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Structures of Metallacarboranes and Coordination Complexes: Coordination Sensors Based on Rhodamine B and Quinolines

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STRUCTURES OF METALLACARBORANES AND COORDINATION COMPLEXES: COORDINATION SENSORS BASED ON RHODAMINE B AND QUINOLINES

by

Agozie Nnaemeka Oyeamalu

A dissertation submitted to the Graduate College in partial fulfillment of the requirements for the degree of Doctor of Philosophy Chemistry Western Michigan University June 2017

Doctoral Committee:

Ekkehard Sinn, Ph.D., Chair
Sherine Obare, Ph.D.
Donald Schreiber, Ph.D.
Daniel Cassidy, Ph.D.
Rhodamine-based ligands that can complex different metals has been designed and synthesized. Using Rhodamine B as starting material, we synthesized and characterized quinoline precursors as well as successfully carried out the oxidation of methyl and aldehyde groups on the quinoline ring, and on the hydroxyl moiety of the quinoline spirolactone ring. These turn-on/off rhodamine fluorescence probes sense Cr$^{3+}$ and Ni$^{2+}$ with high selectivity and sensitivity. These probes can be applied to detect other metal ions that are present in chemical, biological and environmental settings. They were designed to fluoresce when bonded to ions such as cyanide in detecting warfare agents, as well as trivalent chromium, aiming to detect at low concentration levels. Cr$^{3+}$ is considered an important toxic environmental pollutant, and nickel is a potential contaminant in pharmaceuticals. Detection of Cr$^{3+}$ and Ni$^{2+}$ at low concentrations will help combat their adverse health effects, such as cancer or neurodegenerative diseases.

X-ray diffraction of single crystals is another research area that has gained scientific attention over the course of the last few decades. They combine the fundamental theories and applications based on diffraction and statistics in order to provide a complete understanding of the molecular and geometric characteristics of molecules. In this study, we were able to solve structures of new metallacarboranes and other complexes via X-ray crystallography. This
resulted in specifically two crystallographically independent molecules in the unit cell complex of the metallocarborane cluster framework [3,3-(CO)2-3-NO-closo-Re(8-O(CH2)2O(CH2)2I-3,1,2-C3B9H10)]. The ReC2B9 moiety is comprised of the usual closo-icosahedral framework with an η5-coordinated Re center. Such rhenacarborane derivatives can be prime candidates for use as drug-delivery vehicles of amino acids or small peptides across the blood-brain barrier, which might otherwise not be easily transported.

X-ray studies were carried out on some new metal complexes, designed and synthesized for anti-cancer applications. The results show that the actual structures were different than those intended in the original synthetic design. We show that the actual X-Ray structures are compatible with the synthetic design determined are actually predictable and expected based on structural consideration. The intended design included two adjacent 8-membered rings, which would show a significant degree of steric strain. On the other hand, the actual structures contained two adjacent 5-membered rings and constitute a sterically more relaxed system.
I would like to first and foremost give all honor, praise and thanks to my Lord and Savior for his unconditional love, mercy and grace. To my research advisor and Committee Chair Professor Ekkehard Sinn, words cannot express the gratitude and respect I have for you. I thank you for giving me an opportunity, for providing me with the platform to succeed, for believing in my abilities and accepting me as a member of your research group. You provided me with the best working environment any graduate student could possibly ask for and supported my academic pursuits to the fullest. Your leadership, compassionate and loyal nature not only speaks volume, but shows an exceptional and distinguished presence beyond measure. I thank you for all the support and encouragement you rendered during some of the most challenging times. May God continue to bless you and your family.

I would like to give a warm thank you to my dissertation committee members: Professor Sherine Obare, Professor Donald Schreiber, and Professor Daniel Cassidy for their support and accepting to serve as my committee. Special thanks also goes to the Dean of the Graduate College, Dr. Susan Stapleton, for her encouragements and support. I would also like to acknowledge Professor Sinn’s research group members both past and present especially Dr Aruna Weerasinghe and Dr Joseph Kreft. The group comradery will be solely missed and it has been a pleasure knowing and working with all of you.

I would like to acknowledge and thank Western Michigan University Chemistry department and the graduate college for giving me the opportunity to pursue my doctoral studies.
I also thank the Graduate Assistance in Areas of National Need (GAANN), Dr Ekkehard Sinn and the Graduate Education and the Professoriate (GEP) for their financial support.

I would like to thank my parents, brother-in-law (Mr. Chuma Egbu), Mr. Abi Omot, close friends and families for their encouragement and support. May the good Lord continue to bless and protect you all. Finally, I would like to dedicate this dissertation to my sister Dr. (Mrs.) Chioma Adaora Oyeamalu-Egbu. Chi-Chi, continue to rest in perfect peace. You will never be forgotten. I miss you!

Agozie Nnaemeka Oyeamalu
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<tr>
<td>BBB</td>
<td>Blood-Brain-Barrier</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>Chloroform-d</td>
</tr>
<tr>
<td>CD₃CN</td>
<td>Acetonitrile-d₃</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet</td>
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<tr>
<td>DCC</td>
<td>N,N’-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>Electro Spray Ionization - Mass Spectrometry</td>
</tr>
<tr>
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<td>Ethyl acetate</td>
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<tr>
<td>FT-IR</td>
<td>Fourier transform infrared spectroscopy</td>
</tr>
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<td>Hydrochloric acid</td>
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<tr>
<td>IR</td>
<td>Infrared Spectroscopy</td>
</tr>
<tr>
<td>KCl</td>
<td>Potassium Chloride</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography-mass spectrometry</td>
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<tr>
<td>m</td>
<td>multiplet</td>
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<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
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<tr>
<td>mM</td>
<td>Millimolar</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>Magnesium Sulfate</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>Sodium borohydride</td>
</tr>
<tr>
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<td>Sodium Chloride</td>
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<tr>
<td>NaOH</td>
<td>Sodium hydroxide</td>
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<tr>
<td>NMR</td>
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<tr>
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<td>Oak Ridge Thermal Ellipsoid Plot</td>
</tr>
<tr>
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<td>Room Temperature</td>
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<tr>
<td>s</td>
<td>Singlet</td>
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<tr>
<td>SeO₂</td>
<td>Selenium dioxide</td>
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<tr>
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CHAPTER 1
INTRODUCTION

The main purpose of the work is the formation of new metal complexes. The formation of complexes can make dramatic changes in properties such as fluorescence, and these changes can be used for sensitive and selective detection of metal ions. Two particular metals are the transition metals chromium and nickel, where the sensing ligands are based on rhodamine. Detection at very low levels is important as traces of essential elements or as toxins.

Another transition metal is rhenium, complexed to functionalized carborane ligand which has biological applications as drug carriers, or as antitumor agents. Metallacarborane complexes of heavier $d$-block transition metals often demonstrate robust thermodynamic and kinetic stabilities. These stabilities allows metallacarboranes complexes to be considered for potential therapeutic or diagnostic applications as drug-delivery vehicles that resist metabolic degradation. Again the transition metals nickel and cobalt with biologically interesting ligands form complexes which need to be structurally characterized, and the predicted chemistry is corrected in this work. The metals catalyze condensations in the ligands.

1.1 Toxic Metal Ion Agents

Detecting and controlling the concentration of toxic metal ions in the environment, our food and water as well as in the human body continues to be a high priority. There is a constant need for sensing or quantitatively identifying toxic metals, to improve and control metal ion toxic levels. These toxic ions are single ion species or molecular ions that at high levels constitute health concerns. This research investigates the synthesis of sensitive and selective
detection of metal ions based on rhodamine b complexes and quinoline units. The issue here is not just the metals but also their concentrations. The concerns pertaining to these metals include drinking water, food chains, cosmetics products, the environment, waste management systems, chemical and biological agents to name a few.\textsuperscript{1} Recent news release from the U.S Environmental Protection Agency (EPA) addressed concerns and plans to tackle soil, sediments and surface water that are contaminated with chromium and other heavy metals that could cause severe nervous system damage in mammals.\textsuperscript{2} The Occupational Safety and Health Administration (OSHA), also has a national emphasis program that deals with issues pertaining to toxic heavy metals.\textsuperscript{3} Some of the most common trace metals and toxic heavy metals that are of high concern include Chromium, nickel, cobalt, mercury, lead, cadmium, and arsenic. Lead poisoning can have an adverse impact on blood production, brain function, reproductive organs, kidneys and cardiovascular system.\textsuperscript{2} Mental symptoms such as dementia and anorexia can be associated with arsenic exposure, while mercury toxicity potentially results in gingivitis, kidney, and somatic complications.

According to Title 40 Code of Federal Regulations (40 CFR), the government authorizes and approves written regulations that are mandatory and applied to individuals, institutes, private sectors, state and local government. These regulations explain the technical, operational and legal detection limits of different metal compounds that these institutions are required to meet in accordance with the established law.\textsuperscript{4}

1.2 Organo-Phosphorus Agents

Terrorist attacks using Chemical Warfare Agents (CWAs) continue to be a vital topic within the international community. Detection of nerve gas agents has brought about a need to tackle the issue at hand with affordable and reliable measures. From the 1995 Tokyo subway
Sarin terrorist attacks to the 2013 Syrian nerve gas poison attacks that claimed thousands of lives, new efforts are being made to come up detection methods, through sensor based compounds to identify and quantify these toxic warfare agents. Nerve gas agents are highly toxic and stable organo-phosphorous compounds that come in the form of gas, aerosol or liquid. Their toxic effects are quite rapid after binding to acetylcholinesterase, an enzyme which then inhibits normal biological activity when absorbed through the skin or respiration thereby, disrupting the nervous system potentially leading to death within minutes which classifies them as parasympathomimetics. Adverse effects at lower concentrations can include symptoms such as nausea, hallucinations, contraction of the pupils, headache and chest pains. The four most prominent volatile nerve agents that are organo-phosphorous (OP) cholinesterase inhibitors are shown in Figure 1.1. These contain carbon-phosphorus (C-P) bonds and are classified as organophosphonates; they are related and can be derived from phosphonic acid

\[ \text{R}^1\text{O} \overset{\text{P}}{\longrightarrow} \text{OR}^3 \]

\[ \text{R}^2\text{O} \]

which is also derived from phosphate but lack the C-P bond. Derivatives without the C-P bond and with P=S replacing P=O seem to be less toxic to humans and often have been used as pesticides, such as those shown in Figure 1.1 below.

![Malathion](image1.png) ![Diazinon](image2.png)

**Figure 1.1.** Organophosphonates and pesticide agents
Various detecting methods such as fluorescence\textsuperscript{8-12}, electrochemical biosensors\textsuperscript{13-17}, gas chromatography-mass Spectrometry (GC-MS),\textsuperscript{18-21} surface acoustic-wave\textsuperscript{22-23}, nerve gas litmus test, and photoluminescence\textsuperscript{24-26}, have been developed and attempted for analysis and identification of organophosphonates toxins. However, due to lack of selectivity, sensitivity, and complexity in some areas of detection, these methods have been known to encounter a few problems. Malathion for example, an organophosphate insecticide that inhibits cholinesterase activity can be synthesized by reacting O,O-dimethyldithiophosphoric acid (DMDP) with diethyl maleate.\textsuperscript{27-29} Sample preparation is a problem for sensors when you have to take the toxins in the field and then get it ready via some elaborate procedure to get it ready for testing with the sensor. OP’s have a short half-life and therefore, the shorter the lifetime, the less chance there is of it leaching into soil etc. Method development to tackle such problems is needed in order to help minimize the toxic levels and hazardous risks. There is a need to develop quicker, cheaper and easily portable access for detection and sensing.

1.3 Organo-Phosphorus Fluorescence Chemosensors

A wide array of fluorescent sensors has been designed to detect nerve gas agent mimics. A series of sensors have also been developed and reported herein to have advantages over others, or at least to increase the range of sensor compounds available for producing a hand-held device for detecting. Dale et al investigated a range of fluorescence sensor labels that were versatile to various functional chemical devices which resulted in a timely and discernible response output. These fluorescence sensor labels are shown below in Figure 1.2.\textsuperscript{30-32}
Fluorescence enhancement was observed after coupling with the nerve gas agents. Dale et al illustrates one of many examples where a suitable appended fluorophore is attached to an amine species. Acylation of the corresponding alcohol is converted to produce a phosphate ester through a rapid intramolecular N-alkylation process followed by cyclization to generate a quaternary ammonium salt.\textsuperscript{33}

A photoinduced electron transfer (PET) is implemented to control the fluorescence intensity of a sample. The amine residues are readily utilized as fluorescence quenchers for PET where the nonbonding electrons are transferred to a variety of fluorescence compounds including hydroxy oximes\textsuperscript{33}, aromatic hydrocarbons,\textsuperscript{34} coumarins,\textsuperscript{35} proteins\textsuperscript{36} and other derivatives. These types of sensors have been employed to detect changes in pH, metal ions.

\textbf{Figure 1.2.} Nerve gas agents
Another fluorescent sensor developed for detecting nerve gas mimics was reported by Zhang et al where a phosphate ester linkage bond was formed to produce an absorption that thereafter and fluoresces as a reactive phosphate esters. The focus was on the intramolecular cyclization process where a nucleophilic substitution was carried out after a nerve agent was introduced. The highly delocalized intramolecular species is accomplished via the transformation of the nonplanar conjugated chromophore which enables an increase in the resulting emission. Although the phosphate ester formation is a fast process, the cyclization step is slow.

Enzyme-based fluorescence biosensors have also been investigated for detecting warfare agents. The initial development of organophosphate (OP) biosensors used different toxins to trace the inhibition of acetylcholinesterase. Although these biosensors are highly sensitive, their specificity is poor because other substances such as organic compounds and heavy metals present challenges therefore inhibiting the enzymes. Currently, many OP biosensors in their early stages have incorporated other enzymes as the precursor component in an attempt to detect nerve agents, namely organophosphorus hydrolase (OPH) and organophosphorus acid anhydrolase (OPAA). Both enzymes offer high specificity characteristics, they are not affected by non-specific inhibition by other neurotoxins, and are usually employed as catalysis biosensors. Silver et al demonstrated the pattern of acetylcholinesterase inhibition by organophosphates and reactivation by an oxime. Studies have shown that an increase in acidity from the hydrolysis of acetylcholine enhances the AChE-based sensor with a pH-sensitive fluorescent dye.

Supramolecular sensors is another example that exhibits molecular characteristics and qualifies as a potential candidate for the detection of nerve agents. This phenomenon is achieved by using a noncovalent metal-ligand binding interaction with an analyte to detect changes in the chemical properties of the sensor. Rowan and Weder et al proposed a versatile displacement
mechanism for the supramolecular metal-ion based fluorescence. Eu\textsuperscript{3+} organometallic ligand complexes have been shown to exhibit good characteristics when used as chemical sensors. Their narrow excitation, emission bands, long excited-state lifetimes and intense fluorescence not only show remarkable absorption intensity but also display excellent selectivity. The first step related to the sensor turn “on/off” process is carried out via UV-light absorption by a ligand. The ligand to metal binding is observed as a metal-ion fluorescence, this then binds to an organophosphate derivative for detecting nerve agents.\textsuperscript{43-44}

We have worked on modified sensors for nerve gas agents, pesticides and metal-based toxins for a comparative study of the effect of various substituents. Structures of the sensor/substrate complex were determined, and various tests were performed to analyze all the different compounds and metals. Investigation of the metal complexes and sensor-organic substrate complexes formed between materials of interest and the rhodamine derivative ligands that were used as sensors included sensitivity level of detection, and optimization of the new compounds to produce functional devices using the sensors.

1.4 Chemosensors for Ion Detection

The need for continued development of chemosensors has been prevalent for decades especially in recent times where their applications have been valuable to a broad spectrum of research disciplines. Sensors can be categorized in two forms namely, optical and electronic sensors.\textsuperscript{45} Optical sensors are responsible for producing changes in optical properties where as electronic sensors produce signals relevant to changes in the electrochemical properties. The structural design and synthesis of sensitive and selective chemosensors of neutral and ionic species have been profoundly applied to many areas of research and development including chemical, biological, medical applications, diagnosis and environmental areas.\textsuperscript{46} Chemosensors
have been known to deliver information in real time in the presence of selective compounds or ions of complexed molecules. There is a wide array of techniques used in chemical sensors but not limited to fluorescence, luminescence, optical absorption etc. Anions and cations are important in industrial and environmental settings due to the role they play. Cations such as Cr\(^{3+}\), Ni\(^{2+}\), and Cu\(^{2+}\), are not only essential but are relevant in all phases of life. Chromium has been found useful in the textile and aircraft industries. As a result, chromium is ubiquitous at least in small amounts. Significant amounts of chromium metal can be toxic and carcinogenic especially hexavalent chromium. Therefore, selective detection of chromium metals is very crucial. The sensitive and selective detection of nickel is also of importance because it is considered a carcinogen that causes lung cancer, may cause asthma, minute amounts can be found in milk, milk-based products, and canned foods. Some of the common uses include ceramics, Ni-Cd batteries, and arc welding. Therefore, it is considered an environmental pollutant. The controversy over the possible essentiality of Cr is addressed below: it is still recommended as a micronutrient by the FDA, but this has been criticized as encouraging healthy people to take a toxin with no evidence-based benefits.

Copper is important for growth development, and maintenance of many organs such as the heart, connective tissues and brain. It also plays a vital role in the formation of the red blood cells, and the release of necessary proteins and enzymes to sustain life. Copper deficiency could lead to neurological and hematological disorders such as anemia, gastrointestinal complications and Menkes disease, which can be fatal if proper measures, are not taken. In Contrast to cation sensing, anion is another example that includes fluoride, chloride, cyanide and nitrate ion. F\(^-\) ion can be traced to therapeutic treatment of bone diseases such as osteoporosis. Excess levels of fluoride could lead to fluoride toxicity or fluorosis which increases bone density due to F\(^-\) ion
accumulation. Chloride ion also plays important roles in the detection of salt water in our drinking and surface water systems as well as detecting leaks in landfill reservoirs. Monitoring chloride levels can also help trace environmental pollution especially agricultural and acid soils.

Based on the above examples, it is evident that ion detection has proven to be significant to many areas including industry and the environment. It has also been determined that if care is not taken, there could be devastating effects that could be fatal and expensive. Therefore, research efforts have been focusing on ways to reduce costs and design a much more reliable and efficient way to detect ions in solution. This is achieved by designing and developing selective ion receptors for sensing environmental remediation including the most hazardous chemical species. Figure 1.3 illustrates a typical example of a chemosensor design which consists of three constituents; a receptor that recognizes the sample of interest, which is typically achieved at high selectivity, a signaling unit that transforms the binding effects into physical change and a method used to convert those changes into meaningful data. The binding signaling subunit is linked by a covalent bond interaction where the analyte could potentially induce changes in the electronic properties that result in sensing of the target ion.

![Figure 1.3. Chemosensor binding complex](image-url)
1.5 Rhodamine Derivatives as Chemosensors

Chemosensor fluorescence dye compounds such as Rhodamine, Azo, Triarylmethane, Fluorone and Thiazine have been studied and applied to a broad range of research areas. Rhodamine was initially synthesized in 1905 by Noelting and Dzie-Wonsky. Since then, it has been applied to chemical technology as well as biotechnology such as ELISA, and flow cytometry. It can be used to inhibit mitochondrion function by slowing down the respiratory process, as substrate for multidrug resistance-associated proteins, and in potential anti-cancer drugs. Rhodamine B (Figure 1.4) derivatives are ideal to use as chemosensors based on their high molecular absorption coefficient and high fluorescent quantum yield characteristics. They are obtained by condensation of phthalic anhydride with an amino derivative of phenol. They are simple to synthesize in high yield, their water solubility and high sensitivity make them suitable as chemosensors, their excellent photostability and photophysical properties enable easy detection with very high fluorescent quantum yields as well as high absorption coefficients. Ranging from red to pink, the color changes instantly when it binds to analytes such as (Cr³⁺, Ni²⁺) in real time. The change in color and strong fluorescence in solution is promulgated by activation of the carbonyl group in a spirolactam moiety. Therefore, the equilibrium between the nonfluorescent colorless ring-closed form and the highly fluorescent pink-colored ring-open form is highly sensitive to pH of the medium, where the ring-open form is the predominant in acidic environment and conditions. Cations have been known to set off changes in structure between the open ring cycle and spirocyclic form. Therefore, rhodamine-based compounds have been well selected as sensors for metal ions. As a result of its characteristics, Rhodamine B derivatives can be used to detect various heavy metal ions that are highly selective to specific metal cation. Another prime example of rhodamine derivatives is hydrazines as sensors for nerve
agent mimics such as diethyl chlorophosphate (DCP) in the solid phase. Studies have shown that rhodamine hydrazines are better sensors for DCP when compared to rhodamine amides based on functionality provided by the hydrazine nitrogen which binds with the DCP.\textsuperscript{58}

![Rhodamine B Structure](image)

**Figure 1.4.** Structure of Rhodamine B

### 1.6 Coumarin Chemosensors

Coumarin (2H-chromen-2-one) is a fragrant organic compound that was initially isolated as a natural product in 1820. Its derivatives 7-aminocoumarin\textsuperscript{59} and 7-hydroxycoumarin\textsuperscript{60} have been used as fluorescent labeling and starting materials in the synthetic designs of new compounds. Yang et al reportedly designed the intracellular detection of β-D-glucosidase and phosphodiesterase simultaneously and characterized its triple-signaling outputs.\textsuperscript{61} In general, coumarin derivatives incorporate excellent photophysical properties such as high fluorescent quantum yields, large Stokes shift and high photostability.\textsuperscript{62} Fluorescent chemosensors have been known to be of high value pertaining to environmental, bio-medical and analytical chemistry. They have not only provided accurate and low-cost detection of toxic heavy metal ions, but have also provided anions and enzymes with very high sensitivity and selectivity characteristics. The
Introduction of Coumarin molecules including a class of heterocyclic compounds known as benzopyrone have also been investigated with numerous advantages. These benefits include therapeutics of prostatic carcinoma antidiabetic therapeutic candidates, as well as treatment of metastatic renal cell carcinoma. Applications of coumarins can be found in a wide array of research fields from chemistry, biology, medicine, cosmetics and fluorescent dyes. Coumarin precursors have been used to detect enzymes, proteins, nitric oxides hydrogen peroxide, hydroxyl radicals, oxygen, chemical warfare agents, and organic compounds. Furthermore, coumarin precursors have been known to be good fluorescent chemosensors of anions which includes fluoride, cyanide, acetate, pyrophosphate, benzoate and all other types of metal based ions including Pb(II), Cr(III), Fe(III), Zn(II), Cu(II), Ni(II), and Ag(I). However, there are some other coumarin derivatives that display sensitivity at the same time towards two or more different metal ions such as Cu(II) and Ni(II), Co(II) and Ni(II), Hg(II) and Cu(II), or Ni(II)/Pd(II)/Ag(I). Typical types of coumarin derivatives are depicted in Figure 1.5 where 7-aminocoumarin is represented in structure 2 and 7-hydroxycoumarin by structure 3.

