THE GREAT POTENTIAL OF REDOX ACTIVE LIGANDS: APPLICATIONS IN
CANCER RESEARCH AND REDOX ACTIVE CATALYSIS

A thesis submitted in partial fulfillment of the
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By

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Meredith Miles ENTITLED The Great Potential of Redox Active Ligands: Applications in Cancer Research and Redox Active Catalysis BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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ABSTRACT

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The Great Potential of Redox Active Ligands: Applications in Cancer Research and Redox Active Catalysis

Metal N-heterocyclic carbene (NHC) complexes have recently gained much popularity due to their tunable, steric, and electronic properties. Applications for such versatile molecules include organocatalysis\textsuperscript{1,2,3}, olefin metathesis\textsuperscript{4,5,6}, sundry cyclization reactions\textsuperscript{7,8,9}, and materials chemistry\textsuperscript{10,11}. Redox active NHCs are of special interest due to their ability to alter the electronic properties of the metal centers they are ligated to.\textsuperscript{12}

In the first chapter, Au(I)-NHC complexes were synthesized and tested for biological activity in human cancer cell lines. Increasing reactive oxygen species (ROS) in cellular systems has proven to be a successful pathway for treating cancer.\textsuperscript{13,14,15} The redox active group in this case was naphthoquinone which contributed to the oxidative stress applied to the tumor cells. Three Au(I)-NHC complexes were synthesized and analyzed structurally utilizing \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, and X-ray crystallography. Biological studies including IC\textsubscript{50} cell culture lines and cell proliferation analyses were performed to determine the complexes’ efficiency and success as a cancer treatment drug.
The second chapter describes a theoretical approach to synthesize a redox active tetrathiafulvalene (TTF) fused with an iridium-NHC complex to serve as a redox switchable catalyst. The first compound in this synthetic route was successfully synthesized and analyzed structurally with $^1$H and $^{13}$C NMR, UV-Vis spectroscopy, and IR spectroscopy. The electrochemical properties were also investigated. Tetrathiafulvalene possesses the ability to undergo multiple one electron reversible redox transformations.\textsuperscript{16} This unique characteristic paired with the catalytic properties of iridium-NHC could produce a catalyst capable of accessing three or more catalytic species based upon the oxidation state of TTF.
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CHAPTER ONE: DEVELOPMENT OF REDOX CYCLING N-HETEROCYCCLIC CARBENE – GOLD(I) COMPLEXES FOR THERAPEUTIC APPLICATIONS

I. Introduction

i. N-Heterocyclic Carbenes

a. Historical Background

Although N-Heterocyclic carbenes (NHCs) have been known since the late 1960s, it wasn’t until 1991 in which Arduengo et al. was the first to successfully isolate an NHC. Previous isolation attempts had been performed by Wanzlick in 1961, but such efforts erroneously resulted in the formation of dimers. It was later discovered that bulky nitrogen substituents prevented this dimerization. The following scheme illustrates the synthetic strategy carried out by Arguendo and his research team.

![Scheme 1.1: Isolation of a free carbene.](image)

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Arduengo treated the 1,3-di-1-adamantylimidazolium chloride with a catalytic amount of DMSO in the presence of 1 equivalent of sodium hydride in THF at room temperature to produce the carbene. As a second method, the same imidazolium salt was treated with potassium tert-butoxide at room temperature, and the deprotonation occurred with a 96% yield. The carbene remains stable under inert conditions allowing it possible to understand the physical properties that make NHCs crucial in organometallic transformations.\textsuperscript{17}

b. Structural Properties

Free carbenes exist in singlet or triplet states depending on the type of substituent on the nitrogen atoms. Electron donating groups stabilize the singlet state of free carbenes, while electron withdrawing groups stabilize the triplet state through steric and electronic effects. Triplet state carbenes occur when there is an electron in two different orbitals with parallel spins. For this reason, triplet carbenes act as a biradical species. There are two scenarios for singlet state carbenes; the electrons can reside in the $\sigma$ orbital or $p_\pi$ orbital.\textsuperscript{19,20,21,22,23}

For this research, the singlet carbene is of interest. A “push pull” effect occurs due to the lone pair on the nitrogen atoms strongly interacting with the $p_\pi$ orbital of the
carbene carbon.\textsuperscript{22,23} They exhibit a positive mesomeric effect while simultaneously providing a negative inductive effect on the carbene carbon.\textsuperscript{20}

The negative inductive effect is present because the nitrogen atoms are stronger σ electron withdrawing groups in comparison to carbon atoms. This “pulls” the electron density away from the carbene center. The positive mesomeric effect is caused by the lone pair present on the nitrogen atoms, which is capable of delocalization and π-back donation (Figure 1.2). This “pushes” on the carbene carbon. This combination of mesomeric and inductive effects creates a stabilized carbene center, allowing for a facile and strong coordination, particularly to metals.

The tunable steric and electronic properties of NHCs coupled with their stability allow for excellent coordination to transition metal complexes.\textsuperscript{20,23} These characteristics are especially important when considering drug synthesis. The objective of this research was to investigate naphthoquinone fused NHC Au(I) complexes for cancer research. First, it is necessary to look at the two factors related to cancer: reactive oxygen species (ROS) and the thioredoxin reductase system.
Reactive Oxygen Species (ROS)

Reactive Oxygen Species (ROS) are highly reactive radical species present in healthy and diseased cells. The generation of ROS is caused by numerous factors that can be broken into exogenous and endogenous influences. Three primary exogenous factors involve mitochondria, phagocytes, and peroxisomes. Through normal aerobic respiration, mitochondria consume oxygen and break it down in to water. Through this process, ROS is produced. Phagocytes come into play in the presence of chronic inflammations or infections. Phagocytic cells destroy the bacteria while simultaneously releasing nitric oxide, thus producing ROS. Lastly, peroxisomes are responsible for degrading fatty acids. A byproduct of this degradation is H$_2$O$_2$ which is normally degraded by catalase but can sometimes escape into other areas of the body.$^{24,25,26}$

Exogenous factors that produce ROS levels can be attributed to smoking, UV ray exposure, chemotherapeutic agents, pesticides, organic solvents, and radiation. This source of ROS can be fatal if levels of exposure surpass a generous amount.$^{27}$

Although ROS is present throughout the body, cancer cells have been found to contain and thrive amidst higher levels. In cancer cells, this ROS production can be increased from elevated metabolic activity, mitochondrial dysfunction, peroxisome activity, increased cellular receptor signaling, oncogene activity, increased activity of oxidases, cyclooxygenases, lipoxigenases and thymidine phosphorylase, or through crosstalk with infiltrating immune cells.$^{24}$

When ROS levels are elevated, apoptosis occurs. It has been discovered that tumor cells house a higher level of ROS which can accelerate the tumor development.$^{24}$ The idea is that increasing ROS production will cause cancer cells to be in a state of extreme
oxidative stress causing them to die but leaving the healthy cells unharmed. In order to do this, the thioredoxin system needs to be considered as well.

iii. Thioredoxin System

Thioredoxin reductase (TrxR) is an antioxidant flavoenzyme that maintains and regulates redox pathways within a cell. The system is comprised of TrxR, nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), and thioredoxin. Its main function is to reduce disulfide bonds in order to relieve the body of oxidative stress, or elevated reactive oxygen species (ROS) levels. Hence, Trx is a crucial antioxidant system that prevents cellular damage.  

