Electronic Activation and Tuning of Redox-Active Ligand Orbitals

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Abstract

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Department of Chemistry

This dissertation focuses upon the synthesis, characterization and reactivity of thiolate-ligated α-(imino)-N-heterocycle complexes. Chapter 1 provides an introduction to cysteinate ligated metalloenzymes and synthetic model systems containing redox-active ligands. Chapter 2 discusses the synthesis and characterization of three thiolate ligated iron (II) α-(imino)-N-heterocycle complexes displaying unique spectroscopic features. Chapter 3 highlights the unique activation of the α-(imino)-N-heterocycles due to the coordinated thiolate through the role of electrochemistry, sulfur K-edge X-ray absorption spectroscopy and computations. Chapter 4 exhibits the role of the geometry around the metal center and the effect of the thiolate through a cobalt, manganese and thioether derivatives. Chapter 5 presents a unique nucleophilic attack of a thiolate forming a thiazolidine ring structure. The results described will highlight the ability to fine tune these redox-active orbitals which have a large role in multi-electron base metal catalysis.
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<td>Ångström</td>
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<td>Acetate</td>
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<tr>
<td>atm</td>
<td>Atmosphere</td>
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<tr>
<td>BIP</td>
<td>Bis(imino)pyridine</td>
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<td>Boc</td>
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<td>ΔE_Q</td>
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<td>LLCT</td>
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<td>Nicotinamide adenine dinucleotide phosphate</td>
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ppm  parts per million
RDS  Rate determining step
S    Sulfur
SOD  Superoxide Dismutase
SOR  Superoxide Reductase
TD-DFT Time dependent density functional theory
TLC  Thin layer chromatography
Tren N(EtNH$_2$)$_3$
Ts   Tosylate
UV-Vis Ultraviolet-visible
XANES X-ray absorption near edge structure
XAS  X-ray absorption spectroscopy
**List of Numbed Complexes**

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<td>2-benzylsulfanyl methyl-2-methyl-propane-1,3-diol, (C_{12}H_{18}O_2S)</td>
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<td>(3-methanesulfonyl-2-methanesulfonylmethyl-2-methyl-propylsulfanyl)methyl-benzene, (C_{14}H_{22}O_6S_3)</td>
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<td>(3-azido-2azidomethyl-2-methyl-propylsulfanyl)methyl-benzene, (C_{12}H_{16}N_6S)</td>
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<td>6</td>
<td>2-benzylsulfanyl methyl-2-methyl-propane-1,3-diamine, (C_{12}H_{20}N_2S)</td>
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<td>2-benzylsulfanyl methyl-2-methyl-propane-1,3-(tert-Butyloxy carbonyl) diamine, (C_{22}H_{36}N_2O_4S)</td>
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<td>2-thiomethyl-2-methyl-propane-1,3-diamine dihydrogenchloride, (C_6H_{16}Cl_2N_2S)</td>
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<td>([\text{Fe}^{II}(\text{Tame-N}_2\text{SPy}<em>2)]<em>2)(PF_6)<em>2, (C</em>{34}H</em>{38}F</em>{12}Fe_2N_8P_2S_2)</td>
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<td>10-CN</td>
<td>((\text{Fe}^{II}(\text{Tame-N}<em>2\text{SPy}<em>2))\text{CN}, C</em>{18}H</em>{19}FeN_4S_1)</td>
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<td>11</td>
<td>([\text{Fe}^{II}(\text{Tame-N}_2\text{SQu}<em>2)]<em>2)(PF_6)<em>2, (C</em>{50}H</em>{46}F</em>{12}Fe_2N_8P_2S_2)</td>
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<td>11-BPh_4</td>
<td>([\text{Fe}^{II}(\text{Tame-N}_2\text{SQu}_2)]<em>2)(BPh_4)<em>2, (C</em>{96}H</em>{86}B_2Fe_2N_8S_2)</td>
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<td>12</td>
<td>([\text{Fe}^{II}(\text{Tame-N}<em>2\text{Slmid(Me)}<em>2)]<em>2)(PF_6)<em>2, (C</em>{30}H</em>{43}F</em>{12}Fe_2N</em>{12}P_2S_2)</td>
</tr>
<tr>
<td>12ox</td>
<td>([\text{Fe}^{III}(\text{Tame-N}<em>2\text{Slmid})<em>2]<em>2)(PF_6)<em>4, (C</em>{30}H</em>{43}F</em>{24}Fe_2N</em>{12}P_4S_2)</td>
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<td>([\text{Co}^{II}(\text{Tame-N}<em>2\text{Slmid})<em>2]<em>2)(PF_6)<em>2, (C</em>{30}H</em>{43}F</em>{12}Co_2N</em>{12}P_2S_2)</td>
</tr>
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<td>13ox</td>
<td>([\text{Co}^{III}(\text{Tame-N}<em>2\text{Slmid})<em>2]<em>2)(PF_6)<em>4, (C</em>{30}H</em>{43}F</em>{24}Co_2N</em>{12}P_4S_2)</td>
</tr>
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<td>([\text{Fe}^{II}(\text{tame-}(\text{N}<em>2\text{S}^{Im}</em>{6}\text{Im})<em>2(\text{MeCN}))])(PF_6)<em>2, (C</em>{22}H</em>{28}F_{12}FeN_6P_2S)</td>
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<tr>
<td>15</td>
<td>([\text{Mn}^{II}(\text{tame-}(\text{N}<em>2\text{S}^{Me}</em>{6}\text{Im})<em>2\text{Cl})])(PF_6), (C</em>{15}H_{22}ClF_6MnN_6PS)</td>
</tr>
</tbody>
</table>
16  [Fe$^{II}$N$_3$thiazolidineCl]Cl, C$_{25}$H$_{35}$Cl$_2$FeN$_3$S

17  [(Fe$^{II}$N$_3$thiazolidineCl)$_2$Cl]OTf, C$_{51}$H$_{70}$Cl$_3$F$_3$FeN$_6$O$_3$S$_3$
Chapter Contributions

Much of the work detailed in the following chapters would not have been possible without the valuable efforts of a number of collaborators. Their individual contributions are gratefully acknowledged below.

Chapter 2. Roslyn Theisen, Sarah E. Flowers and Werner Kaminsky for the crystallographic characterization of 10-12.

Chapter 3. Julian Rees for the detailed computational results for complexes 10-12 and performing the Mössbauer spectroscopy. Alexander Nyrov and Professor Serena DeBeer for performing the Sulfur K-edge X-ray spectroscopy experiments at the ESRF beamline. Maike Blakely and Werner Kaminsky for the crystallographic characterization of 12\textsuperscript{ox}.

Chapter 4. Sarah E. Flowers, Maike Blakely and Werner Kaminsky for the crystallographic characterization of 13-15 and 13\textsuperscript{ox}.

Chapter 5. Michael Coggins and Werner Kaminsky for the crystallographic charterization of 16 and 17.
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First I would like to thank my graduate advisor Professor Julie Kovacs for all the support. Graduate school had many ups and downs but throughout my time at the University of Washington she has always been there to provide both the scientific and emotional support that was necessary to making me both the scientist and person I am. I am forever grateful for her advice and hopefully I have been a good role model to the next wave of Kovacs students in her laboratory.

I have always admired the ability of my committee members to take the time to discuss my chemistry, both in and out of my examinations. These Professors have provided an excellent source of inspiration in becoming a better chemist. Professors Gamelin and Cossairt have always aided me in understanding the complexities of inorganic chemistry during my examinations. Professor Stenkamp was a wonderful GSR who took the time to read my written portions and provide feedback, both in my writing and presentations. Professors Mayer, Sasaki and Boydston all took the time to sit in and encourage me during my early examinations and taught me to think critically about chemistry. I would be remiss not to acknowledge Professor Heinekey who has made the inorganic division such a wonderful place to work. I am also extremely grateful for the support from Professor Goldberg, who took time to help me, more so than she may realize, through some difficult times.

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chemistry currently underway. Maike Blakely, Maks Dedusko, Penny “Dyme” Poon (King Bob), Alex Downing and Dylan Rogers will undoubtedly carry the lab forward into exciting new frontiers of bioinorganic chemistry.

My chemistry would not be complete without the support of the University of Washington inorganic department. Some of these people have become great friends to this day and I cannot picture a world without them in my life. To the “Diner Club”¹: Tyler Stevens, Sophia Cherry, Mike Cherry, Wilson Bailey, Cecily Ferguson, Jon Goldberg, Karena Smoll, Travis Lekich and Louise Guard, thank you! I would not have gotten through the first couple of exams without the support of my ex-wife, Carolyn Valdez, who helped shaped my understanding of what a great chemist consists of.

My life has been so enjoyable while at the University of Washington thanks to the support of my wonderful girlfriend, Kim Quigley, who has been so patient and supportive throughout this final chapter of graduate school. Words cannot express how much you have helped me get through this, thank you!

Finally, I would not be the person I am without the support of my family, who have been the best role models for me growing up and even to this day. To my sister, Mom and Dad, thank you for all the support. I don’t think this journey would have been this special without you.

¹ Bailey, W. D. Late Transition-Metal Complexes Supported by Pincer Ligands: Applications in Partial Oxidation Catalysis. University of Washington, Seattle, 2016
Dedication

To my family
Chapter 1.

Introduction.
*Metals in Biological Systems*

Proteins are essential to the function of living organisms and perform an array of diverse processes. These macromolecules are constructed of amino acids and predominately composed of carbon, hydrogen, nitrogen and oxygen. However, the function, or structural stability, of these proteins often require cofactors. A common type of cofactor, which makes up over a third of all crystallographically characterized proteins found in the Royal Society’s protein data bank (PBD), is a transition metal, signifying the importance of these elements in the foundation of life. These metals typically perform functions that are not as accessible for non-metal elements, such as providing structural integrity, aiding in electron transport or transporting small substrates. An additional role of proteins is to catalyze reactions. The metal cofactor can afford access to multiple oxidation states, differing coordination numbers and geometries. This contrasts with the main group elements, which have limited oxidation states and coordination numbers available. One goal of bioinorganic chemists is to understand the properties that make these enzymes so efficient, which typically starts at the primary coordination sphere around the metal cofactor. While high-resolution crystal structures have aided in the understanding structural identity of the active site, the reactivity and intermediates that form during the activity of the enzymes have largely remained a mystery.

However, high-resolution crystal structures allow for the targeted synthesis of structural models to comprehend the subtle importance of specific amino acids. These biomimetic models can be designed to have very similar coordination environments around a metal. With these models, bond lengths and spectroscopic features can be compared to the native metalloenzymes to help understand the reactivity of these important proteins.
other amino acid residues on the protein backbone. Additionally, they can help focus on a specific active-site, as there are metalloenzymes that contain multiple metal cofactors, each with unique function. This can cause data from metal specific spectroscopic techniques to be convoluted. These model systems afford an avenue to perform low-temperature experiments to attempt to isolate key intermediates unobservable in the native enzyme. At times, these metastable intermediates in model systems can be crystalized to give structural information that is far from trivial to obtain from native enzymes. A significant example of this was the observation of a $\mu$-$\eta^2$-$\eta^2$ peroxo bridging mode in a copper model complex that mirrored the bridging mode for copper hemocyanin.$^{4,5}$ Understanding the relationship between structure and function is paramount to the biomimetic community.

Cysteinates and Effects of the Thiolate

Many of the metals that are found in metalloenzymes were incorporated due to the abundance found in the earth’s core. To bind these versatile elements, proteins typically coordinate through amino acid side chains, the amide backbone, or porphyrin and small molecule cofactors. Most metalloenzymes have a primary coordination sphere composed of nitrogen and oxygen atoms.$^{1,2}$ However cysteine (Cys) is one amino acid residue that can coordinate through a deprotonated sulfur of the side chain to have a thiolate ligated to the metal cofactor. Cysteinate ligation can be found in metalloenzymes with a variety of first row transition metals including iron (Fe), cobalt (Co), nickel, copper and zinc.$^{3,6}$

Unlike the first row main group atoms like oxygen and nitrogen, sulfur imparts quite different properties when coordinated to first row transition metals. Cysteinates form highly covalent bonds to first row transition metals, which aids in modulating redox potentials to impact
electron transfer and strong bond activation. Many active sites have the cysteinate trans to the open site where small molecule binding and/or activation occurs.$^{3,6}$ The strong σ- and π-donating thiolate has a strong trans effect and can promote requisite substrate release. The covalency of a coordinated cysteinate can also impact the spin state of metal ions due to the large nephelauxetic effect favoring lower spin states.$^{7,8}$

*Cysteinate Ligated Iron Metalloenzymes*

Iron (Fe) is found in abundance in our Earth’s core and unsurprisingly is the most commonly found transition metal in metalloenzymes. Fe-sulfur bonds are found throughout metalloproteins from Fe-S clusters to Fe-heme and Fe-non-heme enzymes.$^1$ Fe-heme enzymes are attractive to study due to our ability to probe them spectroscopically because of their distinct $\pi \rightarrow \pi^*$ soret band; one of more well studied enzymes featuring cysteine ligation is cytochrome P450.$^9$ While this enzyme has seen a wealth of publications, there is less known about non-heme cysteinate-ligated Fe metalloenzymes.$^9$ These enzymes, including superoxide reductase (SOR), cysteine dioxygenase (CDO), nitrile hydratase, penicillin N synthase and peptide deformylases have unique ligation to the metal cofactor that differs from the common “2-his-1-carboxylate” triad found in mononuclear iron enzymes.$^{3,6}$ In each case cysteinate ligation heavily impacts the reactivity of these metalloenzymes.
Cytochrome P450

Cytochrome P450 is primarily responsible for hydroxylating unactivated, strong C-H bonds. The potent oxidant required to perform these difficult transformations is formed through the reduction of O₂. The primary coordination sphere is important for the enzyme’s ability to activate O₂ and consists of the Fe metal center in a square pyramidal geometry with the basal plane consisting of the four nitrogens of a porphyrin ring (Figure 1.01). The enzyme has one conserved cysteinate residue in proximity to the heme cofactor that is essential to the reactivity, and binds in the axial position. This affects the frontier orbitals giving rise to the signature Soret band at 450 nm.

Figure 1.01: Active site of cytochrome P450 containing a basal plane formed from a porphyrin cofactor and an axial cysteinate. N atoms of porphyrin are in blue, Fe in green, S in yellow while C atoms are in gray.
The general reactivity of cytochrome P450 with O₂ has been established based on spectroscopic observation of significant intermediates. The enzyme has an Fe(III) resting oxidation state and reacts upon the hydrocarbon substrate entering the binding pocket (Figure 1.02). A reduction, typically from NAD(P)H, occurs after geometric changes that induce a spin state change from low- to high-spin Fe(III). The reduction potentials are modulated and lower than expected due to the coordinated anionic thiolate. The reduced ferrous complex is then able to coordinate and reduce O₂ forming a transient Fe^{III}-superoxo species. Reduction by a flavin cofactor and protonation yields an Fe^{III}-hydroperoxo intermediate, known as compound 0. EPR measurements have identified this species as low-spin, and in the mutant enzyme, resonance Raman IR spectroscopy has shown vibrational data consistent with a bound peroxo species due to observed ν_{O-O} and ν_{Fe-O} stretch found at 799 cm⁻¹ and 559 cm⁻¹. This was confirmed to be a peroxo intermediate due to the isotopomeric mixture experiment observing the change in the O-
The weak O-O stretch suggests a significant influence of the axial cysteinate and the spin state on the strength of the O-O bond.

Compound 0 then undergoes heterolytic O-O bond cleavage by protonation of the distal oxygen, forming what is proposed to be the active oxidant compound I. Unlike other catalase O₂ activating heme enzymes that have a hydrophilic distal pocket to promote the protonation of the distal oxygen, cytochrome P450 enzymes have a very hydrophobic pocket. The ability to protonate the distal oxygen and induce a heterolytic O-O bond cleavage is thus much weakened in this class of enzymes. Instead of this type of “pull” effect from a hydrogen bonding chain of residues around the distal oxygen, cytochrome P450 enzymes may aid the bond cleavage through a “push” effect from the cysteinate trans to the peroxo unit. The axial cysteinate can donate electron density in a π-type overlap with the iron metal orbitals. This density is then pushed into the peroxo σ* orbital that overlaps in a π-interaction with specific metal orbitals. Increased electron density in the σ* orbital would then help cleave the O-O bond (Figure 1.03). Thus, covalency of the Fe-S bond is essential to the heterolytic O-O bond cleavage and formation of compound I.

![Figure 1.03](image)

**Figure 1.03:** Schematic picture of the thiolate donating electron density through the iron cofactor and into the peroxide σ* of compound 0.

The heterolytic cleavage of the O-O bond would suggest that compound I is an Fe⁵-oxo species. However due to the cooperative effects of both cysteinate-Fe and π-delocalization
around the heme cofactor, this new intermediate is an Fe\textsuperscript{IV}-oxo with a ligand based radical ((Por/S\textsubscript{Cys}º)Fe\textsuperscript{IV}=O).\textsuperscript{22,23} Recent work by Michael Green has established that significant ligand radical character is associated with the axial cysteinate.\textsuperscript{24} This suggests that there is cooperativity between the organic redox reservoirs of the porphyrin ring and the axial cysteinate to produce this important reducing equivalent. The involvement of this organic based redox-reservoir in the mechanism of cytochrome P450 has inspired considerable development of synthetic 1\textsuperscript{st} row transition metal complexes that contain a redox-active ligand, and will be discussed in detail later in this chapter.

Compound I is believed to be the active oxidant and the thiolate is postulated to increase the basicity of the resulting [(Por/S\textsubscript{Cys}º)Fe\textsuperscript{IV}=O] allowing for H-atom abstraction.\textsuperscript{25} The complete hydroxyla-tion of the aliphatic substrate happens through the rebound mechanism. The H-atom abstraction step affords an Fe\textsuperscript{IV}-OH, known as compound II, and a radical based carbon on the substrate. The hydroxide and carbon radical will recombine to release the hydroxylated product and subsequent water coordination will afford the resting ferric state.\textsuperscript{10} The axial cysteinate is proposed to impact many steps of this mechanism and synthesizing model systems to investigate this can help gain insight to the design and function of cytochrome P450.

\textit{Superoxide Reductases}

While O\textsubscript{2} is essential to much of life on earth, its reduced species are strong oxidants that can negatively impact cells. High superoxide (O\textsubscript{2}\textsuperscript{−}) concentration has been linked to a variety of diseases and detrimental conditions such as Parkinson’s and Alzheimer’s diseases, and cancers.\textsuperscript{26} To combat this toxic small molecule oxidant, living organisms have enzymes that are capable of sequestering O\textsubscript{2}\textsuperscript{−} into less harmful products. Most aerobic organisms contain superoxide
dismutase (SOD), which will affect the $1e^-$ disproportionation of $O_2^-$ into the more benign $O_2$ and $H_2O_2$ (Scheme 1.01).27 Both the reduction and oxidation of superoxide occurs at a single redox active metal cofactor active site consisting of either a non-heme Fe, Mn or Cu. Unique to the copper enzyme is a redox-inert zinc cofactor.28

**Scheme 1.01: Disproportionation of O$_2^-$ by SOD**

\[
\begin{align*}
\text{SOD} \\
\text{a} & \quad O_2^- + 2H^+ + Fe^{\text{II}} \rightarrow H_2O_2 + Fe^{\text{III}} \\
\text{b} & \quad O_2^- + Fe^{\text{III}} \rightarrow O_2 + Fe^{\text{II}} \\
& \quad 2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2
\end{align*}
\]

**Scheme 1.02: Sequestering of O$_2^-$ by SOR**

\[
\begin{align*}
\text{SOR} \\
O_2^- + 2H^+ + Fe^{\text{II}} \rightarrow H_2O_2 + Fe^{\text{III}}
\end{align*}
\]

Anaerobic bacteria also have an enzyme that sequesters $O_2^-$ but unlike in SOD it will not produce $O_2$. This enzyme known as superoxide reductase (SOR), will only perform one half of the reaction seen in SOD (Scheme 1.02).29 This enzyme has a primary coordination sphere that is reminiscent of Cytochrome P450. It is known to contain a Fe metal cofactor constrained in a square pyramidal geometry (Figure 1.04). Four nitrogens from histidine residues makeup the basal plane and an axial cysteinate is trans to the open site.3 The location of the active site by the surface of the enzyme may allow proton shuttles that are necessary for enzymatic reactivity.29
Figure 1.04: Active site of superoxide reductase consisting of a basal plane of four histidines and an axial thiolate. N atoms of histidines are in blue, Fe in green, S in yellow while C atoms are in gray.

The enzyme has a high-spin ferric resting state that coordinates a nearby glutamate to the open site, resulting in an octahedral geometry. This glutamate (glu₁₄), as well as a nearby lysine, are essential to the reactivity and could maintain a proton relay or guide the O₂⁻ substrate to the active site. The reduction of the ferric species will release the glutamate and establish the five-coordinate high-spin ferrous active species. Coordination of O₂⁻ and oxidation of the ferrous metal center will generate a metastable high spin ferric species, T₁ (Figure 1.05).

Figure 1.05: Proposed reaction cycle of superoxide reductase indicating two metastable species, T₁ and T₂.
A charge transfer band at 600 nm has been established as the $S_{cys} \rightarrow Fe$ charge transfer transition for the $T_1$ intermediate.\textsuperscript{31} Resonance Raman probed vibrational parameters of this species with a mutant enzyme, using $H_2O_2$ as the oxidant. This species had a weak $\nu_{Fe-O}$ stretch at 438 cm$^{-1}$ but a strong $\nu_{O-O}$ stretch at 850 cm$^{-1}$, which were both isotopically sensitive when $^{18}O$-labeled substrate was added.\textsuperscript{32} At the time this species was tentatively assigned as an $\eta^2$-side-on peroxo species based on synthetic models. Larry Que had established that $\eta^2$-side-on peroxo complexes typically had weaker $\nu_{Fe-O}$ and favored high spin ferric states, while $\eta^1$-end-on peroxos favored low-spin states resulting in stronger $\nu_{Fe-O}$.\textsuperscript{33} However, the crystal structure of this intermediate definitively identified this species as an end-on hydroperoxo species.\textsuperscript{34} It has been hypothesized that the strong $trans$ effect of the axial cysteinate helps to weaken the Fe-O bond and promote product release.

This intermediate suggests that cytochrome P450 and SOR proceed through a structurally similar end-on ferric hydroperoxo. However, unlike the heme enzyme, SOR will not proceed through a high valent Fe=O. Instead of protonating the distal oxygen and favoring O-O cleavage, SOR will protonate the proximal oxygen resulting in the release of $H_2O_2$ and the cleavage of the Fe-O bond.\textsuperscript{3,6} After release of $H_2O_2$, a new ferric species is observed and believed to be an Fe$^{III}$-hydroxide, known as T2. Reduction by NADPH will then regenerate the starting active ferrous state.\textsuperscript{35} The axial cysteinate has been postulated to help promote the critical bond breaking steps of the related Fe$^{III}$-hydroperoxo intermediates in both enzymes, however this cleavage occurs at two different locations (Figure 1.06).
Biomimetic Modeling of Ferric Peroxides

As discussed above, a vast number of pentadentate amine scaffolds have been isolated and has been shown that there is significant differences between high spin metal complexes and low spin complexes. Low-spin systems typically have $\nu_{\text{Fe}-\text{O}}$ around 617-644 cm$^{-1}$ and $\nu_{\text{O}-\text{O}}$ around 781-806 cm$^{-1}$ (Table 1.01).\textsuperscript{33,36,37} Conversely, high-spin complexes have $\nu_{\text{Fe}-\text{O}}$ around 470-495 cm$^{-1}$ and $\nu_{\text{O}-\text{O}}$ around 817-827 cm$^{-1}$ suggesting that SOR could modulate the strong O-O bond by maintaining a high spin iron metal center, favoring protonation of the proximal oxygen and subsequent release of H$_2$O$_2$.\textsuperscript{38,39} The low-spin state of the ferric metal in the cytochrome P450 intermediates can promote O-O bond cleavage instead.

**Table 1.01:** Vibrational data of Fe(III)-peroxo intermediates in selected synthetic model complexes and for some metastable intermediates of enzymes. Table adapted from Ref 33.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\nu_{\text{Fe}-\text{O}}$ (cm$^{-1}$)</th>
<th>$\nu_{\text{O}-\text{O}}$ (cm$^{-1}$)</th>
<th>Spin</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Py5-(OOH)</td>
<td>627</td>
<td>806</td>
<td>1/2</td>
<td>33</td>
</tr>
<tr>
<td>5-Br$_2$N$_4$Py-(OOH)</td>
<td>641</td>
<td>795</td>
<td>1/2</td>
<td>33</td>
</tr>
<tr>
<td>5-(MeO)$_2$N$_4$Py-(OOH)</td>
<td>644</td>
<td>791</td>
<td>1/2</td>
<td>33</td>
</tr>
<tr>
<td>TPEN-OOH</td>
<td>617</td>
<td>796</td>
<td>1/2</td>
<td>36</td>
</tr>
<tr>
<td>S$^{\text{Me}_2}$N$_4$Tren-OOH</td>
<td>562(DFT)</td>
<td>784</td>
<td>1/2</td>
<td>44</td>
</tr>
<tr>
<td>CytP450 compound I</td>
<td>553</td>
<td>792</td>
<td>1/2</td>
<td>12</td>
</tr>
<tr>
<td>N4Py-(OO)</td>
<td>495</td>
<td>827</td>
<td>5/2</td>
<td>33</td>
</tr>
<tr>
<td>EDTA-(OO)</td>
<td>459</td>
<td>816</td>
<td>5/2</td>
<td>39</td>
</tr>
<tr>
<td>BPPA-(OOH)</td>
<td>621</td>
<td>830</td>
<td>5/2</td>
<td>38</td>
</tr>
<tr>
<td>CyclamPrS-(OOH)</td>
<td>419</td>
<td>850</td>
<td>5/2</td>
<td>45</td>
</tr>
<tr>
<td>E47A SOR T1</td>
<td>438</td>
<td>850</td>
<td>5/2</td>
<td>32</td>
</tr>
</tbody>
</table>
However the axial cysteinate in both of these enzymes is critical and is potentially responsible for impacting the vibrational stretches. David Goldberg demonstrated that the incorporation of a thiolate will weaken the Fe-O bond of alkylperoxides. A tetradeutate cyclam amine backbone formed the basal plane around the Fe metal center (Figure 1.07). The incorporation of a *trans* thiolate decreases the \( \nu_{\text{Fe-O}} \) by 90 cm\(^{-1}\) compared to other low-spin ferric alkylperoxides.\(^{41}\) Methylating the backbone affords a spin state change from low-spin to high-spin and, as expected, the vibrational \( \nu_{\text{Fe-O}} \) stretches decreased from 612 cm\(^{-1}\) to 584 cm\(^{-1}\) with the same change of *trans* triflate to an aryl thiolate.\(^{42}\) These results indicate the importance of both the coordinated atoms and the spin state of the metal ion on the strength of the Fe-O bond.

