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Synthesis And Characterization Of Nickel Complexes With Relevance To Nickel Acireductone Dioxygenase And Nickel Superoxide Dismutase

Margo Nicole Montgomery
University of Mississippi

SYNTHESIS AND CHARACTERIZATION OF NICKEL COMPLEXES WITH RELEVANCE TO NICKEL ACIREDUCTONE DIOXYGENASE AND NICKEL SUPEROXIDE DISMUTASE

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The University of Mississippi

by

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ABSTRACT

SYNTHESIS AND CHARACTERIZATION OF NICKEL COMPLEXES WITH RELEVANCE TO NICKEL ACIREDUCTONE DIOXYGENASE AND NICKEL SUPEROXIDE DISMUTASE

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This research presents an investigation of synthetic model complexes with relevance to the active site of Ni(II) acireductone dioxygenase (Ni-ARD) and Ni(II) superoxide dismutase (Ni-SOD).

Acireductone dioxygenases (ARDs) are a unique set of enzymes found in the methionine salvage pathway that catalyze the oxidation reaction of acireductone (1, 2-dihydroxy-3-oxo-5-(methylthio)pent-1-ene). These enzymes share a common polypeptide sequence but bind different metal ions, Ni^{2+} or Fe^{2+}, at the active site. The Ni-ARD enzyme is responsible for the off pathway shunt in the pathway. Using the tridentate nitrogen donor ligands hydrotris(3,5-dimethyl-1-pyrazolyl)borate (Tp*) and the newly developed tris(1, 2-dimethyl-4-imadozyl)carbinol, (4-$TIC^{Me, Me}$) several reactions involving the acireductone analog 2-hydroxy-1, 3-diphenylpropan-1, 3-dione and O_2 were investigated for similarities to the Ni-ARD active site.

Superoxide dismutases (SODs) play a key role in protecting cells against oxidative damage by regulating the cellular concentration of the superoxide radical ($O_2^{\cdot-}$) which is an unwanted byproduct of cellular metabolism. This process is accomplished by converting the superoxide radicals to hydrogen peroxide and molecular oxygen. Several small-molecule complexes were synthesized and characterized in an effort to model the reduced state of the Ni-SOD using the Tp* ligand. The structures for these complexes have been determined using X-Ray Crystallography.

DEDICATION

This dissertation is dedicated to the members of "my village" who were granted their wings in heaven before I was able to cross the finish line;

My Father: Oliver M. Montgomery, Grandparents: Carrie Farries and Oliver L. Montgomery

And Uncles:

Rupert Alexis, Sr. and Kemron Ebanks

LIST OF ABBREVIATIONS AND SYMBOLS

ARD	Acireductone Dioxygenase
SOD	Superoxide Dismutase
MTA	5’-methyl-thioadenosine
6-Ph_2TPA	*N*, *N*-bis((6-phenyl-2-pyridyl)methyl)-*N*-((2-pyridylmethyl)amine)
Tp*	Hydrotris(3,5-dimethylpyrazolyl)borate
4-TIC	Tris(4-imidazolyl)carbiol

ACKNOWLEDGEMENTS

First and foremost, I have to give thanks to my Lord and Savior, Jesus Christ. It was only by his grace and mercy that I was able to complete this journey.

During the past seven years I have had the honor and pleasure of working with a great chemist and mentor, my advisor Dr. Walter E. Cleland, Jr. His guidance and encouragement has made this a thoughtful and rewarding journey. I thank my dissertation committee members: Dr. Maurice Eftink, Dr. Daniell Mattern, Dr. Jason Ritchie and Dr. Donald Cole for their support and encouragement through the years.

I would also like to thank my family and friends, especially my mom: Dawn J. Williams for being the best role model a daughter could ask for. My big/lil sister: Monica M. Montgomery for her motivation and support throughout this entire process. You have supported me from New Hampshire to Mississippi. My brother John and sister Delann for giving me the drive to continue forward. My fiancé: Jamaal Richardson for being so understanding and always allowing me to see the positive side of things.

A special thanks to Ms. Harriet Hearn and Dr. Murrell Godfrey for being there through the good and bad times of graduate school. My fellow classmates Kari Copeland and Jeffrey Veals, we have laughed together, struggled together and now we have earned our Ph.D.'s together.

TABLE OF CONTENTS

LIST OF TABLES

Table Page

LIST OF FIGURES

LIST OF SCHEMES

Scheme Page

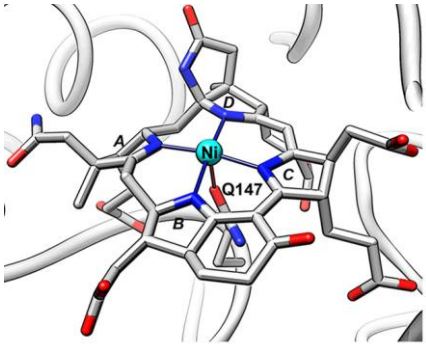
CHAPTER 1

INTRODUCTION

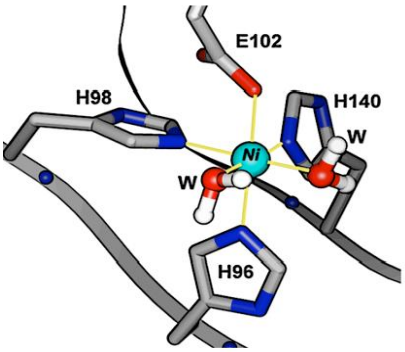
Metalloenzymes catalyze a wide variety of reactions ranging from electron transfer to the insertion of oxygen into carbon-hydrogen bonds. In performing these reactions the metal site can be mononuclear or in a cluster. Even though many of the reactions catalyzed by metalloenzymes are considered biologically essential, they can also catalyze reactions that can be considered harmful to the cell. In an effort to better understand the chemistry behind the reactions associated with metalloenzymes, chemists have developed a strong interest in synthetic analogs which can function as structural and/or functional models of the enzymes.

The nickel metalloenzymes have become the subject of intense research since the discovery of nickel in the active site of Urease in 1975. Urease catalyzes the hydrolysis of urea, which is excreted by vertebrates, into ammonia and carbon dioxide. Since its discovery there have been seven additional enzymes which contain nickel in the active site to be reported: Glyoxylase I (GlxI), Nickel Superoxide Dismutase (SOD), NiFe Hydrogenase, Carbon Monoxide Dehydrogenase (CODH), Acetyl Coenzyme A Synthase, Methyl-CoM Reductase (MCR) and the recently discovered Acireductone Dioxygenase (ARD) (Fig. 1 and 2). Although the role of the nickel varies greatly among theses enzymes there are some

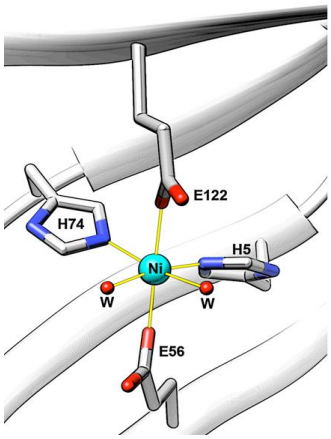
similarities. Most of the enzymes involve the production of gases (carbon monoxide, carbon dioxide, hydrogen, ammonia, methane or oxygen) which play important roles in many natural biological systems.[1-3]



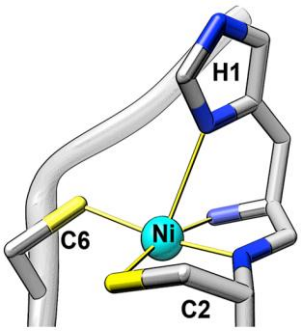
F_{430} in Methyl-CoM Reductase



Acireductone Dioxygenase

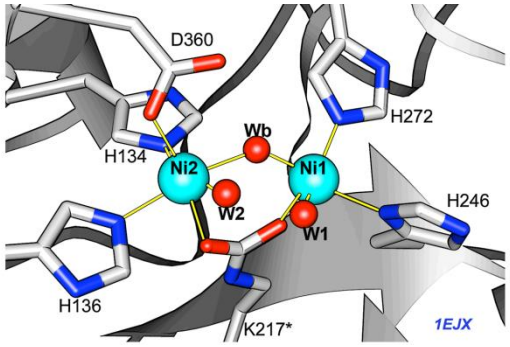


Glyoxylase I

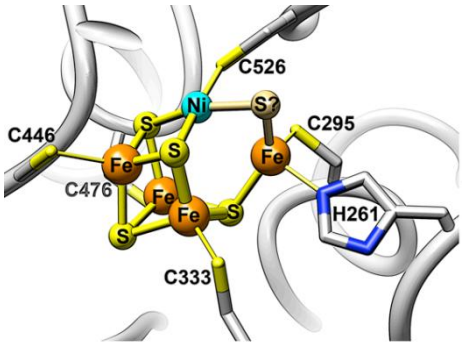


Nickel Superoxide Dismutase

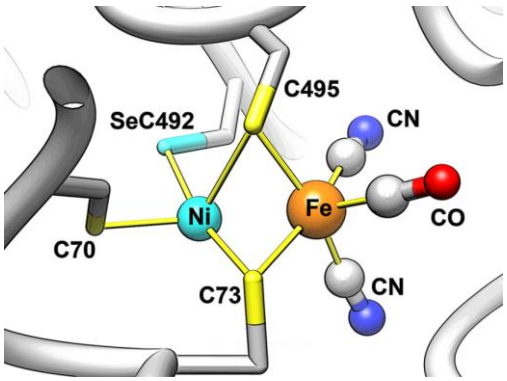
Figure 1. Active sites of the mononuclear nickel metalloenzymes. Reprinted with permission from S. W. Ragsdale (2009) Copyright 2009 American Society for Biochemistry and Molecular Biology [1]



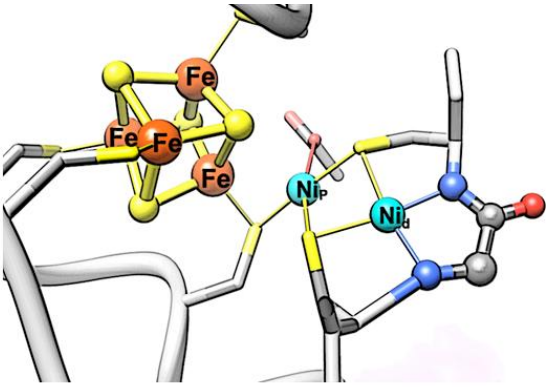
Urease



CO Dehydrogenase



Nickel-Iron Hydrogenase



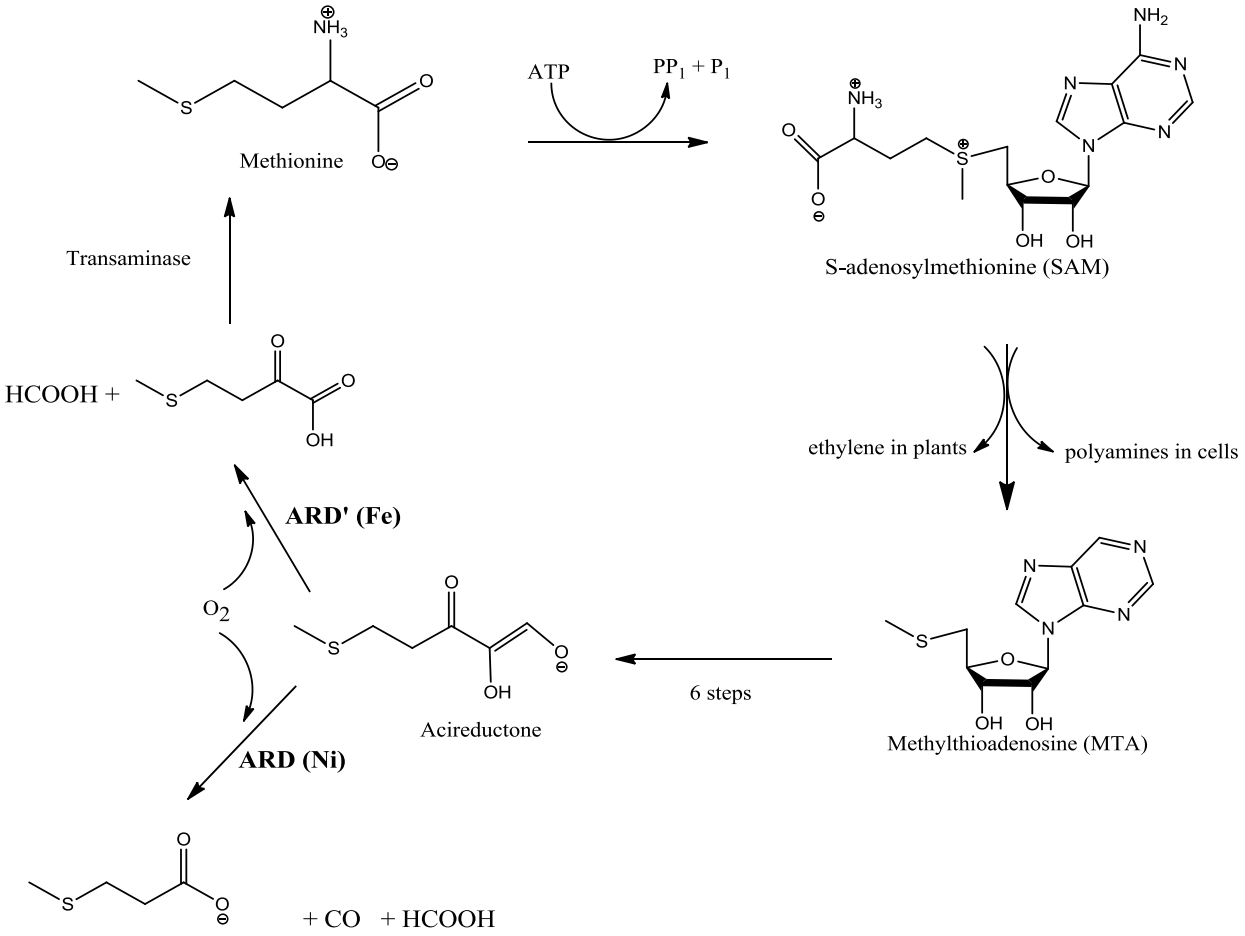
Acetyl Coenzyme A Synthase

Figure 2. Active sites of the polynuclear nickel metalloenzymes. Reprinted with permission from S. W. Ragsdale (2009) Copyright 2009 American Society for Biochemistry and Molecular Biology [1]

A**cireductone Dioxygenase**

The methionine salvage pathway is a universal pathway, found in all types of organisms from unicellular bacteria to plants and animals, which recycles methionine from 5'-methyl-thioadenosine (MTA). The recent investigation of the pathway in the bacteria *Klebsiella pneumonia* has lead to the discovery of a unique set of enzymes called acireductone dioxygenases (ARDs).[4]

Acireductone dioxygenase is used to catalyze two different reactions between 1, 2-dihydroxy-3-oxo-5-(methylthio)pent-1-ene (acireductone), an intermediate in the pathway, and O_2, depending on the metal ion bound in the active site (Scheme 1). These enzymes share a common polypeptide sequence but bind different metal ions, Ni^{2+} or Fe^{2+}, at the active site and can be separated using ion exchange and hydrophobic interaction chromatography. When the iron metal ion is bound in the active site (ARD') the acireductone is cleaved to give formate and methylthioketobutyrate, a precursor for methionine. But when the nickel metal ion is bound in the active site (ARD) the acireductone is cleaved to give formate, carbon monoxide and methylthiopropionate, which is not a precursor for methionine.[5-9] Thus, ARD is considered an off pathway shunt of the methionine salvage pathway. There have been several proposals as to the reason for the off pathway shunt including simply a method of regulating the amount of methionine produced or a method to produce carbon monoxide, which can act as a neurotransmitter or diffusible messenger.[6,10] Despite these proposals the exact reasons for the off pathway shunt remain unclear.



Scheme 1. Methionine salvage pathway in *Klebsiella pneumonia*

Nickel-containing ARD is the first example of a nickel-containing dioxygenase reported in the literature. Using a mouse homolog of ARD, X-ray absorption spectroscopy (XAS) and NMR, the structure of the nickel center in the resting state of ARD has been determined.[11] The reported structure has a six coordinate nickel site composed of oxygen/nitrogen donor ligands, with three being from histidine imidazole nitrogen's. ^{1}H NMR studies revealed several isotropically shifted resonances in the range of 45-75 ppm. These signals are assigned to imidazole protons of the histidine ligands.[9] The carboxylate of glutamate provides the fourth of six ligands required for the pseudo octahedral structure, with the remaining two exogenous ligands reported to be provided by water or substrate (Fig. 3).[5-7]

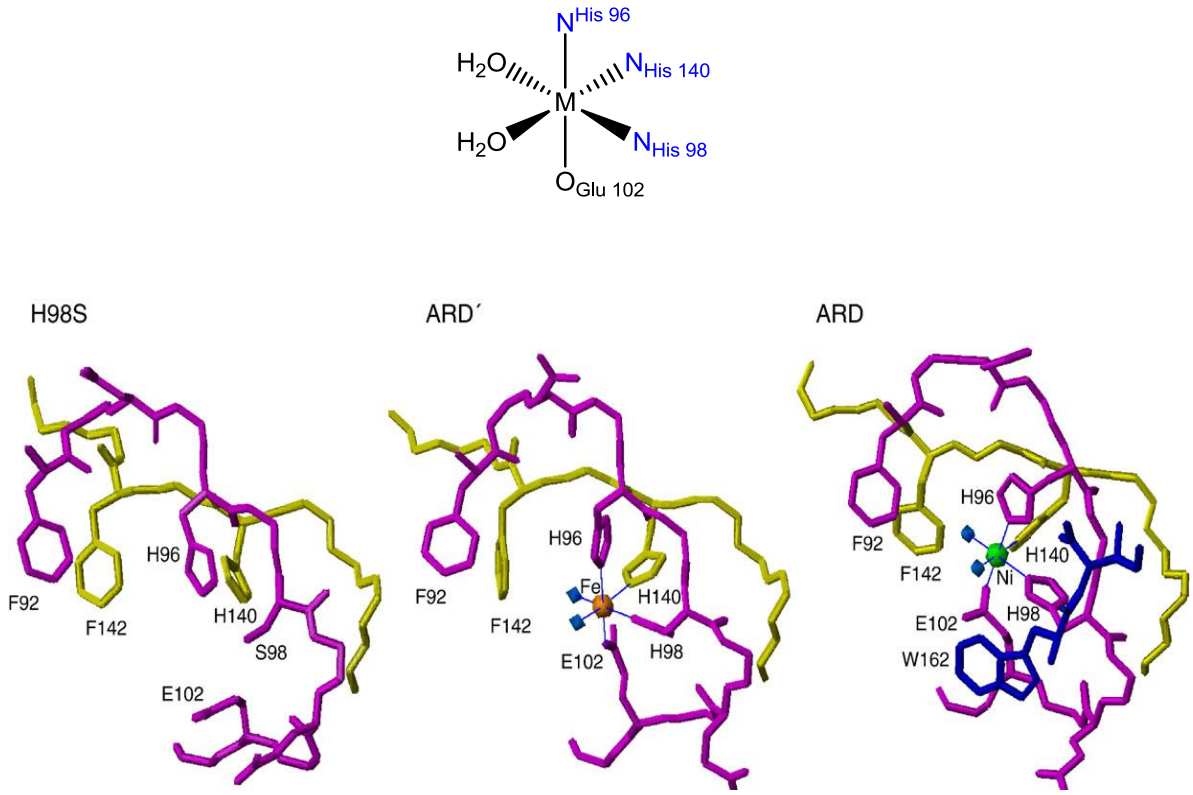
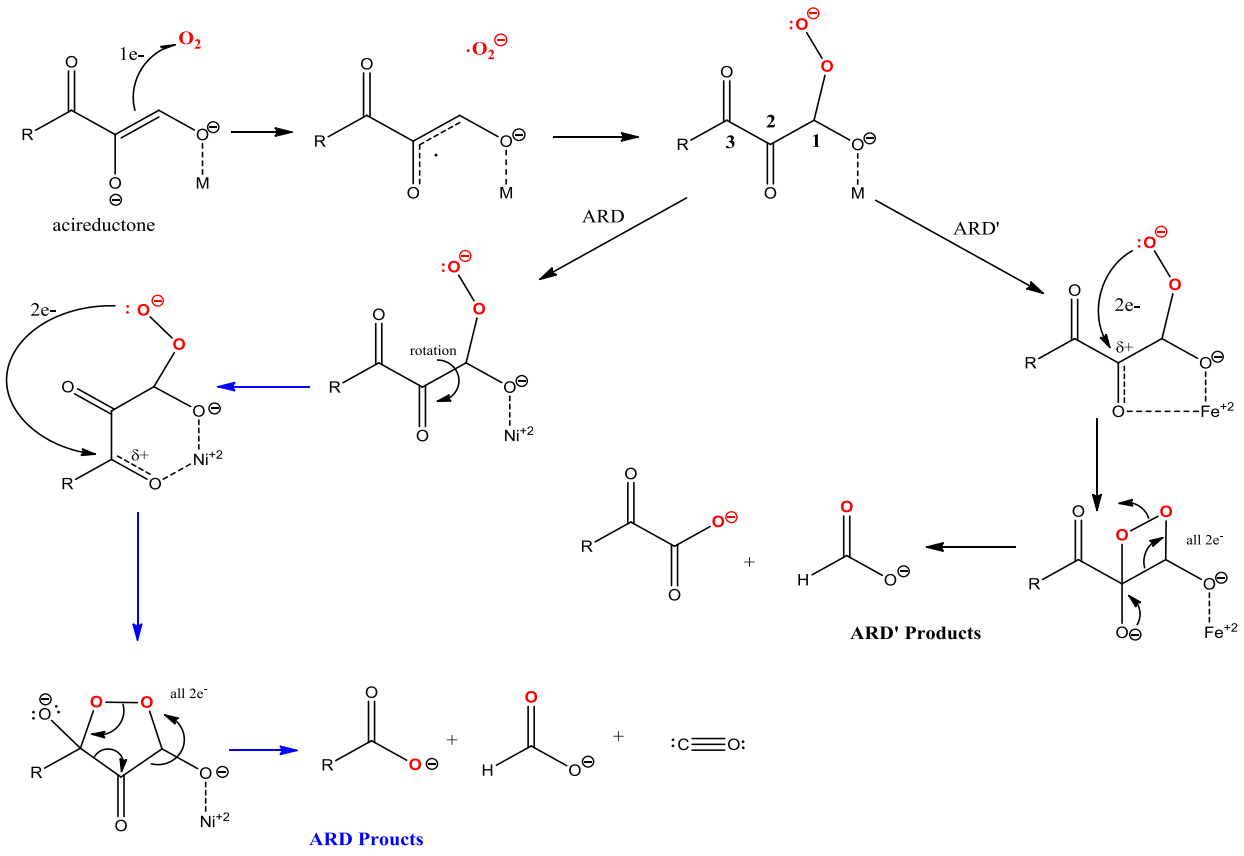


Figure 3. Binding motif and active sites of the Apo, Iron bound (ARD') and Nickel bound (ARD) enzyme. Reprinted with permission from T. Ju, R. B. Goldsmith, S. C. Chai, M. J. Maroney, S. Pochapsky and T. Pochapsky (2006). Copyright 2006 Elsevier.[9]

The most recent mechanism of both the nickel and iron catalyzed reactions has been proposed by Pochapsky and co workers.[6] Here they reported that the nickel and iron catalyzed reactions undertake two different pathways which explains the different sets of products. The pK_a values for the acireductone substrate have been determined to be 4 and 12.2. It is therefore a monoanion at neutral pH. An electronic absorption spectrum of the substrate at pH 7.4 features a λ_{max} equal to 305 nm that shifts to 345 nm at pH 13, which corresponds to the substrate becoming the dianion species. Under anaerobic conditions, binding of the substrate to Ni(II)-ARD causes a red shift in the λ_{max} from 305 to 345 nm, suggesting the dianionic binding of the substrate. Upon addition of the substrate several new resonances appear in the ^1H NMR spectrum of the enzyme/substrate complex, compared to the spectrum of the resting state for enzyme. EXAFS data is consistent with a six coordinate Ni(II) center in the enzyme/substrate complex with a higher O-donor content compared to the resting state of Ni(II)-ARD.[7]

The first step of the mechanism is identical in both reactions; here an electron is transferred from the acireductone substrate to the O_2, which results in the formation of superoxide. The superoxide then reacts to form a C-O bond with C_1 of the substrate. In the Ni(II) catalyzed reaction, the nickel binds to the intermediate via chelation at the 1 and 3 position oxygens forming a 6-membered chelate ring, while in the iron catalyzed reaction, the iron binds to the intermediate at the 1 and 2 positions forming a 5-membered chelate ring. Then a nucleophilic attack at C_3 in the nickel and at C_2 in the iron catalyzed reactions give rise to a 5-membered peroxo-ring intermediate in the nickel catalyzed reaction and a 4-membered peroxo intermediate in the iron catalyzed reaction. The final step of the mechanism is a retro cycloaddition rearrangement for ARD and a fragmentation for ARD' to

form the products of each reaction. Isotopic labeling experiments using $^{18}O_2$ have been conducted to show the nature of oxygen incorporation from the dioxygen into the final products in each mechanism (Scheme 2). In the nickel catalyzed reaction (ARD) you get an off pathway oxidation of acireductone where the $^{18}O_2$, shown in red, is incorporated into C_1 and C_3 with the formation of carbon monoxide, formate, and methylthiopropionate, whereas in the iron catalyzed reaction (ARD'), the $^{18}O_2$ is incorporated into C_1 and C_2 of the substrate which results in the formation of formate and the keto-acid precursor of methionine.[9]



Scheme 2. Proposed mechanisms for ARD' and ARD catalysis of acireductone oxidation. The oxygen atoms in red represent the position of the oxygens derived from O_2 as determined by $^{18}O_2$ labeling.[7]

Synthetic Models for Nickel ARD

Studies involving the reactivity and characterization of complexes with analogs of the ARD substrate coordinated have been very rare. One of the first examples of an acyclic acireductone analog complex to be characterized by X-ray crystallography was reported by Jeffery and coworkers in 1996.[12] The compound $[(Ru(bipy)_2)_2(\mu\text{-}C_4H_4O_3)]\ [PF_6]_2$ (Fig. 4) was prepared using [Ru (bipy) $2Cl_2 \cdot H_2O$], (bipy-2, 2'-bipyridine), and ethylene glycol in the presence of NH_4PF_6. In this complex the acireductone analog is coordinated as a dianion. To date there have been no reactivity studies reported for this compound.

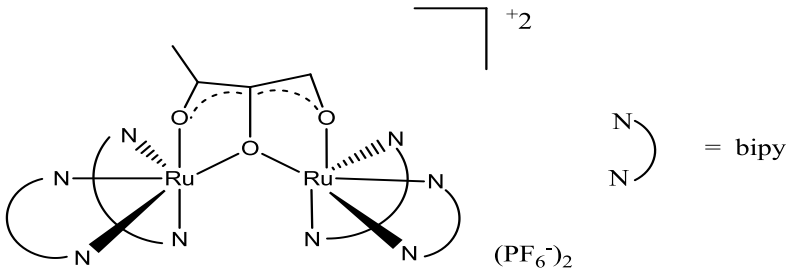


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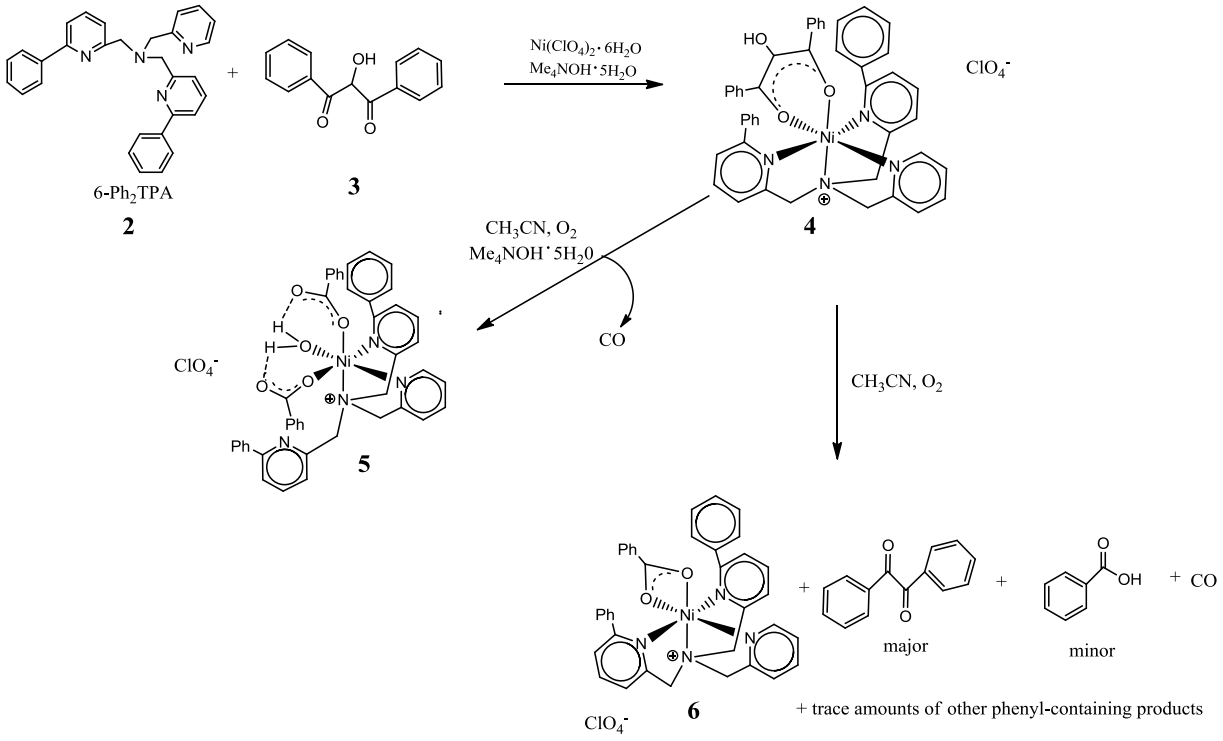
Figure 4. Drawing of $[(Ru\ (bipy)_2)_2(\mu\text{-}C_4H_4O_3)]\ [PF_6]_2$

Berraeu and coworkers have reported a new nickel complex which could be used to model the Ni-ARD enzyme-substrate complex (Scheme 3).[13,14] Using the poly pyridyl-chelate ligand, (*N, N*-bis((6-phenyl-2-pyridyl) methyl)-*N*-((2-pyridyl) methyl) amine) (6-Ph_2TPA, **2**) and the bulky 2-hydroxy-1, 3-diphenylpropan-1, 3-dione (**3**) substrate analog they formed a complex which mimics structurally the Ni-ARD complex (**4**, Scheme 3). Reactivity studies of this complex with O_2 were conducted in the presence or absence of additional base. The reaction in which base was not added produced a complex, in which the bound substrate (**3**) is in the monoanionic form (**6**, Scheme 3), along with several additional organic side products during the reaction. But the reaction in which additional base was added produced a new nickel complex having a coordinated dianionic form of (**3**), as supported by the spectroscopic evidence. Treatment of this complex with excess O_2 results in the formation of (**5**) and CO (Scheme 3). Formation of the dianion is believed to be essential in producing an appropriate rate of reaction involving O_2 and toward limiting the alternative oxidation pathways. This reaction is much cleaner because there was no detection of additional organic products produced.

