DESIGN, SYNTHESIS, AND CHARACTERIZATION OF $[1 \rightarrow 3]; [1 \rightarrow (2 + 1 \text{ Me})]$; $[1 \rightarrow (2 + 1)]$C-BRANCHED DENDRONS AND DENDRITIC ARCHITECTURES

A Dissertation

Presented to

The Graduate Faculty of The University of Akron

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

Kishore Kumar Kotta

May, 2006
DESIGN, SYNTHESIS, AND CHARACTERIZATION OF $[1 \rightarrow 3]; [1 \rightarrow (2 + 1 \text{ Me})];$

$[1 \rightarrow (2 + 1)] C$-BRANCHED DENDRONS AND DENDRITIC ARCHITECTURES

Kishore K. Kotta

Dissertation

Approved:  

Advisor  
Dr. George R. Newkome

Accepted:  

Department Chair  
Dr. Michael J. Taschner

Committee Member  
Dr. Michael J. Taschner

Dean of the College  
Dr. Ronald Levant

Committee Member  
Dr. David A. Modarelli

Dean of the Graduate School  
Dr. George R. Newkome

Committee Member  
Dr. Chrys Wesdemiotis

Date

Committee Member  
Dr. Robert R. Mallik

ii
ABSTRACT

Various dendrons and dendrimers with \([1 \rightarrow 3] ; [1 \rightarrow (2 + 1 \text{ Me})]; [1 \rightarrow (2 + 1)]\) C-branching were designed, synthesized, and studied. Dendrimers with internal PEG linkages were prepared using a convergent approach. Incorporation of triethylene glycol units within the dendritic framework rendered the dendrimer soluble in both polar and apolar solvents. The solubility of lithium triflate salts in chloroform in the presence of PEGed dendrimers is described. Dendrimers from 1\(^\text{st}\) to 5\(^\text{th}\) generation with \([1 \rightarrow (2 + 1 \text{ Me})]-C\)-branched monomer were constructed by iterative methodology. Quantum dots were prepared in the presence of 1\(^\text{st}\) – 5\(^\text{th}\) generation dendrimers and their emission properties studied. The synthesis of cyano-terminated, sol-gel dendrons and their application in capillary microextraction-gas chromatography (CME-GC) are described. A convenient synthesis for the construction of \([1 \rightarrow 3]-C\)-branched dendrons was developed. The design and synthesis of conifer-shaped dendritic architecture as well as its complexation with \(\beta\)-cyclodextrin are described. \(^1\)H NMR, \(^{13}\)C NMR, IR, ESI-MS, and MALDI-TOF MS methods were used to characterize all new intermediates and final products. Potential applications of these dendrons and dendrimers, as polymer electrolytes, solid sorbents, and the unimolecular micelles are envisioned.
ACKNOWLEDGMENTS

I would first like to thank Professor George R. Newkome for being a wonderful advisor during my time at The University of Akron. Professor Newkome is a tremendous chemist from whom I have learned a great deal. He is also the most creative person I have ever met in a chemistry lab and I will never forget witnessing his many brilliant ideas. But more importantly Professor Newkome is a wonderful person. He has created an extremely positive and encouraging work environment that makes it a pleasure to come to work everyday. I am indebted to Dr. Charles N. Moorefield for his detailed assistance with laboratory techniques. I also deeply appreciate his assistance with the writing of my publications.

I would also like to thank Professor Taschner for his continued guidance whenever I needed advise on running a reaction or figuring out a synthetic problem. I also enjoyed taking Professor Taschner’s synthesis class; he was also a great source of entertainment. I would also like to thank my thesis committee, Professor Chrys Wesdemiotis and Professor David Modarelli. Without their guidance, support and understanding this thesis would not have been possible. My special thanks to my collaborators Prof. Abdul Malik and Dr. Abuzar Kabir at the Department of Chemistry, University of South Florida.
The administrative staff (Barbara Smith, Nancy Homa) in the department deserves a good deal of recognition for their help.

Last, but certainly not least I must thank my colleagues who have helped me in so many ways while this research was conducted. All of my labmates over the years have been very generous in sharing equipment and discussions with me on various aspects of research and I feel very fortunate to have worked with them.

To everyone else I did not mention, thanks for making my time at The University of Akron so enjoyable. I wish everyone nothing but the best in the future.
DEDICATION

Dedicated to my parents Smt. Kalavathi and Shri. Hanumantha Rao
# TABLE OF CONTENTS

| LIST OF FIGURES | ix |
| LIST OF SCHEMES | xi |

## CHAPTER

### I. INTRODUCTION

1.1. Synthesis of Dendritic Architectures .................................................................4
1.2. Dendrimers with Poly(ethylene)glycol Moieties ..................................................11
1.3. Dendrimers as Synthetic Hosts .............................................................................16
1.4. Dendrimers in Separation Science ........................................................................19
1.5. Dendrimers as Unimolecular Micelles ................................................................21
1.6. Dendrimers with Heterogeneous Substitution .....................................................23
1.7. References ..............................................................................................................29

### II. SYNTHESIS OF WATER-SOLUBLE, ACID-TERMINATED DENDRONS
AND DENDRIMERS CONTAINING INTERNAL PEG LINKAGES ..........................40

2.1. Introduction ..............................................................................................................40
2.2. Synthesis of Key Extenders ....................................................................................42
2.3. Construction of Extended Dendrons .....................................................................43
2.4. Synthesis of 2\textsuperscript{nd} and Extended 2\textsuperscript{nd} Generation Dendrons ........................................................................44
2.5. Synthesis of Dendrimers .........................................................................................46
VI. DESIGN, SYNTHESES, AND CHARACTERIZATION OF CONIFER-SHAPED DENDRITIC ARCHITECTURES

6.1. Introduction.................................................................138
6.2. Synthesis of Monomers..................................................141
6.3. Experimental Section. General Remarks .......................150
6.4. References........................................................................164

VII. CONCLUSIONS...............................................................169
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Schematic representation of a dendritic architecture</td>
<td>2</td>
</tr>
<tr>
<td>2. Newkome’s arborol and Tomalia’s PAMAM dendritic architectures</td>
<td>3</td>
</tr>
<tr>
<td>3. Divergent and convergent construction for dendrimer synthesis</td>
<td>5</td>
</tr>
<tr>
<td>4. A multivalent, unsymmetrical dendrimer with 16 mannose units and 2 coumarin chromophores</td>
<td>10</td>
</tr>
<tr>
<td>5. Diederich’s dendroclefts with PEG units on the surface</td>
<td>12</td>
</tr>
<tr>
<td>6. Encapsulation of anticancer drugs in PAMAM dendrimer with PEG surface</td>
<td>13</td>
</tr>
<tr>
<td>7. Polyester dendritic architectures with PEG units</td>
<td>13</td>
</tr>
<tr>
<td>8. Grinstaff’s [(G4)-PGLSA---OH]$<em>2$-PEG$</em>{3400}$ dendrimer</td>
<td>16</td>
</tr>
<tr>
<td>9. Dendritic architectures with carborane and metal ions</td>
<td>18</td>
</tr>
<tr>
<td>10. Dendron-based capillary chromatography</td>
<td>20</td>
</tr>
<tr>
<td>11. Newkome’s unimolecular micelle and Meijer’s dendritic box</td>
<td>22</td>
</tr>
<tr>
<td>12. Newkome’s [1 → (2 + 1)]-C-branched dendrimers</td>
<td>28</td>
</tr>
<tr>
<td>13. Fréchet’s unimolecular micelle</td>
<td>72</td>
</tr>
<tr>
<td>14. GPC traces for dendrimers 80, 82, 83, 85, 86, 88, 89, and 90</td>
<td>84</td>
</tr>
<tr>
<td>15. UV-Vis spectrum and photoluminescence spectra for CdS/dendrimer nanocomposites</td>
<td>85</td>
</tr>
<tr>
<td>16. Cyano-terminated dendron with a triethoxysilyl root</td>
<td>109</td>
</tr>
<tr>
<td>17. Surface-bonded sol-gel dendron coating</td>
<td>110</td>
</tr>
</tbody>
</table>
18. Thermogravimetric analysis curve and first derivative of TGA curve for the sol-gel dendron 103

19. CME-GC analysis of polycyclic aromatic hydrocarbons

20. CME-GC analysis of alcohols
## LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Construction of poly(phenylene) dendrimers using double exponential growth</td>
<td>7</td>
</tr>
<tr>
<td>2. Zimmermann’s orthogonal approach</td>
<td>8</td>
</tr>
<tr>
<td>3. Construction of monocyano substituted dendrons</td>
<td>24</td>
</tr>
<tr>
<td>4. Synthesis of dendrons with diverse functional groups on the surface</td>
<td>26</td>
</tr>
<tr>
<td>5. Synthesis of key extenders 50 and 51</td>
<td>43</td>
</tr>
<tr>
<td>6. Construction of extended dendrons 54 and 55</td>
<td>44</td>
</tr>
<tr>
<td>7. Synthesis of dendron 58</td>
<td>45</td>
</tr>
<tr>
<td>8. Synthesis of dendron 60</td>
<td>46</td>
</tr>
<tr>
<td>9. Synthesis of 1st generation dendrimer</td>
<td>47</td>
</tr>
<tr>
<td>10. Synthesis of 2nd generation dendrimer</td>
<td>48</td>
</tr>
<tr>
<td>11. Synthesis of 2nd generation bis-PEG extended dendrimer</td>
<td>49</td>
</tr>
<tr>
<td>12. Synthesis of 1st and 2nd generation dendrons</td>
<td>74</td>
</tr>
<tr>
<td>13. Synthesis of 3rd generation dendron 77</td>
<td>76</td>
</tr>
<tr>
<td>14. Synthesis of 1st generation dendrimers 78 and 79</td>
<td>77</td>
</tr>
<tr>
<td>15. Synthesis of 2nd generation dendrimers 80, 81, and 82</td>
<td>78</td>
</tr>
<tr>
<td>16. Synthesis of 3rd generation dendrimers 83, 84, and 85</td>
<td>80</td>
</tr>
<tr>
<td>17. Synthesis of 4th generation dendrimers 86, 87, and 88</td>
<td>81</td>
</tr>
<tr>
<td>18. Synthesis of 5th generation dendrimers 89, 90, and 91</td>
<td>82</td>
</tr>
</tbody>
</table>
19. Convergent construction of 2\textsuperscript{nd} and 3\textsuperscript{rd} generation dendrimers \textbf{80} and \textbf{83} ..................83
20. Synthesis of key monomers \textbf{93} and \textbf{94} .................................................................106
21. Synthesis of 2\textsuperscript{nd} generation isocyanate dendron \textbf{97} ..................................................107
22. Synthesis of 3\textsuperscript{rd} generation isocyanate dendron \textbf{101} ........................................108
23. Synthesis of 2\textsuperscript{nd} generation dendrons ................................................................124
24. Synthesis of 3\textsuperscript{rd} generation dendrons ................................................................125
25. Synthesis of 2\textsuperscript{nd} generation predendrons \textbf{115} and \textbf{116} ....................................141
26. Synthesis of predendron \textbf{117} ......................................................................................143
27. Synthesis of 3\textsuperscript{rd} generation predendron \textbf{119} ..................................................144
28. Synthesis of extended amine dendron \textbf{121} ........................................................................145
29. Synthesis of 2\textsuperscript{nd} generation extended dendron \textbf{126} ........................................146
30. Synthesis of elongated dendron \textbf{129} ................................................................................147
31. Synthesis of adamantane amine \textbf{135} ..............................................................................148
32. Synthesis of dendritic architecture \textbf{136} and its complexation with β-cyclodextrin ...149
CHAPTER I
INTRODUCTION

The practice of organic synthesis began in the nineteenth century when Wöhler demonstrated the first transformation of an inorganic material into an organic substance. Since then the field of organic synthesis has evolved to a level where molecules that were once only imaginary are now the cures for the world’s diseases, materials for space travel, and the substances, which make everyday life, as we know it safer and more convenient. Dendrimers (Fig. 1) are one of the most exciting and fascinating discoveries in the field of organic synthesis of the twentieth century. Their unique structural properties give rise to a host of potential utilitarian applications.

In 1941, P. J. Flory\textsuperscript{1,2} envisioned the possible synthesis of branched chain macromolecules and disclosed his experimental evidence on branched-chain, three-dimensional macromolecules now known as dendritic architectures. In 1942, he successfully demonstrated the synthesis of highly branched polymers from trifunctional monomers\textsuperscript{3} possessing two different functional groups that were reactive with each other. In 1973, J. M. Lehn\textsuperscript{4} reported the step-wise strategies or iterative synthesis for the construction of macrocyclic rings. In 1978 Fritz Vögtle et al.\textsuperscript{5} reported the first example of an iterative synthesis towards branched architectures; he used the iterative methodology to construct low molecular weight branched architectures and termed them as “cascade molecules.” Although numerous routes exist to construct these highly
branched, 3-dimensional, globular macromolecules, the synthetic strategies fall into one of two categories (Fig. 3): divergent synthesis involving an “inside-out” approach and convergent synthesis involving an “outside-in” approach. Newkome et al. and Tomalia et al. pioneered the divergent approach, while Hawker and Fréchet pioneered convergent approach.

Figure 1. Schematic representation of a dendritic architecture.

In 1985, Newkome et al. published the first molecular tree - an “arborol” (Latin: *arbor*: tree) based on the $1 \rightarrow 3$ branching pattern (1, Fig 2), simultaneously Tomalia published his $1 \rightarrow 2$ branched (2, Fig 2) PAMAMs or “dendrimers” (Greek: *dendron*: tree). Thus, the Greek terminology is today the norm for this class of macromolecular constructs. Both of these initial routes (with three or greater generations – the definition
of a true dendrimer) were synthesized using the divergent approach, which involves the step-wise addition of monomeric units in a radially outward fashion.

Newkome’s series were divergently grown by the use of $[1 \rightarrow 3]$-C-branched monomers; whereas, Tomalia’s dendrimers were built by the use of $[1 \rightarrow 2]$-C-branched monomers. In 1990, Hawker and Fréchet introduced the convergent growth mode as well as the term “dendron” or as today denoted as a “macromonomer.” The convergent approach involves the preparation of dendrons from outside-in fashion; this approach offers the introduction of different functional groups into the dendrimers.

![Figure 2. Newkome’s arborol and Tomalia’s PAMAM dendritic architectures.](image-url)
1.1. Synthesis of the dendritic architectures

Several synthetic strategies have been devised and reported over the years to improve the synthesis of dendrimers. Over the past nearly two decades, more than 7000 papers and patents have appeared and thus the molecular growth is well founded but also their unique structures of dendrimers have introduced scientists and engineers to a growing forest of nanomaterials capable of not only unimolecular aspects but also biological mimics. These molecules provoke a wide interest due to their unique architectural features, which make these nanoscopic-sized dendrimers attractive for potential use in a variety of applications.

Many investigations\textsuperscript{10} have centered upon efficient synthesis of dendritic architectures. Most of the earlier work in the preparation of dendrimers used divergent, convergent or the combination of two approaches. Fréchet and co-workers introduced\textsuperscript{11} the “hypercore” and “hypermonomer” approach for the synthesis of high generation dendrimers with high yields in fewer steps. A series of convergently prepared dendrons is coupled to a preformed central core containing multiple branching sites. The deprotection of dendrimers gave the next generation hypercores, which were treated with $1^{\text{st}}$, $2^{\text{nd}}$ or $3^{\text{rd}}$ generation dendrons to form higher generation dendrimers with high overall yield compared to the standard divergent or convergent approach. This method is the combination of divergent and convergent approaches and is known as the “double stage convergent approach.”
Figure 3. Divergent and convergent construction for dendrimer synthesis.
Later, Moore et al.\textsuperscript{12} reported the construction of poly(phenyl)acetylene dendrimers using another approach and they named this approach as the “double exponential dendrimer growth” (Scheme 1). This strategy uses a building block, which is protected at the focal point as well as the periphery. Selective deprotection and coupling with other building blocks resulted in the next generation dendron. Repeating these steps gave higher generation dendrons in fewer steps than conventional convergent and divergent methods in high yield. For example, building block 3 is doubly protected by silyl groups on one side and with a diethyltriazene group on the other. The diethyltriazene moiety can be easily transformed to an iodide group 4 with MeI at 110 °C in a sealed tube. The terminal silyl groups can be deprotected to generate a building block 5 with terminal alkyne groups. The use of these two sets of reactions afforded different sets of dendrons that are coupled to each other to generate higher generation dendron 6. Ihre and coworkers\textsuperscript{13} reported a similar strategy towards the synthesis of aliphatic polyester using double stage convergent growth.
Zimmermann and coworkers\textsuperscript{14} also reported a rapid synthesis of dendrimers using an orthogonal coupling approach. They used two different building blocks having complementary coupling functional groups (Scheme 2). Starting with diacid 7 the building block 8 was coupled to the carbonyl moieties using Mitsunobu conditions to give iodide 9. Similarly, 2\textsuperscript{nd} generation dendron 11 was synthesized by the Sonagashira coupling of iodide 9 and diyne 10. The use of alternating series of Mitsunobu esterification and Sonagashira reactions generated higher generation dendron 12. This orthogonal approach minimizes the steps necessary for the construction of high
generation dendritic architectures by avoiding protection and deprotection steps. By choosing appropriate functional complementaries, it is possible to synthesize high generation dendrimers with a minimum number of steps.

\[
\text{Scheme 2. Zimmermann’s orthogonal approach.}
\]

Recently, Sharpless et al.\textsuperscript{15} applied “click chemistry” for the construction of dendritic architectures with very high yield and purity. This procedure involves the Cu(I) -catalyzed synthesis of 1,2,3-triazoles from azides and alkynes. A variety of azides and alkyne building blocks can be employed in the synthesis of dendrimers. Analytical
techniques like NMR, MALDI-TOF MS, GPC confirmed the purity of the dendrimers prepared by this method. Fréchet and coworkers\textsuperscript{16} also applied the same click chemistry to prepare dendronized polymeric architectures. Wooley and co-workers further reported\textsuperscript{17} the divergent preparation of dendrimers using click chemistry. Employing divergent construction, a two-directional core with azide groups was treated with an alkyne moiety to generate the 1\textsuperscript{st} generation dendrimer. The transformation of peripheral alcohol to azide groups, followed by treatment with alkyne monomers produced higher generation dendrimers. Dendrimers were obtained in pure form by extraction into dichloromethane or by precipitation into water. Purity of these dendrimers was demonstrated by gel permeation chromatography.

Hawker et al. also reported\textsuperscript{18} the preparation of a library of dendritic macromolecules using Cu(I)-catalyzed alkyne-azide cycloaddition reaction. Dendrimers with peripheral alkyne groups were treated with various azido monomer units to generate a library of dendritic architectures. Hawker and Sharpless successfully employed the click chemistry for the construction of a novel class of asymmetric diblock dendrimers.\textsuperscript{19} A set of dendrons was prepared with focal azide and acetylene groups containing distinct surface groups. The Cu(I)-catalyzed cycloaddition reaction of alkyne and azide dendrons resulted unsymmetrical dendrimers in high yields with different surface groups. The authors ingeniously introduced 16 mannose units on one side and 2 coumarin chromophores on the other side (13; Fig. 4). Liskamp and co-workers\textsuperscript{20} developed microwave-assisted synthesis of multivalent dendrimeric peptides using click chemistry.
Figure 4. A multivalent, unsymmetrical dendrimer with 16 mannose units and 2 coumarin chromophores.
1.2. Dendrimers with Poly(ethylene)glycol Moieties

Recently, research efforts were concentrated on the construction of biodegradable dendrimers. Various monomers were evaluated for the synthesis of biodendrimers, including poly(ethylene)glycol, poly(ethylene)oxide, poly(caproic acid), glycerols, lactic acids, succinic acids, sugars, and amino acids. Poly(ethylene)glycol and their derivatives are widely known for their non-toxic nature, biocompatibility, and solubility in a wide range of solvents. PEG-functionalized proteins and polymers were shown to find applications in the areas of drug delivery systems, high-energy density batteries, electrochemical cells, and electrochromic devices. Many dendrimers have been synthesized with PEG attached at their periphery, or at the core. Very few reports have appeared with the PEG attached as internal linkages. These PEGed dendrimers have increased solubilities in water and can solubilize small hydrophobic drug molecules within the interior of the dendrimer and act as nano-containers in aqueous solutions.

Diederich et al. have prepared a series of dendroclefts and dendritic iron porphyrins with water-soluble PEG units on the surface for the selective molecular recognition of monosaccharides and as model compounds of heme proteins, respectively. The hydrogen bonding between the host dendroclefts and guest monosaccharides was monitored by $^1$H NMR experiments and these interactions have been shown to be generation independent. As the dendrimer generation increased, the enantioselectivity decreased; whereas, the diastereoselectivity to the $\alpha$- and $\beta$-glucoside increased.
Kojima and coworkers\textsuperscript{53} reported the synthesis of PAMAM dendrimers terminated with poly(ethylene)glycol (PEG) chains, which were attached with urethane bonds to encapsulate the anticancer drug molecules such as: adriamycin (ADR) and methotrexate (MTX) (15, Fig. 6). The 3\textsuperscript{rd} and 4\textsuperscript{th} generations of PAMAM dendrimers attached with PEG chains were characterized by \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, and gel permeation chromatography (GPC). The drug molecules were encapsulated by the acid-base interactions of drug molecules and dendrimer interior, respectively. The concentration of encapsulated drug molecules increased with the increasing amounts of the drug, which was supported by UV spectroscopy, and drug release was accomplished by dialysis. Fréchet and coworkers\textsuperscript{13,54} reported the synthesis of polyester dendrimers comprised of 2,2–\textit{bis}(hydroxymethyl)propanoic acid units (16 and 17, Fig. 7). A PEG capped 4\textsuperscript{th} generation dendrimer and a (polyethylene oxide) PEO star-G3-dendrimer conjugate were also evaluated (18, Fig. 7). An anticancer drug doxorubicin (DOX) was used to prepare polymer-drug conjugate; the drug molecule was covalently attached to an acid-labile
hydrazone linkage, which can remain stable under physiological conditions and release in the acidic environment.

Figure 6. Encapsulation of anticancer drugs in a PAMAM dendrimer with PEG surface.

Figure 7. Polyester dendrimer architectures with PEG units.
Meijer et al. reported the surface modification of 1st – 4th poly(propylene imine) dendrimers with hydrophilic 3,4,5-tris(tetraethyleneoxy)benzoyl units and demonstrated the encapsulation of water-soluble xanthene dyes in aqueous solutions.\(^\text{55}\) The host-guest interactions were monitored by UV/Vis titrations and small angle X-ray scattering experiments. Encapsulation within the dendrimer’s interior was suggested by the acid-base interactions between the xanthene guest and poly(propylene imine) dendrimer, respectively.

Poly(ethylene)glycol and their derivatives can act as polymer electrolytes by solvating metal ions with their ethereal oxygen atoms. Hawker et al. reported\(^\text{56}\) the preparation of hyperbranched poly(ethylene)glycols using di-, tri- or hexaethylene glycol units. These hyperbranched poly(ethylene)glycols were characterized by size-exclusion chromatography and soluble in a wide-range of solvents. The glass transition temperature and ionic conductivity were measured for the hyperbranched poly(ethylene)glycol/lithium perchlorate (LiClO\(_4\)) complex. The ionic conductivity was increased with increasing LiClO\(_4\), as well as the temperature. Itoh et al. also studied the ionic conductivity\(^\text{47,57}\) of hyperbranched PEG derivatives in the presence of lithium metal salts [LiCF\(_3\)SO\(_3\) and Li(CF\(_3\)SO\(_2\))\(_2\)N].

Nierengarten and co-workers utilized a series of fullerodendrimers\(^\text{58-61}\) possessing poly(aryl ether) dendrons capped with small, surface PEGed moieties and then studied their photophysical properties in different solvents. The triplet lifetime of the excited fullerene core increased linearly with increasing dendritic generation, indicating the shielding effect of dendritic branches. It was also found that disubstituted branching has more shielding effect on the fullerene core than monosubstituted branching.
Several examples based on dendrimers containing poly(ethylene)glycol as the core unit are known. Gitsov et al. reported a series of linear-dendritic and star amphiphilic copolymers using linear poly(ethylene)glycol, as the focal group, and branched PEG, as the core. The convergently prepared Fréchet-type dendrons with bromine at the focal point were treated with linear and branched poly(ethylene)glycol in the presence of NaH to produce linear-dendritic block copolymers. Gel permeation chromatography (GPC) and MALDI-TOF mass spectrometry were employed for the characterization of these dendrimers.

Bryce and coworkers incorporated small PEG moieties within the dendritic framework of tetrathiafulvalene (TTF) to instill solubility in a variety of solvents. The oxidation states of tetrathiafulvalene were measured using cyclic voltammetry in organic solvents. Recently, Grinstaff and co-workers reported (19, Fig. 8) the encapsulation of Reichardt’s dye and 10-hydroxycamptothecin in the 4th generation poly(glycerol-succinic acid)-poly(ethylene)glycol [(G4)-PGLSA-OH]2-PEG3400 dendrimer. One- and two-dimensional NMR and NOESY experiments predicted the interaction between the protons of the guest molecule and the CH₂, CH protons of succinic acid and glycerol units of the dendrimer. The spin-lattice relaxation time constant T₁ and spin-spin relaxation time constant T₂ values of these guest molecules decreased in the presence of dendrimer, compared to the free guest molecules alone in CD₃OD.
Figure 8. Grinstaff’s [(G4)-PGLSA-OH]_{2}-PEG_{3400} dendrimer.

1.3. Dendrimers as Synthetic Hosts

As a result of their highly branched, well-defined architecture and the large number of functional groups that can be incorporated into the structure, dendrimers have been explored as synthetic hosts. Metal ions have also been incorporated into the dendritic architectures, thus taking advantage of non-covalent interactions. These “metallodendrimers” can have the metals placed at the core, within the branching, at the periphery of the dendrimer or inside the dendrimer cavities.\textsuperscript{64} Transition metal containing dendrimers are of particular interest as a result of their optical, electronic, magnetic, and catalytic properties. Balzani et al.\textsuperscript{65-67} reported the synthesis of polypyridine-transition
metal complexes and studied their electrochemical properties, luminescence, redox properties and electron-transfer behavior. Newkome et al.\textsuperscript{68} described the synthesis of 1,2-dicarba-closo-dodecaborane dendrimer (20, Fig. 9); a four directional dendrimer with four and twelve alkyne moieties in the interior was treated with decaborane to afford boron cluster dendrimers. These dendrimers were soluble in water and characterized by $^1\text{H}$, $^{13}\text{C}$, and $^{11}\text{B}$-NMR spectroscopy.

Crooks et al. described\textsuperscript{69,70} the preparation of dendrimer-encapsulated nanoparticles using transition metal ions and higher generation PAMAM and PPI dendrimers (21, Fig.9). $\text{Cu}^{2+}$, $\text{Pd}^{2+}$, $\text{Pt}^{2+}$, $\text{Ni}^{2+}$, $\text{Fe}^{3+}$, $\text{Au}^{3+}$, and $\text{Ag}^+$ were used as the template metal ion to prepare nanoparticles. Dendrimers at higher generation possess cavities of different size depending on the functional groups that are present in the interior and exterior of the dendrimer, which can be used to trap metal ions. The 4\textsuperscript{th} generation hydroxyl-terminated PAMAM dendrimer was used to trap transition metal ions, which were subsequently reduced to zero valent metals using excess NaBH$_4$ to produce uniform sized nanoparticles inside the dendrimer. The interaction of metal ions with the interior of dendrimer was monitored by UV-vis and EPR spectra. Dendrimer-encapsulated bi-metallic nanoparticles were also prepared.$^{71,72}$ These dendrimer-encapsulated monometallic and bimetallic nanoparticles were found to be useful in homogenous catalysis like hydrogenation,$^{73}$ Heck,$^{74,75}$ Suzuki$^{76,77}$ and Stille$^{78}$ coupling reactions.$^{79}$ The 4\textsuperscript{th} generation hydroxyl-terminated PAMAM dendrimer-encapsulated palladium nanoparticles were used to catalyze the hydrogenation of linear and branched alkenes.$^{73}$ PAMAM dendrimer-encapsulated palladium nanoparticles were used to catalyze Stille$^{78}$ reaction at room temperature in water.
Quantum dots or nanocrystals are semiconductor nanoparticles with unique optical and electronic properties. During the past decade, quantum dots have been extensively studied due to their potential use in biology, nanotechnology, and chemosensors. Quantum dots have also been incorporated into a wide variety of polymers. Murphy et al. reported the preparation of CdS/dendrimer nanocomposites with PAMAM dendrimers and their optoelectronic properties. The dendrimer branches impede the aggregation of CdS nanoparticles to produce small, uniform sized CdS clusters having unique photo-luminescent property, which can also depend on the solvent and pH of the solution. Dynamic light scattering (DLS) experiments and transmission electron microscopy (TEM) revealed the size of the CdS clusters.

![Figure 9. Dendrimers with carborane units and metal ions.](image-url)
1.4. Dendrimers in Separation Science

Due to their highly branched architectures and large internal surface area, dendrimers and dendrons have also found applications in separation sciences, for example in the extraction of trace amounts of analytes from aqueous solutions. Dendrimers have been used as the solid-stationary phase in electrokinetic chromatography, solid-phase microextraction (SPME), capillary electrochromatography, gas chromatography, and in HPLC. Recently, Malik and coworkers reported the use of dendrimers in solid-phase microextraction. Sol-gel dendrimer coatings were prepared by using 3rd generation \( 1 \rightarrow 3 \) C-branched benzyl-terminated dendron with a triethoxysilyl focal moiety (22, Fig. 10). In situ sol-gel networks of these dendrons can be generated by the hydrolysis of triethoxysilyl group in the presence of trifluoroacetic acid. The fused silica capillary inner surface sol-gel dendrimer coatings have high thermal stability and are stable in solution at high temperatures. Numerous analytes, such as: polynuclear hydrocarbons (PAHs), alcohols, phenols, aldehydes and ketones, were extracted from aqueous solutions and analyzed by gas chromatography.
Chao and Hanson reported the use of silica surface-bonded dendrons, as stationary phase, in capillary electrochromatography. The 1<sup>st</sup> and 2<sup>nd</sup> generation of convergent Fréchet type dendrons with hydrophilic alcohol group at the focal point were attached to 3-(triethoxysilyl)propyl isocyanate to obtain the corresponding carbamates. These dendrons were then immobilized on the fused silica capillary inner surface using the sol-gel chemistry. The attachment of dendrons on silica surface was characterized by FTIR, Raman spectroscopy, and UV spectroscopy. The use of the dendron-bonded stationary phase for the extraction of a variety of analytes resulted in a better separation compared to unbonded silica.
1.5. Dendrimers as Unimolecular Micelles

A classic micelle is formed when a molecule with a polar head group and nonpolar tail is added to water. The molecules assemble in such a way that a spherical structure is formed having the polar head groups outside interacting with water and the nonpolar hydrophobic chains clump into center of a spherical structure. Dendritic architectures can act as micelles when they have a hydrophobic interior and hydrophilic exterior; these are known as unimolecular micelles, coined by Newkome and co-workers,\textsuperscript{93-95} who reported the first example of dendrimer (23, Fig. 11) with nonpolar hydrocarbon interior and polar carboxylic acid groups, as the exterior, and was shown to act as an unimolecular micelle. The micellar properties were demonstrated by converting the terminal carboxylic groups into the corresponding ammonium and tetramethylammonium carboxylate derivatives. The molecular inclusion within the interior of the dendritic architecture was evidenced by the UV and fluorescence analyses of the guest dyes pinacyanol chloride, phenol blue, chlortetracycline, and naphthalene. The synthesis of such unimolecular micelles laid the foundations for those that followed. Fréchet\textsuperscript{96} and coworkers reported the encapsulation of pyrene and fluorescent dyes within the water-soluble poly(aryl ether) dendrimer; the solubility of pyrene molecule was increased in water in the presence of the dendrimer.