![Figure 1.07](image)

*Figure 1.07:* Spin states of two Tetradeutate cyclam ferric alkylperoxos with an exogenous aryl thioalate in the axial position.

The Kovacs group has shown the importance of both the spin-state and the location of a coordinated thiolate on functional synthetic models of SOR. While Goldberg had N\(_4\)S ligation around the Fe metal, the thiolate was not tethered to the basal amine framework. Kovacs’ first functional model maintained the N\(_4\)S coordination but the geometry was not similar to that seen in SOR.\(^{43}\) The system, [Fe\(^{II}\)(SMe\(_2\)N\(_4\)(tren))]\(^{+}\), coordinated in a trigonal bipyramidal geometry around the ferrous metal (Figure 1.08 left). A key feature of the enzyme’s active site, the *trans* cysteinate, was not replicated as in this model as the thiolate is *cis* to the open coordination site.
Figure 1.08: Synthetic models designed by Kovacs and coworkers containing a coordinated thiolate in both cis (left) and trans (right) to the open site. Both model the reactivity of SOR.

Even with these differences, superoxide will bind to and oxidize the ferrous metal center to form a metastable intermediate with a charge transfer band at 452 nm. This intermediate was identified to contain a ferric metal center based on the location of this sulfur to Fe charge transfer transition. An axial EPR signal with g-values indicating a low-spin ferric metal center and X-ray absorption data also confirmed this assignment. This species was further identified as a Fe-hydroperoxo species due to the observation of a distal oxygen in the EXAFS spectrum, as well as vibrational data. FT-IR data indicated a Fermi resonance, due to coupling between two vibrations of similar energies, at 788 and 781 cm$^{-1}$. Addition of D$_2$O caused the Fermi resonance to collapse into a single peak at 784 cm$^{-1}$. This suggests that there is a peroxo binding mode due to the $\nu_{O-O}$ stretch in the IR spectrum. Isotopically labeling the oxygens results in a shift of this resonance of 31 cm$^{-1}$ to 753 cm$^{-1}$ as expected by Hooke’s law. The $\nu_{Fe-O}$ stretch was unobserved but calculated by DFT to be at 562 cm$^{-1}$. This weakened O-O bond is not without precedent and similar to the ferric hydroperoxo observed in compound 0, both of which contain a thiolate in the primary coordination sphere.

Protonation of this species by acid will afford a 6-coordinate low-spin ferric complex with the coordinated conjugate base and the release of H$_2$O$_2$ modeling the second step of the
SOR mechanism. An outersphere reductant will regenerate the starting ferrous complex. Addition of another equivalent of potassium superoxide will result in the formation of the same metastable intermediate replicating the chemistry produced by SOR, even with different ferric spin states and geometry of the coordinated thiolate.

While \([\text{Fe}^{II}(\text{S}^{\text{Me}_2}\text{N}_4\text{(tren)})]^+\) did not have a thiolate \textit{trans} to the open site or a similar spin state of the ferric hydroperoxo species seen in SOR, Kovacs and coworkers synthesized a second model system to address these features. The cyclam basal plane was adapted to contain a single arm containing an aliphatic thiolate known as \([\text{Fe}^{II}\text{cyclamPrS}]^+\) \((\text{Figure 1.08 right})\).\(^{45}\) This afforded a square pyramidal \textit{N}_4\textit{S} geometry with the basal plane consisting of the four nitrogens and an apical thiolate consistent with the active site of SOR. Addition of superoxide results in the formation of a metastable species with a visible charge transfer band at 530 nm.

EPR spectroscopy has identified this species as a high-spin ferric complex. The vibrational data collected with resonance Raman spectroscopy suggests that, once again, a ferric-peroxo species is formed. The \(v_{\text{O-O}}\) stretch is exceptionally high at 891 cm\(^{-1}\) while the \(v_{\text{Fe-O}}\) stretch indicates a weak Fe-O bond at 419 cm\(^{-1}\). This Fe-O bond is unusually weak but relates well to the vibrational data observed in SOR. Addition of an acid will produce \(\text{H}_2\text{O}_2\) and a ferric complex with the coordinated conjugate base. Reduction can then reform the ferrous starting complex which can undergo another turnover. The difference in the vibrational data of these two thiolate ligated synthetic models suggests the importance of both the geometry of the complex, the position of the coordinated thiolate, and the spin-state of the metal. Understanding the true effects of both of these factors would be more viable with a larger library of thiolate-ligated model complexes.
Redox-Active Ligands and Their Effect on Catalysis

Typically earth abundant, 1st row transition metals excel at sequential 1e⁻ redox chemistry but Nature has found a way to incorporate these metals to perform multiple electron redox transformations. Water oxidation and nitrogen reduction are two essential transformations that require multiple electrons. To accomplish these difficult transformations, enzymes have adopted active sites that contain multiple metal ions, expanding the number of redox states and making this chemistry viable.¹,²

Cytochrome P450, however, undergoes the 4e⁻ reduction of O₂ at a mononuclear Fe-metal center.⁹ An essential feature of the chemistry of cytochrome P450 is the ability of the porphyrin/cysteinate’s redox reservoir to participate in the critical heterolytic O-O bond cleavage step. This cooperativity between the metal redox orbitals and the organic redox orbitals, so essential to the enzyme, has inspired considerable effort to characterize and understand synthetic systems with similar characteristics.⁴⁶

Recently there has been a wealth of publications on the preparation of 1st row transition metal complexes containing redox-active ligands. Examples of these systems include salen,⁴⁷ dithiolenes,⁴⁸ o-phenylenediamines,⁴⁹ bis(imino)pyridine⁵⁰ and α-(imino)pyridines⁵¹ (Figure 1.09). These first examples were interesting to inorganic chemists due to the electronic structure of these complexes. The observation of redox-activity has been shown in these cases to involve ligand π or π* orbitals that are close in energy to the d-orbitals of the metal center.
Figure 1.09: Structures of typical redox-active ligands.

While these complexes have unique spectroscopic properties, some of them have shown promise at performing multiple electron redox transformations that are typically reserved for noble metals. The Chirik group has reported multiple types of catalytic chemistry with reduced bis(imino)pyridine complexes. For example they have demonstrated the ability of a monomeric Fe complex to perform hydrogenation of olefins. A putative catalytic cycle identified two key 2e⁻ redox transformations, oxidative addition of H₂ and reductive elimination of the alkane. The same complex served as a catalyst for [2π+2π] cycloaddition of dienes where a proposed reductive elimination of the cyclized product is critical. The precatalyst is a doubly reduced ferrous(bis)iminopyridine complex that was later established as an Fe(II) doubly reduced ligand (Figure 1.10). A second generation bis(imino)pyridine pre-catalyst was shown to do hydrogenation where reducing equivalents originate from both the ligand and metal redox orbitals, highlighting the cooperativity between the metal and ligand redox reservoirs. The ability of the ligand redox orbitals to participate in these critical 2 e⁻ steps is essential to preventing complications of high valent or low valent oxidation states of the Fe metal center.
Figure 1.10: Proposed catalytic cycle of a bicyclization consisting of a 2e⁻ reduction of the substrate. The two electrons originate from a ligand based redox orbital. Tobias Ritter has shown the competence of an α-(imino)pyridine catalyst in hydrosilations of dienes. The proposed catalytic cycle is initiated by oxidative addition of silane and is completed with the reductive elimination of the hydrosilation product. Both of these steps require a 2e⁻ redox chemistry to occur at the metal center. The availability of the ligand redox orbitals is thought to be critical to mitigate the electronic demands at the metal center. This property can maximize catalyst turnover by preventing degradation through the formation of an Fe(0) product. Tuning the energetics of the metal redox-orbitals and the ligand-based orbitals is essential for these catalysts to function.

While Chirik and Ritter have showcased the activity of these redox-active ligands in the participation of 1ˢᵗ row transition metal catalysts, there remains much to understand about these unique systems. The Betley group has demonstrated that suitable energetics alone does not guarantee the ligand will participate in redox transformations. The tris(5-mesitylpyrrolyl)ethane (TPE) ligand was shown to undergo a ligand-based oxidation with outer-sphere oxidants when coordinated to 1ˢᵗ row divalent metals. However, inner-sphere oxidants undergo an entirely metal-based oxidation with no participation of the ligand-based redox-orbitals (Scheme 1.03). The Betley group proposes that the π overlap of the ligand redox orbitals with the metal-based d-orbitals prevents ligand-based oxidation. The difference in the
energetics of the ligand-based orbitals and metal-based orbitals may not provide a large enough thermodynamic driving force for an electron transfer from the ligand HOMO orbital to the metal orbital. However, the addition of an inner-sphere would alter the molecular orbitals and could conceivably change the HOMO orbital to be more metal-based as seen with the metal oxidation. Consequently, understanding the interactions between multiple redox-reservoirs around a metal center would be essential for designing future effective homogeneous catalysts.

**Scheme 1.03:** Reactivity of a ferrous TPE complex with both inner-sphere and outer-sphere oxidants.59

![Scheme 1.03](image)

While the design of these catalysts have been influenced by cytochrome P450 and the involvement of the porphyrin redox state, few have incorporated a thiolate. As previously mentioned, there is now belief that significant organic radical character is maintained on the axial cysteinate. Due to the interactions between the cysteinate and the porphyrin it is essential to synthesize and characterize synthetic complexes containing a redox-active ligand along with a coordinated thiolate. Probing these interactions on model systems can impact our understanding of the complex synergy of the multiple pieces of cytochrome P450. As of now, there is a one example of a ferrous bis(imino)pyridine complex with a coordinated thiolate that was reported by David Goldberg.60 This complex has unique structural parameters that may be suggestive of thiolate involvement in the redox-active bis(imino)pyridine framework.
Notes to Chapter 1


Chapter 2.

Synthesis and Characterization of a Family of Fe α-(Imino)-N-Heterocycle complexes; Preliminary Reactivity with Small Substrates.

Portions of this chapter have been adapted from: Leipzig, B. K.; Rees, J. A.; Nyrov, A.; Theisen, R.; Flowers, S. E.; Kaminsky, W.; DeBeer, S.; Kovacs, J. A. In Preparation.¹
Introduction:

Metalloenzymes perform many functions critical to life on earth. The ability of these enzymes to accomplish their catalytic function is dependent on numerous specific geometric arrangements in both the primary and secondary coordination sphere. As discussed in the introductory chapter, the addition of a thiolate can have a remarkable influence on the properties of Fe metalloenzymes, which will be further elaborated here.³,⁴

Our group has shown that the model system [Fe²⁺(S²Me₂N₄(tren))]⁺ has remarkable similarities to the SOR. In this model system, superoxide will bind and oxidize the ferrous metal center to provide a metastable ferric hydroperoxo intermediate (Figure 2.01).⁵,⁶ Akin to the metalloenzyme, this intermediate can be protonated at the proximal oxygen and release H₂O₂; the resulting ferric metal center can be reduced to regenerate the starting complex. While this intermediate is quite similar to that of the T1 species of SOR in regards to the N₄S primary coordination sphere, there are geometric and electronic differences between the two. Unlike the enzyme, which has the cysteinate trans to the peroxo, our model system constrained the thiolate cis to the peroxo.⁷ In addition, the high-spin Fe metal center in SOR is thought to be essential in weakening the Fe-O bond and releasing the hydrogen peroxide, however our model system is a low-spin S=1/2, though still releases H₂O₂.⁸

![Figure 2.01](image-url)

**Figure 2.01:** Synthetic models incorporating a thiolate in the primary coordination sphere.
To further investigate the importance of the thiolate position in SOR, our group has prepared a second model system that incorporates cyclam in the basal plane with a pendant thiolate arm that is trans to the open site. The model system, [Fe^{II}(cyclam-PrS)]^+, also reacts with superoxide and forms an intermediate that has a very low $\nu_{Fe-O}$ stretch at 419 cm$^{-1}$, which is similar to a mutant enzyme which has an $\nu_{Fe-O}$ of 438 cm$^{-1}$.$^9,10$ This is due to the high-spin nature of the Fe in the model complex and the thiolate having a strong trans effect and weakening the Fe-O bond.

To further highlight the importance of the geometry of the primary coordination sphere, more synthetic models need to be prepared. These new model systems will provide benchmark spectroscopic parameters to understand crucial enzymatic intermediates. A new system has been reported by the Kovacs group that incorporates a tripodal backbone with a thiolate and two primary amines. It is hypothesized that the condensation of aromatic pyridines to this tripodal base may impart a rigid basal plane and place the thiolate trans to an open site (Figure 2.02). However, it was observed that this new system does not form a monomeric species in the solid state, rather a bis $\mu$-thiolate dimeric geometry, even in coordinating solvent solutions.$^{11}$ However, two new systems have been designed with differing N-heterocycles (Figure 2.02). This family of complexes has some unique ligand bond lengths that suggests an interesting electronic structure.

![Figure 2.02: Idealized square pyramidal metal complex containing a thiolate trans to the open site using the tripodal tame(N$_2$S) backbone.](image)
Experimental:

General Considerations: Sodium azide, 1-hydroxybenzotriazole (HOBT), dicyclohexylcarbodiimide, 3,3’-aminopropylamine, di-tert-butyl dicarbonate, 2-(tert-butoxycarbonylamino)isobutyric acid, iron(II) acetate, iron(II) chloride, and tetraphenyl phosphonium chloride were all purchased from TCI and used as received. 3-methyl-3-oxetanemethanol (1) was purchased from Sigma-Aldrich and used without further purification. DMSO-d$_6$, CDCl$_3$ and MeCN-d$_3$ were purchased from Cambridge Isotope Labs and used as received. EtOH was purchased from Decon and degassed prior to use. Et$_2$O was purchased from Fischer Scientific and purified using a solvent purification columns housed in a custom stainless steel cabinet and dispensed by a stainless steel Schlenk-line (GlassContour). All other solvents were purchased from Sigma Aldrich. MeOH, MeCN and CH$_2$Cl$_2$ were dried and distilled prior to use. A 48% aqueous solution of hydrobromic acid was purchased from Alfa-Aesar and used as received. Ammonia was obtained from Praxair while all other material was purchased and used as received from Sigma Aldrich.

$^1$H and $^{13}$C NMR spectra were obtained on a Bruker AV300, AV301, DRX499, or AV500. Chemical shifts are listed in parts per million and were reported relative the residual protio solvent. UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer equipped with a fiber optic cable connected to a “dip” ATR probe (C-technologies). A custom-built two neck solution sample holder equipped with a threaded glass connector was sized specifically to fit the “dip” probe. Electrospray ionization mass spectrometry (ESI-MS) was preformed on a Bruker Esquire LC-Ion Trap. X-ray crystallographic data was recorded on a Bruker APEX II single crystal X-ray diffractometer using Mo-radiation. Elemental analysis were preformed by
Atlantic Microlab, Inc. Norcross, Ga. Infrared spectra were recorded on a Bruker Tensor 27 FTIR instrument.

All manipulations were performed using Schlenk techniques or under a N\textsubscript{2} atmosphere in a glovebox. The synthesis of 2-bromomethyl-2-methyl-propane-1,3-diol (2) and 2-benzylsulfanyl methyl-2-methyl-propane-1,3-diol (3) was performed according to a modified literature procedure.\textsuperscript{12}

**Synthesis of (3-methanesulfonyl-2-methanesulfonylmethyl-2-methyl-propylsulfanyl methyl)-benzene (4).** Methanesulfonyl chloride (18.2 g, 159 mmol) was added dropwise to a CH\textsubscript{2}Cl\textsubscript{2} (375 mL) solution containing 3 (9.0 g, 39.8 mmol), triethylamine (TEA) (24.1 g, 239 mmol) and a catalytic amount (0.3 g) of 4-dimethylaminopyridine at 0°C. The orange solution was monitored by TLC through the disappearance of the starting material. The reaction was then allowed to warm to room temperature. Water (300 mL) was added to the solution and extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 300 mL), the combined organics were washed with water and brine (2 x 100 mL each) prior to drying with sodium sulfate. Solvents were removed \textit{in vacuo} and the orange oil was purified to an off yellow oil by column chromatography (1:1 EtOAc:hexanes) in 87% yield. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.33 (m, 5H), 4.09 (d, \(^{2}J=10\) Hz, 2H), 4.03 (d, \(^{2}J=10\) Hz, 2H), 3.75 (s, 2H), 3.01 (s, 6H), 2.53 (s, 2H), 1.08 (s, 3H). ESI-MS: expected \(m/z\) for C\textsubscript{14}H\textsubscript{22}O\textsubscript{6}S\textsubscript{3}= 382.1 found 382.2.

**Synthesis of (3-azido-2azidomethyl-2-methyl-propylsulfanyl methyl)-benzene (5).** (4) (8.0 g, 21 mmol) was added to a solution of sodium azide (12.3 g, 189 mmol) in DMF (130 mL) and refluxed for 3 days. After cooling to room temperature, water (130 mL) was added and the
organics were extracted with EtOAc (3x 200 mL). The combined organics were combined and washed water and brine (2 x 200 mL each) wherein the reaction mixture was dried with sodium sulfate. The solvent was removed in vacuo and the resulting yellow oil was purified by silica gel column chromatography (4:1 hexanes:EtOAc) to yield 5 as an off white oil in 80% yield. $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.34 (m, 5H), 3.74 (s, 2H), 3.29 (d, $^2$J=12 Hz, 2 H), 3.24 (d, $^2$J=12 Hz, 2 H), 2.44 (s, 2H), 0.98 (s, 3H).

**Synthesis of 2-benzylsulfanylmethyl-2-methyl-propane-1,3-diamine (6).** 5 (2.0 g, 7.2 mmol) was added drop wise to a stirred solution of lithium aluminum hydride (LAH) (1.1 g, 28.8 mmol) in ether (150 mL) at 0°C. Once the reaction was complete water was added slowly to quench the excess LAH. The reaction was then filtered through Celite and dried with sodium sulfate. The ether was removed in vacuo and the clear oil was placed in an aqueous solution (10 mL) and acidified to pH 2.0. The aqueous solution was washed with ether (3 x 20 mL) before being basified to pH 12.0. The product was then extracted ether (3 x 40 mL). The combined organics were dried with sodium sulfate and then removed in vacuo to yield 6 as a clear oil in 51% yield. $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.32 (m, 5H), 3.70 (s, 2H), 2.55 (s, 4H), 2.44 (s, 2H), 0.86 (s, 3H). ESI-MS: expected m/z for C₁₂H₂₀N₂S= 224.1, found m/z=225.1.

**Synthesis of 2-benzylsulfanylmethyl-2-methyl-propane-1,3-(tert-Butyloxycarbonyl) diamine (7).** 6 (4.7g, 20 mmol) was dissolved in CH₂Cl₂ (50 mL) and cooled to 0°C. di-tert-butyl dicarbonate (9.1g, 40mmol) was dissolved in CH₂Cl₂ (10 mL) and added dropwise to the solution of 6. This solution was allowed to warm to room temperature overnight. The solution was washed with brine (2 x 50 mL) and dried over Na₂SO₄. Volatiles were removed in vacuo to
afford 7 as a white solid in 95% yield (8.1 g) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.33 (m, 5H), 5.03 (bs, 2H), 3.69 (s, 2H), 3.048 (dd, \(^3\)J=7.5 Hz, \(^2\)J=14.7 Hz, 2H), 2.80 (dd, \(^3\)J=6.3 Hz, \(^2\)J=14.9 Hz 2H), 2.35 (s, 2H), 1.44 (s, 18H), 0.86 (s, 3H). ESI-MS: expected \(m/z\) for C\(_{22}\)H\(_{36}\)N\(_2\)O\(_4\)S= 424.1, found \(m/z=425.1\

**Synthesis of 2-thiomethyl-2-methyl-propane-1,3-(tert-Butyloxycarbonyl) diamine (8).** To a stirred solution of liquid ammonia (50 ml) cooled to -78°C, was added sodium metal (200 mg). 7 (2.9 g, 6.8 mmol) of was added in 0.3 g portions. Additional sodium was periodically added in small proportions to maintain the deep blue color. The completion of the reaction was assumed once the solution maintained its deep blue color for more than 1 h. Ammonium chloride was added until the solution changed from blue to yellow, thus quenching the sodium. The liquid ammonia was evaporated under a stream of N\(_2\). A 50 mL, 0.025M K\(_2\)HPO\(_4\) and 0.025M NaH\(_2\)PO\(_4\) aqueous solution was then added and the reaction was acidified with 37% HCl until the reaction reached a pH of 2. The organic product was extracted with dichloromethane (4 x 75 ml). The organics were then dried with Na\(_2\)SO\(_4\) and the volatiles were removed to afford 8 as a foul smelling oil in 93% yield (2.1 g) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.26 (bs, 2H), 3.00 (m, 4H), 2.41 (d, \(^3\)J=9 Hz 2H), 1.66 (t, \(^3\)J=9 Hz 1H), 1.46 (s, 18H) 0.89 (s, 3H). ESI-MS: expected \(m/z\) for C\(_{15}\)H\(_{30}\)N\(_2\)O\(_4\)S= 334.1, found \(m/z=335.1\

**Synthesis of 2-thiomethyl-2-methyl-propane-1,3-diamine dihydrogenchloride (9).**

5 ml of 4M HCl in dioxane was added to 8 (2.1 g, 6.4 mmol) in methanol (2 mL). Gas evolution was observed and this was allowed to stir overnight. The volatiles were removed to afford a 9 as a white solid in 95% yield (1.2 g) \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.12 (bs, 5H, NH\(_2\)), 2.91 (bs,
4H), 2.65 (s, 2H), 1.02 (s, 3H). ESI-MS: expected $m/z$ for $\text{C}_5\text{H}_{16}\text{Cl}_2\text{N}_2\text{S}= 207.1$, found $m/z=135.1$ (No HCl’s)

**Synthesis of $[\text{Fe}^{\text{II}}(\text{Tame-N}_2\text{SPy}_2)]_2(\text{PF}_6)_2$** (10). 9 (0.2 g, 1 mmol) was added to a vial containing a stirred solution of sodium methoxide (0.156 g, 3 mmol) in of methanol (10 mL). 2-pyridinecarboxaldehyde (0.21g, 2mmol) was then added and the stirred suspension was cooled to -40° C. In a separate vial, iron (II) chloride (0.126 g, 1 mmol) dissolved in methanol (50 mL) and cooled to -40° C. The iron solution was then slowly added to the organic solution. Immediately, the solution became a deep turquoise color. This was stirred for 1h at which time sodium hexafluorophosphate (0.168g, 1mmol) was added. This solution was stirred overnight at which time a dark solid precipitated out. The methanol was removed and the solid was dissolved in acetonitrile, and filtered through celite. The deep turquoise solution was concentrated to a minimal volume (~ 2 mL) upon which Et$_2$O was layered to isolate a deep blue solid in 70% yield (360 mg). Electronic absorption spectrum: $\lambda_{\text{max}}$ (nm) ($\epsilon$ (M$^{-1}$cm$^{-1}$)): (MeCN): 420 (6,150), 580 (9,100), and 650 (11,800)). $^1$H NMR (300 MHz, MeCN-d$_3$) $\delta$ 9.3 (s, 1H), 9.00 (s, 1H), 8.97 (s, 1H) 8.15, (m, 3H), 7.75 (t $^3J$ 7.5 Hz, 1H), 7.45 (m, 2H), 7.09 (t $^3J=7$ Hz, 1H), 4.14 (d $^2J=12.7$ Hz, 1H) 3.77 (m, 3H), 1.04 (s, 3H), 0.90 (d, $^2J=13.3$ Hz 1H), 0.31 (d $^2J=13.4$ Hz, 1H); $^{13}$C NMR (500 MHz, MeCN-d$_3$) $\delta$ 169.2 (s, 2C), 168.5 (s, 2C), 160.2 (s, 2C), 158.9 (s, 2C), 154.4 (s, 2C), 153.3 (s, 2C), 136.9 (s, 2C), 136.1 (s, 2C) 128.8 (s, 2C), 128.1 (s, 2C), 125.4 (s, 2C), 125.2 (s, 2C), 69.0 (s, 2C), 67.0 (s, 2C), 43.4 (s, 2C), 26.6 (s, 2C), 24.8 (s, 2C) ESI-MS: expected $m/z$ for $[\text{C}_{34}\text{H}_{38}\text{N}_8\text{S}_2\text{Fe}_2]^{2+}$ = 367.1, found $m/z=367.1$  

Elemental Analysis for $\text{C}_{34}\text{H}_{38}\text{F}_{12}\text{N}_8\text{P}_2\text{S}_2\text{Fe}_2$  

Calculated: C, 39.86; H, 3.74; N, 10.94. Found C, 39.28; H, 3.73; N, 10.80.
Synthesis of $[(\text{Fe}^{II}(\text{Tame-N}_2\text{SQu}_2))_2]^{2+} (\text{PF}_6)_2$ (11). 11 was isolated following a similar procedure as 10. A deep blue solid was isolated by layering Et$_2$O onto a concentrated solution of 11 in DCM in 67% yield (410 mg). $\lambda_{\text{max}}$ (nm) ($\epsilon$ (M$^{-1}$cm$^{-1}$)): (MeCN): 420 (6,240), 607 (14,830), and 719 (19,500). $^1$H NMR (300 MHz, MeCN-$d_3$) $\delta$ 9.81 (s, 2H), 8.30 (d, $^2J$=8.5Hz, 2H), 8.06 (d, $^2J$=7.8Hz, 2H), 7.58 (t, $^3J$=7.4Hz, 2H), 7.47 (t, $^3J$=7.7Hz, 2H), 6.50 (d, $^2J$=8.3Hz, 2H), 4.77 (d, $^2J$=15.1Hz, 2H) 3.87 (d, $^2J$=15.1Hz, 3H), 0.67 (s, 3H), 0.00 (s, 2H) ESI-MS: expected m/z for $[\text{C}_{50}\text{H}_{46}\text{N}_8\text{S}_2\text{Fe}_2]^{2+}$ = 467.1, found m/z=467.1  Elemental Analysis for $\text{C}_{50}\text{H}_{46}\text{F}_{12}\text{N}_8\text{P}_2\text{S}_2\text{Fe}_2\text{CH}_2\text{Cl}_2$ Calculated: C, 46.77; H, 3.69; N, 8.56. Found C, 46.85; H, 3.73; N; 8.11.

