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Synthetic development and application of compounds with biological relevance

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SYNTHETIC DEVELOPMENT AND
APPLICATION OF COMPOUNDS WITH
BIOLOGICAL RELEVANCE

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

in

The Department of Chemistry

by
Jeffery Caleb Clark
B.S., University of Mississippi, 2000
August, 2005
DEDICATION

This dissertation would not be possible without the contributions from my parents and my grandparents. I would like to thank each of you for your contributions.

Daddy, I really do appreciate your motivation you provide to me. You have been the best example of what a father is to be to his children, and I am fortunate to have that kind of example. I really enjoy our fishing trips out to Bayou Heron where we frequently don’t catch, but always have a good time.

Mom, I would like to thank you for always listening to me when I need to talk. We have so much in common and it’s always easy to talk to someone you identify with so closely. Having someone to listen who is so understanding is priceless.

Also I would like to dedicate this dissertation to my grandparents Mr. Jeffery Hayden and Mrs. Jo Hayden who funded my undergraduate education. Without the “scholarship” you gave, I probably would not have gone to graduate school. I hope that you know how much I appreciate all of your contributions.

_It is not the number of steps you take forward, but more importantly the number of steps that you don’t take back._
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Philippians 4:13
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LIST OF ABBREVIATIONS SYMBOLS

δ - chemical shift
Boc – t-butoxycarbonyl
br - broad
n-BuLi – n-butyl lithium
BNCT - boron neutron capture therapy
$^{13}$C-NMR – carbon 13 nuclear magnetic resonance
Cbz – benzyloxy carbonyl
d - doublet
DBAD - di-t-butyl azodicarboxylate
DBU – 1,8-diazabicyclo[5.4.0]-undec-7-ene
DCM – dichloromethane
DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIA – diisopropylamine
DMAP – dimethylaminopyridine
DPPA – diphenylphosphoryl azide
EtOAc – ethyl acetate
EtOH – ethanol
FAB – fast atom bombardment
Fmoc - 9-fluorenlymethoxycarbonyl
Gly – glycine
$^{1}$H-NMR – proton nuclear magnetic resonance
HPLC – High Performance Liquid Chromatography
h – hour(s)

HPFC – high performance flash chromatography

Hz - hertz

ICD – isopropylcarbodiimide

J - coupling constant

KHMDS – potassium hexamethyldisilazide

LAH – lithium aluminum hydride

LET – linear energy transfer

LHMDS – lithium hexamethyldisilazide

MALDI – matrix assisted laser desorption/ionization

mcpba – m-chloroperoxybenzoic acid

MeOH – methanol

min – minute(s)

MS – mass spectrometry

m/z – mass to charge ratio

NBS – N-bromosuccinimide

NCS – N-chlorosuccinimide

NMP - N-methyl-2-pyrrolidinone

OEP – octaethylporphyrin

PDT – photodynamic therapy

PhSCI – phenylsulfenyl chloride

PhSH – benzenethiol

PLE – pig liver esterase
PME – propionic methyl ester

ppm – parts per million

PyAOP - 7-Azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate

q – quartet

quint - quintet

RBF – round bottom flask

RT – room temperature

s - singlet

t – triplet

TBAF – tetrabutylammonium fluoride

TFA – trifluoroacetic acid

TLC – thin layer chromatography

TPP – 5,10,15,20-tetraphenylporphyrin
ABSTRACT

Nature has provided a vast number of compounds that have medicinal application. The use of these compounds provided by nature however, is limited by the amount of a specific compound that nature provides. The synthesis of these molecules and their derivatives provides an even greater number of compounds for biological screening.

Various pyrroles, the heterocyclic building blocks of porphyrins, can be prepared synthetically over several steps. The implementation of carboranes on pyrrole rings intrinsically provides substrates that can be converted into porphyrins bearing carborane substituents. The condensation of these carboranylpyrroles with carboranylaldehydes provides carboranylporphyrins bearing a higher order of carborane substitution. The conversion of these carboranylporphyrins into their water-soluble nido derivatives provides several compounds whose biological properties are currently being explored.

The use of peptides in the treatment of neurodegenerative diseases such as Alzheimer’s provides a need for novel peptides. Peptides typically are synthesized through extensive use of solid-phase chemistry, protecting group chemistry, and linkers. The manipulation of the reactivity of these groups provides more advanced methods for producing novel peptides. The development of novel protecting groups and linkers on solid-phase resins have been attempted and have shown preliminary success.

The preliminary results of the biological studies of two of the molecules from this dissertation have shown positive activity for potential use in cancer therapy. These results as well as future findings will soon be published.
CHAPTER 1: INTRODUCTION

1.1 Synthesis

Organic synthesis is a powerful tool, which provides an abundance of biologically relevant molecules. Nature has provided a wide variety of compounds, but so many are in such low abundance that extraction from nature is often not worthwhile. Organic synthesis provides methods that can ultimately lead to large amounts of compounds, which in nature may exist in such low abundance. As a result, synthesis of many of these naturally occurring species becomes a valuable tool in obtaining these compounds in large amounts. While many natural systems have shown application toward the treatment of various diseases, synthetically prepared derivatives of natural substrates are sometimes more important than the ones provided by nature. Synthetic preparation of many of these derivatives provides more diversity in the number of compounds to be studied. Two of the many areas of organic chemistry, which produce molecules with biological relevance are porphyrin and peptide syntheses. While many disciplines of chemistry produce biologically significant molecules the contributions made to these porphyrin and peptide chemistry will be discussed in this dissertation. This chapter will give an overview of the basic principles, history, and progress made in porphyrin and peptide chemistry. Because pyrroles are the building blocks and are vital in the synthesis of porphyrins, a brief introduction to their properties, syntheses, and other applications will first be presented. The history of porphyrin chemistry, their syntheses, characterization, and modern medicinal applications will be discussed. Additionally, an introduction to peptide chemistry including their application in the treatment of neurodegenerative diseases such as Alzheimer’s will be followed by a discussion of recent developments in peptide
The use and development of peptide linkers, protecting groups, and solid-phase chemistry to synthesize peptides will be discussed briefly followed by a description of the contents of this dissertation.

1.2 Porphyrs

1.2.1 Introduction

Pyrroles can be tetramerized\(^1\) by various methods to yield porphyrins.\(^2,3\) Porphyrin chemistry for some time has sparked the interest of many scientists in several disciplines. In addition to being encountered in chemistry, porphyrins also are frequently encountered in biochemistry, botany, genetics, physiology, medicine, and materials science.\(^4\) Porphyrins and porphyrin-like compounds are naturally occurring tetrapyrrolic systems that can be obtained from many natural sources.\(^5\) The first porphyrins were isolated from hemoglobin,\(^6\) though earlier studies of iron-free hemat\(i\)n\(^7\) were reported. Because porphyrins exhibit many fascinating physical properties, they have been investigated heavily since the early 19\(^{th}\) century. The first synthetic preparation of a porphyrin was reported by Thudichum in 1867.\(^8\) Many other advances in porphyrin synthesis were made shortly after Thudichum’s synthesis of cruentine, and the first total synthesis of etioporphyrin-III was reported by Fischer in 1926.\(^9\) In that same year Fischer also synthesized octamethylporphyrin.\(^10\) Finally, in 1929 Fischer synthesized and named protoporphyrin-IX,\(^11\) which is the free base porphyrin of hemin. The three porphyrins mentioned above and synthesized by Fischer as well as other historically important porphyrins can be seen in Figure 1.1.

As previously mentioned porphyrins are tetapyrrolic heterocycles, but their structure for many years was unclear. Three ring systems proposed by three early
porphyrin chemists are shown in Figure 1.2. Fischer proposed that porphyrins were eight-membered ring structures \(^a\) joined by a direct vinylic linkage, but Willstätter then proposed that, based on his degradation studies, porphyrins were tetrapyrroleethylene structures \(^b\). In 1912 Küster had proposed the tetrapyrrolic system \(^c\) that we now know to be the correct structure, but in 1921 even Fischer doubted that this type of large ring system was correct. These types of large ring systems were not known at that time. It was not until after Fischer had prepared etioporphyrin-I and octamethylporphyrin that he accepted the ring structure correctly proposed by Küster in 1912.\(^d\)

![Porphyin Structures](image)

**Figure 1.1**: Historically and biologically important porphyrins.

One can imagine that a structured nomenclature system is necessary for porphyrins because of the size of these macrocyclic ring systems. Currently there are two systems of nomenclature in use for the numbering of porphyrins related systems. The older of the two systems is the Fischer system, which identifies the eight \(\beta\) pyrrolic
carbons on the ring by a numerical system. The meso positions of the ring are labeled by a Greek lettering system, and are labeled \(\alpha, \beta, \gamma,\) and \(\delta.\) The four pyrrolic rings are also labeled by the capital letters A, B, C, and D, respectively. Because the Fischer system of nomenclature does not identify all carbons on the porphyrin, its use is diminishing and

![Proposed structures of porphyrins by Fischer, Willstätter, and Küster.](image)

**Figure 1.2:** Proposed structures of porphyrins by Fischer, Willstätter, and Küster.

will not be used in this dissertation. The more modern and more thorough system of nomenclature for porphyrins is the IUPAC system. This system, though more complex, identifies every carbon on the macrocyclic ring. In addition to numbering the carbons on the macrocycle, it also numbers the carbon on the substituents. The substituents are also systematically numbered with a superscripted Arabic numeral to denote the carbons on

![Fischer and IUPAC nomenclature of porphyrins.](image)

**Figure 1.3:** Fischer and IUPAC nomenclature of porphyrins.
the substituent chain. One example of the Fischer system of nomenclature and two examples of the IUPAC nomenclature are shown. The second example using the IUPAC system effectively demonstrates how it could easily be used in more complex systems by numbering the substituents.

1.2.2 Synthesis of Porphyrins

Many different methods to make porphyrins from pyrroles have been developed and improved upon since Fischer first synthesized etioporphyrin-I.\(^9\) The most obvious method is by the tetramerization of a monopyrrole. As in benzene chemistry, the nucleophilicity of a pyrrole is governed by the type of substitution present on the ring. Thus, an electron-donating group such as an alkyl group would enhance the nucleophilicity of a pyrrole. Conversely, the presence of an electron-withdrawing group such as an ester would decrease the reactivity of the pyrrole, and this nucleophilicity is essential for porphyrin synthesis.

The two most commonly studied porphyrins are TPP and OEP. Because the experimental methods to synthesize TPP were employed throughout this dissertation, the history of the development of these methods to make TPP will be discussed here. Three basic method have been developed to synthesize TPP and other related porphyrins. The most primitive of these methods was first developed by Rothemund and Menotti.\(^{15}\) In 1964 an improved method by Adler and Longo synthesized TPP by reacting pyrrole and benzaldehyde in open air while refluxing in propionic acid.\(^{16}\) Finally, in 1986 Lindsey optimized the method for the synthesis of TPP by first forming porphyrinogen under equilibrium conditions followed by a separate oxidation to the porphyrin.\(^{17}\) These methods will now be discussed in further detail. In addition to the development of the
synthesis of TPP, the development of the synthesis of unsymmetrically substituted porphyrins will also be discussed.

Rothemund and Menotti originally showed that TPP could be slowly formed at high temperature by the reaction of benzaldehyde and pyrrole in a sealed tube.\textsuperscript{15} The reaction took place in pyridine, and the highest yield of TPP was about 11\% (Scheme 1.1). The best yield was when the reaction took place in the presence of \( \text{Zn(OAc)}_2 \) at high pressure. Refluxing the same reagents in methanol and pyridine at atmospheric pressure yielded TPP and the chlorin of TPP. This chlorin was referred to as TPC, and it can be oxidized with oxygen to TPP. The Rothemund conditions are compatible with only very few benzaldehydes due to the harshness of the conditions. The use of these conditions is not practical and was rarely used after the development of Adler-Longo conditions.\textsuperscript{16}

\begin{equation}
\text{N} \text{H} \text{N} \text{H} \text{N} \text{Ph} \text{Ph} \text{Ph} \text{NH} \text{CHO} + \text{pyridine} \text{MeOH} \rightarrow \text{TPP} \text{Ph} \text{Ph} \text{Ph} \text{N} \text{HN} \text{Ph} \text{Ph} \\
150^\circ \text{C} \text{24 hr.} \text{11}\%
\end{equation}

\textbf{Scheme 1.1:} Synthesis of TPP using Rothemund conditions.

About 25 years after Rothemund conditions were developed to make TPP, Adler and Longo investigated the synthesis of porphyrins under many different conditions.\textsuperscript{16} Their findings resulted in a new set of conditions that formed TPP by refluxing pyrrole and benzaldehyde in propionic acid. These conditions were relatively mild compared with the earlier Rothemund conditions developed about 25 years before. Adler and Longo studied many solvent systems with a variety of salts present to enhance the formation of
TPP. The Adler-Longo conditions were much faster than Rothemund conditions and yielded TPP in a yield of up to 20%. These milder conditions allowed the synthesis of porphyrins with a wider variety of substituents and in a much higher yield. Even though the Adler-Longo method shown in Scheme 1.2 was a vast improvement over the Rothemund method, it still had its limitations. The conditions are still somewhat harsh, and more sensitive functional groups were not compatible with this method. Another commonly encountered problem with using the Adler-Longo method is the formation of large amounts of tar. Purifications are more difficult with this method because of the formation of tar; however, methods have been developed to suppress tar formation.\textsuperscript{18} Though more modern synthetic methods have been developed, the syntheses of meso-tetraalkylporphyrins are most efficient using this method.

\begin{center}
\textbf{Scheme 1.2:} Synthesis of TPP using Adler-Longo conditions.
\end{center}

In 1987 the synthesis of TPP and related compounds was revolutionized by Lindsey and coworkers (Scheme 1.3).\textsuperscript{17} Lindsey successfully demonstrated that TPP could be formed under equilibrium conditions, and that many functional groups could be tolerated under these conditions. Under Lindsey conditions a colorless porphyrinogen is first formed, followed by the subsequent oxidation with \textit{p}-chloranil or DDQ. The yields of the porphyrins ranged from 30-40\%, which was a large improvement of the yields
using Adler-Longo or Rothemund conditions. Use of \( p \)-chloranil for the oxidation of the porphyrinogen typically gave higher yields than with DDQ.

As mentioned before, the use of Lindsey conditions is a very mild way to more efficiently produce a wider variety of porphyrins. TPP was formed by dissolving benzaldehyde and pyrrole in dichloromethane in a \( 10^{-2} \) M solution. The acid catalyst (\( \text{BF}_3 \cdot \text{Et}_2 \text{O} \) or TFA) was typically added at a dilution of \( 10^{-3} \) M. Lindsey found that the reaction was very sensitive to many factors such as choice of oxidant or reagent, reaction time, or concentration of starting materials and catalyst. Lindsey also found that the rate for the formation of TPP could be altered by the concentration of acid, but the yield was not typically affected by changes in acid concentration. The yields of TPP at various concentrations were monitored and ten-fold higher and ten-fold lower resulted in much lower yield. One problem in all porphyrin syntheses is the formation of polymeric species versus cyclic species, and it was found that the ratio of these products was not concentration dependent. The rate of the oxidation was dependent on which oxidizing agent was chosen. The use of DDQ yielded the porphyrin within minutes, but the use of \( p \)-chloranil yielded the porphyrin within an hour. Lindsey effectively proved that

\[
\begin{align*}
\text{CHO} & + \text{Ph} \\
\xrightarrow{1) \text{acid}} & \xrightarrow{2) \text{oxidant}} \text{Ph} \\
\xrightarrow{1) \text{acid}} & \xrightarrow{2) \text{oxidant}} \text{Ph}
\end{align*}
\]

**Scheme 1.3:** Synthesis of TPP using Lindsey conditions.
tetraarylporphyrins and meso-tetraalkylporphyrins could be formed under equilibrium followed by a subsequent oxidation to produce many porphyrins in unprecedented yields.

In addition to monopyrrole tetramerization, unsymmetrical porphyrins can be prepared by the condensation of two dipyrromethanes. This is often referred to as the MacDonald [2+2] method. Two variations of the MacDonald [2+2] reaction can be seen in Scheme 1.4. The first example of a [2+2] condensation shows that unsymmetrical porphyrins can be produced from the condensation of two dipyrromethanes if one of the dipyrromethanes contains symmetry about the interpyrrolic carbon. The second example of the [2+2] method is the acid catalyzed self-condensation of a monoformyldipyrromethane to yield the porphyrin after oxidation. As can be seen, the MacDonald [2+2] porphyrin synthesis is a powerful strategy and is the most widely used method toward the syntheses of unsymmetrically substituted porphyrins.

In addition to being prepared from dipyrromethanes, unsymmetrical porphyrins can also be prepared from tripyrrolic intermediates via a [3+1] route. This type of condensation involves the condensation of a monopyrrole with a tripyrrane, and an example of this type of condensation can be seen in Scheme 1.5. The use of this approach was first reported by Boudif and Momenteau, where a 2,5-diformylpyrrole and a tripyrrane were condensed with each other.

The development of the synthetic methods to produce porphyrins have been vastly improved upon in recent times. The development of the synthesis of TPP and the methods such as the [2+2] and the [3+1] have given rise to the synthesis of many novel unsymmetrically substituted porphyrins. These more sophisticated methods have seen
many recent improvements, and their use will likely provide synthetic route to a diverse array of substrates.

**Scheme 1.4:** Examples of the syntheses of unsymmetrically substituted porphyrins via MacDonald [2+2] reactions.

**Scheme 1.5:** Synthesis of an unsymmetrically substituted porphyrin via a [3+1] condensation reaction.
1.2.3 Applications of Porphyrins

Porphyrins have many different applications, but because of their ability to selectively localize in tumor tissues they are heavily investigated for application in cancer therapy.\textsuperscript{24} They have been applied in photodynamic therapy (PDT),\textsuperscript{25} boron neutron capture therapy (BNCT),\textsuperscript{26} radiation therapy (RT),\textsuperscript{27} and magnetic resonance imaging (MRI).\textsuperscript{28} PDT and BNCT are binary cancer therapies that involve activation of tissue-localized sensitizers.\textsuperscript{24} The sensitizer in PDT is activated by low energy red light, and low-energy neutrons are used in BNCT.

In PDT the sensitizer has localized to the tumor cells, and is irradiated with light corresponding to the longest wavelength of that particular species. The light absorbed promotes the sensitizer to the excited state. The singlet-excited state undergoes intersystem crossing to the triplet state, which in turn reacts with oxygen producing singlet oxygen, superoxide anions, and hydroxyl radicals. The presence of these species causes irreversible damage specifically to the tumor cell because they have a limited range in tissue.\textsuperscript{24} In BNCT, a boron-containing species is subjected to a low energy neutron beam. The $^{10}\text{B}$ reacts with neutrons and produces $^4\text{He}^{2+}$ and $^7\text{Li}^{3+}$, which are both cytotoxic and also have a limited range in tissue. The equation of the reaction of $^{10}\text{B}$ and a neutron can be seen in Equation 1.1.

\begin{equation}
^{10}\text{B} + \text{n} \rightarrow ^7\text{Li}^{3+} + ^4\text{He}^{2+} + \gamma + 2.4 \text{ MeV}
\end{equation}

\textbf{Equation 1.1:} Nuclear reaction of $^{10}\text{B}$ with a neutron.

$^4\text{He}^{2+}$ and $^7\text{Li}^{3+}$ produced in Equation 1.1 are high linear-energy transfer particles, which damage the tissues where they are present. These particles can only travel approximately the diameter of one cell. This nuclear reaction also produces 2.4 MeV of
kinetic energy per $^{10}$B nucleus, and the particles produced provide a powerful means of destruction of the tissues where they are present. The carboranylporphyrins prepared here are being investigated for use in BNCT, and the results of these studies will be reported in Chapter 4. The use of PDT and BNCT provide local control of the disease with few side effects. The use of BNCT has been shown to treat deep malignant brain tumors and PDT has been shown to treat superficial cancers such as carcinomas and non-superficial small tumors in combination with fiber optic light delivery.\cite{24} One clear advantage of BNCT over PDT is that neutron beams can penetrate tissues up to ten times deeper than light. This deeper penetration allows tumors to be treated up to 6-7 cm in the tissue. The use of both of these types of therapy provide potential alternatives to surgery, chemotherapy, and other conventional cancer therapies.

\section*{1.3 Peptide and Protecting Group Chemistry}

\subsection*{1.3.1 Introduction}

Proteins and peptides are linear polymers consisting of amino acids, which are linked together by amide bonds.\cite{29} Two to forty amino acids linked together are known as peptides, and longer chains are referred to as polypeptides. Proteins are polypeptides, which have defined structures.

In nature there is a large abundance of proteins that are folded into many different types of structures. The proteins have a wide variety of functions, which depend on the shape of the three dimensional structure.\cite{30} Proteins are often found in helices, sheets, loops, and turns. The conformations of the proteins are stabilized by intramolecular interactions such as hydrogen bonding or steric interactions. The misfolding of proteins plays a vital role in the development of neurodegenerative diseases such as Alzheimer’s,
Parkinson’s, and other related diseases. In diseases such as Alzheimer’s abnormal folding of a protein, which is usually soluble, causes it to aggregate and become an insoluble plaque. This is referred to as an amyloid plaque, and its formation is the basis on which Alzheimer’s disease escalates. The design of compounds that prevent this type of aggregation is an area of research which has received recent attention. The synthesis of peptides is proving itself to be valuable in the prevention of these aggregates.

1.3.2 Syntheses of Peptides

Protecting groups are necessary in the synthesis of peptides because without protecting groups their synthesis could not be controlled. Three of the most commonly used protecting groups in peptide chemistry are Fmoc, Cbz, and Boc. Though other protecting groups are used, these shown in Figure 1.4 are three of the most commonly used in peptide synthesis.

Figure 1.4: Three commonly used protecting groups in peptide synthesis.

The facile removal of a protecting group under a given set of conditions is very important, but these conditions may not be used until the removal of the protecting group is desired. As can be seen in Scheme 1.6, the Fmoc protecting group can easily be removed from the peptide by an amine base. As a result, basic conditions must be avoided throughout the synthesis of the peptide if Fmoc is to remain attached to the peptide.
Scheme 1.6: Example of a base-induced removal of a peptide from the Fmoc protecting group.

The removal of the Cbz protecting group can be effected by catalytic hydrogenation, and the removal of the Boc protecting group can be effected by the use of trifluoroacetic acid. The use of these three protecting groups can be applied toward the synthesis of nearly any peptide. Solid-phase chemistry is often used in the synthesis of peptides, and the first synthesis of a peptide on solid-phase was reported in the 1960’s by Merrifield.\textsuperscript{35} The solid phase is typically a polymeric resin with functionality attached to the polymeric bead, which is used to attach a linker to the resin. The most common materials used for solid-support are usually small beads composed of polymers which have appropriate solubility for the reagents used in the reactions. For example, if more polar starting materials are needed a polyethylene glycol resin would be used. If less polar solvents were needed, a less polar polymer would be used such as polystyrene. The polymer absorbs solvent and the bead enlarges. This phenomenon is commonly referred to as swelling, and more swelling exposes more of the functionality to the reagents.

After the peptide has been synthesized on solid-phase it must be removed through the use of a linker. Linkers provide a means of removal as well as a support on which the peptide can be synthesized. Solid-phase chemistry is not as developed as solution-phase chemistry, but its use has advantages over solution-phase chemistry.\textsuperscript{36} Perhaps the largest advantage of solid-phase chemistry is that excess reagents can be used to drive the reaction forward. After the reaction is complete, the excess solution-phase reagents can
be removed by simple filtration. Peptide synthesis is more easily affected on solid phase, and many developments have been made in the methods of solid-phase peptide synthesis. Usually a linker is attached to a solid-phase support, and the peptide is synthesized on that support. The peptide is then cleaved from the linker and the peptide is isolated. A very general schematic of the synthesis of a peptide on a solid-phase resin can be seen in Scheme 1.7.

**Scheme 1.7:** General example of peptide coupling followed by removal from the solid-phase resin by use of a linker.

1.4 References


29 Oguz, U., **2003**. *Design and Synthesis of Constrained Dipeptide Units for Use as β-Sheet Protomers*. Ph.D. Thesis. Louisiana State University, Baton Rouge, LA, USA.


