Synthesis and Solution State Self-Assembly of Linear-Dendritic Block Copolymers

By

Kristoffer Keith Stokes

B.S. Chemistry
Carnegie Mellon University, 2001

M.S. Chemistry
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Submitted to the Department of Chemistry
In Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy in Chemistry

At the

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Abstract

Linear-dendritic block copolymers consisting of a poly(styrene) linear block and poly(amidoamine) dendrimer block were synthesized and examined for their ability to self-assemble in both aqueous environments and organic/aqueous mixtures. These polymers were shown to assemble into vesicle structures under a variety of conditions. Furthermore, size measurements of the dendritic portion were taken by means of Langmuir-Blodgett isotherms, demonstrating both the steric area, as well as the electrostatic area occupied by the dendrimer in a monolayer. Further studies into the rapid synthesis of such systems were also undertaken, with a particular interest in use of the so-called "click" reaction to be used as a facile means toward block copolymer synthesis.

Thesis advisor: Paula T. Hammond
Title: Mark Hyman, Jr., Professor of Chemical Engineering

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Table of Contents

List of Figures

List of Schemes

List of Tables

Chapter 1 : Introduction

1.1.Motivation

Dendrimers are amazing molecules that have myriad uses. The fractal-like nature of the dendritic architecture lends itself towards applications as varied as controlled/targeted drug delivery,[1-5] encapsulation,[6] environmental remediation,[7] and recyclable catalysts.[8,9] Additionally, dendrimers have found applications as optical limiting materials,[10-14] molecular antennae,[15] and nanoparticle synthesis templates.[16-19]

These materials indeed are quite useful, however, dendrimers, as currently envisioned, suffer from several drawbacks. For use as drug delivery agents, their size is simply too small, and are eliminated much too quickly from the body to be of significant therapeutic use.[20] Additionally, many of the encapsulation applications are hindered by the limited void space which host the smaller guest molecules. For example, in a spherical poly(amidoamine) (PAMAM) dendrimer of generation 3-4, studies by Kojima, *et al.* suggest that only six to twenty hydrophobic molecules can be hosted within one dendritic macromolecule.[21] Furthermore, using PAMAM as an electrostatic complexing agent, up to 78 molecules can be complexed per dendrimer.[1] However, this

complex is still roughly a one to one weight ratio, and the controlled delivery is virtually negated in buffered solutions.

Additionally, the symmetrical nature of the molecule reduces the possibilities for differential functionalization on the surface. That is, dendrimers must be customized in the design phase. Using a stock solution of dendrimer to functionalize one side of the molecule in one manner, while functionalizing the other side of the molecule in a different manner, will only result in a statistical distribution of functionalizations, rather than a targeted functionalization as desired. Therefore structures such as amphiphilic dendrimers become difficult to synthesize. There do exist methods[22] to accomplish this task, but again, the molecules must be customized before synthesis with several protection steps, adding to the cost, and thus reducing the utility.

Altering the topology of dendrimers offers an attractive alternative. The addition of a linear polymer delivers the possibility of utilizing block copolymer assembly, in both the bulk phase and solution phase, to accomplish tasks that, alone, PAMAM could not.

1.2.Research Objectives

The goal of this research is to synthesize linear-dendritic hybrid copolymers and explore their solution state aggregation behavior. This is done as fundamental research into the dilute solution behavior to increase the understanding of these molecules. Further understanding of this solution

assembly behavior can lead to advances in encapsulation applications such as drug delivery and environmental remediation. Additionally, explorations into alternative syntheses of these molecules can deliver insight into future work and rapid exploration of structure-property relationships.

1.3.Background

1.3.1.Dendrimers

Dendritic structures have been synthesized for several decades now[23-28]. They are highly functional and predictably branched monodisperse polymers.[29] This is in direct comparison to the so-called hyperbranched polymers, which maintain the high degree and density of functionality that dendrimers exhibit, but without the regularity in branching or monodispersity.[30-32] the regularity and predictability of branching, as well as the monodispersity makes dendrimers more appealing as a subject of fundamental studies into branched polymers.

Dendritic systems are composed of a focal point, or the origin of branching, and *generations* explaining the degree of branching. Similar to the genealogical term, it refers to the distance a particular set of branches is from the original focal point. The term generation is defined differently for different systems. For example, Tomalia, *et al.* define generation 0 in the PAMAM system as the first generation after using a diamine core, a dendrimer with 4 branches.

Therefore, the ethylene diamine core would be generation –1, but is usually referred to as simply, the core. In other systems, the simplest functional group that a dendrimer can be started from can be referred to as either the core or generation 0. It is important that while reading the literature, one is aware of the conventions as applied by the author.

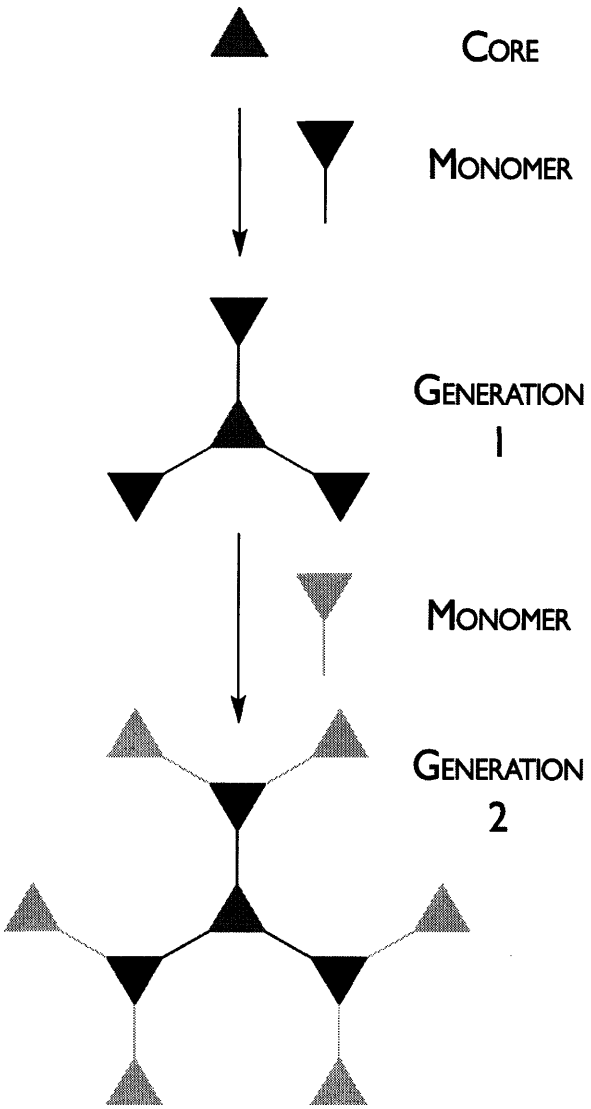

Figure 1.1: Schematic demonstrating the core-to-periphery nature of divergent dendrimer synthesis.

Two methods exist in synthesizing dendritic systems, convergent and divergent. These terms are directly analogous to their usage in general organic synthesis. Divergent methods begin at a focal point and involve a series of reactions to build generation upon generation to arrive at the periphery. The first method is common to many dendritic systems and is easily applied to many different chemistries. Various functionalities including esters,[33] amines,[34] amides,[26,27] and ethers[35] have been used to great effect. Figure 1.1 demonstrates the principle of divergent dendrimer synthesis.

Though the divergent methods dominated the synthetic schemes of the early dendrimer field, convergent methods have been increasingly used by chemists. The convergent methods involve synthesis from the periphery to the core in strict contrast to the divergent method (Figure 1.2). This type of synthesis allows for higher yields and greater purities than can usually be achieved by divergent methods. A more thorough review of the subject can be found elsewhere.[36]

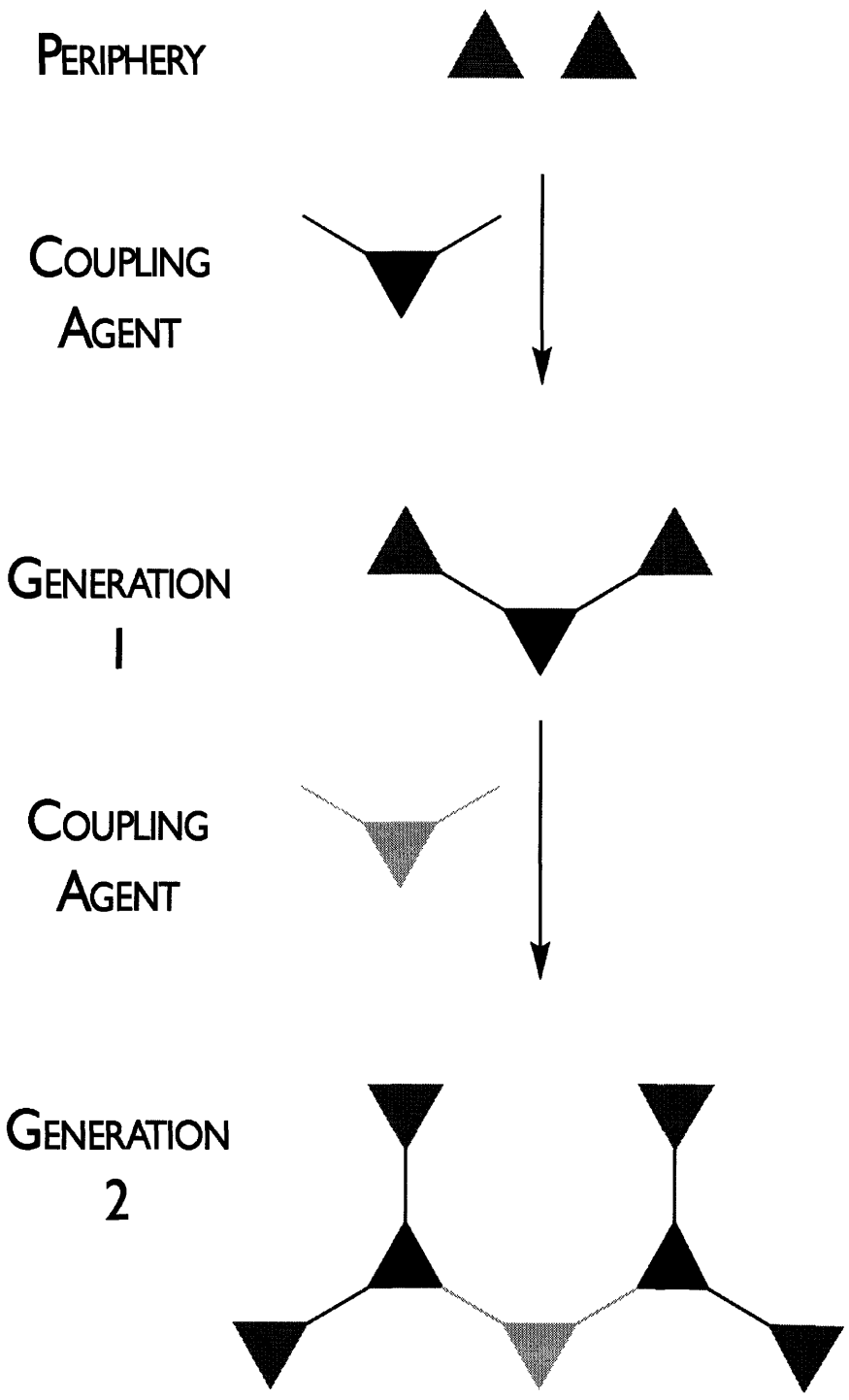

Figure 1.2:Schematic demonstrating the periphery-to-core nature of convergent dendrimer synthesis.

1.3.2. Linear-Dendritic Copolymers

Dendrimers, by themselves, are intrinsically interesting, however, researchers have attempted to increase their utility while exploring the properties of regularly branched molecules by using traditional block copolymer chemistry in conjunction with dendritic macromolecules.[37,38] By attaching a linear polymer, in some manner, to a dendritic polymer, the effect of regular, fractal-like branching on polymer assembly and polymer properties can be explored. The ordinary linkages one might imagine with linear type polymers have also been explored with their dendritic analogues. (Figure 1.3)

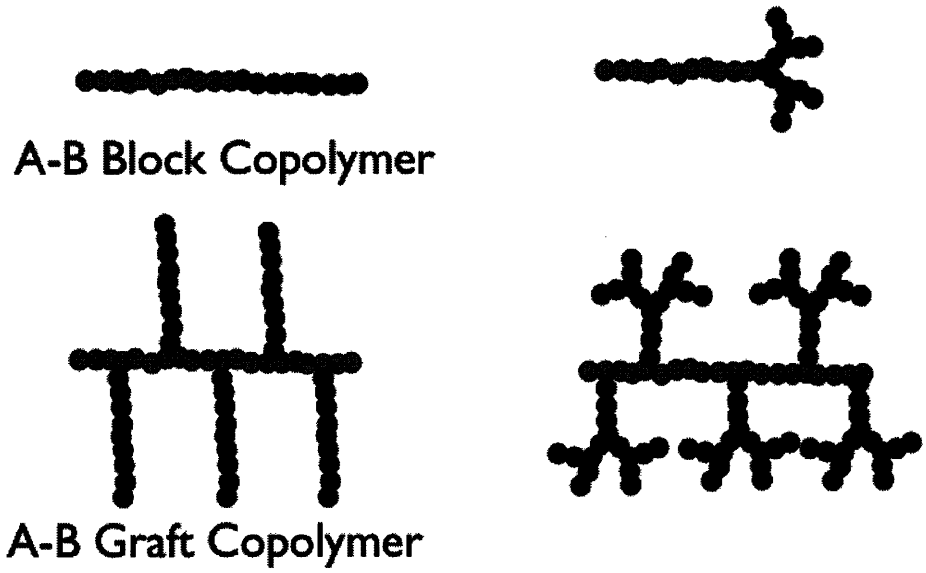

Figure 1.3: Examples of linear-linear block copolymer topologies (left), contrasted against comparable linear-dendritic topologies (right).

Though much work was accomplished in the early 1990s on the synthesis of such molecules,[39,40] the assembly of the linear-dendritic polymers was first

touched upon by Gitsov and Fréchet using a poly(benzyl ether)-*b*-poly(ethylene oxide) copolymer.[41] In this study, the assembly behavior in various solvent systems were analyzed as well as the resulting lyotropic liquid crystalline formation. Later, Meijer, *et Al.* synthesized and characterized the assembly behavior of an amphiphilic polystyrene with a dendritic poly(ethylene imine) block.[42-45] These molecules demonstrated various micellar morphologies as a function of generation and pH. For example, the self-assembly shows vesicle structures for generation 3, whereas generations 4 and 5 led to micellar rods and spherical micelles, respectively.

More recent accomplishments in the field include further synthesis of various combinations of linear blocks and dendrimers. Of particular note is the collected work of the Hammond lab.[46-52] The Hammond group has achieved the synthesis of both block-type and graft-type linear-dendritic block copolymers, as well as various assemblies of these polymers. Solid state,[51] solution state,[49,50] and interfacial assembly[50,52-54] has been explored by this group.

Though much is taken, much abides; these polymers continue to be interesting to researchers for their branching density, solid state morphology, and solution behavior. Further studies into their assembly behavior, however, are necessary to understand how to best utilize their unique structure-property relationship.

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Chapter 2 : Divergent Synthesis of Poly(styrene)-*block*-poly(amidoamine)

2.1.Introduction

Dendritic macromolecules have been synthesized in a variety of ways over the course of several decades.[15,24,36,55,56] These molecules have wonderful encapsulation properties[57,58] and a high density of functional groups[59-61], as well as other unique properties[10,62] that can be directly attributed to their monodispersity and fractal-like, highly branched structure. However, these materials also suffer from drawbacks in applications because of their small physical dimensions. For example, when looking at encapsulation applications, two aspects are immediately evident. The first is the physical size of the dendrimers.

Typical guest-host dendrimer encapsulation relies on hydrophobic void spaces to contain similarly hydrophobic guests. Within each dendritic host, only a few guest molecules can be present due to the limited void space within the dendrimer. Kojima, *et al.* reported 6-26 hydrophobic guest molecules per dendrimer in generations 3 and 4.[21] Other drugs such as ibuprofen interact differently with the PAMAM, instead preferring an electrostatic complex rather than hydrophobic interactions in a 78:1 ibuprofen to dendrimer ratio.[1] Even in this case, the complex requires a nearly 1:1 weight ratio of drug to dendrimer and it retains only modest stability under reasonable drug delivery

conditions. Therefore, in a therapeutic application, there would be a large amount of dendrimer delivered with the therapeutic agent.

Large doses of dendrimer become problematic for two reasons. First, and foremost is the cost of the system. Large dendritic structures are quite expensive due in great part to their purification procedures. Additionally, some dendritic systems, especially PAMAM, are quite cytotoxic,[20,63-65] much to the detriment of the patient. Moreover, it has been seen that dendrimers are removed from the body rapidly upon introduction[20] due to their small size, negating a controlled or targeted delivery application. These are both conditions that are inherent with the use of dendritic systems.

These limitations have forced research into alternative topologies to take advantage of the dendritic architecture, but mitigate the drawbacks.[39,42,66] One approach is to incorporate various types of linear polymers into the architecture. Inclusion of a hydrophobic linear block, for instance, can increase the utility of the dendritic architecture. By creating an amphiphilic macromolecule, higher order superstructures could be formed in solution. Aggregates of such polymer components could nullify the previously listed drawbacks to dendrimers. Such structures can retain the high functional group density of the dendrimers for multivalent interactions[67], but form an expandable dendritic surface around encapsulated molecules, rather than relying on the limited void space inside the dendrimer. Furthermore, aggregates can increase the retention rate *in vivo* due to the increased size.

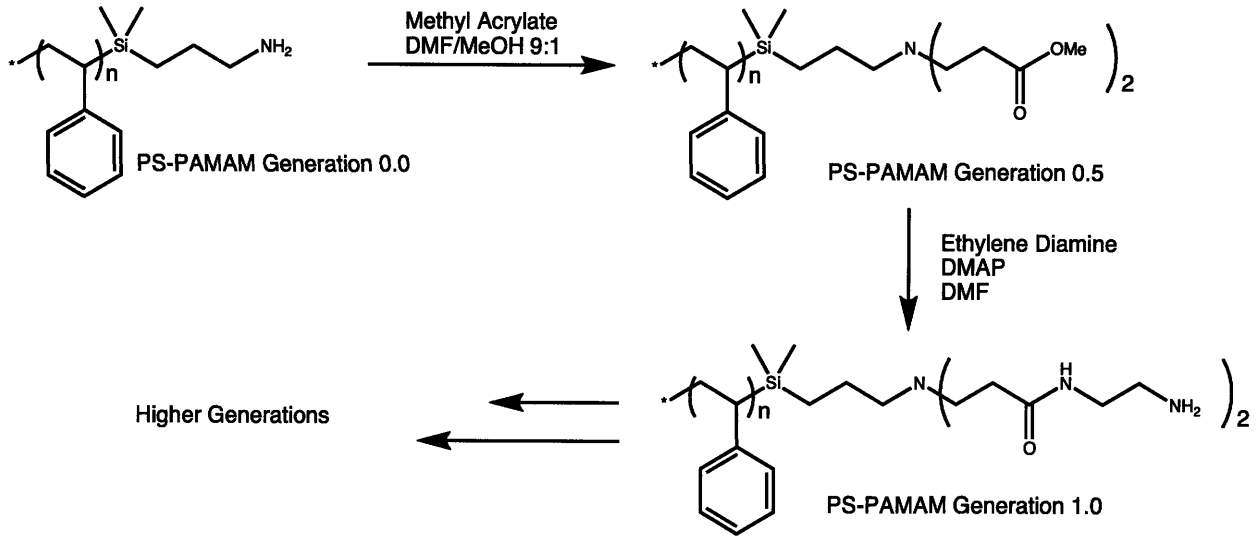
Here we report the synthesis of linear dendritic block copolymers with a poly(styrene) linear block and a poly(amidoamine) dendritic block. Using the poly(styrene) as a linear hydrophobic block, and the poly(amidoamine) as a dendritic hydrophilic block, solution phase supramolecular assemblies can be formed and studied. The creation of such molecules can lend insight into the behavior of highly branched systems and their interactions as a component of a block copolymer.

2.2.Results and Discussion

2.2.1.Synthesis of poly(styrene)-*b*-poly(amidoamine)

The general synthetic scheme is depicted in Scheme 2.1. It is slightly adapted from the Tomalia methodology[24,68] to allow for the hydrophobic nature of a polystyrene block. The exhaustive Michael addition and amidation reactions can be repeated sequentially to build up the desired dendritic generation. An example of the structure of a generation 3.0 PS-PAMAM is illustrated in Figure 2.1.

Scheme 2.1: Synthetic pathway for PS-PAMAM. These two steps are repeated to build higher generations.



Here, an amine-terminated polystyrene is dissolved in dimethylformamide (DMF) and at least 50 equivalents of methyl acrylate. Since each amine can add two molecules of methyl acrylate, that becomes a 100:1 molar ratio of polymer end groups to acrylate molecules. This large excess is used to create favorable conditions for acrylate addition in the presence of considerable steric hindrances and less than favorable solvent conditions.

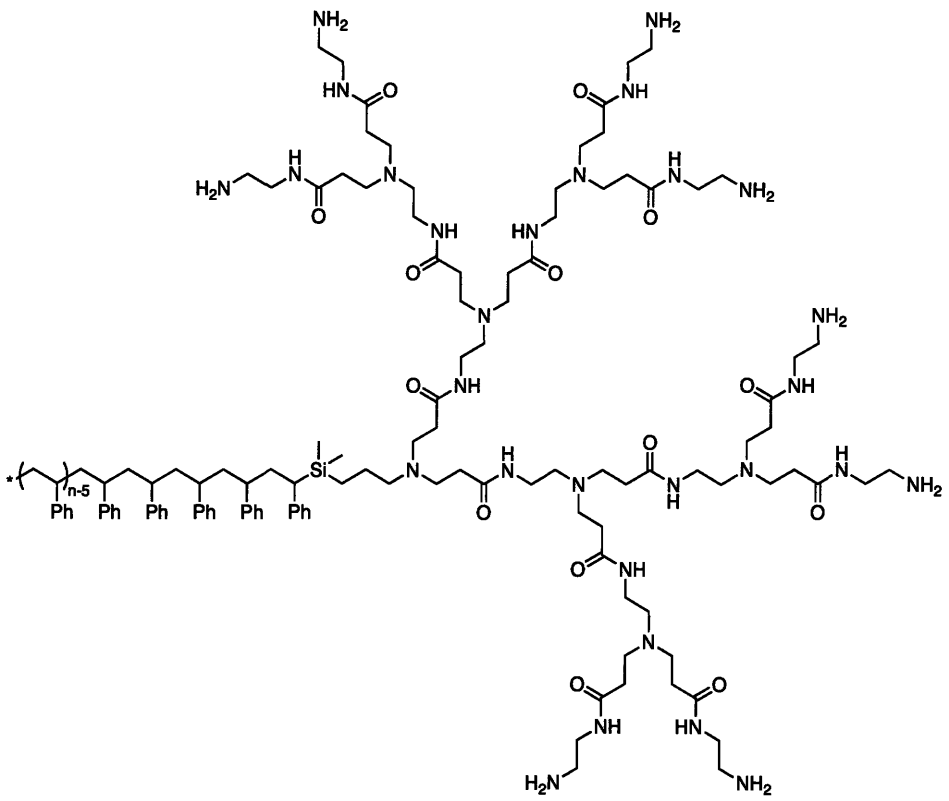


Figure 2.1: Chemical structure of a PS-PAMAM generation 3.0 block copolymer

Additionally, a small portion of methanol is added to the solution to encourage proton transfer during the Michael addition reaction. Methanol will make the PS solution less stable, but one can add methanol until the PS begins to precipitate, followed by an additional portion of DMF to redissolve the polymer. Typically, the solution can be up to 10% methanol before this occurs, but that is dependent on PAMAM generation as well. Reaction times are dependent on generation but for this Michael addition step, they range from 36-72 hours at room temperature, with the longer reaction times reserved for larger generations. (Table 2.1) The long reaction times address two issues. First, it helps ensure complete reaction with each amine. Since each amine end group requires two additions of methyl acrylate, the steric congestion can rapidly become a major

hindrance to complete reaction. Second, since the reaction medium is not ideal for the Michael addition reaction to occur, the longer reaction times are necessary to encourage a complete reaction.

Table 2.1: Reaction time in hours for each generation of PS-PAMAM

	Reaction Time (h)		
Generation	Michael Addition	Generation	Amidation
0.5	36	1.0	48
1.5	36	2.0	72
2.5	36	3.0	96
3.5	48	4.0	120
4.5	48	5.0	144
5.5	72	6.0	168

The amidation reaction to complete the PAMAM generation is also quite simple. A solution of ethylene diamine and DMF is prepared. Additionally, a catalytic amount (*ca.* 20 mol%) of dimethylaminopyridine (DMAP) is added. DMAP acts as an amidation catalyst, helpful in forcing the reaction to completion. The ethylene diamine solution is stirred and heated to 80˚C, at which point the polymer solution is added dropwise over the course of two hours. Slow addition to a large excess of diamine is required to avoid cyclic byproducts of the amidation[68] and encourage the reaction to occur in spite of the large steric hindrances. This portion of the synthesis, much like the Michael addition, has a generation dependent reaction time, ranging from 48 hours to one week (Table 2.1). Similar timescales have been used for other systems where dendritic growth is discouraged.[69]

2.2.2.Characterization

The progress of the reaction can easily be tracked via IR analysis. With each half-generation of dendrimer, the spectrum changes significantly. The ester-type carbonyl peak from a generation X.5 dendrimer is converted At 1739 cm^{-1}, the carbonyl in the ester following the Michael addition appears in the spectrum. Following the reaction with ethylene diamine, the ester peak disappears and is replaced with an increasing amide (1670 cm^{-1}) stretch. Additionally, the amine stretch around 3400 cm^{-1} increases in intensity as a function of generation. Within this broad strech also lies the amide N-H stretch.

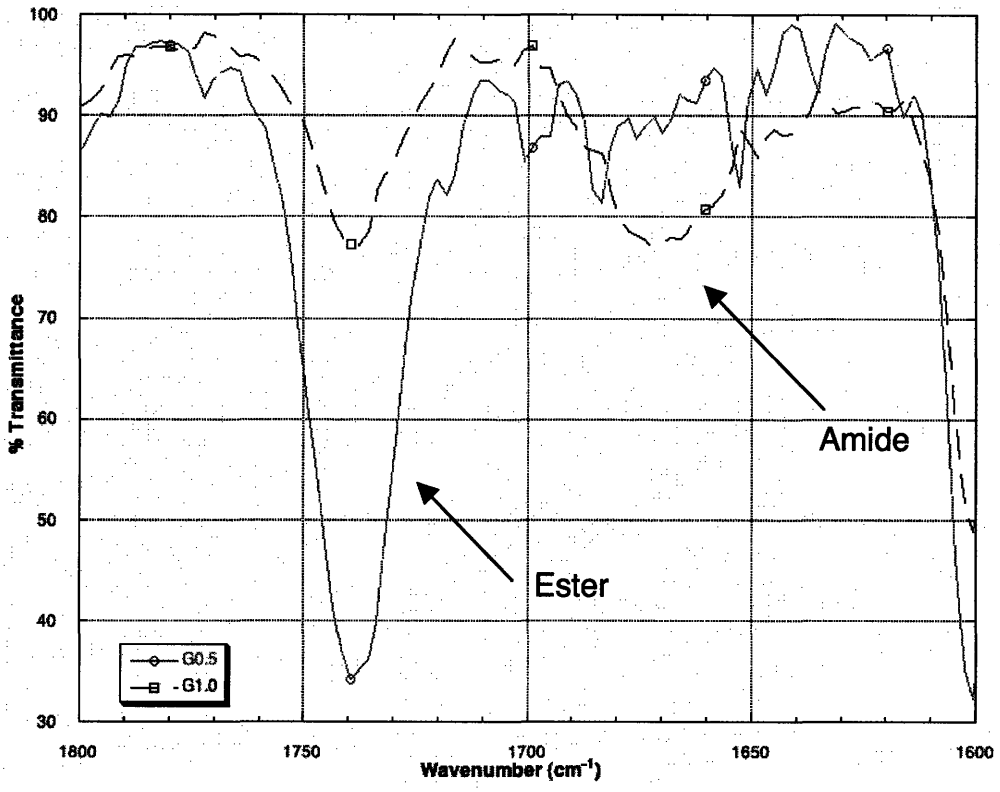


Figure 2.2: IR spectrum comparing G 0.5 to G 1.0. Note the carbonyl absorptions at 1740 (ester) and 1670 (amide).

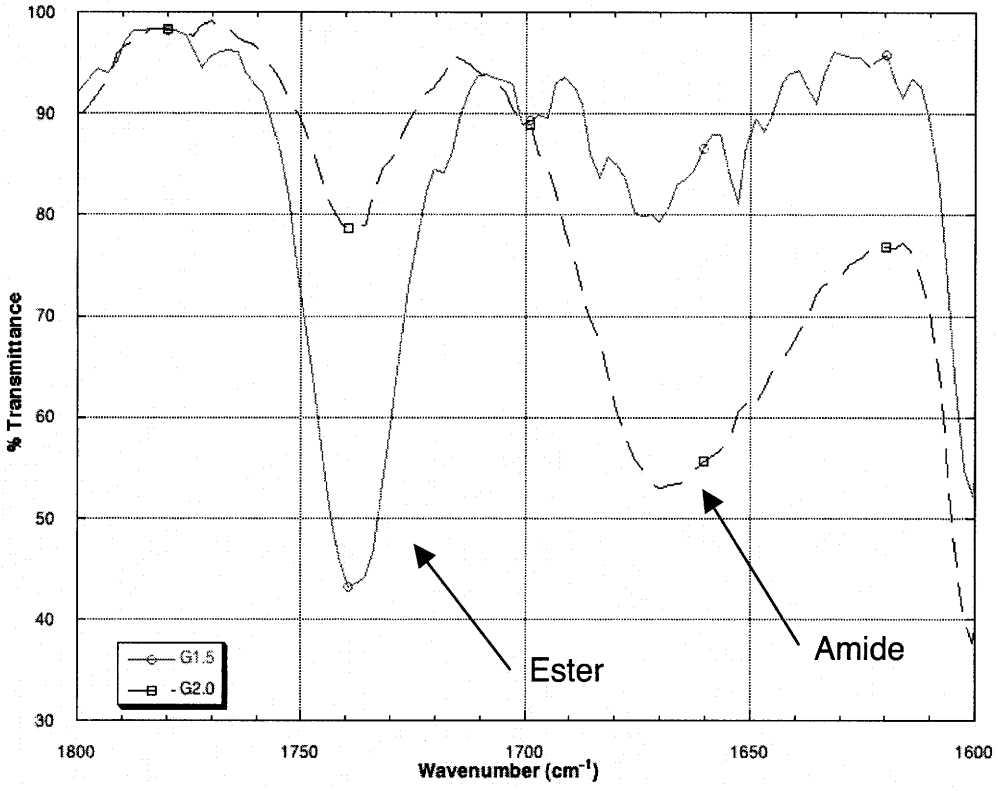


Figure 2.3: IR spectrum comparing G 1.5 to G 2.0. Note the carbonyl absorptions at 1740 (ester) and 1670 (amide).

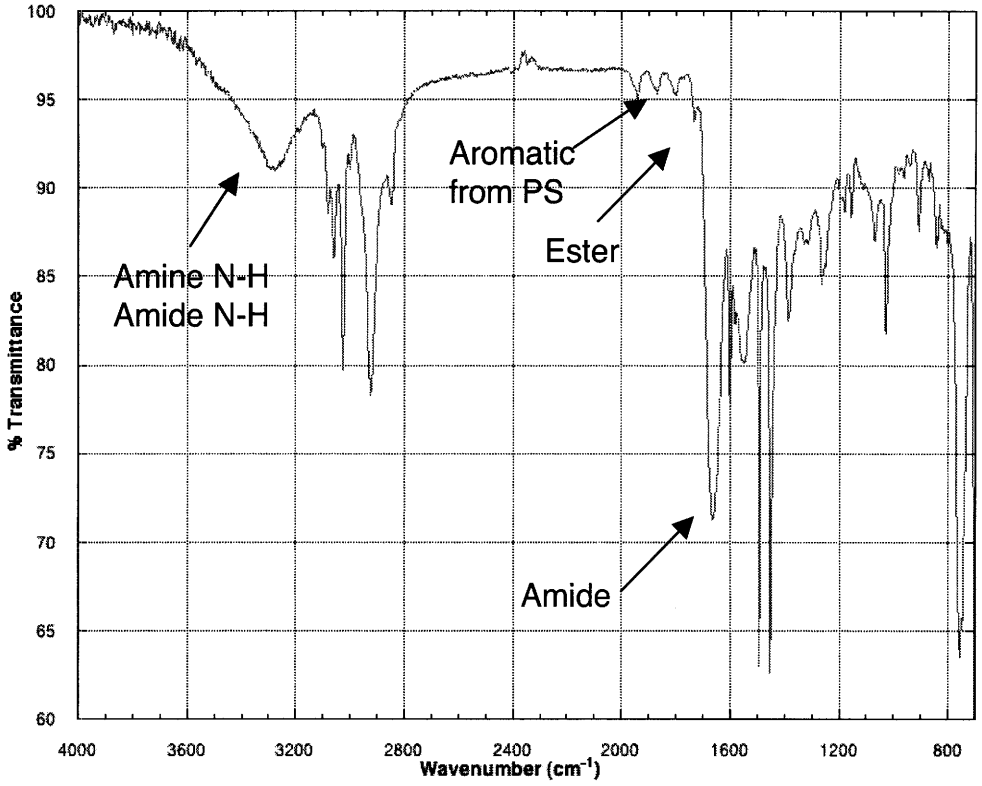


Figure 2.4: FTIR spectrum of PS-PAMAM generation 6.0. Carbonyl contributions arise from PAMAM while aromatic contributions come from PS.

Figure 2.5 depicts the ^{1}H NMR spectrum of PS-PAMAM generations 0.0-3.0. Here, the growth of characteristic PAMAM peaks can be seen clearly as most of the PAMAM resonances appear between 2.0 and 4.0, whereas much PS appears further downfield in the 6.0-7.0 range for the aromatic protons. There does exist some overlap between the aliphatic PS backbone protons and the aliphatic portions of the PAMAM dendrimer. This is marked in the figure.

