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THE SYNTHESIS, CHARACTERIZATION, AND ELECTROCHEMICAL STUDY OF TRIS(PYRAZOLYL)-TYPE IRON(II) COMPLEXES, IRON(II) SULFUR- AND SELENIUM-CONTAINING COMPLEXES, AND TRIS(PYRAZOLYL)-TYPE RUTHENIUM(II) COMPLEXES

A Thesis
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In Partial Fulfillment
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Master of Science
Chemistry

by
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Accepted by:
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ABSTRACT

Highly reactive radical species such as hydroxyl radical cause oxidative stress, resulting in chronic or degenerative diseases. In the biological Fenton reaction, iron(II) generates hydroxyl radical, \( \cdot \text{OH} \), but only within a specific electrochemical potential window (-324 mV to 640 mV). Selenium and sulfur compounds have been extensively studied for their antioxidant properties, and they may exert their effects by binding iron(II) and shifting its electrochemical potential out of this window. This work has investigated the synthesis and electrochemical characterization of iron(II) chalcogenate complexes and iron(II) chalcogenone complexes. Cyclic voltammetry (CV) of \([\text{Fe}(\text{EPh})_4][(\text{PPh}_4)_2] \) (E = S, Se) complexes shows \( \text{Fe}^{2+/3+} \) redox potentials of -723 mV (E = S) and -1010 mV (E = Se) vs. NHE. These electrochemical results suggest that selenium coordination stabilizes iron(II) relative to sulfur coordination and may inhibit iron redox cycling.

Because of synthetic difficulties with iron(II) complexes, ruthenium(II) was substituted for iron(II) due to its inert reaction kinetics and diamagnetism, allowing the use of NMR spectroscopy for characterization. Tris(pyrazolyl)methane ruthenium(II) complexes of the formula \([\text{TpR}^\text{R} \text{Ru} (\text{NCCH}_3)_3]^{2+} \) (R = Me, Ph) and the previously-reported tris(pyrazolyl)borate ruthenium(II) complexes \([\text{Tp}^\text{R} \text{Ru} (\text{NCCH}_3)_3]^+ \) (R = H, Me, Ph) have been synthesized using a new synthetic pathway that reduces the number of required steps on average by 80% and average reaction times by over 95%. Tris(pyrazolyl) (Tp) ligands are used to mimic adenine and guanine coordination to ruthenium(II), known sites of metal localization. CV studies of \([\text{TpRu} (\text{NCCH}_3)_3][\text{BF}_4] \)
(Tp = tris(pyrazolyl)borate) and [Tp*Ru(NCCH\textsubscript{3})\textsubscript{3}][OTf] (Tp* = tris(3,5-dimethylpyrazolyl)borate) determined Ru\textsuperscript{2+/3+} redox potentials of 489 mV and 498 mV, respectively, vs. NHE compared to the Ru\textsuperscript{2+/3+} redox potential for [Ru(NCCH\textsubscript{3})\textsubscript{6}][\textsubscript{2}(BF\textsubscript{4})\textsubscript{2}] of 517 mV. Thus, coordination of Tp-type ligands substantially affects the redox chemistry of ruthenium as well as iron.
DEDICATION

I dedicate this thesis to my father, Mike, who got me interested in anything scientific. I will miss you.

I also dedicate this to my loving wife, Sonia. I love you with all of my heart.
ACKNOWLEDGMENTS

I would first like to thank Dr. Julia L. Brumaghim for allowing me the opportunity to learn about coordination chemistry and its applications in bioinorganic chemistry. The skills she taught me and the guidance she gave me are invaluable and will be an asset to me in my professional career. For this, I am truly grateful.

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I also thank my committee members, Dr. William Pennington and Dr. Rhett Smith, for their guidance in both the preparation of this thesis and in my graduate work, and I also want to thank the staff of the chemistry department for their continued support. Lastly (but certainly not least), I want to thank my family and friends who have been there when I needed them and lifted me up when I was down.
TABLE OF CONTENTS

Page

TITLE PAGE ........................................................................................................................................ i
ABSTRACT......................................................................................................................................... ii
DEDICATION ....................................................................................................................................... iv
ACKNOWLEDGMENTS ..................................................................................................................... v
LIST OF TABLES ............................................................................................................................. viii
LIST OF FIGURES ........................................................................................................................... ix
LIST OF SCHEMES.......................................................................................................................... xii

CHAPTER

I. A BRIEF REVIEW OF THE USES OF IRON AND RUTHENIUM COMPLEXES WITH TRIS(PYRAZOLYL) LIGANDS AND THEIR BIOLOGICAL RELEVANCE .................................................. 1

   Introduction ................................................................................................................................. 1
   Tp-Type Iron Chemistry and Its Applications ................................................................. 5
   Tp-Type Ruthenium Chemistry and Its Applications .................................................. 8
   Biological Applications of Ruthenium ................................................................. 14
   References .......................................................................................................................... 18

II. SYNTHESIS AND CHARACTERIZATION OF IRON(II) COMPLEXES CONTAINING TRIS(PYRAZOLYL) LIGANDS AS WELL AS SULFUR- OR SELENIUM-CONTAINING LIGANDS AND THEIR BIOLOGICAL RELEVANCE ................................................................. 24

   Introduction ............................................................................................................................. 24
   Results and Discussion ........................................................................................................ 31
   Experimental Methods ....................................................................................................... 41
   References .......................................................................................................................... 44
III. SYNTHESIS AND CHARACTERIZATION OF RUTHERNIUM(II) COMPLEXES CONTAINING TRIS(PYRAZOLYL) BORATE AND – METHANE LIGANDS

Introduction ............................................................................................ 48
Results and Discussion .......................................................................... 53
Experimental Methods .......................................................................... 66
References .............................................................................................. 73

APPENDICES

A: Copyright permission for Figure 1.2 A................................................. 76

B: Copyright permission for Figure 1.2 B................................................. 83
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Fe$^{2+/3+}$ potentials for target complexes ($E$ vs. NHE)</td>
</tr>
<tr>
<td>3.1</td>
<td>List of synthetic parameters for selected ruthenium(II) acetonitrile complexes</td>
</tr>
<tr>
<td>3.2</td>
<td>Selected bond lengths [Å] and angles [°] for [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$]</td>
</tr>
<tr>
<td>3.3</td>
<td>Ru$^{2+/3+}$ potentials for target complexes ($E$ vs. NHE)</td>
</tr>
<tr>
<td>3.4</td>
<td>Crystallographic data and structure refinement for [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$]</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The Fenton reaction in biological systems</td>
<td>1</td>
</tr>
<tr>
<td>1.2</td>
<td>(A, left) NMR structure of ATGA segment (red) from DNA showing Fe$^{2+}$ (orange) bound to the N7 of the guanine base and its proximity to the cleaved thymidine deoxyribose (yellow), used with permission (A, right) Fe$^{2+}$ binding to an ATGA segment, drawn for clarity. (B, left) NMR structure the AGGG segment (A in green and GGG in pink) from DNA showing Fe$^{2+}$ (orange) bound to the N7 of the guanine bases and its proximity to the cleaved thymidine deoxyribose (yellow), used with permission. (B, right) Fe$^{2+}$ binding to an AGGG segment, drawn for clarity</td>
<td>3</td>
</tr>
<tr>
<td>1.3</td>
<td>Model of the 2-His-1-carboxylate functionality using non-heme iron(II); X, Y, and Z represent open coordination sites</td>
<td>4</td>
</tr>
<tr>
<td>1.4</td>
<td>Structures of tris(pyrazolyl)borate (Tp$^R$) and tris(pyrazolyl)methane (Tp$^R$) ligands</td>
<td>5</td>
</tr>
<tr>
<td>1.5</td>
<td>Structures of Tp$_2$Fe (R = H, 1), Tp*$_2$Fe (R = Me, 2, top), and Tp$_2$Fe$_2$(µ-O)(µ-O$_2$CCH$_3$) (3, bottom)</td>
<td>7</td>
</tr>
<tr>
<td>1.6</td>
<td>Structures of Tp$^{3p}$Fe(OAc) (4, left) and [NEt$_4$][Tp$^R$Fe(CN)$_3$] (R = H, Me, ³Pr; 5, right)</td>
<td>7</td>
</tr>
<tr>
<td>1.7</td>
<td>Structure of [(Tpm)$_2$Fe][X$_2$] (X = BF$_4^-$, ClO$_4^-$, OTf$^-$; R = H, CH$_3$, ³Pr; 6).............</td>
<td>8</td>
</tr>
<tr>
<td>1.8</td>
<td>Structures of [Tpm<em>RFe(NCE)$_3$(NCCH$_3$)] (E = S, Se; 7, left) and [Tpm</em>RFe(NCCH$_3$)$_3$][(BF$_4$)$_2$] (8, right)</td>
<td>9</td>
</tr>
<tr>
<td>1.9</td>
<td>Structures of TpRuCl(COD) (9, top), TpRu(R)(NCCH$_3$)Me (R = CO, P(CH$_3$)$_3$; 10, middle), and Tp*RuH(COD) (11, bottom)</td>
<td>11</td>
</tr>
<tr>
<td>1.10</td>
<td>Structures of [Tp$^R$Ru(NCCH$_3$)$_3$][X] (R = H, X = PF$_6^-$, 12; R = Me, X = OTf$^-$, 13; R = ³Pr, X = OTf$^-$, 14)</td>
<td>12</td>
</tr>
<tr>
<td>1.11</td>
<td>Structures of fac-[TpmRu(DMSO-S)$_2$(DMSO-O)][(OTf)$_2$] (15, top) and [TpmRu(OH$_2$)$_3$][(OTs)$_2$] (16, bottom)</td>
<td>13</td>
</tr>
</tbody>
</table>
1.12 Structures of [TpmRuCl(NCCH\textsubscript{3})\textsubscript{2}][PF\textsubscript{6}] (17, top) and [(Tpm)\textsubscript{2}RuCl][Cl] (18, bottom) ................................................................. 13

1.13 Structure of NAMI-A (20) .............................................................................. 16

1.14 Structures of [(η\textsuperscript{6}-arene)Ru(X)(Y)(Z)] (21, left), and carboplatin (22, right) ........................................................................................................ 17

2.1 Structures of sulfur-containing amino acids tested for antioxidant activity ................................................................................................. 26

2.2 Structures for the Fe-S clusters in ferredoxin (a) and rubredoxin (b) ........... 27

2.3 Structures of ergothioneine and selenoneine (left) and methimazole (right) ................................................................................................. 28

2.4 Structures of selenium-containing amino acids tested for antioxidant activity ................................................................................................. 29

2.5 Target iron(II) complexes .................................................................................. 30

2.6 Synthesis of [Tp*Fe(NCCH\textsubscript{3})\textsubscript{3}][BPh\textsubscript{4}] (1); yield 65% .......................................................... 31

2.7 Synthesis of [Tpm*Fe(NCCH\textsubscript{3})\textsubscript{3}][(BPh\textsubscript{4})\textsubscript{2}] (2), yield 43% ................................................ 32

2.8 Sulfur- and selenium-containing compounds used in this work ................. 33

2.9 Preparation of [Fe(SePh)\textsubscript{4}][(PPh\textsubscript{4})\textsubscript{2}]\textsuperscript{53} (3) and [Fe(SPh)\textsubscript{4}][(PPh\textsubscript{4})\textsubscript{2}] (4) ...... 34

2.10 Synthesis of [Fe(DImT)\textsubscript{2}][OTf\textsubscript{2}] (5) and [Fe(DImSe)\textsubscript{2}][OTf\textsubscript{2}] (6) ............. 35

2.11 Results of adding Tp-type ligands to the synthesized iron(II) sulfur- and selenium-containing complexes. All reactions were conducted in acetonitrile ......................................................................................... 36

2.12 Depiction of where the potentials of iron(II) complexes lie in relation to the electrochemical window for the Fenton reaction ......................... 40

3.1 Structures of [(η\textsuperscript{6}-arene)Ru(X)(Y)(Z)] (left), and carboplatin (right) ... 49

3.2 Structures of RuH\textsubscript{2}(PPh\textsubscript{3})\textsubscript{4} (left), Grubbs catalyst, 1\textsuperscript{st} generation (Cy = cyclohexane; middle), and Grubbs catalyst, 2\textsuperscript{nd} generation (right) ........ 50

3.3 Structures of RuCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{3} (left) and [RuCl\textsubscript{2}(COD)]\textsubscript{x} (right) ....................... 51
3.4 Structures of target ruthenium(II) complexes discussed in this chapter ......53
3.5 Synthesis of ruthenium(II) starting materials ..................................................55
3.6 Crystal structure diagram of [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$]. Density surfaces show 50% probability ellipsoids .................................................................58
3.7 Packing diagram of [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] viewed along the $a$-axis of the unit cell ........................................................................59
3.8 Synthesis of [Tp$^R$Ru(NCCH$_3$)$_3$][X] ..............................................................60
3.9 Synthesis of [Tpm$^R$Ru(NCCH$_3$)$_3$][(X)$_2$] .......................................................62
3.10 TpRuCl(COD) (left), TpRuCl(PPh$_3$)$_2$ (middle), and [TpmRuCl(PPh$_3$)$_2$][BF$_4$] (right) ..............................................................................63
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Reported catalysis of $\text{H}_2\text{P(\text{CH}_2)_2\text{PH}_2}$ with $[\text{Tpm}^*\text{Fe(\text{NCCH}_3)_3}][\text{(BF}_4\text{)}_2]$</td>
<td>9</td>
</tr>
<tr>
<td>1.2</td>
<td>Reported result of attempted synthesis of $[(\text{Tpm})_2\text{Ru}][(\text{ClO}_4)_2]$ from $[\text{Tpm}_2\text{RuCl}][\text{Cl}]$</td>
<td>15</td>
</tr>
<tr>
<td>3.1</td>
<td>Total reported synthesis of $[\text{TpRu(\text{NCCH}_3)_3}][\text{PF}_6]$</td>
<td>52</td>
</tr>
<tr>
<td>3.2</td>
<td>Total reported synthesis of $[\text{Tp}^*\text{Ru(\text{NCCH}_3)_3}][\text{OTf}]$</td>
<td>52</td>
</tr>
<tr>
<td>3.3</td>
<td>Total reported synthesis of $[\text{TpmRu(OH}_2\text{)}_3][\text{(OTs)}_2]$</td>
<td>53</td>
</tr>
<tr>
<td>3.4</td>
<td>Total reported synthesis of $[\text{Ru(\text{NCCH}_3)_6}][(\text{BF}_4)_2]$</td>
<td>54</td>
</tr>
</tbody>
</table>
CHAPTER ONE

A BRIEF REVIEW OF THE USES OF IRON AND RUTHENIUM COMPLEXES WITH TRIS(PYRAZOLYL) LIGANDS AND THEIR BIOLOGICAL RELEVANCE

Introduction

Iron is an essential metal that is required for the activity of enzymes and proteins. It is vital in the transport of $O_2$ throughout mammalian organisms in hemoglobin,\(^1\) in the electron transport chain of cellular respiration in cytochrome,\(^2\) and the degradation of hydrogen peroxide into oxygen and water in catalase.\(^3\) As a transition metal, non-protein-bound iron is prone to electron transfer reactions that enable it to generate reactive oxygen species (ROS). This labile iron participates in the Fenton reaction generating the ROS hydroxyl radical, $^\cdot OH$ (Figure 1.1). Labile iron(II) generates $^\cdot OH$ by reducing hydrogen peroxide (a byproduct of cellular respiration), thereby oxidizing iron from a +2 oxidation state to +3. Iron(III) is then reduced back to iron(II) by cellular reductants such as nicotinamide adenine dinucleotide (NADH) to complete the cycle.\(^4\)

![Figure 1.1. The Fenton reaction in biological systems.](image-url)
The generated hydroxyl radical can cause oxidative stress in cells, damage to lipids and proteins, and damage to DNA.\(^5\) Hydroxyl radical has been identified as a primary cause of increased risk of life-threatening and chronic or degenerative diseases such as cancer,\(^6\) as well as cardiovascular,\(^7\) Alzheimer’s,\(^8\) and Parkinson’s diseases\(^8-12\) and is a primary factor in the aging process.\(^13\) Therefore, it is of great interest to investigate methods to prevent the formation of hydroxyl radical for disease prevention and treatment.

