ABSTRACT

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Synthesis of Amphiphilic Iron-Sulfur Core Dendrimers and Investigations into Their Encapsulation Abilities in Different Solutions

Dr. Christopher Bigler Gorman, advisor

Several novel amphiphilic iron-sulfur core dendrimers were synthesized by modifying the tips of the dendrons to install hydrophilic peripheries. These dendrimers were synthesized via standard convergent and a "modular" synthetic strategy. The electrochemistry of the dendrimers was investigated in dimethylformamide and dimethylformamide/water solutions. Positive shifts in the redox potential of the iron-sulfur cores corresponding to dendrimer size and periphery type were recorded. Secondary peaks in the anodic wave of cyclic voltammograms of dendrimers in dimethylformamide/water solutions were possible indications of limited access of water molecules to the iron-sulfur cores of some of the dendrimers.

Synthesis of Amphiphilic Iron-Sulfur Core Dendrimers and Investigations into Their Encapsulation Abilities in Different Solutions

by

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Biography

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Table of Contents

Table of Figures v
Table of Tables vi
1. Introduction 1
1.1. The Concept of Molecular Encapsulation 1
1.2. Dendrimers 4
1.3. Dendrimers or Linear Polymers 9
1.4. Dendrimer Cores 10
1.5. Photoactive cores 13
1.5.1. Electroactive Cores 16
1.5.2. Ligand Binding 20
1.6. Dendritic Encapsulation Studies by the Gorman Group 22
1.6.1. Controlling Encapsulation Through Chemical Structure 22
1.6.2. Controlling Encapsulation: Solution vs. "Thick" Film 25
1.6.3. Controlling Encapsulation Through Dendron Conformation 26
1.7. Controlling Encapsulation with Solution Conditions 27
1.8. Water-Soluble Dendrimers 30
1.9. Research Goals 31
2. Synthesis of Amphiphilic Iron-Sulfur Dendrimers 33
2.1. Introduction 33
2.2. Results -- Convergent Dendron Synthesis 35
2.2.1. Synthesis of "Tip" Molecules 35
2.2.2. Synthesis of Amphiphilic Dendrons 38
2.2.3. Dendrimer Assembly Following Convergent Synthesis 42
2.3. Results - Modular Convergent Synthesis 44
2.3.1. Convergent Synthesis of MOM-Dendrons 44
2.3.2. Adding "Tips" to the MOM-Dendrimers 47
2.4. Results - "Split-Tip" Dendrimers 50
2.5. Discussion - Dendron Synthesis and Purification 52
2.5.1. Convergent vs. Modular Synthesis 52
2.6. Summary 54
3. Electrochemistry of Amphphilic Dendrimers 55
3.1. Introduction 55
3.2. Procedure 56
3.3. Results 58
3.3.1. Electrochemistry of Dendrimers in DMF solution 59
3.3.2. Addition of Water to Dendrimer DMF Solutions 63
3.4. Discussion 68
3.4.1. Positive Shifts of Iron-Sulfur Cluster Redox Potentials 68
3.4.2. Water Access to the Iron-Sulfur Core 68
3.5. Summary 70
4. Conclusions 72
4.1. Difficulties With Water-Soluble Iron-Sulfur Core Dendrimers 72

4.2. General Comments on Ligand Exchange and Characterization of Dendrimers .. 74
5. Appendix A – Synthetic Procedures 76
5.1. Triethyleneglycol and Dodecylethylene Monomethyl ether Toluene Sulfonate . 76
5.2. Methyl 3,4,5-tris(Triethylene Glycol Monomethyl Ether)Benzoate..... 77
5.3. 3,4,5-tris(Triethylene Glycol Monomethyl Ether) Benzyl Alcohol..... 78
5.4. 3,4,5-tris(Triethylene Glycol Monomethyl Ether) Benzyl Bromide..... 79
5.5. Phenyl Toluene Sulfonate 80
5.6. Phenyl α-Bromotoluene Sulfonate..... 80
5.7. Deprotection MOM-Gx-Thiocarbamate 81
5.8. Coupling of Phenyl α-Bromotoluene Sulfonate to 4,4'-(bis-phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate 81
5.9. Coupling of PEG3-Tosylate to 4,4'-(bis-Phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate..... 82
5.10. Coupling of triPEG3 Benzyl Bromide to 4,4'-(bis-Phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate..... 84
5.11. Coupling of R-Gx-Tosylate to 4,4'-(bis-Phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate..... 84
5.12. Coupling of PEG12 Tosylate to the Phenylhydroxyydroxy-Gx-Thiocarbamate85
5.13. Synthesis of R-Gx-Amine 86
5.14. DCC-mediated Coupling of R-Gx-Amines and 4-Thiocarbamate Benzoic Acid88
5.15. Basic Deprotection of R-Gx-Thiocarbamate..... 92
5.16. Ligand Exchange and Assembly of Dendrimers..... 94
6. Bibiliography..... 96

Table of Figures

Figure 1.1 Image of Encapsulation 1
Figure 1.2 Crystal Structure of an Iron-Sulfur Protein 4
Figure 1.3 The Modular Dendrimer 5
Figure 1.4 Convergent and Divergent Synthesis 8
Figure 1.5 First Dendritic Encapsulation 14
Figure 1.6 Encapsulation Effect - Control of Core Emission 15
Figure 1.7 Encapsulation Effect - Enhanced Luminescence of the Core 16
Figure 1.8 Encapsulation Effect - Site Isolation of a Zn-Porphyrin Core 18
Figure 1.9 Encapsulation Effect - Directional Control of Electron Transfer 19
Figure 1.10 Site Isolation of Pd-Porphyrins 21
Figure 1.11 "Flexible" and "Rigid" Dendrimers 23
Figure 1.12 Isomer Backfolding 26
Figure 1.13 Effective Electron Transfer Distance 27
Figure 1.14 Conceptual "Unimolecular Memory" 29
Figure 1.15 Proposed Water-soluble Dendrimers 32
Figure 2.1 Hydrophilic "Tip" Molecules for Modification of Dendrons. 37
Figure 2.2 Convergent Synthesis I: Addition of "Tips" and Growth of Dendrons 39
Figure 2.3 Convergent Synthesis II: Addition of "Focal" Group 41
Figure 2.4 Ligand Exchange Reactions for PEG3 and triPEG3 Dendrimers 43
Figure 2.5 Synthesis of MOM G1 Alcohol 44
Figure 2.6 Convergent Synthesis of MOM-G1 and MOM-G2-Dendrons 46
Figure 2.7 Synthesis of MOM-G3-Dendrons 47
Figure 2.8 PEG12 and triPEG3 Dendrimer Assembly 49
Figure 2.9 Synthesis of Generation 1 Half-MOM Dendrons 51
Figure 2.10 "Split-Tip" Dendrimer 52
Figure 3.1 Air-Tight Electrochemical Cell for DMF/Water Solutions 58
Figure 3.2 Cyclic Voltammograms of PEG3 Dendrimers 60
Figure 3.3 Cyclic Voltammograms of PEG12 Dendrimers 61
Figure 3.4 Cyclic Voltammograms of triPEG3 Dendrimers 62
Figure 3.5 Addition of Water to triPEG3 G1 Dendrimer Solution 64
Figure 3.6 Addition of Water to triPEG3 G1 Dendrimer Solution 65
Figure 3.7 Addition of Water to PEG12 G1 Dendrimer Solution 66

Table of Tables

Table 1.1 Functional Cores Used in Dendrimers 12
Table 3.1 Redox Potentials of Amphiphilic Iron-Sulfur Core Dendrimers in DMF..... 63
Table 3.2 Redox Potentials of G1 Dendrimers in DMF/Water Solutions..... 67

1. Introduction

1.1. The Concept of Molecular Encapsulation

A general goal of materials research is the capability to alter or influence the measurable chemical and physical properties of molecules. Encapsulation of molecules is one strategy of this overall effort to control molecular properties. This strategy can be summarized in an initial definition of molecular encapsulation. Molecular encapsulation would be "the act or process of surrounding a core moiety with other polymeric molecules." A baseball, a macroscopic object, serves as a useful starting point to illustrate this preliminary definition of molecular encapsulation (Figure 1.1).



Figure 1.1 Image of Encapsulation
The layering of a baseball is one of the natural images associated with the term "encapsulation"even when referring to block copolymers or dendrimers. While this image may be appropriate for micon scale particles derived from polymers, it does not accurately represent "encapsulation" with regards to nanometer scale dendrimers.

The interior of a baseball is composed of a cork core wrapped by several layers of rubber, thread and ultimately leather (Figure 1.1). The cork core is "encapsulated" by several layers of rubber, thread and a leather cover. This is an image which naturally comes to mind for the term encapsulation and is naturally transposed to the molecular level for the term

"molecular encapsulation". The cork core is replaced by a molecule or cluster of atoms, and polymer molecules replace the rubber, thread, and leather.

This "baseball" image is somewhat misleading when thinking about molecular encapsulation (Figure 1.1). The "baseball" image applies in two ways to the mental "molecular" image. First, in both the macro- and molecular scale images, the encapsulated system was designed to function as a complete unit and has unique properties that are the result of the combination of the encapsulating material and the core. Second, in both cases, encapsulation involves the principle of surrounding a target with an encapsulating material, rubber, twine and leather for a baseball, polymers for molecules.

Despite these two similarities, the true "molecular" encapsulation system deviates significantly from the mental "baseball" image. First, the "baseball" image is macroscopic and thus is a fixed, static system subject to the laws of gravity. This image coincides well for particles formed with block copolymers and inorganic clusters which are micron scale objects and generally fixed structures once formed. However, a "molecular" system covers the angstrom to nanometer scale, is a dynamic system with molecular motion and is subject to quantum mechanical phenomenon.

The "baseball" image also automatically implies that the encapsulated object is centered within a sphere. Again this image would be appropriate for inorganic particles wrapped in a polymer matrix. In most molecular systems, this is not necessarily true. In a biological context, molecular systems such as enzymes, for which crystal and NMR structures can be obtained, demonstrate encapsulation of reactive molecules such as hemes, chlorophylls, and iron-sulfur clusters, by protein, i.e. biological polymers. [1, 2] These reactive

centers can be found in a variety of orientations and locations within a protein, not always in the center of a globular mass. A comparison of the crystal structures of *E. coli* succinate dehydrogenase, a protein analogous to complex II in mitochondrial electron transport system, and the iron-sulfur protein from nitrogenase, illustrate these variations (Figure 1.2).

The baseball image also implies that access to the core object is severely restricted or precluded by outside forces unless extraordinary measures are employed. Such measures usually result in the destruction of the composite object. In biological systems, the encapsulating proteins provide stabilizing support to an encapsulated cluster or molecule and influence its chemical and physical properties while still allowing limited access to the molecule.

While the baseball image serves as a nice general starting point, it has many implications which are contradictory to the goals of molecular encapsulation and a better definition for molecular encapsulation is needed. For the purposes of this dissertation, molecular encapsulation shall be defined as “the act or process of attaching polymeric molecules to a reactive core moiety with the goal(s) of altering or influencing the measurable properties of the core moiety and/or controlling access by the nanoenvironment to the core moiety.” The term "nanoenvironment," first coined by Fréchet, is hereby defined the spherical volume, 2 nm radius, of space surrounding the core moiety.

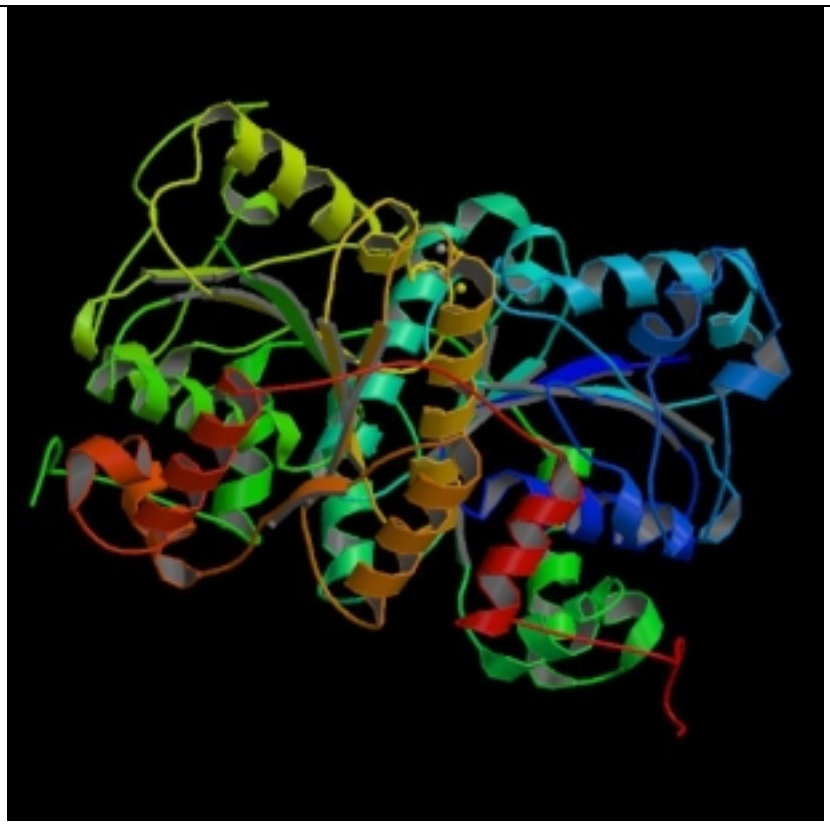


Figure 1.2 Crystal Structure of an Iron-Sulfur Protein
A crystal structure of the all ferrous iron-sulfur protein from the nitrogenase complex from Azotobacter vinelandii. The iron-sulfur cluster is located at thetop edge of the dimer. Picture obtained from Protein Data Bank online.

1.2. Dendrimers

The archetypical systems used in materials research for molecular encapsulation are the class of supramolecules known as dendrimers. Dendrimers are special polymers consisting of one or more hyperbranched arms, dendrons, which extend from a central molecule or cluster. Conceptually, as supramolecules, dendrimers are composed of three distinct components: A core, an interior matrix and a periphery (Figure 1.3). The “core” molecule is the focal point of a dendrimer and can have chemical properties (electrochemistry, reactivity, etc.) or be inert. Influencing chemical properties of a “core” is the usual goal of encapsulation. The “interior matrix” is composed of the hyperbranching

dendrons which extend outward from the "core." Hyperbranching is achieved through the use of ABn monomers (n = 2 or more) instead of the AB or AA monomers used in linear polymers. The "interior matrix" is the immediate chemical environment arround the “core” and has the greatest influence on any chemcial properties. The “periphery” is the outer layer of the dendrimer. The nature of the “periphery” is defined by the chemical nature of the molecules used for the “tips” of the dendrons.

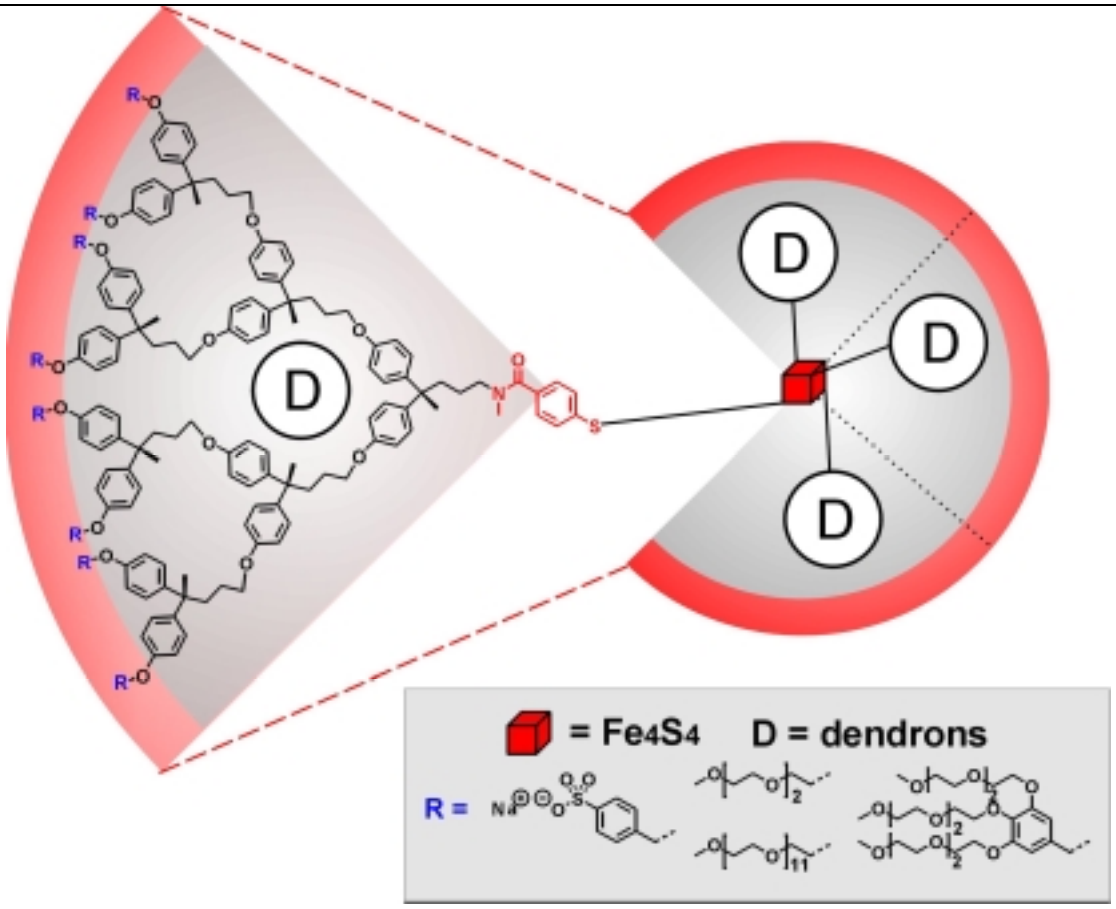


Figure 1.3 The Modular Dendrimer
The hyperbranched arms (4) are known as “dendrons” and are composed of ABn monomers. Focal molecules attach the dendrons to the “core” and tip molecules define the”periphery” of the dendrimer. The chemical nanoenvironment around the “core” is defined by the chemical structure of the “interior."

The defined components of a dendrimer provide context for other aspects of dendrimers. Dendrimer size is defined as “generation” and is the number of branch points on

a dendron from the "core" out to the "periphery." Three branch points would be a generation 3 (G3) dendrimer (Figure 1.3). The "periphery" of the dendrimer is the dominant factor regarding the solubility of the dendrimer. The methodology by which dendrimers can be assembled, convergent or divergent, relates to the fashion in which the "interior" part of a dendron is synthesized relative to the "periphery" and the "core". These two methodologies are well known and have been covered thoroughly. [3-5]

In convergent methodology, dendrimers are synthesized and purified starting with the periphery and ending at the core. Initially "tips", functional groups of molecules intended to be the periphery of a complete dendrimer, are coupled to the B reactive group of an ABn monomer (Figure 1.4). This reaction starts the synthesis of a dendron. The A group of this product is then "activated," if necessary, and "coupled" to the B groups of a second ABn monomer. The ratios of reactants in these coupling reactions is usually 2.2 : 1, although it can be increased if necessary. A layer of branch points is added each time this "activate/couple" cycle is performed. Synthesis of dendrons is complete when a desired size (Gx) is reached and any necessary focal molecule has been added. Dendrimers are assembled by attachment of the dendrons in a final step to the core. The stepwise "activate/couple" cycle allows purification of dendrons at each step, including final assembly, assuming the dendrimer is not too sensitive, resulting in monodisperse dendrimers. If the dendrons are too large, steric hindrance will prevent assembly of a complete dendrimer resulting in a practical limit on the size of the dendrimers via the convergent methodology.

Dendrimers made via divergent methodology are synthesized by growing the dendrons directly from the core in a reaction sequence reminiscent of polymer growth (Figure 1.4). As the size of the dendrimer grows, i.e G2 to G3, the number of reactions occurring on a single dendrimer increases geometrically. In contrast to a convergent synthesis, large excesses of reactants relative to the growing dendrimer are needed to insure complete reactions. Eventually, the number of coupling reactions, which is a function of both dendrimer generation and the number of branches at a branch point, will exceed 100 insuring that errors occur. Unlike convergent synthesis, a complete dendrimer is formed immediately in divergent synthesis. With divergent synthesis, it is possible to make dendrimers which are much larger than the same dendrimers synthesized convergently but some polydispersity is the trade-off.

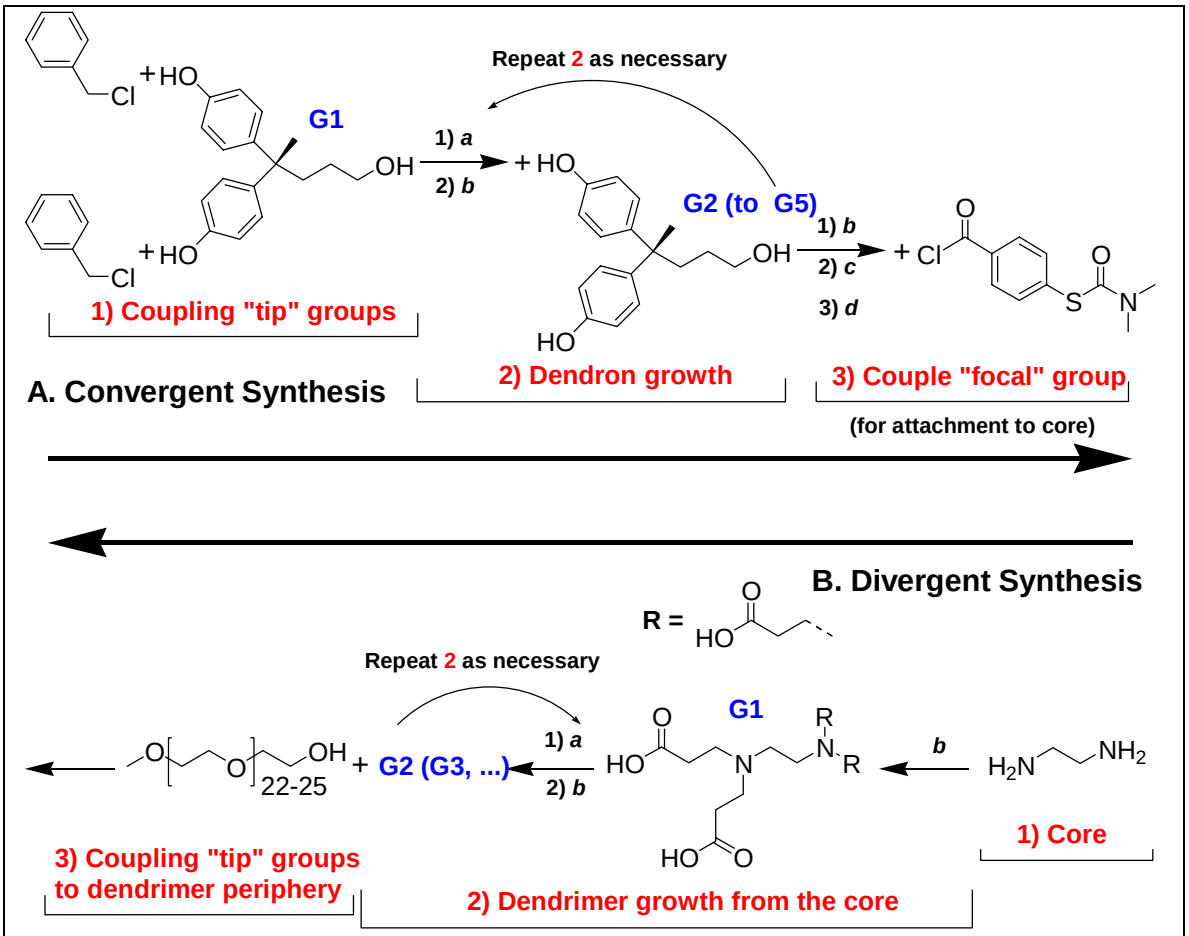


Figure 1.4 Convergent and Divergent Synthesis
The convergent and divergent synthesis of dendrimers is shown. A) Convergent methodology follows a repetitive "activate/couple" cycle in step 2 to couple smaller dendrons to the ABn monomers to make larger dendrons. Eventually, the dendrons must be attached to a core molecule. B) In divergent methodology, dendrimers are synthesized by "growing" directly from the core. Large excesses of reactant are required in second step.

In molecular encapsulation, the majority of the research conducted is on dendrimers with a central core that has measurable physical or chemical properties. These core properties fall into three general categories: photophysics, electrochemistry, and ligand binding. Any changes in the properties of a core molecule correlating to an increase in the size of the dendrimer are attributed to the effects of encapsulation. The primary mechanisms by which the core properties are altered in encapsulation are interaction with the dendrons by

the core, steric interference by the dendrons, controlling access to the core by the local nanoenvironment, or a combination of all. When the properties of a core are frozen or stabilized such that changes cannot be observed the core is said to be "isolated." [6]

1.3. Dendrimers or Linear Polymers

Although encapsulation of molecules and particles can be achieved with conventional linear polymers, dendrimers are much better suited for this particular application. Dendrimers have several unique advantages over conventional polymers.

Dendrimer architecture is structurally predisposed to encapsulation. The entire mass of dendrons is restricted to a defined volume around the core due to the hyperbranching. With a conventional linear polymer, the majority of its mass can distribute in a volume extending outward from a core defined by a maximum radius equal to the length of the linear polymer. Such behavior has been observed in comparison studies of the effectiveness of encapsulation of dendrons vs. linear polymer analogues.[7] While linear polymers can wrap around a core, this usually requires special solvent conditions or polymer core interactions. Fortunately, a large amount of research into solvent/polymer interactions has been published within the past few years and can be put to use for such applications as layering.[8-20] Special solvent conditions are not required for dendrimers. Architecture alone dictates the maximum radius into which the mass of a hyperbranched dendron can be distributed.

A second advantage for dendrimers is greater control over the nanoenvironment via the amount of encapsulation and the chemical nature of the encapsulation. This is a natural result of the stepwise nature of both the convergent and divergent methodologies. Both convergent and divergent methodolgies result in polymeric molecules that are monodisperse

and have regular, layered, and symmetrically branched three-dimensional architectures surrounding cores. The chemical nature of each layer can be tailored by choice of the ABn monomers composing the dendrons.

Any encapsulation of a core via linear polymers must involve induced layering which would be an average layer at best due to polydispersity of the polymers. Differing layers can be achieved with block copolymers but would still require special manipulation of solvent conditions and the resulting particles would certainly still have polydispersity issues. Use of more than two different types of copolymers would greatly increase the structural uncertainties.

The most important advantage of dendrimers over linear polymers is that dendrimers are modular in construction and composition. Thus the "core", the "interior", and the "periphery" can be changed to suit particular applications or needs.[21] This "modular" nature of dendrimers makes them extremely useful in encapsulation research. [22] Gorman et al. have reported several dendrimers with identical peripheries and interiors but a variety of cores. Benzyl ether, "Fréchet-style," interiors have been used in many different dendrimers as cores and peripheries. Wooley et al. demonstrated the facile functionalization of dendrimer peripheries and Tolosa has reported dendrimers specifically designed for easy modification of periphery.[23, 24]

1.4. Dendrimer Cores

The two types of cores in dendrimers are either "nonfunctional" or "functional." "Nonfunctional" cores are molecules that have no intrinsic measurable properties, and serve only as a polyvalent focal point for dendrimer assembly. Dendrimers with "nonfunctional"

cores are primarily for material applications other than encapsulation such as supramolecular constructs, self assembly research, polyvalent scaffolds, drug delivery, and solid-state synthesis.[25-40] "Nonfunctional" cores are not particularly useful for encapsulation studies.