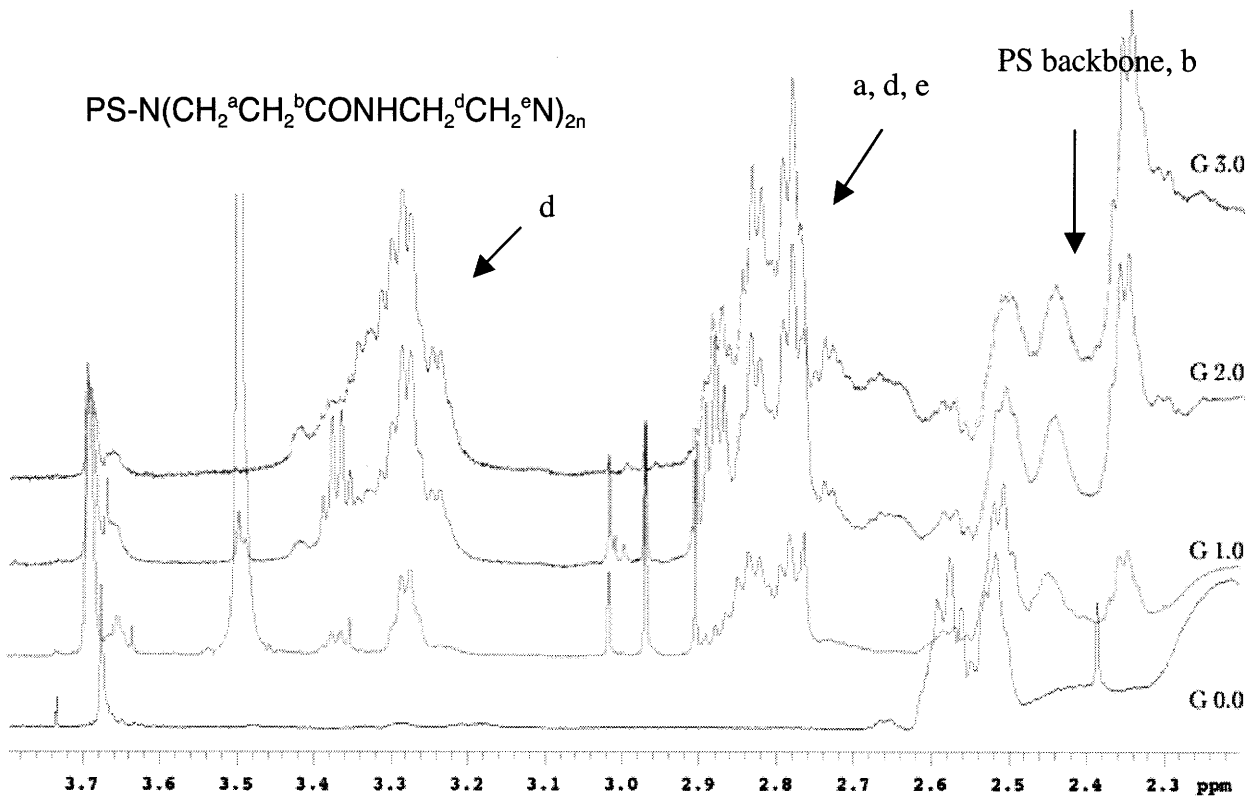


Figure 2.5: NMR of PS-PAMAM G 0.0-3.0. The spectra are enlarged and vertically offset to show the portion of the spectrum where the PAMAM peaks appear.

Molecular weight characterization is a much more difficult task on these polymers. It has been found that the typical characterization of polymers, gel permeation chromatography (GPC), does not provide accurate information for highly branched polymers, such as dendritic systems.[70] This is because GPC columns separate based on the hydrodynamic volume of the polymers, using a relative calibration with linear standards. Unfortunately, with highly branched systems, the relationship between hydrodynamic volume and molecular weight is not directly comparable to the linear block hydrodynamic volume. Whereas the hydrodynamic volume of an unknown linear polymer can be interpolated from a known linear standard

with decent accuracy, an unknown branched polymer cannot be similarly interpolated. Branched polymers add mass at a much greater rate than volume. Thus, the measured values for such a polymer are consistently lower than the theoretical values.

Matrix assisted laser desorption and ionization time of flight mass spectrometry (MALDI-TOF MS) can also be used to determine the molecular weight of polymer systems. This method was also utilized without success to determine the molecular weight of the polymer system. Many different matrices were used, but none were able to properly ionize the polymer for detection purposes. The linear generation 0 polymer was successfully analyzed, however, any amount of dendrimer added on to the polymer made detection impossible.

A third method of molecular weight characterization was also attempted. Static light scattering (SLS) is another means of determining molecular weight, however, the scattering from these molecules made it impossible to determine with any amount of accuracy.

2.3.Experimental

2.3.1.Materials

Amine terminated poly(styrene) with molecular weight of 2,500 $gmol^{-1}$ (PDI=1.15, f=0.98) was purchased from Polymer Source (Montreal, Quebec) and used as received. HPLC grade solvents and N,N-dimethylaminopyridine (DMAP), and were obtained from Sigma-Aldrich and also used as received. Methyl acrylate and ethylene diamine, obtained from Sigma-Aldrich, were distilled from CaH_2 under nitrogen before use. GPC analysis was performed on a Waters Breeze system with Waters separation columns (Styragel HT 3, HT 4, HT 5) and weight distributions recorded by a refractive index detector calibrated with monodisperse polystyrene samples (Sigma-Aldrich).

2.3.2.Procedure

2.3.2.1 Generalized synthesis of PS-PAMAM generation X.5

The synthesis of PAMAM from an amine-terminated polystyrene is straightforward.[68] The generation X.0 polymer is dissolved in a solution of N, N-dimethylformamide (DMF) with approximately 10% methanol cosolvent. Next, 50 equivalents (100 times the number of end groups) of methyl acrylate are added. The solution is then stirred at room temperature over the course of 36-72 hours. After the reaction is completed, the solution is then concentrated by removal of

methyl acrylate under reduced pressure and precipitation into methanol. At higher dendrimer generations or with a lower molecular weight PS, an ice and methanol precipitation may be more effective. The resulting half-generation precipitate is then vacuum filtered and collected for the next step.

2.3.2.2 Generalized synthesis of PS-PAMAM generation X.0

Obtaining the full generation polymer is completed by the addition of an ethylene diamine unit to the methyl ester end groups of the half-generation. The X.5 generation polymer is dissolved in a minimal amount of DMF and added dropwise to a solution of ethylene diamine (50 equivalents) and N, N-dimethylaminopyridine (DMAP, 20 mol%), already heated to 80°C. After the slow addition of the generation X.5 polymer over the course of 2 hours, the solution is stirred, maintaining the temperature for a period of time between 2 days (for low generations) and 7 days (for high generations). After the reaction has completed, the excess ethylene diamine is removed under vacuum, and the resulting solution precipitated in methanol, or for higher generations, ice and methanol. The precipitate is then recovered by vacuum filtration and collected.

2.3.3.Characterization

Polystyrene (2.5k)-PAMAM generation 0.5: ^{1}H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.75 (m, $COOCH_3$), 2.5-3.2 (br, $N\text{-}CH_2$), 2.5-

0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 30.8, 8.7, 6.2. FTIR ν (cm^{-1}) 1739 (Ester C=O).

Polystyrene (2.5k)-PAMAM generation 1.0: ^{1}H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.37 (m, CONHC**H**$_2$), 3.24 (m, CONHC**H**$_2$), 2.9-2.5 (br, NC**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$, partial) δ 39.8, 37.6, 30.8, 6.2. FTIR ν (cm^{-1}) 3400 (N-H), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 1.5: ^{1}H NMR (300 Mhz, $CDCl_3$) 7.3-6.2 (br, aromatic protons from PS), 3.75 (m, COOC**H**$_3$), 2.5-3.2 (br, N-C**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 40.5, 39.8, 37.6, 8.8, 6.4. FTIR ν (cm^{-1}) 1739 (Ester C=O), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 2.0: ^{1}H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.4-3.2 (br, CONHC**H**$_2$), 2.9-2.5 (br, NC**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 39.8, 37.5, 30.8, 24.0, 8.7, 6.0. FTIR ν (cm^{-1}) 3400 (N-H), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 2.5: ^{1}H NMR (300 Mhz, $CDCl_3$) 7.3-6.2 (br, aromatic protons from PS), 3.75 (m, COOC**H**$_3$), 2.5-3.2 (br, N-C**H**$_2$), 2.5-0.3

(br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 40.7, 39.8, 37.5. FTIR ν (cm^{-1}) 1739 (Ester C=O), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 3.0: ^1H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.4-3.2 (br, CONHC**H**$_2$), 2.9-2.5 (br, NC**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 44.3, 39.8, 37.5, 30.8, 6.0. FTIR ν (cm^{-1}) 3400 (N-H), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 3.5: ^1H NMR (300 Mhz, $CDCl_3$) 7.3-6.2 (br, aromatic protons from PS), 3.75 (m, COOC**H**$_3$), 2.5-3.2 (br, N-C**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 44.3, 40.6, FTIR ν (cm^{-1}) 1739 (Ester C=O), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 4.0: ^1H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.4-3.2 (br, CONHC**H**$_2$), 2.9-2.5 (br, NC**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 39.8, 37.5, 8.7, 6.0 FTIR ν (cm^{-1}) 3400 (N-H), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 4.5: ^1H NMR (300 Mhz, $CDCl_3$) 7.3-6.2 (br, aromatic protons from PS), 3.75 (m, COOC**H**$_3$), 2.5-3.2 (br, N-C**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 41 (br). FTIR ν (cm^{-1}) 1739 (Ester C=O), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 5.0: ^{1}H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.4-3.2 (br, CONHC**H**$_2$), 2.9-2.5 (br, NC**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$, partial) δ 39.8, 37.5. FTIR ν (cm^{-1}) 3400 (N-H), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 5.5: ^{1}H NMR (300 Mhz, $CDCl_3$) 7.3-6.2 (br, aromatic protons from PS), 3.75 (m, COOC**H**$_3$), 2.5-3.2 (br, N-C**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 41(br). FTIR ν (cm^{-1}) 1739 (Ester C=O), 1672 (Amide C=O)

Polystyrene (2.5k)-PAMAM generation 6.0: ^{1}H NMR (300 Mhz, $CDCl_3$) δ 7.3-6.2 (br, aromatic protons from PS), 3.4-3.2 (br, CONHC**H**$_2$), 2.9-2.5 (br, NC**H**$_2$), 2.5-0.3 (br, backbone protons from PS). ^{13}C NMR (500 Mhz, $CDCl_3$) δ 128 (br), 41(br), 39.8, 37.5, 30.6, 8.7. FTIR ν (cm^{-1}) 3400 (N-H), 1672 (Amide C=O)

2.3.4.Conclusions

PS-b-PAMAM linear-dendritic block copolymers were synthesized in a divergent manner following a variation of the Tomalia method. FTIR and NMR characterization demonstrate the fractal-like growth of the dendritic block while retaining the styrene moiety. These polymers can be used in a variety of studies based on their unique topological structure.

2.4.References

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Chapter :3 Solution State Assembly of Divergent Poly(styrene)-*block*-poly(amidoamine)

3.1.Introduction

The behavior of amphiphilic self-assembly of block copolymers in solution has been a topic of great interest in recent years.[42,66,71-78] Much of the interest comes from the potential applications stemming from this technology. Micellar systems can use this aggregation behavior for encapsulation type applications, such as drug delivery[79-81] and environmental remediation.[7] Spontaneous formation of superstructures by amphiphilic molecules in solution is well documented[73,82-87]. More recently, block copolymers have sprung to the forefront of dilute solution self-assembly [76,79,88-91].

Micellar assembly is largely controlled via thermodynamics. Decreased solvent interactions with the hydrophobic portion while maintaining minimal unfavorable interactions between headgroups drives this phenomenon. The Israelachvili model of amphiphilic self-assembly[92] relies on molecular dimensions to predict solution state morphology (Figure 3.1).

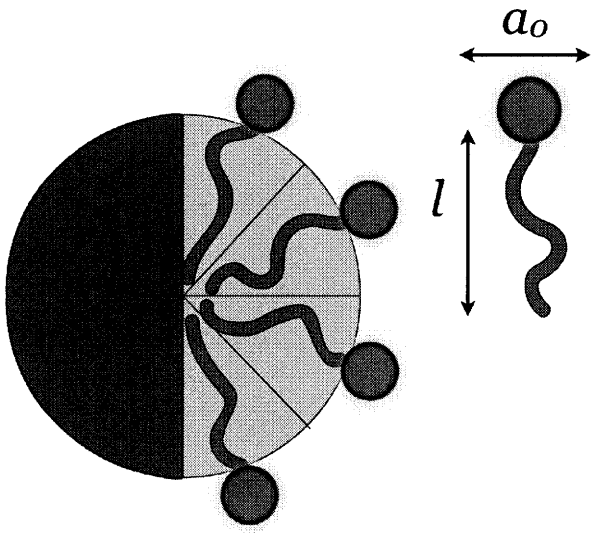

Figure 3.1. Israelachvili model of supramolecular assemblies. The term "*l*" refers to the hydrophobic length and "a_0" is the effective area of the headgroup.

This model takes into account the effective area of the head group area and compares it to the length and volume of the tail portion. What is retrieved from this ratio is a number, the "packing parameter", which serves as a reasonably good prediction of solution state morphology. Essentially, it is a geometric argument useful in determining what sort of molecular "shapes" can reasonably fit within a particular three dimensional geometry.

$$N_s = \frac{\upsilon}{la_o} \qquad (1)$$

The packing parameter (Equation 1) is composed of three important terms: υ, and l, the volume and length of the hydrophobic "tail" portion, respectively; and a_0, the effective area of the hydrophilic "head" group. By obtaining the packing parameter, one can predict whether the solution state morphology will display micelles ($N_s \leq 0.33$), cylinders ($N_s \leq 0.5$), or vesicles/bilayers ($N_s \approx 1.0$) (Figure 3.2).[92]

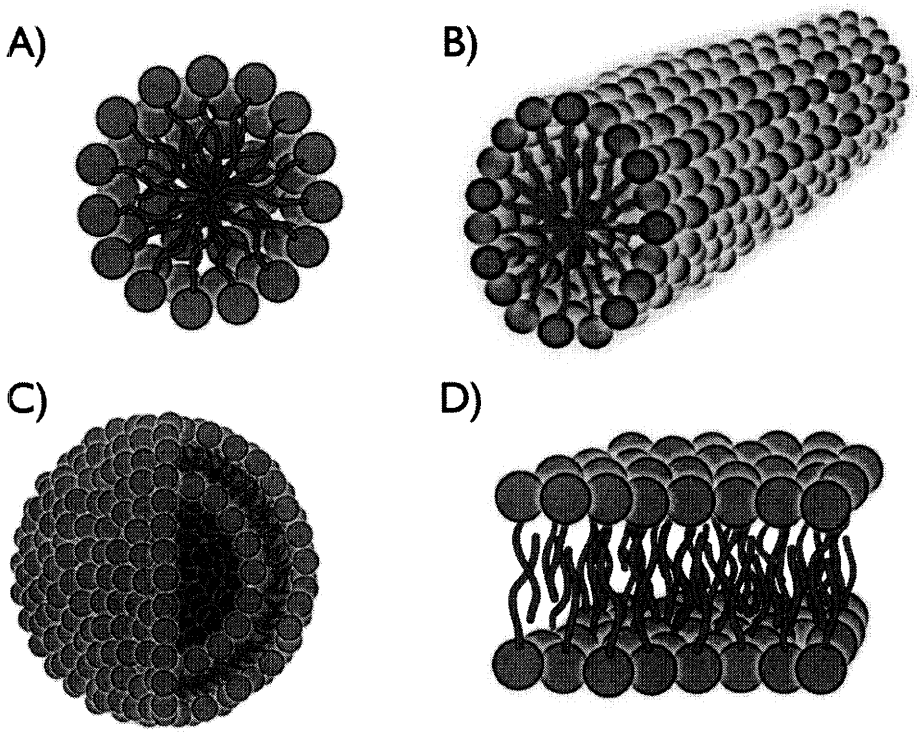

Figure 3.2: Various solution state morphologies: A) Micelle, B) Cylinder, C) Vesicle, D) Bilayer

Note that the term for the head group area is labeled with the term *effective*. This term takes into account not only the expected steric area, but also any interactions between adjacent head groups. By adding repulsive interactions and varying the size of

the head group, one should be able to affect the solution state morphology. Additionally, by changing the electrostatic interactions, the morphological Here we measure the size of the head group of linear-dendritic block copolymer system based on the poly(styrene)-*block*-poly(amidoamine) varied by dendrimer generation and degree of protonation.

3.1.1.Critical Aggregation Concentration

One important aspect of micellar assembly is that of critical aggregation concentration (CAC). Oftentimes, this is also referred to as the critical micelle concentration (CMC), however, for the purposes of this discussion, all aggregates will be considered, rather than only micelle forming systems.

The CAC is an important factor in the properties of amphiphilic systems. The basic scheme of CAC is seen in Figure 3.3. The CAC is determined as the concentration at which aggregates (micelles, vesicles, etc.) begin to form in solution. As amphiphiles are added to a solution, the concentration of individual molecules increases. This will continue until the concentration of added amphiphiles reaches the CAC. Once this concentration has been reached, any further addition of amphiphile will only increase the concentration of aggregates, the concentration of free, non-aggregated species will remain conastant. As depicted Figure 3.3, the discontinuity

delineates the CAC. The CAC also reveals the concentration of molecules that are unimeric* in solution.

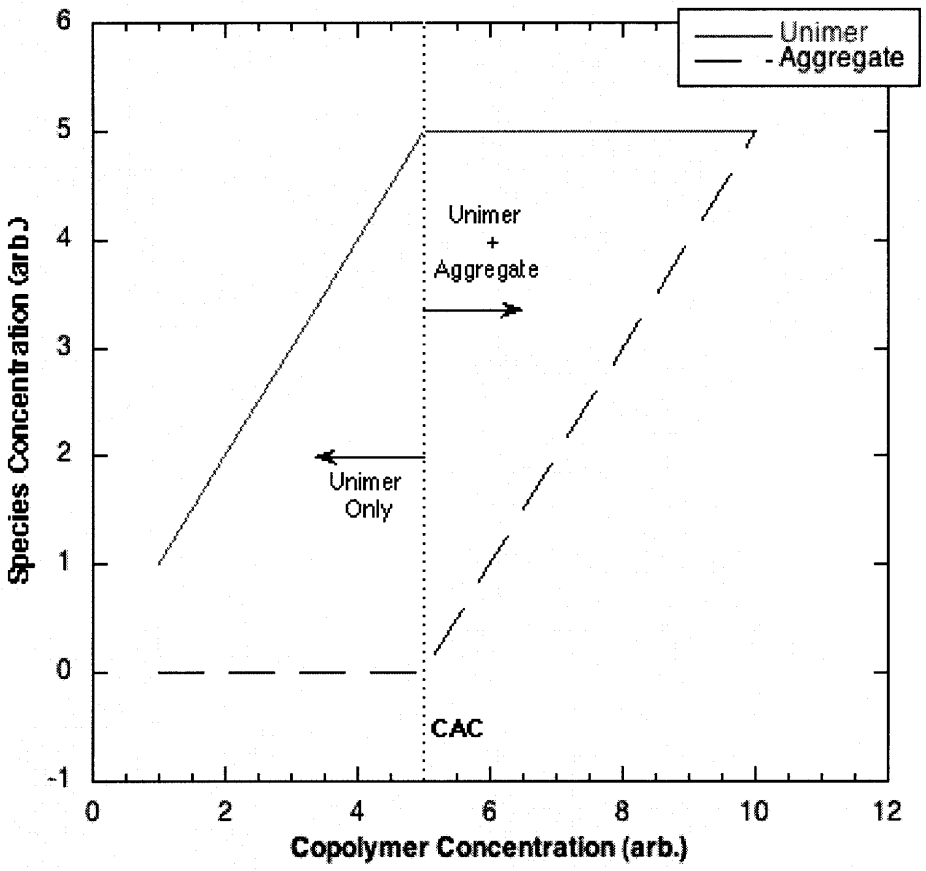

Figure 3.3: The concept of CAC summarized. At concentrations lower than the CAC, single molecules are the only species. Higher concentrations yield both unimer and aggregate species.

For small molecules, such as sodium dodecyl sulfate (SDS), the CAC can be in the millimolar range at room temperature. This number demonstrates that supramolecular aggregates do not form until the concentration is above this millimolar

* Literature will often refer to unaggregated molecules in a micellar solution as "monomer". Here to avoid confusion with the polymer synthesis term, I will refer to molecules that exist in solution but are not part of the aggregate structure as "unimers".

limit. Conversely, it also demonstrates that in a particular solution with aggregates, there is a constant concentration of free molecules equal to the CAC. Thermodynamically, the free energy of aggregation of a given system can be described by Equation 2.[93]

$$\Delta G^{\circ} = RT \ln (CAC) \qquad (2)$$

Therefore, it is immediately obvious that aggregates in systems with low CAC values are more thermodynamically stable relative to those with high CAC values.

Thus, CAC has an important role in the eventual application of supramolecular assemblies. For example, in drug delivery applications[84], it is necessary to keep the CAC of an aggregate system as low as possible to ensure stability as the structures are introduced to a medium with no unimer present. If a solution of aggregates is introduced to a medium, the immediate dilution would cause the already formed aggregates to dissociate until the concentration of unimer is equal to the CAC. In this case, any potential controlled delivery advantage of the colloidal system is negated as some of the aggregates will simply dissolve, immediately releasing whatever guest molecules reside within and destroying any type of controlled or targeted delivery for which the system was designed.

In this case, polymeric systems become attractive to use due to their low CAC values.[94] With CAC values typically below 10^{-6} M,[95] these systems exist mostly as the aggregate form. The aggregation keeps single molecule toxicity low and prevents premature release of the encapsulated treatment.

3.2.Results and Discussion

3.2.1.Critical Aggregation Concentration

Several methods exist for determining CAC values for a system. Techniques such as tensiometry and light scattering have been used to this end. However, these measurements are incapable of ascertaining the low values associated with some systems. Tensiometry was attempted, but was unsuccessful due to the extremely low CAC values. CAC measurements for this system were successfully made using the fluorescence method that has been well documented for block copolymer systems.[93] This method involves utilizing the vibrational structure of pyrene obtained by fluorescence spectroscopy to ascertain the nature of the pyrene environment. Emission spectra of pyrene show the vibronic fine structure quite well. Because of this, one can easily note the differences in the local environment due to the relative ratios of the vibronic peaks.[96] If the pyrene remains in an aqueous environment, as it would in a solution of amphiphiles under the CAC, the ratio of the first (I_1 = 373) and the third (I_3 = 393nm) vibrational modes is nearly unity. Once the concentration of amphiphiles has increased to the point of aggregation, the soluble pyrene can leave the undesirable hydrophilic solvent for the energetically favorable hydrophobic pockets created by the amphiphile assembly. In this case, the ratio then increases as a function of concentration.

Figure 3.4 demonstrates typical spectra obtained from this analysis. Note that this analysis can also be performed on excitation spectra of pyrene, with similar results. In the case of the excitation spectra, the ratio of intensities between the peaks at 335 and 340 can be similarly analyzed.

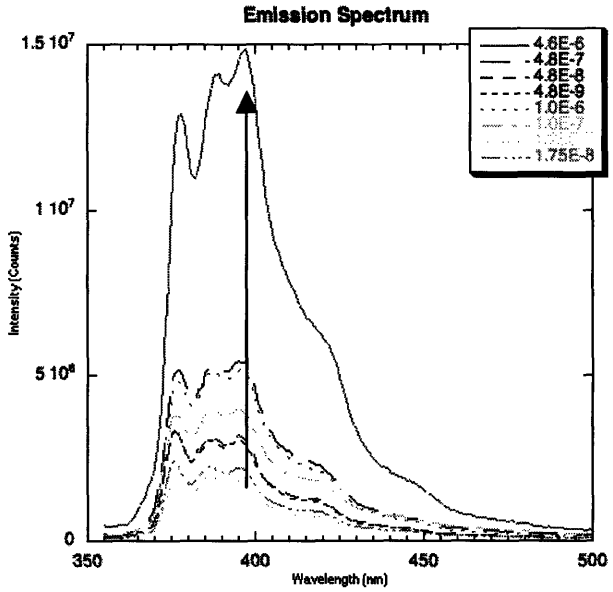

Figure 3.4: Typical emission spectrum from pyrene in solutions of various concentrations of PS-PAMAM generation 3.0. The arrow points in the direction of increasing amphiphile concentration.

A graph of dendrimer generation versus CAC values from the measurements of PS-*b*-PAMAM can be seen in Figure 3.5. Here one can note the difference in CAC as a function of generation. Generations 0, 1, and 2 were not measured because the polymers were unable to form a stable dispersion in water. It can be seen that, generally speaking, the CAC is higher for the low pH system than the high pH system. This can

be attributed to the charging of the PAMAM dendrimer portion of the block copolymer. Two different interactions can contribute to this behavior.

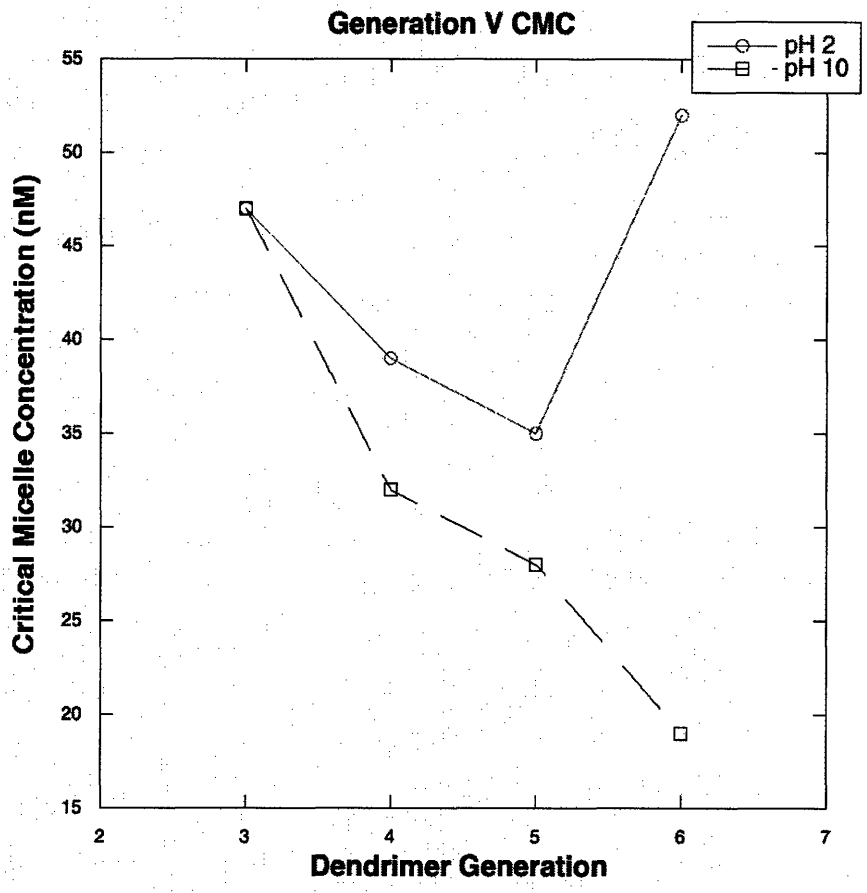

Figure 3.5: Dendrimer generation versus CAC for PS-PAMAM for both fully charged and fully uncharged PAMAM species. These measurements were taken with a constant ion concentration of 0.01 M.

The first is polymer-solvent interactions. With a greater degree of charge on the dendritic portion, it becomes more water soluble. This increases the stability of single chains in solution, decreasing the need for the stabilizing interactions afforded by the amphiphilic assembly. The second interaction is in the form of polymer-polymer

interactions. As the dendrimer portion becomes charged, electrostatic interactions begin to have a greater effect. At large generations, this interaction becomes quite substantial. The energy required to overcome the electrostatic interactions becomes more than the stabilization afforded by aggregation. Thus, the favorability of the aggregate formation is eradicated by the unfavorable intermolecular interactions.

3.2.2.Transmission Electron Microscopy

The establishment of the aggregate forming behavior of the polymers next requires some idea of the nature of the aggregates. Though measures of size can be obtained from light scattering of various sorts, the size distribution obtained is only an indirect means of measurement. A more direct measurement can be obtained by transmission electron micrcoscopy (TEM).

In this system, the glassy behavior of the PS block is sufficient for microscopy of the vesicles with TEM. Using a solvent with high volatility, such as THF, the vesicle structure is preserved for microscopy to be performed. Two methods of staining were used to provide contrast for imaging. One, ruthenium tetraoxide, was applied as a vapor and acts as a general stain. Neither block was preferably stained by this method, however, it provided a good means to visualize the vesicle structures on the substrate. The other method was the use of negatively charged gold nanoparticles to be used to interact with the dendritic portion of the polymer. A comparison between the two methods can be seen in Figure 3.6 and Figure 3.7.

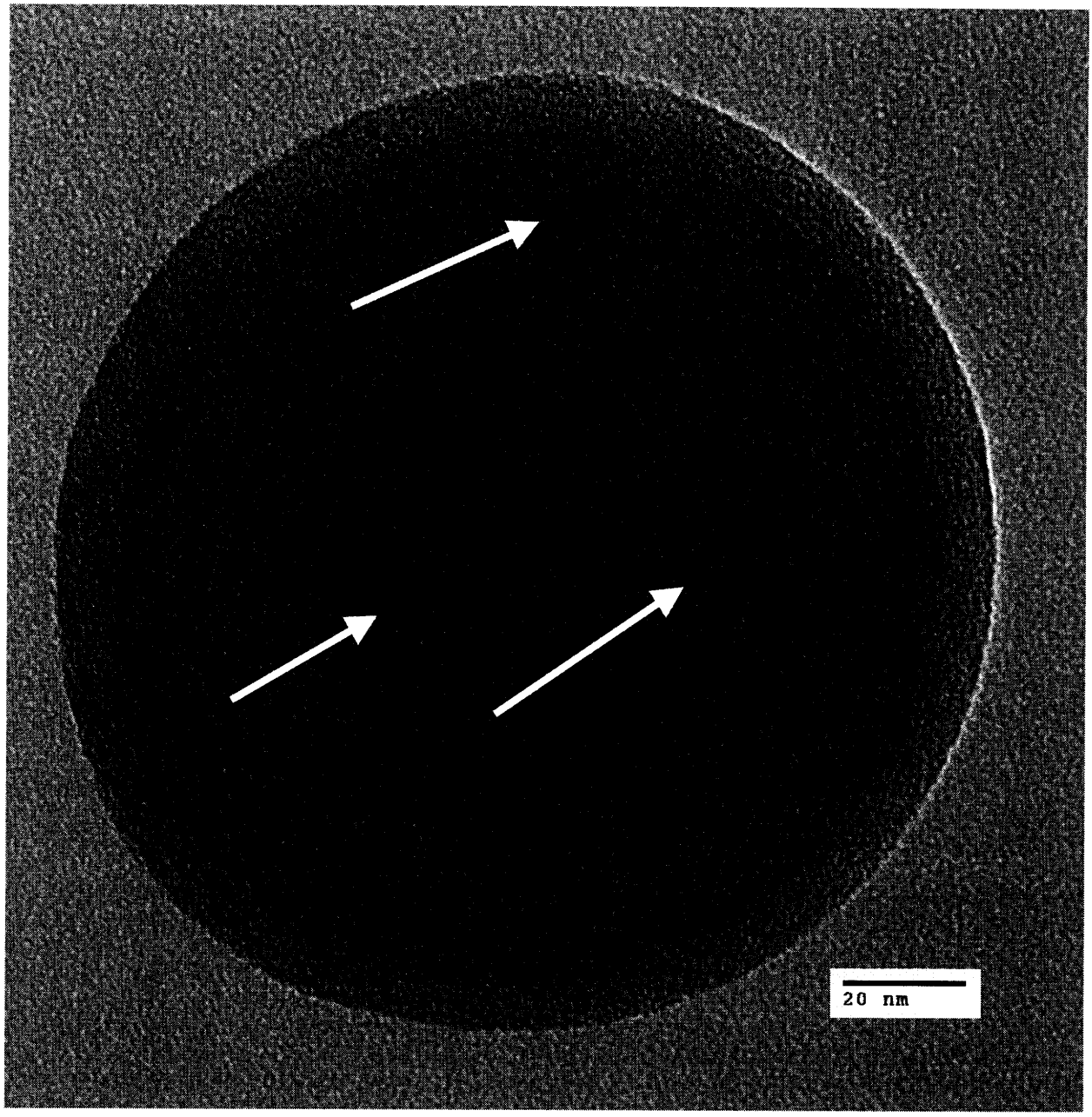

Figure 3.6: PS-PAMAM generation 6.0 vesicle formed in THF/water 60:40 at 0.25 wt% polymer concentration. Sample enhanced by incorporation of gold nanoparticles ca 5 nm in the vesicle bilayer. Arrows highlight gold nanoparticles embedded in the vesicle bilayer.

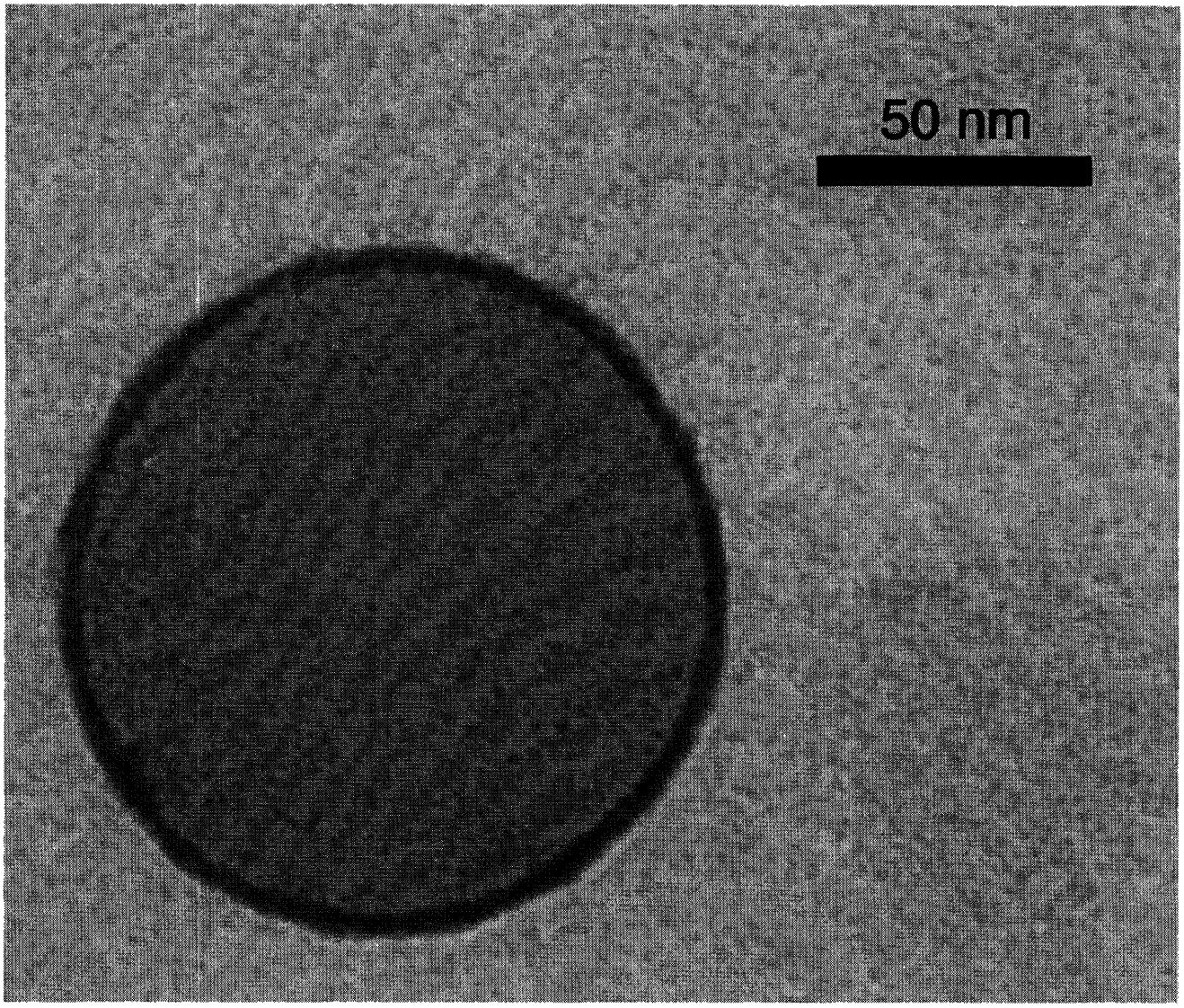

Figure 3.7:PS-PAMAM generation 2.0 vesicle formed in THF/water 60:40 at 0.25 wt% polymer concentration. Sample stained with RuO_4 vapor.

