PREPARATION AND CATALYTIC ACTIVITY OF POLY(PROPYLENE IMINE) DENDRIMERS QUATERNIZED BY METHYLATION

By

JASON L. KREIDER

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Louisiana College

Pineville, Louisiana

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PREPARATION AND CATALYTIC ACTIVITY OF

POLY(PROPYLENE IMINE) DENDRIMERS

QUATERNIZED BY METHYLATION

Thesis approved:

Warren T Ford

Thesis Advisor

Richard A. Reinert

Edward Knobbe

Perry Tang

Marvin Stone

Alfred Larkin

Dean of the Graduate College

PREFACE

Dendrimers are symmetrical, highly branched, three-dimensional macromolecules. Dendrimers differ from other polymers because they are constructed from small molecules that have 3 or more reaction sites resulting in highly branched structures, whereas linear polymers are prepared from small molecules that have 2 reaction sites. Dendrimers are of great interest in chemical, biological, and material research for their unique properties compared to linear polymers and small molecules.

Previously, micelles (soaps), polymer latexes (paints), and dendrimers have been used as catalysts for reactions of oil-like compounds in water. In order to increase the rate of these reactions, the catalyst must be able to bind the oil-like compound. To bind the compound, (+)-charged sites are placed on the catalyst that attract (-) charges in the oil-like molecule and enable the dendrimer to bind the molecule. Inside the catalyst, the oil-like molecule breaks apart faster because there is less water present. One area of interest is to determine the structural location where binding of the organic compound is the most effective. The locations (core or surface) of binding sites in polymer latexes are not, but they are in dendrimers which makes them ideal for this type of investigation.

For this research I chose polyamine dendrimers that were available commercially. Dendrimers of different sizes were prepared that contained (+)-charges 1) at 65% of the surface sites of the dendrimer and 60% of the internal sites 2) throughout the dendrimer, and 3) at the interior of the dendrimer only.

All (+)-charged dendrimers were used to increase the rate of decomposition (loss of carbon dioxide) of an oil-like compound. The dendrimers increased the rate 1.5-4.5 times that in water. Previous dendrimers (which were more oil-like) increased the rate by factors of 25-500. The absence of oil-like groups in my dendrimers makes them less effective at decomposing oil-like compounds in water.

ACKNOWLEDGEMENTS

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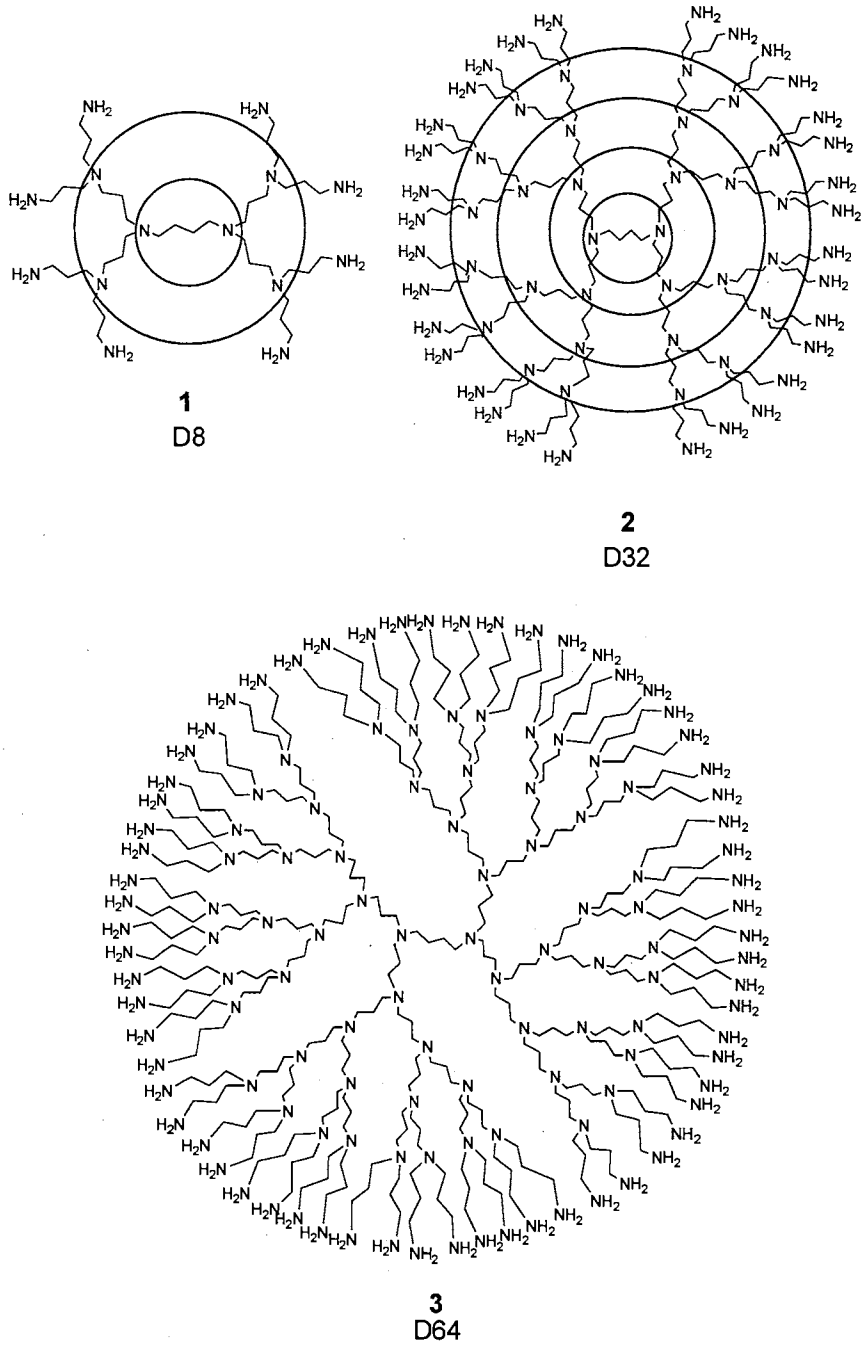
CHAPTER 1

POLY(PROPYLENE IMINE) DENDRIMERS: LOOKING BACK AT THEIR HISTORY AND INTO THEIR FUTURE

Dendrimers are three-dimensional, highly-branched (tree-like), symmetrical, monodisperse, macromolecules. They have three distinct regions: core, internal branches, and chain ends. Dendrimers are prepared by repeated stepwise additions of monomers to multivalent functional groups where each addition adds a new layer to the framework. Therefore, dendrimers are generational materials defined by the number of layers of repeat units added as demonstrated in Figure 1. A dendrimer has a large number of terminal functional groups that primarily determine its properties. The density of chain ends combined with large internal void spaces make dendrimers interesting subjects in a variety of chemically-related fields.

The History of Molecular Trees. Although Vogtle's cascade molecules[1] were the first "tree-like" compounds reported, Tomalia[2] and Newkome[3] are credited with developing dendrimers at macromolecular levels in the mid-80s. Scientific interest in dendritic molecules has increased dramatically over the past fifteen years. Dendrimer research papers can be found in every major chemical journal and have been the subject of numerous articles in some of the most prestigious scientific journals (Science and Nature),[4,5] "mainstream" magazines (Scientific American),[6] and newspapers (The Wall



1
D8

2
D32

3
D64

Figure 1: Generation 2 (D8, **1**), 4 (D32, **2**), and 5 (D64, **3**) poly(propylene imine) dendrimers. Addition of two layers of monomer (acrylonitrile) to D8 gives D32. Addition of one layer of monomers to D32 gives D64. For complete synthesis details see Scheme 1.

Street Journal).[7] This curiosity may have developed because of the unique characteristics, synthetic possibilities, and proposed applications of these "perfect" macromolecules.

Comparison to Other Polymers. Dendritic polymers are the newest class of polymers and include both dendrimers and hyperbranched polymers (Figure 2). Extensively branched structures and better solubility characteristics separate this group of

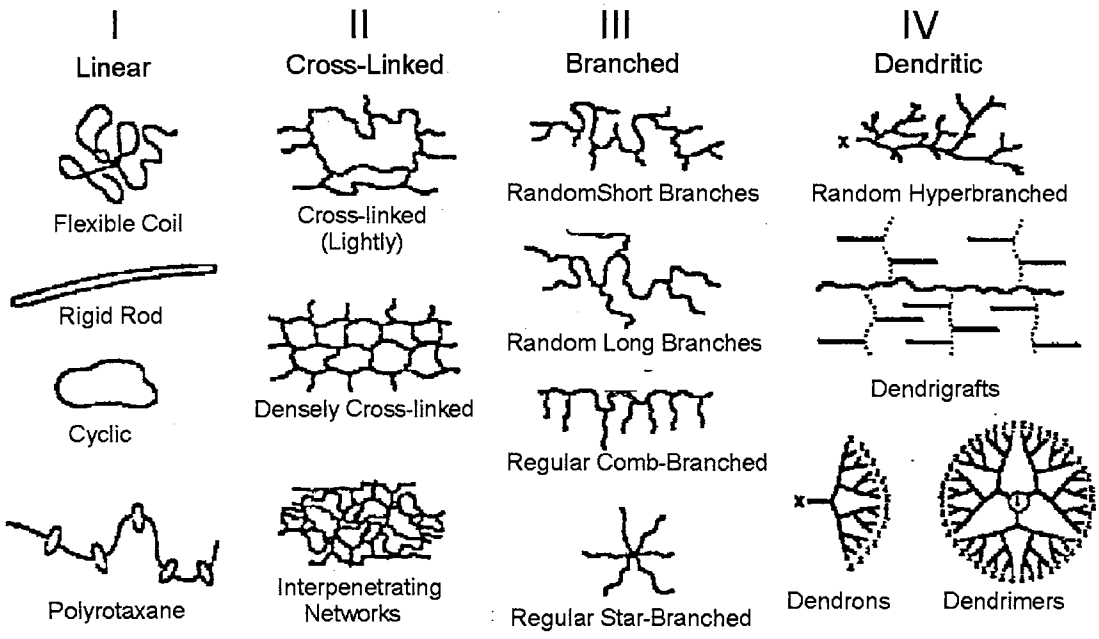


Figure 2: Comparison of the four major groups of polymers (adapted from Dvornic and Tomalia).[8]

polymers from linear (random coil), cross-linked, and branched polymers. Dendrimers are further distinguished from hyperbranched materials by their preparation and structural design. Ideal dendrimers are prepared through a step-wise synthetic approach, are perfectly branched, and have exact chain lengths; whereas, hyperbranched polymers are

synthesized by a single pot, step-growth polymerization, resulting in random branching, and varied chain lengths.[9]

Whereas linear polymers adopt random coil conformations, dendrimers tend to adopt spherical shapes in solution. In addition to their globular shapes, the three-dimensional symmetry of their structure leads to a high concentration of functionalities on the sphere surface as well as a large internal free volume.[10] The dense arrangement of atoms in a restricted volume results in a very low intrinsic viscosity compared to that observed with linear polymers.[11] Figure 3 illustrates the change in geometry of poly(propylene imine) dendrimers (PPIs) with size. Most polymers are soluble in only a limited number of solvents. Additionally, polymer solubility is often not improved or changed by functionalization. Dendrimers are usually soluble in many different solvents. PPIs in amine form are soluble in many common solvents such as water, methanol, methylene chloride, chloroform, and toluene. Modification of PPI functionalities can be accomplished easily through amidation or alkylation reactions. Modification of the primary amine chain ends can drastically change solubility, encapsulation, and/or selective binding characteristics of PPIs.[12]

One of the most distinguishing marks of a synthetic polymer from a simple molecule is the inability to assign a definite molar mass to a polymer. Polymer masses are defined in terms of their number and weight averages (equations 1 and 2, respectively). N_i is the number of molecules of species i of molar mass M_i. The weight average divided by the number average gives the polydispersity index (PDI) of traditional polymers (equation 3).[13]

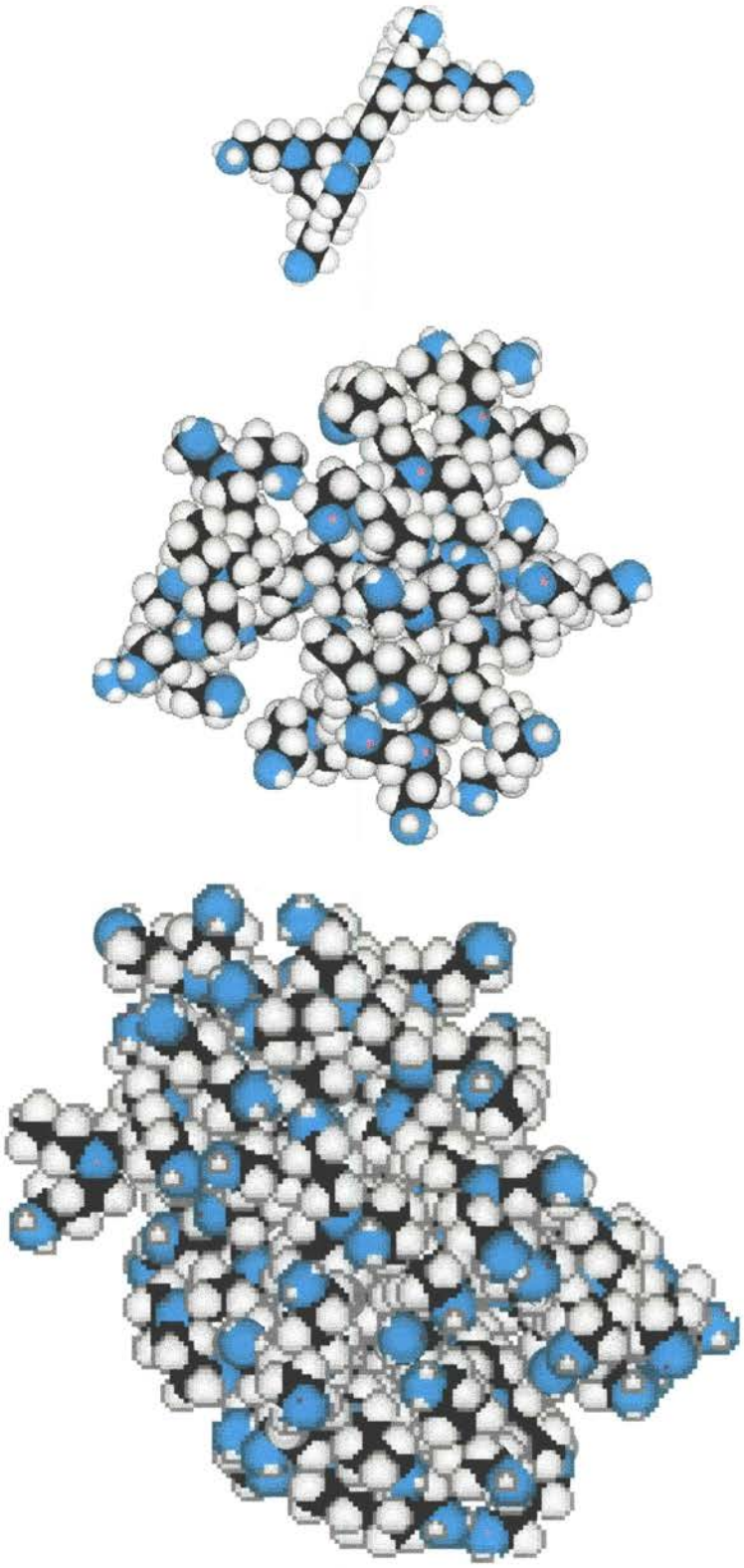


Figure 3: Chem 3-D representation of D8 (**1**), D32 (**2**), and D64 (**3**) (top to bottom) illustrating the change in conformation from open to spherical with increasing generation size.

$$M_n = \Sigma N_i M_i / \Sigma N_i \qquad (1)$$

$$M_w = \Sigma N_i M_i / \Sigma N_i \qquad (2)$$

$$PDI = M_w / M_n \qquad (3)$$

Although dendrimers do contain minor defects that reduce the yield of the perfect structures, they are not polydisperse when compared to other polymers. "Monodisperse" polyethylene oxide has a molecular weight distribution of 1.04, whereas a typical dendrimer, D64 (M = 7168), was found to have a polydispersity of 1.002.[14] Rather than refer to the polydispersity of a sample, dendritic purity is often used to describe the success of a particular dendrimer synthesis.[15] Purity is defined by the weight percentage of perfect dendrimer present in a sample.

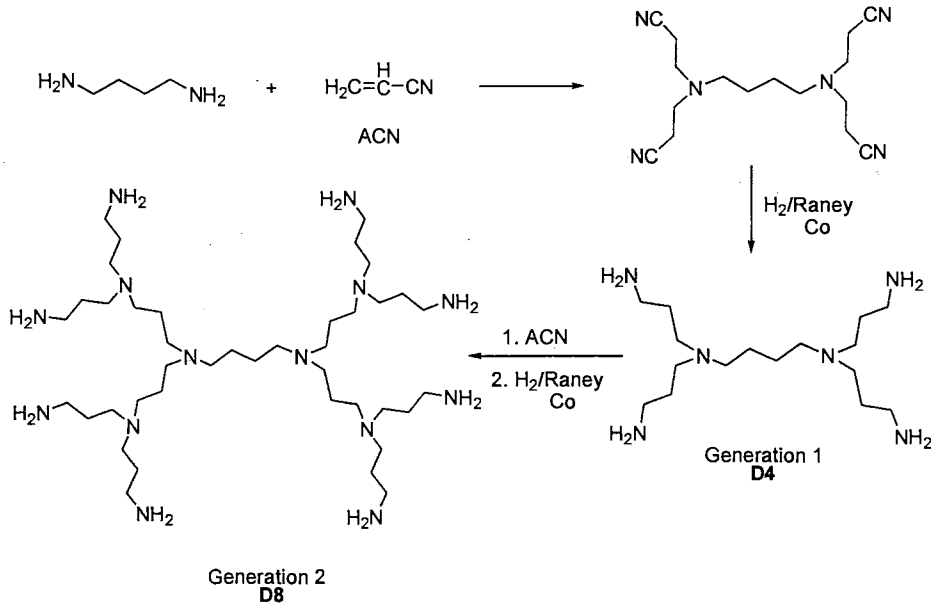
Dendritic polymers consist of three structural domains: core, branch points, and chain ends. A dendritic repeat unit consists of the atoms from the end of one branch to the start of the next. For a PPI dendrimer, the repeat unit is $-CH_2CH_2CH_2N<$ and the core is 1,4 diaminobutane (Scheme 1). Each repeat unit "shell" is often referred to as a generation. Addition of the first set of monomer units to the core is sometimes called generation 0 (polyamidoamine dendrimers or PAMAM's) and other times generation 1 (poly(propylene imine) dendrimers or PPI's). Because of the ambiguity in generation number assignment, it is more consistent to refer to the number of chain ends. The number of chain ends is determined by the number of functional groups at the core, their multiplicity, and the multiplicity of functional groups at the branch points. The molecular weights of dendrimers are exact (not distributions as other polymers) and can

be defined mathematically by Equation 4, where M_c = mass of the core, N_c = multiplicity of the core, M_{RU} = mass of the repeat unit, N_b = multiplicity of branch points, G = generation by PPI methods, and M_t = mass of the terminal group.[15] Using equation 4, the mass of an 8 chain end (Generation 2) PPI dendrimer is calculated: MW= 84 + $4[56(2^2-1)/(2-1) + 1(2)^2]$=772

$$MW = M_c + N_c[M_{RU}(N_b^G-1)/(N_b-1) + M_tN_b^G] \qquad (4)$$

Synthesis and Properties. Dendrimers have been prepared from organic, inorganic, and metal-containing "monomers".[16] Dendrimers can be prepared by two major approaches: convergent[11] or divergent[2] synthesis. The divergent method begins with a core molecule and adds branches in a stepwise manner as demonstrated in Scheme 1. In

Scheme 1: Divergent synthesis of poly(propylene imine) dendrimers.



the convergent approach, dendrons (Figure 2) are prepared from a core that retains a unique functional group (the focal point, X in Figure 2) by a stepwise divergent approach followed by reaction of the focal point with a core molecule in the last step. Other growth processes are modifications, combinations, or improvements of these basic methods.[17]

The stepwise formation of dendritic structures permits analysis of lower generation materials formed after each step of the reaction. The convergent approach often results in higher dendritic purities, since by-products and starting dendrons are usually much smaller than the perfect dendrimers making them easier to remove. However, the convergent approach is size-limited due to increased congestion at the focal point making reaction of dendrons with the core more difficult.[12]

There are many excellent sources that highlight major accomplishments in dendrimer research to date.[16-24] Matthews et al., in their review of dendrimer research, stated "We are now approaching a time when the study of dendrimers becomes inextricably linked with many other fields, leaving the comprehensive reviewer of the subject with a near-impossible task to fulfil."[17] Our work has focused on the modification of PPI dendrimers. In light of the broad expansion of dendrimer research over the past 10 years, the remainder of the discussion will focus on PPI dendrimers.

POLY(PROPYLENE IMINE) DENDRIMERS

PPIs are prepared by divergent synthesis and were first reported by de Brabander[25] and Mulhaupt.[26] As shown in Scheme 1, they are prepared from a 1,4-diaminobutane core by successive additions of acrylonitrile followed by reduction to the amine. Nitrile-ended materials are considered "half-generations". PPIs (nitrile or amine terminated) are commercially available from Aldrich with 4, 8, 16, 32, and 64 chain ends.

Structure and Properties. PPI dendrimers are composed of propylamine repeat units and may have either nitrile or amine chain ends. Primary amine terminated PPIs have been more widely explored as they are more stable polymers than their nitrile ended precursors. The structural conformation of PPI dendrimers changes with generation number or the doubling of chain ends.

As the dendrimer becomes more crowded, shape changes from freely rotating, open chain conformations to a more globular or spherical dense shape. For each increased generation molecular weight is approximately doubled (Equation 4). The volume of the dendrimer may be approximated by calculating an approximate radius based on fully extended chains. Alternatively, the change in volume which encloses most of the extended conformations of the dendrimer as generation increases is approximately $[(G + 2)/(G + 1)]^3$, where G is the generation and the core is assumed to be equivalent to one generation. As the size of dendrimers increases up to D16, the approximated volume increase is greater than the mass increase. From D16 to D32 there is a factor of ~2.0 volume increase, whereas in going from D32 to D64 volume increases by only a factor of ~1.7.

PPIs in general have a low glass transition temperature and flow as a viscous liquid that increases in viscosity in proportion to molecular weight.[12] Amine terminated PPIs are thermally stable compounds.[27] D8 shows no loss in molecular weight at temperatures up to 300 °C. The maximum slope of a TGA curve measured for D8 under nitrogen was 378 °C and for D32 was 470 °C indicating that stability increases with size.[24,25]

End functional groups determine solubility and can be specifically designed for a given solvent.[28] PPI dendrimers are soluble in many polar and nonpolar solvents. Modifications of PPIs by alkylation with long chain hydrocarbons have made them insoluble in water and methanol;[29] whereas, quaternization by methylation of PPIs renders them insoluble in most organic solvents. Poly(propylene imine) dendrimers in dilute solutions (less concentrated than the random close packed sphere volume fraction, X=0.64) disperse as uniform spheres. At low concentration chain ends from different dendrimers do not interpenetrate. At higher concentration, close packing and interpenetration begin to occur and the spheres begin to collapse or deform.[30]

PPIs demonstrate short-ranged repulsive interactions in the manner that they protonate. PPI dendrimers behave more "hard" when placed in acidic solutions due to stretching to separate charges.[34] Duijvenbode et. al. titrated PPIs and demonstrated that protonation alternates shells.[31] For example, D32 would protonate at the end groups followed by the 8 branch shell and then the core. In this way, the protonation scheme of

PPIs approximates a polyelectrolyte effect.[32] Additionally, ^{15}N NMR confirmed a similar protonation pattern.[33]

Analysis and Purification. Although PPI dendrimer synthesis is accomplished stepwise, numerous defects occur in a typical preparation. Defects may be due to cyclization, failed hydrogenation, or failed Michael addition as shown in Figure 4. Since the properties and composition of defective components do not differ greatly from those of the perfect structure, complete purification of PPI dendrimers has proven impossible.

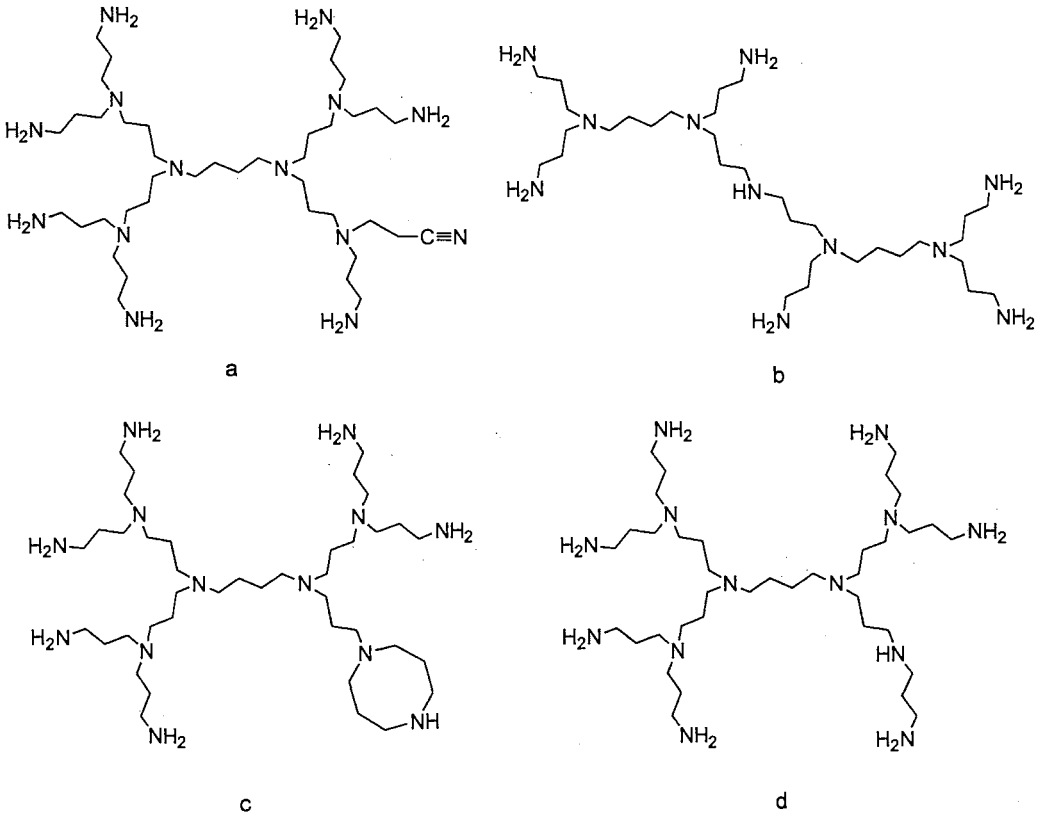


Figure 4: Defect structures proposed by van der Wal et. el.[35], based on exclusion chromatography HPLC-ESIMS analysis of PPIs. Defects result as follows: a, D8 with failed hydrogenation; b, Addition of RNH_2 to R-CN of two D4 molecules; c, D8 with cyclization by addition of RNH_2 to R-CN; d, D8 with one failed Michael addition.

Most dendrimers, especially higher molecular weight materials, lack long range order resulting in the formation of amorphous solid states; therefore, conventional crystallization methods are useful only for low molecular weight solid dendritic polymers.[36] PPI dendrimers at sizes of 8 to 64 chain ends are viscous liquids at room temperature (D4 is a white crystalline solid).

Some purification of PPI dendrimers has been possible through HPLC and gel permeation chromatography.[37] Additionally, recent methods in capillary electrophoresis and mass spectrometry have successfully determined defect structures and analyzed the purity of dendrimers.[38] Using MALDI-TOF MS, a typical batch of poly(propylene imine) dendrimers of the fifth generation (D64) was determined to contain 23% of the perfect structure and have a polydipersity of 1.002.[15] Considering 248 reactions in the preparation of D64 (**1**) from 1,4-diaminobutane statistically $x^{248} = 0.2$, the success of each reaction is 99.5%. Although dendrimers contain defects their polydispersity is not greatly affected; therefore, dendrimers are generally defined by purity rather than polydispersity. MALDI-TOF analysis of the dendritic purity of typical PPI batches are given in Table 1.[19]

Smaller dendrimers have open structures and are flexible and freely rotating in solution, explaining their greater dendritic purity compared to higher generations. Due to increased crowding effects as the dendrimer mass increases more rapidly than the volume of a sphere, defect structures from incomplete reaction increase significantly in going from D32 (**2**) to D64 (**3**).

Table 1. Dendritic purity of PPI Dendrimers based on MALDI-TOF MS analysis.

generation	dendrimer	dendritic purity
1	D4	96 %
2	D8	86.7 %
3	D16	63.8 %
4	D32	41.3 %
5	D64	23.1 %

Characterization. Since ideal PPI dendrimers have a single molecular weight and most dendrimer samples have a low polydispersity, conventional methods of analysis (NMR, MS, elemental analysis, FT-IR, and UV) are frequently used to obtain structural information. PPIs do not form ordered crystal structures; therefore, crystal analysis techniques (x-ray crystallography) are not used. Normally multiple methods are used to determine product composition in a PPI synthesis or modification.

Traditional proton and carbon-13 NMR are useful for lower molecular weight PPIs and continue to have utility through the highest molecular weight materials available; however, line broadening significantly reduces ^{1}H NMR resolution. Carbon NMR is often very useful in determining structure because small defects tend to be more well-resolved in ^{13}C spectra than in proton NMR.

Use of 2-dimensional NMR techniques (specifically, COSY and HMQC) with modified D8 materials makes signal assignment possible in some of the poorly resolved proton spectra. These assignments can be used analogously with higher generation materials.

The success of chain end modifications can usually be determined by NMR. However, if the groups added have or result in near equivalent magnetic environments loss of resolution may result.[29,39,40] ^{15}N NMR has been used to probe the protonation

characteristics of PPI dendrimers but the poor signal to noise of such spectra prevents their widespread use in characterizing PPIs.[33]

Electrospray ionization mass spectrometry (ESIMS) and matrix-assisted laser desorption ionization (MALDI) MS, are widely used in dendrimer characterization. Both are soft ionization techniques that do not induce significant fragmentation of the structure. Although quantitative analysis of the sample is not possible through these methods alone, qualitative analysis of the composition is possible. New methods that couple LC and MS methods have provided some quantitative analysis of dendrimers.[15]

Elemental analysis has some application in the characterization of modified PPIs but does not aid in the analysis of unmodified PPI dendritic purity. Defect structures of unmodified PPIs usually result from a missing C_3H_6N chain. The mass percent of each missing element corresponds to that of the perfect structure; therefore, defects caused by missing chains do not significantly effect elemental analysis percentages. In either case, retention of water by PPIs eliminates the usefulness of the overall analysis, allowing only for a comparison of element ratios.

FT-IR is useful for confirming the presence of primary amine and nitrile functionalities at the chain ends. Presence of amides from chain end modification can also be confirmed. However, the success of reductive amination cannot be determined because the signal for water retained by the dendrimer eclipses the 3100-3500 cm^{-1} region of the spectrum. The signal from secondary amine is not observed even when present on the product.

MODIFICATION OF PPI DENDRIMERS

PPI dendrimers and modified PPIs have been utilized in a variety of scientific fields because of their structural features and synthetic versatility. As was demonstrated in the previous section, PPI properties are primarily determined by the chain ends. For this reason, most modifications focus on adding to or otherwise altering the amine or nitrile chain ends. Examples of core, branch point, and chain end modifications are presented in this section.

Chain End Modifications. Conventional micelles are aggregates of surfactant molecules arranged dynamically in solution so that groups of similar polarity to the solvent face the exterior of the micelle and groups unlike the solvent are oriented in the interior. Individual surfactant molecules cannot form micelles. A unimolecular micelle is a single distinct molecule that in isolation from other molecules continues to exhibit micellar behavior.

Each molecular micelle is able to host or trap one or more organic molecules in an aqueous solution. At high dilutions, micelle aggregates break up (dilution past the critical micelle concentration), losing the capability to function. The advantage of unimolecular micelles is that they do not have a critical micelle concentration, and therefore solubilize compounds at very dilute concentrations.

Amphiphilic Dendrimers. Amphiphilic dendrimers are of great interest as organic molecular hosts. Alkyl-amidated and PEGylated (polyethylene glycol modified) PPI dendrimers have been prepared and tested as molecular hosts. Water solubility and

internal organic character are the main considerations in preparing these types of dendrimers.

PPIs modified at the chain ends with both PEG and octyl groups were prepared through a 4 step process.[29] PPI chain ends were amidated with octanoyl chloride followed by reduction with $LiAlH_4$. The secondary octylamine chain ends were amidated with an acid chloride derivative of triethylene glycol followed by reduction to give octyl and triethylene glycol groups at every chain end.[29] Figure 5 is a possible conformation

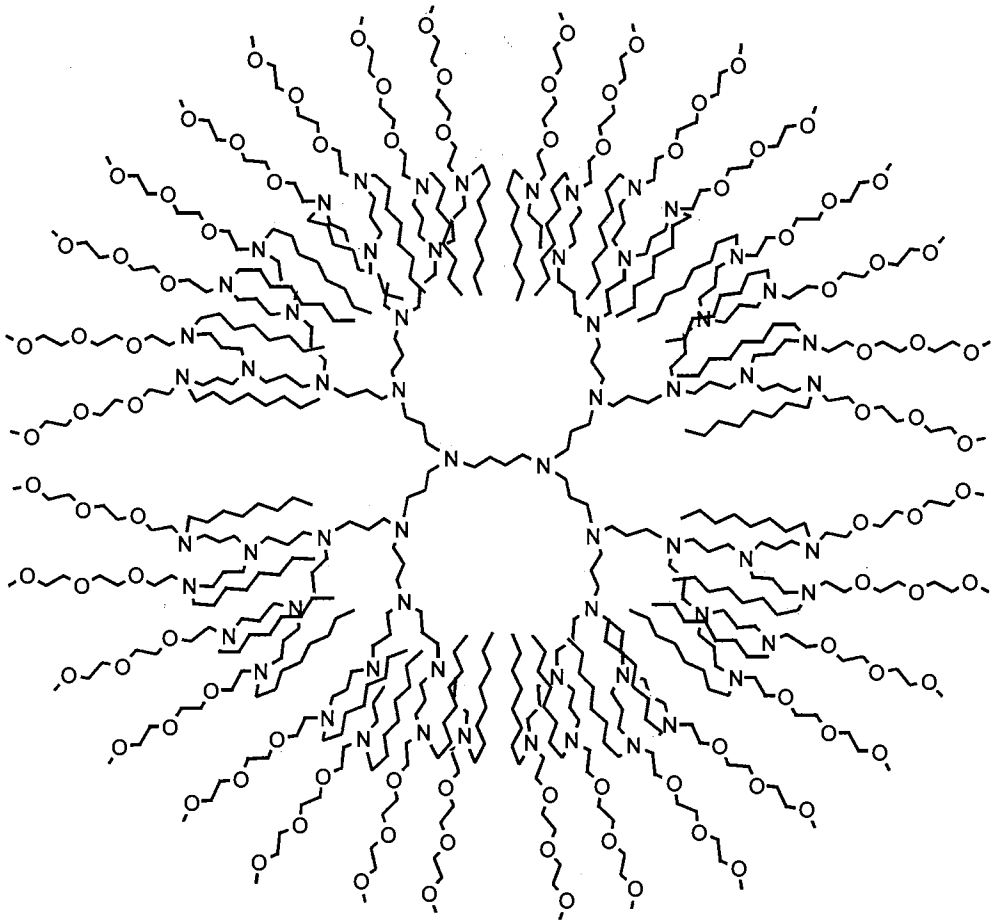


Figure 5: Hydrophobic and hydrophilic moieties at every chain end of D32. This figure demonstrates the backfolding of the octyl chains that occurs in aqueous solutions promoting function as a unimolecular micelle.

of these dendrimers in an aqueous solution. The polyamine dendrimer is soluble in water only at pH $\leq$ 4.6. NMR relaxation times indicate that the octyl chains rotate less freely in methanol than in chloroform.

PPI dendrimers have been modified with fatty acids (octadecanoic, dodecanoic, palmitoyl, acid, etc.) through covalent and non-covalent interactions.[41-43] Covalent preparations utilize the acid chloride or active ester/DCC coupling for amide bond formation. In the noncovalent approach, a 1% fatty acid/toluene solution was added to PPI dendrimers. By acid/base chemistry, the acid protonates the chain ends and ion pairing occurs between the carboxylate and newly formed ammonium ions. Self-assembly of the carboxylate ion with the dendrimer chain ends was confirmed by FT-IR based on the appearance of an asymmetric carboxylate peak at 1557 cm^{-1} and the absence of the acid carboxyl peak at 1710 cm^{-1}.

Dendritic Boxes. Dendritic boxes or non-draining spheres have bulky chain end functionalities that inhibit the passage of small molecules in and out of the dendrimer core. Steric hindrance at the chain ends enables these dendrimers to capture and contain a molecule.

The most well known dendritic box is *tert*-butoxycarbonyl phenylalanine modified D64 (Figure 6) prepared by Meijer et al.[44] Meijer's box was confirmed to trap up to five Bengal Rose dye molecules from a methylene chloride solution.[45] Guest molecules (Bengal Rose and *p*-nitrobenzoic acid, specifically) were trapped in the Meijer Box by constructing the box in the presence of the guests. The box was constructed from D64 (**3**)

and an *L*-phenylalanine derivative.[44] The shell is densely hydrogen-bonded and retains the guest molecules even through dialysis and sonication. This methodology has been extended to functionalize PPI dendrimers with other amino acid derivatives.[46]

A particularly innovative dendritic box was prepared by functionalizing PPI dendrimers with azobenzene groups.[47] Azobenzene compounds undergo photoisomerization of the N-N double bond.[48] The isomerization from a closed cis

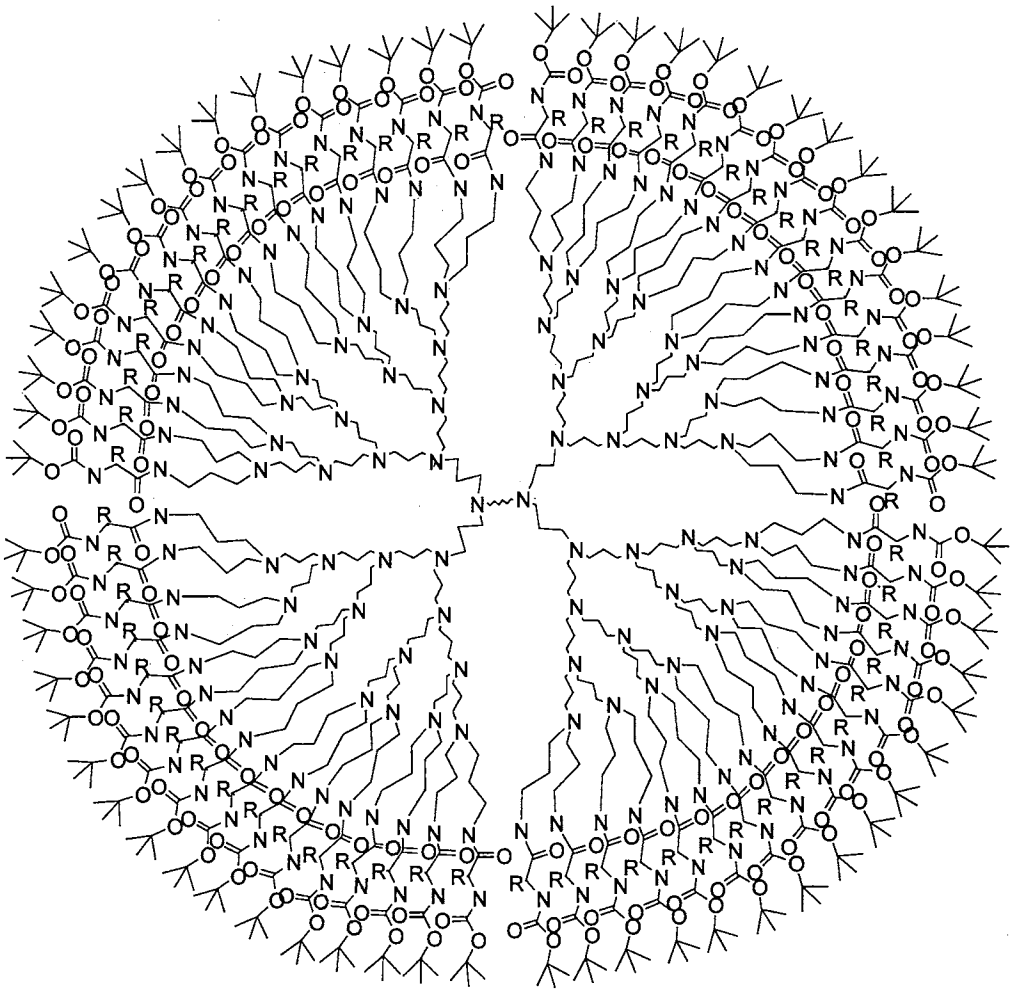


Figure 6: Meijer's dendritic box. D64 (**3**) modified at the chain ends to have tert-butoxyphenyl alanine end groups. R = $CH_2C_6H_5$

conformation to an open trans conformation at the end groups makes the chain end stereochemistry photoswitchable. D32 chain ends were amidated to carboxyamide azobenzene chain ends. The cis conformation was able to trap more Eosin Y (2', 4', 5', 7'-tetrabromofluorescein dianion) than the trans conformation based on fluorecence data.

Trigalactoside-ended dendrimers have been prepared by connecting three saccharide units to form a small branch which is coupled to the dendrimer through an active ester. (Figure 7).[39] Adding different lengths of spacer arms to the small branches before coupling to the dendrimer changes the binding characteristics of the "glycodendrimer".

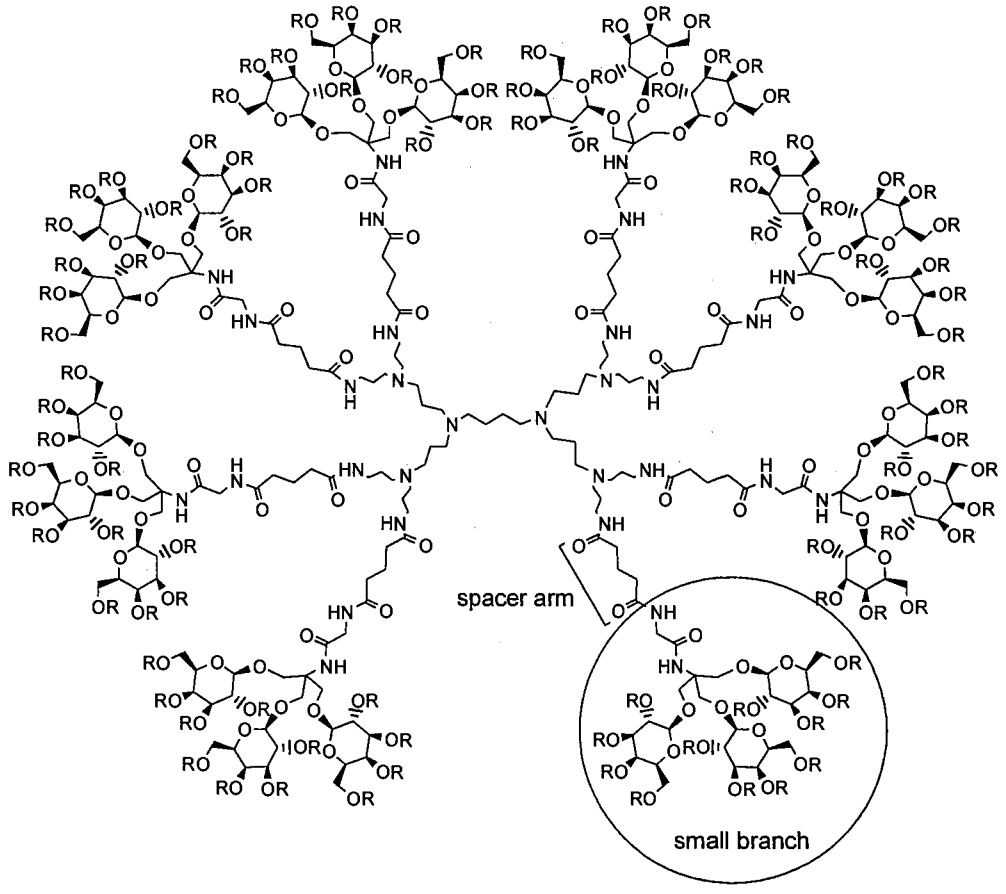
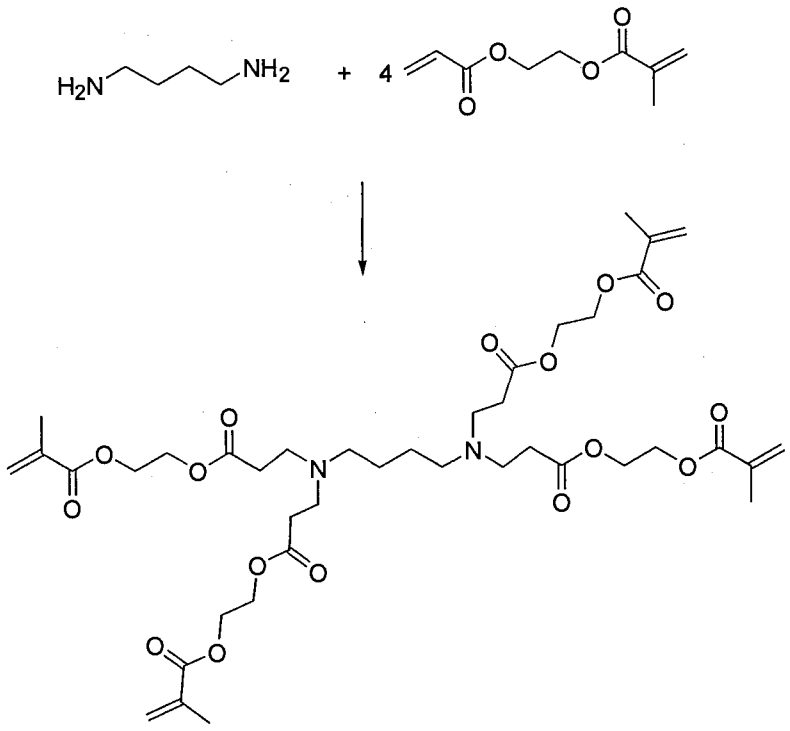


Figure 7: Structure of trigalactosidodendrimers prepared for protein binding. R=Ac or H.

Dendrimer cross-links. Dendrimer methacrylic cross-linking agents have been prepared as shown in Scheme 2 by Michael addition of diacrylate derivatives to the primary amine chain ends of PPIs.[49] The dimethacrylate in Scheme 2 was prepared by esterification of 2-hydroxymethacrylate with acryloyl chloride. AIBN-initiated homo-polymerization of every C-C double bond was reported to occur based on differential scanning calorimetry results confirming the formation of methacrylic, dendrimer cross-linked polymers. Glass transitions for these cross-linked polymers occurred at or below ambient temperature.

Scheme 2: Dendrimer methacrylate polymerization crosslinks.



Aryl functionalitites have been added to PPI chain ends by Michael addition of D8 to ω-(4'-cyanobiphenyl-4-oxy)alkyl acrylate.[50,51] Different flexible spacer arms were used between the dendrimer and cyanobiphenyl groups (Figure 8).

