Diels-Alder reactions of [60]fullerene with 1,2,4,5-tetrazines and additions to [60]fullerene-tetrazine monoadducts

Mark Christopher Tetreau
University of New Hampshire, Durham

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Diels-Alder reactions of $[60]$ fullerene with 1,2,4,5-tetrazines and additions to $[60]$ fullerene-tetrazine monoadducts

Abstract
The Diels-Alder reaction between $[60]$ fullerene and 1,2,4,5-tetrazines was studied. Under conditions of total darkness, $[60]$ fullerene reacts with tetrazines to form bicyclic intermediates which immediately extrudes nitrogen to yield C2nu symmetric monoadducts. Thus, 3,6-diphenyl and 3,6-di-(2’-pyridyl)-1,2,4,5-tetrazines react with $[60]$ fullerene to form the corresponding C2nu symmetric monoadduct. To successfully synthesize these $[60]$ fullerene-tetrazine monoadducts, the Diels-Alder reactions must be run in total darkness. In the presence of light and acid catalyst, the monoadducts are susceptible to nucleophilic attack by water leading to novel hydration/rearrangement products that contain 4,5-dihydropyrazole groups nested atop the $[60]$ fullerene skeleton.

The $[60]$-fullerene-tetrazine monoadducts also react with primary amines in a similar fashion. The proposed mechanism for the reaction between $[60]$ fullerene-tetrazine monoadducts and primary amines is similar to that proposed for the hydration/rearrangement reaction.

The $[60]$ fullerene-tetrazine monoadducts also react with monoprotic nucleophiles such as thiols, alcohols, and secondary amines to yield racemic tetrahydropyridazine products. Nucleophilic attacks by nonanethiol, thiophenol, methanol and dimethylamine have all been studied and are all are proposed to proceed along a similar pathway.

Keywords
Chemistry, Organic
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DIELS-ALDER REACTIONS OF [60]FULLERENE WITH 1,2,4,5-TETRAZINES
AND ADDITIONS TO [60]FULLERENE-TETRAZINE MONOADDUCTS

BY

Mark Christopher Tetreau

B.S. Principia College, 1995

DISSERTATION
Submitted to the University of New Hampshire
in Partial Fulfillment of
the Requirements for the Degree of

Doctor of Philosophy
in
Chemistry
May, 2002
This dissertation has been examined and approved.

Glen P. Miller
Dissertation Director, Glen P. Miller, Associate Professor of Chemistry

Richard P. Johnson, Professor of Chemistry

Roy P. Planalp, Associate Professor of Chemistry

Charles K. Zercher, Associate Professor of Chemistry

Robert Jerald, Professor of Mechanical Engineering

May 3, 2002

Date
DEDICATION

This work is dedicated to my wife, Gillian, who is a constant reminder that "Love never faileth." Without her love, support, and inspiration this work would not have come to fruition.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Dr. Glen Miller. His input and direction kept me on the road to success. I would also like to thank the rest of the faculty on my thesis committee, Dr. Zercher, Dr. Johnson, Dr. Planalp, and Dr. Jerard, for their comments, questions, corrections and suggestions during my stay at the University of New Hampshire. In addition, I would like to thank Dr. Weisman and Dr. Wong, two gentlemen who, while not on my committee, provided valuable suggestions and instruction. Thanks goes out to the rest of the faculty and staff of the UNH chemistry department for their contributions, however small, to this work.

I would like to gratefully acknowledge Dr. Vern Reinhold for providing the mass spectrometry data, and Dr. Alan Balch for providing crystallographic data. I must also thank Kathy Gallagher of the UNH Instrumentation Center for her technical expertise in obtaining NMR spectra.

I would be remiss if I didn't thank the members of the Miller Research Group with whom I had the pleasure of working over the years. James Mack's invaluable advice got me started in the early days, and Steve Mathieu kept it interesting. I want to thank Jon, Julie, and Ingyu for adding to the good working atmosphere in the Miller Group.

Most importantly, I want to thank my family—the Lincolns, Holcombs, Moores, and Tetreaus— for their unceasing support of this endeavour.
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ABSTRACT

DIELS-ALDER REACTIONS OF [60]FULLERENE WITH 1,2,4,5-TETRAZINES
AND ADDITIONS TO [60]FULLERENE-TETRAZINE MONOADDUCTS

By

Mark C. Tetreau

University of New Hampshire, May, 2002

The Diels-Alder reaction between [60]fullerene and 1,2,4,5-tetrazines was studied. Under conditions of total darkness, [60]fullerene reacts with tetrazines to form bicyclic intermediates which immediately extrudes nitrogen to yield C_{2v} symmetric monoadducts. Thus, 3,6-diphenyl and 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazines react with [60]fullerene to form the corresponding C_{2v} symmetric monoadduct. To successfully synthesize these [60]fullerene-tetrazine monoadducts, the Diels-Alder reactions must be run in total darkness. In the presence of light and acid catalyst, the monoadducts are susceptible to nucleophilic attack by water leading to novel hydration/rearrangement products that contain 4,5-dihydropyrazole groups nested atop the [60]fullerene skeleton.

The [60]-fullerene-tetrazine monoadducts also react with primary amines in a similar fashion. The proposed mechanism for the reaction between [60]fullerene-tetrazine monoadducts and primary amines is similar to that proposed for the hydration/rearrangement reaction.
The [60]fullerene-tetrazine monoadducts also react with monoprotic nucleophiles such as thiols, alcohols, and secondary amines to yield racemic tetrahydropyridazine products. Nucleophilic attacks by nonanethiol, thiophenol, methanol and dimethylamine have all been studied and are all proposed to proceed along a similar pathway.
1. INTRODUCTION

1.1 [60] Fullerene

1.1.1 History and Physical Properties of [60] Fullerene. In 1984 three Exxon researchers, Rohlfing, Cox, and Kaldor, reported the results of their experiments with carbon clusters formed using a laser ablation technique. They noticed that in the mass spectra of the clusters they generated, there were both odd-numbered and even-numbered clusters of carbon atoms below a size of twenty carbon atoms. However, when looking at the region of clusters greater than forty atoms, the Exxon group noticed that the clusters were of only even-numbered sizes. The investigators were at a loss to explain this phenomenon.

Harold Kroto, a researcher at Sussex University in Great Britain, was interested in the study of carbon clusters of interstellar origin. Years earlier astrophysicists noted the presence of large carbon clusters that were streaming out of a red giant star. These clusters showed some unusual infrared (IR) emissions that investigators were eager to reproduce in a laboratory setting. In order to generate and study carbon clusters, Kroto began a collaboration with Curl and Smalley at Rice University in Texas.

Smalley and co-workers at Rice University had previously developed a laser vaporization technique based upon the one used at Exxon in order to synthesize and study metallic clusters. Together with Kroto, Curl and coworkers, Smalley modified the apparatus so that carbon clusters could be studied. In the laser ablation technique, a high-
power Nd:YAG laser vaporizes the surface of a rotating graphite disk. The hot carbon plasma is suspended in a high-pressure He atmosphere where the carbon atoms are allowed to cluster. After the clustering time has elapsed (~30-200 µs), the helium gas containing the carbon clusters and unclustered plasma are released into a vacuum. This release into a vacuum results in supersonic cooling and expansion of the He gas which serves to terminate the clustering process. The carbon clusters are then analyzed by mass spectrometry.

In their studies of carbon clusters, Kroto, Curl, Smalley and coworkers noticed the same cluster distribution that the Exxon group had, but they also noticed an unusually large peak for a 60-carbon cluster in their mass spectrum.\textsuperscript{4} By allowing for longer clustering times in their laser ablation procedure, they found that the peak for the 60-carbon cluster could be enhanced relative to the rest of the cluster peaks.

Previous work, both experimental and theoretical, had shown that carbon clusters up to about 10 carbon atoms in size are most stable when in linear chains,\textsuperscript{1} and clusters in the area of 10-30 carbon atoms prefer to be in rings.\textsuperscript{5} Kroto, Curl and Smalley took this work one step further by postulating that the clusters above 40 atoms in size would exist in some sort of cage structure. This follows the procession from 1-dimensional clusters (linear chains) to 2-dimensional clusters (ring systems) to 3-dimensional clusters (the cages proposed by Kroto and Smalley).

Kroto, Smalley and Curl\textsuperscript{4} then correctly inferred that the structure of the C\textsubscript{60} cluster was that of a truncated icosahedron formed by fusing pentagons and hexagons. In the truncated icosahedral structure, there are no dangling bonds and the pentagons are all isolated from each other in order to provide maximum stability (the so-called "isolated
pentagon rule"). Nuclear Magnetic Resonance Spectroscopy (NMR) later confirmed the icosahedral structure of the C\textsubscript{60} molecule. Carbon-13 NMR spectra of the C\textsubscript{60} molecule indicate only one signal at about 143 ppm, confirming the molecule's icosahedral symmetry.

Noting the uncanny resemblance of the C\textsubscript{60} molecule to the geodesic domes designed by the famed architect R. Buckminster Fuller, Kroto, Smalley and coworkers gave the C\textsubscript{60} molecule the name "buckminsterfullerene" and labeled it as such in their paper. Eventually "fullerenes" came to be the name for the entire class of closed cage molecules.

Figure 1. Structure of the C\textsubscript{60} molecule as determined by Kroto, Smalley, and Curl. The molecule was christened "buckminsterfullerene," with the name "fullerene" used to describe any all-carbon cage molecule.
Although Kroto, Smalley and coworkers published the first definitive proof for the existence of C_{60},
theoretical considerations of icosahedral structures are many years older. Renaissance thinkers,
including Leonardo Da Vinci, developed and worked with models of the truncated icosahedron. In the early 20th century, there were a number of theoretical suggestions for icosahedral molecules that predated the work of Kroto, Smalley and Curl by several decades. Osawa theorized in 1970 that an icosahedral C_{60} molecule might be chemically stable. A group of Russian researchers utilized Hückel calculations to determine that C_{60} should have a large HOMO-LUMO gap. It was only after the Kroto-Smalley-Curl contribution that these early works on C_{60} became appreciated.

Although C_{60}, buckminsterfullerene, is the best known of the fullerenes, there are many other fullerenes molecules that can be isolated. The best known examples are those fullerenes with more than 60 carbons. These include C_{70}, C_{76}, C_{78}, C_{84} and higher fullerenes. In principle there is no end to the number of fullerene compounds that can be formed. Those with C_{2n} atoms and all isolated pentagons are expected to be stable.

The major drawback to early fullerene work was that the laser ablation technique used at Rice and in other places could only produce microscopic quantities of fullerene material with which to work and study. This meant only a limited number of researchers could get their hands on a useable quantity of C_{60} and the cost to produce C_{60} and other fullerenes was much too high for most research groups. In 1990 Krätschmer and Huffman broke the field of fullerene research wide open with the publication of a method for the production of fullerenes in much larger quantities.
In the Kratschmer-Huffman method, a 100A current is arced across two carbon rods placed in a low-pressure He atmosphere (~100 torr). The rods are spring-loaded such that there is a constant vaporization of the carbon rods to produce a carbon soot. The current is supplied by a standard arc-welding apparatus. The carbon soot typically contains 7-10% fullerene material.\textsuperscript{13} Kratschmer and Huffman's arc discharge method can produce gram quantities of carbon soot from which fullerenes can be extracted,\textsuperscript{14} enabling even those with a modest research budget to obtain samples of C\textsubscript{60} and higher fullerenes for their own investigations.

In addition to providing large quantities of fullerene material for study and development, Kratschmer and Huffman's method also led to the isolation of carbon nanotubes by Iijima in 1991.\textsuperscript{15} A nanotube, or "buckytube", consists of a sheet of graphene (see Figure 2) rolled into a tube. The tube can be open on both ends or the tube can be capped at one or both ends with what amounts to half of a fullerene.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{The building blocks for carbon nanotubes: (a) a sheet of graphene and (b) a fullerene for the tube cap.}
\end{figure}
Several different types of nanotubes exist including single-walled nanotubes (SWNT) that consist of a monolayer of carbon atoms. Nanotubes with multiple wall layers are known as multi-walled nanotubes (MWNT). The MWNT's consist of several sizes of SWNT's nested inside of each other. SWNT's come in different varieties depending upon the size and symmetry of the fullerene piece that is used to cap the SWNT. If $C_{60}$
is bisected in such a way that the resulting SWNT cap retains a five-fold axis of symmetry, the resulting nanotube is termed an "armchair" SWNT. If, on the other hand, C₆₀ is bisected such that the resulting caps contain a three-fold axis of symmetry, then the nanotube is referred to as a "zigzag" nanotube. A third type of SWNT can be fashioned from a fullerene that has been cut in half in such a way that the resulting pieces have no symmetry. The resulting nanotube is chiral and looks as if the hexagons are spiraling up the sides of the tube. Once considered part of the greater scope of fullerene work, the study of SWNT's and MWNT's has evolved and expanded to such an extent that nanotube science is now considered a unique discipline, separate from fullerenes.

The development of methodologies to separate fullerenes from carbon soot in a straightforward manner increased the utility of Krätschmer and Huffman's method for fullerene generation. A typical separation scheme (Figure 4) first involves a toluene extraction of the carbon soot using a soxhlet extractor. The toluene extracts contain fullerenes from C₆₀ to around C₁₀₀. The residual soot is then subjected to a second soxhlet extraction wherein the soot is extracted with 1,2,4-trichlorobenzene to remove higher fullerenes up to C₂₅₀. Fullerenes larger than C₂₅₀ are for the most part insoluble in organic solvents. Only small amounts of fullerenes between C₁₀₀ and C₂₅₀ are recovered and they cannot be isolated easily.

Smaller fullerenes (e.g. C₆₀ to ~C₁₀₀) can be isolated as shown in Figure 4. Toluene-extracted fullerene material can be separated by column chromatography using a 95:5 solution of hexane:toluene as the eluent with neutral alumina as the stationary phase. The first fullerene to be removed from the column is C₆₀ which makes up the majority of.

7
the fullerene material that is generated in the Krätschmer-Huffman synthesis. The next fullerene isolated from the alumina column is C\textsubscript{70} which is produced in second highest yield behind C\textsubscript{60}. Once the C\textsubscript{70} is isolated, the remaining fullerenes can be separated by HPLC using a C\textsubscript{18} reverse-phase column. HPLC can separate fullerenes such as C\textsubscript{76}, C\textsubscript{78}, and C\textsubscript{84}.

**Figure 4. Chart for fullerene separation and isolation (adapted from ref. 7)**
Since the overwhelming majority of fullerene material produced in the Krätschmer-Huffman method is $C_{60}$, the majority of physical and chemical data for fullerenes comes from studies of $C_{60}$.

Upon looking at a model of $C_{60}$ molecule, it could be reasoned that the molecule is fully aromatic with all $sp^2$-hybridized carbon atoms. In reality, this is not the case. Haddon calculated$^{16}$ the hybridization to be on the order of $sp^{2.278}$. This slight shift towards tetrahedral results from the necessarily curved surface of the fullerene. Another consequence of the slight rehybridization of the carbons atoms is that the $\pi$-orbitals radiate exohedrally further than they extend into the center of the fullerene. This raises the electronegativity of the fullerene.$^{17}$

$C_{60}$ has two distinct types of bonds. There is a shorter double bond, and a longer single bond. All of the double bonds in the molecule are exocyclic to the five-membered rings and the double bonds are endocyclic to the six-membered rings. Placing an endocyclic double bond in a 5-ring would force the 5-ring towards planarity which would induce considerable strain into the fullerene system.$^{18}$ Measurements of the bond-lengths in $C_{60}$ bear this out. The bonds which make up the junction of two 6-membered rings (a 6,6-junction) are exocyclic to the five-membered rings and have more double-bond character. Accordingly the 6,6-bond length is 1.40Å, while the 6,5 bond length is 1.46Å.$^{19}$

$C_{60}$ exhibits solubility in most organic solvents,$^{20}$ with the best solubility seen with aromatic solvents (e.g. benzene, toluene, naphthalene) and sulfur-containing solvents (e.g. carbon disulfide and 2-methylthiophene). In contrast to the black color of solid fullerenes, $C_{60}$ in solution ranges in color from magenta to purple.
1.1.2. Chemistry of C60

1.1.2.1. Endohedral Fullerenes. The first endohedral fullerene compound was synthesized when Kroto, Smalley, Curl and coworkers soaked a graphite disk in LaCl3 before subjecting it to their laser ablation technique. This produced a molecule of C60 with an atom of lanthanum trapped inside the cage. To distinguish an endohedral fullerene compound from an exohedral compound, the symbol "@" was adopted to symbolize an atom or molecule inside a fullerene. Therefore, the metallofullerene with La trapped inside is designated as La@C60. Since Kroto, Smalley, Curl and coworkers first reported La@C60, many endohedral fullerene compounds have been made. One particular endohedral metallofullerene, Sc3N@C80, is reported to be prepared in such high quantities that it is the third most abundant fullerene produced, behind only C60 and C70.

Endohedral fullerene compounds have been prepared with nonmetals inside the fullerene cage. He@C60 and Ne@C60 were detected as by-products of fullerene synthesis in atmospheres of He and Ne, respectively. He@C60 has proven to be a useful substrate for studying exohedral functionalization of C60 by 3He NMR. Another very interesting endohedral compound that has been made is N@C60. Here normally reactive atomic nitrogen sits idyllically inside the C60 cage and does not even interact with the endohedral surface of the fullerene. Functionalization of the exohedral surface has no effect on the trapped N atom.

Most endohedral fullerenes are synthesized by the encapsulation of an atom or molecule during the formation of the carbon cage. Recently, Rubin and coworkers at
UCLA reported the synthesis of a C\textsubscript{60} derivative in which a hole had been opened up on the surface of the fullerene\textsuperscript{27}. The hole was large enough to allow the trapping of He and H\textsubscript{2} inside the fullerene. Although their method required heat and pressure to facilitate the insertion of He and H\textsubscript{2}, the energy requirement was significantly smaller than any previously reported methods. The next step—closing up the fullerene to permanently trap an atom or molecule within—has not yet been reported in the literature.

1.1.2.2. Chemistry On the Exterior Surface of C\textsubscript{60}. The vast majority of chemistry performed on C\textsubscript{60} occurs on the *exohedral* surface of the molecule. Unlike diamond or graphite, the exterior (exohedral) surface of C\textsubscript{60} is quite reactive. Since the \( \pi \)-bonds in C\textsubscript{60} are somewhat distorted from planarity, they possess some strain energy\textsuperscript{28} and they tend to be more reactive than the \( \pi \)-bonds of normal alkenes. Likewise, the majority of the chemistry on the surface of C\textsubscript{60} occurs at the \( \pi \)-bonds of 6,6-junctions.

The reactivity of the 6,6-bonds in conjuction with C\textsubscript{60}’s electronegativity leads to the accurate description of C\textsubscript{60} as a three-dimensional, electron-deficient polyalkene. C\textsubscript{60} then, can undergo the full spectrum of reactions that are typical of electron-deficient alkenes. These reactions include, but are not limited to, hydrogenation, nucleophilic reactions, halogenations, electron-transfer reactions, and cycloadditions such as the Diels-Alder reaction\textsuperscript{29}.

1.1.2.2.1. Hydrogenation. The first successful hydrogenation of C\textsubscript{60} was reported in 1990\textsuperscript{30}. The hydrogenation of C\textsubscript{60} was carried out using a Birch reduction and two products were indentified by electron-impact mass spectrometry: C\textsubscript{60}H\textsubscript{36} and C\textsubscript{60}H\textsubscript{18}. The
structures of these two polyhydrofullerenes have not yet been unambiguously assigned. Further investigations of the Birch reduction products using "softer" MS methods showed that the reaction actually produces a mixture of polyhydrofullerenes from \( \text{C}_{60}\text{H}_{18} \) to \( \text{C}_{60}\text{H}_{36} \) with the major product being \( \text{C}_{60}\text{H}_{32} \).

\( \text{C}_{60}\text{H}_{36} \) is the most highly hydrogenated fullerene that can be isolated. Beyond 36 hydrogens, there arises unfavorable eclipsing interactions on the fullerene surface. The most stable isomer of \( \text{C}_{60}\text{H}_{60} \) ("fullerane") is calculated to be one in which ten of the hydrogen atoms are endohedral.\(^{32}\) Given the high barrier for the insertion of hydrogen into a fullerene, about 2.7 eV/atom,\(^{29}\) \( \text{C}_{60}\text{H}_{60} \) can not be made using current hydrogenation methodology.

Treatment of a mixture of polyhydrofullerenes with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing toluene leads to the recovery of starting \( \text{C}_{60} \). This means that the reduction/oxidation of \( \text{C}_{60} \) is fully reversible with no breakdown of the fullerene cage.\(^{30}\) This discovery has created interest in using fullerenes and carbon nanotubes as hydrogen storage devices for fuel cells.

The first synthesis of the simplest of the hydrofullerenes, \( \text{C}_{60}\text{H}_{2} \), was accomplished by Cahill and Henderson\(^{33}\) using a borane-tetrahydrofuran complex (BH\(_3\)-THF) followed by acidic work-up to achieve the generation of 1,2-dihydro-\( \text{C}_{60} \) (Scheme 1). The 1,2-isomer of \( \text{C}_{60} \) is the lowest in energy of the 23 possible \( \text{C}_{60}\text{H}_{2} \) isomers. All others isomers give rise to at least one unfavorable 6,5-\( \pi \)-bond. Reaction of \( \text{C}_{60}\text{H}_{2} \) with another equivalent of BH\(_3\)-THF leads to the formation of several \( \text{C}_{60}\text{H}_{4} \) isomers of which the 1,2,3,4-tetrahydro isomer dominates.\(^{34}\) \( \text{C}_{60}\text{H}_{6} \) and higher polyhydrofullerenes can also be prepared in this way. Along with hydroboration, the
hydrogenation of C$_{60}$ has been accomplished using hydrozirconation, hydrogen in the presence of Pd/C catalyst, Cr(II) acetate, diimide, transfer hydrogenation, hydrazine, Zn with acid and others methodologies.

Scheme 1. Hydroboration of C$_{60}$ to produce 1,2-dihydro-C$_{60}$.

1.1.2.2. Nucleophilic Reactions. In general, the addition of a nucleophile to C$_{60}$ follows the formula shown in Scheme 2. An equivalent of nucleophile adds to a 6,6-junction and yields a fullerene anion. The reaction is next quenched with an equivalent of electrophile to bring the fullerene back to neutral. Some good examples of nucleophilic addition to C$_{60}$ can be found in the work of Wudl and co-workers. They showed that organometallic reagents such as alkyllithiums and Grignard reagents add into C$_{60}$ and can be quenched with a suitable electrophile like methyl iodide (MeI).
Scheme 2. General formula for nucleophilic addition to $C_{60}$.

Use of a large (60-fold) excess of organometallic leads to the addition of 10 equivalents of nucleophile. By using equimolar amounts of $C_{60}$ and organometallic, a 1:1 adduct can be obtained (Scheme 3).

$$C_{60} + 60 \text{ eq. PhMgBr} \xrightarrow{1) \text{THF, RT}} \xrightarrow{2) \text{60 eq. Mel}} C_{60}\text{Ph}_{10}\text{Me}_{10}$$

$$C_{60} + 60 \text{ eq. } t\text{-BuLi} \xrightarrow{1) \text{THF, RT}} \xrightarrow{2) \text{60 eq. Mel}} C_{60}t\text{-Bu}_{10}\text{Me}_{10}$$

$$C_{60} + 1 \text{ eq. } t\text{-BuLi} \xrightarrow{1) \text{THF, RT}} \xrightarrow{2) \text{1 eq. Mel}} C_{60}t\text{-BuMe}$$

Scheme 3. Additions of organometallic nucleophiles to $C_{60}$. 