Synthesis of $[(\text{Fe}^{II}(\text{Tame-N}_2\text{SQu}_2))_2]^{2+} (\text{BPh}_4)_2$ (11-BPh$_4$). Crystals with the BPh$_4$ counterion were grown by a slow vapor diffusion of MeCN:Et$_2$O. $\lambda_{\text{max}}$ (nm) ($\epsilon$ (M$^{-1}$cm$^{-1}$)): (MeCN): 420 (6,240), 607 (14,830), and 719 (19,500). ESI-MS: expected m/z for $[\text{C}_{50}\text{H}_{46}\text{N}_8\text{S}_2\text{Fe}_2]^{2+}$ = 467.1, found m/z=467.1.

Synthesis of $[(\text{Fe}^{II}(\text{Tame-N}_2\text{SImid(Me)})_2)_2]^{2+} \cdot \text{MeCN(}\text{PF}_6)_2$ (12). 12 was isolated following the same procedure for 11. A royal blue solid was obtained in 85% yield (440 mg) from layering of ether onto a concentrated volume of acetonitrile. Crystals were isolated in a slow diffusion of Et$_2$O into a concentrated volume of acetonitrile. $\lambda_{\text{max}}$ (nm) ($\epsilon$ (M$^{-1}$cm$^{-1}$)): (MeCN): 619 (11,500); (MeOH) 595 (4,600). Magnetic moment (solution MeCN 298K) 2.89$\mu_B$ ESI-MS: expected m/z for $[\text{C}_{30}\text{H}_{43}\text{N}_{12}\text{S}_2\text{Fe}_2]^{2+}$ = 373.5, found m/z=373.1  Elemental Analysis for $\text{C}_{30}\text{H}_{42}\text{F}_{12}\text{N}_{13}\text{P}_2\text{S}_2\text{Fe}_2\text{CH}_3\text{CN}$ Calculated: C, 35.67; H, 4.21; N, 16.90. Found C, 35.57; H, 4.14; N; 16.74.
Reactions with CO\(_{(g)}\). In a typical experiment 15-20mg of 10 or 12 was added to a medium walled J. Young NMR tube in MeCN-\(d_3\). The NMR tube was rigorously degassed and was then pressurized with 5 atm of CO\(_{(g)}\) for about 30 seconds. This NMR tube was then stirred slowly at room temperature over the course of days.

Synthesis of \(\text{(Fe}^{\text{II}}\text{Tame-N}_2\text{SPy}_2\text{)CN (10-CN)}\): 9 (0.1 g, 0.5 mmol) was added to a vial containing a stirred solution of sodium methoxide (0.081 g, 1.5 mmol) in 10ml of methanol. 2-pyridinecarboxaldehyde (0.107 g, 1 mmol) was then added and the stirred suspension was cooled to \(-40^\circ\text{C}\). In a separate vial iron (II) chloride (0.063 g, 0.5 mmol) was dissolved in 5ml of methanol and cooled to \(-40^\circ\text{C}\). The iron solution was then slowly added to the organic solution. Immediately, the solution became a deep turquoise color. This was stirred for 1h at which time sodium cyanide (0.025g, 0.5mmol) was added. This solution was stirred overnight at which time a dark solid precipitated out. The methanol was removed and the solid was dissolved in dichloromethane, and filtered through celite. The deep turquoise solution was concentrated to a minimal volume (~2ml) upon which ether was layered to isolate a deep blue crystalline solid solid in 70% yield (360 mg). Electronic absorption spectrum: \(\lambda_{\text{max}}\) (nm) \(\varepsilon\) (M\(^{-1}\)cm\(^{-1}\)): 353 (3,500), 409 (4600), 577 (3,600) 697 (4,200) (some may have decomposed). (MeCN)\(^{1}\)H NMR (300 MHz, MeCN-\(d_3\)) \(\delta\) 9.76 (d, \(^3J=6\) Hz, 1H), 9.15 (s, 1H), 8.76 (s, 1H) 8.00, (d, \(^3J=12\) Hz 1H), 7.86 (m, 2H), 7.68 (t, \(^3J=12\) 1H), 7.45 (m, 2H), 7.10 (t, \(^3J=10\) Hz, 1H) 4.71 (d \(^3J=16\) Hz, 1H) 3.76 (m, 3H), 1.17 (s, 3H), 2 protons masked by solvent peak. ESI-MS: expected \(m/z\) for \(\text{C}_{18}\text{H}_{19}\text{N}_5\text{SFe}\)= 393.07, found \(m/z=393.1\) IR (solution, CH\(_2\)Cl\(_2\), cm\(^{-1}\)) \(\nu\) (CN) 2087.
**O₂ Reactions:** An inert custom ‘dip’ probe cell was evacuated with Ar\(_{\text{g}}\). To this a 0.05 mM solution of the corresponding complex was added. This custom cell could be immersed in a cold bath or heated to allow temperature control. Once temperature is equilibrated the cell was exposed to atmosphere and scans were recorded in timed intervals.

**X-Ray Crystallographic Structure Determination**

A lustrous green prism, 11, measuring 0.20 x 0.15 x 0.13 mm\(^3\) was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame for all sets. The scan width was 0.5°. Data collection was 100% complete to 25° in θ. A total of 128992 reflections were collected covering the indices, h = -18 to 18, k = -18 to 18, l = -19 to 19. 11639 reflections were symmetry independent and the R\(_{\text{int}}\) = 0.0287 indicated that the data was of better than average quality (0.07). Indexing and unit cell refinement indicated a triclinic lattice. The space group was found to be P ̅1 (No. 2).

A blue piece, 12, measuring 0.10 x 0.05 x 0.05 mm\(^3\) was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 30 seconds per frame for all sets. The scan width was 0.5°. Data collection was 99.9% complete to 25° in θ. A total of 50076 reflections were collected covering the indices, h = -19 to 19, k = -20 to 20, l = -21 to 20. 14435 reflections were symmetry independent and the R\(_{\text{int}}\) = 0.0608 indicated that the data was of slightly better than average quality (0.07). Indexing and unit cell refinement indicated a triclinic lattice. The space group was found to be P ̅1 (No. 2).
A dark blue translucent prism, 10-CN measuring 0.38 x 0.03 x 0.03 mm$^3$ was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 120 seconds per frame for all sets. The scan width was 1°. Data collection was 95.5% complete to 25° in θ. A total of 46138 reflections were collected covering the indices, h = -46 to 46, k = -46 to 46, l = -8 to 8. 3647 reflections were symmetry independent and the R$_{int}$ = 0.3106 indicated that the crystal was not that good and the data quite week. Indexing and unit cell refinement indicated a R-centered trigonal lattice. The space group was found to be R 3 (No.148).

The data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker. Solution by direct methods (SHELXS, SIR97$^{13,14}$) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97$^{15,16}$. Scattering factors are from Waasmair and Kirfel.$^{17}$ Hydrogen atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters U$_{eq}$ were fixed such that they were 1.2U$_{eq}$ of their parent atom Ueq for CH's and 1.5U$_{eq}$ of their parent atom U$_{eq}$ in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares. Crystallographic data for 11, 12 and 10-CN are presented in Table 2.01.
Table 2.01: Crystallographic data for 11, 12 and 10-CN.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>12</th>
<th>10-CN</th>
</tr>
</thead>
<tbody>
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<td><strong>Formula</strong></td>
<td>$\text{C}<em>{98}\text{H}</em>{96}\text{B}_2\text{FeN}_8\text{S}_2$</td>
<td>$\text{C}<em>{70}\text{H}</em>{90}\text{Fe}_{24}\text{Fe}<em>4\text{N}</em>{29}\text{P}_4\text{S}_4$</td>
<td>$\text{C}<em>{70}\text{H}</em>{90}\text{Fe}_{24}\text{Fe}<em>4\text{N}</em>{29}\text{P}_4\text{S}_4$</td>
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<td><strong>MW (g/mol)</strong></td>
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<td>2278.30</td>
<td>2359.75</td>
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<tr>
<td><strong>Crystal System</strong></td>
<td>Triclinic</td>
<td>Triclinic</td>
<td>Trigonal</td>
</tr>
<tr>
<td><strong>Space Group</strong></td>
<td>P-1</td>
<td>P-1</td>
<td>R-3</td>
</tr>
<tr>
<td><strong>Unit Cell Dimensions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a (Å)</td>
<td>13.35249(16)</td>
<td>13.9227(10)</td>
<td>39.021(7)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>13.6085(16)</td>
<td>14.5427(19)</td>
<td>39.021(7)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>14.5700(16)</td>
<td>15.0078(11)</td>
<td>7.0622(14)</td>
</tr>
<tr>
<td>α (deg)</td>
<td>71.249(5)</td>
<td>97.318(6)</td>
<td>90</td>
</tr>
<tr>
<td>β (deg)</td>
<td>66.021(5)</td>
<td>116.683(4)</td>
<td>90</td>
</tr>
<tr>
<td>γ (deg)</td>
<td>78.500(6)</td>
<td>112.025(6)</td>
<td>120</td>
</tr>
<tr>
<td><strong>Final R indices</strong></td>
<td>0.0317</td>
<td>0.0501</td>
<td>0.0987</td>
</tr>
<tr>
<td><strong>R indices (all Data)</strong></td>
<td>0.0363</td>
<td>0.0976</td>
<td>0.2270</td>
</tr>
</tbody>
</table>

**Results and Discussion:**

$N_2S$ **Ligand Design and Synthesis:**

To attempt to fully mimic cysteinate ligated metalloenzymes, which contains the sulfur $trans$ to an open site, a square pyramidal ligand system would have to be designed in which the thiolate is contained in the axial position. Previous work in our group used the $tren$ (N(EtNH$_2)_3$) ligand scaffold, which with the addition of 3-methyl-3-mercapto-2-butanone, forms a trigonal bipyramidal geometry with the thiolate $cis$ to the open site. To enforce a square planar type geometry, a tripodal backbone containing two primary amines and a thiolate was designed by the Kovacs group and is a derivative of 1,1,1 tris-(aminoethyl)ethane (tame).$^{10}$ This tripodal ligand framework should be suited for metal templated Schiff base condensations in order to isolate
pentadentate metal complexes that mimic the active sites of cysteinate ligated metalloenzymes. Ideally the conjugated aromatic rings would form a basal plane forcing the thiolate to retain a position trans to the vacant site. However, a crystal structure obtained in our group of an iron complex indicate these complexes have flexibility, allowing a geometry that places the thiolate cis to the open site and causing dimerization through bridging thiolates. 

Although this tame derivative has been used in the Kovacs lab previously, the ligand synthesis has been optimized and the purity of the final product improved (Scheme 2.01). The 7 step organic synthesis has an overall yield of 29%. The synthesis begins with the ring opening of 2-methyl-3-oxetanemethanol with HBr to generate 2. The thiolate is then incorporated by nucleophilic attack of benzyl mercapton to yield 3. Since thiolates can be oxidized, the benzyl mercapton is essential due to the high stability of this protecting group and the duration of this lengthy organic synthesis.

**Scheme 2.01**: Eight-step synthetic route to isolate TameN₂SH•2HCl with an overall yield of 29%.
While TsCl was used in order to convert the alcohols to a better leaving group, this reaction took 2 days. Using MsCl would convert the alcohols to the mesylate product, 4, in just hours and also afforded improved yields. Addition of sodium azide afforded the azide product 5 and a LAH reduction reduces the azide to the primary amine product 6, essential for the metal template Schiff base condensation.

Previously, 6 is deprotected in one step with sodium metal, however this has proven to be unreliable. Elemental analysis using a one step deprotection indicates significant impurities in the organic product, with as much as 15% of the molar mass unaccounted for. The main issue with the straight deprotection is that isolating the thiolate product from the bi-products is difficult due to the pKas of the ammoniums groups and the thiolate group (pKa’s of 10 and 9 respectively) being closely related. Excess sodium chloride and ammonium salts, which were generated during the workup, and potential alkoxide bi-products may all be present in this one step deprotection, thus lowering the purity of this step. These bi-products will affect the yield of the metal templated Schiff base condensation and the purity of the final metal complexes.

To circumvent these issues, an extra protection step has been added. The boc protection group is unaffected by the sodium reduction and the carboxamide functional group will allow for an organic work up to remove any salt bi-products. Stirring the product of the sodium reduction in an organic solution of HCl will remove the boc groups and afford the desired tripodal backbone as a di-HCl salt 9. The purity of the isolated product was greatly improved through the addition of these two extra steps.
Structural Characterization of a Family of FeTame α-(imino)-N-heterocycle Complexes:

The complete pentadentate ligand was not isolated but instead synthesized coordinated to the metal in a one-pot metal-templated Schiff base condensation (Scheme 2.02). Using two equivalents of 2-pyridinecarboxyaldehyde along with one equivalent of the tripodal ligand and one equivalent of an Fe(II) source, 10 was isolated. When using the longer organic synthesis, much purer metal product was obtained, as confirmed with elemental analysis and yields that were over 30% higher than previously reported. However, the pyridine version does not form the desired monomeric square pyramidal geometry, but instead forms a dimer, bridged through bis-µ-thiolates.

Scheme 2.02: Iron templated Schiff base condensation to form the dimeric solid state structure.

One way to favor monomeric products is to increase the steric bulk or alter the electronic parameters, both of which may be possible through the modification of the aldehyde and N-heterocyclic amine. This was done by incorporating commercially available quinoline and imidazole derivatives of the 2-pyridinecarboxyaldehyde to generate 11 and 12 respectively. Similar to 10 these two analogues form dimeric structures in the solid state (Figure 2.03). To favor a monomeric species, steric bulk is most likely necessary in a more proximal position to the thiolate. Our group has shown that the incorporation of gem-dimethyl groups adjacent to the thiolate stabilizes coordinatively unsaturated monomeric metal-thiolate complexes.18,19 However,
the incorporation of gem-dimethyl groups using this synthesis may not be feasible due to the specific ring opening mechanism of the first step.

![Figure 2.03](image)

**Figure 2.03:** X-ray crystal structures of 10, 11, 12 with 50% probability ellipsoids. Counterions, cosolvents and hydrogens omitted for clarity (top). Corresponding structural representations (bottom).

In addition to the similar bridging µ-thiolates (Figure 2.04), all three complexes have comparable Fe-N bond lengths that are consistent with other low-spin Fe(II) systems (Table 2.02).\(^{20,21}\) When considering the ligand environment it is not surprising that the metal favors a low-spin state. As a π acceptor, the α-imino-N-heterocyle arms would favor a low spin metal center. The thiolate, even as a π-donor that would normally favor higher spin states, forms very covalent bonds with first row transition metals and, due to the nepheloxetic effect, can favor low-spin Fe complexes. In addition, the octahedral geometry would provide a splitting of the \(t_{2g}\) and \(e_g^*\)-like orbitals and thus favor the low spin state.
Figure 2.04: Schematic representation of the four atom core Fe$_2$S$_2$ for complexes 10-12. Also including the S-C bond for reference.

However, there are differences between these three complexes. In contrast to the $C_2$ symmetric 10 and 12, which are bridged only through the sulfur, 11 has $C_{2h}$ symmetry. This may be due to the increase in steric of the quinoline ring which forces the ligand to span both metals, with one $\alpha$-(imino)quinoline arm coordinated to one metal and the other arm to the other. In contrast to the symmetric bis $\mu$-thiolate core of 10 and 11, the Fe-S bonds of 12 are less symmetric and suggest more facile cleavage of this dimer (*vide infra*).

Table 2.02: Selected bond lengths (Å) for complexes 10, 11, 12, 13. *Crystallographic dimers identical bond lengths on each Fe.*

<table>
<thead>
<tr>
<th>Bond Lengths</th>
<th>10$^a$</th>
<th>11$^a$</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe(1)-S(1)</td>
<td>2.284(1)</td>
<td>2.273(1)</td>
<td>2.288(1)</td>
</tr>
<tr>
<td>Fe(1)-S(2/1’)</td>
<td>2.289(1)</td>
<td>2.279(1)</td>
<td>2.311(1)</td>
</tr>
<tr>
<td>Fe(1)-N(1)</td>
<td>1.908(4)</td>
<td>1.949(1)</td>
<td>1.917(2)</td>
</tr>
<tr>
<td>Fe(1)-N(2)</td>
<td>1.916(4)</td>
<td>1.996(1)</td>
<td>1.923(2)</td>
</tr>
<tr>
<td>Fe(1)-N(3)</td>
<td>1.984(4)</td>
<td>1.949(1)</td>
<td>1.955(2)</td>
</tr>
<tr>
<td>Fe(1)-N(4)</td>
<td>1.997(4)</td>
<td>1.987(1)</td>
<td>-</td>
</tr>
<tr>
<td>Fe(1)-N(5)</td>
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<td>-</td>
<td>1.966(2)</td>
</tr>
<tr>
<td>Fe(2)-S(1)</td>
<td>-</td>
<td>-</td>
<td>2.297(1)</td>
</tr>
<tr>
<td>Fe(2)-S(2)</td>
<td>-</td>
<td>-</td>
<td>2.283(1)</td>
</tr>
<tr>
<td>Fe(2)-N(7)</td>
<td>-</td>
<td>-</td>
<td>1.933(2)</td>
</tr>
<tr>
<td>Fe(2)-N(8)</td>
<td>-</td>
<td>-</td>
<td>1.925(2)</td>
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<tr>
<td>Fe(2)-N(9)</td>
<td>-</td>
<td>-</td>
<td>1.970(2)</td>
</tr>
<tr>
<td>Fe(2)-N(10)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fe(2)-N(11)</td>
<td>-</td>
<td>-</td>
<td>1.973(2)</td>
</tr>
</tbody>
</table>

This family of complexes is unique in that it has three “redox-active” components: the metal, the thiolate and the $\alpha$-(imino)-$N$-heterocycle.$^{22,23}$ As seen in nature, first row transition
metals are used by metalloenzymes to perform essential redox transformations. Thiolates can be oxidized and therefore provide a second redox-active site as well to modulate the redox potentials of the metal.\textsuperscript{2,3} Finally the \(\alpha\)-(imino)-\(N\)-heterocycle is part of a growing family of “redox-active ligands” that are more commonly being incorporated into base metal catalysts.\textsuperscript{24,25,26} This \(\alpha\)-(imino)-\(N\)-heterocycle backbone can accept up to two electrons on each arm and have characteristic bond lengths depending on the formal oxidation state of the ligand (Table 2.03).\textsuperscript{23}

\textbf{Table 2.03:} Ligand backbone bond lengths (Å). Average distances of all 4 (\(\alpha\)-imine)\(N\)-heterocycle arms.

<table>
<thead>
<tr>
<th>Bond Lengths(^a)</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>Typical (L(0)^{23})</th>
<th>Typical (L(\prime)^{23})</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-N(\textsubscript{imine})</td>
<td>1.297(3)</td>
<td>1.297(1)</td>
<td>1.297(3)</td>
<td>1.28(1)</td>
<td>1.34(1)</td>
</tr>
<tr>
<td>C-C</td>
<td>1.414(3)</td>
<td>1.440(2)</td>
<td>1.427(3)</td>
<td>1.47(1)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>C-N(\textsubscript{N-heterocycle})</td>
<td>1.364(4)</td>
<td>1.352(1)</td>
<td>1.336(8)</td>
<td>1.35(1)</td>
<td>1.39(1)</td>
</tr>
</tbody>
</table>

Unexpectedly, even without the addition of an external reductant, the bond lengths show increased electron density within this organic framework of the imine bond. All three complexes have elongated imine bonds and shortened C-C bonds (Table 2.03), which are diagnostic of a partially reduced ligand backbone. While there are other complexes with long imine bonds around (1.29 Å) these ferrous complexes do not have the concurrent short C-C bond; these ferrous complexes C-C bonds are around 1.46 Å.\textsuperscript{27,28} This elongation could be caused by either a reduction of the ligand backbone or increased backbonding into the \(\alpha\)-(imino)-\(N\)-heterocycle \(\pi^*\) orbital. Milstein \textit{et al.} have observed an unusual elongation of the imine bond in a similar \(\alpha\)-(imino)pyridine complex and they have attributed this to increased backbonding due to the electronic geometry of the metal complexes.\textsuperscript{29} However his C-C bond does not show the same decrease in bond length that is observed within this family of thiolate ligated ferrous complexes suggesting there may be more electron density present within this redox-active ligand
While there is a wealth of similar α-(imino)pyridine complexes and other similar “redox-active” ligands, there are few with a coordinated thiolate which could influence both the electronics of the metal and other ligands around the metal center. In one similar instance, Goldberg has also observed unusual bond lengths within the imine arms of a singly reduced bis(imino)pyridine system with a pendent thiolate, suggesting that the thiolates may be able to modulate the electron density of other redox ligands coordinated to the metal center.³⁰

**Solution State Structural Analysis of 10, 11 and 12:**

A diamagnetic ¹H NMR spectrum is expected since the metal-ligand bond lengths are consistent with a low-spin ferrous electronic configuration. Indeed, complexes 10 and 11 do have diamagnetic proton spectra that are consistent with the structural geometry of the complex depending on how the ligand bridges the two iron metal centers (Figure 2.05). As seen in the solid state structure, 11 has $C_{2h}$ symmetry, and has two doublets observed at 4.77 ppm ($^2J = 15.1$ Hz) and 3.88 ppm ($^2J = 15.2$ Hz) which are assigned to the diasterotopic protons on the four symmetry related methylene carbons adjacent to the imine nitrogens. Additionally the methylene protons adjacent to the thiolate are equivalent by ¹H NMR spectroscopy, constituting the singlet resonance at 0 ppm. Finally, each quinoline ring is related by symmetry and as such only 6 unique aromatic protons are observed while the protons on the imine carbon are all symmetry related and are observed as a singlet at 9.8 ppm.

Conversely, since the $C_2$ symmetric 10 is of lower symmetry, there are more distinct proton environments observed. The protons on the methylene groups adjacent to the imine nitrogen now consist of four unique protons instead of two and they can be observed as a doublet consisting of one of the protons at 4.15 ppm ($^2J = 12.7$ Hz) and a multiplet containing the other
three protons at 3.77 ppm (Figure 2.05). Similarly the protons on the methylene adjacent to the thiolate are now split into two doublets at 0.90 ppm ($^2J = 13.3$ Hz) and 0.31 ppm ($^2J = 13.4$ Hz). Since the two aromatic rings on each organic backbone are no longer symmetry related, there are 8 peaks corresponding to the 8 unique aromatic protons. The two imine arms are also chemically inequivalent and the protons on the imine carbon are now two singlets at 9.3 and 9.0 ppm. The splitting patterns in these spectra give evidence that the solid-state structure geometry is maintained in solution.

**Figure 2.05:** $^1$H NMR spectra of 10 (top) and 11 (bottom) in MeCN-$d_3$ at 300 MHz and 298 K. Diagrams are showing one half of the dimeric solid state structure as the other half is related by symmetry. $H_{Ar}$ indicates aromatic protons.

However, while a low-spin ferrous metal center would be consistent with the metal-ligand bond lengths, the intra-ligand bond lengths and the diamagnetic $^1$H NMR spectrum, alternative electronic geometries exist that could also explain these observations. Since $\alpha$-(imino)pyridine ligands can be reduced, an internal electronic rearrangement wherein the ferrous metal center reduces the ligand backbone would lead to a complex such as Fe(III)-(L)(L$^-$). It would be expected that, in this geometry the solid state structure would have two asymmetric imine arms according to the oxidation state of each ligand, but Wieghardt has observed with Fe
that the radical can be delocalized across both \( \alpha \)-(imino)pyridine arms leading to bond lengths halfway between a closed shell ligand and a reduced ligand.\(^{23}\) These bond lengths match the bond lengths observed for \( \mathbf{11} \). Additionally, Wieghardt has reported strong antiferromagnetic coupling between a singly reduced \( \alpha \)-(imino)pyridine and a paramagnetic metal center with coupling constants ranging from \( J = -330 \) to \(-1370 \) cm\(^{-1}\).\(^{23}\) As such the diamagnetic \(^1\)H NMR spectra do not discount this electronic configuration.

While the structure of \( \mathbf{12} \) has similar bond lengths to the other two complexes, the \(^1\)H NMR spectrum is distinct. This spectra contains a mixture of paramagnetic and diamagnetic features, indicating that a mixture of species is present in solution. As observed in the solid state, the Fe-S bonds for \( \mathbf{12} \) are asymmetric which may lead to the cleavage of the dimeric solid-state structure. If the solid-state dimer were to cleave, it would be expected that the corresponding five-coordinate monomeric species may have a different metal spin state due to the geometry and could lead to the paramagnetic features. A solution-state effective magnetic moment was evaluated over a range of temperatures by using the Evans method and it clearly shows an increase as a function of temperature deviating from Curie’s law, suggesting the possibility of a monomer-dimer equilibrium in solution (Figure 2.06). If the solid-state dimer were to cleave a monomeric species may be paramagnetic. The ratio of these two would depend on the temperature dependent equilibrium constant (\( K_{eq} \)) giving rise to the variation of \( \mu_{eff} \) on temperature. The possibility of a monomeric species in solution is further supported by this complex’s reactivity with \( \mathbf{O}_2 \).
Electronic Absorption Spectra of 10, 11 and 12:

The electronic absorption spectra of all three of these complexes show intense visible features. These features have very large extinction coefficients, which suggests that these transitions are not ligand field transitions in nature, but charge transfer transitions (Figure 2.07, Figure 2.08 and Table 2.04). Thiolate ligated Fe complexes typically contain intense ligand to metal charge transfers (LMCT) due to the covalent thiolate bond and initially it was hypothesized that these transitions were a result of this type of transition. However, typically our group observes these strongly visible features only when the metal is oxidized to the ferric oxidation state. This could lend confidence to the hypothesis of the electronic rearrangement wherein the correct electronic configuration would consist of an Fe(III)-( L)(L−). However, the nature of the charge transfer is due to the low lying π* ligand orbitals of the α-(imino)pyridines which will be seen in the electronic absorption spectra. This will be further evaluated in Chapter 3.