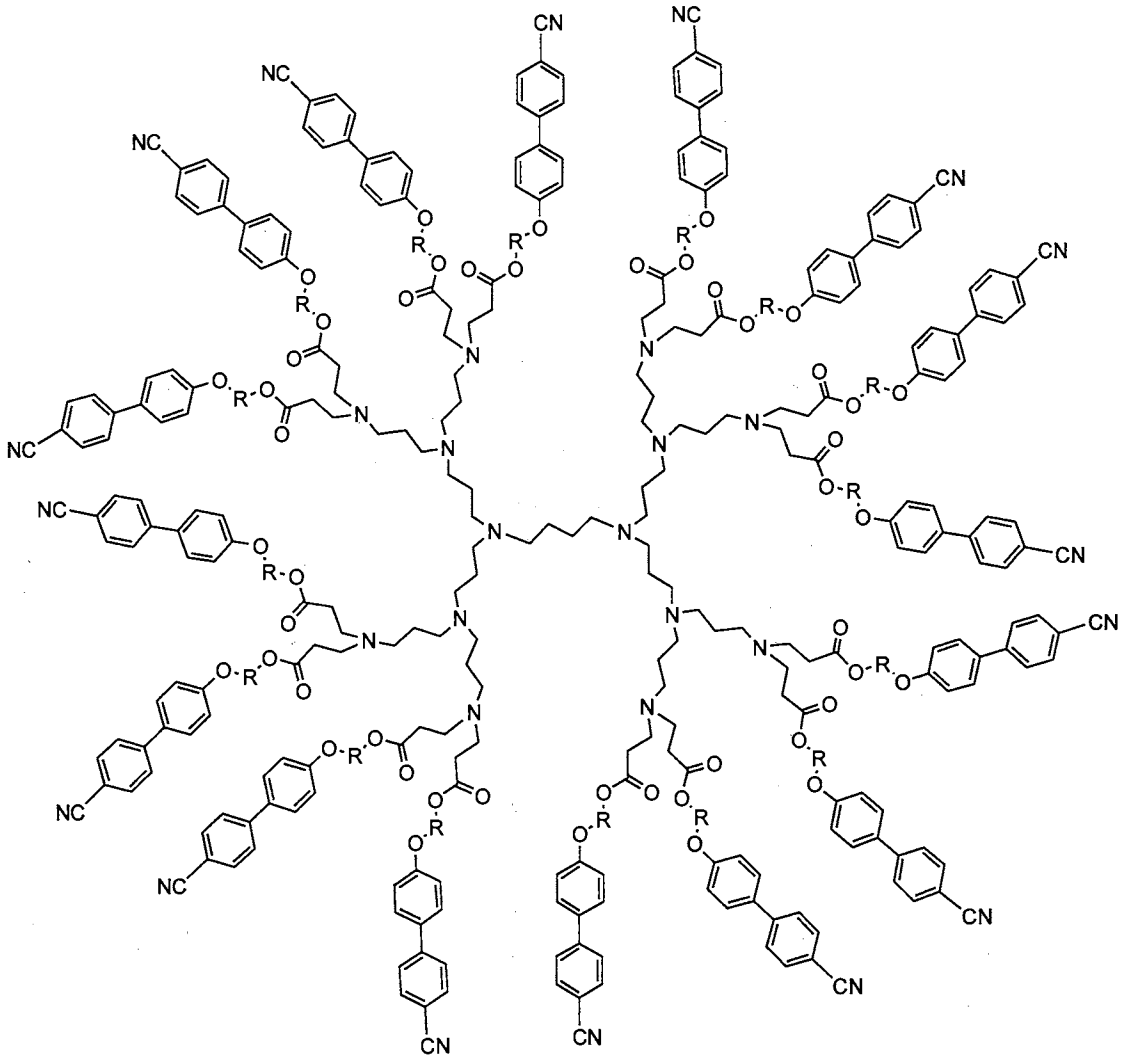


Figure 8: PPI liquid crystal dendrimers (PPILCDs). R = $(CH_2)_n$ with n = 5, 6, 8, 10.

Chain end quaternizations. The PPI dendrimer D16 was quaternized at the chain ends by a two step method. Amidation of the chain ends with 2-chloroethyl isocyanate followed by reaction with dimethyldodecylamine produced dimethyldodecylammonium

chloride functionalities at the chain ends with an amide spacer as shown in Figure 9 structure a.[52]

PPIs have been end quaternized by a ring-opening reaction with glycidyltrimethylammonium chloride (GTACl).[53] Reaction with one GTACl group per end group resulted in a quaternary ammonium chloride chain ends with a hydroxyalkyl spacer as shown in Figure 9 structure b.

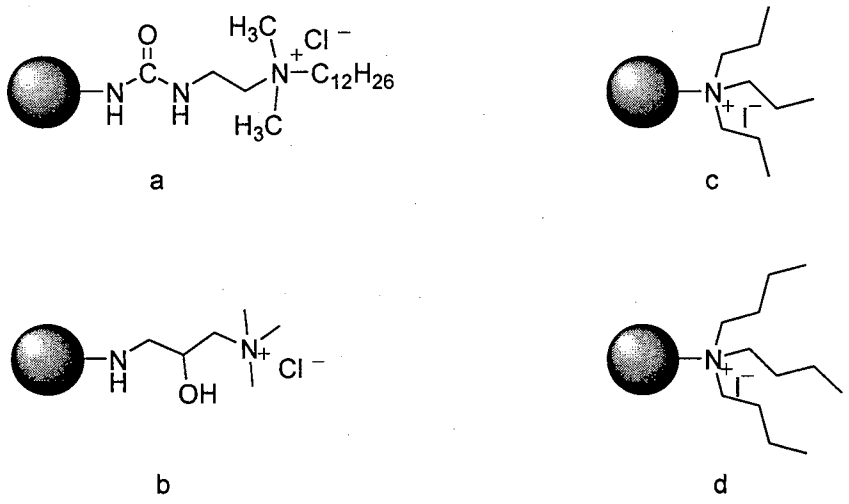


Figure 9: PPI dendrimer chain ends modified to have quaternary ammonium sites. The shaded circles represent the PPI dendrimer.

Other chain end quaternizations have been reported but are not documented with experimental procedures.[24] These chain end quaternizations include propylation and butylation as shown in Figure 9 structures c and d.

Chain End and Branch Point Modification. Complete quaternization of PPI dendrimers has been reported by Pan et al.[24,29] The most successful quaternizations

reported involve iodomethane as the alkylating agent. PEG/octyl-modified PPIs were quaternized with iodomethane to form an amphiphilic dendrimer with 62 charged sites.[29]

Other complete quaternizations have been reported but are not documented with experimental procedures.[24] These quaternizations include permethylation and perethylation of PPIs.

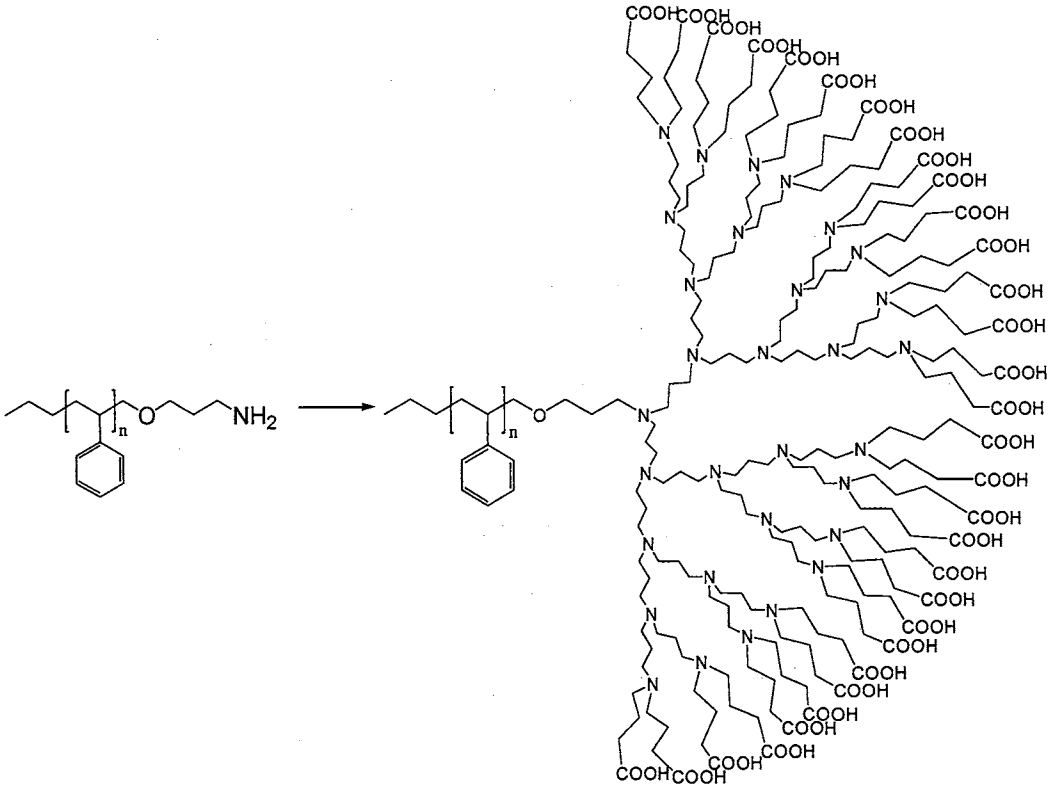
Internal (core and branch point) modifications. Core and branch point modifications are not as common as chain end modifications. Internal modifications are more difficult because of greater steric hindrance and lesser reactivity than the chain ends. Additionally, internal modifications are less attractive as the character of the interior of the dendrimer has less effect on its properties.

Two approaches can be taken for successful internal modification. The PPI dendrimer can be constructed on a new amine source such as an amine-terminated polymer. Alternatively, chain end reactions can be prevented by protection of the chain ends enabling selective reaction at internal sites.

Random Coil/Dendrimer Copolymers. Polystyrene-PPI dendrimers have been prepared by divergent synthesis of the dendrimer onto a primary amine functionalized polystyrene core molecule of MW = 3.2×10^3 as shown in Scheme 3.[54,55] PPI nitrile chain ends were converted to acid functionalities by hydrolysis. These amphiphilic structures exhibited a pH-dependent amphiphilic behavior. At pH=1.9 (0.01M HCl), phase inversion from water to toluene occurred at 70% toluene, whereas at pH=3.5 (0.01M KCl) inversion occurred at 50% toluene based on conductivity measurements.[28] These materials form microdomains of hexagonal (low MW dendrimer blocks) and

lamellar (high MW dendrimer blocks) structures that have segregated the dendrimer "head groups" (microphase-separated block copolymers).[56] The synthesis of quaternary ammonium salt-functionalized block copolymers of PPI dendrimers and polystyrene has also been reported.[57] Protection or amidation of end groups followed by internal modification has not been reported at this point.

Scheme 3: Preparation of polystyrene terminated with a PPI dendrimer.



APPLICATIONS

Non-catalytic application of PPIs.

Molecular Hosts. The ability to host molecules inside a dendrimer has potential application in the areas of catalysis and drug delivery. Dendritic boxes and amphiphilic dendrimers have demonstrated the ability to host molecules. Meijer's box (64 chain ends) was able to host up to 5 Bengal Rose molecules. Hybrid octyl-$MPEG_{164}$ armed PPIs with 32 chain ends were able to solubilize one pyrene molecule per dendrimer. Additionally, glycidyltrimethylammonium chloride chain end functionalized D32 and D64 were active pH-sensitive, controlled release systems based on the ability to solubilize pyrene in water as determined by fluorescence spectroscopy.[53]

Biocides. PPIs with dimethyldodecylammonium chloride chain ends were active biocides against Staphylococcus aureus and Escherichia coli in vitro.[52] Dendrimers modified with fatty acids are currently being evaluated for their cleansing, antifouling and rubber-curing properties.[58]

Liquid Crystals. Liquid crystals are of interest for use in high-speed switches and other liquid crystal devices. PPI liquid crystal dendrimers (PPILCDs) have been prepared by functionalizing chain ends with cyanobiphenyl derivatives utilizing different length spacers (Figure 6).[51] The mesogenic dendrimer oriented into a smectic A mesophase between temperatures of –7 and 89 °C.[50]

Protein recognition. Several sugar residues bound to the dendrimer chain ends by spacers of the appropriate length should be able to form stronger complexes with protein receptors than individual saccharides.[59,60] Dendrimers with trisaccharide units at the

chain ends or "glycodendrimers" were prepared as a new approach to preparing materials which can bind proteins strongly. Each chain end cluster should bind to a single protein receptor site.

Energy transfer. Poly(propylene imine) dendrimers have been functionalized with conjugated oligo(p-phenylene vinylene)s (OPV) through amidation of the end groups.[61] The OPV-PPIs self-assemble at the air-water interface to form homogeneous films. OPV-PPIs were able to efficiently extract dyes into nonpolar organic solvents. Thin films of OPV-PPIs and dyes demonstrated energy transfer based on fluorescent emission experiments. Exciting the OPV chain ends at λ_{ex} = 420 nm results in quenched fluorescence of the OPV and emission of the Sulforhodamine B dye ($\lambda_{em,\ max}$ = 593 nm).[61]

PPIs were sulfonated at the chain ends with 1,3-propane sultone. The sulfonated dendrimer was utilized in a direct methanol fuel cell to prevent methanol crossover (methanol crossover decreases efficiency of the cell). A 2 wt.% solution of the sulfonated PPI reduced methanol crossover by more than 30%.[62]

Dendrimer Catalysts

Because of the relevance that catalysis has to this research, a survey of the types of dendrimer catalysts is appropriate. Dendrimers have been utilized as both heterogeneous and homogeneous catalysts for a variety of organic reactions. The ability to tailor solubility, to design specific structures for enantioselective reactions, to complex metal ions, and to host molecules inside dendrimers have led to a variety of dendrimer catalysts. Dendrimer structures exhibit unique complexing and hosting capabilities as well.

Dendrimer-Metal Complexes. Carbosilane and amino acid based dendrimers have been modified to have "Ni(III)-pincers" at the end groups (Figure 10).[63,64] These metal containing silane based dendrimers were active as homogeneous catalysts of the Karasch addition reaction (1,2-addition of chloroform to methyl methacrylate). Although the dendrimers were not as active as the *ortho*-diamino-aryl pincer alone, their use in a continous process via a membrane reactor has some promise.

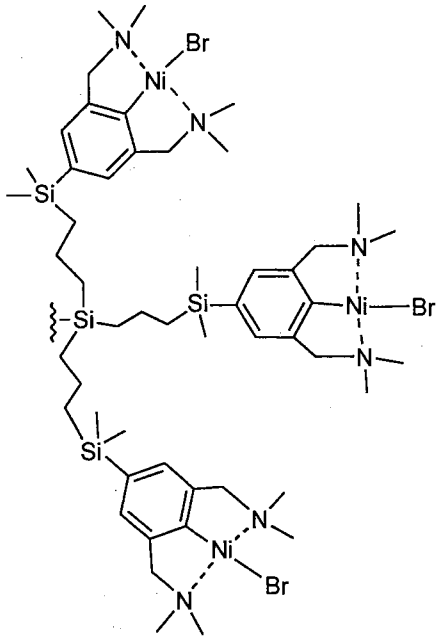


Figure 10: One PPI branch point with Ni-pincer formed on chain ends of a carbosilane-based dendrimer for catalysis of the Karasch addition reaction.

PPI dendrimers complexed with a variety of metal ions have been used in homogeneous catalysis.[65] Vassilev et. al. reported PPI primary amine chain end complexing of Cu(II), Co(III) and Zn(II). The dendrimer complex was used to catalyze

the hydrolysis of bis-*para*-nitrophenyl diphenyl phosphate and para-nitrophenyl diphenyl phosphate.[66,67]

Crooks et. al. reported the immobilization of PPI dendrimers on a gold surface.[68,69] Crooks has also reported 1-2 nm nanoclusters of Cu(II) inside PAMAM dendrimers.[70] Complete displacement of the nanoclusters by more noble metals has also been reported.[71,72] These materials have been reported as homogeneous catalysts for the electrochemical reduction of oxygen.

Hydroformylation reactions have been catalyzed by polyamidoamine (alkyl PAMAM) and polyamidoaryl amine (aryl PAMAM) dendrimers immobilized on a silica gel.[73,74] The alkyl and aryl PAMAM chain ends were diphosphonated facilitating complexation of a rhodium catalyst (Figure 11). Although alkyl derivatives were less effective catalysts the aryl derivatives were found to be excellent catalysts for hydroformylation of olefins such as vinyl acetate and vinyl benzoate.

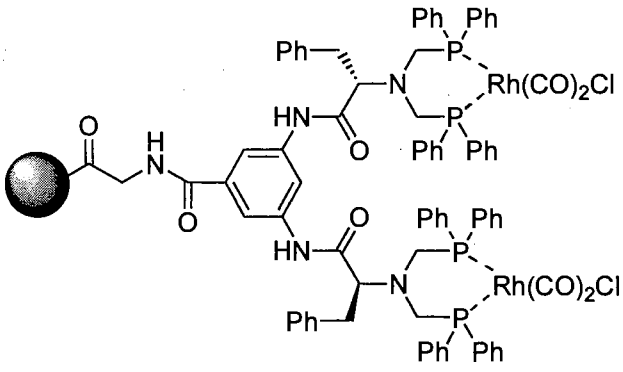


Figure 11: Polyamidoaryl amine diphosphonated dendrimer complexing rhodium. The sphere represents the internal dendrimer structure. These dendrimers were anchored onto silica gel for the hydroformylation reactions.

Amphiphilic dendrimers. A variety of modifications have been directed toward the preparation of dendrimers with chain ends for catalyzing organic reactions in aqueous solutions. Fatty acid modifications through both covalent[75] and noncovalent[41] interactions have been reported. Most approaches have added nonpolar moieties through amide linkages to PPI and PAMAM dendrimers. A pentaerythritol-based dendrimer with amine chain ends quaternized with iodomethane increased the rate of decarboxylation of 6-nitrobenzisoxazole-3-carboxylate by 22 times over the rate in water.[76] The addition of octyl groups and PEG groups to every chain end of PPI dendrimers gave a dendrimer with hydrophobic and hydrophilic character at the chain ends. This dendrimer in quaternized form increased the rate decarboxylation of 6-nitrobenzisoxazole-3-carboxylate 500 times over the rate in water.[29]

Chiral Catalysts. Rhodium complexed cyclophosphazene-based dendrimers containing chiral ferrocenyl ligands have been utilized to asymmetrically hydrogenate dimethyl itaconate with a 98% enantiomeric excess (ee).[77] PAMAM dendrimers with polyhydroxylated chain ends derived from glucose as shown in Figure 12 reduced prochiral ketones to the corresponding alcohols in high yield with over 95% ee.[78] The use of chiral dendrimers with stiff hydrocarbon backbones for the enantioselective addition of dialkylzincs to aldehydes resulted in 86% ee.[79]

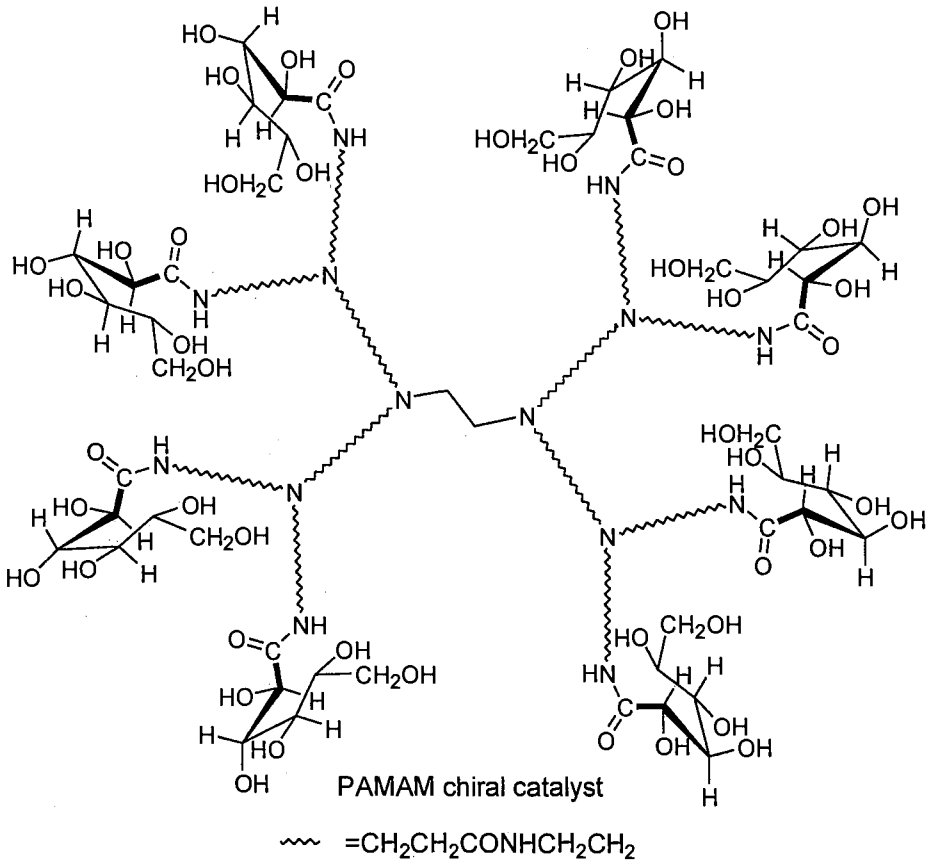


Figure 12: PAMAM with glucose derivatives as chain ends.

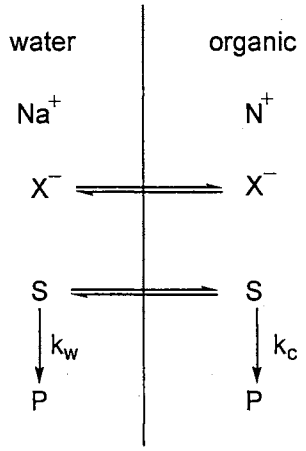
ORGANIC REACTIONS IN AQUEOUS SOLUTIONS

Phase transfer catalysis. Phase transfer catalysis can be defined as the facilitation of reactions between chemical species that are in different phases. Often the reactions are between a salt dissolved in water (X^-) and a mostly nonpolar compound (substrate, S) in an organic medium as shown in Scheme 4. The function of the catalyst (N^+) is to transfer the anions (X^-) of the reacting salt to the organic medium as an ion pair (N^+, X^-). In aprotic solvents the ions are "deshielded" and therefore highly reactive. Therefore, the substrate reaches product through reaction in the aqueous phase and reaction in the organic phase. The overall rate observed is equal to the sum of the rates in the aqueous

and organic phases. Additionally, the rate in water is $k_w[S]_w[X^-]_w$ and rate in organic phase is $k_c[S]_o[X^-]_o$, where concentrations refer to the volumes of the water and organic phases, which can be related to overall concentrations by volume fractions. The rate of reaction of X^- and S is increased when the rate constant k_C for reaction in the organic phase is larger than the rate constant k_W for reaction in the aqueous phase. The major advantage of PTC is the decreased amount of costly (purchase and disposal costs) organic solvents required for a process.

Catalytic Species. The ability of micelles and similar association colloids to alter reaction rates is typically described in terms of pseudophase models, where the micelle or colloid and water are considered as two distinct media.[80] "Pseudo-phase transfer

Scheme 4: General scheme for phase transfer catalysis.



catalysis" (p-PTC) is used to describe this type of catalysis, since p-PTC and PTC differ only by replacement of the organic phase (of PTC processes) with a catalyst pseudo-phase. In pPTC, the catalyst (N^+) has water soluble functionalities at the periphery and nonpolar chains in the interior or core. The substrate (S) is dispersed into the aqueous

phase with the catalyst. Due to the hydrophobic natures of the substrate and the interior of the catalyst, the substrate is extracted from the aqueous phase into the catalyst or organic pseudo-phase. As a result, the substrate becomes concentrated inside the catalyst. The environment of the catalyst core is similar to an apolar organic solvent; that is, there is little hydrogen bonding making ions present highly reactive. Pseudo-phase transfer catalysis can be described by the same equations as normal phase transfer catalysis by considering the catalyst as the organic phase.

Aggregates are groups of molecules that assemble in solution to form a larger particle. Micelles, bilayer vesicles, and microemulsions are aggregates that are collectively known as association colloids.[81,82] Polymers in the form of polyelectrolytes, polyampholytes,[83] polymer latexes,[84,85] ion exchange resins, and most recently dendrimers[29,76] have also been utililized as host systems for these reactions. A short review of these systems and their advantages and disadvantages as catalysts is provided in this chapter.

Micelles and Vesicles. Surfactants consist of a polar head group and a nonpolar hydrocarbon tail. Head groups may be anionic, cationic, or neutral. The nonpolar moiety of a micelle can differ in length, and be made up of multiple chains and/or unsaturated bonds. Aggregation of surfactant molecules is concentration dependent. Surfactant molecules do not aggregate at concentrations below the critical micelle concentration (CMC). Above the CMC, aggregates or micelles form by orienting their nonpolar tails toward each other and their polar heads toward the aqueous solution as demonstrated in Figure 13. Because of the highly organic interior of micelles, they are capable of

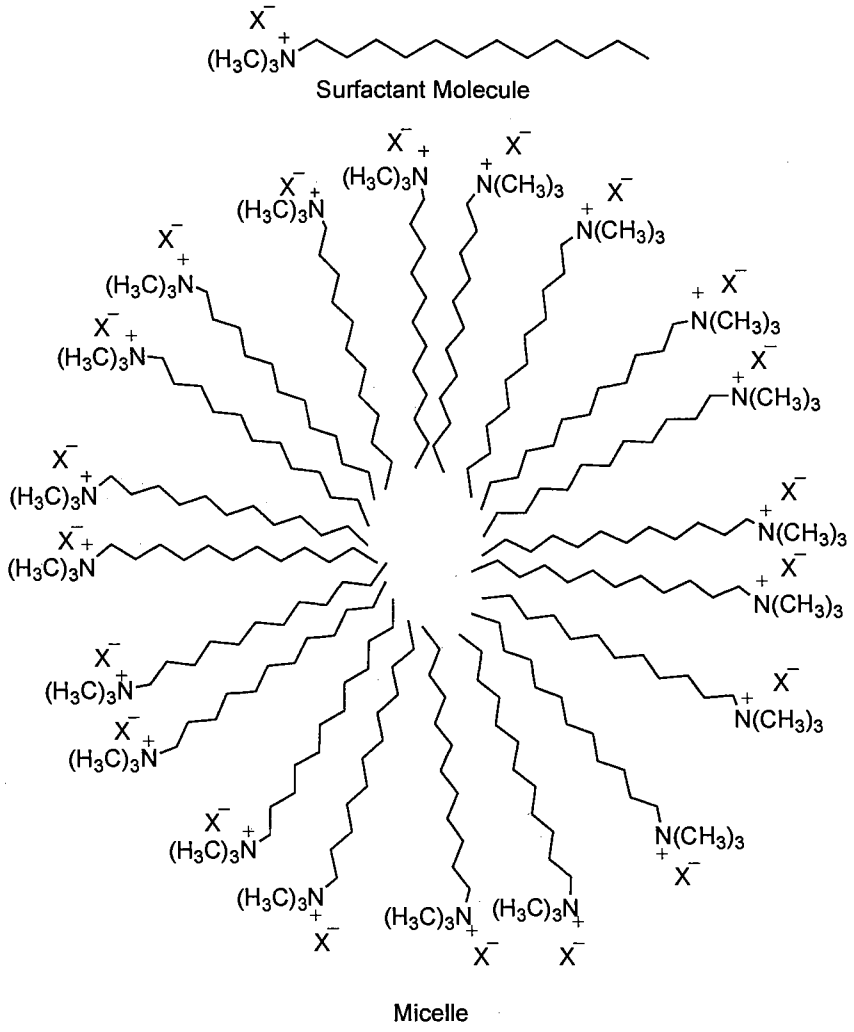


Figure 13: Aggregation of surfactant molecules to form a micelle.

dissolving organic compounds (oils). In organic solvents micelles invert their structure and are capable of dissolving polar molecules.

Vesicles are spherical or ellipsoidal, single or multicomponent, closed bilayer structures.[82] Surfactant vesicles and liposomes (phospholipid vesicles) interact with and trap molecules in three areas based on composition: polar molecules are entrapped in the

aqueous interior of the vesicle; charged species are electrostatically bound to the surface; and hydrophobic substrates are distributed among the alkyl chains of the vesicle.[82] Vesicles are dynamic systems that behave similarly to micelles.

Microemulsions. Microemulsions are stable, optically-transparent, dispersions of oil in water or water in oil. Microemulsions are formed in oil by increasing the surfactant entrapped water pools. In aqueous solutions, progressive addition of a surfactant in the presence or absence of a cosurfactant (usually an alcohol) leads to water-based microemulsions.[82] Structures of oil in water microemulsions are dependent on the type and composition of the surfactant. Although microemulsions are thermodynamically stable, they are sensitive to temperature and relative composition. Changing conditions may cause microemulsions to separate into two phases.

Polyelectrolytes, latexes, polyampholyte latexes, and ion exchange resins. Polyelectrolytes are highly-charged polymer chains that are completely water soluble. Polyelectrolytes dissolve into dilute solutions as isolated chains. With high charge density they form highly expanded coils. At low charge density they more nearly resemble micelles having charged moieties located at the periphery and hydrophobic portions of the polymer in the core.

Latexes are sub-micrometer-sized particles made up of a polymer matrix dispersed in an aqueous solution. They are colloidally stable (do not coagulate and precipitate) because of electrostatic repulsion of charge sites in the surface, and are large enough to scatter light. Additionally, advances in stabilization in high ionic strength solutions have been made by adsorbing or covalently incorporating polyethylene oxides into the polymer

structure.[86] Charge in a latex occurs through charged monomers, charged initiator fragments, or charged molecules absorbed on the surface of the particle.[84,85]

Polyampholyte latexes contain both positive and negative charges on the same polymer chain. Polyampholyte latexes are composed of three types of monomers: negative (e.g. sulfonate functionalized), positive (e.g. ammonium functionalized), and usually neutral (nonpolar, e.g. styrene). A polyampholyte latex in an aqueous solution will orient positive and negative functionalities toward the exterior and the neutral portions will form a core. In a pure aqueous solution, polyampholyte latexes will aggregate and fall out of solution; however, if an electrolyte is added aggregation is prevented by charge separation, making the polyampholyte latex colloidally stable.

Ion exchange resins are water-swollen polymer gels that can contain multiple ionic sites. Anion exchange resins contain cationic sites in their core as well as the periphery; therefore, reactions can occur within the core as well as at the surface. Typical anionic resins are 10 to several hundred micrometers in diameter.

Summary of Catalytic Species. The CMC of micelle formation is the main consideration in their use for catalytic processes. Additionally, volume fraction of micelles and vesicles must be approximated making kinetics more difficult to describe. High concentration requirements make micelles less desirable when considered with catalytic species that can function at low concentration.

Polyelectrolytes' high solubility in water makes them less desirable as catalysts as they are not easily removed. Like micelles, the volume fraction of polyelecrolytes must be approximated, limiting the modeling of kinetic results.

Polyampholyte latexes are colloidal particles that are stable in high ionic strength solutions, and can be removed by ultracentrifugation.[87] They are ideal for reactions that must be carried out under high electrolyte concentrations (sea water), but precipitate from pure aqueous solutions. The location of catalytic sites within a polyampholyte latex is not well-defined and they are dispersed rather than dissolved in the water phase.

A single latex particle is able to solvate or host an organic molecule. Latexes volume fraction can be determined and they can be removed by ultrafiltration. Latexes have been among the most successful catalytic media for these processes and continue to hold much promise.[84,85] However, a complete understanding of these kinetic processes cannot be achieved through latex particles. Latexes are dispersed in solution rather than dissolved, and the location of catalytic sites are not well-defined .

Separation of anion exchange resins from an aqueous solution is easy due to their large size. However, rates of reaction may be slowed by the rate of diffusion of reactants to active sites within the resin, and under intraparticle diffusional control the rate of reaction is inversely proportional to the radius of the particle/molecule.[88] Since resins are large particles (>10 μm), reaction rates in anion exchange resins often are diffusion limited.

Advantages of dendrimer catalysts. Dendrimers can exhibit a variety of solubilities based on the selected monomers and typically are soluble in a number of different solvents. Chain end functionalities determine overall dendrimer solubility and can be modified to change solubilities. They are not dynamic aggregates like surfactant micelles

and vesicles. PPI dendrimers dissolve as individual molecules and are uniformly water soluble at a variety of temperatures and concentrations.

Dendrimers are monodisperse and have well defined structural regions that can be selectively modified. PPIs have a larger number of functionalities per unit mass than any other phase transfer catalyst. PPI dendrimers have diameters of 10-50 Å. Whereas large polymer particles may give diffusion-limited rates due to slow transport of reactant molecules from solution to active sites in the particle, rates of reaction with dendrimers catalysts are not diffusion limited. The well-described structures and distribution of functionalities in PPI dendrimers provide a unique opportunity to alkylate selectively and study the effect of charge location.

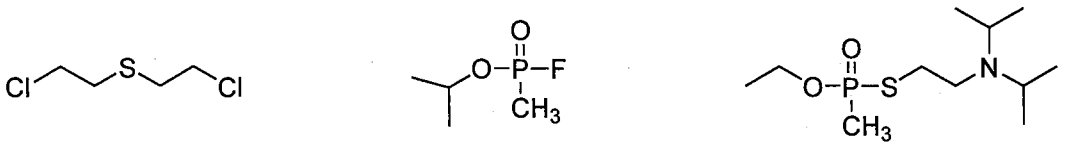
The previously described catalytic species do not have structures that are as well-defined as dendritic polymers. The exact molecular weights and the known number of chain end functionalities make selectively quaternized dendrimers ideal subjects for studying the effect of charge distribution in catalysis.

Applications of Catalysts. A potential application of catalysis by quaternary ammonium ion polymers and colloids in aqueous solutions is decontamination of toxic chemicals. Many industrial processes involve the use or production of hazardous chemicals. New, inexpensive approaches for detoxification of large volumes of these chemicals are needed. Water is an ideal medium for these reactions because it is nontoxic, abundant, and inexpensive. Decontamination of chemical warfare (CW) agents is of particular interest. Since CW agents are generally insoluble in water and their decomposition

occurs slowly in aqueous solutions, a variety of water-soluble aggregates have been designed as organic hosts to enhance the rate of reaction in an organic pseudo-phase.

Currently chemical warfare (CW) agents are stockpiled in many countries, are easily made, and continue to be produced by terrorist nations. Their use or accidents in their transport and/or storage are valid concerns for the future. The existence of CW agents continues to be a threat in times of war and peace. At this time, the most common methods for destruction of stockpiled agents are pyrolysis and high temperature hydrolysis.[89] These approaches are not suitable for decontamination of military equipment, personnel, or civilian areas. New and better methods for decontaminating and destroying CW agents will continue to be sought in the immediate future.

There are three major classes of CW agents: aminophosphonothiolates (VX), phosphonofluoridates (GB and GD), and sulfur mustards as shown in Figure 14. Sulfur mustards are blister agents that attack mucous membranes, whereas VX, sarin (GB), and soman (GD) are nerve agents which inhibit respiratory and nerve functions.[89]



Sulfur mustard Sarin (GB) VX

Figure 14: Structures of the three major classes of chemical warfare agents.

Mustards can be either oxidized or hydrolyzed. Since hydrolysis is rate-limited by the formation of an episulfonium ion, added nucleophiles do not alter the overall reaction rate. Sarin hydrolysis can be catalyzed by nucleophiles, metal-ion complexes, surfactants

or polymer latexes, but sarin does not react with oxidants.[89] The P-S bond of VX is cleaved through hydrolysis with hydrogen peroxide as the nucleophile.[90] Hydrolysis of all agents requires stoichiometric base to neutralize acidic products and therefore must be conducted in basic solutions or in the presence of excess buffer. Although catalysts may increase the rate of hydrolysis, they do not alter the stoichiometry.

OBJECTIVES AND KEY RESULTS

The primary objective of this research is to modify PPI dendrimers by selective quaternization of amine sites in order to study the effects of charge location on catalysis. The structures of PPI dendrimers have amine sites at all branch points and chain ends. The selective methylation of chain ends and branch points to quaternary ammonium sites will be used to determine the effect of charge location on binding and rate constants.

Dendrimers change conformation to become more spherical or globular with increasing molecular weight. This change is significant between D32 and D64 because the mass increases more than the volume of the sphere that encloses the molecule. I chose D8 to test synthetic methods, and D32 and D64 to monitor the effect of changing conformation. Quaternization by methylation was chosen to increase the probability of complete reactions and to retain water solubility.

Preparation of the Target Dendrimers. I chose reductive amination to generate tertiary amine dendrimers (e.g. **4**, structures are numbered in order of appearance in Chapter 2) from primary amine ended PPIs (e.g. **1**) as shown in Figure 15. For the preparation of chain end quaternized PPIs (e.g. **7**), we reacted tertiary amine dendrimer precursors with stoichiometric iodomethane. Permethylated dendrimers (e.g. **11**) were prepared from the tertiary amine form by reaction with excess iodomethane. Dendrimers with PEG-amide chain ends (e.g. **16**) were prepared by reaction of $MPEG_{164}$-acid chloride with primary amine chain ends. Internally quaternized dendrimers (e.g. **18**) were prepared from the amide ended materials by reaction with excess methyl iodide.

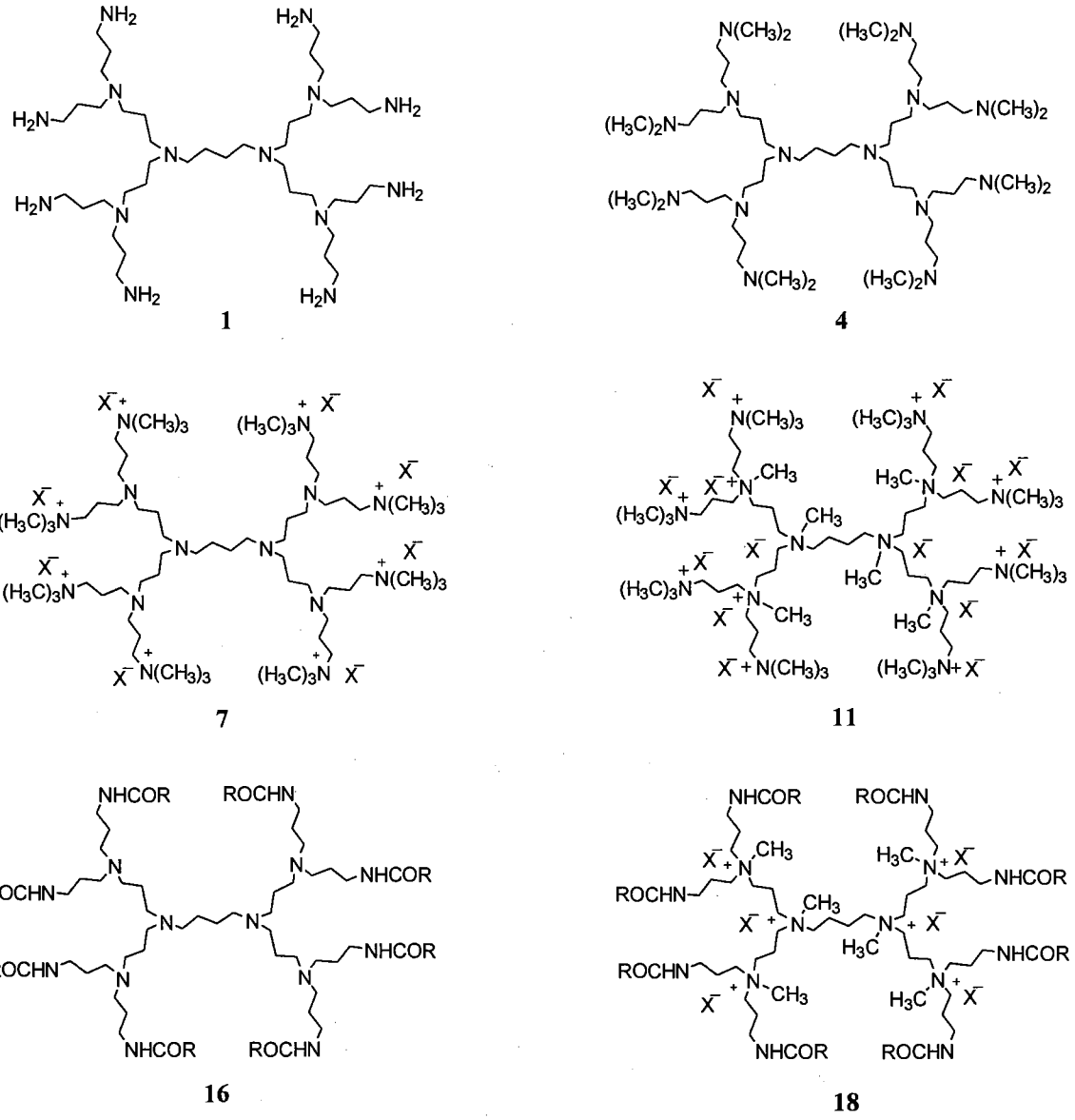


Figure 15: Modifications of PPI dendrimer D8 (**1**) to form new dendrimers with tertiary amine chain ends (**4**), quaternary ammonium chain ends (**7**), quaternary ammonium chain ends and branch points (**11**), amide chain ends (**16**) and quaternary ammonium branches (**18**). X = I or Cl, R = $CH_2OCH_2CH_2OCH_2CH_2OCH_3$. Numbers refer to schemes in Chapter 2.

Characterization of the Target Dendrimers. Product structures were determined by ^{1}H and ^{13}C NMR, electrospray ionization mass spectroscopy (ESIMS), and elemental analysis (EA). Distortionless enhancement by polarization transfer (DEPT), heteronuclear multiple quantum coherence (HMQC) and correlated spectroscopy (COSY) NMR experiments were used to aid in assignment of the D8 materials. NMR spectra of modified D8 materials were used analogously for signal locations in spectra of modified D32 and D64.

Application of the Target Dendrimers. The quaternized PPI dendrimer counterions were converted from iodide to chloride. The catalytic activities of the target molecules were measured for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate in basic (pH=11.5) aqueous solutions. Observed rates were 1.5-4.5 times the reaction rate in pure water. Hydrophobicity promotes both the intrinsic rate constant (by reducing hydrogen bonding) and the binding constant (by reducing the preference of the substrate as the ammonium counterion chloride). The hydrophilicity of methylated dendrimers compared to other known catalysts resulted in lower intrinsic rate constants and binding constants.

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CHAPTER 2

QUATERNIZATION OF POLY(PROPYLENE IMINE DENDRIMERS BY METHYLATION

ABSTRACT

Poly(propylene imine) dendrimers (PPI) were quaternized at chain ends only, at chain ends and branch points, and at branch points only. Primary amine end groups of DAB-*dendr*-$(NH_2)_8$, DAB-*dendr*-$(NH_2)_{32}$, and DAB-*dendr*-$(NH_2)_{64}$ (**1**, **2**, and **3**, respectively) were converted to tertiary amines using formic acid and formaldehyde. Tertiary amine PPI dendrimers were quaternized at the chain ends using stoichiometric amounts of iodomethane. Complete quaternization (chain end and branch point methylation) was accomplished by reacting tertiary amine PPI dendrimers with excess iodomethane. PPI dendrimers **1** and **2** were amidated with 2-[2-(2-methoxyethoxy)ethoxy]acetic acid chloride followed by alkylation with iodomethane to form internally quaternized dendrimers. Product structures were determined by ^{1}H and ^{13}C NMR, electrospray ionization mass spectrometry, and elemental analysis.

INTRODUCTION

Micelles are dynamic aggregates of surfactant molecules that only form when the amount of surfactant in solution exceeds the critical micellar concentration (CMC). At dilution beyond the CMC, micelles do not form.[1] Additionally, surfactant aggregation is ionic strength and temperature dependent. Dendrimers are stable irrespective of concentration, ionic strength, and temperature of the solution since they are constructed with covalent bonds. The stability and unique structural design of dendritic unimolecular micelles has led to applications in the areas of drug delivery,[2] protein recognition,[3] and homogeneous catalysis.[4]

Dendrimers as unimolecular micelles were first proposed by Newkome in 1991.[5] Preparation and use of unimolecular micelles are now widespread.[6] Dendrimers with hydrophobic end groups have been prepared as inverted unimolecular micelles.[7] Utility of hybrid ended (hydrophilic and hydrophobic) dendrimers as unimolecular hosts and catalysts has also been demonstrated.[8,9]

Quaternary ammonium ions catalyze the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate based on their attraction of the carboxylate ion. The effect of charge location in polymer catalysis of this decarboxylation has not been thoroughly examined.[10] The kinetic effect of charge location could be determined using dendrimers, since they are synthetically designed to be perfect structures. Hydrophobic and hydrophilic groups can be selectively added to change the host characterisitics of the dendrimer catalyst. A better understanding of the requirements for catalysts may be gained by preparing differently functionalized dendrimer catalysts.

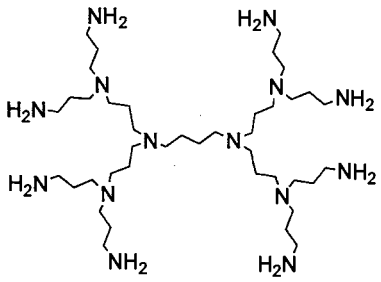
Poly(propylene imine) (PPI) dendrimers contain amine functional groups at chain ends and branch points, that could be selectively modified to study the effects of quaternary ammonium group location on catalytic activity. Through alkylation and amidation a variety of groups can be added at chain ends and branch points. PPI dendrimers with either primary amine or nitrile ends are available commercially from Aldrich with 4, 8, 16, 32, or 64 chain ends.

We chose PPI dendrimers, DAB-*dendr*-$(NH_2)_8$, DAB-*dendr*-$(NH_2)_{32}$, and DAB-*dendr*-$(NH_2)_{64}$ (**1, 2,** and **3**, respectively), as starting materials for this investigation. Dendrimer **1** (D8) was used to determine the success of reactions and the best techniques for purification and analysis. Dendrimers **2** (D32) and **3** (D64) were chosen to assess the effects of rotating open chain conformations of **2** versus the more globular shape of **3** on catalytic activity.[11,12]

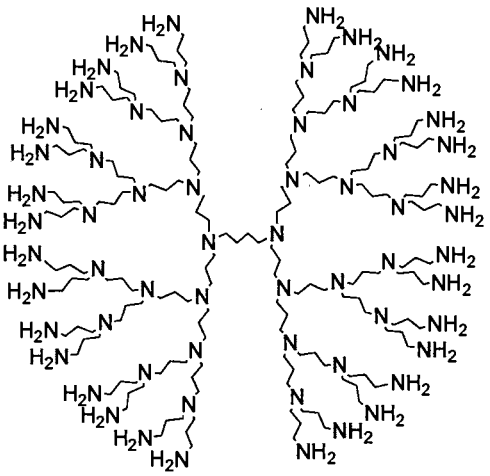
Selective Quaternization Approach. The following methylations provided structures which are similar in order to determine charge location effects: Methylation of amine chain ends only (e.g. **7**); complete permethylation of all amine nitrogens in the dendrimer (e.g. **11**); internal methylation (e.g. **18**) after amidation of chain ends.