Staining with gold nanoparticles affords two advantatges. The first, and perhaps most important, of these advantages is consistency. Using RuO_4 vapors, timing is extremely important, and contrast based on exposure time can vary dramatically between samples. Gold nanoparticles (negatively charged with citric acid stabilizers) introduced in the vesicle forming solution will interact with the positively charged dendrimer and concentrate themselves within the vesicle wall. Additionally, they offer a reference point for picture contrast. Since the gold scatters incident electrons extremely well, the particles become points of absolute black within the micrograph.

After obtaining micrographs of the polymer, they can then be analyzed for their representative vesicle size distribution. Using this type of analysis, one can obtain a real distribution of sizes for each condition. With the TEM sample preparation used here, PS-PAMAM generations 1 and 2 gave very little useful data. These samples only created films and very few vesicle structures. Higher generations, however, produced several interesting sets of vesicles. Generation 3.0 can be seen in Figure 3.8 with the corresponding distribution. Note that in generation 3.0, there is a very large distribution of vesicle sizes. As the dendrimer generation increases in size, generations 5.0 (Figure 3.9) and 6.0 (Figure 3.10) show a much tighter vesicle size distribution.

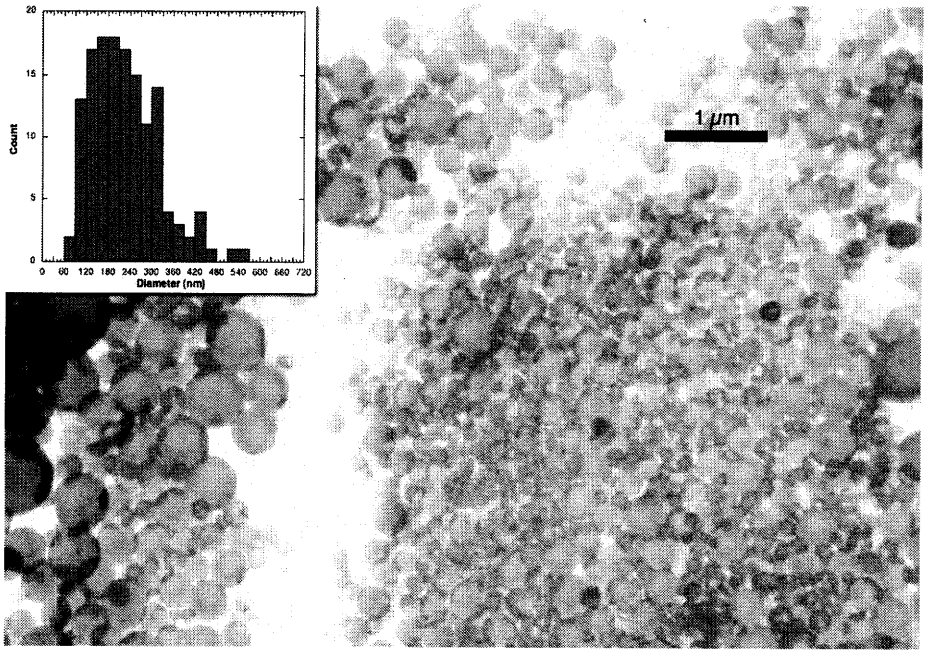

Figure 3.8: Representative distribution of PS-PAMAM G 3.0, 0.5% in water. The mean is 193.4 +/- 71.2 nm.

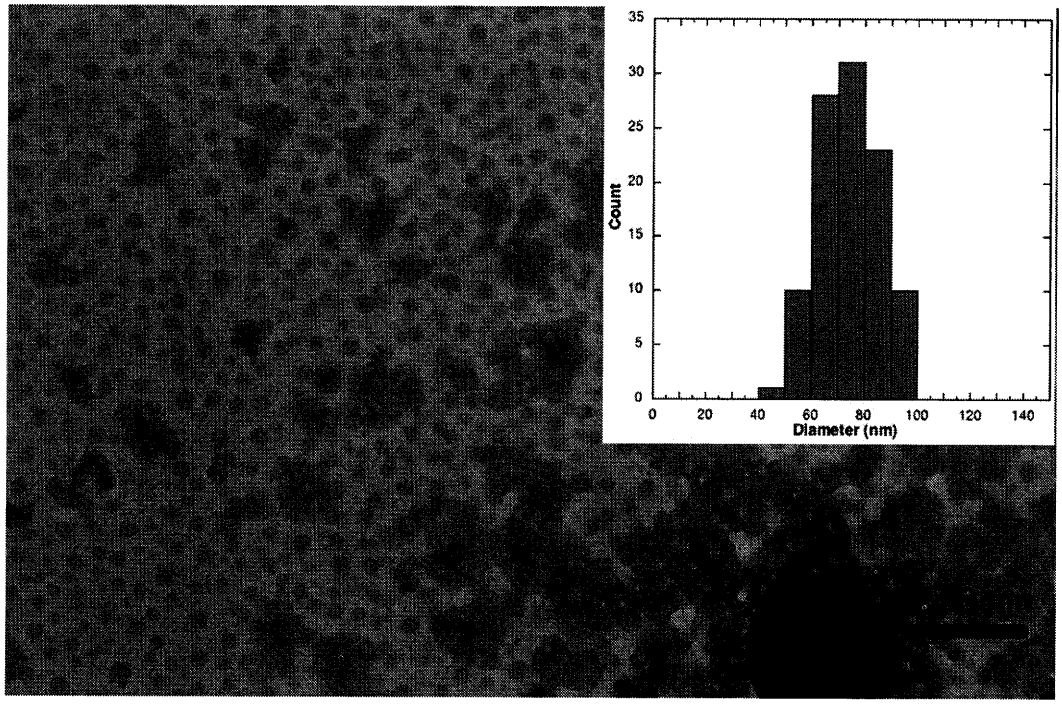

Figure 3.9: Representative distribution of PS-PAMAM G 5.0, 0.5% in water. The mean is 73.6 +/- 11.4 nm.

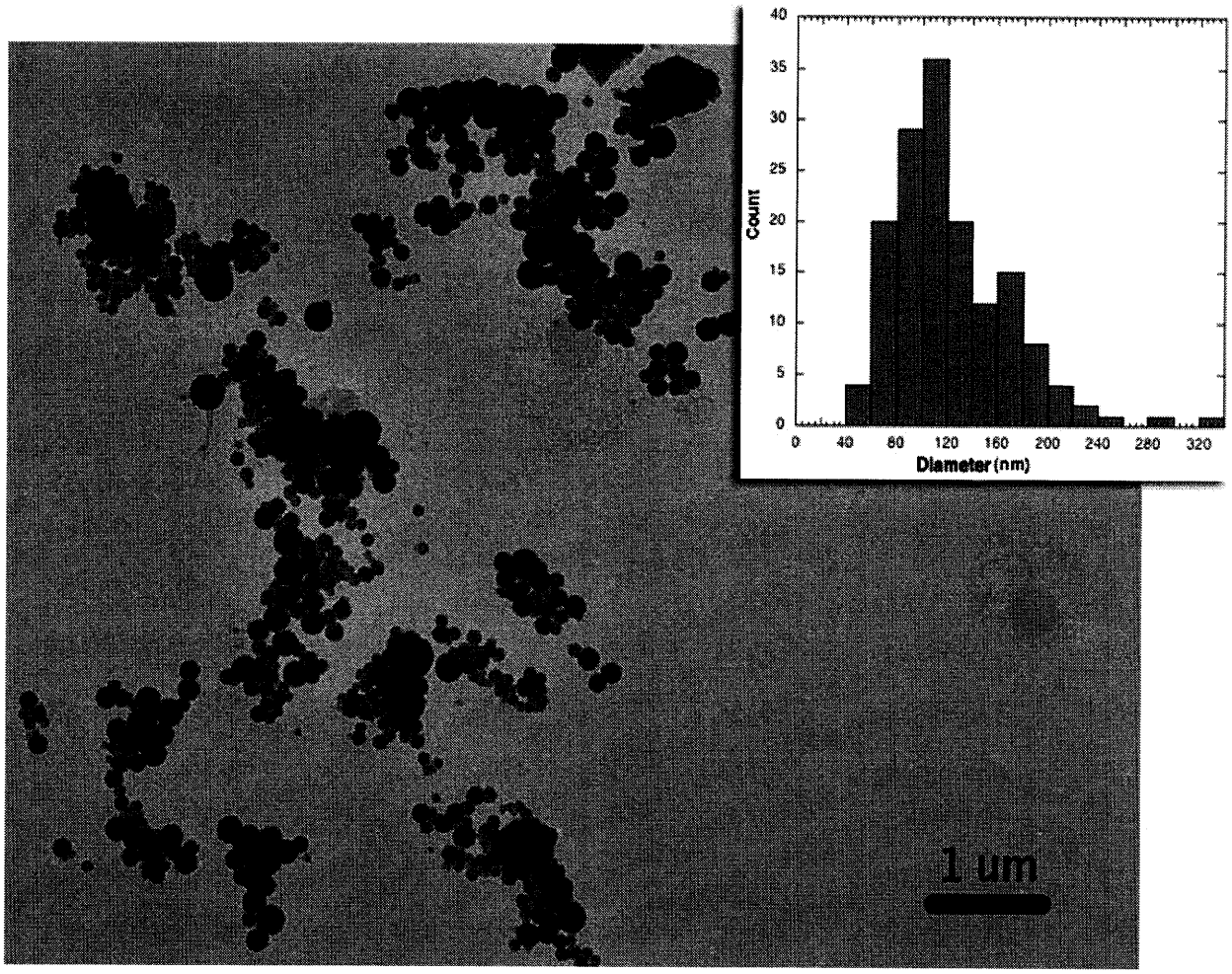

Figure 3.10: Representative distribution of PS-PAMAM G 6.0, 0.5% in water. The mean is 121.7 +/- 45.9 nm.

Large generations can be seen to conform to much smaller radii. The increased steric and electrostatic headsize contribute to the smaller radius of curvature inducing this behavior. Additionally, the differences in imperfectly synthesized dendrimers becomes smaller as the generations increase. For example, one missing branch from a generation 1.0 dendrimer has a much larger difference in size than a generation 6.0 dendrimer with a similar branch missing. Eventually, through the repetition of synthetic steps, an imperfect generation 6.0 will be mostly healed with minor imperfections.

Imperfections at lower generations creates a greater tolerance for variance in curvature radius. Greatly imperfect dendritic structures can act as "kinks" in the vesicle wall, increasing the radius of curvature.

3.2.3.Laser Light Scattering

Laser light scattering can be used to great effect in determining particle sizes. Here, it is used to monitor the aggregation phenomenon in mixed solvents. By introducing a small amount of water to an organic solvent system, the PS-PAMAM polymer can be induced to form aggregates even under conditions where the ratio of good solvent to poor solvent is quite high.

The light scattering results demonstrate the assembly behavior well. A small amount of block selective solvent can force the generation 0.0 system to rapidly assemble into many different types of aggregates. An amine terminated PS (PAMAM generation 0.0) shows several different scattering modes (Figure 3.11). The first of these corresponds to single molecule scattering around 5 nm. The next mode corresponds well to aggregates, followed by a very large scattering mode that most likely corresponds to aggregates of aggregates.

As the generation is increased to generations 1.0 (Figure 3.12) and 2.0 (Figure 3.13), the very large and very small modes are decreased in proportion to the single aggregate scattering. By generation 3 (Figure 3.14), nearly all the scattering arises from the single aggregates around 100 nm. Generations 4 and 5 were similar to generation 3.

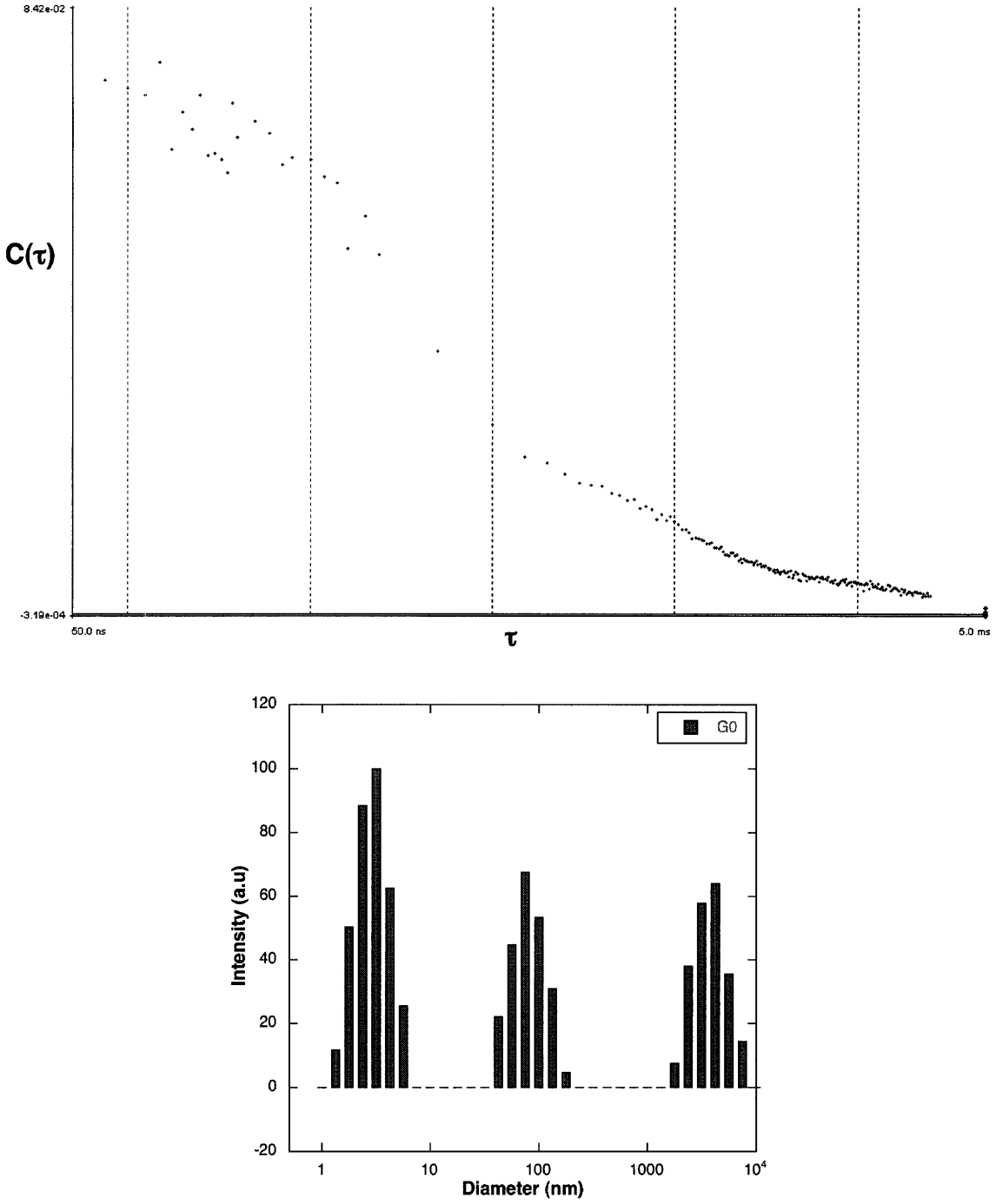

Figure 3.11: DLS correlation function (top) and NNLS number based size distribution (bottom) for PS-PAMAM G 0.0. Polymer 0.1 wt% in THF with 5% water.

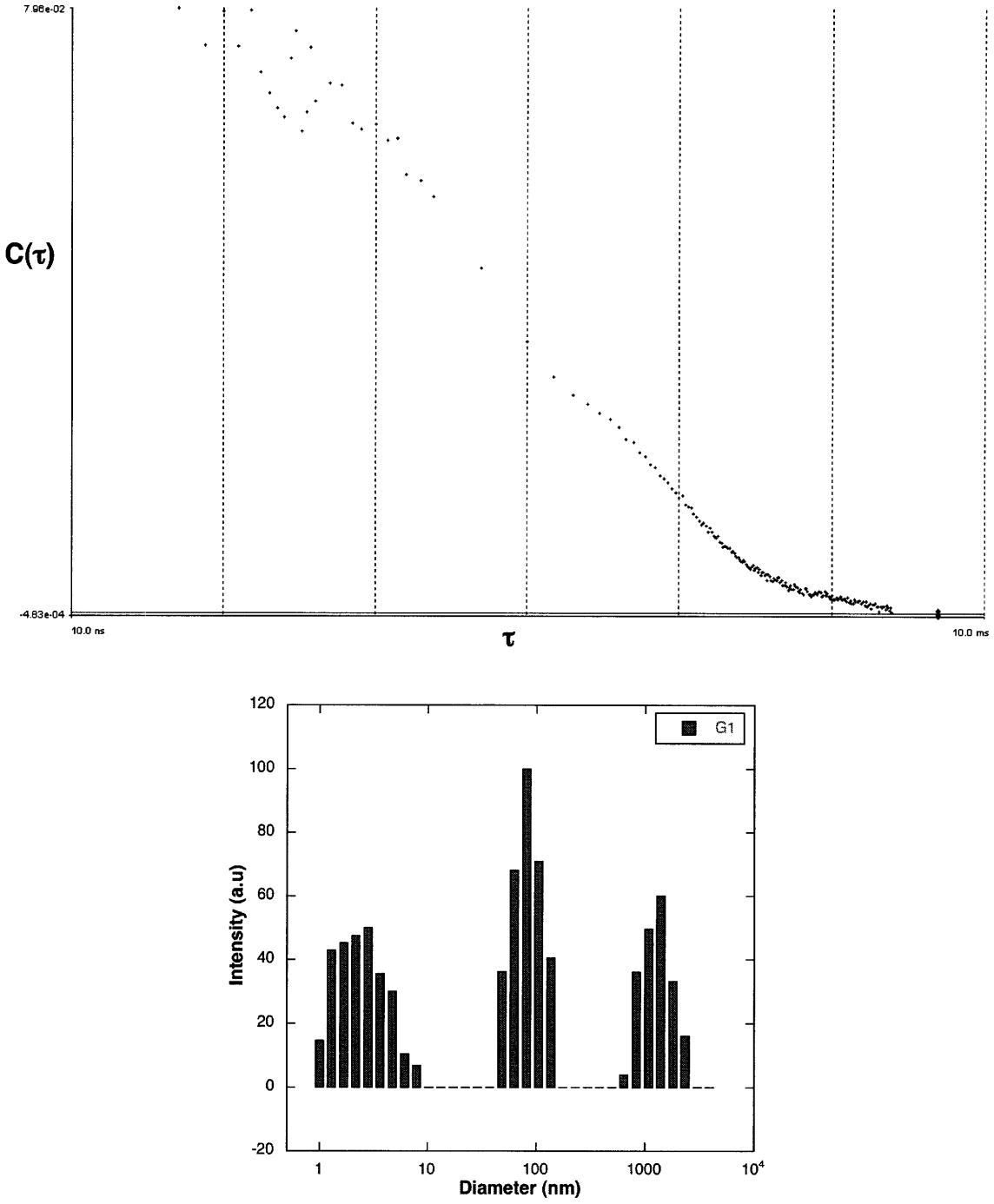

Figure 3.12: DLS correlation function (top) and NNLS number based size distribution (bottom) for PS-PAMAM G 1.0. Polymer 0.1 wt% in THF with 5% water.

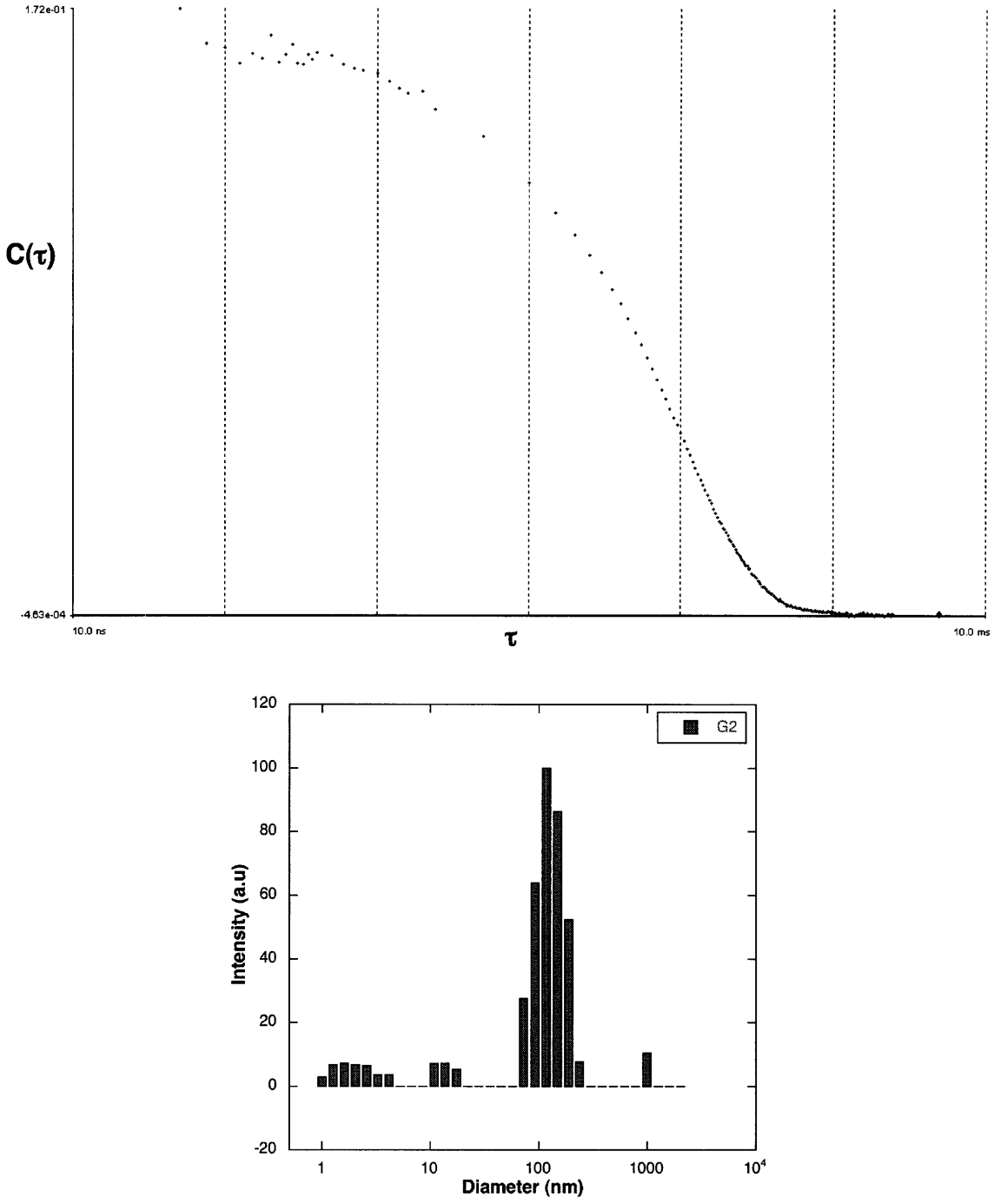

Figure 3.13: DLS correlation function (top) and NNLS number based size distribution (bottom) for PS-PAMAM G 2.0. Polymer 0.1 wt% in THF with 5% water.

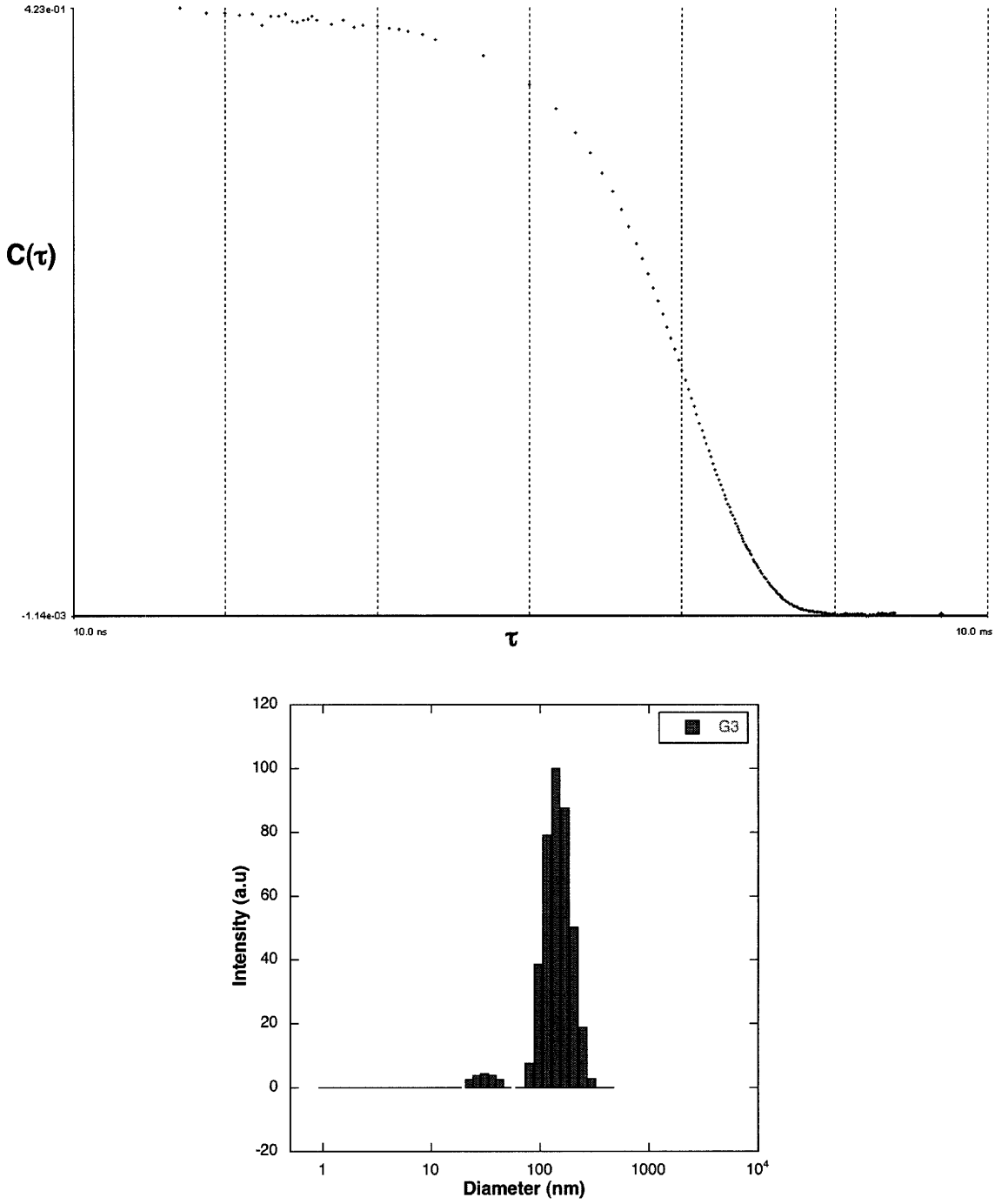

Figure 3.14: DLS correlation function (top) and NNLS number based size distribution (bottom) for PS-PAMAM G 3.0. Polymer 0.1 wt% in THF with 5% water.

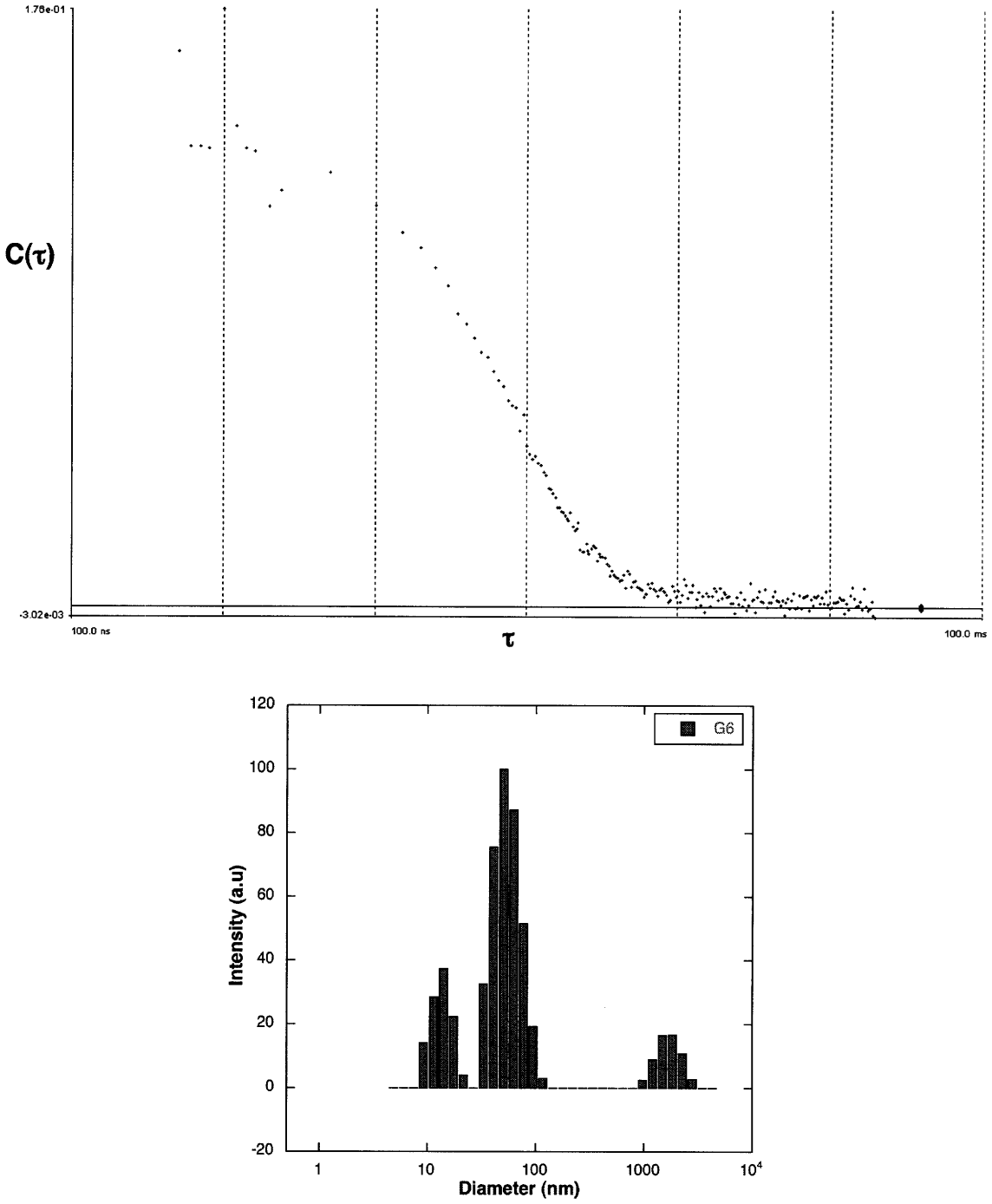

Figure 3.15: DLS correlation function (top) and NNLS number based size distribution (bottom) for PS-PAMAM G 6.0. Polymer 0.1 wt% in THF with 5% water.

Generation 6 (Figure 3.15), has an interesting scattering profile. The single molecule scattering around 10 nm still exists, most likely due to increased solubility in

the THF/water mixture (greater CMC in this particular solvent system), but the single aggregate scattering is greatly decreased in size. This can simply be explained by a shape argument.[†] The growth of the dendritic head group forces a stable aggregate to undertake more curvature to maintain the energy balance between steric and hydrophobic interactions within the aggregate. This, in turn, leads to smaller aggregates. Even at this high generation, large aggregates still form.

3.3.Experimental

3.3.1.Materials

Poly(styrene)-b-poly(amidoamine) (PS-PAMAM) was synthesized as previously described. Deionized water was obtained from a Milipore brand Mili-Q system. Ruthenium Oxide staining agent for electron microscopy was obtained as a 0.1 wt% solution in water from Electron Microscopy Sciences. Copper TEM grids with a carbon coated Formvar substrate were obtained from Ted Pella, Inc. (Redding, CA). Citrate stabilized gold colloid (5 nm) was obtained for staining purposes from Sigma Aldrich.

3.3.2.Procedure

Critical aggregation concentration measurements.

Water based stock suspensions of polymer were obtained by dissolving 5 mg of polymer in ca. 5 ml of tetrahydrofuran (THF). A small amount of water was added to the solution to the point of precipitation, at which point enough THF was added to

[†] This phenomenon is described in more detail in the following chapter.

resolubilize the polymer. The THF cosolvent was then removed by rotary evaporation, leaving behind a water suspension of polymer. This suspension was then diluted to 250 ml, shaken vigorously, and allowed to equilibrate overnight. A stock solution of pyrene was created by dissolving 5 mg of pyrene in 10 ml of dichloromethane and diluting to a final concentration of 10^{-5} M.

An aliquot of the pyrene solution (0.1 ml) was then added to a vial. After the solvent evaporated, the polymer suspension was added, along with an amount of sodium chloride solution, and acid or base if needed for altering the pH of the solution. The amounts added to the vial were dependent on the particular concentration of polymer desired. For CAC measurements, a range of polymer concentrations from 10^{-9}-10^{-4} M was desirable. Additionally, the ratio of salt solution to acid or base added was maintained across polymer concentrations to ensure a standard counterion concentration of 0.1 M for comparison across pH ranges.

