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Chemistry of rhenium(I) tricarbonyl complexes of biomedical relevance

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CHEMISTRY OF RHENIUM(I) TRICARBONYL COMPLEXES OF BIOMEDICAL RELEVANCE

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy in

The Department of Chemistry

by

Theshini Perera
B.Sc. University of Colombo, Sri Lanka, 2004
August 2010
Dedicated with love to my late mother

And to my loving father
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ABSTRACT

fac-[Re\textsuperscript{I}(CO)\textsubscript{3}L\textsuperscript{n}] complexes serve as models for short-lived fac-[\textsuperscript{99m}Tc\textsuperscript{I}(CO)\textsubscript{3}L] imaging tracers. Dangling groups on L, needed to achieve desirable biodistribution, complicate the NMR spectra, which are not readily understood. In fac-[Re\textsuperscript{I}(CO)\textsubscript{3}L\textsuperscript{+}] with less complicated L, NH groups (exo-NH) projecting toward the L face sometimes showed an upfield shift attributable to steric shielding of the exo-NH group from the solvent by the chelate rings. To investigate whether exo-NH groups in six-membered rings exhibit the same effect and whether the presence of dangling groups alters the effect, we prepared new fac-[Re(CO)\textsubscript{3}L\textsuperscript{n}] complexes that allow direct comparisons of exo-NH shifts for six-membered vs. five-membered chelate rings. The use of anions as probes, including the new use of the [ReBr\textsubscript{6}\textsuperscript{2–}] anion as a paramagnetic outer-sphere H-bonding shift reagent, establishes that these NH protons are not well solvated. Lack of solvation, induced by chelate ring bulk, accounts for the upfield shift.

To evaluate syntheses of fac-[Re(CO)\textsubscript{3}L\textsuperscript{+}] complexes in organic solvents, we treated fac-[Re(CO)\textsubscript{3}(CH\textsubscript{3}CN)\textsubscript{3}]PF\textsubscript{6}/BF\textsubscript{4} in acetonitrile with triamine ligands (L). When L had two primary or two tertiary terminal amine groups, the expected fac-[Re(CO)\textsubscript{3}L\textsuperscript{+}] complexes formed. Treatment of fac-[Re(CO)\textsubscript{3}(CH\textsubscript{3}CN)\textsubscript{3}]\textsuperscript{+} with various tridentate amine ligands has produced several novel compounds, which most likely arise from reaction of the coordinated nitrile with ligand terminal amines. The new compounds advance our understanding of the spectral and structural properties of Re analogues of \textsuperscript{99m}Tc radiopharmaceuticals.

In fac-[Re(CO)\textsubscript{3}(5,5′-Me\textsubscript{2}bipy)(HNC(CH\textsubscript{3})NHR)]BF\textsubscript{4} complexes, the monodentate amidine ligand adopts the E, E′, and Z, but not the Z′ configuration in solution. Both amidine CN bonds have double-bond character, leading to slow isomerization on the NMR time scale.
The equilibrium favors the $E'$ isomer as NHR rises above a threshold size or when stacking can occur.

The structural characterization of $fac$-[Re(CO)$_3$L]$^+$ complexes bearing novel ligands having a central sulfonamide group and two pyridine rings has revealed that the central N of the tertiary sulfonamide group binds to Re. These are among the few structurally characterized complexes with a tertiary (neutral) sulfonamide bound to a metal. We show that a sulfonamide can be used to conjugate the $fac$-[Re(CO)$_3$]$^+$ unit to a porphyrin. The new ligands may be used eventually in $^{99m}$Tc imaging.
CHAPTER 1

INTRODUCTION

Metal coordination compounds are extensively used in a variety of medicinal applications. Cisplatin and carboplatin used for the treatment of cancer, gadolinium compounds used as magnetic resonance imaging (MRI) agents, and $^{99m}$Tc and $^{186/188}$Re compounds used as diagnostic and therapeutic agents are some notable examples. 

1.1 Metalloradiopharmaceuticals

Radiopharmaceuticals are used as modern, powerful tools in nuclear medicine to diagnose and treat many common diseases. Various imaging agents are in use today but the need for better resolution and targeted delivery fuels more research in this field. Metalloradiopharmaceuticals consist of a metal nuclide and ligands. The metal nuclides of most interest are $^{99m}$Tc, and $^{186/188}$Re.

$^{99m}$Tc (E = 141 keV, $t_{1/2} = 6h$) is the most widely used radionuclide in nuclear medicine with over 7 million scans performed each year. The 141 keV gamma ray emission is close to optimal for imaging, and commercially available gamma cameras may be used. The 6 h half-life is long enough to allow pharmaceutical preparation and accumulation in the target tissues, but short enough to minimize radiation dose to the patient. The use of $^{186/188}$Re as beta emitters in medical applications is fairly recent. $^{186}$Re (E = 1.07 MeV, $t_{1/2} = 90$ h) and $^{188}$Re (E = 2.12 MeV, $t_{1/2} = 17$ h) are used for therapeutic applications and aim at delivering therapeutic doses of radiation to target tissues without adversely affecting normal tissue.

1.2 $\text{fac-}\{\text{M}^1(\text{CO})_3\}^+$ ($\text{M} = ^{99m}\text{Tc, Re}$) Core

The seminal contributions of Alberto and co-workers to technetium-carbonyl chemistry have allowed facile access to the $\text{fac-}\{\text{M}^1(\text{CO})_3\}^+$ ($\text{M} = ^{99m}\text{Tc, Re}$) core. Understanding the
fundamental chemistry based on the \( \text{fac-}\{\text{M}^I\text{(CO)}_3\}^+ \) core is important to guide efforts to develop new radiopharmaceuticals.\(^8,11\) Radiopharmaceuticals containing the \( \{^{99m}\text{Tc}^I\text{(CO)}_3\}^+ \) core show promise in the advancement of new clinically useful imaging agents\(^12,13\) and the \( \text{fac-Re(CO)}_3\text{L} \) analogue approach (L is a facially coordinated tridentate ligand) has aided in the development of technetium complexes as potential radiopharmaceuticals.\(^14-16\) Several studies, including those from our laboratory, have been instrumental in developing a better understanding of NMR spectral features of \( \text{fac-Re(CO)}_3\text{L} \) complexes bearing simple donor ligands.\(^17-22\)

Renal imaging agents with some target ligands such as polyamino-polycarboxylic ligands form isomers under the aqueous conditions under which they are synthesized.\(^18,23\) We reasoned that reactions in organic media could be more easily followed in real time by using NMR spectroscopy. Thus, precursors such as \( \text{fac-[Re(CO)}_3\text{(CH}_3\text{CN)}_3\text{]}^+ \) and \( \text{fac-[Re(CO)}_3\text{(DMSO)}_3\text{]}^+ \) which are organic soluble, may be utilized.

Another class of \( \text{fac-[Re(CO)}_3\text{L(L′)}} \text{]}^{n\text{a}} \) complexes of interest includes the bisimine complexes, which have recently been shown to be useful as cell imaging agents in fluorescence microscopy.\(^24\) Relative lipophilicity is a desired feature of Re complexes to be used for cell imaging because it leads to cell membrane permeability.\(^24\) Numerous other applications exist for these bisimine complexes, such as precursors in supramolecular chemistry for the design and construction of molecular scale devices for information storage and transfer.\(^25-28\)

A theme of this work has been to understand the solution structure of novel \( \text{fac-Re(CO)}_3 \) complexes and how NMR spectroscopy could be utilized for this purpose. The first part of this work describes the synthesis in water and detailed analysis of \( \text{fac-[Re(CO)}_3\text{L]}^{n\text{a}} \) complexes having six-membered chelate rings and use of small anions to probe solution structure of these complexes.
In the second part, to evaluate syntheses of \( \text{fac-}[\text{Re(CO)}_3\text{L}]^+ \) complexes in organic solvents, the \( \text{fac-}[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]^+ \) precursor was utilized; some unusual Re\(^{\text{i}}\) amidine complexes formed by attack of primary or secondary amine terminal groups of polyamines on coordinated acetonitrile, in one case giving a seven-membered chelate ring. Because an important goal is to interpret how structure affects the NMR spectra of the \( \text{fac-}[\text{Re}^{\text{i}}(\text{CO})_3\text{L}]^n \) complexes, we evaluate the interaction of Cl\(^-\) with some of the new \( \text{fac-}[\text{Re(CO)}_3\text{L}]^n \) complexes that have unusual NH groups. To further assess Re\(^{\text{i}}\) amidine chemistry, we move on to investigate amidine products formed by treating \( \text{fac-}[\text{Re(CO)}_3(5,5'\text{-Me}_2\text{bipy})(\text{CH}_3\text{CN})]\text{BF}_4 \) (a complex with only one coordinated acetonitrile) with ammonia and amines. The configuration is influenced primarily by electronic and steric effects because the ligand is monodentate and the configuration is not restricted.

Finally, novel ligands of potential radiopharmaceutical interest and their \( \text{fac-Re(CO)}_3 \) complexes are synthesized as a preliminary step before \(^{99m}\text{Tc}\) labeling and biological studies of these complexes. This model is also extended to include a Re-porphyrin conjugate.

1.3 References


CHAPTER 2

NH NMR SHIFTS OF NEW, STRUCTURALLY CHARACTERIZED fac-[Re(CO)₃(POLYAMINE)]ⁿ⁺ COMPLEXES PROBED VIA OUTER-SPHERE H-BONDING INTERACTIONS TO ANIONS, INCLUDING THE PARAMAGNETIC [Re⁴⁹Br₆]²⁻ ANION*

2.1 Introduction

fac-[Re(CO)₃L]ⁿ complexes have provided a good model system for interpreting the nature of the analogous fac-[⁹⁹ᵐTc(CO)₃L]ⁿ imaging agents formed in tracer level preparations.¹,² The convenient generation of the fac-[⁹⁹ᵐTc(CO)₃(H₂O)₃⁺ precursor³,⁴ and the straightforward preparation of the fac-[Re(CO)₃(H₂O)₃⁺ precursor⁵ have contributed toward developing new fac-[⁹⁹ᵐTc(CO)₃L]ⁿ radiopharmaceuticals because fac-[Re(CO)₃(H₂O)₃⁺ allows the simulation of the synthesis of ⁹⁹ᵐTc complexes in aqueous media.² Recently Re complexes have been emerging as radiopharmaceuticals in their own right, owing to the possibility of utilizing the {¹⁸⁶/¹⁸⁸Re(CO)₃}⁺ core for therapeutic purposes.⁶,⁷ Additional evidence of the growing importance of this field is found in a recent report of a rapid and versatile microwave synthesis for preparing chelate complexes with the fac-{M¹(CO)₃}⁺ core (M = ⁹⁹ᵐTc, Re).⁸

fac-[⁹⁹ᵐTc(CO)₃L]ⁿ complexes bearing tridentate ligands (L) are rather robust,⁶,⁹ and tridentate ligand systems bearing a dangling group with functional groups for conjugation to biomolecules or for directing the agent to a particular target are widely used.⁹-¹³ Ligands with carboxyl groups on dangling chains are normally evaluated in renal tracer development because the interaction of the renal receptor with the carboxyl group is important for clearance of small peptides.¹⁴-¹⁶ Tridentate ligands being investigated in bioconjugates or in tracers often have the

dangling group attached to a central N anchoring the two chelate rings. Thymidine derivatives functionalized at position N3 of the nucleobase and attached to $^{99m}$Tc or Re by a chain dangling from the central N of diethylenetriamine (dien) are recognized as substrates by human thymidine kinase 1, a promising target for noninvasive imaging and therapy of malignant cells. A recent report describes $\textit{fac}$$^{-}\text{[}^{188}\text{Re(CO)}_3\text{((bis(2-pyridylmethyl)amino)ethylamine)}\text{]}\text{Br}$, a $^{188}\text{Re}$ complex exhibiting promising biomedical properties and having a pyridyl-containing tridentate ligand with a dangling ethylamine group attached to the central N (Chart 2.1).

Ligands named or used in this report are depicted in Chart 2.1. The H at the end of an abbreviation for a ligand name in Chart 2.1 or in the designation of a complex indicates the number of acidic hydrogens retained by the coordinated ligand, or in some cases, such as trenH (tris-(2-aminoethyl)amine), the H indicates that the coordinated ligand has become protonated.

Highly functionalized $\textit{fac}$$^{-}\text{[Re(CO)}_3\text{L]}^n$ complexes are difficult to crystallize, and also the solution structures relevant to the likely structure of the tracer may differ from that in solution. For example, dangling uncoordinated carboxyl groups (which are negatively charged and deprotonated at physiological pH) usually become neutral protonated groups in procedures employed to crystallize the complex. One goal of our study is to interpret how NMR spectra inform us about the solution structure of $\textit{fac}$$^{-}\text{[Re(CO)}_3\text{L]}^n$ complexes. We first became aware that an unusually wide shift range exists for NH signals at amine groups terminating chelate rings (i.e., amines not anchoring two chelate rings) in $\textit{fac}$$^{-}\text{[Re(CO)}_3\text{L]}^n$ complexes in a study of two $\textit{fac}$$^{-}\text{[Re(CO)}_3\text{(ENDACH)}\text{]}$ isomers (ENDACH$_2$ ligand shown in Chart 2.1). For both isomers in the solid state, the coordinated carboxyl group is deprotonated, whereas the dangling carboxyl group is protonated. Two types of terminal NH’s were defined and unambiguously identified through the crystallography of the two isomers. In one isomer, the terminal amine has an endo-NH proton (defined as the proton projecting toward the carbonyl
ligands, Figure 2.1) with a normal relatively downfield shift (5.84 ppm, DMSO-\textit{d}_6) for a terminal secondary amine NH signal. In the other isomer, this amine has an \textit{exo}-NH proton (defined as the proton projecting \textit{away} from the carbonyl ligands, Figure 2.1).\textsuperscript{21} The signal of this terminal secondary amine \textit{exo}-NH proton was observed at a rather upfield position (5.36 ppm, DMSO-\textit{d}_6).

\textbf{Chart 2.1.} Ligands used or mentioned in this study
Figure 2.1. Designation of endo and exo protons in 5-membered (left) and 6-membered (right) rings, as illustrated based on the molecular structure of [Re(CO)₃(aepn)]PF₆. The exo-NH or exo-CH protons point away from the carbonyl ligands and the endo-NH or endo-CH protons point toward the carbonyl ligands.

In later studies,¹,⁵,²³ we found a relatively wide range of NH shifts also for terminal primary amine groups in fac-[Re(CO)₃L]⁺ complexes.¹,²³ When L = lanthionine isomers as the tridentate ligand (LANH₂, Chart 2.1), the fac-[Re(CO)₃(LAN)]⁻ isomers exhibited NH signals differing in shift, but the shift range was not readily understood.¹ For some primary amine groups the two NH signals were well dispersed, whereas for others the shifts of both NH signals were similar.¹ Because the two deprotonated dangling carboxyl groups of the fac-[Re(CO)₃(LAN)]⁻ complex could be influencing shift, we examined fac-[Re(CO)₃L]⁺ complexes with such minimal prototypical ligands as dien or simple dien-related ligands (e.g., daes, Chart 2.1) to establish baseline chemical shift characteristics that define NMR parameters for fac-[Re(CO)₃L]ⁿ complexes.²⁴

For the prototypical fac-[Re(CO)₃L]⁺ complexes, with L lacking dangling groups and forming two 5-membered rings, downfield and upfield NH signals were observed and assigned to endo-NH and exo-NH protons, respectively.²⁴ We hypothesized that the shift differences might be attributable in part to the lower exposure to solvent of the exo-NH protons compared to the
endo-NH protons. We reasoned that the chelate rings forming the face defined by L might provide a steric barrier that inhibits full access of the polyatomic solvent molecules to the exo-NH. As a result, the solvent cannot approach the exo-NH closely enough to allow formation of strong solvent to NH H-bonding interactions (an interaction causing downfield shifts). Therefore, we evaluated the interaction of the small monoatomic Cl\(^-\) anion with these prototypical complexes. We reasoned that the Cl\(^-\) anion would be attracted to the cationic complex, leading to an ion pair with the Cl\(^-\) anion H-bonded preferentially to the poorly solvated exo-NH groups. This interaction caused larger downfield shifts for the exo-NH signal than for the endo-NH signal, consistent with our hypothesis that solvent molecules are too large to access the exo-NH groups well. The extent of solvent accessibility to exo-NH groups might be altered by dangling groups on the ligands, by replacement of one of the groups with other donor types, by chelate ring size, as well as by other possible factors.

In the present study, we investigate fac-[Re(CO)\(_3\)L]\(^{n+}\) complexes bearing polyamine ligands having 6-membered chelate rings to determine if some of the same unusual NH shifts are present in the \(^1\)H NMR spectra of these compounds. Also, we test further our proposal that at least a significant factor influencing shift is solvent exposure by assessing the interaction of anions of increasing size along the series: Cl\(^-\), Br\(^-\), and I\(^-\). We also evaluated the large paramagnetic Re\(^{IV}\) anion, [ReBr\(_6\)]\(^2-\). This series of studies was designed to test the solvent exposure hypothesis that small species are expected to access the sterically hindered face of the octahedron defined by the tridentate ligand better than larger anions. Two-dimensional NMR NH signal assignment is more straightforward for fac-[Re(CO)\(_3\)L]\(^{n+}\) complexes bearing polyamine ligands having two 6-membered chelate rings than for fac-[Re(CO)\(_3\)L]\(^{n+}\) complexes bearing polyamine ligands having 5-membered chelate rings because ring pucker in the latter type of compounds is usually very fluxional and different for the two chelate rings. From now on, we
omit the \textit{fac}- designation when discussing specific compounds because all the new compounds have this geometry.

\textbf{2.2 Experimental Section}

\textbf{Starting Materials.} Tris-(2-aminoethyl)amine (tren), \(N\)-3-(aminopropyl)-1,3-propanediamine (dipn), \(N\)-2-(aminoethyl)-1,3-propanediamine (aepn), 3,3'-diamino-\(N\)-methylidipropylamine (\(N'\)-Medipn), \(N\),\(N\)-dimethyldipropylentriamine (\(N,N\)-Me\(_2\)dipn), tris-(3-aminopropyl)amine (trpn), 1,4,7-triazacyclononane (tacn), and \(\text{Re}_2(\text{CO})_{10}\) from Aldrich were used as received. \([\text{Re(CO)}_3(\text{H}_2\text{O})_3]\text{OTf}\) (OTf = trifluoromethanesulfonate) and \([\text{Bu}_4\text{N}]_2[\text{ReBr}_6]\) were prepared by known methods.\(^5\)\(^{25}\)

\textbf{NMR Measurements.} \(^1\)H (400 MHz) and \(^2\)H NMR (unlocked) spectra were recorded on Bruker spectrometers. Peak positions are relative to TMS by using TMS or in some cases solvent residual peak, referenced in turn to TMS. NMR data were processed with TopSpin and Mestre-C software.

\textbf{X-ray Data Collection and Structure Determination.} Intensity data were collected at 90.0(5) K on a Nonius Kappa CCD diffractometer fitted with an Oxford Cryostream cooler and graphite-monochromated MoK\(\alpha\) (\(\lambda = 0.71073\) Å) radiation. Data reduction included absorption corrections by the multi-scan method, with HKL SCALEPACK.\(^{26}\)

All X-ray structures were determined by direct methods and difference Fourier techniques and refined by full-matrix least squares, using SHELXL97.\(^{27}\) All non-hydrogen atoms were refined anisotropically, except for those in the 6-membered chelate rings of 5, which were disordered into two conformations. Except for those on the water molecule in 1, all H atoms were visible in difference maps. H atoms on C and N were placed in idealized positions, except for the NH hydrogen atoms in 2, 4, and 6. A torsional parameter was refined for each methyl group.
Compound 1 has three independent Re complexes in the asymmetric unit, two of which have disordered (CH$_2$)$_3$ groups. Compound 3 has two formula units in the asymmetric unit. Compound 7 crystallizes in a chiral conformation as an enantiopure crystal, as evidenced by Flack parameter $x = 0.014(6)$.

**Synthesis of fac-[Re(CO)$_3$L]PF$_6$ and fac-[Re(CO)$_3$L]BF$_4$ Complexes.** An aqueous solution of [Re(CO)$_3$(H$_2$O)$_3$]OTf (5 mL, 0.1 mmol) was treated with the ligands, L (0.1 mmol). The pH was adjusted to ∼6 (3 mL of methanol was added to dissolve any precipitate that formed), and the clear reaction mixture was heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature, treated with solid NaPF$_6$ or NaBF$_4$ (∼15 mg), and then left undisturbed. X-ray quality crystals formed within 2-3 days. Specific procedures are detailed below.

[Re(CO)$_3$(dipn)]BF$_4$ (1). Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with dipn (15 µL) as described above afforded [Re(CO)$_3$(dipn)]BF$_4$ as colorless crystals (17 mg, 35% yield) after the addition of NaBF$_4$. The product was characterized by single-crystal X-ray diffraction. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: 6.00 (b, 1H, NH), 5.23 (d, 2H, NH), 3.79 (b, 2H, NH), 3.20 (m, 2H, CH$_2$), 2.90 (m, 2H, CH$_2$), 2.68 (m, 2H, CH$_2$), 2.62 (m, 2H, CH$_2$), 1.88 (m, 2H, CH$_2$), 1.68 (m, 2H, CH$_2$). [Re(CO)$_3$(dipn)]PF$_6$. Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with dipn as described above afforded [Re(CO)$_3$(dipn)]PF$_6$ as colorless crystals (36 mg, 66% yield) after the addition of NaPF$_6$. The product could not be characterized by single-crystal X-ray diffraction because of twinning. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: identical to that of [Re(CO)$_3$(dipn)]BF$_4$.

[Re(CO)$_3$(N′-Medipn)]PF$_6$ (2). Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with N′-Medipn (17 µL) as described above afforded [Re(CO)$_3$(N′-Medipn)]PF$_6$ as colorless crystals (18 mg, 32% yield) after the addition of NaPF$_6$. The product was characterized by single-crystal X-ray
diffraction. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: 5.30 (d, 2H, NH), 3.80 (t, 2H, NH), 3.20 (m, 2H, CH$_2$), 3.02 (m, 2H, CH$_2$), 2.98 (s, 3H, CH$_3$), 2.65 (m, 4H, CH$_2$), 1.90 (m, 2H, CH$_2$), 1.88 (m, 2H, CH$_2$).

[Re(CO)$_3$(N,N-Me$_2$dipn)]BF$_4$ (3). Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with N,N-Me$_2$dipn (18 µL) as described above afforded [Re(CO)$_3$(N,N-Me$_2$dipn)]BF$_4$ as colorless crystals (29 mg, 56% yield) after the addition of NaBF$_4$. The product was characterized by single-crystal X-ray diffraction. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: 6.34 (s, 1H, NH), 5.53 (d, 1H, NH), 3.78 (t, 1H, NH), 3.24 (m, 1H, CH$_2$), 3.01 (s, 3H, CH$_3$), 2.90 (m, 3H, CH$_2$), 2.80 (m, 1H, CH$_2$), 2.71 (m, 3H, CH$_2$), 2.62 (s, 3H, CH$_3$), 1.94 (m, 1H, CH$_2$), 1.86 (m, 1H, CH$_2$), 1.62 (m, 2H, CH$_2$).

[Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4). Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with tren (16 µL) as described above afforded [Re(CO)$_3$(trenH)](PF$_6$)$_2$ as colorless crystals (34 mg, 47% yield) after the addition of NaPF$_6$. The product was characterized by single-crystal X-ray diffraction. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: 7.70 (b, 3H, NH), 5.62 (b, 2H, NH), 4.22 (b, 2H, NH), 3.57 (m, 2H, CH$_2$), 3.09 (m, 2H, CH$_2$), 2.91 (m, 6H, CH$_2$).

[Re(CO)$_3$(trpnH)](PF$_6$)$_2$ (5). Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with trpn (20 µL) as described above afforded [Re(CO)$_3$(trpnH)](PF$_6$)$_2$ as colorless crystals (34 mg, 45% yield) after the addition of NaPF$_6$. The product was characterized by single-crystal X-ray diffraction. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: 7.69 (b, 3H, NH), 5.39 (b, 2H, NH), 3.72 (b, 2H, NH), 3.10 (m, 4H, CH$_2$), 2.85 (m, 4H, CH$_2$), 2.75 (m, 4H, CH$_2$), 1.96 (m, 6H, CH$_2$).

[Re(CO)$_3$(aepn)]PF$_6$ (6). Treatment of [Re(CO)$_3$(H$_2$O)$_3$]OTf with aepn (13 µL) as described above afforded [Re(CO)$_3$(aepn)]PF$_6$ as colorless crystals (30 mg, 56% yield) after the addition of NaPF$_6$. The product was characterized by single-crystal X-ray diffraction. $^1$H NMR spectrum (ppm) in DMSO-$d_6$: 6.47 (b, 1H, NH), 5.50 (d, 1H, NH), 5.24 (d, 1H, NH), 4.08 (b, 1H,
NH), 3.50 (t, 1H, NH), 3.25 (m, 1H, CH₂), 3.04 (m, 1H, CH₂), 2.97 (m, 1H, CH₂), 2.63 (m, 3H, CH₂), 2.57 (m, 1H, CH₂), 2.43 (m, 1H, CH₂), 1.94 (m, 1H, CH₂), 1.74 (m, 1H, CH₂).

[Re(CO)₃(tacn)]PF₆ (7). Treatment of [Re(CO)₃(H₂O)₃]OTf with tacn (13 mg) as described above afforded [Re(CO)₃(tacn)]PF₆ as colorless crystals (30 mg, 55% yield) after the addition of NaPF₆. The product was characterized by single-crystal X-ray diffraction. ¹H NMR spectrum (ppm) in DMSO-d₆: 7.06 (b, 3H, NH), 2.96 (m, 6H, CH₂), 2.88 (m, 6H, CH₂).

Cl⁻ Titration of [Re(CO)₃L]PF₆ Complexes. A 5 mM solution of the desired fac-[Re(CO)₃L]PF₆ complex in DMSO-d₆ or acetonitrile-d₃ (600 µL) was treated with increasing amounts of Et₄NCl (1 to 125 mM), and the solution was monitored by ¹H NMR spectroscopy after each Cl⁻ aliquot was added. All Et₄NCl stock solutions were prepared by using a 5 mM solution of the complex to keep the complex concentration constant throughout the titration. Similar experiments were performed with [Re(CO)₃(dipn)]PF₆ in acetonitrile-d₃ by using Et₄NBr (1 to 125 mM) and Et₄NI (1 to 50 mM, owing to low solubility).

Preparation of [Re(CO)₃(dipn-d₅)]PF₆. The NH NMR signals of a 5 mM solution of [Re(CO)₃(dipn)]PF₆ in acetonitrile-d₃ (600 µL) disappeared within ~40 min after addition of D₂O (5 µL) and K₂CO₃ (2 mg). Therefore, the NH groups of [Re(CO)₃(dipn)]PF₆ (8 mg) in CH₃CN (3 mL) were exchanged by using D₂O (70 µL) and K₂CO₃ (8 mg). The reaction mixture was taken to dryness, the residue dissolved in CH₃CN, and the solution filtered to remove K₂CO₃. The filtrate was taken to dryness, and the residue was re-dissolved in CH₃CN (3 mL) to give a 5 mM [Re(CO)₃(dipn-d₅)]PF₆ stock solution for use in ²H NMR-monitored titrations. Later, [Re(CO)₃(dipn-d₅)]PF₆ was prepared more conveniently by using the volatile Et₃N instead of K₂CO₃.
Addition of \([\text{Bu}_4\text{N}]_2[\text{ReBr}_6]\) to \([\text{Re(CO)}_3(\text{dipn-d}_5)]\text{PF}_6\). A 5 mM solution of \([\text{Re(CO)}_3(\text{dipn-d}_5)]\text{PF}_6\) in CH$_3$CN (600 µL) was treated with increasing amounts of \([\text{Bu}_4\text{N}]_2[\text{ReBr}_6]\) (1 to 12 mM), and the solution was monitored by $^2$H NMR spectroscopy after each \([\text{ReBr}_6]^{2–}\) aliquot was added. An analogous $^1$H NMR experiment was performed with \([\text{Re(CO)}_3(\text{dipn})]\text{PF}_6\) in acetonitrile-$d_3$. The \([\text{Re(CO)}_3(\text{dipn-d}_5)]\text{PF}_6\) concentration was kept constant throughout the titrations as described above.

2.3 Results and Discussion

Synthesis. A \([\text{Re(CO)}_3(\text{H}_2\text{O})_3]\text{OTf}\) aqueous solution\(^5\) (pH ~6) was used to prepare all the complexes crystallized and structurally characterized in this study (Scheme 2.1). All complexes are new except for the tacn complex, which was not previously characterized as a PF$_6$– salt.\(^{28,29}\) This salt was needed for our NMR studies.

Scheme 2.1. Synthesis of complexes
X-ray Crystallography. All complexes possess a distorted octahedral structure, with the three carbonyl ligands occupying one face. The three remaining coordination sites are occupied by amine nitrogen atoms (Figures 2.2-2.4). Crystal data and details of the structural refinement for these complexes are summarized in Table 2.1. Ligands and their abbreviations are depicted in Chart 2.1. The complexes have chelate rings of different sizes: two six-membered chelate rings ([Re(CO)3(dipn)]BF4 (1), [Re(CO)3(N′-Medipn)]PF6 (2), [Re(CO)3(N,N-Me2dipn)]BF4 (3), and [Re(CO)3(trpnH)](PF6)2 (5)); six- and five-membered chelate rings ([Re(CO)3(aepn)]PF6 (6)); two five-membered rings ([Re(CO)3(trenH)](PF6)2 (4)); or three five-membered rings ([Re(CO)3(tacn)]PF6 (7)). For all complexes except [Re(CO)3(tacn)]PF6 (7), N1 and N3 refer to bound terminal nitrogen atoms of the ligand, and N2 denotes the central nitrogen; for [Re(CO)3(trenH)](PF6)2 (4) and [Re(CO)3(trpnH)](PF6)2 (5), the nitrogen atom of the dangling NH3+ group is designated as N4 (Chart 2.1).

Selected Re–N bond lengths and the N–Re–N bond angles are summarized in Table 2.2. The Re–N bond lengths and N–Re–N bond angles are consistent with those found in similar fac-[Re(CO)3L]+ complexes. It is useful to compare the N–Re–N angles for two terminal amine groups of [Re(CO)3(dien)]PF6 (87.14(12)°), which has two 5-membered chelate rings, with those of [Re(CO)3(aepn)]PF6 (86.74(15)°), which has 5- and 6-membered chelate rings (Figure 2.2), and [Re(CO)3(dipn)]BF4 (84.67(10)°), which has two 6-membered rings (Figure 2.2). The N–Re–N angle relating two terminal N’s decreases significantly as the ring size increases (Table 2.2). The non-bonded distances between N1 and N3 are mostly similar for complexes 1-6, ranging from 3.01-3.14 Å (Table 2.3) regardless of the size of the chelate ring.

The presence of a methyl group on N2 of [Re(CO)3(N′-Medipn)]PF6 (2) is reflected in a longer Re–N2 bond distance for 2 (2.299(2) Å) than for [Re(CO)3(dipn)]BF4 (1) (2.244(3) Å).
A similar difference in the Re–N2 bond distance is found for the corresponding complexes with two 5-membered rings (L = dien and N′-Medien, Chart 2.1).\textsuperscript{24} Thus, in [Re(CO)\textsubscript{3}L]\textsuperscript{a} complexes containing either 6- or 5-membered chelate rings, having a methyl substituent on N2 increases the Re–N2 bond distance by a similar small extent. This same conclusion appears to apply when data for [Re(CO)\textsubscript{3}(trenH)](PF\textsubscript{6})\textsubscript{2} (4) and [Re(CO)\textsubscript{3}(trpnH)](PF\textsubscript{6})\textsubscript{2} (5) are considered. The central N in 4 and 5 bears a CH\textsubscript{2}CH\textsubscript{2}NH\textsubscript{3}\textsuperscript{+}; the greater bulkiness of this dangling group does not appear to cause any greater lengthening of the Re–N2 bond than does the methyl group.

**Figure 2.2.** ORTEP plots of the cations of [Re(CO)\textsubscript{3}(dipn)]BF\textsubscript{4} (1), [Re(CO)\textsubscript{3}(N′-Medipn)]PF\textsubscript{6} (2), [Re(CO)\textsubscript{3}(N,N-Me\textsubscript{2}dipn)]BF\textsubscript{4} (3), and [Re(CO)\textsubscript{3}(aepn)]PF\textsubscript{6} (6). Thermal ellipsoids are drawn with 50% probability. Only one of the independent molecules is shown for 1 (Z′ = 3) and for 3 (Z′ = 2).
Figure 2.3. ORTEP plots of the cations of \([\text{Re(CO)}_3(\text{trenH})](\text{PF}_6)_2\) (4) and \([\text{Re(CO)}_3(\text{trpnH})](\text{PF}_6)_2\) (5). Thermal ellipsoids are drawn with 50% probability.

Figure 2.4. ORTEP plot of the cation of \([\text{Re(CO)}_3(\text{tacn})]\text{PF}_6\) (7). Thermal ellipsoids are drawn with 50% probability.
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<sup>a</sup>R = (∑||Fo|| - ||Fc||)/∑||Fo||; <sup>b</sup>wR2 = [∑[w(Fo)² - Fc)²²]/∑[w(Fo)²²][1/2, in which w = 1/[σ²(Fo)² + (dP)² + (eP)] and P = (Fo)² + 2Fc)²/3, d = 0.0356, 0.0245, 0.0412, 0.0241, 0.0294, 0.0225, and 0.0131, and e = 7.9046, 0.3934, 0.4422, 3.894, 2.1227, 2.1782, and 1.8054 for complexes 1-7, respectively.

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### Table 2.2. Selected Bond Distances (Å) and Angles (deg) for \([\text{Re(CO)}_3(\text{dipn})]\text{BF}_4\) (1), \([\text{Re(CO)}_3(N'\text{-Medipn})]\text{PF}_6\) (2), \([\text{Re(CO)}_3(N,N'\text{-Me}_2\text{dipn})]\text{BF}_4\) (3), \([\text{Re(CO)}_3(\text{trenH})](\text{PF}_6)_2\) (4), \([\text{Re(CO)}_3(\text{trpnH})](\text{PF}_6)_2\) (5), \([\text{Re(CO)}_3(\text{aepn})]\text{PF}_6\) (6), and \([\text{Re(CO)}_3(\text{tacn})]\text{PF}_6\) (7)

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### Table 2.3. Selected Non-bonded Distances (Å) for \([\text{Re(CO)}_3(\text{dipn})]\text{BF}_4\) (1), \([\text{Re(CO)}_3(N'\text{-Medipn})]\text{PF}_6\) (2), \([\text{Re(CO)}_3(N,N'\text{-Me}_2\text{dipn})]\text{BF}_4\) (3), \([\text{Re(CO)}_3(\text{trenH})](\text{PF}_6)_2\) (4), \([\text{Re(CO)}_3(\text{trpnH})](\text{PF}_6)_2\) (5), \([\text{Re(CO)}_3(\text{aepn})]\text{PF}_6\) (6), and \([\text{Re(CO)}_3(\text{tacn})]\text{PF}_6\) (7)

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**Chelate Ring Conformation.** In the next subsection on NMR signal assignments, we discuss the use of COSY NMR spectra and chelate ring torsion angles, which depend on chelate ring conformation. Thus, it is useful to consider chelate ring conformations in the new structures and to compare these to conformations found in previous studies.\(^{23,24}\) From Scheme 2.1, it can be
seen that all of the new complexes except 3 and 6 will have a time-averaged plane of symmetry. However, none have such a plane in the solid state (Figures 2.2 and 2.3).