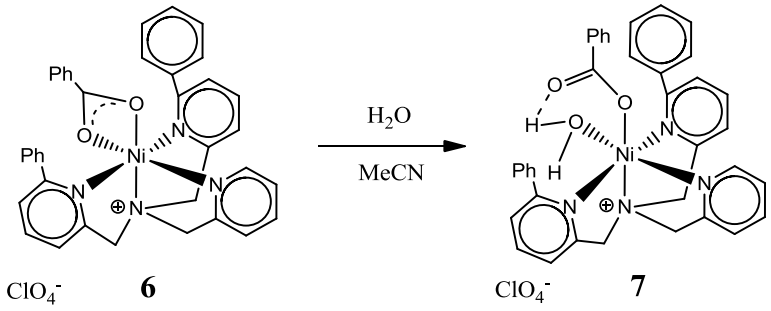


Scheme 3. Model substrate reactions reported by Berraeu

When labeled $^{18}O_2$ was used in the reaction with no additional base, there was approximately 50% incorporation into the benzoate ligand compared to 67% incorporation when base was added to the reaction. These results help confirm the notion that when base is added to the reaction, fewer side products and more of the expected products are formed.[13-16]

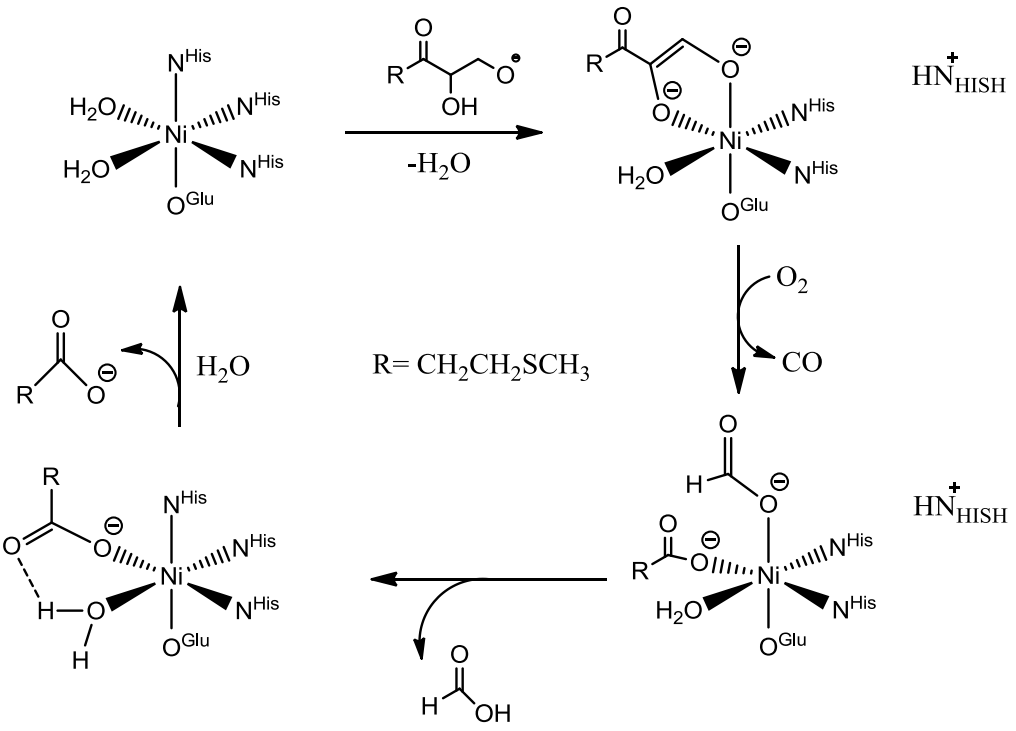
The nickel complexes produced in these reactions contain a tetradentate chelate ligand which contains two hydrophobic phenyl appendages. The purpose of the two phenyl groups was to mimic the possible influence of the two hydrophobic phenylalanine residues that are positioned near the active metal center in Ni-ARD. The reaction conducted in the presence of base produces a complex in which the 6-Ph_2-TPA chelate ligand binds with κ^3-coordination while the reaction conducted in the absence of base had κ^4-coordination of the ligand.

While investigating the carboxylate chemistry of these complexes it has been reported that in the mononuclear complex the carboxylate ligand coordinates differently depending on the presence of water in the reaction. In the relative absence of any water the carboxylate ligand is bidentate but when water is present the ligand is monodentate and forms a hydrogen bonding interaction with a Ni (II)-bound water molecule (Scheme 4).[17]



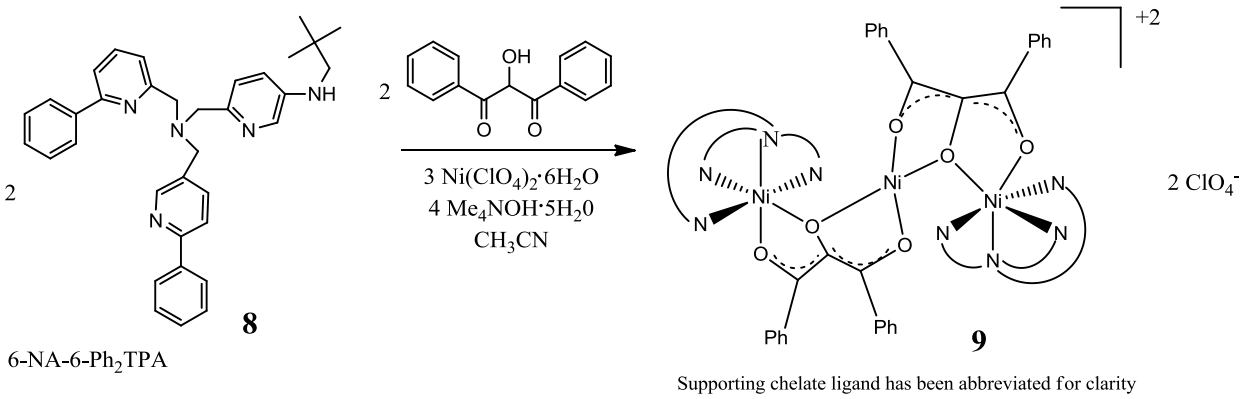
Scheme 4. Reaction of mononuclear nickel complex with water.

These results demonstrate that the coordination properties of a carboxylate ligand can be influenced by the secondary environment surrounding the nickel center in ARD. These studies have also allowed Berreau and coworkers to assemble a preliminary step by step mechanism in which the carboxylate is released from the Ni-ARD (Scheme 5). In this mechanism the coordination of the carboxylate must be monodentate and not bidentate, because the bidentate coordinated species may inhibit the release of the product and reduce the effectiveness of the catalytic cycle.



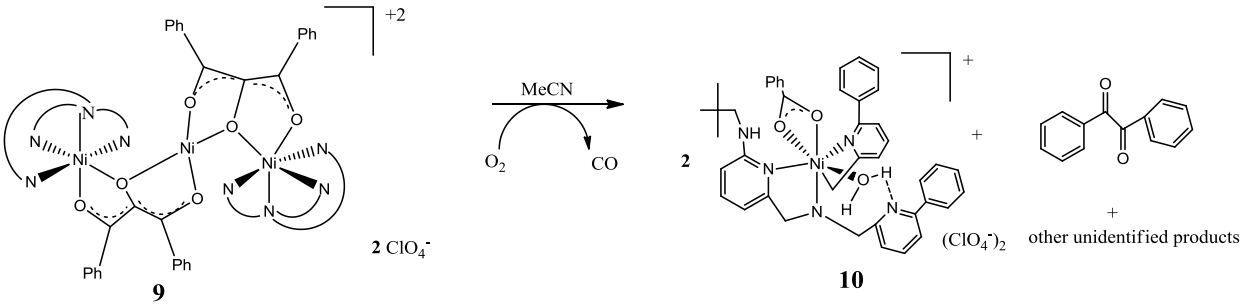
Scheme 5. Propose Stepwise carboxylate product release in Ni-ARD where R=$CH_2CH_2SCH_3$

To further investigate the influence of hydrogen bonding, Berraeu and coworkers developed a new N_4-donor chelate ligand, 6-NA-6-Ph_2TPA (**8**), where a secondary amine hydrogen-bond donor has been incorporated to create a mixed hydrophobic/hydrogen-bond donor environment. The purpose of this ligand was to investigate the influence of a hydrogen bond donor on the chemistry of the nickel (II) complexes. Using the same methods as before, they attempted to prepare a new analog of the 6-Ph_2-TPA complex (**6**); instead of a mononuclear compound they received something relatively different, an orange/brown trinuclear complex (**9**) (Scheme 6). The formation of this complex suggests that the presence of the internal hydrogen donor may be important in promoting dianion coordination of the substrate.[13]



Scheme 6. Synthesize of the trinuclear nickel (II) enedioliate complex

Exposure to O_2 resulted in the rapid loss the orange brown color to give a pale green solution indicating a reaction had taken place (Scheme 7). Using ^1H NMR they have identified several new resonances of the complex. The NMR combined with MS data allowed them to identify one of the main nickel containing products of this reaction, complex **10**.[13]



Scheme 7. O_2 Reactivity of Trinulcear Complex (**9**)

To verify these results an independent synthesis of the product was conducted and the resulting characterization was compared.

The complexes developed by Berreau and coworkers are the only nickel complexes to date which have an acireductone ligand to be reported in the literature. From these studies it has been determined that the nickel (II) coordination chemistry of (**2**) and its analog (**8**) is strongly influenced by the nature of the supporting chelate ligand and the secondary environment surrounding the metal center.

However, even though these complexes make good functional models, the 6-Ph_2TPA ligand does not serve as a good structural representation for the histidine backbone seen in the active site of the enzyme. In the active site of the ARD enzyme the three histidine residues bind in a facial manner but the 6-Ph_2TPA ligands are considered tetradentate ligands with all four nitrogens binding to the metal.

Nickel Superoxide Dismutase

Superoxide dismutases (SODs) protect cells against oxidative damage by regulating the cellular concentration of the superoxide radical ($O_2^{\cdot-}$) which is the unwanted byproduct of cellular metabolism. This process is accomplished by converting the superoxide radicals to hydrogen peroxide and molecular oxygen. The redox-active metal cofactor cycles between oxidized and reduced states that differ by one electron.

$$2\ O_2^{\cdot-} + 2H^+ \longrightarrow H_2O_2 + O_2$$

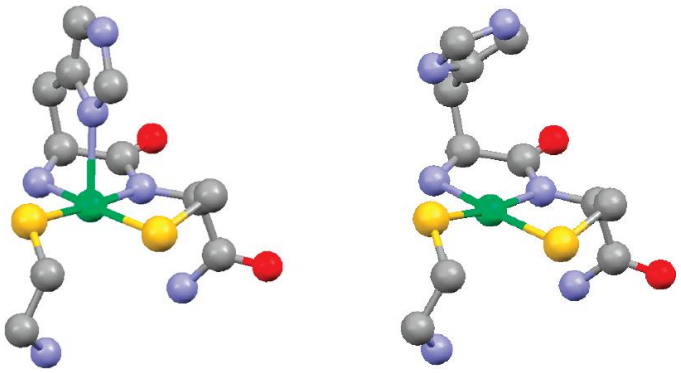
Three classes of superoxide dismutase enzymes have been characterized: copper-zinc superoxide dismutase (CuZnSOD), the structurally related iron and manganese superoxide dismutase (FeSOD and MnSOD), and the nickel superoxide dismutase (NiSOD). The enzymatic reaction can be written as two distinct half reactions, an oxidative half reaction in which the substrate, superoxide, is oxidized to dioxygen and a reductive half reaction in which superoxide is converted to hydrogen peroxide:

$$O_2^{\cdot-} + M^{(n+1)+}SOD \longrightarrow O_2 + M^{n+}SOD$$

$$O_2^{\cdot-} + 2H^+ + M^{n+}SOD \longrightarrow H_2O_2 + M^{(n+1)+}SOD$$

where M = Cu (n=1); Mn (n=2); Fe (n=2); Ni (n=2).

The Ni SODs have many similarities with the Mn/Fe and Cu/Zn SODs, but forms a distinct group based on the metal content and ligand environment of the nickel center and the protein structure. In the active site of the enzyme the nickel geometry cycles from square planar Ni(II), with thiolate and nitrogen ligands, to square pyramidal Ni(III) with an added nitrogen ligand (Fig. 5)



Ni (III) Ni (II)

Figure 5. Geometry of Ni-SOD active site, square pyramidal (left) and square planar (right). Reprinted with permission from H. Ma, G. Wang, g. T. Yee, J. L. Peterson, M. P. Jensen (2009). Copyright 2009 Elsevier. [18]

Synthetic Models for Nickel SOD

Jenson and coworkers recently reported several pentacoordinate complexes using a derivative of the hydrotris(dimethyl-pyrazolyl)borate anion and a dithiocarbamate co-ligand (Fig. 6).[18,19] The complexes were isolated and structural, spectroscopic and reactivity studies were reported.

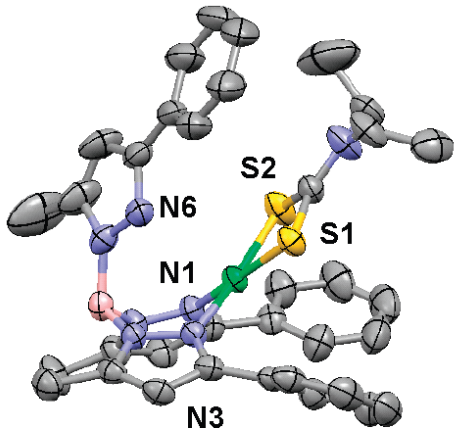


Figure 6. X-ray crystal of $Tp^{Ph,Me}NiS_2CNEt_2$. Reprinted with permission from H. Ma, S. Chattopadhyay, J. L. Peterson and M. P. Jensen(2008). Copyright 2008 American [18]

All of the reported complexes exhibit key properties, tuneable oxidation, axial equilibrium coupled to spin crossover and redox reactivity, which mimic the reduced Ni-SOD enzyme.

Trispyrazolylborate Chemistry

The hydrotrispyrazolyl borate ligands (Tp) were first reported by Trofemenko in 1966 and have been of interest in many areas of inorganic chemistry because of their thermal and oxidative stability along with their ability to stabilize unusual structural features such as highly reactivity or oxygen sensitive metal - ligand fragments.[20] The substituent groups located on the pyrazole ring allow the steric requirement of the ligand to be tuneable. By changing these groups we can adjust the steric demands of the ligand. There have been various substituents in the 3, 4, and 5 positions of the pyrazole ring with the most utilized of these being the 3, 5-dimethylpyrazole derived ligand (Fig. 7).

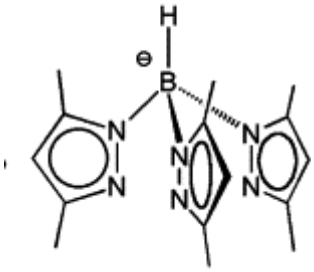


Figure 7. Hydrotris(3, 5-dimethylpyrazolyl)borate, (**11**)

Here the methyl groups in the three position of each ring taken together form a protective steric "pocket" around the metal ion while the methyl groups in the five position offer protection to the B-H bond.

Over a hundred structures containing hydrotrispyrazolyl borate ligands and the nickel metal ion have been deposited into Cambridge Crystallography Structure Database. Many of the structures sited in the search are hydrotrispyrazolyl borate (Tp) mixed ligand complexes (TpNiX), where X can be anything from a simple halide or carboxylate ligand to a more complex nitrogen, oxygen, or sulfur donor ligand (Fig. 8). [21-36]

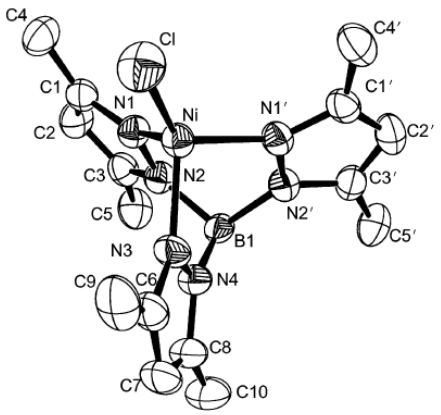


Figure 8. Example of a mixed ligand Tp* complex; ORTEP diagram for Tp*NiCl. Reprinted with permission from P. J. Desrochers, S. LeLievre, R. J. Johnson, B. T. Lamb A. L. Phelps, A. W. Cordes, W. Gu and S. P. Cramer (2002) Copyright 2003 American Chemical Society[37]

The nitrogen donor complexes are the largest subcategory of mixed ligand complexes,[24,28,30,38-61] while sulfur donor ligands complexes (Fig,9) are the [18,52,60,62,63] smallest subcategory of complexes found during the search.

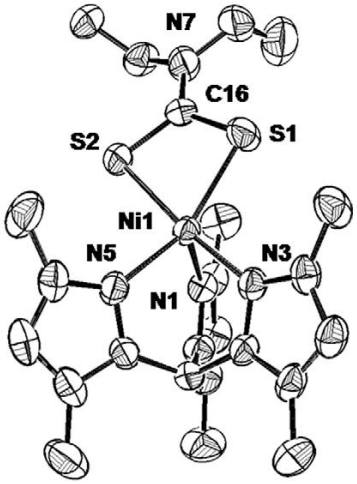


Figure 9. Example of a Tp* complex with a sulfur donor ligand; ORTEP diagram for Tp*NiS_2CNEt_2. Reprinted with permission from H. Ma, G. Wang, G. T. Yee, J. L. Peterson, M. P. Jensen (2009) Copyright 2009 American Chemical Society.[63]

The complexes which contain an oxygen donor ligand (Fig. 10) have the most significance to our research project . [28,30,44,45,48,58,61,64-73]

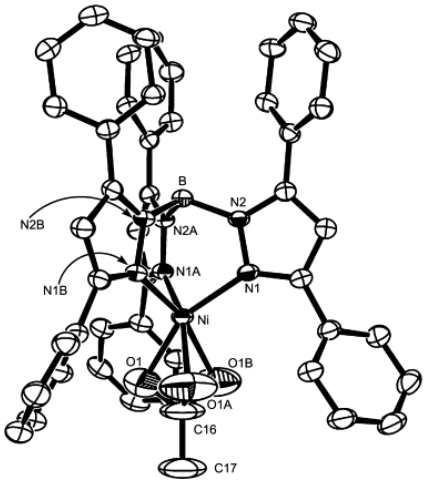


Figure 10. Example of a Tp* complex with an oxygen donor ligand, ORTEP diagram for $Tp^{Ph}{}_2Ni(OAc)$. Reprinted with permission from D.J. Harding, P. Harding, H. Adams and T. Tuntulani (2007) Copyright 2007 Elsevier[71]

There were several dimetallic complexes listed where there are two different metal ions incorporated into the structure; examples include nickel-cobalt and nickel-ruthenium complexes (Fig. 11)[74-77]

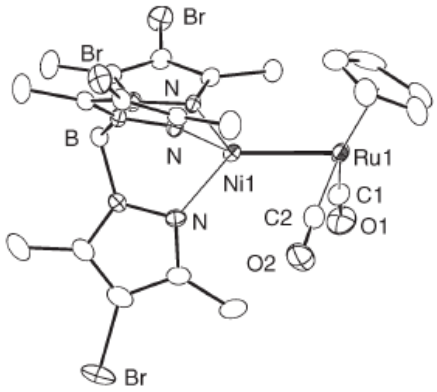


Figure 11. Example of dimetallic Tp* complexes $TpNiRuCp(CO)_2$.

A fair number of bridged complexes were also found; here two TpNi complexes are attached by a bridging ligand (hydroxyl, halide, carboxylate, etc.) to form one complicated structure (Fig. 12). [26,28,48,66,69,70,78-84]

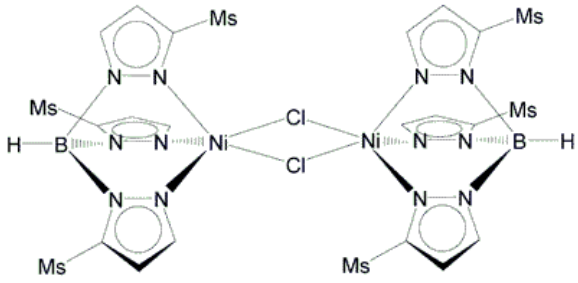
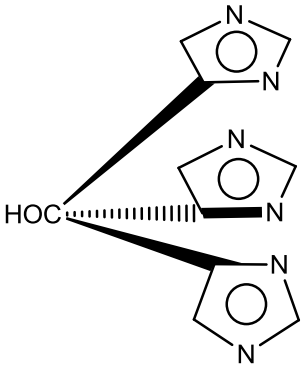


Figure 12. Example of a bridged Tp complex, $[\{TpMs^{**}\}NiCl]_2$.[26]

Tris(4-imidazolyl)carbinol Chemistry

Unlike the hydrotrispyrazolyl borate ligands, the tris (4-imidazolyl)carbinol ligands have seen limited attention with regard to the models of metalloenzymes, despite the fact that imidazole is more biologically relevant. The synthesis of these compounds has been extremely problematic for years but with a recently reported simplified synthesis the coordination properties and catalytic reactivity of their metal complexes can now be studied.[85,86] Only six metal complexes with tris(4-imidazolyl)carbinol (**12**) have been structurally characterized.



12

Figure 13. Drawing of tris(4-imidazolyl)carbinol.

In 2004, Nicholas and co workers reported an improved route to the parent tris(4-imidazolyl)carbinol.[85] They also reported the first structurally characterized metal complex of the tris(4-imidazolyl)carbinol ligand, an Iron (II) complex (Fig. 14).

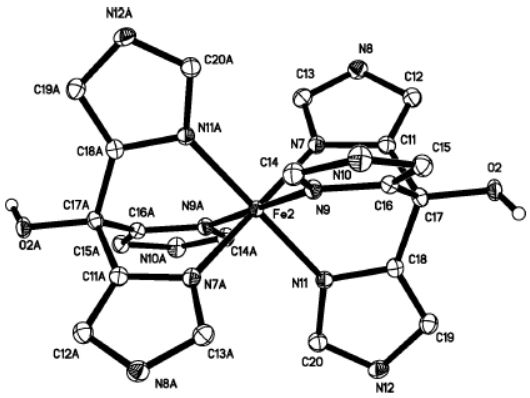


Figure 14. ORTEP diagram for Fe[tris(4-imidazolyl)carbinol]$_2$Cl$_3$.[85]

Kujime and coworkers prepared two copper complexes using the ethyl and isopropyl substituted tris(4-imidazolyl)carbinol ligands.[87] The reported complexes were used for ^{63}Cu NMR spectroscopic studies. The effectiveness of copper bound CO as a ^{63}Cu probe was examined and reported. The paragamagnetic shielding effect by the copper-bound CO induces a large downfield shift of the ^{63}Cu NMR signal for the copper carbonyl complex. Even though two different 4-TIC ligands were used in this study only one crystal structure was reported, [Cu(i-pr-4-TIC)(CO)]ClO$_4$ (Fig. 15).

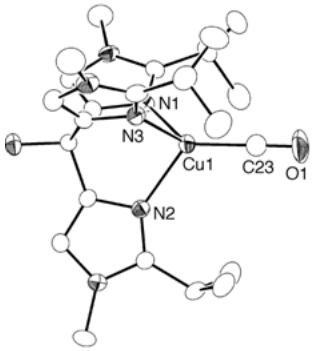
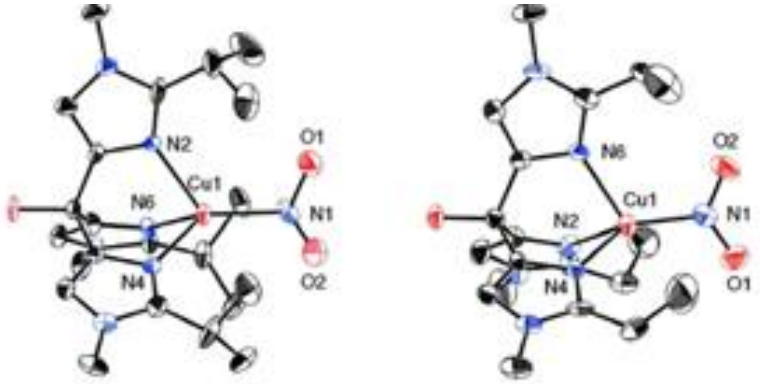


Figure 15. ORTEP drawing of the Cu complex of [Cu(*i*-pr-4-TIC)(CO)]ClO_4.[87]

In an effort to study copper (I) nitrite, a key intermediate of the copper containing nitrite reductase (Cu-NiRs), several functional models were prepared, two of which contained derivatives of the 4-TIC ligand.[88] The copper containing nitrite reductases catalyze the reduction of nitrite to nitric oxide gas in bacterial denitrification. The X-Ray crystal structures of [Cu(i-pr-4-TIC)(NO_2)] and [Cu(Et-4-TIC)(NO_2)] are shown in Figure 16.



A B

Figure 16. ORTEP drawings of (a) [Cu(i-pr-4-TIC)(NO_2)] and (b) [Cu(Et-4-TIC)(NO_2)].[88]

The 4-TIC ligand complexes are soluble in many polar protic solvents (ethanol, methanol and water),

In an effort to increase the solubility of the complexes in aprotic solvents we started investigating disubstituted 4-TIC ligands. The first series of disubstituted 4-TIC ligands were reported by Kujime and coworkers (Fig. 17).[86] These complexes were designed to have a stable NH protecting group in the 1-position and a sterically hindered substituent at the 2-position of each imidazole ring. These substituted ligands were prepared with hopes of stabilizing the reactive species bound to the metal center of many metalloenzymes.

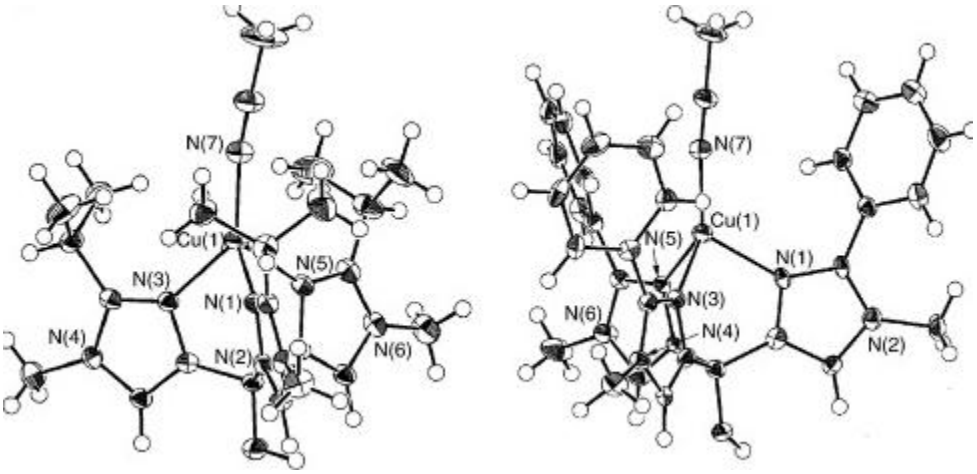


Figure 17. ORTEP drawings of (a) $[HOC(Im^{i\text{-}Pr})_3Cu(CH_3CN)]^+$ and (b) $[HOC(Im^{Ph})_3Cu(CH_3CN)]^+$.[86]

In the proposed mechanism of ARD, the substrate which binds to the metal contains a functional group that has not been reported extensively in the literature as a ligand in metal complexes, the enediol. Using the model ligand reported by Berreau, (**3**) and a tridentate nitrogen binding ligand, that resembles the 3-histidine binding motif in the enzyme, we have prepared several complexes which contain the enediol functional group.