Chain end only and fully quaternized materials were prepared by a stepwise approach through a tertiary amine. Reductive methylation by the Eschweiler-Clarke method was chosen for this transformation since the tertiary amine is formed preferentially.

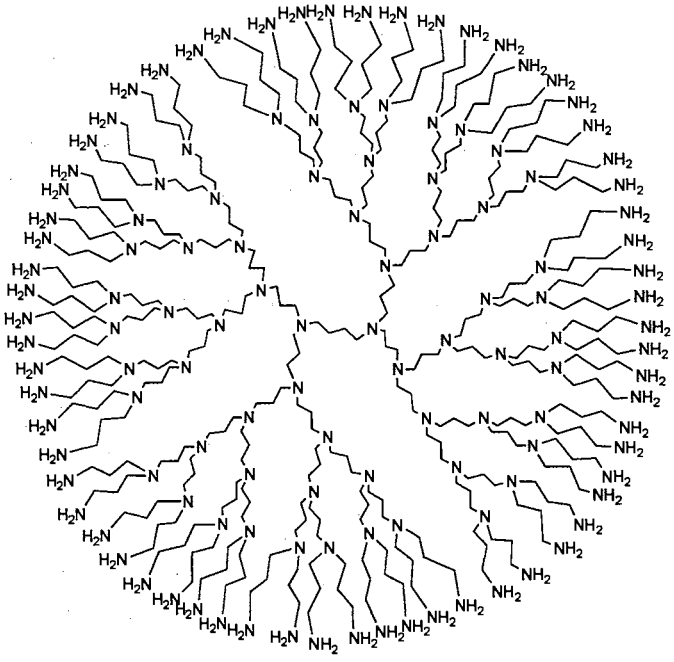
Reductive amination has a long history dating back to Leuckart's alkylation of ammonia with various carbonyl compounds using ammonium formate.[13] Wallach found that alkylation of amines with carbonyl compounds could be accomplished at lower temperatures in the presence of formic acid.[14] Eschweiler and Clarke were the first to



1



2



3

use formic acid and formaldehyde to methylate various amines.[15,16] The technique used to methylate primary amine end groups of **1-3** to tertiary amines was adapted from work done by Pine et. al., with benzylamine.[17]

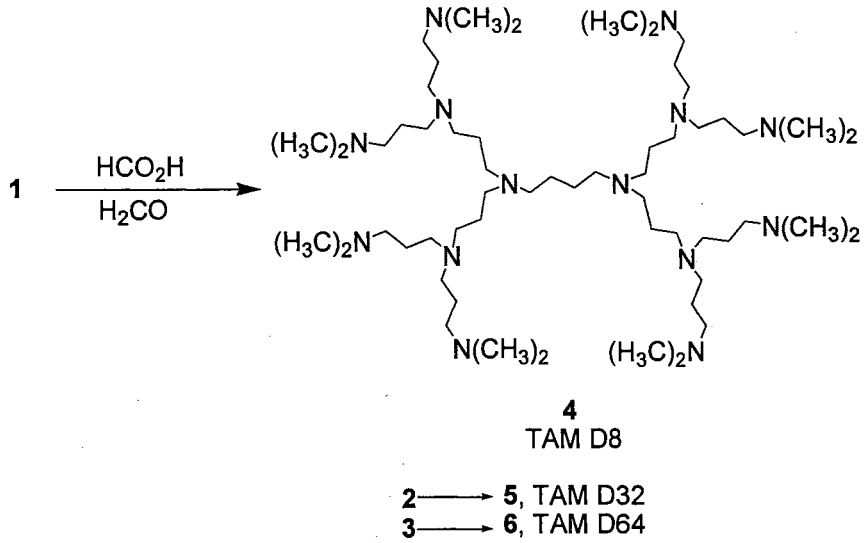
Tertiary amine dendrimers were quaternized at chain ends with stoichiometric iodomethane. Complete permethylation was accomplished with excess iodomethane. Internally quaternized dendrimers (IM) were prepared by amidating with the acid chloride of triethylene glycol monomethyl ether followed by quaternization. Products were identified using NMR, ESIMS, and elemental analysis.

RESULTS

Tertiary Amine Chain Ends. The Eschweiler-Clarke method was utilized to convert primary amine chain ends of dendrimers **1-3** to tertiary amines. Dendrimers **1-3** were methylated with excess formic acid and formaldehyde to give the tertiary amine ended dendrimers **4-6** as shown in Scheme 1.

The Eschweiler-Clarke method was chosen for the formation of tertiary amines since the tertiary amine product is formed preferentially.[15-17] Direct alkylation with iodomethane requires a sterically-hindered strong base such as 1, 2, 2, 6, 6, pentamethylpiperidine (PMP). However, the Eschweiler Clarke reductive methylation does not require PMP. Additionally, the tertiary amine dendrimer can be extracted into an organic solvent providing easy separation and purification of products.

Scheme 1: Reductive methylation of PPI dendrimers.



Dendrimers **4-6** required isolation in free amine form before use in quaternization reactions. Drying the unpurified aqueous reaction mixture under reduced pressure resulted in formation of paraformaldehyde, noted by white deposits on the walls of the flask. Ether extraction of the acidic solution, followed by lyophilization of the aqueous layer, yielded the protonated product which was passed down an Amberlite IRA-95 column to generate the free amine. Although this method worked well, it was tedious and left the amine in an aqueous solution that had to be lyophylized. Due to protonation of amine nitrogen, the tertiary amine dendrimer preferred the aqueous phase predominately pH~12. Deprotonation of the dendrimer using a Group I or II metal hydroxide was avoided to prevent amine-metal ion coordination. Dendrimer amine-metal complexing would reduce extraction yields by retention of the dendrimer in the aqueous phase. Initially, tetramethylammonium hydroxide pentahydrate was used to deprotonate the dendrimers. However, high sodium hydroxide concentrations increased extraction yields by salting the dendrimer out of the aqueous phase.

Reductive methylation appeared to produce dendrimers **4-6** based on ^{1}H NMR integrations and ESI-MS signals. However, extra signals present in the ^{13}C NMR spectra were determined to be methyls on secondary amine nitrogen based on a distortionless enhancement by polarization transfer (DEPT) experiment. The degree of methylation was determined using ratios of the integration of the tertiary amine signals at 45 ppm and the secondary amine signals at 42 ppm. Degrees of methylation achieved with varying conditions are presented in Table 1. The best sample of TAM D8 (**4**(1)) had only 6.5 of

Table 1. Reductive Methylation Experiments.

starting dendrimer	product dendrimer	temp (°C)	time (h)	HCO_2H/ H_2CO/NH_2	$-N(CH_3)_2$/ $-NHCH_3$ [a]	details[b]
1	**4**(1)	90	24	9:3:1	6.5:1.5	used for **11**
1	**4**(2)	90	24	9:9:1	6.3:1.7	pH = 4.5
1	**4**(3)	90	24	9:9:1	6.2:1.8	exc. reag. added
1	**4**(4)	90	48	9:3:1	6.1:1.9	methanol added
4(6)	**4**(5)	90	24	9:3:1	6.1:1.9	additional reag.
4(4)	**4**(6)	-	-	-	6:2	prep. TLC
1	**4**(7)	90	48	9:3:1	6:2	water added
4(6)	**4**(8)	100	48	9:3:1	6:2	sealed rxn
1	**4**(9)	100	48	3:3:1	5.6:2.4	ref 17
1	**4**(10)	80	24	3:3:1	5.3:2.7	used for **7**
1	**4**(11)	100	24	9:3:1	4.9:3.1	sealed rxn
1	**4**(12)	90	24	9:3:1	4.1:3.9	dry, MeOH
2	**5**(1)	90	24	9:3:1	24:7.6	water added
2	**5**(2)	80	24	9:3:1	21.7:10.3	used for **8**
2	**5**(3)	100	48	3:3:1	20:12	used for **12**
3	**6**(1)	80	48	9:3:1	44:20	used for **9**
3	**6**(2)	90	24	9:3:1	42.4:21.6	used for **13**

[a] the ratio of tertiary to secondary amine chain ends were determined by integration of ^{13}C signals at 45.6 and 42.3 ppm. Parentheses designate different experiments.
[b] denotes further modifications to the described procedure or use of the product in a subsequent experiment.

its 8 end groups as tertiary amines (Figure 1). Additionally, the best samples of TAM D32 (**5**(1)) and TAM D64 (**6**(1)) were determined to contain 7.6 and 20 secondary amine end groups, respectively.

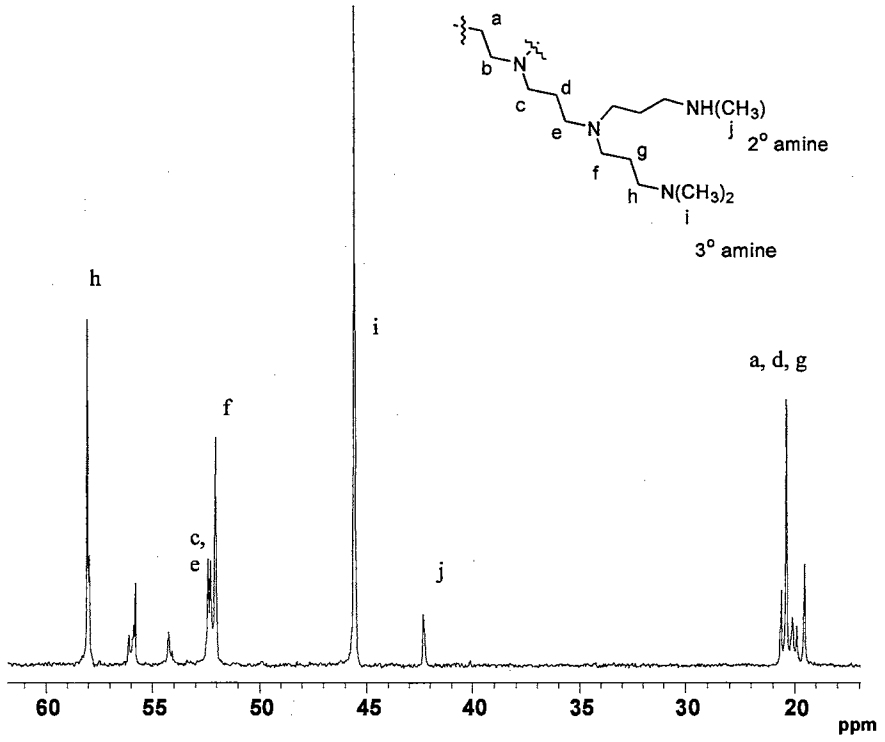


Figure 1: ^{13}C NMR of tertiary amine D8 (**4**(1)). Relative integrations of signals *i* and *j* indicate that 6.5 of 8 end groups are tertiary amines.

In the original Eschweiler-Clarke methylation of benzylamine, 5 moles of formic acid and 2.2 moles of formaldehyde were used per mole of benzylamine.[18] Increasing the molar amount of formic acid in dendrimer amine reactions gave the highest conversion, but did not complete the methylation (**4**(1), **5**(1), and **6**(1)).

Conditions for reductive amination (the Wallach reaction) with carbonyl compounds (not formaldehyde) were examined by Staple and Wagner.[19] Their results indicated that optimum conditions for the alkylation of piperidine with cyclohexanone were temperatures of 123-125 °C, using 150-250% excess formic acid under dry conditions (99% formic acid and $CaSO_4$). In an attempt to replicate similar reactions conditions, **1** was methylated with 96% formaldehyde and paraformaldehyde in methanol at 90 °C (temperature measured inside flask). As reported in Table 1, the reaction produced only 4 of 8 chain ends as tertiary amines (sample **4**(12)). Longer times and higher temperatures (in aqueous solutions) also failed to produce the desired product.

The effect of pH on the kinetics of reductive methylation was studied by Subbaiah et al., and maximum rate was determined at a pH of 4.5 for primary amines.[20] At pH 4.5, reaction of D8 gave **4**(3) with 6.3 of 8 chain ends as tertiary amines.

Reductive methylation was carried out with deuterated formic acid and formaldehyde to form PPIs with CD_3 ends. The same procedure was used for the deuterated approach as was used to form **4**(1) (Table 1). Results are presented in Table 2. Lower degrees of methylation were attributed to a lower equilibrium constant for reaction of *d*-formaldehyde with secondary amine than unlabeled formaldehyde with secondary amine.

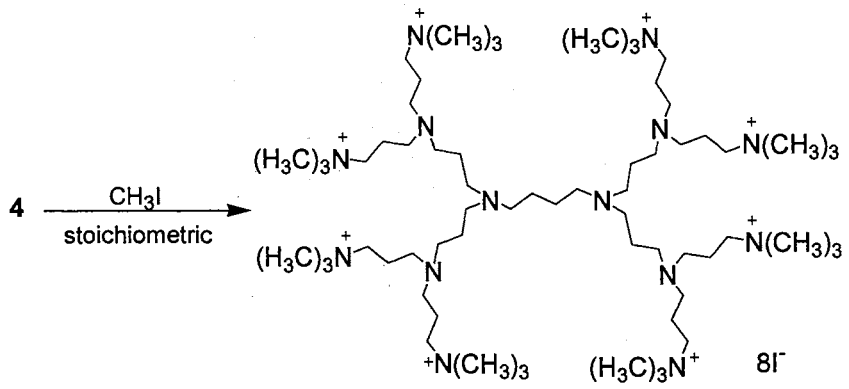
Table 2. Reductive methylations with deuterated reagents.

starting dendrimer	product dendrimer	temp (°C)	time (h)	DCO_2D/ D_2CO/NH_2	$-N(CD_3)_2$/ $-NHCD_3$ [a]
4	**4**(13)	90	24	9:3:1	3.8:4.2
5	**5**(4)	90	48	9:3:1	12.5:19.5
6	**6**(3)	90	48	9:3:1	21.3:42.7

[a] the ratio of tertiary to secondary amine chain ends were determined by integration of ^{13}C signals at ~45 and ~42 ppm.

Quaternary Ammonium Chain Ends. Tertiary amine dendrimers **4-6** were reacted with stoichiometric iodomethane to form dendrimers **7-9** as demonstrated in Scheme 2. Reaction temperature was maintained at 50 °C for 24 h to limit internal methylation. Raising the temperature to 80 °C after 24 h ensured complete reaction of any remaining iodomethane.

Scheme 2: Quaternization of PPI Chain Ends.



7
EGM D8

5 ⟶ **8**, EGM D32
6 ⟶ **9**, EGM D64

Primary amine chain ends were believed to react faster than internal tertiary amine branch points because they are more basic[21] and less hindered. PMP was not required in end group methylations, since internal dendrimer amine sites served as the base for these conversions. Since interior tertiary amines react with iodomethane, some interior quaternization was expected. Maintaining a low level of interior quaternized sites was considered acceptable as an approximate of chain end quaternized dendrimers.

Spectra taken of chain end quaternized PPIs in acidic solutions did not contain the signal for tertiary amine chain ends (~ 45 ppm) indicating that all chain ends are either quaternized or protonated. However, ^{1}H and ^{13}C NMR spectra of basic solutions of **7-9** indicated the presence of both secondary and tertiary amine sites at chain ends. Numbers of tertiary and secondary amine chain ends and quaternary ammonium chain ends and branch points were measured by integration of ^{13}C NMR signals at 45.6 ppm ($RN(CH_3)_2$), 42.3 ppm ($RNHCH_3$), 55.8 ppm ($RN(CH_3)_3^+$), 53.1 ppm ($R_3N(CH_3)^+$) The overall extent of quaternization at chain end and internal nitrogens is given in Table 3. Using PMP (1 mol/chain end) as a base in the D8 chain end quaternization did not change the amount of secondary and tertiary amine present in the product.

Table 3. Chain End Quaternization Results.

Starting dendrimer	dendrimer product	$RN(CH_3)_3^+$	$RN(CH_3)_2$	$RNHCH_3$	$R_3N(CH_3)^+$
4(9)	**7**	6.7	0.5	0.8	2.1
5(2)	**8**	20.5	3.9	7.6	19.1
6(1)	**9**	43.5	5.5	14.7	34.9

Elemental analyses of **7-9** as isolated from the reaction (without base treatment) found C/N and N/I ratios within 7% of the values calculated, assuming the structure contained internal quaternary ammonium sites as determined by ^{13}C NMR and contained HI from reaction of secondary amine sites in the precursors. EGM D8 (**7**) was further examined by ESI-MS, which confirmed the presence of **7** with some signals from over methylation and the retention of HI from the reaction.

Quaternary Ammonium Ions at Both Chain Ends and Branch Points. Permethylated dendrimers **11-13** were obtained by reacting dendrimers **4-6** with excess

iodomethane at 110 °C in a sealed ampoule. Reaction of iodomethane with primary or secondary amines results in protonation at branch points. Protonated branch points do not react with iodomethande. Due to secondary amine sites in the tertiary amine precursors (**4-6**), a stoichiometric amount of PMP (**10**) was required to neutralize acid generated during the reaction.

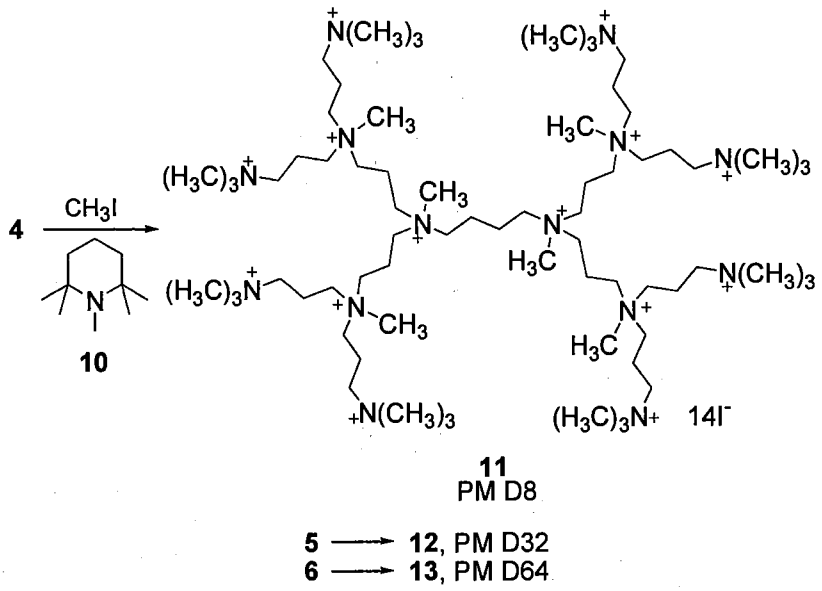
PPI dendrimers D8 (**1**), D32 (**2**), and D64 (**3**) were originally permethylated using excess iodomethane at 100-110 °C in a sealed tube. The one step reaction of PPI dendrimers with excess iodomethane in the presence of PMP (**10**) failed to produce fully quaternized dendrimers. Separation of the product by precipitation from cold methanol followed by reaction with additional iodomethane completed the permethylation, successfully yielding dendrimers PM D8 (**11**), PM D32 (**12**), and PM D64 (**13**). PMP was not required for the second step of the methylation as all dendrimer amines were either tertiary or quaternary after the first reaction with iodomethane/PMP.

Although the reaction went to completion in two steps using iodomethane, using the Eschweiler-Clarke reductive amination with formaldehyde and formic acid generated tertiary amine-ended dendrimers (**4-6**) which could be fully quaternized in a second step with excess iodomethane. For every secondary amine present after reductive methylation, one mole of PMP was required to neutralize the acid. Direct methylation used 2 moles of PMP for every primary amine end group; therefore, use of **4-6** as precursors for quaternization significantly reduced the amount of PMP required.

Characterization by ^{1}H NMR was again somewhat less useful than ^{13}C NMR because of unresolved signals. Spectral assigments were made using heteronuclear multiple quantum coherence (HMQC) and correlated spectroscopy (COSY) experiments to find

correlations between proton signals and carbon signals. ESIMS of **11** contained multiple signals due to the retention of different amounts of iodide during analysis. Signals corresponding to the dendrimers with 14 and 13 quaternary ammonium sites were observed in the spectrum. The $(M - 14I)^{+14}$ species (no retention of iodide, $m/z = 86.0$) of **11** was the most highly charged species observed by ESI-MS. Elemental analysis also confirmed the composition of **11-13** based on C/N and N/I ratios.

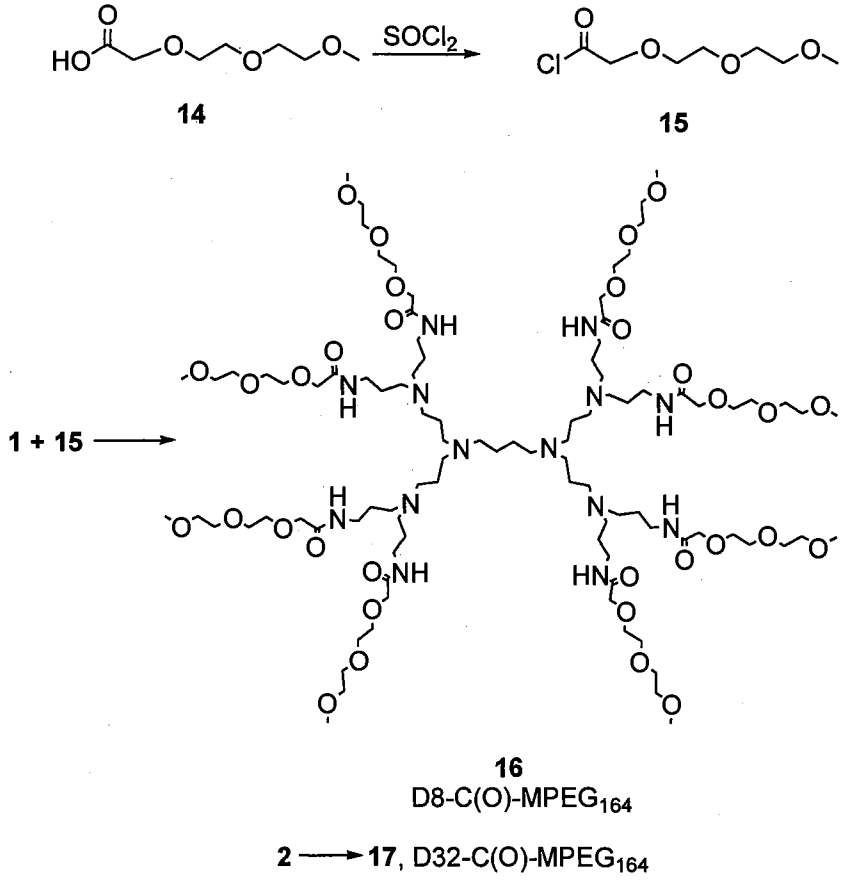
Scheme 3: Quaternization of PPI chain ends and branch points.



Quaternary Ammonium Ions at Branch Points Only. Internally permethylated dendrimers were prepared in two steps from PPI dendrimers **1-3**. Thionyl chloride was reacted with 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (**14**) in the presence of triethylamine to give the acid chloride $MPEG_{164}$-COCl (**15**). Reaction of the acid chloride with **1** and **2** gave the desired amide-ended dendrimers D8-C(O)-$MPEG_{164}$ (**16**) and D32-C(O)-$MPEG_{164}$ (**17**) as shown in Scheme 4. Dimethylformamide was used as the solvent

and catalyzed formation of the amide.[22] Isolation by basic extraction gave the pure product based on ^{1}H (Figure 2) and ^{13}C NMR (Figure 3) results. ESI-MS confirmed the molecular weights of the products. Signals for unreacted dendrimer chain ends were not observed. Column chromatography did not improve the purity based on ^{1}H NMR and resulted in loss of an additional 5 percent of product; therefore, it was not utilized for larger samples.

Scheme 4: Amidation of PPI chain ends.



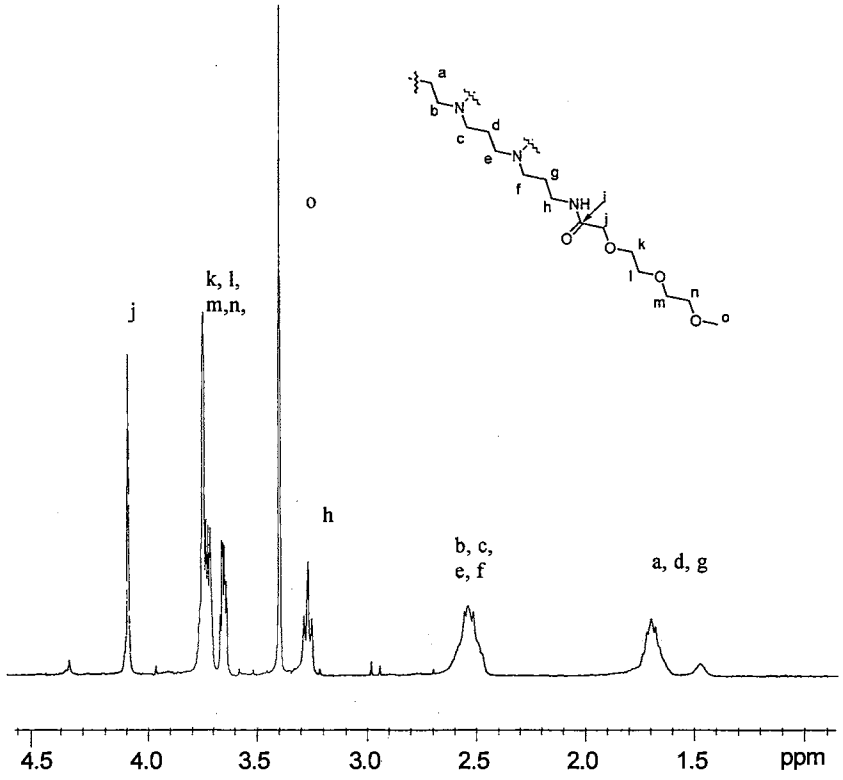


Figure 2: ^{1}H NMR of D8-C(O)-MPEG$_{164}$, **16**.

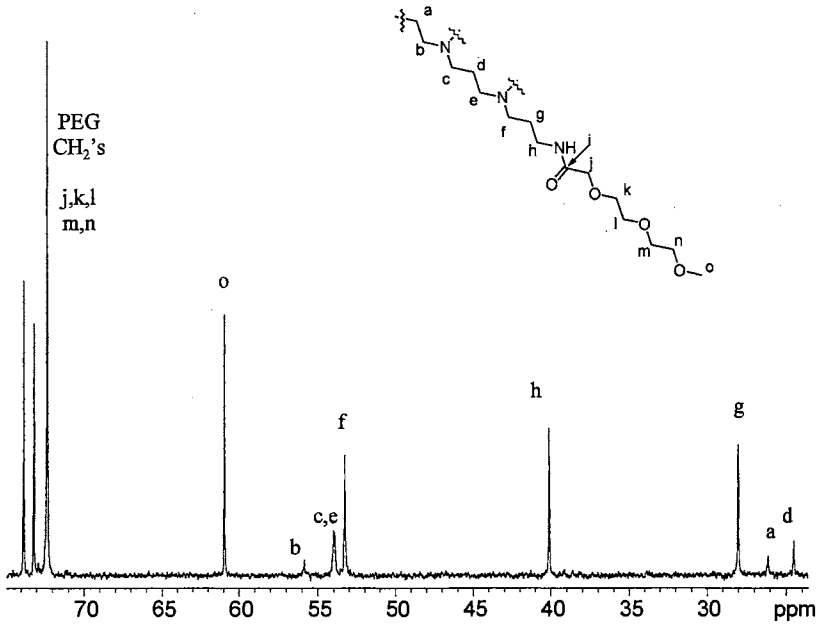
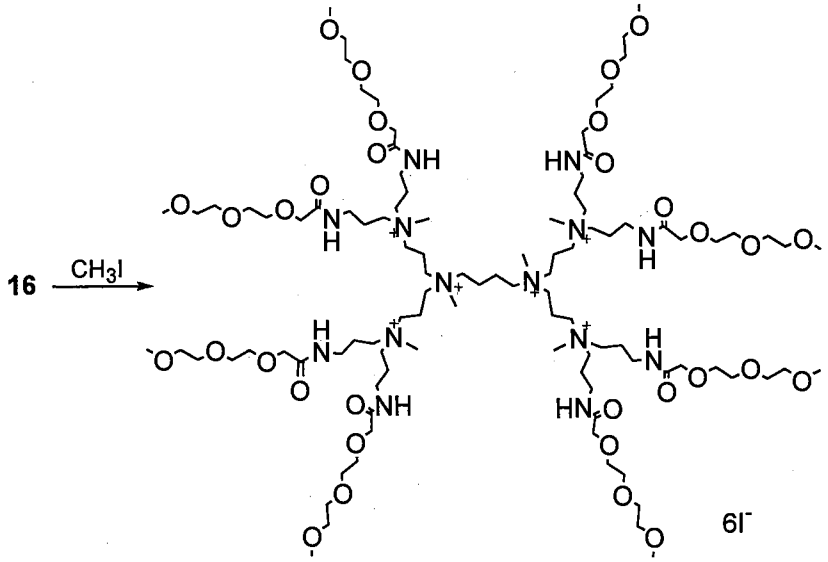


Figure 3: ^{13}C NMR spectrum of D8-C(O)-MPEG$_{164}$, (**16**). The amide carbonyl signal (i) appears at 171.0 ppm.

Dendrimers **18** and **19** were prepared by treatment of the amide-terminated dendrimers **16** and **17** with a 200% excess of iodomethane as shown in Scheme 5. The internally quaternized dendrimers **18-19** were confirmed by ^{1}H and ^{13}C NMR. Although electrospray mass analysis was not successful, elemental analysis results confirmed the product composition.

Scheme 5: Quaternization of PPI branch points.



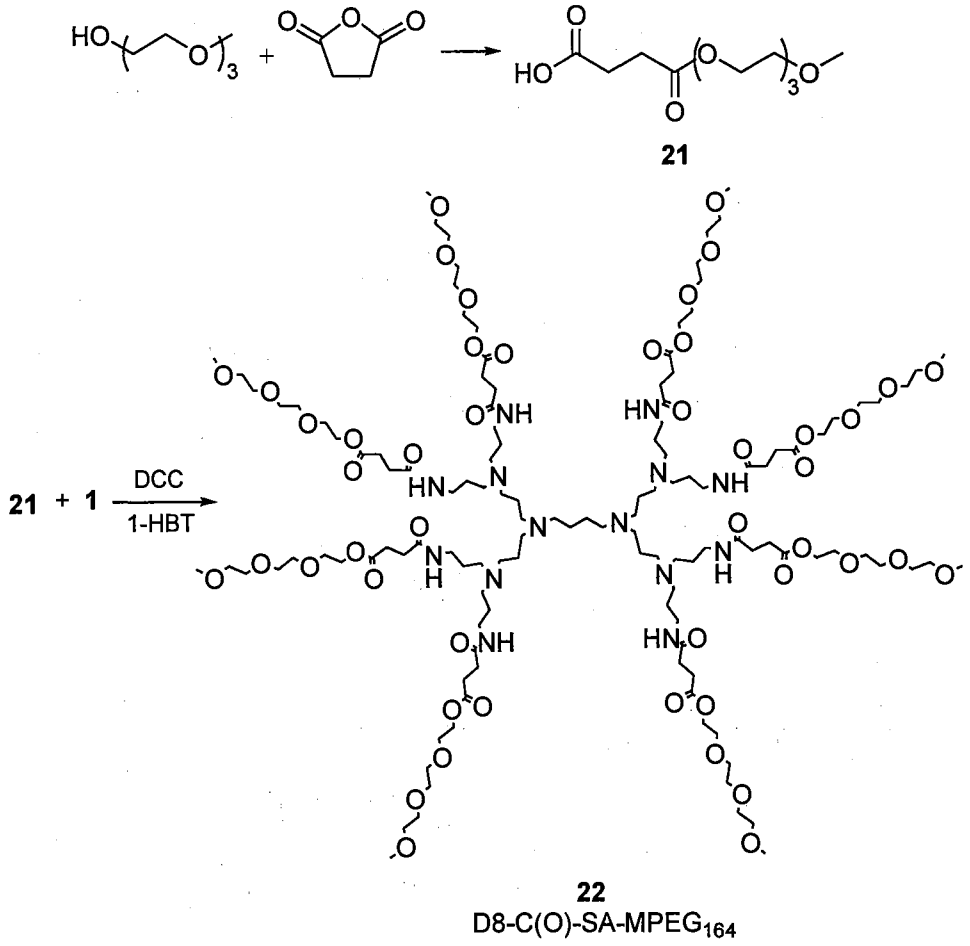
18
IM D8-C(O)-MPEG$_{164}$

17 ⟶ **19**, IM D32-C(O)-MPEG$_{164}$

The first attempts at amidation were made through the active ester of 1-hydroxybenztriazole (1-HBT) with dicyclohexylcarbodiimide (DCC) because of the mild conditions under which the amide is formed.[23,24] MPEG$_{164}$ was converted to the acid MPEG$_{164}$-SA-COOH (**21**) by addition to succinic anhydride. The acid **21** was coupled to D8 (**1**) through formation of the active ester of 1-hydroxybenztriazole (1-HBT) using

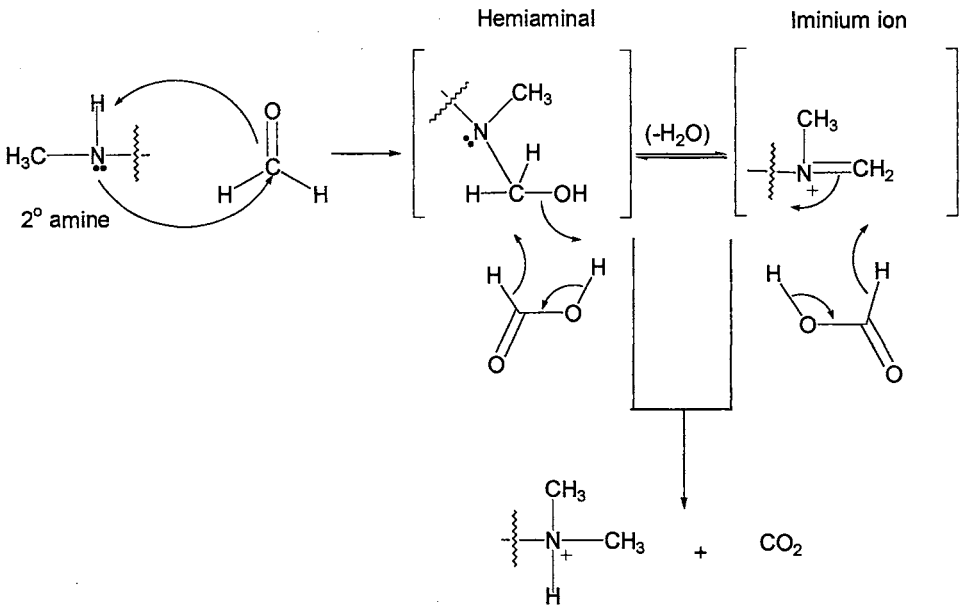
DCC as demonstrated in Scheme 7. Although unreacted DCC and 1-HBT were removed after extraction, a significant amount of the byproduct, dicyclohexyl urea (DCU), remained in the sample as observed by ^{1}H NMR. The byproduct could not be removed by extraction, microfiltration, or chromatography.

Scheme 6: Amidation of **1** using DCC.



Tertiary Amine Chain Ends. The mechanism for reductive methylation demonstrates that different intermediates were produced from addition of formaldehyde to the primary amine versus addition to the secondary amine.[17] Alkylation from primary to secondary amine proceeds through attack on formaldehyde's carbonyl carbon to form the hemiaminal. Loss of water leads to the imine which remains in equilibrium with hemiaminal until reduction. Reduction of both intermediates leads to formation of the secondary amine. Addition of formaldehyde to the secondary amine results in formation of an iminium ion. However, production of the iminium ion does not account for a different reactivity as reduction is the fast step in the reaction.[20] The slow step is reaction of formaldehyde with the amine; therefore, the equilibrium must not favor production of the secondary hemiaminal or iminium ion.

Scheme 7: Mechanism of reductive amination of a secondary amine.



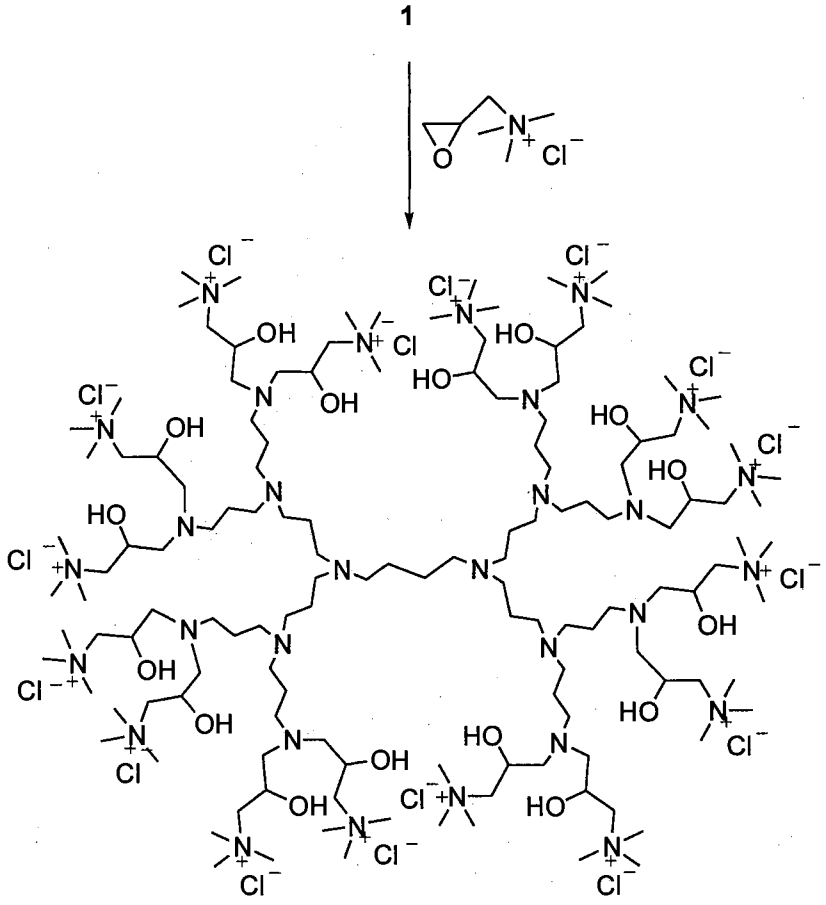
Successful methylation of D8 (**1**) by the Eschweiler-Clarke procedure has been reported;[25] however, the reaction results could not be reproduced in this laboratory. For this project, tertiary amine products were to be used as precursors for permethylations; therefore, the mixed secondary/tertiary amine materials were considered acceptable precursors.

Quaternary Ammonium Chain Ends. End only quaternized dendrimers have been reported previously. Li used iodomethane to quaternize an amine ended dendrimer that had carbon branches (no internal amines).[26] Chen and Cooper reported quaternary ammonium PPI dendrimers prepared by reaction of primary amine chain ends with 2-chloroethyl isocyanate. Tertiary amines (such as dimethyldodecyl amine) were used to quaternize the 2-chloroethyl chain ends. Sideratou et al., recently reacted glycidyltrimethyl ammonium chloride with PPI dendrimers to give secondary amines at dendrimer ends with quaternary ammonium chloride "tails".[27] Use of excess glycidyltrimethylammonium chloride has been considered as a possible route to end only quaternized PPI dendrimers (**20**), as shown in Scheme 8.

Quaternary Ammonium Ions at Both the Chain Ends and Branch Points. Two complete quaternizations of modified PPIs have been previously reported. Pan reported the permethylation of $MPEG_{164}$,octyl-ended PPI dendrimers with iodomethane.[4] These dendrimers were evaluated as unimolecular micelles and catalysts. Quaternization of the PPI portion of PPI-polystyrene block copolymers was reported by Elissen-Román et. al. [28] Alkylation of PPI dendrimers with up to 16 end groups was accomplished using iodomethane. These amphiphilic block copolymers formed stable emulsions in water/toluene mixtures. The block copolymers exhibited opalescence on removal of

toluene indicating formation of large uniform aggregates. The analysis of PPI dendrimers quaternized by methylation dendrimers has not been reported previously.

Scheme 8: Reaction of glycidyltrimethylammonium chloride with **1**.



Quaternary Ammonium Ions at Branch Points Only. Successful amidation of dendritic primary amines with carboxylic acids and DCC and with active esters of fatty acids and saccharides (formed from reaction with *N*-hydroxysuccinimide) has been reported.[29,30] Isolation of products was accomplished by extraction into methylene

chloride. The reported isolations did not involve chromatography or discuss any difficulty in isolating products from DCU. I prepared $MPEG_{164}$ amide ended dendrimers through the active ester of 1-HBT, however DCU was generated as a byproduct during the reaction. Attempts at purification were unsuccessful.

Use of acid chlorides to cap dendrimer end groups with alkyl and PEG chain ends has also been reported.[4,7] The methods used are similar to those reported herein and show similar success. The MPEG capped dendrimers reported by Pan were first reacted with octanoyl chloride which was reduced before reaction with **14**.[9] After reduction and permethylation these hybrid-armed dendrimers were active catalysts in the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate.[4] Based on reviews of the current literature on PPI dendrimers, preparation of PPI dendrimers quaternized only internally has not been reported before. We used MPEG-acylated dendrimers to prepare the first dendrimers **18** and **19** having quaternary ammonium ions only at the branch points.

Completing reductive methylation. Preparation of perfectly methylated tertiary amine dendrimers is still necessary for future quaternization reactions and for preparation of the deuterated materials. Approaches to completing methylation involve either direct reductive methylations, alkylations or amidations followed by reduction.

Alkylations of amines with aldehydes and reducing agents often utilize metal hydrides as the reducing agent.[31] Use of metal hydrides in our experiments had been avoided because of possible coordination with metal cations inhibiting extraction. Since tertiary amine dendrimers have recently been extracted from a 50% aqueous solution of sodium hydroxide, the use of pelletized sodium borohydride with formic acid as an alternative technique for methylation is currently being investigated.[32,33] However, if the rate-

limiting step for this procedure goes through attack of the aldehyde by the secondary amine, it is unlikely that the level of methylation will be improved.

A direct alkylation approach using iodomethane should generate the tertiary amine based on the greater reactivity of chain ends. The pitfall with this route is formation of internal quaternized amine sites. Conditions such as lower temperatures and less polar solvents might aid in limiting the amount of internal quaternization. However, this method is not desirable considering the limited selectivity of iodomethane in the chain end quaternizations.

Generating formamide chain ends followed by reduction is a two step approach that is a feasible but more tedious solution. Acid chlorides have been used to amidate chain ends successfully in this project as well as other research.[4] Formic acid chloride can be generated by reacting hexachloroacetone and triphenylphosphine at –78 °C.[22] However, formic acid chloride is unstable and must be generated at very low temperatures in situ.

Alternatively, formyl acetyl anhydride (a mixed anhydride) can be generated by mixing anhydrous formic acid and acetic anhydride.[34] The formyl group is more reactive than the acetyl group resulting in formation of the formamide derivative. This approach followed by reduction with $LiAlH_4$ should provide the completely methylated tertiary amine dendrimer.

EXPERIMENTAL

Materials. Dendrimers were purchased from DSM Fine Chemicals (Geleen, The Netherlands) or Aldrich and used as pure based on NMR spectra. All other starting materials and solvents were obtained from Aldrich and Fisher. Triethylamine was dried over 3Å molecular sieves for 24 h and freshly distilled. NMR solvents were purchased from Cambridge Isotope Laboratories and Aldrich. Reaction temperatures reported are the oil bath temperature with the flask submerged to the neck or the sealed ampoule completely submerged.

Spectra. ESI mass spectra were obtained on a PE/Sciex API-III Quadra 950 triple quadrupole biomolecular mass analyzer or a Perspective Biosystems Mariner Biospectrometry ESI-TOF Workstation equipped with a Harvard 2000 infusion syringe pump and Protana microspray apparatus at the Oklahoma University Health Sciences Center's NSF Laser Mass facility. Injected solutions were 50/50 H_2O:acetonitrile or 100% methanol acidified with 3% acetic acid. Calculated values were for the lowest isotopomers. NMR spectra were obtained on Varian 300, 400, and 600 MHz instruments at the Oklahoma Statewide Shared NMR Facility, Oklahoma State University, Stillwater, OK. ^{1}H NMR results are reported as H_{found}/H_{calcd} based on NMR integrations. The signals used for integral reference are denoted with an asterisk. Quantitative ^{13}C NMR were obtained with an acquisition time of 0.5 s and a delay of 1.0 s. Increasing the delay to 5 s did not affect the integral ratios. The 2-dimensional NMR (HMQC and COSY) experiments were typically conducted with spectral widths of 6 kHz for ^{1}H and 16 kHz for ^{13}C. Elemental analysis results are reported with C/N and C/I ratios since the hygroscopic nature of the dendrimer makes overall analyses less useful.

Purification of Ion Exchange Resins. A 50-mL sample of the Amberlite IRA-95 was purified and put into tertiary amine form in a column by the following consecutive elutions: 250 mL of water, 250 mL of methanol, 250 mL of water, 50 mL of 2 M NaOH, 500 mL of water, 250 mL methanol, and water until pH of the eluate and pH of the eluent (deionized water) were the same. The purified resin was stored in a glass bottle. Samples were rinsed with 5 bed volumes of water prior to use. By the same method, 50 mL of Amberlite IRA-402 was purified and put into chloride form replacing 2 M NaOH with 2 M HCl.

D8 (1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76-2.68 (t, 16/16H*), 2.52-2.34 (br, 36.4/36H), 1.64-1.5 (br, 24.7/24H), 1.46-1.18 (br, 19/20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.2, 52.4, 52.3, 51.9, 40.7, 31.0, 25.1, 24.6.

D32 (2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94-2.78 (br, 61.7/64H); 2.78-2.40 (br, 179.4/180H); 1.94-1.44 (br, 134.9/124H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.6, 52.4, 52.2, 51.9, 40.8, 30.9, 24.5, 24.4.

D64 (3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88-2.64 (br, 122/128H); 2.59-2.28 (br, 377/372H); 2.28-1.72 (br, 130/128H); 1.72-1.24 (br, 242/252H); ^{13}C NMR (75 MHz, $CDCl_3$) 52.5, 52.4, 52.2, 51.9, 49.5, 40.7, 30.7, 24.4, 16.9.

TAM D8 (4). To 1.32 g (1.71 mmol) of D8 (**1**), 6.45 g (126 mmol) of 88% formic acid and 3.33 g (42 mmol) of 37% formaldehyde were added. The solution was heated to 80 °C under N_2 for 24 h with stirring. Tetramethylammonium hydroxide pentahydrate was added to the solution to pH >14 followed by extraction into methylene chloride. After solvent removal under reduced pressure, 1.24 g (1.24 mmol, 72.5%) of an amber oil (**4**) was recovered. ^{1}H NMR (300 MHz, D_2O) δ 2.58-2.24 (br, 49.8/52H), 2.24-2.12 (s,

46.9/48H), 1.72-1.54 (br, 21.0/20H), 1.52-1.38 (br, 4/4H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.0, 57.9, 55.8, 52.4, 52.3, 52.0, 45.6, 42.3, 25.6, 25.3, 24.4. ESIMS for $C_{56}H_{128}N_{14}$ calcd $(M+H)^{+1}$ 998.1, $(M+2H)^{+2}$ 499.5, $(M+4H)^{+4}$ 250.3, found 997.7, 500.3, 250.1. Anal. Calcd for $C_{54}H_{124}N_{14}$: C, 66.9; H, 12.9; N, 20.2; C/N, 3.86, Found C, 62.9; H, 12.3; N, 17.1; C/N, 4.28.

