Chemical Reactivity and Regioselectivity of Trimetallic Nitride Endohedral Metallofullerenes

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(Abstract)

Endohedral metallofullerenes (EMF) have attracted increasing attention during past decades for their potential applications in the fields of biomedicine and nanomaterials. Trimetallic nitride template endohedral metallofullerenes (TNT EMFs) are some of the most promising fullerene-based materials (e.g., as MRI and X-ray contrast agents) because of their high yields compared to classic endohedral metallofullerenes. This dissertation addresses the chemical reactivity and regioselectivity of TNT EMFs.

Based on the extraordinarily high stability of TNT EMFs relative to empty cage fullerenes and classic endohedral metallofullerenes, macroscopic quantities of high purity TNT EMFs were obtained directly from crude soot in a single facile step by using a cyclopentadiene-functionalized resin to trap the more reactive species via Diels-Alder reactions, allowing the TNT EMFs to pass through. We also developed a support-free chemical separation method of TNT EMFs from Sc- and Lu-based soot extract that makes use of the differing solubilities of unreacted TNT EMFs versus 9-methylanthracene-derivatized empty cage fullerenes.

The exohedral functionalization of metallofullerenes can fine-tune their chemical and physical properties. The first N-methylpyrrolidino derivatives of TNT EMFs ($I_h$ Sc$_3$N@C$_{80}$ and $I_h$ Er$_3$N@C$_{80}$) were synthesized via 1,3-dipolar cycloaddition of N-methylazomethine ylides (Prato reaction). The demonstration of planar symmetry in the N-methylpyrrolidino derivatives by $^{13}$C NMR spectroscopy suggested that the reaction exclusively took place at the 5,6-ring junction. However, both 5,6-ring and 6,6 ring junction adducts were obtained when $I_h$
Sc$_3$N@C$_{80}$ reacted with N-triphenylmethyl-5-oxazolidinone, as characterized by NMR spectroscopy and X-ray crystallography. The kinetically favored 6,6-ring junction adduct was converted to the thermodynamic product, the 5,6-ring junction adduct, upon thermal equilibration. The synthesis of pyrrolidino derivatives was also extended to two other Sc-based TNT EMFs, $D_{5h}$ Sc$_3$N@C$_{80}$ and Sc$_3$N@C$_{78}$. The reactivity and regioselectivity of $D_{5h}$ Sc$_3$N@C$_{80}$ and Sc$_3$N@C$_{78}$ were demonstrated by NMR spectroscopy, X-ray crystallography and theoretical calculations.

Another type of reaction, the Bingel-Hirsch cyclopropanation was carried out with $D_{5h}$ Sc$_3$N@C$_{78}$ for the first time, yielding a single $C_s$-symmetric monoadduct and a dominant $C_{2v}$-symmetric diadduct for the first time. The symmetric diadduct clearly demonstrates the remarkable regioselectivity control exerted by the encapsulated Sc$_3$N cluster. We employed a LUMO electron density surface computational approach to predict multiadduct docking sites on the ellipsoidal fullerene cage surface. We also successfully synthesized the first derivative of a non-IPR fullerene, the diethyl malonate derivative of Sc$_3$N@C$_{68}$ by a Bingel-Hirsch reaction. The reactivity and regioselectivity of Sc$_3$N@C$_{68}$ were investigated by NMR spectroscopy and theoretical calculations.
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Chapter 1

Dissertation Statement

During the past decade, the field of metallofullerenes has developed explosively, driven by the structural novelty and the intriguing properties that offer a wide variety of new possibilities in nanomaterials and biomedical applications. In particular, trimetallic nitride templated endohedral metallofullerenes (TNT EMFs) are some of the most studied metallofullerene-based materials (e.g., as magnetic resonance imaging and X-ray contrast agents).

However, despite the interest in these materials, the limited quantities of isolated material have restricted further investigation into their chemical and physical properties and exohedral functionalizations. In this dissertation, we demonstrate in Chapter 3 that high purity TNT EMFs can be obtained directly from as-prepared soots in a single facile step by taking advantage of their extraordinary kinetic chemical stability with respect to the Diels-Alder reaction with cyclopentadiene-functionalized resin. (This work was published in the Journal of the American Chemical Society: Ge, Z.; Duchamp, J. C.; Cai, T.; Gibson, H. W.; Dorn, H. C.  *J. Am. Chem. Soc.* **2005**, *127*, 16292-16298.) In Chapter 4, we develop a support-free chemical separation method for TNT EMFs from Sc- and Lu-based soot extract that makes use of the differing solubilities of unreacted TNT EMFs versus 9-methylnanthracene-derivatized empty cage fullerenes.
Inspired by the results in Chapter 3, which indicate that it is possible to separate isomers of these TNT EMFs, in Chapter 5, we present the first isolation and full structural characterization of the Sc$_3$N@C$_{80}$ $D_{5h}$ isomer. We discuss the enhanced reactivity of the $D_{5h}$ isomers in comparison with the more common $I_h$ isomers of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ toward Diels-Alder and 1,3-dipolar tritylazomethine ylide cycloaddition reactions. Both cyclic voltammetry and theoretical molecular orbital (MO) calculations demonstrate that the $D_{5h}$ isomers have smaller energy gaps than those of the $I_h$ isomers, which is consistent with the observation of higher reactivity for the $D_{5h}$ isomers. (This work appeared as an article in the Journal of the American Chemical Society: Cai, T.; Xu, L.; Anderson, M. R.; Ge, Z.; Zuo, T.; Wang, X.; Olmstead, M. M.; Balch, A. L.; Gibson, H. W.; Dorn, H. C. *J. Am. Chem. Soc.* 2006, 128, 8581-8589.)

Organic functionalization of these materials is crucial to construct novel organometallofullerene materials for a variety of future applications. The modification of metallofullerene carbon cages can fine-tune their chemical and physical properties. The next five chapters focus on the study of exohedral derivatization of TNT EMFs.

In Chapter 6, we discuss the synthesis and characterization the first TNT endohedral metallofullerenes pyrrolidino derivative via 1,3-dipolar cycloaddition of N-methylazomethine ylides (Prato reaction) to both diamagnetic and paramagnetic TNT EMFs (Sc$_3$N@C$_{80}$ and Er$_3$N@C$_{80}$). (This work appeared as a communication in the Chemical Communication: Cai, T.; Ge, Z.; Iezzi, E. B.; Glass, T. E.; Harich, K.; Gibson, H. W.; Dorn, H. C. *Chem. Commun.* 2005, 28, 3594-3596.)

Under similar conditions used for the efficient 1,3-dipolar cycloaddition reaction of N-methylazomethine ylide to TNT EMFs, two N-tritylpyrrolidino derivatives of $I_h$ Sc$_3$N@C$_{80}$
have been synthesized and characterized by both NMR and X-ray crystallography (Chapter 7). A kinetic study shows that the 6,6-ring junction adduct is the kinetically controlled product; it is converted to the thermodynamic product, the 5,6-ring junction adduct, upon thermal equilibration. This was the first time such an isomerization process was observed for an endohedral metallofullerene. (This work published in the Journal of the American Chemical Society as a full article paper: Cai, T.; Slebodnick, C.; Xu, L.; Harich, K.; Glass, T. E.; Chancellor, C.; Fettinger, J. C.; Olmstead, M. M.; Balch, A. L.; Gibson, H. W.; Dorn, H. C. J. Am. Chem. Soc. 2006, 128, 6486-6492.)

After the initial discovery of the TNT EMF class represented by the prototypical Sc$_3$N@C$_{80}$ (I$_h$ cage), two other Sc$_3$N EMF family members, the $D_{3h}$ symmetrical Sc$_3$N@C$_{78}$ and the $D_3$ symmetrical non-IPR (isolated-pentagon rule) Sc$_3$N@C$_{68}$ were also discovered in relatively low yield. Recent advances in chemical separation techniques of TNT EMFs (Chapter 3 and 4) make it possible to isolate significant quantities of materials in a short period of time for exohedral functionalization studies.

In Chapter 8, we discuss the synthesis and characterization of first N-tritylpyrrolidino derivatives of $D_{3h}$ (78:5) Sc$_3$N@C$_{78}$ utilizing the Prato reaction. These results are compared with previous studies of the homologous Sc$_3$N@C$_{80}$ (Chapter 7), both in terms of chemical reactivity and regioselectivity, as well as crystallographic studies. This represents the first case (in contrast with earlier studies of A$_3$N@C$_{80}$ molecules and other endohedral metallofullerenes) in which the internal trimetallic cluster (Sc$_3$N) is restricted to a horizontal plane in the molecule and thus demonstrates regio-control of adduct docking on a metallofullerene sphere. (This work published in the Journal of the American Chemical
The remarkable regioselectivity control exerted by the encapsulated trimetallic cluster is further demonstrated in Chapter 9. The cyclopropanation of Sc$_3$N@C$_{78}$ with diethyl bromomalonate produces only one monoadduct and one dominant symmetric bisadduct. The C$_1$-symmetric monoadduct and C$_{2v}$-symmetric diadduct were isolated by HPLC and characterized by MS and NMR spectroscopy. Significantly, the selective formation of a symmetric Sc$_3$N@C$_{78}$ bisadduct demonstrates the remarkable regioselective adduct docking control exerted by the encapsulated Sc$_3$N cluster. We also discuss the use of a LUMO electron density surface computational approach to predict multi-adduct docking sites on the fullerene cage surface. (This chapter appeared as a communication paper published in the Journal of the American Chemical Society: Cai, T.; Xu, L.; Shu, C.; Hunter, A. C.; Jonathan, E. R.; Clemens A.; Mark, R. A.; Gibson, H. W.; Dorn, H. C.; J. Am. Chem. Soc. 2008, 130, 2136-2137.)

In Chapter 10, we discuss the synthesis and characterization of a non-IPR fullerene derivative, the diethyl malonate derivative of Sc$_3$N@C$_{68}$. The structure of the Sc$_3$N@C$_{68}$ monoadduct is investigated by the NMR spectroscopy and DFT computations. The proposed addition site of Sc$_3$N@C$_{68}$ monoadduct is in good agreement with the experimental and calculated $^{13}$C NMR spectra, LUMO electron density study and UV-vis spectroscopy.
The structure of this dissertation is shown in the following tree diagram.
Chapter 2

Overview of Fullerenes and Endohedral Metallofullerenes

2.1. INTRODUCTION

2.1.1. Empty Cage Fullerenes

In 1985, the highly stable 60 carbon atom cluster, C$_{60}$, was discovered by Kroto and co-workers when they investigated the mass spectra of laser evaporated carbon in a helium atmosphere.\textsuperscript{1} Shortly thereafter, a very symmetric truncated isosahedral structure was proposed for C$_{60}$ (Figure 1a).\textsuperscript{2} The icosahedral symmetry of the C$_{60}$ molecule was confirmed from $^{13}$C nuclear magnetic resonance (NMR) experiments; where only a single line was observed, consistent with only one type of carbon atom in this molecule.\textsuperscript{3} Nearly all fullerene research in the early stage was limited to theoretical study because only small quantities of material were available.\textsuperscript{4}

The second breakthrough in fullerene research was achieved by Krätschmer, Huffman, and co-workers in 1990. They reported a simple procedure for the preparation macroscopic quantities of fullerenes (C$_{60}$, C$_{70}$, and other empty-cages) from the vaporization of inexpensive graphite rods in a helium atmosphere.\textsuperscript{5} With this invention, scientists opened the way for large scale fullerene research, which spread out explosively into chemistry, physics and material science.\textsuperscript{6}
2.1.2. Endohedral Metallofullerenes

Because fullerenes are hollow molecules, it was expected that it should be possible to trap atoms inside the cage. One week after the discovery of C₆₀, the Kroto research group observed the peak of the first endohedral metallofullerene, La@C₆₀, in a mass spectrum of a sample prepared by the laser vaporization of a LaCl₂ impregnated graphite rod. The symbol @ is used to indicate the atoms in the interior of the fullerene cage. Further evidence that metal atoms were encaged in C₆₀ was reported by Smalley’s group. They found that both C₆₀ and La@C₆₀⁺ complexes did not react with H₂, O₂, NO and NH₃. This suggested that reactive metal atoms were protected from the surrounding gases and were indeed trapped inside closed carbon cages.

In 1991, Chai et al. used high temperature laser vaporization of La₂O₃/graphite composite rods and the corresponding contacted arc technique to produce macroscopic quantities of lanthanofullerenes. The major lanthanofullerene was La@C₈₀ due to its relative high stability. Two and three metal atoms also can be encapsulated into a fullerene. For example, Shinohara et al. produced and isolated a serial of scandium metallofullerenes (Sc@C₈₂, Sc@C₈₂, Sc₂@C₈₄ and Sc₃@C₈₄) in macroscopic quantities (Figure 1b). In recent years, group 3 metals (M=Sc, Y, and La) and most lanthanide metals have been trapped inside the higher fullerenes, such as C₈₀, C₈₂, C₈₄ etc., to provide mono-, di- and trimetallofullerenes. Several metal carbide endohedral fullerenes were also synthesized, such as Sc₂C₂@C₈₄ and Sc₃C₂C₈₀ (Figure 1c).

2.1.3. Trimetallic Nitride Endohedral Metallofullerenes
In 1999, Stevenson and Dorn et al. reported a novel stable four atom molecular cluster endohedral fullerene, icosahedrally (I\textsubscript{h}) symmetrical Sc\textsubscript{3}N@C\textsubscript{80} (Figure 1d).\textsuperscript{14} This new endohedral metallofullerene was formed by a trimetallic nitride template process (vaporizing graphite rods packed with Sc\textsubscript{2}O\textsubscript{3} in a Krätschmer-Huffman generator under He/N\textsubscript{2} atmosphere) in a remarkable high yield (5-10 % of the soluble extract).\textsuperscript{14} Based on this TNT process, a variety of new trimetallic nitride endohedral metallofullerenes with different encapsulated metals and carbon cage structures were synthesized and characterized recently: A\textsubscript{3}N@C\textsubscript{2n} (A= Y, Gd, Tb, Dy, Ho, Er, Tm, and Lu; 38 ≤n ≤ 49).\textsuperscript{15} Furthermore, several mixed TNT endohedral metallofullerenes have been synthesized, isolated and characterized, such as Er\textsubscript{x}Sc\textsubscript{3-x}N@C\textsubscript{80},\textsuperscript{16} CeSc\textsubscript{2}N@C\textsubscript{80}\textsuperscript{17} and four heteroatoms encapsulated ScYE\textsubscript{r}N@C\textsubscript{80}.\textsuperscript{18}

*Figure 1.* The optimized structures of (a) C\textsubscript{60}, (b) Sc\textsubscript{2}@C\textsubscript{84}, (c) Sc\textsubscript{3}C\textsubscript{2}@C\textsubscript{80}, (d) Sc\textsubscript{3}N@C\textsubscript{80}
2.2. PRODUCTION, EXTRACTION AND SEPARATION

2.2.1. Production

A Krätschmer-Huffman generator has been used for producing macroscopic amounts of fullerenes (Figure 2).\textsuperscript{5} The generator mainly consists of an evaporation chamber, which is connected to a pump system and a gas inlet. In arc vaporization of graphite rods\textsuperscript{19,20}, two graphite rods are kept in close but not direct contact. A voltage is applied across the two graphite rods by a dc power supply, which is used to maintain the arc discharge between them. A gap of approximately 4 mm is determined to attain maximum brightness of the plasma. The carbon soot generated in the arc is condensed onto a water-cooled stainless steel cylinder. The fullerenes are subsequently obtained by extracting the crude soot with organic solvents, such as toluene. This technique allows an efficient evaporation of carbon, and a very high yield (up to 44\% extractable material) was reported.\textsuperscript{21}

\textbf{Figure 2.} Apparatus used to produce fullerenes by arc vaporization of graphite rods
2.2.2. Extraction

The most common method for the isolation of fullerenes from soot is extraction with organic solvents.\textsuperscript{5,20,22} In general, toluene is used as the solvent because it is a good solvent for fullerenes and is less toxic than benzene or carbon disulfide (CS\textsubscript{2}). For the metallofullerene extraction, pyridine\textsuperscript{23} and trichlorobenzene\textsuperscript{24} were used in order to increase the efficiency. Khemani et al.\textsuperscript{25} and Parker et al.\textsuperscript{26} found that Soxhlet extraction (Figure 3) worked much better than simple reflux, giving a 26\% yield of soluble material. In contrast, reflux extraction gave only a 14\% yield of soluble material. It has been shown that either high temperature extraction or longer extraction times lead to higher yields of fullerenes.\textsuperscript{26}

2.2.3. Separation

2.2.3.1. Separation Based on High Pressure Liquid Chromatography

The extract of the crude soot from the fullerene generator is a mixture. Separating fullerenes to obtain the individual members is a key step to characterizing them for further application. To date, HPLC (High Pressure Liquid Chromatography) is the most important and useful technique in fullerene separation. It is widely used for separating both empty cage fullerenes and endohedral metallofullerenes. Many novel stationary phases have been designed and synthesized in order to effectively separate fullerenes.
ODS (octadecyl silica) is the most conventional stationary phase in the LC separation of fullerenes.\textsuperscript{27,28} This stationary phase is commercially available and easy to optimize.\textsuperscript{28} Monomeric ODS phases have better retention values than polymeric ODS phases for separation of fullerene mixtures. However, polymeric ODS phases have better selectivity for the separation of fullerene isomers.\textsuperscript{29} Since ODS columns exhibited limited separation effectiveness for higher fullerenes, several novel stationary phases were tried and developed.

Pirkle and Welch\textsuperscript{30,31} developed a novel tris(2,4-dinitrophenoxy)decyl group stationary phase, the so-called Buckyclutcher (Figure 4a). The stationary phase consists of a long chain and two electron-withdrawing nitro substituents on phenyl rings, which allow electron donor-acceptor interactions between the fullerene and polar end groups to occur. In addition, the polar end group forms a cavity that can house a bulky fullerene molecule. The small difference in the size of the fullerenes result in different degrees of interactions.\textsuperscript{28,32,33} The Buckyclutcher column can separate $C_{60}$ and $C_{70}$ very effectively. It is also very useful for the separation of higher fullerenes and metallofullerenes.

PPB (pentabromobenzylxyloxypropylsilyl) (Figure 4b) silica gel is another highly retentive and efficient packing material for the separation of fullerenes.\textsuperscript{34} The stationary phase of the PPB column containing heavy heteroatoms (five bromine atoms) resulted in longer retention of fullerenes. Some solvents in which fullerenes that have high solubility, such as carbon disulfide and 1,2,4-trichlorobenzene, can be used as mobile phases because of the PPB column’s excellent efficiency and capacity in fullerene separation.\textsuperscript{28}
Shinohara *et al.*\(^{35}\) first reported work on the isolation of the endohedral discandium fullerenes (Sc\(_2\)@C\(_{74}\), Sc\(_2\)@C\(_{82}\), Sc\(_2\)@C\(_{84}\)) using a two-stage HPLC process. Stevenson *et al.*\(^{36}\) also isolated Y@C\(_{82}\) and Sc\(_3\)@C\(_{82}\) by using a two-stage HPLC coupled with on-line EPR detection. In the two-stage separation, a polymer column was normally used as the preparative column for removing the dominant empty-cage fullerenes. A column with higher selectivity (for example, a Buckyclutcher column) was used in the second stage for further separation and purification of the metallofullerenes. Yamamoto *et al.*\(^{24}\) reported the first successful isolation of La@C\(_{82}\) in single stage HPLC. He used a novel column called a PYE (2-(1-pyrenyl)ethyl) silica column with toluene as mobile phase (Figure 4c). PYE silica, having the electron-donating pyrenyl group, is highly retentive to the electronegative fullerenes. This type of stationary phase allows for preparative separation of metallofullerenes due to its great loading capacity and especially high efficiency separation of the late-eluting substances.\(^{37}\)
2.2.3.2. Other Separation Methods.

Akasaka et al. reported a convenient separation method for endohedral metallofullerenes and empty fullerenes by an electrochemical process.\(^{38}\) La@C\(_{82}\) and La\(_2@C_{80}\) were selectively reduced from extracts of carbon soot to anions, which exhibit both a high stability and a high solubility in polar solvents, such as mixed acetone/CS\(_2\). Therefore, reduced endohedral metallofullerene and neutral empty fullerenes could be separated via utilization of their different solubilities.\(^{38}\)

Host-guest complexation of endohedral metallofullerene with an azacrown ether was applied to the selective extraction of endohedral metallofullerenes from extracts of crude soot.\(^{39}\) Unlike empty cage fullerene, endohedral metallofullerenes such as La@C\(_{82}\) form complexes with the azacrown ether and precipitate out of solution. The precipitates collected by filtration were subsequently sonicated in CS\(_2\) solution to release free lanthanum metallofullerenes.\(^{39}\)

2.3. STRUCTURE AND ELECTRONIC PROPERTIES

2.3.1. Empty Cage Fullerenes

The soccer-ball shaped C\(_{60}\) is the most abundant fullerene. The icosahedral symmetry point group I\(_h\) is the most stable C\(_{60}\) isomer and it obeys the “isolated pentagon rule” (IPR).\(^{40,41}\) The IPR states that the fullerene structure with all the pentagons surrounded by hexagons is more stable than structure with adjacent pentagons.

C\(_{70}\) is the next most stable and IPR satisfying fullerene. D\(_{5h}\) symmetry was proposed for the C\(_{70}\) carbon cage and consists of 12 pentagonal faces fused to 25 hexagonal faces.\(^{40}\) The \(D_{5h}\) structure determined by X-ray crystallography\(^{42}\) was consistent with the previous \(^{13}\)C
NMR experiment, in which five lines (intensity ratio: 10/20/10/20/10) correspond to the five types of carbon atoms in the C\textsubscript{70} cage.\textsuperscript{22}

With the increase in number of carbons, the number of isomers increases dramatically. The number of allowed fullerene isomers is one for C\textsubscript{60}, C\textsubscript{70} and C\textsubscript{76}, five for C\textsubscript{78}, seven for C\textsubscript{80}, 24 for C\textsubscript{84} and 46 for C\textsubscript{90}.\textsuperscript{43,44} The most symmetrical isomer does not always possess the greatest stability. For example, a $D_{2d}$ isomer of C\textsubscript{84} is the most abundant isomer, instead of the $D_{6h}$ isomer.\textsuperscript{45} Interestingly, some of the fullerenes, for instance, $D_{2}$ of C\textsubscript{76} are chiral. The chiral fullerene C\textsubscript{76} was kinetically resolved by asymmetric osmylation. Optically active enantiomers of C\textsubscript{76} were recovered from the treatment of racemic C\textsubscript{76} with OsO\textsubscript{4} and a chiral alkaloidal ligand.\textsuperscript{46,47} A fullerene smaller than C\textsubscript{60}, the non-isolated pentagon fullerene C\textsubscript{50}, has been isolated as the decachloro-derivative, D\textsubscript{5h} C\textsubscript{50}Cl\textsubscript{10} (Figure 5),\textsuperscript{48} which was prepared by graphite arc discharge in a helium atmosphere with a small amount of carbon tetrachloride (CCl\textsubscript{4}).

![Schematic structure of C\textsubscript{50}Cl\textsubscript{10}](image)

**Figure 5.** Schematic structure of C\textsubscript{50}Cl\textsubscript{10}\textsuperscript{48}

Soon after the discovery of C\textsubscript{60}, a theoretical calculation of molecular orbital levels of C\textsubscript{60} indicated that the lowest unoccupied molecular orbital (LUMO) was triply degenerate.\textsuperscript{49,50,51} Therefore, C\textsubscript{60} was predicted to be able to accept up to six electrons. This
prediction was verified by cyclic voltammetric studies.\textsuperscript{52} Six reduction waves can be observed at comparable potential, which corresponds to the formation of monoanion to hexaanion.\textsuperscript{52} The reduction waves were also found to be reversible and have an equal potential change between each successive reduction.\textsuperscript{52} The LUMO of C\textsubscript{70} was predicted to be only doubly degenerate.\textsuperscript{49} But since the energy difference between the LUMO and the LUMO+1 of C\textsubscript{70} was very small, six reversible reduction waves were also observed for C\textsubscript{70}.\textsuperscript{52} The electrochemical gaps between the first oxidation and the first reduction of C\textsubscript{60} and C\textsubscript{70} were measured at 2.32V and 2.22V, respectively. Electrochemistry of the higher fullerenes C\textsubscript{76}, C\textsubscript{78}, C\textsubscript{82} and C\textsubscript{84} has been reported.\textsuperscript{53} Due to the presence of many different isomers, the observed multiple redox waves were normally complicated to assign.

2.3.2. Monometallofullerenes

The most abundantly extracted and isolated monometallofullerene family is M@C\textsubscript{82} (M=group 3 or lanthanide metals). Although many M@C\textsubscript{82} have been isolated and purified in macroscopic quantities, their paramagnetic properties and instability in air prevent detailed experimental characterization.\textsuperscript{54}

Akasaka and coworkers prepared the anion of La@C\textsubscript{82} by bulk controlled potential electrolysis.\textsuperscript{55,56} They found the anion of La@C\textsubscript{82} was remarkably stable in air. The diamagnetic nature of this anion allowed NMR determination of the structure of La@C\textsubscript{82}.

The C\textsubscript{82} fullerene has nine distinct isomers (C\textsubscript{3v}(a), C\textsubscript{3v}(b), C\textsubscript{2v}, C\textsubscript{2}(a), C\textsubscript{2}(b), C\textsubscript{2}(c), C\textsubscript{s}(a), C\textsubscript{s}(b) and C\textsubscript{s}(c)) that satisfy the IPR.\textsuperscript{57} The \textsuperscript{13}C NMR study of C\textsubscript{82} showed only one isomer with C\textsubscript{2} symmetry abundantly produced.\textsuperscript{58} However, it was predicted that La@C\textsubscript{82} with C\textsubscript{2v}, C\textsubscript{3v} and C\textsubscript{s} symmetry structure were energetically much more favorable\textsuperscript{59} because
the three-electron transfer from the La atom to the C$_{82}$ cage leads to a closed-shell electronic structure. The $^{13}$C NMR spectrum of the anion of M@C$_{82}$ (M=La, Ce and Pr) exhibits 17 distinct lines of near-equal intensities and 7 lines of half-intensity, verifying that M@C$_{82}$ (M=La, Ce and Pr) with $C_{2v}$ structure is the most energetically stable isomer.$^{55,60}$

From cyclic voltammograms of M@C$_{82}$ (M=La, Ce, Gd and Y), the first reversible oxidation potentials were slightly more positive than that of ferrocene, indicating that those lanthanide monometallofullerenes are good electron donors.$^{61}$ In addition, the first reduction potentials of M@C$_{82}$ (M=La, Ce, Gd and Y) were more negative than those of C$_{60}$ and C$_{70}$, suggesting that they are also the stronger electron acceptors than empty cage fullerenes.$^{61}$ The molecular orbital diagram of La@C$_{82}$ demonstrated the presence of an unpaired electron in the HOMO,$^{62}$ which explained the stability of La@C$_{82}$ anion (closed-shell structure) and the relatively easy first reduction. M@C$_{82}$ (M= Y, La, Ce, and Pr) exhibit very similar UV-vis-NIR absorption spectra because of the same cage structure ($C_{2v}$) and electronic state ($C_{82}^{3-}$).$^{63,64,65}$

2.3.3. Dimetallofullerenes

The important progress in the isolation and purification of the representative dimetallofullerenes, Sc$_2$@C$_{84}$, La$_2$@C$_{80}$ and Ce$_2$@C$_{80}$, in macroscopic quantities made it possible to investigate their properties.$^{66,67}$

The C$_{84}$ empty cage fullerene has 24 isomers that satisfy the IPR,$^{57}$ but only two isomers ($D_2$ and $D_{2d}$) are produced abundantly.$^{45}$ However, the most abundant isomer of Sc$_2$@C$_{84}$ has a $D_{2d}$ structure. Based on theoretical calculations,$^{66,68}$ X-ray$^{69}$ and $^{45}$Sc NMR analysis,$^{70}$ the two Sc atoms encapsulated inside isomer $D_{2d}$ are equivalent and transfer 4
electrons to the cage to stabilize the structure. The electronic structure is formally described as \((\text{Sc}^{2+})_2\text{C}_{84}^{4-}\). 66

From the LUMO-HOMO gap study and \(^{13}\text{C}\) NMR analysis of \(\text{C}_{80}\) fullerene\(^{71,72}\), the \(D_2\) isomer is the most stable of the 7 possible isomers. However, from theoretical calculations and NMR analysis, the least stable \(I_h\) isomer turns out to be the most favorable structure when 2 La atoms are encapsulated inside the fullerene cage.\(^{71}\) The explanation is that charge is transferred from the internal metal atoms to the cage, making the whole structure more stable. The \(I_h\) isomer has only two electrons in the four-fold degenerate HOMOs, so it can accept six more electrons from two La atoms to form a stable closed shell electronic structure with a large HOMO-LUMO gap. The electronic structure can be described as \((\text{La}^{3+})_2\text{C}_{80}^{6-}\). 71

The largest fullerene cage isolated to date, a stable \(\text{Dy}_2@\text{C}_{100}\) dimetallofullerene was recently produced and isolated by Dunsch and Yang.\(^{73}\)

2.3.4. Trimetallic Nitride Endohedral Metallofullerenes

The Metallofullerene family, \(\text{Sc}_{3-n}\text{M}_n\text{N}@\text{C}_m\) (\(M=\text{Y, La, and lanthanides; } n=0-3; \) \(m=68,78,80\)) is produced in relatively high yields by the TNT process.\(^{14}\) \(\text{Sc}_3\text{N}@\text{C}_{80}\) is a representative member and its yield even exceeds empty-cage \(\text{C}_{84}\). The structure of \(\text{Sc}_3\text{N}@\text{C}_{80}\) has been investigated by theoretical calculations,\(^{74}\) single crystal X-ray diffraction and \(^{13}\text{C}\) NMR analysis.\(^{14}\) Analogous to the structure of \(\text{La}_2@\text{C}_{80}\) mentioned above, theoretical calculations of the structure of \(\text{Sc}_3\text{N}@\text{C}_{80}\) suggested that the internal \(\text{Sc}_3\text{N}\) cluster transfer six electrons to the \(I_h\) cage (Figure 6a), resulting in a closed shell electronic structure which is described as \((\text{Sc}_3\text{N})^{6+}\text{C}_{80}^{6-}\). 74
The $^{13}$C NMR spectrum of Sc$_3$N@C$_{80}$ displays only two lines with an intensity ratio of 3:1. The $^{45}$Sc NMR spectrum exhibits a single symmetric line. The information from NMR experiments indicated the Sc$_3$N$_{6+}$ cluster rotates rapidly inside the negatively charged cage on the time scale of the NMR experiments. The electrostatic potential map of C$_{80}^{-}$ showed almost concentric circles with no clear minima. This indicates that the encapsulated metal cluster Sc$_3$N$_{6+}$ is not fixed at specific internal bonding sites but can freely rotate inside the C$_{80}$ Cage (Figure 6b), as found for La$_2$@C$_{80}$. 

![Figure 6](image)

**Figure 6.** (a) Charge transfer model for Sc$_3$N@C$_{80}$ (b) Rapid circular motion of the Sc$_3$N cluster inside the I$_h$ C$_{80}$ cage.

A single-crystal X-ray diffraction study of Sc$_3$N@C$_{80}^+$ Co$^{II}$ (OEP)$\cdot$1.5CHCl$_3$$\cdot$0.5C$_6$H$_6$ (OEP is the dianion of octaethylporphyrin) shows that a planar internal Sc$_3$N cluster is favored. The free Sc$_3$N cluster prefers to have the pyramidal structure. However, in Sc$_3$N@C$_{80}$, the large positive charges on Sc are very effective for electrostatic attractive interaction with the negatively charged nitrogen and carbon cage. In order to avoid severe electrostatic repulsions between the Sc atoms, the Sc$_3$N cluster prefers to adopt a planar structure in Sc$_3$N@C$_{80}$ so that the Sc-Sc distance increases.
Besides Sc$_3$N@C$_{80}$, the other horologes, Sc$_3$N@C$_{68}$ and Sc$_3$N@C$_{78}$, are produced in slightly higher abundance than the most prominent non-TNT Sc$_2$@C$_{84}$. According to the isolated-pentagon rule (IPR), for fullerenes smaller than C$_{70}$, only C$_{60}$ has a cage with a classic IPR allowed icosahedral cage. However, the stable Sc$_3$@C$_{68}$ molecule represents the first exception to the IPR with three fused pentagons orthogonal to the C$_3$ axis (Figure 7). The highly symmetric D$_3$ structure for Sc$_3$N@C$_{68}$ has been confirmed by $^{13}$C NMR data and recent X-ray crystallographic study.