This has given us complexes which contain structural components similar to that of the ARD enzyme. Modeling studies can often help in understanding the mechanism of enzyme-catalyzed reactions.

The main goal of this research project is to prepare structural models of the nickel acireductone dioxygenase and superoxide dismutase enzymes. In order to achieve this objective we will focus on the following: 1) preparing nickel complexes that contain a tridentate nitrogen binding ligand which resembles the 3-histidine binding motif of the enzymes and/or 2) exploring the reactivity of these complexes with oxygen.

The nickel ARD has been reported as a pseudo-octahedral structure in which there are three histidines coordinated in an approximate tripodal geometry to the metal site. To mimic this binding motif we will use the tripodal nitrogen binding hydrotris(3,5-pyrazolyl)borate (Tp*) and the di-methyl substituted tris[4(5)imidazolyl]carbinol (4-TIC^{Me,Me}) ligands.

There are very few examples of metal complexes that include a ligand with the binding groups and binding modes found in the enzyme. Interest in ligands of this type is due to the fact that the acireductone substrate which binds to the ARD enzyme contains this functional group. After examining several acireductone and enediol ligands, it has been determined that the 2-hydroxy-1, 3-diphenylpropan-1, 3-dione ligand will be a nice model for the acireductone substrate. Using our tripodal nitrogen complexes as the backbone structure we will attempt to prepare rather simple complexes which contain structural complexes similar to the ARD active site.

The oxygen reactivity of these model complexes will be also be investigated. These results will be compared to that of the ARD substrate and the other reported model complexes in the literature with hopes of gaining a better understanding of the proposed mechanism of the nickel ARD.

The coordination environment of the nickel superoxide dismutase can be modeled by the tripodal nitrogen binding hydrotris(3,5-pyrazolyl)borate (Tp*) and dithiocarbamate ligands. We have prepare and characterized several Tp*Ni(S_2CNR_2) complexes with various ring sizes. These complexes can serve as models for the N_3S_2 coordination environment of the oxidized Ni-SOD.

CHAPTER 2

EXPERIMENTAL

Methods and Materials. All reactions and recrystallizations were carried out aerobically unless otherwise noted. Hexanes, dichloromethane, isopropanol, 1, 2-dichloroethane, acetonitrile, and ethyl acetate were purified by distillation from calcium hydride. Toluene and methanol were purified by distillation from sodium and magnesium methoxide, respectively. Tetrahydrofuran was purified using the Pure Process Technology/Glass Contour Solvent Purification System. All other reagents were of commercial grade and used without further purification. ^{1}H NMR was recorded on a Bruker 300 MHz spectrometer. Elemental analyses were performed by Columbia Analytical Services, Inc., Tucson, Az. UV-Visible-NIR spectra were obtained from an OLIS Cary-14 UV/VIS/NIR double beam spectrophotometer. Mass spectra were measured on a Bruker Autoflex MALDI TOF mass spectrometer or Thermo-Scientific ITQ1100 GC-Ion Trap MS. Infrared spectra were recorded on Bruker IFS-66 FTIR spectrometer with a Graseby-Speac grazing angle reflection accessory. Cyclic voltammetric measurements were preformed in MeCN or CH_2Cl_2 solutions containing 0.1M $[Et_4N]$ $[ClO_4]$ as supporting electrolyte. Potentials were measured against Ag/0.01 $AgNO_3$ in MeCN as reference electrode on an EG & G Princeton Applied Research Corp. Model 283 instrument.

Ligand Synthesis

2-Hydroxy-1,3-diphenylpropan-1,3-dione (3)

A 250 mL round bottom flask with a side arm connected to an oil bubbler was charged with $NaHCO_3$ (0.840 g, 0.010 mol) and a fresh solution of $RuCl_3$ (400 µL, 0.1 M). The suspension was diluted with 4 mL of distilled H_2O, 24 mL of ethyl acetate and 24 mL acetonitrile. The mixture was allowed to stir for a few minutes after which Oxone® (12.2 g, 0.02 mol) was added in one portion to the brown solution, causing gas evolution (as seen from the bubbler). After about 10 min the solution turned a bright yellow color and chalcone (0.833 g, 0.004 mol) was added to the solution. The mixture was allowed to stir for 3 days. The phases were separated and the aqueous layer was extracted with ethyl acetate (x3, 25mL). The yellow organic layers were combined and dried over Na_2SO_4 overnight. The mixture was filtered and solvent was removed from the filtrate under reduced pressure to give a yellow oily substance. Purification of the residue by silica gel flash chromatography using pentanes/ethyl acetate as the eluent (**3**) as a yellow solid; yield 0.20 g (21%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01(d, 4H), 7.56 (m, 2H), 7.47 (m, 4H), 6.09 (s, 1H), 4.65 (s, 1H) ppm, in agreement with the literature.[89]

Potassium hydrotris(3, 5-dimethylpyrazolyl)borate, (13) (KTp*)

A 500 mL three neck flask equipped with a gas inlet adapter and thermometer was charged with KBH_4 (5.39 g, 0.1 mol) and 3, 5-dimethylpyrazole (50 g, 0.5 mol); the flask was degassed and placed under a gentle flow of nitrogen. The mixture was heated with stirring until the evolution of gas ceased, as noted by the external bubbler. Once the mixture reached room temperature, 100 mL of diethyl ether was added to the flask. The solid was

filtered, washed twice with 50 mL of diethyl ether and dried in air to give (**13**) as a white solid; yield 25.80 g (76.7%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.01 (s, 9H), 2.16 (s, 9H) ppm. FTIR: 2435 (ν_{B-H}) 1571, 1537, 1415, 1237, 1183, 1110, 943 cm^{-1}, in agreement with the literature.[90]

Acetylacetonate [hydrotris(3, 5-dimethylpyrazolyl)borato]nickel (II), (14) (Tp*Ni(acac))

A 500 mL round bottom flask was charged with $Ni(acac)_2{\cdot}2H_2O$ (2.56 g, 0.01 mol), **13** (3.36 g, 0.01 mol) and 160 mL of dichloromethane. The mixture was allowed to stir for 18 hours. The white precipitate produced during the reaction was filtered and washed several times with dichloromethane. The washings and filtrate were combined and concentrated under reduced pressure to give a solid. Purification of the solid by silica gel column chromatography using dichloromethane as the eluent gave (**14**) as a blue-green solid; yield 3.26 g (72 %). FTIR: 2505 cm^{-1} (ν_{B-H}), in agreement with the literature.[91]

Bromo [hydrotris(3,5-dimethylpyrazolyl)borato]nickel (II), (15) (Tp*NiBr)

A solution of 48% HBr (0.25 mL) in 20 mL of tetrafydrofuran was added dropwise to (**14**) (1.0 g, 2.2 mmol) in 60 mL of THF in a 200 mL Erlenmeyer flask. The mixture was allowed to stir for 13 hours during which the solution changed from a bluish color to a deep purple color. The solvent was then removed under reduced pressure and the crude product was recrystallized by slow evaporation of dichloromethane at room temperature. The crystals were collected by filtration, washed three times with hexanes and dried in air to give (**15**) as a purple solid; yield 0.50 g (52%) FTIR: 2528 (ν_{B-H}), 1541, 1447, 1178, 1064, 857 cm^{-1} in agreement with the literature.[91]

Tris(1-N,N-dimethylsulphamoyl-2-t-butyldimethylsilyl-5-imidazolyl)carbinol (17)

1-(Dimethylsulfamoyl)imidazole (**16**) (1.85 g, 10.6 mmol) was dissolved in 90 mL of dry THF under nitrogen. With vigorous stirring, the temperature was lowered −78°C and a solution of *n*-BuLi in pentane (11.1 mmol, 5.9 mL of 1.88 M) was added dropwise. After the solution was stirred for 30 min, a solution of *tert*-butyldimethylsilyl chloride (12.7 mmol, 1.91 g in 2 mL of THF) was added via syringe. The reaction was allowed to warm to room-temperature overnight. The mixture was then cooled to −78°C, and a solution of *n*-BuLi (11.7 mmol, 6.2 mL, 1.88 M) was added dropwise. After the solution was stirred for 30 min, neat diethyl carbonate (3.0 mmol, 425 mL) was added dropwise. The mixture was allowed to warm to room temperature over 24 h. Ethyl acetate (50 mL) was added, and the solution was washed three times with 20 mL of brine. The organic layer was dried over $MgSO_4$, and the solvent was rotary evaporated. During evaporation, a white solid precipitated, which was filtered and washed with ethyl acetate. The filtrate was concentrated, and the procedure was repeated to afford 2.19 g of spectroscopically pure (**17**) as a white solid (70% yield).^{1}H NMR (300MHz, $CDCl_3$) δ 6.38 (s, 3H), 5.80 (s, 1H), 2.59 (s, 18H), 1.02 (s, 27H), 0.38 (s, 9H), 0.36 (s, 9H) ppm, in agreement with the literature.[85]

Tris-(4(5)-imidazolyl)carbinol hydrochloric salt (18)

The protected carbinol (**17**) (1.60 g, 1.80 mmol) was refluxed in 50 mL of hydrochloric acid (1.5 M) for 90 min. The solvent was evaporated under reduced pressure. Chromatography of the residue on Dowex 50WX8-100 resin (20 mL) with water followed by 6 M hydrochloric acid yielded 487 mg (80% yield) of hydrochloride salt **18** after solvent

evaporation.^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (s, 1H), 7.74 (s, 1H) ppm, in agreement with the literature.[85]

Tris-(4(5)-imidazolyl)carbinol (12)

The protected Carbinol (**17**)(1.60 g, 1.80 mmol) was refluxed in 50 mL of hydrochloric acid (1.5 M) for 90 min. The solvent was evaporated under reduced pressure. Chromatography of the residue on Dowex 50WX8-100 resin (20 mL) with water followed by 6% NH_4OH yielded **12**. ^{1}H NMR (300MHz, CD_3OH) δ 7.64 (d, 3H), 6.84 (d, 3H) ppm, in agreement with the literature.[85]

4,5-Diiodo-2-methylimidazole (25a)

A solution of 2-methylimidazole (**24a**) (10.0 g, 0.122 mol) in 2M aqueous NaOH (400 mL) was added to a solution of I_2 (61.95 g, 0.244 mol) in CH_2Cl_2 (400 mL). The two phase system was allowed to stir for four days, during which the organic phase became colorless. The aqueous phase was separated and upon neutralized with concentrated acetic acid a white solid precipitated out. The solid was filtered and recrystallized from acetonitrile to give (**25a**) as a white solid; yield 37.65g (93%).^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.12(br, 1H), 2.47 (s, 3H) ppm. Compound (**25b**) was obtained by the same procedure from (**24b**) as a white solid; yield: 16.8 g (89%) . ^{1}H NMR ($CDCl_3$ 300 MHz): δ 8.22 (m, 3H), 7.47 (m, 3H), 2.75 (s, 3H), 2.67 (s, 3H) ppm, in agreement with the literature values.[92]

4-Iodo-2-methylimidazole (26a)

A solution of (**25a**) (10g, 30mmol) and Na_2SO_3 (30g, 0.238 mol) in ethanol (500mL) was refluxed for 24 hrs. The solvent was removed almost to dryness under reduced pressure, to prevent the inorganic salts from precipitating out of the solution and the solid was filtered, washed with distilled water and allowed to dry in air to give (**26a**) as a white solid; yield 4.05g (65%). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.03 (s, 1H), 2.45 (s, 3H) ppm, in agreement with the literature values in agreement with the literature values.[92]

1,2-Dimethyl-4-iodoimidazole (27a)

4,5-Diiodo-1,2-dimethylimidazole(**30a**) (1.57g, 0.00451mol) was dissolved in 20mL of dry THF under a slight pressure of nitrogen. The temperature was lowered to 0˚C and a solution of EtMgBr (0.00519mol, 1.73mL of a 3M solution) in Et_2O was added dropwise. After stirring for 1.5 hrs, the reaction was quenched by the addition of saturated aqueous NH_4Cl (25mL), extracted into ethyl acetate (25mL) and washed 3 times with 25mL of a saturated NaCl solution (brine). The organic layer was dried with Na_2SO_4 overnight. The mixture was filtered and the solvent was removed under reduced pressure to yield a yellow oily residue. Purification of the residue by silica-gel column chromatography using dichloromethane-acetone (9:1) as the eluent gave (**27a**) as a yellow solid: yield 0.58g (58%). ^{1}H NMR ($CDCl_3$, 300MHz): δ 6.871(s, 1H), 3.552 (s, 3H), 2.369 (s, 3H) ppm, in agreement with the literature values.[93]

4-Iodo-1-methyl-2-phenylimidazole (27b)

To a THF suspension (100ml) of NaH (1.43 g, 59.6 mmol) was added (**26b**) (14.2g, 59.6 mmol) and the mixture was stirred for 1hr at room temperature. Iodomethane was added to the mixture and stirred for 12hours at room temperature. The mixture was concentrated and the residue was purified by silica-gel chromatography using dichloromethane/acetone (9:1) as the eluent to give (**27b**) as a white solid; yield 0.67g (35%). ^{1}H NMR 7.61 (d, 2H), 7.47 (m, 3H), 7.07 (s, 1H) 3.74 (s, 3H) ppm, in agreement with the literature.[86]

Tris(1,2-dimethyl-4-imidazolyl)carbinol, (29a) (4-TIC^{me,me})

1,2-Dimethyl-4-iodoimidazole (**27a**) (1.32 g, 0.00594 mol) was dissolved in 50 mL of CH_2Cl_2 under a slight pressure of nitrogen. The temperature was lowered to 0^{o}C and a solution of EtMgBr (0.00653 mol, 2.18 mL of a 3M solution) in Et_2O was added dropwise. After stirring for 2 hrs, fresh $ClCO_2Me$ (0.00198mol, 0.153mL) was added dropwise by way of a syringe. After stirring for 40 hrs, the reaction was quenched by the addition of saturated aqueous NH_4Cl (50mL). The organic layer was separated and concentrated under reduced pressure to give an oily residue. Purification of the residue by alumina column chromatography using dichloromethane-acetone (3:1) as the eluent gave (**29a**) as a white solid; yield 0.17g (27%). ^{1}H NMR ($CDCl_3$, 300MHz): δ 4.046(s, 9H), 2.669 (s, 9H) ppm.

4,5-Diiodo-1,2-dimethylimidazole (30a)

A solution of 4,5-Diiodo-2-methylimidazole (**25a**)(3.20g, 0.00958mol) dissolved in 50mL of dry THF was placed under a slight pressure of nitrogen. The temperature was lowered to 0^{o}C and NaH (0.4598 g, 0.01150 mol) was added slowly. After stirring for 45 minutes, iodomethane (0.656 mL, 0.0150 mol) was added dropwise by way of a syringe and was allowed to stir overnight. Ethyl acetate (50 mL) was added to the reaction, and the solution was washed 3 times with 25mL of a saturated brine solution. The organic layer was dried with Na_2SO_4 overnight. The mixture was filtered and the solvent was removed under reduced pressure to yield a brownish-yellow residue. The residue was treated with chloroform (25mL), and the insoluble part was removed by filtration. The filtrate was concentrated on the rotary evaporator to give (**30a**) as a yellow solid; yield 1.86g (56%). ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.60 (s, 3H), 2.49 (s, 3H) ppm. Compound (**30b**) was obtained by the same procedure from (**25b**) as a white solid; yield 7.6g (74%). ^{1}H NMR ($CDCl_3$ 300 MHz): δ 3.75 (s, 3H), 7.46 (m, 3H), 7.55 (m, 2H) ppm, in agreement with the literature values.[94]

Synthesis of Complexes

Benzoato[hydrotris(3,5-dimethylpyrazolyl)borate]nickel(II), (36) [(Tp*)Ni(OBz)]

Synthesized by two different methods

Method I Reaction of (15) with (3)

A 50 mL flask was charged with (**15**) (0.0726 g, 0.167 mmol) and 8 mL of dichloromethane. The (**3**) (0.0400 g, 0.167 mmol) was added to the flask and the mixture was allowed to stir for a few minutes. Sodium hydroxide (0.33 mL, 0.5M) was added by way of a syringe along with an additional 3 mL of water. The two phase system was then allowed to stir for three hours. A color change in the organic phase from purple to green was observed during the course of the reaction. The green organic phase was separated and evaporated to dryness with a rotary evaporator**.** The residue was chromatographed on silica gel with dichloromethane as the eluent. The green band was collected, evaporated to dryness and recrystallized from dichloromethane/ isopropanol to give (**37**) as a green solid; yield.0483 g (61%) IR 2922, 2511, 1594, 1429, 1517, 1429, 1191, 1060, 864, 808 cm^{-1}, in agreement with the literature values.[95]

Method II Reaction of (14) and (38)

A 50mL round bottom flask was charged with (**14**) (0.25 g, 0.55 mmol) and 10mL of toluene. The mixture was allowed to stir for a few minutes. A solution of (**38**) (0.0675g, 0.55mmol) in toluene (6mL) was added drop wise. The reaction mixture was stirred for 45 minutes. The solvent was removed with a rotary evaporator leaving the crude product. The crude product was recrystallized from dichloromethane/isopropanol to give (**37**) as a green solid; yield 0.1008g (44%) IR 2924, 2511, 1514, 1416, 1188, 1059, 858, 801 cm^{-1}. in agreement with the literature values.[95]

Quantification of Benzoic Acid (38)

The green organic phase from the reaction of (**15**) with (**3**) separated and placed in a 25 mL round bottom flask. Sodium hydroxide (2mL, 0.5M) and 3 mL of distilled water was

added to the flask. The mixture was allowed to stir for approximate 15 minutes. The aqueous phase was separated and the pH was tested (approx. 10). The organic phase was washed three times with 3 mL of distill water and the washings were added to the aqueous phase. The aqueous phase was then extracted three times with approximately 3mL of diethyl ether. The ether was then removed under reduced pressure to give 0.0235g of (**38**). ^{1}H NMR 8.04 (d, 2H), 7.53-7.507 (m, 1H), 7.419-7.369 (m, 2H) ppm, in agreement with literature values.

Reaction of 4-TIC^{me,me} (29a) with (3)

A 25 mL round bottom flask was charged with 4-TIC^{me,me} (0.129g, 0.410 mmol), Ni(acac)$_2$·H$_2$O (0.105g, 0.410 mmol) and 10 mL of acetonitrile. This mixture was allowed to stir overnight after which the solvent was removed on the rotary evaporator to give the crude product as a solid. Crystals were obtained by slow evaporation of 10 mL of an acetonitrile solution to approximately 3 mL. The crystals were collected by filtration, washed with MeOH and dried to give 0.0598 g of product. This material was later identified as Ni(acac)$_2$· 2H$_2$O (**40**) by X-ray crystallography.

Bis(pyrrolidine-1-carbodithioato)nickel (II) (44a) Ni(S$_2$CNR)$_2$

Potassium hydroxide (0.531 g, 10 mmol) was dissolved in 20 mL of distilled H$_2$O. Pyrrrolidine (0.82 mL, 10 mmol) was added dropwise and the mixture was allowed to stir for 15 minutes at room temperature. After which, carbon disulfide (0.60 mL, 10 mmol) was added and the mixture was allowed to continue stirring for an additional 15 minutes. A solution of nickel chloride (1.34 g, 5 mmol) in 5 mL of H$_2$O was added causing the separation of a green precipitate. The solution was allowed to stir for an additional 2 hours

and the precipitate was collected by filtration, washed with water, ethanol and dried in air to give (**44a**) as green solid; yield 1.35 g (77%) Compound (**44b**) and (**44c**) were obtained by the same procedure starting from piperidine and azepane to give (**44b**) and (**44c**) as green solids; (**44b**) yield: 1.59 g (84%); (**44c**) yield: 1.456 g (84%). X-ray crystallography was conducted on all compounds. [96]

Sodium –pyrolidine-1-dithiocarmatae (45a) [Na($S_2CNC_4H_8$)]

Sodium hydroxide (1 g, 0.025 mol) was dissolved in 20 mL of distilled H_2O. The pyrolidine was mixed with 50 mL of ethyl ether and added to the mixture. Carbon disulfide (2g, 0.026 mol) was added dropwise with stirring to produce a white solid. The mixture was allow to stir for 0.5 hour, filtered and the solids were washed with hexanes to give (**45a**) as a yellow solid; yield 2.5 g (68%). Compounds (**45b**) and (**45c**) were obtained by the same procedure starting from piperidine and azepane to give (**45b**) and (**45c**) as yellow solids; (**45b**) yield: 3.75 g (75%); (**45c**) yield: 2.45 g (64%) .[96]

Cyclic amine-1-dithiocarmatae(3,5-dimethylpyrazolyl)boratonickel(II)

[Tp*Ni(S_2CNR)] (46a-c)

A 100 mL round bottom was charged with [Ni($S_2CNR)_2$] (1.5mmol), (**13**) (0.5g 1.5mmol) and 50 mL of toluene. The mixture was degassed and put under a gentle flow of nitrogen and allowed to reflux overnight. Over the course of the reaction, a color change from olive to a bright emerald green was noted. The mixture was cooled to room temperature and filtered. The filtrate was concentrated down on the rotary evaporator to give the crude product. X-ray crystallography was conducted on all complexes.

46a R = pyrrolidine. Recrystallization of this compound from dichloromethane/methanol gave (**46a**) as a green solid; yield 0.5960g (79%). FT IR 2510, 2358, 1542, 1412, 1197, 1057 cm^{-1}; Anal. Calc. $C_{20}H_{30}N_7S_2BNi$: C, 47.84; H, 6.03; N, 19.53. Found: C, 47.71; H, 5.97; N, 19.24.

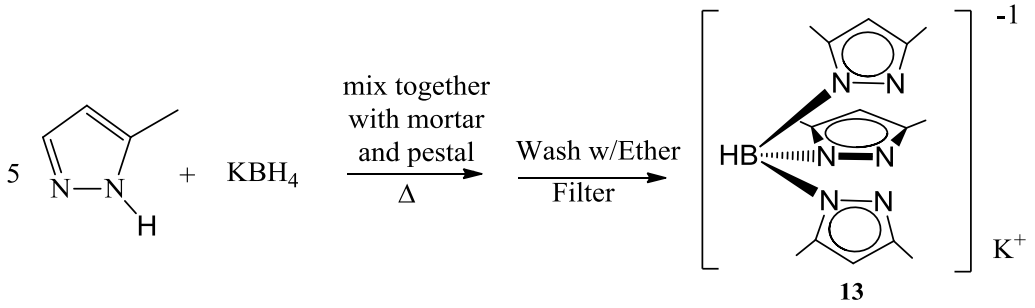
46b R = piperidine. Recrystallization of this compound from dichloro-methane/methanol to gave (**4bc**) as a green solid; yield 0.3351 (65%). FT IR 2514, 2343, 1541, 1416, 1239, 1059 cm^{-1}; Anal. Calc. for $C_{21}H_{32}N_7S_2BNi$: C, 48.86; H, 6.26; N, 18.49. Found: C, 48.63; H, 5.91; N, 18.73.

46c R = azepane. Recrystallization of this compound from toluene/hexanes gave the (**46c**) as a green solid; yield 0.7802 g (89%). FT IR 2513, 1547, 1497, 1262, 983, 803 cm^{-1}; MALDI-MS, m/z 528 (M^+, 100%).

CHAPTER 3

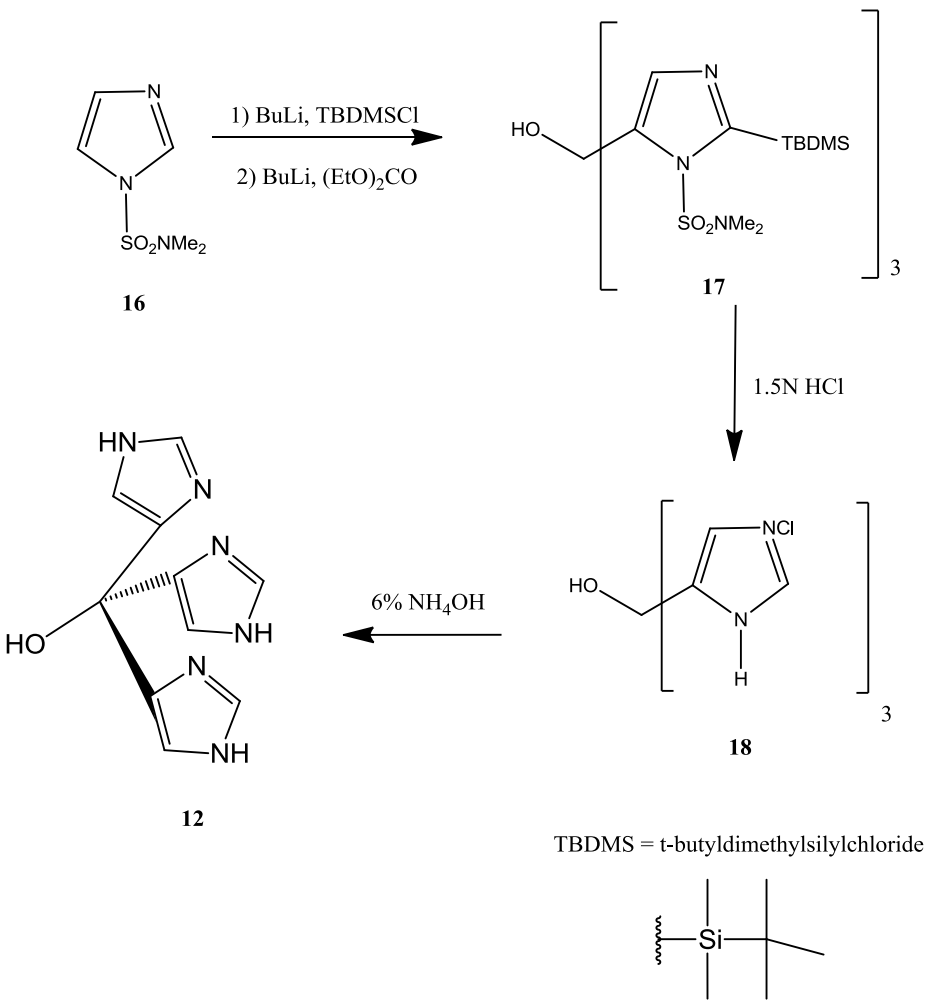
NICKEL ACIREDUCTONE DIOXYGENAGE MODEL COMPLEXES

In an effort to prepare mimics of the nickel ARD active site several mixed ligand nickel complexes which contain a tridentate nitrogen donor were prepared. The reported syntheses for Tp* and 4-TIC (Schemes 8 and 9) given in the literature gave pure material in good yield with no problems, while the synthesis for the alkyl substituted 4-TIC ligands proved to be very problematic.