TAM D32 (5). By the procedure of TAM D8 (**4**), 0.25 g (0.071 mmol) of D32(**2**), 1.08 g (20.6 mmol) of formic acid, and 0.8 g (9.9 mmol) of formaldehyde gave 0.24 g (0.054 mmol, 76%) of an amber oil (**5**). ^{1}H NMR (300 MHz, D_2O) δ 2.57-2.15 (br, 415/436H), 1.72-1.32 (br, 124/124H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.0, 57.9, 56.1, 55.9, 55.8, 53.4, 52.4, 52.2, 52.0, 45.6, 45.5, 42.3, 25.6, 25.4, 25.1, 24.8, 24.4. Anal. Calcd for $C_{238}H_{1530}N_{62}$: C, 67.1; H, 12.5; N, 20.4; C/N, 3.83. Found C, 63.1; H, 12.2; N, 17.7; C/N, 4.14.

TAM D64 (6). By the procedure of TAM D8 (**4**), 0.25g (0.035 mmol) of D64 (**3**), 0.36 g (6.88 mmol) of formic acid, and 0.8 g (9.9 mmol) of formaldehyde gave 0.23 g (0.027 mmol, 77.1%) of an amber oil (**6**). ^{1}H NMR (300 MHz, D_2O) δ 2.68-2.06 (889/884H); 1.78-1.25 (br, 252/252H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.9, 58.0, 57.9, 56.2, 55.9, 55.8, 53.4, 52.5, 52.1, 50.1, 45.6, 45.5, 42.3, 26.0, 25.6, 25.3, 25.1, 24.8, 24.4, 15.3. Anal. Calcd for $C_{484}H_{1096}N_{126}$: C, 63.0; H, 12.4; N, 24.6; I, 45.0; C/N, 3.85. Found: C, 64.5; H, 12.3; N, 18.5; C/N, 4.06.

EGM D8 (7). To 0.612 g (0.614 mmol) of TAM D8 (**4**(9)) in 10 mL of 80% aqueous methanol, 0.959 g (6.75 mmol) of iodomethane was added. The solution was transferred to a thick-walled ampoule frozen in liquid nitrogen and degassed, and the ampoule was sealed under vacuum. After warming to room temperature, the ampoule was heated to 50

°C for 24 h and then to 80 °C for an additional 24 h. After evaporation of water, methanol, and iodomethane, and drying under reduced pressure, 1.07 g (0.552 mmol, 89.9%) of a glassy, amber solid (**7**) was recovered. ^{1}H NMR (300 MHz, D_2O) δ 4.02-2.82 (br, 137/124H), 2.82-1.88 (br, 28/28H*). A concentrated solution of **7** was treated with Amberlite IRA-95 and the solvent was evaporated to give **7** containing no HI. ^{1}H NMR (300 MHz, D_2O) δ 3.68-2.86 (br), 2.74-2.06 (br) 2.06-1.44 (br); ^{13}C NMR (75 MHz, D_2O) δ 67.1, 65.0, 63.8, 63.1, 62.0, 56.5, 54.2, 52.0, 22.4, 20.3, 20.2. ESI-MS for $C_{64}H_{155}N_{14}I_8$ calcd $(M+CH_3I-8I)^{8+}$ 157.4, $(M-7I)^{7+}$ 177.7, $(M+3HI-8I)^{8+}$ 187.6, $(M+CH_3I-7I)^{7+}$ 198.0, $(M+2HI-7I)^{7+}$ 217.6, $(M-6I)^{6+}$ 228.5, Found 157.2, 177.3, 186.8, 199.7, 216.4, 228.4. Anal. Calcd for $C_{64}H_{155}N_{14}I_{11}$: C, 30.5; H, 6.2; N, 7.8; I, 55.5; C/N, 4.58; N/I, 1.27. Found C, 28.1; H, 6.5; N, 6.7; I, 55.1; C/N, 4.89; N/I, 1.10. After ion exchange with Amberlite IRA-402 and recovery,. $I^- < 0.2$.

EGM D32 (8). By the procedure of EGM D8 (**7**), 0.250 g (0.057 mmol) of TAM D32 (**5**(2)) in 10 mL of 80% aqueous methanol and 0.339 g (2.39 mmol) of iodomethane gave 0.46 g (0.051 mmol, 89.5%) of a glassy, amber solid **8**. ^{1}H NMR (300 MHz, D_2O) δ 4.08-2.64 (512/532H); 2.62-1.62 (124/124H*). After treatment with Amberlite IRA-95 as for **7**, HI-free **8** was recovered. ^{1}H NMR (300 MHz, D_2O) δ 3.74-2.98 (br), 2.82-2.18 (br) 2.18-1.94 (br) 1.82-1.64 (br); ^{13}C NMR (75 MHz, D_2O) δ 67.3, 65.8, 64.9, 63.7, 63.1, 61.8, 61.2, 56.3, 56.0, 55.2, 54.0, 51.9, 51.5, 43.8, 25.5, 22.8, 22.4, 20.2. Anal. Calcd for $C_{280}H_{730}N_{62}I_{42}$: C, 32.7; H, 7.1; N, 8.3; I, 51.8; C/N, 4.52; N/I, 1.44. Found C, 30.8; H, 7.5; N, 7.5; I, 53.3; C/N, 4.80; N/I, 1.47. After ion exchange with Amberlite IRA-402 and recovery, $I < 0.1$.

EGM D64 (9). By the procedure of EGM D8 (**7**), 0.100 g (0.011 mmol) of TAM D64 (**6**(1)) in 5 mL of 80% aqueous methanol and 0.131 g (0.924 mmol) of iodomethane gave 0.163 g (0.009 mmol, 81.8%) of a glassy, amber solid **9**. ^{1}H NMR (300 MHz, D_2O) δ 4.18-2.94 (b, 1190/1058H); 2.92-1.64 (252/252H*). After treatment with Amberlite IRA-95 as for **7**, HI-free **9** was recovered. ^{1}H NMR (300 MHz, D_2O) δ 3.80-2.96 (br), 2.84-2.14 (br) 2.14-1.88 (br) 1.80-1.66 (br); ^{13}C NMR (75 MHz, D_2O) δ 65.3, 62.1, 56.8, 54.7, 52.6, 21.5, 20.5. Anal. Calcd for $C_{280}H_{730}N_{62}I_{42}$: C, 33.1; H, 6.6; N, 8.5; I, 51.7; C/N, 4.51; N/I, 1.50. Found C, 27.5; H, 6.1; N, 6.5; I, 45.93; C/N, 4.49; N/I, 1.42. After ion exchange with Amberlite IRA-402 and recovery, I < 0.3.

PM D8 (11). To a solution of 0.18 g (0.23 mmol) of TAM D8 (**4**(1)) in 2 mL of 50% aqueous methanol, 166 μL (0.23 mmol) of 1,2,2,6,6-pentamethyl piperidine (PMP, **10**) was added. The mixture was transferred to a thick-walled, ampoule, and 346 μL (5.5 mmol) of methyl iodide was added. The mixture was degassed by 3 freeze-pump-thaw (in liquid nitrogen) cycles, and the ampoule sealed under vacuum, and annealed. After warming to room temperature, the ampoule was submerged in a 100 ^{0}C oil bath for 48 h. The ampoule cooled to room temperature, then was submerged in liquid nitrogen and opened. At 0 °C the product mixture was amber liquid and a light yellow precipitate. The liquid was pipetted away and the solid was washed 3 times with cold methanol. The solid was dried under vacuum for 24 h, dissolved in 2 mL of deionized water, and passed down a 2.5 x 25 cm column of Amberlite IRA-95 weakly basic anion exchange resin. After lyophilization of the eluate and drying under reduced pressure at 60 °C for 24 h, 0.67 g (0.20 mmol, 87.0%) of a glassy, amber solid (**11**) was recovered. ^{1}H NMR (400 MHz, D_2O) δ 3.80-3.42 (br, 52/54.5H), 3.30 (s, 12.7/12H) 3.27 (s, 6.9/6H) 3.34 (s,

71.8/72H), 2.6-2.47 (br, 24.4/24H), 2.26-2.15 (br, 4/4H*); ^{13}C NMR (100 MHz, D_2O) δ 65.0, 62.0, 56.4, 51.6, 51.5, 37.0, 22.3, 20.2. ESIMS for $C_{70}H_{170}N_{14}I_{14}$: calcd $(M-14I)^{14+}$ 86.2, $(M-13I)^{13+}$ 102.6, $(M-11I)^{+11}$ 144.3, $(M-CH_3I-10I)^{10+}$ 157.3, $(M-CH_3I-8I)^{8+}$ 228.3, $(M-7I)^{7+}$ 299.4, $(M-2CH_3I-6I)^{6+}$ 323.1, $(M-6I)^{6+}$ 370.4, $(M-CH_3I-5I)^{5+}$ 441.5, $(M-5I)^{5+}$ 469.9, $(M-CH_3I-4I)^{4+}$ 583.6, $(M-4I)^{4+}$ 619.1, $(M-CH_3I-3I)^{3+}$ 820.5, $(M-3I)^{3+}$ 867.8, $(M-2I)^{2+}$ 1365.1, found 86.0, 102.1, 144.5, 156.9, 227.9, 299.1, 323.2, 370.1, 441.4, 469.8, 583.6, 619.0, 820.4, 867.8, 1365.2. Anal. Calcd for $C_{70}H_{170}N_{14}I_{14}$: C, 28.2; H, 5.7; N, 6.6; I, 59.5; C/N, 4.98; N/I, 1.00. Found C, 27.9; H, 6.0; N, 6.2; I, 60.5. C/N, 5.25; N/I, 0.93. A solution of **11** was treated with Amberlite IRA-402, and the solvent was evaporated to give **11b**. I < 0.1.

PM D32 (12). By the procedure of PM D8 (**11**), 0.11 g (0.026 mmol) of TAM D32 (**5**(3)) in 5 mL of 50% aqueous methanol, 0.048 g (0.31 mmol) of PMP (**10**) and 0.47 g (3.0 mmol) of iodomethane at 110 ^{0}C for 72 h gave 0.30 g (0.022 mmol, 84.6%) of a glassy, amber solid (**12**). ^{1}H NMR (400 MHz, D_2O) δ 3.96-3.16 (b, 653/622H), 2.66-2.32 (br, 124/124H*); ^{13}C NMR (100 MHz, D_2O) δ 67.0 64.6, 61.5, 56.5, 56.0, 51.8, 22.6, 20.2. Anal. Calcd for $C_{310}H_{746}N_{62}I_{62}$: C, 28.2; H, 5.7; N, 6.6; I, 59.6, C/N, 5.00; N/I, 1.00. Found C, 26.7; H, 6.2; N, 6.4; I, 53.6; C/N, 4.87; N/I, 1.08. A solution of **12** was treated with Amberlite IRA-402, and the solvent was evaporated to give **12b**. Anal. Calcd for $C_{310}H_{746}N_{62}Cl_{62}$: C, 49.4; H, 10.0; N, 11.5; Cl, 29.1; I, 0; C/N, 5.00; N/Cl, 1.00. found C, 38.7; H, 10.1; N, 9.1; Cl, 19.8; I<0.1; C/N, 5.0; N/Cl, 1.16.

PM D64 (13). By the procedure of PM D8 (**11**), 0.300 g (0.035 mmol) of TAM D64 (**6**(1)) in 10 mL of 50% aqueous methanol, 127 μL (0.7 mmol) of PMP, and 0.5 mL (8.2 mmol) of iodomethane at 110 ^{0}C for 72 h gave 0.752 g (0.021 mmol, 82.9%) of a glassy,

amber solid **13**. ^{1}H NMR (400 MHz, D_2O) δ 4.04-3.28 (s, 1376/1262H); 2.72-2.44 (br, 252/252H*); ^{13}C NMR (100 MHz, D_2O) δ 62.6, 59.5, 54.4, 49.8, 18.1. Anal. Calcd for $C_{630}H_{1514}N_{126}I_{126}$: C,28.2; H, 5.7; N, 6.6; I, 59.6; C/N, 4.98; N/I, 1.00. Found C, 26.1; H, 5.8; N, 6.0; I, 56.7; C/N, 5.07; N/I, 0.95. A solution of **13** was treated with Amberlite IRA-402, and the solvent was evaporated to give **13b**. I < 0.07.

D8-C(O)-MPEG$_{164}$ (16). To 1.0 g (1.2 mmol) of D8 (**1**) in 5 mL of anhydrous DMF, 900 mg (8.8 mmol) of triethylamine and 3.0 g (15.3 mmol) of MPEG$_{164}$-COCl were added at 0 °C. The solution was stirred under nitrogen at 70 °C for 24 h. Excess MPEG$_{164}$-COCl was hydrolyzed using 5 mL of water. The resulting solution was rendered basic using 5 g (27 mmol) of tetramethylammonium hydroxide pentahydrate. The basic solution (pH~14) was extracted with three 10-mL portions of dichloromethane. The combined dichloromethane solution was evaporated under reduced pressure, and 1.77 g (0.86 mmol, 72.1%) of a light yellow oil was recovered. ^{1}H NMR (300 MHz, D_2O) δ 4.08 (s, 16/13.2H), 3.86-3.55 (m, 62.5/64H), 3.4 (s, 24.4/24H), 3.22-3.33 (t, 17.4/16H), 2.63-2.37 (b, 33.8/36H), 1.92-1.38 (b, 28/28H*). ^{13}C NMR (100 MHz, D_2O) δ 73.8, 73.2, 72.4, 60.9, 55.8, 54.0, 53.9, 53.3, 40.1, 28.0, 26.1, 24.5. ESIMS for $C_{96}H_{192}N_{14}O_{32}$: calcd $(M+H)^{1+}$ 2054.4, $(M+2H)^{2+}$ 1027.7, $(M+3H)^{3+}$ 685.5, $(M+4H)^{4+}$ 514.4, found 2055.1, 1027.9, 685.6, 514.1. Anal. Calcd for: $C_{96}H_{192}N_{14}O_{32}$: C, 56.12; H, 9.42; N, 9.54; O, 24.92; C/N, 6.86. Found: C, 49.8; H, 9.0, N, 7.9; C/N, 7.35.

D32-C(O)-MPEG$_{164}$ (17). By the procedure of D8-C(O)-MPEG$_{164}$ (**16**) 1.0 g (0.28 mmol) of D32 (**2**) in 10 mL of DMF, 0.9 g (8.8 mmol) of triethylamine, and 3.2 g (16.3 mmol) of MPEG$_{164}$-COCl gave 1.73 g (0.20 mmol, 71.4%) of a light yellow oil (**17**). ^{1}H NMR (300 MHz, D_2O) δ 4.07 (s, 58.3/64H), 3.86-3.55 (m, 259/256H), 3.4 (s, 99.9/96H),

3.22-3.33 (t, 68.7/64H), 2.63-2.37 (b, 176/180H), 1.92-1.38 (b, 124/124H*); ^{13}C NMR (100 MHz, D_2O) 73.8, 73.1, 72.3, 60.9, 54.0, 53.7, 53.2, 40.0, 27.9, 24.4. ESIMS for $C_{408}H_{816}N_{62}O_{128}$: calcd $(M+6H)^{6+}$ 1440.0, $(M+7H)^{7+}$ 1234.4, $(M+8H)^{8+}$ 1080.3, $(M+9H)^{9+}$ 960.3, $(M+10H)^{10+}$ 864.4, $(M+11H)^{11+}$ 785.9, found 1440.6, 1235.1, 1081.4, 961.2, 865.1, 786.3. Anal. Calcd for $C_{408}H_{816}N_{62}O_{128}$: C, 56.7; H, 9.52; N, 10.05; O, 23.71; C/N, 6.55. Found C, 53.38; H, 9.61; N, 9.48; C/N, 6.57.

IM D8-C(O)-MPEG$_{164}$ (18). To 0.200 g (0.097 mmol) of D8-C(O)-MPEG$_{164}$ (**16**) in 10 mL of 50% aqueous methanol, 0.134 g (0.97 mmol) of iodomethane was added. The solution was transferred to a thick-walled ampoule, degassed, and the ampoule sealed under vacuum and annealed. The solution was heated at 90 °C for 48 h. Solvent was removed under reduced pressure, yielding 0.258 g (0.89 mmol, 91.9%) of an amber oil (**18**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14-4.02 (t, 14.4/16H); 4.00-3.20 (156/158H); 2.62-2.08 (b, 28.3/28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.4, 77.3, 77.1, 76.8, 71.8, 71.0, 70.4, 70.3, 70.2, 62.2, 60.6, 59.1, 49.5, 35.8, 23.1, 19.5, 18.5. Anal. Calcd for $C_{102}H_{210}N_{14}I_6O_{32}$: C, 42.2; H, 7.3; N, 6.8; I, 26.2; O, 17.6; C/N, 7.24 N/I, 2.35. Found C, 38.4; H, 7.3; N, 6.5; I, 25.1; C/N, 6.90; N/I, 2.34. A solution of **18** was treated with Amberlite IRA-402, and the solvent was evaporated to give **18b**. I < 0.03.

IM D32-C(O)-MPEG$_{164}$ (19). By the procedure of IM D8-C(O)-MPEG$_{164}$ (**18**), 0.100 g (0.012 mmol) of D32-C(O)-MPEG$_{164}$ (**17**) in 10 mL of 50% aqueous methanol and 0.085 g (0.60 mmol) of iodomethane gave 0.142 g (0.011, 91.7 mmol) of an amber oil (**19**). ^{1}H NMR (300 MHz, D_2O) δ 4.12-4.02 (b, 64.3/64H); 3.86-2.98 (b, 726/686H); 2.64-1.94 (b, 124/124H*); ^{13}C NMR (75 MHz, D_2O) δ 73.8, 73.2, 72.5, 72.4, 72.4, 72.3, 62.7, 62.3, 61.4, 61.0, 60.9, 51.6, 51.3, 38.6, 25.1, 20.3, 19.9. Anal. Calcd. For

$C_{408}H_{816}N_{62}O_{128}$: C, 40.8; H, 7.1; N, 6.7;I, 29.5; O, 15.9; C/N: 7.10, N/I: 2.06. Found: C, 39.37; H, 8.18; N, 6.57; I, 29.98; C/N: 6.99; N/I: 2.01. A solution of **11** was treated with Amberlite IRA-402, and the solvent was evaporated to give **11b**. $I < 0.2$.

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CHAPTER 3

CATALYTIC ACTIVITY OF QUATERNIZED POLY (PROPYLENE IMINE) DENDRIMERS

ABSTRACT

Dendrimer unimolecular micelles have served as the catalytic media for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate (NBC, **23**) by providing a lipophilic environment into which NBC can partition from the aqueous phase.[1,2] Poly(propylene imine) dendrimers (PPIs) quaternized at the chain ends only (**7-9**), at chain ends and branch points (**11-13**) and at the branch points only (**18-19**) were converted from iodide to chloride counterion form using Amberlite IRA-402 chloride exchange resin. These quaternary ammonium chloride dendrimers catalyzed the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate at 25 °C and pH 11.5. The observed rate increase was 1.5 - 4.5 times the rate in water alone. The hydrophilicity of methylated dendrimers compared to other known catalysts resulted in lower intrinsic rate constants and binding constants compared to other known catalysts.

INTRODUCTION

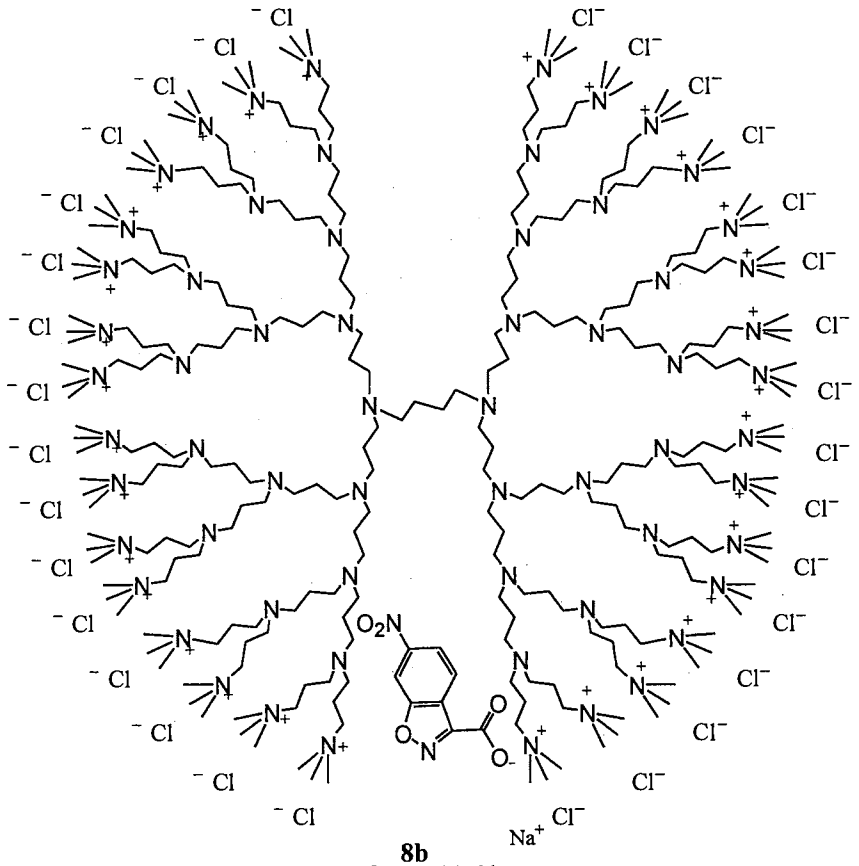
The importance of organic reactions in aqueous media is exhibited throughout nature. These aqueous phase reactions are catalyzed by enzymes in living organisms in a variety of metabolic functions (gluconeogenesis, fatty acid synthesis, citric acid cycle, etc.).[3] Hydrophobic and electrostatic interactions between the organic compound (substrate) and the host are the driving forces for binding of the substrate.[4] Enzyme catalysis requires binding substrate and turnover. Synthetic catalysts (micelles, latexes, dendrimers, etc.) model enzyme behavior as they require binding and intrinsic reactivity. These catalysts provide hydrophobic environments within the aqueous solution.

The use of these catalysts enhances reaction rates in aqueous solutions by concentrating the substrate (organic compound) inside the hydrophobic areas of the catalysts. The hydrophobic environment serves as an organic "pseudo-phase" The kinetics of these catalyzed reactions are described by a surfactant micelle kinetic model.[5] Increased reaction rates observed due to transfer of an organic compound from an aqueous solution into a catalyst has been termed pseudo-phase transfer catalysis.[6] Sites for binding the molecule into the organic pseudo-phase further enhance the function of the catalyst.

Quaternary ammonium functionalities have been widely used in phase and pseudo-phase transfer catalysis to bind anionic substrates by ion exchange.[7] For example, the quaternary ammonium chloride dendrimer **8b** electrostatically attracts 6-nitrobenzisoxazole-3-carboxylate and exchanges a chloride ion for carboxylate (Figure 1). The counterion must not be bound tightly by the quaternary ammonium group or ion

exchange will be inhibited. For this reason, iodide is usually avoided as the counterion for pseudo-phase approaches. The selectivity of the quaternary ammonium site for the substrate is further enhanced by hydrophobic regions within the catalyst structure.

Incorporating quaternary ammonium sites into the structure of an organic polymer or micelle catalyzes the reaction by removing it from a hydrogen-bonding aqueous environment in which the reaction is slow and hosting it inside the polymer or micelle.



8b
EGM D32 Cl

Figure 1: Binding of 6-nitrobenzisoxazole-3-carboxylate to a quaternary ammonium chloride ended PPI dendrimer.

Among the best known "pseudo-phase" catalysts are micelles, polymer latexes, and dendrimers. Micelles are dynamic systems formed by the aggregation of surfactant molecules. The nonpolar tails of surfactant molecules orient to form a hydrophobic core and the polar heads locate at the surface to provide water solubility. However, micelle formation is ionic strength and temperature dependent and micelles dissociate at concentrations below the critical micellar concentration.[7]

Polymer latexes are discrete, colloidal particles that require interparticle charge repulsion to remain dispersed in solution. Latexes have no CMC and consequently bind anions at very low particle concentrations. Although polymer latexes have demonstrated some of the highest activities among catalysts used in these reactions, the location of catalytic sites within the structure is not well-defined.[8,9]

Pseudo-phase transfer catalysis can take place on the surface of the catalyst, at the core or interior, or both. The specific structural location where pseudo-phase transfer catalysis occurs has not been determined. [8] Latexes and other polymeric media cannot be selectively alkylated to have site specific charge. Charge location effects in pseudo-phase transfer catalysis have not been thoroughly examined. The effect of charge location could be studied using dendrimers, as they are synthetically designed to be perfect structures. The hydrophobic and hydrophilic nature of the dendrimer catalyst can be selectively modified to change activity. These dendrimers can function as single entities to solvate small molecules (as unimolecular micelles).

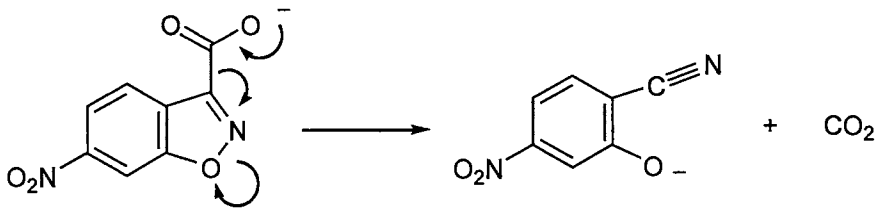
A unimolecular micelle is a water-soluble molecule that contains both hydrophobic and hydrophilic regions. The hydrophobic regions allow the molecule to solublize organic compounds in aqueous solutions. Unimolecular micelles are stable irrespective

of concentration, ionic strength, and temperature of the solution since they are constructed with covalent bonds.[10] Solubility of the unimolecular micelle is determined by the functionalities. Unlike polymer latexes, unimolecular micelles are designed to be soluble in water and do not require charge stabilization to form dispersions. Based on their continued function in dilute solutions and increased stability, unimolecular micelles have better characteristics for these reactions than dynamic systems such as micelles. Dendrimers have well-defined structure that can be easily modified to function as unimolecular micelles.

Dendrimers as unimolecular micelles were first proposed by Newkome in 1991.[11] Dendrimers with hydrophobic end groups have been prepared as inverted unimolecular micelles.[12] Dendrimers with hydrophilic and hydrophobic chain ends (**25**) have solvated one molecule of pyrene/dendrimer and were active decarboxylation catalysts.[13]

The decarboxylation of 6-nitrobenzisoxazole-3-carboxylate (**23**) has been used previously to evaluate the activity of latex and dendrimer catalysts. The mechanism for decarboxylation of **23** is given in Scheme 1. Although this substrate is water soluble, decarboxylation occurs slowly in the aqueous phase due to hydrogen bonding.

Scheme 1: Mechanism for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate.



23 **24**

PPI dendrimers were selectively methylated to study the structural location effects of quaternary ammonium groups on catalytic activity. Through alkylation and amidation, quaternization was accomplished selectively at chain ends and/or branch points. These dendrimers in chloride form were analyzed for activity in the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate.

RESULTS

PPI dendrimers were selectively quaternized with iodomethane as described in Chapter 2. The iodide counterions were anion exchanged for chloride using an Amberlite® resin. Ion exchanged dendrimers contained less than 0.3% iodide by elemental analysis. Unbuffered solutions of these dendrimers at pH 11.5 were used to catalyze the decarboxylation of **23**. The reaction was monitored by UV based on the absorbance of the 2-cyano-5-nitrophenoxide ion (**24**) at 400 nm.

Observed rate constants for the decarboxylation reactions with selectively quaternized PPI dendrimers are reported in Table 1. Selectively quaternized dendrimers increased the rate of decarboxylation by a factor of 4 at best. Increasing the concentration of the dendrimer quaternary ammonium sites from 2.4 mM to 24 mM approximately doubled the rates as illustrated in Figure 2. Dendrimer **25**, having 32 end groups with octyl and $MPEG_{164}$ at every chain end, under the same conditions catalyzed the reaction 44 times faster than the best methylated PPI dendrimers. However, the rate obtained was 5 times less than that obtained by Pan with **25** under similar conditions.[2] The lower rate constants obtained for **25** in my experiments may be due to my reactions being at different dendrimer concentrations or temperatures. Additionally, the exact identity of

the sample was not confirmed. Only a few milligrams were available for the kinetic analysis.

Table 1. Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylate with Selectively Quaternized PPI Dendrimers.[a]

Dendrimer	10^3 [N^+] (M)[b]	$10^5 k_{obsd}$ (s^{-1})	k_{obsd}/k_w[c]
EGM D8 Cl (**7b**)	2.4	0.61	1.97
EGM D8 Cl (**7b**)	24	1.41	4.52
EGM D32 Cl (**8b**)	2.4	1.03	3.32
EGM D32 Cl (**8b**)	24	1.87	6.03
EGM D64 Cl (**9b**)	2.4	0.56	1.81
EGM D64 Cl (**9b**)	24	0.74	2.40
PM D8 Cl (**11b**)	2.4	0.46	1.48
PM D8 Cl (**11b**)	24	1.41	4.52
PM D32 Cl (**12b**)	0.24	0.53	1.71
PM D32 Cl (**12b**)	0.7	0.71	2.29
PM D32 Cl (**12b**)	2.4	1.36	4.39
PM D32 Cl (**12b**)	7.0	2.05	6.61
PM D32 Cl (**12b**)	10.0	2.15	6.94
PM D32 Cl (**12b**)	17	2.37	7.65
PM D32 Cl (**12b**)	24	2.58	8.32
PM D64 Cl (**13b**)	2.4	0.70	2.26
PM D64 Cl (**13b**)	24	2.41	7.77
IM D8 Cl-C(O)-$MPEG_{164}$ (**18b**)	2.4	0.60	1.94
IM D8 Cl-C(O)-$MPEG_{164}$ (**18b**)	24	0.79	2.55
IM D32 Cl-C(O)-$MPEG_{164}$ (**19b**)	2.4	0.79	2.55
IM D32 Cl-C(O)-$MPEG_{164}$ (**19b**)	24	1.73	5.58
PM PO 32 Cl (**25**)	2.4	27.3	88.1
PMPO 32 Cl (**25**)[d]	2.4	151	487

[a] Data were obtained from aqueous solutions of quaternary ammonium chloride dendrimers at pH = 11.5 and 25 °C. Experiments at 2.4 x 10^{-3} M [N^+] were conducted in duplicate or triplicate and differed by ≤ 7%. Maximum absorbance (λ_{max}) of 2-cyano-5-nitrophenoxide was at 398-400 nm.

[b] [6-nitrobenzisoxazole-3-carboxylate] = 7.82 x 10^{-5} M = $[S]_t$

[c] k_w was 3.1 x 10^{-6} s^{-1}

[d] reported by Pan (Ref 2)

Because of the low activity of quaternized materials, the tertiary amine precursors were evaluated as well (Table 2). Although the polyamine dendrimers are more hydrophobic than their quaternary ammonium counterparts, the lack of quaternary ammonium sites to bind the carboxylate ion prevented these dendrimers from changing the rate significantly.

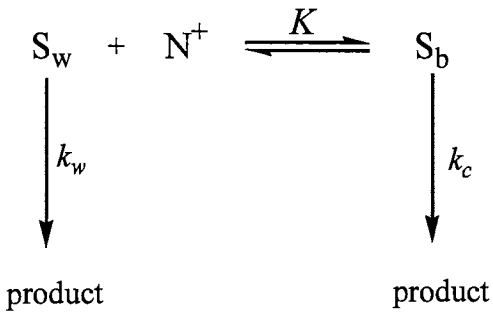
Table 2. Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylate with Tertiary Amine PPI Dendrimers.[a]

Dendrimer	$10^4 k_{obsd}$ (s^{-1})	k_{obsd}/k_w
TAM D8 (**4**)	0.080	2.58
TAM D32 (**5**)	0.061	1.97
TAM D64 (**6**)	0.127	4.10
D8-C(O)-$MPEG_{164}$ (**16**)	0.036	1.16
D32-C(O)-$MPEG_{164}$ (**17**)	0.062	2.00

[a] Conditions were the same as in the footnotes of Table 1. Concentration of amine nitrogen was 2.4×10^{-3}M. All experiments were duplicated and differed by $\leq 7\%$.

From the single site binding model in Scheme 2, which is based on the Menger-Portnoy kinetic model for catalysis by surfactant micelles,[5] the substrate was assumed to distribute between the dendrimer pseudophase and the aqueous phase. Substrate binding was assumed to be reversible. $[S]_w$ represents the substrate concentration in the aqueous phase, $[S]_b$ represents substrate bound in the dendrimer pseudo-phase, and $[N^+]$ is the total concentration of quaternary ammonium sites in solution. The observed rate constant depends on the aqueous phase (k_w) and intrinsic (k_c) rate constants and on the fraction of

Scheme 2: Surfactant micelle kinetic model.



substrate bound to dendrimer ($[S]_b/[S]_t$) as illustrated by Scheme 2 and equation 1. K is the binding constant (eq. 2) and the dependence of k_{obsd} on the concentration of quaternary ammonium sites $[N^+]$ is given by equation 3. The intrinsic rate constants in the dendrimer pseudo-phase (k_c) and binding constants (K) for decarboxylation with **12b** were calculated using a regression analysis and equation 3. Values for k_c and K obtained from a typical non-linear plot (Figure 3) are given in Table 3.

$$k_{obsd} = k_w[S]_w/[S]_t + k_c[S]_b/[S]_t \qquad (1)$$

$$K = [S]_b/([S]_w[N^+]) \qquad (2)$$

$$k_{obsd} = (k_w/K + k_c[N^+])/(1/K + [N^+]) \qquad (3)$$

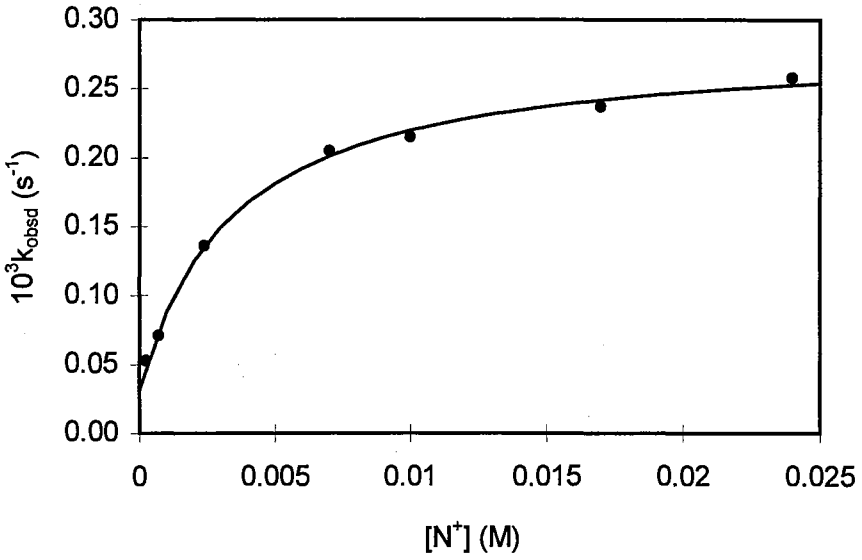


Figure 2: Pseudo-first order rate constants for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid (7.82 x 10^{-5} M) as a function of [N^+] of **12b** at 25 °C. The non-linear plot was used to determine K and k_c using equation 3.

Table 3. Binding Constant and Intrinsic Rate Constants for the Decarboxylation of 23.[a]

Dendrimer	$10^3\,k_c$ (s^{-1})[b]	k_c/k_w	K (M^{-1})
PM D32 (**12b**)	0.028	9.3	291
PMPO 32 Cl (**25**)	1.75	564	2442
PE-TMA 36 (**26**)	0.080	25	1700

[a] conditions were the same as reported in Table 1
[b] k_c is the intrinsic rate constant

DISCUSSION

In the quaternized PPI series presented in Table 1, dendrimers with 32 chain ends resulted in the highest rates. The increase in activity from 8 to 32 chain ends must be a result of the larger more globular dendrimers ability to contain substrate inside the

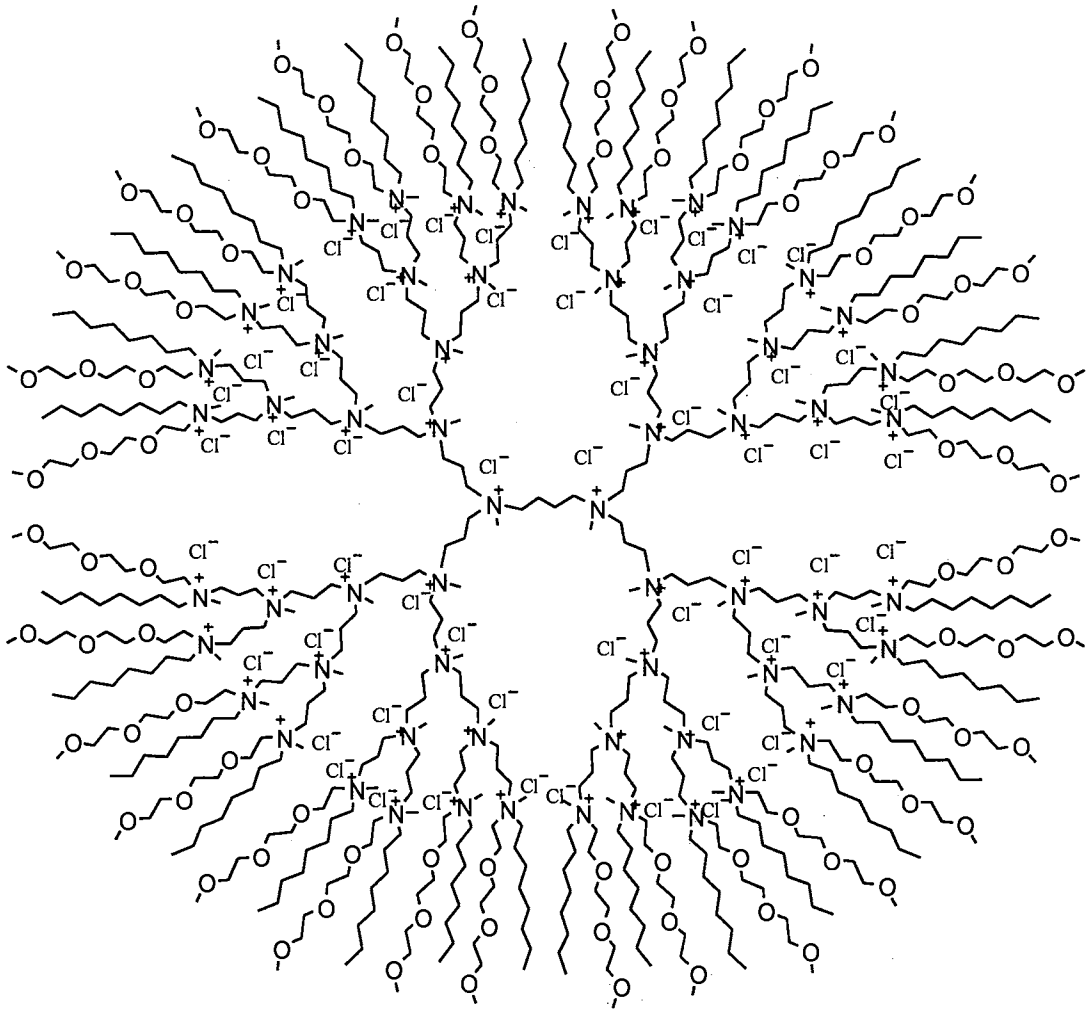
dendrimer pseudophase where it is somewhat less hydrated than when bound to the open structure, 8 chain end materials. Previous dendrimer catalysts have shown a similar trend.[1,2]

In decarboxylations reported previously, the activity of larger dendrimers was not assessed. In general, we would expect size increases to increase the rate until steric effects begin to limit the diffusion into the dendrimer. Larger unimolecular micelles should have more hydrophobic environments as well as a greater internal free volume to enhance their hosting capabilities. The decrease in rate at 64 chain ends may be a result of a sterically hindered ionic surface inhibiting binding in the dendrimer pseudophase. D64 has less volume per quaternary ammonium site than D32. Therefore, D64 quaternized analogs would be more highly ionic and more hydrated than D32 quaternized analogs.

Table 3 demonstrates that both the intrinsic rate constants k_c and binding constants K are much lower for the hydrophilic permethylated dendrimer **12b** than for **25** and **26**. The small value of k_c indicates that the substrate is still strongly stabilized by hydrogen bonding in **12b**. In contrast, PM PO 32 Cl (**25**) and PE-TMA36 (**26**) have more hydrophobic character than **12b** and therefore are able to increase the rate constant k_c due to reduced hydrogen bonding.

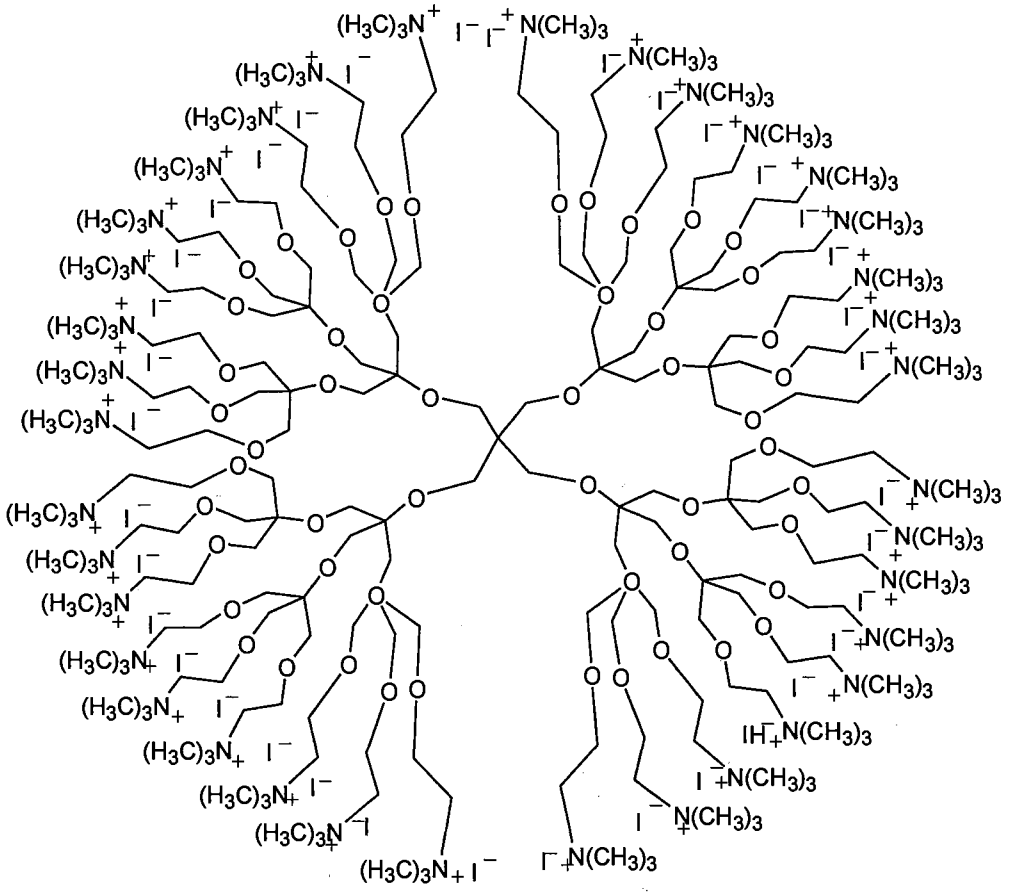
The decreased binding efficiency (K) of **12b** must also be attributed to the lack of hydrophobic groups. Binding still occurs due to the quaternary ammonium groups' attraction of the substrate for ion exchange; however, the dendrimer is highly hydrated decreasing substrate preference for the dendrimer pseudophase. The equilibrium for ion exchange in this case does not significantly favor the carboxylate ion, therefore the

binding constant is reduced. The hydrophobic character of **25** probably increases the size of the binding constant by favoring the carboxylate ion over chloride. The increased binding efficiency of **26** over the selectively methylated dendrimers is somewhat surprising since its counterions were iodide which would be more tightly



25
PMPO 32 Cl

Figure 3: Hybrid armed dendrimer with triethyleneoxy methyl ether and octyl arms at the chain ends.



26
PE-TMA 36

Figure 4: Dendrimer with pentaerythritol type branches quaternized at the end groups only.

bound than the chlorides of the methylated series. However, this further illustrates the effects of hydrophobicity on ion preference and equilibrium between the bound and unbound substrate.

Conclusions. The methylated dendrimer catalysts caused only small increases in the rate of decarboxylation. The low intrinsic rate constants and binding efficiencies were due to the hydrophilic nature of these dendrimers. Polymer latexes of varying alkyl character have been extensively tested in pseudo-phase transfer catalysis. Rates of

decarboxylation of **23** increase with increasing hydrophobic character of the latex [9,15] Increased hydrophobicity in dendrimer catalysts has also led to increased rate constants.[1,2] Dendrimers quaternized at only a few chain ends (such as 8 of 32 ends) might increase activity. Additionally, more lipophilic alkylating agents could be used in the quaternizations.

FUTURE WORK

Two goals are evident for future experiments: preparation of more effective catalysts and preparation of catalysts to demonstrate the effect of charge location on catalysis. Based on the results obtained in this research and comparison to those reported in the literature, it is apparent that effective catalysts tend to be less hydrophilic than the methylated PPI dendrimers. The low activity of methylated dendrimers and the low selectivity in the chain end quaternizations prevents analogies between charge location and relative activities. At this point, the following future work to develop better catalysts and to determine the effect of charge location on pseudo-phase transfer catalysis is proposed.

Developing better dendrimer catalysts for aqueous solutions. The most apparent approach would be to use longer chain alkyl groups. Attempts to prepare benzylated and butylated dendrimers from tertiary amine precursors were made in this research project. Based on integration of ^{13}C NMR signals the highest conversion sample for benzylation contained 7 benzyl groups (of 14 possible). Butylation yielded only 4 of 14 possible butylated sites. Completion of these alkylations in aprotic solvents (i.e. DMF) would lead to dendrimers that should have better activity. However, the most effective samples

will probably contain large water-soluble chains (such as the MPEG chains) and long alkyl chains rather than simple alkylations in which water solubility is inhibited at much shorter chains.

Using the technique developed by Pan, dendrimers with longer MPEG chains can be prepared. The longer MPEG chains maintain water solubility of the catalyst allowing the introduction of longer alkyl chains. Longer alkyl chains should produce a more hydrophobic dendrimer interior. Successive amidation and reduction with a variety of longer alkyl and MPEG chain ends would enable the determination of a maximum in activity for this type of PPI dendrimer. However, these long chains increase steric hindrance and reduce the internal free volume of the dendrimer. Therefore, at some chain length a maximum in rate should be observed. In addition to long chain alkyl groups, the addition of cyclic and aromatic groups may produce interesting kinetic results. Alkyl groups to be used in place of octyl in structure **25** that should change activity of the catalyst are dodecanyl, decanyl, 2-methyl-butyl, and benzyl.