Many types of DNA modifications are caused by \(`\text{OH}`\),\(^14,15\) and several of the \(`\text{OH}`\)-induced DNA modifications are mutagenic.\(^16\) DNA damage from hydroxyl radical occurs at the nucleotide bases and the phosphate backbone via strand breakage.\(^17\) In cells, positively-charged iron ions localize around the negatively-charged phosphate backbone to help stabilize the charge of the oxygen atoms\(^18\) and electron-rich nucleotide bases (specifically at guanine-rich sequences)\(^19-21\) through electrostatic interactions (Figure 1.2). When hydrogen peroxide is in close proximity to localized iron(II) on the DNA phosphate backbone, \(`\text{OH}`\) is formed and can deprotonate the backbone at the 4’ carbon, resulting in a rearrangement reaction that ultimately cleaves the phosphodiester bond between deoxyribose sugars and DNA backbone cleavage.\(^18,19,21,22\)

N,N,N-type donor ligands have been of interest in metalloenzyme modeling, specifically with 2-His-1-carboxylate functionality (Figure 1.3) commonly found in enzymes that contain non-heme iron(II).\(^23\) These ligands coordinate a wide variety of metal centers, specifically late 1\(^{\text{st}}\) row transition metals. Two widely used ligands of the
Figure 1.2. (A, left) NMR structure of ATGA segment (red) from DNA showing Fe$^{2+}$ (orange) bound to the N7 of the guanine base and its proximity to the cleaved thymidine deoxyribose (yellow), used with permission.$^{20}$ (A, right) Fe$^{2+}$ binding to an ATGA segment, drawn for clarity. (B, left) NMR structure the AGGG segment (A in green and GGG in pink) from DNA showing Fe$^{2+}$ (orange) bound to the N7 of the guanine bases and its proximity to the cleaved thymidine deoxyribose (yellow), used with permission.$^{22}$ (B, right) Fe$^{2+}$ binding to an AGGG segment, drawn for clarity.
N,N,N-type are tris(pyrazolyl)borates (Tp<sup>R</sup>; 1; Figure 1.4) and tris(pyrazolyl)methanes (Tpm<sup>R</sup>; 2; Figure 1.4). First synthesized by Trofimenko, Tp and Tpm coordinate to 1<sup>st</sup> and 2<sup>nd</sup> row transition metals, and the properties of these complexes have been extensively studied in terms of structural characterization, reactivity, and electronic properties. Trofimenko and Kitajima have used tris(pyrazolyl)borate (Tp) complexes with N,N,N donor ligands to model several enzymes with the 2-His-1-carboxylate facial triad; however, there were drawbacks in terms of lack of O donation from the ligand, since the O donor increases the stability of the scaffold.<sup>25-31</sup> These trinitrogen donor ligands are widely used in the synthesis of biometallic complexes due to their similar reactivities to the cyclopentadienyl (Cp) family of ligands, especially when bound to iron.<sup>32</sup> No previous reports using Tp-type ligands as DNA coordination mimics exist, but it is believed these ligands can be used to mimic metal binding to adenine and guanine N7, known sites of metal localization (Figure 1.2).<sup>33</sup>

![Figure 1.3. Model of the 2-His-1-carboxylate functionality using non-heme iron(II); X, Y, and Z represent open coordination sites.](image-url)
Figure 1.4. Structures of tris(pyrazolyl)borate (Tp\(^R\)) and tris(pyrazolyl)methane (Tpm\(^R\)) ligands.

A useful property of the N,N,N-type ligands is the ability to tune both their electronic properties, by using a neutral ligand (Tpm\(^R\)) or negatively-charged ligand (Tp\(^R\)), and to tune their steric properties by adding the desired R substituents to control steric bulk. This ability has led to widespread applications of Tp\(^R\) and Tpm\(^R\) ligands in metallocenzyme model chemistry,\(^{29}\) polymerization catalysis,\(^{34}\) C-H bond activation,\(^{35}\) and metal ion extraction.\(^{36}\) There also is intrinsic interest in the electronic characteristics of Tp\(^R\) and Tpm\(^R\) ligands relative to those of other facially-coordinating, six-electron donors such as 1,4,7-triazacyclononane (TACN) and cyclopentadienyl (Cp) ligands.\(^{37,38}\)

**Tp-Type Iron Chemistry and Its Applications**

Tp-type iron complexes have been extensively studied since they were first synthesized by Trofimenko in 1966.\(^{39}\) One of these types of complexes are the octahedral Tp\(_2\)Fe (1) and Tp*\(_2\)Fe (2; Figure 1.5) that can be formed in high yields using iron(II) salts such as FeCl\(_2\), Fe(OAc)\(_2\), and Fe(OTf)\(_2\) with two equivalents of the desired
TpR ligand. These iron(II) complexes have displayed unusual temperature-dependent spin-state crossover behavior.40-45

Another type of complex includes oxo-bridged diiron centers, such as Tp$_2$Fe$_2$(μ-O)(μ-O$_2$CCH$_3$), (3; Figure 1.5) that resembles metalloenzymes such as hemerythrin, ruberythrin, and methane mono-oxygenase. The crystal structure of 3 shows iron coordination by one μ-oxo and two μ-carboxylato bridges with the Tp ligand mimicking three histidine moieties.46 The five-coordinate iron(III) complex Tp$_i$PrFe(OAc) (4; Figure 6) was also synthesized and acts as a mimic for non-heme metalloprotein hemoglobin and cytochrome P-450.47 Facial-capped Tp-type iron complexes are also of interest as synthons for magnetic materials. Iron(III) complexes of the type (R = H, Me, iPr; 5; Figure 1.6) have been synthesized and studied for their electrical and optical properties, but mostly for their ability to self-assemble into bridged chains that have exhibited unusual magnetic properties.48,49

Tris(pyrazolyl)methane iron complexes have also been studied since they were first synthesized by Trofimenko,50 but not as extensively as analogous tris(pyrazolyl)borate iron complexes. Iron complexes of Tpm such as [Tpm$_2$Fe][X$_2$] (X = BF$_4^-$, ClO$_4^-$, OTf; 6; Figure 1.7) can be formed in high yields using iron(II) salts such as Fe(BF$_4$)$_2$, Fe(ClO$_4$)$_2$, and Fe(OTf)$_2$ with two equivalents of the desired Tpm ligand. These iron(II) complexes have also displayed unusual temperature-dependent spin-state crossover behavior similar to that of their Tp$_2$Fe analogs.51

Similarly, Tpm-type iron complexes of considerable interest are the facially-capped synthons. One example are the complex [Tpm*Fe(NCE)$_2$(NCCH$_3$)] (E = S, Se;
Figure 1.5. Structures of Tp$_2$Fe (R = H, 1), Tp*$_2$Fe (R = Me, 2, top), and Tp$_2$Fe$_2$(µ-O)(µ-O$_2$CCH$_3$) (3, bottom).

Figure 1.6. Structures of Tp$^{i}$PrFe(OAc) (4, left) and [NEt$_4$][Tp$^{i}$PrFe(CN)$_3$] (R = H, Me, $^{i}$Pr; 5, right).
Figure 1.7. Structure of [Tpm$_2$Fe][X$_2$] (X = BF$_4^-$, ClO$_4^-$, OTf$^-$; R = H, CH$_3$, $^3$Pr; 6).

9; Figure 1.8) which were studied for spin-crossover behavior and found to be comparable to that of their bis-Tpm analogs.$^{52}$ Another complex, [Tpm$^*$Fe(NCCH$_3$)$_3$][(BF$_4$)$_2$] (10; Figure 1.8), was synthesized and tested to determine if it could generate a nine-membered triphosphorous macrocycle via intramolecular hydrophosphination. The complex was treated with bidentate phosphines such as 1,2-diphosphinoethane in tetrahydrofuran (THF), and was found to undergo ligand disproportionation to form [Tpm$^*$_2Fe][(BF$_4$)$_2$] and the tris-diphosphino iron(II) species (Scheme 1).$^{32}$

**Tp-Type Ruthenium Chemistry and Its Applications**

Ruthenium is in the same group as iron, but it is a soft, inert metal unlike borderline, labile iron(II). Ruthenium(II) is diamagnetic, unlike its paramagnetic iron(II) cousin, making NMR data evaluation of ruthenium(II) complexes more tractable compared to iron(II). These properties make ruthenium(II) ideal for coordination studies related to iron(II).

Tp-type ruthenium(II) complexes also have practical uses outside of being
**Figure 1.8.** Structures of \([\text{Tpm}^*\text{Fe(NCE)}_2(\text{NCCH}_3)]\) (\(E = \text{S, Se}\); 7, left) and \([\text{Tpm}^*\text{Fe(NCCH}_3)_3][\text{BF}_4]_2\) (8, right).

**Scheme 1.1**
suitable substitutes for iron(II) such catalysis applications, but they have mostly been limited to the parent Tp ligand. One example is Tp$_2$Ru (analogous to the iron complex in Figure 1.5), synthesized by combining the thallium salt of Tp with tetrakis(benzonitrile)dichlororuthenium(II) in benzene and heating to reflux for two days before column chromatographic purification. The bis-Tp complex was used as in the catalytic hydrogenation of olefins such as methyl acrylate. Surprisingly, this complex is the only reported bis-Tp ruthenium complex of any kind.

Another more widely used complex is TpRuCl(COD) (COD = cyclooctadiene; Figure 1.9), synthesized by heating the polymeric [RuCl$_2$(COD)$_n$] with KTp to reflux in THF. This Tp-type COD-containing complex has been used as a catalyst in the reactions of phenylacetylene with allyl alcohols to form selective C-O coupled products and trimethylsilylacetylene with allyl alcohols to form an (allyloxy)carbenes. Another ruthenium complex, TpRu(R)(NCCH$_3$)Me (R = CO, PMe$_3$; Figure 1.9), activates C-H bonds in the presence of furan or thiophene to produce methane and TpRu(NCCH$_3$)(aryl) (aryl = 2 furyl or 2-thienyl) and to activate sp$^3$ C-H bonds to form new C-C and C-N bonds when heated in excess acetone or acetonitrile, respectively. Tp$^*$RuH(COD) (11; Figure 1.9) was generated from RuHCl(COD)(Bpm) (Bpm = bis(pyrazolyl)methane) and KTp$^*$ in hopes of producing a saturating species that could activate C-H bonds or perform hydrogen transfer reactions.

The Tp-type ruthenium complexes of the formula [Tp$^k$Ru(NCCH$_3$)$_3$][X] (R = H, Me, Pr; X = PF$_6^-$, OTf$^-$) are of great interest, since these would make excellent synthons for a variety of ruthenium chemistry. [TpRu(NCCH$_3$)$_3$][PF$_6$] (12; Figure 1.10) was
synthesized by heating TpRuCl(COD) and NH₄PF₆ in a 1:1 mixture of dichloromethane and dimethylformamide to reflux and was originally used to study ligand exchange kinetics of its acetonitrile ligands in comparison to the analogous [CpRu(NCCH₃)]⁺. [Tp*Ru(NCCH₃)][OTf] (13; Figure 1.10) was prepared by stirring Tp*RuH(H₂)₂ with triflic acid at -80 °C in THF, and was created as a byproduct when determining the strength of acid needed to create H₂ gas from the Ru(II) starting material. [Tp*PrRu(NCCH₃)][OTf] (14; Figure 1.10) was synthesized by stirring [Tp*PrRu(OH₂)(THF)][(OTf)(THF)₂] in acetonitrile.

![Figure 1.9. Structures of TpRuCl(COD) (9, top), TpRu(R)(NCCH₃)Me (R = CO, P(CH₃)₃; 10, middle), and Tp*RuH(COD) (11, bottom).]
Unlike Tp-type ruthenium complexes, reports of Tpm-type ruthenium complexes are rare. One complex, fac-[TpmRu(DMSO-S)\textsubscript{2}(DMSO-O)][(OTf)\textsubscript{2}] (15; Figure 1.11), was made by heating fac-[Ru(DMSO-O)\textsubscript{3}(DMSO-S)\textsubscript{3}][(OTf)\textsubscript{2}] with Tpm in methanol to reflux. But unlike its Tp-type ruthenium analogs, only two of the three pyrazole rings coordinate to the metal center, as proven through X-ray crystallography.\textsuperscript{63} Another reported complex, [TpmRu(OH)\textsubscript{2}][(OTs)\textsubscript{2}] (16; Figure 1.11), was synthesized by cleaving the diruthenium species Tpm\textsubscript{2}Ru\textsubscript{2}(OH)(\mu-O)(\mu-O\textsubscript{2}PO) with tosylic acid in an aqueous solution in hopes to form dioxygen through electrooxidation of the ruthenium center.\textsuperscript{64}

The most relevant Tpm-type ruthenium(II) complex pertaining to this work is [TpmRuCl(NCCH\textsubscript{3})\textsubscript{2}][PF\textsubscript{6}] (17; Figure 1.12). It is believed that with two weakly-coordinated acetonitrile solvato ligands, this complex would be a valuable synthon to perform subsequent ruthenium chemistry. This Tpm-ruthenium(II) complex was synthesized by heating the ruthenium(III) species TpmRuCl\textsubscript{3} to reflux with Zn dust in acetonitrile, followed by a counterion exchange with NH\textsubscript{4}PF\textsubscript{6}.\textsuperscript{65}
Figure 1.11. Structures of $\text{fac-}[\text{TpmRu(DMSO-S)}_2(\text{DMSO-O})][(\text{OTf})_2]$ (15, top) and $[\text{TpmRu(OH}_2]_3][(\text{OTs})_2]$ (16, bottom).