The N2,N3 6-membered rings in compounds 1, 2, 3, and 6 (Figure 2.2) all have a very similar chair conformation (Chart 2.2). However, the conformation of the N1,N2 ring differs; this ring has the twist boat conformation in 1 (Chart 2.2), the sofa conformation in 2 and 3 (Chart 2.2), and five members in 6 (see below).30,31

When the two chelate rings are not equivalent (as in 3 and 6), L has a 'head' and a 'tail' (htL), and thus the complex is chiral. Also, one of the htL rings may dictate the conformation of the other ring. For 3, in which both rings are 6-membered and flexible, such conformational control of one ring by the other ring is not evident.

Chart 2.2. Conformations of 6-membered rings

In contrast, when one htL ring is 5-membered, the conformation of the ring may be influenced by the other ring. The conformation of 5-membered rings is described by ring pucker (λ or δ) (Figure 2.5). One ring pucker (λ or δ) may be favored. In cases such as [Re(CO)3(tmbSO2-dien)], in which both rings of the htL are 5-membered, this chirality will determine the favored ring pucker of each ring (λ or δ).23 The common pucker designation (λ or δ) is not useful for interpreting NMR data. Instead, we designate the 5-membered ring conformations as *endo*-C and *exo*-C, where the ring carbon bound to the terminal N projects.
toward and away, respectively, from the carbonyl ligands (Figure 2.5). This designation can also be used for 6-membered rings (Figure 2.5). Please note: the ring carbon has both an endo-CH and an exo-CH, regardless of whether or not the carbon is an endo-C or an exo-C. For example, in Figure 2.1, the 6-membered ring shown has an endo-C with its two hydrogens labeled as endo-CH and exo-CH.

![Diagram showing conformations of 5- and 6-membered rings](image)

**Figure 2.5.** Designations of the exo-C and endo-C conformations for 5- and 6-membered rings of fac-[Re(CO)$_3$L]$^n$ complexes. Re is directed away from the viewer and the nitrogens are blue. The terminal N of the ring of interest is on the right, the central N is on the left, and the terminal N (but not the chain methylene groups) of the other ring is in the axial position. Note that for 5-membered rings, the chirality of the ring pucker is also designated.

**NMR Spectroscopy.** Complexes 1–7 were characterized by NMR spectroscopy in DMSO-$d_6$ (Figures 2.6 and A.1, Supporting Information), acetonitrile-$d_3$, and acetone-$d_6$ at 25 °C (Table 2.4). COSY experiments performed for most of the complexes at 25 °C in DMSO-$d_6$, together with torsion angles obtained from the respective molecular structures, were useful in assigning NMR signals.
Figure 2.6. $^1$H NMR spectra of [Re(CO)$_3$(dipn)]PF$_6$ (1), [Re(CO)$_3$(aepn)]PF$_6$ (6), and [Re(CO)$_3$(dien)]PF$_6$ (top) in DMSO-$d_6$ at 25 °C (* water peak). Full spectra for 1 and 6 are presented in Figure A.1 in Supporting Information.

Table 2.4. Selected $^1$H NMR Chemical Shifts (ppm) of [Re(CO)$_3$(dipn)]BF$_4$ (1), [Re(CO)$_3$(N$^\text{Me}$Medipn)]PF$_6$ (2), [Re(CO)$_3$(N,N-Me$_2$dipn)]BF$_4$ (3), [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4), [Re(CO)$_3$(trpnH)](PF$_6$)$_2$ (5), [Re(CO)$_3$(aepn)]PF$_6$ (6), and [Re(CO)$_3$(tacn)]PF$_6$ (7) at 25 °C.$^a$

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$^a$ COSY spectra were used to assign the NH signals of 1-6 in DMSO-$d_6$ and 4 in acetone-$d_6$.$^b$

For 4 and 5, the chemical shift of the dangling NH$_3^+$ group is listed in the rows containing central-NH values. $^c$ The second entry is for the 6-membered ring.
In our previous work, the assignment by COSY or other means of an NH signal to an \textit{exo}-NH or \textit{endo}-NH proton was possible either because the complex contained only one of these types of protons in a secondary amine or because there was only one NH\textsubscript{2} group in a unique 5-membered chelate ring (the ligand was an htL).\textsuperscript{23} For example, the ring with the terminal amine in \([\text{Re(CO)}_3(\text{tmbSO}_2\text{-dien})]\) has an \textit{exo}-C conformation in the solid, and the \textit{endo}-NH exhibited a strong COSY cross-peak to the \textit{exo}-CH. In \([\text{Re(CO)}_3(\text{aepn})]\text{PF}_6 (6), the 5-membered chelate ring has an \textit{endo}-C conformation, and the \textit{exo}-NH signal exhibited a strong COSY cross-peak to the \textit{endo}-CH signal of the \textit{endo}-C.

For a symmetric (non-HTL) complex with two identical ethylene chains such as \([\text{Re(CO)}_3(\text{dien})]\text{PF}_6^{+}, the 5-membered chelate rings undergo rapid change in pucker, with both rings \(\lambda,\lambda\) or both \(\delta,\delta\).\textsuperscript{24} Over time, any given CH\textsubscript{2} group in these rings is alternately \textit{endo} or \textit{exo} with respect to the carbonyl ligands. This rapid conformational interchange process averages the torsion angles such that \textit{endo}-NH and \textit{exo}-NH to CH couplings average. This averaging is found for each of the NH signals to both CH signals (unpublished data). COSY data cannot be used to assign the signals. However, the position in conformational space of the NH groups moves just slightly as the slight rotation about the Re–N bond occurs during the dynamic process. Thus, the \textit{exo}-NH signal remains upfield to the \textit{endo}-NH signal.\textsuperscript{24}

The conformations of 6-membered rings are more diverse than those of 5-membered rings (Chart 2.2), as discussed above. However, the chair conformation is most commonly found for the 6-membered rings in the new structures, and we assume that the solution structures will be dominated by this conformation, even in those symmetrical compounds in which the rings undergo conformational interchange. As will be seen, this assumption is justified by its utility in interpreting the NMR data. In the chair conformation, the \textit{exo}-NH is related to the \textit{endo}-CH by the largest H–N–C–H torsion angle (Table A.1, Figure A.2, Supporting Information); thus, for
the 6-membered ring(s) in 1, 2, 3, and 6 (which exhibit similar COSY NH-CH cross-peaks), the
NH-CH cross-peak having the highest intensity will be the *exo-NH-endo-CH* cross-peak (see
below and Supporting Information).

We begin our discussion with \([\text{Re(CO)}_3(N,N-\text{Me}_2\text{dipn})]\text{BF}_4\) (3, Figure 2.2), a chiral
complex with an unsymmetrical coordinated htL in which dynamic motion cannot interchange
the rings. The ring with the terminal NH$_2$ group has the chair conformation. The expected three
NH signals (central NH and terminal NH$_2$) were observed for 3 in DMSO-$d_6$ (Table 2.4, Figure
A.3, Supporting Information). COSY studies discussed in Supporting Information establish that,
although the chelate ring has six members, the *exo-NH* shift is upfield, as found for 5-membered
chelate rings. However, the *exo-NH-endo-CH* COSY cross-peak is larger than the *endo-NH-exo-
CH* COSY cross-peak, unlike the case of the 5-membered chelate ring of \([\text{Re(CO)}_3(\text{tmbSO}_2-
dien)]\) in a previous study in which the largest H-N-C-H torsion angle was ~157° for a ring in the
*exo-C* conformation (Figure 2.5). For this compound, the *endo-NH-exo-CH* cross-peak was the
strongest HN-CH cross-peak.$^{23}$

As found for 3, COSY data for \([\text{Re(CO)}_3(\text{dipn})]\text{BF}_4\) (1) in DMSO-$d_6$ (Supporting
Information) allowed us to establish that the *exo-NH* signal is upfield. Furthermore, unlike the
case for symmetrical complexes with two 5-membered rings, the NH signals of the complexes
with two 6-membered rings can be assigned unambiguously by COSY to either *exo-NH* or *endo-
NH*. A COSY experiment on \([\text{Re(CO)}_3(aepn)]\text{PF}_6\) (6) in DMSO-$d_6$ showed NH-CH correlations
(Supporting Information) which leave no doubt about the assignment of the NH signals (Figure
2.6) of the 6-membered ring. NMR results indicate that 6-membered rings in 1, 2, 3, and 6 have
an *endo-C* conformation (Figure 2.5).

The COSY spectrum of 6 establishes that pucker of the 5-membered ring is *endo-C* in
solution, the same conformation as in the solid. Thus the 6-membered ring induces a preferred
endo-C conformation in the 5-membered ring in both the solution and solid states. Note that the ring bearing the tmbSO₂ group in the case of [Re(CO)₃(tmbSO₂-dien)] also induces a preferred ring conformation in both states, but this conformation is exo-C.²³

For [Re(CO)₃(trenH)](PF₆)₂ (4), both 5-membered chelate rings will time average between endo-C and exo-C conformations in solution. Thus, as expected for a symmetrical complex with two 5-membered rings, the NH-CH COSY cross-peaks in DMSO-d₆ have similar intensity and do not allow assignment of the signals to a specific proton (Figure A.4, Supporting Information). However, we can use the clear pattern that the upfield NH signal arises from the exo-NH to assign the NH signals of 4 (Table 2.4).

**Factors Influencing Shifts of NH Signals for Six- vs. Five-Membered Rings.**

Assignments and shifts of NH signals of new complexes in several solvents are summarized in Table 2.4. Spectra are shown in Figure 2.6 and in Supporting Information. An important goal of the current study is to understand factors influencing NH shifts for 6-membered rings. Our interest focuses on the dependence of shifts on through-space and solvent effects, and thus we must factor out the through-bond inductive effect on shift of the extra methylene group in the 6-membered rings vs. 5-membered rings of fac-[Re(CO)₃L]n complexes. The through-bond inductive effect is best assessed by considering the shift of the signal of the central NH group.

As illustrated in Figure 2.6, the central NH signal of [Re(CO)₃(dipn)]⁺ in DMSO-d₆, is more upfield (6.01 ppm, Table 2.4) than that of [Re(CO)₃(dien)]⁺ (6.98 ppm).²⁴ The more upfield shift of the NH signal of a central N joining 6-membered rings than for an N joining 5-membered rings²⁴ can also be observed in acetonitrile-d₃ and acetone-d₆ (Table 2.4). Furthermore, the shift of the central NH of [Re(CO)₃(aepn)]⁺ is 6.47 ppm; thus, the shift for the compound with one 5- and one 6-membered ring is almost exactly between the shifts for the 5,5- and 6,6- compounds. This relationship is also found for the central NH signal of [Re(CO)₃(N,N-Me₂dipn)]⁺ (6.34 ppm)
vs. that of its corresponding dien analogue, \([\text{Re(CO)}_3(N,N-\text{Me}_2\text{dien})]^+ (7.02 \text{ ppm})\). Thus, there is an inductive through-bond, upfield-shifting effect of ~0.3 to 0.5 ppm for every 5- to 6-membered ring change. This finding is also true for acetone-\(d_6\) and acetonitrile-\(d_3\), even though the specific values quoted above are for DMSO-\(d_6\).

If this inductive effect alone were influencing the shifts of the \textit{exo}-NH and \textit{endo}-NH signals, then these also would be shifted upfield by ~0.3 to 0.5 ppm for every 5- to 6-membered ring change (Figure 2.6). For \([\text{Re(CO)}_3(\text{dipn})]^+\), in DMSO-\(d_6\), the upfield \textit{exo}-NH signal (3.78 ppm) is more upfield than the \textit{exo}-NH signal for \([\text{Re(CO)}_3(\text{dien})]^+ (4.14 \text{ ppm})\), and the \textit{endo}-NH signal (5.22 ppm) is also more upfield than for \([\text{Re(CO)}_3(\text{dien})]^+ (5.43 \text{ ppm})\). A comparison of NH shifts in DMSO-\(d_6\) for this pair of complexes (Figure 2.6) and several more pairs of complexes [\text{trpnH} vs. \text{trenH} (Supporting Information); \(N^\prime\)-Medipn vs. \(N^\prime\)-Medien;\(^{24}\) and \(N,N\)-\text{Me}_2\text{dipn vs. }\(N,N\)-\text{Me}_2\text{dien}\(^{24}\)] indicates that the \textit{exo}-NH signal is upfield by an average of ~0.4 ppm and the \textit{endo}-NH signal is upfield by an average of ~0.2 ppm for complexes with two 6-membered rings vs. those with two 5-membered rings. We attribute these differences to the inductive effect and suggest that the effect on signals of terminal amine proton signals is smaller than on central secondary amine NH signals. At present not enough information exists to interpret the causes of these small differences, but it is clear that the shifts of the NH\(_2\) signals of one chelate ring depend slightly on the features of the other chelate ring (\textit{cf.} Figure 2.6).

The NH protons of \([\text{Re(CO)}_3(\text{tacn})]^+ (7)\) may be considered to resemble closely the central NH protons of Re tricarbonyl complexes containing 5-membered rings such as \([\text{Re(CO)}_3(\text{dien})]^+\). These NH protons are directed toward solvent, away from the hydrophobic pocket. The \(^1\text{H}\) NMR shifts of the NH signals of \([\text{Re(CO)}_3(\text{tacn})]^+\) in DMSO-\(d_6\) (7.06 ppm), acetonitrile-\(d_3\) (5.57 ppm), and acetone-\(d_6\) (6.62 ppm) are very similar to those of \([\text{Re(CO)}_3(\text{dien})]^+ (6.98, 5.57, \text{ and } 6.57 \text{ ppm in DMSO-}d_6, \text{ acetonitrile-}d_3, \text{ and acetone-}d_6,\)
respectively). Because [Re(CO)₃(tacn)]⁺ lacks competing exo-NH and endo-NH protons, we use [Re(CO)₃(tacn)]⁺ as a control to help interpret the effect of Cl⁻ upon the central NH signals of the new complexes in the studies to be described next.

**Interaction of exo-NH Groups with the Cl⁻ Anion.** The effects of Cl⁻ addition on NH shifts for 5 mM solutions of several complexes in DMSO-d₆ were assessed. Upon the addition of Et₄NCl, the observed shift changes, Δδ, of the exo-NH signals of 1, 2, 4, 5 and 6 (Figures 2.7-2.9 and A.5 and A.6, Supporting Information) were downfield (+ values). (The smaller Δδ’s for the endo-NH and the central NH signals are discussed below.)

For [Re(CO)₃(dipn)]⁺ (1), the shift changes of the exo-NH signal (Δδ = ~1.4 ppm, plateau at [Cl⁻] of ~75 mM, Figure 2.7) were comparable to those for [Re(CO)₃(dien)]⁺ (Δδ = ~1.2 ppm, plateau at [Cl⁻] of ~100 mM). Following a reported treatment of the Δδ data, we calculated the equilibrium constant for ion-pairing ([Re(CO)₃L]ⁿ⁺ + X⁻ᵐ⁻ ↔ [Re(CO)₃L]ⁿ⁺X⁻ᵐ⁻) in DMSO-d₆ at 25 °C. A value of 168 ± 26 M⁻¹ was calculated for the equilibrium constant for [Re(CO)₃(dipn)]⁺ + Cl⁻ ↔ [Re(CO)₃(dipn)]⁺Cl⁻. This value is comparable to that reported for [Re(CO)₃(dien)]⁺ (93 ± 11 M⁻¹). The non-bonded distance between the two exo-NH’s in [Re(CO)₃(N'-Medipn)]PF₆ (2), a complex with two representative 6-membered conformations, is 2.475 Å, a value similar to the 2.509 Å distance in [Re(CO)₃(dien)]PF₆, a representative compound with two 5-membered chelate rings.

The standard method for calculating ion-pairing equilibrium constants in DMSO-d₆ gave values for the [Re(CO)₃(aepn)]⁺,Cl⁻ equilibrium of 210 ± 12 M⁻¹ (exo-N1H Δδ plateau = 1.33 ppm) and 188 ± 13 M⁻¹ (exo-N3H Δδ plateau = 1.49 ppm) for the NH’s. In the molecular structure of 6 (Figure 2.2), the distance between the two exo-NH’s is 2.314 Å. For [Re(CO)₃(trenH)]²⁺ (4), this distance is 2.571 Å, and Cl⁻ ion-pairing caused a large Δδ for the
exo-NH (1.2 ppm). For \([\text{Re(CO)}_3(\text{trpnH})]^2+\) (5), the distance between the exo-NH’s is 2.336 Å, and the exo-NH \(\Delta\delta\) plateau = 1.5 ppm. However, the ion-pairing equilibrium constant could not be determined well, possibly because of the extra charge and the dangling charged group (see below).

**Figure 2.7.** Effect of \(\text{Cl}^-\) on \(\Delta\delta\) of the NH signals of \([\text{Re(CO)}_3(\text{dipn})]\text{PF}_6\) (1) and \([\text{Re(CO)}_3(\text{tacn})]\text{PF}_6\) (7) (designated as tacn-NH) in DMSO-\(d_6\) at 25 °C.

**Figure 2.8.** Effect of \(\text{Cl}^-\) on \(\Delta\delta\) of the NH signals of \([\text{Re(CO)}_3(\text{N’-Medipn})]\text{PF}_6\) (2) in DMSO-\(d_6\) at 25 °C.
Figure 2.9. Effect of Cl\textsuperscript{−} on Δδ of the NH signals of [Re(CO)\textsubscript{3}(aepn)]PF\textsubscript{6} (6) in DMSO-\textit{d\textsubscript{6}} at 25 °C. A COSY spectrum was used to assign the NH signals.

The new results on \textit{exo}-NH signals reported in this section are consistent with our previous interpretations as follows: the chloride ion interacts with the two \textit{exo}-NH groups; this interaction involves the formation of H-bonds to chloride; and the two chelate rings sterically impede access of the solvent to the \textit{exo}-NH’s.

Effect on \textit{endo}-NH and Central NH Signals of Cl\textsuperscript{−} Anion Interaction with the \textit{exo}-NH and Central NH Groups. DMSO-\textit{d\textsubscript{6}} As Solvent. The plots of NH signal shift vs. Cl\textsuperscript{−} concentration (Figures 2.7-2.9 and in Figures A.5 and A.6, Supporting Information) are revealing. As the Cl\textsuperscript{−} concentration is increased, particularly beyond the concentration at which the large Δδ of the \textit{exo}-NH signal plateaus, the \textit{endo}-NH signals (and sometimes the central NH signal) shift upfield (-Δδ). At higher Cl\textsuperscript{−} concentration the shift changes reverse and the signal may shift downfield slightly (+Δδ) from the upfield-shifted position. These Δδ are not large (<0.2 ppm and usually < 0.1 ppm), but similar trends were found both in acetonitrile, see below, and in
earlier studies.\textsuperscript{24} Previously no attempt was made to explain the small shifts, but it is now clear that these small $\Delta \delta$'s are real and are interpretable.

The $\Delta \delta$ for \textit{endo}-NH and central NH signals can be explained by invoking two counteracting factors, one upfield-shifting and the other downfield-shifting. One or the other factor prevails in some cases, and the two nearly cancel each other in the other cases.

The \textit{downfield shifting factor} arises from $\text{Cl}^- \text{H}$ bonding with the NH group as discussed above. However, both the \textit{endo}-NH and central NH groups are H-bonded to solvent and are downfield; thus the the $\Delta \delta$'s are small in comparison to the $\Delta \delta$ observed for the less solvated \textit{exo}-NH groups, which have upfield signals in the absence of $\text{Cl}^-$ and exhibit large downfield $\Delta \delta$'s in the presence of $\text{Cl}^-$.

The \textit{upfield-shifting factor} arises from the fact that $\text{Cl}^-$ H-bonding with an NH group will result in the release of electron density from the N-H bond into the N-Re and N-C bonds. In the present study, the \textit{exo}-NH bonds of the terminal amines are affected by this H-bonding. In turn, the electron density in the \textit{endo}-NH bonds (and less so in the central NH bond) will increase, causing an upfield shift change (-$\Delta \delta$). This explanation, which we believe is compelling, adds additional evidence that the ion-pairing at the \textit{exo}-NH site involves H-bonding. Because the interaction of $\text{Cl}^-$ at the \textit{exo}-NH site is favorable, this \textit{upfield-shifting factor} is most likely to prevail over the \textit{downfield-shifting factor} at low $\text{Cl}^-$ concentration. This reasoning explains the shift changes shown in Figures 2.7 to 2.9 and A.5 to A.9.

For $\text{[Re(CO)\textsubscript{3}(dipn)]}^+$ (1) and $\text{[Re(CO)\textsubscript{3}(aepn)]}^+$ (6) (Figure 2.2), the shift patterns of the two \textit{endo}-NH signals DMSO-$d_6$ (Figures 2.7 and 2.9) are informative. At low $\text{Cl}^-$ concentration the two \textit{endo}-NH signals shift upfield. We believe this behavior is clear evidence for the
preferred ion-pairing of the Cl\(^-\) to the \textit{exo}-NH protons, which causes the electron density to increase near the \textit{endo}-NH protons and the consequent upfield shift.

For \([\text{Re(CO)}_3(\text{dipn})]^+ (1)\), as the Cl\(^-\) concentration is increased and the ion-pairing at the \textit{exo}-NH site is saturated, the Cl\(^-\) added to the solution then builds to a sufficient concentration to interact detectably with the central NH, as can be deduced from the reversal of the direction of shift changes of the central NH signal (Figure 2.7). This H-bonding of the central NH begins to reverse the direction of the shift change around the plateau Cl\(^-\) concentration.

For \([\text{Re(CO)}_3(\text{dipn})]^+\) the \textit{endo}-NH \(\Delta \delta\) is \(\sim -0.1\) ppm. However, for complexes in which the central N has an alkyl group, the \textit{endo}-NH signal upfield shift change is smaller, such as for \([\text{Re(CO)}_3(N'-\text{Medipn})]^+ (2) (\Delta \delta \sim -0.03\) ppm, Figure 2.8), \([\text{Re(CO)}_3(\text{trenH})]^2+ (4) (\Delta \delta \sim -0.04)\) ppm, Figure A.5, Supporting Information), and \([\text{Re(CO)}_3(\text{trpnH})]^2+ (5) (\Delta \delta \sim -0.07)\) ppm, Figure A.6, Supporting Information). This finding is readily explained by the fact that the central NH H-bonding site is absent. Thus, after the first anion to interact binds at the preferred \textit{exo}-NH binding site, the next anion to interact with this ion pair necessarily forms an H-bond to the \textit{endo}-NH proton. As a result, the changes in shift from the two factors (upfield shift from electron density changes from \textit{exo}-NH interaction and downfield shift from \textit{endo}-NH H-bonding) nearly cancel, and only very small \textit{endo}-NH \(\Delta \delta\) values are observed (Figure 2.8 and Figures A.5 and A.6, Supporting Information).

\([\text{Re(CO)}_3(\text{aepn})]^+ (6)\) in DMSO-\(d_6\) exhibits interesting behavior as the Cl\(^-\) concentration increases (Figure 2.9). The secondary Cl\(^-\) anion interaction with the central NH shifts this signal downfield. This is the same shift behavior we observed previously with \([\text{Re(CO)}_3(\text{dien})]^+\).\(^{24}\) As we suggested above, the extra methylene group of the 6-membered rings leads to electron donation to the NH groups. Thus, the central NH is more electron-rich when attached to a 6-
membered ring. The lower electron density of a 5-membered ring of \([\text{Re(CO)}_3(\text{aepn})]^+\) (6) is also indicated by the slight downfield shift of the upfield-shifted 5-membered ring endo-NH signal (Figure 2.9). No such \(\Delta \delta\) is exhibited by the 6-membered ring endo-NH signal for \([\text{Re(CO)}_3(\text{aepn})]^+\) (6) (Figure 2.9).

When Cl\(^-\) was added to a 5 mM solution of \([\text{Re(CO)}_3(\text{tacn})]^+\) (7) in DMSO-\(d_6\), only downfield shifting of the NH signal was observed (maximum \(\Delta \delta = 0.17\) ppm, light blue full circles, Figure 2.7). As mentioned above, the NH protons of 7 are directed toward solvent (Figure 2.4). Also, our analysis above comparing central NH shifts to the \([\text{Re(CO)}_3(\text{tacn})]^+\) NH shift indicates clearly that the NH groups in \([\text{Re(CO)}_3(\text{tacn})]^+\) are like the central NH of linear triamines. Thus, the downfield shift observed supports our interpretation that at high Cl\(^-\) concentration, the central NH groups form H bonds to added Cl\(^-\) anion.

For \([\text{Re(CO)}_3(\text{trenH})]^2+\) (4), the Cl\(^-\) ion-pairing caused a large \(\Delta \delta\) for the exo-NH (1.2 ppm) and a small negative \(\Delta \delta\) for the endo-NH (-0.04 ppm) signal (Figure A.5, Supporting Information). This behavior is similar to that of other complexes without the dangling groups, such as \([\text{Re(CO)}_3(\text{N’-Medipn})]^+\) (2). This similarity suggests no synergism involving the dangling \(\text{NH}_3^+\) (\(\Delta \delta = 0.8\) ppm). Indeed, the protons of the dangling \(\text{NH}_3^+\) group of \([\text{Re(CO)}_3(\text{trenH})]^2+\) cannot come close enough to interact with the Cl\(^-\) hydrogen bonded to the exo-NH groups in the 1:1 ion pair. After rotation of torsion angles using Chem3D software, the closest distance between endo-NH and \(\text{NH}_3^+\) protons is \(\sim 3.65\) Å. Both protons could interact with a Cl\(^-\) anion in an ion pair. However, this type of synergistic ion-pair interaction appears to be unfavorable because neither plateauing of \(\Delta \delta\) at low added Cl\(^-\) anion concentration nor significant endo-NH \(\Delta \delta\) values were observed. Similar results were obtained for \([\text{Re(CO)}_3(\text{trpnH})]^2+\) (5) (Figure A.6, Supporting Information).
**Interaction of Cl⁻, Br⁻ and I⁻ Anions with [Re(CO)₃(dipn)]⁺. Acetonitrile-}_d₃ As Solvent.** In order to compare the effect of halide size on ion-pairing interactions with [Re(CO)₃(dipn)]⁺, the halide titration experiments were performed in acetonitrile-}_d₃, because we were concerned that the larger halide anions might bind too weakly in DMSO-}_d₆.

As expected from past studies with Et₄NCl, the weakness of the interactions of acetonitrile with the NH as compared to DMSO facilitate Cl⁻ interaction with the exo-NH groups, leading to larger Δδ and lower Cl⁻ ion concentration for leveling off of Δδ (Δδ = 3 ppm, plateau at ∼10 mM Cl⁻, Figure A.7 Supporting Information). As found previously, the sharpness of the shift changes makes the NMR method for determining ion pairing equilibrium constants inaccurate.

The above titration was repeated with a “buffering” amount of 50 mM Et₄NPF₆. Aliquots of a stock solution of 150 mM Et₄NCl and 5 mM [Re(CO)₃(dipn)]⁺ were added into a 5 mM [Re(CO)₃(dipn)]⁺ / 50 mM Et₄NPF₆ acetonitrile-}_d₃ solution. The Δδ values obtained (Figure A.7 (right), Supporting Information) were almost identical to those obtained without added PF₆⁻ (Figure A.7 (left), Supporting Information).

When the Et₄NBr salt was used, the final Δδ (2.5 ppm) was slightly less than for Et₄NCl; the plateau occurred at ∼10 mM Br⁻ (Figure A.8, Supporting Information). A much higher Et₄NI concentration (∼15 mM) was required to reach a plateau (Δδ = 1.5 ppm) (Figure A.9, Supporting Information). The interaction of halide ions with the exo-NH groups thus decreases in the order, Cl⁻ > Br⁻ > I⁻ (Figure 2.10).

Of some interest, the two counteracting factors (H-bonding-induced electron density changes at the proton and anion H-bonding) influencing Δδ of the endo-NH signal and the central NH signal in DMSO-}_d₆ also explain the Δδ of these NH signals in acetonitrile-}_d₃. In particular,
as shown in Figure A.9, Supporting Information, the \textit{endo}-NH signal of \([\text{Re(CO)}_3(\text{dipn})]^+\) in acetonitrile-\(d_3\) shifts upfield rather little (\(\Delta\delta = -0.1\) ppm) with added \(\Gamma^-\) compared to the effect of \(\text{Cl}^-\) (\(\Delta\delta = -0.4\) ppm). A small upfield shift could be caused by the downfield shifting effect of direct \(\Gamma^-\) interaction with the \textit{endo}-NH. However, \(\Gamma^-\) has a very small direct effect. Thus, the smallness of the upfield shift undoubtedly arises from the weakness of the interaction of \(\Gamma^-\) with the \textit{endo}-NH group. The interaction of \(\Gamma^-\) causes very little change in electron density at the \textit{endo}-NH proton. The results fully support our conclusions above.

\textbf{Figure 2.10.} Effect of \(\text{Cl}^-\), \(\text{Br}^-\), and \(\Gamma^-\) on \(\Delta\delta\) of the \textit{exo}-NH signals of \([\text{Re(CO)}_3(\text{dipn})]\text{PF}_6\) (1) in acetonitrile-\(d_3\) at 25 °C.

\textbf{Interaction of the Paramagnetic Anion, \([\text{ReBr}_6]^{2-}\), with \([\text{Re(CO)}_3(\text{dipn})]^+\).} When \([\text{Bu}_4\text{N}]_2[\text{ReBr}_6]\) was added to a 5 mM solution of \([\text{Re(CO)}_3(\text{dipn})]^+\) in acetonitrile-\(d_3\), upfield shift changes (negative \(\Delta\delta\)) for the NH signals were observed. At 1.65 mM \([\text{ReBr}_6]^{2-}\), \(\Delta\delta\) for the \textit{exo}-NH (-3.6 ppm) was much greater than for the \textit{endo}-NH (-1 ppm). However, during the
titration, the *exo*-NH signal of 1 was often lost under CH$_2$ multiplets (both from 1 and from [Bu$_4$N]$^+$ ions) in the $^1$H NMR spectral region of 1-3.5 ppm.

We reasoned that by exchanging the NH’s to ND’s to obtain [Re(CO)$_3$(dipn-$d_5$)]$^+$, and by performing $^2$H NMR spectroscopy on the sample in normal solvent (CH$_3$CN), we should be able to obtain exact $\Delta \delta$ values throughout the titration. Accordingly, $^2$H NMR experiments were performed on [Re(CO)$_3$(dipn-$d_5$)]$^+$ (5 mM, 600 µL) in CH$_3$CN, and upfield $\Delta \delta$ were noted upon each addition of aliquots of a 30 mM stock solution of [Bu$_4$N]$_2$[ReBr$_6$] containing 5 mM [Re(CO)$_3$(dipn-$d_5$)]$^+$. Figure 2.11 shows a plot of $\Delta \delta$ vs. [ReBr$_6$]$^{2-}$ concentration. At a final [ReBr$_6$]$^{2-}$ concentration of 10 mM, no further upfield shift was observed for the *exo*-ND signal, and the maximum $\Delta \delta$ was -6.1 ppm. For the *endo*-ND signal, the maximum $\Delta \delta$ was only ca. -1.8 ppm. For the central ND signal, the $\Delta \delta$ was negligible (0.03 ppm). Thus, the greater sensitivity of the *exo*-ND signal of 1 to the large paramagnetic [ReBr$_6$]$^{2-}$ anion indicates clearly that this anion interacts with the *exo*-ND groups. The NMR data indicate strong interactions, and we estimate the ion-pairing constant to be greater than 1,000 M$^{-1}$. However, accurate constants cannot be obtained. We further note that the large negative $\Delta \delta$ values leave no doubt that [ReBr$_6$]$^{2-}$ is acting as an outer-sphere paramagnetic shift reagent.

A preliminary investigation using [Re(CO)$_3$(N,N-Me$_2$dipn)]$^+$ showed that the *exo*-NH group did not interact strongly with the [ReBr$_6$]$^{2-}$ anion. This result is consistent with our interpretation of the nature of the anion interactions. Namely, we propose that the anions interact simultaneously with two *exo*-NH groups. Alternatively, the *exo*-NMe group could sterically prevent the anion from closely approaching the *exo*-NH.
Figure 2.11. Effect of $[\text{ReBr}_6]^{2-}$ on $\Delta \delta$ of the ND signals of $[\text{Re(CO)}_3(\text{dipn-}d_5)]\text{PF}_6$ in DMSO-$d_6$ at 25 °C.

2.4 Conclusions

The introduction of a third CH$_2$ group, changing a dimethylene chain bridging the donor atoms in a 5-membered chelate ring to a trimethylene chain, does not significantly alter the exposure of the exo-NH groups of $\text{fac-}[\text{Re(CO)}_3\text{L}]^n$ complexes to solvent. The exo-NH signal is relatively upfield for both 5- and 6-membered chelate rings. Adding the third CH$_2$ group affects chiefly the ring conformation and the electron richness of the central NH group anchoring the two chelate rings in $\text{fac-}[\text{Re(CO)}_3\text{L}]^n$ complexes.

The 6-membered chelate rings favor the chair conformation in both the solid and solution states. Specifically the most common conformations are designated as being endo-C. Thus, COSY data allow unambiguous assignment of the exo-NH and endo-NH signals, even when L is
a symmetrical ligand. In contrast, the conformational interchange between the $\lambda,\lambda$ and $\delta,\delta$ conformations (or as we designate pucker, between the $\text{endo-C,exo-C}$ and $\text{exo-C,endo-C}$ conformations) precludes the use of COSY to assign NH$_2$ signals when L is a symmetrical ligand with two 5-membered rings. However, at least for L in which there are no dangling groups or in which the dangling group is on the central N, the signals can be assigned by recognizing that the upfield NH signal of the NH$_2$ group is the $\text{exo-NH}$ signal.

The electron richness of the central NH group resulting from the third CH$_2$ group leads to upfield shifts of the NH signal, with the upfield-shifting inductive effect *increasing* along the series: two 5-membered rings < one 5- and one 6-membered ring < two 6-membered rings. Consistent with this trend, the interaction of the Cl$^{-}$ anion with this central NH group (as assessed with $^1$H NMR shift changes) *decreases* along this series, as would be expected from the increase in electron density at the proton. The latter observation reveals the utility of the use of the Cl$^{-}$ anion in combination with $^1$H NMR shift changes to probe the properties of the NH groups of complexes. Our work focuses on $\text{fac-[Re(CO)$_3$L]}^\text{n}$ complexes of potential radiopharmaceutical utility. However, the anion probe method to assess the solvation around complexes and the variation in electron distribution should apply to other types of compounds, including complexes of other metals. Indeed, the [ReBr$_6$]$^{2-}$ anion appears to be a promising H-bonding outer-sphere paramagnetic shift reagent, which complements the halide ions used in this study and earlier.$^{24,32}$

The small upfield shifts observed for the $\text{endo-NH}$ signal support the concept that two $\text{exo-NH}$ groups simultaneously form H-bonds to the anion in the ion pair. These upfield $\text{endo-NH}$ shifts are best understood as arising from the increase of electron density in the $\text{endo-N-H}$ bond resulting from the interaction of the two $\text{exo-NH}$ groups with the anion. Larger halide anions form H-bonds in the ion pair, but the interaction is weaker. The alteration of the electronic
properties of $L$ decreases with increasing halide size. Ion-pair stability decreases with halide size. However, the dianionic charge of the large $[\text{ReBr}_6]^{2-}$ anion overcomes this instability problem to a large extent, and the increased stability provides another reason that this anion should be explored more fully in future as an outer-sphere shift reagent.