Preparing selectively alkylated dendrimers. Determining the effect of charge location on catalysis is still a problem that requires further research. The low activities of the methylated dendrimers prevented the results from being useful in this determination. A significant increase in activity has been observed in catalysts that contain hydrophobic moieties;[1,2] therefore, modifications must contain more hydrophobic groups. The dendrimers in Figure 5 are proposed as similar catalysts that may answer the charge location question. Alternatively, ethylation or propylation could be considered if butylations prove too difficult.

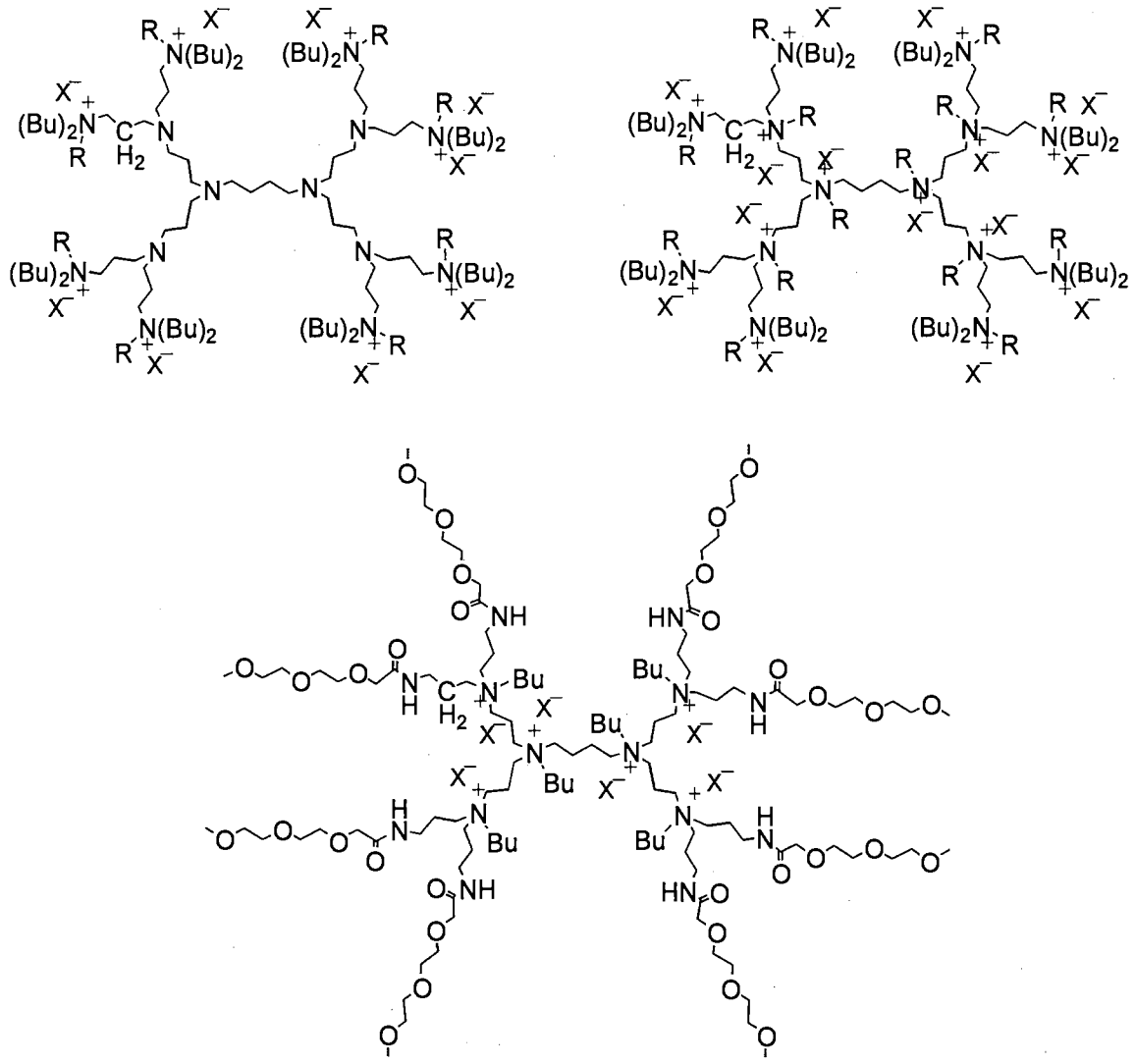


Figure 5: Proposed butylations of PPI dendrimer D8. These compounds should demonstrate the effect of charge location on catalysis. Bu = butyl, X = I or Cl, R = methyl or ethyl.

Chain end quaternization only has been reported to occur with alkyl chains of 3 carbons or greater.[14] In a sealed reaction at high temperature for several days reaction of the TAM D8 (**4**) with stoichiometric iodobutane and PMP gave chain ends with only 4 butyls; therefore, direct butylation of the primary chain ends to tributyl quaternary ammonium sites would be difficult. However, butyl groups could be added by amidation

of primary amine chain ends with butyryl chloride followed by reduction with $LiAlH_4$. The dibutyl amine chain ends could be methylated with stoichiometric iodomethane to yield methyl dibutyl ammonium iodide chain ends. However, selectivity of the methylation is likely to be low. The best approach may be to use 2-chloroethylisocyanate and quaternize with an amine (dibutylmethylamine) to give a specifically chain end quaternized dendrimer.

Perbutylated PPI dendrimers prepared from iodobutane will probably not be possible. However, a near approximation can be obtained by reacting butyryl chloride with primary amine chain ends followed by reduction. Repeating the amidation/reduction yields a tertiary amine that can be quaternized with methyl or ethyl iodide as shown in Figure 5.

Internal butylation might be accomplished from the MPEG amide terminated dendrimers described in chapter 2 (**16-17**). In a sealed reaction, reaction of iodobutane at high temperature in a polar aprotic solvent (DMF) should provide the internally butylated dendrimer. Use of the more reactive reagents may be required if iodobutane reactions do not go to completion.

In summary, the number of modifications of PPI dendrimers that can be proposed is very large. Preparing optimum catalysts and understanding how catalytic activity can be enhanced is very important. Based on what is currently know about these types of catalysts and especially dendrimer catalysts, the best approach to better catalyst is to utilize hydrophilic chains for solubility and hydrophobic chains for preparation of the organic pseudo-phase. Direct alkylations with long chain hydrocarbons will probably

result in water insoluble dendrimers before rate enhancements are observed that are comparable to those of hydrophilic/hydrophobic chain ended dendrimers.

EXPERIMENTAL

Materials. PPI dendrimers were purchased from Aldrich and modified as described in Chapter 2 of this thesis. Amberlite IRA 95 and 402 were obtained from Sigma. Methyl 6-nitro-1,2-benzisoxazole-3-carboxylate was obtained from Pfaltz and Bauer, Inc and was prepared as described by Lee.[15] All other chemicals were obtained from Fisher.

Preparation of Samples for Decarboxylation Kinetics. Standard aqueous solutions of the various quaternary ammonium chloride and tertiary amine dendrimers were prepared using deionized water. Samples were prepared in cuvettes by adding standard dendrimer solutions to 2 mM NaOH to give 2.98 mL of the various N^+ concentrations at pH 11.5. Solutions were allowed to equilibrate in the spectrometer at 25.0 ± 0.2 °C for 20 min. Temperature was maintained by a circulating cooling/heating water bath. The substrate, **23** in an ethanol solution (22 μL of 1.06 x 10^{-2} M), was added to give a 3 mL solution that was 7.82 x 10^{-5} M in **23**.

Kinetic Measurements. All UV-vis spectra were measured from 200-800 nm and kinetic time traces were measured as the averaged absorbance from 390-410 nm, using a Hewlett-Packard model 8452A diode array spectrophotometer, in 1.00 cm polystyrene cells. The kinetic software used for observed rate measurement was the HP 89532A UV/Vis software package. Infinite absorbance values were determined by the experimenter. Reactions were followed by the average absorbance at 390-410 nm, since λ_{max} of the 2-cyano-5-nitrophenoxide in the dendrimer solutions was at ~400 nm. The

rate constants were calculated from data over the first 7% conversion (5000 s) using the first-order kinetic equation: $k_{obsd} = \ln[(A_{inf} - A_o)/(A_{inf} - A_t)]/t$, where *t* represents the time of reaction, and A_o, A_t, and A_{inf} represent the absorbance of 2-cyano-5-nitrophenoxide at time 0, *t*, and infinity, respectively. All experiments were conducted in duplicate or triplicate and averaged. Duplicate experiments agreed to ± 7 %.

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APPENDIX

Figure 1. 400MHz ^{1}H NMR spectrum of D8 (**1**) in $CDCl_3$

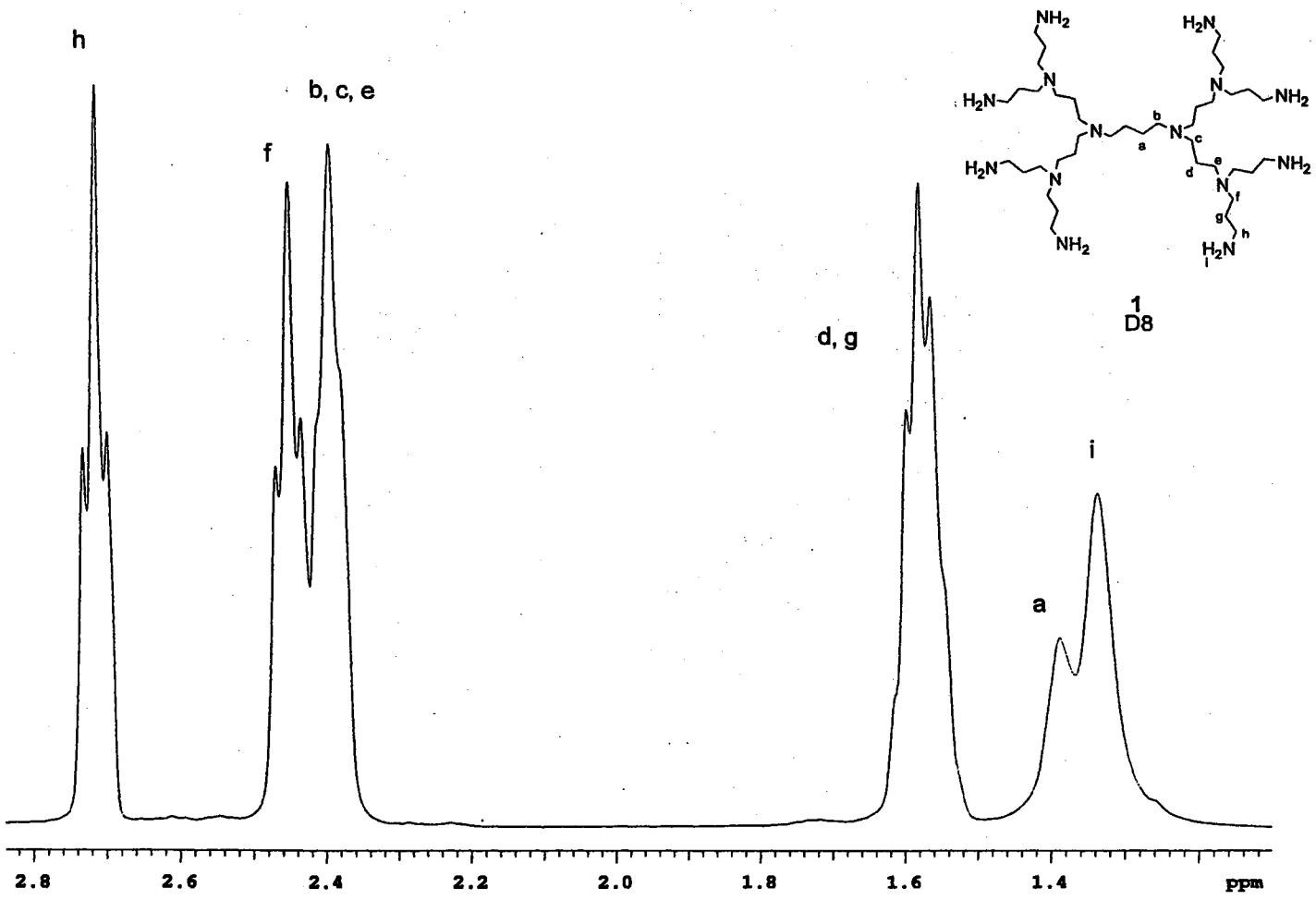


Figure 2. 100MHz ^{13}C NMR spectrum of D8 (1) in $CDCl_3$

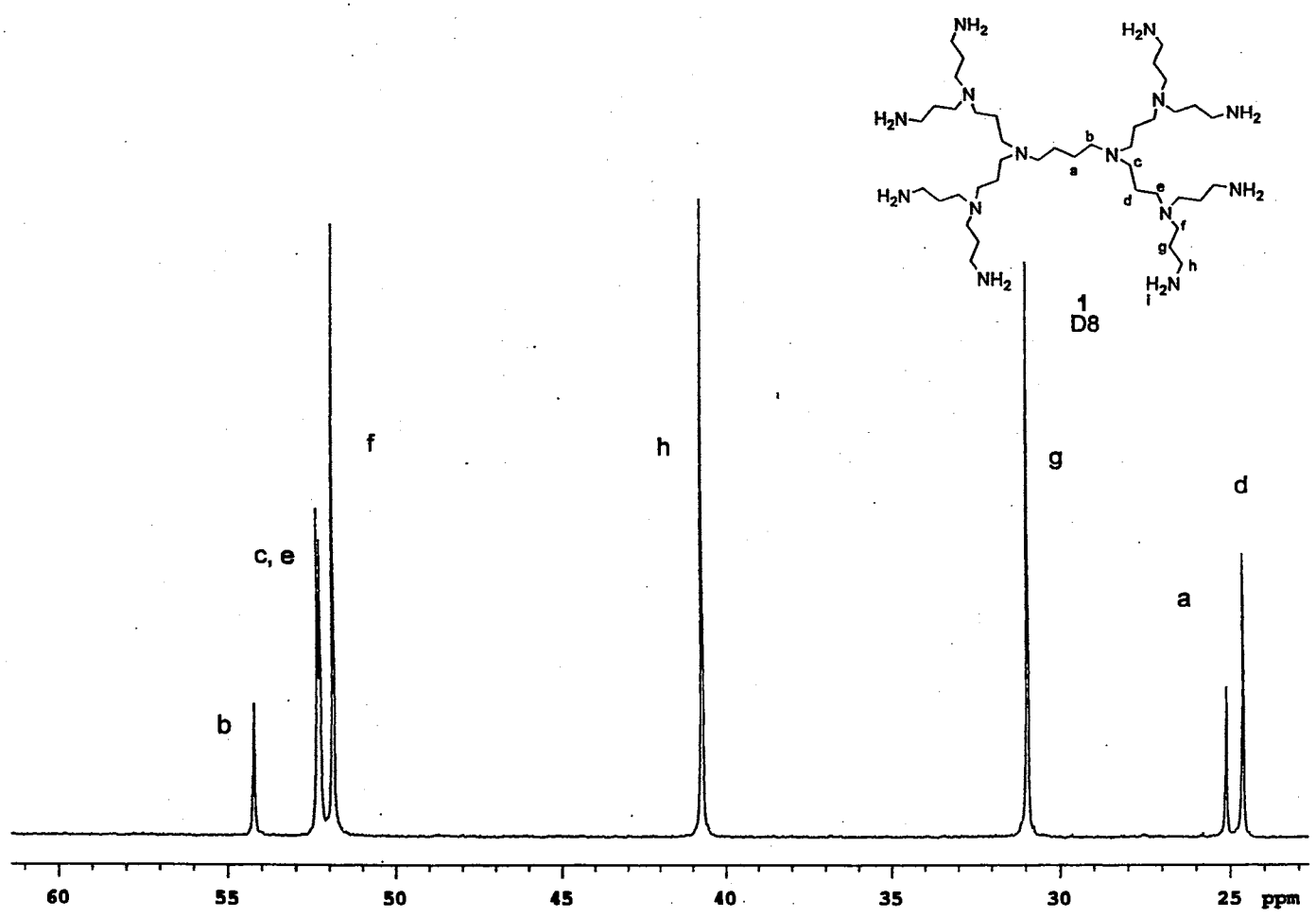


Figure 3. COSY NMR spectrum of D8 (1) in $CDCl_3$ (400 MHz ^1H frequency)

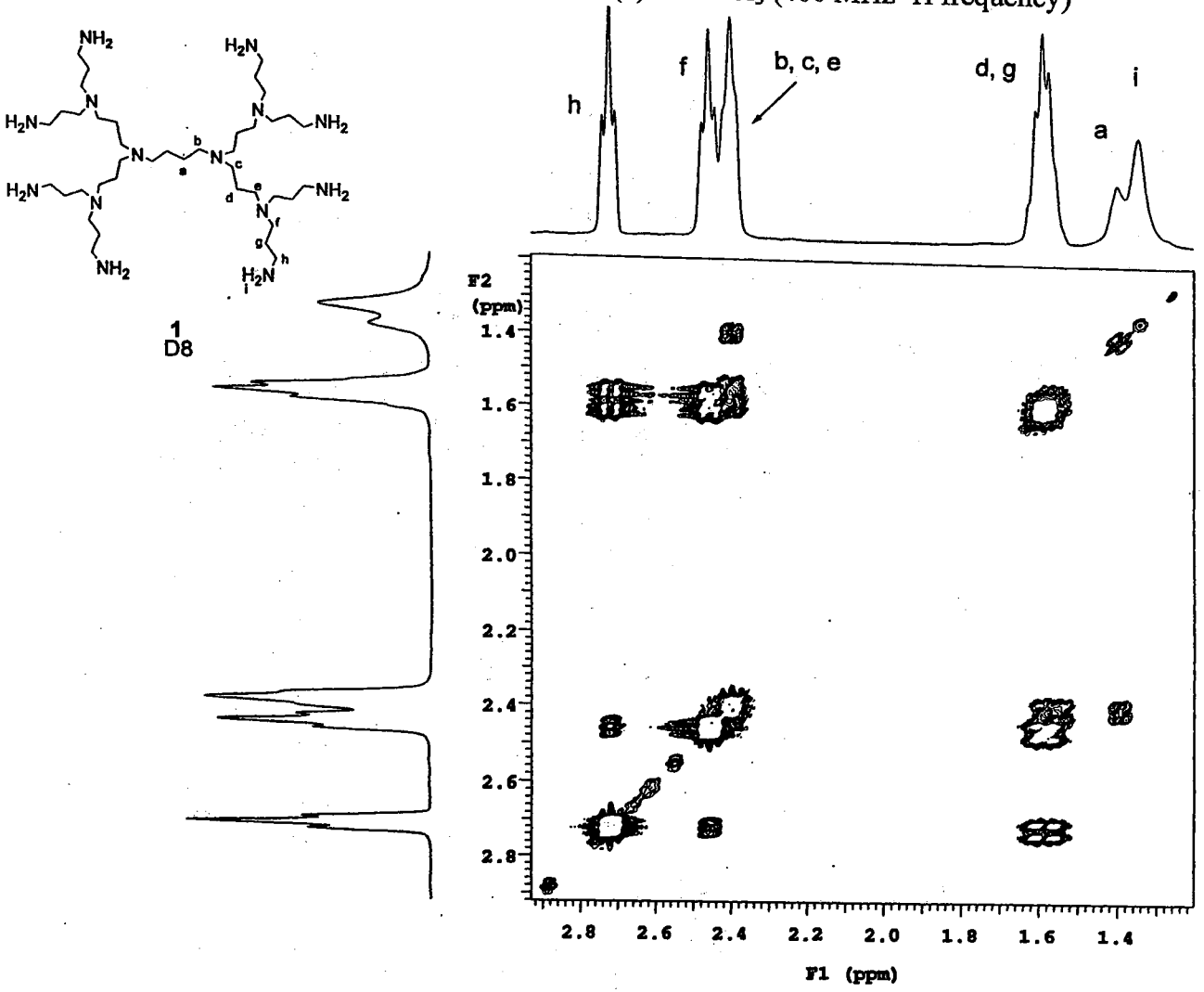


Figure 4. HMQC NMR spectrum of D8 (**1**) in $CDCl_3$ (400 MHz ^1H frequency)

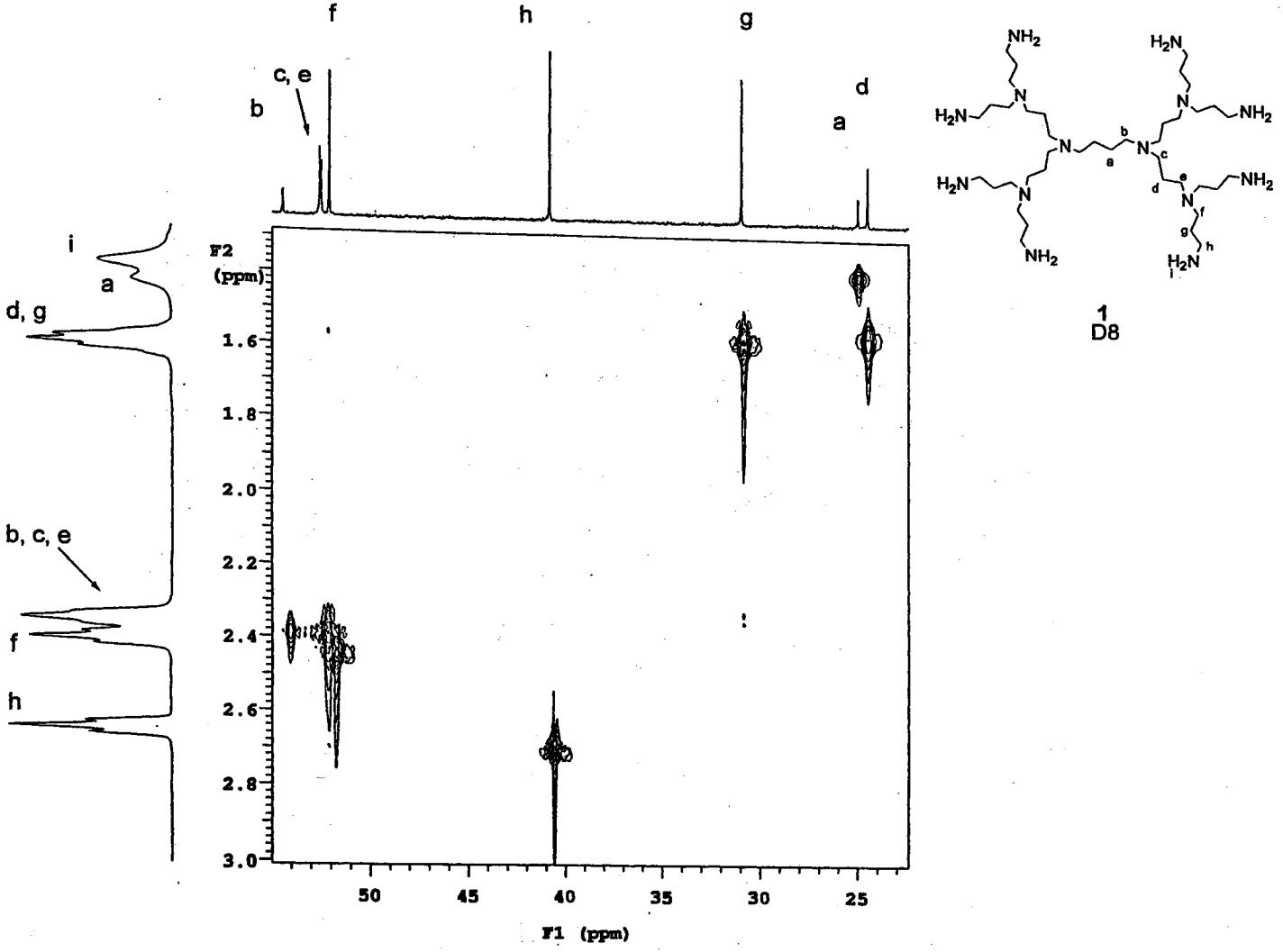


Figure 5. 400MHz ^{1}H NMR spectrum of D32 (**2**) in $CDCl_3$

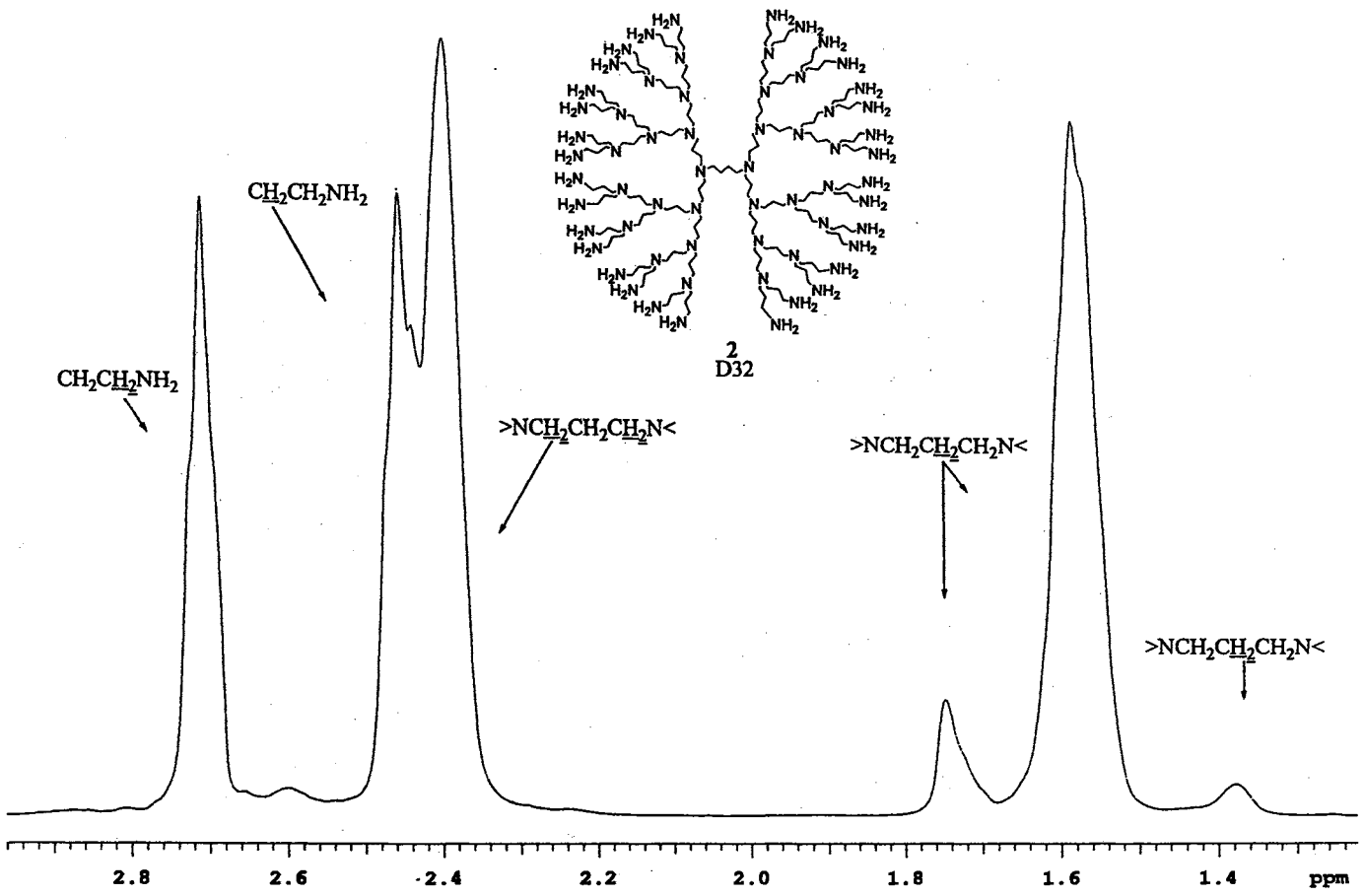


Figure 6. 75 MHz ^{13}C NMR spectrum of D32 (**2**) in $CDCl_3$

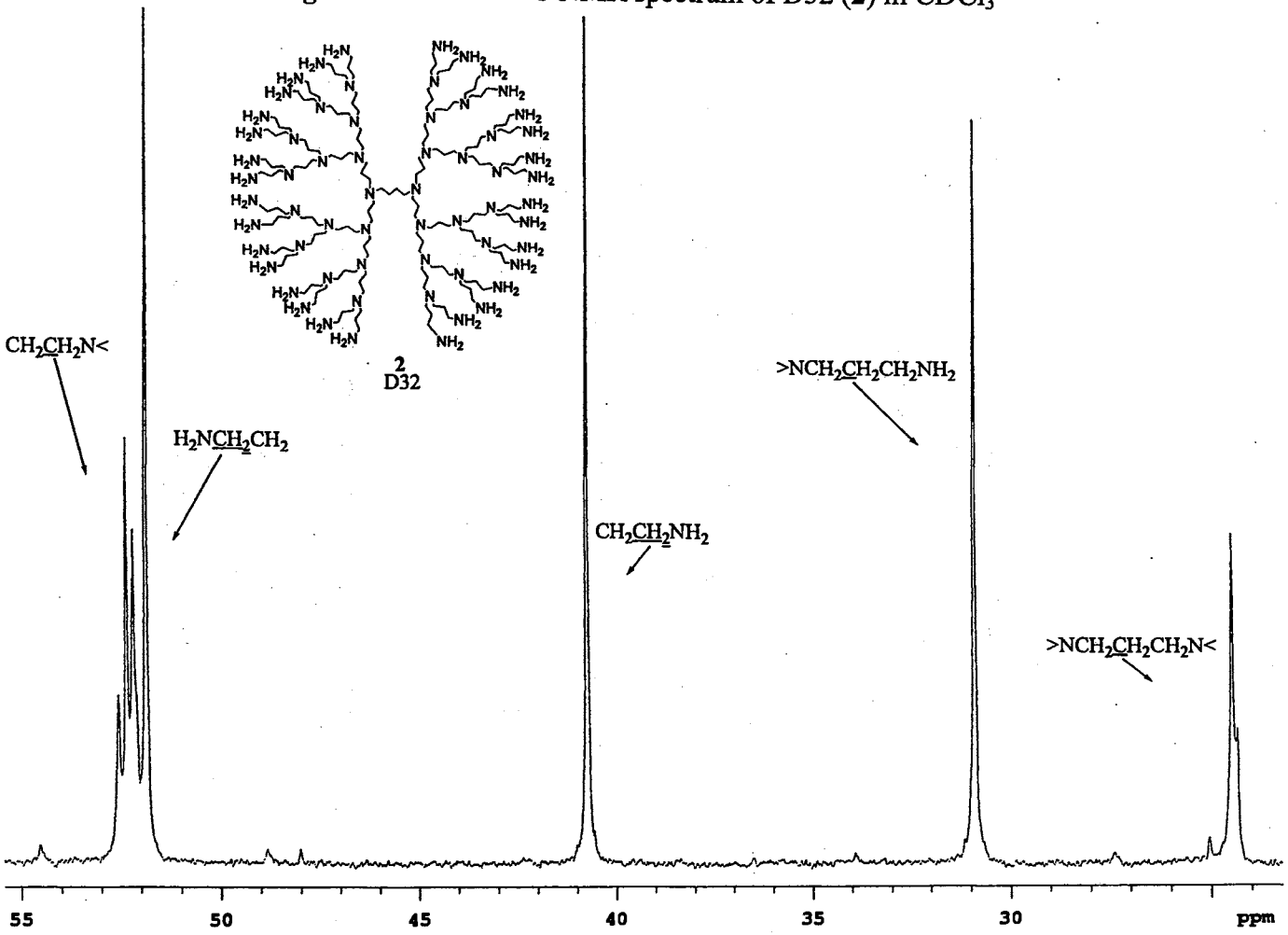


Figure 7. 300MHz ^{1}H NMR spectrum of D64 (**3**) in $CDCl_3$

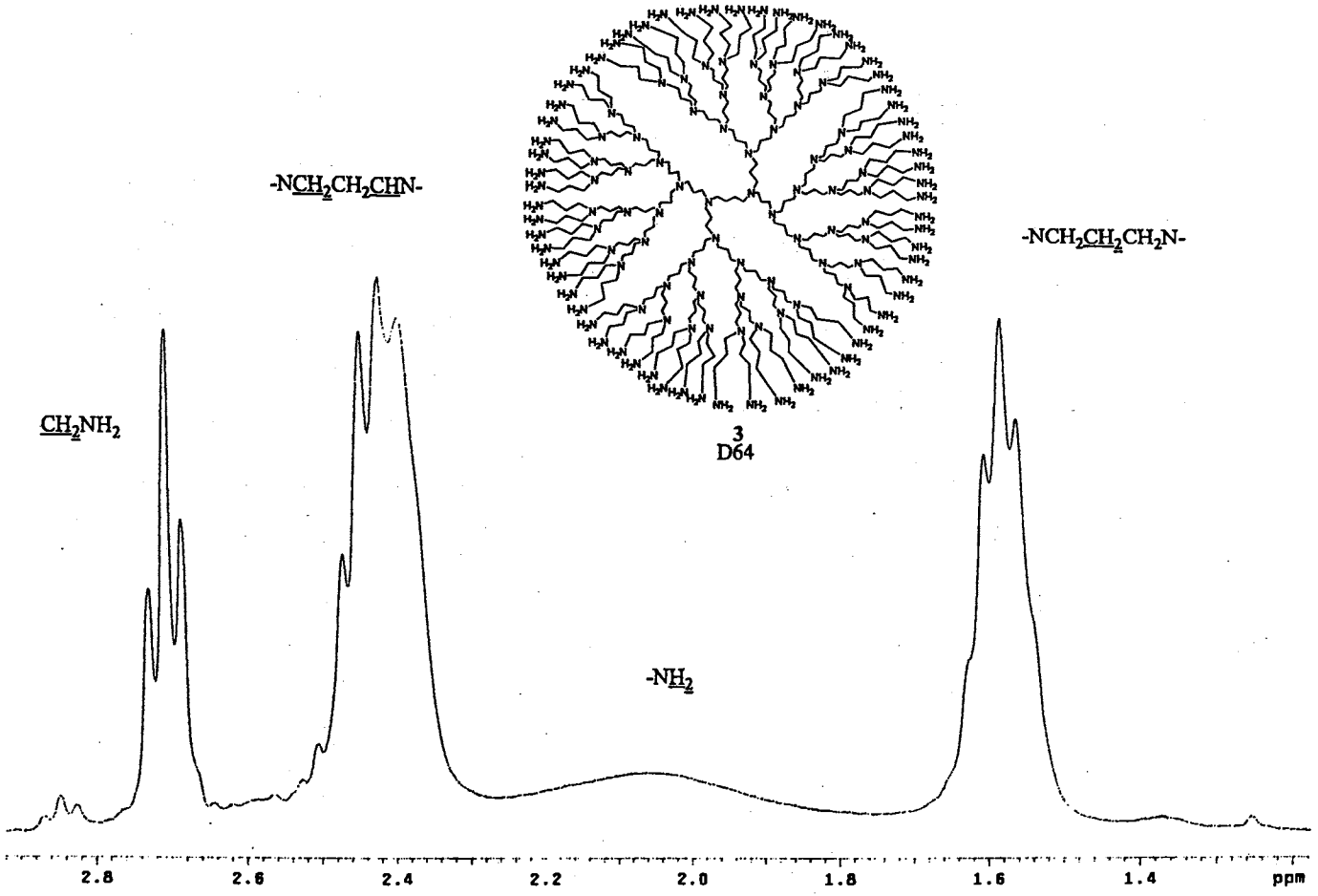


Figure 8. 75 MHz ^{13}C NMR spectrum of D64 (**3**) in $CDCl_3$

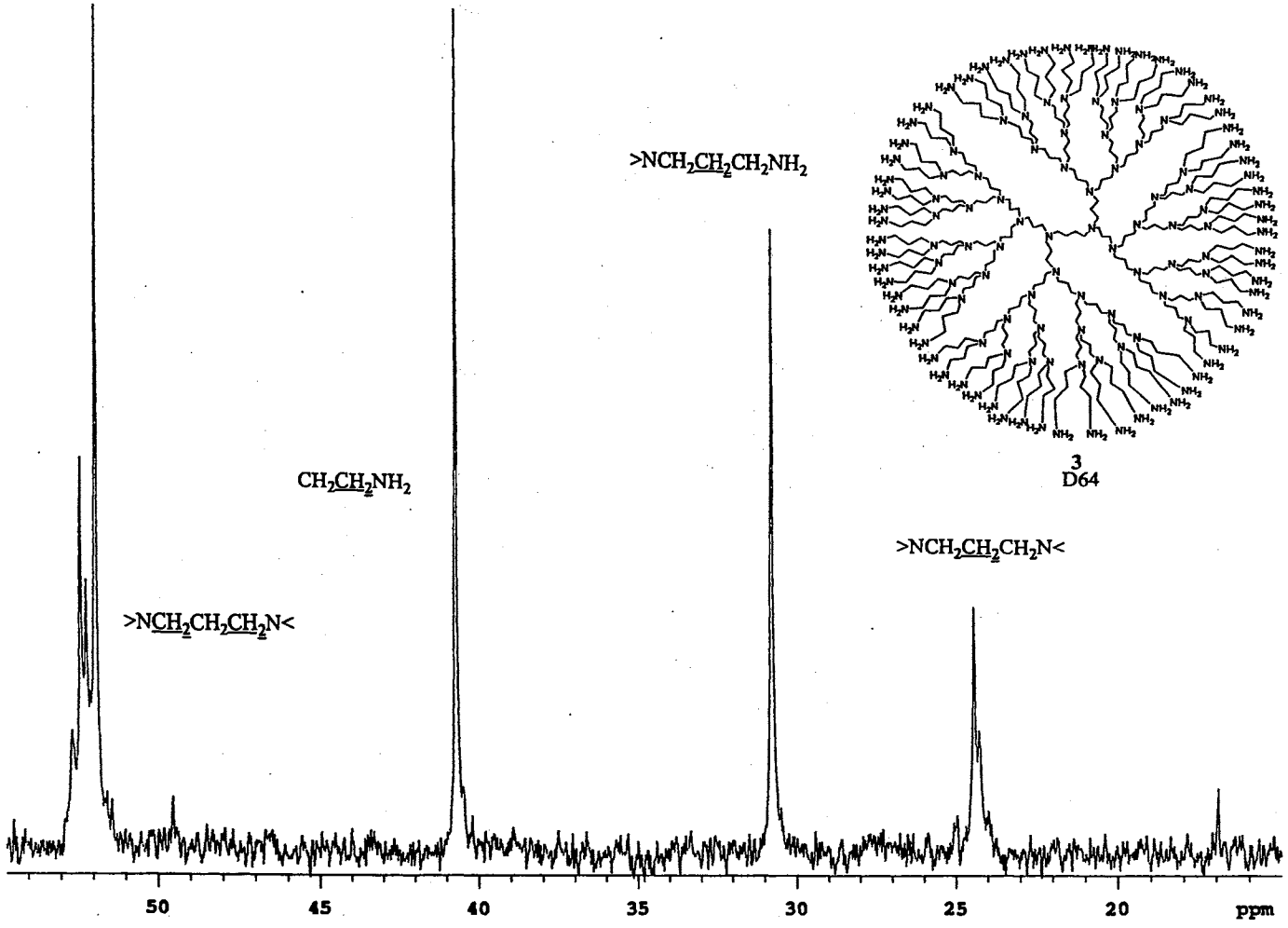
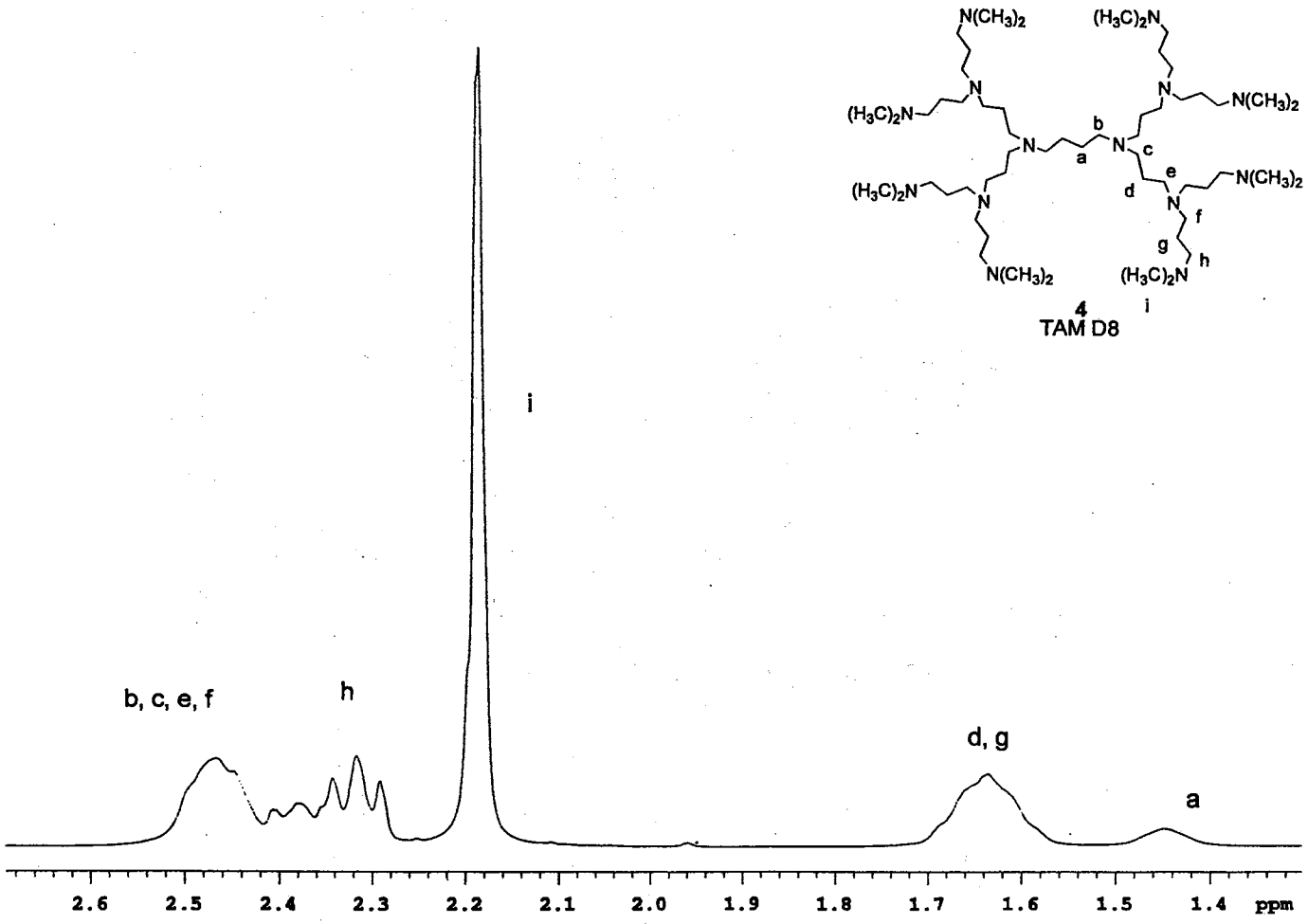


Figure 9. 300MHz ^{1}H NMR spectrum of TAM D8 (**4**) in D_2O



4
TAM D8

Figure 10. 75 MHz ^{13}C NMR spectrum of TAM D8 (4) in $CDCl_3$

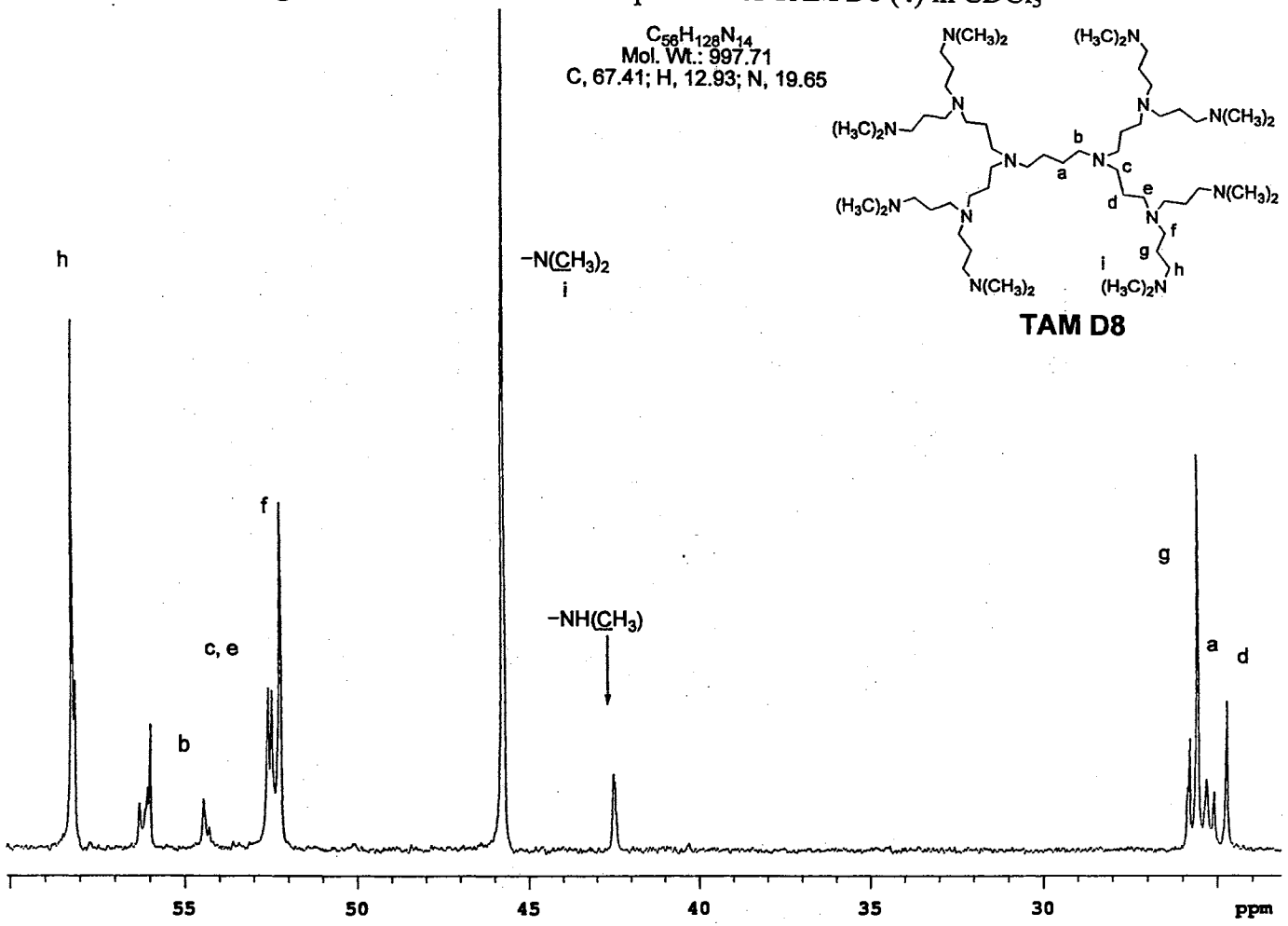


Figure 11. 150 MHz DEPT NMR spectrum of TAM D8 (**4**) in $CDCl_3$

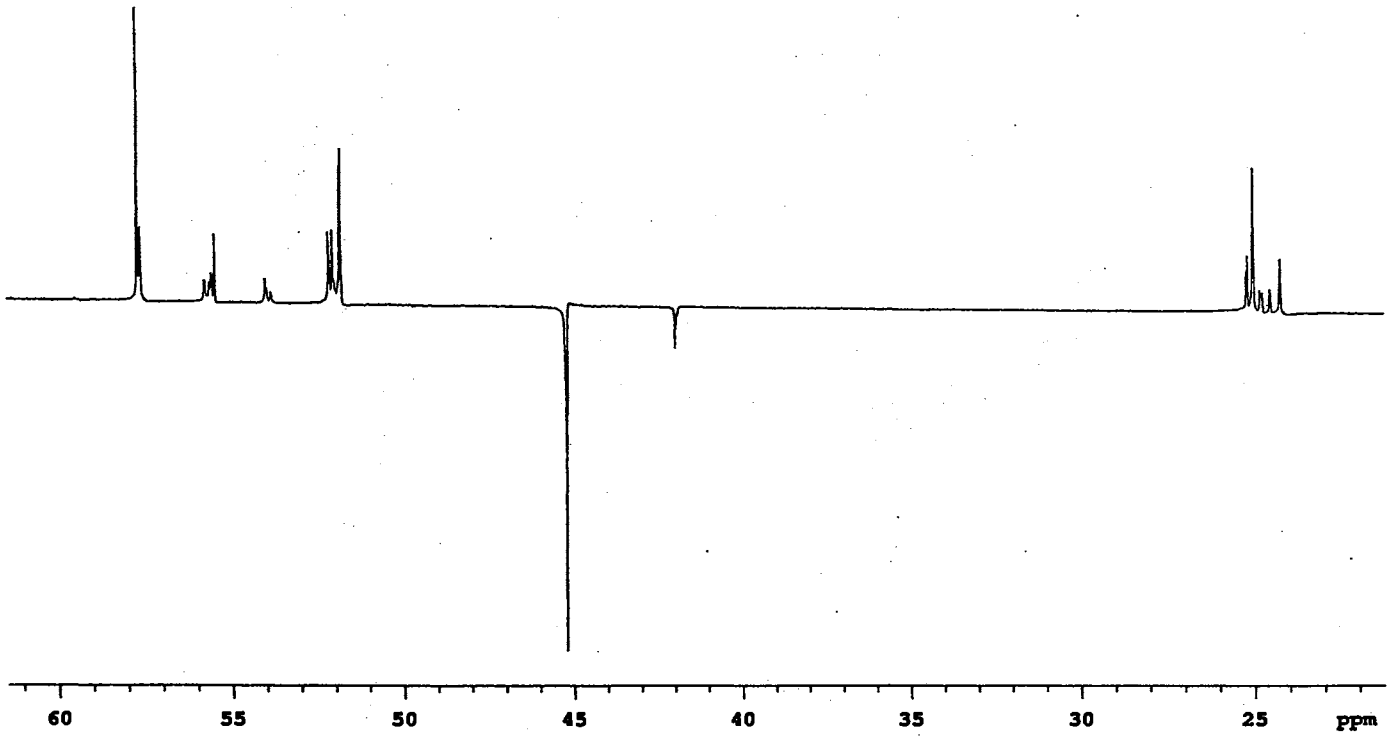


Figure 12. HMQC NMR spectrum of TAM D8 (**4**) in $CDCl_3$ (300 MHz ^1H frequency)