These solutions were then analyzed using a Jobon Yvon Fluoromax fluorimeter in both excitation and emission modes. Excitation spectra of pyrene were obtained over the range of 300-360 nm with an emission wavelength of 390 nm. Emission spectra were recorded with an excitation wavelength of 339 nm. The spectra were then analyzed as described above.

Transmission electron microscopy sample preparation.

Solutions of polymer in THF were prepared at the desired concentration, and water was slowly added. Between each water addition, the solution was agitated until homogenized at which point, more water was added. The solutions were then allowed

to equilibrate overnight under vigorous stirring. A drop of solution was then deposited on a TEM grid and the excess solvent wicked away. The TEM grids were exposed to RuO4 vapor for 45 minutes immediately prior to imaging.

Samples using gold nanoparticles, rather than RuO4, as the staning agent were prepared similarly, though with a minor modification. In these samples, the nanoparticle staining solution was added to the polymer solution before equilibration to maximize particle inclusion. These solutions were then similarly deposited after equilibration with no further staining steps.

Microscopy was completed on JEOL 200, 2000, and 2011 transmission electron microscopes with an accelerating voltage of 200 kV.

Laser light scattering

Solutions were made at the desired concentrations in a THF and filtered through a 0.2 μm polytetrafluoroethylene (PTFE) syringe filter. Water was then added via syringe with an attached 0.2 μm PTFE filter to give the appropriate ratio. Analysis of the correlation curve was performed with the Brookhaven Instruments non-negative least squares (NNLS) analysis.

3.4.Conclusions

Using a sensitive means to measure CAC, PS-PAMAM was found to have extremely low aggregation concentrations, well in the 10-100 nM concentration ranges.

This extremely low CAC value makes these materials excellent candidates for applications where aggregate stability is of utmost importance.

Further analysis of the aggregates with TEM unveiled the vesicle nature of the aggregates. Vesicles were found to spontaneously form under a variety of conditions. Furthermore, the vesicle distribution was found to vary with respect to generation. This is most likely due to the steric bulk of the dendritic block forcing a more uniform radius of curvature upon the aggregate. A clear sign of the dendritic portion taking control of the polymer properties as the weight fraction grows. Further study by dynamic light scattering analysis confirmed the results of the TEM data.

3.5.References

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Chapter 4 Linear-Dendritic Block Copolymers at the Air Water Interface

4.1.Introduction

4.1.1.Langmuir-Blodgett Technique

The Langmuir-Blodgett method[97] is a good means to determining molecular dimensions of amphiphiles. The means by which it does this is through isotherm measurements. A schematic of the isotherm process is shown in Figure 4.1. In this diagram, molecules are spread upon a water subphase at the air-water interface. After some time has passed to allow the molecules to equilibrate, the film is compressed. As the molecules are compressed, they act as a two-dimensional gas (**A**). The amphiphilic nature of the molecules helps to ensure that the compression only occurs laterally on the subphase. A very hydrophobic tail will maintain the presence of molecules on the surface whereas a slightly hydrophilic tail will lead to solubility within the subphase, an undesirable condition for these measurements, but easily recognized by the isotherm results.

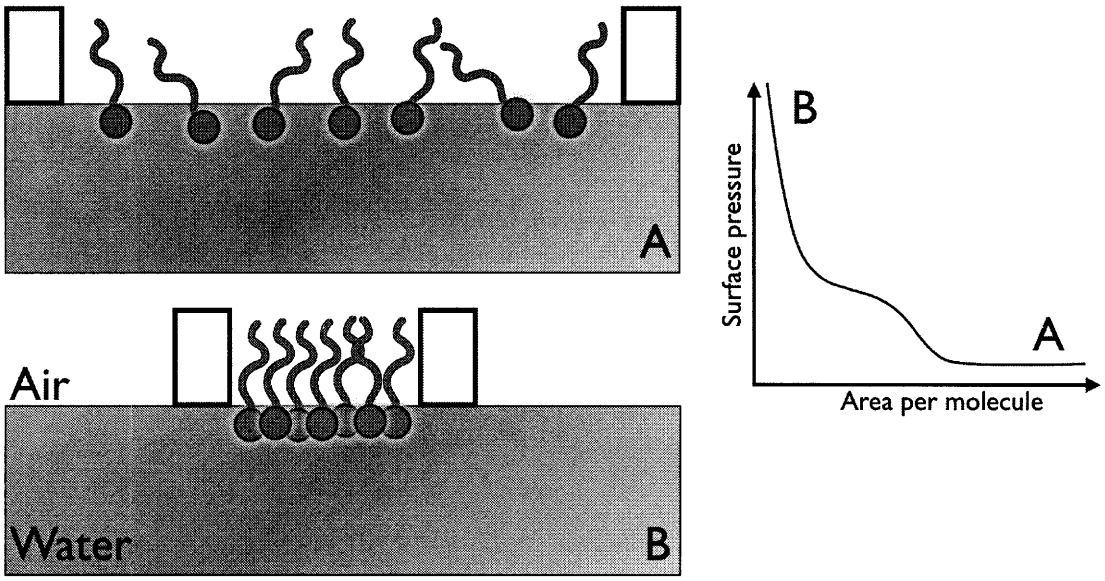

Figure 4.1:Schematic depicting the Langmuir-Blodgett isotherm method. Point A refers to the fully expanded monolayer, point B refers to the fully compressed monolayer.

Immediately, the film is very compressible, but eventually, intermolecular interactions: steric, electrostatic, or otherwise begin to take over. Here, the surface pressure begins to increase sharply. After full compression (**B**), the result is a tightly packed system that acts as a two-dimensional solid, and a greatly increased surface pressure. Often occurring in these types of measurements are intermediate humps that reside between **A** and **B**. These typically suggest an ordered or semi-ordered phase within the film. Determining the nature of this ordered phase is unlikely to be determined from an isotherm alone.

By extrapolation of the steepest part of the compression isotherm to zero pressure, one can obtain molecular dimensions.[98] These molecular dimensions include steric as well as electrostatic interactions. Assuming the head group is the largest part of the amphiphile, this is a useful metric for micellar systems as it is a direct measurement of the effective head group area denoted in the packing parameter equation.

4.2.Experimental

4.2.1.Materials

PS-PAMAM block copolymers were synthesized as described in earlier chapters. Langmuir isotherms were recorded on a Nima Technology 102M Langmuir-Blodgett trough. Water subphases were used from stock solutions. Acidic subphases were acidified with hydrochloric acid; basic subphases were altered by sodium hydroxide. Subphases at pH 5.5 were used as received from a Millipore water purification system.

4.2.2.Procedure

Solutions of polymer (0.5 mg/ml, 25 μl) were made in dichloromethane and gently spread on a pH adjusted water surface. The solvent on the surface was left to evaporate and the sample allowed to equilibrate over the course of 30 minutes. After this period, the film was compressed at 5 cm^2/min and the surface pressure monitored to the point of film collapse.

4.3.Results and Discussion

4.3.1.Langmuir isotherms of poly(styrene)-*b*-poly(amidoamine)

Previously, the Hammond group has explored linear-dendritic block copolymer behavior on the air-water interface with two different systems.[47,54] In the system reported here, the linear block is composed of PS with a M_n = 2500 $gmol^{-1}$. The dendritic block is PAMAM. PAMAM has two pK_a values, 7 for the primary amines at the periphery of the dendrimer, and 5 for the internal tertiary amines.[24] At pH 5.5, the dendrimer should be protonated at the peripheral primary amines and only sparsely protonated at the tertiary amines. This arrangement gives the steric area plus an additional amount of electrostatic repulsion.

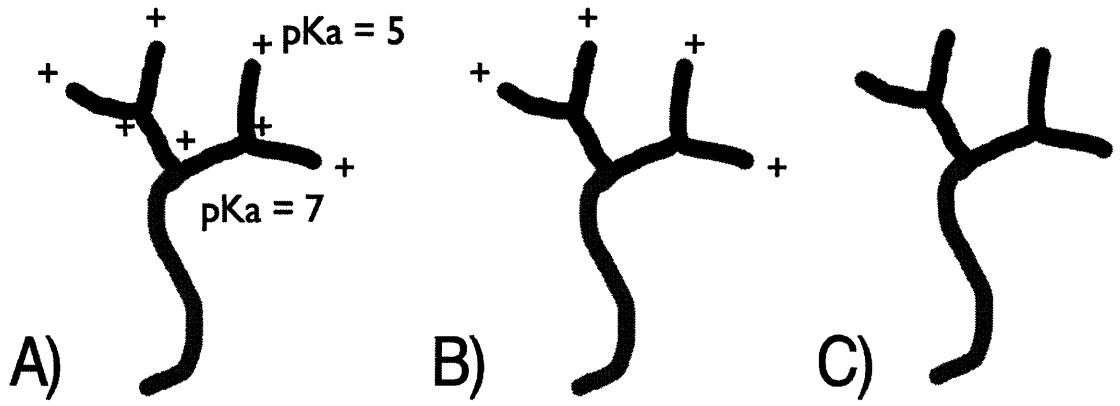

Figure 4.2: Protonation of PAMAM block based on pH. A) pH 2 subphase (fully protonated) B) pH 5.5 subphase (partially protonated) C) pH 10 subphase (no protonation)

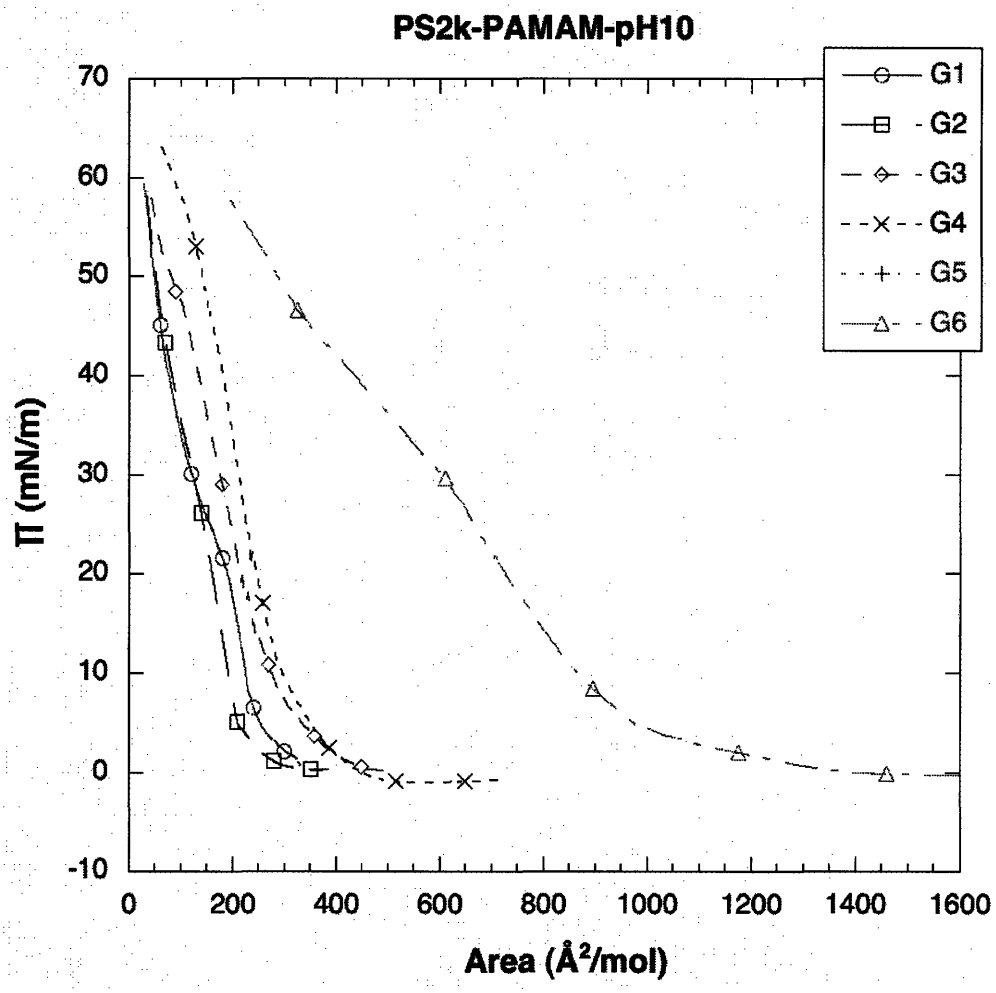

Figure 4.3:Langmuir-Blodgett isotherms of PS-b-PAMAM generations 1-6 on a pH 10 subphase.

At a pH of 10, the primary and tertiary amines are in their free base form. This should create smaller repulsive forces. In Figure 4.3 it can be seen that the area per molecule decreases compared to the same generation on a pH 5.5 subphase. By removing charge from the dendrimer, the effective area of the head group is decreased due to a reduction in electrostatic repulsions between molecules. The decrease could

also be attributed to a decrease in the actual steric size of the dendrimer as the intramolecular electrostatic repulsions will also contribute to the sterics of an individual dendrimer. Unfortunately, under these experimental conditions, the contributions from intermolecular repulsions cannot be extracted from the contributions of increased steric size due to intramolecular interactions. However, no matter what contributes, in high pH conditions, the measurement is as close to the neutral, steric size that can be accomplished with this method.

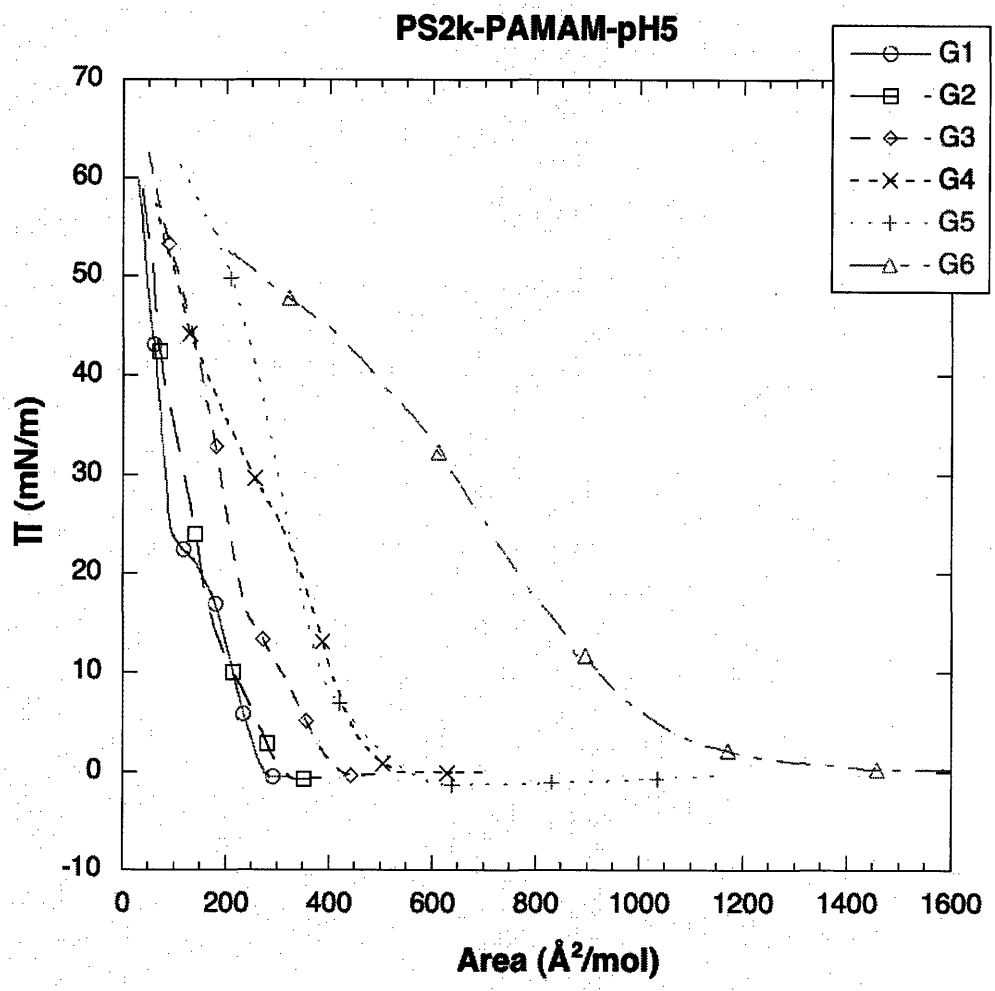

Figure 4.4:Langmuir-Blodgett isotherms of PS-b-PAMAM generations 1-6 on a pH 5.5 subphase.

Figure 4.4 depicts the LB isotherms for generations 1-6 of the PS-PAMAM system on a pH 5.5 water subphase. At this pH, a baseline under mild conditions can be obtained. As seen in Table 4.1, there is a increase in area per molecule across generations. This increase can be attributed directly to the steric area plus any electrostatic repulsions present in the system.

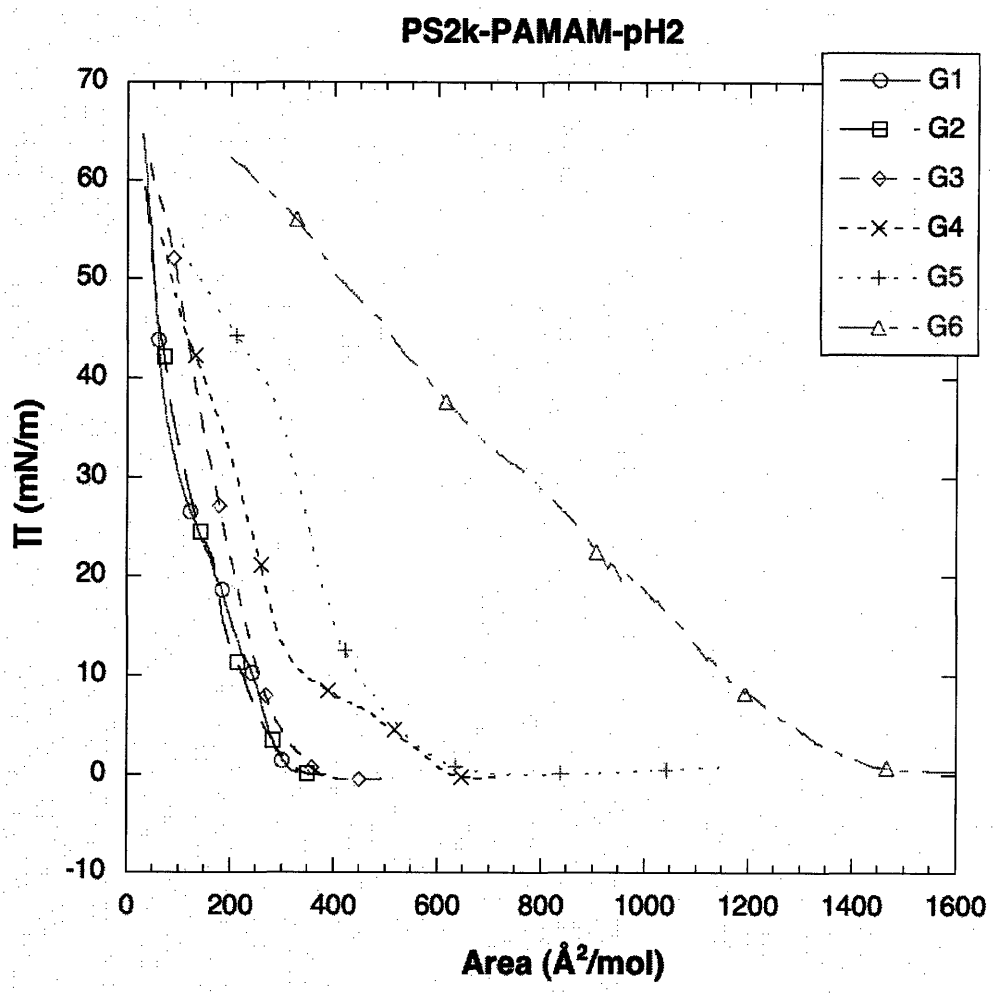

Figure 4.5:Langmuir-Blodgett isotherms of PS-b-PAMAM generations 1-6 on a pH 2 subphase.

An acidic subphase tells a different story. (Figure 4.5) At pH 2, the tertiary amines should also be protonated alongside the primary amines. If one assumes the number of tertiary amines is equal to the number of primary amines, it can be argued that the charge is increased twofold over the pH 10 conditions.[‡] Referring again to Table 4.1, it can be seen that with the increase in dendrimer size along generations, there exists a concomitant increase that is related to the pH conditions.

[‡] A reasonable assumption as the number of primary amines is 2^n, where n is the generation, and the number of tertiary amines is 2^n-1.

Table 4.1: Langmuir-Blodgett isotherm derived area per molecule for PS-PAMAM (PS M_n = 2500 $gmol^{-1}$)

	Subphase pH		
Dendrimer Generation	pH 2 (A^2/molecule)	pH 5 (A^2/molecule)	pH 10 (A^2/molecule)
1	130	130	130
2	175	160	150
3	275	240	215
4	375	350	325
5	725	610	-
6	1275	1000	850

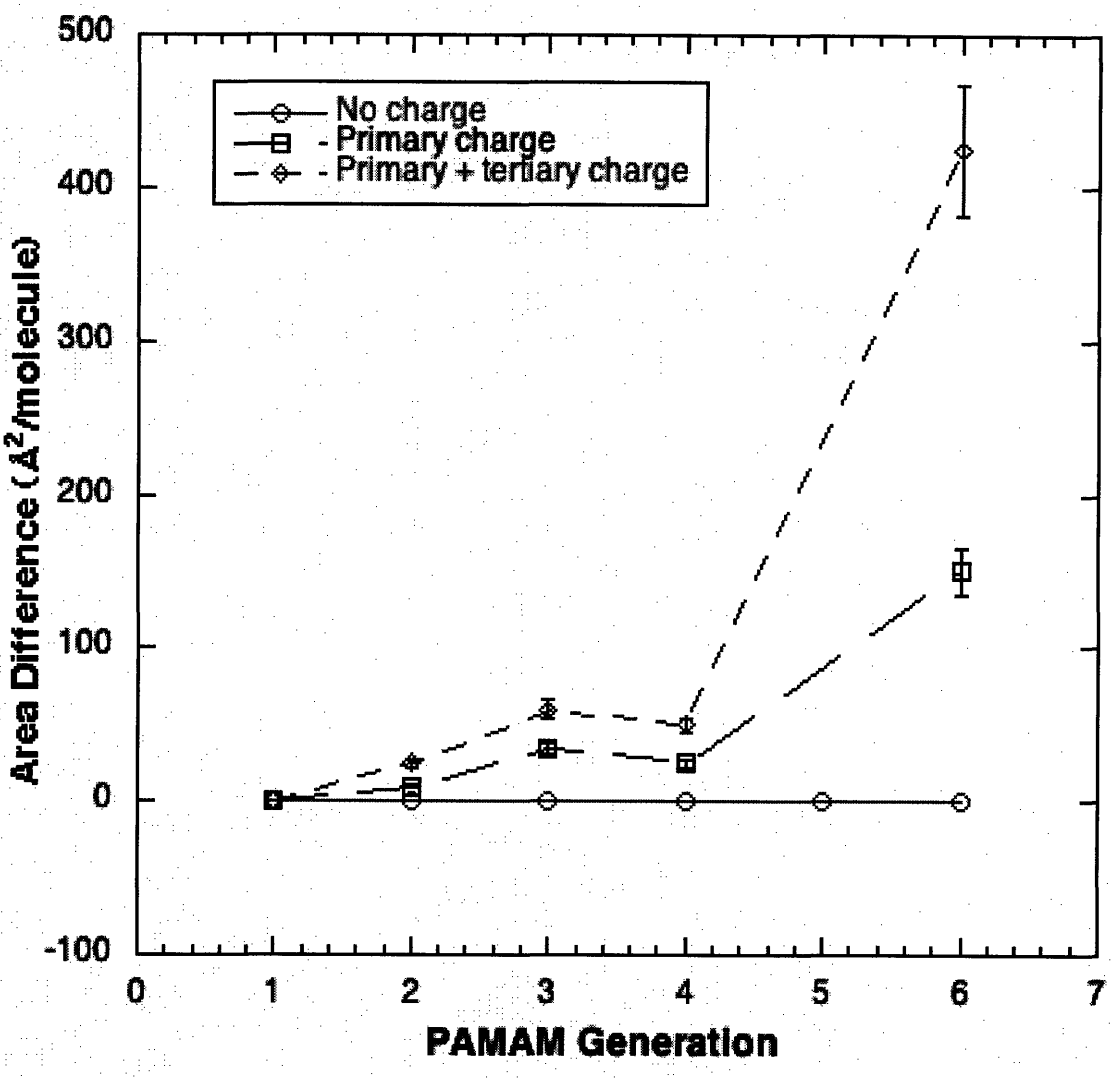

Figure 4.6: Area difference between uncharged PS-PAMAM LB results (pH 10 subphase) and either only primary amine charged PS-PAMAM (pH 5.5 subphase) and fully charged PS-PAMAM (pH 2 subphase).

Figure 4.6 plots the area difference between uncharged PS-PAMAM obtained by spreading the polymer on a pH 10 subphase and both partially charged PS-PAMAM (pH 5.5 subphase) and fully charged PS-PAMAM (pH 2 subphase). Analysis of these differences can be used to determine the contributions from both intermolecular electrostatic interactions as well as intramolecular electrostatic interactions. The number of primary amines in PS-PAMAM can be found with the equation 2^n where n is the (full)

generation number. The number of tertiary amines is described by 2^n-1. Therefore, assuming there is no intramolecular repulsion, the difference between the uncharged and partially charged species should be about half the difference between the uncharged and fully charged species. This assumption, however naïve, can be applied to the early generations of PS-PAMAM

Using this analysis, relative contributions can be determined from the resulting differences. For generations 1-3, the flexibility of the PAMAM is limited as there are fewer branches and the overall electrostatic repulsions define the limit. Generation 6 is influenced by the internal charging more than the previous generations. It can be seen in this figure that the fully charged difference in size is more than twice the difference of the partially charged PS-PAMAM. This is due to the extra contribution of internal electrostatic interactions from the charged tertiary amines enlarging the measured size of the dendritic portion. It should also be noted that there is most certainly an intramolecular repulsion associated with the partially charged PAMAM. Unfortunately, this method cannot fully deconvolute the intermolecular repulsions from the intramolecular repulsions for the partially charged system.

4.4.Conclusions

Using the Langmuir isotherm measurement method, the head group area of an amphihphilic copolymer, poly(styrene)-*b*-poly(amidoamine) (PS-PAMAM) was ascertained. Six generations of poly(styrene)-*b*-poly(amidoamine) were used, each with a poly(styrene) block of 2500 molecular weight. By changing the pH of the subphase, an easy assay of pH effects on the molecular area could be determined. As the subphase pH increased from 2 to 5 the area per molecule decreased in accordance with the pK_a of the internal PAMAM tertiary amines. Furthermore, as the pH of the subphase

increased to 10, the primary amines on the periphery of the dendrimer became uncharged and decreased the area occupied by the dendrimer further.

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Chapter 5: "Convergent" Synthesis of Linear-Dendritic Block Copolymers

5.1. Introduction

Organic chemists frequently attempt to create more "convergent" syntheses. Generally, by utilizing convergent, as opposed to divergent, synthetic routes, molecules can be created more efficiently, with better yields and fewer steps. A perfect example of this phenomenon can be demonstrated in the dendrimer world where there exist dendrimers of both the convergent and divergent varieties.

Divergent dendrimers, such as poly(amidoamine) (PAMAM)[24]. are synthesized starting at a focal point and adding generations stepwise to the periphery. Convergent dendrimers, like the Fréchet polyester dendrimers,[36] are put together piecewise from smaller components from the periphery to the focal point. A comparison of the two methods is demonstrated in Figure 5.1. Dendrimer synthesis by means of a convergent method give rise to several advantages. Generally speaking, convergent methods can produce dendrimers in greater yield and in higher purity than the divergent method.

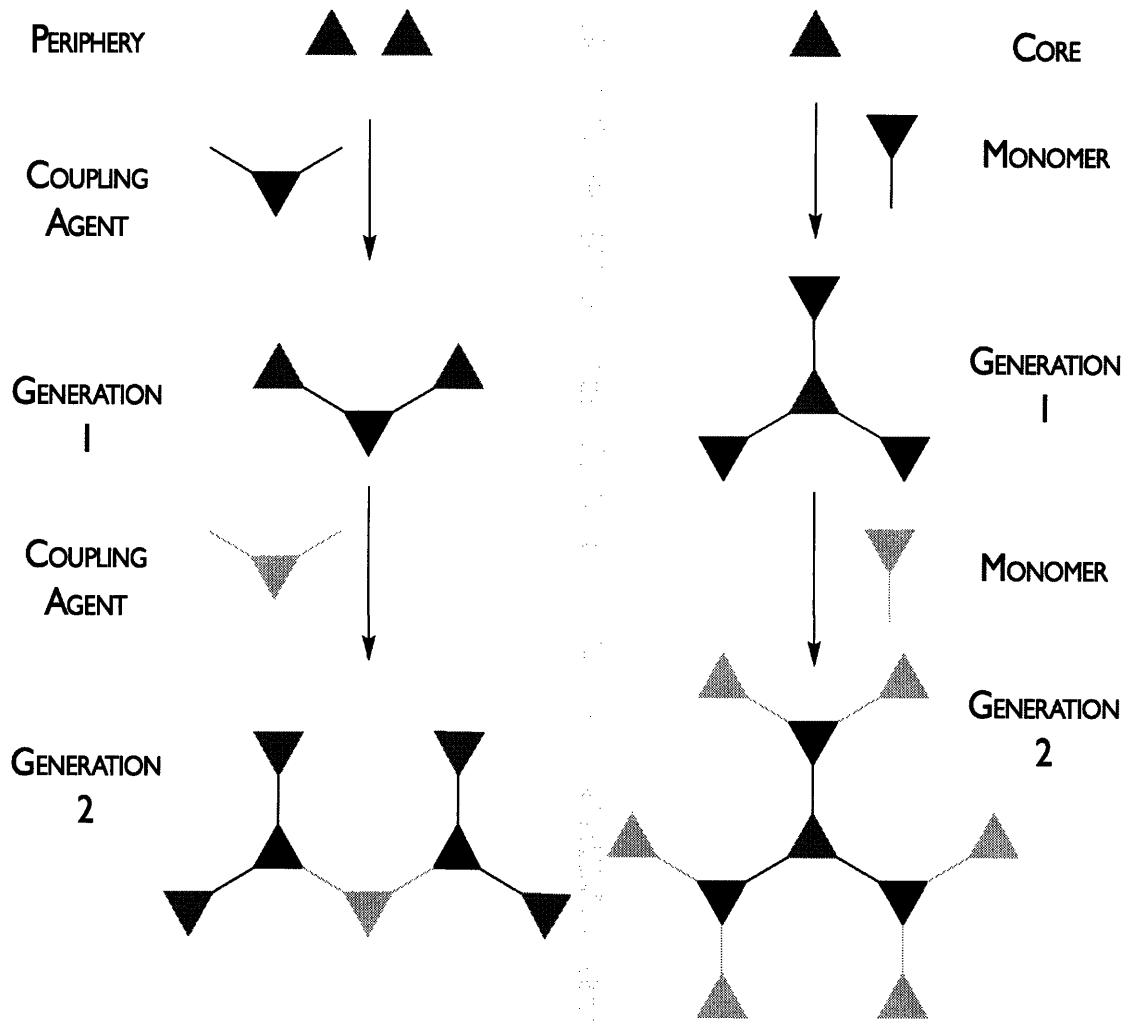


Figure 5.1: Schematic depicting the difference between convergent (left) and divergent (right) dendrimer growth.

Though PAMAM itself cannot currently be synthesized convergently,[§] the architecture of linear-dendritic block copolymers suggests that a more convergent synthesis can be possible. Ideally, the hydrophobic portion can be synthesized in a

[§] There have been many attempts to recreate PAMAM convergently. Only one[99] has been close, although that is still structurally dissimilar from the original Tomalia PAMAM.

medium that facilitates its synthesis, and the hydrophilic portion can be synthesized in a way that increases reaction efficiency and yield. Afterwards, the two could be made linked together in a manner that is amenable to either block. Additionally, this could be done in such a way that could expand the possible linear blocks to include polymers that would, under other circumstances, be incompatible with the harsh chemistries that are used to create PAMAM. Such a synthetic scheme could be immensely useful for structure-property studies where one could rapidly design and synthesize a library of polymeric compounds in an almost combinatorial manner.

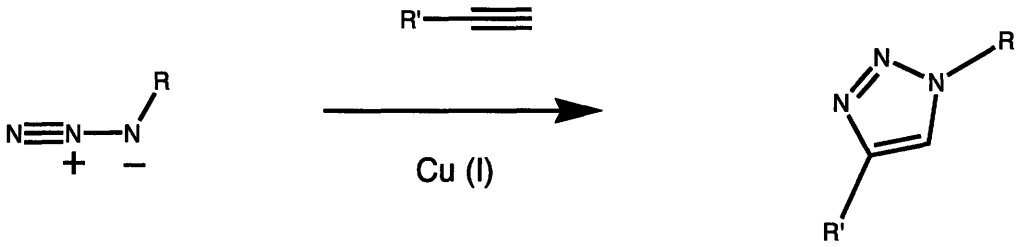
Since PAMAM is synthesized by the use of both electrophilic as well as nucleophilic chemistries, other types of chemistries must be considered when analyzing this problem. The type of reaction required for this system is one that utilizes functional groups that do not interfere or react under either type of conditions. It soon becomes abundantly clear that the only class of reactions suitable for this problem is those of the cycloaddition type.

5.1.1.Click Chemistry

The "click" reactions were named as such by Sharpless, *et al.*, and describe various reactions, all of which have several properties in common. High yield, quick reaction times, and facile workup are among the characteristics that define this class of reactions. These reactions have been utilized to rapidly create various types of small molecules[100] as well as macromolecules[101-104]. One cycloaddition that was named by Sharpless, *et al.* as a key tool is that between alkyne and azide functionalities, a

Huisgen dipolar cycloaddition, one of the most widely used click reactions that were defined (Scheme 5.1).[100] Many typical cycloadditions, are thermoreversible, which is undesirable for systems that would be subjected to thermal testing or where the possibility of reversibility is undesirable. This reaction is not reversible and typically goes to quantitative completion, a trait desirable for polymer chemistry where reactions on end groups prove quite difficult.

Scheme 5.1: Generalized "click" reaction



Though the cycloaddition typically occurs spontaneously at temperatures on or slightly above room temperature, oftentimes a catalyst is added to aid in the reaction. Typically, copper (II) sulfate is reduced *in situ* by sodium ascorbate to produce the Cu(I) species. Addition of Cu(I) aids the reaction in two distinct manners. The first is by increasing the reaction rate. By adding a catalytic amount, the reaction rate is tremendously increased. Perhaps more importantly the reaction, under catalyst guidance, gains regiospecificity. Rather than a mixture of regioisomers, the reaction assumes a preference for the 1,4 substituted rather than the 1,5 substituted regioisomer.