"Functional" cores, in addition to serving as the polyvalent attachment point for the dendrons, have the observable physical/chemical properties necessary to evaluate encapsulation. Encapsulation and site isolation is the predominant research focus for dendrimers containing a "functional" core.

Observable physical/chemical properties fall into three broad categories: photophysics, electrochemistry and ligand binding.[41-48] A variety of molecules are used as "functional" cores: porphyrins/phthalocyanines, inorganic clusters, ionic complexes/organometallics, and fluorescent dyes (Table 1.1).

Molecule	Properties
Porphyrins/Phthallocyanines	
Si- Phthallocyanine	U
Zn-Porphyrin	U, E, F,
Pd-Porphyrin	P, LB
Fe-Porphyrin	U, E
Free base Porphyrin	F
Inorganic Clusters	
$Mo^{V}OS_4$	EPR, E
Fe_4S_4	E
Mo_6Cl_8	
Re_6Se_8	U, E
Organometallic/Ionic	
$Ir(ppy)_3$	L, U
Lanthanide, (Ln^{3+})–$(RCOO^{-}$	FT-IR, U,
Ferrocene	E
Methyl Viologen	E
Dyes	
4-(N-methylamino)-1-	U
p-dimethoxybenzene	F
Tryptophan	F
Coumarin 343,	L
Rhodamine B	F
4-(dicyanomethylene)-2-	F
3-[dimethylamino]phenoxy	F
Coumarin 343	F
Dansyl chloride	FQ
(S)-1,1'-bi-2-naphthol	F, LB

Table 1.1 Functional Cores Used in Dendrimers

The cores listed here are arranged by type and measurable properties. This list is by no means comprehensive. Properties legend: U = UV-vis absorbance, F = fluorescence, FQ = fluorescence quenching, P = phosphorescence, L = luminescence, E = electrochemistry, LB = ligand binding, EPR = electron paramagnetic resonance, FT-IR = FT-IR

While the use of inorganic clusters in dendrimers was originally to mimic cofactors in enzymes, i.e. ligand binding and catalysis, currently, these cores primarily are used for electrochemical and photophysical studies. [49, 50] Ionic and organometallic complexes exhibit photophysical and electrochemical properties and are useful because of the mild conditions

necessary to assemble such dendrimers. [51-53] Fluorescent dyes have been used exclusively for their light emission properties, particularly in the field of organic light emitting diode (OLED) research.

1.5. Photoactive cores

Cores with photophysical properties have proven to be extremely useful for evaluation of encapsulation in dendritic systems. The absorbance and emission of light by a core is easy to measure and non-destructive, and can be influenced by dendritic encapsulation. The usual effect of dendritic encapsulation on these cores is the exclusion of quenching agent by the dendritic material. However, the dendritic encapsulation of cores with photophysical properties has been used to achieve other effects such as enhanced solubility and energy harvesting through an "antenna effect."

The first reported instance of the term "dendritic encapsulation" was used to describe shifts in UV-Vis absorbance maxima of a *p*-dimethylamino-nitrobenzene core (Figure 1.6). These shifts were correlated to the size of the dendrimer by Fréchet and co-workers.[54] Aida and coworkers reported the first instance of site isolation due to dendritic encapsulation.[55] Fluorescence quenching of an encapsulated porphyrin core by free porphyrin molecules was completely inhibited by dendritic material. However, for the same dendrimer, quenching by vitamin K_3, a much smaller molecule, was actually enhanced as the dendrimer grew larger. Presumably, this was due to the ability that water-soluble dendrimers have to extract hydrophobic molecules from aqueous environments.

Moore and coworkers reported shifts in fluorescence maxima for phenylacetylene dendrimers with a p-dimethoxybenzene core.[56] While expected bathochromic shifts were

observed for lower generation dendrimers, at higher generations, shifts were observed that were very solvent dependent. These results indicated that encapsulation of a core does not produce a single, universal effect and that encapsulation might be a controllable phenomenon through means as simple as changing solvent.

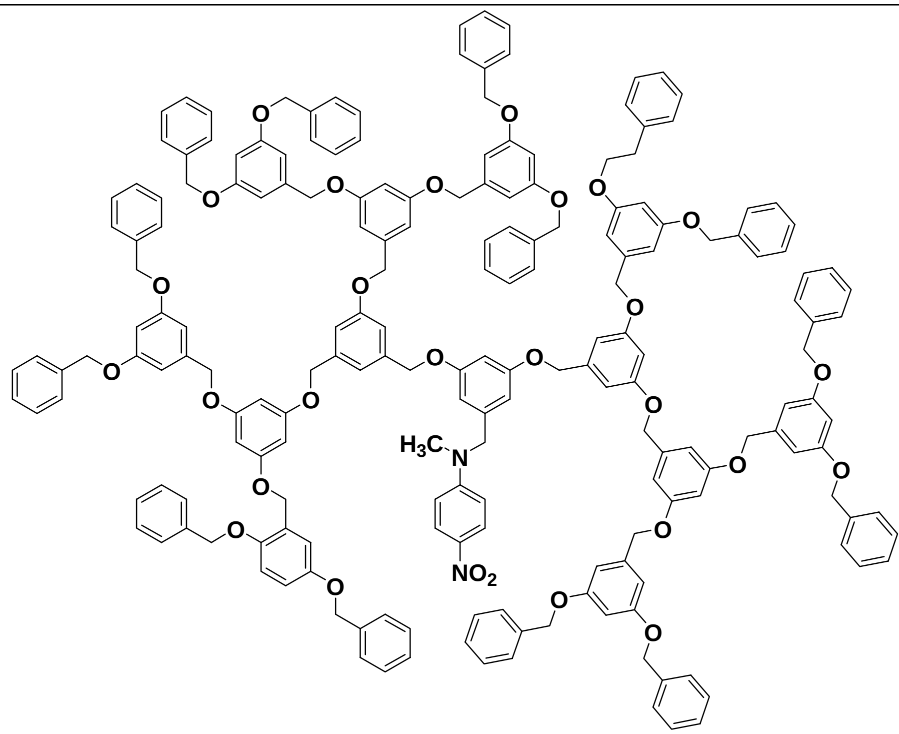


Figure 1.5 First Dendritic Encapsulation
This motif, based upon 3,5-benzyl ether repeat units, is referred to as the classical "Fréchet-style" dendrimer. The actual core is one of the 3,5-dihydroxy benzyl bromide monomers to which a dye molecule has been attached. This was the first instance of the term "encapsulation" being used to describe the relationship between a dendrimer and its core.

Initial experiments demonstrating control of encapsulation were reported by Smith and coworkers using tryptophan-core dendrimers with dendrons capable of hydrogen bonding (Figure 1.6).[57] Vinogradov and coworkers have also demonstrated control of encapsulation with porphyrin-core polyglutamate dendrimers.[58, 59].

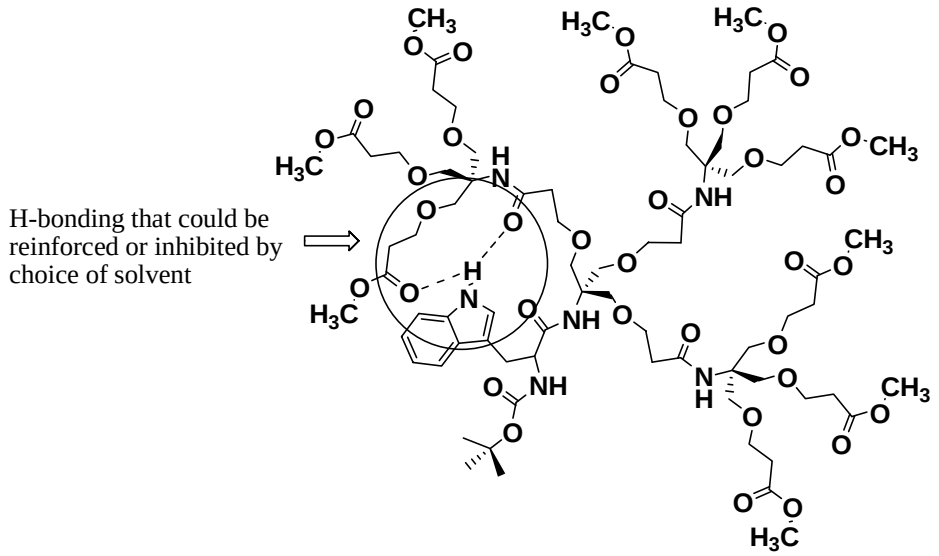


Figure 1.6 Encapsulation Effect - Control of Core Emission
Hydrogen bonding interactions between the tryptophan core and the dendron is illustrated. By selecting solvents capable of competitive hydrogen bonding, such interactions could be enhanced or disrupted. In this fashion, the emission maxima of the tryptophan core could be shifted in a controlled fashion.

Dendritic encapsulation and "site isolation" has been used in organic light emitting diode (OLED) research. Encapsulation of a core prevents self-quenching by other dendrimer cores and it aids in processibility. Otomo and coworkers have spun-cast dendrimer thin films which exhibited mirrorless laser emission with no loss in fluorescence emission intensity.[60] Site isolation and laser emission have also been reported in a dendrimer host/guest system that exhibited nonlinear increases in emission in response to excitation.[61] Markham and coworkers have fashioned green phosphorescence LEDs made from *fac*-tris-2phenylpyridine iridium, $Ir(ppy)_3$, core dendrimers.[21] In addition to site isolation, these dendrimers enabled the $Ir(ppy)_3$ core that would normally be evaporated to form an OLED, to be spin-cast in thin layers up to 20% by weight.

An energy harvesting "antenna" effect has been combined with site isolation and solubility enhancement in photoactive cores. Fréchet and coworkers used the "antenna"

effect to enhance luminescence of lanthanide ion/tricarboxylate core dendrimers (Figure 1.7).[62, 63] In another report, Fréchet and coworkers used the polyvalent nature of dendrimers to enhance this "antenna" effect.[64, 65] The "antenna" effect has been reported to be influenced greatly by the conformation of the dendrimer. Aida and coworkers reported non-linear changes in quantum yields for energy transfer to porphyrin cores that were fully substituted with four dendrons when compared to the partially substituted analogues.[66]

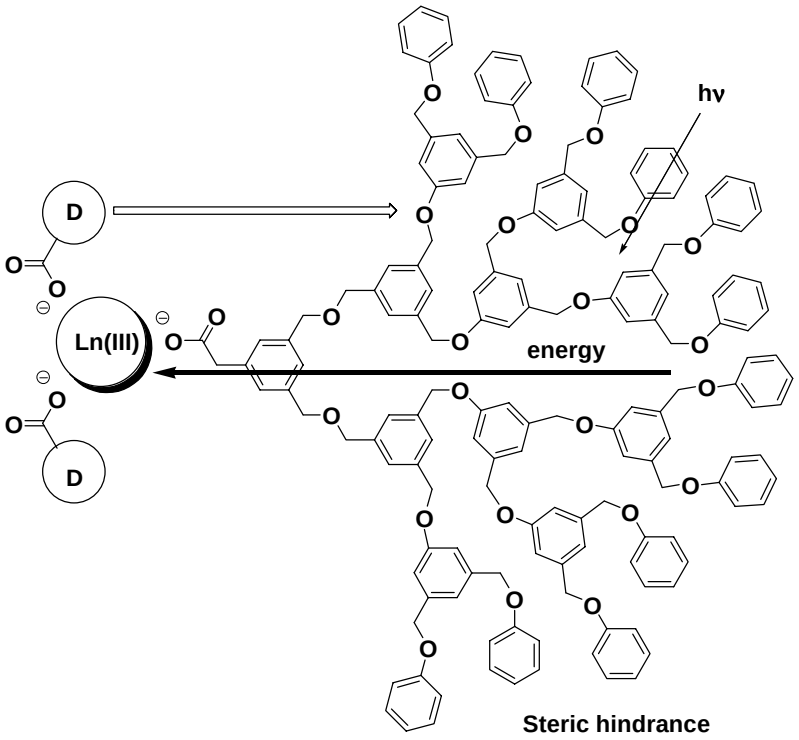


Figure 1.7 Encapsulation Effect - Enhanced Luminescence of the Core
In a lanthanide(III) core dendrimer by Fréchet et al., the dendrons acted as steric hindrance to prevent self-quenching by other cores. and as "antennas" harvesting and funneling energy to the core enhancing its luminescence.

1.5.1. Electroactive Cores

Electrochemically active cores have been used extensively for investigating dendritic encapsulation.[42, 43] Dendritic encapsulation has been shown to affect heterogeneous electron transfer rates. The effect of dendritic encapsulation on heterogeneous electron transfer rates

has been studied extensively and is fairly well understood. The mechanism appears to be simple steric hindrance with distance being the primary factor in influencing the rate of electron transfer. The chemical structure of the dendrons also has an effect on the electron transfer kinetics, as would be expected. Encapsulation effects on redox potential are less well understood, though some progress has been made.[6] The primary factors influenced by encapsulation seem to be the polarity of the local nanoenvironment and solvent/core coordination.

Multiple dendrimers have been reported in which changes in the heterogeneous electron transfer rates are attributed to encapsulation. Diederich and coworkers reported the first correlation between dendrimer size and attenuation of electron transfer rates using Zn-porphyrin-core dendrimers.[67] Fréchet, Abruna, and coworkers demonstrated site isolation for third and fourth generation Zn–porphyrin dendrimers (Figure 1.8).[68] Gorman and coworkers have reported similar results with two iron-sulfur core dendrimers having different chemical structures (Figure 1.11).[69]

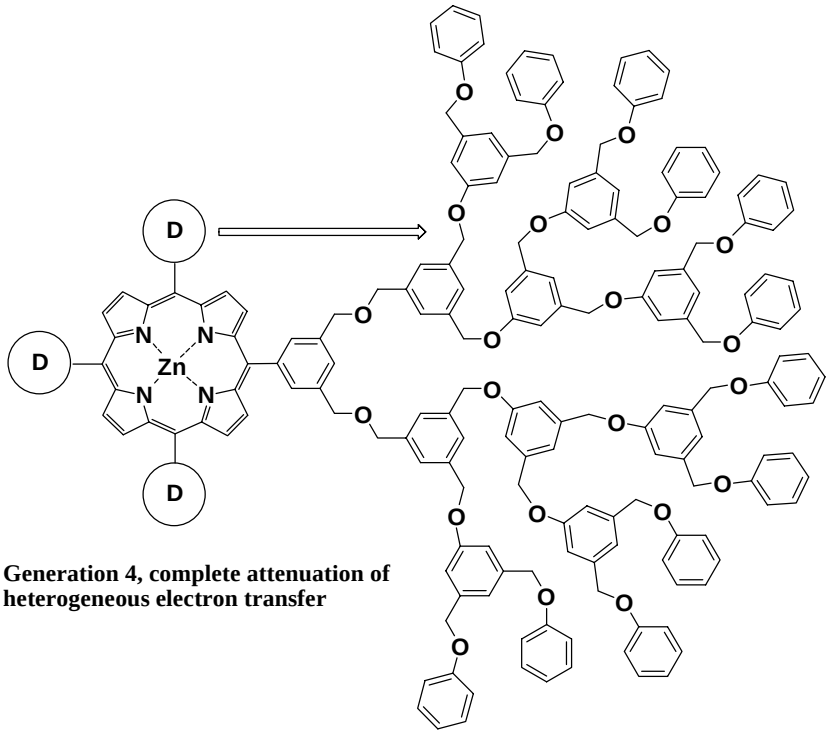


Figure 1.8 Encapsulation Effect - Site Isolation of a Zn-Porphyrin Core
Fréchet and Abruña investigated the effects of encapsulation on the electrochemistryof the porphyrin core of this dendrimer. In the third and fourth generation dendrimers, electron transfer from the core was characterized as irreversible to non-existent.

Kaifer et al. have reported intriguing results using ferrocene-core single-arm offset dendrimers (Figure 1.9). These dendrimers show attenuation of electron transfer rate for in both organic and aqueous solvents.[70] In a particularly elegant experiment, Kaifer and coworkers demonstrated the directional control of electron transfer.[71] Utilizing gold electrodes coated with an amine-terminated alkyl SAM, electron transfer was essentially turned "on and off" by controlling the pH and salt concentration of the electrolyte solution. The carboxylate-tipped dendrimer could be made to orient towards or away from the amine-terminated SAM, depending on protonation state of the respective functional groups (Figure 1.9).

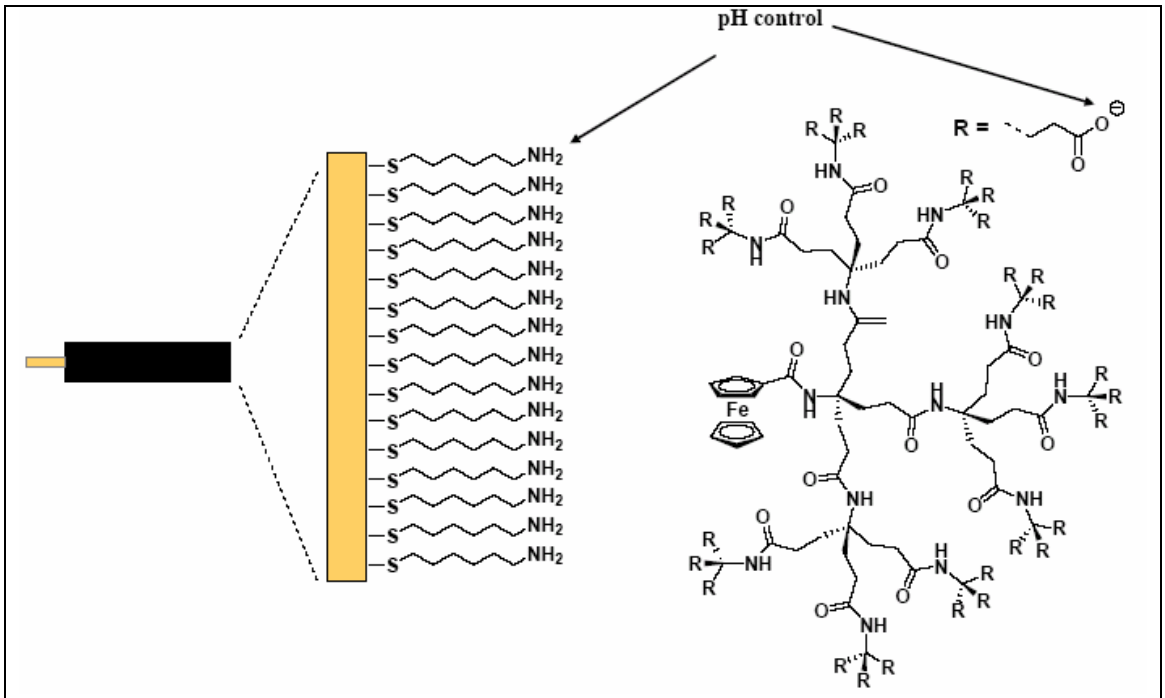


Figure 1.9 Encapsulation Effect - Directional Control of Electron Transfer
The orientation of the carboxylate dendrimer toward the amine SAM was controlled via solution pH. At Around pH 6, the dendrimer oriented towards the SAM, the ferrocene would be oriented away from the electrode surface, essentially shutting off electron transfer. This only occurred when the dendrimer was of sufficient size that the ferrocene was far enough from the electrode that electron transfer did not occur.

While the factors influencing electron transfer via encapsulation are generally well understood, anomalous results have been reported. In two separate, independent papers, both Kaifer and Balzani reported no attenuation of the heterogeneous electron transfer kinetics for identical methylviologen-core dendrimers up to the third generation.[72, 73] The simplest rationale is that the dendrimers were not large enough to sterically shield the core. However, Alvarro et al., working with the exact same system, reported that charge transfer complexes and electron transfer quenching with anthraquinone was inhibited beginning with the second generation dendrimers.[74] It is clear that all aspects concerning encapsulation and attenuation of electron transfer rates have not been uncovered.

The effect of encapsulation on thermodynamic redox potential is an area where more research is needed. In the previously cited research, Abruña and Fréchet also observed redox potential shifts for their Zn-porphyrin.[68] Diederich reported solvent dependent effects for various Fe-porphyrin dendrimers.[67, 75] Stone reported similar effects for ferrocene core dendrimers.[76] Gorman et al. however, observed no significant shift in redox potential of Fe_4S_4 cores for the two differing dendrimer architectures in solution.[69] The same dendrimers in thin films, however, exhibited tremendous changes in redox potential.[77] Clearly, more work needs to be done to elucidate the factors influencing redox potential.

1.5.2. Ligand Binding

The effects of encapsulation on ligand binding to core molecules have been exhibited in diverse dendrimer-core systems. Again, the principle influence is sterics and the type of pockets that can be established around the cores. Aida and coworkers demonstrated inhibition of binding of a dendron-substituted imidazole to a Zn-porphyrin core dendrimer.[78] Suslick and coworkers reported shape selective ligand binding in a series of Zn-porphyrin dendrimers.[79, 80]. Pockets were formed around the Zn-porphyrin core with dendrons, limiting, but not completely eliminating access to the Zn-porphyrin. Using their ferrocene-core dendrimers Kaifer and coworkers demonstrated hindrance of cyclodextrin binding to the ferrocene.[81, 82] Pugh et al. report the ability to discriminate chiral compounds with fluorescent dendrimers.[83] Vinogradov and co-workers showed site-isolation of a Pd-porphyrin core by preventing O_2-quenching (Figure 1.10).[84]

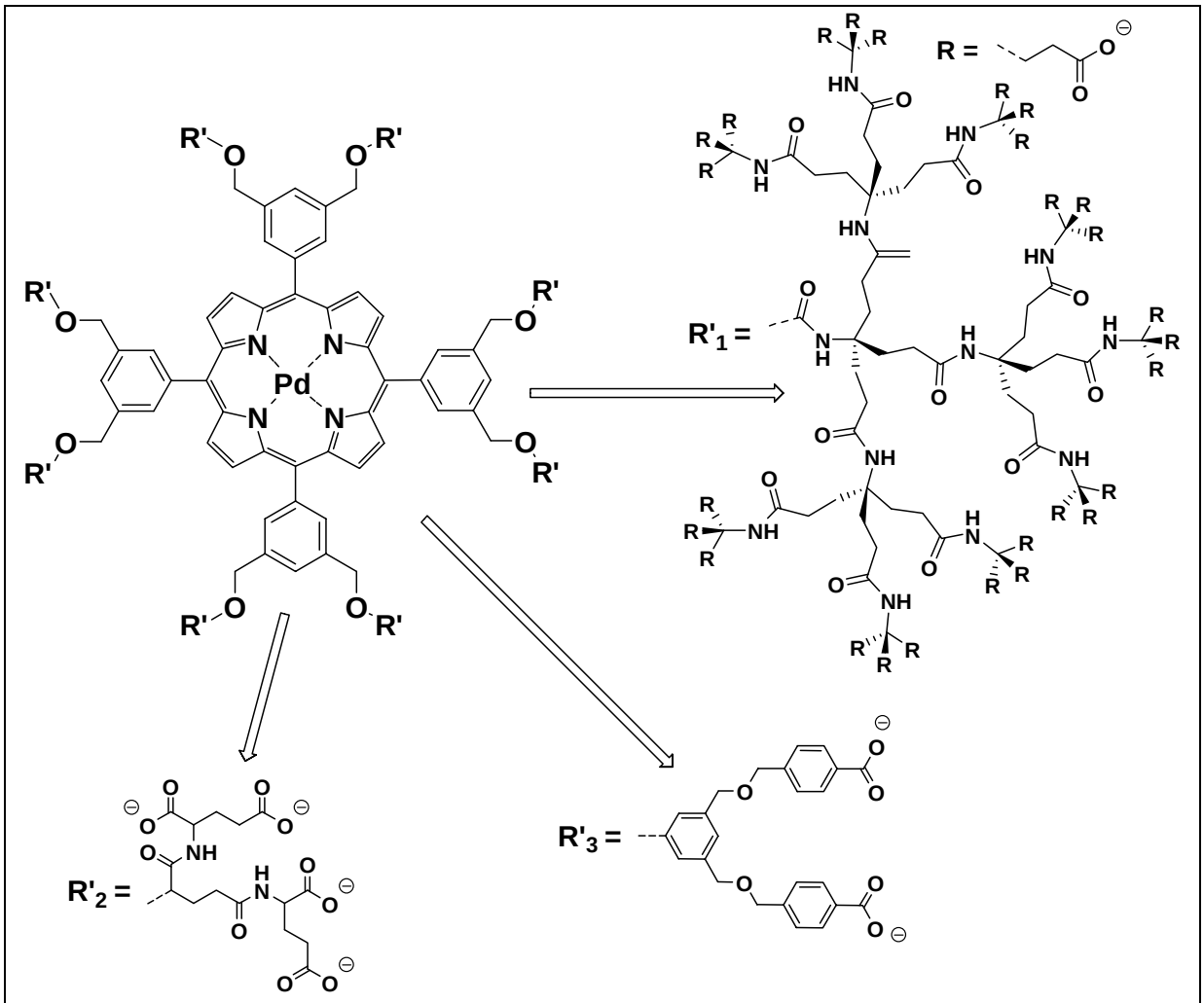


Figure 1.10 Site Isolation of Pd-Porphyrins

Vinogradov et al. have demonstrated site isolation via chemcial structure of the dendrons and solvent choice. Dendrons ***R'1*** *and* ***R'2*** *failed to prevent O_2-quenching of the core luminescence in an aqueous solvent. In contrast, the Fréchet-style dendrimer,* ***R'3****, significantly shielded the core at generation two and almost completely at generation three.*

1.6. Dendritic Encapsulation Studies by the Gorman Group

Over the past few years, Gorman and co-workers have conducted a systematic investigation of dendrimer encapsulation.[6, 69, 85, 86] Utilizing the convergent methodology, dendrimers with a variety of cores and architectures have been assembled.[69, 87] These dendrimers have been analyzed through electrochemistry, NMR and through molecular dynamics modeling. Insights into structure-property relationships in encapsulation have been gained through this research and various potential applications in nanotechnology and biochemistry have arisen from this work. While a variety of cores have been encapsulated by the Gorman research group, the iron-sulfur cluster has been the core which has been the primary core used in the encapsulation research. The redox potetnital of the iron-sulfur cluster is sensitive to the environment. It has stable -2/-3 states and displays reversible kinetics. The ligand exchange reactions to make dendrimers are quantitative and the tetrahedral arrangement of ligands is the simplest geometry that insures 360 degree coverage of a core.