It should be noted that in solution 12 contains two species, one diamagnetic and one paramagnetic, convoluting the analysis of the extinction coefficients. This mixture has a solution
\( \mu_{\text{eff}} \) of 2.9 \( \mu_B \) at 298 K by Evans (Equation 2.01). This is close to the value for an S=1 system (\( \mu_{\text{eff}} \) of 2.9 \( \mu_B \)). This would suggest that the paramagnetic species has high spin S=2 and a solution of 100\% of this species would should have a \( \mu_{\text{eff}} \) of 4.9 \( \mu_B \). The experimental magnetic moment would therefore indicate that the solution consists of 35\% paramagnetic species while 65\% is diamagnetic species at 298 K.\(^{32}\) Using this information, \( K_{\text{eq}} \) of the monomer-dimer equilibrium at room temperature is 0.0034 M for a solution containing 9.1 mM of Fe (Equation 2.02). The relative concentrations of monomer and dimer were then determined for the more dilute UV-Vis samples using this equilibrium constant. By varying these concentrations of iron between 0.228 mM to 0.055 mM they can be used to solve for the extinction coefficients of both species. The monomeric species therefore has a molar absorptivity of 6,100 M\(^{-1}\) cm\(^{-1}\) at 619 nm, while the dimer has a molar absorptivity of 12,400 M\(^{-1}\) cm\(^{-1}\) at 619 nm (Equation 2.03).

\[
\text{FeTIM}_{\text{dimer}} \rightleftharpoons 2 \text{FeTIM}_{\text{monomer}} \quad \text{(eq 2.01)}
\]

\[
K_{\text{eq}} = \frac{[\text{Monomer}]^2}{[\text{Dimer}]} \quad \text{(eq 2.02)}
\]

\[
\text{Abs}_{619} = \varepsilon_{\text{monomer}} \cdot [\text{Monomer}] + \varepsilon_{\text{dimer}} \cdot [\text{Dimer}] \quad \text{(eq 2.03)}
\]

**Table 2.04:** UV-Vis transitions for complexes 10, 11 and 12 in MeCN RT.

<table>
<thead>
<tr>
<th></th>
<th>( \lambda_{\text{max}} ) (nm)</th>
<th>( \varepsilon ) (M(^{-1}) cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>420 (6,150), 580 (9,100), 650 (11,800)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>420 (6,240), 607 (14,830), 719 (19,500)</td>
<td></td>
</tr>
<tr>
<td>12 (monomer)</td>
<td>619 (6,100)</td>
<td></td>
</tr>
<tr>
<td>12 (dimer)</td>
<td>619 (12,400)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2.07: Electronic absorption spectra of 10 and 11 at RT in MeCN.

Figure 2.08: Electronic absorption spectra of 12 consisting of 0.114 mM of a proposed monomeric complex and 0.003 mM concentration of a diamagnetic dimeric complex in MeCN at RT.

Intense, low-energy charge transitions are a hallmark of Fe complexes bearing reduced, conjugated ligands. Assigned as ligand-to-ligand charge transfer (LLCT) transitions, the $\lambda_{\text{max}}$ values are typically in the near infrared region, and extinction coefficients are in excess of $10^4 \text{M}^{-1} \text{cm}^{-1}$. In contrast, closed shell L $^0$ (α-imino)pyridine-ligated iron complexes have Fe$\rightarrow\pi^*$ metal to ligand charge transfer (MLCT) bands with extinction coefficients that range from 700-
6000 \text{ M}^{-1} \text{ cm}^{-1} \text{ and } \lambda_{\text{max}}-\text{values in the range 408-600 nm}.^{19,22} \text{ Thus, the large extinction coefficients of } 1-3 \text{ are more consistent with features expected from a reduced ligand moiety. However, the presence of thiolate ligands has been shown to significantly influence the intensity of MLCT bands to unoccupied } \pi^* \text{ ligand orbitals.}^{35,36} \text{ It is therefore possible that the large extinction coefficients found for } 10-12 \text{ instead reflect enhancement of the MLCT transitions as a result of covalent thiolate donation and will be discussed in full in Chapter 3.}

\textit{Reactivity With Small Molecules:}

While changing the } \text{N-} \text{heterocycle did not produce any desired solid state monomeric species, these could be obtained by the addition of strongly coordinating small molecules. Both } 10 \text{ and } 12 \text{ react with } \text{CO}_{(g)} \text{ and this transformation can be monitored by both } ^1\text{H} \text{ NMR and } ^{13}\text{C} \text{ NMR spectroscopy. } 10 \text{ will react with 5 atm of } \text{CO}_{(g)} \text{ in 12 hours but the identification of a single product is difficult with } ^1\text{H} \text{ NMR spectroscopy. However, a major product is observed by } ^{13}\text{C} \text{ NMR spectroscopy (Figure 2.09). A very small peak at 215 ppm may be the bound } \text{CO carbon while the peak at 185 ppm seems to be consistent with free } \text{CO}_{(g)}. \text{ The pattern of the NMR peaks suggests that a similar ligand geometry is maintained. With 5 aliphatic peaks it seems that the two imine arms are inequivalent by NMR spectroscopy. Ten aromatic proton peaks are observed which is two fewer than expected. The two missing peaks may be masked by the MeCN (solvent) peak. The number of peaks suggests that the imine arms are inequivalent, and if the } \text{CO}_{(g)} \text{ binds it will be in the position vacated by the bridging thiolate and be } \text{cis} \text{ to the remaining thiolate. Upon removal of the } \text{CO atm the complex will revert back to the starting dimeric species. This can then be repressurized to reform the } \text{CO bound product.}
**Figure 2.09**: $^{13}$C NMR spectrum downfield (left) of 10 with the addition of 5 atm CO$_{(g)}$, $^{13}$C NMR spectrum upfield (right) in MeCN-$d_3$.

12 reacts much faster than 10 with 5 atm of CO$_{(g)}$; a noticeable change in the $^1$H and $^{13}$C NMR spectrum in MeCN-$d_3$ is observed immediately after pressurization. While there are still small paramagnetic peaks present, there is a change in the diamagnetic region. If the CO$_{(g)}$ were to bind cis to the thiolate, this six coordinate complex would most likely be low-spin, thus giving rise to a diamagnetic spectrum (Figure 2.10). Although the aliphatic region contains many peaks, there do seem to be six unique peaks in the aromatic region (Figure 2.10). These six peaks represent the four protons on the two asymmetric imidazole rings along with the two imine protons. Similar to 10, the $^{13}$C NMR of 12 seems to only have one major species present. In the aliphatic region all peaks are accounted for including a weak signal at around 45 ppm could be the quaternary carbon of the ligand backbone. Downfield there is a weak signal observed at 218 ppm which is likely the bound CO. There are 7 other peaks but it would be expected to have eight: three carbons within each the imidazole, and the two imine carbons. Two peaks could be too close to each other to resolve or the MeCN solvent peak could mask the last signal. Upon releasing the pressure this complex releases CO and reverts back to the starting species.
The stronger binding, anionic CN\(^{-}\) substrate will also cleave the dimer but binds strongly enough to isolate a solid sample. This complex can be synthesized by adding one equivalent of NaCN at the completion of the metal templated Schiff base condensation instead of the usual non-coordinating counterion (NaPF\(_6\) or NaBPh\(_4\)). Using 10, a new product is observed by \(^1\)H NMR suggesting that CN is bound (Figure 2.11). In accord with the eight unique aromatic protons, this indicates that the complex would have two asymmetric \(\alpha\)-(imino)pyridine arms. The aliphatic region still has a doublet 4.7 ppm and a multiplet 3.8 ppm due to the four protons on the methylene carbons adjacent to the imine. The methyl group on the tame backbone has a large singlet at 1.2 ppm however it seems the two methylene protons adjacent to the thiolate are obscured by the MeCN peak. These protons do indeed appear when the solvent is changed from MeCN-\(d_3\) to \(CD_2Cl_2\) at 2.10 and 2.0 ppm. Indeed, the \(^{13}\)C NMR in MeCN-\(d_3\) confirms that there is one major product with 15 signals. Unfortunately the cyanide complex is not stable and even isolated as a solid will decompose within days at RT in an inert atmosphere. The strong binding
of cyanide could lead to the leaching of the Fe metal center and decomposition of the desired complex.

Figure 2.11: $^1$H NMR spectrum of 10-CN in MeCN-$d_3$.

In addition to NMR spectroscopy, a strong CN stretching feature should be observed by infrared (IR) spectroscopy if CN$^-$ is part of this complex. Indeed, in a solution of CH$_2$Cl$_2$ a peak for the CN$^-$ stretch is observed at 2087 cm$^{-1}$. This is in the region that would be expected if CN$^-$ were to be bound to the ferrous metal center. Que has observed a CN stretch at 2101 cm$^{-1}$ for a ferrous CN complex and “free” CN is expected to be 2052 cm$^{-1}$.\(^{37}\) When the CN is isotopically enriched with $^{13}$C the expected decrease in stretching frequency to 2044 cm$^{-1}$ is observed, consistent with Hooke’s law (Figure 2.12).
Figure 2.12: FT-IR spectra of 10 (Blue), 10-CN (green) and isotopically labeled 10\textsuperscript{13}CN (Red). Solution IR DCM.

The identity of this complex was unambiguously identified by the isolation of a single crystal (Figure 2.13). Unlike the complexes isolated with less coordinating solvents, this forms as a monomer in the solid state. The CN is bound \textit{cis} to the thiolate and in agreement with the NMR spectrum. Although this shows that a monomer may not form with an apical thiolate \textit{trans} to the open site as was the starting goal of this project, it does indicate that some of these dimers may be cleaved.

Figure 2.13: Crystal structure of 10-CN (left). Elipsoids at 50\% probability. Hydrogens and solvent atoms are omitted for clarity. Corresponding structural representations (right).

Similar to the dimeric complexes, this complex seems to have bond lengths consistent with a low-spin metal center, which would be expected with the coordination of a strong field
ligand such as CN	extsuperscript{-}. The Fe-N bond lengths range from 1.916(9)-1.968(9) Å while the Fe-S bond is short at 2.287(9) Å (Table 2.05). Since this has a lower spin-state than that reported by Lawrence Que, a shorter Fe-C bond at 1.945(11) Å is observed in 10-CN, compared to Que’s which has a bond length of 2.21293 Å.\textsuperscript{28} In agreement with the weaker CN	extsuperscript{-} stretching frequency compared to Que’s, we observe a lengthening of the C-N bond length by 0.014(Å). A weaker and longer C-N bond is expected due to the more significant backbonding in 10-CN compared to Que. The lower spin state of 10-CN will populate the \( t_{2g} \)-like orbitals which are capable of backbonding into the \( \pi^* \) orbitals of the CN substrate. Additionally the strongly covalent thiolate will increase the electron density of the metal and as such increase the metals ability to backbond.

**Table 2.05:** selected bond distances (Å) for 10-CN.

<table>
<thead>
<tr>
<th>Metal-Ligand Bond Lengths</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-S(1)</td>
<td>2.287(9)</td>
</tr>
<tr>
<td>Fe-N(1)</td>
<td>1.932(9)</td>
</tr>
<tr>
<td>Fe-N(2)</td>
<td>1.961(10)</td>
</tr>
<tr>
<td>Fe-N(3)</td>
<td>1.916(9)</td>
</tr>
<tr>
<td>Fe-N(4)</td>
<td>1.968(9)</td>
</tr>
<tr>
<td>Fe-C(18)</td>
<td>1.945(11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intra-Ligand Bond Lengths</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(18)-N(5)</td>
<td>1.164(12)</td>
</tr>
<tr>
<td>N(1)-C(5)</td>
<td>1.308(12)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.410(15)</td>
</tr>
<tr>
<td>N(3)-C(12)</td>
<td>1.290(12)</td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.402(14)</td>
</tr>
</tbody>
</table>

While the metal-ligand bond lengths are comparable between 10-CN bound and 10, there are some noticeable differences in the intra-ligand bond lengths. With the CN coordinated to the Fe, the two \( \alpha \)-(imino)pyridine arms do have distinct intra-ligand bond lengths. The imine that is trans to the cyanide has a much shorter imine bond at 1.290(12) Å compared to the imine cis to the CN, which now lengthens to 1.308(12) Å. Both arms have relatively short C-C bonds at
1.402(14) Å and 1.410(15) Å, respectively. The removal of a π-donating thiolate for a strongly π-accepting CN will perturb the $t_{2g}$-like orbitals and the CN$^-$ should have a stronger interaction with the imine arm coordinated *trans* to the CN. As such the CN may influence the electron density in this plane and lessen the amount of electron density within the imine arm compared to the dimeric structure.

Although a crystal structure has been obtained for the pyridine derivative, this complex is not stable and decays over a couple days while in solution, as monitored by $^1$H NMR spectroscopy. In a similar fashion the **12-CN** can be observed but seems to decay faster than the pyridine moiety. The strongly coordinating CN could lead to the decomposition of these species. In contrast the $C_{2v}$ symmetric **11** shows no affinity for these small molecules. This is most likely due to the different bridging mode that prevents easy coordination of small molecules to the metal center.

*Reactivity With Dioxygen:*

Our group has previously shown that thiolate ligation to ferrous complexes lowers the reduction potential and increases its affinity to bind and reduce O$_2$. These three complexes react distinctly with this oxidant; the divergence in reactivity is most likely dependent on the solution state structure of each complex. Akin to its reactivity with small substrates, **11** is inert to O$_2$ and is stable for months. In contrast, **10** reacts slowly with O$_2$ (over the course of several hours) while **12** reacts within minutes, which is similar to our group’s other monomeric thiolate ligated ferrous complexes.

The reaction between **12** and O$_2$ can be easily monitored by the disappearance of the charge transfer band at 619 nm (Figure 2.14). This reaction takes 5 minutes to fully convert and
leaves a small feature at 539 nm. The intensity is much lower than that of the starting band. If the ferrous metal is being oxidized, a thiolate to metal charge transfer should be observed in the visible region. However ESI-MS indicates a small peak that is +32 AMU and could suggest a doubly oxygenated sulfur product. Investigations are ongoing to determine the identity of this product.

**Figure 2.14:** Reaction between 12 and O₂ at RT in MeCN 0.045mM. Scans taken at 1 min intervals.

While this reaction is complete within minutes at RT, the reaction takes longer at -15°C (Figure 2.15). With no observable intermediates it would be likely that the rate determining step (RDS) of this reaction is O₂ reacting with the ferrous starting material. With excess O₂, the expected pseudo first-order kinetic fit for the disappearance of the starting material (Figure 2.15). An induction period is observed but is likely a result of O₂ dissolution into the solvent. The similar fast reactivity with O₂ compared with other monomeric thiolate ligated ferrous
complexes further supports the hypothesis that a significant portion of 12 consists of a monomeric ferrous thiolate in solution as observed with the paramagnetic $^1$H NMR spectrum.

**Figure 2.15:** Reaction between 12 and O$_2$ at -15°C in MeCN (0.045 mM). Inset shows pseudo-first order dependence. Scans taken at 1 min intervals.

While the $^1$H NMR spectra of 10 supports a solution state dimer consistent with the solid state structure, this species will still react with O$_2$. Similar to 12, the reaction can be monitored by UV-Vis through the disappearance of the main charge transfer transition at 640 nm. This reaction takes about 12 hours at RT and the product of this reaction has a weaker feature at 560 nm. This rate can be increased by raising the temperature, but there are no observable intermediates. The reaction appears to be pseudo zeroth-order with respect to the ferrous complex however at higher temperatures the reaction becomes pseudo-first order (**Figure 2.16**). The much slower reactivity could be due to the fact that O$_2$ binds less easily with less facile oxidation at the ferrous metal center as the dimeric solid state structure seems to be retained in solution. Alternatively, there may also be an equilibrium between a monomer and dimer for the
10 as well but, unlike 12, it is almost exclusively favored toward the dimer. This leaves only a small portion of complex that is capable of reacting with O₂. As this monomeric species is consumed it will push the equilibrium to favor the monomeric species. This gradual build-up of monomeric species could be why the reactivity is so much slower for 10 than 12.

![Graph showing absorbance over time and wavelength](image)

Figure 2.16: Reaction between 10 and O₂ at RT in MeCN. Inset shows zeroth order dependence. Scans taken at 2 hour intervals.

Conclusions:

A novel tameN₂S backbone has been used to synthesize three different ferrous species. All three form solid state dimers with bridging μ-thiolates with bond lengths that are consistent with a low-spin ferrous metal center. The condensation of an N-heterocyclic arms affords a unique redox-active ligand arm with unusual ligand bond length perturbations. The bond lengths seem to indicate that there is an increase in electron density present in the ligand backbone. The
activation of this ligand could be due to a metal spin state that is favorable for backbonding to the \( \pi^* \) \( \alpha \)-imino-\( N \)-heterocycle. In addition, the inclusion of the \( \pi \)-donating thiolate can increase and “push” electron density into the \( \alpha \)-(imino)-\( N \)-heterocycle orbitals.

The diamagnetic \(^1\)H NMR spectra of 10 and 11 indicate that the solid state structure seems to be retained in solution. However, it seems that the paramagnetic solution state properties of 12 indicate that in coordinating solvents (MeCN and MeOH), this species will cleave and potentially form a monomeric complex. Indeed, its reactivity in solution with O\(_2\) is similar to other monomeric ferrous thiolates which further confirms that a monomeric species is indeed present in solution. The O\(_2\) reaction product has not been fully characterized but does seem to be a ferric thiolate complex due to a visible charge transfer which is most likely a sulfur to Fe(III) charge transfer. Although no intermediates were observed in this reaction, fully characterizing the final product may yield a better understanding of how this reaction proceeded.

Unlike most previously prepared ferrous thiolates in our group, which have few visible features, these three complexes contain significant charge transfer transitions with large extinction coefficients. The nature of these charge transfers will be discussed in Chapter 3 but seem to include all three of the redox-active functionalities in these molecules. The dimeric structure of the 10 and 12 can be cleaved by the addition of strongly coordinating substrates such as CO\(_{\text{g}}\) and CN\(^-\). It would be interesting to investigate these further as well as other biologically relevant substrates. One promising result could be achieved by treating 10 and 12 with NO\(_{\text{g}}\).
Notes to Chapter 2


Chapter 3.

Spectroscopic Insight Into a Thiolate cis-Type “Push Effect” and its Influence on Auxiliary Redox-Active Ligands.

Portions of this chapter have been adapted from: Leipzig, B. K.; Rees, J. A.; Nyrov, A.; Theisen, R.; Flowers, S. E.; Kaminsky, W.; DeBeer, S.; Kovacs, J. A. In Preparation.¹
Introduction:

Cytochrome P450 has inspired a wealth of synthetic models containing redox-active ligands. Nature has engineered this enzyme to make use of an organic based reductant in the form of a porphyrin and an axial thiolate. This affords the heterolytic O-O bond cleavage of compound 0 and the generation of the high-valent (Por/S_{cys})Fe(IV)=O. This additional redox reservoir expands the formal oxidation states available for this enzyme but also affords the potential to do the necessary direct 2e^- redox reactions.

Numerous synthetic models have been prepared in an attempt to mimic this integral property of cytochrome P450. Performing 2e^- chemical conversions is desirable because this is the required amount of electrons needed to execute both bond making and bond breaking transformations. These transformations are commonly observed with 2nd row transition metals, which generally undergo oxidative addition and reductive elimination to make and break bonds. The redox-active ligand portion of these complexes expands 2e^- chemistry to earth-abundant 1st row transition metal complexes which tend to undergo sequential 1e^- redox processes.

A necessary feature of these complexes is the ability to modulate the redox-potentials of both the metal and ligand to make all redox-reservoirs accessible. This is typically accomplished with high energy filled π orbitals or low energy empty π* orbitals. However, many of these complexes do not incorporate a thiolate which is essential in generating and stabilizing compound I. The axial cysteinate is proposed to help modulate electron density of both the radical, and the peroxo σ*, suggesting it could also regulate the electron density of these redox active ligands.

Exploring the effects of ancillary ligands on reduction potentials and the reactivity of redox-active ligands can aid the design of second-generation catalysts. As explained in the
introductory chapter, these redox-active ligands can accept electron density to mitigate the electronic demands at the metal center. The addition of a coordinated thiolate or other supporting ligand could help tune the electronic demands and modulate the redox-potentials of these complexes even further. Additionally, the size and electronics of the π* systems can be tuned to alter the properties of these ligand frameworks.

**Experimental:**

**General considerations:** ¹H NMR spectra were obtained on a Bruker AV300, AV301, DRX499, or AV500. Chemical shifts are listed in parts per million and were reported relative the residual protio solvent. UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer equipped with a fiber optic cable connected to a “dip” ATR probe (C-technologies). A custom-built two-neck solution sample holder equipped with a threaded glass connector was sized specifically to fit the “dip” probe. Electrospray ionization mass spectrometry (ESI-MS) was performed on a Bruker Esquire LC-Ion Trap. Electron paramagnetic resonance (EPR) spectra were recorded on a Bruker E580 CW-EPR spectrometer operating at X-band frequency between 4 and 10 K with an Oxford helium cryostat. EPR spectra were collected with the following spectrometer parameters: frequency 9.396 GHz, power=2.008 mW, attenuation=20 dB sweep width=6,000 G, gain=1x10³, conversion time 5.4 ms, time constant=5.4 ms. Spectra were fit using EasySpin. Cyclic voltammograms were recorded in MeCN (0.1M nBu₄N[Pf₆] supporting electrolyte) on a PAR 263A potentiostat or a CHI 600E electrochemical work station using a glassy carbon working electrode, platinum auxiliary electrode and an Ag⁺/AgNO₃ reference electrode. X-ray crystallographic data was recorded on a Bruker APEX II single crystal X-ray diffractometer
using Mo-radiation. All manipulations were performed using Schlenk techniques or under a N\textsubscript{2} atmosphere in a glovebox.

**Synthesis of \([\text{Fe}^{\text{III}}(\text{Tame-N}_2\text{Sim}_2)]_2(\text{PF}_6)_4\ (12^{\alpha\text{x}})\):** 12 (50 mg, 0.048 mmols) was added to MeCN (5 mL). To this FcPF\textsubscript{6} (0.033 g, 0.096 mmols) was added as a solid. The solution changed from a deep blue to a reddish brown color and was stirred for 15 hours. The solvent was removed and Et\textsubscript{2}O (3 x 4 mL) was added. The solution was filtered and the filtrate and the Fc product discarded. The solid was washed with DCM (2 x 3 mL) and then redissovled in MeCN (1 mL) and layered with Et\textsubscript{2}O (3 mL) to obtain X-ray diffraction quality crystals. 12\textsuperscript{α\x} was obtained in 47% yield (30mg, 0.023mmol)

**Sulfur K-edge X-Ray Absorption Spectroscopy:** The samples were taken at beam line ID26 at the ESRF using a double crystal Si(111) monochromator. X-Ray size was 250\textmu m (H) x 50\textmu m (V). A Si PIN diode was fixed above the analyzer crystal to allow for additional XANES measurements in total fluorescence yield (TFY). Both the sample and the spectrometer were mounted in a vacuum chamber and kept at about 10\textsuperscript{-6} mbar. Solid samples of 10-12 were diluted in boron nitride and fixed on an aluminum plate by a double sided carbon tape. A 5\textmu m thick polypropylene foil was put on the sample surface to prevent the samples from air during sample mounting. Prior to RIXS measurements, 10-12 were found to be stable for up to 8 minutes of X-ray exposure time by additional XANES measurements. Consequently, RIXS planes were collected in about 100 minutes at different sample positions to exclude radiation damage.
**Computational Methods:** All calculations were performed using the ORCA quantum chemistry package developed by Neese and coworkers.\(^{10}\) All calculations employed the def2-TZVP(-f) basis set and the def2-TZVP/J auxiliary basis set for Coulomb fitting, the atom-pairwise dispersion correction of Grimme (D3BJ),\(^{11,12}\) and tight convergence criteria were required for the SCF solutions. All calculations used the Grid5 (GridX5) integration grid size, the zeroth-order regular approximation (ZORA),\(^{13}\) and the conductor-like screening model (COSMO)\(^{14}\) with acetonitrile as a solvent. Geometries were optimized for all complexes using the BP86 functional with the resolution of the identity (RI) approximation, and initiated from crystallographic coordinates when available.\(^{15,16}\) The calculation was converged to tight optimization criteria. Selected calculations employed the broken-symmetry formalism to model coupled paramagnetic sites. For the calculation of \(^{57}\)Fe Mössbauer parameters, the specialized core properties basis set (CP-PPP) with an integration grid of 7 was selected for Fe. The quadrupole splitting parameters were obtained from the output of the calculation, and the calculated isomer shifts were determined using the calibration study of Römelt et al.\(^{17}\) Time-dependent DFT (TD-DFT) calculations utilized the same parameters but with the CAM-B3LYP\(^{18}\) range-separated hybrid density functional and the RI chain-of-spheres (RIJCOSX) approximation.\(^{19,20}\) Calculation of the electronic absorption and sulfur K-edge X-ray absorption spectra were performed by selecting all available donors and acceptors or by localizing the donor space to the 1s orbitals of sulfur, respectively.\(^{21}\) A Gaussian broadening of 3200 cm\(^{-1}\) (respectively 0.5 eV) full width at half max was applied to the discrete transition moments. Molecular orbital isosurfaces and transition difference densities were visualized using UCSF Chimera.\(^{22}\)
**57Fe Mössbauer Spectroscopy** Mössbauer spectra were recorded in transmission mode with a constant-acceleration Wissel Mössbauer spectrometer, with a $^{57}$Co source in a Rh matrix and a Janis closed-cycle He cryostat operating at 80 K. Samples were anaerobically prepared by grinding crystalline solid into a powder using a mortar and pestle. The powder was then sealed in a shallow Teflon cup. Isomer shifts are reported in mm/s and referenced to iron metal at room temperature. Quadrupole splittings are also reported in mm/s. Experimental data were simulated and fit using the Mfit program.

**X-Ray Crystallographic Structure Determination**

A black prism, $\text{12}^{\text{ax}}$ measuring $0.02 \times 0.01 \times 0.01 \ \text{mm}^3$ was mounted on a loop with oil. Data was collected at $-173^\circ$C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 240 seconds per frame for all sets. The scan width was $1^\circ$. Data collection was 99.2% complete to $25^\circ$ in $\theta$. A total of 66859 reflections were collected covering the indices, $-47 \leq h \leq 47$, $-47 \leq k \leq 47$, $-14 \leq l \leq 14$. 6482 reflections were symmetry independent and the $R_{\text{int}} = 0.1149$ indicated that the sample was quite small. Indexing and unit cell refinement indicated a rhombohedral lattice. The space group was found to be $R \ 3$ (No. 148).