5.1.2.Atom Transfer Radical Polymerization

Atom transfer radical polymerization (ATRP)[105] falls under the category of controlled radical polymerizations. The general reaction mechanism is shown in Figure 5.2. In this figure, the growing polymer chain end is terminated with an active halogen (R-X). Typical initiating species include α-halogen esters and benzyl halogens. The carbon-halogen bond homolytically cleaves in a reaction with a ligand stabilized transition metal catalyst (Mt_n/ ligand) to produce an active radical chain end (R*). Many different transition metals and ligands have been used with great success[106] though copper-amine systems seem to be the most widely used. The resulting radical at the chain end then adds monomer in the manner of a free radical polymerization. This propagation step continues to add monomer until, eventually, the halogenated catalyst reacts with the chain end, restoring the carbon-halogen bond, deactivating the chain end, and allowing other chains to add monomer. The process then begins on other dormant chain ends.

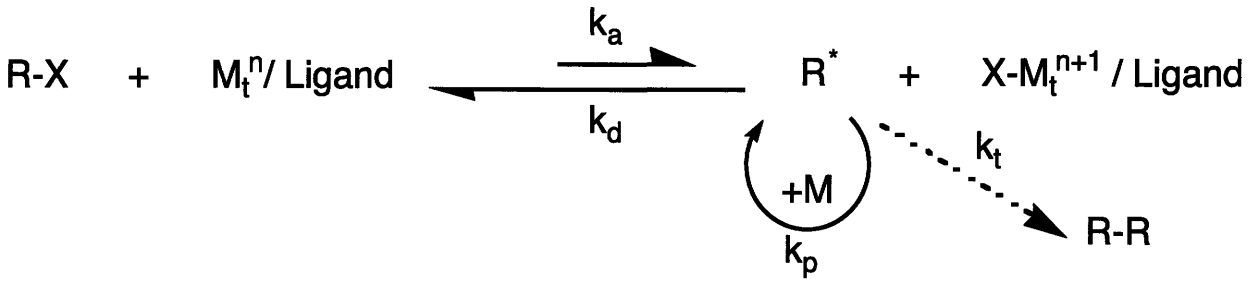


Figure 5.2: Generalized ATRP mechanism. R is the growing polymer chain, X is the halogen substituent, M_t^n is a transition metal of oxidation state n. The activation (k_a), deactivation (k_d), polymerization (k_p), and termination (k_t) rate constants are also included.

An important part of this process is the k_a/k_d ratio. Keeping this reaction under control requires this ratio to be as small as possible. This keeps chain termination events to a minimum by keeping the overall radical concentration low.[107] Transferring the propagating radical in this reversible manner allows all the polymer chains to grow at roughly the same rate. It has the additional benefit of controlling end groups to retain functional telechelic and semi-telechelic polymers.

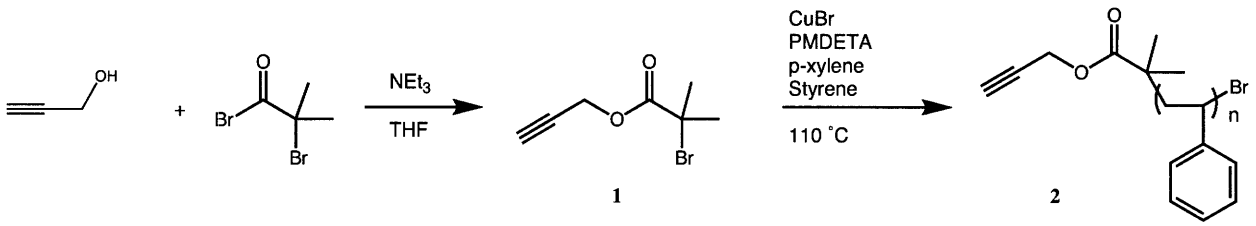
5.2.Results and Discussion

5.2.1.Alkyne functional linear block synthesis.

Alkyne functional linear blocks were prepared using atom transfer radical polymerization (ATRP).[106,108] By using the ATRP method, precise control over molecular weight distribution and end groups can be obtained.[105] It is for these two reasons ATRP was chosen for this system.

Depicted Scheme 5.2 is the synthetic scheme to produce alkyne functional poly(styrene). First, an alkyne functional initiator (**1**) is synthesized by esterification of propargyl alcohol and bromoisobutyryl bromide.[108] This reaction occurs rapidly and is readily purified via vacuum distillation. This compound is then used to initiate polymerization of a desired monomer.

Scheme 5.2: Synthesis of alkyne functional poly(styrene). PMDETA is n, n, n', n", n"-pentamethyldiethylenetriamine



The polymerization is carried out under standard ATRP conditions.[105] A copper source and ligand are added to monomer and initiator, and heated to 110°C for eight hours. The molecular weight can be targeted simply by varying the ratio between monomer and initiator concentrations. Thus, a range of molecular weights can be attained with minimal variation between reactions. In this case, a molecular weight of 7000 $gmol^{-1}$ was targeted for polymer **2**, (Figure 5.3) but could be adjusted for a variety of desirable molecular weights. The slight shoulder in the GPC corresponds to 14k $gmol^{-1}$, and is likely a product of chain coupling.

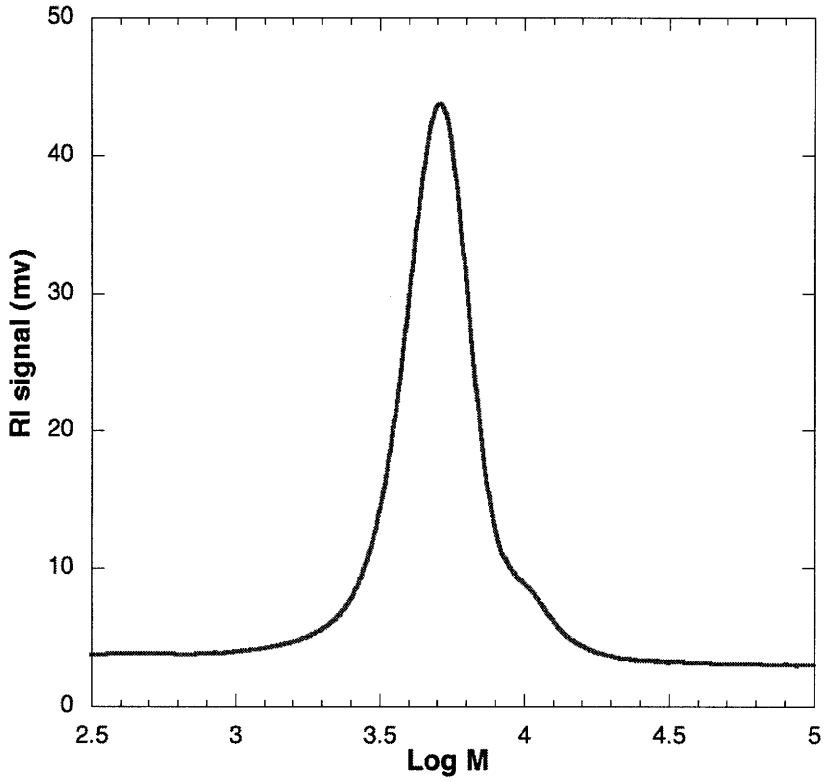


Figure 5.3: GPC trace of alkyne functional poly(styrene). M_n= 7100 $gmol^{-1}$ and PDI = 1.15

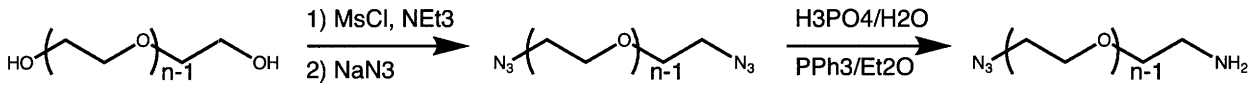
Alternative monomers can also be used, as ATRP is easily applied to other types of polymer systems, including acrylamides and acrylonitriles. Butyl acrylate could be used for a linear block with a low T_g. It would also serve as a good example of a block that would typically be incompatible with the PAMAM synthesis.

5.2.2.Difunctional azido-amino PEG synthesis and PAMAM growth.

Crafting a molecule that contains both an azide for the click reaction, as well as an amine for the dendrimer reaction is slightly more difficult. Here, a poly(ethylene

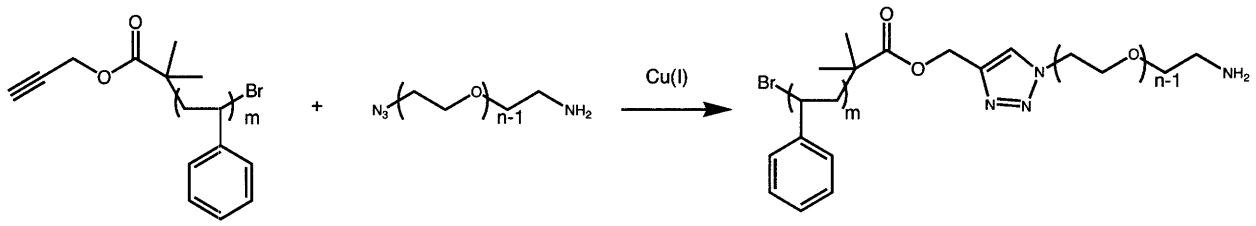
glycol) (PEG) oligomer was chosen for two reasons. First, PEGs are relatively inexpensive, which allows for a less expensive end result. Second, Schwabacher, *et al.* reported on the desymmetrization of PEG oligomers, resulting in α-amino-ω-azido-oligo(ethylene glycol)s.[109] The synthesis is depicted in Scheme 5.3. First, the diol PEG is transformed via nucleophilic substitution to the diazide PEG. The next and crucial step is a biphasic Staudinger reduction. The diazido PEG is dissolved in an acidic water solution and stirred rapidly. Meanwhile, an ether solution of triphenyl phosphine is slowly added to the solution. The biphasic nature of this reaction keeps the reaction working on only the diazido compounds, leaving behind a monoamine to diamine ratio of greater than 100:1.[109] This reaction works best on oligomeric PEGs. Once the molecular weight of the PEG becomes too great, the mono to diamine ratio decreases greatly. This is most likely due to the endgroups having a much smaller effect on solubility compared to the rest of the chain. The PEG then remains in the aqueous phase, decreasing the reaction yield as well as the mono to diamine ratio.

Scheme 5.3. Synthesis of difunctional PEG



5.2.3.Coupling Reaction.

Scheme 5.4: Coupling of PS block with amino-azido PEG.



Once the two components of the block copolymer system have been synthesized, they can be coupled via the "click" reaction. Typically, these reactions take place in a variety of alcohol based solvents: *t*-butanol/water, ethanol/water, methanol/water, etc.[100] Since the polystyrene portion of the polymer is insoluble under these conditions, alternative conditions are required.

Chloroform solvates both portions of the polymer, however, the cycloaddition does not proceed well in this solvent. The reaction was attempted in chloroform under a variety of catalyst conditions, but with little success. only leaving a residue as the desired product.

DMF, however, is compatible with both blocks and still allows the reaction to proceed. A more soluble copper species consisting of copper (I) bromide with PMDETA ligand still did not give promising results. Only by adding a DMF suspension of copper (II) chloride and sodium ascorbate to the reaction, was the reaction able to proceed in reasonable yields. Unfortunately, the only successful reaction conditions were for the

generation 0.0 polymer. The same conditions using larger generation polymers only recovered starting materials.

It is well known that PAMAM binds copper (II) species quite well.[110,111] This is most likely the cause of the inhibition of the click reaction with the dendritic blocks. Figure 5.4 shows the potential ligand structure within the PAMAM dendrimer. Thus, the capability for reaction retardation and inhibition by PAMAM becomes quite realistic. Though the ligand interaction here is quite weak, the ascorbic acid ligands are much weaker.

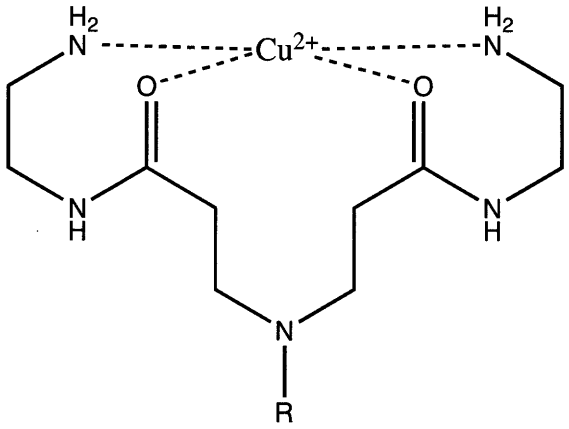


Figure 5.4: Proposed structure of PAMAM Cu(II) complex.

The ligands provided by the ascorbic acid reducing agent are very likely to be acting more as counterions rather than as strongly interacting ligands. Amines present in the PAMAM are much more likely to win in the competitive capture of copper species. Moreover, the proposed mechanism of the click reaction requires the acetylide to coordinate with the copper (I) species. This proposed mechanism explains several aspects of the failed reactions.

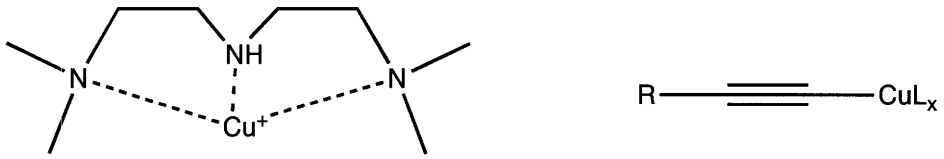


Figure 5.5:PMDETA copper (I) complex (left) and proposed copper acetylide intermediate (right)

First, the reaction does not proceed using a strong ligand (PMDETA) with copper (I) bromide because the copper acetylide species most likely cannot exist in conjunction with the PMDETA complex. PMDETA, as a tridentate ligand, is most likely sterically hindered, and cannot interact with the terminus of the alkyne initiator, (Figure 5.5) much less with the alkyne attached to a polymer in a non-ideal solvent.

Still, it seems quite promising that the generation 0.0 PEG is able to be attached to the PS. This may prove to be a facile means to creation of telechelic and semi telechelic block copolymers that would otherwise be more difficult to synthesize.

5.3.Experimental

5.3.1. Materials

All chemicals were purchased from commercial chemical suppliers and used without further purification, unless noted otherwise. All reactions were performed under dry nitrogen. Butyl acrylate and styrene monomers were distilled over calcium hydride

before use. Copper (I) bromide was stirred in glacial acetic acid overnight then rinsed with methanol, followed by diethyl ether and stored under nitrogen prior to use. GPC analysis was performed on a Waters Breeze system with Waters separation columns (Styragel HT 3, HT 4, HT 5) and weight distributions recorded by a refractive index detector calibrated with monodisperse polystyrene samples (Sigma-Aldrich).

5.3.2. Procedure

Propargyl 2-bromoisobutyrate (1):[108] To a flask charged with 2-bromoisobutyryl bromide (10 g, 43.4 mmol) in tetrahydrofuran (THF, 25 ml) and cooled to 0°C, a solution of triethylamine (6.0 ml, 43.4 mmol) and propargyl alcohol (2.57 ml, 43.4 mmol) in THF (25 ml) was added dropwise over the course of 45 minutes. The resulting mixture was stirred 2 hours, after which, it was extracted with a saturated sodium bicarbonate solution (3 x 50 ml). The collected organic layers were then dried with magnesium sulfate and the solvent removed via rotary evaporation, leaving a yellow oil. Distillation of the oil (30°C/ 0.5 Torr) gave the desired product (3.8g, 42% yield) ^{1}HNMR (300 Mhz, $CDCl_3$): δ 4.78 (d, 2H, CH_2O), 2.51 (t, 1H, C≡CH), 1.96 (s, 6H, $C(CH_3)_2$). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 75.6, 55.1, 53.7, 39.8, 37.6, 30.9, 8.8.

Alkyne functional poly(styrene) (2):[108] Copper (I) bromide (156 mg, 1.1 mmol) was added to a flask which was purged of oxygen by evacuating the flask and refilling it with nitrogen three times. After sparging each with nitrogen (5 minutes) p-xylene solvent (6 ml), styrene monomer (15 ml, 131 mmol) and N, N, N', N", N"-pentamethyldiethylenetriamine (PMDETA) ligand (189 mg, 1.1 mmol) were added.

Initiator **1** (447 mg, 2.2 mmol) was then added and the solution heated to 110˚C for 8 hours. The reaction was quenched by exposure to air and diluted with THF. This solution was then filtered through an alumina column and precipitated in methanol. The white precipitate was subsequently recovered by vacuum filtration and dried to give the desired polymer. ^{1}HNMR (300 Mhz, $CDCl_3$): δ 7.3-6.2 (br, aromatic protons from PS), 4.2 (br, terminal alkyne proton), 2.5-0.3 (br, backbone protons from PS). FTIR ν (cm^{-1}) 3200 (H-C≡C) ^{13}CNMR (500 Mhz, $CDCl_3$): δ 128 (br), 125(br), 41(br), 39.8, 30.8, 8.8.

α, ω-Diazido poly(ethylene glycol) (3):[109] Polyethylene glycol ($M_n \approx$ 600 Da, 20 g, 33.3 mmol) and triethylamine (9.8 ml, 69.9 mmol) were dissolved in THF (80 ml) and chilled to 0˚C. A solution of methanesulfonyl chloride (6.8 ml, 69.9 mmol) in THF (20 ml) was added dropwise. The solution was allowed to warm to room temperature over the course of 5 hours. After this period, the solvent was removed by rotary evaporation and replaced by water (100 ml). Sodium bicarbonate was then slowly added until reaching a solution pH of 8. **WARNING: If the solution is not basic in nature, the following addition of sodium azide will result in formation of a toxic, explosive gas.** Sodium azide (4.5 g, 69.9 mmol) was then added to the solution and the reaction brought to reflux for 24 hours. The solution was extracted with chloroform (5 x 100 ml) with each chloroform layer back extracted with the same saturated salt solution (50 ml). The solvent was then removed from the collected organic layers to leave **3** in quantitative yield. ^{1}HNMR (300 Mhz, $CDCl_3$): δ 3.75-3.5 (br, m, C**H**$_2$O) 3.37 (t, N_3C**H**$_2$). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 68.0, 25.7. FTIR ν (cm^{-1}) 2100 (N_3-R)

α-amino-ω-azido poly(ethylene glycol) (4):[109] Diazido PEG **3** (21 g, 33.3 mmol) was dissolved in a solution of phosphoric acid in water (0.65 M, 200 ml). To this, a solution of triphenylphosphine (9.6 g) in diethyl ether(150 ml) was added dropwise. The biphasic solution was then stirred rapidly over 16 hours. After removal of the ether layer, the water layer was then extracted with diethyl ether (3 x 100 ml). Potassium hydroxide (35 g) was then added to the solution and the mixture refrigerated overnight. The solution was then extracted with chloroform (15 x 50 ml), the organic layers collected, dried, and the solvent removed *in vacuo* revealing the desired product (14.0 g, 66% yield). ^{1}HNMR (300 Mhz, $CDCl_3$): δ 3.75-3.5 (br, m, C**H**$_2$O) 3.37 (t, N_3C**H**$_2$). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 162.8, 132.2, 128.6, 70.6, 50.8, 36.8, 31.7. FTIR ν (cm^{-1}) 3400 (N-H), 2100 (N_3-R)

Azido poly(ethylene glycol)-*b*-poly(amidoamine) generation 0.5: α-amino-ω-azido poly(ethylene glycol) (12 g, 20 mmol) was stirred in a mixture of methanol (50 ml) and methyl acrylate (90 ml, 1 mol) for 24 hours. After this period, the excess methyl acrylate and solvent were removed under high vacuum with no further purification necessary. (14.9 g, 96% yield) ^{1}HNMR (300 Mhz, $CDCl_3$): δ 3.75-3.5 (br, m, C**H**$_2$O), 3.37 (t, N_3C**H**$_2$), 2.7 (t, NC**H**$_2$), 2.33 (t, C**H**$_2$CO). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 72.7, 70.5, 61.6, 51.6, 50.0, 39.8, 32.6. FTIR ν (cm^{-1}) 2100 (N_3-R) 1735 (ester C=O)

Azido poly(ethylene glycol)-*b*-poly(amidoamine) generation 1.0: PEG-PAMAM G 0.5 (14.9 g, 19 mmol) was dissolved in 50 ml of methanol and slowly added to a

solution of ethylene diamine (128 ml, 1.9 mol) in methanol (50 ml). Upon complete addition, the reaction was stirred for 48 hours at room temperature. The solvent and excess ethylene diamine were removed under high vacuum in a constant temperature bath kept at 35°C. To remove salts that formed during the workup, tetrahydrofuran was added, and the precipitate was removed via vacuum filtration. Finally, the solvent was removed to give the desired product (15.5 g, 95% yield) ^{1}HNMR (300 Mhz, $CDCl_3$): δ 3.75-3.5 (br, m, CH_2O), 3.37 (t, N_3CH_2), 2.7 (t, NCH_2), 2.33 (t, CH_2CO). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 70.6, 39.8, 37.6, 30.8, 8.8. FTIR ν (cm^{-1}) 2100 (N_3-R) 1650 (amide C=O)

Azido poly(ethylene glycol)-*b*-poly(amidoamine) generation 1.5: PEG-PAMAM G 1.0 (10.5 g, 12.2 mmol) was stirred at room temperature in a mixture of methanol (50 ml) and methyl acrylate (220 ml, 2.4 mol) for 48 hours. After this period, the solvent and excess reactants were removed under vacuum, leaving the desired product. (18.8 g, quantitative yield). ^{1}HNMR (300 Mhz, $CDCl_3$): δ 3.7-3.4 (br) 3.3 (br), 2.87-2.55 (br), 2.4-2.1 (br m). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 70.6, 39.8, 37.6, 30.8, 8.8. FTIR ν (cm^{-1}) 3400 (N-H) 2100 (N_3-R), 1735 (ester C=O),1650 (amide C=O)

Azido poly(ethylene glycol)-*b*-poly(amidoamine) generation 2.0: PEG-PAMAM G 1.5 (18.8 g, 15.7 mmol) was dissolved in 50 ml of methanol and slowly added to a solution of ethylene diamine (210 ml, 3.15 mol) and methanol (50 ml). Upon complete addition, the reaction was stirred for 72 hours at room temperature. Then, a toluene-methanol (9:1, 200 ml) was added to aid in the removal of ethylene diamine under

vacuum. After several additions of the toluene-methanol solution, only methanol was added to azeotropically remove the excess toluene. Finally, the remaining methanol was removed under high vacuum to give the product as a yellow gum. (18.74 g, 66% yield) ^{1}HNMR (300 Mhz, $CDCl_3$): δ 3.68 (br), 3.60 (br), 3.22 (br), 2.87-2.55 (br), 2.4-2.1 (br) 1.79 (br). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 70.6, 39.8, 37.6. FTIR ν (cm^{-1}) 3400 (N-H), 2100 (N_3-R), 1650 (amide C=O)

Azido poly(ethylene glycol)-*b*-poly(amidoamine) generation 2.5: PEG-PAMAM G 2.0 (13.75 g, 10.5 mmol) was stirred at room temperature in a mixture of methanol (100 ml) and methyl acrylate (130 ml, 846 mmol) for 48 hours. After this period, the solvent and excess reactants were removed under vacuum, leaving the desired product. (26.3 g, quantitative yield). ^{1}HNMR (300 Mhz, $CDCl_3$): δ 2.87-2.55 (br), 2.4-2.1 (br). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 173.1, 70.6, 52.3, 49.3, 39.8, 37.6, 32.8, 30.8, 8.8. FTIR ν (cm^{-1}) 3400 (N-H), 2100 (N_3-R), 1735 (ester C=O), 1650 (amide C=O)

Azido poly(ethylene glycol)-*b*-poly(amidoamine) generation 3.0: PEG-PAMAM G 2.5 (26 g, 15.7 mmol) was dissolved in 100 ml of methanol and slowly added to a solution of ethylene diamine (335 ml, 5 mol) and methanol (50 ml). Upon complete addition, the reaction was stirred for 72 hours at room temperature. Then, a toluene-methanol (9:1, 200 ml) was added to aid in the removal of ethylene diamine under vacuum. After several additions of the toluene-methanol solution, only methanol was added to azeotropically remove the excess toluene. Finally, the remaining methanol

was removed under high vacuum to give the product as a yellow gum. (35.0 g, 95% yield) ^{1}HNMR (300 Mhz, $CDCl_3$): δ 2.87-2.55 (br), 2.4-2.1 (br). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 50.5, 45.0, 39.8, 37.5. FTIR ν (cm^{-1}) 3400 (N-H), 2100 (N_3-R), 1735 (ester C=O), 1650 (amide C=O)

ω-Amino poly(styrene)-*b*-poly(ethylene glycol): Polymers **2** (100 mg, 0.16 mmol)and **4** (0.5 g, 0.06 mmol) were dissolved in DMF (15 ml) and sparged with nitrogen (10 minutes). Meanwhile, sodium ascorbate (50 mg, 0.25 mmol) and copper (II) sulfate (20 mg, 0.12 mmol) were dissolved in a separate flask with previously sparged DMF. The solution was sonicated for 2 minutes and transferred via syringe to the flask containing **2** and **4**. The solution was then stirred for 16 hours at room temperature. After this period, the reaction was then precipitated in ice water and filtered to recover the amine terminated block copolymer. ^{1}HNMR (300 Mhz, $CDCl_3$): δ 7.8, (triazole proton), 7.5 (triazole proton), 7.5-6.4 (br, polystyrene aromatic protons), 4.75-4.5 (br, R-CH_2**C**H**H**PhBr), 4.0-3.5 (br, PEG backbone), 2.5-0.5 (br, PS backbone). ^{13}CNMR (500 Mhz, $CDCl_3$): δ 145, 128, 125, 70.9, 40.5. FTIR ν (cm^{-1}) 2100 (triazole), 1735 (ester C=O), 1650 (amide C=O)

5.4.Conclusion

Click chemistry seems to be a suitable method to rapidly produce new block copolymers in a more combinatorial manner. For many systems, this would be an ideal

procedure for rapid screening of polymers for structure-property relationships. However, the PAMAM system with its polyamine structure, is a poor system for this methodology.

After testing under a variety of conditions, it was found that any amount of dendrimer in the reaction mixture would inhibit the cycloaddition. Presumably, this arises from sequestration of the copper catalyst within the dendritic portion of the molecule. Nonetheless, this method has proven itself worthy of further study, as it can be a rather simple means to create telechelic block copolymers.

5.5.References

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Chapter 6 : Conclusions

6.1.Summary

This study has focused on the synthesis and self assembly behavior of a linear-dendritic block copolymer system comprised of poly(styrene)-*block*-poly(amido amine). Through the synthesis of several generations of this linear-dendritic block copolymer, the solution state self assembly could be observed using TEM and light scattering experiments. In various solvent systems including compositions of water and tetrahydrofuran, the polymers synthesized were able to spontaneously form vesicle structures around 100 nm in diameter.

The area occupied by the amphiphilic headgroup (the dendritic PAMAM portion) of these polymers was determined using the Langmuir Blodgett isotherm method. Obtaining isotherms of these polymers under differing pH conditions allowed for the study of the differing effects of steric as well as electrostatic interactions both intramolecularly and intermolecularly. Additionally, the exponential growth in size could be readily seen via the isotherm analysis.

A more robust means to synthesize linear-dendritic block copolymers was also explored. Using the "click chemistry" methodology, an amine terminated block copolymer of PS-PEG was synthesized, but any further attempts to increase the dendrimer size was met with low yields and difficult purification. It was found that the ability of the PAMAM dendrimer to bind copper salts was a major hindrance in this particular synthetic pathway.

6.2.Future Directions

6.2.1.Rapid convergent synthesis of linear-dendritic block copolymers

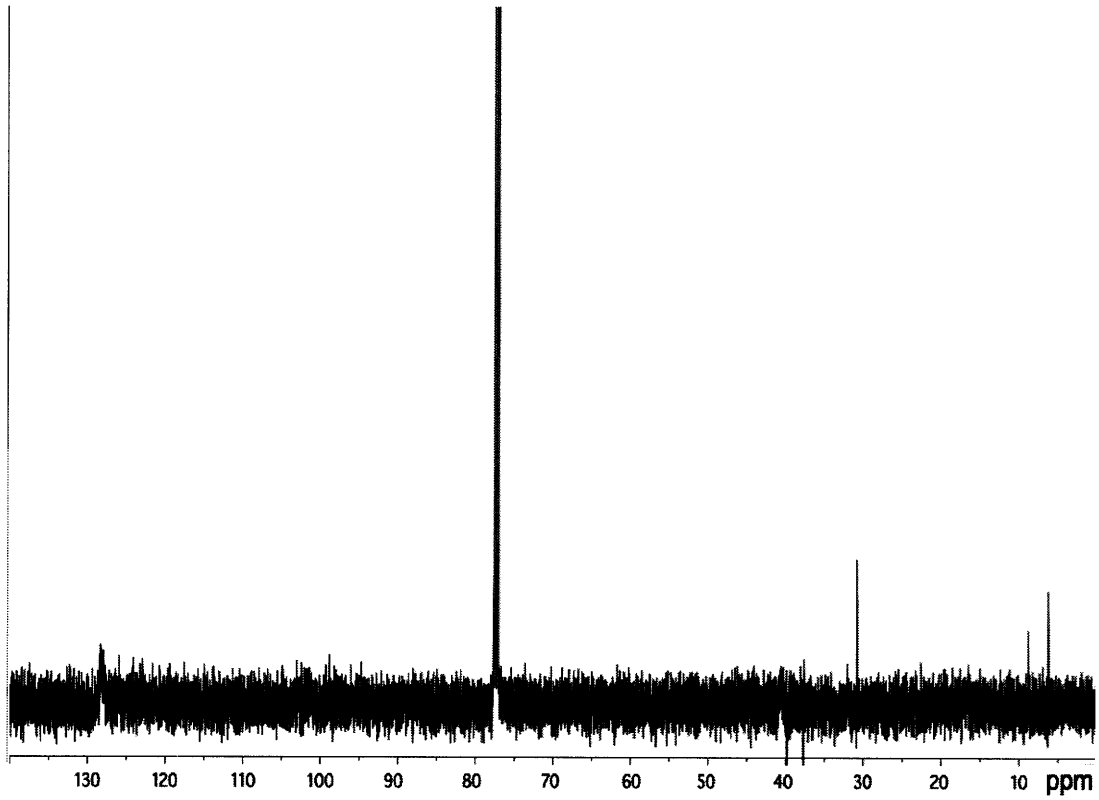
The linear-dendritc block copolymer literature, though brief has several areas where improvements and fundamental studies could be performed. The first of these is a facile synthesis for rapid screening of structure-property relationships. The most important part of this mention is that the synthesis be broad. Most convergently synthesized dendrimers can be readily adapted to rapid synthesis of linear-dendritics, simply because they are created with either orthogonal functional groups or standard protecting groups. Divergently synthesized dendrimers tend to be incompatible with a large number of useful and particularly interesting linear polymers. For example, the PAMAM dendrimer synthesis is chemically incompatible with most polymers. The only polymers remaining for this particular function are the typically "inert" polymers. A synthesis that could rapidly combine dendrimers and linear blocks would create vast new opportunities in this area of polymer chemistry.

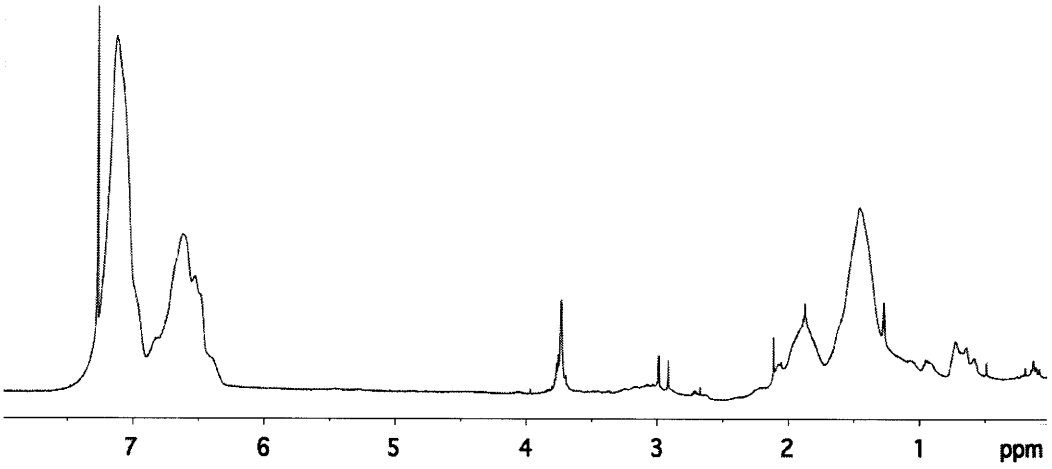
6.2.2.Reversible block copolymer assembly

Along similar lines as the first direction, is the possibility to utilize reversible chemistry to create polymer nanospheres. One example would be a linear-dendritic polymer synthesized with a reversible junction between the two

blocks. This junction could be pH sensitive, light sensitive, heat sensitive, etc., but the main thrust would be to use amphiphilic self assembly to create a desired structure, and "freeze" it into place by removing the solvent stabilizing groups. For the PS-PAMAM system, the PAMAM exterior could be cleaved from the glassy styrene chain leaving 100 nm hollow nanoparticles behind to precipitate out of solution for later characterization. These types of structures could provide long lasting encapsulation solutions as the kinetics for dissociation would be essentially frozen.