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1.1.2.2.3 Halogenation Reactions. The first successful halogenation of C$_{60}$ was fluorination by Smith et al.$^{43}$ By exposing C$_{60}$ to fluorine gas, they obtained a mixture of polyfluorinated fullerenes. The major component of the mixture was C$_{60}$F$_{36}$, which is analogous to the Birch reduction product, C$_{60}$H$_{36}$. Another group of investigators$^{44}$ claimed to have formed C$_{60}$F$_{60}$ by subjecting C$_{60}$ to F$_2$ gas over a period of 12 days. A single peak was seen in the $^{19}$F-NMR spectrum. However, further study showed that the cage structure was most likely lost in the fluorination reaction.$^{45}$

Chlorination of C$_{60}$ with chlorine gas$^{46}$ was accomplished at 250°C in about 5 hours. The polychlorinated product mix had an average formula of C$_{60}$Cl$_{24}$. Increasing the temperature in this reaction led to a decrease in the average amount of chlorine added. Tebbe and co-workers$^{47}$ polychlorinated C$_{60}$ under less forceful conditions. Their method involved the reaction of liquid Cl$_2$ with C$_{60}$ in the absence of light at temperatures around -35°C. Interestingly, Tebbe and coworkers found that in the presence of PPh$_3$, the starting C$_{60}$ could be regenerated in 54-88% yield.

Bromination of C$_{60}$ has afforded researchers products which can be extensively characterized and even studied by x-ray crystallography. Reaction of C$_{60}$ with neat Br$_2$ gave rise to a mixture of C$_{60}$Br$_2$ and C$_{60}$Br$_4$.$^{48}$ With longer reaction times, higher bromination of C$_{60}$ can be achieved.$^{49}$ Birkett, Kroto, et al.$^{50}$ managed to grow crystals of C$_{60}$Br$_6$ and C$_{60}$Br$_8$. Tebbe's group$^{51}$ even obtained a crystal structure for C$_{60}$Br$_{24}$. 

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1.1.2.2.4 Electron-Transfer Reactions. Taking advantage of C_{60}’s ability to be electrochemically reduced up to six times with complete reversibility, reactions involving electron-transfer are quite facile. In the addition of an amine to C_{60},^{52} the first step of the reaction has been shown by electron spin resonance (ESR) spectroscopy^{53} to involve a single-electron transfer from the amine to C_{60} (Scheme 4). The rest of the mechanistic pathway is unclear. Addition of a primary amine yields a molecule where there have been multiple additions to the fullerene surface. Reaction of a secondary amine with C_{60} affords an adduct where the amine group and a proton are arranged in either a 1,2- or a 1,4-fashion.

\[ \text{Scheme 4. Amination of } C_{60} \text{ by a primary or secondary amine.} \]
1.1.2.2.5. Cycloaddition Reactions. $C_{60}$ can undergo most cycloaddition reactions available to an electron-deficient polyalkene. One of the first cycloadditions involving $C_{60}$ is the reaction of $C_{60}$ with osmium tetroxide (OsO$_4$).$^{54}$ Run in the presence of pyridine, the osmylation reaction forms a five-membered osmate ester ring attached to the fullerene (Figure 5), with two pyridine molecules complexing the osmium giving the metal a coordination number of 6. Heating of the osmium complex in a vacuum leads to regeneration of starting fullerene.

![Figure 5. Osmium complex incorporating $C_{60}$](image)

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Like most alkenes, C₆₀ can undergo expoxidation. Methods of epoxidizing C₆₀ include ozonolysis and dimethyl dioxirane (Scheme 5). In the epoxidation of C₆₀, the oxygen can either add across a 6,6- or a 6,5-bond junction. When oxygen adds across the 6,5-junction, the resulting structure contains two destabilizing 6,5-double bonds. The strain is relieved by a bond rearrangement to form a "fulleroid" structure in which a full set of π-bonds (30 for C₆₀) is restored.

Scheme 5. Expoxidation of C₆₀ with dimethyl dioxirane can lead to either a 6,6-fullerene epoxide or a 5,6-oxygen-bridged fulleroid.

Epoxidation across a 6,6-junction is favored for C₆₀. When C₇₀ is epoxidized, addition across a 6,5-junction is preferable. Fullerenes epoxidation is reported to give low yields, due in part to the facile degradation of the epoxide product. One report indicates that upon chromatographic separation of the C₆₀O from unreacted C₆₀, 91% of the C₆₀O reverts to C₆₀.
Scheme 6. The Bingel reaction. Diethylbromomalonate and C\textsubscript{60} in the presence of NaH react to give a dicarboxycyclopropanated fullerene.

Cyclopropanation of C\textsubscript{60} can be accomplished using the Bingel reaction\textsuperscript{58} (Scheme 6). In the Bingel reaction, diethylbromomalonate is deprotonated with sodium hydride (NaH) to give the malonate anion. The anion attacks a \(\pi\)-bond resulting in a fullerene anion which in turn displaces bromide, and forms a three-membered ring. The cyclopropyl ring formed in the Bingel reaction always forms at a 6,6-junction. Hirsch and others\textsuperscript{29} have made extensive use of the Bingel reaction in studies of C\textsubscript{60} functionalization.
Four-membered rings attached to C$_{60}$ can be prepared by [2+2] cycloaddition.

Scheme 7 illustrates the reaction of benzyne with C$_{60}$. Although often used as a dienophile in Diels-Alder reactions, benzyne reacts with C$_{60}$ in a [2+2] fashion. Another [2+2] reaction is the photoinitiated dimerization of C$_{60}$. This reaction gives rise to the "dumbbell" shaped molecule seen in Figure 6.

Scheme 7. Benzyne (formed in situ from anthrinilic acid and isoamyl nitrite) reacts with C$_{60}$ in a thermal [2+2] process.

Figure 6. C$_{120}$ fullerene formed by the [2+2] cycloaddition of two C$_{60}$ molecules.
Formation of five-rings on fullerenes typically involves 1,3-dipolar cycloaddition. Like the Diels-Alder reaction, a 1,3-dipolar addition is a \([4\pi+2\pi]\) cycloaddition.\(^{61}\)

![Generic 1,3-dipolar addition](image)

**Figure 7.** Generic 1,3-dipolar addition to C\(_{60}\).

One example of a 1,3-dipolar addition is the reaction of diphenyldiazomethane with C\(_{60}\).\(^{62}\) As illustrated in Scheme 8, diphenyldiazomethane undergoes a 1,3-dipolar cycloaddition across C\(_{60}\) to yield a pyrazoline unit. The pyrazoline extrudes a molecule of nitrogen leaving behind a fullerene radical and a diphenylmethyl radical which then couple to form either a methanofullerene or a fulleroid structure (Scheme 8). The mixture of methanofullerene and fulleroid is converted to methanofullerene upon heating,\(^{62}\) which suggests that the methanofullerene is thermodynamically preferred over the fulleroid. The methanofullerene/fulleroid relationship and pertinent structural properties have been extensively reviewed.\(^{63}\)

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Scheme 8. 1,3-Dipolar addition of diphenyldiazomethane to $C_{60}$

Similar to the reaction with diazo compounds, azides also undergo a 1,3-dipolar cycloaddition (Scheme 9) to $C_{60}$. Unlike diazo addition, however, the dominant product in this case is the azafulleroid.
A third type of 1,3-dipolar cycloaddition was introduced by Prato and coworkers. They performed a 1,3-dipolar cycloaddition across \( C_{60} \) using an azomethine ylide generated by reacting n-methylglycine with formaldehyde in refluxing toluene (Scheme 10). Addition of amine into formaldehyde and subsequent loss of hydroxide results in an imino acid. Decarboxylation of the imino acid leaves an azomethine ylide for reaction with \( C_{60} \). The N-methylfullerenopyrrolidine was reported in 41% yield.

Prato noted that the imino acid could be isolated as an oxazolidinone and reacted with \( C_{60} \). Reaction of N-triphenylmethyl-5-oxazolidinone (Scheme 11) with \( C_{60} \) led to an N-trityl pyrrolidine adduct. Removal of the trityl group with acid gives rise to the bare...
pyrrolidine which can then be used for further chemistry. This makes for a powerful tool in the synthesis of complex fullerene-containing molecules.

Scheme 10. The Prato Reaction. A 1,3-dipolar cycloaddition of N-methylazomethine ylide.

Scheme 11. A modified Prato Reaction. Reaction of an oxazolidinone with $\text{C}_6\text{O}_6$ and subsequent removal of triphenylmethyl group to afford a reactive pyrrolidine system.
For the formation of six-membered rings on the surface of C\textsubscript{60}, a widespread and versatile reaction is the \([4\pi+2\pi]\) Diels-Alder cycloaddition. The reactive, electron-deficient double-bonds on the surface of the fullerene makes C\textsubscript{60} an ideal choice as a "dienophile" for Diels-Alder reactions. C\textsubscript{60} has been shown to react with a wide variety of dienes and diene-equivalents. These dienes include traditional types of 1,3-dienes, dienes prepared \textit{in situ}, linear acenes, and heterodienes.

A very good example of a "traditional" 1,3-diene for Diels-Alder reactions is cyclopentadiene. Rotello \textit{et al.} reported a Diels-Alder reaction between cyclopentadiene and C\textsubscript{60}.\textsuperscript{66} The cycloaddition reaction, shown in Scheme 12, was run at room temperature in benzene solvent and yielded 74\% of the corresponding Diels-Alder adduct. The cyclopentadiene, as with all Diels-Alder dienes, adds selectively across a 6,6-junction on C\textsubscript{60} with no reported rearrangement to the 6,5-fulleroid. Many Diels-Alder adducts of C\textsubscript{60} are formed reversibly, occasionally limiting the utility of the reaction.

\begin{center}
\textbf{Scheme 12.} Diels-Alder reaction between C\textsubscript{60} and cyclopentadiene.
\end{center}
One way to counteract the reversibility inherent to the Diels-Alder reaction is to generate a very reactive diene that affords a Diels-Alder adduct with a high activation barrier for the "retro" Diels Alder reaction. The reaction between o-quinodimethane with C\textsubscript{60}\textsuperscript{67} illustrates the concept (Scheme 13). o-Quinodimethane is prepared and reacted \textit{in situ} from \(\alpha, \alpha'\)-dibromo-o-xylene. In order for the reaction to reverse, o-quinodimethane would need to be produced again from the aromatic Diels-Alder adduct, an energetically unfavorable prospect.

\begin{center}
\textbf{Scheme 13.} The irreversible Diels-Alder reaction between o-quinodimethane and C\textsubscript{60}.
\end{center}

The reaction between anthracene and C\textsubscript{60}, leads to an interesting structure (Scheme 14) but is readily reversible\textsuperscript{68}. The forward reaction requires slightly elevated temperatures but becomes readily reversible at approximately \(60^\circ\text{C}\).\textsuperscript{68a} The facile reversibility leads leads to a temperature dependent yield. At a temperature of \(50^\circ\text{C}\), the
yield of anthracene-$C_{60}$ adduct is 24%. At 80°C the yield falls to 17%. In boiling toluene (110°C), the yield dips to 8.5%.

Larger linear acenes are also known to react with $C_{60}$, and they are less prone to retro-Diels-Alder reactions. Miller and Mack\textsuperscript{69} reported the reaction between equimolar amounts of pentacene and $C_{60}$ to proceed in a 54% yield (Scheme 15). Komatsu\textsuperscript{70} reported the addition of two $C_{60}$ molecules across a single pentacene using a solid-state vibrational milling technique. He assigned a trans-stereochemistry to the bisadduct formed in 11% yield. Using a diphenyl substituted pentacene, Miller and coworkers\textsuperscript{71} increased the yield to 85% and demonstrated unequivocally that the fullerenes add in a syn fashion to produce cis-bisfullerene adducts of pentacene.

\begin{center}
\textbf{Scheme 14.} Reaction of anthracene with $C_{60}$, a highly reversible process.
\end{center}
Scheme 15. Reaction of pentacene with C\textsubscript{60}. The solution phase cycloaddition occurs exclusively across the central ring of the pentacene.

Heteroatom-containing dienes also react with C\textsubscript{60} in a Diels-Alder fashion.

Eguchi\textsuperscript{72} used a thioacrylamide as a heterodiene in a cycloaddition with C\textsubscript{60} (Scheme 16). The resulting sulfur-containing heterocycle was isolated in 57% yield. The ability to use a heteroatom-containing addent may allow for the fullerene to be attached to natural and biomimetic molecules.

Scheme 16. Addition of a heteroatom-containing diene to C\textsubscript{60}.
1.2. 1,2,4,5-Tetrazines

1.2.1. History and Physical Properties of 1,2,4,5-Tetrazines – 1,2,4,5-Tetrazines are the best known and most studied of the three isomeric tetrazines that are possible. The other tetrazine structures are 1,2,3,4-tetrazine and 1,2,3,5-tetrazine.

![Diagram of tetrazines](image)

Figure 8. The three types of tetrazines.

1,2,3,5-Tetrazine (as-tetrazine), and its 4,6-disubstituted derivatives are not known. However, the 1,2,3,5-tetrazine backbone has been incorporated into polycyclic systems (Figure 9).^3

![Example of a known polycyclic](image)

Figure 9. Example of a known polycyclic incorporating a 1,2,3,5-tetrazine backbone.
Early literature reports of 1,2,3,5-tetrazine structures are in error. These compounds have since been found to be triazole derivatives. In the late 1960's and early 1970's, there were several publications detailing theoretical calculations on the 1,2,3,5-tetrazine system. These publications contain varying conclusions on the potential existence of 1,2,3,5-tetrazines. Some publications suggest that there should be considerable aromatic character in the 1,2,3,5-tetrazines. Other reports suggest that 1,2,3,5-tetrazines could not exist. More recently, ab initio calculations published by Schaefer and coworkers in 1991 predict 1,2,3,5-tetrazine to lie 8 kcal/mol lower in energy than 1,2,4,5-tetrazine.

The isomeric 1,2,3,4-tetrazine (r-tetrazine) has also eluded synthesis, but similar to the case with 1,2,3,5-tetrazine, the 1,2,3,4-tetrazine backbone has been successfully incorporated into larger structures. For example, Ohsawa and coworkers synthesized 6-phenyl[1,2,3]triazolo[4,5,-e]-1,2,3,4-tetrazine by oxidizing a triazolotriazole with lead tetraacetate (Figure 10). The bicyclic product containing a 1,2,3,4-tetrazine unit is unstable to both heat and impact.

Figure 10. Synthesis of a 1,2,3,4-tetrazine.
A 1,2,3,4-tetrazine has also been proposed as a reactive intermediate in the formation of benzyne by the oxidation of 1-aminobenzotriazole. Nonetheless, the scarcity of 1,2,3,4-tetrazine structures in the literature suggests the compounds to be unstable. Indeed, Schaefer et al. calculated 1,2,3,4-tetrazine to lie 22 kcal/mol higher in energy than 1,2,4,5-tetrazine.

By far the most well-studied family of tetrazines is the 1,2,4,5-tetrazine, known formerly as s-tetrazine. The 1,2,4,5-tetrazines are usually symmetrically substituted at the 3- and 6-positions, but several unsymmetrical tetrazines are also known. The unsymmetrical 1,2,4,5-tetrazines are much more difficult to make than their symmetric counterparts. The first reported synthesis of a tetrazine was published by Pinner in 1887 and evolved from work performed in the area of imidate chemistry. Since Pinner's initial publication, hundreds of 1,2,4,5-tetrazines have been prepared and reported. The parent compound, 1,2,4,5-tetrazine (1) was first synthesized by Hantzsch and Lehmann in 1900 by the dimerization of ethyl diazoacetate.

The most commonly synthesized and studied tetrazines include the parent 1, 3,6-dimethyl-1,2,4,5-tetrazine 2, 3,6-bis-(trifluoromethyl)-1,2,4,5 tetrazine 3, 3,6-diphenyl-1,2,4,5-tetrazine 4, 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine 5 and dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate 6 (Figure 11). The preference for these six tetrazines arises from a combination of ease of synthesis and desired physical properties.
1.2,4,5-Tetrazines are all highly colored compounds with shades varying from pink to red to violet. Compound 1 exists as an unstable solid. Storage of 1 for any length of time can only be achieved by storing the compound in the absence of air and at low temperature. 1.2,4,5-Tetrazines with 3,6-dialkyl substituents also tend to be unstable and exist as oils at room temperature. A notable exception is 2, a highly volatile solid. 1.2,4,5-Tetrazines with large alkyl substituents show enhanced stability. For example,
3,6-diundecyl-1,2,4,5-tetrazine, has a melting point of 64°C, and is shelf-stable. To date, the only alicyclic substituted 1,2,4,5-tetrazine known is the 3,6-dicyclopropyl-1,2,4,5-tetrazine, which is a fairly low-melting solid (m.p. 42°C).

1,2,4,5-Tetrazines substituted with arylalkyl, aryl, and/or heterocyclic groups, as in 4 and 5, are much more robust than the dialkylsubstituted 1,2,4,5-tetrazines. They can be stored indefinitely without special precautions. The same can be said of 1,2,4,5-tetrazines with 3,6-dicarboxyl substituents, of which 6 is the best known example.

Almost all 1,2,4,5-tetrazines are highly soluble in organic solvents such as chloroform, acetone, diethyl ether, and toluene. Lower molecular weight tetrazines such as 1 and 2 also exhibit water solubility. 1,2,4,5-Tetrazines tend to be slightly soluble in cold alcohols, making ethanol or methanol the solvents of choice for 1,2,4,5-tetrazine recrystallization.

The spectroscopy of 1,2,4,5-tetrazines is fairly uniform. They generally exhibit an absorption of visible light in the region between 520 and 570 nm. This absorption is believed to result from the promotion of a nitrogen lone-pair electron from a non-bonding orbital to a π* orbital. The UV/Vis spectra also typically include a maximum in the region between 250 and 300 nm resulting from a π to π* transition.

The infrared spectra of 1,2,4,5-tetrazines, are also fairly uniform with expected variations as a function of 3,6-substituents. The IR bands attributed to the 1,2,4,5-tetrazine system include a N-N stretch at 1650 cm⁻¹, C=N stretching at 1430 cm⁻¹, and C-N vibrations at 1375-1400, 1140-1000, and 930-910 cm⁻¹.

NMR spectra, both experimentally determined and estimated, have been reported for 1,2,4,5-tetrazines. Witanowski and co-workers published an estimation of the ¹⁴N
NMR chemical shifts for 1. The $^1$H-NMR spectrum of 1 has not been reported, but the chemical shift for the protons on the tetrazine ring has been estimated to be 10.48 ppm.\textsuperscript{85} This chemical shift was derived by extrapolating from the values for benzene, pyridine, pyridazine and pyrimidine. In 3,6-dialkyltetrazines, the protons attached to the $\alpha$-carbon of the alkyl chain typically shift downfield by 3-3.6 ppm\textsuperscript{74} in comparison to the corresponding alkane. In the cases where the substituents are aryl or heterocyclic, the ortho protons have a strong steric interaction with the nitrogen atoms in the tetrazine ring, causing a marked downfield shift.

The $^{13}$C shifts for 1,2,4,5-tetrazines typically lie in the region of 160-170 ppm\textsuperscript{74} for the carbons in the tetrazine ring. The $\alpha$-carbons of tetrazine substituents usually have a downfield shift of 20-30 ppm compared to the unattached substituent. As in the case with the $^1$H spectra, a strong interaction of the ortho carbons with the tetrazine nitrogens causes a noticeable downfield shift in the ortho carbons of aryl and heterocyclic substituents.

Just as the unsaturated 1,2,4,5-tetrazines have been well studied, the dihydro-, tetrahydro-, and hexahydro-1,2,4,5-tetrazines (Figure 12) have also been extensively studied and documented.\textsuperscript{74} There are four possible dihydro-1,2,4,5-tetrazine isomers: 1,2-, 1,4-, 1,6-, and 3,6-dihydro-isomers, respectively. All four isomers are known in the literature, but the 1,2- and 1,4-dihydropyrrotetrazines are by far the most well-studied. Two tetrahydro-1,2,4,5-tetrazine isomers are known: the 1,2,3,4- and 1,2,3,6-tetrahydrotetrazines. The majority of hexahydrotetrazine compounds reported in the literature are N-substituted tetrazines.\textsuperscript{86}
While unsaturated 1,2,4,5-tetrazines tend to be red in color, dihydrotetrazines are often orange. Tetrahydrotetrazines, on the other hand, are typically a pale yellow color, and hexahydrotetrazines are white.

For the most part, the reduced tetrazines are considered to be very stable compounds and they possess melting points much higher than the corresponding 1,2,4,5-tetrazines. There are however, some notable exceptions. The reported melting points for several 1,2-dihydro-1,2,4,5-tetrazines are the same as those reported for the analogous 1,2,4,5-tetrazine. This likely results from the air oxidation of dihydrotetrazines during the melting point experiment. Another notable exception is that of the 3,6-disubstituted-
1,2,3,4,5,6-hexahydrotetrazines. These compounds must be kept absolutely dry as they will react with ambient water to produce azines.

Substitution aside, the solubility of the reduced 1,2,4,5-tetrazines varies as a function of saturation. Dihydrotetrazines are not as soluble as unsaturated tetrazines in nonpolar organic solvents, but they show improved solubility in polar solvents. Tetrahydrotetrazines are only soluble in polar solvents. Hexahydrotetrazines are only slightly soluble in polar organic solvents and water.

The dihydro- and tetrahydro-tetrazines are of interest as precursors or derivatives of 1,2,4,5-tetrazines. Most of the physical characterization of the dihydro- and tetrahydrotetrazines was done to these ends. In the case of the hexahydrotetrazines, the molecules are treated not as reduced tetrazines, but as cyclic polyamines.
1.2.2. Chemistry of 1,2,4,5-Tetrazines

1.2.2.1. Synthesis of 1,2,4,5-Tetrazines. Several different methods for the synthesis of 1,2,4,5-tetrazines have been published in the chemical literature. The majority of the published methods involve the reaction of hydrazine or hydrazine hydrate upon a substrate with two substituents that can be modified to become leaving groups (Figure 13).

\[
\begin{align*}
&\text{R}^1\text{Y-R}^2 + \text{H}_2\text{N-NH}_2 &\xrightarrow{\text{EtOH}} \text{R}^1\text{R}^2 \text{N}^\equiv\text{N} \quad \text{or} \quad \text{R}^1\text{R}^2 \text{N}^\equiv\text{N} \text{N}^\equiv\text{N} \\
&\xrightarrow{[\text{O}]} &
\end{align*}
\]

Figure 13. A generalized scheme for the synthesis of a 1,2,4,5-tetrazine.

The first formed product resulting from the reaction between starting material and hydrazine is either a 1,2- or a 1,4-dihydropyrrole. The question of whether 1,2- or 1,4-dihydropyrroles are formed in tetrazine syntheses has not been settled. Early tetrazine...
literature is ambiguous on the subject. Several cases exist where investigators made no structural assignment as to the dihydrotetrazines formed. In other cases, both 1,2- and 1,4-dihydrotetrazines have been claimed. Regardless of the dihydrotetrazine formed, the final 1,2,4,5-tetrazines are produced by the oxidation of dihydrotetrazine using a suitable oxidant such as ferric chloride, nitric acid, nitrous acid, hydrogen peroxide, or isoamyl nitrite. Of the oxidants mentioned, nitrous acid tends to be the preferred reagent.