The data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker. Solution by direct methods (SHELXS, SIR97$^{23,24}$) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97$^{25,26}$. Scattering factors are from Waasmair and Kirfel.$^{27}$ Hydrogen atoms were placed in geometrically idealised positions and constrained to
ride on their parent atoms with C--H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters \( U_{eq} \) were fixed such that they were 1.2\( U_{eq} \) of their parent atom \( U_{eq} \) for CH's and 1.5\( U_{eq} \) of their parent atom \( U_{eq} \) in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares. Crystal Data is presented in Table 3.01

**Table 3.01**: Crystallographic data for 12\(^{ox}\)

<table>
<thead>
<tr>
<th></th>
<th>( 12^{ox} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td>( C_{30}H_{42}F_{24}Fe_2N_{12}P_4S_2 )</td>
</tr>
<tr>
<td><strong>MW (g/mol)</strong></td>
<td>1326.46</td>
</tr>
<tr>
<td><strong>Crystal System</strong></td>
<td>Trigonal</td>
</tr>
<tr>
<td><strong>Space Group</strong></td>
<td>R-3</td>
</tr>
<tr>
<td><strong>Unit Cell Dimensions</strong></td>
<td></td>
</tr>
<tr>
<td>( a ) (Å)</td>
<td>39.1499(14)</td>
</tr>
<tr>
<td>( b ) (Å)</td>
<td>39.1499(14)</td>
</tr>
<tr>
<td>( c ) (Å)</td>
<td>11.8458(5)</td>
</tr>
<tr>
<td>( α ) (deg)</td>
<td>90</td>
</tr>
<tr>
<td>( β ) (deg)</td>
<td>90</td>
</tr>
<tr>
<td>( γ ) (deg)</td>
<td>120</td>
</tr>
<tr>
<td><strong>Final R indices</strong></td>
<td>0.0764</td>
</tr>
<tr>
<td><strong>R indices (all Data)</strong></td>
<td>0.1312</td>
</tr>
</tbody>
</table>

**Results and Discussion:**

*Redox Properties of 10, 11 and 12:*

Complexes 10-12 all have multiple redox events within the acetonitrile window. Oxidation and reductions of these complexes can aid in the understanding of the electronic picture of these metal complexes. The Kovacs group has demonstrated that thiolates lower the reduction potential of ferrous complexes and 10-12 behave similarly (Table 3.02).\(^{28,29}\) Compound 10 has two well defined oxidation features; a lower potential that is reversible with an \( E_{1/2} \) of -116mV and an irreversible feature at +466 mV (both vs. Fc/Fc\(^+\)). The first feature is likely to be a Fe\(^{II}/Fe^{III}\) redox couple and the reversibility suggests that there is no change
structurally upon the oxidation in the electrochemical experiment; and reversibility is maintained through many different scan rates (Figure 3.01 Right). Since $^1$H NMR spectroscopic studies suggest that the dimeric structure is maintained in solution, there may be no immediate chemical change upon the oxidation, and we could have generated a mixed valent Fe$^{II}$-Fe$^{III}$ complex. The second irreversible feature could be the oxidation of the second ferrous metal center forming a Fe$^{III}$-Fe$^{III}$ dimeric species. Due to steric factors, this oxidation could force the dimeric structure to cleave, resulting in the observed irreversible redox feature. A similar trend is observed for 11, as it has a reversible feature at +112 mV and an irreversible +830 mV (both vs. Fc/Fc$^+$) (Figure 3.02 and Table 3.02). The same trend should apply to this system also, in which the first redox feature is the oxidation of only one of the Fe atoms making a mixed valence Fe$^{II}$-Fe$^{III}$ complex and the second is the irreversible oxidation to an Fe$^{III}$-Fe$^{III}$ dimeric species, which cleaves.

**Table 3.02: Selected Redox Potentials for 10-12 (vs. Fc/Fc$^+$.)**

<table>
<thead>
<tr>
<th></th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1^{st} E_{1/2}$</td>
<td>-0.116 V</td>
<td>0.112 V</td>
<td>-0.491 V</td>
</tr>
<tr>
<td>$2^{nd} E_{1/2}$</td>
<td>-</td>
<td>-</td>
<td>0.113 V</td>
</tr>
<tr>
<td>$i_{pa}$</td>
<td>0.466 V</td>
<td>0.830 V</td>
<td>0.656 V</td>
</tr>
<tr>
<td>$1^{st}$ Reduction</td>
<td>-1.74 V</td>
<td>-1.39 V</td>
<td>-1.89 V</td>
</tr>
</tbody>
</table>
Figure 3.01: 1mM solution cyclic voltamogram of 10 at room temperature (left). Scans taken in MeCN at 0.1V/s with a glassy carbon working electrode and platinum counter electrode. Potentials referenced to Fc$^+$/Fc and a 0.1M solution of $n$Bu$_4$N[Pf$_6$] supporting electrolyte. Variable scan rate of feature with $E_{1/2}$ at -0.116 V (right).

Figure 3.02: 1mM Cyclic voltamgram of 11 at room temperature. Scans taken in MeCN at 0.1V/s with a glassy carbon working electrode and platinum counter electrode. Potentials referenced to Fc$^+$/Fc and a 0.1M solution of $n$Bu$_4$N[Pf$_6$] supporting electrolyte.

As discussed in Chapter 2, the structure of 12 in an MeCN solution may not be the same as the solid state structure. This is reflected in the cyclic voltammogram (Figure 3.03). Unlike 10 and 11, which both have two prominent oxidation features, the CV of 12 has three notable features in this same region (Table 3.02). The first feature is quasi-reversible with an $E_{1/2}$ of -
There is a second smaller feature that is quasi-reversible at +113 mV. The final feature at +656 mV is more reversible than 10 and 11 observed at 656 mV (all vs. Fc/Fc\(^+\)). Since both \(^1\)H NMR spectroscopy and reactivity studies suggest that there may be an equilibrium between a monomer and dimer in solution, each species should have distinct redox potentials. A similar trend for the dimeric species in solution compared to 10 and 11 should be observable, wherein one feature is assigned to an oxidation of the Fe\(^{II}\)-Fe\(^{II}\)/Fe\(^{III}\)-Fe\(^{III}\) couple and a second one between the Fe\(^{II}\)-Fe\(^{III}\)/Fe\(^{III}\)-Fe\(^{III}\) couple is also expected. As such, the third redox feature observed should consist of the monomeric Fe\(^{II}\)/Fe\(^{III}\) couple.

The highest redox potential should be the second oxidation of the dimeric species (the Fe\(^{II}\)-Fe\(^{II}\)/Fe\(^{III}\)-Fe\(^{III}\) couple) and it may be more reversible than the other two complexes due to the steric factors. If the Fe\(^{III}\)-Fe\(^{III}\) dimer cleaves due to the decrease in bond lengths of the higher oxidation state then the steric constraint associated with this species could be the cause for the irreversibility. Since an imidazole is less sterically encumbered than a pyridine or quinolone this would provide reason for a more reversible feature than seen in 10 and 11. The lowest potential may represent the Fe\(^{II}\)-Fe\(^{II}\)/Fe\(^{III}\)-Fe\(^{III}\) couple. These Fe metal centers in the dimer are ligated by 2 thiolates which would lower the redox potential compared to the monomer, which is ligated by a single thiolate. Also, the 1 mM concentration is more concentrated compared to UV-Vis solutions and should favor dimer formation, which is observed with the larger peak current.
Figure 3.03: Cyclic voltamogram of 12 at room temperature. Scans taken in MeCN at 0.1V/s with a glassy carbon working electrode and platinum counter electrode. Potentials referenced to Fc+/Fc and a 0.1M solution of nBu4N[Pf6] supporting electrolyte.

The lowest redox potential of these three complexes correlates with the size of the N-heterocycle. As the conjugation of the N-heterocyclic ring increases this will stabilize and lower the energy of the empty $\pi^*$-orbital making it closer in energy match to the metal d orbitals. Since these empty $\pi^*$ orbitals have a $\pi$-bonding interaction with the Fe d-orbitals, they will interact with the orbitals that consist primarily of the $d_{xy}$, $d_{xz}$, and $d_{yz}$ which are filled and consist of the HOMO orbitals being probed by CV. The closer in energy these orbitals are to each other the more energy stabilization will be seen in the bonding orbitals, thus stabilizing the filled metal orbitals. This pattern is observed with the $E_{1/2}$ as 11, which should have the most stabilized metal orbitals, is the hardest to oxidize while 12 has the weakest $\pi$-acceptor is the easiest to oxidize.

Chemical oxidation of these complexes allowed for the spectroscopic observation of the oxidized products. Due to the dimeric structure of 11, and the reversibility of the first wave, it
should be possible to isolate a mixed-valent species by treatment with a mild oxidant. Electrochemical oxidation was performed with a 0.4 mM solution of 11 in MeCN in a 1 mm path length cell with a tin-doped indium oxide (ITO) slide as a working electrode, Pt wire counter electrode and a Ag wire reference electrode. The $E_{1/2}$ reversible couple was observed at 570 mV (vs. Ag$^+$/Ag). Holding the potential at 0.7 V (vs. Ag$^+$/Ag) results in the formation of a new species, 11$^{ox}$, with UV/Vis features at 632 nm and 507 nm (Figure 3.04). Isosbestic points at 549 nm, 452 nm, and 407 nm suggest the clean conversion of 11 to 11$^{ox}$. Complete reversibility from 11 to 11$^{ox}$ and back to 11 can be accomplished by varying the potential from 0.4-0.7 V vs. Ag$^+$/Ag and back to 0.4 V at slow scan rates. The same isosbestic points are observed during both the oxidation and reduction.

Figure 3.04: Conversion of 11 to 11$^{ox}$ through electrochemical oxidation. Isosbestic conversion suggests a single species is formed.
Chemical oxidation of 11 with tri-\((p\text{-tolyl})\)aminium hexafluorophosphate \([(p\text{-CH}_3\text{C}_6\text{H}_4)_3\text{N}]\text{[PF}_6]\), \(E^{\circ'} = 0.4\) V vs. \(\text{Fc/Fc}^+\) in MeCN) generates the same 11\(\text{ox}\) with a paramagnetic \(^1\text{H}\) NMR spectrum and an EPR spectrum consistent with an S=1/2 system (Figure 3.05). The EPR spectrum (10 K, 9.396 GHz) was simulated with EasySpin to give a rhombic signal with \(g_1 = 2.330\), \(g_2 = 2.123\) and \(g_3 = 1.932\).\(^\text{30}\) Interestingly, 11\(\text{ox}\) is unstable and converts back to 11 after a period of approximately three hours. Quantitation using the molar absorptivity of the peak at 719 nm indicates that 80% of 11 is regenerated.
Figure 3.06: Regeneration of 11 after oxidation with tri-(p-tolyl)aminium hexafluorophosphate (left). First order kinetics of the reduction of $11^{\text{ox}}$ monitored at 719 nm (right).

The linear relationship between $\ln\left(\frac{(A_t-A_\infty)}{(A_i-A_\infty)}\right)$ at 719 nm vs. time implies that the regeneration is first order ($k_{\text{obs}}(1) = 2.0 \times 10^{-4}$ s$^{-1}$) with respect to 11 (Figure 3.06). The regenerated 11 can be oxidized again to generate the same $11^{\text{ox}}$. This $11^{\text{ox}}$ will again reduce back to 11 in comparable yields (80%) with approximately the same rate ($k_{\text{obs}}(2) = 1.2 \times 10^{-4}$ s$^{-1}$) as the first reduction. This conversion back to 11 is solvent dependent as the $k_{\text{obs}}$ is two orders of magnitude slower in DCM ($k_{\text{obs}}(\text{DCM}) = 6.9 \times 10^{-4}$ s$^{-1}$) than MeCN whereas in MeOH there is no observed conversion to $11^{\text{ox}}$. The regrowth of 11 suggests there is a sacrificial reductant in solution. One possibility is that a disproportionation reaction is responsible for the regeneration of 11. If $11^{\text{ox}}$ is an Fe$^{\text{II}}$-Fe$^{\text{III}}$ mixed valent bimetallic species, a disproportionation would generate 50% Fe$^{\text{III}}$-Fe$^{\text{III}}$ and 50% Fe$^{\text{II}}$-Fe$^{\text{II}}$ (11), which is not consistent with the observed yield. However, the mixed valence, Fe$^{\text{II}}$-Fe$^{\text{III}}$, species may be a source for more than 1 e$^{-}$. The thiolates can act as a reductant and as such more than 1 e$^{-}$ could be obtained from the Fe$^{\text{II}}$-Fe$^{\text{III}}$ bimetallic species, affording a higher yield than would be predicted from a simple disproportionation.
While 10 has what seems to be a reversible 1e⁻ feature in the CV, it takes 2 equivalents of a chemical oxidant ([Fc]PF₆) to fully convert it to a new species. This new species has a feature at 520 nm at half the intensity of the initial feature at 650 nm (Figure 3.07). This new feature will shift upon the addition of small anionic substrates and suggests that it is a monomeric Fe³⁺ thiolate complex. So far attempts to crystallize this new product have been unsuccessful preventing unambiguous assignment. The observation of a visible charge transfer does suggest that this may be a thiolate ligated ferric complex similar to others that have been previously observed in the Kovacs lab.⁴¹,⁴²

![Graph of Absorbance vs. Wavelength](image-url)

**Figure 3.07**: Chemical oxidation of 10 with [Fc]PF₆ in MeCN RT.

In a similar manner the oxidation of 12 also requires 1 equivalent of chemical oxidant ([Fc⁺]PF₆) per Fe equivalent to fully convert to a new species with less intense visible charge transfer transition that is most likely due to a sulfur to metal charge transfer. Interestingly an X-ray quality single crystal was obtained from this reaction however, it had an unusual geometry (Figure 3.08). This solid-state structure maintained a dimeric core with two bis-µ-thiolates. However, unlike the reduced solid state structure which had overall C₂ symmetry, this Fe³⁺ core has C₄ᵥ symmetry, akin to 11. The four counterions support the increase by 1 oxidation state of each Fe. The Fe-S bonds decrease slightly from the reduced 12, however the Fe-N bond lengths
actually elongate slightly (Table 3.03). This is most likely due to the fact that both systems contain a low-spin Fe ion. $\text{1 e}^-$ would be removed from orbitals that are $t_{2g}$-like and do not impact bond lengths as much as the $e_g$-like orbitals, which are $\sigma^*$ in character. However, the $\text{e}^-$ could be removed from a metal orbital that has a $\pi^*$ interaction with the thiolates, which would be responsible for the contraction of the Fe-S bond lengths.

**Figure 3.08:** X-ray crystal structures of $12^{\text{ox}}$ with 50% probability ellipsoids. Counterions, cosolvents and hydrogens omitted for clarity (Left). Unlike 12, which crystalized in $C_2$ symmetry, this crystalized in a $C_{2h}$ symmetry in the solid state. Corresponding structural representations (Right).

**Table 3.03:** Selected bond lengths for $11^{\text{ox}}$.

<table>
<thead>
<tr>
<th>Metal bonds</th>
<th>Bond lengths (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)-Fe(1)</td>
<td>2.2426(16)</td>
</tr>
<tr>
<td>S(1)-Fe(1')</td>
<td>2.2406(15)</td>
</tr>
<tr>
<td>N(1)-Fe(1)</td>
<td>1.983(4)</td>
</tr>
<tr>
<td>N(3)-Fe(1)</td>
<td>1.973(5)</td>
</tr>
<tr>
<td>N(4)-Fe(1)</td>
<td>2.000(4)</td>
</tr>
<tr>
<td>N(5)-Fe(1)</td>
<td>1.979(4)</td>
</tr>
<tr>
<td><strong>Intra-Ligand bonds</strong></td>
<td></td>
</tr>
<tr>
<td>N(1)-C(5)</td>
<td>1.300(7)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.421(8)</td>
</tr>
<tr>
<td>N(4)-C(11)</td>
<td>1.295(6)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.406(7)</td>
</tr>
</tbody>
</table>
Interestingly, the intra-ligand bond lengths do not change much. Even in the oxidized complex, the bond lengths are consistent with an elongated imine, which potentially has electron density residing in the ligand orbitals. This could be due to the fact that the complex is still well suited to have significant backbonding into the imine $\pi^*$ orbital. This complex will still have electron pairs in orbitals that may interact in a backbonding fashion with the imine $\pi^*$ orbital. In addition, the planar Fe$_2$S$_2$ core may cause the thiolates to have significant electron donating ability to the metal and delocalized onto the imine $\pi^*$ orbital, resulting in bond length contraction.

A simple oxidation of this complex would seem unlikely to change the symmetry of the resulting dimeric product. It seems that the geometry and solid state structure of this complex can be controlled by the concentration of the initial metal template condensation. Doubling the concentration of the reaction to make 12 will produce a different $^1$H NMR spectrum and instead of a paramagnetic species in solution, there is primarily a diamagnetic product (Figure 3.09). This diamagnetic product has a splitting pattern that is consistent with a $C_{2h}$ symmetric structure, as in 11. For the $C_{2h}$ symmetric solution state structure, two doublets at 4.83 ppm and 4.30 ppm are associated with the 4 protons on the methylene carbons adjacent to the imine nitrogen. In addition, the methylene protons on the carbon adjacent to the sulfur are not split into two doublets, but instead are a singlet at 1.01 ppm.

However, there is a conversion from the diamagnetic $C_{2h}$ symmetric dimer to the paramagnetic 12 over time (figure 3.09). This conversion is dependent on concentration and, with the addition of an internal standard, is second order with respect to the starting dimeric
complex. A second order rate constant for reactions of this type is unusual, and further studies are ongoing in an attempt to understand the mechanism of this transformation.

Figure 3.09: Conversion of diamagnetic $C_{2h}$ 12 to the paramagnetic species overtime in anaerobic MeCN-$d_3$. *Et$_2$O internal standard.

The change between the two species can also be observed by UV-Vis spectroscopy. The diamagnetic complex has a red-shifted $\lambda_{\text{max}}$ (642 nm) with a slightly larger extinction coefficient (15000 M$^{-1}$ cm$^{-1}$) (Figure 3.10). This could be due to the better orbital overlap between the thiolate, Fe and imine $\pi^*$ orbital. Comparing the solid state structures of 11 and 12, it is observed that the bis-thiolate bis-Fe core is slightly puckered in 12 compared to the planar $C_{2h}$ 11. This will increase the orbital overlap and can be seen in the electronic absorption spectra, as 11 has the highest molar absorptivity of these complexes. Thus, the observed higher molar absorptivity in the diamagnetic 12 would be consistent with this theory. In addition the better $\pi$ overlap of the thiolate should raise the HOMO metal $d$ orbitals resulting in a lower energy charge transfer. The
diamagnetic species reacts slowly with O\textsubscript{2} while after it converts to the paramagnetic species, the same fast reactivity with O\textsubscript{2} is observed. This suggests that the \(C_{2h}\) geometry impacts the ability for these complexes to be oxidized by O\textsubscript{2}, most likely due to the lack of a vacant coordination site.

**Figure 3.10:** Electronic absorption spectrum comparing paramagnetic 12 (red) and diamagnetic 12 (blue). The charge transfer is red shifted for the diamagnetic 12. Starting Fe dimer concentration is 0.058 mM for paramagnetic 12 and 0.047 mM for diamagnetic 12.

**Negative Region of CV of 10, 11, and 12 and Ligand Based Reductions:**

One well-documented aspect of \(\alpha\)-(imino)pyridine ligands is the ability to accept an electron. These reductions are observed at negative redox potentials in the cyclic voltammograms. Weighardt has observed reduction potentials around \(-1\) V vs. Fc/Fc\textsuperscript{+} for a variety of first row metals containing \(\alpha\)-(imino)pyridine.\textsuperscript{7,33} Complexes 10-12 all contain similar features (Figure 3.11). The reduction potentials seem to have the opposite trend of the oxidation potentials with the \(E^0\) 11 > \(E^0\) 10 > \(E^0\) 12 (Table 3.02).
Figure 3.11: 1mM cyclic voltamagrams of 10-12 from -0.7 V to -2.1 V indicating the proposed ligand reduction. The current is normalized. Scans taken in MeCN at 0.1V/s with a glassy carbon working electrode and platinum counter electrode. Potentials referenced to Fc+/Fc and a 0.1M solution of nBu4N[PF6] supporting electrolyte.

The reduction will depend on the imine and the conjugated N-heterocycle. As the conjugation increases, it should lower the energy of the ligand acceptor orbital. As such, 11 has a redox potential observed at -1.39 V vs. Fc/Fc+ due to the much larger 10-atom quinoline. The 6-atom pyridine in 10 is harder to reduce at -1.74V vs. Fc/Fc+, while the smallest 5-atom imidizole, 12, has the most negative reduction potential at -1.89V vs. Fc/Fc+. It should be noted that these reduction potentials are much more negative and harder to reduce than the α-(imino)pyridine complexes that Weighardt et al. observed.6 This may be due to the overall charge of the molecule. While 10-12 are mono-cationic, Weighardt’s un-reduced complexes are dicationic suggesting it should be easier to add electrons to these molecules. Also, when looking at the specific α-(imino)pyridine, it seems that the thiolate and Fe may already be donating electron density to the π* redox orbital, suggesting it would be harder to add further reduce this moiety.
Sulfur X-ray Absorption Spectroscopy of 10, 11, and 12:

Sulfur K-edge X-ray absorption spectroscopy (XAS) has been well-established as a sensitive measure of sulfur-metal covalency.\textsuperscript{34,35} Excitation of a sulfur 1s electron to the LUMOs probes both the energy of the acceptor orbital, typically a metal 3d in the case of first-row transition metals, as well as the extent of sulfur 3p mixing into that acceptor wavefunction and can be observed in the pre-edge region.\textsuperscript{36,37} The sulfur K-edge XAS spectra of solid samples of 10-12 are shown in (Figure 3.12), and exhibit two intense transitions in the 2471-2475 eV region (Figure 3.13 top, Table 3.04). Intriguingly, the first peak, which is assigned as a pre-edge feature, differs in both energy and intensity between compounds, and similar to the electrochemical reduction potentials, is found to correlate with the size of the ligand $N$-heterocycle. Changes in the reduction potentials roughly correspond to changes in the energy of the LUMO. Thus, the similar trend observed in these data suggests that the first S XAS peak may arise from sulfur 1s to LUMO transitions (Figure 3.14).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{sulfur_xas.png}
\caption{Sulfur K-edge X-ray absorption spectra for 10-12. The spectra are normalized to the EXAFS region.}
\end{figure}
Figure 3.1: Pre-edge transitions of sulfur K-edge X-ray absorption spectra for 10-12 (top). The lower energy transition tracks well with ring size. Calculated spectra (bottom) compares favorably with the experimental data and have two transitions (2a and 2b). Visualization of the donor and acceptor states for the first transitions of 11 are shown in inset of bottom spectrum.
Table 3.04: Energy of the two transitions obtained from Sulfur K-edge XAS for 10-12.

<table>
<thead>
<tr>
<th></th>
<th>1st Transition (eV)</th>
<th>2nd Transition (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2471.5</td>
<td>2473.3</td>
</tr>
<tr>
<td>11</td>
<td>2471.2</td>
<td>2473.6</td>
</tr>
<tr>
<td>12</td>
<td>2471.7</td>
<td>2473.4</td>
</tr>
</tbody>
</table>

Figure 3.14: Correlation plot between the S K-edge energy and reduction potential showing good correlation between these two techniques probing the LUMO orbital.

Changes in the higher energy peak do not display the same trend; the peak of quinoline-ligated 11 is highest in energy. In a low-spin ferrous complex, the \( t_{2g} \) orbitals would be completely filled, however transitions into the unoccupied Fe \( e_g^* \) are anticipated. The blue-shifted peak of 11 indicates destabilization of the \( e_g^* \) relative to 10 and 12, which is consistent with 11 having the shortest iron-sulfur bond length. The donor states of this transition were found computationally to contain \( e_g^* \) character in addition to both C-S \( \sigma^* \) and some small amount of sulfur 4p character. This would then be a mixture of pre-edge and edge type transitions and will be discussed in the next section.
**Density Functional Theory Calculations:**

Density functional theory (DFT) calculations were performed to investigate the structural, spectroscopic, and electrochemical properties of these complexes. Geometry optimizations were initiated from crystallographic coordinates, using both closed-shell and broken-symmetry singlet configurations. In all cases the lowest energy closed-shell solution, with neutral ligands and $S=0$ Fe(II) ion. In particular, the distinct crystallographic metrics associated with both the Fe-ligand bond lengths and the intra-ligand bond lengths are reasonably close to the crystallographic metrics (Table 3.05), suggesting that the electronic effects responsible for these structural features are successfully reproduced by the calculations. A qualitative MO diagram for 10 and 12 is shown in Figure 3.15 with 11 having a similar diagram.

Consistent with the diamagnetic ground state, all $t_{2g}$-type orbitals are doubly occupied. The significant mixing between the Fe and S atomic orbitals is observed in the $d_{xy}$ and $d_{xz}$ orbitals as well as the S $p$-orbital, and is typical for thiolate-ligated Fe sites. Again, consistent with the conjugated portion of the ligand scaffold being $\pi$-acidic in nature, the LUMO was found to be imine $\pi^*$, with Fe $e_g$ orbitals higher in energy. Analogous electronic structures were found for 11.

**Table 3.05:** Selected DFT bond metrics for DFT 10-12. Note that the DFT 10 and DFT 11 had symmetric structures while DFT 12 had asymmetry around each Fe atom.