CHAPTER 2: SYNTHESIS, CHARACTERIZATION, AND DERIVATIZATION OF CARBORANYLPYRROLES

2.1 Introduction

Pyrroles are aromatic heterocycles, which are the key building blocks of synthetic and natural porphyrins. Pyrroles are similar to benzene in that the degree of their nucleophilicity depends on type and amount of substitution present on the ring. As with benzene chemistry, electron-donating groups enhance the nucleophilicity. In pyrrole chemistry, this nucleophilicity facilitates porphyrin synthesis. The \( \pi \)-electrons of pyrroles react with electrophiles such as aldehydes to eventually produce porphyrins. Depending on their substitution, pyrroles can have various levels of reactivity. Pyrroles are the precursors to porphyrins, which are macrocyclic ring structures discussed in Chapter 1. It is this nucleophilicity by which the pyrroles can be polymerized giving tetrapyrrolic systems and other polypyrrolic compounds. Polypyrroles are electrical-conducting polymers, which have received recent attention because of their potential application in solid-state devices, energy storage, and sensor applications.

Pyrroles and polypyrroles are found in biological systems. Some commonly encountered tetrapyrrolic systems that are often observed in nature are porphyrins, chlorins, and bacteriochlorins. Several types of pyrrolic and polypyrrolic systems are shown in Figure 2.1. The systems shown have different arrangements of the pyrrole building blocks. The simplest is pyrrole \( a \), which is a monopyrrole. Pyrroles, which consist of more than one pyrrolic unit are referred to as polypyrroles. Two examples of pyrroles containing two pyrrolic systems are \( b \) and \( c \). A dipyrromethane \( b \) is shown and is essentially a methyl group substituted with two pyrroles. A dipyrromethane can be

condensed with another dipyrromethane to make a porphyrin such as \textbf{d} after oxidation. The system containing two pyrroles fused directly to each other with no carbons between them is a bipyrrrole \textbf{c}. Bipyrrroles can be used to make porphycenes \textbf{e}, which are also tetrapyrrolic systems containing direct linkages and two carbon linkages between two pairs of pyrroles. Porphycenes are porphyrin isomers that are synthetically prepared and not found in nature. Another type of tetrapyrrolic system is a corrole \textbf{f}, which contains three one carbon bridges between the pyrroles and one zero carbon bridge between the pyrroles.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{pyrrole_systems.png}
\caption{Examples of various types of pyrrolic and polypyrrolic systems.}
\end{figure}

2.1.1 Synthesis of Pyrroles

Monopyrroles are the key building blocks of porphyrins, and the syntheses of pyrroles are vital in porphyrin synthesis as porphyrins are constructed from monopyrroles. The scope of porphyrin synthesis is limited by the availability of uniquely substituted pyrroles and polypyrroles.\textsuperscript{9} The development of the Barton-Zard reaction allows facile manipulation of these substitution patterns.\textsuperscript{10,11} This synthetic method was developed in order to produce a wide variety of pyrroles with easily removed protecting groups and substitution which could easily be manipulated. The presence of a
protecting group at the 2 or 5 position of a pyrrole allows a high level of stability. Before
the development of the Barton-Zard reaction, the syntheses of pyrroles were based
primarily on the use of the Paal-Knorr synthesis of pyrroles.\textsuperscript{12} This method involves the
reaction of $\alpha$-amino ketones with $\beta$-ketoesters or $\beta$-diketones, and an example of the
Knorr pyrrole synthesis can be seen in Scheme 2.1.\textsuperscript{13} This type of pyrrole synthesis
involves the \textit{in situ} reduction with zinc of an $\alpha$-keto-oxime produced from the reaction of
the ketone with NaNO\textsubscript{2} and acid. This type of conversion does not typically yield these
pyrroles in high yield.

\begin{center}
\textbf{Scheme 2.1:} Synthesis of an $\alpha$-methyl pyrrole \textit{via} Knorr Pyrrole Synthesis.
\end{center}

The Knorr pyrrole synthesis is of value when the presence of highly electron-
withdrawing groups is desired, but removal of these groups involves a high-temperature
saponification. Synthesis of a pyrrole substituted with a \textit{tert}-butyl ester is one of the most
useful, but by Knorr pyrrole synthesis, these \textit{tert}-butyl esters are very difficult to include.
The Barton-Zard reaction easily allows synthesis of a pyrrole with \textit{tert}-butyl ester
functionality, and only one ester group is present in the product. An example of the
Barton-Zard reaction can be seen in Scheme 2.2. In this example a pyrrole substituted
with a \textit{tert}-butyl ester at one of its $\alpha$ positions is formed, and the removal of such an ester
is easily achieved with TFA.

\textbf{2.1.2 Properties of Pyrroles}

Pyrroles are electron rich heterocycles, which in addition to being tetramerized to
porphyrins, can also be polymerized by various methods to form polypyrroles.\textsuperscript{3}
Polypyrroles are stable electrical conducting polymers that have high conductivity and a low oxidation potential. These electrical conducting materials have received so much recent attention because of their applications in solid-state devices, energy storage, and sensor applications. A common method of polymerization of pyrroles to polypyrroles is by electrochemical polymerization. The loss of two electrons and two protons in the electropolymerization in Scheme 2.3 demonstrates the polymerization of a bipyrrrole, which was also formed by the same type of electropolymerization. Pyrrole was first electropolymerized in 1979 and it has since been found that the synthesis of a polypyrrole by electropolymerization is more rapid than the use of chemical methods.

Carboranes are clusters consisting of carbon, boron, and hydrogen. They can exist in neutral or various anionic forms. The charge of a given species is dependent upon the molecular formula of the species in question. The neutral carborane is a closed-cage structure, and an anionic carborane is an open-cage structure. As in other boranes, bonding of carboranes is not analogous to that of hydrocarbons. Due to the electron-deficiency of carborane cages, they are inductively electron-withdrawing. The chemistry of carboranes is very similar to that of benzene because of their electron withdrawing
nature. The nomenclature of carboranes also resembles that of benzene. The position of the carbons on the cage with respect to one another is used to identify the regioisomers of the carboranes as *ortho*, *meta*, and *para*. One can imagine a carborane as a six-membered ring, and the relationship of each carbon to each other are identified as *ortho*, *meta*, or *para*. An example of each can be seen in Figure 2.2, where each of the regioisomers of carborane are shown.

![Carborane Structures](image)

**Figure 2.2:** Examples of ortho, meta, and para isomers of *closo*-carborane.

As with any other electron-withdrawing group, carboranes can very effectively stabilize a negative charge. Because of their nucleophilic behavior, many pyrroles are often not stable over long periods of time. Attaching carborane cages to pyrroles provides additional stability to the pyrroles. The carboranlypyrroles shown in Figure 2.3 have been previously synthesized, and carboranlypyrrole 1 was found to polymerize electrochemically to yield a novel polypyrrolic material. The polymer had electrochemical properties similar to that of the monomer 1. The polypyrrole produced from pyrrole 1 showed enhanced electrochemical and thermal stability compared to polypyrroles doped with small anions.

Since the electropolymerization of the carboranlypyrrole 1 had been successful, the synthesis was repeated in order to convert it from a neutral *closo* compound to its anionic *nido* derivative. This conversion would produce an anion that would be soluble in polar solvents. Once this solubility was obtained its electrochemical properties were
evaluated by Professor Bruno Fabre at the University of Rennes in France. The synthesis
of the anionic derivative will be discussed in detail and the results of these studies
conducted by Dr. Fabre will also be presented.

![Figure 2.3: Examples of previously synthesized carboranylpyrroles.](image)

In addition to the derivatization of carboranylpyrrole 1, two novel carboranylpyrroles were synthesized using methods similar to those previously employed to make carboranylpyrrole 1. Carboranylpyrrole 2 shown in Figure 2.4 contains a bis(methylene) linkage between the pyrrole and the carborane cage. This novel carboranylpyrrole 2 was synthesized in order to provide a less sterically hindered system, which could be readily polymerized to yield a polypyrrole or tetramerized to yield a porphyrin. The carboranylpyrrole 2 was also converted into its nido derivative and polymerizations of the sodium and tetrabutylammonium salts were investigated. In addition, carboranylpyrrole 2 was also N-alkylated with 7-bromo-1-heptene to allow the corresponding polypyrrole to be attached to a solid surface, such as silica gel. These reactions as well as the results of their electrochemical studies will be discussed.

A third carboranylpyrrole 3 containing two carborane cages linked to the pyrrole ring through two bis(methylene) linkages was synthesized. The two carboranes are introduced via a self cross-metathesis reaction. The conversions following the initial
alkylation are very similar and are actually higher yielding than the reactions to make the carboranylpyrrole 2.

![Figure 2.4: Carboranylpyrroles synthesized in this study.](image)

All of the carboranylpyrroles shown in Figure 2.4 were prepared in high overall yields following similar synthetic methods. All three of these pyrroles have alkyl linkages between the carborane cage and the β-pyrrolic positions. In addition to full characterization of each intermediate, X-ray crystal structures were obtained for several of the reactive intermediates and for all three precursor Boc-protected carboranylpyrroles.

In addition to being electropolymerized, carboranylpyrrole 1 was also previously cyclotetramerized by reduction of the α-ethyl ester of 1 to a 2-carbinol. The carbinol was condensed with acid, and oxidized to yield a mixture of type I-IV porphyrin isomers in 15% yield. The low yield of this tetramerization was due to the electron withdrawing effect of the carborane cage and its steric bulk. The condensation of novel carboranylpyrrole 2 with benzaldehydes gave high yields of novel β-substituted carboranylporphyrins, which are discussed in Chapter 3.
2.2 Results and Discussion:

The carboranylpyrrole 1 prepared previously by Vicente and coworkers was electropolymerized to form an electroactive polymeric film, which exhibited an increased resistance to overoxidation compared to unsubstituted polypyrroles.\textsuperscript{20} To continue these electrochemical studies, the synthesis of carboranylpyrrole 1 was repeated in order to convert it to its anionic \textit{nido} derivative. Such a derivative would be soluble in polar solvents such as acetonitrile or water, depending on the nature of the counter ion. To prepare a less sterically-hindered and less electronegative system, carboranylpyrrole 2 was synthesized. Because of its bis(methylene) linkage between the pyrrolic unit and the carborane cage, there is less of a steric effect compared to that of carboranylpyrrole 1.\textsuperscript{21} Carboranylpyrrole 3 was also prepared containing two (bis)methylene linkages between the carboranes and the pyrrole ring. The synthesis and characterization of all three pyrroles and the preparation of some of their derivatives is discussed here in full detail.

The synthetic route to carboranylpyrrole 1 is shown in Scheme 2.4 and Scheme 2.5. The first step involved the alkylation of 1-methyl-o-carborane, which was first dissolved in THF and deprotonated with \textit{n}-BuLi at 0 °C.\textsuperscript{22} Allyl bromide dissolved in THF was then added at -78 °C. The desired alkylated product 4 was initially formed, but under basic conditions over a 12 h period, the terminal alkene 4 rearranged to the more stable internal alkene 5. On the first attempt, the reaction was found to have exclusively produced the more stable internal alkene 5 in a 60% yield after purification via column chromatography. This base-catalyzed rearrangement was first observed by \textsuperscript{1}H-NMR spectroscopy, and confirmed by the X-ray crystal structure seen in Figure 2.5.
**Scheme 2.4:** Alkylation and subsequent addition of phenylsulfenyl chloride.

Following the reaction closely by TLC and quenching the reaction after about 2 h after all material had been converted to alkene 4 allowed successful isolation product in 68% yield. The reaction was quenched by the addition of water, saturated NaCl, and then extracted into EtOAc. The crude reaction mixture was dried, filtered, concentrated under reduced pressure, and purified by column chromatography. The product must not come in contact with dry silica gel, as it lowers the yield.\(^{23,24}\) The alkene 4 was isolated as a colorless oil, and its \(^1\)H-NMR spectrum can be seen in Figure 2.6.

After the alkylation product 4 was purified, phenylsulfenyl chloride was added to the alkene \textit{via} an anti-Markovnikov addition to yield thioether 6.\(^{25}\) The phenylsulfenyl chloride was generated \textit{in situ} by heating NCS in DCM to reflux temperature. Initially one drop of benzenethiol was added to initiate the reaction, and the solution turned yellow indicating the formation of PhSCl. If the solution did not turn yellow it was found to be necessary to repeat the procedure because the radical intermediates are sensitive to moisture. After the initial addition of benzenethiol, the reaction was stirred at reflux for 30 min when no further color change was apparent. At this point the heat was removed and the remaining benzenethiol was added very slowly to prevent formation of
Figure 2.5: X-Ray crystal structure of internal alkene 5.
unwanted diphenyldisulfide dimer. After all of the benzenethiol had been added, the reaction became slightly darker producing an amber-colored slurry.

After 2 h of constant stirring, the flask was cooled to -78 °C and the carboranylalkene 4 was added in one portion to ensure anti-Markovnikov orientation of thio ether 6. If alkene 4 was not added in one portion, it was observed that more of the Markovnikov oriented product formed. After the addition of the alkene 4 in dry DCM the reaction progress was followed closely by TLC. After 2 h, all starting material had been consumed and converted to thioether 6. At this time the reaction was complete, so hexane was added to the reaction mixture until succinimide precipitated from the solution. The reaction mixture was filtered through a short plug of silica, and the resulting crude product was purified via column chromatography in 95% hexane: 5% EtOAc. The $^1$H-NMR spectrum of the product obtained was not conclusive of the regiochemistry of the product, so the product was recrystallized using a mixture of DCM and hexane. The resulting large crystals were submitted for X-ray crystallographic analysis and the structure of the sulfide 6 can be seen in Figure 2.7.

Sulfide 6 was then converted into sulfone 7 by oxidation with mcpba. Even though this reaction seemed trivial, it presented the problem of incomplete oxidation. The first attempt at this reaction yielded two products, which were separated via column chromatography. The two products isolated were found to be the sulfone 7 and the corresponding sulfoxide 10. The $^1$H-NMR spectra of both products were very similar except that the proton α to the sulfone in the more polar product sulfone 7 was more downfield than that in sulfoxide 10. The similarities between the $^1$H-NMR spectra gave
Figure 2.6: $^1$H-NMR spectrum of alkene 4.
Figure 2.7: X-Ray crystal structure of sulfide 6.
evidence that both products were forming. The FAB-MS of the more polar product verified that the sulfone 7 was forming; however, the FAB-MS of the less polar product was exactly the same as that of sulfide 6. This loss of OH via the McLafferty rearrangement during mass spectrometry analysis is common with sulfoxides. Sulfones do not undergo this type of rearrangement. The FAB-MS evidenced rearrangement and the 1H-NMR also evidenced the predominant formation of sulfoxide 10 over sulfone 7. Another unusual phenomenon in this pathway was the immediate formation of a more polar spot, which had the same polarity as the sulfone. Allowing the reaction to proceed for additional time resulted in the formation and isolation of the sulfoxide, but quenching the reaction shortly after the addition of mcpba results in the isolation of the desired sulfone 7 in 95% yield.

Two solutions for the oxidation reaction were found. The first solution was to proceed using the sulfoxide 10 in Scheme 2.5, and the other was to quench the reaction shortly after the addition of mcpba. Quenching the reaction shortly after the addition of mcpba led to a 95% yield of the sulfone after recrystallization from EtOH. Both pathways in Scheme 2.5 ultimately led to the same α-free carboranylpyrrole 1, following similar reactions.

To make a substrate suitable for the Barton-Zard reaction the β-chlorosulfone 7 must be converted into an α,β-unsaturated sulfone 8. This conversion was easily accomplished by a dehydrochlorination reaction using DBU. This reaction is very straightforward if not more than one equivalent of DBU is used. If excess DBU was used, a rearrangement to the more stable internal alkene would have occurred. This rearrangement was avoided by the use of 0.9 equivalents of DBU. The sulfone 7 was
initially dissolved in dry THF and cooled to 0 °C before adding DBU dissolved in THF. Upon the addition of DBU, a white precipitate immediately formed. According to TLC the reaction was complete, so it was filtered to separate the salt byproduct then extracted from an aqueous solution. This product was then purified by column chromatography or by recrystallization. On a larger scale (i.e. 1 g), recrystallization gave a more pure compound in high yield, and on a smaller scale, column chromatography gave a higher yield (i.e. 97%). The $^1$H-NMR spectrum of the elimination product 8 can be seen in Figure 2.8.

The $\alpha,\beta$-unsaturated sulfone 8 was converted into the $\alpha$-Boc pyrrole 9 via the Barton-Zard reaction.$^{29}$ In order to make a pyrrole bearing an easily removed protecting group, the pyrrole was protected with a Boc group.$^{30}$ The Boc-protected pyrrole 9 can easily be converted to the $\alpha$-free pyrrole 1 in 95% yield by reacting with TFA at RT for five minutes. Interestingly, the Barton-Zard reaction of the sulfone gave one regioisomer and the Barton-Zard reaction of the sulfoxide 11 gave the other regioisomer 12. In Scheme 2.2 it can be see that despite differences in reactivity, the sulfone 8 and the sulfoxide 11 ultimately led to the same $\alpha$-free pyrrole 1.

A possible mechanistic explanation for the formation of different regioisomers of carboranylpyrroles 9 and 12 is found in Scheme 2.6. The sulfoxide 11 is not as able to stabilize the negative charge, so the initial cyclization could proceed through a concerted mechanism. The sulfone 8 is more capable of stabilizing a negative charge of intermediate 8a, so the reaction undergoes a typical stepwise reaction when the sulfone is used. Intermediate 8a then undergoes an intramolecular nucleophilic attack to form
Scheme 2.5: Synthesis of carboranylpyrrole 1.
Figure 2.8: $^1$H-NMR spectrum of unsaturated sulfone 8.
Intermediate 8b. Intermediates 8b and 11a then eliminate and undergo proton transfer to produce pyrroles 9 and 12. A concerted mechanism still does not answer the question of the regioselectivity of the Barton-Zard reaction. This preference could be explained by the difference in the electronic properties of α,β-unsaturated sulfones and α,β-unsaturated sulfoxides. The β position of the sulfoxide is more electron rich and the β position of the sulfone is very electron poor. The hard-soft properties of the sulfoxide 11 vs. the sulfone 8 along with the nucleophilic properties of the anionic isocyanate govern the regiochemistry of the pyrroles 9 and 12 formed.

To make the α-Boc pyrrole 9 by the Barton-Zard reaction, the α,β-unsaturated sulfone 8 or sulfoxide 11 and tert-butyl isocyanoacetate are dissolved in dry THF. The chosen base, NaO’Bu, was dissolved and the resulting solution was added to a solution containing sulfone 8 or sulfoxide 11 and tert-butyl isocyanoacetate. Immediately following the addition of NaO’Bu, the solution turned yellow. The solution then became cloudy and was stirred at reflux for 6 h and at RT for an additional 8 h. After this time the reaction mixture was quenched by the addition of saturated NaCl and H2O. The aqueous layer was extracted with EtOAc, and the resulting organic layer was dried, filtered, and concentrated to yield the crude α-Boc protected pyrrole 9. The pyrrole was purified by column chromatography using 75% hexane: 25% EtOAc for elution. As can be seen in Scheme 2.6, the regiochemistry of the pyrrole is governed by whether the sulfone 8 or the sulfoxide 11 is used.
The differing chemical shifts of the pyrrolic peaks hinted that both isomers were forming. The *only* difference between the $^1$H-NMR of both isomers was the chemical shift of the pyrrolic protons. This suspicion has since been confirmed by obtaining a molecular structure for each isomer. These structures can be seen in Figure 2.8 and Figure 2.9 below.

**Scheme 2.6:** Proposed mechanism for the formation of pyrroles 9 and 12.

Though sulfone 8 and sulfoxide 11 led to different regioisomers, they ultimately produced the same $\alpha$-free pyrrole 1. This pyrrole 1 was previously characterized and was found to readily electropolymerize forming an electroactive polymeric film which showed increased resistance to oxidation. The removal of the Boc group from the pyrrole occurs at room temperature by dissolving the Boc-protected pyrroles 9 or 12 in neat TFA, but later it was found that applying only a small amount of heat causes the reaction to occur quickly producing the $\alpha$-free pyrrole 1 in a nearly quantitative yield. Deprotection without applying heat is very slow and a slightly more polar side product also forms. This side-product is likely the dimer of the pyrrole. After the reaction was determined to be complete by TLC, the reaction mixture was quenched with saturated
Na₂SO₃ in order to neutralize excess TFA. The reaction mixture was washed further with saturated Na₂SO₃ until the washes were basic, then with NaHCO₃, and finally with NaCl. Drying over anhydrous MgSO₄ followed by filtration through a celite cake yielded the crude pyrrole. The crude material was then dissolved into a 1:1 mixture of DCM:hexane and filtered through a plug of silica gel yielding the pure α-free pyrrole 1 in a 100% yield.

Previously, pyrrole 9 was cyclotetramerized by reducing the ester group to the corresponding pyrrole carbinol with LAH followed by condensation in the presence of TFA.¹⁹ The porphyrinogen was then oxidized with p-chloranil to yield a mixture of type I-IV porphyrins in 15% yield. The porphyrins obtained showed a single molecular peak in the MALDI-MS, an etio type visible spectrum, and multiple resonances in the ¹H-NMR spectrum indicating the formation of the four isomers.³¹

The low yield obtained for this porphyrin was due to steric hindrance of the bulky carborane group and the electronegativity of the carborane groups. We rationalized that a carboranylpyrrole with a bis(methylene) linkage such as 2 could be more efficiently tetramerized to the carboranylporphyrin.²¹ Pyrrole 2 was synthesized by the same methods using a similar synthetic strategy as in the preparation of carboranylpyrrole 1, bearing only one methylene spacer. The synthetic route to pyrrole 2 is seen in Scheme 2.7, and this desired pyrrole 2 was produced in 55% overall yield.

As with pyrrole 1, 1-methyl-o-carborane was first alkylated with a terminal alkene.²² The alkylation of the long chain was catalyzed with LiI because the reactivity of allyl bromide is higher than that of 4-bromo-1-butene. The starting material,
Figure 2.9: X-Ray crystal structure of Boc-protected carboranylpyrrole 9.
Figure 2.10: X-Ray crystal structure of Boc-protected carboranylypyrrole 12.
1-methyl-α-carborane, was first deprotonated with \( n \)-BuLi solution and allowed to stir for 30 min. while warming to room temperature. After this time, the solution was then cooled to \(-78^\circ C\) and a THF solution of 4-bromo-1-butene was added followed by the addition of a THF solution of LiI to catalyze the reaction. The resulting solution was then allowed to warm to room temperature for 16 h. Initially the reaction only yielded the alkylated carborane 13 in a 55% yield after purification, but later it was found that allowing the reaction to proceed for up to one week slowly increased the yield to 74% after purification. Other reaction conditions were also explored such as changing the sequence of addition of LiI and 4-bromo-1-butene. This, in addition to refluxing the solution did not improve the yield to any noteworthy extent. Even using one equivalent of LiI did not improve the yield. Allowing the reaction to proceed for a long period of time was found to be the only way to improve the yield. After the reaction had been allowed one week, it was quenched by the addition of water and saturated NaCl. The aqueous layer was extracted with EtOAc and the alkylated carborane 13 along with remaining starting material are dried, filtered, and concentrated. Then the crude reaction mixture was purified by column chromatography in 90% hexane: 10% EtOAc to yield the alkylated carborane 13. The remaining material was unreacted starting material, which was easily purified for reuse.

The following reaction was an anti-Markovnikov addition of PhSCl, which produced a thio ether. The PhSCl was generated \textit{in situ} the same way as described above, and alkene 13 was added very slowly at \(-78^\circ C\). Surprisingly the reaction formed a large amount of the unwanted Markovnikov product, which preferentially formed crystals.
These large crystals were submitted for X-ray crystallographic analysis, and the results can be seen in Figure 2.11.

In previous examples of this type of reaction the alkene was always added quickly in one portion. Adding the alkene all in one portion produced the anti-Markovnikov product exclusively. This quick addition of the alkene to phenylsulfenyl chloride was a very simple solution that easily prevented the formation of the unwanted Markovnikov product. After the addition of the alkene 13 the reaction is nearly complete by TLC, but it is allowed to proceed for and additional h to allow full conversion. At first this reaction gave problems with the purification because of the excess NCS, succinimide, and diphenyldisulfide produced in the generation of phenylsulfenyl chloride were all present in the reaction mixture. Filtering through a plug of silica remedied this problem by removing the unreacted NCS and succinimide produced in the generation of phenylsulfenyl chloride. After filtration, the reaction mixture was recrystallized in a
mixture of DCM/hexane to yield the anti-Markovnikov product 14 as a white crystalline material. Recrystallization proved to be an effective yet unreliable method for purifying the product because sometimes it starts to precipitate the sulfide and then eventually becomes an oily residue. The best way found to purify this mixture was using column chromatography with 85% hexane: 15% EtOAc for elution. This yielded still a mixture of the product along with a small amount of the dimer. Attempting the next reaction on the impure material and purifying after the reaction has completed is not a way to remove the dimer from the mixture. Column chromatography is actually a very effective method of purification if the reaction mixture is dried on silica gel, loaded on the column, and the column washed with pure hexane until the dimer passes through the column. After this time, the solvent system can be changed to 95% hexane: 5% EtOAc and the sulfide passes quickly through the column. The pure anti-Markovnikov product 14 was isolated in 92% yield.