Figure 1.5. Structure of Coumarin and its derivatives

1.7. Fluorogenic Chemosensors

Recent developments of fluorogenic chemosensors including those used for the recognition of Hg$^{2+}$ through the use of naphthalimide based sensor derivatives have been
investigated. Naphthlimide precursors have been recognized based on their excellent fluorophores characteristics. Their high stability and quantum yield have made these fluorophores excellent candidates for the preparation of fluorescent chemosensors. Naphthlimide incorporates a unit capable of absorbing energy and emitting fluorescence at long wavelengths. The nature of substituent counterparts of the amino or nitro group as well as the substitution patterns (ortho, meta, para substitution), also exhibits high functional building units. Banerjee et al recently investigated and demonstrated that 1,8-naphthalimides were very sensitive when substitution of aromatic rings was incorporated. A high energy excited state resulted in a broad absorption band for nitro functional groups. The amino acid functional groups represent a push-pull internal charge transfer state and ultimately adds to the emission and absorption bands. A schematic diagram representing the Hg\(^{2+}\) chemosensor with the 1,8-naphthalimides derivatives is depicted in Figure 1.6. The 1,8-naphthalimides derivatives acknowledge fluorescent turn-off signals through the formation of the imide-Hg\(^{2+}\) complex.

![Figure 1.6. Hg\(^{2+}\) chemosensor using 1,8-naphthalimides derivatives](image)

Figure adapted with permission from ref 68 (see Appendix C). Copyright © 2013 Elsevier.

**Figure 1.6.** Hg\(^{2+}\) chemosensor using 1,8-naphthalimides derivatives\(^{68}\)

\[ \text{Hg}^{2+} \text{ chemosensor is determined based on the fluorescence quenching turn-off mechanisms. Very few chemosensors are applied for the fluorescence enhancement turn-on for the recognition of Hg}^{2+} \text{ in aqueous solutions. Fluorescence enhancement approach is preferred for the design of chemosensors because it allows for the low detection limit to be achieved for} \]
specific target compounds. Based on the fluorescence enhancement theory, the development of two acetic carboxylic species annexed to the 1,8-naphthalimide fluorescence-based chemosensor was determined to exhibit high sensitivity and selectivity for the detection of Hg$^{2+}$ ion.

1.8. Chemosensors for Pyrophosphate

Selective detection of pyrophosphate ions continues to become a very important area of medicinal chemistry, diagnostics and cancer research. This has ultimately led to many interests in the development of selective receptors and sensors for anionic phosphate derivatives. Under cellular conditions, pyrophosphate ions are involved in the target of many biological molecules that produces ATP hydrolysis, DNA replication to name a few in real time sequencing method. One of the most common avenues for pyrophosphate ion, proton pump inhibitor (PPI) chemosensors has been channeled through a conventional hydrogen bonding interaction for a direct anion binding. These binding sites typically are covalently bonded to the chemosensor by providing a direct response after pyrophosphate binding. A few examples of hydrogen bond donors include imidazoliums, pyrrols, and amides. Although some receptors harbor multiple hydrogen donors, they are designed to implement a binding site for the pyrophosphate ion. Most of these same receptors that contain hydrogen bond interactions also have some disadvantages including the ability of sensing pyrophosphate ions in organic solvents or aqueous compounds only. One way of solving such a problem involves the combination of hydrogen bonding interactions with positively charged binding sites such as Zn$^{2+}$ with dipicolylamine (DPA) and has been known to be effective as binding targets for phosphate derivatives. Reverse binding of PPI is also another way of solving the problem by interacting metal ion binding sites with phosphate groups. When it comes to the applications in biological systems for instance, activity normally requires selectivity of ADP and ATP. So far, the application of the metal ion complex
as a binding site for PPI has been known to be the preferred choice because the binding affinity
between metal ions and PPI have allowed the detection of PPI in 100% aqueous solutions.

1.9 Selective Detection of Ni$^{2+}$

The design and synthesis of sensors for metal ions have been increasingly developing
particularly in areas such as waste management, biological and the environment.\textsuperscript{73-76} The
selective and detection of nickel is important because of its carcinogenic character and it is thus
considered an environmental pollutant but with some biological interest.\textsuperscript{77-79} The presence of
divalent nickel can possibly lead to diseases such as lung cancer, and dermatitis. Nickel has been
known to enter the environment through its use in jewelry, batteries, arc welding and in
ceramics.\textsuperscript{80} Very little concentrations of divalent nickel have also been found in food products
such as dairy, meat and canned foods. As a result of this, better detectors are necessary to target
these problems especially when it comes to the environment. Some of the methods used for
nickel detection includes ICP-AES, furnace atomic absorption spectrometry, and flame
photometry.\textsuperscript{81} The draw back in using these techniques includes sample pretreatment and the
need for a technician who is an expert in dealing with such instruments and analytical
procedures. Therefore a much-needed sensor that can operate outside the laboratory settings is
needed. Attempts have been made in order to develop turn-on sensors for Ni$^{2+}$. The design and
synthesis of Nickel-sensor 1 (NS1) with BODIPY dye and N/O/S receptor bonded to a metal was
used to develop a fluorescence Ni$^{2+}$ probe.\textsuperscript{82} Ni$^{2+}$ binding was observed following a 25-fold
fluorescence increase with 50 equivalents of Ni$^{2+}$ used to detect low levels of Ni$^{2+}$ in live
mammalian cells. An increase in fluorescence for Ni$^{2+}$ was observed when live cells were
injected with 1 mM NiCl$_2$ and stained with a probe for 18 h duration time. Thus the levels if Ni$^{2+}$
is not destructive to cancer cells but can cause cell death with a 2-10 mM of a Ni$^{2+}$ species.
The development of 1-aminoantracene-9,10-dione based chemogenic sensor for sensing multiple analytes such as Ni$^{2+}$, Cu$^{2+}$, and Co$^{2+}$ has also been investigated. Chemosensor A (Figure 1.7) generated two distinctive bathochromic shifts after binding with Cu$^{2+}$ and Ni$^{2+}$. This resulted in the selective identification of both metal ions.

**Figure 1.7.** Chemosensors A, B

Chemosensor B was also synthesized and allowed for the selective identification of Co$^{2+}$ and Cu$^{2+}$ or Co$^{2+}$ and Ni$^{2+}$.

### 1.10 Selective Detection of Trivalent Chromium Ions

Trivalent chromium (Cr$^{3+}$) is an essential part of the human development and plays a crucial role in the metabolism of carbohydrates, proteins and nucleic acids.\(^{84-85}\) It was suggested that insufficient absorption of Cr$^{3+}$ could potentially increase the risk of cardiovascular diseases and diabetes.\(^ {86}\) However, whether Cr is an essential element is now at best controversial. It was proposed as an essential element in 1959, with the isolation of a chromium complex from extracts of brewers’ yeast which enhanced the action of insulin in controlling normal levels of blood sugar.\(^ {87}\) However this complex, so-called “glucose tolerance factor,” thought to contain CrIII and nicotinate and glutathione as ligands, was never fully characterized, and the glucose
tolerance factor itself was subsequently shown not to contain Cr.\textsuperscript{88} Cr\textsuperscript{III}tris(picolinate) is widely marketed as a mineral supplement for weightloss and bodybuilding, although there is concern about possible damage to DNA.\textsuperscript{88} The US Food and Drug Administration (FDA) still recommends a daily adult intake of about 30μg Cr per day, even though its essentiality is dubious. According to Vincent\textsuperscript{89} Cr should be removed from the list of essential trace elements because it has sufficiently proven that it has no beneficial effects on human body mass or composition.\textsuperscript{89}

On the other hand, an excessive intake risks lead to genotoxic effects. Effective, accurate and rapid detection of Cr\textsuperscript{3+} amounts in the environment is necessary to address the issues because the pollutants accumulate as a result of industrial and agricultural settings. Analytical methods such as atomic absorption spectrometry and inductively-coupled plasma atomic emission spectrometry had been employed for the detection for Cr\textsuperscript{3+}. Though these methods allow for the detection of Cr\textsuperscript{3+} they are time consuming and the sample preparation can be time consuming and tedious.\textsuperscript{90-92} Since there is a need for rapid and accurate detection, Fluorometric detection has advantage over the other methods mentioned because it is simple to perform them with high selectivity, sensitivity, high frequency rate, very low cost of equipment and results are obtained at a faster rate. The design and construction of fluorescent probes specific for Cr\textsuperscript{3+} will be valuable especially for other areas of research.\textsuperscript{93}

Although many chemosensors for Cr\textsuperscript{3+} are developed, a vast majority are turn-off chemosensors for Cr\textsuperscript{3+}. However, when it comes to the paramagnetic nature of Cr\textsuperscript{3+}, the development of turn-on sensors is still a challenge. Zhou et al developed a fluorescent turn-on sensor where the main objective here was to design a sensor that would observe the (Fluorescence Resonance Energy Transfer) FRET-based fluorescence enhancement binding with Cr\textsuperscript{3+}. An
absorption band was observed at 380 nm with a yellow fluorescence centered at 544 nm. The addition of Cr\(^{3+}\) produced a fluorescence band at 594 nm with an excitation at 405 nm. There is an observed decrease in the intensity of the fluorescence band at 544 nm based on the FRET behavior with an association constant of 9.4 \(\times 10^{-3}\) M\(^{-1}\) for Cr\(^{3+}\).\(^{94}\) Mao et al designed and developed another selective and sensitive Cr\(^{3+}\) sensor. In this case, a rhodamine based moiety is applied to a four coordinating area that binds with Cr\(^{3+}\). Results showed that the binding constant generated was 4.1 \(\times 10^{4}\) M\(^{-1}\) and higher when compared to the FRET-based moiety.\(^{95}\)

1.11 Detection of CN

Rhodamine-based Cr\(^{3+}\) or Ni\(^{2+}\) complexes are capable of detecting CN due to its strong binding affinity to the metal ions. The displacement of CN typically results in a turn “off” or a ring-closed spirolactam structure which goes from pink to colorless. The color change can be detected instantly by the naked eye making it a naked-eye sensor for CN.\(^{96}\) Cyanide is known to be a very toxic waste. It can be found and applied to a wide range of places such as pharmaceutical manufacturing, metallurgy, metal cleaning, synthetic rubbers and plastics.\(^{96}\) CN is a well known poison that binds to cytochrome a\(_3\) inhibiting the electron transport chain including the production of ATP in cells of organisms which affects the central nervous system.\(^{97}\) This means that the level of cyanide in natural waters ought to be maintained below 0.1 ppm.\(^{98}\) Therefore, detection of cyanide at low level concentrations is necessary including several detection methods that have been applied and reported for free cyanide, naked eye visual detection, electrometric,\(^{99}\) chromatographic,\(^{100}\) and fluorometric detection.\(^{101}\) Unfortunately, some of the drawbacks relating to these detection methods include expensive laboratory equipment and long sample preparation time.
An example of a CN sensor metal displacement approach of a 4,5-disubstituted-1,8-naphthalimide based on Cu\(^{2+}\) complex has been reported.\(^{102}\) The free sensor compound showed a broad emission band at 534 nm, showing a decrease in intensity following the addition of Cu\(^{2+}\). A new emission band at 478 nm also started to appear while the addition of cyanide resulted in the disappearance of the emission peak at 478 nm with an increase in the band at 534 nm due to the release of Cu\(^{2+}\).\(^{102}\)

1.12 Conclusion

In conclusion, the design and synthesis of chemosensors for certain cations, anions, organophosphorus and rhodamine derivatives are rapidly growing in different areas of research. Selective and sensitive detection of toxic heavy metals such as nickel, chromium, cobalt, lead, mercury and arsenic are important in solving environmental, biological and waste management problems. Minute concentrations of some of these metals can be found in various food products including canned food, chocolates and milk-based products while others can be found in our drinking water, our homes and laboratory settings. As a result of this, there could be potential chronic or acute effect on human health as well as marine species.

Several methods are available are available for detection of the metals such as flow injection spectrometry, flame and graphite furnace atomic absorption spectrometry, ICP-AES and flame photometry. The disadvantages of these techniques include the need for sample pretreatment, expensive equipments and expert personnel to handle the instruments. We now present a “naked eye” sensor that is easy to operate.

1.13 References


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CHAPTER 2

COORDINATION SENSORS BASED ON RHODAMINE B AND QUINOLINES

2.1 Fluorescence Spectroscopy

Fluorescence spectroscopy typically focuses on electronic and vibrational energy level states. Figure 2.1 depicts a general contour map scheme illustrating the excited and ground state through absorbing light of molecules at a particular wavelength.\(^1\)\(^-\)\(^2\) In general, once a target molecule has been identified, it transitions from an excited state in the highest vibrational state to the lowest vibrational level. Transition to the excited state typically takes place when the absorbed energy is equal to the difference between the energy in the ground state and excited state or the energy gap. The change in energy between these two states usually remains constant and is indicative of the molecular structure or atomic configuration. A photon is then emitted which enables relaxation to its ground state. Different energies and frequencies with their relative intensities will be observed in the process therefore, structural determination of the vibrational levels can be obtained. Typically in a fluorescence emission measurement, one would observe variation in the detection wavelength within the area of interest while the excitation wavelength remains fixed. Under the right conditions, an excited molecule will retreat back to the ground state by emitting energy in the form of photons and heat. A combined range of excitation wavelengths is usually obtained from the emission map by measuring the emission spectra. When compared to phosphorescence \((10^{-4} \text{ to } 10 \text{ sec or more})\) fluorescence has a short life time of \((\sim 10^{-8} \text{ sec})\).
Since the emission energy of these photons is equal to the difference between the two energy states, potential loss of energy from the molecule is encountered in the excited state through heat. This will ultimately result from the emitted energy being less when compared to the exciting energy. For this reason, quantification of fluorescence methods will be applied through the use of spectral properties of both the emission and excitation peaks. The general process used to understand this phenomenon is through application of the Stokes’ shift ($\Delta \nu, \text{cm}^{-1}$) which can be defined as the difference in wavelength or frequency between the positions of the bands maxima of the absorption and emission fluorescence spectra based on the same electronic transition. The Stoke shift equation is denoted as:

**Figure 2.1.** Jablonski diagram$^2$
where $\lambda_{\text{abs(max)}}$ and $\lambda_{\text{em(max)}}$ illustrate the maximum absorbance and emission in cm$^1$ respectively. Figure 2.2 illustrates a typical example of an absorption and emission spectra of a molecule. The absorption spectrum can be determined by fixing the emission intensity at a fixed wavelength, while varying the excitation wavelength.

![Stokes' shift illustrating the absorption and emission spectra](image)

**Figure 2.2.** Stoke shift illustrating the absorption and emission spectra$^5$

### 2.2 UV-Absorption on Metal Sensor Compounds

Ultraviolet absorption spectrometers have been in use for over thirty-five years. During this period, it has become one of the most important instrumental methods in present day laboratories. When it comes to applications, many other techniques could be used but few can compete with UV-Visible spectrometry due to its accuracy, cost-effectiveness, speed rate, and simplicity. Ultraviolet and visible (UV-Vis) absorption spectroscopy is the primarily used to measure light when it passes through a sample. It is also a method that is dependent on the
electronic structure and environment of the molecule that is being excited when keeping in mind the effect of changes in solvent polarity and would induce the characterization of an analyte. The absorption of light typically corresponds to the excitation of a molecule’s outer electron. Generally, when a molecule absorbs energy the outermost electrons in the molecule is excited from the Highest Occupied Molecular Orbital (HOMO) to the Lowest Unoccupied Molecular Orbital (LUMO). Figure 2.3 shows an example of a transition and electronic energy levels where the occupied molecular orbitals are known as \( \sigma \) orbitals, while at slightly higher energy they are known as \( \pi \) orbitals.

![Diagram](image-url)

**Figure 2.3.** Transition state and electronic energy level

The absorption can be measured at either a single wavelength, or spectral extended range. Ultraviolet and visible spectroscopy requires sufficient energies to excite the outer electrons into
high energy levels and is quite useful for quantitative measurements. Beer’s Law is applied to determine the concentration of a specific analyte by measuring the absorbance at different wavelengths. The relationship between the absorbance and concentration can be written as:

\[ A = \varepsilon cl \]  

where \( A \) is the absorbance, \( \varepsilon \) is the molar absorptivity expressed in units of \( \text{L \ mol}^{-1} \text{ cm}^{-1} \), \( c \) is the concentration of the sample and its expressed in unit of \( \text{mol L}^{-1} \) and \( l \) is the length of the analyte sample cell expressed in units centimeters.

### 2.3 2-Photon Absorption

The technological developments in laser and optical accessories have contributed enormously to the advancement of science and research especially in the areas of nonlinear optical spectroscopy (NLO). Understanding the NLO properties and structure-property relationships have been of great interest of research for several decades.\(^7\) The development of synthetic methods and techniques for fabrication and material design has also been of interest and has contributed to this area. Although much progress has been accomplished there is still the need for novel materials that are capable of producing large nonlinear optical responses. The first working laser was studied and demonstrated by Theodore Maiman in 1961. Since then, there has been a rapid growth in laser technology including very complexed and sophisticated laser systems.\(^7\) Different qualities of high intensity lasers can be attributed to the basic emergence of modern fields of nonlinear optics. Some of the promising features of laser lights include but not limited to their properties of monochromaticity, and high intensity, which are prerequisites for the study of nonlinear optics. A few examples of nonlinear optical characteristics include the interaction of monochromatic light with a material to transform into the light of another
wavelength or the combination of multiple beams to generate a light beam which can affect the refractive index of a material by an amount proportional to the intensity of the beam. The change in nature of the scattering light while still in the presence of an incident light beam, the excitation of a material by using two or more photons that are absorbed simultaneously or multi-photon absorption are a few examples of NLO materials. One of the most fundamental multi-photon absorption properties is the absorption of two-photons together, even when there could be three or more photon absorption.

Nonlinear optical spectroscopy can be explained in-terms of incorporating a beam of light through it. The order of the nonlinear properties of materials ultimately depends on the electric field strength of the incident radiation. As the intensity of the radiation increases, the higher-order frequency effect occurs. When the optical property of an organic media changes based on the intensity of the applied field, a nonlinear approach also known as 2-Photon absorption develops. There is a function that explains the polarization based on the displacement of charges the occurs in the nonlinear organic material, \( P(t) \) while interacting with an electric field. This function can be described as an anharmonic oscillator as shown in equation 2.3

\[
P(t) = \chi^{(1)} E(t) + \chi^{(2)} E^2(t) + \chi^{(3)} E^3(t) \ldots 
\]

\( \chi^{(1)} E(t) \) represents the individual polarization and its linearity associated with the applied electric field, while \( \chi \) and \( E \) are associated with the linear susceptibility of the electric field and medium. The intense electric fields are related to the higher and second term where the higher order is key when it comes to describing polarization. \( \chi^{(1)} \), \( \chi^{(2)} \), and \( \chi^{(3)} \) represents the second, third and fourth nonlinear medium susceptibilities. The induced polarization can develop the fundamental frequency to a lower wavelength. For this reason, different types of frequencies can be obtained depending on the degree of nonlinearity the material displays and can also provide
supplementary options for studying NLO materials. This dissertation will focus on two-photon absorption (2PA) properties of fluorescence compounds.

2.4 2-Photon Absorption (2PA) on Fluorescence Sensors

2PA on fluorescence sensors has many significant advantages when compared to two-photon absorption. One of the numerous applications of 2PA is the development of a 3D data storage material, which can enhance the storage and transfer of large quantities of digital information. Some of the properties associated with 2PA relevant to data storage include greater penetration, reduced scattering, penetration depth and smaller focusing volumes. Rentzepis et al investigated the very first 3D optical data storage unit where they investigated simultaneous interactions between two photons with a non-linear material inorder to achieve optical reading in 3D and data storage. Light absorption by two-photon generates a photochemical reaction leading to the formation of a colored absorption spectrum which shifts to the visible region. A typical example depicted in Figure 2.4 shows different materials composed of organic dye and compositions of various chemical structures in an acidic or basic environment. Rhodamine B for example is an organic dye that we have investigated and currently use as a precursor in our research group. Depending on the acidity or polarity of the solvent being used, Rhodamine B can be in the form of an acid or base with the basic form having non-fluorescent and colorless characteristics while the acid form is more stable with a noticeable fluorescence colorful dye. Therefore, the acid-base transformation is quite possible when it comes to the storage of materials that is based on a “read and write” process.
Figure 2.4. Write and read process\textsuperscript{9}

The first step in the write process is to develop an acid form of a compound by using light to excite the energy level with the application of an acid-generator. The second integral part of the process involves an organic dye precursor and can also be represented as Rhodamine B. It reacts with the acid that was converted from the photochemical process to generate a colored dye. A strong fluorescence is finally accomplished in the read process by reacting the photochemical species with the colored dye. Scheme 2.1 shows an example of the reaction mechanism for the writing and reading processes.
Scheme 2.1. Writing and reading reaction mechanism

The examples above illustrates the writing and reading processes where Scheme I addresses the formation of the precursor dye after Rhodamine B base reacts with an acid proton. Scheme II’s mechanism introduces a memory material species where 1-nitro-2-naphthaldehyde (NNA) is represented as an acid generator. The acid generator passes through a photochemical type arrangement in the presence of a light source to produce the nitroso-acid product. Experimental results based on the absorption spectra showed a strong efficiency beam of 1064 and 532 nm for 2-photon writing. Their overall work was based on detecting light through a photodiode. The right selection of compounds that contributes to the spectral separation and interpretation is of great importance since it allows for the ‘written’ compounds to emit light which can be attained from the written memory being read.
2.5 Mass Spectrometry – General Information

Mass spectrometry (MS) is an analytical technique that is used to determine the mass-to-charge ratio (m/z) of ions in the gas phase. It provides unique information about the analyte of choice, including their molecular structure, composition and purity. There is three parts associated with a mass spectrometer: (1) Ion source, whose main aim is to ionize the analyte while being transferred to the gas phase. (2) Mass analyzer, which is a device that is used to separate ions based on their mass-to-charge ratio (m/z) values. (3) A detector, which is mainly used to measure the ion current. Once a spectrum is achieved, it can be interpreted in order to characterize the analyte of choice. The interpreted data can also be attained through the assistance for a library database of known compounds based on the mass/charge ratios that best fits the analyte being investigated. For compounds such as the sensor complexes, the principal researcher proceeds by analyzing the spectra for identification of peaks based on the mass until all are resolved. Electrospray ionization methods (ESI-MS) were used for the complexes studied in this dissertation.