Several Trx inhibiting drugs have been discovered, including the popular antirheumatic agent, auranofin. The exact mechanism of action is not completely known due to the complex structure of Trx and conflicting literature results, but a general idea has been conjured. Trx consists of two significant redox active sites: the FADH center and a selenocysteine (SEC)-cysteine (CYS) couple. FADH, like NADPH, is an antioxidant responsible for storing electrons during normal redox transformations such as metabolism. The SEC-CYS couple is considered a redox active site because of its disulfide bond composition. Recently, inhibiting these redox sites utilizing inorganic compounds has become of interest for anti-cancer applications.

iv. Previous Work

Previous work has proven that gold(I)-NHC complexes show therapeutic activity. Our previous work proved that generating reactive oxygen species (ROS) and inhibiting the Trx system simultaneously induced apoptosis. A combination of
ferrocenylated (Fc) imidazolium salts and ferrocenylated bis Au(I) complexes were tested.

Figure 1.3: Complexes studied in previous work.

A key feature of ferrocene is its one electron reversible redox nature (Fc$^{2+}\rightarrow$Fc$^{3+}$), making it possible to increase intercellular ROS levels. These complexes were tested against auranofin, and the biological studies proved an inhibition of Trx with the production of ROS.$^{13}$

v. This Work

As previously described, gold(I) NHC complexes inhibit the Trx system. Hence, combining this functional group with a redox cycling agent would also increase the level of ROS. The inhibition of the Trx system allows for a redefined threshold, and the redox cycling agent will apply exogenous ROS pushing the level above the threshold and causing cell death (Figure 1.4).
Modifying the N-substituents and fusing the NHC-gold(I) complex with naphthoquinone will further enhance this oxidative-stress pathway to kill the tumor cells due to the quinone’s ability to undergo multiple redox transformations. Three naphthoquinone fused NHC-gold(I) complexes were synthesized and confirmed structurally with $^1$H and $^{13}$C NMR, UV-Vis spectroscopy, IR spectroscopy, and X-ray crystallography. The redox properties of the complexes were confirmed with various electrochemical techniques to prove the complexes’ stability. In addition, several biological studies were conducted to analyze their efficacy in killing tumor cells.
Scheme 1.2: Synthesis of Au(I) NHC complexes.

All three complexes were synthesized utilizing 1,3-dimesitylnaphthoquinimidazolium chloride (4[H][Cl]) as the precursor. By altering the equivalents of (C₄H₈S)AuCl, two bis complexes (1 and 2) and one mono complex (3) were produced with high yields.
II. Experimental

$^1$H and $^{13}$C NMR spectra were recorded on Bruker 300 MHz spectrometer, and the spectra were referenced to the residual solvent as an internal standard ($^1$H NMR: CD$_2$Cl$_2$, 5.32 ppm and $^{13}$C NMR: CD$_2$Cl$_2$, 53.84 ppm). UV-vis spectra were obtained at ambient temperature with a Hewlett-Packard 8452A diode array spectrophotometer and molar absorptivities reported in M$^{-1}$ cm$^{-1}$. A Thermo Scientific Nicolet 6700 FT-IR was used to acquire the Infrared spectra (IR) utilizing KBr pellets. High-resolution mass spectra (HRMS) were obtained with a VG analytical ZAB2-E or a Karatos MS9 instrument (ESI or CI) and are reported as m/z (relative intensity). 1,3-dimesitylnaphthoquinimidazolium chloride, (1,3-dimesityl-4,5-naphthoquino-imidazol-2-ylidene)-silver(I) chloride, (C$_4$H$_2$S)AuCl were prepared according to the literature procedures.$^{32}$ Other reagents were purchased from commercial sources and used as received. CD$_2$Cl$_2$ (99.9%) was purchased from Acros Laboratories and dried over 3 Å molecular sieves prior to use. Solvents were either dried with a solvent purification system from the Inert Innovative Technology, Inc. (dichloromethane, diethyl ether, hexanes, tetrahydrofuran and toluene) or freshly distilled over 3 Å molecular sieves and degassed using three consecutive freeze-pump-thaw cycles prior to use. All reactions and manipulations were conducted under an atmosphere of nitrogen unless otherwise indicated. Electrochemical measurements were performed on a CHI620E electrochemical workstation using a silver wire quasi-reference electrode, a platinum disk working
electrode, and a Pt wire auxiliary electrode in a gas tight three-electrode cell under an atmosphere of nitrogen. Unless specified otherwise, the measurements were performed using 1.0 mM solutions of the analyte in dry DMSO with 0.1 M \([\text{N}(n\text{Bu})_4][\text{PF}_6]\) as the electrolyte and ferrocene (Fc) as the internal standard. Differential pulse voltammetry measurements were performed with 50 mV pulse amplitudes and 2 mV data intervals. All potentials listed herein were determined by cyclic voltammetry at 100 mV s\(^{-1}\) scan rates and referenced to a saturated calomel electrode (SCE) by shifting ferrocene\(^{0/+}\) to 0.435 V (DMSO). Elemental analyses were performed by Midwest Microlab, LLC in Indianapolis, IN.