Appendix A: Chapter 2 Compound Spectra





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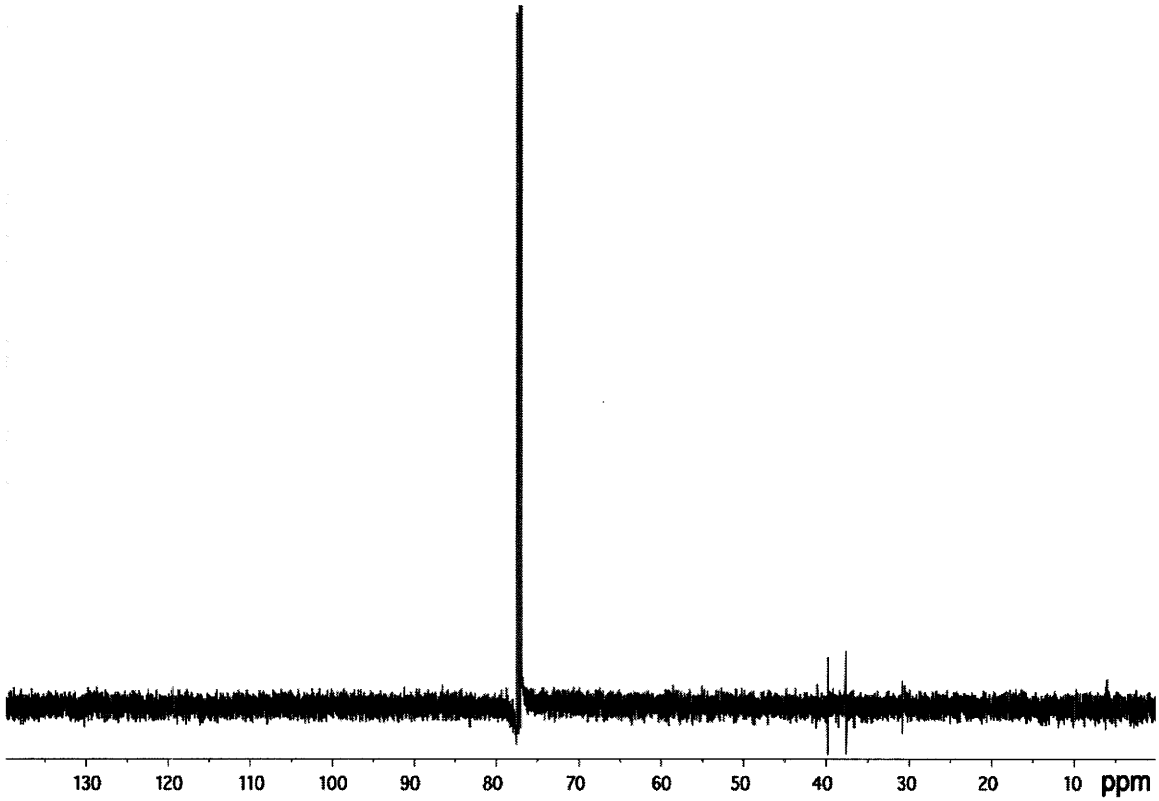

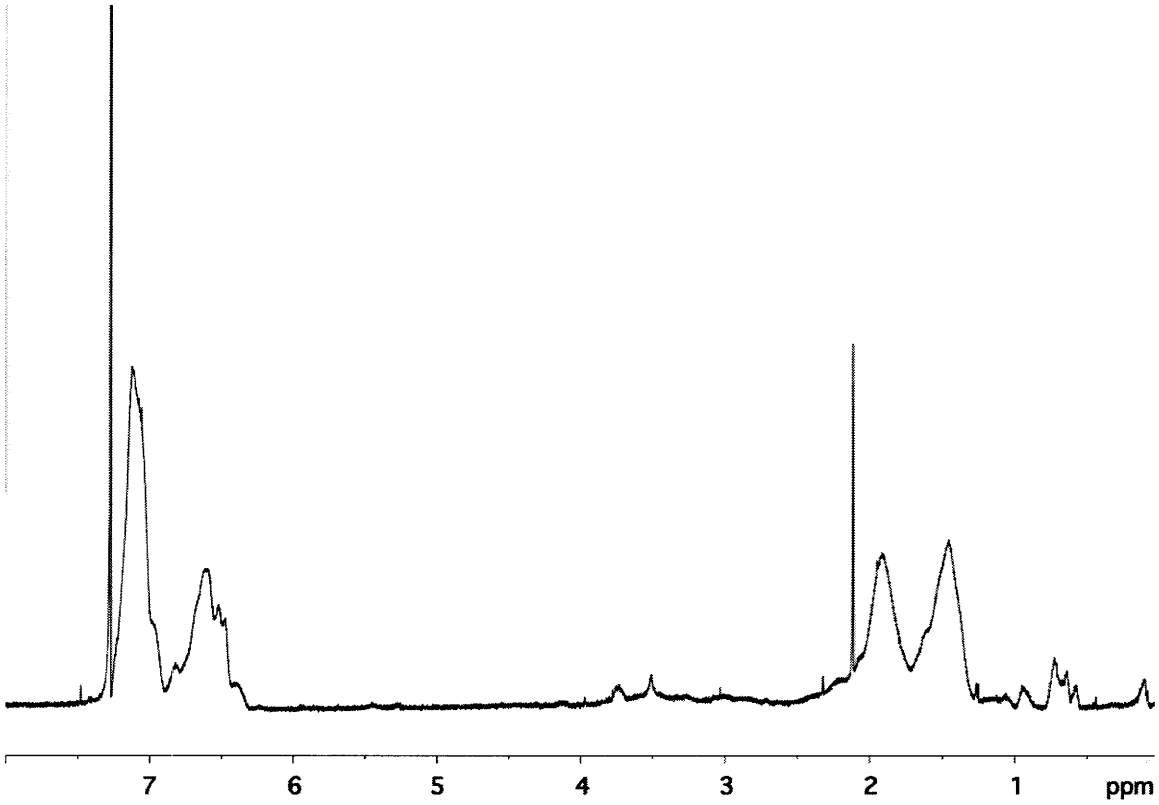

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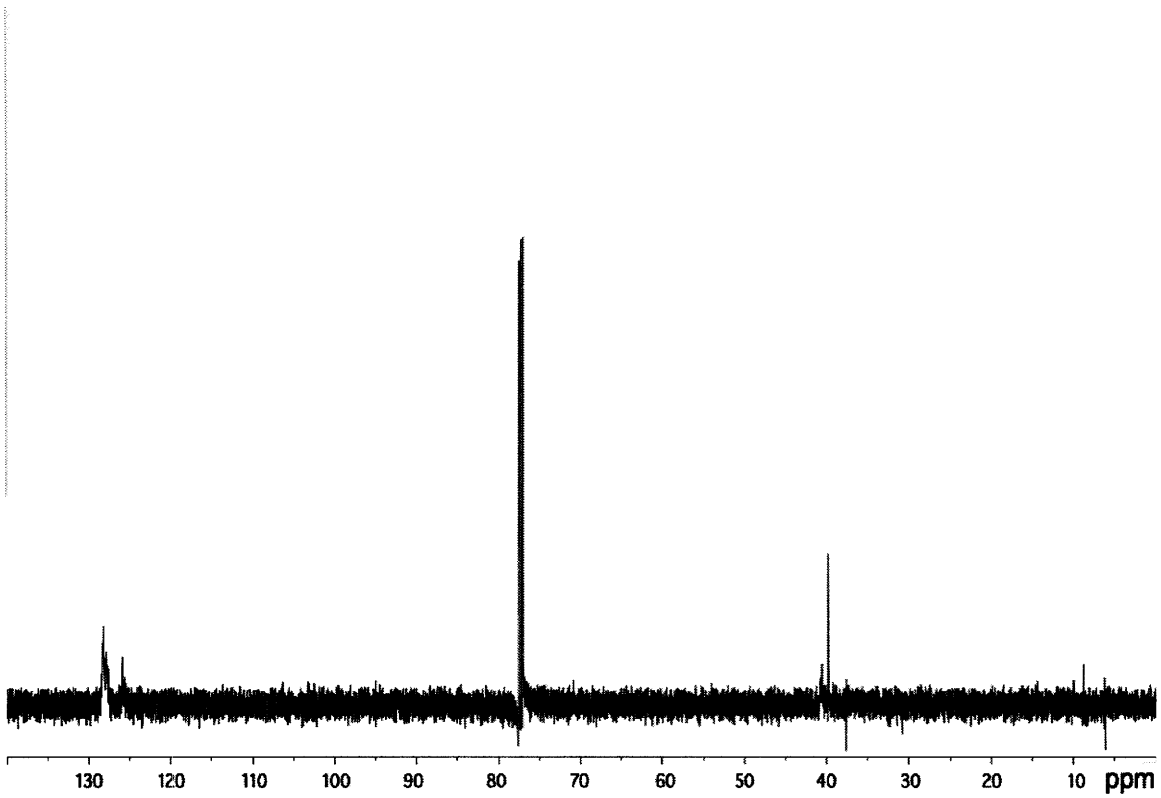

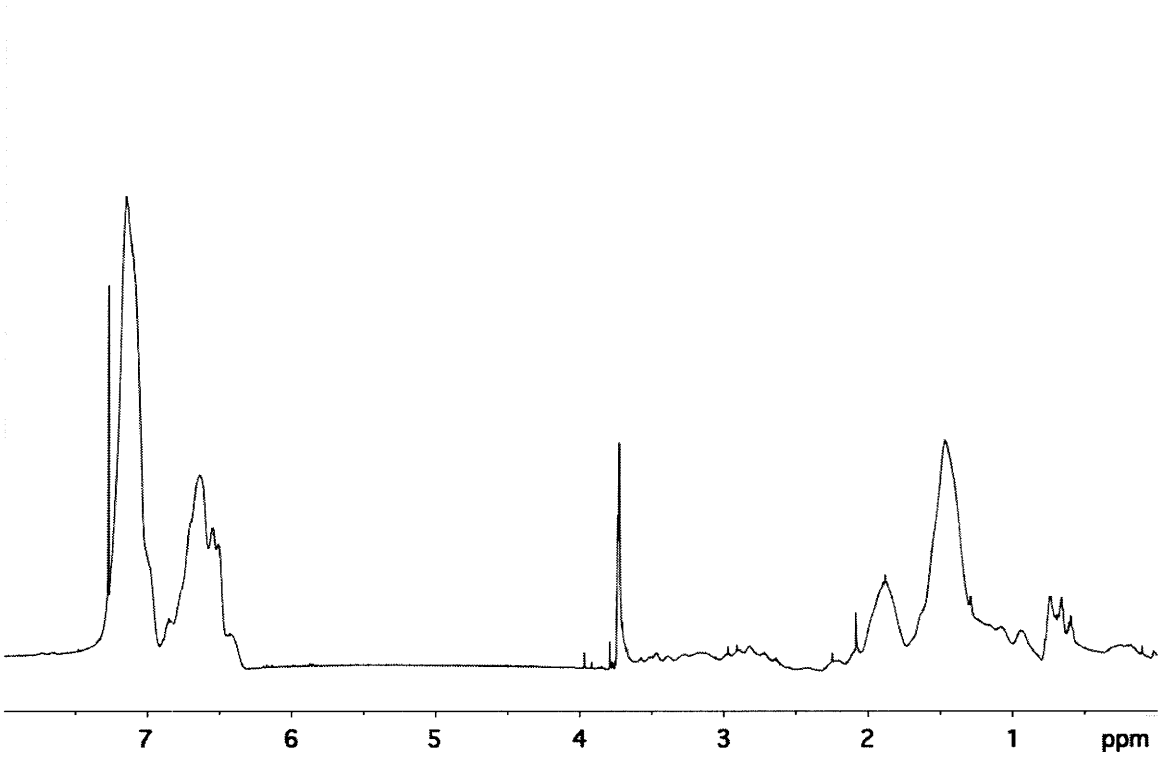

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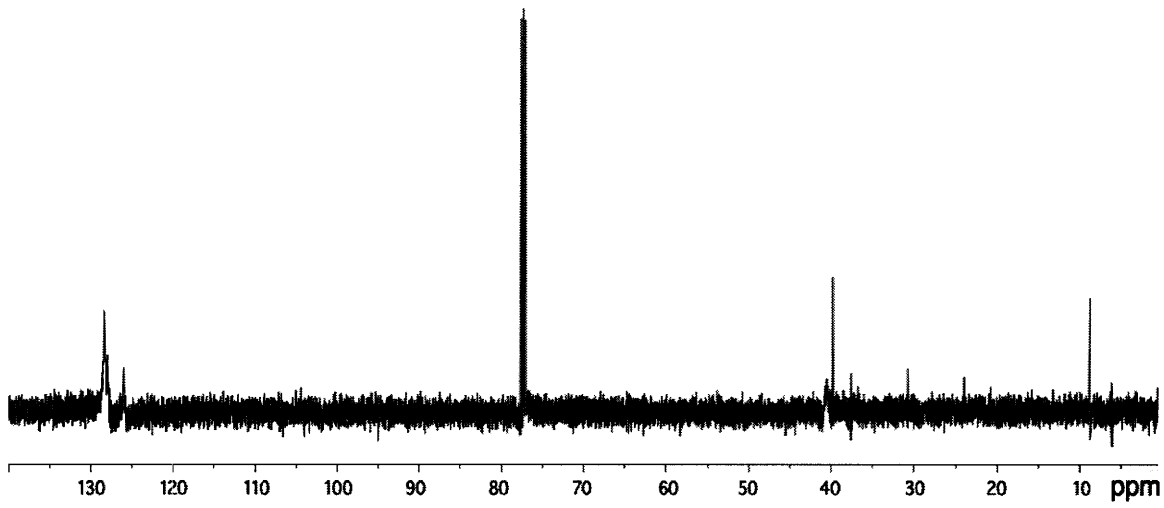

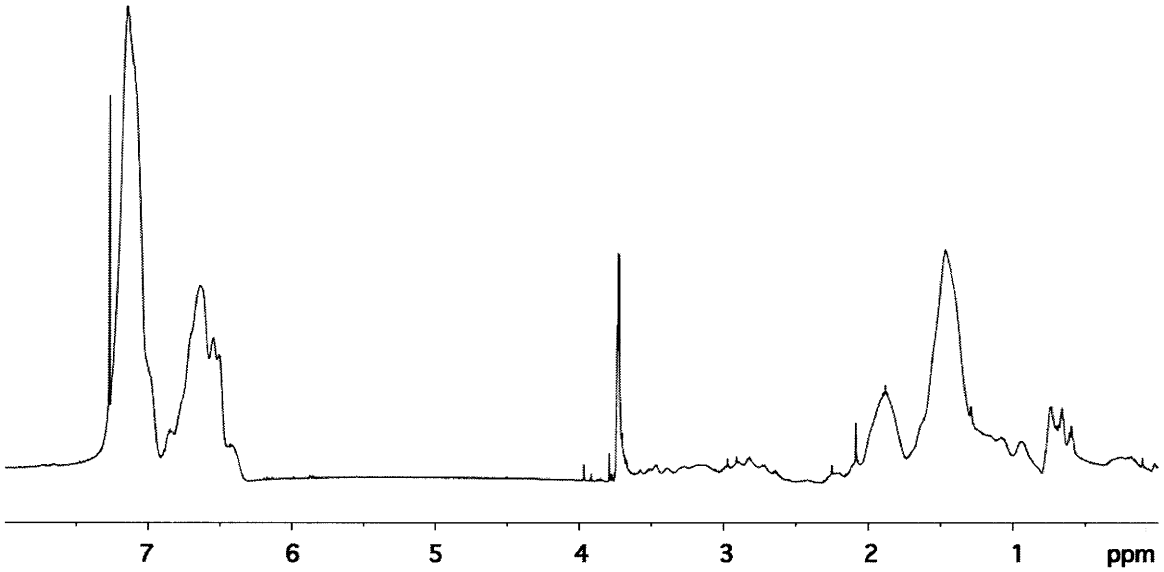

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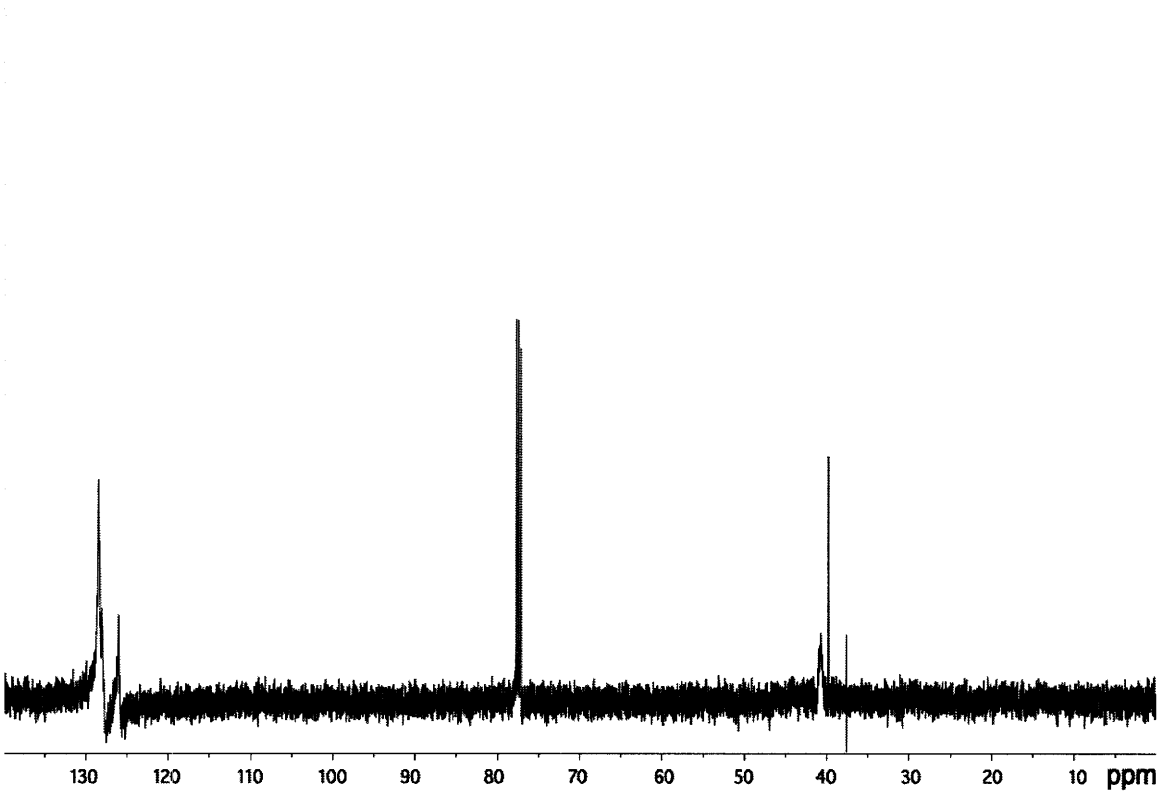

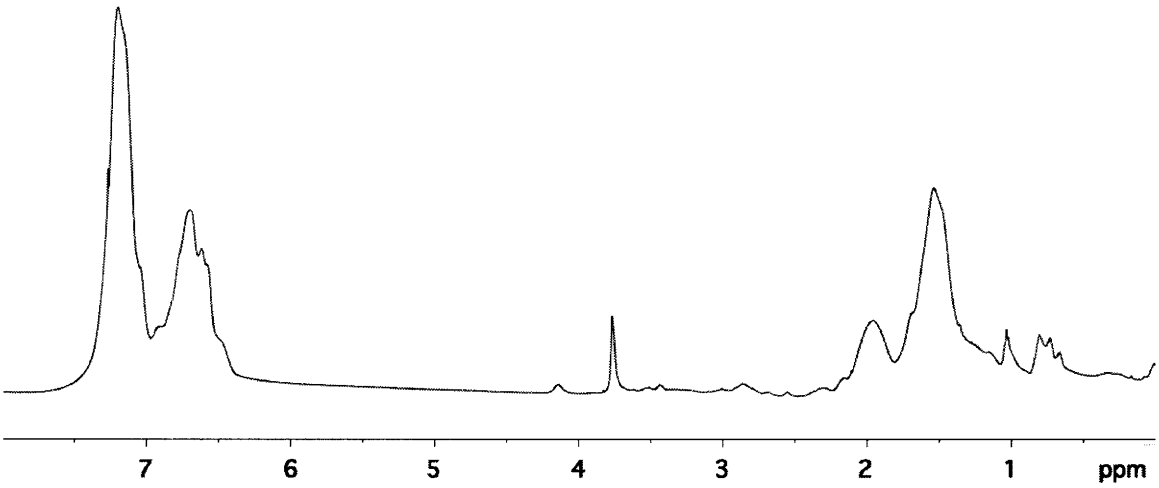

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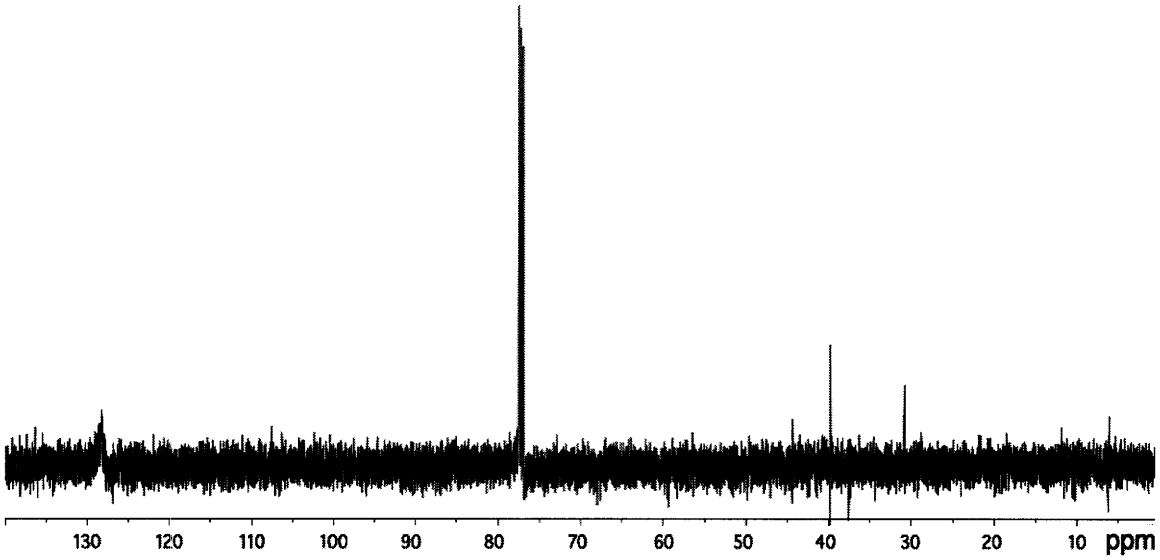

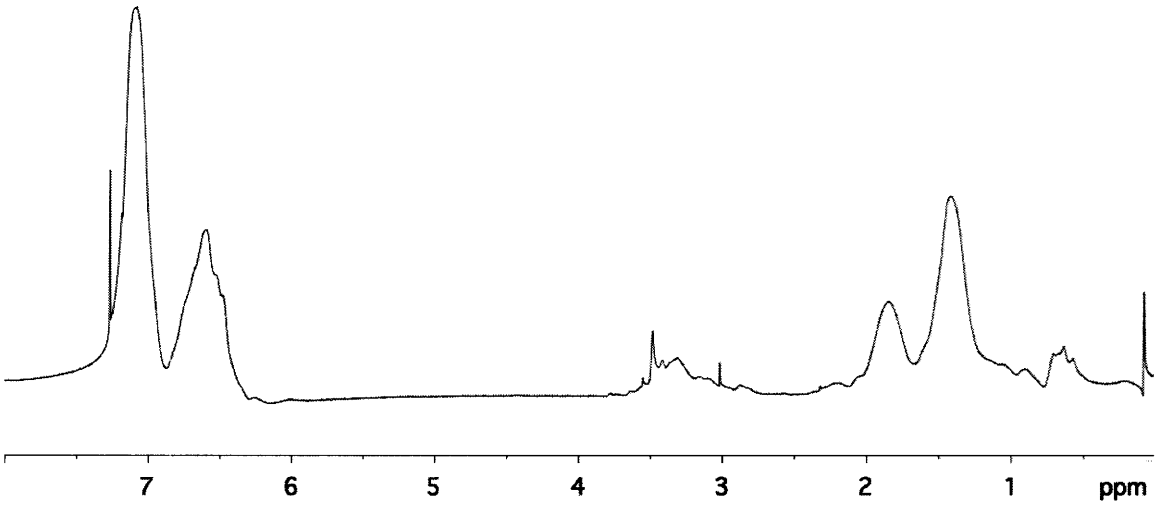

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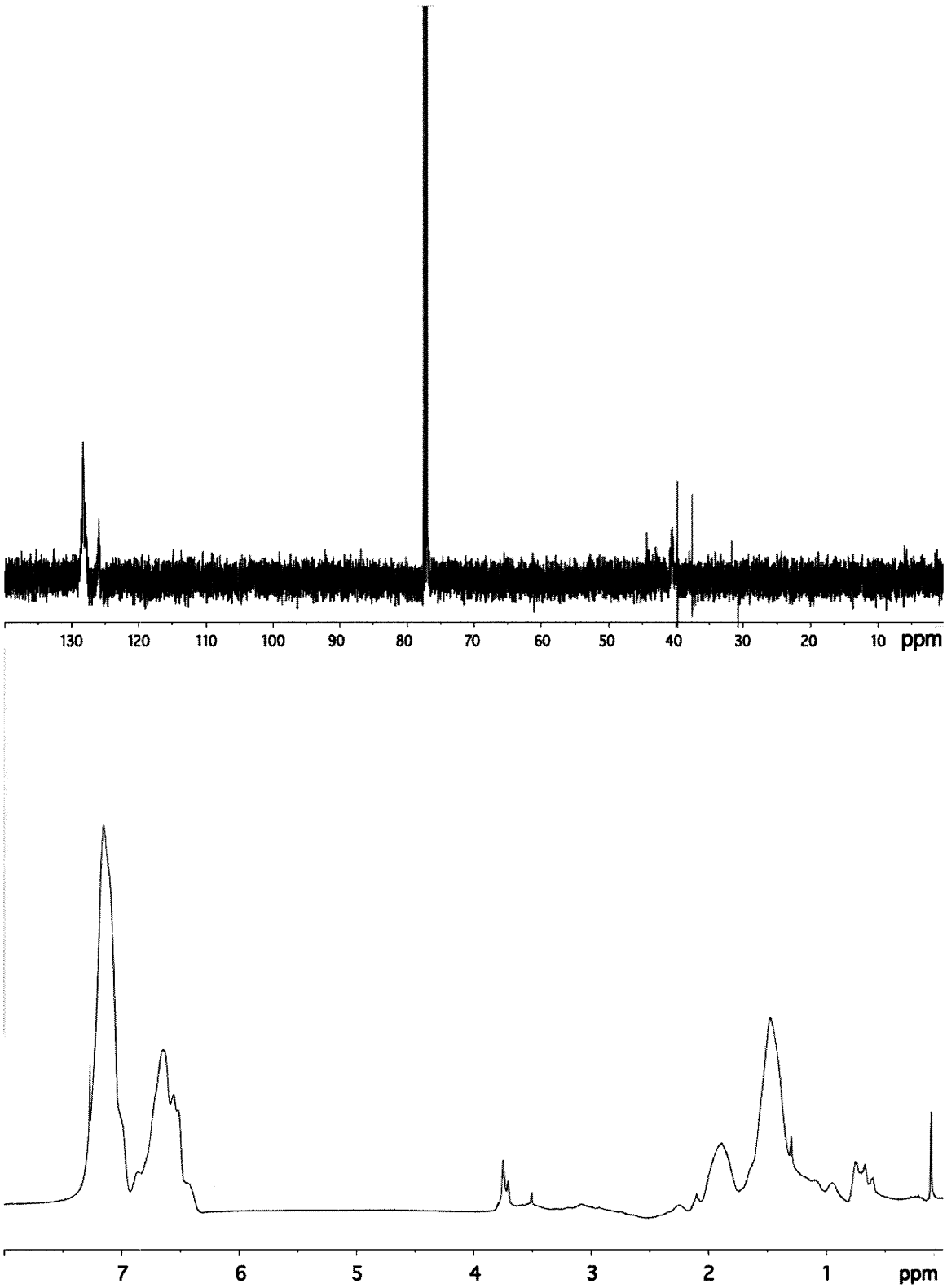

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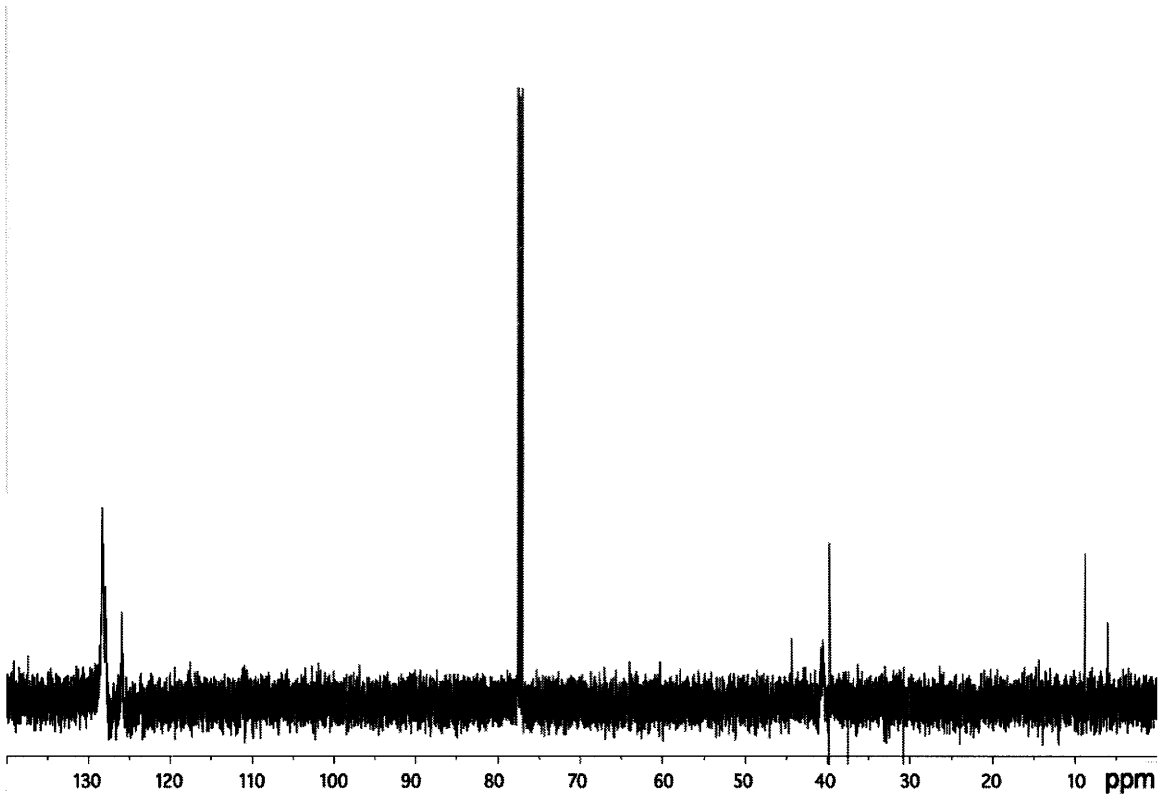

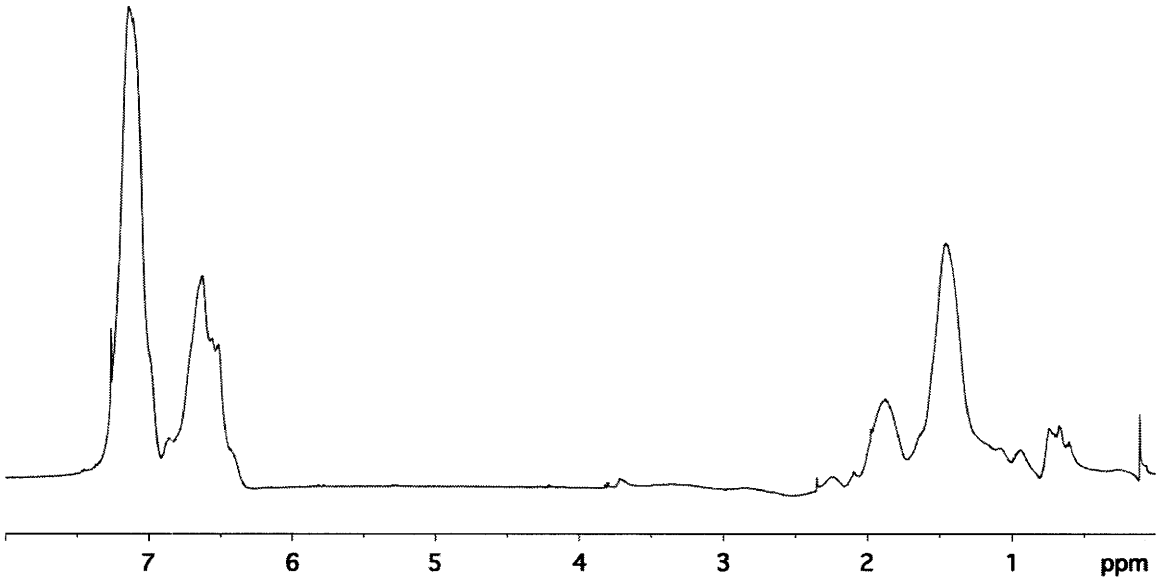

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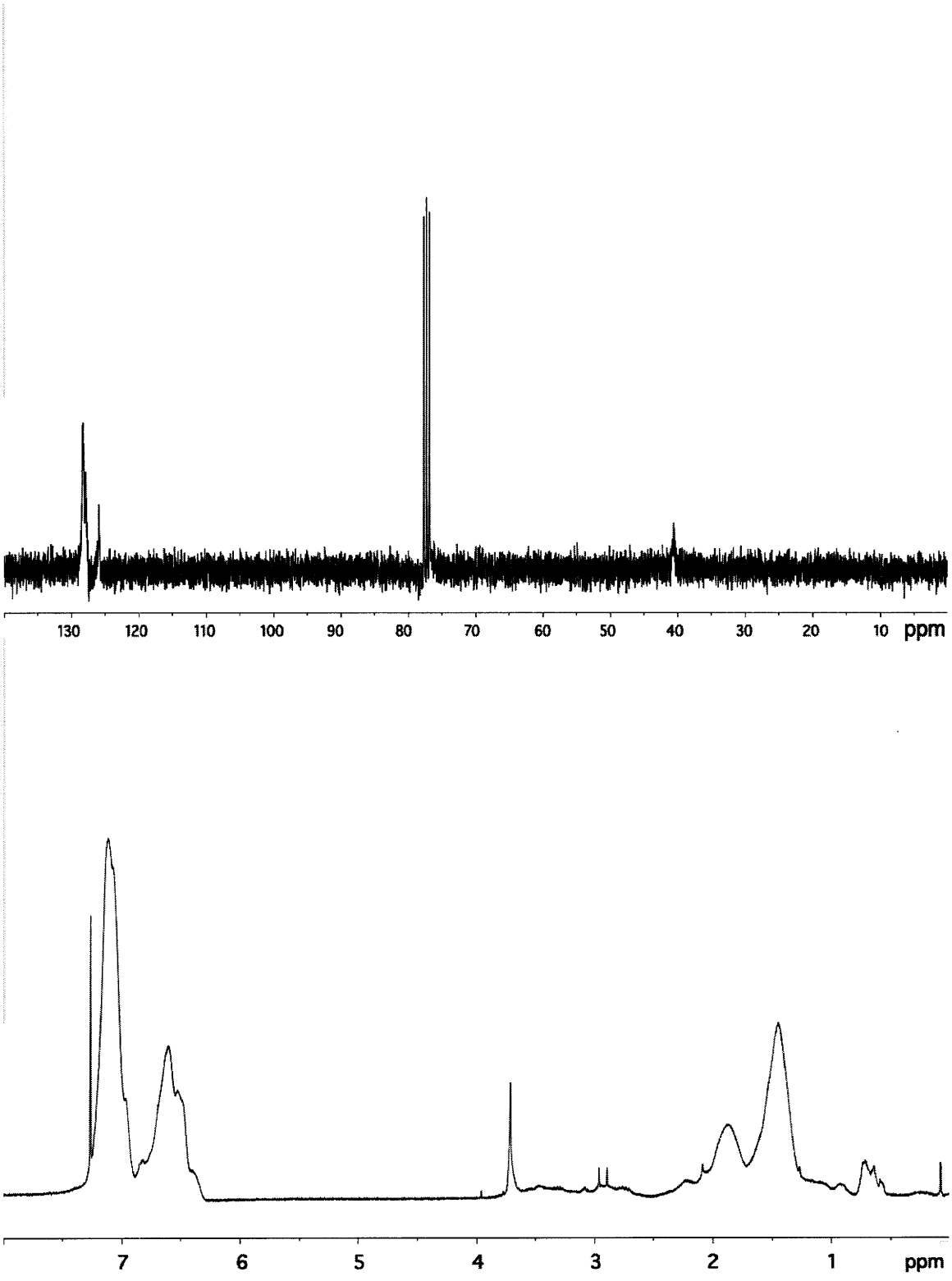

