POLYAMIDE AND POLYAMINE DENDRIMERS: SYNTHESIS, CHARACTERIZATION AND APPLICATION AS UNIMOLECULAR MICELLES AND HOMOGENEOUS CATALYSTS

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PREFACE

Dendrimers are highly branched, three-dimensional macromolecules with a regular tree-like symmetric branches. Dendrimers display unique physical properties which are significantly different from those of both linear macromolecules and small molecules. Dendrimer chemistry has been a topic of great interest to organic, polymer and material chemists for the last decade. The well-engineered and diverse structures of dendritic molecules provide chemists with both challenges and exciting opportunities. It is not surprising that many chemists interested in dendrimer chemistry find the preparation and application of such fascinating globular macromolecules both interesting and rewarding.

Dendrimer materials are relatively new class of macromolecules. Our knowledge of their structure and property relationship and their synthesis are is quite limited, and only few dendrimers are commercially available. It is relatively difficult to predict their properties such as their solubilities in different solvents. Therefore, successful synthesis and application of a new class of dendrimers often require both in-depth understanding of the structure-activity relationship and painstaking trial-and-error in the structural design and synthesis of the new dendrimers.

In this work, we synthesized three families of dendritic macromolecules, and we also put considerable effort in the development of applications for those dendrimers. We are interested in using those dendrimers as potential unimolecular micelles to absorb or concentrate lipophilic organic substrates in aqueous solution and using those amphiphilic

dendrimers as potential homogeneous catalysts to catalyze certain organic reactions in aqueous solution. The aqueous solution of the dendrimers can concentrate neutral organic substrates in an environment which would lead to a more favorable reaction condition. It is the involvement of this work which is responsible for the design and development of new families of dendrimers for such exciting applications.

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CHAPTER I

FUNCTIONALIZED DENDRIMERS: FROM A MOLECULAR TREE TOWARDS THE NEXT GENERATION OF TECHNOLOGIES

ABSTRACT

This chapter discusses the most important structural features and unique properties of dendrimer materials. The historical origins, important synthetic examples and potential applications of dendrimers are reviewed. The most commonly used strategies for the synthesis, purification and characterization of dendrimers are briefly discussed. The potential applications of these fascinating advanced materials for catalysis, molecular recognition and energy transfer are also briefly reviewed. Finally, the objects and key results of this study are summarized.

INTRODUCTION

Structural Features and Unique Properties. Dendrimers are highly branched, three-dimensional macromolecules with a regular tree-like array of symmetric branches. Unlike synthetic linear macromolecules with random coil conformations, dendrimers adopt spherical structures in solution.[1] The structural diversity and the unique molecular architecture of dendrimers have held a deep fascination for chemists in the field of organic chemistry, polymer chemistry, and materials science as well as analytical

chemistry and biochemistry, and this is perhaps one of the reasons why dendrimer chemistry has risen rapidly to a position of international prominence in the past ten years.[2]

Dendrimers possess a number of fascinating structural features, such as the globular shapes, the void interiors, the highly branched architecture with three dimensional symmetry and the large number of terminal functional groups on the periphery of the molecules. These molecular architectures allow the formation of highly dense molecular networks in a well engineered fashion in solution without gelation.[3] Dendrimers display unique physical properties which are significantly different from those of materials made from both linear macromolecules and small molecules. The globular macromolecules with a dense arrangement of atoms in an extremely limited volume cause low intrinsic viscosity,[4] contrary to the well-known behavior of linear macromolecules. The presence of a large number of end groups offers possibilities of modulating the peripheral functionalities and allows the end groups to be efficiently utilized for their potential applications. The internal void can be used to encapsulate guest molecules, and a selective binding can be achieved by controlling the close packing degree of the dendritic shell.[5]

Figure 1 shows the three-dimensional, computer-generated ball-stick models of surface modified poly(propylene imine) dendrimers at generations 2 and 5 (Chapter II). Molecular models show that the dendrimer at generation 5 has extremely dense and compact packing of atoms and functional groups on the surface, while the dendrimer at generation 2 still has a quite open structure.

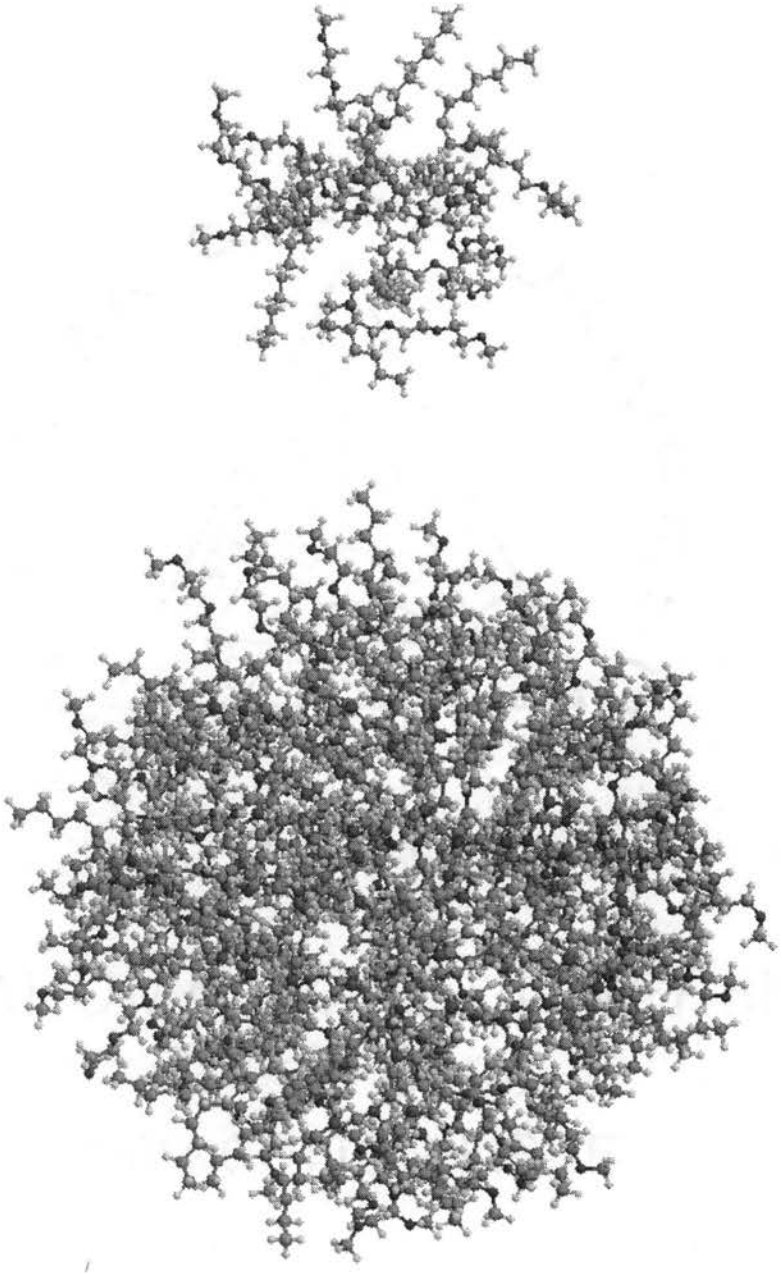
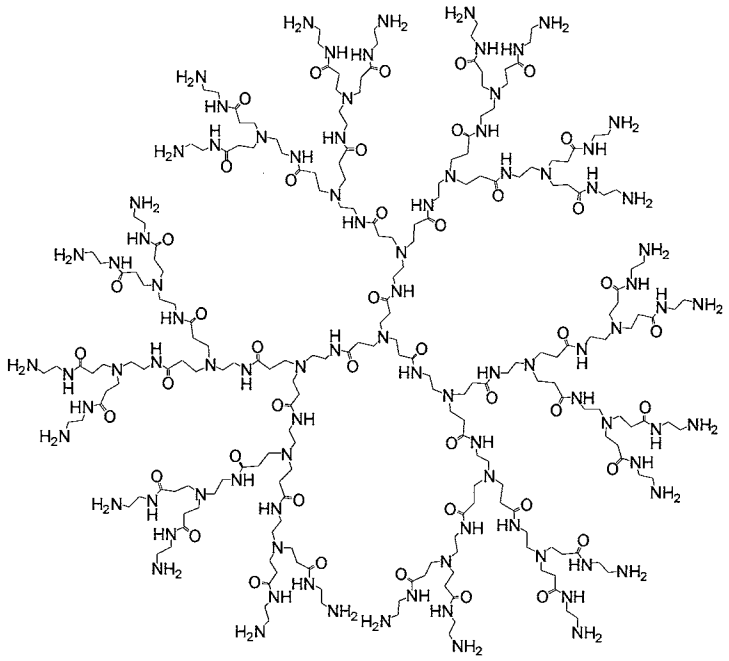


Figure 1. 3D representations (ball-stick model) of poly(propylene imine) dendrimers at generation 2 (top) and generation 5 (bottom).

Historical Origins. Since the initial report on this class of molecules by Vögtle in 1978,[6] many different structural classes of dendritic macromolecules have been reported. The synthesis of poly(propylene imine) dendrimers was reported by Mülhaupt and de Brabander.[7] Tomalia's group devised a stepwise synthetic route to prepare highly branched polyamidoamine dendrimers, such as **1**, using double Michael addition of methyl acrylate to a primary amine.[8]



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Newkome and co-workers reported an approach for the synthesis of hydrophilic carboxylic acid terminated dendrimers with hybrid polyether and polyamide generations in the interiors.[9] Hawker and Frèchet synthesized a series of ester, cyano, amide or ether terminated polybenzyl ether dendrimers by Williamson ether synthesis.[10] Miller, Neenan and co-workers prepared all-carbon aromatic dendrimers using aryl Grignard reagents and the Suzuki coupling reaction for the construction of the branching C-C linkages.[11] Moore and co-workers synthesized aryl-acetylene dendrimers by a repetitive strategy involving

palladium-catalyzed cross-coupling of a terminal acetylene to an aryl diiodide.[12] A wide range of new classes of dendrimers has been developed in the past few years, and many good review articles have appeared in the literature.[1-2,13-16]

SYNTHESIS OF DENDRIMERS

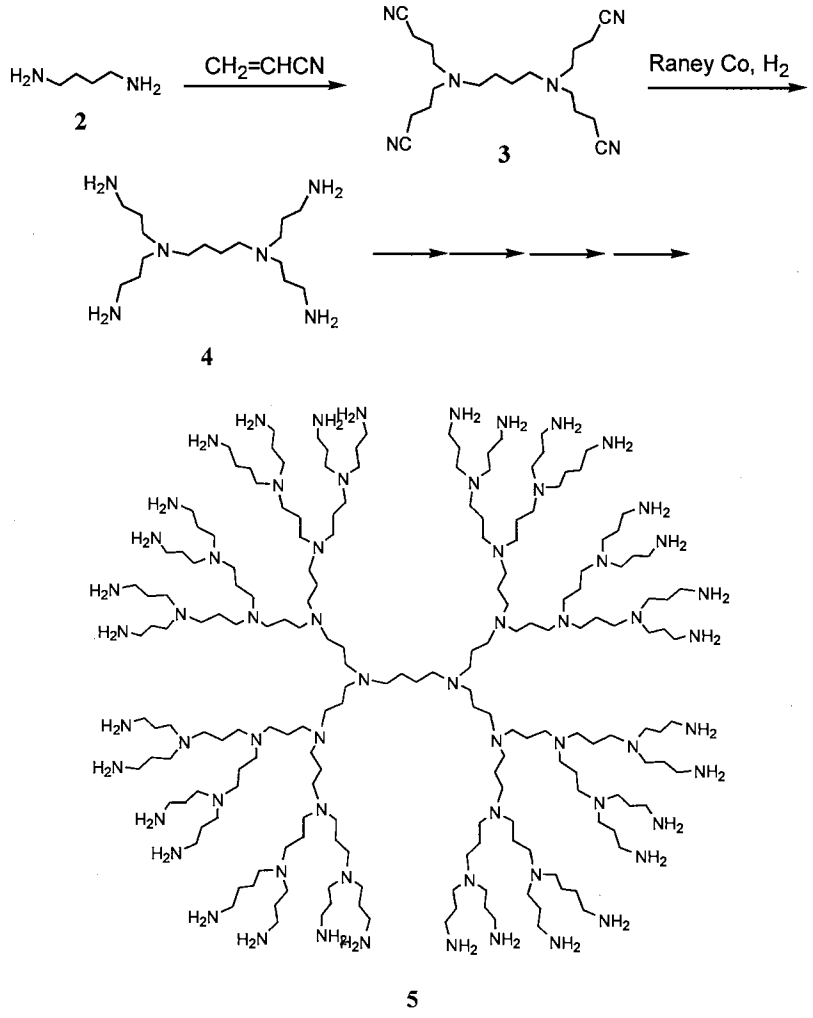
Dendrimers are constructed in repeated synthetic steps. Each repetition cycle adds one more layer to the dendrimer framework. Therefore, the number of generations is equal to the number of repetition cycles performed. The synthetic reactions used for the synthesis of dendrimers must be highly reliable and clean (like the well established Williamson ether synthesis, Michael addition and peptide-related amidation[17]) if a perfect and relatively large dendrimer is desired.

The synthesis of dendritic macromolecules is distinguished from the synthesis of normal polymers in two critical ways. First, dendrimers are constructed from AB_2 or AB_3 monomers to generate the hyperbranched structures, while the normal linear polymers are constructed from standard AB monomers. Secondly, dendrimers are constructed in repeated synthetic steps in the fashion of multi-step synthesis. Two main synthetic strategies for synthesizing dendrimers have emerged over the past decade: the convergent and divergent approaches. Both methods have their strengths and their weaknesses.

Divergent Synthesis. In the divergent strategy, dendrimers are synthesized from the central cores outwards to the peripheries. In each repeat step the reactive groups on the periphery react with monomer units to add a new generation to the surface of the

dendrimer. Examples of divergent synthesis come from Meijer (Scheme 1),[18] Tomalia[19], Diederich[20] and Newkome.[21]

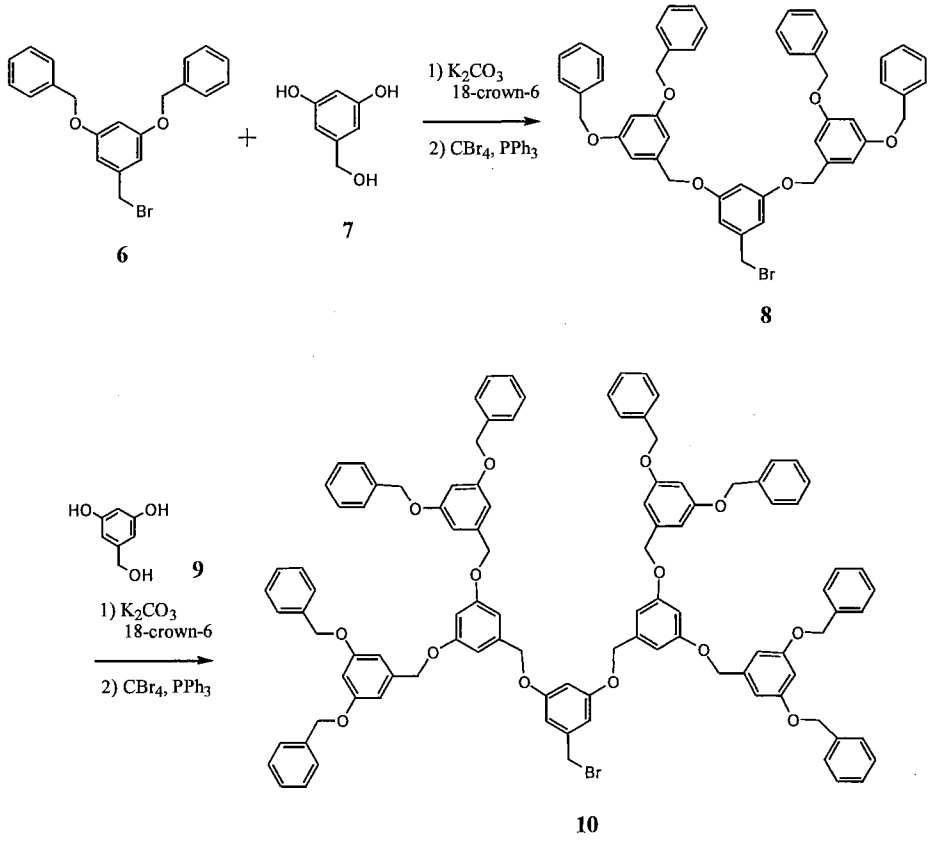
Scheme 1. Meijer's divergent synthesis of poly(propylene imine) dendrimers.



The divergent strategy is often used for the synthesis of dendrimers with higher generations since it is superior in its ability to reach high molecular weight. Dendrimers prepared by divergent synthesis are drawn as monomolecular species, but it should be understood that they contain numerous defects.[22]

Convergent Synthesis. In contrast to divergent strategy, the convergent approach synthesizes dendrimers from the periphery towards the central core, the initial building blocks ultimately reside on the periphery of dendrimers, while the subsequent constructions take place from a *focal point*. Hawker and Fréchet reported the first convergent strategy for the synthesis of polybenzyl ether dendrimers based on the following synthetic steps: (1) the selective alkylation of phenolic hydroxyl groups with a benzyl bromide group of a dendritic synthon (dendron) **6**; (2) conversion of a benzylic alcohol group of the higher generation dendron to a benzylic bromide. This sequence was repeated to synthesize a dendron up to the sixth generation (Scheme 2).[23]

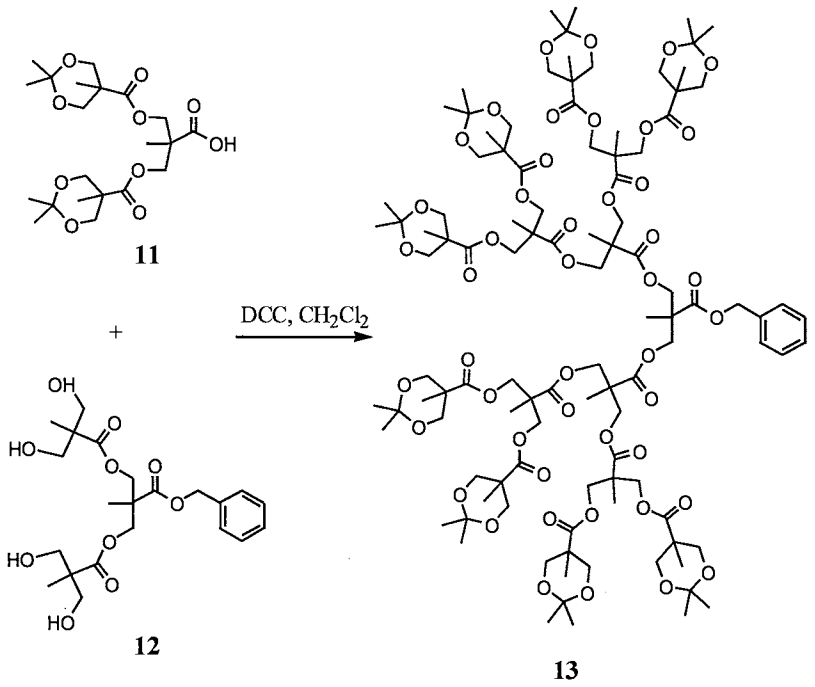
Scheme 2. Hawker and Fréchet's convergent synthetic strategy.



Other examples of the convergent approach to dendrimer synthesis can be found in the work of Miller,[24] Stoddart[25] and Wolf.[26] Dendrimers prepared by convergent synthesis are generally more homogeneous and free of defects, since by-products and starting dendrons are usually much smaller than the perfect dendritic products and are removed at the completion of each synthetic step. However, the convergent strategy is often limited to the synthesis of dendrimers with low generations. The problem is that the reactive focal point becomes increasingly congested when the number of generation increases, and further reaction at the focal point becomes more and more difficult.[27]

Double Exponential Growth. The recent fundamental breakthrough in the synthesis of dendrimers is the concept and implementation of *double exponential* growth, also called *double-stage* convergent synthesis.[28-29] This approach can be envisaged to accelerate the synthesis of higher generation dendrons by using AB_4 or AB_8 monomers instead of AB_2 monomers. Hult and co-workers reported a double-stage convergent approach for the synthesis of functionalized dendritic aliphatic polyesters (Scheme 3).[29b] The strategy represents a simplified and fast method for the synthesis of dendrons as compared with the conventional convergent approach.

Scheme 3. Hult's convergent strategy for the synthesis of a dendritic polyester.



PURIFICATION AND CHARACTERIZATION OF DENDRIMERS

Dendrimers are constructed in repeated synthetic steps, and by-products and defects are often removed at the completion of each synthetic step. However, the structures of the desired dendritic products are extremely close to those of the defects and starting dendritic materials in the reaction mixtures. Liquid chromatography has been extensively used for the purification of dendrimers synthesized by convergent methods, despite the extreme difficulty in separating the desired dendritic products from the mixtures. The conventional crystallization only can be used for low generation solid dendritic molecules.[30] For high molecular weight dendritic molecules, this technique is useless due to the lack of any long range order in the polymeric structures. Dendrimers can also be

purified from reaction mixtures by preparative HPLC and gel permeation chromatography.[31]

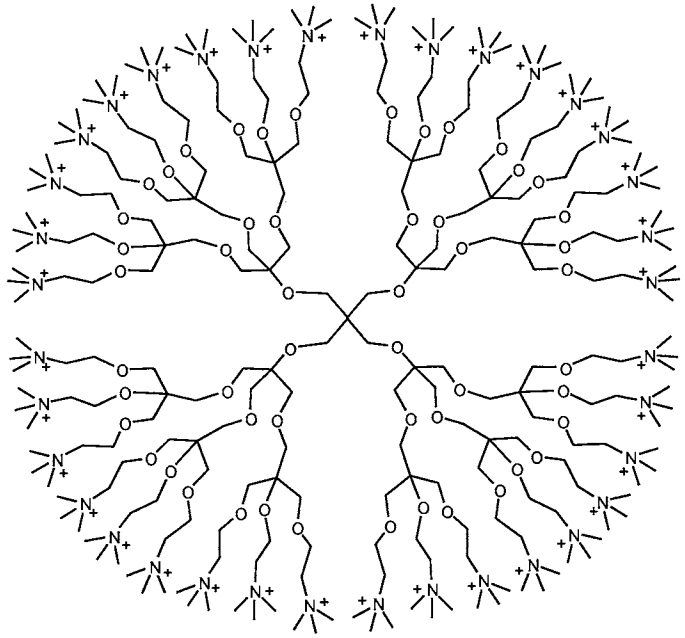
Dendrimers are highly branched macromolecules with well-defined structures which are relatively easy to characterize because they possess a single molecular weight. The precise structures and distinct molecular weights allow them to be characterized in the same way as small molecules. The standard instrumental analyses such as ^{1}H and ^{13}C NMR, FT-IR, UV and FAB-MS are widely used for their structural characterization. The characterization of dendritic molecules using standard NMR can detect some impurities and defects but lacks sensitivity. The determination of the crystal structures of the dendrimers has proved impossible since their solid state structures lack long range order. Elemental analysis is also seldom useful since the compositions of dendrons and dendrimers within the same family vary little. The structural determination of dendrimers with high molecular weights requires the development of new analytical methodology. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) and electrospray ionization mass spectrometry (ESI-MS) are among the most useful analytical techniques for the structure determination of dendritic materials, and many results have been obtained from MALDI-TOF and ESI-MS analysis.[32-34]

APPLICATIONS

The synthetic versatility and the structural diversity of dendrimers, combined with their wide range of sizes and functionalities, make them versatile materials for a wide range of applications, such as catalysis, molecular recognition, drug delivery and energy

transfer. Many potential applications for dendrimers have been stated in the increasing number of review articles.[1-2, 13-15]

Dendritic Catalysts. A number of examples of dendritic catalysts were reported.[35-38] The promises of using dendrimers as catalysts arise from the possibility of creating large dendrimers with densely arranged active sites in a single molecule. Dendritic catalysts may be considered as intermediate between heterogeneous and homogeneous catalysts, and the catalytic activity and the selectivity become modulated or enhanced by the unique dendritic microenvironments.



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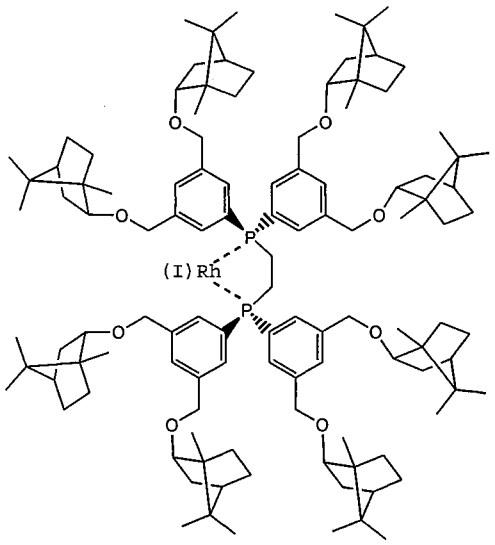
Ford and Lee reported a polycationic dendritic catalyst **14** for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate and bimolecular hydrolysis of *p*-nitrophenyl diphenyl phosphate in aqueous solution.[37] The quaternary ammonium ion terminated polyether dendrimer has a high concentration of catalytic sites on the surface and hydrophobic

polyether branches in the interior. It was concluded that the rate enhancement could result from a favorable binding of the substrate to the dendrimer in aqueous media.

Another example involved the use of dendritic transition-metal complex **15** as a catalyst for the stereoselective hydrogenation of acetamidocinnamic acid.[38] Low enantioselectivity was obtained for the hydrogenation catalyzed by the chiral dendritic catalyst, which suggests that the dendritic substituents are highly flexible and the dendritic structures lack long range order.



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Molecular Encapsulation, Recognition and Unimolecular Micelle. There has been considerable interest in using dendritic architectures for complexation with guest molecules. Meijer and co-workers reported the preparation of a derivative of the fifth generation poly(propylene imine) dendrimer in which the 64 terminal amine groups were modified with *N-tert*-butoxycarbonyl-*L*-phenylalanine, and examined the function of the interior as a "dendritic box" capable of retaining substrates trapped during synthesis.[39] UV-vis spectroscopy indicated that rose bengal was encapsulated in the dendritic box.

The diffusion of the trapped rose bengal molecules out of the box was very slow since the close packed end groups on the periphery prevented them from diffusing outwards. The dendritic material has potential application as a slow-release system for drug delivery (Figure 2).

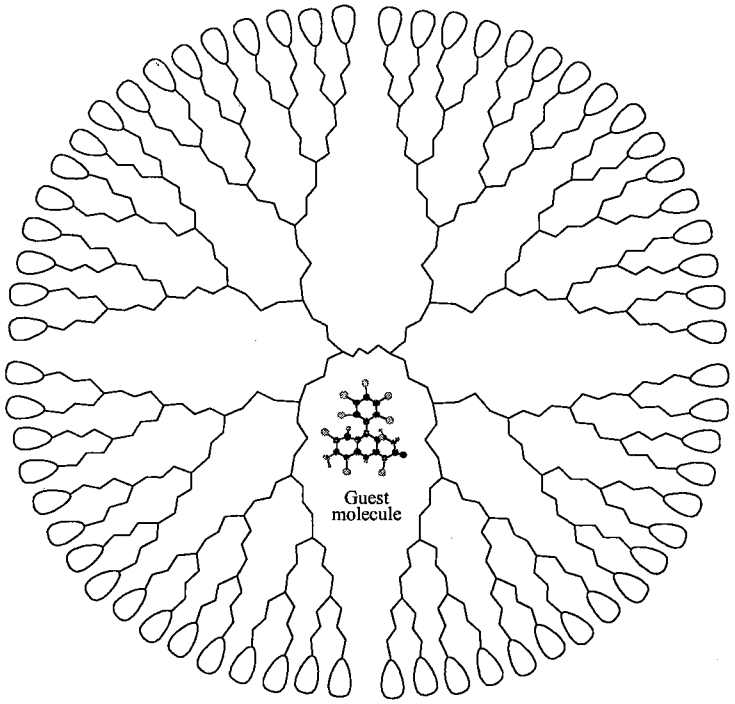

Figure 2. Molecular encapsulation inside a dendrimer.

Newkome and co-workers reported water-soluble hydrophobic dendrimers with a completely hydrophobic alkane interior.[40] The dendrimers containing hydrophobic core and branches and hydrophilic Me_3N^+- end groups acted as unimolecular micelles capable of including lipophilic molecules. The structure of the covalently bonded unimolecular micelle was independent of temperature, concentration and ionic strength of the solution.

In contrast to the "normal" unimolecular micelle, an "inverted" dendritic unimolecular micelle with hydrophilic core and hydrophobic fluorinated surface was recently used to extract hydrophilic methyl orange from water.[41]

Energy Transfer by Dendritic Branches. Energy transfer plays an important role in photosynthesis in plants, in which carotenoids act as "antennae" and absorb solar radiation. Dendrimeric architectures have attracted increasing attention as artificial antennae for energy transduction, as they are similar to natural light harvesting systems, and the dendritic structures are suitable for energy transfer from the branched chain ends to the core. Moore and his co-workers reported a rigid polyaromatic ethyne-linked dendron with a fluorescent perylene chromophore at the focal point.[42] When the dendrons were irradiated at the absorption band of the closely packed end groups, the fluorescent chromophore at the focal point emitted at a longer wavelength with a quantum yield approaching 98%, which indicates that singlet energy transfer occurs in the dendron. The light-harvesting ability increased with increasing number of generations, while the efficiency of the emission process decreased.

Aida and Jiang reported dendritic porphyrins with five-layered dendron subunits at the *meso*-position of a porphyrin for singlet energy transduction.[43] Upon excitation of the dendron subunits in CH_2Cl_2 at 20 °C, the dendritic porphyrin showed an intramolecular singlet energy transfer from the end groups of the dendron to the porphyrin core with energy transfer quantum yields of up to 80.3%.

OBJECTIVES AND KEY RESULTS OF THIS STUDY

Design of the Target Dendrimers. The primary goal of this study is to design, synthesize and characterize functionalized amphiphilic dendrimers for applications as unimolecular micelles and homogeneous catalysts in aqueous solution. Since the dendritic properties become obvious only when the number of generations increases beyond a certain point, it is very difficult to predict the properties, such as the solubilities in different media and the capabilities of hosting lipophilic substrates in aqueous solution, until the certain point is reached. Therefore, successful synthesis and application of a new class of dendrimers often require both in-depth understanding of the structure-activity relationship and painstaking trial-and-error in the structural design and synthesis of the new dendrimers.

As unimolecular micelles in aqueous media, the target dendrimers should have both hydrophilic terminal groups and hydrophobic moieties. The hydrophilic terminal groups should make the materials soluble in aqueous media, and the hydrophobic moieties can be used to hold lipophilic substrates in aqueous solution through lipophilic-lipophilic interaction. As homogeneous catalysts in aqueous solution, the target dendrimers should also have catalytic sites for potential reactions. In this study, quaternary ammonium sites were chosen as the active sites in the structures of the target dendritic catalysts.

Synthesis of the Target Dendrimers. Three families of the target dendrimers were synthesized using different synthetic strategies. The three classes were: 1) amphiphilic dendrimers with alternating arms; 2) amphiphilic dendrimers with alternating generations; 3) ester and amide terminated dendrimers. A representative example of

amphiphilic dendrimers with alternating arms on the periphery is shown in Figure 3, a representative example of amphiphilic dendrimers with alternating generations is shown in Figure 4 and an example of ester terminated dendrimers is shown in Figure 5.

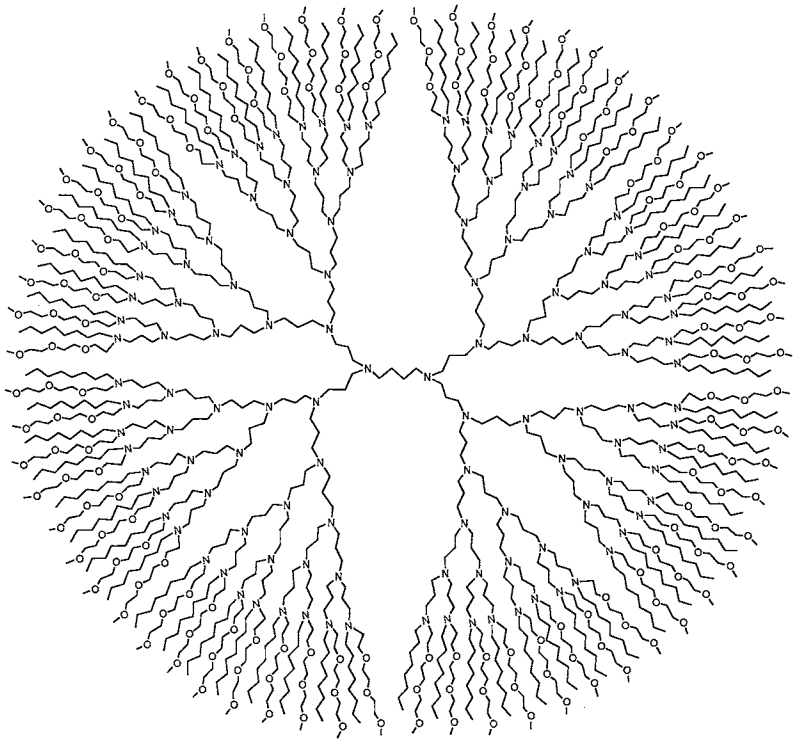

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Figure 3. Generation 5 amphiphilic dendrimer with both hydrophilic and hydrophobic arms. Molecular formula $C_{1336}H_{2800}N_{126}O_{192}$ and molecular weight 23689.32

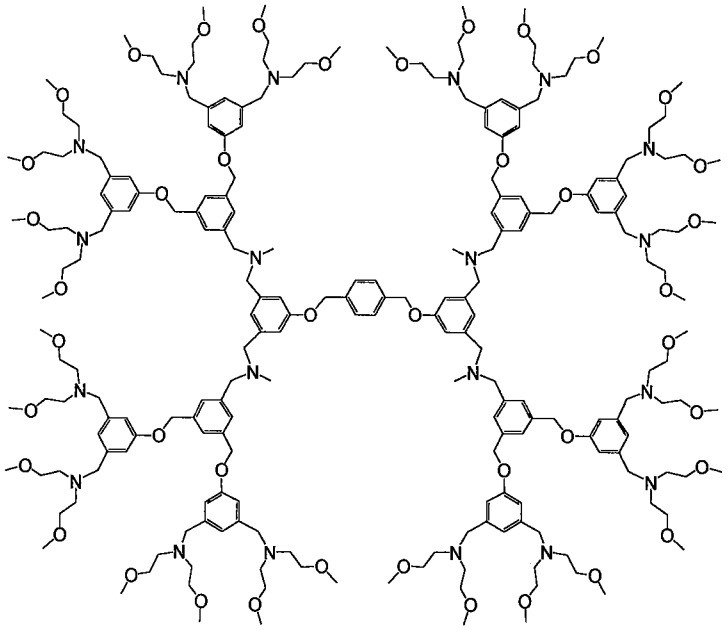

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Figure 4. Dendrimer with alternating ether and amine generations. Molecular formula $C_{224}H_{350}N_{20}O_{42}$ and molecular weight 3992.59

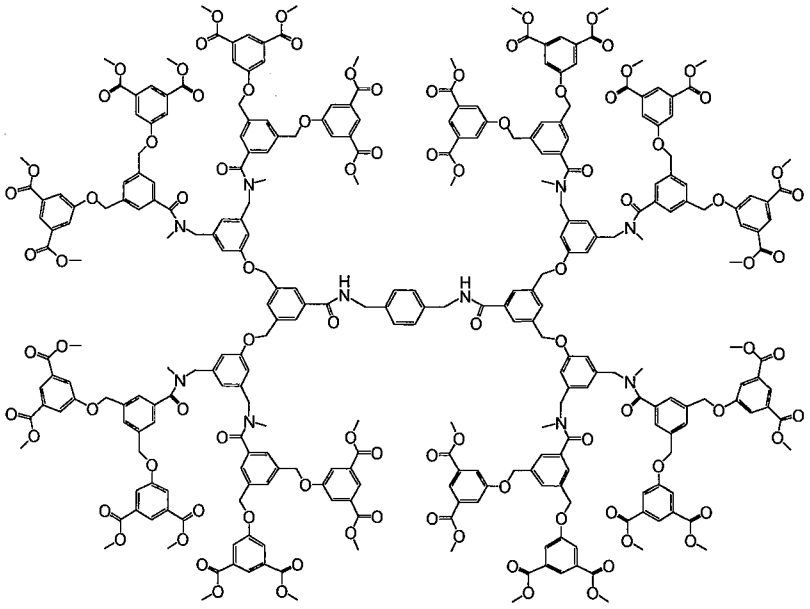

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Figure 5. Ester-terminated dendrimer with alternating ether and amide generations. Molecular formula $C_{298}H_{276}N_{10}O_{94}$ and molecular weight 5497.71

Characterization of the Target Dendrimers. The structures of the target dendrimers are characterized by FT-IR, ^{1}H and ^{13}C NMR, FAB-MS, MALDI-TOF and ESI-MS analysis. The conformations of the target dendrimers were determined by both ^{1}H NMR spectra and ^{1}H and ^{13}C NMR relaxation time analysis. The hydrodynamic sizes of the target dendrimers were determined by dynamic light scattering (DLS) measurement. Computer modeling for the molecular simulations was used to get some insight into the microenvironments of the target dendrimers.