**Compound [1]: [Bis(1,3-dimesityl-4,5-naphthoquino-imidazol-2-ylidene)-gold(I)] [Silver(I) dichloride].**

![Compound Structure](image)

(1,3-dimesitylnaphthoquinimidazol-2-ylidene)-silver chloride (117.4 mg, 0.203 mmol, 1.0 eq) and (C\(_4\)H\(_8\)S)AuCl (29.3 mg, 0.0914 mmol, 0.45 eq) were combined in a 20 mL scintillation vial with 4 mL THF under an inert atmosphere. After stirring at 60°C for 16 hours, the mixture was decanted, and the dark solid was washed with 3 \(\times\) 5 mL of Et\(_2\)O to reveal a yellow product. This was dissolved in minimal CH\(_2\)Cl\(_2\) and filtered through a plug of Celite into a pre-weighed 20 mL scintillation vial; the solvent was removed under reduced pressure. Yield: 82.1\%. \(^1\)H NMR (\(\delta\), CD\(_2\)Cl\(_2\), 300 MHz): 1.63 (s, 24H, Mes),
2.43 (s, 12H, Mes), 6.97 (s 8H, Mes), 7.71-7.77 (m, 4H, NQ), 7.95-8.00 (m, 4H, NQ). $^{13}$C NMR (δ, CD$_2$Cl$_2$, 300 MHz): 17.6, 21.6, 127.7, 129.9, 132.3, 132.5, 132.7, 134.4, 135.6, 141.0, 174.4, 192.6. HRMS (ESI) for [C$_{58}$H$_{52}$N$_4$O$_4$Au] $^+\text{M}$ Calcd. 1065.3654 Found 1065.3656. Anal. Calcd. for: C$_{58}$H$_{52}$N$_4$O$_4$AuAgCl$_2$: C, 55.96; H, 4.21; N, 4.50; Found: C, 56.48; H, 4.34; N, 4.56. IR (cm$^{-1}$): 1681 (KBr).

**Compound [2]: Bis(1,3-dimesityl-4,5-naphthoquino-imidazol-2-ylidene)-gold(I) Chloride.**

![Chemical Structure]

1,3-Dimesitylnaphthoquinimidazolium Chloride (85.2 mg, 0.1809 mmol, 1.0 eq) was added to NaHMDS (33.2 mg, 0.1809 mmol, 1.0 eq) in a 20 mL scintillation vial and stirred at 25°C for 16 h in 2 mL of toluene. The resulting mixture was filtered through a plug of Celite into a pre-weighed 20 mL scintillation vial containing (C$_4$H$_8$S)AuCl (26.1 mg, 0.081 mmol, 0.45 eq) and stirred at 25°C for thirty minutes. The dark precipitate was subjected to a series of washes (2 × 4 mL of toluene and then 3 × 4 mL of Et$_2$O) to yield a yellow solid (67.0 mg). Yield: 74.7%. $^1$H NMR (δ, CD$_2$Cl$_2$, 300 MHz): 1.74 (s, 24H, Mes), 2.55 (s, 12H, Mes), 7.08 (s 8H, Mes), 7.83-7.89 (m, 4H, NQ), 8.06-8.12 (m, 4H, NQ). $^{13}$C NMR (δ, CD$_2$Cl$_2$, 75 MHz): 17.6, 21.6, 127.7, 129.9, 132.2, 132.5, 132.7, 134.4, 135.6, 141.0, 174.4, 192.6. HRMS (ESI) for [C$_{58}$H$_{52}$N$_4$O$_4$Au] $^+\text{M}$ Calcd. 1065.3654 Found 1065.3656.
1065.3654 Found 1065.3665. Anal. Calcd. for: C₅₈H₅₂N₄O₄AuCl: C, 63.24; H, 4.76; N, 5.09; Found: C, 63.33; H, 4.73; N, 5.05. IR (cm⁻¹): 1681 (KBr).

**Compound [3]: (1,3-Dimesityl-4,5-naphthoquino-imidazol-2-ylidene)-gold(I) Chloride.**

![Compound Structure](image)

(1,3-Dimesitylnaphthoquinimidazol-2-ylidene)-silver Chloride (119.4 mg, 0.206 mmol, 1.0 eq) and (C₄H₈S)AuCl (66.1 mg, 0.206 mmol, 1 eq) were combined in a 20 mL scintillation vial with 4 mL THF under an inert atmosphere. After stirring at 40°C for 5 h, the opaque reaction mixture was stirred for an additional 12 h at 25°C. This was then filtered through a plug of Celite into a pre-weighed 20 mL scintillation vial, and the solvent was removed under reduced pressure. The resulting solid was washed successfully with 3 × 5 mL of Et₂O to reveal a yellow product. Yield: 67.8%. ¹H NMR (δ, CD₂Cl₂, 300 MHz): 2.15 (s, 12H, Mes), 2.49 (s, 6H, Mes), 7.20 (s 4H, Mes), 7.83-7.89 (m, 4H, NQ), 8.11-8.16 (m, 4H, NQ). ¹³C NMR (δ, CD₂Cl₂, 300 MHz): 18.2, 21.5, 127.5, 130.0, 132.3, 132.4, 133.4, 134.6, 135.3, 141.1, 174.6, 183.4. HRMS (ESI) for [C₂₀H₂₆N₂O₂AuCl] [M + Na]⁺ Calcd. 689.1246 Found 689.1230. Anal. Calcd. for: C₂₀H₂₆N₂O₂AuCl: C, 52.23; H, 3.93; N, 4.20; Found: C, 51.98; H, 3.85; N, 4.12. IR (cm⁻¹): 1679 (KBr).
III. Results and Discussion

i. Synthesis and Characterization for Compound [1]

The reactant equivalents from the synthesis of [2] and the environmental conditions from the synthesis of [3] were applied to produce Bis(1,3-dimesityl-4,5-naphthoquinone-imidazol-2-ylidene)-gold(I) Silver(I) dichloride [1]. The reactant equivalents to synthesize [1] were one equivalent of the (NHC)AgCl\textsuperscript{33,34} with 0.45 equivalents of (C\textsubscript{4}H\textsubscript{8}S)AuCl. The mixture was stirred at 60°C for 16 h, and the precipitate was collected and subjected to a series of washes with diethyl ether for an 82.1% yield. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR analyses in CD\textsubscript{2}Cl\textsubscript{2} proved consistent with the molecular structure.

\textsuperscript{1}H NMR (CD\textsubscript{2}Cl\textsubscript{2}) chemical shifts for [1] from mesityl-CH\textsubscript{3} were observed at 1.63 ppm (24H) and 2.43 (12H). The significant upfield shift of the mesityl (ortho-CH\textsubscript{3}) hydrogens are indicative of the bis moiety, as observed for other [bis(NHC)Au]\textsuperscript{+} complexes.\textsuperscript{35} The \textsuperscript{13}C NMR (CD\textsubscript{2}Cl\textsubscript{2}) signal corresponding to the \(\delta\) Au–C\textsubscript{carbene} for [1] was observed at 192.6 ppm. This value was shifted downfield compared to other reported (NHC)Au–Cl complexes indicative of the electron-withdrawing nature of the quinone annulated NHC via \(\pi\)-backbonding.\textsuperscript{13,31,33,35} (Figure 1.5 and Figure 1.6).
Figure 1.5: $^1$H NMR for compound [1].