13

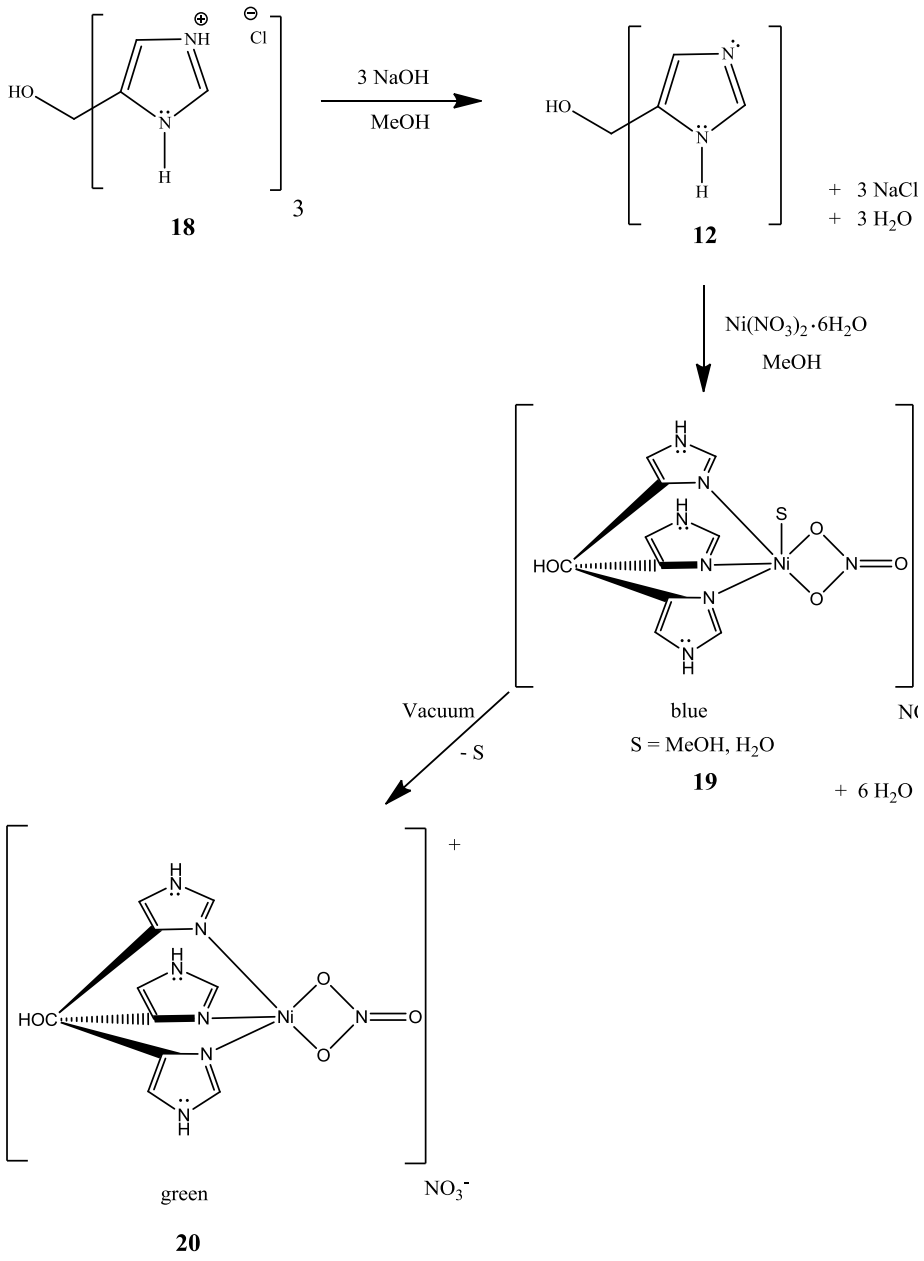
Scheme 8. Synthesis of (**13**) as reported in the literature.[90]



Scheme 9. Reported synthesis of (**12**) as reported in the literature[85]

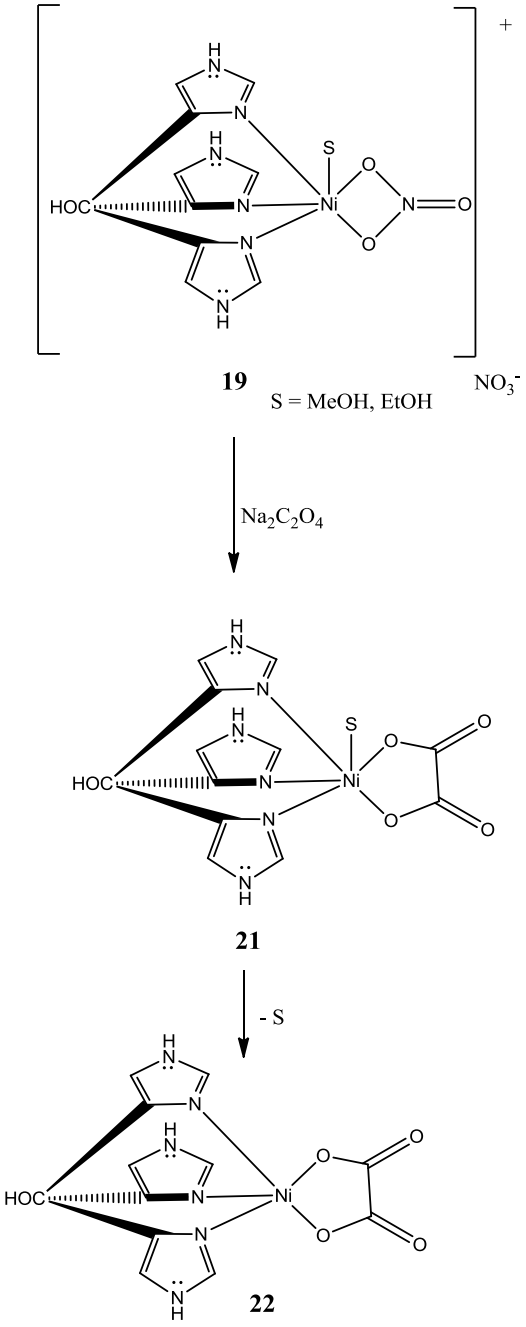
Several preliminary complexes of nickel (II) with the 4-TIC ligand were prepared. Reaction of (**18**) with nickel nitrate led to the synthesis of several mixed ligand nickel containing complexes (**19-23**) which contain the tris(4-imidazolyl)carbinol ligand (Schemes 10 - 12). IR data from complexes (**20**, **22** and **23**) confirmed the presence of the tridentate ligand (**12**) in each of the complexes. In solution, (**19** and **21**) were a blue color

but once the solvent was removed under vacuum the complexes turned a green color (**20** and **22**). The color change is believed to be due to the fact that in solution the solvent is coordinated to the complex making it six coordinate but once removed the complex now has a five coordinate geometry. The optical spectra of (**19** and **21**) contained three absorption maxima in the range of 2000-330 nm, which is characteristic of six coordinated nickel complex. The purple bis 4-TIC complex (**23**) was a purple color and only slightly soluble in most solvent. Because of the low solubility an optical spectra was not taken. Based on previously reported Tp* chemistry data we were able to confirm the synthesis of these complexes.[91] The 4-TIC ligand complexes are soluble in many polar protic solvents (ethanol, methanol and water), which is a desired attribute for many functional and structural models of metalloenzymes, but the low solubility in polar aprotic organic solvents (dichloromethane, tetrahydrofuran, ethyl acetate and acetonitrile) makes them less useful for our purposes.

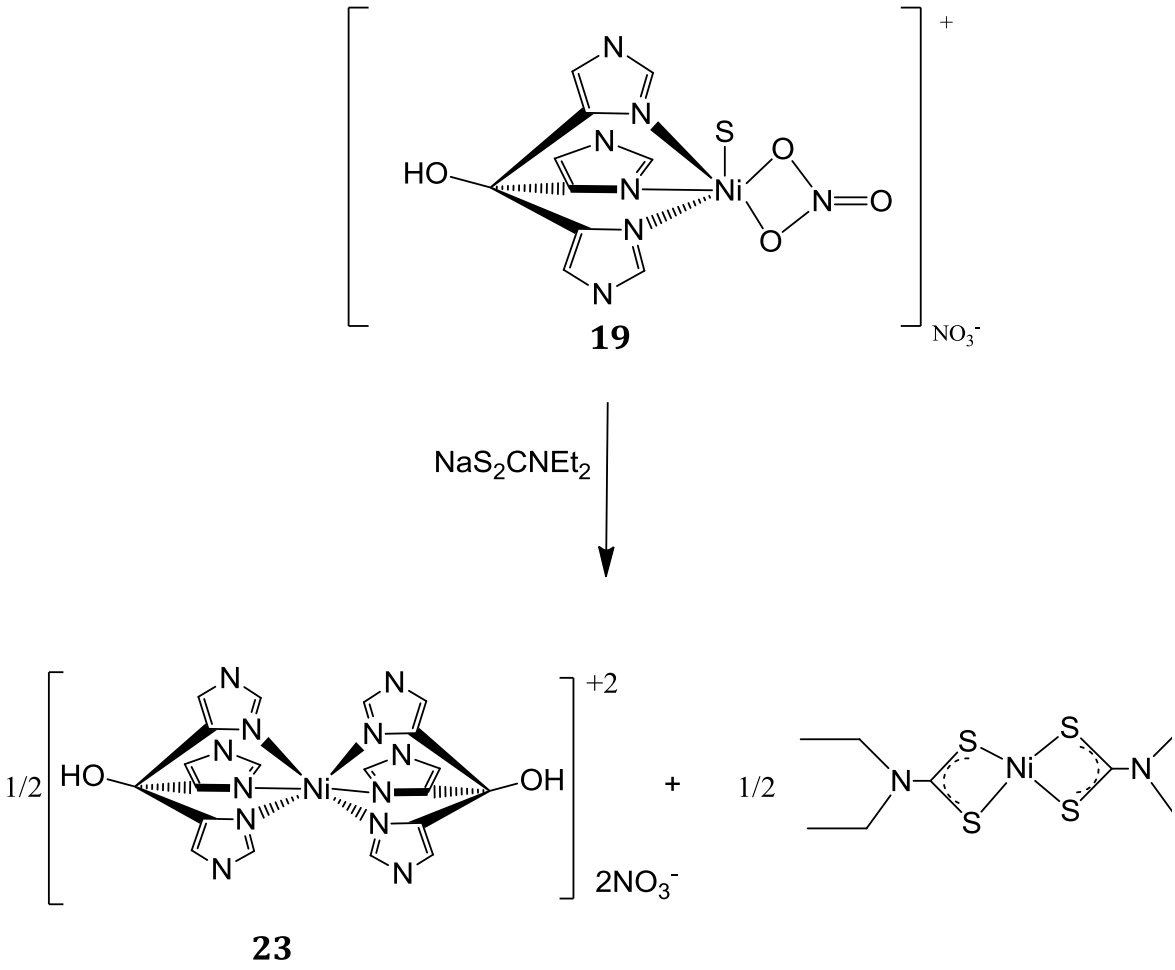


18 **12** **19** **20**

Scheme 10. Synthesis of the Nickel (II) mixed ligand 4-TIC complex (**20**).

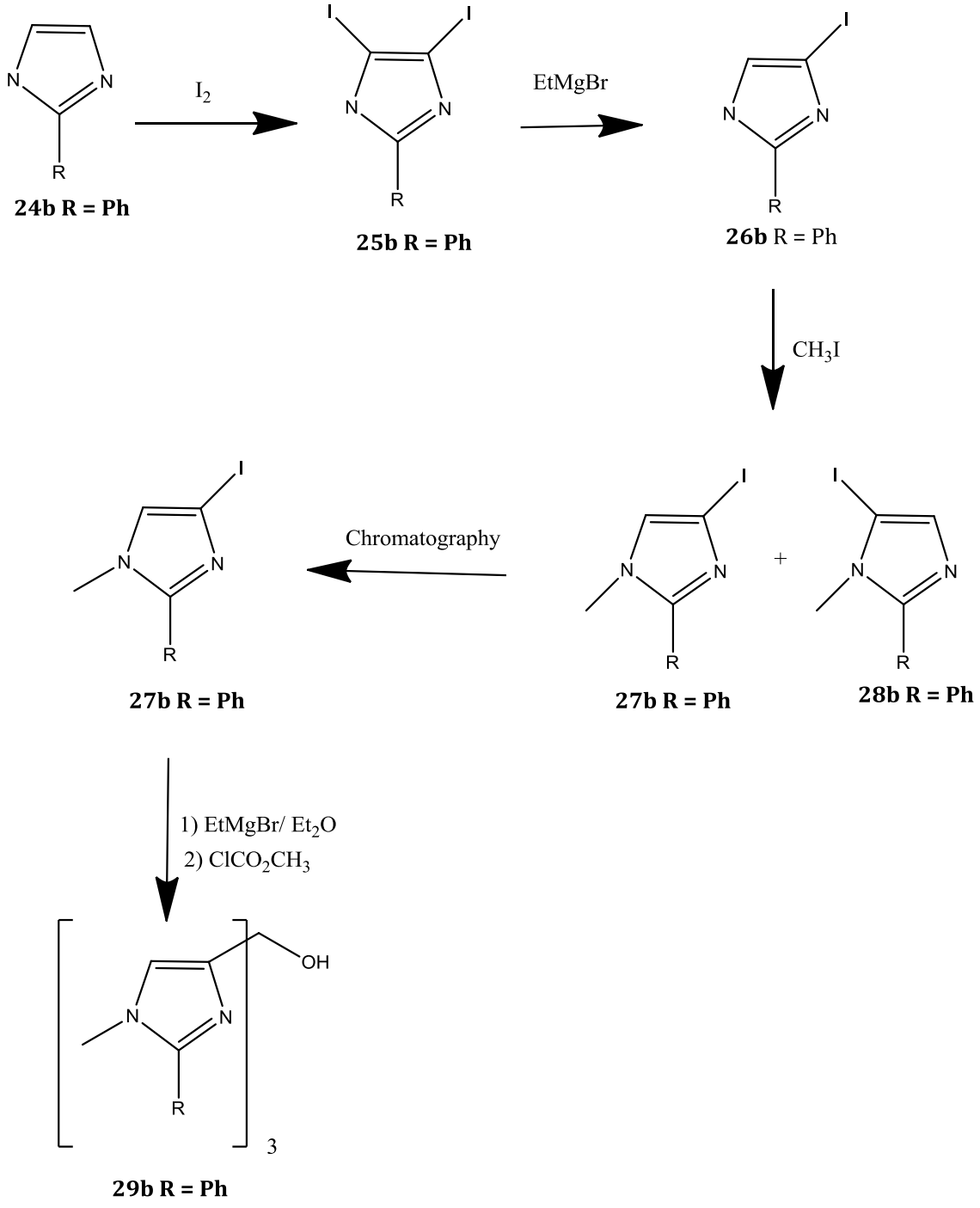


Scheme 11. Synthesis of the Nickel (II) mixed ligand 4-TIC complex (**22**).

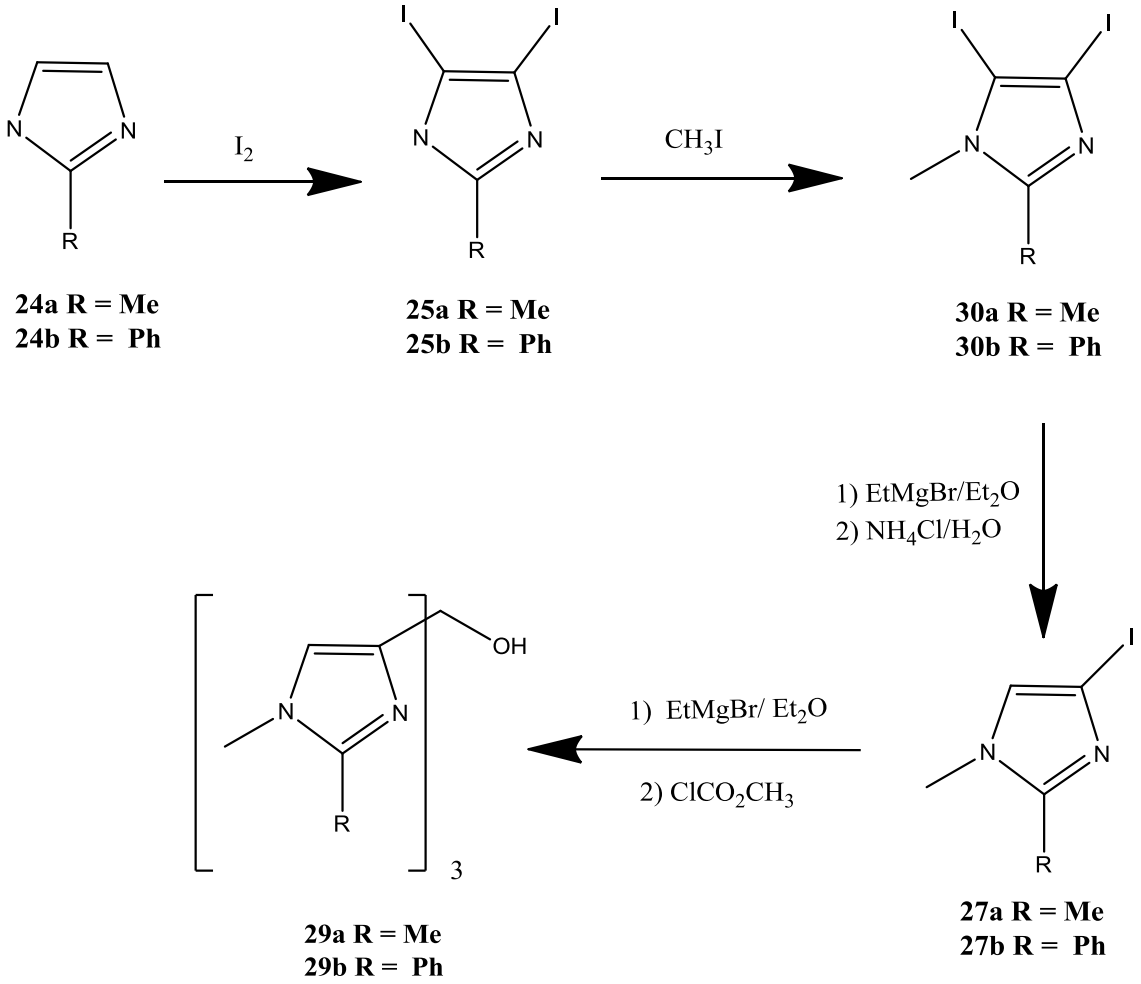


Scheme 12. Synthesis of the Nickel(II) bis 4-TIC complex (**23**).

The synthesis of the 1-methyl-2-phenyl alkyl substituted analog of 4-TIC was not reported until 2005 by Kujime and Fujii.[38] Starting with a simple 2-substituted imidazole they produced the 4-iodo (**27b**) and 5-iodo (**28b**) isomers of a substituted imidazole (Scheme 13). The isomers were separated by column chromatography and **27b** was then used to make the 1-methyl-2-phenyl substituted analog of 4-TIC (**29b**). The separation by column chromatography of the two isomers was very problematic, so instead, we modified the procedure to achieve only the desired (**27b**) (Scheme 14) which was confirmed by ^{13}C NMR. Instead of removing the iodide in the second step we added the methyl group by way of a iodomethane reaction. By adding the methyl group first we were able to set up a reaction which would be regioselective for one isomer, hence eliminating the need for separation by chromatography.

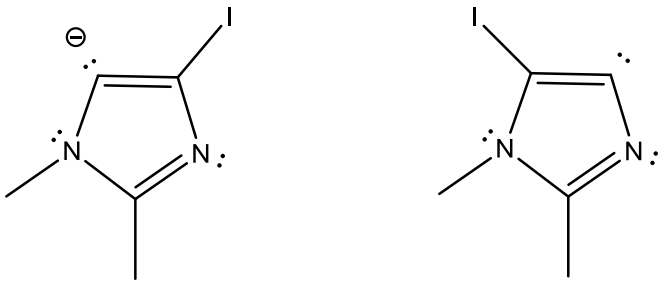


Scheme 13. Synthesis of the alkyl substituted analog of the 4-TIC ligand as reported in the literature.[86]



Scheme 14. Revised synthesis of the alkyl disubstituted 4-TIC ligand

The stability of the intermediate is the reason why the (**27**) is favored. There are two possible intermediates which can form during the third step of the synthesis. In order to get the 5-iodo isomer (**28**) the reaction would have to go through an intermediate with lone pairs on adjacent atoms in the same plane (**32**), making the compound unstable. The 4-iodo (**27**) reaction produces an intermediate in which the lone pairs are considered to be in resonance with the imidazole ring (**31**), hence making a more stable compound (Fig. 18). This route has also been used to prepare the 1, 2-dimethyl substituted analog of 4-TIC (**29a**).



31 **32**

Figure 18. Intermediates formed during the synthesis of the dialkyl substituted 4-TIC (**29**).

ARD Chemistry

The active site of nickel ARD contains an enediol type ligand called acireductone. There are very few examples of metal complexes that include an enediol ligand, an alkene with two cis-hydroxyl groups. After looking at several possible acireductone and enediol ligands (Fig. 19) to mimic the substrate, it was determined that the 2-hydroxy-1, 3-diphenylpropan-1, 3-dione ligand (**3**) would be the best example of an acireductone substrate analog for our research. Many of the ligands considered could only form the five member or six member intermediate but (**3**) has the ability to form both the five and six member intermediate.

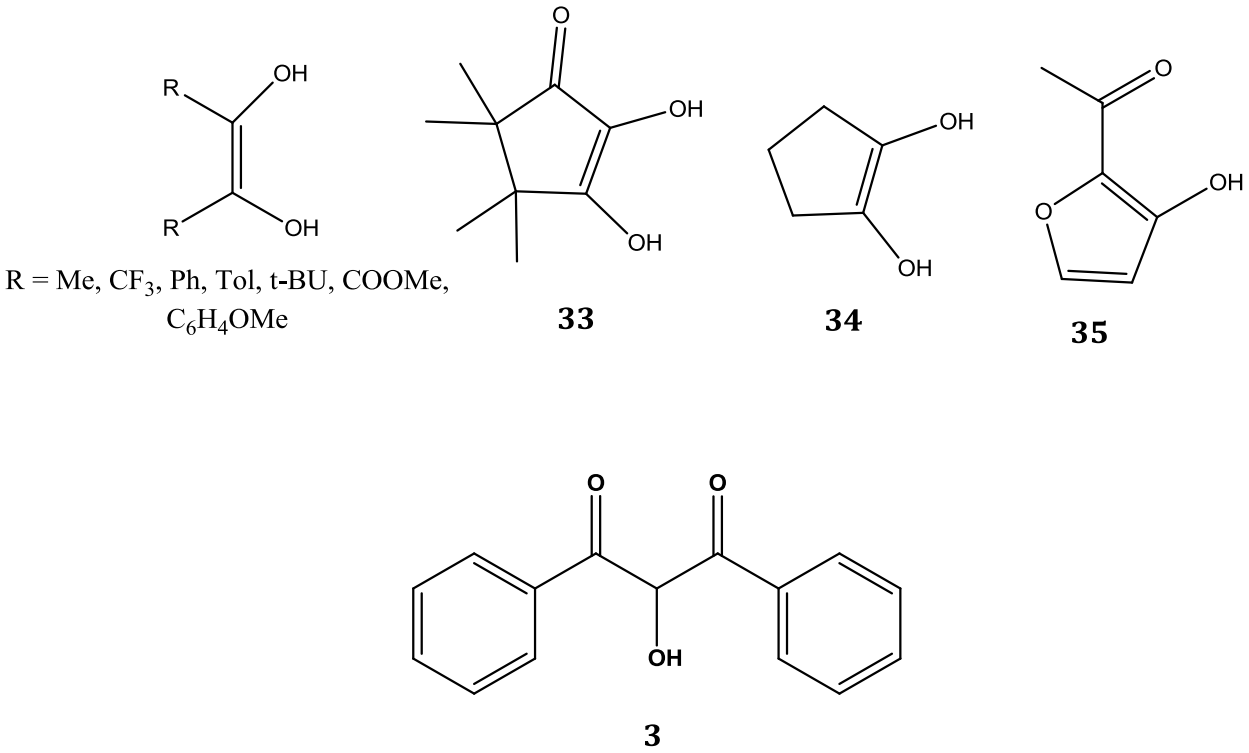
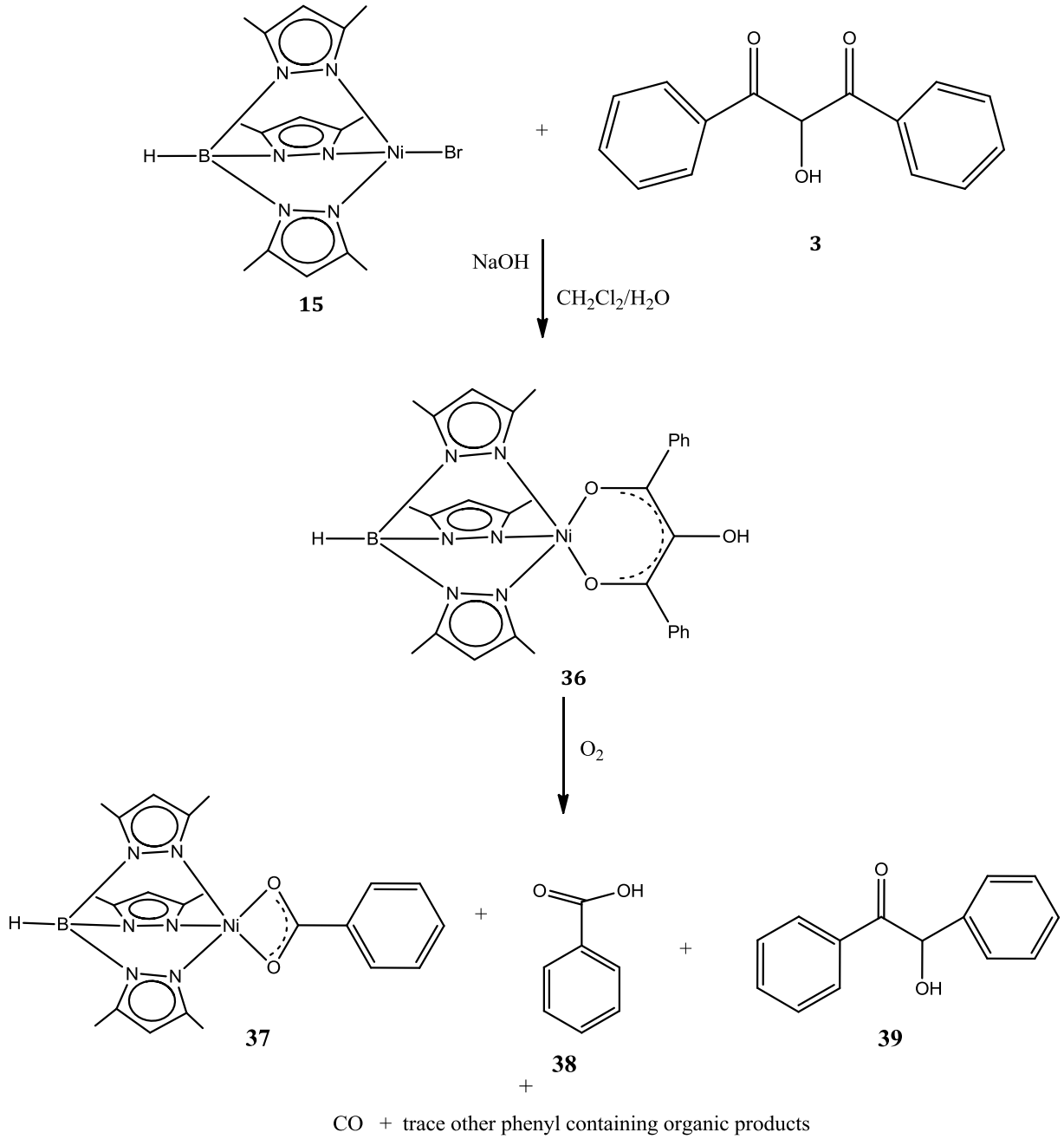


Figure 19. Examples of ligands with the enediol functional group which could mimic the acireductone substrate.

Synthesis of Tp*Complexes with Acireductone Analog

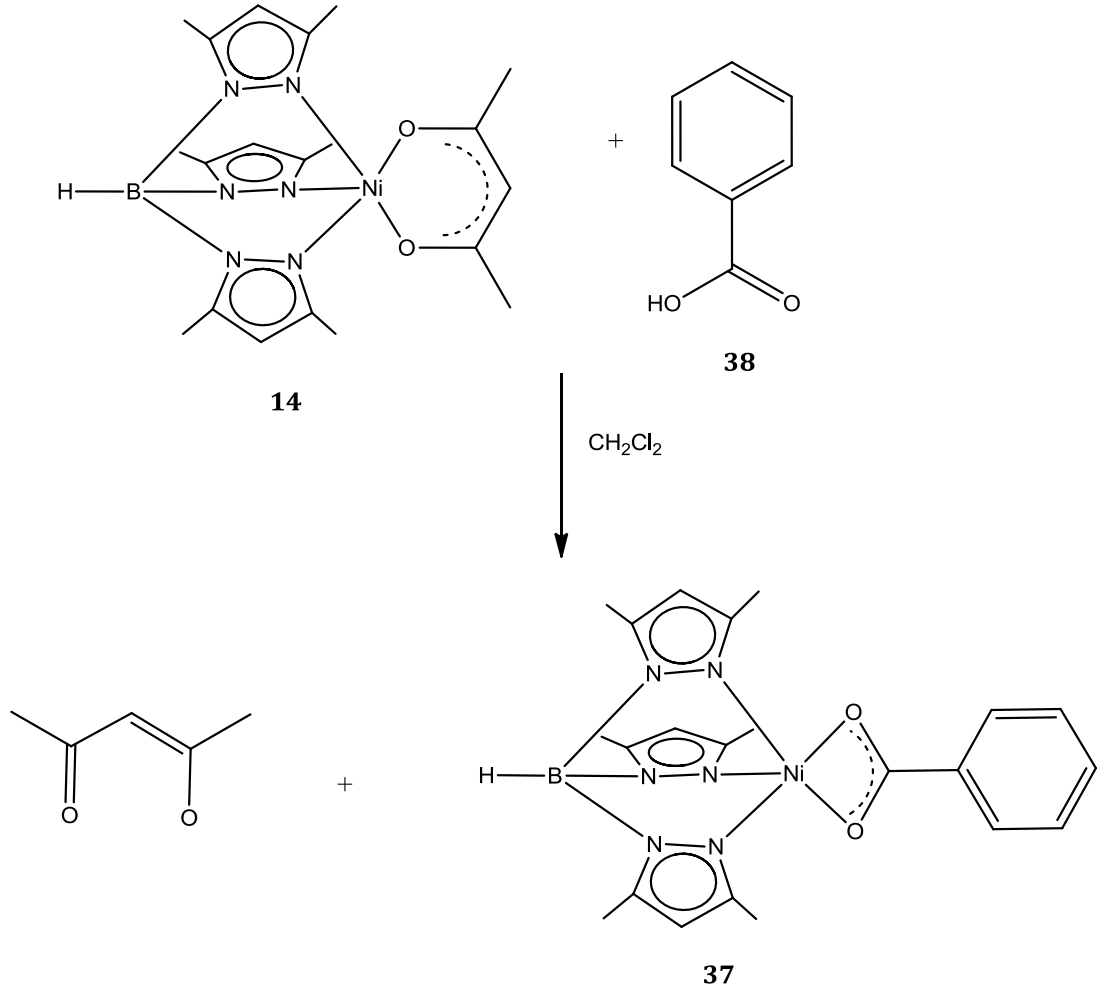
The Tp* nickel complexes with the acireductone model substrate, (**3**) were prepared aerobically using a two phase system. The Tp* ligand and substrate were dissolved in dichloromethane and an aqueous solution of base was added dropwise to the mixture (Scheme 15).