2.6 Overview of Mass Spectrometry

Mass spectrometry has become a virtually ubiquitous research tool to many areas of research since its discovery. Scientific breakthroughs made possible by mass spectrometry have included determination of atomic weights, isotopes, isotope labeling, rapid identification of environmental trace pollutants, and characterization of molecular structures. The first mass spectrometer was discovered by John Thomson in 1913 and appeared in the market by 1943. Since then, many research projects have been conducted using...
mass spectrometry instrumentation, including a mass analyzer. Mass analyzers are used in other analytical methods such as time-of-flight (TOF)\textsuperscript{11}, ion trap,\textsuperscript{12} ion cyclotron resonance (ICR)\textsuperscript{13} and quadrupole.\textsuperscript{14} Gas chromatography-mass spectrometry (GC/MS)\textsuperscript{15} was not developed until the 1960s leading to the analysis and data acquisitions of compounds with complexed mixtures. Tandem mass spectrometry (MS/MS)\textsuperscript{16} and chemical ionization (CI)\textsuperscript{17} were also developed during the same time frame. Mass spectrometry became a standard analytical technique for testing volatile organic compounds. Nonvolatile compounds however are usually thermally labile and therefore are limited in the number of useful techniques for ionization. As a result of these limitations, several soft ionization techniques such as electrospray ionization were introduced.

2.7 Ionization

Ionization techniques typically exist in various forms including gas phase methods such as chemical ionization (CI), electron impact (EI), desorption methods that includes matrix assisted laser desorption ionization (MALDI), field desorption (FD), plasma desorption, fast atom bombardment (FAD) and evaporation ionization methods including thermospray and electrospray ionization (ESI). ESI is being described here as the method used in this dissertation. Atmospheric pressure chemical ionization (APCI) is a method that uses a similar source as ESI. The difference being instead of putting a voltage directly on the spray chamber, the voltage is inserted into a needle that creates a discharge at atmospheric pressure. Therefore, ESI is a form of APCI since ESI can be assembled to ionize at atmospheric pressure. ESI in this case will be the ionization method used.
2.8 Electrospray Ionization (ESI)

In the last several decades, ionization methods based on ESI have increased for analyzing complex compounds in many fields especially in food safety, forensic and quality control. The ability of ESI to generate ions and ranges in mass beyond 100 kilodaltons (kDa) also makes it a special technique.

ESI-MS has emerged in many areas of research and applications especially in the last couple of decades. Its ability to deliver analytes at the right flow rate, pressure and capillary size makes it a unique ionization method with great ion efficiency. The schematic diagram shown in Figure 2.5 illustrates a typical electrospray ionization technique where a direct sample source is introduced followed by an ionization process where the sample and analyte are separated into two steps. The sample is initially introduced through a gas flow chamber. It travels through an electrospray plume where the analytes are ionized and into an MS inlet where data acquisition is obtained and analyzed.\(^\text{18}\)

![Electrospray ionization source](image_url)
2.9 Fourier Transform Infrared Spectrometer (FTIR)

FTIR spectrometer (Fourier Transform Infrared Spectrometer) is a technique widely used in organic synthesis, petrochemical, polymer science, pharmaceuticals and food industries. IR spectrometer was initially invented in the late 1950’s where scientists applied prism optical splitting system made of sodium chloride. The problem with such technique included a very strict particle size and narrow scan range. In the 1960’s a second-generation IR spectrometer was introduced where a grating monochromator was employed. Scientists later found out that the performance of the second-generation IR spectrometer was much better than the prism monochromator with several weaknesses including weak wavelength accuracy, low sensitivity and scan speed. This lead to the invention of the third-generation IR spectrometer or Fourier transform infrared spectrometer (FTIR) where an interferometer was included. By replacing the monochromator with the interferometer, IR became extremely powerful and consequently many applications of IR spectrometer have been utilized. A typical FTIR spectrometer is depicted in Figure 2.6 where it starts with a source that generates light across the analyte of interest. A monochromator separates the source radiation into different wavelengths. The wavelengths are selected by a slit, which shines through the analyte at any given time. In the case of a double beam operation, a beam splitter is used to separate the incident beam into two parts in which the first half goes to the analyte while the other goes to a reference. The analyte absorbs light based on its chemical properties while a detector is put in place to collect the radiation that goes through the sample. The detector utilizes an electrical signal, which is sent to an analog recorder and subsequently allows the user to record energy as a function of frequency or wavelength.
In basic terms, IR can be viewed as absorption measurements of IR frequencies where the electromagnetic radiation is lower in energy compared to visible radiation. Molecules absorb IR radiation, and the energized molecules begin to stretch, vibrate and bend. These motions are observed as varying levels of molecular energies. It is important to note that when it comes to different functional groups and bonds, absorption will be observed at different wavelengths.

Typically, there are three parts of the electromagnetic spectrum of an infrared region and consists of the near, mid and far region. The near region can be observed between 1400-4000 cm\(^{-1}\), while the mid region lies between 4000 – 200. The far region is also observed between 200 – 10 cm\(^{-1}\).

Absorption of energy takes place when the electromagnetic radiation of the infrared region falls on the molecule and is sufficient for the vibrational, bending and stretching motion to begin to occur. A bond in an inorganic molecule will either stretch or bend with other bonds. Also, when it comes to stretching motions, the nuclear distance within two atoms may increase or decrease but the overall atom remains unchanged at the same axis. Figure 2.7 explains how the change in bond length along the axis represents an example of vibration stretching and can be either symmetrical or asymmetrical.
In contrast to vibration stretching, when it comes to bending motions, the bond position changes when compared to its original bond axis. Figure 2.8 depicts an example by showing how the bending motion produces a change in angle between two bonds.

Bending vibrations can also be linked to molecules being in-plane or out of the plane when two atoms move in the same direction. A specific amount of energy is often required when it comes to stretching and bending vibration of a compound. Those vibrations of molecules are efficient for absorbing infrared radiations and can cause a change in its dipole moment. These types of vibrations are generally referred to as IR active vibration, which also appears in the IR spectrum while the peak intensity is proportional to the change in dipole moment.
2.10 Experimental

2.10.1 Materials and Methods

All synthesis reagents were purchased from Sigma-Aldrich and used directly without any purification. Thin layer chromatography was carried out using silica gel plates. Column chromatography was performed using silica gel, 70-230 mesh (60 Å pore size). ACS grade solvents (Hexanes, ethyl acetate, chloroform) were used for the column chromatography while ethanol was used for recrystallization.

All the $^{1}\text{H}$ and $^{13}\text{C}$ NMR spectra were obtained by using the JEOL Eclipse (400 MHz) delta oxford instrument using chloroform-$d$, DMSO-$d$. Chemical shift values are reported in ppm with multiplicities indicated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Coupling constant value ($J$) are reported in Hz.

UV-VIS absorbance was performed and recorded on a Shimadzu UV-2101PC using a spectroscopic grade acetonitrile. Florescence spectra were obtained on a Hitachi F-2500 using spectroscopic grade acetonitrile. 2-Photon Absorption spectra were recorded on an Edinburgh-Millennia V spectrometer using a spectroscopic grade acetonitrile. Electron Spray Ionization Mass Spectra (ESI-MS) in the positive mode was recorded on a water synapt G1 spectrometer using a LC-MS grade methanol. Fourier transform infrared (FT-IR) spectra were recorded on a Mattson FTIR spectrometer using a spectroscopic grade chloroform. All spectra were recorded at room temperature. Single X-Ray diffraction analysis were performed and recorded on a Bruker SMART APEX2 crystallography system. Schemes 2.2, 2.3, and 2.4 show the synthesis of rhodamine B derivatives with electron rich furan moiety. Different substituent groups were used in the furan ring to study the effects of the sensitivity and selectivity of various metal ions.
Scheme 2.2. Synthesis of 1-5

Synthesis of Compound 1: A solution of Rhodamine B (2.40 g, 5.01 mmol) was added with ethanol (60 mL) under room temperature. The reaction mixture was stirred at room temp for 2 minutes. Hydrazine hydrate (6.0 mL) was added dropwise with vigorous stirring for a period of 1 minute while mixture was allowed to reflux for 2 hrs. The resulting mixture was allowed to
cool to room temperature. 1 M HCl was added to the mixture, while 1 M NaOH was also added until pH 14. The reaction mixture was filtered (vacuum), washed twice with 15 mL DI water, and allowed to dry for 1 hr to obtain Compound 1 as a pink solid (2.10 g, 83%). mp: 245 - 246 °C. 1H NMR (400 MHz, CDCl₃): δ 7.93 (1H, m), 7.45 (2H, m), 7.11 (1H, m), 6.46 (2H, d), 6.41 (2H, d), 6.29 (2H, dd), 3.68(2H, s), 3.35 (8H, q), 1.17 (12H, t). 13C NMR (400 MHz, CDCl₃): δ 166.2, 153.9, 151.6, 148.9, 132.5, 130.1, 128.1, 129.9, 123.0, 108.0, 104.6, 98.0, 65.9, 44.4, 12.6. ESI-MS Calcd for C₂₈H₃₂N₄O₂ m/z [M]⁺ 456.58. Found: 457.20 [M + H]⁺, 479.19 [M + Na]⁺.

Synthesis of Compound 2: A solution of 2 (2.05 g, 14.94 mmol) was added with 1.5N HCl under room temperature. The reaction mixture was allowed to stir under reflux temp for 10 minutes or until all solids dissolved. Crotonaldehyde (1.50 mL) was added dropwise for a period of 2 hr while mixture refluxed for 2 hr. The resulting mixture was allowed to cool to room temperature. Aqueous ammonia was added to the mixture until pH 3. The reaction mixture was extracted twice with methylene chloride (50 mL). The Organic layer was separated, dried over MgSO₄ and evaporated to dryness. Crude product was recrystallized from ethanol (20 mL), evaporated to dryness and dried in vacuo overnight to obtain compound 2 as a light brown solid (1.33 g, 89%). mp: 155 - 156 °C. 1H NMR (400 MHz, CDCl₃): δ 8.77 (1H, d), 8.28 (1H, d), 8.05 (1H, d), 7.68 (1H, dd), 7.46 (1H, d), 2.83 (3H, s). 13C NMR (400 MHz, CDCl₃): δ 167.6, 158.0, 145.0, 138.8, 135.2, 132.7, 126.5, 124.1, 122.8, 122.1, 24.9. ESI-MS Calcd for C₁₁H₉NO₂ m/z [M]⁺ 187.20. Found: 188.05 [M+H]⁺.

Synthesis of Compound 3: A Solution of compound 2 (0.75 g, 5.46 mmol) in dichloromethane (30 mL) at 0°C was added with N,N-DiCyclohexylCarbodiimide (DCC) (1.26 g, 6.1 mmol) and 4(DiMethylAmino)Pyridine (DMAP) (0.48 g, 3.9 mmol). The reaction mixture was allowed to stir for 20 minutes before compound 1 (1.63 g, 3.40 mmol) was added. The
mixture was allowed to stir at room temperature for 5 days and the precipitate was filtered off. The filtrate was evaporated and purified on a silica gel column using EtOAc/CHCl₃ (1:4) as the mobile phase to obtain 3 as a brown solid (1.10 g, 76%) mp: 259 - 260 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.71 (1H, dd), 8.18 (1H, d), 7.91 (1H, m), 7.81 (1H, dd), 7.43 (1H, d), 7.42 (2H, m), 7.15 (1H, d), 7.11 (1H, m), 6.43 (2H, d), 6.39 (2H, dd), 6.29 (2H, d), 3.31 (8H, q), 2.16 (3H, s), 1.12 (12H, t). ¹³C NMR (400 MHz, CDCl₃): δ 166.2, 154.5, 153.9, 151.6, 148.9, 143.9, 139.9, 132.5, 130.1, 128.1, 123.9, 123.0, 108.0, 106.6, 104.6, 98.0, 97.9, 65.9, 55.8, 44.4, 44.3, 40.5, 39.2, 35.0, 34.0, 25.5, 24.7, 12.6. ESI-MS Calcd for C₃₉H₃₉N₅O₃ m/z [M]+ 625.31. Found: 626.19 [M + H]+, 648.17 [M + Na]+, 664.14 [M + K]+.

**Synthesis of Compound 4:** A solution of compound 3 (0.35 g, 0.55 mmol) in 1,4-dioxane (35 mL) was heated to 60 °C and SeO₂ (124 mg, 1.1 mmol) was added. The reaction mixture was allowed to heat at 80 °C for 4 hours. The mixture was allowed to cool down to room temperature, filtered and evaporated to dryness. The crude product was purified on a silica gel column using EtOAc/Hexane (2:1) as the mobile phase to generate compound 4 as a red solid (0.21 g, 62%). mp: 277 - 278 °C. ¹H NMR (400 MHz, CDCl₃): δ 13.08 (1H, s), 8.71 (1H, s), 8.69 (1H, d), 8.00 (1H, d), 7.48 (1H, d), 7.46 (1H, d), 6.92 (1H, d), 6.37 (1H, t), 6.29 (1H, d), 4.05 (2H, d), 3.31 (2H, d), 3.29 (2H, d), 3.27 (8H, m), 1.14 (12H, t). ¹³C NMR (400 MHz, CDCl₃): δ 164.4, 164.0, 158.5, 156.8, 153.6, 148.8, 144.7, 137.6, 134.4, 132.7, 129.4, 125.4, 123.8, 123.5, 121.6, 108.1, 104.9, 97.6, 65.9, 49.1, 44.3, 34.0, 25.7, 25.0, 24.7, 12.7. ESI-MS Calcd for C₃₉H₃₇N₅O₄ m/z [M]+ 639.28. Found: 640.14 [M + H]+.

**Synthesis of Compound 5:** Compound 4 (0.15 g, 0.23 mmol) was dissolved in 25 mL of ethanol and NaBH₄ (9 mg, 0.23 mmol) was added and the mixture was allowed to stir at room temperature for 5 hours. The mixture was evaporated to dryness, dissolved in chloroform (30
ml) and extracted twice with 15 ml water. The organic layer was separated, dried under MgSO₄ and evaporated to dryness. The crude product was purified on a silica gel column using EtoAC/Hexane (1:1) as the mobile phase, recrystallized with Ethanol to obtain 5 as a white solid (95 mg, 60%) mp: 240 - 241 °C. ¹H NMR (400 MHz, CDCl₃): δ 13.08 (1H, s), 8.72 (1H, d), 8.70 (1H, d), 8.01 (1H, d), 7.45 (1H, d), 6.94 (1H, d), 6.92 (2H, d), 6.37 (2H, dd), 6.29 (2H, d), 4.01 (2H, s), 3.31 (8H, q), 3.29 (1H, s), 1.10 (12H, t). ¹³C NMR (400 MHz, CDCl₃): δ 207.0, 164.4, 164.0, 157.0, 153.6, 149.1, 148.8, 144.7, 129.3, 129.2, 128.0, 125.4, 123.8, 123.4, 108.0, 104.8, 97.6, 66.0, 48.9, 44.5, 44.3, 39.1, 33.9, 31.1, 30.9, 25.6, 25.0, 12.6, 12.5. ESI-MS Calcd for C₁₉H₁₉N₂O₄ m/z [M]+ 641.30: Found: 642.38 [M+H]+

Scheme 2.3. Synthesis of 6-9
Synthesis of Compound 6: A solution of 6 (2.05 g, 14.94 mmol) was added with 1.5N HCl under room temperature. Reaction mixture was allowed to stir under reflux temp for 10 minutes or until all solids dissolved. Crotonaldehyde (1.50 mL) was added dropwise for a period of 2 hr while mixture refluxed for 2 hr. The resulting mixture was allowed to cool to room temperature. Aqueous ammonia was added to the mixture until pH 3. The reaction mixture was extracted twice with methylene chloride (50 mL). The organic layer was separated, dried over MgSO4 and evaporated to dryness. Crude product was recrystallized from ethanol (20 mL), evaporated to dryness and dried in vacuo overnight to obtain compound 6 as a brown solid. (1.00 g, 66%). mp: 279 - 280 °C. 1H NMR (400 MHz, DMSO-d): δ 9.16 (1H, d), 8.32 (1H, d), 8.16 (1H, d), 7.80 (1H, dd), 7.51 (1H, d), 2.62 (3H, s). 13C NMR (400 MHz, CDCl3): δ 172.3, 148.5, 148.4, 130.2, 129.3, 119.1, 118.2, 118.1, 113.7, 113.6, 31.5. ESI-MS Calcd for C11H9NO2 m/z [M]+ 187.20 : Found: 188.03 [M+H]+

Synthesis of Compound 7: A solution of compound 6 (0.51 g, 2.72 mmol) in dichloromethane (30 mL) at 0°C was added with N,N-DiCyclohexylCarbodiimide (DCC) (0.83 g, 4.0 mmol) and 4(Dimethylamino)pyridine (DMAP) (0.35 g, 2.8 mmol). The reaction mixture was allowed to stir for 20 minutes before compound 1 (1.10 g, 2.4 mmol) was added. The mixture was allowed to stir at room temperature for 5 days and the precipitate was filtered off. The filtrate was evaporated and purified on a silica gel column using EtOAc/CHCl3 (1:4) as the mobile phase to obtain 7 as a brown solid (1.04 g, 72%) mp: 246 - 247 °C. 1H NMR (400 MHz, CDCl3): δ 10.16 (1H, dd), 8.19 (1H, d), 7.91 (1H, m), 7.43 (1H, d), 7.42 (2H, d), 7.10 (1H, d), 6.89 (1H, m), 6.43 (2H, d), 6.39 (2H, dd), 3.31 (8H, q), 2.15 (3H, s), 1.13 (12H, t). 13C NMR (400 MHz, CDCl3): δ 207.5, 166.4, 156.8, 153.9, 148.9, 143.9, 132.5, 130.1, 128.1, 123.9, 123.0,
Synthesis of Compound 8: A solution of compound 7 (0.25 g, 0.40 mmol) in dioxane (25 mL) was heated to 70 °C and SeO₂ (88 mg, 0.7 mmol) was added. The reaction mixture heated at 80 °C for 4 hrs. The mixture was allowed to cool to room temperature, filtered and evaporated to dryness. The crude product was purified on a silica gel column using EtOAc/Hexane (2:1) as the mobile phase to generate compound 8 as a pink solid (0.175 g, 72%). mp: 270 - 271 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.13 (1H, d), 8.11 (1H, d), 7.61 (1H, t), 6.71 (2H, d), 6.69 (2H, d), 6.57 (2H, d), 3.45 (8H, m), 1.09 (12H, t). ¹³C NMR (400 MHz, CDCl₃): δ 157.34, 157.01, 139.32, 130.64, 129.71, 106.62, 96.83, 77.11, 76.79, 67.17, 49.18, 45.35, 40.24, 33.98, 31.04, 25.69, 25.02, 12.66. C₃⁹H₃₇N₅O₄ m/z [M]⁺ 639.28. Found: 640.38 [M + H]⁺

Synthesis of Compound 9: Compound 8 (0.172 g, 0.26 mmol) was dissolved in 34 mL of ethanol. The reaction mixture was allowed to stir at room temp for 5 mins. NaBH₄ (10 mg) was added and the mixture stirred at room temperature for 5 hours. The solution was evaporated to dryness, dissolved in chloroform (40 ml) and extracted twice with water (15 ml). The organic layer was separated, dried over MgSO₄ and evaporated to dryness. The crude product was purified on a silica gel column using EtoAC/Hexane (1:1) as the mobile phase, recrystallized with Ethanol to obtain 9 as a pink solid (0.11 g, 64%) mp: 234 - 235 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.19 (1H, d), 7.99 (1H, d), 7.60 (1H, d), 7.51 (1H, d), 7.58 (1H, d), 7.20 (1H, t), 6.54 (3H, m), 6.52 (1H, d), 6.41 (2H, d), 6.31 (2H, dd), 6.32 (2H, d), 5.12 (2H, s), 4.08 (8H, q), 3.00 (1H, Br s), 1.07 (12H, t). ¹³C NMR (400 MHz, CDCl₃): δ 169.8, 156.7, 153.4, 149.5, 134.4,
129.2, 129.0, 124.8, 124.2, 108.0, 106.0, 98.0, 97.6, 49.2, 44.5, 44.4, 39.2, 34.0, 25.6, 25.0, 12.7, 12.6. ESI-MS Calcd for C_{39}H_{39}N_{5}O_{4} m/z [M]^+ 641.30: Found: 642.32 [M+H]^+

Scheme 2.4. Synthesis of 10-13

Synthesis of Compound 10: A solution of 2 (2.05 g, 14.9 mmol) was added with 1.5N HCl under room temperature. The reaction mixture was stirred under reflux temp for 10 minutes or until all solids dissolved. Crotonaldehyde (1.50 mL) was added dropwise for a period of 2 hr while mixture refluxed for 2 hr. The resulting mixture was allowed to cool to room temperature. Aqueous ammonia was added to the mixture until pH 3. Reaction mixture was extracted twice.
with methylene chloride (50 mL). The Organic layer was separated, dried over MgSO\textsubscript{4} and evaporated to dryness. Crude product was recrystallized from ethanol (20 mL), evaporated to dryness and dried in vacuo overnight to obtain compound 10 as a brown solid. (1.10 g, 73%). mp: 250 - 251 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 8.62 (1H, d), 8.30 (1H, d), 8.18 (1H, d), 7.91 (1H, dd), 7.89 (1H, d), 2.81 (3H, s). \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 171.9, 161.8, 152.7, 152.5, 138.0, 132.4, 131.5, 126.8, 117.2, 117.0, 25.3. ESI-MS Calcd for C\textsubscript{11}H\textsubscript{9}NO\textsubscript{2} m/z [M]+ 187.20. Found: 188.06 [M+H]+

**Synthesis of Compound 11:** A Solution of compound 10 (0.62 g, 3.31 mmol) in dichloromethane (25 mL) at 0 °C was added with DCC (0.95 g, 4.60 mmol) and DMAP (0.45 g, 3.68 mmol). The reaction mixture was allowed to stir for 20 minutes before compound 1 (1.20 g, 2.62 mmol) was added. The mixture was allowed to stir at room temperature for 5 days and the precipitate was filtered (vaccum). The filtrate was evaporated and purified on a silica gel column using EtOAc/CHCl\textsubscript{3} (1:4) as the mobile phase to obtain 11 as a brown solid (0.95 g, 66%) mp: 253 - 254 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 10.15 (1H, s), 8.52 (1H, dd), 8.18 (1H, d), 7.82 (1H, m), 7.43 (1H, d), 7.42 (2H, m), 7.15 (1H, d), 7.12 (1H, m), 6.42 (2H, d), 6.39 (2H, dd), 6.38 (2H, d), 3.30 (8H, q), 2.14 (3H, s), 1.12 (12H, t). \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 208.5, 166.0, 156.8, 154.7, 153.9, 148.9, 148.4, 143.8, 132.5, 130.1, 128.1, 123.9, 123.0, 108.2, 108.0, 106.6, 104.5, 98.0, 65.9, 49.1, 44.4, 40.5, 39.2, 34.0, 31.0, 25.7, 25.0, 12.6. ESI-MS Calcd for C\textsubscript{39}H\textsubscript{39}N\textsubscript{5}O\textsubscript{3} m/z [M]+ 625.31. Found: 626.35 [M + H]+.