Figure 1.6: $^{13}$C NMR for compound [1].
The Uv-Vis spectrum of [1] (Figure 1.14) shows an absorption at 345 nm, signifying the 1,4-naphthoquinone moiety comparable to literature.\textsuperscript{32,36} This red shift is indicative of the substituted quinone. The IR spectrum of compound [1] also clearly shows the presence of the carbonyls located on the quinone at 1681 cm\textsuperscript{-1} (Figure 1.16).\textsuperscript{32}

A crystal structure for compound [1] was acquired by slowly diffusing hexanes into a concentrated 1,2-dichloroethane solution. The Au-C\_carbene bond distance was observed at 2.012(5) Å which agrees to previously reported complexes.\textsuperscript{35,37}

\textbf{ii. Synthesis and Characterization for Compound [2]}

Bis(1,3-dimesityl-4,5-naphthoquino-imidazol-2-ylidene)-gold(I) Chloride [2] was produced by reacting free carbenes generated \textit{in situ} with 0.45 equivalents of (C\textsubscript{4}H\textsubscript{8}S)AuCl. The reaction was run under an inert atmosphere at 25°C for 16 h in order to generate the free carbene; 0.45 equivalents of (C\textsubscript{4}H\textsubscript{8}S)AuCl was then added. Due to the readily available NHC, the reaction was stirred for thirty more minutes, and the collected product was
subjected to a series of washes with toluene and diethyl ether. Complex [2] was tested in $^1$H NMR utilizing CD$_2$Cl$_2$ as the solvent, and spectral integrations proved consistent with the molecular structure.

$^1$H NMR (CD$_2$Cl$_2$) chemical shifts for [2] from mesityl-CH$_3$ were observed at 1.74 ppm (24H) and 2.54 (12H). The significant upfield shift of the mesityl (ortho-CH$_3$) hydrogens are indicative of the bis moiety, as observed for other [bis(NHC)Au]$^+$ complexes.$^{35}$ The $^{13}$C NMR (CD$_2$Cl$_2$) signal corresponding to the the $\delta$ Au–C$_\text{carbene}$ for [2] was observed at 192.6 ppm. Again, this shift in comparison to [3] is downfield due to the fused electron withdrawing quinone that supports $\pi$ backbonding.$^{13,31,33,35}$ (Figure 1.19 and Figure 1.20)

Similar to compound [1], the UV-Vis spectrum (Figure 1.14) indicated a substituted quinone absorption at 345 nm and an IR spectrum (Figure 1.17) absorption at 1681 cm$^{-1}$. These values are similar to literature sources.$^{32}$

A crystal structure for compound [2] was acquired by slowly diffusing benzene into a concentrated 1,2-dichloroethane solution (Figure 1.9). The Au-C$_\text{carbene}$ bond distance was observed at 2.018(5) Å which agrees to previously reported complexes.$^{37}$
iii. Synthesis and Characterization for Compound [3]

(1,3-Dimesityl-4,5-naphthoquinol-imidazol-2-ylidene)-gold(I) Chloride [3] was successfully synthesized by independently treating one equivalent of the (NHC)AgCl with one equivalent of (C₄H₈S)AuCl. Although not originally desired, this complex was generated due to its simplistic nature in comparison to the bis moieties. Varying the temperature and duration of time at which the reaction occurred was determined from several ¹H NMR analyses in CDCl₃; to maximize efficiency and production, the reaction was stirred for 5 h at 40°C and 12 h at 25°C. The complex was subjected to a series of washes with diethyl ether and allowed to dry in vacuo to result in a 67.8% yield.

¹H NMR (CD₂Cl₂) chemical shifts from mesityl-CH₃ of [3] were observed at 2.15 ppm (12H) and 2.49 ppm (6H). These peaks are significantly closer in distance compared to the bis moieties. The diagnostic ¹³C NMR (CD₂Cl₂) signal corresponding to the δ Au–C carbene for [3] was observed at 183.4 ppm.
The UV-Vis spectrum of [3] (Figure 1.14) shows an absorption at 345 nm, signifying the quinone moiety. Literature sources report similar absorptions. This red shift is indicative of the substituted quinone. The IR spectrum of compound [1] also clearly shows the presence of the carbonyls located on the quinone at 1681 cm$^{-1}$.

A crystal structure for compound [3] was acquired by slowly diffusing hexanes into a concentrated 1,2-dichloroethane solution (Figure 1.9). The Au-C$_{\text{carbene}}$ bond distance was observed at 2.009(4) Å which agrees to previously reported complexes.$^{37}$

![Crystal structure of compound [3]](image)

**Figure 1.9: Crystal structure of compound [3].**

**iv. Electrochemical Analyses**

A series of electrochemical tests, including cyclic voltammetry (CV) and differentiated pulse voltammetry (DPV), were carried out with tetrabutylammonium hexafluorophosphate in 5 mL of anhydrous dimethyl sulphoxide (DMSO) in order to
evaluate electronic properties within the three complexes as well as the starting material, 1,3-dimesitylnaphthoquinimidazolium chloride (4[H][Cl]). [N(nBu)4]+ [PF6]- was utilized as the electrolyte at 0.1M while the analyte concentration was held at 0.001M. These tests were performed using a CHI620E potentiostat and a three-electrode system under an inert atmosphere with a scan rate of 0.1 mV s\(^{-1}\). The platinum working electrode was polished between each use with a 15µM diamond paste, and the silver wire reference electrode and platinum wire counter electrode were routinely washed with acetone. All electrochemical data were calibrated using ferrocene as an internal standard with respect to SCE.

Figure 1.10 illustrates the two step, one electron sequential oxidation of the quinone. The first oxidation (a) to the semiquinone appeared as a reversible peak, while the second (b) appeared as a quasi-reversible transformation.\(^{38}\)

![Diagram of redox behavior of NHC annulated quinone](image)

Figure 1.10: Redox behavior of NHC annulated quinone.

The cyclic voltammogram (CV) can be seen in Figure 1.11. All three compounds showed similar voltammograms representing the two step, one electron oxidation of the quinone.
As seen in Table 1.1, compound 4[H][Cl] displayed a much lower potential at -0.38 V corresponding with the positively charge imidazolium ring. The bis and mono complexes had similar potentials.  

Table 1.1: Redox potentials of compounds 1-3 along with 4[H][Cl].

