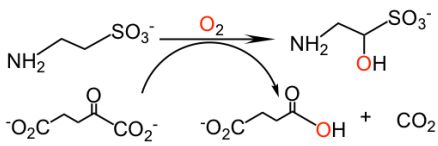
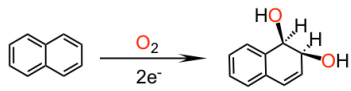
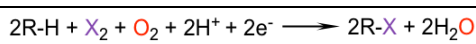
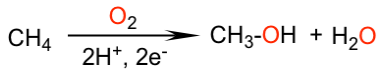
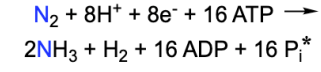
The functionalization of C-H/C=C bonds belong to the most important but still challenging organic transformations. In nature, many metalloenzymes that contain a single metal center within their active sites can affect such transformations by means of high-valent metal intermediates.[1–6] The formation and reactivity of active high-valent metal intermediates in biological systems are complex processes that often remain incompletely understood. However, recent advancements in spectroscopic and computational techniques have shed light on the structures and functions of several such intermediates. [3,7–14]

Inspired by the efficiencies of such metalloenzymes, researchers have devoted considerable efforts to developing related biomimetic model complexes in order to gain understanding of the fundamental chemical processes involving the enzyme active sites, paving the way to design of effective and economical catalysts that can functionalize C-H/C=C bonds with high efficiencies and that may be used in the development of novel catalytic strategies for the synthesis of pharmaceuticals and other valuable chemicals.[5,15–19]

1.1 A brief introduction to iron enzymes

Iron enzymes are a noteworthy class of metalloenzymes that feature iron as a vital constituent of their active sites. These enzymes play pivotal roles in various biological processes, such as hydroxylation, halogenation, desaturation, epoxidation, *cis*-dihydroxylation, N-dealkylation, and aromatic ring cleavage (Table 1.1). Additionally, iron enzymes are involved in oxygen metabolism, electron transport, and the generation of reactive oxygen species. Based on their structural and functional properties, iron enzymes can be classified into three categories: heme enzymes, mononuclear non-heme enzymes, and multinuclear non-heme enzymes (Table 1.1).

Table 1.1. A list of some essential iron enzymes in biology.

Iron enzymes	Sample catalytic reactions	Ref
Heme enzymes		
Cytochrome P450 (Mononuclear)		12,20
Mononuclear non-heme enzymes		
α–ketoglutarate-dependent dioxygenases		2,13
Rieske dioxygenases		21
Halogenases		22,23
Multinuclear non-heme enzymes		
Soluble Methane monooxygenase (Dinuclear)		24
Dinitrogenase Dinitrogenase reductase		25

*P_i = HPO_4^{2-}/ $H_2PO_4^-$

Heme enzymes, such as the cytochrome P450 family, contain a heme group as the active site (Fig. 1.1). The heme group provides a binding site for oxygen, allowing these enzymes to participate in redox reactions. The cytochrome P450 enzymes are involved in a wide range of biochemical processes, including drug metabolism, oxygen transport, and oxidative reactions (Table 1.1). [12,20]

Multinuclear non-heme iron enzymes, such as soluble methane monooxygenase (Fig. 1.1) and some purple acid phosphatases, contain two iron atoms that are bridged by amino acid carboxylate groups or other ligands. These enzymes are involved in such biochemical processes as methane oxidation, phosphate hydrolysis, and epoxidation of alkenes (Table 1.1). [24] The multiple iron atoms in some enzyme active sites, such as the Fe-Mo cofactor of nitrogenase, can facilitate electron transfer and redox chemistry (Table 1.1, Fig. 1.14).[26]

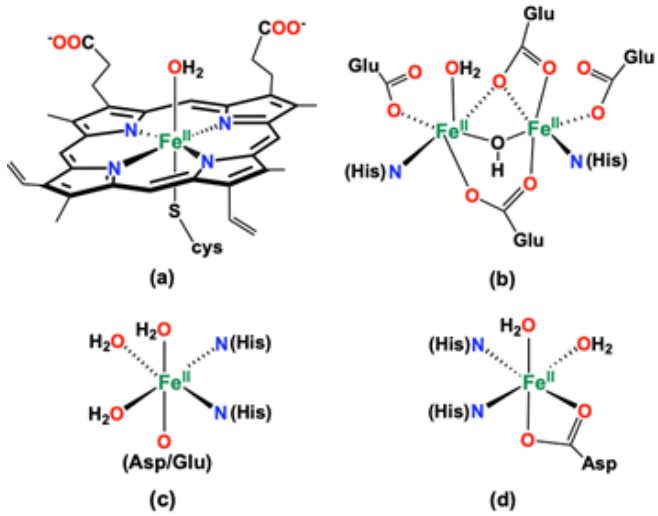


Fig. 1.1. General structures of the active sites of four (classes) of iron enzymes. (a) cytochrome P450; (b) soluble methane monooxygenase (sMMO); (c) α-ketoglutarate-dependent dioxygenases; (d) Rieske oxygenases.

Mononuclear non-heme enzymes, including α-ketoglutarate-dependent dioxygenases, [2,13] Rieske dioxygenases, [24] and halogenases, [22,23] possess a single iron atom in their active sites (as shown in Figure 1.1). These enzymes are involved in essential biochemical processes such as nucleotide synthesis, protein hydroxylation, DNA repair, aromatic compound oxidation, and halogenation of organic substrates (Table 1.1).

Overall, iron enzymes are integral components of numerous biological processes, playing a crucial role in catalyzing a diverse range of reactions that are vital for maintaining cellular function. Consequently, it is essential to gain a comprehensive understanding of the critical functions of iron enzymes in biological systems. Doing so will also enable us to elucidate the underlying mechanisms that drive these processes.

1.2 High valent Iron-oxo complexes

1.2.1 Iron-oxo intermediates in biology

Fe^{IV}=O species have been proven to be the active intermediates of Cytochrome P450 enzymes [21] (Fig. 1.2) and other nonheme enzymes, such as tyrosine hydroxylase (TyrH) and phenylalanine hydroxylase (PheH),[27,28] halogenase CytC3/SyrB2,[23,29] and α-ketoglutarate hydroxylases, including taurine dixoygenase (TauD-J) and

prolyl 4-hydroxylase (P4H) (Fig. 1.3).

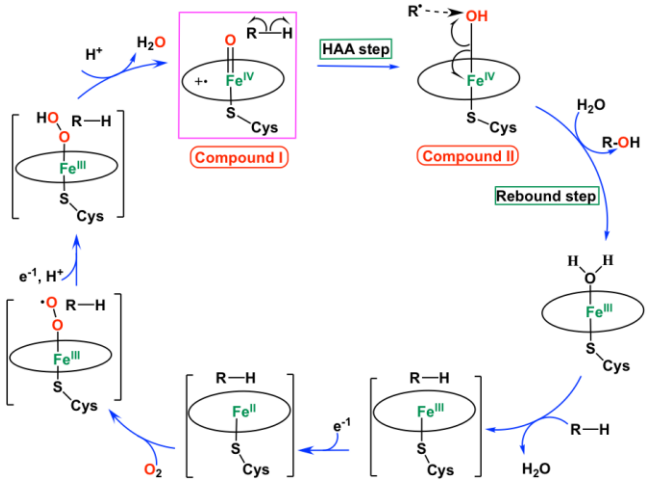


Fig.1.2. Schematic mechanism for C – H hydroxylation by Cytochrome P450 (adapted from ref. [21]); HAA: Hydrogen atom abstraction.

These intermediates have been characterized using Raman and electron paramagnetic resonance spectroscopy, along with computational studies. Interestingly, the Fe^{IV}=O intermediates in all these enzymes exhibit a high spin d_4 configuration[10,12–17] and display remarkable catalytic behaviors, including high reactivities, regio- and stereospecificities. [2,8,9,30,31]

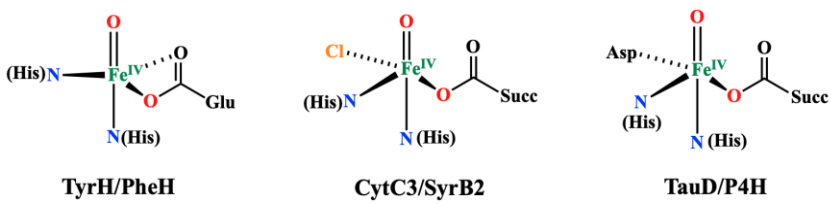


Fig.1.3. The proposed active site structure of pterin-dependent enzymes tyrosine hydroxylase (TyrH) and phenylalanine hydroxylase (PheH), halogenase CyC3/SyrB2, and taurine: α-ketoglutarate dioxygenase (TauD/P4H) in C-H oxidation (succ = succinate).

Further studies have revealed the biological processes catalyzed by non-heme-containing enzymes, such as soluble methane monooxygenase (Fig. 1.4), Rieske dioxygenases (Fig. 1.5), α-ketoglutarate-dependent oxygenases (Fig. 1.6), and halogenase CytC3 (Fig. 1.7). In addition, Fe^{V}=O entities have been identified as the reactive intermediates in Rieske dioxygenases.

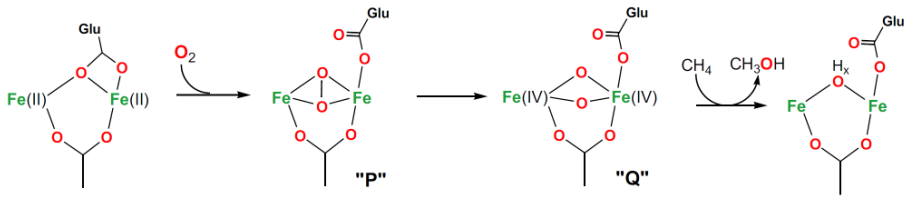


Fig. 1.4. Schematic mechanism for C–H hydroxylation by soluble methane monooxygenase (sMMO) (adapted from ref. [24]).

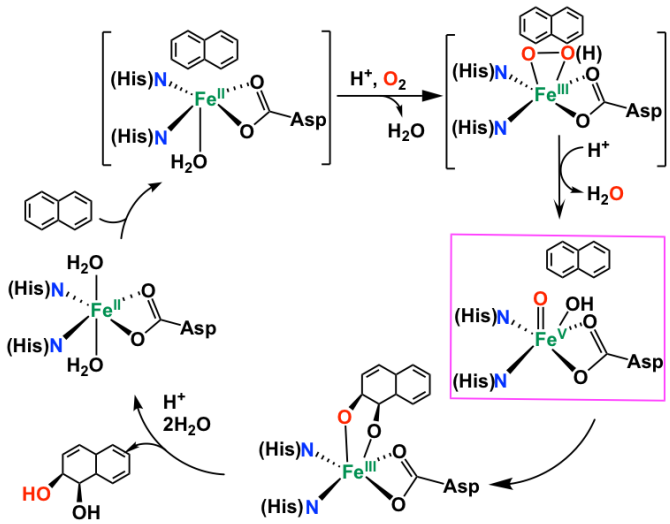


Fig. 1.5. The schematic mechanism for C–H hydroxylation by Rieske oxygenases center (adapted from ref. [21]).

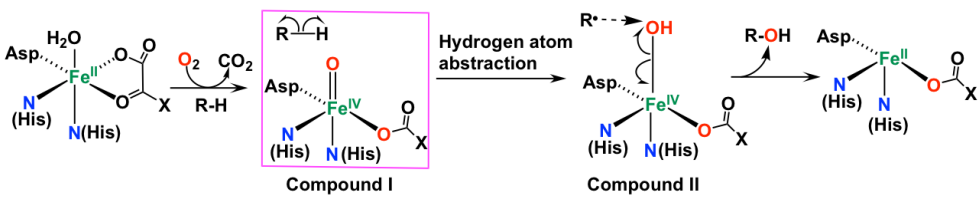


Fig. 1.6. Schematic mechanism for C–H hydroxylation by α-ketoglutarate-dependent oxygenases (adapted from refs. [2,11,13]).

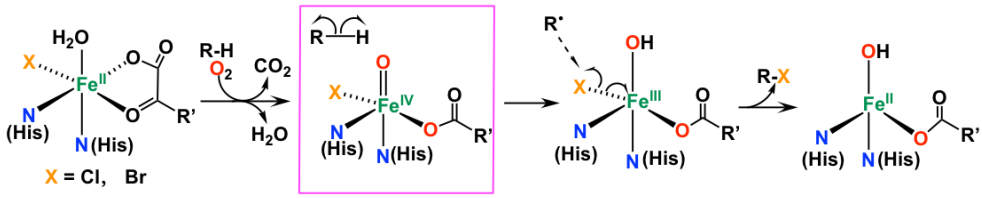


Fig. 1.7. Schematic mechanism for C – H aliphatic chlorination by the halogenase CytC3 (adapted from refs. [2,11,13]).

1.2.2 Bioinspired non-heme iron-oxo complexes

Studying metal intermediates in enzymes is essential not only for understanding their reactivities and replicating their activities but also for discovering new synthetic possibilities in chemical synthesis. However, the high reactivities and short lifespans of these intermediates make them difficult to detect and analyze directly. To address the challenge of understanding high-valent iron-oxo intermediates in non-heme iron enzymes, chemists have invested considerable efforts in developing bioinspired iron complexes with thermal stabilities. Such complexes are usually based on polydentate ligands containing N- and O-based donors and exhibit a diverse range of catalytic activities.[15,17,18,32,33]

In biology, high-spin (S =2) Fe^{IV}=O intermediates have been identified as active oxidizing species.[7,9,10,14,31,34,35] However, most of the synthesized Fe^{IV}=O cores show a low-spin (S = 1) ground state (Figs. 1.8 and 1.9).[17,18,36–39] Due to their thermal stabilities, several low-spin Fe^{IV}=O complexes have been used to study the role of the ligands in controlling the reactivities and selectivities of high-valent iron intermediates. For example, ligands can be used to modulate the electronic structure and redox properties of the iron center, leading to changes in the reactivity and selectivity of the complex.[36,37]

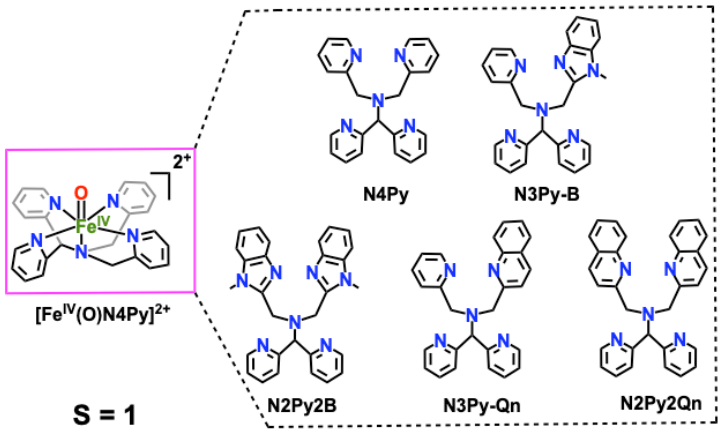


Fig. 1.8. Examples of biomimetic S=1 Fe^{IV}=O units stabilized by enforcing a *C*$_4$ symmetry around the Fe^{IV}=O center.