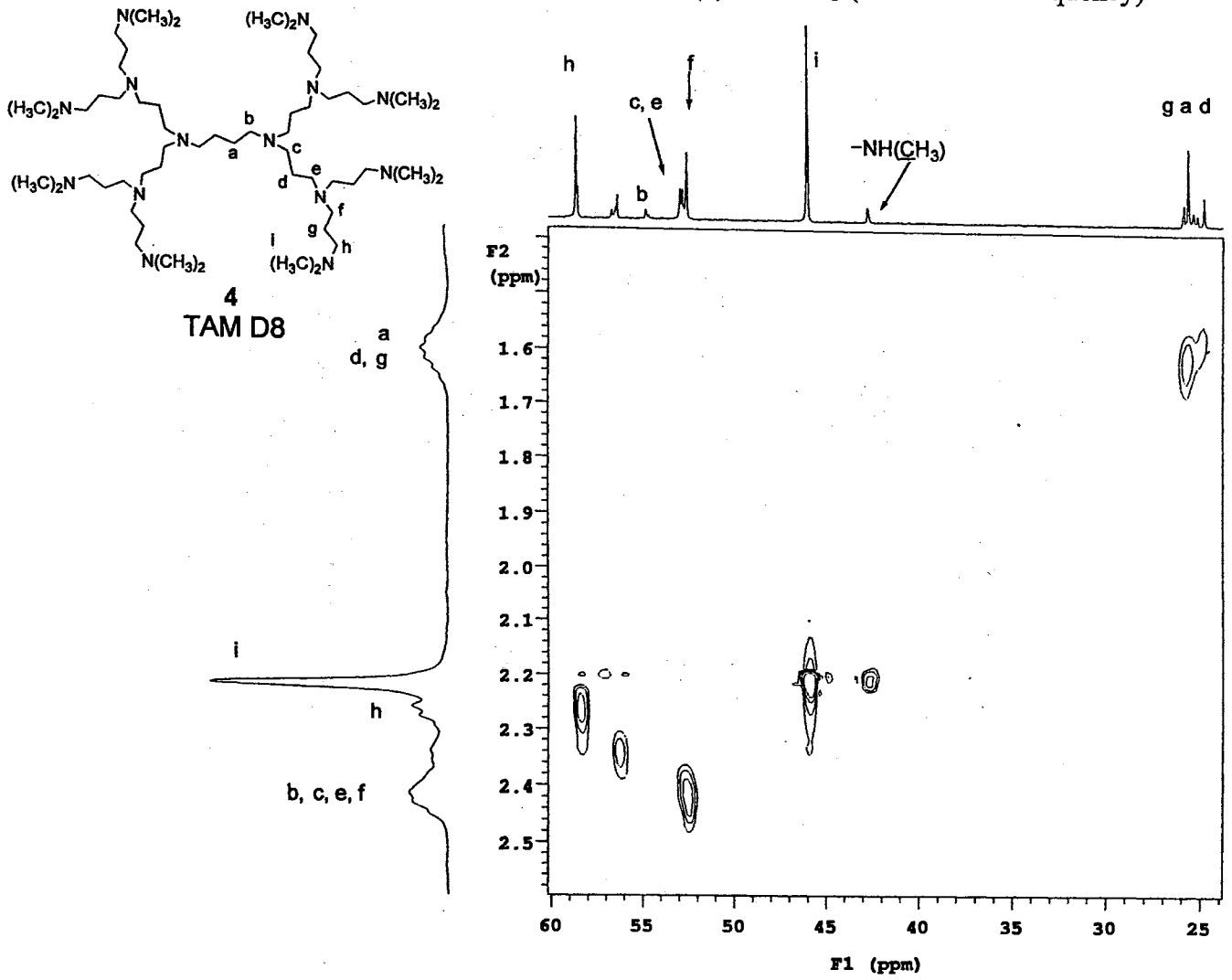


Figure 13. ESI-MS spectrum of TAM D8 (4)

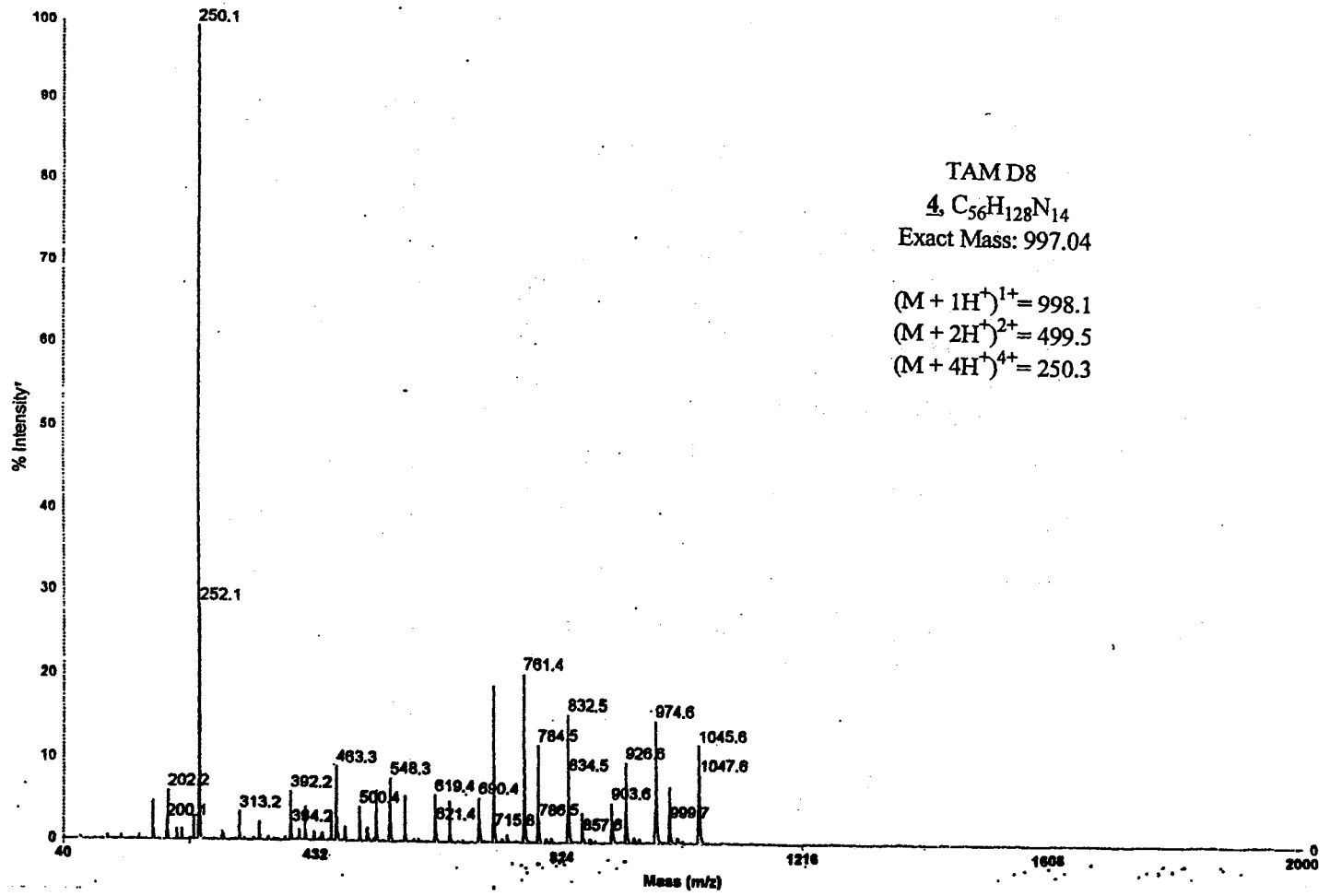
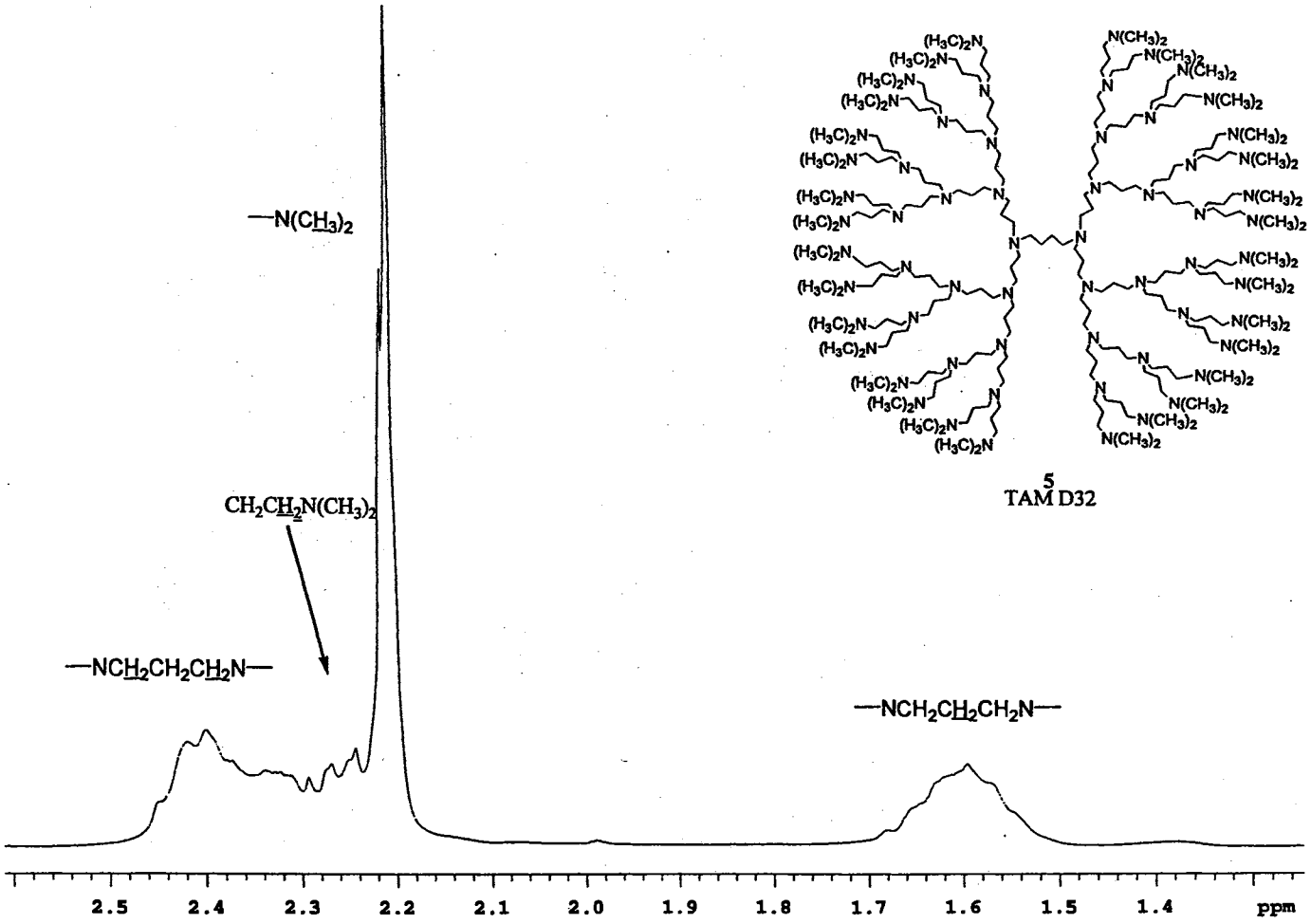


Figure 14. 300 MHz ^{1}H NMR spectrum of TAM D32 (**5**) in $CDCl_3$



5
TAM D32

Figure 15. 75 MHz ^{13}C NMR spectrum of TAM D32 (**5**) in $CDCl_3$

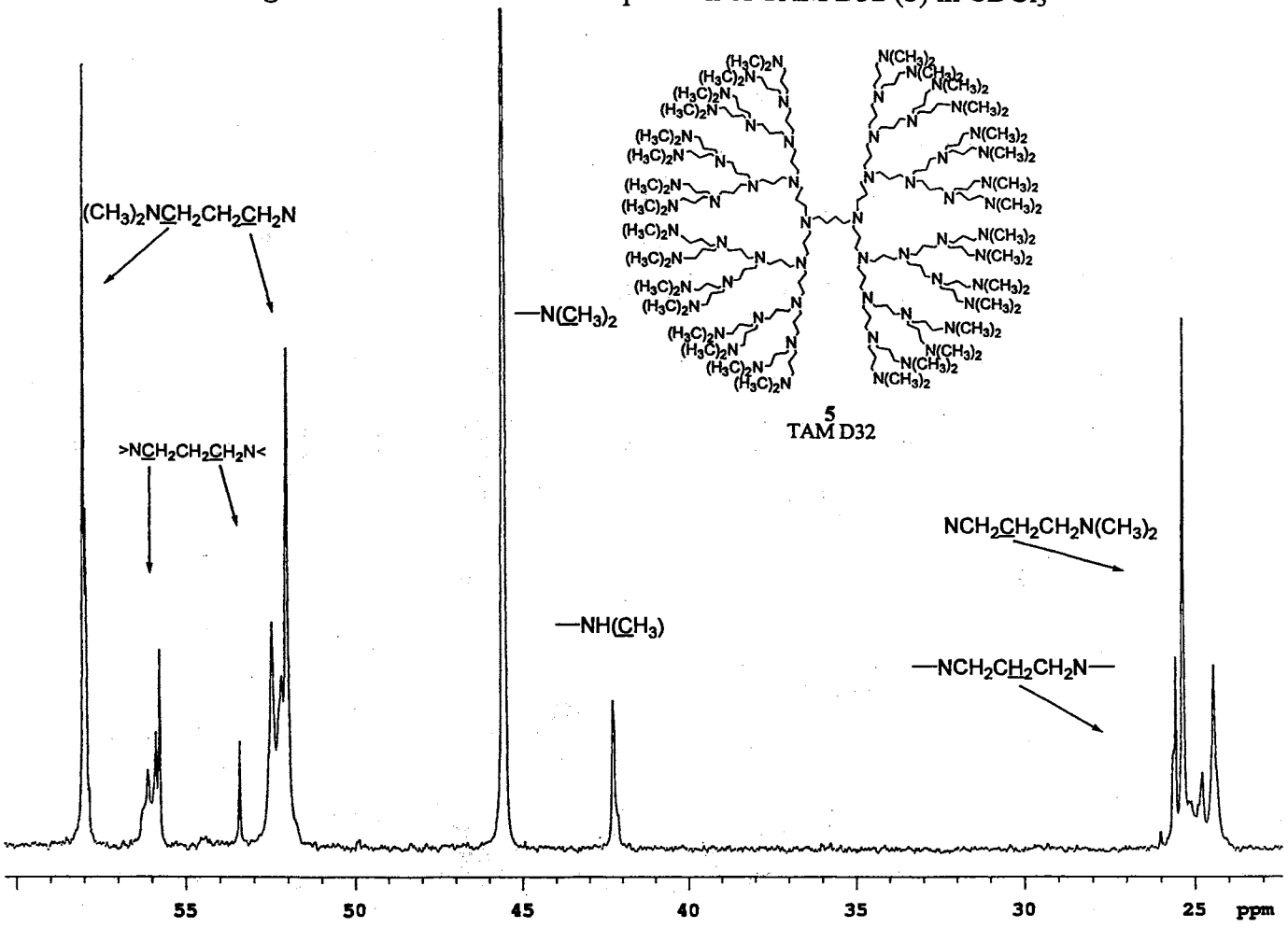
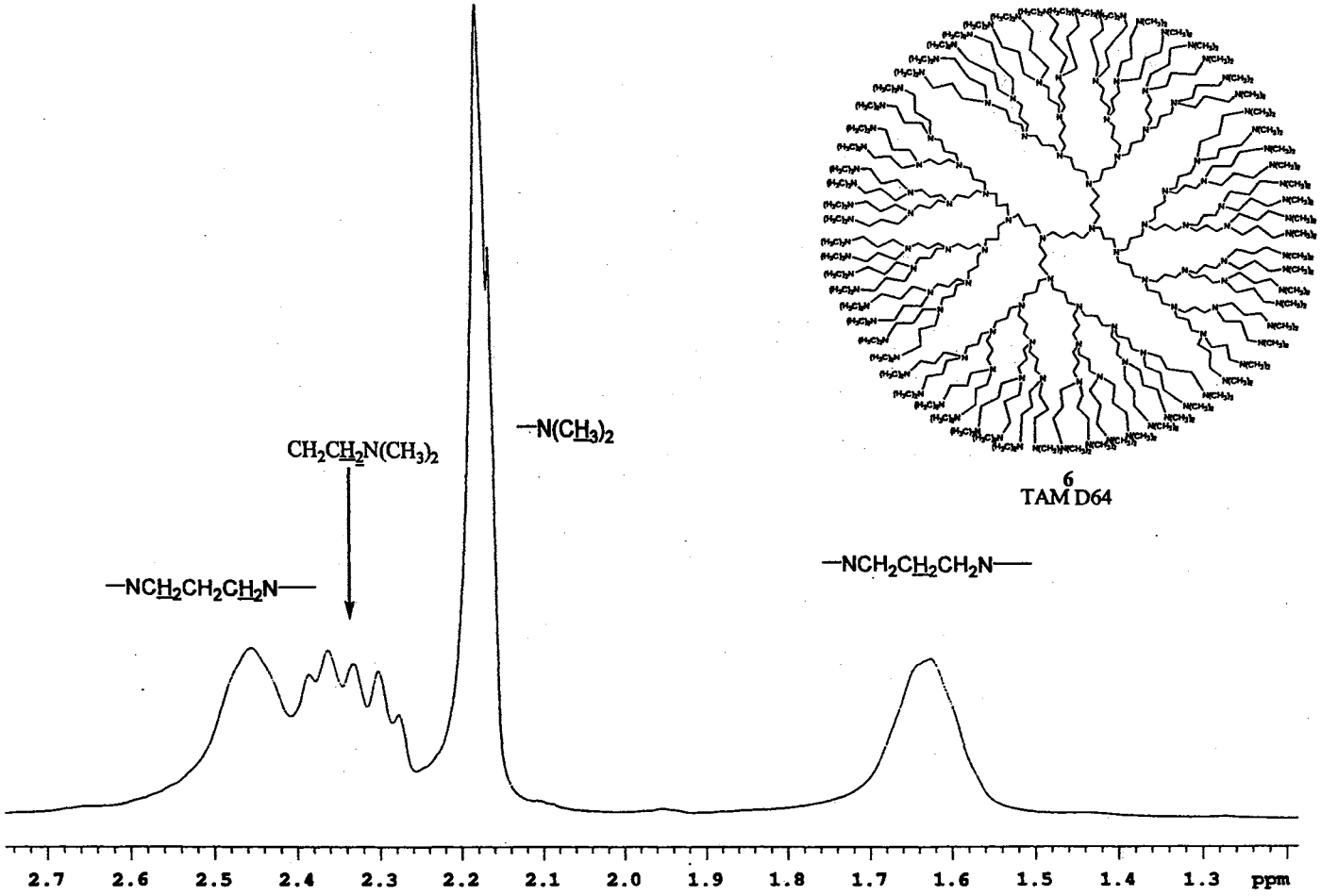


Figure 16. 300 MHz ^{13}C NMR spectrum of TAM D64 (**6**) in $CDCl_3$



6
TAM D64

Figure 17. 75 MHz ^{13}C NMR spectrum of TAM D64 (**6**) in $CDCl_3$

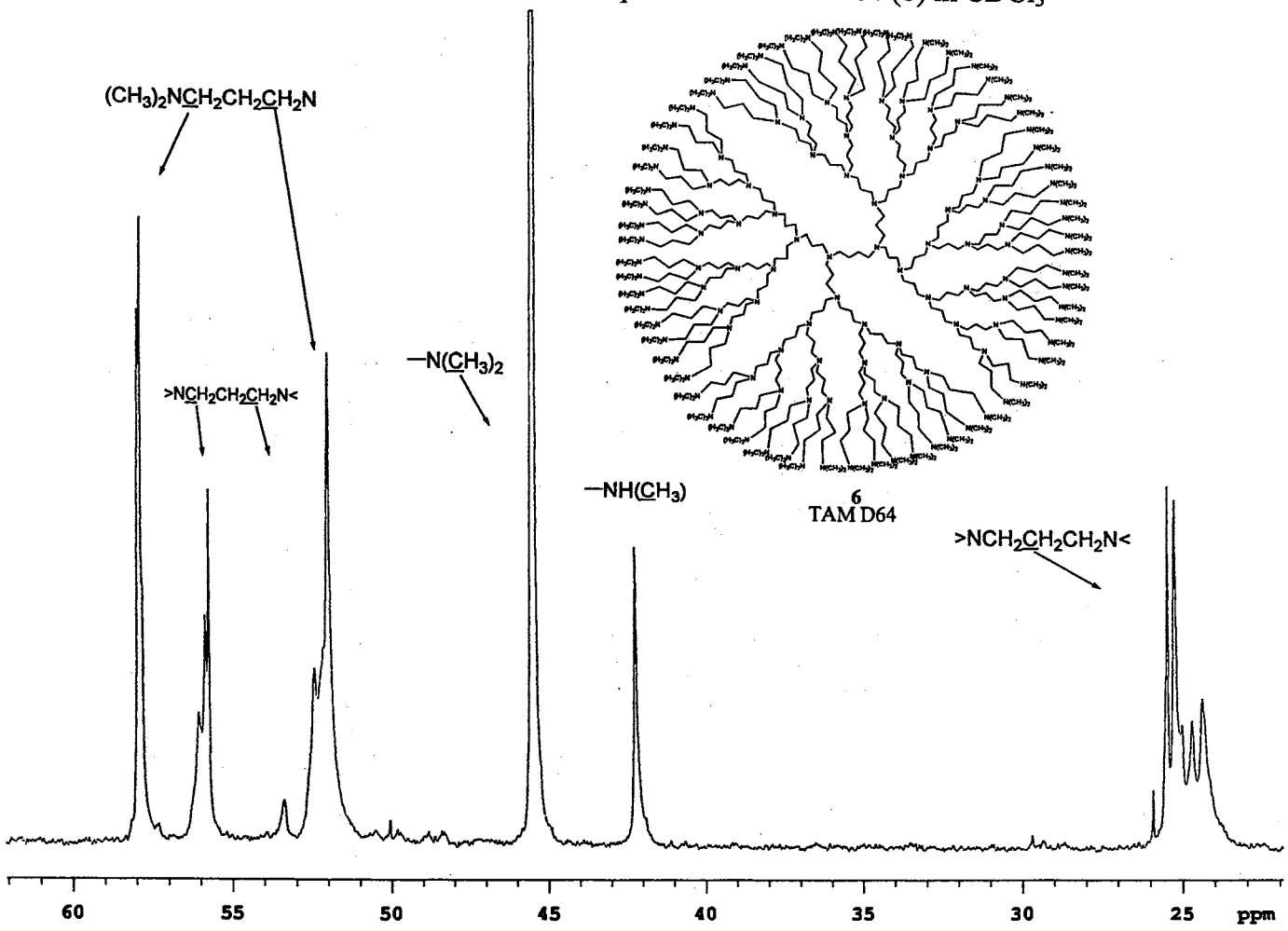
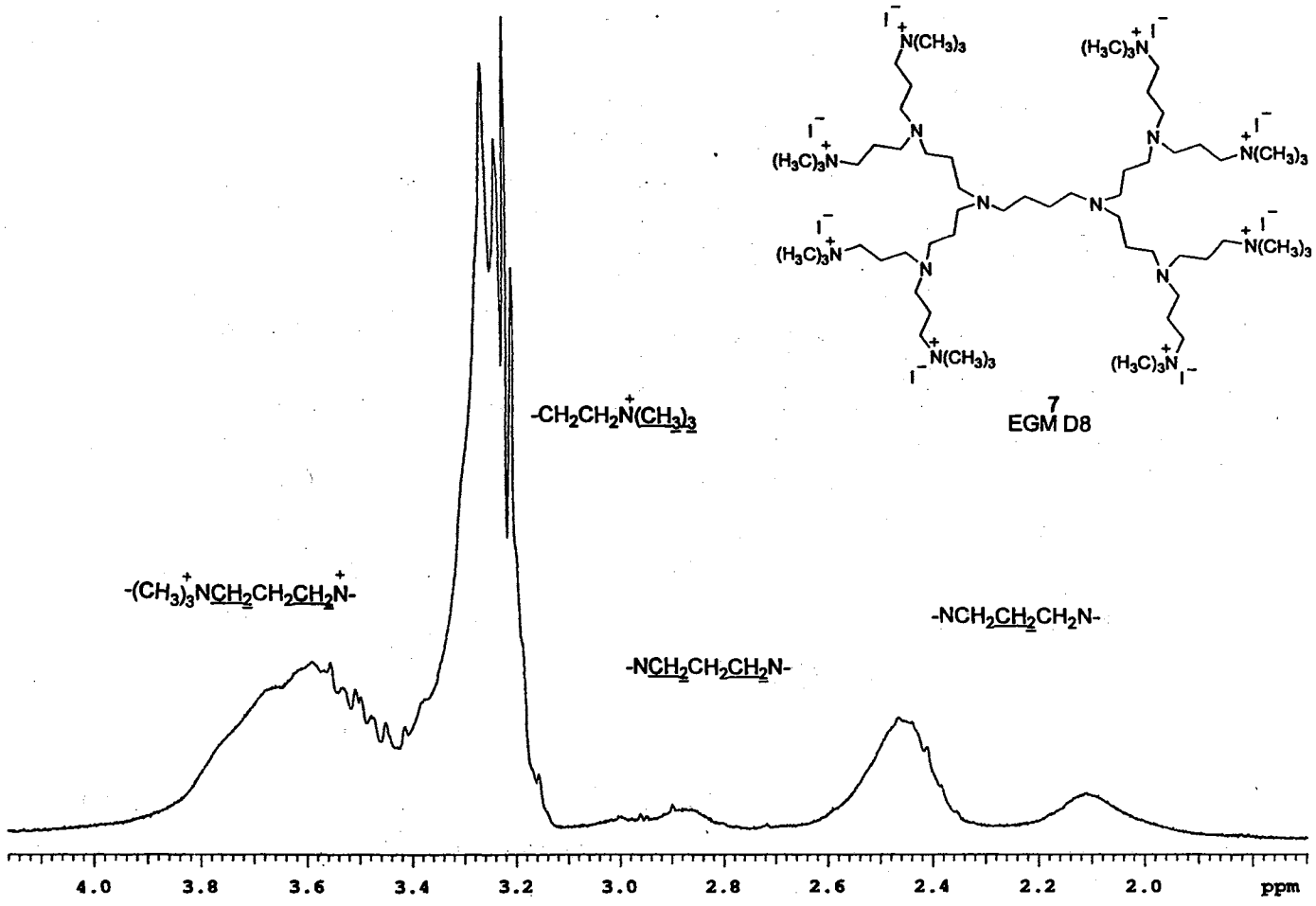
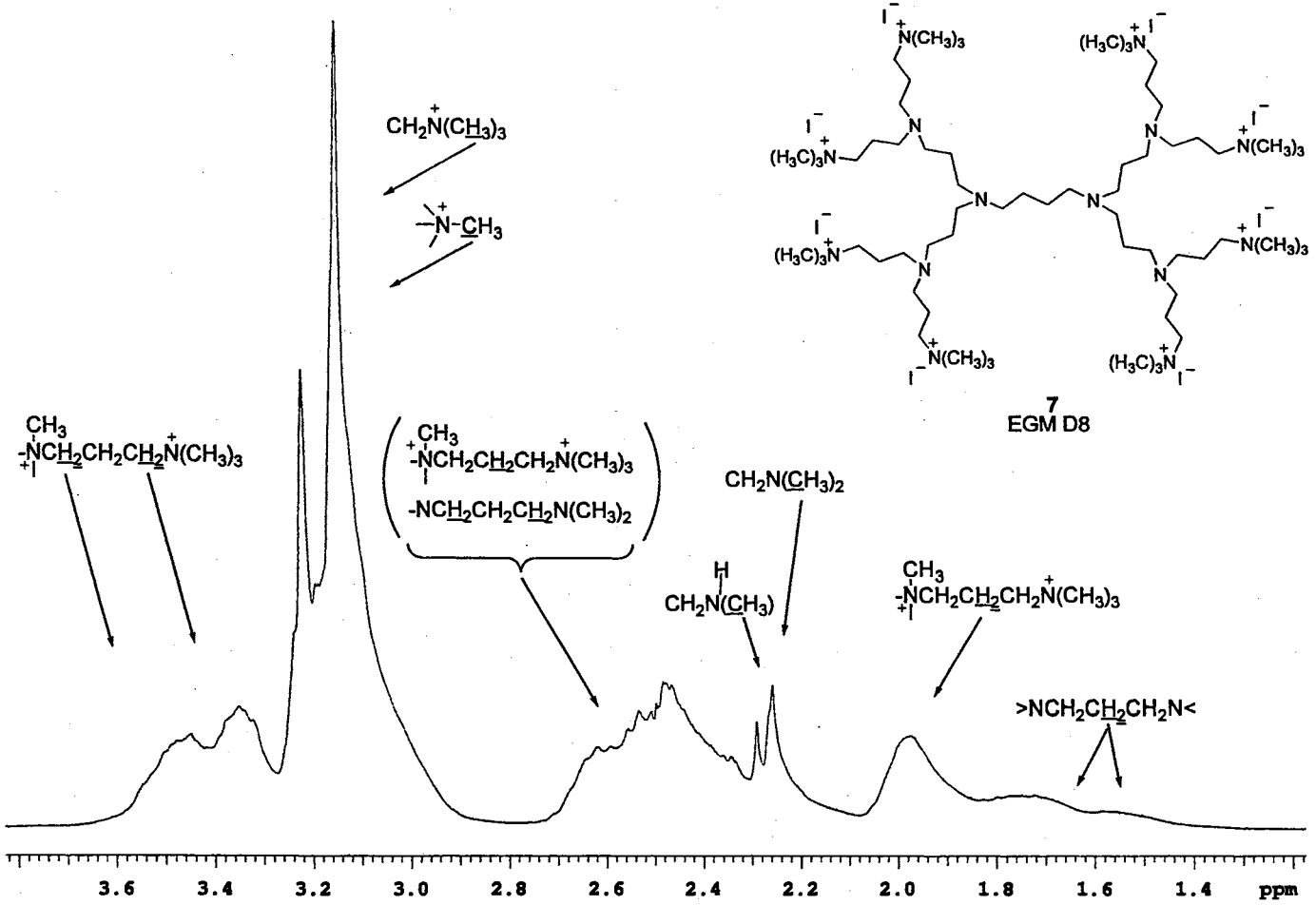


Figure 18a. 300 MHz ^{1}H NMR spectrum of EGM D8 in HI form (7) in D_2O



7
EGM D8

Figure 18b. 300 MHz ^{1}H NMR spectrum of EGM D8 (7) in amine form in D_2O



7
EGM D8

Figure 19. 75 MHz ^{13}C NMR spectrum of EGM D8 (7) in amine form in D_2O

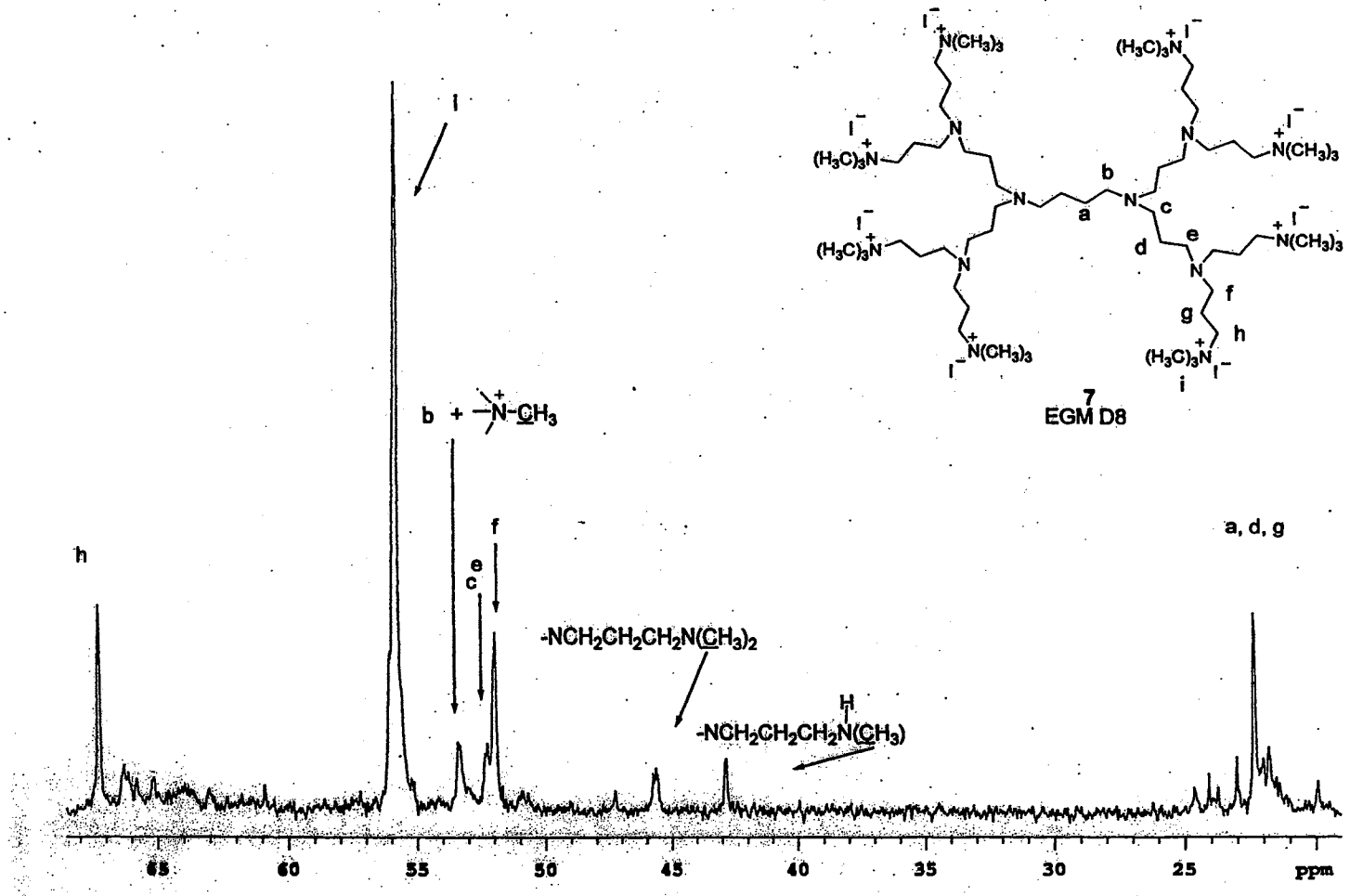


Figure 20. ESI-MS spectrum of EGM D8 (7)

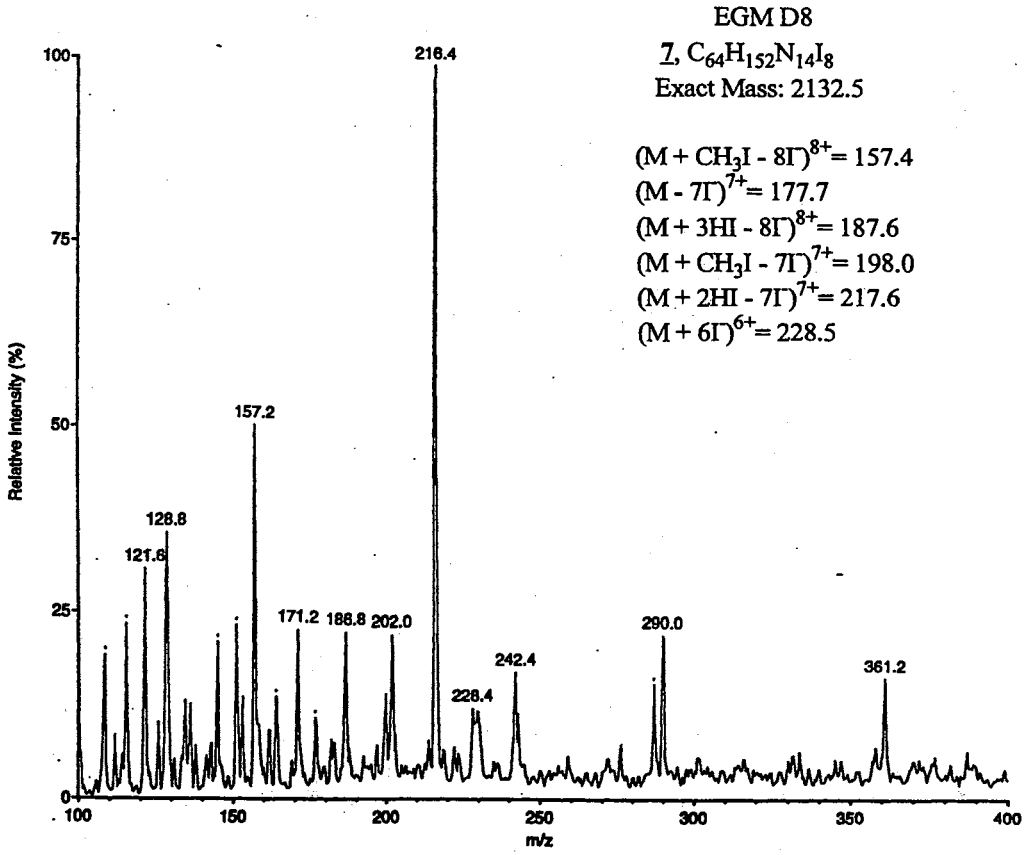
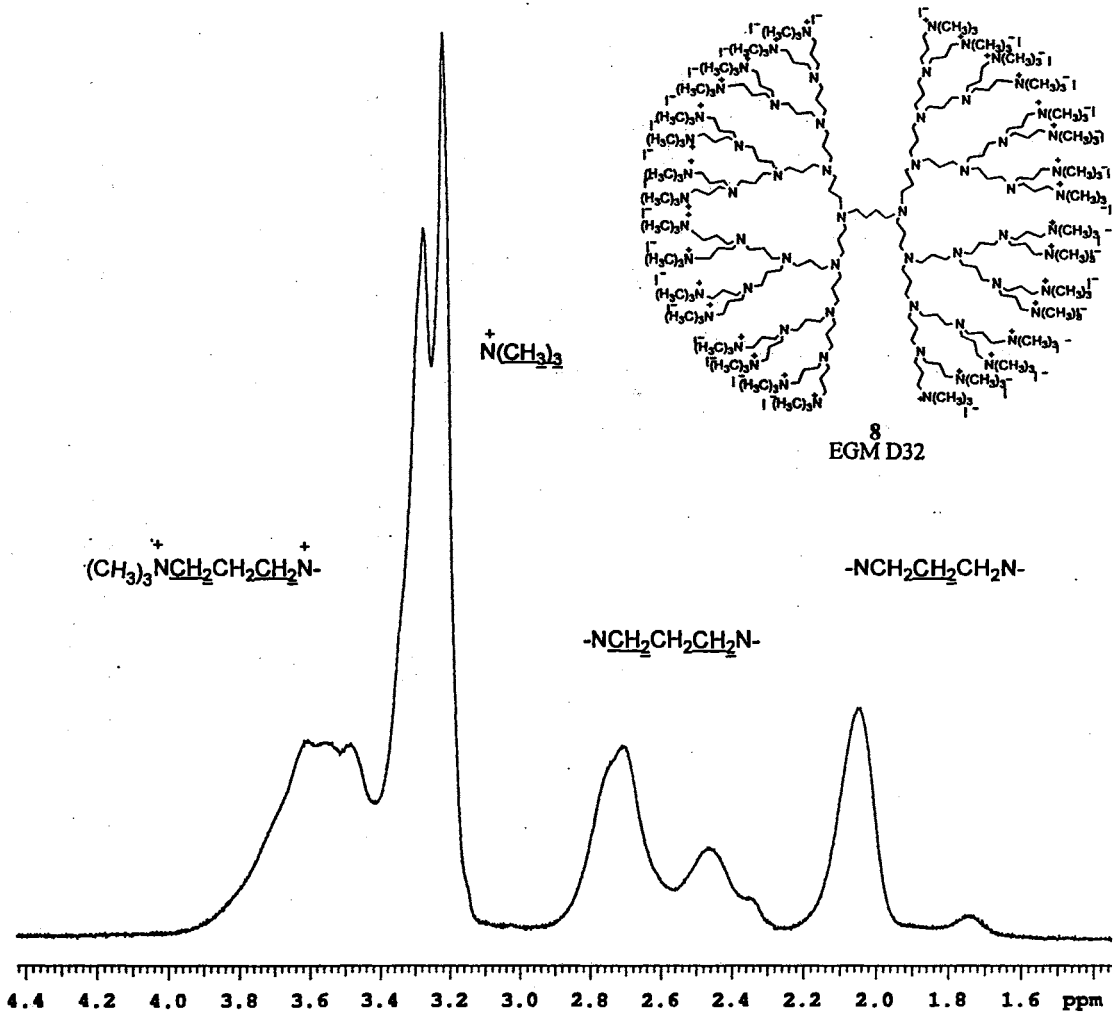