<table>
<thead>
<tr>
<th>Compound</th>
<th>CV $E_{1/2}^a$ (V)</th>
<th>CV $E_{1/2}^b$ (V)</th>
<th>DPV $E_{1/2}^a$ (V)</th>
<th>DPV $E_{1/2}^b$ (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>-0.45</td>
<td>-1.31</td>
<td>-0.42</td>
<td>-1.31</td>
</tr>
<tr>
<td>[2]</td>
<td>-0.46</td>
<td>-1.31</td>
<td>-0.46</td>
<td>-1.31</td>
</tr>
<tr>
<td>[3]</td>
<td>-0.46</td>
<td>-1.29</td>
<td>-0.47</td>
<td>-1.31</td>
</tr>
<tr>
<td>4[H][Cl]</td>
<td>-0.38</td>
<td>-1.15</td>
<td>-0.38</td>
<td>-1.15</td>
</tr>
</tbody>
</table>

To test the stability of the complexes when undergoing a redox transformation, UV-Vis spectroelectrochemical studies were performed on complex [2]. A special quartz electrochemical cell suitable for the UV-Vis instrument was utilized. Inside this cell was
0.0001M of [2] and 0.1M [N(nBu)₄]⁺[PF₆]⁻ in 3 mL of DMSO. The bulk reduction was held at -1.5 V (vs. AgCl) while the oxidation was held at -0.1V (vs. AgCl). These values were obtained from the data given in Table 1.1.

Upon bulk reduction, the quinone moiety was probed to undergo both reductions to form the quinone dianion (NQ→NQ²⁻). The arrows indicate the direction of the spectral change over time.

![Figure 1.12: Bulk reduction of [2] held at -1.5 V (vs. AgCl) in DMSO at 25°C.](image)
The bulk oxidation (NQ²⁻→NQ) successfully reformed the neutral complex based on spectral traces, indicating the stability of the complex during redox transformations.
The original UV-Vis spectrum can be seen in Figure 1.14. Upon reduction, the pale yellow solution changed red which has been observed with other quinone species. There was an increase in absorbance at 460 nm when the species was reducing to form the quinone dianion ($NQ \rightarrow NQ^{2-}$). This gain in absorbance was immediately lost when oxidized, causing the spectra to return to its original state ($NQ^{2-} \rightarrow NQ$).\textsuperscript{32,39}
v. Biological Studies

To examine the efficacy of complexes 1-3, several biological studies were carried out including cell proliferation assays in A549 lung cancer cells.\textsuperscript{41} Doxorubicin, an FDA-approved drug, Auranofin, and a bis(1-benzyl-3-mesityl-imidazol-2-ylidene)-gold(I) chloride) complex (5) were used as control complexes. Doxorubicin is a conjugated multi-ring quinone-based complex capable of either DNA intercalation or ROS accentuation (depending on locus of action), while auranofin contains an Au(I)-phosphine coordination motif known to inhibit TrxR activity.\textsuperscript{41} Complex 5 contains no redox cycling component, but has been previously reported to inhibit TrxR (Figure 1.15).
Figure 1.15: Control complexes for cell proliferation assays. a) Doxorubicin b) Auranofin c) bis(1-benzyl-3-mesityl-imidazol-2-ylidene)-gold(I) chloride) complex (5)

A cocktail of 4[H][Cl] and 5 (2:1 molar ratio, respectively) was also tested to compare the benefits of a dual targeting drug opposed to a mixture of the crucial components. The dosing entailed for this cocktail reflected the relative component stoichiometry in complex [1].

Table 1.2: Cell proliferation data in A549 lung cancer cells.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC_{50} (μM)</th>
<th>Std Error (+/-)</th>
<th>Fold Difference Relative to [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>0.103</td>
<td>0.023</td>
<td>1.41</td>
</tr>
<tr>
<td>Auranofin</td>
<td>1.67</td>
<td>0.05</td>
<td>22.9</td>
</tr>
<tr>
<td>1</td>
<td>0.073</td>
<td>0.016</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.075</td>
<td>0.013</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>12.06</td>
<td>0.18</td>
<td>165</td>
</tr>
<tr>
<td>4[H][Cl]</td>
<td>0.994</td>
<td>0.12</td>
<td>13.6</td>
</tr>
<tr>
<td>5</td>
<td>0.71</td>
<td>0.06</td>
<td>9.72</td>
</tr>
<tr>
<td>4[H][Cl] + 5</td>
<td>0.197</td>
<td>0.057</td>
<td>2.70</td>
</tr>
</tbody>
</table>
From the data seen in Table 1.2, complex [1] and [2] showed inhibition values better than that of the commercial drug, Doxorubicin.\textsuperscript{13,42} At 0.072µM ± 0.016µM, complex [1] showed to be most effective when inhibiting tumor growth. Complex [3] proved to be inactive, showing concentrations more than 150 times less potent than complex [1]. The cocktail of 4[H][Cl] and 5 had an IC\textsubscript{50} value of 0.197µM ± 0.057µM. Although this value is comparable to Doxorubicin, complex [1] still demonstrated a higher potency.
IV. Conclusion

Three naphthoquinone fused NHC-gold(I) complexes were synthesized and confirmed structurally with $^1$H and $^{13}$C NMR, UV-Vis spectroscopy, IR spectroscopy, and X-ray crystallography. All three can be produced with high yields and without using any strenuous purification techniques (i.e., column chromatography, distillation, etc.).

The electrochemical analyses for all three complexes proved their stability when the naphthoquinone moiety was undergoing electron transformations. This was crucial information to obtain to confirm its ability to emphasize reactive oxygen species (ROS) production inside the cell.

When comparing the IC$_{50}$ data with those of commercially available drugs (Doxorubicin and Auronafin), it was evident that complex [1] and [2] had a higher potency against A549 lung cancer cells. Complex [3] proved essentially inactive.
Figure 1.16: IR (KBr) for compound [1].

Figure 1.17: IR (KBr) for compound [2].
Figure 1.18: IR (KBr) for compound [3].

Figure 1.19: $^1$H NMR of compound [2].
Figure 1.20: $^{13}$C NMR of compound [2].

Figure 1.21: $^1$H NMR of compound [3].
Figure 1.22: $^{13}$C NMR of compound [3].

Figure 1.23: DPV of compound [1] with 0.1M [N(nBu)$_4$][PF$_6$] in DMSO (1mM) as referenced to SCE at a scan rate of 0.1 mV s$^{-1}$. (internal standard ferrocene, adjusted to 0.435 V vs. SCE).
Figure 1.24: CV of compound [2] with 0.1M [N(nBu)4][PF6] in DMSO (1mM) as referenced to SCE at a scan rate of 0.1 mV s⁻¹. (internal standard ferrocene, adjusted to 0.435 V vs. SCE).