Pinner's original synthesis\(^8\) of a 1,2,4,5-tetrazine involved the intermediacy of an imidate ester hydrochloride. Dry HCl gas is bubbled through an alcoholic solution of a nitrile for approximately 12-24 hours forming an imidate ester hydrochloride salt. The imidate ester hydrochloride salt is then precipitated from solution by chilling the alcoholic solution to 0 °C for 24 hours (Scheme 17).
In the next step of the Pinner synthesis, the imidate ester hydrochloride salt is suspended in ethanol and stirred at 0 °C. A slight excess of hydrazine hydrate is added dropwise to the ethanol solution, yielding the orange-colored dihydrotetrazine. For the final oxidation, the dihydrotetrazine is suspended in water, stirred and chilled with an ice/water bath. An excess amount of sodium or potassium nitrite is dissolved in the water. Acid is added dropwise to the stirred solution at such a rate as to keep the reaction solution at or near 0 °C. The resulting tetrazine is filtered off and dried.

Although the Pinner synthesis was first developed for 1,2,4,5-tetrazines in 1887, it remains one of the most commonly used methods. Pinner's synthesis has been successfully employed for the preparation of aryl, arylalkyl, alkyl and heterocyclic substituted 1,2,4,5-tetrazines. Still, tetrazine yields are generally poor, with the best yields coming from reactions run under strictly anhydrous conditions and starting from an aromatic imidate ester.

Scheme 17. Pinner's 1,2,4,5-tetrazine synthesis.
A second widely-used synthesis of tetrazines is similar to the Pinner synthesis in that the starting substrate is a nitrile. In this modified Pinner synthesis however, the formation of the imidate ester is skipped and the nitrile is reacted directly with hydrazine or hydrazine hydrate, usually at boiling ethanol temperature (78 °C) (Scheme 18).

\[
\begin{align*}
R-C=\text{N} & \quad \overset{\text{H}_2\text{NNH}_2\cdot\text{H}_2\text{O}}{\text{EtOH, 78°C}} \quad \left[ \begin{array}{c} \text{R} & \text{NH} \\ \text{N} & \text{NH} & \text{NH}_2 \end{array} \right] \quad \text{dimerization} \\
\end{align*}
\]

\[ \text{R} \quad \begin{array}{c} \text{N} \\ \text{N} \end{array} \quad \text{or} \quad \begin{array}{c} \text{N} \\ \text{N} \end{array} \]

**Scheme 18.** Modified Pinner synthesis of 1,2,4,5-tetrazines.

The dihydrotetrazine that forms typically falls out of solution upon cooling the alcohol solution to room temperature. The dihydrotetrazines can then be filtered and either recrystallized or carried on directly to the oxidation step.

The pathway for the reaction illustrated in Scheme 18 is subject to speculation. Müller and Herrdegen\cite{Muller1994} proposed an alternative path illustrated in Scheme 19. Nucleophilic attack of the hydrazine on the nitrile leads to imine hydrazide a, that can react with another molecule of hydrazine to give structure b. The next proposed step is
Scheme 19. Müller and Herrdegen’s proposed path for the synthesis of a dihydrotetrazine.

the condensation of \( a \) and \( b \) to give ultimately a dihydrotetrazine. Evidence for this pathway consists of the fact that imine hydrazides react with hydrazine to form dihydrotetrazines,\(^8\) and that triazoles (presumably formed by the dimerization of \( a \)) are by-products in some tetrazine syntheses. There is little else to support the path, and some consider it to be an unnecessarily complex process.

As with the original Pinner synthesis, yields from the modified Pinner synthesis are low, varying from just a few tenths of a percent to greater than 50%, depending upon substituents. One interesting report stated that the addition of sulfur flowers or sulfurous compounds (like thiols) to the reaction mixture greatly increases the yields of tetrazine.\(^9\) Another group of researchers, however, claim that the addition of sulfur leads to triazole products.\(^1\) Raney nickel has also been reported to increase yields\(^2\) but as with the
addition of sulfur, counter-claims suggest that the addition of Raney nickel leads to triazole formation.\textsuperscript{93}

There have been several other synthetic methods reported\textsuperscript{74} for the formation of tetrazines, almost all involving the reaction of hydrazine upon a substrate containing a C=X electrophilic group where X is S, O, or NH. The majority of these syntheses, some of which are illustrated in Scheme 20, have only one or two literature examples. The first four syntheses in the scheme, those starting from a thioamide, thiohydrazide, dithioacid, and amidehydrazone, involve the formation of a dihydrotetrazine intermediate. In the final case, starting from an aldehyde, a hexahydrotetrazine intermediate is implicated. Oxidation of the hexahydrotetrazine with PtO\textsubscript{2} gives a 3,6-dihydrotetrazine which is further oxidized by nitrous acid to give the desired 1,2,4,5-tetrazine.
Scheme 20. Some reported syntheses of 1,2,4,5-tetrazines involving non-nitrile substrates.

A third method for the formation of tetrazines is used mainly for the production of 3,6-dicarboxytetrazines and 1. This method was developed by Hantzsch and Lehmann\textsuperscript{81} in 1900 and has been subsequently improved by others.\textsuperscript{74} This is unique in that hydrazine is not involved in the synthesis. Instead, the tetrazine structure is formed by the dimerization of ethyl diazaoacetate in an aqueous NaOH solution. In the reaction, the dimerization of ethyl diazaoacetate leads to a dihydrotetrazine (presumed to be 1,2-) 3,6-dicarboxylate sodium salt (Scheme 21). To form 1, the intermediate is acidified,
oxidized with nitrous acid fumes, and then decarboxylated by heating to 150°C.

Unsubstituted tetrazine I is isolated by sublimation.

Scheme 21. Synthesis of the unsubstituted 1,2,4,5-tetrazine from ethyldiazoacetate.

In the synthesis of 3,6-dicarboxysubstituted 1,2,4,5-tetrazines, the carboxylic acid or ester functional group are fixed upon the dihydrotetrazine intermediate prior to final oxidation. This reaction sequence is necessitated by the relative instability of tetrazines to strongly acidic or basic conditions, a topic discussed in section 1.2.2.2. A good example of the synthesis of a dicarboxytetrazine is provided by Boger and coworkers and illustrated in Scheme 22.94
Scheme 22. Synthesis of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate (Bogar and coworkers, ref. 94).

Bogar and coworkers first dimerized ethyl diazoacetate in aqueous NaOH followed by acidification with concentrated HCl. After neutralizing the solution, the diacid was esterified by refluxing in methanol in the presence of thionyl chloride. After formation of the diester, Bogar and coworkers undertook the oxidation of the dihydrotetrazine to the desired 1,2,4,5-tetrazine. They found that attempting the sequence in a different order (i.e., oxidizing the dihydrotetrazine before performing the esterification) led to either no reaction or a decomposition of the tetrazine.
1.2.2.2. Reactions of 1,2,4,5-Tetrazines. As mentioned in section 1.2.2.1, 1,2,4,5-tetrazines can undergo an acid catalyzed hydrolysis reaction. The acid catalyzed hydrolysis of a tetrazine leads to the formation of hydrazine, nitrogen, and either an acid or an aldehyde. This has been a point of controversy in the literature, some groups reporting aldehyde and others not. A probable path for the acid hydrolysis of a 1,2,4,5-tetrazine is illustrated in Scheme 23. In the first part of the reaction, two successive acid catalyzed hydrations occur yielding a molecule of hydrazine and a diacylhydrazone. This is followed by another acid catalyzed hydration producing a carboxylic acid and a hydrazide.

**Scheme 23.** Pathway for the acid hydrolysis of a 1,2,4,5-tetrazine.
Finally, the hydrazide is hydrolyzed yielding another equivalent of acid and an equivalent of diimide. Presumably the diimide can reduce an equivalent of acid to an aldehyde. It has been hypothesized\textsuperscript{74} that the discrepancies in the literature concerning the formation of carboxylic acid or aldehyde is a result from some groups missing the formation of the aldehyde, possibly as a result of the reaction work-up.

Scheme 24 illustrates a base catalyzed hydrolysis of a 1,2,4,5-tetrazine. Initially, the same acid, aldehyde, hydrazine and nitrogen are seen as in the acid catalyzed hydrolysis. Under basic conditions, however, the acid, aldehyde and hydrazine combine to give an acyl hydrazone. Pinner\textsuperscript{96} and Libman and Slack\textsuperscript{97} demonstrated the base catalyzed hydrolysis of 3,6-diphenyl-1,2,4,5-tetrazine 4 using aqueous KOH and the base catalyzed hydrolysis of 3,6-bis-(3'-pyridyl)-1,2,4,5-tetrazine with sodium carbonate solution, respectively.
Scheme 24. The base catalyzed hydrolysis of a 1,2,4,5-tetrazine to yield an acylhydrazone.

Under strongly oxidizing or strongly reducing conditions, 1,2,4,5-tetrazines react to form five-membered rings. Oxidation of a tetrazine with a peracid yields a 1,3,4-oxadiazole. An example of a peracid oxidation is shown in Scheme 25. Compound 4 reacts with peracetic acid to give 2,5-diphenyl-1,3,4-oxadiazole. Presumably a molecule of N₂ is evolved in the oxidation.
Scheme 25. Reaction of a 1,2,4,5-tetrazine with a strong oxidizing agent.

Reaction of a 1,2,4,5-tetrazine with a strongly reducing system such as zinc and acetic acid gives rise to a 1,3,4-triazole (Scheme 26). In this reaction, the tetrazine is first reduced to a 1,2-dihydrotetrazine. The dihydrotetrazine undergoes a rearrangement to a 4-amino-2,5-disubstituted-1,3,5-triazole. Further reduction by the Zn/acid system yields triazole.

Scheme 26. Reaction of a 1,2,4,5-tetrazine with a strong reducing agent.
Under the influence of mild reducing agents such as hydrogen sulfide\textsuperscript{100} and sodium dithionite,\textsuperscript{101} 1,2,4,5-tetrazines are readily reduced to their corresponding dihydrotetrazine. As with the formation of dihydrotetrazines from nitriles and hydrazine, it is unclear if the dihydrotetrazine is of the 1,2- or 1,4- variety. A similar reduction of a 1,2,4,5-tetrazine was accomplished photochemically in methanol solvent.\textsuperscript{102} It is hypothesized that in the photochemical case, the excited triplet state of the tetrazine abstracts protons from the solvent. Reductions of tetrazines have also been carried out electrochemically, but products of the reaction were not specified.\textsuperscript{103} An interesting reduction of tetrazine 2 involves the corresponding dimethyl-hexahydrotetrazine (Scheme 27).\textsuperscript{104}

![Scheme 27. Reduction of 3,6-dimethyl-1,2,4,5-tetrazine with 3,6-dimethyl-1,2,3,4,5,6-hexahydrotetrazine to give a 1,4 dihydrotetrazine and a 1,2,3,4-tetrahydrotetrazine.]

Attempts to reduce compound 4 with stronger reducing agents such as lithium aluminum hydride or sodium borohydride prompted a breakdown of the 1,2,4,5-tetrazine to benzaldehyde azine and hydrazine.\textsuperscript{99}

There are several examples of 1,2,4,5-tetrazine radical anion formation. Dialkyltetrazines have been shown by ESR spectroscopy to form radical anions in the
presence of potassium $t$-butoxide or a sodium/potassium amalgam.\textsuperscript{105} The radical anion of 3,6-dimethyl-1,2,4,5-tetrazine was reported by Skorianetz and Kováts\textsuperscript{104} via electron transfer from the corresponding 1,4-dihydro-3,6-dimethyl-1,2,4,5-tetrazine (Scheme 28).

![Scheme 28. Formation of a charge-transfer complex between 3,6-dimethyl-1,2,4,5-tetrazine and the corresponding 1,4-dihydrotetrazine.](image)

Compounds like 3,6-bis-(2'-pyridyl)-1,2,4,5-tetrazine 5 and its substituted analogs have been found to form stable complexes with 3$d$ transition metals.\textsuperscript{106} The tetrazines are bidentate, and they form 1:1 complexes with metal-halide salts such as FeCl$_2$, ZnCl$_2$, and CuCl$_2$.

The most important reaction of 1,2,4,5-tetrazines was first reported by Carboni and Lindsay.\textsuperscript{107} This reaction is a [4+2] Diels-Alder where the 1,2,4,5-tetrazine acts as a diene. An example is illustrated in Scheme 29.
Scheme 29. A general Diels -Alder reaction between a tetrazine and ethylene producing ultimately a pyridazine.

The tetrazine undergoes a Diels-Alder reaction with ethylene to give the bicyclic intermediate \( a \). This bicyclic structure is short-lived and extrudes a molecule of \( \text{N}_2 \) in a retro-Diels-Alder reaction to give a 1,2-dihydropyridazine \( b \). \textit{Ab initio} calculations suggest\(^\text{108}\) that the ground-state energy for \( a \) is very close to the transition-state energy for the Diels-Alder reaction that leads to \( a \). Not surprisingly, \( a \) has not been isolated. If there are accessible protons, \( b \) will often isomerize to a 1,4-dihydrotetrazine \( c \). The 1,3-hydrogen shift from \( b \) to \( c \) occurs readily in the presence of trace acid. It has been shown\(^\text{109}\) that a small amount of triethylamine added to a solution of \( b \) will serve to
inhibit the 1,3-H shift. There are several cases known where a dihydropyridazine oxidizes in the presence of air to yield a pyridazine (d).

This type of Diels-Alder reaction in which a 1,2,4,5-tetrazine is the diene is known as an “inverse electron demand” Diels-Alder reaction. The term “inverse electron-demand” implies that the HOMO-LUMO interactions of a Diels-Alder reaction is reversed. In a “normal” Diels-Alder reaction, the HOMO of an electron-rich diene interacts with the LUMO of an electron-poor dienophile to give a six-membered ring. An example of a “normal” Diels-Alder reaction is the reaction of 2,3-dimethylbutadiene with maleic anhydride as illustrated in Scheme 30.

Scheme 30. An example of a “normal” Diels-Alder reaction between an electron-rich diene (2,3-dimethylbutadiene) and an electron-poor dienophile (maleic anhydride).

In the case of an “inverse electron-demand” Diels-Alder reaction, it is the LUMO of an electron-poor diene and the HOMO of an electron-rich dienophile that interacts with one another. Since 1,2,4,5-tetrazines are electron-poor molecules, they are ideal for the inverse-electron-demand Diels-Alder reaction. Indeed, 1,2,4,5-tetrazines are the most widely used diene in this type of Diels-Alder reaction.
A good example of the inverse electron-demand Diels-Alder reaction is the reaction of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate with styrene (Figure 14) to give a dihydropyridazine. In dioxane solvent the reaction proceeds in 80% yield.

Because the electron-withdrawing nature of the tetrazine is increased in the presence of carbonyl substituents and because the alkene had an electron-rich phenyl group attached, the reaction is complete at room temperature in only 10 minutes. Upon making the alkene more electron-donating with a p-methoxyphenyl substituent, the time requirement can be cut in half and the yield is increased to 98%.

Although 1,2,4,5-tetrazines prefer to react with electron-rich alkenes, there is nothing to bar a tetrazine from reacting with an electron-deficient alkene. However, the
energy and time requirements increase greatly. Referring once again to Figure 14, the reaction of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate with methyl acrylate requires 20 hours in refluxing dioxane (101°C) to achieve yields analogous to those observed with styrene.

Reaction conditions for the Diels-Alder reactions of tetrazines are also highly affected by the substituents on the tetrazine. Tetrazines with electron-donating substituents typically require severe conditions to react with an electron-rich dienophile in comparison to tetrazines bearing electron-withdrawing groups.

![Scheme 31](image.png)

**Scheme 31.** The substituents on a 1,2,4,5-tetrazines play a large role in determining the conditions necessary for an inverse electron-demand Diels-Alder reaction.
Scheme 31 illustrates substituent effect. Both reactions involve the reaction of a tetrazine with N,N-diethylaminopropene.\(^\text{111}\) In the first case, dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate reacts at 25°C to give a 73% yield of product. In the second case, N,N-diethylaminopropene undergoing an inverse electron-demand Diels-Alder reaction with 3,6-diphenyltetrazine. Since the phenyl groups are electron-donating, the temperature required for reaction is 110°C, and the yield only reaches 65%.

A reaction that approaches the electronic requirements for a "normal" Diels-Alder reaction is shown in Scheme 32. This is the reaction between 3,6-diphenyl-1,2,4,5-tetrazine and acrylonitrile.\(^\text{107b}\) The reaction conditions need to be quite rigorous: five days of heating at 100°C.

![Scheme 32. A reaction between a 1,2,4,5-tetrazine and an electron-poor alkene that approaches the requirements for being a "normal" Diels-Alder reaction.](image)

Are all Diels-Alder reactions where 1,2,4,5-tetrazines act as dienes classified as inverse electron-demand Diels-Alder reactions? According to the "Alder rule,"\(^\text{112}\) the reaction rate for a normal Diels-Alder reaction is increased by electron-donating substituents on the diene and electron-withdrawing substituents on the dienophile. Scheme 32 apparently fulfills the requirements of a normal Diels-Alder reaction. Is it
possible that, depending upon substituent effects, 1,2,4,5-tetrazines can act as dienes in both normal and inverse electron-demand Diels-Alder reactions?

There have been kinetic studies reported in the literature\textsuperscript{113} addressing this question. The results of these kinetic studies suggest that in all cases where the diene is a 1,2,4,5-tetrazine the Diels-Alder reaction is inverse electron-demand. The kinetic studies, however, were performed on a narrow range of 1,2,4,5-tetrazines and dienophiles. The kinetic results, therefore, do not conclusively indicate whether or not all Diels-Alder reactions where 1,2,4,5-tetrazines act as dienes are inverse electron-demand. Further kinetic studies involving a wide range of tetrazines and dienophiles are required.

The review by Boger\textsuperscript{114} of the Diels-Alder chemistry of azadienes includes an extensive summary of reported Diels-Alder reactions involving 1,2,4,5-tetrazines and a wide range of dienophiles.

C\textsubscript{60} has shown extensive utility as a dienophile in the Diels-Alder [4+2] cycloaddition. Its electron-deficient nature makes it well-suited for reactions with electron-rich dienes such as cyclopentadiene, \textit{o}-quinodimethane, linear acenes, and various heterodienes. Although its reactivity is well documented with electron-rich dienes, its reactions with electron-poor dienes like 1,2,4,5-tetrazines are unknown.

1,2,4,5-Tetrazines are among the compounds most commonly used as dienes in inverse electron-demand Diels-Alder reactions. The reactions of 1,2,4,5-tetrazines with electron-rich dienophiles are generally quite facile and require little additional heating beyond room temperature. 1,2,4,5-tetrazines will also undergo inverse electron-demand Diels-Alder reactions with electron-poor dienophiles, albeit under more forcing
conditions. It is expected therefore that a 1,2,4,5-tetrazine will react across a 6,6-junction of C\textsubscript{60} under fairly vigorous conditions as illustrated in Scheme 33.

Tetrazine cycloaddition across a 6,6-junction of C\textsubscript{60} gives a tetraazobicyclic intermediate which should immediately and irreversibly extrude a molecule of N\textsubscript{2} in a "retro" Diels-Alder reaction. N\textsubscript{2} extrusion leaves a C\textsubscript{2}\textsubscript{v}-symmetric 3,6-disubstituted-4,5-dihydro-4,5-[60]fullerenopyridazine.

The addition of an electron-deficient tetrazine to an electron-deficient fullerene should produce a molecule that is exceedingly electron-deficient and susceptible to nucleophilic attack.

Scheme 33. Expected reaction pathway for the reaction of a tetrazine with C\textsubscript{60} to ultimately give rise to a dihydrofullerenopyridazine.
2. RESULTS AND DISCUSSION

2.1. Synthesis of 1,2,4,5-Tetrazines

Before the chemistry between C\textsubscript{60} and 1,2,4,5-tetrazines could be studied, the 1,2,4,5-tetrazines needed to be synthesized. Among the tetrazines originally chosen for study were 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (5), 3,6-diphenyl-1,2,4,5-tetrazine (4) and 3,6-dimethyl-1,2,4,5-tetrazine (2). Both 4 and 5 are commercially available, but it was determined that undertaking the synthesis of 4 and 5 would be beneficial practice for the synthesis of other tetrazine structures.

The synthetic scheme for the synthesis of 5 (Scheme 34) was modified relative to that reported in the literature. A quantity of 2-cyanopyridine is dissolved in anhydrous ethanol (water can interfere with tetrazine formation, so anhydrous ethanol is preferred over 95% ethanol) and an excess of anhydrous hydrazine is added. Literature examples use hydrazine hydrate to accomplish the tetrazine formation, but as previously mentioned water can lower tetrazine yields. The vessel is heated to reflux (78 °C) for a period of 17 to 24 hours during which time the color of the solution changes from clear to yellow to orange. Presumably, hydrazine reacts with 2-cyanopyridine to give a yellow amidrazone (7) intermediate that dimerizes with loss of ammonia to yield the orange colored 1,4-dihydro-3,6-di-(2’pyridyl)-1,2,4,5-tetrazine (8).
Scheme 34. The synthesis of 5 from 2-cyanopyridine.

Once the reaction flask has been cooled to room temperature and then to 0 °C in an ice/water bath, the orange crystals of 8 can be isolated by vacuum filtration in reasonably good yields (56%).

Oxidation of 8 to 5 is accomplished by suspending the dihydrotetrazine in CHCl₃ and refluxing the suspension in the presence of isoamyl nitrite. The solution quickly turns from orange to a magenta color characteristic of 1,2,4,5-tetrazines. Removal of the chloroform and isoamyl nitrite affords a magenta solid which can be recrystallized from 95% EtOH to give 5 as shiny magenta crystals in 90-95% yield from 8. This overall yield from starting 2-cyanopyridine is 50-53%.
The synthesis of 4 is similar to that of 5 with one difference (Scheme 35). Early attempts to synthesize 4 involved the dissolution of benzonitrile in absolute ethanol followed by the addition of hydrazine and heating of the ethanol solution to reflux. Yields of 1,4-dihydro-3,6-diphenyl-1,2,4,5-tetrazine (10) were discouragingly low with the recovery of most of the starting benzonitrile. Upon switching to a higher boiling alcohol, yields improved. Thus, the reaction using 1-propanol (b.p. 97°C) as solvent gave 10 in 44% crude yield. Pale orange 10 is considerably less air-stable than 8 and readily oxidizes to the corresponding tetrazine 4. Complete oxidation of 10 is accomplished by heating of a CHCl₃ suspension in the presence of isoamyl nitrite. After recrystallization, the red/purple crystals of 4 were isolated in 95% yield from 10 (42% from benzonitrile).

Dimethyl 1,2,4,5-tetrazine 2 could not be satisfactorily synthesized by the reaction of hydrazine with acetonitrile. Instead the starting material of choice is thioacetamide (Scheme 36). Thioacetamide is much more reactive towards hydrazine than acetonitrile, enabling the synthesis of 2 at room temperature. Considering the volatility of 2, a room temperature reaction is much preferred.
Scheme 35. The synthesis of 4 from benzonitrile.

Scheme 36. The synthesis of 2 from thioacetamide.
The reaction of thioacetamide with hydrazine at room temperature evolves an equivalent of \( \text{H}_2\text{S} \) (NOTE: \( \text{H}_2\text{S} \) is a toxic gas and an aqueous base gas trap should be employed) while producing the desired amidrazone which dimerizes to form dihydrotetrazine 11. Compound 11 is even less air-stable than 10 and undergoes rapid and essentially complete air oxidation during work-up. Thus, during an ether extraction, the oxygen dissolved in the \( \text{Et}_2\text{O} \) caused an immediate oxidation of 11 to 2, thereby preventing the isolation and characterization of 11. Combining ether extracts afforded a pink solution. The ether solution was concentrated to a volume of 10 ml using rotary evaporation at 0°C. The remaining ether was removed by subjecting the solution to a vacuum and trapping the solid 2 on a dry ice/acetone coldfinger. In this manner, 2 was isolated as a red solid in 47% crude yield.