Application of the Target Dendrimers. The dendritic microenvironments and the unimolecular micellar capabilities of the target dendrimers are examined by UV spectroscopy using Reichardt's dye and pyrene as environment polarity indicators. The catalytic activities of the target dendritic catalysts are determined by kinetic studies of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate in aqueous solution.

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CHAPTER II

SYNTHESIS AND CHARACTERIZATION OF AMPHIPHILIC DENDRIMERS AND THEIR APPLICATION AS UNIMOLECULAR MICELLES AND HOMOGENEOUS CATALYSTS

ABSTRACT

Amphiphilic dendrimers of three different generations with alternating hydrophilic and hydrophobic chain ends at the periphery and fully quaternized ammonium sites in the interior were synthesized based on the surface modification of DAB-*dendr*-$(NH_2)_n$ (n = 8, 32 and 64) dendrimers using multi-step sequential amidations and $LiAlH_4$ reductions. The dendrimers with 'hybrid' arms on the periphery and quaternary ammonium chloride sites in the interior are soluble in both common organic solvents and water. The amphiphilic dendrimers can change their conformations with respect to the change in solvent polarity as demonstrated by ^{13}C spin-lattice relaxation time (T_1) measurements. The amphiphilic dendrimers can solubilize lipophilic substrates, such as pyrene and Reichardt's dye, in aqueous solution. The limiting solubilization of pyrene in aqueous solution of quaternary ammonium chloride dendrimer **5b** (9.16×10^{-4} M) is 1.04×10^{-3} M, corresponding to one pyrene per dendrimer molecule. The rates of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid in aqueous solution catalyzed by the cationic dendrimers are 200-500 times faster than the rate of the control experiment.

INTRODUCTION

Conventional micelles are formed dynamically only when the amounts of surfactants exceed the critical micellar concentration (CMC) in solution, below the CMC there are no micellar structures.[1] The micellar structures are also dependent on the ionic strength and temperature of the solution. In contrast to conventional micelles, dendritic unimolecular micelles can retain their colloidal structure regardless of concentration, ionic strength or temperature of the solution, since the micellar structures of the dendrimers are constructed by covalent bonds which form a regular array of symmetric branches.[2] Dendritic unimolecular micelles have been reported as catalysts, and they have advantages over conventional micellar catalysts.[3] For example, covalently bonded dendritic unimolecular micelles can retain their catalytic activities even at very low concentrations and high ionic strength. These unique properties of dendritic unimolecular micelles may enable applications in the areas of molecular encapsulation,[4] homogeneous catalysis,[3] drug delivery and nanoscopic transport.[5]

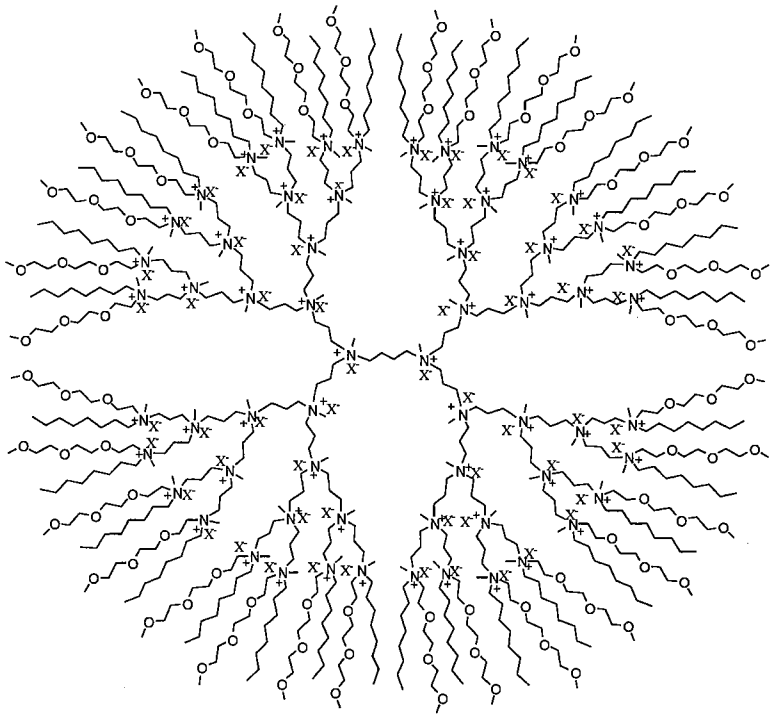
The use of dendrimers as unimolecular micelles was proposed and implemented by Newkome.[6] Since then, dendritic macromolecules having unimolecular micellar structures have been synthesized by several research groups.[7-9] The capability of hosting lipophilic guest molecules has been demonstrated by dissolving pyrene in dendrimer solutions.[10] Hawker and Fréchet demonstrated that the polar CO_2H end groups control solubility of the benzyl-ether dendrimers, and the less polar cores and branching units can solubilize hydrophobic molecules.[11] The synthesis of inverted dendritic micelles having hydrophobic end groups by modifying the hydrophilic end groups of poly(propylene-

imine) dendrimers DAB-*dendr*-$(NH_2)_{64}$ was reported by Meijer and co-workers.[12] The unimolecular micellar dendrimers with half hydrophobic and half hydrophilic shells were reported by Hawker and Fréchet and used to solvate water-insoluble pyrene into aqueous solution,[13] and the dendritic solubilization agents were recyclable. Gitsov and Fréchet reported a stimuli responsive hybrid star macromolecular amphiphilic system which changed conformations as the solvent polarity was varied.[14]

In this study, we report a synthetic approach to amphiphilic dendrimers containing both hydrophilic and hydrophobic chain ends on the periphery and fully quaternized ammonium sites on both the internal branches and the dendritic shells. The periphery of the dendrimers is functionalized with both $CH_3(OCH_2CH_2)_2$ (PEO) and octyl arms. The dendrimers with the 'hybrid' arms on the periphery and quaternary ammonium chloride sites in the interior are soluble in both common organic solvents and water. The dendrimers can be expected to change their conformations between normal and inverted micellar structures in response to changes in solvent polarity, and the conversion from one conformation to the other can be achieved with only minimal rearrangement of the arms at the periphery due to the adjacent, alternating and hybrid nature of the arms. The water-soluble dendrimers having hydrophobic moieties can solubilize water-insoluble lipophilic substrates, such as pyrene, in aqueous solution, and the amphiphilic dendrimers with quaternary ammonium ion sites in the interior show catalytic activity for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid in aqueous media.

The target amphiphilic dendrimers were synthesized by modifying commercially available poly(propylene imine) dendrimers through six individual steps. The terminal primary amine NH_2 groups of the starting material DAB-*dendr*-$(NH_2)_n$ (n = 8, 32 and 64)

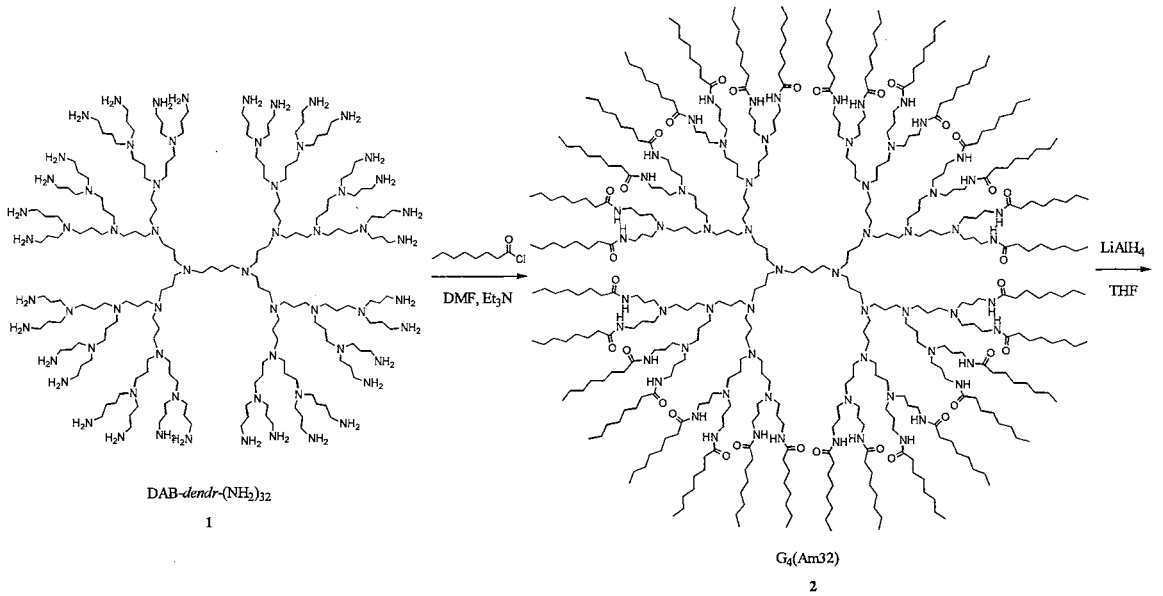
allow the formation of two different arms at each NH_2 group. We took this advantage to introduce both hydrophobic octyl chains and hydrophilic triethyleneoxy methyl ether (TEO) chains to each NH_2 group by sequential amidations and reductions. The polyamine dendrimers were converted to completely methylated quaternary ammonium ion derivatives. One of those polyammonium ion dendrimers is shown in following structure. To the best of our knowledge, this is the first study on the design and synthesis of such 'hybrid' arm dendrimers.

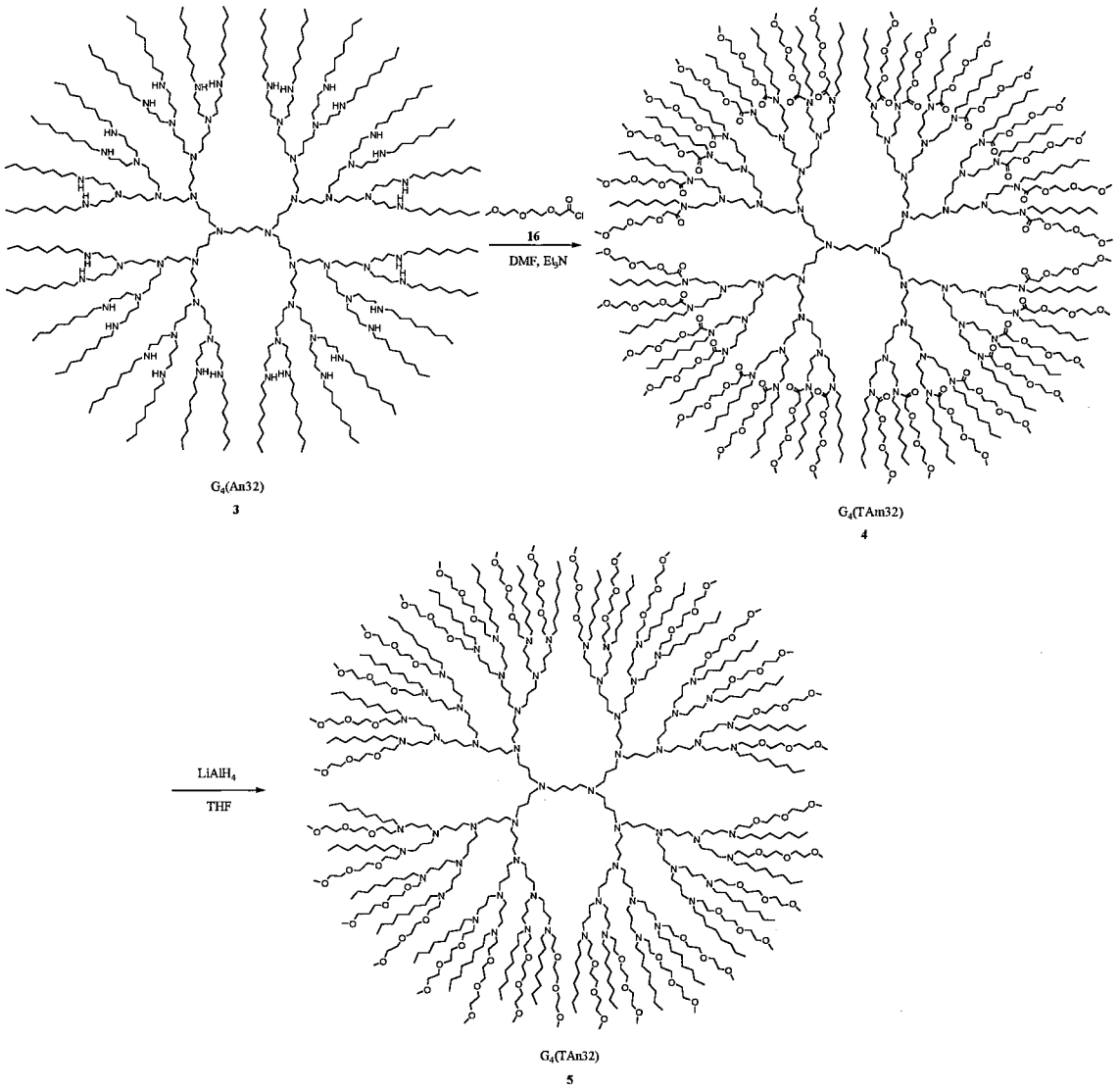


5a X=I
5b X=Cl

Synthesis of Amphiphilic Polyamine Dendrimers. The synthesis of the amphiphilic polyamine dendrimer was achieved through four individual steps from poly(propylene imine) dendrimers DAB-*dendr*-$(NH_2)_{32}$ **1** as shown in Scheme 1. The hydrophobic octyl arms were introduced by an amidation of the surface NH_2 groups with octanoyl chloride to give polyamide terminated dendrimer **2**. The octyl-modified dendrimer **2** is soluble in most common organic solvents, which allows the desired product to be easily isolated and purified by extraction and chromatography. Dendrimer **2** was reduced to **3** by $LiAlH_4$, and the hydrophilic TEO arms were introduced by another amidation of the resulting secondary amines **4** with acid chloride $CH_3O(CH_2CH_2O)_2CH_2COCl$ **16**, followed by another $LiAlH_4$ reduction to afford polyamine dendrimer **5**.

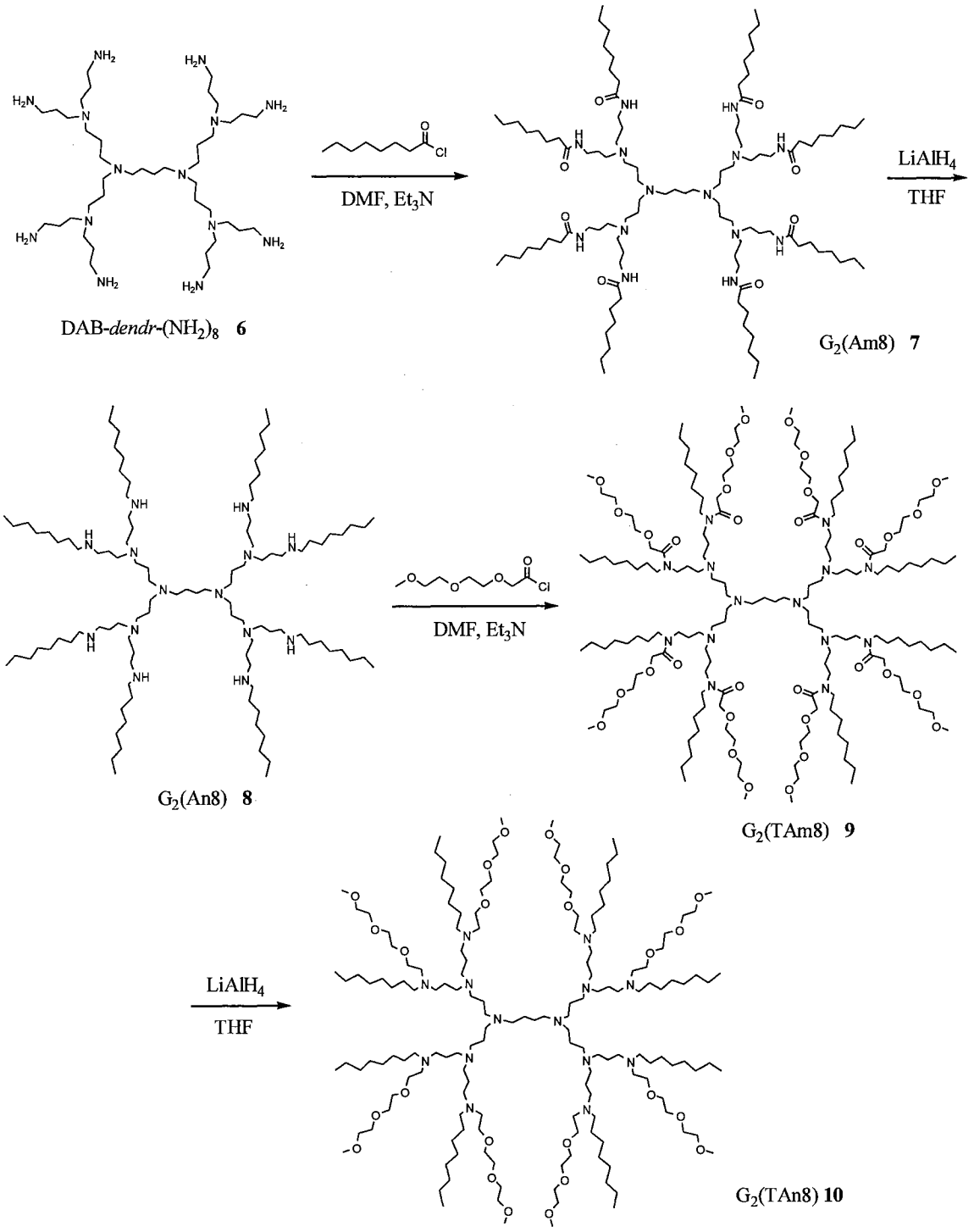
Scheme 1. Synthesis of generation 4 polyamine dendrimer **5**





Generation 2 dendrimer G_2(TAn8) (**10**) with eight terminal amines and generation 5 dendrimer G_5(TAn64) (**15**) with sixty-four terminal amines were also synthesized from DAB-*dendr*-$(NH_2)_8$ (**6**) and DAB-*dendr*-$(NH_2)_{64}$ (**11**), respectively, using the same procedure as described for the synthesis of dendrimer **5** (Scheme 2 and Scheme 3).

Scheme 2. Synthesis of generation 2 polyamine dendrimer **10**



DAB-*dendr*-$(NH_2)_8$ **6**

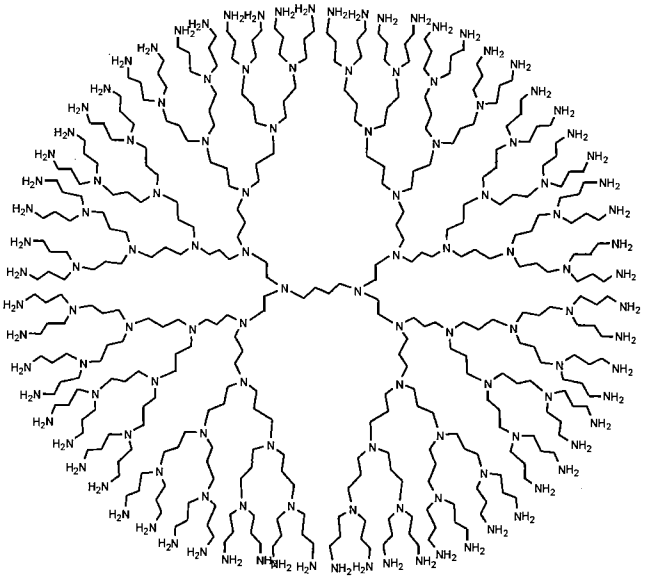
G_2(Am8) **7**

G_2(An8) **8**

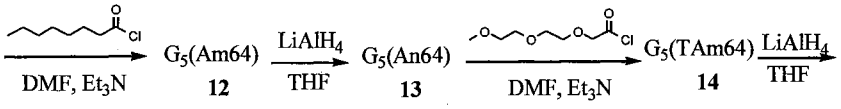
G_2(TAm8) **9**

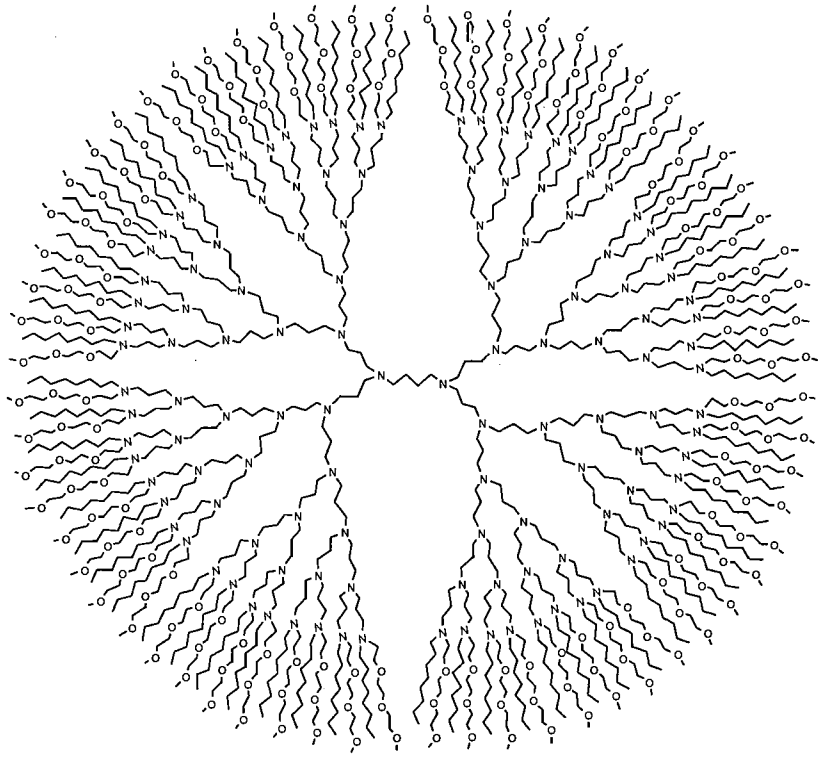
G_2(TAn8) **10**

Scheme 3. Synthesis of generation 5 polyamine dendrimer **15**



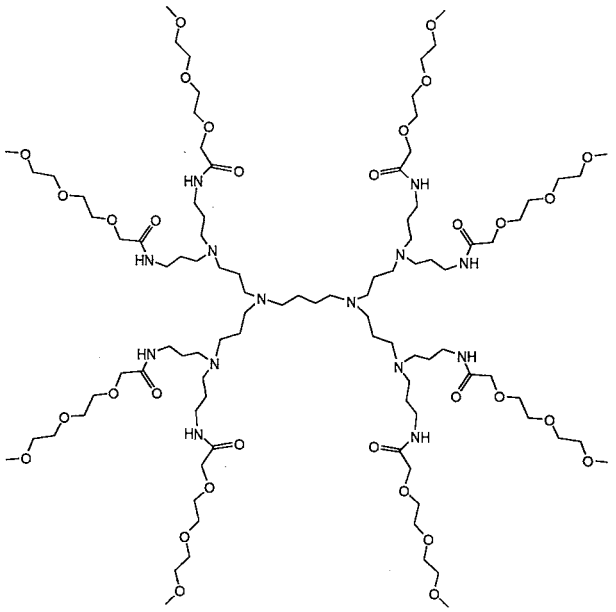
DAB-*dendr*-$(NH_2)_{64}$ **11**





G_5(TAn64) **15**

We also synthesized TEO-modified DAB-*dendr*-$(NH_2)_8$ dendrimer **16** in the framework of our studies on the amphiphilic dendrimers. The product was soluble only in water and alcohols due to the highly hydrophilic TEO-amide end groups on the periphery. The purification and further reaction of the hydrophilic dendrimer proved to be extremely difficult due to the poor solubility in common organic solvents such as chloroform and THF. The lack of any significant hydrophobic moiety in the dendrimer structure precluded the highly hydrophilic dendrimer from being used as a potential unimolecular micelle and catalyst in this study.



16

On the other hand, the octyl modified-DAB-*dendr*-$(NH_2)_n$ (n = 8, 32 and 64) dendrimers G_2(Am32) (**2**), G_4(Am8) (**7**) and G_5(Am64) (**12**) were insoluble in aqueous solution even when the internal polyamine sites are protonated at pH 1.0. It suggests that the solubilities of the dendrimers are primarily determined by the nature of the terminal groups. The poor solubilities of the octyl modified dendrimers in water excluded the

highly hydrophobic dendrimers from being used as potential unimolecular micelles and homogeneous catalysts in aqueous media.

Therefore, we used both the octyl and TEO end groups to modify the peripheries of DAB-*dendr*-$(NH_2)_n$ (n = 8, 32 and 64) dendrimers to synthesize a new class of amphiphilic dendrimers with desired solubilities in both organic solvents and water. The primary amine NH_2 end group allowed two different arms to be introduced in a sequential way, and that was the main strategy of the synthesis in current study.

It needs to be mentioned that if both the triethyleneoxy methyl ether (TEO) arms and octyl arms are to be attached to the periphery of the dendrimers, the octyl arms must be introduced *before* the TEO arms, since the excellent solubilities of the octyl-modified dendrimers in organic solvents can greatly facilitate the subsequent $LiAlH_4$ reduction, amidation and purification.

Preparation of Water-soluble Amphiphilic Polyammonium Dendrimers. The *tertiary amine dendrimers* G_4(**TAn**32) (**5**), G_2(**TAn**8) (**10**) and G_5(**TAn**64) (**15**) are not sufficiently soluble in water due to the densely arranged aliphatic octyl chain ends on the peripheries. Therefore, the polyamine sites of dendrimers **5** and **10** were fully quaternized with excess methyl iodide to give the corresponding *polyammonium iodide dendrimers* G_4(PM**I**32) (**5a**) and G_2(PM**I**8) (**10a**). The ^{1}H NMR spectra of **5a** and **10a** show the absence of the N*C*H_2 and N*C*H_2CH_2O peaks of **5** and **10** at 2.40 and 2.62 ppm. The water-soluble *polyammonium chloride dendrimers* G_4(PM**Cl**32) (**5b**) and G_2(PM**Cl**8) (**10b**) were obtained by converting the quaternary ammonium iodide to the corresponding chloride via ion exchange. The completeness of the conversion from iodides **5a** and **10a**

to the corresponding chlorides **5b** and **10b** using the combination of ion exchange and extraction techniques was confirmed by the integration of a newly formed $OCH_2CH_2N^+Cl^-$ peak of **5b** at 4.32 ppm with respect to the alkyl CH_3 peak at 0.84 ppm ($OCH_2CH_2N^+Cl^-/CH_3$ 2/3).

Characterization. The products were purified using basic aluminum oxide (Baker, 50 μm) flash chromatography, and the purity was checked by TLC (silica gel plates pretreated with trimethylamine). The products were characterized by FT-IR, ^1H and ^{13}C NMR analysis, and the products from DAB-*dendr*-$(NH_2)_8$ were also characterized by ESI-MS analysis in H_2O/CH_3CN (50:50) solution. The ESI-MS analyses for the products from DAB-*dendr*-$(NH_2)_{32}$ and DAB-*dendr*-$(NH_2)_{64}$ were not successful due to instrumental limitation and/or possible aggregation of the products in the H_2O/CH_3CN solution in which the ESI-MS experiments were conducted.

The structures of the intermediate and final dendrimers were confirmed by their ^1H and ^{13}C NMR spectra. Figure 1 shows the ^{13}C NMR spectrum of dendrimer **10**, and the empirical calculations of the chemical shifts using Sadtler Suite™ ^{13}C NMR database (BIO-RAD). The experimental results fit the calculated data extremely well (Figure 1).

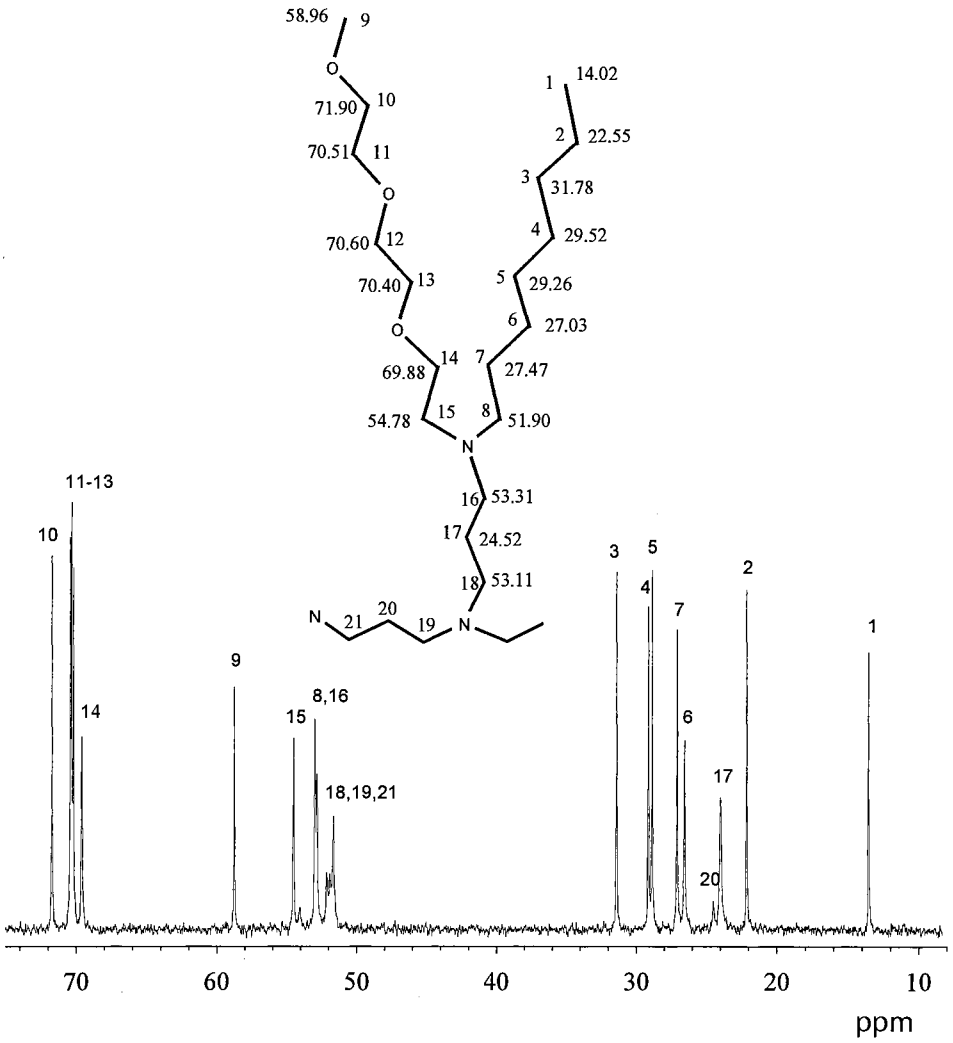


Figure 1. 75 MHz ^{13}C chemical shift assignments of dendrimer **10**.

The formation of the amide groups and the subsequent conversion of the amide groups to amine groups were monitored by FT-IR. The strong absorption of the amide

C=O stretching band at 1640-1650 cm^{-1} indicates a successful formation of the polyamide dendrimers, while the disappearance of the same absorbance after $LiAlH_4$ reduction indicates the completeness of the reduction.

Solubilities of the Polyamine and Polyammonium Dendrimers. The polyamine dendrimers G_4(TAn32) **(5)**, G_2(TAn8) **(10)** and G_5(TAn64) **(15)** are soluble in toluene, ether, THF, chloroform, acetone and MeOH, but they are not soluble in water despite the TEO (triethyleneoxy methyl ether) end groups on the periphery. The polyammonium iodide dendrimers G_4(PMI32) **(5a)** and G_2(PMI8) **(10a)** are only slightly soluble in water and very readily soluble in common organic solvents such as THF, acetone, ether and MeOH. The polyammonium chloride dendrimers G_4(PMCl32) **(5b)** and G_2(PMCl8) **(10b)** are readily soluble in both organic solvents and water, and can be extracted quantitatitively from water by chlorinated solvents (CH_2Cl_2 and $CHCl_3$). This observation indicates that the octyl end groups play an important role in determining the solubilities of the amphiphilic dendrimers, and the amphiphilic dendrimers are still highly hydrophobic although they are soluble in water.

The data from Table 1 indicate that all of the polyamine, polyammonium iodide and chloride dendrimers are readily soluble in common organic solvents. The excellent solibilities allow those products to be purified easily by normal extraction and chromatography. The presence of such hydrophobic moieties in the target dendrimers are highly desired for their potential application as unimolecular micelles and homogeneous catalysts in aqueous solutions.

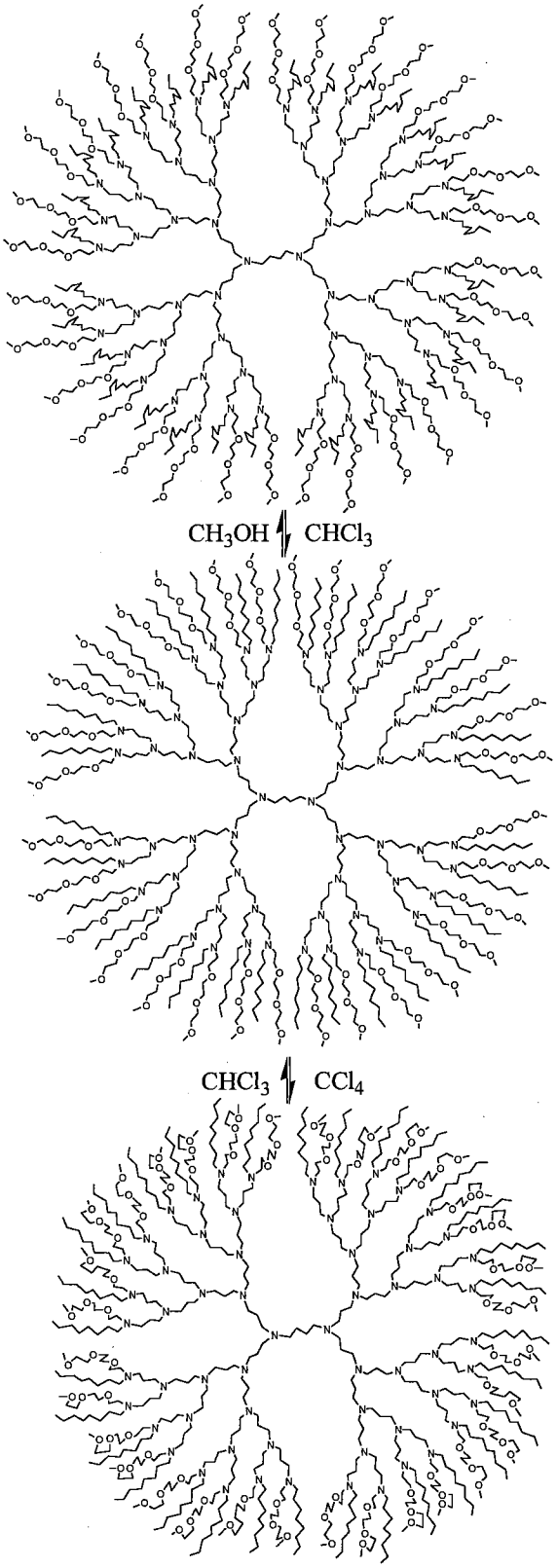
Table 1. Solubilities of Generation 2, 4 and 5 Polyamine, Polyammonium Iodide and Chloride Dendrimers [a]

dendrimer	MeOH, EtOH, THF, CH_2Cl_2, $CHCl_3$	H_2O
G_4(TAn32) (**5**)	✔	×
G_2(TAn8) (**10**)	✔	×
G_5(TAn64) (**15**)	✔	×
G_4(PMI32) (**5a**)	✔	Slightly
G_2(PMI8) (**10a**)	✔	Slightly
G_4 (PMCl32) (**5b**)	✔	✔
G_2(PMCl8) (**10b**)	✔	✔

[a] Solubilities were tested at room temperature.
[b] Symbol '✔' represents good solubility and '×' represents poor solubility.

Mobilities of the Chain Ends. The amphiphilic dendrimers with alternating hydrophilic and hydrophobic arms are expected to change their conformations, especially the conformations of the end groups on the periphery of the dendrimers, with respect to the change in solvent polarity. In other words, the conformations of the polyamine dendrimers are solvent polarity dependent. In chloroform, both the TEO and the alkyl arms are readily solvated, and they adopt their fully extended conformations on the surface of the dendrimers. In polar solvents such as MeOH and water, the alkyl arms contract and are shielded by the TEO arms, and the peripheries of the dendrimers are predominantly covered by the hydrophilic chain ends (Scheme 4). Therefore, when the solvent polarity was changed, the conformation of dendrimer **5** switched to another vastly different conformation simply by a minimal rearrangement of the two different arms.

Scheme 4. Conformations of dendrimer **5** with respect to the solvent polarities.