1.6.1. Controlling Encapsulation Through Chemical Structure

Utilizing Fe_4S_4 chemistry reported by Holm et al. and ligand exchange reactions Brandon Parkhurst, Dr. Kang Yi Chen, Dr. Michael Hager and Dr. Jennifer Smith synthesized and characterized Fe_4S_4-core dendrimers with two different chemical structures (Figure 1.11). [88, 89] The dendrimer employing Fréchet's 4,4'-bis(hydroxyphenyl)pentanol ABn monomer was desiganted "flexible" and the other dendrimer employing Moore's 1,3,5-phenylacetylene ABn monomer was designated "rigid." [69, 90, 91]

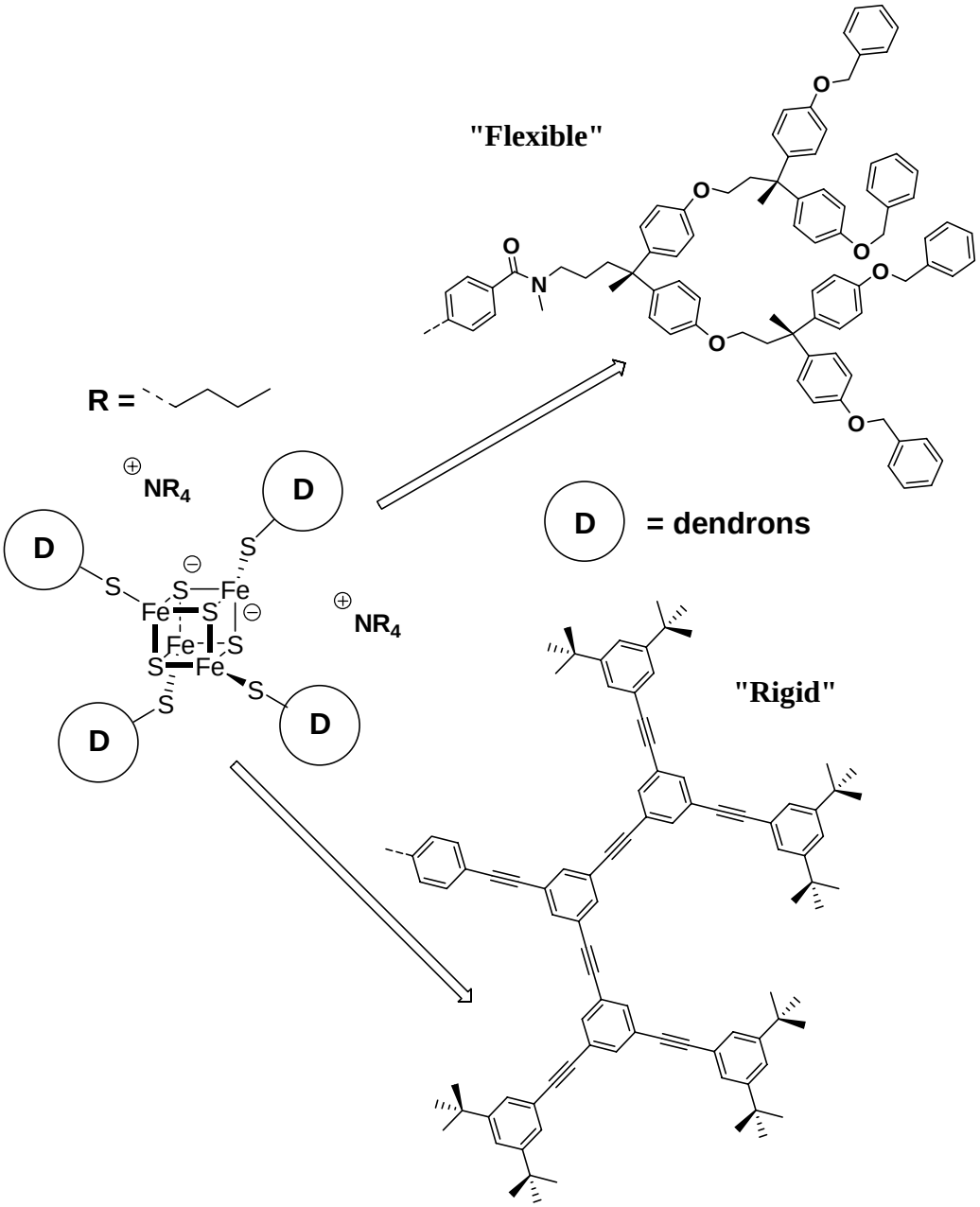


Figure 1.11 "Flexible" and "Rigid" Dendrimers
Control of the heterogeneous electron transfer rates between the iron-sulfur core and platinum electrodes was demonstrated by synthesizing dendrimers with different chemical structures. This research represented the first systematic investigation of the effect of the chemical nature of the dendrons on encapsulation properties.

Different attenuations of the heterogeneous electron transfer rates between the two dendrimers were measured via Osteryoung square wave voltammetry. The attenuation of

electron transfer rates by the rigid architectures was found to be larger than that in the flexible architectures. These results were consistent with data obtained for most other electroactive dendrimers.[42] The results from conformational searching computations on these two architectures suggested that flexible architectures permitted substantial mobility of the core (the origin of "flexible" and "rigid") throughout the architecture compared to the stiffer phenylacetylene architecture. The electrochemical data and computer modeling suggested that generic, flexible dendrimer architectures do not sterically shield the core as much as might be expected merely by examination of their primary structure. In essence, the effective average radius from the core to an electrode surface could quite easily have been smaller in the "flexible" dendrimer than the "rigid". However, comparison of attenuated transfer rates versus the apparent radius of the dendrimer, revealed that the "rigid" architecture was actually performing worse than the "flexible" architecture. Thus, distance was not the only factor influencing the electron transfer rates. The phenylacetylene repeat units of the "rigid" architecture, while cross-conjugated, are still primarily a π-bonded system from the core to the tips of the dendrons. Through-bond electron tunneling from the core to the surface may have been easier due to the multitude of π-systems. The "flexible" architecture, on the other hand, was primarily an aliphatic system composed of sigma bonds and isolated π-systems (Figure 1.11). While the heterogeneous electron transfer rates were affected by encapsulation, the thermodynamic redox potentials of the cores for the "flexible" and "rigid" dendrimers in DMF solution were not.

The lack of effect on the redox potential of the iron-sulfur cores dendrimers was puzzling since these particular cores were thought to be very sensitive to environmental

effects. A simple explanation is that the nanoenvironment around the iron-sulfur core did not change significantly as the dendrimer generation increased, however such an explanation would need to be rationalized for the two differing architectures. The indication of substantial core mobility for the "flexible" dendrimers implies solvent access to the core. The computer structure modeling of the "rigid" dendrimers yielded a relatively open structure in the dendrimer interior. Solvent access via open spaces as in Meijer's "dendritic box" seems likely.[92] Exposure to solvent seems likely for both dendrimer architectures at all generations. The polarity of the nanoenvironment around the core would never change regardless of dendrimer size, and solvent/core interactions would always be possible. Thus no change in redox potential would be expected.

1.6.2. Controlling Encapsulation: Solution vs. "Thick" Film

When the same series of "flexible" and "rigid" dendrimers were spun-cast onto a platinum electrode surface, dramatic differences with the solution electrochemistry were observed. The thermodynamic redox potential shifted with increasing dendrimer generation while the kinetic electron transfer rates were virtually unchanged.[77] Compaction of the dendrons in the films could lead to exclusion of solvent and the formation of less polar environments around the iron-sulfur cores. It is unknown whether the formation of nonpolar nanoenvironments around the core would result in a negative shift in the redox potentials. The concept of core mobility is further reinforced in these "thick" film experiments by the rapid electron transfer kinetics observed for the "flexible architecture and the slow electron transfer rates observed in the "rigid" dendrimer thick films.

1.6.3. Controlling Encapsulation Through Dendron Conformation

A series of constitutional isomers of iron-sulfur core dendrimers were designed to bias the conformations of the dendrons towards backfolding.(Figure 1.12) The structurally biased backfolding was predicted to increase the steric congestion around the iron-sulfur core and lead to better encapsulation. Dr. Tyson Chasse synthesized and characterized these constitutional isomers.[86]

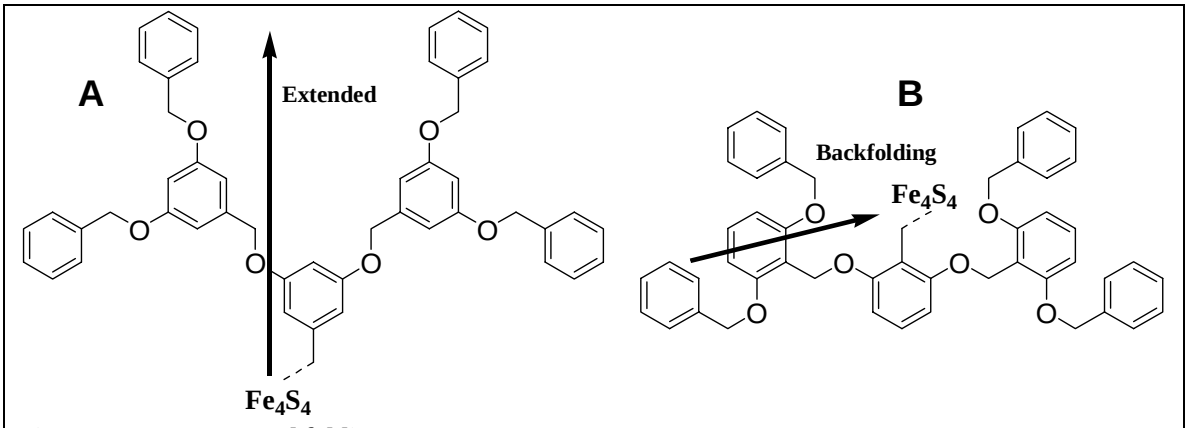


Figure 1.12 Isomer Backfolding
A) *A single dendron showing no backfolding. B) A dendron isomer showing designed backfolding due to chemical structure.*

The backfolded isomers were found to be better encapsulants for the iron-sulfur core. Although more compact and having a smaller hydrodynamic radius, the backfolded dendrimers had heterogeneous electron transfer kinetics 3 to 5 times slower than their non-backfolded analogues. The steric congestion created by the designed backfolding of the dendrons reduced core mobility within the dendrimer. With the core confined more centrally in the smaller backfolded dendrimers, the effective distance from the core to the electrode was still greater than in the corresponding, larger non-backfolded isomers (Figure 1.13). This same "effective electron transfer distance" model was elegantly demonstrated in Kaifer's directional control of electron transfer (Figure 1.9).[71]

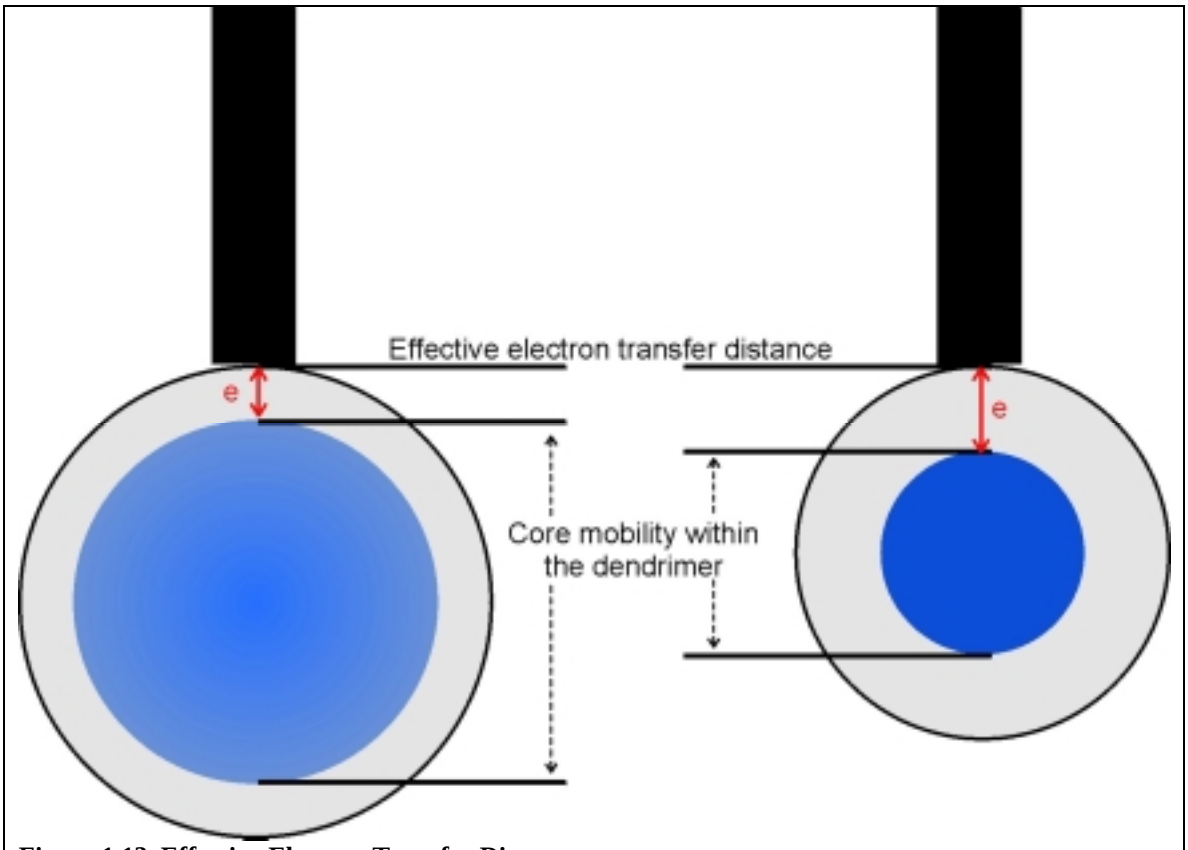


Figure 1.13 Effective Electron Transfer Distance
For any encapsulated core, the dendrimer size does not dictate the heterogeneous electron transfer kinetics. The kinetics are determined by how close the core can come to the periphery of the dendrimer. This is a function of the core's mobility within a dendrimer. Thus, a small dendrimer with a less mobile core can have larger effective electron transfer distance to an electrode than a large dendrimer with a very mobile core.

The redox potentials of the cores of the backfolded dendrimers also shifted more negative. The steric congestion excluded solvent and surrounded the charged iron-sulfur core with a nonpolar environment in much the same fashion as was seen in the "thick" film experiments.

1.7. Controlling Encapsulation with Solution Conditions

The control of core properties through encapsulation demonstrated by Gorman is extremely interesting in terms of potential applications. For instance, the iron-sulfur cores

used in the dendrimers have multiple, stable oxidation states. Any stable difference in two states, such as a –2/–3 redox couple, can be translated into "0" and "1". Thus, iron-sulfur core dendrimers could potentially be used as "uni-molecular" memory, i.e. "one molecule = one bit of information" in nanotechnology (Figure 1.14). One square centimeter of unimolecular memory formed from an addressable array of iron-sulfur dendrimers, 10 nm x 10 nm, potentially represents 1 terabyte of information storage capacity.

Two criteria must be met in order for a dendrimer to be useful uni-molecular memory. First, the dendrimers must "isolate" the cores by encapsulation to prevent "information scrambling" by the shuttling of electrons between two cores, in close proximity, and with different oxidation states. Second, memory is not useful if one cannot "write" to it. Therefore, access to the cores at certain times is necessary in order to change the oxidation states.

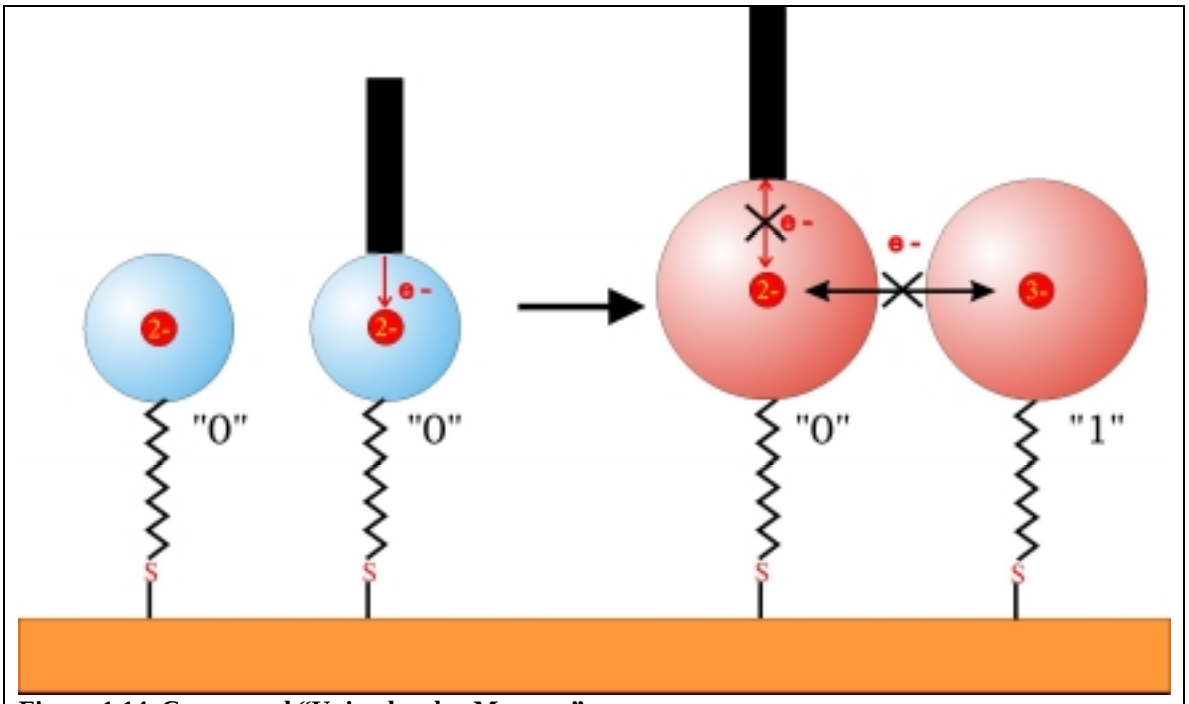


Figure 1.14 Conceptual "Unimolecular Memory"
In order to "write" information to the dendrimers, access to the core would be under specific conditions. Once information was stored, conditions would be changed and the dendrimers would "isolate" the cores to block access and prevent self-scrambling. Dendrimers that could change encapsulation properties in response to environmental conditions would be ideal for this nanotechnology application.

The previously described dendrimers are not suitable for hypothetical "uni-molecular memory" system. In each dendrimer described, the effect due to encapsulation on the electrochemical properties of the iron-sulfur cores was either an irreversible process (thick film formation) or the result of a change in the chemical structure of the dendrimer (requiring the total synthesis of a new series of dendrimers). Such measures are impractical for "unimolecular memory." The ideal dendrimer would be one in which the encapsulation ability of the dendrimers was controllable. A dendrimer motif that changed its encapsulation properties in response to environmental changes, as occurred with Kaifer and Vinogradov's dendrimers, would be extremely useful.

1.8. Water-Soluble Dendrimers

The easiest way to change the environment of a dendrimer is by altering solvent conditions. Smith achieved changes in dendritic encapsulation by changing the actual solvents.[57] It is even easier, though to change solution conditions through the addition of solute, especially in aqueous solutions. Vinogradov and Kaifer have demonstrated control of encapsulation in aqueous solvent via pH.[71 58, 59] Water-soluble dendrimers also change size in response to pH. [93] Water-soluble dendrimers with hydrophobic interiors have been swollen by the addition of tetrahydrofuran to an aqueous solution.[94] A swelling mechanism could be employed with water-soluble iron-sulfur core dendrimers enabling the "effective electron transfer distance" tobe easily altered.

Swelling behavior would also be useful for investigating the role of water coordination on the redox potentials of iron-sulfur clusters. Holm et al. has shown that the iron-sulfur cluster becomes easier to reduce as water was added to DMSO solutions. [95] The redox potentials of iron-sulfur proteins are known to vary widely. With water-soluble iron-sulfur core dendrimers, it may be possible to progressively exclude water from access to the core through a combination of increasing dendrimer size and addition of organic solvents. These dendrimers could serve as synthetic models for studying the effects of water coordination on the thermodynamic redox potential of iron-sulfur proteins.

A second way to alter solvent conditions is by the addition of water to miscible organic solvents such as tetrahydrofuran, THF and dimethylformammide, DMF. The size and morphology of vesicles formed from amphiphilic block co-polymers has been controlled in this fashion.[16, 19, 20] Water-soluble dendrimers are hyperbranched hybrid block co-

polymers and have been referred to as "unimolecular micelles." [37, 96-100] Dendrimers composed of amphiphilic dendrons should exhibit morphologic changes in aqueous/organic mixed solvents similar to those observed in amphiphilic block co-polymers. In experiments involving effects of solution on size and morphology, the dendrimer concentration will need to be kept below the critical micelle concentration to insure that they behave as independent molecules and do not aggregate.[101]

1.9. Research Goals

The goals of this research project are three-fold. The periphery of the "flexible" architecture dendrimers, previously synthesized in the Gorman research group, will be modified with hydrophilic functional groups (Figure 1.15). After the peripheries are suitably modified and dendrimers assembled, the iron-sulfur core dendrimers will be characterized by cyclic voltammetry in dimethyl formamaide (DMF) and DMF/water mixtures to determine if changes in dendrimer conformation and size can be detected. Finally, the electrochemistry of the water-soluble iron-sulfur core dendrimers will be determined so that the effects of water on the thermodynamic redox potential on the iron-sulfur cluster can be assessed.

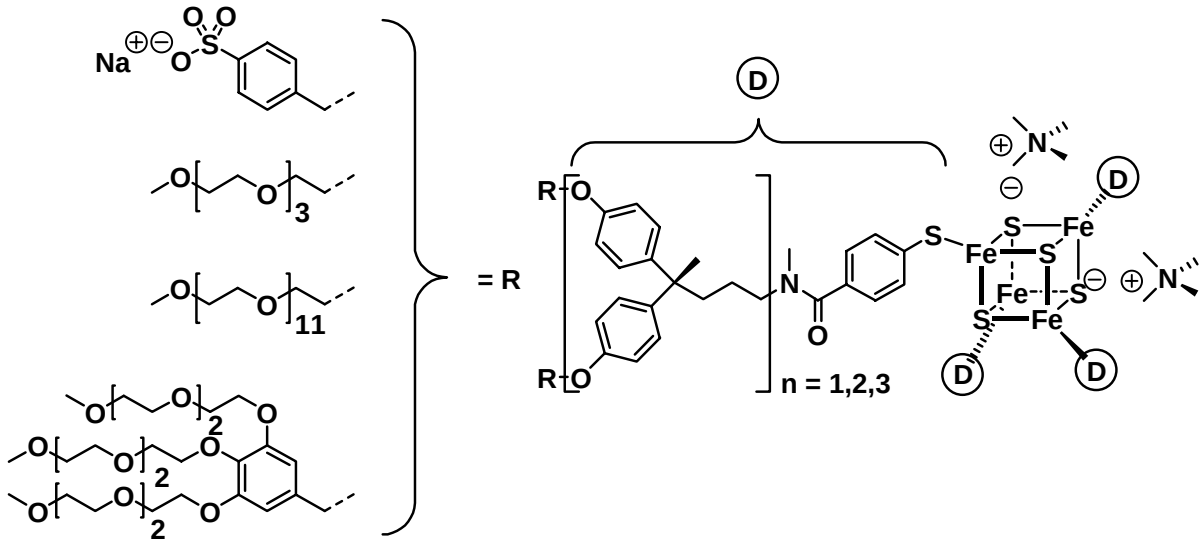


Figure 1.15 Proposed Water-soluble Dendrimers

Water-soluble dendrimers are to be synthesized by modifying the dendron "tips" such that the dendrimer periphery is hydrophilic. With these dendrimers it should be possible to investigate what effects water exposure has on the electrochemistry of the iron-sulfur core. A variety of tips were tried to achieve water-solubility.

2. Synthesis of Amphiphilic Iron-Sulfur Dendrimers

2.1. Introduction

It is well established that the solubility of dendrimers is heavily dependent upon the chemical structure of the functional groups at the periphery of dendrimers.[102, 103] To this end, water soluble dendrimers have been synthesized by the addition of hydrophilic functional groups to the "tips" of dendrons.[104-107] Amphiphilic dendrimers without functional cores have been proposed as "unimicelle" drug delivery agents since it is possible to encapsulate hydrophobic drugs in interior of the dendrimers.[33, 98, 108-113] Amphiphilic dendrimers with functional cores, including electrochemically-active cores, have been proposed as models for enzyme active sites.[41, 49, 50, 67-69, 76, 114-122]

Despite the projection of amphiphilic dendrimers with functional cores as enzyme models, very little electrochemistry has been done in aqueous solution with these molecules.[71, 81, 117, 123] This is particularly surprising since redox centers, such as porphyrins and iron-sulfur clusters, are key components in enzyme active sites. Given the importance and value of synthetic models for enzyme active sites, the lack of papers reporting the synthesis of amphiphilic dendrimers with electrochemically active cores implies that such a task is very difficult.

The iron-sulfur cluster (Fe_4S_4) is an extremely important biological center for controlling electron flow across cellular membranes and in biochemical reactions. This center has been synthesized artificially and characterized electrochemically in dimethylformamide (DMF) as the cluster with ligands and when encapsulated by dendrimers.[69, 77, 86, 95, 124, 125] These studies have provided insight into factors influencing the

heterogeneous transfer kinetics of the cluster, but factors influencing the redox potential, specifically the role of water coordination, are less clear. Even in point mutation proteins, the effects of water and solvent accessibility on the potential of iron-sulfur cores cannot be predicted reliably.[126] Thus, an amphiphilic iron-sulfur core dendrimer which could progressively encapsulate and exclude water would be extremely valuable in studying and understanding the role of water and solvent coordination on redox potentials

It is reported here the synthesis of amphiphilic iron-sulfur core dendrimers based upon the chemical structures reported by Chen et al.[87] Benzyl "tips" were replaced with hydrophilic functional groups. Initially, "tip" modification was performed via straight convergent synthetic methodology but was later changed to a more generally useful "modular" convergent strategy based upon methoxymethyl (MOM) protection/deprotection. This strategy was adopted to facilitate faster, more efficient dendron synthesis and greater "tip" modification than was possible with straight convergent synthesis. Similar protection/deprotection strategies with convergent synthesis have been reported. [50, 114] The efficiency of this "modular" convergent strategy was demonstrated with the rapid synthesis of a variety of "functionalized" dendrons and the usefulness of this strategy was shown by the synthesis of novel split-"tip" dendrons and other dendrons that could not be made via normal convergent strategy.

2.2. Results -- Convergent Dendron Synthesis

The modification of the dendrimer periphery by the addition of hydrophilic functional groups proceeded in three stages. First, individual hydrophilic "tip" molecules, three different polyethylene glycols and a protected sulfonate were synthesized. These hydrophilic "tips" were used to synthesize amphiphilic dendrons either via the convergent synthesis scheme or the "modular" convergent synthesis scheme. Finally, the amphiphilic dendrons were deprotected and iron-sulfur core dendrimers were assembled via ligand exchange reactions. Detailed synthetic procedures for the PEG3 convergent synthesis were included in Appendix A.

2.2.1. Synthesis of "Tip" Molecules

Polyethylene glycol-based tips were synthesized by activation of either triethylene glycol monomethyl ether (PEG3) or dodecylethylene glycol monomethyl ether (PEG12) with *p*-toluene sulfonyl chloride to produce, **1** and **2** respectively (Figure 2.1).[50, 75, 97, 98, 127-130] These reactions were performed on large scales (50-85 g) with purification being simple extraction with water.[131] The reported reaction used methanesulfonyl chloride for activation of the aliphatic alcohol. However, the ethylene glycol molecules with the mesyl group attached were sufficiently water-soluble that separate organic and aqueous phases would not form. Changing to *p*-toluene sulfonyl chloride for activation lowered the polarity of the PEG3 molecules sufficiently that extraction with brine resulted in separate organic and aqueous phases.

A third "tip" molecule was synthesized in which the number of triethylene glycols at the dendron ends was the tripled.[67, 116, 117] These tri-triethylene glycol "tips," (triPEG3) were

synthesized by reacting activated PEG3, **1,** with methyl 3,4,5-trihydroxybenzoate to yield the substituted methyl ester, **3**. This coupling of the PEG3 chains to the aromatic ring was a necessary first step. Methyl 3,4,5-trihydroxybenzoate was very similar in structure to quinones and a reduction with lithium aluminum hydride produced dark green precipitates that were not the desired benzylic alcohol. The triPEG3 methyl ester, **3**, could be reduced to the benzylic alcohol, **4**, which was stored until needed (Figure 2.1). Immediately prior to coupling reactions with the triPEG3 "tips", the benzyl alcohol, **4**, would be activated by conversion to the benzylic bromide, **5**, with phosphorus tribromide.