<table>
<thead>
<tr>
<th></th>
<th>DFT 10 (Å)</th>
<th>DFT 11 (Å)</th>
<th>DFT 12 Fe(1) (Å)</th>
<th>DFT 12 Fe(2) (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-S(1)</td>
<td>2.270</td>
<td>2.243</td>
<td>2.323</td>
<td>2.320</td>
</tr>
<tr>
<td>Fe-S(2)</td>
<td>2.283</td>
<td>2.243</td>
<td>2.322</td>
<td>2.328</td>
</tr>
<tr>
<td>Fe-N$_{\text{heterocycle}}$(1)</td>
<td>1.957</td>
<td>1.937</td>
<td>1.982</td>
<td>1.980</td>
</tr>
<tr>
<td>Fe-N$_{\text{heterocycle}}$(2)</td>
<td>1.962</td>
<td>1.936</td>
<td>1.990</td>
<td>1.982</td>
</tr>
<tr>
<td>Fe-N$_{\text{imine}}$(1)</td>
<td>1.900</td>
<td>1.925</td>
<td>1.949</td>
<td>1.956</td>
</tr>
<tr>
<td>Fe-N$_{\text{imine}}$(1)</td>
<td>1.890</td>
<td>1.927</td>
<td>1.954</td>
<td>1.960</td>
</tr>
<tr>
<td>N$_{\text{imine}}$(1)-C</td>
<td>1.310</td>
<td>1.313</td>
<td>1.293</td>
<td>1.293</td>
</tr>
<tr>
<td>N$_{\text{imine}}$(2)-C</td>
<td>1.306</td>
<td>1.313</td>
<td>1.290</td>
<td>1.290</td>
</tr>
<tr>
<td>C-C</td>
<td>1.432</td>
<td>1.439</td>
<td>1.426</td>
<td>1.428</td>
</tr>
<tr>
<td>N$_{\text{imine}}$(2)-C</td>
<td>1.306</td>
<td>1.313</td>
<td>1.290</td>
<td>1.290</td>
</tr>
<tr>
<td>C-C</td>
<td>1.434</td>
<td>1.439</td>
<td>1.429</td>
<td>1.430</td>
</tr>
</tbody>
</table>
Figure 3.15: DFT calculated molecular orbital for 10 (Left) and 12 (right) with the contributions from each atomic orbital present on the sides. 11 has a very similar electronic structure and all three optimize to a diamagnetic Fe metal center. The LUMO orbitals seem to be composed primarily of ligand based redox orbitals.

These results are consistent with the correlations between LUMO energy and the ring size of the N-heterocycle observed in the electrochemical reduction potentials and the first sulfur XAS transitions. While this energetic ordering of the molecular orbitals is not surprising in light of the abundant literature precedent in this field, the apparent involvement of the thiolate in these redox-active orbitals is unusual. In particular, strong optical and X-ray absorption transitions imply substantial orbital communication between the sulfur 3p and ligand π* orbitals. The nature of the underlying electronic transitions in both absorption spectroscopies was investigated using TD-DFT calculations.
The putative charge-transfer nature of the transitions in the electronic absorption spectra prompted the use of the range-separated hybrid density functional CAM-B3LYP for these calculations. As shown in Figure 3.16, the TD-DFT-calculated electronic absorption spectra of 10 and 11 both have intense transitions in the visible region. The relative energies and intensities are in good agreement, though the absolute transition energies are overestimated by approximately 200 nm when compared to the experimental electronic absorption spectra; a well-known shortcoming of TD-DFT.\textsuperscript{38} However, the nature of these transitions can be examined with reasonable fidelity via the transition difference densities. For both complexes, the intense visible CT transitions are found to have donors and acceptors that are mixed Fe/S and imine π* in character, respectively. The iron 3d-orbitals thus appear to mediate charge transfer from the thiolate 3p to the formally orthogonal ligand π* LUMO.

Figure 3.16: CAM-B3LYP TD-DFT computed electronic absorption spectra for 10 and 11 (bottom) along with the difference states diagrams of these transitions (top). Donor states in teal blue and acceptor states in purple.
As discussed previously, sulfur K-edge XAS provides a more focused probe of the thiolate bonding in these complexes. Figure 3.13 bottom shows the TD-DFT-calculated S K-edge XAS spectra of 10-12. Comparison with the experimental spectra above reveals that the energetic trends observed in both peaks are successfully reproduced. Examination of the transition difference densities reveals that the lower-energy feature indeed corresponds to sulfur 1s → ligand π* LUMO transitions, as proposed above. The higher-energy feature in the sulfur XAS spectra of 10-12 is found to be due to transitions to the unoccupied Fe e_g-type orbitals but does have mixing of the C-S σ* and even sulfur 4p character as shown in the full assignment stick spectra for all three complexes (Figure 3.17). This would make the peak a mixture of both edge and pre-edge features. While the TD-DFT calculations do not reproduce the intensity trend of the first pre-edge peak, the dramatic charge-transfer nature of these transitions make them subject to another known methodological shortcoming of TD-DFT. The experimental intensities provide clear evidence of decreased sulfur 3p / ligand π* LUMO mixing within the series, with 11 > 10 > 12. Importantly, the intensities of the higher-energy transitions are relatively unchanged compared to the variations in the low-energy pre-edge peak. This implies that the covalency of the Fe-S bonds is mostly constant for all three complexes, and that the changes in sulfur 3p / ligand π* mixing are not due to decreased iron-thiolate interactions. Instead, thiolate π donation into the LUMO ligand π* could be mediated by backbonding of the Fe t_{2g}-type orbitals, which presumably changes as a function of ring size and LUMO energy.
Figure 3.17: Full assignment of the second transition in sulfur K-edge XAS for 10-12. Stick spectra shows contribution of all acceptor orbitals and indicates the complex mixture of transitions for the higher energy peak including $e_g^*$, C-S $\sigma^*$ and even sulfur 4p character.

**Role of the Thiolate and an Observation of a cis “Push Effect”:**

The direct involvement of thiolate-based electron density in promoting the activation of the ligand $\pi^*$ orbitals in 10-12 is shown by the S K-edge XAS data, wherein electronic transitions from the localized thiolate 1s orbital into the LUMO $\pi^*$ can be observed. This transition intensity is engendered by the presence of thiolate 3p character in the unoccupied $\pi^*$ orbitals; thus ligand $\pi^*$ character is expected in the occupied thiolate 3p orbitals. The absence of direct thiolate-$\pi^*$ bonds predicates this interaction on orbital mixing mediated by the metal 3d orbitals of appropriate symmetry. This is akin to the proposed “push effect” in cytochrome P450, where electronic donation from the thiolate orbitals into the iron 3d populates the O-O $\sigma^*$ orbital of the ferric hydroperoxo compound 0.\textsuperscript{39,40} Notably, while this thiolate $\pi$ push effect in cytochrome P450 activates the trans ligand, the 4-fold symmetry of the relevant $t_{2g}$ orbital should enable similar activation of cis ligands, as observed in the present system.
Assignment of the first feature in the S K-edge XAS spectra of 10-12 is supported by the correlation of the transition energy and intensity with ring size. These data suggest that energies of the ligand-based redox-active orbitals can be effectively tuned via modulation of the size of the conjugated π system. Given this interpretation, the relative energies of these same LUMO orbitals can also be probed by electrochemical reduction. In fact, quantitative comparison of the first reduction potentials of 10-12 with the corresponding first transition energies, from S K-edge XAS, and the LUMO (α-imino)N-heterocycle orbital energies, obtained from the DFT calculations, are in excellent agreement (Figure 3.18). An important aspect of this class of base metal catalysts is the ability to mitigate electronic demands at the metal via facile redox communication with ligand-based orbitals. Therefore, tuning the energies of these ligand-based orbitals through altering the size of the ligand π system may present an effective design strategy.

Figure 3.18: DFT calculated energy levels overlaid with normalized S XAS and the 1st reduction potential of 10-12.

Additionally, Betley and coworkers have shown that communication between ligand and metal orbitals is predicated on effective orbital overlap.\textsuperscript{41,42} Thus, modulating the extent of
metal-ligand redox orbital coupling may provide a means to fine tune the cooperativity of the molecular redox orbitals. The intensities of electronic transitions provide an effective means of quantifying orbital coupling. As observed in the S K-edge XAS spectra of 10-12, diminished sulfur 1s → LUMO π* transition intensity is found to correlate with decreasing ring size. It should be noted that the intensities of the UV-visible charge-transfer transitions of 10 and 11 display the same trend, however the ambiguous solution-state speciation of 12 precludes similar comparison. While it may not be surprising that an improved orbital energetic match leads to better overlap, the importance of this coupling for effective redox cooperativity should not be overlooked.

$^{57}$Fe Mössbauer Spectroscopy of 10, 11 and 12:

The local electronic structure of the Fe atoms was also investigated by $^{57}$Fe Mössbauer spectroscopy.$^{43,44}$ The zero-field $^{57}$Fe Mössbauer spectra of 10 is shown in Figure 3.19 while, 11 and 12 are shown in Figure 3.20 and the calculated and experimental parameters are reported in Table 3.06. The isomer shift δ (the midpoint of the quadrupole doublet) is primarily sensitive to perturbations in Fe 4s electron density $\rho_0$ at the Fe nucleus, which can be modulated by the 3d orbital population due to shielding. While the 3d$^6$ electron count of Fe(II) ions often results in larger isomer shifts than those observed for 10-12, values in the range $\delta = 0.3 - 0.45$ mm/s are typical for low-spin Fe(II) hemes.$^{45}$ The π-acidic nature of the heme prosthetic group promotes π backbonding, which lowers the effective 3d orbital population. As discussed above, the α-(imino)-N-heterocycle moieties in 10-12 also act as π backbonding acceptors. Importantly, the extent of π backbonding can be expected to manifest in the value of $\delta$, with decreased backbonding leading to more electron-rich 3d orbitals and a high isomer shift. Thus, π
backbonding appears to be smallest in 12 ($\delta = 0.41$ mm/s) and comparable in 10 and 11 (both $\delta = 0.36$ mm/s). While the former conclusion is in good agreement with the previous spectroscopic data, 11 could be anticipated to have more $\pi$ backbonding than 10, based on the sulfur K-edge XAS spectra and TD-DFT calculations. However, just as $\pi$-accepting ligands can depopulate the $3d$ orbitals, $\pi$-donating ligands, like thiolates, can increase the effective $3d$ orbital population.

Comparison of the metrical parameters of 10 and 11 indeed reveals that the Fe-S bonds in 11 are shorter; indicative of increased $\pi$ donation. Thus, the thiolate ligands in 11 compensate for the increased $\pi$-backbonding through more significant $\pi$ donation, leading to the identical isomer shifts of 11 and 12.

Figure 3.19: Mössbauer spectrum of 10. Mössbauer spectra were taken in the solid state.
Figure 3.20: Mössbauer spectra of 11 (bottom) and 12 (top). Isomer shift is consistent with a π-acidic ligand framework low-spin Fe(II). Mössbauer spectra were taken in the solid state.

Table 3.06: Mössbauer parameters for 10-12 and the computed parameters.

<table>
<thead>
<tr>
<th></th>
<th>Isomer shift (δ) (mm/s)</th>
<th>Quadrupole Splitting (ΔE_q) (mm/s)</th>
<th>DFT Isomer shift (δ) (mm/s)</th>
<th>DFT Quadrupole Splitting (ΔE_q) (mm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.36</td>
<td>0.87</td>
<td>0.22</td>
<td>1.07</td>
</tr>
<tr>
<td>11</td>
<td>0.36</td>
<td>0.85</td>
<td>0.22</td>
<td>-1.09</td>
</tr>
<tr>
<td>12</td>
<td>0.41</td>
<td>0.38</td>
<td>0.39</td>
<td>0.82</td>
</tr>
</tbody>
</table>

While δ, is sensitive to the electron density at the $^{57}\text{Fe}$ nucleus, the quadrupole splitting $\Delta E_Q$ provides a measure of the asymmetry of the electric field gradient (EFG) at the nucleus. In the limit of crystal field theory, an $S=0$ d$^6$ Fe ion has a spherically symmetric EFG that should
result in the coalescence of the two peaks of the quadrupole doublet. However, the π-donating thiolate and π-accepting α-(imino)-N-heterocycle should perturb the effective d-orbital populations and the symmetry of the EFG. As with the isomer shift, the quadrupole splitting parameter of 12 ($\Delta E_Q = 0.38$ mm/s) is smaller than that of 10 ($\Delta E_Q = 0.87$) and 11 ($\Delta E_Q = 0.85$). This is again consistent with decreased π-backbonding in 12. Interestingly, the quadrupole splitting of 11 is smaller than that of 10. While the 0.02 mm/s difference is perhaps not so significant, it is contrary to the expected change resulting from increased π-backbonding in 11.

It should be noted, that in fact, the zero-field $^{57}$Fe Mössbauer experiment measures the absolute value of $\Delta E_Q$, despite the quadrupole splitting being a signed quantity. The quadrupole splitting arises from the interaction of the $I=3/2$ nuclear excited state quadrupole moment with the EFG tensor. The main component of the EFG tensor, $V_{zz}$, is influenced by both the bonding orbitals of the ligands and the effective d-orbital population. The competing contributions from these two sources, modulated by covalency and π backbonding, can determine the sign of $V_{zz}$ as detailed in a recent study of Fe-N$_2$ complexes.$^{46}$

The DFT-calculated Mössbauer parameters are given in Table 3.06, and show excellent agreement with the experimentally observed trends. Interestingly, the calculated $\Delta E_Q$ of complexes 10 and 12 are positive, while that of 11 is negative. Importantly, the magnitudes of $\Delta E_Q$ for 10 and 11 are comparable, consistent with experiment.$^{16}$ The calculations thus suggest that in complexes 10 and 12, the dominant contribution to EFG asymmetry is from the covalent ligand orbitals (the thiolates), while in 11 strong perturbations to the local d shell from π backbonding invert the sign of $\Delta E_Q$. Indeed, the unique geometry of 11 (vide supra) provides excellent rationale for this conclusion. The seemingly activated imine bonds of all three complexes suggest that the imine π* serves as a π backbonding acceptor. The imine ligands are
positioned *cis* to each other in the $C_2$ geometries of 10 and 12, and thus $\pi$ backbonding occurs from two distinct $t_{2g}$-type 3$d$ orbitals (along two axes). In contrast, they are in fact *trans* in the $C_{2v}$ geometry of 11, and so only a single 3$d$ orbital has the correct symmetry to $\pi$ backbond. This “double” depopulation of one of the $t_{2g}$-type 3$d$ orbitals along a single axis engenders significant asymmetry to the local 3$d$ shell; so much so that it becomes the stronger contributor to $V_{zz}$ and inverts the sign of $\Delta E_Q$. In summary, the $^{57}$Fe Mössbauer data and accompanying DFT calculations suggest that the extent of $\pi$ backbonding correlates with the size of the $N$-heterocycle, as proposed above, and evidence a compensatory contraction of the Fe-S bonds in 11 due to stronger $\pi$ backbonding. Furthermore, the unique geometry of 11 inverts the sign of the quadrupole splitting, and leads to an observed $|\Delta E_Q|$ that is coincidentally similar in magnitude to 10.

**Conclusions:**

The combined spectroscopic, electrochemical and computational experiments provide insight into the complicated electronic pictures of these complexes. Each of these complexes redox orbitals are convoluted by the inclusion of the redox-active $\alpha$-(imino)-$N$-heterocycle and sulfur as well as the metal $d$-orbitals. The solid-state structure displays a lengthening of the imine and C-C bond lengths which suggests that electron density is populating that ligand orbital. The reduction potentials at -1.38 to -1.89 V for 10-12 suggest that the LUMO orbital is indeed ligand based, as observed with other literature complexes. The ability of the thiolate to push electron density was one potential reason for the bond lengthening and the observation of a second peak in the sulfur K-edge XAS suggests that there is some degree of covalency between
the two ligand based redox orbitals. The observed pattern of increase in the LUMO orbitals energy tracks well with the ligand reduction potentials, the S K-edge XAS and the DFT energies.

The potential ability of the thiolate to modulate the electron density around the metal and help push electron density into ligand redox orbitals may prove beneficial for the design of future catalysts incorporating redox-active ligand frameworks. These organic redox orbitals are designed to limit the amount of electronic demands located at the 1st row metal centers aiding them in performing sequential 2e⁻ redox reactions. The thiolate may increase the ability of these complexes to promote the movement of electron density from the metal center. Additionally it is shown that the size of the N-heterocycle clearly effects the LUMO of these redox orbitals. As such, larger ring sizes will lower the energy of these LUMO’s making them a better match with the orbitals of the metal center. Matching the ligand orbitals with the metal orbitals can help facilitate the transfer of electron density between the two redox centers.
Notes to Chapter 3


Chapter 4.

Electronic and Geometric Factors Influencing the Structural Metrics of $\alpha$-(Imino)-Imidizoles.

Portions of this chapter have been adapted from: Leipzig, B. K.; Rees, J. A.; Nyrov, A.; Theisen, R.; Flowers, S. E.; Kaminsky, W.; DeBeer, S.; Kovacs, J. A. In Preparation.¹
**Introduction:**

Redox-active ligands will have bond lengths that elongate and shorten due to the amount of electron density within the molecular orbitals. The structural and spectroscopic data for 10-12 suggests there is unusual electronic activation of the ligand framework that may be, in part, due to the effect of the thiolate and the low-spin state of the ferrous metal center. The bond lengths are suggestive either of significant π-backbonding or a reduction of the imine backbone. Preparation of a number of complexes with this ligand environment can help highlight the major factors that influence the redistribution of electron density.

A reduction could be caused by an electron transfer from the metal redox orbital to the ligand π*-orbital. For this to occur the ligand π* orbitals were to fall lower in energy than the filled metal orbitals. The incorporation of a coordinated thiolate could buffer the electron density on the metal, lower the redox potential and, as a π-donor, raise the energy of the metal t_{2g}-like orbitals. Alternatively, backbonding from the metal to the imine π* orbital has been observed previously and is possible in this system. This will be heavily influenced by the electronic arrangement of the metal’s d orbital electrons. Additionally, the thiolate could also play a significant role and push electron density into the metal d orbitals, which in turn donate onto the π-accepting imine bond. This would be akin to the “push” effect in cytochrome P450.

Altering the electronic configuration and the number of electron pair’s was accomplished by oxidation reactions, and the sole crystalized example of this, 12^ox, showed no change in the intra-ligand bond lengths, potentially indicating the influence of the coordinating thiolates. To assess the importance of the configuration, different metal complexes were synthesized. The effect of the thiolate was investigated with two complexes that do not incorporate a coordinated thiolate.
Experimental:

General Considerations: DMSO-$d_6$ and CDCl$_3$ were purchased from Cambridge Isotope Labs and used as received. EtOH was purchased from Decon and degassed prior to use. Et$_2$O was purchased from Fischer Scientific and purified using solvent purification columns housed in a custom stainless steel cabinet and dispensed by a stainless steel Schlenk-line (GlassContour). All other solvents were purchased from Sigma Aldrich. MeOH, MeCN and CH$_2$Cl$_2$ were dried and distilled prior to use. A 48% aqueous solution of hydrobromic acid was purchased from Alfa-Aesar and used as received. Ammonia was obtained from Praxair while all other material was purchased and used as received from Sigma Aldrich.

$^1$H NMR spectra were obtained on a Bruker AV300, AV301, DRX499, or AV500. Chemical shifts are listed in parts per million and were reported relative the residual protio solvent. UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer equipped with a fiber optic cable connected to a “dip” ATR probe (C-technologies). A custom-built two neck solution sample holder equipped with a threaded glass connector was sized specifically to fit the “dip” probe. Electrospray ionization mass spectrometry (ESI-MS) was preformed on a Bruker Esquire LC-Ion Trap. Cyclic voltammograms (CV were recorded in MeCN (0.1M $^+$Bu$_4$N[Pf$_6$] supporting electrolyte) on a PAR 263A potentiostat or a CHI 600E electrochemical work station utilizing a classy carbon working electrode, platinum auxiliary electrode and an Ag$^+/AgNO_3$ reference electrode. X-ray crystallographic data was recorded on a Bruker APEX II single crystal X-ray diffractometer using Mo-radiation. Elemental analysis were preformed by Atlantic Microlab, Inc. Norcross, Ga. All manipulations were performed using Schlenk techniques or under a N$_2$ atmosphere in a glovebox.
Synthesis of [(Co$^{II}$)(Tame-$N_2$Sim$_2$)$_2$](PF$_6$)$_2$ (13). 9 (0.2 g, 1 mmol) was added to a vial containing a stirred solution of sodium methoxide (0.156 g, 3 mmol) in methanol (10 mL). 1-methyl-2-imidizolecarboxaldehyde (0.21 g, 2 mmol) was then added and the stirred suspension was cooled to -40°C. In a separate vial cobalt (II) chloride dissolved in MeOH (5mL) and cooled to -40°C. The cobalt solution was then slowly added to the organic solution. This was stirred for 1h, at which time sodium hexafluorophosphate (0.168 g, 1 mmol) was added. This solution was stirred overnight at which time an orange solid had precipitated. The MeOH was removed in vacuo and the solid was dissolved in MeCN (2 mL), and filtered through celite. The MeCN was removed to a minimal volume and layered with Et$_2$O (5 mL) to isolated a red powder in 93% yield (265 mg). A slow diffusion of MeCN:Et$_2$O X-ray quality crystals $\lambda_{\text{max}}$ (nm) ($\varepsilon$ (M$^{-1}$cm$^{-1}$)): (MeCN): 512 sh (654). Magnetic moment (solution, MeCN, 298K) 3.98µB/Co ESI-MS: expected m/z for [C$_{30}$H$_{43}$N$_{12}$S$_2$Co$_2$]$^{2+}$ = 376.1, found m/z = 376.2. Elemental Analysis for C$_{30}$H$_{43}$F$_{12}$N$_{12}$P$_2$S$_2$Co$_2$ Calculated: C, 34.56; H, 4.06; N, 16.12. Found: C, 34.41; H, 4.04; N; 15.95.

Synthesis of [(Co$^{III}$)(Tame-$N_2$Sim$_2$)$_2$](PF$_6$)$_4$ (13ox). 13 (55mg , 0.05 mmol) was dissolved in MeCN (5 mL). To this, stoichiometric amounts [Fc]PF$_6$ (35mg, 0.1mmol) per cobalt was added. This solution was allowed to stir for 15h, after which the volatiles were evaporated. The resulting red solid was washed with Et$_2$O (3 x 4 mL) to yield a yellow filtrate containing the Fc byproduct. The red precipitate was once again dissolved in MeCN (1 mL), and layered with Et$_2$O (3 mL) and cooled in a freezer (-40°C). Red crystals were obtained in 71% yield (50 mg). $^1$H NMR (300 MHz, MeCN-$d_3$) δ 8.62 (s, 1H), 8.97 (s, 1H) 8.35, (S, 1H), 7.57 (s, 1H), 7.43 (s,
1H), 7.10 (s, 1H), 6.48 (s, 1H) 4.08 (s, 6H), 3.76 (m, 2H), 3.51 (m, 2H), 1.25 (s, 3H), 1.05(d, \(J = 15\) Hz, 1H), 0.91 (d, \(J = 15\) Hz, 1H).

**Synthesis of Thioether-ligated \([\text{Fe}^{II}(\text{tame-}(\text{N}_2\text{S}^{\text{Bz}}(\text{MeIm})_2(\text{MeCN})))](\text{PF}_6)_2\) (14).** 6 (0.1 g, 0.44 mmol) was added to a vial and dissolved in MeOH (8 mL). 1-methyl-2-imidizolecarboxaldehyde (0.1 g, 0.88 mmol) was then added and the solution was cooled to -40° C. In a separate vial iron (II) chloride (0.055 g, 0.44 mmol) was dissolved in MeOH (3 mL) and cooled to -40° C. The iron solution was then slowly added to the organic solution. Immediately, the solution became red. This was stirred for 1h at which time sodium hexafluorophosphate (0.148 g, 0.88 mmol) was added. The MeOH was removed *in vacuo* and the solid was dissolved in MeCN (2 mL), and filtered through celite. The red solution was concentrated to a minimal volume (2ml) upon which Et₂O (5 mL) was layered to isolate a deep red solid in 45% yield (150 mg). \(\lambda_{\text{max}}\) (nm) (\(\varepsilon\) (M⁻¹cm⁻¹)): (MeCN): 512 (2850). Magnetic moment (solution, MeCN, 298K) 5.04µB

**Elemental Analysis for C_{24}H_{31}F_{12}N_{7}P_{2}SFe** Calculated: C, 36.24; H, 3.93; N, 12.33 Found: C, 35.74; H, 3.97; N; 12.41.

**Synthesis of \([\text{Mn}^{II}(\text{tame-}(\text{N}_2\text{S}^{\text{MeIm}})_2\text{Cl}]) (\text{PF}_6)\) (15).** 9 (0.2 g, 1 mmol) was added to a vial containing a stirred solution of sodium methoxide (0.156 g, 3 mmol) in MeOH (10 mL). 1-methyl-2-imidizolecarboxaldehyde (0.21 g, 2 mmol) was then added and the stirred suspension was cooled to -40° C. In a separate vial manganese (II) chloride dissolved in MeOH (5 mL) and cooled to -40° C. The manganese solution was then slowly added to the organic solution. This was stirred for 1h, at which time sodium hexafluorophosphate (0.168 g, 1 mmol) was added. This solution was stirred for 15h, at which time a white solid precipitated. The MeOH was
removed *in vacuo* and the solid was dissolved in MeCN (5 mL), and filtered through celite. This was reduced to 1 ml, layered with Et$_2$O (3 ml) and cooled to -40° C for 48h. White crystals were isolated in 70% yield (193 mg). A slow diffusion of MeCN:Et$_2$O yielded X-ray quality crystals.

ESI-MS: expected $m/z$ for \([C_{30}H_{43}N_6SMn]^{2+}\) = 372.1, found $m/z$ = 372.1.

**X-Ray Crystallographic Structure Determination**

A red piece, 13, measuring 0.15 x 0.05 x 0.05 mm$^3$ was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame for all sets. The scan width was 0.5°. Data collection was 99.9% complete to 25° in θ. A total of 107396 reflections were collected covering the indices, h = -15 to 15, k = -18 to 18, l = -25 to 25. 15125 reflections were symmetry independent and the $R_{int} = 0.0643$ indicated that the data was of better than average quality (0.07). Indexing and unit cell refinement indicated a triclinic lattice. The space group was found to be P 1 (No. 2).

A clear red prism, 13$^{95}$, measuring 0.12 x 0.03 x 0.03 mm$^3$ was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 240 seconds per frame for all sets. The scan width was 0.5°. Data collection was 99.8% complete to 25° in θ. A total of 34803 reflections were collected covering the indices, h = -15 to 15, k = -22 to 22, l = -19 to 27. 10456 reflections were symmetry independent and the $R_{int} = 0.2136$ indicated that the data was of less than average quality (0.07). Indexing and unit cell refinement indicated a primitive orthorhombic lattice. The space group was found to be P 21 21 21 (No.19).
A purple block, 14, measuring 0.08 x 0.03 x 0.03 mm$^3$ was mounted on a loop with oil. Data was collected at -173$^\circ$C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 30 seconds per frame for all sets. The scan width was 0.5$^\circ$. Data collection was 99.2% complete to 25$^\circ$ in $\theta$. A total of 21050 reflections were collected covering the indices, h = -13 to 13, k = -15 to 15, l = -15 to 15. 6841 reflections were symmetry independent and the $R_{int} = 0.0820$ indicated that the data was of average quality. Indexing and unit cell refinement indicated a triclinic lattice. The space group was found to be $P\bar{1}$ (No. 2).