2.5 References


CHAPTER 3

SEVERAL NOVEL N-DONOR TRIDENTATE LIGANDS FORMED IN CHEMICAL STUDIES OF NEW \( \text{fac-Re(CO)}_3 \) COMPLEXES RELEVANT TO \( \text{fac-}^{99m}\text{Tc(CO)}_3 \) RADIOPHARMACEUTICALS. ATTACK OF A TERMINAL AMINE ON COORDINATED ACETONITRILE

3.1 Introduction

Radiopharmaceuticals containing the \( \text{fac-}^{99m}\text{Tc}^I(\text{CO})_3 \)^+ core hold promise for the development of new clinically useful imaging agents, \( \text{fac-}^{99m}\text{Tc}^I(\text{CO})_3L^n \) (L is a facially coordinated tridentate ligand). The development of \( ^{99m}\text{Tc} \) radiopharmaceutical agents benefits from an understanding of the features of \( \text{fac-}[\text{Re}^I(\text{CO})_3L]^n \) analogues. Also, \( ^{186}\text{Re} \) and \( ^{188}\text{Re} \) are among the most promising radionuclides for therapeutic applications. Many ligands having the ability to chelate facially with three donors such as N or a combination of N and O donors form stable and kinetically inert complexes with the \( \text{fac-}[\text{M}^I(\text{CO})_3]^+ \) core \( (\text{M} = ^{99m}\text{Tc, Re}) \).

Although N donor groups are superior to the carboxylate O donor group in enhancing the ability of L to form \( \text{fac-}^{99m}\text{Tc}^I(\text{CO})_3L^n \) complexes, carboxylate groups generally have superior biological properties as radiopharmaceutical renal imaging agents. \( ^{1,7} \text{fac-}[^{99m}\text{Tc}^I(\text{CO})_3(\text{NTA})]^2^- \) \( (\text{NTAH}_3 = \text{nitrilotriacetic acid}) \) was recently reported to have pharmacodynamic renal clearance properties in rats good enough to merit testing in humans. This radiopharmaceutical is based on an aminopolycarboxylate ligand that can realistically form only one isomer. However, renal imaging agents with other target ligands, which usually have more N donors (such as polyaminopolycarboxylic acid ligands), form isomers under the normal aqueous conditions in which they are made. The presence of isomers complicates biomedical imaging.

While much of our work has centered on examining preparations of fac-[M(CO)₃L]ⁿ (M = Re or ⁹⁹mTc) complexes in water,¹,⁷,⁸,¹⁰-¹⁴ for a number of reasons we wished to explore preparative chemistry in non-aqueous solvents. First, understanding the non-aqueous chemistry might allow us to prepare renal agents with only one or mainly one isomer. Second, isostructural technetium (radioactive imaging) and rhenium (fluorescence microscopic imaging) compounds allow correlation of images from in vivo and in vitro studies, respectively.⁴,¹⁵,¹⁶ However, the ligands needed to prepare fluorescent compounds are often only sparingly soluble in aqueous media. Third, for some L, the preparation of fac-[M(CO)₃L]ⁿ (M = Re or ⁹⁹mTc) complexes in water was not successful. Reasoning that reactions in organic solvents might be followed more easily in real time by NMR spectroscopy, we decided to evaluate fac-[Re(CO)₃(CH₃CN)₃]⁺ as a soluble precursor for synthesizing fac-[Re(CO)₃L]ⁿ compounds in organic solvents. We began our work with relatively simple tridentate amine ligands because complexes of several of these ligands had already been prepared in water.

Treatment of fac-[Re(CO)₃(CH₃CN)₃]⁺ with various tridentate amine ligands has produced several novel compounds, which most likely arise from reaction of the coordinated nitrile with ligand terminal amines. The reactivity of coordinated nitriles is an important, well-studied topic, and the reader is referred to several excellent recent reviews and articles for background information.¹⁷-²⁰

An important goal is to interpret how structure affects the NMR spectra of the fac-[Re¹(CO)₃L]ⁿ complexes. Previous work having this goal benefited from the study of the interaction of the chloride anion with the protons of the Re-NH groups of fac-[Re(CO)₃L]ⁿ complexes.¹⁰ The topic of metal complexes as anion receptors is currently under intense study.²¹-²³ Thus, we utilize here the same approach to evaluate the interaction of Cl⁻ with some of the new fac-[Re(CO)₃L]ⁿ complexes because these complexes have unusual NH groups. When
discussing specific compounds, we generally do not use the \textit{fac}- designation because all the new compounds have this geometry.

\subsection*{3.2 Experimental Section}

\textbf{Materials.} Re(CO)$_{10}$, diethylenetriamine (dien), \(N,N',N'\prime\)-trimethyldiethylenetriamine (\(N,N',N'\prime\)-Me$_3$dien), \(N,N',N',N'\prime\prime\)-pentamethyldiethylenetriamine (\(N,N',N',N'\prime\prime\)-Me$_5$dien), tetraethylammonium chloride, AgPF$_6$ and AgBF$_4$ from Aldrich, \(N,N\)-dimethyldiethylenetriamine (\(N,N\)-Me$_2$dien) from Ames Laboratories, \(N,N',N'\prime\)-triethylidienetriamine (\(N,N',N'\prime\)-Et$_3$dien) from City Chemical LLC, and \(N'\)-methyldiethylenetriamine (\(N'\)-Medien) from TCI America were used as received. Re(CO)$_5$Br, and [Re(CO)$_3$(CH$_3$CN)$_3$]$^+$ salts were synthesized by using slight modifications of known methods.$^{24-26}$ [Re(CO)$_3$(dien)]PF$_6$ was prepared as previously reported.$^{10}$

\textbf{NMR Measurements.} $^1$H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Peak positions are relative to TMS or solvent residual peak, with TMS as reference. All NMR data were processed with TopSpin and Mestre-C software.

\textbf{X-ray Data Collection and Structure Determination.} Colorless single crystals were placed in a cooled nitrogen gas stream at 90 K on a Nonius Kappa CCD diffractometer fitted with an Oxford Cryostream cooler with graphite-monochromated Mo K\(\alpha\) (0.71073 Å) radiation. Data reduction included absorption corrections by the multi-scan method, with HKL SCALEPACK.$^{27}$ All X-ray structures were determined by direct methods and difference Fourier techniques and were refined by full-matrix least squares by using SHELXL97.$^{28}$ All non-hydrogen atoms were refined anisotropically. All H atoms were visible in difference maps, but were placed in idealized positions, except for some on N, which were refined when their positions were not unambiguously predictable. A torsional parameter was refined for each methyl group. The anion in [Re(CO)$_3$(EAE)]BF$_4$ also exhibits both orientational and substitutional
disorder. The F atoms of the BF$_4^-$ occupy two sets of sites, and a site of apparent $\sim$5% occupancy by Br$^-$ lies near the B position.

\[
[\text{Re(CO)}_3(\text{DAE})]\text{BF}_4 \quad (\text{DAE} = (Z)-N'-'(2-(2-(\text{dimethylamino})\text{ethylamino})\text{ethyl})\text{acetimidamide}).
\]

$N,N'$-Me$_2$dien (15 µL, 0.10 mmol) was added to a solution of
\[
[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{BF}_4 \quad (48 \text{ mg, 0.10 mmol})
\]
in 6 mL of acetonitrile, and the reaction mixture was heated at reflux for 24 h. The volume was reduced to $\sim$2 mL, and diethyl ether was added until a fine precipitate was just visible. The reaction mixture was allowed to stand at room temperature; colorless crystals were observed in 2-3 days (15 mg, 28% yield). $^1$H NMR signals (ppm) in DMSO-$d_6$: 7.99 (s, 1H, NH), 7.28 (s, 1H, NH), 7.10 (s, 1H, NH), 3.19 (m, 4H, CH$_2$), 3.03 (s, 3H, CH$_3$), 2.97 (m, 2H, CH$_2$), 2.63 (m, 2H, CH$_2$), 2.44 (s, 3H, CH$_3$), 2.31 (s, 3H, CH$_3$).

The product was characterized by single-crystal X-ray diffraction.

\[
[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6 \quad (\text{MAE} = N'-'N-(2-(\text{methyl})-(2-(\text{methylamino})\text{ethyl})\text{amino})\text{ethyl})\text{acetimidamid}.e
\]

A 10% excess of $N,N',N'-'$-Me$_2$dien (16 µL, 0.11 mmol) was added to a solution of
\[
[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{PF}_6 \quad (54 \text{ mg, 0.10 mmol})
\]
in 10 mL of acetonitrile. The reaction mixture was heated at reflux for 24 h. A white powder was collected, which later gave X-ray quality crystals upon slow evaporation of a methanol solution (29 mg, 48% yield). $^1$H NMR signals (ppm) in DMSO-$d_6$: 7.17 (s, 1H, NH), 4.50 (s, 1H, NH), 4.22 (m, 1H, CH$_2$), 3.20 (m, 1H, CH$_2$), 3.10 (s, 3H, CH$_3$), 3.03 (m, 2H, CH$_2$), 2.98 (s, 3H, CH$_3$), 2.91 (d, 3H, N1CH$_3$), 2.80 (m, 2H, CH$_2$), 2.60 (m, 2H, CH$_2$), 2.14 (s, 3H, CH$_3$). The above complex can be prepared more readily and reliably by the following procedure: $N,N',N'-'$-Me$_2$dien (14 µL, 0.10 mmol) was added to a solution of
\[
[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{PF}_6 \quad (54 \text{ mg, 0.10 mmol})
\]
in 8 mL of acetonitrile, and the reaction mixture was heated at reflux for 16 h, whereupon a very small amount of a fine precipitate was visible. The reaction mixture was transferred to a vial and allowed to evaporate to
dryness at room temperature. The residue was dissolved in methanol, an excess of diethyl ether was added, and the mixture was left at room temperature. The white precipitate that had aggregated into clumps after 2 days was scraped from the walls of the vial, placed on a filter, and washed with diethyl ether. The NMR spectrum of this precipitate was identical to that of the crystals described above. The BF$_4^-$ salt could also be obtained by using a similar procedure, which yielded a white precipitate having an NMR spectrum identical to that of the PF$_6^-$ crystals; however, the precipitate could not be crystallized.

**[Re(CO)$_3$(MAEH)F]PF$_6$.** Crystallization of the precipitate obtained during one of the syntheses of [Re(CO)$_3$(MAE)]PF$_6$ produced two types of crystals. One type, which was more abundant, was that just described for [Re(CO)$_3$(MAE)]PF$_6$, as confirmed by measurement of the unit cell dimensions. The less abundant type of crystals (needle-like), characterized by single-crystal X-ray diffraction, contained [Re(CO)$_3$(MAEH)F]PF$_6$. $^1$H NMR signals (ppm) of the mixture in DMSO-$d_6$ attributable to [Re(CO)$_3$(MAEH)F]PF$_6$: 6.93 (s, N4H), 6.19 (s, N1H), 3.03 (s, CH$_3$), 2.99 (s, CH$_3$), 2.56 (d, N1CH$_3$), 2.23 (s, C12H$_3$).

**[Re(CO)$_3$(EAE)]BF$_4$ (EAE = N-ethyl-N-(2-ethyl-(2-(ethylamino)ethyl)amino)ethyl)acetimidamide).** A 10% excess of $N,N',N''$-Et$_3$dien (20 µL, 0.11 mmol) was added to a solution of [Re(CO)$_3$(CH$_3$CN)$_3$]BF$_4$ (48 mg, 0.10 mmol) in 6 mL of acetonitrile, and the reaction mixture was heated at reflux for 16 h. The volume was reduced to ~2 mL, and diethyl ether (10-15 mL) was added, whereupon a fine precipitate formed. After about 30 min the precipitate was collected on a filter and washed with diethyl ether (24 mg, 40% yield). (When the precipitate was too fine to filter, crystals could be obtained by letting the mixture stand covered and undisturbed for 1 day.) Crystals suitable for single-crystal X-ray diffraction grew upon slow evaporation of a solution of the compound in methanol. $^1$H NMR signals (ppm) in DMSO-$d_6$: 7.03 (s, 1H, NH), 4.40 (s, 1H, NH), 4.15 (m, 1H, CH$_2$), 3.42 (m, 2H, CH$_2$), 3.20 (m, 2H, CH$_2$).
3.08 (m, 5H, CH₂), 2.80 (m, 2H, CH₂), 2.62 (m, 2H, CH₂), 2.18 (s, 3H, CH₃), 1.23 (t, 3H, CH₃), 1.14 (overlapping triplets, 6H, CH₃). The PF₆⁻ salt could also be obtained by using a similar procedure, which yielded a white precipitate having an NMR spectrum identical to that of [Re(CO)₃(EAE)]BF₄.

**Cl⁻ Titrations.** Aliquots of a NEt₄Cl stock solution containing 5 mM of the desired fac-[Re(CO)₃(L)]⁺ complex in DMSO-d₆ or acetonitrile-d₃ was added to 600 µL of a 5 mM solution of the complex, giving 1 to 140-150 mM Cl⁻. The solution was monitored by ¹H NMR spectroscopy upon each addition.

**Addition of Base to [Re(CO)₃(MAE)]PF₆ and [Re(CO)₃(EAE)]BF₄.** A 5 mM solution of [Re(CO)₃(MAE)]PF₆ crystals in DMSO-d₆ (600 µL) was treated with aqueous sodium hydroxide (0.1 M, 10 µL), and the solution was monitored by ¹H NMR spectroscopy. Similar experiments were conducted with a dilute NaOH solution (0.033 M, 10 µL) and with [Re(CO)₃(EAE)]BF₄ (0.1 M, 10 µL).

### 3.3 Results and Discussion

**Synthetic Results.** New [Re(CO)₃L]ⁿ products prepared from [Re(CO)₃(CH₃CN)₃]PF₆/BF₄ in acetonitrile are shown in Scheme 3.1. In water starting with [Re(CO)₃(H₂O)₃]⁺, the ligands in Scheme 3.1 coordinate unchanged in a tridentate fashion to form normal [Re(CO)₃L]ⁿ products.¹⁰ Because dien and N,N,N’,N”-Me₅dien gave the same normal [Re(CO)₃L]ⁿ products in acetonitrile starting with [Re(CO)₃(CH₃CN)₃]PF₆/BF₄ (details not given) or in water starting with [Re(CO)₃(H₂O)₃]⁺,¹⁰ the formation of different products in acetonitrile than in water for N,N-Me₂dien, N,N’,N”-Me₅dien, and N,N’,N”-Et₃dien is attributable to the presence in these ligands of both steric bulk and NH groups. The reaction pathways in acetonitrile leading to the
compounds in Scheme 3.1 are best discussed after we describe the structures of the new \([\text{Re(CO)}_3\text{L}]^\text{b}\) complexes.

\[ \text{Scheme 3.1.} \] Products obtained in the syntheses using acetonitrile as a solvent. The compound numbers correspond to the structures in Figures 3.1 and 3.2. Adventitious HF from the decomposition of PF\(_6^-\) transformed some of 2a to 2b.

**Structural Results.** All complexes reported here exhibit a pseudo octahedral structure, with the three carbonyl ligands occupying one face and having typical Re–CO bond distances.\(^{10}\) The remaining three coordination sites are occupied by three nitrogen atoms of novel ligands in \([\text{Re(CO)}_3(\text{DAE})]\text{BF}_4\) (Figure 3.1), \([\text{Re(CO)}_3(\text{MAE})]\text{PF}_6\) (Figure 3.2a), and \([\text{Re(CO)}_3(\text{EAE})]\text{BF}_4\) (Figure 3.2c). However, in \([\text{Re(CO)}_3(\text{MAEH})\text{F}]\text{PF}_6\), two coordination sites are occupied by nitrogens and the third by fluoride (Figure 3.2b). Crystal data and details of the structural refinement for all these complexes are summarized in Table 3.1. The atom numbering systems in
the ORTEP figures are used to describe the solid-state data. All complexes in Table 3.2 have a five-membered chelate ring with comparable N1–Re–N2 angles.

**Figure 3.1.** ORTEP plot of the cation in [Re(CO)₃(DAE)]BF₄. Thermal ellipsoids are drawn with 50% probability.

**Figure 3.2.** ORTEP plots of the cations in (a) [Re(CO)₃(MAE)]PF₆, (b) [Re(CO)₃(MAEH)F]PF₆, and (c) [Re(CO)₃(EAE)]BF₄. Thermal ellipsoids are drawn with 50% probability.
Table 3.1. Crystal Data and Structure Refinement for [Re(CO)$_3$(DAE)]BF$_4$ (1), [Re(CO)$_3$(MAE)]PF$_6$ (2), [Re(CO)$_3$(MAEH)F]PF$_6$ (3), and [Re(CO)$_3$(EAE)]BF$_4$ (4)

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$^a R = (\sum |F_o| - |F_c|)/\sum |F_o|; \quad ^b wR2 = [\sum [w(F_o^2 - F_c^2)^2]/\sum w(F_o^2)]^{1/2}, \quad$ in which $w = 1/[(\sigma^2(F_o^2) + (dP)^2 + (eP))]$ and $P = (F_o^2 + 2F_c^2)/3, d = 0.0368, 0.0192, 0.0151, \text{ and } 0.0305 \text{ and } e = 5, 5.2495, 4.1664, \text{ and } 1.826 \text{ for } [\text{Re(CO)}_3(\text{DAE})]\text{BF}_4, [\text{Re(CO)}_3(\text{MAE})]\text{PF}_6, [\text{Re(CO)}_3(\text{MAEH})F]\text{PF}_6, \text{ and } [\text{Re(CO)}_3(\text{EAE})]\text{BF}_4, \text{ respectively.}$
Table 3.2. Selected Bond Distances (Å) and Angles (deg) for [Re(CO)$_3$(DAE)]BF$_4$ (1), [Re(CO)$_3$(MAE)]PF$_6$ (2), [Re(CO)$_3$(MAEH)F]PF$_6$ (3), and [Re(CO)$_3$(EAE)]BF$_4$ (4)

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* The N3–C10 bond distance of 1 should be compared with the N3–C11 bond distance of complexes 2-4.  
  b Nx = N3.  
  c N4.  
  d Cx = C10.  
  e Cx = C11.

The molecular structure of [Re(CO)$_3$(DAE)]BF$_4$ (Figure 3.1) reveals that the bound tridentate DAE ligand is an addition product between N,N-Me$_2$dien and acetonitrile. None of the Re-bound N’s are derived from acetonitrile. One of the two five-membered chelate rings anchored by the central N (N2) is terminated by N3, the original N,N-Me$_2$dien primary amine N.
The relatively short N3–C10 bond (1.293(6) Å; C10 is the original nitrile C) indicates double-bond character and an sp\(^2\) N. The other chelate ring is terminated by N1, the original \(N,N'\)-Me\(_2\)dien tertiary amine N.

In \([\text{Re(CO)}_3(\text{MAE})]\text{PF}_6\) (Figure 3.2a), one terminal amine N of the \(N,N',N''\)-Me\(_3\)dien ligand has now become an endocyclic nitrogen (N3) having three bonds to C and no NH bonds. This N has characteristics of an sp\(^2\) N and is part of a seven-membered chelate ring terminated by N4 (the original nitrile N) and anchored by N2, the original \(N,N',N''\)-Me\(_3\)dien central N. N2 anchors the other chelate ring, and thus an uncommon five-membered/seven-membered chelate ring combination is created.

The bond lengths and angles centered on N3, N4 and C11 show that these are sp\(^2\) hybridized (relatively planar, bond angles near 120°) and that the N4–C11–N3 grouping exhibits electron delocalization. The N4–C11 (1.318(3) Å) and N3–C11 (1.344(3) Å) bonds show double-bond character. \([\text{Re(CO)}_3(\text{EAE})]\text{BF}_4\) (Figure 3.2c) has a structure very similar to that of \([\text{Re(CO)}_3(\text{MAE})]\text{PF}_6\), differing only in having ethyl groups instead of methyl groups at N1, N2, and N3.

Compared to \([\text{Re(CO)}_3(\text{MAE})]\text{PF}_6\), the molecular structure of \([\text{Re(CO)}_3(\text{MAEH})\text{F}]\text{PF}_6\) (Figure 3.2b) has the striking feature that N4 (derived from acetonitrile) is no longer part of an NH group bound to Re; the N4H has been protonated to become a dangling NH\(_2\) group, as found in \([\text{Re(CO)}_3(\text{DAE})]\text{BF}_4\). This NH\(_2\) group forms a hydrogen bond to F, which is directly bound to Re.

Other complexes are known to have a seven-membered chelate ring similar to the type found in the MAE and EAE complexes.\(^{29-32}\) One example is cis-\([\text{Pt(NH}=\text{CPhNBu}^t\text{CH}_2\text{CH}_2\text{NH}^t\text{Bu}^t]\text{Cl}_2\); Natile and co-workers\(^{30}\) described this pseudo square
planar Pt\textsuperscript{II} compound as the final product of the addition of \(N,N'\text{-Bu}_2\text{ethylenediamine}\) to coordinated benzonitrile. The obvious difference in geometry between six-coordinate Re\textsuperscript{I} tricarbonyl complexes versus four-coordinate Pt\textsuperscript{II} complexes might suggest that useful comparisons are not possible because octahedral complexes are usually subject to greater interligand steric interactions. However, Re\textsuperscript{I} tricarbonyl complexes are sterically undemanding because of the small size of the CO ligands and the relatively long bonds made by Re\textsuperscript{I}. Bond distances involving Re\textsuperscript{I} are longer than those involving Pt\textsuperscript{II}.\textsuperscript{11,25,33,34} N–M–N bite angles for chelate rings in related Pt\textsuperscript{II} and Re\textsuperscript{I} compounds are more acute in Re\textsuperscript{I} compounds.\textsuperscript{11,35} We believe this is true because the chelate rings normally adopt a preferred conformation or pucker; this conformation fixes the N-to-N non-bonded distance. However, the angles in the Pt\textsuperscript{II} and the Re\textsuperscript{I} seven-membered chelate rings being compared here have similar values, 89.0(7) and 90.47(7)°, in contrast to the normal situation. Also in contrast to the normal situation, the non-bonded distance between these N atoms is much smaller in the Pt complex (2.79(2) Å) than in the Re complex (3.178(3) Å). The seven-membered chelate ring may be inherently strained and, unlike in other cases, the longer Re–N bond distances seem to allow the ring to reduce strain, explaining the unusually long N-to-N non-bonded distance, the large N–Re\textsuperscript{I}–N bite angle, and the low chelate ring pucker in Re\textsuperscript{I} vs. Pt\textsuperscript{II} (Figure B.1, Supporting Information). This strain aids in the transformation of the seven-membered chelate ring to a five-membered chelate ring as discussed next.

Implications for the Reaction Pathway Forming [Re(CO)\textsubscript{3}(DAE)]BF\textsubscript{4} from the Structures of [Re(CO)\textsubscript{3}(MAE)]PF\textsubscript{6} and [Re(CO)\textsubscript{3}(MAEH)F]PF\textsubscript{6}. We believe that a complex of the [Re(CO)\textsubscript{3}(MAE)]\textsuperscript{+} type initially formed as an intermediate, which then rearranged to give [Re(CO)\textsubscript{3}(DAE)]\textsuperscript{+} (Scheme 3.2). We propose that the early phase of the reaction between \(N,N\text{-Me}_2\text{dien}\) and [Re(CO)\textsubscript{3}(CH\textsubscript{3}CN)\textsubscript{3}]BF\textsubscript{4} includes an attack of a terminal amine on the sp carbon of
a coordinated acetonitrile. This attack leads to formation of a seven-membered ring (as found in
$[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6$); this ring then rearranges to give the $[\text{Re(CO)}_3(\text{DAE})]\text{BF}_4$ product. The
key reason that the rearrangement is possible relates to the fact that the putative
$[\text{Re(CO)}_3(\text{MAE})]^+$ type intermediate on the pathway to the $[\text{Re(CO)}_3(\text{DAE})]\text{BF}_4$ product would
have an endocyclic NH (N3H) rather than an N3Me group in the seven-membered ring of
$[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6$ (Scheme 3.3).

**Scheme 3.2.** The likely pathway for DAE ligand formation from $N,N$-Me$_2$dien and acetonitrile
(green). Stars indicate the location of the lone pair on the nitrogens known to be used or likely to
be used in Re coordination at each stage of the process. The $\text{fac-}\{\text{Re(CO)}_3\}^+$ fragment is not shown.

**Scheme 3.3.** The likely pathway for MAE ligand formation from $N,N',N''$-Me$_3$dien and
acetonitrile (green). Stars indicate the location of the lone pair on the nitrogens known to be used or likely to
be used in Re coordination at each stage of the process. The $\text{fac-}\{\text{Re(CO)}_3\}^+$ fragment is not shown. Only one proton can be transferred (in the second step). The hypothetical step
which would be needed to form the DAE analogue does not occur because the methyl group can not transfer.

The stable $[\text{Re(CO)}_3(\text{MAE})]^+$ and $[\text{Re(CO)}_3(\text{EAE})]^+$ compounds share with the stable Pt
compound, $\text{cis-}\{\text{Pt(NH=CPhNBu'CH}_2\text{CH}_2\text{NHBu')Cl}_2\}$, the feature that the endocyclic non-
coordinated nitrogen does not have a bound proton. All bonds to N3 in $[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6$ are
to carbon. The N3 atom in this ring has no lone pair available to coordinate to Re. However, the
similarly situated N3 of the postulated seven-membered ring of the intermediate on the pathway
to [Re(CO)₃(DAE)]BF₄ has one bound proton; this N3H could release its proton as it generates the lone pair needed to form the Re–N3 bond. This proton can serve as the proton needed to convert the dissociating N4H to a NH₂ group (Scheme 3.2); this process could be stepwise or concerted. In the Supporting Information, we illustrate some of these points using a scheme based on the X-ray structures.

The large angle within the chelate ring involving N4 (Re–N4–C11 ~ 139°) of [Re(CO)₃(MAE)]PF₆ provides evidence that strain may predispose N4 to dissociate. The molecular structure of [Re(CO)₃(MAEH)F]PF₆ (Figure 3.2b) may provide some evidence as to the tendency of N4H to dissociate and be protonated to form an NH₂ group. Although the process involves a proton from the HF formed in situ from the PF₆⁻ anion or present as an impurity in the AgPF₆ reagent, [Re(CO)₃(MAEH)F]PF₆ may be considered to resemble a species that could be present in the rearrangement pathway discussed in the preceding paragraph if the process is not concerted.

**NMR Spectroscopy.** All complexes reported were characterized by NMR spectroscopy in DMSO-"d₆" and acetonitrile-"d₃". On the basis of the molecular structure of [Re(CO)₃(MAE)]PF₆, two different types of NH groups are present, as illustrated in Figure 3.3. For fac-[Re(CO)₃L]ⁿ complexes,⁷,¹⁰ N1H is referred to as an exo-NH proton, as it points away from the carbonyl groups (versus an endo-NH proton pointing toward the carbonyl groups). The N4H is not classified in this way because N4 is sp² hybridized. Two ¹H NMR peaks of [Re(CO)₃(MAE)]PF₆ in DMSO-"d₆" decreased in size when D₂O was added, indicating that these are NH signals. The broad NH signal at 4.50 ppm (Table 3.3), assigned to the exo-N1H from the COSY cross-peak to the N1CH₃ doublet at 2.91 ppm (Figure B.2, Supporting Information), falls within the range observed for exo-NH’s.¹⁰ Of the four methyl peaks for [Re(CO)₃(MAE)]PF₆, only N1CH₃ could
be a doublet. The sharp NH peak at 7.17 ppm, which must be from N4H, has a COSY cross-peak to a singlet at 2.14 ppm; this must be the C12H$_3$ signal.

**Figure 3.3.** Designation of the *exo*-NH proton (pointing away from the carbonyl groups and toward the hydrophobic pocket of the ligand) of [Re(CO)$_3$(MAE)]PF$_6$ and [Re(CO)$_3$(EAE)]BF$_4$. N4H is not classified as either *endo* or *exo*.

**Table 3.3.** $^1$H NMR Chemical Shifts (ppm) of [Re(CO)$_3$(DAE)]BF$_4$ (1), [Re(CO)$_3$(MAE)]PF$_6$ (2), and [Re(CO)$_3$(EAE)]BF$_4$ (4) in DMSO-$d_6$ at 25 °C and Selected NH Shifts in Acetonitrile-$d_3$.

<table>
<thead>
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<th></th>
<th>1</th>
<th>2</th>
<th>4</th>
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<tbody>
<tr>
<td><em>exo</em>-N1H</td>
<td>4.50 (3.39)</td>
<td>4.40 (3.22)</td>
<td></td>
</tr>
<tr>
<td>N2H</td>
<td>7.10 (5.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N4H/N4Ha</td>
<td>7.28 (6.02)</td>
<td>7.17 (6.41)</td>
<td>7.03 (6.28)</td>
</tr>
<tr>
<td>N4Hb</td>
<td>7.99 (6.48)</td>
<td></td>
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</tr>
<tr>
<td>CH$_3$CN-derived CH$_3$</td>
<td>2.31</td>
<td>2.14</td>
<td>2.18</td>
</tr>
<tr>
<td>C7H$_2$</td>
<td>3.19</td>
<td>4.22, 3.20</td>
<td>4.15, 3.42</td>
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$^a$ Assignments of the NH signals were verified by COSY spectra in DMSO-$d_6$. NH shifts in acetonitrile-$d_3$ are enclosed in parentheses.

Additional confirmation for the C12H$_3$ signal assignment comes from the presence of a similar methyl singlet at 2.18 ppm in the spectrum of [Re(CO)$_3$(EAE)]BF$_4$, which can have only the C12H$_3$ signal as a singlet because the other three methyl groups are in the ethyl groups. Many
signals such as a multiplet at \( \sim 4.2 \) ppm (assigned by COSY to one of the protons of the C7H\textsubscript{2} methylene group bonded to the delocalized N3–C11–N4 amidine group) and the NH signals have similar shifts for both [Re(CO)\textsubscript{3}(MAE)]PF\textsubscript{6} and [Re(CO)\textsubscript{3}(EAE)]BF\textsubscript{4} (Table 3.3). For both, the NH signals are more upfield in acetonitrile versus DMSO, a finding attributable to the weaker interaction of acetonitrile with the NH groups.

For [Re(CO)\textsubscript{3}(DAE)]BF\textsubscript{4} (Figure 3.1), 2D NMR experiments were used to assign the signals in DMSO-\( d_6 \) (Figures B.3 and B.4, Supporting Information), and NH signals were identified by addition of D\textsubscript{2}O (Table 3.3). The N1CH\textsubscript{3} signals were assigned from an NOE cross-peak at 3.03 and 2.44 ppm. The peak of the central NH (N2H, 7.10 ppm) was identified by COSY and NOE correlations with two multiplets, at 3.19 and 2.97 ppm, from the N2-CH\textsubscript{2} groups. The COSY cross-peak between the relatively sharp NH peak at 7.28 ppm (Figure 3.4) and the CCH\textsubscript{3} signal at 2.31 ppm (Figure B.4, Supporting Information) assigns these to N4Ha and the methyl group derived from acetonitrile. (See Figure 3.5 for the designations of the N4Ha and N4Hb protons.) This assignment was confirmed by the relatively stronger NOE cross-peak from the CCH\textsubscript{3} peak to the N4Hb signal (7.99 ppm) than to the N4Ha signal.

In general, the NH signals of the new compounds were sharp at 25 \(^\circ\)C. In contrast, for [Re(CO)\textsubscript{3}(DAE)]BF\textsubscript{4} the NH\textsubscript{2} peaks were sharp in DMSO-\( d_6 \) but broad in acetonitrile-\( d_3 \) (Figure 3.4), a solvent that interacts weakly with NH groups. We reasoned that the NH\textsubscript{2} group may rotate at room temperature, but that DMSO may restrict this rotation by H-bonding to the NH\textsubscript{2} protons. Indeed, all three NH signals were sharp in acetonitrile-\( d_3 \) at -5 \(^\circ\)C. Increasing the temperature resulted in considerable broadening of the NH\textsubscript{2} signals (Figure B.5, Supporting Information). The peak width of the central NH (N2H) was hardly affected. The behavior of the NH\textsubscript{2} signals above 25 \(^\circ\)C was complicated, suggesting that a dynamic process in addition to rotation about the C–N bond occurs at elevated temperatures. Therefore, we performed a ROESY experiment at -5 \(^\circ\)C in
acetonitrile-$d_3$. The spectrum contained a negative cross-peak between NH signals at 6.58 and 6.02 ppm (Figure B.6, Supporting Information). The magnitude was larger than a negative N4Ha-N4Hb exchange cross-peak in a ROESY spectrum recorded in DMSO-$d_6$ at room temperature (Figure B.3, Supporting Information). Thus, the rate of rotation of the N4H$_2$ group is faster in acetonitrile-$d_3$ at –5 °C than in DMSO-$d_6$ at 25 °C.

**Figure 3.4.** $^1$H NMR spectrum showing NH signals of [Re(CO)$_3$(DAE)]BF$_4$ in DMSO-$d_6$ at 25 °C (top), in acetonitrile-$d_3$ at 25 °C (middle), and in acetonitrile-$d_3$ at -5 °C (bottom).

**Figure 3.5.** Designation of the N4Ha and N4Hb protons of [Re(CO)$_3$(DAE)]BF$_4$, indicating the proximity of N4Hb to the methyl group and the rotation of the NH$_2$ group.

**NH to ND Exchange.** After addition of D$_2$O (100 µL) to DMSO-$d_6$ solutions (5 mM, 600 µL), the two NH$_2$ protons of [Re(CO)$_3$(DAE)]BF$_4$ underwent immediate H to D exchange, whereas the central N2H had an exchange half-life of ~5 min. A similar experiment for
[Re(CO)\(_3\)(MAE)]PF\(_6\) showed that the \textit{exo}-NH in the terminal NH(CH\(_3\)) group had a half-life of \(\sim 30\) min, and N4H had a half-life of 24 h. The N4H exchange half-life of [Re(CO)\(_3\)(EAE)]BF\(_4\) (24 h) was the same as that of [Re(CO)\(_3\)(MAE)]PF\(_6\). However, the half-life of the exchange of the \textit{exo}-N1H of [Re(CO)\(_3\)(EAE)]BF\(_4\) was longer (~1 h) than that of [Re(CO)\(_3\)(MAE)]PF\(_6\), undoubtedly because of the better electron donation of Et vs. Me. These results indicate that the Re-bound sp\(^2\) N of the seven-membered ring is relatively electron rich and therefore could protonate and dissociate.

Under similar experimental conditions, the exchange half-lives of the [Re(CO)\(_3\)(dien)]PF\(_6\) complex were found to be \(\sim 1\) h, 2 h, and 12 h for the central, \textit{exo}-NH and \textit{endo}-NH protons, respectively.