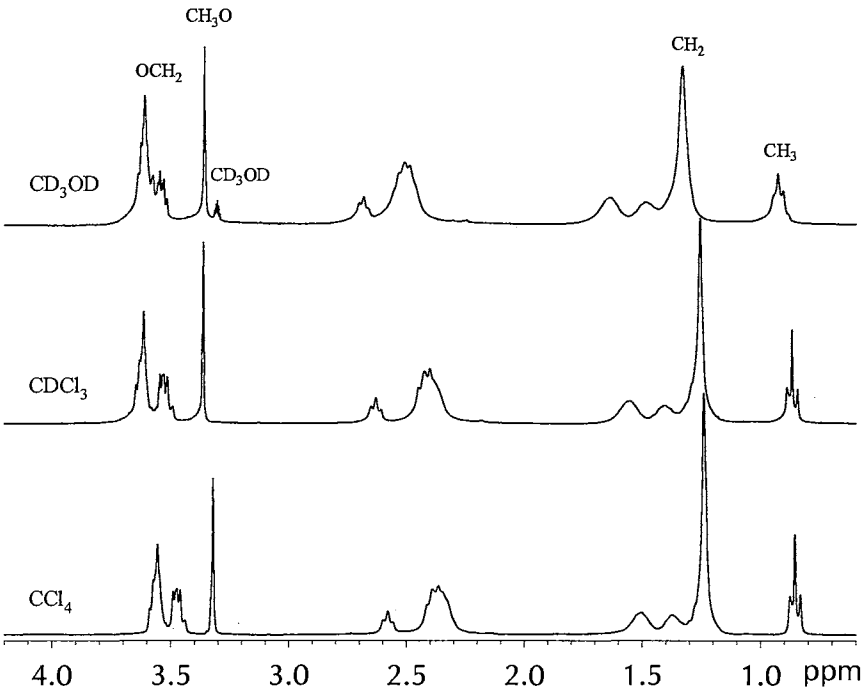


Figure 2. 300 MHz ^{1}H NMR spectra of polyamine dendrimer **5** in $CCl_4/CDCl_3$ (bottom, CCl_4:$CDCl_3$ 9:1), $CDCl_3$ (middle) and CD_3OD (top). ^{1}H NMR spectra were measured using 20 mg of **5** in 0.8 mL of the solvents at 22 °C.

The above rationale was supported by both ^{1}H NMR spectra and ^{13}C NMR T_1 relaxation time measurements in solvents with different polarity. The ^{1}H NMR spectra of the polyamine dendrimer G_4(TAn32) (**5**) indicate that both the CH_3 and CH_2 peaks of the alkyl arms and the OCH_3 and OCH_2 peaks of the TEO arms are sharp in chloroform. In MeOH, the TEO peaks remain sharp while the alkyl peaks are broader (the integrals are the same). In $CCl_4/CDCl_3$ (9:1), the alkyl peaks become sharper while the PEO peaks are

broader (the integrals are the same). The pattern in the *O*-methylene area (3.4-3.7 ppm) also changes with the polarities of the solvents (Figure 2). The octyl peak broadening with increased polarities of the solvents resulted from the increased through-space interaction of the octyl arms with their microenvironments, which implies that the octyl arms contract when solvent polarity increases.

^{13}C spin-lattice relaxation times T_1 also provided information about mobilities of the pendant groups. T_1 relaxation in large organic molecules is usually through a *dipolar mechanism*. The strength of the dipole-dipole interaction is inversely proportional to r^6, where r is the distance between nuclei. A shorter T_1 value can be expected if the motion of a part of the molecule is restricted by steric effects.[15]

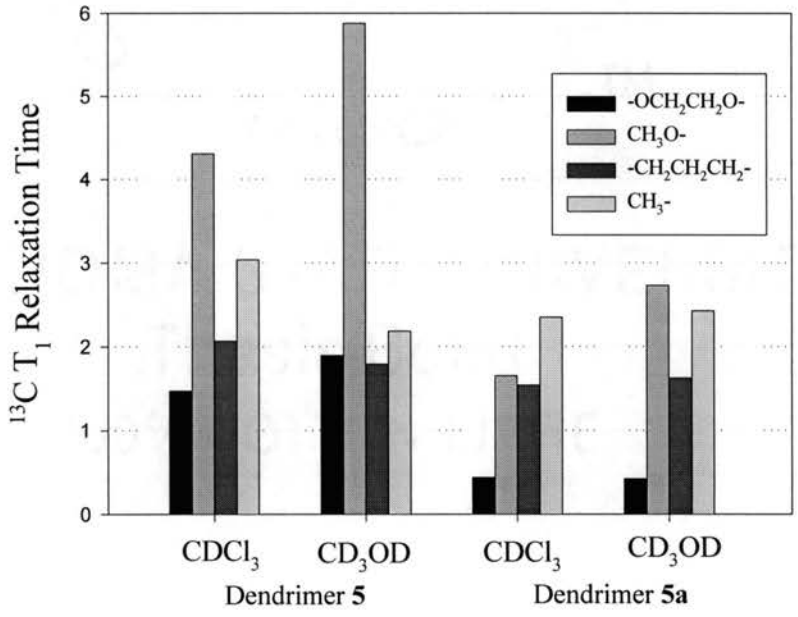


Figure 3. 75 MHz ^{13}C T_1 values of dendrimers **5** and **5a** in MeOH and chloroform. Data were collected using 126 mg of **5** and 108 mg of **5a** in 0.8 mL of the solvents at 22 °C.

Table 2. ^{13}C T_1 Values of the chain ends of 5, 5a and 5b in $CDCl_3$ and CD_3OD [a]

	Dendrimer **5**		Dendrimer **5a**		Dendrimer **5b**	
	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD
CH_3OCH_2	1.48	1.90	0.43	0.42	0.62	0.71
OCH_3	4.31	5.88	1.66	2.73	2.43	3.00
CH_2 [b]	2.07	1.79	1.54	1.63	1.42	1.84
CH_3	3.04	2.19	2.35	2.43	2.43	3.02

[a] 75 MHz ^{13}C T_1 data were collected by the inversion-recovery method using 126 mg of **5**, 108 mg of **5a** and 101 mg of **5b** in 0.8 mL of the solvents at 22 °C.
[b] C-2 of the octyl arms.

The T_1 relaxation time data of G_4(TAn32) **(5)** show that the T_1 values of the TEO arms increase and the T_1 values of the alkyl arms decrease when the solvent changes from $CDCl_3$ to CD_3OD (Figure 3 and Table 2). The results imply that in MeOH the motion of the alkyl arms in **5** decreases by adopting their contracted conformations, while the motion of the TEO arms increases due to the reduced steric restrictions from the adjacent alkyl arms. In both $CDCl_3$ and CD_3OD, the T_1 values of TEO chain ends in **5a** and **5b** are significantly less than those in **5**, which indicates that motion of the TEO arms was slowed by ion-dipole attraction of the internal quaternary ammonium sites in **5a** and **5b**, and such ion-dipole attraction is more significant in $CDCl_3$ than in CD_3OD.

The Microenvironments of the Dendritic Shell. The densely packed chain segments on the outer shell of the globular dendrimer molecules represent one of most important characteristics of dendritic structures. Both carbon T_1 relaxation time measurements and

proton NMR analysis were used to get some insight into the microenvironments of the dendritic shells in generation 2, 4 and 5 dendrimers.

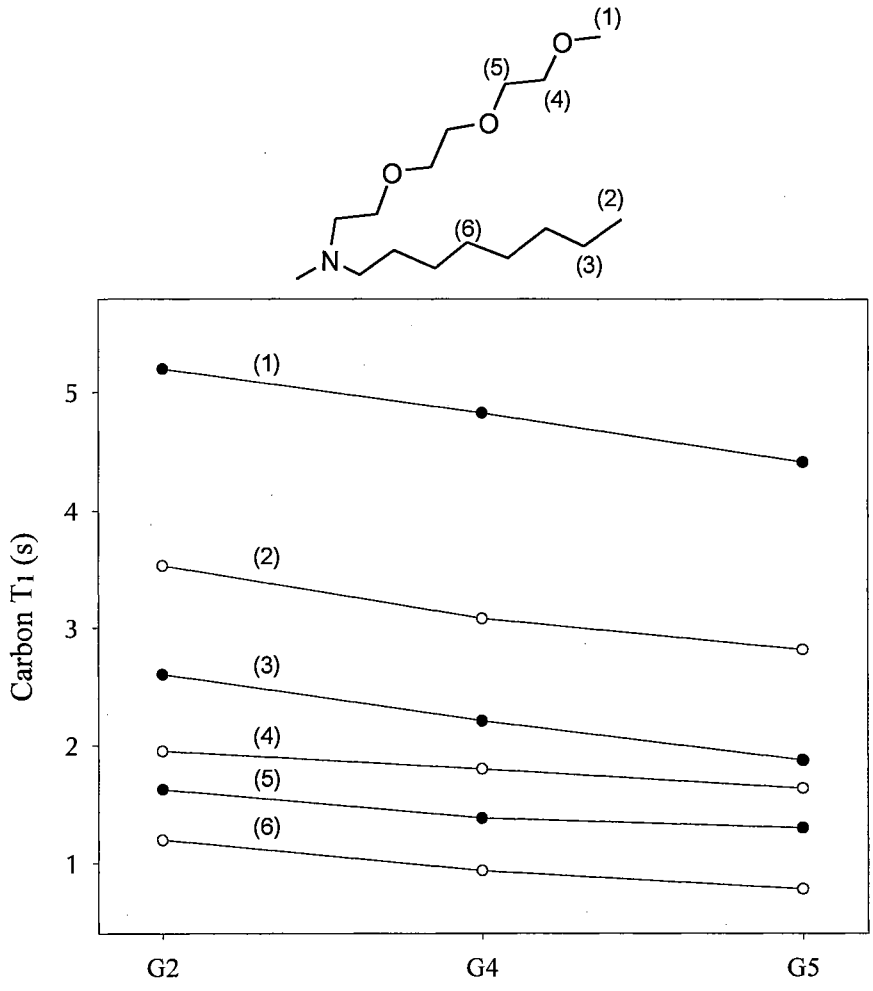


Figure 4. 75 MHz ^{13}C T_1 values of polyamine dendrimers with increasing number of generations. The T_1 data of selected atoms from the arms of G_2, G_4 and G_5 polyamine dendrimers **5**, **10** and **15** were collected in 0.8 mL of $CDCl_3$ at 22 °C.

The carbon spin-lattice (T_1) relaxation data as a function of the dendrimer size are given in Figure 4. The T_1 relaxation values of a large number of atoms from the end

groups of the dendrimers decrease steadily with increasing number of generations, which suggests that these atoms of higher generation dendrimers are less mobile than those of lower generation dendrimers. The continually decreasing T_1 values of the amphiphilic dendrimers from generation 4 to 5 suggest that the alternating arms (especially the atoms near the ends of the arms) on the surface of the generation 5 dendrimer are still flexible, and small molecules may still permeate through the non-solid-like shell. This permeation is crucial to potential applications such as unimolecular micelles and homogeneous catalysis.

Proton NMR chemical shifts of the secondary amide $C_7H_{15}CO\mathbf{NH}$- end groups also provided very useful information about the microenvironments of the dendritic shell. The CO**NH**- functional groups can interact with each other through hydrogen bonding, and the strength of the intramolecular hydrogen bonding can reveal the details about the close packing of the end groups as demonstrated by Meijer.[12] A downfield shifting of the chemical shifts of the amide CO**NH** groups was recorded with increasing number of generations (Figure 5) by ^{1}H NMR spectroscopy, which results from the increasing intramolecular hydrogen bonding in higher generation dendrimers. The results suggest that the intramolecular and intra-arm hydrogen bonding of the CO**NH** groups in the higher generation dendrimers is more extensive than that in lower generation dendrimers because of the increased close packing of the arms in the higher generation dendrimers.

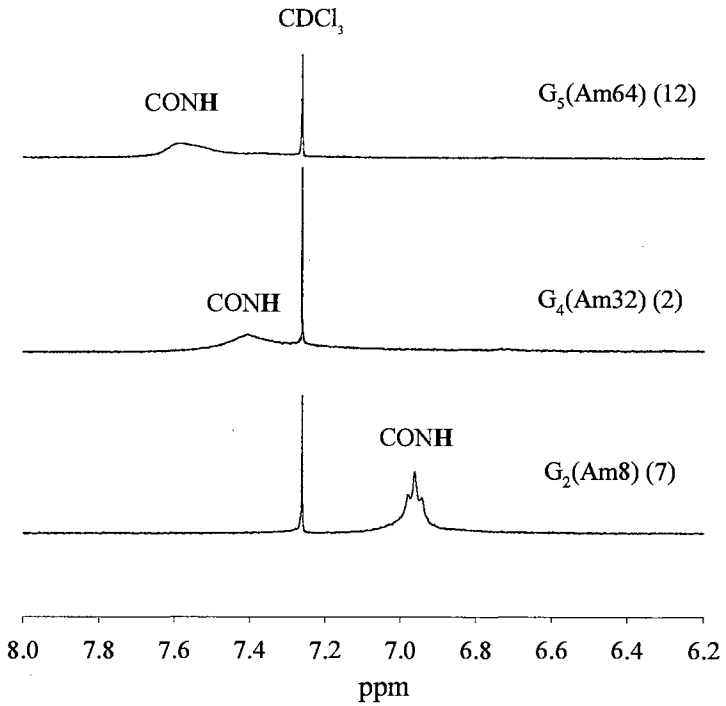


Figure 5. 300 MHz ^{1}H NMR of the CO*NH* signals of the polyamide dendrimers in $CDCl_3$ with increasing number of generations.

Molecular Inclusion. The lipophilic alkyl arms not only enable the dendrimers to be soluble in organic solvents, which can greatly facilitate the synthesis and purification of the dendrimers, but also provide the lipophilic moieties which can host lipophilic substrates from aqueous solutions through hydrophobic interactions. We use a water-insoluble, highly sensitive pyridinium-*N*-phenoxide betaine (Reichardt's dye), whose solvatochromic bands (λ_{max}) can shift from 452 nm to 810 nm when the solvent changes

from water to diphenyl ether,[17-18] as solvatochromic probe to test the solvating behavior of dendrimer G_4(PMClD32) (**5b**) in aqueous solution. (Figure 6).

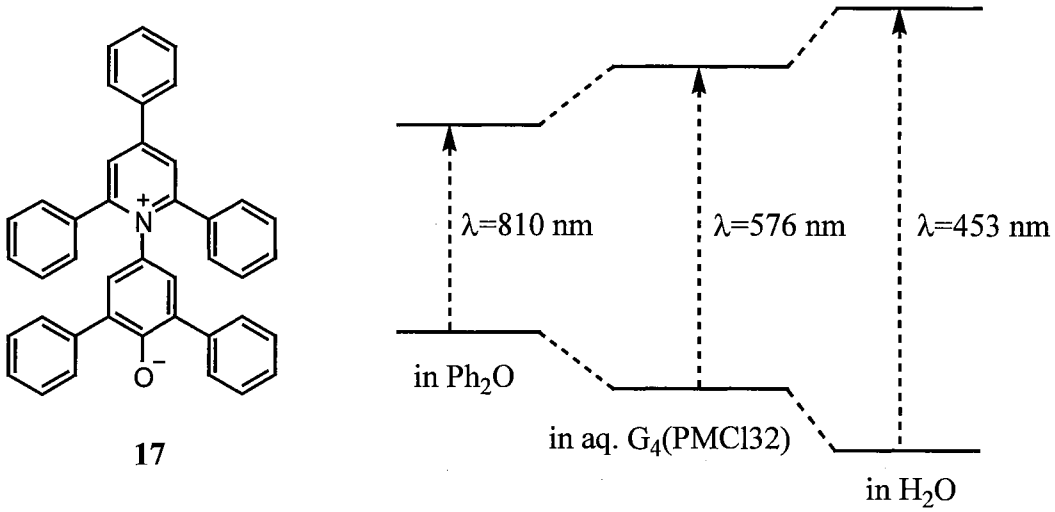


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Figure 6. Solvent dependence of π–π^* transition of Reichardt's dye.

The water-insoluble dye can be solubilized by dendrimer **5b** to form a stable and clear aqueous solution, which indicates that the system developed in this study was capable of hosting lipophilic molecules from aqueous solution. The λ_{max} of the dye in aqueous solution of polyammonium chloride dendrimer G_4(PMCl32) was recorded at 576 nm. Compared with the λ_{max} of the dye in water at 452 nm, a 123 nm $\Delta\lambda_{max}$ was observed. The large λ_{max} shift from water to the aqueous solution of the amphiphilic dendrimer suggests that the dye molecules are solubilized by the hydrophobic moieties of the dendrimer, and the energy gap between the ground state and excited state is significantly reduced (Figure 7).

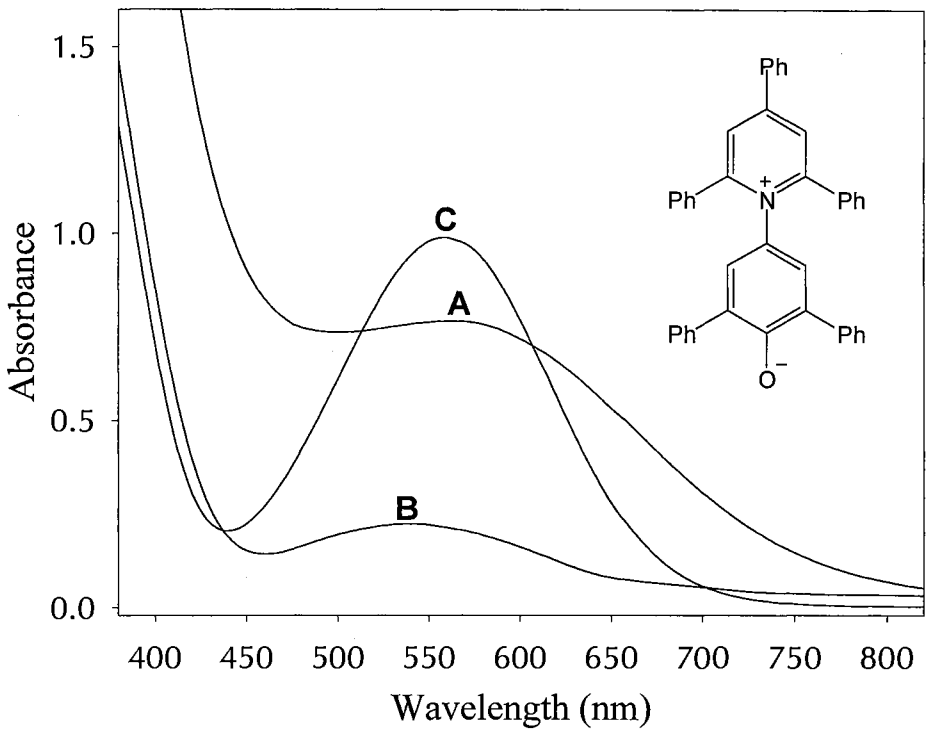


Figure 7. UV-vis absorption spectra of Reichardt's dye in media with different polarities. (A): aqueous solution of polyammonium chloride dendrimer **5b** (7.0×10^{-4} M or 36 mg/3.20 mL) and dye (9.6×10^{-4} M); (B): CTAC (3.5×10^{-3} M or 3.7 mg/3.20 mL) and dye (9.6×10^{-4} M); (C): benzyl alcohol (neat) and dye (3.2×10^{-4} M).

Figure 7 shows the UV-vis absorption of Reichardt's dye in an aqueous solution of dendrimer G_4(PMCl32) (**5b**), and the absorption is compared with those of the dye in aqueous cetyltrimethylammonium chloride (CTAC) solution and in pure benzyl alcohol. A long wavelength absorption (576 nm) for dendrimer **5b** and a short wavelength absorption (542 nm) for CTAC were observed, which implies that the environment of the

dye in the unimolecular micelle system is more hydrophobic than in the dynamically aggregated CTAC micelle, although the length of cetyl chains (C_{16}) in CTAC is twice as that of the octyl chains (C_8) in **5b**. The UV-vis absorption of the dye in aqueous **5b** (λ_{max} = 576 nm) is quite close to that in pure benzyl alcohol (λ_{max} = 567 nm), which implies that the polarity of the overall microenvironment of **5b** in water is somewhat close to the polarity of neat benzyl alcohol.

The limiting solubilization of pyrene in an aqueous solution of **5b** (9.16×10^{-4} M) is 1.04×10^{-3} M as measured by UV-vis absorption spectroscopy, corresponding to one pyrene per dendrimer molecule. The concentration of pyrene in aqueous dendrimer **5b** is nearly 1,300 times higher than the concentration in pure water (8×10^{-7} M). A concern for pyrene probe is that it may aggregate in aqueous solution, resulting in concentration-dependent λ_{max} shifts. The UV-vis absorption spectra of pyrene in dendrimer **5b** with increasing pyrene concentrations were recorded (Figure 8). The λ_{max} values are concentration-independent, which implies a lack of pyrene aggregation in the aqueous solution. The linearity in the plot of absorbance at λ_{max} versus concentration obeys Beer's Law over a wide range of pyrene concentration, and pyrene remains within the hydrophobic moieties of the dendrimer.

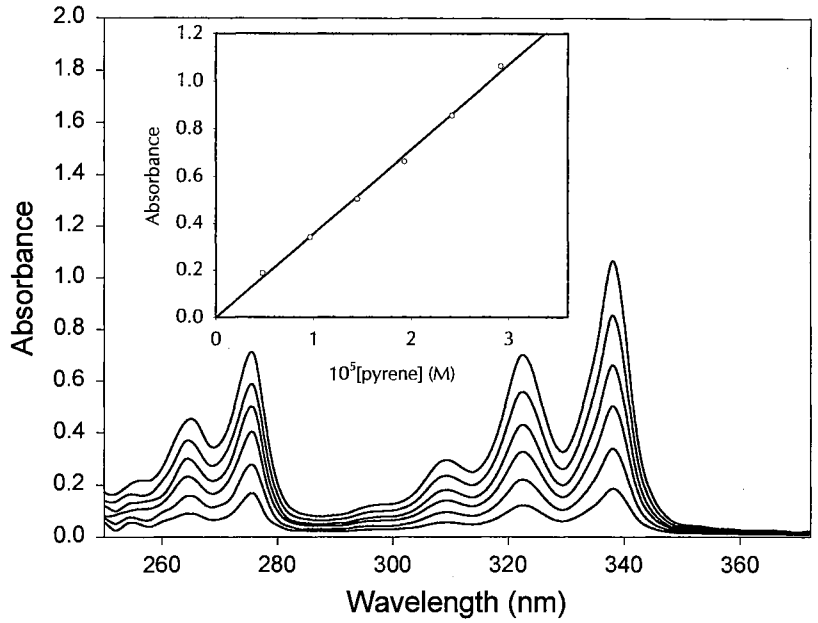


Figure 8. UV-vis absorption spectra of pyrene in 9.16 x 10^{-4} mol/L aqueous dendrimer **5b** with increasing pyrene concentrations (0.48, 0.97, 1.45, 1.93, 2.42 and 2.90 x 10^{-5} M). The inset shows that absorbance at 338 nm obeys Beer's Law.

Molecular Simulations. Molecular simulations (on Insight II and Discovery) were used to investigate the sizes, conformations and molecular characteristics of the dendrimers. One of the reasonable conformations of dendrimer G_4(TAn32) (**5**) is shown in Figure 9 in close-packing model, and the stick models of the dendrimers G_2(TAn8) **(10),** G_2(TAn8) **(5)** and G_2(TAn8) **(15)** are shown in Figure 10. The diameters of monomeric dendrimers were estimated by molecular simulation using the standard feature of Insight II on SGI and HyperChem 5.1 on Windows, and the results are shown in Table 3. Dynamic light scattering (DLS) and small-angle neutron scattering experiments have been widely used for the measurement of hydrodynamic sizes of

dendrimers in the literature.[19] In this study, the sizes of the dendritic particles were also measured by DLS at the scattering angle 90 ° and at 20 °C (Table 3). The sizes measured by DLS fit the estimated values from molecular modeling quite well.

Table 3. Molecular Sizes of Generation 2, 4 and 5 Dendrimers

Dendrimer	Diameter by Modeling (Å) *a*	Diameter by DLS (Å) *b*
G_2(TAn8) (**10**)	21.5	-----
G_4(TAn32) (**5**)	35.4	34.7
G_5(TAn64) (**15**)	44.1	42.4

a The diameter measurement by molecular modeling was performed using Insight II on SGI (MSI).
b DLS was measured using the dendrimers in MeOH solution at 20 °C.

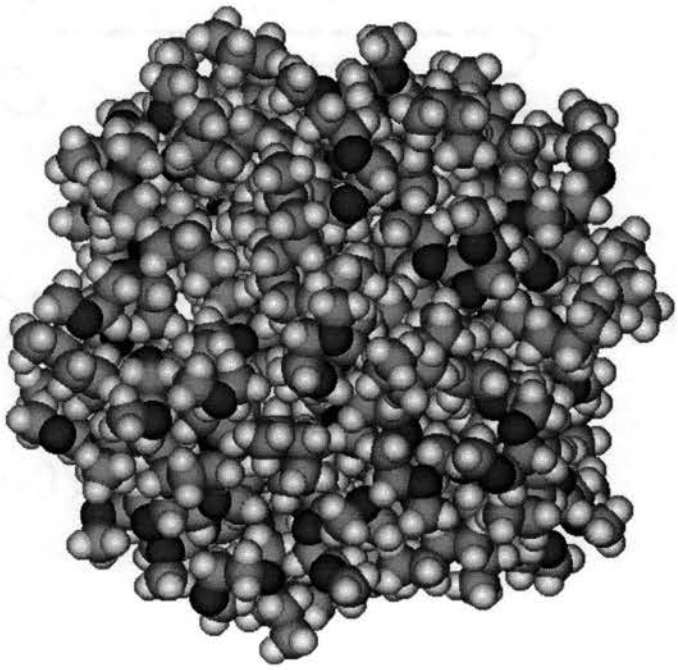


Figure 9. 3D view (close packing model) of dendrimer **5.** Atoms in order of increasing lightness are nitrogen, oxygen, carbon and hydrogen.

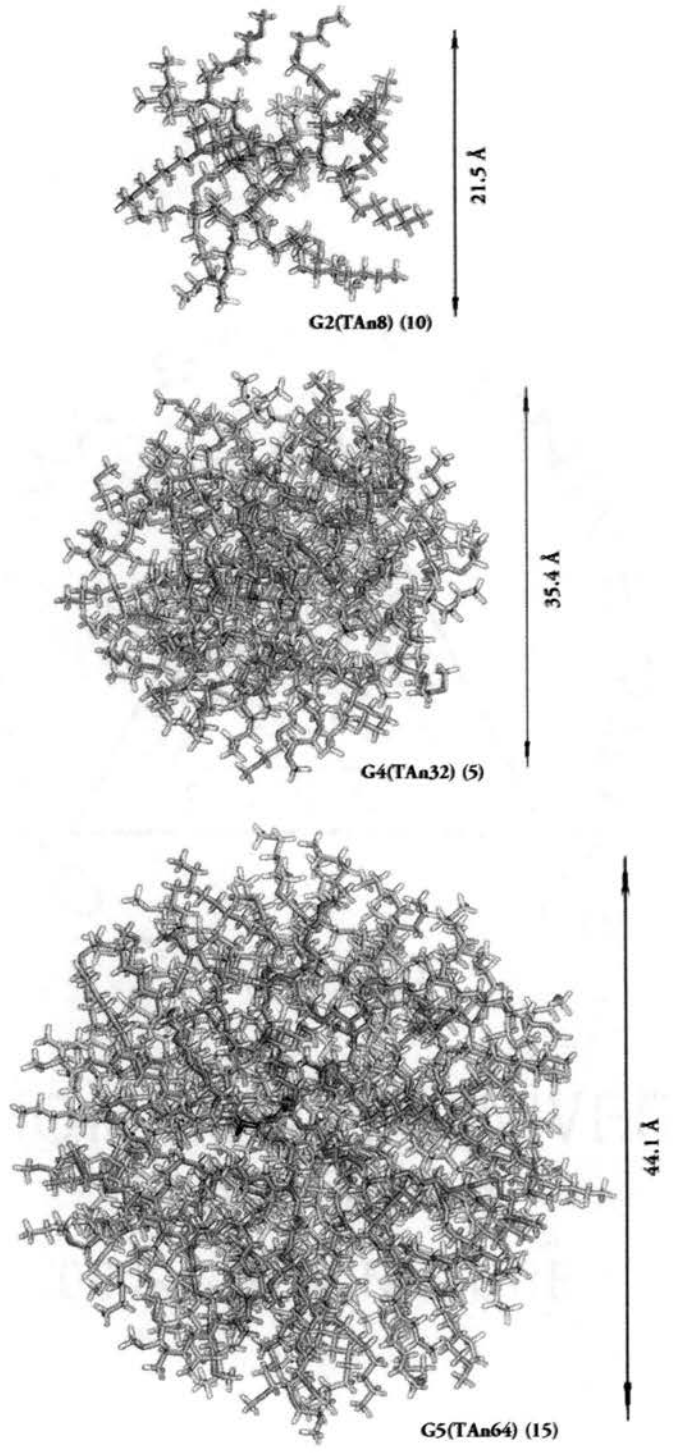


Figure 10. 3D views (stick model) and hydrodynamic sizes of dendrimers G_2(TAn8) **(10),** G_2(TAn8) **(5)** and G_2(TAn8) **(15)** as estimated by molecular simulations.

The average distances between the carbon atoms of octyl and TEO chain ends on the same nitrogen atoms in dendrimers G_3(TAn16) (not synthesized), G_4(TAn32) (**5**) and G_5(TAn64) (**15**) were calculated based on their 3D coordinates from a reasonable conformation after energy minimization. The decreasing average distances with increasing number of generations (G_3(TAn16): 13.03 Å, G_4(TAn32) (**5**): 11.14 Å and G_5(TAn64) (**15**): 10.72 Å) result from closer packing of the dendritic shells.

The distribution of the atoms on a shell at radius r was obtained using an in-house program developed from OpenGL computer graphic interface. All the atoms in the dendrimers were sorted based on their distances (r_i) to the centers of the molecules, and only the atoms having distances between $r - R_{atom}$ and $r + R_{atom}$ ($r - R_{atom} \leq r_i \leq r + R_{atom}$) were used for the calculation and visualization, while R_{atom} stands for the covalent radii of the atoms (hydrogen: 0.32 Å, carbon: 0.68 Å, nitrogen: 0.75 Å and oxygen: 0.73 Å). The ratio of the total area occupied by those atoms on the shell to the total area of the shell was defined as the *Occupied Area Ratio* Φ ($\Phi = \Sigma\pi R_{atom}^2/4\pi r^2$) and calculated according to 3D coordinate data from the reasonable conformations after energy minimization.

The atoms of dendrimer G_5(TAn64) **15** on a shell at r = 21.5 Å (left) and a shell at r = 11.5 Å (right) were visualized as shown in Figure 11. The number of atoms at r = 21.5 Å (corresponding to the compact dendritic shell) is near four times as that at r = 11.5 Å in the interior, while their occupied area ratio is on the same order since the increase of the total area of the shell is proportional to r^2.

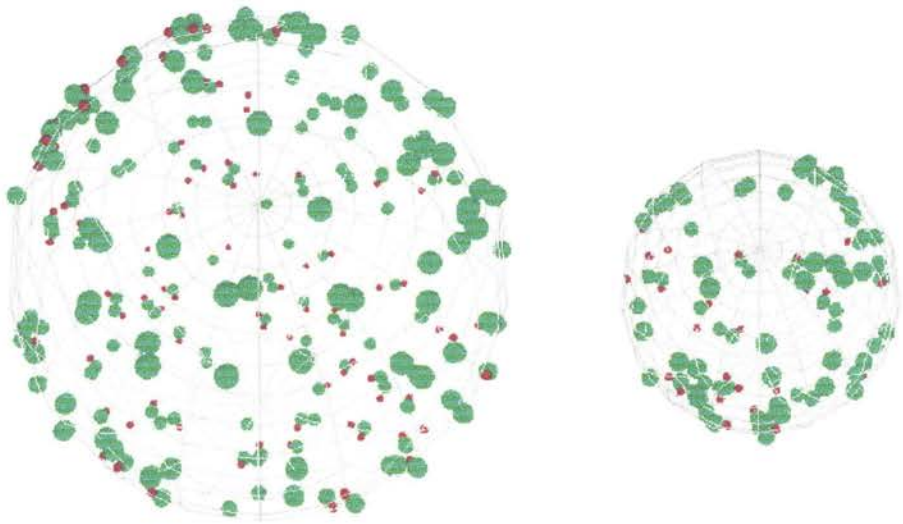


Figure 11. Visualization of the atoms of dendrimer G_5(TAn64) **15** on a shell at r = 21.5 Å (left) and a shell at r = 11.5 Å (right). Only the atoms having the distances (r_i) to the center in the range of $r - R_{atom} \leq r_i \leq r + R_{atom}$ are visualized.

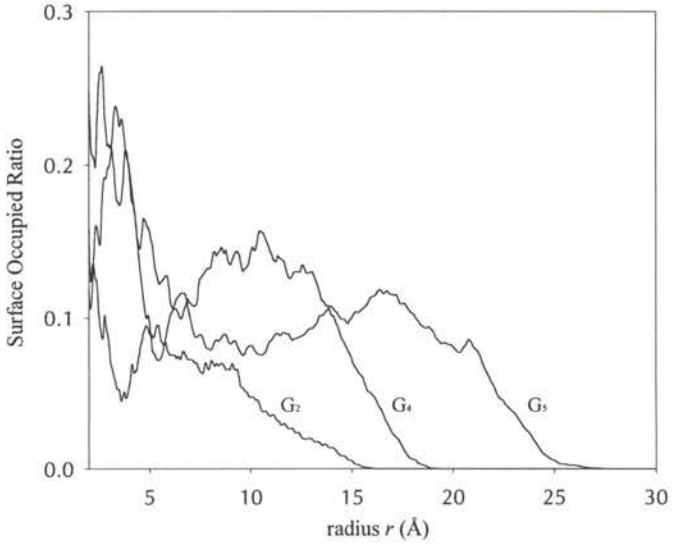
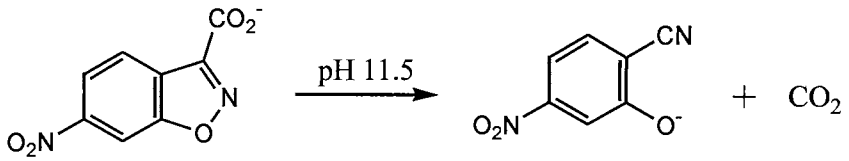


Figure 12. Radial distribution of the occupied surface ratio of G_2(TAn8) (**10**), G_4(TAn32) (**5**) and G_5(TAn64) (**15**) from the cores toward the peripheries.

The radial distributions of the occupied area ratio of dendrimers G_2(TAn8) (**10**), G_4(TAn32) (**5**) and G_5(TAn64) (**15**) versus the radius *r* were plotted (Figure 12). The occupied area ratio of dendrimers G_2(TAn8) (**10**), G_4(TAn32) (**5**) and G_5(TAn64) (**15**) have maximum around *r* = 9.2, 13.5 and 21.5 Å, which is in agreement with their hydrodynamic sizes estimated by Insight II (Table 2). The occupied area ratio may provide some insight into the molecular characteristics of the dendrimers such as the possibility of allowing small molecules to permeate through the compact shells.

Kinetic Study of the Decarboxylation of 6-Nitrobenzisoxazole-3-Carboxylic Acid Catalyzed by Dendrimers 5b and 10b. Chemical reactions catalyzed by enzymes in aqueous media are important in living organisms, and hydrophobic and electrostatic interactions are major driving forces for the binding of substrates to enzymes.[20] We aim to use the amphiphilic dendrimers as mimics for the natural environments of enzymes. The internal quaternary ammonium ions can be considered as catalytic sites for a variety of reactions. One particular useful reaction to probe the catalytic effects of the dendrimers is the unimolecular concerted decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid. The rate of decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid in the aqueous solution of the dendrimers at pH 11.4 was used to determine the extent of hydrogen bonding of water to the reactive anion in the dendrimers and the catalytic activities of the water-soluble amphiphilic dendrimers (Scheme 5).[21]

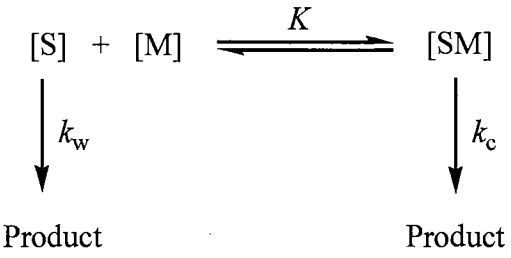
Scheme 5. Decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid.