Meijer and coworkers\textsuperscript{97-99} described the stunning example of dendritic box and demonstrated the physical encapsulation of small guest molecules within the dendrimer (24, Fig. 11). The 5\textsuperscript{th} generation poly(propylene imine) dendrimer was treated with \textit{t}-BOC-protected phenylalanine in the presence of guests molecules like 3-carboxyproxyl-
such as Rose Bengal and 7,7,8,8-tetracyanoquinodimethane. As a result of the dense shell of the dendrimer, these molecules were trapped within the dendrimer. Evidence of the encapsulation of the guest molecules was studied by EPR, UV spectroscopy, and fluorescence analysis.

Figure 11. Newkome unimolecular micelle (23) and Meijer’s dendritic box (24).

Meijer et al.\textsuperscript{100} also reported synthesis of an inverse micelle comprised of hydrophilic interiors and hydrophobic exterior. The amine-terminated poly(propylene imine) dendrimers were treated with nonpolar alkyl acid chlorides. Hydrophilic guests, such as Rose Bengal, were trapped within the dendrimer as evidenced by the \textsuperscript{1}H NMR and dynamic light scattering studies. More recently, Thayumanavan and co-workers\textsuperscript{26,101} reported the preparation of dendrimers possessing hydrophobic and hydrophilic substituents. These authors demonstrated that these dendrimers act as hydrophilic
nanocontainers in the presence of non-polar solvents and as hydrophobic nanocontainers in the presence of polar solvents. These amphiphilic dendritic molecules encapsulated nonpolar Reichardt’s dye in aqueous solution of dendrimer as well as polar Proflavin dye in nonpolar toluene. Encapsulation studies were performed using UV spectroscopy.

1.6. Dendrimers with heterogeneous substitution

Fréchet et al. reported an elegant example\textsuperscript{102} of surface functionalization of dendrons by placing a limited number of functional groups on the periphery. The convergent approach was applied for the construction of 1\textsuperscript{st} through 4\textsuperscript{th} generation dendrons with a monosubstituted cyano group on the periphery; these dendrons were finally coupled to a three-directional core. The monosubstituted aldehyde 25 was constructed from benzyl bromide and excess 3,5-dihydroxybenzaldehyde in the presence of K\textsubscript{2}CO\textsubscript{3} and 18-crown-6. The free hydroxyl moiety was now available for the attachment of $p$-cyanobenzyl bromide to generate a dendron 29 with heterogeneous substitution. The reduction of aldehyde group and conversion of the resultant benzyl alcohol to a benzyl bromide afforded a reactive focal moiety 31, which was coupled with monosubstituted alcohol thus creating the 2\textsuperscript{nd} generation dendron 34 with single cyano group on the surface (Scheme 3). Repetition of these reaction sequences afforded higher generation dendrons in pure form. The $^1$H NMR of 3\textsuperscript{rd} generation monocyano-substituted and unsubstituted benzyl bromide revealed the expected degeneracy and chemical shifts due to the disturbance of the symmetry in monocyano-substituted dendron.
Scheme 3. Construction of monocyano substituted dendrons.

Hawker and Fréchet also reported\textsuperscript{103} the synthesis of dendritic unimolecular reverse micelles with internal functional groups and studied their catalytic activity towards unimolecular elimination [E1] reactions as well as bimolecular nucleophilic substitution [S\textsubscript{N}2] reactions. The monomer was constructed from tetradecylbenzyl bromide and methyl dihydroxybenzoate. Deprotection of the focal group followed by activation with CBr\textsubscript{4}/PPh\textsubscript{3} and treatment with diphenol generated the next generation dendrons. The 1\textsuperscript{st} – 4\textsuperscript{th} generation dendrons were constructed and coupled with a three-
directional core to produce 1st–4th generation dendrimers. The internal ester groups were reduced to corresponding alcohols using LiAlH₄ reaction conditions. Due to the nonpolar alkyl chains on the surface and polar hydroxyl groups inside of the dendrimer, these dendrimers act as unimolecular reverse micelles. Elimination reactions were performed using 2-iodo-2-methylpropane and 2-iodo-2-methylheptane in the presence of these types of dendrimers. The dendrimer’s polar interior stabilized the polar transition state using non-covalent interactions; once products (nonpolar) formed, they pass through the dendrimer’s interior. It was noted that highest catalytic activity was observed for the 4th generation dendrimer.

Schlüter and co-workers have developed the similar strategy to incorporate bromo functionalities at various locations within the dendritic framework. Structural control was achieved by the preparation of the dendron using convergent approach. These bromides were later coupled with p-tert-butylphenylboronic acids under Suzuki coupling conditions. The introduction of functional groups on the surface, at the branching or within the dendritic architectures allows the investigation of the chemical and physical properties of the dendrimer’s interior and surface.

In recent years, Thayumanavan and co-workers reported a series of dendritic architectures with diverse functional groups on the periphery (Scheme 4). The branched monomers were prepared convergently for achieving internal functional group diversity. The nature of the convergent approach allowed the precise control of the spatial placement of the monomer units. The authors employed different approaches for the preparation of sequencing dendrimers, using an AB₂ monomer, where one of the B group is protected. They selected monoallyl-protected 3,5-dihydroxybenzyl alcohol 34 to
initiate their synthesis. Treatment with one equivalent of alkylating agent, followed by the deprotection of allyl group afforded the monosubstituted dendron 36, which has a free phenoxy group for the second alkylation. When this compound was treated with a different alkylating agent, a dendron 37 with different functionalities resulted. Activation of the focal moiety and repetition of the above procedures gave dendrons 42 and 43 with diverse functional groups on the periphery.

Scheme 4. Synthesis of dendrons with diverse functional groups on the surface.
In another approach, they used ABH monomer, where one of the B groups is more reactive than other. The monomers must be carefully selected such that only one of the B functionalities has a higher reactivity over the other. By taking advantage of the differences in the reactivity of the phenol and alcohol groups towards alkylating agents, the authors selectively introduced different functional groups into the dendritic architectures. Upon treatment of ethyl 3-hydroxy-5-(hydroxymethyl)benzoate with 3-bromobenzyl bromide in the presence of K$_2$CO$_3$ and 18-crown-6, only phenolic alkylation was realized leaving the hydroxymethyl group intact. Subsequent treatment with 3-methylbenzyl bromide in the presence of NaH resulted in the formation of a dendron with two different functionalities on the surface. These alkylations were conducted using a different set of alkyl halides to generate dendrons with different functional groups on the surface. The reduction of the focal ester group, followed by conversion into reactive bromides and attaching to 3-hydroxy-5-(hydroxymethyl)benzoate using the above reaction sequence produced the 7-mer dendron. The reiteration of these reaction sequences yielded the 15-mer dendron with diverse functionalities on the periphery.

In 2002, Newkome et al. devised a new series of [1 $\rightarrow$ (2 + 1)] C-branched dendrons so that specific functionality could be introduced while still continuing to branch by means of the remaining two sites. This permitted the access to complex dendritic spherical structures but still possessing a single (or controlled number) locus per dendron or four unique sites per a four-directional dendrimer (44 and 45, Fig. 12). A series of 1$^{st}$ and 2$^{nd}$ generation dendrimers were constructed using different [1 $\rightarrow$ (2 + 1)] C-branched dendrons to demonstrate the methodology.
For any type of dendritic construct where structural evidence and purity are important, a wide variety of analytical techniques are available for the complete characterization of these fractal-like structures.\textsuperscript{112} Nuclear magnetic resonance (NMR) is the most popular and widely used technique for structure identification of most organic compounds.\textsuperscript{113,114} NMR can easily be applied for the characterization of the dendrimers. The electrospray ionization (ESI) and matrix-assisted laser desorption time-of-flight (MALDI-TOF) mass spectrometry are used for the molecular weight analysis of the dendrimers, although this MS analysis does not give definitive information concerning purity. Size-exclusion chromatography (SEC) with multi-angle
laser light scattering is also used extensively for the molecular distribution of dendrimers and dendritic polymers. High performance liquid chromatography (HPLC),\textsuperscript{115} capillary electrophoresis,\textsuperscript{116,117} and gel electrophoresis\textsuperscript{118} are also widely used for the purification of dendrimers.

The increasing interest in the field of dendritic chemistry has led to the construction of numerous branched tailored architectures with various monomer units, as the starting materials. It has been recognized that functional dendrimers find umpteen applications such as unimolecular micelles, drug delivery systems, MRI contrast agents, solid sorbents, and catalysts. Our interest in the design and application of dendrimers led us to synthesize a series of $[1 \rightarrow 3]$ C-, $[1 \rightarrow (2 + 1 \text{ Me})]$ C- and $[1 \rightarrow (2 + 1)]$ C-branched dendrons and dendrimers. Their application in the areas of unimolecular micelles and separation science will be discussed in the following chapters.

1.7. References


CHAPTER II

SYNTHESIS OF WATER-SOLUBLE, ACID-TERMINATED DENDRONS AND
DENDRIMERS CONTAINING INTERNAL PEG LINKAGES

2.1. Introduction

During this past decade, the syntheses, characterization, and applications of dendrimers have been introduced into diverse fields of research.\textsuperscript{1,2} These highly branched, 3-dimensional, globular macromolecules have shown promising utility in molecular electronic devices, such as light emitting diodes,\textsuperscript{3,4} molecular antennae,\textsuperscript{5,6} and light harvesting systems,\textsuperscript{7,8} drug delivery systems,\textsuperscript{9,10} chemical sensors,\textsuperscript{11} receptors in molecular recognition processes,\textsuperscript{12,13} enhanced binding or sensor effects,\textsuperscript{14,15} and luminescent materials,\textsuperscript{16-19} to mention but a few.

Polyethylene glycols (PEGs) and their derivatives are important biocompatible materials that exhibit a wide range of solubilities\textsuperscript{20,21} and are generally nontoxic.\textsuperscript{22} Hence, their use as drug carriers,\textsuperscript{9,23,24} anchors for biological receptors,\textsuperscript{25} and metal ion binding for ion transport\textsuperscript{26} is well documented. In tethered, bi-layer membrane systems, where they are employed as hydrophilic linkers, PEG units act as the integral component of an ion channel switch biosensor.\textsuperscript{27} Further, ether-, ester-, and amine-based linear polymers
with short PEG units in the presence of inorganic salts have potential applications in high-energy density batteries, electrochemical cells, and electrochromic devices.\textsuperscript{28-31}

For dendritic architectures incorporating the PEG moiety, the most common attachment of PEG moieties is onto their surface in order to instill aqueous solubility to water-insoluble species. In that dendrimers have three structural regions in which a PEG unit can be introduced, namely: the core,\textsuperscript{32-42} internal connective moieties,\textsuperscript{43-47} and surface groups,\textsuperscript{9,36,48-82} the former and later attachment predominate due to the ease of instillation; also, dendrons have been focally PEGed.\textsuperscript{38,83-89} Gitsov et al.\textsuperscript{32,36} reported linear-dendritic block copolymers using large PEG components, as the internal core as well as surface unit(s), and studied their properties; a review by Gitsov\textsuperscript{90} has recently appeared. Diederich et al. utilized a series of dendroclefts\textsuperscript{53,60,64} and heme proteins\textsuperscript{50,59,61,68,70,91,92} possessing $[1 \rightarrow 3]$ C-branched monomers capped with small, surface PEGed subunits then studied their unique properties such as their selective recognition of monosaccharides. Phthalocyanines\textsuperscript{65,93} and related benzoporphyrins\textsuperscript{77} as well as metalloclusters\textsuperscript{94} have also been made readily water-soluble by the attachment of small PEG units. Nierengarten recently reviewed\textsuperscript{79} examples of dendritic encapsulation, which is, in part, based on related PEGed-surfaces. The highly stable PEG functionalized saturated hydrocarbon–type dendrimers act as electrolytes and were shown to improve the efficiency\textsuperscript{95,96} of a lithium rocking-chair battery. More recently, Itoh et al.\textsuperscript{44,97} studied the ionic conductivity of hyperbranched PEG derivatives in the presence of lithium metal salts [LiCF$_3$SO$_3$ and Li(CF$_3$SO$_2$)$_2$N] to determine their effectiveness as polymer electrolyte. Only three examples of PEG units being used as non-core, internal linkages have appeared, to the best of our knowledge; functionalization of tetrathiafulvalene
hyperbranched Fréchet-type materials,\textsuperscript{47,97,98} and in the solid-phase peptide synthesis of multimeric \textit{cyclo-(RGDE)-peptides}.\textsuperscript{45}

Our interest in the design and application of dendrimers led us to synthesize a series of useful PEGed dendrons and dendrimers, which utilize a combination of (1) amide connectivity affording minimal internal hydrolytic cleavage in that most PEGed dendrimers possess ester connectivity; (2) $[1 \rightarrow 3]$ C-branching motif; and (3) a non-core, internal PEG linkage, derived from commercially available triethylene glycol. Incorporation of PEG functionality within the dendritic framework is also envisioned to enhance the dendrimer’s potential to facilitate the transport of alkali metal species such as is required of polymer electrolytes in solid-state batteries.

2.2. Synthesis of Key Extenders

The treatment (Scheme 5) of triethylene glycol with ethyl diazoacetate in presence of BF$_3$·Et$_2$O gave the monoester \textsuperscript{48}, which with mesyl chloride in the presence of Et$_3$N, followed by NaN$_3$ in DMF at 60 °C gave (95 %) the desired azidoester \textsuperscript{50}, which was supported ($^1$H NMR) by the up-field shift (3.64 to 3.06 ppm) for the $\omega$-CH$_2$ triplet upon substitution. Ester \textsuperscript{50} was then saponified to give (96 %) the azidoacid \textsuperscript{51}, which was identical to a sample generated in four-steps from chlorotriethylene glycol.\textsuperscript{99} Both ester \textsuperscript{50} and acid \textsuperscript{51} will be used as simple PEG connectors between branching points within a dendrimer framework.
Scheme 5. Synthesis of key extenders 50 and 51: a) N₂CHCO₂CH₂CH₃, BF₃·THF, 25 °C, 12 h; b) CH₃SO₂Cl, C₆H₅Me, Et₃N, 6 h; c) excess NaN₃, dry DMF, 60 °C, 3 h; d) KOH, H₂O, THF, 25 °C, 6 h.

2.3. Construction of Extended Dendrons

Treatment (Scheme 6) of the azido acid 51 with Behera’s amine¹⁰⁰,¹⁰¹ 52 under peptide coupling conditions¹⁰²,¹⁰³ afforded (92 %) the PEG-extended branched amide 53, which is supported by the 3:1 integration (¹H NMR) of the triplet (1.87 ppm) for the α-CH₂CO₂R to the singlet for the α-OCH₂CON as well as the MS peak at m/z 632 for the desired parent ion.

Deprotection of 53 with formic acid at 25 °C quantitatively generates the corresponding triacid 55, evidenced by the absence of the tert-butyl resonances and appearance of a peak at 9.54 ppm for the carboxylic acid. Whereas, subjecting 53 to reductive conditions using Pd on carbon gave (94 %) the desired amine 54, which was spectrally (¹H and ¹³C NMR) similar to the azide except for the shift noted for the N₃CH₂- to H₂NCH₂- conversion; the mass spectral data showed a peak at m/z 606 for the [M + H⁺] further supporting the assignment.
Scheme 6. Construction of extended dendrons 54 and 55: a) DCC, 1-HOBT, THF, 25 °C, 15 h; b) EtOH, 10% Pd/C, H₂ (60 psi), 20 °C, 16 h; c) HCO₂H, 25 °C, 6 h.

2.4. Synthesis of 2nd and Extended 2nd Generation Dendrons

The PEG-extended dendron 58 was constructed (Scheme 7) by initially treating 4-(2-carboxyethyl)-4-nitroheptanedioic acid¹⁰¹,¹⁰⁴,¹⁰⁵ 56 with amine 54 under typical amidation conditions to give (70 %) the 2nd generation predendron 57, which was chromatographed to remove the excess DCC and urea by-products.

The ¹³C NMR spectral data revealed peaks at 57.31, 57.96, and 80.67 ppm for the three different quaternary centers representing the two branching carbons and intact termini; the three carbonyl groups (169.33, 172.54, and 172.58 ppm) as well as MALDI-TOF MS peak at 2,056.2 (M + Na⁺) support the successful amidation. Reduction of the focal nitro substituent was accomplished using T1 Raney Nickel catalyst to afford (80 %) the corresponding amine 58, which was supported by the shift (¹³C NMR) for the O₂NC to H₂NC conversion (92.8 to 57.9 ppm) and the MS peak at 2,030.34 (M + Na⁺).
Scheme 7. Synthesis of dendron 58: a) DCC, 1-HOBT, dry THF, 25 °C, 24 h; b) H₂ (60 psi), Raney Ni, EtOH, 50 °C, 12 h.

The double PEG-extended 60 was obtained in two-steps (Scheme 8) from azide 55 with amine 54 using the same amidation procedure, except using EDC, to give (65 %) the heptaamide intermediate 59; catalytic reduction using Pd/C at 60 p.s.i. hydrogen then transformed (94 %) the azide moiety to the corresponding amine 60. The ¹³C NMR data confirm this structure: 169.15, 170.08, 172.39 ppm for the three different amide carbons, and the expected shift for the N₃CH₂ to H₂NCH₂ (50.4 to 39.6 ppm) conversion as well as the observed mass peak for the parent ion 2218.34 (M + Na⁺).
Scheme 8. Synthesis of dendron 60: a) EDC, 1-HOB, anhydrous DMF, 25 ºC, 24 h; b) EtOH, 10% Pd/C, H₂ (60 psi), 25 ºC, 24 h.

2.5. Synthesis of Dendrimers

Treatment of 4.4 equiv. of amine 54 and tetraacyl chloride⁶¹⁶⁶ 61 in presence of Et₃N afforded the desired polyester 62 (Scheme 9). The ¹³C NMR spectrum of dodecaester 62 showed peaks at 45.12 ppm for the core quaternary carbon and peaks at 168.80, 171.07, 172.03 ppm for the three distinct carbonyl groups as well as the MALDI-TOF MS showed a peak at 2792.35 (M + Na⁺) supporting dendrimer formation.

When amine 58 was subjected to the same procedure (Scheme 10), pure dendrimer 64 was isolated (70 %) and characterized (¹³C NMR) by the peaks (45.33, 57.17, 57.71 ppm) for the three different quaternary centers representing one central and two branching carbons as well as the presence of four different carbonyl groups (169.00, 172.41, 173.29, 173.36 ppm); the peak (MALDI-TOF MS) at 8,406.1 (M + Na⁺) confirms the formation of the four new internal amide connections.
Scheme 10. Synthesis of 2\textsuperscript{nd} generation dendrimer: a) Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, amine 58, 25 °C, 6 h; b) HCO\textsubscript{2}H, 25 °C, 12 h.

The related 2\textsuperscript{nd} generation dendrimer 66 was assembled (63 %) from the bis-PEG-extended amine 60 using the same procedure (Scheme 11); its \textsuperscript{13}C NMR spectral data showed peaks for five carbonyl (168.95, 169.35, 171.25, 172.28, 172.95 ppm) groups and its MALDI-TOF MS showed a peak for molecular ion at 9,115.98 (M + Na\textsuperscript{+}) supporting the formation of the desired dendrimer 66.
Subsequent treatment of dendrimers 62, 64, and 66 with formic acid gave the desire acid-terminated dendrimers 63, 65, and 67, respectively. Their structures were evidenced by their $^{13}$C NMR spectra that exhibited the new signal for the CO$_2$H moiety as well as the disappearance of tert-butyl chemical shifts. In addition, the ESI-MS and MALDI-TOF MS at $m/z$ 2,067.35 (63: calc. $m/z$ 2,067.12 [M - H$^+$]), $m/z$ 6,360.72 (65: calc. $m/z$ 6,361.58 [M - H$^+$]) and $m/z$ 7,116.45 (67: calc. $m/z$ 7142.42 [M - H$^+$]) further characterized the deprotection of t-butyl esters.

Scheme 11. Synthesis of 2$^{nd}$ generation bis-PEG-extended dendrimer: a) Et$_3$N, CH$_2$Cl$_2$, amine 60, 25 °C, 6 h; b) HCO$_2$H, 25 °C, 12 h.
All these dendrimers are waxy solids and the differential scanning calorimetry (DSC) data of the dendrimers 62, 64, and 66 ($T_g = 5.9$, 2.6, and $-5.8 \, ^\circ\text{C}$, respectively) revealed a gradual decrease in the glass transition temperature ($T_g$) with increasing dendrimer generation; all are soluble in most common organic solvents (i.e., Et$_2$O, CHCl$_3$, hexane, DMF, MeOH, and EtOH) as well as in aqueous solution. These dendrimers were also shown to solubilize lithium metal salts in organic media. In order to exclude traces of encapsulated water associated with the ethereal oxygen atoms of triethylene glycol units, the dendrimers were dried in vacuo for extended periods of time, then the lithium triflate was added to the dendrimers in CDCl$_3$. The lithium triflate readily dissolved; whereas, the lithium triflate salt was not soluble in either CDCl$_3$ alone or the corresponding non-PEGed counterparts. The $^{13}$C NMR spectrum of the dendrimer-Li salt complex showed broadened peaks for ethylene glycol units and a quartet peak for the CF$_3$ group.

2.6. Experimental Section. General Remarks.

Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. All of chemicals were purchased from Aldrich Co. except for Behera’s amine. Tetrahydrofuran (THF) was dried by refluxing over benzophenone/Na under N$_2$. Dichloromethane was dried over CaH$_2$. All other commercially available solvents were used without further purification. Column chromatography was conducted using silica gel (60-200 mesh) from Fisher Scientific with the stipulated solvent mixture. $^1$H and $^{13}$C NMR spectra were obtained in CDCl$_3$,
except where noted, and are recorded at 300 and 75 MHz, respectively. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded on an ATI Mattson Genesis Series FTIR spectrometer. Mass spectral data were obtained using an Esquire electron ionization mass spectrometer (ESI) and are reported as: (assignment, relative intensity); ESI samples were typically prepared in MeOH/H2O/TFA (70:30:01) for positive ion mode or Me2CHOH/H2O/NH3 (70:30:1) for negative ion mode and matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer.

**Ethyl [2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy]acetate (48).** To the stirred solution of triethylene glycol 47 (20 g, 133 mmol) and BF3·THF (2 drops) in CH2Cl2 (500 mL) under N2, ethyl diazoacetate (15.4 g, 133 mmol) was added drop wise in CH2Cl2 (50 mL) over 1 h. After stirring at 20 °C for 12 h, the organic phase was washed with water (50 mL, 2X), dried (MgSO4), filtered, and evaporated in vacuo to give (70 %) 48, as a colorless oil: 21.4 g; Rf 0.41 [SiO2: EtOAc/hexane (1:1)]; 1H NMR δ 1.12 (t, 3 H, CH3, J = 7.2 Hz), 3.22 (t, 2 H, HOCH2, J = 5.4 Hz), 3.43-3.57 (m, 10 H), 3.98 (s, 2 H, OCH2CO), 4.05 (q, 2 H, OCH2CH3, J = 7.2 Hz); 13C NMR δ 13.91 (CH3), 60.50 (OCH2CH3), 61.25 (HOCH2), 68.32-72.35, 170.20 (CO2); IR 3500 (OH), 1751 (C=O), 1127 (C-O) cm−1; FAB-MS: m/z = 258.9 (M + H+); calcd. m/z = 259.2 (M + H+).

**Ethyl [2-[2-(2-Mesyloxyethoxy)ethoxy]ethoxy]acetate (49).** To the stirred solution of ester 48 (10 g, 42 mmol), Et3N (4.30 g, 43 mmol), and toluene (50 mL), a solution of mesyl chloride (4.85 g, 43 mmol) was added drop wise in toluene (10 mL) for 30 min at −10 °C. The mixture was stirred for 3 h at 25 °C, then concentrated in vacuo to
give a residue, which was column chromatographed eluting with EtOAc/ CH$_2$Cl$_2$ (20:80) to give (90 %) mesylate 49, as a viscous oil: 12.0 g; R$_f$ = 0.34; $^1$H NMR $\delta$ 1.15 (t, 3 H, OCH$_2$CH$_3$, $J$ = 7.2 Hz), 2.96 (s, 3 H, SO$_2$CH$_3$), 3.54-3.59 (m, 10 H), 3.64 (t, 2 H, MsOCH$_2$, $J$ = 4.5 Hz), 4.00 (s, 2 H, OCH$_2$CO), 4.09 (q, 2 H, OCH$_2$CH$_3$, $J$ = 7.2 Hz); $^{13}$C NMR $\delta$ 13.94 (OCH$_2$CH$_3$), 37.31 (SO$_2$CH$_3$), 60.48 (OCH$_2$CH$_3$), 68.29-70.51, 170.10 (CO$_2$); IR 1750 (C=O), 1174 (C-O) cm$^{-1}$; FAB-MS: m/z = 336.9 (M + Na$^+$); calcd. m/z = 337.3 (M + Na$^+$).

**Ethyl [2-[2-(2-Azidoethoxy)ethoxy]ethoxy]acetate (50).** A stirred mixture of 49 (10 g, 32 mmol) and excess NaN$_3$ (3X) in dry DMF (200 mL) was maintained at 60 °C for 3 h. The mixture was filtered, concentrated in vacuo, and column chromatographed (SiO$_2$) eluting with an EtOAc/hexane mixture (1:1) to give (95 %) the desired azide 50, as a yellow oil: 7.90 g; R$_f$ = 0.55; $^1$H NMR $\delta$ 0.95 (t, 3 H, OCH$_2$CH$_3$, $J$ = 7.2 Hz), 3.06 (t, 2 H, N$_3$CH$_2$, $J$ = 4.2 Hz), 3.33 (m, 10 H), 3.81 (s, 2 H, CH$_2$CO), 3.87 (q, 2 H, OCH$_2$CH$_3$, $J$ = 7.2 Hz); $^{13}$C NMR $\delta$ 13.19 (CH$_3$), 49.66 (N$_3$CH$_2$), 59.65 (CH$_3$CH$_2$O), 67.51-69.75, 169.47 (CO$_2$); IR 2108 (N$_3$), 1751 (C=O), 1125 (C-O) cm$^{-1}$; ESI-MS m/z = 336.9 (M + Na$^+$), calcd. m/z = 337.3 (M + Na$^+$).

**[2-[2-(2-Azidoethoxy)ethoxy]ethoxy]acetic Acid (51).** Ester 50 (5 g, 19.1 mmol) was hydrolyzed in aq. KOH at 20 °C for 6 h. The resultant solution was neutralized with 10 % aq. HCl, then concentrated in vacuo to give an oil, which was extracted with THF, filtered, and evaporated in vacuo to give (96 %) the pure acid 51, as a colorless oil: 4.3 g; $^1$H NMR $\delta$ 3.26 (t, 2 H, N$_3$CH$_2$, 4.5 Hz), 3.57 (m, 10 H), 4.01 (s, 2
H, OCH$_2$CO), 10.66 (s, 1 H, CO$_2$H); $^{13}$C NMR δ 50.31 (N$_3$CH$_2$), 68.02-70.71, 173.54 (CO$_2$); IR 3450 (CO$_2$H), 2108 (N$_3$), 1743 (C=O), 1123 (C-O) cm$^{-1}$; ESI-MS m/z = 234 (M + H$^+$), calcd. m/z = 234.22 (M + H$^+$).

**Synthesis of Dendron 53.** To the stirred solution of acid 51 (560 mg, 2 mmol), DCC (496 mg, 2 mmol), and HOBT (325 mg, 2 mmol), Behera’s amine$^{100,101}$ (52; 1 g, 2 mmol) was added; the mixture was stirred at 25 °C for 15 h. After filtration, the solvent was evaporated *in vacuo* to give a viscous oil, which was column chromatographed (SiO$_2$) eluting with 95% CH$_2$Cl$_2$/EtOAc to give (92 %) pure azide 53, as a viscous oil: 1.4 g; $^1$H NMR δ 1.32 (s, 27 H, CH$_3$), 1.87 (t, 6 H, CH$_2$CH$_2$CO, $J = 8.4$ Hz), 2.09 (t, 6 H, CH$_2$CO, $J = 8.4$ Hz), 3.28 (t, 2 H, N$_3$CH$_2$, $J = 4.5$ Hz), 3.58-3.59 (m, 10 H), 3.78 (s, 2 H, OCH$_2$CO) 6.40 (s, 1 H, NH); $^{13}$C NMR δ 28.18 (CH$_3$), 29.69, 29.78 (CH$_2$CH$_2$CO), 50.74 (N$_3$CH$_2$), 57.28 (NHC), 70.16-71.33, 80.54 (CMe$_3$), 169.09 (CONH), 172.53 (CO$_2$); IR 2106 (N$_3$), 1726 (C=O), 1677 (C=O), 1153 (C-O) cm$^{-1}$; FAB-MS m/z = 632 (M + H$^+$), calcd. m/z = 631.77 (M + H$^+$).

**Synthesis of Dendron 54.** A suspension of azide 53 (3 g, 4.7 mmol) in EtOH (30 mL) with 10 % Pd-C under 60 p.s.i. hydrogen at 20 °C was stirred for 16 h, then carefully filtered to remove the catalyst (care: *pyrophoric*) and concentrated *in vacuo* to give a viscous liquid, which was column chromatographed (SiO$_2$) eluting with EtOAc → 10 % MeOH/EtOAc to afford (94 %) amine 54: 2.7 g; $^1$H NMR δ 1.30 (s, 27 H, CH$_3$), 1.84 (t, 6 H, CH$_2$CH$_2$O, $J = 6.6$ Hz), 2.07 (t, 6 H, CH$_2$O, $J = 6.6$ Hz), 3.04 (t, 2 H, H$_2$NCH$_2$, $J = 4.5$ Hz), 3.57-3.79 (m, 10 H), 3.84 (s, 2 H, CH$_2$CO), 5.21 (s, 1 H, NH), 6.56 (s, 2 H,
\( ^{13} \)C NMR \( \delta \) 27.94 (CH\(_3\)), 29.50 , 29.56 (CH\(_2\)CH\(_2\)O), 39.92 (H\(_2\)NCH\(_2\)), 57.24 (NHC), 67.86-70.57, 80.49 (CMe\(_3\)), 169.37 (CONH), 172.52 (CO\(_2\)); IR 3371 (NH\(_2\)), 1726 (C=O), 1661 (C=O), 1153 (C-O) cm\(^{-1}\); FAB-MS \( m/z = 606 \) (M + H\(^{+}\)), calcd. \( m/z = 605.77 \) (M + H\(^{+}\)).

**Synthesis of Dendron 55.** To the stirred solution of azide 53 (3 g, 4.7 mmol), HCO\(_2\)H was added, and then stirred for 6 h at 25 °C. The excess reagent was evaporated in vacuo, then toluene was added and again evaporated in vacuo to remove the last traces of formic acid to afford (95 %) the pure triacid 55: 2.08 g; \(^1\)H NMR \( \delta \) 2.03 (t, 6 H, CH\(_2\)CH\(_2\)O, \( J = 6.3 \) Hz), 2.26 (t, 6 H, CH\(_2\)O, \( J = 6.3 \) Hz), 3.18 (t, 2 H, N\(_3\)CH\(_2\), \( J = 4.5 \) Hz), 3.62-3.66 (m, 10 H), 3.87 (s, 2 H, CH\(_2\)CO), 6.56 (s, 1 H, NH), 9.54 (s, 3 H, CO\(_2\)H); \(^{13} \)C NMR \( \delta \) 28.15 (CH\(_2\)CO), 29.22 (CH\(_2\)CH\(_2\)CO), 50.06 (N\(_3\)CH\(_2\)), 56.60 (NHC), 69.32-70.41, 168.86 (CONH), 174.50 (CO\(_2\)H); IR 3358 (CO\(_2\)H), 2110 (N\(_3\)), 1716 (C=O), 1668 (C=O), 1104 (C-O) cm\(^{-1}\); FAB-MS \( m/z = 463 \) (M + H\(^{+}\)), calcd. \( m/z = 463.45 \) (M + H\(^{+}\)).