In contrast to the planar structures of trimetallic nitride clusters in the Sc$_3$N@C$_{2n}$ (2n = 68, 78 and 80) and Lu$_3$N@C$_{80}$, the X-ray crystal structure of Gd$_3$N@C$_{80}$ revealed that the Gd$_3$N unit within the I$_h$ C$_{80}$ cage is pyramidal, with the nitrogen atom displaced about 0.5 Å out of the Gd$_3$ plane. The differences in pyramidalization of the nitrogen atom were interpreted by the discrepancy in the ionic radii of the metals involved. The radius of Gd$^{3+}$ (1.08 Å) is significantly larger than either Sc$^{3+}$ (0.88 Å) or Lu$^{3+}$ (1.00 Å).

Recently, the egg-shaped fullerene Tb$_3$N@C$_{84}$ was reported by Zuo et al (Figure 8a). The carbon cage of Tb$_3$N@C$_{84}$ violated the isolated pentagon rule with C$_s$ symmetry and a single site where two pentagonal rings fused. It is remarkable that egg-shaped Tb$_3$N@C$_{84}$ adopts one of the 51568 possible non-IPR structures for the C$_{84}$ cage. Mixed-metal nitride cluster metallofullerene CeSc$_2$N@C$_{80}$ (Figure 8b) has been synthesized and characterized by NMR spectroscopy and X-ray crystallography. Analogous to Sc$_3$N@C$_{80}$, the $^{13}$C NMR spectrum of CeSc$_2$N@C$_{80}$ exhibited only two lines with chemical shifts 142.85 and 135.90
ppm (3 to 1 intensity ratio) for the icosahedral $C_{80}$ cage carbons. Temperature dependent $^{45}\text{Sc}$ NMR spectroscopic studies showed that the internal motion provided the same average electronic environment for the two Sc atoms in the CeSc$_2$N cluster. The temperature-dependent Curie up-field chemical shift for the $^{45}\text{Sc}$ signal of CeSc$_2$N@C$_{80}$ was caused by buried f-electron spin remaining on the Ce$^{3+}$($4f^15d^0$) ion.

![Figure 8](image)

**Figure 8.** (a) X-ray crystal structure of Tb$_3$N@C$_{84}$ (b) Schematic structure of CeSc$_2$N@C$_{80}$

Encapsulation of larger metal ions in the TNT process produces families of endohedral fullerenes that include carbon cages larger than $C_{80}$ but in relatively lower yield. For instance, a family of dysprosium-based trimetallic nitride endohedral fullerenes Dy$_3$N@C$_{2n}$ ($39 \leq 2n \leq 44$) was produced and isolated by Yang et al. (Figure 9a). The electronic absorptions of dysprosium-based trimetallic nitride endohedral fullerenes were found to be sensitive to the cage size. The UV/Vis/NIR spectra of the Dy$_3$N@C$_{2n}$ ($39 \leq 2n \leq 44$) exhibited characteristic spectral onsets and absorption peaks. Since the optical band gap could be calculated from the onset of the electronic absorption spectrum, Dunsch et al. classified the band gap of the Dy$_3$N@C$_{2n}$ ($39 \leq 2n \leq 44$) into two ranges: 1.38(5) to 1.51 eV (1) (for n=39–41; large-bandgap materials) and 0.80(9) to 0.84 eV (7, 8) (for n=42–44; small-bandgap materials).
On the basis of their different absorption properties, the Dy$_3$N@C$_{2n}$ (39 ≤ 2n ≤ 44) showed a variety of colors, as illustrated in the inset of Figure 9b. The spectroscopic studies for other lanthanide trimetallic nitride endohedral fullerenes M$_3$N@C$_{2n}$ (M = Gd, Tm and Tb; 39 ≤ 2n ≤ 44) have been reported as well.

Figure 9. (a) HPLC trace of Dy$_3$N@C$_{2n}$ (39 ≤ 2n ≤ 44) fullerene extract (linear combination of two 4.6×250 mm Buckyprep columns; flow rate 1.6 mL min$^{-1}$; injection volume 500 μL; toluene as eluent) (b) UV/Vis/NIR spectra of Dy$_3$N@C$_{2n}$ (39 ≤ 2n ≤ 44) 1–9 dissolved in toluene. Inset: Photographs of a Dy$_3$N@C$_{2n}$ fullerene extract mixture and 1–9 dissolved in toluene.

2.4. CHEMICAL REACTIVITIES

2.4.1. Chemical Reactivity of C$_{60}$

Because of the accessibility of fullerenes in macroscopic quantities, many modified fullerenes have been prepared by different chemical approaches developed during the last
decade. Most reactivity studies have been carried out with C_{60} due to its large abundance and behavior similar to C_{70} and higher fullerenes.

2.4.1.1. Reduction and Reaction with Nucleophiles

Chemical reduction of C_{60} can be easily achieved by reaction with electropositive metals. For example, the anion C_{60}^{n-} (n=1~5) can be produced by titrating a suspension of C_{60} in liquid ammonia with a solution of Rb (Scheme 1a). C_{60} also can be reduced to anionic species by treatment of Li metal in THF with ultrasound (Scheme 1b).

\[ \text{Scheme 1.} \]

(a) \[ C_{60} + n\text{Rb} \rightarrow C_{60}^{n-} + n\text{Rb}^+ \] \[ \text{Liquid NH}_3 \] \[ n=1\sim5 \]

(b) \[ C_{60} \rightarrow C_{60}^{n-} \] \[ \text{Li/THF} \]
[ ultrasound ]

The chemical and electrochemical experiments show that C_{60} is an electron deficient species. So it readily undergoes many nucleophilic additions. C_{60} reacts with organolithium (Scheme 2a) and Grignard compounds (Scheme 2b) to form hydrofullerene derivatives C_{60}H_{R_n} upon quenching of the resultant anion. The formation of intermediate RC_{60}^{-} is very fast. In order to maximize yields of monoadducts, C_{60}HR, the nucleophile was added stepwise (titration), followed by quantitative protonation.

\[ \text{Scheme 2.} \]

(a) \[ C_{60} + 1.2 \text{eq. RLi} \rightarrow C_{60}^{-} \rightarrow 0.01 \text{M HCl} \]

(b) \[ C_{60} + \text{Excess RMgBr} \rightarrow 0.01 \text{M HCl} \]
Bingel\textsuperscript{91} reported a very useful cyclopropanation reaction (Scheme 3). \(C_{60}\) reacts with the nucleophile, the stabilized \(\alpha\)-halomalonate anion, and the addition is followed by an intramolecular displacement of the halide by the anionic center on the fullerene. The reaction is fast, clean and proceeds in good yield. The cyclopropanation of \(C_{60}\) with diethyl bromomalonate in toluene with NaH as the base proceeds at room temperature. The cycloaddition site is regioselectively at 6,6 ring junction of \(C_{60}\) cage.

\textbf{Scheme 3.}

Hirsch \textit{et al.}\textsuperscript{92} extended this methodology to synthesize a series of \(C_{60}\) diethyl malonate diadducts. Of the eight theoretically possible diadducts, seven were isolated by HPLC from the reaction mixture. (Figure 10) Based on the different symmetries of the diadducts, the structures were identified by \(^{13}\text{C}\) NMR spectra and the correlation between their calculated polarities and retention times on an HPLC trace. The second nucleophilic cyclopropanations of \(C_{60}\) preferentially occur at \textit{equatorial} and \textit{trans-3} bonds, relative to the addent already bound to the fullerene core. Hirsch \textit{et al.} also reported the stepwise synthesis of a \(T_h\)-symmetric hexakisadduct (Figure 11).\textsuperscript{93} In fact, \textit{equatorial} bonds of products at each addition step showed an increasing regioselectivity toward further addition.
Figure 10. Eight different diadducts and yields (R=COOEt)

Figure 11. Schematic structure of T₄-symmetric hexakisadduct (R=COOEt)
The reaction of C\textsubscript{60} with α-bromomalonate derivatives (Bingel-Hirsch reaction) has proven to be a very powerful way to functionalize C\textsubscript{60} due to its versatility and the ready availability of the starting material. For example, a liquid-crystalline methanofullerene (Figure 12a) was synthesized by the cyclopropanation of C\textsubscript{60} with a malonic ester bearing two cholesterol groups.\textsuperscript{94} The preparation of a C\textsubscript{60} derivative with four phosphonate groups (C\textsubscript{60}[C(PO\textsubscript{3}Et\textsubscript{2})\textsubscript{2}]) (Figure 12b) was also achieved by Bingel-Hirsch-type reaction. Wilson \textit{et al.} subsequently hydrolyzed C\textsubscript{60}[C(PO\textsubscript{3}Et\textsubscript{2})\textsubscript{2}]\textsubscript{2} to obtain the corresponding water-soluble diphosphonic acid C\textsubscript{60} derivative.\textsuperscript{95}

\textbf{Figure 12.} (a) liquid-crystalline methanofullerene derivative (b) bis(methylene-diphosphonate) derivative of C\textsubscript{60}

Aliphatic amines undergo nucleophilic addition to C\textsubscript{60} (Scheme 4).\textsuperscript{96,97} First, a single electron is transferred from the amine to the C\textsubscript{60} to generate a radical anionic species. Then the C\textsubscript{60} radical anion recombined with the positively charged amino radical anion and gives neutral addition products by quick proton transfer. The color of the anion complex is typically green and changes to a brown reaction product after several hours. The reaction process was followed by EPR measurements. The signal intensity of the radical increased at the beginning, and then decreased because of formation of the diamagnetic product.\textsuperscript{98}
2.4.1.2. Oxidation and Reactions with Electrophiles

Although the reduction of C\textsubscript{60} is much easier than its oxidation, there are still some oxidative functionalizations as well as electrophilic additions that have been carried out\textsuperscript{99-102}.

Oxygenated fullerene C\textsubscript{60}O\textsubscript{n} (n up to 5) is produced by electrochemical oxidation of C\textsubscript{60}\textsuperscript{99} or photolysis of the crude fullerene extract\textsuperscript{100}. It is generated together with the fullerenes by graphite vaporization due to a small amount of oxygen present in the generator\textsuperscript{99}.

Hawkins reported the oxidation of C\textsubscript{60} by the strong and selective oxidizing reagent osmium tetroxide.\textsuperscript{101} The treatment of C\textsubscript{60} with an equivalent amount of OsO\textsubscript{4} in presence of 70\% pyridine, or with excess OsO\textsubscript{4} and pyridine yielded the monoadduct. (Scheme 5) The addition of an osmyl unit to C\textsubscript{60} successfully gave the first crystal structure of a fullerene, which confirmed the soccer ball-shaped carbon framework.\textsuperscript{101}

2.4.1.3. [4+2] Cycloaddition

In addition, halogenations of C\textsubscript{60} forming C\textsubscript{60}X\textsubscript{n} (X=Br, Cl, F) have been reported for a wide variety of n values.\textsuperscript{102}
A large variety of cycloaddition reactions ([4+2], [3+2], [2+2], [1+2]) have been carried out with C_{60}. These reactions are very useful for the introduction of functional groups to C_{60}.

Fullerenes readily undergo Diels-Alder cycloaddition with a variety of reactive dienes, such as cyclopentadiene, furan and anthracene. The 6-6 double bonds of C_{60} always act as a dienophile in the Diels-Alder reaction. The reaction conditions for cycloadduct formation strongly depend on the reactivity of the diene. For example, C_{60} reacts quickly with cyclopentadiene at room temperature, giving the monoadduct in 68% yield. However, in a study of [4+2] cycloaddition of C_{60} with anthracene, only a 13% yield of cycloadduct was observed after using 10 eq. of diene in refluxing benzene for three days.

Many cycloadducts prepared by the reaction of C_{60} with dienes are thermally unstable, and rapidly revert to the original diene and the free fullerene upon heating. For example, Giovane studied the kinetic stability of the C_{60}-cyclopentadiene Diels-Alder adduct. They found that the cycloadduct undergoes reversion rapidly at 95°C.

In contrast to those thermally unstable cycloadducts, the adducts obtained from oQDM (ortho-quinodimethanes) showed great thermal stability. The parent quinodimethane, a cis-diene, is a very reactive intermediate in the Diels-Alder reaction. The Diels-Alder reaction of...
C$_{60}$ with oQDM has been carried out from different precursors shown in scheme 7.\textsuperscript{107} Most reports describe stabilities to temperatures above 200°C.\textsuperscript{108}

### Scheme 7.

![Scheme 7](image)

### 2.4.1.4. [3+2] Cycloaddition

Five membered ring adducts of C$_{60}$ can be synthesized by [3+2] cycloaddition of an azomethine ylides, which are very reactive 1-3 dipolar planar species. Prato \textit{et al.} first reported the reaction of N-methylglycine with CH$_2$O to form an azomethine ylide by decarboxylation. The ylide undergoes [3+2] cycloaddition to C$_{60}$ to give the N-methylpyrrolidine derivative (Scheme 8).\textsuperscript{109}

### Scheme 8.

![Scheme 8](image)

1,3-Dipolar cycloaddition of azomethine ylides to fullerenes (the Prato reaction) is one of the most useful reactions for obtaining functionalized fullerene derivatives. The use of a
different starting aldehyde allows the synthesis of 2-substituted N-methyl-3,4-fulleropyrrolidines. On the other hand, N-substituted fulleropyrrolidines can be produced by condensation of a variety of N-functionalized glycines with aldehydes.\textsuperscript{110}

**Scheme 9.**

\[
\begin{align*}
R_1\text{NHCH}_2\text{CHOOH} + R_2\text{CHO} & \xrightarrow{\Delta} C_{60} \\
\end{align*}
\]

A main advantage of the Prato reaction is that two functional chains can be simultaneously incorporated on the nitrogen and adjacent carbon atom of the pyrrolidine ring (Scheme 9). For instance, Martin and Guldi reported the synthesis of several fullerene-\(\pi\)-extended tetrathiafulvalene (exTTF) dyads (Figure 13) by the Prato reaction.\textsuperscript{111,112} The electron-donating dyads connected to the electron-accepting \(C_{60}\) through a vinylene linker on the side chain of pyrrolidino ring provided long distance charge-separated states. Moreover, a tri(ethylene glycol) monomethyl ether (mTEG) chain was introduced to provide solubility in organic solvents.

**Figure 13.** Fullerene-\(\pi\)-extended tetrathiafulvalene dyads
Recently, retro-cycloaddition reactions of pyrrolidinofullerenes under thermal and catalytic conditions were reported by Martin and Echegoyen et al.\textsuperscript{113}

### 2.4.1.5. [2+2] Cycloaddition

The addition of benzynes to $C_{60}$ leads to [2+2] cycloadducts. Hoke and coworkers\textsuperscript{114} reported [2+2] cycloaddition of a benzyne and $C_{60}$ by using anthranilic acid as a precursor (Scheme 10). Along with the monobenzyne product, some dibenzyne and tribenzyne products were also found from mass spectra. In addition, either photochemical or thermal [2+2] cycloadditions of $C_{60}$ with enones, quadricyclane and electron rich alkynes have been reported.\textsuperscript{102}

**Scheme 10.**

![Scheme 10](image)

### 2.4.1.6. [2+1] Cycloaddition

[2+1] cycloaddition is one of many very efficient reactions for the preparation of fullerene derivatives. Numerous reactions of $C_{60}$ with diazo compounds have been performed and their stereochemistry studied. For instance, in the addition of diazomethane to $C_{60}$, the elimination of $N_2$ can be achieved both thermally and photochemically.\textsuperscript{115} The photolysis gives a mixture of [6,5]-open and [6,6]-closed, whereas the thermolysis leads almost exclusively to [6,5]-open product (Scheme 10).
In theory, it is possible to form four isomers: [6,5]-open, [6,5]-closed, [6,6]-open, and [6,6]-closed, depending on whether addition takes place at 6,6 or 6,5 bonds and whether that bond breaks or not. But experimentally, the 6,5-closed and the 6,6-open isomer are not observed because they are energetically disfavored.\textsuperscript{116}

A carbene can exclusively add to the [6,6]-ring junction of C\textsubscript{60} to generate the [1+2] cycloadduct.\textsuperscript{116} For example, the O-benzyl and O-pivaloyl protected diazirine can be used to produce nucleophilic carbenes thermally by elimination of a molecule of N\textsubscript{2} (Scheme 13).\textsuperscript{117} The carbene subsequently reacts with C\textsubscript{60} to give the monoglycosylate adduct. The fullerene derivatives are chiral and enantiomerically pure. The deprotection of the sugar residues would generate fullerenes and provide potential application, in biochemical and pharmacological fields.
2.4.2. Chemical Reactivity of Metallofullerenes

Compared with C\textsubscript{60}, less work has been done on the functionalization of metallofullerenes because of the slow progress with the isolation and purification of sufficient quantities of metallofullerenes. However, fullerenes with metals inside may have novel properties and potential applications in many fields, such as medicine, electronic materials.\textsuperscript{118} This has motivated scientists to keep exploring the functionalization of metallofullerenes.

2.4.2.1. Reaction with Disilirane

Akasaka and coworkers first reported the exohedral adducts of La@C\textsubscript{82}.\textsuperscript{119} La@C\textsubscript{82} reacts with 1,1,2,2-tetrakis(2,4,6-trimethylphenyl)-1,2-disilirane (Mes = 2,4,6-trimethylphenyl) in toluene upon photoirradiation at 20 °C with a tungsten-halogen lamp. The 1:1 adduct was verified by means of mass spectrometry. Interestingly, they found that both Gd@C\textsubscript{82} and La@C\textsubscript{82} are thermally reactive towards disilirane (Scheme 13)\textsuperscript{119,120}, whereas empty cage fullerene, C\textsubscript{60}\textsuperscript{121} and C\textsubscript{70}\textsuperscript{122} did not react. The high thermal reactivity of La@C\textsubscript{82} and Gd@C\textsubscript{82} towards disilirane can be explained by their characteristic electronic properties.\textsuperscript{119,120,123} A non-local density function calculation predicts that the ionization potential (I\textsubscript{p}) and electron affinity (E\textsubscript{a}) of La@C\textsubscript{82} and Gd@C\textsubscript{82} are much smaller and larger, respectively than those for C\textsubscript{60} and C\textsubscript{70}. This strongly agrees with the fact that both La@C\textsubscript{82} and Gd@C\textsubscript{82} have lower oxidation and reduction potentials than C\textsubscript{60} and C\textsubscript{70}. They are stronger electron donors and acceptors than empty fullerenes.
Recently, Akasaka et al. reported that the reactivity of $\text{Sc}_3\text{N}@\text{C}_{80}$ toward 1,1,2,2-tetramesityl-1,2-disilirane was much different from that of $\text{La}_2@\text{C}_{80}$. $\text{La}_2@\text{C}_{80}$ reacted both photochemically and thermally with 1,1,2,2-tetramesityl-1,2-disilirane. However, $\text{Sc}_3\text{N}@\text{C}_{80}$ reacted only photochemically with the disilirane reagent. Although these two metallofullerenes have the same carbon cage ($I_h$) and electronic structure $\text{C}_{80}^{6-}$, the internal metal clusters exhibited significant control on the reactivities. Both theoretical calculations and electrochemical studies have demonstrated that $\text{Sc}_3\text{N}@\text{C}_{80}$ has a much larger energy gap than $\text{La}_2@\text{C}_{80}$, resulting in a low thermal reactivity toward the disilirane reagent.

The dynamic behavior of metals encapsulated inside fullerene cages has attracted a great deal of interest. In early studies, by analyzing the $^{13}\text{C}$ and $^{139}\text{La}$ NMR of $\text{La}_2@\text{C}_{80}$, Akasaka et al. reported that the two La atoms were not stabilized at specific sites, but could rotate freely in three dimensions inside the $\text{C}_{80}$ cage. Interestingly, recent X-ray crystallographic and variable-temperature $^{139}\text{La}$ NMR analyses of $\text{La}_2@\text{C}_{80}$ revealed that the free random motion of two La atoms was restricted to two-dimensional hopping motion between two sites along the equator of the $\text{C}_{80}$ cage after the exohedral functionalization with 1,1,2,2-tetrakis(2,4,6-trimethylphenyl)-1,2-disilirane. (Figure 14)
2.4.2.2. Bingel-Hirsch Reactions

The Bingel-Hirsch reaction of La@C₈₂ was carried out with diethyl bromomalonate in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU).¹²⁸,¹²⁹ Five monoadducts were isolated and characterized. Four of the monoadducts (mono-A, -B, -C, and -D) were ESR-inactive and singly bonded regioisomers (Figure 15a), suggested by X-ray crystal structure and NMR spectroscopy. One monoadduct (mono-E) was an ESR-active conventional cyclopropanated Bingel-Hirsch adduct. The singly bonded monoadducts were quite unstable. They underwent the retro-Bingel reaction either under thermal treatment or during electrochemical reductions. However, mono-E showed the remarkable thermal stability and reversibility on electrochemical redoxations. Under the same approach, Akasaka et al. also reported the synthesis and characterization of the first La@C₈₂ bisadduct.¹³⁰ X-ray crystallographic analysis showed that a pair of enantiomers of this bisadduct linked together to form a dimer in the single crystal. (Figure 15b)
Very recently, Echegoyen et al. reported the cycloaddition of bromomalonates to Y$_3$N@C$_{80}$, while Sc$_3$N@C$_{80}$ did not react under the same experimental conditions.$^{131}$ The crystal structure of the Bingel-Hirsch adduct Y$_3$N@C$_{80}$-C(CO$_2$CH$_2$Ph)$_2$ clearly showed that the original C1-C9 bond were lengthened to 2.30Å upon addition (Figure 16a).$^{132}$ Y-1 in Y$_3$N@C$_{80}$-C(CO$_2$CH$_2$Ph)$_2$ is located immediately adjacent to the site of addition with full crystallographic occupancy. However, Y-2 and Y-3 were strongly disordered. This suggested that the dynamic motion of Y$_3$N group is free to spin along the N-Y-1 axis as shown in Figure 16b.
2.4.2.3. Hydroxylation

Cagle and coworkers\textsuperscript{133} prepared Ho\textsubscript{x}@C\textsubscript{82}(OH)\textsubscript{y} (x=1,2; y \approx 16) by stirring a solution containing Ho\textsubscript{x}@C\textsubscript{82}, KOH and the phase-transfer catalyst, TBAOH (tetrabutylammonium hydroxide). Sun et al.\textsuperscript{134} synthesized Pr@C\textsubscript{82}O\textsubscript{m}(OH)\textsubscript{n} (M \approx 10 and n \approx 10) by treatment with nitric acid, followed by hydrolysis. The first water-soluble trimetallic nitride endohedral metallofullerene Sc\textsubscript{3}N@C\textsubscript{80}(OH)\textsubscript{10}O\textsubscript{10} was synthesized by Iezzi et al (Scheme 14).\textsuperscript{135} A toluene solution of Sc\textsubscript{3}N@C\textsubscript{80} was reduced by sodium metal to produce a black polyanionic radical precipitate. The exposure of this mixture to water and air then oxidized the precipitate to produce the water-soluble TNT endohedral metallofullerols.
2.4.2.4. Diels-Alder Cycloaddition

Iezzi *et al.* synthesized the first [4+2] cycloadduct of a TNT metallofullerene.\textsuperscript{136} The \textsuperscript{13}C labeled metallofullerene monoadduct was obtained by Diels-Alder cycloaddition of highly reactive \textsuperscript{13}C labeled 6,7-dimethoxyisochroman-3-one and Sc\textsubscript{3}N@C\textsubscript{80} in 1,2,4-trichlorobenzene (TCB) solution.\textsuperscript{(Scheme 15)}

The single narrow signal in the \textsuperscript{13}C NMR spectrum of the \textsuperscript{13}C labeled adduct indicated the presence of a plane of symmetry in the adduct. The HMQC (Heteronuclear Multiple Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) spectra verified the symmetric attachment of the functional group to the C\textsubscript{80} cage.\textsuperscript{136} For the three possible reactive sites on I\textsubscript{h} Sc\textsubscript{3}N@C\textsubscript{80} cage

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17}
\caption{(a-c) Possible reactive sites (green) on the I\textsubscript{h} Sc\textsubscript{3}N@C\textsubscript{80} cage (d) Gauss View structure mono-adduct 4 from addend addition at a [5,6] bond-juncture (site “b”) on the Sc\textsubscript{3}N@C\textsubscript{80} cage.\textsuperscript{136}}
\end{figure}
(Figure 17), b turns out to be the actual reaction site due to its smallest strain effect, as verified by X-ray crystallography.\textsuperscript{137}

The yield of the Sc\textsubscript{3}N@C\textsubscript{80} monoadduct was only slightly greater than 10% when a ten-fold excess of reagent was used. This suggested that Sc\textsubscript{3}N@C\textsubscript{80} was much less reactive than the empty-cage fullerene C\textsubscript{60}, which produced 47% monoadduct and 22% bisadduct in the reaction with nearly equivalent 6,7-dimethoxyisochroman-3-one.\textsuperscript{138} Stevenson \textit{et al.} recently reported that Gd\textsubscript{3}N@C\textsubscript{80} was more reactive than Sc\textsubscript{3}N@C\textsubscript{80} towards to 6,7-dimethoxyisochroman-3-one.\textsuperscript{139} 10-20\% of the bisadduct of Gd\textsubscript{3}N@C\textsubscript{80} was isolated under the same Diels-Alder cycloaddition condition as used for Sc\textsubscript{3}N@C\textsubscript{80}.\textsuperscript{139}

2.5. APPLICATIONS

2.5.1. Biomedical Applications

Soon after the discovery of fullerenes, many efforts were devoted to the application of fullerenes and their derivatives. The interesting properties of fullerenes attract scientists to study and show significant potential application in medicine. However, the bottleneck for fullerenes to be used in medicinal chemistry is their poor solubility in polar solvents. In order to make fullerenes more bio-available, various functionalizations have been utilized to increase their hydrophilicity (e.g.-OH, -COOH, -NH\textsubscript{2}). Water-soluble fullerenes have been investigated as neuroprotective agents, HIV protease inhibitors, MRI contrast agents, etc.\textsuperscript{140}

2.5.1.1. Fullerenes as Antioxidants and Neuroprotective Agents

Many neurodegenerative disorders, such as Parkinson’s disease, are attributed to the action of the oxygen or nitric oxide radicals. These species induce cellular instability, leading
to a programmed cell death. “Free radical scavengers,” such as C<sub>60</sub>, can be used to decrease excitotoxic neuronal death because it can easily react with oxygen radical species such as the superoxide (O<sub>2</sub>·<sup>-</sup>) and the hydroxyl (·OH) radical.<sup>141, 142</sup>

Water-soluble carboxylic acid C<sub>60</sub> derivatives, containing three malonic acid groups per molecule, have been demonstrated to act as effective neuroprotective antioxidants <em>in vitro</em> and <em>in vivo</em>.<sup>142</sup> Hirsch, first synthesized this compound through the reaction of C<sub>60</sub> with diethyl bromomalonate in the presence of excess NaOH, followed by hydrolysis of the ester bonds (Scheme 16).<sup>143</sup> The mono and bisadduct were also produced, but they are less soluble than the triadducts.

**Scheme 16.**

There are two isomers for the triadducts (C<sub>3</sub> and D<sub>3</sub> Symmetry). EPR studies shows both isomers are unusually potent scavengers of the hydroxyl radical and superoxide radical anion in solution. However, in a study of neuroprotection against excitotoxic injury in vitro, the C<sub>3</sub> isomer turns out more effective than D<sub>3</sub> because all the carboxylic groups of C<sub>3</sub> are on the same hemisphere. Therefore, the C<sub>3</sub> isomer has a greater ability to enter lipid membranes.<sup>142</sup>
It is found that when the number of addends on fullerenes increases, the radical scavenging ability decreases. The loading capability of fullerenes decreases as well, due to steric effects.\(^{144}\) Hirsch and Brettreich developed a synthesis of a highly water-soluble monoadduct, which is obtained by covalently attaching a dendrimer to C\(_{60}\) (Figure 18).\(^{145}\) This monoadduct has 18 carboxylic groups and reaches the highest water-solubility for C\(_{60}\) (34mg/ml at pH 7.4) known to date.

![Figure 18. Highly water-soluble dendro[60] fullerene](image)

### 2.5.2.1. Inhibition of HIV-P

The protease of human immunodeficiency virus (HIV-P) is a fundamental enzyme for virus survival.\(^{140}\) The HIV-P cleaves a polyprotein shortly after viral budding, and is essential for the completion of the life cycle of HIV-1. The HIV-P active site is an open-ended cylindrical hydrophobic cavity. On the surface of the cavity, two acidic amino acid residues, Asp25 and Asp125, catalyze the hydration of the peptide bonds of the substrate.\(^{140}\) In 1993, Wudl and coworkers\(^{146}\) performed molecular modeling studies and they found HIV-P could be inhibited by introducing a C\(_{60}\) derivative into its catalytic cavity of HIV-P. This is due to the diameter of that C\(_{60}\) derivative which is close to the diameter of this cavity.
The same research group synthesized the first generation fullerene inhibitor of HIV-P (Figure 19a),¹⁴⁷ which can fit into the active site of the cavity through strong van der Waals interactions. Friedman suggested a stable interaction in which the two aspartic residues could increase the efficiency of the potential inhibitions.¹⁴⁷ On this basis, Prato and coworkers synthesized a C₆₀ derivative bearing two ammonium groups (Figure 19b) via 1,3-dipolar cycloaddition of an azomethine to C₆₀.¹⁴⁸

\[
R = \text{HOC(O)(CH}_2\text{)}_2\text{C(O)NH(CH}_2\text{)}_2
\]

![Figure 19](image)

**Figure 19.** Fullerene inhibitor of HIV protease

The distance between the two-ammonium functional groups was 5.1 Å, a value very close to the distance for efficient electrostatic interactions and hydrogen bonding with two aspartic residues. Molecular modeling studies show that this derivative can fit well inside the HIV-P cavity (Figure 20), and the interactions between the ammonium groups and the aspartic residues stabilize the complexation of the enzyme with the derivative.¹⁴⁸,¹⁴⁹
2.5.3.3. Fullerene Based Protein

The first water-soluble C_{60}-peptide conjugate was synthesized and characterized by Toniolo et al. A methanofullerene carboxylic acid was covalently linked to the amino group of the hydrophilic C-terminal 4-8 sequence of peptide T (Scheme 17). The biological and pharmacological activities of this fullerene-peptide T conjugate [4–8] were studied. Analogous to the parent peptide T [4–8] (a cellular receptor), the C_{60}-peptide conjugate also activates human monocyte chemotaxis through the CD_{4}/T_{4} antigen.

Scheme 17.

The formation of the C_{60}-derivatized protein can also be achieved by using
fulleropyrrolidine as the precursor (Scheme 18). The N-H fulleropyrrolidine was generated by treating N-tritylfulleropyrrolidines with trifluoromethanesulfonic acid and pyridine. The N-H fulleropyrrolidine was subsequently reacted with 3-maleimidopropionyl chloride to produce a thiol selective fullerenomaleimide. Azurin is a redox protein which can bind copper ions and act as an electron transfer agent in the denitrification chains of several bacteria. Kurz et al. mutated azurin protein by introducing an exposed Cys residue in order to facilitate further linking with thiol selective fullerenomaleimide to form a C₆₀-based thiol adduct. The electrochemical behavior of this fullerene-protein conjugate showed a direct communication between the two moieties and that no protein denaturation occurred during the redox process. Capaccio et al. reported a similar approach to attach fullerenes to biomolecules that involves the use of molecular adapters biotin. The biotin unit was incorporated into a fulleropyrrolidine by dicyclohexylcarbodiimide (DCC) coupling of 6-((biotinoyl)-amino)hexanoic acid (biotin-X) with N-H fulleropyrrolidine. Streptavidin was used as a molecular adapter to facilitate the attachment of biotin-conjugated proteins to biotinylated fullerene through strong biotin-streptavidin interaction. The feasibility of this two step coupling approach was demonstrated by binding fluorescein-conjugated streptavidin and biotinylated alkaline phosphatase.

In addition, Hirsch et al. reported noncovalent complexation of positively charged ZnCytc (zinc cytochrome c) with polyanionic dendrofullerenes through electrostatic interaction.
Scheme 18. Coupling proteins to fulleropyrrolidine (a) trifluoromethanesulfonic acid and pyridine (b) 3-maleimidopropionyl chloride (c) DCC and Biotin-X

2.5.4.4. Metallofullerene as Radiotracer and MRI Contrast Agents

One of most important applications of endohedral metallofullerenes is in the nuclear medicine field. Cagle and coworkers studied the biodistribution of water-soluble radioactive metallofullerene compounds Hoₙ@C₈₂(OH)ₙ (x=1,2; y=16) by using BALB/C mice. The biodistribution, studied over a 48-hour period, showed that the $^{166}$Ho tracer displayed slow clearance from most tissue, and then selectively localized in the liver and bone. The
distribution and relocation of metallofullerene derivatives in selected organs offers the opportunity for “organ-specific targeting”.