18 **19**

The substrate is assumed to distribute between the aqueous phase and the dendritic unimolecular micelles. We assume that the substrate binding is reversible, and that the binding equilibrium fits the so-called Menger-Portnoy kinetic model which was developed and used for catalysis by surfactant micelles (Scheme 6).[22-24]

Scheme 6. Kinetic model of the decarboxylation



The symbols K and k_c represent the binding constant and the intrinsic rate constant inside the dendritic systems, [S] is the concentration of the substrate in aqueous phase, [M] is the concentration of the unimolecular micelles, and [SM] is the concentration of the substrate bound to the unimolecular micelles. The pseudo-first-order rate constants k_{obsd} and the rate enhancements k_{obsd}/k_w for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid are listed in Table 4, the binding constants K and intrinsic rate constances k_c are shown in Table 5, and the plot of data used to determine K and k_c by regression analysis is shown in Figure 13.

Table 4. Rate Constants of Decarboxylation of 6-Nitrobenzisoxazole-3-Carboxylic acid [a]

Dendrimer	10^3 [N^+] (M) [b]	$10^3 k_{obsd}$ (s^{-1})	k_{obsd}/k_w [c]
G_4(PMCl32) (**5b**)	0.79	1.16	374
G_4(PMCl32) (**5b**)	1.58	1.37	442
G_4(PMCl32) (**5b**)	2.37	1.51	487
G_4(PMCl32) (**5b**)	4.74	1.61	519
G_2(PMCl8) (**10b**)	0.83	0.63	203
G_2(PMCl8) (**10b**)	1.66	0.77	248
G_2(PMCl8) (**10b**)	2.49	0.84	271
G_2(PMCl8) (**10b**)	4.98	0.91	294

[a] Data were obtained in aqueous solution of **5b** and **10b** at pH 11.4 and 25.0 °C. Reaction was followed by the average absorbance between 400-430 nm while the λ_{max} of 2-cyano-5-nitrophenoxide is at 418 nm.
[b] Concentration of the quaternary ammonium ions [N^+] was in excess over the substrate concentration: [S] = 7.82 x 10^{-5} M.
[c] The first order rate constant in water at pH 11.5 was k_w = 3.1 x 10^{-6} s^{-1} (ref. 22).

Table 5. Binding Constants and Intrinsic Rate Constants of Decarboxylation of 6-Nitrobenzisoxazole-3-Carboxylic Acid in Aqueous 5b and 10b at 25.0 °C

Dendrimer	$10^3 k_c$ (s^{-1}) [a]	k_c/k_w [b]	K (M^{-1})
G_4(PMCl32) (**5b**)	1.75	564	2442
G_2(PMCl8) (**10b**)	1.00	323	2043
PE-TMA36 [c]	0.08	25	1700

[a] k_c = intrinsic rate constant in the dendrimer pseudophase.
[b] The first order rate constant in water k_w = 3.1 x 10^{-6} s^{-1} at pH 11.5.
[c] A dendrimer catalyst with quaternary ammonium ions on the surface (ref. 22).

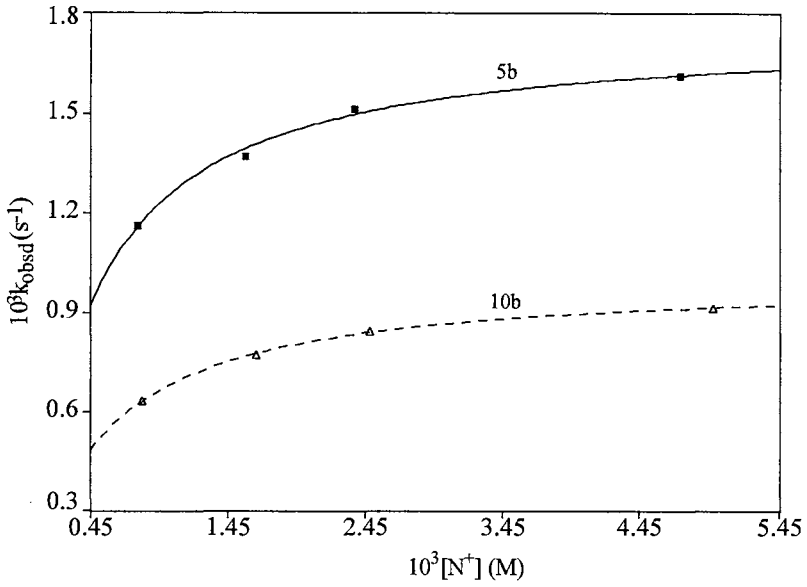


Figure 13. Pseudo-first-order rate constants for decarboxylation of 7.82 x 10^{-5} M 6-nitrobenzisoxazole-3-carboxylic acid solution as a function of $[N^+]$ units of **5b** and **10b** at 25 °C. The non-linear plots were used to determine k_c and K using equation $k_{obsd} = (k_w/K + k_c*[N^+])/(1/K + [N^+])$ (ref. 24).

Table 5 shows that dendrimers G_4(PMCl32) **(5b)** and G_2(PMCl8) **(10b)** have much higher values of k_c than a dendrimer catalyst PE-TMA36 with quaternary ammonium ion sites on the surface as reported earlier in this laboratory.[21] Since the surface environments of dendrimers G_4(PMCl32) **(5b)** and G_2(PMCl8) **(10b)** are much more lipophilic than dendrimer PE-TMA36, the increases in the rates are the result of a more favorable equilibrium binding between the substrate and the amphiphilic dendrimers which have a large number of octyl lipophilic moieties around the quaternary ammonium ion sites in the dendritic structures. Both the equilibrium binding constants K and the intrinsic rate

constants k_c played a key role in the kinetic process of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid since the rate constants k_c in the unimolecular micelles are much larger than the rate constant of water k_w (Scheme 6 and Table 5).

The kinetic results also show that dendrimer G_4(PMCl32) (**5b**) gives higher observed rate constants than dendrimer G_2(PMCl8) (**10b**). The larger ionic radius of G_4(PMCl32) (**5b**) reduces its ion-dipolar attraction for water so that the lipophilic molecules of the substrate are bound to dendrimer **5b** in a much less aqueous environment. As a consequence, a higher catalytic activity of the amphiphilic dendrimer with a larger size was observed.

One interesting feature of the dendrimer catalysts is that the quaternary ammonium ion sites are surrounded by a large hydrophobic shell which can absorb lipophilic substrates nearby in the same molecule, and the surface of the whole system is covered by the amphiphilic TEO arms as indicated earlier in this chapter.

EXPERIMENTAL SECTION

All starting materials were from Aldrich and were used as received unless otherwise stated. THF was freshly distilled from sodium. Triethylamine was dried over anhydrous 3 Å molecular sieves and freshly distilled. ^{1}H NMR spectra (400 or 300 MHz) and ^{13}C NMR spectra (100.6 or 75.4 MHz) were recorded with the solvent signal as the reference. Analytical TLC was performed on Kodak thin-layer chromatography plates with silica gel GF_{254}. Basic aluminum oxide (Baker, 50 μm) was used for flash chromatography. Amberlite IRA 402 anion exchange resin in Cl^- form (Sigma) was used for the conversion

of the polyammonium iodide dendrimers to chloride dendrimers, and the resin was washed with aqueous NaOH, deionized water, aqueous HCl, deionized water and MeOH. Analytical TLC was performed on Kodak thin-layer chromatography plates with silica gel GF_{254}, and the plates were pretreated with trimethylamine vapor and activated at 60 °C for 2 h. Dynamic light scattering (DLS) was studied using a Brookhaven Instruments BI-200SM Goniometer and BI-9000AT multi-τ-digital correlator at a 90° scattering angle and 20 °C. The light source was a coherent INNOVA-90 argon laser (488 nm). The samples for DLS were prepared by dissolving the dendrimers (50-60 mg) in 2.50 mL of MeOH. UV-vis spectra and kinetic time traces were obtained in 3.00 cm polystyrene cells using a Hewlett-Packard model 8452A diode array spectrophotometer. ESI-MS spectra were obtained on a PE/Sciex API-III Quadra 950 triple quadrupole biomolecular mass analyzer at University of Oklahoma Health Science Center. Injected solutions were prepared in either 50/50 (v/v) H_2O:acetonitrile or 50/50 (v/v) H_2O:MeOH acidified with 3% acetic acid. Calculated *m/z* values are for the lowest isotopomers.

G_4(Am32) (2). Octanoyl chloride (1.98 g, 12.2 mmol) was added to a solution of DAB-*dendr*-$(NH_2)_{32}$ **1** (940 mg, 0.268 mmol), DMF (3.0 mL) and triethylamine (1.51 g, 15.0 mmol) at 0 °C, and the solution was stirred under nitrogen at 70 °C for 24 h. Water (2.0 mL) was added, and the solution was stirred for 10 min, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 1% aqueous K_2CO_3 (2 x 15 mL) and brine, dried (K_2CO_3), and concentrated. The oily crude product was purified on an aluminum oxide column (MeOH/$CHCl_3$, 2:98) to give 1.64 g (82%) of **2** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3295, 3089, 1651 cm^{-1}; ^1H

NMR ($CDCl_3$, δ): 0.91 (t, J = 6.57, CH_3), 1.12-1.40 (m, CH_2), 1.42-1.80 (m, $NCH_2CH_2CH_2NCO$, $NCH_2CH_2CH_2N$ and $NHCOCH_2CH_2$), 2.20 (t, $NHCOCH_2$), 2.40 (m, $CH_2N(CH_2)_2$), 3.26 (q, CH_2NHCO), 7.18 (br, $NHCO$); ^{13}C NMR ($CDCl_3$, δ): 13.98 (alkyl C1), 22.52 (alkyl C2), 25.87 ($NCH_2CH_2CH_2NH$), 26.94 (alkyl C6), 29.05 (alkyl C5), 29.30 (alkyl C4), 31.69 (alkyl C3), 36.51 (alkyl C7), 37.57 ($NCH_2CH_2CH_2NH$), 51.29 ($NCH_2CH_2CH_2NH$), 52.05 ($NCH_2CH_2CH_2N$), 174.00 (C=O).

G_4(An32) (3). A solution of **2** (1.04 g, 0.138 mmol) in THF (6.0 mL) was slowly added to a suspension of $LiAlH_4$ (400 mg, 11.6 mmol) in THF (50 mL) under nitrogen with stirring at 0 °C. The suspension was stirred at reflux for 24 h, and transferred slowly into saturated aqueous Na_2SO_4 solution (40 mL) at 5-10 °C. The THF layer was collected, and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic phase was washed with 4% aqueous K_2CO_3 (3 x 20 mL), dried (K_2CO_3) and concentrated. The oily crude product was purified on an Al_2O_3 column ($MeOH/CHCl_3$, 2:98) to give 880 mg (90%) of **3** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3295, 1474, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.86 (t, J = 6.62, CH_3), 1.18-1.38 (m, CH_2), 1.38-1.70 (m, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$), 2.31-2.50 (m, $CH_2N(CH_2)_2$), 2.51-2.70 (m, CH_2NH); ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 22.55 (alkyl C2), 24.23 ($NCH_2CH_2CH_2N$), 27.39 (alkyl C6 and $NCH_2CH_2CH_2NH$), 29.20 (alkyl C5), 29.49 (alkyl C4), 30.17 (alkyl C7), 31.75 (alkyl C3), 48.76 ($NCH_2CH_2CH_2NH$), 50.26 (alkyl C8), 52.22 ($NCH_2CH_2CH_2NH$), 53.20 ($NCH_2CH_2CH_2N$).

G_4(TAm32) (4). [2-(2-Methoxyethoxy)ethoxy]acetyl chloride **16** (1.28 g, 6.50 mmol) was added to a solution of **3** (920 mg, 0.130 mmol), DMF (3.0 mL) and triethylamine

(445 mg, 4.4 mmol) at 0 °C, and the solution was stirred under nitrogen at 70 °C for 24 h. Water (2.0 mL) was added, and the solution was stirred for 10 min and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL), washed with 1% aqueous K_2CO_3 (3 x 10 mL), dried (K_2CO_3) and concentrated. The oily crude product was purified on an Al_2O_3 column (MeOH/$CHCl_3$, 2:98) to give 1.14 g (72%) of **4** as a yellow thick oil. IR (film on NaCl) ν_{max}: 1651, 1474, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.89 (m, *CH_3*), 1.18-1.42 (br, *CH_2*), 1.42-1.80 (m, *CH_2*CH_2NCO, NCH_2*CH_2*CH_2N), 2.39 (br, NCH_2CH_2*CH_2*N), 3.23-3.32 (m, *CH_2*NCO), 3.38 (s, *CH_3*O), 3.52-3.80 (m, O*CH_2*CH_2*), 4.20 (s, NCO*CH_2*O); ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 22.50 (alkyl C2), 24.98 (NCH_2*CH_2*CH_2N), 26.46 and 26.77 (NCH_2*CH_2*CH_2NCO), 26.92 (alkyl C6), 27.47 and 28.94 (alkyl C7), 29.17 (alkyl C5), 29.29 (alkyl C4), 31.67 (alkyl C3), 44.15, 44.74 and 45.45 (NCH_2CH_2*CH_2*NCO), 47.03 (alkyl C8), 51.00 and 52.16 (N*CH_2*CH_2*CH_2*N), 58.95 (*CH_3*O), 63.68, 70.00 (CO*CH_2*O), 70.46 (*CH_2*O), 70.57 (*CH_2*O), 70.84 (*CH_2*O), 71.86 (CH_3O*CH_2*CH_2*O).

G_4(TAn32) (5). A solution of **4** (1.66 g, 0.136 mmol) in THF (4.0 mL) was slowly added to a suspension of $LiAlH_4$ (300 mg, 7.89 mmol) in THF (30 mL) under nitrogen with stirring at 0 °C. The suspension was stirred at reflux for 24 h, cooled, and quenched by transferring into saturated aqueous Na_2SO_4 solution (30 mL) at 5-10 °C. The THF layer was collected and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic phase was washed with 4% aqueous K_2CO_3 (3 x 10 mL), dried (K_2CO_3) and concentrated. The oily crude product was purified on an Al_2O_3 column (MeOH/$CHCl_3$, 2:98) to give 1.21 g (75%) of **5** as a light yellow thick oil. IR (film on

NaCl) ν_{max}: 1473, 1118 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.18, CH_3CH_2), 1.16-1.36 (m, CH_2), 1.36-1.70 (m, $NCH_2CH_2CH_2N$), 2.30-2.50 (m, $NCH_2CH_2CH_2N$), 2.61 (t, NCH_2CH_2O), 3.34 (s, CH_3O), 3.50 (m, OCH_2CH_2O), 3.62 (m, NCH_2CH_2O and OCH_2CH_2O); ^{13}C NMR ($CDCl_3$, δ): 14.02 (alkyl C1), 22.55 (alkyl C2), 24.52 ($NCH_2CH_2CH_2N$), 27.03 (alkyl C6), 27.47 (alkyl C7), 29.26 (alkyl C5), 29.52 (alkyl C4), 31.78 (alkyl C3), 51.90 (alkyl C8), 53.11 (NCH_2), 53.31 (CH_2N), 54.78 (NCH_2CH_2O), 58.96 (CH_3O), 69.87 (NCH_2CH_2O), 70.40 (OCH_2CH_2O), 70.50 (OCH_2CH_2O), 70.60 (OCH_2CH_2O), 71.90 (CH_2OCH_3).

G_4(PMI32) (5a). Methyl iodide (10.0 g, 70.0 mmol) was slowly added to a solution of **5** (680 mg, 0.0577 mmol) in CH_2Cl_2 (3.0 mL) in a thick-walled ampoule at 0 °C. The ampoule was sealed at -110 °C under vacuum and heated at 100 °C for 48 h. The excess methyl iodide and the solvent were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with aqueous $Na_2S_2O_3$ and NaI, dried (Na_2SO_4), concentrated under reduced pressure, and dried under vacuum at 60 °C for 24 h to give 986 mg (83%) of **5a** as a yellow powder. ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.46, CH_3CH_2), 1.16-1.58 (m, CH_2), 1.82 (m, $NCH_2CH_2CH_2N$), 2.62-2.92 (m, $NCH_2CH_2CH_2N$, NCH_2CH_2 and NCH_3), 3.38 (s, CH_3O), 3.42-4.32 (m, NCH_2CH_2O, CH_2O); ^{13}C NMR ($CDCl_3$, δ): 13.94, 18.76, 22.46, 22.75, 26.22, 29.06, 31.56, 49.76, 59.01, 64.65, 70.16, 70.29, 71.75.

G_4(PMCl32) (5b). A solution of dendrimer **5a** (600 mg, 0.0291 mmol) in MeOH (1.0 mL) and water (0.5 mL) was placed on a column packed with Amberlite IRA 402 in Cl^- form and eluted using 1.2:1 MeOH/H_2O. The eluate was evaporated under reduced pressure. The residue was dissolved in a mixture of MeOH (2.0 mL) and aqueous

saturated NaCl (10 mL) and stirred for 24 h. The MeOH was removed under reduced pressure, and the aqueous solution was extracted with CH_2Cl_2 (3 x 10 mL). The extracts were washed with brine and water, concentrated under reduced pressure and dried under vacuum at 60 °C for 24 h to give 308 mg (71%) of **5b** as a light yellow powder. ^{1}H NMR ($CDCl_3$, δ): 0.84 (t, J = 5.91, CH_3CH_2), 1.21-1.42 (m, CH_2), 1.60-1.78 (br, $N^+CH_2CH_2CH_2N^+$), 2.58, 3.32 (s, CH_3O), 3.34-4.18 (m, OCH_2CH_2O, N^+CH_2 and N^+CH_3), 4.22-4.42 (br, $OCH_2CH_2N^+$); ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 17.57 (br), 22.53 (alkyl C2), 26.36 (alkyl C6 and C7), 29.11 (alkyl C4), 29.20 (alkyl C5), 31.67 (alkyl C3), 49.00-51.00 (m, N^+CH_3), 58.90 (CH_3O), 57.10-61.69 (m, N^+CH_2), 64.78 ($N^+CH_2CH_2O$), 70.23 (OCH_2CH_2O), 71.73 (CH_2OCH_3).

G_2(Am8) (7). By the procedure for **G_4(Am32) (2),** DAB-*dendr*-$(NH_2)_8$ **6** (773 mg, 1.00 mmol), octanoyl chloride (1.60 g, 9.80 mmol), triethylamine (1.51 g, 15.0 mmol) and DMF (2.0 mL) gave **7** (1.60 g, 90%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3296, 3089, 1650, 1553 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 0.93 (t, J = 6.60, CH_3), 1.20-1.42 (m, CH_2), 1.43-1.81 (m, $NCH_2CH_2CH_2NCO$, $NCH_2CH_2CH_2N$ and $NHCOCH_2CH_2$), 2.20 (t, $NHCOCH_2$), 2.40 (m, $CH_2N(CH_2)_2$), 3.24 (q, CH_2NHCO), 6.92 (br, $NHCO$); ^{13}C NMR ($CDCl_3$, δ): 13.92 (alkyl C1), 22.47 (alkyl C2), 25.78 ($NCH_2CH_2CH_2NH$), 26.83 (alkyl C6), 28.94 (alkyl C5), 29.24 (alkyl C4), 31.62 (alkyl C3), 36.57 (alkyl C7), 37.68 ($NCH_2CH_2CH_2NH$), 51.40 ($NCH_2CH_2CH_2NH$), 52.92 ($NCH_2CH_2CH_2N$), 173.81 (C=O); MS (ESI) calcd for $C_{104}H_{208}N_{14}O_8$ 1781.63, found: 1783.6 $(M+H)^+$, 892.4 $(M+2H)^{2+}$, 595.2 $(M+3H)^{3+}$.

G_2(An8) (8). By the procedure for **G_4(An32) (3)**, compound **7** (800 mg, 0.448 mmol), THF (40 mL) and $LiAlH_4$ (380 mg, 10.0 mmol) gave **8** (680 mg, 91%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3298, 1475, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.86 (t, J = 6.73, CH_3), 1.18-1.39 (m, CH_2), 1.38-1.72 (m, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$), 2.30-2.51 (m, $CH_2N(CH_2)_2$), 2.52-2.72 (m, CH_2NH); ^{13}C NMR ($CDCl_3$, δ): 13.96 (alkyl C1), 22.54 (alkyl C2), 24.39 ($NCH_2CH_2CH_2N$), 24.99 ($NCH_2CH_2CH_2CH_2N$), 27.36 (alkyl C6 and $NCH_2CH_2CH_2NH$), 29.18 (alkyl C5), 29.47 (alkyl C4), 30.12 (alkyl C7), 31.73 (alkyl C3), 48.74 ($NCH_2CH_2CH_2NH$), 50.23 (alkyl C8), 52.24 ($NCH_2CH_2CH_2NH$), 54.22 ($NCH_2CH_2CH_2N$); MS (ESI) calcd for $C_{104}H_{224}N_{14}$ 1669.80, found: 1672.0 $(M+H)^+$, 836.4 $(M+2H)^{2+}$, 557.6 $(M+3H)^{3+}$.

G_2(TAm8) (9). By the procedure for **G_4(TAm32) (4)**, compound **8** (600 mg, 0.36 mmol), 2-[2-(2-methoxyethoxy)ethoxy]acetyl chloride (845 mg, 4.30 mmol), DMF (3.0 mL) and triethylamine (445 mg, 4.40 mmol) gave **9** (806 mg, 76%) as a yellow thick oil. IR (film on NaCl) ν_{max}: 1652, 1475, 1106 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.94 (m, CH_3), 1.25 (br, CH_2), 1.42-1.78 (m, CH_2CH_2NCO, $NCH_2CH_2CH_2N$), 2.40 (br, $NCH_2CH_2CH_2N$), 3.23-3.32 (m, CH_2NCO), 3.39 (s, CH_3O), 3.50-3.81 (m, OCH_2CH_2), 4.22 (s, $NCOCH_2O$); ^{13}C NMR ($CDCl_3$, δ): 13.96 (alkyl C1), 22.50 (alkyl C2), 24.22 and 24.93 ($NCH_2CH_2CH_2N$), 26.45 and 26.80 ($NCH_2CH_2CH_2NCO$), 26.92 (alkyl C6), 27.45 and 28.91 (alkyl C7), 29.15 (alkyl C5), 29.27 (alkyl C4), 31.66 (alkyl C3), 44.18, 44.74 and 45.48 ($NCH_2CH_2CH_2NCO$), 47.06 (alkyl C8), 51.12 and 52.16 ($NCH_2CH_2CH_2N$), 58.97 (CH_3O), 69.97 ($COCH_2O$), 70.47 (CH_2O), 70.58 (CH_2O), 70.84 (CH_2O), 71.86

($CH_3OCH_2CH_2O$); MS (ESI) calcd for $C_{160}H_{320}N_{14}O_{32}$ 2950.38, found: 1476.8 $(M+2H)^{2+}$, 985.2 $(M+3H)^{3+}$, 738.8 $(M+4H)^{4+}$.

G_2(TAn8) (10). By the procedure for **G_4(TAn32) (5)**, compound **9** (660 mg, 0.224 mmol), THF (20 mL) and $LiAlH_4$ (102 mg, 2.68 mmol) gave **10** (584 mg, 92%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1473, 1118 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.86 (t, J = 6.66, CH_3CH_2), 1.2 (br, CH_2), 1.32-1.52 (m, $NCH_2CH_2CH_2N$), 2.30-2.51 (m, $NCH_2CH_2CH_2N$), 2.62 (t, NCH_2CH_2O), 3.36 (s, CH_3O), 3.52 (m, OCH_2CH_2O), 3.62 (m, NCH_2CH_2O and OCH_2CH_2O); ^{13}C NMR ($CDCl_3$, δ): 14.06 (alkyl C1), 22.55 (alkyl C2), 24.40 ($NCH_2CH_2CH_2N$), 24.93 ($NCH_2CH_2CH_2N$), 26.95 (alkyl C6), 27.47 (alkyl C7), 29.24 (alkyl C5), 29.52 (alkyl C4), 31.76 (alkyl C3), 51.93 (alkyl C8), 52.40, 53.12 (NCH_2), 53.25 (CH_2N), 54.77 (NCH_2CH_2O), 58.97 (CH_3O), 69.81 (NCH_2CH_2O), 70.38 (OCH_2CH_2O), 70.51 (OCH_2CH_2O), 70.60 (OCH_2CH_2O), 71.89 (CH_2OCH_3); MS (ESI) calcd for $C_{160}H_{336}N_{14}O_{24}$ 2838.55, found: 1420.8 $(M+2H)^{2+}$, 947.6 $(M+3H)^{3+}$, 710.8 $(M+4H)^{4+}$, 568.8 $(M+5H)^{5+}$.

G_2(PMI8) (10a). By the procedure for **G_4(PMI32) (5a)**, **10a** was obtained as brown powder. ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.73, CH_3CH_2), 1.16-1.50 (m, CH_2), 1.78 (br, $NCH_2CH_2CH_2N$), 2.52 (br, NCH_3, $NCH_2CH_2CH_2N$ and NCH_2CH_2), 3.38 (s, CH_3O), 3.42-4.32 (m, NCH_2CH_2O, CH_2O); ^{13}C NMR ($CDCl_3$, δ): 13.98, 18.29, 22.47, 22.70, 26.21, 29.03, 31.56, 49.59, 52.20, 59.02, 60.76, 63.22, 64.62, 66.03, 70.17, 70.32, 71.76, 72.49.

G_2(PMCl8) (10b). By the procedure for **G_4(PMCl32) (5b), 10b** was obtained as a light yellow powder. ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.58, CH_3CH_2), 1.21-1.42 (m, CH_2CH_2), 1.60-1.78 (br, $N^+CH_2CH_2CH_2N^+$), 2.58, 3.32 (s, CH_3O), 3.34-4.18 (m,

OCH_2CH_2O, N^+CH_2 and N^+CH_3), 4.22-4.42 (br, $OCH_2CH_2N^+$); ^{13}C NMR ($CDCl_3$, δ): 13.99 (alkyl C1), 17.57 (m), 22.53 (alkyl C2), 26.36 (alkyl C6 and C7), 29.11 (alkyl C4), 29.20 (alkyl C5), 31.67 (alkyl C3), 49.00-51.00 (m, N^+CH_3), 58.90 (CH_3O), 57.10-61.69 (m, N^+CH_2), 64.78 ($N^+CH_2CH_2O$), 70.23 (OCH_2CH_2O), 71.73 (CH_2OCH_3).

G_5(Am64) (12). By the procedure for **G_4(Am32) (2)**, octanoyl chloride (2.30 g, 14.0 mmol), DAB-*dendr*-$(NH_2)_{64}$ **11** (1.00 g, 0.140 mmol), DMF (3.0 mL) and triethylamine (1.60 g, 15.8 mmol) gave 1.98 g (93%) of **12** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3294, 3090, 1650, 1550 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.91 (t, J = 6.60, CH_3), 1.12-1.40 (m, CH_2), 1.42-1.80 (m, $NCH_2CH_2CH_2NCO$, $NCH_2CH_2CH_2N$ and NHCOCH2CH_2), 2.18 (br, $NHCOCH_2$), 2.40 (br, $CH_2N(CH_2)_2$), 3.26 (q, CH_2NHCO), 7.58 (br, *NH*CO); ^{13}C NMR ($CDCl_3$, δ): 14.37 (alkyl C1), 22.90 (alkyl C2), 25.30 ($NCH_2CH_2CH_2NH$), 26.29 and 27.41 (alkyl C6), 28.94 (alkyl C5), 29.44 (alkyl C4), 29.72, 31.99 (alkyl C3), 32.07, 36.84 (alkyl C7), 37.93 and 38.25 ($NCH_2CH_2CH_2NH$), 51.56 ($NCH_2CH_2CH_2NH$), 52.47 ($NCH_2CH_2CH_2N$), 174.06 (C=O).

G_5(An64) (13). By the procedure for **G_4(An32) (3)**, compound **12** (1.95 g, 0.128 mmol), THF (38 mL) and $LiAlH_4$ (660 mg, 17.3 mmol) gave **13** (1.68 g, 91%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3300, 1476, 1135 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.86 (t, J = 6.61, CH_3), 1.18-1.38 (m, CH_2), 1.38-1.70 (m, $NCH_2CH_2CH_2N$, $NCH_2CH_2CH_2$), 2.31-2.50 (m, $CH_2N(CH_2)_2$), 2.51-2.70 (m, CH_2NH); ^{13}C NMR ($CDCl_3$, δ): 13.97 (alkyl C1), 22.56 (alkyl C2), 27.41 (alkyl C6 and $NCH_2CH_2CH_2NH$), 29.21 (alkyl C5), 29.49 (alkyl C4), 30.15 (alkyl C7), 31.74 (alkyl C3), 48.75 ($NCH_2CH_2CH_2NH$), 50.24 (alkyl C8), 52.24 ($NCH_2CH_2CH_2N$).

G_5(TAm64) (14). By the procedure for **G_4(TAm32) (4)**, compound **13** (1.00 g, 0.070 mmol), 2-[2-(2-methoxyethoxy)ethoxy]acetic acid chloride (1.38 g, 7.00 mmol), Et_3N (0.76 g, 7.5 mmol) and DMF (2.0 mL) gave **14** (1.18 g, 69%) as a yellow thick oil. IR (film on NaCl) ν_{max}: 1653, 1476, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.89 (m, CH_3), 1.18-1.42 (br, CH_2), 1.42-1.80 (m, CH_2CH_2NCO, $NCH_2CH_2CH_2N$), 2.39 (br, $NCH_2CH_2CH_2N$), 3.23-3.32 (m, CH_2NCO), 3.38 (s, CH_3O), 3.52-3.80 (m, OCH_2CH_2), 4.20 (s, $NCOCH_2O$); ^{13}C NMR ($CDCl_3$, δ): 14.02 (alkyl C1), 22.55 (alkyl C2), 25.05 ($NCH_2CH_2CH_2N$), 26.50 and 26.84 ($NCH_2CH_2CH_2NCO$), 26.96 (alkyl C6), 27.51 and 28.98 (alkyl C7), 29.30 (alkyl C5), 29.38 (alkyl C4), 31.66 (alkyl C3), 44.18, 44.75 and 45.49 ($NCH_2CH_2CH_2NCO$), 47.06 (alkyl C8), 51.11 and 52.15 ($NCH_2CH_2CH_2N$), 58.97 (CH_3O), 70.01 ($COCH_2O$), 70.47 (CH_2O), 70.58 (CH_2O), 70.85 (CH_2O), 71.86 ($CH_3OCH_2CH_2O$).

G_5(TAn64) (15). By the procedure for **G_4(TAn32) (5),** compound **14** (1.07 g, 0.044 mmol), THF (32 mL) and $LiAlH_4$ (420 mg, 10.6 mmol) gave **15** (0.82 g, 78%) as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1474, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.84 (t, J = 6.66, CH_3CH_2), 1.16-1.36 (m, CH_2), 1.36-1.70 (m, $NCH_2CH_2CH_2N$), 2.30-2.50 (m, $NCH_2CH_2CH_2N$), 2.61 (t, NCH_2CH_2O), 3.34 (s, CH_3O), 3.50 (m, OCH_2CH_2O), 3.62 (m, NCH_2CH_2O and OCH_2CH_2O); ^{13}C NMR ($CDCl_3$, δ): 14.12 (alkyl C1), 22.61 (alkyl C2), 24.58 ($CH_2CH_2CH_2$), 27.09 (alkyl C6), 27.51 (alkyl C7), 29.32 (alkyl C5), 29.58 (alkyl C4), 31.82 (alkyl C3), 51.85 (alkyl C8), 53.30 (CH_2N), 54.75 (NCH_2CH_2O), 58.92 (CH_3O), 69.85 (OCH_2CH_2N), 70.35 (OCH_2CH_2O), 70.46 (OCH_2CH_2O), 70.55 (OCH_2CH_2O), 71.86 (CH_2OCH_3).

2-[2-(2-Methoxyethoxy)ethoxy]acetyl Chloride (16). The acid chloride was prepared by reacting 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (5.34 g, 30.0 mmol) with thionyl chloride (5.95 g, 50.0 mmol) in toluene (3.0 mL) for 4 h at 65 °C. The solvent and excess reagent were removed under reduced pressure, and the residue was dried at 60 °C under vacuum to give a light yellow oil which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, δ): 3.40 (s, CH_3O, 3H), 3.57 (m, OCH_2CH_2O, 2H), 3.63 (m, OCH_2CH_2O, 2H), 3.70 (m, OCH_2CH_2O, 2H), 3.80 (m, OCH_2CH_2O, 2H), 4.52 (s, CH_2OCO, 2H); ^{13}C NMR ($CDCl_3$, δ): 58.91, 70.44, 70.64, 71.17, 71.70, 76.55, 171.97.

Kinetic Experiments and Calculations. The pH of the dendrimer solution was adjusted to 11.4 using aqueous NaOH, and the sample was placed into a polystyrene cuvette and diluted with aqueous NaOH (pH 11.4) to give a 3.0 mL of solution with certain concentration of N^+ units. The solution was allowed to equilibrate to 25.0 °C for 10 min. The substrate 6-nitrobenzisoxazole-3-carboxylic acid in ethanol solution (22 μL of 1.06 x 10^{-2} M solution) was added to produce a 3.0 mL solution with final substrate concentration at 7.82 x 10^{-5} M. Reaction was followed by the average absorbance at 400-430 nm, since the λ_{max} of 2-cyano-5-nitrophenoxide is at 418 nm. The rates were calculated based on the data over the first 25% conversion using the first-order kinetic equation: $k_{obsd} = \ln((A_{inf}-A_0)/(A_{inf}-A_t))/t$, where t represents the time of reaction, and A_0, A_t and A_{inf} represent the absorbance of 2-cyano-5-nitrophenoxide at time 0, t and infinity.

Molecular Dynamics. The 3D structures of the amphiphilic dendrimers were built by means of ChemSketch application (ACD Labs) running on Windows to ensure the reasonable starting conformations and to minimize the possible entanglements of the

chain segments during molecular dynamics. The molecular dynamics were performed on a Silicon Graphics Indigo (SGI) workstation using Insight II and Discovery (3.0.0). The all-atom consistent valent force field (CVFF) was used for the molecular dynamics, and reasonable conformations were obtained by combining a simulated annealing procedure and energy minimization. The calculation of the average distances between the carbon atoms of octyl and TEO chain ends on the same nitrogen atoms were based on the structural data collected from reasonable minimum energy structures. The coordinate values of the interesting atoms in 3D space from the equilibrium conformation were taken from the corresponding PDB (protein data bank) data files.

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CHAPTER III

SYNTHESIS AND CHARACTERIZATION OF DENDRIMERS WITH ALTERNATING AMINE AND ETHER GENERATIONS

ABSTRACT

Polyamine dendrimers having up to sixteen bis(2-methoxyethyl)amine end groups and four internal tertiary amines were synthesized. The aryl benzyl ether generations were constructed by Willamson ether synthesis, and the tertiary amine generations were created by the amidation of secondary amines with carboxylic acid chlorides followed by $LiAlH_4$ reductions. These 'hybrid' globular macromolecules consists of both hydrophilic and hydrophobic moieties, and the two distinct moieties alternate from the core toward the surface. The structures of the intermediates and final products were characterized by ^1H, ^{13}C NMR, FT-IR and ESI-MS analysis.

The hybrid amphiphilic dendrimers were soluble in both common organic solvents and aqueous buffer solutions up to pH 4.7. The microenvironment of the hydrophobic interior of the bis(2-methoxyethyl)amine-terminated polyamine dendrimers was probed by solubilizing pyrene in the aqueous solution of the dendrimer at pH 3.0. The limiting solubility of pyrene is 2.50×10^{-5} M as measured by UV-vis absorption spectroscopy, which is nearly 31 times higher than the concentration in pure water (8×10^{-7} M).