A colorless prism, 15, measuring 0.03 x 0.01 x 0.01 mm$^3$ was mounted on a loop with oil. Data was collected at -173$^\circ$C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 240 seconds per frame for all sets. The scan width was 1.0$^\circ$. Data collection was 99.3% complete to 25$^\circ$ in $\theta$. A total of 13868 reflections were collected covering the indices, h = -9 to 9, k = -13 to 13, l = -17 to 17. 4521 reflections were symmetry independent and the $R_{int} = 0.1009$ indicated that the data was appropriate. Indexing and unit cell refinement indicated a triclinic lattice. The space group was found to be $P\bar{1}$ (No.2).

All data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker.$^8$ All solution by direct methods (SHELXS, SIR97$^{9,10}$) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97.$^{11,12}$ Scattering factors are from Waasmair and Kirfel.$^{13}$ Hydrogen atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters $U_{eq}$ were fixed such that they were 1.2$U_{eq}$ of their parent atom $U_{eq}$ for CH's
and $1.5U_{eq}$ of their parent atom $U_{eq}$ in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares. Crystal Data is presented in Table 4.01.

**Table 4.01**: Crystallographic data for 13-15 and 13°x.

<table>
<thead>
<tr>
<th></th>
<th>13</th>
<th>13°x</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td>C$<em>{30}$H$</em>{42}$Co$<em>2$F$</em>{12}$N$_{12}$P$_2$S$_2$</td>
<td>C$<em>{30}$H$</em>{42}$Co$<em>2$F$</em>{24}$N$_{12}$P$_4$S$_2$</td>
<td>C$<em>{26}$H$</em>{34}$F$_{12}$FeN$_8$PS</td>
<td>C$<em>{17}$H$</em>{25}$ClF$_6$MnN$_7$PS</td>
</tr>
<tr>
<td><strong>MW (g/mol)</strong></td>
<td>1165.84</td>
<td>1470.93</td>
<td>836.46</td>
<td>594.86</td>
</tr>
<tr>
<td><strong>Crystal System</strong></td>
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<td>Orthorhombic</td>
<td>Triclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td><strong>Space Group</strong></td>
<td>P-1</td>
<td>P 21 21 21</td>
<td>P-1</td>
<td>P-1</td>
</tr>
<tr>
<td><strong>Unit Cell Dimensions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a (Å)</td>
<td>10.9597(3)</td>
<td>13.1337(12)</td>
<td>11.2287(11)</td>
<td>7.8232(12)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>13.0171(4)</td>
<td>18.726(2)</td>
<td>12.2948(13)</td>
<td>11.4274(16)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>17.9975(5)</td>
<td>22.973(3)</td>
<td>12.7375(14)</td>
<td>14.851(2)</td>
</tr>
<tr>
<td>α (deg)</td>
<td>93.948(2)</td>
<td>90</td>
<td>88.369(5)</td>
<td>70.691(9)</td>
</tr>
<tr>
<td>β (deg)</td>
<td>102.099(2)</td>
<td>90</td>
<td>74.465(5)</td>
<td>88.291(9)</td>
</tr>
<tr>
<td>γ (deg)</td>
<td>95.177(2)</td>
<td>90</td>
<td>84.959(5)</td>
<td>82.748(10)</td>
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<tr>
<td><strong>Final R indices</strong></td>
<td>0.0374</td>
<td>0.0712</td>
<td>0.0598</td>
<td>0.0602</td>
</tr>
<tr>
<td><strong>R indices (all Data)</strong></td>
<td>0.0657</td>
<td>0.2034</td>
<td>0.1222</td>
<td>0.1268</td>
</tr>
</tbody>
</table>

**Results and Discussion:**

**Cobalt Derivative of 12:**

Variation of the d-electron count was accomplished by isolating a cobalt derivative of 12. This Co complex, 13, was synthesized in the same Schiff base condensation as 12 (Chapter 2) and shown to form a similar $C_2$ symmetric dimer in the solid state (Figure 4.01). The Co-ligand bond lengths are consistent with a high-spin Co (II) metal ion. Unlike the Fe complexes, that have a very uniform bis-µ-thiolate core, 13 does not. One Co-S bond length is much shorter (2.393(1) Å) than the other Co-S bond (2.465(1) Å). This lengthening of the bridging Co may allow more facile cleavage of this dimeric structure. In addition to the asymmetry of the bond
lengths, the Co$_2$S$_2$ core is much more puckered as observed by a much larger calculated least squares plane fit. The distance between the M-M and S-S centroids is 0.72 Å for 13 whereas it is 0.34 Å for the Fe$_2$S$_2$ core of 12 (Table 4.02).

**Figure 4.01:** X-ray crystal structures of 13 with 50% probability ellipsoids. Counterions, cosolvents and hydrogens omitted for clarity (Left). Corresponding structural representations (Right).

**Table 4.02:** Selected Metal-ligand bond lengths and metrical parameters for 13 and 13$^{ox}$.

<table>
<thead>
<tr>
<th>Bonds</th>
<th>13</th>
<th>13$^{ox}$</th>
</tr>
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<tbody>
<tr>
<td>Co-S(1)</td>
<td>2.393(1)</td>
<td>2.229(3)</td>
</tr>
<tr>
<td>Co-S(2)</td>
<td>2.465(1)</td>
<td>2.232(3)</td>
</tr>
<tr>
<td>Co-N(1)</td>
<td>2.162(2)</td>
<td>1.903(8)</td>
</tr>
<tr>
<td>Co-N(2)</td>
<td>2.121(2)</td>
<td></td>
</tr>
<tr>
<td>Co(1)-N(3)</td>
<td>-</td>
<td>1.934(8)</td>
</tr>
<tr>
<td>Co(1)-N(4)</td>
<td>2.145(2)</td>
<td></td>
</tr>
<tr>
<td>Co(1)-N(5)</td>
<td>2.141(2)</td>
<td>1.934(8)</td>
</tr>
<tr>
<td>Co(1)-N(6)</td>
<td>-</td>
<td>1.898(8)</td>
</tr>
<tr>
<td>Co(2)-S(1)</td>
<td>2.462(1)</td>
<td>2.225(3)</td>
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<tr>
<td>Co(2)-S(2)</td>
<td>2.391(1)</td>
<td>2.226(3)</td>
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<tr>
<td>Co(2)-N(7)</td>
<td>2.123(2)</td>
<td>1.891(9)</td>
</tr>
<tr>
<td>Co(2)-N(8)</td>
<td>2.156(2)</td>
<td></td>
</tr>
<tr>
<td>Co(2)-N(9)</td>
<td>-</td>
<td>1.953(7)</td>
</tr>
<tr>
<td>Co(2)-N(10)</td>
<td>2.209(2)</td>
<td></td>
</tr>
<tr>
<td>Co(2)-N(11)</td>
<td>2.121(2)</td>
<td>1.915(8)</td>
</tr>
<tr>
<td>Co(2)-N(12)</td>
<td>-</td>
<td>1.924(8)</td>
</tr>
</tbody>
</table>

Least square fit Co$_2$S$_2$ 0.34 0.15
A solution state magnetic moment of 3.98 BM would be consistent with a high spin Co(II) metal ion and be indicative of either a monomeric species, where the bridging thiolates are cleaved in solution, or dimeric species, with no coupling through this puckered core. The high-spin state of the Co complex seems to influence the intra-ligand bond lengths. Unlike Fe complexes 10-12, this Co complex has a very short average imine bond length of 1.276 Å (Table 4.03). This contraction of the imine bond may, in part, be a result of the change in electronic configuration and will be discussed further in this chapter. While the Fe complexes have intense electronic absorption features in the visible region, 13 has only a small shoulder at 512 nm with a much smaller extinction coefficient of around 600 M⁻¹cm⁻¹ (Figure 4.02). If mixing of the sulfur contributes to the large intensity seen in complexes 10-12, then the weakening of the orbital overlap by the distorted geometry of the 13 could cause the intensity to decrease significantly.

Table 4.03: Intra-ligand bond lengths for 13 and 13ox.

<table>
<thead>
<tr>
<th></th>
<th>13 (Å)</th>
<th>13⁰x (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(5)</td>
<td>1.275(2)</td>
<td>1.277(10)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.447(3)</td>
<td>1.458(13)</td>
</tr>
<tr>
<td>N(4)-C(11)</td>
<td>1.274(2)</td>
<td>1.293(12)</td>
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<tr>
<td>C(11)-C(12)</td>
<td>1.449(3)</td>
<td>1.431(14)</td>
</tr>
<tr>
<td>N(7)-C(20)</td>
<td>1.283(2)</td>
<td>1.316(12)</td>
</tr>
<tr>
<td>C(20)-C(21)</td>
<td>1.442(3)</td>
<td>1.427(13)</td>
</tr>
<tr>
<td>N(10)-C(26)</td>
<td>1.272(2)</td>
<td>1.309(11)</td>
</tr>
<tr>
<td>C(26)-C(27)</td>
<td>1.451(3)</td>
<td>1.373(12)</td>
</tr>
</tbody>
</table>
Figure 4.02: Electronic absorption of 13 in MeCN at RT.

Although there could be monomeric species in solution, the electrochemical CV shows two reversible features at $E_{1/2}=-466\text{mV}$ and $E_{1/2}=-824\text{mV}$ vs. Fc/Fc$^+$ (Figure 4.03). Since there are two reversible features, one possibility exists that the dimer is present in solution. The first oxidation would form a mixed valent Co$^{II}$-Co$^{III}$ species with the second oxidation forming a Co$^{III}$-Co$^{III}$ dimeric species. Since there is no geometric change to this dimeric species upon oxidation, a reversible feature would be expected with each oxidation at different potentials. A monomeric Co(II) species would be unlikely to have two reversible features. An electrochemical oxidation would likely result in a Co(III) species, which would most likely have a spin-state change to a low-spin electronic configuration. Chemically, a low-spin Co(III) would typically prefer to be six coordinate and bind an MeCN solvent molecule. This type of oxidation would be unlikely to maintain the geometry throughout the electrochemical experiment which would probably involve an irreversible reduction event. However, this complex is ligated by a thiolate, which may stabilize a coordinatively unsaturated five coordinate Co(III) complex, as has been observed previously our group before and accounts for the reversible reduction feature.$^{14,15}$
observance of two sequential reversible features seem unlikely to portend a monomeric species in solution.

**Figure 4.03:** 1mM Cyclic voltamogram of 13 at RT. Scans taken in MeCN at 0.1V/s with a glassy carbon working electrode and platinum counter electrode. Scan from 1 V to -1 V and potentials referenced to Fc/Fc⁺ and a 0.1M solution of "Bu₄(N)[PF₆] supporting electrolyte.

Similar to the Fe complexes, there seems to be a large reduction feature at more negative values (**Figure 4.04**). There is a cathodic peak potential, $E_{pc}$, of -1.59V and a very small anodic peak potential, $E_{pa}$, of -1.44V. The anodic and cathodic peak current for these two features ($I_{pc}$ and $I_{pa}$ respectfully) are clearly indicative of an irreversible process. As seen with the Fe complexes, this irreversible feature may be due to the change in the chemical environment due to the change from a $\pi$-acceptor imine orbital to a $\pi$-donating amide ligand. There is a significant decrease in the energy required to reduce this complex compared to the analogous ferrous complex 12, this trend seems to hold based on the limited electronic activation of the imine and will be discussed later.
Figure 4.04: 1mM Cyclic voltamogram of 13 at RT. Scans taken in MeCN at 0.1V/s with a glassy carbon working electrode and platinum counter electrode. Scan from -1.1V to -2V and potentials referenced to Fc/Fc$^+$ and a 0.1M solution of $^n$Bu$_4$N[PFe] supporting electrolyte.

A small change is observed in the electronic absorption spectrum when 2 equivalents of Fc$^+$ are added to the dimeric 13. However, a clear indication that the desired reaction took place was observed by $^1$H NMR spectroscopy, where an observed diamagnetic product is consistent with a low-spin Co(III) species (Figure 4.05). The peaks in the $^1$H NMR spectrum are consistent with two unique imidazole arms, similar to the $C_2$ symmetric 10. The imine protons are observed at 8.54 and 8.26 ppm while four distinct aromatic peaks are observed at 7.57, 7.42, 7.04 and 6.46 ppm. There are two unique methyl groups on the imidazole rings which are seen as two singlets at 4.09 and 4.06 ppm while a multiplet between 3.70 and 3.39 ppm is the result of the methylene protons adjacent to the nitrogen of the imine. Finally, a singlet at 1.20 ppm would be consistent with the methyl group on the tame backbone and two roofing doublets at 0.92 and 0.82 ppm are the result of the protons of the methylene adjacent to the thiolate.
**Figure 4.05:** $^1$H NMR spectrum of $^{13}\text{ox}$ in MeCN at RT.

The solid-state structure was verified crystallographically (**Figure 4.06**). In the solid state, this complex, $^{13}\text{ox}$, has the same $C_2$ symmetry as the reduced version, $^{13}$, and is consistent with the splitting pattern observed in the $^1$H NMR spectrum (**Figure 4.05**). There is a noticeable decrease in the Co-N bond lengths compared to $^{13}$. On average the Co-N bond length decreased from 2.15 Å in the high spin Co(II) of $^{13}$ to 1.92 Å in $^{13}\text{ox}$ (**Table 4.02**). This suggests that, not only has the Co been oxidized to Co(III), but also that it is low-spin, consistent with the diamagnetic NMR spectrum. This low-spin Co(III) complex would be isoelectronic to the low spin ferrous derivative $^{12}$. Similarly, the thiolate bond lengths contract with bond lengths ranging from 2.225(3) to 2.232(3) Å. In addition to the shorter Co-S bond lengths, the asymmetry of the Co$_2$S$_2$ core that was observed in $^{13}$ is now much more symmetric for the oxidized product. Finally, unlike $^{13}$, $^{13}\text{ox}$ has a very planar Co$_2$S$_2$ suggesting a more octahedral like structure and better π-overlap between the Co and ligands with the least square plane fit now 0.15 (0.35 in $^{13}$) (**Figure 4.07**).
Figure 4.06: X-ray crystal structures of $\text{13}^{\text{ox}}$ with 50% probability ellipsoids. Counterions, cosolvents and hydrogens omitted for clarity (Left). Corresponding structural representations (Right).

Figure 4.07: Chemdraw depiction of the four atom core $(\text{Co}_2\text{S}_2)$ of $\text{13}$ and $\text{13}^{\text{ox}}$ indicating the methyl carbon adjacent to the thiolates.

While the contraction of the Co-ligand bond lengths are expected, the lengthening of the imine bonds are somewhat unexpected. Around Co(1) the two imine bond lengths are 1.277(10) and 1.293(12) Å suggesting some activation when compared to $\text{13}$ (Table 4.03). However, the imine bond lengths are lengthened around Co(2), with an imine bond length of 1.309(11) and 1.316(12) Å indicating a possible activation of this ligand fragment.

The observed ligand bond lengths in $\text{12}$, $\text{13}$ and $\text{13}^{\text{ox}}$ can be explained through the differences in both spin state and geometry around the metal ion. It seems that the low-spin state of $\text{12}$ and $\text{13}^{\text{ox}}$ suggests that the metal ion is capable of backbonding into the $\pi^*$ imine orbital.
Conversely, 13 has a high spin state and fewer electron pairs (one $t_{2g}$-orbital is half filled) in metal orbitals capable of backbonding into the accepting imine orbital. Additionally, angular orbital overlap between the $\pi$-donating thiolate into the metal ion would be increased as the M$_2$S$_2$ core becomes more planar. This increases a “push”-like $\pi$-effect from the donating thiolate through the metal orbital and out into the imine $\pi^*$ orbital. The bent nature of 13 hinders the thiolate ability to donate electron density and activate these ligands. A shorter M-thiolate distance will increase the effect of the thiolate and it is seen that 13, which has no activation and the longest M-S bond lengths has the least activated intra-ligand bond lengths.

These properties are important to keep in mind when designing future base-metal catalysts. An important feature in these redox-active ligand frameworks is the ability for the ligand to mitigate the amount of electronic demand at the metal center. This will afford 2 e$^-$ redox chemistry for 1st row transition metals which typically undergo sequential 1 e$^-$ redox reactions. This case study indicates that the addition of strong $\pi$-donating ligands may be able to influence the amount of electronic activation of the ligands and aid future catalysts in the efficiency of using both redox reservoirs.

The ability for the thiolate to modulate electron density into other ligand orbitals is proposed in the mechanism of cytochrome P450. A critical step is the heterolytic cleavage of the O-O bond which is aided by the “push”-effect of the axial cysteinate. The thiolate will donate electron density through the $\pi$-framework of the metal and into the peroxide $\sigma^*$-orbital, weakening the O-O bond. Even though this density is pushed into a $\sigma^*$-bond, it has $\pi$ overlap with the metal orbitals. Using redox-active ligands that will accept electron density and have changes in bond lengths allows observation of a thiolate effect.
**Thiolate Effect:**

In order to specifically investigate the importance of the thiolate, a benzyl protected thioether complex, 14, was synthesized. This complex was prepared using the diamine benzyl protected organic precursor, 6 (Figure 4.08). A similar Schiff base condensation yields a monomeric ferrous complex. The geometry of this thioether complex is square pyramidal with the two α-(imino)-imidizoles in the basal plane and an axial thioether (Figure 4.08). As evidenced by the Fe-N bond lengths (all < 2.0 Å) and a short Fe-S bond length of 2.27 Å, the ferrous ion appears to be in a low-spin $S=0$ state (Table 4.04). However, the $^1$H NMR spectrum of 14 at room temperature did not display the expected diamagnetic signals; instead, paramagnetically shifted peaks were observed. This could be readily rationalized by solvent dissociation at higher temperatures, however a solution magnetic moment $\mu_{\text{eff}} = 5.04$ µB by Evan’s method suggests a high-spin state in solution. Difference in spin states between solution state and solid state crystal structures are seen in the literature and could be due to the differences in the temperature of these two experimental techniques.\(^{19}\)

![Reaction of 6 and 1-methyl-2-imidazolecarboxaldehyde to produce 14 and Corresponding structural representations (Left). X-ray crystal structures of 14 with 50% probability ellipsoids. Counterions, cosolvents and hydrogens omitted for clarity (Right).](image)
Table 4.04: Metrical parameters for 14.

<table>
<thead>
<tr>
<th>Metal-Ligand Distances</th>
<th>14 (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-S(1)</td>
<td>2.275(13)</td>
</tr>
<tr>
<td>Fe-N(1)</td>
<td>1.948(4)</td>
</tr>
<tr>
<td>Fe-N(2)</td>
<td>1.996(4)</td>
</tr>
<tr>
<td>Fe-N(4)</td>
<td>1.941(4)</td>
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<td>Fe-N(5)</td>
<td>1.981(4)</td>
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<tr>
<td>Fe-N(7)</td>
<td>1.947(4)</td>
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</table>

<table>
<thead>
<tr>
<th>Intra-Ligand Distances</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(6)</td>
<td>1.281(5)</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.432(6)</td>
</tr>
<tr>
<td>N(4)-C(12)</td>
<td>1.287(5)</td>
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<tr>
<td>C(12)-C(13)</td>
<td>1.436(6)</td>
</tr>
</tbody>
</table>

Since 14 shares a similar solid-state metal spin state to 12, the only difference is the change from other ligands, which alters the activation of the intra-ligand bond lengths (Table 4.04). The substitution of a neutral L-type thioether for a π-donating anionic thiolate indicates the importance of the thiolate in ligand activation. It seems that, in the right geometry, the thiolate can “push” electron density through the metal $t_{2g}$-like orbitals into the π-accepting ligand orbital.

Furthermore, while 14 retains a CT transition in the visible region of the electronic absorption spectrum, it is to higher energy and much lower intensity ($\lambda_{\text{max}} (\varepsilon, \text{M}^{-1}\text{cm}^{-1}) = 512 (2850)$) nm when compared to that of thiolate-ligated 12 ($\lambda_{\text{max}} (\varepsilon, \text{M}^{-1}\text{cm}^{-1}) = 619 (11500)$) nm. An interpretation of this spectra is that the there is no longer any thiolate-mixing that was observed by DFT for 12. These differences in the C-N imine bond and the C-C bond metrical parameters, as well as electronic absorption spectra, suggest that the thiolate ligand plays a critical role in promoting the intense optical transitions and distinct intra-ligand metrical parameters observed for 10-12.

The electrochemistry of 14 is indicative of the difference between thiolate ligation and thioether ligation. A fairly reversible feature is observed at 480 mV vs. Fc/Fc$^+$ (Figure 4.09).
The more positive reduction potential is expected as the overall charge of the complex is more positive. In addition the thiolate will lower the reduction potential, as has been observed with other systems. Also, unlike 10-12 which had multiple features, this monomeric ferrous complex only has one. Similar to 13, there is a noticeable shift to higher potentials for the $E_{pc}$ which is observed, at -1.68 V (Figure 4.10). There seems to be an $E_{pa}$ at -1.28 V that is dependent on the initial cathodic feature.

**Figure 4.09**: 1 mM Cyclic voltamagram of 14 at RT. Scans taken in MeCN at 0.1 V/s with a glassy carbon working electrode and platinum counter electrode. Scan from 1.1 V to -0.1 V and potentials referenced to Fc/Fc$^+$ and a 0.1 M solution of $n$Bu$_4$N[PF$_6$] supporting electrolyte.
Figure 4.10: 1 mM Cyclic voltamagram of 14 at room temperature (left). Scans taken in MeCN at 0.1 V/s with a glassy carbon working electrode and platinum counter electrode. Scan from -0.8 V to -2.1 V and potentials referenced to Fc/Fc$^+$ and a 0.1 M solution of $^{n}$Bu$_4$N[PF$_6$] supporting electrolyte.

A Manganese derivative of 12:

Using MnCl$_2$ in an analogous procedure to the one that was used to isolate 12 and 13, afforded an unusual complex, 15. A white solid was isolated, which had a parent peak at 372.1 m/z$^+$, that is consistent with the desired monomeric Mn(II) with the fully condensed ligand present. This product seemed to have no reactivity with O$_2$, which is in stark contrast to our related Mn(DPEN) system.$^{20,21}$ Typically our thiolates afford low reduction potentials that aid in the reactivity of these complexes with O$_2$. Although as we observed with the analogous Fe complex 10, there is a possibility that a dimer could be formed, which would leave no open site for O$_2$ to perform inner-sphere oxidation.
The cyclic voltamogram shows small anodic features that could be the Mn$^{III}$-Mn$^{II}$ redox couple but they are at high potentials (over 1V vs. Fc/Fc$^+$). This high oxidation potential is unlike similar thiolate ligated Mn complexes that our group has reported.$^{19,22}$ This is consistent with the observed lack of O$_2$ reactivity. However like the 13 and 14 complex, this Mn complex has an $E_{pc}$ of -1.58V which is a more positive compared to 12 and is assigned as the ligand reduction (Figure 4.11).
This unexpected thiolate reactivity explains the observed electrochemical patterns and the $O_2$ reactivity.

Figure 4.12: X-ray crystal structures of 15 with 50% probability ellipsoids. Counterions, cosolvents and hydrogens omitted for clarity (Left). Corresponding structural representations (Right).

Table 4.05: Selected metrical parameters for 15

<table>
<thead>
<tr>
<th>Metal-ligand Bond Lengths</th>
<th>15 (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn-N(1)</td>
<td>2.215(4)</td>
</tr>
<tr>
<td>Mn-N(3)</td>
<td>2.328(4)</td>
</tr>
<tr>
<td>Mn-N(4)</td>
<td>2.366(4)</td>
</tr>
<tr>
<td>Mn-N(5)</td>
<td>2.178(4)</td>
</tr>
<tr>
<td>Mn-Cl(1)</td>
<td>2.4128(15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intra-Ligand Bond Lengths</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N(3)-C(5)</td>
<td>1.468(6)</td>
</tr>
<tr>
<td>C(5)-C(4)</td>
<td>1.482(7)</td>
</tr>
<tr>
<td>S(1)-C(5)</td>
<td>1.836(5)</td>
</tr>
<tr>
<td>N(4)-C(11)</td>
<td>1.275(6)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.443(7)</td>
</tr>
<tr>
<td>$\tau$ value</td>
<td>0.072</td>
</tr>
</tbody>
</table>

The unusual reactivity of the thiolate generates two noticeably different C-N bond lengths. The nucleophilic attack of the sulfur prevents imine formation and it is reflected in an elongated C-N bond. This bond length of 1.468(6) Å is similar to an expected C-N single bond.²

The other side of this molecule contains an intact $\alpha$-(imino)-imidazole with no coordinated sulfur
and its bond length is similar to an unactivated imine bond of 1.275(6) Å and a longer 1.443(7) Å C-C bond.

The effect of the thiolate itself was observed in both the 14 and 15. 14 structurally seems to be isoelectronic to the family of Fe-thiolate complexes. The only difference between these is the variation between the π-donating anionic thiolate to the L-type coordinated thioether. As observed, the imine bond length contracts compared to the related thiolate complex. While the electronic geometry of 12 and 14 in the solid state are equivalent, suggesting that the backbonding effect of the metal is similar the thioether will have significantly less push-effect from the thiolate and this is consistent with observations of the intra-ligand bond lengths. This similar effect is observed in 15 which has no sulfur coordination and the imine bond length is suggestive of an unactivated imine.