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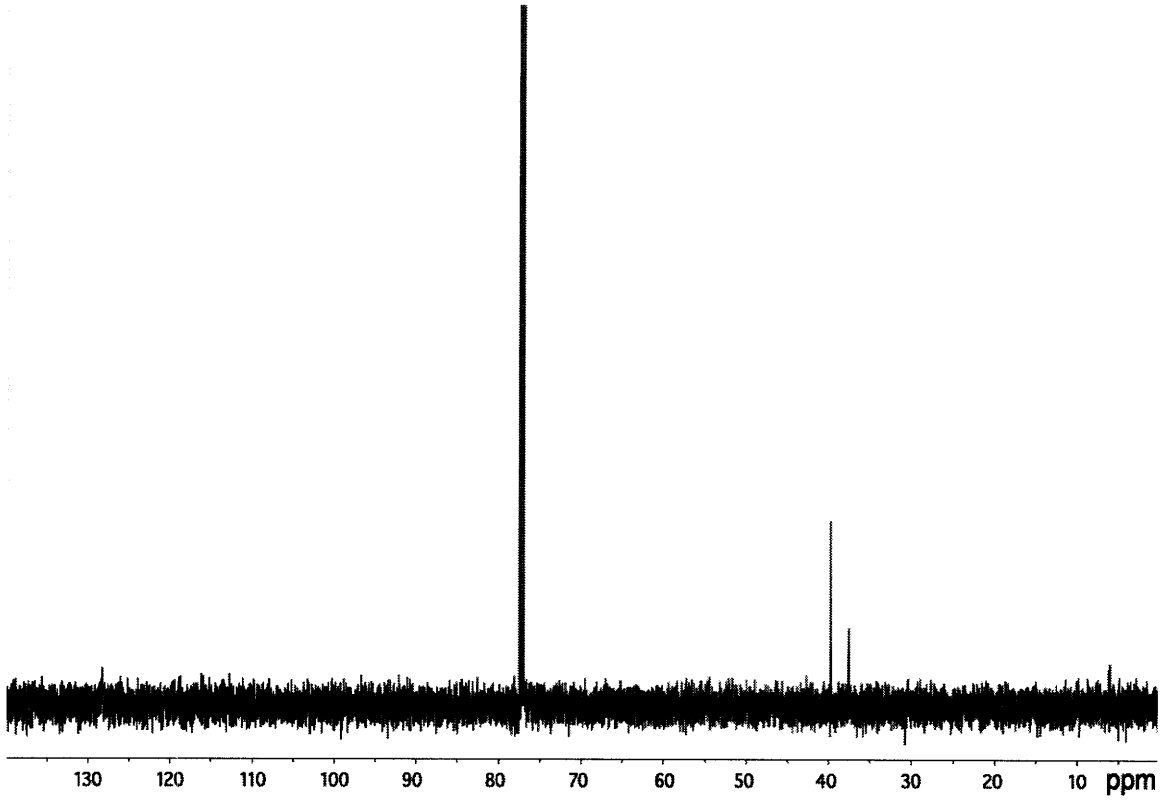

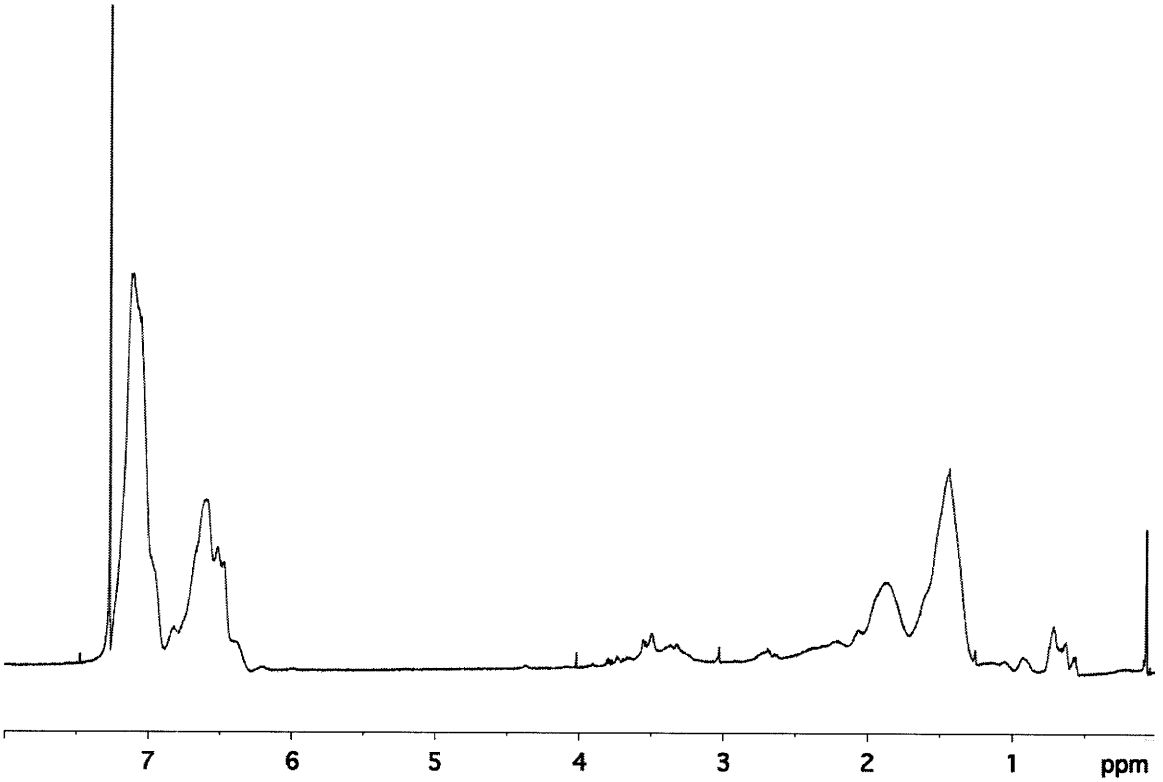

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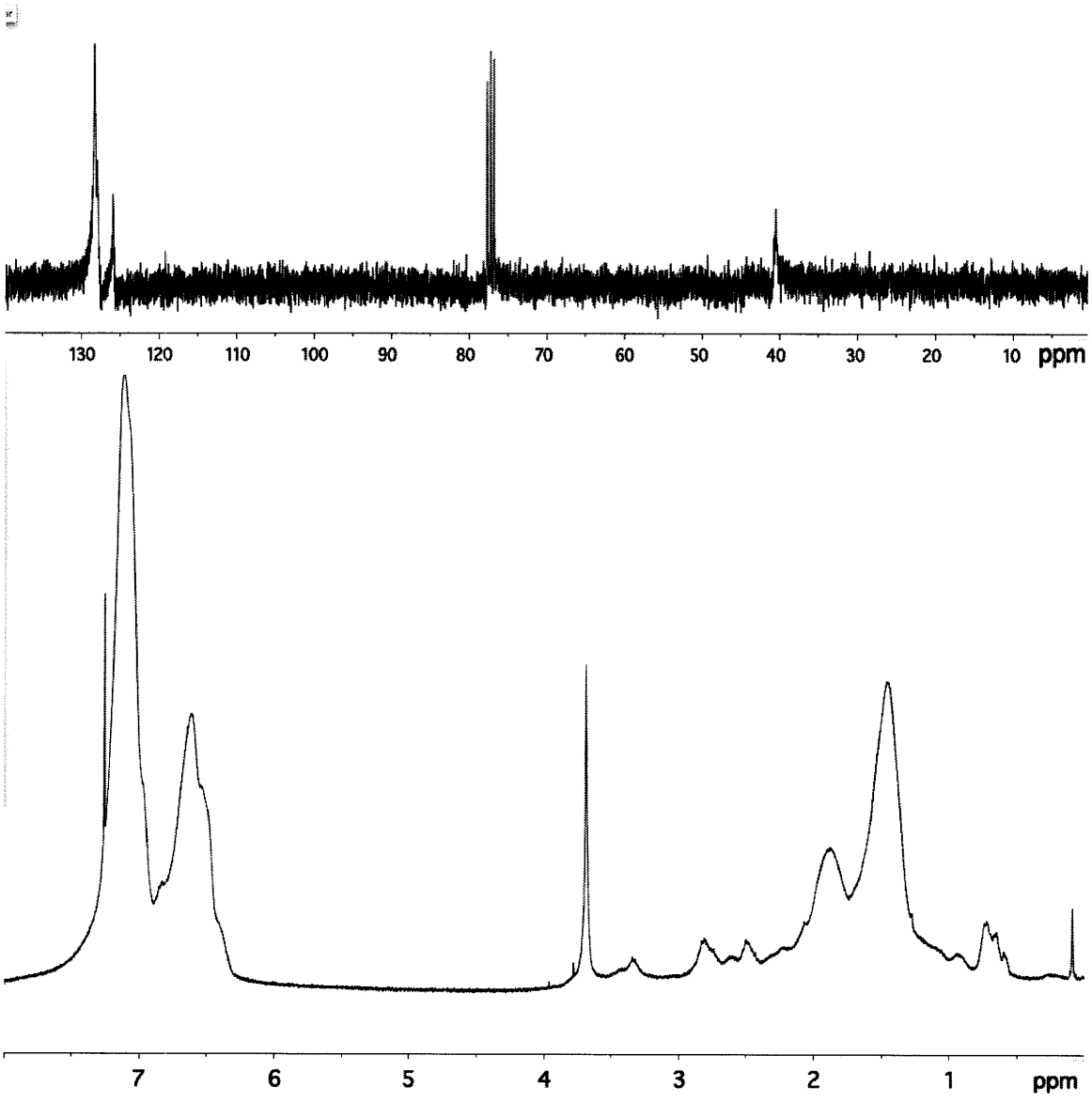

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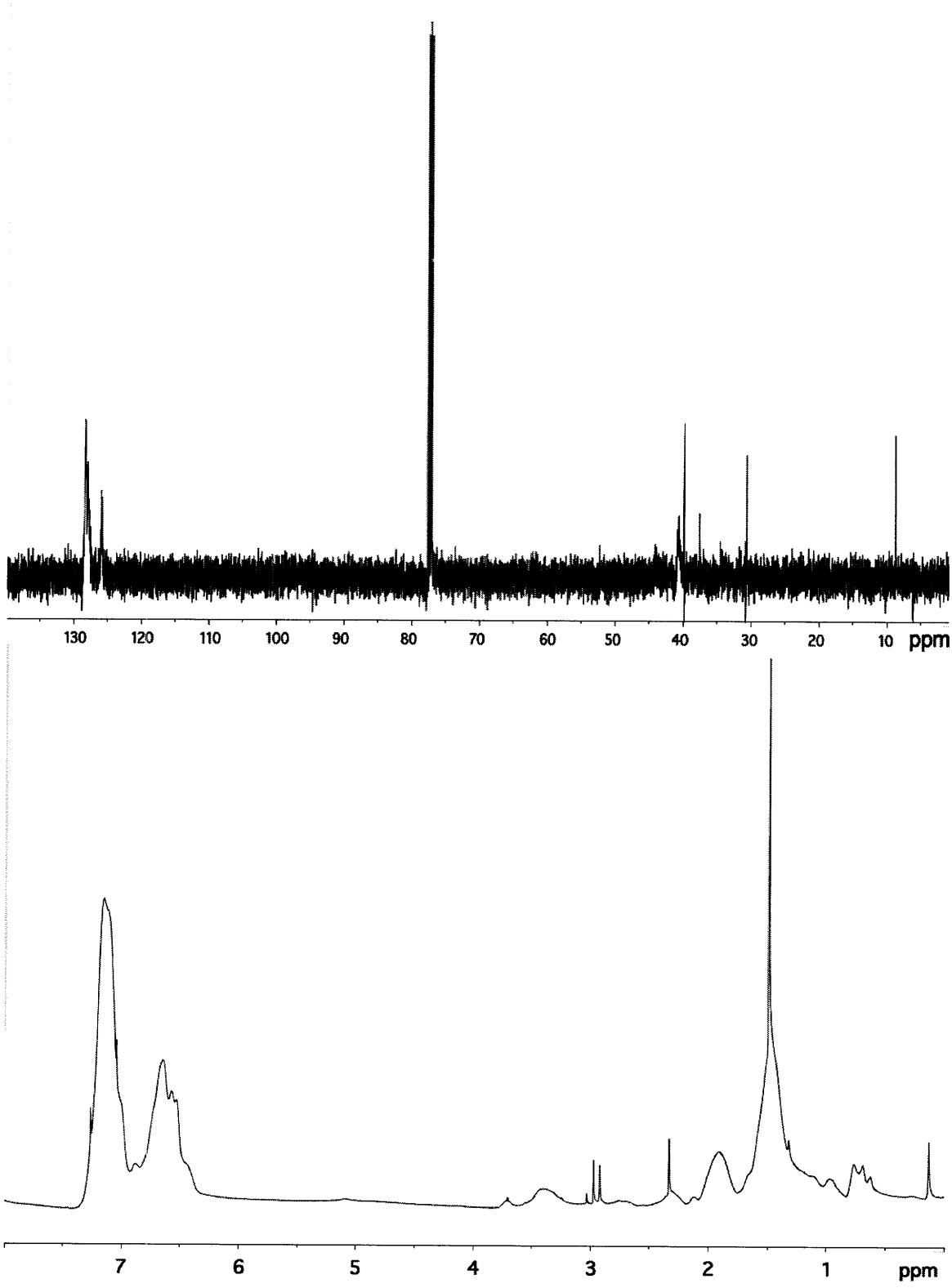

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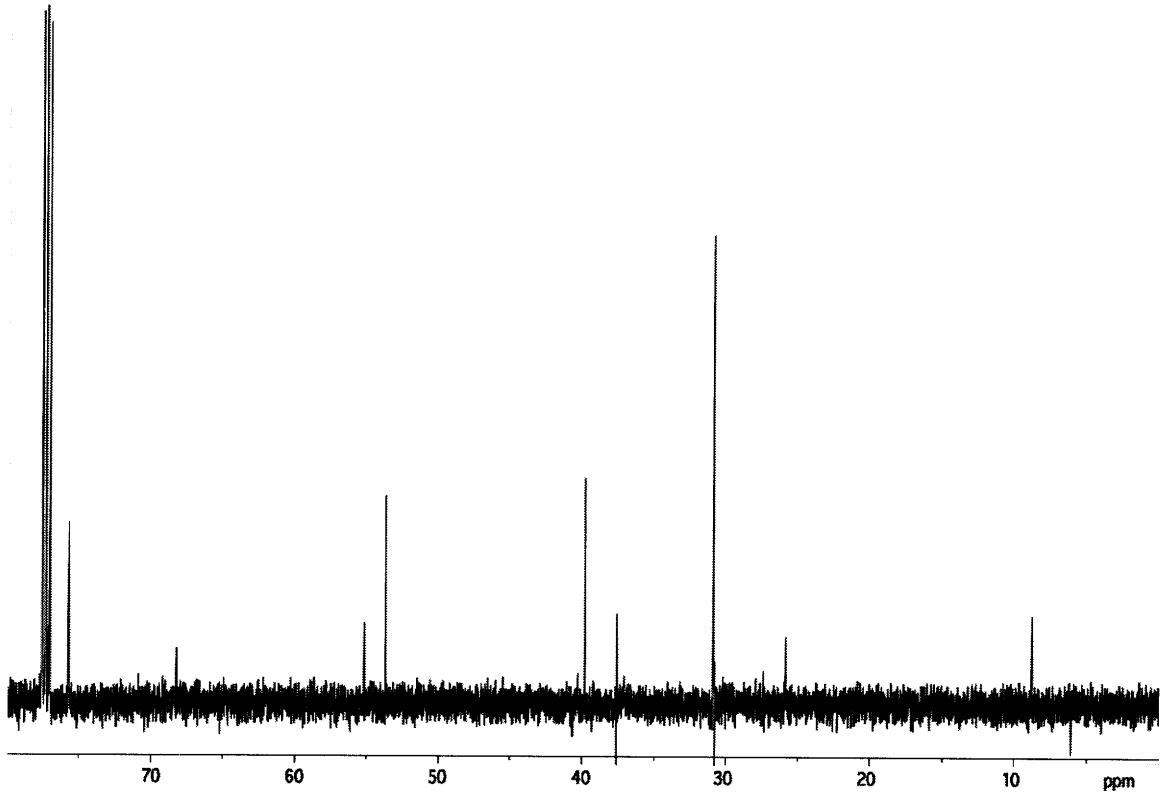
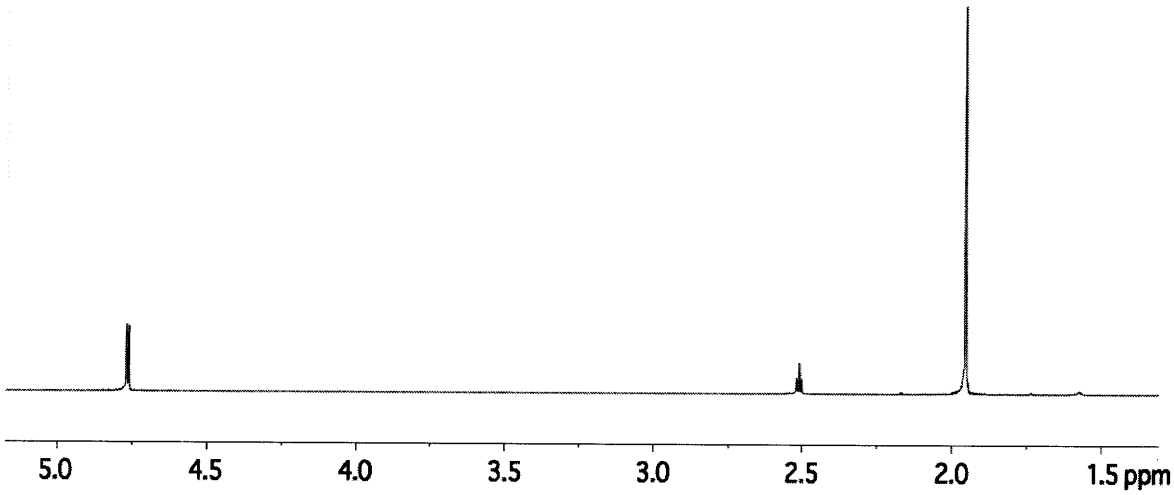
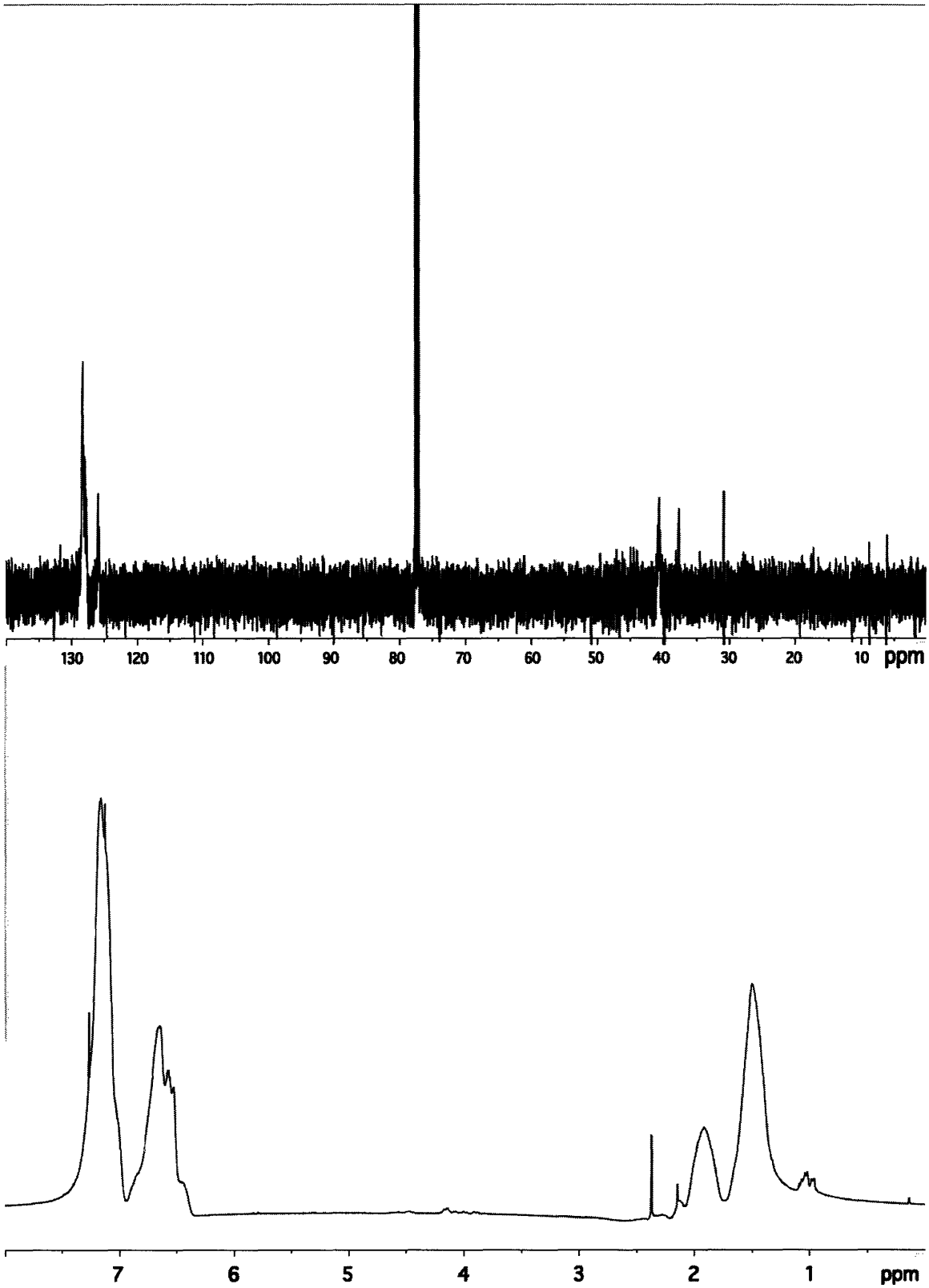
Appendix B: Chapter 5 Compound Spectra





Compound 1



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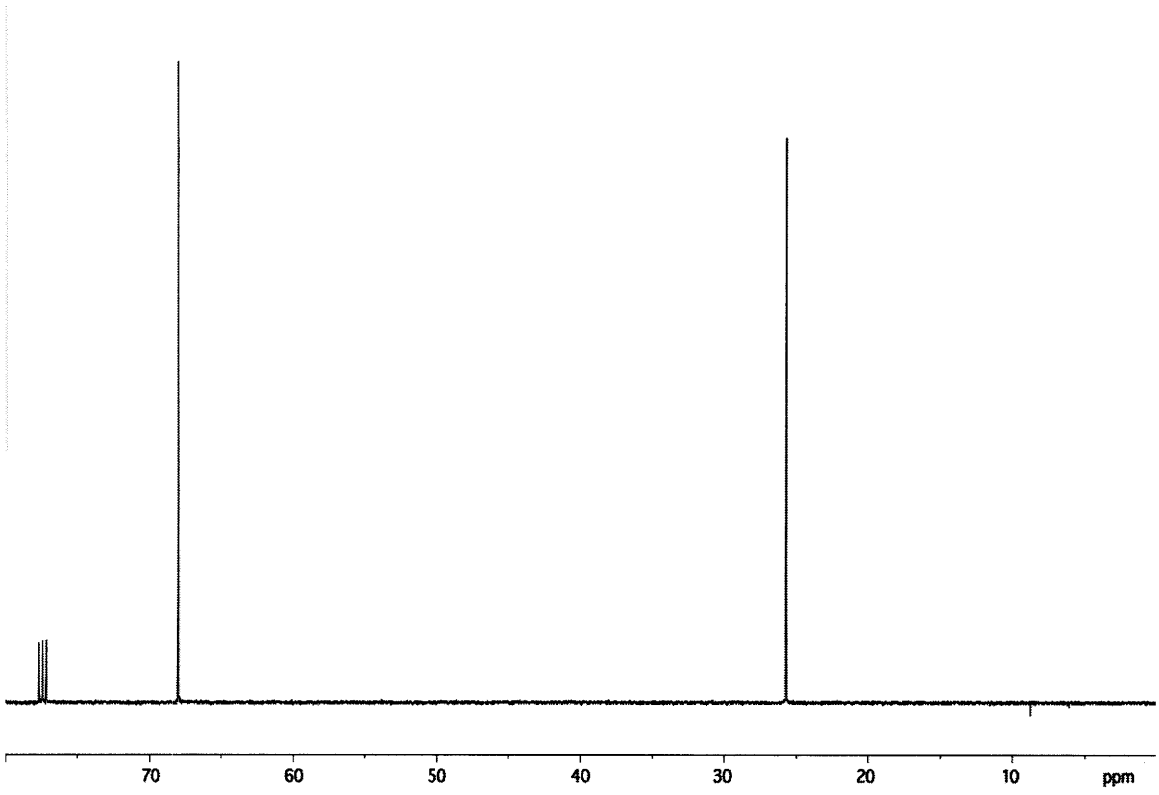

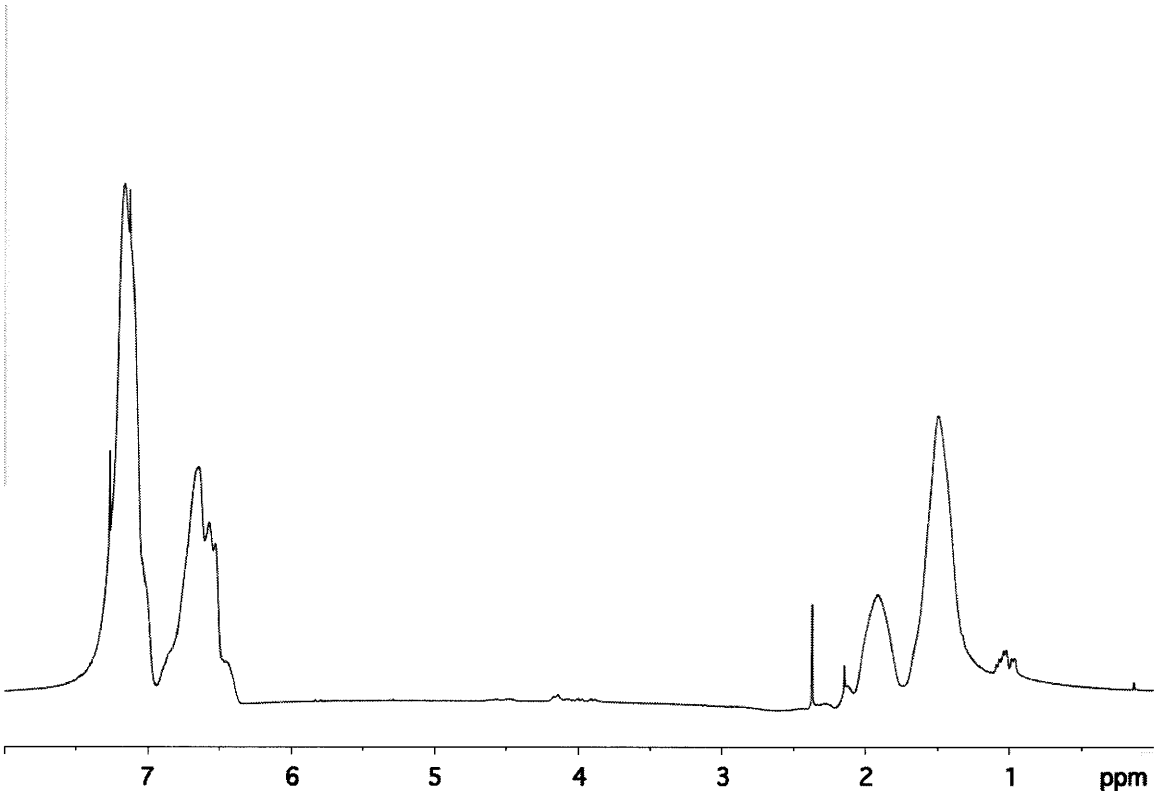

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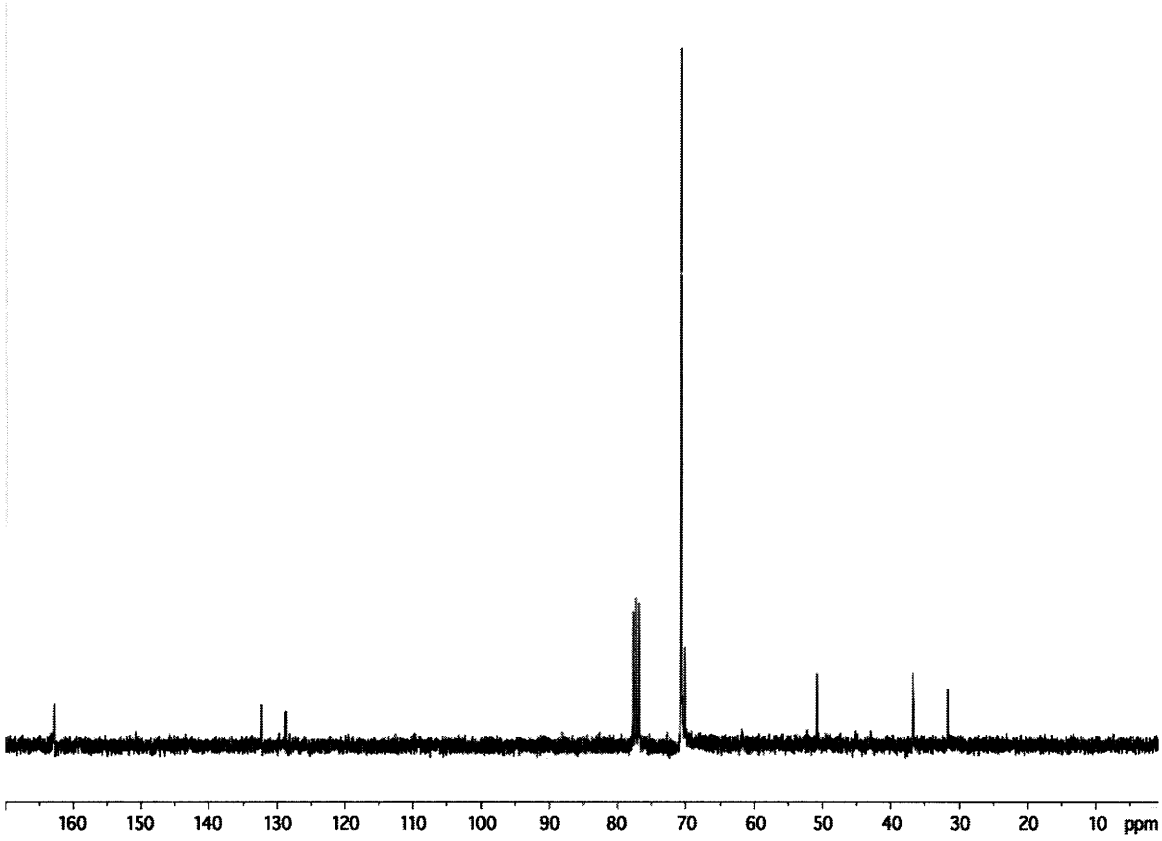
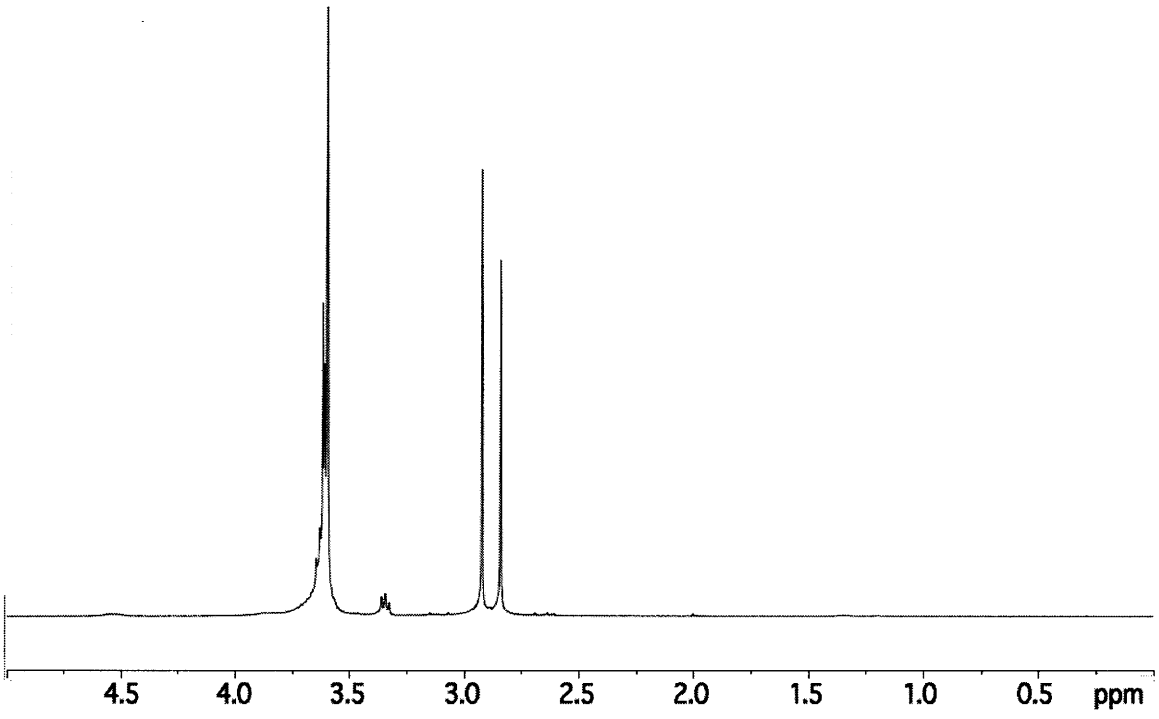
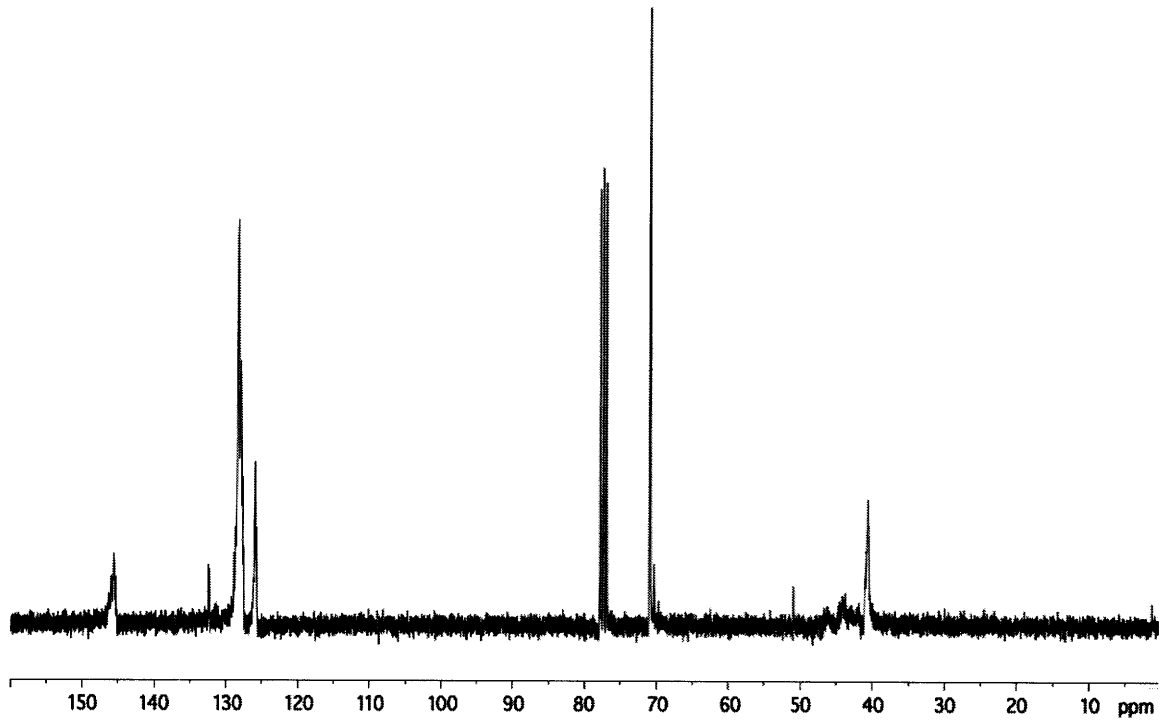
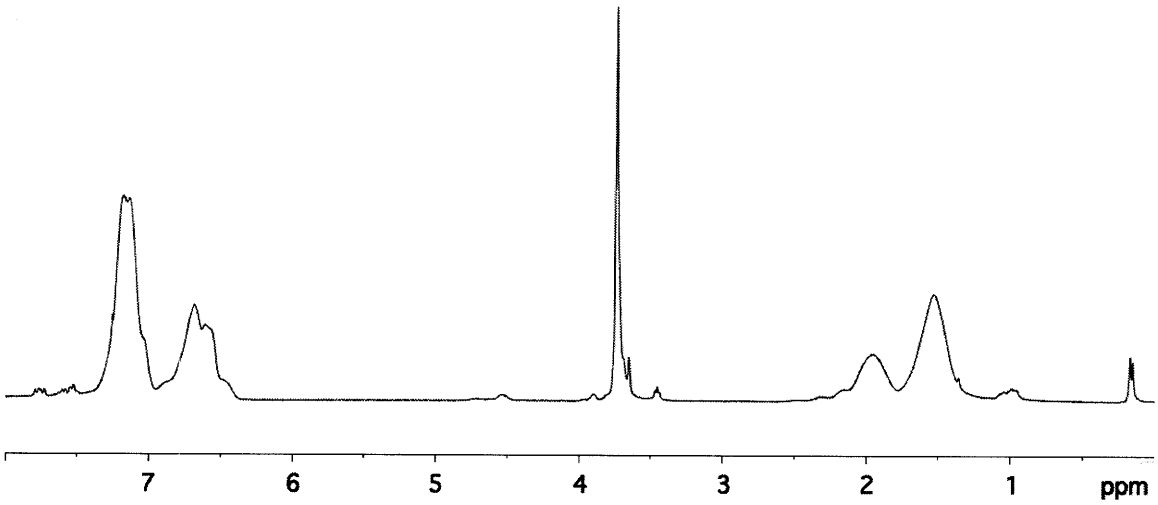