The oxidation of sulfide 14 to sulfone 15 was very easy if the starting material contained no impurities from the previous reaction. If the starting material contained even a small amount of dimer, the resulting mixture formed by the oxidation was very difficult to purify. The starting material was first dissolved in DCM and cooled to 0 °C. Solid mcpba was dissolved in DCM and added to the reaction mixture and the resulting mixture was stirred. According to TLC, the reaction mixture was complete immediately following the addition of mcpba. The reaction mixture was then washed with saturated aqueous Na₂SO₃ to remove excess TFA until the washes were basic, then with saturated aqueous NaHCO₃, and finally with saturated aqueous NaCl. Drying and concentrating...
Figure 2.11: X-Ray crystal structure of Markovnikov product 14.
under reduced pressure afforded the sulfone 15, which was recrystallized from hot EtOH to yield the pure compound as a white solid in nearly a quantitative yield.

To make α,β-unsaturated sulfone 16 for the Barton-Zard reaction, the sulfone 15 must be dehydrohalogenated with base.\textsuperscript{25} Assuming the longer chain would not rearrange, excess base was initially used to maximize the amount of product. TLC indicated the formation of four different products, three of which had very similar polarity. One of the products was very non-polar according to TLC, and was correctly predicted to be diene 17 produced in the double elimination of the sulfone. This non-polar product was very crystalline and the X-ray crystal structure in Figure 2.12 was used to verify that a double elimination occurred. The complete separation of the more polar products was very difficult and all of them were not completely separated from each other. The desired sulfone 16 was purified and was isolated in only 15% yield. The carboranyldiene 17 was the major product isolated in 52% yield. To solve the problem of this side reaction, 0.9 eq. of DBU was added very slowly. This did solve the problem and the pure unsaturated sulfone 16 was isolated as a fluffy white solid in 90% yield after recrystallization.

The $^1$H-NMR spectrum of unsaturated sulfone 16 showed no impurities, but had a very unusual peak, which resembled a four-proton singlet. The protons α to the alkene and α to the carboranyl group had the same chemical shift. This seemed unusual, but the integral of the mentioned protons corresponded to four protons, which was consistent with the correct area of the methylene groups. The $^1$H-NMR of α,β-unsaturated sulfone 17 can be seen in Figure 2.13.
Figure 2.12: X-Ray crystal structure of rearranged diene 16.*
Figure 2.13: $^1$H-NMR spectrum of $\alpha,\beta$-unsaturated sulfone 16.
The α,β-unsaturated sulfone 16 is a suitable substrate for the Barton-Zard reaction, and can be converted to an α-protected pyrrole. The Barton-Zard reaction yielded a Boc-protected pyrrole 18, which was deprotected by dissolving in TFA to yield the α-free pyrrole 2. As before, tert-butyl isocyanatoacetate was used in the Barton-Zard reaction because it produced a Boc-protected pyrrole. A Boc group is easily removed and tert-butyl isocyanatoacetate is commercially available. The Cbz protecting group is also removed easily, but benzyl isocyanatoacetate is not commercially available.

First, the unsaturated sulfone 17 was combined with tert-butyl isocyanatoacetate in THF, the mixture was heated to reflux temperature, and NaO'Bu was added in a minimal amount of THF. Immediately following the addition of even a small amount of base results in a distinct color change from a clear solution to a bright yellow solution, which eventually becomes turbid. Dissolving NaO'Bu in anhydrous THF can be quite difficult, and a large amount of THF is required to dissolve it completely. Shortly after the addition of NaO'Bu the reaction appeared to be nearly complete according to TLC, but the reaction mixture was stirred at room temperature for 12 h to insure completion. After the reaction was complete, it was quenched with aqueous saturated NaCl and extracted into EtOAc.

The first attempt at this reaction as well as every other time gave excellent yields, but the removal of tert-butyl isocyanatoacetate was very difficult because initially three equivalents of it were used. The next time, slightly less than one equivalent of tert-butyl isocyanatoacetate was used in order to consume all of it. Even with 0.95 equivalents of tert-butyl isocyanatoacetate the yields were still excellent, and the purification was very easy. Column chromatography with 80% hexane; 20% ethyl acetate allowed a very easy
separation. The less polar Boc-protected pyrrole 18 eluted quickly through the column yielding the Boc-protected pyrrole in a 92% yield. The $^1$H-NMR spectrum of Boc-protected pyrrole 18 can be seen in Figure 2.14.

Many solvent systems for recrystallization were explored to make crystals for obtaining a molecular structure. The systems that usually worked for many of the intermediates did not produce large crystals. Dissolving the pyrrole in a very small amount of DCM, adding a small amount of hexane, and allowing the DCM to slowly evaporate yielded long thread-like needles. The next method employed was dissolving the pyrrole in EtOH and allowing the solvent to slowly evaporate. This method also yielded small needles. A similar method using DMF was attempted, but it too was not successful. Finally, dissolving the pyrrole in toluene by applying heat to dissolve all material and allowing the toluene to slowly evaporate gave very large crystals. The resulting crystals were analyzed by X-ray crystallographic analysis and the X-ray crystal structure of the Boc-protected pyrrole 18 can be seen in Figure 2.15.

The Boc-group at the α position can be easily removed with TFA to form the α-free pyrrole 2. Initially the Boc group was removed by dissolving the pyrrole 18 in TFA and allowing the reaction mixture to stir at room temperature. The Boc-protected pyrrole 18 dissolved immediately in TFA, but after a short period of time a solid precipitated from the reaction mixture. According to TLC this precipitate is a very polar intermediate, which is the carboxylic acid of the Boc ester. Later it was discovered that the reaction could be completed in higher yield and more quickly by just applying enough heat to dissolve all contents of the flask. Applying heat more than likely assists in the
Figure 2.14: $^1$H-NMR spectrum of Boc-protected pyrrole 18.
decarboxylation of the pyrrole, because without heat the decarboxylation step is very slow.

The deprotection of a pyrrole must be monitored closely by TLC, because pyrroles tend to polymerize in TFA. Heating actually gives the pyrrole so little time to polymerize that this circumvents this problem. Once the reaction is determined to be complete by TLC, it is stopped by the addition of a saturated solution of Na$_2$SO$_3$ and EtOAc, and washed with Na$_2$SO$_3$ until the washes are basic. After all of the TFA was neutralized, the reaction mixture was washed with saturated NaHCO$_3$ then with saturated NaCl.

The facile electropolymerization of pyrrole 1 gave reason to pursue pyrroles that are soluble in more polar solvents such as water or acetonitrile. This type of solubility could be achieved by base degradation of the closo carborane cage to the nido carborane cage. This involves the loss of a boron atom to yield an anionic species. The nature of the counter ion on the nido compound could be used to manipulate its solubility. For example, a tetrabutylammonium salt would be more soluble in organic solvents and a metal salt such as potassium would be more water-soluble. The simple base degradation of the closo carborane cage to the anionic nido analogue could be employed to achieve solubility in more polar solvents.

Though there are many different methods for degrading carborane cages, the degradation with 3:1 mixture of pyridine and piperidine was first attempted. This basic solution was added to the pyrrole and the final mixture was stirred at room temperature for 12 h. After this time the starting material had completely disappeared by TLC and the product was assumed to have formed. Surprisingly, the desired product had not formed.
Figure 2.15: X-Ray crystal structure of the Boc-protected carboranylpyrrole 18.∗
According to mass spectrometry a neutral intermediate 19 shown in Scheme 2.8 was forming and could not be fully converted to the anion.\textsuperscript{33}

In the mechanism of the degradation, the base attacks a boron atom adjacent to the carbon atom of the carborane cage and the amine leaves along with a boron atom from the cage. This intermediate with the nitrogen bound to the boron was not converting to the \textit{nido} anion by the loss of boron. Another way to degrade a carborane was attempted using a solution of KOH in EtOH and refluxing for 30 min.\textsuperscript{34} This method also did not yield the desired product, but a third method using a dilute solution of TBAF gave high yield of the tetrabutyl ammonium salt 20.\textsuperscript{35}

\textbf{Scheme 2.8:} Attempted deboronation of carboranylpyrrole 1.

The pyrrole 1 was combined with TBAF in the presence of H\textsubscript{2}O in THF. Initially the reaction was not proceeding to any large degree, so a slight amount of heat was applied. The reaction was monitored closely by TLC, and within 2 h all of the starting material had completely disappeared. The tetrabutylammonium salt 20 was produced by the method shown in Scheme 2.9. After all of the starting material had disappeared, THF was removed under reduced pressure and DCM was added. The DCM layer was washed with 3 portions of H\textsubscript{2}O to remove excess TBAF. The DCM layer was then dried over MgSO\textsubscript{4}, filtered through a celite cake, and concentrated under reduced pressure. The off-white solid was then recrystallized in EtOH and the \textit{nido} carboranylpyrrole 20 was
collected in high yield. The product of this reaction was a tetrabutylammonium salt that was soluble in DCM and easily purified.

**Scheme 2.9:** Base degradation of carboranylpyrrole 1 with TBAF.

The *nido* anion of pyrrole 21 was also prepared. The same procedure using TBAF was used to make the long chain *nido* carboranylpyrrole 21 and is shown in Scheme 2.10. The bis(methylene) linkage could possibly relieve strain and make the pyrroles more reactive toward electropolymerization. Unfortunately the long chain *nido* pyrrole 21 also would not electropolymerize. Initially it was thought that the steric effect of the large counter ion was causing the pyrrole to not polymerize, so it was converted into the potassium salt. Surprisingly the potassium salt 22 also would not polymerize to yield any polymeric material. This result evidences an electronic effect because the much smaller potassium salt also would not polymerize. This type of effect could be because an anion would not be as withdrawing as the neutral *closo* carborane cage in carboranylpyrrole 1.

**Scheme 2.10:** Base degradation and ion exchange of carboranylpyrrole 1.

The $^1$H-NMR spectrum of the long chain tetrabutylammonium salt 21 can be seen in Figure 2.16. The broad peak in the negative region of the $^1$H-NMR spectrum is
attributed to the bridged hydride remaining on the \textit{nido} cluster after deboronation with base.

In order to attach the polypyrrole to silica gel to make a polymeric film, the pyrrole was alkylated with an olefin. With this objective in mind the alkylation of the N-position of the long chain pyrrole with 7-bromo-1-heptene was investigated. To initially explore this type of reaction, the alkylation of pyrrole with 4-bromo-1-butene was studied. The first base used in this alkylation was \textit{n}-BuLi. The reaction mixture turned black after a short period of time and did not yield an appreciable amount of desired alkylated product. A procedure using KOH by Smith and coworkers was found, so this method using KOH in DMSO was attempted on Boc-protected pyrrole 9.\textsuperscript{36} The use of a polar-aprotic solvent was used to enhance the nucleophilicity of the anionic pyrrole. A large amount of a less polar product was detected by TLC, so finely ground KOH was used in the deprotonation of the Boc-protected pyrrole 9 and 7-bromo-1-heptene was used in the subsequent alkylation. After the pyrrole 9 was added to the reaction mixture, the contents of the flask immediately turned light yellow. To insure complete deprotonation, the reaction mixture was stirred for an additional 30 min. After that time had elapsed, 7-bromo-1-heptene was added, and the reaction was monitored constantly by TLC. The reaction was not fast, but according to TLC did go nearly to completion. The reaction mixture was quenched by the addition of saturated NaCl, distilled water, and extracted into EtOAc. To insure complete removal of the DMSO the organic layer was washed with three portions of distilled water and the product was isolated in a 55\% yield after purification by column chromatography. In order to have an \textit{α}-free pyrrole for the
Figure 2.16: $^1$H-NMR spectrum of tetrabutylammonium salt 21.
electropolymerization, the Boc group was removed under the conditions described earlier in this chapter.

The same reaction was attempted on the α-free pyrrole 2 as shown in Scheme 2.12. Unfortunately, this avenue yielded the desired product in only 23% yield using KOH as the base. Because of such a large difference in polarity the starting material was easily separated from the N-alkylated pyrrole using column chromatography. The starting material was recovered and the procedure was repeated until the starting material had all been consumed. This difference in yield between the pyrrole 9 and the pyrrole 2 is probably due to the presence of the Boc group in pyrrole 9. The α-free pyrrole 2 is

more basic, and the deprotonated pyrrole could be causing an E2 elimination to occur. An elimination reaction would regenerate the starting material by reprotonation of the pyrrole and would lower the yield of the N-alkylated product. Another possible explanation for the low yield with the α-free pyrrole is that the deprotonation with KOH does not go to completion. The Boc-protected pyrrole 9 is more acidic at the N-position because of the withdrawing effect of the Boc group. In order to improve the yield of the alkylation of the α-free pyrrole it was decided to apply a small amount of heat.

\[ \text{Scheme 2.11: N-alkylation of carboranylpyrrole 9.} \]

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Unfortunately this quickly decomposed the product and starting material into many undesired products. The small amount of product initially present disappeared quickly from the TLC, and no product was recovered.

Scheme 2.12: N-alkylation of carboranylpyrrole 2.

In need of a higher yield it was found that an alternative method for the N-alkylation of the long chain pyrrole 2 was necessary. The more efficient conversion of the pyrrole 9 to the N-alkylated pyrrole 23 gave reason to attempt the N-alkylation on the Boc-protected pyrrole followed by the subsequent removal of the Boc group. This same procedure by Smith and coworkers also used NaH to deprotonate the pyrrole. The Boc-protected pyrrole 18 in Scheme 2.13 was first alkylated then the Boc group was removed. A 60% dispersion of NaH in mineral oil was weighed out into a flask and the flask was purged with Ar. After the atmosphere of the flask was inert, the NaH was washed with dry hexane to remove the mineral oil. The flask was evacuated, charged with dry DMF, stirred, and the pyrrole 18 dissolved in DMF was added. The addition of the pyrrole immediately resulted in a yellow solution, which was stirred for 30 min. After this time had elapsed, 7-bromo-1-heptene was added in DMF, and within one hour all of the
starting material had been completely converted to the Boc-protected derivative of pyrrole 24. As with the pyrrole 9 the reaction was quenched by the addition of water and saturated NaCl, dried, filtered, and concentrated. The resulting oil was dissolved in TFA and pyrrole 24 isolated in 68% yield. The resulting crude product was filtered through a plug of silica gel to yield a light-yellow oil, which needed no further purification according to the $^1$H-NMR spectrum shown in Figure 2.17.

The improvement of this yield in Scheme 2.13 is more than likely a combination of the use of NaH instead of KOH and the use of the Boc-protected pyrrole 18 instead of the $\alpha$-free pyrrole 2. Because the Boc-protected pyrrole 9 was N-alkylated using KOH in 55% yield it seems that the Boc-protected pyrrole was alkylated more efficiently than the $\alpha$-free pyrrole.

One obvious feature of pyrroles is that they are five-membered rings, which do not contain as much symmetry as six-membered rings. The synthesis of a symmetrical pyrrole would provide a porphyrin similar to OEP or octamethylporphyrin. The tetramerization of a symmetrical pyrrole will give only one product. All of the pyrroles prepared up to this point contained very little symmetry, so I began to envision a way to make a carboranlypyrrole with more than just one plane of symmetry. This type of
Figure 2.17: $^1$H-NMR spectrum of N-alkylated pyrrole 24.
symmetrical molecule would require two carborane cages both substituted with the same
type of linkages. Previously Vicente and coworkers\textsuperscript{19} prepared a symmetrical
carboranylpyrrole using Eschemoser’s salt and a silyl protected pyrrole, but it was
prepared in low yield and only had one methylene linkage between the carborane groups
and the pyrrole ring.

To prepare the dicarboranylpyrrole 3 with two bis(methylene) linkages, a new
methodology was explored. A ruthenium-catalyzed cross-metathesis reaction was
attempted to self-couple carborane 13. Unfortunately, the self cross-metathesis reaction
and Hoyveda’s catalyst shown in Scheme 2.14 to make the symmetrical carboranylalkene
25 did not yield the desired product. As an alternative to the cross-metathesis to make
the dicarboranylalkene 25 in Scheme 2.14, a McMurry reaction was attempted on the
aldehyde 26 prepared by ozonolysis. Starting with the alkene 13 dissolved in DCM,
ozone was bubbled through the reaction flask. A small aliquot of the reaction mixture
was taken from the reaction mixture and a drop of dimethyl sulfide was added. The
reaction was monitored closely by TLC, because leaving the reaction too long in the
presence of oxygen oxidizes the aldehyde 26 to the corresponding carboxylic acid
lowering the yield of the aldehyde.

After all of the alkene had been consumed dimethylsulfide was added and the reaction
mixture was stirred. There were two major products formed, and aldehyde 26 was
isolated in 60% yield after column chromatography with 85% hexane: 15% EtOAc. A
similar procedure used a 1:1 DCM: methanol mixture, and the pure aldehyde 26 was
isolated in a 92% yield after purification with column chromatography. The \textsuperscript{1}H-NMR
spectrum of aldehyde 26 can be seen in Figure 2.18. To make the desired
Scheme 2.14: Attempted synthesis of precursor to carboranylpyrrole 3.

dicarboranylalkene, a McMurry reaction was attempted on the carboranylaldehyde 26 to make the dicarboranylalkene 25, but the product obtained was very polar and according to $^1$H-NMR was not the desired alkene. This procedure was not thoroughly investigated, and some variation of the McMurry reaction could have likely produced the desired alkene.

An alternative to the McMurry reaction using 1,6-dibromo-3-hexene did produce the dicarboranylalkene 25. A slight modification to a procedure by Crowe and coworkers$^{37}$ produced 1,6-dibromo-3-hexene in a 68% yield. 4-Bromo-1-butene was dissolved in DCM and Hoyveda’s ruthenium catalyst was added to the flask. The reaction mixture contained no 4-bromo-1-butene, so the reaction was assumed to be complete. To isolate the product, the reaction mixture was filtered through a plug of silica gel and concentrated under reduced pressure to give pure 1,6-dibromo-3-hexene.

To make the dicarboranylalkene 25 in Scheme 2.15, 1,6-dibromo-3-hexene was alkylated with 2-lithium-1-methyl-o-carborane using LiI catalysis.$^{22}$ In an attempt to improve the yield of the desired dicarboranylalkene 25, three equivalents of 1-methyl-o-carborane were used.$^{38}$ Two products were isolated by column chromatography from this reaction.
The first product isolated was a non-polar conjugated diene 27 and was identified as the product of an elimination reaction after the first site had been alkylation. Despite the large amount of this by-product formed, the desired dicarboranylalkene 25 was isolated in 44% yield. In an attempt to improve the yield of the desired product, suppression the formation of the diene by using less base was attempted. The amount of 2-lithium-1-methyl-o-carborane was lowered from 3 equivalents to 2.5 equivalents. This did not improve the yield of the dicarboranyl alkene 25.

After the dicarboranylalkene 25 was isolated, the remaining steps in Scheme 2.15 to make the dicarboranylpyrrole 3 gave excellent yields using the same type of reaction sequence used to prepare the other carboranylpyrroles. As in the addition reactions before, phenylsulfenyl chloride was generated and added to alkene 25 at -78 °C. At that temperature the addition was very slow, so the reaction was warmed slowly to room temperature. By the time the reaction mixture had reached room temperature the addition product 28 had completely formed. The TLC showed that only a small amount of diphenyldisulfide dimer had formed, and no other impurities were detected by TLC. Hexane was added until succinimide and NCS precipitated, and the resulting precipitate was removed by filtering through a plug of silica gel. The thio ether 28 was easily isolated in 99% yield as a fluffy white material, after column chromatography using 70% hexane: 30% DCM. The ¹H-NMR spectrum of sulfide 28 can be seen in Figure 2.19.

Because the sulfide 28 was not stable over long periods of time in previous syntheses, it was immediately oxidized to the sulfone 29 by the same procedure with mcpba. The sulfide 28 was dissolved in DCM, and mcpba dissolved in DCM was added very slowly at 0 °C. Unlike the sulfide 14, the oxidation of dicarboranyl sulfide 28 did
Figure 2.18: $^1$H-NMR spectrum of aldehyde 26.
not occur immediately, but over a period of 16 h. To remove the excess mcpba, the reaction mixture was washed first with a saturated solution of Na$_2$SO$_3$, NaHCO$_3$, then NaCl. The crude mixture was dried and filtered through a plug of silica gel and the sulfone 29 was isolated in 93% yield and needed no further purification according to $^1$H-NMR.

To make an $\alpha,\beta$-unsaturated sulfone 30 for the Barton-Zard reaction, the same type of elimination reaction using DBU was employed. Because of past experience with unwanted rearrangements when attempting these elimination reactions, 0.9 equivalents of

**Scheme 2.15:** Synthesis of dicarboranylpyrrole 3.
DBU was used. Sulfone 29 was dissolved in THF at 0 °C, and DBU dissolved into THF was added dropwise. The addition of DBU to the reaction mixture immediately resulted in the formation of a cloudy precipitate. The reaction was determined to be complete by TLC, so the reaction was quenched with aqueous saturated NaCl. The resulting mixture was stirred and extracted into EtOAc, dried, and concentrated under reduced pressure to yield the product as a white powder.

Expecting the formation of both the E and Z isomers in the dehydrohalogenation, it was surprising that only one sulfone isomer 30 was formed according to ¹H- NMR spectrum. The formation of only one product gives some insight into the reaction mechanism. Only one spot could be seen by TLC, although TLC does not conclusively determine the presence of one or more products. The ¹H-NMR of the dehydrohalogenation product was unusually clean, indicating the formation of only one product. The one peak in the olefinic region was a distinct triplet, and there are no other peaks in that region that could be the other isomer. The ¹H-NMR spectrum does not conclude which isomer is formed because there are no olefinic coupling constants to compare with known data. The ¹H-NMR spectrum in Figure 2.13 of α,β-unsaturated sulfone 16 showed two olefinic peaks, both of which were terminal. The peaks both appeared to be doublets and were dramatically different from each other. These olefinic doublets appeared at 6.41 and 5.81 ppm, and were separated to such a large degree because their cis-trans relationships with the sulfonyl group. The presence of only one triplet in the olefinic region of the ¹H-NMR spectrum indicates the formation of only one product.
Figure 2.19: $^1$H-NMR of sulfide 28.
The unexpected formation of only one product in the dehydrohalogenation reaction could possibly be accounted for by an E1-conjugate base (E1-CB) mechanism. The proton α to the sulfone is acidic because of the strong electron withdrawing effect of the sulfonyl group. The conjugate base formed after the deprotonation with DBU is very stable, and at 0 °C the subsequent elimination of the chloro group may be slow. If the chloro group leaves slowly, the conjugate base may have time to orient in the most stable conformation. This would be an example of a thermodynamic product formation. It is also possible that an E2 reaction could be occurring because of a steric effect of the carborane groups. These groups would orient furthest from each other before the elimination reaction.

The same Barton-Zard reaction conditions were used to make the Boc-protected dicarboranlypyrrole 31, and as with the other Barton-Zard reactions this procedure was high yielding. The α,β-unsaturated sulfone 30 formed in the dehydrohalogenation was a suitable substrate for the Barton-Zard reaction with tert-butyl isocyanate and as before NaO'Bu was used to promote the reaction. As before the Boc-protected dicarboranlypyrrole was prepared because of the ease in removal of a Boc group from the α position of a pyrrole. The α,β-unsaturated sulfone 30 was combined with tert-butyl isocyanate, heated to reflux temperature, and NaO'Bu dissolved into the minimal amount of dry THF was added rapidly. The addition of NaO'Bu quickly induced a color change from a clear solution to a yellow solution, which became turbid after just a few minutes. The reaction was followed by TLC over a 5 h period and was found to be proceeding very slowly. Though the Barton-Zard reaction was very slow, it was steadily
converting the sulfone 30 to the Boc-protected pyrrole 31. After 5 h the heat was removed and the solution was stirred overnight.

After 16 h, TLC indicated the complete consumption of starting material, so the reaction was quenched by the addition of water and saturated NaCl. The reaction mixture was extracted with EtOAc, dried, filtered, and concentrated under reduced pressure. Although TLC indicated complete consumption of the sulfone 30 starting material a small amount of a non-polar by-product was detected. This side-product was never characterized, but is probably a diene analogous to the carboranyldiene produced in the double elimination. Despite the small amount of by-product isolated, the desired dicarboranylpyrrole is isolated as a white solid in a 94% yield, after column chromatography (70% hexane: 30% EtOAc). In order to obtain an X-ray crystal structure of the dicarboranylpyrrole, the pure compound was recrystallized several times in various solvent systems used to recrystallize many of the other compounds. This was very soluble in many systems, but when precipitation began the compound always precipitated as a powder. The solvents were varied in order to prevent such precipitation, but I could find no solvent that could precipitate the compound as large crystals formed. Finally, because of the unusual solubility of this compound it precipitated in DCM. The formation of crystals in this type of solvent system was very surprising, but the needle-like crystals were suitable for X-ray crystallography. The X-ray crystal structure and the $^1$H-NMR spectrum can be seen in Figure 2.21 and Figure 2.22.