Chemists have made several efforts to synthesize high-spin S = 2 Fe^{IV}=O complexes in order to model enzymatic intermediates more accurately. A qualitative d-orbital splitting diagram for the d_4 Fe^{IV}=O center (Fig. 1.9) shows that stabilization of S = 2 state can be achieved by enforcing a *C*$_3$ symmetry around the Fe^{IV}=O center or decreasing the energy gap between the d_{x2-y2} and d_{xy} orbitals in *C*$_4$ symmetry Fe^{IV}=O complexes.[40] Therefore, two strategies can be employed for this purpose: (1) In a pseudo-octahedral field (*C*$_4$ symmetry), introduce weaker-field equatorial ligands to diminish the energy gap between d_{x2-y2} and d_{xy} orbitals, which will stabilize the S = 2 ground state. [40] (2) Enforce the trigonal-bipyramidal geometry (*C*$_3$ symmetry) by employing bulky tripodal ligands around the Fe^{IV}=O center, which will lead to the degeneration of d_{x2-y2} and d_{xy} orbitals (Figs. 1.9 and 1.10). However, synthetic high-spin Fe^{IV}=O complexes have shown limited abilities to cleave substrate C-H bonds due to hindered substrate access.[18]

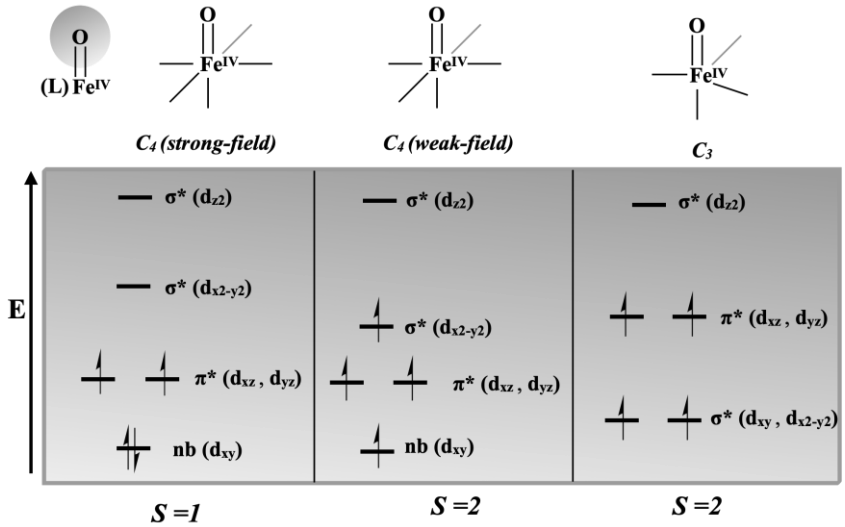


Fig. 1.9. Qualitative d-orbital splitting diagrams for Fe^{IV}=O complexes with tetragonal (strong- and weak-field) and trigonal symmetries (nb = non-bonding, adapted from ref. [15]).

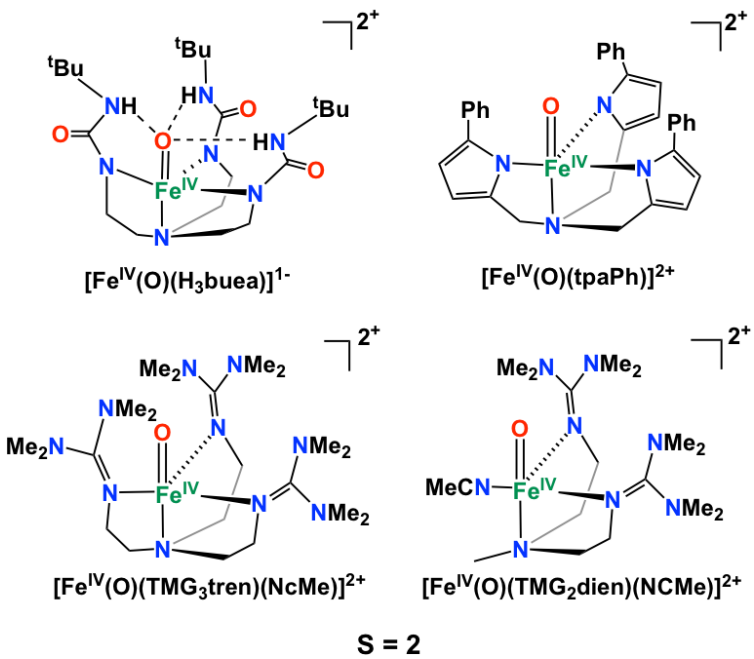


Fig. 1.10. Synthetic trigonal-bipyramidal S = 2 Fe^{IV}=O units obtained by enforcing a C_3 symmetry around the Fe^{IV} center (adapted from ref. [15]).

A comparison of tetragonal $[Fe^{IV}(O)(L)(NCMe)]^{2+}$ complexes (L = tris(2-pyridylmethyl)amine (TPA), (2-quinolylmethyl)bis-(2-pyridylmethyl)amine (QBPA), and tris(2-quinolylmethyl)amine (TQA), as shown in Fig. 1.11) has revealed that $[Fe^{IV}(O)(TPA)(NCMe)]^{2+}$ and $[Fe^{IV}(O)(QBPA)(NCMe)]^{2+}$ adopt the standard S = 1 configuration, while $[Fe^{IV}(O)(TQA)(NCMe)]^{2+}$ includes S = 2 state, indicating the possibility of a high-spin Fe^{IV}=O unit in a tetragonal geometry under a suitable ligand field.[40–43]

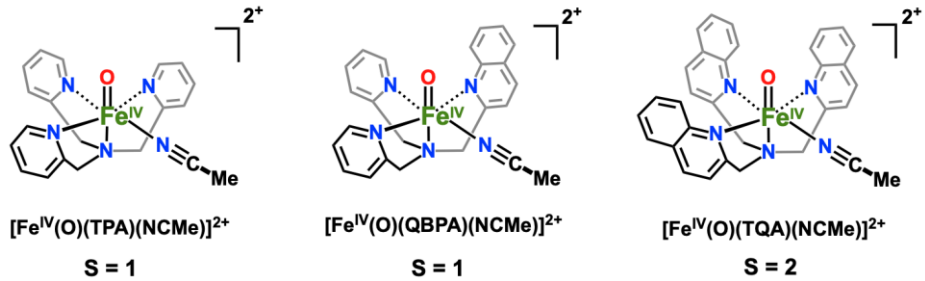


Fig. 1.11. Examples of biomimetic Fe^{IV}=O units with tetragonal geometry.

High-spin (S = 2) Fe^{IV}=O complexes are predicted to exhibit higher reactivity than their S = 1 counterparts due to several factors. As shown in Fig. 1.12, in tetragonal Fe^{IV}=O complexes, hydrogen atom transfer from σ(C-H) to S = 1 Fe^{IV}=O via the 'π attack' pathway results in stronger steric interactions between the substrate and equatorial ligands compared to the 'σ attack' pathway of S = 2 counterparts. Furthermore, electron transfer into the empty d_{z2} orbital of the S = 2 Fe^{IV}=O complex brings in exchange-enhanced stabilization by creating four new exchange interactions, while the 'π attack' in S = 1 counterparts reduces one stabilizing exchange interaction.[4,44] It should be noted that the reactivities of S = 2 Fe^{IV}=O complexes can also be influenced by factors such as the nature of the ligands and the coordination geometry of the complex.

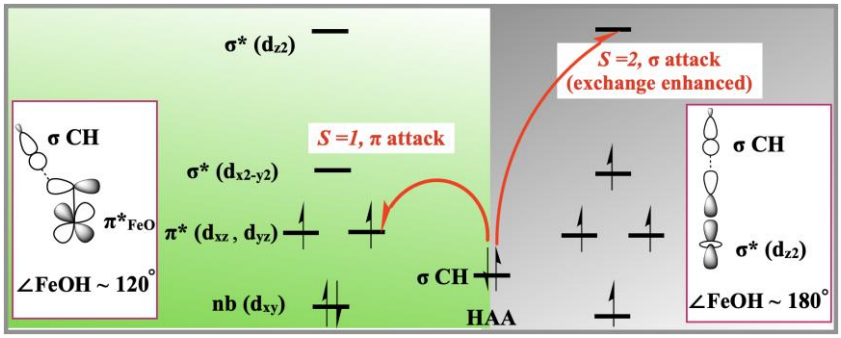


Fig. 1.12. Comparison of the frontier molecular orbitals (FMOs) involved in the hydrogen atom abstraction processes carried out by tetragonal Fe^{IV}=O complexes on S = 1 and S = 2 surfaces (adapted from ref. [4]).

1.3 High valent iron-nitrido and iron-imido complexes

1.3.1 Iron-nitrido and Iron-imido intermediates in biology

Iron-nitrido and imido complexes, which share electronic characteristics with iron-oxo complexes, are proposed to be critical intermediates in several significant biological transformations.[26,45–47] Although direct evidence for the participation of iron-nitrido or imido intermediates in biology remains elusive, mechanistic proposals that involve such intermediates have been put forward based on indirect evidence from various biochemical experiments.[45,48–50] For example, an iron(IV)-tosylimido (Fe^{IV}=NTs) porphyrin species has been suggested as the reactive intermediate in nitrogen-atom-transfer reactions catalyzed by cytochrome P450-LM-3,4 enzymes (Fig. 1.13).[26,51,52]

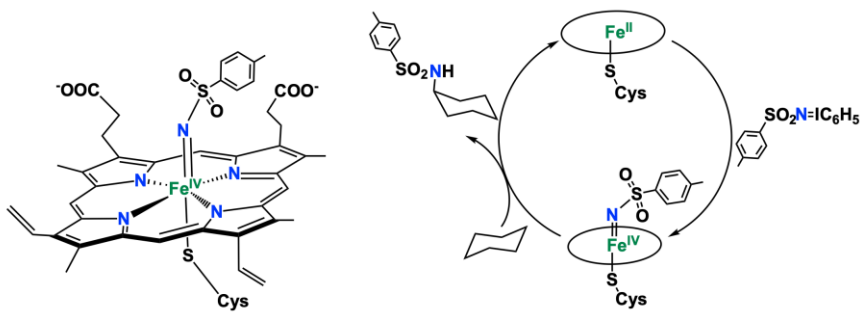


Fig. 1.13. Left: Proposed structure of the Fe^{IV}=NTs porphyrin intermediate that has been suggested for cytochrome-P450 catalyzed nitrogen group transfer reactions; Right: The proposed mechanism of the nitrogen transfer reaction (adapted from ref. [51]).

Iron(IV)-nitrido/imido (Fe^{IV}≡N/Fe^{IV}=N-R) species have been identified as potential catalytic intermediates in nitrogenase enzymes. Specifically, Fe^{IV}≡N and Fe^{III}=NH entities are believed to be formed during nitrogen reduction by the Fe-Mo cofactor of the nitrogenase enzyme (Fig. 1.14).[46,50]

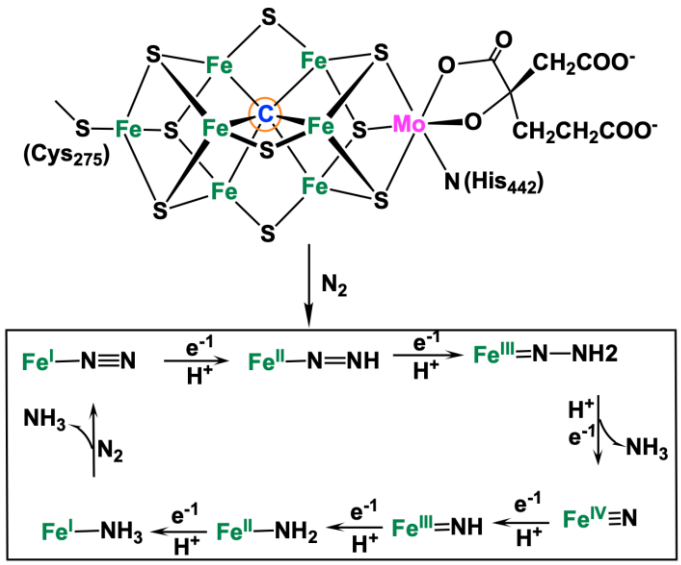


Fig. 1.14. The Fe-Mo cofactor of the nitrogenase enzyme with a central carbide (C), and the proposed intermediates (in the box) of the dinitrogen activation process occurring at a single iron site (adapted from ref.[26]).

1.3.2 Bioinspired non-heme high-valent FeIV=N-R complexes

Bioinspired non-heme Fe^{IV}=N-R complexes have garnered significant attention in the field of bioinorganic chemistry due to their resemblance to the active sites of various iron-containing enzymes. These complexes are capable of carrying out a range of important chemical transformations, including C-H activation, epoxidation, and nitrogen fixation.[26,53–58] However, despite this interest, relatively few models of Fe^{IV}=N-R species have been reported, in contrast to the successful syntheses of many biomimetic Fe^{IV}=O complexes.[26,53–56,59–66]

In 2006, Que and co–workers synthesized the first octahedral iron(IV)-tosylimido (Fe^{IV}=NTs) species, by reaction of $[Fe^{II}(N4Py)(NCMe)]^{2+}$ with the tosylimido transfer agent PhINTs (Fig. 1.15).[54] Some years later, a comparison of catalytic properties between these two analogs ($[Fe^{IV}(X)(N4Py)]^{2+}$ X = O, NTs) was performed by Sastri, de Visser *et al*.[57,58] In principle, as analogs of Fe^{IV}=O species, Fe^{IV}=NTs complexes tend to exhibit similar strong oxidative power to catalyze amination reactions. However, it has been experimentally and theoretically

demonstrated that there are differences in the electronic structure of the two types of species, which bring significantly different reactivities.