The fourth "tip" molecule synthesized was a phenyl-protected benzenesulfonate. Polysulfonates are common in amphiphilic block copolymers, form the polar head for sodium dodecyl sulfonate, and have been used in amphiphilic dendrimers.[105, 132] The phenyl benzenesulfonate tips were synthesized by first reacting phenol with *p*-toluene sulfonyl chloride to yield phenyl *p*-toluene sulfonate, **6**. This coupling reaction was followed by a radical bromination with N-bromosuccinimide to yield the benzylic brominated molecule, **7** (Figure 2.1). The radical bromination reaction always resulted in a mixture of approximately 63-72% mono-brominated, **7**, 5% dibrominated side-product, **7a**, and 28-32% starting material, **6**. Separation of the three components of these mixtures was virtually impossible. All three products would co-crystallize and separation with a silica column was impractical due to low solubility in the solvents necessary for purification. Purification was not necessary since in the mixture of products, the starting material **6** did not react in coupling reactions and any side products from the reaction of **7a** could be removed during subsequent purifications.

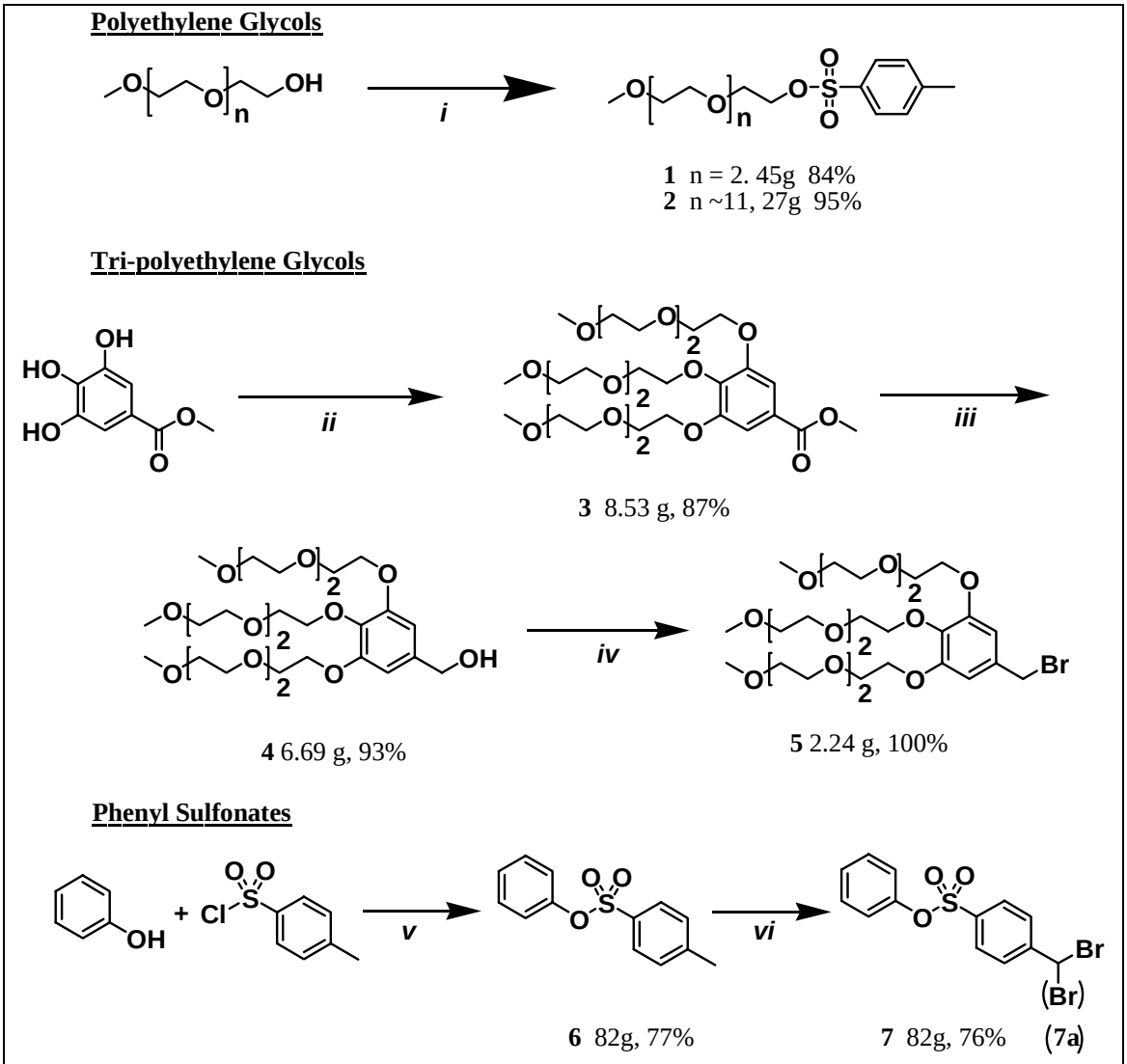


Figure 2.1 Hydrophilic "Tip" Molecules for Modification of Dendrons.
Theses molecules were prepared in large batches, stored, and used as needed. ***i****) p-Tosyl Chloride, NaOH(aq)/THF, 0 °C to RT, 2 hrs.* ***ii****)* K_2CO_3*, 18-O-6, Acetone,* ***iii****) LAH, THF 0 °C to RT, 2 hrs.* ***iv****) 0.33 eq.* PBr_3 ***v****)* K_2CO_3*, DCM* ***vi****)* Δ *0.9 eq. NBS, AIBN, DCM, 60 °C*

2.2.2. Synthesis of Amphiphilic Dendrons

Generations 1, 2 and 3 of dendrons with PEG3 "tips" and generation 1 dendrons with phenyl benzenesulfonate and triPEG3 "tips" were synthesized by following a convergent scheme similar to that reported by Chen at al (Figure 2.2).[87] The same ABn monomer used by Chen was employed and where possible, improvements were made in the synthetic scheme.

"Tip" precursor molecules, **1**, **5**, or **7** replaced the original reported benzyl tips and were coupled to the ABn monomer, **8**, to create the G1 alcohols, **9a**, **12a**, and **13a** (Figure 2.2). The resulting G1 alcohols, **9a**, **12a**, or **13a**, were then activated by reacting either with methanesulfonyl chloride or with *p*-toluene sulfonyl chloride. Higher generation dendrimers with PEG3 tips were synthesized by reacting the appropriate G1 or G2 mesylates, **9b**, and **10b**, with the ABn monomer, **8**, to produce the PEG3 G2 and G3 alcohols, **10a**, and **11a**. Phenyl-benzene sulfonate-tipped dendrons were not carried beyond G1 dendrons due to extreme fragility observed when sulfonate dendrimers were assembled via ligand exchange reactions. TriPEG3 dendrons could not be synthesized beyond G1 level via the convergent synthetic scheme due to difficulties in purification. Generations 2 and 3 of the triPEG3 dendrimers had to be produced by using the "modular" convergent strategy.

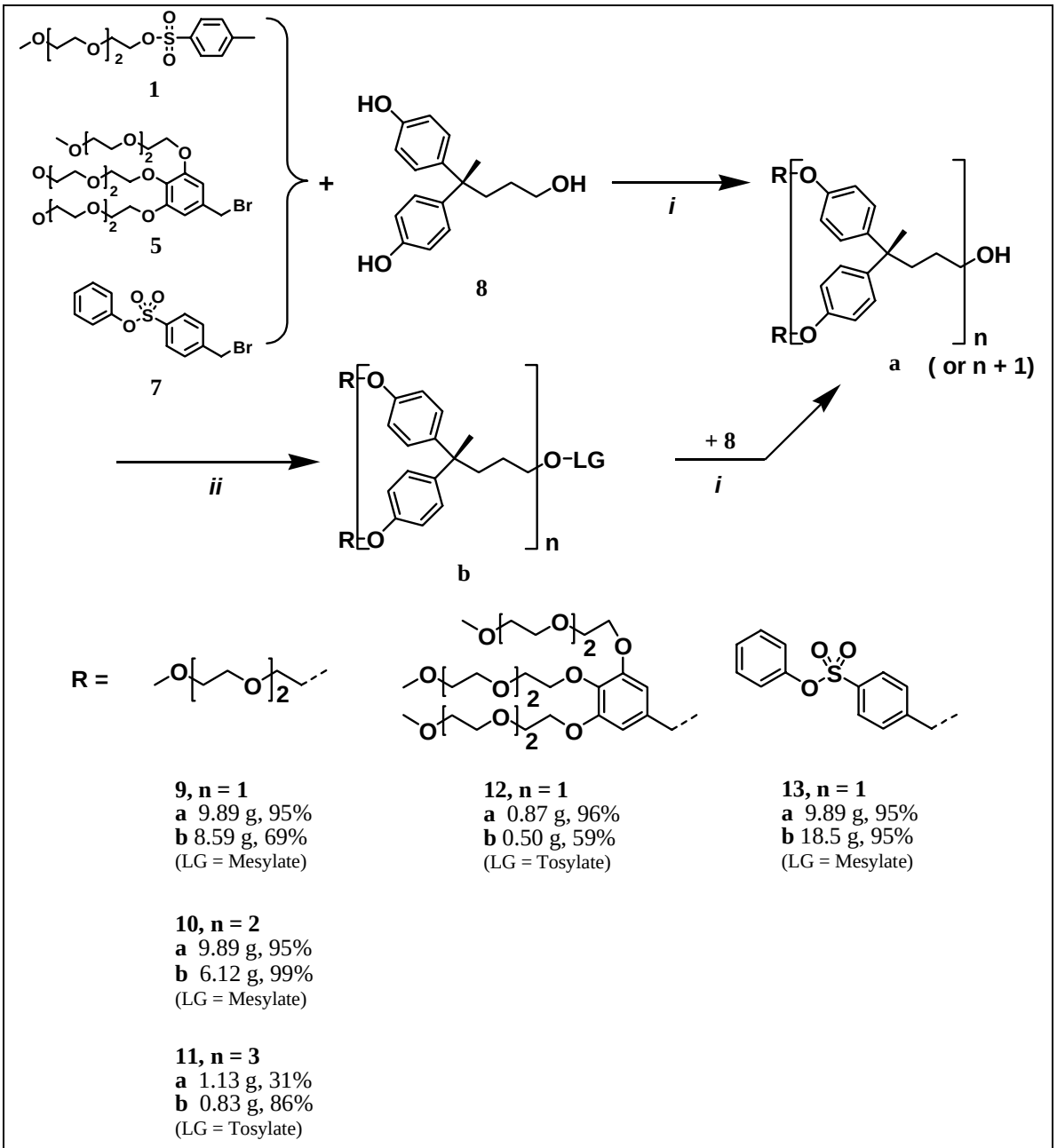


Figure 2.2 Convergent Synthesis I: Addition of "Tips" and Growth of Dendrons

"Tips" were initially added to the ABn monomer. Growth of the dendrons is achieved by activating the aliphatic alcohols and reacting them with the ABn monomer, 8, in a cyclic fashion. Dendrons are numbered according to generation, n, and focal group: ***a*** *for –OH and* ***b*** *for -OLG. i) K_2CO_3, 18-crown-6, acetone, Δ,12 hrs. ii) p-Toluenesulfonyl chloride or methanesulfonyl chloride, triethylamine, methylene chloride*

The convergent syntheses of amphiphilic dendrons were completed by converting the activated precursors, **9b**, **10b**, **11b**, **12b**, and **13b**, to the secondary amines, **9c**, **10c**, and **11c, 12c, and 13c** (Figure 2.3). The conversion to the secondary amine was performed by heating in THF and aqueous methylamine instead of reacting in DMSO saturated with gaseous methylamine. This reaction was an improvement in the sequence reported by Chen et al.[87] The resulting secondary amines were reacted with the acid chloride of the thiocarbamate focal group, **14**, to produce the completed dendrons, **9d**, **10d**, **11d**, **12d**, and **13d**.

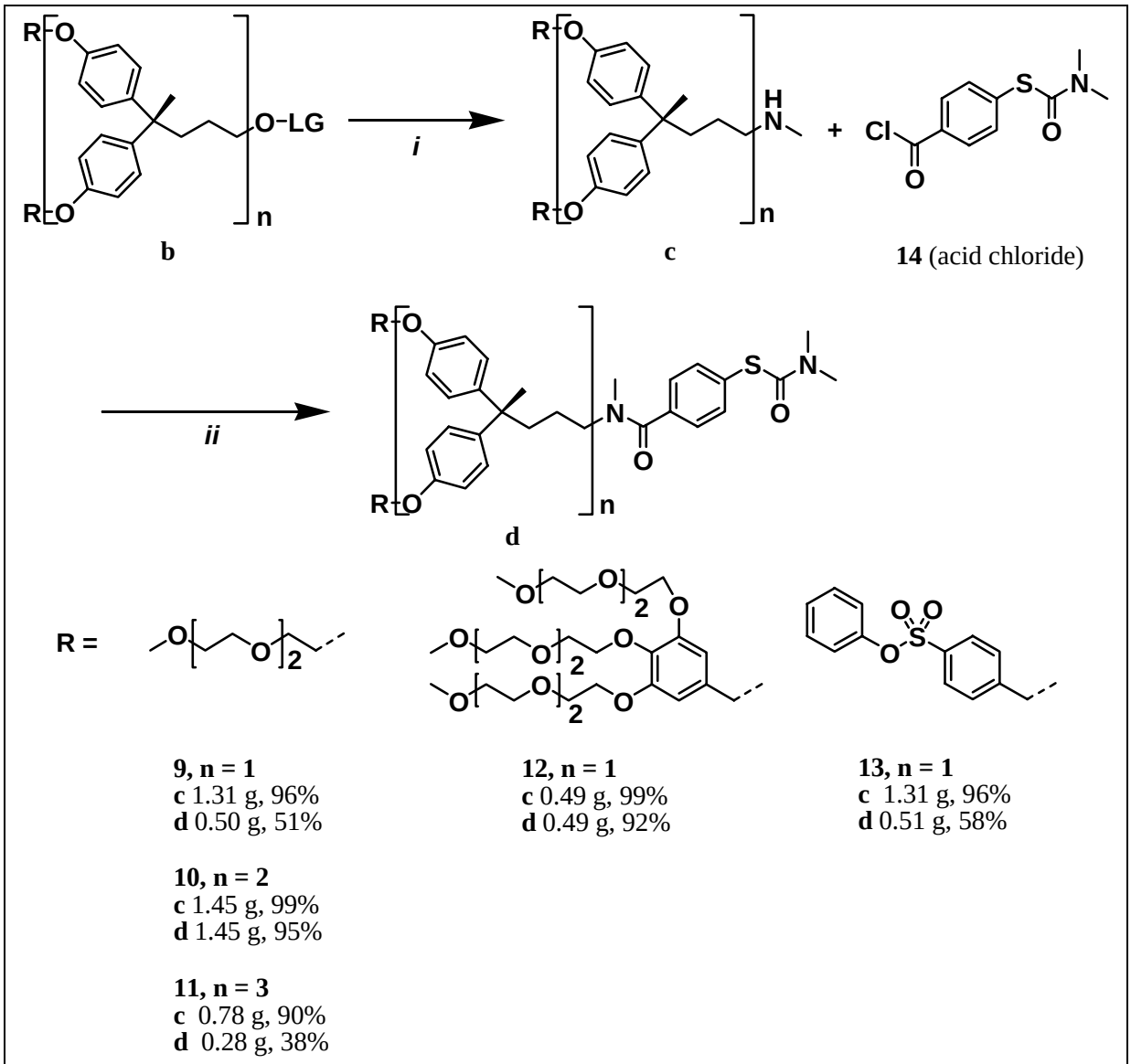


Figure 2.3 Convergent Synthesis II: Addition of "Focal" Group

Focal groups were attached to dendrons of an appropriate size. Instead of reaction with the ABn monomer 8, the activated dendrons, -OLG, were converted to a secondary amine which was used to form an amide bond with the acid chloride of the focal aromatic thiol, ***14****. i) THF, methylamine(aq), 60 °C, 2h. ii) 3 eq. Triethylamine, methylene chloride, 0 °C to RT, 12 h.*

2.2.3. Dendrimer Assembly Following Convergent Synthesis

After convergent synthesis of amphiphilic dendrons, **9d**, **10d**, **11d**, **12d**, and **13d,** iron-sulfur core dendrimers were assembled via ligand exchange reactions as reported by Smith et al.[69] The aromatic thiols were deprotected by refluxing with base under an N_2 blanket, followed by neutralization with 12N hydrochloric acid. The resulting dendrons were dried under vacuum and added inside an N_2 dry box to an iron-sulfur cluster dimethylformamide solution. In this fashion, PEG3-periphery G1, G2, and G3 iron-sulfur core dendrimers, **15**, **16**, and **17**, and triPEG3-periphery G1 iron-sulfur core dendrimers, **18**, were assembled. Physical observations (red-wine color and thiol odor), ^{1}H NMR spectra, and cyclic voltammetry indicated successful ligand exchange. The PEG3-dendrimers were also checked by MALDI-TOF.

Ligand exchange reactions were tried several times with the phenyl-benzenesulfonate dendron, **13d**, following the simultaneous basic deprotection/neutralization of both the focal aromatic thiol and the phenyl protected sulfonate "tips." These reactions had characteristic signs of success, (red-wine color and thiol odor) however, the dendrimers were found to be extremely unstable. The characteristic burgundy color of the iron-sulfur dendrimer faded, even when stored inside an N_2 dry box. It was not possible to collect ^{1}H NMR spectra of an intact dendrimer. While the possibility exists that acid was left in the flask after the initial deprotection steps, this does not seem likely given that other successful ligand exchange reactions that had been performed following the same protocol.

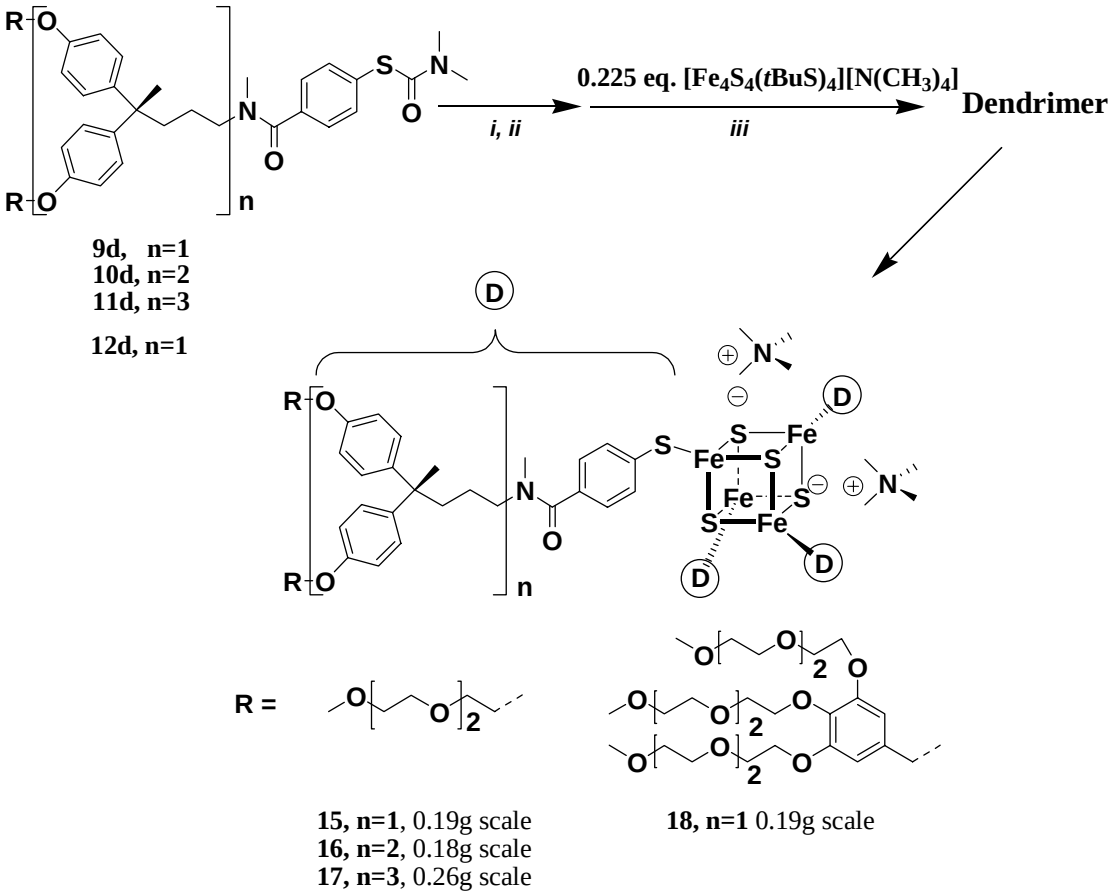


Figure 2.4 Ligand Exchange Reactions for PEG3 and triPEG3 Dendrimers

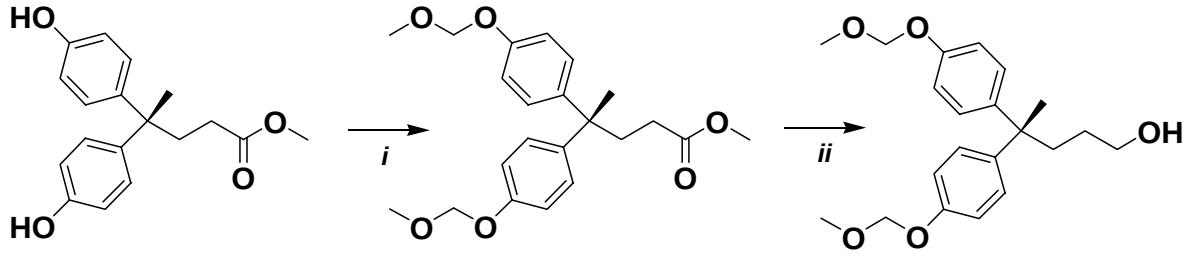
The dendrons were deprotected by basic reflux under a nitrogen blanket. After acid neutralization, the reactions were dried in a vacuum line and mixed with iron-sulfur cluster in DMF. A red-wine color and thiol smell indicated successful ligand exchange reactions. i) THF/methanol/water, 3 eq. sodium hydroxide, N_2, Δ, 12 h. ii) 3.1 eq. conc. HCl/THF. iii) N_2, RT, 5 mins.

2.3. Results - Modular Convergent Synthesis

While the PEG3-tipped dendrons were synthesized successfully via a convergent methodology, PEG12 and triPEG3 dendrimers were not. Difficulties with purification were encountered, when the length or number of polyethylene glycol tips on the dendrons was increased. Also the inefficiency of convergent strategy was evident since changing the "tips" of a dendron always required a completely new synthesis. To avoid the purification problems encountered and to increase the efficiency of the synthetic process, the new "modular" convergent synthetic scheme was adopted based upon MOM-protected phenols. Detailed synthetic procedures for the "modular" synthetic schemes were very similar to the procedures for the PEG3 convergent synthesis. (Appendix A)

2.3.1. Convergent Synthesis of MOM-Dendrons

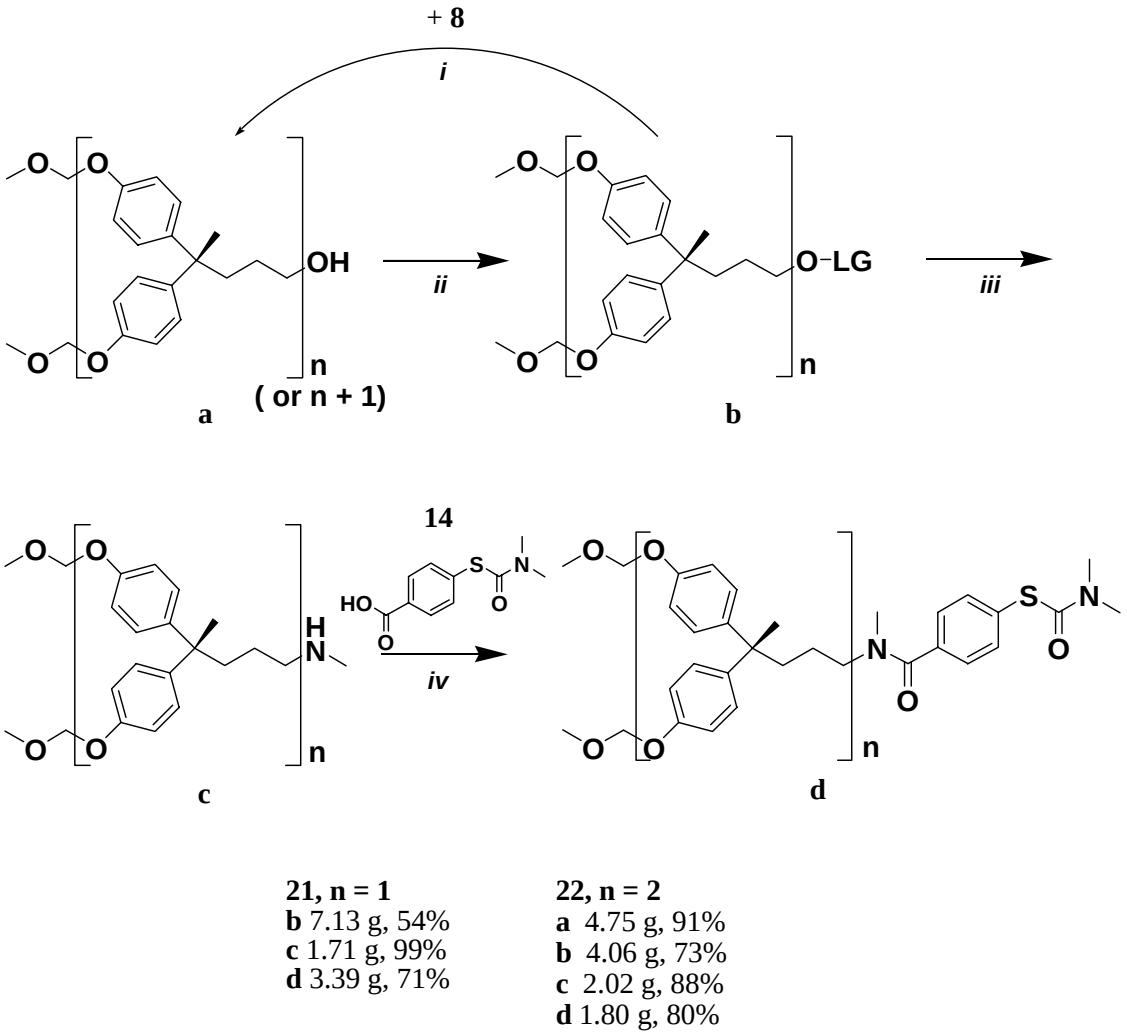
Direct protection of the phenol groups of the ABn monomer, **8**, with MOM groups was not possible without also protecting the aliphatic alcohol. Therefore, the phenols on the methyl ester, **19**, were protected by reaction with methoxymethyl chloride (Figure 2.5). The protected ester, **20**, was then reduced with lithium aluminum hydride to the alcohol, MOM-G1-OH, **21a**.



19 **20** 19.02 g, 70% **21a** 17.5 g, 99%

Figure 2.5 Synthesis of MOM G1 Alcohol
The phenol groups on the methyl ester were protected with the methoxymethyl groups (MOM) first. Reaction of the MOM-chloride with the ABn monomer, 8, would result in the protection of all alcohols. i) Methoxymethyl chloride, triethylamine, Δ, 48 hrs. ii) Lithium aluminum hydride, THF, 0 ^{o}C to room temperature, 2 hrs.