Figure 1.12. Structures of $[\text{TpmRuCl(NCCH}_3)_2][\text{PF}_6]$ (17, top) and $[\text{Tpm}_2\text{RuCl}][\text{Cl}]$ (18, bottom).
No reports exist for the synthesis of bis-Tpm ruthenium(II) complexes. The closest structure to a true bis-Tpm ruthenium(II) complex, where all six coordination sites are occupied by two Tpm ligands, is [Tpm$_2$RuCl][Cl] (18; Figure 1.12), made by combining a solution of the ruthenium(III) species TpmRuCl$_3$ and LiCl in water and a solution of Tpm and triethylamine in ethanol and heating to reflux. As proven by $^1$H and $^{13}$C NMR spectroscopy, only five of the six pyrazole rings are bound to the metal center. Upon removing the chloride with AgClO$_4$ and heating the reaction mixture in acetonitrile to reflux to allow for the sixth ring to bind, $^1$H and $^{13}$C NMR spectroscopy showed that the metal center exchanged the chloride for an acetonitrile ligand instead of binding the sixth nitrogen of the Tpm ligand (19; Scheme 1.2).

**Biological Applications of Ruthenium**

Although ruthenium is not an essential metal, ruthenium complexes are also of biological interest in cancer treatment. Since the discovery of cisplatin-resistant forms of cancer, research has been conducted to discover other transition metal-based chemotherapeutic drugs to help combat more aggressive cancer cell lines. One of these ruthenium drugs is trans-[HIm]-[Ru$_{III}$Cl$_4$(DMSO)(Im)] (NAMI-A, or new anti-tumor metathesis inhibitor-A; 20; Figure 1.13). Unlike other ruthenium-based complexes, NAMI-A has the ability to eradicate tumor metastases. This property may be due to the ability of NAMI-A and other Ru(III) complexes with similar structures to be transported by vacant Fe(II) sites in transferrin and lactoferrin to distant cancer cells. Once these complexes reach target cancer cells, they then interact with either
extracellular matrix components or some form of cellular receptor to enter the cell via endocytosis. Upon entering the cancerous cell, it is currently believed that the Ru(III) center is then reduced to Ru(II) by glutathione. Finally, the complex binds to the target cell’s DNA via guanine, causing DNA crosslinks and inhibiting the function of topoisomerase II.

One study of particular interest is the use of ruthenium(II) arene complexes of the type $[(\eta^6\text{-arene})\text{Ru}(X)(Y)(Z)]$ (arene = substituted benzene; X, Y, Z = halides,
acetonitrile, isonicotinamide; 21; Figure 1.14), that were synthesized and tested in A2780 (ovarian) cancer cell growth inhibition assays. These ruthenium(II) complexes inhibited cell growth similarly to that of carboplatin (22; Figure 1.14), and ¹H NMR spectroscopy indicated that the metal center was strongly bound to the guanine N7 in DNA.⁷⁶ This reinforces the proposal that ruthenium(II) may be a useful mimic for iron(II) in biological studies. It also shows ruthenium complexes of Tp-type ligands may be useful for studying metal-ion interactions with DNA.

An example of Tp-type ruthenium complexes that are of biological interest is the aforementioned [TpmRuCl(NCCH₃)₂][PF₆] (17; Figure 1.12). This complex was originally made as a starting material so that bidentate phosphine ligands could be added. The resulting complex was tested in vitro against breast (MCF-7) and cervical (HeLa) cancer cell lines. Complex 17 has shown significant cytotoxicity based on 3-(4,5-
Figure 1.14. Structures of [(η⁶-arene)Ru(X)(Y)(Z)] (21, left), and carboplatin (22, right).

dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays,⁶⁵ a colorimetric assay used to measure enzyme activity that can be used to assess the viability and proliferation of cells.⁷⁵ Due to structural similarities of 17 with the arene complex 21, it is likely this complex may also bind DNA to exert its anticancer effects.

This review shows Tp-type iron(II) and ruthenium(II) complexes have uses in catalysis, as biomimetics, and in biological studies. It also shows that this class of complexes has the potential to be used in biologically-relevant studies of DNA. The research presented in Chapter 2 describes the synthesis and characterization of tris(pyrazolyl)borate and tris(pyrazolyl)methane complexes of iron(II), with an emphasis on electrochemical studies. Novel iron(II) complexes containing chalcogenates and chalcogenones were also synthesized and the studies conducted on these complexes show the effects sulfur and selenium have on the electrochemical behavior of iron(II). These studies help us understand how changing the electrochemical behavior of iron(II) affects its ability to undergo the Fenton reaction.
An improved synthetic method for the synthesis of tris(pyrazolyl)borate ruthenium(II) complexes as well as the synthesis and characterization of novel tris(pyrazolyl)methane complexes of ruthenium(II) are presented in Chapter 3. The improved syntheses of these Tp-type complexes also yields a quick and effective pathway for making ruthenium(II) synthons to use in catalysis or as building blocks for subsequent synthetic chemistry. Cyclic voltammetry studies conducted on these species show how the coordination of Tp-type ligands alters the electrochemical behavior of ruthenium(II). These electrochemical studies show that the coordination of N,N,N-type donors such as Tp also affect the redox chemistry of ruthenium.

References


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CHAPTER TWO
SYNTHESIS AND CHARACTERIZATION OF IRON(II) COMPLEXES
CONTAINING TRIS(PYRAZOLYL) LIGANDS AS WELL AS SULFUR- OR
SELENIUM-CONTAINING LIGANDS AND THEIR BIOLOGICAL RELEVANCE

Introduction

In cells, unbound iron(II) is prone to electron transfer reactions that enable it to
generate hydroxyl radical (‘OH) in the Fenton reaction (Reaction 1).\(^1\) The generated
hydroxyl radical can cause oxidative stress in cells and damage to DNA.\(^2\) Hydroxyl
radical is an underlying cause of chronic or degenerative diseases and is also a primary
factor in the aging process.\(^3\)-\(^{10}\) Therefore it is of great interest to investigate methods to
prevent hydroxyl radical formation for disease prevention and treatment.

$$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^- \quad (1)$$

Selenium is a required dietary micronutrient for most animals,\(^1,^5\) and selenium
compounds have also been reported as vital antioxidants,\(^11,^12\) protecting and
strengthening the immune system by preventing radical formation. World population
studies show that where the soil is rich in selenium, there are significantly lower levels of
cancers.\(^13\) The Nutritional Prevention of Cancer (NPC) trial found that a regular
supplement of dietary selenium in humans (200 µg/day) can reduce the occurrence of
prostate cancer by 63%, colorectal cancer by 58%, carcinoma by 45%, and lung cancer
by 48% over a ten year period,\textsuperscript{14} though a larger study of selenium and vitamin E supplementation on prostate cancer, the SELECT trial, found that selenium supplementation using yeast enriched with primarily L-selenomethionine (200 \(\mu\)g/day; SeMet; Figure 2.1) was not as effective in preventing prostate cancer as once thought.\textsuperscript{15} Many population studies have also shown that selenium is a protective nutrient against the development of heart and artery disease.\textsuperscript{16} These findings have led to the development of organoselenium drugs, which are less toxic than inorganic selenium and appear to be bioavailable.\textsuperscript{6,7} In Japanese clinical trials, the selenium-containing drug ebselen was found effective for treatment of stroke, and 1,2-diselenone-3-pentanoic acid, the selenium analog of \(\alpha\)-lipoic acid, is a well-studied naturally-occurring antioxidant.\textsuperscript{17}

Selenium can be found as selenocysteine (SeCys; Figure 2.1) and selenomethionine (Figure 2.1) in plants, which naturally replace sulfur in cysteine and methionine with selenium absorbed from the soil.\textsuperscript{18} Selenocysteine is also specifically incorporated into the active sites of antioxidant proteins such as glutathione peroxidase (GPx),\textsuperscript{17} thioredoxin reductase,\textsuperscript{19} and selenoproteins P, W, and R.\textsuperscript{20}

Selenolates (RSe\(^-\)) in biological systems coordinate metal ions similarly to thiolates (RS\(^-\)). Iron thiolate complexes can mimic ferridoxins (Figure 2.2), iron-sulfur proteins that are involved in the transfer of electrons in metabolic processes, such as those found in the mitochondria of anaerobic bacteria\textsuperscript{21} and the chloroplasts of plants.\textsuperscript{22} Another example of iron thiolate complexes is the family of rubredoxins (Figure 2.2), iron-sulfur proteins that are also involved in electron transfer reactions and found exclusively in sulfur-processing archaebacteria.\textsuperscript{23} Selenolate-metal coordination is
found in the [NiFeSe] hydrogenases, a group of metalloenzymes also found in sulfur-processing archaebacteria that catalyze the hydrolysis of hydrogen gas into hydrogen ions and electrons. They are generally heterodimeric, contain three iron–sulfur clusters in their small subunit and a nickel-iron-containing active site in their large subunit that incorporates a SeCys residue bound to nickel(II).24
Figure 2.2. Structures for the Fe-S clusters in ferredoxin (a) and rubredoxin (b).

The heterocyclic chalcogenone ergothioneine (Figure 2.3), widely found in actinobacteria, is an amino acid that is a thiourea derivative of histidine. Its selenium analog, selenoneine (Figure 2.3), mostly found in fish such as bluefin tuna (430 nmol/g), is a major dietary source of selenium for largely fish eating cultures. These chalcogenones resemble methimazole, a drug currently used in the treatment of hyperthyroidism. Heterocyclic chalcogenones such as those shown in Figure 2.3 also coordinate iron(II) well, since they are σ- and π-donors as well as π-acceptors. Raper, Akrivos, Spicer et al., and Pettinari have previously reviewed the coordination chemistry of selones and thiones with transition metals and halogens.
Small-molecule sulfur and selenium antioxidants help prevent or minimize widespread cellular damage from reactive oxygen species including 'OH. Studies by Battin et al. have shown using gel electrophoresis DNA damage assays that the sulfur-containing cellular antioxidants reduced glutathione (GSH) and oxidized glutathione (GSSG; Figure 2.1) inhibit iron-mediated DNA damage. GSH inhibited iron-mediated DNA damage (23.0 ± 8.4% inhibition at 10,000 µM) at a concentration well within biological concentrations (up to 15,000 µM in the nucleus). GSSG also inhibited iron-mediated DNA damage (50.2 ± 4.5% inhibition at 10,000 µM), giving credence as to why glutathione is the primary sulfur-containing cellular antioxidant. In contrast, the sulfur-containing amino acids cysteine (Cys), cystine (Cys$_2$), and methionine (Met; Figure 2.1) do not effectively inhibit iron-mediated DNA damage. It was determined that metal coordination is required for the majority of glutathione antioxidant activity, as determined by similar studies conducted with chelated iron (in the form of [Fe(EDTA)]$^{2-}$) using gel electrophoresis.$^{32}$
Selenium concentrations in biological systems are small,\textsuperscript{33} so it is believed that no more than one selenium-containing ligand would typically be involved in biological metal coordination. Battin \textit{et al.} also used DNA damage assays to study the ability of selenium-containing compounds found in biological systems to inhibit iron-mediated DNA damage. Of the 12 selenium compounds studied, only methyl-selenocysteine (MeSeCys; Figure 2.4; IC\textsubscript{50} of 378.4 ± 0.1 µM) and selenocystamine (SeCysta; Figure 2.4; IC\textsubscript{50} of 121.4 ± 0.3 µM) inhibited iron-mediated DNA damage, although these concentrations are much higher than biological selenium concentrations. It was determined, as for the previously tested sulfur-containing compounds, that iron coordination is required for the majority of this antioxidant activity.\textsuperscript{34}

\begin{center}
\begin{tabular}{ll}
\textbf{selenocysteine (SeCys)} & \textbf{selenomethionine (SeMet)} \\
\begin{tabular}{c}
\text{HO} \\
\text{SeH} \\
\text{NH}_2 \\
\end{tabular} & \begin{tabular}{c}
\text{HO} \\
\text{Se} \\
\text{NH}_2 \\
\end{tabular} \\
\text{selenocysteine (SeCys)} & \text{selenomethionine (SeMet)} \\
\text{methyl-selenocysteine (MeSeCys)} & \text{selenocystamine (SeCysta)} \\
\begin{tabular}{c}
\text{HO} \\
\text{Se} \\
\text{NH}_2 \\
\end{tabular} & \begin{tabular}{c}
\text{H}_2\text{N} \\
\text{Se} \\
\text{Se} \\
\text{NH}_2 \\
\end{tabular}
\end{tabular}
\end{center}

\textbf{Figure 2.4.} Structures of selenium-containing amino acids tested for antioxidant activity.
Based on these data, synthesis and electrochemical study of biologically-relevant Tp-type iron(II) complexes (Figure 2.5) containing chalcogenates and chalcogenone ligands may help understand how changing the electrochemical behavior of iron(II) affects its ability to undergo the Fenton reaction. In the attempts to synthesize these complexes, two different methods are employed. One method entailed the chelation of iron(II) with Tp-type ligands to form Tp-type iron(II) complexes with labile solvato ligands, such as acetonitrile. Labile solvato ligands were used so that they can be replaced with sulfur- or selenium-containing ligands in subsequent steps. This reaction was followed by addition of the chalcogenate or chalcogenone ligands. The second method involved initial coordination of the chalcogenate or chalcogenone ligands to form iron(II)-sulfur and -selenium complexes, followed by chelation of the Tp-type ligand.