**Synthesis of Predendron 57.** To a stirred solution of 4-(2-carboxyethyl)-4-nitroheptanedioic acid\(^{104,105} \) (530 mg, 1.91 mmol), HOBT (780 mg, 5.7 mmol), and DCC (1.2 g, 5.7 mmol) in THF (50 mL) at 25 °C, amine 54 (3.5 g, 5.7 mmol) was added. After 48 h, the mixture was filtered, then the solvent removed in vacuo to give the crude dendron, which was column chromatographed (SiO\(_2\)) eluting with hexane to remove the excess DCC, then 10 % MeOH in CH\(_2\)Cl\(_2\) to afford (70 %) the desired predendron 57: 2.7 g; \(^1\)H NMR \( \delta \) 1.33 (s, 81 H, CH\(_3\)), 1.88 (t, 24 H, CH\(_2\)CH\(_2\)CO, \( J = 7.2 \) Hz), 2.10 (t, 24 H, CH\(_2\)CO, \( J = 7.2 \) Hz), 3.31 (t, 2 H, NHCH\(_2\), \( J = 4.8 \) Hz), 3.41-3.58 (m, 30 H), 3.84 (s, 6 H, NH\(_2\)).
CH₂CO), 6.42 (s, 3 H, NH), 6.72 (s, 3 H, NHCH₂); ¹³C NMR δ 28.04 (CH₃), 29.59, 29.70 (CH₂CH₂CO), 30.36, 30.78 (CH₂CH₂CO), 39.36 (NHCH₂), 57.18 (NHC), 69.77-70.81, 80.49 (CMe₃), 92.80 (O₂NC), 169.22 (CONH), 171.04 (CONH), 172.46 (CO₂); IR 1726 (C=O), 1670 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 2056.2 (M + Na⁺); calcd. m/z = 2059.23 (M + Na⁺)

**Synthesis of Dendron 58.** The predendron 57 (1 g, 490 µmol) was reduced (H₂, Raney Ni, 60 p.s.i, EtOH, 50 °C), to give (80 %) the corresponding amine 58, as a pale yellow liquid: 780 mg; ¹H NMR δ 1.24 (t, 24 H, CH₂CH₂CO, J = 6.9 Hz), 1.43 (s, 81 H, CH₃), 1.97 (t, 18 H, CH₂CO, J = 7.5 Hz), 2.20 (t, 6 H, CH₂CO, J = 7.5 Hz), 3.41 (t, 6 H, NHCH₂, J = 4.8 Hz), 3.53-3.69 (m, 30 H), 3.97 (s, 6 H, CH₂CO); ¹³C NMR δ 27.90 (CH₃), 29.43, 29.54, 30.52, 34.72 (CH₂CH₂CO), 39.10 (NHCH₂), 57.02 (NHC), 57.96 (H₂NC), 69.71-70.77, 80.33 (CMe₃), 169.02 (CONH), 172.27 (CONH), 173.25 (CO₂); IR 3333 (NH₂), 1728 (C=O), 1672 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 2030.34 (M + Na⁺), calcd. m/z = 2030.55 (M + Na⁺).

**Synthesis of Azide 59.** To the stirred solution of 55 (1 g, 2.16 mmol), EDC (1.24 g, 6.4 mmol), and HOBT (880 mg, 6.4 mmol), amine 54 (3.9 g, 6.4 mmol) was added in DMF (50 mL) at 25 °C. After 15h, the residue was filtered and the solution evaporated in vacuo to afford the crude product, which was column chromatographed eluting with 10% MeOH in CHCl₃ to give (65 %) pure azide 59: 3.12 g; ¹H NMR δ 1.31 (s, 81 H, CH₃), 1.88 (br m, 24 H, CH₂CH₂CO), 2.08 (br, 24 H, CH₂CO), 3.27 (t, 6 H, H₂NCH₂, J = 4.5 Hz), 3.41 (t, 2 H, N₃CH₂, J = 4.5 Hz), 3.52-3.57 (m, 40 H), 3.80 (s, 8 H, OCH₂CO), 6.41
(s, 3 H, NH), 6.43 (t, 3 H, NHCH2, J = 6 Hz), 6.45 (s, 1 H, NHC); 13C NMR δ 27.82 (CH3), 28.05, 29.39 (CH2CH2CO), 30.31, 30.68 (CH2CH2CO), 39.09 (NHCH2), 50.42 (N3CH2), 56.98 (NHC), 57.68 (NHC), 69.64-70.80, 80.26 (CMe3), 168.92 (CONH), 169.06 (CONH), 172.23 (CONH), 172.51 (CO2); IR 3335 (NH), 2106 (N3), 1726 (C=O), 1673 (C=O), 1152 (C-O) cm⁻¹; MALDI-TOF MS m/z = 2,245.76 (M + Na⁺), calcd. m/z = 2,245.76 (M + Na⁺).

**Synthesis of the 2nd Generation Dendron 60.** Azide 59 (2 gm, 890 µmol) was converted to its corresponding amine 60 by reduction with 10 % Pd/C at 60 p.s.i at 25 °C, as noted above. After 24 h, the mixture was filtered through the celite to remove the catalyst (care: pyrophoric), then the solvent was removed in vacuo to give (94 %) the pure amine 60: 1.85 g; 1H NMR δ 1.36 (s, 81 H, CH3), 1.99 (br m, 24 H, CH2CH2CO), 2.20 (br m, 24 H, CH2CO), 3.41 (br m, 8 H, NHCH2, CH2N3), 3.49-3.69 (m, 40 H), 3.94 (s, 8 H, OCH2CO), 6.52 (s, 3 H, NH), 7.31 (s, 5 H, NHCH2, H2NCH2), 7.44 (s, 1 H, NHC); 13C NMR δ 28.01 (CH3), 29.53, 29.67 (CH2CH2CO), 30.55, 31.23 (CH2CH2CO), 39.22 (NHCH2), 39.63 (NH2CH2), 57.15 (NHC), 58.19 (NHC), 69.53-70.92, 80.46 (CMe3), 169.15 (CONH), 170.08 (CONH), 172.39 (CONH), 173.60 (CO2); IR 3334 (NH2), 1724 (C=O), 1670 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 2,218.40 (M + Na⁺), calcd. m/z = 2,218.34 (M + Na⁺).

**Synthesis of 1st Generation Dendrimer 62. General Procedure.** To a stirred solution of amine 54 (2.5 g, 4.13 mmol) and NEt3 (2 g, 19.6 mmol) in dry CH2Cl2 (50 mL), was added tetraacid chloride 61 (500 mg, 1.0 mmol), prepared from the
corresponding tetraacid\(^{109}\) in CH\(_2\)Cl\(_2\) added drop wise. The mixture was stirred for 30 min at 0 °C and then 6 h at 25 °C. The mixture was washed sequentially with 10 % cold HCl, water, and satd. brine solution, then dried (MgSO\(_4\)), evaporated \textit{in vacuo} to give the crude product, which was column chromatographed (SiO\(_2\)) eluting with 7 % MeOH in CH\(_2\)Cl\(_2\) to afford (83 %) the pure dendrimer 62, as a viscous oil: 2.2 g; \(^1\)H NMR \(\delta\) 1.44 (s, 108 H, C\(\text{H}_3\)), 1.98 (t, 24 H, CH\(_2\)CH\(_2\)CO, \(J = 8.7\) Hz), 2.21 (t, 24 H, CH\(_2\)CO, \(J = 8.7\) Hz), 2.44 (t, 8 H, OCH\(_2\)CH\(_2\)CO, \(J = 6.0\) Hz), 3.31 (s, 8 H, OCH\(_2\)), 3.45 (t, 8 H, OCH\(_2\)CH\(_2\)CO, \(J = 4.8\) Hz), 3.56 (t, 8 H, NHCH\(_2\), \(J = 4.8\) Hz), 3.66-3.68 (m, 40 H), 3.93 (s, 8 H, OCH\(_2\)CO), 6.47 (s, 4 H, NH), 6.83 (t, 4 H, NHCH\(_2\), \(J = 2.0\) Hz); \(^{13}\)C NMR \(\delta\) 27.71 (C\(\text{H}_3\)), 29.26, 29.40 (C\(\text{H}_2\)C\(\text{H}_2\)), 36.34 (CH\(_2\)CO), 38.92 (NHCH\(_2\)), 45.12 (\(\text{C}^4\)C), 56.85 (NHC), 67.04 (OCH\(_2\)CH\(_2\)), 68.80 (CH\(_2\)OCH\(_2\)), 69.57-70.67 (OCH\(_2\)), 80.04 (CMe\(_3\)), 168.80 (CONH), 171.07 (CONH), 172.03 (CO\(_2\)); IR 3342 (NH), 1724 (C=O), 1672 (C=O), 1153 (C-O) cm\(^{-1}\); MALDI-TOF MS \(m/z = 2,792.35\) (M + Na\(^+\)), calcd. \(m/z = 2,794.50\) (M + Na\(^+\)).

**Synthesis of 1\(^{st}\) Generation Dendrimer Acid 63.** A solution of dodecaester 62 (1 g, 360 µmol) in 95% formic acid (50 mL) was stirred for 12 h. After concentration, toluene (50 mL) was added and the solution was again concentrated \textit{in vacuo} to afford (95 %) viscous oil: 720 mg; \(^1\)H NMR \(\delta\) 1.98 (t, 24 H, CH\(_2\)CH\(_2\)CO, \(J = 8.7\) Hz), 2.21 (t, 24 H, CH\(_2\)CO, \(J = 8.7\) Hz), 2.44 (t, 8 H, OCH\(_2\)CH\(_2\)CO, \(J = 6.0\) Hz), 3.31 (s, 8 H, OCH\(_2\)), 3.45 (t, 8 H, OCH\(_2\)CH\(_2\)CO, \(J = 4.8\) Hz), 3.56 (t, 8 H, NHCH\(_2\), \(J = 4.8\) Hz), 3.66-3.68 (m, 40 H), 3.93 (s, 8 H, OCH\(_2\)CO), 6.47 (s, 4 H, NH), 6.83 (t, 4 H, NHCH\(_2\), \(J = 2.0\) Hz); \(^{13}\)C NMR \(\delta\) 29.29, 30.71 (CH\(_2\)CH\(_2\)CO), 37.68 (CH\(_2\)CO), 40.46 (NHCH\(_2\)), 46.74 (\(\text{C}^4\)C), 58.82 (NHC), 68.71 (OCH\(_2\)CH\(_2\)), 70.61 (CH\(_2\)OCH\(_2\)), 71.26-72.12 (OCH\(_2\)), 172.10 (CONH),
174.31 (CONH), 176.94 (CO₂H); IR 3342 (NH), 1724 (C=O), 1672 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 2,067.35 (M - H⁺), calcd. m/z = 2,067.12 (M - H⁺).

**Synthesis of 2nd Generation Mono-PEG Extended Dendrimer 64.** The 2nd generation dendrimer was prepared using the amine 58 (8.1 g, 4.03 mmol) and tetraacyl chloride (500 mg, 1.0 mmol), following the above General Procedure. Purification was accomplished by chromatography eluting with 5% MeOH in CH₂Cl₂ to afford (70 %) the pure dendrimer 64, as a waxy semisolid: 5.8 g; ¹H NMR δ 1.33 (s, 324 H, CH₃), 1.88 (t, 96 H, CH₂CH₂CO, J = 7.5 Hz), 2.16 (t, 96 H, CH₂CO, J = 7.5 Hz), 2.78 (t, 8 H, OCH₂CH₂, J = 3.9 Hz), 3.28 (s, 8 H, CH₂O), 3.33 (s, 8 H, OCH₂), 3.42 (t, 8 H, OCH₂CH₂CO, J = 3.9 Hz), 3.54 (t, 24 H, NHCH₂, J = 6.0 Hz), 3.59 (m, 120 H), 3.82 (s, 24 H, OCH₂CO), 6.38 (s, 12 H, NH), 6.81 (s, 4 H, NHCH₂), 6.92 (s, 4 H, NH); ¹³C NMR δ 28.05 (CH₃), 29.60, 29.77 (CH₂CH₂CO), 30.5, 30.72 (CH₂CH₂CO), 37.47 (CH₂CO), 39.29 (NHCH₂), 45.33 (¹⁴C), 57.17 (NHC), 57.71 (NHC), 66.19 (CH₂OCH₂), 67.80 (CH₂OCH₂), 69.75-70.97 (OCH₂), 80.48 (CMe₃), 169.00 (CONH), 172.41 (CONH), 173.29 (CONH), 173.36 (CO₂); IR 3331 (NH), 1726 (C=O), 1669 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 8,406.10 (M + Na⁺), calcd. m/z = 8,405.59 (M + Na⁺).

**Synthesis of 2nd Generation Mono-PEG Extended Dendrimer Acid 65.** Dendrimer 64 (500 mg, 59 µmol) was deprotected in a procedure similar to that of 62 to give (90 %) the corresponding dendritic acid 65, as a waxy solid: 340 mg; ¹H NMR δ 1.88 (t, 96H, CH₂CH₂CO, J = 7.5 Hz), 2.16 (t, 96 H, CH₂CO, J = 7.5 Hz), 2.78 (t, 8 H, OCH₂CH₂, J = 3.9 Hz), 3.28 (s, 8 H, CH₂O), 3.33 (s, 8 H, OCH₂), 3.42 (t, 8 H, OCH₂CH₂, J = 3.9 Hz), 3.54 (t, 24 H, NHCH₂, J = 6.0 Hz), 3.59 (m, 120 H), 3.82 (s, 24 H, OCH₂CO), 6.38 (s, 12 H, NH), 6.81 (s, 4 H, NHCH₂), 6.92 (s, 4 H, NH); ¹³C NMR δ 28.05 (CH₃), 29.60, 29.77 (CH₂CH₂CO), 30.5, 30.72 (CH₂CH₂CO), 37.47 (CH₂CO), 39.29 (NHCH₂), 45.33 (¹⁴C), 57.17 (NHC), 57.71 (NHC), 66.19 (CH₂OCH₂), 67.80 (CH₂OCH₂), 69.75-70.97 (OCH₂), 80.48 (CMe₃), 169.00 (CONH), 172.41 (CONH), 173.29 (CONH), 173.36 (CO₂); IR 3331 (NH), 1726 (C=O), 1669 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 8,406.10 (M + Na⁺), calcd. m/z = 8,405.59 (M + Na⁺).
OCH₂CH₂CO, J = 3.9 Hz), 3.54 (t, 24 H, NHCH₂, J = 6.0 Hz), 3.59 (m, 120 H), 3.82 (s, 24 H, OCH₂CO), 6.38 (s, 12 H, NH), 6.81 (s, 4 H, NHCH₂), 6.92 (s, 4 H, NH); ¹³C NMR δ 29.37, 30.74 (CH₂CH₂CO), 32.15, 32.65 (CH₂CH₂CO), 38.35 (CH₂CO), 40.54 (NHCH₂), 46.53 (³⁴C), 57.18 (NHC), 58.86 (NHC), 67.21 (CH₂OCH₂), 67.95 (CH₂OCH₂), 70.56-72.11 (OCH₂), 172.15 (CONH), 173.65 (CONH), 175.94 (CONH), 177.09 (CO₂H); IR 3331 (NH), 1726 (C=O), 1669 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 6,360.72 (M - H⁺), calcd. m/z = 6,361.58 (M - H⁺).

Synthesis of 2nd Generation Bis-PEG Extended Dendrimer 66. The 2nd generation dendrimer can be prepared via amine 60 (1.75 g, 790 µmol) and tetraacyl chloride 61 (100 mg, 200 µmol) using the General Procedure. The residual solid was column chromatographed (SiO₂) eluting with 5% MeOH in CH₂Cl₂ to give (63%) the pure dendrimer 66, as a waxy solid: 1.1 g; ¹H NMR δ 1.29 (s, 324 H, CH₃), 1.84 (t, 96 H, CH₂CH₂CO, J = 8.4 Hz), 2.06 (t, 96 H, CH₂CO, J = 8.4 Hz), 2.29 (t, 8 H, OCH₂CH₂, J = 4.8 Hz), 3.26 (t, 8 H, OCH₂, J = 4.8 Hz), 3.39 (t, 32 H, NHCH₂, NHCH₂ J = 5.1 Hz), 3.50-3.55 (br m, 160 H), 3.78 (s, 32 H, OCH₂CO), 6.37 (s, 16 H, NH), 6.69 (br m, 16 H, NHCH₂); ¹³C NMR δ 27.90 (CH₃), 29.44, 29.58 (CH₂CH₂CO), 30.40, 30.85 (CH₂CH₂CO), 36.46 (CH₂CO), 39.13 (NHCH₂), 45.38 (C), 57.04, 57.76 (2 NHC), 67.26, 68.97 (2 CH₂OCH₂), 69.61-70.78 (OCH₂), 80.32 (CMe₃), 168.95, 169.35, 171.25, 172.28 (4 CONH), 172.95 (CO₂); IR 3334 (NH), 1724 (C=O), 1670 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 9,115.98 (M + Na⁺), calcd. m/z = 9,120.36 (M + Na⁺).
Synthesis of 2nd Generation Bis-PEG Extended Dendrimer Acid 67.

Dendrimer 66 (500 mg, 54 µmol) was dissolved in 95% formic acid (50 mL) and stirred for 24 h to afford (88%) pure dendrimer acid 67, as a waxy solid: 340 mg; 1H NMR δ 1.84 (t, 96 H, CH₂CH₂CO, J = 8.4 Hz), 2.06 (t, 96 H, CH₂CO, J = 8.4 Hz), 2.29 (t, 8 H, OCH₂CH₂, J = 4.8 Hz), 3.26 (t, 8 H, OCH₂, J = 4.8 Hz), 3.39 (t, 32 H, NHCH₂J = 5.1 Hz), 3.50-3.55 (br m, 160 H), 3.78 (s, 32 H, OCH₂CO), 6.37 (s, 16 H, NH), 6.69 (br m, 16 H, NHCH₂); 13C NMR δ 29.40, 29.85 (CH₂CH₂CO), 30.79, 31.22 (CH₂CH₂CO), 35.87 (CH₂CO), 40.59 (NHCH₂), 45.89 (C), 58.87, 58.96 (2 NHC), 67.26, 68.97 (2 CH₂OCH₂), 69.61-70.78 (OCH₂), 171.25, 172.15, 172.28 174.10 (4 CONH), 177.07 (CO₂H); IR 3334 (NH), 1724 (C=O), 1670 (C=O), 1153 (C-O) cm⁻¹; MALDI-TOF MS m/z = 7,116.45 (M - H⁺), calcd. m/z = 7,118.42 (M - H⁺).

2.7. References


85. Choi, J. S.; Lee, E. J.; Choi, Y. H.; Jeong, Y. J.; Park, J. S. Poly(ethylene glycol)-


CHAPTER III

TAILORING OF DENDRITIC POROSITY: SYNTHESIS OF A \([1 \rightarrow 2] C\)-BRANCHED MONOMER AND CONVERSION TO \([1 \rightarrow 2]\) AND \([(1 \rightarrow 2) + (1 \rightarrow 3)]\) \(C\)-BRANCHED DENDRIMERS

3.1. Introduction

Dendrimers,\(^1\)\(^-\)\(^4\) with their generally globular structure,\(^5\) have been shown to act as highly branched, unimolecular micelles\(^6\)-\(^13\) owing to their propensity to encapsulate guest molecules\(^14\)-\(^21\) by classical lipophilic/hydrophilic and \(H\)-bonding interactions or by steric-induced, internal “void” region trapping based on surface congestion at higher generations or simple capping with bulky termini. Newkome et al. first proposed\(^6\) and then reported\(^22,23\) an example of a unimolecular micelle that incorporated the lipophilic/hydrophilic features of a classical micelle into a single molecule (23, Fig. 11). Molecular probes, used for traditional micellar characterization such as pinacyanol chloride, phenol blue, chlortetracycline, and naphthalene, were each encapsulated as demonstrated by UV and fluorescence techniques.\(^24\) As well, fluorescence lifetime decay experiments using \((1,6\text{-dicyclohexyl})\text{hexatriene}\), as the guest, were used and examine the lipophilic character of the hydrocarbon infrastructure. Meijer et al.\(^25\) reported the elegant
synthesis of a “dendritic box,” which was comprised of the 5th generation poly(propylenimine) dendrimer possessing ideally 64 amine termini (24, Fig.11). This dendrimer in the presence of dye molecules, e.g. Rose Bengal, was capped with bulky, Boc-protected L-phenylalanine moieties, which successfully trapped the dye within the dendrimer, as shown by EPR, UV, and fluorescence studies. As the degree-of-branching increased or the synthetic perfection increased, the number of guests (dye molecules) decreased, indicating the importance to control the degree-of-branching as well as the homogeneity of the internal superstructure. Properties, such as functional group density, void volume, hydrophobicity, and internal molecular recognition can be modified by the preparation of building blocks that facilitate a modular synthetic approach.

Fréchet et al. reported the encapsulation of pyrene and fluorescent dyes within the water-soluble poly(aryl)ether dendrimer as supported by the enhanced solubility of pyrene in water in the presence of the dendrimer. Grinstaff et al. prepared poly-(glycerol-succinic acid) dendrimer, which encapsulated solvatochromic dye and anticancer drugs, such as: Reichardt’s dye and 10-hydroxycamptothecin, respectively. Crooks et al. prepared metal-encapsulated dendrimers using PAMAM and PPI dendrimers capitalizing on these inner cavities; these dendrimers were shown to be useful in catalysis. More recently, Thayumanavan and co-workers reported the preparation of dendrimers possessing hydrophobic and hydrophilic substituents. The authors demonstrated that these dendrimers act as hydrophilic nanocontainers in the presence of non-polar solvents and as hydrophobic nanocontainers in the presence of polar solvents. Moore et al. showed that longer linkers or connectors permitted attachment of bulky
dendrons to a core, thus introducing an alternative route to control the size of the internal void regions.

Previously, monomers possessing $[1 \rightarrow 3],[35-38]$ $[1 \rightarrow (2 + 1)]^{39}$ C-branching motifs were created to control the speed-of-construction as well as the location of internal functionality within the molecular confines. The related linear $[1 \rightarrow (1 + 2 \text{ Me})]$ C-analogue$^{40}$ was prepared so that there would be a more traditional benchmark for comparative purposes. Herein, is reported the synthesis of the missing $[1 \rightarrow (2 + 1 \text{ Me})]$ C-branched monomer to complete the family of related building blocks. The construction of the dendritic family up to the 5$^{th}$ generation based on this monomer was prepared by

Figure 13. Fréchet’s unimolecular micelle.
convergent and divergent approaches; these products were characterized by $^1$H NMR, $^{13}$C NMR, ESI, MALDI-TOF MS, and GPC techniques. Also the $[(1 \rightarrow 2) + (1 \rightarrow 3)]$ branched dendrons were prepared and transformed to the corresponding four-directional dendrimer.

3.2. Synthesis of dendrons.

The addition of 2 equivalents of tert-butyl acrylate to nitroethane (Scheme 12) in the presence of tetramethylguanidine (TMG) in dimethoxymethane generated (73 %) the predendron 68, which was structurally confirmed ($^{13}$C NMR) by the presence of a singlet at 170.8 ppm for the ester carbonyl as well as two peaks at 89.6 (O$_2$NC) and 80.4 ppm (Me$_3$C), as well as the ESI-MS at $m/z = 354.0$ [M + Na$^+$]. Reduction of nitro group with T-1 Raney nickel in EtOH at 50 °C gave (95 %) the corresponding amino diester 69, which was characterized by the distinctive up-field shift from 89.6 to 51.6 ppm for the O$_2$NC; there were no significant changes for other peaks.

Deprotection of 68 with 95% formic acid at 25 °C quantitatively gave the corresponding diacid 70, which showed the absence ($^1$H NMR) of tert-butyl peaks and appearance of a peak at 9.4 ppm for the carboxylic acid protons, as well as the down field shift ($^{13}$C NMR) of carbonyl group from 170.8 (ester C=O) to 173.4 (acid C=O) ppm further confirming the complete conversion.

The treatment (Scheme 12) of acid 70 with two equivalents of amine 69 under typical peptide conditions$^{41,42}$ gave (80 %) the 2$^{nd}$ generation predendron 71, which was easily purified by column chromatography. The $^{13}$C NMR spectral data showed two
peaks for the two methyl groups at 21.7 and 23.6 ppm and two carbonyl groups 170.4 and 173.2 ppm as well as ESI-MS peak at 808.6 [M + Na$^+$]. The nitro group was reduced with T-1 Raney Ni catalyst to afford (90%) the corresponding amine 72, which was supported by the chemical shift for the CNO$_2$ to CNH$_2$ conversion (90.5 to 55.8 ppm) and the MS peak at 778.6 [M + Na$^+$]. Hydrolysis of 71 with formic acid gave the 4-acid 75, which was confirmed by the signal at 174.8 ppm (CO$_2$H) and the disappearance of the tert-butyl peaks (80.6 ppm, $\text{CMes}$; 28.1 ppm, $\text{CH}_3$). The ESI-MS spectrum further confirmed its identity, showing a molecular ion peak at $m/z$ = 560.2 [M - H$^+$] (calc. $m/z$ = 560.5 [M - H$^+$]).

![Scheme 12. Synthesis of 1$^\text{st}$ and 2$^\text{nd}$ generation dendrons; a) CH$_2$=CHCO$_2$t-bu, TMG; b) H$_2$, Raney Ni, EtOH, 50 ºC, 12 h; c) HCO$_2$H, 25 ºC, 7 h; d) DCC, HOBT, THF, amine 69, 25 ºC, 12 h; e) DCC, HOBT, Behera’s amine [H$_2$NC(CH$_2$CH$_2$CO$_2$t-bu)$_3$], THF, 25 ºC, 12 h.](image)
The 2\textsuperscript{nd} generation [1 $\rightarrow$ 2] C-branched capped with [1 $\rightarrow$ 3] C-branched predendron 73 was prepared in a similar way to that of 71 except for the substitution of 69 with Behera’s amine.\textsuperscript{38} The hexaester 73 was identified by the presence (\textsuperscript{13}C NMR) of one single peak for methyl group at 21.8 ppm and two peaks at 170.5, 173.0 ppm for carbonyl groups, as well as MS peak at 1036.7 [M + Na\textsuperscript{+}]. The catalytic reduction of 73 (Scheme 12) with T-1 Raney nickel gave (90 \%) the desired amine 74, which was confirmed by the up-field chemical shift (\textsuperscript{13}C NMR) for the CNO\textsubscript{2} to CNH\textsubscript{2} (90.5 to 51.5 ppm) conversion and the MS peak at 1006.8 [M + Na\textsuperscript{+}].

The 3\textsuperscript{rd} generation predendron 76 was prepared in the same manner (Scheme 13) as that for 2\textsuperscript{nd} generation nitro dendron by the treatment of 4-acid 75 with diester amine 69. The structure of 76 was identified by the appearance of an additional new carbonyl group (CONH) and the ESI-MS spectrum exhibited the expected molecular ion signal at m/z 1718.6 [M + Na\textsuperscript{+}] (calc. m/z 1718.2 [M + Na\textsuperscript{+}]). Reduction of the nitro group of 76 with T-1 Raney Ni in absolute EtOH at 50 °C gave 3\textsuperscript{rd} generation amine 77. This was supported by the chemical shift for the quaternary carbon from 90.2 to 50.7 ppm (R\textsubscript{3}CNO\textsubscript{2} and R\textsubscript{3}CNH\textsubscript{2}, respectively). The molecular ion peak at m/z 1688.1 [M + Na\textsuperscript{+}] (calc. m/z 1688.2 [M + Na\textsuperscript{+}]) in ESI-MS further supported the identity of the amine dendron 77.
Scheme 13. Synthesis of 3rd generation dendron 77; a) HCO₂H, 25 °C, 7 h; b) DCC, HOBT, DMF, amine 69, 15 h.; c) H₂, Raney Ni, EtOH, 50 °C, 15 h.


The treatment of tetraacyl chloride 61 with excess amine 69 in the presence of triethylamine (Et₃N) in dry CH₂Cl₂ afforded (80 %) the corresponding 1st generation dendrimer 78 (Scheme 14). Evidence for the formation of the dendrimer 78 was confirmed by the presence (¹³C NMR) of two carbonyl groups at 170.5 and 172.5 ppm, three quaternary carbon peaks at 79.7 (Me₃C), 54.7 (HNC), and 45.0 (C⁴°) ppm as well as the molecular ion peak in ESI-MS spectrum at 1579.7 (M + Na⁺).

Formation of the octacarboxylic acid dendrimer 79 was accomplished (90 %) by the treatment of 78 with formic acid at 25 °C for 12 hours. The total loss of the signals at 27.7 (CH₃) and 79.7 (CMe₃) ppm (¹³C NMR) for the tert-buty1 carbons confirms the deprotection. The ESI-MS peak showed a single peak at m/z 1109.6 [M - H⁺; calc. mass
and the IR spectrum revealed the expected broad stretch for O-H stretching (3500-3000 cm\(^{-1}\)) and C=O absorption (1700 cm\(^{-1}\) for carboxylic acid vs 1730 cm\(^{-1}\) for the ester peak of 78) for the COOH moiety to confirm the transformation.

Scheme 14. Synthesis of 1\(^{\text{st}}\) generation dendrimers 78 and 79: a) Et\(_3\)N, CH\(_2\)Cl\(_2\), amine 68, 25 °C, 6 h; b) HCO\(_2\)H, 25 °C, 12 h.

Octaacid 79 was further treated with excess diester amine 69 in the presence of DCC and 1-HOBT to yield (75 %) the 2\(^{\text{nd}}\) generation dendrimer 80 (Scheme 15) possessing a molecular weight of 3397.2 amu (MALDI-TOF MS: \(m/z\) 3396.9 [M + Na\(^+\)]).

Further evidence for the formation of 80 is the presence (\(^{13}\)C NMR) of two peaks for two methyl groups at 23.6 and 24.0 ppm as well as two new peaks at 55.5 and 173.0 ppm corresponding to \(^{4}\)CNH and CONH carbon signals from the new generation. Repetition
of the reaction sequences used in the conversion of 1\textsuperscript{st} generation octaester 78 to 2\textsuperscript{nd} generation dendrimer 80 afforded the construction of 3\textsuperscript{rd} generation dendrimer 83. Thus, hydrolysis of 80 with formic acid yielded (83 \%) polyacid 81 with a 2478.3 amu (calculated formula weight 2477.8 amu). The $^{13}$C NMR spectrum in DMSO-d$_6$ revealed loss of the $\tau$-butyl ester related peaks at 28.0, 80.2, and 173.1 ppm. A new peak at 177.5 ppm was observed for the carbonyl carbon of the carboxylic acid (CO$_2$H) group. The broad peak in the IR spectrum of 81 for the OH stretching (3550-3000 cm$^{-1}$) and the intense absorption (1700 cm$^{-1}$) for the C=O absorption indicated the conversion of ester to acid functionality.

Scheme 15. Synthesis of 2\textsuperscript{nd} generation dendrimers 80, 81, and 82: a) DCC, 1-HOBT, amine 69, 25 °C, 24 h; b) Et$_3$N, Behera’s amine, CH$_2$Cl$_2$, 25 °C, 6 h; c) HCO$_2$H, 25 °C, 24 h.
This polyacid 81 on further treatment with diester amine under the traditional coupling conditions using DCC and 1-HOBT in DMF afforded (67 %) (Scheme 16), which has 32 tert-butyl ester groups in the periphery of the resultant dendrimer. Evidence for the formation of 83 was obtained from $^{13}$C NMR spectra and MALDI-TOF MS ($m/z = 7038.5$ [M + Na$^+$], calcd $m/z = 7036.3$). The carbons from the tetrakis-core located in the dendritic interior appeared as small signals compared with the intense peaks observed for those of the 32 peripheral tert-butyl ester moieties. Three peaks for three methyl groups at 23.9, 24.0, and 24.2 ppm and three peaks at 55.2, 55.6, and 55.8 ppm corresponding to the three unique set of quaternary carbons ($^{4^\circ}$CNH), which are the branching points for each generation provided the key evidence for the formation of 83.