Figure 1.25: DPV of compound [2] with 0.1M [N(nBu)4][PF6] in DMSO (1mM) as referenced to SCE at a scan rate of 0.1 mV s⁻¹. (internal standard ferrocene, adjusted to 0.435 V vs. SCE).
Figure 1.26: CV of compound [3] with 0.1M [N(nBu)4][PF6] in DMSO (1mM) as referenced to SCE at a scan rate of 0.1 mV s⁻¹. (internal standard ferrocene, adjusted to 0.435 V vs. SCE).

Figure 1.27: DPV of compound [3] with 0.1M [N(nBu)4][PF6] in DMSO (1mM) as referenced to SCE at a scan rate of 0.1 mV s⁻¹. (internal standard ferrocene, adjusted to 0.435 V vs. SCE).
CHAPTER TWO: DEVELOPMENT OF A REDOX-ACTIVE LIGAND FOR
POTENTIAL CATALYTIC APPLICATIONS

I. Introduction

i. Historical Background of Redox Active Ligands

In 1913, Alfred Werner received the Nobel Prize for his work on the linkage of atoms in transition metal complexes. His insight earned him the title, “Founder of Coordination Chemistry.” His examples gave the inorganic community answers regarding “innocent” ligands. In other words, these complexes contained ligands that allowed a definitive oxidation state on the metal center. In 1966, nearly fifty years later, C.K. Jorgenson stated, “ligands are innocent when they allow oxidation states of the central atoms to be defined. The simplest case of a suspect ligand is NO.”

When looking at the molecular orbital diagram for nitric oxide, there are 11 valence electrons, leaving an unpaired electron in the $\pi^*$ orbital.
When considering NO as a ligand, it can exist as NO$^+$ or NO$. In the cationic state, nitric oxide acts as a three-electron donor when in contact with a metal. One electron from the NO center is donated to the metal resulting in a cationic species. This lone pair on the nitrogen can then coordinate with the metal creating a linear species.$^{46,47}$

$$\begin{align*}
\text{O}=\text{N}^+ & \quad + \text{M}^- \\
\text{O} & \quad \text{N}^+ \quad \text{M}^-
\end{align*}$$

In the anionic example, nitric oxide acts as a one electron donor. One electron from the metal center is donated to the NO center, producing the nitric oxide anion. A lone pair on the nitrogen is then donated back to the metal to create the coordination. Overall, this is considered a one electron donation and created a bent species.$^{46}$
This introduction of a “suspect ligand” or “non-innocent ligand” became attractive for inorganic chemists due to their multifunctional characteristics. Within this new category of ligands are the redox active ligands for catalytic applications. These types of ligands can either function as spectators or actors. Herein, an example of each are explored to gain a better understanding of the term “redox active.” These examples include situations in which the ligand acted as an electron reservoir, assisted in making a bond, induced a radical type reactivity, and increased the Lewis acidity of the metal.\textsuperscript{48}

b. Making a Bond

A notorious example of an active redox active ligand is the enzyme, galactose oxidase (Figure 2.2). This copper(II) tyrosyl is responsible for the oxidation of an alcohol into an aldehyde while simultaneously reducing O\textsubscript{2} into H\textsubscript{2}O\textsubscript{2} (Scheme 2.3).\textsuperscript{49} This transformation from D-galactose into D-galacto-hexodialdose occurs in several types of fungi.

Scheme 2.2: Metal to nitric oxide coordination to form a bent bond.

\[
\left[ \dot{\text{O}}=\text{N}:: \right]^+ + M^+ \rightarrow +M=\dot{\text{N}}\text{O}.
\]
Scheme 2.3: Oxidation of galactose into galacto-hexodialdose.

The catalyst begins as an “inactive” form, and it is oxidized into a one-electron oxidized tyrosyl radical that is stabilized by a nearby tryptophan. This redox-active ligand plays a prominent role in the bond-activation processes leading to oxidation of the alcohol substrate.\textsuperscript{49}

c. Induced Radical Type Reactivity

A second example of an “actor” redox ligand is when radical type reactivity is induced.\textsuperscript{50} The concept is similar to the making a bond example; a common example is the usage of a cobalt porphyrin catalyst (Figure 2.3).\textsuperscript{51}

Figure 2.3: Cobalt porphyrin catalyst.

These cobalt (II) porphyrin catalysts are easily tunable and stabilized due to the macrocyclic effect. Dimerizations are commonly reported, but utilizing this catalyst avoids that issue. As seen in Scheme 2.4, the catalyst reacts with a diazo compound,
eliminating N₂. This forms a ligand centered radical that can react further with various alkenes to form the cyclic product.⁵¹

![Scheme 2.4: Cobalt catalyzed cyclopropanation of an alkene.](image)

**a. Electron Reservoir**

One of the most common examples of a spectator redox ligand is when it acts as an electron reservoir for catalytic transformations.⁴⁸,⁵²,⁵³ Several expensive metals, such as platinum and rhodium, are involved in catalytic reactions that involve multiple electron transfers. In order to allow less expensive metals to do this, such as iron⁵² or ruthenium⁵⁴, a redox ligand can be used. The ligand acts as an electron acceptor so the metal can participate successfully in the reaction. The following example is from Chirik and coworkers. An iron catalyzed (2π⁺2π) cycloaddition was performed with pyridine as the redox active ligand.⁵²
As outlined in Scheme 2.5, the catalyst being used is a bis(imino)-pyridine iron bis(dinitrogen) complex. While thermally forbidden and photochemically allowed, the addition of the metal catalyst circumvents constraints from orbital symmetry.