Figure 21a. 300 MHz ^{1}H NMR spectrum of EGM D32 (**8**) in HI form in D_2O



8
EGM D32

Figure 21b. 300 MHz ^{1}H NMR spectrum of EGM D32 (**8**) in amine form in D_2O

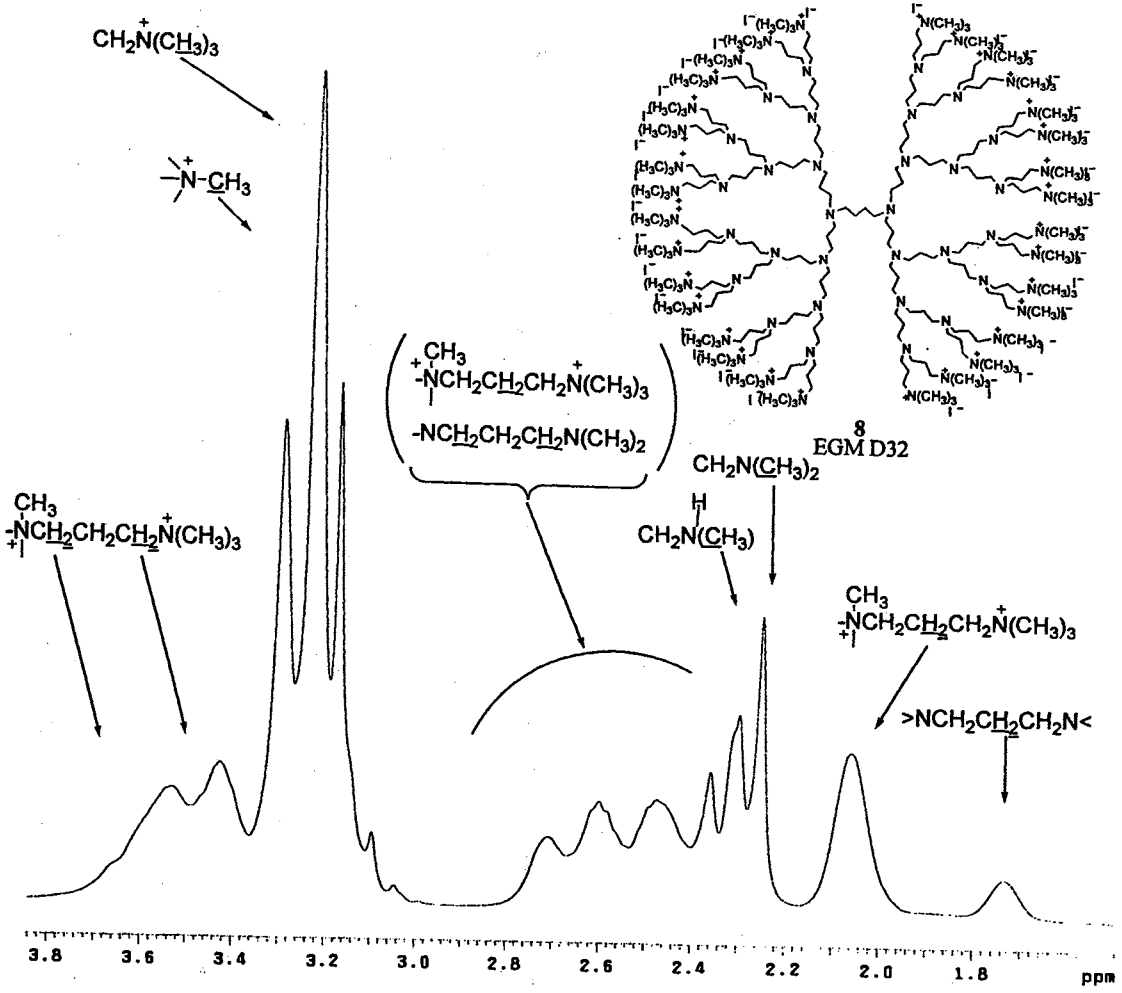
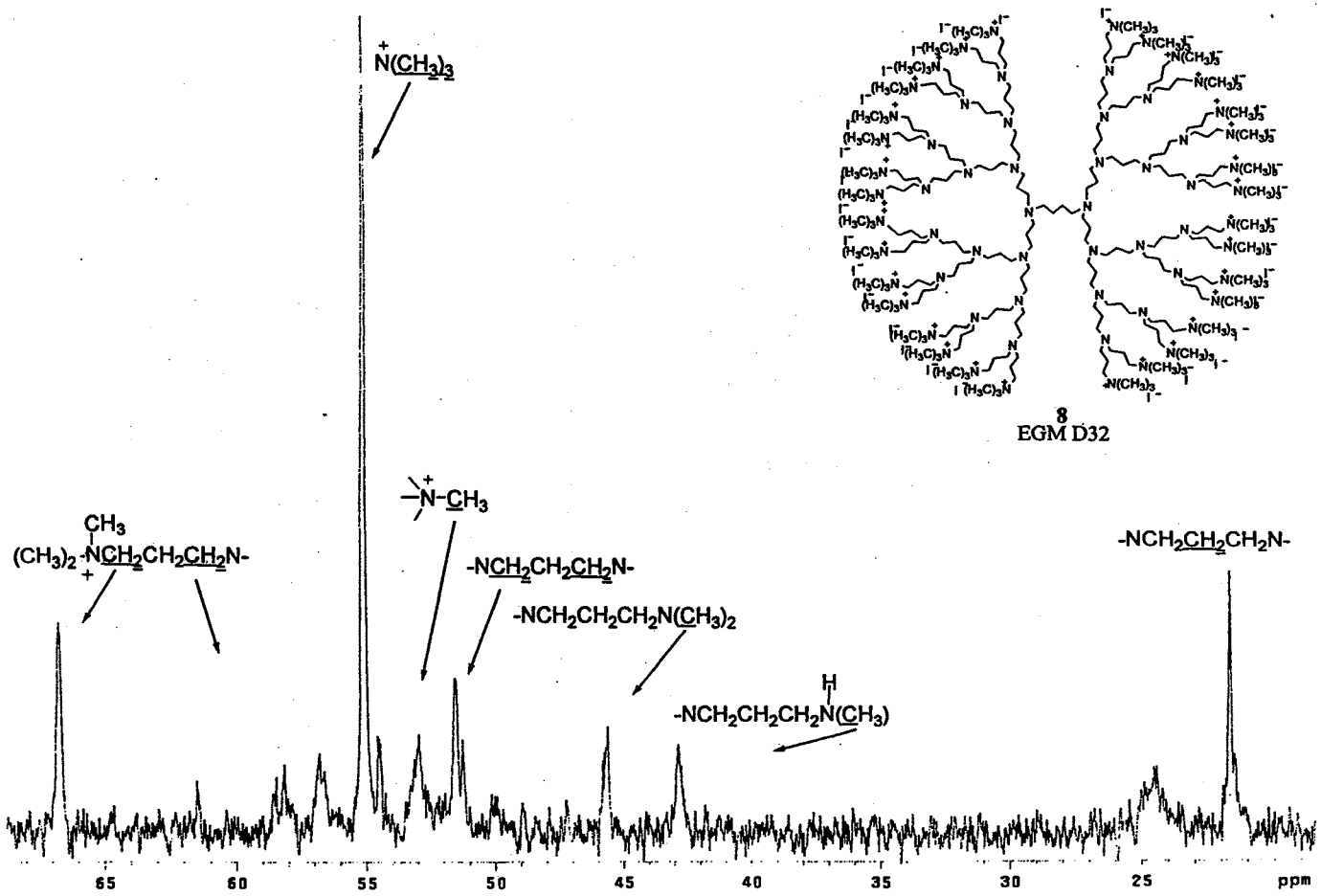


Figure 22. 75 MHz ^{13}C NMR spectrum of EGM D32 (**8**) in amine form in D_2O



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EGM D32

Figure 23. 300 MHz ^{1}H NMR spectrum of EGM D64 (**9**) in HI form in D_2O

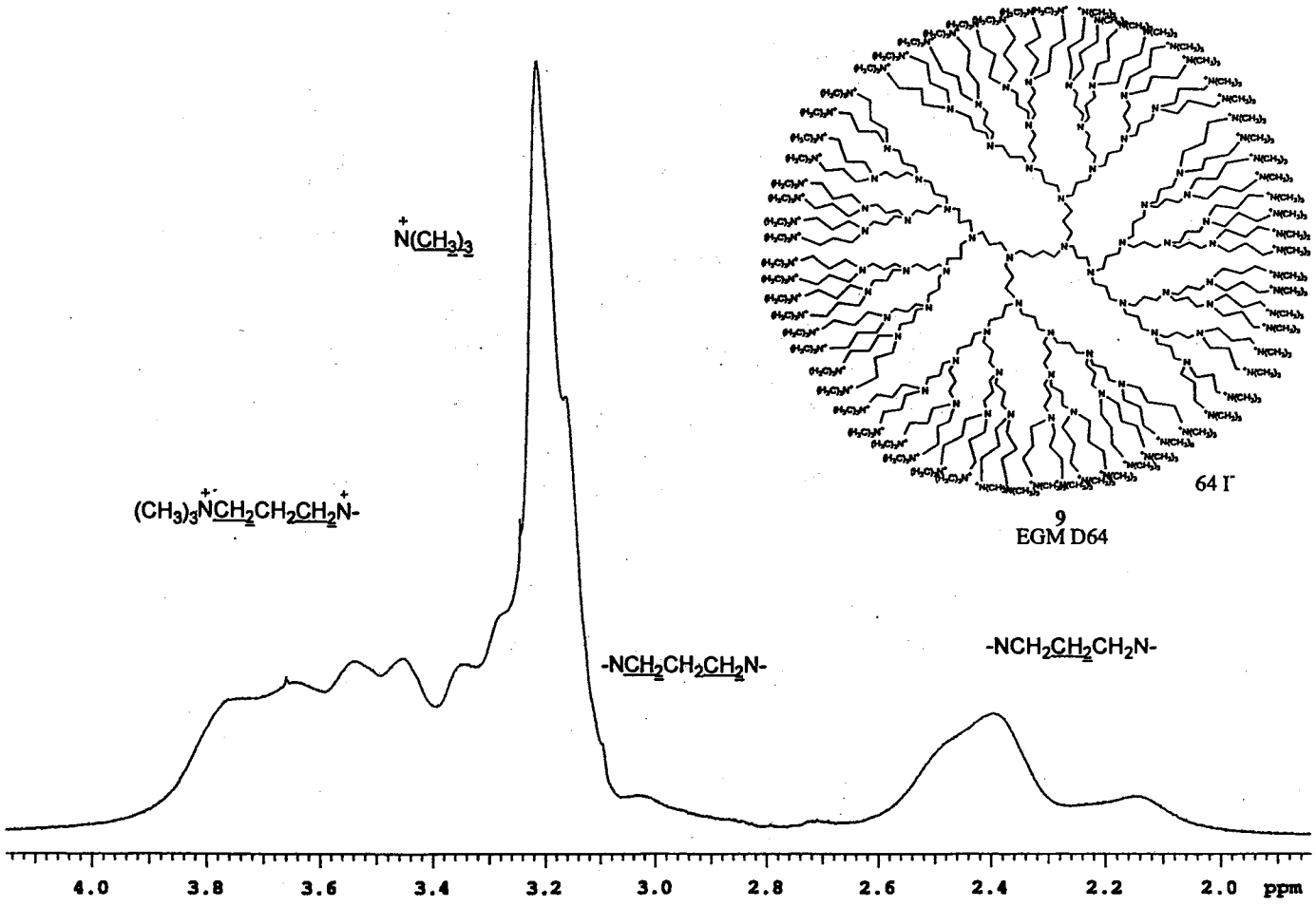


Figure 23b. 300 MHz ^{1}H NMR spectrum of EGM D64 (**9**) in amine form in D_2O

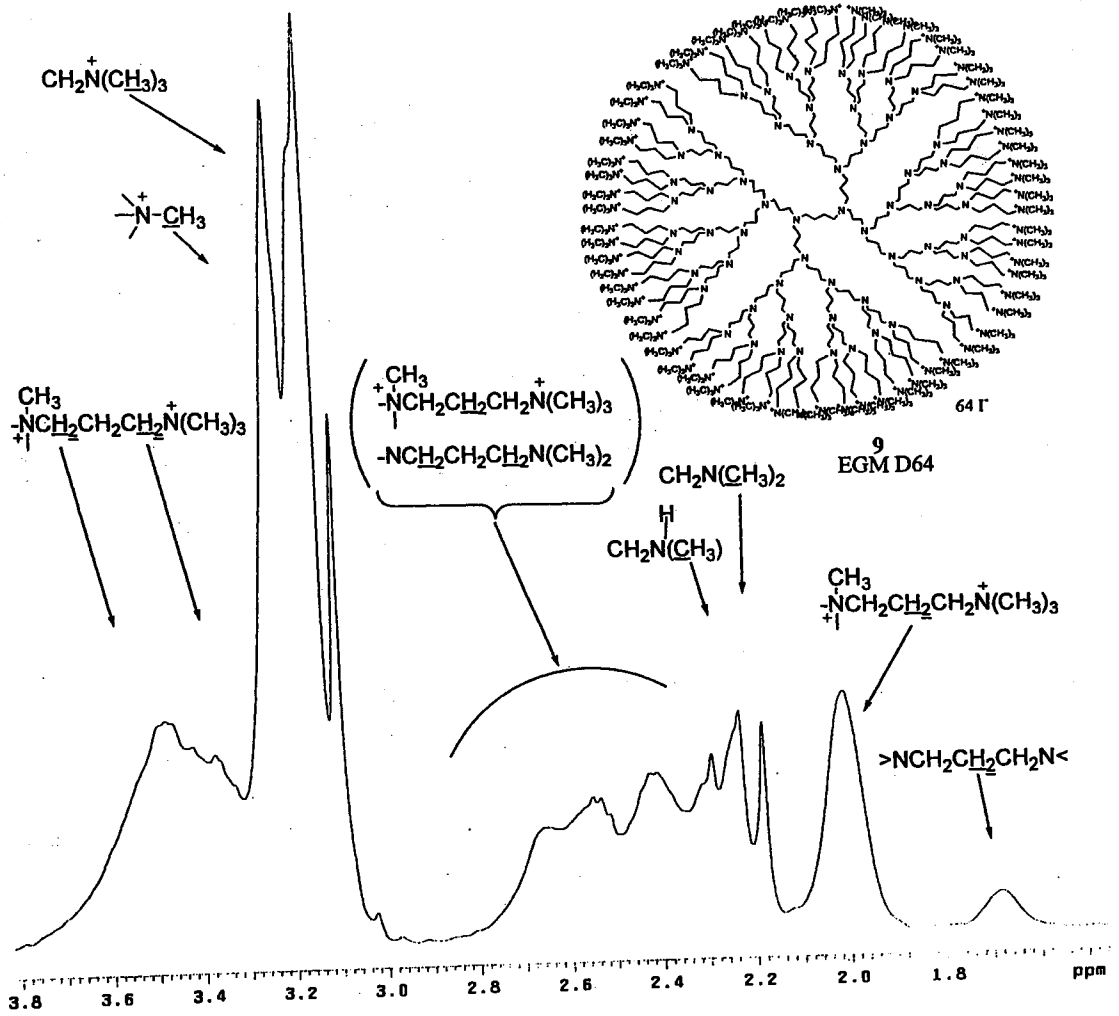


Figure 24. 75 MHz ^{13}C NMR spectrum of EGM D64 (**9**) in amine form in D_2O

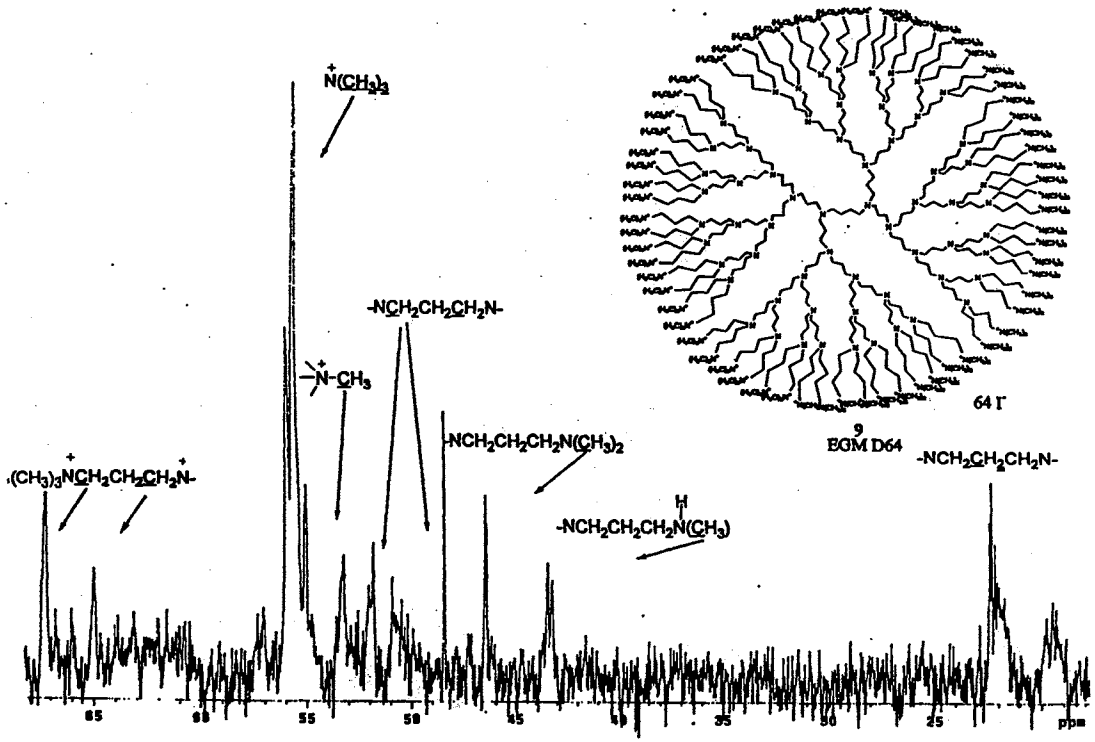


Figure 25. 400 MHz ^{1}H NMR spectrum of PM D8 (**11**) in D_2O

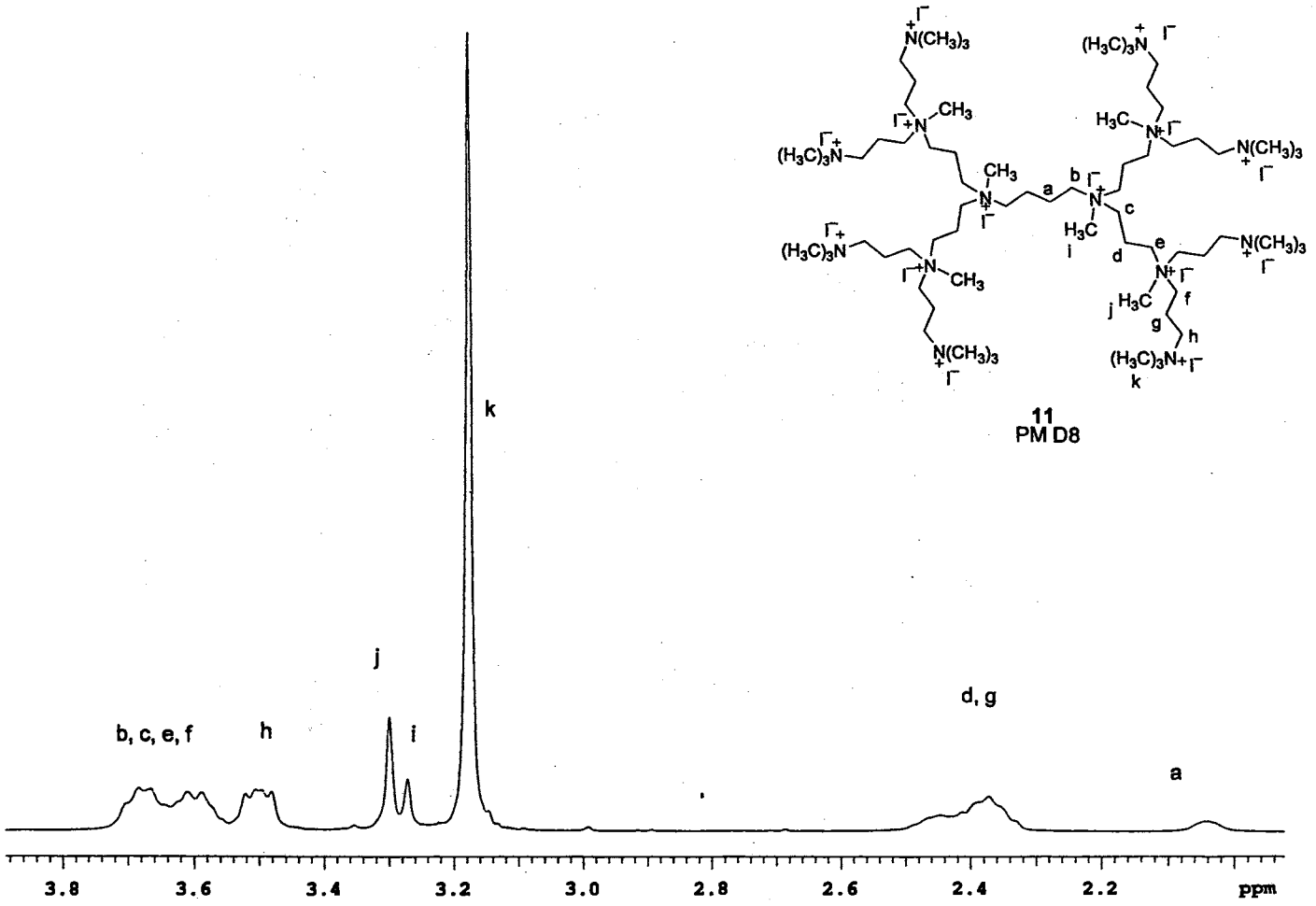


Figure 26. 100 MHz ^{13}C NMR spectrum of PM D8 (11) in D_2O

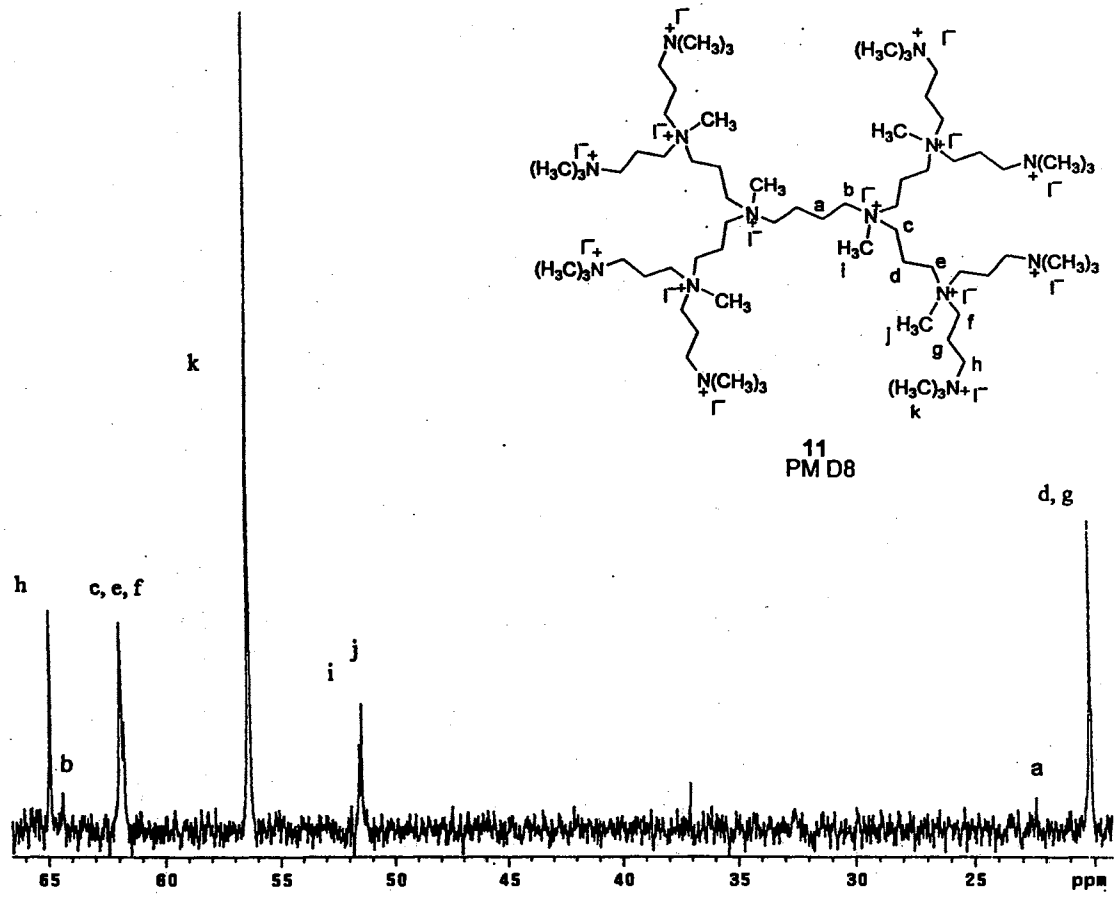


Figure 27. COSY NMR spectrum of PM D8 (**11**) in D_2O (400 MHz ^1H frequency)

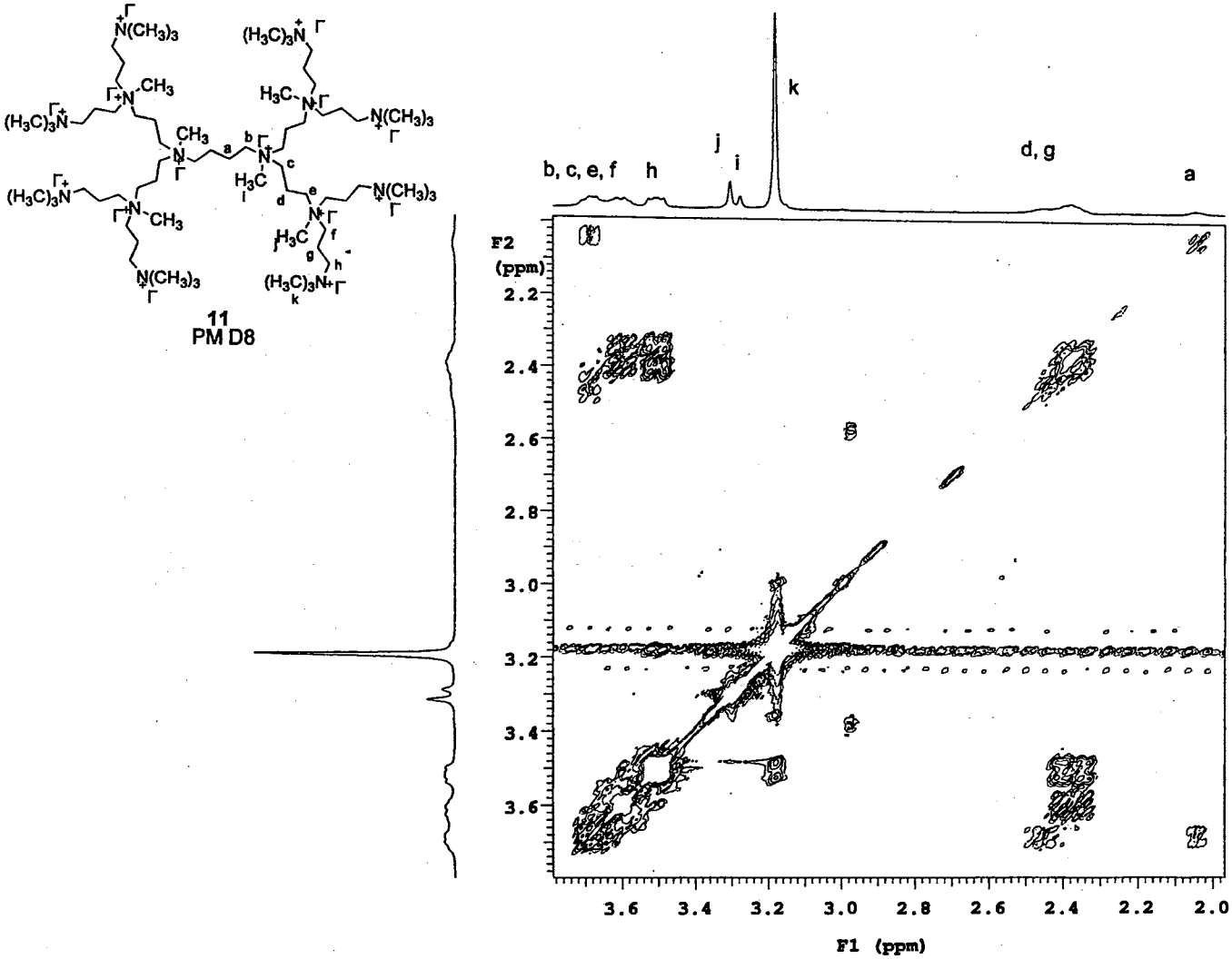


Figure 28. HMQC NMR spectrum of PM D8 (**11**) in D_2O (400 MHz ^1H frequency)

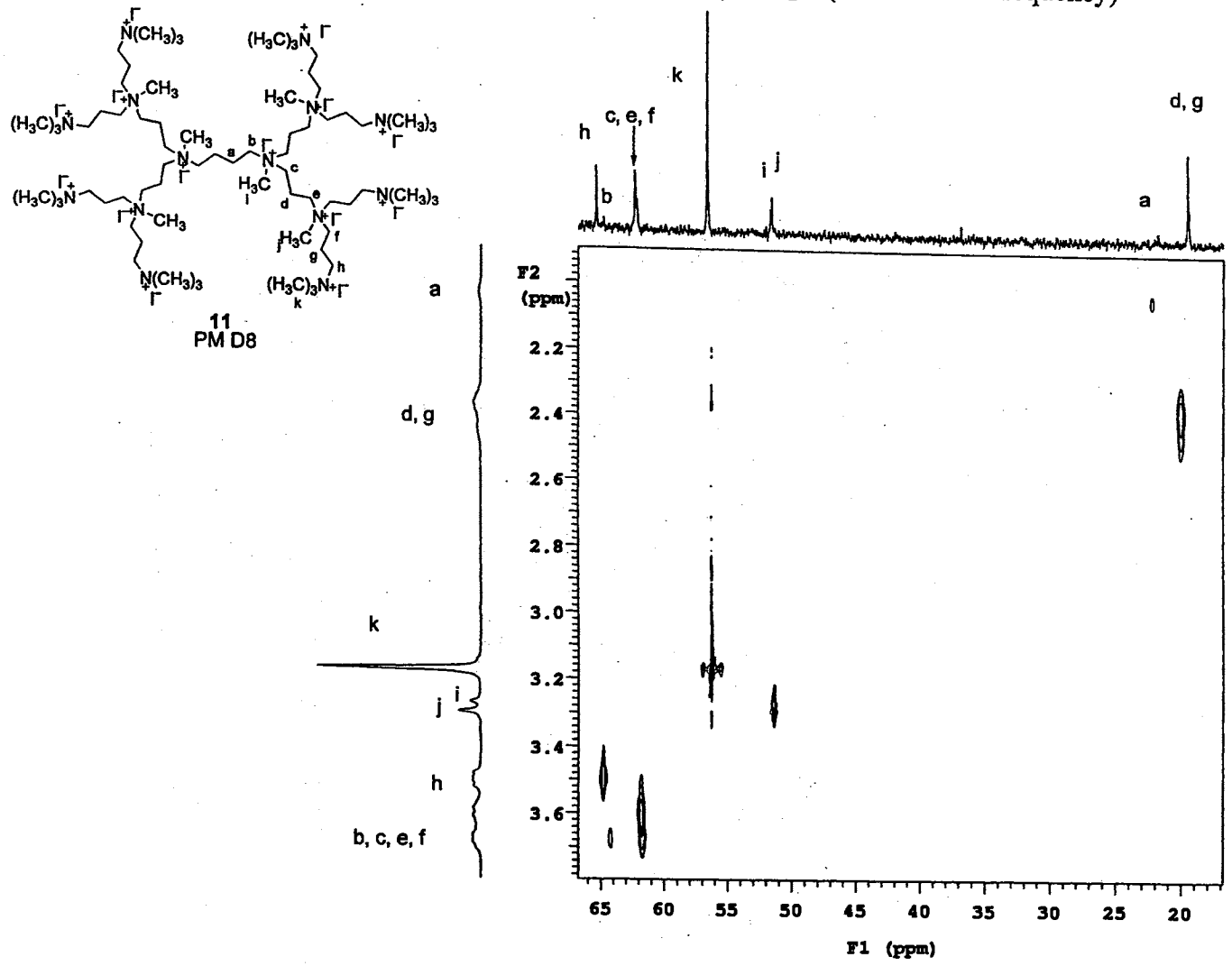


Figure 29a. ESI-MS spectrum of PM D8 (11) in D_2O (0-400 m/z)

PM D8
11, $C_{70}H_{170}N_{14}I_{14}$
Exact Mass: 2984.2

$(M - 14I)^{14+} = 86.2$
$(M - 13I)^{13+} = 102.6$
$(M - 11I)^{11+} = 144.3$
$(M - CH_3I - 10I)^{10+} = 157.3$
$(M - CH_3I - 8I)^{8+} = 228.3$
$(M - 7I)^{7+} = 299.4$
$(M - 2CH_3I - 6I)^{6+} = 323.1$
$(M - 6I)^{6+} = 370.4$

Signals at 100.0 and 115.5 were residual in the detector.

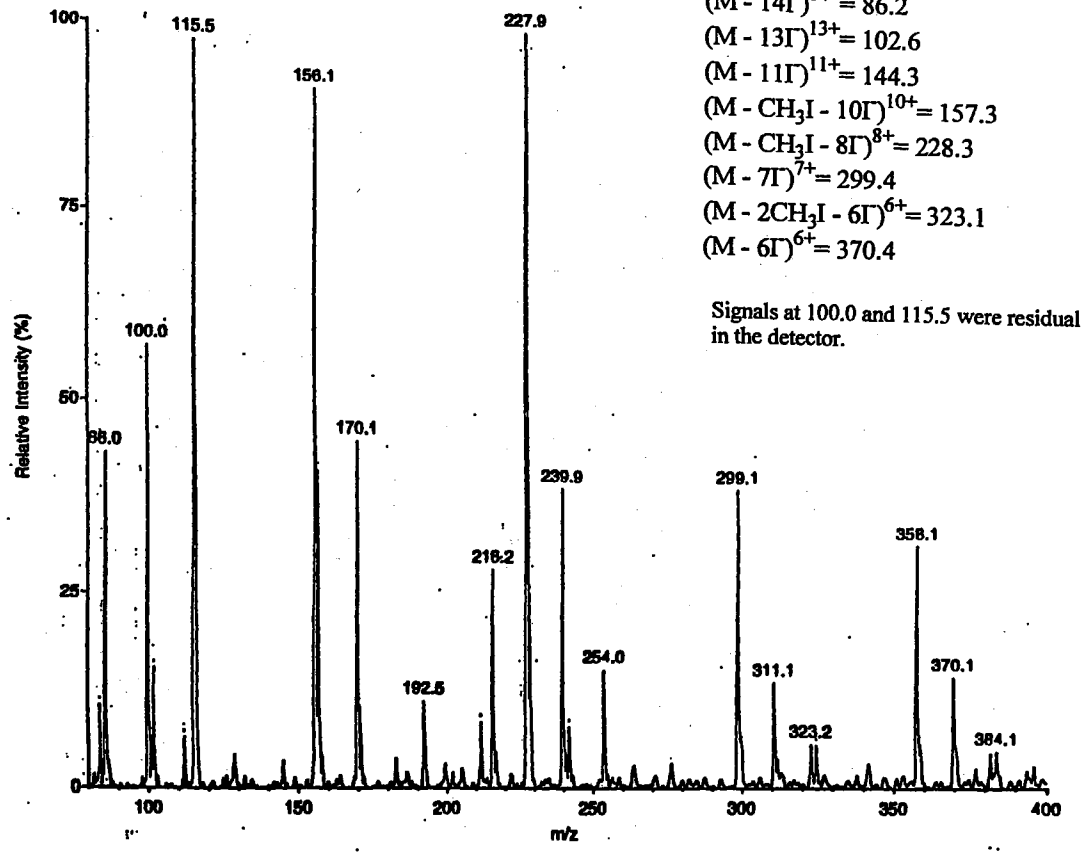


Figure 29b. ESI-MS spectrum of PM D8 (**11**) (400-1400 m/z)

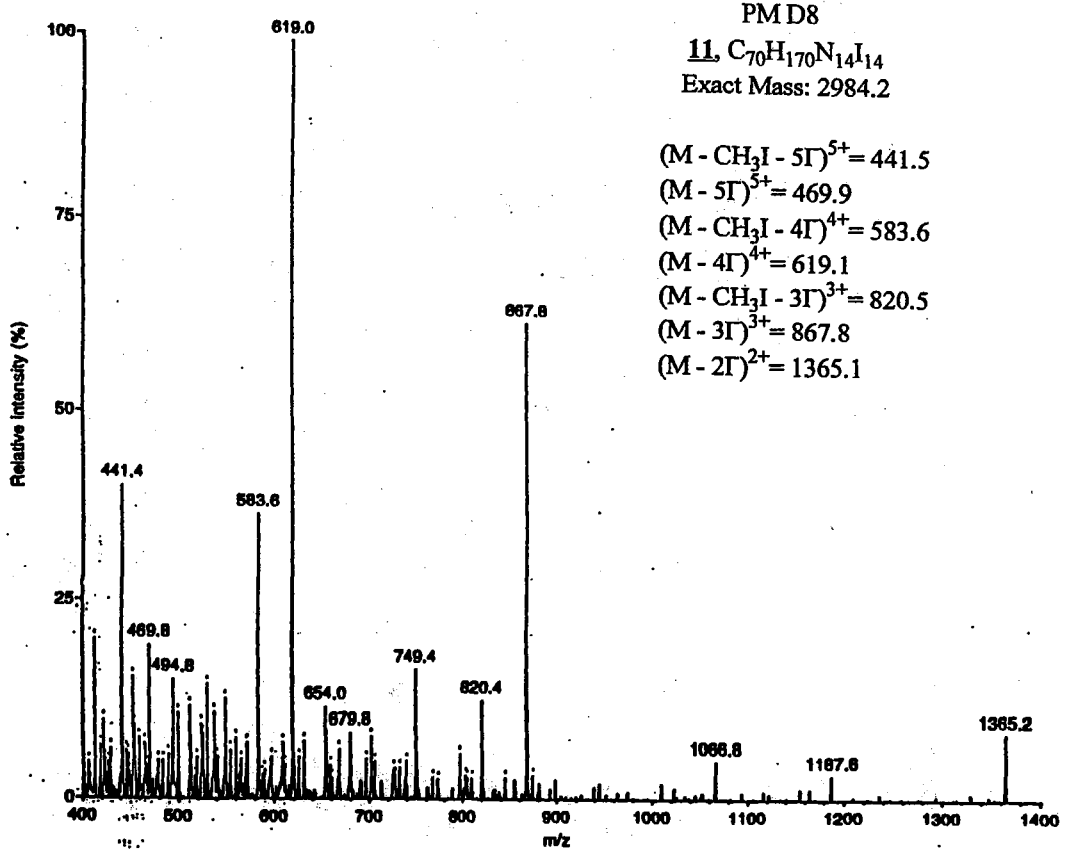


Figure 30. 400 MHz ^{1}H NMR spectrum of PM D32 (**12**) in D_2O

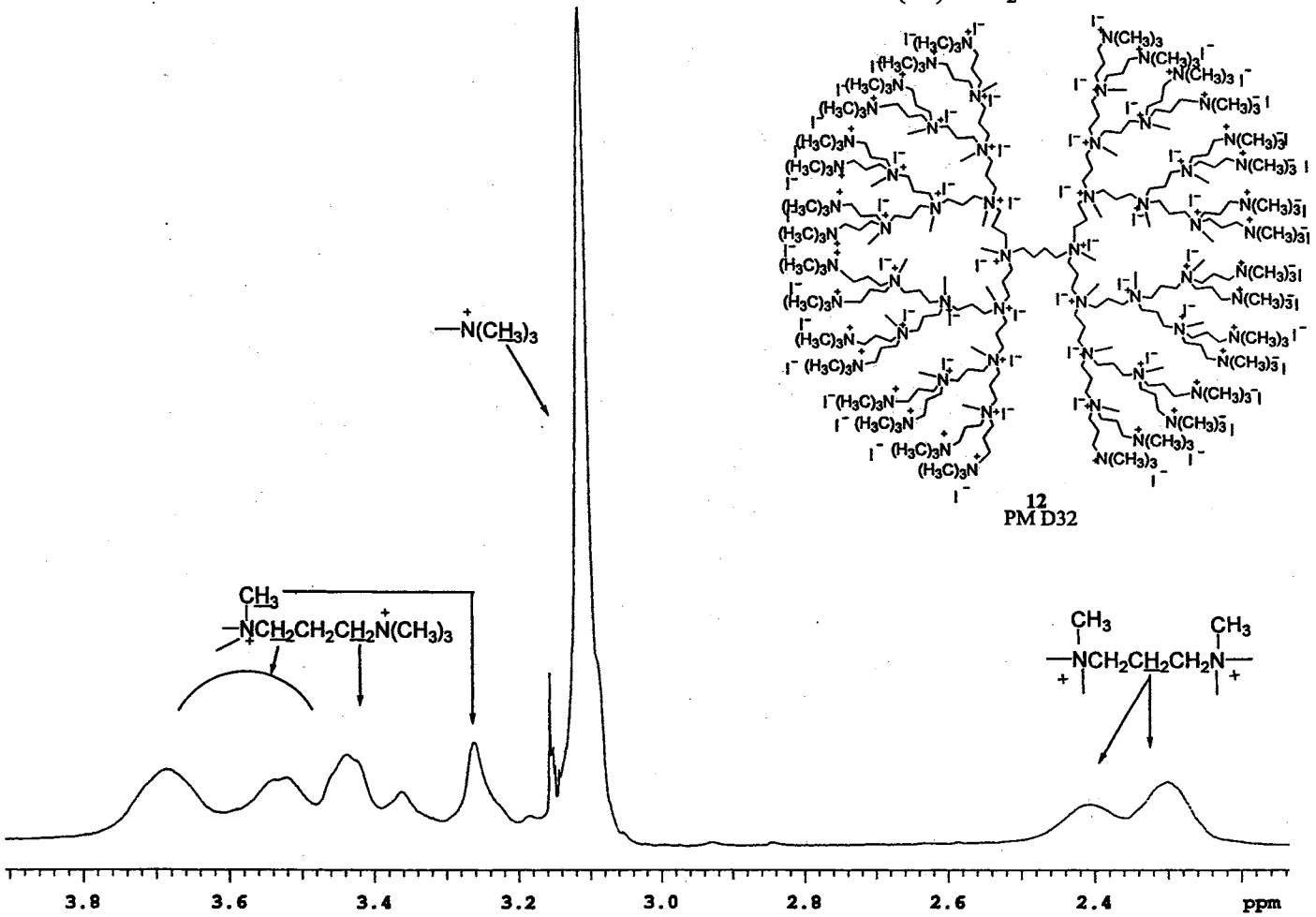
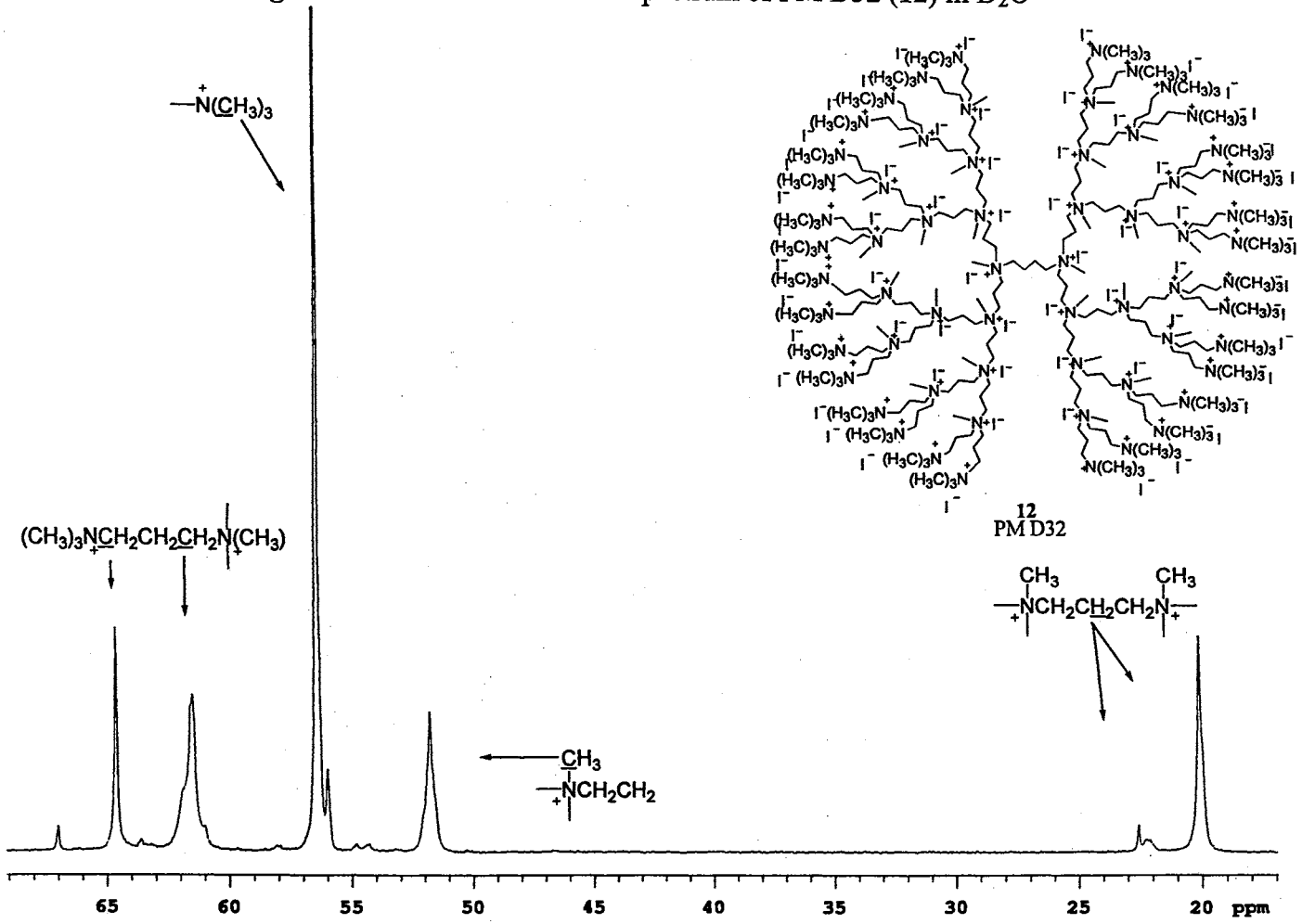