Dendrimer 83 on treatment with formic acid afforded (70 %) the 3rd generation dendrimer acid with 32 acid groups 84, which gave a molecular ion peak in the MALDI-TOF MS spectrum at $m/z = 5217.6$ [M - H$^+$]. The conversion of 83 to 84 was inferred from the loss of the intense peak at 1725 cm$^{-1}$ (ester C=O) and the appearance of a broad peak between 3560-3000 cm$^{-1}$ (O-H stretch) and an intense C=O absorption at 1700 cm$^{-1}$. DCC coupling reaction of (excess) diester amine 69 with the 3rd generation acid 84 in DMF, as the solvent, yielded 4th generation dendrimer 86 (Scheme 17). Key signals in the $^{13}$C NMR spectrum at 57.4, 57.6 ($^{4^\circ}$CNH), 173.2 (CONH, CO$_2$) ppm; and a sharp peak at $m/z = 14,308.7$ [M + Na$^+$] (calcd $m/z = 14,310.1$ [M + Na$^+$]) supported the assigned structure of 86.

Deprotection of the 64 peripheral tert-butyl ester groups of 86 was effected by the treatment with formic acid at 25 ºC for 36 h affording (80 %) the 4th generation acid 87. Residual formic acid was removed by dialysis of 87 in a methanol and water mixture using a 1000 MWCO membrane. The superstructure of 87 was established (¹³C NMR) by the total absence of the distinctive signals for the tert-butyl group carbons at 28.0 and 80.3 ppm, and appearance of a downfield signal at δ 177.8 for the terminal acid carbon atom.

The 64-acid 87 was coupled with di-tert-butyl 4-amino-4-methylheptanedioate (69) in the presence of DCC and 1-HOBT in dry DMF to afford (45 %) the 5th generation dendrimer 89 (Scheme 18), which was characterized by the ¹³C NMR spectrum, which showed new signals corresponding to the terminal generation at 28.1 (CH₃), 80.5 (CMe₃) ppm and other expected signals. The molecular ion peak in MALDI-TOF MS at m/z 28,894.3 [M + Na⁺] (calc. 28,892.6) further proved the formation of dendrimer. The 5th generation dendrimer 89 was then deprotected with 95% formic acid at 25 °C for 48 h to quantitatively give the 128-acid 91, which was confirmed by the disappearance of the tert-butyl absorptions in ¹³C NMR as well as the expected downfield shift for the carboxylic carbonyl group to 175.3 ppm; the MALDI-TOF MS revealed a molecular ion peak at m/z 21,653.6 [M - H⁺].

The 2nd - 5th generation dendrimers capped with Behera’s amine were prepared in a similar manner to the above dendrimers by treating 1st, 2nd, 3rd, and 4th generation dendrimer acids (71, 81, 84, and 87, respectively) with Behera’s amine in the presence of DCC and 1-HOBT in DMF.

3.4. B. Convergent Approach.

Dendrimers up to three generations were also prepared by the convergent approach (Scheme 19) by the reaction between the tetraacyl chloride and the 1st, 2nd, and 3rd generation dendrons (78, 80, and 83, respectively) to produce corresponding
dendrimers. These dendrimers were exactly the same to those prepared by divergent approach.

Scheme 19. Convergent construction of 2\textsuperscript{nd} and 3\textsuperscript{rd} generation dendrimers 80 and 83: a) Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, amine 72, 25 ºC, 6 h; b) Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, amine 77, 25 ºC, 7 h.

The formation of dendrimers was also characterized by gel permeation chromatography (Figure 14). All of the dendritic architectures exhibited narrow molar mass distribution (polydispersity: 1.01-1.07). The molecular weights obtained from GPC are in good agreement with ESI-MS and MALDI-TOF MS spectrometry. The physical properties of these dendrimers are very similar to that of [1 \rightarrow 3] C-branched dendritic family. All the tert-butyl protected dendrons and dendrimers are fairly soluble in a wide range of organic solvents such as CHCl\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, EtOAc, MeOH, and THF and the acid-terminated dendrons and dendrimers are soluble in MeOH, and water.
3.5. Preparation of Quantum Dots.

Quantum dots or nanocrystals are semiconductor nanoparticles with unique optical and electronic properties. During the past decade, quantum dots have been extensively studied due to their potential use in biology, nanotechnology, and specifically chemosensors. Quantum dots have also been incorporated into a wide variety of polymers as well as dendritic architectures.

The stable CdS/dendrimer nanocomposites were prepared following the method of Murphy et al. using 4th and 5th generation \([1 \to (2 + 1 \text{ Me})] \) C-branched dendrimer acids \((1.2 \times 10^{-4} \text{ M})\) and the stock solutions of \(\text{Cd}^{2+}\) and \(\text{S}^{2-}\) \((2.0 \text{ mM})\). The dendrimer/CdS nanocomposites were excited with a light at a wavelength of 350 nm to
measure luminescence spectra, which showed emission maxima at 530 nm (Figure 15). The dendrimer encapsulated CdS quantum dots may be useful for fabricating photovoltaic devices, and other chemosensors.

![Figure 15](image)

Figure 15. UV-vis spectrum and photoluminescence spectra (inset) for CdS/dendrimer nanocomposites.


Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. All of chemicals were purchased from Aldrich Co. except for Behera’s amine. Tetrahydrofuran (THF) was dried by refluxing over benzophenone/Na under N₂. Dichloromethane was dried over CaH₂. All other commercially available solvents were used without further purification. Column
chromatography was conducted using silica gel (60-200 mesh) from Fisher Scientific with the stipulated solvent mixture. $^1$H and $^{13}$C NMR spectra were obtained in CDCl$_3$, except where noted, and are recorded at 300 and 75 MHz, respectively. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded on an ATI Mattson Genesis Series FTIR spectrometer. Mass spectral data were obtained using an Esquire electron ionization mass spectrometer (ESI) and are reported as: (assignment, relative intensity); ESI samples were typically prepared in MeOH/H$_2$O/TFA (70:30:01) for positive ion mode or Me$_2$CHOH/H$_2$O/NH$_3$ (70:30:1) for negative ion mode and matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer.

**Di-tert-butyl 4-Methyl-4-nitroheptanedioate (67).** Tert-butyl acrylate was added (37.6 g, 66.3 mmol, 2.2 equiv.) portion-wise over a period of 20 min to a stirred solution of nitroethane (10 g, 30 mmol) and tetramethylguanidine (TMG) in EtOH (200 mL). After stirring at 50 °C for 15 h, the solvent was concentrated *in vacuo* to give crude oil, which was dissolved in CHCl$_3$ and washed with water, then sat. brine, dried (MgSO$_4$), filtered, and concentrated *in vacuo* to afford (73 %) the desired diester 67, as a white solid: 31.4 g; mp 55-57 °C; $^1$H NMR $\delta$ 1.44 (s, 6H, CH$_3$), 1.53 (s, 3H, CH$_3$), 2.20 (t, 4H, CH$_2$CH$_2$, $J = 7.4$ Hz), 2.27 (t, 4H, CH$_2$CH$_2$, $J = 7.4$ Hz); $^{13}$C NMR $\delta$ 21.4 (CH$_3$), 27.7 (CMe$_3$), 29.8 (CH$_2$CH$_2$CO), 33.9 (CH$_2$CO), 80.4 (CMe$_3$), 89.6 (O$_2$NC), 170.8 (CO$_2$); IR 1731 (C=O), 1540 (NO$_2$) cm$^{-1}$; ESI-MS: $m/z = 354.4$ [M + Na$^+$]; calc. $m/z = 354.4$ [M + Na$^+$].
**Di-**tert-**butyl 4-Amino-4-methylheptanedioate (68).** A solution of di-**tert-**butyl ester 67 (5 g, 16 mmol) in EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (60 p.s.i) at 50 °C for 15 h. After the solution was cautiously (pyrophoric) filtered through celite, the solvent was removed in vacuo to afford (95 %) amine 68, as a viscous liquid: 4.3 g; ¹H NMR δ 1.0 (s, 3H, CCH₃), 1.41 (s, 6H, CH₃), 1.57 (t, 4H, CH₂CO, J = 8.1 Hz), 2.21 (t, 4H, CH₂CH₂CO, J = 8.1 Hz), 5.83 (s, 2H, NH₂); ¹³C NMR δ 21.1 (CH₃), 28.1 (CH₃), 29.9 (CH₂CO), 35.2 (CH₂CH₂CO), 51.6 (H₂NC), 81.1 (CMe₃), 173.0 (CO₂); IR 3378 (NH₂), 1728 (C=O) cm⁻¹; ESI-MS: m/z = 324.0 [M + Na⁺], calc. m/z = 324.4 [M + Na⁺].

**4-Methyl-4-nitroheptanedioic Acid (69).** A solution of di-**tert-**butyl ester 67 (7 g, 21 mmol) in 95 % formic acid (50 mL) was stirred at 25 °C for 12 h. After concentration in vacuo, toluene (2 x 25 mL) was added and the solution was again concentrated in vacuo to afford a crude solid, which was solidified from water to give (86.5%) diacid 69, as a white powder: 4.0 g; mp 114-116 °C; ¹H NMR δ 1.55 (s, 6H, CH₃), 2.35 (t, 4H, CH₂CH₂, J = 7.2 Hz), 2.81 (t, 4H, CH₂CH₂, J = 7.2 Hz); ¹³C NMR δ 21.4 (CH₃), 28.6 (CH₂CH₂CO), 33.6 (CH₂CO), 90.4 (CNO₂), 173.4 (CO₂H); IR 3360 (br, acid OH), 1730 (C=O), 1535 (NO₂) cm⁻¹; ESI-MS: m/z = 218.9 [M - H⁺], calc. m/z = 218.1 [M - H⁺].

**Synthesis of Predendron 70.** To a stirred solution of 4-methyl-4-nitroheptanedioic acid (69; 1.9 g, 8.66 mmol) in dry THF (100 mL), was added DCC (4.5 g, 21 mmol) and 1-HOBT (2.9 g, 21 mmol) at 25 °C. After 30 min, amine 68 (6.6 g, 21
mmol) was added. The mixture was stirred for an additional 24 h, after which the white precipitate was filtered. The filtrate was concentrated \textit{in vacuo} to give a crude oil, which was column chromatographed (SiO$_2$) eluting with CHCl$_3$ to afford (78 %) the 2\textsuperscript{nd} generation dendron 70, as a white solid: 5.3 g; mp 160-161 °C; $^1$H NMR $\delta$ 1.28 (s, 6H, CCH$_3$), 1.52 (s, 3H, CH$_3$), 1.63 (t, 8H, CH$_2$CO, $J = 4.2$ Hz), 1.90 (t, 8H, CH$_2$CH$_2$CO, $J = 4.2$ Hz), 2.04 (t, 4H, CH$_2$CH$_2$CO, $J = 7.2$ Hz), 2.24 (t, 4H, CH$_2$CH$_2$CO, $J = 7.2$ Hz), 5.94 (s, 2H, NH); $^{13}$C NMR $\delta$ 21.7 (CH$_3$), 23.6 (CH$_3$), 28.1 (CH$_3$), 30.3 (CH$_2$CH$_2$CO), 31.5 (CH$_2$CO), 80.6 (CMe$_3$), 90.5 (O$_2$N), 170.4 (CONH), 173.2 (CO$_2$); IR 1728 (ester C=O), 1653 (amide C=O) cm$^{-1}$; ESI-MS: $m/z = 808.6$ [M + Na$^+$], calc. $m/z = 809.0$ [M + Na$^+$].

**Synthesis of Dendron 71.** The nitro dendron 70 (5 g, 6.36 mmol) was reduced (H$_2$, Raney Ni, 60 p.s.i., EtOH, 50 °C), in a procedure similar to that of 68, to give (94 %) corresponding amine 71, as a white solid: 4.5 g; mp 151-152 °C; $^1$H NMR $\delta$ 1.05 (s, 6H, CH$_3$), 1.24 (t, 8H, CH$_2$CH$_2$CO, $J = 6.0$ Hz), 1.43 (s, 36H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.66 (t, 8H, CH$_2$CO, $J = 6.0$ Hz), 1.96 (t, 4H, CH$_2$CH$_2$CO, $J = 6.3$ Hz), 2.22 (t, 4H, CH$_2$CO, $J = 6.4$ Hz), 6.10 (s, 1H, NH), 6.12 (s, 2H, NH$_2$); $^{13}$C NMR $\delta$ 23.6 (CH$_3$), 27.5 (CH$_3$), 28.0 (CMe$_3$), 30.2 (CH$_2$CH$_2$CO), 32.1 (CH$_2$CO), 33.2 (CH$_2$CH$_2$CO), 37.9 (CH$_2$CO), 50.9 (HNC), 55.8 (H$_2$N), 80.3 (CMe$_3$), 172.7 (CONH), 173.0 (CO$_2$); IR 3330 (br, NH$_2$), 1730 (ester C=O), 1653 (amide C=O) cm$^{-1}$; ESI-MS: $m/z = 778.6$ [M + Na$^+$]; calc. $m/z = 779.0$ [M + Na$^+$].

**Synthesis of Predendron 72.** To a stirred solution of 4-methyl-4-nitroheptanedioic acid (69; 2 g, 9.12 mmol) in dry THF (100 mL) was added DCC (4.7 g,
23 mmol) then 1-HOBT (3.08 g, 23 mmol) at 25 °C. After 30 min, Behera’s amine 51 (9.5 g, 23 mmol) was added. The mixture was stirred for an additional 24 h, and then the precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed (SiO\textsubscript{2}) eluting with a 10% EtOAc in CHCl\textsubscript{3} solvent mixture to afford (73 %) the 2\textsuperscript{nd} generation nitro predendron 72, as a white solid: 6.75 g; mp 191-192 °C; ¹\textsuperscript{H} NMR δ 1.44 (s, 54H, CH\textsubscript{3}), 1.52 (s, 3H, CH\textsubscript{3}), 1.96 (t, 16H, CH\textsubscript{2}CH\textsubscript{2}CO, CH\textsubscript{2}CO, J = 7.5 Hz), 2.21 (t, 16H, CH\textsubscript{2}CO, CH\textsubscript{2}CH\textsubscript{2}CO, J = 7.5 Hz), 6.16 (s, 1H, NH); ¹³C NMR δ 21.8 (CH\textsubscript{3}), 28.2 (CH\textsubscript{3}), 30.0 (CH\textsubscript{2}CH\textsubscript{2}CO), 31.7 (CH\textsubscript{2}CO), 35.1 (CH\textsubscript{2}CH\textsubscript{2}CO), 57.7 (HNC), 80.9 (CMe\textsubscript{3}), 90.5 (CNO\textsubscript{2}), 170.5 (CONH), 173.0 (CO\textsubscript{2}); IR 1730 (ester C=O), 1651 (amide C=O), 1531 (NO\textsubscript{2}) cm\textsuperscript{-1}; ESI-MS m/z = 1,036.7 [M + Na\textsuperscript{+}]; calc. m/z = 1,037.2 [M + Na\textsuperscript{+}].

**Synthesis of Dendron 73.** The nitro predendron 72 (1 g, 980 mmol) was reduced (H\textsubscript{2}, Raney Ni, 60 p.s.i., EtOH, 50 °C) in a procedure similar to that of 68 to give (92 %) the corresponding amine 73, as a white solid: 900 mg; mp 172-173 °C; ¹\textsuperscript{H} NMR δ 1.05 (s, 3H, CH\textsubscript{3}), 1.25 (t, 4H, CH\textsubscript{2}CH\textsubscript{2}CO, J = 6.0 Hz), 1.44 (s, 54H, CH\textsubscript{3}), 1.67 (t, 4H, CH\textsubscript{2}CO, J = 6.0 Hz), 1.96 (t, 12H, CH\textsubscript{2}CH\textsubscript{2}CO, J = 7.8 Hz), 2.22 (t, 4H, CH\textsubscript{2}CO, J = 7.8 Hz), 6.11 (s, 3H, NH, NH\textsubscript{2}); ¹³C NMR δ 27.2 (CH\textsubscript{3}), 28.1 (CH\textsubscript{3}), 29.9 (CH\textsubscript{2}CH\textsubscript{2}CO), 30.0 (CH\textsubscript{2}CO), 32.2 (CH\textsubscript{2}CH\textsubscript{2}CO), 37.9 (CH\textsubscript{2}CO), 51.5 (H\textsubscript{2}NC), 57.4 (HNC), 80.6 (CMe\textsubscript{3}), 172.6 (CONH), 172.9 (CO\textsubscript{2}); IR 3356 (br, NH\textsubscript{2}), 1728 (ester C=O), 1651 (amide C=O) cm\textsuperscript{-1}; ESI-MS: m/z = 1,006.8 [M + Na\textsuperscript{+}], calc. m/z = 1,007.3 [M + Na\textsuperscript{+}].
Synthesis of Tetraacid 74. A solution of tetraester 70 (5 g, 6.36 mmol) in 95% formic acid (70 mL) was stirred at 25 °C for 12 h. After concentration in vacuo, toluene (2 x 25 mL) was added and the solution was again concentrated in vacuo to afford a crude solid, which was recrystallized from water to give (96%) the acid 74, as a white powder: 3.4 g; mp 209-210 °C; \( ^1 \)H NMR \( \delta 1.27 \) (s, 6H, CH₃), 1.29 (s, 3H, CH₃), 1.65 (t, 8H, CH₂CO, \( J = 4.5 \) Hz), 1.92 (t, 8H, CH₂CH₂CO, \( J = 4.5 \) Hz), 2.01 (t, 4H, CH₂CO, \( J = 7.0 \) Hz), 2.26 (t, 4H, CH₂CH₂CO, \( J = 7.0 \) Hz), 5.94 (s, 2H, NH), 10.31 (br m, 4H, CO₂H); \( ^{13} \)C NMR \( \delta 21.1 \) (CH₃), 23.3 (CH₃), 28.7, 30.5 (CH₂CH₂CO₂H), 32.9, 34.8 (CH₂CH₂CO), 54.3 (NHC), 91.0 (O₂NC), 170.6 (CONH), 174.8 (CO₂H); IR 3358 (br, acid OH), 1728 (ester C=O), 1650 (amide C=O), 1535 (NO₂ cm\(^{-1}\)); ESI-MS: \( m/z = 560.2 \) [M - H\(^+\)], calc. \( m/z = 560.5 \) [M - H\(^+\)].

3\(^{rd}\) Generation [1 \( \rightarrow \) 2] C-Branched Predendron 75. To a solution of tetraacid 74 (2 g, 3.5 mmol) in dry DMF (100 mL) were added DCC (3 g, 14.5 mmol) and 1-HOBT (2 g, 14.5 mmol) at 25 °C. The mixture was stirred for 30 min and then amine 68 (4.4 g, 14.5 mmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed eluting with EtOAc/hexane (1:2) to yield (67%) the 3\(^{rd}\) generation nitro predendron 75, as a solid foam: 4.0 g; mp 113-115 °C; \( ^1 \)H NMR \( \delta 1.23 \) (s, 12H, CH₃), 1.25 (s, 6H, CH₃), 1.27 (s, 3H, CH₃), 1.45 (s, 72H, CCH₃), 1.90 (br, 28H, CH₂CH₂CO, CH₂CH₂CONH), 2.23 (br m, 28H, CH₂CO, CH₂CONH), 6.41 (s, 6H, NH); \( ^{13} \)C NMR \( \delta 22.2 \) (CH₃), 23.5 (CH₃), 23.6 (CH₃), 27.9 (CH₃), 30.1 (CH₂CH₂CO), 31.2 (CH₂CO), 31.6 (CH₂CH₂CONH), 33.1 (CH₂CONH), 34.2 (CH₂CH₂CONH), 34.3
(CH$_2$CONH), 54.9 (NHC), 55.3 (NHC), 80.1 (CMe$_3$), 90.2 (O$_2$NC), 170.8 (CONH), 172.8 (CONH), 172.9 (CO$_2$); IR 1728 (ester C=O), 1653 (amide C=O), 1539 (NO$_2$) cm$^{-1}$; ESI-MS: $m/z$ = 1,718.6 [M + Na$^+$], calc. $m/z$ = 1,718.2 [M + Na$^+$].

3$^{rd}$ Generation [1 $\rightarrow$ 2] C-Branched Dendron 76. A mixture of nitro predendron 75 (4 g, 2.3 mmol), and T-1 Raney Ni in absolute EtOH (150 mL) was hydrogenated at 60 psi at 50 °C for 24 h. The solution was cautiously filtered through celite. The solvent was concentrated in vacuo and the residue was chromatographed (SiO$_2$) eluting with EtOAc to give (82 %) amine 76, as a foam solid: 3.2 g; mp 88-89 °C; $^1$H NMR $\delta$ 1.21 (s, 12H, CH$_3$), 1.24 (s, 6H, CH$_3$), 1.25 (s, 3H, CH$_3$), 1.44 (s, 72H, C$\text{C}_3$H$_3$), 1.93 (br, 28H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CONH), 2.25 (br, 28H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CONH), 6.43 (s, 8H, NH); $^{13}$C NMR $\delta$ 23.3 (CH$_3$), 23.5 (CH$_3$), 27.3 (CH$_3$), 27.7 (CCH$_3$), 30.0 (CH$_2$CH$_2$CO), 31.4 (CH$_2$CO), 31.8 (CH$_2$CH$_2$CONH), 32.9 (CH$_2$CONH), 34.1 (CH$_2$CH$_2$CONH), 37.8 (CH$_2$CONH), 50.7 (H$_2$NC), 54.7 (NHC), 54.9 (NHC), 79.8 (CMe$_3$), 172.7 (CONH), 172.7 (CONH), 173.1 (CO$_2$); IR 3330 (br, NH$_2$), 1730 (ester C=O), 1653 (amide C=O) cm$^{-1}$; ESI-MS: $m/z$ = 1,688.1 [M + Na$^+$], calc. $m/z$ = 1,688.2 [M + Na$^+$].

Synthesis of Dendrimers: 1$^{st}$ Generation Dendrimer 77. General Procedure

A. To a stirred solution of amine 68 (2.5 g, 4.13 mmol) and Et$_3$N (2 g, 19.6 mmol) in dry CH$_2$Cl$_2$ (100 mL) was added drop wise tetraacid chloride 60 (500 mg, 1.0 mmol), prepared from the corresponding tetraacid,$^{36}$ in CH$_2$Cl$_2$ (30 mL). The mixture was stirred for 30 min at 0 °C, then 6 h at 25 °C. The mixture was washed sequentially with 10 % cold HCl, water, and satd. brine solution, then dried (MgSO$_4$) and evaporated in vacuo to
give the crude product, which was column chromatographed (SiO₂) eluting with an
EtOAc/CHCl₃ (1:1) mixture to afford (80 %) the 1ˢᵗ generation dendrimer 77, as a white
solid: 1.24 g; mp 104-105 °C; ¹H NMR δ 1.24 (s, 12H, CH₃), 1.43 (s, 72H, CH₃), 1.90 (t,
16H, CH₂CH₂CO, J = 7.5 Hz), 2.23 (t, 16H, CH₃CO, J = 7.5 Hz), 2.35 (t, 8H, OCH₂CH₂,
J = 5.7 Hz), 3.32 (s, 8H, CH₂O), 3.65 (t, 8H, OCH₂CH₂, J = 5.7 Hz), 6.39 (s, 4H, NH);
¹³C NMR δ 23.4 (CH₃), 27.7 (CH₃), 29.9 (CH₂CH₂CO), 32.9 (CH₂CO), 36.9, (CH₂CO),
45.0 (CCH₂O), 54.7 (HNC), 67.1 (CH₂OCH₂), 68.5 (OCH₂), 79.7 (CMe₃), 170.5
(CONH), 172.5 (CO₂); IR 3343 (br, NH), 1730 (ester C=O), 1650 (amide C=O) cm⁻¹;
ESI-MS: m/z = 1,579.7 [M + Na⁺]; calc. m/z = 1,581.0 [M + Na⁺].

1ˢᵗ Generation Dendritic Acid 78. A solution of dendrimer 77 (5 g, 3.2 mmol) in
formic acid (50 mL) was stirred at 25 °C for 12 h. After concentration, water was added
and the solution was again concentrated in vacuo to afford (90 %) octaacid 78, as a white
solid: 3.2 g; ¹H NMR δ 1.26 (s, 12H, CH₃), 1.91 (t, 16H, CH₂CH₂CO, J = 4.8 Hz), 2.32
(t, 16H, CH₂CO, J = 4.8 Hz), 2.40 (t, 8H, OCH₂CH₂, J = 5.4 Hz), 3.41 (s, 8H, CH₂O),
3.64 (t, 8H, OCH₂CH₂, J = 5.4 Hz), 6.39 (s, 4H, NH), 9.4 (s, 8H, COOH); ¹³C NMR δ
24.3 (CH₃), 30.2 (CH₂CH₂CO), 34.7 (CH₂CO), 38.5, (CH₂CO), 46.8 (CCH₂O), 56.6
(HNC), 69.0 (CH₂OCH₂), 71.4 (CH₂OCH₂), 174.1 (CONH), 178.0 (CO₂H); IR 3500 (br,
acid OH), 1700 (acid C=O), 1652 (amide C=O) cm⁻¹; ESI-MS: m/z = 1,109.6 [M - H⁺];
calc. m/z = 1,108.1 [M - H⁺].

2ⁿᵈ Generation Dendrimer 79 was prepared using amine 71 (6.9 g, 9.12 mmol)
and tetraacid chloride (1 g, 2.0 mmol) by General Procedure A. Purification was
accomplished by column chromatography (SiO<sub>2</sub>) eluting with EtOAc to afford (75 %) pure 2<sup>nd</sup> generation dendrimer 79, as a white solid: 5.1 g; mp 83-84 °C; <sup>1</sup>H NMR δ 1.22 (s, 24H, CH<sub>3</sub>), 1.26 (s, 12H, CH<sub>3</sub>), 1.43 (s, 144H, CH<sub>3</sub>), 1.90 (t, 32H, CH<sub>2</sub>CH<sub>2</sub>CO, J = 8.4 Hz), 2.08 (t, 32H, CH<sub>2</sub>CO, J = 8.4 Hz), 2.10 (t, 16H, CH<sub>2</sub>CH<sub>2</sub>CNHNH, J = 7.5 Hz), 2.22 (t, 16H, CH<sub>2</sub>CNHNH, J = 7.5 Hz), 2.34 (t, 16H, CH<sub>2</sub>CONH, J = 7.5 Hz), 3.34 (s, 8H, CH<sub>2</sub>O), 3.62 (t, 8H, CH<sub>2</sub>OCH<sub>2</sub>), 6.40 (s, 8H, NH), 6.8 (s, 4H, NH); <sup>13</sup>C NMR δ 23.6 (CH<sub>3</sub>), 24.0 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 30.3 (CH<sub>2</sub>CH<sub>2</sub>CO), 31.9 (CH<sub>2</sub>CO), 33.2 (CH<sub>2</sub>CH<sub>2</sub>CNHNH), 34.5 (CH<sub>2</sub>CNHNH), 37.8 (CH<sub>2</sub>CO), 45.3 (CCH<sub>2</sub>O), 55.0 (HNC), 55.5 (HNC), 67.7 (CH<sub>2</sub>OCH<sub>2</sub>), 69.5 (CH<sub>2</sub>OCH<sub>2</sub>), 80.2 (CMe<sub>3</sub>), 171.2 (CONH), 173.0 (CONH), 173.1 (CO<sub>2</sub>); IR 3330 (br, NH), 1729 (ester C=O), 1650 (amide C=O) cm<sup>-1</sup>; MALDI-TOF MS m/z = 3,396.9 [M + Na<sup>+</sup>], calc. m/z = 3,397.2 [M + Na<sup>+</sup>].

2<sup>nd</sup> Generation Dendritic Acid 80 was prepared from 2<sup>nd</sup> generation dendrimer (1 g, 296 µmol) ester by following the procedure for 78. The product 80 was obtained (83 %) as a white solid: 610 mg; mp 153-154 °C; <sup>1</sup>H NMR δ 1.25 (s, 24H, CH<sub>3</sub>), 1.30 (s, 12H, CH<sub>3</sub>), 1.91 (t, 32H, CH<sub>2</sub>CH<sub>2</sub>CO, J = 5.1 Hz), 2.09 (t, 32H, CH<sub>2</sub>CO, J = 5.1 Hz), 2.24 (t, 16H, CH<sub>2</sub>CH<sub>2</sub>CNHNH, J = 5.4 Hz), 2.30 (t, 16H, CH<sub>2</sub>CNHNH, J = 5.4 Hz), 2.44 (t, 8H, CH<sub>2</sub>CONH, J = 5.4 Hz), 3.39 (s, 8H, CH<sub>2</sub>O), 3.66 (t, 8H, CH<sub>2</sub>CO), 7.44 (s, 8H, NH), 7.57 (s, 4H, NH), 9.44 (s, 16H, COOH); <sup>13</sup>C NMR δ 23.9 (CH<sub>3</sub>), 24.36 (CH<sub>3</sub>), 29.9 (CH<sub>2</sub>CH<sub>2</sub>CO), 32.6 (CH<sub>2</sub>CO), 34.4 (CH<sub>2</sub>CH<sub>2</sub>CNHNH), 35.6 (CH<sub>2</sub>CNHNH), 38.49 (CH<sub>2</sub>CO), 46.7 (CCH<sub>2</sub>O), 56.2 (HNC), 56.3 (HNC), 69.0 (CH<sub>2</sub>OCH<sub>2</sub>), 70.5 (CH<sub>2</sub>OCH<sub>2</sub>), 173.7 (CONH), 175.7 (CONH), 177.5 (CO<sub>2</sub>H); IR 3550 (br, acid OH), 1700
(acid C=O), 1650 (amide C=O) cm\(^{-1}\); MALDI-TOF MS \(m/z = 2,478.3\ [M - H^+]\), calc. \(m/z = 2,477.8\ [M - H^+]\).

**2nd Generation \([1 \rightarrow 2]\) C-Branched Dendrimer with \([1 \rightarrow 3]\) C-Branched Exterior 81** was prepared using amine 72 (3.9 g, 3.9 mmol) and tetraacid chloride (500 mg, 1.0 mmol) using Route A. Purification was accomplished by column chromatography (SiO\(_2\)) eluting with EtOAc to afford (75 %) pure 2\(^{nd}\) generation dendrimer 81, as a white solid: 3.2 g; mp 91-92 °C; \(^1\)H NMR \(\delta\) 1.22 (s, 12H, C\(_H_3\)), 1.44 (s, 216H, C\(_H_3\)), 1.96 (t, 64H, CH\(_2\)CH\(_2\)CO, CH\(_2\)CH\(_2\)CONH, \(J = 7.5\) Hz), 2.21 (t, 64H, CH\(_2\)CH\(_2\)CO, CH\(_2\)CH\(_2\)CONH, \(J = 7.5\) Hz), 2.36 (t, 8H, OCH\(_2\)CH\(_2\), \(J = 7.5\) Hz), 3.36 (s, 8H, CH\(_2\)O), 3.63 (t, 8H, OCH\(_2\)CH\(_2\), \(J = 7.5\) Hz), 6.30 (s, 8H, NH), 7.00 (s, 4H, NH); \(^13\)C NMR \(\delta\) 24.2 (CH\(_3\)), 28.0 (CH\(_3\)), 28.3 (CH\(_2\)CH\(_2\)CO), 29.7 (CH\(_2\)CO), 32.0 (CH\(_2\)CH\(_2\)CONH), 34.6 (CH\(_2\)CONH), 37.4 (CH\(_2\)CONH), 45.3 (CCH\(_2\)O), 55.6 (HNC), 57.2 (HNC), 67.7 (CH\(_2\)OCH\(_2\)), 69.5 (CH\(_2\)OCH\(_2\)), 80.4 (CMe\(_3\)), 171.2 (CONH), 172.6 (CONH), 172.9 (CO\(_2\)); IR 3331 (br, NH), 3331 (ester C=O), 1653 (amide C=O) cm\(^{-1}\); MALDI-TOF MS \(m/z = 4,309.5\ [M + Na^+]\), calc. \(m/z = 4,312.5\ [M + Na^+]\).