Although the yield of 2 was acceptable, its highly volatile nature makes it a difficult tetrazine to work with. A less volatile tetrazine was desired. Since alkyl substituted tetrazines tend to be volatile liquids at room temperature, the synthesis of an arylalkyl tetrazines such as 3,6-dibenzyl-1,2,4,5-tetrazine was desired. Because 4'-methoxyphenylacetonitrile was available, 3,6-di-(4'-methoxyphenylmethyl)-1,2,4,5-tetrazine (12) was prepared.

A modified Pinner synthesis of 12 was used (Scheme 37). In Pinner’s original synthesis\(^8\) (Scheme 17), the starting nitrile is dissolved in ethanol and dry HCl gas is bubbled through the solution for a period of 24 hours.
Scheme 37. Synthesis of 12 from 4'-methoxyphenylacetonitrile using a modification of the Pinner synthesis.

Once the HCl addition is complete, the reaction solution is cooled to 0°C for an extended period of time, causing the precipitation of an imidate ester hydrochloride of the starting nitrile. In the synthesis of 12, a commercially available 5N HCl·iPrOH solution was used in place of HCl gas. Using an HCl·iPrOH solution eliminates the need for a prolonged (24 hr) period of bubbling.

Thus, to a flask containing 4'-methoxyphenylacetonitrile is added enough 5N HCl·iPrOH to dissolve the nitrile. This solution is cooled to 0°C for a 24-hour period.
During cooling the imidate ester hydrochloride (13) is formed and precipitates from solution. Once the cooling period is complete, 13 is isolated by vacuum filtration, washed, and dried. The white crystals of 13 are next suspended in ethanol which has been cooled in an ice/water bath. An excess of anhydrous hydrazine is added to the stirred, cooled suspension. Once again, anhydrous hydrazine is used in place of hydrazine hydrate in order to eliminate interference from water. The attack of hydrazine upon 13 leads to the elimination of isopropanol and ammonium chloride (NH₃, HCl) and the formation of an amidrazone which dimerizes with loss of another equivalent of ammonia to give the dihydrotetrazine 14. Compound 14 can be isolated by vacuum filtration to yield orange-yellow crystals. Upon exposure to air, 14 immediately begins to oxidize, and any significant amount of air-drying leads to a mixture of 14 and the pink-red tetrazine 12.

Full oxidation of 14 to 12 is accomplished using nitrous acid as oxidant. Solid 14 is suspended in a solution of aq. NaNO₂. The solution is magnetically stirred and cooled to <5°C by an ice/water bath. Glacial acetic acid is added dropwise to the suspension. The rate of addition is controlled so that the temperature of the suspension does not exceed 5°C. Once the acetic acid addition is complete, the mixture is stirred for 2 hours at 0°C, then for another hour at room temperature. The pink-red crystals of 12 are vacuum filtered and recrystallized from 95% ethanol.

Attempts were made to synthesize 12 using direct hydrazine addition to 4'-methoxyphenylacetonitrile as in the synthesis of tetrazines 4 and 5. The product isolated, however, was not a dihydrotetrazine, but rather aminotriazole 15. Aminotriazole 15 is pale, fluffy, pink solid that is sparingly soluble in organic solvents. Compound 15 also
has a higher melting point than 12 and possesses both a $^1$H NMR resonance and an FT-IR stretch consistent with an amine functionality. Interestingly, there are several literature examples of compounds that were as assigned originally as tetrazines, but are known to be aminotriazoles.

Scheme 38. The reaction of $p$-methoxyphenylacetonitrile with hydrazine in refluxing ethanol does not produce the dihydrotetrazine 14, but rather the aminotriazole 15.
Although there have been no papers describing a mechanism for the formation of aminotriazoles from nitriles and hydrazine, one can speculate that the aminotriazole forms from a rearrangement of a 1,2-dihydrotetrazine as in Scheme 39. The first part of the mechanism is similar to those invoked for the formation of the 1,4-dihydrotetrazines 8 and 10. The starting nitrile reacts with hydrazine to form an amidrazone which dimerizes with loss of ammonia to give the 1,4-dihydrotetrazine. At elevated temperature (boiling ethanol, 78°C), the 1,4-dihydrotetrazine can isomerize to a 1,2-dihydrotetrazine. The next step involves the attack of an amino nitrogen upon an imino carbon produces a zwitterionic tetraazobicyclic intermediate. Rearrangement affords an aminotriazole.

![Scheme 39. Proposed pathway for aminotriazole formation.](image-url)
Literature observations\textsuperscript{74,91,95} support the proposed pathway. Authentic samples of alkyldihydrotetrazine, prepared by the reduction of the corresponding tetrazine, are known to rearrange to aminotriazoles when heated.\textsuperscript{91} This reaction is reversible at elevated temperatures.\textsuperscript{95} These data suggest that formation of the aminotriazole should pass through a dihydrotetrazine intermediate. Another piece of evidence supporting the proposed pathway concerns the observed substituent effect. If the substituents are aromatic, heteroaromatic or heterocyclic, the rearrangement does not occur. Presumably, aromatic, heteroaromatic, or heterocyclic groups possess enough electron-donating character to deactivate the imine carbons from attack by an amino nitrogen. An alkyl group is less electron-donating and should not deactivate the imine carbons from nucleophilic attack. An interesting test case for the second point would be whether or not a rearrangement to the aminotriazole would occur in a dihydrotetrazine possessing trifluoromethyl (\(-\text{CF}_3\)) substituents. If the pathway proposed in Scheme 39 is valid, the rearrangement from a bis-trifluoromethylidihydrotetrazine to a bis-trifluoromethyltriazole should be a facile process.
2.2. Reaction Between C$_{60}$ and 1,2,4,5-Tetrazines

Tetrazine 5 reacts with C$_{60}$ to give monoadduct 16. An equimolar amount of C$_{60}$ and 5 are weighed into a round-bottom flask that has been oven-dried and wrapped in aluminum foil. Toluene is added (ca. 1 ml for every mg of C$_{60}$) and the flask is attached to a reflux condenser which is also wrapped in foil. The solution is heated at toluene reflux (110°C) for 24 hours, after which time the toluene is removed by rotary evaporation making sure that the flask and its contents remain in the dark. After removal of the solvent, crude brown solid is recovered. It is possible to use lower boiling solvents such as carbon disulfide (bp 46 °C) and benzene (bp 80 °C), or higher boiling solvents, such as o-dichlorobenzene (ODCB, bp 182 °C). There are however, caveats associated with each type of solvent. In the case of the lower boiling solvents, the reaction times necessary for a reasonable yield of crude product are increased dramatically (~72 hours for carbon disulfide). The use of ODCB cuts down the required reaction time to about 4 hours, but there is a high occurrence of thermal degradation of tetrazine which reduces the yield. Another problem with ODCB is its low volatility which complicates removal from the crude product mix.

Separation of 16 from the crude mixture is performed in the dark. The simplest way to accomplish this is to wrap all flasks, filtering funnels, etc. in aluminum foil. The crude product mixture is rinsed several times with acetone to remove any unreacted tetrazine. Once all of the unreacted tetrazine (pink color) is removed, the resulting precipitate is then washed several times with CHCl$_3$. The resulting filtrates are a dark brown color which get lighter with each subsequent CHCl$_3$ rinse. When all of the brown
color (dissolved 16) is gone from the filtrate, the CHCl₃ washes are combined. The remaining precipitate can be taken up in CS₂ and they analyze for pure unreacted C₆₀. Evaporation of CHCl₃ leaves brown solid 16 in approximately 56% crude yield. The separation scheme for the isolation of 16 is illustrated in Figure 15.

**Figure 15.** Diagram illustrating the isolation of 16 using washing of the crude product mix with different solvents.
The expected pathway for the reaction of 5 with C₆₀ is illustrated in Scheme 40. Tetrazine 5 and C₆₀ react to give bicyclic intermediate 17, immediately extrudes a molecule of N₂ in retro-Diels-Alder fashion to give 3,6-di-(2'-pyridyl)-4,5-dihydro-4,5-[60]fullerenopyridazine 16.

Tetrazine adduct 16 is expected to possess C₂ᵥ symmetry and its ¹H and ¹³C NMR spectra are consistent with such a structure. In the ¹H NMR spectrum (Figure 22), the only resonances observed are those for the pyridine protons, the only protons on the molecule. Because the two pyridine rings are equivalent, only four ¹H NMR resonances are observed. Since only four ¹H NMR are observed (none broadened), it is safe to assume that the pyridine rings on 16 rotate freely on the NMR time scale.

Scheme 40. Expected pathway for the reaction of C₆₀ with 5 to form 16.
It is also possible to predict the $^{13}$C NMR spectrum for 16. Due to the C$_{2v}$ symmetry, there should be 5 carbon resonances for the pyridine rings and 1 resonance for the carbons in the pyridazine unit attached to pyridine rings. It is known that C$_{2v}$ fullerene adducts give rise to 16 resonances for the C$_{60}$ cage. There are 15 resonances predicted for the sp$^2$-like carbons in the cage and there should be a single resonance for the sp$^3$ carbons in the cage that are annealed to the pyridazine unit. By analyzing the NMR spectra and also using mass spectrometry (16 would have a m/z of 928) it should be fairly easy to determine if 16 is indeed produced in the reaction of C$_{60}$ with 5.

A close examination of the $^1$H NMR spectrum for 16 (360 MHz, CS$_2$/CDCl$_3$), shows three sets of resonances that integrate in a 1:2:1 ratio, consistent with 16. This inspection also reveals that the sample of 16 is not entirely clean, a consequence of using solvent washes rather than chromatographic methods to isolate product.

**Figure 16.** $^1$H NMR spectrum of 16. The singlet at $\delta$ 7.27 is CHCl$_3$. 

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The $^{13}$C NMR spectrum (90.56 MHz, CS$_2$/CDCl$_3$) for 16 (Figure 17) is also consistent with the proposed structure. There is a single resonance at $\delta$ 63.1 which corresponds to the two quaternary $sp^3$-hybridized carbons on the fullerene cage. There are only five pyridine carbon signals and only one resonance for both $sp^3$ carbons of the dihydropyridazine moiety, all consistent with a C$_2v$ adduct. Finally, there are fifteen resonances for the $sp^2$-like carbons in the fullerene cage. These fifteen resonances, along with the single resonance for the fullerene $sp^3$ carbons, gives a total of sixteen signals for the fullerene skeleton, exactly as expected for a C$_2v$ symmetric fullerene monoadduct. Also present in the spectrum is a single peak at $\delta$ 143 which corresponds to unreacted C$_{60}$, a common contaminant. Electrospray mass spectrometry gives an M+1 peak of 929 amu for 16-H$^-$, consistent with the C$_{72}$N$_4$H$_8$ formula for 16.
Likewise, the reaction between C\textsubscript{60} and tetrazine 4 yields 3,6-diphenyl-4,5-dihydro-4,5-[60]fullerenopyridazine 18 (Scheme 41). As with 16, 18 is C\textsubscript{2\text{v}} symmetric. Equimolar amounts of C\textsubscript{60} and 4 are added to a dry, foil-wrapped round-bottom flask. The reactants are dissolved in toluene (ca. 1 ml toluene per mg of C\textsubscript{60}). As in the synthesis of 16, the reaction solution is heated to reflux (110 °C) in the dark for 48 hrs. At the end of the reflux period, the brown-colored crude product solution is cooled to room temperature and the solvent is removed by rotary evaporator.

![Scheme 41. Reaction pathway to produce 18.](image)

Isolation of 18 from the crude product mix is accomplished in much the same fashion as described for 16. The main difference between the two procedures is the diethyl ether solvent washes rather than acetone are used on the crude product mixture containing 18. This is because 4 shows better solubility in diethyl ether than in acetone, while for 5 the reverse is true. Beyond the substitution of diethyl ether for acetone, the
isolation procedure is essentially the same (Figure 18). Once the CHCl₃ washings are combined, the chloroform is removed with rotary evaporation. Tetrazine adduct 18 is obtained as a dark brown solid in 52% crude yield.

**Figure 18.** Flowchart for the isolation of 18.

The $^1$H NMR (360 MHz, CS₂/CDCl₃) spectrum for 18, shows only two resonances (Figure 19) integrating in a 2:3 ratio. The downfield signals integrate for 4H.
and correspond to the ortho-protons on the phenyl rings. The upfield multiplet integrating for 6H arises from the meta- and para-protons.

An examination of the $^{13}$C NMR (90.56 MHz, CS$_2$/CDCl$_3$) spectrum for 18 (Figure 20) reveals an upfield peak at $\delta$ 60 corresponding to the two $sp^3$-hybridized carbons of the fullerene cage. There are fifteen carbon signals in the range of $\delta$ 130-150 corresponding to the rest of the C$_{60}$ cage, for a total of 16 fullerenic carbon signals. As with the spectrum of 16, the presence of sixteen fullerenic carbon resonances in the $^{13}$C NMR spectrum of 18 indicates C$_{2v}$ symmetry.

**Figure 19.** $^1$H NMR spectrum of 18. The signal at $\delta$ 7.27 is CHCl$_3$. 
It is worth noting the differing reactions conditions and times required to accomplish the synthesis of 16 and 18. To produce 16, C_{60} and 5 are heated in boiling carbon disulfide (46°C). For the synthesis of 18, C_{60} and tetrazine 4 must be heated in refluxing toluene (110°C). Monoadduct 16 is produced in reasonable yields (>50%) after 24 hours in refluxing toluene. To obtain comparable yields of 18, the reaction requires approximately 48 hours in refluxing toluene. The experimental data suggest that the C_{60} is more reactive towards 5 than 4.

Regardless of the times and temperatures employed in the syntheses of 16 and 18, the reaction and work-up steps must be performed in the dark. Exposure to light induces both monoadducts to undergo a complete conversion to compounds which will be discussed in section 2.2.
Diels-Alder reactions between C$_{60}$ and aryl substituted tetrazines (4 and 5) yield C$_2v$ symmetric monoadducts (18 and 16). It therefore seems logical to expect that the reaction of C$_{60}$ with an alkyl substituted tetrazine, 12, should yield an analogous monoadduct (19). However, when C$_{60}$ and 12 are reacted in refluxing toluene, the product isolated is not 19. Instead, a C$_v$-symmetric adduct 20, is formed with no 19 observed (Scheme 42).

Apparently, the pyridazine unit on 19 undergoes an immediate 1,3-hydrogen shift to form 20. Similar 1,3-H shifts are well known phenomena in tetrazine chemistry.$^{85}$ and almost always occur when there is an accessible hydrogen in a position $\beta$ to a pyridazine nitrogen. Most literature examples of this rearrangement involve $\beta$-hydrogens that are endocyclic. However the endocyclic $\beta$-positions in C$_{60}$-tetrazine are quaternary necessitating an exocyclic 1,3 hydrogen shift.

For the reaction of C60 with tetrazine 12, equimolar amounts of fullerene and tetrazine are added to a dry round-bottom flask that is covered in foil. Toluene is added to the flask and the solution is heated in the dark at 110 °C for 24 hours. Upon cooling the solution to room temperature, the foil is removed and the toluene is evaporated with a rotary evaporator to give a crude brown solid.
Scheme 42. Pathway for the reaction of C\textsubscript{60} with 12 to yield 19 which rearranges to 20 using a 1,3-H shift.
Isolation of the product (20) from the crude mixture is accomplished using either column chromatography or preparative thin-layer chromatography, depending upon the scale of the reaction. In both cases the stationary phase is silica gel and the mobile phase is 10:1 CS₂:ethyl acetate. The first band to elute is unreacted C₆₀ followed by 20 as a brown band. Unreacted 12 follows. Evaporation of the solvent from the collected band gives 20 as a brown solid in 20% yield.

Examination of the 'H and 13C NMR spectra for 20 (Figures 21 and 22, respectively) confirm the assigned structure. In the 'H NMR spectrum (360 MHz, CS₂/CDCl₃), there are two separate signals (δ 3.8 and 3.9) for the two methoxy groups indicating a loss of symmetry. There is only one peak for the benzyl protons at δ 4.5, integrating for only 2 H. In the range of δ 6.8-7.5 there are four multiplets which integrate for nine protons. These multiplets can be assigned to the eight phenyl protons and the one olefinic proton. Finally, there is a slightly broadened singlet at δ 8.3 which is characteristic for an amine proton in which the nitrogen is connected to an imine nitrogen.

The 13C NMR spectrum (90 MHz, CS₂/CDCl₃) for 20 corroborates the 'H NMR assignment. Thus two signals are observed for the methoxy carbons (δ 55.0 and 55.2), one for the benzyl carbon (δ 40.2) and one resonance for the styrenyl carbon bearing a proton (δ 110.3). Two resonances for the two unique sp² carbons in the pyridazine ring (δ 158.5 and 159.1), and eight 13C signals denoting the eight unique carbons in the two phenyl rings are observed. As expected for a Cᵥ symmetric adduct, a total of 32 13C
Figure 21. $^1$H NMR spectrum of 20.

Figure 22. $^{13}$C NMR spectrum of 20. The triplet at $\delta 77.25$ is CDCl$_3$. 

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signals are observed for the fullerene skeleton. Two signals at \( \delta 67.4 \) and 68.6 correspond to the quaternary \( sp^3 \) hybridized carbons that are annealed to the dihydropyridazine ring. An additional 30 \(^{13}\)C signals are observed between \( \delta 135 \) and 150 corresponding to the \( sp^2 \) carbons of the fullerene cage.

An intriguing aspect of the reactions that produce 16, 18, and 20 is the fact that the product slate for each reaction consists exclusively of the \( C_{60}\)-tetrazine monoadduct. Several attempts were made to produce a bistetrazine adduct of \( C_{60} \), but only monoadduct was observed. These attempts included the use of a large excess (10-fold) of tetrazine while running the reaction in refluxing ODCB for multiple days. Even under these fairly forcing conditions, the only product observed was monoadduct. Presumably, the \( C_{60}\)-tetrazine monoadduct is much too electron-deficient to react with another equivalent of tetrazine. However, the \( C_{60}\)-tetrazine monoadduct will readily react with pentacene to produce several adducts. Since the electron-deficient tetrazine does not react with the very electron-deficient \( C_{60}\)-tetrazine monoadduct and pentacene does react, one can assume that the Diels-Alder reaction between 1,2,4,5-tetrazines and \( C_{60} \) is an inverse electron-demand Diels-Alder reaction.

Also attempted was the reaction of monoadduct 16 with another equivalent of \( C_{60} \) in the hopes of preparing a bisfullerene adduct of a 1,2,4,5-tetrazine. Even with a large excess of \( C_{60} \) in refluxing ODCB, the reaction failed to produce observable product.
2.3. Hydration of C₆₀-Tetrazine Monoadducts

In the reactions that produce 16 and 18, the procedure for separating the monoadducts from the starting materials involves various solvent washes performed in the dark which takes advantage of the differing solubilities of the products and the starting materials. Although this is a convenient method for isolating 16 and 18, a look at their NMR spectra reveals that these compounds are not entirely free of impurities. Typical approaches to isolate 16 and 18 free of impurities would include some type of chromatography like, e.g., column chromatography, preparative thin-layer chromatography, or HPLC. However, when subject to normal phase chromatographic conditions, 16 and 18 undergo a rapid hydration with novel rearrangement. Thus, after reacting C₆₀ with tetrazine 5 in refluxing toluene and in total darkness, evaporation of toluene leaves a brown solid as crude product. The crude product mixture is separated by flash silica column chromatography using a 20:1 CS₂:ethyl acetate mixture as eluent. The first band to elute is unreacted C₆₀, and this is followed by a second band that analyzes for hydration product ±21 (Scheme 43). Changing eluent to 20:1 CHCl₃:MeOH enables the collection of unreacted tetrazine. Tetrazine monoadduct 16 is not recovered.

An examination of ±21 reveals that it is chiral and, having been synthesized from achiral precursors, must exist as a racemic mixture of enantiomers. From an NMR standpoint, this means that all of the protons and carbons in the molecule are chemically and magnetically unique. The hydration of 16 is accompanied by a rearrangement that places two protons on the fullerene skeleton in a 1,4-fashion.
Scheme 43. Formation of $\pm 21$ via hydration/rearrangement of 16.
An interesting feature of ±21 is that the ring appended to the fullerene is now a five-membered amido dihydropyrazole system as compared to the dihydropyridazine unit in 16. Moreover, the dihydropyrazole ring in ±21 is fused to the fullerene at a 5,6-junction. In 16, the dihydropyridazine ring is fused to the fullerene at a 6,6-junction. Typically, a cycloaddend fused to a fullerene at a 5,6-junction is accompanied by unfavorable 6,5-double bonds. However, the 1,4-fullerenic hydrogens on ±21 eliminates the existence of such high-strain features.

Compound ±21 gives an electrospray mass spectrometric M+1 peak of 947 amu, 16 amu higher than the M+1 for 16 (929 amu).

![Figure 23. 1H NMR spectrum of ±21. The singlet at δ 7.27 is CHCl₃.](Image)

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The $^1$H NMR spectrum (360 MHz, CS$_2$/CDCl$_3$) of $\pm$21 (Figure 23) indicates a lack of symmetry as seven multiplets between $\delta$ 7.3 and 9.0 corresponding to the eight protons of the pyridine rings (one multiplet integrates for 2 H) are observed. Two doublets ($^5J$=1.8 Hz) centered at $\delta$ 6.5 are indicative of protons attached to the fullerene cage. Several examples of hydrogenated fullerenes with chemical shifts in this range are known.$^{40}$ Moreover, a 1.8 Hz coupling constant is uniquely consistent with a 1,4-arrangement of fullerenic protons. Representative $^3J$, $^4J$, and $^5J$ for fullerenic protons are 14, -9.6, and 1.7 Hz, respectively.$^{37}$

![Graph showing NMR spectrum with peaks at 6.0 to 6.7 ppm](image)

**Figure 24.** An expansion of the area between 6.0 and 7.0 ppm in the $^1$H NMR spectrum for $\pm$21.
The $^{13}$C NMR spectrum (90.56 MHz, CS$_2$/CDCl$_3$) for ±21 is also consistent with a racemic fullerene adduct and includes many structural clues.

Figure 25. $^{13}$C NMR spectrum of ±21. The triplet at δ 77.25 is CDCl$_3$. 

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Four $^{13}$C signals are observed between 45 and 90 ppm (Figure 26) corresponding to 4 unique $sp^3$ carbons. The two upfield peaks at 54.3 ppm and 55.7 ppm are assigned to the hydrogen-bearing methine carbons on the fullerene cage. The chemical shifts for these two carbons are consistent with published shifts for methine carbons on hydrogenated fullerene structures.\textsuperscript{40} The relatively high s/n associated with these signals results from NOE effects. The two downfield peaks lower intensity in Figure 26 (disregarding the CDCl$_3$ triplet) are assigned to the $sp^3$ carbons of the C$_{60}$ cage that bridge the dihydropyrazole moiety. The signal at 80.8 ppm can be assigned to the cage carbon bound directly to nitrogen.
Figure 27. Expansion of the $^{13}$C NMR spectrum of ±21 for the region from 120-170 ppm.