Shinohara and colleagues synthesized and characterized water-soluble multi-hydroxyl lanthanoid (La, Ce, Gd, Dy and Er) endohedral metallofullerenes for the use of magnetic resonance imaging (MRI) contrast agents. Good contrast agents, having high $r_1$ and $r_2$ (longitudinal and transverse relaxivities for water protons) values, can enhance the resolution of the image and provide better sensitivity. Among that series of lanthanoid metallofullerenols, Gd@C$_{82}$(OH)$_m$ show highest water proton relaxivity: $r_1$=73, $r_2$=80 (20 MHz, 19±1°C, pH=7±1). These values are much higher than that of commercial MRI contrast agents, such as the gadolinium chelate compound Gd-DTDA ($r_1$=4.4, $r_2$=5.5). An extremely strong signal enhancement can be observed for Gd metallofullerenols in phantom MRI studies (Figure 21).
Bolskar and coworkers developed the first soluble M@C_{60} derivative MRI contrast agent. The new compound Gd@C_{60}[C(COOH)_{2}]_{10} with sufficient carboxylic groups is highly soluble, air stable and also available since it is based on the more abundant M@C_{60} fraction: r_1 relaxivity in water for Gd@C_{60}[C(COOH)_{2}]_{10} is 4.6 mM^{-1}S^{-1}, which is comparable to the commercial MRI contrast agent gadodiamide (r_1=4.3 mM^{-1}S^{-1}). Wilson et al. reported that the proton relaxivities for Gd@C_{60}[C(COOH)_{2}]_{10} increased strongly with decreasing pH (pH: 3-12). Dynamic light scattering studies showed that the pH dependency of the proton relaxivity of Gd@C_{60}[C(COOH)_{2}]_{10} was caused by particle aggregations.

Recently, Fatouros, Dorn and Gibson et al. reported the water-soluble poly(ethylene glycol) functionalized and hydroxylated Gd_3N@C_{80} MRI contrast agent, Gd_3N@C_{80}[DiPEG_{5000}(OH)_x] (Figure 22a). The measured r_1 and r_2 relaxivities for this nanoparticle were significantly higher than that for gadodiamide at 0.35, 2.4, and 9.4 T. In studies of in vitro agarose gel infusion, 30 times less concentrated Gd_3N@C_{80}[DiPEG_{5000}(OH)_x] showed equivalent image intensities in comparison with gadodiamide (Figure 22b). Lower diffusion rates were observed for Gd_3N@C_{80}[DiPEG_{5000}(OH)_x] relative to gadodiamide in live normal rat brain tissue. Directly infusing Gd_3N@C_{80}[DiPEG_{5000}(OH)_x] into a tumor-bearing brain suggested an improved tumor delineation in comparison with the conventional intravenous injection of gadodiamide. The functionalized trimetallic nitride endohedral metallofullerene species Gd_3N@C_{80}[DiPEG_{5000}(OH)_x] is expected to be a new MRI contrast agent, as demonstrated with in vitro relaxivity and MR imaging studies, in infusion experiments with agarose gel and in vivo rat brain tumor studies.
Figure 22. (a) Pegylated-hydroxylated metallofullerenes: \( \text{Gd}_3\text{N@C}_{80}[\text{DiPEG}_{5000}(\text{OH})_x] \), (b) \( T_1 \)-weighted MR image (700/10) of aqueous solutions of \( \text{Gd}_3\text{N@C}_{80}[\text{DiPEG}_{5000}(\text{OH})_x] \) (inner ring, concentration decreasing in clockwise direction: 0.2020, 0.0101, 0.0505, 0.0252, 0.0126, 0.0063, 0.0032, and 0.0016 mmol/L) and gadodiamide (outer ring, concentration decreasing in clockwise direction: 5.0, 3.0, 1.0, 0.70, 0.50, 0.30, 0.10, and 0.050 mmol/L). Note the substantially lower concentrations required for \( \text{Gd}_3\text{N@C}_{80}[\text{DiPEG}_{5000}(\text{OH})_x] \) for achieving equivalent image intensities to gadodiamide.\(^{158}\)

2.5.2. Fullerene-Based Solar Cells

\( \text{C}_{60} \) is a strong electron acceptor, which can be electrochemically reduced accepting up to six electrons.\(^52\) It is a useful material in photovoltaic devices because photoinduced electron transfer occurs from donor-type semiconducting polymers onto acceptor-type \( \text{C}_{60} \) molecules. However, the low solubility of \( \text{C}_{60} \) in common organic solvents limits its applications in composite (donor-acceptor) layer and bulk heterojunction devices. Wudl et al. in 1995 reported the synthesis of a soluble \( \text{C}_{60} \) derivative, [60]-PCBM (phenyl \( \text{C}_{61} \) butyric acid methyl ester)\(^{159}\), which has been extensively studied in polymer/fullerene solar cells over the past decade.

The synthesis of [60]-PCBM is outlined in Scheme 19. The unstable diazo compound was generated by based-induced decomposition of tosylhydrazone, then rapidly reacted with \( \text{C}_{60} \) to form
diazoline intermediate through 1,3-dipolar addition. The “open ”[5,6]-PCBM was obtained by nitrogen elimination and isomerized to [6,6]-PCBM through heating.

**Scheme 19.**

PCBM has been applied in photovoltaic research mainly as a component in bulk heterojunction-type composite photoactive layers. The PCBM bulk heterojunction solar cells are fabricated in sandwich geometry (Figure 23). Transparent, conducting electrodes, glass or plastic covered with ITO (indium tin oxide), are used as substrate. Conductive polymers, PEDOT:PSS [poly(ethylene-dioxythiophene) doped with polystyrenesulfonic acid)], are coated above the transparent conducting substrate. This PEDOT:PSS layer is of importance to improve the surface quality of the ITO electrode and facilitate hole injection/extraction. The active layer is the PCBM-based bulk-heterojunction, a blend of the donor and acceptor components. The active layers can be spin coated with solutions or vacuum deposited. The aluminum is evaporated on the top of device as the electrode. The overall process of converting light into electric current in a PCBM-based bulk
heterojunction solar cells is accomplished by three consecutive steps; (1) Absorption of a photon leading to the generation of the electron-hole pair (exciton). (2) Photon-induced electron transfer from the donor-type semiconducting polymer to the acceptor PCBM introduces free charge carries. (3) Charge transport to the anode (Al) and cathode (ITO) to supply a direct electric current for the consumer load.161

Figure 23. Device structure for polymer/fullerene bulk heterojunction solar cell

In 2001, Hummelen et al. reported a 2.5% efficient solar cell, which was obtained from a bulk-heterojunction of soluble poly[2-methoxy-5-(3′,7′-dimethyloctyloxy)-1,4-phenylene vinylene] (MDMO-PPV) and [60]-PCBM.162 Chlorobenzene was used as a solvent for spincoating in the weight ratio of 1:4 for MDMO-PPV to optimize the power conversion efficiency of 2.5%.162 Later, by replacing the C60 moiety of [60]-PCBM by the C70 fullerene derivative, Hummelen et al. also reported a 3.0% efficient [70]-PCBM:MDMO-PPV photovoltaic cell.163 Compared with [60]-PCBM, the less symmetric [70]-PCBM (phenyl C71 butyric acid methyl ester) displayed a significantly improved light absorption/harvesting in
the visible region.\textsuperscript{163} [70]-PCBM:MDMO-PPV films showed the best photovoltaic behavior by spin-coating from o-dichlorobenzene due to the optimized nanoscale morphology in the blend.\textsuperscript{163}

Another type of commonly studied fullerene-based bulk heterojunction solar cells is prepared with poly(3-alkylthiophenes)s and PCBM as active layer materials. P3HT (poly(3-hexylthiophene)), P3OT(poly(3-octylthiophene)) and P3DDT(poly(3-dodecylthiophene)) were used as electron donors in bulk heterojunction solar cell with high power conversion efficiencies up to 5%.\textsuperscript{164} Recently, Heeger \textit{et al.} reported that more than 6\% power-conversion efficiencies could be achieved by using tandem solar cells, in which two solar cells with different absorption characteristics were linked to improve solar absorption.\textsuperscript{165} [70]-PCBM:P3HT and [60]-PCBM:PCPDTBT (poly[2,6-(4,4-bis-(2-ethylhexyl)-4H-cyclopenta[2,1-b;3,4-b'] dithiophene)-alt-4,7-(2,1,3-benzothiadiazole)]) were used as bulk heterojunction materials in two active layers of tandem solar cell.\textsuperscript{165}

So far, less photovoltaic research has been done on metallofullerenes. Shinohara \textit{et al.} demonstrated the conductivity and an \textit{n}-type field effect transistor with La$_2$@C$_{80}$ thin film.\textsuperscript{166} The 10 nm thick La$_2$@C$_{80}$ film was made by a molecular beam deposition technique.\textsuperscript{166} The mobility of electron carriers in La$_2$@C$_{80}$ is $1.1 \times 10^{-4}$cm$^2$/Vs; which is much lower than that of C$_{60}$ ($8 \times 10^{-2}$cm$^2$/Vs)\textsuperscript{167} and C$_{70}$ ($2 \times 10^{-3}$cm$^2$/Vs).\textsuperscript{168} The low mobilities for La$_2$@C$_{80}$ were explained by small intermolecular overlap of La$_2$@C$_{80}$ LUMO.\textsuperscript{166} Unlike C$_{60}$ where the LUMO is effectively delocalized over the whole molecule, the LUMO of La$_2$@C$_{80}$ is localized on the encapsulated La metals.\textsuperscript{124}
REFERENCES


Chapter 3

Purification Trimetallic Nitride Template Endohedral Metallofullerenes
by Cyclopentadiene-Functionalized Merrifields Peptide Resin

3.1. INTRODUCTION

The scarcity of purified, homogeneous samples has hampered wider study and application of carbonaceous nanomaterials (fullerenes, endohedral metallofullerenes, and nanotubes).¹ Production of single-walled nanotubes usually leads to distributions in terms of diameter, chirality, and length, and formation of multiwalled nanotubes. The usual Krätschmer-Huffman (KH) electric-arc generator produces a mixture of fullerenes including C₆₀, C₇₀, C₇₆, C₇₈, C₈₄, etc.² The complexity is even greater for endohedral metallofullerenes because of the presence of multiple isomers of both the fullerenes and metallofullerenes.³ Until now, the only reliable methods for obtaining purified fullerene and endohedral metallofullerene (EMF) samples involved extensive, repetitive, time-consuming chromatographic procedures that required large volumes of solvent. Herein, we report that pure trimetallic nitride templated (TNT) EMFs,⁴ ⁵ ⁶ A₃N@C₂₅n (A = Sc and Lu, 39 ≤ 2n ≤ 44) can be obtained from crude soot extracts in a single, facile step based on selective chemical reactivity. TNT EMFs are currently being seriously investigated for a number of diagnostic (MRI and X-ray contrast agents) and therapeutic medical applications.⁷ ⁸

Our purification protocol is based on the kinetic stability of the TNT EMFs relative
to empty-cage fullerenes and classical EMFs, such as $A_x@C_{2y}$ ($x = 1-3, y = 30-50$), which are concomitantly produced and also of interest in medical imaging.\textsuperscript{8,9,10} Computational and experimental results demonstrate significant charge transfer (6 electrons) to the icosahedral ($I_h$ symmetrical) cage of TNT EMFs, e.g., $[Sc_3N]^{[6]@[C_{80}]}^{-6}$.\textsuperscript{11,12}

Aihara has calculated the minimum bond resonance energies (min BRE) for numerous fullerenes and metallofullerenes; negative BREs represent kinetic instability and higher chemically reactivity.\textsuperscript{12} This leads to the prediction of exceptional kinetic and thermodynamic stability of the icosahedral $[C_{80}]^{-6}$ cage of $A_3N@C_{80}$ that is significantly greater than neutral empty-cages $C_{60}$ and $C_{70}$, which are the major products of the K-H process (Table 1).\textsuperscript{12} Note that the min BRE value for the icosahedral $[C_{80}]^{-6}$ cage is the highest on the list, meaning it should be the least reactive in general. Consistent with this prediction, $Sc_3N@C_{80}$ is stable in air to temperatures of 600-650 K\textsuperscript{13} and in nanotube “peapods” in vacuo to temperatures in excess of 1300 K.\textsuperscript{14} An isochromanone derivative of $Sc_3N@C_{80}$ can be prepared only at elevated temperatures\textsuperscript{15}, in comparison with the analogous lower temperature reaction with the empty-cage fullerene $C_{60}$\textsuperscript{16}. Similarly, the Prato reaction of $Sc_3N@C_{80}$ produces a monoadduct under conditions which yield multi-adducts with empty cage fullerenes and classical endohedral metallofullerenes.\textsuperscript{17,18} Recently, the low reactivity of $Sc_3N@C_{80}$ in comparison to $La_2@C_{80}$ (a singlet ground state in which the cage has been assigned as the $I_h$ hexaanion, $C_{80}^{-6}$) in photochemical disilane cycloadditions has been reported and rationalized in terms of redox potentials.\textsuperscript{19} Obviously, the nature of the endohedral species plays a role in the reactivity and even regiochemistry, as recently demonstrated for $A_3N@C_{80}$ ($A = Y$ and Sc)\textsuperscript{20} and the recent
production of a diadduct from reaction of Gd$_3$N@C$_{80}$ with the o-quinodimethane derived from 6,7-dimethoxyisochromanaone in less time (1h @ 214 °C)\textsuperscript{21} than for production of the monoadduct (predominantly) of the Sc$_3$N@C$_{80}$ analogue (24h @ 214°C).\textsuperscript{15} Nonetheless, although not an absolute predictor of reactivities, the min BREs provide a useful framework for predicting and understanding the relative reactivities of fullerenes, EMFs and TNT EMFs.

**Table 1.** Minimum Bond Resonance Energies of Reported Fullerenes (from ref. 12) \textsuperscript{a}

Highest reactivity = 1. \textsuperscript{b} Not yet an isolated/identified isomer.

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3.2. RESULTS AND DISCUSSION

3.2.1. Preparation of Reactive Resin for Purification of TNT EMFs

*Scheme 1.*

On the basis of the observed low reactivity of the TNT EMFs, we reasoned that a suitably designed insoluble resin system could remove more reactive fullerenes from mixtures produced in the K-H process and allow the purification of the TNT EMFs in a facile manner. Fullerenes act as dienophiles in Diels-Alder cycloaddition reactions.\(^{22,23}\)

We prepared a cyclopentadiene-functionalized styrene-divinylbenzene resin (2) from the chloromethylated (Merrifield) resin 1 in a fashion similar to the procedure reported by Rotello *et al.* (Scheme 1).\(^{24}\) However, we used a lower level of cross-linking (1% vs 2%) and a higher loading of chloromethylated sites (3.5-4.5 vs 1.04 meq of Cl/g) for synthesis of resin 2.
3.2.2. Purification of Sc$_3$N@C$_{80}$ Soot Extract.

**Figure 1.** (a) and (b) Separation of TNT EMFs from empty cage fullerenes by selective cycloadditions with resin 2. (c) Recovery of the empty-cage fullerenes from resin 2 upon heating.

Figure 1a and 1b illustrate the concept; as the solution of the fullerene mixture passes through a column packed with the cyclopentadienyl resin 2, the empty cage fullerenes (red ball: C$_{60}$, C$_{70}$, C$_{76}$, C$_{78}$, C$_{84}$) are bound to the resin by Diels-Alder cycloaddition (Scheme 2). TNT EMFs (blue ball) are left unbound and can be isolated in a pure state in the eluent solution by taking advantage of the high kinetic stability of TNT EMFs.

**Scheme 2**
Figure 2. HPLC (PYE column, toluene, 3mL/min, detection at 390 nm) traces of (a) the toluene extract of “scandium soot”, (b) the room-temperature toluene eluent from application of the extract to a column packed with cyclopentadiene-functionalized resin; the peak at 27.9 min corresponds to Sc$_3$N@C$_{80}$; there are minor peaks due to Sc$_3$N@C$_{68}$ (16 min) and Sc$_3$N@C$_{78}$ (27 min) and at retention times of 5-10 min due to unreactive polycyclic aromatic hydrocarbons from the soot; see further discussion below and (c) the eluent from the column after elution (b) upon heating at 85 °C in the presence of maleic anhydride.

Next we applied the purification protocol to the toluene extract of the soot produced from a K-H preparation of Sc$_3$N@C$_{80}$. The soot from the arc process with Sc$_2$O$_3$-loaded graphite rods was subjected to Soxhlet extraction with toluene. Figure 2a shows the HPLC trace of the toluene extract containing both empty cage fullerenes and Sc$_3$N@C$_{80}$. Figure 3 contains the CI mass spectrum of the extract, demonstrating the presence of empty cage fullerenes C$_{60}$, C$_{70}$, C$_{76}$, C$_{78}$, C$_{82}$, C$_{84}$, C$_{86}$ (m/z 1032), C$_{88}$ (m/z 1056), C$_{90}$ (m/z 1080), C$_{92}$ (m/z 1104), C$_{94}$ (m/z 1128) and C$_{96}$ (m/z 1152), along with TNT
EMFs Sc$_3$N@C$_{68}$, Sc$_3$N@C$_{78}$, and Sc$_3$N@C$_{80}$. The concentrated extract was applied to a column packed with resin 2 and the column was flushed slowly with toluene. As demonstrated above with the simple binary mixtures and in accord with Figure 1, the empty-cage fullerenes present in the extract react with the cyclopentadiene-functionalized resin by Diels-Alder cycloaddition, allowing the less reactive TNT EMF, Sc$_3$N@C$_{80}$ (see Table 1), to pass through (essentially completely unreacted as demonstrated below), thus affording relatively pure Sc$_3$N@C$_{80}$ (Figure 3b); see also the discussion of purification of the raw “scandium soot” below.

![Figure 3](image.png)

**Figure 3.** Chemical ionization mass spectrum (negative ion) of the toluene extract of soot made from graphite rods packed with Sc$_2$O$_3$; as indicated, empty cage fullerenes and TNT EMFs are present.

The Diels-Alder reaction is thermally reversible and Rotello et al. investigated recovery of C$_{60}$ from similar cyclopentadiene-functionalized supports upon heating.
Saunders et al. utilized the reversibility for isomer release after anthracene Diels-Alder adducts had been purified.

**Scheme 3.**

![Scheme 3 Diagram](image)

Figure 1c illustrates the recovery of the empty-cage fullerenes trapped by resin 2 by heating the column in the presence of more reactive dienophile maleic anhydride. Figure 2c shows the HPLC trace of the eluent from the column upon heating at 85 °C in the presence of maleic anhydride. The overall recovery of empty cage fullerenes was 60% relative to the extract initially applied to the resin. Note that no or very little Sc3N@C80 had been bound to the resin, in accord with its greatly diminished reactivity relative to the other species in the complex mixture; however, see the discussion below. It is noteworthy that exposure of the extract to resin 2 and the recovery process resulted in a change in the ratio of C78 isomers as shown by comparison of Figure 3, parts a and c, in accord with the differing reactivities of the three known isomers predicted by the calculations shown in Table 1.

No attempt was made in the present work to optimize the recovery process, but it should be noted that Rotello et al. achieved 48% recovery of bound C60 using their cyclopentadiene-functionalized resin and 94% of bound C60 and 41% of bound C70 using an analogous cyclopentadiene-functionalized silica.
3.3. CONCLUSIONS

High purity lanthanide trimetallic nitride endohedral metallofullerenes, \( \text{A}_3\text{N} @ \text{C}_{80} \) (\( \text{A} = \) lanthanide atom, e.g., Gd, Ho, Lu, Sc), can be obtained directly from as-prepared soots in a single facile step by taking advantage of their extraordinary kinetic chemical stability with respect to the Diels-Alder reaction with cyclopentadiene-functionalized resin. The present results indicate that it is possible to separate isomers of these TNT EMFs as well as various empty cage fullerenes. The thermal reversibility of the Diels-Alder reaction can, in principle, provide selective elution of fullerenes and endohedral metallofullerenes from the resin column as a function of temperature, flow rate, stoichiometry, and addition of competitive dienophiles. Moreover, complete removal of the bonded fullerenes would allow multiple cycles with the same resin, providing a purification approach that is scalable and consistent with Green Chemistry practices. We are currently pursuing these refinements of this protocol. This new purification protocol has two advantages relative to the use of the HPLC method. First, the yields are higher by about 2-fold. This is due to the use of a lower temperature extraction solvent with reduced exposure to oxygen, hence decreased oxidative losses. In addition, repeated losses in the chromatographic process from multiple injections are avoided. A second major advantage is the time for obtention of pure endohedral trimetallic nitride fullerene samples, which is reduced from ca. 30 days to one (1) day.

3.4. EXPERIMENTAL SECTION

Materials and Methods
Graphite rods (99.9995% C, 6.15 mm × 152 mm) and graphite powder (99.9995% C) were obtained from Alfa Aesar. The graphite rods were drilled longitudinally to provide a 5/32” (4 mm) hole, which was packed with the metal oxide, Fe₃N and graphite powder (2-15 μm); the latter three components were mixed with a mortar and pestle and the graphite rod was packed with the resultant mixture using a cotton tip applicator, followed by the blunt end of the 5/32” drill bit. Scandium (III) oxide (Sc₂O₃, 99.999%), lutetium (III) oxide (Lu₂O₃, 99.995%), holmium (III) oxide (Ho₂O₃, 99.999%) and gadolinium (III) oxide (Gd₂O₃, 99.995%) were obtained from Stanford Materials Corporation. Iron nitride (99.9%, FeₓN, x = 2-4) was obtained from Cerac Specialty Inorganic Chemicals. Merrifield’s resin (chloromethylated styrene-1% divinylbenzene copolymer, 3.5-4.5 meq of Cl/g) and sodium cyclopentadienylide (2.0 M solution in tetrahydrofuran) were obtained from Sigma-Aldrich. C₆₀ was obtained from Mer Corporation and used as received. A semipreparative Buckyclutcher column (10 x 250 mm, Regis Chemical Company) was used in HPLC for both analysis and purification. HPLC was also carried out on a PYE column (10×250 mm, Alltech Associates) and a PBB column (4.6×250 mm, Alltech Associates).

**Cyclopentadiene-Functionalized Resin 2.**

A suspension of chloromethylated styrene-divinylbenzene copolymer (1 g) in toluene (200 mL) was cooled to -20 °C. To the stirred suspension, sodium cyclopentadienylide (16 mL of a 2.0 M solution in tetrahydrofuran, 32 mmol, ~8 equiv.) was added dropwise. Then the mixture was stirred for 2 h at 20°C and filtered; the beads were washed with toluene (600 mL) to give the dark brown cyclopentadiene-functionalized resin 2.
**Sc$_3$N@C$_{80}$**. Sc$_3$N@C$_{80}$ was prepared by arc-vaporization of graphite rods packed with Sc$_2$O$_3$ (0.73 g, 5.3 mmol), Fe,N (0.40 g) and graphite powder (1.00 g, total carbon ~2.5 g, 0.21 g at) in a K-H generator under a dynamic N$_2$ (20 mL/min)/He (~900 mL/min) atmosphere (at 300 Torr total pressure). The graphite rods were typically baked at ~1100 °C under N$_2$ for ~18 h just prior to arc-vaporization. A potential difference of 31 V was applied between the ends of the rods and maintained via electronic control. After each rod had been consumed (~45 min), the resulting soot was collected.

**Purification of Sc$_3$N@C$_{80}$ Soot Extract Using Resin 2 and Recovery of Other Fullerenes.**

The raw soot from three graphite rods packed with Sc$_2$O$_3$ was collected and extracted in a Soxhlet device with toluene for 12 h, yielding 38.3 mg of mixed fullerenes and endohedral metallofullerenes after removing the solvent in vacuo; see Figure 3 for the mass spectrum of this material. This extract was redissolved in toluene and applied to a glass column (28×22 mm, d×h) packed with ~20 g of cyclopentadiene-functionalized resin 2 (~180 mmol of reactive sites based on the starting chloromethylated resin capacity) in toluene. Toluene was flushed through by gravity feed (~6 mL/h) during 48 h. Sc$_3$N@C$_{80}$ was obtained after removing the solvent from the eluent. To study the reversibility of the covalent binding process, the column was wrapped with heating tape and a digital thermometer was inserted into the resin. At room temperature, two column volumes of toluene saturated with maleic anhydride were flushed through the column; no fullerenes were eluted. The column was then heated to 85 °C and kept at this temperature overnight. The solution in the column turned red, which indicated that the empty cage fullerenes had
been released and replaced by the more reactive dienophile, maleic anhydride. The column was flushed with toluene saturated with maleic anhydride at 85 °C over a 2 h period. The red solution was subsequently passed through a silica gel column to remove a small amount of maleic anhydride; removal of the solvent yielded 22.4 mg of recovered fullerenes; total recovery from extract: 23.4 mg, 61% (Figure 2c).

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Chapter 4

Purification of Trimetallic Nitride Template Endohedral Metallofullerenes
by Chemical Reaction of Eutectic 9-methylanthracene with Fullerenes

4.1. INTRODUCTION

Since the inception of fullerene science, endohedral metallofullerenes have attracted attention due to the unique properties that result from the encapsulation of metal atoms inside the carbon cage.\(^1\) \(^2\) In particular, trimetallic nitride templated endohedral metallofullerenes (TNT EMFs)\(^3\) are considered one of the most important fullerene-based families of materials due to their abundance and diversity (e.g., various metals, cage sizes and symmetries).\(^4\)-\(^11\) The diversity of TMFs coupled with the interesting properties of metals surrounded by an organic cage makes them potentially useful for a wide variety of applications, for example, MRI contrast agents.\(^12\)

So far, the inadequate availability of pure endohedral metallofullerenes has hindered research on these new nanomaterials. Although the trimetallic nitride template method of fullerene production can afford macroscopic quantities of materials such as Sc\(_3\)N@C\(_{80}\),\(^3\) the mixed fullerenes created in a Krätschmer-Huffman electric arc generator are still dominated by empty-cage fullerenes (e.g. C\(_{60}\), C\(_{70}\), etc.), and considerable purification is necessary. Traditionally, endohedral metallofullerenes have been isolated by multi-step liquid chromatographic method.\(^13\)-\(^15\) However, the poor solubility of endohedral metallofullerenes limits the sample loading; thus, it is very time and solvent consuming to obtain them in
macroscopic quantities. Alternatively, chemical separations have been recently used to isolate TMFs. Two such methods have been reported so far: the selective binding of empty-cage fullerenes to cyclopentadiene functionalized Merrifield’s peptide resin\textsuperscript{16} and a similar reaction with amino-capped silica gel.\textsuperscript{17}

While these two chemical separation methods differ in mechanism, the principle of how they work is the same. $C_{60}$ and other empty-cage fullerenes are electron deficient olefins and therefore are fairly reactive species in many reactions, such as cycloadditions. However, theoretical calculations demonstrate that TNT EMFs are stabilized by the transfer of six electrons from the internal trimetallic nitride (A$_3$N) cluster to the carbon cage, resulting in a closed shell electronic structure and a large energy gap.\textsuperscript{18-24} The lower reactivity of TNT EMFs relative to empty-cage fullerenes in cycloadditions has been demonstrated: functionalization of TMFs requires more severe reaction conditions (i.e., elevated temperatures or large reagent excesses) than similar reactions on empty-cage fullerenes.\textsuperscript{25-27}

The support-based purification methods noted above are effective at yielding TNT EMF samples of >98% purity, however both methods are fairly expensive and time consuming (requiring a minimum of two days to achieve effective separation). Also, neither method has demonstrated to complete release of the reacted fullerenes from the support in order to be completely recyclable. Seeking to reduce the amount of time and the cost of obtaining pure TNT EMFs, we believe a support-free method of isolation would be an effective alternative. In this case a support-free separation method would theoretically take less time by eliminating the use of time to synthesize the support and avoiding lengthy reaction/elution times. A support-free separation method would also reduce cost by being fully reversible and recyclable. Many studies on Diels-Alder reactions and retro-reactions of $C_{60}$ with acenes have been reported.\textsuperscript{28-32} Saunders and coworkers also reported that the separation of $C_{84}$ isomers by using the reversible
Diels-Alder reaction of C\textsubscript{84} with 9,10-dimethylanthracene.\textsuperscript{33} A similar isolation procedure for C\textsubscript{60} from a C\textsubscript{60}-C\textsubscript{70} mixture was reported by Wang and coworkers.\textsuperscript{34} Kräutler and coworkers found that the most efficient method of forming Diels-Alder adducts with anthracene and C\textsubscript{60} is to perform a solvent-free reaction in which the reaction mixture is heated above the melting point of the anthracene.\textsuperscript{30,35}

Using a variation of Kräutler’s solvent-free method of forming anthracene-C\textsubscript{60} adducts (Scheme 1), we herein discuss the reaction of a large excess of a low melting anthracene, 9-methylanthracene, with Sc- and Lu-based soot extracts and the separation of the reacted empty-cage fullerenes from the unreacted TNT EMFs.

![Scheme 1](image)

**Scheme 1:** Fullerene extract reaction with 9-methylanthracene

### 4.2. RESULTS AND DISCUSSION

The overall approach is illustrated in Figure 1 and HPLC chromatograms are shown of the soot extract at each step in the process for Sc\textsubscript{3}N@C\textsubscript{80} (Figure 2). After mixing and heating with 9-methylanthracene at 140-145°C for 30 minutes, all of the fullerenes in the soot extract were derivatized except Sc\textsubscript{3}N@C\textsubscript{80} and negligible amounts of C\textsubscript{60}, C\textsubscript{70}, C\textsubscript{84}, and Sc\textsubscript{3}N@C\textsubscript{78} (Figure 2b). Formation of the derivative is evidenced by the dramatic decrease in the size of the empty-cage peaks, and the appearance of large peaks just after the dead-time. The large peaks observed between 7 and 12 minutes in the HPLC trace of the reaction mixture (Figure 2b) were assigned to unreacted 9-methylanthracene and 9-methylanthracene/ fullerene adducts; this
assignment is supported by mass spectrometric data, which show that the 8 minute peak is 9-methylnaphthacene, and the 9 and 12 minute peaks are derivatives of mixed fullerenes, each showing peaks for \(C_{60}\), \(C_{70}\) and \(C_{84}\). (Supporting Information) The shorter retention times are due to increased solubility of the 9-methyl anthryl derivatives in toluene.

**Figure 1.** Schematic of isolation \(Sc_{3}N@C_{80}\) from empty-cage fullerenes by reaction with 9-methylnaphthacene, a support-free method.

As seen in comparing Figures 2a and 2b, the derivatization of the empty-cage fullerenes is very dramatic. From the areas calculated by the HPLC integration, the \(Sc_{3}N@C_{80}\) peak in the soot extract (Figure 2a) was 0.3 times the size of the \(C_{70}\) peak, but after reaction with 9-methylnaphthacene (Figure 2b), the \(Sc_{3}N@C_{80}\) peak was 42 times the size of the \(C_{70}\) peak. This is a 140-fold increase in the ratio of \(Sc_{3}N@C_{80}\) to \(C_{70}\). To perform the solid-liquid extraction, the solid reaction mixture was pulverized, sonicated in ether, centrifuged, and subsequently the supernatant was removed with a pipette. This method afforded \(Sc_{3}N@C_{80}\) that was \(~35\%\) pure (Figure 2c) and \(Lu_{3}N@C_{80}\) (Figure 5c) that was \(~19\%\); a 2.5- and 3.5-fold increase in purity, respectively. Considering the large difference in the retention time of adducts and TMFs on the HPLC column, a short HPLC column could be used to pass sample through in a significantly
reduced amount of time for final clean-up of TMFs. This method has the potential to greatly reduce the time and cost necessary to obtain pure TMFs.

**Figure 2.** HPLC chromatograms of (a) extract of scandium soot (b) extract of scandium soot after heating with 9-methylanthracene (c) extract of scandium soot after heating with 9-methylanthracene and washing with ether (d) final purification by HPLC. HPLC conditions: 10 mm × 250 mm PYE column at 2.0 mL min⁻¹ flow rate with toluene, 390 nm detection

After extensive washing, removal of the ether-soluble derivatives was accompanied by loss of small quantity of TMF, either due to solid particles that did not settle out, or particles that were disturbed in the removal of the liquid.