**3rd Generation \([1 \rightarrow 2]\) C-Branched Dendrimer 82.** To a stirred solution of 16-acid 80 (1 g, 400 µmol) in dry DMF (50 mL), was added DCC (1.4 g, 6.7 mmol), then 1-HOBT (900 mg, 6.7 mmol) at 25 °C. After 1h, amine 68 (1.95 g, 6.7 mmol) was added. The mixture was stirred for 48 h, after which the white precipitate was filtered. The filtrate was concentrated *in vacuo* to give a crude oil, which was column chromatographed (SiO\(_2\)) eluting 10 % MeOH in EtOAc to afford (67 %) the 3\(^{rd}\)
generation dendrimer 82, as a white solid: 950 mg; mp 85-86 ºC; $^1$H NMR $\delta$ 1.21 (br, 84 H, CH$_3$), 1.43 (s, 288 H, CH$_3$), 1.88 (br m, 112H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CONH), 2.02 (br m, 112H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CONH), 2.91 (br m, 8H, OCH$_2$CH$_2$), 3.25 (s, 8H, CH$_2$O), 3.63 (br m, 8H, OCH$_2$CH$_2$), 6.82 (s, 28H, NH); $^{13}$C NMR $\delta$ 23.9 (CH$_3$), 24.0 (CH$_3$), 24.2 (CH$_3$), 28.3 (CMe$_3$), 30.6 (CH$_2$CH$_2$CO), 31.9 (CH$_2$CO), 33.5 (CH$_2$CH$_2$CONH), 34.3 (CH$_2$CONH), 34.5 (CH$_2$CH$_2$CONH), 37.8 (CH$_2$CONH), 45.7 (CCH$_2$O), 55.2 (HNC), 55.6 (HNC), 55.8 (HNC), 67.5 (CH$_2$OCH$_2$), 69.5 (CH$_2$OCH$_2$), 80.4 (CMe$_3$), 171.3 (CONH), 173.2 (CONH), 173.3 (CONH), 173.3 (CO$_2$); IR 3332 (br, NH), 1725 (ester C=O) cm$^{-1}$; MALDI-TOF MS $m/z$ = 7,038.5 [M + Na$^+$]; calc. $m/z$ = 7,036.3 [M + Na$^+$].

3rd Generation Dendritic Acid 83. The tert-butyl groups were removed using similar procedure to that of 78 to afford (70 %) the 3rd generation acid 83, as a white solid: 410 mg; mp 118-119 ºC; $^1$H NMR $\delta$ 1.27 (br, 84 H, CH$_3$), 1.88 (br m, 112 H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CONH), 2.02 (br m, 112H, CH$_2$CO, CH$_2$CONH), 2.91 (br m, 8H, OCH$_2$CH$_2$), 3.25 (s, 8H, CH$_2$O), 3.63 (br m, 8H, OCH$_2$CH$_2$), 6.82 (br m, 28H, NH), 9.23 (br m, 32H, CO$_2$H); $^{13}$C NMR $\delta$ 22.8 (CH$_3$), 23.1 (CH$_3$), 23.3 (CH$_3$), 28.9 (CH$_2$CH$_2$CO), 31.4 (CH$_2$CO), 33.3 (CH$_2$CH$_2$CONH), 34.3 (CH$_2$CONH), 34.5 (CH$_2$CH$_2$CONH), 37.3 (CH$_2$CO), 45.6 (CCH$_2$O), 55.1 (HNC), 55.2 (HNC), 55.6 (HNC), 67.5 (CH$_2$OCH$_2$), 69.5 (CH$_2$OCH$_2$), 172.5 (CONH), 174.6 (CONH), 176.5 (CONH), 178.3 (CO$_2$); IR 3560-3000 (br, acid OH), 1700 (acid C=O), 1646 (amide C=O) cm$^{-1}$; MALDI-TOF MS: $m/z$ = 5,217.6 [M - H$^+$]; calc. $m/z$ = 5,216.8 [M - H$^+$].
3rd Generation [1 → 2] C-Branched Dendrimer with [1 → 3] C-Branched

Exterior 84 was prepared using similar procedure to that of 81 to afford (65%) 3rd generation dendrimer 84, as a white solid: 2.3 g; mp 83-85 °C; 1H NMR δ 1.23 (s, 24H, CH3), 1.27 (s, 12H, CH3), 1.43 (s, 432H, CCH3), 1.92 (br m, 144H, CH2CH2CO, CH2CH2CONH), 2.23 (br m, 144H, CH2CO, CH2CONH), 2.38 (br m, 8H, OCH2CH2), 3.32 (s, 8H, CH2O), 3.65 (br m, 8H, OCH2CH2), 6.41 (br m, 28H, NH); 13C NMR δ 23.7 (CH3), 25.1 (CH3), 28.0 (CH3), 29.7 (CH2CH2CO), 31.7 (CH2CO), 34.4 (CH2CH2CONH), 37.4 (CH2CH2CONH), 46.7 (C), 55.4 (HNC), 57.2 (HNC), 65.7 (CH2O), 67.8 (OCH2), 80.3 (CMe3), 172.7 (CONH), 172.9 (CO2); IR 3332 (br, NH), 1752 (ester C=O), 1652 (amide C=O) cm⁻¹; MALDI-TOF MS: m/z = 8,861.92 [M + Na⁺], calc. m/z = 8,862.7 [M + Na⁺].

4th Generation [1 → 2] C-Branched Dendrimer 85 was prepared using a similar procedure to that of 82; the product was purified using 1000 MWCO membrane in MeOH to afford (57%) pure dendrimer 85, as a white solid: 1.5 g; mp 78-79 °C; 1H NMR δ 1.25 (br, 180H, CH3), 1.45 (s, 576H, CCH3), 1.94 (br m, 240H), 2.23 (br m, 240H), 2.35 (br m, 8H, OCH2CH2), 3.34 (s, 8H, CH2O), 3.82 (br m, 8H, OCH2CH2), 6.43 (br s, 60H, NH); 13C NMR δ 23.7 (br, CH3), 28.0 (CH3), 30.3 (CH2CH2CO), 31.7 (CH2CO), 33.2 (CH2CH2CONH), 35.5 (CH2CH2CONH), 37.4 (CH2CO), 46.4 (C), 57.4 (HNC), 57.6 (HNC), 80.1 (CMe3), 173.0 (CONH, CO2); IR 3334 (br, NH), 1752 (ester C=O), 1653 (amide C=O) cm⁻¹; MALDI-TOF MS m/z = 14,311.7 [M + Na⁺], calc. m/z = 14,310.1 [M + Na⁺].
4th Generation [1 → 2] C-Branched Dendritic Acid 86 was prepared (80 %) from dendrimer ester 85 (1 g, 7 µmol) using formic acid: 590 mg; mp 96-97 ºC; 1H NMR δ 1.28 (br, 180H, CH₃), 1.96 (br m, 240H), 2.27 (br m, 240H), 2.39 (br m, 8H, OCH₂CH₂), 3.37 (s, 8H, CH₂O), 3.85 (br m, 8H, OCH₂CH₂), 6.49 (br s, 60H, NH), 9.1 (br, 64H, CO₂H); 13C NMR δ 24.0 (CH₃), 24.2 (CH₃), 24.3 (CH₃), 24.6 (CH₃), 30.0 (CH₂CH₂CO), 32.6 (CH₂CH₂CO), 34.5 (CH₂CH₂CO), 34.7 (CH₂CH₂CO), 35.5 (CH₂CO), 46.4 (C), 56.3 (HNC), 56.6 (HNC), 58.3 (HNC), 173.4 (CONH), 175.53 (CO₂H); IR 3540 (br, acid OH), 1700 (acid C=O), 1653 (amide C=O) cm⁻¹; MALDI-TOF MS m/z = 10,697.2 [M - H⁺], calc. m/z = 10,695.0 [M - H⁺].

4th Generation [1 → 2] C-Branched Dendrimer with [1 → 3] C-Branched Exterior 87 was prepared (55 %) using acid 32-acid 83 (1 g, 190 µmol) and Behera’s amine (2.54 g, 6.1 mmol) in the presence of DCC (1.26 g, 6.1 mmol), HOBT (820 mg, 6.1 mmol) in DMF (50 mL). The reaction mixture was stirred for 2 days, the crude dendrimer was purified by dialysis using 1000 MWCO membrane in a 10% water-MeOH solution: 1.9 g; mp 82-83 ºC; 1H NMR δ 1.23 (br, 84H, CH₃), 1.46 (s, 864H, CCH₃), 1.92 (br m, 304H), 2.27 (br m, 304H), 2.36 (br m, 8H, OCH₂CH₂), 3.32 (s, 8H, CH₂O), 3.85 (br m, 8H, OCH₂CH₂), 6.42 (60H, NH); 13C NMR δ 23.8 (CH₃), 25.1 (CH₃), 28.1 (CH₃), 29.77 (CH₂CH₂CO), 31.8 (CH₂CH₂CO), 34.3 (CH₂CH₂CO), 37.5 (CH₂CH₂CO), 46.7 (C), 51.6 (HNC), 55.4 (HNC), 57.2 (HNC), 65.7 (CH₂O), 67.8 (OCH₂), 80.3 (CMe₃), 172.7 (CONH), 173.0 (CO₂); IR 3540 (br, NH), 1700 (acid C=O), 1653 (amide C=O); MALDI-TOF MS m/z = 17,964.10 [M + Na⁺], calc. m/z = 17,963.0 [M + Na⁺].
5\textsuperscript{th} Generation 1 → 2 C-Branched Dendrimer 88 was prepared using acid 86 (500 mg, 460 µmol) and amine 68 (900 mg, 2.9 mmol) to afford (45 %) 88 as a white solid: 600 mg; mp 77-78 ºC; \(^1\)H NMR \(\delta\) 1.27 (br, 372H, \(CH_3\)), 1.42 (s, 1152H, CCH\(_3\)), 1.95 (br m, 496H), 2.27 (br m, 496H), 2.36 (br m, 8H, OCH\(_2\)CH\(_2\)), 3.35 (s, 8H, CH\(_2\)O), 3.81 (br m, 8H, OCH\(_2\)CH\(_2\)), 6.46 (124H, NH); \(^{13}\)C NMR \(\delta\) 23.5 (br, \(CH_3\)), 28.1 (CH\(_3\)), 29.4 (br, CH\(_2\)CO), 29.8 (br, CH\(_2\)CH\(_2\)CO), 45.8 (br, \(\beta-C\)), 57.3-57.9 (br, NHC), 80.5 (CMe\(_3\)), 172.9 (CONH), 173.6 (CO\(_2\)); IR, 3345 (br, NH), 1753 (ester C=O), 1653 (amide C=O) cm\(^{-1}\); MALDI-TOF MS \(m/z\) = 28,894.3 [M + Na\(^+\)]; calc. \(m/z\) = 28,892.6 [M + Na\(^+\)].

5\textsuperscript{th} Generation [1 → 2] C-Branched Dendrimer with [1 → 3] C-Branched Exterior 89. Acid 86 (500 mg, 460 µmol) was treated with Behera’s amine (1.4 g, 3.3 mmol) to obtain (48 %) the 5\textsuperscript{th} generation dendrimer 89, as a white solid: 200 mg; mp 77-78 ºC; \(^1\)H NMR \(\delta\) 1.25 (br, 180H, \(CH_3\)), 1.43 (s, 1728H, CCH\(_3\)), 1.94 (br m, 624H), 2.26 (br m, 624H), 2.39 (br m, 8H, OCH\(_2\)CH\(_2\)), 3.31 (s, 8H, CH\(_2\)O), 3.83 (br m, 8H, OCH\(_2\)CH\(_2\)), 6.45 (br s, 124H, NH); \(^{13}\)C NMR \(\delta\) 23.7 (br, \(CH_3\)), 27.9 (CH\(_3\)), 28.5 (CH\(_2\)CH\(_2\)CO), 29.6 (CH\(_2\)CH\(_2\)CO), 45.6 (C), 57.9 (br, NHC), 80.2 (CMe\(_3\)), 172.5 (CONH), 173.5 (CO\(_2\)); IR 3339 (br, NH), 1751 (ester C=O), 1650 (amide C=O) cm\(^{-1}\); MALDI-TOF MS \(m/z\) = 36,199.3 [M + Na\(^+\)]; calc. \(m/z\) = 36,198.6 [M + Na\(^+\)].

5\textsuperscript{th} Generation [1 → 2] C-Branched Dendritic Acid 90 was prepared (76 %) from dendrimer ester 90 (1 g, 3.4 µmol) using formic acid: 560 mg; mp 85-86 ºC; \(^1\)H NMR \(\delta\) 1.23 (br, 372H, \(CH_3\)), 1.91 (br m, 496H), 2.23 (br m, 496H), 2.32 (br m, 8H,
OCH$_2$CH$_2$), 3.34 (s, 8H, CH$_2$O), 3.80 (br m, 8H, OCH$_2$CH$_2$), 6.41 (124H, NH), 8.9 (br, 128H, CO$_2$H); $^{13}$C NMR δ 23.4 (br, CH$_3$), 29.2 (br, CH$_2$CO), 29.7 (br, CH$_2$CH$_2$CO), 45.5 (br, $^{44}$C), 57.3-57.9 (br, NHC), 172.9 (CONH), 175.3 (CO$_2$H); IR, 3545 (br, acid OH), 1705 (acid C=O), 1650 (amide C=O) cm$^{-1}$; MALDI-TOF MS m/z = 21,653.6 [M - H$^+$]; calc. m/z = 21,651.4 [M - H$^+$].

**Preparation of Quantum dots:** The 4$^{th}$ (64-Acid) and 5$^{th}$ (128-Acid) generation [1 → (2 + 1Me)] C-branched dendrimer acids were dissolved in MeOH as ca. 1.2 × 10$^{-4}$ M solution. The 2.0 mM stock solutions of Cd$^{2+}$ and S$^{2-}$ were freshly prepared by dissolving 12.4 mg of Cd(NO$_3$)$_2$ · 4H$_2$O in 20 mL of MeOH, and by dissolving 3.0 mg of Na$_2$S in 20 mL of MeOH. In the standard incremental addition procedure, a Cd$^{2+}$ methanolic stock solution was added to dendrimer methanolic stock solution at 0 ºC, followed by addition of S$^{2-}$ methanolic solution. UV/Vis absorption spectra were obtained on Hewlett-Packard UV/Vis spectrophotometer. Photoluminescence spectra were obtained using a Perkin-Elmer LS55 spectrometer.

3.7. References


4.1. Introduction

The design and synthesis of dendrimers and dendritic polymers gained considerable attention during the last two decades due to their tailor-made applications.\textsuperscript{1} The large number of functional groups and globular shape at higher generations cause dendritic architectures to behave differently when compared to the linear polymers, in that dendrimers have high solubility and low viscosity in organic solvents. Although numerous synthetic pathways are available for the construction of dendritic architectures, there are mainly two categories: divergent construction\textsuperscript{2} where the growth begins from the core to periphery and convergent construction,\textsuperscript{3} dendritic branches or dendrons are connected to the central core moiety. Many functional dendrimers were prepared and exploited in the areas of unimolecular micelles,\textsuperscript{4,5} drug delivery,\textsuperscript{6,7} immunoassays,\textsuperscript{8} catalysis,\textsuperscript{9} MRI contrast agents\textsuperscript{10,11} sensors,\textsuperscript{12} light harvesting molecules,\textsuperscript{13,14} liquid crystals,\textsuperscript{15} chromatography,\textsuperscript{16-21} and light-emitting diodes.\textsuperscript{22,23}
Recently, we reported\textsuperscript{21,24} the synthesis and application of benzyl-terminated sol-gel dendrons in capillary microextraction. Efficient extraction of a wide range of analytes from their aqueous solutions was accomplished using sol-gel, dendron-coated, fused-silica capillaries. Low parts-per-trillion level detection limits were achieved in capillary microextraction-gas chromatography (CME-GC) for both polar and nonpolar analytes including polyaromatic hydrocarbons (PAHs), aldehydes, ketones, phenols, and alcohols.

Here, the synthesis of cyano-terminated, sol-gel dendrons and their application in CME-GC are reported. Characterization of the sol-gel cyano-dendron-coating was done using Fourier Transform-InfraRed (FT-IR) and Thermogravimetric Analysis (TGA). TGA data were indicative of high thermal stability of sol-gel cyano-dendron-coating. CME-GC experiments indicated that sol-gel cyano-dendron coating possesses several advantageous features over conventional coatings, for example, faster mass transfer rate, significantly higher thermal and solvent stability, wide-range of applications for both polar and nonpolar analytes. Both aliphatic and aromatic alcohols and high molecular weight polycyclic aromatic hydrocarbons were extracted using sol-gel cyano-dendron-coated capillaries. To our knowledge, this is the first report of high temperature (350 °C) polar capillary microextraction sorbent.

4.2. Synthesis of Dendrons

The treatment of ‘tris’ and acrylonitrile in dioxane with 40 % KOH gave the Lin’s amine \textsuperscript{93} (Scheme 20), which was previously reported by Newkome et al,\textsuperscript{25} the appearance (\textsuperscript{13}C
NMR) of a peak at 117.9 ppm for C≡N and the molecular peak at \( m/z \) 303.2 [M + Na\(^+\)] in the ESI-MS supports the structural assignment. Subsequent treatment of amine 93 with triphosgene in the presence of Et\(_3\)N in dry THF afforded (80 %) the desired isocyanate building block 94, which was structurally established (\(^{13}\)C NMR) by the new signal (126.1 ppm) for OCNC and the molecular ion peak (ESI-MS) at \( m/z \) 329.3 [M + Na\(^+\)].

![Scheme 20. Synthesis of key monomers 93 and 94: a) H\(_2\)C=CH-CN, 40 % KOH, dioxane, 25 ºC, 15 h; b) Et\(_3\)N, triphosgene, 0 ºC, 3 h.](image)

Synthesis of the 2\(^{nd}\) generation nitro dendron 95 was achieved (Scheme 21) by the DCC-mediated coupling reaction of 4-(2-carboxyethyl)-4-nitroheptanedioic acid (94) and three equivalents of Lin’s amine 93 in dry THF at 25 ºC for 15 h. The presence of new peaks (\(^{13}\)C NMR) at 92.3, 171.0 ppm attributed to the O\(_2\)NC, CONH moiety respectively, as well as a peak at 117.9 ppm for C≡N moiety, along with the mass peak (ESI-MS) at \( m/z \) 1086.6 [M + Na\(^+\)] provided evidence for the structure.

Reduction of the nitro moiety of 95 with 10% Pd/C and NaBH\(_4\) in MeOH afforded (67 %) the 2\(^{nd}\) generation amino-dendron 96, which was supported by the chemical shift (\(^{13}\)C NMR) for the quaternary carbon from 92.3 (O\(_2\)NC) to 60.2 (H\(_2\)NC) ppm and the molecular ion peak (ESI-MS) at \( m/z \) 1057.6 [M + Na\(^+\)]. Subsequent
treatment of amine 96 with 0.5 equiv. of triphosgene in the presence of Et₃N in dry THF gave the 2nd generation isocyanate 97. In the ¹³C NMR spectra of 97, a significant down field shift of the signal at 60.2 to 62.4 ppm corresponding to the ONCC and the appearance of a new absorption at 123.2 ppm (NCO) support the formation of isocyanate. The molecular ion peak at m/z 1082.3 [M + Na⁺] further supported the transformation of amine group.


The 3rd generation predendron 99 was synthesized (Scheme 22) by the DCC coupling of nonaacid, which was previously prepared from nonaester and excess Lin’s amine 93 in DMF at 25 °C for 48 h. The structure of 99 was supported (¹³C NMR) by the
appearance of new chemical shifts at 173.1 ppm for the carbonyl CONH as well as at 92.8 ppm for the quaternary carbon O₂NC signal, 68.6 ppm for the CH₂O, 118.2 ppm for the C≡N moiety and the molecular ion peak (MALDI-TOF MS) at m/z 3346.9 [M + Na⁺].

Reduction of the focal nitro group with 10% Pd/C and NaBH₄ in MeOH at 50 ºC smoothly afforded (58%) desired amino dendron 100, as evidence by the up-field chemical shift (¹³C NMR) of the signal at 55.3 ppm assigned to the R₃CNH₂ moiety and the molecular ion peak (MALDI-TOF MS) at m/z 3312.38 [M + Na⁺].

![Chemical structures](image)


Treatment of amine 100 with 0.5 equiv. of triphosgene in the presence of Et₃N in dry THF gave the corresponding isocyanates 101. The structure was evidenced by the ¹³C
NMR spectra that exhibited chemical shifts for the $R_3CNCO$ signals from 60.2 to 61.0 ppm, as well as the presence of new absorption at 122.4 ppm assigned to the NCO group. In addition, the IR spectra of 101 showed isocyanate peak (2260 cm$^{-1}$). The MALDI-TOF of 101 showed a molecular ion peak at $m/z$ 3342.3 [M + Na$^+$.]

The treatment of isocyanate 101 with 3-(triethoxysilyl)propyl amine in dry CH$_2$Cl$_2$ at 25 ºC for 1h quantitatively afforded 102 (Fig. 16). Its preparation was confirmed ($^{13}$C NMR) by the presence of a new urea (NHCONH) carbon peak at 158.2 ppm and peaks at 65.5, 68.6 ppm corresponding to OCH$_2$, CH$_2$O, as well as new absorbance peaks (IR) at 1100 and 1650 cm$^{-1}$ for the silane group (Si-O) and urea carbonyl group, respectively.

Figure 16. Cyano-terminated dendron with a triethoxysilyl root.
The dendritic silane reagent 102 with triethoxysilyl root, when treated with a catalytic amount of trifluoroacetic acid (TFA) in the presence of methyltrimethoxysilane (MTMS) undergoes hydrolysis and subsequent polycondensation with MTMS as well as inner surface walls of the fused silica capillary to form an organic-inorganic hybrid network. When this reaction was performed within a fused silica capillary column, the surface silanol groups were deactivated and the dendrons were immobilized with chemical bonding (Fig 17).

Figure 17. Surface-bonded sol-gel dendron coating.

The capillary microextraction gas-chromatography experiments were carried out using sol-gel dendron-coated capillaries with a variety of analytes ranging from nonpolar
polycyclic aromatic hydrocarbons (PAHs) and polar aliphatic alcohols. Figure 19 represents the GC separation of five polycyclic aromatic hydrocarbons. They were extracted from an aqueous sample (each PAH at 10 ppb). Figure 20 represents a chromatogram illustrating GC separation of mixture of aliphatic alcohols (10 ppb concentration of each).

![Figure 18. Thermogravimetric analysis curve (continuous line) and first derivative of TGA curve (dotted line) for the sol-gel dendron 103.](image)

Figure 18. Thermogravimetric analysis curve (continuous line) and first derivative of TGA curve (dotted line) for the sol-gel dendron 103.
Figure 19. CME-GC analysis of PAHs at 10 ppb concentration using sol-gel dendron-coated microextraction capillary. Extraction conditions: 13 cm X 0.32 mm i.d. microextraction capillary; extraction time, 30 min. GC analysis conditions: 10 m X 0.25 mm i.d. sol-gel PDMS column; split-less injection; injector temperature, initial 30 °C, program rate 100 °C/min, final 350 °C; GC oven temperature programmed from 30 °C (hold for 5 min) to 350 °C at a rate of 20 °C/min; helium carrier gas; FID temperature 350 °C. Peak identification: 1) acenaphthene, 2) fluorene, 3) phenanthrene, 4) fluoranthene, 5) pyrene.
Figure 20. CME-GC analysis of alcohols at 10 ppb concentration using sol-gel dendron-coated microextraction capillary. Extraction conditions: 13 cm X 0.32 mm i.d. microextraction capillary; extraction time, 30 min. GC analysis conditions: 10 m X 0.25 mm i.d. sol-gel PEG column; split-less injection; injector temperature, initial 30 ºC, program rate 100 ºC/min, final 350 ºC; GC oven temperature programmed from 30 ºC (hold for 5 min) to 350 ºC at a rate of 20 ºC/min; helium carrier gas; FID temperature 350 ºC. Peak identification: 1) 1-octanol, 2) 1-nonanol, 3) 1-decanol, 4) 1-undecanol, 5) 1-dodecanol.

In summary, sol-gel technology has proven to be a powerful tool for the attachment of silica to highly branched dendritic architectures containing cyano terminal groups. The treatment of 3rd generation dendron with unique isocyanate group at the focal point with 3-(triethoxysilyl)propyl amine generated dendritic silane reagent with a stable
urea linkage. Sol-gel dendron-coated capillaries were prepared and used for microextraction of polar alcohols and nonpolar polycyclic aromatic hydrocarbons (PAHs) from aqueous samples. Gas chromatography was used for the analysis of extracted analytes.

4.3. Experimental Section

5-Amino-1,9-dicyano-5-(4-cyano-2-oxabutyl)-3,7-dioxanonane (93). In a 300-mL, one-necked, round-bottomed flask equipped with a magnetic stirring was placed ‘tris’ (5 g, 41.2 mmol), dioxane (100 mL), and 40% KOH solution, respectively. The solution was stirred for 15 minutes at 25 °C. Acrylonitrile (6.8 g, 128 mmol, 3.1eq) was added to the above stirred solution and the reaction mixture was stirred for overnight. Then CH$_2$Cl$_2$ (200 mL) was added to the solution and washed with water, brine (100 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to give viscous yellow oil, which was column chromatographed (SiO$_2$) eluting with EtOAc/hexane (1 : 1) affording (70 %) 93, as a pure viscous oil: 8.1 g; $^1$H NMR: δ 2.06 (s, H$_2$N, 2H), 2.61 (t, 6H, CH$_2$CN, J = 6 Hz), 3.45 (s, H$_2$CO, 6H), 3.69 (t, 6H, OCH$_2$CH$_2$, J = 6 Hz); $^{13}$C NMR: δ 18.4 (CH$_2$CN), 55.7 (H$_2$NC), 65.4 (OCH$_2$), 72.1 (H$_2$CO), 117.9 (CN); IR (neat) 3390, 2933, 2882, 2251 cm$^{-1}$; ESI-MS: m/z = 303.2 [M + Na$^+$], calc m/z = 303.32 [M + Na$^+$].

5-Isocyanato-1,9-dicyano-5-(4-cyano-2-oxabutyl)-3,7-dioxanonane (94). To a round bottom flask containing 5-amino-1,9-dicyano-5-(4-cyano-2-oxabutyl)-3,7-dioxanonane (93; 2 g, 7.1 mmol) and Et$_3$N (1.1 g, 10.8 mmol) in dry THF (100 mL) was
added triphosgene (1.1 g, 3.7 mmol) in THF (50 mL) over a period of 20 min. The reaction mixture was maintained at 0 ºC for 3 h. The solvent was concentrated in vacuo to give a solid, which was dissolved in CHCl₃, washed with water, and brine solution. The combined organic solution was dried, filtered and concentrated in vacuo to give a solid, which was column chromatographed (SiO₂) eluting with 20 % EtOAc in CHCl₃ affording (80 %) pure isocyanate 93, as a colorless oil: 1.7 g; ¹H NMR: δ 2.65 (t, 6H, H₂CCN, J = 6.3 Hz), 3.51 (s, 6H, H₂CO), 3.68 (t, 6H, OCH₂CH₂, J = 6.3 Hz); ¹³C NMR: δ 17.8 (CH₂CN), 62.9 (OCNC), 65.3 (OCH₂), 69.9 (H₂CO), 117.7 (CN), 126.1 (OCN); IR (neat) 2932, 2880, 2250, 2261 cm⁻¹; ESI-MS: m/z = 329.3 [M + Na⁺], calc m/z = 329.32 [M + Na⁺].

2nd Generation Predendron 95. To a stirred solution of 4-(2-carboxyethyl)-4-nitroheptanedioic acid (94; 1 g, 3.6 mmol) in dry THF (50 mL) were added DCC (2.3 g, 11.1 mmol) and 1-HOBT (1.5 g, 11.1 mmol) at 25 ºC. After 30 min. Lin’s amine (93; 3.1 g, 11.1 mmol) was added. The mixture was stirred for 15 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed (SiO₂) eluting with an EtOAc/hexane (1 : 2) mixture to afford (78 %) the 2nd generation 95, as a viscous oil: 3.0 g; ¹H NMR: δ1.66 (br s, 6H, CH₂CH₂CONH), 2.19 (br s, 6H, CH₂CONH), 2.63 (t, 18H, H₂CCN, J = 5.7 Hz), 3.69 (t, 18H, OH₂CCH₂, J = 5.7 Hz), 3.81 (s, 18H, H₂CO), 6.03 (s, 3H, NH); ¹³C NMR: δ 18.2 (CH₂CN), 30.2, 30.4 (CH₂CH₂CONH), 59.3 (HNC), 65.2 (OCH₂), 68.2 (H₂CO), 92.3 (O₂NC), 117.9 (CN), 171.0 (CONH); IR (neat) 3360, 2933, 2882, 2251, 1735, 1535 cm⁻¹; ESI-MS: m/z = 1,086.6 [M + Na⁺], calc m/z = 1,087.15 [M + Na⁺].
2nd Generation Amine 96. A solution of 2nd generation predendron 95 (1 g, 930 µmol) in dry THF (50 mL) was added 10 % Pd/C (300 mg), and cooled the reaction mixture to 0 °C, then NaBH₄ (100 mg) was added as portion-wise over 10 min. The reaction mixture was stirred for 12 h at 25 °C, filtered through celite, and the solvent was removed in vacuo to afford (65 %) amine 96, as a viscous liquid: 630 mg; ¹H NMR: δ 1.93 (t, 6H, CH₂CONH, J = 6.3 Hz), 2.19 (t, 6H, CH₂CH₂CONH, J = 6.3 Hz), 2.63 (t, 18H, HC=CH₂, J = 6 Hz), 3.69 (t, 18H, OCH₂CH₂, J = 6 Hz), 3.80 (s, 18H, CH₂CO), 5.3 (s, 2H, NH₂), 6.09 (s, 3H, NH); ¹³C NMR: δ 18.2 (CH₂CN), 27.9, 30.5 (CH₂CH₂CO₂), 59.5 (HNC), 60.2 (H₂NC), 65.5 (OCH₂), 68.6 (H₂CO), 118.1 (CN), 173.6 (CONH); IR (neat) 3360, 2930, 2882, 2250, 1735 cm⁻¹; ESI-MS: m/z = 1,057.6 [M + Na⁺], calc. m/z = 1,057.17 [M + Na⁺].

2nd Generation Isocyanate 97. To a round bottom flask containing 2nd generation amine (96; 1 g, 960 µmol) and Et₃N (200 mg, 1.9 mmol) in dry THF (100 mL), triphosgene (150 mg, 500 µmol) in THF (50 mL) was added over a period of 20 min. The reaction mixture was maintained at 0 °C for 5 h. The solvent was concentrated in vacuo to give a crude oil, which was dissolved in CHCl₃, washed with water, then brine. The combined organic solution was dried (MgSO₄), filtered, and concentrated in vacuo to give a solid, which was column chromatographed (SiO₂) eluting with EtOAc/CHCl₃ (1 : 1) to afford (63 %) pure isocyanate 97, as a viscous oil: 640 mg; ¹H NMR: δ 2.06 (m, 12H, CH₂CH₂CONH), 2.65 (t, 18H, HC=CH₂, J = 6 Hz), 3.65 (t, 18H, OCH₂CH₂, J = 6 Hz), 3.79 (s, 18H, H₂CO), 6.09 (s, 3H, NH); ¹³C NMR: δ 18.2 (CH₂CN), 27.9, 30.5 (CH₂CH₂CONH), 59.9 (HNC), 62.4 (OCNC), 65.4 (OCH₂), 68.7 (H₂CO), 117.9 (CN),
123.2 (OCN), 172.4 (CONH); IR (neat) 3365, 2933, 2882, 2255, 2251, 1735 cm$^{-1}$; ESI-MS: $m/z = 1,082.3$ [M + Na$^+$], calc. $m/z = 1,083.16$ [M + Na$^+$].