**Interaction of NH Protons with the Cl\(^-\) Anion.** When Cl\(^-\) was added to 5 mM solutions of \textit{fac}-[Re(CO)\(_3\)L\(^+\)] complexes, downfield shift changes, \(\Delta \delta\), were observed.\(^{10}\) The \(\Delta \delta\) of the relatively upfield [Re(CO)\(_3\)(MAE)]PF\(_6\) \textit{exo}-N1H signal reached a plateau of \(\sim 1.3\) ppm at 100 mM Cl\(^-\) in DMSO-\(d_6\) (Figure 3.6). This behavior is in agreement with the finding that the \textit{exo}-NH group typically shifts downfield by \(\sim 1\) ppm in DMSO-\(d_6\) on addition of Cl\(^-\) to \textit{fac}-[Re(CO)\(_3\)L\(^+\)] complexes having L = dien or simple dien-related derivatives.\(^{10}\) Because H-bonding to solvent causes downfield shifts, the relatively upfield shift of \textit{exo}-NH signals was attributed to steric hindrance to solvation of the \textit{exo}-NH groups of [Re(CO)\(_3\)(dien)]PF\(_6\) by virtue of their being located in the pocket (as illustrated for [Re(CO)\(_3\)(MAE)]PF\(_6\) in Figure 3.3 above). This \(\Delta \delta\) behavior was explained by suggesting that the Cl\(^-\) anion, owing to its small size, can enter the sterically hindered pocket and form H-bonds to the two \textit{exo}-NH’s. These \textit{exo}-NH’s are close enough (~2.5 Å) to interact simultaneously with the chloride ion; this two-proton interaction was more favorable than when only one \textit{exo}-NH was present in the complex.\(^{10}\) A similar explanation
accounts for the $\Delta \delta$ of the \textit{exo}-NH signal of $[\text{Re}(\text{CO})_3(\text{MAE})]\text{PF}_6$. The plot in Figure 3.6 is very close to that for the \textit{exo}-NH of $[\text{Re}(\text{CO})_3(\text{dien})]\text{PF}_6$.\textsuperscript{10} The $\Delta \delta$ of the N4H signal of $[\text{Re}(\text{CO})_3(\text{MAE})]\text{PF}_6$ exactly paralleled that of the \textit{exo}-NH, but $\Delta \delta$ was only $\sim$0.6 ppm. These results are consistent with synergistic interaction with chloride of both NH protons, which are separated by $\sim$2.5 Å (Figure 3.3).

**Figure 3.6.** Change in chemical shift ($\Delta \delta$, ppm) of the NH signals of $[\text{Re}(\text{CO})_3(\text{MAE})]\text{PF}_6$ (5 mM) caused by added Cl$^-$ in DMSO-$d_6$ at 25 °C.

In acetonitrile-$d_3$, on addition of Cl$^-$ the relatively upfield $[\text{Re}(\text{CO})_3(\text{MAE})]\text{PF}_6$ \textit{exo}-N1H signal (at 3.39 ppm, Table 3.3) shifted downfield ($\Delta \delta \sim 3.3$ ppm). The N4H signal (at 6.41 ppm) shifted downfield only $\sim$ 1.8 ppm. The maximum shift change was observed at a much lower concentration of Cl$^-$ in acetonitrile-$d_3$ (20 mM, Figure 3.7) than in DMSO-$d_6$ ($\sim$100 mM), consistent with the weaker H-bonding of the acetonitrile solvent. The plots for $\Delta \delta$ for both signals are parallel for the reason given in the preceding paragraph, namely both protons interact with chloride ion.
Figure 3.7. Change in chemical shift (Δδ, ppm) of the NH signals of [Re(CO)₃(MAE)]PF₆ (5 mM) caused by added Cl⁻ in acetonitrile-d₃ at 25 °C.

When Cl⁻ was added to a solution of [Re(CO)₃(DAE)]BF₄ in acetonitrile-d₃, the three NH signals shifted downfield in parallel (Δδ plateau values at ~110 mM Cl⁻ = ~1.5, ~0.8, and ~2 ppm for N4Ha, N4Hb, and the central NH, respectively, Figure 3.8). A Δδ of 2 ppm is large for a central NH signal, as the maximum change in shift for the central NH of related N donor L’s in fac-[Re(CO)₃L]ⁿ complexes is ≤ 1 ppm and occurs at higher Cl⁻ concentration (unpublished results).¹⁰ The NH₂ group of [Re(CO)₃(DAE)]BF₄ is not close enough to the central NH to interact synergistically with Cl⁻. In other cases in which the central NH group was present, the complex had exo-NH groups that could cooperatively bind the Cl⁻ anion.¹⁰ Thus, Cl⁻ interacted preferentially at this site. The resulting H-bonded ion pair would have zero overall charge, decreasing the interaction of a second Cl⁻ with the central NH of the complex, which is now a neutral ion pair. However, the competing NH₂ site of [Re(CO)₃(DAE)]BF₄ is far from the positive metal center (Figure 3.5), and this group interacts relatively weakly with Cl⁻. Thus, the interaction of Cl⁻ with the central NH may be more favorable than in previous cases.¹⁰ Nevertheless, this interaction is relatively weak because a fairly high Cl⁻ concentration is needed for Δδ of the central NH signal of [Re(CO)₃(DAE)]BF₄ to plateau (Figure 3.8).
Isomerization of $[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6$. One important issue relevant to radiopharmaceuticals is the stereochemistry of coordinated secondary amines, which have two configurations that can interconvert via base catalysis.\textsuperscript{7,10} We assessed isomerization at N1 of $[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6$, resulting from addition of aqueous NaOH to a DMSO-$d_6$ solution. An initial NMR spectrum (Figure 3.9, top) recorded before addition of OH\textsuperscript{−} confirmed that the complex was isomerically pure. After addition of OH\textsuperscript{−} (1.7 mM), a new set of signals observable in the first recorded spectrum (5 min) grew within 20 min to its final intensity (13% new signals vs. 87% initial signals). The new product has a sharp and a broad NH signal (Figure 3.9, bottom) and a methyl doublet (not shown). The broad signal and an associated methyl doublet allow us to establish that the new signals come from the isomer of $[\text{Re(CO)}_3(\text{MAE})]\text{PF}_6$ having the inverted N1 configuration ($\text{endo} \text{NH}$, the H points toward the carbonyls). Upon addition of D\textsubscript{2}O to this base-isomerized sample, the N1CH\textsubscript{3} doublet for both isomers immediately became singlets. The new $\text{endo}$-NH signal is more downfield (6.19 ppm) than the $\text{exo}$-NH signal (4.50 ppm), and the
new \textit{exo}-N1CH$_3$ signal (2.56 ppm) is more upfield than the \textit{endo}-N1CH$_3$ signal (2.91 ppm). The more downfield NH signal correlates with the more upfield CH$_3$ signal. These shift values and correlations agree well with data for chiral [Re(CO)$_3$(N,N',N''$\textprime$-Me$_3$dien)]PF$_6$ (ppm: \textit{endo}-N1H, 6.39, \textit{exo}-N1CH$_3$ doublet 2.66; and \textit{exo}-N1H 5.15, \textit{endo}-N1CH$_3$ doublet 2.94).$^{10}$ The sharp signal (6.90 ppm, Figure 3.9) upfield of the initial N4H signal (7.18 ppm) was assigned to the N4H of this new \textit{endo}-N1H/\textit{exo}-N1CH$_3$ isomer.

![NMR spectra](image)

\textbf{Figure 3.9.} $^1$H NMR spectra of [Re(CO)$_3$(MAE)]PF$_6$ (5 mM) in DMSO-$d_6$ at 25 °C before (top) and 20 min after (bottom) addition of OH$^-$ (1.7 mM). The multiplet at ~4.2 ppm arises from one of the C7H$_2$ protons.

To confirm that OH$^-$ is acting as a catalyst and does not coordinate directly to Re, a 1.7 mM NaOH and a 0.54 mM NaOH solution were prepared from the same stock solution of [Re(CO)$_3$(MAE)]PF$_6$. If hydroxide adds to Re and is not acting as a catalyst, decreasing the hydroxide concentration to 0.54 mM would not only decrease the rate of reaction but would also decrease the percentage of the new product. When the solutions were monitored by NMR spectroscopy, the 1.7 mM NaOH sample reached equilibrium in 20 min as before, whereas the 0.54 mM NaOH sample required more time (1-2 h) to reach equilibrium, as expected. In both solutions, the new product abundance was the same (13%). Thus, hydroxide is not coordinating but is acting as a catalyst.
In the identical 1.7 mM NaOH study, but with [Re(CO)\(_3\)(EAE)]BF\(_4\), the new minor set of signals appeared and reached its maximum intensity in 40 min (12% minor isomer, 88% major isomer). The new *endo*-NH signal appears more downfield (5.78 ppm) than the *exo*-NH signal (4.40 ppm) of the original isomer. The new N4H signal appeared upfield (6.77 ppm) of the initial N4H signal (7.03 ppm). The faster rate of isomerization of [Re(CO)\(_3\)(MAE)]PF\(_6\) versus [Re(CO)\(_3\)(EAE)]BF\(_4\) is attributable to the slightly greater N1H acidity of [Re(CO)\(_3\)(MAE)]PF\(_6\), as suggested by its shorter NH to ND exchange half-life than that of [Re(CO)\(_3\)(EAE)]BF\(_4\).

When Cl\(^-\) was added to a base-isomerized sample of [Re(CO)\(_3\)(MAE)]PF\(_6\), the N1H signal of the minor *endo*-N1H/*exo*-N1CH\(_3\) isomer shifted only minimally downfield (\(\Delta\delta \sim 0.28\) ppm at 150 mM Cl\(^-\)), while the N4H signal was not shifted. The NH signals of the starting major *exo*-N1H/*endo*-N1CH\(_3\) isomer shifted as described previously. This observation highlights a new application of Cl\(^-\) addition as an aid in identifying which isomer of a fac-[Re(CO)\(_3\)L]\(^n\) complex has an *endo*-NH/*exo*-alkyl and which has an *exo*-NH/*endo*-alkyl terminal amine. The small \(\Delta\delta\) for the N4H signal further indicates that this proton is not very acidic. The isomerization at N1 should have no effect on the electronic character of N4. This result and the relatively long half-life for H to D exchange indicate a lower acidity for the N4H. This lower acidity in turn means that N4 is relatively electron rich, and thus N4 is poised to accept a proton during the reaction pathway to [Re(CO)\(_3\)(DAE)]BF\(_4\) (Scheme 3.2).

### 3.4 Conclusions

As shown by Natile et al.\(^{30}\) for a stable Pt\(^{II}\) compound with a closely related seven-membered ring, we conclude that the Re\(^I\) seven-membered chelate rings in [Re(CO)\(_3\)(MAE)]PF\(_6\) and [Re(CO)\(_3\)(EAE)]BF\(_4\) products shown in Scheme 3.1 arise from intramolecular attack by a terminal amine on a coordinated acetonitrile. The novel DAE ligand in [Re(CO)\(_3\)(DAE)]BF\(_4\) provides an interesting and highly unusual variation having an sp\(^2\) N donor derived from an sp\(^3\)
primary amine. Complexed DAE has a five-membered chelate ring and a dangling NH$_2$ group. DAE is formed via a series of steps, and the likely pathway has two proton transfer steps and a Re–N bond disruption step, Scheme 3.2. The stable Pt$^{II}$ and Re$^I$ complexes with seven-membered chelate rings cannot convert to a complex with the DAE-type ligand (Scheme 3.3), because the endocyclic nitrogen bears an alkyl or aryl group rather than the proton needed for the second proton transfer step forming the dangling NH$_2$ group in DAE, as shown in Scheme 3.2. Thus, the seven-membered chelate ring of the MAE-type ligand serves as a model for one likely intermediate in the formation of the DAE ligand. Two types of evidence suggest that the sp$^2$ NH donor bound to Re in this MAE-type ring is poised to undergo dissociation and protonation. First, [Re(CO)$_3$(MAE)]PF$_6$ has a large Re–N4–C11 angle, indicating strain and favoring Re–N bond breaking. Second, N4H is relatively non-acidic (revealed by slow H to D exchange and by weak interaction with chloride ion of the N4H of the minor endo-N1H/exo-N1CH$_3$ isomer of [Re(CO)$_3$(MAE)]PF$_6$), indicating an electron-rich N ready to accept a second proton.

Our studies on chloride interaction complement reports of the use in anion receptors$^{36}$ of transition-metal fragments to serve as scaffolds onto which H-bonding donor groups can be connected.$^{23}$ Chloride and other anions interact with the pyrazole NH’s of fac-[Re$^I$(CO)$_3$(generic pyrazole)$_3$]$^+$ cations.$^{22}$ This work is related to our present findings on chloride interactions with six-coordinate Re$^I$ tricarbonyl complexes. However, we expand the field of the interaction of anions with NH groups in metal complexes by showing that such interactions provide a useful approach for both interpreting NMR data and for elucidating the structure of isomers; such information is useful for probing properties of Re analogues of $^{99m}$Tc radiopharmaceuticals.

3.5 References


CHAPTER 4

SUPERBASIC AMIDINE MONODENTATE LIGANDS IN $fac$-[Re(CO)$_3$(5,5′-
Me$_2$Bipy)(AMIDINE)]BF$_4$ COMPLEXES: DEPENDENCE OF AMIDINE
CONFIGURATION ON THE REMOTE NITROGEN SUBSTITUENTS

4.1 Introduction

The chemistry of amidine complexes of several metals (including platinum, iridium,
cobalt, and manganese) has been described in several reviews.$^{1-3}$ Because the $fac$-$\{\text{M}^1(\text{CO})_3\} \ (\text{M} = \text{Tc or Re})$ core is important in radiopharmaceuticals,$^{4-6}$ the acetonitrile reaction chemistry of
Re$^1$ complexes has recently become a subject of scrutiny.$^{7-9}$

Both of the amidine carbon-to-nitrogen bonds have double-bond character. The bond
between the amidine carbon and the superbasic coordinated nitrogen$^{10-12}$ leads to two
configurations dictating the description of amidine stereochemistry as $E$ or $Z$ (Figure 4.1). When
the remote nitrogen has two different substituents, the two resulting configurations about the
bond to the amidine carbon lead to a total of four conceivable configurations depicted in Figure
4.1 ($E, E’, Z,$ and $Z’$ labels follow previous usage).$^{13,14}$ Whereas detection of isomers involving
the two configurations about the bond between the amidine carbon and the metal-bound nitrogen
is a common occurrence for amidine ligands as well as iminoether ligands,$^{15}$ there have been few
reports of isomers resulting from restricted rotation about the other amidine carbon-to-nitrogen
bond, in part because amidine ligands often have a symmetrical remote NH$_2$ or NR$_2$ grouping,
thus precluding such isomers. Also, in previously studied Re$^1$ carbonyl compounds, ring
formation restricted the amidine stereochemistry.$^{7,8}$

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Marzilli, P. A.; Marzilli, L. G., “Superbasic Amidine Monodentate Ligands in $fac$-[Re(CO)$_3$(5,5′-
Me$_2$Bipy)(Amidine)]BF$_4$ Complexes: Dependence of Amidine Configuration on the Remote
Chemical Society.
Most reports on monodentate amidine ligands of interest to the current study on complexes with the \( \text{fac-}[\text{Re}^\text{I}(\text{CO})_3] \) core involve pseudo square planar Pt\( ^\text{II} \) complexes, about which many studies have been performed in view of the demonstrated cytotoxicity of many iminoether and amidine Pt complexes.\(^\text{13,16-18} \) Iminoether and amidine ligands are related. Natatile and co-workers have contributed substantially to this field because the first Pt\( ^\text{II} \) compound with a trans configuration shown to have anticancer activity was an iminoether complex;\(^\text{19} \) these and other investigators later extended such studies to the evaluation of ketimine\(^\text{20} \) and amidine\(^\text{13,21,22} \) Pt complexes.

**Figure 4.1.** Conceivable \( \text{fac-}[\text{Re}(\text{CO})_3(L)(\text{HNC(CH}_3\text{)}\text{NHR})]^+ \) isomers, in which \( L \) is a bidentate ligand denoted by N–N donor atoms.

In reports on Pt complexes, the dependence of the amidine ligand configuration on the bulk and the presence of NH groups of the remote amidine NR\(_2\), NHR, or NH\(_2\) group in the ligand have been assessed.\(^\text{14,22,23} \) Both amidine ligands in \( \text{trans-}[\text{Pt(HNC(CH}_3\text{)NHCH}_3\text{)}_2\text{Cl}_2] \) have the \( Z \) configuration,\(^\text{22} \) thought to be stabilized by strong intramolecular H-bonds between chloride and the remote NH group.\(^\text{22} \) The amidine ligands in \( \text{cis-}[\text{Pt(HNC(CH}_3\text{)N(CH}_3\text{)}_2\text{Cl}_2] \) lack a remote NH group, however, and adopt the \( E \) configuration.\(^\text{23} \) Belluco et al. reported that, on the basis of \(^1\text{H NMR data, the addition reactions of primary amines and secondary amines to}
cis- and trans-[PtCl₂(PhCN)₂] afforded a complicated mixture of amidine complexes, with the amidine having a mixture of \(E\), \(E'\), \(Z\), and \(Z'\) configurations in CD₂Cl₂.¹⁴ In a more recent study, Marzano et al. conducted additional chemical studies of some of these amidine complexes because they have promising antitumor activity.¹³ These investigators noted that the reaction forming cis-[PtCl₂(HNC(Ph)NHCH₃)₂] afforded a mixture of \(E\), \(E'\), \(Z\), and \(Z'\) isomers, unlike such reactions with acetonitrile derivatives; heating converted the product to the \(Z\) isomer stabilized by intramolecular H-bonding to chloride ligands.¹³ Both steric effects and H-bonding play a role in dictating stereochemistry in these Pt amidine complexes.²²,²³

Nucleophilic attack of pyrazole on a coordinated, metal-activated nitrile resulted in the formation of a pyrazolylamidino chelate ring in Re⁠¹ carbonyl compounds.⁷ We recently reported some unusual Re⁠¹ amidine complexes formed by attack of primary or secondary amine terminal groups of polyamines on coordinated acetonitrile, in one case giving a seven-membered chelate ring.⁸ The starting complex in that study⁸ had three coordinated acetonitrile ligands, and the attacking amines were complicated.

To assess Re⁠¹ amidine chemistry, we have now investigated amidine products formed by treating \(\text{fac-[Re(CO)}₃(5,5’-\text{Me}_2\text{bipy})(\text{CH}_3\text{CN})]\text{BF}_4\) (a complex with only one coordinated acetonitrile) with ammonia and amines (Figure 4.2). In the resulting complexes, such as \(\text{fac-[Re(CO)}₃(5,5’-\text{Me}_2\text{bipy})(\text{HNC(\text{CH}_3)NH})]\text{BF}_4\), the monodentate amidine ligand can conceivably have any of the four possible configurations. Unlike in the cases of many other Re and Pt complexes, these configurations will not be confounded by H-bonding interactions or controlled by ring formation. Only steric and solvent effects and intrinsic electronic structures of the amidine ligands will influence geometry and stability. Two-dimensional NMR spectroscopy, in conjunction with structural characterization of several complexes by single-crystal X-ray
crystallography, has been utilized to evaluate which monodentate amidine ligand configurations (Figure 4.1) are favored in solution.

![Figure 4.1](image)

**Figure 4.2.** [Re(CO)$_3$(L)(HNC(CH$_3$)NHR)]$^+$ isomers observed upon treatment of [Re(CO)$_3$(5,5$'$-Me$_2$bipy)(CH$_3$CN)]$^+$ with RNH$_2$ in acetonitrile at 25 °C.

*Note:* We omit the fac-designation when discussing specific complexes. Also, to simplify the text, we shall use the terms, $E$, $E'$, $Z$, or $Z'$ isomer, to designate the isomers of the entire complex with the amidine ligand in the respective configurations.

### 4.2 Experimental Section

**Starting Materials.** Re(CO)$_5$Br was synthesized as described in the literature.$^{24}$ Re$_2$(CO)$_{10}$, 5,5$'$-dimethyl-2,2$'$-bipyridine (5,5$'$-Me$_2$bipy), isopropylamine, isobutylamine, tert-butylamine, benzylamine, anhydrous methyamine and ammonia in steel cylinders, and AgBF$_4$ were obtained from Aldrich. [Re(CO)$_3$(CH$_3$CN)$_3$]BF$_4$ was synthesized by a slight modification of a known procedure.$^{25}$ The synthesis of [Re(CO)$_3$(5,5$'$-Me$_2$bipy)(CH$_3$CN)]BF$_4$ (I) from [Re(CO)$_3$(CH$_3$CN)$_3$]BF$_4$ is described elsewhere.$^{26}$ Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.
**NMR Measurements.** $^1$H NMR spectra were recorded on a 400 MHz Bruker spectrometer. Peak positions are relative to TMS or solvent residual peak, with TMS as reference. All NMR data were processed with TopSpin and Mestre-C software. For specific assignments of signals listed in the synthetic section below, please see tables in the text and Supporting Information.

**X-ray Data Collection and Structure Determination.** Intensity data were collected at low temperature on a Nonius Kappa CCD diffractometer fitted with an Oxford Cryostream cooler with graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation. Data reduction included absorption corrections by the multi-scan method, with HKL SCALEPACK. All X-ray structures were determined by direct methods and difference Fourier techniques and refined by full-matrix least squares by using SHELXL97. All non-hydrogen atoms were refined anisotropically. All H atoms were visible in difference maps, but were placed in idealized positions, except for N-H hydrogen atoms, which were refined individually where possible. A torsional parameter was refined for each methyl group. For compound 3, the contribution to the structure factors from disordered solvent was removed by using SQUEEZE, amounting to 4/3 molecules of acetonitrile per unit cell. For compounds 3 and 4, BF$_4^-$ sites were shared by a small amount of bromide, and the occupancies of BF$_4^-$ and Br$^-$ were constrained to sum to unity. The occupancies were fixed in final refinements for 3. The structure of compound 6 was determined from a crystal having more substantial substitutional disorder for the anion, apparently about 52% BF$_4^-$ and 48% ReO$_4^-$.

In compound 3, the isobutyl group of one of the two independent cations is disordered into two orientations with 0.725(7)/0.275(7) occupancy. Crystal data and details of refinements are listed in Table 4.1, except for compound 6, for which the cation is illustrated in Supporting Information.
Table 4.1. Crystal Data and Structural Refinement for [Re(CO)$_3$(5,5'-Me$_2$-bipy)(HNC(CH$_3$)NHR)]BF$_4$ Complexes

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$^a$R = ($\Sigma||F_o|-|F_c||)/\Sigma|F_o|$; $^b$wR2 = [\(\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\)]$^{1/2}$, in which w = 1/[$\sigma^2(F_o^2) + (dP)^2 + (eP)$] and P = ($F_o^2 + 2F_c^2$)/3, d = 0.0218, 0.0341, 0.0284, 0.0275, and 0.0331, and e = 1.2987, 0.9602, 0, 1.9993, and 2.9329 for complexes 2-5 and 7, respectively.
Synthesis of $[\text{Re(CO)}_3(5,5'$-Me$_2$ bipy)(HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2).

Isopropylamine (52 $\mu$L, 0.60 mmol) was added to an acetonitrile solution (6 mL) of $[\text{Re(CO)}_3(5,5'$-Me$_2$ bipy)(CH$_3$CN)]BF$_4$ (1, 0.04 g, 0.06 mmol), and the reaction mixture was stirred at room temperature for 24 h. The volume was reduced to $\sim$1 mL by rotary evaporation, and addition of diethyl ether ($\sim$10 mL) produced a yellow crystalline material, which was collected on a filter and washed with diethyl ether and dried; yield, 40 mg (63%). An NMR spectrum recorded immediately upon dissolution of this material showed mostly one set of signals. $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.84 (s, 2H, H6/6$'$), 8.28 (d, 2H, H3/3$'$), 8.04 (d, 2H, H4/4$'$), 6.10 (b, 1H, NH), 4.51(1H, NH), 3.14 (m, 1H, CH), 2.47 (s, 6H, 5/5$'$-CH$_3$), 2.07 (s, 3H, CCH$_3$), 0.74 (d, 6H, 2CH$_3$). However, an NMR spectrum recorded after 15 min shows an equilibrium mixture of $E'$ and $Z$ isomer signals, as observed in the reactions monitored by NMR spectroscopy and described below.

Amine reactions of 1 (10 mM in acetonitrile-$d_3$, 600 $\mu$L) were monitored by NMR spectroscopy; we refer to this as the 10 mM solution. The first spectrum recorded at 5 min showed only reactants. On addition of a 10% excess of isopropylamine (5 $\mu$L) to the 10 mM solution, NMR signals indicative of a mixture of $E'$ and $Z$ isomers of 2 were observed within 30 min (at 6 h, $E'/Z = 64:36$), and these signals continued to grow (while maintaining the same ratio of isomers) until no starting complex remained the next day. $^1$H NMR signals (ppm) in acetonitrile-$d_3$ (cf. Figure 4.2 for atom numbering): 8.84 (s, H6/6$'$), 8.74 (s, H6/6$'$), 8.28 (overlapping d, H3/3$'$), 8.04 (d, H4/4$'$), 6.10 (b, NH), 5.57 (b, NH), 5.33(NH), 4.51(NH), 3.69 (m, CH), 3.14 (m, CH), 2.47 (s, 5/5$'$-CH$_3$), 2.07 (s, CCH$_3$), 1.89 (s, CCH$_3$), 1.21 (d, 2CH$_3$), 0.74
(d, 2CH₃). Slow evaporation of this acetonitrile solution yielded X-ray quality crystals of the E′ isomer. ¹H NMR spectrum in acetonitrile-d₃: identical to that of the bulk precipitate.

[Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHCH₂CH(CH₃)₂)]BF₄ (3). The method described above but with isobutylamine (60 µL, 0.60 mmol) produced a yellow crystalline material; yield, 35 mg (54%). ¹H NMR signals (ppm) in acetonitrile-d₃: 8.84 (s, 2H, H6/6′), 8.29 (d, 2H, H3/3′), 8.04 (d, 2H, H4/4′), 6.29 (b, 1H, NH), 4.52 (1H, NH), 2.49 (m, 2H, CH₂), 2.47 (s, 6H, 5/5′-CH₃), 2.08 (s, 3H, CCH₃), 1.82 (m, 1H, CH), 0.56 (d, 6H, CH₃).

On addition of a 10% excess of isobutylamine (6 µL) to the 10 mM solution, NMR signals of a mixture of E′ and Z isomers of 3 were observed within 10 min, and the reaction was complete the next day. ¹H NMR signals (ppm) in acetonitrile-d₃: 8.84 (s, H6/6′), 8.73 (s, H6/6′), 8.29 (overlapping d, H3/3′), 8.05 (d, H4/4′), 6.29 (b, NH), 5.85 (b, NH), 5.34 (NH), 4.52 (NH), 3.06 (m, CH₂), 2.49 (m, CH₂), 2.47 (s, 5/5′-CH₃), 2.08 (s, CCH₃), 1.87 (s, CCH₃), 1.82 (m, CH), 1.22 (m, CH), 0.95 (d, CH₃), 0.56 (d, CH₃).

X-ray quality crystals of the E′ isomer of 3 were produced upon slow evaporation of the solution of the crystalline material (10 mg) in a 1:5 (v/v) mixture of acetonitrile/diethyl ether.

[Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHCH₂CH(CH₃)₃)]BF₄ (4). The method described above but with tert-butylamine (65 µL, 0.60 mmol) produced a yellow crystalline precipitate (yield, 32 mg, 49%), but the reaction time was longer (4 days). ¹H NMR signals (ppm) in acetonitrile-d₃: 8.85 (s, 2H, H6/6′), 8.30 (d, 2H, H3/3′), 8.06 (d, 2H, H4/4′), 6.11 (b, 1H, NH), 4.30 (1H, NH), 2.47 (s, 6H, 5/5′-CH₃), 2.01 (s, 3H, CCH₃), 0.80 (s, 9H, CH₃).

On addition of a 10% excess of tert-butyl amine (6.5 µL) to the 10 mM solution, NMR signals of a mixture of E′ and Z isomers of 4 were observed only after 1 h (reaction time, ~4
days). $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.85 (s, H6/6'), 8.73 (s, H6/6'), 8.30 (overlapping d, H3/3'), 8.06 (d, H4/4'), 6.11 (b, NH), 5.97 (b, NH), 5.38 (NH), 4.30 (NH), 2.47 (s, 5/5'-CH$_3$), 2.01 (s, CCH$_3$), 1.95 (s), 1.38 (s, CH$_3$), 0.80 (s, CH$_3$). The resulting solution yielded X-ray quality crystals upon slow evaporation.

$\text{[Re(CO)}_3(5,5'\text{-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{NHCH}_2\text{C}_6\text{H}_5)]BF_4$ (5). The method described above but with benzylamine (66 µL, 0.60 mmol) produced a yellow crystalline precipitate; yield, 38 mg (55%). $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.64 (s, 2H, H6/6'), 7.96 (d, 2H, H3/3'), 8.05 (d, 2H, H4/4'), 7.15 (t, 1H), 7.06 (t, 2H), 6.91 (b, 1H, NH), 6.09 (d, 2H), 4.38 (1H, NH), 3.94 (m, 2H, CH$_2$), 2.47 (s, 6H, 5/5'-CH$_3$), 2.18 (s, 3H, CCH$_3$).

On addition of a 10% excess of benzylamine (7 µL) to the 10 mM solution, NMR signals of a mixture of $E'$ and $Z$ isomers of 5 were observed within 15 min, and the reaction was complete the next day. $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.76 (s, H6/6'), 8.64 (s, H6/6'), 8.27 (d, H4/4'), 8.05 (overlapping d, H3/3' Z and H4/4' $E'$), 7.96 (d, H4/4'), 7.38 (t, benzyl), 7.31 (t, benzyl), 7.22 (d, benzyl), 7.15 (t, benzyl), 7.06 (t, benzyl), 6.91 (b, NH), 6.32 (b, NH), 6.09 (d, benzyl), 5.54 (NH), 4.45 (m, CH$_2$), 4.30 (NH), 3.94 (m, CH$_2$), 2.44 (s, 5/5'-CH$_3$), 2.18 (s, CCH$_3$), 1.84 (s, CH$_3$). The resulting solution yielded X-ray quality crystals upon slow evaporation.

**Synthesis of $\text{[Re(CO)}_3(5,5'\text{-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{NHCH}_3)]BF_4$ (6).** The method described above but with methylamine (~30 µL, volume approximate because the volatile methylamine was added from an inverted container) produced a yellow precipitate; yield, 32 mg (52%). $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.83 (s, 2H, H6/6'), 8.28 (d, 2H, H3/3'), 8.05 (d, 2H, H4/4'), 6.80 (b, 1H, NH), 4.50 (1H, NH), 2.25 (d, 3H, NCH$_3$), 2.47 (s, 6H, 5/5'-CH$_3$), 2.07
On addition of a 10% excess of methylamine (∼5 µL) to the 10 mM solution, NMR signals indicative of a mixture of $E'$ and $Z$ isomers of 6 were observed within 20 min ($E'Z = 66:34$) and continued to grow, maintaining the same ratio of isomers until no starting complex signal remained (∼6 h). $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.83 (s, H6/6'), 8.73 (s, H6/6'), 8.28 (overlapping d, H3/3'), 8.05 (d, H4/4'), 6.80 (b, NH), 5.90 (b, NH), 5.29 (NH), 4.50 (NH), 2.87 (d, NCH3), 2.25 (d, NCH3), 2.47 (s, 5/5'-CH3), 2.07 (s, CCH3), 1.86 (s, CCH3). Upon slow evaporation, the resulting solution yielded X-ray quality crystals of the $E'$ isomer.

**Synthesis of [Re(CO)3(5,5'-Me₂bipy)(HNC(CH3)NH2)]BF4 (7).** The method described above but with ammonia bubbling through for ~5 min (medium flow rate) produced a yellow crystalline precipitate; yield, 25 mg (41%). $^1$H NMR spectrum in acetonitrile-$d_3$: identical to that given below. Ammonia gas was bubbled through a 10 mM solution of [Re(CO)3(5,5'-Me₂bipy)(CH₃CN)]BF4 in acetonitrile-$d_3$ (600 µL), and the solution was monitored by NMR spectroscopy. NMR signals of a mixture of $E'$ and $Z$ isomers of 7 were observed. $^1$H NMR signals (ppm) in acetonitrile-$d_3$: 8.79 (s, H6/6'), 8.75 (s, H6/6'), 8.29 (overlapping d, H3/3'), 8.04 (d, H4/4'), 6.30 (b, NH), 5.93 (b, NH), 5.45 (NH), 5.33 (NH), 2.48 (s, 5/5'-CH3), 2.12 (s, CCH3), 1.83 (s, CCH3). When the experiment was repeated in CDCl3, a mixture of isomers formed. $^1$H NMR signals (ppm) in CDCl3: 8.75 (s, H6/6'), 8.60 (s, H6/6'), 8.27 (overlapping d, H3/3'), 7.92 (d, H4/4'), 6.15 (b, NH), 5.86 (b, NH), 5.58 (NH), 2.50 (s, 5/5'-CH3), 2.21 (s, CCH3), 2.17 (s, CCH3). Slow evaporation of this chloroform solution yielded X-ray quality crystals.
**Challenge Reactions.** A 5 mM solution of [Re(CO)$_3$(5,5′-Me$_2$bipy)](HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2) in acetonitrile-$d_3$ (600 µL) was treated with a fivefold excess of 4-dimethylaminopyridine (2.0 mg, 25 mM), and the solution was monitored by $^1$H NMR spectroscopy. A similar experiment was conducted in CDCl$_3$.

**4.3 Results and Discussion**

**Synthesis.** Syntheses of [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NHR)]BF$_4$ complexes were carried out in acetonitrile (R = isopropyl (2), isobutyl (3), tert-butyl (4), benzyl (5), and methyl (6)) at room temperature (Figure 4.2). For R = H (7), acetonitrile or chloroform was used. Reactions were monitored at intervals of 10 min, 1 h, and 1 to 4 days (sometimes also 5 min, 30 min, or 6 h) by NMR spectroscopy. Times required for completion of reaction varied (∼6 h for 6; ∼1 day for 2, 3, 5, 6, and 7; and ∼4 days for 4). For compounds 2 to 6, the ratio of E′ to Z isomers remained the same throughout the course of the reaction. For 7, which has a symmetrical remote nitrogen group, the isomer designation is restricted to E and Z; experimentally, a trace amount of the E isomer was observed in addition to the major isomer, Z.

**Structural Results.** Complexes structurally characterized here, having the general formula, [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NHR)]BF$_4$ (R = alkyl, benzyl or H, Figures 4.3 and 4.4, and Figure C.1, Supporting Information), exhibit a distorted octahedral structure, with the three carbonyl ligands occupying one face. The remaining three coordination sites are occupied by the two nitrogen atoms of the 5,5′-Me$_2$bipy ligand and a nitrogen atom of the neutral monodentate amidine ligand. Crystal data and details of the structural refinement for these complexes are summarized in Table 4.1. The atom numbering systems in the ORTEP figures are used to describe the solid-state data. The Re–C bond distances (not shown) involving the CO
group trans to the amidine group are not significantly different from those of the other Re–C bonds.

Figure 4.3. ORTEP plots of the cations in [Re(CO)$_3$(5,5′-Me$_2$bipy)(E′-HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2), [Re(CO)$_3$(5,5′-Me$_2$bipy)(E′-HNC(CH$_3$)NHCH$_2$CH(CH$_3$)$_2$)]BF$_4$ (3), [Re(CO)$_3$(5,5′-Me$_2$bipy)(E′-HNC(CH$_3$)NHCH$_2$C$_6$H$_5$)]BF$_4$ (4), and [Re(CO)$_3$(5,5′-Me$_2$bipy)(E′-HNC(CH$_3$)NHCH$_2$C$_6$H$_5$)]BF$_4$ (5). Thermal ellipsoids are drawn with 50% probability.
Figure 4.4. ORTEP plot of the cation in [Re(CO)₃(5,5′-Me₂bipy)(Z-HNC(CH₃)NH₂)]BF₄ (7). Thermal ellipsoids are drawn with 50% probability.

These [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHR)]BF₄ complexes (R = isopropyl (2), isobutyl (3), tert-butyl (4), benzyl (5), and methyl (6)) have an amidine ligand in the E′ configuration in the solid state (Figures 4.3, and Figure C.1, Supporting Information), even though NMR data show that both E′ and Z isomers exist in acetonitrile (discussed below). The molecular structure of [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NH₂)]BF₄ (7) reveals that this nonbulky amidine ligand has the Z configuration (Figure 4.4), in contrast to the structures found here for all other crystals.