MOM-tipped G1 and G2 dendrons, **21d** and **22d**, were then synthesized from the MOM-G1-OH, **21a,** via the convergent methodology (Figure 2.6). Another change in the synthesis scheme was the use of N,N-dicyclohexylcarboxydiimide (DCC)-mediated amide formation for attachment of the thiocarbamate focal unit, **14**,. The DCC-mediated coupling reaction was easier than the acid chloride-based coupling reactions, produced better yields, and required less focal reactant, **14**.

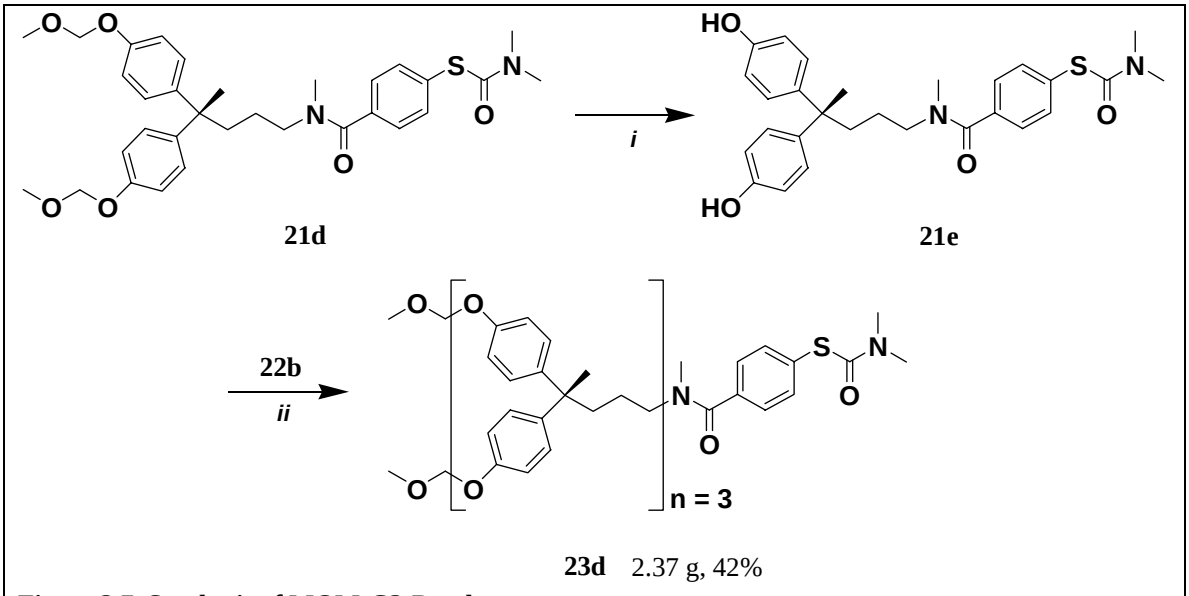


21, n = 1
b 7.13 g, 54%
c 1.71 g, 99%
d 3.39 g, 71%

22, n = 2
a 4.75 g, 91%
b 4.06 g, 73%
c 2.02 g, 88%
d 1.80 g, 80%

Figure 2.6 Convergent Synthesis of MOM-G1 and MOM-G2-Dendrons
MOM-protected G1 and G2 dendrons were made via convergent synthesis Compound number is derived from the generation, n, and identical focal groups across generations are indicated by letter, a, b, c, or d. ***i)*** *K_2CO_3, 18-crown-6, acetone, Δ, 12 hrs.* ***ii)*** *p-Toluenesulfonyl chloride, triethylamine, methylene chloride* ***iii)*** *Methylamine, 40% aqueous, THF, 60 ^oC, 4 hours.* ***iv)*** *1 eq.* ***14****, dicyclohexylcarbodiimide, dimethylaminopyridine (DMAP), methylene chloride, 2 hrs.*

The "modular" nature of the dendrons was then employed to synthesize the MOM-G3-Thiocabamate, **23d** (Figure 2.7). MOM-G1-Thiocarbamate, **21d**, was deprotected by refluxing in methanol/hydrochloric acid. After deprotection of the phenols, HO-G1-Thiocarbamate, **21e**, was coupled to MOM-G2-Tos, **22b,** to yield MOM-G3-Thiocarbamate, **23d**.



23d 2.37 g, 42%

Figure 2.7 Synthesis of MOM-G3-Dendrons
The MOM groups were removed and the resulting phenol groups were reacted with MOM-G2-Tos. i) *Methanol, 4 drops conc. hydrochloric acid, Δ, 2 hrs.* ***ii)*** *2.2 eq.* ***21b****, K_2CO_3, 18-crown-6, acetone, Δ 12 hrs.*

2.3.2. Adding "Tips" to the MOM-Dendrimers

With the MOM-dendrons, it was possible to incorporate novel tips that were not possible with the straight convergent methodology (Figure 2.8). MOM-G1, MOM-G2, and MOM-G3-Thiocarbamates, **21d**, **22d**, and **23d**, were deprotected and then coupled to new "tip" molecules using standard acetone/potassium carbonate S_N2 reactions. To insure complete reactions, the amount of "tip" reactant molecules was doubled, i.e. four equivalents

instead of two for a G1 dendron. Purification was not attempted for functionalized dendrons. Thus, once coupling of new "tips" was begun, the reaction mixtures were carried through deprotection to the ligand exchange reactions.

One problem encountered during the addition of activated dodecylethylene glycol tips, **2**, in the acetone/K_2CO_3 coupling reactions was clumping of the K_2CO_3. This clumping was possibly due to dodecylethylene glycol chains coordinating with the potassium ions. Similar clumping was also observed with triPEG3 "tips," but not to the extent observed with the dodecylethylene glycol tips. This problem was not observed with coupling reactions involving PEG3 "tips".

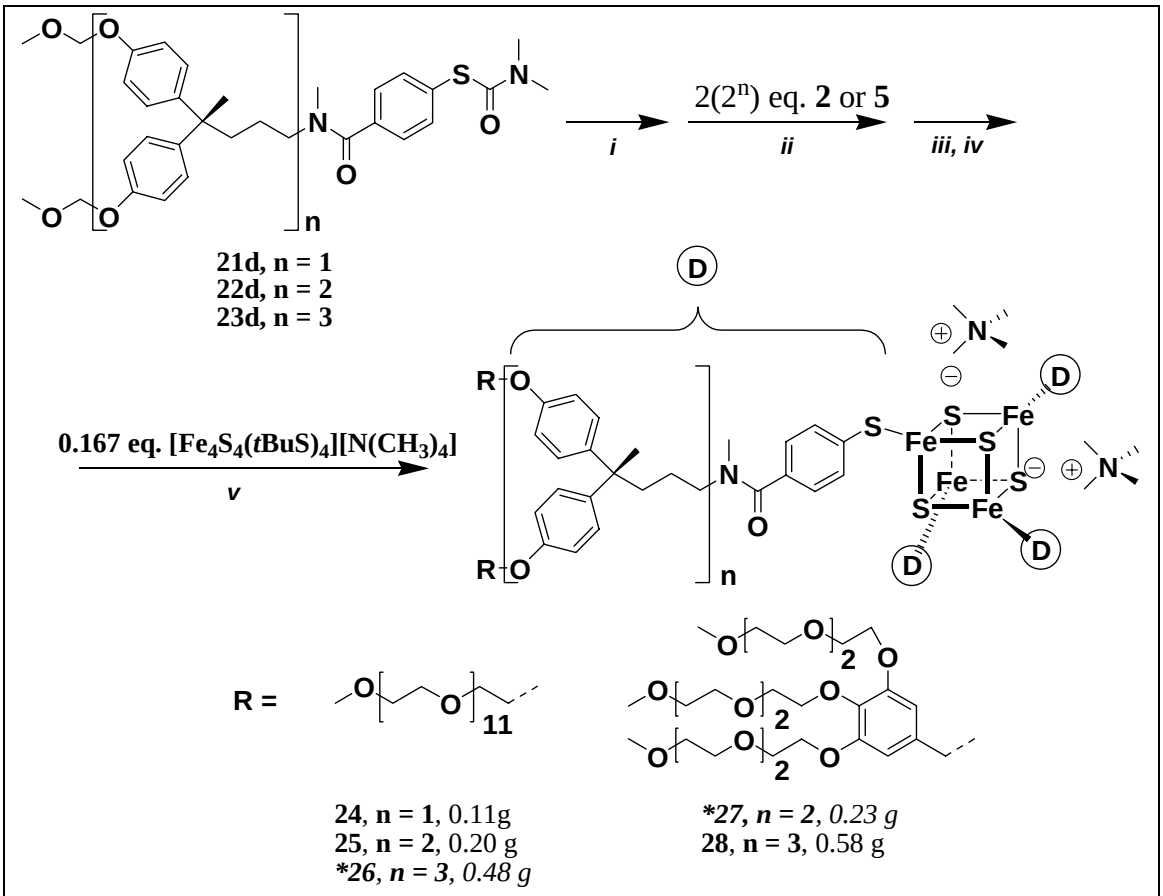


Figure 2.8 PEG12 and triPEG3 Dendrimer Assembly
*The purification of products and calculation of yields was not possible for the polyethylene tipped dendrons. Thus, scale of first reaction in the sequence is shown. The * indicates reactions that were tried but were unsuccessful.. i) Methanol, 4 drops conc. hydrochloric acid, Δ, 2 hrs. ii) K_2CO_3, 18-crown-6, acetone, Δ, 12 hrs.* ***iii****) THF/methanol/water, 3 eq. sodium hydroxide, N_2, Δ, 12 h.* ***iv****) 3.1 eq. conc. HCl/THF.* ***v****) N_2, RT, 5 mins.*

Using the products of the modular strategy, dodecylethylene glycol-tipped G1 and G2 dendrimers, **24** and **25**, and tri-triethylene glycol-tipped G3 dendrimers, **28**, were assembled. Reactions for the PEG12 G3 dendrimer and the triPEG3 glycol-tipped G2 dendrimers were attempted however assembly of the dendrimer was unsuccessful. These results emphasized the difficulties of working with these dendrons even with a synthetic strategy that was known to work.

2.4. Results - “Split-Tip” Dendrimers

The usefulness of a modular convergent strategy was further demonstrated in the synthesis of novel “split-tip” dendrimers. The synthetic work was performed by Peyton Hassinger with graduate supervision. These “split-tip” dendrimers were designed to be soluble in both aqueous and organic solutions and responsive to changing solution conditions. Zubarev and coworkers have reported Y-shaped and hexa-arm amphiphilic molecules with alternating polyethylene glycol and long chain aliphatic tips that are very responsive to solution conditions. [133-136]

The methyl ester, **19**, was reacted sequentially with one equivalent of methoxymethyl chloride and one equivalent of 1-bromoundecane to yield a ½ MOM, ½ undecane ester (Figure 2.9). This ester, **29**, was reduced to the alcohol, which was then carried through the same reactions as the MOM dendrons to yield a split-tip MOM-undecane G1 thiocarbamate, **34** (Figure 2.6).

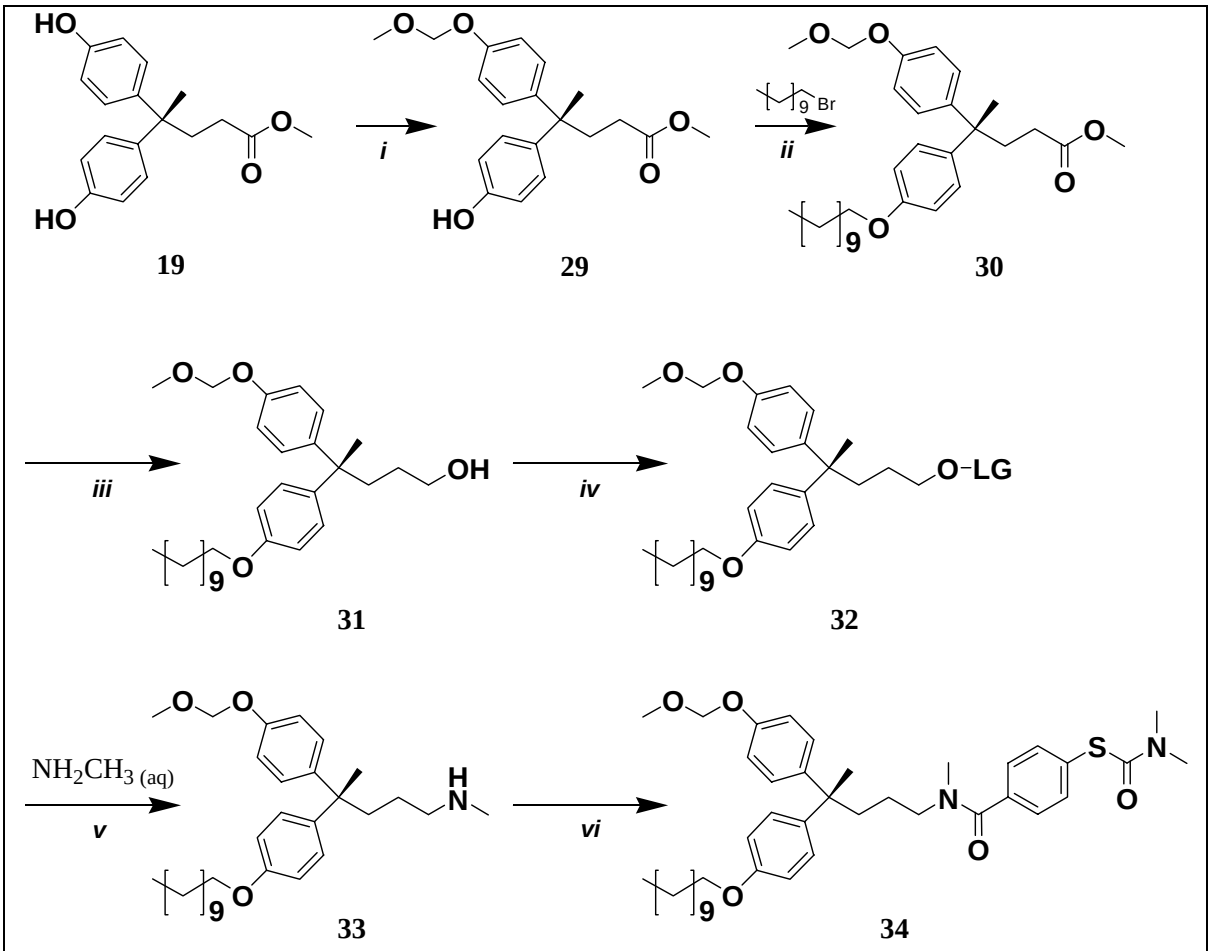


Figure 2.9 Synthesis of Generation 1 Half-MOM Dendrons

No yields have been calculated for this scheme. This synthesis was performed by P. Hassinger and is shown only to demonstrate the usefulness of the "modular" approach. i) Methoxymethyl chloride, triethylamine, Δ, 48 hrs. ii) K_2CO_3, 18-crown-6, acetone, Δ, 12 hrs. iii) Lithium aluminum hydride, THF, 0 °C to RT, 2 hrs. iv) p-Toluenesulfonyl chloride, triethylamine, methylene chloride, 0 °C v) Methylamine, 40% aqueous, THF, 60 °C, 4 hours. vi) Dicyclohexylcarbodiimide, dimethylaminopyridine, methylene chloride, 2 hrs., RT

Dendrimers were then prepared by removing the MOM group and reacting the free phenols with activated PEG12 tosylate, **2**. No purification was attempted after coupling of the "tips" and reaction products were carried directly to deprotection and ligand exchange. A first generation dendrimer was prepared using this scheme. (Figure 2.10)

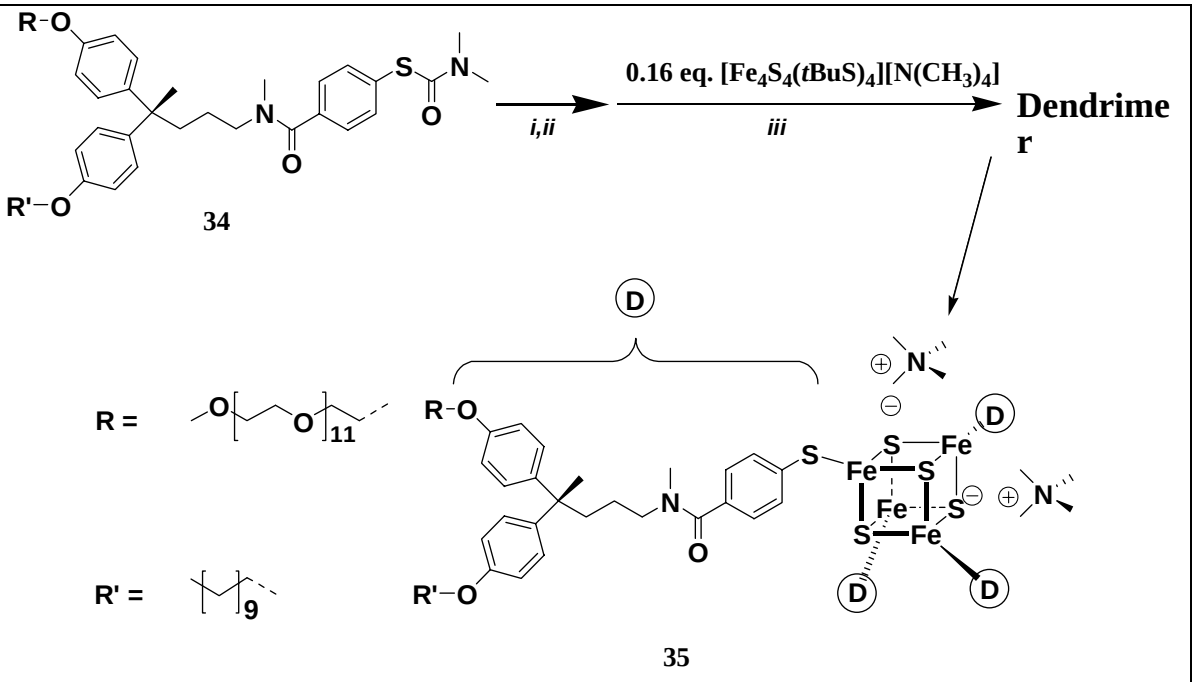


Figure 2.10 "Split-Tip" Dendrimer

The usefulness of the modular scheme was demonstrated by the synthesis the split-tip dendrons. Each dendron has alternating "tip" units. ***i****) NaOH, THF/H_2O, Δ ii) 1 eq. conc. HCl/THF* ***iii****) N_2, RT, 5 min*

2.5. Discussion - Dendron Synthesis and Purification

2.5.1. Convergent vs. Modular Synthesis

Iron-sulfur core dendrimers with triethylene glycol (PEG3) peripheries assembled via convergent methodology were not soluble in water. This result was unexpected given Diederich's success with triethylene tips.[75] There were significant structural differences between the these iron-sulfur core dendrimers and Diederich's dendrimers. Diederich's dendrimers possessed three times the number of triethylene glycol tips per generation with a polar interior matrix capable of forming hydrogen bonds. While the nature and number of periphery functional groups strongly influences dendrimer solubility, the polarity of the dendrimer interior also plays a significant role.

Alternative hydrophilic functional groups were tried as “tips” in order to assemble water-soluble iron-sulfur core dendrimers. Two problems were encountered.. Each new convergent synthesis, G1-3, required a significant investment in time, effort and money for each new “tip.” After the results obtained with the PEG3 tips, there was no assurance that new “tips” would impart water-solubility or if a certain size of dendrimer was necessary in order to be water-soluble. Second, the use of certain “tips” made it impossible to purify dendrons via column, precipitation, or crystallization during the convergent synthesis. It was not possible to carry the reaction mixtures forward without purification due to the repetition of reactions in the “activate/couple” cycle. A polydisperse mixture of partially substituted G2 and G3 dendrons would have resulted negating the strength of a convergent synthesis.

The “modular” convergent scheme was adopted to overcome these two problems. Generation 1 and 2 dendrons with methoxymethyl groups protecting the reactive phenols could be synthesized and purified via the convergent strategy insuring monodispersity and eliminating the need for a complete new synthesis for each new “tip”. The efficiency of the "modular" approach was seen in the ability screen a variety of tips after deprotection of the phenol groups and in the synthesis of the MOM-G3 dendrons (Figure 2.7).

PEG12 and triPEG3 dendrons, G1-3, were synthesized via this modular strategy and used in ligand exchange reactions to make amphiphilic iron-sulfur core dendrimers (Figure 2.8). The PEG12 dendrimers were found to be water-soluble at generation 1 and it was expected that the triPEG3 dendrimers would also prove to be water-soluble, based upon Diederich’s results and the solubility of the “tip” molecules **4** and **5**.[75] Further optimization of the “modular” convergent strategy was needed due to excess “tip” reactant molecules

remaining after the functionalization steps leading to dendrimer assembly. This excess “tip” reactant could react with the aromatic thiolate focal group produced during basic deprotection reactions (Figure 2.8). Such side reactions may have lead to the inability to produce PEG12 G3 dendrimer and triPEG3 G2 dendrimers. The excess “tip” reactant molecules also could not be removed from completed dendrimers via selective precipitation.. ^{1}H NMR spectra of crude reaction mixtures of dendrimers following a series of functionalization reactions possessed characteristic ^{1}H signal shifts due to pseudo-Fermi contacts with the paramagnetic iron-sulfur core. However identification of other signals was very difficult and the integration was not possible. It might be to use solid-phase substrates, such as polystyrene-phenol beads, as scavengers for excess "tip" reactants immediately prior to “focal” group deprotection.

2.6. Summary

The synthesis and assembly of amphiphilic iron-sulfur core dendrimers involved a much different strategy than originally envisioned. While the actual synthetic reactions were not difficult, the addition of tips that imparted water solubility in completed dendrimer made purification of dendrons impossible. In order to avoid this roadblock, the "modular" strategy was adopted in which the dendron tips were only added immediately before ligand exchange reactions leading to dendrimer assembly. While this methodology still possessed significant hurdles with regards to purification of the final product, it did prove to be a viable strategy to produce water-soluble iron-sulfur core dendrimers.

3. Electrochemistry of Amphphilic Dendrimers

3.1. Introduction

The effects of dendritic encapsulation on core molecules which have measurable properties have been reviewed in numerous papers. [6, 41-43, 53] Although dendrimers have been proposed as synthetic models for enzyme active sites with cofactors, there have been few actual studies of such dendrimers in aqueous solutions. [116, 121]The results of these reported studies, though, have been impressive and show many similarities to reactions in biological systems. Kaifer et al. demonstrated directional control of electron transfer for dendrimers in an aqueous systems.[71, 81] Vinogradov and coworkers have demonstrated pH–dependent shielding of Zn-porphyrins and site isolation of Pd-porphyrins and control of ligand binding in aqueous solutions by varying the hydrophobicity of the dendrimer interior.[58, 84] Diederich and co- workers have shown positive thermodynamic shifts in the redox potential of Fe(II) porphyrin core dendrimers in aqueous solutions.[75]

One particular core that has been studied extensively either as a cluster with small ligands or encapsulated in dendrimers is the iron-sulfur cluster. [6, 69, 77, 86, 95, 124, 137] These studies have elucidated structure-property relationships that affect the heterogeneous electron transfer kinetics of iron-sulfur core dendrimers in organic solutions.[6] Structure-property relationships for dendritic encapsulation that affect the thermodynamic redox potential are less-well understood.

Electrochemical studies of the iron-sulfur cluster are very important given its ubiquitous and vital role in biological systems. [138] An understanding of the structure-property relationships controlling the electron transfer kinetics and thermodynamic redox potentials of

iron-sulfur clusters represents a “holy grail” for the biological sciences. Much recent biochemical research has been conducted to understand structure property relationships concerning protein structure and thermodynamic redox potential of iron-sulfur clusters. [139-145] The synthesis of iron-sulfur clusters and iron-sulfur core dendrimers have been important steps in the development of model compounds to aid in the study of the electrochemistry of these clusters. All of this research has, however, been in organic solution, and currently, nothing is known concerning either the kinetics or potential of synthetic iron-sulfur cluster models in aqueous solutions.

Holm reports positive shifts in the redox potential of synthetic iron-sulfur clusters as the water content of organic solutions is increased.[95] Hydrogen bonding has been shown to cause redox potentials of iron-sulfur clusters to shift to more positive values.[140, 146] In contrast, point-mutation studies on iron-sulfur proteins are not as consistent with regards to redox potential shifts especially concerning increased water exposure.[1, 126, 147] We report here positive redox potential shifts in iron-sulfur clusters encapsulated by ethylene glycol periphery dendrimers.

3.2. Procedure

Cyclic voltammograms (CVs) were recorded for triethylene (PEG3), dodecylethylene (PEG12), and tri-triethylene (triPEG3) periphery iron-sulfur core dendrimers (1 mM) in dimethylformamide solution with tetraethylammonium tetrafluoroborate as the electrolyte (100 mM, recrystallized three times). The thermodynamic potentials of the dendrimers were measured against the Ag/Ag^+ standard used by Gorman et al.[69, 86] Electrochemical measurements were performed in a special, air-tight cell made from a 25 mL sample vial

(Fisher) with a open-top cap and a teflon/rubber septa with 5/16" and 3/16",holes for the electrodes (Figure 3.1). A platinum wire counter electrode was inserted through the septum using an 18 gauge needle.

Cyclic voltammetry measurements that involved addition of water to the DMF dendrimer solutions were performed with the cell. DMF solutions of dendrimer were prepared in a N_2 drybox. The cell was sealed and initial cyclic voltammograms of dendrimers in pure DMF solution were recorded. The entire cell was then removed from the N_2 drybox and aliquots of aqueous TEA BF_4 (100 mM, degassed by boiling and sparging through a septum with nitrogen) were added and cyclic voltammograms were recorded after each addition. Final percentages of water were 0, 3, 6, 9, 12, and 15% by volume. Only G1 dendrimers were used in such water addition experiments

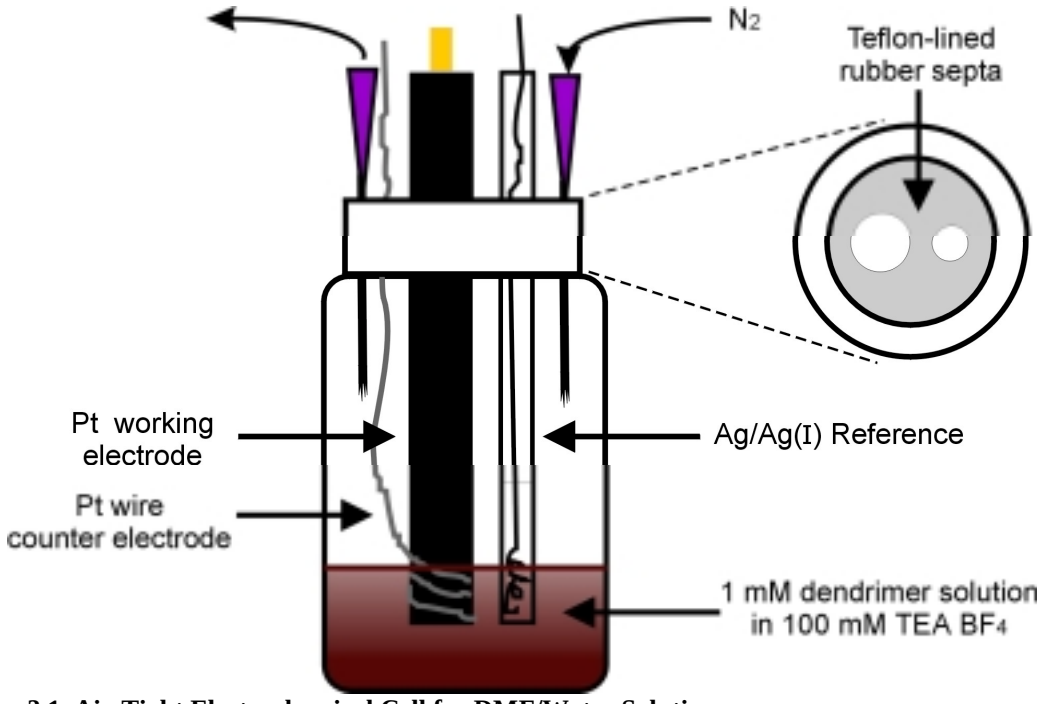


Figure 3.1 Air-Tight Electrochemical Cell for DMF/Water Solutions
This cell setup was used for the DMF/water solutions electrochemistry outside the N_2 drybox. It was also used for the electrochemistry of dendrimers in water.