**3$^{rd}$ Generation Predendron 99.** To a round bottom flask containing nonaacid (98; 1 g, 1.0 mmol) in dry DMF, DCC (2.1 g, 10.3 mmol) and 1-HOBT (1.4 g, 10.3 mmol) were added at 25 °C under nitrogen. The mixture was stirred for 30 min. and then Lin’s amine (93; 2.9 g, 10.3 mmol) was added. The mixture was stirred for 48 h, after which the white precipitate was filtered. The filtrate was concentrated *in vacuo* to give a crude oil, which was column chromatographed (SiO$_2$) eluting with EtOAc to yield (70 %) the 3$^{rd}$ generation predendron 99, as colorless oil: 2.4 g; $^1$H NMR: $\delta$ 2.13 (m, 12H, $\text{CH}_2\text{CH}_2\text{CONH}$), 2.25 (m, 36H, $\text{CH}_2\text{CH}_2\text{CONH}$), 2.63 (t, 54H, $\text{CH}_2\text{CN}$, $J = 6$ Hz), 3.67 (t, 54H, OCH$_2$CH$_2$, $J = 6$ Hz), 3.80 (s, 54H, H$_2$CO), 6.13 (s, 9H, NH), 6.25 (s, 3H, HN); $^{13}$C NMR: $\delta$ 18.6 (CH$_2$CN), 27.9, 30.8, 31.0 (CH$_2$CH$_2$CONH, CH$_2$CH$_2$CONH), 57.5 (HNC), 59.5 (HNC), 65.5 (OCH$_2$), 68.6 (H$_2$CO), 92.8 (O$_2$NC), 118.2 (CN), 170.7 (CONH), 173.1 (CONH); IR (neat) 3400, 2933, 2822, 2250, 1735, 1672, 1540 cm$^{-1}$, ESI-MS: $m/z = 3,346.39$ [M + Na$^+$], calc $m/z = 3,348.69$ [M + Na$^+$].

**3$^{rd}$ Generation Dendron 100.** To a solution of 3$^{rd}$ generation predendron 99 (1 g, 300 µmol) in dry THF (50 mL), 10% Pd/C (500 mg) was added, and then the reaction mixture was cooled to 0 °C, then NaBH$_4$ (50 mg, 1.3 mmol) was added as portion-wise over 10 min. The reaction mixture was stirred for 24 h at 50 °C, filtered through celite, and the solvent was removed *in vacuo* to afford (58 %) amine 100, as a viscous liquid: 570 mg; $^1$H NMR: $\delta$ 1.92 (m, 12H, $\text{CH}_2\text{CH}_2\text{CONH}$), 2.15 (m, 36H, $\text{CH}_2\text{CH}_2\text{CONH}$),
2.66 (t, 54H, CH₂CN, J = 6 Hz), 3.69 (t, 54H, OCH₂CH₂, J = 6 Hz), 3.81 (s, 54H, H₂CO), 6.13 (s, 2H, H₂N), 6.18 (s, 9H, NH), 6.53 (s, 3H, HN); $^{13}$C NMR: δ 18.4 (CH₂CN), 27.7, 30.8 (CH₂CH₂CONH, CH₂CH₂CONH), 55.3 (H₂NC), 57.2 (HNC), 59.4 (HNC), 65.4 (OCH₂), 68.4 (H₂CO), 118.2 (CN), 171.7 (CONH), 173.2 (CONH); IR (neat) 3400, 2930, 2821, 2251, 1735, 1670 cm⁻¹; ESI-MS: m/z = 3,312.38 [M + Na⁺], calc m/z = 3,318.7 [M + Na⁺].

3rd Generation Isocyanate 101. To a round bottom flask containing 3rd generation dendron 100 (1 g, 300 µmol) and Et₃N (8.5 µl, 600 µmol) in dry THF (100 mL), triphosgene (450 mg, 150 µmol) in THF (50 mL) was added over a period of 20 min. The reaction mixture was stirred for 15 h at 25 °C. The solvent was concentrated in vacuo to give a crude oil, which was dissolved in CHCl₃, washed with water, then brine. The combined organic solution was dried (MgSO₄), filtered, and concentrated in vacuo to give a solid, which was column chromatographed (SiO₂) eluting with EtOAc to afford (45 %) of pure isocyanate 101, as a viscous oil: 450 mg; $^1$H NMR: δ 1.96 (m, 12H, CH₂CH₂CONH), 2.18 (m, 36H, CH₂CH₂CONH), 2.65 (t, 54H, CH₂CN, J = 6 Hz), 3.69 (t, 54H, OCH₂CH₂, J = 6 Hz), 3.82 (s, 54H, H₂CO), 6.05 (s, 9H, NH), 6.10 (s, 3H, HN); $^{13}$C NMR: δ 18.6 (CH₂CN), 31.0, 31.2 (CH₂CH₂CONH, CH₂CH₂CONH), 57.5 (HNC), 59.5 (HNC), 61.0 (OCNC), 65.5 (OCH₂), 68.6 (H₂CO), 118.1 (CN), 122.4 (OCN), 170.7 (CONH), 173.1 (CONH); IR (neat) 3400, 2930, 2822, 2260, 2251, 1735, 1672 cm⁻¹; ESI-MS: m/z = 3,342.3 [M + Na⁺], calc m/z = 3,344.7 [M + Na⁺].
Synthesis of Dendron 102. To a round bottom flask containing 3rd generation isocyanate 101 (500 mg, 150 µmol) in dry DCM (5 mL), 3-(triethoxysilyl)propylamine (35 mg, 150 µmol) in dry DCM (2 mL) was added at 25 ºC. The reaction mixture was stirred for 1 h then the reaction was complete by TLC (50 % EtOAc/CH₂Cl₂). The solvent was concentrated in vacuo to afford an almost quantitative of pure dendritic silane reagent 102, as a viscous liquid: 530 mg; ¹H NMR: δ 0.63 (t, 2H, SiCH₂, J = 7.5 Hz), 1.25 (t, 9H, OCH₂CH₃, J = 6.5 Hz), 1.59 (m, 2H, CH₂CH₂NH) 1.97 (m, 12H, CH₂CH₂CONH), 2.16 (m, 36H, CH₂CH₂CONH), 2.64 (t, 54H, CH₂CN, J = 6 Hz), 3.17 (t, 2H, CH₂NH, J = 7.3 Hz), 3.69 (t, 54H, OCH₂CH₂, J = 6 Hz), 3.81 (s, 54H, H₂CO), 6.10 (s, 9H, NH), 6.14 (s, 3H, HN); ¹³C NMR: δ 7.6 (SiCH₂), 18.3 (OCH₂CH₃), 18.8 (CH₂CN), 31.1, 31.4 (CH₂CH₂CONH, CH₂CH₂CONH), 42.5 (H₂CNH), 57.9 (HNC), 59.3 (HNC), 59.5 (HNC), 65.5 (OCH₂), 68.6 (H₂CO), 118.1 (CN), 158.2 (HNCNH), 170.7 (CONH), 173.1 (CONH); MALDI TOF-MS: m/z = 3,569.8 [M + Na⁺], calc. m/z = 3,566.1 [M + Na⁺].

4.4. References


CHAPTER V
CONVENIENT SYNTHESIS OF [1 → 3] C-BRANCHED DENDRONS

5.1. Introduction

Both in the convergent construction of dendrimers and the dendrimerization or dendron-coating of materials and surfaces, dendrons of different size and functionality have been shown to play a key role in structurally tailored materials.\(^1\) In 1991, the [1 → 3] C-branched monomer, di-tert-butyl 4-[2-(tert-butoxycarbonyl)ethyl]-4-amino heptanedioate\(^ {2-4}\) (“Behera’s Amine;” \(52\), Scheme 1) was first introduced and its use in the divergent synthesis of a family of dendrimers using amide-based connectivity was demonstrated. The facile conversion of amine \(52\) to the corresponding isocyanate\(^ {5-7}\) has further expanded its utilitarian uses. Brettreich and Hirsch\(^8\) convergently created the related 2\(^{\text{nd}}\) and 3\(^{\text{rd}}\) generation dendrons, which were subsequently attached to the \(C\(_{60}\)\) surface.\(^ {9-19}\) These [1 → 3] C-branched monomers have received considerable attention\(^ {20-35}\) in that they (1) are easily attached to a great variety of starting cores, surfaces\(^ {36}\) and polymers,\(^ {37}\) (2) have a specific molecular canopy, and (3) are easily transformed to the corresponding acidic surface for further modification.
The reported convergent route\(^8\) to the higher generation dendrons used the typical amidation coupling reaction in which a combination of DCC (dicyclohexylcarbodiimide) and 1-HOBT (1-hydroxybenzotriazole) in DMF was used as the reagents of choice and the solvent, respectively. We herein report a new high-yield preparation of these [1 \(\rightarrow\) 3] \(\mathrm{C}\)-branched dendrons, thus eliminating the need to remove a high boiling solvent, multiple by-products, and circumvents unwanted side reactions, such as that derived from \(N\)-acylurea formation that can occur in DCC amidations.

5.2. Synthesis of Dendrons

Behera’s amine 52, previously synthesized (>95 % overall) in two-steps\(^{2,4}\) from \(\text{MeNO}_2\) and tert-butyl acrylate, followed by catalytic reduction of the nitro group, was treated with one equivalent of acryloyl chloride in the presence of \(\text{Et}_3\text{N}\) in \(\text{CH}_2\text{Cl}_2\) to give (>96 %) the \(N\)-substituted amide 104 (Scheme 23), which was confirmed by the new peaks (\(^{13}\text{C} \text{NMR}\)) assigned to the new amido carbonyl group at 164.7 ppm (C=O), as well as the expected downfield chemical shift (52.0 to 57.4 ppm) for the newly acylated \(\text{R}_3\text{CNH}\) moiety. The ESI-MS further confirmed the assignment by a peak at \(m/z\) 492.2 [M + Na\(^+\)].

Michael-type addition of \(\text{MeNO}_2\) to acrylamide triester 104 in the presence of the water-soluble base tetramethylguanidine (TMG) afforded (93 %) the homologated nitrotriester 105, whose structure was supported (\(^{13}\text{C} \text{NMR}\)) by the appearance of a new resonance (74.5 ppm) for the primary \(\text{CH}_2\text{NO}_2\) group as well as an absence of olefinic signals. Subsequent reaction of two equivalents of acrylamide 104 with the nitroalkane
reagent \textbf{105} in the presence of TMG (THF, 50 °C, 15 h) gave (91 %) the desired 2\textsuperscript{nd} generation nitro-nonaester predendron \textbf{106}. A notable downfield chemical shift (\textsuperscript{13}CNMR) for the resonance assigned to the R\textsubscript{3}CNO\textsubscript{2} group from 74.5 to 92.1 ppm supported the coupling procedure.

Different acryl amide monomers derived from other branched monomers can also be attached to afford easy access to heterogeneously functionalized higher generation dendrons. One-step treatment of MeNO\textsubscript{2} with three equivalents of the acryl amide \textbf{104} in the presence of TMG in THF afforded a near quantitative yield of the predendron \textbf{106}. Reduction of the focal nitro group with Raney-Ni\textsuperscript{38} in absolute EtOH at 40 °C smoothly afforded (>95 %) the desired amino-nonaester dendron \textbf{107}, as evidenced by the up-field

Scheme 23. Synthesis of 2\textsuperscript{nd} generation dendrons: i) Et\textsubscript{3}N, CH\textsubscript{2}=CHCOCl, 0 °C, 3 h; ii) excess CH\textsubscript{3}NO\textsubscript{2}, CHCl\textsubscript{3}, TMG, 25 °C, 24 h; iii) \textbf{104}, THF, TMG, 50 °C, 15 h; iv) EtOH, H\textsubscript{2} (65 psi), 50 °C, 12 h; v) Et\textsubscript{3}N, Triphosgene, THF, 25 °C, 3 h.
chemical shift ($^{13}$C NMR) of the signal assigned to the $R_3CNH_2$ moiety from 92.1 to 52.3 ppm; this sample is identical in all respects to one prepared by the convergent acrylamide alkylation coupling procedure.

![Scheme 24](image)

Scheme 24. Synthesis of 3$^{\text{rd}}$ generation dendrons: i) Et$_3$N, CH$_2$Cl$_2$, CH$_2$=CHCOCl, 0 $^\circ$C; ii) excess CH$_3$NO$_2$, THF, TMG, 50 $^\circ$C, 24 h; iii) 2 eq. 109, THF, TMG, 50 $^\circ$C, 24 h; iv) Raney Ni, EtOH, H$_2$ (65 psi), 50 $^\circ$C, 24 h; v) Et$_3$N, Triphosgene, THF, 25 $^\circ$C, 8 h.

Synthesis of the 2$^{\text{nd}}$ generation acrylamide 109 (Scheme 24) was achieved (93 %) by the treatment of acryloyl chloride with 2$^{\text{nd}}$ generation amine 107 in the presence of Et$_3$N in dry DCM. The appearance of three different carbonyl signals in its $^{13}$C NMR spectrum and the molecular peak at $m/z$ 1516.2 [M + Na$^+$] in the ESI-MS support the amidation. Subjecting the 2$^{\text{nd}}$ generation acrylamide 109 to MeNO$_2$ alkylation in the presence of TMG in refluxing THF for 24 h lead (82 %) to predendron 111, which was
structurally established ($^{13}$C NMR) by the new signal (74.8 ppm) for RCH$_2$NO$_2$ and the molecular ion peak (MALDI-TOF MS) at $m/z$ 4567.2 [M + Na$^+$].

Alkylation of 110 using two equivalents of the acrylamide 109 then gave (70 %) the fully substituted quaternary carbon center of nitro-polyester 111. The presence of ($^{13}$C NMR) a new absorption at 92.7 ppm attributed to the R$_3$CNO$_2$ moiety along with the mass peak (MALDI-TOF MS) at $m/z$ 4537.3 [M + Na$^+$] provided evidence for the structure. Reduction of the nitro moiety of 111 with Raney Ni catalyst in absolute ethanol at 50 °C then afforded (85 %) the 3rd generation amino-polyester dendron 112, which was supported by the chemical shift ($^{13}$C NMR) for the quaternary carbon from 92.7 to 52.3 ppm (R$_3$CNO$_2$ and R$_3$CNH$_2$, respectively) and the molecular ion peak (MALDI-TOF MS) at $m/z$ 4537.4 [M + Na$^+$].

Subsequent treatment of amines 107 and 112 with 0.5 equiv. of triphosgene in the presence of Et$_3$N in dry THF gave the desired isocyanates 108 and 113, respectively. Their structures were evidenced by their $^{13}$C NMR spectra that exhibited chemical shifts for the R$_3$CNCO signals from 52.3 and 52.4 ppm to 62.3 and 59.9 ppm, respectively, as well as the presence of new absorptions at 122.4 and 125.5 ppm assigned to the NCO group. In addition, the IR spectra of both displayed isocyanate peaks (108, 2261 cm$^{-1}$; and 113, 2256 cm$^{-1}$ and signals (ESI-MS and MALDI-TOF MS) at $m/z$ 1512.1 [M + Na$^+$] (108: calc. $m/z$ 1510.9 [M + Na$^+$]) and $m/z$ 4565.2 [M + Na$^+$] (113: calc. $m/z$ 4561.9 [M + Na$^+$]) further characterized the transformation of the amine group.

In conclusion, the [1 → 3] C-branched amine dendrons have been synthesized via a new, high yield route, then transformed to the corresponding isocyanate derivatives. The structures of these monomers were characterized by means of $^1$H and $^{13}$C NMR, as
well as mass spectrometry. Use of this protocol facilitates the purification of the dendrons at each stage of the synthesis and removes the potential for unwanted by-products, such as N-acylureas, that are commonly observed in DCC-based carboxylic acid–amine coupling reactions, as well as provides high yield access to new multifunctional dendrons.

5.3. Experimental Section. General Remarks.

Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. All of chemicals were purchased from Aldrich Co. except for Behera’s amine.\textsuperscript{39} Tetrahydrofuran (THF) was dried by refluxing over benzophenone/Na under N\textsubscript{2}. Dichloromethane was dried over CaH\textsubscript{2}. All other commercially available solvents were used, without further purification. Column chromatography was conducted using silica gel (60-200 mesh) from Fisher Scientific with the stipulated solvent mixture. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were obtained in CDCl\textsubscript{3}, except where noted, and are recorded at 300 and 75 MHz, respectively. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded on an ATI Mattson Genesis Series FTIR spectrometer. Mass spectral data were obtained using an Esquire electron ionization mass spectrometer (ESI) and are reported as: (assignment, relative intensity); ESI samples were typically prepared in MeOH/H\textsubscript{2}O/TFA (70:30:01) for positive ion mode or Me\textsubscript{2}CHOH/H\textsubscript{2}O/NH\textsubscript{3} (70:30:1) for negative ion mode and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer.
Synthesis of Di-\textit{tert}-butyl 4-Acryloylamino-4-(2-\textit{tert}-butoxycarbonylethyl)-heptanedioate (104). To a stirred solution of Behera’s amine\textsuperscript{4} (52; 4.6 g, 11 mmol) and Et\textsubscript{3}N (3.1 mL, 22 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} at 0 °C, acryloyl chloride (1 g, 11 mmol) was added. After 2h at 25 °C, the reaction mixture was washed with water then satd. brine. The organic solution was dried (MgSO\textsubscript{4}), filtered, and concentrated \textit{in vacuo} to give a crude solid, which was chromatographed (SiO\textsubscript{2}) eluting with a 10 % EtOAc in CHCl\textsubscript{3} mixture to afford (96 %) amide 104, as a white solid: 5.3 g; m. p. 144-145 °C; \textsuperscript{1}H NMR $\delta$ 1.44 (s, 27H, CH\textsubscript{3}), 2.04 (t, 6H, $J = 7.5$ Hz, CH\textsubscript{2}CH\textsubscript{2}CO), 2.26 (t, 6H, $J = 7.5$ Hz, CH\textsubscript{2}CO), 5.59 (dd, $J = 12$, 1.5 Hz, 1H, CH\textsubscript{2}=CH), 6.03 (dd, $J = 19.0$, 10.0 Hz, 1H, CH\textsubscript{2}=CH), 6.20 (s, 1H, NH), 6.22 (dd, $J = 18.0$, 1.5 Hz, 1H, CH\textsubscript{2}=CH); \textsuperscript{13}C NMR $\delta$ 27.9 (CH\textsubscript{3}), 29.6 (CH\textsubscript{2}CO\textsubscript{2}), 29.9 (CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}), 57.4 (NHC), 80.3 (CMe\textsubscript{3}), 125.5 (CH\textsubscript{2}=CH), 131.7 (CH\textsubscript{2}=CH), 164.7 (CONH), 172.7 (CO\textsubscript{2}); IR 3290, 1710, 1654, 1622 cm\textsuperscript{-1}; ESI-MS $m/z$ = 492.2 [M + Na\textsuperscript{+}]; calcd. $m/z$ = 492.3 [M + Na\textsuperscript{+}]. \textit{Anal.} (C\textsubscript{25}H\textsubscript{43}NO\textsubscript{7}) Found: C, 63.68; H, 9.30; N, 2.84. Calcd. C, 63.94; H, 9.23; N, 2.98.

Synthesis of Nitro Amide 105. To a stirred solution of acrylamide 104 (2 g, 4.2 mmol) in a MeNO\textsubscript{2}/CHCl\textsubscript{3} mixture (1:1; 100 mL), TMG (200 µL) was added and maintained at 25 °C for 24 h. The mixture was then concentrated \textit{in vacuo} to give a crude solid, which was dissolved in CHCl\textsubscript{3} then sequentially washed with dilute aq. HCl, water, and satd. brine. The organic solution was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated \textit{in vacuo} to give a crude oil, which was column chromatographed (SiO\textsubscript{2}) eluting with 25 % EtOAc in hexane to give (93 %) amide 105, as a white solid: 2.1 g; m. p. 140-141 °C; \textsuperscript{1}H NMR $\delta$ 1.45 (s, 27H, CH\textsubscript{3}), 1.99 (t, 6H, $J = 7.5$ Hz, CH\textsubscript{2}CH\textsubscript{2}CO), 2.24 (t, 6H, $J = 7.5$ Hz, 128
\( \text{CH}_2\text{CO} \), 2.26 (m, 4H, \text{CH}_2\text{CH}_2\text{CO} \), 4.47 (t, 2H, \( J = 6 \) Hz, \text{O}_2\text{NCH}_2 \), 6.19 (s, 1H, NH); 

\(^{13}\text{C}\) NMR \( \delta \) 22.8 (\text{CH}_3\text{CO}), 27.7 (\text{CH}_3), 29.6 (\text{CH}_2\text{CO}), 29.8 (\text{CH}_2\text{CH}_2\text{CO}), 32.4 (\text{O}_2\text{NCH}_2\text{CH}_2), 57.3 (\text{NHC}), 74.5 (\text{O}_2\text{NCH}_2), 80.2 (\text{CMe}_3), 170.1 (\text{CONH}), 172.4 (\text{CO}_2); 

IR 3300, 1710, 1670, 1552 cm\(^{-1}\); ESI-MS \( m/z = 553.3 \) [M + Na\(^{+}\)]; calcd. \( m/z = 553.3 \) [M + Na\(^{+}\)]. 

**Anal.** (C\(_{26}\)H\(_{46}\)N\(_2\)O\(_9\)) Found C, 57.94; H, 8.66; N, 5.20. Calcd. C, 58.85; H, 8.74; N, 5.28.

**Synthesis of 2\(^{nd}\) Generation Nitro Predendron 106.** Acryl amide 104 (1.9 g, 4.0 mmol) and TMG (250 µL) were added to a stirred solution of amide 105 (1 g, 1.9 mmol) in dry THF (100 mL). After the mixture was stirred for 15 h at 50 °C, the solution was concentrated \textit{in vacuo} to give a solid residue, which was dissolved in CHCl\(_3\) and then sequentially washed with dilute aq. HCl, water, and satd. brine. The organic solution was dried (Na\(_2\)SO\(_4\)), filtered, and reduced \textit{in vacuo} to give a oil, which was column chromatographed (SiO\(_2\)) eluting with EtOAc/hexane (1:2) mixture to give (91 %) 106, as a white solid: 2.5 g; m.p. 157-158 °C; \(^1\text{H}\) NMR \( \delta \) 1.44 (s, 8\text{H}, \text{CH}_3), 1.93 (t, 18\text{H}, \text{CH}_2\text{CH}_2\text{CO}_, \( J = 7.0 \) Hz) 2.12 (t, 30\text{H}, \text{CH}_2\text{CH}_2\text{CO}_2, \text{CH}_2\text{CH}_2\text{CONH}, \( J = 7.0 \) Hz), 6.20 (s, 3\text{H}, \text{CONH}); \(^{13}\text{C}\) NMR \( \delta \) 28.2 (\text{CH}_3), 29.8, 29.9 (\text{CH}_2\text{CH}_2\text{CO}), 31.4 (\text{CH}_2\text{CH}_2\text{CONH}), 57.7 (\text{CONHC}), 80.8 (\text{CMe}_3), 92.6 (\text{O}_2\text{NC}), 170.6 (\text{CONH}), 172.9 (\text{CO}_2); IR: 3360, 2979, 1731, 1681 cm\(^{-1}\); ESI-MS \( m/z = 1493.4 \) [M + Na\(^{+}\)]; calcd. \( m/z = 1492.9 \) [M + Na\(^{+}\)].

**2\(^{nd}\) Generation Amine Dendron 107** was generated by a catalytic hydrogenation of the predendron 106 with T-1 Raney Ni in absolute EtOH at 65 psi at 50 °C for 15 h.
The solution was cautiously (pyrophoric) filtered through celite, then the filtrate was concentrated in vacuo to give (>95 %) pure amine dendron 107:  m. p. 193-194 °C; $^1$H NMR δ 1.51 (s, 81H, CH$_3$), 2.01 (t, 18H, CH$_2$CH$_2$CO$_2$,  $J = 7.0$ Hz), 2.12 (t, 30H, CH$_2$CH$_2$CO$_2$, CH$_2$CH$_2$CONH,  $J = 7.0$ Hz), 6.22 (s, 3H, CON$_2$H), 6.31 (s, 2H, NH$_2$); $^{13}$C NMR δ 28.2 (CH$_3$), 29.8, 29.9 (CH$_2$CH$_2$CO$_2$), 31.4 (CH$_2$CH$_2$CONH), 57.7 (CONHC), 52.3 (H$_2$NC), 80.8 (CMe$_3$), 170.6 (CONH), 172.9 (CO$_2$); IR 3360, 2979, 1731, 1681cm$^{-1}$; ESI-MS $m/z = 1493.4$ [M + Na$^+$]; calc. $m/z = 1492.9$ [M + Na$^+$].

**Synthesis of 2$^{nd}$ Generation Isocyanate 108.** The 2$^{nd}$ generation amine 107 (500 mg, 340 µmol) was dissolved in dry THF (20 mL) and Et$_3$N (50 µL, 680 µmol) was added under nitrogen atmosphere, then cooled to 0 °C. A solution of triphosgene (51 mg, 170 µmol) in THF (5 mL) was added drop-wise at 0 °C over 20 min. After the addition was completed, the stirred reaction mixture was allowed to warm to 25 °C; after 3h, the white precipitate was removed by filtered and the filtrate was concentrated in vacuo to give a residue, which was dissolved in CHCl$_3$ washed with water, dried (MgSO$_4$), and then concentrated in vacuo to give a solid, which column chromatographed (SiO$_2$) eluting with EtOAc/hexane (1:3) to afford (710 mg, 70 %) the 2$^{nd}$ generation isocyanate 108, as a white solid:  m. p. 163-165 °C; $^1$H NMR δ 1.49 (s, 81H, CH$_3$), 2.0 (br m, 18H, CH$_2$CH$_2$CO$_2$), 2.12 (br m, 30H, CH$_2$CH$_2$COO, CH$_2$CH$_2$CONH), 6.33 (s, 3H, CONH); $^{13}$C NMR δ 27.5 (CH$_3$), 29.3, 29.6 (CH$_2$CH$_2$CO$_2$), 31.1, 31.7 (CH$_2$CH$_2$CONH), 57.4 (CONHC), 62.3 (OCN), 80.2 (CMe$_3$), 122.4 (NCO), 171.2 (CONH), 172.9 (CO$_2$); IR 3363, 2978, 2936, 2260 (N CO),1730 (ester C=O), 1680 (amide C=O) cm$^{-1}$; ESI-MS $m/z = 1512.1$ [M + Na$^+$]; calcd. $m/z = 1510.9$ [M + Na$^+$].
**Synthesis of Amide 109.** To a stirred solution of 2nd generation amine 107 (5 g, 3.5 mmol) and Et₃N (1.0 mL, 9.8 mmol) in anhydrous THF (50 mL), was added acroyl chloride (310 mg, 3.5 mmol) in THF (20 mL) under nitrogen atmosphere at 0 ºC, then maintained for 3 hr at 25 ºC. The reaction mixture was filtered and concentrated *in vacuo* to give the crude product, which was dissolved in CHCl₃ and washed with satd. brine solution, followed by water, dried (MgSO₄), filtered and concentrated *in vacuo* to get a foam solid, which was chromatographed (SiO₂) eluting with EtOAc/hexane (1:2) to afford (93 %) of 109, as a white solid: 4.8 g; H NMR δ 1.44 (s, 81H, CH₃), 1.95 (t, 18H, J = 6.9 Hz), 2.04 (br m, 12H), 2.20 (t, 18H, J = 6.9 Hz), 5.54 (dd, J = 12, 1.5 Hz, 1H, CH₂=CH), 6.06 (dd, J = 19.0, 10.0 Hz, 1H, CH₂=CH), 6.11 (br, 2H, NH), 6.21 (dd, J = 18.0, 1.5 Hz, 1H, CH₂=CH); C NMR δ 27.9 (CH₃), 29.7, 29.9 (CH₂CH₂CO₂), 31.6, 32.0 (CH₂CH₂CONH), 57.3 (CONHC), 57.7 (HNC), 80.4 (CMe₃), 125.4, (CH₂=CH), 132.1 (CH₂=CH), 165.5 (CONH), 172.5 (CONH), 172.9 (CO₂); IR 3280, 1710 (ester C=O), 1654 (amide C=O), 1622 cm⁻¹; ESI-MS m/z = 1516.2 [M + Na⁺]; calcd. m/z = 1515.6 [M + Na⁺]. Anal. (C₇₉H₁₃₆N₄O₂₂) Found: C, 63.04; H, 9.13; N, 3.74. Calcd. C, 63.51; H, 9.18; N, 3.75.

**Synthesis of Extended Nitro Dendron 110.** Acrylamide 109 (2 g, 1.3 mmol) was dissolved in anhydrous THF/MeNO₂ mixture (1:1; 100 mL), and TMG (250 uL) was added to the above solution at 25 ºC, the reaction mixture was stirred for 24 h at 50 ºC. The mixture was then concentrated *in vacuo* to give a crude solid, which was dissolved in CHCl₃ then sequentially washed with dilute aq. HCl, water, and satd. brine. The organic solution was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give a crude oil,
which was column chromatographed (SiO₂) eluting with 25 % EtoAc in CHCl₃ to give (88 %) amide 110, as a white solid: 1.83 g; mp 122-123 °C; ¹H NMR δ 1.44 (s, 81H, CH₃), 1.95 (t, 18H, CH₂CH₂CO₂, J = 5.4 Hz), 2.01 (2H, O₂NCH₂CH₂CO₂, J = 5.1 Hz), 2.20 (t, 30H, CH₂CH₂CO₂, CH₂CH₂CONH), 2.30 (m, 2H, O₂NCH₂CH₂), 4.51 (t, 2H, O₂NCH₂, J = 4.8 Hz), 6.04 (s, 3H, CONH), 7.94 (s, 1H, CONH); ¹³C NMR δ 22.8 (CH₂CO), 27.92 (CH₃), 29.6 (CH₂CO), 29.7 (CH₂CH₂CO₂), 31.4 (CH₂CO, CH₂CH₂CO₂), 32.5 (O₂NCH₂CH₂), 57.2 (NHC), 57.6 (NHC), 74.8 (O₂NCH₂), 80.3 (CMe₃), 170.7 (CONH), 172.5 (CONH), 172.7 (CO₂); IR 3320, 1715, 1670, 1550 cm⁻¹; ESI-MS m/z = 1577.9 [M + Na⁺]; calcd. m/z = 1577.98 [M + Na⁺]. Anal. (C₈₀H₁₃₉N₅O₂₄) Found: C, 61.80; H, 8.96; N, 4.62. Calcd. C, 61.79; H, 9.01; N, 4.50.

**Synthesis of 3rd Generation Predendron 111.** Nitroamide 110 (500 mg, 0.32 µmol) and TMG (100 µL) were dissolved in (25 mL) of anhydrous THF, the 2nd generation acrylamide 109 (960 mg, 0.064 µmol) in THF (50 mL) was added. The mixture was refluxed under nitrogen for 12 h, cooled, and concentrated in vacuo to give the crude product, which was dissolved in CHCl₃, washed with water, dried (MgSO₄), filtered, and concentrated in vacuo to give a solid, which was column chromatographed (SiO₂) eluting with EtoAc/hexane (1:2) to afford (70 %) the 3rd generation predendron 111, as a white solid: 1.0 g; mp 161-162 °C; ¹H NMR δ 1.42 (s, 243H, CH₃), 1.93 (br m, 78H, CH₂CH₂CO₂, CH₂CH₂CONH), 2.12 (br m, 78H, CH₂CO₂, CH₂CONH), 6.19 (s, 12H, CONH); ¹³C NMR δ 27.3 (CH₃), 29.2 (CH₂CH₂CO₂), 33.6 (CH₂CH₂CONH), 56.7 (CONH₂CH₂CO₂), 57.5 (CONHC), 80.1 (CMe₃), 92.7 (O₂NC), 170.5 (CONH), 132
170.9 (CONH), 172.5 (CO₂); IR: 3358, 2978, 2936 1730 (ester C=O), 1654 (amide C=O) cm⁻¹; MALDI-TOF MS m/z = 4567.2 [M + Na⁺]; calcd. m/z = 4565.8 [M + Na⁺].