In order to electropolymerize the dicarboranylpyrrole or to make a carboranylporphyrin the $\alpha$-Boc pyrrole 31 must be converted into an $\alpha$-free pyrrole 3. This is accomplished by the use of TFA and heat. The deprotection of the
Figure 2.20: $^1$H-NMR of unsaturated sulfone 30.
dicarboranylpyrrole 31 was not as efficient as in previous carboranylpyrroles. The first attempt at the deprotection followed the same method as before, but because of poor solubility it yielded the α-free pyrrole in only a modest 50% yield. It was first attempted to dissolve the Boc-protected dicarboranylpyrrole 31 directly into TFA, but it would not dissolve even at elevated temperature. A large amount of DCM had to be added in order to dissolve all materials, and the reaction was quenched by the addition of a saturated solution of Na₂SO₃, a saturated solution of NaHCO₃, and then a saturated solution of NaCl. The free pyrrole 3 was isolated after drying and filtering through a plug of silica gel as an off-white solid in 52% yield.

To improve this yield, the compound was dissolved into a minimal amount of DCM and then TFA was added. Shortly after the addition of TFA a precipitate formed, but only a small amount of DCM was required to redissolve it. A very small amount of heat was added, and the reaction was stirred in DCM at reflux temperature for 15 min. After this time TFA and DCM were removed under reduced pressure. TLC indicated that the reaction was complete, and the reaction mixture was dissolved into a minimal amount of DCM and filtered through a plug of silica gel. According to ¹H-NMR and ¹³C-NMR spectrum of α-free pyrrole was very pure and needed no further purification. The ¹³C-NMR spectrum of the α-free dicarboranylpyrrole can be seen in Figure 2.22, and the ¹H-NMR spectrum can be seen in Figure 2.23.

2.3 Conclusions and Future Direction

The overall yields of all of the carboranylpyrroles have been optimized to produce the carboranylpyrroles in excellent yield. All steps after the first two are very high and cleanly produce the desired product with little or no need for purification. In fact, the
Figure 2.21: X-Ray crystal structure of Boc-protected dicarboranylpyrrole 31.
Figure 2.22: $^1$H-NMR spectrum of Boc-protected dicarboranylpyrrole 31.
Figure 2.23: $^{13}$C-NMR spectrum of α-free dicarboranylpyrrole 3.
Figure 2.24: $^1$H-NMR spectrum of $\alpha$-free dicarboranylpyrrole 3.
reactions work well on the crude material, but all intermediates were intensely purified in order to properly characterize them. For example, after the alkylation and addition products in Scheme 2.4 were thoroughly purified, the crude intermediates of the following steps work very well to produce the Boc-protected pyrroles. The Boc-protected pyrroles can then be easily purified by column chromatography or recrystallization from EtOH. This would allow an excellent overall yield of all three carboranlypyrroles. The alkylation step of the synthesis of the dicarboranlypyrrole could probably be optimized by the use of only two equivalents of 1-methyl-2-lithium-o-carborane. Using only two equivalents of this would inhibit the formation of the diene in this step. This is the only step, which could possibly be improved.

Most applications of the carboranlypyrrole 2 have been explored, such as its N-alkylated derivative, its nido derivatives, and even its neutral derivatives. Unfortunately many of the derivatives did not yield positive results, because they would not polymerize. Fortunately, there is still much to learn about the dicarboranlypyrrole. The synthesis of this pyrrole gives excellent yields, and because of this many things can still be explored with this molecule. Tetramerization of the dicarboranlypyrrole was attempted, but the porphyrin was not successfully synthesized. This pyrrole was envisioned with the porphyrin in mind, because of the symmetry this molecule contains. The attempts of making a porphyrin from this pyrrole 3 will be discussed in Chapter 3.

2.4 Experimental

All experiments were performed under inert argon atmosphere using a Schlenk line. Melting points were measured with an Electrothermal melting point apparatus. The $^1$H-NMR spectra were obtained using either a Bruker ARX-300 or a DPX-250 for the 300
MHz and the 250 MHz, respectively. Reactions were all monitored using silica gel TLC plates from Sorbent Technologies (200 µm). 1-Methyl-o-carborane was purchased from Dexasil and all other starting materials and reagents were purchased from Sigma-Aldrich and required no purification before using. Silica gel was purchased from Sorbent Technologies (60 Å, 40-75 µm). All solvents were purchased from Fisher. DCM was dried by distilling over CaH₂ and THF was dried by distilling first over LiAlH₄ then distilling over sodium and benzophenone. The low resolution MS experiments reported as FAB (Fast Atom Bombardment) were measured with Finnigan MAT 900, and the High Resolution MS (HRMS) experiments were measured using an Applied Biosystems Q Star XL electrospray (ESI) MS. Elemental analysis experiments were performed by Midwest Microlab, LLC.

2-Methyl-1-(2-propenyl)-o-carborane (4):

1-Methyl-o-carborane (2.50 g, 15.9 mmol) was dissolved into THF (40 mL) in a 3-neck RBF equipped with magnetic stirring, and cooled to 0 °C. A 2.5 M solution of n-BuLi in hexanes (11.1 mL, 27.8 mmol) was added slowly to the cooled solution, and upon the addition of n-BuLi the solution became turbid yellow. The solution was then warmed to room temperature and stirred for 30 min after reaching room temperature. Allyl bromide (2.89 g, 23.9 mmol) was weighed out into a 25 mL RBF and dissolved into THF (20 mL). The solution of 1-methyl-o-carborane and n-BuLi was cooled to –78 °C and the allyl bromide solution was added via syringe. The solution was allowed to react for only 1.5 h because of isomerization to the more stable internal alkene in the presence of excess base. Saturated NaCl (20 mL) and H₂O (30 mL) were added to the reaction mixture and it was stirred for 5 min. The mixture was extracted with EtOAc (3 x 100 mL), dried over
MgSO₄ and purified by column chromatography yielding the title compound as a clear oil (3.15 g) in a 68% yield. Note: Do not allow product to come in contact with dry silica gel.

ESI MS m/z 197 [M⁺]; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 5.84-5.73 (m, 1H), 5.23-5.08 (m, 2H), 2.96 (d, 2H, J = 7.5), 2.03 (s, 3H), 1.03-3.20 (br m, 10H).

2-Methyl-1-(2-phenylthio-3-chloropropyl)-o-carborane (6):
NCS (2.56 g, 12.91 mmol) was weighed out into a 250 mL RBF equipped with magnetic stirring and was dried under high vacuum. Freshly distilled DCM (30 mL) was added to dissolve most of the NCS. The suspension was heated to reflux. Then, PhSH (1.56 g, 14.20 mmol) was added dropwise via syringe. Upon the addition of one drop of PhSH, the solution became bright yellow, and upon further addition, it turned amber. The resulting solution was refluxed for 20 min, then cooled to room temp and stirred for 2 h. The starting material, 2-methyl-1-(2-propenyl)-o-carborane 8 (2.56 g, 12.91 mmol), was added in one portion in 10 mL DCM at −78 °C. The reaction was followed closely by TLC, and after 10 min, it appeared that the reaction was almost complete; however, the reaction was given 1 h to insure completion. The reaction mixture was filtered through a plug of silica gel, concentrated under reduced pressure, and a reddish oil was isolated. The oil was recrystallized in hot EtOH to yield the title compound as white crystals (3.97 g) in a 90% yield.

m.p. = 89-92 °C; FAB MS m/z 343.1 [M+H⁺]; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 7.49-7.37 (m, 5H), 3.76 (dd, 1H, J = 11, 3 Hz), 3.49 (dd, 1H, J = 9, 10.5 Hz), 3.47-3.40 (m, 1H), 2.90 (dd, 1H, J = 3, 16 Hz), 2.28 (dd, 1H, J = 8, 16 Hz), 2.05 (s, 3H), 1.20-3.50 (br m, 10H).
2-Methyl-1-(2-phenylsulfonyl-3-chloropropyl)-o-carborane (7):

2-Methyl-1-(2-phenylthio-3-chloropropyl)-o-carborane 9 (1.75 g, 5.09 mmol) was placed in a 250 mL RBF equipped with magnetic stirring and was dissolved into 15 mL DCM and cooled to 0 °C with constant stirring. A solution of mcpba (3.51 g, 20.3 mmol) dissolved into 50 mL DCM was added dropwise to the solution of 1-methyl-2-(2-phenylthio-3-chloropropyl)-o-carborane with constant stirring. The reaction was monitored closely by TLC and upon formation of the more polar sulfone the reaction was stopped. The mcpba which precipitated from the reaction mixture upon cooling was removed via filtration. The DCM layer was washed with saturated Na$_2$SO$_3$ until the washes were basic, NaHCO$_3$ (100 mL), then NaCl (100 mL). The remaining organic layer was washed with MgSO$_4$, and concentrated to yield a viscous oil. The oil was recrystallized in hot MeOH to yield the title compound as white crystals (1.74 g) in a 95% yield.

m.p. = 124-126 °C; FAB MS m/z 374.2 [M+H$^+$]; $^1$H-NMR (250 MHz, CDCl$_3$, δ ppm)
7.94-7.90 (m, 2H, Ar-H) 7.75-7.61 (m, 3H), 4.48-4.34 (m, 1H), 3.57-3.41 (m, 2H), 2.67 (dd, 2H, J = 16, 9 Hz), 2.11 (s, 3H), 3.50-1.20 (br m, 10H).

2-Methyl-1-(2-phenylsulfanyl-2-propenyl)-o-carborane (8):

1-Methyl-2-(2-phenylsulfonyl-3-chloropropyl)-o-carborane (0.27 g, 0.752 mmol) was placed in a 100 mL RBF equipped with magnetic stirring and dissolved into 25 mL THF. DBU (0.091 g, 0.59 mmol) was weighed out into a vial and dissolved into 10 mL THF. The solution of 1-methyl-2-(2-phenylsulfinyl-3-chloropropyl)-o-carborane was cooled to 0 °C with constant stirring. The solution of DBU was added via syringe, and upon addition a precipitate formed. The precipitate was removed via filtration and the filtrate
was concentrated under reduced pressure. The product was purified by column chromatography (80% hexanes:20% EtOAc) to yield the title compound as a white solid (0.194 g) in a 97% yield.

m.p. = 138-140 °C; FAB MS m/z 339.0 [M+H⁺]; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 7.87-7.83 (m, 2H, Ar-H), 7.71-7.61 (m, 3H, Ar-H), 6.09 (quint, 1H, J=7.5), 5.73 (d, 1H, J = 15 Hz), 3.86 (dd, 2H, J = 8, 1 Hz), 1.83 (s, 3H), 1.20-3.18 (m, 10H).

**tert-Butyl-4-Methyl-(2-methyl-o-carboranyl)pyrrole-2-carboxylate (9):** 1-methyl-2-(2-phenylsulfonyl-3-propenyl)-o-carborane (0.350 g, 1.09 mmol) and tert-butylisocyanoacetate (CNCH₂Boc) (0.169 g, 1.19 mmol) were dissolved in 60 mL THF in a 250 mL RBF equipped with magnetic stirring and refluxed. NaOttBu was dissolved in 40 mL THF and added to the refluxing mixture. The solution turned from clear to a turbid yellow color immediately following the addition of NaOttBu. The reaction was followed by TLC, and the product appeared to be forming immediately. To insure the reaction was going to completion, the reaction mixture was stirred overnight at RT. Saturated NaCl (40 mL) and H₂O (40 mL) were added and the reaction mixture was stirred for 20 min. The aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The product was dissolved in DCM (20 mL), activated carbon was added, and the reaction mixture was heated to reflux temperature. The carbon was removed by filtration through a celite cake. The product was further purified by recrystallization in hot MeOH to yield the title compound (0.334 g) as fine needle like crystals in 91% yield.

m.p. = 156-158 °C; FAB MS m/z = 337.5 [M⁺ - ‘Bu]; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 9.25 (br s, 1H), 6.79-6.75 (m, 1H), 6.68-6.65 (s, 1H ), 3.37 (s, 2H), 2.12 (s, 3H),
1.57 (s, 9H); Anal. Calcd for C$_{13}$H$_{27}$B$_{10}$NO$_2$: C, 46.26; H, 8.08; N, 4.15. Found: C, 46.52; H, 7.95; N, 4.08.

(2-Methyl-o-carboranyl)-3-methylpyrrole (1):

tert-Butyl-4-Methyl-(2-methyl-o-carboranyl)-1$H$-pyrrole-2-carboxylate (0.130 g) was dissolved into a minimal amount of TFA (approximately 5 mL) and stirred for 2.5 h or until the slightly more polar α-free pyrrole was shown to be present by TLC. Saturated NaCl (25 mL), H$_2$O (50 mL), and EtOAc (50 mL) were added to the reaction mixture and stirred for 20 min. The reaction mixture was washed saturated with Na$_2$SO$_3$ until the washes were basic, then with saturated NaHCO$_3$ (2 x 100 mL), and then with saturated NaCl (100 mL). The organic layer was then dried over MgSO$_4$ and concentrated under reduced pressure. The product was a light brown oil which was dissolved into 20% EtOAc: 80% hexanes and filtered through a plug of silica gel to yield the title compound (0.091 g) as an oil in a 100% yield and needed no further purification according to NMR. FAB MS (M$^+$) m/z 237.4 [M + H$^+$]; $^1$H-NMR (250 MHz, CDCl$_3$, δ ppm) 8.20 (broad s, 1H), 6.79–6.70 (m, 1H), 6.70–6.61 (m, 1H), 6.14–6.05 (m, 1H), 3.40 (s, 2H), 2.11 (s, 3H).

1-(3-Butenyl)-2-methyl-o-carborane (13):

1-Methyl-o-carborane (1.00 g, 6.36 mmol) was dissolved into freshly distilled THF (60 mL) in a 250 mL RBF equipped with magnetic stirring, and cooled to 0 °C. A 2.5 M solution in hexane of n-BuLi (3.05 mL, 7.63 mmol) was added slowly to the cooled solution, and upon its addition, the solution became a turbid yellow solution. The solution was warmed to RT, stirred for 1 h after reaching RT, and then cooled to ~78 °C. 4-Bromo-1-butene (1.12 g, 8.27 mmol) was placed into a 25 mL RBF and dissolved into 20 mL THF and LiI (0.17 g, 1.27 mmol) was added. Immediately the resulting solution
became bright yellow and was added to the carborane containing solution at –78 °C. The solution was slowly warmed to RT and left stirring for 36 h. According to TLC, the reaction was not complete, but no further reaction progress was apparent. Saturated NaCl (20 mL) and H₂O (30 mL) were added, and the reaction mixture was stirred for an additional 5 min. The aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layer was dried over MgSO₄ and purified via column chromatography (90% hexanes:10% EtOAc) to yield the title compound as a white solid (1.00 g) in a 74% yield. m. p. = 70-71 °C; FAB MS m/z 211.2 [M+H⁺]; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 5.84-5.68 (m, 1H), 5.13-5.08 (m, 1H), 5.08-5.03 (m, 1H), 2.44-2.41 (m, 4H), 2.02 (s, 3H), 3.67-0.95 (br, 10H, BH).

**2-Methyl-1-(3-phenylthio-4-chlorobutyl)-o-carborane (14):**

NCS (1.95 g, 14.6 mmol) was weighed and placed into a 3-neck 250 mL RBF equipped with magnetic stirring and dried under reduced pressure. DCM (30 mL) was added via syringe and the suspension was heated to reflux. Four drops of benzenethiol were added to initiate the reaction, and the remainder of the benzenethiol (0.62 g, 5.65 mmol) was added via a 1 mL syringe to the stirring solution at a rate sufficient to maintain reflux. The resulting solution was stirred for 2 h and cooled to –78 °C, then the 1-(3-butenyl)-2-methyl-o-carborane 1 was dissolved into THF (20 mL) and added via syringe to the stirring PhSCl solution. The progress of the reaction was followed by TLC, and excess NCS was removed by filtration after the reaction was complete. The resulting solution was filtered through a plug of silica in 85% Hexanes:15% EtOAc, and concentrated under reduced pressure. The remaining material was purified by column chromatography in 85% hexanes: 15% EtOAc. Column chromatography did not yield completely pure
material, so the impure material was recrystallized in hexanes at \(-78^\circ\text{C}\) to yield the title compound as a white solid (1.43 g) in 90% purified yield. 

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\text{m. p.} = 65-66^\circ\text{C}; \ FAB\ MS\ m/z\ 357.2\ [M+H^+]\; ;\ \hbox{\textsuperscript{1}H-NMR}\ (300\ MHz, \text{CDCl}_3, \delta\ \text{ppm})\ 7.42-7.36\ (m,\ 2H,\ Ar-H),\ 7.36-7.32\ (m,\ 3H,\ Ar-H),\ 3.75\ (dd,\ 1H,\ J = 11,\ 4Hz),\ 3.47\ (dd,\ 1H,\ J = 11,\ 11Hz),\ 3.01-3.20\ (m,\ 1H),\ 2.85-2.52\ (m,\ 2H),\ 2.37-2.25\ (m,\ 2H),\ 2.05\ (s,\ 3H),\ 3.10-1.10\ (br\ m,\ 10H,\ BH).
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2-Methyl-1-(3-phenylsulfonyl-4-chlorobutyl)-o-carborane (15): 

2-Methyl-1-(3-phenylthio-4-chlorobutyl)-o-carborane 2 (0.334 g, 0.936 mmol) was dissolved in DCM (5 mL) in a 50 mL RBF equipped with magnetic stirring. Solid mcpba (1.61 g, 9.36 mmol) dried under high vacuum was dissolved into 10 mL anhydrous DCM and the resulting solution was added dropwise to the solution of starting material at 0 \(^{\circ}\text{C}\). A white precipitate was observed after the addition of mcpba and TLC indicated the reaction was complete. To remove the excess mcpba, the solution was concentrated under reduced pressure to remove DCM, EtOAc was added, and the resulting solution was transferred to a separatory funnel. The solution was washed with saturated \(\text{Na}_2\text{SO}_3\) until the washes were basic, then washed with \(\text{NaHCO}_3\) (3 x 100 mL), then with saturated \(\text{NaCl}\) (100 mL). The organic layer was dried over \(\text{MgSO}_4\) and concentrated under reduced pressure to yield a viscous oil which was recrystallized in EtOH to yield the title compound as fluffy white crystals (0.338 g) in a 93% yield. 

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\text{m.p.} = 125-127^\circ\text{C};\ \hbox{HRMS}\ (\text{ESI TOF})\ \text{for}\ C_{13}\text{H}_{26}\text{B}_{10}\text{O}_2\text{S}_3\ 390.2337\ (\text{calc.}\ 390.2332)\; ;\ \hbox{\textsuperscript{1}H-NMR}\ (300\ MHz, \text{CDCl}_3, \delta\ \text{ppm})\ 7.89-7.86\ (m,\ 2H,\ Ar-H),\ 7.75-7.73\ (m,\ 1H,\ Ar-H),\ 7.66-7.61\ (m,\ 2H,\ Ar-H),\ 3.83\ (dd,\ 1H,\ J = 4,\ 12\ Hz),\ 3.58\ (dd,\ 1H,\ J = 12,\ 10\ Hz),\ 3.28-
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3.16 (m, 1H), 2.50-2.40 (m, 2H), 2.30-2.10 (m, 2H), 2.03 (s, 3H), 3.10-1.00 (br m, 10H, BH).

2-Methyl-1-(3-phenylsulfonyl-3-butenyl)-o-carborane (16):

2-Methyl-1-(3-phenylsulfonyl-4-chlorobutyl)-o-carborane 3 (1.80 g, 4.64 mmol) was dissolved into freshly distilled THF (20 mL) in a 100 mL RBF. DBU (0.670 g, 4.40 mmol) was weighed out into a vial and dissolved into THF (5 mL). The solution containing the 1-methyl-2-(3-phenylsulfonyl-4-chlorobutyl)-o-carborane was cooled to 0 °C and the solution of DBU was added dropwise very slowly. Upon the addition of DBU, a precipitate formed immediately and the reaction was complete according to TLC. The reaction mixture was filtered to remove the precipitate and to the organic layer was added EtOAc (100 mL). The solution was then transferred to a separatory funnel and H₂O (100 mL) was added. The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layer was dried over MgSO₄, and concentrated under reduced pressure to yield a white solid which was recrystallized in EtOH to yield the title compound as white crystals (1.26 g) in 77% yield.

m. p. = 145-147 °C; HRMS (ESI TOF) for C₁₃H₂₅O₂SB₁₀ 353.2579 (calc. 353.2585)¹H-NMR (250 MHz, CDCl₃, δ ppm) 7.89-7.85 (m, 2H, Ar-H), 7.59-7.73 (m, 3H), 6.41 (d, 1H, J = 1 Hz), 5.81 (d, 1H, J = 1 Hz), 2.46-2.41 (m, 4H), 1.99 (s, 3H).

tert-Butyl-2-(2-Methyl-o-carboranyl)-4-ethyl -1H-pyrrole-2-carboxylate (18):

2-Methyl-1-(3-phenylsulfonyl-4-butenyl)-o-carborane 4 (0.244 g, 0.69 mmol) and tert-butyl isocyanatoacetate (0.097 g, 0.69 mmol) were dissolved into THF (20 mL) in a 250 mL RBF equipped with magnetic stirring and a reflux condenser. The solution was heated to reflux, and in a separate flask NaOtBu (0.066, 0.69 mmol) was dissolved into
THF (80 mL). The solution containing NaOtBu was added to the solution containing 1-methyl-2-(3-phenylsulfonyl-4-butenyl)-o-carborane and tert-butyl isocyanateacetate, and immediately the solution turned yellow and eventually a turbid yellow solution resulted. TLC indicated that the reaction was complete, but the reaction was refluxed for 4 h and allowed to stir at RT for an additional 12 h. After this time, EtOAc (50 mL), saturated NaCl (50 mL), and H2O (100 mL) were added to the flask and stirred for 15 min. The contents of the RBF were transferred to a separatory funnel and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layer was dried over MgSO4, concentrated under reduced pressure, and purified via column chromatography (70% hexanes: 30% EtOAc) to yield the title compound as a white solid in a 92% yield (0.222 g).

m. p. = 208-9 °C; FAB MS m/z 296.2 [M+H+ - tBu]; 1H-NMR (250 MHz, CDCl3, δ ppm) 9.44 (br s, 1H), 6.77-6.71 (m, 1H) 6.68-6.62 (m, 1H), 2.78-2.68 (m, 2H), 2.48-2.37 (m, 2H), 2.03 (s, 3H), 1.57 (s, 9H), 3.78-1.90 (br m, 1H, BH); Anal. Calcd for C14H29B10NO2: C, 47.83; H, 8.33; N, 3.99. Found: C, 48.27; H, 8.34; N, 3.75.

2-(2-Methyl-o-carboranyl)- 3-ethylpyrrole (2):

tert-Butyl-2-(2-Methyl-o-carboranyl)-4-ethyl-1H-pyrrole-2-carboxylate (0.100 g) was weighed and placed in a 100 mL RBF equipped with magnetic stirring. Sufficient trifluoroacetic acid (TFA) was added to dissolve the starting material (approximately 5 mL). Shortly after adding the TFA the pyrrole precipitated and the reaction was heated until all contents of the flask were dissolved. At this point, the reaction was determined to be complete by TLC. Immediately following the addition of TFA, the very polar acid was found to be the major product, but after heating the flask the free pyrrole was the
The major product. The polarity of the free pyrrole was only slightly more than that of the starting material. Saturated Na$_2$SO$_3$ (10 mL) was added and the reaction was stirred. At this point EtOAc (50 mL) was added and the organic layer was washed with NaHCO$_3$ until the washes were found to be basic. The organic layer was dried over MgSO$_4$, filtered through a celite cake, and concentrated under reduced pressure. The resulting product was then dissolved into 1 mL of an 80% hexane: 20% EtOAc mixture and filtered through a plug of silica gel. The product was then collected in a 100 mL RBF and concentrated under reduced pressure to yield the title compound as an off-white solid (0.067 g) in a 94% yield, which required no further purification.

m. p. = 67-69 °C; HRMS (ESI-TOF) for C$_9$H$_{22}$B$_{10}$N 252.2767 (calc. 252.2759); $^1$H-NMR (250 MHz, CDCl$_3$, δ ppm) 8.10 (br s, 1H), 6.76 (dd, 1H, J = 2, 3 Hz) 6.63-6.59 (m, 1H), 6.09 (dd, 1H, J = 2, 3 Hz), 2.89-2.65 (m, 2H), 2.50-2.37 (m, 2H), 2.08 (s, 3H), 3.78-1.90 (br m, 1H, BH).