The organic phase which contained the crude product was purified by chromatography. Dark green crystals of the pure product were obtained by a liquid-liquid diffusion of dichromethane and isopropanol.



Scheme 15. Synthesis of (**37**) from (**15**) with (**3**).

The Tp ligands (**12**) have been reported to stabilize unusual structural features, such as high reactive or oxygen sensitive metal-ligand fragments and unusual oxidation states. Because of these properties we initially believed that the Tp* ligand (**15**) could perhaps stabilize the complex of the monoanion of (**3**) in air but upon investigation of the products it was determined that the analog bound complex was indeed reactive with O_2 yielding (**37**) instead of (**36**). To verify the products of this reaction (**37**) was prepared independently using benzoic acid (**38**) and (**14**) as the starting reagents (Scheme 16).



14 **38** **37**

Scheme 16. Independent synthesis of (**37**)..

The products of both reactions were characterized using IR and UV-Vis with the results being essentially identical. This was proof that the reaction involving the acireductone analog was indeed O_2 reactive.

If strict ARD-type reactivity occurs in this reaction, two equivalents of (**38**) should be formed along with one equivalent of CO. Because CO is somewhat harder to quantitate relative to benzoic acid we ran the reaction and quantitated the amount of (**38**) produced. The two-phase reaction shown in Scheme 15 to produce (**36**) was set up and after 1 hour was worked up by first treating with excess base to free the benzoate ligand from the metal and convert all of the benzoic acid produced into the benzoate, which should extract quantitatively in the aqueous phase. The phases were separated and the aqueous phase was acidified to form benzoic acid and repeatedly extracted with ether to extract all of the benzoic acid. The organic phase was then separated and the solvent evaporated to leave solid benzoic acid. The solid was dried and a ^{1}H NMR was obtained that showed pure benzoic acid, uncontaminated with other products. Careful weighing showed that 1.2 equivalents of benzoic acid were produced in the reaction instead of the expected 2.0 equivalents.

Berreau and coworkers showed that in their system using the 6-Ph_2TPA chelate ligand and the same model substrate (**3**) that instead of two equivalents of benzoic acid, they obtained other organic products including benzil, PhC(O)C(O)Ph, and less than two, but greater than one equivalent of benzoic acid.[14] They did not quantitate the benzil, nor the benzoic acid. They concluded that strict ARD-type reactivity was not followed and that at least one other reaction pathway must be in operation in this reaction. They offered that formation of

benzil could be derived from coupling of two benzoyl radicals, PhCO•. With this in mind, we ran our reaction again and investigated the reaction mixture by GC-MS. Perhaps not surprisingly, the two main products were benzoic acid and, benzoin, PhC(O)CH(OH)Ph, together with trace amounts of other phenyl-containing products. This result demonstrates that while the ARD-type pathway is likely to occur, benzoin and the other products must arise from an alternate reaction pathway. Interestingly, we do not observe benzil, as the Berreau observed in their 6-Ph_2TPA-based reaction system, but rather benzoin. This may be due to the tridentate N_3 coordination of Tp* compared to the tetradentate N_4 coordination of the 6-Ph_2TPA ligand. This leads to a reduced coordination number of five versus six for our complex and leaves a coordination position open and available for reaction in non-coordinating solvents such as dichloromethane, a common solvent in this work.

The optical spectra of the product of the reaction of (**15**) with (**3**) and the independent synthesis of (**37**) (Figures 20 -21) were recorded in polar and non-polar solvents. The product from the reaction of (**15**) with (**3**) was recorded in non-polar (CH_2Cl_2) and polar (MeCN and DMF) solvents. In CH_2Cl_2 the complex is believed to be five coordinate which is characterized by four absorption maxima in the range 300-2000 nm. The complex becomes six coordinate when a coordinating polar solvent is used to record the spectra as seen with MeCN and DMF; this is characterized by three absorption maxima. The five-coordinate complex was a nice green color in solution while the six coordinate complexes exhibited a blue color in solution.

All of the five coordinated green nickel complexes exhibited four absorption bands. These bands can be tentatively assigned to the spin-allowed transitions $^3A_2 \longrightarrow {}^3E$, $^3A_2 \longrightarrow {}^3A_{1\ or}$ ^3E, $^3A_2 \longrightarrow {}^3A_2$, and $^3A_2(F) \longrightarrow 3E(P)$ or $3A_2(P)$.

The blue six-coordinated solvent adducts seen by (**37**) are characterized by three absorption bands which can be tentatively assigned to the three spin allowed transitions arising from $^3A_2 \longrightarrow {}^3T_2$, $^3A_2 \longrightarrow {}^3T_1$ and $^3A_2(F) \longrightarrow {}^3T_2(P)$.

The spectrum from the independent synthesis of (**37**) was recorded in non-polar (CH_2Cl_2) and polar (MeCN) solvents. In the CH_2Cl_2 the complex is considered five coordinate which is characterized by the four absorption maxima while the MeCN the complex is six coordinate, characterized by the three absorption maxima in the range 300-2000nm. The molar extinction coefficients seen in Table 1 for the reaction product of (**37**) with (**3**) and the independent synthesis of (**37**) are very close which is to be expected if they are the same complexes synthesized from two different routes.

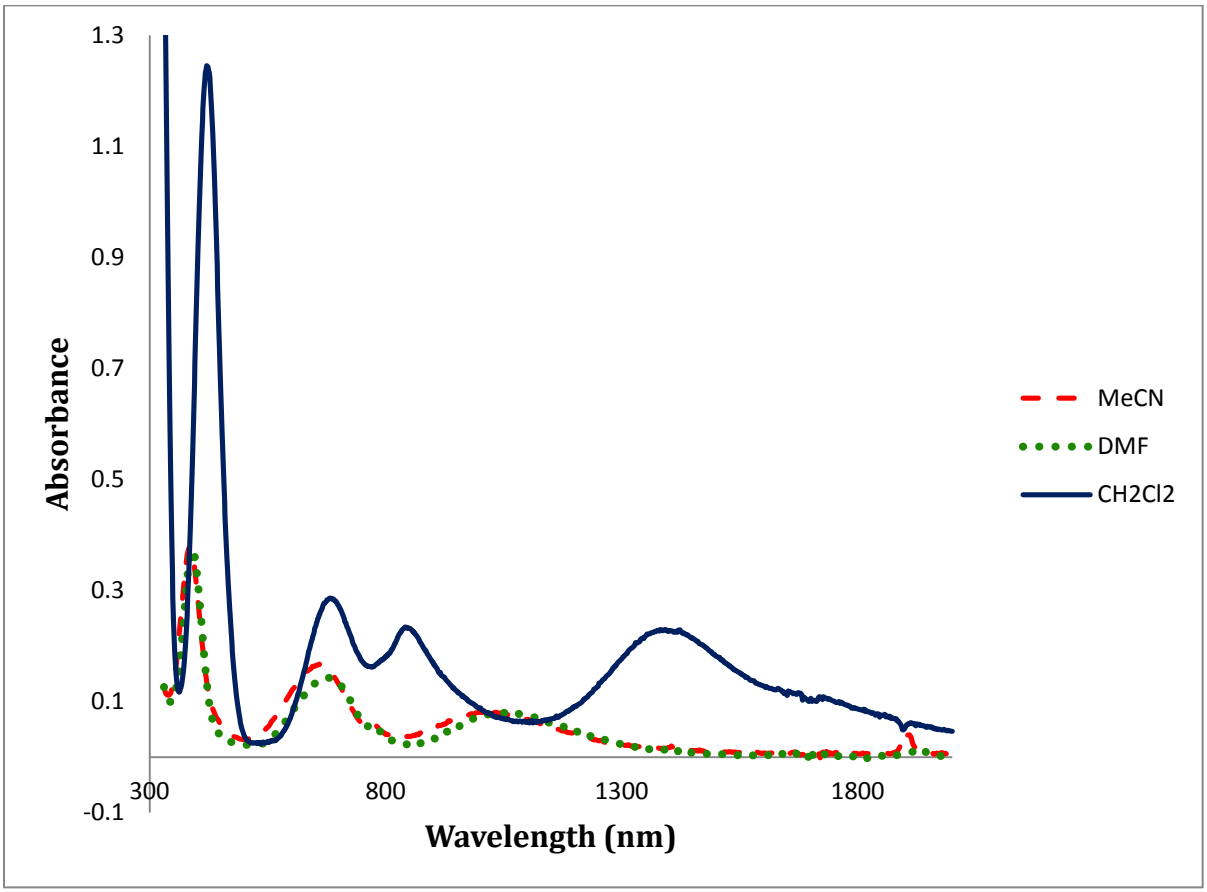


Figure 20. Optical spectrum of a 5.0 x 10^{-3} M solution of (**37**) from the reaction of (**14**) with (**3**) in a 1cm cell at room temperature.

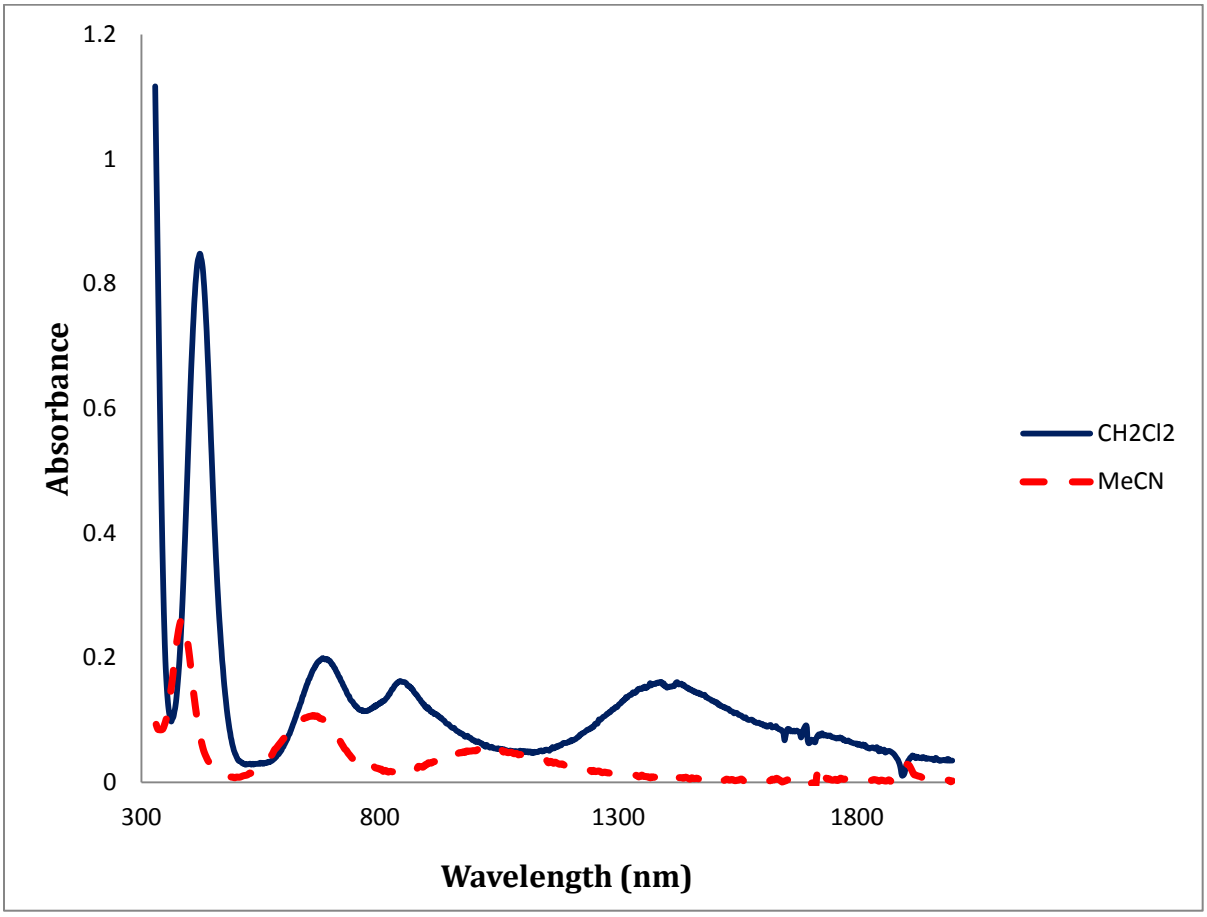


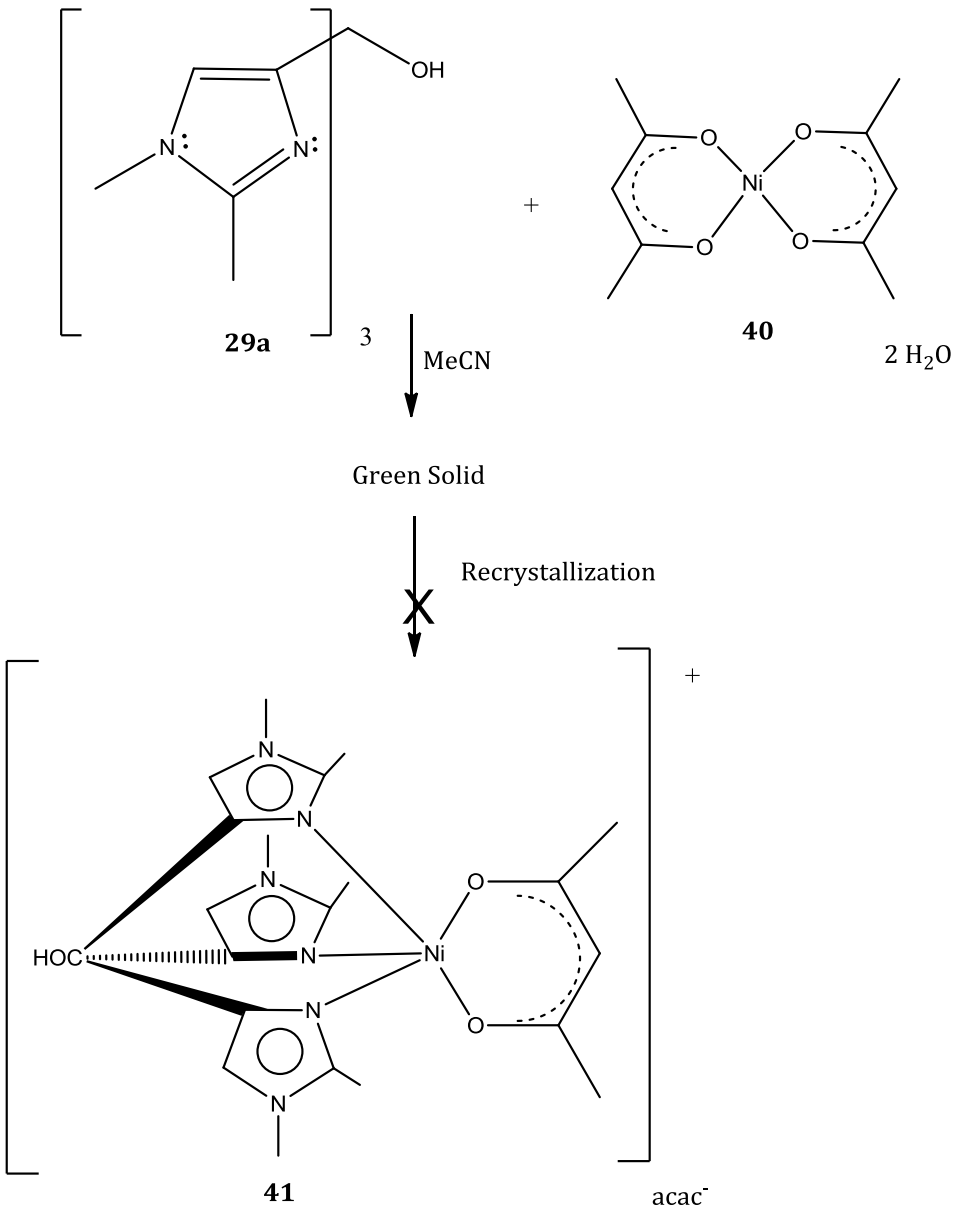
Figure 21. Optical spectrum of a 5.0 x 10^{-3} M solution of (**37**) from the independent synthesis reaction in a 1cm cell at room temperature.

Table 1. Electronic spectra features data for (**37**).

Complex	Solvent	Absorption Maxima nm (ε_M)			
Synthesis of (**37**) from reaction of (**15**) and (**3**)	CH_2Cl_2	1423 (46)	842 (47)	682 (57)	421 (249)
	MeCN	1020 (16)		656 (37)	387 (29)
	DMF	1061 (16)		677 (75)	388 (74)
Independent synthesis of (**37**)	CH_2Cl_2	1424 (32)	843 (33)	680 (40)	422 (170)
	MeCN	1027 (10)		659 (21)	383 (52)

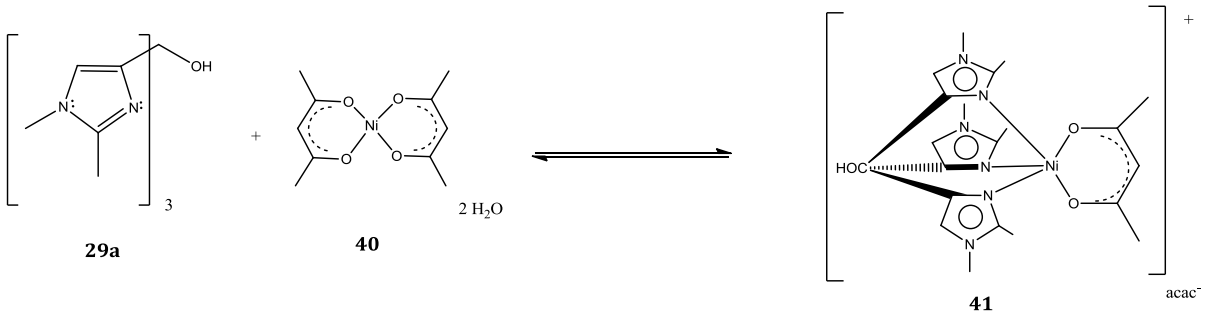
Synthesis of Complexes with 4-TIC^{me,me}

In an attempt to synthesis model complexes with the neutral imidazole ligand 4-TIC$^{Me, Me}$, several reactions similar to that of the Tp* were attempted. The first reaction we investigated was the synthesis of (4-TIC$^{Me, Me}$)Ni(acac)](acac) (Scheme 17).



Scheme 17. Attempted synthesis of [(4-TIC^{Me,Me})Ni(acac)]$^{+}$ (acac)$^{-}$

The recrystallization by slow evaporation of fresh acetonitrile produced nice green crystals but instead of the nickel complex which contained the 4-TIC$^{Me, Me}$ ligand the crystals turned out to be starting material $Ni(acac)_2 \cdot 2H_2O$ (**40**). The IR taken after the initial reaction indicated that the ligand was present but it seems that during the recrystallization process the equilibrium was pushed back toward the reactants (Scheme 18).



Scheme 18. Equilibrium of the $[(4\text{-}TIC^{Me,Me})Ni(acac)]^+ (acac)^-$

As the crystals started growing the intensity of the color of the filtrate began to fade. The larger the crystals got the lighter the filtrate became. As the concentration the solvent decreased the equilibrium shifted towards the reactants causing the least soluble reagent to come out of solution. The products of this reaction were verified with X-Ray Crystallography (Fig. 22)

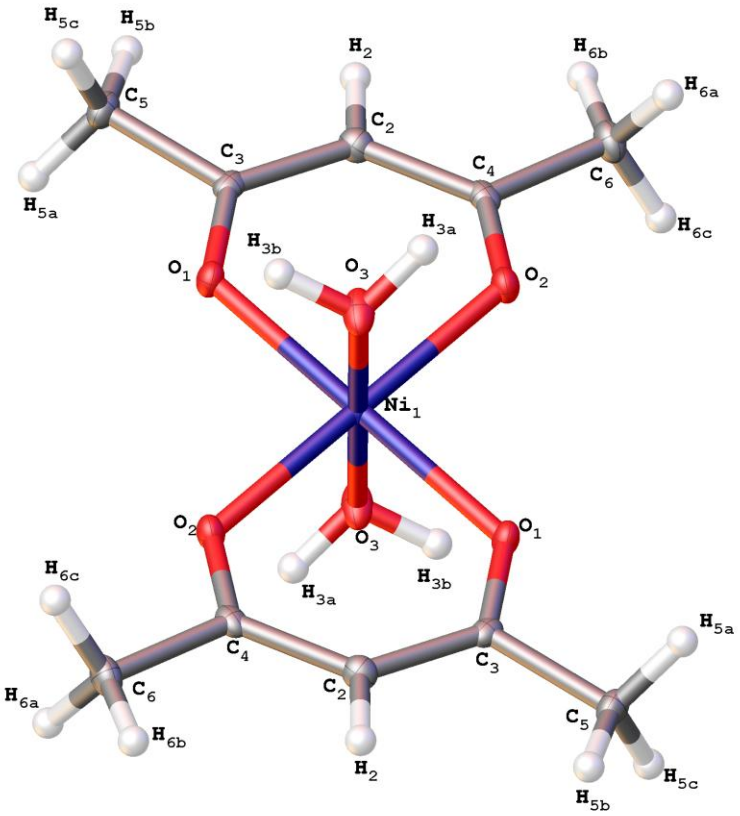


Figure 22. X-ray structure of $Ni(acac)_2 \cdot 2H_2O$ (**40**).

Table 2. Selected Bond Distances (Å) and Bond Angles (deg.) for $Ni(acac)_2 \cdot 2H_2O$ (**40**)

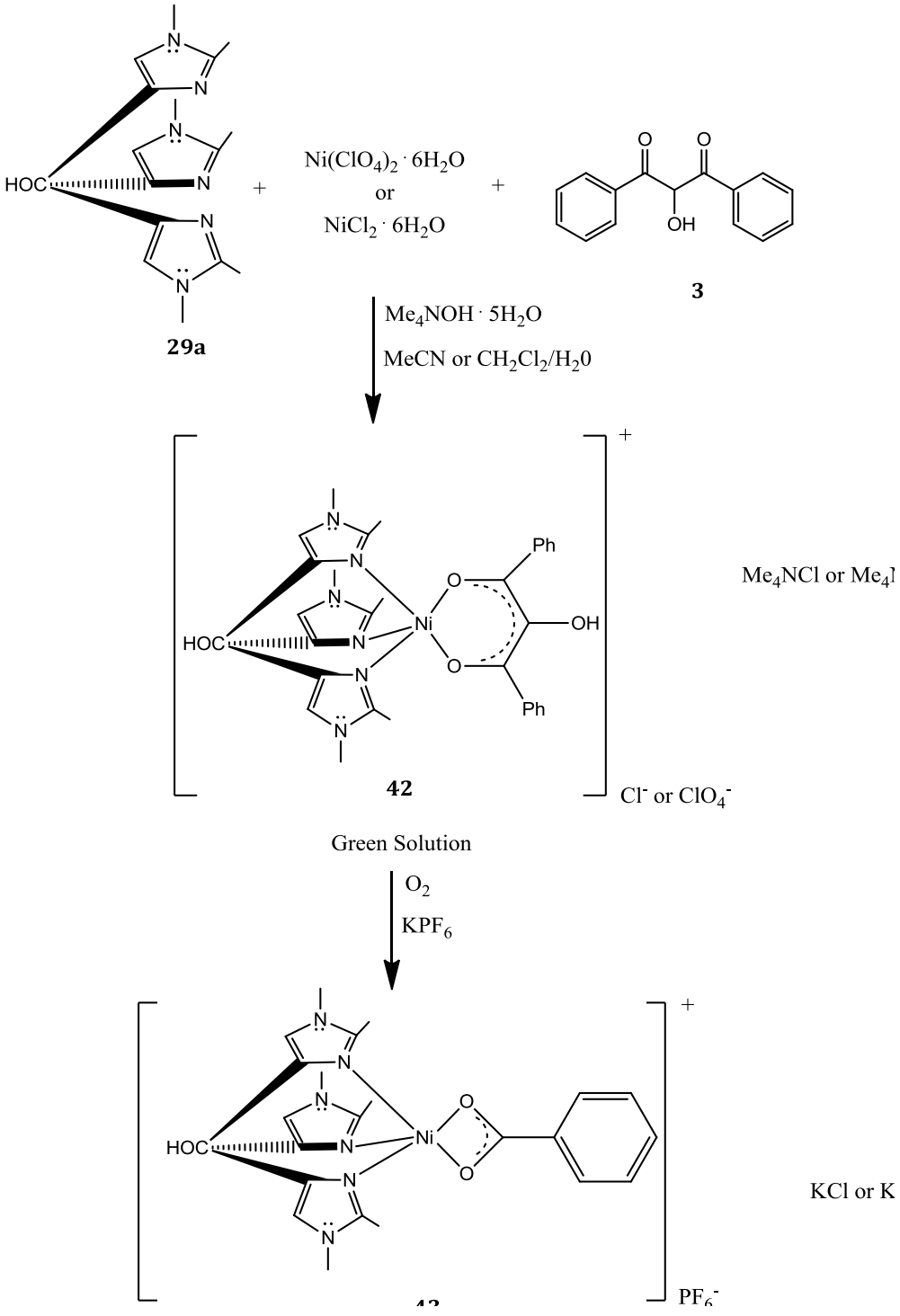
Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	$O1^1$	2.0085 (11)	O1	Ni	$O1^1$	180.0
Ni	O1	2.0085 (11)	$O1^1$	Ni	O3	89.10 (5)
Ni	$O2^1$	1.9978 (11)	$O1^1$	Ni	$O3^1$	90.90 (5)
Ni	O2	1.9978 (11)	O1	Ni	$O3^1$	89.10 (5)
Ni	$O3^1$	2.1097 (11)	O1	Ni	O3	90.90 (5)
Ni	O3	2.1097 (11)	$O2^1$	Ni	O1	87.98 (5)
			O2	Ni	O1	92.02 (5)
			$O2^1$	Ni	$O1^1$	92.02 (5)
			O2	Ni	$O1^1$	87.98 (5)
			$O2^1$	Ni	O2	180.0
			O2	Ni	$O3^1$	91.78 (5)
			$O2^1$	Ni	O3	91.78 (5)
			O2	Ni	O3	88.22 (5)
			$O2^1$	Ni	$O3^1$	88.22 (5)
			O3	Ni	$O3^1$	180.0

Numbers in parentheses are estimated standard deviations in the least significant digits.

The X-ray crystal structure of (**40)** is shown in Figure 23 and the selected bond distances and angles are listed in Table 2. The nickel atom is hexacoordinate, surrounded by six oxygen atoms which constitute a octahedral geometry. The $O1^1$-O1 and $O2^1$-O1 form the square planar base around the Ni atom. All of the Ni-O bond angles are very close to 90^o, which is expected for an octahedral geometry. The Ni-O2 and Ni-O1 bond distances are approximately 2.0Å, which indicates symmetrical bonding of the acetylacetonate ions. The C-O bond distances fall within the normal organic compound ranges.

Synthesis of Model Substrate Complexes with 4-TIC^{Me,Me}

The 4-TIC$^{Me, Me}$ complexes (**41**) and (**42**) were attempted using two different routes with a series of conditions. The first attempt was modeled after the procedure reported by Berreau [15] and co-workers. For this reaction the nickel source was $NiClO_4 \cdot 6H_2O$ and the base used to depronate (**3**) was Me_4NOH. The reaction was set up in acetonitrile and allowed to stir overnight. A bright green solution which was believed to be the oxidative product was produced. In an effort to precipitate out the complex, one equivalent of KPF_6 was added to the reaction flask but unfortunately a green solid was not recovered. The reaction was repeated with $NiCl_2 \cdot 6H_2O$ only to give similar results (Scheme 19).

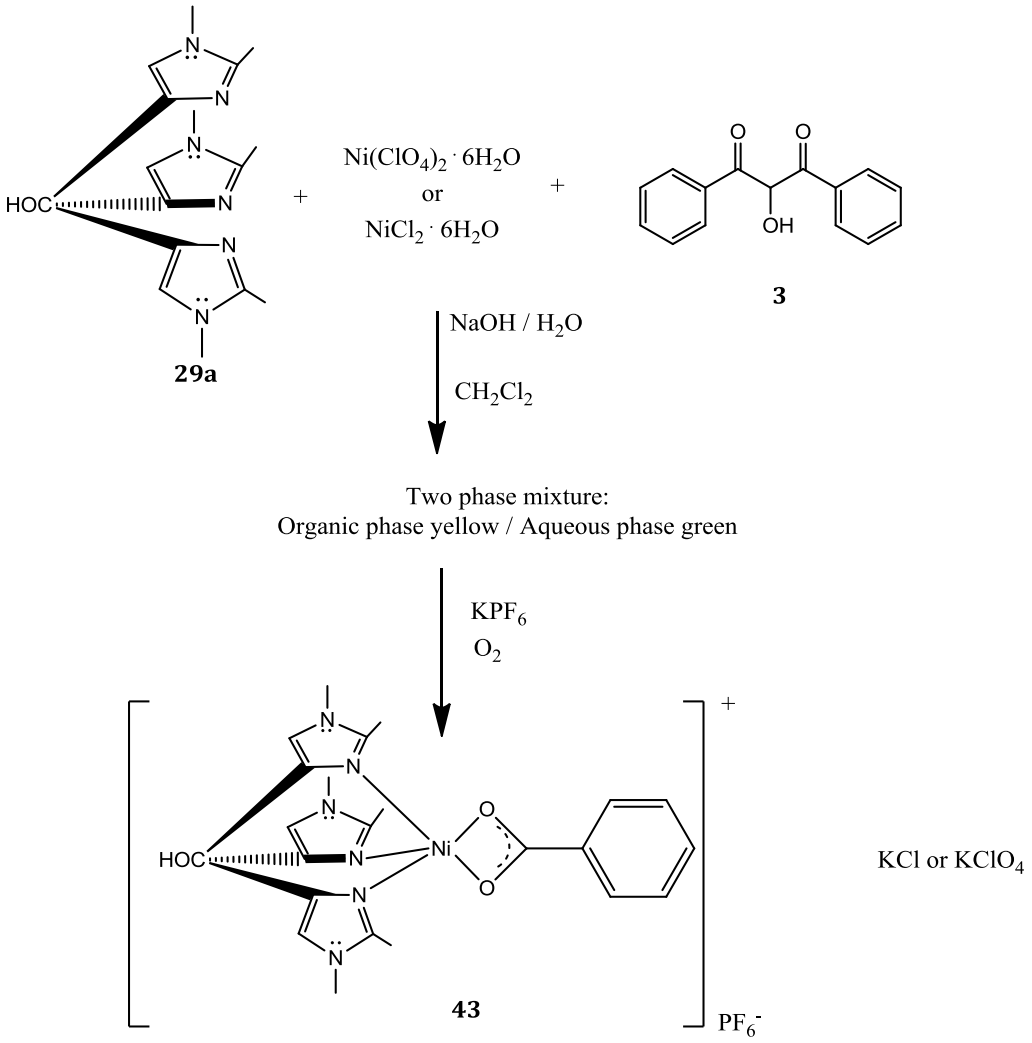


Scheme 19. Attempted synthesis of (**43**) from Me_4NOH.