Although a crowded region of the $^{13}$C spectrum, several structural clues are can be gathered by examining the Csp$^2$ region of the spectrum of ±21 (Figure 27). The signals of greatest intensity in the sp$^3$ region can be assigned to hydrogen bearing carbons of the two pyridine rings (NOE effects). The signal at lowest field can be assigned to the amide carbonyl carbon and the next most downfield signal (153 ppm) to the sole sp$^2$ carbon of the dihydropyrazole ring. The remaining 58 $^{13}$C signals correspond to the two unique ipso carbons of the pyridine rings plus the 56 remaining sp$^2$ carbons of the fullerene skeleton. An FT-IR spectrum of ±21 reveals multiple features including a C=O stretching vibration at 1650 cm$^{-1}$ consistent with an amide functionality.
Compound 18 undergoes an analogous hydration/rearrangement reaction when similarly subjected to chromatographic conditions. Thus, reaction between C₆₀ and 1,2,4,5-tetrazine 4 in refluxing toluene and total darkness yields crude 18 that hydrates and rearranges to ±22 when subject to normal phase chromatographic conditions (flash silica column, 20:1: CS₂:ethyl acetate eluent) as illustrated in Scheme 44.

Scheme 44. Formation of ±22 via the hydration/rearrangement of 18.
The $^1$H and $^{13}$C NMR spectra for ±22 (Figures 28 and 29, respectively) contain features that are very similar to those reported for ±21. The $^1$H NMR spectrum (360 MHz, CS$_2$/CDCl$_3$) of ±22 contains a pair of AB doublets at 6.6 ppm and 6.7 ppm with a $^\text{H}$ of 1.8 Hz, indicating a pair of 1,4-hydrogens on the fullerene surface. The $^1$H NMR spectrum also includes three partially overlapping aryl multiplets that integrate for a total of 10 protons.

Figure 28. $^1$H NMR spectrum of ±22.
The $^{13}$C NMR spectrum (90.56 MHz, CS$_2$/CDCl$_3$) of ±22 reveals two signals at δ 54 and 56 that correspond to the fullerenic carbons bearing hydrogen (Figure 29). The two resonances at δ 70 and 80 can be assigned to the $sp^3$ hybridized carbons of the fullerene that bridge the dihydropyrazoline ring. Like the $^{13}$C NMR spectrum of ±21, the spectrum of ±22 includes a peak at 165 ppm corresponding to the amide carbonyl carbon.

Unlike 16 and 18, compound 20 does not undergo a hydration and subsequent rearrangement upon exposure to acidic aqueous conditions. The rapid 1,3-hydrogen shift experienced by 19 apparently deactivates the resulting structure, 20, from hydration. Likewise, 20 can be chromatographed on silica gel without complication.

In a series of control experiments, the conditions required to convert 16 and 18 to ±21 and ±22, respectively, were ascertained. The role of ambient light was initially
studied. In separate side by side reactions, C\textsubscript{60} and tetrazine 5 were allowed to react in refluxing toluene. One reaction was run in complete darkness and the other in ambient light. Following evaporation of the toluene solvent (performed in the dark for the dark reaction), \textsuperscript{1}H NMR spectra of the crude reaction mixtures revealed major differences. The spectrum for the reaction run in total darkness revealed unreacted 5 plus monoadduct 16 with little or no ±21. Conversely, the \textsuperscript{1}H NMR spectrum for the reaction run in ambient light revealed unreacted 5, dihydrotetrazine 8, and ±21. Compound 16 was not observed. It is concluded from these experiments that ambient light is required for the facile conversion of 16 and 18 to ±21 and ±22, respectively.

In another set of control experiments, separate reactions between C\textsubscript{60} and 5 were run in three solvents, toluene, toluene-d\textsubscript{8}, and ODCB. The solvents were used without purification. After separately refluxing C\textsubscript{60} and 5 in each solvent in ambient light, the solvents were evaporated and the crude reaction mixtures were characterized by \textsuperscript{1}H NMR spectroscopy. Each crude spectrum revealed the presence of ±21 with no 16. These control experiments demonstrated that the hydration/rearrangement reaction is neither solvent nor temperature dependent. Furthermore, the new fullerene C-H bonds on ±21 and ±22 were not formed by abstraction of hydrogen from organic solvent molecules.

In a third set of control experiments, the role of atmospheric oxygen was investigated. Two reactions between C\textsubscript{60} and 5 were set up to be run in ambient light. The first reaction was run in the ambient air while the second reaction was run under a nitrogen atmosphere. After refluxing in toluene for 24 hours and removing solvent, both \textsuperscript{1}H NMR spectra for the separate crude product mixtures revealed ±21 but no 16. These control experiments indicate that oxygen plays no role in the conversion of 16 to ±21.
In a fourth set of control experiments, the role of water was investigated. Side by side reactions between C₆₀ and 5 were again run. The first reaction was carried out under scrupulously dry conditions. The reaction flask was flame-dried before use, freshly distilled toluene from Na°/benzophenone was used and the reaction was run under a blanket of dry nitrogen in ambient light. In the second reaction, the reaction flask was washed and air-dried before use. Toluene was used as provided from the vendor, and the reaction was run under a blanket of nitrogen and in ambient light. The crude ¹H NMR spectrum of the "dry" reaction showed 16, but no evidence of ±21. Conversely, the ¹H NMR spectrum for the "wet" reaction revealed ±21, but no 16. These control experiments indicate that water plays a large role in the conversion of 16 to ±21 and that ±21 can be viewed as a hydration product of 16.

The first four sets of control experiments revealed that water and light are required for the conversion of 16 to ±21, but that the reaction is not influenced by the choice of temperature or the presence of atmospheric oxygen. In a fifth set of control experiments, the role of water and light were reexamined. In particular, we tested to see if both water and light are simultaneously required for conversion of 16 to ±21. A "wet" reaction between C₆₀ and 5 (toluene solvent used as is from vendor bottle; air-dried glassware) was run in total darkness. After refluxing for 24 hours and evaporating toluene solvent in the dark, a ¹H NMR spectrum of the crude product mixture showed 16 but no sign of ±21. Combined with the "dry" reaction discussed above, it is evident that both water and light are simultaneously necessary to convert 16 to ±21.
Reactions between C\textsubscript{60} and 5 run in the much lower boiling solvent CS\textsubscript{2} (b.p. 46 °C) produce 16, but in lower yield that the analogous reactions run in either toluene (b.p. 110 °C) or ODCB (b.p. 182 °C). Interestingly, the CS\textsubscript{2} reactions run under "wet" conditions and in ambient light produce 16 with little or no ±21 observed. However the addition of acid rapidly catalyzes the rearrangement. Thus upon reacting C\textsubscript{60} and 5 in refluxing CS\textsubscript{2} under "wet" conditions and in ambient light, a \textsuperscript{1}H NMR spectrum of the crude product mixture shows only 16 (no ±21). After adding a tiny amount of silica gel, the tube was shaken and a second spectrum was taken. This time, ±21 is present. A similar experiment was performed again, but instead of SiO\textsubscript{2}, a drop of concentrated HCl was added to the NMR tube. Once again ±21 was quickly formed. The hydration/rearrangement reaction is acid catalyzed. In the absence of acid catalyst, temperatures in excess of 46 °C are required. In the presence of acid catalyst, milder reaction conditions may be employed.

In a final set of control experiments the combined roles of light, water, and acid were tested. Upon forming 16 from C\textsubscript{60} and 5 in dry, dark refluxing CS\textsubscript{2}, addition of an organic acid, dry p-toluenesulfonic acid (TsOH), did not promote formation of ±21. Acid alone was not enough. Upon forming 16 from C\textsubscript{60} and 5 in wet, dark refluxing CS\textsubscript{2}, addition of TsOH did not effect a rearrangement. Water and acid are not enough. Upon forming 16 from C\textsubscript{60} and 5 in dry refluxing CS\textsubscript{2} in ambient light, addition of TsOH did not induce rearrangement of 16 to ±21. Light and acid are not enough. These control experiments demonstrate that while the hydration/rearrangement of 16 to ±21 is catalyzed by acid, the reaction will not occur in the absence of either light or water.
Figure 30. Summary of control experiments designed to determine the conditions required for the conversion of 16 to ±21. The first part of the table indicates that the hydration/rearrangement reaction occurs regardless of solvent or atmosphere, and that the hydrogens on the fullerene cage do not come from solvent. The second part indicates that light, water, and acid catalyst must be present for the hydration/rearrangement to occur.
With the conditions required for the formation of ±21 in hand, it is possible to propose a mechanism for the hydration and rearrangement of 16 to yield ±21. This mechanism, illustrated in Scheme 45, begins with an acid catalyzed protonation of one of the pyridazine nitrogens in 16. Protonation activates 16 towards a reversible nucleophilic attack by water to give structure 23 with regeneration of the acid catalyst. A ring opening of the pyridazine unit is proposed to yield 24, a zwitterionic structure consisting of an oxonium cation and a fullerene anion. Proton transfer affords the neutral structure 25. It would appear that 25 should be an isolable intermediate. However in the reactions between C60 and tetrazines, there is a total mass balance of the fullerene. All of the C60 is either recovered as unreacted C60 or as ±21 after chromatography. In addition, NMR examinations of crude product mixtures shows no indication of 25 regardless of reaction conditions. It is proposed that 25 undergoes a photoinitiated intramolecular electron transfer resulting in 26 which rapidly rearranges to ±21 (Scheme 45). Numerous reactions of C60 involving photoinduced electron transfer are known.29
Scheme 45. Possible mechanism for the formation of ±21 from 16.
While $C_{60}$ is a good electron-acceptor, photoexcited $C_{60}$ is an even better electron-acceptor. A single-electron transfer then occurs where the $C_{60}$ accepts an electron from a suitable donor forming a fullerene radical anion and a donor radical cation. Species 26, contains a fullerene radical anion, known to be a relatively stable entity, tethered to a resonance-stabilized nitrogen radical cation. Nitrogen radical cations are acidic species capable of protonating a fullerene radical anion to yield the neutral diradical 27. A simple intramolecular radical coupling yields a 3,4-dihydropyrazole ring fused at a 6,5-junction of $\pm 21$. 

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2.4. Addition of Primary Amines to C₆₀-Tetrazine Monoadducts

Since water added regioselectively to an activated imine carbon in 16 to form ±21, the possibility that other diprotic nucleophiles could add to 16 in a similar fashion was explored. An obvious choice of diprotic nucleophiles for these studies are primary amines. It is known⁵²,⁵³ that primary and secondary amines react with C₆₀ in a single-electron-transfer reaction (SET, Scheme 46) to form an amine radical cation and a fullerene radical anion that then combine to form a C₆₀-amine adduct. When equimolar amounts of C₆₀ and amine are used in a relatively nonpolar solvent, the coupling reaction is a photoinduced process.¹¹⁵

Since the reaction that forms ±21 is also a photoinduced reaction, the addition of a primary amine to 16 becomes an interesting test case for the chemoselectivity of a functionalized fullerene. One possible reaction path involves nucleophilic attack of the primary amine on an imine carbon of 16 with a subsequent rearrangement to yield an amine analog of ±21. A second potential reaction involves a SET from the amine to 16 followed by the addition of the amine to the fullerene surface to give rise to a pyridazino-analog of product structure shown in Scheme 46.
Scheme 46. The reaction of a primary or secondary aliphatic amine with C$_{60}$ to yield is believed to involve a SET step. When a stoichiometric amount of amine is used in a relatively nonpolar solvent, the reaction is a photoinduced process.

An equimolar amount of C$_{60}$ and tetrazine 5 were dissolved in toluene and heated to reflux in the dark for approximately one day, taking care to keep the reaction scrupulously dry. Once the heating time had elapsed, the crude reaction mixture was allowed to cool to room temperature. While still keeping the reaction flask in the dark, 16 was isolated as previously described and dissolved in CHCl$_3$. To this solution was added 1.2 equivalents of $n$-hexylamine. The flask was equipped for magnetic stirring, the
foil was removed, and the reaction was stirred for 24 hours at room temperature in ambient light.

Once the reaction time was complete, the CHCl₃ solvent was evaporated to leave the crude product mixture as a brown solid. Separation of the crude was performed using column chromatography (20:1 CS₂:ethyl acetate on silica gel). The first band to elute was unreacted C₆₀ that was not removed during the isolation of 16. The product of amine addition to 16 was the second band to be isolated as a brown solution. Following the product band, unreacted C₆₀-tetrazine monoadduct, in the form of ±21, eluted. Switching the eluent to a more polar mixture (20:1 CHCl₃:MeOH) allows for the isolation of any unreacted 5 that may have not been removed during the isolation of 16.

The solvent was evaporated from the product band (the second band) and the ¹H and ¹³C NMR spectra were acquired. The product was assigned the structure ±28 (Scheme 47). Compound ±28 is an amine analog of ±21. No other amine-addition adducts are detected, including amine adducts of unreacted C₆₀. This result implies that primary aliphatic amines add chemoselectively to the pyridazine moiety of 16 rather than the unreacted fullerene skeleton. Since primary aliphatic amines are not reacting with C₆₀ under these conditions, it seemed plausible that the amine could be added to the crude product mixture containing 16, 5, and the unreacted C₆₀ rather than performing the separation steps to isolate purified 16. Control experiments established that hexylamine does not react with 5, further implying that the amine should add only to 16. Addition of hexylamine to the crude product mixture containing 16 results in a product slate similar to that obtained upon adding hexylamine to a purified sample of 16. Thus the reaction producing ±28 can be run as a "one-pot" synthesis from C₆₀.
Unlike the hydration/rearrangement reaction leading to ±21, the reaction leading to ±28 does not require light. One-pot reactions run in total darkness produce comparable yields of ±28. The lack of photoinduction in the addition of hexylamine to 16 implies that the formation of ±28 does not involve an electron-transfer step. Another schematic difference in the formation of ±28 is the lack of an acid catalysis requirement for a facile reaction. Compound ±28 forms smoothly at room temperature in the absence of an acid catalyst. This observation is entirely consistent with the idea that nitrogen (of the primary aliphatic amine) is a better nucleophile than oxygen (of water).

The ¹H NMR and ¹³C NMR spectra of ±28 (Figures 31 and 32, respectively) contain many features similar to those seen in the analogous spectra for ±21. In the ¹H NMR spectrum (360 MHz, CS₂), the multiplets associated with the aromatic protons of the pyridine rings are similar to those seen for ±21. Each pyridine proton is unique.
Compound ±28 also contains a set of doublets centered at δ 6.5. Like the $^1$H spectrum for ±21, the coupling constant is 1.8 Hz, consistent with a $^5J_{HH}$ coupling between two protons attached to the fullerene cage in a 1,4-fashion. Since ±28 is racemic, the methylene protons on the hexyl chain are diastereotopic. If the product formed from amination of 16 was symmetric then the splitting pattern for the methylene protons closest to the nitrogen atom (the methylene farthest downfield) would exist as a neat triplet integrating for 2H. In the case of ±28, this methylene unit (at δ 3.3) appears as a complex multiplet. The multiplet does indeed integrate for the 2H, but there is extra $^2J$ and $^3J$ coupling because all of the protons are diastereotopic.

![Figure 31](image)

**Figure 31.** $^1$H NMR spectrum of ±28 in CS$_2$. 

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Figure 32. $^{13}$C NMR spectrum of ±28 in CS$_2$/CDCl$_3$. The triplet at 77.25 ppm is due to CDCl$_3$.

In the $^{13}$C NMR spectrum (90.56 MHz, CS$_2$/CDCl$_3$) of ±28, there are several identifying features. There are the six individual hexyl carbon signals from 10-50 ppm. Like ±21, there are two signals at δ 54 and 56 which are consistent with protons attached to the fullerene cage. Also visible are the signals at 70 and 80 ppm which correspond to the quaternary $sp^3$ carbons of the 4,5-dihydropyrazole moiety. Another structural feature that can be seen in the $^{13}$C NMR spectrum is the lack of symmetry in ±28. All of the pyridine, fullerene and pyrazole carbons are inequivalent to one another and consequently the $^{13}$C NMR spectrum shows 68 distinct carbon signals in the region between δ 120 and 160.
Figure 33 compares the $^1$H NMR spectra of ±21 and ±28. In both spectra, there are two doublets centered at approximately δ 6.5. In both spectra the corresponding $^5J_{HH}$ coupling constant is 1.8 Hz. Since the chemical shifts and coupling constants are similar, it is reasonable to assume that these protons attached to the fullerene cage in ±28 and ±21 are experiencing a similar electronic environment.

Figure 33. A comparison of the $^1$H NMR spectra for ±28 (a) and ±21 (b). Both spectra are an expansion of the region between 6.2 and 9.4 ppm. The hexyl protons for ±28 are therefore not pictured. In both spectra the singlet at δ 7.27 corresponds to residual CHCl$_3$. 

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Figure 34. A comparison of the $^{13}$C NMR spectra for ±28 (a) and ±21 (b). Both spectra are expansion of the region from 40-160 ppm. Thus, the five upfield carbon signals for the hexyl chain in ±28 are not shown. The resonance at 50 ppm in spectrum a is the downfield methylene carbon of ±28. In both spectra, the triplet at 77.25 ppm is due to CDCl$_3$ solvent.

As with the $^1$H NMR spectra, the $^{13}$C NMR spectra of ±28 and ±21 (Figure 34) are quite similar further suggesting similar molecular structures. In both cases there are two resonances near 54 and 56 ppm corresponding to the carbons bearing hydrogen on the fullerene cage. Both spectra also contain two fullerene $sp^3$ carbon resonances near δ 70 and 80 corresponding to the $sp^3$ fullerenic carbons of the pyrazole moieties. Since the chemical shifts of the four peaks between 50 and 80 ppm are similar for ±28 and ±21,
the substitution pattern on the fullerene cages should also be similar. The spectra show similarities in the range between 120 and 160 ppm as well. The chemical shift pattern for the pyridine carbons and the sp\(^2\)-hybridized carbons are comparable. The only significant difference between the \(^{13}\)C NMR spectra of ±28 and ±21 is the peak at 163 ppm in the spectrum for ±21. The peak corresponds to the carbonyl carbon between the dihydropyrazole ring and a pyridine ring. In ±28 the corresponding carbon is an imine carbon that appears at a higher field in the \(^{13}\)C spectrum.

The addition of water and hexylamine leads to ±21 and ±28, respectively. These racemic mixtures have not yet been resolved into their respective enantiomers. Addition of a chiral amine, however, should produce a potentially separable mix of diastereomers. The chiral amine chosen for this reaction was (R)-(+)/-\(\alpha\)-methylbenzylamine (29).

Equimolar amounts of C\(_{60}\) and 5 were dissolved in toluene and heated in the dark at reflux (110°C) for 24 hours (Scheme 48). Upon cooling of the solution to room temperature, a slight excess (1.2 equivalents) of 29 was added to the crude mixture containing 16. The reaction solution was stirred for 24 hours at room temperature. Evaporation of the toluene afforded a crude product mixture as a brown solid. The crude product was separated by column chromatography (20:1 CS\(_2\):ethyl acetate on silica gel). The amination/rearrangement product eluted as the third band from the column. Evaporation of the CS\(_2\):ethyl acetate eluent afforded the product, 30, as a mix of diastereomers. Attempts at separating the diastereomers proved unsuccessful and 30 was analyzed as a diastereomeric mixture.
Scheme 48. Synthesis of the diastereomeric mixture 30 from the reaction of 16 with 29.

Analysis of 30 using mass spectrometry was performed using both Fast-Atom Bombardment (FAB-MS) and Matrix-Assisted Laser Disorption (MALDI-MS) methods. The FAB-MS technique gave an M⁺ peak of 1050 m/z. The MALDI-MS technique afforded a MH⁺ peak of 1051 m/z. Both peaks are consistent for a parent ion of 1050 m/z. Examination of the ¹H and ¹³C NMR spectra of 30 shows that it is indeed a mixture of diastereomers. The upfield region (Figure 35) of the ¹H NMR spectrum for 30 (360 MHz, CS₂) reveals two doublets at 1.56 and 1.63 ppm, each integrating for 3H, and corresponding to the two unique α-methyl groups on the diastereomers. Another feature of Figure 42 is the quartet at 4.49 ppm. This quartet integrates for 2H and has the same coupling constant, 6.4 Hz, as the two upfield doublets. It is assigned to the single benzylic protons on the diastereomers. The chemical shifts for the two benzylic protons coincidentally overlap giving rise to a single quartet that integrates for 2H.
Figure 35. $^1$H NMR spectrum of 30 from $\delta$ 1.5-5.

Figure 36. Expansion of $^1$H NMR spectrum of 30 between 6 and 7 ppm.
Figure 36 shows an expansion of the $\delta$ 6-7 region of the $^1$H NMR spectrum for 30. In this narrow 1 ppm region, there exists four doublets each with a coupling constant of 1.8 Hz. The coupling constant and chemical shifts (6.50, 6.52, 6.67, and 6.82 ppm) are consistent with a pair of $1,4$-hydrogens bound to the fullerene cage of the two diastereomers. These shifts and couplings compare well to the fullerenic proton signals seen in the spectra for $\pm 28$ and $\pm 21$.

The aromatic region of the $^1$H NMR spectrum of 30 is complicated and provides only limited information. The collection of aromatic multiplets integrate for a total of 26 protons, which breaks down to 13 aromatic protons per diastereomer as expected for structures containing 1 set of phenyl protons (5H) and two sets of pyridine protons (8H) per diastereomer. Also discernible from the aromatic region of the $^1$H NMR spectrum is the lack of symmetry in each diastereomer.
In the $^{13}$C NMR spectrum (90.56 MHz, CS$_2$) of 30, the $sp^3$ region between 120 and 160 ppm is quite complicated. A total of 134 carbon resonances are expected in this region. Careful peak picking suggests a minimum of 102 signals with multiple cases of coincidental overlap, consistent with asymmetric 30. The $sp^3$ region of the $^{13}$C spectrum between 25 and 90 ppm reveals several structural clues (Figure 37). As in the $^1$H NMR spectrum, there are separate $^{13}$C resonances for each $\alpha$-methyl groups of the diastereomers, but only a single benzylic $^{13}$C signal for the two unique benzylic carbons. The benzylic chemical shifts coincidentally overlap. Four $^{13}$C signals are observed between 59 and 61 ppm corresponding to the fullerenic $sp^3$ carbons bearing hydrogen, two on each diastereomer. Likewise, there are four signals between 70 and 80 ppm corresponding to the four unique fullerenic $sp^3$ carbons attached to the dihydropyrazole

Figure 37. Expansion of the $^{13}$C NMR spectrum of 30 in the 25-90 ppm region.
rings of the two diastereomers. The shifts for these signals are reasonably close to those for analogous quaternary, fullerene $sp^3$ carbons on $\pm 28$ and $\pm 21$.

NMR and mass spectrometry data alone are not enough to conclusively assign the structure of 30 to the molecule that is the product of the reaction of 29 with 16. Other analytical methods must be employed to accurately assign the product structure. Towards this end, crystals of 30 were grown for analysis by X-ray diffraction. The crystals were grown first by slow evaporation of CS$_2$ solvent and then later by diffusion of hexane into a CS$_2$ solution. The crystals submitted for x-ray diffraction studies were black in color. X-ray analysis indicates that the empirical formula for the crystal is C$_{80}$H$_{19}$N$_5$-2CS$_2$, meaning that two molecules of CS$_2$ co-crystallized with a molecule of 30. Both diastereomers are present in the crystal, leading to disorder in the crystal lattice. The co-crystallization of the diastereomers of 30 can be related to orientational disorder seen in many fullerene crystals.