INTRODUCTION

Since the pioneering syntheses of Tomalia,[1] Newkome,[2] and Fréchet,[3] many different types of dendritic macromolecules have been synthesized.[4] Dendritic macromolecules having amphiphilic unimolecular micelle structures may be valuable for molecular encapsulation and catalysis.[5] Their polar end groups control solubility, and their less polar cores and branching units can solvate hydrophobic molecules.[6] Carboxylic acid terminated dendrimers serve as micelle substitutes for the separation of parabens via electrokinetic capillary chromatography.[7] The internal volume of eight carboxylic acid terminated poly(amidoamine) (PAMAM) dendrimer provided confined sites for the polymerization of lipophilic monomers in aqueous solution.[8] Dendrimers with terminal ammonium salts and long all-hydrocarbon core and branching units trap lipophilic guest molecules such as diphenylhexatriene, naphthalene and dyes in aqueous solutions.[9] Carboxylic acid terminated PAMAM dendrimers having a long aliphatic chain in the core host hydrophobic dyes in aqueous solution.[10] Dendritic unimolecular micelles, unlike dynamically aggregated surfactant micelles, retain their colloid structure no matter how dilute the solution, and can solubilize organic solutes regardless of the pH, temperature and ionic strength of the solution. These unique properties of dendrimers may enable applications in the areas of drug delivery, membrane transport and catalysis.[11]

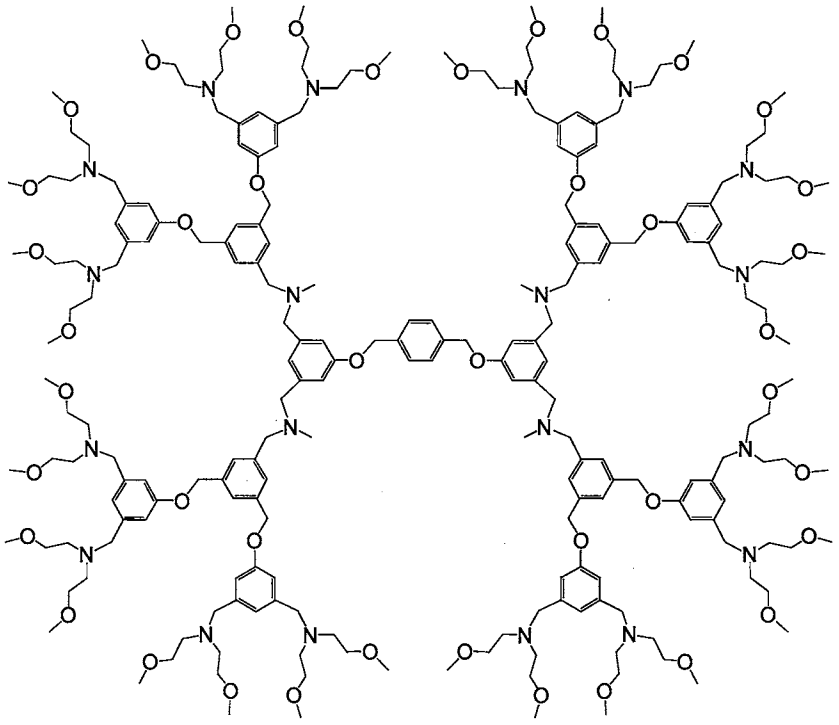
The cores and branch parts as well as the end groups of a dendrimer can be reactive functional groups. The widely investigated poly(propylene imine) (PPI) and polyamidoamine (PAMAM) dendrimers have internal tertiary amines with a variety of functionalities on the chain ends. Both the PPI and PAMAM are prepared by repetitive

conjugate addition of a primary amine to acrylonitrile or methyl acrylate, followed by conversion to primary amines via hydrogenation of the resulting nitriles,[11] or by amidation of the methyl esters with excess ethylenediamine.[13] The preparation of polyamine dendrimers by the reduction of amides is rare,[14] although the amide connectivity is highly useful in dendrimer synthesis because of its chemical stability and because many high yield amidation methods are available from synthesis of polyamides and polypeptides.[15]

Our aim with amine dendrimers is to evaluate their potential as catalysts of reactions in aqueous solutions. Nonpolar organic compounds will partition into the less polar interiors of the dendrimers. Primary and tertiary amine end groups and tertiary amine branch points can serve as ligands for metal ion complexes. Conversion of the tertiary amines to quaternary ammonium ions gives compact polyelectrolyte structures that bind counterions as reagents or catalysts. In our first study of dendrimer catalysis the activity of a terminal quaternary ammonium dendrimer with no internal active sites and little free volume was much less than that of poly[(styrylmethyl)trialkylammonium] latexes for decarboxylation of 6-nitrobenzisoxazole-3-carboxylate and for *o*-iodosobenzoate-catalyzed hydrolysis of *p*-nitrophenyl diphenyl phosphate.[16]

Here we report the synthesis of dendrimers with both terminal and internal tertiary amines. An example is dendrimer **1** which has sixteen bis(2-methoxyethyl)amine end groups. This 'hybrid' globular macromolecule consists of both hydrophilic and hydrophobic generations, and the two distinct moieties alternate from the core toward the surface of the globular macromolecules. The structure is analogous to *layer block*

copolymers and may solubilize lipophilic molecules inside the multiple hydrophobic layers. Such structures cannot be obtained from dynamically aggregated surfactants.



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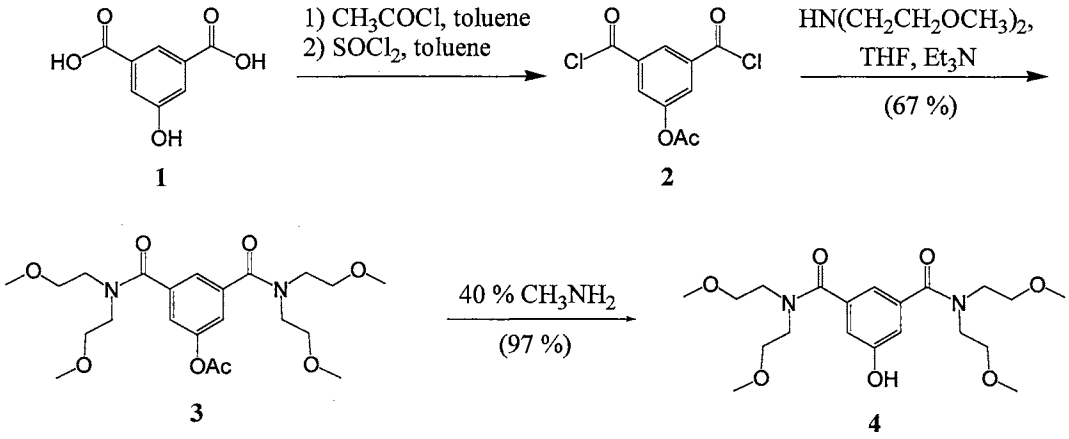
RESULTS AND DISCUSSION

The overall strategy for the syntheses of **1** and related dendrimers with alternating ether and amine generations is based on the construction of ether layers using the Williamson ether synthesis, amidation and formation of tertiary amines by reduction of amides of secondary amines. The outer layer of end groups and terminal branches of a dendrimer count for at least half of the mass and are the interface between dendrimer and medium that mainly determines its solubility.

Bis(2-methoxyethyl)amine Terminated Dendron. Polyamides frequently are insoluble in common organic solvents, and so highly solubilizing bis(2-methoxyethyl)amine and amide end groups were used throughout. The amide terminated dendron **4** was synthesized by the method of Scheme 1.

Scheme 1. Synthesis of monomer **4** from compound **1**

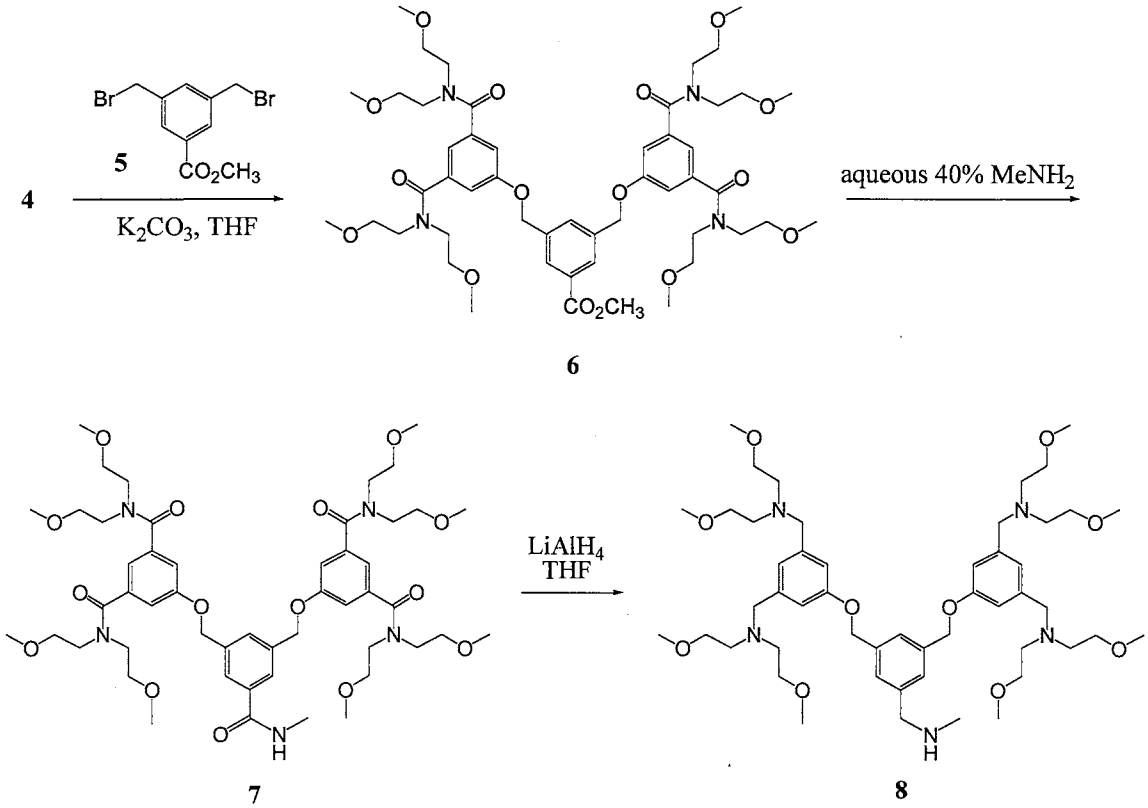


The hydroxyl group of 5-hydroxyisophthalic acid was protected using acetyl chloride, and the two carboxylic acid groups were converted to acid chlorides using thionyl chloride to give **2**. The crude product **2** was treated with bis(2-methoxyethyl)amine to form dendron **3,** and the protecting group of **3** was subsequently removed by aqueous methylamine to give the corresponding phenol **4**.

Branching monomer **5** was prepared by *N*-bromosuccinimide (NBS) bromination of methyl 3,5-dimethylbenzoate in 60% yield.[17] The syntheses of the amide terminated amide dendron **7** and the amine terminated amine dendron **8** are shown in Scheme 2. Ester **6** was synthesized by etherification of two equivalents of phenol **4** with one equivalent of dibromide **5**, and was converted to amide **7** using 40% aqueous $MeNH_2$.

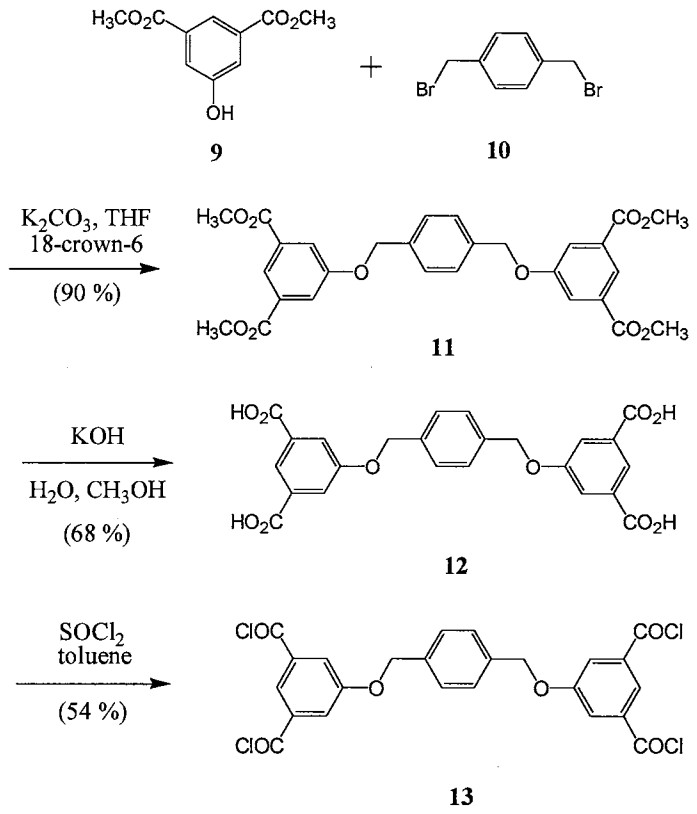
Both the terminal and the focal amide groups of **7** were converted to amine groups by $LiAlH_4$ in THF to give amine **8** in 91% yield. The secondary amine formed at the focal point of **8** becomes the site for subsequent coupling reactions (Scheme 2). The bis(2-methoxyethyl)amine groups were stable to the conditions of both amidation and $LiAlH_4$ reduction, and they may even serve as proton acceptors in the coupling of polyamine dendrons with the core units.

Scheme 2. Synthesis of dendron **8**



Tetraacid chloride **13** was synthesized as shown in Scheme 3. Two equivalents of dimethyl 5-hydroxyisophthalate (**9**) and one equivalent of α,α'-dibromo-*p*-xylene (**10**) gave tetraester **11**, which was hydrolyzed to tetraacid **12** and converted to acid chloride **13** by reaction with thionyl chloride in toluene (Scheme 3).[18]

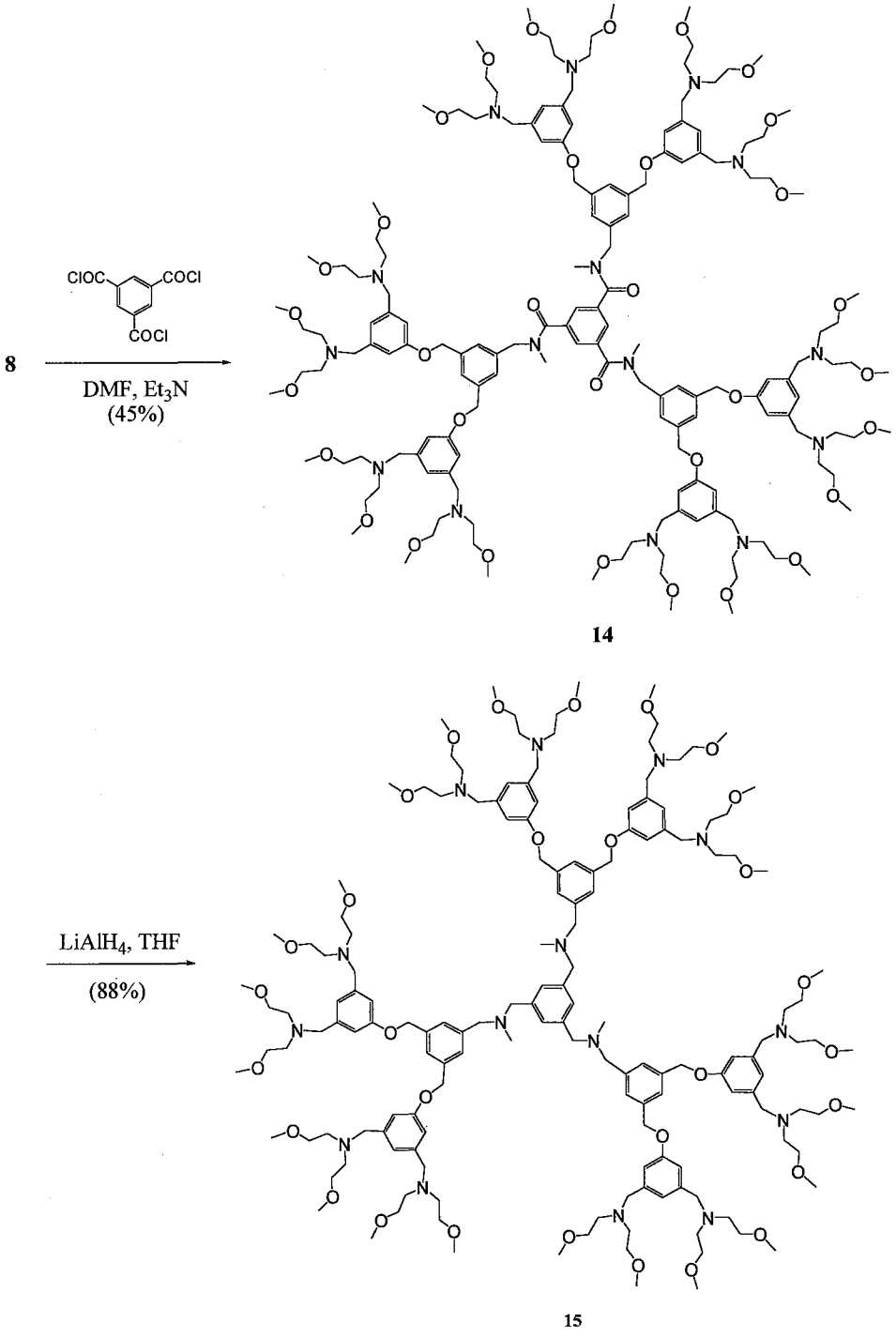
Scheme 3. Synthesis of the core unit.



Coupling of Dendrons to Cores. Internal amide groups in the layer block dendrimers were formed by amidation of carboxylic acid chloride cores, and were reduced to tertiary amines. The terminal amides were directly converted to tertiary amines in the dendron *prior to* the formation of the dendrimers. Thus amine **8** reacted with benzene-1,3,5-tricarboxylic acid chloride in DMF to give dendrimer **14** in 45% isolated yield as shown in Scheme 4. The relatively low yield resulted from the difficulty in separating **14** from excess starting material **8**. The two compounds tailed during chromatography on normal silica gel. Dendrimer **14** was purified using preparative silica gel plates pretreated with trimethylamine, and purity was confirmed by NMR, ESI-MS,

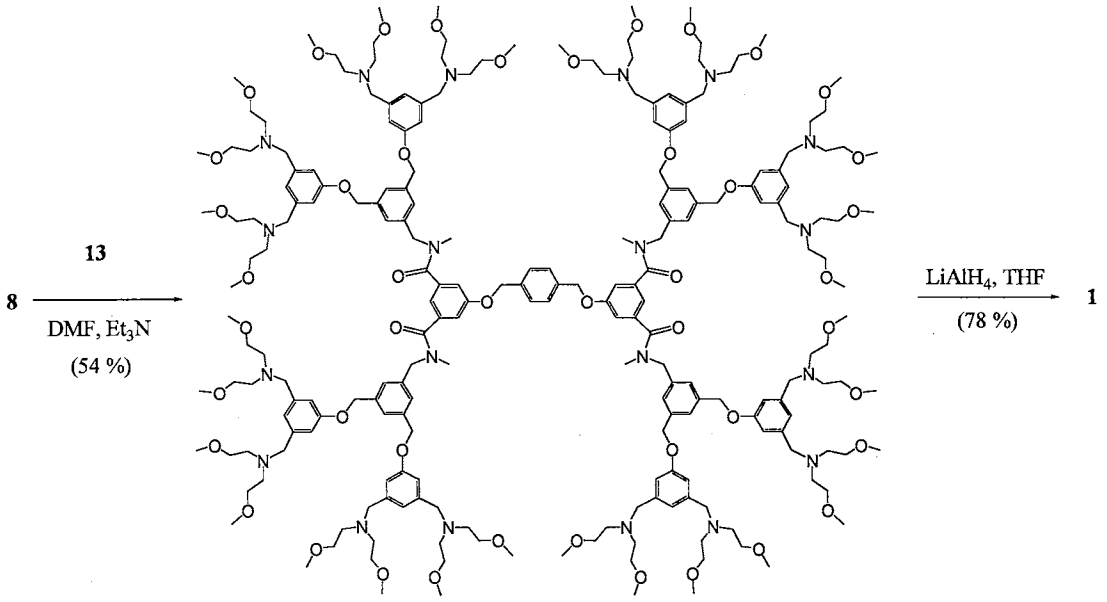
TLC and HPLC analysis. The reduction of **14** by $LiAlH_4$ in THF gave the polyamine dendrimer **15** in 88% yield (Scheme 4).

Scheme 4. Synthesis of polyamine dendrimer **15**



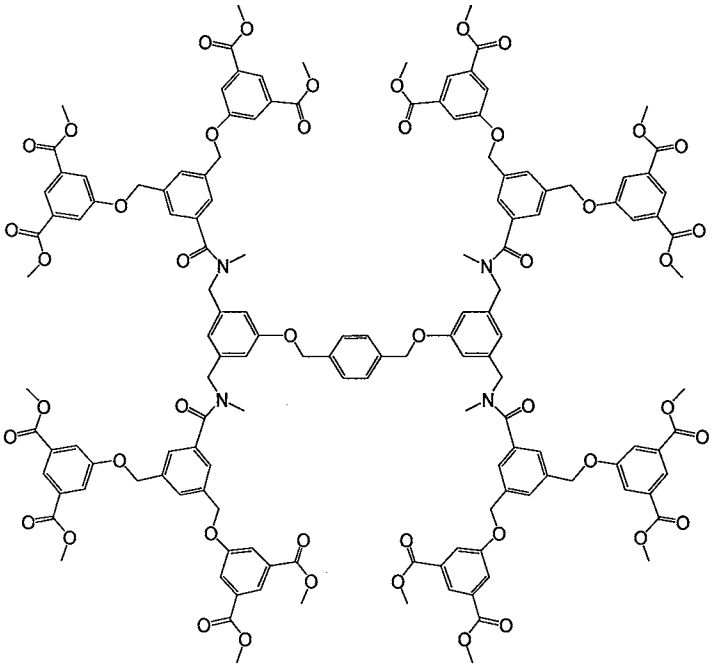
Dendrimer **16** with sixteen terminal tertiary amine groups was prepared using the reaction of excess of amine **8** with the core unit **13** in DMF. The amide-amine **16** was purified using preparative silica gel plates pretreated with trimethylamine, and the internal polyamide groups were reduced to the internal polyamine groups by $LiAlH_4$ to afford the polyamine dendrimer **1** (Scheme 5).

Scheme 5. Synthesis of polyamine dendrimer **1**



Other Approaches to Alternating Amide-Ether Dendrimers. Some other approaches to terminal amide functionality gave low yields or separation difficulties. Reactions of the 16-methyl esters dendrimer **17** with methylamine and benzylamine gave secondary terminal amides in good yield, but the amide dendrimers were soluble only in DMF and DMSO, and attempts to use borane or $LiAlH_4$ to reduce the polyamides to polyamines were not successful due to their poor solubility in THF and dioxane and the formation of insoluble gel-like materials. The poor solubility of the MeNHCO- amide-

terminated dendrons and dendrimers in common organic solvents excluded them from being use feasible synthetic building blocks or targets because there is no suitable way to purify and react those products subsequently.



17

Amidations of the terminal ester groups of **17** with secondary amines suffered from incomplete conversions even at elevated temperature and with NaCN as a catalyst. Therefore, a suitable terminal must be placed into the building block of the shell units at the very beginning of the convergent synthesis. This is the strategy used in this study for the synthesis of the amphiphilic dendrimers with alternating generations.

Characterization. The polyamine dendron **8** and dendrimers **14-16** and **1** were characterized by IR, ^{1}H and ^{13}C NMR, and ESI-MS. LSI-MS analysis was used for amide dendrons and monomers. Purities were analyzed by TLC and HPLC. FT-IR was very useful for determining the completeness of the amidations from the disappearance of the carbonyl chloride absorbance of the core units, and for determining the completeness of

$LiAlH_4$ reduction from the disappearance of amide bond absorbance in the region of 1640-1650 cm^{-1} (Figure 1).

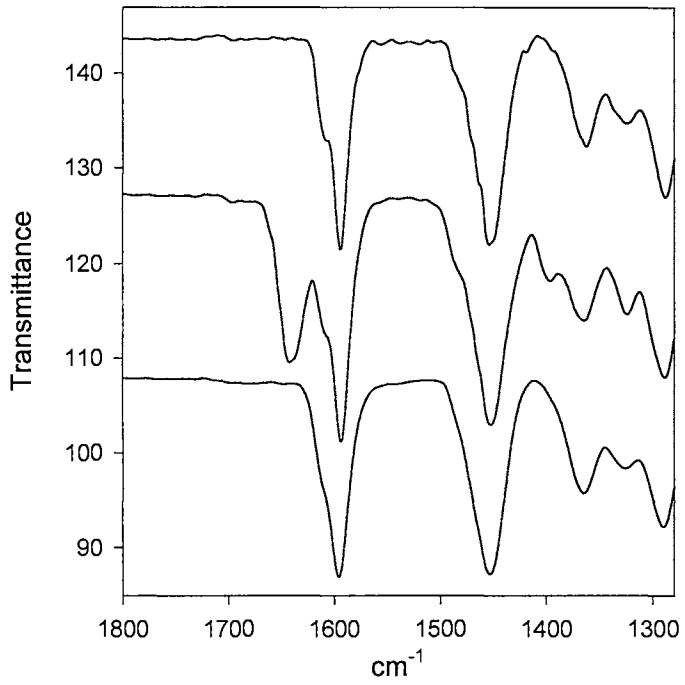


Figure 1. FT-IR spectra of polyamine dendron **8** (top), polyamine/polyamide dendrimer **16** (middle) and polyamine dendrimer **1** (bottom).

NMR analysis was of little use for the characterization of the aromatic tertiary amide dendrimers because each amide group exists in two conformations due to slow rotation about the carbonyl C-N bond, and each conformation gives its own spectrum (Chapter IV). However, the NMR spectra of the polyamine dendrimers were much clearer, the ^1H

NMR spectra of the interior amide dendrimer **16** and the wholly polyamine dendrimer **1** are compared in Figure 2.

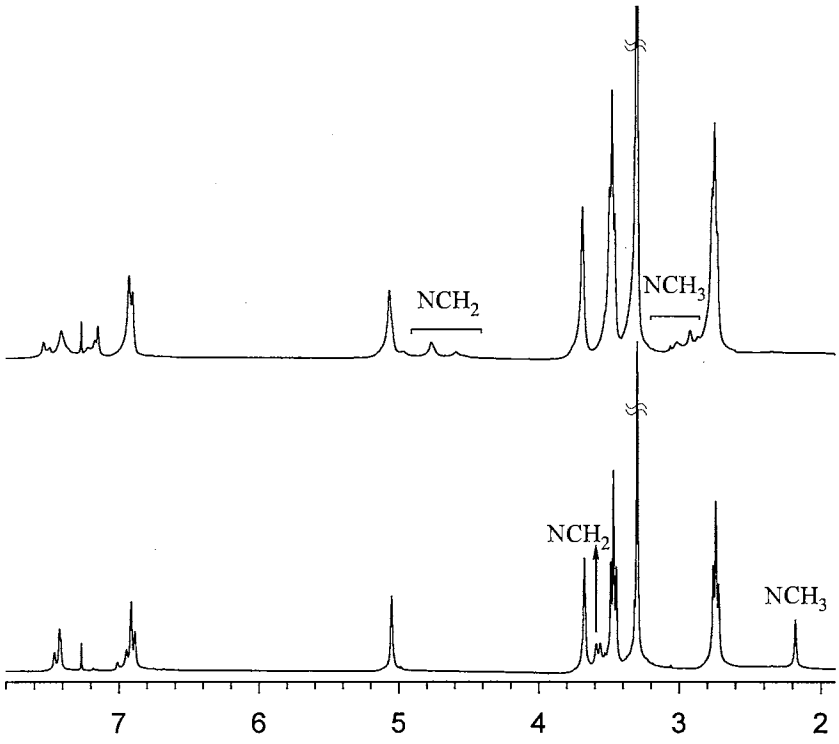


Figure 2. 400 MHz ^{1}H NMR spectra of the polyamine/polyamide dendrimer **16** (top) and the polyamine dendrimer **1** (bottom).

The ESI-MS spectrum of dendron **8** from water/acetonitrile/acetic acid (50:50:0.5) predominantly contained $(M+H)^{+}$ and $(M+2H)^{+}$ ions, while the spectra of dendrimers **14-16** and **1** mainly contained ions with 2+ to 7+ charge in which one charge was due to

sodium or potassium and the rest were due to protons. These data indicate that the desired dendron and dendrimers are the predominant species in the samples. The ESI-MS of dendrimers **14** and **16** showed no peaks from the starting material **8**.

Solubility of the Dendrimers. The bis(2-methoxyethyl)amine terminated polyamide and polyamine dendrimers are readily soluble in toluene, ether, THF, chloroform, acetone, MeOH, and DMF. The solubility of the dendrimers in organic solvent is essential for the synthesis and purification. The good solubility in toluene indicates that dendrimer **1** and **15** are compatible with lipophilic materials. Dendrimers **1** and **15** are also soluble in aqueous buffer solutions at pH 4.74. Both the amphiphilic bis(2-methoxyethyl)amine end groups and the protonation of the tertiary amine units determine the solubility of the polyamine dendrimers possessing internal hydrophobic moieties in acidic aqueous solution. The lipophilic compatability and the solubility in aqueous solution are desired properties for the potential application of the polyamine dendrimers as unimolecular micelles and homogeneous catalysts.

Measurement of Unimolecular Micellar Behavior. The amphiphilic dendrimers are expected to be able to host lipophilic substrates from aqueous solution because of the large hydrophobic moieties in the first and third generations. For dendrimer **1,** pyrene and methylnaphthalene were used to determine its ability to host lipophilic substrates in aqueous solution at pH 3.0. A clear solution was obtained after the introduction of pyrene or methylnaphthalene, while an introduction of the same amount of pyrene or methylnaphyhalene into pure water resulted in a cloudy solution or even precipitation.

The microenvironment of the hydrophobic interior of the bis(2-methoxyethyl)amine terminated polyamine dendrimers was probed by solubilizing pyrene in aqueous solution

at pH 3.0. Figure 3 shows the UV-vis absorption of pyrene in aqueous solution of dendrimer **1,** and the absorption is compared with those of pyrene in aqueous cetyltrimethylammonium chloride (CTAC) solution and in pure ethanol. It can be seen that the UV-vis absorption of pyrene in an aqueous solution of dendrimer **1** is similar to that in aqueous CTAC, which implies that the lipophilic microevironment in the hydrophobic generations of dendrimer **1** is quite close to that of CTAC.

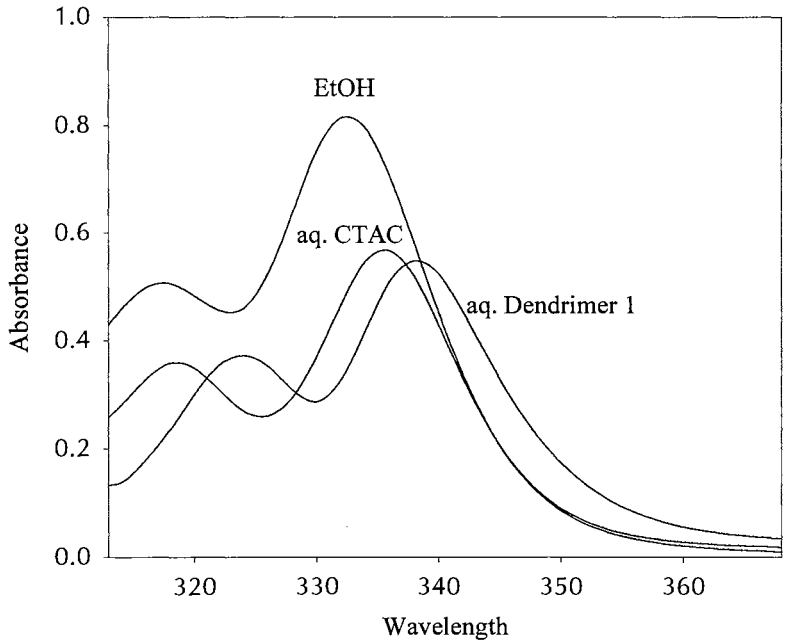


Figure 3. UV-vis absorption spectra of pyrene in aqueous solution of dendrimer **1**, CTAC and pure ethanol.

The limiting solubility of pyrene (2.50×10^{-5} M) in aqueous dendrimer **1** (2.80×10^{-3} M) as measured by UV-vis absorption spectroscopy is nearly 31 times higher than the

concentration in pure water (8 x 10^{-7} M).[19] The UV-vis absorption spectra of pyrene with increasing pyrene concentration in dendrimer **1** were recorded and the absorption obeys Beer's Law when concentration of pyrene is below the limiting solubility (2.31 x 10^{-5} M) (Figure 4). The linearity in the plot of absorbance at λ_{max} versus concentration of pyrene suggests that pyrene remains within the hydrophobic interior of the dendrimer in accordance with Beer's law. The λ_{max} values are concentration-independent, which implies a lack of pyrene aggregation in the aqueous solution.

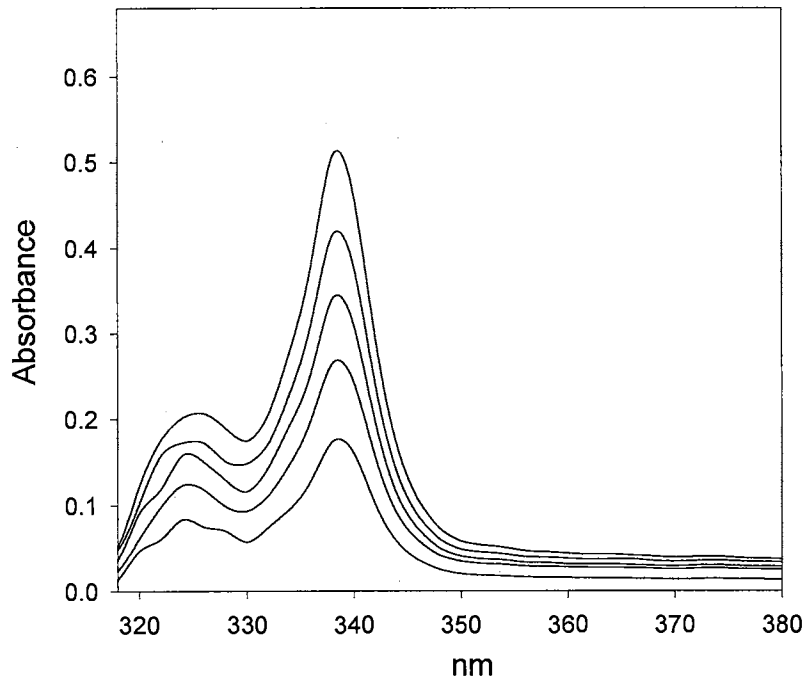


Figure 4. UV-vis absorption spectra of pyrene in 2.80 x 10^{-3} M aqueous dendrimer **1** at pH 3.0 with increasing pyrene concentration (0.77, 1.16, 1.54, 1.92 and 2.31 x 10^{-5} M).

EXPERIMENTAL SECTION

All starting materials were from Aldrich and were used as received unless otherwise stated. THF was freshly distilled from sodium. Pyridine and triethylamine were dried over 3 Å molecular sieves and freshly distilled. All glassware was dried at 200 °C before use. ^{1}H NMR spectra at 400 or 300 MHz NMR spectra and ^{13}C NMR spectra at 100 or 75 MHz were recorded with the solvent proton signal as the reference. Liquid secondary ion mass spectra (LSIMS) were obtained on a ZAB-SE2 spectrometer using 25 keV primary Cs^{+} ion beam and 3-nitrobenzyl alcohol matrix. Electrospray mass spectra were acquired on a PE/Sciex API-III Quadra 950 triple quadrupole biomolecular mass analyzer equipped with an atmospheric pressure ion source, and positive ions produced from a pneumatically assisted electrospray interface using the samples in water, acetonitrile or methanol and acetic acid (50:50:0.5) solutions; ions were analyzed by scanning the first quadrupole in 0.2 amu increments. Calculated *m/z* values are for the lowest isotopomers. Analytical TLC was performed on Kodak thin-layer chromatography plates with silica gel GF_{254}. Preparative TLC was performed on Aldrich silica gel GF plates (1000 μm thick), and the plates were pre-developed with 2% trimethylamine in CH_2Cl_2 and activated at 60 °C for 6 h. Baker silica gel (40 μm) was used for flash chromatography. HPLC was carried out with a reversed phase C_{18} column, UV detection at 350 nm and MeOH/$CHCl_3$ (50:50) as the solvent. UV-vis spectra were measured using a Hewlett-Packard model 8452A diode array spectrophotometer in 1.00 cm polystyrene cells.

5-Acetoxy-1,3-bis[*N,N*-di(2-methoxyethyl)]benzenedicarboxamide (3). A mixture of 6.01 g (33.0 mmol) of 5-hydroxyisophthalic acid, 10.80 g (138.0 mmol) of acetyl chloride and 10 mL of toluene was stirred under reflux for 6 h. Thionyl chloride (11.0 g, 92.0 mmol) was added, the mixture was stirred for 7 h under reflux, and was concentrated under reduced pressure. The oily residue **2** was dissolved in 10 mL of THF. A solution of 9.06 g (68.0 mmol) of bis(2-methoxyethyl)amine in 15 mL of THF and 8.10 g (80.0 mmol) of triethylamine were added slowly with stirring at 0 °C, and the mixture was stirred for 30 min at 0 °C and 4 h at room temperature, added to 30 mL of water, extracted with $CHCl_3$ (2 × 50 mL), washed with water, dried ($MgSO_4$), and evaporated to a light yellow oil, which was purified by column chromatography (SiO_2, MeOH/$CHCl_3$ 2:98) to give 10.11 g (67%) of **3** as a thick oil. IR (film on NaCl) ν_{max}: 1738, 1638, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.36 (s, 3H), 3.31 (d, 12H), 3.35-3.80 (m, 16H), 7.22 (s, 2H), 7.40 (s, 1H); ^{13}C NMR ($CDCl_3$, δ): 20.34, 44.70, 49.09, 58.22, 69.65, 70.14, 120.75, 122.46, 137.48, 149.58, 168.09, 169.77; MS (LSI) calcd for $C_{22}H_{34}N_2O_8$ 454.23, found 455 $(MH)^+$.

5-Hydroxy-1,3-bis[*N,N*-di(2-methoxyethyl)]benzenedicarboxamide (4). Acetate **3** (10.00 g, 22.00 mmol), 10 mL of methanol, and 20 mL of 40% aqueous $MeNH_2$ were stirred for 8 h at room temperature. The mixture was concentrated on a rotary evaporator, acidified to pH 4-5 using 2% aqueous HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4), and evaporated to give 9.70 g (97%) of **4** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 3195, 1638, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.34 (d, 12H), 3.35-3.78 (m, 16H), 6.82 (s, 2H), 6.85 (s, 1H), 8.58 (br, 1H);

^{13}C NMR ($CDCl_3$, δ): 44.63, 49.40, 58.00, 69.73, 70.33, 120.80, 122.25, 137.80, 149.75, 168.01; MS (LSI) calcd for $C_{20}H_{32}N_2O_7$ 412.22, found 413 $(MH)^+$.