Figure 31. 100 MHz ^{13}C NMR spectrum of PM D32 (**12**) in D_2O



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PM D32

Figure 32. 400 MHz ^{1}H NMR spectrum of PM D64 (**13**) in D_2O

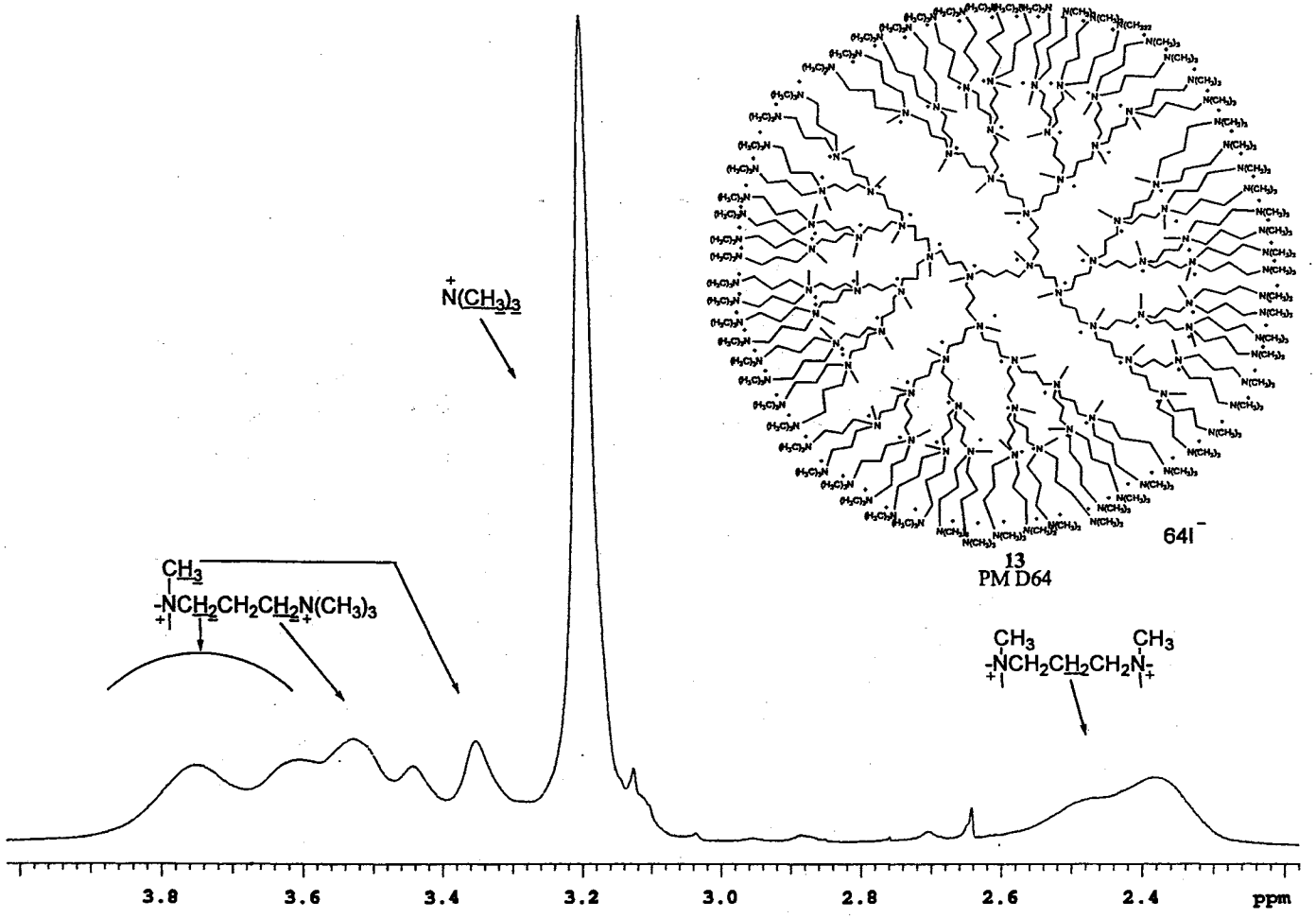


Figure 33. 100 MHz ^{13}C NMR spectrum of PM D64 (**13**) in D_2O

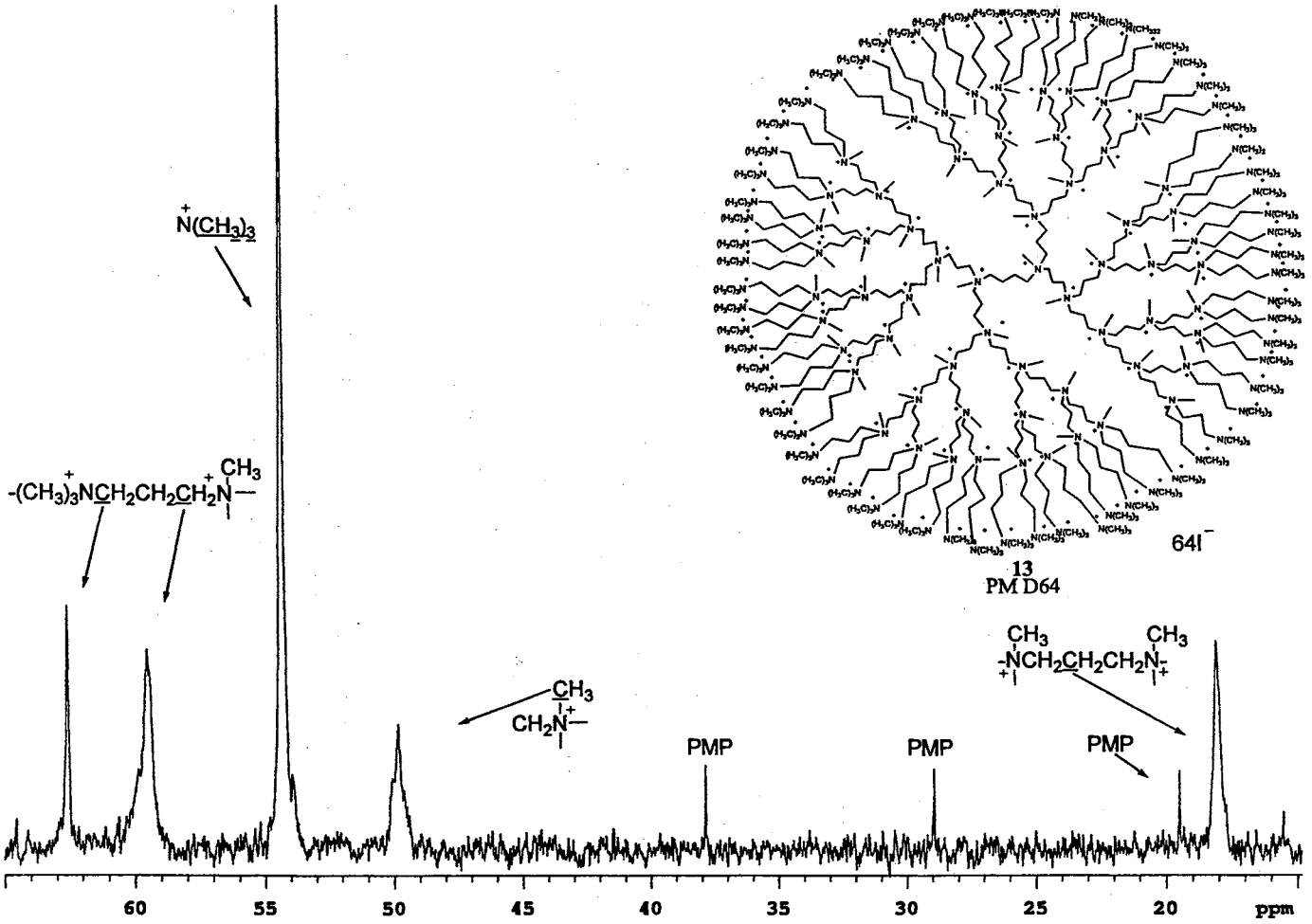


Figure 34. 300 MHz ^{1}H NMR spectrum of D8-C(O)-MPEG$_{164}$ (**16**) in D_2O

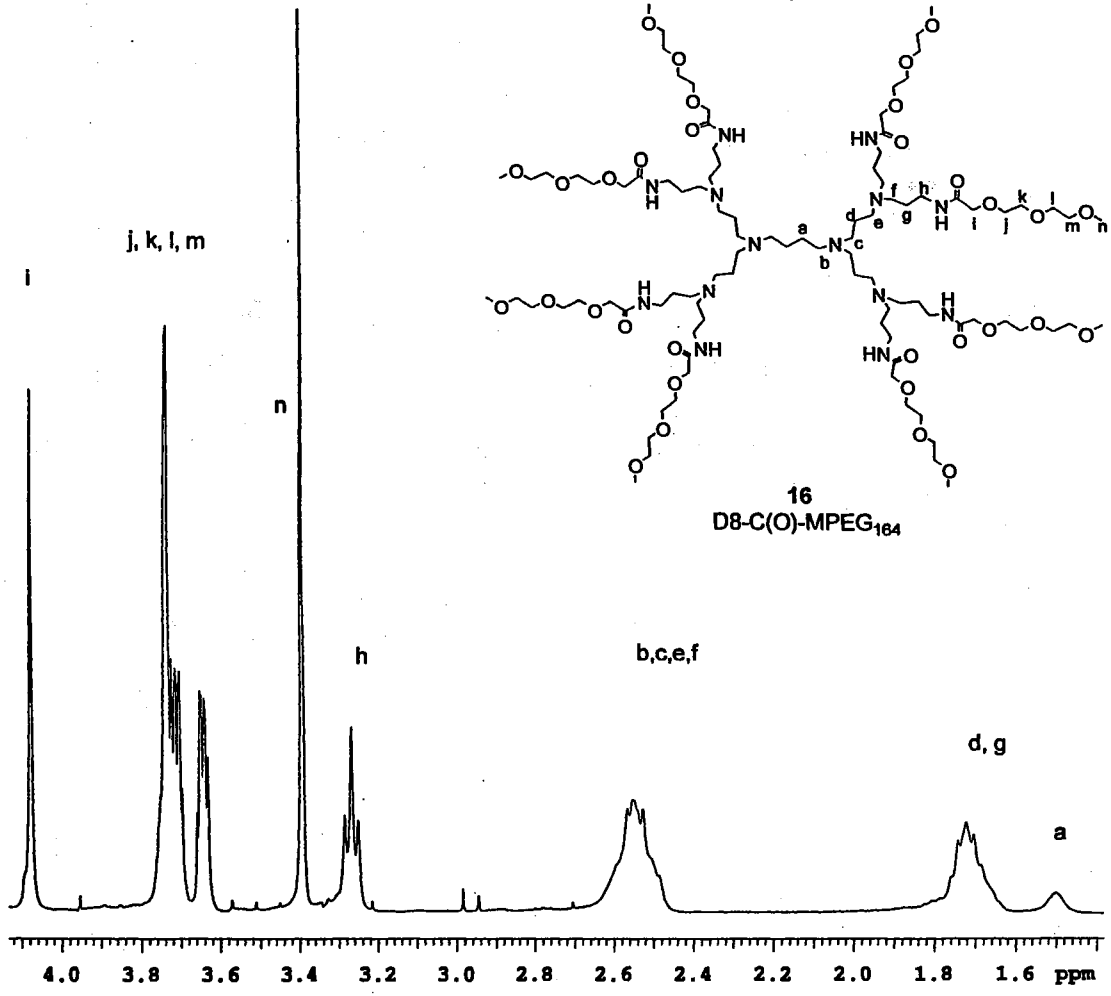


Figure 35. 100 MHz ^{13}C NMR spectrum of D8-C(O)-MPEG$_{164}$ (**16**) in D_2O

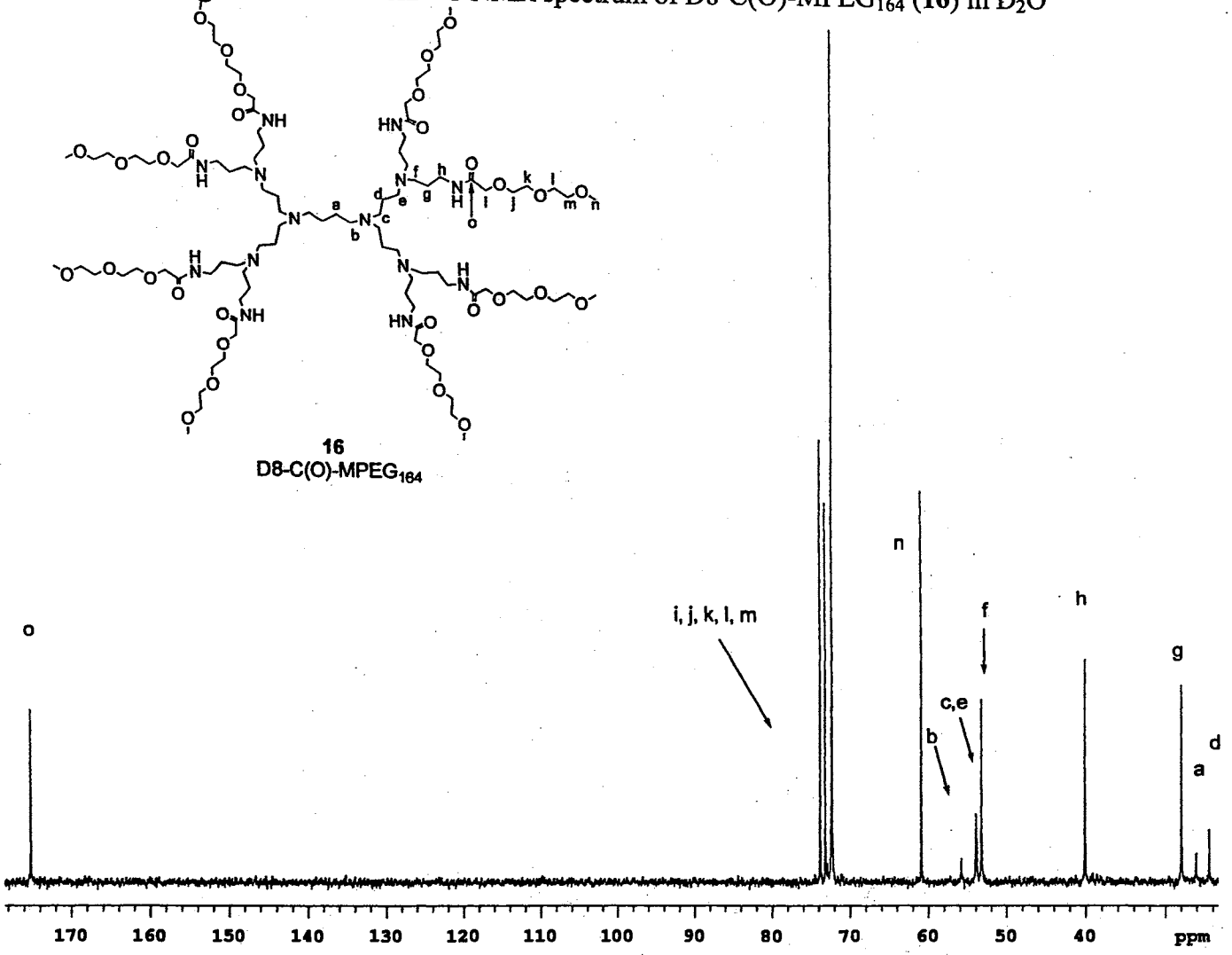


Figure 36. ESI-MS spectrum of D8-C(O)-MPEG$_{164}$ (**16**)

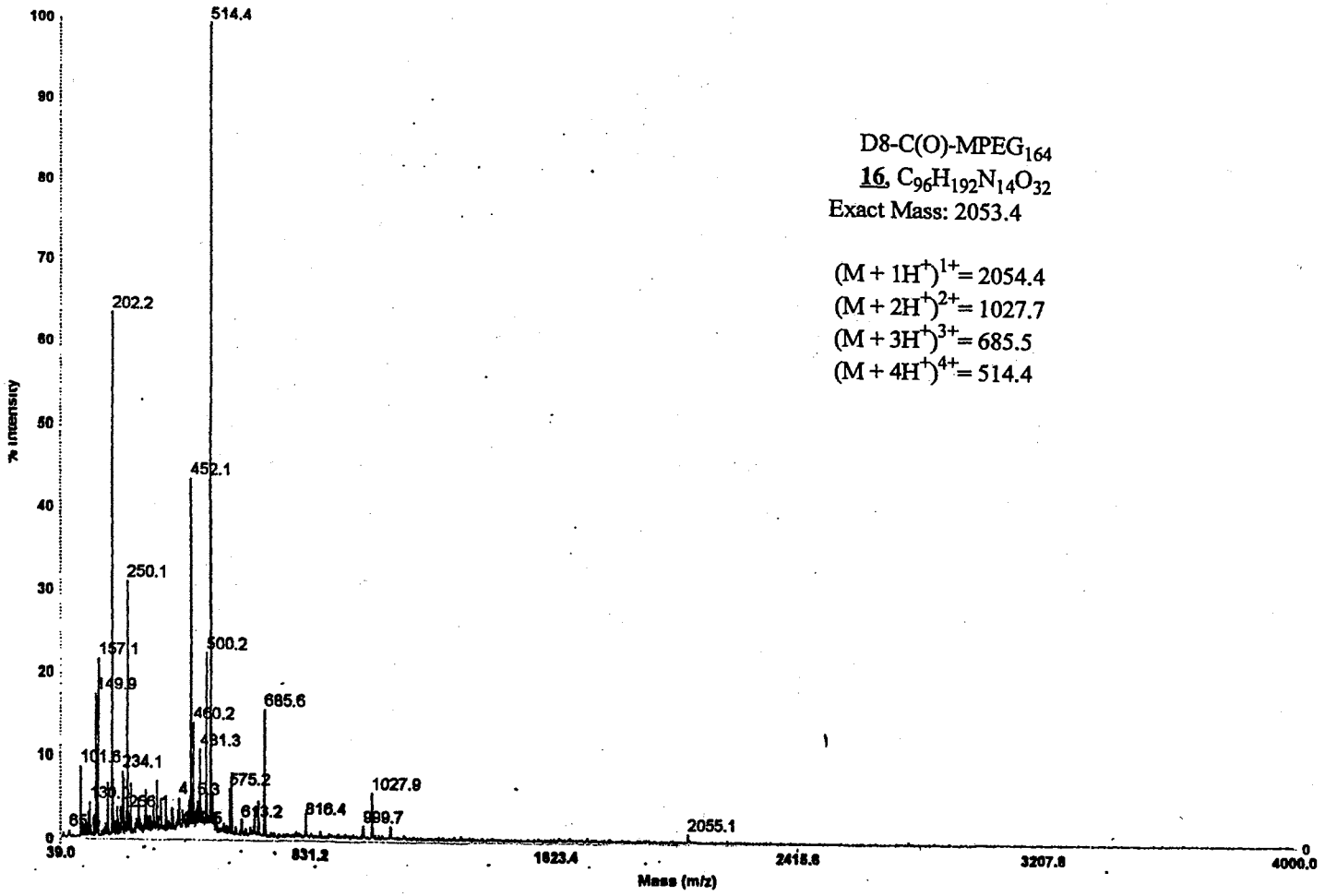


Figure 37. 300 MHz ^{1}H NMR spectrum of D32-C(O)-MPEG$_{164}$ (**17**) in D_2O

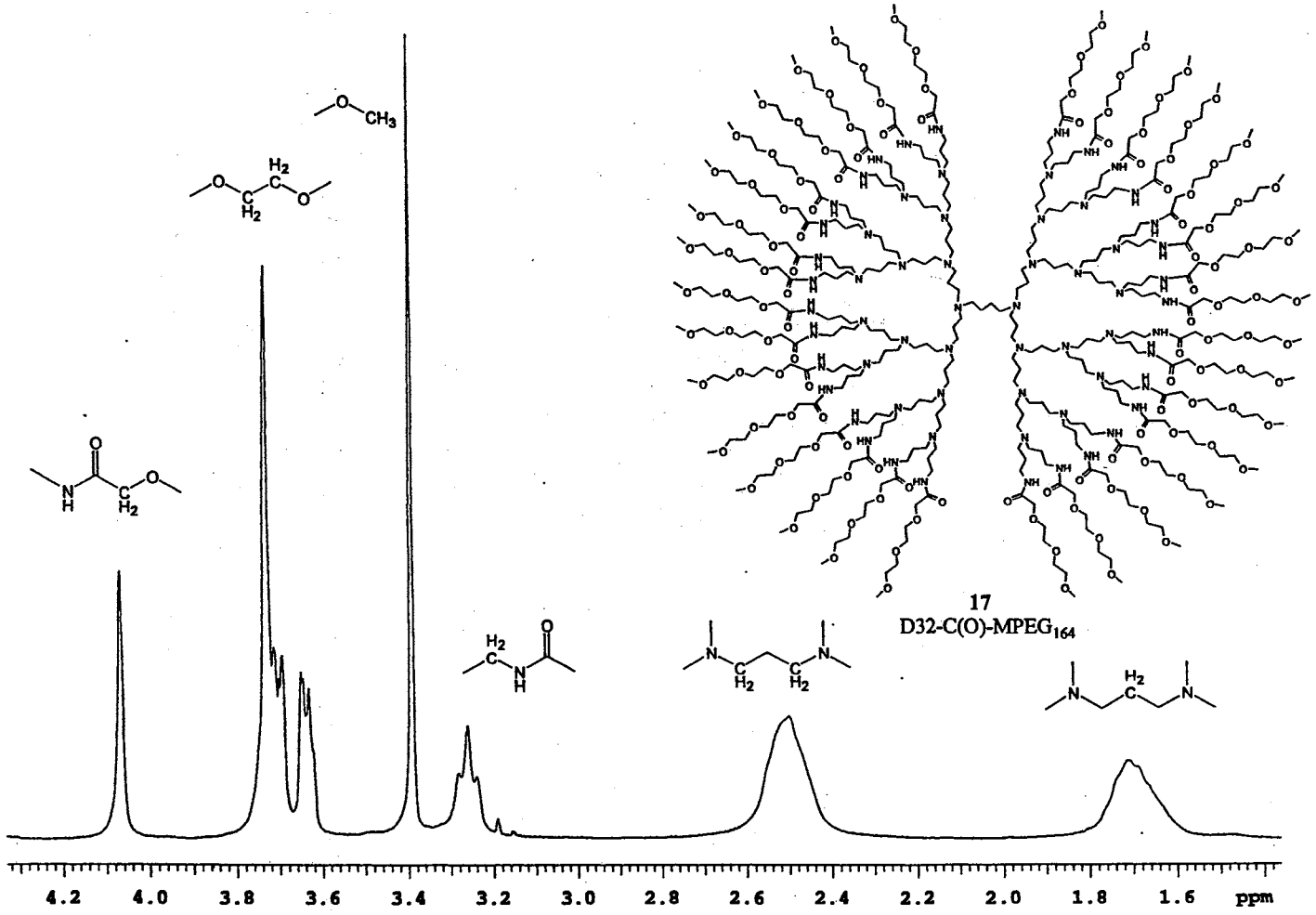


Figure 38. 100 MHz ^{13}C NMR spectrum of D32-C(O)-MPEG$_{164}$ (**17**) in D_2O

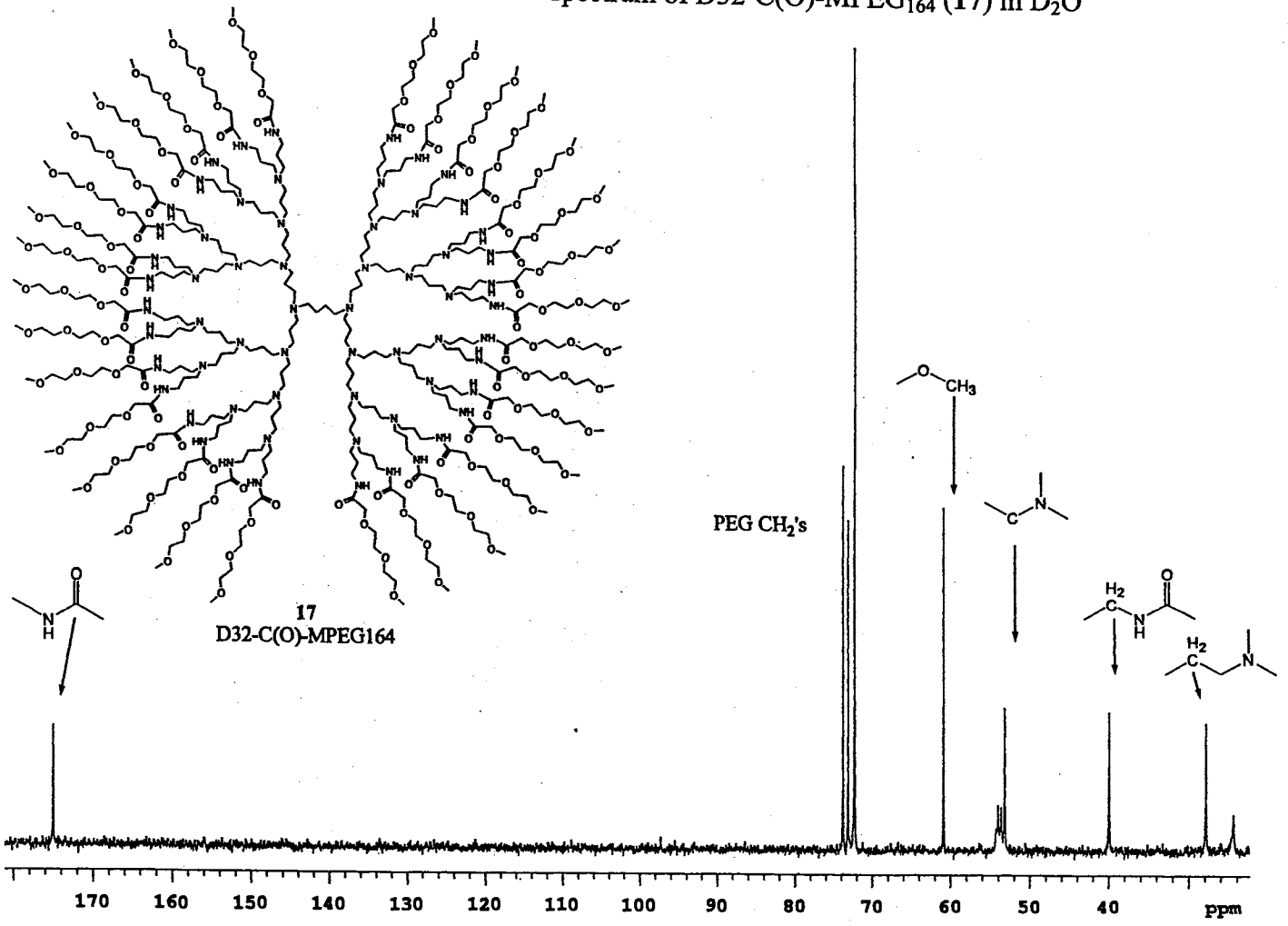


Figure 39. ESI-MS spectrum of D32-C(O)-MPEG$_{164}$ (**17**)

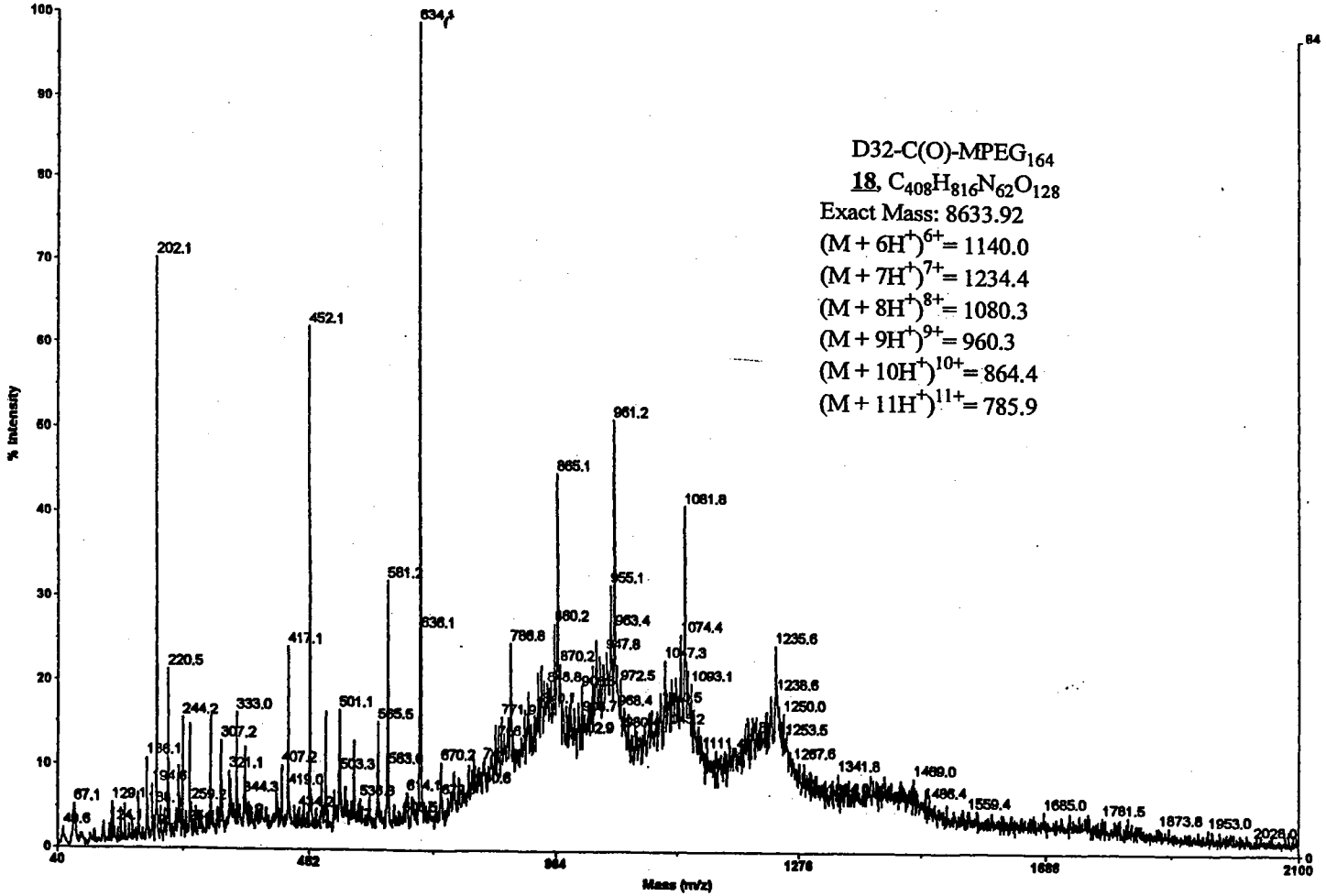


Figure 40. 400 MHz ^{1}H NMR spectrum of IM D8-C(O)-MPEG$_{164}$ (**18**) in $CDCl_3$

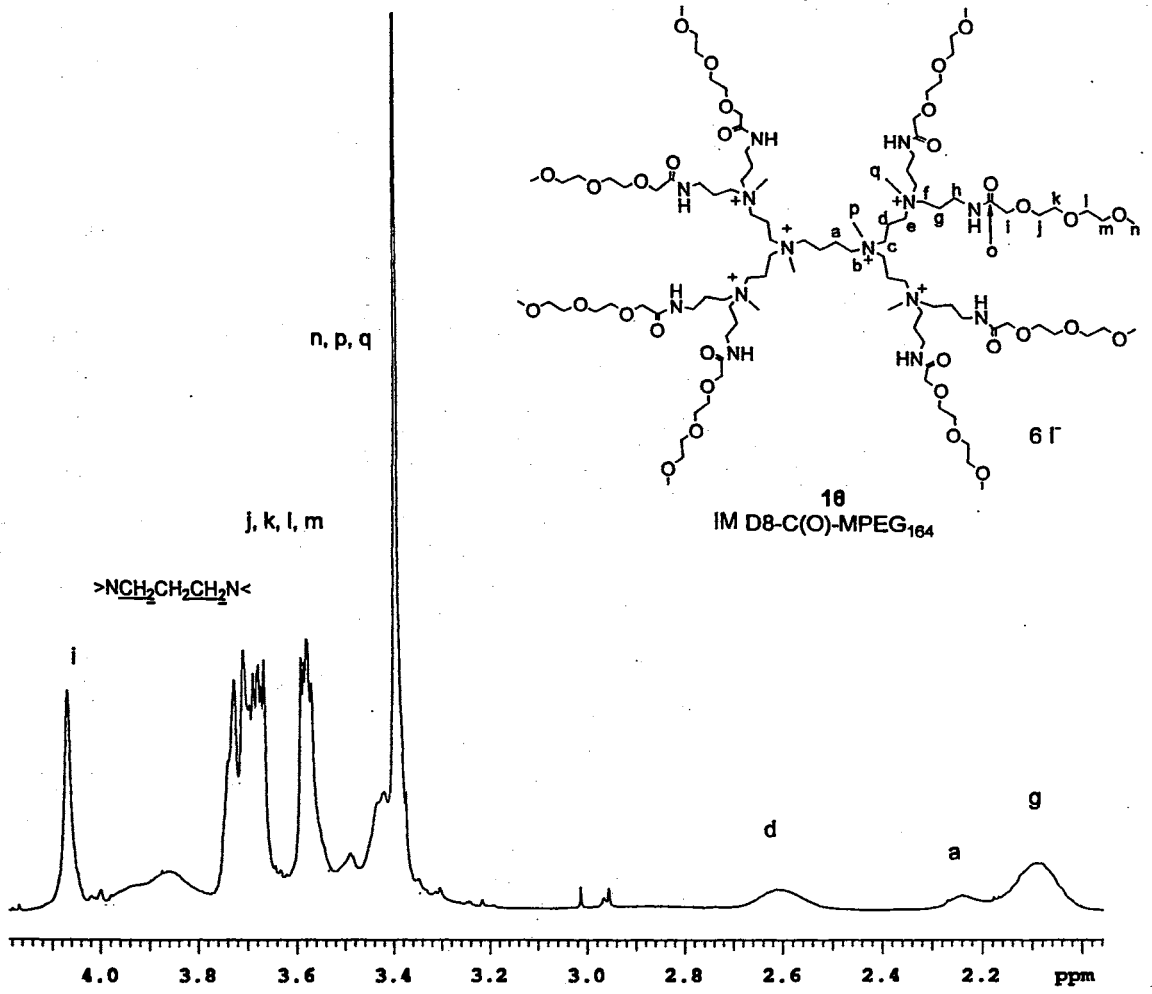


Figure 41. 100 MHz ^{13}C NMR spectrum of IM D8-C(O)-MPEG$_{164}$ (**18**) in $CDCl_3$

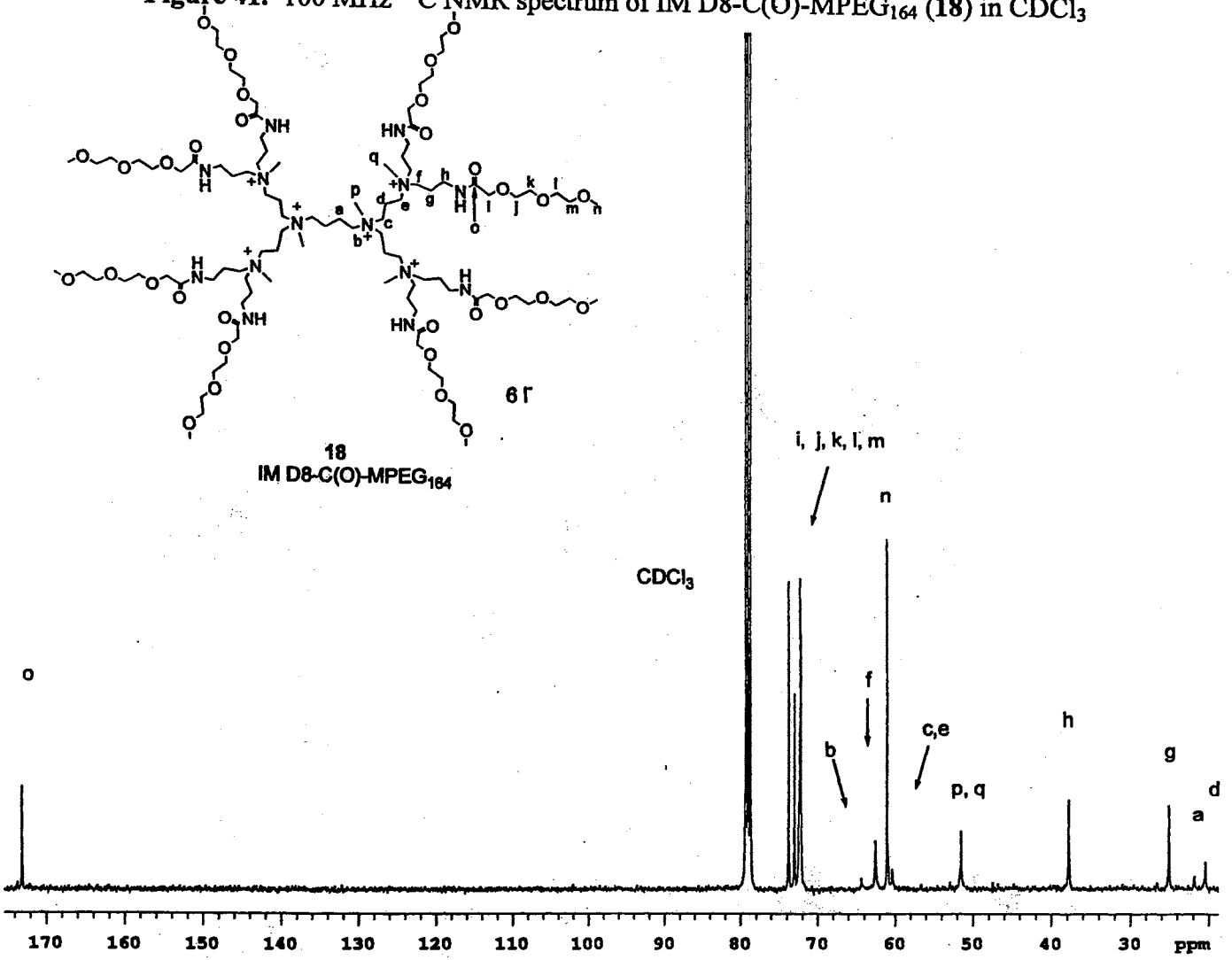


Figure 42. 300 MHz ^{1}H NMR spectrum of IM D32-C(O)-MPEG$_{164}$ (**19**) in $CDCl_3$

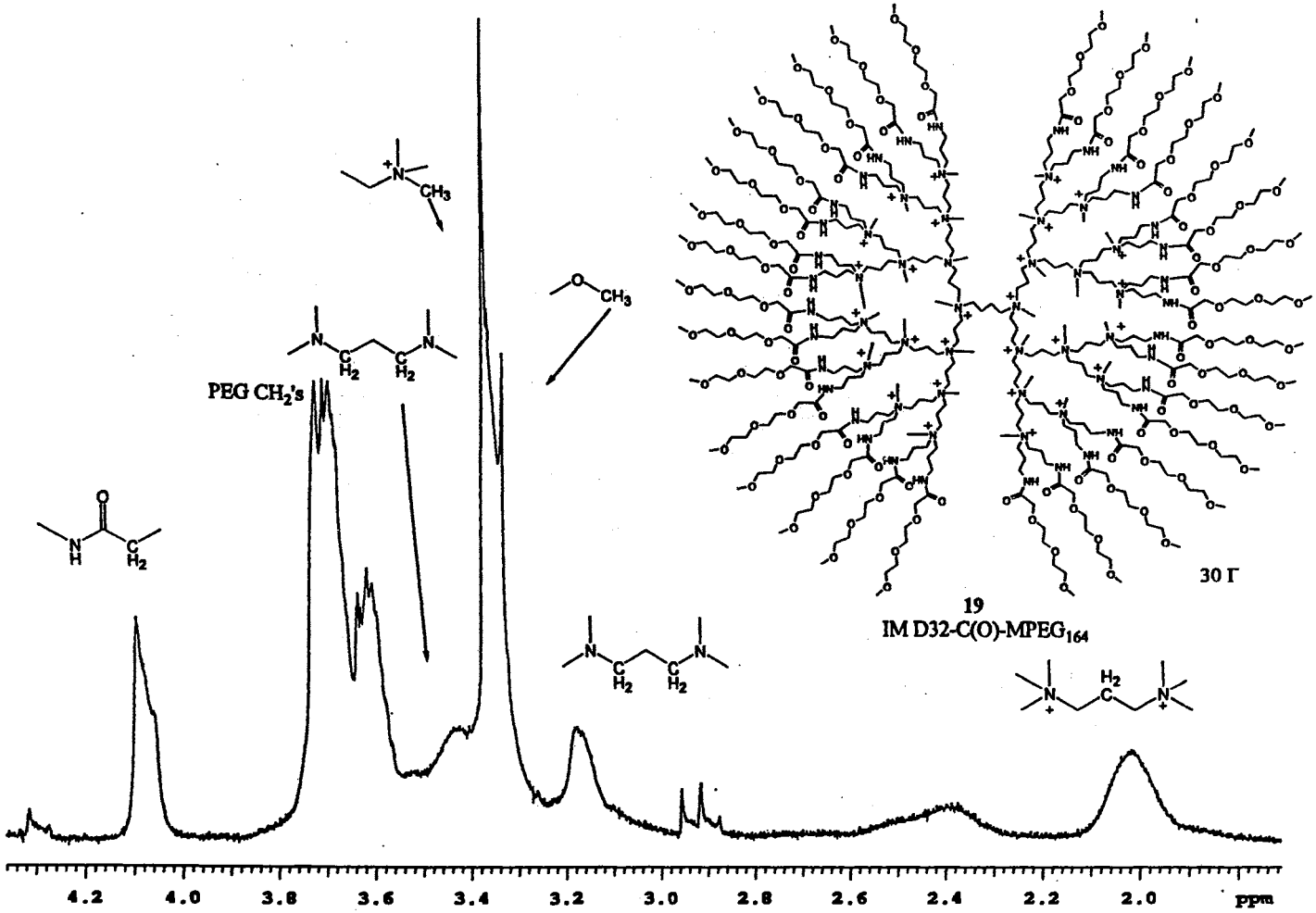


Figure 43. 75 MHz ^{13}C NMR spectrum of IM D32-C(O)-MPEG$_{164}$ (**19**) in D_2O

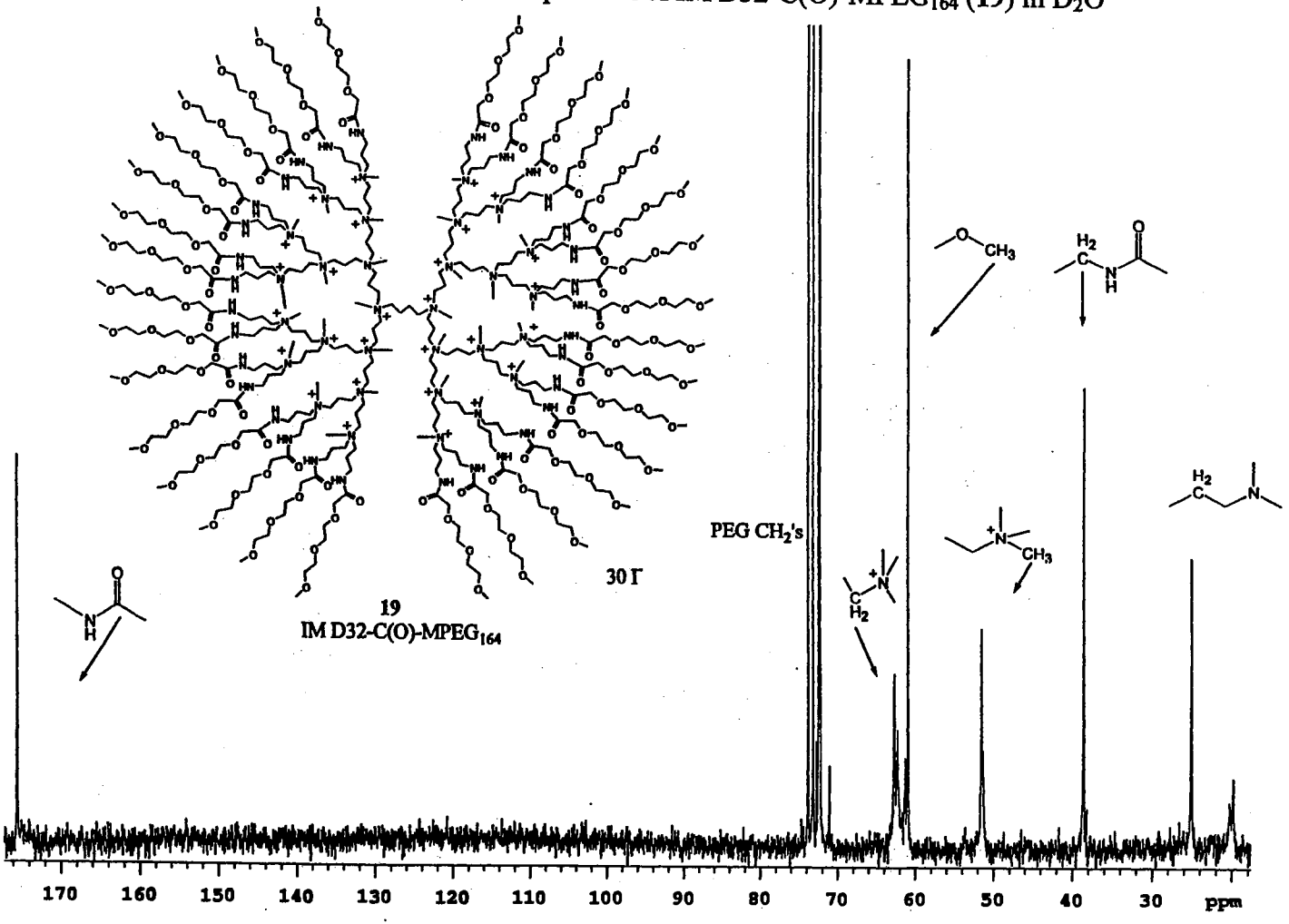
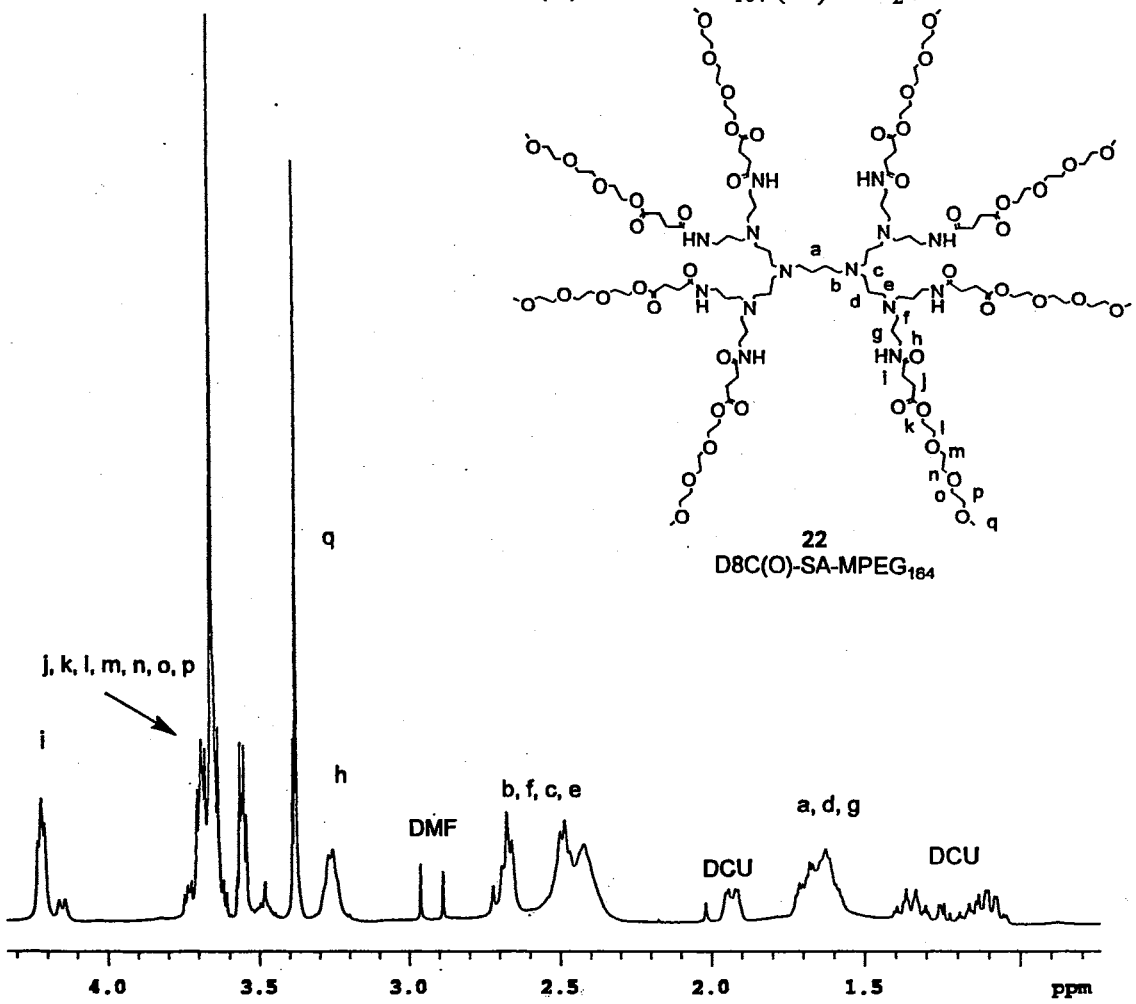


Figure 44. 300 MHz ^{1}H NMR spectrum of D8-C(O)-SA-MPEG$_{164}$ (**22**) in D_2O



VITA

Jason L. Kreider

Candidate for the Degree of

Doctor of Philosophy

Thesis: PREPARATION AND CATALYTIC ACTIVITY OF POLY(PROPYLENE IMINE) DENDRIMERS QUATERNIZED BY METHYLATION

Major Field: Chemistry

Biographical:

Personal Data: Born in Columbia, Missouri on August 10, 1972, son of Jack and Sandra Kreider. Married to Angela Baughman on June 27, 1998.

Education: Received Bachelor of Science Degree in Chemistry and in Biology at Louisiana College, Pineville, Louisiana in May 1994. Completed the requirements for the Doctor of Philosophy with a major in Chemistry at Oklahoma State University, Stillwater, Oklahoma in December, 2000.

Experience: Research Assistant. Department of Chemistry, Oklahoma State University. 1995-2000. Industrial Research Intern. Baker Petrolite, Sugar Land, Texas. 1997. Teaching Assistant. Department of Chemistry Oklahoma State University. 1994-1997. Teaching Assistant. Department of Chemistry and Physics, Lousiana College 1991-1994.

Professional Memberships: American Chemical Society, Phi Lambda Upsilon Honorary Chemical Society.