3.3. Results

During initial cyclic voltammetry measurements in DMF, increases in redox potential were observed for PEG12 and triPEG3 periphery dendrimers when compared to corresponding generations of PEG3 periphery dendrimers. Upon the addition of aliquots of water to DMF solutions of PEG12 G1 and triPEG3 G1 dendrimers, degradation of the cyclic voltammetry wave was observed. No such degradation was observed for PEG3 G1 dendrimers.

3.3.1. Electrochemistry of Dendrimers in DMF solution

Cyclic voltammograms were recorded for 1 mM DMF solutions of PEG3 periphery dendrimers (Figure 3.2), PEG12 periphery dendrimers, (Figure 3.3) ,and triPEG3 periphery dendrimers (Figure 3.4). Individual pairs of redox peaks in each voltammogram were observed for each series of dendrimers indicating the presence of a single electroactive species in solution. Cyclic voltammograms of "Flex" G1 iron-sulfur core dendrimer and β-mercaptoethanol (BME) iron-sulfur cluster were include in each plot as references indicating the shift in thermodynamic redox potentials observed for each change in dendrimer size and periphery functional groups.

The measured redox potentials for the PEG3 dendrimers, generations 1-3 were slightly more negative than those reported for corresponding "flex" dendrimers as reported by Gorman et al (Table 3.1).[69] The decrease in the redox potential correlated to an increase in dendrimer generation and size. This behavior was analogous to that reported previously for the 'Flex' dendrimers.

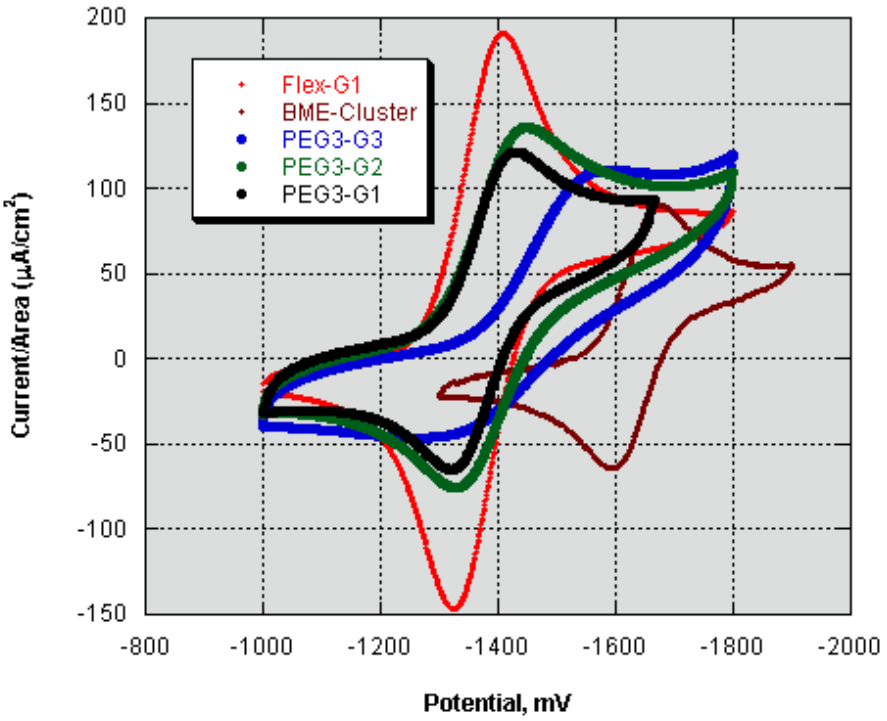


Figure 3.2 Cyclic Voltammograms of PEG3 Dendrimers
The redox potentials of generations 1,2 and 3 were measured. Solution conditions were 1 mM dendrimer with 100 mM TEA BF_4 in DMF. The scan rate was 100 mV/s.

From the cyclic voltammograms, an increase in redox potentials could be observed for the PEG12 G1 and G2 dendrimers (Figure 3.3). This shift correlated with increasing dendrimer generation and size and was opposite the shifts observed in the PEG3 series dendrimers and the reported 'Flex' dendrimers (Table 3.1).[69]

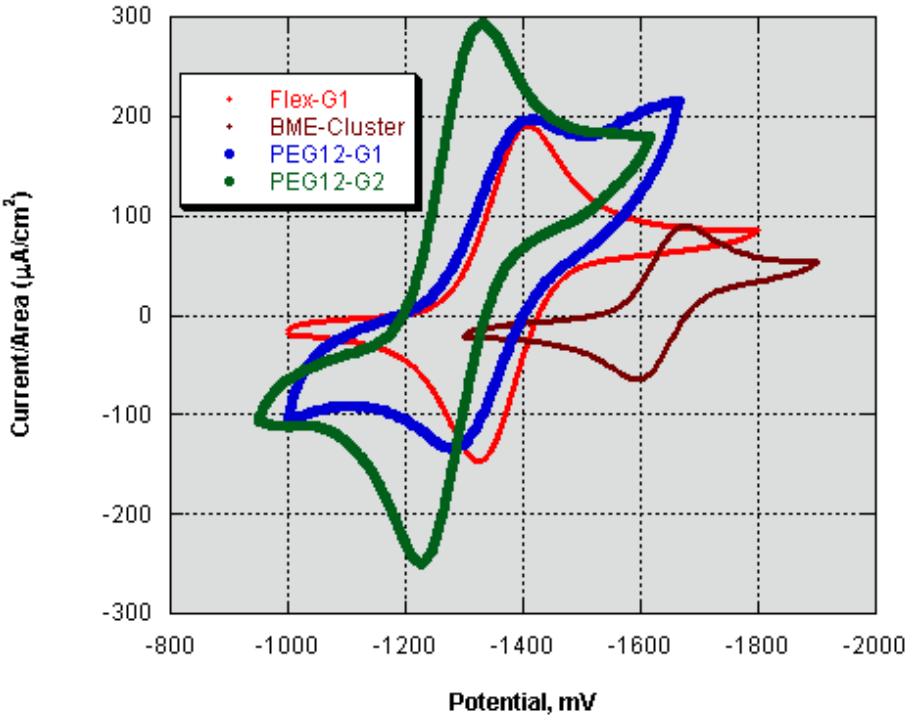


Figure 3.3 Cyclic Voltammograms of PEG12 Dendrimers
The redox potentials of generations 1 and 2 were measured. Solution conditions were 1 mM dendrimer with 100 mM TEA BF_4 in DMF. The scan rate was 100 mV/s.

Increases in the redox potential, relative to the "Flex" G1 dendrimer, and similar to those seen for PEG12 dendrimers were observed for the triPEG3 G1 and G3 dendrimers (Figure 3.4). This shift also correlated with increasing dendrimer generation and size. The increase in potential per generation for the triPEG3 dendrimers did not appear to be as great as that observed for the PEG12 dendrimers. While the PEG12 and triPEG3 G1 dendrimers had virtually identical redox potentials, the redox potential of the PEG12 G2 dendrimer measured more positive, (-1278.5 mV) than the triPEG3 G3 dendrimer, (-1292 mV) (Table 3.1).

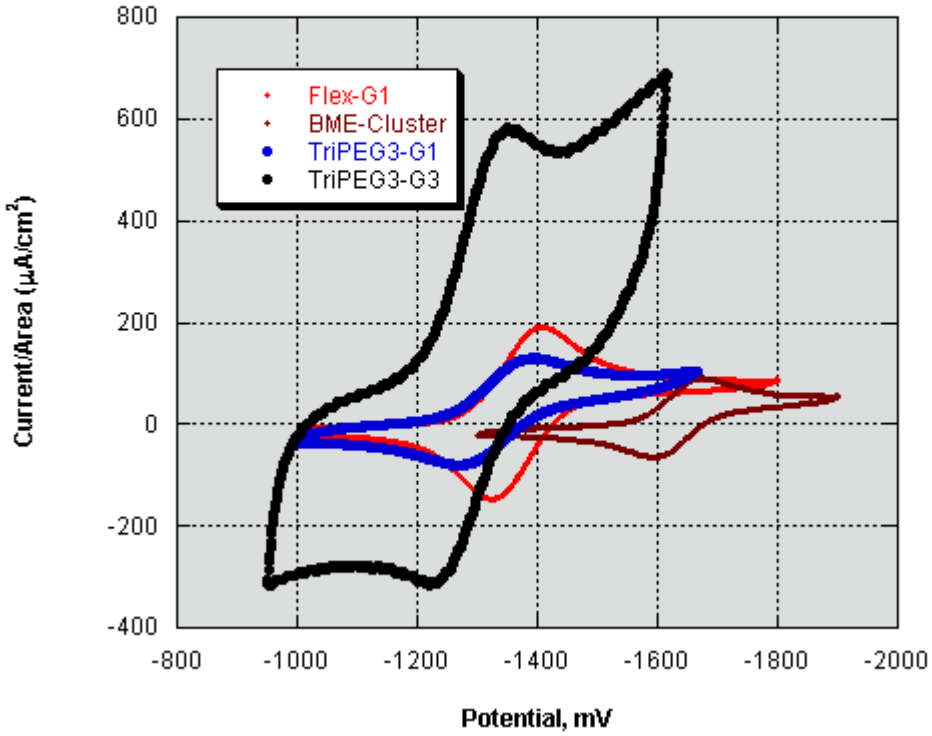


Figure 3.4 Cyclic Voltammograms of triPEG3 Dendrimers
The redox potentials of generations 1 and 3 were measured. Solution conditions were 1 mM dendrimer with 100 mM TEA BF_4 in DMF. The scan rate was 100 mV/s.

Thermodynamic Redox Potentials of Iron-Sulfur Core Dendrimers (1 mM in DMF, 100 mM TEA BF_4, 100 mV/s)				
Dendrimer	Anodic Peak (mV)	Cathodic Peak (mV)	Δ Peak (mV)	$E_{1/2}$ (mV)
PEG3 G1	-1321	-1430	-109	-1376
PEG3 G2	-1326	-1443	-117	-1384
PEG3 G3	-1268	-1588	-320	-1428
PEG12 G1	-1265	-1407	-142	-1336
PEG12 G2	-1226	-1331	-105	-1279
triPEG3 G1	-1273	-1396	-123	-1334
triPEG3 G3	-1302	-1350	-116	-1292
Flex G1				-1360
Flex G2				-1366
Flex G3				-1371

Table 3.1 Redox Potentials of Amphiphilic Iron-Sulfur Core Dendrimers in DMF

The redox potentials for the "Flex" series of dendrimers were derived from reported literature.

3.3.2. Addition of Water to Dendrimer DMF Solutions

Positive redox potential shifts were observed in cyclic voltammograms as the percentage of water was increased in the DMF solutions of PEG3, PEG12 and triPEG3 G1 dendrimers. The PEG12 and triPEG3 dendrimers appeared to be more sensitive to the addition of water than the PEG3 dendrimer.

A slight positive shift in the redox potential with each addition of water was recorded in the cyclic voltammograms of the PEG3-G1 dendrimer (Figure 3.5). Single peaks in the

cathodic and anodic waves indicated the presence of a single electroactive species throughout the experiment. Potentials were determined from raw data (Table 3.2).

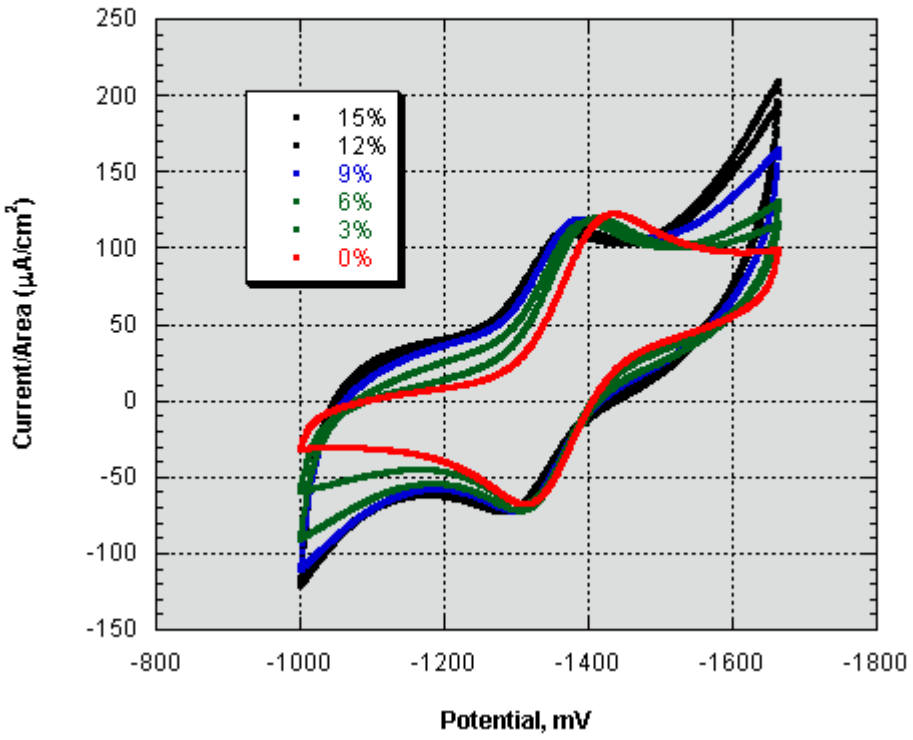


Figure 3.5 Addition of Water to triPEG3 G1 Dendrimer Solution

The redox potentials were measured as a function of the percentage water in solution. A second peak appears as the percent water increased. Initial solution conditions were 1 mM dendrimer with 100 mM TEA BF4 in DMF. The scan rate was 100 mV/s. Water was added as aqueous 100 mM TEA BF4 .

In contrast to the cyclic voltammograms recorded for the PEG3 dendrimer solution, second peaks in the anodic waves were recorded for the triPEG3 and PEG12 dendrimer solutions as the water percentage increased.(Figure 3.6) (Figure 3.7) For the triPEG3

dendrimer, the appearance of a second peak in the anodic wave occurred at 9% water indicated the presence of a second electroactive species with only a single peak was recorded for the cathodic wave. Potentials at 12 and 15% water had to be estimated from the cyclic voltammograms.(Figure 3.6)

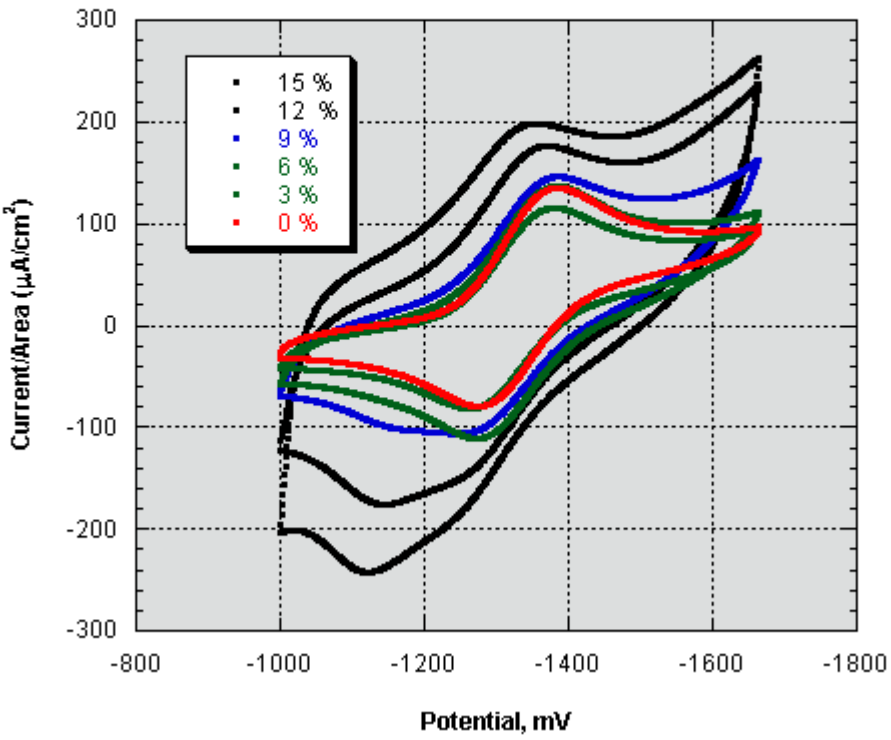


Figure 3.6 Addition of Water to triPEG3 G1 Dendrimer Solution
The redox potentials were measured as a function of the percentage water in solution. A second peak appears as the percent water increased. Initial solution conditions were 1 mM dendrimer with 100 mM TEA BF_4 in DMF. The scan rate was 100 mV/s. Water was added as aqueous 100 mM TEA BF_4 .

For the PEG12 dendrimer solutions, the second peak in the anodic wave was first recorded at 6% water compared to 9% for the triPEG3 G1 dendrimer. Only a single peak

was recorded for the cathodic wave. For the PEG12 dendrimer solutions, redox potential shifts had to be estimated from the cyclic voltammograms. (Table 3.2)

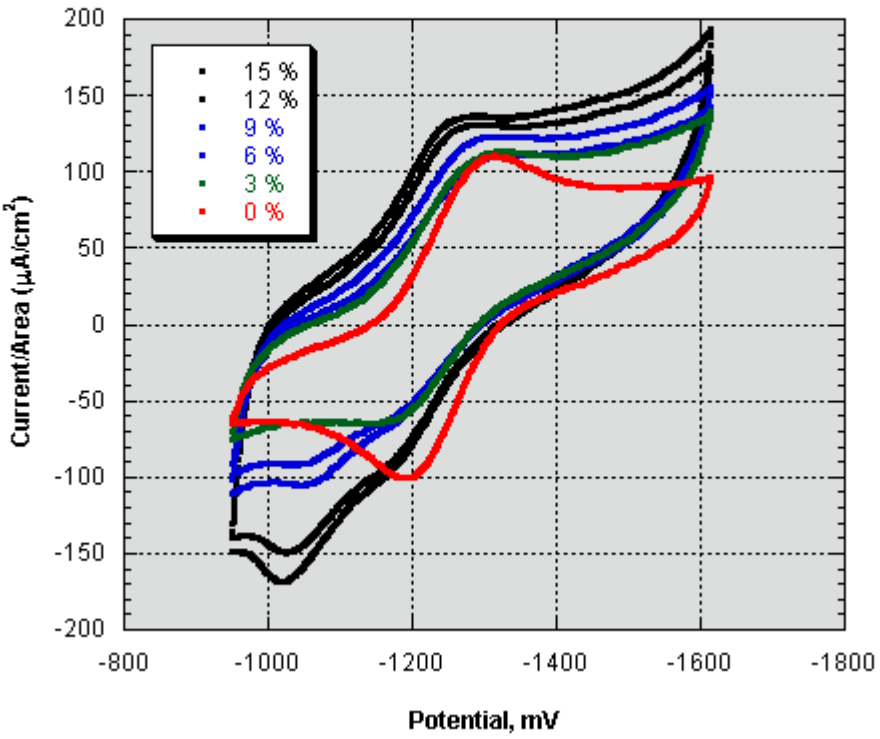


Figure 3.7 Addition of Water to PEG12 G1 Dendrimer Solution
The redox potentials were measured as a function of the percentage water in solution. A second peak appears as the percent water increased. Initial solution conditions were 1 mM dendrimer with 100 mM TEA BF_4 in DMF. The scan rate was 100 mV/s. Water was added as aqueous 100 mM TEA BF_4 .

Effect of Water on the Redox Potentials of Various Iron-Sulfur Core Dendrimers						
Periphery	Water, %	Cathodic (mV)	Anodic 1 (mV)	$E_{½}$ 1 (mV)	Anodic 2 (mV)	$E_{½}$ 2 (mV)
PEG 3	0	-1475	-1284	-1379.5	--	
	3	-1436	-1298	-1367	--	
	6	-1415	-1300	-1357.5	--	
	9	-1414	-1289	-1351.5	--	
	12	-1412	-1288	-1350	--	
	15	-1411	-1285	-1348	--	
triPEG3	0	-1380	-1274	-1327	--	
	3	-1381	-1264	-1322.5	--	
	6	-1384	-1273	-1328.5	--	
2^{nd} peak	9	-1385	-1258	-1321.5	-1186	-1285
	12	-1370	-1258	-1314	-1146	-1258
	15	-1355	-1247	-1301	-1123	-1239
PEG12	0	-1314	-1190	-1252	--	
	3	-1300	-1176	-1238	--	
2^{nd} peak	6	-1295	-1170	-1232.5	-1057	-1176
	9	-1283	-1170	-1226.5	-1051	-1167
	12	-1267	-1160	-1213.5	-1028	-1148
	15	-1262	-1160	-1211	-1023	-1143

Table 3.2 Redox Potentials of G1 Dendrimers in DMF/Water Solutions
Peak positions were determined from the raw CV data where possible. Peak positions for the Anodic 2 peak positions and Anodic peak 1 positions were estimated from the CV plots

3.4. Discussion

3.4.1. Positive Shifts of Iron-Sulfur Cluster Redox Potentials

While the measured redox potentials of the PEG3 dendrimers correlated well with the potentials reported by Gorman et al. for "flex" dendrimers, the positive shifts in the measured potentials for the PEG12 and triPEG3 periphery dendrimers were unexpected (Table 3.1).[69] These shifts for the PEG12 and triPEG3 dendrimers appeared to be related to the number or length of the polyethylene glycol tips. This indicated that the periphery functional groups were interacting in some unknown fashion with the iron-sulfur core. Coordination of the lone pairs of electrons of the oxygen atoms to the iron(II) and iron(III) ions in the cluster would be expected to decrease, not increase, the redox potential Point mutation studies of the 4Fe-forms of *P. furiosus* ferredoxin have shown that electron donation by coordinating ligands into an iron-sulfur center decreases the redox potential while electron withdrawal by coordinating ligands leads to a reduction in the potential.[147] Point mutation studies of *A. vinelandii* ferredoxin I have shown that introduction of positive dipoles in close proximity to the iron-sulfur cluster can cause a positive shift in the redox potential.[126] Holm et al. and Ueno et al. have shown that electron withdrawing groups result in positive shifts in synthetic iron-sulfur cluster models. [124, 146]

3.4.2. Water Access to the Iron-Sulfur Core

With two apparent anodic peaks in the triPEG3 and PEG12 G1 dendrimers, two separate redox potentials, E1 and E2, can be estimated from the cyclic voltammograms of the water addition experiments.(Figure 3.6)(Figure 3.7) The first potential, E1 , for the triPEG3 and PEG12 G1 dendrimers was calculated from the peak corresponding to the position of the

anodic peak in the PEG3 G1 dendrimer solution which was used as a reference. Using the PEG3 G1 dendrimer as a reference point, the potential shifts (31, 26, and 41 mV) correlated with the addition of water for all three dendrimer solutions. The relatively small increase in redox potential observed as the percent water increased does not match the reports of a +200 mV shift in 20% water/ DMSO solutions of iron-sulfur clusters by Holm et al.[148] Holm's experiments involved synthetic clusters that were less sterically hindered than the iron-sulfur core dendrimers and the relatively small potential shift observed here could be due to encapsulation of the cores by the hydrophobic dendrimer interiors.

Although encapsulation is generally thought to occur in dendrimers around generation 3, there are reports of differing behavior. Vinodgradov and co-workers report data indicative of encapsulation at generation 2.[84] In contrast, Kaifer and co workers and Balzani report in separate papers an apparent lack of encapsulation in generation 3 dendrimers.[72, 149] The second redox potential, E2, may be due to periphery of the PEG12 and triPEG3 dendrimers aiding the access of water molecules to the iron-sulfur cores. The size of E2, +108 mV for the PEG12 dendrimer and +87 mV for the triPEG3 dendrimer, would be closer to the +200 mV shift reported by Holm and coworkers. [95, 124] The difference could be attributed to the encapsulation effect of the hydrophobic interior of the dendrimers and a smaller number of water molecules with access to the core.

The size of the second peak in the anodic wave increases with higher water percentages with the effect being more pronounced and observed at a lower water percentage for the PEG12 dendrimer. This behavior would be expected if backfolding of the polyethylene glycol tips and interactions between water molecules and the hydrophilic tips

was necessary for access to the core. Individual triethylene glycol tips may not have been sufficiently long enough to facilitate water access to the core and greater numbers were required to achieve effects similar to those observed for individual dodecylethylene glycol tips.

Due to the synthetic methodology used to assemble these dendrimers, it was not possible to remove completely the excess reactants used to add the polyethylene glycol groups to the PEG12 and triPEG3 dendrimers. This excess material could have interacted with the iron-sulfur cluster. However, successful ligand exchange reactions were performed with these excess contaminants which were also present during the measurement of redox potentials in pure DMF solution. The effect, if any, of these contaminants is currently unknown. Further experiments without the excess polyethylene glycol material are desired but a methodology to successfully purify these particular dendrimers is not apparent.

3.5. Summary

Cyclic voltammetry experiments were performed to measure the thermodynamic redox potentials on a series of triethylene (PEG3) glycol periphery, dodecylethylene (PEG12) glycol periphery, and tri-triethylene (triPEG3) glycol periphery iron-sulfur core dendrimers in DMF solutions. Unexpected increases in redox potential were recorded for the PEG12 and triPEG3 series dendrimers. These increases in potential correlated with increasing size and differing periphery functionality. The addition of water to solutions of all three dendrimers also resulted in increased redox potentials but not to the extent reported in literature. The small increase in redox potential may be evidence of dendritic encapsulation at

G1 and longer or more numerous polyethylene glycol tips may be able to overcome the encapsulation effect.

4. Conclusions

Two of the three goals of this research project were accomplished. A synthetic scheme by which the tips of the "flexible" dendrons could be modified with hydrophilic functional groups was developed (Figure 1.15). Initial testing indicated success in terms of water-solubility. Initial characterizations of the iron-sulfur core dendrimers by cyclic voltammetry in dimethyl formamaide (DMF) and DMF/water mixtures performed. It was not possible to determine whether or not size changes occurred in the dendrimers. However, interesting shifts in the redox potential were observed. These shifts merit further investigation since the lack of observed shifts in the original electrochemistry was a motivating factor for this research. Electrochemistry on aqueous solution of the iron-sulfur core dendrimers was tried however no anodic or cathodic peaks were recorded in the cyclic voltammograms. The inability to complete all three goals was a source of frustration. The synthetic work took far longer than anticipated. The anecdote below provides a glimpse of the difficulties

4.1. Difficulties With Water-Soluble Iron-Sulfur Core Dendrimers

The difficulties of this project can be illustrated with a brief description of the synthesis and assembly of the PEG3 periphery dendrimers. The convergent synthesis of these dendrimers went well. However, the dendrimers were not water-soluble. The analysis below offers a glimpse into the thought processes and synthetic work that had to be done in order to overcome the difficulties. This account covers only one of the stumbling blocks encountered during this research.