The relative amounts of each diastereomer found in the analyzed crystal were unequal with the major diastereomer having a population of 0.529(3). Figure 38 depicts the structure of the major diastereomer found. The x-ray crystal structure confirms the structural assignment of 30 as a fullerene derivative bearing a 1,4-dihydropyrazole ring fused to the fullerene skeleton.
Figure 38. A perspective view of the x-ray crystal structure for the major diastereomer of 30. The only hydrogen atoms shown are those on the fullerene cage at C1 and C4.
As expected, two hydrogens are attached to the C\textsubscript{60} skeleton at C1 and C4. The pyrazole ring in nearly flat and coplanar with one pyridine ring. Distortion of the fullerene cage is limited to the sites of attachment as is usual with fullerenes\textsuperscript{117}. The C1-C2 and C3-C4 bonds at 6,6-junctions on the fullerene skeleton are 1.670(8) and 1.712(10) Å for the major diastereomer and 1.720(8) and 1.731(11) Å for the minor diastereomer. In C\textsubscript{60}, the length of a 6,6-bond is 1.38Å. Also elongated is the C2-C3 bond. The C2-C3 bond in 30 is 1.622(5)Å but only 1.46Å in C\textsubscript{60}.

The structure of 30 (both major and minor diastereomers) has thus been assigned unequivocally. Since the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of 30 and ±28, are so similar, it seems reasonable that the analogous structures assigned to ±28 is also correct. It is possible to postulate a mechanism(Scheme 49) for the addition of primary amines to 16. The mechanism is similar to that already proposed for the formation of ±21 and ±22. However, reaction conditions for the formation of ±28 and 30 differ from those necessary for ±21 and ±22. Unlike hydration/rearrangement of 16, the amination/rearrangement reaction of 16 requires neither light nor acid catalyst. An acid catalyst is not needed as the amino nitrogen, a better nucleophile than oxygen, does not require an activated imine carbon for reaction. Since the amination/rearrangement reaction occurs in the dark, it is not likely that SET chemistry is involved.
Scheme 49. Proposed mechanism for the amination/rearrangement of 16.

(±28: R=n-hexyl; 30: R=(R)-(−)-α-methylbenzyl)
The proposed mechanism begins with attack of the amine nitrogen of the primary aliphatic amine upon 16 followed by H⁻ transfer to give intermediate i. Intermediate i then ring-opens to yield ii, a zwitterion with an iminium cation and a fullerene anion. Proton transfer from the iminium ion to the fullerene creates neutral ketazine iii. Addition of a ketazine nitrogen to the fullerene surface creates a 4,5-dihydropyrazole ring (iv). Proton transfer from the iminium ion of intermediate iv to the surface of the fullerene affords neutral adduct ±v, a generic structure for ±28 and ±30.

Scheme 50. Compound ±28 can be hydrolyzed to ±21, but iminohydrazide ±21 is not easily aminated to give “Schiff base” ±28.
Formally, ±28 and 30 are “Schiff base” derivatives of iminohydrazide ±21. However, addition of hexylamine or (R)-(+)−α-methylbenzylamine to ±21 under acidic conditions does not produce ±28 or 30, respectively (Scheme 47). Thus, iminohydrazide ±21 is not an intermediate in the synthesis of ±28 and 30. Interestingly, ±28 and 30 are converted to ±21, under fairly harsh hydrolysis conditions (conc. HCl, 80°C), thereby confirming the structural assignment for ±21.

The reaction between the monoadduct 16 and propanolamine was also studied in order to expand the repertoire of primary aliphatic amines that can be added to 16. Adduct ±31 was prepared in the same fashion as ±28 and 30. The reaction produced exclusively the amine addition product ±31 and no alcohol addition products (Scheme 51). Compound ±31, with its reactive primary alcohol function can be reacted further. The functionalized fullerene could act as a seed for polymer (including hyperbranched polymer) synthesis and could even be tethered to a solid support/resin.

![Scheme 51](image)

**Scheme 51.** Reaction between 16 and propanolamine to yield ±31.
2.5. Reaction of Monoprotic Nucleophiles with C_{60}-Tetrazine Monoadducts

C_{60}-tetrazine monoadduct 16 reacts smoothly with water and primary aliphatic amines, both diprotic nucleophiles. We sought to study the reactivity between 16 and several monoprotic nucleophiles thiols, alcohols, and secondary aliphatic amines.

2.5.1. Towards Formation of a “Holey” Fullerene. It can be speculated from the reaction of 16 with water and primary amines that the addition of a generic monoprotic nucleophile, R-XH (where X= S, O) or R_2NH would initially produce species i of Scheme 52. With only one proton available for transfer, rearrangement to a dihydropyrazole ring system should not occur. Since species i is unlikely to rearrange to a dihydropyrazole, it seems plausible that a second equivalent of RXH could add to give the diastereomeric mixture ii of Scheme 52. Species ii is a hexahydropyridazine that can be viewed as a cyclic, substituted hydrazine. We considered that the reaction of ii with a suitable oxidant such as lead tetraacetate (Pb(OAc)_4) would produce a diimide (species iii of Scheme 52) that could extrude N_2 leaving a fullerene fused cyclobutane, species iv of Scheme 52. A “retro [2+2]” reaction would effectively open structure iv to produce “holey” fullerene v that is calculated to be energetically preferred to species iv.
Scheme 52. Proposed route to a “holey” fullerene starting with the addition of two equivalents of a monoprotic nucleophile to C₆₀-tetrazine monoadduct 16.

The diameter of the opening in species v is calculated to be approximately 2.7 Å. It is anticipated that with the aid of heat and/or pressure, small molecules such as H₂, He and CO could be placed in the endohedral cavity of v. Insertion of H₂ into the fullerene...
cage could be detectable by $^1$H NMR spectroscopy as the resonance for the H$_2$, normally 4.2 ppm, would move upfield of 0 ppm due to shielding by the fullerene cage. The same type of upfield shift would be seen in the $^{13}$C NMR spectrum of $^{13}$CO inserted into the endohedral cavity of a fullerene cage. He insertion would be detectable using the $^3$He NMR technique developed by Saunders and coworkers at Yale.

### 2.5.2 Addition of aliphatic thiols to 16.

$n$-Nonanethiol, 32, was the first monoprotic nucleophile to be reacted with 16. Equimolar amounts of C$_{60}$ and 5 were heated in refluxing toluene overnight in the absence of light. Cooling the reaction solution to room temperature afforded 16 in a crude product mixture along with unreacted C$_{60}$ and 5. Since nonanethiol is unreactive towards both C$_{60}$ and 5, isolation of 16 was not necessary. To the crude mixture of 16 was added 2.2 equivalents of nonanethiol. The reaction pot was equipped for magnetic stirring and stirred for 24 hours at room temperature in total darkness (foil-wrapped glassware). Evaporation of the solvent gave a crude product mixture as a brown solid. $^1$H NMR spectra of the crude product mixture showed that there was no reaction between 32 and 16 under these reaction conditions. As with the addition of water to 16, the aliphatic thiol sulfur may require a catalyst in order to attack an unactivated imine carbon in 16.

With this in mind, the aliphatic thiol addition was repeated (Scheme 53), with an excess of 32 and in the presence of acidic SiO$_2$. This time, the crude $^1$H NMR spectrum showed evidence for a reaction and the crude product mixture was separated by flash silica column chromatography. The eluent used was 20:1 CS$_2$:ethyl acetate. The
product, ±33, elutes second after unreacted C₆₀. Upon evaporation of the column eluent, ±33 was obtained as a brown solid in 34% yield. Adduct ±33 shows a significant solubility in organic solvents and is particularly soluble in CS₂ and mixed solvents containing CS₂.

Scheme 53. Reaction between nonanethiol 32 and 16 and in the presence of acidic SiO₂ to produce ±33.
The aromatic region (7-9 ppm) of the $^1$H NMR spectrum for ±33 (Figure 39, 360 MHz, CS$_2$/CDCl$_3$), reveals a series of overlapping multiplets that integrate or a total of 9 protons. The lack of symmetry implies the addition of only one equivalent of 32 to the C$_{60}$-tetrazine monoadduct. Also, an N-H signal is apparently buried in the multiplet at approximately 8.6 ppm.

Figure 39. Expansion of the 7-9 ppm region of the $^1$H NMR spectrum for ±33. The singlet at 7.27 ppm is residual CHCl$_3$. 

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In the region between 0.5 and 3 ppm (Figure 40), the resonances for the protons on the C₉ chain can be seen. The two multiplets farthest downfield in this region, at 2.29 and 2.52 ppm, respectively, each integrate for 1H and correspond to the two diastereotopic protons attached to the methylene carbon closest to the sulfur atom on the nonyl chain. The diastereotopic nature of the protons is consistent with ±33. The diastereotopicity can also be seen in the multiplet centered at δ 1.55 that arises from the two protons attached to the methylene carbon β- to the sulfur. The rest of the alkyl protons can be seen in the multiplet at 1.3 ppm (12H) and the triplet-like resonance at 0.86 ppm (3H).
The corresponding $^{13}$C NMR spectrum (125 MHz, CS$_2$/CDCl$_3$) is also consistent with the assigned structure ±33. In the downfield region of the spectrum (100-160 ppm), over 60 $^{13}$C signals can easily be identified. These signals arise from 10 pyridyl carbons, the lone $sp^2$ hybridized carbon on the tetrahydropyridazine unit, and the 58 distinct $sp^2$ hybridized carbons of the fullerene moiety. The upfield portion of the spectrum (0-100 ppm) shows nine signals corresponding to the nine carbons of the nonyl chain in the in the region between 10 and 50 ppm. Between 60 and 85 ppm, another three resonances are observed which correspond to the three quaternary carbons in ±33.

One equivalent of nonanethiol, 32, adds smoothly to 16 in the presence of acidic SiO$_2$ to afford ±33. The path to the “holey fullerene” of Scheme 52, however, requires the addition of two molecules of 32 to the C$_{60}$-tetrazine monoadduct. Towards this end, the addition of a second equivalent of 32 to ±33 was attempted. A second equivalent of 32 could add to ±33 to give a mixture of cis (34) and trans (35) addition products (Scheme 54). An examination of molecular models suggest greater steric strain in 34. One might therefore anticipate 35 to be the major diastereomer formed.
Scheme 54. Possible products from the addition of a second equivalent of 32 to ±33.

To a solution of ±33 in CHCl₃ was added an excess of 32 and a catalytic amount of SiO₂. The CHCl₃ was heated to reflux for 17 hours. Upon completion of the reflux, the solvent was evaporated and the crude product mixture was examined by ¹H NMR spectroscopy. The ¹H NMR spectrum showed that no reaction had occurred in the refluxing CHCl₃. The experiment was attempted again with toluene (bp. 111°C) as solvent. The toluene reaction was heated to reflux for 17 hours the toluene solvent was evaporated, and the crude product again examined by ¹H NMR spectroscopy. The ¹H NMR spectrum revealed complete conversion of ±33 to ±21. The transformation of ±33 to ±21 is illustrated in Scheme 55. Instead of an acid catalyzed addition of a second equivalent of 32 to ±33, the SiO₂ apparently catalyzes the removal of nonylthiol from ±33 to yield 16. In, ambient light the hydration/rearrangement of 16 yielded ±21.

Presumably, the the imine system is stabilized by the new amine nitrogen, thus
preventing nucleophilic attack. While unintentional, the conversion of \( \pm 33 \) to \( \pm 21 \) does provide evidence for the structure assigned to \( \pm 33 \). Formation of \( \pm 21 \) must proceed through tetrazine monoadduct 16. Since 16 is the starting material from which \( \pm 33 \) is produced, conversion of \( \pm 33 \) to 16 should involve the reverse reaction.

\[
\begin{align*}
34.35 & \xrightarrow{\text{32, cat. } SiO_2, \text{ toluene, } 110^\circ C} \pm 33 \\
& \xrightarrow{\text{32, cat. } SiO_2, \text{ toluene, } 110^\circ C} \pm 21 \\
& \xrightarrow{\text{SiO}_2, \text{ hv, water}} 16
\end{align*}
\]

**Scheme 55.** Conversion of \( \pm 33 \) to \( \pm 21 \) in refluxing toluene and in the presence of silica gel and ambient light.
2.5.3. Addition of Aromatic Thiols to 16. In order to expand the repertoire of thiols that can be added to 16, the aromatic thiols thiophenol (36) and 1-naphthalenethiol (37) were studied. In the addition of 36 to 16, 2.2 equivalents of thiol was added to a crude product solution of 16 in toluene. The solution was stirred at room temperature in the absence of light for 17-24 hours. Upon evaporation of the toluene solvent, the crude product mixture was separated by silica gel column chromatography using 20:1 CS$_2$:ethyl acetate as the eluent. The purple-colored band of unreacted C$_{60}$ elutes first from the column followed the product of thiophenol addition to 16. This product is assigned the structure ±38. The third band to elute is ±21 resulting from the hydration/rearrangement of unreacted 16 on the silica gel column in ambient light. Switching the mobile phases from CS$_2$:ethyl acetate to a more polar CHCl$_3$:MeOH (20:1) solution affords recovery of unreacted 5 and small quantities of non-fullerene by-product.
Scheme 56. Thiophenol (36) will add once to 16 giving rise to the racemate ±38, but not twice to give the diastereomeric mixture 39.

Like nonanethiol 32, thiophenol 36 adds only once to 16 (Scheme 56) to afford ±38. Evidence for this structure can be found in the examination of the $^1$H and $^{13}$C NMR spectra for ±38. In the $^1$H NMR spectrum of ±38 (Figure 41, 360 MHz, CS$_2$/CDCl$_3$) all of the proton resonances for the molecule can be found in the region between δ 7.0 and 9.0. The resonances in this region integrate for a total of 14 protons: 8 pyridine, 5 phenyl and 1 N-H. The ratio of pyridine to phenyl protons (8:5) indicates only one thiophenol addition. The multiplet pattern seen implies a lack of symmetry in ±38, a situation reminiscent of ±33. The broad singlet at 7.85 ppm is assigned to the N-H proton of ±38.
Figure 41. $^1$H NMR spectrum of $\pm 38$. The singlet at 7.27 is residual CHCl$_3$.

The $^{13}$C NMR spectrum of $\pm 38$ (125 MHz, CS$_2$) serves to reinforce some of the conclusions drawn from the $^1$H spectrum. A look at the full spectrum reveals the lack of symmetry seen in $\pm 38$, with 70+ resonances observed. Compound $\pm 38$ is predicted to have a total of 78 $^{13}$C signals. In the region between 60 and 85 ppm, three $^{13}$C signal are expected. In order to detect all three $^{13}$C signals, a paramagnetic relaxation agent must be employed. In the course of working with the C$_{60}$-tetrazine monoadducts, it was noticed
that the $sp^3$ hybridized carbons of the various compounds were exceedingly slow to relax on the NMR timescale. Since slow relaxation causes a decrease in signal intensity, failure to use a paramagnetic relaxation agent such as chromium (III) acetoacetate results in the observation of only two $^{13}$C signals in the 60 to 85 ppm region.

Chemical testing also sheds some light on the relationship between ±33 and ±38. A sample of ±38 was subjected to the same conditions that caused the transformation of ±33 to ±21, refluxing in toluene in the presence of acidic SiO$_2$. If ±38 is structurally similar to ±33, then it should behave in a similar way when subjected to the same hydrolysis conditions. A 15 mg sample of ±38 was dissolved in toluene along with 10 mg of silica gel. The toluene solution was heated to reflux for 17 hours after which time the silica was filtered off. Evaporation of the toluene afforded a brown solid. Upon removing the reaction flask from the rotary evaporator, the strong smell of thiophenol was instantly noticed. The crude was washed twice with hexane to remove the thiophenol and then examined by $^1$H NMR spectroscopy. The NMR spectrum showed a mixture of ±38 and ±21, mirroring the result obtained with ±33 and implying that ±33 and ±38 have similar structures.

In order to further probe the chemistry between aromatic thiol and C$_{60}$-tetrazine monoadduct 16, the reaction between naphthlanethiol 37 and 16 was also studied. Under conditions identical to those that give ±38, the naphthyl analog ±40 is produced in 36% isolated yield (Scheme 57). The $^1$H NMR spectrum (360 MHz, CS$_2$) of ±40 is similar to that of ±38. The $^1$H NMR spectrum integrates for a total of 16 protons, with the pyridine to naphthalene ratio (8:7) consistent with a single addition of 37. The abundance of multiplets suggests a lack of symmetry. In the $^{13}$C NMR spectrum of ±40 (90 MHz,
two carbon peaks are missing in the region between 60 and 90 ppm presumably due to slow carbon relaxation.

Scheme 57. Reaction between 37 and 16 to produce ±40, the naphthalene analog of ±38.

In the addition of the aromatic thiols 36 and 37 to 16 to produce ±38 and ±40, respectively, the nucleophilic attack of the sulfur upon an imine carbon is accomplished without the aid of a catalyst. The lack of a need for an acid may be related to the acidic character of an aromatic thiol proton. Deprotonation of the thiol leads to a stable aromatic thiolate anion. The thiolate anion is a much better nucleophile than a neutral thiol. Since 16 contains both pyridazine and pyridine nitrogens, it is reasonable to conclude that the aromatic thiols 36 and 37 are first deprotonated to give the
corresponding thiolate anions that then add smoothly across and imine bond in 16 to give ±38 or ±40 (Scheme 58).

Scheme 58. Proposed pathway for the addition of aromatic thiols to 16.
2.5.4. Addition of Alcohols to the C₆₀-Tetrazine Monoadduct. Following the successful addition of aromatic and aliphatic thiols to 16, a study of the reaction of alcohols and 16 was undertaken. The first alcohol to be reacted with 16 was the simplest alcohol, methanol. As with the thiol-addition reactions, a crude solution of 16 was first prepared by refluxing an equimolar amount of C₆₀ and 5 in toluene with the rigorous exclusion of light. With a crude solution of 16 in hand, a slight excess of methanol was added to the toluene solution along with approximately 50 mg of SiO₂. Care was taken to keep the reaction solution in total darkness. The reaction flask was equipped with a magnetic stirrer and stirred at room temperature for 17-24 hours. Upon completion of the reaction, the solvent was removed with a rotary evaporator and the crude product mixture separated by column chromatography (silica gel, 10:1 CS₂:ethyl acetate). The first band to elute is unreacted C₆₀ followed by ±21. Hydration/rearrangement product ±21 presumably forms from unreacted 16 on the silica column. The third band removed from the column is the methanol addition product assigned structure ±41. Changing the eluent to a more polar mixture of 20:1 CHCl₃:MeOH removes unreacted 5 and some tetrazine-degradation products.
Scheme 59. Formation of methanol addition product, ±41.

The proposed pathway for the formation of ±41 is similar to that proposed for the addition of aliphatic thiols. The acid catalyst activates one of the imine carbons of the dihydropyridazine moiety towards nucleophilic attack. Methanol proceeds to attack the activated imine carbon followed by proton-transfer to give ±41. The $^1$H NMR spectrum for ±41 (360 MHz, CS$_2$) contains features that aid in the structural assignment. First, there is a singlet at 3.50 ppm which corresponds to the methoxy protons. This singlet integrates for 3H indicating that methanol adds just once to 16. In the aromatic region ($\delta$ 7-9), eight resonances are observed for the eight unique pyridine protons. Also in the aromatic region, a broad singlet is observed and assigned to the N-H proton in the tetrahydropyridazine moiety of ±41. An acceptable $^{13}$C NMR spectrum for ±41 was not obtained due to poor solubility.
2.5.5. Addition of Secondary Amines to the C₆₀-Tetrazine Monoadduct. The reaction between secondary aliphatic amines and 16 was also studied. The simplest of the secondary amines, dimethylamine, was chosen for addition. In order to prevent possible side-reactions with water, dimethylamine was distilled from its commercially available 40% aqueous solution.

A crude solution of 16 was prepared by reacting C₆₀ with 5 in refluxing toluene while rigorously excluding light. To the toluene solution was added a slight molar excess of dimethylamine and approximately 50 mg of SiO₂. The reaction solution was stirred in the dark at room temperature for 20 hours. ¹H NMR spectra of the crude product mixture reveals the presence of weak signals that could be assigned to a dimethylamine adduct of 16 (tentatively assigned ±42). Separation by preparatory TLC gives the product in such small quantities (<2 mg) that proper structural assignment by spectroscopic methods is nearly impossible. C₆₀, ±21 and 5 are recovered in reasonable yields suggesting the reaction between dimethylamine and 16 is quite sluggish and proceeds in low yield.

A possible explanation for the low yielding reaction is the steric interaction between 16 and dimethylamine. Even though the imine carbon is activated towards nucleophilic attack by the acid catalyst, the imine carbon is quite crowded, a bulky fullerene one side and a pyridyl ring on the other. Secondary amines may be sufficiently bulky to preclude facile addition.

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Scheme 60. Proposed low-yielding reaction between dimethylamine and 16 to form ±42.
2.6. Other Reactions Involving C₆₀-Tetrazine Monoadducts

2.6.1. Addition of Electrophiles to C₆₀-Tetrazine Monoadducts. Nucleophiles, both diprotic and monoprotic, add to C₆₀-tetrazine monoadducts smoothly and in chemoselective fashion. C₆₀-tetrazine monoadducts should also be susceptible to electrophile addition, a process that could lead to a “holey” fullerene as described above. Molecular halogens Cl₂ and Br₂ are known to undergo electrophilic additions to alkenes and seemed a reasonable choice for addition to a C₆₀-tetrazine monoadduct. A proposed pathway for halogenation of 18 is illustrated in Scheme 61. An imine carbon of 18 attacks a polarizeable molecule of halogen leading to the stabilized cation i. The halide counter-ion (X') attacks the cation affording the dihalide ii which could then extrude a molecule of N₂ giving rise to the fullerenocyclobutane iii. A "retro" [2+2] electrocyclic ring-opening of iii leads to the desired "holey" fullerene, iv of Scheme 61.
Scheme 61. Proposed halogenation of 18 to produce the open fullerene iv.

The addition of Cl₂ to ketazines (Scheme 62) is reported in the literature. Benzophenone ketazine adds Cl₂ in a 1,4-fashion to give a dihalodiimide. Since the pyridazine unit in 18 is a cyclic ketazine, it was hypothesized that halogens could add in the desired 1,4-fashion. However, McBride reports that cyclic ketazines avoid 1,4-halogenation producing little or no cyclic diimide. He hypothesized that cyclic ketazines...
are not able to stabilize the intermediate carbocation formed to the same extent as an acyclic ketazine (Scheme 62), thus explaining their reduced reactivity.

Scheme 62. McBride reports that acyclic ketazines halogenate in 1,4-fashion much more readily than cyclic ketazines suggesting the importance of a linear heterocumulene-like cationic intermediate that is less significant in a cyclic structure.
The C₆₀-tetrazine monoadduct 18 was prepared and isolated as described in Section 2.2. Monoadduct 18 was dissolved in CHCl₃ and chilled in an ice/water bath with magnetic stirring. Light was rigorously excluded from the reaction. Chlorine gas was bubbled into the solution of 18 over a period of 24 hours while the solution was allowed to warm from 0 °C to room temperature. Once the reaction period had ended, nitrogen was bubbled through the reaction solution to purge unreacted chlorine gas from solution. The solvent was evaporated and the crude reaction mixture was examined by ¹H NMR. The ¹H NMR spectrum indicates a vast array of chlorination products. The formation of a large product slate indicates halogenation of the fullerene surface, not entirely unexpected considering that C₆₀ is known to halogenate under similar reaction conditions,⁴⁷ and a huge excess of Cl₂ was employed. In order to probe this point, the reaction would need to be performed again using a stoichiometric quantity of Cl₂.