Methyl 3,5-bis(bromomethyl)benzoate (5). White solid; mp 91-93 °C (lit. mp 92-93 °C);[17a] IR (film on NaCl) ν_{max}: 1730, 1438, 1317, 1231, 776, 705, 698 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.92 (s, 3H), 4.50 (s, 4H), 7.59 (s, 1H), 7.93 (t, 2H); ^{13}C NMR ($CDCl_3$, δ): 52.10, 81.74, 129.82, 133.27, 133.40, 138.70, 164.50; MS (LSI) calcd for $C_{10}H_{10}Br_2O_2$ 321.99, found 323 $(MH)^+$.

Ester 6. A solution of 3.34 g (8.10 mmol) of phenol **4**, 1.30 g (4.04 mmol) of bromide **5**, and 1.66 g (12.0 mmol) of K_2CO_3 in 38 mL of THF was stirred under nitrogen at 65 °C for 24 h. The mixture was concentrated and water (20 mL) was added. The mixture was extracted with $CHCl_3$, washed with 1% aqueous Na_2CO_3 and water, and dried ($MgSO_4$). Flash chromatography (MeOH/$CHCl_3$, 2:98) afforded 3.03 g (77%) of **6** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1730, 1638, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.34 (d, 24H), 3.35-3.78 (m, 32H), 3.95 (s, 3H), 5.18 (s, 4H), 7.08 (s, 2H), 7.12 (s, 4H), 7.72 (s, 1H), 8.08 (s, 2H); ^{13}C NMR ($CDCl_3$, δ): 45.37, 49.86, 52.49, 59.02, 69.61, 70.54, 70.94, 114.60, 118.49, 128.40, 130.76, 131.21, 137.62, 138.52, 158.38, 166.59, 171.22; MS (LSI) calcd for $C_{50}H_{72}N_4O_{16}$ 984.49, found 985 $(MH)^+$.

Amide 7. A solution of 3.20 g (3.25 mmol) of ester **6** in 6 mL of methanol and 18 mL of 40% aqueous $MeNH_2$ was stirred at room temperature for 24 h. The mixture was concentrated, acidified to pH 4 using 2% aqueous HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4), concentrated, and flash chromatographed (MeOH/$CHCl_3$, 2:98) to give 2.12 g (71%) of **7** as a colorless thick oil.

IR (film on NaCl) ν_{max}: 3359, 1637, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.96 (d, 3H), 3.34 (d, 12H), 3.35-3.78 (m, 16H), 5.18 (s, 4H), 7.18 (6H), 7.59 (s, 1H), 7.82 (s, 2H); ^{13}C NMR ($CDCl_3$, δ): 26.51, 44.93, 49.39, 58.56, 69.32, 70.07, 70.45, 114.31, 118.01, 125.63, 128.70, 135.40, 137.09, 138.05, 157.94, 167.22, 170.77; MS (LSI) calcd for $C_{50}H_{73}N_5O_{15}$ 983.51, found 984 $(MH)^+$.

Amine 8. A suspension of 98 mg (2.6 mmol) of $LiAlH_4$ and 16 mL of THF under nitrogen was cooled to 0 °C, and 998 mg (1.01 mmol) of **7** in 4 mL of THF was added slowly with stirring at 0 °C. The mixture was stirred at 70 °C for 24 h, cooled, and slowly poured into 20 mL of saturated aqueous Na_2SO_4 solution at 0 °C. The mixture was acidified to pH 1 using 6 M aqueous HCl, washed with ether (2 × 5 mL), added to 10 M aqueous NaOH to pH 12, and extracted with ether (3 × 15 mL). The organic solution was washed with water, dried (K_2CO_3), evaporated, and dried under vacuum to give 722 mg (80%) of **8** as a thick oil. IR (film on NaCl) ν_{max}: 1593 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.76 (t, 16H), 3.34 (s, 24H), 3.48 (t, 16H), 3.68 (s, 5.18 (s, 4H), 7.18 (6H), 7.59 (s, 1H), 7.82 (s, 2H); ^{13}C NMR ($CDCl_3$, δ): 26.51, 44.93, 49.39, 58.56, 69.32, 70.07, 70.45, 114.31, 118.01, 125.63, 128.70, 135.40, 137.09, 138.05, 157.94, 167.22, 170.77; MS (ESI) calcd for $C_{50}H_{83}N_5O_{10}$ 913.61, found 914.8 $(MH)^+$, 457.9 $(M+2H)^{2+}$.

Tetramethyl 5,5'-[1,4-phenylenebis(methyleneoxy)]diisophthalate (11). A mixture of 2.10 g (10.0 mmol) of dimethyl 5-hydroxyisophthalate (**9**), 1.29 g (4.90 mmol) of α,α'-dibromo-*p*-xylene (**10**), 2.21 g (16.0 mmol) of K_2CO_3, 0.10 g of 18-crown-6, and 38 mL of THF was stirred under nitrogen at 65 °C for 24 h. The mixture was concentrated, and 1% aqueous Na_2CO_3 (20 mL) was added at 0 °C. The solid was collected, washed

with water and ether, and dried under vacuum at 50 °C to give 2.31 g (90%) of **11** as a white powder; mp 186-188 °C; IR (KBr) ν_{max}: 1730, 1602, 1459, 1346, 1246, 1040, 755 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.96 (s, 12H), 5.19 (s, 4H), 7.28 (s, 4H), 7.82 (s, 4H), 8.32 (s, 2H); ^{13}C NMR ($CDCl_3$, δ): 52.40, 70.08, 120.22, 123.38, 127.95, 131.94, 136.25, 158.83, 166.23; MS (LSI) calcd for $C_{28}H_{26}O_{10}$ 522.15, found 523 $(MH)^+$.

5,5'-[1,4-Phenylenebis(methyleneoxy)]diisophthalic Acid (12). A solution of 1.02 g (1.95 mmol) of ester **11**, 10 mL of methanol, 450 mg (8.02 mmol) of KOH, and 10 mL of water (10 mL) was stirred under nitrogen at 50-60 °C for 48 h. The mixture was concentrated, and 6 M aqueous HCl was added slowly at 0 °C. The precipitate was collected, washed with water, and dried under vacuum to give 0.62 g (68%) of acid **12** as a white solid. IR (KBr) ν_{max}: 3500-2500, 1708, 1602 cm^{-1}; ^1H NMR (DMSO-d_6, δ): 5.29 (s, 4H, CH_2O), 7.58 (s, 4H), 7.81 (s, 4H), 8.18 (s, 2H), 13.40 (br, 4H);[18] ^{13}C NMR (DMSO-d_6, δ): 65.30, 115.43, 118.43, 123.79, 128.60, 132.27, 154.49, 162.38.

5,5'-[1,4-Phenylenebis(methyleneoxy)]diisophthalic Acid Chloride (13). A mixture of 400 mg (0.850 mmol) of acid **12**, 4 mL of toluene, and 4 mL of $SOCl_2$ was stirred under nitrogen at 70-75 °C for 48 h. The precipitate was collected, washed with ether (2 × 3 mL), and dried under vacuum to give 250 mg (54%) of **13** as a light yellow solid; mp 189-192 °C; IR (KBr) ν_{max}: 1765, 1597, 1304, 681 cm^{-1}; ^1H NMR (DMSO-d_6, δ): 5.25 (s, 4H, CH_2O), 7.58 (s, 4H), 7.78 (s, 4H), 8.10 (s, 2H); ^{13}C NMR (DMSO-d_6, δ): 65.49, 119.64, 122.60, 127.97, 132.74, 136.46, 166.49.

Dendrimer 14. To a solution of 645 mg (0.706 mmol) of amine **8** in 4.0 mL of DMF, 60 mg (0.23 mmol) of 1,3,5-benzenetricarboxylic acid chloride and 63 mg (0.80 mmol)

of pyridine were added, and the mixture was stirred under nitrogen at 60 °C for 24 h. The DMF was removed under reduced pressure. The residue was dissolved in 1.5 M aqueous HCl, washed with ether (2 × 5 mL), and aqueous 5 M NaOH was added slowly at 0 °C to pH 11. The aqueous mixture was extracted with ether (3×10 mL), and the combined organic solution was washed with water, dried (K_2CO_3), and concentrated. The oily crude product was purified on trimethylamine pretreated preparative TLC plates (Me_3N/MeOH/$CHCl_3$, 0.5:2.5:97) to give 300 mg (45%) of **14** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1641, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.81 (m, 48H), 2.81-3.14 (br, 9H), 3.40 (s, 72H), 3.56 (m, 48H), 3.78 (s, 24H), 4.40-4.84 (br, 6H), 5.06 (s, 12H); ^{13}C NMR ($CDCl_3$, δ): 45.31, 53.57, 58.64, 59.47, 69.46, 69.66, 71.14, 113.56, 113.63, 121.89, 125.58, 126.35, 127.81, 137.55, 138.26, 139.66, 140.95, 141.06, 158.96; MS (ESI) calcd for $C_{159}H_{249}N_{15}O_{33}$ 2896.83, found 1450.4 $(M+2H)^{2+}$, 967.2 $(M+3H)^{3+}$, 725.6 $(M+4H)^{4+}$, 580.4 $(M+5H)^{5+}$.

Dendrimer 15. By the procedure for amine **8**, 38 mg (1.0 mmol) of $LiAlH_4$, 17 mL of THF, and 250 mg (0.0862 mmol) of **14** gave 216 mg (88%) of **15** as a thick oil. IR (film on NaCl) ν_{max}: 1590 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.18 (s, 9H), 2.76 (t, 48H), 3.34 (s, 72H), 3.46 (t, 48H), 3.58 (m, 12H), 3.68 (s, 24H), 5.18 (s, 12H), 6.84 (m, 18H); ^{13}C NMR ($CDCl_3$, δ): 44.98, 53.58, 58.70, 59.50, 61.72, 69.78, 71.10, 113.80, 122.10, 125.71, 127.90, 137.52, 137.78, 139.90, 140.81, 158.99; MS (ESI) calcd for $C_{159}H_{255}N_{15}O_{30}$ 2854.89, found 1429.2 $(M+2H)^{2+}$.

Dendrimer 16. By the method for dendrimer **14**, 548 mg (0.600 mmol) of amine **8,** 4.0 mL of DMF, 70 mg (0.13 mmol) of **13,** and 60 mg (1.93 mmol) of trimethylamine

gave 280 mg (54%) of **16** as a light yellow thick oil. IR (film on NaCl) ν_{max}: 1648, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.81 (m, 64H), 2.81-3.14 (br, 12H), 3.40 (s, 96H), 3.56 (m, 64H), 3.78 (s, 32H), 4.4-4.84 (br, 8H), 5.06 (s, 16H); ^{13}C NMR ($CDCl_3$, δ): 53.55, 58.70, 59.47, 69.58, 71.02, 113.82, 122.24, 126.32, 127.26, 127.95, 138.20, 140.83, 158.95; MS (ESI) calcd for $C_{224}H_{342}N_{20}O_{46}$ 4048.50, found 2026.4 $(M+2H)^{2+}$, 1351.2 $(M+3H)^{3+}$, 1014.0 $(M+4H)^{4+}$, 811.2 $(M+5H)^{5+}$, 676.0 $(M+6H)^{6+}$.

Dendrimer 1. By the method for amine **8,** 38 mg (1.0 mmol) of $LiAlH_4$, 17 mL of THF, and 220 mg (0.0543 mmol) of **16** gave 169 mg (78%) of **1** as a thick oil. IR (film on NaCl) ν_{max}: 1591 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.19 (s, 12H), 2.76 (t, 64H), 3.34 (s, 96H), 3.46 (t, 64H), 3.58 (m, 16H), 3.60 (s, 32H), 5.08 (s, 16H); ^{13}C NMR ($CDCl_3$, δ): 41.93, 53.60, 58.70, 59.52, 61.81, 62.19, 69.81, 71.10, 113.83, 122.07, 125.77, 127.88, 138.81, 137.58, 140.84, 159.07; MS (ESI) calcd for $C_{224}H_{350}N_{20}O_{42}$ 3992.59, found 1998.8 $(M+2H)^{2+}$, 1332.8 $(M+3H)^{3+}$, 1000.0 $(M+4H)^{4+}$, 800.0 $(M+5H)^{5+}$, 666.8 $(M+6H)^{6+}$, 571.6 $(M+7H)^{7+}$.

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CHAPTER IV

ESTER AND AMIDE TERMINATED DENDRIMERS WITH ALTERNATING AMIDE AND ETHER GENERATIONS

ABSTRACT

Ester-terminated polyamide dendrimers up to the third generation and amide-terminated polyamide dendrimers at the first generation were synthesized by a convergent growth method. The Williamson ether synthesis and diphenylphosphoryl azide (DPPA) coupling were used for the construction of the dendrimers having alternate ether and amide generations. The CH_3OCO- and $(CH_3CH_2)_2NCO$-terminated dendrimers are readily soluble in common organic solvents, while the CH_3NHCO- and $PhCH_2NHCO$-terminated dendritic molecules are soluble only in DMF and DMSO. Both the end and internal amide groups of the $(CH_3CH_2)_2NCO$-terminated dendrimer were reduced to polyamine groups by $LiAlH_4$. The products were characterized by NMR, MALDI-TOF or ESI mass analysis and elemental analysis.

INTRODUCTION

The rapid growth of research in the area of dendritic macromolecules has led to the synthesis of a variety of structurally intriguing materials with a number of potential applications such as catalysis, molecular recognition, drug delivery and energy transfer (Chapter I). In the framework of our studies on polyamine and polyammonium ion

dendrimers as unimolecular micelles and homogeneous catalysts in aqueous media, we have been extremely interested in polyamide (especially aromatic polyamide) dendrimers because of their excellent chemical stability, and because many high yield amidation methods are available from synthesis of polyamides and polypeptides.[1]

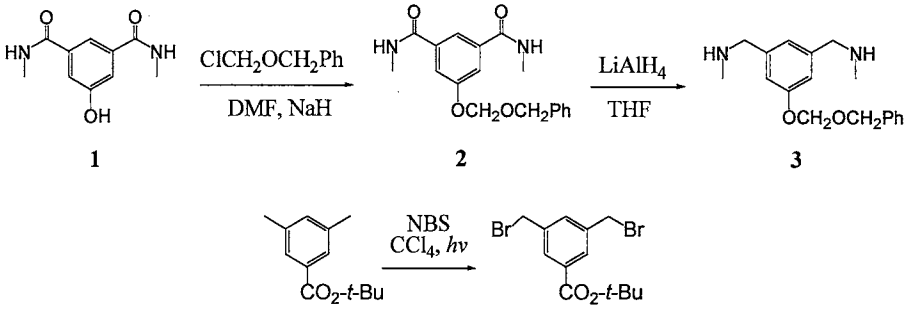
The synthesis of dendrimers having polyamide branching units has been extensively studied. However, dendrimers having aromatic polyamide branching units are relatively rare. Miller and Neenan reported a preparation of polyaromatic amide dendrimers based on the coupling of two equivalents of aniline with 5-nitroisophthalic acid chloride, followed by a conversion of the NO_2 group to an NH_2 group. The dendron containing the NH_2 at the focal point was treated with triacyl core to afford the three-directional dendrimer up to the second generation of polyamide branching units.[2a] Newkome and Lin reported a convergent synthesis of a hybrid polyamide/polyether dendrimer with one ether generation and two polyamide generations based on the same strategy.[2b] Frèchet and co-workers reported a preparation of aromatic amide terminated dendrimers, and the preparation was accomplished by converting the methyl isophthalate end groups of an aryl benzyl ether dendrimer to the aromatic amide end groups using excess of benzylamine.[2c] Feast et al. reported a convergent construction of aromatic polyamide dendrimers up to the second generation.[3] Nagasaki et al. reported a synthesis of "crowned" dendrimers, having linear aromatic polyamido crown ether units incorporated into a dendron with ether branching units.[4] Liskamp and co-workers reported amino acid based dendrimers by coupling of three equivalents of *N*-BOC-protected aminodicarboxylic acid with a dendron having three terminal amines and a methyl benzoate. The methyl benzoate at the focal point was hydrolyzed to benzoic acid which

was again coupled with the dendron to build a dendron up to the third amide generation.[5] Stoddart and co-workers recently used a double exponential growth step to form a new family of ester-terminated aromatic polyamide dendrimers using the DCC-HOBt (1-hydroxybenzotriazole) coupling technique.[6] Ashton et al. reported a convergent approach to carbohydrate-containing dendrimers with a trifunctional 1,3,5-benzenetricarbonyl amide in the core.[7] Aromatic polyamide dendrimers are much less soluble in common organic solvents than their aliphatic counterparts, and the aromatic amide-terminated polyaryl benzyl ether dendrimer prepared by Frèchet's group is only soluble in DMF and DMSO.[2c] The poor solubilities of aromatic polyamide dendrimers in common organic solvents make the subsequent reaction and purification very difficult. NMR analysis is not very useful for dendrimers having aromatic amide (especially tertiary aromatic amide) branching units since the restricted rotation of the aromatic amide C-N bounds makes both proton and carbon NMR peaks split into multiplets or broad peaks.

The synthesis of both ester and amide terminated aromatic polyamide dendrimers containing alternating ether-amide generations were studied in this research. The target dendrimers were synthesized by a convergent method. The Williamson ether synthesis and coupling of carboxylic acids with amines were used as key steps for the construction of the target dendrimers. The products were characterized by ^{1}H and ^{13}C NMR, MALDI-TOF or ESI-MS, and elemental analysis. The target dendrimers having alternate ether and amide generations are layer blocked, and the two different chemical links are placed at varying generations throughout the dendrimers.

Synthesis of Ester Terminated Dendrimers. Solubilities of dendrimers are primarily determined by terminal groups.[8] The methyl ester group CH_3OCO was chosen as terminal functionality for the target dendrimers due to its excellent compatibility with most common organic solvents. Scheme 1 shows the synthesis of monomers **3** and **5**, the building blocks for the construction of the target dendrimers. The phenol group of **1** was protected to give the benzyloxymethyl ether (BME ether) **2**, and diamine **3** was obtained by $LiAlH_4$ reduction of **2**. Ester **4** was prepared from 3,5-dimethylbenzoic acid via the esterification of 3,5-dimethylbenzoyl chloride with *tert*-butyl alcohol. Compound **4** was converted to bromide **5** by *N*-bromosuccinimide (NBS) in 61% yield.

Scheme 1. Synthesis of monomers **3** and **5**.

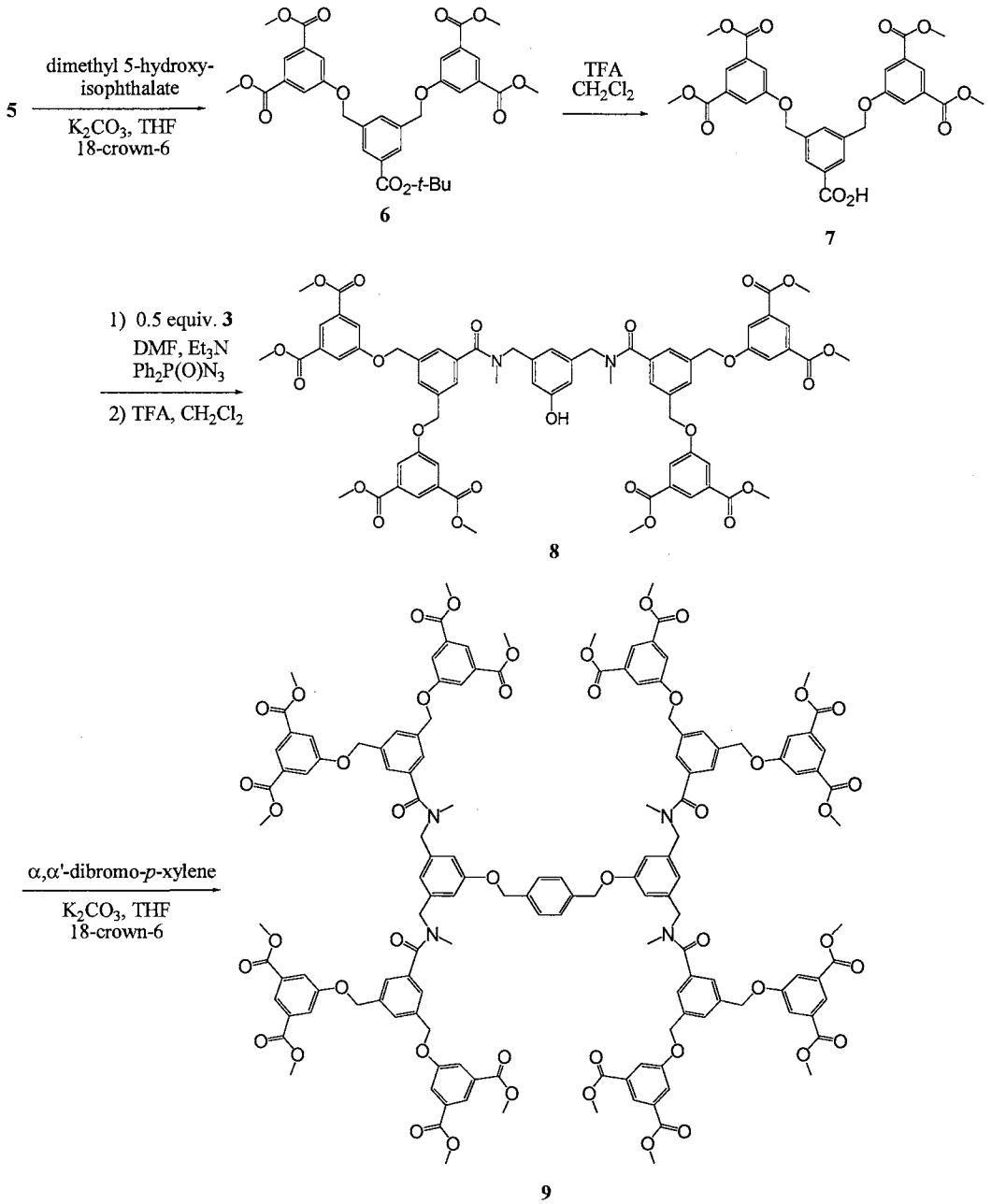


1 2 3 4 5

The synthesis of dendrimer G_2(16est) (**9**) from monomers **3** and **5** is shown in Scheme 2. The coupling of dimethyl 5-hydroxylisophthalate with 0.5 equivalents of bromide **5** via the Williamson ether synthesis gave dendron G_0(4est-CO_2-*t*-Bu) (**6**) in 80% yield. The *tert*-butyl ester group of **6** was removed by trifluoroacetic acid (TFA) to give acid G_0(4est-CO_2H) (**7**) quantitatively. Acid dendron **7** was activated *in situ* by

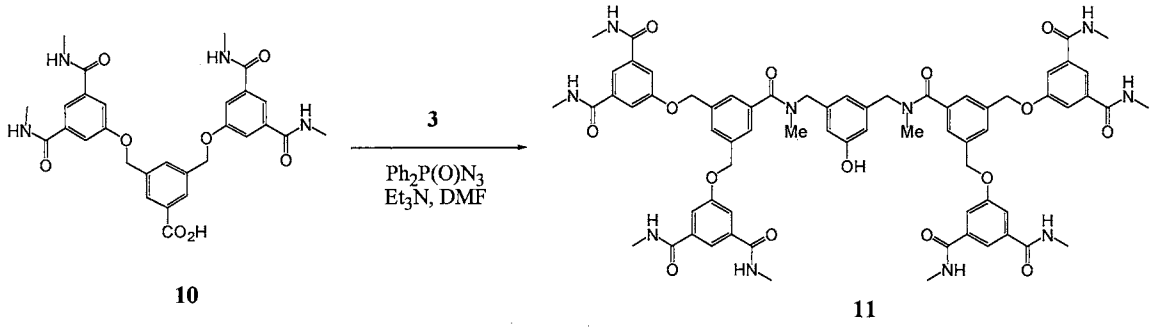
diphenylphosphoryl azide (DPPA) and coupled with 0.5 equivalents of amine **3**, followed by a TFA deprotection to give G_1(8est-OH) (**8**) in 45% yield. The generation 2 dendrimer G_2(16est) (**9**) was prepared by coupling of **8** with α,α'-dibromo-*p*-xylene.

Scheme 2. Synthesis of dendrimer G_2(16est) (**9**).



An amide-terminated dendron G_1(8amide-OH) (**11**) was also prepared by a similar synthetic method from G_0(4amide-CO_2H) (**10**) as shown in Scheme 3. Dendron **11** terminated with eight CH_3NHCO-amide end groups is insoluble in THF, chloroform, acetone and methanol. The poor solubility of dendron **11** excluded it as a useful synthon because there is no appropriate solvent available for subsequent purification and reaction.

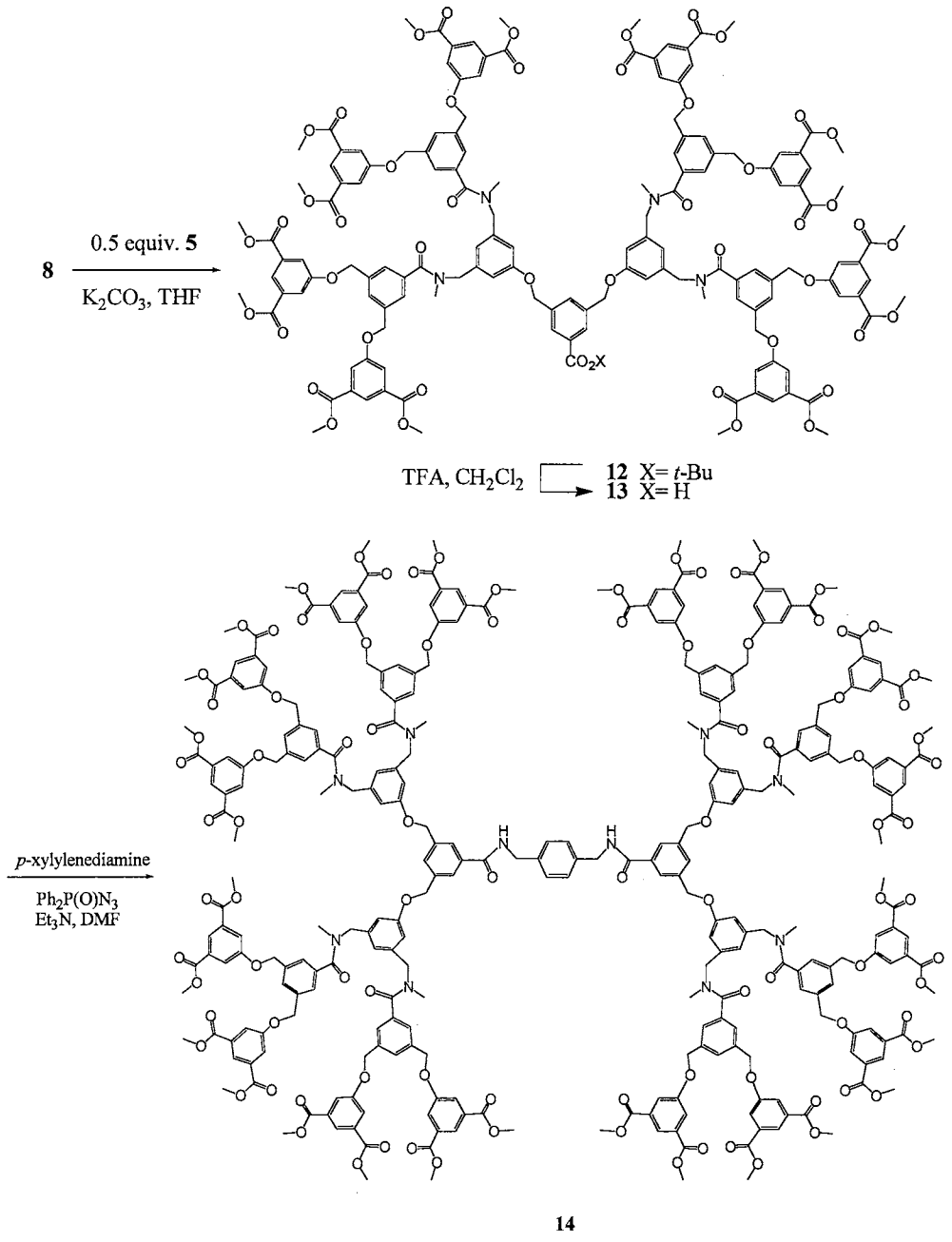
Scheme 3. Synthesis of amide-terminated G_1 dendron **11**.



10 **11**

Scheme 4 shows the synthesis of the third generation dendrimer G_3(32est) (**14**) from G_1(8est-OH) (**8**). Dendron **8** was coupled with bromide **5** to give G_2(16est-CO_2-*t*-Bu) (**12**) in 79% yield, and **12** was deprotected by TFA to give G_2(16est-CO_2H) (**13**) quantitatively. Dendrimer G_3(32est) (**14**) was prepared by coupling of **13** with 0.5 equivalents of *p*-xylylenediamine in 32% yield.

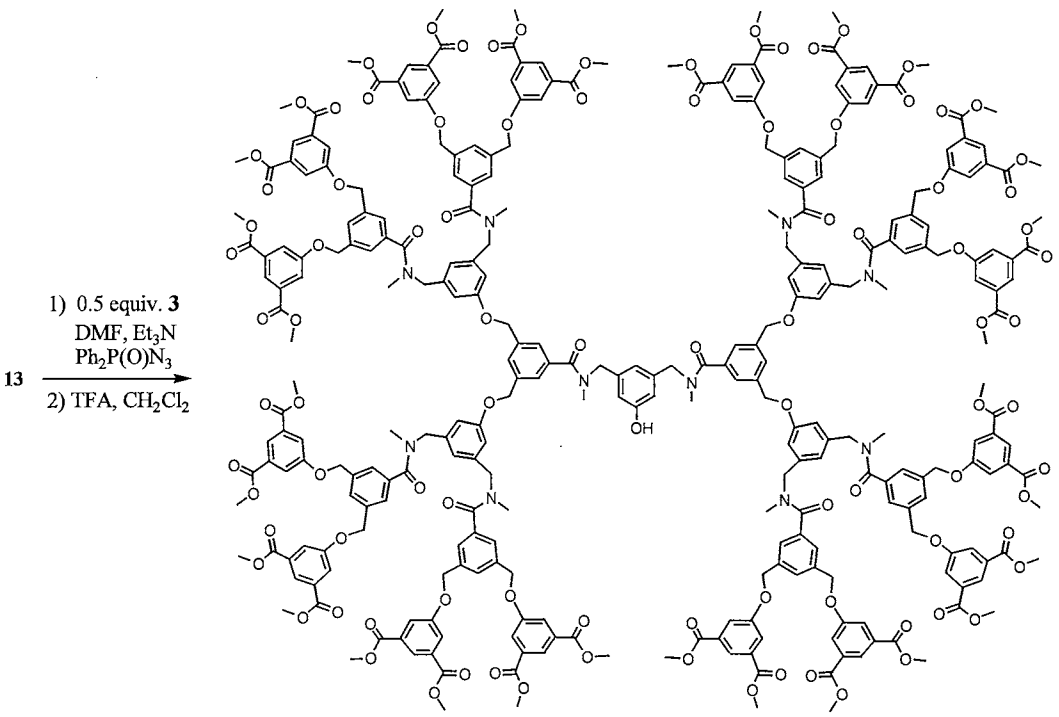
Scheme 4. Synthesis of dendrimer G_3(32est) (**14**).



14

A generation 3 dendron G_3(32est-OH) (**15**) was prepared by coupling of **13** with amine **3** using $(PhO)_2P(O)N_3$ in 29% yield as shown in Scheme 5.

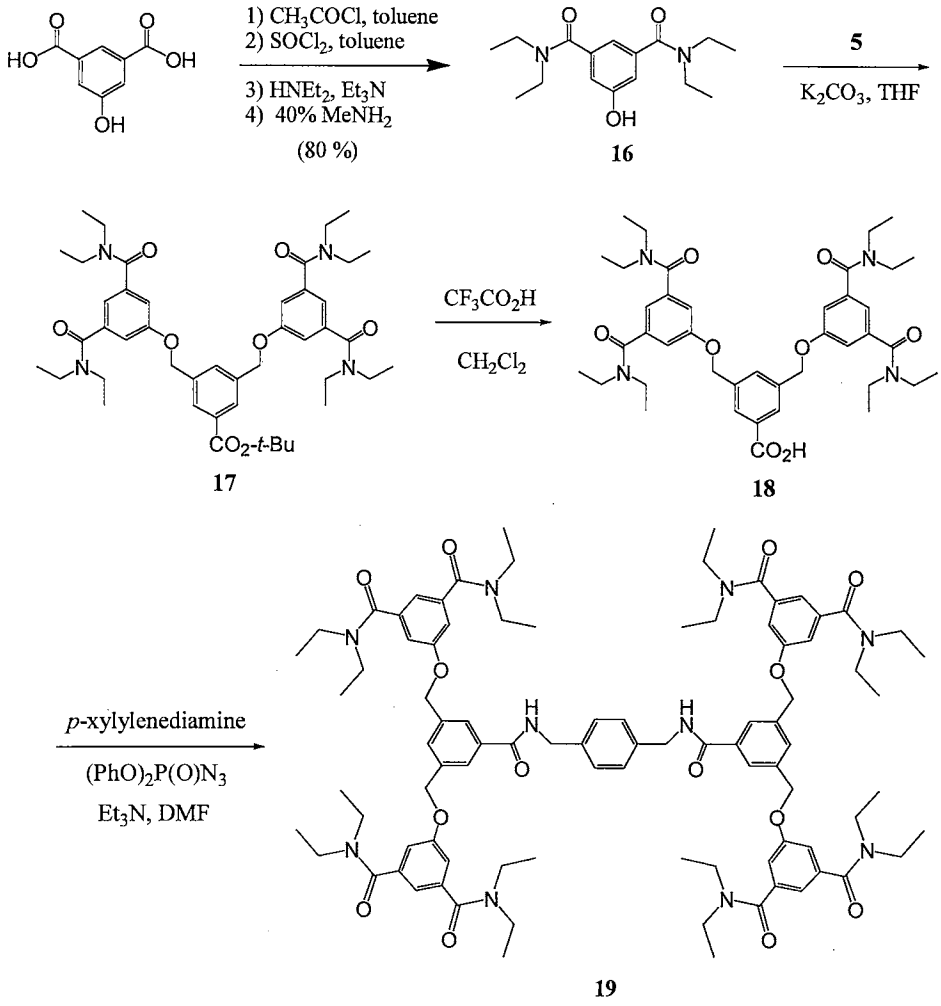
Scheme 5. Synthesis of generation 3 dendron **15**.



15

Synthesis of Amide Terminated Dendrimers. We attempted to convert the ester end groups of dendrimer G_2(16est) (**9**) to $PhCH_2NHCO$-amide end groups by reacting **9** with excess benzylamine. The $PhCH_2NHCO$-amide terminated dendrimer is only soluble in DMF and DMSO, and attempts to purify the product or reduce the amide end groups to amines by $LiAlH_4$ in THF or dioxane were not successful due to the poor solubility of the product in chloroform, THF and dioxane. Therefore, $(CH_3CH_2)_2NCO$-amide was chosen as the terminal functionality of polyamide-terminated dendrimer **19** shown in Scheme **6.**

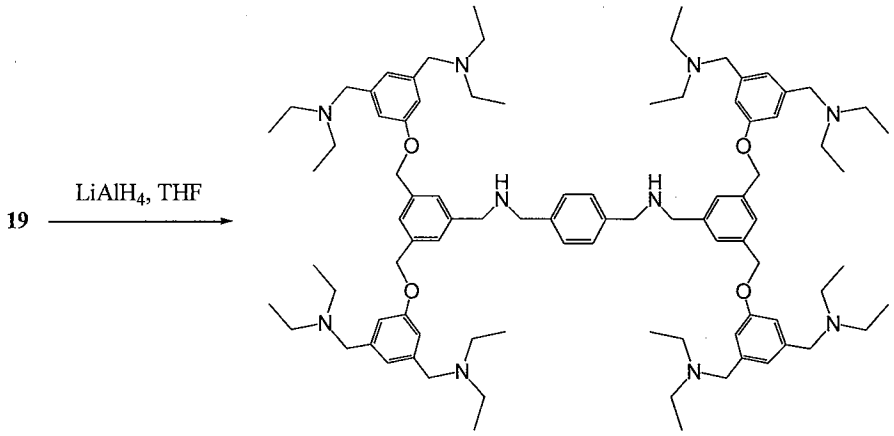
Scheme 6. Synthesis of amide terminated dendrimer **19**.