The reaction was then attempted using a different solvent combination, dicholormethane/water. It was believed that the complex would be soluble in the organic phase while the by-products (Me_4NCl or Me_4NClO_4) would stay in the aqueous phase making it easier to crystallize the desired product. Unfortunately the desired product was not recovered using the method.

Continuing with the goal of isolating the 4-TIC complex with the acireductone analog a second synthesis was investigated. Here the base was replaced with NaOH and the solvent system was the two phase system dicholormethane / water (Scheme 20). During this reaction a different problem developed: the nickel product would not go into the organic phase. Even when the nickel source ($NiCl_2 \cdot 6H_2O$ or $NiClO_4 \cdot H_2O$) was changed the aqueous remained green, indicating the presence of nickel, while the organic phase remained yellow.

The reason behind the difficulty with isolating the 4-TIC ^{Me,Me} complex is unclear. These results do provide evidence that even though the 4-TIC ligands have a better resemblance to the actual active site, the synthesis is much more complicated than that of the pyrazol base ligands. The Tp* complexes were synthesized with no problems.



Scheme 20. Attempted synthesis of (**43**) from NaOH.

Conclusions

Preliminary studies with the parent 4-TIC ligand resulted in several complexes of low solubility necessitating the need to design and prepare alkyl substituted 4-TIC ligands. By developing a innovative route to key intermediate (**27a**) we were able to prepare the new 4-TIC^{Me,Me} ligand (**29a**). Efforts to prepare (**41**)as a convenient starting complex resulted in isolation of crystalline (**40**) which was determined by X-ray crystallography analysis.

An ARD model substrate (**3**) was prepared by a modulation of the literature procedure and used to prepare ARD-type reactions in model complexes. The reaction of (**15**) with (**3**) in a two phase reaction produced ARD-type products along with phenyl containing organic products that could not arise from ARD-type reactivity. Product analysis by ^{1}H NMR, gravimetry, GC-MS analysis and the independent synthesis of (**37**) together shows that ARD-type reactivity is observed along with an alternative pathway.

Optical spectra in the UV-Vis-NIR regions was obtained and tentative assignments were made for the observed bands. These spectra were consistent with the observed structures. Reactions of (**29a**) with (**3**), in with the Tp* reaction gave inconclusive results. While spectroscopic evidence indicated that (**43**) was produced, it was not isolated in pure crystalline form.

The two tridentate ligands, (**29**) and (**13**) are good structural models for the tris-histidine bonding seen in the Nickel(II) Acireductone Dioxygenase enzyme. Reactions involving the acireductone substrate analog (**3**) were consistent with the reported ARD activity along with another possible reaction pathway.

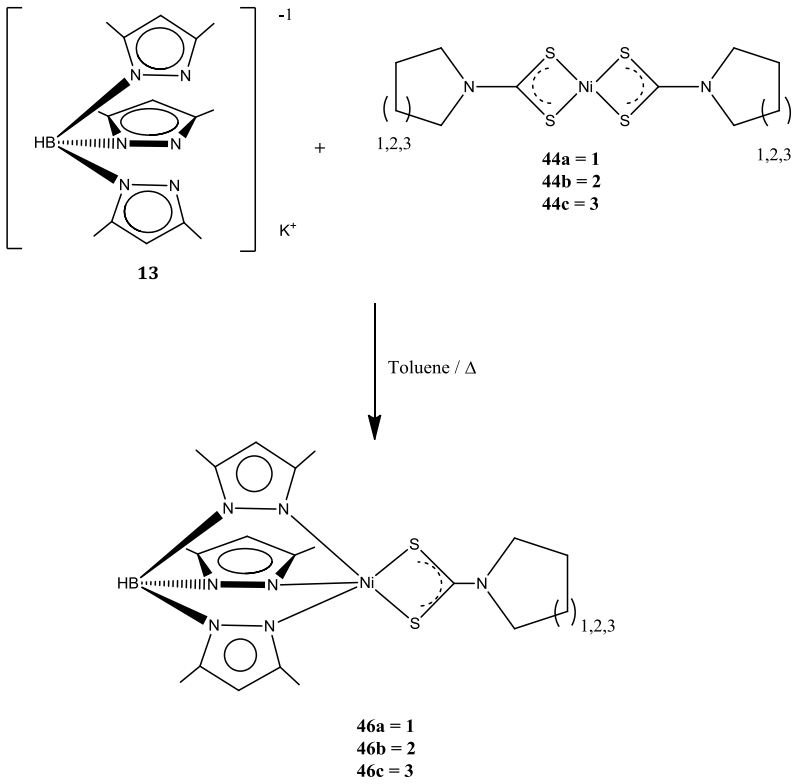
CHAPTER 4

NICKEL SUPEROXIDE DISMUSTASE MODEL COMPLEXES

The active site of the Ni-SOD enzyme in the oxidized form supports an unusual Ni^{+3} ion in a square-pyramidal $N_3S_2^{-3}$ ligand field comprised of an amine, imidazole from an histidine, an adjacent backbone amide, and thiolates from cysteine residues. A series of five coordinate nickel complexes were prepared in an effort to mimic this binding motif. The hydrotris(3,5-pyrazolyl)borate ligand was utilized to mimic the nitrogen donor backbone of the active site. Chelating dithiocarbamates were used as co-ligands to mimic the two binding thiolates. The synthetic strategy is to prepare the Ni^{+2} complexes and examine their redox chemistry with cyclic voltametry. A series of three complexes with different ring sizes will be prepared in order to vary the solubility and other physical properties.

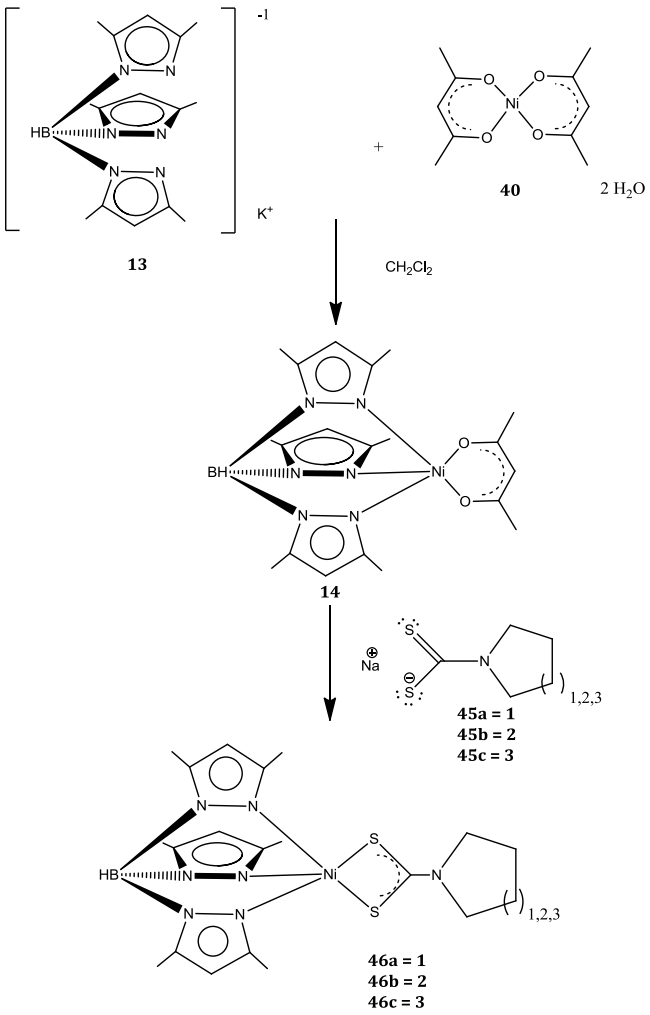
Synthesis of Tp* complexes with a dithiocarbamate ligand

The bright green nickel mixed ligand complexes containing the Tp* and a dithiocarbamte ligands can be prepared by two different synthetic routes. In the first route the bis dithocarbamate nickel complex $[Ni(S_2CNR_2)_2]$ (**44**) is combined with the potassium salt of the Tp* (**13**) and allowed to reflux in a solution of hot toluene (Scheme 21).



Scheme 21. Synthesis of (**46a-c**) using $Ni(S_2CNR)_2$ (**44**).

The second route which can be employed to prepare these complexes uses (**14**) and the sodium salt of the dithiocarbamate (**45a-c**) as starting reagents (Scheme 22).



Scheme 22. Synthesis of (**46a-c**) using Na(S_2CNR) (**45**).

At the start of the both reactions the color of the mixture was an olive color but after the addition of the dithiocarbamate the color changed rather quickly to a bright emerald green color. The crude products were recrystallized by liquid-liquid diffusion to give nice green crystals of the pure complexes in good yields.

Optical Spectra of Complexes

The absorption spectra of complexes (**46a-c**) have been recorded in the nonpolar solvent CH_2Cl_2. All of these complexes are five coordinate and exhibit four absorption maxima in the range of 300 – 2000 nm. The spectral data are collected in Table 3. The spectra of (**49 a-c**) are shown in Figures 23-25. One low intensity band is located in the near infrared region, three absorptions fall in the visible region.

Spectra of complexes with known pseudo- trigional bipyramidal (TB) or –square pyramid (SP) geometry have been interpreted satisfactorily using calculated energy level diagrams. The reported spectrum of complexes with an intermediate geometry is more difficult to interpret due to their lower symmetry.[97,98] The present set of complexes (**46a-c**) have intermediate geometries. The first three maxima can tentatively be assigned to the three spin allowed bands arising from splitting of the ^3F free ion term $^3E' \longrightarrow {}^3E''$; $^3E' \longrightarrow {}^3A_1''$ and $^3E \longrightarrow {}^3A_2''$, and the fourth band to one of the transitions from the ^3F to the ^3P manifold, $^3E' \longrightarrow {}^3E'(P)$.

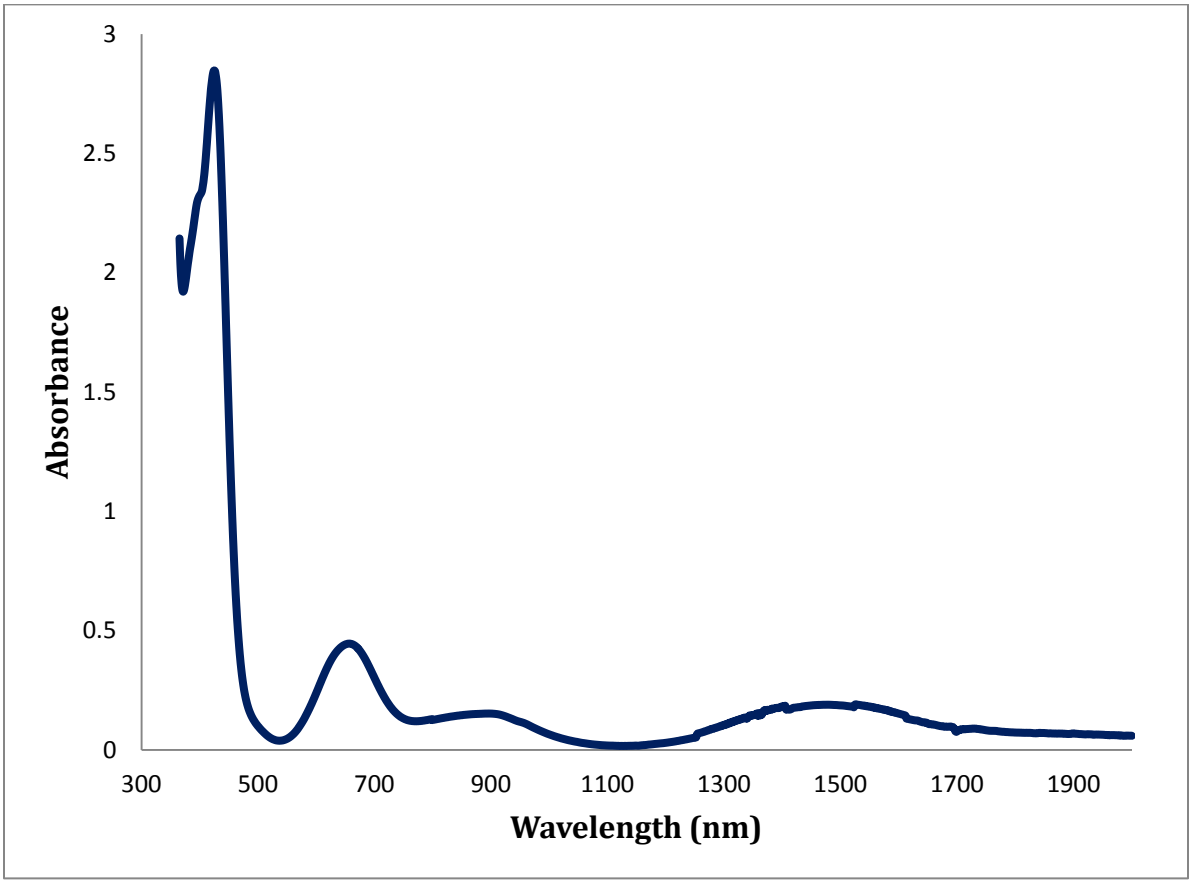


Figure 23. Optical spectra of a 5 x 10^{-3} M CH_2Cl_2 solution of (**46a**) in a 1cm cell at room temperature.

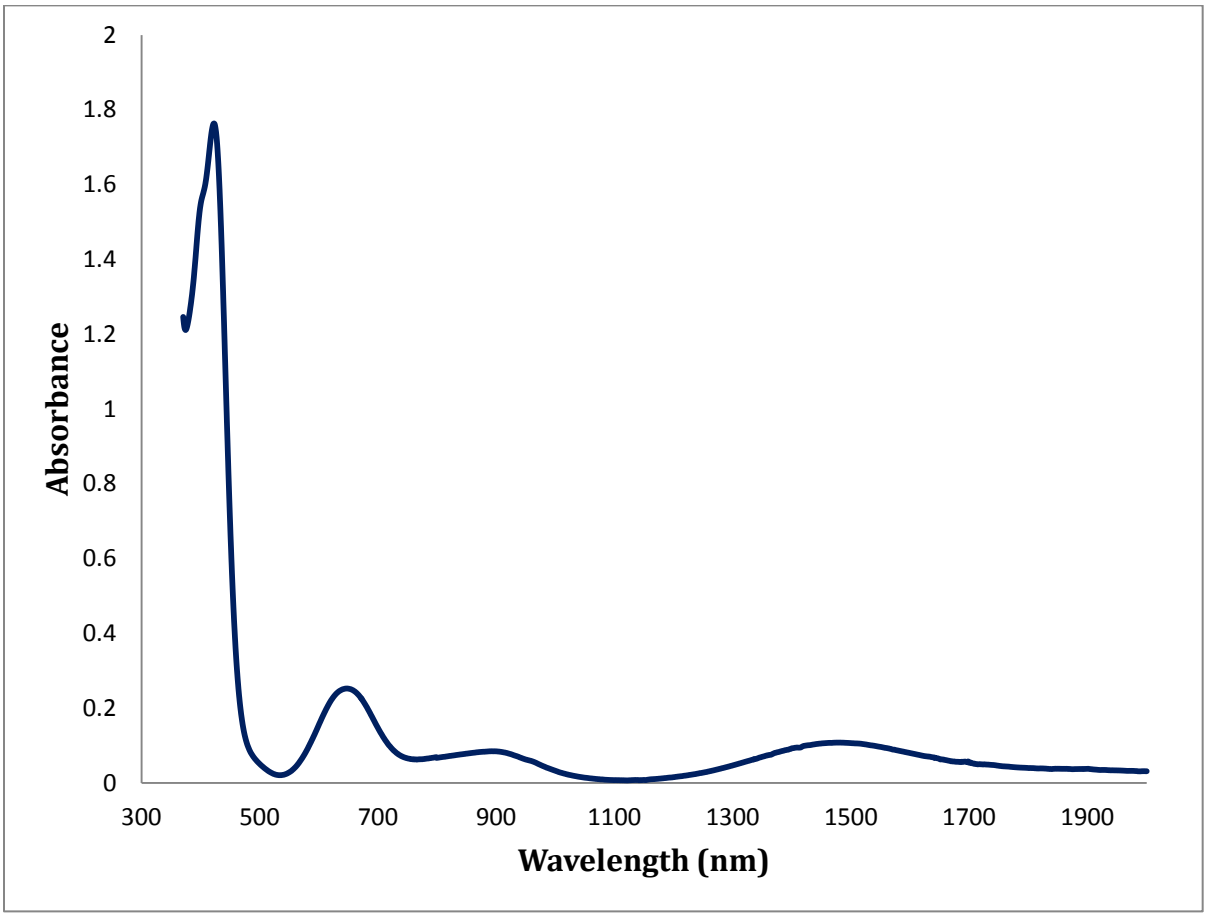


Figure 24. Optical spectra of a 3.5 x 10^{-3} M solution CH_2Cl_2 of (**46b**) in a 1cm cell at room temperature.

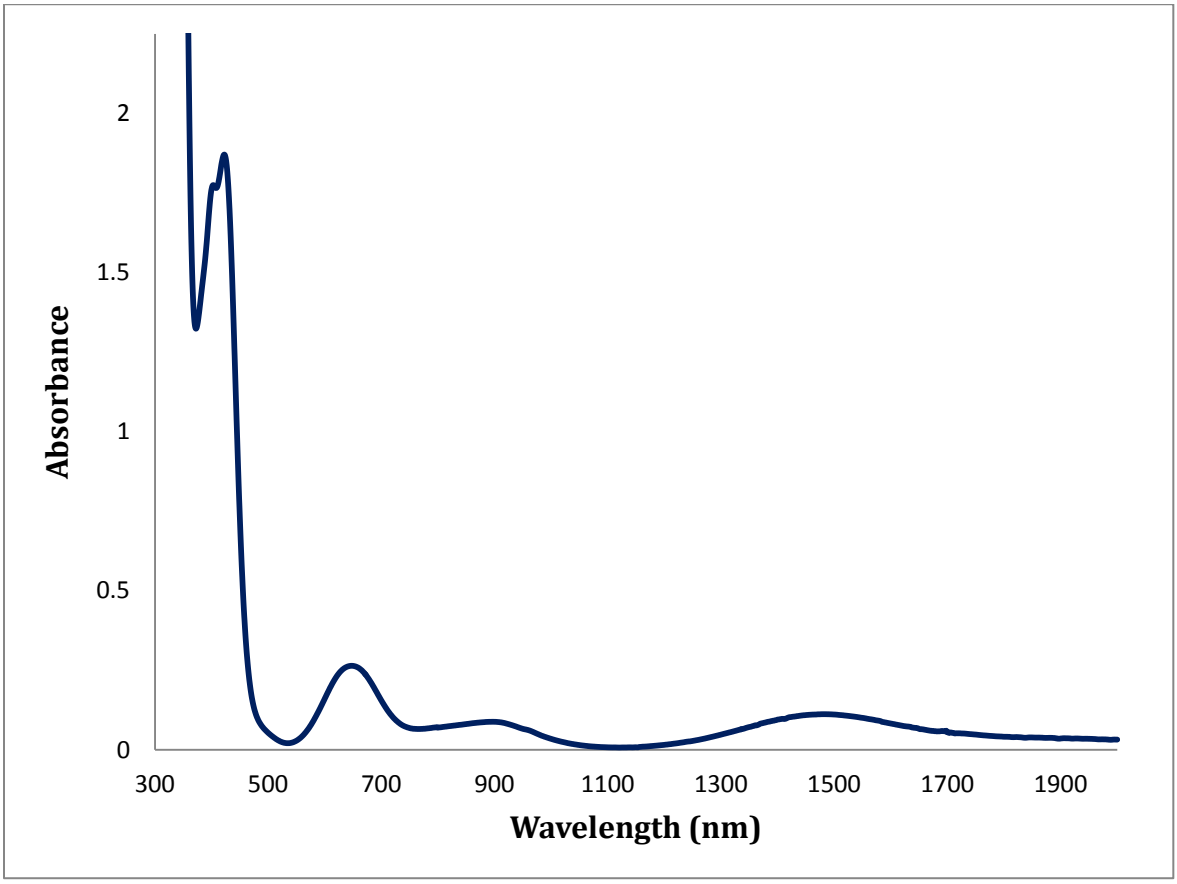


Figure 25. Optical spectra of a 3.5 x 10^{-3} M CH_2Cl_2 solution of (**46c**) in a 1cm cell at room temperature.

Table 3. Electronic Spectra Features Data for **(46a-c).**

Complex	Solvent	Absorption Maxima nm (ε_M)			
Tp*Ni($S_2CN(C_4H_8)$) (**46a**)	CH_2Cl_2	1478 (38)	896 (31)	657 (89)	424 (569)
Tp*Ni($S_2CN(C_5H_{10})$) (**46b**)	CH_2Cl_2	1482 (30)	904 (24)	647 (72)	422 (504)
Tp*Ni($S_2CN(C_5H_{12})$) (**46c**)	CH_2Cl_2	1482 (32)	895 (25)	646 (76)	422 (536)

X-ray Crystallography

$Ni(S_2CNR)_2$ (46a-c)

During the synthesis of (**46a-c**) starting with the bis-nickel complex (Scheme 18) we also produced and crystallized out the starting material $Ni(S_2CNR)_2$ (**44a-c**). The crystal structures for these compounds determined by single crystal X-ray diffraction are shown in Figures 26-28. The selected bond distances and angles are listed in Tables 4-6. All three of the structures are considered four coordinate with a square planar geometry around the nickel atom. All of the Ni-S bond distances are within approximately one one thousand angstrom of each other and within 3σ of each other. These are typical distances for a nickel dithiocarbamate. The "bite angle" ($S2^1$-Ni-S2) of the dithiocarbamate was 79-80° which is also typical of the dithiocarbamate complexes. The two ligands thus bind to the nickel in a symmetrical square planar geometry.

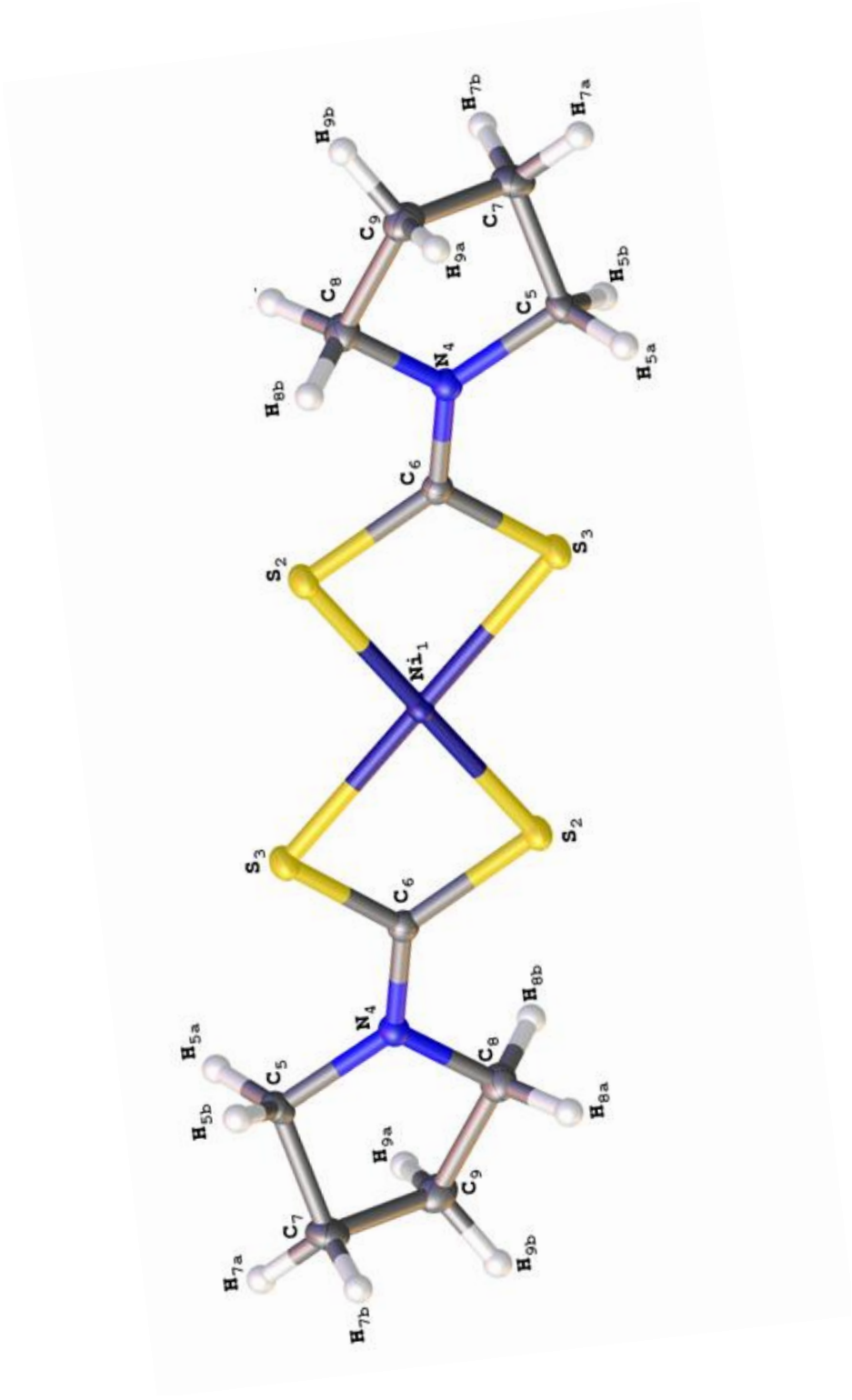


Figure 26. X-ray structure of (**44a**).

Table 4. Selected Bond Distances (Å) and Bond Angles (deg.) for $Ni(S_2CN(C_4H_8))_2$ **(44a)**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	$S2^1$	2.2109 (3)	$S2^1$	Ni	S2	179.999 (9)
Ni	S2	2.2109 (3)	S2	Ni	$S3^1$	100.316 (10)
Ni	$S3^1$	2.2126 (3)	$S2^1$	Ni	$S3^1$	79.685 (10)
Ni	S3	2.2127 (3)	S2	Ni	S3	79.683 (10)
			$S2^1$	Ni	S3	100.316 (10)
			$S3^1$	Ni	S3	180

Numbers in parentheses are estimated standard deviations in the least significant digits.