In order to further characterize the derivatization process, the ratio of empty-cage fullerenes to Sc₃N@C₈₀ was examined as a function of temperature for reaction time of 30 minutes. It was determined that increasing the temperature to ~145°C increased the reaction of empty-cages, while increasing the temperature above 145°C facilitated the retro-reaction
Predictably, we also found that increasing the mass ratio of 9-methylandthracene to soot increased the yield of derivatives, but only up to a point after which little increase seemed to occur. The mass ratio for maximum yield of empty-cage derivatives from scandium soot extract was found to be 5:1 (Figure 4).

**Figure 3.** Enrichment of Sc$_3$N@C$_{80}$ vs. C$_{70}$ as a function of the reaction temperature (10:1 mass ratio of 9-methylandthracene to soot extract).

**Figure 4.** Enrichment of Sc$_3$N@C$_{80}$ vs. C$_{70}$ as a function of the mass ratio of 9-methylandthracene to Sc soot extract (85-90°C)

It is worth noting that to determine the extent of reaction, the ratio of the HPLC peak area of Sc$_3$N@C$_{80}$ to C$_{70}$ was calculated. We decided to use the area of the C$_{70}$ peak as a reference instead of the total area of the unreacted fullerene peaks (C$_{60}$, C$_{70}$, C$_{84}$, etc.) because the C$_{70}$ peak was better resolved. Also, C$_{70}$ seemed to undergo the retro-reaction most easily of
all of the derivatives; therefore monitoring the TMF peak relative to it was the most sensitive measure of determining optimal conditions.

![Figure 5](image)

**Figure 5.** HPLC chromatograms of (a) extract of lutetium soot (b) extract of lutetium soot after heating with 9-methylanthracene (c) extract of scandium soot after heating with 9-methylanthracene and washing with ether (d) final purification by HPLC. HPLC conditions: 10 mm × 250 mm PYE column at 2.0 mL min-1 flow rate with toluene, 390 nm detection.

To test the applicability of this method to other C₈₀ cage TNT EMFs, a reaction using Lu-based soot was run under the optimal conditions determined for Sc soot extract (i.e., 30 minutes at 145°C, with 5:1 mass ratio) (Figure 5). Analogous to the Sc-based soot extract, the empty-cage derivatives were almost completely reacted (Figure 5b). In the soot extract (Figure 5a) the ratio of Lu₃N@C₈₀ to C₇₀ was 0.11, but after reacting with 9-methylanthracene (Figure 5b) the ratio was 5.6, a 51-fold increase in the ratio of Lu₃N@C₈₀ to C₇₀. It is worth noting that
Unlike those empty-cage fullerenes, two isomers of dimetallofullerenes Lu$_2@C$_82, Lu$_2@C$_82 (I) and Lu$_2@C$_82 (II) remain unreacted in the mixture after heating with 9-methylenanthracene (MS see supporting information). This could be attributed to the low reactivity of Lu$_2@C$_82 or rapid retro-reaction of Lu$_2@C$_82 with 9-methylenanthracene.

The reaction of 9-methylenanthracene with Lu-based soot extract did not have as high a “yield” (as determined by the ratio of Lu$_3N@C$_80 to C$_70$) of derivative as for the Sc-based soot extract; this may be due to the fact that the Lu-based soot extract had a lower percent TMF, and therefore there were many more empty-cage fullerenes in 25 mg of Lu-based soot extract than in 25 mg Sc-based soot extract. In general, soot extracts with lower percentages of TNT EMFs seem to require a larger mass ratio of 9-methylenanthracene to soot extract in order to reduce the unreacted fullerenes to a negligible amount.

It is conceivable that other conventional separation methods could be used to separate 9-methylenanthracene derivatives of empty-cage fullerenes from unreacted TMF molecules more effectively. Komatsu and coworkers were able to separate C$_{60}$ from 9-hydroxymethylenanthracene/C$_{60}$ derivatives on silica column with toluene as the eluent. Although we were not able to completely separate empty cage 9-methylenanthracene derivatives and TNFs by silica column, the enrichment of TMF could be further improved with using ether/toluene solvent system on silica column. For instance, the solid of Sc soot extract after heating with 9-methylenanthracene and washing thoroughly with ether (Figure 6a) was applied to a silica column. The column was initially flushed with ethyl/toluene (v/v: 3/7). As shown in Figure 6b, the first fraction eluting out of column consisted of mainly derivatives along with 10% Sc$_3N@C$_80. The second fraction was collected when the column was subsequently flushed.
with toluene. From HPLC trace of the second fraction (Figure 6c), the percentage of Sc$_3$N@C$_{80}$ in the mixture increased to 60%.

**Figure 6.** HPLC chromatograms of (a) solid extract of scandium soot after heating with 9-methylnaphthalene and washing with ether; (b) the first fraction from the silica column with ethyl/toluene (v/v: 3/7) as eluent; (c) the second fraction from the silica column with toluene as eluent. HPLC conditions: 10 mm × 250 mm PYE column at 2.0 mL min$^{-1}$ flow rate with toluene, 390 nm detection.

### 4.3. CONCLUSIONS

We develop a support-free chemical separation method of TMFs from Sc- and Lu-based soot extract that makes use of the differing solubilities of unreacted TMFs versus 9-methylnaphthalene-derivatized empty-cage fullerenes. Empty-cage fullerene (e.g. C$_{60}$, C$_{70}$, etc.) are much more reactive than trimetallic nitride metallofullerenes (TMFs) towards 9-
methylanthracene via Diels-Alder cycloaddition. After heating of 9-methylanthracene with Sc- or Lu-based soot extract, the most 9-methylanthracene-derivatized empty cage fullerenes could be removed by washing with ether. The remaining unreacted TMFs were easily isolated by one-stage HPLC from TMFs enriched extracts. This support-free chemical separation method has the advantages of being inexpensive, easily scalable, and faster than current purification methods. This method has the potential to greatly reduce the time and cost necessary to obtain a large quantity of pure TNT EMFs.

4.4. EXPERIMENTAL SECTION

Materials and Methods. Graphite rods (99.9995% C, 12.7 mm ×152 mm) and graphite powder (99.9995% C) were obtained from Alfa Aesar. The graphite rods were drilled longitudinally to provide a 5/16” (8 mm) hole, which was packed with the metal oxide, Fe_xN, and graphite powder; the latter three components were mixed with a mortar and pestle and the graphite rod was packed with the resultant mixture placed in the rod and tamped down with the blunt end of the 5/16” drill bit. Scandium (III) oxide (Sc_2O_3, 99.999%) and lutetium (III) oxide (Lu_2O_3 99.995%) were obtained from Stanford Materials Corporation. Iron nitride (99.9%, Fe_xN, x =2-4) and 9-methylanthracene (99%) were obtained from Alfa Aesar. Anhydrous diethyl ether was obtained from Fisher Scientific. A β-(1-pyrenyl)ethyl silica (PYE) column (10 × 250 mm, Alltech Associates) was used in high pressure liquid chromatography (HPLC) for both analysis and purification.

Sc_3N@C_{80}-Containing Soot Extract. Sc_3N@C_{80} was prepared by arc-vaporization of graphite rods packed with Sc_2O_3 (4.9 g, 35.5 mmol), Fe_xN (0.28 g) and graphite powder (1.82 g, total carbon ~12.5 g) in a K-H generator under a dynamic N_2 (33 mL/min)/He (545 mL/min)
atmosphere (at 300 Torr total pressure). The graphite rods were typically baked at ~1025 °C under N₂ for 8 h and allowed to cool under N₂ just prior to arc-vaporization. A potential difference of 27 V was applied between the ends of the rods and maintained via electronic control. After each rod had been consumed (~60 min), the resulting soot was collected. The soot from 10 rods was combined and run through a Soxhlet extraction with o-xylene for 18 h to obtain soot extract (mixed fullerenes).

Lu₃N@C₈₀-Containing Soot Extract. Lu₃N@C₈₀ was prepared from graphite rods packed with Lu₂O₃ (7.68 g 19.3 mmol), Fe₃N (0.48 g), and graphite powder (3.84 g, total carbon ~14.84 g). The soot from 28 rods was combined and subjected to Soxhlet extraction with o-xylene for 18 h to obtain the soot extract (mixed fullerenes).

Purification of Sc₃N@C₈₀ from Soot Extract. The extract was rinsed with diethyl ether to render it powdery, and 25 mg was mixed with 125 mg 9-methylanthracene in a 13 × 100 mm test tube. The mixture was placed in an oil bath at 140-145°C and heated for 30 minutes, followed by cooling under tap water. The resulting black solid was pulverized, placed in about 40 mL diethyl ether, sonicated for 30 seconds, centrifuged, and the supernatant was removed with a pipette; the washing process was performed a total of six times. The ether-insoluble solid TNT EMF-enriched sample (7mg) was subsequently dissolved in toluene. In the final stage, high pressure liquid chromatography (HPLC) was utilized to provided 2 mgs of high purity (> 99%) Sc₃N@C₈₀.

Purification of Lu₃N@C₈₀ from Soot Extract. The Lu soot extract was treated identically to the Sc soot extract.
4.4. SUPPORTING INFORMATIONS

Figure S1. The negative ion DCI MS spectra of Sc soot extract in Figure 2a

Figure S2. MALDI-TOF mass spectrum of peaks between 9~12 mins in Figure 2b (9-nitroanthracene matrix and negative ionization)
**Figure S3.** The negative ion DCI MS spectra of pure Sc₃N@C₈₀ in Figure 2d

**Figure S4.** HPLC chromatograms of extract of lutetium soot. Inset: MALDI-TOF mass spectrum of the mixture of Lu₃N@C₈₀ and Lu₂@C₈₂.

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Chapter 5

The Structures and Enhanced Reactivities of the $D_{5h}$ Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ Metallofullerene Isomers: The Importance of the Pyracylene Motif

5.1. INTRODUCTION

Endohedral metallofullerenes (EMF) have attracted increasing attention during past decades for their potential applications in the fields of biomedicine and nanomaterial sciences. The chemical and electronic properties and exohedral chemical functionalizations for various mono- and di-metallofullerenes have been extensively studied. In 1999, a novel stable four-atom molecular cluster endohedral fullerene, icosahedrally (I$_h$) symmetrical Sc$_3$N@C$_{80}$, was prepared in remarkably high yield by the use of the trimetallic nitride template (TNT) process. Computational and experimental results demonstrate that the C$_{80}$ cage is stabilized by transfer of six electrons from the internal trimetallic nitride cluster, resulting in a closed shell electronic structure, i.e., (Sc$_3$N)$^{6+}$C$_{80}$$^{6-}$. Long-time molecular dynamics simulations followed by quantitative DFT-NMR calculations of the $^{13}$C NMR chemical shifts of Sc$_3$N@C$_{80}$ I$_h$ isomer reproduced the two-line experimental spectrum. Two other Sc$_3$N EMF family members, the $D_{3h}$ symmetrical Sc$_3$N@C$_{78}$ and the $D_3$ symmetrical non-IPR (isolated-pentagon rule) Sc$_3$N@C$_{68}$, were also discovered. Thus far the family of TNT EMFs, has been expanded to other metals A$_3$N@C$_{2n}$ (A=Y, Gd, Tb, Dy, Ho, Er, Tm and Lu; 38 ≤ n ≤49).
In an earlier study,\textsuperscript{9} we proposed that a relatively small amount of the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ existed in samples dominated by the $I_h$ isomer based on high performance liquid chromatography (HPLC) and $^{13}$C NMR. The structures of these two isomers are compared in Figure 1. Figure 2 shows a schematic diagram of the $D_{5h}$ isomer of the C$_{80}$ cage with its six different types of carbon atoms arranged into six colored layers.

\textbf{Figure 1.} (Left) Sc$_3$N@C$_{80}$ $I_h$ isomer (Right) Sc$_3$N@C$_{80}$ $D_{5h}$ isomer.

\textbf{Figure 2.} A schematic diagram of the carbon cage of the $D_{5h}$ C$_{80}$ isomer showing the six bands of different types of carbon atoms.
Dunsch and co-workers used HPLC to separate $I_h$ and $D_{5h}$ isomers for various trimetallic nitride endohedral metallofullerenes, including $\text{Sc}_3\text{N}@\text{C}_{80}$, $\text{Tm}_3\text{N}@\text{C}_{80}$, and $\text{Dy}_3\text{N}@\text{C}_{80}$. Since the retention times of the two isomers are similar, in order to achieve better separation, a linear combination of two HPLC columns and multiple injections were applied to afford the pure isomers. Compared with the $I_h$ isomer, a relatively smaller optical energy gap, i.e., a longer onset wavelength $\lambda_{\text{max}}$ value, was reported for the $D_{5h}$ isomers by visible-NIR spectroscopy. On the basis of different oxidation potentials for $\text{Sc}_3\text{N}@\text{C}_{80}$ $I_h$ and $D_{5h}$ isomers, Echegoyen and co-workers reported an electrochemical method to oxidize the $D_{5h}$ isomer selectively. The unoxidized $I_h$ isomer was purified by removing the radical cation of the $D_{5h}$ isomer from the silica column. Based on density functional theoretical (DFT) methods and Gibbs energy calculations, Slanina and Nagase recently calculated the observed populations of 10% and 17% for the $D_{5h}$ $\text{Sc}_3\text{N}@\text{C}_{80}$ isomer at temperatures of 2100 K and 2340 K, respectively. Very recently, Yang and Dunsch reported the third stable trimetallic nitride encapsulated $\text{C}_{80}$ cage; the $\text{Dy}_3\text{N}@\text{C}_{80}$ isomer with a proposed $D_{5d}$ symmetrical structure was isolated and characterized by optical and vibrational spectroscopy.

In this chapter, we explore the Diels-Alder cycloaddition reactions of $A_3\text{N}@\text{C}_{80}$ ($A = \text{Sc, Lu}$) with cyclopentadiene-functionalized resin as a method for purification of mixtures of $I_h$ and $D_{5h}$ TNT EMFs. Both $D_{5h}$ $\text{Sc}_3\text{N}@\text{C}_{80}$ and $D_{5h}$ $\text{Lu}_3\text{N}@\text{C}_{80}$ exhibit higher reactivities than the respective $I_h$ isomers. Cyclic voltammetry and theoretical molecular orbital (MO) calculations have also been carried out for $\text{Sc}_3\text{N}@\text{C}_{80}$ and $\text{Lu}_3\text{N}@\text{C}_{80}$ in order to understand the relative stabilities and reactivities of the $D_{5h}$ and $I_h$ isomers. Although several exohedral derivatives of TNT EMF $I_h$ isomers have been synthesized and characterized, no derivatives of the $D_{5h}$ isomers have been previously reported. Herein, for the first time we report the synthesis and characterization of N-tritylpyrrolidino mono- and di-adducts of the
The possible cycloaddition reaction sites for the two monoadducts of the \( D_{5h} \) isomer are discussed based on \(^1\)H NMR evidence and other data deduced from DFT calculations, electrochemistry, and X-ray crystallography.

5.2. RESULTS AND DISCUSSION

5.2.1. Crystallographic Determination of the Structure of the \( D_{5h} \) isomer of Sc\(_3\)N@C\(_{80}\)

Since we have repeatedly demonstrated that co-crystallization with metallo-octaethylporphyrins, M\(^{II}\)(OEP) (M=Ni, Co) produces samples with sufficient order to allow structure determination,\(^{3,4c,6,7b,17}\) benzene solutions of the \( D_{5h} \) isomer of Sc\(_3\)N@C\(_{80}\) and Ni\(^{II}\)(OEP) were allowed to slowly diffuse together. Black parallelepipeds of the product were obtained and utilized in the crystal structure determination.

Figure 3 shows a drawing of the four molecules present in the asymmetric unit of the compound. None of these has any crystallographically imposed symmetry. As usual, all eight ethyl groups of the porphyrin surround the fullerene. The closest contact between the porphyrin and the endohedral is the 2.812(3) Å separation between Ni and C46. Remarkably, both the carbon cage and its contents are fully ordered.
Figure 3. A view of the contents of the asymmetric unit in the $D_{5h}$ isomer of \( \text{Sc}_3\text{N}@\text{C}_{80}\text{-Ni(OEP)}\text{-2benzene} \) with 50% thermal ellipsoids.

Figure 4 shows two drawings of the fullerene itself. Part A shows a view down the non-crystallographic, five-fold axis of the cage, while part B shows a view perpendicular to that five-fold axis. As these drawings show, the Sc$_3$N portion is strictly planar (the sum of the three Sc-N angles is 359.94°), but the plane of these four atoms is tipped out of the non-crystallographic horizontal mirror plane of the fullerene by 30°. The geometry of the Sc$_3$N portion is rather irregular with a variety of Sc-N distances (Sc1-N, 2.014(2), Sc2-N, 2.031(2); Sc3-N, 2.041(2) Å) and N-Sc-N angles (Sc1-N-Sc2, 121.12(11); Sc1-N-Sc3, 107.21(10); Sc2-N-Sc3, 131.61(11) °). Each scandium ion is in close proximity to a pair of carbon atoms of the fullerene. Sc1 is located over a c-d bond involving C64 and C44, Sc2 sits over an e-e bond involving C24 and C57, and Sc3 is situated near a d-e bond involving C31 and C32.
Figure 4. Two views of the endohedral fullerene in the $D_{3h}$ isomer of Sc$_3$N@C$_{30}$•Ni(OEP)•2benzene. Upper, looking down the fullerene five-fold axis. Lower, looking perpendicular to the fullerene five-fold axis which is vertical in this view. For clarity, all atom positions are show as circles of uniform size depending upon atom type.
The C-C bond distances in the carbon cage of $D_{5h}$ Sc$_3$N@C$_{80}$ show greater variation than was observed in the corresponding $I_h$ isomer. In $I_h$ Sc$_3$N@C$_{80}$ there are only two types of C-C bonds. Those at the junction of two hexagons have an average distance of 1.421(18) Å, while those at the junction of a pentagon and a hexagon have an average distance of 1.437(15) Å. In the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$, the f-f bonds are the longest C-C bonds, while the e-e bonds are the shortest. These bonds alternate about the horizontal plane of the cage and lie in a direction parallel to the five-fold axis. The short C-C e-e bonds (average distance, 1.396 Å) are in pyracylene sites where two hexagons abut with pentagons at either end, while the long f-f bonds (average distance 1.462 Å) are in pyrene sites. This is the first crystallographically characterized fullerene cage to have such pyrene sites. The other C-C bond lengths have the following average values: a-a, 1.434; a-b, 1.420; b-c, 1.419; c-c, 1.438; c-d, 1.451; d-e, 1.434; d-f, 1.432. In all cases the C-C bonds nearest the three scandium ions have been omitted in calculating these average distances. The proximities of these pairs of carbon atoms closest to the scandium atoms appear to lengthen the C-C bonds between them.

The pyramidalization angles, $\theta_p$, (for graphite = 0°; $\theta_p$ for C$_{60}$ = 11.6°) for the individual fullerene carbons of $D_{5h}$ Sc$_3$N@C$_{80}$ also show some interesting variations. The average pyramidalization angles for the different types of carbon atoms are: a, 10.6; b, 8.9; c, 10.1; d, 10.2; e, 10.5; and f, 8.4°. In averaging these values, those carbon atoms nearest the scandium ions have been omitted since the carbons atoms near scandium have particularly high pyramidalization as follows: C64, 13.0; C44, 12.9; C24, 13.9; C57, 11.3; C31, 12.5; C32, 13.8°. Similarly high pyramidalization angles were seen for those carbon atoms nearest the scandium ions in a functionalized version of $I_h$ isomer of Sc$_3$N@C$_{80}$. The carbon atom nearest the porphyrin, C46, exhibits an unusually low $\theta_p$ of 8.7° for a carbon atom of the d-type. Likewise C47 which is the next nearest carbon to the porphyrin has a low $\theta_p$ of 7.6°, the
lowest $\theta_p$ value seen for any of the f-type carbon atoms. For the other carbon atoms, the highest pyramidalization is seen for the a-type carbon atoms at the poles of the carbon cage and for the e-type carbon atoms that surround the middle of the molecule. Notice that there is a pronounced alternation about the middle of the fullerene with the e-type carbons atoms showing a high degree of pyramidalization and the f-type carbon atoms displaying the lowest degree of pyramidalization seen anywhere in the molecule.

The combination of short bond length and high degree of pyramidalization for the central carbon atoms of the pyracylene sites at the center of the carbon cage suggest that these may be the sites of greatest reactivity in the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$. The two carbons atoms at the center of pyracylene sites are generally the positions of highest chemical reactivity on empty cage fullerenes, but the $I_h$ isomer of Sc$_3$N@C$_{80}$ lacks such sites. The lack of this structural feature offers some insight into the low degree of chemical reactivity of the $I_h$ isomer of Sc$_3$N@C$_{80}$. In contrast the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ is more reactive and the NMR data for the mono-(N-tritylpyrrolidino) derivative of the $D_{5h}$ isomer described below is consistent with the crystallographic work suggesting that the e-e bonds at the middle of this metallofullerene are the initial sites of addition.

5.2.2. Reactivity Comparisons

5.2.2.1. Kinetic Stability

Recently, using cyclopentadiene-functionalized resin 1, macroscopic quantities of high purity TNT EMF were directly and expeditiously obtained from crude soots or extracts by taking advantage of significantly different kinetic stabilities between TNT EMFs and other fullerenes (empty cage fullerenes and classical endohedral metallofullerenes). In order to explore the reactivity differences between $I_h$ and $D_{5h}$ isomers of TNT EMFs, mixtures of
A3N@C80 (A = Sc or Lu) \(I_h\) and \(D_{5h}\) were treated with large excesses of the cyclopentadiene-functionalized resin 1 (finely ground) under vigorous stirring at room temperature. The Diels-Alder cycloaddition reactions of TNT EMFs with resin 1 were assumed to be under pseudo-first order conditions. The concentration of A3N@C80 was monitored by HPLC.

Aihara’s minimum bond resonance energy (min BRE) calculations\(^{20a}\) and the calculated HOMO-LUMO energy gaps for the C\(_{80}\) \(6^-\) isomers,\(^{20a,22}\) suggested that the \(D_{5h}\) C\(_{80}\) cage with six negative charges is slightly more reactive than the \(I_h\) analog. Figure 5 illustrates the different reactivities between TNT EMF \(I_h\) and \(D_{5h}\) isomers with cyclopentadiene-functionalized resin 1. In Figure 5a, the \(D_{5h}\) Sc\(_3\)N@C\(_{80}\) eluted later than the \(I_h\) isomer and appeared as a shoulder on the \(I_h\) chromatographic peak. The ratio of \(I_h\) to \(D_{5h}\) isomer peaks increased with reaction time, indicating that the \(D_{5h}\) isomer reacted faster than the \(I_h\) isomer in this competitive reaction. The \(D_{5h}\) Sc\(_3\)N@C\(_{80}\) was almost completely removed from the original mixture after two weeks. A similar reactivity pattern was also observed for \(I_h\) and \(D_{5h}\) isomers of Lu\(_3\)N@C\(_{80}\) (Figure 5b). The isomers of Lu\(_3\)N@C\(_{80}\) were better resolved than those of Sc\(_3\)N@C\(_{80}\) under the same HPLC conditions. The short elution time peak was the \(I_h\) Lu\(_3\)N@C\(_{80}\) \(^{8f}\) and the later one was the \(D_{5h}\) isomer. These assignments were confirmed by both mass spectrometry and \(^{13}\)C NMR spectroscopy.

In the \(^{13}\)C NMR spectrum of \(D_{5h}\) Lu\(_3\)N@C\(_{80}\) (see Supporting Information), the chemical shifts for the six peaks (135.5, 138.1, 138.2, 143.2, 144.7 and 149.0 ppm), representing the six different types of carbon atoms on the \(D_{5h}\) C\(_{80}\) cage, and their relative intensities are very consistent with the reported assignment for \(^{13}\)C NMR spectrum of the Sc\(_3\)N@C\(_{80}\) \(D_{5h}\) isomer.\(^9\) After normalizing the \(I_h\) chromatographic peaks to the same height, the peaks for the \(D_{5h}\) Lu\(_3\)N@C\(_{80}\) were found to decrease with increasing reaction time, again indicating the higher reactivity of the \(D_{5h}\) isomer. As a result of the distinctly different
reactivities for $I_h$ and $D_{5h}$ TNT EMFs toward resin 1 and the thermal reversibility of Diels-Alder cycloaddition,\textsuperscript{19,23} it is feasible to establish a non-chromatographic strategy to separate the $I_h$ and $D_{5h}$ isomers; the resin produced after the $D_{5h}$ isomer is consumed can be subjected to retro-Diels-Alder conditions to free this isomer (see Supporting information for preliminary results). However, the purified $D_{5h}$ samples utilized in the current study \textit{vide infra} were purified by repetitive chromatography methods.

\textbf{Scheme 1.} Reaction of TNT EMFs with cyclopentadiene-functionalized resin 1, A = Sc or Lu.
Figure 5. HPLC (PYE column, toluene, 1 mL/min, detection at 390 nm) traces (a) The $I_h$ and $D_{5h}$ Sc$_3$N@C$_{80}$ mixture after reaction with resin 1 in toluene at room temperature for 0 day, 3 days, 1 week, 2 weeks, and 3 weeks. (b) The $I_h$ and $D_{5h}$ Lu$_3$N@C$_{80}$ mixture after reaction with resin 1 in toluene at room temperature for 0 day, 3 days, 1 week, 2 weeks, 3 weeks, and 5 weeks. The heights of the $I_h$ Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ peaks were adjusted to be the same for all reaction times.

5.2.2.2. Electrochemistry

The electrochemical behavior for the $I_h$ and $D_{5h}$ isomers of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ were determined by cyclic voltammetry (Figure 6) and the results are summarized in Table 1. Two reduction peaks and one oxidation peak were observed for each sample. The first reduction potentials ($\text{red}E_1$) for the $D_{5h}$ isomers of Sc$_3$N@C$_{80}$ (-1.333 V) and Lu$_3$N@C$_{80}$ (-1.409 V) are slightly more negative than the $I_h$ isomers of Sc$_3$N@C$_{80}$ (-1.274 V) and Lu$_3$N@C$_{80}$ (-1.402 V), respectively. The oxidation potentials ($\text{ox}E_1$) of both Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ $D_{5h}$ isomers, however, are approximately 0.2 V less positive than those of the $I_h$ isomers. The resulting electrochemical gaps ($\text{ox}E_1 - \text{red}E_1$) for the $D_{5h}$ isomers of Sc$_3$N@C$_{80}$ (1.675 V) and Lu$_3$N@C$_{80}$ (1.855 V) are approximately 0.18 V smaller than the electrochemical gaps for the $I_h$ isomers of Sc$_3$N@C$_{80}$ (1.842 V) and Lu$_3$N@C$_{80}$ (2.044 V). The observation of less positive first oxidation potentials for the $D_{5h}$ isomers is consistent with the assignments made by Echegoyen and co-workers from the cyclic voltammogram of the isomeric mixture of Sc$_3$N@C$_{80}$.11

It is worth noting that both oxidation and reduction potentials for $I_h$ and $D_{5h}$ isomers were shifted by changing the internal trimetallic nitride cluster. The electrochemical gaps for the Lu$_3$N@C$_{80}$ $I_h$ (2.044 V) and $D_{5h}$ isomers (1.855 V) are approximately 0.2 V larger than the Sc$_3$N@C$_{80}$ $I_h$ (1.842 V) and $D_{5h}$ (1.675 V) isomers, respectively. However, the differences in the electrochemical gaps between the lanthanide TNT EMFs are relatively small. For
example, the electrochemical gap of $I_h$ Lu$_3$N@C$_{80}$ (2.044 V) is comparable to that of $I_h$ Tm$_3$N@C$_{80}$ (1.99 V).$^{24}$

**Table 1.** Electrochemical Redox Potentials (V versus Fe/Fe$^+$ in o-dichlorobenzene, 0.1 M TBABF$_4$) and HOMO/LUMO levels (eV) for the $I_h$ and $D_{5h}$ isomers of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$

<table>
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<th>compound</th>
<th>$\alpha E_1$</th>
<th>$\text{red} E_1$</th>
<th>$\alpha E_1$-$\text{red} E_1$</th>
<th>HOMO</th>
<th>LUMO</th>
<th>HOMO-LUMO</th>
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<tr>
<td>Sc$<em>3$N@C$</em>{80}$ ($I_h$)</td>
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<td>-1.274</td>
<td>1.842</td>
<td>-5.44</td>
<td>-2.91</td>
<td>2.53</td>
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<td>0.342</td>
<td>-1.333</td>
<td>1.675</td>
<td>-5.29</td>
<td>-3.01</td>
<td>2.28</td>
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<td>-1.402</td>
<td>2.044</td>
<td>-5.44</td>
<td>-2.89</td>
<td>2.55</td>
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<tr>
<td>Lu$<em>3$N@C$</em>{80}$ ($D_{5h}$)</td>
<td>0.446</td>
<td>-1.409</td>
<td>1.855</td>
<td>-5.23</td>
<td>-2.94</td>
<td>2.29</td>
</tr>
</tbody>
</table>

![Graph showing electrochemical behavior](attachment:image.png)
Figure 6. Cyclic voltammogram of the $I_h$ and $D_{5h}$ isomers of (a) Sc$_3$N@C$_{80}$ and (b) Lu$_3$N@C$_{80}$ in o-dichlorobenzene, 0.1 M TBABF$_4$, 500 mV/s scan rate.

5.2.2.3. Theoretical Calculations

DFT calculations have provided the molecular orbital energy level diagrams of the TNT EMF isomers of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ (Figure 7). The LUMOs of the $D_{5h}$ isomers (Sc$_3$N@C$_{80} = -3.01$ eV, Lu$_3$N@C$_{80} = -2.94$ eV) are comparable to those of the $I_h$ isomers (Sc$_3$N@C$_{80} = -2.91$ eV, Lu$_3$N@C$_{80} = -2.89$ eV). However, the HOMOs of the $D_{5h}$ isomers (Sc$_3$N@C$_{80} = -5.29$ eV, Lu$_3$N@C$_{80} = -5.24$ eV) are higher than those of the $I_h$ isomers (Sc$_3$N@C$_{80} = -5.45$ eV, Lu$_3$N@C$_{80} = -5.44$ eV). Therefore, the HOMO-LUMO gaps for the $D_{5h}$ isomers are about 0.25 eV smaller than those of the $I_h$ isomers. These are still relatively small differences and are perhaps fortuitous agreement with the electrochemically determined potential differences (Table 1). They also agree well with the observation of the higher
reactivity for $D_{5h}$ isomers in the competition reactions with $I_h$ isomers towards the
cyclopentadiene-functionalized resin by Diels-Alder cycloaddition (Figure 5).

Interestingly, the $I_h$ isomer of La$_2$@C$_{80}$ has almost the same HOMO level but a
significantly different LUMO level compared with the $I_h$ isomer of Sc$_3$N@C$_{80}$.
In contrast, for the same TNT cluster but different C$_{80}$ cage symmetry, $I_h$ vs. $D_{5h}$, the changes of the
HOMO levels are more obvious than those of the LUMO levels. Therefore, in general the
LUMO energies of EMFs are more sensitive to the internal metallic cluster, while the HOMO
levels are more sensitive to the structure and symmetry of the outside carbon cage, as
expected on the basis of the $(A_3N)^+6C_{80}^-6$ formulation. Figure 8 shows that the HOMO
levels of the $I_h$ isomers are very different from those of the $D_{5h}$ isomers, which are locally
distributed onto one hemisphere. Similar to the localized LUMO for La$_2$@C$_{80}$ that results in
high reactivity, the higher reactivity of the $D_{5h}$ isomer relative to the $I_h$ isomer is presumably
due to its more localized HOMO orbital.