The reaction between monoadduct 18 and molecular bromine, Br₂, was also studied. Bromine is also known to add readily to C₆₀,⁴⁸-⁵¹ so issues of chemoselectivity were considered. To a solution of monoadduct 18 in CHCl₃ was added 1.2 equivalents of Br₂ predissolved in chloroform. The reaction was stirred in the dark at 0°C for 24 hours. After evaporation of the solvent and any residual bromine, the crude product mixture was examined by ¹H NMR spectroscopy. As with the chlorination reaction NMR spectra of the crude reaction mixture show a large mixture of compounds, indicating bromination of the fullerene surface and a lack of the desired chemoselectivity.

The reaction between monoadduct 18 and I₂ was also studied. Iodine does not add to C₆₀ and would therefore seem to be a better candidate for chemoselective addition to the dihydropyridazine moiety. Towards this end, 1.5 equivalents of molecular iodine
was added to a CH$_2$Cl$_2$ solution containing 18. The solution was stirred in the dark at room temperature for 24 hours. Upon evaporation of the solvent and removal of excess iodine, the crude reaction mixture was examined by $^1$H NMR spectroscopy. Unlike the chlorination and bromination reactions, NMR spectra of the crude reaction mixture from iodine addition show no reaction between the iodine and monoadduct 18. It appears that I$_2$ is sluggish to react with fullerene and the dihydropyridazine on 18.

Although more experiments are needed, it appears that bromination and chlorination of C$_{60}$-tetrazine monoadducts may lack the desired chemoselectivity to be useful. A careful study of the addition of stronger electrophiles including carbocations would be useful.
2.6.2. Free-Radical Addition to C₆₀-Tetrazine Monoadducts. Free radical additions to C₆₀-tetrazine monoadducts have also been studied as they, too, potentially offer a route to a "holey" fullerene. In the proposed pathway, Scheme 63, one equivalent of a radical adds to monoadduct 18 resulting in resonance stabilized radical i. A second radical addition produces diimide ii that could extrude N₂ followed by a retro-[2+2] ring-opening to give an opened ("holey") fullerene structure.

Scheme 63. Proposed free-radical addition to monoadduct 18.
The first free radical addition reaction attempted was the reaction of the free-radical initiator azoisobisbutyronitrile (AIBN) with 18. Under conditions of heat, AIBN is known to degrade to two equivalents of radical that can which reacts with 18 to produce a cyclic diimide. The reaction was carried out using a freshly prepared sample of 18 dissolved in dry THF with the reaction flask covered in foil to exclude light. A stoichiometric quantity of AIBN was added to the flask. The flask containing the reaction solution was heated to reflux (66 °C) for 24 hours. Upon completion of the reflux time, the solvent and excess AIBN was removed. The crude product mixture was examined by ¹H NMR spectroscopy. The NMR spectrum indicated no reaction between 18 and any free-radicals as the only compound detected was the unreacted monoadduct 18

Another free-radical approach was tried. In the literature it is known that lead tetraacetate (Pb(OAc)₄) will react with a ketazine to yield a diacetyl compound according to Scheme 64.¹¹⁸ In the reaction, an acetyl radical fragments from the Pb(OAc)₄ forming ·OAc and Pb(III)(OAc)₃. The acetyl radical adds to the ketazine to give a resonance-stabilized radical intermediate that can add a second ·OAc fragments to produce lead(II) acetate and a diacetyl diimide.
Scheme 64. Free radical addition of Pb(OAc)$_4$ to a ketazine to produce a diacetyldiimide.

For the reaction of Pb(OAc)$_4$ with 18, a freshly prepared solution of 18 in CH$_2$Cl$_2$ was covered in foil to exclude light. A stoichiometric quantity of Pb(OAc)$_4$ was added to the solution and heated at reflux (40 °C) for 24 hours. Once the heating was finished, the solution was washed several times with water to remove excess Pb(OAc)$_4$ and dried over sodium sulfate. Evaporation of the solvent left the brown crude reaction mixture for examination by $^1$H NMR. The NMR spectrum revealed that there was no reaction between 18 and the lead tetraacetate. The reasons for the lack of reactivity are currently unclear.
2.6.3. Electro cyclic Additions to C_{60}-Tetrazine Monoadducts. A final attempt to form the open fullerene involved a [4+2] Diels-Alder cycloaddition to a C_{60}-tetrazine monoadduct. Using the dihydropyridazine moiety as a diene (Scheme 65), reaction with a suitable dienophile could produce a tricyclic structure that can extrude N\textsubscript{2} leaving a bicyclic cyclobutane fused fullerene that could ring-open to an open fullerene structure.

![Scheme 65. Proposed reaction of monoadduct 16 as a diene with a dienophile (cyclopentene) to produce an open ("holey") fullerene.](image)

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The reaction was attempted using both 16 and 18 as dienes. For use as
dienophiles, the electron-rich norbornene and the electron-deficient N-phenylmaleimide
were studied. There is literature evidence to suggest that the addition of trifluoroacetic
acid (TFA) can serve to catalyze Diels-Alder reactions involving pyridazines as the
diene.\textsuperscript{109} With this information in hand, each Diels-Alder reaction was tried both with
and without TFA as catalyst. The general reaction conditions involved a freshly prepared
solution of either 16 or 18 dissolved in toluene. To the solution of 16 or 18 was added a
stoichiometric amount of dienophile. The reaction solution was heated to reflux
overnight. The solvent was evaporated and the crude product mixture examined by \textsuperscript{1}H
NMR spectroscopy. In the cases where TFA was used as a catalyst the reflux solvent
was changed to THF as TFA boils at 78°C. Since SiO\textsubscript{2} was used successfully to catalyze
the addition of nucleophiles to 19, silica gel was also utilized as a catalyst in refluxing
toluene.

In all cases, crude \textsuperscript{1}H NMR spectra indicated that no reaction had occurred
regardless of dienophile or of catalyst present. In the cases of fullerene adducts 19 and
21, the aryl substituents on the dihydropyridazine rings are forced in a configuration that
is nearly orthogonal to the pyridazine ring. It is conceivable that these substituents
interfere with approaching dienophiles, further slowing down the Diels-Alder reaction.
2.7. Miscellaneous Reactions with $C_{60}$

An early reaction of $C_{60}$ was the formation of the $C_{120}$ molecule by the photodimerization of two equivalents of $C_{60}$. If one considers $C_{120}$ as two $C_{60}$'s connected by a 0 carbon bridge, then it is conceivable that a series of all-carbon molecules could be formed by the connection of two (or more) fullerenes by bridges $n$ carbons in length. In order to build such a series the synthesis of the next bridged fullerene, $C_{121}$, was undertaken (Figure 42).

Figure 42. The two “dumbbell” shaped molecules $C_{120}$ and $C_{121}$.

The reagent chosen for the formation of the one-carbon bridge in $C_{121}$ was carbon suboxide ($O=\overset{\equiv}{C}=\overset{\equiv}{C}=\overset{\equiv}{C}=O$). Carbon suboxide reacts with alkenes, either
photochemically or thermally, in a reaction such that a carbon is inserted into the alkene to form an allene with the generation of two equivalents of CO (Scheme 66). The first step is the photochemical or thermal extrusion of CO from the carbon suboxide forming a ketenylidene carbene which adds across the double-bond of an alkene to afford a cyclopropyl ketene. Next, another equivalent of CO is extruded leaving behind a cyclopropylidene carbene which rearranges to an allene.

\[
\begin{align*}
O=C&=C=C=O \xrightarrow{\text{hv or } \Delta} O=C&=C&=O \+ CO \\
\downarrow & \quad \downarrow \\
H_2C&=CH_2 & \xrightarrow{\text{hv or } \Delta} \xrightarrow{-CO} O=C&=C
\end{align*}
\]

Scheme 66. Reaction of carbon suboxide with ethylene to form allene.

If, however, the cyclopropylidene carbene was unable to rearrange to an allene, then the carbene would be able to react with another equivalent of alkene to form spiro-fused cyclopropane rings. In the reaction of C_{60} with carbon suboxide, rearrangement to allene is not possible and therefore C_{121} should form (Scheme 67).
Scheme 67. Reaction of C<sub>60</sub> with carbon suboxide to form C<sub>121</sub>.

Carbon suboxide (b.p. 6.7°C) was formed by the double dehydration of malonic acid with P<sub>2</sub>O<sub>5</sub> at 150°C using the apparatus illustrated in Figure 43. Malonic acid and P<sub>2</sub>O<sub>5</sub> (10-fold excess by weight) were thoroughly mixed in round-bottom flask a. Trap b was cooled with an ice/water bath and trap e was cooled with liquid N<sub>2</sub>. Stainless steel bomb d was charged with C<sub>60</sub> predissolved in ODCB and cooled with a dry ice/acetone bath. The system was placed under vacuum. The low pressure in conjunction with the
Figure 43. Apparatus for the synthesis of carbon suboxide. The apparatus consists of a round bottom-flask a heated connected in series with trap b, trap c and stainless steel bomb d. The bomb can be removed from the system for heating.

bath $P_2O_5$ served to dry the apparatus. Flask a was heated under vacuum to 150°C with an oil bath prompting the solid state dehydration of malonic acid to form carbon suboxide. The carbon suboxide gas, along with the by-products CO$_2$ and water and the side product acetic acid, traveled through trap b which condensed out most of the water and acetic acid. The gas stream next traveled to trap c where all compounds were frozen by the liquid nitrogen. When gas evolution in flask a stopped, the heat was removed and the apparatus allowed to come to atmospheric pressure. The liquid nitrogen bath was next removed from trap c which caused the vaporization of the CO$_2$ and the carbon suboxide, and leaving behind more water and acetic acid. The gases next traveled through the chilled bomb d where the carbon suboxide gas liquified and was trapped in the bomb, with the CO$_2$ allowed to escape to the atmosphere.
When all carbon suboxide has been trapped in bomb d, it was removed from the carbon suboxide generating apparatus and allowed to come to room temperature, thus melting the ODCB and allowing some of the carbon suboxide to dissolve in the fullerene solution.

Reaction of the carbon suboxide with C$_{60}$ was achieved by heating the bomb at temperatures between 260° and 300°C for 24 hours. The crude product mixture was separated by column chromatography (CS$_2$ as eluent), which resulted in the isolation of a brown solid product which was sparingly soluble in CS$_2$ and ODCB and insoluble in other organic solvents. $^{13}$C NMR in conjunction with FAB Mass Spectrometry did not lead to a definite structural assignment of the product. The overwhelming excess of carbon suboxide present in the reaction coupled with the poor solubility of the product leads to the conclusion that the brown solid is most likely a mixture of oligomeric fullerene species.
3. CONCLUSION AND FUTURE WORK

Several 1,2,4,5-tetrazines, specifically 4, 5, and 12, undergo an inverse electron-demand Diels-Alder reaction with C_{60}. The reactions produce a non-isolable bicyclic intermediate that rapidly extrudes nitrogen to afford C_{60}-tetrazine monoadducts 16, 18, and 20 (after a 1,3-H shift). Monoprotic and diprotic nucleophiles readily add to the C_{60}-tetrazine monoadducts. In the case of the diprotic nucleophiles (water, primary amines), the resulting compounds, a rapid rearrangement to form dihydropyrazole moieties follows nucleophilic addition. The rearrangement involves the formation of new 1,4-fullerenic C-H bonds adjacent to the dihydropyrazole function. Monoprotic nucleophiles (thiols, alcohols, secondary amines) add to C_{60}-tetrazine monoadducts in a 1:1 fashion giving rise to racemic tetrahydropyridazine structures. These tetrahydropyridazines can be viewed as the first step of a reaction sequence leading to “holey” fullerene structures in which a 6,6-fullerenic bond has been cleaved.

Future directions for this work are threefold. It would be advantageous to synthesize more C_{60}-tetrazine monoadducts in order to further probe the reactivity trends seen and to begin an extensive electrochemical study. Second, it is desirable to expand the study of nucleophilic addition chemistry with the addition of new diprotic and monoprotic nucleophiles. Moreover, the addition of nonprotic nucleophiles such as alkyl lithium or Grignard reagents should be studied. Since these nonprotic nucleophiles are much stronger than the mono- or diprotic reagents used, they may be better suited for chemo-selective and regio-selective addition across the dihydropyridazine moiety of C_{60}-
tetrazine monoadducts. Finally, the demonstration of successful electrophilic, electrocyclic, and free-radical additions to C₆₀-tetrazine monoadducts should be undertaken. Only a small amount of work has been done so far in these areas to date.
4. EXPERIMENTAL

4.1. General Methods

**\(^1\)H NMR Spectra.** \(^1\)H NMR spectra were obtained on a Bruker AM 360 FT-NMR operating at 360 MHz and a Varian INOVA 500 FT NMR operating at 500 MHz. All chemical shift (\(\delta_H\)) values are reported in parts per million (ppm) relative to (CH\(_3\))\(_4\)Si (TMS).

**\(^13\)C NMR Spectra.** \(^13\)C NMR spectra were obtained on a Bruker AM 360 FT-NMR operating at 90 MHz and a Varian INOVA 500 FT-NMR operating at 125 MHz. All chemical shift (\(\delta_C\)) values are reported in parts per million (ppm) relative to (CH\(_3\))\(_4\)Si (TMS).

**Infrared Spectra.** IR spectra were obtained on a Nicolet 205 FT-IR and reported in wavenumbers (cm\(^{-1}\)).
4.2. Solvents

All solvents were used without further purification unless otherwise noted.

Acetic Acid (CH₃CO₂H) was obtained from J.T. Baker Chemical Co.

Acetone (reagent grade) was obtained from Fischer Chemical Company.

Benzene (C₆H₆) was obtained from EM Science.

Carbon Disulfide (CS₂) was obtained from EM Science.

Chloroform (CHCl₃) was obtained from EM Science.

Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories.

1,2-Dichlorobenzene (ODCB) was obtained from Acros Organics Co.

Dichloromethane (CH₂Cl₂) was obtained from EM Science.

Diethyl Ether ((CH₃CH₂)₂O) was obtained from VWR Chemical Co.

Ethanol (anhydrous) was obtained from Pharmco.

Ethanol (95%) was obtained from Pharmco.

Ethyl Acetate (CH₃CO₂CH₂CH₃) was obtained from Pharmco.

Methanol (CH₃OH) was obtained from Pharmco.
Tetrahydrofuran (THF) was obtained from Acros Organics Co. It was distilled over Na° from a solution containing benzophenone as indicator.

Toluene (PhCH₃) was obtained from EM Science and distilled over Na° in some cases.

4.3. Chromatography

Sand was obtained from Fischer Chemical Co.

Silica Gel (40 μm Flash Chromatography Packing) was obtained from J.T. Baker.

Silica Gel (38-75 μm Flash Chromatography Packing) was obtained from Natland International Co.
4.4. Reagents

*All reagents were used without further purification unless otherwise noted.*

3-Aminopropanol (propanolamine) was obtained from Acros Organics Co.

Azobisisobutyronitrile (AIBN) was obtained from Aldrich Chemical Co.

Benzonitrile (PhCN) was obtained from J.T. Baker Co. and Aldrich Chemical Co.

Bromine (Br₂) was obtained from Acros Organics Co.

[60]-Fullerene (C₆₀) was obtained from MER Co.

2-Cyanopyridine (C₆H₄N₂) was obtained from Aldrich Chemical Co.

Diemethylamine (40 % aq.) was obtained from Alfa Aesar Chemical Co. and distilled prior to use.

n-Hexylamine (C₆H₁₃NH₂) was obtained from Aldrich Chemical Co.

5N Hydrochloric Acid in Isopropanol (5N HCl-iProH) was obtained from Acros Organics Co.

Hydrazine (anhydrous) was obtained from Alfa Aesar Chemical Co.

Isoamyl Nitrite was obtained from Acros Organics Co.

Iodine (I₂) was obtained from Mallincrodt Chemical Co.
4-Methoxyphenylacetonitrile was obtained from Aldrich Chemical Co.

(R)-(+) α-Methylbenzylamine was obtained from Aldrich Chemical Co.

1-Naphthalenethiol was obtained from Eastman Kodak Co.

n-Nonanethiol (C₉H₁₉SH) was obtained from Aldrich Chemical Co.

Norbornene was obtained from Aldrich Chemical Co.

N-Phenylmaleimide was obtained from Aldrich Chemical Co.

Thioacetamide (CH₃CSNH₂) was obtained from Aldrich Chemical Company.

Thiophenol was obtained from Aldrich Chemical Company.

Trifluoroacetic Acid (TFA) was obtained from Aldrich Chemical Company.
4.5. Syntheses

3,6-dimethyl-1,2,4,5-tetrazine (2) - To a 100 mL round-bottom flask filled with 50 mL of anhydrous EtOH was added thioacetamide (1.12 g, 0.015 mol). The flask was equipped for magnetic stirring. To the thioacetamide solution was added 0.5 mL (0.02 mol) anhydrous hydrazine. The H₂S which evolves from the reaction was trapped using a 10% aq. NaOH solution. The reaction was stirred 20 hours to ensure that the reaction reached completion and also to ensure that all evolved H₂S had been trapped. Water was added to the yellow/green crude solution. The aqueous ethanol solution was then extracted with diethyl ether. Ambient oxygen caused all 9 present in the alcohol/water solution to oxidize to 2 preventing isolation of the dihydrotetrazine. After several ether extractions, the ether extracts were combined and the resulting ethereal solution was concentrated to a volume of approximately 10 mL. Removal of the ether solvent was accomplished using a rotary evaporator at 0°C. Tetrazine 2 was isolated from the ether solution by subjecting the solution to a vacuum and trapping the tetrazine on a dry ice/acetone coldfinger. Compound 2 (0.760 g, 0.007 mol) was isolated in 47% crude yield as a highly volatile magenta solid.

2: ¹H NMR (360 MHz, CDCl₃) δ 2.72 (s, 6H); ¹³C NMR (90.56 MHz, CDCl₃) δ 15.6, 165.3.
3,6-diphenyl-1,2,4,5-tetrazine (4)- To 25 mL of 1-propanol in a 100 mL round-bottom flask was added 5g (0.049 mol) benzonitrile (PhCN). To the ethanol solution was next added 2g (0.0625 mol) anhydrous H\textsubscript{2}NNH\textsubscript{2}. The solution was heated to reflux for 48 hours during which the solution color changed from a pale yellow to orange. The solution was cooled first to room temperature and then to 0°C with an ice/water bath. The crude dihydrotetrazine 10 fell out of solution as orange plates. The crystals were collected by vacuum filtration and washed several times with cold 95% ethanol. The isolated 10, upon exposure to air, immediately began to oxidize. Compound 10 was suspended in CHCl\textsubscript{3} An excess of isoamyl nitrite was added to the CHCl\textsubscript{3} suspension. The reaction solution was heated to reflux for 45 min. Upon cooling to room temperature, the CHCl\textsubscript{3} and isoamyl nitrite were removed with a rotary evaporator. The crude tetrazine 4 was recrystallized from 95% ethanol and isolated as a shiny magenta solid in 42% yield.

4: \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \delta 7.63 (m, 6H), 8.66 (m, 4H); \textsuperscript{13}C NMR (90.56 MHz, CDCl\textsubscript{3}) 5128.0, 129.3, 131.8, 132.7, 164.0.

3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (5)- Dihydrotetrazine 8 (2.1 g, 8.78 mmol) was suspended in 50 mL of CHCl\textsubscript{3}. To the CHCl\textsubscript{3} suspension was added excess isoamyl nitrite. The suspension of was heated to reflux for 1.5 hours. Upon cooling to room temperature, the CHCl\textsubscript{3} and isoamyl nitrite were removed with a rotary evaporator. The crude tetrazine 5 was recrystallized from 95% EtOH. and isolated as bright red crystals in 91% yield (1.88 g, 8.0 mmol).
5: M.P. - 206°C; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.57 (m, 2H), 8.0 (m, 2H), 8.75 (m, 2H), 8.97 (m, 2H); $^{13}$C NMR (90.56 MHz, CDCl$_3$) $\delta$ 124.5, 126.59, 137.49, 150.1, 151.0, 163.9.

1,4-dihydro-3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (8) - To a 100 ml round-bottom flask filled with 50 ml of anhydrous EtOH was added 2-cyanopyridine (3.72 g, 0.036 mol). To the ethanol solution was added anhydrous hydrazine (2.8 g, 0.088 mol). The reaction was heated to reflux for 22 hours. The solution was cooled first to room temperature and then to 0°C in an ice/water bath. Upon cooling, orange crystals precipitated from the ethanol solution. The orange crystals were collected by vacuum filtration and washed several times with cold 95% ethanol. 2.41 (0.010 mol) of 8 was isolated in 56% yield.

8: $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.35 (m, 2H), 7.75 (m, 2H), 8.04 (m, 2H), 8.49 (s, 2H), 8.57 (m, 2H); $^{13}$C NMR (90.56 MHz, CDCl$_3$) $\delta$ 121.3, 124.7, 136.5, 146.2, 147.7, 148.3.

3,6-di-(4'-methoxyphenylmethyl)-1,2,4,5-tetrazine (12) - To 5 g (.034 mmol) of 4-methoxyphenylacetonitrile was added 20 mL 5N HCl-iPrOH. The solution was stirred at room temperature for 1 hour, then cooled to 0°C for 24 hours. While cooling, intermediate 13 precipitates from solution. Compound 13 is collected via vacuum filtration, washed several times with water, and dried. Compound 13 was suspended in anhydrous EtOH and cooled to 0°C. To the suspension was added an excess (1.2 molar equivalents) of 98% H$_2$NNH$_2$. The suspension was stirred at 0°C for 2 hours. The
resulting orange dihydrotetrazine 14 was collected via vacuum filtration, washed several times with cold 95% ethanol, and dried. Upon exposure to air 14 immediately began to oxidize. Compound 14 was suspended in an 50 mL aqueous NaNO₂ (7.0 g, 0.101 mol). The solution was cooled to 0°C with magnetic stirring. Glacial acetic acid (5 mL) was added dropwise making sure to keep the solution temperature below 5°C. Once acetic acid addition was complete, the solution was stirred at 0°C for 2 hours, followed by 1 hour of stirring at room temperature. The pink/red tetrazine 12 was isolated by vacuum filtration and washed several times with cold water. Recrystallization from 95% ethanol yielded 12 in 36% yield (4.23 g).

12 ¹H NMR (360 MHz, CDCl₃) δ 3.76 (s, 6H), 4.50 (s, 4H), 6.89 (m, 4H), 7.27 (m, 4H); ¹³C NMR (90.56 MHz, CDCl₃) δ 40.6, 55.0, 114.3, 127.9, 130.3, 158.8, 169.1.

3,6-di-(2'-pyridyl)-4,5-dihydro-4,5-(1,2-[60]fullereno)-pyridazine (16)- All reaction and isolation steps were performed as to rigorously exclude light and water. C₆₀ (50 mg, 0.069 mmol) and 5 (16.3 mg, 0.069 mmol) were added to an oven-dried 100 ml round-bottom flask covered in foil. To the flask was added 50 ml dry toluene. The flask was attached to a reflux condenser (also wrapped in foil) and heated to reflux (110°C) in the dark for 22 hours. Upon cooling of the toluene solution to room temperature, the solvent was removed by rotary evaporation making sure that the crude product mixture was kept dark. The crude product mixture was washed with acetone and filtered several times until the acetone filtrate ran clear. The undissolved solids were next washed with CHCl₃ and filtered several times. Washing with CHCl₃ was performed until the filtrate
ran clear. The CHCl₃ solutions were combined and the solvent removed. Evaporation of the solvent yielded 16 (35 mg, 0.038 mmol) as a brown solid in 56 % crude yield.