Tetrabutylammonium (nido 2-Methyl-o-carboranyl)-3-methylpyrrole (20):

(2-Methyl-o-carboranyl)-3-methyl-1H-pyrrole (0.150 g, 0.59) was weighed out into a 50 mL RBF equipped with magnetic stirring. To a 1.0 M solution of tetrabutyl ammonium fluoride (2.98 mL, 2.98 mmol) was added distilled H$_2$O (0.43, 24.8 mmol). The resulting solution was added to the flask containing starting material and the solution was stirred until dissolved. The flask was heated and gently refluxed. The disappearance of starting material indicated the completion of the reaction. DCM (100 mL) was added to the flask and the contents of the flask were transferred to a 250 mL separatory funnel and the DCM layer was washed with H$_2$O (3 x 100 mL). The organic layer was dried over MgSO$_4$, filtered through a celite cake, and concentrated under reduced pressure, The
resulting oil was recrystallized in EtOH and the resulting crystals were filtered and washed with cold EtOH to yield the title compound as off-white crystals (0.240 g) in an 86% yield.

m. p. = 98-100 °C; ESI-MS m/z 227.27 [M⁺ - NBu₄⁺]; ¹H-NMR (300 MHz, CDCl₃, δ ppm) 8.01 (br s, 1H), 6.76-6.73 (m, 1H), 6.67 (dd, 1H, J = 19, 2 Hz), 6.16 (dd, 1H, J = 2.5, 1.5 Hz), 3.17-3.12 (m, 3H), 2.96 (s, 2H), 1.68-1.52 (m, 8H), 1.50-1.38 (m, 9H), 1.25 (s, 3H) 1.01 (t, 12H, J = 7 Hz), 2.50-0.50 (br m, 10H, BH), -2.35(br s, 1H, B-H-B); Anal. Calcd for C₁₄H₂₉B₁₀NO₂: C, 61.46; H, 11.84; N, 5.97. Found: C, 60.91; H, 12.42; N, 5.55.

Tetrabutylammonium 2-(nido 2-Methyl-o-carboranyl)-3-ethylpyrrole (21):

2-(2-Methyl-o-carboranyl)- 3-ethyl-1H-pyrrole 6 (0.150 g, 0.59) was weighed out into a 50 mL RBF equipped with magnetic stirring. To a 1.0 M solution of tetrabutylammonium fluoride (2.98 mL, 2.98 mmol) was added distilled H₂O (0.43, 24.8 mmol). The resulting solution was added to the flask containing starting material and the solution was stirred until dissolved. The flask was heated and gently refluxed. TLC indicated the disappearance of starting material and that the reaction was complete. DCM (100 mL) was added to the flask and the contents of the flask were transferred to a 250 mL separatory funnel and the DCM layer was washed with H₂O (3 x 100 mL). The organic layer was dried over MgSO₄, filtered through a celite cake, and concentrated under reduced pressure. The resulting oil was recrystallized in EtOH and the resulting crystals were filtered and washed with cold EtOH to yield the title compound as off-white crystals (0.240 g) in 86% yield.
m. p. = 152-3 °C; MALDI MS m/z 240.8 [M⁺ - NBu₄]; ¹H-NMR (300 MHz, CDCl₃, δ ppm) 8.15 (br s, 1H), 6.68 (d, 1H, J = 2 Hz), 6.59-6.52 (m, 1H), 6.08-6.02 (m, 1H), 3.15 (t, 3H, J = 8 Hz), 2.75-2.55 (m, 2H), 2.15-1.80 (m, 2H), 1.60-1.55 (dd, 8H, J = 7, 8 Hz), 1.50 (s, 3H), 1.42 (q, 8H, J = 7 Hz), 1.02 (t, 12H, J = 7 Hz), 2.50-0.50 (br m, 10H, BH), -2.44(br s, 1H, B-H-B).

2-(2-Methyl-o-carboranyl)- 3-ethyl-1-(6-heptenyl)pyrrole (24):

A dispersion of NaH (60% in mineral oil) (0.006 g, 0.25 mmol) was weighed and placed into a 50 mL RBF equipped with magnetic stirring. The NaH was blanketed by Ar and then washed with dry hexane. The hexane was then removed and to the washed NaH was added the tert-Butyl-2-(2-Methyl-o-carboranyl)-4-ethyl - 2-carboxylate (0.018, 0.05 mmol) dissolved in 2 mL DMF. The suspension was then stirred at RT for 30 min and cooled to 0 °C. 7-Bromo-1-heptene (0.018 g, 0.10 mmol) was weighed into a vial and dissolved into 1 mL DMF. The reaction was followed by TLC and within 1 h all starting material had been converted to product. H₂O (30 mL) was added and a cloudy solution resulted. The solution was transferred to a 500 mL separator funnel. To the funnel was added EtOAc (150 mL). The organic layer was washed with saturated aqueous NaCl (3 x 150 mL) to remove all DMF. The resulting organic layer was dried over Na₂SO₄, filtered through a celite cake, and concentrated under reduced pressure. The crude product was then dissolved into 3 mL TFA and according to TLC all had been immediately converted to the α-free pyrrole. Ethyl acetate (100 mL) was added and the TFA was removed by washing with Na₂SO₃, NaHCO₃, and NaCl then the remaining organic layer was dried over Na₂SO₄. The organic layer concentrated under reduced pressure to yield the N-
alkylated pyrrole 7 (0.013 g) as a yellow oil in a 76% yield after purification by column chromatography (90 % hexanes: 10 % EtOAc).

HRMS (MALDI-TOF) for C_{16}H_{34}B_{10}N 348.3682 (calc. 348.3702); \textsuperscript{1}H-NMR (250 MHz, CDCl\textsubscript{3}, δ ppm) 6.49 (t, 1H, J = 2.4 Hz), 6.37 (t, 1H, J = 1.9 Hz), 5.87 (t, 1H, J = 2.1 Hz), 5.80 – 5.63 (m, 1H), 4.97 – 4.84 (m, 2H), 3.72 (t, 2H, J = 7.2 Hz), 2.68 – 2.58 (m, 2H), 2.40 – 2.31 (m, 2H), 2.04 – 1.92 (m, 2H), 1.95 (s, 3H), 1.67 (quint, 2H, J = 7.2), 1.41 – 1.15 (m, 4H); \textsuperscript{13}C-NMR (60 MHz, CDCl\textsubscript{3}, δ ppm) 139.05, 121.43, 121.20, 121.20, 118.40, 115.01, 107.81, 79.26, 75.15, 50.03, 37.39, 33.99, 31.81, 28.86, 27.66, 26.64, 23.60.

\textbf{1,6-Dibromo-3-hexene:} 4-Bromo-1-butene (1.00 g, 7.41 mmol) was dissolved into freshly distilled DCM (10 mL) and Hoyveda’s catalyst (0.046 g, 0.741 mmol) dissolved into DCM (1 mL) was added via pipette. The reaction was monitored by TLC (staining with I\textsubscript{2}). The reaction turned from green to brown within 30 min, and the reaction was complete according to TLC. Hexane (10 mL) was added and the reaction was filtered through a plug of silica to remove catalyst. The product was concentrated under reduced pressure and isolated as a clear liquid 1.79 g in a 68% yield.

\textsuperscript{1}H-NMR (250 MHz, CDCl\textsubscript{3}, δ ppm) 5.58 – 5.52 (m, 2H), 3.40 (d of d, 4H, J = 1.7 Hz, J = 7.0 Hz), 2.69 – 2.54 (m, 2H).

\textbf{1,6-Di-(2-methyl-o-carboranyl)-3-hexene (25):}  
1-Methyl-o-carborane was dissolved into THF (20 mL) in a 100 mL RBF equipped with magnetic stirring. n-Butyl lithium (1.94 mL, 3.10 mmol) (1.6 M in hexane) was added to the stirring solution at 0 ºC and stirred for 1 h. Solid LiI (0.04 g, 0.31 mmol) was dissolved into THF (5 mL) and the 1,6-dibromo-3-hexene (0.25 g, 1.03 mmol) was
dissolved into THF (2 mL) and added to the solution of LiI. The solution containing 1-methyl-o-carborane and n-BuLi was cooled to -78 °C and the solution containing LiI and 1,6-dibromo-3-hexene was added slowly. The reaction was stirred for 36 h and allowed to warm to RT. H₂O (50 mL) was added and the product was extracted into DCM (3 x 50 mL). The organic layer was dried over MgSO₄, filtered through celite and concentrated under reduced pressure. The reaction mixture was purified in 90% hexane: 10% EtOAc to yield the title compound as a white solid (0.180 g) in 44% yield.

m.p. 228 – 231 °C; ESI-MS m/z 396.57 [M⁺]; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 5.47 – 5.41 (m, 2H), 2.26 – 2.20 (m, 8H), 2.01 (s, 6H), 3.75 – 0.90 (m, 20 H, BH).

3-(2-Methyl-o-carboranyl)-propanal (26):
1-(3-Butenyl)-2-methyl-o-carborane (0.810 g, 3.81 mmol) was dissolved into DCM (10 mL) and MeOH (10 mL) and O₃ was bubbled through the flask for 2 h or until all starting material had been consumed according to TLC. After this time, Me₂S (1 mL) was added and the flask was stirred at RT for an additional 1 h. Solvent was removed under reduced pressure and the reaction mixture was purified by column chromatography (25% EtOAc: 75 % hexane) to yield the title compound as a white solid in 92% yield (0.75 g).

m.p. = 62 - 64 °C; HRMS (ESI-TOF) for C₆H₁₇B₁₀O 213.2295 (calc. 213.2285); ¹H-NMR (300 MHz, CDCl₃, δ ppm) 9.77 (s, 1H), 2.85 – 2.78 (m, 2H), 2.52 (t, 2H, J = 8 Hz).

4-Chloro-3-phenylthio-1,6-di(2-methyl-o-carboranyl)hexane (28):
A suspension of NCS (0.108 g, 0.81 mmol) in DCM (1 mL) was heated to reflux and PhSH dissolved in DCM (1 mL) was added slowly dropwise. The addition of PhSH resulted in a yellow solution, which turned darker upon stirring at RT. This solution was cooled to -78 °C and 1,6-dibromo-3-hexene (0.106 g, 0.27 mmol) was added all at once
in DCM (3 mL). The reaction was warmed to RT and within 30 min starting material had been consumed. Hexane was added until the NCS and precipitated. The solution was filtered through a short plug of silica gel. The resulting clear solution was concentrated and purified via column chromatography (70% hexane: 30% DCM) to yield the title compound (0.145 g) as a white fluffy solid in 99% yield.

m.p. = 58-60 °C; ESI-MS m/z 540.23 [M-H]; $^1$H-NMR (300 MHz, CDCl$_3$, δ ppm) 7.43 – 7.34 (m, 5H), 3.87 – 3.78 (m, 1H), 3.08 (d of t, 1H, J = 2.3 Hz, J = 7.4 Hz), 2.70 – 2.20 (m, 8H), 2.02 (s, 3H), 1.99 (s, 3H), 3.10 – 1.25 (m, 20H, BH).

4-Chloro-3-phenylsulfonyl-1,6-di(2-methyl-o-carboranyl)hexane (29):

4-Chloro-3-phenylthio-1,6-di(2-methyl-o-carboranyl)hexane (0.143 g, 0.26 mmol) was dissolved into DCM (3 mL) and cooled to 0 °C. Mcpba (0.182 g, 1.06 mmol) was dissolved into 3 mL DCM (3 mL) and added dropwise. The reaction was followed by TLC and after 16 h it had gone to completion. EtOAc (50 mL) was added and the organic layer was washed with saturated Na$_2$SO$_3$ until the washes were basic, with saturated NaHCO$_3$ (100 mL), with saturated NaCl (100 mL). The organic layer was dried over MgSO$_4$, filtered through a plug of silica gel, and concentrated under reduced pressure to give the title compound (0.151 g) as a white solid in 93% yield.

m.p. = 75–78 °C; ESI-MS m/z 571.03 [M-H$_2$]; $^1$H-NMR (250 MHz, CDCl$_3$, δ ppm) 7.93 – 7.88 (m, 2H), 7.83 – 7.40 (m, 1H), 7.70 – 7.63 (m, 2H), 4.41 – 4.33 (m, 1H), 3.18 – 3.10 (m, 1H), 2.60 – 1.80 (m, 8H), 2.03 (s, 3H), 2.02 (s, 3H), 3.20 – 1.00 (m, 20H, BH).

3-Phenylsulfonyl-1,6-di(2-methyl-o-carboranyl)-3-hexene (30):

4-Chloro-3-phenylsulfonyl-1,6-di(2-methyl-o-carboranyl)hexane (0.062 g, 0.11 mmol) was dissolved into THF (3 mL), stirred, and cooled to 0 °C. DBU (0.015 g, 0.097 mmol)
dissolved into THF (2 mL) was added dropwise and immediate precipitation was observed. The organic layer was combined with H\textsubscript{2}O (50 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered through a plug of celite, and concentrated under reduced pressure to yield the pure title compound as a white solid (0.052 g) in 100% yield.

m.p. = 190–193 °C; ESI-MS m/z 536.10 [M]; \textsuperscript{1}H-NMR (250 MHz, CDCl\textsubscript{3}, \delta ppm) 7.85 – 7.80 (m, 2H), 7.73–7.65 (m, 1H), 7.63 – 7.56 (m, 2H), 6.87 (t, 1H, J = 5), 2.50 – 2.25 (m, 8H), 2.05 (s, 3H), 2.00 (s, 3H), 3.30 – 1.00 (m, 20H, BH).

**tert-Butyl-3,4-Di[ethyl-2-(2-methyl-o-carboranyl)]-2-carboxylate (31):**

3-Phenylsulfonyl-1,6-di(2-methyl-o-carboranyl)-3-hexene (0.048 g, 0.089 mmol) and \textit{t}-butylisocyanatoacetate (0.014 g, 0.10 mmol) were dissolved into THF (10 mL) and heated to reflux temperature. NaO\textsubscript{B}u (0.010 g, 0.10 mmol) dissolved into a minimal amount of solvent was added to the solution at reflux. The solution turned from clear to light yellow then became turbid after stirring for approximately 1 min. The reaction was refluxed for 24 h and cooled to RT. To the reaction H\textsubscript{2}O (25 mL) and EtOAc (50 mL) were added. The aqueous layer was extracted with an additional portion of EtOAc (50 mL), dried over MgSO\textsubscript{4}, filtered through a celite cake, and concentrated under reduced pressure. The crude reaction mixture was then purified via column chromatography (70% hexane: 30% EtOAc) to give the pure title compound as a white solid (0.045 g) in 94% yield.

m.p. = 270-273 °C; MALDI-MS m/z 536.93 [M+H]; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}, \delta ppm) 8.75 (br s, 1H), 6.64 (d, 1H, J = 3), 2.96 – 2.87 (m, 2H), 2.67 – 2.59 (m, 2H), 2.38 – 2.29 (m, 4H), 2.08 (s, 3H), 2.05 (s, 3H), 1.56 (s, 9H), 3.25 – 1.50 (m, 20H, BH).
3,4-di[ethyl-2-(2-methyl-o-carboranyl)]pyrrole (3):

3,4-di[ethyl-2-(2-methyl-o-carboranyl)]-2-carboxylic acid tert-butyl ester-1H-pyrrole (0.078 g, 0.15 mmol) was dissolved in a mimimal amount of DCM (˜5 mL) and TFA (5 mL) was added. The solution began to precipitate and the solution was heated to reflux temperature. After 1 h, the precipitate had dissolved and TLC indicated the complete formation of the slightly more polar α-free dicarboranylpyrrole. The TFA and DCM were removed under reduced pressure and the resulting white solid was dissolved in DCM (2 mL) and filtered through a plug of silica to yield the title compound (0.040 g) as an off-white solid in 63% yield.

m.p. = 182-185 °C; ESI-MS m/z 434.42 [M – H]+; 1H-NMR (300 MHz, CDCl3, δ ppm); 7.99 (br s, 1H), 6.54 (d, 2H, J = 2.4 Hz), 2.68 – 2.58 (m, 4H), 2.43 – 2.33 (m, 4H), 2.04 (s, 6H), 3.50 – 0.5 (m, 20H, BH); 13C-NMR (63 MHz, CDCl3, δ ppm) 121.79, 117.80, 80.30, 77.51, 38.47, 36.67, 27.65, 25.44.

2.4 References


3.1 Introduction

The use of porphyrins in BNCT has created a high demand for water-soluble carboranylporphyrins. There is a two-fold advantage to attaching carboranes to porphyrins. First, carboranes have a high percent boron by weight, which in BNCT provide a large amount of boron to a specific area. Secondly, closo carboranes can be readily converted into their corresponding nido derivatives. If the counter ion of the nido derivative is a metal cation, it will likely be water-soluble. This two-fold advantage gives reason to synthesize water-soluble carboranylporphyrins. Many examples of meso substituted carboranylporphyrins have been reported, but no examples produce β-carboranylporphyrins in high yield. There are no previous examples of carboranylporphyrins with β and meso carborane substituents on the porphyrin. The synthesis of the carboranylpyrroles 1 - 3 from Chapter 2 provides substrates which can easily be tetramerized to carboranylporphyrins containing carborane substitution at their β positions.

By nature porphyrins tend to specifically localize in tumor tissues, and 10B nuclei produce cytotoxic particles after irradiation with a neutron beam. Before this reaction with neutrons, carboranylporphyrins exhibit low toxicity and high stability relative to other boron-containing compounds.

3.2 Results and Discussion

Porphyrins can be synthesized by various methods, which have been under development since the first synthesis of a porphyrin in 1867. One of the simplest
methods to synthesize a porphyrin is by reduction of an ester at the 2 position of a pyrrole to its corresponding 2-carbinol pyrrole. The 2-carbinol can then tetramerized in the presence of TFA to yield a porphyrin. The reduction of pyrrole 1 is shown in Scheme 3.1 where LAH was used to reduce pyrrole 1 to its corresponding 2-carbinol followed by tetramerization with TFA. Interestingly, the reduction of the Boc ester with LAH was not successful, because of the bulkiness of the tert-butyl ester. The reduction with LAH was slow, but when allowing the reaction to proceed for a long period of time the carborane cage began to degrade. The unusually stable 2-carbinol was purified on neutral alumina and dissolved in DCM. A very small amount of TFA was added to the flask and within minutes the reaction mixture turned black. After 2 h the addition of solid DDQ resulted in a colorless mixture, which no longer contained a Soret band. The earlier presence of a Soret band evidenced the oxidation was occurring with ambient oxygen, which may have been present in the reaction mixture in low abundance.

Scheme 3.1: Attempted synthesis of carboranylporphyrin 2.

The inefficiency of the reduction of the Boc group gave reason to use Lindsey’s high-dilution conditions to condense carboranylpyrrole 3 with benzaldehyde to yield carboranylporphyrin 4. The condensation in Scheme 3.2 produced the first novel β-
carboranylporphyrin in high yield following subsequent oxidation with \( p \)-chloranil. Carboranylpyrrole 3 was combined with benzaldehyde and dissolved into DCM to produce a \( 10^{-2} \) M solution and a catalytic amount of BF\(_3\)•Et\(_2\)O was added. Upon the addition of the first drop of acid catalyst the solution turned bright yellow, and after 2 h the solution turned purple. The oxidation was then achieved by the addition of solid \( p \)-chloranil, which immediately turned the reaction mixture dark. The resulting mixture was added to EtOAc and washed with saturated aqueous NaHCO\(_3\) until the washes were basic. The resulting mixture was then filtered through a plug of silica gel to remove polar byproducts. Carboranylporphyrin 4 was observed to be very basic, so the insertion of Zn (II) assisted in purification. Porphyrin 4 was dissolved in DCM and Zn(OAc)\(_2\) dissolved in MeOH was added. Within minutes, UV-visible spectroscopy showed that the insertion of Zn (II) was complete because of the disappearance of the characteristic four Q-bands in the free base. The resulting complex was easily purified via column chromatography eluting with toluene. The UV-visible spectrum of carboranylporphyrin 5 can be seen in Figure 3.1, and the X-ray crystal structure of the type II isomer of carboranylporphyrin 5 which crystallized preferentially from toluene can be seen in Figure 3.2.\(^4\)

The removal of Zn (II) from porphyrin 4 was achieved by the addition of TFA. After TFA was added the purple solution immediately turned bright green. To remove excess TFA the solution was washed with NaHCO\(_3\). The mixture of four porphyrins was then concentrated under reduced pressure after drying over MgSO\(_4\). The \(^1\)H-NMR of carboranylporphyrin 4 can be seen in Figure 3.3.
Scheme 3.2: Efficient synthesis of a novel carboranylporphyrin.

With the need for water-soluble carboranylporphyrins of high boron content for BNCT the synthesis of octa-carboranylporphyrin 6 was undertaken.\(^1\) Never before had a carboranylporphyrin bearing meso and \(\beta\) carborane cages been reported. The condensation of carboranylpyrrole 3 with carboranylbenzaldehyde 6\(^2\) produced the novel carboranylporphyrin 7. Initially the same reactions conditions with BF\(_3\)•Et\(_2\)O catalysis used to produce carboranylporphyrin 4 were used, but carboranylporphyrin 7 was obtained in only 10% yield after purification. The yield of carboranylporphyrin 7 was improved to 20% with the use of TFA as the catalyst and DDQ as the oxidant. The reaction mixture was then washed with saturated aqueous NaHCO\(_3\), dried over anhydrous MgSO\(_4\), and filtered through a short plug of silica gel. Carboranylporphyrin 7 was purified by column chromatography on silica gel eluting with toluene after the insertion of zinc (II) to form carboranylporphyrin 8.
Figure 3.1: UV-visible and fluorescence emission spectra of carboranylporphyrin 5.
Figure 3.2: X-Ray crystal structure of the type II isomer of carboranylporphyrin 5.
Figure 3.3: $^1$H-NMR spectrum of carboranylporphyrins 4.
Scheme 3.3: Synthesis of a novel octacarboranylporphyrin.

As with carboranylporphyrin 5, zinc (II) can easily be removed from the core of the porphyrin by the dropwise addition of TFA until the solution becomes bright green. The reaction mixture was then washed with NaHCO$_3$ until the washes were basic and by this time the green solution turned dark red. The solution was then dried over MgSO$_4$, filtered, and concentrated under reduced pressure to yield a purple solid in a 16% yield after metalation, purification, and demetalation.

The base degradation of the closo-carboranylporphyrins (Scheme 3.4) to their water-soluble nido derivatives was first attempted with a 3:1 mixture of pyridine:piperidine. The conversion was not successful using this method. The success of the degradation of carboranylpyrrole 3 with TBAF in Chapter 2 gave sufficient reason to attempt the same degradation using only 1.5 equivalents of TBAF per carborane ring. This relatively low concentration of TBAF (compared to the degradation of carboranylpyrrole 3) was because of the concern of fluorination of the porphyrin ring.
Fortunately, the degradation of the closo-carborane cages with TBAF yielded the unfluorinated \textit{nido} tetrabutylammonium salts of porphyrins $9$ and $10$.

Tetrabutylammonium salts $9$ and $10$ were dissolved in a very small amount of acetone and converted to their potassium salts by ion exchange chromatography using Dowex ion exchange resin. Initially the salt was eluted with 70\% acetone: 30\% water followed by elution with 30\% acetone: 70\% water. After ion exchange, the potassium salts of porphyrins $9$ and $10$ were found to be water-soluble and are currently being evaluated for potential use in BNCT.

After carboranylporphyrins $4$ had been degraded to their \textit{nido} derivatives, HPLC was used to verify that the four isomers had indeed formed. The formation of isomers of types I – IV was verified by the development of an HPLC method to separate these isomers, which could not be separated by TLC, HPFC, or column chromatography. The first attempt at separating these isomers with HPLC was with carboranylporphyrin $5$, but the removal of zinc (II) on silica gel also posed this problem on the HPLC column. The next attempt to separate the isomers of carboranylporphyrin $4$ used acetonitrile for elution, but the free base also protonated quickly on the HPLC column. The final attempt used a phosphate buffer to prevent protonation and a gradient of MeOH. The results of the HPLC and the gradient used can be seen in Figure 3.4.