In addition, the energy levels of HOMO and HOMO minus orbitals for Sc$_3$N@C$_{80}$ and
Lu$_3$N@C$_{80}$ are similar, and the electron density distributions around both endohedral
metallofullerenes are similar; these result from the six electrons transferred from the
encapsulated cluster to the cage.
5.2.3. 1,3-Dipolar Cycloaddition Reaction of N-Tritylazomethine Ylide with $D_{5h}$ Sc$_3$N@C$_{80}$

Recently, we reported the synthesis and characterization of mono- and di-(N-tritylpyrrolidino) derivatives of the $I_h$ isomer of Sc$_3$N@C$_{80}$.\textsuperscript{26} It was found that the addition of the N-tritylazomethine ylide occurs at both the 5,6- and 6,6-ring junctions of the Sc$_3$N@C$_{80}$ $I_h$ cage, yielding the thermodynamic and kinetic products, respectively. In the present work, however, we have found that the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ exhibits significantly higher reactivity with the 1,3-dipolar tritylazomethine ylide (Scheme 2) in comparison with the $I_h$ isomer. The HPLC chromatogram of the original sample of Sc$_3$N@C$_{80}$ (Figure 8a) consisted mainly of the $I_h$ isomer with a small amount of $D_{5h}$ isomer, which appears as a shoulder at 91.0 min under slow flow rate conditions utilizing a PYE column. The purified Sc$_3$N@C$_{80}$

Figure 7. The Molecular Orbital (MO) diagrams of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ ($I_h$ and $D_{5h}$ isomers).
$D_{5h}$ isomer (Figure 8d) was allowed to react with N-triphenylmethyl-5-oxazolidinone under the same conditions as the $I_h$ isomer. After 4 hours two strong peaks for monoadducts $2a$ (40.0 min) and $2b$ (43.0 min) were observed (Figure 8e) in contrast with the much weaker peaks observed for the $I_h$ isomer (Figure 8c). In addition, the $I_h$ isomer exhibited only one small peak for a diadduct after 12 hours of reaction time; whereas, two peaks were identified as the diadducts ($2c$, $2d$) of the $D_{5h}$ isomer after just 4 hours reaction time (Figure 8e). These data clearly indicate that the Sc$_3$N@C$_{80}$ $D_{5h}$ isomer is more reactive than the $I_h$ isomer. The mono- and di-tritylpyrrolidino $D_{5h}$ derivatives were characterized by MALDI-TOF mass spectra (Figure 9) and exhibited mass distribution patterns similar to those reported for the corresponding $I_h$ derivatives.

Scheme 2. 1,3-Dipolar cycloaddition reaction of the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ with N-triphenylmethyl-5-oxazolidinone
Figure 8. HPLC chromatograms: (a) a mixture of Sc$_3$N@C$_{80}$ $I_h$ and $D_{5h}$ isomers, (b) pure Sc$_3$N@C$_{80}$ $I_h$ isomer, (c) reaction mixture of the Sc$_3$N@C$_{80}$ $I_h$ isomer with N-triphenylmethyl-5-oxazolidinone at $\sim$132°C for 4 hours. (d) pure Sc$_3$N@C$_{80}$ $D_{5h}$ isomer, (e) reaction mixture of the Sc$_3$N@C$_{80}$ $D_{5h}$ isomer with N-triphenylmethyl-5-oxazolidinone at $\sim$132°C for 4 hours. HPLC conditions: 10 × 250 mm PYE at 1.0 mL min$^{-1}$ flow rate with toluene, 390 nm detection. * Traces (b) and (c) are reproduced from Ref. 26.

Figure 9. MALDI-TOF mass spectra using a 9-nitroanthracene matrix and negative ionization: (a) monoadduct 2a, (b) monoadduct 2b, (c) bisadduct 2c, (d) bisadduct 2d. Calculated for monoadducts: m/z 1394; calculated to bisadducts: m/z 1679.

The $^1$H NMR spectrum of 2a exhibits four doublets (H$_a$, H$_b$, H$_c$ and H$_d$) for the methylene protons of the pyrrolidine ring. Moreover, the $^1$H COSY spectrum of 2a (Figure 10a) demonstrates that H$_a$-H$_b$ and H$_c$-H$_d$ are coupled with each other; this means that H$_a$-H$_b$
and H_c-H_b are on the two different methylene carbons, respectively. Unlike the spectrum of 2a, in which the four methylene protons are in different chemical environments, the COSY spectrum of 2b exhibits a broad singlet at 3.19 ppm (Figure 10b), which indicates four equivalent methylene protons on the pyrrolidine ring.

Figure 10. 500 MHz COSY spectra of the Sc_3N@C_{80} D_{5h} isomer monoadducts (a) 2a and (b) 2b ([Solvent: 1,2-dichlorobenzene-d_4], 55 °C).
Table 2. NMR chemical shifts of methylene protons for Sc$_3$N@C$_{80}$ $I_h$ isomer derivatives 1a and 1b;\textsuperscript{a}

$D_{5h}$ isomer derivatives 2a and 2b.

<table>
<thead>
<tr>
<th>N-Tritylpyrrolidino Sc$<em>3$N@C$</em>{80}$ Derivative</th>
<th>$\delta$H (ppm)</th>
<th>Rings Junction</th>
<th>Addition Pattern $^a$</th>
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</thead>
<tbody>
<tr>
<td>$I_h$ 1a *</td>
<td>2.53(d), 3.95(d)</td>
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<td>Symmetric</td>
</tr>
<tr>
<td>$I_h$ 1b *</td>
<td>2.82(s), 3.11(s)</td>
<td>6,6</td>
<td>Asymmetric</td>
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<tr>
<td>$D_{5h}$ 2a</td>
<td>3.53(d) 3.44(d) 3.13(d) 2.95(d)</td>
<td>6,6</td>
<td>Asymmetric</td>
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<tr>
<td>$D_{5h}$ 2b</td>
<td>3.19 (s)</td>
<td>6,6</td>
<td>Symmetric</td>
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</table>

* Ref 26.\textsuperscript{a} Addition pattern symmetry is based on the methylene carbons of the pyrrolidine ring on the derivatives.

There are a total of nine different types of C-C bonds on the $D_{5h}$ C$_{80}$ cage as shown in Figure 2; the statistical numbers of bonds of each type, ring junction, addition patterns, and bond lengths are summarized in Table 3. It is clear from previous studies with the $I_h$ pyrrolidine derivatives\textsuperscript{15,26,27}, that the symmetric 5,6-ring junction adduct exhibits large chemical shift differences (1.2~1.4 ppm) for the diastereotopic methylene protons of the pyrrolidine ring, which are due to differential shielding effects from carbon cage ring currents and the nitrogen atom of pyrrolidine ring. Since the $^1$H NMR spectrum of 2b exhibits only one singlet peak for the methylene protons of the pyrrolidine ring, the asymmetric 5,6-ring (c-d, d-e), the asymmetric 6,6-ring (a-b, b-c, d-f), and the symmetric 5,6-ring (a-a, c-e) junction adducts can be excluded as possible sites for cycloaddition adduct 2b. As illustrated in Figure 2, only the e-e and f-f bonds can produce the symmetric 6,6-ring junction adduct 2b. Furthermore, both experimental and theoretical calculated bond lengths demonstrate that e-e is the shortest bond and should be more reactive compared with the other bonds. Therefore,
the pyracylene type e-e bond is the most likely addition site for the 2b monoadduct (Table 3) as predicted from the crystallographic results. Based on the above discussions, and the limited ¹H COSY spectrum for 2a, we predict that 2a is the asymmetric 6,6-ring junction cycloaddition adduct. The three most likely cycloaddition sites for adduct 2a are at the a-b, b-c, and d-f bonds as summarized in Table 3 and further studies to elucidate this structure are in progress.

Table 3. $D_{5h}$ Sc$_3$N@C$_{80}$: Comparison of X-ray and Computational Structural Parameters (average bond lengths)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond numbers</th>
<th>Rings junction</th>
<th>Addition patterna</th>
<th>Experimental bond length (Å) b</th>
<th>Theoretical calculated bond length (Å) b</th>
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</table>

*Symmetry is discussed based on the methylene carbons of the pyrrolidine ring on the derivatives. baverage bond lengths * Possible reaction sites for isomeric monoadduct 2a.

In a previous study we found that upon heating the 6,6-ring junction adduct of the $I_h$ isomer converted into the 5,6-ring junction adduct and we proposed a single bond migration mechanism based on the concept of microscopic reversibility. After 3 hours in a solution of chlorobenzene at 160 °C purified isomer 2b was unchanged, whereas, under these conditions 2a was partially converted to other unidentified monoadduct isomers. As expected, these results also indicate that 2b is the thermodynamically stable product. There is remarkable similarity in the cycloaddition reactions of the $D_{5h}$ and $I_h$ isomers of Sc$_3$N@C$_{80}$ in providing
only two mono-adducts. However, a key difference is the presence of the pyracylene motif in the $D_{5h}$ isomer, which undoubtedly leads to the enhanced reactivity of the $D_{5h}$ Sc$_3$N@C$_{80}$ isomer. This is consistent with reactivity patterns for empty-cage fullerenes. We are currently investigating the regioselectivity of $D_{5h}$ C$_{80}$ cages with other metal clusters (e.g., yttrium, holmium, thulium, etc.).

5.3. CONCLUSIONS

The structure of the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ has been determined crystallographically. The planar Sc$_3$N portion is tipped out of the non-crystallographic, horizontal mirror plane of the carbon cage by 30°. The short C-C bond length and high degree of pyramidalization for the central carbon atoms of the pyracylene sites of the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ suggest that these C-C bonds are the ones most likely to undergo addition reactions.

The $D_{5h}$ isomers of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ exhibit higher reactivity than the $I_h$ isomers toward cyclopentadiene-functionalized resin 1 under Diels-Alder cycloaddition. Both cyclic voltammetry and theoretical molecular orbital (MO) calculations demonstrate that the $D_{5h}$ isomers have smaller energy gaps than the $I_h$ isomers, which is consistent with the observation of higher reactivity for the $D_{5h}$ isomers. The differences between the first oxidation potentials and HOMO levels for the $I_h$ and $D_{5h}$ isomers are larger than those of the reduction potentials and LUMO levels; these results show that, as expected on the basis of the transfer of six electrons from the cluster to the C$_{80}$ carbon cage, the isomeric nature of the cage structure plays a more important role in determining the HOMO level than the internal metallic cluster.

The $D_{5h}$ Sc$_3$N@C$_{80}$ isomer also proves to be more reactive towards 1,3-dipolar cycloaddition of N-tritylazomethine ylide than the $I_h$ isomer under same reaction conditions.
Two $D_{5h}$ Sc$_3$N@C$_{80}$ monoadducts and two diadducts were isolated and characterized by MALDI-TOF MS spectroscopies. Monoadduct 2a is assigned as an asymmetric product based on its $^1$H NMR and COSY spectra. Monoadduct 2b exhibits a single methylene proton signal in its $^1$H NMR spectrum, which indicates a symmetrical addition at the 6,6-ring junction in the pyracylene unit, consistent with its highly reactive character. Preliminary studies show that monoadduct 2b is thermally stable to isomerization, but 2a is converted to other products upon heating.

5.4. EXPERIMENTAL SECTION

Materials and Methods:

The Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ $I_h$ and $D_{5h}$ isomer mixture was obtained by the chemical separation method. Pure Sc$_3$N@C$_{80}$ $I_h$ and $D_{5h}$ isomers were isolated from the original mixture by HPLC using a PYE column, with toluene @ 1.0mL/min, $\lambda = 390$nm. Toluene (HPLC Grade $\geq$99.9%) and o-dichlorobenzene (99.9%) were used as obtained from Aldrich. A semi-preparative PYE [$\beta$2-(1-pyrenyl)ethyl silica] column (10 $\times$ 250 mm) and a guard PYE column (10 $\times$ 20 mm) were used for both analysis and purification. HPLC system: Acure series III pump, 757 Absorbance Detector (Applied Biosystems).

The $^{13}$C NMR spectrum of the Lu$_3$N@C$_{80}$ $D_{5h}$ isomer was obtained by using a Varian Inova 800 instrument (Georgia Institute of Technology). The Lu$_3$N@C$_{80}$ $D_{5h}$ isomer sample was dissolved in CS$_2$/D-acetone (v/v: 10/1) and doped with chromium acetylacetonate. A JEOL ECP 500 MHz instrument was used for Sc$_3$N@C$_{80}$ $D_{5h}$ derivatives’ $^1$H NMR and COSY measurements.
Cyclic voltammetric measurements were conducted using a CH Instruments model 600A potentiostat (Austin, TX) and a microelectrochemical cell described previously. This cell allows measurement down to 50 μL of sample solution. Measurements were conducted using 1,2-dichlorobenzene solutions containing 0.100 M tetra-\textit{n}-butylammonium tetrafluoroborate and approximately 5x10^{-4} M concentration of the TNT fullerene. Potentials are reported relative to the reversible ferrocene oxidation couple. Solution resistance was compensated 95% for all measurements.

**X-ray Crystallography and Data Collection:**

The crystals were removed from the glass tube in which they were grown together with a small amount of mother liquor and immediately coated with a hydrocarbon oil on the microscope slide. A suitable crystal was mounted on a glass fiber with silicone grease and placed on the goniometer head in the cold dinitrogen stream from a CRYO Industries low-temperature apparatus at 90(2) K. The diffractometer was a Bruker SMART Apex with an Apex II CCD and utilized MoKα radiation. No decay was observed in 50 duplicate frames at the end of data collection. Crystal data are given below. The structure was solved by direct methods and refined using all data (based on $F^2$) with the software of SHELXTL 5.1. A semiempirical method utilizing equivalents was employed to correct for absorption. Hydrogen atoms were added geometrically and refined with a riding model.

**Crystal data for C_{128}H_{56}N_{5}NiSc_{3}:** black parallelepiped, triclinic, space group P\bar{1}, $a = 14.505(3)$ Å, $b = 14.878(3)$ Å, $c = 19.855(4)$ Å, $\alpha = 85.052(3)$ °, $\beta = 86.758(3)$ °, $\gamma = 61.016(3)$ °, $V = 3733.6(12)$ Å$^3$, $Z = 2$, $D_\text{c} = 1.652$ Mg/m$^3$, $T = 90(2)$ K; R1 = 0.112, wR2 = 0.124 for all data; conventional R1 = 0.052 computed for 13289 observed data ($I > 2\sigma(I)$) with 0 restraints and 1235 parameters.
**Computations:** Full geometry optimization were conducted at the B3LYP level\textsuperscript{20,31,32} using the Gaussian 03 program.\textsuperscript{33} The effective core potential and the corresponding basis set were used for Sc and Lu. The basis sets employed were LanL2DZ for Sc,\textsuperscript{34} Stuttgart RSC Segmented/ECP for Lu,\textsuperscript{35} and 6-31G* for C and N.\textsuperscript{36} The computed structure of Sc\textsubscript{3}N@C\textsubscript{80} is referred to the crystallographic data. We have assumed that Lu\textsubscript{3}N@C\textsubscript{80} exhibits a structure similar to that of Sc\textsubscript{3}N@C\textsubscript{80} for the computations. All the calculations (\textit{Ih} and \textit{D}_{5h} isomers) were subjected to frequency analysis, performed at the same level as the geometry optimization. As a result, no imaginary frequencies are reported for the optimized structures.

**Synthesis of N-Tritylpyrrolidino Derivatives of the \textit{D}_{5h} Isomer of Sc\textsubscript{3}N@C\textsubscript{80}:**

A solution of 0.4 mg (0.4 μmol) of Sc\textsubscript{3}N@C\textsubscript{80} D\textsubscript{5h} isomer and 6 mg (0.02 mmol) of N-triphenylmethyl-5-oxazolidinone in 7 mL of chlorobenzene was heated at reflux under nitrogen. The solvent was removed by a rotary evaporator. The crude solid was redissolved in toluene and then injected into an HPLC for analysis. 2\textsubscript{a}, 2\textsubscript{b}, 2\textsubscript{c} and 2\textsubscript{d} were isolated by HPLC using a PYE column, with toluene @ 1.0 mL/min, \(\lambda = 390\) nm.

**5.5. SUPPORTING INFORMATION**

**Figure S1.** 200 MHz \textsuperscript{13}C NMR Spectrum (CS\textsubscript{2}/d\textsubscript{6}-acetone, V/V: 10/1) for the Lu\textsubscript{3}N@C\textsubscript{80} \textit{D}_{5h} Isomer
<table>
<thead>
<tr>
<th>( ^{13}\text{C} \delta/\text{ppm} )</th>
<th>Lu(<em>3\text{N}@\text{C}</em>{80}) D(_{5h}) isomer</th>
<th>Sc(<em>3\text{N}@\text{C}</em>{80}) D(_{5h}) isomer (Ref. 9)</th>
<th>Relative intensities</th>
</tr>
</thead>
<tbody>
<tr>
<td>149.0</td>
<td>149.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>144.7</td>
<td>145.0</td>
<td>2</td>
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<tr>
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<td>143.9</td>
<td>2</td>
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</tr>
<tr>
<td>138.2</td>
<td>139.3</td>
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<td>1</td>
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<tr>
<td>135.5</td>
<td>135.2</td>
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</table>

Scheme for Separation and Purification of Sc\(_3\text{N}@\text{C}_{80}\) \(I_h\) and \(D_{5h}\) Isomers.
The initial toluene solution of Sc$_3$N@C$_{80}$ (~10 mgs) (trace a) contained about 80\% $I_h$ and 20\% $D_{5h}$ isomers. The solution was stirred in the presence of cyclopentadiene-functionalized resin 1 (~15g) for three weeks and then the suspension was filtered. The resulting solution (trace b) contained about 90\% $I_h$ Sc$_3$N@C$_{80}$ and 10\% $D_{5h}$ Sc$_3$N@C$_{80}$. After filtering, the reacted resin was collected, then heated at 100 $^\circ$C for 10 hours in the presence of excess maleic anhydride to release the bonded Sc$_3$N@C$_{80}$ $I_h$ and $D_{5h}$ isomers. After filtering to remove the resin, the solution (trace c) contained recovered the Sc$_3$N@C$_{80}$ with an enriched content of the $D_{5h}$ isomer (ratio: 50:50). Repetition of these steps does lead to the pure $D_{5h}$ isomer, but with the drawback of time and lower yield.

**REFERENCES**


Chapter 6.

Synthesis and Characterization of the First Trimetallic Nitride Templated Pyrrolidino Endohedral Metallofullerenes

6.1. INTRODUCTION

Trimetallic nitride templated (TNT) endohedral metallofullerenes,\textsuperscript{1, 2} the most abundantly formed endohedral metallofullerenes, are under current active investigation as powerful, next generation magnetic resonance imaging (MRI) agents and radiotracers,\textsuperscript{3} as are other endohedral metallofullerenes.\textsuperscript{4, 5} In order to function as medical imaging and therapeutic agents these fullerenes need to be properly functionalized. Previously we have shown that these species undergo the Bingel–Hirsch cyclopropanation reaction.\textsuperscript{6} We also demonstrated that these new fullerenes are capable of undergoing cycloaddition reactions with quinodimethanes.\textsuperscript{7, 8} Among the wide variety of functionalization methods of C\textsubscript{60}, the 1,3-dipolar cycloaddition of azomethine ylides to fullerenes (the Prato reaction) is one of the most useful; it entails the formation of pyrrolidino fullerene derivatives by reactions with azomethine ylides formed in situ from aldehydes and N-substituted glycines.\textsuperscript{9, 10} Herein, we report functionalization of TNT endohedral metallofullerenes by the Prato reaction on both diamagnetic Sc\textsubscript{3}N@C\textsubscript{80} (1a) and paramagnetic Er\textsubscript{3}N@C\textsubscript{80} (1b), as a means of diversifying the chemistry of these valuable new species.

6.2. RESULTS AND DISCUSSION

The synthesis of TNT endohedral pyrrolidinometallofullerenes 2 was carried out
by heating o-dichlorobenzene solutions containing A$_3$N@C$_{80}$ (1, 1 equiv.), $^{13}$C labeled formaldehyde (12 equiv.) and N-methylglycine (4 equiv.) at 110 °C for 10 h (Scheme 1). Monoadducts 2a and 2b were isolated in 30–40% yield after silica gel column chromatography using o-dichlorobenzene as eluent and subsequently purified by high pressure liquid chromatography (HPLC), using a PYE [2-(1′-pyrenyl)ethyl silica] column with CS$_2$ as eluent (Figure 1). The monoadducts are well soluble in CS$_2$ and o-dichlorobenzene, but not in toluene, behavior similar to that of the monoadduct of La@C$_{82}$. The dominant formation of the monoadducts of the TNT endohedral metallofullerenes is consistent with our previous observations that trimetallic nitride endohedral metallofullerenes are less reactive than mono-metallofullerenes, e.g., with Gd@C$_{82}$ up to octaadducts were observed in the Prato reaction. The lower reactivity of the TNT endohedrals is due to the transfer of six electrons from the metal nitride cluster to the I$_h$ symmetric C$_{80}$ cage, resulting in a closed shell electronic structure and higher chemical kinetic stability.

Scheme 1. Cycloaddition of azomethine ylides to Sc$_3$N@C$_{80}$ (1a) and Er$_3$N@C$_{80}$ (1b).

The matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass
spectra of the endohedral Prato monoadducts 2a and 2b were observed as strong M⁻ peaks at m/z 1167 and m/z 1534, respectively. The peaks at m/z 1109 and 1476 for M⁻ of 1a and 1b are due to loss of the exohedral functional groups [(CH₂)₂NCH₃] from 2a and 2b, respectively, a common feature in mass spectra of fullerene derivatives. The peak of monoadduct 2b is about twice as broad as that of 2a because of the isotopic distribution of Er, in good agreement with the calculated distributions (see supporting information).

Figure 1. HPLC chromatograms (1 x 25 cm PYE column at 0.5ml/min flow rate with CS₂ eluent) and MALDI-TOF mass spectrum (9-nitroanthracene as matrix and negative ionization) of pure monoadducts (a) 2a; (b) 2b.

In 1,3-dipolar cycloadditions of N-methylazomethine ylides the TNT endohedral metallofullerenes behave as 1,3 dipolarophiles and reactive 2π components. Therefore, the
*N*-methylazomethine ylide can only react with a localized double bond at one of the two types of ring juncture available on the I₆ symmetric C₈₀ cage. These are the 5,6-ring juncture that is abutted by two six-membered rings (A in Scheme 2) and the 6,6-ring juncture abutted by one five- and one six-membered ring (C in Scheme 2). The 5,6-ring juncture proved to be the reaction site, as clearly demonstrated by the ¹³C NMR spectrum of ¹³C labeled adduct 2a, which exhibits a single narrow signal at 71.6 ppm for the equivalent methylene carbon atoms of product B. Addition to the 6,6- juncture was thus ruled out because it would have led to an adduct (product D) with non-equivalent methylene carbon atoms. This result is consistent with our earlier report of Diels–Alder isochromanone-derived quinodimethane adduct formation with Sc₃N@C₈₀ (1a) at the same double bond site, as confirmed by X-ray structural analysis.⁷,⁸

**Scheme 2.** Prato reaction at the 5,6-ring junction (A→B) and at the 6,6-ring junction (C→D). A and B have a horizontal plane of symmetry, while C and D have a vertical plane of symmetry. In B the methylene carbons are equivalent, while in D they are non-equivalent.
Further confirmation of this mode of addition came from $^1$H NMR spectroscopy. Unlike the analogous C$_{60}$ monoadduct (obtained in 41% yield) in which all the methylene hydrogens are equivalent,$^9$ the $^1$H spectrum of derivative 2a without the $^{13}$C label (Figure 2) exhibits signals for the diastereotopic geminal methylene hydrogens. These diastereotopic hydrogens differ in chemical shift by 1.2 ppm. One set (designated H$_a$) resonates at 2.87 ppm and the other (designated H$_b$) at 4.02 ppm. Interestingly, these chemical shifts are nearly equally spaced from the diastereotopic methylene protons observed in the six-membered quinodimethane cycloadduct, 3.57 and 3.41 ppm.$^7$ This means that differential ring currents in the 5- and 6-membered rings adjacent to the reaction site cannot be the sole source of the large chemical shift difference. Both sets of signals are, however, shifted upfield from that of the corresponding C$_{60}$ derivative, in which the methylene protons appear as a singlet at 4.38 ppm,$^9$ this overall 0.9 ppm shielding increase is attributed to the increased ring current in the more electron rich TNT endohedral metallofullerene cage relative to C$_{60}$. If the nitrogen lone pair of electrons prefers to be away from the cage for electrostatic reasons, there are two potentially interconvertible diastereomeric adducts as shown in Figure 3. It has long been known that trans lone pairs and cis N–C bonds in unsaturated heterocycles cause significant shielding of $\alpha$-protons.$^{17}$ This effect, coupled with the inherent local asymmetry, leads to the large chemical shift differences of the intrinsically diastereotopic methylene protons in 2a.
**Figure 2.** The 500 MHz COSY spectrum of 2a without the $^{13}$C label in CS$_2$-CDCl$_3$. $^1$H NMR: $\delta$ 4.02 (d, $^2J_{H-H} = 10$ Hz, 2H), 2.87 (d, $^2J_{H-H} = 10$ Hz, 2H), 2.74 (s, 3H).

**Figure 3.** Proposed diastereomeric partial structures of the Prato adducts 2a and 2b assuming the nitrogen lone pair of electrons is pseudoaxial for electrostatic reasons. (a) Left: CH$_3$ over five-membered ring. (b) Right: CH$_3$ over six-membered ring.

The heteronuclear multiple quantum coherence (HMQC) spectrum (Figure 4) verifies the proton assignments. The $^{13}$C labeled methylene carbon is coupled to its diastereotopic, geminal methylene hydrogens, $H_a^*$ and $H_b^*$, producing a doublet of
doublets for both protons symmetrically disposed about the signals of the geminal methylene protons on the non-labeled carbon, Hₐ and Hₐ*, that appear at 4.02 and 2.87 ppm, as in Figure 2. That is, the signal for proton Hₐ* at 4.02 ppm is a doublet of doublets with $^2J_{H-H} = 10$ Hz and $^1J_{C-H} = 145$ Hz and the signal for proton Hₐ* at 2.87 ppm is a doublet of doublets with $^2J_{H-H} = 10$ Hz and $^1J_{C-H} = 133$ Hz; note that one of the $^{13}$C-split doublets for Hₐ* lies under the methyl signal at 2.74 ppm. Additionally, other $^{13}$C splittings are observed. The methyl protons now appear as a doublet with $^3J_{C-H} = 8$ Hz. The signal for Hₐ on the non-labeled carbon is also split with a small $J_{C-H}$, yielding a multiplet that is part of a complex pattern. There is also long range $^{13}$C coupling to its geminal partner Hₐ with $J_{C-H} = 3$ Hz, yielding a doublet of doublets for Hₐ at 2.87 ppm. We were unable to obtain high-resolution $^1$H and $^{13}$C NMR spectra for the $^{13}$C labeled erbium adduct 2b. This observation, coupled with significant line broadening (factor of 2) of the $^1$H solvent line (chloroform), strongly suggests that the pyrrolidinometallofullerene 2b is paramagnetic, as expected. In addition, the T₂ spin–spin relaxation time for the $^1$H chloroform signal in the presence of adduct 2b (~0.2 mM) is 1.2 s versus 2.4 s (9.4 T) for the chloroform-CS₂ solvent without adduct 2b. UV–vis absorption spectra of the TNT endohedral metallofullerenes 1a-b are similar to those of their monoadducts 2a-b (Figure 5), indicating that the pyrrolidine derivatives retain the main aromatic cage features of the parent metallofullerenes.¹,³
Figure 4. The 500 MHz HMQC spectrum for purified $^{13}$C-labeled 2a in CS$_2$–CDCl$_3$. The impurity peak centered at ~3.65 ppm does not exhibit any correlation and is not present in the natural abundance sample (Figure 2).

Figure 5. UV–vis spectra (solvent: CS$_2$): (a) 1a (solid line) and 2a (dotted line); (b) 1b (solid line) and 2b (dotted line).
6.3. CONCLUSIONS

In summary, we have successfully synthesized and characterized the first TNT endohedral pyrrolidinometallofullerenes via 1,3-dipolar cycloaddition of azomethine ylides to both diamagnetic and paramagnetic TNT endohedral metallofullerenes. The development of the Prato reaction on TNT endohedral metallofullerenes is noteworthy because it affords access to various derivatives that have great potential for applications in medical and materials science. We are currently trying to obtain single crystals of these compounds for X-ray structural analysis to verify their structures; we are also examining the magnetic (e.g., low temperature ESR on 2b) and MRI relaxation properties of these and related lanthanide TNT pyrrolidinometallofullerenes.

6.4. EXPERIMENTAL SECTION

♦ Synthesis and Isolation

1. Sc₃N@C₈₀ pyrrolidine derivative 2a (natural abundance carbon):

To a solution of 5.0 mg (4.5 μmol) of Sc₃N@C₈₀ in 50 ml of o-dichlorobenzene, 1.2 mg (14 μmol) of N-methylglycine and 1.6 mg (53 μmol) of paraformaldehyde were added. The mixture was heated at 110°C in oil bath for 10 h. The solvent was removed in vacuo and the crude solid was purified by silica gel column chromatography (eluent: o-dichlorobenzene). The collected solid was dissolved in CS₂ and injected into an HPLC for final purification. HPLC condition: PYE column (10 × 250 mm), mobile phase (CS₂), flow rate: 0.5ml/min, λ = 390nm. This led to the isolation of 2 mg (40%) of pure 2a as a black solid.
2. Sc$_3$N@C$_{80}$ pyrrolidine derivative 2a (99% $^{13}$C labeled)

To a solution of 2.0 mg (1.8 μmol) of Sc$_3$N@C$_{80}$ in 30 ml of o-dichlorobenzene, 0.7 mg (9 μmol) of N-methylglycine and 3 μl (0.03 mmol) of formaldehyde (99% $^{13}$C, ~20% W/W in H$_2$O) (Cambridge Isotope Laboratory, Inc.) were added. The product was purified as indicated above. This led to the isolation of 0.6 mg (30%) of pure 2a as a black solid.

3. Er$_3$N@C$_{80}$ pyrrolidine derivative 2b (99% $^{13}$C labeled)

To a solution of 2.2 mg (1.5 μmol) of Er$_3$N@C$_{80}$ in 30 ml of o-dichlorobenzene, 0.6 mg (7 μmol) of N-methylglycine and 2~3 μl (0.02 mmol) of formaldehyde (99% 13C, ~20% W/W in H$_2$O) (Cambridge Isotope Laboratory, Inc.) were added. The product was purified as indicated above. This led to the isolation of 0.7 mg (30%) of pure 2b as a black solid.

**Figure S1.** HPLC trace of monoadduct 2a and unreacted Sc$_3$N@C$_{80}$ (1a).

Retention times: 30.12 min (Sc$_3$N@C$_{80}$); 31.79 min (2a)
**Figure S2.** HPLC trace of monoadduct 2b and unreacted Er$_3$N@C$_{80}$ (1b).

Retention times: 30.96 min (Er$_3$N@C$_{80}$); 32.18 min (2b)

**Figure S3.** Comparison of computer simulated mass spectra with experimental mass spectra (Assuming A$_3$N$_2$C$_{83}$H$_8$ is equivalent to A$_3$N$_2$C$_{83}$H$_7$ with one carbon which is 100% $^{13}$C labeled)

(a) Computer simulated mass spectrum of the molecule with formular of Sc$_3$N$_2$C$_{83}$H$_8$ (top)
Experimental mass spectrum of 2a (99% $^{13}$C labeled) (bottom)
(b) Computer simulated mass spectrum of the molecule with formula of Er₃N₂C₈₃H₈ (top)  
Experimental mass spectrum of 2b (99% ¹³C labeled) (bottom)

REFERENCES


Chapter 7

A Pirouette on a Metallofullerene Sphere: Interconversion of Isomers of N-Tritylpyrrolidino \( \text{I}_h \text{Sc}_3\text{N@C}_{80} \)

7.1. INTRODUCTION

Endohedral metallofullerenes (EMFs) are novel molecules that encapsulate metal atoms in carbon cages. Because of their unique structures various potential applications have been proposed since their discovery.\(^1\) In particular, trimetallic nitride template TNT EMFs (\( \text{A}_3\text{N@C}_{80}, \text{A} = \text{lanthanide atom} \))\(^2\) are some of the most promising fullerene-based materials (e.g., MRI and X-ray contrast agents\(^3\)) because of their high yields compared to classic endohedral metallofullerenes. Theoretical calculations demonstrate that the TNT EMFs are stabilized by six electrons transferred from the trimetallic nitride (\( \text{A}_3\text{N} \)) cluster to the \( \text{C}_{80} \) cage, resulting in a closed shell electronic structure described as \( \text{A}_3\text{N}^{6+}@\text{C}_{80}^{6-} \).\(^4\) Based on the extraordinarily high stability of TNT EMFs relative to empty cage fullerenes and classic endohedral metallofullerenes,\(^5\) macroscopic quantities of high purity TNT EMFs were recently obtained directly from crude soots in a single facile step by using a cyclopentadiene-functionalized resin to trap the more reactive species via Diels-Alder reactions, allowing the TNT EMFs to pass through.\(^7\)

Based on the reaction of \( \text{C}_{60} \) reported by Prato et al.,\(^8\) we recently synthesized and isolated the first N-methylpyrrolidino derivatives of both diamagnetic and paramagnetic TNT EMFs via 1,3-dipolar cycloaddition of azomethine ylides.\(^9\) The demonstration of planar symmetry in the N-methylpyrrolidino derivatives by \( ^{13}\text{C} \) NMR spectroscopy suggested that
the reaction took place at the 5,6-ring junction, as we observed earlier for an isochromanone Diels-Alder adduct.\textsuperscript{10} Echegoyen et al. reported selective 5,6-ring junction cycloaddition of N-ethylazomethine ylide to \( I_h \) symmetrical Sc\(_3\)N@C\(_{80}\).\textsuperscript{11} Echegoyen et al. also reported the impact of changing the metal of the internal cluster from Sc to Y; the cycloaddition of N-ethylazomethine ylide to Y\(_3\)N@C\(_{80}\) was reported to occur exclusively at 6,6-ring junction of the \( I_h \) symmetrical C\(_{80}\) cage.\textsuperscript{12} The thermal retro-cycloaddition reaction of N-ethylpyrrolidino-[5,6]-Sc\(_3\)N@C\(_{80}\) has also been reported.\textsuperscript{13} Campanera et al. recently predicted that the 5,6-ring junction is the most reactive site in the case of both the free \( I_h \) C\(_{80}\) cage and the TNT encapsulated C\(_{80}\) cage, taking into account the double bond character and the pyramidalization angle of the C-C bonds.\textsuperscript{14}

Very recently, Asasaka and coworkers have reported the synthesis and characterization of N-tritylpyrrolidino adduct of the \( I_h \) isomer of La\(_2\)@C\(_{80}\).\textsuperscript{15} In that study both the 5,6- and 6,6-ring junction adduct isomers were formed, but it was the 6,6-isomer that could be separated through crystallization. Both experimental and theoretical studies suggested that the two La atoms are localized in the 6,6-adduct C\(_{80}\) cage.