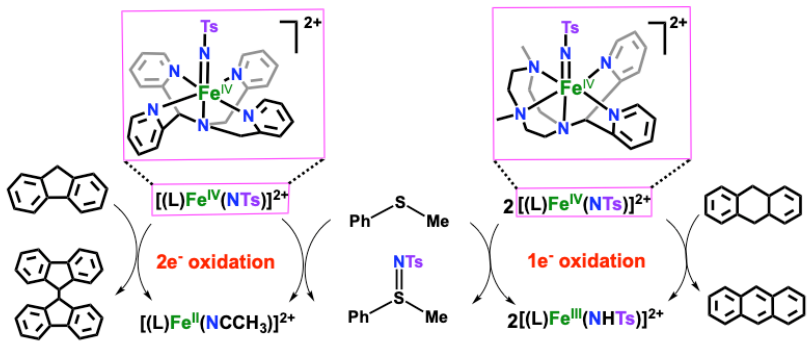


Fig. 1.15. Schematic drawings of $[(N4Py)Fe^{IV}(NTs)]^{2+}$,[57] $[(Me_2(CHPy_2)tacn)Fe^{IV}(NTs)]^{2+}$,[56] and the general mechanisms in H-atom abstraction reaction/N-atom transfer reactions.

On the basis of DFT calculations, it was argued that hydrogen atom transfer (HAT) reactions with $[(N4Py)Fe^{IV}(NTs)]^{2+}$ proceed through a two-step mechanism.[58] The electron affinity of $[(N4Py)Fe^{IV}(NTs)]^{2+}$ is high enough to accept electrons from substrates at a large distance, forming an $[(N4Py)Fe^{III}(NTs)]^{+}$ species that subsequently undergoes a proton transfer reaction. Although strictly not directly comparable, the greater electrophilicity of $[(N4Py)Fe^{IV}(O)]^{2+}$ relative to the tosylimido species $[(N4Py)Fe^{III}(NTs)]^{+}$ means that HAT reactions proceed at faster rates for the oxo species.[58]

In 2019, Costas reported another two rare octahedral examples of Fe^{IV}=NTs complexes with tacn-based ligands.[56] It was concluded that $[(MePy_2tacn)Fe^{IV}(NTs)]^{2+}$ and $[(Me_2(CHPy_2)tacn)Fe^{IV}(NTs)]^{2+}$, behave as a single-electron oxidant, while $[(N4Py)Fe^{IV}(NTs)]^{+}$ act as a two-electron oxidant (Fig. 1.15).[56,58] This difference in the mechanism can be attributed to the different ligand properties (see Chapter 3 for further details).

Overall, the mechanisms of reactions involving Fe^{IV}=NTs have been found to be more complex than those of their Fe^{IV}=O analogs. As less studies have been made in comparison to their Fe^{IV}=O analogs, more research is needed to gain a deeper understanding of the reactions of Fe^{IV}=NR complexes.

1.4 Summary, motivation and scope of this thesis

In conclusion, controlling catalytic oxidation reactions is challenging due to the formation of unwanted by-products and catalyst degradation. Therefore, the development of effective, affordable, and environmentally friendly regio- and stereoselective oxidation catalysts is highly desirable. Enzymes containing transition metals in their active sites create a unique chemical environment that allows selective catalytic substrate oxidation by activating dioxygen/nitrogen. Understanding the short-lived metal-based oxidants in critical oxidation processes is fundamental to developing greener oxidation catalysts. Bioinspired model complexes, especially those with high-valent intermediates such as iron-oxo and -imido species, provide powerful tools for investigating the reactivity and selectivity of analogous enzyme active sites. Insights obtained from these studies can be used to design new catalysts with enhanced properties for various industrial and environmental applications.

This thesis is concerned with the synthesis and reactivity studies of bioinspired high-valent iron complexes that can affect atom and group transfer reactions, as functional mimicry of active sites in mononuclear non-heme iron enzymes, specific to Fe^{IV}=O and Fe^{IV}=NR intermediates. Chapter 2 (Papers I and IV) discusses bioinspired model complexes for high-valent iron-oxo intermediates in biology. Four non-heme Fe^{IV}=O complexes based on new pentadentate N5-donor ligands have been prepared and characterized, which provides detailed investigations into the reactivities of these complexes towards hydrogen atom transfer and oxygen transfer reactions, and highlights how the electronic and steric properties influence reactivities of high-valent iron-oxo complexes. Chapter 3 (Paper II) describes the preparation and reactivity of a Fe^{IV}=NR complex that combines good stability with high reactivity. A comparative kinetic study was conducted to examine the reactivity patterns of the new imido complex versus its oxido congener. Chapter 4 (Paper III) describes catalytic epoxidation reactions affected by iron complexes by Fe^{II} complexes based on the newly synthesized pentadentate ligands, which sheds light on the role of electronic effects of the ligand in the reactivity of olefin epoxidation.

Chapter 2: Electronic and steric influence by ligands on the reactivities of non-heme iron-oxo complexes

2.1 Bioinspired nonheme Fe^{IV}=O complexes.

A number of bioinspired Fe^{IV}=O complexes with a wide range of pentadentate and tetradentate ligands have been synthesized and characterized in the past two decades.[15,17,36,37] Unlike the high-spin (S = 2) Fe^{IV}=O intermediates found in non-heme enzymes, most of the synthesized complexes are found to be in the low-spin (S = 1) state (Table 2.1).[67,68] High-spin (S = 2) Fe^{IV}=O units have been predicted to be more reactive towards C-H abstraction than their low-spin (S = 1) counterparts due to a lower steric contribution at the transition state and an increase in the number of exchange interactions resulting from the transfer of an electron into the empty d_{z2} orbital (*vide* Chapter 1).[69,70]

Only a few synthetic efforts have successfully stabilized S = 2 Fe^{IV}=O units by enforcing a C_3 symmetry around the Fe^{IV}=O center (Table 2.1 and Fig. 2.1 (a)). However, due to bulky ligands hindering access to substrates, these complexes have shown limited efficacy in cleaving substrate C-H bonds. A highly reactive Fe^{IV}=O complex with C_4 symmetry, $[Fe^{IV}(TQA)(NCMe)]^{2+}$ (Fig. 2.1 (b)), decreases the energy gap between the d_{x2-y2} and d_{xy} orbitals to give an S = 2 ground state. It shows the best reactivity of all synthetic S = 2 Fe^{IV}=O complexes and is the closest functional model of the enzymatic intermediate, TauD-J.[68]

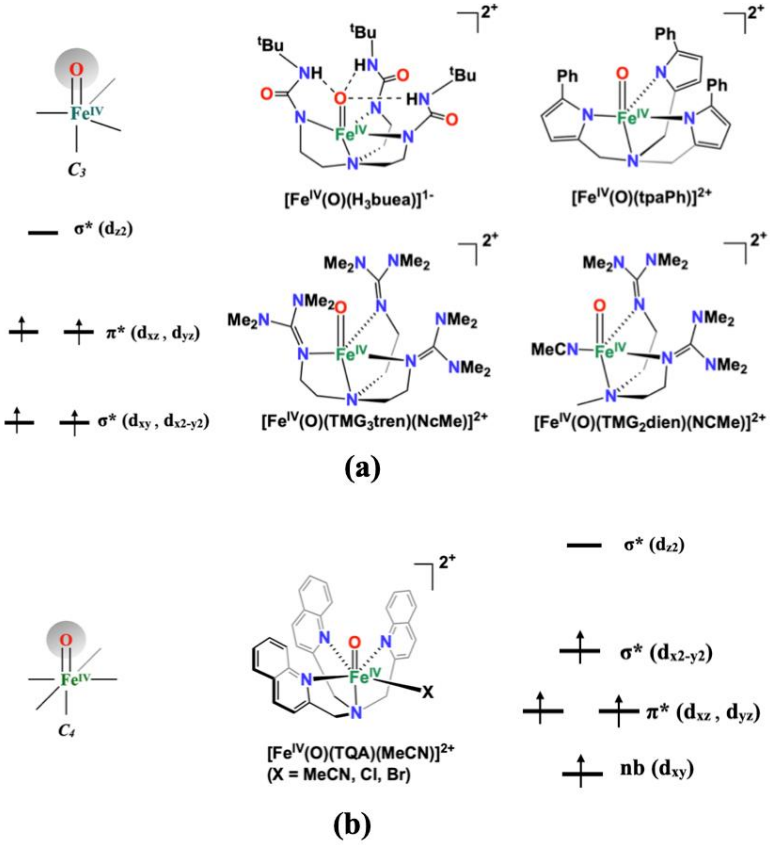


Fig. 2.1. Examples of biomimetic S = 2 Fe^{IV}=O units with C_3 (a) or C_4 (b) symmetry.

Table 2.1. Spectroscopic and structural properties of enzymatic and synthetic nonheme iron-oxo complexes.

Complexes[a]	S[b]	near-IR bands (nm)	δ (mm s^{-1})	ΔE_Q (mm s^{-1})	D (cm^{-1})	Ref(s)
Biological Fe^{IV}=O species						
Taurine dixoygenase (TauD-J)	2		0.30	-0.88	10.5	[11]
Halogenase CytC3	2		0.30, 0.22	-1.09, -0.70	8.1	[22]
Halogenase SyrB2	*2*		0.30, 0.23	1.09, 0.76		[23]
Tyrosine hydroxylase (TyrH)	2		0.25	1.27	12.5	[71]
Prolyl 4-hydroxylase (P4H)	2		0.30	-0.82	15.5	[72]
Phenylalanine hydroxylase (PheH)	2		0.28	1.26		[28]
S = 1 Fe^{IV}=O species						
$[Fe^{IV}(O)(N4Py)]^{2+}$	1	695	-0.04	0.93	22	[73]
$[Fe^{IV}(O)(N2Py2B)]^{2+}$	1	725	-0.02	1.34	25(1)	[74]
$[Fe^{IV}(O)$ (N3Py-(NMB))$]^{2+}$	1	708	-0.03	1.1		[74]
$[Fe^{IV}(O)$ (TMC) (MeCN)$]^{2+}$	1	824	0.17	1.24	27	[75]
$[Fe^{IV}(O)(Bn\text{-}tpen)]^{2}$	1	740	0.01	0.87		[73]
$[Fe^{IV}(O)(N2Py2Qn)]^{2+}$	1	770	0.03	0.56	26(2)	[76]
$[Fe^{IV}(O)(TPA)(NCMe)]^{2}$	1	724	0.01	0.92	28(2)	[77]
$[Fe^{IV}(O)(QBPA)(NCMe)]^{2}$	1	770				[78]
$[Fe^{IV}(O)(Me_3NTB)(NCMe)]^{2}$	1	770	0.02	1.53	28(7)	[79]
S = 2 Fe^{IV}=O species						
$[Fe^{IV}(O)(OH_2)_5]^{2+}$	2		0.38	0.33	9.7(7)	[80]
$[Fe^{IV}(O)(TQA)(NCMe)]^{2}$	2	650, 900	0.24	-1.05	17(1)	[81]
$[Fe^{IV}(O)(TMG_3tren)]^{2+}$	2	825	0.09	-0.29	5.0(5)	[82]
$[Fe^{IV}(O)(H_3buea)]^{1-}$	2	808	0.02	0.43	4.0(5)	[83]
$[Fe^{IV}(O)(TMG_2dien)(X)]^{+/2+}$						[84]
X = MeCN	2	724, 805	0.08	0.58	4.5(5)	
X = Cl	2	745, 803	0.08	0.41	4.0(5)	
$X = N_3$	2	827	0.12	-0.30	4.6(5)	
$[Fe^{IV}(O)(tpa^{Ph})]^{1-}$	2	~900	0.09	0.51	4.3	[85]

Researchers have found that for low-spin (S = 1) Fe^{IV}=O complexes, ligand modifications can also significantly affect the electronic structure and redox properties of the iron center, leading to changes in reactivities and selectivities of

the complexes (vide infra).[17,18,36,37] To rationalize the differences in reactivity observed among various S = 1 Fe^{IV}=O complexes, the two-state-reactivity (TSR) model has been developed by Shaik and coworkers (Fig. 2.2).[86,87] This model suggests that the net activation barrier for breaking a C-H bond is a combination of the barriers for both the ground triplet and excited quintet states.[70] Consequently, it is hypothesized that ligand-field effects which diminish the energy gap between the triplet and quintet states (ΔE_{TQ}) are able to enhance C-H bond cleavage by S = 1 Fe^{IV}=O complexes.

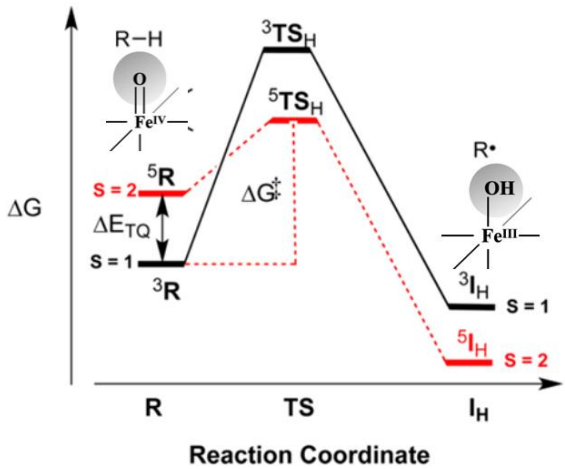


Fig. 2.2. Representation of the two-state reactivity (TSR) scenario during a hydrogen atom abstraction reaction of an Fe^{IV}=O complex in a tetragonal geometry (adapted from ref. [86,87]).

2.2 Ligand effects on S = 1 Fe^{IV}=O complexes.

The reactivities and selectivities of these complexes in diverse chemical reactions can be profoundly influenced by the electronic and steric effects of their ligand environment. A comprehensive understanding of these effects can help design more efficient and selective catalysts for specific applications.