![Figure 2.5. Target iron(II) complexes.](image)
Results and Discussion

Synthesis of $T_p$-type iron(II) tris(acetonitrile) complexes.

$[T_p^*Fe(NCCH_3)_3][BPh_4]$ (1) was synthesized by slow cannula addition of the potassium salt of $T_p^*$ ($T_p$, $R = \text{Me}$) in acetonitrile to iron(II) triflate in acetonitrile. Immediately, a light pink solution formed and potassium triflate (KOTf) precipitated as a white solid. After separating the KOTf by cannula filtration, NaBPh$_4$ was added to the solution to perform a counteranion exchange, and the mixture was stirred overnight to yield a red solution. The volume of the solvent was reduced, and diethyl ether was added to precipitate a white solid (Figure 2.6). The $^1$H NMR spectrum for 1 is quite similar to that reported for its Fe-$T_p$m* analog. The BH proton appears as a broad singlet at $\delta$ -12, the two methyl groups at $\delta$ 39 and $\delta$ 14, and the 4-H of the pyrazole appears at $\delta$ 58. A sharp peak at $\delta$ -79 in $^{19}$F{$^1$H} NMR indicates the presence of uncoordinated triflate ion.

![Reaction Scheme](image)

**Figure 2.6.** Synthesis of $[T_p^*Fe(NCCH_3)_3][BPh_4]$ (1): yield 65%.

The IR spectrum of the free $T_p^*$ ligand shows a B-H stretching vibration at 2470 cm$^{-1}$, and the bound acetonitrile on iron(II) triflate of the form Fe(OTf)$_2$(NCCH$_3$)$_2$ has a nitrile stretching vibration at 2292 cm$^{-1}$. Upon $T_p^*$ coordination to iron(II) triflate, the B-
H stretch shifts to 2924 cm\(^{-1}\), a significantly higher energy relative to the unbound ligand, indicative of strong donor bonding to iron. The nitrile stretch from the iron-bound acetonitrile ligands shifts to 2319 cm\(^{-1}\), a higher energy, indicating stronger donor bonds between iron and acetonitrile upon addition of both Tp* and an acetonitrile solvato ligand.

\[[\text{Tpm*Fe(NCCH}_3)_3][\text{(BPh}_4)_2] \quad (2)\]

was synthesized similarly to a reported procedure (Tp* = Tpm, R = Me;\(^{35}\) Figure 2.7). The \(^1\)H NMR spectrum shows a broad resonance at \(\delta\) -42.2, characteristic of the apical CH proton. Broad resonances at \(\delta\) 54 (4-H on the pyrazole ring), 35 (3-methyl), and 12.7 (5-methyl) are due to Tpm* coordination to the metal ion. The \(^{19}\)F{\(^1\)H} NMR spectra shows a singlet at -79 ppm, indicating the presence of uncoordinated triflate anion.

\[
\begin{align*}
\text{Fe(Otlf)}_2 \cdot 2 \text{CH}_3\text{CN} + \text{Tpm*} & \quad \xrightarrow{\text{CH}_3\text{CN}} \quad \text{TPm*Fe(NCCH}_3)_3][\text{(BPh}_4)_2] + 2 \text{NaOTf}
\end{align*}
\]

**Figure 2.7.** Synthesis of \([\text{Tpm*Fe(NCCH}_3)_3][\text{(BPh}_4)_2] \quad (2), \) yield 43%.

Attempts to coordinate sulfur- and selenium-containing ligands using sodium phenylthiolate (NaSPh), sodium phenylselenolate (NaSePh), 1,3-dimethylimidazole-2-thione (DImT), and 1,3-dimethylimidazole-2-selone (DImSe; Figure 2.8) to
tris(acetonitrile) complexes 1 and 2 afforded products that could not be separated from the reaction mixture, as determined from paramagnetic $^1$H NMR spectra.

**Synthesis of iron(II) sulfur and selenium compounds.** Since sulfur- and selenium-containing ligands do not provide clean products with Tp-type iron(II) complexes, Fe(EPh)$_4^{2-}$ complexes (E = S, Se; Figure 2.9) were synthesized to attempt to synthesize the target iron(II) complexes. This approach differs as it involves coordinating the chalcogen to the metal before addition of the Tp-type ligand.

![Diagram of iron(II) complexes](image)

sodium phenylthiolate (NaSPh), E = S
sodium phenylselenolate (NaSePh), E = Se
1,3-dimethylimidazole-2-thione, E = S
1,3-dimethylimidazole-2-selone, E = Se

**Figure 2.8.** Sulfur- and selenium-containing compounds used in this work.

The iron(II) selenolate complex (3) was prepared as previously reported, but was modified to prepare the iron(II) thiolate complex (4). Addition of hydrated iron(II) chloride to sodium phenylthiolate yielded a dark purple solution and purple crystals of 4 upon cooling overnight. Comparison of the paramagnetic $^1$H NMR spectra of 3 and 4 to the reported values for the phenylselenolate complex suggest that the protons of the ortho, meta, and para positions from the phenylselenolate ligands are reversed from what was reported. Specifically, the resonances for the ortho and para protons have a positive
chemical shift ($\delta$ 18 and 16, respectively, compared to $\delta$ -16 and -18 reported) and the meta proton has a negative chemical shift ($\delta$ -16.5 compared to the reported $\delta$ 16).

To compare iron(II) complexes with different sulfur- and selenium-containing ligands, [Fe(DImE)$_2$][(OTf)$_2$] compounds were synthesized, where E is again sulfur (5) or selenium (6; Figure 2.10). Paramagnetic $^1$H NMR spectra of 5 shows a downfield shift from $\delta$ 3.5 (N-Me) and $\delta$ 6 (olefinic) for the free thione to $\delta$ 11 and $\delta$ 10, respectively, for the bound thione ligand. The spectra also show two resonances each for the methyl and olefinic protons, suggesting that the protons of the imidazole ligands have different environments. This same phenomenon is seen in the $^1$H NMR spectrum of 6.

The IR spectrum of the free thione shows a C=S stretching vibration at 1181 cm$^{-1}$, whereas the free selone has a C=Se stretching vibration at ~1148 cm$^{-1}$, consistent with previous reports for DImT, 1,1'-methylenebis(1,3-dihydro-3-methyl-2H-imidazole-2-
Figure 2.10. Synthesis of [Fe(DImT)₂][OTf₂] (5) and [Fe(DImSe)₂][OTf₂] (6).

thione) (Mbit), and 1,1’-methylene-bis(1,3-dihydro-3-methyl-2H-imidazole-2-selone) (Mbis). Upon DImT coordination to iron(II) triflate, the C=S stretch shifts to 1174 cm⁻¹, a lower energy relative to the unbound ligand indicative of weak iron backbonding to the thione ligand. Coordination of DImSe to iron(II) triflate results in a shift of the C=Se stretch to 1155 cm⁻¹, a slightly higher energy, indicating that iron backbonding interactions with this ligand are not significant. A similar difference in vibrational energies is seen for DImT and DImSe binding to copper(I).

Attempts at coordinating Tp* and Tpm* to both types of sulfur- and selenium-containing complexes yield a variety of results. Paramagnetic ¹H NMR spectra indicate that addition of Tp* and Tpm* to complexes 3 – 6 yielded results ranging from no reaction to ligand disproportionation upon addition of TpR ligands (Figure 2.11).

A comparison of the electrochemistry of iron(II) complexes. Cyclic voltammetry was performed on the new iron(II) complexes to understand how coordination of both
Figure 2.11. Results of adding Tp-type ligands to the synthesized iron(II) sulfur- and selenium-containing complexes. All reactions were performed in acetonitrile.

Tp-type ligands and sulfur- and selenium-containing ligands to iron(II) affects its redox chemistry. Changing the redox chemistry may affect the ability of iron(II) to generate hydroxyl radical in the Fenton reaction.

Upon comparing the measured Fe$^{2+}$/Fe$^{3+}$ potentials (Table 2.1) of the Tp-containing iron complexes with the sulfur- and selenium-containing iron complexes, it is clear that addition of a single Tp-type ligand to iron(II) triflate generally results in more positive Fe$^{2+}$/Fe$^{3+}$ potentials. These potentials indicate that iron(II) is less stable relative to iron(III). On the other hand, the addition of sulfur- and selenium-containing ligands to iron(II) triflate yields negative potentials, indicating that sulfur and selenium coordination stabilizes iron(II) relative to iron(III).

The potentials in Table 2.1 show that the addition of multiple Tp* ligands to iron result in lower Fe$^{2+}$/Fe$^{3+}$ potentials. For example, the bis Tp-type analog, Tp*$_2$Fe, has a more negative reversible Fe$^{2+}$/Fe$^{3+}$ potential of 0.241 V vs. normalized hydrogen electrode
Table 2.1: $\text{Fe}^{2+/3+}$ potentials for target complexes ($E$ vs. NHE).

<table>
<thead>
<tr>
<th>Complex</th>
<th>$E_{\text{pa}}$ (V)</th>
<th>$E_{\text{pc}}$ (V)</th>
<th>$E_{\text{1/2}, \text{Fe}^{2+/3+}}$ (V)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe(OTf)$_2$(NCCH$_3$)$_2$</td>
<td>0.633</td>
<td>0.913</td>
<td>0.771</td>
<td>This work</td>
</tr>
<tr>
<td>Tp*$_2$Fe</td>
<td>0.189</td>
<td>0.294</td>
<td>0.241</td>
<td>41</td>
</tr>
<tr>
<td>[Tp*$_2$Fe][[OTf]$_2$</td>
<td>0.916</td>
<td>1.02</td>
<td>0.968</td>
<td>41</td>
</tr>
<tr>
<td>[Tp*Fe(NCCH$_3$)$_3$][BPh$_4$] (1)</td>
<td>0.698</td>
<td>0.850</td>
<td>0.776</td>
<td>41</td>
</tr>
<tr>
<td>[Tp*Fe(NCCH$_3$)$_3$][(BPh$_4$)$_2$] (2)</td>
<td>0.879</td>
<td>1.04</td>
<td>0.761</td>
<td>41</td>
</tr>
<tr>
<td>[Fe(SPh)$_4$][(PPh$_4$)$_2$] (3)</td>
<td>-0.650</td>
<td>-0.796</td>
<td>-0.723</td>
<td>This work</td>
</tr>
<tr>
<td>[Fe(SePh)$_4$][(PPh$_4$)$_2$] (4)</td>
<td>-1.07</td>
<td>-0.942</td>
<td>-1.01</td>
<td>This work</td>
</tr>
<tr>
<td>[Fe(DImT)$_2$][(OTf)$_2$] (5)</td>
<td>-1.31</td>
<td>-0.176</td>
<td>-0.547</td>
<td>This work</td>
</tr>
<tr>
<td>[Fe(DImSe)$_2$][(OTf)$_2$] (6)</td>
<td>-0.401</td>
<td>-0.047</td>
<td>-0.047</td>
<td>This work</td>
</tr>
</tbody>
</table>

The potentials show that the coordination of multiple Tp* ligands stabilizes iron(III) relative to iron(II) better than does a single Tp* ligand due to the negative charge of the Tp* ligand. Conversely, the potentials in Table 2.1 show that addition of multiple neutral Tpm* ligands to iron yields a more positive potential than having one neutral Tpm* ligand coordinated to iron(II). The Tpm analog, [Tpm*$_2$Fe][[OTf]$_2$], has a more positive reversible $\text{Fe}^{2+/3+}$ potential of 0.968 V vs. NHE than that of the mono Tpm analog 2 (0.761 V). Also note that 2 has a slightly lower potential than iron(II) triflate (0.771 V). This trend can be explained due to the presence of the acetonitrile solvato ligands. Recall that the IR spectrum of iron(II) triflate of the form Fe(OTf)$_2$(NCCH$_3$)$_2$ has a nitrile stretching vibration for its bound acetonitriles at 2292 cm$^{-1}$. The nitrile stretching
vibration for 2 is shifted to a lower energy, 2283 cm$^{-1}$, upon addition of both Tpm* and an additional acetonitrile. The coordinated nitrogens of acetonitrile have the ability to $\sigma$-donate and $\pi$-accept when bound to a metal center, resulting in backbonding of its d orbitals to the empty $\pi^*$ orbital of the acetonitrile nitrogens, which is indicated by the lower vibrational energy. Thus, since $[\text{Tpm}^*\text{Fe}(\text{NCCH}_3)_3][\text{BPh}_4]_2$ (2) gains one solvato ligand, it yields the slightly lower potential regardless of Tpm* coordination; the bis analog has no solvato ligands from which it can backbond compared to 2, thus the higher potential. Thus the addition of multiple neutral Tpm* ligands better stabilizes iron(II) relative to iron(III) than does adding one Tpm* ligand.

However, the previous trend only holds true if more than one charged N,N,N-type donor is added to the metal center. $[\text{Tp}^*\text{Fe}(\text{NCCH}_3)_3][\text{BPh}_4]$ (1; 0.776 V) has a reversible Fe$^{2+/3+}$ potential that only differs by 15 mV as compared to complex 2 (0.761 V). But when more than one trinitrogen donor is added, the difference in potential widens greatly between Tp*$_2$Fe and $[\text{Tpm}^*$_2$\text{Fe}][(\text{OTf})_2]$ (727 mV). The potentials again show that the addition of charged species results in the stabilization of iron(II) over iron(III). The potentials also show that the charge of the trinitrogen donor has minimal effect on potential when only one ligand is coordinated to the metal center.

Comparing the Fe$^{2+/3+}$ potentials for the iron chalcogenate complexes, it can be seen that selenolate coordination of 4 (-1.01 V) negatively shifts the potential of the iron(II) compared to its thiolate analog, 3 (-0.723 V). This is because the selenolate is a softer base than the thiolate, meaning that the selenolate has more polarizable valence electrons than the thiolate. Although iron(II) is a borderline acid, the softer selenolate
will donate its pair of electrons through σ-donation more effectively than the thiolate, more effectively stabilizing iron(II) over iron(III).

In contrast, comparing the electrochemical potentials of complexes 5 and 6 show that the thione (-0.547 V) has a more negative potential than the selone (-0.047 V). The results can be explained using previously-discussed IR data for 5 and 6. Recall that the C=S stretch for 5 shifts to a lower energy relative to the unbound thione ligand, whereas the C=Se for 6 shifts to a slightly higher energy compared to unbound selone. Thus, backbonding to the thione ligand is more significant than to the selone ligand, indicating that the electrons from the thione ligand are not as readily donated to the iron center than with the selone ligand. These data show that both the thione and selone stabilize the iron(II) metal center relative to iron(III), but the selone is more effective at stabilizing the iron(II) center than the thione.