In this paper we report that the addition of the N-tritylazomethine ylide occurs at both the 5,6- and 6,6-ring junctions of the Sc\(_3\)N@C\(_{80}\) \( I_h \) cage. Two monoadducts are fully characterized by NMR spectroscopy and X-ray crystallography. A kinetic study suggests that the 6,6 ring junction adduct is the kinetically controlled product, but it can interconvert into thermodynamic product 6,5 ring junction adduct at elevated temperatures. In addition, the partial characterization of the bisadducts of \( I_h \) Sc\(_3\)N@C\(_{80}\) is also reported.

### 7.2. RESULTS AND DISCUSSION
7.2.1. Prato Reaction on $I_h$ Sc$_3$N@C$_{80}$ Reaction Kinetics and Product Isolation

A chlorobenzene solution of the pure $I_h$ isomer of Sc$_3$N@C$_{80}$ and N-triphenylmethyl-5-oxazolidineone (in excess) was heated at reflux under nitrogen (Scheme 1). The progress of the reaction was monitored by high performance liquid chromatography (HPLC) as shown in Figure 1. After 4 hours’ reaction (Figure 1b), two new peaks appeared at 38.6 min ($1a$) and 43.7 min ($1b$); these are assigned as the N-tritylpyrrolidino monoadducts of $I_h$ Sc$_3$N@C$_{80}$. Unreacted $I_h$ Sc$_3$N@C$_{80}$ was later eluted at 87.8 min. $1a$ and $1b$ were eluted earlier than Sc$_3$N@C$_{80}$ because of significant differences in the polarizability and solubility caused by the trityl groups. From the HPLC trace for 4 hours reaction time (Figure 1b), the intensity of peak for $1b$ is higher than that of $1a$. However, after 8 hours, the amounts of product $1a$ and $1b$ became nearly equivalent (Figure 1c). After 12 hours, the amount of $1a$ exceeded that of $1b$, becoming the major product. According to the time evolution of the relative intensities of $1a$ and $1b$ in the HPLC traces, it appeared that $1a$ was the thermodynamically stable product, but product $1b$ was kinetically favored.

Scheme 1. 1,3-Dipolar cycloadditon reaction of Sc$_3$N@C$_{80}$ with N-triphenylmethyl-5-oxazolidineone
Figure 1. HPLC chromatograms of a reaction mixture for the Sc$_3$N@C$_{80}$ I$_5$ isomer at times (a) 0 (b) 4 h (c) 8 h (d) 12 h. HPLC conditions: 10 × 250 mm PYE column at 1.0 mL min$^{-1}$ flow rate with toluene, 390 nm detection.

MALDI-TOF mass spectra of 1a and 1b (Figure 2a, 2b), under negative ionization conditions, both show strong M$^-$ peaks at m/z 1395 and fragment peaks of the parent cage Sc$_3$N@C$_{80}$ at m/z 1109. With positive ionization, MALDI-TOF mass spectra of 1a and 1b revealed the loss of the trityl group (Supporting Information), as expected on the basis of the high stability of the trityl cation.

A small amount of bisadduct 1c was observed after 12 hours of reaction (Figure 1d). In a fashion analogous to the MALDI-TOF mass spectrum for the first bisadduct of Gd$_3$N@C$_{80}$ reported by Stevenson et al.,$^{16}$ we observed a strong M$^-$ signal at m/z 1682 for the isolated bisadduct sample 1c (Figure 2c). The fragment peak at m/z 1438 results from the loss of the trityl group from one of the tritylpyrrolidino groups of 1c. The fragment peak at m/z 1396 is due to complete loss of one of the tritylpyrrolidino groups. Complete loss of both tritylpyrrolidino groups (M-572) gives the Sc$_3$N@C$_{80}$ ion fragment peak at m/z 1110. It is
worth noting that the retention time for the bisadduct is significantly shorter than those of the monoadducts, in accord with solubility and polarizability changes reflective of two exohedral trityl functional groups.

**Figure 2.** MALDI-TOF mass spectra using a 9-nitroanthracene matrix and negative ionization: (a) 1a, (b) 1b, (c) 1c.

### 7.2.2. Structure Determination of the Products

The TNT endohedral metallofullerenes behave as 1,3 dipolarophiles and reactive $2\pi$ components in 1,3-dipolar cycloadditions with azomethine ylides. Therefore, the N-tritylazomethine ylide can only react with a localized double bond at one of the two types of ring junction available on the $I_h$ symmetric $C_{80}$ cage. The 5,6-ring junction is abutted by two six membered rings (Figure 3A) and the 6,6-ring junction is abutted by one five- and one six-
membered ring (Figure 3B). Moreover, there is statistically the same number for the two types of double bonds per molecule (60 total 5,6 and 60 6,6 ring junction bonds, respectively). The 5,6-ring junction has a horizontal plane of symmetry that leads to a tritylpyrrolidino derivative with two equivalent methylene carbons each bearing non-equivalent geminal protons in the pyrrolidine ring (Figure 3C). In contrast, since there is no horizontal symmetric plane, the 6,6-ring junction adduct has two non-equivalent methylene carbons and the two sets of protons on these carbons are non-equivalent (Figure 3D). Because of the non-planar nature of the pyrrolidine ring, the 6,6-isomer will exist as a pair of enantiomers that can interconvert through inversion of the pyrrolidine ring.

![Figure 3](image)

**Figure 3.** (A and B) two addition sites on the Sc$_3$N@C$_{80}$I$_6$ symmetrical cage; (C) symmetric 5,6-ring junction addition model; (D) asymmetric 6,6-ring junction addition model.

Monoadduct 1a displayed $^1$H and $^{13}$C NMR (Figures 4a, 5a), COSY and HMQC spectra (Supporting Information) analogous to those of our previously reported N-methyl
analog from the $I_h$ isomer$^9$ and thus we assigned 1a the structure resulting from addition across the 5,6-ring junction, producing equivalent carbon atoms (62.6 ppm) in the pyrrolidine ring, but diastereotopic geminal protons (2.53, 3.95 ppm) in each of the methylene groups, producing an equivalent AB quartet for each pair. The NMR data of 1a also agree with the reported assignment for the 5,6 ring junction adduct of La$_2$@C$_{80}$.\textsuperscript{15}

Figure 4. $^1$H NMR spectra (500 MHz) of the Sc$_3$N@C$_{80}$ $I_h$ isomer monoadducts (a) 1a in 10:90 (v:v) CD$_3$COCD$_3$:CS$_2$ at 25 °C; (b) 1b in 10:90 (v:v) CD$_3$COCD$_3$:CS$_2$ at 25 °C; (c) 1b in CDCl$_3$ at 55 °C.
The proton NMR spectrum of 1b at room temperature in 10:90 CD$_3$COCD$_3$:CS$_2$ exhibits two broad singlets for the methylene protons at 2.82 (H$_a$) and 3.11 (H$_b$) ppm (Figure 4b), but at 55ºC in CDCl$_3$ pyrrolidine ring inversion occurs more rapidly, yielding time-averaged signals that integrate to a ~2:2 ratio (Figure 4c). The COSY spectrum (not shown) demonstrates that these methylene proton signals are not coupled; therefore, the two signals are consistent with two pairs of geminal protons in non-equivalent chemical environments.

The $^{13}$C NMR spectrum of 1b (with $^{13}$C enriched methylene carbons in the pyrrolidine ring by use of labeled formaldehyde) shows two resonances of equal intensity at 65.6 and 57.6 ppm (Figure 5b). Furthermore, the HMQC spectrum (Supporting Information) reveals that the two protons are correlated to two non-equivalent carbon atoms. Thus, unlike 1a, in which the two carbons of the pyrrolidine ring are equivalent (Figure 5a), the methylene carbons of 1b are non-equivalent. Therefore, the addition pattern for 1b must be asymmetric. This conclusion is consistent with Echegoyen et al.’s results for the asymmetric addition of azomethine ylides on $I_h$ Y$_3$N@C$_{80}$; the pyrrolidine ring carbons and geminal hydrogens in this case have similar NMR shift differences, but are significantly more deshielded. Whereas, the methylene proton signals for the 6,6-ring junction La$_2$@C$_{80}$ adduct show two singlet signals at 3.22 and 3.45 ppm, which is quite similar to our finding for 1b. Thus, we assign 1b as the 6,6-ring junction adduct for the $I_h$ isomer of Sc$_3$N@C$_{80}$ (Figure 3D).
Figure 6. UV-vis spectra of Sc₃N@C₈₀ Ih isomer (black line), 1a (red line) and 1b (blue line) in CS₂ solution.

The UV-vis spectrum (Figure 6) of monoadduct 1a is similar to pristine Ih Sc₃N@C₈₀. However, it is worth noting that there is a broad spectral absorption peak centered at 800-820 nm for 1b which is not present in 1a. In previous studies of bisadducts and triadducts of C₆₀ fulleropyrrolidines, these C₆₀ regioisomeric adducts exhibited distinct absorption patterns in the corresponding UV-vis spectra¹⁷,¹⁸ and this was found to be a useful tool for addition pattern assignments. Specifically, the spectra do not appear to be dependent on the nature of the addend but are characteristic of the regiochemistry for each isomer.¹⁷ Therefore, the characteristic absorption behavior centered at 800 nm for 1b could be associated with the regio-addition site on the Ih C₈₀ cage; namely, the [6,6] adduct. In addition, the distinctive differences in the ¹H NMR spectra for 1a and 1b suggests that the aromaticity of the fullerene cage has been significantly altered for [6,6] when compared with the [6,5] ring junction mono-addition product.

The X-ray crystal structure of the solvate of the 5,6 isomer 1a•2.15C₆H₆•0.35C₅H₁₂ confirms that symmetric addition has occurred at the 5,6-ring junction as shown in Figure 7. The trityl group on the pyrrolidine ring is positioned to minimize contact with the fullerene. The lone pair of electrons on the nitrogen atom in the pyrrolidine ring is located over the
pentagonal ring rather than over the hexagonal ring on the C₈₀ cage. As a result of adduct formation, the C1-C2 length (1.619(4) Å) at the site of addition is longer than the average C-C bond length (1.437 Å) expected for the carbon atoms in a 5,6 ring junction.¹⁰ᵇ

The molecule contains disordered scandium positions that fall into two Sc₃N sets, with a common nitrogen atom for each. The two sets of three scandium atoms, {Sc1, Sc2, Sc3} and {Sc4, Sc5, Sc6} refined to occupancies of 0.90(3) and 0.10(7), respectively. The major Sc₃N set is planar with the sum of the three Sc-N-Sc angles equaling 359.79 °; the minor set is similar with the sum of the other three angle Sc-N-Sc equaling 357.9 °. Figure 7 shows only the location of the major set. The orientation of the major planar Sc₃N unit is surprisingly similar to that of the previously reported Diels-Alder adduct in which the internal cluster is positioned well away from the external functionalization site.¹⁰ The dihedral angle of the planes of the Sc₃N cluster and the pyrrolidino ring (C₁-C₂-C₈₁-C₈₂) is 26.35°, which is very close to that in the Diels-Alder adduct (27.06 °). The N-Sc distances in the major form [2.031(2), 2.030(3) and 2.029(2) Å] are also very comparable to those in the Diels-Alder adduct [2.032(3), 2.020(3) and 2.029(3) Å].¹⁵
**Figure 7.** Two orthogonal views of the 5,6 isomer in 1a•2.15C₆H₆•0.35C₅H₁₂ with thermal ellipsoids at 30% probability. The solvent molecules are omitted for clarity.

Similarly, the X-ray crystal structure of the solvate 1b•2.25CS₂•0.75C₆H₆ confirms that addition has occurred at a 6,6-ring junction. Figure 8 shows drawings of the structure as determined crystallographically. The two orthogonal views of one enantiomer of the major form are shown at the top of Figure 8. Since the compound crystallizes in the centrosymmetric space group $P\overline{1}$, the other enantiomer is present and generated by symmetry. There is disorder in the cage location. Only the major form, which has 0.75 occupancy, is shown in the two views at the top of Figure 8. In addition to the orientation shown in the two views at the top of Figure 8, there is a second orientation of the fullerene cage that interchanges the positions of the five- and six-membered rings that radiate from the sites of addition. This situation arises because the two enantiomers of the 6,6 isomer crystallize in unequal amounts at a common site. A line drawing showing a portion of both orientations (enantiomers) superimposed is shown in the lower part of Figure 8. Note that this disorder does not jeopardize the conclusion that addition has occurred at a 6,6-ring junction. As a result of adduct formation the C1-C9 bond length (1.619(7) Å) is longer than the average C-C bond length (1.421 Å) at an unfunctionalized 6,6 ring junction.\(^{10b}\)

There is also disorder in the interior of the C₈₀ that involves the locations of the scandium atoms. There are ten scandium atom sites with site occupation factors (SOF's) ranging from 0.187 to 0.398. These were refined with anisotropic thermal parameters. There are five additional scandium atom sites with SOF's ranging from 0.065 to 0.097, and these were assigned isotropic thermal parameters. The occupancies of these scandium positions were independently varied but were constrained to sum to 3.00000. No clear correlation
between the occupancies of these fifteen sites could be discerned. All fifteen sites are shown in Figure 8. Notice, however, that none of these scandium atom sites is near the site of external adduct formation. The presence of fifteen sites for scandium atoms within this endohedral is consistent with earlier calculations that show little energetic differences between varying orientations of the Sc$_3$N group within the Ih isomer of unfunctionalized C$_{80}$.$^{19}$ The structure also contains disorder in the solvate CS$_2$ and benzene molecules, which are not shown in the figure. The structure of the fullerene cage and the appended group of the tritylpyrrolidino 6,6-adduct of La$_2$@C$_{80}$ is similar to that of the 6,6-isomer 1b reported here.$^{15}$ That adduct also crystallized as a racemate in the space group $P\overline{1}$.
**Figure 8.** Top, two orthogonal views of the 6,6 isomer in 1b•2.25CS₂•0.75C₆H₆ showing the position of the major cage site (with 0.75 occupancy) with thermal ellipsoids at 30% probability. The positions of the 15 sites containing scandium ions with fractional occupancies ranging from 0.40 to 0.06 are shown in red. Bottom, a drawing of a portion of the fullerene cage 1b showing the orientation of the minor form, shown with dashed lines, relative to the major form, shown with solid lines.

### 7.2.3. Interconversion of Isomeric Prato Mono-adducts 1a and 1b

To demonstrate that the 6,6-adduct 1b is indeed the kinetic product and the 5,6-adduct 1a is the thermodynamic product we carried out an interconversion study. A chlorobenzene solution of pure 6,6-junction adduct 1b, the purported kinetic product, was heated at reflux for 2 days; the composition of the solution was monitored via HPLC. The results of this study are shown in Figures 9 and 10. Over time the 6,6-adduct 1b is converted to >90% 5,6-adduct 1a, the thermodynamically more stable isomer. If we assume the interconversion process is the first order reaction, then the half-life for this process is 11.5 hours (at ~ 130 °C); the calculated reaction rate \( k \) is 0.0604 min⁻¹.
Figure 9. HPLC chromatograms of interconversion of 1b to 1a, (a) pure 1a, (b) t = 0, pure 1b, (c) t = 10.5 h, (d) t = 24.5 h, (e) t = 34.5 h, (f) t = 46.5 h.
Figure 10. The change of composition of 1b and 1a during the interconversion process.

Mechanistically the interconversion of the isomers of the monoadducts 1a and 1b is an interesting process. Although such equilibrations have been reported for C$_{60}$ derivatives, to our knowledge, this is the first such isomerization process to be observed for an endohedral metallofullerene. Based on the principle of microscopic reversibility, the expected mechanism for this process involves the same intermediate that is presumed to be involved in the initial formation of 1b, i.e., the zwitterionic species resulting from initial attack of the azomethine ylide, which has a negative charge on the C$_{80}$ cage and a positive charge on the azomethine ylide moiety (Figure 11, middle). After rotation about the CH$_2$-C$_{80}$ bond, bond formation at the 5,6-ring juncture would then yield the thermodynamic product 1a (Figure 11).
Figure 11. Proposed mechanism of interconversion of 1b to 1a through the pirouette of the addend.

7.3. CONCLUSIONS

Both the kinetically and thermodynamically controlled N-tritylpyrrrolidino derivatives of \( \text{I}_h \) Sc\(_3\)N@C\(_{80}\) have been synthesized and isolated. Kinetic studies clearly demonstrate that the 5,6-ring junction adduct (1a) is the thermodynamic product, whereas the 6,6-ring junction adduct (1b) is the kinetic product. The structures of the 5,6- and 6,6-adducts were confirmed by X-ray crystallography. The kinetic product 1b was converted to the thermodynamic product 1a in refluxing chlorobenzene at 130 °C. By acid-catalyzed removal of the trityl protecting group, these N-tritylpyrrrolidino derivatives promise to be useful precursors for various applications as shown with C\(_{60}\) analogs.\(^{22}\)

7.4. EXPERIMENTAL SECTION

Materials and Methods: The Sc\(_3\)N@C\(_{80}\) \( I_h \) and \( D_{5h} \) isomer mixture was obtained by the chemical separation method, as reported in detail earlier.\(^7\) N-Triphenylmethyl-5-
oxazolidineone was synthesized according to previous work.\textsuperscript{8} Formaldehyde (99\% $^{13}$C, ~20\% w/w in H$_2$O, Cambridge Isotope Laboratory, Inc.) was used for synthesizing $^{13}$C enriched N-triphenylmethyl-5-oxazolidineone. Toluene (HPLC Grade $\geq$99.9\%) and chlorobenzene (99\%) were used as obtained from Aldrich. A semi-preparative PYE [β-(1-pyrenyl)ethyl silica] column (10 × 250 mm) and a guard PYE column (10 × 20 mm) were used for both analysis and purification. HPLC system: Acure series III pump, 757 Absorbance Detector (Applied Biosystems). A JEOL ECP 500 MHz instrument was used for all NMR measurements. Mass spectrometry was performed on a Kratos Analytical Kompact SEQ MALDI-TOF mass spectrometer. Samples were dissolved in carbon disulfide and 0.5 ul of solution was placed on the stainless steel target plates. An equal volume of saturated solution of the 9-nitroanthracene matrix in toluene was added, and the mixture was evaporated to dryness. Analysis was performed in the typical manner, whereby the dried sample on the target plate was subjected to irradiation from a nitrogen laser (227 nm) and the resulting ions formed were detected and recorded. The accelerating voltage applied was 20 kV. Minimal laser power was used in order to achieve sufficient sensitivity, while avoiding degradation of the signal in terms of resolution and noise.

**Purification of Isomeric Sc$_3$N@C$_{80}$:** The Sc$_3$N@C$_{80}$ $I_h$ and $D_{5h}$ isomer mixture was dissolved in toluene. Pure Sc$_3$N@C$_{80}$ $I_h$ isomer was isolated from the original mixture by HPLC using a PYE column, with toluene at 1.0mL/min, $\lambda$ = 390nm.

**Reaction of $I_h$ Isomer of Sc$_3$N@C$_{80}$ with N-trityloxazolidineone:** A solution of 2.0 mg (1.8 $\mu$mol) of Sc$_3$N@C$_{80}$ $I_h$ isomer and 30 mg (91 $\mu$mol) of N-triphenylmethyl-5-oxazolidineone in 35 mL of chlorobenzene was heated at reflux under nitrogen. The solvent was removed by a rotary evaporator. The residue was dissolved in toluene and then injected into an HPLC for analysis. 1a, 1b and 1c were isolated by HPLC using the same conditions as indicated above.
X-ray Crystallographic Analysis of the 5,6-Isomer 1a: Black needles of the 5,6 isomer 1a•2.15C₆H₆•0.35C₅H₁₂ crystallized from benzene/pentane by slow vapor diffusion of the latter at room temperature. The crystals were removed from the glass tubes in which they were grown together with a small amount of mother liquor and immediately coated with a hydrocarbon oil on a microscope slide. A suitable crystal was mounted on a glass fiber with silicone grease and placed in the cold dinitrogen stream of a Bruker Apex II CCD with graphite-monochromated Mo Kα radiation at 90(2) K. No decay was observed in 50 duplicate frames at the end of each data collection. Crystal data are given below. The structures were solved by direct methods and refined using all data (based on $F^2$) using the software of SHELXTL 5.1.23 A semiempirical method utilizing equivalents was employed to correct for absorption.24 Hydrogen atoms were added geometrically and refined with a riding model.

The molecule contains disordered scandium atoms that can be assigned to two Sc₃N sets, with a common nitrogen atom in each. The two sets of three scandium atoms, {Sc1, Sc2, Sc3} and {Sc4, Sc5, Sc6} refined to set occupancies of 0.90(3) and 0.10(7), respectively. The structure contains a region of disordered solvent that was modeled with three half-occupied molecules of benzene and a molecule of $n$-pentane at 0.35 fractional occupancy. These molecules were refined as rigid groups. In addition, there is a molecule of benzene located on a position of inversion symmetry.

Crystal Data for the 5,6-Isomer 1a•2.15C₆H₆•0.35C₅H₁₂. Black needles, C₁₁₅.₆₃H₃₆.₁₀N₂Sc₃, crystal size 0.24 x 0.09 x 0.013 mm³, triclinic, space group $P\overline{1}$, $a = 11.0242(11)$ Å, $b = 16.5046(18)$ Å, $c = 18.8995(19)$, $\alpha = 74.045(2)^\circ$, $\beta = 77.655(3)^\circ$, $\gamma = 76.840(2)^\circ$, $V =$
X-ray Crystallographic Analysis of the 6,6 Isomer 1b: Black plates of the 6,6 isomer 1b•2.25CS₂•0.75C₆H₆ were formed by layering 0.5 mL of benzene over a solution of 2 to 5 mg of 1b in 0.5 mL of carbon disulfide in a 6 mm inside diameter glass tube. Methanol (0.5 mL) was layered over the benzene layer, and the tube was capped with a permeable rubber septum. Crystals grew in one to two weeks. Crystals were harvested and data collected as described above for the 5,6 isomer 1a. The structure contains disorder in the solvate CS₂ and benzene molecules.

Crystal Data for the 6,6 Isomer 1b•2.25CS₂•0.75C₆H₆. Black plates, C₁₀₇.₇₅H₂₃.₅₀N₂S₄.₅₀Sc₃, crystal size 0.24 x 0.11 x 0.016 mm³, triclinic, space group P1̅, a = 11.0127(8), b = 16.3870(8), c = 18.7355(11) Å, α= 99.521(1), β = 106.034(1), γ = 102.488(1)°, V = 3080.0(3) Å³, Z = 2, d(calcd) = 1.752 Mg/m³, F(000) = 1638, λ(MoKα) = 0.71073 Å, μ(MoKα) = 0.543 mm⁻¹, θ range for data collection 1.95 to 27.50°, T = 90(2) K; reflections collected 35232; independent reflections 14160 [R(int) = 0.0445], Completeness to θ = 27.50° 99.9 %, Refinement method - Full-matrix least-squares on F²; data/restraints/parameters: 14160 / 463 /1214; Goodness-of-fit on F² 1.104; Final R indices [I>2σ(I)]: R1 = 0.099, wR2 = 0.281; R indices (all data): R1 = 0.141, wR2 = 0.30525; Largest diff. peak and hole: 1.819 and -1.509 e.Å⁻³.
7.5 SUPPORTING INFORMATION

**Figure S1a.** 5,6-(N-Tritylpyrrolidino) adduct of $I_h$ Sc$_3$N@C$_{80}$ (1a)

**Figure S1b.** 6,6-(N-Tritylpyrrolidino) adduct of $I_h$ Sc$_3$N@C$_{80}$ (1b)
**Figure S2.** 500MHz COSY spectrum of 5,6-(N-tritylpyrrolidino) adduct of $I_h$ Sc$_3$N@C$_{80}$ (1a) [solvent: 10/90 (v/v) CD$_3$COCD$_3$/CS$_2$], 25 ºC.

![COSY spectrum](image)

**Figure S3.** 500MHz HMQC spectrum of 5,6-(N-tritylpyrrolidino) adduct of $I_h$ Sc$_3$N@C$_{80}$ (1a) [solvent: 10/90 (v/v) CD$_3$COCD$_3$/CS$_2$], 25 ºC.

![HMQC spectrum](image)
**Figure S4.** 500MHz HMQC spectrum of 6,6-(N-tritylpyrrolidino) adduct of \( I_6 \) Sc\(_3\)N@C\(_{80}\) (1b) [solvent: CDCl\(_3\), 55\(^\circ\)C].

**REFERENCES**


Chapter 8

Sc$_3$N@C$_{78}$: Encapsulated Cluster Regio-Control of Adduct Docking on an Ellipsoidal Metallofullerene Sphere

8.1. INTRODUCTION

The chemistry of endohedral metallofullerene has developed rapidly during the past decade, driven by the remarkable chemical and physical features that could provide many important applications in nanomaterials and biomedical science.$^{1-6}$ Since their discovery in 1999,$^7$ a large variety of trimetallic nitride templated endohedral metallofullerenes (TNT EMFs) with different encapsulated metals, cage sizes, and symmetries have been synthesized and isolated.$^7-^{16}$

After the initial discovery of the TNT EMF class represented by the prototypical Sc$_3$N@C$_{80}$ ($I_h$ cage),$^7$ Sc$_3$N@C$_{78}$ was also discovered and X-ray crystallographic analysis revealed that it possesses $D_{3h}$ (78:5) symmetry (Figure 1).$^9$ Both crystallography and DFT calculations of Sc$_3$N@C$_{78}$ show that the scandium atoms are localized over the three pyracylene patches.$^9,^{17}$ Studies on the electronic and vibrational structures of Sc$_3$N@C$_{78}$ suggest that there are strong interactions between the Sc$_3$N cluster and the fullerene cage carbon atoms.$^{18, 19}$ Two other C$_{78}$ endohedral metallofullerenes, La$_2$@C$_{78}$$^{20}$ and Ti$_2$C$_2$@C$_{78}$$^{21, 22}$ were reported to have the same $D_{3h}$ (78:5) symmetry. Tm$_3$N@C$_{78}$, Dy$_3$N@C$_{78}$ (I) and Dy$_3$N@C$_{78}$ (II) were also isolated and characterized.$^{12, 13}$ Compared with $D_{3h}$ (78:5) Sc$_3$N@C$_{78}$, Tm$_3$N@C$_{78}$, Dy$_3$N@C$_{78}$ (I) and Dy$_3$N@C$_{78}$ (II) have significantly longer
chromatography retention times and distinct absorption spectra which suggest for the different cage structures.\textsuperscript{12, 13}

Functionalization of the TNT EMFs is necessary to provide unique nanomaterials useful for various further applications, for example, MRI contrast agents.\textsuperscript{23} However, organic functionalization chemistry of Sc$_3$N@C$_{78}$ has not been extensively explored because only small amounts of the material were previously available. Recently, by taking advantage of the high kinetic stability of TNT EMFs, it has been found that high purity TNT EMFs can be obtained directly from soot or its extract by selectively trapping empty cage fullerenes and classic EMFs on a functionalized support.\textsuperscript{24, 25} This breakthrough makes it possible to isolate significant quantities of Sc$_3$N@C$_{78}$ in a short period of time.

In this chapter, we report the synthesis and characterization of first N-tritylpyrrolidino derivatives of $D_{3h}$ (78:5) Sc$_3$N@C$_{78}$ utilizing the Prato reaction.\textsuperscript{26, 27} These results are compared with previous studies of the homologous Sc$_3$N@C$_{80}$, both in terms of chemical reactivity and regioselectivity, as well as crystallographic studies.

\textbf{Figure 1.} A schematic diagram of the carbon cage of the $D_{3h}$ (78:5) C$_{78}$ isomer showing the 8 bands of different types of carbon atoms. The 3-fold axis is aligned vertically and the horizontal mirror plane passes through the h-type carbon atoms. There are two $D_{3h}$ isomers of C$_{78}$ that obey the isolated pentagon rule. Throughout this article we are concerned only with the specific isomer (78:5) shown here.\textsuperscript{9}
8.2. RESULTS AND DISCUSSION

Recently, pyrrolidino derivatives of icosahedrally symmetric \((I_h)\) Sc\(_3\)N@C\(_{80}\) were synthesized via 1,3-dipolar cycloaddition of azomethine ylides to the fullerene cage and characterized.\(^{28-30}\) A kinetic study showed that the 6,6-ring junction adduct is the kinetically controlled product; it is converted to the thermodynamic product, the 5,6-ring junction adduct, upon thermal equilibration.\(^{30-32}\) On the other hand, the minor Sc\(_3\)N@C\(_{80}\) isomer, with \(D_{5h}\) symmetry, exhibits higher reactivity in the Prato reaction with the tritylazomethine ylide in comparison with the \(I_h\) analog and yields the thermodynamically stable monoadduct by addition across the 6,6–ring junction of a pyracylene unit.\(^{14}\)

In the present work, two mono- and one di-N-tritylpyrrolidino Sc\(_3\)N@C\(_{78}\) derivatives were obtained after 3 hours’ reflux with N-trityloxazolideneone in chlorobenzene (Scheme 1) (Figure 2). From high performance liquid chromatography (HPLC) trace of reaction mixture (Figure 2), product 1\(a\) (18.6 min) and 1\(b\) (22.0 min) were identified as the monoadducts by MALDI-TOF MS (Figure 3a,3b). A small quantity of bisadduct 1\(e\) was also isolated and characterized by MALDI-TOF MS (Figure 3c). Molecular ion peak of bisadduct 1\(e\) was observed at m/z 1656. The fragment peak at m/z 1373 was due to loss of one of the tritylpyrrolidino groups. The fragment peak at m/z 1413 and m/z 1128 resulted from the loss of the trityl groups from tritylpyrrolidino groups of 1\(e\), as expected on the basis of the high stability of the trityl cation. Complete loss of both tritylpyrrolidino groups gave the Sc\(_3\)N@C\(_{78}\) ion fragment peak at m/z 1085. The shorter retention time of the bisadduct 1\(e\) (12.0 min) is analogous to bisadducts of the \(I_h\) and \(D_{5h}\) isomers of Sc\(_3\)N@C\(_{80}\).\(^{14,30}\) However,
the reactivity of Sc$_3$N@C$_{78}$ is significantly higher than Sc$_3$N@C$_{80}$ by comparison of the reaction yield and high yield of bisadduct in a shorter time period$^{30}$.