2.2.1 Electronic effects of Ligands

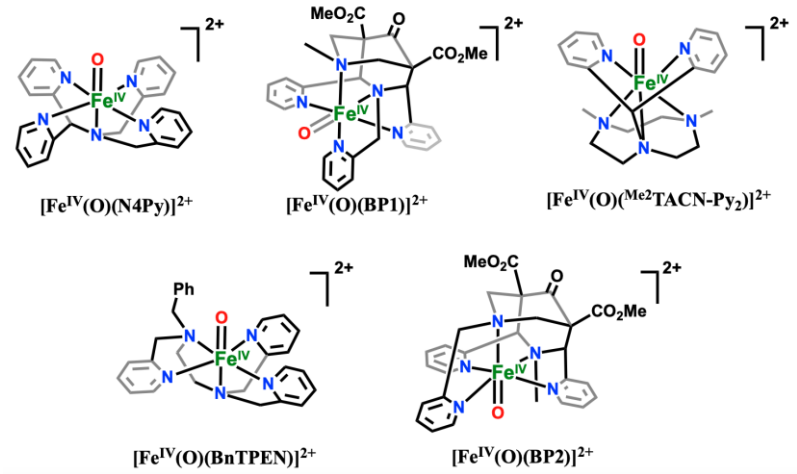


Fig. 2.3. Schematic drawings of nonheme S = 1 Fe^{IV}=O complexes based on pentadentate N5 ligands with different equatorial electron-donating properties (adapted from ref. [88]).

The electronic effects (electron-donating properties) of the ligand(s) will influence the electron density of the Fe^{IV}=O unit and may therefore significantly influence the reactivities of Fe^{IV}=O complexes. In 2013, Que and coworkers carried out a study on a series of S = 1 $[Fe^{IV}(O)(L)]^{2+}$ complexes with pentadentate N5-donor ligands containing one tertiary amine ligand *trans* to the oxo group but with different equatorial electron-donating groups (Fig. 2.3).[88] The ligands with low equatorial electron-donating properties would lead to increased Fe^{III}-OH/Fe^{IV}=O potential. For the first time, the redox potentials for $[Fe^{IV}(O)(L)]^{2+}$ complexes ($E_{1/2}$(IV/III)) were determined by spectropotentiometry, which showed a difference of 0.3-0.4 V in the Fe^{III}-OH/Fe^{IV}=O potentials. It was also found that oxygen atom transfer reactivities of the complexes correlated linearly with $E_{1/2}$(IV/III values (Fig. 2.4). As the axial ligands of these complexes are tertiary amines in all complexes, the electronic and reactivity differences were attributed to the electron-donating or electron-withdrawing properties of the equatorial ligands. [18] Even though it is the electron-donating properties of the various donor units that directly influence the property of the Fe^{IV}=O center, the steric effects of the α-H atom on the perpendicular pyridine donor in ligands BP1 and BP2 (Fig. 2.3), were considered to weaken equatorial fields by lengthening Fe-N distances. [18]

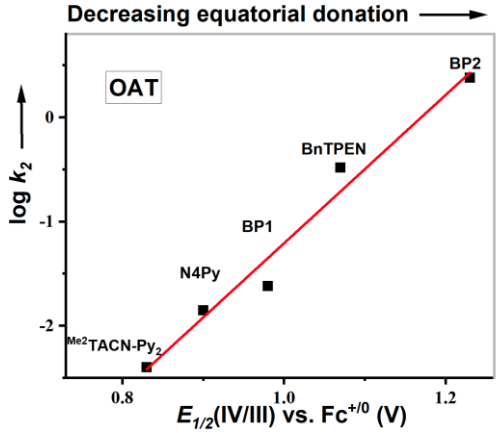


Fig. 2.4. Plots of the logarithms of the second-order rate constants (*log* k_2) for the OAT (PhSMe at -10 ºC) reactivities in CH_3CN versus the Fe^{III}-OH/Fe^{IV}=O redox potential values measured by spectropotentiometry for a series the complexes in Fig. 2.3 (adapted from ref.[88]).

In 2015, Chang and co-workers carried out a study on a series of $[Fe^{II}(CH_3CN)(PY5Me_2\text{-}X)]^{2+}$ complexes with different electron-withdrawing functionalities of the axial pyridine ligands (*trans* to the CH_3CN ligand) ($PY5Me_2$ = 2,6-bis(1,1-bis(2-pyridyl)ethyl)pyridine; X = CF_3, H, Me, or NMe_2), in which the Fe^{III}/Fe^{II} redox potentials were found to correlate well with the Hammett parameter (σ_p) of the added substituents, where electron-rich derivatives are more easily oxidized from Fe^{II} to Fe^{III} (Fig. 2.5).[89]

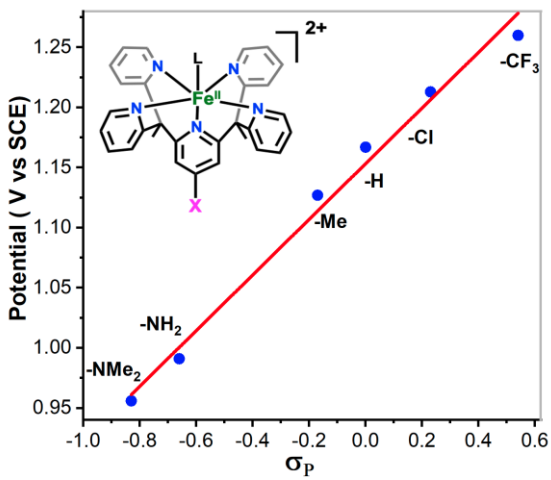


Fig. 2.5. The relationship between Fe^{III}/Fe^{II} redox couples of Fe^{II}-X complexes and Hammett Parameters (σ_p) of the X-substituents (adapted from ref.[42]).

The oxidative reactivities of these $[Fe^{IV}(O)(PY5Me_2\text{-}X)]^{2+}$ ferryl species were found to correlate with the electronic properties of the axial pyridine ligands (Fig. 2.6).

The $[Fe^{IV}(O)(PY5Me_2\text{-}X)]^{2+}$ derivatives with electron-poor axial ligands showed faster rates of HAT and OAT compared to their counterparts supported by electron-rich axial donors.

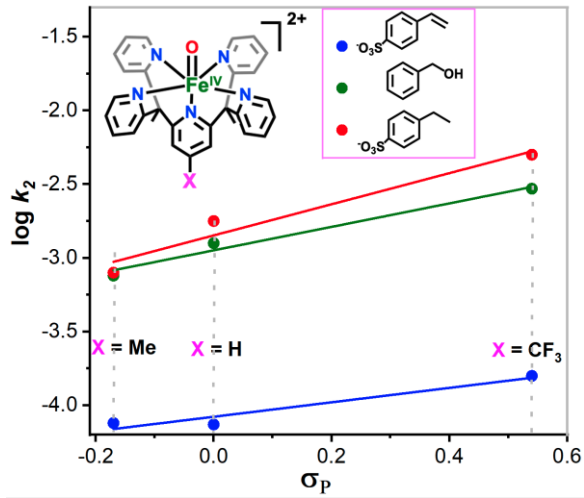


Fig. 2.6. The relationship between Hammett parameters (σ_p) of the X-substituents and (pseudo-first-order) reaction rate constants for oxidation of hydrocarbon substrates by Fe^{IV}=O-X (adapted from ref. [89]).

In conclusion, electron-withdrawing functionalities in the axial position (*trans* to the oxido ligand) were found to result in more positive Fe^{III}/Fe^{II} redox potentials, and more reactive $[Fe^{IV}(O)(PY5Me_2\text{-}X)]^{2+}$ species toward HAT and OAT reactions.

2.2.2 Steric effects of ligands

Steric effects, determined by the spatial arrangement and size of the ligands, modulate the accessibility of substrates to the metal center. For example, as discussed above, although computational studies suggest that S = 2 nonheme Fe^{IV}=O complexes should be more reactive than their S = 1 counterparts, trigonal-bipyramidal S = 2 Fe^{IV}=O complexes with bulky C_3-symmetric ligands (*e.g.* $[(TMG_3tren)Fe^{IV}(O)]^{2+}$ in Fig. 2.1), always exhibit a rather sluggish reactivity, which could be attributed to the steric encumbrance provided by the ligand framework hindering the substrate from the substrates.[15,68]

On the other hand, de Visser and coworkers made a joint experimental and computational study on steric and electronic factors by applying selective substitutions in the N4Py framework.[36] The sudden drop in reactivity for $[Fe^{IV}(O)(^{Me}N4Py)]^{2+}$ and $[Fe^{IV}(O)(N4Py^{Me})]^{2+}$ with triphenylmethane verified the steric hindrance effect of the methyl group (Fig. 2.7). Compared to the other two complexes, $[Fe^{IV}(O)(N4Py^{Me})]^{2+}$ showed much more enhanced reactivity in both HAT and OAT reactions. The computational modeling showed that $[Fe^{IV}(O)(N4Py)]^{2+}$, $[Fe^{IV}(O)(^{Me}N4Py)]^{2+}$ and $[Fe^{IV}(O)(N4Py^{Me})]^{2+}$ have similar physicochemical properties, but methyl substituents in the 6-positions of $[Fe^{IV}(O)(N4Py^{Me})]^{2+}$ are able to guide substrates in their approach to the Fe^{IV}=O center and thereby influence reactions efficiently, which resembles functions of enzymatic catalysts that can channel the substrate and position the oxidant in an ideal conformation.[90]

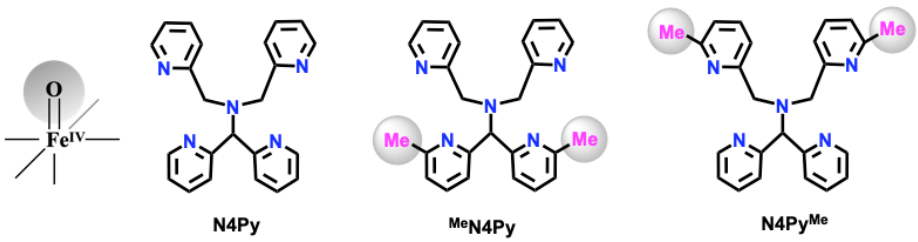


Fig. 2.7. Schematic drawings of pentadentate ligands for Fe^{IV}=O complexes discussed in ref [36].

Even though the S = 1 spin state complexes are predicted to be less reactive than their S = 2 counterparts, the S = 1 $[Fe^{IV}(O)(Me_3NTB)]^{2+}$ complex (Fig. 2.8) is as reactive as the S = 2 $[Fe^{IV}(O)(TQA)]^{2+}$ that is discussed above.[79,91] Several investigations have been done to study how the introduction of (*N*-methyl)benzimidazolyl moieties in ligand frameworks affects the properties of Fe^{IV}=O complexes (Fig. 2.8).[74,91–93]

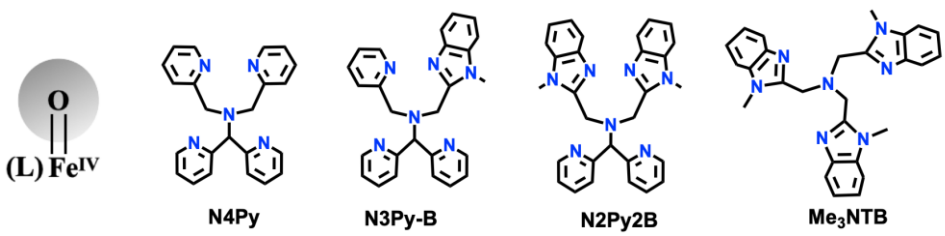


Fig. 2.8. Schematic drawings of pentadentate ligands for Fe^{IV}=O complexes discussed in ref. [18].

Although the ligands in Fig. 2.8 are not strictly comparable, Fig. 2.9 indicates that HAT and OAT activities can be enhanced gradually by the replacement of pyridyl

units by 1-3 (*N*-methyl)benzimidazolyl moieties. The differences in reactivities among this set of complexes can largely be attributed to steric factors, as the relative donor capacities of pyridine and benzimidazole can be estimated to be quite similar by comparing the pKa values of their conjugate acids (5.22 for pyridine and 5.41 for benzimidazole).[94] The sp^2 character and the rigidity of the (*N*-methyl)benzimidazolyl substituent should enforce a higher steric demand in the equatorial plane than the α-H substituent on the perpendicular pyridine donors. As a result, the introduction of one or two (*N*-methyl)benzimidazolyl donors in the N4Py framework (ligands N3Py-B and N2Py2B, Fig. 2.8) leads to weaker Fe-N interactions in the equatorial plane of $[Fe^{IV}(O)(L)]^{2+}$ complexes (L= N3Py-B and N2Py2B) than the parent complex $[Fe^{IV}(O)(N4Py)]^{2+}$, which is demonstrated by the longer wavelengths of the characteristic absorptions in the near-IR region of their UV-vis spectra. In the case of the parent complex $[Fe^{IV}(O)(N4Py)]^{2+}$, Que, Solomon and coworkers have determined that this near-IR absorption originates from d-d transitions and red-shifts in wavelength indicate weaker equatorial ligand fields.[88,95]

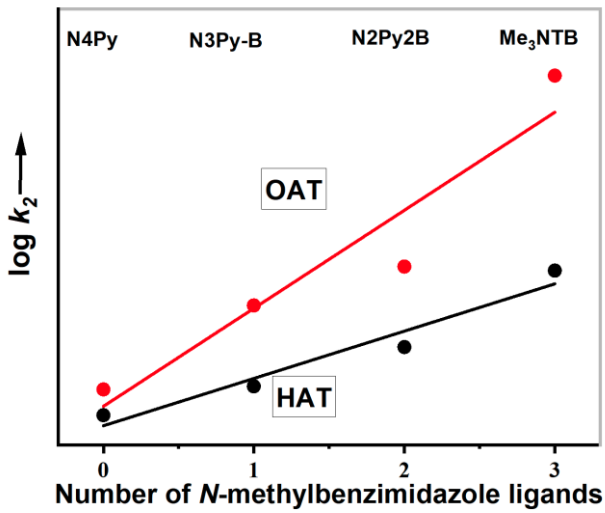


Fig. 2.9. Plots of the log k_2 values for OAT (PhSMe at -30 ºC) and HAT (C_6H_{12} at 25 ºC) reactivities in CH_3CN versus the number of N-methylbenzimidazole donors in the supporting ligands for a series of Fe^{IV}=O complexes (adapted from ref. [18]).