3rd Generation Dendron 112. The predendron 111 (1 g, 220 µmol), dissolved in absolute EtOH (50 mL) with T-1 Raney Ni, was hydrogenated at 65 psi at 50 °C for 24 h. The solution was cautiously filtered through celite being careful not to allow the catalyst to become dry due to its pyrophoric nature. The filtrate was concentrated in vacuo to give a crude compound, which was purified by column chromatography (SiO₂) eluting with EtOAc to give (73 %) 112, as a white solid: 720 mg; ¹H NMR δ 1.22 (s, 243H, CH₃), 1.77 (br m, 78H, CH₂CH₂CO₂, CH₂CH₂CONH), 2.00 (br m, 78H, CH₂CH₂CO₂, CH₂CH₂CONH), 6.14 (s, 12H, CONH); ¹³C NMR δ 27.6 (CH₃), 29.5 (CH₂CH₂CO₂), 31.3 (CH₂CH₂CONH), 52.4 (H₂NC), 57.0 (CONHCCH₂CH₂CO₂), 57.5 (CONHC), 80.1 (CMe₃), 172.3 (CONH), 172.9 (CO₂); IR 3361, 3334, 2978, 2934, 1730 (ester C=O), 1653 (amide C=O) cm⁻¹; MALDI-TOF MS m/z = 4537.3 [M + Na⁺]; calcd. m/z = 4534.9 [M + Na⁺].

Synthesis of 3rd Generation Isocyanate 113 followed that of 108 (1 g, 220 µmol) in which the crude reaction mixture was column chromatographed (SiO₂) eluting with EtOAc/hexane (1:1) to give (57 %) the pure isocyanate 113: 570 mg; ¹H NMR δ 1.24 (s, 243H, CH₃), 1.75 (br m, 78H, CH₂CH₂CO₂, CH₂CH₂CONH), 2.01 (br m, 78H, CH₂CH₂CO₂, CH₂CH₂CONH), 6.21 (s, 12H, CONH); ¹³C NMR δ 28.0 (CH₃), 29.6 (CH₂CH₂CO₂), 31.5 (CH₂CH₂CONH), 57.3 (CONHCCH₂CH₂CO₂), 57.7 (CONHC), 59.9 (OCNC), 80.2 (CMe₃), 125.5 (OCN), 171.9 (CONH), 172.8 (CO₂); IR 3324, 2978, 2934, 2930, 1730, 1653 (ester C=O) cm⁻¹; MALDI-TOF MS m/z = 4537.3 [M + Na⁺]; calcd. m/z = 4534.9 [M + Na⁺].
2933, 2256 (O=C=N), 1731 (amide C=O), 1655 (ester C=O) cm⁻¹; MALDI-TOF MS m/z = 4565.2 [M + Na⁺]; calcd. m/z = 4561.9 [M + Na⁺].

5.4. References


CHAPTER VI

DESIGN, SYNTHESIS, AND CHARACTERIZATION OF CONIFER-SHAPED DENDRITIC ARCHITECTURES

6.1. Introduction

Traditional dendritic growth has generally led to uniform, spherical morphologies since the monomers used in their construction are generally uniform throughout their infrastructure. In light of the step-wise synthesis associated with the divergent construction of dendrimers, the utilization of different but yet similar branched monomers permits the construction of non-spherical shapes and sizes, thus expanding their applications in the areas of supramolecular chemistry. As well, most of the dendritic architectures thus far reported have a homogeneous surface, and are assembled in a uniform manner, due to the use of identical monomers or dendrons at each successive generation. And the design and synthesis of these architectures including dendronized polymers\textsuperscript{2,3} for various applications in such areas of unimolecular micelles\textsuperscript{4,5}, molecular encapsulation\textsuperscript{4,6-9}, drug delivery\textsuperscript{10-12}, and catalysis\textsuperscript{13,14} have become an important part of supramacromolecular chemistry.\textsuperscript{15} The general spherical shape and molecular weight of these unimolecular, nanoscale materials can be controlled by their now well-known step-wise construction based on either a divergent strategy\textsuperscript{16,17} involving an “inside-out”
approach or a convergent strategy\textsuperscript{18-20} utilizing an “outside-in” methodology. Accelerated procedures such as the orthogonal construction\textsuperscript{21,22} and the double exponential growth method\textsuperscript{23} have also been applied to the synthesis of dendrimers in order to reduce the overall number of steps. The chemical and physical properties of most dendrimers can be tuned by the introduction of appropriate terminal functional groups as well as internal components.

The majority of dendritic constructs have a homogeneous surface in that the same functionality appears at each terminus. Although there have been limited examples of combinatorial-type\textsuperscript{24} heterogeneous surfaces, Fréchet et al.\textsuperscript{25} reported an initial example of the functionalization of a dendron surface by placing a unique functional group on it’s periphery; whereby, this convergent approach was applied to the construction of generation 1\textsuperscript{st} – 4\textsuperscript{th} dendrons possessing a single cyano group on the surface of each dendron. These dendrons were finally coupled at their focal site to a three-directional core to produce a dendrimer with three unique termini. Schlüter et al.\textsuperscript{26} applied a similar strategy to incorporate bromo functionality at specific locations within their dendritic framework.

More recently, Thayumanavan et al.\textsuperscript{27} reported a series of dendrimers with various terminal groups in which the branched dendrons were convergently prepared to instill a pattern of substitution into the ultimate dendrimer; multiple approaches involving monomers possessing either different [1 → 2]-branched terminal protecting groups\textsuperscript{28} or different terminal reactivities\textsuperscript{29} affording varied functional groups on the periphery have been reported. Kozaki and Okada presented\textsuperscript{30} the preparation of snowflake-shaped dendrimers by using a combination of Suzuki and Sonogashira cross-coupling reactions.
Majoral et al. reported\textsuperscript{31-34} the preparation of phosphorous-containing dendrimers with P=N-P=S linkages, followed by internal site-specific functionalization leading to heterogeneous substitution. These authors also selectively functionalized one of the peripheral P(X)Cl\textsubscript{2} (X = S, O) moieties by displacement of a simple chlorine leaving the other chlorine atom intact for further dendritic growth.\textsuperscript{35}

In 2002, we devised a simple, utilitarian series of [1 → (2 + 1)]-C-branched dendrons\textsuperscript{36-39} so that specific functionality could be introduced but branching could still continue by means of the remaining two sites. This permitted access to complex dendritic spherical structures that possessed a single (or a controlled number) unique locus per dendron. This enhanced our general ability to preselect the number of unique sites at each generation of a particular dendrimer. Since these [1 → (2 + 1)]-C-branched predendrons and dendrons are easily created, when combined with [1 → 3]-C-branching monomers and dendrons, there is an infinite number of architectural possibilities. Since the vast majority of dendritic structures are spherical, or nearly so depending on generation, we, set as our goal the construction of different sizes and forms of nanoscopic macromolecular trees.

Herein, we describe our initial simple strategy aimed at the synthesis of nonspherical-shaped dendrons using the convergent protocol by the selective combination of [1 → (2 + 1)]- and [(1 → 3)]-C-branching building blocks.
6.2. Synthesis of Monomers

Diacid 114, prepared\textsuperscript{36} by treatment of benzyl 4-nitrobutanoate with a slight excess of tert-butyl acrylate followed by butyl ester cleavage (HCO\textsubscript{2}H), was treated with 2 equivalents of [1 → 3]-C-branched amine\textsuperscript{40,41} 52 in the presence of DCC and 1-HOBT to yield (93 \%) heptaester 115 (Scheme 25). The formation of ester 115 is supported (\textsuperscript{13}C NMR) by the presence of two new peaks at 57.7 and 170.2 ppm corresponding to the HNC and CONH carbon signals supporting tier assembly; the molecular weight of 1185.3 amu (ESI-MS) was demonstrated. Catalytic deprotection of monomer 115 with 10\% Pd/C afforded (100 \%) the bis(amido) acid 116, as shown by the disappearance (\textsuperscript{13}C NMR) of the benzyl group absorptions and the observed new peak at 174.0 ppm (CO\textsubscript{2}H). The definitive molecular ion peak (ESI-MS) at \textit{m/z} 1073.33 [M - H\textsuperscript{+}] also supported the structure.

In order to construct a larger wedge, a [1 → 2]-C-branching pattern was inserted into the synthetic protocol affording a less congested internal environment deemed necessary for later coupling of the components. Treatment of diacid 114 with aminodiester building block42 69 using DCC amidation conditions gave (96 %) pentaester 117 (Scheme 26). The $^{13}$C NMR spectral data for 6 showed two carbonyl groups [170.4 (amide) and 173.2 ppm (ester)] as well as an ESI-MS peak at 957.3 [M + Na$^+$. Pentaester 117 was then deprotected with 95 % formic acid at 25 ºC for 15 h to quantitatively give the tetraacid 118, which was confirmed by the disappearance of the tert-butyl absorptions in $^{13}$C NMR as well as the expected downfield shift for the carboxylic carbonyl group to 174.0 ppm; the ESI-MS revealed a molecular ion peak at $m/z$ 708.3 [M - H$^-$].

The tetraacid 118 was coupled with Behera’s amine 52 under similar amidation conditions to afford (85 %) predendron 119 (Scheme 27), which was identified by the appearance ($^{13}$C NMR) of a singlet at 24.0 ppm for the unique methyl groups and four distinctive carbonyl absorptions at 170.9, 172.2, 172.9, and 173.0 ppm, as well as the appropriate MALDI-TOF MS peak at 2321.6 [M + Na$^+$]. Hydrogenolysis of the benzyl group with 10% Pd/C at 60 p.s.i and 25 ºC for 48 h liberated the internal acid moiety generating the desired dodecaester 120 as demonstrated by the appearance of a new peak at 174.9 ppm for this carbonyl group while still retaining all other core functionality as verified by ($^{13}$C NMR). A shift (1730 → 1700) of the C=O adsorption (IR) as well as observed broad peak for the OH stretching (3660-3000 cm$^{-1}$) further confirmed the transformation. The combination of these different monomers in the assembly process ensures a high outer surface density while leaving the internal infrastructure open for subsequent elaboration.

In order to instill the elongated component into the framework, Behera’s amine 52, when treated with one equivalent of acryloyl chloride in the presence of Et₃N in dry THF gave (> 96 %) the N-substituted amide 104 (Scheme 28), which was subsequently subjected to a 1:1 Michael-type addition with MeNO₂ in the presence of the water-soluble base tetramethylguanidine (TMG) to generate (ca. 90 % overall) the homologated nitrotriester 43 105. Reduction of the nitro moiety with Raney-Ni catalyst in absolute EtOH at 50 ºC afforded (98 %) the desired extended amine dendron 121, whose structure was identified (¹³C NMR) by the anticipated upfield chemical shift from 74.5 to 41.0 ppm (O₂NCH₂ and H₂NCH₂, respectively) and the molecular ion peak (ESI-MS) at m/z 523.1 [M + Na⁺].

With most of the key components of this elongated molecular structure in-hand, assembly of the sections started with the top tier 121, which will be connected to the middle tier 116, then to the bottom tier 120, and lastly it will be extended with a novel focal section. Thus, the DCC-mediated coupling of monoacid 116 and amine 121 afforded (92 %) top-section predendron 122 (Scheme 29), which was characterized by the appearance (¹³C NMR) of peaks at 80.6 and 80.7 ppm for two different tert-butyl quaternary carbons, the presence of 3 peaks for the three different amide carbonyl moieties, and a definitive molecular ion (ESI-MS) peak at m/z 1577.8 [M + Na⁺]. The focal nitro group of this predendron 122 was then reduced quantitatively to the corresponding amine group by catalytic hydrogenation to generate the [1 + 2]-poly functional dendron 123. Formation of amine 123 was demonstrated by the downfield
shift ($^{13}$C NMR) of the peak assigned to the focal quaternary carbon from 93.1 to 55.3 ppm and a molecular ion peak (ESI-MS) at $m/z$ 1547.8 [M + Na$^+$.]

Scheme 28. Synthesis of the extended amine dendron 121: a) H$_2$C=CHCOCl, Et$_3$N, CH$_2$Cl$_2$, 25 °C, 2 h; b) CH$_3$NO$_2$, CHCl$_3$, 25 °C, 24 h; c) H$_2$, Raney Ni, EtOH, 50 °C, 15 h.

To instill the extended focal functionality necessary to penetrate into and attach the lower tier 3, the synthesis of acrylamide 124 (Scheme 29) was achieved (93 %) by the treatment of amine 123 with acryloyl chloride in the presence of Et$_3$N in dry THF. The new acrylamide signal ($^{13}$C NMR) at 165.5 ppm (CONH) and olefinic peaks at 125.5, 132.1 ppm as well as a molecular ion peak (ESI-MS) at $m/z$ 1602.1 [M + Na$^+$] provided evidence for the initial extension stage. Reacting the acrylamide 124 with MeNO$_2$ in the presence of TMG in refluxing THF for 24 h gave (82 %) predendron 125, which was structurally established ($^{13}$C NMR) by the new signal (74.9 ppm) for the O$_2$NCH$_2$R moiety and the molecular ion peak (ESI-MS) at $m/z$ 1662.9 amu [M + Na$^+$]. Reduction of the nitro moiety with Raney Ni catalyst in absolute EtOH at 50 °C created (95 %) the desired extended amino dendron 126, which was supported by the spectral similarity to the previous predendrons in this synthetic series with the exception of the notable...
chemical shift ($^{13}$C NMR) from 74.9 to 39.9 ppm ($\text{O}_2\text{NCH}_2$ and $\text{H}_2\text{NCH}_2$, respectively) and the molecular ion peak (ESI-MS) at $m/z$ 1633.0 [M + Na$^+$].

Scheme 29. Synthesis of 2$^{\text{nd}}$ generation extended dendron 126: a) DCC, 1-HOBT, THF, 25 °C, 24 h; b) H$_2$, T1-Raney Ni, EtOH, 50 °C, 15 h; c) H$_2$C=CHCOCl, Et$_3$N, THF, 25 °C, 5 h; d) CH$_3$NO$_2$, TMG, 50 °C, 15 h; e) H$_2$, Raney Ni, EtOH, 50 °C, 15 h.

The assembly of the combined tiers 1 and 2 in extended amine 126 with the lower tier 120 portion was accomplished by treatment of the acid 120 with amine 126 by the DCC coupling procedure to generate (65 %) the desired predendron 127 (Scheme 30), whose structure was confirmed ($^{13}$C NMR) by observation of the peaks assigned to the 10
different carbonyl groups and the molecular ion peak at \( m/z \) 3825.5 \([M + Na^+]\) in the MALDI-TOF MS. Reduction of the nitro moiety with Raney-Ni in absolute EtOH at 50 °C for 36 h afforded (85 %) the corresponding amine 128 that was characterized by the chemical shift (\(^{13}\)C NMR) for the \( H_2NC \) from 92.3 to 55.6 ppm and the molecular ion peak in MALDI-TOF MS at \( m/z \) 3796.2 \([M + Na^+]\). Amino dendron 128 was next treated with triphosgene in the presence of \( Et_3N \) to afford (75 %) the desired isocyanate dendron 129. New peaks at 62.3 (OCNC), 123.2 (OCN) ppm supported the assigned structure of 129; in addition, a \([M + Na^+]\) peak at \( m/z \) 3819.6 (calcd. mass 3820.9) and appearance of the unique peak at 2210 cm\(^{-1}\) (FTIR) further characterized the proposed structure.

Scheme 30. Synthesis of elongated dendron 129: a) DCC, 1-HOBT, DMF, 25 °C, 24 h; b) \( H_2 \), Raney Ni, EtOH, 50 °C, 48 h; c) Triphosgene, \( Et_3N \), THF, 25 °C, 12 h.
Construction of an adamantane-based focal molecular anchor was undertaken next; the strategy for the synthesis of alkyl amine modified adamantane 135 is shown in Scheme 31. Using the standard amidation conditions, 1-adamantanecarboxylic acid treated with aminopentanol using the above amidation conditions to generate (87 %) alcohol 132, as evidenced by the appearance ($^{13}$C NMR) of a carbonyl peak at 178.2 ppm for the amide and the ESI-MS data revealing the expected molecular ion at 288.1 amu [M + Na$^+$]. Alcohol 132 was subsequently reacted with mesyl chloride in the presence of Et$_3$N in THF to produce (90 %) mesylate 133; the downfield shift (62.2 to 69.9 ppm) for OCH$_2$ and the appearance of a peak at 37.3 ppm for SO$_2$CH$_3$ ($^{13}$C NMR) as well as the molecular ion peak (ESI-MS) at 366.2 amu [M + Na$^+$] confirm the transformation. Nucleophilic substitution of the mesyl group with NaN$_3$ in DMF at 60 ºC afforded (93 %) azide 134, which was catalytically hydrogenated to give (95 %) the corresponding amine 135 whose structure was supported by an upfield shift (51.2 → 40.8 ppm) of the absorption corresponding to the CH$_2$NH$_2$ moiety and a molecular ion peak (ESI-MS) at m/z 287.3 [M + Na$^+$].

Scheme 31. Synthesis of adamantane amine 135: a) DCC, 1-HOBT, THF, 25 ºC, 5 h; b) Et$_3$N, MsCl, THF, 25 ºC, 3 h; c) NaN$_3$, DMF, 50 ºC, 7 h; d) H$_2$, 10% Pd/C, EtOH, 25 ºC, 12 h.
Synthesis of the desired elongated macromolecule 136 was achieved (95%) by the reaction between isocyanate 129 and amine 135 in dry CH₂Cl₂. Evidence for the formation of 136 was supported by the appearance (¹³C NMR) of the new urea carbonyl group at 158.3 ppm and the molecular ion peak (MALDI-TOF) at m/z 4085.0 [M + Na⁺]. Finally the adamantane-terminated dendron was planted into a molecular container, β-cyclodextrin (β-CD), by treatment of a 1:1 mixture of 136 and β-CD in DMSO. The host-guest interactions of adamantane moiety within the β-cyclodextrin cavity were monitored by ¹H NMR spectroscopy. The H-3 peak of the uncomplexed cyclodextrin at 4.47 ppm was shifted to upfield (Δδ = -0.023 ppm) upon complexation with adamantane-terminated dendron due to the guest (adamantane) inclusion compared to the other protons of cyclodextrin.

In summary, new types of dendritic frameworks, in which different, branched layers were synthesized from the key intermediates 120 and 126, which in turn were readily prepared from the combination of [1 $\to$ (2 + 1)]- and [1 $\to$ 3]-C-branched building blocks. The amine dendron 128 has been synthesized, then transformed to the corresponding isocyanate dendron using triphosgene. Treatment of isocyanate 129 with amine 135 afforded conical-shaped dendron 136, which was subsequently planted in $\beta$-cyclodextrin. All the new dendrons were isolated as either white solids or clear viscous liquids, which were soluble in common organic solvents such as CHCl$_3$, CH$_2$Cl$_2$, THF, and MeOH and were fully characterized by $^1$H NMR, $^{13}$C NMR, ESI, MALDI-TOF MS, and IR spectroscopy. Today when one buys an evergreen tree in a nursery, the balled root system is in a plastic bucket, thus the creation of coniferous-shaped molecular trees and their protected sites for attachment is possible and may be available in the future to build molecular gardens and forests. One realizes that two-dimensional representations do not accurately depict three-dimensional molecular assemblies – but having appropriate branched monomers permits the construction of novel non-uniform, tree-shaped structures.

6.3. Experimental Section: General Remarks.

Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. All of chemicals were purchased from Aldrich Co. except for Behera’s amine.$^{44}$ Tetrahydrofuran (THF) was dried by refluxing
over benzophenone/Na under N\textsubscript{2}. Dichloromethane was dried over CaH\textsubscript{2}. All other commercially available solvents were used without further purification. Column chromatography was conducted using silica gel (60-200 mesh) from Fisher Scientific with the stipulated solvent mixture. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were obtained in CDCl\textsubscript{3}, except where noted, and are recorded at 300 and 75 MHz, respectively. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded on an ATI Mattson Genesis Series FTIR spectrometer. Mass spectral data were obtained using an Esquire electron ionization mass spectrometer (ESI) and are reported as: (assignment, relative intensity); ESI samples were typically prepared in MeOH/H\textsubscript{2}O/TFA (70:30:01) for positive ion mode or Me\textsubscript{2}CHOH/H\textsubscript{2}O/NH\textsubscript{3} (70:30:1) for negative ion mode and matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer.

**Preparation of Activated Raney Nickel Catalyst.**\textsuperscript{45} In a beaker with distilled water (2 L), NaOH (300 g) was added carefully with stirring. After dissolution, Al-Ni alloy (120 g) was added in small portions. The temperature suddenly increased with the evolution of hydrogen gas. The beaker was covered with a watch glass and the temperature was maintained at 80-90 °C by warming on a hot plate/stirrer for one hour. The supernatant solution was then decanted; the catalyst was washed several times with distilled water and then 3 times with EtOH. *Throughout this process, caution must be taken to keep the catalyst wet; the activated catalyst is highly pyrophoric.*

**Heptaester 115** was previously prepared\textsuperscript{36} as a white solid: 5.9 g; mp 110-111 °C; \textsuperscript{1}H NMR: \( \delta \) 1.43 [s, 54H, C(CH\textsubscript{3})\textsubscript{3}], 1.95 (t, \( J = 7.2 \) Hz, 12H, \( CH_2CH_2CO_2 \)), 2.09 (t, 6H, \( J \) \( \text{Hz} \)).
= 8.4 Hz, CH₂CH₂CONH, CH₂CH₂CO₂), 2.21 (t, 12H, J = 7.2 Hz, CH₂CO₂), 2.40 (t, 6H, J = 8.4 Hz, CH₂CONH, CH₂CO₂CH₂), 5.12 (s, 2H, CH2Ph), 6.16, (s, 2H, CONH), 7.35 (s, 5H, Ph); ¹³C NMR: δ 28.1 [C(CH₃)₃], 28.7 (CH₂CH₂CH₂CO₂, 29.9 (CH₂CH₂CONH, CH₂CH₂CO₂), 30.0 (CH₂CO₂CH₂), 31.3 (CH₂CONH), 31.4 (CH₂CO₂), 57.7 (NHC), 66.8 (OCH₂Ph), 80.8 (CMe₃), 92.5 (O₂NC), 128.4 (4-PhC), 128.5 (3-PhC), 128.6 (2-PhC), 135.6 (1-PhC), 170.2 (CONH), 172.0 (CO₂CH₂), 172.9 (CO₂); IR: 1725 (C=O), 1715 (C=O), 1535 (NO₂) cm⁻¹; ESI-MS m/z = 1184.90 [M + Na⁺]; calcd. m/z = 1185.45 [M + Na⁺].

Bis(amido)acid 116 was previously prepared³⁶ as a white solid: 5.4 g; mp 113-114 ºC; ¹H NMR: δ 1.36 [s, 54H, C(CH₃)₃], 1.89 (m, 12H, CH₂CH₂CO₂), 2.12 (m, 20H, CH₂CO₂, CH₂CH₂CONH, CH₂CH₂CO₂CH₂), 2.26 (m, 2H, CH₂CO₂CH₂), 6.21 (s, 2H, CON) 9.14 (s, 1H, CO₂H); ¹³C NMR: δ 28.2 [C(CH₃)₃], 28.4 (CH₂CH₂CO₂H), 28.6 (CH₂CO₂H), 30.0 (CH₂CH₂CO₂), 30.3 (CH₂CO₂), 31.3 (CH₂CH₂CONH), 31.5 (CH₂CONH), 57.7 (NHC), 81.1 (CMe₃), 93.4 (O₂NC), 170.8 (CONH), 173.3 (CO₂), 174.2 (CO₂H); IR: 1730 (C=O), 1700 (C=O), 1530 (NO₂) cm⁻¹; ESI-MS m/z = 1094.80 [M + Na⁺]; calcd. m/z = 1095.33 [M + Na⁺].

Synthesis of Pentaester 117. To a stirred solution of acid³⁶ 1 (mp 96-97 ºC; 1 g, 2.7 mmol) in dry DMF (30 mL), DCC (1.2 g, 5.7 mmol) and 1-HOBT (770 mg, 5.7 mmol) were added at 25 ºC; after 2 h, diester amine⁴² 5 (1.7 g, 5.7 mmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed
(SiO$_2$) eluting with 15% EtOAc in hexane to afford (96%) 117, as viscous oil: 2.5 g; $^1$H NMR: $\delta$ 1.27 (s, 6H, CH$_3$), 1.43 [s, 36H, C(CH$_3$)$_3$], 1.89 (t, 8H, $J$ = 7.5 Hz, CH$_2$CH$_2$CO$_2$), 2.01 (t, 4H, $J$ = 7.5 Hz, CH$_2$CH$_2$CO$_2$CH$_2$), 2.08 (t, 8H, $J$ = 6 Hz, CH$_2$CO$_2$), 2.23 (t, 6H, $J$ = 7.5 Hz, CH$_2$CH$_2$CONH, CH$_2$CH$_2$CO$_2$CH$_2$), 2.39 (t, 2H, $J$ = 8.4 Hz, CH$_2$COCH$_2$), 5.11 (s, 2H, OC$_2$H$_2$), 6.05 (s, 2H, NH), 7.35 (s, 5H, Ph); $^{13}$C NMR: $\delta$ 23.5 (CH$_3$), 27.9 [C(CH$_3$)$_3$], 28.5 (CH$_2$CH$_2$CO$_2$CH$_2$), 29.9 (CH$_2$CH$_2$CONH), 30.1 (CH$_2$CH$_2$CO$_2$), 30.9 (CH$_2$CO$_2$CH$_2$), 31.0 (CH$_2$CONH), 33.1 (CH$_2$CO$_2$), 55.3 (NHC), 66.5 (H$_2$CO), 80.3 (CMe$_3$), 92.6 (O$_2$NC), 128.1 (4-PhC), 128.2 (3-PhC), 128.4 (2-PhC), 135.5 (1-PhC), 170.2 (CONH), 171.7 (CO$_2$CH$_2$), 173.0 (CO$_2$); IR: 1725 (C=O), 1715 (C=O), 1530 (NO$_2$) cm$^{-1}$; ESI-MS: $m/z$ = 956.8 [M + Na$^+$], calcd. $m/z$ = 957.16 [M + Na$^+$].

Synthesis of Tetraacid 118. A solution of pentaester 6 (5 g, 5.3 mmol) in HCO$_2$H (100 mL, 95%) was stirred at 25 ºC for 15 h. After concentration in vacuo, toluene (2 X 50 mL) was added and the solution was again evaporated in vacuo to afford (95%) pure tetraacid 118, as viscous liquid: 3.6 g; $^1$H NMR: $\delta$ 1.29 (s, 6H, CH$_3$), 1.93 (br m, 8H, CH$_2$CH$_2$CO$_2$), 2.10 (t, 2H, $J$ = 7.5 Hz, CH$_2$CO$_2$CH$_2$), 2.15 (t, 8H, $J$ = 6 Hz, CH$_2$CO$_2$), 2.35 (t, 6H, $J$ = 7.5 Hz, CH$_2$CH$_2$CONH, CH$_2$CO$_2$CH$_2$), 2.43 (t, 4H, $J$ = 8.4 Hz, CH$_2$CONH), 5.19 (s, 2H, OCH$_2$), 6.18 (s, 2H, NH), 7.41 (s, 5H, Ph); $^{13}$C NMR: $\delta$ 23.8 (CH$_3$), 26.5 (CH$_2$CH$_2$CO$_2$CH$_2$), 29.6 (CH$_2$CH$_2$CONH), 29.9 (CH$_2$CH$_2$CO$_2$), 31.3 (CH$_2$CO$_2$CH$_2$), 31.7 (CH$_2$CONH), 34.4 (CH$_2$CO$_2$), 56.4 (NHC), 67.7 (H$_2$CO), 94.1 (O$_2$NC), 129.3 (4-PhC), 129.4 (3-PhC), 129.6 (2-PhC), 137.4 (1-PhC), 173.7 (CONH), 173.9 (CO$_2$CH$_2$), 177.5 (CO$_2$); IR: 3400-3000 (OH), 1725 (C=O), 1700 (C=O), 1535 (NO$_2$) cm$^{-1}$; ESI-MS: $m/z$ = 708.30 [M - H$^+$], calcd. $m/z$ = 708.74 [M - H$^+$].
**Synthesis of Predendron 119.** To a stirred solution of tetraacid 118 (1 g, 1.4 mmol) in dry DMF (30 mL), DCC (1.2 g, 5.7 mmol) and 1-HOBT (780 mg, 5.7 mmol) were added at 25 °C; after 2 h, Behera’s amine \(^{44}\) 52 (2.4 g, 5.7 mmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated *in vacuo* to give a crude oil, which was column chromatographed (SiO\(_2\)) eluting with 40% EtOAc in CHCl\(_3\) to afford (85 %) 119, as a white solid: 2.8 g; mp 127-128 °C; \(^1\)H NMR: \(\delta\) 1.24 (s, 6H, C\(\text{CH}_3\)), 1.43 [s, 10H, C(C\(\text{CH}_3\))], 1.53 (br m, 12H, C\(\text{CH}_2\)CH\(_2\)CONH), 1.67 (br m, 12H, CH\(_2\)CONH), 1.95 (t, 24H, \(J = 7.8\) Hz, CH\(_2\)CH\(_2\)CO\(_2\)), 2.02 (br m, 2H, CH\(_2\)CH\(_2\)CO\(_2\)CH\(_2\)), 2.20 (t, 24H, CH\(_2\)CO\(_2\)), 2.41 (br m, 2H, CH\(_2\)CO\(_2\)CH\(_2\)), 5.12 (s, 2H, OCH\(_2\)), 6.12 (s, 4H, NH), 6.88 (s, 2H, NH), 7.35 (s, 5H, Ph); \(^{13}\)C NMR: \(\delta\) 24.0 (C\(\text{CH}_3\)), 28.2 [C(C\(\text{CH}_3\))], 28.9 (CH\(_2\)CH\(_2\)CO\(_2\)CH\(_2\)), 29.9 (CH\(_2\)CH\(_2\)CO\(_2\)), 30.1 (CH\(_2\)CO\(_2\)), 30.4 (CH\(_2\)COCH\(_2\)), 30.8 (CH\(_2\)CH\(_2\)CONH), 31.3 (CH\(_2\)CONH), 32.1 (CH\(_2\)CH\(_2\)CONH), 34.6 (CH\(_2\)CONH), 55.7 (HNC), 57.5 (HNC), 66.8 (H\(_2\)CO), 80.7 (CMe\(_3\)), 92.8 (O\(_2\)NC), 128.4 (4-PhC), 128.7 (3-PhC), 128.8 (2-PhC), 135.8 (1-PhC), 170.9 (CONH), 172.2 (CO\(_2\)CH\(_2\)), 172.9 (CONH), 173.0 (CO\(_2\)); IR: 1730 (C=O), 1725 (C=O), 1535 (NO\(_2\)) cm\(^{-1}\); ESI-MS: \(m/z = 2322.0\) [M + Na\(^+\)], calcd. \(m/z = 2322.33\) [M + Na\(^+\)].

**Synthesis of Acid 120.** An absolute EtOH (100 mL) solution of ester 119 (1 g, 430 \(\mu\)mol) in the presence of 10% Pd on activated carbon (1 g) was hydrogenated at 60 psi at 25 °C for 12 h. The solution was cautiously filtered through Celite and the solvent was reduced *in vacuo* to give (90 %) monoacid 120, as a white solid: 860 mg; mp 135-137 °C; \(^1\)H NMR: \(\delta\) 1.26 (s, 6H, CH\(_3\)), 1.44 [s, 108H, C(CH\(_3\))], 1.96 (t, 64H, \(J = 7.2\) Hz, 154
CH$_2$CH$_2$CO$_2$, CH$_2$CH$_2$CONH), 2.19 (br m, 8H, CH$_2$CH$_2$CONH), 2.39 (br m, 4H, CH$_2$CH$_2$CO$_2$CH$_2$), 6.25 (s, 4H, NH), 6.59 (s, 2H, NH); $^{13}$C NMR: δ 23.8 (CH$_3$), 28.0 [C(CH$_3$)$_3$], 28.4 (CH$_2$CH$_2$CO$_2$CH$_2$), 29.7 (CH$_2$CH$_2$CO$_2$), 30.1 (CH$_2$CO$_2$), 30.8 (CH$_2$CH$_2$CONH), 31.2 (CH$_2$CO$_2$CH$_2$), 31.9 (CH$_2$CONH), 34.5 (CH$_2$CH$_2$CONH), 34.8 (CH$_2$CONH), 55.5 (HN$_2$C), 57.4 (HN$_2$C), 80.5 (CMe$_3$), 93.3 (O$_2$N$_2$C), 171.1 (CONH), 172.7 (CONH), 173.1 (CO$_2$), 174.9 (CO$_2$H); IR: 1735 (C=O), 1720 (C=O), 1700 (C=O), 1535 (NO$_2$) cm$^{-1}$; ESI-MS: m/z = 2231.41 [M + Na$^+$], calcd. m/z = 2232.81 [M + Na$^+$].