**Scheme 1.** The Prato Reaction of Sc$_3$N@C$_{78}$ with N-Triphenylmethyl-5-oxazolidineone.

**Figure 2.** HPLC chromatograms of (a) the initial Sc$_3$N@C$_{78}$ (b) the product mixture from the Prato reaction. HPLC conditions: 10 × 250 mm PYE [2-(1'-pyrenyl)ethyl silica] column at 2.0 mL min$^{-1}$ flow rate with toluene, 390 nm detection.
Figure 3. Matrix Assisted Laser Desorption Ionization Time-of-flight (MALDI-TOF) mass spectra using a 9-nitroanthracene matrix and negative ionization: (a) monoadduct 1a, (b) monoadduct 1b, (c) bisadduct 1c. Calculated for monoadducts: m/z 1372 ; calculated to bisadducts: m/z 1655.
The $^{13}$C NMR spectrum of 1a (with $^{13}$C-enriched methylene carbon atoms in the pyrrolidine ring by use of $^{13}$C labeled starting material) exhibits peaks at 59.3 and 67.3 ppm, indicating that methylene carbon atoms $C_a$ and $C_b$ are nonequivalent (Figure 4a). The $^1$H NMR spectrum of 1a contains two triplets (at 3.79 and 3.31 ppm) for the methylene hydrogens $H_a$ and $H_b$ (triplets due to coupling with adjacent $^{13}$C labeled methylene carbon, $^{1}J_{C-H}=141$Hz). The heteronuclear multiple quantum coherence (HMQC) spectrum confirms the assignment; the methylene carbon atoms $C_a$ and $C_b$ are coupled to the adjacent methylene hydrogen atoms $H_a$ and $H_b$, respectively (Figure 4a). The correlation spectroscopy (COSY) spectrum (Figure 4b) confirms that these methylene protons are not coupled. In addition, based on previous studies with the pyrrolidino metallofullerene derivatives, differential shielding effects from pentagon-hexagon ring currents on the surface cage and the nitrogen atom of the pyrrolidine ring, the 5,6-ring junction adduct always exhibits large chemical shift differences (1.2-1.4 ppm) for the diastereotopic methylene protons of the pyrrolidine ring.$^{28-30, 33}$ In contrast, the 6,6-junction adducts have either no or much smaller shift differences (~0.2 ppm)$^{14, 30, 33, 34}$ Therefore, we conclude that 1a is a 6,6-ring junction adduct with the equivalent methylene protons (assuming rapid inversion of the pyrrolidine ring) but non-equivalent methylene carbons.
Figure 4. 500 MHz (a) HMQC (b) COSY spectra of the Sc$_3$N@C$_{78}$ N-tritylpyrrolidino monoadducts 1a. [Solvent: 1,2-dichlorobenzene-d$_4$.]

The $^{13}$C NMR spectrum of 1b (with $^{13}$C-enriched methylene carbons in the pyrrolidine ring by use of $^{13}$C labeled starting material) exhibits peaks at 56.2 and 66.8, indicating nonequivalent methylene carbon atoms C$_a$ and C$_b$. However, in contrast to 1a in which the geminal methylene hydrogens on each carbon are equivalent (no diastereotopic methylene protons were observed), in the $^1$H NMR spectrum of 1b (Figure 5a) the geminal methylene hydrogen atoms on each carbon are nonequivalent. The HMQC spectrum of 1b shows that H$_a$ (3.24 ppm) and H$_a'$ (3.07 ppm) are coupled with C$_a$, and H$_b$ (3.16 ppm) and H$_b'$ (3.05 ppm) couple with C$_b$. The H$_a$-H$_a'$ and H$_b$-H$_b'$ couplings are confirmed by the COSY spectrum (Figure 5b). Therefore, we conclude that 1b is also a 6,6-ring junction adduct, but with both nonequivalent methylene carbons and hydrogens.
Figure 5. 500 MHz (a) HMQC (b) COSY spectra of the Sc$_3$N@C$_{78}$ N-tritylpyrrolidino monoadducts 1b. For good resolution, methylene carbons are not $^{13}$C-enriched in the 1D proton spectrum of 1b. [Solvent: 1,2-dichlorobenzene-$d_4$].

The $D_{3h}$ (78:5) ellipsoidal Sc$_3$N@C$_{78}$ carbon cage has 8 different types of carbon atoms and 13 sets of C-C bonds as shown in Figure 1. The statistical numbers of bonds of each type, the type of ring junction involved and the symmetry of the addition patterns are summerized in Table 1. As suggested by the NMR data for 1a, the c-f bond is the only possible 6,6-ring junction reaction site that produces non-equivalent methylene carbon atoms.
but equivalent geminal methylene protons. The reaction site for 1b, based on Table 1 and the NMR data, has three possibilities: the b-d, d-e and f-g bonds; these three sites yield 6,6-ring junction adducts with both nonequivalent methylene carbon atoms and hydrogen atoms. DFT calculations were performed for these three 1b adducts. Among them, the b-d bond adduct has a significantly lower relative thermodynamic energy (~20 kcal/mol) and larger HOMO-LUMO gap (0.4~0.6 eV) than those of the d-e and f-g bond adducts (Table 2). However, the differences in the relative thermodynamic energies and the HOMO-LUMO gaps for the b-d bond adduct and c-f adduct 1a are quite small (2.1 kcal/mol and 0.04 eV), accounting for the experimental observed production of two kinetically favored monoadducts. Therefore, d-e and f-g bond sites can be ruled out, and we suggest that the b-d bond is the most likely addition site for the monoadduct 1b. Consistent with our calculations and experimental result, Campanera et al. also suggested that the c-f and b-d bond are the two most reactive site in pristine Sc3N@C78 based on the higher Mayer Bond Order (MBO) values (Table 2) compared with other bond sites.35

**Table 1.** Comparison of symmetries for $D_{3h}$ (78:5) Sc$_3$N@C$_{78}$ N-tritylpyrrolidino monoadducts at different addition sites

<table>
<thead>
<tr>
<th>Site of Addition</th>
<th>Ring junction type</th>
<th>Number of equivalent bonds</th>
<th>Symmetry of the methylene carbon atoms</th>
<th>Symmetry of the methylene hydrogen atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-a</td>
<td>6,6</td>
<td>6</td>
<td>Symmetric</td>
<td>Symmetric</td>
</tr>
<tr>
<td>a-a</td>
<td>6,5</td>
<td>6</td>
<td>Symmetric</td>
<td>Symmetric</td>
</tr>
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<td>a-b</td>
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<td>Asymmetric</td>
</tr>
<tr>
<td>b-d</td>
<td>6,6</td>
<td>12</td>
<td>Asymmetric</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>d-d</td>
<td>6,6</td>
<td>6</td>
<td>Symmetric</td>
<td>Asymmetric</td>
</tr>
</tbody>
</table>
Table 2. Thermodynamic relative energies (kcal/mol) and HOMO/LUMO levels (eV) for Sc$_3$N@C$_{78}$ N-tritylpyrrolidino monoadducts

<table>
<thead>
<tr>
<th>Site of Addition</th>
<th>Thermodynamic Relative Energy of Sc$<em>3$N@C$</em>{78}$ N-tritylpyrrolidino monoadduct</th>
<th>HOMO Level of Sc$<em>3$N@C$</em>{78}$ N-tritylpyrrolidino monoadduct</th>
<th>LUMO Level of Sc$<em>3$N@C$</em>{78}$ N-tritylpyrrolidino monoadduct</th>
<th>HOMO-LUMO Gap of Sc$<em>3$N@C$</em>{78}$ N-tritylpyrrolidino monoadduct</th>
<th>Final MBO for Sc$<em>3$N@C$</em>{78}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-f</td>
<td>0.00</td>
<td>-5.28</td>
<td>-3.11</td>
<td>2.17</td>
<td>1.280</td>
</tr>
<tr>
<td>b-d</td>
<td>2.13</td>
<td>-5.23</td>
<td>-3.11</td>
<td>2.13</td>
<td>1.271</td>
</tr>
<tr>
<td>d-e</td>
<td>21.89</td>
<td>-5.02</td>
<td>-3.51</td>
<td>1.51</td>
<td>1.097</td>
</tr>
<tr>
<td>f-g</td>
<td>23.50</td>
<td>-5.10</td>
<td>-3.33</td>
<td>1.77</td>
<td>1.165</td>
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</tbody>
</table>

Black crystals of 1a suitable for single crystal X-ray diffraction were obtained by evaporation of a benzene solution. Figure 6 shows two drawings of the adduct. The upper drawing shows a view in which the flat Sc$_3$N unit lies in the horizontal plane. This view looks down what would have been the three-fold axis of the parent Sc$_3$N@C$_{78}$. The lower drawing shows a clearer view of the attachment of the addend to the cage. Addition has occurred at a c-f bond in the endohedral fullerene and this adduct addition site is above, but equidistant from the Sc3 and Sc1 atoms that define the plane of the Sc$_3$N unit. Thus, three pyracylene patches in the plane of the Sc$_3$N unit and the h-type carbon atoms are not susceptible to external attack by the adjacent metals, and the addend avoids any interaction with the Sc$_3$N unit, which remains in the horizontal plane of the C$_{78}$ cage. The Sc-N distances are: Sc1-N1
2.001(2), Sc2-N1 1.999(2), and Sc3-N1 2.001(2) Å. The Sc-N distances are similar to those in other endohedrals containing the planar Sc₃N unit.³⁶

**Figure 6.** Two drawings of Sc₃N@C₇₈-(CH₂)₂NC(C₆H₅)₃, 1a, with 50 % thermal ellipsoids. The top view looks down what would be the 3-fold axis of the unfunctionalized endohedral, while the lower view is arranged to show the disposition of the addend. The benzene molecules in the solvate are not shown.
The scandium ion resides at the center of a pyracylene patch in the middle of the C\textsubscript{78} cage. The shortest Sc-C distances are: Sc1-C27, 2.213(3); Sc1-C28, 2.271(3); Sc2-C34, 2.238(3); Sc2-C35, 2.250(3); Sc3-C42, 2.210(3); and Sc3-C41 2.269(3) Å. The positioning of the metal ions within the C\textsubscript{78} cage corresponds to that seen in the parent endohedral. However, in that structural study which involved the cocrystal, Sc\textsubscript{3}N@C\textsubscript{78} • Co\textsuperscript{II}(OEP) • 1.5C\textsubscript{6}H\textsubscript{6} • 0.3CHCl\textsubscript{3}, there were three different orientations of the cage and three orientation of the Sc\textsubscript{3}N unit to consider. The present structure does not display any disorder.

The variations seen in the C-C distances in the C\textsubscript{78} cage are larger than those seen in Sc\textsubscript{3}N@C\textsubscript{80} where there are only two types of C-C bonds with corresponding distances of 1.437(15) Å at the 5:6 ring junctions and 1.421(18) Å at the 6:6 ring junctions. In 1\textsubscript{a} the average C-C distances for the shortest C-C bonds are 1.394 Å for the a-a bonds at 6:6 ring junctions and 1.394 Å for the c-f bonds. The c-f bond at the site of additions has been excluded from this averaging. Other average C-C distances are: 1.441 Å for the a-a bonds at 5:6 ring junctions, 1.420 Å for the a-b bonds (5:6 junction), 1.445 Å for the b-c bonds (6:6 junction), 1.468 for the d-d bonds (6:6 junction), 1.450 for the d-e bonds (6:6 junction), 1.441 Å for the e-g bonds (5:6 junction), 1.429 for the f-g bonds (6:6 junction), 1.419 Å for the g-g bonds (6:6 junction), 1.443 Å for the h-e bonds (5:6 junctions), and 1.436 for the h-h bonds (6:6 junction), which are the carbon atoms nearest the scandium ions.

8.3. CONCLUSIONS

In conclusion, we have synthesized and isolated the first derivatives of Sc\textsubscript{3}N@C\textsubscript{78} via 1,3-dipolar cycloaddition of tritylazomethine ylides. The addition sites of two kinetic stable N-tritylpyrrolidino monoadducts 1\textsubscript{a} and 1\textsubscript{b} were located at c-f and b-d bonds on the
Sc$_3$N@C$_{78}$ cage respectively (Figure 7), based on NMR spectra and DFT calculations. The first single crystal X-ray diffraction study of Sc$_3$N@C$_{78}$ derivative 1a confirms that the addition has occurred at the c-f bond on the ellipsoidal metallofullerene $D_{3h}$ (78:5) Sc$_3$N@C$_{78}$. The Sc$_3$N unit remains in the horizontal plane of the $D_{3h}$ (78:5) cage after exohedral derivatization and does not interact directly with the site of addition. This represents the first case (in contrast with earlier studies of A$_3$N@C$_{80}$ molecules and other endohedral metallofullerenes) where the internal trimetallic cluster (Sc$_3$N) is restricted to a horizontal plane in the molecule and thus, demonstrates regio-control of adduct docking on a metallofullerene sphere.

![Figure 7. Two addition sites c-f and b-d bond (yellow) on $D_{3h}$ (78:5) Sc$_3$N@C$_{78}$ cage](image)

8.4. EXPERIMENTAL SECTION

Materials and Methods: The Sc$_3$N@C$_{68}$, Sc$_3$N@C$_{78}$ and Sc$_3$N@C$_{80}$ mixture was obtained by the chemical separation method, as reported in detail earlier.$^{24}$ Pure Sc$_3$N@C$_{78}$ sample was isolated and purified by HPLC at retention time of 41.2 min (PYE column, 10 x 250 mm, toluene, 2 mL/min). N-tritylpyrrolidino derivatives of Sc$_3$N@C$_{78}$ were synthesized by heating
a solution of 2.0 mg (1.8 μmol) of Sc$_3$N@C$_{78}$ and 12.2 mg (37 μmol) of N-triphenylmethyl-5-oxazolidinone in 25 mL of chlorobenzene at reflux for 3 h under N$_2$. The solvent was removed under a stream of nitrogen overnight. The crude solid was dissolved in toluene and then injected into an HPLC for isolation and analysis (PYE column, 10 x 250 mm, toluene, 2 mL/min). The yields of two monoadducts are both around 20%. HPLC system and MALDI-TOF Mass spectrometry are the same as were used in the previous study.$^{30}$ A JEOL ECP 500 MHz instrument was used for Sc$_3$N@C$_{78}$ NMR measurements.

**Computations:** Full geometry optimizations were conducted at the B3LYP level$^{37-39}$ using the Gaussian 03 program.$^{40}$ The effective core potential and the corresponding basis set were used for Sc. The basis sets employed were LanL2DZ for Sc,$^{41}$ and 3-21G* for C,N and H.$^{42}$ For the computed structure of the c-f bond adduct of Sc$_3$N@C$_{78}$, we referred to the crystallographic data. As for structures of the b-d, d-e, and f-g bond adducts, we assumed that the functional group would connect to the carbon as far away as possible from the positions of the metal atoms. All the calculations were subjected to frequency analyses, which were performed at the same level as that of the geometry optimization. As a result, no imaginary frequencies are reported for optimized structures.

**Crystals of Sc$_3$N@C$_{78}$-(CH$_2$)$_2$N(C(C$_6$H$_5$)$_3$)$\cdot$2.5(C$_6$H$_6$)** were obtained by slow evaporation of a benzene solution of the compound. Crystal data for Sc$_3$N@C$_{78}$-(CH$_2$)$_2$N(C(C$_6$H$_5$)$_3$)$\cdot$2.5(C$_6$H$_6$): black needle, 0.27 x 0.05 x 0.05 mm, triclinic, space group $P\overline{1}$, $a = 10.923(2)$, $b = 16.311(3)$, $c = 18.734(3)$ Å, $\alpha = 75.545(2)$, $\beta = 76.371(2)$, $\gamma = 77.167(2)$ °, $V = 3093.4(9)$ Å$^3$, $\lambda = 0.71073$ Å, $Z = 2$, $D_c = 1.682$ Mg m$^{-3}$; $\mu$ (Mo Kα) = 0.391 mm$^{-1}$; $T = 90(2)$ K; Bruker Apex II; scans, $2\theta_{\text{max}} = 66.46$ °; 25065 reflections collected; min/max transmission = 0.90/0.98; Patterson and difference Fourier methods solution (SHELXS-97, Sheldrick, 1990);
full-matrix least squares based on \( F^2 \) (SHELXL-97; Sheldrick, 1998); \( R = 0.1802 \) for all data; conventional \( R_I = 0.0679 \) computed for 9806 observed data (>2\( \sigma(I) \)) with 1043 parameters and no restraints.

8.5. SUPPORTING INFORMATION

*Figure S1.* UV-Vis Spectrum of 1a

![UV-Vis Spectrum of 1a](image)

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Chapter 9

Selective Formation of a Symmetric Sc$_3$N@C$_{78}$ Diadduct: Adduct Docking Controlled by an Internal Trimetallic Nitride Cluster

9.1. INTRODUCTION

Organic functionalization of endohedral metallofullerenes is essential to construct novel organo-metallofullerene materials for a variety of future applications. Many recent experimental and theoretical studies suggest that the chemical reactivity and regioselectivity of endohedral metallofullerenes are influenced by the encapsulated cluster, metal species, carbon cage size, and symmetry.\textsuperscript{1} Trimetallic nitride endohedral metallofullerenes are the most abundant families of metallofullerenes formed in the Krätschmer-Huffmann generator.\textsuperscript{2} The synthesis and characterization of Sc$_3$N@C$_{78}$ was first reported in 2001.\textsuperscript{3} X-ray crystallographic analysis revealed that its C$_{78}$ cage possesses $D_{3h}$ (78:5) symmetry. The planar Sc$_3$N cluster lies on the horizontal mirror plane of the C$_{78}$ cage, while the scandium atoms are localized over the three pyracylene patches. The 3-fold axis is aligned vertically and the horizontal mirror plane passes through the h-type carbon atoms (Figure 1).\textsuperscript{3} Unlike the Sc$_3$N@C$_{80}$ I$_h$ isomer, in which the Sc$_3$N cluster can freely rotate inside the C$_{80}$ cage, the rotation of the Sc$_3$N cluster in the C$_{78}$ cage is restricted to the two-dimensional horizontal mirror plane.\textsuperscript{4} The strong interactions between the Sc$_3$N cluster and the C$_{78}$ cage have been demonstrated in several studies.\textsuperscript{4-6}
To date, studies of exohedral derivatization of trimetallic nitride endohedral metallofullerenes have focused on the isolation and characterization of monoaddition products. For example, we recently reported that the 1,3-dipolar cycloaddition sites for two N-tritylpyrrolidino \( \text{Sc}_3\text{N}@\text{C}_{78} \) monoadducts were across c-f and b-d bonds at elevated temperatures,\(^7\) consistent with the theoretical prediction by Poblet \textit{et al.}\(^8\) Herein, we describe selective kinetic control via a Bingel-Hirsch reaction affording a single mono and single symmetric di-ethyl malonate derivative of \( \text{Sc}_3\text{N}@\text{C}_{78} \).\(^9,\)\(^10\) Thus, the structures of the mono- and di-adducts demonstrate the remarkable regioselectivity control (adduct docking) exerted by the encapsulated \( \text{Sc}_3\text{N} \) cluster. More importantly, we describe a LUMO electron density surface computational approach that predicts multi-adduct docking sites on the fullerene cage surface.

**9.2. RESULTS AND DISCUSSION**

The Bingel-Hirsch cyclopropanation of \( \text{Sc}_3\text{N}@\text{C}_{78} \) was carried out at room temperature with excess diethyl bromomalonate in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in \( \text{o-dichlorobenzene} \) over 5 hrs under argon (Scheme 1). Surprisingly, at
conditions of higher dilution and a large excess of diethyl bromomalonate only monoadduct 1
and diadduct 2 dominate (>70%) the reaction mixture with only relatively minor amounts of
the tri-, tetra-, and penta- adducts formed (Figure 2a). In contrast, under the same
cyclopropanation reaction conditions $I_h$ Sc$_3$N@C$_{80}$ does not react.\textsuperscript{11} This also indicates that
$D_{3h}$ Sc$_3$N@C$_{78}$ has significantly higher reactivity than $I_h$ Sc$_3$N@C$_{80}$.

Scheme 1. Cyclopropanation of Sc$_3$N@C$_{78}$

Figure 2. HPLC trace of the reaction mixture (a) 1.0 mg Sc$_3$N@C$_{78}$ with 8\mu l diethyl bromomalonate
and 5\mu l of DBU in 6.5 ml o-dichlorobenzene (10 mm × 250 mm PYE column, toluene, 2 mL/min,
detection at 390 nm) (b) 1.0 mg Sc$_3$N@C$_{78}$ with 8μl diethyl bromomalonate and 5μl of DBU in 3 ml o-
dichlorobenzene (10 mm × 250 mm PYE column and a 10 mm × 20 mm guard PYE column, toluene, 2 mL/min, detection at 390 nm)

The $^1$H NMR spectrum of 1 (Figure 3) contains a single triplet at 1.44 ppm and a single quartet at 4.45 ppm, indicating that the ethyl groups of monoadduct 1 are chemically equivalent. Since the two ethyl groups of 1 are equivalent based on the $^1$H NMR spectrum, we believe that the c-f bond is the cyclopropanation site for the monoadduct 1 on the basis of symmetry considerations consistent with our earlier results for 1,3-dipolar cycloaddition. If the monoadduct had formed at the b-d bond, non-equivalent ethyl groups would be predicted.

![Figure 3. 500 MHz $^1$H NMR spectrum of the Sc$_3$N@C$_{78}$ monoadduct 1 (solvent: CDCl$_3$-CS$_2$, * denotes toluene impurity, one of triplet peaks is buried under the H$_2$O peak).](image)

The mirror symmetry of 1 was further confirmed by the $^{13}$C NMR spectrum (Figure 4); there are a total of 38 lines in the aromatic region. Two half intensity peaks at 127.08 and 151.54 ppm are due to two sp$^2$-hybridized carbons on the cage. The remaining 36 peaks represent the other 74 sp$^2$-hybridized carbons on the fullerene cage; the double intensity peak at 142.12 ppm represents four carbons due to coincidental overlap. The other two peaks at 45.54 and 52.49 ppm correspond to sp$^3$-hybridized carbon atoms in the cyclopropane ring.
These data clearly suggest that monoadduct 1 possesses a “closed” cyclopropyl structure (Figure 5a) as opposed to the ring-opened norcaradiene type structure found for the Y₃N@C₈₀ and La@C₈₂ Bingel-Hirsch adducts.¹⁴ The peaks at 14.47, 63.29 and 162.34 ppm correspond to the pairs of equivalent methyl, methylene and carbonyl carbons, respectively. The peak at 60.21 ppm is assigned to the methano bridge carbon.

Figure 4. 150 MHz¹³C NMR spectra of Sc₃N@C₇₈ monoadduct 1 (a) and diadduct 2 (b) [solvent: CD₃COCD₃: CS₂]. × denotes toluene peaks.
Figure 5. The optimized structure of a) monoadduct 1, b) diadduct 2.

Figure 6. 500 MHz $^1$H NMR spectrum of the Sc$_3$N@C$_{78}$ diadduct 2 (solvent: CDCl$_3$-CS$_2$, one of triplet peaks is buried under the H$_2$O peak).

Surprisingly, the $^1$H NMR spectrum of 2 (Figure 6) is nearly identical to the corresponding $^1$H NMR spectrum of 1. It contains only one triplet for the twelve methyl protons at $\delta = 1.43$ ppm, and one quartet for the eight methylene protons at $\delta = 4.44$ ppm, showing that all four ethyl groups of bisadduct 2 are equivalent. The 150 MHz $^{13}$C NMR spectrum for ~200 $\mu$gs of 2 (Figure 4b) exhibits only 20 peaks in the range typical of $sp^2$-hybridized carbon atoms on the fullerene cage ($\delta = 125 \sim 160$ ppm). This further supports the higher symmetry of bisadduct 2 compared with monoadduct 1. Based on the $C_{2v}$ symmetry of 2 shown in Figure 3b, 17 full intensity peaks ($\delta = 125 \sim 160$ ppm) account for a total of 68 $sp^2$-hybridized carbons atoms on the cage. Three half intensity peaks at 137.03, 137.63 and 142.15 ppm are consistent for the six $h$-labelled $sp^2$-hybridized carbon atoms in the equatorial plane containing the Sc$_3$N cluster. Two half intensity peaks at 42.73 and 45.70 ppm correspond to the four $sp^3$-hybridized fullerene carbons in the cyclopropane rings. The carbon chemical shifts of the exohedral functional groups in the diadduct 2 are very similar to those
of monoadduct 1. Methyl, methylene, carbonyl, and methano bridge carbons each appear as single signals at 14.47, 63.25, 162.75 and 60.21 ppm, respectively.

Figure 7. UV/Vis spectra of Sc$_3$N@C$_{78}$, monoadduct 1 and diadduct 2 in toluene.

The UV/Vis absorption spectrum of 1 is similar to that of 2 (Figure 7). However, after derivatization, the characteristic Sc$_3$N@C$_{78}$ absorption at 614 nm is not observed in 1 or 2; this indicates significant alteration of the electronic character of the C$_{78}$ carbon cage. Cyclic voltammetric study of Sc$_3$N@C$_{78}$ and monoadduct 1 exhibit ($^{ox}_E$-$^{red}_E$) values of 1.637 V and 1.560 V, respectively. These values are significantly lower than those of Sc$_3$N@C$_{80}$ $I_h$ isomer but close to those of $D_{5h}$ isomer. These data are consistent with the higher reactivity of Sc$_3$N@C$_{78}$. However, an even lower ($^{ox}_E$-$^{red}_E$) value for Sc$_3$N@C$_{78}$ in toluene was reported by Zhang et al.\textsuperscript{15}

Under the conditions of our study, the cyclopropanation of Sc$_3$N@C$_{78}$ with diethyl bromomalonate produced only one monoadduct and one dominant symmetric diadduct. Significantly, the second addition for the major diadduct 2 occurs at the anti-$1$ bond instead of syn-$1$ or anti-$2$ bonds, which all appear as equivalent bonds on the Sc$_3$N@C$_{78}$ cage (Figure 8a). The high regioselectivity is supported by the highest LUMO surface electron density
value for the \textit{anti-1} bond (Figure 8b), which corresponds to the kinetically preferred site for nucleophilic attack\textsuperscript{16}. The novel $C_{2v}$-adduct 2 represents the first example of a symmetric endohedral metallofullerene diadduct in which the second reaction site is clearly controlled by the internal trimetallic nitride cluster. For comparison, in similar cyclopropanation reactions of $C_{60}$\textsuperscript{10} and $C_{70}$\textsuperscript{17} the symmetric diadducts do not dominate relative to the other diadducts. Therefore, the remarkable regioselectivity for diadduct 2 is attributed to the strong influence of the internal trimetallic nitride cluster. This finding provides new insight and rationale for the study of multi-adducts of other endohedral metallofullerenes.

\textbf{Figure 8.} a) The three most preferred sites for the second addition b) Projection of the LUMO onto the electron density surface of 1.

\section*{9.3. CONCLUSIONS}

We report the first syntheses of mono- and di-(ethyl malonate) derivatives of Sc$_3$N@C$_{78}$ via the Bingel-Hirsch reaction. The $Cs$-symmetric monoadduct 1 and $C_{2v}$-symmetric diadduct 2 were isolated by HPLC and characterized by MS and NMR spectroscopy. The symmetric diadduct 2 clearly demonstrate the remarkable regioselectivity control exerted by the encapsulated Sc$_3$N cluster. The LUMO electron density surface
computational approach predicts certain specific multi-adduct docking sites on the fullerene cage surface.

9.4. EXPERIMENTAL SECTION

Pure Sc$_3$N@C$_{78}$ was isolated by the chemical separation method, as reported in detail earlier. Diethyl malonate derivatives of Sc$_3$N@C$_{78}$ were synthesized by adding 5 µl (33 µmol) of DBU to a solution of 1.0 mg (0.9 µmol) of Sc$_3$N@C$_{78}$ and 8 µl (50 µmol) diethyl bromomalonate in 3 or 6.5 mL of o-dichlorobenzene. The reaction mixture was stirred at room temperature for 5 h under argon. The solvent was removed under a stream of nitrogen overnight. The crude solid was dissolved in toluene, then filtered and injected into an HPLC for analysis (PYE column, toluene, 2 mL/min). The $^{13}$C NMR spectra (150 MHz) were obtained utilizing a 600 MHz Bruker Instrument with a Z-gradient high resolution cryoprobe.

Sc$_3$N@C$_{78}$ Monoadduct I: MALDI-TOF MS (matrix: 1,1,4,4-tetrapenyl-1,3-butadiene) $m/z$:1243 [M$^+$]; $^1$H NMR (500 MHz, CDCl$_3$/CS$_2$ 1:2(v:v) 298 K): $\delta = 1.44$ (t, $J = 7.1$ Hz, 6H), 4.46 (q, $J = 7.1$ Hz, 4H) ; $^{13}$C NMR (150 MHz, CS$_2$/[D$_6$]-acetone 7:1(v:v), doped with chromium acetylacetonate, 4000 scans at 298K): $\delta = 162.34$ (2C), 157.33 (2C), 155.51 (2C), 154.86 (2C), 152.04 (2C), 151.54 (1C), 150.77 (2C), 150.39 (2C), 150.04 (2C), 149.66 (2C), 149.29 (2C), 149.17 (2C), 148.93 (2C), 147.35 (2C), 147.23 (2C), 146.42 (2C), 142.55 (2C), 142.12 (4C), 141.88 (2C), 140.33 (2C), 139.99 (2C), 139.86 (2C), 136.16 (2C), 135.55 (2C), 135.53 (2C), 135.27 (2C), 134.89 (2C), 134.62 (2C), 134.33 (2C), 133.69 (2C), 132.83 (2C), 132.74 (2C), 132.24 (2C), 130.38 (2C), 130.29 (2C), 129.61 (2C), 127.08 (1C), 126.75 (2C), 125.19 (2C), 63.29 (2C), 60.21 (1C), 52.49 (1C), 45.54 (1C), 14.47 (1C).
Sc$_3$N@C$_{78}$ Diadduct 2: MALDI-TOF MS (matrix: 1,8,9-trihydroxyanthracene) $m/z$: 1402 [M$^+$]; $^1$H NMR (500 MHz, CDCl$_3$/CS$_2$ 1:2(v:v) 298 K): $\delta$ = 1.43 (t, $J$ = 7.1 Hz, 12H), 4.44 (q, $J$ = 7.1 Hz, 8H); $^{13}$C NMR (150 MHz, CS$_2$/[D$_6$]-acetone 7:1(v:v), doped with chromium acetylacetonate, 24000 scans at 298K): $\delta$ = 162.75 (4C), 157.41 (4C), 149.47 (4C), 149.23 (4C), 149.22 (4C), 148.01 (4C), 146.14 (4C), 144.19 (4C), 142.57 (4C), 142.15 (2C), 140.33 (4C), 137.63 (2C), 137.03 (2C), 135.91 (4C), 134.90 (4C), 132.63 (4C), 131.70 (4C), 131.55 (4C), 130.33 (4C), 125.80 (4C), 124.04 (4C), 63.25 (4C), 59.52 (2C), 45.70 (2C), 42.73 (2C), 14.47 (4C).

All geometry optimizations and calculation were conducted at the B3LYP level $^{19-21}$ using the Gaussian 03 program$^{22}$. The effective core potential and the corresponding basis set were used for Sc$^{23}$. The basis sets employed were LanL2DZ for Sc, and 3-21G* for C,N and H$^{24}$. All the calculations were subjected to frequency analyses, which were performed at the same level as that of the geometry optimization. As a result, no imaginary frequencies were reported for optimized structures.

Cyclic voltammetric measurements were conducted using a CH Instruments model 600A potentiostat (Austin, TX) and a single compartment microelectrochemical cell. The working electrode was a 2 mm glassy carbon disk electrode along with a Pt auxiliary and Ag/AgCl as a reference. Measurements were conducted using o-dichlorobenzene solutions containing 0.100 M tetra-n-butylammonium tetrafluoroborate and approximately $5 \times 10^{-4}$ M concentration of samples. Potentials are reported relative to ferrocene and solution resistance was compensated at least 97% for all measurements.
Figure S1. MALDI-TOF mass spectrum of 1 (matrix: 1,1,4,4-tetrapenyl-1,3-butadiene)

Figure S2. MALDI-TOF mass spectrum of 2 (matrix: 1,8,9-trihydroxyanthracene)
Figure S3. MALDI-TOF mass spectrum of fraction 3 (8.5~10.5 min). (matrix: 1,1,4,4-tetrapenyl-1,3-butadiene)

Figure S4. MALDI-TOF mass spectrum of fraction 4 (7.5~8.5 min). (matrix: 1,1,4,4-tetrapenyl-1,3-butadiene)
Figure S5. MALDI-TOF mass spectrum of fraction 5 (7~12 min).

Figure S6. 500 MHz COSY spectrum of monoadduct 1 (solvent: d-chloroform).

Figure S7. 500 MHz HMQC spectrum of monoadduct 1 (solvent: d-chloroform)
Figure S8. Expanded 150 MHz $^{13}$C NMR Spectrum of Monoadduct 1.
Figure S9. Expanded 150 MHz $^{13}$C NMR Spectrum of diadduct 2.
Figure S10. Cyclic voltammogram of Sc$_3$N@C$_{78}$ (Red) and Sc$_3$N@C$_{78}$ monoadduct 1 (Blue) in o-dichlorobenzene, 0.1 M TBABF$_4$, 50 mV/s scan rate.