The PEG3 G1 dendrons were initially synthesized via convergent methodology and the PEG3 G1 dendrimers were assembled via ligand exchange with the iron-sulfur clusters as outlined (Chapter 2). Diederich had successfully used the triethylene glycol tips with heme core dendrimers. When tested, the PEG3 G1 dendrimers were not water-soluble. Three rationales for the lack of water solubility were considered: 1) the hydrophobic nature of the dendrimer interior matrix counteracted the hydrophilic nature of the "tips", 2) the solubility constant of the iron-sulfur dendrimer and its "greasy" tetra-n-butyl ammonium counterions was too low, 3) the relatively short length of the triethylene glycol tips was not sufficient to solubilize the dendrimer. Alteration of the dendrimer interior matrix was not an option since that would require a completely new synthetic scheme and would make any comparisons to previous iron-sulfur core dendrimers impossible. Thus, the decision was to alter the counterion and polyethylene glycol tip length.

New iron-sulfur cluster with tetramethylammonium counterions was synthesized for ligand exchange reactions with PEG3 G1 dendron. This change initially appeared to be effective. The resulting dendrimers had very nice ^{1}H NMR spectrum in DMF-d6 and appeared to be soluble in deuterium oxide. However, there was a distinct color change from burgundy to green and not signal shift due to pseudo-Fermi contacts was observed in the ^{1}H NMR spectrum. They were not soluble in aqueous 100 mM tetraethylammonium tetrafluoroborate either, precluding any possibility of electrochemistry. After discussion of these problems, PEG3 G2 and G3 dendrimers were assembled with the expectation that increasing dendrimer size with the associated increase in number of PEG3 tips would eventually lead to water solubility. This expectation was not fulfilled as neither the G2 nor

G3 dendrimers were soluble in water. Thus, a large amount of synthetic work was performed to arrive at a dead end. Dr. Christopher Gorman was fond of quoting a former graduate student from another group: “Seventy-two steps of synthesis and the ring won’t close”

4.2. General Comments on Ligand Exchange and Characterization of Dendrimers

All successful ligand exchange reactions were initially identified by a color change and a characteristic odor. A solution of iron-sulfur cluster in DMF was green-black in color. Upon addition of any aromatic thiol, there was an almost instantaneous color change in the solution from the green-black to wine-red with a simultaneous release of 2-methyl-2-propane thiol. The smell of 2-methyl-2-propane thiol was quite potent and the molecule itself was toxic. Thus, all ligand exchange reactions were carried out either in a hood, on a vacuum double manifold line with the vacuum pump venting into a hood, or in the N_2 drybox. Even with such measures, the characteristic odor was unmistakable. Frequent vacuum pump oil changes and regenerations of the N_2 drybox were necessary.

The observation of the color change and a strong thiol odor in a ligand exchange, the reaction solvent, usually DMF, would be removed by placing the Schlenk flask under vacuum on the double vacuum manifold. Upon removal of all solvent a dark red residue would be left in the flask, and a ^{1}H NMR spectrum would be collected on this residue. The iron-sulfur cluster used in these reactions was paramagnetic and thus, the aromatic protons adjacent to the cluster were subject to the effects of pseudo-Fermi contacts. In the ^{1}H NMR spectra, these were observed as chemical shifts downfield for protons in the ortho- position and upfield for the meta- position. These proton signals were also broadened which led to their designation as “lumpies.”

As stated above, one of the difficulties with the "modular" convergent strategy was that purification was impractical once the MOM groups were removed from the dendrons and coupling of new "tips" was begun. Assessment of the efficacy of the "tip" coupling reactions and the deprotection reactions was not possible. In order to insure complete dendrimers were formed several assumptions were made. First, an excess of "tip" molecules, 2 equivalents instead of 1 for every free phenol , was used to insure complete reactions of the dendrons in the coupling reactions (Figure 2.8). In addition, the thiol deprotection reaction was assumed to be 80% effective based upon Chen's original yields.[87] The amount of cluster used in the ligand reactions was calculated from the original amount of MOM protected dendron when a "tip" functionalization/focal deprotection/ligand exchange reaction sequence was begun. The target ratios were 6 equivalents of dendron to 1 equivalent of cluster. Ratios less than 6 to 1 gave poor results with the ligand exchange reactions.

As a final characterization, cyclic voltammograms were recorded for 1 mM dendrimer solutions in DMF with 100 mM TEA BF_4 as an electrolyte. A single clean voltammetric wave in conjunction with the other characteristic signatures (color, odor, spectrum) was interpreted as a single electroactive species in solution and therefore a successful ligand exchange.

5. Appendix A – Synthetic Procedures

5.1. Triethyleneglycol and Dodecylethylene Monomethyl ether Toluene Sulfonate

The procedure for the activation of the aliphatic alcohol was similar for both triethylene monomethyl ether and dodecylethylene monomethyl ether [131]. Triethylene glycol, monomethyl ether (20.03 g, 0.122 moles) was dissolved in 30 mL of THF and cooled to 4 ^{o}C. Aqueous sodium hydroxide (20 mL, 12 N) was slowly added and two distinct layers formed in the round bottom flask. *p*-Tosyl chloride (22.2 g, 0.117 moles) was added and mixture was allowed to stir for 2 hours at 4 ^{o}C. The reaction mixture was diluted with 600 ml of diethyl ether and the organic and aqueous phases were separated. The organic phase was then extracted repeatedly with DI water until the aqueous phase no longer registered as basic to pH paper. The organic phase was dried with magnesium sulfate and the solvent removed under reduced pressure via rotary evaporation. The desired product PEG3-Tos, **1**, was a clear, colorless syrup (31.7g, 0.10 moles, 85% yield).

The activation of the dodecylethylene monomethyl ether (23.3 g, 0.042 moles) used 10 mL of 5 N NaOH(aq) as the base and the reaction was allowed to proceed overnight. The reaction mixture was diluted with ethyl acetate due to the difference in solubilities between triethylene and dodecylethylene monomethyl ethers. The extraction and drying steps were identical. The product PEG12-Tos, **2**, was a clear, pale green syrup (26.8g, 0.038 moles, 96% yield). The dodecylethylene glycol *p*-toluene sulfonate was very hygroscopic.

Triethylene Glycol Monomethyl Ether Toluene Sulfonate (PEG3-Tos), **1**:
^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.37 (s, 3H), 3.52 (t, 2H, J = 6 Hz), 3.59 (m, 2H), 3.68 (t, 2H, J = 6 Hz), 4.16 (t, 2H, J = 6 Hz), 7.34 (d, 2H, J = 9 Hz), 7.80 (d, 2H, J = 9 Hz)
^{13}C NMR ($CDCl_3$) δ 21.46, 58.80, 68.45, 69.21, 70.33, 70.50, 71.71, 127.77, 129.73, 132.79, 144.71
FT-IR (cm^{-1}) 2876, 1451, 1355, 1176
EA Theoretical C(52.81) H(6.96) O(30.15) S(10.07) Actual C(52.90) H(6.85) S(10.07)

Dodecylethylene Glycol Monomethyl Ether Toluene Sulfonate (PEG12-Tos), **2**:
^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.37 (s, 3H), 3.52 (t, 2H, J = 6 Hz), 3.59 (m, 2H), 3.68 (t, 2H, J = 6 Hz), 4.16 (d, 2H, J = 6 Hz), 7.34 (d, 2H, J = 9 Hz), 7.80 (d, 2H, J = 9 Hz)

5.2. Methyl 3,4,5-tris(Triethylene Glycol Monomethyl Ether)Benzoate

In a clean, oven dried 250 mL round-bottom flask, PEG3-Tos, **2**, (15.73g, 0.0494 mole) was combined with methyl 3,4,5-trihydroxybenzoate (2.90g, 0.0157 mole, RS I 80) in 50 ml of HPLC-grade acetone. The reaction mixture was allowed to reflux overnight with potassium carbonate (12.8 , 0.0942 mole) and 18-crown-6 (0.41g, 0.00157 moles). The following morning, the solids were removed via filtered and the reaction was diluted with 200 ml of ethyl acetate. The organic phase was extracted twice with aqueous 2N sodium hydroxide. The aqueous phase was retained and extracted twice with methylene chloride. All organic phases were combined, dried over magnesium sulfate, and the solvents removed under reduced pressure via rotary evaporation. The clear syrupy product triPEG3 Ester, **3**, (8.53 g, 0.0137 mole, 87% yield) was applied to a Biotage 40M silica cartridge, washed with a mixture of methylene chloride/ tetrahydrofuran/ methanol (94:5:1) and eluted with a mixture of methylene chloride/ tetrahydrofuran/ methanol (93.3:5:1.7).

Methyl 3,4,5-tris(Triethylene Glycol Monomethyl Ether) Benzenoate (triPEG3 Ester), **3**:
^{1}H NMR($CDCl_3$) δ 2.45 (s, 3H), 3.37 (s, 3H), 3.52 (t, 2H, J = 6 Hz), 3.59 (m, 2H), 3.68 (t, 2H, J = 6 Hz), 4.16 (d, 2H, J = 6 Hz), 7.34 (d, 2H, J = 9 Hz), 7.80 (d, 2H, J = 9 Hz)
^{13}C NMR($CDCl_3$) δ 5.95 (br, 8H),
EA $C_{29}H_{50}O_{14}$ Theoretical C(55.94) H(8.09) Actual C(55.63) H(8.09)

5.3. 3,4,5-tris(Triethylene Glycol Monomethyl Ether) Benzyl Alcohol

In a clean, oven dried 500 mL Ehrlenmeyer flask, triPEG3 ester, **3**, (7.46 g, 0.0120 mole) was dissolved in 100 ml of dry THF and cooled to 0 ^{o}C. Dry powdered lithium aluminum hydride (LAH) (0.91g, 0.024 mole) was slowly added by spatula (approximately 15') to the vigoruosly stirring solution. After complete addition of the LAH, the reaction was allowed to warm slowly to room temp and stir overnight. The extra time was not really necessary since the reaction was complete after two hours. The reaction was quenched by the addition of water (1 ml/1g of LAH) followed by 2N sulfuric acid (25 ml/g of LAH). The aqueous and organic layers were separated and the organic phase was diluted with ethyl acetate (or methylene chloride) and extracted with water. The addition of extra organic solvent was very important. The presence of three triethylene glycol chains combined with a benzyl hydroxyl group made the product, **4**, very amphiphilic. Unless the organic phase was diluted with ethyl acetate prior to extraction with water, no phase separation would occur in the separatory funnel. The two aqueous phases were combined and extracted five with 100 ml portions of ethyl acetate or methylene chloride. All organic phases were combined, dried over magnesium sulfate, and the solvents removed under reduced pressure via rotary evaporation. The product triPEG3 benzyl alcohol, **4**, (6.69g, 0.0112 mole, 93% yield) was recovered as a clear syrup.

3,4,5-tris(Triethylene Glycol Monomethyl Ether) Benzyl Alcohol (triPEG3 OH), **4**:
^{1}H NMR($CDCl_3$) δ 3.37 (s, 9H), 3.51-3.75 (m, 24H), 3.78 (t, 2H, J = 6 Hz), 3.85 (t, 4H, J = 6 Hz) 4.14 (t, 2H, J = 6 Hz), 4.16 (t, 4H, J = 6 Hz) 4.56 (s, 2H),6.61 (s, 2H) ^{13}C NMR ($CDCl_3$) δ 59.24, 69.00, 70.00, 70.71, 70.91, 70.97, 72.12, 72.45, 106.70, 136.98, 152.86, 163.26 FT-IR (cm $^{-1}$) 3490, 2923, 2876, 1112

EA $C_{28}H_{50}O_{13}$ Theoretical C(56.55) H(8.47) O(34.97) Actual C(56.27) H(8.57)

5.4. 3,4,5-tris(Triethylene Glycol Monomethyl Ether) Benzyl Bromide

The benzyl bromination of triPEG3 benzyl alcohol was virtually identical to the procedure used by Dr. Tyson Chasse [86]. This bromination reaction was always carried out immediately prior to a coupling reaction in which triPEG3 tips would be added to a molecule.

In a clean, oven dried 50 mL round-bottom flask, triPEG3 benzyl alcohol, **4**, (0.52g, 0.00087 mole) was dissolved in 5 mL of dry THF and cooled to 4 ^{o}C. Phosphorous tribromide, PBr_3, (0.094 g, 0.00035 mole) was added and the reaction was allowed to stir for 1 hour at 4 ^{o}C. The addition of the PBr_3 was very tricky due to the small amounts, the reactivity of the compound, and its density. The progress of the reaction was very difficult to follow since the presence of the trithylene glycol chains on both the benzyl alcohol, **4**, and the benzyl bromide, **5**, resulted in very little difference in Rf values when checked by TLC. Methylene chloride/THF (60:40) was the best eluent. After one hour, the reaction was diluted with ethyl acetate and washed three times with 25 mL of saturated aqueous sodium bicarbonate solution. The aqueous portions were combined and washed repeatedly with 50 mL portions of methylene chloride. The extraction with the methylene chloride was very important since the presence of three triethylene glycol chains made the product triPEG3 benzyl bromide, **5**, very amphiphilic. The triPEG3 benzyl bromide, **5,** was purified with a quick silica plug column using methylene chloride/THF (60:40) and was recovered as a clear, thick syrup (0.57 g, 0.0087 mole, 100 % yield). Analysis of the product via ^{1}H NMR was difficult as it was found that the chemical shift of the benzyl protons for the alcohol, **4**, and the bromide, **5**, were almost identical.

5.5. Phenyl Toluene Sulfonate

In a clean, oven dried 1000 mL round-bottom flask, phenol, 34 g (0.41 mol) and potassium carbonate 84 g (0.62 mol) were combined in 500 mL of methylene chloride and cooled to 0 ^{o}C. Para-toluene sulfonyl chloride, 98 g (0.52 mol) was dissolved in 50 mL of methylene chloride and added slowly, with vigorous stirring, to the phenol/K_2CO_3 slurry. Due to the lowered temperature, the slurry tended to clump and it was necessary to continually break clumps. The reaction was allowed to warm slowly to room temperature and proceed overnight. The following morning, the reaction was extracted repeatedly with deionized water until no more solid was evident, followed by a single extraction with brine. The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure via rotary evaporation. The resulting white solid product, **6**, was recrystallized from methylene chloride by the addition of hexane and cooling to 4^{o}C.

Phenyl Toluene Sulfonate, **6**:
^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H) 6.97 (d, 2H, J = 9.0 Hz), 7.25-7.31 (m, 3H), 7.69 (d, 2H, J = 9.0 Hz)

5.6. Phenyl α-Bromotoluene Sulfonate

In a clean, oven dried 1000 mL round-bottom flask, phenyl toluene sulfonate, **6,** 82 g, was dissolved in 250 ml of methylene chloride and mixed with N-bromosuccinimide, 58 g, (recrystallized from hot water, vacuum dried). The reaction mixture was heated to 60 ^{o}C to increase the solubility of N-bromosuccinimide in methylene chloride. The reaction was initiated by the addition of a few grains of recrystallizeed AIBN and the mixture was allowed to reflux overnight. Solid crystals of succinimide formed in the bottom of the flask and the solution turned an orange color characteristic of the formation of small amounts of bromine.

The reaction solution was diluted with methylene chloride and extracted twice with aqueous 1 N sodium hydroxide and once with 1 N hydrochloric acid. The organic phase was dried with magnesium sulfate and the solvent was removed under reduced pressure via rotary evaporation. Attempts were made to recrystallize the resulting white solid ethyl acetate by the addition of hexane (1EA:9H). A mixture of fine white crystals consisting of unreacted starting material, **6** (15%), monobrominated product, **7** (72%), and dibrominated side product, **7a** (13%) was recovered. The molar ratios were determined by integration of the benzyl proton signals of each species.

Phenyl α-Bromotoluene Sulfonate, **7**:
^{1}H NMR ($CDCl_3$) δ 4.51 (s, 2H), 6.97 (d, 2H, J = 9.0 Hz), 7.25-7.31 (m, 3H), 7.53 (d, 2H, J = 9.0 Hz) 7.80 (d, 2H, J = 9.0 Hz)

5.7. Deprotection MOM-Gx-Thiocarbamate

The removal of methoxymethyl (MOM) protecting groups from the phenols of the MOM-Gx-thiocarbamates was very straightforward. The thiocarbamate was dissolved in methanol and refluxed with 3 or 4 drops of concentrated hydrohcloric acid for 1 hour. The product was used without purification. This reaction cannot be carried out using THF as a solvent.

5.8. Coupling of Phenyl α-Bromotoluene Sulfonate to 4,4'-(bis-phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate

This reaction coupled the phenyl sulfonate tips to the triOH monomer, **8,** and could be used with the deprotected phenols from the MOM-Gx_thiocarbamates, **21d**, **22d** or **23d**. Amounts of reactants would have to be adjusted appropriately.

In a clean, oven dried 500 mL round-bottom flask, triOH monomer, **8**, (31.1g, 0.114 moles) was combined with the phenyl sulfonate tip mixture, **6**, **7** and **7a** (81.8 g 0.25 moles) in 250 ml of HPLC-grade acetone. The amount of the phenyl sulfonate tip mixture was determined from the molar ratio of the mono-brominated **7** to the unbrominated **6** and the dibrominated side product **7a** in the tip mixture. Oven dried potassium carbonate (77.5 g 0.57 mol) and 18-crown-6 (2.90 g 0.011 mol) were added and the mixture was refluxed overnight. After refluxing, the solid was filtered and the solvent was removed under reduced pressure via rotary evaporation. The white solid was resuspended in 500 ml of ethyl acetate and extracted with 200 ml of 2N aqueous sodium hydroxide. The organic portion was dried over magnesium sulfate and the solvent removed by rotary evaporation. The product, **13a**, was purified using a large silica column, 85 mM ID, packed with eight inches of silica gel over a one inch bed of sand. A layer of one inch of sand also covered the top of the silica bed. Product, **13a**, would be applied to the sand and allowed to soak into the top of the silica bed. The column was washed with methylene chloride and the desired product eluted with methylene chloride/10% ethyl acetate.

Phenylsulfonate-G1-OH, **13a**
F^1H NMR($CDCl_3$) δ 1.27-1.40 (m, 2H), 1.61 (s, 3H) 2.10-2.15 (m, 2H), 3.60 (t, 2H, J = 6 Hz), 5.12 (s, 4H), 6.87 (d, 4H,J = 9 Hz), 6.98 (d, 4H, J = 8 Hz), 7.12 (d, 4H, J = 9Hz), 7.24-7.30 (m, 6H), 7.58 (d, 4H, J = 9 Hz), 7.83 (d, 4H, J = 9 Hz)
^{13}C NMR ($CDCl_3$) δ 28.00, 28.31, 38.13, 44.93, 63.45, 68.86, 114.32, 122.45, 127.36, 127.57, 128.54, 128.87, 129.83, 134.66, 142.82, 144.40, 149.65, 156.16

5.9. Coupling of PEG3-Tosylate to 4,4'-(bis-Phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate

This general reaction coupled triethylene glycol tips to the triOH monomer, **8,** or to the deprotected phenols from the MOM-Gx-thiocarbamates, **21d**, **22d** or **23d.** In a clean,

oven dried 250 mL round-bottom flask, triOH monomer, **8**, (4.84 g, 0.018 mol) was combined with the PEG3-tosylate, **2**, (11.92 g, 0.037 mol) in 50 ml of HPLC-grade acetone. Oven dried potassium carbonate (12.2 g 0.0.090 mol) and 18-crown-6 (0.47 g 0.0018 mol) were added and the mixture was refluxed overnight. The following day, the solid was filtered, rinsed, and the solvent was removed under reduced pressure via rotary evaporation. The clear syrup was resuspended in 500 ml of ethyl acetate and extracted with 200 ml of 2N sodium hydroxide$_{(aq)}$. The organic portion was dried over magnesium sulfate and the solvent removed by rotary evaporation. The clear, colorless syrup, **9a**, was purified from the golden crude by elution (DCM/ 3% methanol) from Biotage 40M silica cartridge.

This same procedure could also be used to couple the PEG12-Tos, **2**, to the triOH monomer, **8**, or the ester that was the precursor to **8**. However, Purification was not possible for the products of either reaction. The addition of PEG12 to any molecule eliminated the use of silica columns for purification.

PEG3-G1-OH **9a**
^{1}H NMR($CDCl_3$) δ 1.31-1.35 (m, 2H), 1.56 (s, 3H) 2.05-2.09 (m, 2H), 3.36 (s, 6H), 3.52-3.57 (m, 8H, J = 6 Hz), 3.62-3.67 (m, 8H, J = 6 Hz), 3.71 (t, 4H), 3.82 (t, 4H, J = 6 Hz), 4.08 (t, 4H, J = 6 Hz) 6.78 (d, 4H, J = 9.0 Hz) 7.06 (d, 4H, J = 9.0 Hz) ^{13}C NMR($CDCl_3$) δ 28.05, 28.42, 38.15, 44.84, 59.18, 63.53, 67.41, 69.91, 70.70, 70.79, 70.93, 72.06, 114.04, 128.34, 142.21, 156.72
EA $C_{31}H_{48}O_9$Theoretical C(65.93) H(8.57) Actual C(65.72) H(8.69)

MOM-G1-OH, **21a**
^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2H), 1.59 (s, 3H) 2.07-2.12 (m, 2H), 3.48 (s, 6H), 3.59 (t, 2H, J = 6 Hz), 5.14 (s, 4H), 6.93 (d, 4H, J = 9.0 Hz), 7.10 (d, 4H, J = 9.0 Hz)
^{13}C NMR ($CDCl_3$) δ 25.28, 27.95, 38.52, 44.84, 55.04, 55.86, 68.21, 94.39, 96.31, 115.57, 128.29, 143.01, 155.10
FT-IR (cm $^{-1}$) 3402, 2944, 1509, 1237, 1153, 1006

5.10. Coupling of triPEG3 Benzyl Bromide to 4,4'-(bis-Phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate

3,4,5-Tris(triethylene glycol monomethyl ether) benzyl alcohol, **4**, was converted to 3,4,5-Tris(triethylene glycol monomethyl ether) benzyl bromide, **5**, as outlined immediately prior to use in this reaction. In a clean, oven dried 100 mL round-bottom flask, triOH monomer, **8**, (0.18 g, 0.0.00064 mol) and the benzyl bromide, **5**, (0.93 g, 0.0014 mol) were dissolved in 50 ml of HPLC-grade acetone. Oven dried potassium carbonate (0.95 g 0.032 mol) and 18-crown-6 (0.037 g 0.00014 mol) was added and the mixture was allowed to reflux 8 hours. After refluxing, the solid was filtered, rinsed and the solvent was removed under reduced pressure via rotary evaporation. A clear, colorless syrup, **12a**, was purified from the golden crude by elution (DCM/5% methanol) from a 40M Biotage silica cartridge.

5.11. Coupling of R-Gx-Tosylate to 4,4'-(bis-Phenylhydroxy)pentanol or Phenylhydroxy-Gx-Thiocarbamate

This general procedure is essentially the same as outlined by Chen et al. [87] It is used to couple any activated dendron precursor, i.e tosylate, to the triOH monomer, **8**, to produce the next generation dendron alcohol or with deprotected phenylhydroxy-Gx-thiocarbamate to produce a completed dendron. In the example given here, MOM-G3-thiocarbamate is produced by reacting MOM-G2-Tosylate, **22b**, with pheylhydroxy-G1-thiocarbamate, **21e**.

MOM-G1-thiocarbamate, **21d**, (1.39 g, 0.0024 mol) was deprotected as outlined to yield phenylhydroxy-G1-thiocarbamate, **21e**. The sticky white solid was dissolved along with MOM-G2 Tosylate, **24b**, (5.44 g, 0.0049 mol) in 25 mL of HPLC-grade acetone. Oven dried potassium carbonate (1.36 g, 0.012 mol) and 18-crown-6 (0.063 g, 0.00024 mol) were added and the mixture was refluxed for 6 hours.. The white solid was filtered, rinsed and the

solvent removed by rotary evaporation. The clear, colorless syrup, **23d**, was purified from the golden crude by a step gradient [1) ethyl acetate/35% hexane: 2)ethyl acetate/30% hexane: 3) ethyl acetate/25% hexane] elution from a 40M Biotage silica cartridge.

PEG3-G2-OH, **10a**
^{1}H NMR($CDCl_3$) δ 1.29 (m, 2H), 1.53 (s, 3H), 1.56 (s, 6H), 2.02-2.04 (m, 2H), 2.13-2.17 (m, 4H) 3.32 (s, 12H), 3.48-3.50 (m, 16H, J = 6 Hz), 3.59-3.63 (m, 16H, J = 6 Hz), 3.67-3.69 (t, 8H), 3.78 (t, 8H, J = 6 Hz), 4.05 (t, 8H, J = 6 Hz) 6.70 (d, 4H, J = 9.0 Hz) 6.78 (d, 8H, J = 9Hz), 7.01 (d, 2H, J = 9Hz), 7.06 (d, 8H, J = 9.0 Hz) ^{13}C NMR
($CDCl_3$) δ 24.80, 27.81, 38.15, 44.47, 58.80, 62.89, 67.08, 68.02, 69.55, 70.33, 70.44, 70.06, 71.71, 113.53, 113.76, 128.03, 141.63, 141.72, 156.41, 156.57
FT-IR (cm $^{-1}$) 3492, 2924, 2868, 1608, 1510, 1248, 1108
EA $C_{79}H_{112}O_{19}$ Theoretical C(69.48) H(8.27) Actual C(69.30) H(8.43)

PEG3-G3-OH, **11a**
^{1}H NMR($CDCl_3$) δ 1.35 (m, 6H), 1.52-1.59 (m, 40H), 2.02-2.09 (m, 4H), 2.15-2.19 (m, 12H), 3.37 (s, 24H), 3.53-3.56 (m, 16H), 3.63-3.68 (m, 32H), 3.71-3.74 (m, 16H), 3.83 (t, 27H, J = 6 Hz), 4.09 (t, 16H, J = 6 Hz), 6.69-6.81 (m, 32H), 6.99-7.10 (m, 32H) ^{13}C NMR($CDCl_3$) δ 25.16, 28.12, 38.55, 44.95, 59.20, 63.62, 67.44, 68.50, 69.94, 70.71, 70.81, 70.95, 72.09, 113.91, 114.10, 114.93, 128.40, 141.79, 142.16, 149.89, 156.74, 157.02
FT-IR (cm $^{-1}$) 3493, 2924, 2878, 1608, 1511, 1247, 1108

5.12. Coupling of PEG12 Tosylate to the Phenylhydroxyydroxy-Gx-Thiocarbamate

This general procedure describes the coupling of PEG12-Tos, **2**, to the phenylydroxy-G1-thiocarbamate, **21e**. This general procedure was used to functionalize the deprotected MOM-Gx-thiocarbamates with tips that hindered normal purification attempts via column, precipitation and crystallization. Once functionalization of the dendrons was begun, products of all reactions were carried through to ligand exchange and dendrimer assembly without purification. The same flask used for the initial MOM deprotection is used for the coupling reaction.

Phenylydroxy-G1-thiocarbamate, **21e,** (0.10 g, 0.00020 mol) was combined with PEG12-tosylate, **2**, (0.60g, 0.00080 mol) in 50 ml of HPLC-grade acetone. A large excess of

oven dried potassium carbonate (77.5 g 0.57 mol) and 18-crown-6 (2.90 g 0.011 mol) were added and the mixture was allowed to reflux overnight. The excess of potassium carbonate was necessary to overcome a clumping problem observed in reactions involving PEG12-tosylate, **2**. After refluxing, the solid was filtered, rinsed and the solvent was removed under reduced pressure via rotary evaporation. The crude was carried to the next reaction, basic deprotection of the thiocarbamate as outlined under ligand exchange.