In 2018, Que and coworkers successfully crystallized two $[Fe^{IV}(O)(L)]^{2+}$ complexes supported by pentadentate ligands, which provided direct evidence of the influence of ligand-modifications (Fig. 2.10**).**[37]

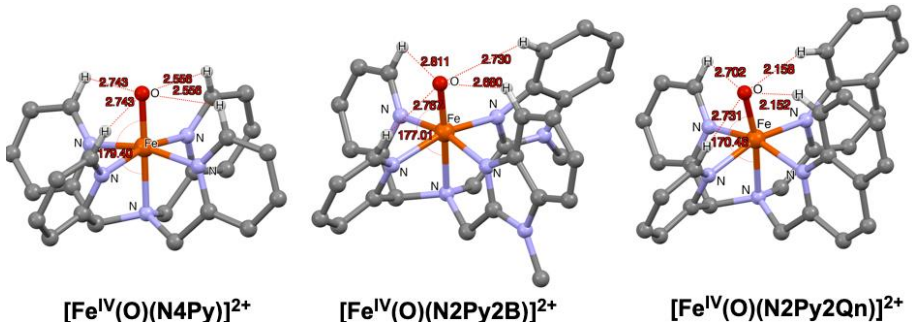


Fig. 2.10. Mercury plots of crystallographically determined Fe^{IV}=O complexes with ellipsoids set at 50% probability. Counterions and selected hydrogen atoms have been omitted for clarity. The dotted lines show the Fe-N bond lengths (Å) and angles (º).

Especially, the sterically bulky quinoline donors in $[Fe^{IV}(O)(N2PyQn)]^{2+}$ are found to tilt the Fe=O unit away from a linear N_{ax}-Fe=O arrangement by 10º and also increase the average Fe-N bond length, resulting in higher HAT and OAT rates relative to $[Fe^{IV}(O)(N4Py)]^{2+}$ and $[Fe^{IV}(O)(N2Py2B)]^{2+}$ (Figs. 2.10 and 2.11**)**. These longer distances correlate linearly with log k_2' values for O- and H-atom transfer rates, suggesting that weakening the ligand fields can increase the electrophilicity of the Fe=O center.[37,94]

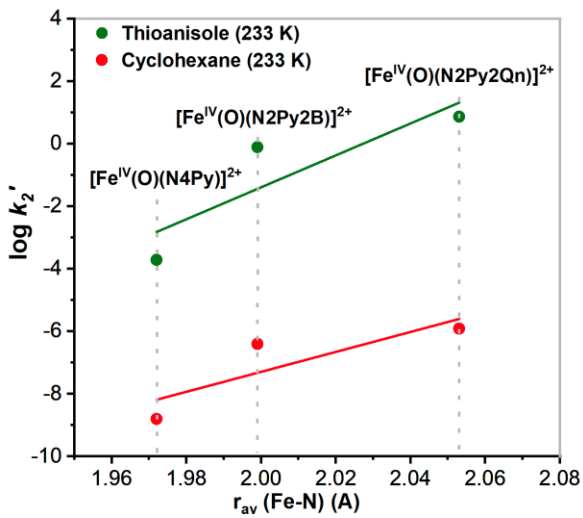


Fig. 2.11. Correlation of log k_2' values for thioanisole and cyclohexane at -40 ºC versus the average Fe-N bond lengths for complexes (adapted from ref. [94]).

In conclusion, ligand fields around the Fe^{IV}=O center are of paramount importance for the physicochemical properties and reactivities of ferryl complexes. Modifications of the ligands always bring in both steric and electronic effects. Weak ligand fields can enhance reactivity. Steric effects can hinder the substrate approach to the Fe=O unit, but sometimes steric effects can also help the reaction to take place by directing the substrates to the Fe=O center. Also, as discussed above, steric effects can result in weak ligand fields by influencing the interaction (bond distances) between the ligand and the iron center. Therefore, optimization of the ligand scaffolds is very tricky, and further research on electronic and steric effects generated by substituents is needed to pave the way to more efficient and selective systems.

2.4 Electronic influence of N5-donor ligands in a series of new Fe^{IV}=O complexes (Paper I).

The complex $[Fe^{IV}(O)(N4Py)]^{2+}$ based on the pentadentate N4Py ligand has been demonstrated to possess strong oxidative reactivity towards alkanes and arenes, making it capable of cleaving strong C-H bonds. Additionally, the complex exhibits significant thermal stability, allowing for in-depth studies of its properties.[96] As a result, various derivatives of the N4Py ligand have been synthesized to examine how modifications to the ligand affect the electronic and steric properties of the iron complexes and their reactivities. [36,37] Specifically, as N-donor entities, (N-methyl)benzimidazole and quinoline have been found to be amongst the best substituents to make reactive nonheme Fe^{IV}=O complexes. The steric effects arising from the introduction of either of these two moieties into the N4Py scaffold are thought to be the main reasons for the elongation of Fe-N distances, which weakens the ligand field and increases the electrophilicity of the Fe^{IV}=O center.[18,37] The basicities/electron-donating properties of the (N-methyl)benzimidazolyl and quinolinyl substituents of the ligands may also influence the reactivity of the Fe^{IV}=O center, although it is difficult to assess the precise influence of the electronic effects of the ligands because they are compounded with the electronic effects. To investigate the influence of electronic-donating properties of N4Py-like ligands on the reactivities of their iron complexes, four new pentadentate ligands (Fig. 2.12 and Paper I) similar to the N2Py2Qn and N2Py2B frameworks were designed and synthesized. Due to the sizes and orientations of the imidazolyl and isoquinolinyl moieties in these new ligands, it was anticipated that their coordination with the iron center would lead to relatively open structures with minor steric influences on the Fe^{IV}=O units. Therefore, the reactivities of non-heme Fe^{IV}=O complexes of these ligands may be mainly attributed to the electronic effects of the ligands.

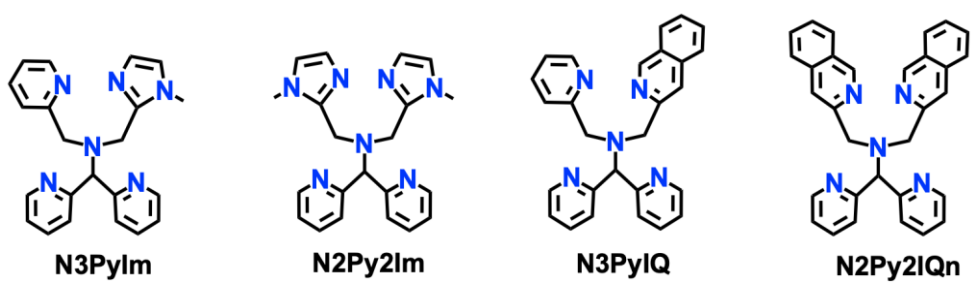


Fig. 2.12. Schematic drawings of pentadentate ligands discussed in Paper I.

In Paper I, the synthesis and characterization of four new Fe^{IV}=O complexes (Fig. 2.13) based on the four new pentadentate ligands are reported. UV-vis spectra and Mössbauer spectra confirmed the S = 1 state of these Fe^{IV}=O complexes. Crystal structures proved that steric influences on the central Fe^{IV}=O units exerted by the four new ligands are negligible (see Paper I). Cyclic voltammetry was applied on Fe^{II} complexes to indicate the electrophilicity of iron centers. The order of half-wave potentials of Fe^{II}/Fe^{III} redox couples is $[Fe^{II}(CH_3CN)(N2Py2Im)]^{2+}$ < $[Fe^{II}(CH_3CN)(N3PyIm)]^{2+}$ < $[Fe^{II}(CH_3CN)(N3PyIm)]^{2+}$ < $[Fe^{II}(CH_3CN)(N2Py2Im)]^{2+}$ < $[Fe^{II}(CH_3CN)(N4Py)]^{2+}$ (*cf.* Paper I, Fig. 2.13), which is consistent with the fact that (N-methyl)imidazolyl moiety is essentially a pure sigma-donor ligand and isoquinoline/pyridyl substituents are σ-donors and π-acceptors (see Paper I). Therefore, N2Py2Im is expected to have the weakest ligand field. [89]

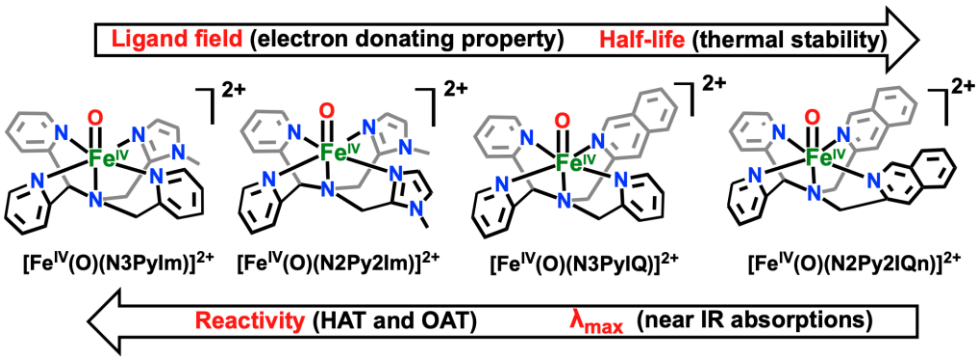


Fig. 2.13. Schematic drawings of the Fe^{IV}=O complexes discussed in Paper I.

The sequence of λ_{max} for the characteristic near IR absorptions of Fe^{IV}=O complexes was found to be 721 nm ($[Fe^{IV}(O)(N2Py2Im)]^{2+}$) > 706 nm ($[Fe^{IV}(O)(N3PyIm)]^{2+}$) > 696 nm ($[Fe^{IV}(O)(N3PyIQn)]^{2+}$) ⩾ 695 nm ($[Fe^{IV}(O)(N2Py2IQn)]^{2+}$) ≈ 695 nm ($[Fe^{IV}(O)(N4Py)]^{2+}$), and the thermal stabilities increased in the opposite direction (Fig. 2.13). [51] Consequently, the kinetics study of OAT and HAT reactions proved that $[Fe^{IV}(O)(N2Py2Im)]^{2+}$ is the most reactive species (Fig. 2.13). All evidence demonstrated the N2PyIm ligand to exhibit the weakest ligand field. As the steric influences on the central Fe^{IV}=O units exerted by the four new ligands are negligible (see Paper I), the electronic effects are the primary contributor to the differences in properties of the Fe^{IV}=O complexes.

2.5 Steric influence of ligands on the reactivity of $Fe^{V}(O)(OH)$ species in stereospecific C-H hydroxylation (Paper IV).

In contrast to the observations in Paper I, where reactivities of Fe^{IV}=O units are primarily dictated by the electronic properties of the ligands with little or no steric restrictions, Paper IV provides an example of a ligand framework where the steric restrictions of the specific ligand dictates the substrate accessibility to two $Fe^{V}(O)(OH)$ tautomers (Fig. 2.14) and any electronic influence by the donor moieties appears to be of secondary importance

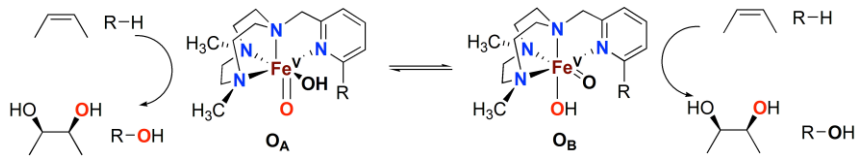


Fig. 2.14. Oxidation of alkanes (R-H) and alkenes by the two tautomers, $\mathbf{O_A}$ and $\mathbf{O_B}$, observed in reactions catalyzed by the Fe(PyTACN) family of complexes.

In previous studies, Costas and coworkers[97,98] have observed that products, and product distributions, in oxidations of alkanes by the Fe(PyTACN) family of complexes, are consistent with the formation of $Fe^{V}(O)(OH)$ intermediates that emulate the reactivities of Rieske oxygenases (*cf.* Chapter I for a discussion of Rieske oxygenases). Furthermore, it could be shown by ^{18}O-labeling of substrates that the two possible tautomers can be formed (Fig. 2.14) which exhibit different reactivities. The tautomer labelled O_A, where the oxido ligand lies in the PyTACN ligand plane, is sterically more shielded for oxo atom transfer than tautomer O_B and the steric properties of the pendant "arm" of the PyTACN ligand therefore affects the relative reactivities – and thus the product distributions – of the two tautomers.

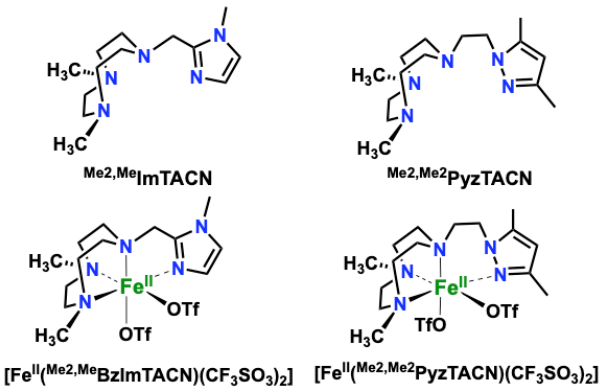


Fig. 2.15. Structures of tetradentate ligands and related Fe^{II} complexes described in Paper IV.

In Paper IV, the synthesis and characterization of two new members of the R-TACN family of ligands, *viz.* ^{Me2,Me}ImTACN and ^{Me2,Me2Pyz}TACN (Fig. 2.15) are described. Both ligands were used to synthesize the Fe^{II} complexes ([Fe^{II}(^{Me2,Me}BzImTACN)(CF_3SO_3)$_2$] and [Fe^{II}(^{Me2,Me2}PyzTACN)(CF_3SO_3)$_2$]), in which the pendant arms (pyrazole and imidazole) of the ligands contain sterically bulky nitrogen donors. My contribution to this work was the synthesis of ligand ^{Me2,Me2}PyzTACN and [Fe^{II}(^{Me2,Me2}PyzTACN)(CF_3SO_3)$_2$]. The C-H hydroxylation reactions of a number of substrates using H_2O_2 as the oxidant were investigated using the two new complexes, as described in the Ph. D. thesis of Mainak Mitra. [99] As the oxo ligand in O_A originates from water,[97,98] by using ^{18}O-labelled hydrogen peroxide and ^{18}O-labelled water in separate oxidation experiments, the relative presence of the two tautomers O_A and O_B could be ascertained for the two complexes and related to the results obtained for a number of related complexes. On the basis of experimental results (different incorporation of labeled oxygen into the oxidation products), it was thus possible to gauge the relative steric influence of the pendant arms of the different R-TACN ligands, and this steric influence could be confirmed by buried volume calculations (see Paper IV and Fig. 2.16).