**Biological implications of this work.** The biological Fenton reaction occurs only over a specific electrochemical range (-0.324 V to 0.460 V). To illustrate the biological implications of the potentials in Table 2.1, Figure 2.13 shows the potentials of the iron complexes relative to the electrochemical window in which the Fenton reaction can occur. Previous reports have shown that complexation of iron(II) alters its electrochemical properties compared to iron(II). Based on the electrochemical potentials for the iron(II) complexes, chelation of either the DNA mimic Tp-type ligands or sulfur and selenium may inhibit the Fenton reaction. Tp-type coordination to iron(II) may stabilize iron(II) to H₂O₂ oxidation, whereas sulfur and selenium coordination may stabilize iron(III) to NADH reduction, preventing iron redox cycling. These findings are
consistent with the findings of Battin et al., where coordination of selected sulfur- and selenium-containing compounds is a mechanism for preventing iron-mediated DNA damage.\textsuperscript{32,34}

\textbf{Figure 2.12.} Depiction of where the potentials of iron(II) complexes lie in relation to the electrochemical window for the biological Fenton reaction.

Based on the findings presented in this chapter, it can be concluded that coordination of ligands to iron can significantly alter its electrochemical behavior. The ability to stabilize either oxidation state of iron (+2 or +3) is important not only to biological systems, but could also be used to tune the reactivity of iron complexes for use in catalysis.
Experimental Methods

General air-sensitive techniques under argon were used to synthesize the complexes unless otherwise stated. $^1$H and $^{19}$F{$^1$H} NMR spectra were obtained using a Bruker-AVANCE NMR spectrometer at 300 MHz. $^1$H NMR chemical shifts are reported in $\delta$ relative to tetramethylsilane (TMS) and referenced to solvent. $^{19}$F{$^1$H} NMR spectra were externally referenced to CCl$_3$F ($\delta$ 0).$^{43}$ Infrared spectra were obtained using Nujol mulls on KBr salt plates with a Magna 550 IR spectrometer. Abbreviations used in the description of vibrational data are as follows: vs, very strong; s, strong; m, medium; w, weak; b, broad. Electrospray ionization mass spectrometry (ESI-MS) was conducted using a QSTAR XL Hybrid MS/MS System from Applied Biosystems via direct injection of sample (0.05 mL/min flow rate) into a Turbo Ionspray ionization source. Samples were run under positive mode in methanol, with ionspray voltage of 5500 V, and in TOF scan mode. Peak envelopes match theoretical calculations for their ions. Elemental analyses were performed in-house on a Perkin Elmer 2400 Series II CHNS/O Elemental analyzer.

Methyl iodide, potassium borohydride, 3,5-dimethylpyrazole, precipitated sulfur, sulfur powder, and tetra-$n$-butylammonium bromide were purchased from Alfa Aesar; sodium hydride, diethyl ether, hydrated iron(II) chloride, diphenyl diselenide, and iron powder were purchased from Fisher/Acros; methanol, and acetonitrile were purchased from Mallinkrodt; chloroform and sodium sulfate were purchased from BDH; sodium tetraphenylborate was purchased from Lancaster; dry methanol was purchased from
Burdick; and diphenyl disulfide, 1-methylimidazole, and tetraphenylphosphonium chloride were purchased from TCI.

Iron(II) triflate,\textsuperscript{44} KTp*,\textsuperscript{45} Tpm*,\textsuperscript{46} sodium phenylselenolate (NaSePh),\textsuperscript{47,48} sodium phenylthiolate (NaSPh),\textsuperscript{47,48} 1,3-dimethylimidazole-2-thione,\textsuperscript{49} 1,3-dimethylimidazole-2-selone,\textsuperscript{49} and [Fe(SePh)\textsubscript{4}][(PPh\textsubscript{4})\textsubscript{2}]\textsuperscript{36} were synthesized using reported procedures. [Tpm*Fe(NCCH\textsubscript{3})\textsubscript{3}][(BPh\textsubscript{4})\textsubscript{2}] was synthesized according to the procedure reported for synthesizing [(Tpm*)Fe(NCCH\textsubscript{3})\textsubscript{3}][(BF\textsubscript{4})\textsubscript{2}].\textsuperscript{35}

\textit{Synthesis of [Tp*Fe(NCCH\textsubscript{3})\textsubscript{3}][BPh\textsubscript{4}], 3.} The potassium salt of Tp* (1) (0.168 g, 0.5 mmol) dissolved in acetonitrile (10 mL) was added dropwise using a cannula to a solution of Fe(OTf)\textsubscript{2} \cdot 2 CH\textsubscript{3}CN (0.5 mmol, 0.22 g) in acetonitrile (10 mL), and the solution was stirred for 30 min. A white precipitate formed and the solution turned gradually to a pale pinkish-red color. The white solid was separated using cannula filtration, and a solution of NaBPh\textsubscript{4} (0.171 g, 0.5 mmol) dissolved in acetonitrile (15 mL) was added and stirred overnight. The solution was concentrated by reducing the volume of the solvent to 2 mL, and a dull white solid precipitated. Ether (10 mL) was added to facilitate precipitation, and the light pink solid was separated by cannula filtration, washed with ether (2 × 5 mL), and vacuum dried. Total yield: 0.258 g, 65%. \textsuperscript{1}H NMR (acetone-d\textsubscript{6}): δ 59 (3H, 4-H(pz)), 39 (9H, -Me), 14 (9H, -Me), 6.95 (t, -Ph), 6.75 (t, -Ph). IR (cm\textsuperscript{-1}): 486 w, 596 w, 652 w, 721 m, 847 w, 1030 w, 1152 w, 1304 w, 1543 w, 1578 w, 2265 w, 2326 w, 2360 w, 2665 w, 2730 w.

\textit{Synthesis of [Fe(SPh)\textsubscript{4}][(PPh\textsubscript{4})\textsubscript{2}], 5.} Hydrated iron(II) chloride (1.0 g, 4.27 mmol) in acetonitrile (50 mL) was added dropwise to a stirring solution of sodium
phenylthiolate (2.31 g, 17.5 mmol) in acetonitrile (30 mL) and the resulting brown solution was then heated to 60°C for 30 min. Tetraphosphonium chloride (3.36 g, 8.96 mmol) was added and heated for an additional 15 min and filtered. Diethyl ether (40 mL) was added to the solution to facilitate crystallization, and the solution was stored overnight at -20°C to afford purplish-brown crystals. Total yield: 4.4 g, 88%. $^1$H NMR (DMSO-d$_6$): δ -24 (s, 8H, SPh m-H), 7.37 (s, 8H, PPh m-H), 7.79 (s, 4H, PPh o-H), 7.95 (s, 8H, PPh m-H), 20.5 (s, 8H, SPh m-H), 21.5 (s, 4H, SPh o-H).

**Synthesis of Fe(DImT)$_2$(OTf)$_2$.** 7. A mixture of 1,3-dimethylimidazole-2-thione (0.151 g, 1.2 mmol) and iron(II) triflate (0.25 g, 0.6 mmol) was dissolved in methanol (15 mL) and stirred for 12 h, resulting in a yellow solution. The solvent was removed *in vacuo*, and the green solid was extracted with dichloromethane (2 × 7 mL) and filtered. The filtrate was dried *in vacuo* to yield a bluish-green solid. Total yield: 0.269 g, 74%. $^1$H NMR (CD$_3$CN): δ 15.2 (2H, Im-H), 10 (2H, Im-H), 6.2 (3H, Im-Me), 5.9 (6H, Im-Me). $^{19}$F$^\{^1\text{H}\}$ NMR (CD$_3$CN): δ -74.5 (s). IR (cm$^{-1}$): 635 s, 678 w, 757 w, 801 w, 1035 vs, 1091 w, 1174 vs, 1260 vs, 1561 m, 1655 w, 2345 w, 2373 w, 3126 m, 3152 m, 3484 b. Mass spectrum (ESI-MS): m/z 460.9 [Fe(DImT)$_2$(OTf)]$^+$, 318.9 [Fe(DImT)$_2$]+. Anal. Calc. for FeC$_{12}$H$_{16}$S$_4$F$_6$O$_6$N$_4$: C, 19.66; N, 10.49; H, 2.62. Found: C, 18.77; N, 10.91; H, 3.01.

**Synthesis of Fe(DImSe)$_2$(OTf)$_2$.** 8. A mixture of 1,3-dimethylimidazole-2-selone (0.208 g, 1.2 mmol) and iron(II) triflate (0.25 g, 0.6 mmol) was dissolved in methanol (20 mL) and stirred for 12 h, resulting in an orange solution. The solvent was removed *in vacuo*, extracted with dichloromethane (2 × 7 mL), and filtered. The filtrate was dried *in vacuo*,
vacuo to yield a dark red solid. Total yield: 0.193 g, 46%. $^1$H NMR (CD$_3$CN): $\delta$ 16.3 (2H, Im-H), 11.2 (2H, Im-H), 6.2 (3H, Im-Me), 5.9 (6H, Im-Me). $^{19}$F{$^1$H} NMR (CD$_3$CN): $\delta$ -75 (s). IR (cm$^{-1}$): 638 w, 740 w, 798 m, 1029 vs, 1094 m, 1155 s, 1259 vs, 1561 m, 1655 w, 2345 w, 2373 w, 3108 m, 3142 m, 3449 b. Calc. for FeC$_{12}$H$_{16}$S$_2$F$_6$O$_6$N$_4$Se$_2$: C, 17.04; N, 9.09; H, 2.27. Found: C, 18.07; N, 10.21; H, 2.31.

**Electrochemical studies of synthesized iron(II) complexes.** Cyclic voltammetry (CV) experiments were carried out using CHI Electrochemical analyzer and employed a three-electrode cell consisting of glassy carbon working electrode, a Ag/AgCl reference electrode, and a platinum wire auxiliary electrode. The glassy carbon electrode was polished with alumina prior to each trial. CV experiments were conducted in acetonitrile containing 0.1 mM complex and 0.1 M tetra-n-butyl ammonium hexafluorophosphate (TBAPF$_6$) at a scan speed of 0.1 V/s from -1.25 V to 1.25 V. Solutions were deoxygenated with dry nitrogen gas and maintained under a blanket of nitrogen during measurements, and voltammograms were referenced to the ferrocene/ferricenium couple (Fc$^{+/0}$) at 0.46 V.$^{50}$ Formal potentials were evaluated as $E_{1/2} = (E_{pa}+E_{pc})/2$, where $E_{pa}$ and $E_{pc}$ are anodic and cathodic peak potentials.

**References**


(41) Sathyamurthy, R.; Brumaghim, J. L., unpublished results.


CHAPTER THREE
SYNTHESIS AND CHARACTERIZATION OF RUTHENIUM(II) COMPLEXES
CONTAINING TRIS(PYRAZOLYL) BORATE AND –METHANE LIGANDS

Introduction

Although ruthenium is not a biologically essential metal like iron, ruthenium complexes are of biological interest. They have been shown to aid in the treatment of the rejection of cadaver skin grafting,\textsuperscript{1} autoimmune deficiencies,\textsuperscript{2} and the kinetic study of glutathione oxidation.\textsuperscript{3} It is also of interest in cancer treatment; the discovery of cisplatin-resistant forms of cancer has lead researchers to investigate transition metal-based chemotherapeutic drugs in addition to platinum drugs that could interact with DNA, such as the ruthenium-containing compound NAMI-A, to help combat aggressive cancer cell lines.\textsuperscript{4,5} The advantage to using ruthenium in this work is that it is in the same group as iron, but it is a soft, inert metal unlike borderline iron(II). Ruthenium(II) is also diamagnetic, unlike its paramagnetic iron(II) cousin, making NMR data evaluation more tractable. These properties make ruthenium(II) ideal for coordination studies related to iron(II) and can also be a useful substitute for iron(II) in biological studies of DNA binding.

Ruthenium(II) arene complexes of the type [(η\textsuperscript{6}-arene)Ru(X)(Y)(Z)] (arene = substituted benzene, X, Y, Z = halides, acetonitrile, isonicotinamide; Figure 3.1) exhibit a similar inhibition of cell growth to that of carboplatin, an analog of cisplatin (Figure 3.1), and \textsuperscript{1}H NMR spectroscopy indicated that the metal center was strongly bound to the
The use of capping N,N,N-type ligands, such as the Tp-type ligands, in ruthenium-based complexes may allow the study of how ruthenium(II) interacts with DNA. Tp-type ruthenium complexes, such as $[\text{TpmRuCl(NCCH}_3)_2][\text{PF}_6]$, have shown significant cytotoxicity against breast (MCF-7) and cervical (HeLa) cancer cell lines. 

![Figure 3.1. Structures of $[(\eta^6\text{-arene})\text{Ru}(X)(Y)(Z)]$ (left), and carboplatin (right).](image)

Much work is also being conducted to develop ruthenium catalysts that improve reaction efficiency in an effort to advance the principles of green chemistry. Various coordination complexes of ruthenium exhibit industrially-significant catalytic properties. For example, the complex $\text{RuH}_2(\text{PPh}_3)_4$ (Figure 3.2) catalyzes the conversion of nitriles to amides, esterification using alcohols and nitriles, and the polymerization of nylon-6,6, among other reactions. The most notable ruthenium-based catalysts, the Grubbs catalysts (Figure 3.2), enable various olefinic metatheses such as in ring-opening polymerization and ring closures. By using these catalytic synthetic methods,
improvements can be made in various organic reactions’ atom efficiencies and their selectivity.

Figure 3.2. Structures of RuH₂(PPh₃)₄ (left), Grubbs catalyst, 1st generation (Cy = cyclohexane; middle), and Grubbs catalyst, 2nd generation (right).

The primary ruthenium source for organometallic and coordination chemistry is ruthenium(III) chloride hydrate, used to synthesize the commonly-used synthons RuCl₂(PPh₃)₃¹⁰ and polymeric [RuCl₂(COD)]ₓ¹¹ (COD = 1,5-cyclooctadiene; Figure 3.3). Use of RuCl₂(PPh₃)₃ and [RuCl₂(COD)]ₓ in subsequent reactions results in complexes that contain triphenylphosphine or COD ligands, substituents that are undesirable in further substitution reactions due to their tendency to crowd available coordination sites because of their steric bulk. Another reported ruthenium starting material, [Ru(NCCH₃)₆][ZnCl₄]¹² does not have the issues with sterically-bulk ligands in its coordination sphere, but is an undesirable material to use in subsequent coordination reactions, since competitive binding of the coordinating ligands may occur between the ruthenium cation and the zincate anion.