**Synthesis of Compound 12:** A Solution of compound 11 (0.26 g, 0.41 mmol) in dioxane (30 mL) was heated to 70 C and SeO\textsubscript{2} (92 mg, 0.82 mmol) was added. The reaction mixture was allowed to heat at 80 °C for 12 hrs. The mixture was allowed to cool to room temperature, and evaporated. The crude product was purified on a silica gel column using EtOAc/Hexane (2:1) as
the mobile phase to generate compound 12 as a pink solid (0.15 g, 44%). mp: 242 - 243 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.14 (1 H, s), 8.13 (1 H, d), 8.11 (1 H, d), 7.61 (1 H, t), 7.45 (2 H, m), 7.20 (1 H, d), 6.71 (2 H, d), 6.69 (2 H, d), 6.51 (2 H, d), 3.24 (8 H, m), 1.14 (12 H, t). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 170.0, 156.9, 153.4, 152.9, 149.6, 143.2, 134.4, 129.2, 129.0, 124.8, 124.3, 108.1, 106.6, 106.0, 98.0, 97.6, 67.1, 49.1, 44.5, 44.4, 40.5, 39.8, 34.0, 25.7, 25.0, 12.6. ESI-MS Calcd for C\(_{39}\)H\(_{37}\)N\(_5\)O\(_4\) m/z [M]+ 639.28. Found: 640.08 [M + H]+

Synthesis of Compound 13: Compound 12 (0.10 g, 0.15 mmol) was dissolved in 20 mL of ethanol. The reaction mixture was allowed to stir at room temp for 5 mins. NaBH\(_4\) (6 mg, 0.15 mmol) was added and the mixture stirred at room temperature for 5 hours. The solution was evaporated to dryness, dissolved in chloroform (25 ml) and extracted with water. The organic layer was separated, dried over MgSO\(_4\) and evaporated to dryness. The crude product was purified on a silica gel column using EtoAC/Hexane (1:1) as the mobile phase, recrystallized with Ethanol to obtain 13 as a white solid (73 mg, 49%) mp: 238 - 239 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.21 (1 H, d), 8.01 (1 H, d), 7.65 (1 H, d), 7.70 (1 H, d), 7.40 (1 H, d), 7.21 (3 H, m), 6.52 (2 H, d), 6.49, (2 H, dd), 6.25 (2 H, d), 4.14 (2 H, s), 3.34 (8 H, q), 2.99 (1 H, Br s), 1.08 (12 H, t). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 156.2, 155.0, 153.0, 152.1, 149.5, 149.3, 147.3, 134.0, 131.2, 129.0, 128.1, 113.0, 108.0, 107.6, 106.5, 98.5, 97.6, 49.2, 44.5, 44.3, 37.5, 39.5, 34.0, 25.6, 25.0, 12.7, 12.6. ESI-MS Calcd for C\(_{39}\)H\(_{30}\)N\(_5\)O\(_4\) m/z [M]+ 641.30: Found: 642.07 [M+H]+

2.11 Results and Discussion

2.11.1 Synthesis

Derivatives of rhodamine B was carried out with an electron rich pyran moiety. (Scheme 2.2). We attempted to attach different substituent groups on the pyran ring to study the effects of
these on the electronic and molecular sensitivity of the sensor towards toxic heavy metals. We expected to achieve selectivity and sensitivity of certain metal ions by bonding through the carbonyl Oxygen, and the amino group. One of the main sensors in this study, compound 5 was synthesized in a moderate yield of 60%. Compound 5 was synthesized from a one-step route that involved coupling compound 4 using sodium borohydride in ethanol. The reaction mixture was allowed to stir for a 5 hr period at room temperature to generate the alcohol substituent. Chemosensors 5,9 and 13 were synthesized by applying a Schiff-base condensation technique between the amine containing compounds 4,8,12 and the corresponding aldehyde in ethanol. Compounds 2, 6 and 10 with substituents at the ortho, meta, and para positions were obtained in moderate to high yields after a solution of 1.0 equivalent of the amine in 1.5N HCl reacted with 1.2 equivalents of crotonaldehyde to form a red solution. Compound 1 was reacted with the corresponding methylquinoline carboxylic acids in the presence of DCC and DMAP in methylene chloride to produce compounds 3, 7 and 11 in good yields. The 2-methyl group in the quinoline ring was then oxidized to generate the aldehyde group in the presence of SeO₂ and then the aldehyde was reduced back to the alcohol group with NaBH₄. There are four coordination sites that can potentially coordinate to Compound 5 with specific metal ions such as Cr³⁺. All the structures were characterized using ¹H NMR, ¹³C NMR, mass spectrometry, and infrared spectroscopy.

### 2.11.2 Association Constants

Association constants were calculated using the Benesi-Hildebrand equation.

\[
\frac{1}{A-A_0} = \frac{1}{K(A_{\text{max}}-A_0)}[M^{x+}]_0 + (A_{\text{max}}-A_0)
\]

where \( A_0 \) is the absorbance of 5 without analyte, \( A \) is the absorbance of 5 with the analyte and \( A_{\text{max}} \) is the absorbance with \( [M^{x+}]_0 \) max.
All spectroscopic studies were performed in CDCl$_3$, CHCl$_3$, CH$_3$CN and DMSO. Synthesized compounds were stable for a prolong time duration. In general, Rhodamine-based compounds are protonated in an acidic environment and emit a strong fluorescence. The colorless solutions showed weak fluorescence and no absorption peaks above 450 nm, which is a strong characteristic of the ring-closed spirolactam form.

2.11.3 Solution Preparation for UV Absorption and Emission Studies

Chemosensor stock solutions of the metal ions were prepared using chlorides and nitrate salt complexes in acetonitrile. The chloride salts used were CuCl$_2$.2H$_2$O CoCl$_2$.2H$_2$O CaCl$_2$.2H$_2$O FeCl$_2$. CdCl$_2$.FeCl$_3$ while the nitrates used were NaNO$_3$, KNO$_3$, Zn(NO$_3$)$_2$.6H$_2$O, Cr(NO$_3$)$_3$.9H$_2$O, Mg(NO$_3$)$_2$, 6H$_2$O, Pb(NO$_3$)$_2$. Ni(NO$_3$)$_2$.6H$_2$O, Na$_2$HAsO$_4$.7H$_2$O and Hg (OAC)$_2$ were also prepared. Fluorescence and UV absorption studies were performed using a 20 µM solution of the compound with appropriate amounts of the analytes. Once the solutions were prepared, they were allowed to sit for 10 minutes before fluorescence measurements took place. The fluorescence analysis was performed based on a 510 nm excitation, while the emission and excitation slit width were at 2 nm. A change in the fluorescence intensity was observed for compound 5 (20 µM) after the addition of acetonitrile. It showed a relatively high sensitivity and selectivity towards Cr$^{3+}$ (Figure 2.7). Also, an immediate color change from clear to pink was observed which also indicated that the sensor could also be used as a “naked eye” chemosensor. An increase in fluorescence intensity was observed after a continued addition of Cr$^{3+}$ to a point of saturation.

2.11.4 Detection of Ni$^{2+}$ and Cr$^{3+}$

We have designed and synthesized new sensors based on rhodamine-B bearing a 2-methanol quinoline moiety (5), coupled through an amide linkage shown in Scheme 2.2.
Fluorescence probe 5 forms a colorless solution in acetonitrile that shows a very weak fluorescence at 580 nm upon excitation at 510 nm. This is indicative of trace amounts of the ring-open form among the predominantly non-fluorescent ring-closed spirolactam. The fluorescence intensity changes of 5 (20 μM) upon addition of the metal ions (20 μM) in acetonitrile showed a sensitivity and selectivity towards Cr$^{3+}$ (Figure 2.9). The observed fluorescence enhancement at 580 nm ($\lambda_{ex} = 510$ nm) was over 1100-fold, which is remarkably high when compared to the other metals (Figure 2.16). This high fluorescence enhancement is credited to the formation of the ring-open spirolactam in the presence of Cr$^{3+}$. The fluorescence enhancement is also associated with a strong color change from colorless to pink which has the advantage of allowing “naked-eye” detection of Cr$^{3+}$. A high sensitivity and selectivity of any metal ion will make a good sensor. To demonstrate the selectivity of the sensor system, compounds were tested with metal ions including Na$^+$, K$^+$, Fe$^{3+}$, Fe$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, and Hg$^{2+}$.
Figure 2.9. Fluorescence spectra of compound 5 (20 μM) with Na⁺, K⁺, Fe³⁺, Fe²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺, Hg²⁺ (20 μM) in CH₃CN (λₑₓ = 510 nm)

The results showed no major fluorescence enhancement for most of the tested metal ions. But Cr³⁺ which showed the greatest enhancement while Zn²⁺ (54 fold) and Fe³⁺ (40 fold) were the only two other metals that showed minor fluorescence enhancement.

The emission spectra for 5 above (highly selective for Cr³⁺) are quite different to the absorption spectra which are selective for Ni²⁺. Even though compound 5 showed no significant fluorescent enhancement with Ni²⁺, the addition of one equivalent of Ni²⁺ to solution 5 (20 μM) produced a dramatic absorption enhancement with a new absorption band at 560 nm (ε = 4.1 x 10⁴ M⁻¹ cm⁻¹) (Figure 2.17). The linearity of the graph I/I₀ vs 1/[Ni²⁺] confirms the 1:1 binding between 5 and Ni²⁺ while the association constant was found to be 4.25 x 10⁵ M⁻¹ (Figure 2.10). The absorption data were used to calculate the binding constant for 5 with Cr³⁺.
(Figure 2.17) and it could be compared with the value for Ni\(^{2+}\). The graph shown in Figure 2.10 \(I/A-A_0\) vs \(1/[Ni^{2+}]\) is a linear relationship which confirms the 1:1 binding stoichiometry with a binding constant of \(3.47 \times 10^4\) M\(^{-1}\). The absorption enhancement was found to be high (183 fold) compared to other metals.

![Graph showing binding constants](image)

**Figure 2.10.** Binding constants of 5 \(I/A-A_0\) vs \(1/[Ni^{2+}]\)

There was also an immediate change from colorless to pink. On the other hand, Co\(^{2+}\) and Cr\(^{3+}\) showed the next highest enhancement at 56 and 55 respectively. The absorption spectra of 5 with a continuous addition of Ni\(^{2+}\) showed a continuous increase in the absorption at 560 nm (Figure 2.12). Apart from detecting Cr\(^{3+}\) through fluorescence change, 5 can also be used as an independent Ni\(^{2+}\) sensor as a result of a strong absorption enhancement.

The job’s plot (Figure 2.11) indicated a 1:1 binding stoichiometry between the sensor 5 and Cr\(^{3+}\) with an association constant of \(2.0 \times 10^4\) M\(^{-1}\).
Figure 2.11. Job’s plot of 5 (10 μM) with Cr$^{3+}$ (10 μM) in CH$_3$CN

Figure 2.12. UV-Vis spectra of compound 5 (20 μM) with metal ions (20 μM) in CH$_3$CN

A photograph of 5 (20 μM) with 1 μM of the metal ions shows a color development with Ni$^{2+}$, while other metals showed no color change (Figure 2.13). This makes sensor 5 extremely
sensitive and selective for Ni$^{2+}$ (detection limit: 0.3 $\mu$M) that could qualify it as possibly being the first rhodamine-based Ni$^{2+}$ sensor.

![Figure 2.13](image)

**Figure 2.13.** Photograph of 5 (20 $\mu$M) with (1 $\mu$M) metal ions (From left to right: 5, free, Ni$^{2+}$, Na$^+$, K$^+$, Cr$^{3+}$, Fe$^{2+}$, Fe$^{3+}$, Co$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Hg$^{2+}$)

The fluorescence properties of 3 were also tested with solutions of acetonitrile dissolved metal ions in order to investigate the structural needs of sensors in detecting metal ions. Compound 3 also formed a colorless solution in acetonitrile which is weakly fluorescent upon excitation at 510 nm. The fluorescence profiles were very similar when compared to those of sensor 5: once again, Cr$^{3+}$ registered the highest fluorescence enhancement while other metals showed no significant enhancement (Figure 2.14). Since sensors 3 and 5 are very selective and sensitive for Cr$^{3+}$, the hydroxyl functionality on the quinoline ring is not important in Cr$^{3+}$ binding.
Figure 2.14. Fluorescence spectra of compound 3 (20 μM) with metal ions (20 μM) in CH$_3$CN ($\lambda_{\text{ex}} = 510$ nm)

However, the absorbance showed an interesting trend, the addition of one equivalent of Ni$^{2+}$ did not give any absorption enhancement which is completely opposite of what is observed with 5. This behavior can be attributed to the structural changes between 3 and 5, which is the oxidation of the methyl group on the quinoline ring of 3 to –CH$_2$OH (Scheme 2.2) in 5. Both Cr$^{3+}$ and Cu$^{2+}$ showed an immediate color change with 3. Even though both Cr$^{3+}$ and Cu$^{2+}$ gave color changes with 3, they are easily identified separately via the large fluorescence enhancement with Cr$^{3+}$ (Figure 2.14).

2.11.5 Detection of CN

A stock solution of compound 5 (4 x 10$^{-4}$ M) was prepared in CH$_3$CN. Free 5 formed a colorless non-visible solution in CH$_3$CN. Since the 5-Cr$^{3+}$ complex is highly fluorescent, we
decided to choose it as the optimal cyanide detector, via the metal displacement approach method. Cyanide complexes strongly with \( \text{Cr}^{3+} \). Figure 2.15 shows the addition of 20 µM of anions \( \text{CN}, \text{Cl}, \text{Br}, \text{I}, \text{CH}_3\text{COO}, \) and \( \text{SO}_4^{2-} \) to \(5\)-\(\text{Cr}^{3+}\) (1:1) \(\text{CN}\) alone quenches the fluorescence with a very slight effect for acetate, indicating high selectivity for \(\text{CN}\). Gradual addition of \(\text{CN}\) results in a continuous decrease in the emission intensity at 580 nm (Figure 2.20). The system is highly sensitive for \(\text{CN}\) as the addition of 20 µM of \(\text{CN}\) quenches the \(5\)-\(\text{Cr}^{3+}\) complex (Figure 2.18). Based on the fluorescence data, the detection limit of \(5\)-\(\text{Cr}^{3+}\) for \(\text{CN}^-\) was calculated at 5.4 µM. Also, the color change from pink to colorless allows for a naked eye identification of \(\text{CN}\). The addition of 20 µM of \(\text{CN}\) did not show any significant absorption change with the non-fluorescent \(5\)-\(\text{Ni}^{2+}\) complex.

![Fluorescence spectra of compound 5-Cr\(^{3+}\) (1:1) with CN\(^-\), Cl\(^-\), Br\(^-\), I\(^-\), SO\(_4^{2-}\), Acetate (20 µM) (λ\(_{ex}\) = 510 nm)\(^{20}\)](image)

**Figure 2.15.** Fluorescence spectra of compound \(5\)-\(\text{Cr}^{3+}\) (1:1) with \(\text{CN}^-\), \(\text{Cl}^-\), \(\text{Br}^-\), \(\text{I}^-\), \(\text{SO}_4^{2-}\), Acetate (20 µM) (λ\(_{ex}\) = 510 nm)\(^{20}\)
Figure 2.16. Bar graph illustrating fluorescence enhancement of 5 (20 μM) at 580 nm (λ_{ex} = 510 nm) with metals (20 μM)

Figure 2.17. Fluorescence spectra of 5 (20 μM) with Cr^{3+} (0-36 μM) in CH₃CN (λ_{ex} = 510 nm)
However, the absorption spectra revealed a different orientation. After the addition of 1 equivalent of Ni$^{2+}$ to compound 5 (20 μM), a new peak was observed at 560 nm. The enhancement was quite high with Ni$^2$ when compared to other metals (Figure 2.12). There was also a change in color observation as it changed from colorless to pink. The absorption spectra of 5 were noted with a continuous addition of Ni$^{2+}$ which showed an increase in the absorption band at 560 nm (Figure 2.18). Cr$^{3+}$ and Ni$^{2+}$ both have intense fluorescence selectivity and sensitivity and can be very well used as rhodamine-based sensors.

**Scheme 2.5.** Proposed binding mechanism of 5 with Ni$^{2+}$

**Figure 2.18.** UV-Vis spectra of compound 5 (20 μM) with Ni$^{2+}$ in CH$_3$CN
The System is highly sensitive for CN as the addition of 20 μM of CN essentially removes all the Cr\textsuperscript{3+} bounded to 5 as shown in (Figure 2.19). Clearly one can observe a striking color change from pink to colorless indicating a optimal cyanide detector.

**Figure 2.19.** Compound 5 (20 μM), free (left), with (20 μM) Cr\textsuperscript{3+} (middle), with (20 μM) Cr\textsuperscript{3+} and CN (right).

Gradual addition addition of CN results in a continuous decrease in the emission intensity at 580 nm (Figure 2.20).

**Figure 2.20.** Fluorescence spectra of 5-Cr\textsuperscript{3+} (1:1) with consecutive addition of CN\textsuperscript{-} (λ\textsubscript{ex} = 510 nm).
The fluorescence properties of compound 9 were also tested with other metal ions in acetonitrile to explore the structural needs of sensors in detecting metal ions. Figure 2.21 showed that Compound 9 was sensitive to cadmium but not selective to any of the other metals that were tested. However, the absorption properties showed sensitivity to chromium but there were no selectivity of any of the other metals (Figure 2.22). The emission properties of compound 13 showed sensitivity towards magnesium but there were no selectivity for the other metal ions (Figure 2.23). On the other the absorption properties were neither sensitive nor selective to all the metals that were tested. (Figure 2.24).

Figure 2.21. Fluorescence spectra of compound 9 (20 µM) with metal ions (20 µM) in CH$_3$CN ($\lambda_{ex} = 510$ nm)
Figure 2.22. UV-Vis spectra of compound 9 (20 µM) with metal ions in CH$_3$CN

Figure 2.23. Fluorescence spectra of compound 13 (20 µM) with metal ions (20 µM) in CH$_3$CN ($\lambda_{ex} = 510$ nm)
Figure 2.24. UV-Vis spectra of compound 13 (20 μM) with metal ions in CH₃CN

2.11.6 ¹H NMR Study

Compounds 3 and 5 showed approximately equal fluorescence enhancements with Cr³⁺ indicating the unimportance of the quinoline hydroxyl group in Cr³⁺ binding. Compound 5 on the other hand, showed a much higher affinity towards Ni²⁺ indicating the importance of the hydroxyl in Ni²⁺ binding. Binding of Ni²⁺ with 5 was studied using ¹H NMR (Figure 2.25) in a mixture of CD₃CN and CDCl₃ due to the limited solubility of 5 in CD₃CN at higher concentrations.
Figure 2.25. $^1$H NMR titration of 5 with Ni$^{2+}$ in CD$_3$CN/CDCl$_3$ (0,1,2,3,4 equiv from bottom to top)

After the addition of 1 equivalent of the Ni$^{2+}$ ion the hydroxyl proton at $\delta$ 3.05 disappeared which indicated that the OH group was involved in the binding with Ni$^{2+}$. There was also a peak broadening at $\delta$ 8.06, 7.76 and 7.43 which corresponded to H$_b$, H$_c$, and H$_a$ respectively. Once the addition of 4 equivalents Ni$^{2+}$ was employed, the triplet signal at $\delta$ 7.35 corresponding to H$_4$ was also broadened. (Figure 2.25). This was probably due to the nitrogen ring binding to the Ni$^{2+}$. More additions of the Ni$^{2+}$ resulted in the decrease of the intensities and broadening of the xanthene protons at $\delta$ 6.63 (H$_h$), 6.20 (H$_g$), and 6.07 (H$_f$) based on the formation of the high fluorescent ring-open form (Scheme 2.5). Ni$^{2+}$ can form a strong diamagnetic planar or paramagnetic tetrahedral, five-coordinated or octahedral complex with four donor atoms from 5 participating in the complexation. The planar binding geometry is ruled out, while tetrahedral is made unlikely by the donor atom configuration in the coordinating pocket of 5. In addition, with the set of N and O donor atoms, the metal is expected to seek
future donor atoms to octahedral or 5-coordinate geometry. The rest of the coordination sites would be occupied by nitrates or solvent molecules. Octahedral complexes of Ni$^{2+}$ are paramagnetic. This explains the extremely low fluorescence enhancement for the 5-Ni$^{2+}$ complex.

### 2.11.7 Fluorescence Sensing: Two Photon Excitation

Two photon excitation measurements were carried out with an excitation at 800 nm for sensor compounds 5, 9 and 13. Two-photon excitation of compound 5 showed an increase in emission and sensitivity for Cr$^{3+}$ (Figure 2.26). However compounds 9 and 13 showed sensitivity for zinc and cobalt respectively (Figures 2.27, 2.28). Two-photon cross section measurements have shown an inter-rhodamine interaction in the presence of metal ions and cross section enhancement.

![Figure 2.26. 2-Photon excitation spectra of compound 5 (20 μM) with metal ions in CH$_3$CN](image)
**Figure 2.27.** 2-Photon excitation spectra of compound 9 (20 μM) with metal ions in CH₃CN

**Figure 2.28.** 2-Photon excitation spectra of compound 13 (20 μM) with metal ions in CH₃CN

### 2.12 Conclusion

In conclusion, the application of spirocyclic derivatives of rhodamine dyes are extremely versatile and promising for the fluorescent enhancement structural change of the ring-opening process. Sensor compounds pose as good candidates for a colorimetric detector. Sensor
compounds are reversible with a distinctive color change upon binding and can be used on a solid surface. Schemes 2.1, 2.2, and 2.3 describe the new compounds synthesized in this work. The synthesis of very stable fluorescent chemosensors in CH$_3$CN has been accomplished. Sensors 3 and 5 were the rhodamine-B bearing 2-methyl quinoline and 2-methanol quinoline. These showed high sensitivity and selectivity enhancement towards Cr$^{3+}$. Compound 5 is a selective sensor for both Cr$^{3+}$ and Ni$^{2+}$, it showed sensitivity towards Ni$^{2+}$ which included the hydroxyl group on the quinoline ring and a key part of its structural binding. Both Cr$^{3+}$ and Ni$^{2+}$ showed an instant color change on reaction with 5 but showed different fluorescence properties, which enabled them to be identified separately. While compound 5-Cr$^{3+}$ has fluorescence characteristics, 5-Ni$^{2+}$ complexes are nonfluorescent and usually adopts a tetrahedron or octahedron geometry. Sensor 5 showed a greater absorption enhancement with Ni$^{2+}$ when compared to Cr$^{3+}$ or Co$^{3+}$ and showed fluorescence enhancement for Cr$^{3+}$ but no fluorescence for Ni$^{2+}$ and Co$^{3+}$. It shows that even though sensor 5 can selectively identify Ni$^{2+}$ and Cr$^{3+}$ it is not a sensor for Co$^{3+}$. Compound 3 also gave a color change with Cr$^{3+}$ and Cu$^{2+}$. However, 5-Cu$^{2+}$ did not show any signs of fluorescence activity, which proves that they should be identified separately. The 5-Cr$^{3+}$ complex was also attempted to detect CN through the metal-displacement approach because it showed an excellent selectivity and sensitivity towards CN. Sensors 9 and 13 as potential new sensor were synthesized. Sensor 9 was sensitive to Hg, while sensor 13 was sensitive to Mg. Other metals interfere strongly but were not selective to any of the metals. The sensors form strongly bound complexes with the metal. Therefore, in principle, one should be able to isolate the complex with the metal, in single crystal form. However despite all the attempts, we were unable to grow crystals. It should be noted that no crystal structures of such
complexes have yet been reported; therefore other researchers have not been successful in growing suitable crystals either.