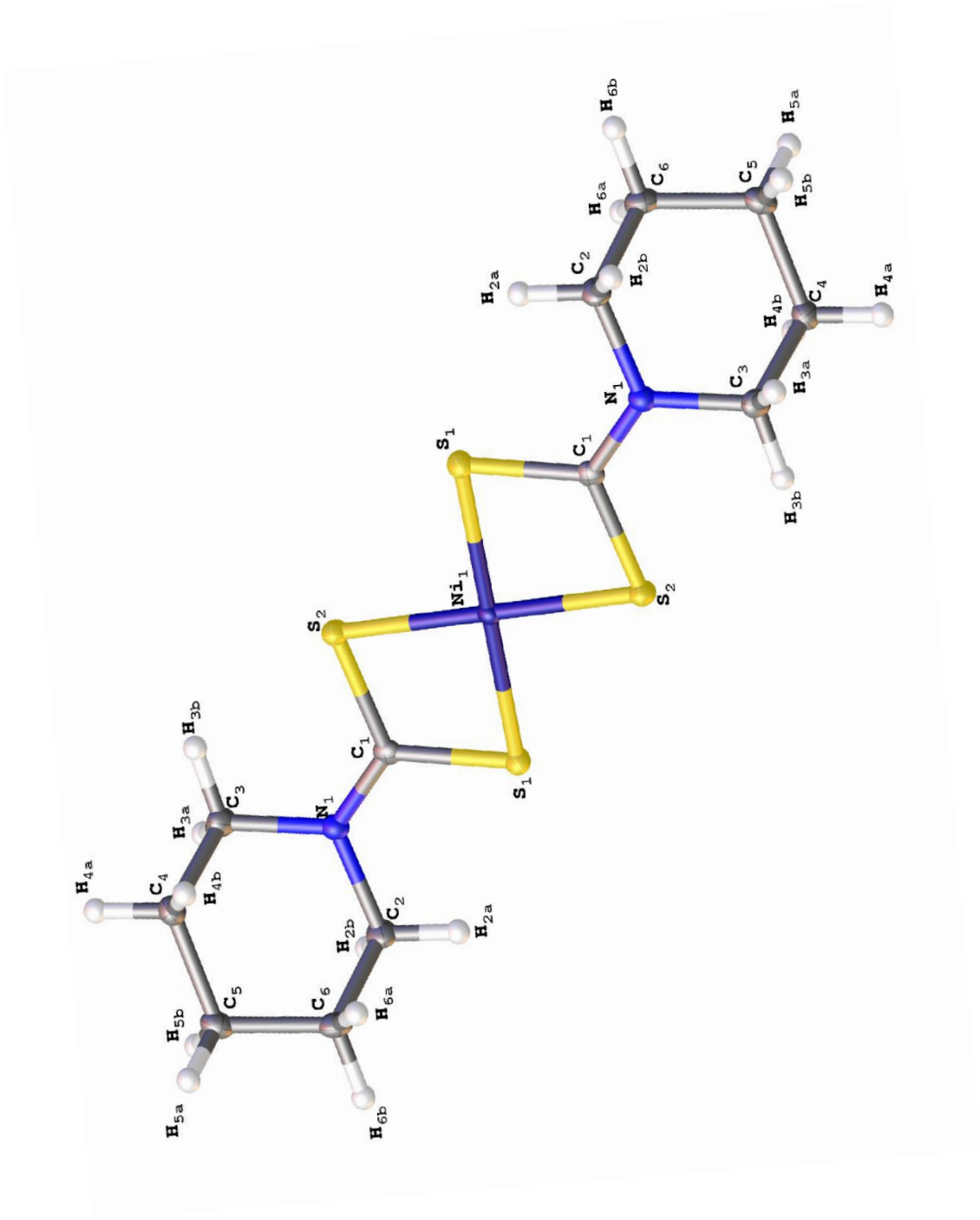


Figure 27. X-ray structure of (**44b**).

Table 5. Selected Bond Distances (Å) and Bond Angles (deg.) for $Ni(S_2CN(C_5H_{10})_2)$ **(44b)**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	$S2^1$	2.203(4)	$S3^1$	Ni	S3	180
Ni	S2	2.203(4)	S2	Ni	$S2^1$	180
Ni	$S3^1$	2.196(4)	$S3^1$	Ni	$S2^1$	79.49(14)
Ni	S3	2.196(4)	S3	Ni	S2	79.50(14)
			$S3^1$	Ni	S2	100.50(14)
			$S2^1$	Ni	S3	100.50(14)

Numbers in parentheses are estimated standard deviations in the least significant digits.

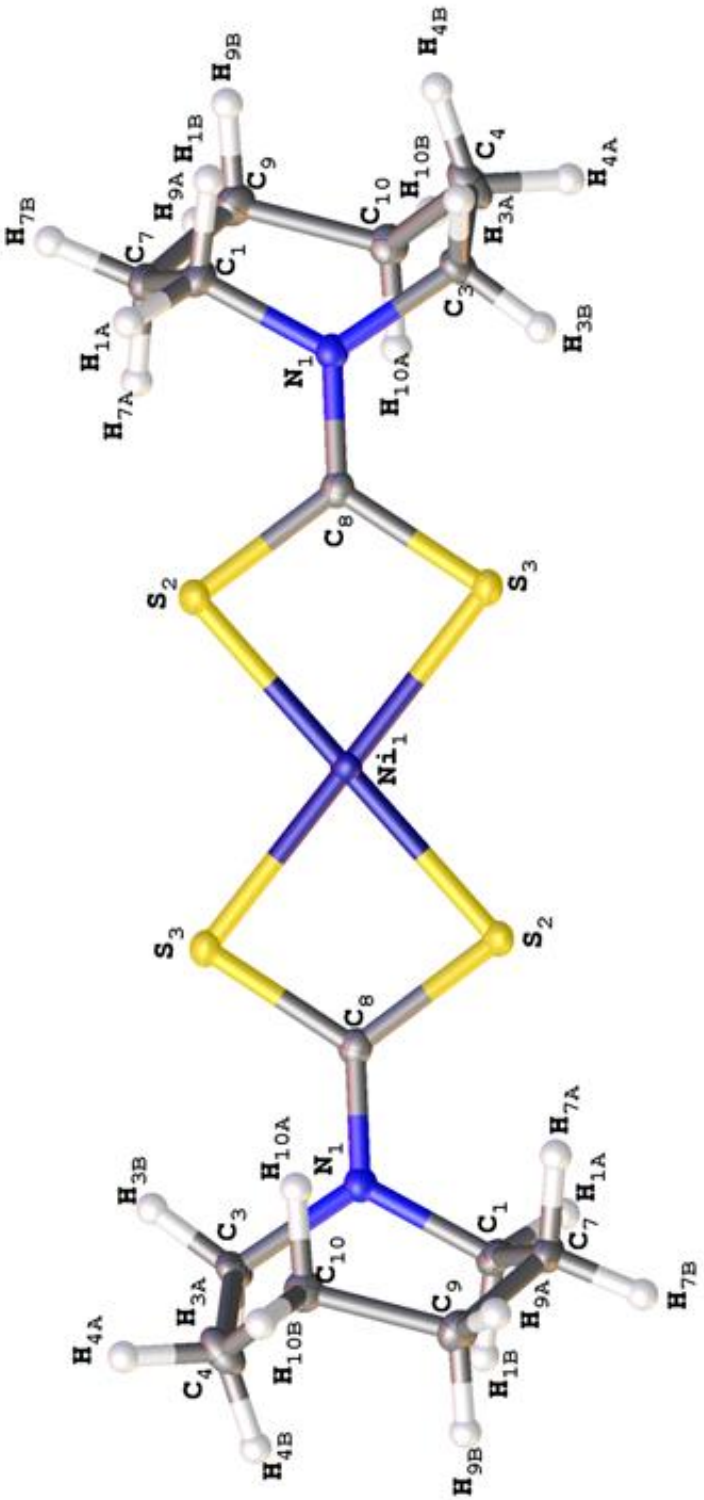


Figure 28. X-ray structure of (**44c**).

Table 6. Selected Bond Distances (Å) and Bond Angles (deg.) for $Ni(S_2CN(C_6H_{12})_2)$ **(44c)**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	S3[1]	2.203(5)	S3[1]	Ni	S3	180
Ni	S2	2.210(5)	S3	Ni	S2[1]	100.50(17)
Ni	S2[1]	2.210(5)	S3[1]	Ni	S2[1]	79.50(17)
Ni	S3	2.203(5)	S3	Ni	S2	79.50(17)
			S3[1]	Ni	S2	100.50(17)
			S2[1]	Ni	S2	180

Numbers in parentheses are estimated standard deviations in the least significant digits.

The crystal structures of Tp*Ni(S_2CNR_2) (**46a-c**) were determined by single crystal X-ray diffraction. The coordination environment in all three structures is considered pentacoordinate, with the nickel atom surrounded by three nitrogen atoms and two sulfur atoms. All three of the molecules exhibit a distorted square pyramidal coordination geometry. The nickel atom in each complex is coordinated to the hydrotris(3,5-dimthyl)pyrazolyl ligand (Tp*)and a bidentate dithiocarbamate ligand. The nickel metal atom resides in a "pocket" formed by the methyl groups at the three positions of each pyrazolyl ring. The square planar base found in these complexes is formed by the two sulfur atom and two nitrogen atoms in each structure. Details of the individual structures are given below:

Tp*Ni($S_2CN(C_4H_8)$) (46a)

The structure of (**46a**) is shown in Figure 29 and the selected bond distances and angles are listed in Table 7. The structure reveals N8 is at the apex and N11-S2 and N9-S3 form the base of the square pyramid.

Tp*Ni($S_2CN(C_5H_{10})$) (46b)

The structure of (**46b**) is shown in Figure 30 and the selected bond distances and angles are listed in Table 8. The structure reveals N1 is at the apex and N5-S2 and N3-S1 form the base of the square pyramid.

Tp*Ni($S_2CN(C_6H_{12})$) (46c)

The structure of (**46c**) is shown in Figure 31 and the selected bond distances and angles are listed in Table 9. The structure reveals N8 is at the apex and N4-S2 and N6-S3 form the base of the square pyramid.

The three Ni-N bond distances in each of these complexes are nearly equal and are at the usual distance for Ni^{+2}-imidazol pyridine or pyrazole. This indicates that the pyrazolyborato ligand is symmetrically coordinated to the nickel ion in each structure. The N-Ni-N bond angles in all three complexes represent the typical values for the pyrazolyl rings in pyrazolylborato metal complexes.

The Ni-S distances for (**46a**) and (**46b**) show that the dithiocarbamate ligand in these complexes is not symmetrically coordinated to the nickel atom. By comparison the coordination of the dithiocarbamate ligands in (**44a-c**) are symmetrically coordinated. In addition the Ni-S distances in (**46a-c**) are outside the range of 2.21903 (3)-2.2127(3) found for (**44a-c**). This is consistent with the smaller "bite angle" (1S-Ni-S)of the approximately 74^o for (**46a-c**) compared to 79-80^o for (**44a-c**). These differences in the structural features can be attributed to the difference in coordination number between the two sets of complexes. The Ni-S bond distances in (**46c**) are rather symmetrical compared to (**46a, b**) probably die to crystal packing forces.

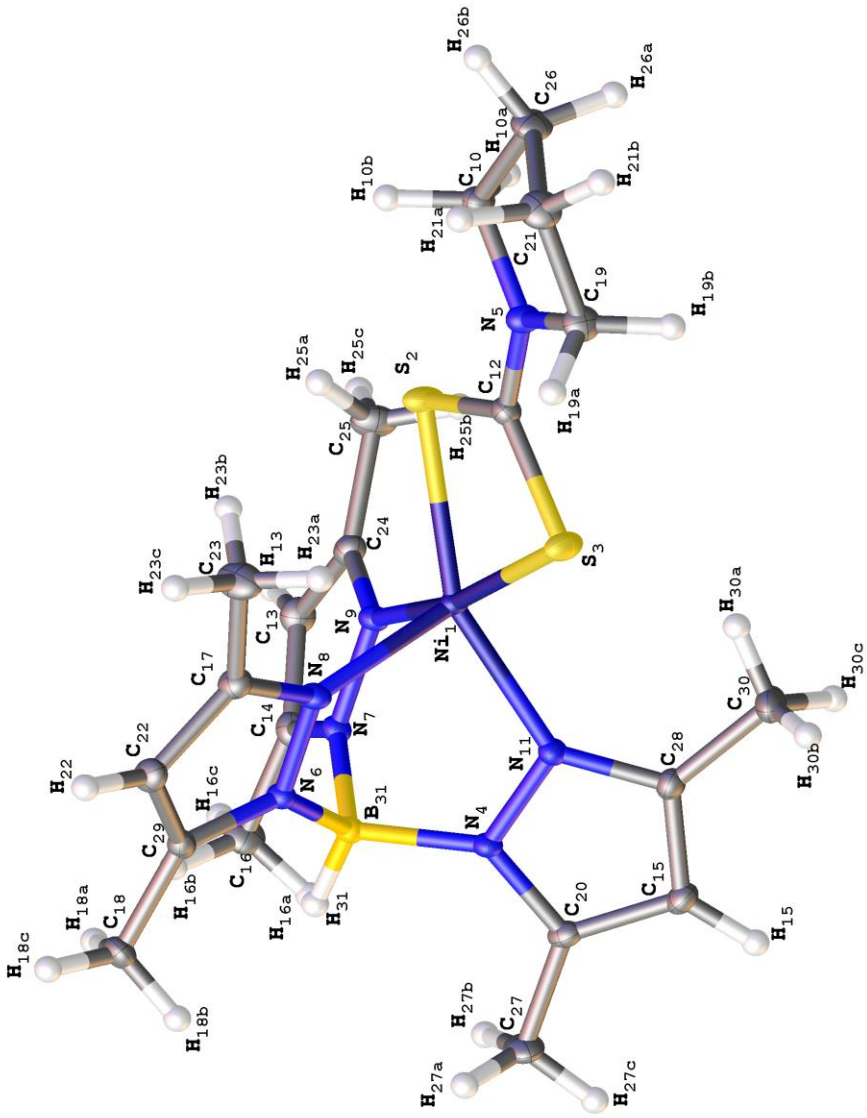


Figure 29. X-ray structure of (**46a**).

Table 7. Selected Bond Distances (Å) and Bond Angles (deg.) for [(Tp*)Ni($S_2CNC_4H_8$)] (**46a**)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	S2	2.3640 (4)	N8	Ni	N9	88.50 (4)
Ni	S3	2.4598 (5)	N8	Ni	S2	112.55 (3)
Ni	N8	2.0287 (10)	N11	Ni	S2	154.72 (10)
Ni	N9	2.0625 (11)	N9	Ni	S2	96.14 (3)
Ni	N11	2.044 (5)	N8	Ni	S3	101.56 (3)
			N9	Ni	S3	168.03 (3)
			S2	Ni	S3	74.11 (1)
			N11	Ni	N9	89.0 (3)
			N11	Ni	S3	97.0 (3)
			N8	Ni	N11	92.28 (6)

Numbers in parentheses are estimated standard deviations in the least significant digits.

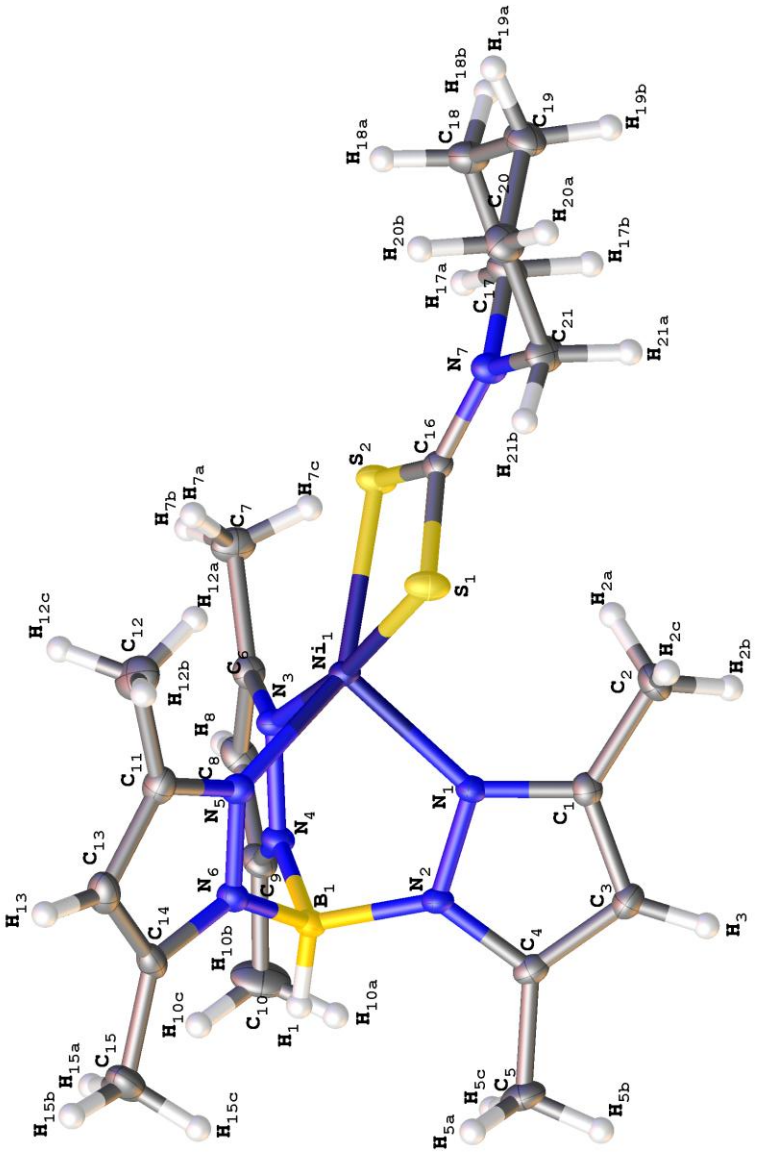


Figure 30. X-ray structure of (**46b**).

Table 8. Selected Bond Distances (Å) and Bond Angles (deg.) for [(Tp*)Ni($S_2CNC_5H_{10}$)] (**46b**)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	S1	2.4732 (3)	S2	Ni	S1	73.994 (10)
Ni	S2	2.3182 (3)	N1	Ni	S1	96.93 (3)
Ni	N1	2.0146 (10)	N1	Ni	S2	119.54 (3)
Ni	N3	2.0888 (10)	N1	Ni	N3	88.04 (4)
Ni	N5	2.0164 (10)	N1	Ni	N5	94.01 (4)
			N3	Ni	S1	171.92 (3)
			N3	Ni	S2	98.02 (3)
			N5	Ni	S1	99.00(3)
			N5	Ni	S2	146.13 (3)
			N5	Ni	N3	86.97 (4)

Numbers in parentheses are estimated standard deviations in the least significant digits.

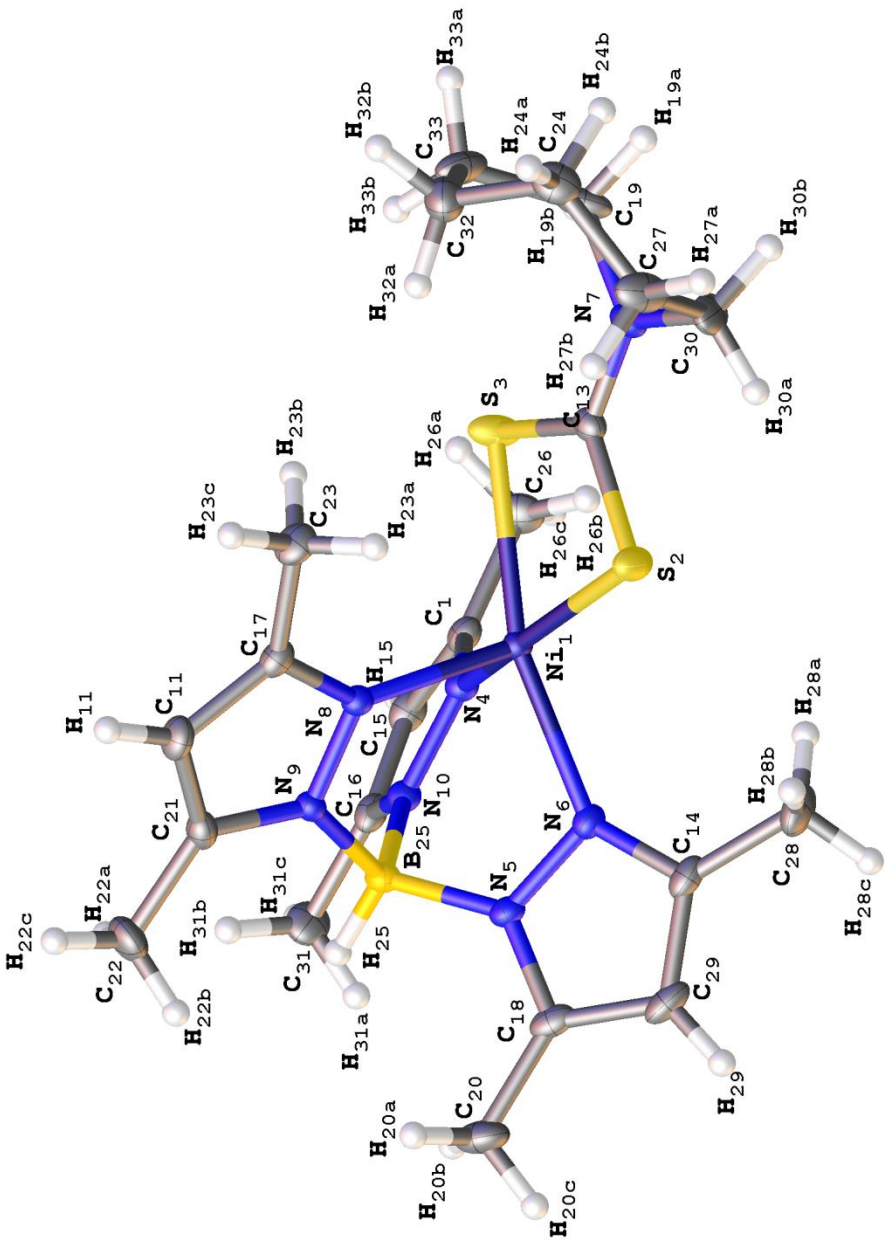


Figure 31. X-ray structure of (**46c**).

Table 9. Selected Bond Distances (Å) and Bond Angles (deg.) for [(Tp*)Ni($S_2CNC_6H_{12}$)] (**46c**)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 2	Angle
Ni	S2	2.378(4)	S3	Ni	S2	75.03(12)
Ni	S3	2.381(4)	N4	Ni	S2	161.00(3)
Ni	N4	2.062(11)	N4	Ni	S3	96.51(3)
Ni	N6	2.098(11)	N6	Ni	S2	96.65(3)
Ni	N8	2.014(11)	N6	Ni	S3	164.05(3)
			N6	Ni	N4	87.17(4)
			N8	Ni	S2	107.30(3)
			N8	Ni	S3	103.67(3)
			N8	Ni	N4	91.12(4)
			N8	Ni	N6	91.73(4)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Electrochemistry

The electrochemical behavior of complexes (**46a-c**) was examined using cyclic voltammetric techniques. The poor solubility of the compounds in good electrochemical solvents significantly affected the results. The measurements for (**46c**) were made in MeCN but because of the low solubility of the smaller rings was insufficient we switch to CH_2Cl_2 for complexes (**46a-b**). All three complexes were electrochemically active within the potential window of ($^{+}2.0$ - $^{-}2.0$). Parameters obtained from the voltammograms include peak potential separation (ΔE_p) and the peak current ratio (i_a/i_c)). For a reversible one-electron process, the theoretical values of the parameters are ΔE_p=59 mV and i_a/i_c = 1.0.[99] The oxidation processes observed for these complexes have wider ΔEp and larger i_a/i_c values than expected. The poor conductivity of the solvent, even with 0.1Met_4NClO_4 supporting electrolyte hampered obtaining good results. A typical voltamogram is shown in Figure 32. Values are recorded in Table 10. All of the complexes show an oxidative wave, presumably from $Ni^{+2/+3}$. The larger ΔEp values indicate a slow e- transfer and the larger i_a/i_c values indicate that the e- transfers are apparently not chemically reversible. The sample used for compounds (**46c**) exhibited another oxidative wave and we attribute that to contamination by (**44c**). Previous studies on similar compounds[91] showed much more reversible one electron processes. Apparently our cell geometry in combination with solvent and electrolyte led to the present results. Further electrochemical investigations are planned.

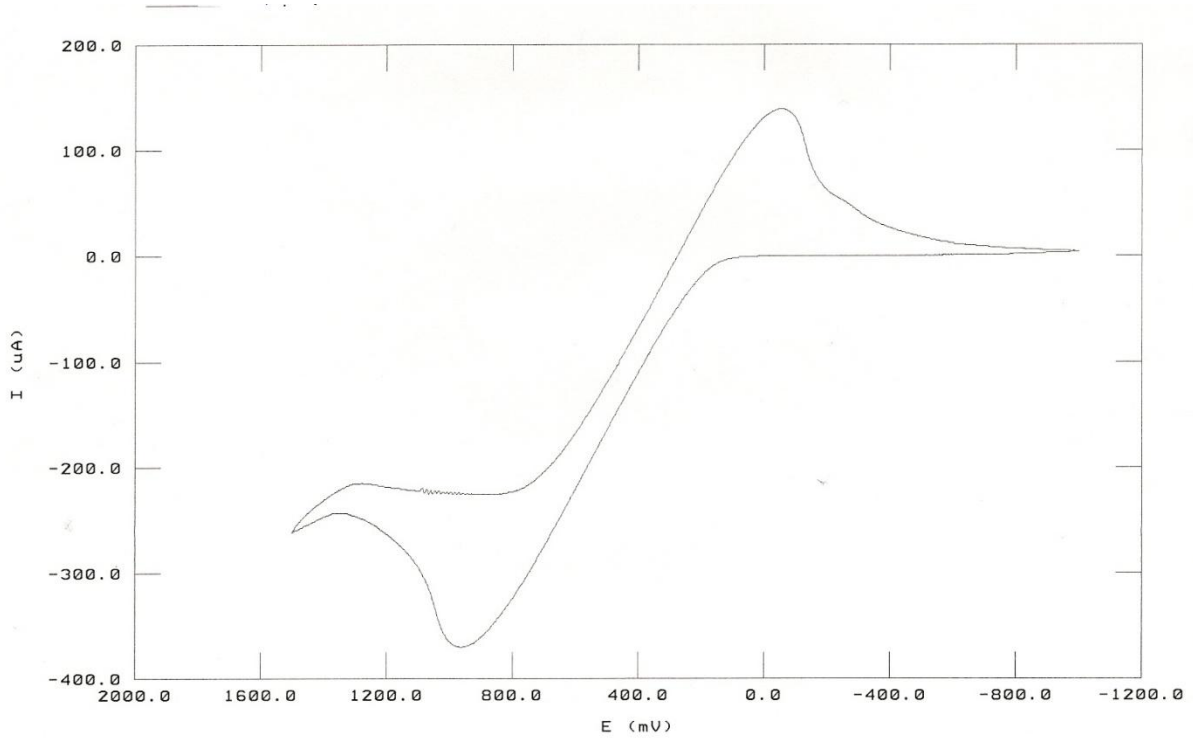


Figure 32. Cyclic voltammogram of 3mM (**46b**) in CH_2Cl_2 at a platinum electrode at room temperature.

Table 10 Electrochemical Data for **(46a-c).**

Complex	**Electrode**	**ΔEp(mv)**	**$E_{1/2}$(V)**	**i_a/i_c**
Tp*Ni($S_2CN(C_4H_8)$) (**46a**)				
	Glassy-Carbon	1050	0.553	3.3
	Platinum	1187	0.643	4.9
Tp*Ni($S_2CN(C_5H_{10})$) (**46b**)				
	Glassy-Carbon	851	0.44	2.8
	Platinum	900	0.51	0.3
Tp*Ni($S_2CN(C_6H_{12})$) (**46c**)				
	Glassy-Carbon	128	0.585	5.4
		99	0.187	19.5
	Platinum	121	0.433	4.6
		92	0.176	33

*Scan 50 mV/s

Conclusions

We were able to prepare in good yield the TpNi(S_2CNR_2) complexes (**46a-c**) with varying ring sizes on the dithiocarbamate by two routes. In the first route we used the square planar nickel complexes (**44a-c**) and the second started from (**14**). The electronic absorption spectra of (**46a-c**) support the distorted square pyramid geometry observed in the crystal structure.

X-ray crystal structure determination for (**44a-c**) and (**46a-c**) were obtained. The structures of (44a-c) show one Tp* and one dithiocarbamate coordinated to the Ni+2 ion. A square pyramidal geometry is observed with a N_2S_2 square base and one pyrazoyl group at the apical position to complete the square planar coordination unit.

Even though the electrochemical studies of (**46a-c**) did not exhibit the expected results we still believe that the results from the other analysis demonstrate that the Tp*Ni(S_2CNR_2) complexes are reasonable models for the oxidative form of Ni-SOD.