The family of tris(acetonitrile) tris(pyrazolyl) ruthenium(II) complexes are of great interest, since these would make excellent synthons for a variety of ruthenium
chemistry. However, there are few reports of the synthesis of these complexes. Synthesis of Tp-type ruthenium(II) complexes of the formula [Tp\(^R\)Ru(NCCH\(_3\))\(_3\)]\([X]\) (R = H, Me, \(^i\)Pr; X = PF\(_6\), OTf) requires multiple steps and the use of many chemicals, but synthesis of [TpRu(NCCH\(_3\))\(_3\)]\([PF_6]\)\(^{13}\) (Scheme 3.1), [Tp\(^*\)Ru(NCCH\(_3\))\(_3\)]\([OTf]\)\(^{14}\) (Scheme 3.2), and [TpiPrRu(NCCH\(_3\))\(_3\)]\([OTf]\)\(^{15}\) (Scheme 3.2) have all been reported. Interestingly, there are no reports of syntheses of analogous Tpm-type ruthenium(II) complexes of the formula [Tpm\(^R\)Ru(NCCH\(_3\))\(_3\)]\([X]^2\) (R = H, Me, \(^i\)Pr, Ph; X = PF\(_6\), OTf). Closely related Tpm-type ruthenium(II) complexes that have been reported also require many steps to synthesize, including [TpmRuCl(NCCH\(_3\))\(_2\)]\([PF_6]\)\(^6\) (Scheme 3.3) and [TpmRu(OH\(_2\))\(_3\)]\([OTs]^2\)\(^{16}\) (Scheme 3.3). This chapter presents a new method to synthesize hexakis(acetonitrile) ruthenium(II) complexes containing uncoordinated nonmetallic counteranions and tris(acetonitrile) tris(pyrazolyl)borato ruthenium(II) complexes with reduced reaction times, and a general method to synthesize novel tris(acetonitrile) tris(pyrazolyl)methano ruthenium(II) complexes (Figure 3.4).
Scheme 3.1

\[
\text{RuCl}_3 \cdot 3 \text{H}_2\text{O} \xrightarrow{\text{COD, EtOH, reflux 24 h}} \left(\begin{array}{c}
\text{Ru} \\
\text{Cl} \\
\text{Cl}
\end{array}\right)_n
\]

\[
n \text{KTP} \xrightarrow{\text{THF, reflux 5 h}}
\]

Scheme 3.2

\[
\text{EtOH, reflux 3 h}
\]

\[
\text{LiB(CH}_3\text{CH}_3)_3\text{H} \xrightarrow{\text{THF, -78°C 1 h}}
\]

\[
\text{KTP}^R \\
R = \text{CH}_3, \text{iPr}
\]

\[
\text{CF}_3\text{SO}_3\text{H} \xrightarrow{\text{THF, -80°C 1 h, r.t. 1 h}}
\]

\[
\text{H}_2 \xrightarrow{\text{pentane, 15 h}}
\]
Scheme 3.3

Scheme 3.4. Structures of target ruthenium(II) complexes discussed in this chapter.

Results and Discussion

Synthesis and characterization of hexakis(acetonitrile) ruthenium(II) starting materials. The only reported syntheses of hexakis(acetonitrile) ruthenium(II) starting materials are those of [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] (1),$^{20}$ reported in 1974, and [Ru(NCCH$_3$)$_6$][ZnCl$_4$],$^{12}$ reported in 2001. Surprisingly, these complexes have not been
utilized as starting materials for additional ruthenium chemistry; this is most likely because 1 requires many steps to synthesize (Scheme 3.4) and the ruthenium(II) zincate species contains a counteranion capable of ligand coordination that would cause undesired competitive binding. Reported characterization was limited to IR and $^1$H NMR spectroscopy, as well as elemental analysis, for both reported [Ru(NCCH$_3$)$_6$]$^{2+}$ species.

Scheme 3.4

Using an improved synthetic method, two [Ru(NCCH$_3$)$_6$][(X)$_2$] complexes (X = BF$_4^-$; 1 and X = OTf$^-$; 2) were prepared similarly to that of [Ru(NCCH$_3$)$_6$][ZnCl$_4$],$^{12}$ but with a counteranion exchange step (with NaBF$_4$ or NaOTf) after reduction of the
ruthenium to remove the zincate anion. After workup, a light yellow solid is obtained (Figure 3.5). Using this procedure, 1 and 2 were obtained in yields of 66% and 60%, respectively, as compared to 80% for the previous preparation of 1 and 36% for the zincate species. Overall, synthesis of 1 using this method is significantly shorter with three fewer steps, and results in a product without a counterion capable of ligand coordination (Table 3.1).

\[
\begin{align*}
2 \text{RuCl}_3 \cdot 3 \text{H}_2\text{O} & \xrightarrow{\text{Zn, CH}_3\text{CN, reflux 1 h}} \text{[Ru(NCCH}_3)_6][\text{ZnCl}_4] + \text{RuCl}_2(\text{NCCH}_3)_4 \\
& \xrightarrow{4 \text{NaX, reflux 16 h}} 2 \text{[Ru(NCCH}_3)_6][(\text{X})_2] + 4 \text{NaCl} + \text{ZnCl}_2
\end{align*}
\]

\[X = BF_4^- , OTf^-\]

**Figure 3.5.** Synthesis of ruthenium(II) starting materials.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Steps</th>
<th>Reaction Time</th>
<th>% Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ru(NCCH(_3)_3][BF(_4)]_2</td>
<td>4</td>
<td>60 h</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>[Ru(NCCH(_3)_3][ZnCl(_4)]</td>
<td>1</td>
<td>2 h</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>[Ru(NCCH(_3)_3][BF(_4)]_2</td>
<td>1</td>
<td>13 h</td>
<td>66</td>
<td>This work</td>
</tr>
<tr>
<td>[TpRu(NCCH(_3)_3][PF_6]</td>
<td>3</td>
<td>33 h</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>[TpRu(NCCH(_3)_3][BF(_4)]_2</td>
<td>1</td>
<td>1 h</td>
<td>56</td>
<td>This work</td>
</tr>
<tr>
<td>[Tp*Ru(NCCH(_3)_3][OTf]</td>
<td>7</td>
<td>46 h</td>
<td>72</td>
<td>14</td>
</tr>
<tr>
<td>[Tp*Ru(NCCH(_3)_3][OTf]</td>
<td>1</td>
<td>30 min</td>
<td>65</td>
<td>This work</td>
</tr>
<tr>
<td>[Tp(^\text{Ph})Ru(NCCH(_3)_3][OTf]</td>
<td>1</td>
<td>15 min</td>
<td>53</td>
<td>This work</td>
</tr>
<tr>
<td>[Tpm*Ru(NCCH(_3)_3][BF(_4)]_2</td>
<td>1</td>
<td>12 h</td>
<td>72</td>
<td>This work</td>
</tr>
<tr>
<td>[Tpm(^\text{Ph})Ru(NCCH(_3)_3][OTf]_2]</td>
<td>1</td>
<td>8 h</td>
<td>22</td>
<td>This work</td>
</tr>
</tbody>
</table>

**Table 3.1.** List of synthetic parameters for selected ruthenium(II) acetonitrile complexes.
Characterization of 1 and 2 matches reported values for $^1$H NMR and IR spectra. In both cases, the bound acetonitrile shifts downfield in the $^1$H NMR spectrum to δ 2.68 and 2.52, respectively, compared to δ 2.10 for unbound acetonitrile. The IR spectra for both 1 and 2 show nitrile stretching frequencies of 2326 cm$^{-1}$ and 2373 cm$^{-1}$, consistent with reported values of 2300 cm$^{-1}$ and 2325 cm$^{-1}$ for nitrile stretches of 1 and the ruthenium(II) zincate species. This shift to higher energies upon ruthenium(II) binding relative to free acetonitrile (2250 cm$^{-1}$) indicates an increased nitrile bond strength due to donor bond formation upon ruthenium(II) complexation.

Single crystal X-ray diffraction data was collected for [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] (1), which crystallized as colorless cubes by slow vapor diffusion of diethyl ether into an acetonitrile solution, and compared to the reported structure of [Ru(NCCH$_3$)$_6$][ZnCl$_4$]. Selected bond lengths for 1 are summarized in Table 3.2, and its structure is shown in Figure 3.6. 1 crystallized with a unit cell in the monoclinic $P2_1/c$ with unit cell dimensions of $a = 8.0993(16)$, $b = 8.1969(16)$, $c = 15.877(3)$ Å, $\alpha = 90.00$, $\beta = 92.78(3)$, $\gamma = 90.00^\circ$, whereas the zincate species crystallized with a unit cell in the trigonal $R-3$ space group with larger unit cell dimensions than 1 ($a = 11.744$, $b = 11.744$, $c = 30.932$ Å, $\alpha = 90.000$, $\beta = 90.000$, $\gamma = 120.00^\circ$). Similar average Ru-N bond distances of 2.03(7) Å were observed for the two [Ru(NCCH$_3$)$_6$]$^{2+}$ species. The packing structure of 1 shows a close contact between F(2) and the H on C(6) (2.50 Å) that is smaller than the sum of their van der Waal radii (2.67 Å) and can be seen in the packing diagram viewed along the $a$-axis (Figure 3.7). No interactions are observed between ions for the [Ru(NCCH$_3$)$_6$][ZnCl$_4$] structure. With an improved synthetic method for
Ru[(NCCH$_3$)$_6$]$^{2+}$ species 1 and 2, these materials can be used as synthons to synthesize tris(acetonitrile) ruthenium(II) complexes with trinitrogen donor ligands.

Table 3.2. Selected bond lengths [Å] and angles [°] for [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] (1).

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Distance/Angle [Å/°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru(1)-N(2)</td>
<td>2.023(3)</td>
</tr>
<tr>
<td>Ru(1)-N(3)</td>
<td>2.024(3)</td>
</tr>
<tr>
<td>Ru(1)-N(1)</td>
<td>2.028(3)</td>
</tr>
<tr>
<td>N(2)-C(5)</td>
<td>1.133(4)</td>
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<tr>
<td>N(3)-C(7)</td>
<td>1.130(4)</td>
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<td>N(1)-C(3)</td>
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<tr>
<td>F(2)-B(1)</td>
<td>1.395(6)</td>
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<td>F(3)-B(1)</td>
<td>1.398(6)</td>
</tr>
<tr>
<td>F(4)-B(1)</td>
<td>1.397(5)</td>
</tr>
<tr>
<td>F(1)-B(1)</td>
<td>1.390(6)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.449(5)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.461(5)</td>
</tr>
<tr>
<td>C(6)-C(5)</td>
<td>1.451(5)</td>
</tr>
<tr>
<td>N(2)-Ru(1)-N(3)</td>
<td>90.14(11)</td>
</tr>
<tr>
<td>N(2)-Ru(1)-N(1)</td>
<td>89.30(11)</td>
</tr>
<tr>
<td>N(3)-Ru(1)-N(1)</td>
<td>91.79(11)</td>
</tr>
<tr>
<td>C(5)-N(2)-Ru(1)</td>
<td>175.8(3)</td>
</tr>
<tr>
<td>C(7)-N(3)-Ru(1)</td>
<td>174.6(3)</td>
</tr>
<tr>
<td>C(3)-N(1)-Ru(1)</td>
<td>173.4(3)</td>
</tr>
<tr>
<td>F(1)-B(1)-F(2)</td>
<td>108.2(4)</td>
</tr>
<tr>
<td>F(1)-B(1)-F(4)</td>
<td>110.8(4)</td>
</tr>
<tr>
<td>F(2)-B(1)-F(4)</td>
<td>108.6(4)</td>
</tr>
<tr>
<td>F(1)-B(1)-F(3)</td>
<td>109.9(4)</td>
</tr>
<tr>
<td>F(2)-B(1)-F(3)</td>
<td>109.7(4)</td>
</tr>
<tr>
<td>F(4)-B(1)-F(3)</td>
<td>109.5(4)</td>
</tr>
<tr>
<td>N(3)-C(7)-C(8)</td>
<td>179.4(4)</td>
</tr>
<tr>
<td>N(1)-C(3)-C(4)</td>
<td>178.0(4)</td>
</tr>
<tr>
<td>N(2)-C(5)-C(6)</td>
<td>178.7(4)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms: -x+2,-y,-z+2
Figure 3.6. Crystal structure diagram of [Ru(NCCH\textsubscript{3})\textsubscript{6}][(BF\textsubscript{4})\textsubscript{2}]. Density surfaces show 50% probability ellipsoids.

Synthesis and characterization of the tris(pyrazolyl)borato-type tris(acetonitrile) ruthenium(II) complexes. The only reported complexes of the formula [Tp\textsuperscript{R}Ru(NCCH\textsubscript{3})\textsubscript{3}]\textsuperscript{+} are [TpRu(NCCH\textsubscript{3})\textsubscript{3}][PF\textsubscript{6}],\textsuperscript{13} [Tp\textsuperscript{*}Ru(NCCH\textsubscript{3})\textsubscript{3}][OTf],\textsuperscript{14} and [Tp\textsuperscript{ip}Ru(NCCH\textsubscript{3})\textsubscript{3}][OTf].\textsuperscript{15} These complexes have not been utilized as starting materials for other ruthenium chemistry, likely because of the time and number of steps required to synthesize the materials (Schemes 3.1 and 3.2). Using [Ru(NCCH\textsubscript{3})\textsubscript{6}]\textsuperscript{2+} complexes 1 and 2 as starting materials, complexes of the formula
Figure 3.7. Packing diagram of [Ru(NCCH\(_3\))\(_6\)][(BF\(_4\))]\(_2\) viewed along the \(a\)-axis of the unit cell.

[Tp\(^8\)Ru(NCCH\(_3\))\(_3\)][X] (R = H, Me, Ph; X = BF\(_4\), OTf) were synthesized according to a new procedure (Figure 3.8; Table 3.1).