2.13 References

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CHAPTER 3
SINGLE CRYSTAL X-RAY DIFFRACTION

3.1 Background

Since x-ray crystallography is one of the most important techniques used in this work, a more detailed background is given. More recent development in crystallography is discussed. After the background section, some more recent developments in crystallography are discussed. This includes crystallography of variable temperature crystallography\(^1\), and protein crystallography.\(^2\)

In the past few years the achievements of modern crystallography such as protein crystallography have been recognized due to breakthroughs in theoretical and technical advancements especially in terms of technology developments. From the direct and phasing methods to other powerful x-ray sources such as synchrotron radiation (SR); to more efficient and sensitive detectors, the rapid development of protein crystallography has been revolutionized by the invention and applications of DNA technologies such as DNA double helix\(^3\), myoglobin structure\(^4\), hemoglobin\(^5\), and vitamin B structure\(^6\). Protein crystallography not only solves the structures in high resolution and accuracy but also helps in understanding vital life processes including mechanisms of diseases and medicinal discoveries. These developments can produce any protein of interest in substantial amounts with less tedious work. New methods and technologies for automation and high-throughput have enabled for the development of big-scale, high efficiency macromolecular crystallography in areas such as structural genomics (SG)\(^7\), and recently x-ray free-electron laser (XFEL)\(^8\) and its application in protein crystallography. Protein
crystallography continues to show great potential as it continues to change and grow exponentially. Variable temperature crystallography is another modern technique where studies have been conducted by combining thermal analysis with x-ray diffraction analysis. Variable-temperature single x-ray diffraction analysis has been used to characterize complex pharmaceutical solid-state reactions including crystal transformations. This technique is powerful because it permits simultaneous quantification of multiple solid phases. It can also be used to determine the effect of heat generated during compression on the transformation of an analyte.

3.2 Theory

Molecular and electronic structure are important concepts of Chemistry. The theoretical and experimental design can be generated by understanding the connectivity between the atomic and molecular conformations. The fastest and easiest way to determine and solve molecular structures is through x-ray diffraction methods by the theory of statistics, space and light. While diffraction techniques can apply to many other fields, the explanation here will be focused on a single molecule x-ray crystallography technique. On average, it takes one hour to select a good crystal, mount and center the crystal, and approximately one day to run the sample and solve the crystal structure. To solve the structure, different parameters are considered such as intermolecular interactions, bond lengths, bond angles, crystal system space groups and hydrogen bonding which are all performed under one experiment. X-ray structures in addition to other measurements such as magnetic susceptibility techniques, electrochemical properties, reaction rates and many other characteristics all contribute to providing a complete picture of how different molecular structures are formed. The following chapter will illustrate the theory and application of X-ray crystallography as well as projects that were performed. A general
background including comparisons between the molecular and electronic structure and elucidation by magnetic measurements will be discussed in subsequent chapters.

3.3 History of X-ray

As far back as 1895 the properties of x-rays were investigated and a new form of electromagnetic radiation was introduced and described by a world-renowned pioneer in Röntgen. This phenomenon covers a range in wavelength from $10^{-8} - 10^{-10}$ m which rapidly contributed to new applications of x-Ray radiation from biomedical to physical and chemical applications. Since then, the application and properties have exceeded expectations and grown exponentially. August 2013 commemorated the hundredth-year anniversary for the determination of the very first crystal structure. The first x-ray absorption spectroscopy measurements were conducted to show absorption K-edges of Ag and Br in 1913 by a French physicist Louis de Broglie. X-ray scattering primarily provides information about the size and shape of macromolecules but has since transitioned into other techniques including small angle x-ray scattering (SAXS). Scattering of light through diffraction is another X-ray technique where light passes through narrow slits to generate bands that are parallel to one another. X-ray diffraction was originally investigated by von Laue where he conducted experiments based on x-ray spectrum and geometry that produced a pattern of spots. Each of those spots corresponded to a reflection of the x-ray beam of the crystal plane. This led to Bragg’s introduction of 3D x-ray diffraction of a molecular structure where it was experimentally shown that solid NaCl and KCl did not result from individual molecules but were linked to an array of cations and chloride ions. In 1929 Kathaleen Lonsdale used x-ray diffraction methods to prove that six equidistant bonds of benzene ring were symmetrically flat. The molecular structure of vitamin B$_{12}$ and myoglobin was determined by Dorothy Hodgkin in 1954, while Max Perutz and Sir John Cowdery Kendrew
were responsible for the structure determination of approximately 150 amino acids.\textsuperscript{16} With a mass increase in computational speed and power of three or more orders of magnitude, a new generation of routine problem-solving techniques of small molecules can be feasible.

The diffraction pattern and molecular structure determination can be challenging and complex. Although modern technology allows users to avoid an in-depth knowledge of all the steps and protocols needed to grasp and understand the techniques required, this could lead to a lack of general understanding which may result in unsolved structures, poor quality determination and experimental errors. To understand the entire scope of diffraction through a single crystal or crystals, one would have to understand the theory behind X-ray crystallography.

3.4 Diffraction

Electromagnetic radiation or “light” can have a very wide range of wavelengths but has many common properties, such as the ability to undergo diffraction. Xrays are light with a wavelength much shorter than the visible. The diffraction process starts when a beam of light from the source hits an object with a regular pattern that can then send out new beamslets; for visible lights this can be slits cut in a barrier, for the (longer) IR it can conveniently be a regularly spaced grating from which the beamlets reflect; for the (shorter) Xrays it can be regularly individual atoms from which the beamlets are reemitted. Light passes through is reflected/remitted, scatters and spreads into a region where it can constructively or destructively interfere. This phenomenon is known as diffraction. Huygen’s principle best describes diffraction by rationalizing that every point on the remitted wave front can be considered as a source of tiny wavelets which spreads out typically in the forward direction at the speed of the wave.\textsuperscript{17} Therefore, an image pattern or transformation will be formed when a light wave encounters an object and bending of visible light rays. In this diffraction pattern, lighter and
darker image sections are distributed in a specific unique arrangement. The intensity depends on the relative path lengths of the wavelets which usually depends on the scattering angle of the wavelets while the intensity differences result from the constructive and destructive interference that is also caused by the phase relationship of the wavelets obtained at the object. The angular spread of the diffraction pattern usually depends on the ratio of the wavelength (\( \lambda \)) of the radiation used to the very minimum dimension (x), causing scattering of the object. The larger the angular spread of the diffraction pattern, the larger the value of \( \lambda/x \).18

The interference of wave that results in the diffraction pattern is described by Young’s 1801 double slit experiment (Figure 3.1) where a monochromatic light source passes through the slits while diffracting at different angles. The following scheme in Figure 3.1 a, b, and c shows how the individual waves meet at a screen in phase at the constructive and destructive interference point. As the diffraction angle (\( \theta \)) of the waves increases, so does the distance. Therefore, the distance between the travel and screen becomes larger from one wave to the other. Constructive interference is produced when the distance traveled by one wave is equal to \( n\lambda \) where \( n=1,2,3..., \) whereas, if \( \theta \) happens to be at a position where the distance of travel for a single wave is \( 1/2\lambda \), both waves will reach a point where a dark line will be generated from the destructive interference which will be considered out of phase in Figure 3.1c. Where the phase difference is between 0 and \( \frac{1}{2} \), neither constructive nor destructive interference are present. Therefore, the intermediate intensities are observed on the screen. Since diffraction occurs on both sides of the slits, the combined interference between waves of the same slit and scattering at the same angle determines the intensity of the diffraction. The screens are illuminated depending on the distance between the slits. Therefore, if the spacing between the slits is narrow the illuminated region will
become wide. By adding more slits of equal spacing will result in a narrow constructive illumination which ends up with sharp lines.

![Diagram of interference from two slits at different scattering angles](image)

**Figure 3.1.** Interference from two slits at different scattering angles\(^{17}\)

The combination of a 1D grating of a known slit spacing with another 1D grating of a different slit spacing will generate a 2D diffraction pattern that shows reciprocal spacing perpendicular to the original orientation. It is the basic correlation between the orientation and distances in real time, where the atoms exist, where the distances are in reciprocal space and where diffraction pattern exists.

### 3.5 Diffraction Through a 3D Lattice

In 1912, Max von Laue, Friedrich and Knipping discovered that X-rays fired into a crystal of copper sulfate produced a characteristic diffraction pattern.\(^{19}\) Laue described the theory of diffraction based on a 3D arrays of reciprocal lattice, and although it did not seem practical at the time, it should be possible, in principle, to determine the exact arrangement of the atoms in the copper sulfate crystal. Bragg’s equation \((n\lambda = 2d \sin \theta)\) has become one of the most trusted models used to calculate crystal structures. Braggs describes the diffraction pattern in terms of
real space and not in terms of reciprocal lattice as von Laue had originally predicted. In order words, if the atomic planes of atoms extended between points of a crystal lattice, the diffracted beam will be labeled as “reflecting” off the atomic planes so that the angle of incidence is equal to that of the angle of reflection. Constructive interference occurs when waves from the adjacent parallel planes are scattered to yield an integral multiple wavelength of radiation (Figure 3.2). This relationship can be explained by the equation \( n\lambda = 2d \sin \theta \), where \( n \) is an integer, \( \lambda \) is the wavelength of radiation, \( d \) is the perpendicular distance between adjacent planes, while \( \theta \) is the angle of scatter complement. \( 2\theta \) is the scattering angle that is between the radiation and incident beam.

![Figure 3.2](image)

**Figure 3.2.** Constructive interference of adjacent parallel planes

### 3.6 Intensities

By adding adjacent slits to sharpen the diffraction maxima lines in one dimension while combining two of the 1D gratings, the diffraction maxima become sharpened in two dimensions to generate circles. These defined spheres in reciprocal spaces are determined based on the uniformly stacked adjacent gratings in three dimensions. These spheres are referred to as
“reflections” within the confines of the X-rays and demonstrate specific intensities and positions. In the case of constructive interference, where the location depends on the distance between slits, the angular position depends on the dimensions of the repeated lattice. Each diffraction sphere has an intensity that is based on the types of atoms and their arrangements within the unit cell.

As each individual electron interacts with the electromagnetic radiation, the scattered waves from an atom in the direction of the beam scatters in phase. This scattering leads to the sum of their amplitude, which contributes to the intensity of the diffraction of the atom. The scattering of the total electrons of an atom is referred to as the atomic scattering factor, f, which is proportional to the number of electrons retained by the atom. Scattering from different angles of each electron combines with different phases and partially destructively interfere which causes a decrease in the scattering intensity with increasing angle, 2θ. When waves diffract from electrons in an atom, the difference in magnitude will be proportional therefore, causing greater interference if the radiation has a shorter wavelength. The atomic scattering factor is relatively common. It is relative to the diffraction angle and wavelength, \( \sin \theta / \lambda \). (Figure 3.3).

![Figure 3.3](image_url)  

Figure 3.3. Atomic scattering factors, f, for ions or atoms vs \( \sin \theta / \lambda \).
The Atomic scattering factor of an atom in Figure 3.3 is equal to the ratio of the amplitude of a wave scattered by the atom to that of a wave scattered by a single electron. The scattering factor provides a measure of the scatter caused by each atom that coincides with the scattering within the entire structure and unit cell. It can be approximated by summing up the independent scattering contributions of the constituent atoms and knowing that scattering waves both have phase and amplitude. An atom, j, of a scattered wave can be expressed as

\[ F_j = F_j (\cos \alpha_j + i \sin \alpha_j) \]  

where \( f_j \) is the atomic scattering factor or amplitude and \( \alpha_j \) is the phase. There will be a difference in phase when adding the scattering from different atoms. The difference in phase depends on the fractional coordinates \( (x,y,z) \) of the atom within the unit cell together with the indices of reflection \( (h,k,l) \) which is expressed in the equation

\[ \alpha = 2\pi(hx + ky + Iz) \]  

By combining both equations and summing up the overall atoms in the unit cell one would generate the equation

\[ F_{hkl} = \sum_j f_j \left[ \cos 2\pi(hx_j + ky_j + Iz_j) + i \sin 2\pi(hx_j + ky_j + Iz_j) \right] \]  

where \( F_{hkl} \) is called the structure factor, whose amplitude square is directly proportional to the intensity of the diffracted beam.

\[ |F_{hkl}|^2 \propto I_{hkl} \]  

It is quite important to understand that every atom in the unit cell all contribute to the entire structure factor, \( F_{hkl} \), in regards to its position in the unit cell and identity. Each reflection can be described mathematically by the structure factor equation describing the diffracted wave light from the crystal lattice.
3.7. Phase Problems

The ultimate goal of any crystallography experiment is to determine the atom positions of the x,y,z within the unit cell. The structure factor in equation (3.1.3) which contains both a phase and magnitude typically provides a method for calculating x,y,z for any reflection of a certain h,k,l value. The downside is that the X-ray diffraction technique only allows a direct intensity measurement, which enables the user to manipulate the amplitude but not the sign (+ or −) from the structure factor, \( F_{hkl} \). As a result, one will run into a “phase problem,” which in crystallography terms simply means that the phase information needed to solve the structure factor equation is lost.

In theory, if the phases existed, calculation of the atomic positions is conducted by a mathematical operation that is based on a Fourier transform. The Fourier transform theorem can be referred to any function of a continuous single-valued frequency domain of a series of sinusoidal curves.\(^{23}\) This mathematical operation can be related to the structure factor equation (equation 3.1.3) in addition to the electron density equation illustrated below.

\[
\rho_{x,y,z} = \frac{1}{V} \sum_{hkl} F_{hkl} \exp \left[ -i2\pi(hx + ky + Iz) \right]
\]

where \( \rho_{x,y,z} \) is the electron density at any position \((x,y,z)\) in the unit cell, \( V \) represents the volume of the unit cell and the sum of the equation is over all the values of h,k, and l. The structure of the unit cell contents can be geometrically constructed by placing atoms in areas that contain the highest electron density.

3.8 Patterson Methods

To produce the phase of different waves, it will be advantageous to investigate the phase problems in different ways. The Patterson method was initially introduced in 1935 and became
an effective method used between the 1930s and 60s. The Patterson function, \( P(u,v,w) \) mainly consists of a Fourier series which only depends on the indices, \((h,k,l)\) while the \( |F|^2 \) values are within the confines of the diffracted beam.

\[
P( u,v,w ) = \frac{1}{v} \sum_{hkl} |F|^2 \cos 2\pi (hu + kv + lw) \tag{3.1.6}
\]

\( u,v,w \) is usually represented as a coordinate system which is also referred to as the Patterson space or vector map that is related to the electron density. It is also the size and shape of a unit cell. Whenever a separation by a vector \((u,v,w)\) occurs between two atoms in the unit cell, a peak in the Patterson map at \((u,v,w)\) will be observed. Every peak in the Patterson map corresponds to both the orientation and length between two atoms in a vector. The vector peak heights are proportional to the product of the atomic numbers of the atom which occurs at the end of the vector. Since the origin of the vector can be located anywhere, it makes interpretation of the Patterson vector rather complicated unless there is a peak of unusual height at \( u,v,w \) which coincides with many pairs of atoms with high atomic numbers. The positions at the largest peak correspond to the heaviest atom and could potentially represent a starting point for determination of other atoms by further investigation of other Fourier methods or the Patterson map. In general, the Patterson method can be used to solve phase problems by performing a Fourier synthesis of the structure factor equation without the phases. \(^{21}\)

### 3.9 Direct Methods

As technology continued to improve in the late 1960s, the Direct method was introduced for determining the phases of the reflection. Although it is important to understand that the electron density must have a nonnegative value throughout the unit cell and must acquire spherical peaks, however, there are also limits to the phase angles for individual reflections. In
the crystallographic community, there are relationships such as the Sayre probability relationship which states that for any three reflections in a centrosymmetric structure, the sign in one phase has to attain the product of signs of two other phases. The relationship between the three reflections can be described in such a way that \( h,k,l \) and \( h',k',l' \) are related to \( h'',k'',l'' \) by their difference, \( h'' = h' - h'', k'' = k' - k'' \) and \( l'' = l' - l'' \). Also, by introducing a normalized structure factor, \( E \), and assuming that atoms have no thermal motion from diffraction, a distribution of \( E \)-values can well be generated.

\[
E^2 = \frac{|F|^2}{\langle |F|^2 \rangle}
\]

(3.1.7)

where \( \langle |F|^2 \rangle \) is the average structure factor magnitude in a shell of \( (\sin \theta)/\lambda \). The \( E \)-value distribution is dependent on the absence or presence of the center of symmetry. The \( E \)-value distribution is also used to determine the quality of the data in such a way that if the average \( |E^2 - 1| \) value is close to a certain figure such as 0.678 the structure will become non-centrosymmetric. On the other hand, if it is close to 0.858, the structure will become centrosymmetric. Other methods are also used to determine and optimize the phases of the reflections to generate the \( E \)-maps where the atomic positions can be determined.

3.10 Symmetry

So far, the basic knowledge and understanding of diffraction have been used to describe how the types and positions of atoms in the unit cell affect the phases and intensities of the diffracted radiation. The measured intensities and estimated phases are used to generate a 3D map of the structure. However, a property of crystals in real space that affects the diffraction pattern in reciprocal space which is the symmetry of the crystal.
3.11 Conclusion

X-ray crystallography of single crystals has become one of the most valuable and unique techniques in many research areas. By combining the fundamental theories and applications, a complete understanding of the molecular and geometric characteristics of molecules is better understood. Structural characterization by X-ray diffraction as well as optical detection of ions is also of great interest for environmental as well as biological detection. The process of selecting a good crystal to a diffraction pattern and finally molecular structures can be tedious. Failure to understand basic knowledge of the selecting process may lead to unsolved structures, poor quality determinations and errors. Therefore, a complete understanding of the theory of x-ray crystallography should start with a firm grasp of diffraction, specifically diffraction through crystals.

X-ray radiation is unique for analyzing the structures of different molecules due to its wavelength being of equal size to the distance between atoms. The diffraction pattern is analyzed where the measured intensities of the reflection provide information regarding the electron density in each crystal plane that satisfies the diffraction condition, \( n\lambda = 2d \sin \theta \).

3.12 References


23. Lake, C.; Craven, B.M. *Small Molecule Crystallography*. **2003**.
CHAPTER 4
CRYSTAL AND MOLECULAR STRUCTURE OF NEW METALLACARBORANES

4.1 Lattice Types and Unit Cell

A crystal can be defined as a microscopic arrangement of homogeneous atoms with a three dimensional long-range internal order. A unit cell is defined as the smallest building block of a crystal consisting of atoms, ion or molecules whose repetition at regular intervals creates a three dimensional form of a crystal lattice with lengths of a, b, c and angles α, β, γ as depicted in Figure 4.1.

<table>
<thead>
<tr>
<th>Crystal System</th>
<th>Restrictions on axes and angles</th>
<th>Bravais Lattice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triclinic</td>
<td>None</td>
<td><img src="image" alt="Triclinic" /></td>
</tr>
<tr>
<td>Monoclinic</td>
<td>α = γ = 90°</td>
<td><img src="image" alt="Monoclinic" /></td>
</tr>
<tr>
<td>Orthorhombic</td>
<td>α = β = γ = 90°</td>
<td><img src="image" alt="Orthorhombic" /></td>
</tr>
<tr>
<td>Tetragonal</td>
<td>a = b, α = β = γ = 90°</td>
<td><img src="image" alt="Tetragonal" /></td>
</tr>
<tr>
<td>Trigonal</td>
<td>a = b = c, α = β = γ or α = b</td>
<td><img src="image" alt="Trigonal" /></td>
</tr>
<tr>
<td></td>
<td>a = β = 90°, γ = 120°</td>
<td></td>
</tr>
<tr>
<td>Hexagonal</td>
<td>a = b, α = β = 90°, γ = 120°</td>
<td><img src="image" alt="Hexagonal" /></td>
</tr>
<tr>
<td>Cubic</td>
<td>a = b = c, α = β = γ = 90°</td>
<td><img src="image" alt="Cubic" /></td>
</tr>
</tbody>
</table>

**Figure 4.1.** Unit cell, crystal and lattice are represented with symbols\(^1\)
There is more than one choice of Bravais lattice or “parallelepiped” that are available for most crystal systems. The unit cell chosen typically represents the translational and rotational symmetry of the entire crystal structure with the smallest length and bond angles close to 90°. The unit cell morphology is grouped into seven categories known as the crystal system and they depend on their rotational symmetry (Figure 4.1). Dating back to the mid-1800’s, Bravais and Frankenheimer systematically proved that by centering the unit cell in such a way that an additional lattice point is in the body center, face center, or at the edge-center of the unit cell, the unit cell may incorporate more of the crystal symmetry compared to the primitive or one lattice point unit cell. By combining all seven crystal systems, and four lattice types, the Bravais lattices shown in Figure 4.1 are produced. It is imperative to understand that the lattice coordinate system is a series of imaginary points that is used to describe the symmetry of the atom structure that comprises the crystal. By combining the Bravais lattices with the translational symmetry, only 230 possible arrangements are generated in order to pack atoms in the regular repeating pattern found in crystalline solids. The 230 arrangements or crystallographic space groups can be found in the International Tables of Crystallography.¹

4.2 Point and Space Groups

The perception of symmetry has been studied and understood by scientists. In order words, if an object can be rotated, reflected or turned inside and out without altering any unique characteristics, it retains symmetry. The symmetry elements usually consist of rotation around the axes, the plane of an object that is being reflected, and the center point where the object is inverted. The symmetry operation is the action of the symmetry element that leaves an object looking the same after it has been carried out. For example, the operation of rotation, reflection and inversion are all point-symmetry operations because they all leave a point within the object
stationary. Rotation axes are determined by an integer, \( n \), in such a way that when the object is rotated \( 360^\circ/n \), it is unchanged from its starting point. Although an object or molecule may have a local rotation axis of 5, 7, or 8, it has been known that only rotation axes of 1, 2, 3, 4 and 6 are capable for structures built on 3D lattices. Roto-inversion axes are designated by \( n \), where the structure is rotated by \( 360^\circ/n \) but inverted through a point on the axes to generate its original object. Mirror planes, \( m \), are reflected through a plane that is equivalent to a two-fold roto-inversion axis, \( 2 \), that are oriented perpendicular to the plane. Chirality of a molecule will change whenever a mirror plane converts right hands into left hands. Based on the total number of possibilities to combine the rotation axes, 1, 2, 3, 4, 5, 6, and the roto-inversion axes, \( 1, 2, 3, 4, 5, 6 \), there is only a total of 32 three dimensional combinations which are known as the crystallographic point groups.