Synthesis of carboranylporphyrin $12$ with an alkyl linkage between the carborane and the porphyrin ring could easily be achieved by the conensation of aldehyde $11$ with pyrrole (Scheme 3.5). This type of porphyrin with only one methylene spacer between the carboranes and the porphyrin ring had been previously synthesized before Lindsey conditions were developed.\footnote{The more primitive Adler-Longo method\cite{Adler-Longo} had been used,}
and the porphyrin was produced in 16% yield. The use of the milder Lindsey conditions could provide a porphyrin with (bis)methylene linkages between the carboranes and the porphyrin. Ozonolysis\textsuperscript{10} was previously used to make an aldehyde from vinylcarborane, but the corresponding porphyrin could not be synthesized because of the close proximity of the carborane cages to the porphyrin ring.

\begin{center}
\includegraphics[width=\textwidth]{scheme3_4.png}
\end{center}

**Scheme 3.4:** Basic degradation of closo carboranes to their nido derivatives.

Initially, Lindsey conditions were attempted with aldehyde 11 and pyrrole. The yield was so low that another method had to be attempted. The use of less dilute conditions is common in the synthesis of meso-tetraalkylporphyrins,\textsuperscript{11} so a concentration of 10\textsuperscript{-1} M was applied in the synthesis of carboranylporphyrin 12. Synthesis of carboranylporphyrin 12 was not successful under Lindsey conditions, so Adler-Longo methods were then employed using a variation that prevents formation of tar.\textsuperscript{12} This method used pyridine, excess pyrrole, and water to prevent tar formation. Initially it was
**Figure 3.4:** HPLC of carboranylporphyrin 9.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% A</th>
<th>% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>100</td>
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<td>25</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

**Solvent A:** 50% Phosphate Buffer pH = 8
50% MeOH

**Solvent B:** 10% Phosphate Buffer pH = 8
90% MeOH

**Table:**

- **Time (min)**: The time in minutes for the HPLC analysis.
- **% A**: The percentage of Solvent A.
- **% B**: The percentage of Solvent B.
thought that this method also was not producing the porphyrin, but the presence of a sharp Soret band in the UV-visible spectrum indicated otherwise. It became apparent that the reaction was occurring, but poor solubility caused problems in the purification of porphyrin 12.

Scheme 3.5: Synthesis of meso tetraalkylcarboranylporphyrin 12.

The synthesis of a similar porphyrin with meso phenyl substitution could improve its solubility. The use of dipyrromethanes to make porphyrins by MacDonald [2+2] route\(^{13}\) could provide a less symmetrical but more soluble dicarboranylporphyrin 13.\(^{14}\) This porphyrin 13 contained only two carborane groups and would likely be more soluble because of the presence of meso phenyl substitution. Phenylidipyrromethane was synthesized and condensed with aldehyde 11 in the presence of Amberlyst-15 cation exchange resin \textit{via} a MacDonald [2+2] condensation.\(^{15}\) This aldehyde was combined with phenylidipyrromethane under acid catalysis and stirred for 12 h followed by subsequent oxidation with \textit{p}-chloranil. Initially the sharp Soret and Q-bands in the reaction mixture gave strong indication that the reaction had been successful. The \(^1\text{H-}\)NMR also indicated that the product had been formed, but the MALDI-MS indicated that other products were also forming. Careful examination of the \(^1\text{H-}\)NMR spectrum showed
the presence of unexplained coupling and integrations that were not consistent with the pure product. MALDI-MS indicated the products in Scheme 3.6 were forming in addition to the trans isomer of the dicarboranylporphyrin shown. Unfortunately, scrambling of porphyrinogens is a common problem in MacDonald [2+2] reactions, and this condensation yielded at least the three shown porphyrin products shown in Scheme 3.6.\(^{16}\)

Scheme 3.6: MacDonald [2+2] condensation yielding carboranylporphyrins.

3.3 Conclusions and Future Direction

Great strides were made toward the synthesis of novel β-carboranylporphyrins from pyrrole 3. The β-carboranylporphyrins have been explored to quite a large extent, but on the other hand, the purification of carboranylporphyrin 12 needs improvement. The presence of a strong Soret Band and four Q-bands in the UV-Visible spectrum during the synthesis of carboranylporphyrin 12 indicates that the reaction is working to a large degree. The purification could possibly be improved by recrystallization of the tetrabutylammonium salt of the nido derivative of carboranylporphyrin 12 followed by ion exchange to produce the potassium salt.
3.4 Experimental

β,β',β'',β'''-Tetra[2-(2-Methyl-o-carboranyl)-ethyl]-5,10,15,20-tetraphenylporphyrin (4):

2-(2-Methyl-o-carboranyl)-3-ethylpyrrole 3 (0.062 g, 0.25 mmol) was dried under reduced pressure to remove ambient moisture and flushed with Ar to remove ambient oxygen. Freshly distilled DCM (25 mL) was added to a 250 mL 3 neck RBF equipped with magnetic stirring. The solution was stirred to dissolve pyrrole 3 and distilled benzaldehyde (0.027 g, 0.25 mmol) dissolved in freshly distilled DCM (25 mL) was added. The solution was shielded from light and BF₃•Et₂O (3.55 µL, 0.025 mmol) was added dropwise. Upon the addition the solution immediately turned yellow then after 2 h the solution was purple. After 2 h, solid p-chloranil (0.184 g, 0.75 mmol) was added directly to the reaction mixture. The reaction remained purple and was stirred for 13 h. The solvent was removed under reduced pressure and EtOAc (100 mL) was added to dissolve the reaction mixture. The organic layer was washed with NaCl (150 mL), and NaHCO₃ in 150 mL portions until the washes were clear and basic indicating that all of the reduced p-chloranil had been removed by the bicarbonate solution. The organic layer was then washed again with NaCl (150 mL), the organic layer was dried over MgSO₄ and concentrated. The mixture was first chromatographed on silica gel (60% hexanes: 40% EtOAc) to remove any non-polar by-products. DCM was then used to flush any remaining porphyrin products through the column. The reaction mixture was concentrated under reduced pressure and dissolved in DCM in an RBF and 1 mL TEA was added with Zn(OAc)₂ (0.122 g, 0.56). The product was then filtered through a plug of silica gel and concentrated under reduced pressure. The crude zinc complex was then purified by column chromatography eluting with toluene. The four isomers were
dissolved into 5 mL DCM and 1 mL TFA was added. The reddish solution immediately became bright green and was immediately washed with saturated NaHCO₃ until washes were basic. The organic layer was then dried over MgSO₄, filtered through a celite cake, and concentrated under reduced pressure give a mixture of the four isomeric porphyrins (types I – IV) in a 49% yield (0.041 g).

m.p. > 300 °C; HRMS (MALDI-TOF) for C₆₄H₉₅B₄₀N₄ 1353.1622 (calc. 1352.1580); UV-Vis (CH₂Cl₂) λₘₐₓ 423.5 (ε 352, 900), 520 (26, 600), 589.0 (13,650), 651 (6,700) nm; ¹H-NMR (250 MHz, CDCl₃, δ ppm) 8.27-8.05 (m, 12H, β and o Ar-H), 7.94-7.83 (m, 12H, p and m Ar-H), 3.11-2.75 (m, 8H, αCH₂), 2.45-2.02 (m, 8H, βCH₂), 1.83-1.77 (m, 12H, CH₃), 3.11-0.70 (br m, 40H, BH), -2.44 (br s, 2H, NH).

**Tetra-Potassium β,β’,β”’,β’’’-Tetra[2-(2-methyl-o-nido-carboranyl)-ethyl]-5,10,15,20-tetraphenylporphyrin (9):**

Tetra-β,β’,β”’,β’’’-Tetra-[2-(2-Methyl-o-carboranyl)-ethyl]-5,10,15,20-tetraphenyl porphyrin 7 (0.010 g, 0.007 mmol) was weighed out and placed into an RBF equipped with magnetic stirring. A solution of TBAF (1 M in THF) (0.044 mL, 0.044 mmol) was added and the solution turned from red to green. To the resulting solution were added THF (10 mL) and H₂O (0.006 mL, 0.35 mmol) and the resulting solution was stirred for 12 h. Little reaction progress was apparent, so the reaction was heated for 2 h at mild reflux. After 1 h the TLC indicated the presence of no starting material in the reaction mixture, but the reaction was stirred for an additional 2 h. Solvent was removed under reduced pressure at elevated temperature. The reaction mixture was extracted into DCM (2 x 100 mL) and the green solution was washed with water (3 x 100 mL) to remove the excess TBAF and side products produced in the reaction. The solution was dried over Na₂SO₄, filtered through a celite cake, and concentrated under reduced pressure to yield
the corresponding tetrabutylammonium salt. The title compound was converted to the
title compound by passing through Dowex cation exchange resin which had been
activated with a 1M solution of KOH and washed with H₂O. The salt was first dissolved
into acetone (0.7 mL) and H₂O (0.3 mL) was added. The resulting solution was loaded to
the column and eluted with 70% acetone: 30% H₂O. The solubility of the salt in the
mobile phase had been greatly enhanced by passing once through the column, so to
insure all cations had been exchanged, the salt was eluted once more in the same mobile
phase then with 30% acetone: 70% H₂O. The salt was then concentrated under reduced
pressure and dissolved into acetone to remove any undesired impurities from the resin,
which were not soluble in acetone. The mother liquors were concentrated under reduced
pressure to yield the title compound in an 83% yield (0.009 g).
m.p. > 300 °C; MALDI-MS for C₆₄H₉₇B₃₆N₄Na 1335.84 (calc. 1335.12); UV-Vis
(CH₂Cl₂) λₘₐₓ 417 (ε 316,100), 512 (17,500), 546 (9,700), 587 (8,800) nm; ¹H-NMR
(250 MHz, CDCl₃, δ ppm) 8.05-7.95 (m, 12H, β and o Ar-H), 7.94-7.83 (m, 12H, p and
m Ar-H), 3.64-3.05 (m, 8H, αCH₂), 2.36-2.20 (m, 8H, βCH₂), 1.40-1.20 (m, 12H, CH₃),
3.50-0.60 (br m, 40H, BH), - 2.47 (br s, 6H, NH).

β,β’,β”,β’’’-Tetra[2-(2-Methyl-o-carboranyl)-ethyl]-5,10,15,20-tetra-(2-methyl-o-
carboranyl)-methyl tetraphenyl porphyrin (7):

2-(2-Methyl-o-carboranyl)-3-ethylpyrrole 3 (0.028 g, 0.11 mmol) and p-(2-methyl-o-
carboranyl)methyl benzaldehyde 6 (0.031 g, 0.11 mmol) were placed into a 250 mL RBF
and dissolved in freshly distilled DCM (22 mL). BF₃•Et₂O (5 µL, 0.033 mmol), was
added and the solution turned yellow then eventually red after 2 h. Solid DDQ (0.075 g,
0.33 mmol) was added and the red solution quickly turned black and stirred at RT for 40
min. UV-vis showed a Soret band and the reaction was washed with saturated NaHCO₃
until the washes were basic and clear. The resulting dark brown solution was concentrated under reduced pressure and purified by column chromatography eluting with DCM. The resulting product was dissolved into 15 mL DCM and Zn(OAc)$_2$ (0.244 g, 1.11 mmol) was added resulting in a dark red solution. The reaction was monitored by TLC and UV-Vis. Once the reaction was complete, the solution was filtered through a plug of silica gel and purified via column chromatography eluting with toluene. The resulting material was concentrated under reduced pressure and isolated the mixture of four porphyrins in a 16% yield (0.009 g).

m. p. > 300 °C; HRMS (MALDI-TOF) for C$_{80}$H$_{151}$B$_{80}$N$_4$ 2033.9923 (calc. 2033.9987);

UV-Vis (CH$_2$Cl$_2$)$\lambda_{\text{max}}$423.5 (ε 240,000), 520.0 (15,500), 594.0 (6,400), 648.0 (3,400) nm;

$^1$H-NMR (400 MHz, CDCl$_3$, δ ppm) 8.36-8.25 (m, 4H, β-H), 8.22-8.05 (m, 8H, o-Ar-H), 7.78-7.55 (m, 8H, m-Ar-H), 3.88-3.54 (m, 8H, benzylic CH$_2$), 3.13-2.82 (m, 8H, αCH$_2$), 2.70-2.50 (m, 8H, βCH$_2$), 2.41-2.31 (m, 12H, CH$_3$), 2.00-1.92 (m, 12H, CH$_3$), 3.13-0.70 (br m, 80H, BH), -2.81 (br s, 2H, NH).

**Tetra potassium β,β’,β”,β’’'-tetra potassium[2-(2-Methyl-o-nido-carboranyl)-ethyl]-5,10,15,20-tetra(2-methyl-o-nido-carboranyl)-methyl tetraphenylporphyrin (10):**

β,β’,β”,β’’'-Tetra[2-(2-Methyl-o-carboranyl)-ethyl]-5,10,15,20-tetra-(2-methyl-o-carboranyl)-methyl tetraphenylporphyrin 8 (0.007 g, 0.003 mmol) was placed in a 100 mL RBF equipped with magnetic stirring, and a THF solution of TBAF (1 M) (0.041 mL, 0.041 mmol) was added. Two drops of water were added, and the resulting solution was heated gently. Additional THF was added (5 mL) to keep the reaction mixture from drying. After 2 h TLC indicated no more starting material remained, but the reaction was heated for an additional 2 h. The solvent was removed under reduced pressure and H$_2$O
(50 mL) and DCM (50 mL) were added. The aqueous layer was extracted with DCM (2 x 50 mL), dried over Na₂SO₄, filtered through a celite cake, and concentrated under reduced pressure to yield the tetrabutylammonium salt. As above, the tetrabutylammonium salt was converted to the potassium salt by ion exchange chromatography to yield the title compound as a reddish solid (0.006 g) in a 77% yield.

m. p. > 300 °C; MALDI-MS for C₇₇H₁₃₈B₆₃N₄Na₇ 1962.62 (calc. 1962.65); UV-Vis (CH₂Cl₂)λₑₓₕ₄₂₅.₅(ε 176,600), 555.0 (29,500), 601.5 (24.200); ¹H-NMR (250 MHz, acetone–d6, δ ppm) 7.92 (d, 8H, J = 8.2 Hz, o-Ar-H) 7.75 – 7.38 (m, 4H, β-H), 7.25 (d, 8H, J = 4.15 Hz, m-Ar-H), 3.52 – 3.46 (m, 8H, benzylic CH₂), 3.40 - 3.36 (m, 8H, αCH₂), 2.12 – 2.07 (m, 8H, βCH₃), 1.27 (s, 12H, CH₃), 1.19 (s, 12H, CH₃), 2.30 – 1.70 (br m, 80H, BH), - 2.52 (br s, 10H, B-H-B, NH).

3.5 References


CHAPTER 4: DERIVATIZATION OF NATURAL PORPHYRINS

4.1 Introduction

The syntheses of hemes labeled with $^2$H and $^{13}$C have previously been used in paramagnetic heme protein NMR. The chemical shifts of for example the methyls of heme give information on the unpaired spin density of each methyl, and therefore on the electronic structure of heme in the protein. Methyls (because there is one per pyrrole substituent) are excellent spectroscopic probes, but assignments must be made for each of the four methyl groups. Placing labels on methyls through $^2$H and $^{13}$C provides this information through difference spectroscopy.

Deuterium has been incorporated into the porphyrin by total synthesis from deuterated acetylacetone and by exchange of intact porphyrins. $^{13}$C has also been incorporated from the pyrrole stage using $^{13}$C DMF and POCl$_3$. The development of the Suzuki reaction$^2$ to directly place methyl groups on the porphyrin will more easily allow these studies to be undertaken.

Naturally derived porphyrins possessing substitution patterns of natural tetrapyrrolic systems have been shown to be efficient photosensitizers in PDT.$^{3,4}$ In addition to application in PDT, porphyrins and metalloporphyrins have been applied in materials science$^5$ and organometallic chemistry.$^6$ Previously, palladium-mediated cross-coupling between arylboronic acids and halogenated porphyrins were used to produce porphyrin oligomers,$^7$ and such oligomers were shown to be efficient photosensitizers in PDT.$^8$ Suzuki cross-coupling methods have been shown to produce biaryls under relatively mild conditions.$^9$ These types of reactions are not particularly sensitive to water, and many different types of functionality can be tolerated. To date no examples of
alkyl boronic acids have been used to implement alkyl functionality on the β positions of deuteroporphyrin-IX. The derivitization of natural porphyrins can be used to efficiently provide a means of conversion to other natural porphyrins in high yield. These types of porphyrins have been used as sensitizers in PDT, and because of their natural abundance they can be produced in high yield.

Deuteroporphyrin-IX contains two unsubstituted β positions. These positions are readily brominated to form 3,8-dibromodeuteroporphyrin-IX, which is a suitable substrate for the Suzuki reaction. Protoporphyrin-IX is a naturally derived porphyrin, which can be easily converted to deuteroporphyrin-IX by devinylation in resorcinol.

4.2 Results and Discussion

Commercially available hemin chloride was converted to deuteroporphyrin-IX dimethyl ester by devinylation in a rescorcinol melt followed by esterification with gaseous HCl in the presence of MeOH. Hemin chloride was weighed and ground with resorcinol using a mortar and pestle. The resulting powder was placed in an RBF and heated until a molten solution resulted. As this dark solution was heated, resorcinol began to sublime, so the flask walls were scraped to return the sublimed resorcinol to the melt. This solution was stirred for 45 min in an inert atmosphere at 165 °C. To the resulting solution ether was added and a brown solid precipitated. The solid was isolated by filtration, dried over a 2 h period, and dissolved in pyridine.

To demetalate hemin, FeSO₄•7H₂O was added in MeOH and gaseous HCl was bubbled into the flask until a peak on the UV-vis appeared at 550 nm representing the dication of the porphyrin. Porphyrin I was extracted into DCM, purified by column
chromatography on grade III alumina eluting with DCM, and was isolated in a 51% yield. The $^1$H-NMR spectrum of porphyrin 1 can be seen in Figure 4.1.

To brominate the β positions, porphyrin 1 was dissolved into DCM and a slight excess of solid NBS was added to the reaction mixture. Excess NBS could be used because the meso positions were too sterically hindered for bromination. Immediately following the addition of NBS UV-vis indicated the formation of the brominated porphyrin 2, so the crude mixture was dissolved in DCM and filtered through a short plug of grade III alumina to remove succinimide.

Porphyrin 2 had limited solubility in DCM, but was dissolved in DCM to form a maroon colored slurry. To insert zinc into porphyrin 2, Zn(OAc)$_2$ dissolved in MeOH
was added to the solution and stirred until UV-vis indicated the disappearance of a set of four Q-bands\textsuperscript{15} and the appearance of a set of two Q-bands. After the insertion of Zn was complete, the solution had higher solubility in DCM and had turned from maroon to bright red. The resulting solution was washed with an aqueous solution of NaCl to remove excess Zn(OAc)\textsubscript{2}. The resulting solution was dried and concentrated under reduced pressure. The resulting crude mixture was recrystallized in cold MeOH, and porphyrin 3 was isolated as a red solid in 90% yield. The \textsuperscript{1}H-NMR spectrum of porphyrin 3 shows the absence of β protons and this spectrum can be seen in Figure 4.2.

The methylation of porphyrin 3 was first attempted using the Suzuki reaction with solution phase Pd(PPh\textsubscript{3})\textsubscript{4} in a 1:1 mixture of toluene and DMF, but a more polar product formed. As an alternative method to the Suzuki reaction, the Negishi reaction was attempted in THF with ZnCl\textsubscript{2}, MeLi, and solid-phase palladium.\textsuperscript{16} The ZnCl\textsubscript{2} was ground, placed in a flask, heated, and MeLi was added. After the addition of MeLi, a precipitate formed and solid-phase palladium and porphyrin 3 were added. Initially, the Negishi reaction appeared to be progressing, but later MALDI confirmed that this was not the case.

\textbf{Scheme 4.2:} Attempted coupling reactions of porphyrin 3.
Figure 4.1: $^1$H-NMR spectrum of deuteroporphyrin-IX dimethyl ester 2.
**Figure 4.2:** $^1$H-NMR spectrum of 3,8-dibromodeuteroporphyrin-IX (Zinc II) dimethyl ester 3.
The more polar product containing the aromatic protons was likely an adduct of palladium and halogenated porphyrin 3, so the Suzuki reaction was attempted with polystyrene bound palladium. All materials including K₂CO₃ were combined in a flask, evacuated, and refilled with Ar.³ After an inert atmosphere was obtained, a solution of toluene and DMF was added to dissolve all soluble contents of the flask. The dark solution was stirred for 4 days, and the progress of the reaction was followed by MALDI-MS. After 4 days, MALDI confirmed the complete conversion to porphyrin 4. The reaction was stopped by filtration through a celite cake to remove palladium catalyst. The reaction mixture was then extracted into DCM to remove DMF. The ¹H-NMR spectrum of porphyrin 4 shows the symmetry of the molecule and can be seen in Figure 4.3. Additionally, porphyrin 4 crystallized from THF to produce red crystals whose X-ray crystal structure can be seen in Figure 4.5.

Scheme 4.3: Methylation of DP-IX dimethyl ester.

Scheme 4.4: Formation of propionic methyl ester boronic ester by anti-Markovnikov addition.
4.3 **Future Direction**

The alkylations of porphyrin 3 with ethyl boronic acid and isopropyl boronic acid are currently being investigated, and alkylation with propionic methyl ester boronic ester will then be attempted. The anti-Markovnikov addition of borane 5 to vinyl ester 6 shown in Figure 4.4 will afford the boronic ester 7, which can be used in a Suzuki coupling between porphyrin 3 and boronic ester 7. The conversions in Scheme 4.5 using the Suzuki reaction will provide a direct pathway to coproporphyrin-III.

In addition to direct conversion to coproporphyrin-III, the development of the Suzuki reaction has provided an economical means to place deuterated methyl groups on deuteroporphyrin-IX. The use of dibromodeuteroporphyrin-IX readily provides a substrate that can be isotopically labeled and used to investigate the magnetic properties of these labeled hemes.

**Scheme 4.5:** Direct conversion to coproporphyrin-III by Suzuki coupling.

![Chemical structures](image-url)
Figure 4.4: $^1$H-NMR spectrum of 3,8-dimethyldeuteroporphyrin-IX (Zinc II) dimethyl ester 4.
Figure 4.5: X-ray crystal structure of porphyrin 4.
4.4 Experimental

Deuteroporphrin-IX dimethyl ester:

To resorcinol (4.0 g) was added commercial hemin chloride (1.0 g). The powders were ground using a mortar and pestle, and placed in a 100 mL RBF equipped with magnetic stirring, and heated to 165 °C under a stream of N₂ for 45 min. The mixture was allowed to cool and ether (25 mL) was added. The brown solution was vacuum filtered and the crude deuterohemin precipitate was rinsed with ether until the filtrate was nearly colorless. The air dried hemin was dissolved in pyridine (8 mL) and MeOH (3 mL) after which MeOH (37 mL) and FeSO₄•7H₂O (2.5 g) were added. The reaction vessel was chilled in an ice bath as dry gaseous HCl was rapidly bubbled through the solution. After 10 min the demetalation was complete as determined by the presence of the porphyrin dication absorption at 550 nm, the solution was carefully poured into a 500 mL separatory funnel containing ice water (100 mL) and DCM (100 mL). The porphyrin was extracted from the acidic aqueous layer with several portions of DCM and the combined organic fractions were washed repeatedly with water (3 x 50 mL). The organic layer was collected, the solvent removed, and the residue was chromatographed on grade III alumina with DCM. The main fraction was collected and crystallized from DCM/hexanes to give the title compound as a dark red solid (0.420 g) in 51% yield. 

m.p. = 220-221 °C (lit.¹² 223–225 °C); (250 MHz, CDCl₃, δ ppm) 10.22 (s, 1H), 10.18 (s, 1H), 10.14 (s, 1H), 10.10 (s, 1H), 9.18 (d, 2H, J = 2.5), 4.43 (t, 4H, J = 7.6 Hz), 3.76 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.67 (s, 6H), 3.03 (t, 4H, J = 7.7 Hz).
3,8-Dibromodeuteroporphyrin-IX Dimethyl Ester:
Freshly recrystallized NBS (0.129 g, 0.725 mmol) was added to a solution of
deuteroporphyrin-IX dimethyl ester (0.186 g, 0.345 mmol) dissolved in DCM (25 mL).
The solution was stirred at RT for 1 h. After 1 h, the reaction mixture was washed with
H₂O (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The
remaining crude material was dissolved into DCM and filtered through grade III alumina
to yield the title compound as a purple solid (0.230 g) in 96% yield.
m.p. = 278-279 °C (lit.¹⁴b 277 °C); (250 MHz, CDCl₃, δ ppm) 9.79 (s, 1H), 9.75 (s, 1H),
9.61 (s, 1H), 9.59 (s, 1H), 4.34 (t, 2H, J = 7.6 Hz), 3.65 (s, 6H), 3.57 (s, 3H), 3.50 (s, 6H),
3.48 (s, 3H), 3.21 (d of t, 6H, J = 7.4 Hz, J = 2.3 Hz).