The Re–N bond lengths of the amidine complexes (Table 4.2) are comparable to those found for typical Re sp² nitrogen bond lengths, which range from 2.14 to 2.18 Å. Likewise, in all cases the bond distances from the amidine carbon (C16) to the two nitrogen atoms, N3 and N4 (see Figure 4.2), are closer to the average sp² C double-bond length to N (C=N, ~1.28 Å) than to the average sp³ C single-bond length to N (C–N, 1.47 Å). For example, in [Re(CO)₃(5,5′-
Me₂bipy)(HNC(CH₃)NHCH(CH₃)₂)BF₄ (2) (Figure 4.3), the bond distances are 1.308(3) Å (N3–C16) and 1.339(3) Å (N4–C16). The N3–C16 (1.266(12) Å) and N4–C16 (1.359(12) Å) bond distances of 7 (Figure 4.4) are generally similar to the relevant distances (Table 4.2) of [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHR)]BF₄ complexes 2 to 5.

Table 4.2. Selected Bond Distances (Å) and Angles (deg) for [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHR)]BF₄ Complexes

<table>
<thead>
<tr>
<th>R = isopropyl</th>
<th>R = isobutyl</th>
<th>R = tert-butyl</th>
<th>R = benzyl</th>
<th>R = H</th>
</tr>
</thead>
<tbody>
<tr>
<td>bond distances</td>
<td>bond distances</td>
<td>bond distances</td>
<td>bond distances</td>
<td>bond distances</td>
</tr>
<tr>
<td>Re–N1</td>
<td>2.1829(19)</td>
<td>2.167(3)</td>
<td>2.183(2)</td>
<td>2.1746(19)</td>
</tr>
<tr>
<td>Re–N2</td>
<td>2.1819(18)</td>
<td>2.178(3)</td>
<td>2.178(3)</td>
<td>2.1874(18)</td>
</tr>
<tr>
<td>Re–N3</td>
<td>2.1810(18)</td>
<td>2.174(3)</td>
<td>2.158(2)</td>
<td>2.181(2)</td>
</tr>
<tr>
<td>N3–C16</td>
<td>1.308(3)</td>
<td>1.307(4)</td>
<td>1.302(4)</td>
<td>1.298(3)</td>
</tr>
<tr>
<td>N4–C16</td>
<td>1.339(3)</td>
<td>1.331(4)</td>
<td>1.340(4)</td>
<td>1.341(3)</td>
</tr>
<tr>
<td>bond angles</td>
<td>bond angles</td>
<td>bond angles</td>
<td>bond angles</td>
<td>bond angles</td>
</tr>
<tr>
<td>N1–Re–N2</td>
<td>75.14(7)</td>
<td>74.89(10)</td>
<td>74.88(9)</td>
<td>75.24(7)</td>
</tr>
<tr>
<td>N1–Re–N3</td>
<td>85.31(7)</td>
<td>83.92(10)</td>
<td>79.73(9)</td>
<td>85.78(7)</td>
</tr>
<tr>
<td>N2–Re–N3</td>
<td>81.33(7)</td>
<td>80.76(10)</td>
<td>79.89(9)</td>
<td>77.56(7)</td>
</tr>
<tr>
<td>Re–N3–H3N</td>
<td>109.5(18)</td>
<td>111(3)</td>
<td>111(2)</td>
<td>115(2)</td>
</tr>
<tr>
<td>Re–N3–C16</td>
<td>135.43(16)</td>
<td>135.4(2)</td>
<td>138.7(2)</td>
<td>135.59(16)</td>
</tr>
<tr>
<td>C16–N3–H3N</td>
<td>114.9(18)</td>
<td>113(3)</td>
<td>110(2)</td>
<td>110(2)</td>
</tr>
<tr>
<td>N3–C16–N4</td>
<td>122.9(2)</td>
<td>123.1(3)</td>
<td>123.6(3)</td>
<td>123.4(2)</td>
</tr>
<tr>
<td>N3–C16–C17</td>
<td>121.45(19)</td>
<td>121.4(3)</td>
<td>120.2(3)</td>
<td>120.8(2)</td>
</tr>
<tr>
<td>N4–C16–C17</td>
<td>115.64(18)</td>
<td>115.4(3)</td>
<td>116.2(3)</td>
<td>115.8(2)</td>
</tr>
<tr>
<td>C16–N4–C18</td>
<td>125.25(18)</td>
<td>124.9(3)</td>
<td>126.8(2)</td>
<td>123.9(2)</td>
</tr>
</tbody>
</table>

a H41 is in place of C18.
The relevant angles of the amidine moiety are all ~120° (Table 4.2), and these facts all indicate electron delocalization along the N–C–N bonds. Furthermore, in all cases as exemplified by 2, the N4–C16 bond is slightly but significantly longer than the N3–C16 bond (Table 4.2), suggesting slightly less double-bond character. These slight differences are reflected in the ease of rotation about the N–C bonds.

The orientation of the amidine ligand of 4 is different from that of compounds 2, 3, and 7. (Figure C.2, Supporting Information shows different orientations of the amidine ligands when the Me₂bipy plane is oriented in a similar manner). These differences in orientation are present in the solid state; there are no indications to imply their presence in solution.

The molecular structure of the benzylamidine complex, [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHCH₂C₆H₅)]BF₄ (5, Figure 4.3), shows that the phenyl ring of the amidine moiety is stacked above the bipyridine ligand. The closest C-to-C non-bonded distances are 3.584, 3.586, and 3.953 Å. Stacking is depicted in side and top-down views of the stacked rings in Supporting Information (Figure C.3). Effects of this stacking on NMR shifts of the bipyridine signals are discussed later.

**NMR Spectroscopy. General Considerations.** All complexes reported in this study were characterized by NMR spectroscopy in acetonitrile-d₃, and selected complexes were studied in other solvents. COSY and ROESY experiments aided in the assignment of the signals of complexes 2, 3, and 4 in acetonitrile-d₃ and of 2 in CDCl₃ and CD₂Cl₂. (For the NMR discussion, the atom numbering in Figure 4.2 is used.) NMR spectra recorded immediately after dissolving crystals of [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHR)]BF₄ (R = isopropyl (2), isobutyl (3), tert-butyl (4), benzyl (5) and methyl (6)) complexes in several solvents showed two to three sets of
signals, which changed in intensity until equilibrium was reached. In general, one set of signals grew slowly, and all other sets (one or two sets, depending on solvent) decreased with time.

Because rotation about the bond between the amidine carbon and the Re-bound N is expected to be slow compared to the rotation about the bond between the amidine carbon and the remote N, this behavior indicates that the first signals observed are from the $E'$ or $E$ isomer (the solid has the $E'$ isomer). This reasoning allowed us to assign unambiguously the initial set(s) of peaks to an isomer with the amidine ligand in the $E'$ or $E$ configuration and the second set to the isomer with the amidine ligand in the $Z'$ or $Z$ configuration. However, 2D NMR data in combination with studies in several solvents and in mixtures of solvents allowed us to conclude that in every case the $E'$ and $Z$ isomers of $\text{[Re(CO)\textsubscript{3}(5,5'\text{-Me\textsubscript{2}bipy})(HNC(CH\textsubscript{3})NHR)]BF\textsubscript{4}}$ complexes coexisted in polar solvents such as acetonitrile-$d\textsubscript{3}$. Only in solvents of low polarity do we observe signals for the $E$ isomer. The $Z'$ isomer was not found in any solvent. As an illustration of our solution studies and 2D NMR analysis of amidine complexes in polar solvents, we first discuss 2 (Figure 4.3) in acetonitrile-$d\textsubscript{3}$; we then extend the discussion to other compounds in this solvent and eventually to other solvents.

**NMR Studies of $\text{[Re(CO)\textsubscript{3}(5,5'\text{-Me\textsubscript{2}bipy})(HNC(CH\textsubscript{3})NHCH(CH\textsubscript{3})\textsubscript{2})]BF\textsubscript{4}}$ (2) in Acetonitrile-$d\textsubscript{3}$**. Upon dissolution of 2 (Figure 4.3) in acetonitrile-$d\textsubscript{3}$, the NMR spectrum showed two sets of signals (Figure 4.5). The less intense set of signals grew in intensity until equilibrium was reached (~15 min, Figure 4.5). Integration as well as the slow isomerization of the complex on dissolution allowed us to identify all signals attributable to each of the two sets. Two singlets for the CCH\textsubscript{3} groups derived from acetonitrile occur at 1.89 ($Z'$ or $Z$) and 2.07 ($E'$ or $E$) ppm. The four broad peaks between 4.5 and 6.1 ppm (Figure 4.6) were identified as NH signals by addition of K\textsubscript{2}CO\textsubscript{3}/D\textsubscript{2}O. A CH multiplet at 3.15 ppm (integrating to one proton) for the $E'$ or $E$ isomer has
a COSY cross-peak with the CH$_3$ doublet (0.74 ppm) from the isopropyl group (Figure 4.7). This CH multiplet correlated in turn with an NH signal at 6.10 ppm, assigning this signal to N4H (Table 4.3). (See Figure 4.2 for designations of the N3H and N4H protons.) Likewise, a similar correlation was observed for peaks of the Z’ or Z isomer of 2; the CH$_3$ doublet (ppm) correlated with the CH multiplet (3.69 ppm), which correlated with the N4H signal at 5.57 ppm (Figure 4.7).

![Figure 4.5](image)

**Figure 4.5.** $^1$H NMR spectra as a function of time after crystals of the $E'$ isomer of [Re(CO)$_3$(5,5'-Me$_2$bipy)(HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2) were dissolved in acetonitrile-$d_3$ at 25 °C.

![Figure 4.6](image)

**Figure 4.6.** $^1$H NMR spectrum of [Re(CO)$_3$(5,5'-Me$_2$bipy)(HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2) in acetonitrile-$d_3$ at 25 °C.
Figure 4.7. $^1$H-$^1$H COSY NMR spectrum of [Re(CO)$_3$(5,5′-Me$_2$-bipy)(HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2) in acetonitrile-$d_3$ at 25 °C.

Table 4.3. Selected $^1$H NMR Shifts (ppm) for Re(CO)$_3$[(5,5′-Me$_2$-bipy)(HNC(CH$_3$)NHR)]BF$_4$ in Acetonitrile-$d_3$ at 25 °C

<table>
<thead>
<tr>
<th>R</th>
<th>isomer</th>
<th>N3H</th>
<th>N4H</th>
<th>CH$_3$ (formerly CH$_3$CN)</th>
<th>N4CH$_n$ $^a$</th>
<th>H6/6′</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl (6)</td>
<td>$E'$</td>
<td>4.50</td>
<td>6.80</td>
<td>2.07</td>
<td>2.25(d) $^b$</td>
<td>8.83</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>5.29</td>
<td>5.90</td>
<td>1.86</td>
<td>2.87(d) $^b$</td>
<td>8.73</td>
</tr>
<tr>
<td>isopropyl (2)</td>
<td>$E'$</td>
<td>4.51</td>
<td>6.10</td>
<td>2.07(s)</td>
<td>3.14(m) $^c$</td>
<td>8.84</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>5.33</td>
<td>5.57</td>
<td>1.89(s)</td>
<td>3.69(m) $^c$</td>
<td>8.74</td>
</tr>
<tr>
<td>isobutyl (3)</td>
<td>$E'$</td>
<td>4.52</td>
<td>6.29</td>
<td>2.08(s)</td>
<td>2.49(m) $^d$</td>
<td>8.84</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>5.34</td>
<td>5.85</td>
<td>1.87(s)</td>
<td>3.06(m) $^d$</td>
<td>8.73</td>
</tr>
<tr>
<td>tert-butyl (4)</td>
<td>$E'$</td>
<td>4.30</td>
<td>6.11</td>
<td>2.01(s)</td>
<td>$^e$</td>
<td>8.85</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>5.38</td>
<td>5.97</td>
<td>1.95(s)</td>
<td>$^e$</td>
<td>8.73</td>
</tr>
<tr>
<td>benzyl (5)</td>
<td>$E'$</td>
<td>4.30</td>
<td>6.91</td>
<td>2.18</td>
<td>3.94(m) $^d$</td>
<td>8.64</td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>5.54</td>
<td>6.32</td>
<td>1.84</td>
<td>4.45(m) $^d$</td>
<td>8.76</td>
</tr>
<tr>
<td>H (7)</td>
<td>$E'$</td>
<td>5.45</td>
<td>6.30, 5.93(b)</td>
<td>2.12</td>
<td>8.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z</td>
<td>5.45</td>
<td>6.30, 5.93(b)</td>
<td>1.83</td>
<td>8.75</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ The N4CH$_n$ signals vary in multiplicity according to the R group. $^b$ n = 3. $^c$ n = 1. $^d$ n = 2. $^e$ n = 0. $^f$ Not observed.
A strong NOE cross-peak seen in the ROESY spectrum (Figure C.4, Supporting Information) between the N3H signal (5.33 ppm) and the CCH$_3$ singlet (1.89 ppm) for the $Z$' or Z isomer, together with a strong NOE peak between this CCH$_3$ singlet and the CH multiplet (3.69 ppm), establishes that this is the Z isomer. The absence of a N4H-CCH$_3$ NOE cross-peak excludes the presence of the $Z$' isomer. There is no NOE peak between the N3H signal (4.51 ppm) and the CCH$_3$ signal (2.07 ppm) attributable to the $E$' or E isomer, a result consistent with the assignment of these signals to the $E$' isomer. The presence of a very strong NOE peak between the N3H signal (4.51 ppm) and the CH multiplet (3.15 ppm) confirms beyond doubt that this isomer indeed has the $E$' configuration because the distance between the N3H and CH protons is short for the $E$' isomer (2.18 Å) but is too long (3.51 to 4.39 Å, Supporting Information) to give a strong NOE peak for all of the other isomers. Thus, we conclude that the two sets of signals observed for 2 in acetonitrile-$d_3$ arise from the $E$' and Z isomers. The alternative conclusion that the signals arise from a mixture of rapidly interconverting ($E$/E and $Z$/Z) isomers is not supported by the solvent and temperature dependence studies described below.

The 5,5'-Me$_2$bipy signals of 2 were completely assigned by using NOE and COSY cross-peaks between the 5/5' CH$_3$ signals and the H6/6' and H4/4' signals for 2 (Figure C.5, Supporting Information). The occurrence of only one set of 5,5'-Me$_2$bipy signals for each isomer indicates rapid rotation about the Re–N3 bond.

**NMR Studies of Other [Re(CO)$_3$(5,5'-Me$_2$bipy)(amidine)]BF$_4$ Complexes in Acetonitrile-$d_3$.** The same methods described above revealed that two isomers formed upon dissolution of crystals for compounds 3 to 6. For all except 5 (see below), the clear chemical shift patterns for the H6/6' signals in acetonitrile-$d_3$ (Table 4.3) indicate that these are $E$' and Z
isomers. For 3 and 4, these conclusions were supported by 2D NMR spectra. For both isomers of $	ext{[Re(CO)}_3(5,5^\prime\text{-Me}_2\text{bipy})(\text{HNC(CH}_3\text{)NHHR})]\text{BF}_4$ ($R$ = isopropyl (2), isobutyl (3), tert-butyl (4), and methyl (6)) complexes, the N3H signals (N bound to Re) are more upfield (4.30-5.34 ppm) than the N4H signals (5.57-6.80 ppm) in acetonitrile-$d_3$. The signals of the methyl group derived from acetonitrile range from 2.01-2.08 ppm for the $E^\prime$ isomers and from 1.86-1.95 ppm for the $Z$ isomers. Thus, for the typical $R$ group, the isomers are easily identified.

### Upfield 5,5$^\prime$-Me$_2$bipy Signals of [Re(CO)$_3$(5,5$^\prime$-Me$_2$bipy)]

(HNC(CH$_3$)NHCH$_2$C$_6$H$_5$)]BF$_4$ (5) Arising from Stacking. For complexes 2, 3, 4 and 6, with non-anisotropic $R$ groups, the average shifts in acetonitrile-$d_3$ are 8.84 (H6/6$'$), 8.04 (H4/4$'$), and 8.27 (H3/3$'$) ppm for $E^\prime$ isomer signals and 8.73 (H6/6$'$), 8.04 (H4/4$'$), and 8.29 (H3/3$'$) ppm for $Z$ isomer signals. (The H4/4$'$ and H3/3$'$ signals of the $E^\prime$ isomer overlap with the H4/4$'$ and H3/3$'$ signals of the $Z$ isomer, in some cases.) For [Re(CO)$_3$(5,5$^\prime$-Me$_2$bipy)]

(HNC(CH$_3$)NHCH$_2$C$_6$H$_5$)]BF$_4$ (5, Figure 4.3), the $Z$ isomer H6/6$'$, H4/4$'$ and H3/3$'$ signals (8.76, 8.05, and 8.27 ppm, respectively) have the typical values; however, the signals for the $E^\prime$ isomer all appear upfield (8.64, 7.96 and 8.05 ppm, respectively) to typical values of the $E^\prime$ isomer of compounds 2, 3, 4, and 6. (For 5, the upfield-shifted H3/3$'$ doublet of the $E^\prime$ isomer overlaps with the H4/4$'$ doublet of the $Z$ isomer.)

The upfield shifts of the 5,5$^\prime$-Me$_2$bipy signals of the $E^\prime$ isomer of 5 can be reasonably explained only by the stacking of the phenyl moiety over the 5,5$^\prime$-Me$_2$bipy ligand in solution. This explanation was apparent when the complex was first prepared, and it derived support when the solid-state structure showed a stacking interaction (Figure C.3, Supporting Information). As we noted above and for reasons expanded upon below, the major form that can be present upon dissolution has to be either the $E^\prime$ or $E$ isomer. The $E$ isomer (Figure 4.1) cannot stack and can be
excluded because the upfield shifts cannot be explained without phenyl/5,5′-Me₂bipy stacking. Free rotation around the Re–N3 bond, which must occur in solution, explains both the presence of one signal for each type of 5,5′-Me₂bipy proton and the upfield shifts of the H6/6′ and H4/4′ signals.

**Influence of Isomerization Rate on NMR Spectra of [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHCH₂CH(CH₃)₂)]BF₄ (3).** ¹H NMR spectra of 3 (5 mM) recorded from -15 to 55 °C in acetonitrile-d₃, showed no change in the equilibrium ratios of the H6/6′ and the NH NMR signals and no major shift in these signals. Thus, the E′-to-Z interchange is too slow on the NMR time scale to influence spectra. The presence of only small EXSY cross-peaks at 65 °C in a ROESY spectrum in acetonitrile-d₃ (not shown) further confirms that the interchange between the E′ and Z isomers of 3 is slow on the NMR time scale. In addition, at -15 °C no additional signals, which would indicate the presence of the E or Z′ isomers, were observed.

**Dependence of the E′:Z Equilibrium Ratio on the Nature of R in Acetonitrile.** NMR data for a series of amidine complexes in acetonitrile-d₃ at room temperature allowed us to determine the E′:Z equilibrium ratio (Table 4.4). The similarity of these E′:Z ratios for 2 (R = isopropyl), 3 (R = isobutyl), and 6 (R = methyl) indicates that a ratio of ~65:35 may be the ‘normal’ ratio of E′ to Z isomers in acetonitrile. Put differently, the ratio is dictated by the relative bulk of the N4H and the CCH₃, which project toward the equatorial plane, and by the natural relative energy of the molecular orbitals. The higher equilibrium ratio (E′:Z = 82:18) for 4 (R = tert-butyl) than the baseline value establishes that as the bulk of the amidine ligand R substituent rises above a threshold size, such as for R = tert-butyl, the high bulk favors the E′
isomer. Likewise, although the benzyl group in 7 has only moderate bulk, phenyl/5,5′-Me₂bipy stacking favors the E′ isomer in acetonitrile (Table 4.4).

**Table 4.4.** Distribution (%) of E′ and Z Isomers of [Re(CO)_3(5,5′-Me₂bipy)(HNC(CH₃)NHR)]BF₄ in Acetonitrile-d₃ at 25 °C

<table>
<thead>
<tr>
<th>R</th>
<th>E′</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl (6)</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>isopropyl (2)</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>isobutyl (3)</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>tert-butyl (4)</td>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>benzyl (5)</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>H (7)</td>
<td>12</td>
<td>88</td>
</tr>
</tbody>
</table>

**Isomers of 2 Present in Less Polar Solvents, CD₂Cl₂ and CDCl₃.** When crystals of [Re(CO)_3(5,5′-Me₂bipy)(HNC(CH₃)NHCH(CH₃)₂)]BF₄ (2) were dissolved in CD₂Cl₂ and CDCl₃, signals for three isomers were observed (Figures 4.8 and C.6, Supporting Information). Two sets of signals maintained the same ratio and decreased with time. The third set grew in intensity and has all the characteristics expected for the Z isomer.

In CDCl₃, of the two sets of signals that decreased with time, one set had medium intensity (designated as m), and the other had weak intensity (designated as w). In a ROESY spectrum of 2 (Figure C.6, Supporting Information) in CDCl₃ at 25 °C, EXSY peaks between the respective signals of the m and w sets are present as follows (ppm): CH multiplets, 3.50 (m) and 3.13 (w); N3H, 5.22 (m) and 4.30 (w); N4H, 6.07 (m) and 5.77 (w); and CH₃ doublets, 1.07 (m) and 0.80 (w). The m signals were assigned to the E isomer by an N4H-N3H NOE peak. Also, an NOE cross-peak between the CCH₃ (2.23 ppm) signal and the CH multiplet (3.50 ppm) establishes without doubt that the m set belongs to the E isomer. The w signals belong to the E′ isomer, as confirmed by EXSY peaks above. The most intense set of signals was assigned to the
Z isomer by NOE cross-peaks relating the CCH$_3$ signal (2.03 ppm) to the N3H signal (5.75 ppm) and to the CH multiplet of the isopropyl group (3.67 ppm). A CCH$_3$-N3H NOE peak together with a CCH$_3$-CH NOE peak is uniquely expected for the Z isomer (Figure 4.1). Thus, the three sets of $^1$H NMR signals observed for 2 in CDCl$_3$ belong to the $E'$, $E$, and Z isomers present in the equilibrium ratio of 5:32:63, respectively.

**Figure 4.8.** $^1$H NMR spectra illustrating the distribution of $E'$, $E$, and Z isomers of [Re(CO)$_3$(5,5'-Me$_2$bipy)(HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2) in CD$_2$Cl$_2$ (with percent acetonitrile-$d_3$ noted on trace) and acetonitrile-$d_3$ at 25 °C. *Note*: the bottom two spectra were recorded before equilibrium was reached.

In CD$_2$Cl$_2$, as found in the less polar CDCl$_3$ solvent, 2 exhibits three sets of $^1$H NMR signals. Two sets of these signals have essentially equal intensity and are connected by $E$-$E$ EXSY peaks (ROESY spectrum at 0 °C, not shown) as follows (ppm): CH multiplets, 3.51 and 2.95; N3H,
5.11 and 4.06; N4H, 5.96 and 5.85; and CH₃ doublets, 1.03 and 0.80. The third set of signals is established as belonging to the Z isomer by NOE peaks relating the CCH₃ signal (1.97 ppm) to the N3H signal (5.16 ppm) and to the CH multiplet of the isopropyl group (3.67 ppm). Equilibrium for 2 in CD₂Cl₂ (E′:E:Z = 19:19:62) is reached in 3 h.

Mixed-Solvent Studies Exploring the E′ Isomer Signals of 2. As mentioned above, in the polar solvent acetonitrile-d₃, the signals for the E′ isomer could alternatively represent a rapidly interconverting mixture of E and E′ isomers. In solvents such as CD₂Cl₂, the separate signals for these isomers can be observed. Thus, in solvents of low polarity, it is clear that both isomers are present and that interchange is slow on the NMR time scale. We designed an experiment to assess whether in acetonitrile-d₃ a significant amount of an E isomer in rapid exchange with the major E′ isomer might be present but undetectable in acetonitrile-d₃.

We initiated our study with a freshly prepared CD₂Cl₂ solution because equilibrium was not reached for ~3 h after crystals of 2 were dissolved in CD₂Cl₂. The E isomer was initially abundant (E′:E:Z = 37:37:28; Figure 4.8, bottom). Addition of 1% and then 2% of acetonitrile-d₃ into the CD₂Cl₂ solution of 2 (these first two additions were recorded prior to equilibrium in order to have abundant E′ and E isomers) showed an increase in the relative abundance of the E′ isomer, as reflected in the intensities of the H6/6′ signals (Figure 4.8). At 21% acetonitrile-d₃, the E′ isomer H6/6′ signal was observed but not the E isomer signal (Figure 4.8). Thus, the one set of signals observed in 100% acetonitrile-d₃ is that of the E′ isomer, with a negligible (if any) contribution of an E isomer.

NMR Studies of Other [Re(CO)₃(5,5′-Me₂bipy)(amidine)]BF₄ Complexes in CD₂Cl₂ and CDCl₃. ¹H NMR data for complexes 2, 3, and 4 in CD₂Cl₂ and CDCl₃ (Table C.1, Supporting Information) indicate that complexes 3 and 4 have E′, E (in most cases), and Z
isomers, as found above for 2. In CDCl₃ and CD₂Cl₂ (as in acetonitrile-d₃), the signals of the methyl group derived from acetonitrile have a more downfield shift (∼2.2 ppm) characteristic for the E and E′ isomers and a more upfield shift (∼2.0 ppm) characteristic for the Z isomer. An N3H signal having a shift upfield of 4.60 ppm in acetonitrile-d₃, CD₂Cl₂, or CDCl₃ was another indication allowing the assignment of signals to the E′ isomer. As found in the case of every solvent for compounds with non-anisotropic R groups, the H6/6′ signal of the E′ isomer in CD₂Cl₂ or CDCl₃ is more downfield than that of the E isomer, which in turn is more downfield than this signal for the Z isomer (Table C.1). This relationship holds true for all solvents, including DMSO-d₆ (see below).

These shift analogies were supported by the spectral changes upon dissolution of crystals, which also aided in the assignments. Dissolution of crystals of 3 (R = isobutyl) in CDCl₃ gave NMR features (Table C.2) similar to those observed for 2. A ¹H NMR spectrum recorded in 5 min contained mostly one large set of peaks of the E isomer, identified by NMR shifts that closely resemble those of the E isomer of 2. Dissolution of crystals of 3 in CD₂Cl₂ also gave NMR features similar to those observed for 2 (Tables C.1 and C.2), for which three distinct sets of signals were observed, with features expected for the three isomers.

A ¹H NMR spectrum of 4 (R = tert-butyl) initially recorded within 5 min of dissolution in CDCl₃ showed signals for the three isomers with the E and E′ isomers in abundance. With time, peaks assignable to the Z isomer grew. However, the spectrum obtained upon dissolution of 4 in CD₂Cl₂ has only two sets of signals. The peaks clearly assignable to the Z isomer were sharp, and these grew with time. Although the signals attributable to the E′ isomer were broad at 25 °C, all signals in the regions characteristic of the E and E′ isomers, including the informative H6/6′
signal, were sharp at 0 °C; these results are consistent with the absence of the E isomer in this solvent (Tables C.1 and C.2).

**Dependence of the E:Z Ratios on Solvent and Remote N Group Bulk.**

Some E:Z equilibrium ratios have been mentioned above for different solvents. In this section we discuss the data further. Because the situation is complicated, we begin with a brief summary. The E′ isomer is favored by high bulk and polar solvents. The E isomer is insensitive to bulk but favored by low solvent polarity. The Z isomer is favored by low bulk and low solvent polarity.

For 2, E:Z equilibrium ratios in CDCl₃ (5:32:63) versus CD₂Cl₂ (19:19:62) show that while the percentage of the E′ isomer has increased, the abundance of the Z isomer has remained more or less constant. In other words, E′ has increased and E has decreased as the dielectric constant of the solvent increased from 4.8 (CDCl₃) to 9.1 (CD₂Cl₂). This same relationship is valid for 3, and as mentioned above, signals for the E isomer of 4 are no longer observed even in the relatively low polarity solvent, CD₂Cl₂ (Table C.2). For all [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)NHR)]BF₄ compounds, the E′ isomer is least abundant in CDCl₃ (5-15%). As shown in Table C.2, the abundance of the E′ isomer (64-82%) was greater in the higher dielectric constant (37.5) solvent, acetonitrile-d₃, and even higher in DMSO-d₆ (dielectric constant = 47.2). Although we do not discuss the NMR studies in DMSO-d₆ in detail, the isomer and signal assignments followed the methods discussed for other solvents. For example, an NMR spectrum of 2 recorded in DMSO-d₆ showed mostly one set of signals (E′) initially, and a second set of peaks grew with time, reaching equilibrium within 30 min (E′:Z = 78:22). The N4H signals of both the E′ and Z isomers appear more downfield in DMSO-d₆ than in acetonitrile, consistent with the good H-bonding and solvation properties of DMSO.
Compared to all solvents used for 2, 3, and 4, the abundance of the Z isomer was lowest (13-22%) in DMSO-$d_6$ (Table C.2). The Z isomer was favored most in CDCl$_3$ (57-64% abundance). Thus, a low dielectric solvent favors the Z isomer for all [Re(CO)$_3$(5,5$'$-Me$_2$biyp)(HNC(CH$_3$)NHR)]BF$_4$ compounds studied.

**The Z$''$ Isomer.** While we have observed evidence for the presence of $E'$, $E$, and Z isomers for complexes 2 and 3 in CDCl$_3$ and CD$_2$Cl$_2$, the Z$'$ isomer appears not to be present in several solvents ranging from CDCl$_3$ to DMSO-$d_6$. The Z$'$ isomer is probably destabilized by interligand steric clashes involving the basal plane defined by the 5,5$'$-Me$_2$biyp N atoms and the trans carbonyl C atoms (Figure C.7, Supporting Information). Such clashes are likely to be severe in octahedral complexes but are likely to be less important in square-planar complexes, and the Z$'$ isomer has been reported for Pt$^\text{II}$. Complexes with the $fac$-$\{\text{Re}^\text{I}(CO)_3\}$ core are generally sterically undemanding compared to other octahedral complexes because Re$^\text{I}$–N bonds are longer than typical M–N bonds for metal ions in an octahedral environment and the CO ligands are relatively non-bulky. Nevertheless, even in this favorable case, steric clashes appear to preclude formation of significant amounts of the Z$'$ isomer.

The unstable nature of the Z$'$ isomer suggests that the pathway for the interconversion of the $E'$ to Z isomers passes through the $E$ isomer and not through the Z$'$ isomer. Furthermore, the findings for 2 in CDCl$_3$, namely that the $E'$/$E$ ratio remained constant while the amount of Z increased with time and that only $E'$-$to$-$E$ EXSY cross-peaks were present in the ROESY spectrum, suggest that the $E'$-$to$-$E$ interconversion is facile. Thus, the slow steps in the $E'$-$to$-$Z$ interconversion are the $E$-$to$-$Z$ interconversion. A likely reaction pathway scheme is shown in Figure C.8, Supporting Information.
NMR Studies of \( \text{[Re(CO)}_3(5,5\text{'-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{NH}_2)]BF}_4 \) (7). NMR spectra of 7 in acetonitrile-\( d_3 \) at 25 °C recorded at 15 min and 1 day were very similar, containing two very broad NH signals (6.30 and 5.93 ppm) and one fairly sharp NH signal at 5.45 ppm (each integrating to one proton) for the major Z isomer. Sharp H6/6’ signals were observed, with the smaller signal downfield, suggesting that \(~12\%\) \( E \)’ isomer was also present. The signal at 5.45 ppm did not shift with temperature and can be assigned to N3H of the Z isomer. At 5 °C, the two broad NH signals of equal intensity became sharp (6.60 and 5.81 ppm). At 35 °C, the broad signals merged to give one peak (6.09 ppm), the total intensity remaining the same. These results indicate that the signals are from the –NH\(_2\) group of \( \text{[Re(CO)}_3(5,5\text{'-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{NH}_2)]BF}_4 \) and that elevated temperature increases the rate of rotation around the C–NH\(_2\) bond. The NH peaks of the minor \( E \)’ isomer could not be identified. The H6/6’ and amidine CH\(_3\) signals were used to obtain the ratio of the \( E \)’ and Z isomers (Table 4.4).

Structural analysis of \( \text{fac-[Re(CO)}_3(5,5\text{'-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{OCH}_3)]BF}_4 \), an iminoether analogue of the amide complexes in this study, has revealed that the iminoether ligand has the Z configuration in the solid state.\(^{26}\) The oxygen of the iminoether ligand is sterically less bulky than the NHR group of \( \text{[Re(CO)}_3(5,5\text{'-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{NHR)]BF}_4 \) complexes. Combining these findings for \( \text{[Re(CO)}_3(5,5\text{'-Me}_2\text{bipy})(\text{ligand)]BF}_4 \) complexes in which the ligand is an amidine or an iminoether, we suggest that the Z configuration is favored electronically, but the \( E \)’ configuration is favored by steric effects.

Robustness of the Isopropylamidine Ligation. When \( \text{[Re(CO)}_3(5,5\text{'-Me}_2\text{bipy})(\text{HNC(CH}_3)\text{NHCH(CH}_3)_2)]BF}_4 \) (2) in acetonitrile-\( d_3 \) or CDCl\(_3\) was treated with a fivefold excess of 4-dimethylaminopyridine, no major changes in spectral features of the amidine complex were observed, even up to 2 months, indicating that the isopropylamidine ligand is not readily
replaced. [Re(CO)$_3$(5,5′-Me$_2$bipy)(4-dimethylaminopyridine)]BF$_4$ was synthesized, and the NMR shifts were recorded in acetonitrile-$d_3$ and CDCl$_3$ as a control.

4.4 Conclusions

The [Re(CO)$_3$(5,5′-Me$_2$bipy)(CH$_3$CN)]BF$_4$ complex (1) readily forms [Re(CO)$_3$(5,5′-Me$_2$bipy)(amidine)]BF$_4$ complexes. The facility of this reaction for a low-oxidation-state, third-row transition metal complex very likely reflects the fact that the CO ligands reduce the electron density on the metal via $\pi$ back-bonding. In these complexes, the amidine ligand is attached robustly, but it does not exhibit a trans influence.

Because the amidine grouping is not in a ring and the ligand is monodentate, the configuration is not restricted. Furthermore, there is no interligand hydrogen bonding possible to influence the stereochemistry. Thus, the configuration is influenced primarily by electronic and steric effects. The $E'$ isomer crystallized for [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NHR)]BF$_4$ (R = methyl, isopropyl, isobutyl, tert-butyl, and benzyl), whereas the $Z$ isomer crystallized for [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NH$_2$)]BF$_4$. Increased bulk of the R group favors the $E'$ configuration of the amidine ligand because the alkyl group projects away from the basal plane. The $Z$ configuration is favored electronically, as evidenced by the structure of [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NH$_2$)]BF$_4$ and also by the structure of several [Re(CO)$_3$(L)(iminoether)]BF$_4$ complexes analyzed in unpublished work.

The exchange reaction between the $E'$ and $Z$ isomers of [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NHR)]BF$_4$ (R = isopropyl, isobutyl and tert-butyl) complexes is too slow to be observed on the NMR time scale. The isomerization rate is slow because there is double-bond character in the bond between the amidine C and the N bound to Re. However, the isomerization rate between the $E'$ and $E$ isomers is fast because there is less double-bond character in the bond.
between the amidine C and the remote N. Exchange between the \( E' \) and \( Z \) isomers is likely to follow a pathway through the \( E \) isomer because the \( Z' \) isomer (not observed) is likely to be unstable as a result of strong steric clashes between the R group and the basal ligands in this isomer.