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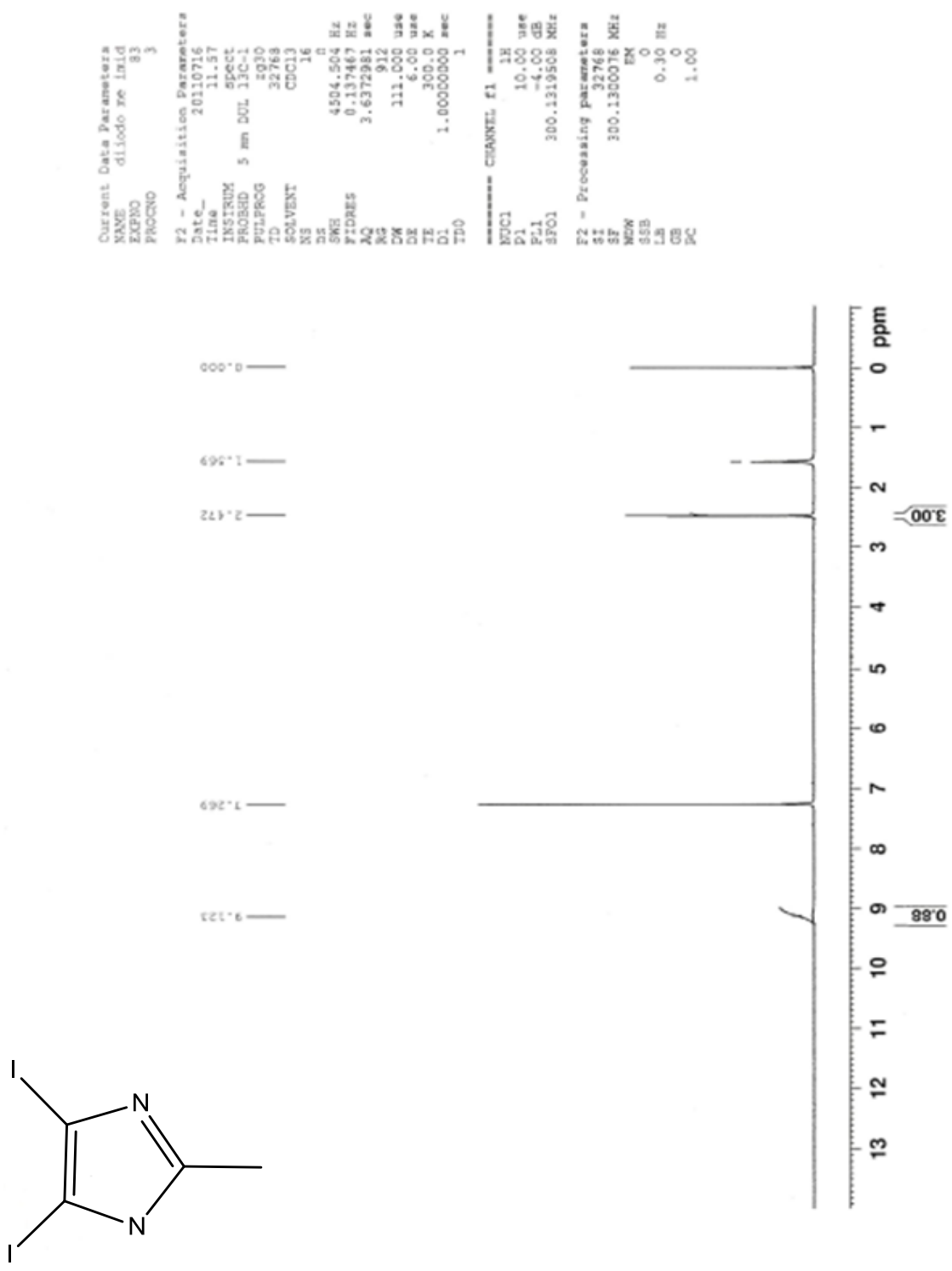
LIST OF APPENDICIES

APPENDIX: I

SPECTRA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TE 300.0 K
D1 1.00000000 sec
TD0 1
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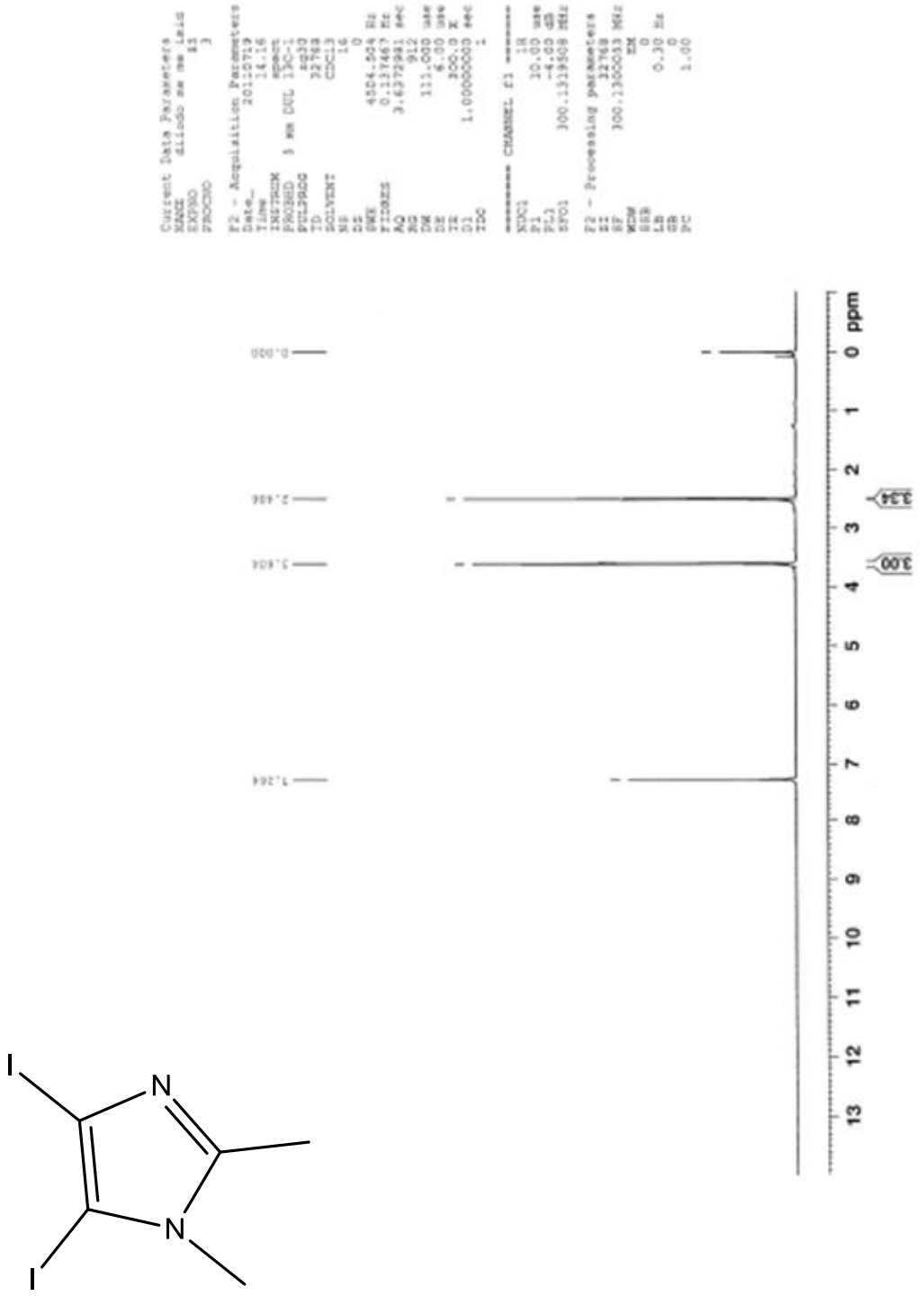
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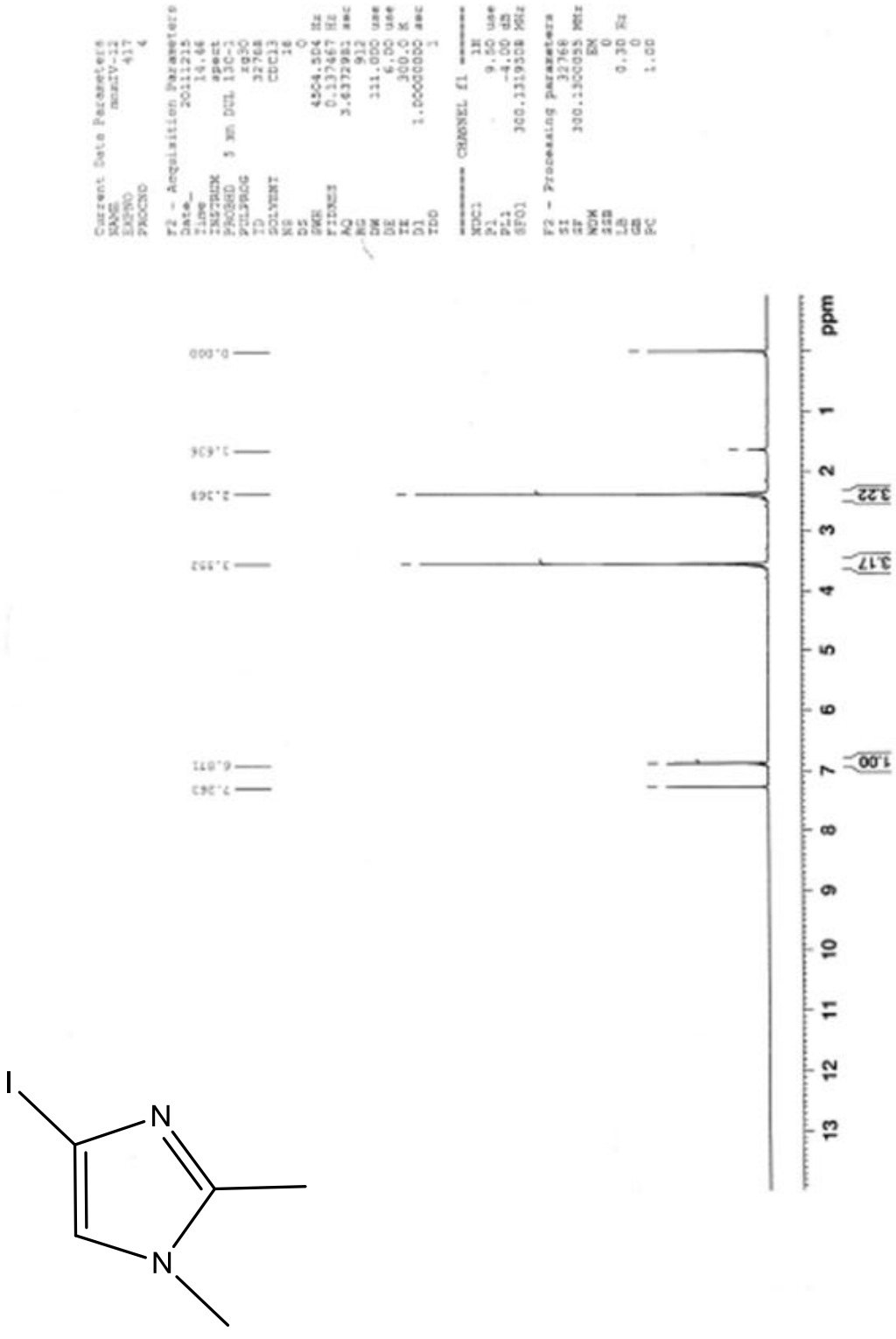
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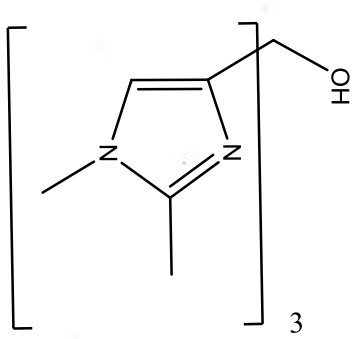


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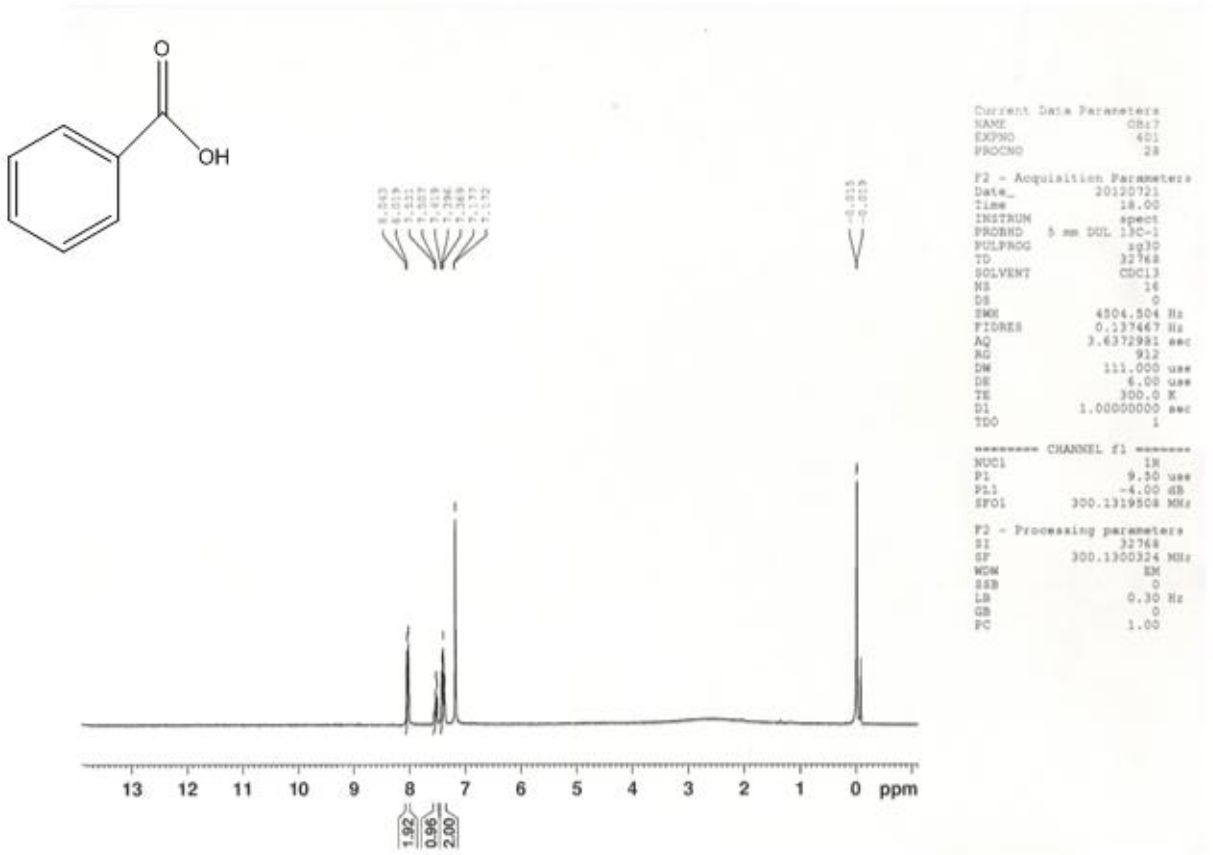
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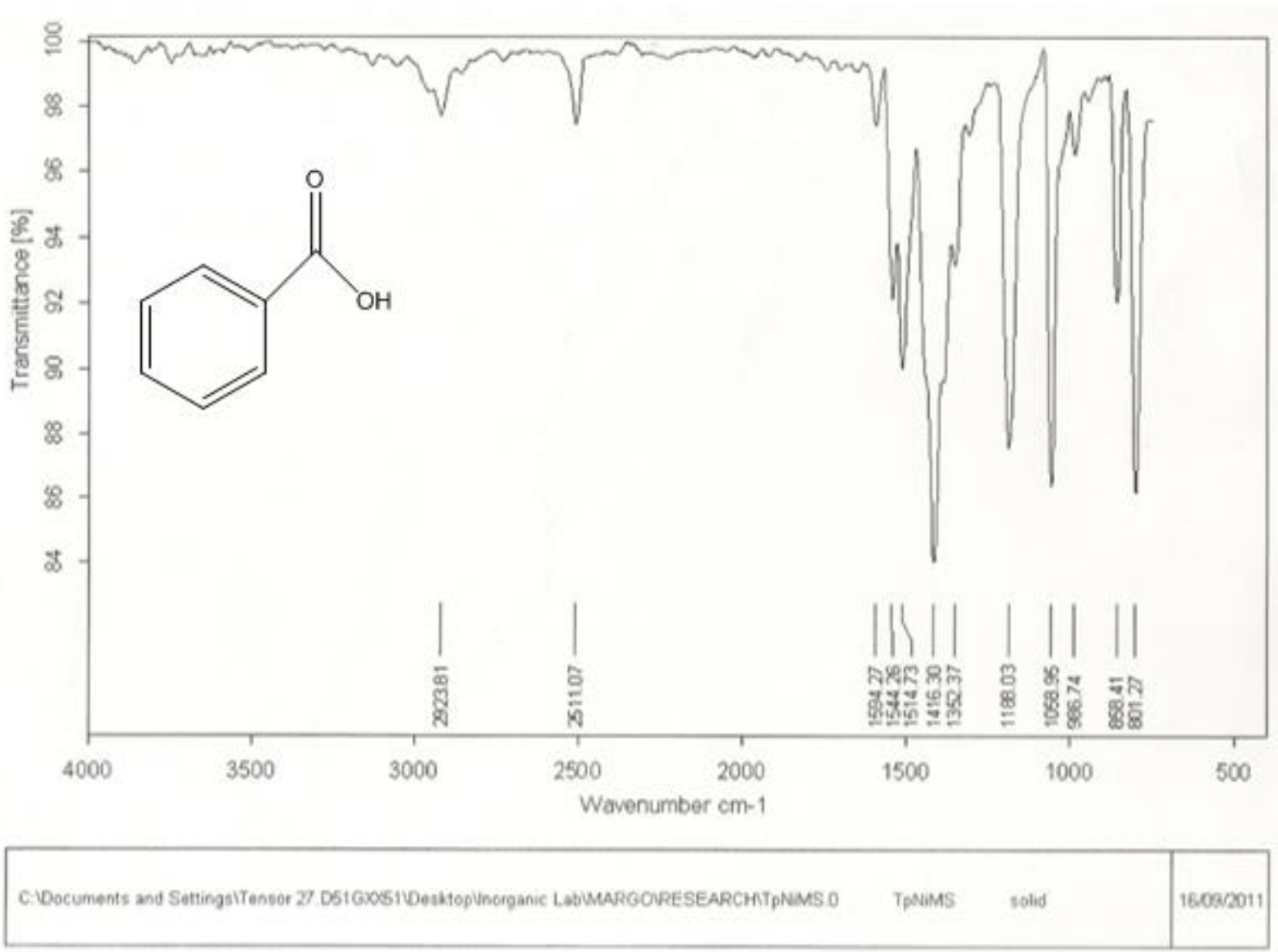
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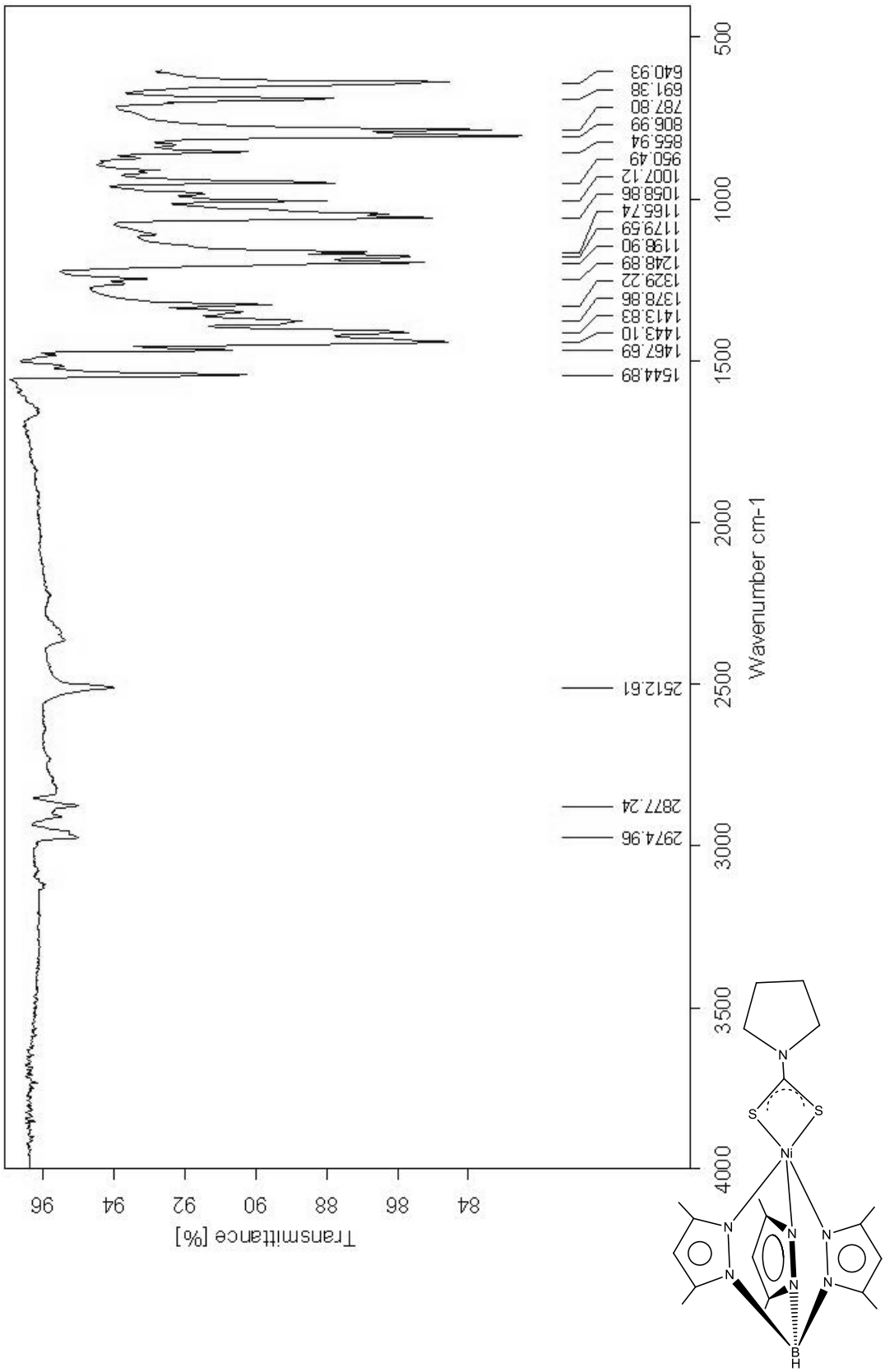
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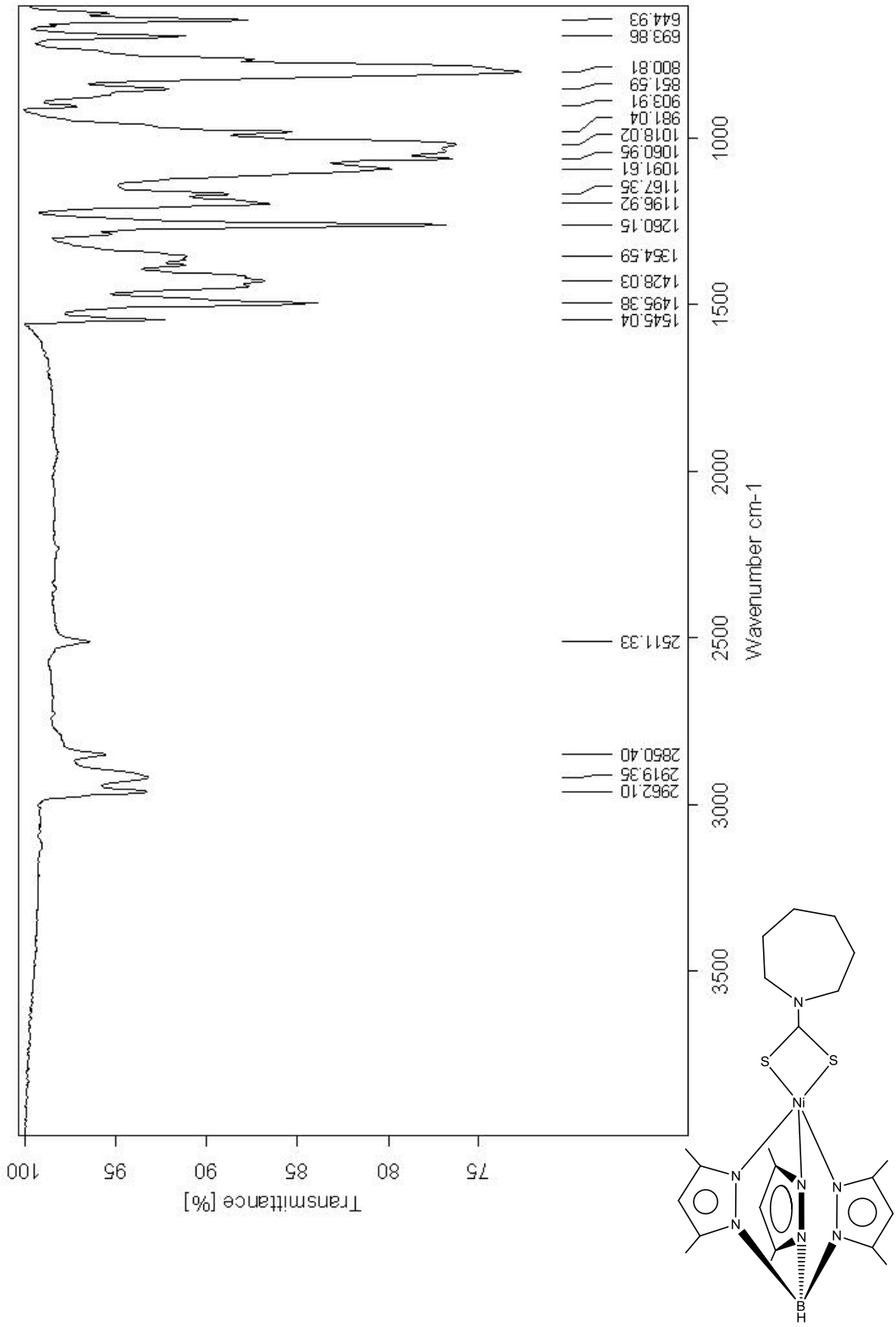
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Wavenumber cm-1
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APPENDIX: II

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Title: Effect of a Tridentate Ligand on the Structure, Electronic Structure, and Reactivity of the Copper(I) Nitrite Complex: Role of the Conserved Three-Histidine Ligand Environment of the Type-2 Copper Site in Copper-Containing Nitrite Reductases

Author: Masato Kujime et al.

Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

Date: May 1, 2008

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Margo N. Montgomery

EDUCATION

The University of Mississippi, University, MS
Doctor of Philosophy, Inorgani**c** Chemistry, Anticipated Date: August 2012
Dissertation: *Synthesis and Characterization of Nickel Complexes with Relevance to Acireductone Dioxygenase* Advisor: Dr. Walter E. Cleland, Jr.

Xavier University of Louisiana, New Orleans, LA
Bachelor of Science, Chemistry May 2003

AWARDS

Mississippi Space Grant Consortium Graduate Research Fellow 2008 - 2011
Amount Awarded: $17,000/year
K-12 Outreach Component:

Oxford Learning Center, (Alternative School), Oxford, MS
Teaching Assistant/Intern, 1day/week 2009-2011
Developed inquiry based experiments for students in grades 6-12, coordinated its first science fair, with the winners going on to the regional fair and ultimately advancing on to the state fair.

University of Mississippi Graduate Student Travel Award 2009, 2010

NOBCChE Advancing Science Award 2007, 2008

Alliance for Graduate Education in Mississippi Doctoral Scholar 2005 – 2007
Amount Awarded: $9,000/year

TEACHING EXPERIENCE

Northwest Mississippi Community College, Senatobia, MS Fall 2011
Adjunct Instructor- General Chemistry

The University of Mississippi, University, MS
Teaching Assistant – "General Chemistry Lecture" 2011 - present
Managed on-line content for course.

Teaching Assistant – "Advanced Inorganic Lab" 2009 – 2011
"General Chemistry Lab" 2007 – 2008
"Survey of Chemistry Lab" 2005 – 2007

RESEARCH EXPERIENCE

Research Assistant, University of Mississippi 2005-Prseent
Advisor: Dr. Walter E. Cleland, Jr.
Synthesized model complexes specifically designed to mimic the structural, spectroscopic and reactivity features of the nickel dependant enzyme, acireductone dioxygenase.

Research Assistant, University of New Hampshire 2003-2005
Advisor: Dr. Glen P. Miller
Using organic polyamines investigated the chemistry of the regioselective hydrogenation process of fullerenes.

Research Assistant, Xavier University of Louisiana 2002-2003
Advisor: Dr. Kathleen M. Morgan
Developed a new and improved synthesis for 1-aza-2-adamantanone, (Kirby's most twisted amide).

PRESENTATIONS

M. N. Montgomery and W. E. Cleland, "*Preparation and properties of the tris[4(5)imidazolyl]carbinol ligand complexes*" Joint 66th Southwest and 62nd Southeastern Regional Meeting of the American Chemical Society Poster Presentation, December 2010, New Orleans, LA.

M. N. Montgomery, S. Liao, W. Chen. B. Engine, W. E. Cleland, *"Synthesis and characterization of nickel trispyrazolylborate complexes with dithioacid coligands"* 238th American Chemical Society National Meeting Poster Presentation, August 2009, Washington, D.C.

April R. Noble, **Margo N. Montgomery**, Kathleen M. Morgan, *"Synthesis of the twisted amide"* 225th American Chemical Society National Meeting, March 2003, New Orleans, LA

PUBLICATIONS

M. N. Montgomery and W.E. Cleland, Jr. *"Synthesis and Characterization of Tris(4-imidazolyl)carbinol Ligands and their Nickel(II) Complexes Related to Nickel Acireductone Dioxygenase"* In preparation

M. N. Montgomery and W.E. Cleland, Jr. "*Hydrotris(3,5-dimethylpyrazolyl)borate Based Synthetic Models for the Active Site of Nickel Acireductone Dioxygenase."* In preparation

W. Chen, L. Zhao, S. Liao, **M. N. Montgomery** and W. E. Cleland, Jr. *"Nickel polypyrazolylborate chemistry: Synthesis and characterization of a series of dialklydithiocarbamato hydrotris(3,5-dimethylpyrazolyl)borato nickel complexes."* In preparation

J. B. Briggs, **M. N. Montgomery**, L. Silva and G. P. Miller. "*Facile, Scalable, Reegioselective Synthesis of $C_{3v}C_{60}H_{18}$ Using Organic Polyamines."* Organic Letters. 2005, 7, 5553-5555.

K. Morgan, M. L. Rawlins, **M. N. Montgomery**. "*Influence of methyl substituents on the stability of 1-aza-2-adamantanone, Kirby's most twisted amide."* Journal of Physical Organic Chemistry, 2005, 18, 310-314.

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