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

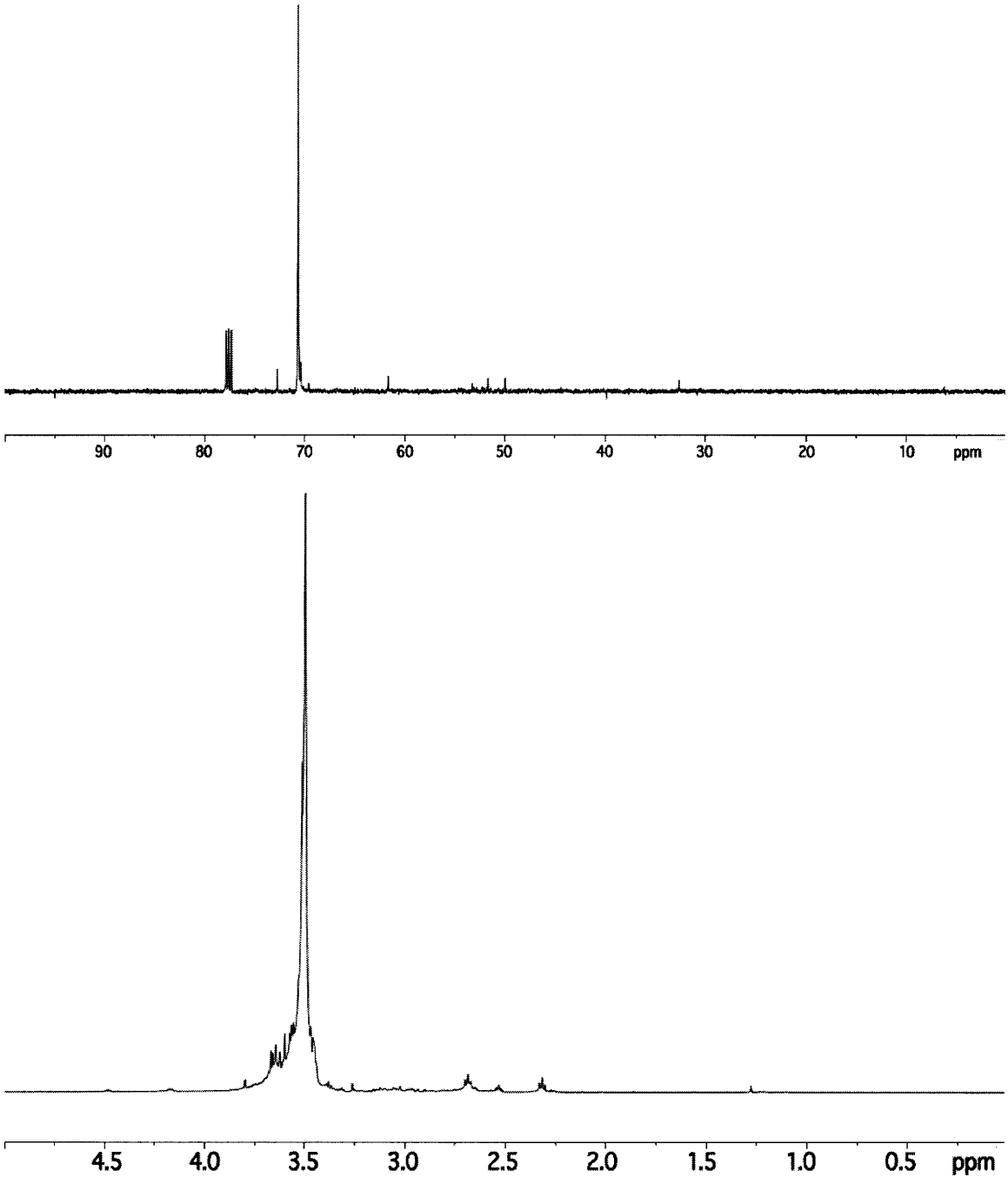

4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

Compound 4

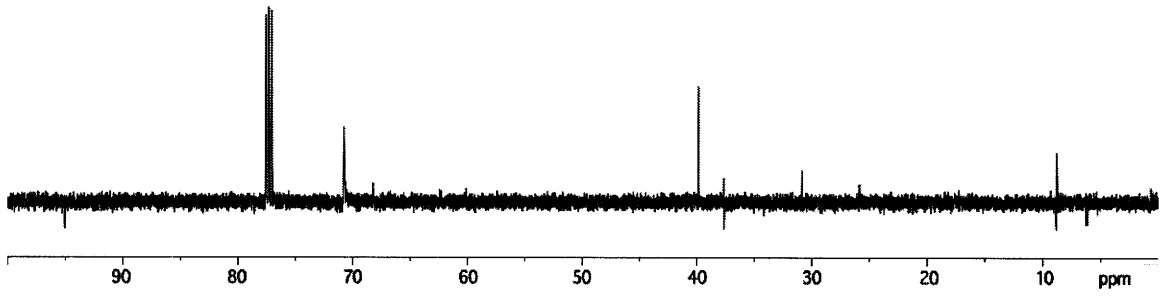


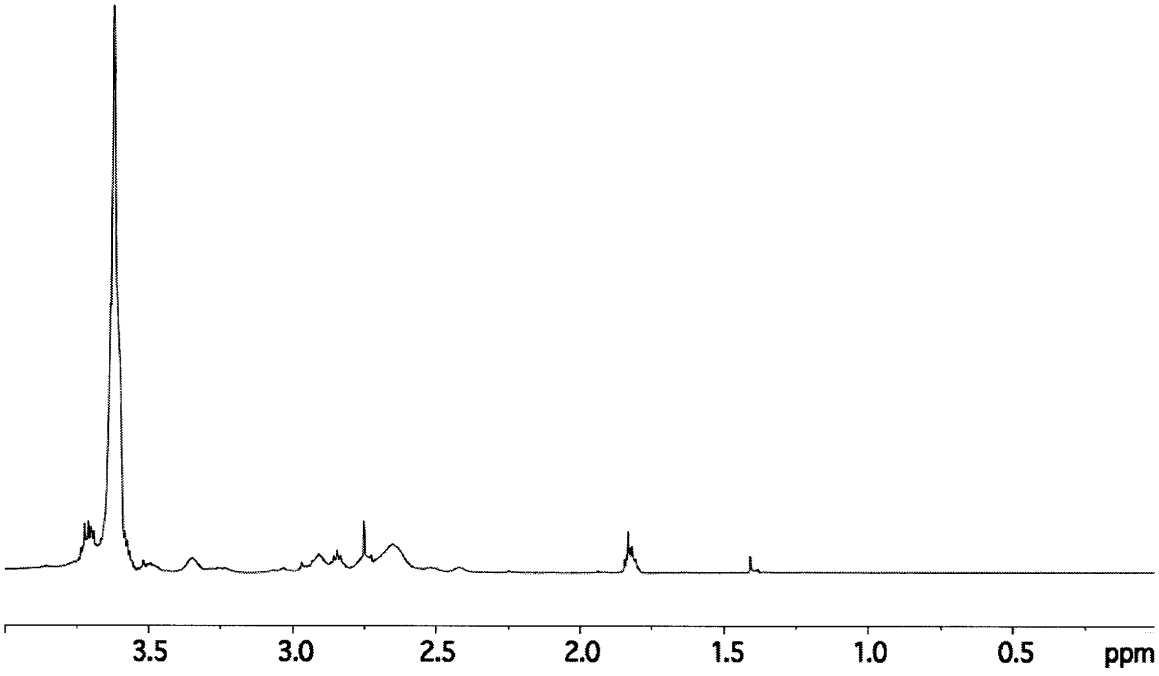


Compound 5

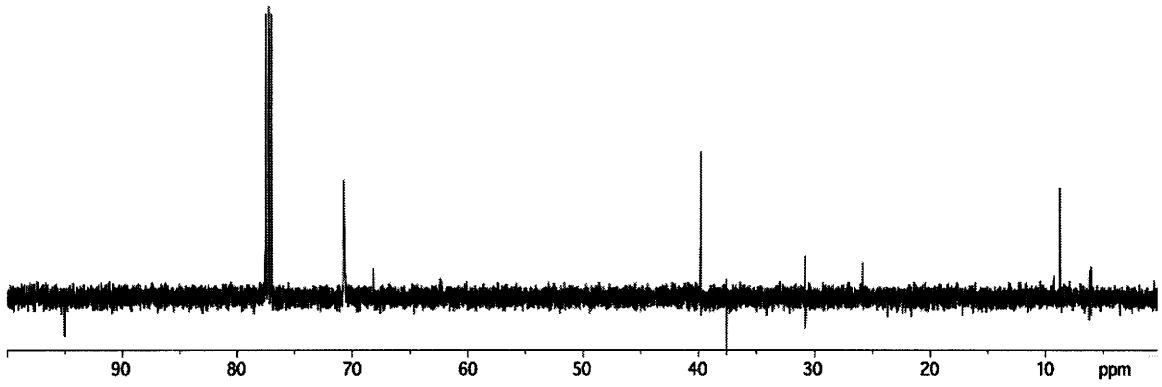


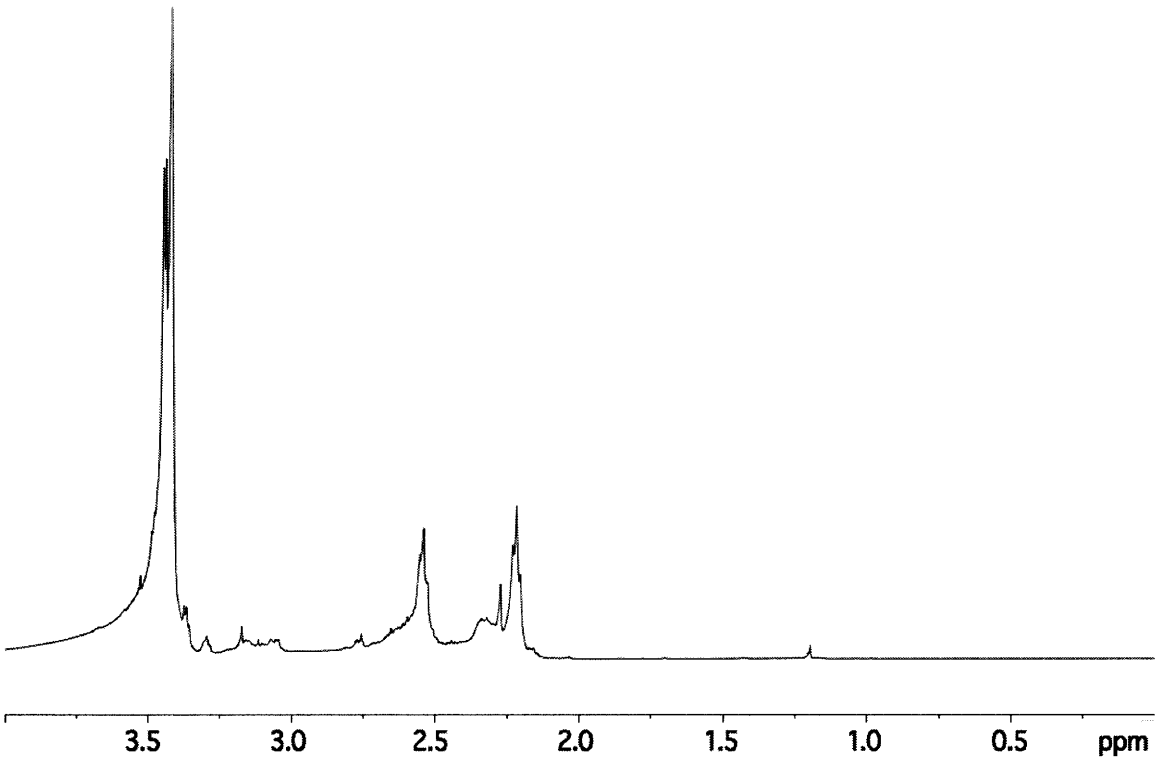
Azide-PEG-PAMAM G 0.5





Azide-PEG-PAMAM G 1.0





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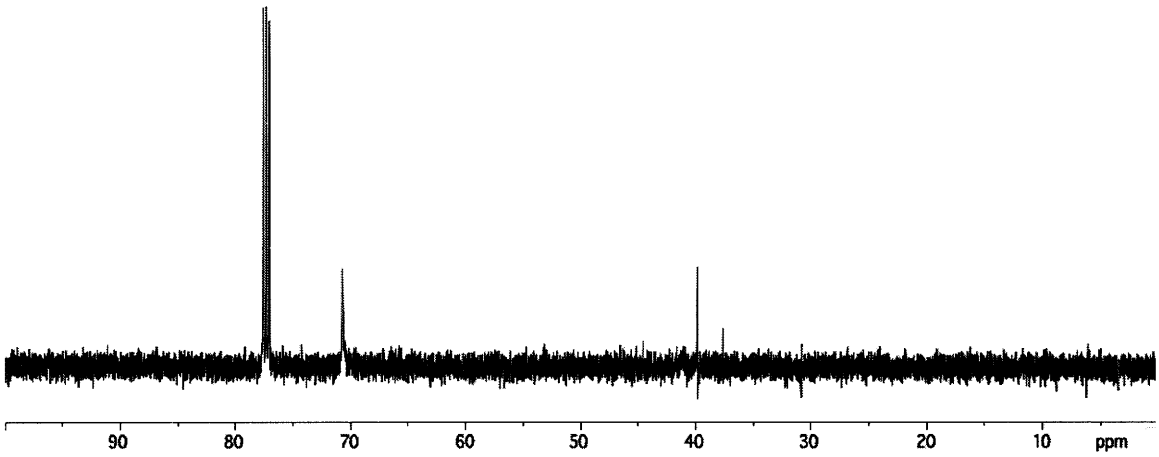
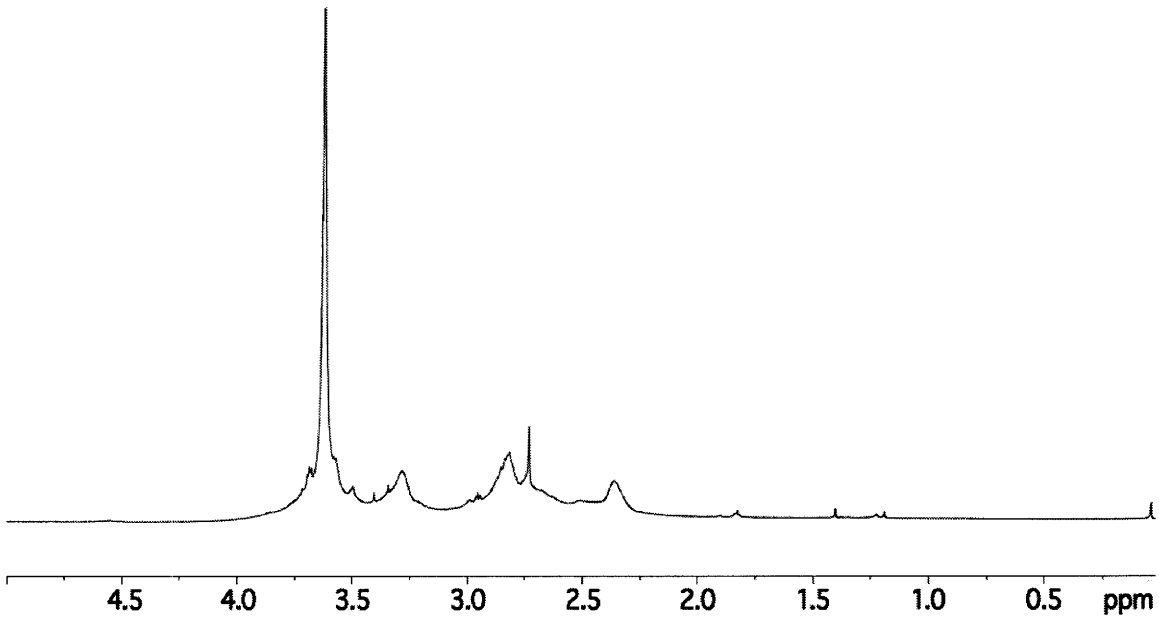
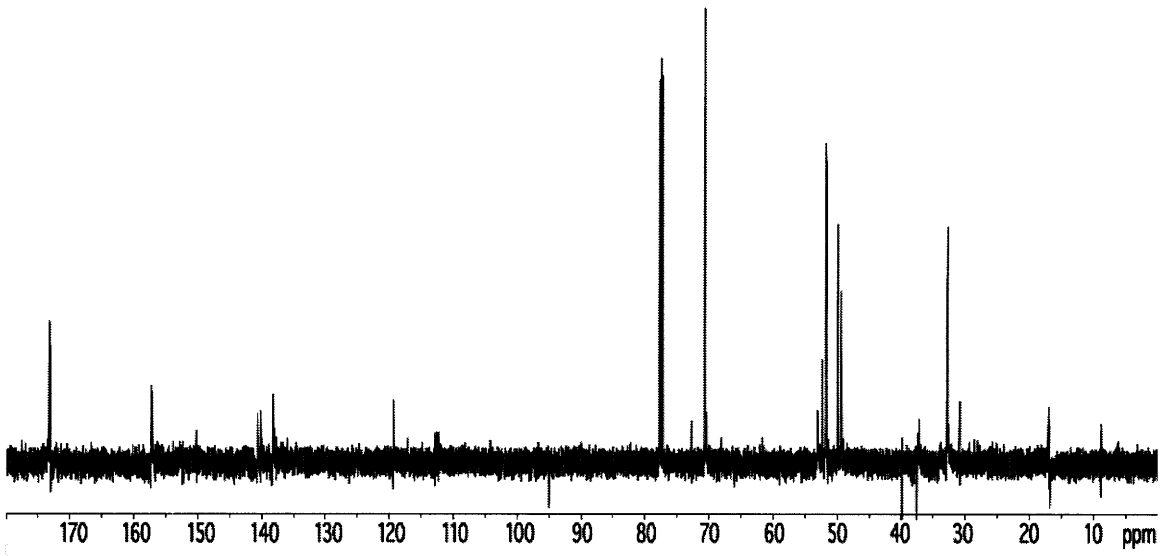
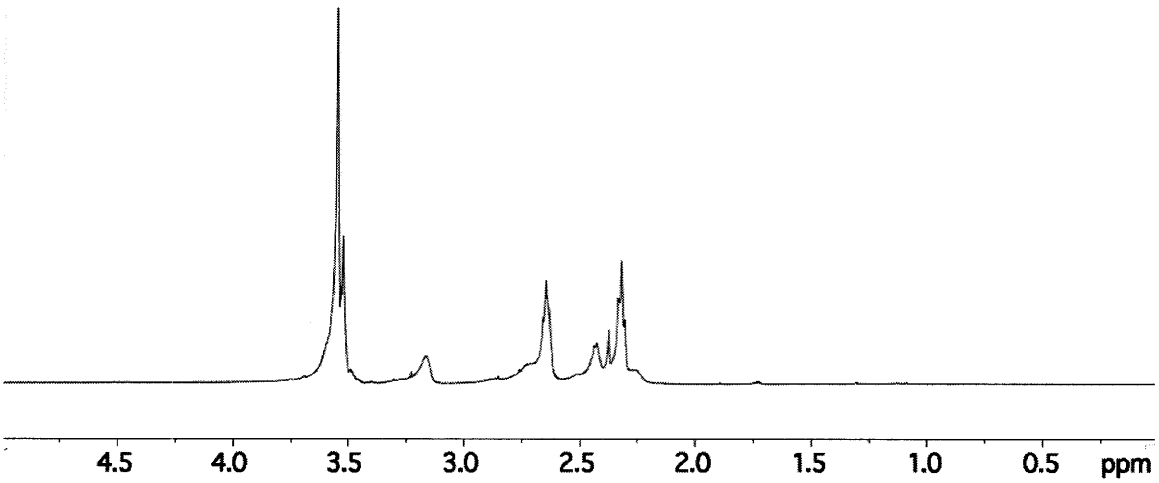




Azide-PEG-PAMAM G 2.0





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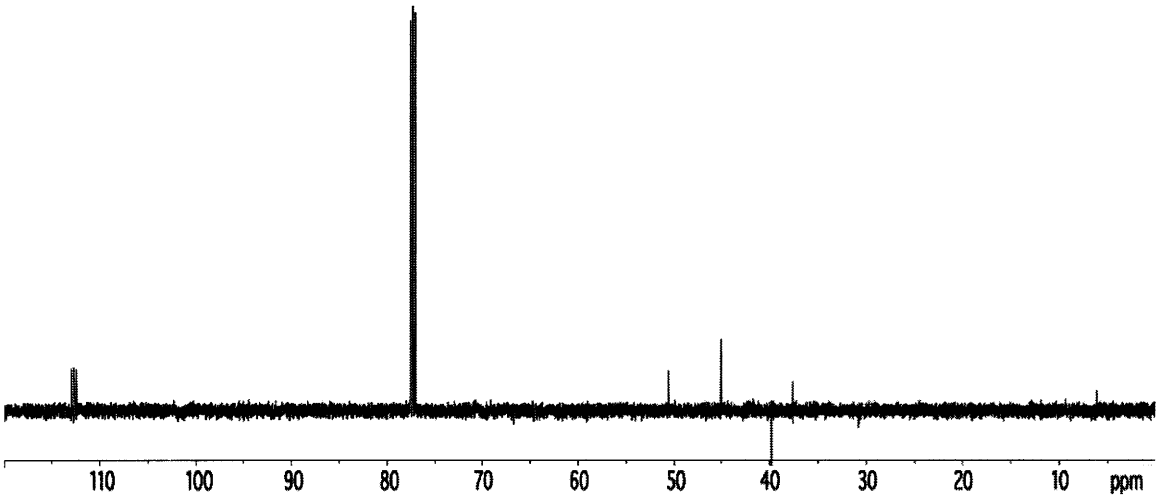

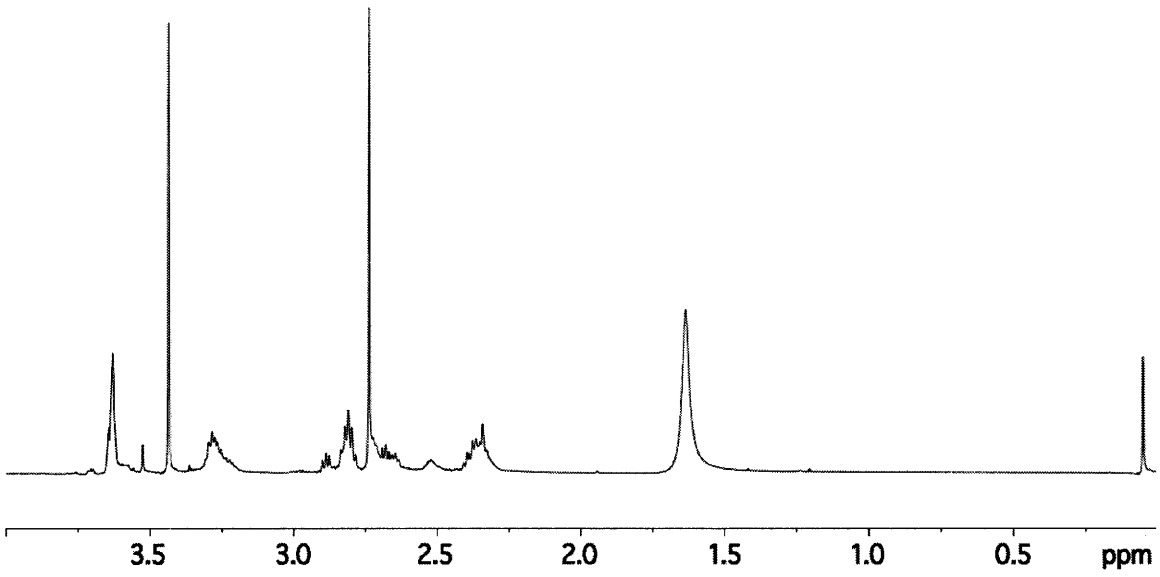

Azide-PEG-PAMAM G 3.0

Appendix C: List of Acronyms

AFM- Atomic Force Microscopy

CAC- Critical Aggregation Concentration

CMC- Critical Micelle Concentration

DLS- Dynamic Light Scattering

DMAP- Dimethylaminopyridine

DMF- Dimethylformamide

LB- Langmuir-Blodgett

MALDI-TOF MS- Matrix assisted laser desorption time of flight mass spectrometry

NNLS- Non-negative Least Squares

PAMAM- Poly(amidoamine)

PEG- Poly(ethylene glycol)

PEO- Poly(ethylene oxide)

PMDETA- n, n, n', n", n"-Pentamethyldiethyltriamine

PS- Polystyrene

PTFE- Polytetrafluoroethylene

SDS- Sodium Dodecyl Sulfate

SLS- Static Light Scattering

TEM- Transmission Electron Microscopy

THF- Tetrahydrofuran

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e-mail: kstokes@alumni.cmu.edu

OBJECTIVE

Seeking employment at a research facility requiring a highly skilled polymer chemist with a strong background in organic synthesis and the physical characterization of polymeric materials

EDUCATION

Massachusetts Institute of Technology *Cambridge, MA*
Ph. D. Chemistry January 2007
- Thesis Advisor: Paula T. Hammond
- Thesis Title: *Synthesis and Solution State Assembly of Linear-Dendritic Block Copolymers*

Carnegie Mellon University *Pittsburgh, PA*
M.S. Chemistry - May 2001
- Thesis Advisor: Richard D. McCullough
- Thesis Title: Synthesis and Development of Processable Polythiophenes

B.S. Chemistry w/ Polymer Science Option - May 2001

WORK EXPERIENCE

Graduate Scientist - *Massachusetts Institute of Technology* *Cambridge, MA*
W/ Dr. Paula Hammond (January 2002-Present)
- Designed and synthesized linear-dendritic block copolymers
- Characterized solution state self-assembly behavior
- Maintained and repaired several pieces of equipment, including two glove boxes, a gel permeation chromatograph, and several vacuum lines
- Presented occasional lectures on polymer chemistry

Technical Consultant - *A123Systems* *Boston, MA*
W/ Dr. Andrew Loxley (January 2003-March 2003)
- Aided design and execution of synthetic pathways central to long term company objectives
- Taught Schlenk line chemistry techniques to company staff

Computer Programmer - *Harvard School of Public Health* *Boston, MA*
W/ Dr. Sue Goldie (May 2002-August 2003)
- Developed and maintained a Monte Carlo cervical cancer simulation in C++
- Collaborated with students to incorporate real data into the semi-empirical model

Research Scientist - *E Ink Corporation* *Cambridge, MA*
W/ Dr. Anthony Pullen (June 2001-August 2001)
- Synthesized innovative organic, electronically-active materials

Visiting Scientist - *University of Copenhagen* *Copenhagen, Denmark*
W/ Dr. Thomas Bjørnholm (June 2000-January 2001)
- Synthesized novel polythiophenes derived from uniquely functional monomers
- Active in general lab upkeep

Undergraduate Research Scientist - *Carnegie Mellon University* *Pittsburgh, PA*
W/ Dr. Richard McCullough (September 1998-May 2001)
- Synthesized and purified functional polythiophenes and polythiophene copolymers
- Contributed to general lab upkeep
- Presented results at various symposia

Teaching Assistant - *Carnegie Mellon University* *Pittsburgh, PA*
W/ Richard Pattis (August 1998-May 2000)
- Conducted computer lab hours and led help sessions for students
- Involved in grading of assignments
- Presented intermittent lectures

Kristoffer K. Stokes – (617) 767-3955 *kstokes@alumni.cmu.edu*

LABORATORY SKILLS

Synthesis: Organic, organometallic, and polymeric compounds under anhydrous, anaerobic, and cryogenic conditions; Langmuir-Blodgett films
Instruments: NMR (Varian, Bruker), GC/MS (Agilent/HP), HPLC, GPC (Waters), MALDITOF-MS, TEM, Tensiometry

COMPUTER SKILLS

Programming languages: C/C++, perl, bash, awk, xml
Operating Systems: Mac OS, UNIX, MS Windows

ACADEMIC HONORS

MIT Presidential Fellow - 2001
Phi Beta Kappa - Member 2001
Warner Prize - 2001
ACS Analytical Division Award - 2000
Howard Hughes Medical Institute Fellow - 1999
Dr. Paul Snyder Scholarship - 1999
Undergraduate Research Presentation Award - August 1999
Small Undergraduate Research Grant Recipient - Spring 1999

PUBLICATIONS

Stokes, K. K.; Hammond, P. T. "Synthesis and Solution Self-Assembly of a Block Copolymer with a Unique Topology". *Polymer Preprints* **2004**, 45(1), 751.

Stokes, K. K.; Heuzé, K.; McCullough, R. D. "New Phosphonic Acid Functionalized, Regioregular Polythiophenes". *Macromolecules* **2003,** *36*, 7114.

Stokes, K. K.; Ibrahim, S. H.; Hammond, P. T. "Synthesis and Characterization of Amphiphilic Linear-Dendritic Diblock Copolymers for Functional Micelle Formation". *Polymer Preprints* **2003**, *44(1)*, 1026.

Zhai, L.; Pilston, R. L.; Zaiger, K. L.; Stokes, K. K.; McCullough, R. D. "A Simple Method to Generate Side-Chain Derivatives of Regioregular Polythiophene via the GRIM Metathesis and Post-polymerization Functionalization". *Macromolecules* **2003,** *36 (1)*; 61.

Costanzo, P. J.; Stokes, K. K. "Synthesis and Characterization of Poly(Methyl Acrylate) grafted from Poly(Thiophene) to Form Solid State Fluorescent Materials". *Macromolecules* **2002,** *35*, 6804.

Stokes, K. K.; Johnson, M. A.; Hammond, P. T. "Morphological Self-Assembly and Nanoparticle Formation in PEO-PAMAM Linear Dendritic Diblock Copolymers". *Polymer Preprints* **2002**, *43(2)*, 430.

PRESENTATIONS

"Synthesis and Solution Self-Assembly of a Block Copolymer with a Unique Topology". Talk at the National American Chemical Society Meeting, Anaheim, CA. **2004.**

"Self-Assembly of Linear-Dendritic Diblock Copolymers". Poster at the National American Chemical Society Meeting, Boston, MA. **2002**.

"Synthesis of a Novel Polythiophene: Addition of Phosphonate Side Chains".Poster at the National American Chemical Society Meeting, New Orleans, LA. **1999.**

"Effects of Phosphonate Side Chains on Polythiophene Monolayer Formation".Poster at the Pittsburgh Polymer and Colloid Minisymposium, Pittsburgh, PA. **1999.**