Comparison of Redox Trends:

While 13-15 do not indicate much electronic activation of the ligand they are consistent in terms of the reduction feature in the CV (Table 4.06). Usually, redox-active ligands have similar redox-features because the reduction potentials do not change between different metal centers.23,24 However these complexes do have distinct redox features to 12. These redox features are all shifted to higher potential compared to 12 suggesting that the latter is the hardest to reduce in this family of α-(imino)imidazoles. This fits in with the pattern of ligand activation as if there is less electron density being pushed into the ligand backbone it will be easier to add an electron within this redox reservoir. Thus, the increase in the ligand redox potential suggests that there is less backbonding (or push effect) from the thiolate in 13, 14 and 15 which parallels the structural parameters that were observed in the X-ray crystal structures.
Table 4.06: Comparison of ligand redox potentials for 12-15.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$E_{pc}$ (V vs. Fc/Fc$^+$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>-1.89</td>
</tr>
<tr>
<td>13</td>
<td>-1.59</td>
</tr>
<tr>
<td>14</td>
<td>-1.68</td>
</tr>
<tr>
<td>15</td>
<td>-1.58</td>
</tr>
</tbody>
</table>

Conclusions:

Four analogues of 12 have been structurally characterized. Unlike 10-12, 13-15 display little to no ligand activation. This is due to both the mode of thiolate coordination as in 13 or the lack of thiolate coordination as observed for 14 and 15. In addition, 13 and 15 have a high-spin electronic structure at the metal ion suggesting that activation could result in strong backbonding from a metal center only if it contains filled $t_{2g}$-like orbitals. The lack of structural activation of the imine is consistent with the much more positive reduction potentials seen in the CVs of 13-15 compared to 12 (Table 4.06), which could be promising for attempting to reduce these complexes.
Notes to Chapter 4


Chapter 5:

Thiazolidine-Ligated Ferrous Metal Complexes.
Introduction:

While the \(\alpha\)-(imino)pyridine complexes have found some use in catalytic chemistry,\textsuperscript{1} the more common redox-active bis(imino)pyridine ligand backbone has been extensively used in base metal catalysis due to its much more rigid pincer framework. They have been shown to catalyze polymerization,\textsuperscript{2,3} hydrogenation,\textsuperscript{4,5} and cyclization\textsuperscript{6,7} transformations due to the ligand’s ability to both accept and donate electron density to and from the metal active site. This pincer ligand also provides a rigid tridentate backbone that can mimic the tri-histidine coordination of a variety of metalloenzymes.\textsuperscript{8}

Scheme 5.01: Oxygenation of a coordinated aromatic thiolate at a ferrous metal center using a redox active bis(imino)pyridine ligand backbone reported by Goldberg.

Goldberg has shown that an asymmetric bis(imino)pyridine Fe complex is a competent cysteine dioxygenase mimic (Scheme 5.01).\textsuperscript{9} They were able to tether on an aromatic thiolate that was coordinated to the bis(imino)pyridine framework to form a tetradentate ligand that, when exposed to \(\text{O}_2\), would oxygenate the coordinated thiolate. In a different study, it was observed that, if the thiolate was not tethered to the ligand backbone, different reactivity would be seen depending on the strength of the coordinated counterion.\textsuperscript{10} While both the enzyme active species and Goldberg’s mimic both contain a coordinated thiolate, there can be subtle differences between an aromatic thiolate and an aliphatic thiolate.\textsuperscript{11}
While Goldberg was able to coordinate the aromatic thiolate to an Fe metal center, attempts to coordinate the aliphatic thiolate were unsuccessful. Similar to 15, there was unusual reactivity in the metal template condensation step. A carbon-sulfur bond similar to 15 was observed in the solid state structure, however the smaller 5 membered ring is structurally similar to the thiazolidine ring structure produced in the enzyme isopennicilin N-synthase.\textsuperscript{12}

**Experimental:**

**General Considerations:** DMSO-\textit{d}_6 and CDCl\textsubscript{3} were purchased from Cambridge Isotope Labs and used as received. Ethanol was purchased from Decon and degassed prior to use. Et\textsubscript{2}O was purchased from Fischer Scientific and purified using a solvent purification columns housed in a custom stainless steel cabinet and dispensed by a stainless steel Schlenk-line (GlassContour). All other solvents were purchased from Sigma Aldrich. MeOH, MeCN and CH\textsubscript{2}Cl\textsubscript{2} were dried and distilled prior to use.

\textsuperscript{1}H NMR spectra were obtained on a Bruker AV300, AV301, DRX499, or AV500. Chemical shifts are listed in parts per million and were reported relative the residual protio solvent. UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer equipped with a fiber optic cable connected to a “dip” ATR probe (C-technologies). A custom-built two neck solution sample holder equipped with a threaded glass connector was sized specifically to fit the “dip” probe. Matrix-Assisted Laser Desorption/Ionization (MALDI) mass spectrometry (ESI-MS) was preformed on a Bruker Autoflex II and used pyrene as a charge transfer matrix. All manipulations were performed using Schlenk
techniques or under a N₂ atmosphere in a glovebox. The asymmetric ketone was synthesized according to literature procedure.¹¹

**Synthesis of [Fe^{II}N₃thiazolidineCl]Cl (16):** The asymmetric ketone (0.05 g, 0.16 mmol) and FeCl₂ (0.020 g, 0.16 mmol) were stirred in THF (2 mL). To this solution 2-propanethiol, 1-amino-2-methyl hydrochloride salt (0.022 g, 0.16 mmol) and triethylamine (0.031 g, 0.31 mmol) were added. This solution was stirred for 14 hours and monitored by mass spectroscopy. A peak at 464m/z indicated the formation of the product. The solution was then evacuated *in vacuo* and redissolved in MeCN (4 mL). Salts were filtered and the solution was evacuated to a minimal volume and layered with Et₂O. A blue solid, 16, was collected in 47% yield (0.04 g, 0.087 mmol). X-ray quality crystals were grown through slow vapor diffusion of Et₂O into an MeCN solution. \( \lambda_{\text{max}} \) (nm) \( (\varepsilon \text{ (M}^{-1}\text{cm}^{-1})) \): (MeCN): 599 (500), (MeOH): 638 (545), (DCM): 620 (480), THF: 681 (419). MALDI-MS: expected \( m/z \) for \([C_{25}H_{35}N_{3}SFeCl]^{+}=499.5\), found \( m/z=464.1 \) (no chloride coordinated).

**Synthesis of [(Fe^{II}N₃thiazolidineCl)₂Cl]OTf (17):** 17 was synthesized in the same manner as 16 but Fe(OTf)₂ was used instead of FeCl₂. \( \lambda_{\text{max}} \) (nm) \( (\varepsilon \text{ (M}^{-1}\text{cm}^{-1})) \): (THF): 625 (453). MALDI-MS \( m/z \) for \([C_{25}H_{35}N_{3}SFeCl]^{+}=499.5\), found \( m/z=464.1 \). The MS shows a similar pattern to the monomer suggesting that the dimer cleaves under MS conditions.
X-Ray Crystallographic Structure Determination

A blue twinned twinned crystal, 16, measuring 0.15 x 0.05 x 0.05 mm³ was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 90 seconds per degree for all sets. The scan width was 0.5°. Data collection was 97.2% complete to 25° in θ. The sample seemed to consist of at least three individuals. The raw data appeared conglomerated. With CELL_NOW three individual data sets were isolated which, if not separated, would cause considerable overlap of diffraction peak intensities. Multi-domain integration with SAINT within the APEX2 software package by Bruker and absorption correction with twinabs removed the overlap. A total of 5887 independent reflections were collected covering the indices, h = -11 to 9, k = -16 to 15, l = -9 to 16 with R_int = 0.1268 indicated that the twin-refined data was of less than average quality (0.07). Indexing and unit cell refinement indicated then a triclinic P lattice. The space group was found to be P 1̅ (No.2).

A red prism, 17, measuring 0.22 x 0.07 x 0.05 mm³ was mounted on a loop with oil. Data was collected at -173°C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame for all sets. The scan width was 0.5°. Data collection was 99.6% complete to 25° in θ. A total of 225743 reflections were collected covering the indices, h = -15 to 15, k = -27 to 28, l = -38 to 37. 17222 reflections were symmetry independent and the R_int = 0.0904 indicated that the data was of slightly less than average quality (0.07). Indexing and unit cell refinement indicated a primitive monoclinic lattice. The space group was found to be P 2/c (No.14).

Solution by direct methods (SHELXS, SIR97) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed
by difference Fourier synthesis with SHELXL97.\textsuperscript{17,18} Scattering factors are from Waasmair and Kirfel.\textsuperscript{19} Hydrogen atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters $U_{\text{eq}}$ were fixed such that they were 1.2$U_{\text{eq}}$ of their parent atom $U_{\text{eq}}$ for CH's and 1.5$U_{\text{eq}}$ of their parent atom $U_{\text{eq}}$ in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares. Crystal Data is presented in Table 5.01.

### Table 5.01: Crystallographic data for 16 and 17.

<table>
<thead>
<tr>
<th></th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td>$C_{25}H_{35}Cl_{2}FeN_{3}S$</td>
<td>$C_{111}H_{162}Cl_{14}Fe_{4}N_{12}O_{8}S_{6}$</td>
</tr>
<tr>
<td><strong>MW (g/mol)</strong></td>
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<td>2818.59</td>
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<tr>
<td><strong>Crystal System</strong></td>
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<tr>
<td><strong>Space Group</strong></td>
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<td>$P 1 21/c$</td>
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<tr>
<td><strong>Unit Cell Dimensions</strong></td>
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<tr>
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<td>21.003(2)</td>
</tr>
<tr>
<td>$c$ (Å)</td>
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<td>90</td>
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<td>90</td>
</tr>
<tr>
<td><strong>Final R indices</strong></td>
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<tr>
<td><strong>R indices (all Data)</strong></td>
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<td>0.1174</td>
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### Results and Discussion:

**Thiazoldine Ligated Iron Complexes:**

The unsymmetrical ketone was prepared following an adapted literature procedure by performing an acid catalyzed mono condensation to 2,6-diacetylpyridine (Scheme 5.02).\textsuperscript{20} The imine substituent was 2,6-diisopropylphenyl, which imparts significant steric
bulk around the metal center. Although the yield was low (34%) the low cost of the starting materials led to the facile and inexpensive preparation of large quantities of this precursor.

**Scheme 5.02:** Synthesis of asymmetric ketone (top), and metal template Schiff base condensation (bottom).

Treating 2-propanethiol,1-amino-2-methyl hydrochloride salt with this precursor in the presence of an Fe(II) source produced a deep blue mixture suggesting that there was coordination to the metal in the templated Schiff base condensation. MALDI-mass spectroscopy provided evidence that the condensed ligand was coordinated to the ferrous metal ion (Figure 5.01). The peak is consistent with the entire ligand coordinated to the metal ion and the isotopic pattern matches with what would be expected for a monomeric Fe metal complex due to the M-2 peak at 462.1 m/z.
Figure 5.01: MALDI-MS of 16 (left) indicating the peak associated with the coordinated complex at 464.1 m/z. Comparison of the isotopic pattern of the peak at 464.1 and the theoretical m/z of 16 (right).

Using ferrous chloride as the initial Fe source afforded the crystals of the template product, 16 (Figure 5.02). X-ray diffractometry identified this as a monomeric ferrous complex. This five coordinate complex has the three nitrogens of the ligand backbone coordinated to the metal and two chlorides creating a distorted square pyramidal geometry with a $\tau$-value of 0.092 (Table 5.02). Unlike many other complexes from our group that form strong covalent Fe-S bonds, this complex does not have a thiolate coordinated to the metal center. Instead, a new carbon-thiolate single bond is formed making a five-membered thiozolidine ring.

Figure 5.02: ORTEP of 16 showing 50% probability ellipsoids (Left). Hydrogen atoms and solvents of crystallization were removed for clarity. Corresponding structural representation of 16 (Right).
It seems that, during the Schiff base condensation, instead of the thiolate coordinating to the metal it participates in the condensation reaction by nucleophilically attacking the partially positive carbon atom. A plausible mechanism for this reactivity would be that the Fe serves as a Lewis acid to activate the carbonyl for nucleophilic attack of the primary amine. Instead of the imine formation to release water, the thiolate will participate in an intramolecular nucleophilic attack at the carbon releasing the water (path A, Scheme 5.03). Alternatively the thiolate could attack first followed by the primary amine to release the water (path B, Scheme 5.03).

**Scheme 5.03:** Possible thiazolidine ring cyclization at the Fe center. Path A (top) has initial nucleophilic attack by the primary imine while Path B (bottom) has the initial nucleophillic attack by the thiolate.
The formation of a thermodynamically stable 5-membered ring may be the driving force for this type of reactivity. Typically our group uses 3-methyl,3-mercapto-2-butanone to add the thiolate during the Schiff base condensation. In using this reagent, it is unlikely to observe the same nucleophilic attack of the thiolate instead of the imine due to its location in relation to the carbonyl group. Since the carbonyl carbon in this substrate is only 2 bonds away from the thiolate the product of a nucleophilic attack would be a highly strained 3-membered ring containing a thioether which would favor thiolate coordination to the ferrous ion.\textsuperscript{21}

The Fe-N bond lengths of this complex are all above 2.1 Å and are consistent with a high spin ferrous complex (Table 5.02). The thioether has equivalent S-C bond lengths (1.859(6) Å and 1.848(5) Å) suggesting that a strongly covalent carbon-sulfur bond has been formed. The two chlorides have equivalent bond lengths (2.3035(16) and 2.3008(17)) and no counter ions are observed further supporting the assignment of a ferrous oxidation state. The strongly coordinating chlorides from the starting FeCl\textsubscript{2} could inhibit coordination of the thiolate and favor thiazolidine formation.

Due to the thiazolidine ring formation, this complex would be more similar to an α-(imino)pyridine instead of the targeted bis(imino)pyridine. Unlike the α-(imino)-N-heterocycles described in chapters 2-4, this complex shows no activation of the imine bond, with a C-N 1.283(6) Å (Table 5.03). This lack of activation would be expected with no strong donation from a coordinated thiolate or the strong backbonding from a low-spin ferrous metal center.
Table 5.02: Selected geometrical parameters for 16 and 17. *indicates the bridging chloride.

<table>
<thead>
<tr>
<th></th>
<th>16 Distance (Å)</th>
<th>17 Fe(1) Distance (Å)</th>
<th>17 Fe(2) Distance (Å)</th>
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<tr>
<td>Fe-N(1)</td>
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<td>Fe(1)-N(1) 2.237(4)</td>
<td>Fe(2)-N(4) 2.233(4)</td>
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<td>Fe-N(2)</td>
<td>2.120(4)</td>
<td>Fe(1)-N(2) 2.088(4)</td>
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<td>Fe-N(3)</td>
<td>2.233(4)</td>
<td>Fe(1)-N(3) 2.199(4)</td>
<td>Fe(2)-N(6) 2.234(4)</td>
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<td>Fe-Cl(1)</td>
<td>2.3035(16)</td>
<td>Fe(1)-Cl(1)* 2.4066(13)</td>
<td>Fe(2)-Cl(1)* 2.3617(16)</td>
</tr>
<tr>
<td>Fe-Cl(2)</td>
<td>2.3008(17)</td>
<td>Fe(1)-Cl(2) 2.2859(13)</td>
<td>Fe(2)-Cl(3) 2.2767(17)</td>
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<tr>
<td>S-C(3)</td>
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<td>S(1)-C(3) 1.835(5)</td>
<td>S(2)-C(28) 1.838(5)</td>
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<td>S(1)-C(5) 1.861(5)</td>
<td>S(2)-C(5) 1.840(5)</td>
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<table>
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<tr>
<th></th>
<th>16 Bond angle (deg)</th>
<th>17 Fe(1) Bond angle (deg)</th>
<th>17 Fe(2) Bond angle (deg)</th>
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<tr>
<td>N(1)-Fe-N(3)</td>
<td>144.70(15)</td>
<td>N(2)-Fe(1)-Cl(2) 150.59(11)</td>
<td>N(4)-Fe(2)-N(6) 145.95(15)</td>
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<td>N(2)-Fe-Cl(1)</td>
<td>139.20(13)</td>
<td>N(3)-Fe(1)-N(1) 148.86(14)</td>
<td>N(5)-Fe(2)-Cl(1) 133.88(11)</td>
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<td>N(2)-Fe-Cl(2)</td>
<td>111.02(12)</td>
<td>Cl(2)-Fe(1)-Cl(1) 105.96(5)</td>
<td>N(5)-Fe(2)-Cl(3) 118.45(11)</td>
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<tr>
<td>τ</td>
<td>0.092</td>
<td>τ= 0.0144</td>
<td>τ= 0.100</td>
</tr>
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Table 5.03: Selected intra-ligand bond lengths for 16 and 17.

<table>
<thead>
<tr>
<th>Monomeric Complex</th>
<th>Distance (Å)</th>
<th>Dimeric Complex Fe(1) Distance (Å)</th>
<th>Dimeric Complex Fe(2) Distance (Å)</th>
</tr>
</thead>
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<tr>
<td>N(3)-C(12)</td>
<td>1.283(6)</td>
<td>N(3)-C(12) 1.286(6)</td>
<td>N(4)-C(37) 1.283(6)</td>
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<tr>
<td>C(11)-C(12)</td>
<td>1.474(7)</td>
<td>C(11)-C(12) 1.495(6)</td>
<td>C(36)-C(37) 1.484(7)</td>
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<tr>
<td>C(11)-N(2)</td>
<td>1.354(6)</td>
<td>C(11)-N(2) 1.348(6)</td>
<td>C(36)-N(5) 1.355(6)</td>
</tr>
<tr>
<td>N(1)-C(5)</td>
<td>1.473(6)</td>
<td>N(1)-C(5) 1.470(6)</td>
<td>N(6)-C(30) 1.480(6)</td>
</tr>
<tr>
<td>C(5)-C(7)</td>
<td>1.504(7)</td>
<td>C(5)-C(7) 1.521(6)</td>
<td>C(30)-C(32) 1.530(7)</td>
</tr>
<tr>
<td>C(7)-N(2)</td>
<td>1.333(6)</td>
<td>C(7)-N(2) 1.336(6)</td>
<td>C(32)-N(5) 1.322(6)</td>
</tr>
</tbody>
</table>
In an attempt to prevent the thiazolidine ring formation, and to isolate a monomeric thiolate ligated ferrous complex, Fe(OTf)₂ was used as the Fe source instead of FeCl₂. The loss of the two chlorides could provide easier coordination for the thiolate. However, the same cyclization and carbon-sulfur bond formation occurred (Figure 5.03) but this time yielded a bimetallic structure, 17. Both Fe metal centers are coordinated by three nitrogens and two chlorides, one of which bridges the two centers. As with 16 both of the Fe’s in 17 are contained in a distorted square pyramidal geometry, as evidenced by a τ-value of 0.014 for Fe(1) and 0.10 for Fe(2). While both irons are in a similar geometry, the orientation is slightly different between the two. The bridging chloride, Cl(1), is in the axial position around Fe(1) while but in the basal plane around Fe(2) with Cl(3) occupying in the axial position. The chlorides could originate from the starting 2-propanethiol, 1-amino-2-methyl hydrochloride salt. The sterics of this bi-metallic structure may cause a slight disruption of the geometry of these two Fe metal

Figure 5.03: ORTEP of 17 showing 50% probability ellipsoid. All hydrogen atoms and counterions omitted for clarity. Corresponding structural representation of 17 (right).
centers. If the bridging chloride were to be in the axial position for both centers there may be a steric clash between the isopropyl groups of the phenyl ring or the bulky gem-
di-methyl groups adjacent to the sulfur in the thiazolidine ring structure.

Similar to 16 the bond lengths in the solid state suggests that both Fe have a high spin state (Table 5.02). The bridging chloride has a much longer Fe-Cl bond lengths (2.4066(13) Å and 2.3617(13) Å) than the non-bridging chlorides (2.2859(13) Å and 2.2767(13) Å), which is to be expected. A single crystalized OTf counteranion along with the three coordinated chlorides suggest a ferrous oxidation state for both metal centers and is consistent with the bond lengths observed. The C-S bond lengths are consistent suggesting the formation of a carbon-sulfur sigma bond. It seems that the weaker coordinated bridging chloride does not effect the spin state or the ability of the Fe to backbond with the α-(imino)pyridine. The imine bond lengths of 1.286(6) and 1.283(6) Å are consistent with an unactivated ligand (Table 5.03).

The formation of a 5-membered thiazolidine ring was not predicted but similar to the ring formation in isopenicillin N-synthase.22 One difference is Isopenicillin N-synthase forms a thiazolidine ring structure through reactivity with O₂.12 High-valent Fe dioxygen species are responsible for activating C-H bonds and forming a C-S bond.23,24 The C-S bond formed in these complexes seems to be formed through much different chemistry but the final product still has some structural similarities to this important substrate.

Thiazolidine ring structures are observed in other areas of bioinorganic chemistry such as those seen in the reactivity of siderophores.25 Bacteria use siderophores to scavenge important metals from outside the cell.26 These metals are then integrated into
important metalloenzymes that will help with DNA synthesis and electron transfer, among other important applications. The virulence of two bacteria *Yersinia pestis*, which causes the bubonic plague, and *Yersinia enterocolitica*, a food borne pathogen, both depend on the amount of Fe available in the environment. These bacteria, among others, scavenge Fe ions through the siderophore yersiniabactin (**Figure 5.04**), which contains thiazoldine rings to bind Fe in the environment. The upregulation in siderophores and the scavenging of metals will precede an increase in virulence factors of bacteria. Understanding how thiozolidines bind to transition metals would aid in understanding how to disrupt and minimize the effects of these toxic bacteria.

**Figure 5.04:** Structure of yersiniabactin indicating multiple thiazolidines within the substrate.

*Electronic Absorption Spectroscopy of 16 and 17:*

Similar to the ferrous $\alpha$-(imino)-$N$-heterocycles described in chapters 2 and 3, these two complexes, 16 and 17, contain charge transfer bands in the visible region. 16 has a charge transfer in MeOH at 638 nm. This charge transfer is much less intense than that observed for compounds 10-12 and has a molar absorptivity of 545 M$^{-1}$cm$^{-1}$ (**Figure 5.05**). The lower intensity is in line with molar absorptivities for other non thiolate ligated ferrous $\alpha$-(imino)pyridines.$^{28,29}$

This charge transfer is most likely a Fe to $\alpha$-(imino)pyridine $\pi^*$ transition as this ligand still has redox-active low lying empty orbitals. The decrease in molar absorptivity
compared to complexes 10-12 is most likely due to the fact that there is no mixing of the sulfur in this transition. 16 does have a solvent dependence on the charge transfer as in the $\lambda_{\text{max}}$ is red shifted in THF to 681 nm while in CH$_2$Cl$_2$ and MeCN it is blue shifted to 620 nm and 559 nm respectively. The molar absorptivities are all relatively similar ranging between 419 M$^{-1}$cm$^{-1}$ to 545 M$^{-1}$cm$^{-1}$.

**Figure 5.05:** Electronic absorption spectrum of 16 in various organic solvents at RT.

The geometry and electronics of this complex could play a role in its solvent-dependent electronic absorption spectra. Since this complex is 5-coordinate and high spin there is a chance that in solution a solvent molecule could coordinate and slightly alter the electronic structure. The change of the $d$-orbital manifold would then impact the energy of the MLCT transition. One observation is that the highest energy charge transfer is observed in MeCN, which could behave more as an L-type or even a $\pi$-accepting ligand. This would then lower the metal $d$-orbitals that could backbond, have a transition to the ligand $\pi^*$ orbital, and also raise the energy of this charge transfer transition. Conversely, if MeOH or THF coordinated they may behave more as a $\pi$-donating ligand and raise the
metal $d$-orbitals and lower the MLCT transition, as observed in the UV-Vis spectrum (Figure 5.05).

The $\lambda_{\text{max}}$ of 17 (625 nm) is actually blue-shifted in THF compared to the monomeric structure. This could be due to the much weaker interaction of the bridging chloride compared to a singly coordinated chloride. The X-type $\pi$-donating chloride would have a much stronger interaction on the Fe $d$-orbitals when it is not bridging, raising the $d$-orbitals and lowering the energy of the MLCT transition observed for the monomeric chloride. If the metal template Schiff base condensation is heated, then the $\lambda_{\text{max}}$ of the product in THF will shift to 689 nm, similar to the monomeric species. This would be consistent with the thermal splitting of the dimeric structure.

$O_2$ Reactivity:

There are examples of monomeric non-heme Fe(II) enzymes that react with $O_2$.\textsuperscript{30,31} Although this complex is not a model for non-heme cysteinate ligated metalloenzyme, these coordinatively unsaturated complexes could still react with $O_2$. The reactivity with small molecule substrates can have significant differences in protic and aprotic solvents. In protic solvents such as MeOH and EtOH, all that is observed when 16 and 17 are treated with $O_2$ is the decay of the charge transfer transition. In contrast, there seems to be an intermediate observed when these reactions are performed in THF or CH$_2$Cl$_2$. 
Figure 5.06: Reactivity of 16 with O$_2$. A metastable stable species is observed at 524 nm.

16 has a new charge transfer band when ambient pressure O$_2$ is added in THF. This peak has an intense $\lambda_{\text{max}}$ at 524 nm (Figure 5.06). While this new peak grows in rapidly at room temperature, it maintains a shoulder at 681 nm suggesting that the starting complex may be still present. This intermediate will decay quickly resulting in a final spectrum very similar to the starting complex. The $\lambda_{\text{max}}$ of the final spectrum is blue shifted by only 20 nm to 660 nm (Figure 5.07). Since the feature at 680 nm does not change with the addition of O$_2$ throughout the reaction it may mean an unidentified complex is responsible for reacting with O$_2$ and generating a metastable species at 524 nm.
Figure 5.07: Decay of the metastable species at 524 nm.

While this metastable species is unstable at room temperature, it is much longer lived at low temperatures. At -40°C the peak at 524 nm is stable for hours suggesting a potential way for isolating this species. At low temperatures it is much easier to resolve the feature of the starting band at 680 nm while the intermediate is present suggesting that the species responsible for this band may not react with O₂. Similar to the room temperature reactivity, the peak at 524 nm will decay and the resulting spectrum will look similar to the starting spectrum with a peak at 660 nm.

17 will also react with O₂. Similar to 16 a band grows in around 520 nm however, it is not as defined (Figure 5.08). This new absorption band persists and does not convert back to a spectra similar to the starting material, as observed for 16. Overall, O₂ will react with a product from both of these reactions however, the fact that the end and starting spectra are so similar suggests that the complex responsible for the main band at 680 nm may not react with O₂.
Figure 5.08: Reactivity of 17 with O$_2$ at RT.

Conclusions:

Two ferrous complexes have been structurally synthesized, each containing a five membered thiozolidine ring. This ring was formed during the Schiff base condensation and prevented the desired thiolate coordination to the ferrous metal center. These thiozolidine rings are similar to those observed in isopennicilin $N$-synthase and in certain siderophores. Although these complexes do not have a thiolate coordinated to the metal atom, some species seems to react with O$_2$ due to the observance of a metastable species. With the lack of a coordinated thiolate and the change in spin state, the imine bond in 16 and 17 seems to be much less activated than those observed in 10-12.
Notes to Chapter 5


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