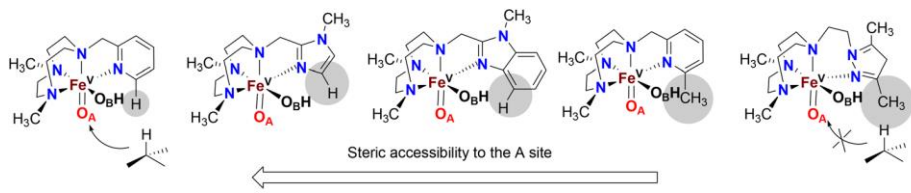


Fig. 2.16. Schematic depictions (top) and space-filling models (bottom) of the Fe^{V}(O)(OH) species obtained by modifying the crystal structures of Fe^{II} complexes.

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Chapter 3: High valent Fe^{IV} imido complexes: reactivities towards H- and N-atom transfer process

3.1 Fe=N-R intermediates in mononuclear non-heme enzymes

Iron-nitrido and imido complexes have been suggested to be critical intermediates in numerous significant biological processes.[26,45–47] For instance, during the biosynthesis of ammonia, $Fe^{IV}{\equiv}N$ and $Fe^{III}{=}NH$ entities are proposed to be key intermediates in the Fe-Mo cofactor of nitrogenase.[46,50] In 1985, Breslow, Dawson, and coworkers used purified cytochrome $P450_{LM3,4}$ enzyme from rabbit liver microsomes to facilitate nitrogen transfer *in vitro*.[51] $P450_{LM3,4}$ has been found to catalyze reactions such as intramolecular amination of [(2,5-diisopropylphenyl)sulfonyl]iminophenyliodinane and intermolecular amination of cyclohexane, using a $Fe^{IV}{=}NR$ species as the reactive intermediate (*vide* chapter 1).[51] Since then, a number of engineered hemoproteins have been prepared and have shown reactivity in a variety of nitrene transfer reactions via reactive $Fe^{IV}{=}NR$ intermediates (Fig. 3.1).[100–103] In 2018, the first cytochrome P450 nitrene transferase 'BezE' was discovered in nature by Ohnishi, Tsutsumi and coworkers, and $Fe^{IV/V}{=}NR$ entities were proposed to be key intermediates in the catalytic cycle of the enzyme.[104]

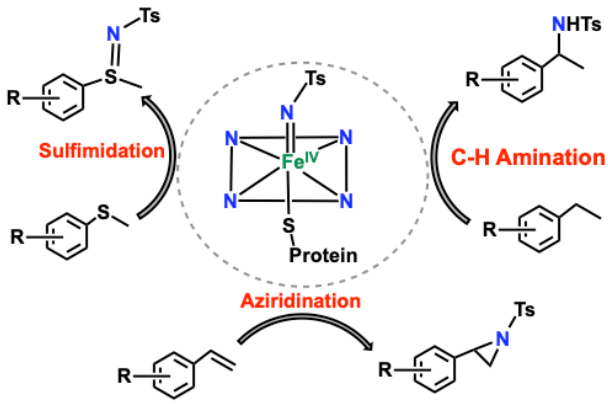

Fig. 3.1. Nitrene transfer reactions via C-H amination,[101] sulfimidation[102] and aziridination catalyzed by engineered hemoproteins (adapted from ref. [10]).

3.2 Bioinspired nonheme Fe=N-R complexes

Researchers are highly interested in nitrogen-functionalization of organic molecules, particularly in the field of pharmaceutical synthesis. To achieve this, mimicking the metal intermediates in relevant enzymes is critical to understanding reaction mechanisms, duplicating their functions, and discovering new synthetic pathways in chemical synthesis. In 2000, Lee and coworkers isolated the first structurally characterized Fe=NR complex, where this unit forms a part of an $Fe_4(NR)_4$ cubane cluster.[64] Since then, quite a few Fe=NR bioinspired complexes have been developed, which have led to significant progress in the understanding of their chemical properties (Fig. 3.2).[105–110] As shown in Fig. 3.2, most of the isolated iron imido complexes have a low-coordinate ligand environment in approximate threefold symmetry. It has been suggested that a low-coordinate environment is essential for the stabilization of Fe=NR species.[26,61] In contrast, 5- or 6-coordinate Fe-imido complexes are typically regarded as highly unstable, leading to challenges in their generation and characterization. [61]

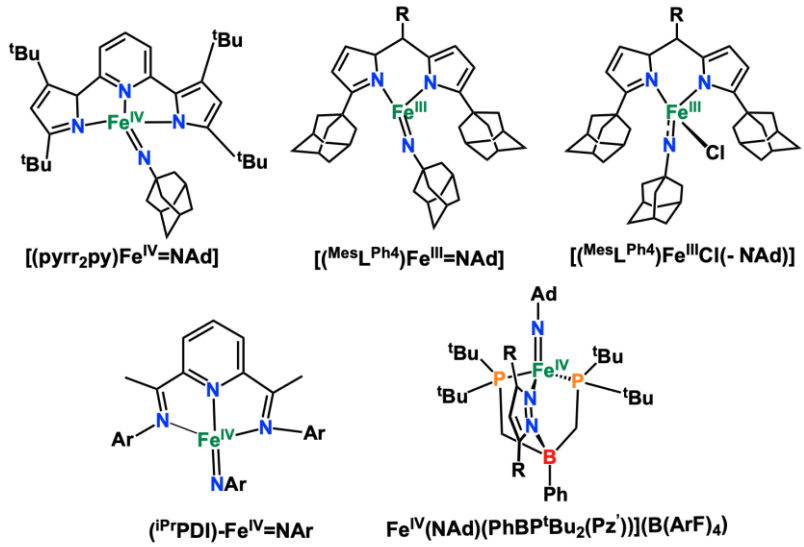

Fig. 3.2. Representative examples of low-coordinate Fe=N-R complexes (Ad = adamantyl).

In 2017, Nam and coworkers isolated the first mononuclear nonheme Fe^{V}=N-R complex, *viz.* $[(TAML)Fe^{V}(NTs)]^{-}$, which is capable of C-H functionalization and sulfimidation (Fig. 3.3).[59] Soon after that, they succeed to oxidize it to $[(TAML^{+\bullet})Fe^{V}(NTs)]$ using a one-electron oxidant, such as $[Fe^{III}(bpy)_3]^{3+}$ or $[Ru^{III}(bpy)_3]^{3+}$.[111] The one-electron oxidized ligand ($TAML^{+\bullet}$) was demonstrated to enhance reactivity in nitrene transfer reaction by four orders of magnitude. DFT calculations attributed the reactivity enhancement to the substantial increase in the electron affinity of $[(TAML^{+\bullet})Fe^{V}(NTs)]$ upon ligand oxidation.[111] On the other hand, the similar N-H bond dissociation energies of $[(TAML^{+\bullet})Fe^{IV}(NHTs)]$ and $[(TAML)Fe^{IV}(NHTs)]^{-}$ indicated similar driving forces in C-H bond activation reactions for the two complexes, which can explain their similar activities.[112] As the reason that the imido ligand binding to the metal center is weaker than the oxo ligand, which results in less orbital hybridization and the destabilization of valence antibonding orbitals, Fe^{V}=NR complexes can access more complicated electronic configurations and display more reaction patterns.[112]

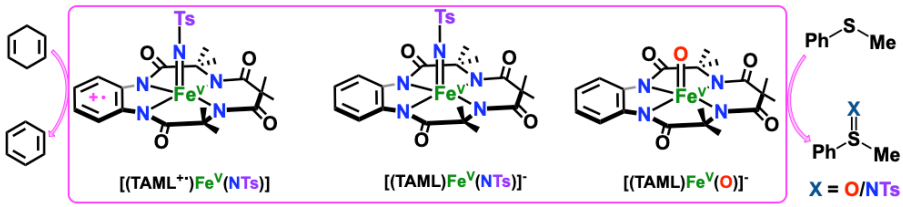

Fig. 3.3. Chemical structures of $[(TAML^{+\bullet})Fe^{V}(NTs)]$, $[(TAML)Fe^{V}(NTs)]^{-}$ and $[(TAML)Fe^{V}(O)]^{-}$ and their substrate oxidation reactions (adapted from ref. [112])

In 2006, Que and coworkers isolated and characterized the first octahedral Fe^{IV} imido complex based on the N4Py N5-donor ligand, *viz.* $[(N4Py)Fe^{IV}(NTs)]^{2+}$ (Fig. 3.4), the long lifetime of which makes it suitable for reactivity studies.[54] The first comparative study on the reactivity patterns of $[(N4Py)Fe^{IV}(NTs)]^{2+}$ *vs* $[(N4Py)Fe^{IV}(O)]^{2+}$ has also been investigated by Sastri, de Visser and coworkers who found that the $Fe^{IV}(NTs)$ species exhibited higher reactivity to transfer the –NTs moiety to nucleophilic substrates (sulfides), whereas the reverse trend was found in hydrogen atom abstraction reactions.[113] Another combined kinetics and computational study by de Visser and coworkers found that the substantially larger electron affinity of $[(N4Py)Fe^{IV}(NTs)]^{2+}$ versus $[(N4Py)Fe^{IV}(O)]^{2+}$ makes it possible that electrophilic addition reactions such as sunfimidation happen more efficiently than sulfoxidation.[58] On the other hand, in hydrogen atom transfer reactions, the electron affinity of $[(N4Py)Fe^{IV}(NTs)]^{2+}$ is sufficiently high to accept electrons from substrates at a large distance, forming an iron(III)-imido species first. As a result, it is the reduced species $[N4Py)Fe^{III}(NTs)]^{+}$ that subsequently performs hydrogen atom abstraction (Fig. 3.5). The $[(N4Py)Fe^{III}(NTs)]^{+}$ complex is catalytically much less potent than $[(N4Py)Fe^{IV}(O)]^{2+}$; this makes the HAT reactions of the Fe(III) imido complex proceed at slower rates.[58] Fukuzumi and co–workers recently found that in the dimerization of N,N–dimethylaniline, $[(N4Py)Fe^{IV}(NTs)]^{2+}$ is a more effective oxidant and easier to reduce to the analogous Fe(III) species than $[(N4Py)Fe^{IV}(O)]^{2+}$. Conversely, $[(N4Py)Fe^{III}(NTs)]^{+}$ was found to be less basic than the (putative) $[(N4Py)Fe^{III}(O)]^{+}$ analog,[114] which is in agreement with the results of de Visser and coworkers.[58]

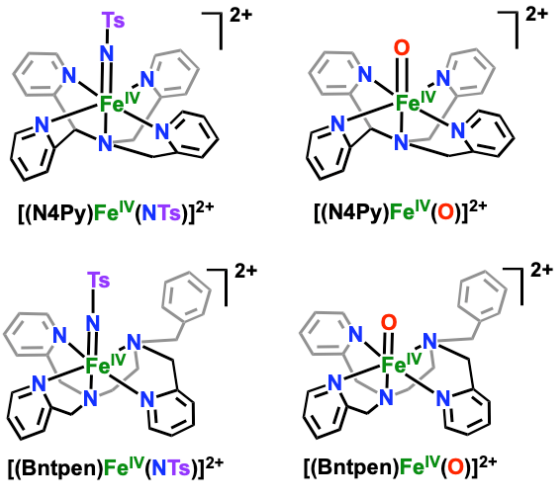

Fig. 3.4. Chemical structures of $[(N4Py)Fe^{IV}(NTs)]^{2+}$, $[(N4Py)Fe^{IV}(NTs)]^{2+}$, $[(Bntpen)Fe^{IV}(NTs)]^{2+}$ and $[(Bntpen)Fe^{IV}(O)]^{2+}$.

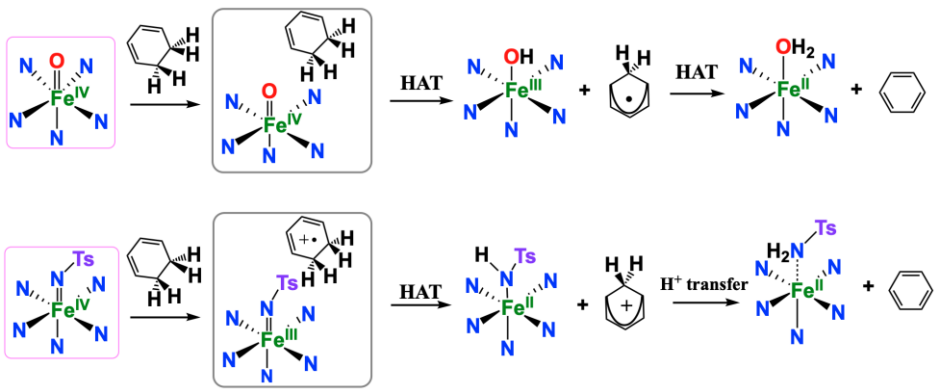

Fig. 3.5. Reaction mechanisms established for $[(N4Py)Fe^{IV}(O)]^{2+}$ and $[(N4Py)Fe^{IV}(NTs)]^{2+}$ (adapted from [58]).

In 2020, de Visser and coworkers provided valuable insights into the properties and reactivities of Fe^{IV}=O/Fe^{IV}=NTs complexes with two analogous pentadentate ligands, Bntpen and N4Py (Fig. 3.4).[53] For HAT reactions catalyzed by the Bntpen system, Fe^{IV}=O reacts 300 times faster than Fe^{IV}=NTs, which is consistent with the N4Py system. However, in the catalytic oxidation of thioanisole by the Bntpen system, Fe^{IV}=O is surprisingly more reactive in sulfoxidation than Fe^{IV}=NTs is in sulfimidation, which is opposite to the N4Py system. Furthermore, for HAT reactions, the $[(Bntpen)Fe^{IV}(O)]^{2+}$ is ten times more reactive than $[(N4Py)Fe^{IV}(O)]^{2+}$ while $[(Bntpen)Fe^{IV}(NTs)]^{2+}$ is four times slower than $[(N4Py)Fe^{IV}(NTs)]^{2}$. In conclusion, the sixth ligand (oxido *vs* nitrido) can affect the physicochemical properties of the Fe^{IV}=X entities (X= 6th ligand) and therefore influence the mechanism of the reaction, which is critical to reactivity.