### 4.5 References


CHAPTER 5
IMINOETHER COMPLEXES OF THE TYPE, \( \text{fac-}[\text{Re(CO)}_3L(\text{HNC(CH}_3\text{OCH}_3))]\text{BF}_4 \) (\( L = \text{BIPYRIDINE AND SUBSTITUTED BIPYRIDINE} \)): SYNTHETIC, X-RAY CRYSTALLOGRAPHIC, AND NMR SPECTRAL FEATURES

5.1 Introduction

\( \text{fac-}[\text{Re(CO)}_3L(L')]^n \) complexes, containing bisimine ligands, have recently found use as cell imaging agents in fluorescence microscopy.\(^1\) Complexes of the type, \( \text{fac-}[\text{Re(CO)}_3L(L')]^n \), in which \( L' = \text{dimethyl sulfoxide (DMSO), pyridine, or pyridine derivatives with various charges and lipophilicities and in which } L = 2,2'-\text{bipyridine (bipy) or a substituted bipyridine, have also sparked much interest.}^2 \) This interest arises because the excited state is localized on one bipyridine unit, making such complexes excellent candidates as probes responsive to their environment.\(^1\) These complexes are also important as precursors in supramolecular chemistry.\(^3,4\)

\( \text{fac-}[\text{Re(CO)}_3(\text{bipy})(\text{DMSO})]^+ \) has found use as a precursor for binding the luminescent \( [\text{Re(CO)}_3(\text{bipy})]^+ \) fragment to polytopic ligands for the construction of more elaborate assemblies.\(^5\)

A desirable feature in Re complexes designed for use in cell imaging is lipophilicity, which favors cell membrane permeability.\(^1\) While investigating the properties of \( \text{fac-}[\text{Re(CO)}_3(N-N)L]^+ \) complexes to be utilized as fluorescent probes, we noted that ligands needed to prepare fluorescent compounds are often only sparingly soluble in water, the solvent in which the common precursor is prepared.\(^6\) In addition, various pH conditions lead to different linkage isomers or mixtures of isomers for complicated ligands.\(^7,8\) Also, monitoring reaction mixtures is inconvenient under aqueous conditions. Therefore, we have evaluated the \( \text{fac-}[\text{Re(CO)}_3(\text{CH}_3\text{CN})]^+ \) precursor as a means of synthesizing Re compounds in organic solvents. In a previous study,\(^9\) we reported several novel compounds, which arose from reaction of the coordinated nitrile with ligand terminal amines upon treatment of \( \text{fac-}[\text{Re(CO)}_3(\text{CH}_3\text{CN})]^+ \) with
various tridentate amine ligands. Treatment of \( \text{fac-}[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]^+ \) with bidentate aromatic N-donor \( L \) using acetonitrile or benzene as solvent gave the desired \( \text{fac-}[\text{Re(CO)}_3(\text{N–N})(\text{CH}_3\text{CN})]^+ \) complexes in excellent yield. We discovered that synthetic reactions in methanol led to addition of solvent to a bound acetonitrile, giving iminoether complexes (Scheme 5.1).

**Scheme 5.1.** Synthesis of \([\text{Re(CO)}_3L(\text{HNC(\text{CH}_3})\text{OR}])\text{BF}_4\) complexes

![Scheme 5.1](image)

Iminoether metal complexes (\( \text{MHNC(\text{R})OR'} \)) are formed by the reaction of \( \text{M-N≡CR} \) with \( \text{R'OH} \), and two configurations of the iminoether ligand (\( E \) and \( Z \)) are possible with the \( \text{OR'} \) group being \( \text{cis} \) or \( \text{trans} \) to rhenium (Chart 5.1). Specifically when \( \text{R'OH} = \text{methanol} \) and \( \text{R} = \text{methyl} \), we will refer to this ligand (\( \text{HNC(\text{CH}_3})\text{OCH}_3 \)) as acetimidate. Although there have been no previous reports of \( \text{Re}^1 \) iminoether complexes, the synthesis, characterization, and stereochemistry of iminoether complexes of platinum are well documented.\(^1\) Some of these platinum iminoether complexes are known to have antitumor activity.\(^1\) Natile and co-workers reported that the addition of alcohols to coordinated nitriles takes place under basic conditions, initially forming the \( Z \) isomer; subsequently the \( Z \) isomer isomerizes to the \( E \) isomer.\(^1\) A large steric bulk of the alcohol \( \text{R'} \) group was reported to stabilize \( E \) over \( Z \) and increasing steric bulk of the nitrile \( \text{R} \) group was reported to stabilize the \( Z \) isomer.\(^1\)
In a recent review, Bokach et al. noted that the conditions needed for the reactions of alcohols with coordinated nitriles depend substantially on the oxidation state of the metal and that the addition of ROH to RCN in metal complexes of low to moderate oxidation state such as Pt$^{II}$, Pd$^{II}$, Ni$^{II}$, Ir$^{III}$, and Cu$^{II}$ requires alkali or base. Bokach also pointed out the need for investigating more examples of $E/Z$ configuration addition/transformation at different metal centers before a general conclusion as to the factors influencing the relative stability of the $E$ or $Z$ configuration of bound iminoether ligands can be reached. The low oxidation state of Re$^{I}$, the formation of iminoether complexes in the absence of base, and the lack of a complete understanding of the factors influencing the $E/Z$ ratio all prompted us to expand our study.

We have synthesized a series of fac-[Re(CO)$_3$L(HNC(CH$_3$)OR')]BF$_4$ complexes bearing the substituted bipyridine moiety and iminoether ligands. We report here the first examples of an iminoether ligand bound to a Re$^{I}$ center, as well as the first solid-state evidence of the configuration of the iminoether ligand bound to Re$^{I}$. However, Re$^{IV}$ compounds (cis-[Re(HNC(CH$_3$)OCH$_3$)$_2$Cl$_4$] and [Re(HNC(CH$_3$)OCH$_2$CH$_3$)$_2$Cl$_4$]) were prepared in 1968 by Rouschias et al., and the crystal structure of cis-[Re(HNC(CH$_3$)OCH$_3$)$_2$Cl$_4$], formed during an attempted crystallization of cis-[Re$^{IV}$(CH$_3$CN)$_2$Cl$_4$] in methanol, was reported recently.
We have utilized a series of dimethyl-2,2’-bipyridine ligands to evaluate distortions in planarity of \( \text{fac-}[\text{Re(CO)}_3 L(\text{HNC(CH}_3\text{OCH}_3))\text{]}\text{BF}_4 \). Our study thus also provides a structural comparison of \( \text{Re}^1 \) complexes bearing the same ligand system, in which only the position of the methyl substituent in the bipyridine moiety is varied. Below, we do not use the \( \text{fac-} \) designation when discussing specific compounds because all the new compounds have this geometry.

5.2 Experimental Section

**Starting Materials.** \( \text{Re(CO)}_5 \text{Br} \) was synthesized as described in the literature.\(^{21}\) \( \text{Re}_2(\text{CO})_{10}, 2,2’\)-bipyridine, 4,4’-dimethyl-2,2’-bipyridine (4,4’-Me\(_2\)bipy), 5,5’-dimethyl-2,2’-bipyridine (5,5’-Me\(_2\)bipy), 6,6’-dimethyl-2,2’-bipyridine (6,6’-Me\(_2\)bipy), \( \text{AgPF}_6 \) and \( \text{AgBF}_4 \) were obtained from Aldrich. \( \text{[Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{PF}_6 \) and \( \text{[Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{BF}_4 \) were synthesized by a slight modification of a known procedure\(^{22}\) (see below).

**NMR Measurements.** \(^1\)H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Peak positions are relative to TMS or solvent residual peak, with TMS as reference. All NMR data were processed with TopSpin and Mestre-C software.

**X-ray Data Collection and Structure Determination.** Single crystals were placed in a cooled nitrogen gas stream at 90 K on a Nonius Kappa CCD diffractometer fitted with an Oxford Cryostream cooler with graphite-monochromated Mo \( \text{K}\alpha \) (0.71073 Å) radiation. Data reduction included absorption corrections by the multi-scan method, with HKL SCALEPACK.\(^{23}\) All X-ray structures were determined by direct methods and difference Fourier techniques and refined by full-matrix least squares by using SHELXL97.\(^{24}\) All non-hydrogen atoms were refined anisotropically. All H atoms were visible in difference maps, but were placed in idealized positions. A torsional parameter was refined for each methyl group.
[Re(CO)_3(CH_3CN)_3]PF_6 (1a). [Re(CO)_3(CH_3CN)_3]PF_6 was synthesized by a slight modification of a known procedure, in which AgPF_6 was used instead of AgClO_4. A solution of Re(CO)_3Br (1.62 g, 4 mmol) and AgPF_6 (1.02 g, 4 mmol) in acetonitrile (20 mL) was heated at reflux for 16 h. After the reaction mixture was filtered, the solvent was removed by rotary evaporation to give a white solid, which was recrystallized by adding diethyl ether (~30 mL) to a solution of the solid in acetonitrile (~5 mL) and allowing the mixture to stand undisturbed for 1 h (1.75 g, 81% yield). X-ray quality crystals were obtained from acetonitrile/isopropyl ether solution. ^1H NMR signal (ppm) in CDCl_3: 2.52 (s, CH_3), in DMSO-d_6; 2.65 ppm, in acetone-d_6; 2.66 ppm, in acetonitrile-d_3; 2.43 ppm.

[Re(CO)_3(CH_3CN)_3]BF_4 (1b). Substituting AgBF_4 for AgPF_6 in the above procedure produced [Re(CO)_3(CH_3CN)_3]BF_4 as a white crystalline precipitate (1.62 g, 84% yield). X-ray quality crystals were obtained from a solution of the compound in acetonitrile/isopropyl ether. The ^1H NMR spectra were identical to that of the PF_6^- crystals given above. We report the crystallographic data of this compound obtained at 90 K in Supporting Information. (An X-ray structural characterization using data collected at room temperature has been reported.)

Synthesis of [Re(CO)_3L(HNC(CH_3)OCH_3)]BF_4 Complexes. Two methods (A and B) were employed to obtain [Re(CO)_3L(HNC(CH_3)OCH_3)]BF_4 complexes. Method A involved heating a benzene solution (10 mL) of [Re(CO)_3(CH_3CN)_3]BF_4 (0.1 mmol, 48 mg) and L (0.1 mmol) at reflux for 16 h. The solvent was removed by rotary evaporation, and the resulting solid was dissolved in ~1 mL of acetonitrile; diethyl ether (~25 mL) was then added to give [Re(CO)_3L(CH_3CN)]BF_4 as a crystalline precipitate. This precipitate was washed well with diethyl ether and dried. [Re(CO)_3L(CH_3CN)]BF_4, in 10 mL of a 1:1 acetonitrile:ethanol mixture, was then heated at reflux for 24 h. The resulting solution was cooled to room temperature and taken to dryness by rotary evaporation. The residue was dissolved in acetonitrile;
addition of diethyl ether produced an orange precipitate, which was collected on a filter and washed with diethyl ether and dried. Method A resulted in high yields of crystalline material. Method B, employed to obtain X-ray quality crystals, involved first stirring an acetonitrile solution (10 mL) of [Re(CO)\(_3\)(CH\(_3\)CN)\(_3\)]BF\(_4\) (0.1 mmol, 0.0481 g) and L (0.1 mmol) at room temperature and then heating the solution at reflux for 2-3 days. The reaction mixture was monitored by NMR spectroscopy to ensure that the reaction went to completion. An equal volume of methanol was then added, and the mixture was heated at reflux for 1 day. The resulting solution yielded X-ray quality crystals upon slow evaporation. The yields reported below are based on the initial concentration of [Re(CO)\(_3\)(CH\(_3\)CN)\(_3\)]BF\(_4\) (0.1 mmol, 48 mg).

\[\text{[Re(CO)\(_3\)(bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\)}\] (2). Method A just described yielded the intermediate product, [Re(CO)\(_3\)(bipy)(CH\(_3\)CN)]BF\(_4\), as a yellow crystalline precipitate (39 mg, 76% yield). \(^1\)H NMR signals (ppm) in CDCl\(_3\): 8.91 (d, H6/6’), 8.56 (d, H3/3’), 8.26 (t, H4/4’), 7.64 (t, H5/5’), 2.21 (s, CCH\(_3\)). (The synthesis of [Re(CO)\(_3\)(bipy)(CH\(_3\)CN)]BF\(_4\) was reported by Amoroso et al., but synthetic details and NMR data were not provided and different starting materials were used.\(^1\) The synthesis of [Re(CO)\(_3\)(bipy)(CH\(_3\)CN)]PF\(_6\) has been reported,\(^{26}\) but NMR data were not provided.) Method A afforded [Re(CO)\(_3\)(bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) as an orange-colored precipitate (39 mg, 63% yield). Method B afforded X-ray quality crystals (21 mg, 36% yield). \(^1\)H NMR (ppm) in CDCl\(_3\): 8.90 (d, H6/6’), 8.37 (d, H3/3’), 8.16 (t, H4/4’), 7.62 (b, NH), 7.56 (t, H5/5’), 3.92 (s, OCH\(_3\)), 2.17 (s, CCH\(_3\)).

\[\text{[Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\)}\] (3). The intermediate product, [Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(CH\(_3\)CN)]BF\(_4\), was obtained as a yellow crystalline precipitate (41 mg, 69% yield). \(^1\)H NMR signals (ppm) in CDCl\(_3\): 8.71 (d, H6/6’), 8.35 (d, H3/3’), 7.39 (d, H5/5’), 2.65 (s, 4/4′-CH\(_3\)), 2.20 (s, CCH\(_3\)). (\([\text{Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(CH\(_3\)CN)]PF\(_6\}\) has been synthesized

\[\text{[Re(CO)\(_3\)(bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\)}\] (2). Method A just described yielded the intermediate product, [Re(CO)\(_3\)(bipy)(CH\(_3\)CN)]BF\(_4\), as a yellow crystalline precipitate (39 mg, 76% yield). \(^1\)H NMR signals (ppm) in CDCl\(_3\): 8.91 (d, H6/6’), 8.56 (d, H3/3’), 8.26 (t, H4/4’), 7.64 (t, H5/5’), 2.21 (s, CCH\(_3\)). (The synthesis of [Re(CO)\(_3\)(bipy)(CH\(_3\)CN)]BF\(_4\) was reported by Amoroso et al., but synthetic details and NMR data were not provided and different starting materials were used.\(^1\) The synthesis of [Re(CO)\(_3\)(bipy)(CH\(_3\)CN)]PF\(_6\) has been reported,\(^{26}\) but NMR data were not provided.) Method A afforded [Re(CO)\(_3\)(bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) as an orange-colored precipitate (39 mg, 63% yield). Method B afforded X-ray quality crystals (21 mg, 36% yield). \(^1\)H NMR (ppm) in CDCl\(_3\): 8.90 (d, H6/6’), 8.37 (d, H3/3’), 8.16 (t, H4/4’), 7.62 (b, NH), 7.56 (t, H5/5’), 3.92 (s, OCH\(_3\)), 2.17 (s, CCH\(_3\)).

\[\text{[Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\)}\] (3). The intermediate product, [Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(CH\(_3\)CN)]BF\(_4\), was obtained as a yellow crystalline precipitate (41 mg, 69% yield). \(^1\)H NMR signals (ppm) in CDCl\(_3\): 8.71 (d, H6/6’), 8.35 (d, H3/3’), 7.39 (d, H5/5’), 2.65 (s, 4/4′-CH\(_3\)), 2.20 (s, CCH\(_3\)). (\([\text{Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(CH\(_3\)CN)]PF\(_6\}\) has been synthesized
previously, but details were not reported. No NMR data were provided.) Method A afforded [Re(CO)$_3$(4,4′-Me$_2$bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$ as an orange-colored precipitate (38 mg, 62% yield). Method B afforded X-ray quality crystals (21 mg, 34% yield). $^1$H NMR (ppm) in CDCl$_3$: 8.69 (d, H$_6$/6′), 8.14 (s, H$_3$/3′), 7.41 (b, NH), 7.33 (d, H$_5$/5′), 3.90 (s, OCH$_3$), 2.59 (s, 4/4′-CH$_3$), 2.14 (s, CCH$_3$).

[Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$ (4). The intermediate product, [Re(CO)$_3$(5,5′-Me$_2$bipy)(CH$_3$CN)]BF$_4$, was obtained as a yellow crystalline precipitate (50 mg, 70% yield). $^1$H NMR signals (ppm) in CDCl$_3$: 8.68 (s, H$_6$/6′), 8.35 (d, H$_3$/3′), 8.01 (d, H$_4$/4′), 2.53 (s, 5/5′-CH$_3$), 2.22 (s, CCH$_3$). X-ray quality crystals were obtained by slow evaporation from a chloroform solution. (Meyer et al. have reported the synthesis of [Re(CO)$_3$(5,5′-Me$_2$bipy)(CH$_3$CN)]PF$_6$ from Re(CO)$_3$(5,5′-Me$_2$bipy)Cl, which was heated at reflux in acetonitrile with AgClO$_4$•H$_2$O. The product was obtained by addition of a saturated aqueous solution of NH$_4$PF$_6$. No NMR data were provided.) Method A afforded [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$ as an orange-colored precipitate (41 mg, 67% yield). Method B afforded X-ray quality crystals (23 mg, 37%). $^1$H NMR signals (ppm) in CDCl$_3$: 8.43 (d, H$_3$/3′), 8.09 (t, H$_4$/4′), 7.54 (d, H$_5$/5′), 3.06 (s, 6/6′-CH$_3$), 2.22 (s, CCH$_3$). Method A afforded [Re(CO)$_3$(6,6′-Me$_2$bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$•0.5(6,6′-Me$_2$bipy) (5). The intermediate product, [Re(CO)$_3$(6,6′-Me$_2$bipy)(CH$_3$CN)]BF$_4$, was obtained as a yellow crystalline precipitate (42 mg, 72% yield). $^1$H NMR signals (ppm) in CDCl$_3$: 8.43 (d, H$_3$/3′), 8.09 (t, H$_4$/4′), 7.54 (d, H$_5$/5′), 3.06 (s, 6/6′-CH$_3$), 2.22 (s, CCH$_3$). Method A afforded [Re(CO)$_3$(6,6′-Me$_2$bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$ as an orange-colored precipitate (39 mg, 63% yield). Method B afforded X-ray quality crystals (20 mg, 33%). These crystals contained
uncomplexed ligand, and a set of signals in the NMR spectrum provided evidence of the free 6,6′-Me₂bipy ligand. 

\(^1\)H NMR (ppm) in CDCl₃: for [Re(CO)₃(6,6′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄: 8.15 (d, H3/3′), 7.97 (t, H4/4′), 7.59 (b, NH), 7.49 (d, H5/5′), 3.81 (s, OCH₃), 3.04 (s, 6/6′-CH₃), 2.15 (s, CCH₃) and for the 6,6′-Me₂bipy of solvation: 8.18 (d, H3/3′), 7.66 (t, H4/4′), 7.14 (d, H5/5′), 2.62 (s, 6/6′-CH₃).

[Re(CO)₃(5,5′'-Me₂bipy)(HNC(CH₃)OCH₂CH₃)]BF₄ (6). Using ethanol instead of methanol in the general procedure described above for 4 afforded [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)OCH₂CH₃)]BF₄ as an orange-colored precipitate (50 mg, 76% yield). Method B afforded X-ray quality crystals (29 mg, 46%). \(^1\)H NMR signals (ppm) in CDCl₃: 8.66 (s, H6/6′), 8.17 (d, H3/3′), 7.90 (d, H4/4′), 7.45 (b, NH), 4.18 (q, OCH₂), 2.49 (s, 5/5′-CH₃), 2.17 (s, CCH₃), 1.49 (t, CH₃).

Cl⁻ Titration of [Re(CO)₃(5,5′'-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄. A 5 mM solution of [Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄ in DMSO-d₆ (600 µL) was treated with increasing amounts of Cl⁻ (1 to 150 mM) and the solution was monitored by \(^1\)H NMR spectroscopy upon each addition of Cl⁻. The complex concentration was kept constant throughout the titration by using a 5 mM solution of the complex in DMSO-d₆ to prepare the Cl⁻ stock solution.

5.3 Results and Discussion

Structural Results. All complexes reported here exhibit a pseudo octahedral structure, with the three carbonyl ligands occupying one face. The remaining three coordination sites are occupied by N donors. The N donors consist of acetonitrile molecules for [Re(CO)₃(CH₃CN)₃]PF₆ (1a) (Figure 5.1), or two nitrogen atoms of 2,2′-bipyridine or of a substituted 2,2′-bipyridine and a nitrogen of an acetimidate ligand for complexes having the
The general formula, \([\text{Re(CO)}_3\text{L(HNC(CH}_3\text{)OCH}_3)]\text{BF}_4\) (Figure 5.2). Crystal data and details of the structural refinement for all these complexes are summarized in Table 5.1. The atom numbering in Figure 5.2 is used to describe the solid-state data.

**Figure 5.1.** ORTEP plot of \([\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{PF}_6\). Thermal ellipsoids are drawn with 50% probability.

The \([\text{Re(CO)}_3\text{L(HNC(CH}_3\text{)OCH}_3)]\text{BF}_4\) complexes (\(\text{L} = \text{bipy (2), 4,4}'\text{-Me}_2\text{bipy (3), 5,5}'\text{-Me}_2\text{bipy (4), and 6,6}'\text{-Me}_2\text{bipy (5)}\)) have an acetimidate ligand in the Z configuration in the solid state (Figure 5.2). This observation is also true for \([\text{Re(CO)}_3(5,5]'\text{-Me}_2\text{bipy)(HNC(CH}_3\text{)OCH}_2\text{CH}_3)]\text{BF}_4\) (Figure D1, Supporting Information).

In all of the \([\text{Re(CO)}_3\text{L(HNC(CH}_3\text{)OCH}_3)]\text{BF}_4\) structures (2-5, Figure 5.2), the distance of the Re–CO bond trans to the acetimidate group does not differ significantly from those of the other Re–CO bonds (not shown); the acetimidate ligand has no trans influence. However, a negative trans influence is present for \([\text{Re(CO)}_3(4,4]'\text{-Me}_2\text{bipy)}\text{BF}_4\]) (unpublished results), in which the distance of the Re–CO bond trans to Re–F is significantly shorter (1.902(2) Å) than the other Re–CO bond distances (1.920(2) Å and 1.928(2) Å).
Figure 5.2. ORTEP plots of the cations of (a) [Re(CO)\(\text{bipy}\)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) (2), (b) [Re(CO)\(\text{3,4′-Me\text{bipy}}\)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) (3), (c) [Re(CO)\(\text{3,5′-Me\text{bipy}}\)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) (4) and (d) [Re(CO)\(\text{3,6′-Me\text{bipy}}\)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) (5). The uncomplexed 6,6′-Me\(_2\text{bipy}\) ligand in 5 is omitted for clarity. Thermal ellipsoids are drawn with 50% probability.
Table 5.1. Crystal Data and Structure Refinement for $[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{PF}_6$ and $[\text{Re(CO)}_3(L) (\text{HNC(CH}_3\text{OCH}_3))]\text{BF}_4$ (L = bipy, 4,4′-Me₂bipy, 5,5′-Me₂bipy, and 6,6′-Me₂bipy)

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<th>5,5′-Me₂bipy</th>
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$^aR = \frac{\sum|F_o| - |F_c|}{\sum|F_o|}$. $^b$wR$^2 = \frac{\sum[w(F_o^2 - F_c^2)]^2}{\sum[w(F_o^2)^2]}$, in which $w = 1/[\sigma^2(F_o^2) + (dP)^2 + (eP)]$ and $P = (F_o^2 + 2F_c^2)/3$, and $d = 0.0388, 0.0104, 0.0167, 0.0203$, and 0.0274 and $e = 4.4179, 2.0041, 2.412, 1.2932$, and 4.5142 for $[\text{Re(CO)}_3(\text{CH}_3\text{CN})_3]\text{PF}_6$, and $[\text{Re(CO)}_3(L) (\text{HNC(CH}_3\text{OCH}_3))]\text{BF}_4$, in which L = bipy, 4,4′-Me₂bipy, 5,5′-Me₂bipy, and 6,6′-Me₂bipy, respectively.
The Re–N (Figure 5.2) bond lengths of complexes 2-4 are comparable with typical Re sp² nitrogen bond lengths, which range from 2.14 to 2.18 Å. However, the Re–N1 (2.211(3) Å) and Re–N2 (2.213(3) Å) bond lengths for 5, \((L = 6,6′\text{-Me}_2\text{bipy})\), are significantly longer than the next longest Re–N bond length of the other complexes reported in this study (Re–N3 of \([\text{Re(CO)}_3(5,5′\text{-Me}_2\text{bipy})(\text{HNC(\text{CH}_3)OCH}_3)]\text{BF}_4 (4) = (2.1860(18) \text{ Å})\). The Re–N1 and Re–N2 bond distances are thus longer for \([\text{Re(CO)}_3(6,6′\text{-Me}_2\text{bipy})(\text{HNC(\text{CH}_3)OCH}_3)]\text{BF}_4 (5), in which the highest distortion in planar aromatic ligands is expected. Also, it should be noted that the Re–N3 bond lengths of \([\text{Re(CO)}_3(\text{Me}_2\text{bipy})(\text{HNC(\text{CH}_3)OCH}_3)]\text{BF}_4\) do not depend on the position of the methyl substituents, but are longer than the 2.084(5) Å Re–N bond length of \([\text{Re(HNC(\text{CH}_3)OCH}_3]_2\text{Cl}_4\), the only reported molecular structure to contain a Re–acetimidate bond.

Figure 5.3 shows that the plane of the iminoether ligand is projected along the length of the bipyridine plane except \([\text{Re(CO)}_3(4,4′\text{-Me}_2\text{bipy})(\text{HNC(\text{CH}_3)OCH}_3)]\text{BF}_4 (3), in which the acetimidate ligand is almost perpendicular. Hydrogen bonding between the N3H and F1 of the BF$_4^-$ anion in 3 may contribute toward this difference. Thus, the orientation of the iminoether ligand does not depend on bipy bulk. Even with the bulkiness of the methyl groups at the 6,6′ position of the 6,6′-Me$_2$bipy ligand, the orientation of the acetimidate ligand is similar to that of the unsubstituted bipy. Figure 5.4 compares the molecular structures of 2 and 5 through overlaying Re atoms and N and O atoms of the acetimidate ligand, rms = 0.033.

For \([\text{Re(CO)}_3L(\text{HNC(\text{CH}_3)OCH}_3)]\text{BF}_4\) complexes (see Figure 5.2 for atom numbering), the bond angles range between 74.44(7) and 75.21(5)° for N1–Re–N2, 81.49(6) to 86.72(5)° for N1–Re–N3, and 80.33(5) to 81.66(7)° for N2–Re–N3. Although most of the differences are significant, no distinct trend could be identified.
Figure 5.3. Relative orientations of [Re(CO)$_3$L(HNC(CH$_3$)OCH$_3$)]BF$_4$ when the structures are viewed with the aromatic rings in the plane and the acetimidate ligand projected toward the viewer. L = bipy (a), 4,4′-Me$_2$bipy (b), 5,5′-Me$_2$bipy (c), and 6,6′-Me$_2$bipy (d).

Figure 5.4. Overlay of Re, N3, and O4 atoms of the acetimidate ligands of [Re(CO)$_3$(bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$ (gold) and [Re(CO)$_3$(6,6′-Me$_2$bipy) (HNC(CH$_3$)OCH$_3$)]BF$_4$ (purple) when the structure is viewed with the aromatic ring of the least distorted structure on the plane and the iminoether ligand projected along the y axis (r.m.s. = 0.033).
For complexes 2-5 (Figure 5.2), the iminoether N-to-C (N3–C16) bond shows typical double-bond character, while the iminoether N-to-O (C16–O4) distance is longer than the typical sp\(^2\) C=O bond length (1.21 Å) and closer to, though somewhat less than that of the average sp\(^2\) C–O bond length (1.34 Å).\(^2\) As an example, in [Re(CO)\(_3\)(4,4′-Me\(_2\)bipy)(HNC(CH\(_3\)OCH\(_3\))]BF\(_4\) (3), these bond distances are 1.279(3) Å (N3–C16) and 1.327(3) Å (C16–O4). In complexes 2-5, even though extensive delocalization is not reflected in the bond lengths, the C16–O4–C18 angle is close to 120° (Table 5.2), as observed by Natile and co-workers in iminoether Pt\(^{II}\) complexes,\(^10\) and may support the resonance argument (a lone pair of electrons on oxygen contributes to the formation of a delocalized system having double-bond character along the O–C–N bonds). This argument has also been proposed for Ir\(^{III}\) complexes bearing an iminoether ligand.\(^16\) Resonance may also explain the quasi-planarity of the acetimidate ligand, as evidenced by N–C–O–C torsion angles ranging from 171.67(18)° to 177.55(18)° (Table 5.2).

In a previous study,\(^29\) we noted that the electron delocalization along the N-C-N bonds was supported by relevant bond lengths and angles for monodentate amidine ligands in [Re(CO)\(_3\)(5,5′-Me\(_2\)bipy)(HNC(CH\(_3\))NHR)]BF\(_4\) (R = isopropyl, isobutyl, tert-butyl, and benzyl). In those complexes the N-to-C bond distance of the Re-bound N was only slightly shorter than the other amidine C–N bond. These observations were reflected in the ease of rotation about the N–C bonds giving rise to different configurations about N–C bonds in amidine complexes. However, only the E′ isomers formed crystals in the above complexes.\(^29\) When R = H as in [Re(CO)\(_3\)(5,5′-Me\(_2\)bipy)(HNC(CH\(_3\))NH\(_2\))]BF\(_4\), the Z isomer crystallized.\(^29\) All of the structures having an iminoether ligand reported in this study have the Z configuration as noted above. The Z configuration is sterically favored as the oxygen of the iminoether ligand is less bulky than the NHR group of amidine ligands.
Table 5.2. Selected Bond Distances (Å) and Angles (deg) for [Re(CO)₃L(HNC(CH₃)OCH₃)]BF₄ (L = Bidentate Ligand)

<table>
<thead>
<tr>
<th></th>
<th>bipy</th>
<th>4,4′-Me₂bipy</th>
<th>5,5′-Me₂bipy</th>
<th>6,6′-Me₂bipy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bond distances</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re–N1</td>
<td>2.1767(14)</td>
<td>2.1750(18)</td>
<td>2.1778(16)</td>
<td>2.211(3)</td>
</tr>
<tr>
<td>Re–N2</td>
<td>2.1721(14)</td>
<td>2.1786(18)</td>
<td>2.1706(17)</td>
<td>2.213(3)</td>
</tr>
<tr>
<td>Re–N3</td>
<td>2.1705(15)</td>
<td>2.1771(18)</td>
<td>2.1860(18)</td>
<td>2.175(3)</td>
</tr>
<tr>
<td>N3–C16</td>
<td>1.288(2)ₐ</td>
<td>1.279(3)</td>
<td>1.285(3)</td>
<td>1.294(4)</td>
</tr>
<tr>
<td>C16–O4</td>
<td>1.331(2)ₐ</td>
<td>1.327(3)</td>
<td>1.337(3)</td>
<td>1.331(4)</td>
</tr>
<tr>
<td>bond angles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1–Re–N2</td>
<td>75.21(5)</td>
<td>74.44(7)</td>
<td>75.08(6)</td>
<td>75.19(10)</td>
</tr>
<tr>
<td>N1–Re–N3</td>
<td>86.72(5)</td>
<td>82.55(7)</td>
<td>81.49(6)</td>
<td>83.33(11)</td>
</tr>
<tr>
<td>N2–Re–N3</td>
<td>80.33(5)</td>
<td>81.66(7)</td>
<td>80.72(6)</td>
<td>80.38(10)</td>
</tr>
<tr>
<td>C16–O4–C18</td>
<td>118.33(16)ₐ</td>
<td>120.2(2)</td>
<td>120.21(17)</td>
<td>119.6(3)</td>
</tr>
<tr>
<td>N3–C16–O4–C18</td>
<td>171.67(18)</td>
<td>176.2(2)</td>
<td>177.55(18)</td>
<td>174.4(3)</td>
</tr>
</tbody>
</table>

ₐ C16 = C14

**Out-of-Plane Distortions.** Bipyridines in metal complexes having M–N distances within the typical range (~2.0-2.2 Å) are not planar,° out-of-plane distortions of these complexes can be described by several parameters: bowing (θₗ), twisting (θₜ) and S-shaped deformation (dₛ).° Among the Re¹ acetimidate complexes studied here (Table 5.3), [Re(CO)₃(6,6′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄ is the most distorted, with an exceptionally large twist angle (θₜ = 12.4°) and a large bow angle (θₗ = 11.0°). This result may arise from steric repulsion between the methyl groups at the 6,6′ positions and the carbonyl ligands. [Re(CO)₃(6,6′-
Me₂bipy)(HNC(CH₃)OCH₃)BF₄ also has the largest dihedral angle ($\theta_{\text{di}} = 16.7^\circ$) of the acetimidate complexes reported here.

Earlier studies from our laboratory have focused on the effects on structure of ligand bulk on [PtLCl₂] complexes. Bearing in mind that Re–N bond distances are longer than Pt–N bond distances, we sought to analyze the effect of Re–N bond distances on distortions of Reᴵ bipyridine complexes studied here. Typical Pt–N bond distances of [PtLCl₂] complexes, where L = bipy, Me₂bipy, ranged from 2.017(3) - 2.032(3) Å. For acetimidate complexes the Re–N bond distances (pyridyl N) varied from 2.1706(17) - 2.1786(18) Å, with the notable exception of [Re(CO)₃(6,6′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄, in which the Re–N bond distances are ∼2.21 Å (as discussed above). This complex is also distinguished by its exceptionally large twist angle ($\theta_T = 12.4^\circ$) compared to [Pt(6,6′-Me₂bipy)Cl₂] ($\theta_T = 6.1^\circ$).

**Table 5.3. Ligand Deformation in Octahedral Rhenium Complexes**

<table>
<thead>
<tr>
<th>compound</th>
<th>twist angle ($\theta_T$)</th>
<th>bow angle ($\theta_B$)</th>
<th>S-shaped distortion ($d_s$)</th>
<th>in-plane distortion ($\theta_P$)</th>
<th>dihedral angle ($\theta_{\text{di}}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Re(CO)₃(bipy)(HNC(CH₃)OCH₃)]BF₄</td>
<td>0.1</td>
<td>1.9</td>
<td>0.022</td>
<td>6.6</td>
<td>1.9</td>
</tr>
<tr>
<td>[Re(CO)₃(4,4′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄</td>
<td>2.0</td>
<td>4.3</td>
<td>0.014</td>
<td>6.8</td>
<td>4.7</td>
</tr>
<tr>
<td>[Re(CO)₃(5,5′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄</td>
<td>0.6</td>
<td>5.8</td>
<td>0.005</td>
<td>8.0</td>
<td>5.8</td>
</tr>
<tr>
<td>[Re(CO)₃(6,6′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄</td>
<td>12.4</td>
<td>11.0</td>
<td>0.087</td>
<td>4.0</td>
<td>16.7</td>
</tr>
</tbody>
</table>

a $d_s$ (in Ångstroms) and $\theta_T, \theta_B, \theta_P, \text{and } \theta_{\text{di}}$ values (in degrees) were calculated by using a Fortran program provided by Dr. Alan Hazell. $\theta_{\text{di}}$ values calculated using SHELXL97 agreed with those from the Fortran program.