The first step is a two-electron oxidative addition in which the iron coordinates to the double bonds of the reactant. The electrons stem from the 2,6-diiminepyridine ligand. This allows the iron to stay in its Fe$^{II}$ oxidation state instead of adopting the less stable Fe$^{IV}$. The second step is a two-electron reduction that allows the iron to stay as Fe$^{II}$ instead of adopting the high energy, thus unstable, Fe$^{0}$. High yields (~90%) were seen when “E” was a larger alkyl chain.\cite{52}

d. Increased Lewis Acidity

The last example, and most comparable to this research, is when the redox active ligand is responsible for increasing or decreasing the Lewis acidity of the metal center. This can be seen in many examples of redox active catalysis.\cite{55,56,57} Previous work with a
ferrocenylated Grubbs-Hoveyda catalyst proved that it was possible to alter the metal’s catalytic reactivity by “switching” the oxidation state of the ferrocene.\textsuperscript{58}

\begin{center}
\textbf{Scheme 2.6}: Redox “switching” of the ferrocenylated Hoveyda-Grubbs catalyst.\textsuperscript{58}
\end{center}

The catalyst was subjected to the ring closing metathesis of diethyl diallylmalonate to its respective cyclic product. This was done in deuterated dichloromethane, and the percent conversion was monitored with \textsuperscript{1}H NMR.

\begin{center}
\textbf{Scheme 2.7}: Ring opening metathesis of diethyl diallylmalonate.\textsuperscript{58}
\end{center}

In its neutral state (Fe\textsuperscript{II}), the complex was able to successfully catalyze the ring opening metathesis. After 16 minutes, ferrocenium tetrafluoroborate was added to oxidize the complex (Fe\textsuperscript{II}→Fe\textsuperscript{III}). Once oxidized, the complex’s catalytic reactivity decreased significantly. It is hypothesized that the electron deficiency of Fe\textsuperscript{III} caused a pull of electrons from the metal center through inductive effects. This in turn, decreased the efficiency of the metal as a catalyst.\textsuperscript{58}
The ring closing metathesis was performed a second time, in which the catalyst was “switched” twice leading to the same result. When in the oxidized form, the catalyst was less effective than in the neutral state.

**iii. Current Work**

Previous work with a redox active ligand coupled with an NHC metal catalyst proved effective in changing the catalyst’s reactivity. Current work is focused on developing a catalyst with a redox ligand capable of changing its selectivity. This idea, outlined in Scheme 2.8, aims to produce a redox active complex capable of accessing multiple catalytic species based upon the oxidation state.
When in its neutral state, the catalyst coupled with a redox active group (RAG) will be able to catalyze reactant A into product B. Upon oxidation of this RAG, the complex will either no longer be able to catalyze A into B, or it will do so at a much slower rate ($k_1 \neq k_2$). Instead, the oxidized catalyst will be capable of converting reactant C into product D. In order to achieve this type of catalyst, two groups need to be considered: the catalyst and the redox active ligand. The focus of this work is on synthesizing the redox active ligand.

a. N-Heterocyclic Carbene Metal Catalyst

As stated earlier, N Heterocyclic carbenes are stable and tunable ligands that coordinate strongly to metals. They have been used as the backbone for catalysts for years; prevalent examples including the second-generation Grubbs’ catalyst and Grubbs-Hoveyda catalyst. $^{59,60,61}$ Common metals for these NHC catalyst include palladium, ruthenium, nickel, iridium, rhodium, copper, and platinum. $^{62}$ Each metal is capable of catalyzing specific reactions. Iridium has proven to be less reactive than other metals, which will make the analyses of the catalyst easier for future work.
b. Redox Active Ligand: Tetrathiafulvalene

Tetrathiafulvalene (TTF) was first discovered as a salt in 1972 by Wudl and coworkers. Material applications for these stable molecules include superconductors, photovoltaics, optics, and electronics. They are also commonly utilized for supramolecular chemistry.

The attractive feature of TTF is its ability to undergo multiple reversible one electron transformations (Scheme 2.9).

Scheme 2.9: The redox behavior of TTF.
These redox potentials occur at lower oxidation potentials, proving the compound’s ease of gaining and losing an electron.\textsuperscript{72} In its neutral state, TTF exists as a 14π electron nonaromatic system. After each one electron oxidation, it gains aromaticity due to Hückel’s rule, making it more stable.\textsuperscript{16} TTF is also capable of stacking leading to self-assemblies through π-π and S-S interactions.\textsuperscript{72} In addition to its complex and stable redox behavior, TTF is easily tunable, making a great base for a redox ligand.

Herein, the development of a tetrathiafulvalene ligand is described (Compound [1], Scheme 2.10). Two amine groups are present on the ring fused to the TTF in order to form the metal NHC catalyst in the future. It is possible to arylate/alkylate the nitrogen atoms by utilizing a Buchwald-Hartwig reaction.\textsuperscript{73} In this instance, several different types of substituents can be added. A cyclization of the free amines by utilizing triethylorthoformate in acidic conditions can then be performed to form the imidazolium salt.\textsuperscript{73,74} From this, a simple deprotonation reaction can be done, and a metal can be added to coordinate to the carbene carbon.
Scheme 2.10: Proposed scheme to synthesize a redox active catalyst. (R= aryl group)

Structurally, [1] was confirmed via $^1$H and $^{13}$C NMR. The electronic properties were analyzed by electrochemical methods.
II. Experimental

$^1$H and $^{13}$C NMR spectra were recorded on Bruker 300 MHz spectrometer, and the spectra were referenced to the residual solvent as an internal standard ($^1$H NMR: $\text{C}_2\text{D}_6\text{OS}$, 2.50 ppm and $^{13}$C NMR: CD$_2$Cl$_2$, 39.52 ppm). UV-vis spectra were obtained at ambient temperature with a Hewlett-Packard 8452A diode array spectrophotometer and molar absorptivities reported in M$^{-1}$ cm$^{-1}$. A Thermo Scientific Nicolet 6700 FT-IR was used to acquire the Infrared spectra (IR) utilizing NaCl salt plates. An Agilent 6120B Liquid Chromatograph - Quadrupole Mass Spectrometer was used to acquire the mass data. 1,2-diaminobenzene-4,5-bis(thiocyanate), 5,6-diaminobenzene-1,3-dithiole-2-thione, and 4,5-Dimethyl-1,3-dithiol-2-one were synthesized according to literature procedures. Other reagents were purchased from commercial sources and used as received. Solvents were either dried with a solvent purification system from the Inert Innovative Technology, Inc. (dichloromethane, diethyl ether, hexanes, tetrahydrofuran and toluene) or freshly distilled over 3 Å molecular sieves and degassed using three consecutive freeze-pump-thaw cycles prior to use. All reactions and manipulations were conducted under an atmosphere of nitrogen unless otherwise indicated.
Compound [1]: 4,5-Dimethyltetraethylvalene-1,3-(5,6-diaminobenzene)