The overall symmetry operation of a structure and how it relates to other neighboring structures including space symmetry is vital and should to be considered. Since the unit cell is defined by side by side stacking in three dimensions, it not only provides a translation of the entire unit cell along one dimension, but it can also develop other space symmetry operations such as screw axes and glide planes which result from a mirror operation and a translation. A screw axis, \( n_s \), is applied to a combination of a rotation of \( 360^\circ/n \) and a translation that is parallel to the axis, \( 3_1 \), along the b axis that will rotate the structure by \( 120^\circ \) then translate \( 1/3 \) of the unit cell length along axis b. A glide plane will cause a halfway translation along the unit cell edge since mirrors are two-fold, and can also be an a-glide, b-glide or c-glide depending on the parallel axis. By combining all 32 crystallographic point groups and space- symmetry operations, will ultimately lead to 230 different ways of packing objects in three dimensions in such a way that the properties of the unit cell are arranged the same way for the entire solid.
4.3 Systematic Absences

Translational symmetry consists of the lattice centering, screw axes and glide planes in real space and encounters some implications when dealing with the diffraction pattern that is generated in reciprocal space. These translational elements can cause certain reflections that usually satisfy the diffraction conditions \( n\lambda = 2d\sin\theta \) to be absent. It can be caused by the translation symmetry element to produce a plane of atoms where one would not exist in the absence of translational symmetry. The plane of atoms that have the exact same electron density will also have the same structure factor amplitude and therefore cause complete destructive interference for specific sets of planes. For example, for any plane, \( h,k,l \) that is in a C-centered lattice, the reflection where \( h+k=2n+1 \) is present will not be observed in the diffraction pattern. Systemic absences in general, help to classify the diffraction pattern to space group that illustrates the specific combination of translational symmetry elements.\(^1\)

4.4 Symmetry in Both Spaces

The symmetry relation between real and reciprocal spaces usually allows for certain similarities and differences. There is certain symmetry that is present in real space such as the four-fold rotation and mirrors. It transfers as a four-fold mirror symmetry in reciprocal space. Whereas, diffraction patterns are centrosymmetric while translational symmetry does not cause translational symmetry in reciprocal space. The symmetry of the diffraction pattern in reciprocal space is arranged as part of the eleven Laue point groups that is used to determine which part of the diffraction data is unique or redundant.\(^2\)
4.5 Summary

X-ray diffraction is best known for determining and solving crystal structures from simple to complex molecules. The size of the wavelength is proportional to the distance between the atoms in such a way that the repeating arrays of atoms diffract the X-ray into noticeable patterns. The spacing of the reflection within the confines of the diffraction pattern provides a measurement of the unit cell lengths and angles by understanding that any distance, d in real space is 1/d in reciprocal space. By identifying the space group of a crystal will also help in identifying parts of a molecule and simplify the analysis of the diffraction pattern by identifying different sections that are equal. In general, before a space group is determined the symmetry of the diffraction pattern, and the Laue point must be determined. In addition to that, the statistical analysis of the normalized structure factors, \( |E^2 - 1| \) allows for the determination of centrosymmetry of the crystal. As the reflection is found to be symmetrically absent, the lattice and translational symmetry are ascertained which in most cases restrains the space groups to a short list. Again, the diffraction pattern is analyzed where the measured intensities of the reflection provide information about the electron density that is present in each crystal plane which satisfies the diffraction condition, \( n\lambda = 2d\sin \theta \). By combining the space group with the intensities, the estimated phases are determined while producing an electron density map that shows atom positions in real space.

4.6 Practice

Theory and practice are required for the crystallographer to stay up to date with the ever-changing toolbox. While some users may be discouraged, others are encouraged by the tools one generation developed in exchange for the tools of another. Currently, the mathematical and
manual precisions have been revamped by software manipulations techniques while understanding the data analysis and is also applied to X-ray crystallography techniques. However, it is important to note that the process from a diffraction pattern point of view to a complete structure solution will require an in-depth understanding of the theory and practical knowledge to apply them. Without such acquired knowledge, it will be challenging to interpret meaningful data information regardless of the simple or complexity of the sample.

4.7 Sample

There are limits to every technique based on their size, type, stability, chemical and physical properties that are associated with the sample in order to produce meaningful results. Many factors are considered when it comes to crystallography samples due to its specificity, the amount of time the sample run is repeated, and the nature or quality of the single crystal solid being investigated. It is imperative to note that the crystal selected for measurement must be the right size in dimension. Depending on the diameter of the X-ray beam, the size may vary from 0.01 mm in terms of the micro-focus X-ray source to 0.8 mm for a tube source. It is vital for the crystal to remain intact within the beam for the entire duration of the sample collection process in order to guarantee accurate corrections for absorption.

For a single crystal to attain the best possible result, the sample must be free of any potential impurities, cracks, and defects. Although genuine crystals will have some of these characteristics, they can also occur in growth regions that can be tilted. The structured domain of crystals requires real crystals be rotated between 90 and 180 degrees in order for each of the domain to have the opportunity to satisfy the diffraction condition and thereby contribute to the intensity of the reflection. Single crystals usually exhibit birefringence to generate sharp extinction when it is rotated on a microscope. When choosing a crystal, it is important to keep in
mind the representative of the sample from which it was taken, the shape as well as the crystal habit to prevent the possibility of twinning which occurs when part of the crystal is extinguished. Some of the questions that may arise while attempting to run a crystal sample includes if they are homogeneous? This means that if a sample contains platelets, or needle type crystals in the same sample it will most likely contain a mixture of compounds and impurities.

It is quite important to have a stable compound before attempting to run an X-ray diffraction experiment. This stable compound is important because crystals that are volatile often dry out under ambient conditions and in most cases will not remain in the beam long enough for the entire experiment to take place. At higher temperatures some crystals will either melt or sublime while others may react with oxygen from the air or moisture. The optimum method used to solve such problems is accomplished by cooling the sample during the entire course of the measurement. By using this approach, the lower temperature in the nitrogen atmosphere will enable the sample to remain stable and not dissociate or be destroyed. Also, there will be a decrease in the molecular movement of atoms, which results in a better diffraction pattern. The process of growing a crystal can be tedious and sometimes complexed, but the quality and size of a crystal depend on it. When growing a crystal from solution different factors come into play such as lowering the saturation point in a slow manner as well as controlling the rate of nucleation to allow a few large crystals to form. When it comes to growing good crystals, there are various methods and variations in which one can explore. Some of these methods include solvent evaporation, solvent diffusion, slow cooling, and sublimation. The best crystals are formed over a long period of time by controlling the temperature, pH and ionic strength in such a way that the molecules can form.
4.8 Diffractometer

Single crystal X-ray diffraction data collection and analysis were conducted on a Bruker SMART APEX II diffractometer with $K_\alpha$ Mo source ($\lambda = 0.71074$ Å), a graphite monochromator and CCD detector. Crystals were measured under room temperature while the unit cell refinement and integration of the diffraction frames were performed with Bruker. Hydrogens were either placed from the difference map with their positions refined, or placed in calculated positions and isotropically refined using a model. Just like most radiation techniques, the hardware constituents necessary to perform the experiment lies under a source, sample and a detector. When it comes to the source a monochromatic beam of light is chosen for diffraction experiments. It is produced by applying a high-energy electron beam towards a metal target such as Mo, Cu or Ag. The electrons from the sample interact with the electrons of the target at a certain voltage and is able to ionize an inner core electron. By filling the inner hole of the outer electron, it will lead to the energy release of the X-ray wavelength. $K_\alpha$ transition represents the transition from the L-shell to the K-shell. Relaxation from the M-shell to the K-shell is designated as a $K_\beta$ x-ray emission. Some of the other X-rays with lower intensity such as white radiation is emitted as a result of an incomplete energy transfer between the high-energy electron and the metal electrons. The $K_\beta$ wavelength and a great amount of the white radiation are removed either by a monochromator or a filter. The $K_\alpha$ radiation of the sample is the average of two different energy transitions from the s and p subshells and the L shell that are very close in energy to be separated. For example, Mo $K_\alpha 1$ emits a wavelength at 0.70926 Å and Mo $K_\alpha 2$ is at approximately 0.71069 Å.

Before running a crystal sample, the crystal is carefully selected through a microscope and carefully placed at the end of a glass fiber. The selected crystal is attached to the fiber with
an oil, epoxy or glue and mounted onto a sample holder or goniometer. The goniometer is used to rotate the crystal sample to measure the angles between the crystal faces and to obtain a complete diffraction set of data. The center of the goniometer is where you will find the location of the crystal sample. It is also a region where the X-rays are directed from the source. A schematic diagram showing the Eulerian geometry of the goniometer with four degrees of freedom at $\phi, \omega, \chi$ and $2\theta$ is shown in Figure 4.2 where the Cartesian coordinate system $X_1, Y_1, Z_1$ are centered around the four degrees of freedom. The angles of $2\theta$ and $\omega$ are known to be concentric around the $Z_1$ axis while the detector is mounted on a $2\theta$ arm in such a way that the position of the detector is equal to the $2\theta$ value for a diffracted reflection. 

![Goniometer geometry diagram](image)

**Figure 4.2.** Goniometer geometry showing the coordinate axes and the 4 rotational degrees of freedom

The $X_1$ axis is aligned with the source radiation while the $Y_1$ axis and crystal contribute to form the goniometer equatorial plane.
The advancement of X-ray detectors from film method to image plates and scintillation counters to CCD detectors continue to have major impact on most instruments. CCD detectors are beneficial because they combine the automation of scintillation counters with measuring multiple reflections in a 2D image. The first step occurs when the X-ray hits the detector by exciting the phosphorescent material that emits visible photons paired with a CCD chip through fiber optics. The CCD converts the electrical charge into a digital number that is stored. The crystal axes does not have to be aligned with the diffractometer’s axes. The two dimensional images that contains the quantitative data for sets of angles is referred to as a frame. Typically, there are hundreds of frames with thousands reflections that are observed for one structure determination. Therefore, the spatial resolution, detector speed and range play a huge role. The diffraction pattern is accomplished during the experiment while determining the structure based on the application of the theories involved. Figure 4.3 illustrates a typical process that is used.

**Figure 4.3.** Steps for determining crystal structures
The general experimental process can be described in a chronological and practical manner where each step and specifications of the software program is used. Understanding the software program will enable the X-ray user to become proficient in the research that is being carried out.

4.9 Obtaining the Diffraction Pattern

In general, the initial measurements taken are indicative of reciprocal spaces. As soon as the crystal is centered on the diffractometer, a series of diffraction frames are taken by a host software. It is vital that the series are orthogonal and they overlap to get a representative sample of reciprocal space due to the fact that the unit cell dimensions and lattice type are generated from the frames.

During the experiment run, high intensity reflections are located in such a way that the intensity, I, is greater than three times the intensity standard deviation, \( \sigma \). The geometric positions of the reflections are used as defined in the Cartesian lab frame to determine the directions and lengths of the reciprocal lattice vectors. There are three non-coplanar reciprocal lattice vectors which gives rise to reciprocal unit cell vectors of \( a^*, b^*, c^* \). The orientation matrix is then calculated by incorporating a series of matrix manipulations and geometry with the use of computer technology. The orientation matrix is used to convert the reciprocal lattice vectors which is expressed in Cartesian lab space coordinates \((X_1, Y_1, Z_1)\) to reciprocal lattice vectors and expressed in reciprocal space dimensions \((a^*, b^*, c^*)\). The term indexing is used to identify the order, \( n \), of the reflection that distributes \((n\lambda = 2d\sin\theta)\) in all three dimensions which provides the values for \( h, k, l \). The \( h, k, l \) values that is based on a reflection is designated by the position of the reflection relative to the origin of the reciprocal lattice. When it comes to the
indices of reflection and diffractometer angle, the accuracy of the orientation matrix becomes important. Refining the orientation matrix is accomplished based on sets of three indexed, linearly independent reflections that can ultimately determine the orientation matrix and unit cell. The variations in the orientation matrix make it possible for a more accurate value for the matrix. If the unit cell is primitive and consist of the shortest non-planar vectors of the reciprocal lattice, it will lead to a mathematical transformation into only one Bravais lattice type. In most cases, the symmetry inherent of the Bravais lattice is equivalent to that of the metric symmetry of the unit cell. Take for instance a monoclinic unit cell that has a $\beta$ close to $90^0$, a reduced cell will suggest an orthorhombic unit cell. Choosing the wrong unit cell at this stage in the experiment can be avoided if the intensities of diffracted reflections are not considered using Friedel’s law.

Friedel’s law states that the intensity of the diffracted wave from the reflection planes of $h,k,l$ are equal to the planes of $-h, -k, -l$ which are centro-symmetrically related. Both intensities are represented differently in each diffraction pattern which depends on the lattice type. For instance, a triclinic lattice produces four pairs of equivalent reflections; $i_{hkl} = l^h_k l^k_l$ and $l^h_k l^k_l$ = $l^h_-k_-l$ = $l^h_-k_-l$ = $l^h_-k_-l$ = $l^h_-k_-l$.$^{144}$

The metric system of a crystal is usually higher than the Laue symmetry of a diffraction pattern.

So far, the Bravais lattice, the orientation matrix, and unit cell dimensions including errors have all been determined by applying the three orthogonal images. This method has become a standard for the derivation of instrumental conditions that is needed for collection of the diffracted pattern. Different factors such as run time, redundancy, resolution and completeness all play a huge factor when it comes to calculating the collection strategy. The maximum resolution, $d$, for a crystal with high quality where all the reflections are collected has a value of $0.459\lambda$ and calculated from the equation, $d = \lambda = 2d\sin(\theta_{\text{max}})$ where $d$ represents the
distance between the peaks. For Mo the radiation, \( d = 0.33 \, \text{Å} \) can provide resolution where the bonds are in the order of 1-3 \( \text{Å} \). Reflections with the highest resolution usually contain those with high diffraction angles. Reflection data with low reflection angles will ultimately lead to a poor quality crystal in which the diffracted peak will remain unresolved.\(^3\) The quality of the crystal is determined by the minimum resolution and the wavelength is calculated from the number of frames that has been measured. Typically, the minimum resolution that is used to satisfy a crystal structure is 0.84 \( \text{Å} \). The crystal symmetry is used to determine the completeness and redundancy of the diffracted pattern being collected. Ideally, if a crystal structure is more symmetric then the diffraction pattern will also be more symmetric. Therefore, the equivalent reflection will be observed in an area of reciprocal space. When combined with Friedel’s law it causes redundancy especially when the same reflection gets recorded from the same crystal orientation or a different one. To achieve better data or error determination, it is recommended to have a certain degree of redundancy. The diffraction completeness of the pattern is determined if the entire reflections have been collected to solve the structure of the smallest area which is unrelated to the symmetry, or the asymmetric unit. If the Bravais lattice is found to be of high symmetry such as orthorhombic then a smaller fragment of the reciprocal space is needed to determine the overall structure. The desired completeness when running any crystal sample is 100\%, but there are times during the experiments when the completeness is below 100\% but also acceptable. By combining the parameters such as redundancy, resolution completeness and experiment time at optimum levels, the data collecting process will proceed in a timely manner. Advancement in technology has made it possible to collect diffraction images in less than 24 hours compared to days or weeks for similar or better quality data. During the experimental run, if no reflections are observed at high scattering angles then collecting the data at a higher
resolution will be a waste of time. Increasing the redundancy will help improve the accuracy and error of the data but may require the sampling of reciprocal space. When it comes to the structure completeness of a sample there is no compromise for time except for when a sample is unstable. An unstable diffracted crystal will require a longer time exposure to X-rays in order to increase their intensity, while other crystals maybe unstable to the point of decomposition from X-ray exposure. The X-ray data collection strategy is the key to obtaining the highest possible qualities of diffraction data that are determined from different parameters such as wavelength, attenuation, detector-to-crystal distance, exposure time, range, angles and rotations. It also helps when necessary to sample the portion of diffraction space which reflections will be measured first. X-ray data collection is an easy process but the most important steps include, the detector that uses an oscillation method for collecting the frames. Any one frame with an $\omega$-scan, the angle $2\theta$, $\varphi$ and $\chi$ are all fixed while at $0.5^\circ$ the crystal is rotated in the $\omega$ direction. On the other hand, while $2\theta$, $\varphi$ and $\omega$ are fixed, the crystal is rotated about $\varphi$ in a $\varphi$-scan because of the mosaic spread of real crystals (~0.1-0.2°) and also, the beam is not perfectly monochromic. Therefore, the diffraction condition is fulfilled over a small angular range.³

4.10 Analyzing the Diffraction Pattern

A considerable amount of parameters is pertinent with the intensity of the reflections in different patterns. Therefore, it is quite important that the integration of the reflection is accurate. When it comes to the 2D detector, each of the pixel records an intensity with one reflection spanning multiple frames within a range of $\omega$ angles. The intensity should be summed throughout a 3D box and if the box contains one reflection, then the background is resolved from the average pixel intensity located outside the reflection area. There is a linear variation in the
background throughout the box that can be subtracted from each pixel within the box. When it comes to scanning, it takes a finite time to run it and the intensity is normalized to counts per second to record the frame. A broadening of the box method estimates that the profile peak of a subset of reflections that occur in the same area of reciprocal space will be similar but the difference will be by a scale factor. The profile fitting method vastly enhances the quality of the data sets and grants the individual analysis to overlap the reflections as they should exist.

Systemic error has been found to affect the accuracy of diffracting experiments, which normally requires some modification of the measured intensities before the structure is solved. The prevalent corrections for each of the integrated intensities \( I_{hkl} \), are the Lorentz-polarization factor, \( L_{hkl} \), the X-ray absorption factor \( A_{hkl} \), the extinction factor, \( y_{hkl} \) and a scaling factor \( K_{hkl} \) which are expressed in the following equation.

\[
I_{hkl} = L_{hkl} \cdot A_{hkl} \cdot y_{hkl} \cdot K_{hkl} \cdot |F_{hkl}|^2
\]

The Lorentz-polarization factor is essentially a combination of two factors due to their dependence on the scattering angle. When it comes to the Lorentz-polarization factor, the number of photons from a reflection depends on the time of the crystal plane that causes the reflection to remain in the diffraction orientation during a measurement. The time is usually calculated from known constants like the scan rate of the diffractometer but dependent on the location of the reflection, \( \sin 2\theta \). The intensity measured is divided by the time, and is directly dependent on the position in such a way that \( L_{hkl} = 1/(\sin(2\theta_{hkl})) \). When the incident beam is known to be unpolarized, or the monochromator not being utilized, the interaction with the crystal sample will cause the diffracted beam to become either partially or completely polarized with no intensity in each perpendicular direction. The degree of polarization is also a function of
the position in each of the reflection in such a way that the polarization correction takes place
without mediating constants in the XY plane, and is equal to \( P_{hk} = (1 + \cos^2 \theta_{hk})/2 \). While the
combined \( L_p \) factor is:

\[
L_{hk} = (1 + \cos^2 \theta_{hk}) /[2(\sin(2\theta_{hk}))]
\]

The extinction factor, derived by Darwin originates from the interference of waves within
the crystal. The initial extinction takes place when the reflected beam occurs in the right position
to be re-diffracted by other lattice planes, resulting in a loss of intensity from the original
reflection.\(^2\) The loss in intensity would come to about 50\% of the crystal when the lattice plane is
being diffracted in tandem. On the other hand, if a certain mosaic spread is present, it will lead to
a fraction of the lattice planes to become present in the diffraction condition simultaneously,
therefore minimizing the extinction effect. The expression for the extinction factor is related to
the size of a mosaic block of unknown crystal. The extinction factor is therefore, calculated
empirically but generally not large enough to be compelling for most crystal samples and
therefore, can be overlooked. However, it may be enforced as part of the refinement process.

The absorption correction is the most notable source of error for the intensities. When the
X-ray passes through a crystal, the atom absorbs a specific amount of energy while some of it is
diffracted. The absorbed energy all depends on the thickness of the crystal as well as the type of
atoms in the crystal. The crystal thickness within the beam changes at different angles of rotation
therefore, varying the absorbed energy and energy available for diffraction. The following
equation depicts a general form of the absorption factor:

\[
A_{hk} = 1/v \int V \exp[ -\mu (r_\alpha - r_\beta)]dV
\]

where \( V \) is the crystal volume, \( \mu \) is the linear absorption coefficient for both the crystal and
radiation being used, \( r_\alpha \) and \( r_\beta \) are path lengths which comes from the element of the crystal
volume $dV$ to the surface of the crystal with the incident and diffracted rays.\(^2\) To calculate the absorption factor, two methods are used which are either empirically or numerically from the measured intensities. When selecting a crystal, and if the crystal edges and faces are well defined, the indexes are then measured by using an optical microscope with a known orientation to the lab reference frame. Therefore, the unique path that passes through the crystal for each other scattered ray can be determined. There are instances where one attempts to grow a crystal but does not form with well-defined angles and faces. In such cases, calculation of the absorption factor is enforced by comparing the measured intensities of equivalent reflections from other orientations of the crystal. The measured intensities are numbers that relate to the experimental settings. When it comes to the structure factor, it is rather incorrect to impose the experimental settings to dictate the magnitude of the intensity that is being used. Consequently, the intensities have to be converted from the relative scale of the experiment to the electron density scale of the entire structure.\(^3\) The scaling factor, $K_{hkl}$, originates from the ratio of the relative intensities to the calculated intensities of the reflections. The calculated intensities are based on the finite set of the reflections and combined information from a series of constants from other correction factors and unit cell dimensions. Once the reflection intensities have been corrected, the next step is the symmetry analysis.