**Synthesis of Amine 121.** A suspension of nitro amide$^{43}$ 105 (3 g, 5.6 mmol) and T-1 Raney-Ni (2 g) in abs. EtOH (100 mL) was hydrogenated at 60 psi at 50 ºC for 15 h. The solution was cautiously filtered (Pyrophoric) through Celite, after which the solvent was removed in vacuo to afford (96 %) 121, as a white solid: 2.7 g; mp 110-112 ºC; $^1$H NMR: δ 1.44 (s, 27H, CH$_3$), 1.88 (t, 2H, J = 6.6 Hz, CH$_2$CO), 1.96 (t, 6H, J = 7.5 Hz, CH$_2$CH$_2$CO), 2.22 (t, 6H, J = 7.5 Hz, CH$_2$CO), 2.33 (t, 2H, J = 6 Hz, CH$_2$CONH), 2.89 (t, 2H, J = 6 Hz, H$_2$NCH$_2$), 4.27 (s, 2H, NH$_2$), 6.19 (s, 1H, NH); $^{13}$C NMR: δ 22.8 (CH$_2$CO), 28.2 [C(CH$_3$)$_3$], 30.0 (CH$_2$CO, CH$_2$CH$_2$CO), 34.7 (H$_2$NCH$_2$CH$_2$), 41.0 (H$_2$NCH$_2$), 57.6 (HNC), 80.8 (CMe$_3$), 172.3 (CONH), 173.1 (CO$_2$); IR: 3300-3000 (NH$_2$), 1710 (C=O), 1670 (C=O) cm$^{-1}$; ESI-MS: m/z = 523.12 [M + Na$^+$], Calcd. m/z = 523.67 [M + Na$^+$].

**Synthesis of the Extended Predendron 122.** To a stirred solution of acid$^{36}$ 116 (2 g, 1.8 mmol) in dry DMF (50 mL), DCC (385 mg, 1.8 mmol) and 1-HOBT (255 mg, 1.8 mmol) at 25 ºC were added; after 2 h, extended amine 121 (930 mg, 1.8 mmol) was
added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated \textit{in vacuo} to give a crude oil, which was column chromatographed (SiO$_2$) eluting with 20% EtOAc in hexane to afford (91%) 122, as a white solid: 1.8 g; $^1$H NMR: $\delta$ 1.43 (s, 81H, CH$_3$), 1.78 (t, 2H, $J = 5.1$ Hz, CH$_2$CO), 1.96 (br m, 36H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CO), 2.09 (t, 2H, $J = 4.5$ Hz, CH$_2$CH$_2$CO), 2.19 (m, 12H, CH$_2$CH$_2$CONH, CH$_2$CH$_2$CONH), 3.25 (t, 2H, $J = 4.8$ Hz, NHCH$_2$), 6.12 (s, 2H, NH), 6.21 (s, 1H, NH), 6.40 (t, $J = 3.9$ Hz, 1H, NHCH$_2$); $^{13}$C NMR: $\delta$ 25.71 (CH$_2$CO), 28.1 (CH$_3$), 29.8 (CH$_2$CH$_2$CO$_2$), 29.9 (CH$_2$CO$_2$), 29.99 (CH$_2$CH$_2$CO$_2$), 30.4 (CH$_2$CH$_2$CONH), 30.8 (CH$_2$CONH), 31.4 (CH$_2$CO$_2$), 34.5 (HNCH$_2$CH$_2$), 39.1 (HNCH$_2$), 57.5 (HNC), 57.6 (HNC), 80.6, 80.7 (2 CMe$_3$), 93.1 (O$_2$NC), 170.6, 171.7, 172.2 (3 CONH), 172.8, 172.9 (2 CO$_2$); IR: 3300 (NH), 1730 (C=O), 1720 (C=O), 1550 (NO$_2$) cm$^{-1}$; ESI-MS: $m/z = 1577.80$ [M + Na$^+$], calcd. $m/z = 1577.98$ [M + Na$^+$].

**Synthesis of Amino Dendron 123.** A solution of nitro ester 122 (2 g, 1.3 mmol) in abs. EtOH (150 mL) with T-1 Raney Ni (3 g) was hydrogenated (60 p.s.i) at 50 ºC for 15 h. The solution was cautiously filtered, as in the above procedure, through Celite, then concentrated \textit{in vacuo} to give (95%) the amino ester 123, as a viscous oil: 1.86 g; $^1$H NMR: $\delta$ 1.41 (s, 81H, CH$_3$), 1.81 (t, 2H, $J = 5.1$ Hz, CH$_2$CO), 1.96 (br m, 36H, CH$_2$CH$_2$CO, CH$_2$CH$_2$CO), 2.22 (m, 2H, CH$_2$CH$_2$CO), 2.35 (m, 12H, CH$_2$CH$_2$CONH, CH$_2$CONH), 3.27 (t, 2H, $J = 4.8$ Hz, NHCH$_2$), 6.42 (s, 2H, NH), 6.51 (s, 1H, NH), 6.41 (br s, $J = 3.9$ Hz, 1H, NHCH$_2$), 7.35 (s, 2H, NH$_2$); $^{13}$C NMR: $\delta$ 25.7 (CH$_2$CO), 28.0 (CH$_3$), 29.6 (CH$_2$CH$_2$CO$_2$), 29.7 (CH$_2$CO$_2$), 30.2 (CH$_2$CH$_2$CONH), 30.8 (CH$_2$CONH), 32.4 (CH$_2$CH$_2$CONH, CH$_2$CONH), 34.3 (HNCH$_2$CH$_2$), 38.7 (HNCH$_2$), 55.3 (H$_2$NC), 156
57.4, 57.7 (3 HNC), 80.3, 80.4 (2 CMe₃), 172.5, 172.6, 172.8 (3 CONH), 172.9, 173.2 (2 CO₂); IR: 3400-3000 (NH₂), 1730 (C=O), 1725 (C=O) cm⁻¹; ESI-MS: m/z = 1547.8 [M + Na⁺], calcd. m/z = 1548.0 [M + Na⁺].

Synthesis of Acrylamide 124. To a stirred solution of amine 123 (1 g, 650 µmol) and Et₃N (184 µL, 1.3 mmol) in dry THF at 0 ºC, acryloyl chloride (60 mg, 650 µmol) was added. After 5 h at 25 ºC, the reaction mixture was washed with water, then satd. brine. The organic solution was dried (MgSO₄), filtered, and concentrated in vacuo to give a crude solid, which was chromatographed (SiO₂) eluting with a 30 % EtOAc in CHCl₃ mixture to afford (96 %) amide 124, as a white solid: 990 mg; ¹H NMR: δ 1.44 (s, 81H, CH₃), 1.79 (t, 2H, J = 5.1 Hz, CH₂CO), 1.98 (br m, 36H, CH₂CH₂CO, CH₂CO), 2.21 (t, 2H, J = 4.5 Hz, CH₂CH₂CO), 2.27 (m, 12H, CH₂CH₂CONH, CH₂CONH), 3.25 (t, 2H, J = 4.8 Hz, NHCH₂), 5.58 (br m, 1H, CH₂=CH), 6.12 (br m, 1H, CH₂=CH), 6.21 (br m, 1H, CH₂=CH), 6.41 (s, 2H, NH), 6.51 (s, 2H, NH), 6.41 (s, 1H, NHCH₂), 7.35 (s, 2H, NH₂); ¹³C NMR: δ 25.7 (CH₂CO), 28.0 (CH₃), 29.5 (CH₂CH₂CO₂), 29.7 (CH₂CO₂), 30.9 (CH₂CH₂CO), 31.6 (CH₂CH₂CONH), 31.9 (CH₂CO₂), 33.1 (CH₂CH₂CONH), 34.3 (CH₂CONH), 35.3 (HNCH₂CH₂), 38.8 (HNCH₂), 57.3, 57.9 (3 HNC), 80.3, 80.4 (2 CMe₃), 125.5 (CH₂=CH), 132.1 (CH₂=CH), 165.5, 172.1, 172.6, 172.7 (4 CONH), 172.9, 173.7 (2 CO₂); IR: 3350 (NH), 1730 (C=O), 1720 (C=O), 1620 (C=C), 1670 (C=O) cm⁻¹; ESI-MS: m/z = 1602.1 [M + Na⁺], calcd. m/z = 1602.4 [M + Na⁺].

Synthesis of Extended Nitroamide 125. To a stirred solution of acrylamide 124 (1 g, 630 µmol) in a MeNO₂/CHCl₃ mixture (1:1; 50 mL), TMG (250 µL) was added and
maintained at 50 ºC for 15 h. The mixture was then concentrated in vacuo to give a crude solid, which was dissolved in CHCl₃ then sequentially washed with dilute aq. HCl, water, and satd. brine. The organic solution was dried (Na₂SO₄), filtered, and concentrated in vacuo to give a crude oil, which was column chromatographed (SiO₂) eluting with 40 % EtOAc in CHCl₃ to give (87 %) amide 125, as a white solid: 900 mg; ¹H NMR: δ 1.44 (s, 81H, CH₃), 1.79 (t, 2H, J = 5.1 Hz, CH₂CO), 1.96 (br m, 36H, CH₂CH₂CO, CH₂CH₂CO), 2.15 (br s, 2H, CH₂CO), 2.21 (br m, 2H, CH₂CH₂CO), 3.27 (t, 2H, J = 4.8 Hz, O₂NCH₂), 6.09 (s, 2H, NH), 6.25 (s, 2H, NH), 6.43 (t, J = 3.9 Hz, 1H, NHCH₂); ¹³C NMR: δ 22.8 (CH₂CO), 25.7 (CH₂CO), 27.9 (CH₃), 29.6 (CH₂CH₂CO₂, CH₂CO), 31.3 (CH₂CH₂CONH), 31.4 (CH₂CONH), 32.6 (O₂NCH₂CH₂), 34.3 (HNCH₂CH₂), 34.7 (CH₂CONH), 38.8 (HNCH₂), 57.2, 57.7 (4 HNC), 74.9 (O₂NCH₂), 80.3, 80.4 (2 CMe₃), 170.8, 172.0, 172.5, 172.7 (4 CONH), 172.7, 173.5 (2 CO₂); IR: 3350 (NH), 1735 (C=O), 1720 (C=O), 1550 (NO₂) cm⁻¹; ESI-MS: m/z = 1662.90 [M + Na⁺], calcd. m/z = 1663.08 [M + Na⁺].

Synthesis of Aminoamide 126. A solution of predendron 125 (1 g, 610 µmol) in abs. EtOH (150 mL) with T-1 Raney Ni (3 g) was hydrogenated (60 p.s.i) at 50 ºC for 24 h. The solution was cautiously filtered, as in the above procedure, through Celite, then concentrated in vacuo to give (95 %) the amino ester 126: 930 mg; ¹H NMR: δ 1.44 (s, 81H, CH₃), 1.79 (t, 2H, J = 5.1 Hz, CH₂CO), 1.96 (br m, 36H, CH₂CH₂CO, CH₂CH₂CO), 2.15 (br s, 2H, CH₂CO), 2.21 (br m, 2H, CH₂CH₂CO), 2.27 (m, 12H, CH₂CH₂CONH, CH₂CONH), 2.30 (t, 4H, CH₂CH₂), 2.80 (t, 2H, J = 4.8 Hz, NHCH₂), 3.25 (m, 2H,
H₂NCH₂), 6.09 (s, 2H, NH), 6.25 (s, 2H, NH), 6.96 (t, J = 3.9 Hz, 1H, NHCH₂); ¹³C NMR: δ 23.1 (CH₂CO), 26.0 (CH₂CO), 28.0 (CH₃), 29.7 (CH₂CH₂CO₂, CH₂CO₂), 30.7 (CH₂CH₂CONH), 31.0 (CH₂CONH), 31.2 (CH₂CH₂CONH), 31.3 (CH₂CONH), 33.9 (HNCH₂CH₂), 34.3 (H₂NCH₂CH₂), 38.4 (HNCH₂), 39.9 (H₂NCH₂), 57.3, 57.4, 57.7 (4 HNC), 80.3, 80.4 (2 CMe₃), 172.7, 172.8, 172.9, 173.0 (4 CONH), 173.3, 173.9 (2 CO₂); IR: 3400-3000 (NH₂), 1735 (C=O), 1720 (C=O) cm⁻¹; ESI-MS: m/z = 1633.0 [M + Na⁺], calcd. m/z = 1633.10 [M + Na⁺].

**Synthesis of Predendron 127.** To a stirred solution of acid 120 (1 g, 450 µmol) in dry DMF (30 mL), DCC (93 mg, 450 µmol) and 1-HOBT (61 mg, 450 µmol) were added at 25 ºC; after 2 h, extended amine 126 (930 mg, 450 µmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated *in vacuo* to give a crude oil, which was column chromatographed (SiO₂) eluting with EtOAc to afford (65 %) predendron 127, as a white solid: 1.1 g; ¹H NMR: δ 1.23 (s, 6H, CH₃), 1.44 (s, 189H, CH₃), 1.95 (br m, 84H, CH₂CH₂CO₂), 2.20 (br m, 48H, CH₂CH₂CONH), 3.24 (br m, 4H, HNCH₂), 6.10 (s, 6H, NH), 6.52 (s, 3H, NH), 6.55 (s, 2H, NH); ¹³C NMR: δ 23.8 (CH₃), 24.1 (CH₂CO), 26.2 (CH₂CH₂), 28.5 (CH₃), 29.8, 31.0, 31.3, 32.1, 33.9, 34.4, 34.9 (CH₂CH₂CO, CH₂CH₂CONH), 38.8 (HNCH₂), 55.5, 55.6, 57.3, 57.4 (4 HNC), 80.4, 80.5, 80.6 (3 CMe₃), 93.4 (O₂NC), 171.0, 171.8, 172.2, 172.4, 172.7, 172.8, 172.9 (7 CONH), 173.0, 173.1, 173.7 (3 CO₂); IR: 3350 (NH), 1735 (C=O), 1720 (C=O), 1550 (NO₂) cm⁻¹; MALDI-TOF MS: m/z = 3825.5 [M + Na⁺], calcd. m/z = 3824.9 [M + Na⁺].
**Synthesis of Amine 128.** Suspension of 127 (1 g, 263 µmol) and T-1 Raney-Ni (3 g) in absolute EtOH (50 mL) was hydrogenated at 60 psi at 50 ºC for 48 h. The solution was cautiously filtered (pyrophoric) through Celite, after which the solvent was concentrated *in vacuo* to afford (78 %) of amine 128, as a white solid: 770 mg; \(^1\)H NMR: \(\delta 1.24 (s, 6H, CH_3), 1.43 (s, 189H, CH_3), 1.91 (br s, 84H, CH_2CH_2CO_2), 2.20 (br s, 48H, CH_2CH_2CONH), 3.20 (br s, 2H, HNCH_2), 4.18 (br s, 2H, HNCH_2), 6.15 (s, 6H, NH), 6.52 (s, 3H, NH), 6.55 (s, 4H, NH, H2N); \(^1^3\)C NMR: \(\delta 24.1 (CH_3), 24.5 (CH_2CO), 26.4 (CH_2CH_2), 28.3 (CH_3), 29.7, 31.0, 31.5, 32.3, 33.9, 34.4, 34.9 (CH_2CH_2CO, CH_2CH_2CONH), 38.8 (NHC), 53.2 (H_2NCC), 55.6, 57.3, 57.4, (3 HNC), 80.4, 80.5, 80.6 (3 CMe_3), 171.3, 172.4, 173.5 (3 CONH), 173.9 (CO_2); IR: 3400-3000 (NH_2), 1730 (C=O), 1720 (C=O) cm\(^{-1}\); MALDI-TOF MS: \(m/z = 3794.6 [M + Na^+]\), calcd. \(m/z = 3794.9 [M + Na^+]\).

**Synthesis of Isocyanate Dendron 129.** To a stirred solution of amine 128 (500 mg, 132 µmol), Et_3N (26 µL, 264 µmol) in dry THF (25 mL), triphosgene (23 mg, 79 µmol) in THF (10 mL) was added at 0 ºC. The solution was stirred for 12 hours, and the solution was filtered, concentrated *in vacuo* to afford crude solid, which was columnchromatographed (SiO_2) eluting with EtOAc afforded (75 %) of isocyanate 129, as a solid: 380 mg; \(^1\)H NMR: \(\delta 1.25 (s, 6H, CH_3), 1.44 (s, 189H, CH_3), 1.95 (br s, 84H, CH_2CH_2CO_2), 2.20 (br s, 48H, CH_2CH_2CONH), 3.24 (br s, HNCH_2), 3.52 (br s, HNCH_2), 6.10 (s, NH), 6.52 (s, NH), 6.55 (s, NH); \(^1^3\)C NMR: \(\delta 23.8 (CH_3), 24.1 (CH_2CO), 26.2 (CH_2CH_2), 28.5 (CH_3), 29.8, 31.0, 31.3, 32.1, 33.9, 34.4, 34.9, 38.8 (CH_2CH_2CO, CH_2CH_2CONH), 55.6, 57.3, 57.4 (3 HNC), 62.3 (OCNC), 80.4, 80.5, 80.6 (3 CMe_3),
123.2 (OCN), 171.2, 172.4, 172.7 (3 CONH), 172.8 (CO₂); IR: 3300 (NH), 2210 (OCN),
1730 (C=O), 1720 (C=O) cm⁻¹; MALDI-TOF MS: m/z = 3822.87 [M + Na⁺], calcd. m/z =
3820.91 [M + Na⁺].

**Synthesis of Amide 132.** To a stirred solution of adamantane acid 130 (2 g, 11
mmol) in dry DMF (50 mL), DCC (2.3 g, 11 mmol) and 1-HOBT (1.5 g, 11 mol) were
added at 25 ºC; after 2 h, aminopentanol 131 (1.15 g, 11 mmol) was added. The mixture
was stirred for 5 h, after which the white precipitate was filtered. The filtrate was
concentrated *in vacuo* to give a crude oil, which was column chromatographed (SiO₂)
eluting with 20% EtOAc in hexane to afford (87 %) the amide 132, as a white solid: 2.5
g; mp 103-104 ºC; ¹H NMR: δ 1.37-1.51 (br m, 6H, CH₂CH₂CH₂), 1.72-1.85 (br m, 15H,
adamantane), 2.01 (s, 1H, OH), 3.25 (t, 2H, J = 6.9 Hz, HNCH₂), 3.65 (t, 2H, J = 6.3 Hz,
HOCH₂), 5.60 (s, 1H, NH); ¹³C NMR: δ 23.0 (CH₂), 28.1 (CH of adamantane), 29.4
(CH₂), 32.2 (CH₂CH₂NH), 36.5 (CH₂ of adamantane), 36.7 (CH₂CH₂OH), 39.1 (C⁴⁻ of
adamantane), 39.2 (CH₂ of adamantane), 40.5 (HNCH₂), 62.2 (HOCH₂), 178.2 (CONH);
IR: 3450-3000 (OH), 1720 (C=O) cm⁻¹; ESI-MS: m/z 288.0 [M + Na⁺], calcd. m/z
288.39 [M + Na⁺].

**Synthesis of Mesylate 133.** To a stirred solution of 132 (1 g, 3.7 mmol), Et₃N
(570 µL, 5.6 mmol) in dry THF (50 mL), mesyl chloride (431 mg, 3.7 mmol) in THF (20
mL) was added at 0 ºC. The solution was stirred for 3 h at 25 ºC. After filtration, the
solvent was removed *in vacuo* to give a residue, which was dissolved in CHCl₃ (100 mL)
and washed with water (100 mL, 2X) and then saturated brine. The organic phase was
dried (MgSO₄) and concentrated *in vacuo* to give a solid that was column chromatographed (SiO₂) eluting with 20% EtOAc in hexane to give (90 %) 133, as a white solid: 1.15 g; mp 108-109 ºC; ¹H NMR: δ 1.44-1.67 (br m, 6H, CH₂CH₂CH₂), 1.72-1.85 (br m, 15H, adamantane), 3.01 (s, 3H, O₂SCH₃), 3.25 (t, 2H, J = 6.6 Hz, NHCH₂), 4.24 (t, 2H, J = 6.3 Hz, OCH₂), 5.62 (s, 1H, NH); ¹³C NMR: δ 22.7, 28.1 (CH of adamantane), 28.7 (CH₂), 29.0 (CH₂), 36.5 (CH₂ of adamantane), 37.3 (O₂SCH₃), 38.8 (C₄ of adamantane), 39.3 (CH₂ of adamantane), 40.5 (HNCH₂), 69.9 (OCH₂), 178.0 (CONH); IR: 3300 (NH), 2110 (N₃), 1720 (C=O) cm⁻¹; ESI-MS: m/z 366.0 [M + Na⁺], calcd. m/z 366.48 [M + Na⁺].

**Synthesis of Azide 134.** A stirred solution of mesylate 133 (1 g, 2.9 mmol) and NaN₃ (560 mg, 8.7 mmol) in DMF (50 mL) was refluxed for 7 h. After filtration, solvent was concentrated *in vacuo* to give a residue, which was dissolved in CHCl₃ and then sequentially washed with water and saturated brine. The solution was dried (MgSO₄), filtered, and concentrated *in vacuo* to give a crude solid, which was column chromatographed (SiO₂) eluting with 20 % EtOAc in hexane to afford (93 %) azide 133, as a viscous oil: 785 mg; ¹H NMR: δ 1.36-1.65 (br m, 6H, CH₂CH₂CH₂), 1.72-1.85 (br m, 15H, adamantane), 3.22 (t, 2H, J = 6.9 Hz, N₃CH₂), 3.30 (t, 2H, J = 6.6 Hz, NHCH₂), 5.60 (s, 1H, NH); ¹³C NMR: δ 24.0 (CH₂), 28.1 (CH₂), 28.5 (CH of adamantane), 29.2, 36.5 (CH₂ of adamantane), 39.0 (C₄ of adamantane), 39.3 (CH₂ of adamantane), 40.6 (HNCH₂), 51.2 (N₃CH₂), 178.0 (CONH); ESI-MS: m/z 313.2 [M + Na⁺]; IR: 3300 (NH), 2110 (N₃), 1720 (C=O) cm⁻¹; ESI-MS: 313.0 [M + Na⁺], calcd. m/z 313.40 [M + Na⁺].
Synthesis of Amine 135. A suspension of azide 134 (500 mg, 1.7 mmol) and 10% Pd on activated carbon (200 mg) in EtOH (30 mL) was hydrogenated at 60 psi at 25 °C for 12 h. The solution was then cautiously filtered through Celite (pyrophoric) and then the solvent was concentrated in vacuo to afford (95 %) amine 135, as a white solid: 432 mg; mp 82-83 ºC; $^1$H NMR: δ 1.35-1.63 (br m, 6H, C\textsubscript{6}H\textsubscript{2}C\textsubscript{6}H\textsubscript{2}C\textsubscript{6}H\textsubscript{2}), 1.70-1.83 (br m, 15H, adamantane), 2.70 (t, 2H, $J$ = 6.6 Hz, NHC\textsubscript{2}H), 3.23 (t, 2H, $J$ = 6.6 Hz, NH\textsubscript{2}CH\textsubscript{2}); $^{13}$C NMR: δ 24.0 (CH\textsubscript{2}), 27.1 (CH\textsubscript{2}), 28.2 (CH of adamantane), 29.2 (CH\textsubscript{2}), 36.6 (CH\textsubscript{2} of adamantane), 39.4 (C\textsuperscript{4º} of adamantane), 39.9 (CH\textsubscript{2} of adamantane), 40.6 (HNCH\textsubscript{2}), 40.8 (H\textsubscript{2}NCH\textsubscript{2}), 179.0 (CONH); IR: 3400-3000 (NH\textsubscript{2}), 1720 (C=O) cm$^{-1}$; ESI-MS: $m/z$ 265.10 [M + H$^+$], calcd. $m/z$ 265.41 [M + H$^+$].

Synthesis of Adamantane Dendrimer 136. To a stirred solution of isocyanate 129 (200 mg, 52 µmol) in dry CH\textsubscript{2}Cl\textsubscript{2} amine 135 (14 mg, 52 µmol) was added at 25 ºC. The reaction mixture was stirred for 6 h, after which the solvent was concentrated in vacuo to quantitatively afford 136, as a viscous liquid: 210 mg; $^1$H NMR: δ 1.44 (s, 189H, CH\textsubscript{3}), 1.5-1.67 (br m, 15H, adamantane), 1.71 (s, 6H, CH\textsubscript{3}), 1.84 (br m, 36H, CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}), 1.95 (br m, 48H, CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}), 2.20 (br m, 36H, CH\textsubscript{2}CH\textsubscript{2}CONH, CH\textsubscript{2}CH\textsubscript{2}CO) 2.50 (br m, 12H, CH\textsubscript{2}CH\textsubscript{2}CONH), 3.24 (br m, 2H, HNCH\textsubscript{2}), 3.52 (br m, 2H, HNCH\textsubscript{2}), 6.10 (s, 6H, NH), 6.52 (s, 3H, NH), 6.55 (s, 4H, NH, H\textsubscript{2}N); $^{13}$C NMR: δ 23.8 (CH\textsubscript{3}), 24.1 (CH\textsubscript{2}CO), 26.0 (CH\textsubscript{2}CH\textsubscript{2}CO), 26.2 (CH of adamantane), 28.5 (CH\textsubscript{3}), 29.8, 31.0, 31.3, 32.1, 33.9, 34.4, 34.9, 38.8, 53.2, 55.6, 57.3, 57.4 (4 HNC), 80.4, 80.5, 80.6 (3 CMe\textsubscript{3}), 158.3 (HNCONH), 172.4, 172.9, 173.0, 173.4 (4 CONH), 174.2 (CO\textsubscript{2}).
178.4 (CONH, adamantane); IR: 3400 (NH), 1730 (C=O), 1720 (C=O), 1650 (C=O) cm\(^{-1}\); MALDI-TOF MS: \(m/z = 4085.0\) [M + Na\(^+\)], calcd. \(m/z = 4085.31\) [M + Na\(^+\)].

**Preparation of Dendron 136 · β-Cyclodextrin Complex.** To a solution of β-CD (10 mg, 8.8 \(\mu\)mol) in DMSO, was added the dendron 136 (35 mg, 8.8 \(\mu\)mol), then the mixture was ultrasonicated for 30 min, affording a clear solution of the 136 · β-CD complex. \(^1\)H NMR: \(\delta 1.22\) (s, 6H, CH\(_3\)), 1.38 (s, 189H, CH\(_3\)), 1.54-1.67 (br m, 15H, adamantane), 1.74 (br m, 36H, CH\(_2\)CH\(_2\)CO\(_2\)), 2.05 (br m, 48H, CH\(_2\)CH\(_2\)CO\(_2\)), 2.10 (br m, 36H, CH\(_2\)CH\(_2\)CONH, CH\(_2\)CH\(_2\)CO) 2.49 (br s, 12H, CH\(_2\)CH\(_2\)CONH), 3.01 (br m, 2H, HNCH\(_2\)), 3.63 (t, 2H, \(J = 5.1\) Hz, HNCH\(_2\)), 4.44, 4.82, 5.66, 5.72 (CH\(_2\), CH of cyclodextrin), 7.15 (s, 6H, NH), 7.17 (s, 3H, NH), 7.26 (t, 4H, \(J = 4.2\) Hz, NH, H\(_2\)N); \(^{13}\)C NMR: \(\delta 23.8\) (CH\(_3\)), 25.9 (CH\(_2\)CO), 27.8 (CH\(_3\)), 29.0 (CH of adamantane), 29.1 (CH\(_2\)CH\(_2\)CO), 29.7, 30.6, 31.5, 32.0, 33.7, 36.2, 38.3, 38.5, 55.6, 56.4, 56.5 (4 HNC), 60.0, 79.1, 79.2, 79.6 (3 CMe\(_3\)), 81.6, 102.0, 157.2 (HNCONH), 171.8, 172.2, 172.5, 176.9 (CONH, adamantane).

6.4. References


20. Grayson, S. M.; Fréchet, J. M. J. Convergent Dendrons and Dendrimers: from


(11), 4252-4261.

Epperson, J. D. Isocyanate-Based Dendritic Building Blocks: Combinatorial Tier

25. Hawker, C. J.; Fréchet, J. M. J. Control of Surface Functionality in the Synthesis of
Dendritic Macromolecules Using the Convergent-Growth Approach. *Macromolecules*
**1990**, 23 (21), 4726-4729.

26. Bo, Z.; Schäfer, A.; Franke, P.; Schlüter, A. D. A Facile Synthetic Route to a Third-

27. Bharathi, P.; Zhao, H.; Thayumanavan, S. Toward Globular Macromolecules with
Functionalized Interiors: Design and Synthesis of Dendrons with an Interesting

28. Sivanandan, K.; Vutukuri, D.; Thayumanavan, S. Functional Group Diversity in

29. Vutukuri, D. R.; Sivanandan, K.; Thayumanavan, S. Synthesis of dendrimers with
multifunctional periphery using an ABB' monomer. *Chem. Commun.* **2003**, (6), 796-
797.

30. Kozaki, M.; Okada, K. Snowflake-Like Dendrimers via Site-Selective Synthesis of


CHAPTER VII
CONCLUSIONS

The potential for dendrons and dendritic architectures as the scaffolds in mimicking\textsuperscript{1} biological macromolecules and expand into numerous research areas such as unimolecular micelles,\textsuperscript{2,3} molecular encapsulation,\textsuperscript{4,5} drug delivery,\textsuperscript{6,7} and catalysis\textsuperscript{8} is now widely recognized. The design and synthesis of various dendritic architectures are the key steps in investigating the plethora of applications.

A systematic series of dendrons and dendritic architectures based on $[1 \rightarrow 3] C$-,
\[ [1 \rightarrow (2 + 1 \text{ Me})] C, [1 \rightarrow (2 + 1)] C \] branched monomers have been synthesized and characterized. Using triethyleneglycol unit, as the starting material, three different extended dendrons have been synthesized utilizing DCC-mediated coupling reaction. The four directional dendrimers, possessing internal PEG units within the branching framework were prepared and characterized. These dendrimers demonstrated to solubilize lithium triflate salts in nonaqueous environments, such as chloroform.

Monomer possessing $[1 \rightarrow (2 + 1 \text{ Me})] C$-branching motif was prepared and dendrimers were constructed up to the 5\textsuperscript{th} generation using convergent and divergent approaches. The 2\textsuperscript{nd} - 5\textsuperscript{th} generation dendrimers capped with Behera’s amine were also prepared and fully characterized. Gel permeation chromatography (GPC) was employed to check the purity of the dendrimers. CdS quantum dots were prepared in the presence of
4th and 5th generation [1 → (2 + 1 Me)] C-branched dendrimers and their absorption emission spectra was measured.

Cyano-terminated sol-gel dendrons have been prepared and explored in capillary microextraction-gas chromatography (CME-GC). Thermogravimetric analysis revealed the high thermal stability of the sol-gel dendron coating. Aliphatic, aromatic alcohols and polycyclic aromatic hydrocarbons (PAHs) were extracted using sol-gel cyano-dendron coated capillaries. Gas chromatograms of extracted analytes were also reported.

We developed an efficient synthesis of [1 → 3] C-branched dendrons without the use of DCC and 1-HOBT. Treatment of [1 → 3] C-branched amines with acryloyl chloride, generated acrylamides, which upon treatment with nitromethane gave extended nitro amides. The Michael addition reaction of nitro amide with 2 equiv of acrylamide afforded the higher generation dendron.

Finally, conifer-shaped dendritic architectures were designed and synthesized using the selective combination of [1 → 3] C- and [1 → (2 + 1)] C-branched monomers. The adamantane-terminated elongated dendron was complexed with β-cyclodextrin in DMSO. The host-guest interactions of adamantane moiety and β-cyclodextrin were monitored by 1H NMR spectroscopy.

The application of these dendrons and dendrimers in the areas such as polyelectrolytes, separation science, unimolecular micelle, and drug delivery applications is envisioned.