The $(CH_3CH_2)_2NCO$-amide groups were placed into the potential shell units of the building block **16** at the beginning of the convergent synthesis. Dendrons **17** and **18** and dendrimer **19** terminated with the $(CH_3CH_2)_2NCO$-amide functionality have excellent solubilities in most common organic solvents such as THF, $CHCl_3$, acetone and methanol, which greatly facilitates the purification and subsequent synthesis. The amide-terminated dendron **16** was synthesized from 5-hydroxyisophthalic acid in an one-pot reaction. The hydroxyl group of 5-hydroxyisophthalic acid was protected using acetyl

chloride, and the two carboxylic acid groups were converted to acid chloride groups using thionyl chloride. The acid chlorides were reacted with diethylamine in THF followed by removal of the acetyl protecting group with aqueous methylamine to give phenol **16**. Ester **17** was synthesized by etherification of phenol **16** with dibromide **5** (0.5 equivalent) and was converted to acid **18** using TFA deprotection. The carboxylic acid at the focal point coupled with *p*-xylylenediamine (0.5 equivalent) to afford dendrimer **19** in 78% yield.

Scheme 7. Synthesis of amine terminated dendrimer **20**.



The polyamide dendrimer **19** was successfully reduced to polyamine **20** in THF by $LiAlH_4$ as shown in Scheme 7. The product was purified on a basic Al_2O_3 column and characterized by ^1H and ^{13}C NMR and ESI-MS analysis.

Solubilities of the Ester and Amide-terminated Dendrons and Dendrimers. The ester terminated dendrimers are soluble in chloroform, THF and acetone as well as in DMF and DMSO. The benzyl ether linkages in the alternating generations of the products enhance the solubilities of the aromatic polyamide dendrimers, and the solubilities of the

dendrons and dendrimers are crucial for the purification of the products by liquid chromatography and for the subsequent reactions. The octa(methylamide) dendron **11** and the $PhCH_2NHCO$-amide terminated dendrimer prepared from the ester-terminated dendrimer **9** are soluble only in strong polar solvents such as DMF and DMSO. The *N,N*-diethylamide terminated dendrimer **19** is readily soluble in THF, acetone, methanol and ether.

Table 1. Solubilities of Ester and Amide-terminated Dendrons and Dendrimers [a, b]

	THF, $CHCl_3$	MeOH, EtOH	DMF, DMSO
G_1(8est-OH) (**8**)	✔		✔
G_2(16est) (**9**)	✔		✔
G_3(32est) (**14**)	✔		✔
G_0(4amide-CO_2H) (**10**)	×	✔	✔
G_1(8amide-OH) (**11**)	×	×	✔
G_0(4amide-CO_2H) (**18**)	✔	✔	✔
G_1(8amide) (**19**)	✔	✔	✔

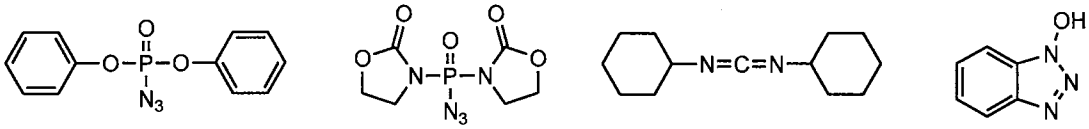
[a] Solubilities were tested at room temperature.
[b] Symbol '✔' represents good solubility and symbol '×' represents poor solubility.

The solubilities of the dendritic materials are mainly determined by the properties and the number of their end groups. The solubility of a higher generation dendron may be dramatically different from that of its precursor. For example, dendron G_0(4amide-CO_2H) (**10**) having four *N*-methylamide end groups is readily soluble in methanol, while dendron G_1(8amide-OH) (**11**) terminated with eight *N*-methylamide end groups is only soluble in hot DMF and DMSO.

NBS Bromination. The preparation of dibromide **5** by NBS bromination required strong UV irradiation and benzoyl peroxide initiator. The by-products of the reaction were monobromide and tribromide. The reaction on a 1-3 gram scale was used, good selectivity of the dibromide was achieved, and the desired dibromide was easily recrystallized from hexane. When the reaction was performed in the dark, with a relatively weak light source, or on a 5 gram scale where the light efficiency was poor, considerable amounts of the by-products were obtained. It was quite difficult to separate the desired dibromide from the reaction mixture by crystallization or chromatography.[9]

Coupling Reactions of Aromatic Carboxylic Acids with Diamines. The formation of the amide generations in the aromatic polyamide dendrimers required a highly efficient coupling method. Coupling techniques of carboxylic acids with amines using the DCC,[10] DPPA,[11,12] DCC-HOBT[13] and BOP-Cl[14] as activating reagents have been well established for synthesis of peptides (Scheme 8).

Scheme 8. Coupling agents for the formation of amide bonds.

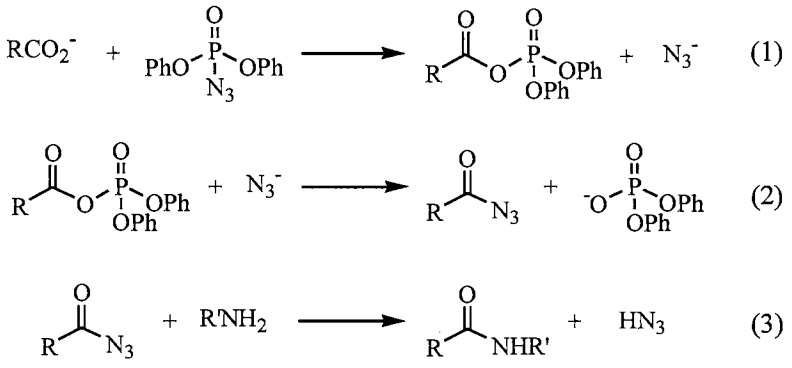


DPPA BOP-Cl DCC HOBT

Those coupling methods have also been widely used for synthesis of dendrimers having aliphatic polyamide generations.[6,15] In this study, the couplings of dendrons **7**, **13** and **18** with secondary and primary amines using the DCC-HOBT, BOP-Cl and DPPA were examined. DPPA proved to be the most useful coupling agent for the formation of the aromatic amide bonds. The postulated mechanism involves formation of acyl azide as

a reactive intermediate (Scheme 9). The aromatic acid anion is less nucleophilic to DPPA than the aliphatic acid anion, and the aromatic acyl azide intermediate is less reactive to amines due to the conjugation of the carbonyl of the acyl azide with the aromatic system and the steric hindrance of the aromatic rings having two large branching units. Therefore, it is expected that the aromatic carboxylic acid groups at the focal points of dendrons **7**, **13** and **18** are less reactive towards amines (especially secondary amines) than their aliphatic counterparts. The coupling reactions of acids **7** and **18** with *p*-xylylenediamine using DPPA as the activating reagent gave the BME ether of dendron G_1(8est-OH) (**8**) and dendrimer G_1(8amide) (**19**) in 74% and 78% yields, respectively, while the coupling of acid **13** with *p*-xylylenediamine afforded G_3(32est) (**14**) in 32% yield, and the coupling of acid **13** with secondary amine **3** gave G_3(32est-OH) (**15**) in 29% yield. These results suggest that the steric hindrance of aromatic acid **13** having two large branching units significantly reduced the reactivity of the acid group at the focal point, and the NCH_3 group of secondary amine **3** imposed an additional steric effect on the reaction between the amine and the reactive acyl azide intermediate.

Scheme 9. Mechanism of DPPA coupling reaction.



Influence of Slow Amide C-N Rotation on NMR Peak Broadening. Spectroscopic characterization of the aromatic polyamide dendrimers by ^{1}H and ^{13}C NMR proved difficult due to the broad signals in the spectra. The ^{1}H NMR spectrum of dendron **8** at 20 °C shown in Figure 1 has the OCH_2, OCH_3, NCH_2 and NCH_3 signals spread out over a wide range of chemical shifts.

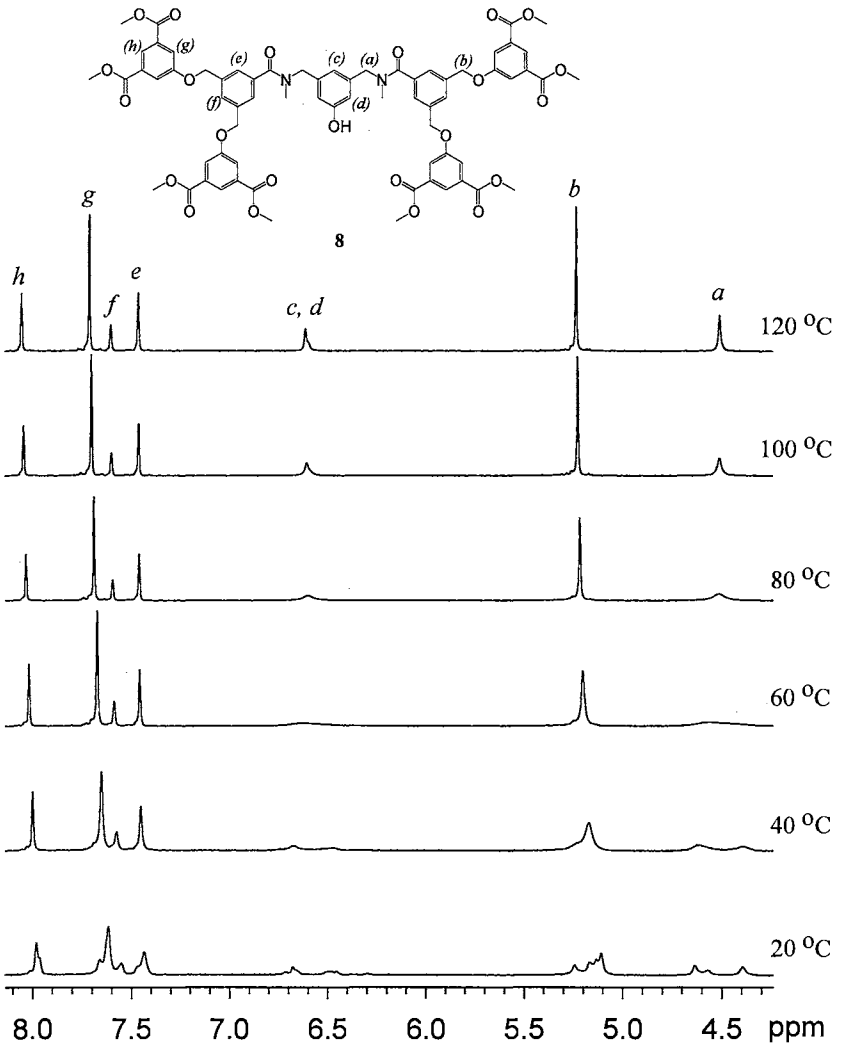


Figure 1. 400 MHz ^{1}H NMR spectra of dendron **8** at varied temperature.

Using DMSO as solvent at 100 and 120 °C, the signals become sharp and well resolved. The NMR spectra of dendrimers **14** and **15** show broad OCH_2, OCH_3, NCH_2 and NCH_3 signals even at 120 °C. The peak broadening from the slow rotation of the amide C-N bonds become more extensive with increasing generation

EXPERIMENTAL SECTION

All starting materials were purchased from Aldrich and used as received unless otherwise stated. Benzyl chloromethyl ether was purchased from TCI America. THF was freshly distilled from sodium. Pyridine and triethylamine were dried over 3 Å molecular sieves and freshly distilled. All glassware was oven-dried before use. ^1H NMR spectra (400 or 300 MHz) and ^{13}C spectra (100 or 75 MHz) were recorded with the solvent signal as reference. MALDI-TOF mass spectra were obtained by using indoleacrylic acid as matrix. Liquid secondary ion mass spectra were obtained by using 2-nitrobenzyl alcohol as matrix. Electrospray mass spectra were acquired on PE/Sciex API-III Quadra 950 triple quadrupole biomolecular mass analyzer equipped with an atmospheric pressure ion source, and positive ions produced from a pneumatically assisted electrospray interface using the samples in water, methanol and acetic acid (50:50:0.5) solution. Ions were analyzed by scanning the first quadrupole in 0.2 amu increments. Calculated *m/z* values are for the lowest isotopomers.

3,5-Bis(*N*-methylcarboxamido)phenol (1). A solution of dimethyl 5-hydroxyisophthalate (14.0 g, 66.7 mmol) and 40% aqueous $MeNH_2$ (20.0 mL, 222 mmol) was stirred for 10 h at room temperature. The solution was concentrated under

reduced pressure, and dried *in vacuo* to remove the excess amine. Aqueous ethanol (20%, 15 mL) was added to the residue. The solution was cooled to 0 °C, and the precipitate was collected and washed with cold water and ether to give **1** (10.38 g, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.76 (d, J=4.2 Hz, 6H), 7.31 (s, 2H), 7.71 (s, 1H), 8.41 (d, J=4.2 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.34, 116.73, 136.40, 157.60, 166.73.

3,5-Bis(*N*-methylcarboxamido)phenyl benzyloxymethyl ether (2). To a suspension of NaH (0.90 g, 50% dispersion in oil, 18 mmol) in dry DMF (30 mL) cooled to 0 °C was added **1** (3.12 g, 15.0 mmol). After stirring at 23 °C for 60 min, a solution of benzyl chloromethyl ether (2.67 g, 16.6 mmol) in DMF (5.0 mL) was added, and the suspension was stirred at room temperature for 2 h. The suspension was poured into water, neutralized with 1% aqueous HCl to pH 7, and extracted with chloroform (3×60 mL). The combined organic phase was washed with water, dried (K_2CO_3), and concentrated *in vacuo*. The residue was precipitated by adding ether, and the solid was washed with cold hexane to give **2** (4.68 g, 95%), mp 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (d, 6 H, NCH_3), 4.74 (s, 2H, OCH_2Ph), 5.28 (d, 2H, OCH_2O), 6.58 (br, 2H, NH), 7.37 (m, 5H, Ph), 7.58 (s, 2H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.86, 70.30, 92.21, 117.65, 118.47, 127.99, 128.03, 128.48, 136.30, 136.82, 157.50, 167.14. MS (LSI) calcd for $C_{18}H_{20}N_2O_4$ 328.1, found 329 (MH^+).

3,5-Bis(methylaminomethyl)phenyl benzyloxymethyl ether (3). Powdered $LiAlH_4$ (1.53 g, 38.0 mmol) was slowly added to a solution of **2** (3.12 g, 9.50 mmol) in THF (85 mL) at 0 °C. After stirring at 65 °C for 6 h, the suspension was slowly added to saturated

aqueous Na_2SO_4 at 5-10 °C. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic phase was washed with water, dried (K_2CO_3) and concentrated to give **3** (2.68 g, 94%) as a thick oil which was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H, NCH_3), 3.76 (d, 4H, NCH_2), 4.74 (s, 2H, OCH_2Ph), 5.28 (d, 2H, OCH_2O), 6.92 (s, 3H), 7.37 (m, 5H); ^{13}C NMR (100 MHz, CDCl3): δ 36.02, 55.89, 69.84, 92.12, 114.50, 121.40, 127.80, 128.80, 128.38, 128.42, 137.23, 141.88, 157.46. MS (LSI) calcd for $C_{18}H_{24}N_2O_2$ 300.1, found 301 (MH^+).

***tert*-Butyl 3,5-dimethylbenzoate (4).** A suspension of 3,5-dimethylbenzoic acid (10.0 g, 66.6 mmol), toluene (8.0 mL) and thionyl chloride (10 mL, 137 mmol) was stirred under reflux for 4 h. Toluene and excess thionyl chloride were removed by evaporation under reduced pressure. A solution of *t*-BuOH (8.00 g, 108 mmol) and pyridine (5.53 g, 70.0 mmol) in CH_2Cl_2 (20 mL) were added to the residue. The solution was stirred at room temperature for 6 h, cooled to 0 °C, and the precipitate was filtered off. The filtrate was concentrated, dissolved in CH_2Cl_2, washed with 4.0 M cold HCl, water, 2.0 M NaOH and water, and dried (K_2CO_3). The solvent was removed and the residue was distilled under reduced pressure to give **4** (12.2 g, 89%) as colorless liquid: bp 80-85 °C/2 torr. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 9H), 2.38 (s, 6H), 7.16 (s, 1H), 7.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.03, 28.07, 80.70, 127.17, 131.95, 134.11, 137.86, 166.28. MS(LSI) calcd for $C_{13}H_{18}O_2$ 206.13, found: 206 (M^+).

***tert*-Butyl 3,5-bis(bromomethyl)benzoate (5).** A suspension of **4** (1.03 g, 5.00 mmol), NBS (1.83 g, 10.3 mmol), benzoyl peroxide (10.6 mg) and CCl_4 (16 mL) was

stirred and heated under mild refluxing with an IR lamp and irradiated with a medium-pressure 450 W Hg UV lamp located 4 cm away for 60 min. The suspension was cooled to room temperature, and the precipitate was filtered and washed with CH_2Cl_2. The combined organic solution was washed with 1% aqueous Na_2CO_3 and water, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue was dried *in vacuo* at 50-60 °C for 4 h. The residue was crystallized from hexane at -20 °C to afford **5** (1.12 g, 61%) as a white solid: mp 115-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 9H), 4.50 (s, 4H, CH_2Br), 7.59 (s, 1H), 7.93 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.13, 32.02, 81.74, 129.82, 133.27, 133.40, 138.70, 164.50.

G_0(4est-*t*-Bu) (6). A suspension of **5** (1.00 g, 2.75 mmol), dimethyl 5-hydroxyisophthalate (1.20 g, 5.72 mmol), K_2CO_3 (1.00 g, 7.24 mmol, dried for 4 h at 180 °C), 18-crown-6 (0.1 g) and THF (40 mL) was stirred and heated under mild reflux for 24 h. The suspension was concentrated *in vacuo*. The residue was extracted with chloroform, washed with 1% aq. NaOH and water, and dried ($MgSO_4$). The solvent was removed *in vacuo,* and the residue was crystallized from a mixture of methanol/acetone/ether (1:1:6). The resulting solid was collected and washed with the above solvent mixture, dried *in vacuo* to give **6** (1.36 g, 80%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 9H), 3.94 (s, 12H, CO_2CH_3), 5.20 (s, 4H, CH_2O), 7.70 (s, 1H), 7.82 (s, 4H), 8.18 (s, 2H), 8.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 28.37, 52.65, 69.98, 81.82, 120.28, 123.68, 128.50, 130.52, 132.11, 133.17, 137.12, 158.73, 165.24, 166.22; MS (LSI) calcd for $C_{33}H_{34}O_{12}$ 622.21, found 567.0 (MH^+-C_4H_8). Anal. Calcd for $C_{33}H_{34}O_{12}$: C, 63.66; H, 5.50. Found: C, 63.99; H, 5.81.

G_0(4est-CO_2H) (7). Trifluoroacetic acid (3.0 mL) was added to a solution of G_0(4est-Bu) (**6**) (0.18 g, 0.30 mmol) in CH_2Cl_2 (10 mL). The solution was stirred at room temperature for 0.5 h, TFA and the solvent were removed under reduced pressure at 50-60 °C. Acetone/ether (2:1, 5.0 mL) was added to the residue, and the solid was collected and washed with ether to give **7** (0.15 g, 91%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 12H, CO_2CH_3), 5.21 (s, 4H, CH_2O), 7.80 (s, 1H), 7.83 (s, 4H), 8.18 (s, 2H), 8.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.46, 69.53, 120.16, 123.67, 128.96, 130.19, 131.50, 132.04, 137.55, 158.58, 166.17, 170.39; MS (LSI) calcd for $C_{29}H_{26}O_{12}$ 566.1, found 567.0 (MH^+); Anal. Calcd for $C_{29}H_{26}O_{12}$: C, 59.59; H, 4.83. Found: C, 60.29; H, 4.38.

G_1(8est-OH) (8). A suspension of G_0(4est-CO_2H) (**7**) (590 mg, 1.04 mmol), amine **3** (156 mg, 0.52 mmol) and DMF (8.0 mL) was stirred at room temperature until all of the solid dissolved. DPPA (310 mg, 1.08 mmol) and triethylamine (1.0 mL) were added, and the solution was stirred at 50 °C for 24 h. The reaction was quenched with water (10 mL), and the solution was extracted with chloroform (3 x 20 mL). The combined organic layers were washed with cold 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography using chloroform as the eluant. After concentration under reduced pressure, the oily residue was dissolved in CH_2Cl_2 (8.0 mL), and TFA (4.0 mL) was added. The solution was stirred at room temperature for 36 h. The excess TFA and CH_2Cl_2 were evaporated under reduced pressure, and 5% aqueous $NaHCO_3$ was added to the residue. The solid was collected, washed with water, and dried *in vacuo*. The crude

product was purified by column chromatography by using chloroform-MeOH (99:1) as eluant to give **8** (265 mg, 54%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 3.00 (m, 6H, NCH_3), 3.94 (s, 24H, CO_2CH_3), 4.50 (m, 4H, NCH_2), 5.21 (s, 8H, OCH_2), 6.60 (br, 3H), 7.42 (s, 4H), 7.56 (s, 8H), 7.60 (s, 2H), 7.82 (s, 4H), 9.08 (bs, 1H, OH); MS (MALDI-TOF) calcd for $C_{68}H_{64}N_2O_{23}$ 1276.39, found 1300.38 (MNa^+); Anal. Calcd for $C_{68}H_{64}N_2O_{23}\cdot H_2O$: C, 63.06; H, 5.14; N, 2.16. Found: C, 63.31; H, 5.07; N, 2.01.

G_2(16est) Dendrimer (9). A suspension of G_1(8est-OH) (**8**) (138 mg, 0.108 mmol), α,α'-dibromo-*p*-xylene (13.6 mg, 0.0500 mmol), K_2CO_3 (20.8 mg, 0.150 mmol) and DMF (4.0 mL) was stirred at 80 °C for 24 h. The solvent was evaporated under reduced pressure. The residue was extracted with chloroform, washed with 1.0 M aqueous NaOH and water, and dried ($MgSO_4$). The crude product was purified by flash chromatography using gradient $CHCl_3$-MeOH (92:8-85:15) as eluant to afford **9** (100 mg) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90 (br, 12H, NCH_3), 3.92 (s, 48H, CO_2CH_3), 4.42 and 4.65 (br, 8H, NCH_2), 5.21 (br, 16H, OCH_2), 6.60 (br, 3H), 6.84 (br, 4H), 7.48 (br, 12H), 7.70 (br, 16H), 8.20 (br, 8H). MS (MALDI-TOF) calcd for $C_{144}H_{134}N_4O_{46}$ 2654.83, found 2678.98 (MNa^+).

G_2(16estCO_2-*t*-Bu) (12). By the procedure for **6**, G_1(8est-OH) (**8**) (640 mg, 0.502 mmol), bromide **5** (86 mg, 0.23 mmol), K_2CO_3 (108 mg, 0.780 mmol), 18-crown-6 (30 mg) and acetone (15 mL) afforded **12** (510 mg) as a white powder (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (br, 9H, *t*-Bu), 2.90 (m, 12H, NCH_3), 3.92 (s, 48H, CO_2CH_3), 4.42 and 4.65 (m, 8H, NCH_2), 5.21 (br, 20H, OCH_2), 6.60-6.90 (m, 6H), 7.48 (br, 12H), 7.70

(br, 16H), 8.20 (br, 8H). MS (MALDI-TOF) calcd for $C_{149}H_{142}N_4O_{48}$ 2754.88, found 2779.8 (MNa^+). Anal. Calcd for $C_{149}H_{142}N_4O_{48} \cdot H_2O$: C, 64.50; H, 5.23; N, 2.02. Found: C, 64.28; H, 4.91; N, 2.01.

G_2(16est-CO_2H) (13). By the procedure for acid **7**, TFA (4.0 mL) and **12** (486 mg, 0.176 mmol) in CH_2Cl_2 (6.0 mL) gave product **13** (470 mg, 99%) as a white powder which was used for the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (m, 12H, NCH_3), 3.92 (s, 48H, CO_2CH_3), 4.42 and 4.65 (m, 8H, NCH_2), 5.21 (m, 20H, OCH_2), 6.60-6.90 (m, 6H), 7.48 (br, 12H), 7.70 (br, 16H), 8.20 (br, 8H); MS (MALDI-TOF) calcd for $C_{145}H_{134}N_4O_{48}$ 2698.82, found 2723.6 (MNa^+).

Dendrimer G_3(32est) (14). By the procedure for **8**, G_2(16est-CO_2H) (**13**) (334 mg, 0.124 mmol), DMF (4.0 mL), triethylamine (25 mg, 0.25 mmol), DPPA (38.6 mg, 0.140 mmol) and *p*-xylylenediamine (8.2 mg, 0.060 mmol) gave **14** (106 mg, 32%) as a light yellow powder. ^1H NMR (400 MHz, $CDCl_3$): δ 2.98 (m, 24H, NCH_3), 3.92 (s, 96H, CO_2CH_3), 4.45 and 4.80 (m, 20H, NCH_2), 5.16 (br, 40H, OCH_2), 7.56 (br, 24H), 7.70 (br, 32H), 8.28 (br, 16H). MS (MALDI-TOF) calcd for $C_{298}H_{276}N_{10}O_{94}$ 5497.71, found 5523.97 (MNa^+).

Dendron G_3(32est-OH) (15). By the procedure for **8**, G_2(16est-CO_2H) (**13**) (352 mg, 0.130 mmol), DMF (4.0 mL), triethylamine (25 mg, 0.25 mmol), DPPA (38.6 mg, 0.14 mmol) and amine **3** (21 mg, 0.07 mmol) gave **15** (106 mg, 29%) as a white powder. ^1H NMR (300 MHz, $CDCl_3$): δ 2.95 (m, 30H, NCH_3), 3.92 (s, 96H, CO_2CH_3), 4.42-4.65 (m, 20H, NCH_2), 5.16 (br, 40H, OCH_2), 6.60-6.90 (m, 15H), 7.56 (br, 24H), 7.70 (br,

32H), 8.00 (br, 3H), 8.28 (br, 16H), 9.98 (br, 1H, OH). MS (MALDI-TOF) calcd for $C_{300}H_{280}N_{10}O_{95}$ 5541.74, found 5568.5 (MNa^+).

Dendron 16. A suspension of 5-hydroxyisophthalic acid (6.0 g, 33 mmol), acetyl chloride (10.8 g, 138 mmol) and toluene (10 mL) was stirred under reflux for 6 h. Thionyl chloride (11.0 g, 92.0 mmol) was added. The suspension was stirred for 7 h under reflux, and concentrated under reduced pressure. The oily residue was dissolved in THF (10 mL). A solution of diethylamine (5.0 g, 68 mmol) in THF (12 mL) and triethylamine (8.1 g, 80 mmol) was added slowly with stirring at 0 °C, and the suspension was stirred for 30 min at 0 °C and 4 h at room temperature. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (50 mL) and washed with water (2 x 30 mL). The solvent was evaporated, and methanol (10 mL) and aqueous $MeNH_2$ (40%, 20 mL) was added to the residue. The solution was stirred for 8 h at room temperature, concentrated on a rotary evaporator, acidified to pH 4-5 using 2% aqueous HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water and dried (Na_2SO_4). The solvent was evaporated to give a light yellow oil which was eluted through a short column chromatography using MeOH/$CHCl_3$ (2:98) as eluant to give **16** (7.51 g, 78%) as a thick oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (m, CH_3CH_2N, 12H), 3.40 (m, CH_3CH_2N, 8H), 6.74 (s, 1H), 6.79 (s, 2H), 9.22 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.05, 14.43, 39.69, 43.74, 114.66, 115.19, 138.11, 157.79, 171.26; MS (LSI) calcd for $C_{16}H_{24}N_2O_3$ 292.18, found 293 (MH^+).

Dendron G_0(4Am-*t*-Bu) (17). By the procedure for **6**, bromide **5** (2.00 g, 5.50 mmol), **16** (3.65 g, 11.4 mmol), K_2CO_3 (2.00 g, 14.5 mmol), 18-crown-6 (0.18 g) and THF (70

mL) gave **17** (3.30 g, 77%) as a thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, 24H, CH_3CH_2), 1.60 (s, 9H, *t*-Bu), 3.40 (d, 16H, CH_3CH_2), 5.16 (s, 4H, CH_2O), 6.98 (s, 2H), 7.02 (s, 4H), 7.64 (s, 1H), 8.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.02, 14.40, 28.32, 39.42, 43.49, 69.77, 113.72, 116.92, 128.31, 130.32, 133.10, 137.32, 139.19, 158.69, 165.15, 170.19. MS (LSI) calcd for $C_{45}H_{62}N_4O_8$ 786.46, found 732 (MH^+-C_4H_8).

Dendron G_0(4amide-COOH) (18). By the procedure for acid **7**, TFA (6.0 mL) and G_0(4Am-*t*-Bu) **17** (2.18 g, 2.77 mmol) in CH_2Cl_2 (20 mL) gave **18** (1.8 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, 24H, CH_2CH_3), 3.40 (d, 16H, CH_2CH_3), 5.16 (s, 4H, CH_2O), 6.98 (s, 2H), 7.02 (s, 4H), 7.74 (s, 1H), 8.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.35, 13.68, 39.93, 43.63, 69.47, 112.95, 113.97, 116.37, 116.76, 128.73, 131.04, 137.17, 137.40, 158.19, 158.68, 169.00, 171.18; MS (LSI) calcd for $C_{41}H_{54}N_4O_8$ 730.39, found 732 (MH^+).

G_1(8amide) (19). A suspension of G_0(4est-CO_2H) **18** (556 mg, 0.761 mmol), *p*-xylylenediamine (51 mg, 0.37 mmol), DMF (4.0 mL), DPPA (223 mg, 0.81 mmol) and triethylamine (154 mg, 1.52 mmol) was stirred at 50 °C for 24 h. The reaction was quenched with cold water (10 mL), and the solvent was removed under reduced pressure. The residue was dissolved in chloroform, washed with 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography using chloroform-MeOH (98:2) as eluant to give **19** (450 mg, 78%) as a light yellow thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.2 (d, 48H, CH_2CH_3), 3.21 (d, 32H, CH_2CH_3), 4.61 (d, 4H, NCH_2), 5.06 (s, 8H, OCH_2), and

aromatics. MS (MALDI-TOF) calcd for $C_{90}H_{116}N_{10}O_{14}$ 1560.87, found: 1562.46 $(MH)^+$, 1584.38 $(MNa)^+$.

G_1(8amine) (20). G_1(8amide) **19** (296 mg, 0.190 mmol) was dissolved in THF (10 mL) in a 25 mL of flask. The solution was cooled to 0 °C, and $LiAlH_4$ (77 mg, 2.0 mmol) was added slowly. The suspension was stirred under N_2 at 65 °C for 24 h, and was added slowly to saturated aqueous Na_2SO_4 at 5-10 °C. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phase was washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue was purified on an Al_2O_3 column (MeOH/$CHCl_3$, 2:98) to give **20** (242 mg, 90%) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, 48H, CH_2CH_3), 2.51 (q, 32H, CH_2CH_3), 3.41 (s, 2H, NH), 3.56 (s, 16H, NCH_2), 3.80 (d, 4H, NCH_2), 5.06 (s, 8H, OCH_2), 6.90 (s, 12H), 7.10-7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.68, 46.72, 52.99, 57.44, 64.16, 69.76, 113.65, 122.19, 125.43, 126.84, 127.72, 128.26, 137.58, 137.69, 138.91, 140.95, 141.10, 158.80; MS (ESI) calcd for $C_{90}H_{136}N_{10}O_4$ 1421.07, found 1422.0 $(MH)^+$, 711.6 $(M+2H)^{2+}$, 474.8 $(M+3H)^{3+}$.

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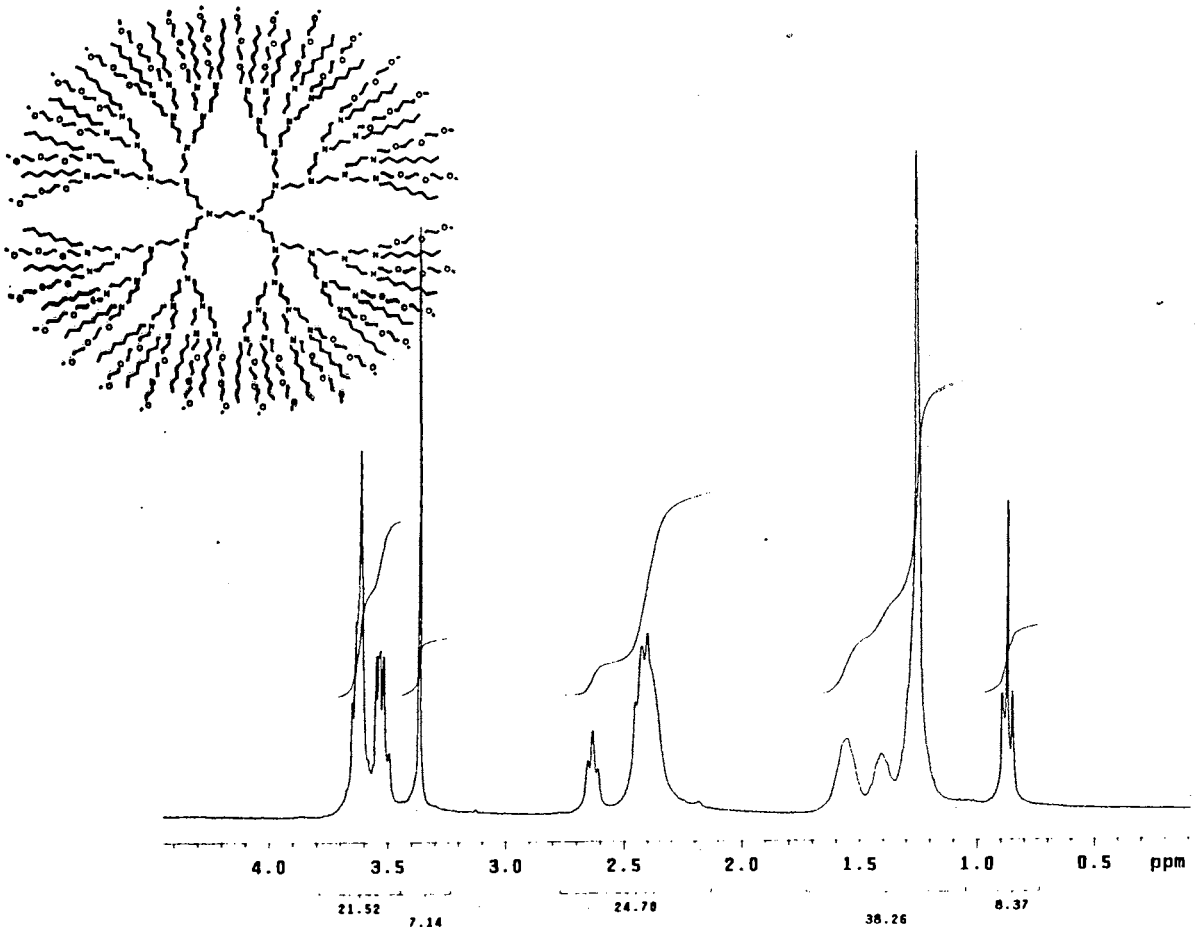
Figure 1. ^{1}H NMR spectrum of polyamine dendrimer G_4(TAn32) **5** in Chapter II.



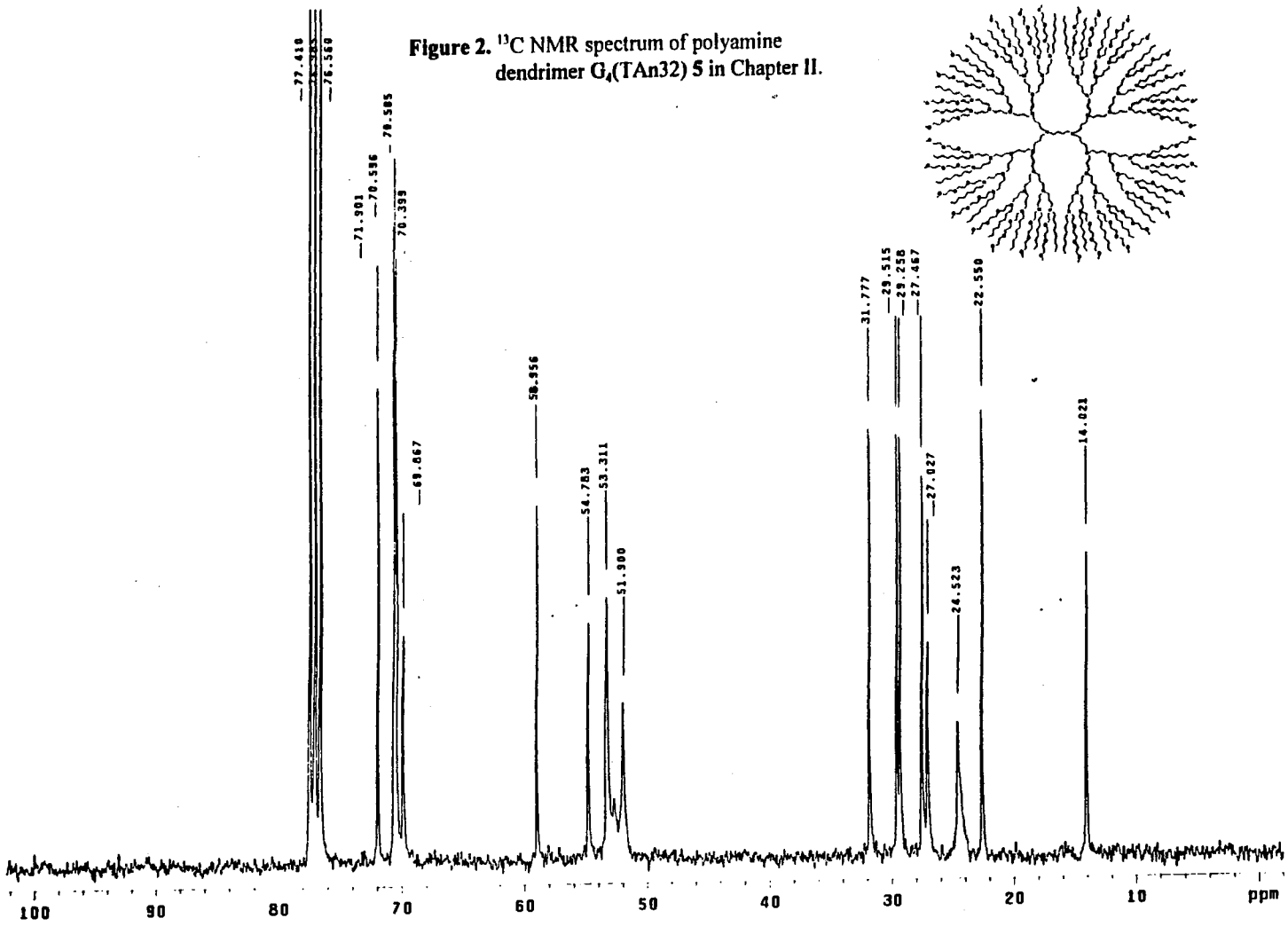


Figure 2. ^{13}C NMR spectrum of polyamine dendrimer G_4(TAn32) **5** in Chapter II.