The symmetry analysis process takes place in a step by step fashion starting from the unit cell, combining the reflections. This is done based on the lattice type with the application of Friedel’s law. Next, the systematic absences are checked in-order to determine the most reasonable space group of the structure. Based on the data derived from the experiment, unit cell dimensions, space group, and corrected intensities it will be possible to attempt in determining the structure by generating the electron density map. One can apply either the direct method or
Patterson method when trying to calculate the phases which are combined with the measured intensities in-order to calculate the structure factor, $F$, followed by a Fourier transform method to generate an electron density distribution map showing the structure. For larger atoms, the Patterson method is the preferred choice, while the direct method is the best choice for solving lighter structures. It is important to note that the initial structure has been known to be a trial structure with approximate figures compared with the true structure. This approach is ultimately applied and refined in order to remove any possible discrepancies.

4.11 Refining the Structure and Results

When it comes to refinement of the trial structure, the process typically involves the systematic variation of the atomic parameters to generate the optimum solution between the measured structure factor amplitude and the ones calculated from the proposed structure. Typically, the trial structure is not accurate because of the use of estimated phrases in such a way that the atoms and hydrogen atoms may be the wrong type or not present and the atom’s position is inaccurate. Nonetheless, the trial structure is adjusted by applying geometrical methods of bonding to designate better positions for the atoms. This approach is used to allow for better determination of the phrases and improve the electron density map. The electron density map is typically referred to as the difference map, $F_o - F_c$. It is the difference between two structure factors, the observed structure factor, $F_o$, that is calculated from the observed structure factor amplitude with the calculated phases from the atomic model. The calculated structure factor, $F_c$, is calculated from both the structure factor amplitudes and the phrases from the atomic model. To minimize the difference between the $F_c$ and $F_o$, refinement is implemented by the means of least squares.²
The method of Least Squares is a standard approach that is applied to determine the optimum fit of a model to a set of experimental data. Least squares are successful whenever there is a lot more experimental data than parameters to work with. Some of the parameters include but not limited to the coordinate and displacement parameters of each atom and the scaling factor. To qualify as a good refinement, the ratio between the data to the parameter is suggested to be 10:1. However, the best parameters are attained by minimizing the sum of the squares (M) based on the deviations between the model and experimental quantities. This is then applied to the structure factors with the following equation:

\[ M = \sum w(F_{0}^2 - F_{c}^2)^2 \]  

where \( w \) is represented as the weighting factor based on the error (\( \sigma \)) of the measurement in such a way that the greater the estimated standard deviation for a measurement, the lower the weight that is designated for that measurement.\(^2\) The function in equation 4.4 can be minimized and seen graphically with a value that is close to zero over the entire difference map. This will indicate that the experimental observations will coincide with the expected calculation from the model structure.

The X-ray experimental results are determined based on the positions of the atoms within the structure and their parameter displacement in which the inter and intra-atomic distances are shown. This data is usually revealed in an ORTEP (Oak Ridge Thermal Ellipsoid Plot) diagram of the entire structure. Though much of the refinement process relies heavily on the principal researcher’s arrangement of the model and the actual fit of that model, it would be appropriate to incorporate some quantitative factors to compare it with. The quality if the diagram is often base on three R-factors, namely the weighted-R, wR, \( R_1 \), and the goodness of fit, s. \( R_1 \) is known to be the most common value that is based on the structure factors \( F \), and not the squares of the
structure value, $F^2$. For a crystal sample to be acceptable with good quality, the $R_1$ values have to be 5% or lower. The weighted-$R$ is closely related to the refinement against $F^2$ therefore, a value of <12% would be considered reasonable. The goodness of fit typically contains the parameter and has a value close to 1.0 and can be considered to be a good fit. The following figure illustrates the equation for the weighted-$R$, R-factors and the goodness of fit, $S$. Figure 4.4 illustrated the equation of the R-values where $N_R$ is the number of independent reflections, and $N_P$ is the number of refined parameters.

\[
\begin{align*}
wR &= \left( \frac{\sum w(F_0^2 - F_c^2)}{\sum wF_0^2} \right)^{1/2} \\
R &= \left( \frac{\sum |F_0| - |F_c|}{\sum F_0} \right)^{1/2} \\
S &= \left( \frac{\sum w(F_0^2 - F_c^2)}{(N_R - N_P)} \right)^{1/2} 
\end{align*}
\]

**Figure 4.4.** Equation of the residual R-values including the goodness of fit, $S^2$

### 4.12 Carborane Chemistry-Bonding and Structure

Beginning with the initial synthesis in the mid 1960’s, carbroane chemistry based on the $C_nB_{n-2}H_n$ framework have been investigated and studied. Apart from their unique characteristics as attaining high symmetry, the chemistry generated by the carborane species continues to grow enormously. Carboranes can be described as a group of polyhedral compounds that contain both carbon and boron atoms in the same atomic molecule. Polyhedrons contain between one to four carbon atoms however, those with two carbon atoms are most prominent. Carboranes can be grouped into three different classes namely: the *closo*, *nido* and *arachno*, which are based on their formulas. The *closo* or closed carborane is the most important classes of carborane chemistry. It has a general formula of $C_nB_{n-2}H_n$, where $n$ is between 5 to 12. The *nido-
Carboranes typically conform to the general formula $C_2B_{n-2}H_n$ or $C_2B_{n-2}H_n^{2-}$, and the arachno-carboranes formula are $C_2B_{n-6}H_n$ to $C_2B_{n-2}H_n^{4-}$.

The names suggest the structure: closo is the most closed, arachno (“spider-like”) is the most open, and nido (“netlike”) is between the two. The factor in which the three is observed is determined by the electron-count, which increases from closo through arachno, so the observed crystal structure we can count electrons and, for example, describe the oxidation state of a transition metal fused into the carborane. Electron counting rules have been enunciated by Wade and are discussed below.

The closo dicarbadodecaboranes have been known to be the highest members of the closo carborane species. Figure 4.5 shows a few examples of the atoms in the polyhedra consisting of a terminal hydrogen. The presence of two carbon atoms typically produces three distinctive isomers namely the ortho, meta and para carborane.

![Figure 4.5. Polyhedra Closo-carborane](image)
The carborane structures can be justified in terms of Wade’s rule used to predict the shapes of borane and substituted carborane cluster compounds based on the number of electron pair that is available for bonding. In general, by considering a B-H bonding unit complex, and if a single sp orbital is used in the formation of the exo B-H bond, this will ultimately result in one remaining sp orbital towards the center of the polyhedron and two p orbitals. Each B-H unit can donate two electrons for bonding and consequently, a C-H unit can also donate three electrons shown in Figure 4.6.6

![Figure 4.6. Skeleton bonding of sp orbitals](image)

Thus for carborane or borane compounds, Wades rule shows that for a polyhedron with n vertices, the \textit{closo} structure will have the skeleton electron pair of n+1, \textit{nido} with an electron pair of n+2 and \textit{arach}o with a n+3 electron pair. So for example, the dicarbadodecarboranes (C$_2$H$_{10}$H$_{12}$) complex has a total of 13 electron pairs and they are available for the skeletal bonding especially for the \textit{closo} ring and also have 12 vertices. This results in the formation of icosahedral structure it is bonded by three center units. Delocalization of the electron typically takes place when the C-H and B-H units of the skeletal bonding donate them hence have led to the description of carboranes as semi-aromatic compounds. Icosahedral carboranes and their anion species have also been studies and applied to. There are also areas where icosahedral
carborane anions are investigated as weakly coordinating anions and as conjugate bases for relatively strong acids. The properties of icosahedral carboranes are quite promising for the boron cluster chemistry that provides the $C_nB_{n-2}H_n$ and its derivatives with a diverse approach. The typical icosahedral cluster of $CB_{11}H_{12}^-$ is isoelectronic with the dianion icosahedral species $B_{12}H_{12}^{2-}$ and is recognized as a very stable cluster. The stability of these clusters is credited due to their high delocalization s-bonding over a skeleton of the boron species which contains roughly about 26 electrons in 13 bonding molecular orbitals. In theory, a general molecular orbital calculation of icosahedral clusters proves that a large HOMO-LUMO gap is consistent with the UV transparency.

4.13 Functionalization of Rhenacarboranes Towards Their Use as Drug Delivery Vehicles

Metallocarboranes and its application to inorganic medicinal chemistry are another area that also continues to grow rapidly ever since its discovery. Over ten years have elapsed since the chemistry of metallocarboranes was first introduced. The merging of two diverse areas of chemistry in the transition metals and boron hydrides through the discovery of metallocarborane complexes continues to grow enormously. The polyhedral expansion of carboranes has been recognized as being an overall method for the synthesis of metallocarboranes. The synthesis of metallocarboranes through low temperature or thermal metal approach even in their early stage of development could also pave the way for new synthetic methods. Recent studies based on the chemistry of metallocarboranes have shown the oxidative addition to the polyhedral boron vertex $\{BH\}$. Also, there are certain catalytic exchange on boron hydride, carboranes and metallocarboranes that occur when introduced to a few transition metal complex ligands.

Icosahedral carboranes and their anion characteristics can also be applied medically based on their flexible derivatization chemistry as well as the highly stable carborane
characteristics under biological conditions. Also, their low toxicity is encouraging and contributes to their being good candidates for medical applications. One example takes advantage of the high nuclear cross-section of $^{10}\text{B}$. 

$$^{10}\text{B} + n_{\text{Therm}} \rightarrow [^{11}\text{B}] \rightarrow ^{4}\alpha + ^{7}\text{Li} (+2.31 \text{ MeV}).$$

The boron is bombarded with thermal neutrons in order to produce $\alpha$-particles, and performed in live tissue that could potentially result in tissue destruction restricted to a single cell.$^{10}$ This however could potentially lead to the development of Boron Neutron Capture Therapy (BNCT). It could also lead to the treatment of various cancers at the cellular level including some of the most recent ones such as the treatment of rheumatoid arthritis through the development and evaluation of Boron Neutron Capture Synovectomy.$^{11}$ While there are numerous boron-containing compounds such as those based on the neutral $\text{C}_2\text{B}_{10}\text{H}_{12}$ cage, it has been investigated as probable therapeutic neutron-capture agents, the aspect of $\text{CB}_{11}\text{H}_{12}^-$ derivatives has recently been addressed, together with the hydroxylated and alkoxyalted recursor moieties. Substituted counterparts of $\text{CB}_{11}\text{H}_{12}^-$ have been investigated for various medical applications. When it comes to iodinated molecules, the ability of the cage for potentially containing halogen atoms has been employed for use as x-ray agents, $^{124}\text{I}$ positron emission tomography$^{13}$ (PET) agents,$^{12}$ and $^{123}\text{I}$ single photon emission tomography (SPECT) imaging agents. Their unique capability to carry a high mass percentage of iodine, their chemical inertness, resilience and control where they are derivatized makes these same $\text{CB}_{11}\text{H}_{12}^-$ agents encouraging preferences to the current iodinated compounds which are based on substituted phenyl rings.$^{14}$

The blood-brain barrier (BBB) is a diffusion barrier that aims to regulate the gateway of most compounds from blood to the brain and extracellular fluid that is in the central nervous
system. The main goal here is for proper communication channels for homeostatic regulation to take place. One of the major obstacles in overcoming the delivery of bioactive compounds into neurological tissues is the capillary bed of endothelial cells in the vascular BBB.

There are many avenues of crossover in the BBB including but not limited to, vesicle passage, transport protein and passive diffusion which helps many hydrophobic molecules with lower molecular weights to diffuse through the membrane easier. In a typical drug delivery system, a drug is administered either orally or via injection into the vein, or muscle. The drug molecules enter the blood circulation and its transported to various organs throughout the body. The drug molecules are transported to the cells and interstitial space from microcirculation. There are a few challenges associated with the passage of most therapeutic substances via systematic delivery across the blood brain barrier. Some of these challenges include therapeutic relevant concentrations where the dose concentration amount is critical in-order for effective transport across the BBB. In particular, lipid-mediated diffusion to the brain is limited to high lipid solubility and low molecular weight drugs of less than about 400 Daltons. Other challenges include side effects of the drug while binding to other proteins within the body.

On the other hand, neutral carboranes and their metallo-derivatives and stability can be very lipid-soluble due to their hydrophobic charge distribution. However, they are not affected by the size constraint in crossing over the BBB and accumulates in neutral tissues which are a nonfactor since they are not precursors in the metabolic pathways for p-glycoprotein. Metallocarbrane complexes are quite unique because they encounter heavier d-block transition metal characteristics and results in the kinetic and thermodynamic stabilities. What this does is to potentially allow the metallocarboranes to be considered for potential cancer therapeutic agents or diagnostic applications as drug-delivery vehicles that could potentially
resist metabolic degradation. Valliant et al have investigated the chemistry of rhenacarborane complexes as part of a strategy for the development of a few synthetic pathways to imaging reagent that incorporated the rhenium congener technetium, which is considered as one of the most commonly used imaging radioisotope. The development of rhenacarborane complexes has been of great interest due to its useful precursor Cs[3,3,3-(CO)₃-closo-3,1,2-ReC₂B₉H₁₁] (1) (Figure 4.7) as drug delivery vehicles for the central nervous system (CNS).

![Figure 4.7](image_url)

Figure 4.7. Prototype of the rhenacarborane complexes
Based on the preliminary studies with the $^{131}$I-labeled prototypical rhenacarborane complex $[3$-$\text{NO}$-$3,3$-$\text{K}^2$-$(2,2'$$\text{-N}_2$-$C_{10}$-$\text{H}_6$(Me})$\text{)}_{(\text{CH}_2)_{7}}^{131}$I$^{4,4'}$-$\text{closo}$-$3,1,2$-$\text{ReC}_2$-$\text{B}_9$-$\text{H}_{11}]$ (2) have shown the ability of a rhenacarborane to penetrate the BBB.\textsuperscript{18} The rapid uptake as well as the equilibrium phases have been determined based on the steady state injection dose that is being taken up per gram of the CD-1 male mouse brain. The $^{131}$I-labeled compound showed stability in the brain, blood and enzymatic resistance and therefore, qualifies as a great successor for targeting the CNS. Although the partition coefficient of Complex 2 at optimum levels has a lipophilic characteristic to cross the BBB, it also plays an important role by ensuring that it does not get trapped in the membrane. There is also a challenge associated with the synthesis because it contains an asymmetric 2,2'$\text{-bipyridyl}$ ligand. However, efforts are being made to study different routes in the synthetic process but in the confines of rhenacarborane delivery vehicles to complex 2.

The nitrosyl complex of $[3$-$\text{NO}$-$3,3$-$\text{(CO)}_2$-$\text{closo}$-$3,1,2$-$\text{ReC}_2$-$\text{B}_9$-$\text{H}_{11}]$ (3) was investigated a number of years ago.\textsuperscript{18} Based on its neutral, non-polar rhenacarborane complex, it was determined to be lipophilic enough to be soluble in hexanes therefore, making it a good candidate for a BBB delivery vehicle as well as pharmacological payloads.

### 4.14 Results and Discussion

A translucent light yellow-red leaf-like specimen of $C_{6}$-$H_{18}$-$B_{9}$-$\text{IN}_{2}$-$\text{O}_{5}$-$\text{Re}$, approximate dimensions $0.040$ mm $\times$ $0.180$ mm $\times$ $0.190$ mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Smart Apex II-D8 diffractometer using Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å) at 1446(2) K. A total of 6243 frames were collected. The total exposure time was 17.34 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic
unit cell yielded a total of 94263 reflections to a maximum θ angle of 29.93° (0.71 Å resolution), of which 10297 were independent (average redundancy 9.154, completeness = 97.3%, \(R_{\text{int}} = 4.03\), \(R_{\text{sig}} = 2.18\)) and 9596 (93.19%) were greater than 2σ(\(F^2\)). The final cell constants of \(a = 12.2638(4)\) Å, \(b = 12.8143(4)\) Å, \(c = 13.5752(5)\) Å, \(\alpha = 107.089(2)°\), \(\beta = 114.700(2)°\), \(\gamma = 91.129(2)°\), volume = 1827.50(11) Å³, are based upon the refinement of the XYZ-centroids of 9672 reflections above 20 σ(I) with 4.701° < 2θ < 59.80°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to the maximum apparent transmission was 0.585. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.3000 and 0.7310. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group \(P\overline{1}\), with \(Z = 4\) for the formula unit, \(\text{C}_6\text{H}_{13}\text{B}_9\text{IN}_2\text{O}_5\text{Re}\). The final anisotropic full-matrix least squares refinement on \(F^2\) with 596 variables converged at \(R1 = 2.93\)%, for the observed data and \(wR2 = 7.99\)% for all data. The goodness-of-fit was 1.061. The largest peak in the final difference electron density synthesis was 6.286 e/Å³ and the largest hole was –1.659 e/Å³ with an RMS deviation of 0.228 e/Å³. On the basis of the final model, the calculated density was 2.248 g/cm³ and \(F(000)\), 1144 e.

To demonstrate that these nitrosylrhenacarborane complexes could be produced with a diether group, an X-ray crystallography study was conducted on complex 6c. Single crystals were grown from a dichloromethane (CH₂Cl₂) solution with a complex layered with hexanes. The complex readily crystallizes as two independent molecules in a triclinic \(P1-1\) unit cell as shown in (Figure 4.8). The two molecular structures appear to have very few intramolecular structural differences between them and therefore, due to the sake of brevity one of the structures will be discussed. The \(\text{ReC}_2\text{B}_9\) moiety contains the \textit{closo}-icosahedral framework with an \(\eta^5\)-coordinated Re center. The distance from the metal to the unique β-B is longer (Re3-B8-2.368
than the other two (Re3-B4 2.338, Re3-B7 2.306 Å) and is associated with the presence of the O6 atom (B8-O6 1.428 Å). The metal vertex consists of a Re(CO)2NO tripod arrangement with near-linear nitrosyl (Re-N3-O3 171.76°) and carbonyls (Re3-C4-O4 175.21, Re3-C5-O5 177.80°). The existence of the iodine atom at the end of the O(CH2)O(CH2)2 chain is also confirmed (C9-11 2.157 Å).

Figure adapted with permission from ref 15 (see Appendix C). Copyright © 2015 Elsevier.

Figure 4.8. Independent molecular structures of complex 6c displaying diether chain orientations

The disposition of the pendant O(CH2)2O(CH2)2 group is of interest to us with respect to the metallocarborane cluster framework. The chain extends away from the metallocarborane that includes both independent molecules with no evidence of interaction with the C2B9H11 ligand. A clearer picture can be seen in the crystallographic packing diagram that can be viewed down the b axis of the unit cell as depicted in Figure 4.9. This viewpoint reveals a layered arrangement with a two-dimensional aggregation of carborane cages along the ac faces and the ReNO(CO)2 and O(CH2)2O(CH2)2I groups intertwined in the space between. The more polar
O(CH₂)₂O(CH₂)₂I chains show little interaction with the more hydrophobic carborane cage, which could potentially be expected to influence the membrane transport properties of the complex once a pharmacological target is attached.

Figure adapted with permission from ref 15 (see Appendix C). Copyright © 2015 Elsevier.

**Figure 4.9.** Crystallographic packing diagram of 6c down the b axis of the unit cell

In this metallocarborane, the structure is *closa*, to form an irregular icosahedron. The icosahedron is necessarily irregular because there are three different kinds of atoms forming it: B, C and Re. There are also substituents on some of the atoms. To get a regular icosahedron, the first requirement would be to make all the atoms alike, as in N(C₈H₁₉)₄.Au₂₅(SCH₂CH₂.C₆H₅)₁₈, which has an icosahedral core.

**4.14.1 The Au₂₅(SCH₂CH₂.C₆H₅)₁₈ Ion**

The compound N(C₈H₁₉)₄.Au₂₅(SCH₂CH₂.C₆H₅)₁₈ was prepared by a fellow graduate student, Mr Viraj Thanthirige. For Mr Thanthirige, studies on atomically precise nanoclusters, and we re-determined the structure at several temperatures to see how it varied as a function of
temperature. The variation in temperature only caused an increase in the crystallographic disorder in the octyl chains of the cation \(N(C_8H_{19})_4^+\) which is of no real interest. The anion \(N(C_8H_{19})_4Au_{25}(SCH_2CH_2C_6H_5)_{18}^-\) had the same structure at all the temperatures, so there was no variation and nothing new was revealed. But the icosahedral structure was interesting. It is shown below to compare the icosahedron with the nitrosylrhenacarborane.

![Figure 4.10. Structure of the icosahedral core (left) and the entire \(Au_{25}(SCH_2CH_2C_6H_5)_{18}^-\) anion (right)](image)

4.15 Conclusion

Rhenacarborane derivatives have become a promising class of boron-containing compounds that could act as delivery vehicles if able to cross the blood-brain-barrier. Metallacarborane complexes of heavier \(d\)-block transition metals demonstrate robust thermodynamic and kinetic stabilities. This allows them to be considered for potential diagnostic and therapeutic applications as drug delivery vehicles that resist metabolic degradation. In this work, structures of new metallacarborane and other complexes were solved via X-ray crystallography. The structure showed what the metallacarborane cage looked like and the
location of the three hetero-atoms (non boron). The cage occurs in all the related compounds in these reactions. Therefore, knowing the structure of the cage is important. It shows the three hetero-atoms (two C’s and one Re) makeup one triangular face of the icosahedral cage. It also shows where the substituent alkoxy-iodo chain is located, as well as the positions of the carbonyl and nitrosyl groups on the metal.

This work resulted in two crystallographically independent molecules in the unit cell complex of the metallacarborane cluster framework [3,3-(CO)₂-3-NO-closo-Re(8-O(CH₂)₂O(CH₂)₂I-3,1,2-C₃B₉H₁₀)]. The ReC₂B₉ moiety is comprised of the usual closo-icosahedral framework with an η⁵-coordinated Re center. These results show that rhenacarborane derivatives was enzymatically resistant and able to cross the BBB by transmembrane diffusion and accumulate in the brain in substantial amounts. This supports their use as therapeutic agents and prime candidates for use as drug-delivery vehicles of amino acids or small peptides across the blood-brain barrier, which might otherwise not be easily transported. Future synthesis on these vehicle-peptide bio-conjugates will hopefully shed the light onto the central nervous system therapeutics.

4.16 References


CHAPTER 5

CHARACTERISTICS OF METAL COMPLEXES BASED ON PYRUVIC ACID CONDENSATES WITH ORGANIC HYDRAZINE COMPOUNDS

5.1 X-ray Studies of Metal Coordination Complexes

Guanidine derivatives have demonstrated a wide array of applications. Its physiological and pharmacological viewpoints also make it a distinctive module for the semiessential amino acid arginine.\(^1\) In general, the molecular recognition mechanism in certain enzymes including signaling proteins also involve guanidine based receptors which have been known for protein stability conformation through hydrogen bonding based on their hydrophilic characteristics. Aminoguanidine on the other hand, is a molecular fragment present in various forms of drugs demonstrating different activities which includes but not limited to catalysis, anti-cancer, anti-aging, anti-diabetic, anti-obesity and anti-hyperglycemic properties, etc. This idea has provided an attractive platform in coordination and organometallic chemistry.\(^2\) In spite of all the diverse applications, amine derivatization into N-heterocyclic species without interrupting the guanyl moiety is rare which makes it an attractive research area in crystal engineering. Scheme 5.1 depicts a general example of a guanidine derivative complex with a metal. Aminoguanidine derivatives can also be found under protonated, deprotonated, or neutral form depending on the pH which can also display various coordination mechanisms.