In 2019, Costas presented another two rare octahedral Fe^{IV}(NTs) complexes with pentadentate ligands based on the tacn platform, specifically $[(MePy_2tacn)Fe^{IV}(NTs)]^{2+}$ and $[(Me_2(CHPy_2)tacn)Fe^{IV}(NTs)]^{2+}$ (Fig. 3.6).[56] These complexes were found to behave as single-electron oxidants (Figs. 3.7 and 3.8), in contrast to $[(N4Py)Fe^{IV}(NTs)]^{+}$ that acts as a two-electron oxidant (Fig. 3.5).[56,58] The reactivities towards thioanisole substrates involved an initial NTs transfer and a subsequent reaction with another Fe^{IV}(NTs) molecule, ultimately forming ferric complexes (Figs. 3.7). Moreover, these complexes reacted with hydrocarbons containing weak C–H bonds through a two-step process where initial substrate binding is followed by a rate-determining HAT reaction (Fig. 3.8). The mechanistic differences between tacn and N4Py systems can be attributed to the different ligand properties. For example, the N4Py ligand may provide a sterically more demanding scaffold than the tacn-based ligands, so N4Py system limits the bimolecular reactions and favors dissociation in sulfimidation of thioanisole, which is different from the bimolecular reactions by the tacn system.

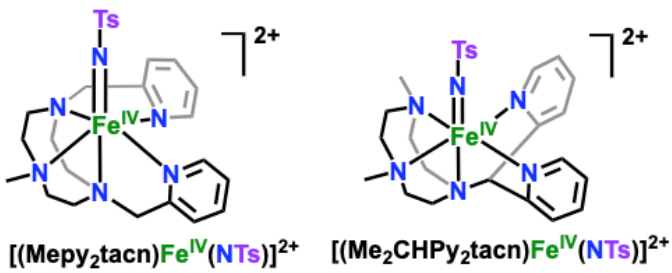

Fig. 3.6. Chemical structures of $[(MePy_2tacn)Fe^{IV}(NTs)]^{2+}$ and $[(Me_2(CHPy_2)tacn)Fe^{IV}(NTs)]^{2+}$ (adapted from ref. [56]).

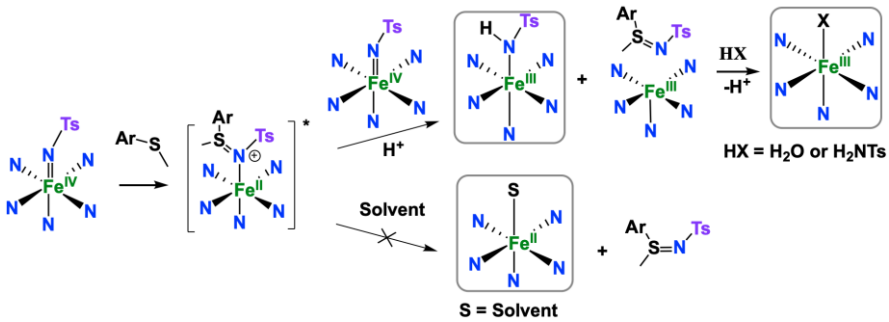

Fig. 3.7. Reaction mechanisms established for $[(MePy_2tacn)Fe^{IV}(NTs)]^{2+}$ and $[(Me_2(CHPy_2)tacn)Fe^{IV}(NTs)]^{2+}$ with thioanisole substrates. S stands for solvent molecule (adapted from ref. [56]).

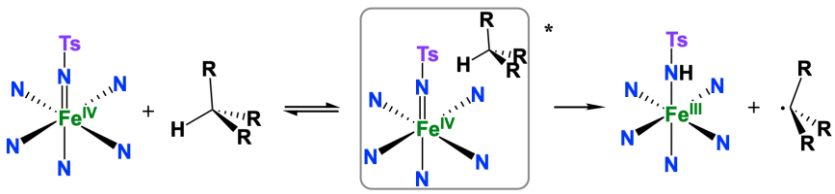

Fig. 3.8. Reaction mechanisms established for $[(MePy_2tacn)Fe^{IV}(NTs)]^{2+}$ and $[(Me_2(CHPy_2)tacn)Fe^{IV}(NTs)]^{2+}$ with hydrocarbons (adapted from ref. [56]).

In conclusion, the study of various iron-imido complexes has shed light on their geometries, chemical properties and reactivities, revealing the critical role of ligand properties and metal-ligand systems in shaping reaction mechanisms. These imido complexes exhibit more unique and diverse reactivities than their oxo counterparts, mainly due to the capacity of the imido complexes to access a wider range of electromers, resulting in complex electron configurations and reaction pathways. The metal-ligand system plays a vital role in determining reactivity, as it influences the physicochemical properties, such as redox potential, which serves as the main driving force for reaction mechanisms with substrates.

3.3 Motivation behind the work

Compared to their oxo analogs, iron-imido complexes have been much less studied. Chapter 2 of this thesis includes several Fe^{IV}=O complexes based on the well-known N4Py platform. Given the stabilities and the knowledge obtained for the Fe^{IV}=O complexes based on the isoquinoline-containing ligands, it was decided to prepare their Fe^{IV}=NTs analogs and compare their reactivities to the previously described Fe^{IV}=O/Fe^{IV}=NTs complexes based on analogous N4Py ligands.

3.4 Finds in this thesis

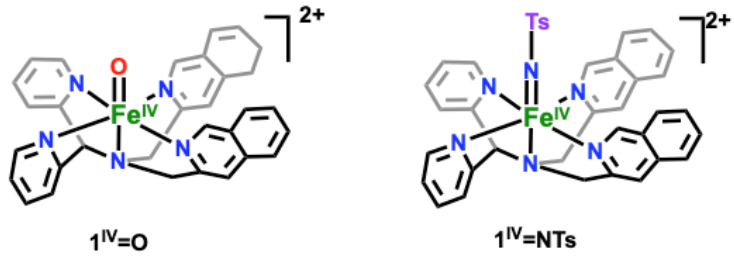

Fig. 3.9. Schematic drawings of $[(N2Py2IQn)Fe^{IV}(O)]^{2+}$ (**1^{IV}=O**) and $[(N2Py2IQn)Fe^{IV}(NTs)]^{2+}$ (**1^{IV}=NTs**).

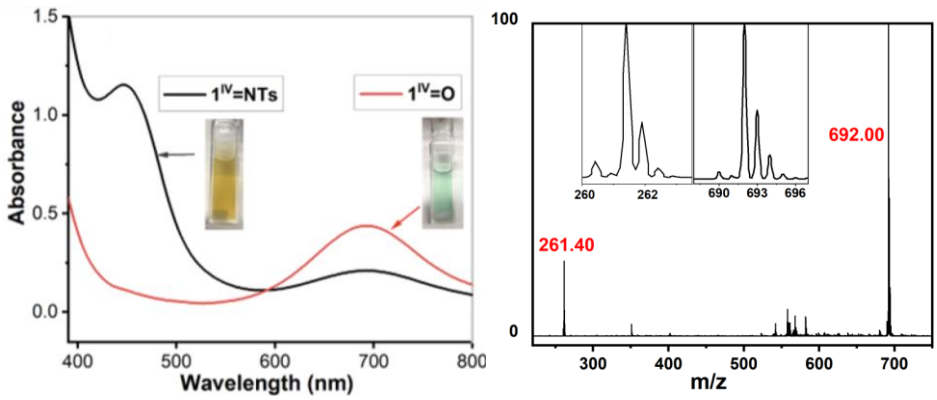

Fig. 3.10. Left: UV-vis spectra of **1^{IV}=O** and **1^{IV}=NTs** in acetonitrile; Right: ESI-MS spectrum of $[Fe^{IV}(N2Py2IQn)(NTs)]^{1+}$.

The non-heme Fe^{IV}=NTs complex $[(N2Py2IQn)Fe^{IV}(NTs)](BF_4)_2$ (**1^{IV}=NTs**·$(BF_4)_2$) based on the pentadentate ligand N2Py2IQn, was synthesized and characterized by a number of spectroscopic techniques (Figs. 3.9 and 3.10, *cf.* paper II for details).

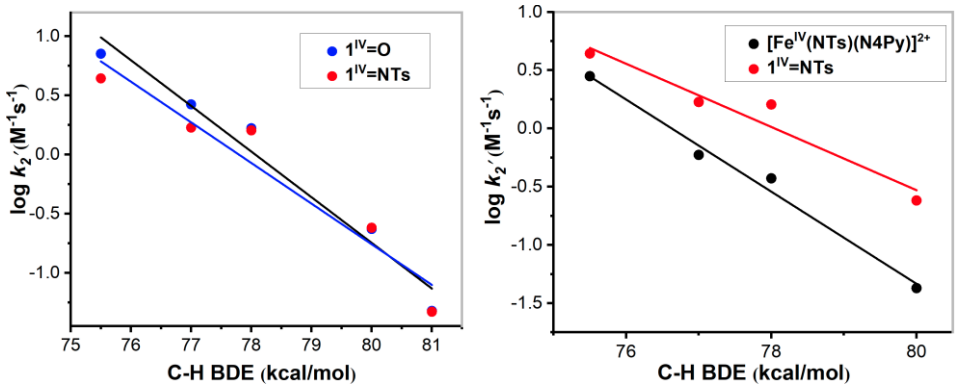

Fig. 3.11. Left: Plot of log k_2' versus C-H bond dissociation energies of different alkane substrates for **1^{IV}=O** and **1^{IV}=NTs**; Right: Plot of log k_2' versus C-H bond dissociation energies of different alkane substrates for **1^{IV}=NTs** and [Fe^{IV}(NTs)(N4Py)]$^{2+}$ at 288K.

A comparative investigation was performed to explore the reactivity patterns of [(N2Py2IQn)Fe^{IV}(NTs)](ClO$_4$)$_2$ (**1^{IV}=NTs**·(ClO$_4$)$_2$) to its oxido analog [(N2Py2IQn)Fe^{IV}(O)](ClO$_4$)$_2$ (**1^{IV}=O**·(ClO$_4$)$_2$). It was found that complexes **1^{IV}=NTs** and **1^{IV}=O** exhibit comparable reactivities in relation to both hydrogen atom transfer and nitrene transfer reactions (Fig. 3.11). Such behavior is different from earlier comparative studies on Fe^{IV}=O and Fe^{IV} =NTs analogs. As discussed above, Fe^{IV} =NTs complexes have previously been found to display very different reactivities from their oxido analogs. On the other hand, compared to [Fe^{IV}(NTs)(N4Py)]$^{2+}$, **1^{IV}=NTs** is more reactive with hydrogen atom transfer reactions. Given the very similar activities of **1^{IV}=NTs** and **1^{IV}=O** during the above-mentioned reactions, control experiments were carried out to ascertain whether the oxido complex could be formed as a side-product in the reactions of **1^{IV}=NTs**. NMR spectroscopy showed that it is difficult to hydrolyze PhINTs by trace water. Reaction of **1^{IV}=NTs** with oxygen atom donors (*m*-CPBA) did not result in formation of **1^{IV}=O**. Product analysis indicated that only sulfimidation occurred with thioether substrates. As the metal-ligand system is proposed to be the main driving force for reaction behaviors with substrates, computational work needs to be done to analyze what is the key point of this ligand to drive the similar reactivities of its imido and oxido counterparts.

Chapter 4: Electronic influence by ligands on the reactivities and mechanisms in the oxidation of alkenes by non-heme Fe^{IV}=O complexes

4.1 Introduction

Epoxides are important building blocks in organic synthesis and have a wide range of industrial and pharmaceutical applications. For example, epoxides react with a broad range of nucleophiles, which is the basis of the production of epoxy glues and glycols.[115] Epoxides are also used to produce surfactants and polyethers[116,117] and are used as intermediates in the production of solvents, plastics, and pharmaceuticals, among other products. Therefore, the development of efficient, selective, and practical methods for epoxidation is an important area of research in synthetic chemistry.

4.2 Synthetic non-heme iron catalysts for epoxidation of alkenes

Heme enzymes of the Cytochrome P450 family and the non-heme iron enzyme methane monooxygenase are proven to be able to catalyze the epoxidation of alkenes.[118,119] Inspired by Nature, many biomimetic nonheme iron catalysts have been synthesized as catalysts for alkene epoxidation. Tetradentate N4 ligand-based iron complexes, which possess two *cis*-labile coordination sites on the iron center for peroxide binding and activation, are the most well-known catalysts for alkene

epoxidation.[120,121] In reactions with H_2O_2 as the oxidant, it is proposed that the active species is an Fe^{V}=O complex that is formed from an Fe^{III}(OOH) intermediate via O-O bond heterolysis, which can be promoted by the coordinated carboxylic acid or water (Fig. 4.1).[122] Therefore, the catalytic activities and selectivities in these reactions can be enhanced by the addition of AcOH/H_2O.

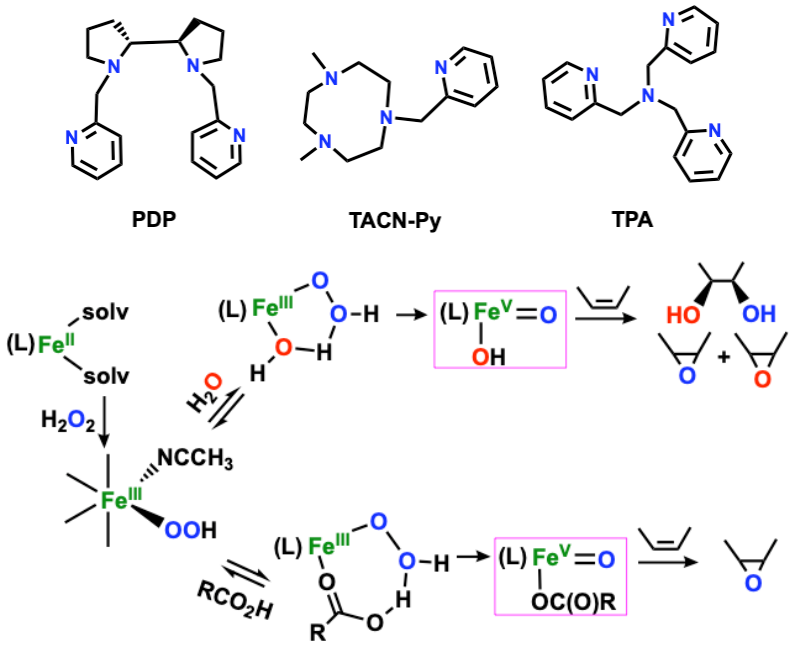

Fig. 4.1. Examples of ligands and proposed mechanisms of alkene epoxidations by Fe^{II} catalysts supported by tetradentate N4 ligands.