Figure 3a. ^{1}H NMR spectrum of polyammonium iodide dendrimer G_4(PMI32) **5a** in Chapter II.

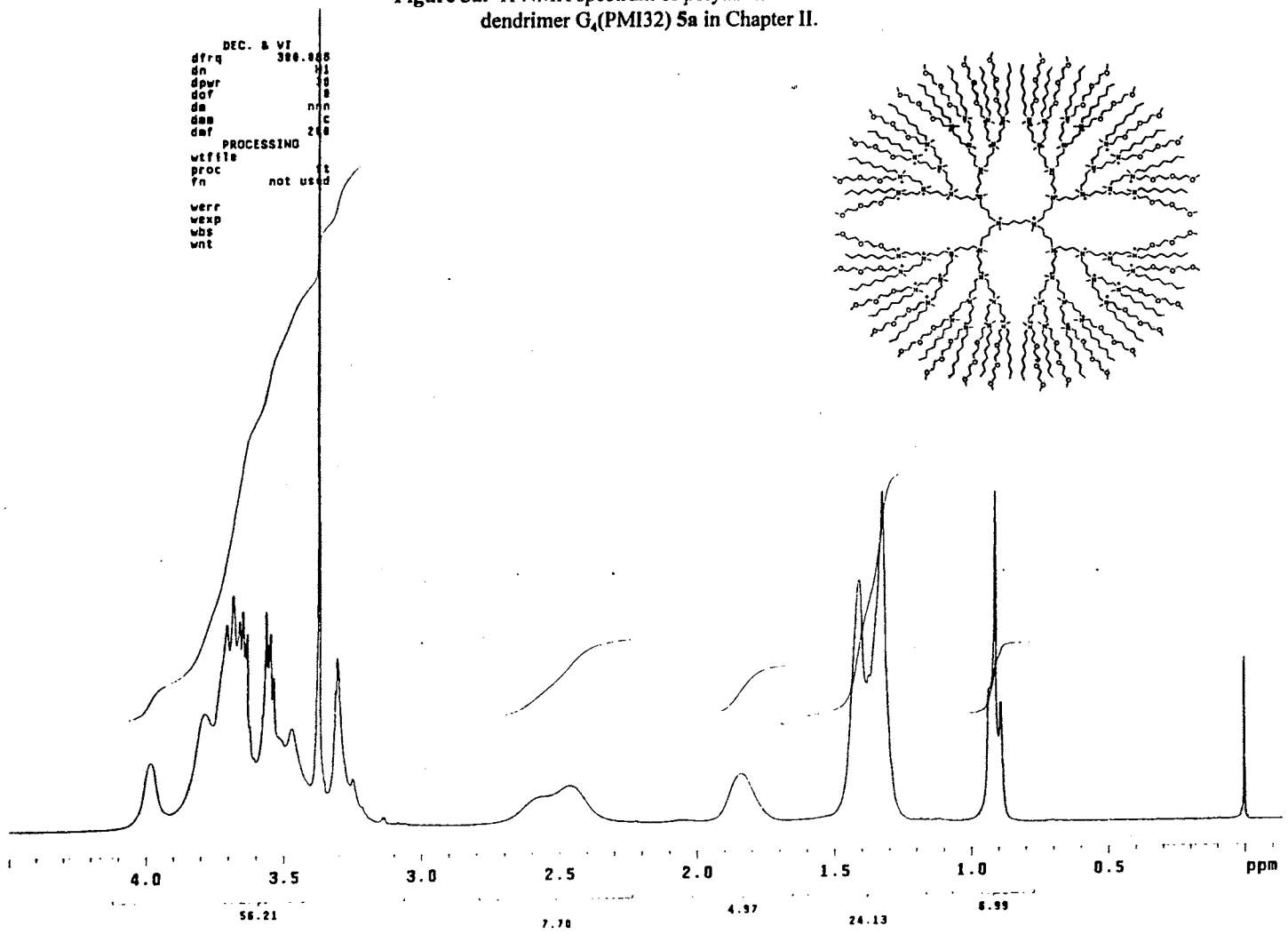
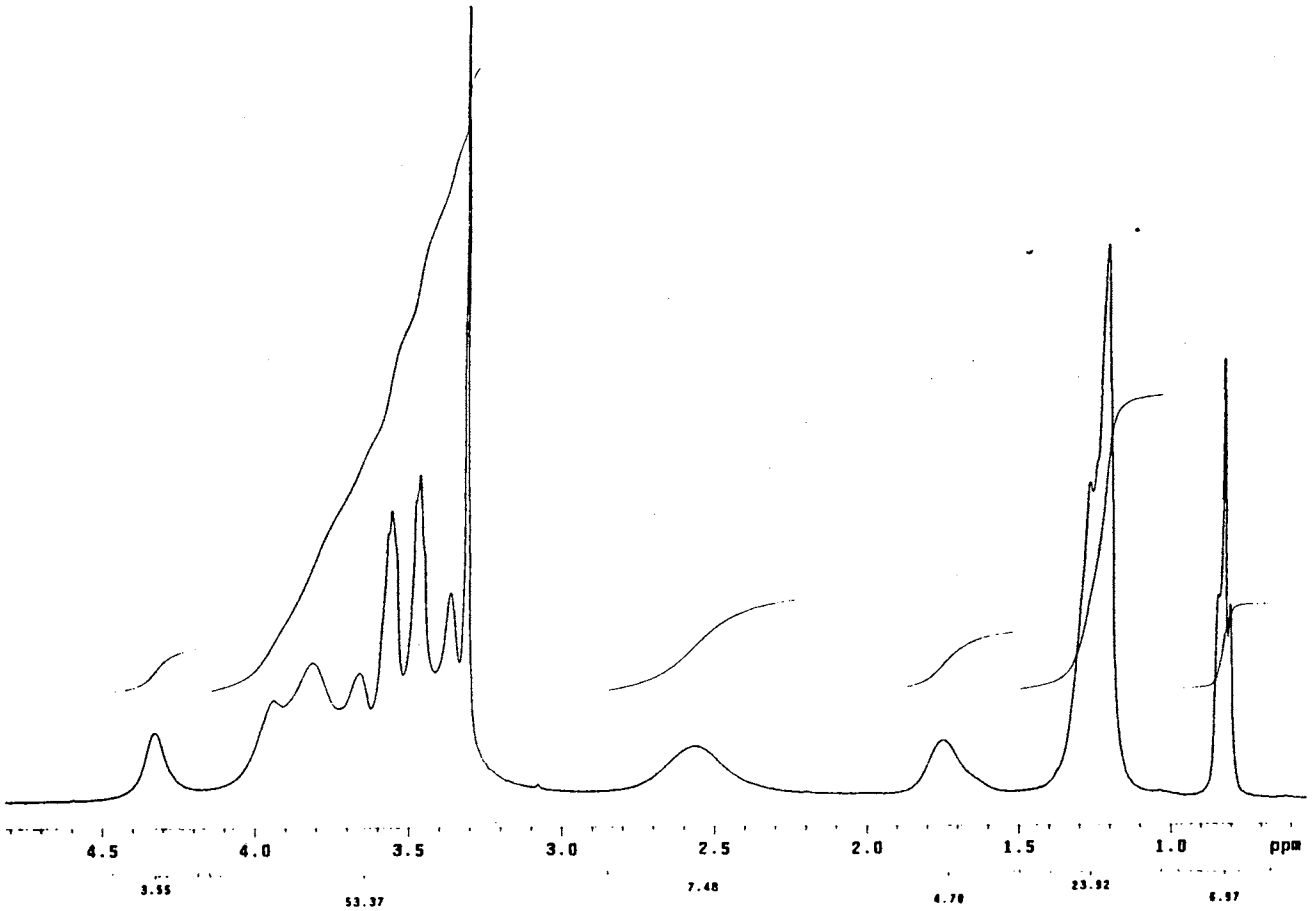


Figure 3b. ^{1}H NMR spectrum of polyammonium chloride dendrimer G_4(PMCl32) **5b** in Chapter II.



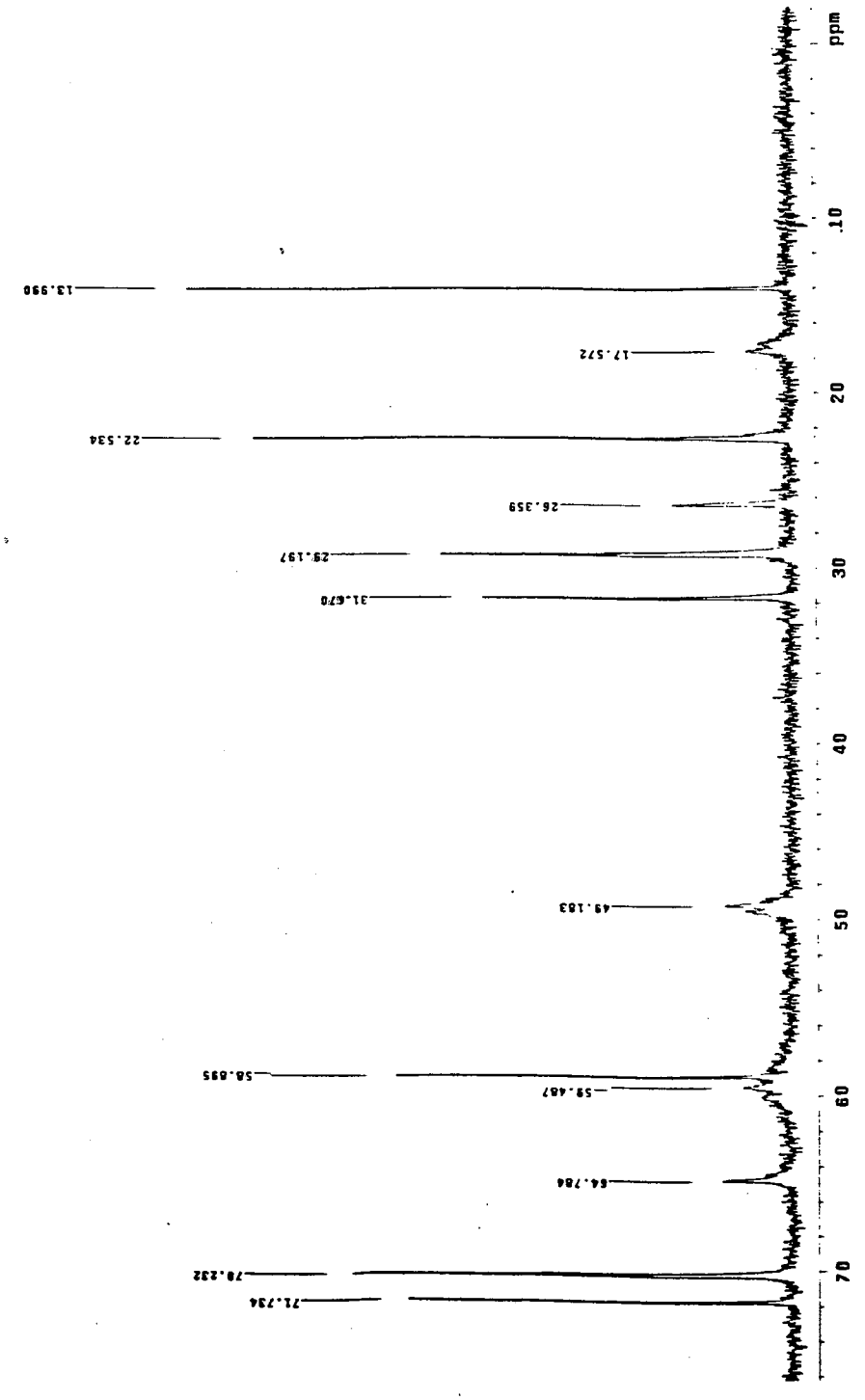


Figure 4. ^{13}C NMR spectrum of polyammonium chloride dendrimer $G_4(PMCl32)$ **5b** in Chapter II.

Figure 5. ESI-MS spectrum of polyamine dendrimer G_2(TAn8) **10** in Chapter II.

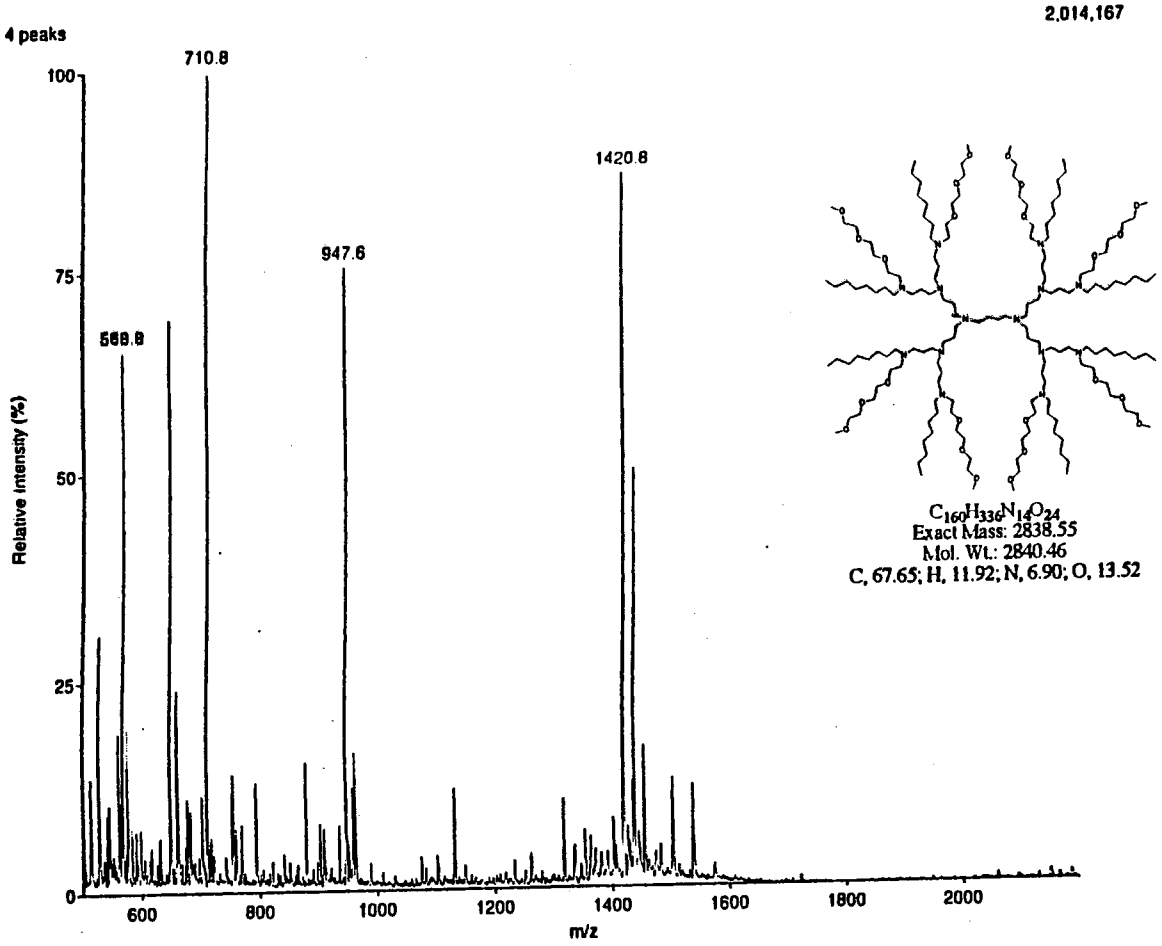
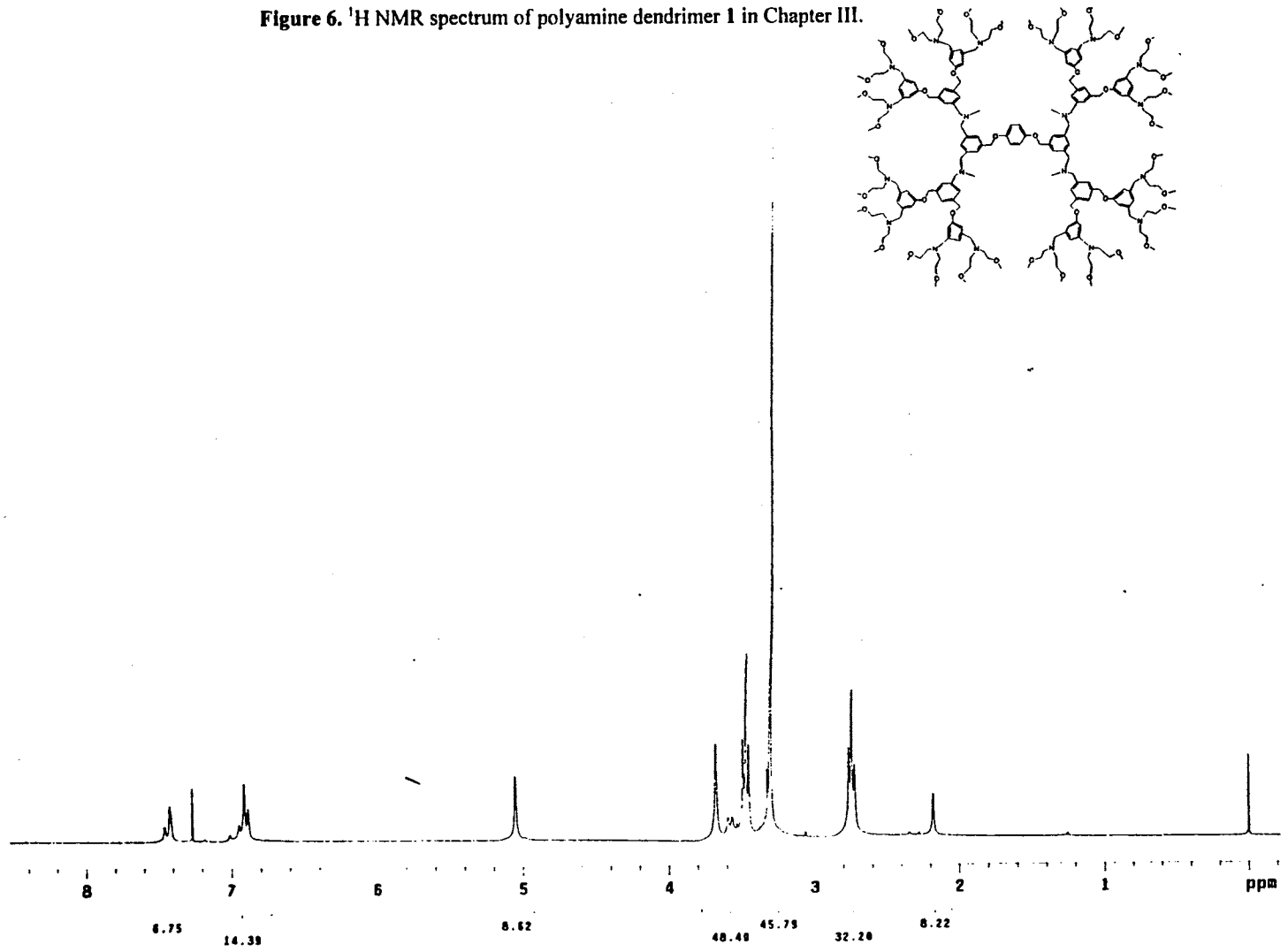


Figure 6. ^{1}H NMR spectrum of polyamine dendrimer **1** in Chapter III.



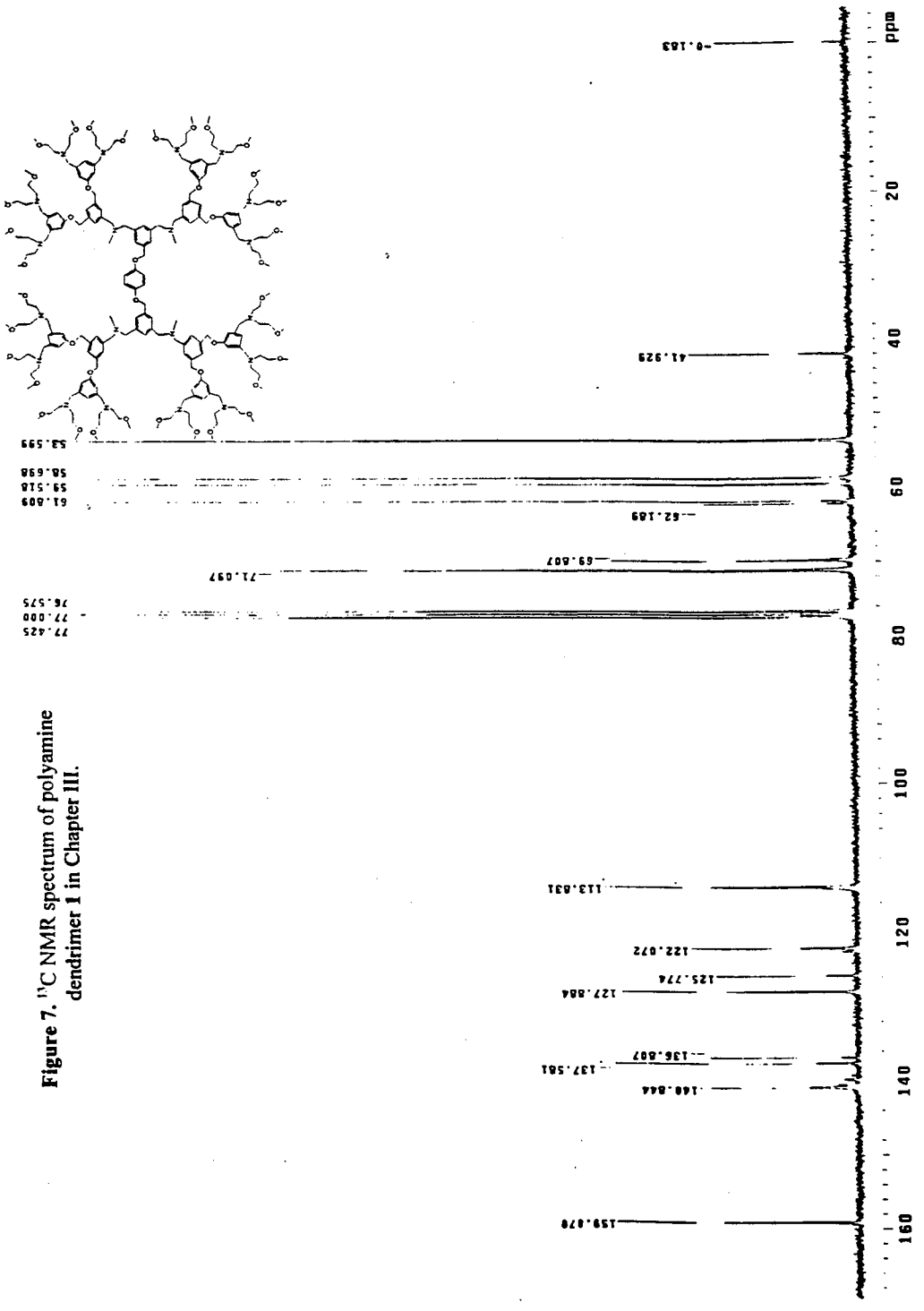


Figure 7. ^{13}C NMR spectrum of polyamine dendrimer **1** in Chapter III.

Figure 8. ESI-MS spectrum of polyamine/polyamide dendrimer **16** in Chapter III.

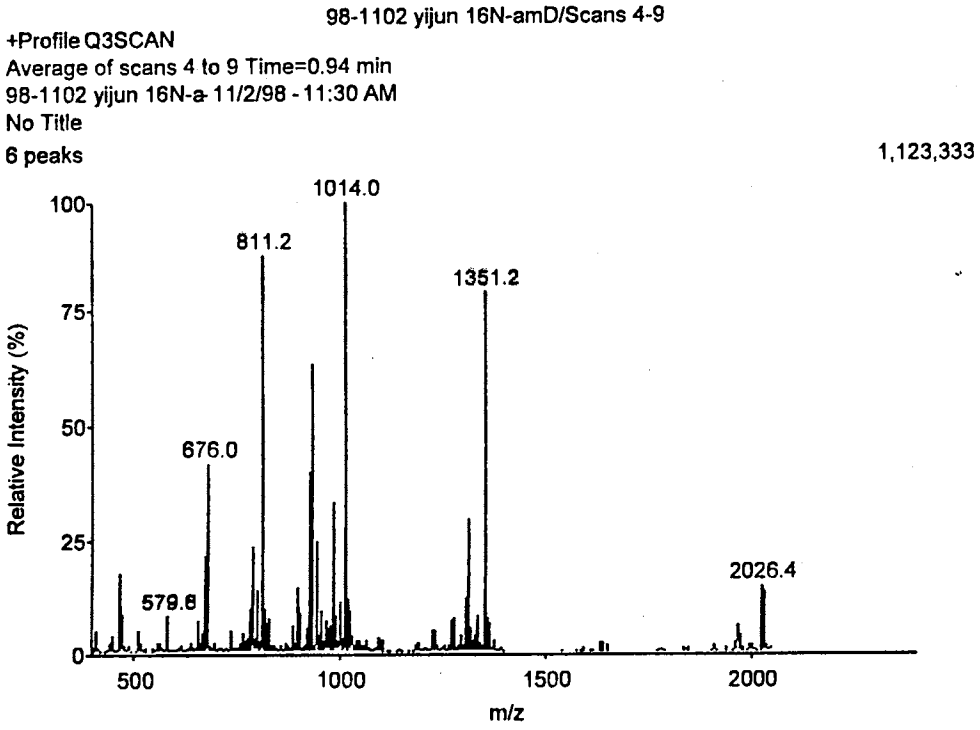


Figure 9. ESI-MS spectrum of polyamine dendrimer **1** in Chapter III.

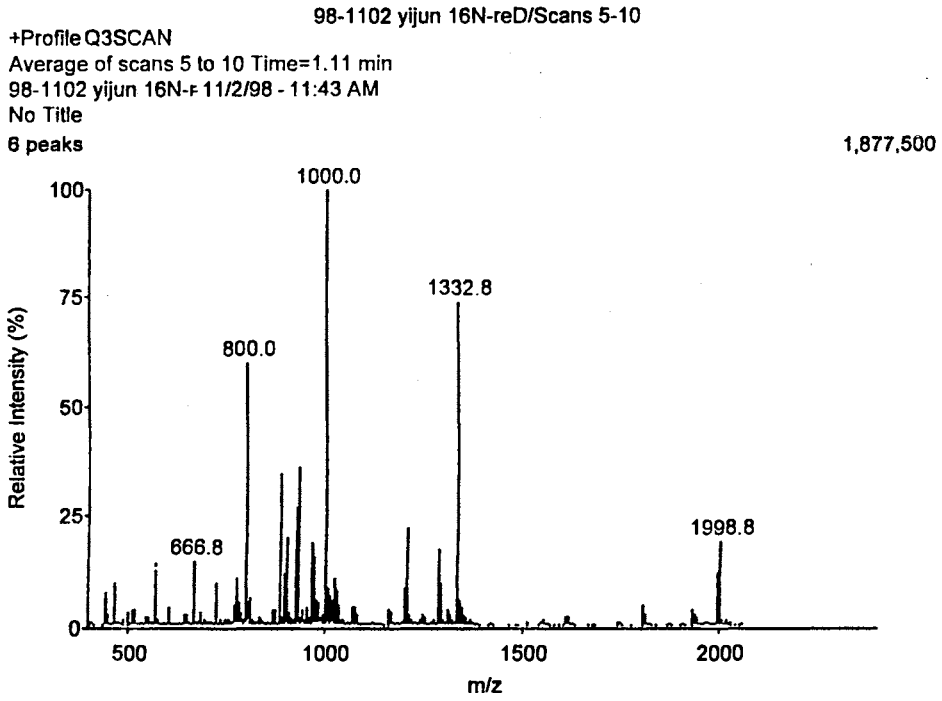


Figure 10. ^{1}H NMR spectra of ester-terminated dendrimer **15** in Chapter IV.

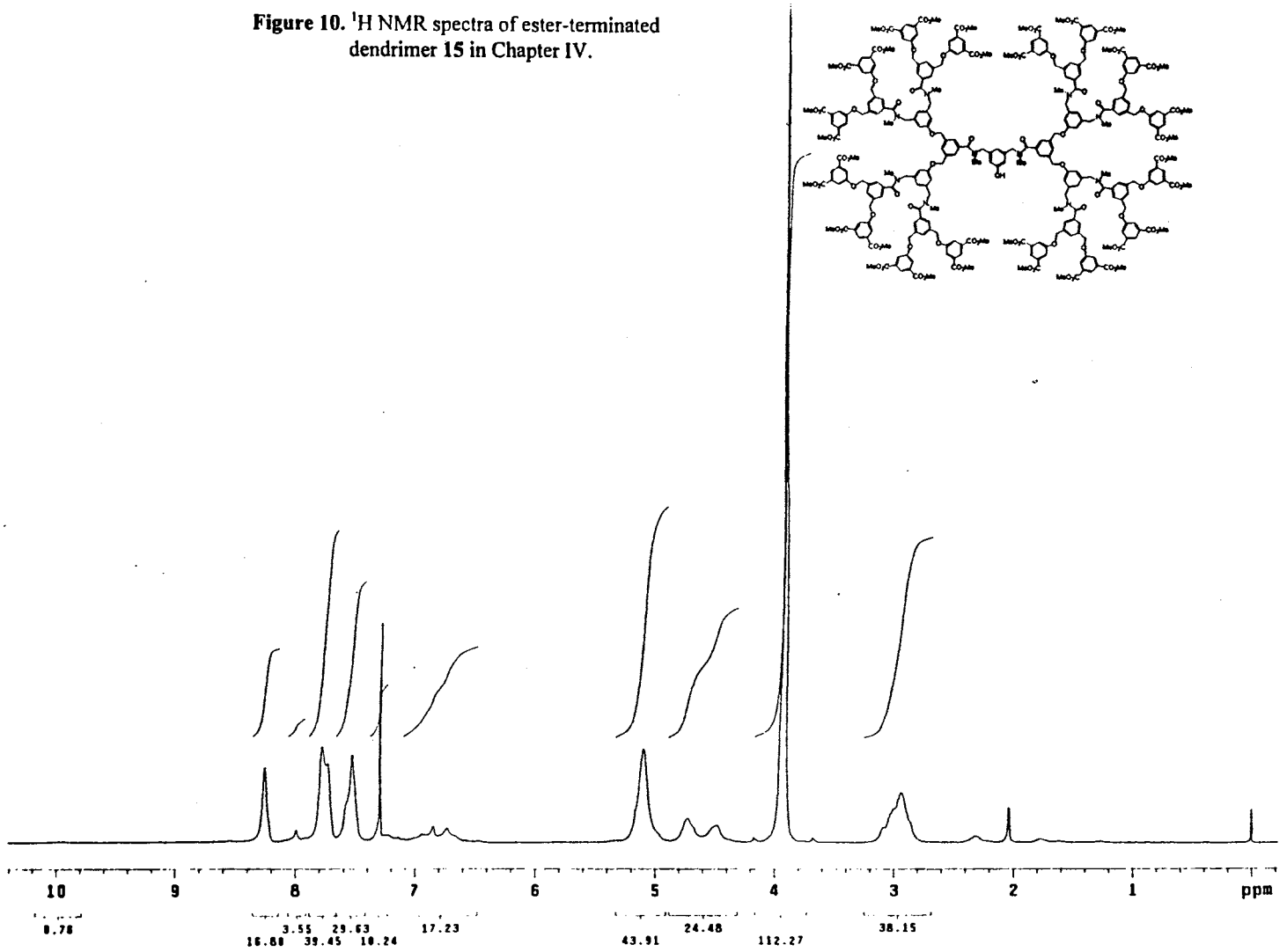
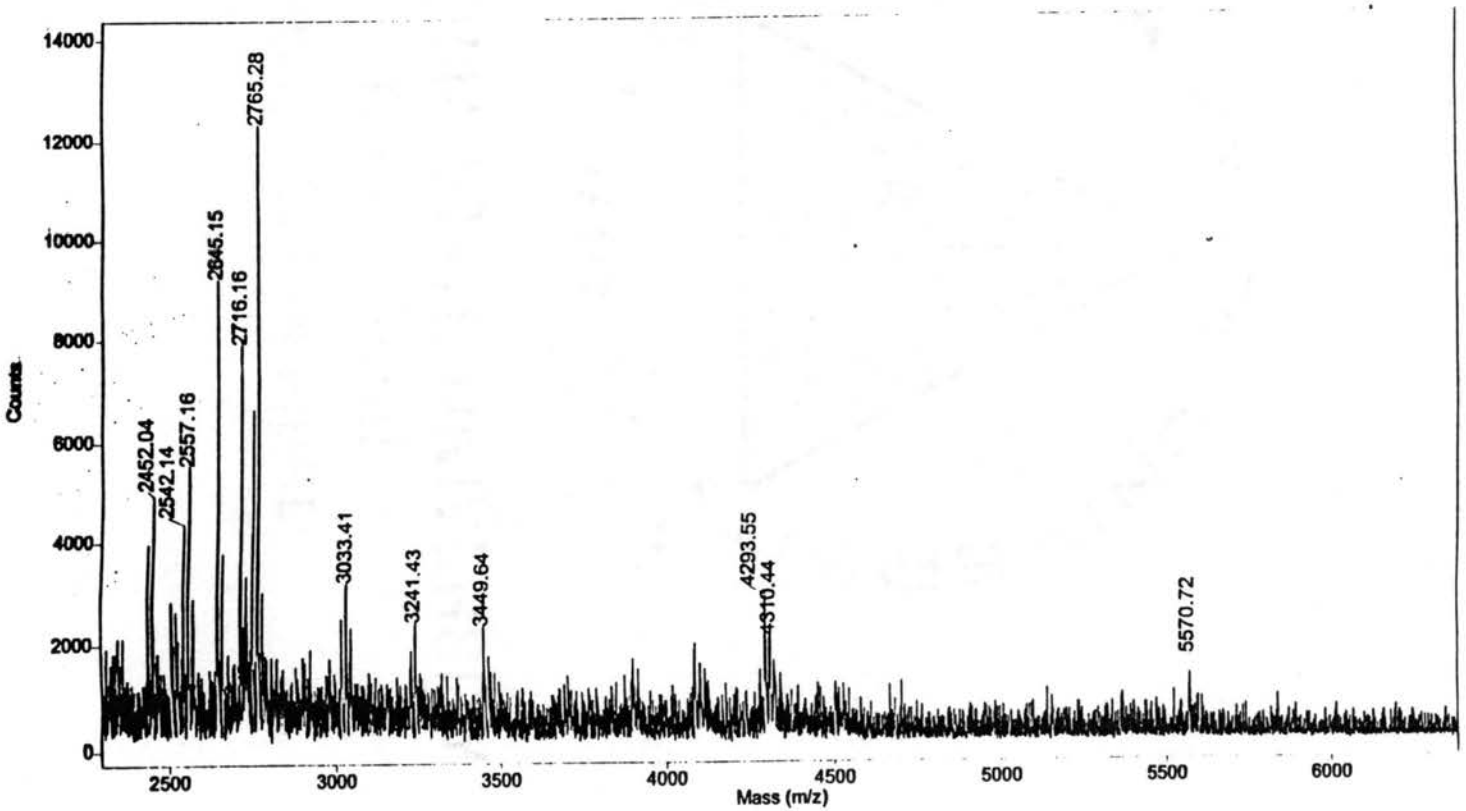


Figure 11. MALDI-TOF spectrumof ester-terminated dendron **15** in Chapter IV.



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