**In-plane Bending.** The in-plane bending for the Reᴵ bipyridine complexes reported here is within the range ($\theta_P = 2.9 - 12.5^\circ$) reported by Hazell, who also noted that $\theta_P$ decreases with increasing M–N distance. This finding is valid for the comparison of [Re(CO)₃(6,6′-Me₂bipy)(HNC(CH₃)OCH₃)]BF₄ with other Reᴵ complexes in this study (the other complexes reported here have very similar M-N distances and a generalization cannot be made regarding
them). For \([\text{Pt}(6,6^\prime-\text{Me}_2\text{bipy})\text{Cl}_2]\) the \(\theta_P\) value (\(\theta_P = 10.9^\circ\)) is comparatively larger than for isomers having methyl groups at the 4,4\(^\prime\) and 5,5\(^\prime\) positions, but \([\text{Re}(\text{CO})_3(6,6^\prime-\text{Me}_2\text{bipy})(\text{HNC(CH}_3\text{OCH}_3))]\text{BF}_4\) has the smallest \(\theta_P\) value (\(\theta_P = 4.0^\circ\)) in comparison with others in the series. In \(\text{PtLCl}_2\), distortion is characterized more by twisting than bowing, except for \([\text{Pt}(6,6^\prime-\text{Me}_2\text{bipy})\text{Cl}_2]\). But for the Re complexes reported here, distortion is characterized more by bowing than by twisting, except when \(L = 6,6^\prime-\text{Me}_2\text{bipy}\) (Table 5.3). Among the complexes discussed in Table 5.3, \([\text{Re}(\text{CO})_3(6,6^\prime-\text{Me}_2\text{bipy})(\text{HNC(CH}_3\text{OCH}_3))]\text{BF}_4\) (5) has the highest dihedral angle (\(\theta_{di} = 16.7^\circ\)). A dihedral angle of 20.2\(^\circ\) in \([\text{Pt}(6,6^\prime-\text{Me}_2\text{bipy})\text{Cl}_2]\) reveals that the 6,6\(^\prime\) isomer had the highest dihedral angle in \(\text{PtLCl}_2\) complexes. Thus, the highest dihedral angle is for the 6,6\(^\prime\) isomer, irrespective of whether the complex is square planar or octahedral.

**NMR Spectroscopy.** All complexes reported were characterized by NMR spectroscopy in several solvents (CDCl\(_3\), DMSO-\(d_6\) and acetonitrile-\(d_3\)). The iminoether NH signals appear more downfield in DMSO-\(d_6\) (8.57-8.72 ppm) than in CDCl\(_3\) (7.41-7.62 ppm) or in acetonitrile-\(d_3\) (7.18-7.31 ppm). The more downfield chemical shifts of the N3H signals in DMSO-\(d_6\) may be explained by looking at the molecular structures of these complexes (Figure 5.2), in which N3H points toward the solvent; thus, more downfield signals are observed in hydrogen bonding solvents vs. non-hydrogen bonding solvents. Addition of D\(_2\)O (100 \(\mu\)L) to \([\text{Re}(\text{CO})_3\text{L}(\text{HNC(CH}_3\text{OCH}_3))]\text{BF}_4\) (5 mM, 550 \(\mu\)L DMSO-\(d_6\)) showed that the half-life for the exchange reaction of N3H with D\(_2\)O is \(~40\) min. In a similar study of Re\(^I\) complexes bearing unusual amidine ligands (having seven-membered chelate rings), the NH of the sp\(^2\)N took longer for NH-ND exchange in DMSO-\(d_6\) (half life = 1 day).\(^9\)

In a study of complexes of the type \([\text{Re}(\text{CO})_3(5,5^\prime-\text{Me}_2\text{bipy})(\text{HNC(CH}_3\text{NHR})]\text{BF}_4\) out of four conceivable isomers, \(E^\prime\) and \(Z\) isomers were observed in acetonitrile-\(d_3\) and \(E, E^\prime\) and \(Z\)
isomers were observed in CDCl$_3$ and CD$_2$Cl$_2$; the exchange reaction between the $E$ and $E'$ isomers was fast enough to be observed on the NMR time scale, even though the exchange reaction between $E'$ and $Z$ isomers was slow.\textsuperscript{29} The bond distance of the Re-bound N and C is shorter for iminoether complexes ($\sim$1.28 Å) than for amidine complexes ($\sim$1.31 Å). Thus, the double bond character of the bond between the Re-bound N and C is higher in iminoether complexes (Table 5.2) versus amidine complexes, indicating that $E$ to $Z$ interchange is slow, leading to possible absence of the $E$ isomer.

**Interaction of NH Protons with the Cl$^-$ Anion.** Downfield shift changes, $\Delta\delta$, for NH groups directed away from solvent were observed when Cl$^-$ was added to 5 mM solutions of fac-[Re(CO)$_3$L]$^+$ complexes.\textsuperscript{9,34} When Cl$^-$ was added to a solution of [Re(CO)$_3$(5,5'-Me$_2$bipy)(HNC(CH$_3$)OCH$_3$)]BF$_4$ in DMSO-$d_6$, the already downfield NH signal of the acetimidate ligand shifted only slightly downfield ($\Delta\delta \sim 0.21$ ppm, plot not included).

### 5.4 Conclusions

Because the fac-[Re(CO)$_3$L(L')]$^+$ compounds containing acetonitrile as the labile ligand isolated here in good yield and purity can be used as intermediates, we propose that fac-[Re(CO)$_3$(CH$_3$CN)$_3$]$^+$ is a versatile precursor. Iminoether complexes of Re$^1$ bearing dimethyl-2,2'-bipyridine ligands favor the $Z$ configuration in the solid state; there is no evidence from NMR spectra that the $E$ or $E'$ isomers exist in solution. This finding is in contrast to that of amidine complexes, where, $E$, $E'$ and $Z$ isomers were observed in CDCl$_3$ in [Re(CO)$_3$(5,5'-Me$_2$bipy)(amidine)]BF$_4$ complexes obtained by the addition of aliphatic amines at the rhenium-coordinated nitrile.\textsuperscript{29}

For fac-[Re(CO)$_3$L(HNC(CH$_3$)OR')]BF$_4$ bearing the bipy moiety and iminoether ligands reported here, distortion is characterized more by bowing, than by twisting, except when L =
6,6′-Me₂bipy; in PtLCl₂, distortion is characterized more by twisting than bowing, except for [Pt(6,6′-Me₂bipy)Cl₂].

5.5 References


CHAPTER 6
NEW N,N,N-DONOR LIGANDS BEARING A TERTIARY SUFONAMIDO LINKAGE.
SYNTHETIC, X-RAY CRYSTALLOGRAPHIC, AND NMR SPECTRAL FEATURES OF
fac-Re(CO)₃ COMPLEXES

6.1 Introduction

Radiopharmaceuticals containing the \(\{^{99m}\text{Tc} (\text{CO})_3\}\)^+ core have received widespread attention in the past two decades.\(^1\)-\(^6\) Many factors have contributed to this interest, including the convenient generation of the \(\text{fac-}[^{99m}\text{Tc} (\text{CO})_3(\text{H}_2\text{O})_3]^+\) precursor\(^7,8\) and the utility of \(\text{fac-}[\text{Re} (\text{CO})_3 \text{L}]^\circ\) analogues (L is a facially coordinated tridentate ligand) to serve as model systems allowing the chemistry of the short-lived radioactive \(\text{fac-}[^{99m}\text{Tc} (\text{CO})_3 \text{L}]^n\) imaging agents to be understood.\(^4,9\)-\(^11\) Also \(^{186}\text{Re}\) and \(^{188}\text{Re}\) are among the most promising radionuclides for therapeutic applications.\(^12\) Tridentate ligands form stable and kinetically inert complexes containing the \(\{\text{M} (\text{CO})_3\}\)^+ core (M = \(^{99m}\text{Tc}, \text{Re}\)).\(^12\)

Luminescent probes based on Re(I) are particularly useful for studying biological processes by virtue of their long lifetime, polarized emission, and large Stokes shift.\(^13\)-\(^15\) Recently \(\text{fac-Re(CO)}_3\) complexes bearing di(2-picolyl)amine (N(H)dpa) derivatives have generated much interest in biomedical research.\(^13,16,17\) In naming ligands in this article, the \(\text{N}\) designates the central \(\text{sp}^3\) nitrogen, with the substituent replacing the \(\text{NH}\) proton. Zubieta and co-workers have based some of their work relating to the bifunctional chelate design for \(\{\text{M} (\text{CO})_3\}\)^+ (M = \(^{99m}\text{Tc}, \text{Re}\)) on the tridentate ligand, N(H)dpa,\(^13,18\) in which the amine nitrogen provides a site for tethering additional functional groups. A \(^{188}\text{Re}\) complex containing the N(amoenoethyl)dpa ligand functionalized at the central \(\text{N}\) with a dangling ethylamine group, \(\text{fac-}[^{188}\text{Re} (\text{CO})_3 (\text{N(amoenoethyl)dpa})]\text{Br}\), has been reported to show promising biomedical properties.\(^17\) \(\text{fac-[M(CO)}_3(\text{N(CH}_2\text{COglucosyl)}\text{dpa})]\text{Br}\) (M = \(^{99m}\text{Tc}, \text{186Re and Re}\) conjugates were synthesized in an effort to develop stable carbohydrate-appended imaging and therapeutic
agents. Also \( \text{fac-}^{99m}\text{Tc(CO)}_3(N(3,5\text{-dimethoxybenzyl})\text{dpa})^+ \) has been developed and evaluated for cardiac uptake. Highly lipophilic cations are thought to be required for high uptake and retention in the myocardium; the \( \text{N(H)dpa} \) moiety was chosen because it allows the lipophilicity to be modulated through easy derivation of the central \( \text{N} \) and because the size and lipophilicity of the ligands could be varied without the formation of isomers.

The fact that no new \( ^{99m}\text{Tc} \) imaging agent has received FDA approval for over a decade clearly indicates the need for exploring novel ligands that could impart superior characteristics into such agents. In designing ligands with new methods of conjugation, it is important to consider and take advantage of geometric constraints. As an example, in designing tetradentate ligands to form octahedral cobalt complexes that adopt a specific geometry, the NSNN donor set was used, taking advantage of the fact that S atoms act as internal donor atoms with a known stereochemical preference to bind pyramidal (i.e., enforce a facial coordination mode).

Evaluating literature examples, we found that although the usual situation is that sulfonamide \( \text{N} \) atoms do not coordinate metals unless they are deprotonated, a few examples exist in which a tertiary sulfonamide is coordinated to a metal, albeit in cyclic ligands. Paralleling this observation are cases in which tertiary sulfonamide groups do not bind metals; the tertiary sulfonamide nitrogen did not bind metals in porphyrins containing only tertiary sulfonamide groups and in square planar Pd complexes. Such coordination ordinarily would require that the \( \text{N} \) permits meridional coordination.

In this study, we report on the synthesis of new ligands bearing central sulfonyl groups on the \( \text{dpa} \) unit \( (\text{N(SO}_2\text{R})\text{dpa}, \text{R} = \text{Me, tmb, and 5-(dimethylamino)-naphthalene; see Figure 6.1 for ligands and their abbreviations}) \) and their \( \text{fac-}[\text{Re(CO)}_3\text{L}]^+ \) complexes. As mentioned, the study of nonradioactive Re analogues is important in guiding ligand design and is useful for understanding the chemistry of \( ^{99m}\text{Tc} \) agents. Treatment of \( \text{fac-}[\text{Re(CO)}_3(\text{H}_2\text{O})]^+ \) with tridentate
ligands L (novel ligands bearing central sulfonyl groups, and two pyridine rings) afforded \( \text{fac-[Re(CO)}_3L]^+ \) complexes bearing a tertiary sulfonamide linkage. This study is the first structural characterization of a tertiary neutral sulfonamide to be linked to the \( \text{fac-Re(CO)}_3 \) core. It is also the first such study of open-chain sulfonamides with any metal.

![Figure 6.1. Ligands used in this study: \( N,N\)-di(2-picolyl)methanesulfonamide (\( \text{N(SO}_2\text{Me)}dpa \)), \( N,N\)-di(2-picolyl)-2,4,6-trimethylbenzenesulfonamide (\( \text{N(SO}_2\text{tmb)}dpa \)), \( N,N\)-di(2-picolyl)-5-(dimethylamino)-naphthalene-1-sulfonamide (\( \text{N(dansyl)}dpa \)).](image)

We test our conjugation method by utilizing a tetraarylporphyrin (\( \text{T(N(SO}_2\text{C}_6\text{H}_4)dpa)P} \)) which contains four peripheral dpa moieties linked to the porphyrin via a tertiary sulfonamide (Scheme 6.1) and by evaluating the formation of a 1:4 porphyrin:Re adduct. The results demonstrate that the tertiary sulfonamide linkage may be utilized to tether biologically important molecules and propose that it may be extended to the \( \text{\{}^{99m}\text{Tc(CO)}_3\text{\}}^+ \) core. From now on, we omit the \( \text{fac-} \) designation when discussing specific compounds because all the new compounds have this geometry.
6.2 Experimental Section

**Starting Materials.** Methanesulfonyl chloride (MeSO₂Cl), 2,4,6-trimethylbenzenesulfonyl chloride (tmbSO₂Cl), 5-(dimethylamino)naphthalene-1-sulfonyl chloride (dansyl chloride), di(2-picoly)lamine (N(H)dpa), and Re₂(CO)₁₀ were used as received from Aldrich. [Re(CO)₃(H₂O)₃]OTf (OTf = trifluoromethanesulfonate) was prepared by a known method.³² [Re(CO)₃(CH₃CN)₃]BF₄ and *meso*-tetra-(4-chlorosulfonylphenyl)porphyrin (TCISO₃PP) were synthesized as described elsewhere,³³,³⁴ and the ¹H NMR chemical shifts matched the reported values.

**NMR Measurements.** ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Peak positions are relative to tetramethylsilane (TMS) or solvent residual peak with TMS as reference. All NMR data were processed with TopSpin and Mestre-C software.

**X-ray Data Collection and Structure Determination.** Single crystals were placed in a cooled nitrogen gas stream at 90 K on a Nonius Kappa CCD diffractometer fitted with an Oxford
Cryostream cooler with graphite-monochromated Mo Kα (0.71073 Å) radiation. Data reduction included absorption corrections by the multi-scan method, with HKL SCALEPACK.\textsuperscript{35} All X-ray structures were determined by direct methods and difference Fourier techniques and refined by full-matrix least squares by using \textit{SHELXL97}.\textsuperscript{36} All non-hydrogen atoms were refined anisotropically. All H atoms were visible in difference maps, but were placed in idealized positions. A torsional parameter was refined for each methyl group.

\textbf{Synthesis of [Re(CO)\textsubscript{3}L]PF\textsubscript{6} and [Re(CO)\textsubscript{3}L]BF\textsubscript{4} Complexes.} The following general procedure was employed to obtain the $N$(SO\textsubscript{2}R)dpa ligands. A solution of the sulfonyl chloride (5 mmol) in 25 mL of dioxane was added dropwise over a period of 2 h to a solution of $N$(H)dpa, (10 mmol) in 100 mL of dioxane at 20 °C. The reaction mixture was stirred at room temperature for 24 h and then filtered to remove any precipitate before the dioxane was completely removed by rotary evaporation. Water (30 mL) was added to the resulting oil, and the product was extracted into CH\textsubscript{2}Cl\textsubscript{2} (2 × 25 mL). The CH\textsubscript{2}Cl\textsubscript{2} portions were combined, washed with water (2 × 25 mL), and taken to dryness to yield an oil, which was used to synthesize [Re(CO)\textsubscript{3}L]PF\textsubscript{6} and [Re(CO)\textsubscript{3}L]BF\textsubscript{4} in the general procedure outlined here. An aqueous solution of the ligand (0.1 mmol in 2 mL) was treated with an aqueous solution of [Re(CO)\textsubscript{3}(H\textsubscript{2}O)\textsubscript{3}]\textsuperscript{+} (0.1 mmol in 3 mL). Methanol (2-3 mL) was added to dissolve any precipitate that formed, and the clear reaction mixture was heated at reflux for 12 h. A slight excess of NaPF\textsubscript{6} or NaBF\textsubscript{4} was added to the clear solution, and the resulting precipitate was collected on a filter, washed with water, and air dried. (If the pH of the final reaction mixture was below 6, it was adjusted to 7 before adding NaPF\textsubscript{6}; for $N$(SO\textsubscript{2}tmb)dpa and $N$(dansyl)dpa, methanol (~1 mL) was used initially to dissolve the ligand).
[Re(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ (1). The general method described above, with MeSO$_2$Cl (0.39 mL) and N(H)dpa (1.80 mL), yielded the crude N(SO$_2$Me)dpa ligand as a deep red oil (1.40 g, 76% yield). $^1$H NMR signals (ppm) in DMSO-$d_6$: 8.50 (s, 2H, H6/6'), 7.75 (t, 2H, H4/4'), 7.34 (d, 2H, H3/3'), 7.27 (t, 2H, H5/5'), 4.48 (s, 4H, CH$_2$), 3.11 (s, 3H, CH$_3$). The general method described, with N(SO$_2$Me)dpa (28 mg) and [Re(CO)$_3$(H$_2$O)$_3$]$^+$ (0.1 mmol), afforded [Re(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ as a white precipitate (38 mg, 54% yield) after the addition of NaPF$_6$ (∼15 mg). Slow evaporation of a solution of the compound in acetone produced colorless, needle-like crystals that were characterized by single-crystal X-ray crystallography. $^1$H NMR signals (ppm) in DMSO-$d_6$: 8.89 (d, 2H, H6/6'), 8.09 (t, 2H, H4/4'), 7.57 (d, 2H, H3/3'), 7.53 (t, 2H, H5/5'), 5.44 (d, 2H, CH$_2$), 5.13 (d, 2H, CH$_2$), 3.87 (s, 3H, CH$_3$).

[Re(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ (2). The general method described above, with tmbSO$_2$Cl (1.10 g) and N(H)dpa (1.80 mL), yielded N(SO$_2$tmb)dpa as a pale orange oil (1.75 g, 92% yield). $^1$H NMR signals (ppm) in DMSO-$d_6$: 8.43 (s, 2H, H6/6'), 8.09 (t, 2H, H4/4'), 7.53 (t, 2H, H3/3'), 7.53 (t, 2H, H5/5'), 6.97 (s, 2H), 4.54 (s, 4H, CH$_2$), 2.53 (s, 6H, CH$_3$), 2.23 (s, 3H, CH$_3$). The general method above, with N(SO$_2$tmb)dpa (38 mg) and [Re(CO)$_3$(H$_2$O)$_3$]$^+$ (0.1 mmol), afforded [Re(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ as a white precipitate (51 mg, 64% yield) after the addition of NaPF$_6$ (∼15 mg). Slow evaporation of a solution of the compound in chloroform produced colorless, block-like crystals that were characterized by single-crystal X-ray crystallography. $^1$H NMR signals (ppm) in DMSO-$d_6$: 8.90 (d, 2H, H6/6'), 8.05 (t, 2H, H4/4'), 7.64 (d, 2H, H3/3'), 7.49 (t, 2H, H5/5'), 7.46 (s, 2H), 5.22 (d, 2H, CH$_2$), 4.53 (d, 2H, CH$_2$), 2.78 (s, 6H, CH$_3$), 2.43 (s, 3H, CH$_3$).

[Re(CO)$_3$(N(dansyl)dpa)]BF$_4$ (3). The general method described above, with dansyl chloride (1.42 g) and N(H)dpa (1.8 mL), yielded N(dansyl)dpa as a pale orange oil (1.96 g, 91%
yield). \(^1H\) NMR signals (ppm) in DMSO-\(d_6\): 8.44 (d, 1H), 8.37 (d, 2H), 8.20 (d, 1H), 8.16 (d, 1H), 7.58 (t, 2H), 7.54 (m, 2H), 7.23 (d, 1H), 7.18 (t, 2H), 7.12(d, 2H), 4.72 (s, 4H, CH\(_2\)), 2.82 (s, 6H, CH\(_3\)). The general method described, with \(N\)(dansyl)dpa (43 mg) and [Re(CO)\(_3\)(H\(_2\)O)\(_3\)]\(^+\) (0.1 mmol), afforded [Re(CO)\(_3\)(\(N\)(dansyl)dpa)]BF\(_4\) as yellow block-like crystals (38 mg, 44% yield) after the addition of NaBF\(_4\) (~15 mg). The product was characterized by single-crystal X-ray crystallography. \(^1H\) NMR signals (ppm) in DMSO-\(d_6\): 8.90 (m, 3H), 8.71 (d, 1H), 8.58 (d, 1H), 7.98 (t, 1H), 7.92 (t, 1H), 7.78 (t, 1H), 7.47 (t, 2H), 7.42 (d, 2H), 7.39 (d, 1H), 5.64 (d, 2H), 4.53 (d, 2H, CH\(_2\)), 2.91 (s, 6H, CH\(_3\)).

\(T(N(SO_2C_6H_4)dpa)P\). A solution of TCISO\(_2\)PP (0.4 g, 0.39 mmol) in CH\(_2\)Cl\(_2\) (50 mL) was treated with \(N\)(H)dpa (3.7 mL, 1.98 mmol), and the reaction mixture was stirred at room temperature for 24 h. Impurities in this mixture were then extracted with water (3 \times 25 mL); the organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and the solvent removed under vacuum. The purple residue was crystallized from CH\(_2\)Cl\(_2\)/hexane and washed with hexane (0.32 g, 49% yield). \(^1H\) NMR signals (ppm) in DMSO-\(d_6\): 8.87 (s, 8H, \(\beta\)H), 8.55 (d, 8H, H6/6'), 8.37 (d, 8H, oH), 8.24 (d, 8H, mH), 7.83 (t, 8H, H4/4'), 7.49 (d, 8H, H3/3'), 7.34 (t, 8H, H5/5'), 4.90 (s, 16H, CH\(_2\)), -2.96 (s, 2H, NH). ESI-MS(m/z): [M + H]\(^+\) = 1660.4881, [M + 2H]\(^+2\) = 830.7465. Calcd for [M + H]\(^+\) = 1660.4886, [M + 2H]\(^+2\) = 830.7443.

\([\{\text{Re(CO)}_3\}_4T(N(SO_2C_6H_4)dpa)P](\text{BF}_4)_4\) (4). [Re(CO)\(_3\)(CH\(_3\)CN)\(_3\)]BF\(_4\) (28 mg, 0.058 mmol) was added to a solution of T(N(SO\(_2\)C\(_6\)H\(_4\))dpa)P (20 mg, 0.012 mmol) in a mixture of chloroform/acetone (25 mL/5 mL). The reaction mixture was heated at reflux for 16 h and reduced to dryness by rotary evaporation. The resulting maroon residue was quickly washed with CH\(_2\)Cl\(_2\), dissolved in acetone, and the resultant solution layered with hexane to give a maroon precipitate (15 mg, 40% yield). \(^1H\) NMR signals (ppm) in DMSO-\(d_6\): 9.19 (s, 8H, \(\beta\)H), 9.01 (d,
8H, H6/6'), 8.84 (s, 16H, o,nH), 8.14 (t, 8H, H4/4'), 7.71 (d, 8H, H3/3'), 7.58 (t, 8H, H5/5'), 5.98 (d, 8H, CH2), 4.97 (d, 8H, CH2), -2.81 (s, 2H, NH).

6.3 Results and Discussion

**Synthesis of N(SO2R)dpa and [Re(CO)3(N(SO2R)dpa)]PF6.** We have synthesized potential tridentate ligands bearing MeSO2, tmbSO2, and dansyl groups at the central N (Figure 6.1) by coupling N(H)dpa with the desired sulfonyle chloride. The ligands were obtained in good yield and quite pure, as indicated by NMR spectral data (Experimental Section). NMR spectra of the new ligands are given in Supporting Information and show no N(H)dpa left in sample. A [Re(CO)3(H2O)3]OTf aqueous solution32 was used to prepare complexes 1-3 (Scheme 6.2).

**Scheme 6.2.** Synthesis of [Re(CO)3(N(SO2R)dpa)]+ complexes

$$
\text{fac-[Re(CO)3(H2O)3]OTf}
\begin{array}{c}
\rightarrow \\
N(SO2R)dpa
\end{array}
\begin{array}{c}
\rightarrow \\
\text{R}
\end{array}
$$

$$
\begin{align*}
\text{fac-[Re(CO)3(N(SO2R)dpa)]}^+ \\
\text{R} &= \text{methyl} \quad (1) \\
\text{R} &= 2,4,6\text{-trimethylbenzene} \quad (2) \\
\text{R} &= 5\text{-dimethylamino}n\text{-naphthalene} \quad (3)
\end{align*}
$$

**Synthesis of the Porphyrin T(N(SO2C6H4)dpa)P and its 1:4 Re Adduct, [(Re(CO)3)4T(N(SO2C6H4)dpa)P][BF4]4.** We have utilized the synthetic approach reported by members of our group39 to prepare T(R1R2NSO2C6H4)P (R1 = N-py-n-CH2 (n = 2 or 4) and R2 = alkyl) in order to synthesize a porphyrin (T(N(SO2C6H4)dpa)P) bearing four dpa moieties linked
via tertiary sulfonamide groups (Scheme 6.1). Because the porphyrin is not water-soluble, we utilized the [Re(CO)\(_3\)(CH\(_3\)CN)\(_3\)]\(^+\) precursor to form a 1:4 adduct between T(N(SO\(_2\)C\(_6\)H\(_4\))dpa)P and Re (see below). Alessio and co-workers utilized the [Re(CO)\(_3\)(DMSO)\(_3\)]\(^+\) precursor to synthesize [Re(CO)\(_3\)(bipyridine)(DMSO)]\(^+\),\(^{37}\) which was then used to prepare 1:1 and 1:4 adducts between meso-tetra(4-pyridyl)porphyrin (TpyP(4)) and Re(CO)\(_3\)(bipyridine) units.\(^{38}\) In these porphyrin-Re conjugates a peripheral meso pyridyl group was directly bound to Re. In [{Re(CO)\(_3\)}\(_4\)T(N(SO\(_2\)C\(_6\)H\(_4\))dpa)]\((BF_4)_4\), three of the Re-bound atoms (a peripheral tertiary sulfonamide and two pyridyl groups) are to the porphyrin but linked via an aryl group.

**Structural Results.** The Re complexes reported here exhibit a pseudo octahedral structure, with the three carbonyl ligands occupying one face. The remaining three coordination sites are occupied by three nitrogen atoms of new tridentate ligands in [Re(CO)\(_3\)(N(SO\(_2\)Me)dpa)]PF\(_6\) (1) (Figure 6.2), [Re(CO)\(_3\)(N(SO\(_2\)tmb)dpa)]PF\(_6\) (2) (Figure 6.3), and [Re(CO)\(_3\)(N(dansyl)dpa)]BF\(_4\) (3) (Figure 6.4). The unusual and most interesting structural feature is that the central N, N2, is bound to Re. Crystal data and details of the structural refinement for these complexes are summarized in Table 6.1. The atom numbering systems in the ORTEP figures are used to describe the solid-state data. The asymmetric unit of 1 contains one [Re(CO)\(_3\)(N(SO\(_2\)Me)dpa)]\(^+\) cation and half of two crystallographically independent PF\(_6^-\) anions; one anion lies on an inversion center, and the other anion lies on a twofold axis and is disordered.

In the molecular structure of [Re(CO)\(_3\)(N(SO\(_2\)Me)dpa)]PF\(_6\) (1) (Figure 6.2), the Re–N2 bond distance (2.2826(16) Å) involving the central nitrogen is significantly longer than the Re–N1 (2.1736(17) Å) and the Re–N3 (2.1948(18) Å) bond distances (Table 6.1). The complex of the parent amine, [Re(CO)\(_3\)(N(H)dpa)]Br, has a central N–Re bond distance of 2.187(4) Å,\(^{18}\) but when the NH proton is replaced by a CH\(_2\)CO\(_2\)H substituent (in [Re(CO)\(_3\)(N(CH\(_2\)CO\(_2\)H)dpa)]Br) the N–Re bond distance is longer (2.230(5) Å).\(^{18}\) Because such bond lengthening can be
attributed to steric rather than to electronic effects, the similar length of the Re–N bond for this sp³ tertiary N and for the sulfonamide N (N2) indicates that the sulfonamide N is a relatively strong donor. In [Re(CO)₃(N(SO₂Me)dpa)]PF₆ (1) (Figure 6.2), the angles of the sulfonamide nitrogen are close to 109° (Table 6.2), a result clearly illustrating that the hybridization of the sulfonamide nitrogen has changed from sp² to sp³ upon binding to Re. Re–N(sp³) bond distances in [Re(CO)₃L]⁺ complexes with prototypical aliphatic NNN donor ligands are ~2.23-2.29 Å,³⁹,⁴⁰ and Re–N(sp²) bond distances are ~2.17-2.19 Å.⁴¹ The Re–N(pyridyl) bond distances of 1 (2.1736(17) and 2.1948(18) Å) and [Re(CO)₃(dpa)]Br (2.177(5) and 2.183(5) Å)¹⁸ are statistically very similar, and thus any effects of having a tertiary sulfonamide N anchoring the two chelate rings versus having a traditional sp³ nitrogen anchoring the rings are minimal.

**Figure 6.2.** ORTEP plots of the cations in [Re(CO)₃(N(SO₂Me)dpa)]PF₆ (1). Thermal ellipsoids are drawn with 50% probability.
Figure 6.3. ORTEP plots of the cations in [Re(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ (2). Thermal ellipsoids are drawn with 50% probability.

Figure 6.4. ORTEP plots of the cations in [Re(CO)$_3$(N(dansyl)dpa)]BF$_4$ (3). Thermal ellipsoids are drawn with 50% probability.
Table 6.1. Crystal Data and Structure Refinement for [Re(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ (1), [Re(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ (2), and [Re(CO)$_3$(N(dansyl)dpa)]BF$_4$ (3)

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$^a$ $R = (\sum||F_o|-|F_c||)/\sum|F_o|$; $^b$ $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$, in which $w = 1/[\sigma^2(F_o^2) + (dP)^2 + (eP)]$ and $P = (F_o^2 + 2F_c^2)/3$, $d = 0.0368$, 0.0463, and 0.0399, and $e = 5$, 0, and 2.129 for [Re(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ (1), [Re(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ (2), and [Re(CO)$_3$(N(dansyl)dpa)]BF$_4$ (3), respectively.
Table 6.2. Selected Bond Distances (Å) and Angles (deg) for [Re(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ (1)
and [Re(CO)$_3$(N(SO$_2$tmdbpa)]PF$_6$ (2) and [Re(CO)$_3$(N(dansyl)dpa)]BF$_4$ (3)

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The Re–N1, Re–N2, and Re–N3 bond distances of [Re(CO)3(N(SO2tmb)dpa)]PF6 (2) (Figure 6.3) and [Re(CO)3(N(dansyl)dpa)]BF4 (3) (Figure 6.4) are not statistically different from the relevant bond distances of 1 (Table 1). In both 2 and 3, the Re–N2 bond distance is significantly longer than the Re–N1 and Re–N2 bond distances, as found for 1.

To the best of our knowledge, there are four literature examples in which tertiary sulfonamides have been shown to bind to metals.24,26-28 In all these previous cases, the N is positioned advantageously by ligand rings. In three of these examples, the likelihood of the tertiary sulfonamides coordinating to the metal is improved via good positioning of the group within a macrocyclic cavity created by chelating N binding sites.24,26,27 The fourth example is a cyclic 7-azanorbornadiene derivative of Fe(CO)3.28 In each of these examples, the metal-bound tertiary sulfonamide nitrogen and the donors of the adjacent chelate rings occupy the face of an octahedron24 or have a similar arrangement in complexes with other geometries.26,27 In no case do these three donor atoms and the metal atom define a common plane.

In Pt(N(SO2Me)dpa)Cl2, a Pt complex containing the (N(SO2Me)dpa) ligand (Supporting Information), the central nitrogen is not bound to Pt; the bidentate ligand binding mode is confirmed by X-ray crystallography. Bond angles pertaining to the relevant angles of the sulfonamide nitrogen are close to 120° (not shown) and indicate sp2 hybridization. In contrast to the clear evidence that binding of the tertiary sulfonamide nitrogen in 1 changes hybridization at the central nitrogen from sp2 to sp3, a Cu complex of a pyridine containing macrocycle having tertiary sulfonamide nitrogens that are bound and unbound to Cu,26 has bond angles of 110.58°, 114.91°, 100.89°, and 98.84° at the bound sulfonamide nitrogen and 114.00°, 114.17°, and 112.71° at the unbound sulfonamide nitrogen. This observation suggests constrained bond angles. The Cu-N bond length of 2.346(7) Å is within the range of a typical Cu-N bond length.26
However, there is no clear evidence to indicate either sp$^2$ or sp$^3$ hybridization at the sulfonamide nitrogen.

**NMR Spectroscopy.** All complexes reported were characterized by NMR spectroscopy in DMSO-$d_6$. In the free ligands ($N$(SO$_2$Me)dpa, $N$(SO$_2$tmb)dpa, and $N$(dansyl)dpa), the methylene groups appear as a singlet (Table 6.3). Upon coordination to metal, regardless of the bi or tri dentate binding mode, the methylene groups appear as two doublets because the methylene protons are no longer magnetically equivalent.

Table 6.3. Selected $^1$H NMR Shifts (ppm) in DMSO-$d_6$ for dpaSO$_2$Me, $[\text{Re}$(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ (1), Pt($N$(SO$_2$Me)dpa)Cl$_2$, dpaSO$_2$tmb, $[\text{Re}$(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ (2), and Pt($N$(SO$_2$tmb)dpa)Cl$_2$

<table>
<thead>
<tr>
<th></th>
<th>H6/H6′</th>
<th>H5/5′</th>
<th>H4/4′</th>
<th>H3/3′</th>
<th>CH$_2$</th>
<th>CH$_3$SO$_2$</th>
<th>tmbSO$_2$</th>
<th>H4, H6</th>
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<tr>
<td>$N$(SO$_2$Me)dpa</td>
<td>8.50</td>
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<td>7.75</td>
<td>7.34</td>
<td>4.48</td>
<td>3.11</td>
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<tr>
<td>$[\text{Re}$(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$</td>
<td>8.89</td>
<td>7.53</td>
<td>8.09</td>
<td>7.57</td>
<td>5.44, 5.13</td>
<td>3.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt($N$(SO$_2$Me)dpa)Cl$_2$</td>
<td>9.24</td>
<td>7.49</td>
<td>7.93</td>
<td>7.51</td>
<td>6.04, 5.21</td>
<td>3.21</td>
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<td></td>
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<td>$N$(SO$_2$tmb)dpa</td>
<td>8.43</td>
<td>7.22</td>
<td>7.65</td>
<td>7.09</td>
<td>4.53</td>
<td>6.97</td>
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</tr>
<tr>
<td>$[\text{Re}$(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$</td>
<td>8.90</td>
<td>7.49</td>
<td>8.05</td>
<td>7.64</td>
<td>5.22, 4.53</td>
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</tr>
<tr>
<td>Pt($N$(SO$_2$tmb)dpa)Cl$_2$</td>
<td>9.27</td>
<td>7.47</td>
<td>7.81</td>
<td>7.14</td>
<td>6.09, 5.08</td>
<td>7.04</td>
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<td></td>
</tr>
</tbody>
</table>

As mentioned above, $N$(SO$_2$Me)dpa acts as a bidentate ligand in Pt($N$(SO$_2$Me)dpa)Cl$_2$ (unpublished results) and as a tridentate ligand in $[\text{Re}$(CO)$_3$(N(SO$_2$Me)dpa)]PF$_6$ (1). For 1 the signals of the methylene protons appear as two doublets and have a coupling constant ($J = 16.6$ Hz) indicating geminal coupling. For Pt($N$(SO$_2$Me)dpa)Cl$_2$, the coupling constant, although still indicative of geminal coupling, is smaller ($J = 15.0$ Hz) than that in the tridentate complex 1. However, the coupling constants of $[\text{Re}$(CO)$_3$(N(SO$_2$tmb)dpa)]PF$_6$ (2), ($J = 16.0$ Hz) and Pt($N$(SO$_2$tmb)dpa)Cl$_2$ (unpublished results, $J = 15.6$ Hz) are not much different. Thus, the value
of \( J \) is not indicative of bidentate versus tridentate binding mode. There is no trend in shift to suggest that the NMR signals (Table 6.3) of the methylene protons can be used to distinguish between bidentate and tridentate ligand binding modes.