A 200mL Schlenk flask equipped with a condenser and stir bar was charged with 5,6-diaminobenzene-1,3-dithiole-2-thione (1.83g, 0.0085 mol, 1 eq) and 4,5-dimethyl-1,3-dithiol-2-one (2.48g, 0.017 mol, 2 eq). Freshly degassed triethyl phosphite (60 mL) and anhydrous toluene (60mL) was then added under nitrogen. The mixture was allowed to reflux at 120°C for 8 hours. The solvent was evaporated off under reduced pressure to reveal a dark red oil. The oil was washed with 3 × 25mL hexanes to reveal a orange/red solid. The crude product was purified via column chromatography (silica gel, hexane/EtOAc, 40%/60%) and subsequently washed with 3 × 25mL Et₂O to yield a pale yellow solid (147.2mg, 5.5%). ^1H NMR (δ, C₂D₆OS, 300 MHz): 1.94 (s, 6H), 4.68 (s, 4H), 6.53 (s, 2H). ^13C NMR (δ, C₂D₆OS, 300 MHz): 13.39, 107.47, 108.59, 117.41, 121.59, 122.58, 134.69. LC-MS (MeCN) for [C₁₂H₁₂S₄N₂] Calcd. 311.98 Found. 312.00; IR (cm⁻¹): 3492.92, 2998.93, 2913.30, 1663.96, 1436.77, 1310.95 (NaCl).
III. Results and Discussion

i. Synthesis and Characterization of [1]

5,6-diaminobenzene-1,3-dithiole-2-thione, and 4,5-dimethyl-1,3-dithiol-2-one were synthesized utilizing literature procedures.\textsuperscript{75,76,77} Compound [1] was synthesized by a triethyl phosphite mediated coupling reaction of these two reactants. One equivalent of thione was combined with two equivalents of the dithiol ketone in 60 mL of triethyl phosphite and 60 mL of toluene. The extremely air and moisture sensitive reaction was monitored via TLC to ensure complete conversion. The coupling of the ketone and dithiol thione resulted in several by-products including homo and hetero coupled products that needed to be purified via column chromatography.

\textsuperscript{1}H NMR and \textsuperscript{13}C NMR chemical shifts proved consistent with similar literature compounds.\textsuperscript{76} A chemical shift at 6.53 ppm was indicative of the para positioned protons on the ring. The amine protons can be seen at 4.68 ppm and the aliphatic protons can be seen at 1.94 ppm. There is a significant downfield shift from the starting material for the aromatic and amine protons; this is indicative of the electronegative sulfur atoms.
The $^{13}$C NMR also indicated a successful product. The absence of peaks in the quaternary region proves the absence of the dithiol ketone and thione. Six peaks in the aromatic region and one peak in the aliphatic region are characteristic of compound [1].
The IR spectra of compound [1] can be seen in Figure 2.8. Peaks at 3492.92 cm\(^{-1}\) and 1663.96 cm\(^{-1}\) are indicative of the amine groups and C=C, respectively. These are similar to literature values.\(^7^6\)
Figure 2.8: IR spectra (NaCl) for compound [1].

To observe the absorption properties, a UV-Vis spectra was taken in DMSO. The spectra shows a distinct absorption at 320 nm, characteristic of the $\pi \rightarrow \pi^*$ transitions from the compound’s high conjugation (Figure 2.9).
Figure 2.9: UV-Vis spectra for compound [I] (DMSO).

ii. Electrochemical Analyses

A series of electrochemical tests, including cyclic voltammetry (CV) and differentiated pulse voltammetry (DPV), were carried out with tetrabutylammonium hexafluorophosphate in 5 mL of anhydrous acetonitrile in order to evaluate electronic properties of the tetrathiafulvalene compound. \([\text{N}(\text{nBu})_4]^+ \text{[PF}_6^-\text{]}\) was utilized as the electrolyte at 0.1M while the analyte concentration was held at 0.001M. These tests were performed using a CHI620E potentiostat and a three-electrode system under an inert atmosphere with a scan rate of 0.1 mV s\(^{-1}\). The platinum working electrode was polished between each use with a 15\(\mu\)M diamond paste, and the silver wire reference electrode and platinum wire counter electrode were routinely washed with acetone. All electrochemical data were calibrated using decamethylferrocene as an internal standard with respect to SCE.
Compound [1] displayed two reversible one electron oxidations. The first oxidation (TTF → TTF$^{+}$) occurred at 0.14 V (vs. SCE) while the second oxidation (TTF$^{+}$ → TTF$^{2+}$) occurred at 0.43 V (vs. SCE). These values were confirmed with CV and DPV in Figure 2.11 and Figure 2.12, respectively. Both oxidations proved reversible at various scan rates (0.05, 0.1, 0.25, 0.5, and 0.75 mV s$^{-1}$).

In comparison to an unsubstituted tetrathiafulvalene (Figure 2.10), these oxidation values are shifted significantly lower most likely due to the annulated diaminobenzene. Compounds of similar structure showed comparable oxidation values.$^{79}$
Figure 2.11: CV of compound [1] with 0.1 M \([N(nBu)]\)[PF$_6$] in DMSO (1 mM) as referenced to SCE at a scan rate of 0.1 mV s$^{-1}$. (internal standard decamethylferrocene, adjusted to -0.125 V vs. SCE).

Figure 2.12: DPV of compound [1] with 0.1 M \([N(nBu)]\)[PF$_6$] in DMSO (1 mM) as referenced to SCE at a scan rate of 0.1 mV s$^{-1}$. (internal standard decamethylferrocene, adjusted to -0.125 V vs. SCE).
IV. Conclusion

A redox active ligand was synthesized and confirmed structurally with $^1$H and $^{13}$C NMR, UV-Vis spectroscopy, and IR spectroscopy. Compound [1] was successfully made by a triethyl phosphite mediated coupling of 5,6-diaminobenzene-1,3-dithiole-2-thione, and 4,5-Dimethyl-1,3-dithiol-2-one. Although the yield was low, the workup and purification of this compound was achieved by simple column chromatography.

A theoretical synthetic route has also been outlined utilizing compound [1] as the starting material. It is possible to arylate/alkylate the nitrogen atoms by utilizing a Buchwald-Hartwig reaction. In this instance, it is possible to add several different types of substituents. A cyclization of the free amines by utilizing triethylorthofomate in acidic conditions can then be performed to form the imidazolium salt. From this, a simple deprotonation reaction can be done, and a metal can be added to coordinate to the carbene carbon. An attractive characteristic of this method is the ability to tune the substituents on the tetrathiafulvalene; this could lead to higher yields than the dimethyl system.

The electrochemical analyses of compound [1] proved its redox stability, confirming its success as a non-innocent ligand. The compound underwent two redox transformations to form the cation (TTF$^{+}$) and dication (TTF$^{2+}$). Once fused with a metal NHC, it is possible to access multiple catalytic species based upon the oxidation state of the TTF ligand.
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