Even though a number of pentadentate N5 ligand-coordinated iron complexes have been proven to be active in C-H oxidation, such complexes are relatively little explored for epoxidation reactions. Que and others reported several N5-ligand based Fe^{II} catalysts (Fig. 4.2) for alkene epoxidations, which involve *in situ* generated Fe^{IV}=O active units that were produced from low-spin Fe^{III}-OOH intermediates.[123]

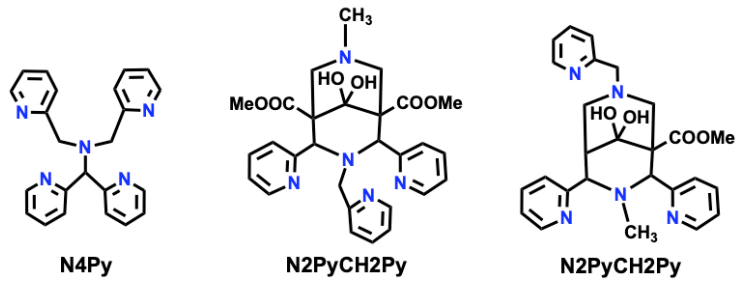

Fig. 4.2. Pentadentate N5 ligands used for Fe^{II} catalysts for alkene epoxidations.

Although such nonheme Fe^{IV}=O complexes can react with alkenes to give epoxides, the mechanisms of these reactions remain elusive. For example, $[Fe^{IV}(O)(N4Py)]^{2+}$ is not strong enough to oxidize the styrene derivatives in acetonitrile at 298 K, but the epoxidation reactions occur efficiently by adding trifluoroacetic (triflic) acid (HOTf). The reactivity enhancement by HOTf is proposed to occur via proton-coupled electron transfer from the substrates to the diprotonated Fe^{IV}=O center, which is the rate-determining step.[124]

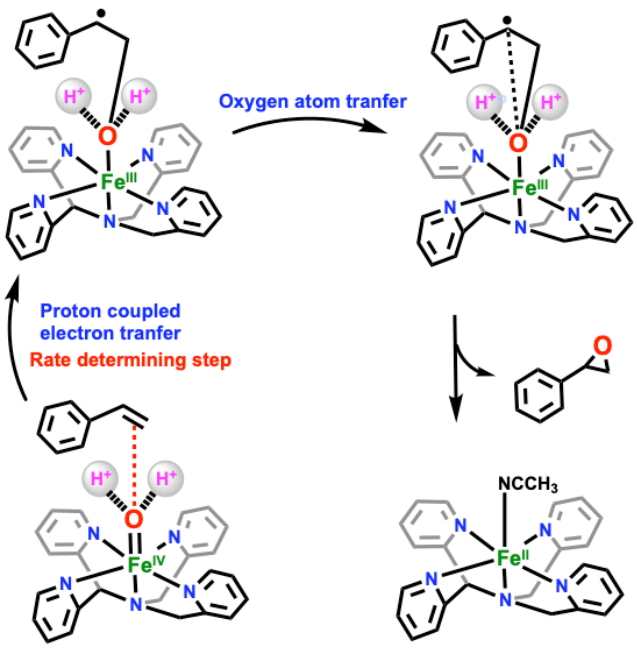

Fig. 4.3. Proposed mechanisms of C=C epoxidation by Fe^{II} catalysts in the presence of HOTf.

Similarly, the alkene epoxidation efficiency of iron complexes can also be significantly promoted by adding non-redox metal ions such as Sc^{3+}.[125] The Fe^{V}=O species is proposed to be much more favorable for oxygen transfer to alkenes than lower oxidation state species (Fe^{III}OOH and Fe^{IV}=O). However, Lewis acids like Sc^{3+} can make Fe^{III}OOH and Fe^{IV}=O species transfer oxygen to alkenes as well as Fe^{V}=O species, which opens up multiple channels for oxygen transfer.[125]

Another study applied $[Fe^{IV}(O)(N2Py2Q)]^{2+}$ to alkene epoxidation, which shed light on the effect of the ligand backbone on the reactivity and mechanism of alkene epoxidation by this kind of nonheme iron complexes.[126] As the electron transfer from alkenes to the Fe^{IV}=O center is the rate-determining step, the stronger electrophilicity of the $[Fe^{IV}(O)(N2Py2Q)]^{2}$ contributes to the extent of reactivity, which originates from the weaker donating property of N2Py2Q vs N4Py. Especially, the bulky 2PyN2Q ligand increases the steric hindrance and restricts pathway I, resulting in the mechanistic shuttle between OAT pathway I and isomerization pathway II, so that a mixture of *cis-trans* epoxides is found to be the products of the reaction between $[Fe^{IV}(O)(N2Py2Q)]^{2+}$ with sterically bulky substrates (*cis*-stilbene) (Fig. 4.4).

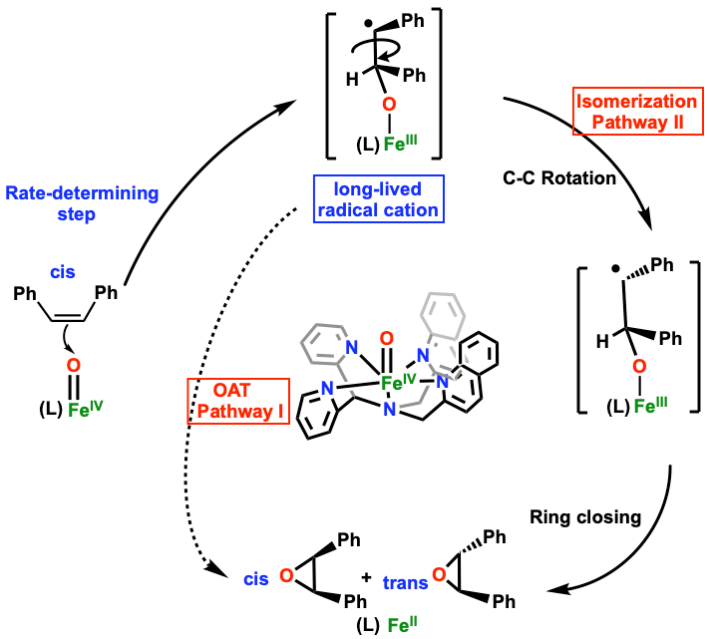

Fig. 4.4. Proposed mechanistic cycle of alkene epoxidation by $[Fe^{IV}(O)(N2Py2Q)]^{2+}$. [126]

4.3 Motivation behind the work

As discussed above, the mechanism of epoxidation reactions mediated by iron-oxo complexes coordinated by pentadentate ligands is complicated, and still not much explored. Electron transfer from the alkene to the Fe^{IV}=O center is the rate-determining step, so the electrophilicity of the active site is vital to the reactivity. However, the significant steric and electronic effects exerted by the ligands in complexes such as $[Fe^{IV}(O)(N2Py2Q)]^2$ make it difficult to clearly identify the impact of the electronic effect on the epoxidation reaction, as it is overshadowed by the steric effect.

4.4 Findings in this thesis

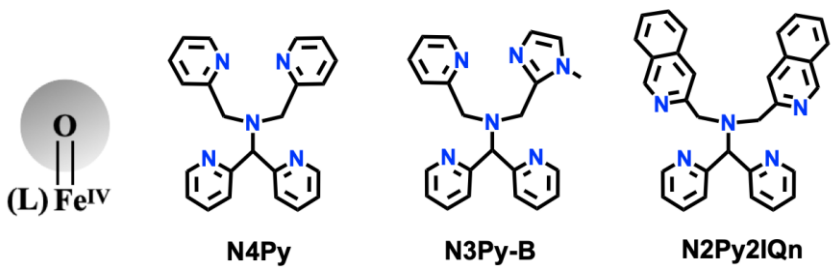

Fig. 4.5. Pentadentate N5 ligands used to synthesize Fe^{IV}=O complexes.

In Paper III, a study of alkene epoxidations catalyzed by two of the new Fe^{IV}=O complexes described in Chapter 1 (Fig. 4.5) is presented. Epoxidations of para-substituted styrene derivatives were studied (Fig. 4.6). The negative Hammett ρ values (0.96/0.72 for $[Fe^{IV}(O)(N2Py2Q)]^{2+}$/$[Fe^{IV}(O)(N3PyIm)]^{2+}$ indicate their electrophilic properties and that electron transfer from the alkene substrates to the Fe^{IV}=O center during the oxidation process can be the rate-determining step. By comparing the reactivities of the Fe^{IV}=O units in different ligand systems, it can be concluded that the ligands with weaker ligand fields can significantly enhance the reactivity of alkene epoxidation through an OAT pathway.

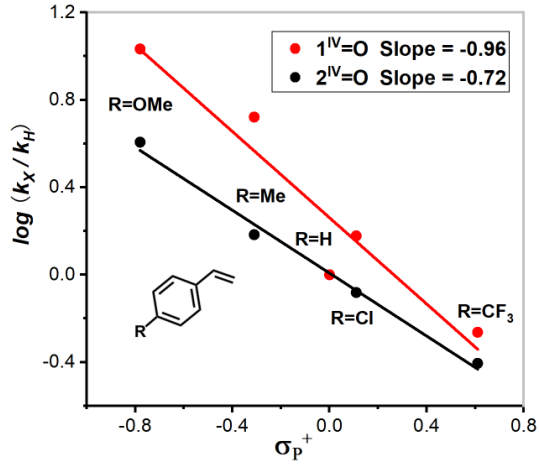

Fig. 4.6. Hammett–Brown plot for the epoxidation of para-substituted styrenes by 1^{IV}=O/2^{IV}=O.

Moreover, *trans*-stilbene oxide was found to be the primary product in the reaction of both *cis*-stilbene and *trans*-stilbene, which may be explained by the isomerization of the stilbene radical cation being faster than the oxygen-transfer to the *cis*-stilbene within the cage of the putative $\{Fe^{III}(O)\}^{+}$ intermediate. Another speculation is that weak ligand fields tend to stabilize the cage of such an $\{Fe^{III}(O)\}^{+}$ intermediate, which makes it sufficiently long-lived so that C-C rotation of *cis*-stilbene radical can take place (Fig. 4.4).

This investigation shows how different ligands affect the reactivity and mechanistic properties of epoxidation reactions catalyzed by nonheme Fe^{IV}=O complexes. As the minor steric influence of the ligands has been established (*vide* Chapter 1), we attribute the ligand effects to their electron-donating property.

Chapter 5: Conclusions and Outlook

Metalloenzymes play critical roles in various biological processes, which has inspired chemists to perform biomimetic studies of the active sites involved. Most of such research is divided into two aspects: (i) To understand the mechanisms of biological processes involving specific metalloenzymes. (ii) To design effective and economical catalysts based on biomimetic studies of such enzymes.

In general, steric and electronic effects of ligands can have a significant impact on the properties of biomimetic catalysts. Understanding and controlling these effects can be an important aspect of designing and optimizing bioinspired catalysts for specific applications. The steric effects of the ligands can affect the accessibility of the "active site" and the orientation of the reactants, which can in turn affect the electronic properties of the catalyst. Therefore, it can be challenging to assess the precise influence of the electronic effects of ligands on a catalyst because they are often compounded with steric effects.

In this thesis, four new pentadentate N5 ligands with minor steric restrictions have been developed. The reactivities of relative Fe^{IV}=O complexes in HAT and OAT reactions have been investigated in detail. As the ligands are designed on the basis of the same framework and include negligible steric restrictions, it is possible to assess how electron-donating properties can influence the reactivity of Fe^{IV}=O complexes. Moreover, the study of alkene epoxidation by such Fe^{IV}=O complexes has been done to shed light on the influence of electron-donating properties on the reactivity and mechanism of alkene epoxidation. Furthermore, a pair of Fe^{IV}=NR and Fe^{IV}=O complexes, which contain the same ligand with little strict effect, have been synthesized and a comparative study on the structure and reactivity patterns of this couple has been conducted.

In addition to the above-mentioned ligands with negligible steric effects, the steric influence of two tetradentate N4 ligands on the reactivity of Fe^{V}(O)(OH) complexes has been assessed and gauged relative to other related ligands. This study provides an example of how the steric restrictions of the specific ligand can dominate the reactivity of active units.

In conclusion, with the design of the ligands in this thesis, it is possible to tease apart the individual contributions of steric and electronic effects on the reactivity and selectivity of specific types of high-valent mononuclear iron catalysts. This information may be used to optimize the design of ligands and catalysts for specific

chemical reactions. Further study of how electronic effects can influence the reactivity and selectivity of Fe^{IV}=NR complexes will be conducted based on the four new N5 ligands with minor steric effects.

However, enzymes in biology are typically found in very specific environments that can be difficult to replicate in a laboratory setting. For example, enzymes may require a specific pH or temperature range in order to function optimally. Enzymes may also require specific co-factors or metal ions in order to function properly. Furthermore, enzymes in biology are often surrounded by other molecules or cellular structures that can affect their function. Overall, replicating the specific environment of enzymes in biology can be a significant challenge for researchers to mimic these enzymes in a laboratory setting. However, advances in biotechnology and synthetic biology are enabling researchers to overcome many of these challenges and create increasingly sophisticated biomimetic catalysts. For example, the use of synthetic biomimetic catalysts embedded in protein structures is an emerging field that has the potential to revolutionize various industries. In the future, this approach may lead to the development of more efficient and effective catalysts for a range of applications, from drug synthesis to bioremediation. Additionally, the ability to simulate the activity of synthetic catalysts in biological environments may lead to a better understanding of biological processes and pave the way for the development of new therapies and treatments. Overall, the outlook for this field is promising, and continued research and development are likely to yield exciting advances and discoveries.

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