5.13. Synthesis of R-Gx-Amine

The general procedure to convert R-Gx-mesylates and R-Gx-tosylates, where R is MOM, PEG3, etc., was modified to use aqueous methylamine (40% by weight) instead of the gaseous methylamine. The reaction conditions for all amine conversion reactions were identical regardless of starting material.

MOM-G1-Tosylate, **21b**, (2.82 g, 0.0055 mol) was dissolved in 20 mL of tetrahydrofuran in a 40 mL sample vial. A ten-fold excess of aqueous methylamine (5 mL, 40% bwt) was added and the vial was sealed with a teflon coated rubber septa. The solution was heated to 60 ^{o}C for 4 hours with stirring. The reaction vessel was unsealed and solution was diluted with methylene chloride. The mixture was extracted with 50 mL of 1N hydrochloric acid followed by 50 mL of saturated aqueous sodium carbonate. The second extraction with base was essential to deprotonate the methylammonium cation from the first extraction. The organic phase was dried over magnesium sulfate and the solvent removed via rotary evaporation. The clear syrup was used without pruification.

PEG3-G1-OMs, **9b**

^{1}H NMR($CDCl_3$) δ 1.52 (m, 2H), 1.57 (s, 3H) 2.10-2.15 (m, 2H), 2.86 (s, 3H), 3.36 (s, 3H), 3.54 (d, 2H, J = 6 Hz), 3.56 (d, 2H, J = 6 Hz), 3.64-3.69 (m, 8H, J = 6 Hz), 3.72-3.75 (m, 4H), 3.84 (t, 4H, J = 6 Hz), 4.10 (t, 4H, J = 6 Hz), 4.15 (t, 2H, J = 6 Hz), 6.80 (d, 4H, J = 9.0 Hz) 7.05 (d, 4H, J = 9.0 Hz)
^{13}C NMR($CDCl_3$) δ 28.05, 28.42, 38.15, 44.84, 59.18, 63.53, 67.41, 69.91, 70.70, 70.79, 70.93, 72.06, 114.04, 128.34, 142.21, 156.72

PEG3-G1-Methylamine, **9c**
^{1}H NMR($CDCl_3$) δ 1.34 (m, 2H), 1.56 (s, 3H) 2.05-2.10 (m, 2H), 2.39 (s, 3H), 2.60 (t, 2H, J = 7 Hz), 3.37 (s, 3H), 3.53 (d, 2H, J = 6 Hz), 3.55 (d, 2H, J = 6 Hz), 3.63-3.69 (m, 8H, J = 6 Hz), 3.71-3.74 (m, 4H), 3.83 (t, 4H, J = 6 Hz), 4.09 (t, 4H, J = 6 Hz), 6.79 (d, 4H, J = 9.0 Hz) 7.07 (d, 4H, J = 9.0 Hz)

PEG3-G2-OTos, **10b**
^{1}H NMR($CDCl_3$) δ 1.40 (m, 2H), 1.49 (s, 3H), 1.56, (m, 4H), 1.60 (s, 6H), 21.96-2.01 (m, 2H), 2.15-2.21 (m, 4H) 2.43, (s, 3H), 3.36 (s, 12H), 3.53-3.55 (m, 16H, J = 6 Hz), 3.63-3.68 (m, 16H, J = 6 Hz), 3.71-3.74 (m, 8H), 3.82-3.86 (m, 10H), 3.95 (t, 2H, J = 6Hz) 4.10 (t, 8H, J = 6 Hz), 6.72 (d, 4H, J = 9.0 Hz), 6.80 (d, 8H, J = 9Hz), 6.97 (d, 2H, J = 9Hz), 7.09 (d, 8H, J = 9.0 Hz), 7.31 (d, 2H, J = 9.0 Hz), 7.74 (d, 2H, J = 9.0 Hz)
^{13}C NMR ($CDCl_3$) δ 21.87, 24.88, 25.24, 28.18, 37.96, 38.60,44.76, 45.01, 59.24, 67.54, 68.56, 69.99, 70.78, 70.87, 71.02, 71.50, 72.16, 114.03, 114.19, 128.10, 128.31, 128.45, 130.05, 141.34, 142.19, 156.85, 157.20
EA $C_{86}H_{118}O_{21}S$ Theoretical C(67.96) H(7.83) S(2.11) Actual C(67.77) H(7.80) S(1.99)

PEG3-G2-Methylamine, **10c**
^{1}H NMR($CDCl_3$) δ 1.61 (m, 2H), 1.44 (m, 4H), 1.48, (s, 3H), 1.53 (s, 6H), 1.86-2.0 (m, 2H), 2.08-2.14 (m, 4H), 2.19 (s, 3H), 2.41 (t, 2H, J = 6 Hz), 3.20 (s, 12H), 3.38-3.42 (m, 26H), 3.46-3.57 (m, 25H), 3.69 (t, 8H,J = 6 Hz), 3.84 (t, 4H, J = 6Hz), 4.02 (t, 8H, J = 6 Hz), 6.73 (d, 4H, J = 9.0 Hz), 6.81 (d, 8H, J = 9Hz), 7.00 (d, 4H, J = 9Hz), 7.05 (d, 8H, J = 9.0 Hz)

PEG3-G3-OTos, **11b**
FT-IR (cm^{-1}) 3036, 2918, 2873, 1608, 1510, 1248, 1109

PEG3-G3-Methylamine, **11c**
FT-IR (cm^{-1}) 3036, 2925, 2873, 1608, 1510, 1248, 1109

triPEG3-G1-OTos, **12b**
^{1}H NMR($CDCl_3$) δ 1.42 (m, 2H), 1.53 (s, 3H) 2.00-2.04 (m, 2H), 2.42 (s, 3H), 3.38 (s, 18H), 3.51-3.75 (m, 48H), 3.79 (t, 2H, J = 6 Hz), 3.85 (t, 4H, J = 6 Hz), 3.96 (t,2H J = 6 Hz), 4.10-4.18 (m, 12H), 4.88 (s, 4H), 6.65 (s, 4H) 6.81 (d, 4H, J = 9.0 Hz) 7.03 (d, 4H, J = 9.0 Hz) 7.32 (d, 2H, J = 9.0 Hz) 7.73 (d, 4H, J = 9.0 Hz)

triPEG3-G1-Methylamine, **12c**

^{1}H NMR($CDCl_3$) δ 1.26 (m, 2H), 1.58 (s, 3H) 2.03-2.10 (m, 2H), 2.39 (s, 3H), 2.54 (t,2H J = 6 Hz), 3.38 (s, 18H), 3.51-3.75 (m, 48H), 3.79 (t, 2H, J = 6 Hz), 3.85 (t, 4H, J = 6 Hz), 4.18 (m, 12H), 4.88 (s, 4H), 6.65 (s, 4H) 6.85 (d, 4H, J = 9.0 Hz) 7.11 (d, 4H, J = 9.0 Hz)

Phenylsulfonate-G1-OMs, **13b**
^{1}H NMR($CDCl_3$) δ 1.55 (m, 2H), 1.61 (s, 3H) 2.17 (m, 2H), 2.91 (s, 3H), 4.17 (t, 2H, J = 6 Hz), 5.13 (s, 4H), 6.87 (d, 4H,J = 9 Hz), 6.98 (d, 4H, J = 8 Hz), 7.12 (d, 4H, J = 9Hz), 7.24-7.30 (m, 6H), 7.58 (d, 4H, J = 9 Hz), 7.83 (d, 4H, J = 9 Hz)
^{13}C NMR ($CDCl_3$) δ 25.04, 27.96, 37.43, 37.75, 44.84, 68.85, 70.69, 114.45, 122.44, 127.36, 127.57, 128.46, 128.87, 129.83, 134.69, 142.16, 144.32, 149.65, 156.31

Phenylsulfonate-G1-Methylamine, **13c**
^{1}H NMR($CDCl_3$) δ 1.34 (m, 2H), 1.61 (s, 3H) 2.07-2.12 (m, 2H), 2.40 (s, 3H), 2.62 (t, 2H, J = 6 Hz), 5.13 (s, 4H), 6.87 (d, 4H,J = 9 Hz), 6.98 (d, 4H, J = 8 Hz), 7.12 (d, 4H, J = 9Hz), 7.24-7.30 (m, 6H), 7.58 (d, 4H, J = 9 Hz), 7.83 (d, 4H, J = 9 Hz)
^{13}C NMR ($CDCl_3$) δ 25.62, 28.50, 36.90, 40.17, 41.62, 45.59, 53.09, 69.38, 114.87, 122.98, 127.93, 127.93, 128.15, 129.09, 129.38, 130.38 135.13, 143.40, 145.02, 150.19, 156.68

MOM-G1-OTos, **21b**
^{1}H NMR ($CDCl_3$) δ 1.41 (m, 2H), 1.52 (s, 3H), 1.98-2.03 (m, 2H), 2.45 (s, 3H), 3.48 (s, 6H), 3.97 (t, 2H, J = 6 Hz), 5.14 (s, 4H), 6.92 (d, 4H, J = 9.0 Hz), 7.00 (d, 4H, J = 9.0 Hz), 7.33 (d, 2H, J = 9.0 Hz) 7.76 (d, 2H, J = 9.0 Hz)
^{13}C NMR ($CDCl_3$) δ 20.31, 21.83, 23.63, 24.78, 27.99, 37.84, 44.84, 56.19, 71.38, 94.63, 115.81, 128.07, 128.35, 130.01, 133.30, 142.57, 144.89, 155.34
FT-IR (cm $^{-1}$) 2961, 1509, 1177, 1153, 1003
EA $C_{28}H_{34}O_7S$ Theoretical C(65.35) H(6.66) Actual C(65.29) H(6.62)

MOM-G1-Methylamine, **21c**
^{1}H NMR($CDCl_3$) δ 1.26 (m, 2H), 1.58 (s, 3H), 2.03-2.06 (m, 2H), 2.37 (s, 3H), 2.53 (t, 2H, J=6 Hz), 3.48 (s, 6H), 3.59 (t, 2H, J = 6 Hz), 5.14 (s, 4H), 6.92 (d, 4H, J = 9.0 Hz), 7.09 (d, 4H, J = 9.0 Hz)

MOM-G2-OTos, **22b**
^{1}H NMR ($CDCl_3$) δ 1.38-1.42 (m, 2H), 1.50-1.63 (m), 1.97-2.03 (m, 2H), 2.17-2.22 (m, 4H), 2.43 (s, 3H), 3.48 (s, 6H), 3.83 (t, 4H, J = 6 Hz), 3.97 (t, 2H, J=6 Hz), 5.14 (s, 8H), 6.73 (d, 4H, J = 9.0 Hz), 6.90 (d, 8H, J=6 Hz), 6.98 (d, 4H, J = 9.0 Hz), 7.13 (d, 8H, J=9 Hz), 7.33 (d, 2H, J = 9.0 Hz) 7.78 (d, 2H, J = 9.0 Hz)

5.14. DCC-mediated Coupling of R-Gx-Amines and 4-Thiocarbamate Benzoic Acid

This general procedure details the N,N-dicyclohexylcarbodiimide, DCC, mediated amide bond formation between any R-Gx-amine and 4-thiocarbamic benzoic acid. It is

replaces the acid chloride reaction reported by Chen et al. The example reaction given is the coupling of the thiocarbamate focal group, **14**, to PEG3-G2-amine, **10c**,

In a clean, oven dried 100 mL round-bottom flask, PEG3-G2-amine, **10c**, (0.30g, 0.00017 mol) was dissolved with 4-thiocarbamate benzoic acid, **14**, (0.076 g, 0.00034 mol) in 25 mL of dry, distilled methylene chloride. N,N-dicyclohexylcarbodiimide, DCC, (0.035 g, 0.00017 mol) and catalytic 4-dimethylaminopyridine, DMAP, were added and the reaction was allowed to stir at room temperature for 2 hours. A successful reactionw as indicated by the presence of fine, needle crystals floating on top of the methylene chloride solution. The crystals were filtered and the crude loaded onto a Biotage 40S silica cartridge. The clear, colorless product, **10d**, was eluted with a two step gradient [1) DCM/ 4% methanol: 2) DCM/ 10% methanol].

PEG3-G1-Thiocarbamate, **9d**
^{1}H NMR($CDCl_3$) δ 1.29 (m, 1H), 1.41 (m, 1H), 1.50 (m, 1H), 1.57 (m, 1H), 1.80 (m, 15H), 2.08 (m, 1H), 2.76 (s, 1.5H) 2.89 (s, 1.5H), 3.05 (br, 6H), 3.17 (m, 1H), 3.35 (s, 3H), 3.48 (m, 1H), 3.51 (d, 2H, J = 6 Hz), 3.54 (d, 2H, J = 6 Hz), 3.62-3.67 (m, 8H, J = 6 Hz), 3.70-3.73 (m, 4H), 3.82 (t, 4H, J = 6 Hz), 4.09 (t, 4H, J = 6 Hz), 6.78 (d, 4H, J = 9.0 Hz) 6.97-7.08 (dd, 4H) 7.27-7.37 (dd, 2H), 7.50 (d, 2H, J = 9.0 Hz)
^{13}C NMR($CDCl_3$) δ 22.45, 23.88, 27.98, 29.80, 32.68, 37.07, 38.42, 44.83, 51.65,59.14, 67.41, 69.88, 70.67, 70.76, 70.90, 72.04, 114.10, 127.18, 127.42, 128.21, 130.44, 135.51, 137.39, 141.68, 142.07, 156.77
EA $C_{42}H_{60}N_2O_{10}S$ Theoretical C(64.26) H(7.70) N(3.57) S(4.08) Actual C(63.95) H(7.75) N(3.57) S(4.01)

PEG3-G2-Thiocarbamate, **10d**
^{1}H NMR($CDCl_3$) δ 1.23 (m, 1H), 1.43 (m, 1H), 1.50 (m, 1H), 1.57 (m, 1H), 1.80 (m, 1H), 2.10 (m, 1H), 2.20 (m, 8H), 2.76 (s, 1.5H), 2.89 (s, 1.5H), 3.05 (m, 3H), 3.13 (s, 3H), 3.17 (m, 1H), 3.37 (s, 12H), 3.48 (m, 1H), 3.55 (m, 8H), 3.62-3.67 (m, 16H), 3.70-3.73 (m, 8H), 3.82 (t, 8H, J = 6 Hz), 4.13 (t, 8H, J = 6 Hz), 6.78 (d, 4H, J = 9.0 Hz), 6.81 (d, 8H, J=9 Hz), 6.97-7.08 (dd, 4H), 7.09 (d, 8H, J=9 Hz), 7.27-7.37 (dd, 2H), 7.50 (d, 2H, J = 9.0 Hz)
^{13}C NMR($CDCl_3$) δ 21.27, 28.10, 44.87, 58.71, 67.32, 67.61, 69.66, 70.28, 70.48, 70.60, 71.94, 100.09, 101.21, 114.44, 124.80, 128.59, 135.82, 142.09, 156.88, 156.98
EA $C_{90}H_{124}N_2O_{20}S$ Theoretical C(68.16) H(7.88) N(1.77) S(2.02) Actual C(67.95) H(7.83) N(1.89) S(2.00)

PEG3-G3-Thiocarbamate, **11d**
^{1}H NMR($CDCl_3$) δ 1.52-1.62 (m, 32H), 2.07-2.13 (m, 2H), 2.16-2.20 (m, 12H), 2.76 (s, 1.5H), 2.85-2.86 (m, 1H), 2.91 (s, 1.5H), 3.03 (m, 3H), 3.08 (s, 3H), 3.17 (m, 1H), 3.37 (s, 24H), 3.53-3.55 (m, 16H), 3.64-3.68 (m, 32H), 3.72-3.74 (m, 16H), 3.84 (t, 27H, J = 6 Hz), 4.10 (t, 16H, J = 6 Hz), 6.74 (d, 12H, J = 9.0 Hz), 6.80 (d, 16H, J=9 Hz), 6.97-7.13 (m, 28H), 7.29-7.38 (m, 2H), 7.51 (d, 2H, J = 9.0 Hz) ^{13}C NMR($CDCl_3$) δ 25.11, 28.05, 38.45, 44.87, 59.15, 67.37, 68.40, 69.87, 70.67, 70.76, 70.89, 72.03, 113.82, 114.02, 128.33, 135.50, 141.76, 142.06, 156.70, 156.97
FT-IR (cm^{-1}) 2924, 2868, 1671, 1635, 1608, 1509, 1247, 1107

triPEG3-G1-Thiocarbamate, **12d**
^{1}H NMR($CDCl_3$) δ 1.29 (m, 1H), 1.41 (m, 1H), 1.50 (m, 1H), 1.57 (m, 1H), 1.80 (m, 15H), 2.08 (m, 1H), 2.76 (s, 1.5H) 2.89 (s, 1.5H), 3.05 (br, 6H), 3.17 (m, 1H), 3.38 (s, 18H), 3.51-3.75 (m, 48H), 3.79 (t, 2H, J = 6 Hz), 3.85 (t, 4H, J = 6 Hz), 4.18 (m, 12H), 4.88 (s, 4H), 6.65 (s, 4H), 6.78 (d, 4H, J = 9.0 Hz) 6.97-7.08 (dd, 4H) 7.27-7.37 (dd, 2H), 7.50 (d, 2H, J = 9.0 Hz)

Phenylsulfonate-G1-Thiocarbamate, **13d**
^{1}H NMR($CDCl_3$) δ 1.55 (m, 2H), 1.61 (s, 3H) 2.17 (m, 2H), 2.91 (s, 3H), 4.17 (t, 2H, J = 6 Hz), 5.13 (s, 4H), 6.87 (d, 4H,J = 9 Hz), 6.98 (d, 4H, J = 8 Hz), 7.12 (d, 4H, J = 9Hz), 7.24-7.30 (m, 6H), 7.58 (d, 4H, J = 9 Hz), 7.83 (d, 4H, J = 9 Hz)
^{13}C NMR($CDCl_3$) δ 25.04, 27.96, 37.43, 37.75, 44.84, 68.85, 70.69, 114.45, 122.44, 127.36, 127.57, 128.46, 128.87, 129.83, 134.69, 142.16, 144.32, 149.65, 156.31

MOM-G1-Thiocarbamate, **21d**
^{1}H NMR($CDCl_3$) δ 1.29 (m, 1H), 1.41 (m, 1H), 1.50 (m, 1H), 1.57 (m, 1H), 1.80 (m, 15H), 2.08 (m, 1H), 2.76 (s, 1.5H) 2.89 (s, 1.5H), 3.05 (br, 6H), 3.17 (m, 1H), 3.48 (s, 6H), 3.59 (t, 2H, J = 6 Hz), 5.14 (s, 4H), 6.92 (d, 4H, J = 9.0 Hz), 7.02-7.11 (dd, 4H), 7.28-7.37 (dd, 2H), 7.51 (dd, 5H, J = 9.0 Hz)

MOM-G2-Thiocarbamate, **22d**
^{1}H NMR($CDCl_3$) δ 1.29 (m), 1.41 (m), 1.50 (m), 1.57 (m), 1.57-73 (m, 12H), 1.85 (m, 1H) 2.03 (m, 1H), 2.13-2.30 (m 4H) 2.76 (s, 1.5H) 2.89 (s, 1.5H), 3.05 (br, 6H), 3.17 (m, 1H), 3.48 (s, 12H), 3.55 (m, 1H), 3.90 (m, 8H), 5.14 (s, 4H), 6.75-6.83 (m, 4H) 6.95 (d, 4H, J = 9.0 Hz), 7.01-7.20 (m, 16H), 7.23-7.32 (dd, 2H), 7.57 (d, 2H, J = 9.0 Hz)

MOM-G3-Thiocarbamate, **23d**
^{1}H NMR($CDCl_3$) δ 1.39-63 (m, 50H), 1.85 (m, 1H) 2.0-2.23 (m 24H) 2.76 (s, 1.5H) 2.89 (s, 1.5H), 3.05 (br, 6H), 3.17 (m, 1H), 3.48 (s, 24H), 3.85 (m, 14H), 5.14 (s, 16H), 6.75 (d, 8H) 6.95 (d, 4H, J = 9.0 Hz), 6.99-7.13 (m, 28H), 7.27-7.32 (dd, 2H), 7.53 (d, 2H, J = 9.0 Hz)

5.15. Basic Deprotection of R-Gx-Thiocarbamate

This general procedure details the removal of the thiocarbamate protecting group and the regeneration of aromatic thiol for amphiphilic dendrons. It follows closely the procedure by Chen et al.[87] It is extremely important that no water be introduced to the reaction solution prior to or during the basic deprotection of the carbamate group. Inclusion of water results in the formation of disulfides presumably due to oxygen being introduced by the basic aqueous solution. The solvent mixture used in the deprotection reaction may have to be adjusted depending upon the functional groups incorporated as amphiphilic groups on the dendrons, however, a significant portion of methanol should always be included. It will be necessary to adjust the number of equivalents of sodium hydroxide used if amphiphilic functional "tip" groups are also being deprotected . Since both verification that the carbamate deprotection reaction has occurred and purification of the reaction mixture are difficult at best for amphiphilic dendrons, it is recommended that at least 2 equivalents of sodium hydroxide be employed for each functional group to be deprotected. The reactions are refluxed at least twelve hours under a nitrogen blanket. Once the aromatic thiols have been deprotected, they are stable.

The following illustrative deprotection reaction was performed first and employed PEG3-G1- Thiocarbamate dendron for several reasons. This dendron was the easiest to remake if something went wrong. Deprotection reactions and ligand exchange had been

performed successfully with this molecule. Verification of carbamate removal, thiol formation, and purification of the thiol were possible.

The dendron, PEG3-G1 Thiocarbamate, **9d**, (0.16 g, 0.00020 mol), and solid sodium hydroxide (0.16 g, 0.00040 mol) were combined in a Schlenk flask, sealed, and placed under vacuum for one hour using a double manifold vacuum line. This flask was back-filled with nitrogen and, under approximately 4 psi of nitrogen pressure above atmospheric, the flask was fitted with a reflux condenser that was sealed with a rubber septum. Three, 3, mLs. each of dry, distilled tetrahydrofuran and methanol were added to the flask via syringe. The flask was purged with nitrogen for one more hour using an 18 gauge outlet needle in the septum while the sodium hydroxide dissolved. The flow of nitrogen was stopped and the fully sealed system was allowed to reflux overnight. The reaction solution developed a yellow color during this time. After refluxing, the reaction solution was allowed to cool and was quenched by the addition of four drops of 12N hydrochloric acid dissolved in 1 mL of dry, distilled tetrahydrofuran. The reflux condenser was removed and the solvent removed from the Schlenk flask via rotary evaporation. The residue was dissolved in methylene chloride and dried over magnesium sulfate. The methylene chloride was removed via rotary evaporation and vacuum was applied to the flask to remove any residual hydrochloric acid. Although it was possible to purify the polyethylene glycol tipped dendrons, this was not done. The residue was spotted on silica TLC plate along with a small sample of residue that had been treated with iodine. The TLC plate was eluted with DCM/3% methanol and two spots were observed for the untreated sample, one corresponding to thiol and the other to disulfide as determined from the single spot corresponding to the iodine treated sample.

NMR of the residue revealed the disappearance of the carbamate protecting group and a single proton in the expected region for an aromatic thiol. The residue was carried on to the ligand exchange reaction.

5.16. Ligand Exchange and Assembly of Dendrimers

The following general procedure details the ligand exchange reactions with amphiphilic aromatic thiol dendrons. These dendrons are immediately after basic deprotection of the carbamate protecting group, protonation of the aromatic thiolate with concentrated hydrochloric acid and drying under vacuum as described. The ligand exchange reactshould be increased from 4.4:1 to 6:1 to allow for any disulfide that might form during quenching. Although the ligand exchange is possible in any solvent, dimethylformamide is the standard choice here . Volume is not particularly important. The reaction is complete within a minute.

After a successful ligand exchange reaction, the DMF was removed using the vacuum line and the dendrimer purified by successive cycles of dissolution/precipitation using appropriate oxygen-free solvents and non-solvents preferably obtained fresh from a solvent still. The precipitated material was isolated via centrifugation at 2500 rpm for 3 min.. It was imperative that blue Falcon-brand tubes be used for centrifugation.

A specific ligand exchange was as follows: dendron PEG3-G1-Thiol (0.14g, 0.000190 mole), product of the deprotection reaction, was placed in an open Schlenk flask and “pumped” into the nitrogen dry box. Iron-sulfur cluster, $[Fe_4S_4(S\text{-}t\text{-}Bu)_4](Me_4N)_2$ (0.0278g, 0.000033 mole) was weighed in the N_2 dry box. The thiol dendron was dissolved in 5 mLs of dimethylformamide and a small amount of the preweighed iron-sulfur cluster

was added to this solution. Rapid development of burgundy color confirmed the presence of the aromatic thiol and the remaining cluster was dissolved in ~2mLs. dimethylformamide and transferred to the reaction Schlenk flask. The flask was sealed, removed from the N_2 drybox, and the DMF was removed under vacuum on a double manifold vacuum line. The resulting PEG3-G1 iron-sulfur core dendrimer was purified by dissolving the residue in 2 mLs dry distilled DCM followed by precipitation by the addition of 8 mLs. dry distilled ether. Solid product was isolated via centrifugation.

PEG3-G1, **15**
^{1}H NMR(DMF-d6$_3$) δ 1.37 (m), 1.58 (m), 1.88-2.17 (m), 3.27 (s), 3.36 (s), 3.42-3.66 (m), 3.79 (s, 16H), 4.12 (s, 16H), 5.92 (br, 8H), 6.89 (m, 16H), 7.11 (m 16H), 8.20 (br, 8H)

PEG3-G2, **16**
^{1}H NMR(DMF-d6$_3$) δ 1.54-1.63 (m, 48H), 2.24 (m, 12H), 3.29-3.69 (m, 268H), 3.81, (m, 32H), 3.95 (m, 16H), 4.12 (m, 32H) 5.92 (br, 8H), 6.85-6.90 (m, 48H), 7.05-7.20 (m 48H), 8.22 (m, 8H)

PEG3-G3, **17**
^{1}H NMR(DMF-d6$_3$) δ 1.60-1.78 (m, 124H), 2.31-2.41 (m, 52H), 3.42 (s, 96H),3.51-3.85 (m, 298H), 3.96, (m, 64H), 4.09 (m, 48H), 4.27 (m, 64H) 6.08 (br, 8H), 6.95-7.09 (m, 112H), 7.17-7.37 (m 112H), 8.24 (br, 8H)

triPEG3-G1, **18**
^{1}H NMR(DMF-d6$_3$) δ 1.40-2.40, 3.42 (s), 3.53 (s), 3.56-3.82 (m), 3.88 (s, 16H), 4.00 (s, 32H), 4.25 (s, 16H), 4.33(s, 32H), 5.15 (s, 16H), 6.09 (br, 8H), 7.00-7.36 (48H), 8.42 (br, 4H)

triPEG3-G3, **28** crude

PEG12-G1, **24** crude
^{1}H NMR(DMF-d6$_3$) δ 1.24-2.20, 3.20-3.71, 3.80, 4.14, 5.94 (br), 6.71, 6.86, 7.00-7.14, 8.28 (br)

PEG12-G2, **25** crude
^{1}H NMR(DMF-d6$_3$) δ 1.24-2.20 (60H), 3.20-3.71, 3.80, 3.97, 4.15, 5.95 (br), 6.71 (d, 8H), 6.86, 7.00-7.14, 8.34 (br)

6. Bibiliography

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