Table S1. Redox potentials (V) of Sc$_3$N@C$_{78}$ and Sc$_3$N@C$_{78}$ monoadduct 1

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<tr>
<th>Compound</th>
<th>$^{ox}E_1$</th>
<th>$^{red}E_1$</th>
<th>$^{ox}E_1 - ^{red}E_1$</th>
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<td>-1.637</td>
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<tr>
<td>1</td>
<td>0.136</td>
<td>-1.424</td>
<td>-1.560</td>
</tr>
</tbody>
</table>
Figure S11. (a) Optimized structure of diethyl malonate C₆₀ monoadduct (b) LUMO of diethyl malonate C₆₀ monoadduct (c) Projection of the LUMO onto the electron density surface of diethyl malonate C₆₀ monoadduct (The density of the surface is 0.002 electron / au³). e position has the highest electron density surface value, and is the most kinetic preferred sites for nucleophilic attack. These results agree with Hirsch’s previous study with using MO calculations (AM1). (Hirsch, A.; Lamparth, L.; Grosser, T. J. Am. Chem. Soc. 1994, 116, 9385; Hirsch, A.; Lamparth, I.; Karfunkel, H. R. Angew. Chem. Int. Ed. 1994, 33, 437)

Figure S12. Projection of the LUMO onto the electron density surface of Sc₃N@C₇₈ monoadduct 1 (The density of the surface is 0.002 electron / au³) (a) front view (b) back view
Figure S13. HOMO and LUMO orbitals of Sc₃N@C₇₈ monoadduct 1 and diadduct 2.

REFERENCES


Chapter 10.

Synthesis and Characterization of a Non-IPR Fullerene Derivative: Sc$_3$N@C$_{68}$[C(COOC$_2$H$_5$)$_2$]

10.1. INTRODUCTION

It is well known that empty cage fullerenes, such as C$_{60}$, strictly obey the isolated pentagon rule (IPR). Nevertheless, during the past several years, a few Non-IPR fullerenes containing metal ions or clusters have been successfully produced, isolated and characterized. The kinetic and thermodynamic stabilities of these non-IPR fullerenes can be mainly rationalized by both charge transfer from the encapsulated metal clusters to the fullerene cages and the strong coordination of the metal ions to the pentalene (fused pentagons) portion of carbon cages.

Soon after the discovery of the first trimetallic nitride endohedral metallofullerenes Sc$_3$N@C$_{80}$, $^{14}$ $^{1}$C NMR analysis and computational study of another homologue, Sc$_3$N@C$_{68}$, revealed that the C$_{68}$ carbon cage violates the isolated pentagon rule (IPR) with three pentalenes orthogonal to the C$_3$ axis. $^3$ Later an X-ray crystallographic study confirmed the folded pentalene structure of Sc$_3$N@C$_{68}$ (isomer 6140) with the scandium atoms localized over the centers of pentalene portions (Figure 1). $^{15}$ Due to the relatively small cage size and the remarkable coordination of each Sc atom to a pentalene site, density functional theory (DFT) calculations demonstrated that rotation of Sc$_3$N within the C$_{68}$ cage around the C$_3$ axis was entirely hindered by a very large energy barrier. $^{12}$
Figure 1. The optimized structure of \(D_3\) Sc\(_3\)N@C\(_{68}\) (left) top view, (right) side view. (White atoms = Sc; blue atoms = N; yellow highlighted atoms are pentalene carbons)

Although many examples of the non-IPR fullerene have been reported, chemical reactivity and regioselectivity of non-IPR fullerenes have not been explored due to their scarcity. In particular, the reactivity of the unique 5,5-ring junction in non-IPR fullerenes is still unknown. Herein, via the commonly used Bingel-Hirsch reaction\(^{16,17}\), for the first time we report the synthesis and isolation of a non-IPR fullerene derivative, the diethyl malonate adduct of Sc\(_3\)N@C\(_{68}\). The structure of the Sc\(_3\)N@C\(_{68}\) monoadduct was investigated by NMR spectroscopy and a DFT computational approach.

10.2. RESULTS AND DISCUSSION

Scheme 1

The Bingel-Hirsch cyclopropanation of Sc\(_3\)N@C\(_{68}\) was carried out at room
temperature with excess diethyl bromomalonate in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in o-dichlorobenzene over 3 hrs under argon (Scheme 1). From high performance liquid chromatography (HPLC) of the reaction mixture (Figure 2) one monoadduct 1 (13.2 min) was observed and identified by MALDI-TOF mass spectroscopy (m/z 1123) (Figure 3a). The MALDI-TOF mass spectrum of fraction 2 (8.72 min) revealed a mixture containing the di-, tri-, tetra- and pentadducts (Figure 3b). Unreacted Sc$_3$N@C$_{68}$ was eluted at 24.7 min on PYE column under flow rate of 2.00 ml/min.

**Figure 2.** HPLC trace of the reaction mixture (HPLC conditions: 10 × 250 mm PYE [2-(1’-pyrenyl)ethyl silica] column at 2.0 mL min$^{-1}$ flow rate with toluene, 390 nm detection.)

In contrast to the symmetric monoadduct of Sc$_3$N@C$_{78}$ whose methyl and methylene hydrogens appeared as equivalent in the $^1$H NMR spectrum,$^{18}$ the structure of Sc$_3$N@C$_{68}$ monoadduct 1 seems to be asymmetric based on the $^1$H NMR spectrum (Figure 4), which exhibited triplets at 1.32 and 1.44 ppm corresponding to two different methyl groups. Because of the asymmetric addition, the diastereotopic methylene hydrogens were
geminally coupled in addition to the coupling with the methyl protons. Therefore, in the $^1$H NMR spectrum of 1, the four non-equivalent methylene hydrogens appeared as four quartets at 4.3 ~ 4.6 ppm (two overlapped at 4.5 ppm). According to the COSY spectrum (see supporting information), the peaks from 4.29 ~ 4.43 ppm were due to the two non-equivalent methylene hydrogens attached to the same carbon and the peaks from 4.45 ~ 4.51 ppm were due to two methylene hydrogens from the other ethyl group.

**Figure 3.** (a) MALDI-TOF mass spectrum of 1 (matrix: 1,1,4,4-tetrapenyl-1,3-butadiene). (b) MALDI-TOF mass spectrum of 2 (matrix: 9-nitroanthracene)

**Figure 4.** 500 MHz $^1$H NMR spectrum of the Sc$_2$N@C$_{68}$ monoadduct 1 (solvent: CS$_2$-[D$_6$]-acetone 7:1:v:v), peaks in the region of 2.0~2.4 ppm due to acetone, toluene and other
impurities in the solvent)

The $^{13}$C NMR spectrum of pristine $D_3$-symmetric Sc$_3$N@C$_{68}$ contains twelve different carbon signals, eleven of full intensity and one of one third intensity.\textsuperscript{3} Since the $D_3$ symmetry of Sc$_3$N@C$_{68}$ was broken by the exohedral functionalization, the $^{13}$C NMR spectrum of the monoadduct 1 exhibited a total of 64 peaks in the aromatic region (Figure 5), which account for 66 $sp^2$-hybridized carbons on the cage (two double intensity peak at 147.99 and 137.31 ppm correspond to four carbons due to coincidental overlap). The remaining two carbons on the C$_{68}$ cage, the two $sp^3$-hybridized atoms in the cyclopropane ring (Ce and Ce'), appeared at 71.08 and 67.40 ppm. The peak at 53.45 ppm was assigned to the methano bridge carbon (Cd). The signals at 14.22 and 14.36, 63.77 and 63.87 ppm correspond to the pairs of non-equivalent methyl carbons (Ca and Ca') and methylene carbons (Cb and Cb'), respectively. The assignment for the ethyl groups of monoadduct 1 were confirmed by the HSQC spectrum (see supporting information). The two non-equivalent carbonyl carbons (Ce and Ce') appeared at 163.56 and 164.04 ppm.
The HPLC trace and NMR spectra of \( {\text{I}} \) demonstrated that the exohedral derivatization of \( {\text{Sc}}_3{\text{N}}@{\text{C}}_{68} \) was remarkably regioselective, affording only a single monoadduct which was similar to our recent finding on the Bingle-Hirsch reaction of \( {\text{Sc}}_3{\text{N}}@{\text{C}}_{78} \).\(^{18} \) The cycloaddition site of the \( {\text{Sc}}_3{\text{N}}@{\text{C}}_{78} \) monoadduct was consistent with the theoretical prediction by Poblet and coworkers;\(^{18,19} \) unfortunately, none of the C-C bonds on the \( {\text{Sc}}_3{\text{N}}@{\text{C}}_{68} \) cage could be clearly identified as the most reactive site.\(^{19} \) As was previously pointed out by Poblet \textit{et al.}, the \( {\text{Sc}}_3{\text{N}}@{\text{C}}_{68} \) cage is more complicated than normal IPR allowed fullerenes, containing six different types of C-C bonding motifs.
A, B and C type C-C bonds are 6,6 ring junctions; D and F type are 5,6-ring junctions; the E type C-C bond is a 5,5-ring junction abutted by two hexagons. Type E and F only exist in non-IPR fullerenes. As for the Sc$_3$N@C$_{68}$ monoadduct 1, addition to the 5,6-ring junction (Type D and F) can probably be ruled out because of differential shielding effects from the pentagon-hexagon ring currents on the cage surface which would yield large chemical shift differences for the diastereotopic methylene and methyl hydrogens,\textsuperscript{20-22} which were not observed in the $^1$H NMR spectrum of 1.

![Figure 6. Six different types of C-C bonds in non-IPR fullerene Sc$_3$N@C$_{68}$](image)

Thus, the addition site for the Sc$_3$N@C$_{68}$ monoadduct 1 should be one of the nine different sets of C-C bonds listed in Table 1. We performed DFT calculations for all the possible Sc$_3$N@C$_{68}$ monoadducts. The bond length at the addition site, relative thermodynamic energies and HOMO/LUMO levels for the different Sc$_3$N@C$_{68}$ monoadducts are summarized in Table 1. However, neither HOMO/LUMO gaps nor relative thermodynamic relative energies could provide identification of the addition site.
It is worth noting that the bond lengths between the two substituted carbon atoms of Sc$_3$N@C$_{68}$ monoadducts varied from 1.65 Å up to 2.32 Å. Echegoyen and coworkers reported a single crystal X-ray structure of an “open” methano malonate derivative of Y$_3$N@C$_{80}$ in which C-C distances at the addition site are 2.30 Å. In the carbene derivatives of La@C$_{82}$, Sc$_2$C$_2$@C$_{82}$ and M$_2$@C$_{80}$ (M = La and Ce), “open” structures have been characterized by spectroscopic and crystallographic analyses. Recently, we proposed “open” structures for malonate methano derivatives of $I_h$ Sc$_3$N@C$_{80}$. The “closed” methano structure for $I_h$ Sc$_3$N@C$_{80}$ proved to be energetically unstable by geometry optimization and always led to the open form with a C-C distance at the addition site up to 2.19 Å.

Table 1. Calculated bond length (Å) at the addition site, relative thermodynamic energies (kcal/mol) and HOMO/LUMO levels (eV) for Sc$_3$N@C$_{68}$ monoadducts

<table>
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<th>C-C bond for the Addition Site$^a$</th>
<th>Type</th>
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<th>HOMO-LUMO Gap</th>
<th>Relative Thermodynamic Energy</th>
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<td>2.08</td>
<td>12.17</td>
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<td>11,12</td>
<td>B</td>
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<td>2.10</td>
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<td>15,27</td>
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<td>1.97</td>
<td>2.18</td>
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<td>12,22</td>
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<td>E</td>
<td>2.05</td>
<td>2.19</td>
<td>13.47</td>
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$^a$ The carbon atoms are labeled as given in Figure 7.
The $^{13}$C chemical shifts of the two substituted carbons in the “open” methano metallofullerene derivative have been reported by Feng and Akasaka et al.\textsuperscript{28} In the $^{13}$C NMR spectrum of La@C\textsubscript{82} monoadduct-E, two signals at 111.26 and 94.52 ppm were assigned for the two substituted carbons due to their retained sp\textsuperscript{2}-hybridized properties.\textsuperscript{28} In contrast, we recently found that the diethyl malonate derivative of Sc\textsubscript{3}N@C\textsubscript{78} possessed a “closed” structure, which has not been reported before in methano metallofullerene derivatives.\textsuperscript{18} As evidenced by the $^{13}$C NMR spectroscopy, the two substituted carbons appeared in the sp\textsuperscript{3}-hybridized carbon region ($\delta$ = 60.21 and 45.54 ppm). In the geometrically optimized structure of the Sc\textsubscript{3}N@C\textsubscript{78} monoadduct the C-C bond of the addition site has a bond length of 1.57 Å.\textsuperscript{18} As for the Sc\textsubscript{3}N@C\textsubscript{68} monoadduct I, the two substituted carbons exhibited resonances at 71.08 and 67.40 ppm between the values of the two substituted carbons reported for the “open” and “closed” structures mentioned above.
In order to further identify the structure of monoadduct 1, we performed $^{13}$C NMR spectrum simulations for all of the possible Sc$_3$N@C$_{68}$ monoadducts. As shown in Table 2, the calculated chemical shifts of methyl ($C_a$ and $C_{a'}$), methylene ($C_b$ and $C_{b'}$) and carbonyl carbons ($C_c$ and $C_{c'}$) for the different Sc$_3$N@C$_{68}$ monoadducts were very close, shifting systematically by 2.8~7.7 ppm to lower field compared with the experimental results. However, the difference between the calculated and measured signals for the methano bridge carbons ($C_d$) and the two substituted carbons ($C_e$ and $C_{e'}$) were distinct for different monoadducts. The C12-C13 adduct can be clearly ruled out because the chemical shift of its methano bridge carbon (26.3 ppm) was significantly different from the experimental observation (53.45 ppm). For the chemical shifts of the two substituted carbons ($C_e$ and $C_{e'}$), except for C15-C27 and C12-C22 adducts, the simulations for the rest of the monoadducts differed strongly from the experimental results by upfield shifts of 15 ~ 40 ppm. However, comparison of the down-field regions of the $^{13}$C NMR spectra for C15-C27 and C12-C22 adducts suggest that only the C12-C22 adduct displays a pattern consistent with the experimental results (Figure 8). For example, four aromatic carbon signals are found experimentally at high-field (115~130 ppm) (Figure 8a). The calculated $^{13}$C NMR spectrum for the C12-C22 adduct (Figure 8b) exhibits exactly four signals in that region, which were not observed in the C15-C27 adduct (Figure 8c). Furthermore, the overall $^{13}$C NMR spectral agreement of C12-C22 adduct is much better in comparison with the C15-C27 adduct.

Table 2. Comparison of computed $^{13}$C NMR chemical shifts (ppm) of Sc$_3$N@C$_{68}$ monoadducts with experimental results
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<th>Monoadduct</th>
<th>C&lt;sub&gt;a&lt;/sub&gt;</th>
<th>C&lt;sub&gt;a'&lt;/sub&gt;</th>
<th>C&lt;sub&gt;b'&lt;/sub&gt;</th>
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<td>53.49</td>
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* The atoms are labeled as given in Figure 7, <sup>13</sup>C NMR chemical shifts with respect to TMS (δ<sub>TMS</sub> in ppm).
Hirsch and coworkers reported that two equatorial positions of the diethyl malonate monoadduct of C₆₀ had the highest LUMO orbital coefficients and correspond to preferred sites for the second nucleophilic attack.²⁹ Using a similar approach for Sc₃N@C₇₈, we used the highest LUMO surface electron density value of the Sc₃N@C₇₈ monoadduct to predict the second addition site, which was consistent with experimental results.¹⁸ In the present case of Sc₃N@C₆₈, the highest LUMO surface electron densities are located at the C22-C12, C4-C29 and C8-C36 bonds. These studies supported our conclusion that the C22-C12 bond of Sc₃N@C₆₈ is the position where the cycloaddition occurs; the C4-C29 and C8-C36 bonds are identical to the C22-C12 bond due to the D₃ symmetry.

**Figure 9.** (a) The optimized structure of Sc₃N@C₆₈ (b) Projection of the LUMO onto the electron density surface of Sc₃N@C₆₈ (The density of the surface is 0.002 electron / au³). The UV-vis spectrum of 1 was almost identical to that of pristine Sc₃N@C₆₈. It confirms that the “open” structure of Sc₃N@C₆₈ monoadduct 1 retains the same
aromaticity of the C\textsubscript{68} fullerene cage after the exohedral derivatization because of the two \textit{sp}\textsuperscript{2}-hybridized substituted carbons at the initially attacked double bond. This finding is consistent with other reported malonate methano metallofullerene derivatives with “open” structures,\textsuperscript{23, 27, 28} whereas the recently reported the UV-vis spectra of “closed” malonate methano derivatives of Sc\textsubscript{3}N@C\textsubscript{78} changed dramatically compared to the Sc\textsubscript{3}N@C\textsubscript{78}.\textsuperscript{18}

**Figure 10.** UV-vis spectra of Sc\textsubscript{3}N@C\textsubscript{68} (red line) and monoadducts 1 (blue line)

### 10.3. CONCLUSIONS

In summary, we have synthesized and isolated the first non-IPR fullerene derivative, diethyl malonate adduct of Sc\textsubscript{3}N@C\textsubscript{68}. The Sc\textsubscript{3}N@C\textsubscript{68} monoadduct 1 was characterized by HPLC, Mass and NMR spectroscopy. The proposed addition site of Sc\textsubscript{3}N@C\textsubscript{68} monoadduct 1 was in good agreement with the experimental and calculated \textsuperscript{13}C NMR spectra, LUMO electron density study and UV-vis spectroscopy.
10.4. EXPERIMENTAL SECTION

Pure Sc$_3$N@C$_{68}$ was isolated by the chemical separation method, as reported in detail earlier.$^{30}$ Diethyl malonate derivatives of Sc$_3$N@C$_{68}$ were synthesized by adding 5 μl (33 μmol) of DBU to a solution of 1.0 mg (0.9 μmol) of Sc$_3$N@C$_{78}$ and 8 μl (50 μmol) diethyl bromomalonate in 5 mL of o-dichlorobenzene. The reaction mixture was stirred at room temperature for 3 h under argon. The solvent was removed under a stream of nitrogen overnight. The crude solid was dissolved in toluene, then filtered and injected into an HPLC for analysis (PYE column, toluene, 2 mL/min). The $^{13}$C NMR spectra (150 MHz) were obtained utilizing a 600 MHz Bruker Instrument with a Z-gradient high resolution cryoprobe.

Sc$_3$N@C$_{68}$ Monoadduct 1: $^1$H NMR (500 MHz, CS$_2$/d$_6$-acetone 7:1(v:v), 298 K): δ = 1.33 (t, $^2$J$_{H-H}$ = 7.1 Hz, 3H), 1.44 (t, $^2$J$_{H-H}$ = 7.1 Hz, 3H), 4.38 (m, 2H), 4.48 (m, 2H);

$^{13}$C NMR (150 MHz, CS$_2$/CCl$_3$D 6:4(v:v), doped with chromium acetylacetonate, 8000 scans at 298K): δ = 164.04 (1C), 163.56 (1C), 159.78 (1C), 158.16 (1C), 156.85 (1C), 155.74 (1C), 154.82 (1C), 153.59 (1C), 153.09 (1C), 151.27 (1C), 150.76 (1C), 150.60 (1C), 149.63 (1C), 149.59 (1C), 149.36 (1C), 149.11 (1C), 148.10 (1C), 147.99 (2C), 147.48 (1C), 147.26 (1C), 146.46 (1C), 145.89 (1C), 145.64 (1C), 145.14 (1C), 145.04 (1C), 144.61 (1C), 144.28 (1C), 143.91 (1C), 143.68 (1C), 143.08 (1C), 142.85 (1C), 142.82 (1C), 142.07 (1C), 141.83 (1C), 141.34 (1C), 141.32 (1C), 140.76 (1C), 140.49 (1C), 140.34 (1C), 140.24 (1C), 140.04 (1C), 139.14 (1C), 138.67 (1C), 137.78 (1C), 137.48 (1C), 137.31 (2C), 137.12 (1C), 136.55 (1C), 136.41 (1C), 136.25 (1C), 136.11 (1C), 135.88 (1C), 135.64 (1C), 135.20 (1C), 134.39 (1C), 134.24 (1C), 134.08 (1C),
133.73 (1C), 131.72 (1C), 131.44 (1C), 131.36 (1C), 130.24 (1C), 127.13 (1C), 125.36 (1C), 121.51 (1C), 117.24 (1C), 71.08 (1C), 67.40 (1C), 63.87 (1C), 63.77 (1C), 53.45 (1C), 14.36 (1C), 14.22 (1C).

All geometry optimizations and calculation were conducted at the B3LYP level \cite{31-33} using the Gaussian 03 program \cite{34}. The effective core potential and the corresponding basis set were used for Sc \cite{35}. The basis sets employed were LanL2DZ for Sc, and 3-21G* for C, N and H \cite{36}. All the calculations were subjected to frequency analyses, which were performed at the same level as that of the geometry optimization. As a result, no imaginary frequencies were reported for optimized structures. NMR chemical shielding tensors were evaluated employing the gauge-independent atomic orbital (GIAO) method at the B3LYP/6-31G* level of theory. Based on the computed chemical shielding tensors, theoretical $^{13}$C NMR chemical shifts were calculated relative to C$_{60}$ and converted to the TMS (tetramethylsilane) scale using the experimental value for C$_{60}$ (142.68 ppm) \cite{37}.

10.5. SUPPORTING INFORMATION

**Figure S1.** 500MHz COSY spectrum of Sc$_3$N@C$_{68}$ monoadduct 1
**Figure S2.** 600 MHz HSQC Spectrum of Sc₃N@C₆₈ monoadduct 1

**Figure S3.** Simulated $^{13}$C NMR spectrum of C12-C13 adduct
Figure S4. Simulated $^{13}$C NMR spectrum of C14-C24 adduct

Figure S5. Simulated $^{13}$C NMR spectrum of C1-C2 adduct

Figure S6. Simulated $^{13}$C NMR spectrum of C24-C25 adduct
**Figure S7.** Simulated $^{13}$C NMR spectrum of C11-C12 adduct

![SCF GIAO Magnetic shielding](image)

**Figure S8.** Simulated $^{13}$C NMR spectrum of C15-C27 adduct

![SCF GIAO Magnetic shielding](image)

**Figure S9.** Simulated $^{13}$C NMR spectrum of C12-C22 adduct

![SCF GIAO Magnetic shielding](image)
Figure S10. Simulated $^{13}$C NMR spectrum of C23-C24 adduct

Figure S11. Simulated $^{13}$C NMR spectrum of C21-C42 adduct
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Chapter 11

Summary and Future Work

11.1. Summary

The research presented in this dissertation focused on studies of reactivity and regioselectivity of trimetallic nitride template endohedral metallofullerenes (TNT EMFs). Two chemical separation methods for purifying TNT EMFs were discussed. Several organic derivatives of TNT EMFs have been successfully synthesized and characterized.

The availability of pure sample is a major hurdle in the study of TNT EMFs. The traditional liquid chromatographic method to remove dominant empty-cage fullerenes is expensive and time consuming. High purity TNT EMFs can be obtained in pure form directly from as-prepared soots or extracts in a single facile step by taking advantage of their extraordinary kinetic chemical stability with respect to the other fullerenes in Diels-Alder reactions with a cyclopentadiene-functionalized resin. In addition, since the Diels-Alder reaction is thermally reversible, we demonstrated that the bound empty-cage fullerenes can be recovered by displacement with maleic anhydride at 85°C. Another alternative way to purify TNT EMFs is so a called support-free chemical separation method. 9-Methyllanthracene reacts selectively with empty-cage fullerenes in the Sc- and Lu-based soot extracts. After heating of 9-methyllanthracene with Sc- or Lu-based soot extracts, most of the 9-methyllanthracene-derivatized empty cage fullerenes can be removed by washing with ether. The remaining unreacted TNT EMFs were easily isolated by single-stage HPLC from the TNT EMFs.
enriched extracts. The two chemical separation methods have the potential to greatly reduce the time and cost necessary to obtain large quantities of pure TNT EMFs.

Organic functionalization of these materials is crucial to construct novel organo-metallofullerene materials for a variety of future applications. Modification of metallofullerene carbon cages can fine-tune their chemical and physical properties.

1,3-dipolar cycloaddition of azomethine ylides to fullerenes (the Prato reaction) is one of the most useful reactions for obtaining functionalized fullerene derivatives. A main advantage of Prato reaction is that two functional groups can be simultaneously incorporated into the resulting pyrrolidino ring. We reported the synthesis and characterization the first TNT endohedral pyrrolidinometallofullerenes via 1,3-dipolar cycloaddition of N-methylazomethine ylides to both diamagnetic and paramagnetic TNT EMFs (Sc$_3$N@C$_{80}$ and Er$_3$N@C$_{80}$). The existence of planar symmetry in the N-methylpyrrolidino derivatives from $^{13}$C NMR spectrum indicates that the reaction took place at the 5,6 ring junction. Under the similar conditions, both 5,6- and 6,6-ring junction N-tritylpyrrolidino adducts of $I_h$ Sc$_3$N@C$_{80}$ were synthesized and characterized by MALDI-TOF MS, NMR, UV-vis spectroscopy and X-ray crystallography. A kinetic study showed that the 6,6-ring junction adduct is the kinetically controlled product; it is converted to the thermodynamic product, the 5,6-ring junction adduct, upon thermal equilibration. This is for the first time such an isomerization process has been observed for an endohedral metallofullerene.

The structure of the $D_{5h}$ isomer of Sc$_3$N@C$_{80}$ was determined through X-ray crystallography. The enhanced reactivity of the $D_{5h}$ isomers in comparison with the more common $I_h$ isomers of Sc$_3$N@C$_{80}$ and Lu$_3$N@C$_{80}$ toward Diels-Alder and 1,3-dipolar tritylazomethine ylide cycloaddition reactions were discovered. The combination of short
bond length and high degree of pyramidization for the central carbon atoms of the pyracylene sites situated along a belt that is perpendicular to the \(C_5\) axis suggests that these are the sites of greatest reactivity in the \(D_{5h}\) isomer of \(\text{Sc}_3\text{N}@(\text{C}_{80})\). Consistent with the observation of higher reactivity observed for the \(D_{5h}\) isomers, cyclic voltammetry and molecular orbital (MO) calculations demonstrate that the \(D_{5h}\) isomers have slightly smaller energy gaps than those of the \(I_h\) isomers.

The first N-tritylpyrrolidino derivatives of \(\text{Sc}_3\text{N}@(\text{C}_{78})\) were successfully synthesized and isolated. The addition sites for the two nearly equivalent kinetic monoadducts are across two different 6,6-junction sites on the \(\text{Sc}_3\text{N}@(\text{C}_{78})\) cage that are offset from the horizontal plane defined by the \(\text{Sc}_3\text{N}\) cluster. These adducts were characterized by NMR experiments, DFT calculations and X-ray crystallographic analysis of \(\text{Sc}_3\text{N}@(\text{C}_{78})\) derivative 1a. The \(\text{Sc}_3\text{N}\) unit remains in the horizontal plane of the \(D_{3h}\) (78:5) cage after exohedral derivatization and does not interact directly with the site of addition.

For the first time, we successfully synthesized the ethyl malonate derivatives of \(\text{Sc}_3\text{N}@(\text{C}_{78})\) via the Bingel-Hirsch reaction. The Bingel-Hirsch cyclopropanation of \(\text{Sc}_3\text{N}@(\text{C}_{78})\) was carried out at room temperature with excess diethyl bromomalonate in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). The \(C_1\)-symmetric monoadduct 1 and \(C_{2v}\)-symmetric diadduct 2 were isolated by HPLC and characterized by MS, UV-vis, and NMR spectroscopy. The novel \(C_{2v}\)-adduct 2 represents the first example of a symmetric endohedral metallofullerene diadduct in which the second reaction site is clearly controlled by the internal trimetallic nitride cluster. We also employed a LUMO electron density surface computational approach to predict multiadduct docking sites on the ellipsoidal fullerene cage surface. The first non-IPR fullerene derivative, a diethyl malonate adduct of \(\text{Sc}_3\text{N}@(\text{C}_{68})\) was synthesized,
isolated and characterized by mass spectrometry and NMR spectroscopy. The proposed addition site of Sc$_3$N@C$_{68}$ monoadduct was in good agreement with the experimental and calculated $^{13}$C NMR spectra, LUMO electron density study and UV-vis spectroscopy.

11.2 Future Work

The chemical reactivity and regioselectivity of empty-cage fullerenes have been extensively studied over the past two decades. However, the study of chemical reactivity and regioselectivity of TNT EMFs is just in its very beginning and many important questions are still open. For instance: in Chapter 9, we reported the selective formation of a symmetric Sc$_3$N@C$_{78}$ diadduct. We believe the remarkable regioselectivity is controlled by the encapsulated Sc$_3$N cluster. If our assumption is correct, the formation of higher adducts of Sc$_3$N@C$_{78}$ will keep following this rule and ultimately lead to a $D_{3h}$ symmetric hexa-adduct of Sc$_3$N@C$_{78}$ as shown in Figure 1. One problem for the study of multi-adducts of Sc$_3$N@C$_{78}$ is the separation method. Preliminary results showed the tri-, tetra- and penta-adducts of Sc$_3$N@C$_{78}$ all co-eluted from PYE column at the dead time. A different stationary phase HPLC column (e.g. C$_{18}$ silica column) and a mixed solvent system are suggested to achieve better separation for those multiadducts.
Nitroxide compounds are widely used as stable spin labels and also in the design of organic magnetic materials. Covalently linked TNT EMFs to a nitroxide radical will allow the study of the intramolecular interactions of a radical species with the carbon cage and the encapsulated trimetallic nitride cluster.\(^1\) The unique TNT EMF nitroxide derivatives are expected to have many interesting chemical and physical properties, such as superconductivity, ferromagnetism and optical limiting.\(^2\) Some synthetic approaches are suggested to covalently attach nitroxide radicals to TNT EMFs (Scheme 1). For example, a nitroxide methano derivative of \(\text{A}_3\text{N@C}_{80}\) can be synthesized by the Bingel-Hirsch reaction of \(\text{A}_3\text{N@C}_{80}\) and the corresponding nitroxide ether of malonic acid in the presence of tetrabromomethane and DBU (Scheme 1a).\(^3\) Condensation of N-methylglycine with 4-formyl-TEMPO can generate an azomethine ylide that will undergo 1,3-dipolar cycloaddition to \(\text{A}_3\text{N@C}_{80}\) to give the nitroxide metallofulleropyrrolidino derivative (Scheme 1b).\(^4\) Another approach to make a nitroxide metallofulleropyrrolidino derivative is to synthesize a 2,2,5,5-tetramethylpyrrolidine derivative of \(\text{A}_3\text{N@C}_{80}\) as the precursor. The metallofulleropyrrolidino precursor compound can be subsequently oxidized with m-chloroperbenzoic acid (MCPBA) to yield a nitroxide metallofulleropyrrolidino derivative (Scheme 1c).\(^2\)

**Scheme 1.** Synthetic approaches of covalently attaching nitroxide radicals to TNT EMFs
MetalloFullerene dimers and multi-metallofullerene assemblies attract increasing attention because of their interesting physicochemical properties, which may have potential applications in several directions, such as spin electronics and quantum computing. In a reaction analogous to previously reported work on the C\textsubscript{60} dimer\textsuperscript{6-8} we have successfully synthesized a monofunctionalized Sc\textsubscript{3}N@C\textsubscript{80}\textsuperscript{1} (Scheme 2). Monofunctionalized Sc\textsubscript{3}N@C\textsubscript{80}\textsuperscript{1} was isolated from a PYE column at 33.4 min and characterized by MALDI-TOF MS (Figure 2). Unfortunately we couldn’t detect any Sc\textsubscript{3}N@C\textsubscript{80} dimer\textsuperscript{2} formed in the reaction mixture. There is some future works suggested for the synthesis of Sc\textsubscript{3}N@C\textsubscript{80} dimer\textsuperscript{2}. Instead of synthesizing dimer\textsuperscript{2} in an one pot reaction, two individual steps could possibly be employed. Using monofunctionalized Sc\textsubscript{3}N@C\textsubscript{80}\textsuperscript{1} as the reactant for subsequent cycloaddition is expected to give a higher yield of Sc\textsubscript{3}N@C\textsubscript{80} dimer\textsuperscript{2}. In addition, since fullerene dimers normally have very lower solubility in toluene, some other solvents could be
used in the reaction, such as DMF, o-dichlorobenzene or trichlorobenzene.

**Scheme 2.**

![Scheme 2 diagram]

**Figure 2.** HPLC trace of the reaction mixture of Sc$_3$N@C$_{80}$ with 1,2,4,5-tetrakis(bromomethyl)-benzene in the presence of KI and 18-crown-6. Inset: MALDI-TOF mass spectrum of monoadduct 1.
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