16: Electrospray MS- 929 (M+1), \(^1\)H NMR (360 MHz, CS₂/CDCl₃) \(\delta\) 7.36 (m, 1H), 7.90 (m, 2H), 8.60 (m, 1H); \(^{13}\)C NMR (CS₂/CDCl₃, 90.56 MHz) \(\delta\) 63.1, 124.1, 126.0, 134.5, 136.7, 139.2, 141.5, 141.7, 142.5, 142.9, 143.1, 144.3, 145.4, 145.6, 146.2, 146.4, 146.7, 147.2, 147.5, 147.6, 148.1, 153.5, 155.0.

3,6-diphenyl-4,5-dihydro-4,5-(1,2-[60]fullereno)-pyridazine (18) - All reaction and isolation steps were performed as to rigorously exclude light and water. C₆₀ (50 mg, 0.069 mmol) and 4 (16 mg, 0.069 mmol) were added to an oven-dried 100 ml round-bottom flask covered in foil. To the flask was added 50 ml dry toluene. The flask was attached to a reflux condenser (also wrapped in foil) and heated to reflux in the dark for 48 hours. Upon cooling to room temperature, the solvent was removed by rotary evaporation making sure that the crude product mixture was kept dark. The crude product mixture was washed with diethyl ether and filtered several times until the ether filtrate ran clear. The undissolved solids were next washed with CHCl₃ and filtered several times. Washing with CHCl₃ was performed until the filtrate ran clear. The CHCl₃ solutions were combined, and the solvent removed. Evaporation of the solvent yielded 18 (33 mg, 0.038 mmol) as a brown solid in 52 % crude yield.

18: \(^1\)H NMR (360 MHz, CS₂/CDCl₃) \(\delta\) 7.52-7.59 (m, 6H), 8.14 (m, 4H); \(^{13}\)C NMR (90.56 MHz, CS₂/CDCl₃) \(\delta\) 78.4, 128.0, 129.2, 129.8, 14.4, 136.7, 139.5, 141.5, 141.7, 142.4, 142.9, 143.3, 144.4, 145.6, 145.7, 146.5, 146.8, 147.0, 147.1, 147.7, 155.3.
1,4,5-Trihydro-3-(4'-methoxyphenylmethyl)-6-(4'-methoxystyryl)-4,5-(1,2-[60]-fullereno)-pyridazine (20)- To an oven-dried round-bottom flask that had been covered in foil was added C_{60} (47 mg, .065 mmol), 12 (22 mg, .068 mmol) and 20 mL dry toluene. The round-bottom flask was attached to a reflux condenser which also was wrapped in foil. The toluene solution was heated to reflux for 48 hours. Upon cooling to room temperature, the toluene solvent was removed with a rotary evaporator to yield a dark brown solid. The crude product mixture was separated by flash silica column chromatography (10:1 CS₂: ethyl acetate on silica gel). Compound 20 eluted second from the column as a brown solution. Upon removal of the solvent, 20 was isolated as a brown solid in 20% yield (13.7 mg, 0.013 mmol).

20: \textsuperscript{1}H NMR (360 MHz, CS₂/CDC₁₃) δ 3.80 (s, 3H), 3.91 (s, 3H), 4.49 (s, 2H), 6.81 (m, 2H), 7.02 (s, 1H), 7.04 (m, 2H), 7.29 (m, 2H), 7.50 (m, 2H), 8.28 (s, 1H); \textsuperscript{13}C NMR (90.56 MHz, CS₂/CDC₁₃) δ 40.2, 55.0, 55.2, 67.4, 68.6, 110.3, 114.2, 115.0, 127.5, 129.3, 129.8, 130.4, 134.8, 135.8, 138.5, 139.7, 140.2, 141.8, 141.9, 142.1, 142.4, 142.9, 143.2 (4C), 143.3, 144.7, 144.8, 145.5 (3C), 146.0, 146.1, 146.3 (2C), 146.47 (2C), 146.51, 146.6, 147.8, 149.6, 152.2, 153.4, 158.5, 159.1.
(±)-2-(2'-pyridylketo)-5-(2'-pyridyl)-3,4-dihydro-3,4-(1,6-(2',5'-dihydro)-[60]fullereno)-pyrazole (±21)- To a 100 mL round-bottom flask wrapped in foil was added 50 mg (0.069 mmol) C\textsubscript{60}, and an equimolar amount (16.4 mg) of 5. To the flask was added 40 mL of reagent grade toluene. The toluene solution was heated to reflux in the dark for 22 hours. Upon cooling of the reaction solution, the toluene solvent was removed by rotary evaporation to yield a brown crude product mixture. The crude product mixture was separated by flash silica gel column chromatography, with 20:1 CS\textsubscript{2}:ethyl acetate eluent. Compound ±21 eluted second from the column. Residual by-products can be removed from the column with a 10:1 mixture of CH\textsubscript{2}Cl\textsubscript{2}:MeOH. The product was isolated as a brown solid in 51% yield (33 mg, .035 mmol).

±21: Electrospray MS 947 m/z (M+1); \textsuperscript{1}H NMR (360 MHz, CS\textsubscript{2}/CDCl\textsubscript{3}) δ 6.60 (d,1H, 5\textsubscript{JHH} 1.8 Hz), 6.65 (d,1H, 5\textsubscript{JHH} 1.8 Hz), 7.44 (m, 1H), 7.56-7.60 (m, 1H), 7.85 (m, 1H), 7.97-8.00 (m, 2H), 8.81 (m, 1H), 8.91 (m, 1H); \textsuperscript{13}C NMR (90.56 MHz, CS\textsubscript{2}/CDCl\textsubscript{3}) δ 54.2, 55.7, 70.7, 80.1, 123.1, 124.2, 124.7, 125.1, 136.40, 136.42, 137.4, 137.5, 138.7, 139.0, 140.0, 141.0, 141.4, 141.7, 141.8, 142.0, 142.10, 142.13, 142.5, 142.6, 142.9, 143.2, 143.3, 143.6, 143.9, 144.06, 144.09, 144.19, 144.23, 144.30, 144.32, 144.35, 144.39, 144.42, 144.51, 144.57, 144.6, 144.92, 145.0, 145.2, 145.5, 145.7, 145.8, 146.32, 146.36, 146.75, 147.09, 147.17, 147.39, 147.47, 148.1, 148.4, 148.8, 148.9, 149.3, 150.2, 150.5, 151.5, 153.6, 153.9, 165.5.
To a 100 mL round-bottom flask which had been wrapped in foil and attached to a reflux condenser was added 50 mg (0.069 mmol) C₆₀ and an equimolar amount (16.4 mg) of 4. The reactants were dissolved in 40 mL of reagent grade toluene. The fullerene-tetrazine solution was heated to reflux in the dark for 22 hours. Upon cooling of the reaction solution, the toluene solvent was removed by rotary evaporation to yield a crude brown product mixture. The crude product mixture was separated by flash silica column chromatography, using 20:1 CS₂:ethyl acetate solution as eluent. Compound ±22 was the third band to elute after unreacted [60]fullerene and unreacted 4. Residual by-products can be removed from the column with a 10:1 mixture of CH₂Cl₂:MeOH.

±22: ¹H-NMR (360 MHz, CS₂/CDCl₃) δ 6.42 (d, 1H, ⁵JHH 1.8 Hz), 6.58 (d, 1H, ⁵JHH 1.8 Hz), 7.56-7.67 (m, 6H), 8.3 (m, 2H), 8.67 (m, 2H); ¹³C NMR (90.56 MHz, CS₂/CDCl₃) δ 54.1, 56.9, 71.2, 81.4, 128.45, 128.48, 128.7, 129.8, 130.0, 131.2, 131.5, 131.9, 133.0, 135.0, 136.6, 137.2, 137.3, 137.9, 138.4, 139.6, 140.3, 141.8, 141.92, 141.95, 142.5, 142.8, 142.9, 143.06, 143.13, 143.2, 143.5 (coincidental overlap), 143.9, 144.3, 144.55, 144.64, 144.7, 144.83, 144.87, 144.93, 145.0, 145.16, 145.25, 145.5, 146.5, 146.1, 146.4, 146.5, 146.9, 147.0, 147.3, 147.6, 147.75, 147.85, 147.9, 148.5, 148.95, 149.0, 149.4, 149.8, 149.9, 150.1, 152.3, 153.0, 160.4, 165.8.
(±)-2-(2′pyridyl)-hexylimino-5-(2′-pyridyl), 3,4-dihydro-3,4-(1,6-(2′,5′-dihydro)-[60]fullereno-pyrazoline (±28)- To a 100 ml round-bottom flask covered in foil was added C60 (50 mg, 0.069 mmol), 5 (17.2 mg, 0.073 mmol) and 40 ml toluene. The flask was attached to a reflux condenser (also covered in foil) and the toluene solution was heated to reflux (110°C) for 19 hr. Upon cooling the reaction solution, one molar equivalent of hexylamine (7.0 mg dissolved in CHCl3) was added to the reaction flask, making sure to exclude light from the reaction solution. The flask was equipped for magnetic stirring and the solution was stirred at room temperature in the dark for 15 hr. The foil was removed from the flask and the toluene was removed by rotary evaporator. The crude product mixture was isolated by silica gel column chromatography (20:1 CS2:ethyl acetate). Compound ±28 eluted second from the column as a brown/red solution. Upon removal of solvent, ±28 is isolated as a brown solid in 32% isolated yield (22.6 mg, 0.022 mmol).

±28: 1H NMR (360 MHz, CS2) δ 0.79 (t, 3H), 1.10-1.40 (m,6H), 1.62 (m,2H), 3.28 (m, 2H), 6.48 (d, 1H, 5JHH 1.8 Hz), 6.68 (d, 1H, 5JHH 1.8 Hz), 7.23 (m, 1H), 7.43 (m,2H), 7.62 (m, 1H), 7.73 (m, 1H); 7.87 (m, 1H), 8.65 (m, 1H), 8.80 (m, 1H); 13C NMR (90 MHz, CS2) δ 14.5, 23.2, 27.8, 30.1, 32.2, 50.8, 54., 55.2, 70.7, 81.0,121.7, 123.1, 123.3, 123.5, 135.8, 135.9, 137.6, 137.9, 138.4, 138.5, 141.0, 141.4, 141.5, 141.8, 141.9, 142.2, 142.3, 142.4, 142.5, 142.7, 143.00, 143.03, 143.10, 143.15, 143.24, 143.5, 143.6, 143.9, 144.0, 144.1 (2C), 144.18, 144.28, 144.34 (2C), 144.39 (2C), 144.42 (2C), 144.44, 144.7, 144.8, 145.1, 145.2, 145.48, 145.52, 145.58, 146.10, 146.13, 146.6, 146.9, 147.0, 147.7, 147.8, 147.9, 148.1, 148.2, 148.6, 148.9, 148.9, 149.11, 149.14, 149.6, 150.96, 150.99, 152.7, 152.8, 153.0.
2-(2'pyridyl)-α-methyl-benzylimino-5-(2'-pyridyl)-4,5-dihydro-4,5-(1,6-(2',5'-dihydro)-[60]-fullereno)pyrazoline (30)- To a 100 ml round-bottom flask covered in foil was added C_{60} (51 mg, 0.071 mmol), 5 (17.2 mg, 0.073 mmol) and 40 ml toluene. The flask was attached to a reflux condenser (also covered in foil) and the toluene solution was heated to reflux (110°C) for 19 hr. Upon cooling the reaction solution, one molar equivalent of (R)-α-methylbenzylamine (8.6 mg, 0.071 mmol) was added to the reaction flask, making sure to exclude light from the reaction solution. The flask was equipped for magnetic stirring and the solution was stirred at room temperature in the dark for 15 hr. The foil was removed from the flask and the toluene was removed by rotary evaporator. The crude product mixture was isolated by silica gel column chromatography (20:1 CS2:ethyl acetate). 30 elutes third from the column as a brown solution. Upon removal of solvent, 30 is isolated as a brown solid in 30% isolated yield (22.1 mg, 0.021 mmol).

30: FAB-MS: m/z 1050 (M^+); MALDI-MS: m/z 1051 (MH^+); 'H NMR (360 MHz, CS2) δ 1.56 (d, 3H, 3J 6.4 Hz), 1.63 (d, 3H, 3J 6.4 Hz), 4.49 (q, 2H, both diastereomers, 3J 6.4 Hz), 6.50 (d, 1H, 5J 1.8 Hz), 6.52 (d, 1H, 5J 1.8 Hz), 6.67 (d, 1H, 5J 1.8 Hz), 6.82 (d, 1H, 5J 1.8 Hz), 7.0-7.3 (m, 12H), 7.41-7.56 (m, 4H), 7.61-7.68 (m, 2H), 7.73-7.78 (m, 2H), 8.69 (m, 2H), 8.88 (m, 1H), 8.97 (m, 1H); 13C NMR (90.56 MHz, CS2) δ 30.6, 35.1 (both diastereomers), 59.1, 59.3, 60.0, 60.1, 75.5, 75.6, 85.8, 85.9, 126.71, 126.75, 128.07, 128.10, 128.13, 128.21, 128.24, 131.50, 131.56, 131.59, 131.7, 133.1, 133.2, 140.2, 140.5, 140.6, 142.46, 142.50, 142.8, 143.1, 143.26, 143.32, 143.4, 143.5, 146.0 (2C), 146.1, 146.36, 146.41 (2C), 146.5, 146.8 (2C), 146.9, 147.18, 147.23, 147.27 (2C), 147.33, 147.6, 147.7, 147.92 (2C), 147.97, 148.02, 148.2 (2C), 148.3, 148.5, 148.6 (2C), 148.73, 148.77, 148.87 (2C), 148.89, 149.04, 149.05, 149.10, 149.15, 149.19 (2C), 149.19 (2C), 149.22, 149.25 (2C), 149.28, 149.30, 149.37, 149.56, 149.57, 149.7 (2C), 149.9, 150.1 (2C), 150.39, 150.43, 150.44, 150.47 (2C), 150.7, 150.8, 150.99 (2C), 151.01, 151.47, 151.48, 151.73, 151.78, 151.80 (2C), 151.83.
(±)-2-(2’pyridyl)-hydroxyethylimino-5-(2’-pyridyl), 3,4-dihydro-3,4-(1,6-
(2’,5’-dihydro)-[60]fullereno-pyrazoline (±31)- To a 100 ml round-bottom flask
covered in foil was added C₆₀ (75 mg 0.104 mmol), 5 (26 mg, 0.110 mmol) and 50 ml
benzene. The flask was attached to a reflux condenser (also covered in foil) and the
benzene solution was heated to reflux for 48 hr. Upon cooling the reaction solution, a
molar excess (1.5 equivalents) of 3-aminopropanol was added to the reaction flask,
making sure to exclude light from the reaction solution. The flask was equipped for
magnetic stirring and the solution was stirred at room temperature in the dark for 24 hr.
The foil was removed from the flask and the solvent was removed rotary evaporator. The
crude product mixture was isolated by flash silica coloumn chromatography (10:1
CS₂:ethyl acetate). Compound ±31 elutes fourth from the column as a brown solution.
Upon removal of the solvent, ±31 was isolated as a brown solid in 14% yield (14 mg,
0.014 mm).

±31: ¹H NMR (360 MHz, CS₂) δ 2.05-2.2 (m, 2H), 3.6-4.0 (m, 4H), 6.79 (d, 1H,
J=1.8 Hz), 6.98 (, 1H, ²J=1.8 Hz), 7.54 (m, 1H), 7.80 (m, 1H), 7.91 (m, 2H), 8.05 (m,
1H), 8.26 (m, 1H), 8.96 (m, 1H), 9.07 (m, 1H); ¹³C NMR (90 MHz, CS₂) δ 34.6, 47.8,
54.7, 55.6, 60.1, 70.9, 81.4, 122.1, 123.6, 123.9, 124.08, 128.6, 136.1, 136.5, 138.7,
141.5, 141.6, 141.8, 141.9, 142.4, 142.7, 142.8, 143.1, 143.2, 143.4, 143.5, 143.6, 143.7,
143.8, 144.0, 144.2, 144.4, 144.6, 144.7, 145.1, 145.2, 145.6, 145.8, 145.9, 146.0, 146.5,
(±)-3,6-di-(2'-pyridyl)-3-nonylthio-2,3,4,5-tetrahydro-4,5-(1,2-[60]fullereno)-pyridazine (±33) - To a 100 mL round-bottom flask wrapped in foil was added C₆₀ (48 mg, 0.067 mmol), a molar excess of 5 (22.5 mg, 0.095 mmol), and 40 mL benzene. The flask was attached to a reflux condenser (also covered in foil) and the benzene solution was heated to reflux (80°C) for 48 hr. Upon cooling the crude solution, an excess of 32 and 50 mg SiO₂ was added to the reaction flask making sure to exclude light from the reaction. The flask was equipped for magnetic stirring and stirred for in the dark for 24 hr. The foil was removed from the flask and the solvent removed by rotary evaporator. The crude product mixture was isolated by flash silica column chromatography (20:1 CS₂:ethyl acetate). Compound ±33 eluted from the column as the second band. Upon removal of the solvent, ±33 was isolated as a brown solid in 34% yield.

±33: ¹H NMR (500 MHz, CS₂/CDCl₃) δ 0.92 (t, 3H), 1.21-1.37 (m, 12H), 1.55 (m, 2H), 2.29 (m, 1H), 2.52 (m, 1H), 7.25-7.32 (m, 2H), 7.72-7.81 (m, 2H), 8.02 (m, 2H), 8.60 (m, 2H), 8.71 (m, 1H); ¹³C NMR (125.66 MHz, CS₂/CDCl₃) δ 14.8, 23.4, 28.5, 29.74, 29.77, 28.9, 30.3, 30.1, 32.4, 67.3, 79.0, 79.9, 123.3, 123.6, 125.8, 127.4, 134.8, 135.2, 136.0, 136.5, 137.6, 138.67, 138.72, 139.1, 139.7, 141.3, 141.4, 141.5, 141.6, 142.0, 142.2, 142.4, 142.5, 142.6, 142.7 (2C), 142.9 (2C), 143.0 (2C), 143.2, 143.5, 144.5, 144.7, 144.9, 145.1, 145.36, 145.39, 145.42, 145.5, 145.68 (2C), 145.72, 145.75, 145.86 (2C), 146.1, 146.33, 146.38, 146.44, 146.47, 146.68, 146.71, 146.8 (2C), 147.2,
(±)-3,6-di-(2'-pyridyl)-3-phenylthio-2,3,4,5-tetrahydro-4,5-(1,2-[60]fullereno)-pyridazine (±38)- To a dry 250 ml round-bottom flask wrapped in foil was added C₆₀ (214 mg, 0.297 mmol), a molar excess of 5 (79 mg, 0.333 mmol), and 110 ml benzene. The flask was attached to a reflux condenser (also covered in foil) and the benzene solution was heated to reflux (80°C) for 48 hr. Upon cooling the reaction solution, an excess of 36 was added to the reaction flask, making sure to exclude light from the reaction. The flask was equipped for magnetic stirring and stirred in the dark for 24 hr. The foil was removed from the flask and the solvent removed by rotary evaporator. The crude product mixture was isolated by flash silica column chromatography (20:1 CS₂:ethyl acetate). Compound ±38 elutes from the column as the third band. Upon removal of the solvent, ±38 was isolated as a brown solid in 30% yield (83 mg, 0.08 mmol).

±38: ¹H NMR (360 MHz, CS₂/CDCl₃) δ 7.16-7.26 (m, 2H), 7.28-7.35 (m, 5H), 7.68 (s, 1H), 7.80-7.86 (m, 2H), 8.02 (m, 1H), 8.65-8.70 (m, 3H); ¹³C NMR (125 MHz, CS₂/DMSO-d₆) δ 77.3, 81.4, 123.2, 123.3, 125.5, 127.8, 129.1 (2C), 129.5, 131.4, 134.5, 135.0, 135.5, 135.6, 136.3, 136.5 (2C), 136.7, 137.6, 138.5, 138.7, 138.9, 139.0, 139.7, 141.3, 141.5, 141.6, 141.8, 142.2, 142.47, 142.51, 142.6, 142.72, 142.79, 142.89, 142.94, 143.0 (2C), 143.2, 143.5, 144.5, 144.8, 144.9, 145.2, 145.3, 145.4, 145.59, 145.60, 145.65, 145.73, 145.77, 145.78, 146.1, 146.2, 146.31, 146.34, 146.46, 146.50, 146.72, 146.80 (2C), 146.86 (2C), 147.5, 147.7, 147.8, 147.9, 148.0, 148.5, 148.6, 150.1.
To a dry 100 ml round-bottom flask covered in foil was added C_{60} (46 mg, 0.064 mmol), an excess of 5 (21.3 mg, 0.09 mmol), and 40 ml benzene. The reaction flask was attached to a reflux condenser (also wrapped in foil) and the solution was heated to reflux (80°C) for 48 hr. Upon cooling the reaction, 37 (34.7 mg, 0.22 mmol) was added to the reaction flask, making sure to exclude light from the reaction solution. The flask was equipped for magnetic stirring and stirred in the dark for 24 hr. The foil was removed from the flask and the solvent removed by rotary evaporator. The crude product mixture was separated by flash silica column chromatography (20:1 CS\textsubscript{2}:ethyl acetate). Compound \pm 40 eluted from the column as the third band, and was isolated as a brown solid in 36% yield (25.5 mg, 0.023 mmol).

\pm 40: \textit{^1}H NMR (360 MHz, CS\textsubscript{2}) \delta 6.93 (m, 1H), 7.11 (m, 1H), 7.20-7.32 (m, 4H), 7.67-7.91 (m, 7H), 8.61-8.74 (m, 3H); \textit{^{13}}C NMR (125 MHz, CS\textsubscript{2}) \delta 82.53, 141.37, 141.40, 141.41, 141.49, 141.59, 141.63, 141.65, 142.47, 142.50, 142.54, 142.55, 142.68, 142.77, 142.79, 142.8, 143.0, 143.1, 143.2, 143.3, 143.37, 143.38, 143.56, 143.58, 144.5, 144.83, 144.88, 145.1, 145.3, 145.33, 145.34, 145.4, 145.40, 145.47, 145.52, 145.57, 145.7, 145.8, 145.9, 146.04, 146.08, 146.4, 146.5, 146.6, 146.81, 146.85, 146.89, 147.6, 147.8, 147.90, 147.94, 149.0, 150.7, 152.3, 153.5, 153.7, 155.4, 158.0.
(±)-3,6-di-(2'-pyridyl)-3-methoxy-2,3,4,5-tetrahydro-4,5-(1,2-[60]fullereno)-pyridazine (±41)- To a 100 mL round-bottom flask wrapped in foil was added C₆₀ (51 mg, 0.071 mmol), 5 (17 mg, 0.072 mmol), and 40 mL benzene. The reaction flask was attached to a reflux condenser (also wrapped in foil) and the solution was heated to reflux (80°C) for 48 hr. Upon cooling the solution of 16, an excess of methanol and 50 mg SiO₂ were added to the reaction flask, making sure exclude light from the reaction solution. The reaction flask was equipped for magnetic stirring and the solution was stirred in the dark for 24 hr. The foil was removed and the benzene was removed by rotary evaporator. Compound ±41 was isolated flash silica column chromatography (10:1 CS₂: ethyl acetate). Compound ±41 eluted fourth from the column as a brown band. Upon removal of the solvent 17 mg (0.018 mmol) of ±41 was isolated as a brown solid in 25.3 % yield.

±41: ¹H NMR (360 MHz, CS₂) δ 3.48 (s, 3H), 7.27 (m, 1H), 7.37 (m, 1H), 7.79 (m, 3H), 7.97 (m, 1H), 8.04 (m, 1H), 8.52 (m, 1H), 8.76, (m, 1H).
5. APPENDIX
30
1 of 2 diastereomers

(ppm)
6. REFERENCES


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