Zinc(II) 3,8-dibromodeuteroporphyrin-IX Dimethyl Ester:
3,8-Dibromodeuteroporphyrin-IX dimethyl ester (0.200 g, 0.287 mmol) was dissolved
into DCM (15 mL) and Zn(OAc)₂ (0.460 g, 2.87 mmol) dissolved in MeOH (5 mL) was
added to the solution. The resulting solution turned from purple to bright red within 30
min, but the solution was stirred for an additional 1 h to insure complete metalation.
After 1.5 h, the organic layer was washed with H₂O (50 mL) and saturated aqueous NaCl
(50 mL) to remove excess Zn(OAc)₂. The organic layer was then dried over Na₂SO₄,
concentrated under reduced pressure, and recrystallized in MeOH to give the title
compound as a bright red solid (0.196 g) in 90% yield.
m.p. = 276-278 °C (lit.¹⁴b 279-280 °C); MALDI MS m/z 755.496; (250 MHz, CDCl₃, δ
ppm) 9.26 (s, 1H), 9.10 (s, 1H), 8.94 (s, 1H), 8.88 (s, 1H), 4.05 – 4.15 (m, 4H), 3.58 (s,
3H), 3.57 (s, 3H), 3.37 (s, 3H), 3.25 (s, 3H), 3.24 (s, 3H), 3.16 (s, 3H), 3.02 (q, 4H, J =
7.6 Hz).
Zinc(II) 3,8-Dimethyldeuteroporphyrin-IX Dimethyl Ester:

Zinc(II)-3,8-dibromodeuteroporphyrin-IX dimethyl ester (0.050 g, 0.066 mmol), K₂CO₃ (0.091 g, 0.658 mmol), methylboronic acid (0.008 g, 0.132 mmol), and polystyrene bound Pd(PPh₃)₄ (0.132 g, 0.013 mmol) were weighed in a 3 neck RBF equipped with magnetic stirring. The resulting mixture was dissolved in DMF (5 mL) and toluene (5 mL). This solution was heated to 95 °C and stirred for 36 h. The reaction was monitored closely by TLC, was quenched by the addition of saturated aqueous NaCl (50 mL), and then extracted into DCM (50 mL). The resulting organic layer was dried over anhydrous Na₂SO₄, filtered through a celite cake, and concentrated under reduced pressure. The resulting crude product was dissolved in a minimal amount of EtOAc and filtered through a short plug of silica to give the pure title compound as a red solid (0.027 g) in 44% yield. m.p. > 300 °C; MALDI-MS m/z 625.257; UV-Vis (CH₂Cl₂)λ_max 405 (ε 219,800), 535 (ε 28,600), 571 (ε 29,000); (250 MHz, CDCl₃, δ ppm) 9.46 (s, 1H), 9.37 (s, 2H), 9.14 (s, 1H), 4.27 (t, 4H, J = 7.4 Hz), 3.68 (s, 6H), 3.47 (s, 3H), 3.39 (s, 3H), 3.34 (s, 3H), 3.15 (t, 4H, J = 7.5 Hz).

4.5 References


CHAPTER 5: SYNTHESIS OF PEPTIDE LINKERS PROTECTING GROUPS,
AND DIAMINO ACIDS FOR THE FACILITATION OF PEPTIDE SYNTHESIS*

5.1 Introduction

The synthesis of peptide linkers, protecting groups, and diamino acids in this chapter employ many methods which range from commonly known organic techniques to novel reactions. The key focus of this chapter is the facilitation of peptide synthesis, and in many instances to apply olefin metathesis reactions using ruthenium based catalysis. Olefin metathesis is a relatively new type of reaction which uses ruthenium catalysis to synthesize olefins. There are three types of olefin metathesis reactions in organic chemistry - ring closing metathesis,\(^5\) cross metathesis,\(^13\) and ring opening metathesis.\(^11\) The metathesis reactions used here employ two catalysts 1 and 2,\(^9,17\) shown below in Figure 5.1.

![Catalysts](image_url)

**Figure 5.1:** Catalysts used commonly in olefin metathesis.

The first project involved the chemistry and application of a peptide protecting group 3 shown in Scheme 5.2 which is more synthetically useful than the Fmoc

![Scheme](image_url)

**Scheme 5.1:** A general example of olefin cross metathesis.\(^31\)

Scheme 5.2: Ring closing metathesis to control cleavage from protecting group. Unlike Fmoc shown in Scheme 5.3, this protecting group is not fully assembled until after the peptide has been synthesized and removal from the protecting group is desired. The synthetic usefulness of this approach in Scheme 5.2 is that removal can be controlled more precisely than in the case of Fmoc in Scheme 5.3.

Scheme 5.3: Clevage of a peptide from the Fmoc protecting group.

A second project involved a solid phase linker, and also used a base to remove the peptide from a resin. This project relates to the Fmoc analogue project mentioned above in that the peptide can not be eliminated by base until an olefin metathesis reaction has taken place. This also allows for removal of the peptide to be controlled more precisely (Scheme 5.4).

Scheme 5.4: Cross metathesis reaction to control removal of peptide.

The resin-bound peptide was removed from the resin via an olefin cross metathesis with an olefin containing an electron withdrawing substituent, or a functional
group which could be easily converted into an electron withdrawing group in high yield. This conversion will make the elimination of the peptide from the linker possible with a base such as DBU, as is shown in Scheme 5.4.

The final project in this chapter involved the synthesis of novel amino acids using Williams template as a chiral auxiliary. These diamino acids will help to provide rigidity in β sheets by forming a peptide which is conformationally locked. This would cause the peptide to be a very rigid structure. The amino acids will be one of the types of amino acids in this rigid peptide. The diamino acid is the moiety of the peptide in red in peptide, and the other moiety in black has previously been synthesized by a coworker in the McLaughlin group. The reactions of Williams template are stereoselective and allow the synthesis of chiral amino acids.

Scheme 5.5: Synthesis of a diamino acid using Williams template.

The template was first alkylated and then the amino group was attempted first by an electrophilic azo transfer using trisyl azide, but the azo transfer was not successful. Then a Michael addition was the next attempted using DBAD as the Michael acceptor to be later removed by hydrogenolysis, but this reaction was also unsuccessful.

Another interesting method for the synthesis of these amino acids is to start with the hydrochloride salt of diethyl amino malonate, protect with Cbz, then to alkylate with an alkyl halide (Scheme 5.6).
Scheme 5.6: Synthesis of a diamino acid though an enzymatic reaction.

The achiral diester was hydrolyzed with PLE to the chiral acid. 28 The Curtius rearrangement was then attempted with *tert*-butanol and the diprotected chiral amino acid should have been formed with one of the amino groups Boc protected and the other Cbz protected. The remaining ester would then be hydrolyzed with base and isolated. Unfortunately, the Curtius rearrangement on this particular substrate was unsuccessful.

5.2 Results and Discussion

The Fmoc analogue project mentioned in the introduction had many difficulties, and took several turns as seen in Scheme 5.7. Initially, the project involved a Heck coupling 1,2,35 of dibromobenzene 8 with propene, but yields were very low and after purification, dialkene 9 was obtained in only a 6% yield. The Heck reaction also required a high pressure of propene. Propene is not an ideal gas, and large amounts of propene are required to obtain a high pressure. The propene must be condensed then added to the cooled autoclave. After the product was purified via column chromatography, the monobromination of the dialkene 9 to make the brominated dialkene 10 was attempted with NBS and benzoyl peroxide as the radical initiator. The reaction appeared to be successful, but upon chromatography using silica gel the compound decomposed.

After four attempts to obtain an acceptable yield, the Heck reaction was abandoned and the Sonagashira reaction 3 in Scheme 5.8 was implemented to couple dibromobenzene with propyne.
Scheme 5.7: Synthesis of the Fmoc analogue.

The Sonagashira reaction in Scheme 5.8 was more practical, but still gave only a 7% yield of the desired product 11. The Sonagashira reaction required tri (t-butyl) phosphine, which is a very expensive catalyst used in the Sonagashira coupling. The reaction also required palladium, which is expensive. The dialkyne 11 was then hydrogenated with Lindlar’s catalyst under 50 psi of hydrogen. The hydrogenation of the dialkyne afforded the cis dialkene 12 in a quantitative yield. The dialkene 12 was then brominated with NBS at the allylic position with one equivalent of NBS and a catalytic amount of benzoyl peroxide, but as before the halide decomposed on silica gel, so the formation of aGrignard reagent was attempted on the crude material and was also not successful.

Scheme 5.8: Synthesis of the dialkene using Sonagashira reaction.
The alternative route of reacting 2-bromostyrene with excess lithium, butadiene monoxide, and BF₃•Et₂O posed a very efficient synthesis of the target molecule in essentially one step as indicated in Scheme 5.9. ⁶,⁸

Scheme 5.9: Synthesis of the Fmoc analogue.

Unfortunately, the polymerization of styrene was initiated by the presence of the lithium anion of o-bromostyrene 14, so the use of a Grignard reagent was pursued instead. Many difficulties were encountered in preparing the Grignard reagent 2-bromostyrene. Eventually, the preparation of Rieke magnesium³² was accomplished and was very successful. Because butadiene oxide was very expensive, the Grignard reagent 16 was prepared and reacted with DMF to make 2-formyl styrene 17 in a 93% yield in order to verify the formation of the Grignard reagent. Once the 2-formylstyrene was characterized, the Grignard was prepared and reacted with butadiene oxide. Because of the complexity of the ¹H NMR and ¹³C NMR spectra, further characterization was required, and the MS indicated that the reaction had not yielded the desired product.
Scheme 5.10: Synthesis of solid-phase linker through a non-conjugated approach.

The project involving the solid phase peptide linker in Scheme 5.10 also took several turns. All of the solid-phase reactions took place in a 50 mL syringe with a filter to prevent the resin from escaping the syringe.

The project began by coupling 4-pentenoic acid 18 to clear resin 19 to make the amide 20 using DIA to deprotonate the resin and PyAOP as the coupling reagent as indicated in Scheme 5.10. The solvent used to swell the resin was acetonitrile. The reaction was given one day of constant swirling to give all the amine functionality on the resin sufficient time to react. The next step involved the cross metathesis of the terminal olefin coupled to the resin with 3-buten-1-ol 21 to make the resin-bound alcohol 22. The alcohol, 3-buten-1-ol, 21 was added to the resin already swollen with DCM. After the addition of the alcohol 21 to the resin the contents of the syringe were stirred gently to prevent crushing of the resin. The catalyst 1 was weighed out into a 5 mL vial and was dissolved into 3 mL DCM. The catalyst was added very
slowly to the syringe and immediately ethylene began to bubble out of the syringe vigorously. After an hour, the bubbling stopped completely and more catalyst 1 was added. After adding the second lot of catalyst the bubbling resumed. This indicated that the catalyst is not stable in the presence of ethylene. A third lot of catalyst was added and few bubbles formed. The contents of the syringe were then drained, more alcohol was added to the syringe, and the procedure of adding two more lots of catalyst was repeated twice. The reaction was presumed to be complete; however, after placing fresh 3-buten-1-ol 21 into the syringe the bubbles are just as vigorous as previously. This indicates that most of the bubbles are likely coming from the self cross metathesis of 3-buten-1-ol; however, solid state NMR indicated the presence of vinylic peaks, which evidenced that the reaction was working. The next step involved doing a standard coupling reaction with glycine protected with carbobenzyloxy (Cbz) to make the monopeptide 23. Cbz protection would show aromatic protons in the solid state NMR and verify that the
coupling reaction had occurred. The coupling reaction took place in DMF because the starting materials as well as the products were soluble in DMF. The coupling reaction with Cbz-glycine took place in the presence of ICD, and a catalytic amount of DMAP. The ICD receives the water released in the esterification reaction and forms diisopropyl urea. The final step seemed easy, but was the most difficult. This step was to do a cross metathesis with an olefin containing a conjugated electron withdrawing group. The electron withdrawing group would allow the $\alpha$-proton to be easily deprotonated and an elimination would cleave the peptide from the molecule with DBU. This cross metathesis was nothing like the cross metathesis of the terminal olefin and 3-buten-1-ol 21. The steric hindrance seemed to play a huge role in preventing this reaction from occurring. The first olefin chosen was methylvinylketone, but it coupled so quickly with itself that it was not useful. The coupled product would not react with the peptide on the resin. Some of the other olefins tried were acrylonitrile and acrolein diethylacetal.

Neither of the cross metathesis reactions with the olefins mentioned were successful with Hoyveda’s catalyst 1. Another possibility for removing the peptide from the resin was to react the solid phase directly with ethylene and Hoyveda’s catalyst 1. Reactions of this type have been reported in the literature. 36 The reaction worked in a 10% yield to give the olefin 24. The next step involved trying to test the reactivity of the product which came off the resin by synthesizing more of it in solution and trying to find a cross metathesis substrate which would work in a desirable yield.

Unfortunately in the initial stages, the solid phase linker project was tested in solution using benzoic acid instead of an amino acid as seen in Scheme 5.11. The results
led to an unexpected product of a cross metathesis reaction, and the product isolated was the coupled ester 26.

![Scheme 5.11: Synthesis of diyl benzoate through self cross metathesis.](image)

The results of the attempted cross metathesis led to the production of large crystals from the self cross-metathesis reaction. The crystals were formed by the slow removal of EtOAc, which slowly deposited crystals in the flask. The X-ray crystal structure of diester 26 can be seen in Figure 5.2 and these results were published in Acta Crystallographica.

The project was then revised at this point as shown in Scheme 5.12. The use of allyl alcohol 27 instead of 3-buten-1-ol 21 and use of a non-conjugated approach to the cross metathesis reaction could successfully yield the desired product.

The ester of allyl alcohol and Cbz-glycine was made using ICD and a catalytic amount of DMAP, with allyl alcohol as the reagent and solvent. As the reaction proceeds diisopropyl urea is precipitated and crystals formed overnight. The crystals are removed via vacuum filtration and the allyl alcohol is removed under reduced pressure. There was a limited number of substrates to do the cross-metathesis reactions, and these substrates are shown in Table 5.2. The reactions were attempted first using Hoyveda’s catalyst 1 and the ester with allyl cyanide and butenal diethyl acetal. Neither of the reactions were successful with Hoyveda’s catalyst, but the reaction of the ester with butenal diethyl acetal and Grubb’s catalyst yielded the desired product 30b. The structure of the product
was verified by $^1$H-NMR spectroscopy and purification yielded a yellow oil in a 10% yield. These positive results gave the incentive to begin the solid phase synthesis shown in Scheme 5.12.

The first step was to couple the clear resin with 4-pentenoic acid using DIA, and PyAOP with acetonitrile as the swelling solvent. The resin was then reacted with the coupling reagent and DIA. The terminal olefin 20 bound to the solid phase was swollen with anhydrous DCM then allyl alcohol 27 was added to the syringe. The catalyst was dissolved in DCM then added via a pipette. Upon the addition of catalyst 1, vigorous bubbling began and did not completely stop until an hour later. After the bubbling stopped, more catalyst was added and bubbling continued again though not as vigorously as before. Another aliquot of catalyst was added and bubbling did not occur.

The syringe was drained, the resin was washed, and the procedure with allyl alcohol and Hoyveda’s catalyst was repeated. This yielded a primary alcohol 28 which could easily be coupled to an amino acid by the same method discussed before, using isopropyl carbodiimide and a catalytic amount of DMAP. The resin was rinsed with DCM, then DMF. Cbz-glycine, ICD, and DMAP were dissolved in DMF and added to the syringe. The contents of the syringe were swirled overnight and then the procedure was repeated to insure all positions were esterfified to yield the product 29. After the esterification, the peptide along with the linker were removed from the resin via a cross metathesis in anhydrous DCM, mimicking the similar reaction done in solution with 3-butenal-diethyl acetal. The reaction mixture was filtered through a plug of silica gel and
Figure 5.2: X-Ray crystal structure of cross metathesis product 26.
Scheme 5.12: Synthesis of solid-phase linker through a non-conjugated approach.

Table 5.2: Electron-withdrawing groups used to promote cross metathesis reactions in Scheme 5.12.

<table>
<thead>
<tr>
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<th>Metathesis Reaction Mediator</th>
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<tbody>
<tr>
<td>a</td>
<td>OEt</td>
</tr>
<tr>
<td>b</td>
<td>- - =N</td>
</tr>
</tbody>
</table>

then the coupled acetal byproduct was removed by high performance flash chromatography. If the yield had been higher, the acetal 30b would have been hydrolyzed to the aldehyde and then the product would be eliminated and isolated.

The most current project in Scheme 5.13 involves the synthesis of a series of amino acids. The first attempt at obtaining these acids was to alkylate the Williams amino acid template 4 with LiHMDS and benzyl bromide then to do a seemingly facile azo transfer with KHMDS and trisyl azide. Trisyl azide was prepared in a 73% yield in aqueous MeOH by a displacement on trisyl chloride with sodium azide. The product was recrystallized in MeOH to form large crystals, whose X-ray crystal structure can be seen
in Figure 5.3. The alkylation of Williams template in Scheme 5.13 posed no problems, but the azo transfer was not successful with this template.

**Scheme 5.13**: Attempted synthesis of a diamino acid using Williams template and trisyl azide.

The alkylation was carried out at −78 °C and a THF solution of LiHMDS was added dropwise to the THF solution of the template. After addition of the LiHMDS solution, excess benzyl bromide was added very slowly to ensure the benzyl group would be added on the correct face of the template. After 2 h, the reaction was warmed to room temperature, quenched with H₂O, and a saturated solution of NaCl was added. The product 31 was extracted with EtOAc then purified via column chromatography with silica to yield the alkylated template 31. The product 31 was then dried under high vacuum and dissolved in anhydrous THF. The solution was cooled to −78 °C then a THF solution of KHMDS was added dropwise to the solution of the alkylated template 31. The solution was stirred for 2 h, warmed to room temperature, then cooled back to −78 °C. After cooling to −78 °C a THF solution of trisyl azide was added via cannula transfer, the reaction was allowed to react for 30 min, then worked up with HOAc and KOAc. The solution containing HOAc and KOAc was stirred for 1.5 h. The reaction never yielded the desired azide 32 and the product could not be identified because it always decomposed over time. Because an unexplained product appeared on the TLC plate, which decomposed over a such a short period of time, the hydrogenolysis was attempted but the only product obtained was trisyl sulfonamide which crystallized into
large rhombohedral shaped crystals, which were identified by crystallographic analysis. This compound had only been identified by powder diffraction, results of single crystal data were published.\textsuperscript{38} The crystal structure of trisyl sulfonamide can be found in Figure 5.4. Because there was no evidence that the enolate of the alkylated template \textbf{32} was being formed, it was decided to try to alkylate with methylbromo acetate to verify the formation of the enolate. The reaction worked on the first attempt, and gave an 85\% yield of the desired product. The formation of this compound was verified by MS.

It was decided to then try a different method of putting the amino group on the template. The method employed the use of DBAD\textsuperscript{22,23} in a Michael reaction, then hydrogenolysis of the product with H\textsubscript{2} and Pd/C, but FAB MS indicated that this reaction had not worked.

\begin{center}
\includegraphics[width=\textwidth]{Scheme_5.14.png}
\end{center}

\textbf{Scheme 5.14:} Synthesis of a diamino acid using Williams template and DBAD.

The Curtius rearrangement\textsuperscript{27} (Scheme 5.15) was also attempted to make these novel diamino acids. First the chiral amine was produced using pig liver esterase\textsuperscript{28} to enantioselectively hydrolyze one of the ester functionalities on the diester to make the carboxylic acid. The acid was attempted using DPPA in t-BuOH, but the Curtius rearrangement\textsuperscript{29} was not successful in the presence of the amino group. No explanation can be reached for the lack of reactivity of this substrate to the Curtius rearrangement. This would be a very elegant and short synthesis for the desired product, but the results in this synthesis did not show promise of success.
Figure 5.3: X-Ray crystal structure of trisyl azide.
Figure 5.4: X-Ray crystal structure of trisylsulfonamide.
Figure 5.4: X-Ray crystal structure of the amine transfer reagent.
Scheme 5.15: Synthesis of a diamino acid using pig liver esterase.

The final attempt toward the synthesis involved a rarely used amine transfer reagent, which has previously been synthesized by a more difficult method than we have attempted. Previously, hydroxylamine was reacted with phosphoryl chloride. The lack of regioselectivity, in addition to the difficulty to characterize this material, gave incentive to use the Cbz-protected hydroxylamine. The product was a solid material which formed large crystals whose X-ray crystal structure can be seen in Figure 5.5.

5.3 Experimental

1,2 Dipropenylbenzene:

To a slurry of dibromobenzene (4.72 g, 20.01 mmol), Pd(OAc)₂ (0.44 g, 1.96 mmol), Bu₄NBr (12.9 g, 40.00 mmol), LiCl(8.48 g, 200.1 mmol), and KHCO₃ (8.0 g, 79.9 mmol) in) NMP (400 mL) was added condensed propene. The slurry in a 600 mL autoclave was reacted for 3 days at 100 °C. Due to low pressure, the solution was allowed to cool to RT. At RT there was no pressure, indicating there was not sufficient propene for the reaction to occur, so additional propene was added. The autoclave was cooled in dry ice to -78 °C. The propene was condensed with dry ice in the condenser, and liquid N₂ in the dewar. Propene (30 mL) was added to the autoclave in the dry ice acetone bath. The autoclave was allowed to warm to RT, and the pressure equilibrated to 20 psi. Heat was
applied and the pressure surprisingly dropped at 45 °C to 15 psi. At 120°C the pressure was 22.46 psi. Heat was removed and the pressure dropped to 4.5 psi. The reaction mixture was filtered through a celite cake and then extracted with hexane (3 × 200 mL), and backwashed to remove NMP with tap water (3 × 100 mL). The organic layer was dried over MgSO₄, and concentrated under reduced pressure and the title compound was isolated as a clear liquid in 6% yield.

^1^HNMR (250 MHz, CDCl₃) δ 7.68 (d, 2H), 7.20 (d, 2H), 6.90 (d, 2H), 6.35 (m, 2H), 2.02 (d, 6H).

2-Formylstyrene:

The Rieke Mg slurry (0.333 g, 13.7 mmol) was prepared^32 and stirred in THF (20 mL). 2-Bromostyrene (0.5 g, 2.73 mmol) was added via syringe. An exothermic reaction was observed immediately after addition of 2-bromostyrene. The resulting solution was stirred for 1.5 h, DMF was added in THF (3 mL) at –78 °C, and the solution was stirred for 14 h. Saturated NH₄Cl was added to quench the reaction and consume the remaining Rieke Mg. After Rieke Mg was consumed, the reaction mixture was filtered through a celite cake to remove MgCl₂. The reaction mixture was extracted with EtOAc (3 × 100 mL), dried over K₂CO₃, filtered through a plug of celite, and concentrated under reduced pressure. The crude reaction mixture was purified via column chromatography in 92.5% hexanes: 7.5% EtOAc to yield the title compound as a yellow liquid in a 75% yield.

^1^H-NMR (250 MHz, CDCl₃) δ 10.27 (s, 1H), 7.83 (m, 1H), 7.59 (m, 4H), 5.73 (d, 1H), 5.53 (d, 1H).
2-Bromobenzaldehyde Ethylene Glycol Acetal:
2-Bromobenzaldehyde (10 g, 54 mmol) was weighed and placed in a 500 mL RBF equipped with magnetic stirring and ethylene glycol (3.60 g, 58 mmol) was added to the flask via syringe. The contents of the flask were then dissolved in to toluene (50 mL). PTSA•H₂O (0.21 g, 1.08 mmol) was added directly to flask via a powder funnel. H₂O was removed from equilibrium via Dean and Stark trap. The reaction was allowed to heat for 24 h while removing water. The reaction mixture was then stirred with saturated NaHCO₃ solution (250 mL), washed with brine, dried over K₂CO₃, and concentrated under reduced pressure. The reaction mixture was then purified by column chromatography in 90% hexane: 10% ethyl acetate to yield the title compound in 79% yield.

\[ ^1H-NMR \ (250 \text{ MHz, CDCl}_3) \delta \ 7.64 \ (m, 4H), \ 6.12 \ (s, 1H), \ 4.17 \ (m, 4H). \]

But-3-enyl Benzoate:
3-Buten-1-ol (3.0 g, 41.58 mmol), DMAP (0.255 g, 2.079 mmol), and TEA (5.04 g, 49.92 mmol) were dissolved into THF (30 mL), and benzoyl chloride (7.02 g, 49.92 mmol) was dissolved into DCM (20 mL). The solution of benzoyl chloride was added and allowed to react at RT for 2 h. The reaction was closely followed by TLC. When reaction was complete the reaction mixture was transferred to a 500 mL RBF containing a saturated NaHCO₃ solution (350 mL). The reaction was extracted with DCM (3 x 200 mL). The DCM layer was washed with 1 M HCl (250 mL). The organic layer was dried over MgSO₄, and concentrated under reduced pressure. TLC indicated product was pure and the title compound was isolated as a clear oil in 90% yield.
$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 7.52 (m, 5H), 5.79 (d, 1H), 5.27 (d, 1H), 4.56 (m, 1H), 3.72 (q, 2H), 2.35 (q, 2H).