The first complexes made using the improved procedure, [TpRu(NCCH\(_3\))\(_3\)][BF\(_4\)] (3) and [Tp\(^*\)Ru(NCCH\(_3\))\(_3\)][OTf] (4), have yields of 56% and 65%, respectively as compared to reported yields of 70% and 72%, respectively\(^{13,14}\). However, the improved synthetic method significantly cuts the number of steps (by two for 3, six for 4) and the amount of time to obtain a final product (by 35 h and 44 h for 3 and 4, respectively) with only an average yield reduction of 15%. Previous reports have characterized 3 using IR, \(^1\)H, and \(^{13}\)C{\(^1\)H} NMR spectroscopies as well as elemental analysis\(^{13}\), whereas 4 was
Figure 3.8. Synthesis of [Tp^R-Ru(NCCH_3)_3][X].

previously characterized using ^1H NMR spectroscopy and elemental analysis. Characterization of 3 and 4 match reported values for ^1H NMR spectra, and the ^19F{^1H} NMR spectra shows a single resonance for 3 and 4 (δ -148.3 and -77.8, respectively), indicating that the counteranion is not coordinated to the ruthenium center. The IR spectra of both 3 and 4 showed a vibrational energy for the bound acetonitrile ligands at 2344 cm^{-1} and 2472 cm^{-1}, respectively, compared to 2326 and 2373 cm^{-1} for [Ru(NCCH_3)_6]^{2+} species 1 and 2, respectively. The increased nitrile bond energy for both 3 and 4 indicates stronger σ-bonding of the bound acetonitriles occurs upon addition of a Tp-type ligand.

A new complex, [Tp^Ph-Ru(NCCH_3)_3][OTf] (5), was also synthesized using this new procedure with a yield of 53%. In the ^1H NMR spectrum for 5, two separate resonances are now observed for both the ortho and meta protons on the phenyl
substituents, indicating that the corresponding protons on the phenyl rings are not equivalent. The \(^{19}\text{F}\{^{1}\text{H}\}\) NMR spectrum shows a slight downfield shift to \(\delta\) -77.7 as compared to \(\delta\) -79.3 for 2, indicating that the triflate counteranion is still not coordinated to the ruthenium center, although there may be some competition in binding between the triflate and the Tp\(^{\text{Ph}}\) ligand. The IR spectrum of 5 showed an decreased vibrational energy for the bound acetonitrile ligands of 2345 cm\(^{-1}\) compared to 2373 cm\(^{-1}\) for [Ru(NCCH\(_{3}\))\(_{6}\])\(^{2+}\) species 2, similar to the shift observed for the Tp\(^{*}\) analog 4. This result shows stronger backbonding of the acetonitriles to the ruthenium center, even with the increased steric bulk on the Tp\(^{\text{Ph}}\) ligand.

*Synthesis and characterization of new tris(pyrazolyl)methane-type tris(acetonitrile) ruthenium(II) complexes.* Two new complexes of the formula [Tpm\(^{R}\)Ru(NCCH\(_{3}\))\(_{3}\])\(^{2+}\) were synthesized using the same improved procedure for synthesizing the [Tp\(^{R}\)Ru(NCCH\(_{3}\))\(_{3}\])\(^{+}\) complexes. Synthesis of [Tpm\(^{*}\)Ru(NCCH\(_{3}\))\(_{3}\][(BF\(_{4}\))\(_{2}\)] (6) and [Tpm\(^{\text{Ph}}\)Ru(NCCH\(_{3}\))\(_{3}\][(OTf)\(_{2}\)] (7) takes only one step and 16 h (including work-up) to prepare (Figure 3.9) with yields of 72% and 22%, respectively (Table 3.1). The \(^{1}\text{H}\) NMR spectra for 6 and 7 show the same pattern of resonances observed for analogous Tp\(^{*}\) and Tp\(^{\text{Ph}}\) ruthenium complexes, 4 and 5, respectively. As seen for these Tp\(^{R}\) ruthenium complexes, the resonance for the bound acetonitrile ligands shifts downfield (\(\delta\) 1.60 and 2.62 for 6 and 7, respectively), compared to \(\delta\) 2.68 and 2.52 for the bound acetonitrile in [Ru(NCCH\(_{3}\))\(_{6}\])\(^{2+}\) starting materials 1 and 2, respectively. The \(^{13}\text{C}\{^{1}\text{H}\}\) NMR spectrum of 6 show similar shifting to the Tp\(^{R}\) analogs 4. The \(^{19}\text{F}\{^{1}\text{H}\}\) NMR spectra for 6 and 7 indicate that the counteranion is not
coordinated to the ruthenium center, as their $^{19}$F resonances did not shift compared to the resonances of the $[\text{Ru(NCCH}_3)_6]^{2+}$ starting materials.

\[ [\text{Ru(NCCH}_3)_6][\text{X}]_2 \xrightarrow{\text{Tpm}^R} \text{CH}_3\text{OH}, \text{reflux 18 h} \]

\[ 6: R = \text{Me}, \text{X} = \text{BF}_4^- \]

\[ 7: R = \text{Ph}, \text{X} = \text{OTf}^- \]

**Figure 3.9.** Synthesis of $[\text{Tpm}^R\text{Ru(NCCH}_3)_3][\text{X}]_2$.

The IR spectra of $[(\text{Tpm}^K)\text{Ru(NCCH}_3)_3][\text{X}]_2$ complexes 6 (R = Me, X = BF$_4^-$) and 7 (R = Ph, X = OTf) both show a nitrile stretching frequency of 2345 cm$^{-1}$, compared to 2326 and 2373 cm$^{-1}$ for $[\text{Ru(NCCH}_3)_6]^{2+}$ species 1 and 2, respectively. The increased nitrile bond energy for 6 indicates that stronger $\sigma$-bonding of the bound acetonitrile ligands occurs upon addition of a Tpm$^*$ ligand, whereas the decreased nitrile bond energy for 7 indicates stronger backbonding of the bound acetonitrile ligands to the ruthenium center upon adding a Tpm$^{\text{Ph}}$ ligand.

Many attempts were made to synthesize $[\text{TpmRu(NCCH}_3)_3][\text{X}]_2$ (X = BF$_4$, OTf) without success. The synthetic procedure outlined in Figure 3.9 was attempted in
multiple solvents (acetonitrile, methanol, ethanol, THF, dichloromethane, DMF, toluene), varying reaction times (4 h to 60 h), and varying temperatures (from room temperature to reflux). All \(^1\)H NMR spectra of the reaction mixtures indicated no coordination of the Tpm ligand to ruthenium(II).

Comparison of the syntheses of tris(pyrazolyl) ruthenium(II) complexes. The data in Table 3.2 clearly shows that synthesis of the reported complexes 3 – 7 require a large number of steps and long times, making these synthons less desirable to use in ruthenium chemistry than the commonly used synthons such as TpRuCl(COD),\(^{17}\) TpRuCl(PPh\(_3\))\(_2\),\(^{18}\) and [TpmRuCl(PPh\(_3\))\(_2\)][BF\(_4\)]\(^{19}\) (Figure 3.10). In contrast, complexes of the formula [Tp\(^R\)Ru(NCCH\(_3\))\(_3\)][X] (R = H, Me, Ph; X = BF\(_4\), OTf) synthesized according to the new procedure (Figure 3.5) require only one step and 5 h preparation times. This procedure has also enabled synthesis of new Tpm\(^R\) complexes [Tpm\(^*\)Ru(NCCH\(_3\))\(_3\)][(BF\(_4\))]\(_2\) and [Tpm\(^\text{Ph}\)Ru(NCCH\(_3\))\(_3\)][(OTf)]\(_2\) in one step with up to 16 h preparation times.

![Figure 3.10](image-url)  
*Figure 3.10.* (Tp)RuCl(COD) (left), (Tp)RuCl(PPh\(_3\))\(_2\) (middle), and [(Tpm)RuCl(PPh\(_3\))\(_2\)][BF\(_4\)] (right).
The reaction times needed to synthesize the Tp⁰ (15 min to 1 h) ruthenium(II) complexes are surprisingly fast considering the inert nature of ruthenium(II), and they follow a trend based on the ligand charge and their steric bulk. Charged trinitrogen donor ligands expectedly require less reaction time than uncharged donors (8 to 12 h for the Tpm* and Tpm⁰ complexes, respectively), thus in increasing reaction time, Tp⁰ < Tp* < Tp < Tpm⁰ < Tpm*. The syntheses also decrease in reaction time as the steric bulk of the trinitrogen donor is increased in the order Tp⁰ < Tp* < Tp and Tpm⁰ < Tpm*.

**Electrochemistry of ruthenium(II) complexes.** Cyclic voltammetry was performed on ruthenium(II) acetonitrile-containing complexes 1 and 3 – 7 to determine how changing the charge and steric bulk of the Tp-type ligands affects the Ru²⁺/³⁺ redox potentials (Table 3.3). The Ru²⁺/³⁺ potentials indicate that the charge on Tp-type ligands has a significant effect on Ru²⁺/³⁺ electrochemical potentials. The Tp* analog 4 (0.498 V vs. NHE) has a slightly higher potential than its Tpm* analog, 6 (0.390 V), and the Tp⁰ analog 5 (0.595 V) has a slightly higher potential than its Tpm⁰ analog 7 (0.552 V), indicating that charged Tp-type ligands better stabilize ruthenium(III) relative to ruthenium(II). These results agree with the nitrile bond frequencies for 4 and 6, (2472 cm⁻¹ and 2345 cm⁻¹, respectively) indicating that σ-donor bonding of the bound acetonitriles in 4 is more significant than in 6.

The Ru²⁺/³⁺ potentials in Table 3.3 also indicate that [TpRu(NCCH₃)₃]⁺ (3) has a lower Ru²⁺/³⁺ potential (0.489 V vs. NHE) than both the Tp* analog 4 (0.498 V) and the Tp⁰ analog 5 (0.595 V). A similar trend of increasing potentials is also observed for the neutral Tpm* complex 6 (0.390 V) and the Tpm⁰ complex 7 (0.552 V). Comparison of
Table 3.3. Ru$^{2+/3+}$ potentials for target complexes ($E$ vs. NHE).

<table>
<thead>
<tr>
<th>Complex</th>
<th>$E_{pa}$ (V)</th>
<th>$E_{pc}$ (V)</th>
<th>$\Delta E$ (V)</th>
<th>$E_{1/2}$ (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] (1)</td>
<td>0.410</td>
<td>0.623</td>
<td>0.213</td>
<td>0.517</td>
</tr>
<tr>
<td>[TpRu(NCCH$_3$)$_3$][BF$_4$] (3)</td>
<td>0.352</td>
<td>0.625</td>
<td>0.273</td>
<td>0.489</td>
</tr>
<tr>
<td>[Tp*Ru(NCCH$_3$)$_3$][OTf] (4)</td>
<td>0.415</td>
<td>0.580</td>
<td>0.165</td>
<td>0.498</td>
</tr>
<tr>
<td>[Tp$_{Ph}$Ru(NCCH$_3$)$_3$][BF$_4$] (5)</td>
<td>-0.457</td>
<td>1.65</td>
<td>2.11</td>
<td>0.595</td>
</tr>
<tr>
<td>[Tpm*Ru(NCCH$_3$)$_3$][(BF$_4$)$_2$] (6)</td>
<td>0.099</td>
<td>0.681</td>
<td>0.582</td>
<td>0.390</td>
</tr>
<tr>
<td>[Tpm$_{Ph}$Ru(NCCH$_3$)$_3$][(BF$_4$)$_2$] (7)</td>
<td>-0.500</td>
<td>1.603</td>
<td>2.10</td>
<td>0.552</td>
</tr>
</tbody>
</table>

The Ru$^{2+/3+}$ potentials of these complexes shows that the steric bulk of analogous Tp$^R$-type ligands ($R = H, Me, Ph$) has a modest effect on the redox potential of ruthenium(II), stabilizing ruthenium(II) relative to ruthenium(III), where $Tp_{Ph}^R < Tp^* < Tp$ and $Tpm_{Ph}^R < Tpm^*$. A similar trend was also observed for the Tp-type complexes of copper(I) complexes of the formula $Tp^R Cu(NCCH_3)$ and $[Tpm^R Cu(NCCH_3)][X]$ ($R = H, Me, iPr; X = Cl, BF_4$). Overall, using Tp-type ligands of varying steric bulk can change the Ru$^{2+/3+}$ potential by over 200 mV.

Conclusions. An improved synthetic method has been developed for [Ru(NCCH$_3$)$_6$]$^{2+}$ starting materials and the Tp-type ruthenium(II) tris(acetonitrile) series of complexes that only requires one step in the synthetic procedure. Using a similar synthetic pathway, a novel series of Tpm-type ruthenium(II) tris(acetonitrile) complexes were synthesized that may be used for comparative purposes with its Tp-type analogs. This new synthetic method to synthesize these Tp- and Tpm-type tris(acetonitrile) ruthenium(II) complexes will help open up ruthenium chemistry in catalysis and DNA
binding, where these complexes can be used as synthons.

Understanding the redox chemistry of ruthenium with nitrogen donor ligands can give us insight into how ruthenium complexes behave in biological systems. Coordination of Tp-type ligands to ruthenium can significantly alter Ru$^{2+/3+}$ electrochemical potentials from 0.390 V to 0.595 V. Steric bulk, rather than the charge of the Tp-type ligands, is the predominant factor that controls Ru$^{2+/3+}$ redox potential. This ability to stabilize either oxidation state of ruthenium (+2 or +3) may be used to tune catalytic reactions and provide insight into how ruthenium may behave when bound to DNA.

**Experimental Methods**

General air-sensitive techniques under argon were used to synthesize the complexes unless otherwise stated. $^1$H, $^{13}$C{$^1$H}, and $^{19}$F{$^1$H} NMR spectra were obtained using 300 and 500 MHz Bruker-AVANCE NMR spectrometers. $^1$H and $^{13}$C{$^1$H} NMR chemical shifts are reported in $\delta$ relative to tetramethylsilane (TMS) and referenced to solvent. $^{19}$F{$^1$H} NMR spectra were externally referenced to CCl$_3$F ($\delta$ 0$^{19}$). Infrared spectra were obtained using Nujol mulls on KBr salt plates with a Magna 550 IR spectrometer. Abbreviations used in the description of vibrational data are as follows: vs, very strong; s, strong; m, medium; w, weak; b, broad. Electrospray ionization mass spectrometry (ESI-MS) was conducted using a QSTAR XL Hybrid MS/MS System from Applied Biosystems via direct injection of sample (0.05 mL/min flow rate) into a Turbo Ionspray ionization source. Samples were run under positive mode in methanol, with
ionspray voltage of 5500 V, and in TOF scan mode. Peak envelopes match theoretical calculations for their ions.