![Scheme 5.1. Stoichiometry of metal geometry in guanidine derivative complexes](#)

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Its resonance structure is peculiar (Scheme 5.2) due to the electronic and sterically flexibility, also its proton affinity and Y-conjugation introduces a unique interest in other areas of chemistry.³

![Scheme 5.2. Resonance structure of substituted aminoguanidinium ion](image)

Naik et al demonstrated the functionalized aminoguanidine and diaminoguanidines as novel classes of supramolecular complexes in crystal structure applications (Scheme 5.3). As a result, an amine exchange led to the formation of two ligands namely N-4H-1,2,4-triazol-4-yl-guanidine hydrochloride (L1) and 3,4-diamino-4H-1,2,4-triazole hydrochloride (L2). The unique features of aminoguanidine derivative structures are adequate in reacting as derivatives of hydrazine or guanidine and can be used as a platform in medicinal chemistry.⁴ The authors presented examples of the trans-amination for the functionalization of the amine group from the aminoguanidine and diaminguanidines as hydrochloride salts. Both ligands L1 and L2 were isolated as semisolids following the separation from benzene. The transformation is a single step synthesis that involves a non-flash chromatography technique. This technique is preferred and has an advantage over synthesis of the 4-substituted-1,2,4-triazole complex.⁵
Scheme 5.3. Functionalization of amine group in 1,2,4-triazole

The mechanistic routes for L1 and L2 is shown in Scheme 5.4 where the 2-amino group is cyclized into 1,2,4-triazole to form L1 via route (a) of the mechanism. However, the diaminoguanidine did not lead to the bis-1,2,4-triazole compound that may have been expected. Rather, cyclization took place through an unexpected cyclization route (b) to generate the corresponding L2 or 3,4-diamino-4H-1,2,4-triazole. Depending on the R substituent, the intermediate could produce different results. R = H corresponded to the route (a), while R = NH₂ corresponds to route (b).
Scheme 5.4. Mechanism routes of L1 and L2

The present work stems from recent progresses in diverse amines; including biologically relevant aminoacids. This prompted the introduction and investigation of functionalized diaminoguanidine, pyruvic acid as well as carbohydrazide as ligands complexes. The versatility and applicability of the synthetic protocol persuaded us to introduce and functionalize diaminoguanidine as new classes of molecular synthons in crystal chemistry. There were some specific preferred structures that were attained after attempting some chemistry work but different product was produced. Therefore, we attempted to investigate this problem through crystal structure inorder to correct the expected chemistry, determine what happened and guide the future of the project, details of the synthesis and further characterization. Our colleagues
provided the crystals that were intended to confirm the proposed structures in Figure 5.1; we know that they had carried out condensations of pyruvic acid with three organic hydrazine compounds. Ultimately, the preferred structure (Figure 5.1) was not what we had originally expected based on our X-ray results. Apart from many biological importance associated with this topic, one of the main reasons why we decided to get involved in this research topic was because literature has shown that there is a lack of or little study associated with ketone complexes, metals typically stick better to nitrogen that contains aliphatic or aromatic nitrogen compounds. Also, this research is being studied based on its potential for medicinal applications, cancer treatment, and some of the main causes of cancer. Another reason why this research is of great interest will be to investigate the anaerobic metabolic process as well as aerobic respiration that serve as the main source of cellular energy.

The condensed bases with pyruvic acid are shown in Scheme 5.5. Carbohydrazides and Thio-carbohydrazides both have important applications. Carbohydrazide, O=C(NHNH$_2$)$_2$, is a white crystalline solid melting with decomposition at 153-154°C. Its density is 1.616 g/cc (measured at –5°C). It is very soluble in water, practically insoluble in the usual organic solvents, and sparingly so in dimethylformamide and dimethyl sulfoxide. The pH of a 1% aqueous solution is approximately 7.4. Its derivatives are used in drugs, herbicides, plant growth regulators, and dyes. Carbohydrazide acts as a denaturing agent for bovine serum albumin and for DNA. The effect is attributed to stabilization of the denatured DNA relative to native DNA by a decrease in the ion-solvating power and an increase in the hydrophobic character of the solvent. A projectile propellant has been developed which consists of carbohydrazide, nitric acid, and water.
Thiocarbhydrodrazide, \( S=\text{C(NHNH}_2\text{)}_2 \), is a white, crystalline solid, melting with decomposition at 168°C. It may be recrystallized from water. Thiocarbhydrodrazide is almost completely nonhygroscopic. Thiocarbhydrodrazide is useful as an osmiophilic reagent for demonstrating the presence of aldehyde-containing macromolecules, originating from iodic acid oxidation of tissue, and of lipid-containing membranes in osmium tetroxide-fixed tissue. Thiocarbhydrodrazide is a better reagent than thiosemicarbazide for demonstrating the presence of a wide variety of oxidized macromolecules. Thiocarbhydrodrazide is active \textit{in vitro} against tubercle bacilli (strain H37RV) in concentration 10^-5; against Micrococcus pyogenes var. aureus (strain Londres) (1 mg/ml, corresponding to 1.02 pg/ml of penicillin), against Escherichia coli (1 mg/ml, corresponding to 1.2 pg/ml of chloramphenicol), and against Mycobacterium tuberculosis (BCG strain). Thiocarbhydrodrazide and carbohydrazide exhibit a toxicity toward the house-fly comparable to that of DDT. They were equally toxic to a DDT-resistant strain as to a susceptible strain.  

Metabolic pathway (Scheme 5.6) involved in cellular respiration is typically divided into three main areas namely glycolysis, which occurs in the cytoplasm, kreb cycle that occurs in the matrix of the mitochondria and electron transport chain that occurs in the inner membrane of the mitochondria. Cellular respiration absorbs food such as glucose, oxidizes and uses it to create adenosine triphosphate (ATP), which the cell uses for energy in the presence of oxygen.
Scheme 5.5. Condensed bases with pyruvic acid

Scheme 5.6. Metabolic pathway in cellular respiration⁹
Glucose is broken down into pyruvic acid that supplies energy to the cell via the kreb cycle in the presence of oxygen or aerobic respiration.

Figure 5.1. Originally proposed structures of the metal complexes

There were five compounds investigated namely, Nickel pyruvic diaminoguanidine (NIPD), Cobalt pyruvic diaminoguanidine (COPD), Nickel pyruvic carbohydrazide (NIPC) and Cobalt pyruvic triaminoguanidine (COPT). The original structure in Scheme 5.7 also included specific ligands attached to the structure. For COPD and NIPD, the ligand used were diaminoguanidine and pyruvic acid, while NIPC and CUPC had carbohydrazide and pyruvic acid.
The results we expected to achieve were different from what was originally proposed. The original structure was an 8-membered aliphatic ring (Figure 5.1) where they started out with three compounds condensed with pyruvic acid to generate new ligands but in actuality, what we got was a 5-membered ring. Our proposed mechanism is depicted in Scheme 5.7 where we start off with a pyruvic diaminoguanidine species with no metal bounded to the complex. In this case, the condensation of carbohydrazine with pyruvic acid under certain reaction conditions will become the main focal point.

Next, they proposed a mechanism where pyruvic triaminoguanidine (Scheme 5.8) was attempted in the condensation process. This time, a metal ligand was introduced with an amine group. Again, what they expected was not what we observed.
**Scheme 5.8.** Pyruvic triaminoguanidine

**Scheme 5.9.** Pyruvic triaminoguanidine with a metal
Our deduction of how the proposed condensation of pyruvic acid and diaminoguanidine was supposed to have worked, to ultimately form the Metal-PD complexes. Note the strained PD ligand in MPD with two adjacent 8-membered metal-coordination rings.

How the condensation of pyruvic acid and diaminoguanidine actually worked, based on X-ray evidence. Note the unstrained structure of the complex with two adjacent 5-membered metal-coordination rings. The more extensive condensation mechanism is presumably metal-catalyzed. The diagram in Scheme 5.10 shows the “PD” condensation in the presence of metal ion of pyruvic acid and diaminoguanidine to form the MPD-type metal complexes. In order to understand this diagram, it should be taken together with Scheme 5.16 below, which shows the observed condensed ligand, and the CoPD complex as redrawn from the crystal structure. The ligand and complex are shown with their systematic names, as obtained from ChemBioDraw.

Scheme 5.10. Condensation of pyruvic acid
The ChemBioDraw pictures in Scheme 5.11 should be viewed together with the ORTP representation of the Co(PD)₂ structure. Note that the structure determination shows the two tridentate ligands to be chemically equivalent. This indicates that they are deprotonated only at the acid group of the ligand as seen in Scheme 5.3, and it further indicates that the oxidation state of the metal is most likely Co²⁺.

Scheme 5.11. Chemdraw pictures of the free ligand as deduced, and the re-drawn crystal structure of the Co(PD)₂ molecule.
Scheme 5.12 ORTEP representation of the molecular structure of “CoPD”, actually Co(PD)$_2$. The two tridentate ligands are essentially flat and chemically equivalent. Consequently oxidation Co$^{II}$ is postulated. The molecular structure (“packing diagram”) of shown as an ORTEP in Scheme 5.13 shows the individual complex molecules in the Co(PD)$_2$.2H$_2$O. The complex co-crystallizes with two waters of crystallization. The complete crystal structure (Scheme 5.13) shows that, aside from hydrogen bonding interactions with the co-crystallized H$_2$O, the Co(PD)$_2$ molecules are independent and well-isolated from each other.

**Scheme 5.12.** Crystal structure for cobalt complex Co(II)PD
When it comes to the supramolecular structure of Co(PD)$_2$.2H$_2$O the hydrogen-bonding likes the water molecules to the Co(PD)$_2$ molecules into an infinite array. One water molecule ("O8") forms H-bonds (shorter than 3.1 Å) with three distinct Co(PD)$_2$ molecules, via the O5 ligand of one, the N5 ligand of another, and the N9 ligand of the third. The Co(PD)$_2$ molecules in turn each bond to three distinct "O8" water molecules, thereby continuing the link into 3-D. Scheme 5.14 shows these linkages together with the crystallographic symmetry labels of these atoms. Thus this water molecule H-bond-links one Co(PD)$_2$ molecule to the next one along the crystal b-axis, and at the same time links each of these to the next ones along the xz diagonal, and so on in 3-D. Meanwhile, the other water molecule, "O7", makes weaker 3-D links (longer than 3.1 Å) between different Co(PD)$_2$ molecules (Scheme 5.15).
Scheme 5.14. H-bonding linkage for water molecule “O8”

Scheme 5.15 shows the general way the metal complex structure should have looked when ligan PT was formed from pyruvic acid and triaminoguanidine, $\text{NH}_2\text{-N} = \text{C(NH-NH}_2)_2$, shown here as the hydrochloride.
Scheme 5.15. Intermolecular linkage for water molecule “O7” CoPT condensation and structure

Figure 5.2. Structure of triaminoguanidine\textsuperscript{10}
Once again, the proposed structure type in Figure 5.1 would have been a highly strained molecule with adjacent strained 8-membered coordination rings. In the presence of the metal ion, the condensation is more extensive. The X-ray data were good enough to enable finding some H-atoms. Scheme 5.16 shows the actual molecular structure of CoPT as an ORTEP diagram with and without the H-atom positions included.

**Scheme 5.16.** Crystal structure of CoPT
ORTEP representation of CoPT; (Scheme 5.13) with observed H-atoms included, and (Scheme 5.14) with H-atoms omitted for clarity. Note that the two tridentate ligands have the same essential skeleton, but are chemically different in their binding modes.

Scheme 5.17. ORTEP representation of CoPT in another orientation

In Schemes 5.18 and 5.19, it can be seen that the ligands have the same skeleton but have different binding modes, so that when they are coordinated they become chemically non-equivalent. The different coordination modes may be imposed by a need to provide an extra negative charge by losing a H-atom so as to accommodate a Co$^{III}$ oxidation state. One way to see this is to note that on “Ligand 1,” the six-membered condensed organic ring, N11-C14-N9-N8-C16-C15, is not bonded to the metal atom. The amine group on N11 of the ring instead coordinates to the metal atom. On the other hand “Ligand 2” has the six-membered organic ring bonded directly to the metal.
Scheme 5.18. ORTEP representations of “Ligand1” and “Ligand2”
The condensation mechanism of thiocarbohydrazine with pyruvic acid with diaminoguanidine is depicted in Scheme 5.20. Once again, the extensive mechanism is metal catalyzed. However, the diagram shown above shows the expected CoPS with no presence of the metal-catalyzed species. In contrary, Scheme 5.21 shows a predictable metal catalyzed ligand where the proposed condensation of thiocarbohydrazine with pyruvic acid could lead to a Metal-PS complex. The PS ligand in MPS with the two adjacent 8-membered metal-coordination rings is also strained.
Scheme 5.20. Condensation of NH with thiocarbohydrazine and pyruvic acid

Scheme 5.21. Condensation of NH with thiocarbohydrazine with a metal complex
5.2 Conclusion

In this work, the condensation of pyruvic acid with different ligands was investigated. X-ray studies were carried out on some new metal complexes that were designed and synthesized for anti-cancer applications. The results of this study show that the actual structures were different than those intended by our Indian collaborators in the original synthetic design. Additionally, the actual X-Ray structures are compatible with the synthetic design determined, and are predictable and expected based on structural consideration. The intended design included two adjacent 8-membered rings, which should show a significant degree of steric strain. However, the accrual structures contained two adjacent 5-membered rings and constitute a sterically more relaxed system.

5.3 References

10. www.chemspider.com\Chemical-Structure.71560.html
Appendix A

$^1$H NMR, $^{13}$C NMR, ESI-MS, IR, Data of Rhodamine Derivatives
$^{1}$H NMR of Compound 1 in CDCl$_3$
$^{13}$C NMR of Compound 1 in CDCl$_3$
ESI-MS of Compound 1

Low Mass: 60-1000 in MeOH

OD: 50 G6-1H-DAMINE.COMPL. POS/AM: 1 1.034 AM: 1.688 AM: 1.000 AM: 0.00 0.701 CH (1.00)

TOF/MS ES+
2.063
IR of Compound 1 in CDCl$_3$
$^1$H NMR of Compound 2

$^{13}$C NMR of
Compound 2
IR of Compound 2
NMR of Compound 3
$^{13}$C NMR of Compound 3
ESI-MS of Compound 3
IR of Compound 3

Synthesis of Compound 3 ANO
$^{1}H$ NMR of Compound 4
$^{13}$C NMR of Compound 4
ESI-MS of Compound 4
IR of Compound 4
$^1$H NMR of Compound 5
$^{13}$C NMR of Compound 5
IR of Compound 5

Synthesis of Compound 5 ANO

\(^1\text{H}\)
NMR of Compound 6
$^{13}$C NMR of Compound 6
ESI-MS of Compound 6
IR of Compound 6
$^1$H NMR of Compound 7
$^{13}$C NMR of Compound 7
ESI-MS of Compound 7

**Figure Description:**
- The figure appears to be a graph or chart, possibly showing mass spectrometry data for Compound 7.
- The x-axis and y-axis are labeled, though the specific values are not clear.
- There are several data points plotted, possibly indicating mass or intensity values.

**Related Information:**
- The context suggests analysis of a chemical compound using ESI-MS (Electrospray Ionization Mass Spectrometry).
- The graph may be used to determine the molecular weight or other properties of the compound.

**Notes:**
- The exact details of the graph are not fully legible in the provided image.
- Further analysis or discussion of the graph's implications would require a clearer view or additional context.
IR of Compound 7
$^1$H NMR of Compound 8
$^{13}$C NMR of Compound 8
ESI-MS of Compound 8
IR of Compound 8
\textsuperscript{1}H NMR of Compound 9
$^{13}$C NMR of Compound 9
ESI-MS of Compound 9
IR of Compound 9

Synthesis of Compound 9 ANO
$^1$H NMR of Compound 10
$^{13}$C NMR of Compound 10
IR of Compound 10
$^1$H NMR of Compound 11
$^{13}$C NMR of Compound 11
ESI-MS of Compound **11**
IR of Compound 11

Synthesis of Compound 11 ANO
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$^{13}$C NMR of Compound 12
ESI-MS of Compound 12
IR of Compound 12
$^1$H NMR of Compound 13
$^{13}$C NMR of Compound 13
ESI-MS of Compound 13

IR of
Compound 13
Appendix B

X-ray Crystallography Data of Metallacarborane Structures
Crystal Structure Report for REIJ2

A translucent light yellow-red leaf-like specimen of C$_2$H$_{18}$Br$_2$N$_2$O$_3$Re, approximate dimensions 0.040 mm x 0.180 mm x 0.190 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

**Table 1: Data collection details for REIJ2.**

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A total of 6243 frames were collected. The total exposure time was 17.34 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 9463 reflections to a maximum 2θ angle of 29.93° (0.71 Å resolution), of which 10297 were independent (average redundancy 9.154, completeness = 97.3%, Rint = 4.03%, Rag = 2.18%) and 9596 (93.19%) were
greater than 2σ(I^2). The final cell constants of a = 12.2638(4) Å, b = 12.8143(4) Å, c = 13.5752(5) Å, α = 107.689(2)^°, β = 114.700(2)^°, γ = 91.120(2)^°, volume = 1827.50(11) Å^3, are based upon the refinement of the XYZ-centroids of 9672 reflections above 20 a(I) with 3.701 < 20 < 59.80^°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.585. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.3000 and 0.7510.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 4 for the formula unit, C_{38}H_{54}B_{5}N_{3}O_{2}K_{4}. The final anisotropic full-matrix least-squares refinement on F^2 with 596 variables converged at R1 = 2.93%, for the observed data and wR2 = 7.99% for all data. The goodness-of-fit was 1.061. The largest peak in the final difference electron density synthesis was 0.228 e/Å^3 and the largest hole was -1.659 e/Å^3 with an RMS deviation of 0.228 e/Å^3. On the basis of the final model, the calculated density was 2.248 g/cm^3 and F(000), 1144 e^−.
Table 2. Sample and crystal data for REIJ2.

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Table 6. Bond angles (°) for REIJ2.
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| C2-Re3-B4 | 73.29(13) | B7-Re3-B4 | 77.08(14)  |
| C1-Re3-B4 | 43.01(13) | N3-Re3-B8 | 109.91(14) |
| C4-Re3-B8 | 84.85(15) | C5-Re3-B8 | 156.63(15) |
| C2-Re3-B8 | 75.48(13) | B7-Re3-B8 | 45.81(14)  |
| C1-Re3-B8 | 75.12(13) | B4-Re3-B8 | 46.33(14)  |
| C6-O6-B6 | 116.3(3)  | C7-O7-C8  | 115.2(4)   |
| O5-N3-Re3 | 171.5(3)  | C2-C1-B5  | 111.4(5)   |
| C2-C1-H4  | 111.9(3)  | B5-C1-B4  | 63.2(2)    |
| C3-C1-H6  | 61.6(2)   | B5-C1-B6  | 62.4(2)    |
| B4-C1-H6  | 115.1(3)  | C3-C1-Re3 | 68.43(18)  |
| B5-C1-Re3 | 128.5(2)  | B4-C1-Re3 | 60.50(19)  |
| B6-C1-Re3 | 127.5(2)  | C2-C1-H1  | 118.3      |
| B5-C1-H1  | 118.3(3)  | C3-C1-H1  | 104.3      |
| B6-C1-H1  | 113.3(3)  | C1-C2-B6  | 62.2(2)    |
| C1-C2-B1  | 111.3(3)  | C1-C2-B7  | 62.2(2)    |
| B11-C2-B6 | 62.4(2)   | C1-C2-B7  | 111.3(3)   |
| B11-C2-B7 | 62.3(2)   | B6-C2-B7  | 114.6(3)   |
| C1-C2-Re3 | 70.05(18) | B11-C2-Re3| 127.2(2)   |
| B6-C2-Re3 | 129.6(2)  | B7-C2-Re3 | 68.43(19)  |
| C1-C2-H2  | 117.3(3)  | H11-C2-H2 | 124.3      |
| B6-C2-H2  | 112.3(3)  | B7-C2-H2  | 114.6(3)   |
| Re3-C2-H2 | 103.3     | O4-C4-Re3 | 175.4(4)   |
| O5-C5-Ba4 | 174.6(3)  | O6-C6-C7  | 111.4(4)   |
| O6-C6-H61 | 114(3)    | C7-C6-H61 | 107.3      |
| O6-C6-H62 | 112(3)    | C7-C6-H62 | 113.3      |
| H61-C6-H62| 109(4)    | O7-C7-C6  | 111.1(4)   |
| O7-C7-H71 | 107(3)    | C6-C7-H71 | 113.3      |
| O7-C7-H72 | 121(3)    | C6-C7-H72 | 99.5       |
| H71-C7-H72| 106(6)    | O7-C8-C9  | 110.2(4)   |
| O7-C8-H81 | 119(3)    | C9-C8-H81 | 115.3      |
| O7-C8-H82 | 109(3)    | C9-C8-H82 | 106.3      |
| H81-C8-H82| 96.6(4)   | C8-C9-H1  | 109.2(3)   |
| C8-C9-H91 | 115.3     | H1-C9-H91 | 102.3      |
| C8-C9-H92 | 118(3)    | H1-C9-H92 | 98.3       |
| H91-C9-H92| 112.3     | C1-B4-B9  | 103.9(3)   |
| C1-B4-B5  | 58.3(2)   | C1-B4-B5  | 59.8(2)    |
| C1-B4-B8  | 106.5(3)  | B9-B4-B8  | 59.5(2)    |
| B5-B4-B8  | 108.6(3)  | C1-B4-Re3 | 67.40(7)   |
| B9-B4-Re3 | 121.2(2)  | B5-B4-Re3 | 122.1(2)   |
| B5-B4-Re3 | 67.7(3)   | C1-B4-H4  | 120(3)     |
| B9-B4-H4  | 119(3)    | B3-B4-H4  | 109(3)     |
| B5-B4-H4  | 131.3     | Re3-B4-H4 | 115(3)     |
| C1-B5-B9  | 104(0)    | C1-B5-B6  | 59.7(2)    |
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| B9-B5-B4  | 59.8(2)   | B6-B5-B4  | 109.0(3)   |
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**Table 7. Torsion angles (°) for REI1J2.**

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Table 8. Anisotropic atomic displacement parameters (A²) for REIJ2.

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Table 9. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å²) for
Appendix C

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Publisher: Elsevier
Date: 1 March 1997
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