**Isopropoxybenzaldehyde:**

To a slurry of CsCO$_3$ (6.67 g, 20.47 mmol) and K$_2$CO$_3$ (11.88 g, 85.98 mmol) in DMF (50 mL) was added salicylaldehyde (5.0 g, 40.94 mmol) via syringe. The solution was allowed to stir for 20 min. Isopropyl iodide (14.62 g, 85.98 mmol) was added via syringe and allowed to stir for 7 hrs at RT. The reaction mixture was poured into H$_2$O (100 mL) and stirred for 10 min. The reaction mixture was extracted with EtOAc (3 x 100 mL). The organic layer was washed with a saturated NaCl solution (3 x 100 mL), dried over Na$_2$SO$_4$, concentrated under reduced pressure and the title compound was isolated as a clear liquid in a 95% yield.

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 10.46 (s, 1H), 7.80 (m, 4H), 4.65 (m, 1H), 1.40 (m, 6H).

**Isopropoxystyrene:**

To a stirred slurry of Ph$_3$PCH$_3$Br (14.38 g, 40.26 mmol) in THF (60 mL) was added a 2.5 M solution of n-BuLi (28.5 mL, 71.37 mmol) dropwise at $-78$ °C. Upon addition of n-BuLi, a yellow color developed immediately, and solution was stirred for 2 h. The solution was added via cannula to a solution of isopropoxybenzaldehyde in THF (10 mL) at $-78$ °C. The reaction mixture was warmed to RT and reacted for 23 h. A saturated NaCl solution (100 mL) was added to flask, EtOAc (75 mL) was added, and the reaction mixture was extracted with EtOAc (3 x 100 mL). The reaction mixture was dried over MgSO$_4$ and concentrated under reduced pressure. The resulting mixture of starting material and product were separated via column chromatography in 90% hexanes: 10% EtOAc, to yield the title compound in 51% yield.
$^1$H-NMR (250 MHz, CDCl$_3$) δ 7.52 (m, 5H), 5.79 (d, 1H), 5.27 (d, 1H), 4.56 (m, 1H), 1.38 (d, 6H).

**Hoyveda’s Catalyst:**

To a 250 mL RBF equipped with magnetic stirring were added Grubb’s catalyst 2 (1.1 g, 1.27 mmol) and CuCl (0.171 g, 1.27 mmol) and dissolved into DCM (20 mL). In a separate RBF isopropoxystyrene (0.164 g, 1.19 mmol) was dissolved in DCM (20 mL) and the resulting solution was transferred via pipette into the other flask containing catalyst 2 and CuCl. The reaction mixture was allowed to react at RT for 2.5 h. A black solution with a green tint resulted and the mixture was filtered through a celite cake. The TLC of the reaction relative to starting mixture indicated the reaction was complete. A greenish-brown precipitate was removed and the mother liquors were concentrated. The mother liquors contained the product, which was purified via column chromatography in 90% Hexane: 10% EtOAc.

$^1$H-NMR (250 MHz, CDCl$_3$) δ 16.54 (s, 1H), 7.07 (m, 8H), 4.95 (m, 1H), 4.17 (s, 4H), 2.48 (d, 6H), 2.17 (s, 6H), 1.28 (s, 12H).

**(E)-3-Hexene-1,6-diyl dibenzoate (41):**

A 100 mL RBF equipped with magnetic stirring was charged with 15 mL THF. Ester 2 (0.10 g, 0.56 mmol), and methyl vinyl ketone (0.85 g, 11.2 mmol) were charged into the flask. Hoyveda’s catalyst 1 (0.018 g, 0.028 mmol) was added to the flask in DCM (5 mL). The reaction mixture was purified by column chromatography to obtain 3 after removing solvent. The crystals formed in flask and were submitted for crystallographic analysis and trans olefin geometry was determined in the second product.

$^1$H-NMR (250 MHz, CDCl$_3$) δ 8.06 (m, 10H), 5.68 (t, 2H), 4.38 (t, 4H), 2.61 (m, 4H).
Resin-bound 4-pentenamide (29):

In a 25 mL RBF DIA (0.838 g, 8.28 mmol) was added to 4-pentenoic acid (0.781 g, 7.80 mmol) in H$_3$CCN (5 mL). An exothermic acid-base reaction was observed. Clear resin (5 g, 0.39 meq/g) was weighed out into a 50 mL syringe. PyAOP (4.30 g, 8.25 mmol) was weighed out into a 25 mL RBF then dissolved into a minimal amount of solvent by swirling. The resin was swollen in a minimal amount of solvent. The solution of PYAOP was added to the syringe, then the solution of diisopropyl amine and 4-pentenoic acid was added to the syringe. The syringe was swirled for 4 h at RT, then the solution was filtered. The resin was washed with DCM, H$_3$CCN, DMF, then with DCM.

Resin-bound 4-heptenamide-7-ol (30):

The dry resin 29 (1.95 mmol) remained in syringe from previous reaction. 3-Buten-1-ol (7.03 g, 97.5 mmol) was placed into syringe containing resin via pipette. DCM was added to swell resin. The catalyst 1 (0.063 g, 0.098 mmol) was dissolved into DCM (5 mL) and added dropwise to syringe. Upon addition of catalyst, bubbles were observed immediately. The contents of the syringe turned brown while bubbling. Contents were allowed to swirl overnight, then argon was bubbled to remove any remaining ethylene. Two more portions of catalyst were added to insure reaction was going to completion, and after the second addition bubbling continued as before. The third lot of catalyst did not induce bubbling, resin was drained and washed with DCM followed by DMF.

Resin-bound Cbz glycine carboxylate 4-heptenamide (31):

Into a 50 mL flask equipped with magnetic stirring, Cbz-glycine (0.450 g, 2.15 mmol), ICD (0.269 g, 2.13 mmol), and DMAP (0.215 g, 1.95 mmol) were dissolved into a minimal amount of DMF. Enough DMF was added to swell the resin, then the solution
of Cbz-glycine, ICD, and DMAP was transferred to the syringe. The mixture was allowed to react with constant swirling for 6 h. The syringe was drained, washed with DMF, then the procedure was repeated with new reagents. This reaction was allowed to proceed overnight. The syringe was drained, washed with DMF, then DCM.

Resin-bound 4-hexenamide-6-ol (37):
The dry resin 29 (1.95 mmol) remained in syringe from previous reaction. Allyl alcohol (5.66 g, 97.5 mmol) was placed into syringe containing resin via pipette. DCM was added to swell resin. The catalyst 1 (0.061 g, 0.098 mmol) was dissolved into DCM (5 mL) and added dropwise to syringe. Upon addition of catalyst, bubbles were observed immediately. Contents of syringe turned brown while bubbling. Contents were allowed to swirl overnight, then argon was bubbled to remove any ethylene. Two more portions of catalyst were added to insure reaction was going to completion, and after the second addition bubbling continued as before. The third lot of catalyst did not induce bubbling, so resin was drained and washed with DCM followed by DMF.

Resin-Bound Cbz-glycine carboxylate 4-hexenamide (38):
Into a 50 mL flask equipped with magnetic stirring, Cbz-glycine (0.450 g, 2.15 mmol), ICD (0.271 g, 2.15 mmol), and DMAP (0.215 g, 1.95 mmol) were dissolved into a minimal amount of DMF. Enough DMF was added to swell the resin, then the solution of Cbz-glycine, ICD, and DMAP was transferred to the syringe. The mixture was allowed to react with constant swirling for 6 h. The syringe was drained, washed with DMF, then the same procedure was repeated with new reagents. This reaction was allowed to proceed overnight. The syringe was drained, washed with DMF, then with DCM.
**tert-Butyl-3-Benzyl-2-oxo-5,6-diphenyl-morpholine-4-carboxylate (16):**

Williams template 12 (1.0 g, 2.82 mmol) was weighed out into a 100 mL RBF equipped with magnetic stirring, and dissolved into THF (20 mL). Solution was stirred at RT until 12 was completely dissolved, then the solution was cooled to –78°C. Then a 1 M THF solution of LiHMDS (3 mL, 3 mmol, 1.06 eq.) was added dropwise via syringe. The solution was stirred for 30 min after addition of LiHMDS, then benzyl bromide (3.37 mmol, 28.2 mmol) was added dropwise and the reaction was allowed to proceed for 4 h. The TLC of the reaction mixture relative to starting material indicated that the reaction was complete. H₂O (40 mL) and a saturated solution of NaCl (30 mL) were added to the reaction mixture and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The material contained benzyl bromide and product. The mixture was purified via column chromatography in 85% Hexanes: 15% EtOAc and the title compound was isolated as a white solid in an 88% yield.

M+H⁺ = 444.6

**tert-Butyl-3-Benzyl-3-methoxycarbonylmethyl-2-oxo-5,6-diphenyl-morpholine-4-carboxylate:**

The starting material 16 (0.600 g, 1.35 mmol) was weighed out into a 100 mL RBF equipped with magnetic stirring, flushed with argon, then dissolved into anhydrous THF (5 mL). A 0.5 M toluene solution of KHMDS (5.4 mL, 2.7 mmol) was added dropwise at –78°C, stirred for 15 min, warmed to RT, stirred for 45 min, then cooled to –78 °C. Methylbromoacetate (1.03 g, 6.75 mmol) was added via syringe dropwise and the solution was allowed to stir for 2 h. H₂O (40 mL) was added and the solution was stirred for 5 min., extracted with EtOAc (3 x 100 mL), dried over MgSO₄, and concentrated.
under reduced pressure. Product was purified via column chromatography in 90% Hexanes: 10% EtOAc to yield the pure title compound as a fluffy white solid in an 85% yield.

$\text{M+H}^+ = 516.6$.

**N-Cbz-Diethylaminomalonate (48):**

Diethylethylaminomalonate hydrochloride 14 (5.08 g, 24.00 mmol) was weighed out into a 250 mL Erlenmeyer flask then a 5% NaHCO$_3$ solution was added until the pH was 8. The solution was poured into a 500 mL RBF equipped with magnetic stirring, then 200 mL Et$_2$O were added. Benzylchloroformate (4.09 g, 24.00 mmol) was dissolved into Et$_2$O (50 mL) in a 150 mL Erlenmeyer flask. The benzylchloroformate solution was added slowly to the flask containing the starting material. Immediately upon addition of benzylchloroformate, the Et$_2$O layer turned cloudy. The reaction mixture was extracted with ether (3 x 150 mL), dried over MgSO$_4$, concentrated under reduced pressure and the title compound was isolated as a white solid without further purification in an 84% yield.

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 7.34 (m, 5H), 5.10 (s, 1H), 4.64 (s, 2H), 4.29 (q, 4H), 2.40 (s, 1H), 1.27 (t, 6H).

**Benzyl-N-Cbz-Diethylaminomalonate (49):**

N-Cbz-Diethylaminomalonate 48 (2.094 g, 6.74 mmol) was dissolved in 10 mL dry EtOH and Na° (0.209 g, 9.08 mmol) in a 250 mL RBF equipped with magnetic stirring. The reaction was stirred for 18 h, then benzyl bromide (1.24 g, 7.26 mmol) dissolved in EtOH (10 mL) was added dropwise and allowed to stir for 36 h. EtOH was removed under reduced pressure and H$_2$O (25 mL) was added to the reaction mixture. The
aqueous layer was extracted with EtOAc (3 x 100 mL) to yield the title compound as a white solid.

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 7.41 (m, 10H), 6.00 (s, 1H), 5.17 (s, 2H), 4.30 (q, 4H), 3.64 (s, 2H), 2.05 (s, 1H), 1.30 (t, 6H).

2-Benzylxocarbonylamino-malonic Acid Monoethyl Ester:

2-Benzylxocarbonylamino-malonic acid diethyl ester (1.51 g, 4.85 mmol) was weighed out into a 500 mL RBF, 75 mL phosphate buffer was added, then 7.5 mL H$_3$CCN. PLE (0.118g) was added directly to the flask. Throughout the course of the reaction the pH was monitored and adjusted to 7.5 with a 5% solution of NaHCO$_3$. After 72 h, the reaction was acidified to a pH of about 4, filtered through a celite cake, extracted in EtOAc (3 x 100 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The title compound was isolated in an 84% yield without need for further purification. $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 11.83 (s, 1H), 7.35 (s, 5H), 6.01 (d, 1H), 5.19 (m, 1H), 4.93 (s, 1H), 4.29 (q, 2H), 1.32 (t, 3H).

5.4 References


APPENDIX A: LETTERS OF PERMISSION

To: Peter Strickland
From: J. Caleb Clark

Re: Permission Letter

I am a graduate student at Louisiana State University, and I have two publications in Acta Crystallographica Section E. I would like permission to use crystallographic data and figures found in the two articles noted below.


Thank You for your consideration on this request, and would appreciate it if you would e-mail your response to jclar21@lsu.edu.

J. Caleb Clark
P.O. Box 22575
Baton Rouge, LA 70894 USA
Phone: (225)281-4340
Fax: (225)578-3458
Dear Caleb

Thank you for your email.

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Best wishes

Peter Strickland
Managing Editor
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Yours sincerely
Helen Gainford
Rights Manager
APPENDIX B: SELECT CRYSTALLOGRAPHIC DATA

Carboranylpyrrole from Figure 2.10:

Experimental

Crystal data
C₁₃H₂₇B₁₆NO₂
Mᵣ = 337.46
Monoclinic
P2₃/c
a = 12.288 (3) Å
b = 7.449 (2) Å
c = 22.062 (7) Å
β = 104.011 (10)°
V = 1959.3 (9) Å³
Z = 4
Dᵣ = 1.144 Mg m⁻³
Dₘ not measured

Mo Kα radiation
λ = 0.71073 Å
Cell parameters from 3872 reflections
θ = 2.5–26.7°
μ = 0.065 mm⁻¹
T = 105 K
Needle
Colorless
0.40 × 0.12 × 0.10 mm
Crystal source: local laboratory

Data collection
KappaCCD (with Oxford Cryostream) diffractometer
ω scans with κ offsets
Absorption correction: none
16244 measured reflections
4155 independent reflections
2824 reflections with
I > 2σ(I)
R(int) = 0.043
θ(max) = 26.7°
h = −15→15
k = −9→9
l = −27→27
intensity decay: <2%

Refinement
Refinement on F²
R(F² > 2σ(F²)) = 0.0517
wR(F²) = 0.126
S = 1.030
4155 reflections
243 parameters
H atoms treated by a mixture of independent
and constrained refinement

w=1/[σ²(F²) + (0.0528P)² + 0.6488P]
where P = (F² + 2F₂)/3
(Δ/σ)max = 0.000
Δρ(max) = 0.26 e Å⁻³
Δρ(_min) = −0.21 e Å⁻³
Extinction correction: SHELXL
Extinction coefficient: 0.0034 (10)
Scattering factors from International Tables
for Crystallography (Vol. C)
Experimental

Crystal data
C\textsubscript{14}H\textsubscript{29}B\textsubscript{10}NO\textsubscript{2}·0.5(C\textsubscript{7}H\textsubscript{8})
\(M_r = 397.05\)
Monoclinic
\(P2_1/n\)
\(a = 8.1767 (10) \text{ Å}\)
\(b = 24.045 (3) \text{ Å}\)
\(c = 11.935 (2) \text{ Å}\)
\(\beta = 93.920 (5)°\)
\(V = 2341.0 (6) \text{ Å}^3\)
\(Z = 4\)
\(D_a = 1.127 \text{ Mg m}^{-3}\)
\(D_m\) not measured

Mo \(K\alpha\) radiation
\(\lambda = 0.71073 \text{ Å}\)
Cell parameters from 8245 reflections
\(\theta = 2.5-32.6°\)
\(\mu = 0.064 \text{ mm}^{-1}\)
Prism
Colorless
0.47 \times 0.40 \times 0.38 \text{ mm}
Crystal source: local laboratory

Data collection
KappaCCD (with Oxford Cryostream) diffractometer
\(\omega\) scans with \(\kappa\) offsets
Absorption correction: none
41340 measured reflections
8512 independent reflections
5665 reflections with
\(I > 2\sigma(I)\)
\(R_{int} = 0.035\)
\(\theta_{\text{max}} = 32.6°\)
\(h = -12 \rightarrow 12\)
\(k = -36 \rightarrow 36\)
\(l = -18 \rightarrow 18\)

intensity decay: <2%

Refinement
Refinement on \(F^2\)
\(R[F^2 > 2\sigma(F^2)] = 0.058\)
\(wR(F^2) = 0.170\)
\(S = 1.032\)
8512 reflections
302 parameters
H-atom parameters constrained

\(w=1/\left[\sigma^2(F_o^2) + (0.0884P)^2 + 0.3766P\right]\)
where \(P = (F_o^2 + 2F_c^2)/3\)
\((\Delta/\sigma)_{\text{max}} = 0.010\)
\(\Delta\rho_{\text{max}} = 0.45 \text{ e Å}^{-3}\)
\(\Delta\rho_{\text{min}} = -0.24 \text{ e Å}^{-3}\)
Extinction correction: none
Scattering factors from International Tables for Crystallography (Vol. C)
Dicarboranylpyrrole from Figure 2.21:

Experimental

Crystal data  
C_{10}H_{45}B_{20}NO_{2}.CH_{2}Cl_{2}  
M_r = 620.69  
Monoclinic  
P2_1/c  
\( a = 8.390 \) (3) Å  
\( b = 30.373 \) (13) Å  
\( c = 13.846 \) (6) Å  
\( \beta = 96.28 \) (2)°  
\( V = 3507 \) (2) Å³  
\( Z = 4 \)  
\( D_x = 1.176 \) Mg m⁻³  
\( D_m \) not measured

Mo Kα radiation  
\( \lambda = 0.71073 \) Å  
Cell parameters from 4220 reflections  
\( \theta = 2.5\text{–}23.0° \)  
\( \mu = 0.209 \text{ mm}^{-1} \)  
Needle  
Colorless  
0.45 × 0.05 × 0.03 mm  
Crystal source: local laboratory

Data collection  
KappaCCD (with Oxford Cryostream) diffractometer  
ω scans with κ offsets  
Absorption correction:  
multi-scan Denzo and Scalepack  
(OTWINOWSKI & MINOR, 1997)  
\( T_{\text{min}} = 0.912, T_{\text{max}} = 0.994 \)  
19525 measured reflections  
4745 independent reflections  
2177 reflections with  
\( I > 2\sigma(I) \)  
\( R_{\text{int}} = 0.114 \)  
\( \theta_{\text{max}} = 23.0° \)  
\( h = -9 \rightarrow 9 \)  
\( k = -33 \rightarrow 32 \)  
\( l = -15 \rightarrow 15 \)  
intensity decay: <2%

Refinement  
Refinement on \( F^2 \)  
\( R[F^2 > 2\sigma(F^2)] = 0.071 \) \( \)  
\( wR(F^2) = 0.152 \)  
\( S = 0.971 \)  
4745 reflections  
411 parameters  
H-atom parameters constrained

\[ w = 1/\sigma^2(F^2) + (0.0578P)^2 \]  
where \( P = (F^2 + 2F'^2)/3 \)  
\( \Delta_{\text{max}} = 0.002 \)  
\( \Delta_{\text{max}} = 0.49 \text{ e Å}^{-3} \)  
\( \Delta_{\text{min}} = -0.26 \text{ e Å}^{-3} \)  
Extinction correction: none  
Scattering factors from *International Tables for Crystallography* (Vol. C)
Experimental

Crystal data
C_{64}H_{88}B_{30}N_{5}Zn.5(C_{7}H_{8})
M_r = 1875.86
Triclinic
P\overline{1}
\alpha = 12.480 (3) Å
\beta = 12.710 (2) Å
\gamma = 16.746 (4) Å
\alpha = 81.854 (8)°
\beta = 82.884 (8)°
\gamma = 89.518 (9)°
V = 2609.1 (10) Å^3
Z = 1
D_x = 1.194 Mg m\(^{-3}\)
D_m not measured
Mo K\alpha radiation
\lambda = 0.71073 Å
\mu = 0.285 mm\(^{-1}\)
T = 105 K
Plate
Red
0.40 x 0.15 x 0.05 mm
Crystal source: local laboratory

Data collection
KappaCCD (with Oxford Cryostream) diffractometer
\omega scans with \kappa offsets
Absorption correction:
multi-scan HKL Scalepack (Otwinowski & Minor 1997)
\theta_{\text{min}} = 0.911, \theta_{\text{max}} = 0.986
51445 measured reflections
12856 independent reflections
8124 reflections with
I > 2\sigma(I)
R_{\text{int}} = 0.076
\theta_{\text{max}} = 28.3°
h = -16 → 16
k = -16 → 16
l = -22 → 22
intensity decay: <2%

Refinement
Refinement on F^2
R(F^2 > 2\sigma(F^2)) = 0.074
wR(F^2) = 0.168
S = 1.009
12856 reflections
630 parameters
H-atom parameters constrained
\omega = 1/\sigma^2(F_o^2) + (0.0578P)^2 + 3.4871P
where P = (F_o^2 + 2F_c^2)/3
(\Delta/\sigma)_{\text{max}} = 0.000
\Delta\rho_{\text{max}} = 1.03 e Å\(^{-3}\)
\Delta\rho_{\text{min}} = -0.42 e Å\(^{-3}\)
Extinction correction: none
Scattering factors from International Tables for Crystallography (Vol. C)

Carboranylporphyrin from Figure 3.2:
Experimental

Crystal data

$\text{C}_{34}\text{H}_{36}\text{N}_{3}\text{O}_{4}\text{Zn}$

$M_r = 630.04$

Triclinic

$P\overline{1}$

$a = 5.8154 (10)$ Å

$b = 11.450 (2)$ Å

$c = 21.928 (4)$ Å

$\alpha = 77.001 (8)^\circ$

$\beta = 88.645 (9)^\circ$

$\gamma = 87.879 (10)^\circ$

$V = 1421.5 (4)$ Å$^3$

$Z = 2$

$D_x = 1.472$ Mg m$^{-3}$

$D_m$ not measured

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 4993 reflections

$\theta = 2.5^\circ$–$26.0^\circ$

$\mu = 0.912$ mm$^{-1}$

Needle

$T = 110$ K

Red

0.27 × 0.03 × 0.01 mm

Crystal source: local laboratory

Data collection

KappaCCD (with Oxford Cryostream) diffractometer

$\omega$ scans with $\kappa$ offsets

Absorption correction:

multi-scan HKL Scalepack (Otwinowski & Minor 1997)

$T_{\text{min}} = 0.791$, $T_{\text{max}} = 0.991$

18950 measured reflections

5516 independent reflections

2906 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.097$

$\theta_{\text{max}} = 26.0^\circ$

$h = -7 \rightarrow 7$

$k = -14 \rightarrow 14$

$l = -26 \rightarrow 27$

18950 measured reflections

5516 independent reflections

Refinement

Refinement on $F^2$

$R[F^2 > 2\sigma(F^2)] = 0.059$

$wR(F^2) = 0.106$

$S = 0.981$

5516 reflections

396 parameters

H-atom parameters constrained

$w=1/[(\sigma^2(F_o^2) + (0.0260P)^2)]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} = 0.001$

$\Delta\rho_{\text{max}} = 0.448$ e Å$^{-3}$

$\Delta\rho_{\text{min}} = -0.35$ e Å$^{-3}$

Extinction correction: none

Scattering factors from International Tables for Crystallography (Vol. C)
VITA

Caleb Clark was born in Pascagoula, Mississippi, to Wiley and Cynthia Clark on August 28, 1977. He graduated from Moss Point High School on May 26, 1995, and the University of Mississippi on May 13, 2000, with a Bachelor of Science in chemistry. He joined the research group of M. Graça H. Vicente and Kevin Smith at Louisiana State University. He will receive his Doctor of Philosophy degree in chemistry on August 11, 2005. Caleb enjoys running, fishing, softball, photography, and lifting weights.