Elemental analyses were performed in-house on a Perkin Elmer 2400 Series II CHNS/O Elemental analyzer. The elemental analysis for the acetonitrile-containing ruthenium complexes (1 – 7) were within 3% of the values calculated for the tetrahedral complexes resulting from the loss of two acetonitrile ligands. This loss of two acetonitrile ligands resulted from drying in vacuo for approximately 4 h., as has been previously reported for the iron(II) triflate complex.  

Ruthenium(III) chloride hydrate was purchased from Pressure Chemical; potassium borohydride, 3,5-dimethylpyrazole, sodium tetrafluoroborate, and tetra-n-butylammonium bromide were purchased from Alfa Aesar; diethyl ether was purchased from Fisher/Acros; methanol and acetonitrile were purchased from Mallinkrodt; chloroform was purchased from BDH; sodium triflate was purchased from TCI; and dry methanol was purchased from Burdick. KTp, KTp*, KTpPh, Tpm, Tpm*, and TpmPh were synthesized using reported procedures.

Syntheses of [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] (1) and [Ru(NCCH$_3$)$_6$][(OTf)$_2$] (2). A new method was used to synthesize 1. Zinc powder (0.23 g, 3.60 mmol) was added to a solution of ruthenium(III) chloride hydrate (2.0 g, 7.15 mmol) in acetonitrile (150 mL) and the mixture was heated to reflux for 30 min. The mixture turned from black to yellow during this time. The reaction mixture was filtered, sodium tetrafluoroborate (1.65 g, 15.0 mmol) was added to the filtrate, and the solution was heated to reflux for an additional 12 h, during which time a white precipitate formed. The solution was again
filtered and the solvent was removed *in vacuo*. The light yellow powder was washed with ether to remove any excess zinc salts. Crystals of X-ray quality were grown by vapor diffusion of diethyl ether into acetonitrile. Yield: 2.47 g (66%). The synthesis for 2 is the same as for 1, except that sodium triflate (2.59 g, 15.0 mmol) was added instead of sodium tetrafluoroborate. Yield: 2.78 g (60%). $^1$H NMR ($d_6$-DMSO) and IR (Nujol, cm$^{-1}$) spectra of 1 and 2 match reported values.$^{12,21}$ For 1: $^{13}$C{$^1$H} NMR ($d_6$-DMSO): $\delta$ 4.01 (CH$_3$CN), 126.9 (CH$_3$CN). $^{19}$F{$^1$H} NMR ($d_6$-DMSO): $\delta$ -148.3 (s). Anal. Calc. for RuC$_8$H$_{10}$F$_8$N$_4$: C, 21.88; N, 12.76. Found: C, 22.92; N, 13.32.

For 2: $^{13}$C{$^1$H} NMR spectrum identical to 1. $^{19}$F{$^1$H} NMR ($d_6$-DMSO): $\delta$ -79.3 (s). Anal. Calc. for RuC$_{10}$H$_{10}$S$_2$F$_6$O$_6$N$_4$: C, 21.30; N, 9.94. Found: C, 20.64; N, 8.11; H, 2.12.

*Synthesis of [TpRu(NCCH$_3$)$_3$][BF$_4$] (3)*. We have synthesized this previously reported complex$^3$ using our improved method. KTp (88.1 mg, 0.35 mmol) dissolved in methanol (10 mL) was added dropwise using a cannula to a solution of 1 (200 mg, 0.38 mmol) in methanol (25 mL), and the solution was stirred for 30 min. A white precipitate formed and was separated using cannula filtration. The filtrate was concentrated by reducing the volume of the solvent to 10 mL, and a dull white solid precipitated. Ether (15 mL) was added to facilitate precipitation, and the light yellow powder was separated by cannula filtration, washed with ether (10 mL), and dried *in vacuo*. Yield: 103 mg (56%). $^1$H and $^{13}$C{$^1$H} NMR ($d_6$-DMSO) and IR (Nujol, cm$^{-1}$) spectra match previously reported values.$^3$ $^{19}$F{$^1$H} NMR ($d_6$-DMSO): $\delta$ -148.3 (s). Anal. Calc. for RuC$_{11}$H$_{13}$F$_4$N$_7$B: C, 27.39; N, 22.19; H, 2.94. Found: C, 28.95; N, 20.4; H, 3.05.
Synthesis of [$Tp^*Ru(NCCH_3)_3][OTf]$ (4). We have made this previously reported complex\textsuperscript{14} using our improved method. Synthesis of 4 is similar to the method used to synthesize complex 3, except that [Ru(NCCH\textsubscript{3})\textsubscript{6}][(OTf)\textsubscript{2}] (2) was used instead of [Ru(NCCH\textsubscript{3})\textsubscript{6}][(BF\textsubscript{4})\textsubscript{2}] (1), and KTp* (101 mg, 0.30 mmol) was used instead of KTp. A light yellow powder was obtained after work-up. Yield: 235 mg (65\%). \textsuperscript{1}H and \textsuperscript{13}C\{}\textsuperscript{1}H\}\textsuperscript{NMR (d\textsubscript{6}-DMSO) spectra match previously reported values.\textsuperscript{14} \textsuperscript{19}F\{}\textsuperscript{1}H\}\textsuperscript{NMR (d\textsubscript{6}-DMSO): \(\delta\) -77.8 (s). IR (Nujol, cm\textsuperscript{-1}): 719 m, 759 w, 1048 s, 1110 s, 1207 m, 1261 m, 1303 s, 1403 s, 1459 s, 1500 m, 2344 w, 2374 w, 2472 m, 2854 s, 2923 s, 3117 w, 3394 w. Anal. Calc. for RuC\textsubscript{18}H\textsubscript{25}SF\textsubscript{3}O\textsubscript{3}N\textsubscript{7}B: C, 36.73; N, 16.67; H, 4.25. Found: C, 35.76; N, 17.65; H, 4.20.

Synthesis of [$Tp^*PhRu(NCCH_3)_3][OTf]$ (5). KTp\textsuperscript{Ph} (212 mg, 0.30 mmol) dissolved in a 1:1 solution of methanol/acetone (15 mL) was added dropwise using a cannula to a solution of 2 (100 mg, 0.30 mmol) in methanol (15 mL), and the solution was stirred for 15 min, during which time a white precipitate formed. The reaction was dried \textit{in vacuo} and the residue was extracted with acetone. The mixture was filtered and the filtrate was dried \textit{in vacuo} to yield a light yellow powder. Yield: 86 mg (53\%). \textsuperscript{1}H NMR (d\textsubscript{6}-DMSO): \(\delta\) 2.70 (s, 9H, CH\textsubscript{3}CN), 6.66 (s, 3H, 4-pz), 7.03 (br s, 6H, \textit{p}-Ph), 7.20 (s, 3H), 7.31 (t, 6H, \textit{m}-5-Ph), 7.46 (br t, 6H, \textit{m}-3-Ph), 7.79 (d, 6H, \textit{o}-5-Ph), 7.81 (br d, 6H, \textit{o}-3-Ph). \textsuperscript{19}F\{}\textsuperscript{1}H\}\textsuperscript{NMR (d\textsubscript{6}-DMSO): \(\delta\) -77.8 (s). IR (Nujol, cm\textsuperscript{-1}): 688 w, 754 m, 800 w, 975 w, 1031 m, 1076 w, 1170 w, 1261 m, 1377 w, 1459 vs, 1655 w, 1686 w, 2345 w, 2373 w, 2854 vs, 2924 vs, 3448 w. Anal. Calc. for RuC\textsubscript{48}H\textsubscript{36}SF\textsubscript{3}O\textsubscript{3}N\textsubscript{7}B: C, 59.63; N, 10.14; H, 3.83. Found: C, 59.75; N, 10.91; H, 3.80.
Synthesis of $[\text{Tpm}^*\text{Ru(NCCH}_3\text{)}_3][(\text{BF}_4)_2]$ (6). $\text{Tpm}^*$ (119 mg, 0.40 mmol) was added to a solution of 1 (200 mg, 0.38 mmol) in methanol (25 mL), and the solution was heated to reflux for 12 h. The reaction mixture was filtered and the solvent was removed in vacuo. The residue was washed with ether (10 mL) and dried in vacuo to yield a light brown solid. Yield: 190 mg (72%). $^1\text{H NMR}$ (d$_6$-DMSO): $\delta$ 1.60 (s, 9H, CH$_3$CN), 2.66 (s, 9H, 3-Me), 2.72 (s, 9H, 5-Me), 6.33 (s, 3H, 4-pz), 8.09 (s, 1H, H$^{\text{api}}$). $^{13}\text{C}\{{^1\text{H}}\} \text{NMR}$ (d$_6$-DMSO): $\delta$ 3.95 (CH$_3$CN), 11.2 (3-Me), 12.0 (5-Me), 67.5 (C$^{\text{api}}$), 108.2 (C-4), 127.0 (CH$_3$CN), 143.7 (C-3), 152.9 (C-5). $^{19}\text{F}\{{^1\text{H}}\} \text{NMR}$ (d$_6$-DMSO): $\delta$ -148.3 (s). Mass spectrum (ESI-MS): $m/z$ 431.2 [(Tpm$^*$)Ru(OMe)]$^+$. IR (Nujol, cm$^{-1}$): 724 m, 760 w, 1058 s, 1282 w, 1377 s, 1459 vs, 2344 w, 2373 w, 2855 s, 2924 vs. Anal. Calc. for RuC$_{18}$H$_{25}$F$_8$N$_4$B$_2$: C, 35.20; N, 15.97; H, 4.07. Found: C, 34.57; N, 14.17; H, 3.49.

Synthesis of $[\text{Tpm}^\text{Ph}\text{Ru(NCCH}_3\text{)}_3][(\text{OTf})_2]$ (7). $\text{Tpm}^\text{Ph}$ (121 mg, 0.30 mmol) was added to a solution of 2 (100 mg, 0.30 mmol) in THF (25 mL), and the solution was stirred for 8 h at room temperature. The solution was filtered and the filtrate was dried in vacuo. The residue was extracted with dichloromethane, filtered, and the filtrate dried in vacuo to yield a yellow solid. Yield: 40 mg (22%). $^1\text{H NMR}$ (d$_6$-DMSO): $\delta$ 2.69 (s, 9H, CH$_3$CN), 7.14 (s, 3H, 4-pz), 7.20-7.49 (m, 18H, m-, p-Ph), 7.85-7.91 (m, 12H, o-Ph), 7.97 (s, 1H, H$^{\text{api}}$). $^{19}\text{F}\{{^1\text{H}}\} \text{NMR}$ (d$_6$-DMSO): $\delta$ -78.8 (s). IR (Nujol, cm$^{-1}$): 576 w, 638 w, 694 s, 761 m, 799 s, 917 w, 954 w, 1028 s, 1094 s, 1261 s, 1377 w, 1459 vs, 1655 w, 1686 w, 2344 w, 2373 w, 2854 vs, 2924 vs. Anal. Calc. for RuC$_{50}$H$_{36}$S$_2$F$_6$O$_6$N$_7$: C, 53.75; N, 8.78; H, 3.31. Found: C, 52.04; N, 8.54; H, 3.83.

X-ray data collection and structural determination of $[\text{Ru(NCCH}_3\text{)}_6][(\text{BF}_4)_2]$ (1).
Single crystals of \([\text{Ru(NCCH}_3\text{)}_6][(\text{BF}_4)_2]\) were grown from slow vapor diffusion of diethyl ether into an acetonitrile solution and were mounted on a glass filament with silicon grease and immediately cooled to 168.15 K in a cold nitrogen gas stream. Intensity data were collected using a Rigaku Mercury CCD detector and an AFC-8S diffractometer. The space group \(P2_1/c\) was determined from the observed systematic absences. Data reduction including the application of Lorentz and polarization effects (\(L_p\)) and absorption corrections used the CrystalClear\textsuperscript{28} program. The structure was solved by direct methods and subsequent Fourier difference techniques, and refined anisotropically, by full-matrix least squares, on \(F^2\) using SHELXTL 6.10\textsuperscript{29} The quantity minimized by the least square program was \(\Sigma w = (F_o^2 - F_c^2)^2\) where \(w = \{[\sigma^2(F_o^2)] + (0.0422P)^2 + 1.87P]\} \) where \(P = (F_o^2 + 2F_c^2)/3\}. In the final cycle of least squares, independent anisotropic displacement factors were refined for the non-hydrogen atoms and the methyl hydrogen atoms were fixed in "idealized" positions with C-H = 0.96 Å. Their isotropic displacement parameters were set equal to 1.5 times \(U_{eq}\) of the attached carbon atom. The largest peak in the final Fourier difference map (0.88 eÅ\(^{-3}\)) was located 1.61 Å from N1 and the lowest peak (-0.49 eÅ\(^{-3}\)) was located at a distance of 0.86 Å from Ru1. Final refinement parameters for the structure of \([\text{Ru(NCCH}_3\text{)}_6][(\text{BF}_4)_2]\) (1) are given in Table 3.4.

**Electrochemical studies of synthesized ruthenium(II) complexes.** Cyclic voltammetry (CV) experiments were carried out using CHI Electrochemical analyzer and employed a three-electrode cell consisting of glassy carbon working electrode, a Ag/AgCl reference electrode, and a platinum wire auxiliary electrode. The glassy carbon
electrode was polished with alumina prior to each trial. CV experiments were conducted in acetonitrile containing 0.1 mM complex and 0.1 M tetra-n-butyl ammonium hexafluorophosphate (TBAPF$_6$) at a scan speed of 0.1 V/s from -1.25 V to 1.25 V. Solutions were deoxygenated with dry nitrogen gas and maintained under a blanket of nitrogen during measurements, and voltammograms were referenced to the ferrocene/ferricenium couple (Fc$^{+}/$0) at 0.46 V. Formal potentials were evaluated as $E_{1/2} = (E_{pa} + E_{pc})/2$, where $E_{pa}$ and $E_{pc}$ are anodic and cathodic peak potentials. Peak potential separations were evaluated as $\Delta E = |E_{pa} - E_{pc}|$.

Table 3.4. Crystallographic data and structure refinement for [Ru(NCCH$_3$)$_6$][(BF$_4$)$_2$] (I).

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