The methyl group \(^{13}\)C NMR signal in the free \( N(SO_2Me)dpa \) ligand appears at 39.24 ppm. The signal does not shift much in Pt(\( N(SO_2Me)dpa \))Cl\(_2\) (37.17 ppm) but it has a considerably different shift in 1 (32.88 ppm); the signal is thus upfield compared to free ligand. Ordinarily, one expects that metal coordination will produce a downfield shift. These results indicate that \(^{13}\)C NMR shifts of the methyl group may be used to distinguish between bidentate and tridentate binding modes of the ligand in \([Re(CO)_3(N(SO_2Me)dpa)]PF_6\) (1) and Pt(\( N(SO_2Me)dpa \))Cl\(_2\). The upfield shift in 1 can be attributed to the rehybridization of the N.

However, the most convenient NMR signal to distinguish between the bidentate and tridentate ligand binding modes of the \( N(SO_2Me)dpa \) ligand is the methyl \(^1\)H signal. In 1, the \(^1\)H methyl signal moves downfield by 0.76 ppm upon binding of the \( N(SO_2Me)dpa \) ligand to Re; however, upon binding of the \( N(SO_2Me)dpa \) ligand to Pt, the methyl signal shifts downfield by only 0.10 ppm. This observation can best be explained by the inductive effect resulting from a direct N–Re bond in 1 (Figure 6.2) and the absence of a N–Pt bond in Pt(\( N(SO_2Me)dpa \))Cl\(_2\) (Supporting Information).

COSY spectra of the free \( N(SO_2Me)dpa \) ligand and \([Re(CO)_3(N(SO_2Me)dpa)]PF_6\) (1, Figure 6.2) in DMSO-\( d_6 \) aided in the assignment of the aromatic signals. The most downfield doublet (8.50 ppm) of the \( N(SO_2Me)dpa \) ligand belongs to the pyridyl H6/\(^6\) protons (explained by the close proximity to nitrogen). In 1 (Figure 6.2), the pyridyl H6/\(^6\) signal appears at 8.89 ppm. All the aromatic signals appear more downfield for 1 than in the free ligand. Selected \(^1\)H NMR shifts of the \( N(SO_2Me)dpa \) ligand, \([Re(CO)_3(N(SO_2Me)dpa)]PF_6\) (1), and
Pt(N(SO₂Me)dpa)Cl₂ (unpublished results) are given in Table 6.3. The pyridyl H6/6′ protons of Pt(N(SO₂Me)dpa)Cl₂ appear more downfield than in 1. The same trend is observed for N(SO₂tmb)dpa, [Re(CO)₃(N(SO₂tmb)dpa)]PF₆ (2), and Pt(N(SO₂tmb)dpa)Cl₂.

2D NMR spectroscopy aided in the assignment of signals for T(N(SO₂C₆H₄)dpa)P and [{Re(CO)₃}₄T(N(SO₂C₆H₄)dpa)P](BF₄)₄ (4). A ¹H NMR spectrum of 4 in DMSO-d₆ (Figure 6.5) shows that the beta hydrogen signal (Hβ, Scheme 6.1) is downfield by 0.30 ppm when compared to the corresponding signal of the free porphyrin (Table 6.4). The pyridyl H6/6′ signal of 4 appears at 9.01 ppm versus 8.55 ppm of T(N(SO₂C₆H₄)dpa)P, indicating the presence of a Re–N(pyridyl) bond. An interesting spectral change found upon coordination of the four Re moieties to T(N(SO₂C₆H₄)dpa)P is that the phenylene signals give rise to a singlet for 4 (Figure 6.5). Upon binding of the porphyrin to Re, the signals of the phenylene ortho and meta protons of the aryl group have a similar chemical shift (8.84 ppm) because the signal of the phenylene meta protons (the protons closest to Re) shifts downfield (by 0.60 ppm) for 1 versus the smaller shift of the ortho proton signal (0.37 ppm). Then the resulting similar shifts lead to non-first-order spectra in this region, a result confirming the structure proposed.

Table 6.4. Selected ¹H NMR Shifts (ppm) in DMSO-d₆ for T(N(SO₂C₆H₄)dpa)P and [{Re(CO)₃}₄T(N(SO₂C₆H₄)dpa)P](BF₄)₄ (4)

<table>
<thead>
<tr>
<th></th>
<th>H6/H6′</th>
<th>H5/5′</th>
<th>H4/4′</th>
<th>H3/3′</th>
<th>CH₂</th>
<th>Hβ</th>
<th>oH</th>
<th>mH</th>
<th>NH</th>
</tr>
</thead>
<tbody>
<tr>
<td>T(N(SO₂C₆H₄)dpa)P</td>
<td>8.55</td>
<td>7.34</td>
<td>7.83</td>
<td>7.49</td>
<td>4.90</td>
<td>8.87</td>
<td>8.37</td>
<td>8.24</td>
<td>-2.96</td>
</tr>
<tr>
<td><a href="BF%E2%82%84">{Re(CO)₃}₄T(N(SO₂C₆H₄)dpa)P</a>₄</td>
<td>9.01</td>
<td>7.58</td>
<td>8.14</td>
<td>7.71</td>
<td>5.97, 4.97</td>
<td>9.20</td>
<td>8.84</td>
<td>-2.81</td>
<td></td>
</tr>
</tbody>
</table>

In the ¹H NMR spectrum for [{Re(CO)₃}₄T(N(SO₂C₆H₄)dpa)P](BF₄)₄ (4) in DMSO-d₆ (Figure 6.5), the methylene group signals appear as two doublets (J = 16.6 Hz), a value identical to that of 1 (J = 16.6 Hz). The methylene protons of 4 projecting toward and away from the
carbonyl ligands are designated as *endo-* and *exo-CH* protons, respectively. An NOE cross-peak seen in the ROESY spectrum of 4 in DMSO-$d_6$, between phenylene signal (8.84 ppm) and the methylene signal (5.97 ppm) aided in assigning this CH signal to the *endo-CH* proton. An NOE cross-peak between the pyridyl H3/3′ the methylene signal (4.97 ppm) signal allowed assignment of the latter signal to *exo-CH*. For the free T(N(SO$_2$C$_6$H$_4$)dpa)P ligand in DMSO-$d_6$, the methylene CH$_2$ singlet at 4.90 ppm has NOE cross-peaks with the pyridyl H3/3′ signal as well as phenylene $m$H. This observation further illustrates that the equivalence and free rotation of the methylene groups in the free ligands is lost in the complex, [{Re(CO)$_3$}$_4$T(N(SO$_2$C$_6$H$_4$)dpa)P](BF$_4$)$_4$. Also the assignment of the methylene signals of [{Re(CO)$_3$}$_4$T(N(SO$_2$C$_6$H$_4$)dpa)P](BF$_4$)$_4$ described above can be extended to assign the relatively downfield methylene $^1$H NMR signal to the *endo-CH* signal and the upfield signal to the *exo-CH* signal in complexes 1 and 2.

![Figure 6.5](image.png)

**Figure 6.5.** Comparison of the $^1$H NMR spectra of T(N(SO$_2$C$_6$H$_4$)dpa)P (bottom) and [{Re(CO)$_3$}$_4$T(N(SO$_2$C$_6$H$_4$)dpa)P](BF$_4$)$_4$ (top) in DMSO-$d_6$ at 25 °C.

### 6.4 Summary and Conclusions

Three novel ligands and their [Re(CO)$_3$L]PF$_6$ complexes have been synthesized and characterized as a prelude to radiopharmaceutical studies. In two of these complexes, structural
evidence establishes the existence of a bond between a tertiary sulfonamide N and Re. Because there are distinctive NMR spectral features associated with such binding in the $N(SO_2R)\text{dpa}$ ligands, it is clear that in all cases the tertiary sulfonamide N binds.

Tertiary sulfonamides when coordinated appear to be relatively good donors, as judged by the Re–N bond length. However, monodentate tertiary sulfonamides generally do not bind metals. Thus, tertiary sulfonamides have been observed to bind metals only when geometrical restraints are enforced.\textsuperscript{24,26-28} The tertiary sulfonamide nitrogen, when bound as an internal donor atom anchoring two chelate rings, adopts a pyramidal stereochemical preference with the result that the N enforces a facial tridentate geometry. This binding is favored in octahedral complexes such as the [Re(CO)\textsubscript{3}L]\textsuperscript{+} complexes presented in this study. In square planar complexes, however, binding at tertiary sulfonamide N does not take place because coordination of the other donors of the adjacent chelate rings so created would not force the sulfonamide N into the coordination plane.

The conjugation approach described here has potentially wide applications. This prospect is supported by our results showing that a sulfonamide can be used to conjugate the \{Re(CO)\textsubscript{3}\}\textsuperscript{+} unit to a porphyrin. We do not see any limitation in conjugating other molecules to such a core or to extending this chemistry to $^{99m}\text{Tc}$ analogues.

6.5 References


CHAPTER 7

CONCLUSIONS

New \textit{fac}-Re(CO)$_3$ complexes bearing tridentate chelators and a combination of bidentate and monodendate ligands have been synthesized and studied in detail.

In general, this dissertation research contributes toward advancing our understanding of \textit{fac}-[Re(CO)$_3$L]$^+$ complexes of potential radiopharmaceutical utility. The structural and NMR spectral investigation of \textit{fac}-[Re(CO)$_3$(polyamine)]$^+$ complexes with six-membered chelate rings has revealed that changing a dimethylene chain bridging the donor atoms to a trimethylene chain does not alter exposure of \textit{exo} and \textit{endo}-NH groups. The upfield signal for \textit{exo}-NH’s of five and six-membered chelate rings is consistent with difference in solvent exposure.

A new conjugation approach is presented through the synthesis of novel sulfonamide ligands and their Re complexes. In these complexes, the tertiary sulfonamide N binds and this binding is favored in the \textit{fac}-[Re(CO)$_3$L]$^+$ complexes presented in this study because it allows a facial coordination mode of a tridentate ligand with a central tertiary sulfonamide N donor. Our results show that a sulfonamide can be used to conjugate the \textit{fac}-{Re(CO)$_3$}$_3$$^+$ unit to a porphyrin. We believe this method could be used to conjugate other molecules to such a core and that this chemistry may be extended to $^{99}$mTc analogues.

In general, work presented in this dissertation will help guide successful design and evaluation of diagnostic and therapeutic radiopharmaceuticals.
APPENDIX A

SUPPLEMENTARY MATERIAL FOR CHAPTER 2

A.1 NMR Signal Assignments for [Re(CO)$_3$(N$_2$N-Me$_2$dipn)]BF$_4$ (3), [Re(CO)$_3$(dipn)]BF$_4$ (1), [Re(CO)$_3$(N$′$-Medipn)]PF$_6$ (2), [Re(CO)$_3$(aepn)]PF$_6$ (6), [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4), and [Re(CO)$_3$(tacn)]PF$_6$ (7)

[Re(CO)$_3$(N$_2$N-Me$_2$dipn)]BF$_4$ (3, Figure 2.2) is a chiral complex with an unsymmetrical coordinated htL in which dynamic motion cannot interchange the rings, as was the case in previous studies (see main text). Thus 3 is a good example for initiating this detailed discussion of the assignment strategy. The ring of 3 with the terminal NH$_2$ group has the chair conformation. The expected three NH signals (central NH and terminal NH$_2$) were observed for 3 in DMSO-$d_6$ (Table 2.4, Figures A.1 and A.3). The upfield NH signal (3.78 ppm) has a COSY cross-peak (Figure A.3) to another NH signal (5.53 ppm), assigning these as the signals of the coordinated terminal NH$_2$ group; these NH signals have a COSY cross-peak with a different CH signal. According to the Karplus equation, the coupling between two protons connected by three bonds is larger the greater the difference between the torsion angle relating the two protons and $90^\circ$.\(^1\)

The relevant H–N–C–H torsion angle for 3 (Figure A.2, Table A.1) differs more from $90^\circ$ for the exo-NH ($\sim$174$^\circ$) than for the endo-NH ($\sim$47$^\circ$). The stronger NH-CH COSY peak allowed assignment of the upfield 3.78 ppm signal to the exo-NH, and the weaker NH-CH cross-peak allowed assignment of the 5.53 ppm signal to the endo-NH. The NH-CH cross-peaks allowed assignment of the methylene CH signals (endo-CH 2.80 and exo-CH 3.24 ppm). In summary, although the chelate ring has six members, the exo-NH shift is upfield, as found for 5-membered chelate rings. However, the exo-NH-endo-CH COSY cross-peak is larger than the endo-NH-exo-CH COSY cross-peak, unlike the case of the 5-membered chelate ring of [Re(CO)$_3$(tmbSO$_2$-
in a previous study in which the largest H-N-C-H torsion angle was ~157° for a ring in the
exo-C conformation (Figure 2.5). For this compound, the endo-NH-exo-CH cross-peak was the
strongest HN-CH cross-peak.²

For [Re(CO)₃(dipn)]BF₄ (1) in DMSO-d₆, a COSY cross-peak between two NH signals
(each integrating to 2 protons) assigned these as terminal NH₂ signals (the third NH peak at 6.01
ppm, integrating for one proton, did not correlate with any NH peaks, assigning it to the central
NH). The two rings are equivalent on the NMR time scale. However, the atom numbering
scheme for 1 (Figure A.2) is complicated because the two rings have different conformations and
are not equivalent in the solid state. Nevertheless, the largest H-N-C-H torsion angles for both
rings (Table A.1) predict strong exo-NH-endo-CH coupling as for 3. The NH-CH COSY cross-
peak intensities allowed assignment of the 3.78 ppm NH signal to the exo-NH and the multiplet
at 2.62 ppm to endo-CH and assignment of the 5.22 ppm NH signal to the endo-NH and the
multiplet at 3.2 ppm to exo-CH. An endo-NH-endo-CH cross-peak and an exo-NH-exo-CH
cross-peak (both smaller than the exo-NH-endo-CH cross-peak) were also seen. The CH₂ signals
of 1 in acetonitrile-d₃ at 3.23 (exo-CH) and 2.92 (endo-CH) ppm were assigned by using a similar
procedure (NH signals in acetonitrile-d₃ are given in Table 2.4). The COSY spectrum of
[Re(CO)₃(N'-Medipn)]PF₆ (2) in DMSO-d₆ (not shown) has an NH-NH cross-peak identifying
the two terminal NH₂ signals. The largest H-N-C-H torsion angle of the N2,N3 ring (Table A.1
and Figure A.2) predicts a strong exo-NH-endo-CH coupling. The exo-NH signal at 3.80 ppm has
a strong cross-peak to a CH multiplet (2.65 ppm).

A COSY experiment on [Re(CO)₃(aepn)]PF₆ (6) in DMSO-d₆ showed correlations
between two sets of NH peaks: at 4.07 and 5.50 ppm; and at 3.50 and 5.24 ppm. Because one CH
signal is so far upfield (1.74 ppm), it can be assigned to the central CH₂ group. This signal has
strong coupling to a 1.94 ppm signal, indicating geminal coupling. This 1.94 ppm CH signal of
the central CH$_2$ group has a strong cross-peak to a CH signal at 2.55 ppm. Because the largest
torsion angle (172°) is between the endo-CH and the exo-CH of the central CH$_2$, this 1.94 ppm
signal is assigned to the exo-CH. In turn the CH signal at 2.55 ppm assigned as an endo-CH
signal exhibits strong coupling to the NH signal at 3.50 ppm, identifying it as the exo-NH of the
6-membered ring of 6. This coupling to the CH$_2$ signals leaves no doubt about the assignment of
the NH’s of the 6-membered ring.

As above, from the torsion angles (170° and 179°) obtained from the molecular structure,
the exo-NH signals will give the largest NH-CH COSY cross-peaks. Indeed, the upfield NH
signal for each ring has a strong cross-peak to a CH signal, assigning these signals to the exo-
NH’s and endo-CH’s. The pucker of the 5-membered ring is endo-C in the solid, and the COSY
peak confirms this conformation in solution.

For [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4) in DMSO-$d_6$, the most downfield NH signal (7.70 ppm),
which showed no cross-peaks with the other NH signals, immediately disappeared upon addition
of D$_2$O. This rapid NH to ND exchange assigns this signal to the NH$_3^+$ in the dangling group.
The upfield NH signal (4.22 ppm) has a COSY cross-peak (Figure A.4) to a moderately
downfield NH signal (5.62 ppm). Both of these signals of the terminal amine have moderately
strong COSY cross-peaks to two CH signals. Thus, we are able to assign the CH signals to the
CH$_2$ groups adjacent to the NH$_2$ groups. Because the cation is unsymmetrical in the solid state
(Figure 2.3), the two rings are not equivalent in the crystal. The H-N-C-H torsion angles (Table
A.1) predict strong COSY NH-CH cross-peaks involving the exo-NH for one ring and the endo-
NH for the other ring. However, as noted (see main text), both chelate rings will time average
between endo-C and exo-C conformations in solution. Thus, as expected for a symmetrical
complex with two 5-membered rings, the NH-CH COSY cross-peaks have similar intensity and
do not allow assignment of the signals to a specific proton (Figure A.4). However, we can use the clear pattern that the upfield NH signal arises from the $\text{exo}$-NH to assign the NH signals of 4 (Table 2.4).

Shifts in acetone-$d_6$ are more upfield than in other solvents for the dangling NH$_3^+$ group of 4 and 5. For 4, a COSY experiment in acetone-$d_6$ showed that an upfield NH signal ($\text{exo}$) and the downfield NH signal ($\text{endo}$) correlate, while an upfield NH signal showed no cross-peaks with the other NH signals, assigning this latter upfield signal to the dangling NH$_3^+$ signal.

No COSY data were needed for [Re(CO)$_3$(tacn)]PF$_6$ (7) because the three NH’s are identical.
Figure A.1. $^1$H NMR spectra of $[\text{Re(CO)}_3(\text{dipn})]\text{PF}_6$ (1), $[\text{Re(CO)}_3(N'\text{-Medipn})]\text{PF}_6$ (2), $[\text{Re(CO)}_3(N,N\text{-Me}_2\text{dipn})]\text{BF}_4$ (3), $[\text{Re(CO)}_3(\text{aepn})]\text{PF}_6$ (6), and $[\text{Re(CO)}_3(\text{trenH})]\text{(PF}_6)_2$ (4), and $[\text{Re(CO)}_3(\text{trpnH})]\text{(PF}_6)_2$ (5) in DMSO-$d_6$ at 25 °C (* water and solvent residual peaks).
Table A.1. Selected Torsion Angles (deg) for [Re(CO)$_3$(dipn)]BF$_4$ (1), [Re(CO)$_3$(N'-Medipn)]PF$_6$ (2), [Re(CO)$_3$(N,N-Me$_2$dipn)]BF$_4$ (3) [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4), and [Re(CO)$_3$(aepn)]PF$_6$ (6).

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<td>H12–N1–C4–H4a</td>
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<td>33.20$^a$</td>
<td>27.89$^b$</td>
<td>51.18</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ For 2, H11 = H21, H12 = H22. $^b$ For 4, C4 = C5, C9 = C7, H4 = H5, and H9 = H7. $^c$ For 6, C9 = C8 and H9 = H8.

Figure A.2. Drawing of the cations of [Re(CO)$_3$(dipn)]BF$_4$ (1), [Re(CO)$_3$(N'-Medipn)]PF$_6$ (2), [Re(CO)$_3$(N,N-Me$_2$dipn)]BF$_4$ (3) [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4), and [Re(CO)$_3$(aepn)]PF$_6$ (6) showing the torsion angle between N3H and C4H. H31 and H12 are designated as exo-NH. Large torsion angles for exo-NH and small torsion angles for endo-NH were observed for 1, 3, and 6.
Figure A.3. $^1$H-$^1$H COSY NMR spectrum of [Re(CO)$_3$(N,N-Me$_2$dipn)]BF$_4$ (3) in DMSO-$d_6$ at 25 °C.

Figure A.4. $^1$H-$^1$H COSY NMR spectrum of [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4) in DMSO-$d_6$ at 25 °C.
Figure A.5. Effect of Cl$^-$ on the change in chemical shift ($\Delta\delta$, ppm) of the NH signals of [Re(CO)$_3$(trenH)](PF$_6$)$_2$ (4) in DMSO-$d_6$ at 25 °C. The metal complex concentration was maintained at 5 mM throughout the titration. Addition of up to 300 mM Cl$^-$ produced no further increase in $\Delta\delta$.

Figure A.6. Effect of Cl$^-$ on $\Delta\delta$ of the NH signals of [Re(CO)$_3$(trpnH)](PF$_6$)$_2$ (5) in DMSO-$d_6$ at 25 °C.
Figure A.7. Effect of Cl⁻ on $\Delta\delta$ of the NH signals of [Re(CO)$_3$(dipn)]PF$_6$ (1) in acetonitrile-$d_3$ at 25 °C (top, left) and in the presence of 50 mM Et$_4$NPF$_6$ (top, right). An overlay of these two plots is also shown (bottom, middle).
Figure A.8. Effect of Br⁻ on ∆δ of the NH signals of [Re(CO)₃(dipn)]PF₆ (1) in acetonitrile-d₃ at 25 °C.

Figure A.9. Effect of I⁻ on ∆δ of the NH signals of [Re(CO)₃(dipn)]PF₆ (1) in acetonitrile-d₃ at 25 °C.

References


Scheme B.1. Top: Proton transfer and Re–N4 to Re–N3 rearrangement processes that occur in the mechanism suggested for formation of the [Re(CO)$_3$(DAE)]$^+$ cation through an MAE-type intermediate. Bottom: When N3 in the seven-membered chelate ring has bonds only to carbon, the DAE-type ligand cannot form.

Figure B.1. Overlay of N–M–N atoms in the seven-membered chelate ring of [Re(CO)$_3$(MAE)]PF$_6$ (purple) and cis-[Pt(NH=CPnBu'CH$_2$CH$_2$NHBu')Cl$_2$] (gold), in which the metal projects toward the viewer (top) and away from the viewer (bottom).
Figure B.2. $^1$H-$^1$H COSY NMR spectrum of [Re(CO)$_3$(MAE)]PF$_6$ in DMSO-$d_6$ at 25 °C.

Figure B.3. ROESY spectrum of [Re(CO)$_3$(DAE)]BF$_4$ in DMSO-$d_6$ at 25 °C showing negative EXSY cross-peaks (circled) between the $\text{–NH}_2$ signals.
Figure B.4. $^1$H-^1$H$ COSY NMR spectrum of $[\text{Re(CO)}_3(DAE)]\text{BF}_4$ in DMSO-$d_6$ at 25 °C.

Figure B.5. Dependence on temperature of NH $^1$H NMR signals of $[\text{Re(CO)}_3(DAE)]\text{BF}_4$ in acetonitrile-$d_3$. 
Figure B.6. ROESY spectrum of [Re(CO)$_3$(DAE)]BF$_4$ in acetonitrile-$d_3$ at –5 °C showing negative EXSY cross-peaks (circled) between the –NH$_2$ signals.
Figure C.1. ORTEP plot of the cation in $\text{[Re(CO)}_3(5,5^{\prime}\text{-Me}_2\text{bipy})(\text{HNC(CH}_3\text{NHCH}_3))\text{NHCH}_3\text{]}\text{][BF}_4\text{)}_{0.52}(\text{ReO}_4)_{0.48}$ (6). Crystal data: monoclinic $P2_1/c$, $a = 10.2235(15)$, $b = 13.703(2)$, $c = 15.391(2)$ Å, $\beta = 98.671(10)^\circ$ at $T = 90$ K, $Z = 4$, $R = 0.065$. Thermal ellipsoids are drawn with 50% probability. The data for this compound leave no doubt about the structure of the cation. However, because of the uncertainty surrounding the disordered anion, the structure is not included in the main text.

Figure C.2. Depictions of several amidine complex cations with the $\{\text{Re(CO)}_3\}^+$ core positioned in the same orientation. (a) $\text{[Re(CO)}_3(5,5^{\prime}\text{-Me}_2\text{bipy})(Z\text{-HNC(CH}_3\text{NH}_2))\text{][BF}_4\text{]}$ (7); (b) $\text{[Re(CO)}_3(5,5^{\prime}\text{-Me}_2\text{bipy})(E^{\prime}\text{-HNC(CH}_3\text{NHCH(CH}_3_2))\text{][BF}_4\text{]}$ (2); and (c) $\text{[Re(CO)}_3(5,5^{\prime}\text{-Me}_2\text{bipy})(E^{\prime}\text{-HNC(CH}_3\text{NHC(CH}_3_3))\text{][BF}_4\text{]}$ (4). Figure illustrates that the amidine ligand is oriented differently in these products.
Figure C.3. Depiction of stacking of the phenyl ring of the amidine moiety (gold) above one ring of the bipyridine ligand (green) in [Re(CO)$_3$(5,5′-Me$_2$-bipy)(HNC(CH$_3$)NHCH$_2$C$_6$H$_5$)]BF$_4$ (5) in the solid state.

Figure C.4. ROESY spectrum of [Re(CO)$_3$(5,5′-Me$_2$-bipy)(HNC(CH$_3$)NHCH(CH$_3$)$_2$)]BF$_4$ (2) in acetonitrile-$d_3$ at 25 °C, showing NOE peaks.
Figure C.5. NOE (top) and COSY (bottom) cross-peaks in ROESY and COSY spectra of [Re(CO)$_3$(5,5'-Me$_2$-bipy)(HNC(CH$_3$))NHCH(2CH$_3$)$_2$)]BF$_4$ (2) in acetonitrile-$d_3$ at 25 °C.

Figure C.6. ROESY spectrum of [Re(CO)$_3$(5,5'-Me$_2$-bipy)(HNC(CH$_3$))NHCH(2CH$_3$)$_2$)]BF$_4$ (2) in CDCl$_3$ at 25 °C, showing negative EXSY cross-peaks (circled) and NOE peaks.
Figure C.7. Starting with the structure of the $E'$ isomer of $[\text{Re(CO)}_3(5,5'\text{-Me}_2\text{bipy})(\text{HNC(CH}_3\text{)NHCH(CH}_3\text{)}_2)]^+$ (2), $E$, $Z$, and $Z'$ isomer models were constructed by using Chem3D Pro software. Rotations were performed to create short N3H-to-CH(isopropyl) nonbonded distances. Nonbonded distances were measured by using Mercury software, and all structures are illustrated as space-filling models by using this software. The closest N3H-to-CH(isopropyl) distances found were 2.18, 4.18, 4.39 and 3.51 Å for the $E'$, $E$, $Z$, and $Z'$ isomers, respectively. Note that in the $Z'$ isomer the isopropyl group would clash with atoms in the equatorial plane defined by the 5,5'-Me$_2$bipy ligand. It is evident that, while this distance is favorably long in both the $E'$ and $E$ isomers, in the $E$ isomer the isopropyl group would be rather close to the methyl group on the amidine carbon. This proximity can lead to clashes as the size of the R group increases.
Figure C.8. Scheme relating the identified isomers of [Re(CO)$_3$(L)(HNC(CH$_3$)NHR)]$^+$ cations. The figure illustrates the likely pathway between the $Z$ and the $E'$ isomers, passing through the $E$ isomer. Faster interconversion occurs between $E$ and $E'$ isomers, as rotation about the bond between the amidine C and the remote N is expected to be faster compared to rotation about the bond between the amidine C and the N bound to Re.
Table C.1. Selected $^1$H NMR Shifts (ppm) for Re(CO)$_3$[(5,5′-Me$_2$bipy)(HNC(CH$_3$)NHR)]BF$_4$ in CDCl$_3$ and in CD$_2$Cl$_2$ at 25 °C

<table>
<thead>
<tr>
<th>R isomer</th>
<th>N3H</th>
<th>N4H</th>
<th>CH$_3$ (formerly CH$_3$CN)</th>
<th>N4CH$_n$</th>
<th>H6/6′</th>
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<tr>
<td>E′</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isopropyl (2)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>4.30</td>
<td>5.77</td>
<td>2.20</td>
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<td>8.64</td>
</tr>
<tr>
<td>Z</td>
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<td>5.61</td>
<td>2.03</td>
<td>3.67</td>
<td>8.55</td>
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<tr>
<td>isobutyl (3)</td>
<td></td>
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</tr>
<tr>
<td>E</td>
<td>4.37</td>
<td>6.05</td>
<td>2.22</td>
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<tr>
<td>Z</td>
<td>5.83</td>
<td>5.75</td>
<td>2.0</td>
<td>3.06</td>
<td>8.55</td>
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<td>tert-butyl (4)</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>E</td>
<td>4.26</td>
<td>5.57</td>
<td>2.25</td>
<td>8.68</td>
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<td>Z</td>
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<tr>
<th>R isomer</th>
<th>N3H</th>
<th>N4H</th>
<th>CH$_3$ (formerly CH$_3$CN)</th>
<th>N4CH$_n$</th>
<th>H6/6′</th>
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<tr>
<td>E′</td>
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<td></td>
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</tr>
<tr>
<td>isopropyl (2)</td>
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<td>8.69</td>
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<td>tert-butyl (4)</td>
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<td>2.19</td>
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<tr>
<td>Z</td>
<td>4.32</td>
<td>6.10</td>
<td>2.10</td>
<td>8.63</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ The N4CH$_n$ signals vary in multiplicity according to the R group. $^b$ Shoulder, some overlap.

Table C.2. Distribution (%) of E, E′, and Z isomers of [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)NHR)]BF$_4$ at 25 °C

<table>
<thead>
<tr>
<th>R isomer</th>
<th>CDCl$_3$</th>
<th>CD$_2$Cl$_2$</th>
<th>acetonitrile-d$_3$</th>
<th>DMSO-d$_6$</th>
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<tr>
<td></td>
<td>E′</td>
<td>E</td>
<td>Z</td>
<td>E′</td>
</tr>
<tr>
<td>isopropyl (2)</td>
<td>5</td>
<td>32</td>
<td>63</td>
<td>19</td>
</tr>
<tr>
<td>isobutyl (3)</td>
<td>7</td>
<td>29</td>
<td>64</td>
<td>21</td>
</tr>
<tr>
<td>tert-butyl (4)</td>
<td>15</td>
<td>28</td>
<td>57</td>
<td>53</td>
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</table>

$^a$ Not observed.
Figure D1. ORTEP plot of \([\text{Re(CO)}_3(5,5\text{'}-\text{Me}_2\text{bipy})(\text{HNC(CH}_3\text{)OCH}_2\text{CH}_3)]\text{BF}_4\). Thermal ellipsoids are drawn with 50% probability.
<table>
<thead>
<tr>
<th></th>
<th>[Re(CO)$_3$(CH$_3$CN)$_3$]BF$_4$</th>
<th>[Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)OCH$_2$CH$_3$)]BF$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1a</strong></td>
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<td></td>
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<tr>
<td>empirical formula</td>
<td>C$_9$H$_9$N$_3$O$_3$Re·BF$_4$</td>
<td>C$<em>{19}$H$</em>{21}$N$_3$O$_4$Re·BF$_4$</td>
</tr>
<tr>
<td>fw</td>
<td>480.20</td>
<td>628.40</td>
</tr>
<tr>
<td>space group</td>
<td>P$_2_1/m$</td>
<td>P$_2_1/n$</td>
</tr>
<tr>
<td>a (Å)</td>
<td>6.6439(10)</td>
<td>12.6191(15)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>10.0721(14)</td>
<td>8.7045(7)</td>
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<tr>
<td>c (Å)</td>
<td>11.3365(15)</td>
<td>20.759(3)</td>
</tr>
<tr>
<td>α (deg)</td>
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<td>90</td>
</tr>
<tr>
<td>β (deg)</td>
<td>101.518(8)</td>
<td>95.076(4)</td>
</tr>
<tr>
<td>γ (deg)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>V (Å$^3$)</td>
<td>743.34(18)</td>
<td>2271.3(5)</td>
</tr>
<tr>
<td>T (K)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>$\rho_{\text{calc}}$ (mg/m$^3$)</td>
<td>2.145</td>
<td>1.838</td>
</tr>
<tr>
<td>abs coeff (mm$^{-1}$)</td>
<td>8.23</td>
<td>5.41</td>
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<tr>
<td>2θ$_{\text{max}}$ (°)</td>
<td>80.4</td>
<td>72.6</td>
</tr>
<tr>
<td>$R$ indices$^a$</td>
<td>0.024</td>
<td>0.029</td>
</tr>
<tr>
<td>wR2 = [$I &gt; 2\sigma(I)$]$^b$</td>
<td>0.058</td>
<td>0.069</td>
</tr>
<tr>
<td>data/param</td>
<td>4776/111</td>
<td>10573/311</td>
</tr>
</tbody>
</table>

$^a$R = (\sum|F_o| - |F_c|)/\sum|F_o|.$ $^b$wR2 = \[\frac{\sum[w(F_o^2 - F_c^2)^2]}{\sum[w(F_o^2)^2]}\]$. In which w = 1/[σ$^2$(F$_o^2$) + (dP$^2$) + (eP)] and P = (F$_o^2$ + 2F$_c^2$)/3, and d = 0.0214 and 0.0286 and e = 1.5711 and 3.2659 for [Re(CO)$_3$(CH$_3$CN)$_3$]BF$_4$, and [Re(CO)$_3$(5,5′-Me$_2$bipy)(HNC(CH$_3$)OCH$_2$CH$_3$)]BF$_4$. 

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APPENDIX E

SUPPLEMENTARY MATERIAL FOR CHAPTER 6

Figure E.1. $^1$H NMR spectra of $N$(SO$_2$Me)dpa (bottom), $N$(SO$_2$tmb)dpa (middle), and $N$(dansyl)dpa (top) in DMSO-$d_6$ at 25 °C.

Figure E.2. ORTEP plots of Pt($N$(SO$_2$Me)dpa)Cl$_2$ (left), and Pt($N$(SO$_2$tmb)dpa)Cl$_2$ (right). Thermal ellipsoids are drawn with 50% probability.
APPENDIX F

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VITA

Theshini Perera was born in Colombo, Sri Lanka, to Mahima and Newton Perera as the youngest and only daughter, and was brought up as the apple of everyone’s eye! She had her primary and secondary education at Ladies’ College, Colombo, where she was Head Girl and was awarded the most outstanding girl of the year award in 1996. She entered the University of Colombo in year 2000 and graduated with an Honors Degree in chemistry in 2004.

After serving for a few months as a teaching assistant at the Department of Chemistry, University of Colombo, she moved on to the academic staff at the University of Sri Jayewardenepura, where she was hired as a lecturer in chemistry.

She arrived in the United States in August 2006 with her husband Inoka, after celebrating only their first anniversary in her home country. She joined the laboratory of Prof. Luigi Marzilli in January 2007 where she carried out her doctoral research work on Retricarbonyl complexes of biomedical relevance. She is a candidate for the degree of Doctor of Philosophy in the Summer Commencement 2010. She is looking forward to returning to her motherland where she will continue to educate young undergraduates.