

Synthesis and Characterization of Novel Azacrown Core Dendrimers and Functional Dendrons with Long Alkyl Chain Spacers

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We report the synthesis of novel azacrown core dendrimers and siloxy and hydroxy focal point dendrons containing long alkyl chain spacers up to 3rd generation. The starting materials were reacted with methylacrylate in Michael addition followed by amidation. In each step, dendrimer/dendron was characterized by spectroscopic methods. The dendrimers/dendrons are expected to have specific behavior for solubilization in their cavernous interiors suitable for encapsulation of doping reagents.

Key words: poly(amido amine), dendrimer, dendron, long alkyl chain spacer, synthesis, characterization

1. INTRODUCTION

Dendrimers have attracted attention of the chemists in recent years due to their unique properties and applications in various fields[1,2]. Dendrimers are monodisperse and have many end functional groups that can be linked with other chemical moieties[3]. Thus the physico-chemical properties of dendrimers can be greatly modified. Furthermore, considering the internal space in dendrimer, a variety of biologically active reagents and metal nanoparticles can be incorporated into dendrimers[4-6]. Many important theoretical suggestions have been developed to test models[7], and actual synthesis of materials is still challenging[8,9].

Dendrons have structures that contain multiple branch points as traverse from the focal point to the peripheral points of the molecular structure. Such a structure has been found great utility in the preparation of dendrimers in which several of the dendrons are covalently linked to core structure[10]. Using dendrons as building blocks, many novel architectures can be developed. These might include dendrons attached via their focal points to substrate and the use of the dendrons as highly branched ligands surrounding a metallic or semiconducting nanoparticle [4,5,11]. In the present work we report the synthesis of novel functional long alkyl chain spacers dendrimers and dendrons useful in supramolecular chemistry, nanoparticle science, and drug delivery system[12].

2. EXPERIMENTAL

2.1. Materials

1,4,7,10,13,16-hexaazacyclo octadecane (Cyclen), methylacrylate, hexamethylenediamine, methanol, CH₃ONa, 3-aminopropyltriethoxysilane, 2-amino ethanol, were received either from Aldrich or Tokyo Kasei Kogyo Co. Ltd. and were used without further purification.

2.2. Synthesis of dendrimers and dendrons

Azacrown core-containing poly(amido amine)

(PAMAM) dendrimers (G0.5Aza to G3Aza, G: generation) were synthesized by repeating two steps as Michael addition and amidation reactions. Excess reagents and solvents were removed completely, and the products were characterized before starting next reaction. Typical dendrimer synthesis was carried as follows: G2Aza (1.0 g, 5.6 mmol) was dissolved into 20 cm³ methanol, and a methanol solution of methylacrylate (5.0 cm³, 0.1 mol) was added dropwise. A methanol solution of CH₃ONa (1 to 2 drops) was added as catalyst. The mixture was stirred in the dark at room temperature for 6 days. The solvent and excess methylacrylate were removed under vacuum to give yellow oil-like half generation (2.3 g, 80 % yield). (G2.5Aza) elemental analysis (FW 5389) (C₂₇₀H₄₉₈N₄₂O₆₆) Calculated C60.17, H9.31, N10.91; Observed C59.88, H9.60, N10.60; FTIR(neat) 3343, 2942, 2859, 2822, 1730, 1641, 1549, 1433, 1354, 1325, 1273, 1201, 1030 cm⁻¹.

Amidation reaction was performed as follows: Half generation product (G2.5, 1.3 g) was dissolved in 40 cm³ methanol and hexamethylene diamine (2.0 g, 3 mol) was added dropwise. The mixture was stirred in the dark at room temperature for 6 days and the excess of solvent and hexamethylene diamine was removed under vacuum to give a viscous yellow oily product (2.2 g, 98 % yield). (G3Aza) elemental analysis (FW 7445) (C₃₉₀H₈₂₂N₉₀O₄₂) Calculated C62.91, H11.12, N16.93; Observed C63.05, H11.49, N17.34; FTIR(neat) 3304, 3196, 3096, 2928, 2857, 1643, 1555, 1456, 1377, 1319, 1124, 1059 cm⁻¹; UV-Vis (methanol) $\lambda_{\max}(\epsilon) = 210 \text{ nm} (9.34 \times 10^9 \text{ mol}^{-1} \text{ cm}^2)$; ¹H-NMR (500MHz, CD₃OD) $\delta = 1.30\text{-}1.31 \text{ (m, 128 H)}, 1.42\text{-}1.46 \text{ (m, 128 H)}, 2.27\text{-}2.29 \text{ (t, 48 H)}, 2.31\text{-}2.33 \text{ (t, 48 H)}, 2.39\text{-}2.41 \text{ (t, 84 H)}, 2.51\text{-}2.54 \text{ (t, 84 H)}, 2.56\text{-}2.58 \text{ (t, 168 H)}, 2.68\text{-}2.69 \text{ (t, 84 H)}, 2.75\text{-}2.77 \text{ (t, 84 H)}, 3.10\text{-}3.12$

(t, 24 H), 3.25-3.26 (t, 42 H) ppm.

Synthesis of functional dendrons, siloxy functional dendron (Den A) hydroxy functional dendron (Den B) (G1 to G3) was performed in two steps of Michael addition and amidation by repeating the two steps. Typical dendron synthesis for Den A has been presented as below: On a Michael addition reaction, 50 cm³ double necked round bottom flask equipped with nitrogen gas inlet and water reflux condenser, methylacrylate (12.0 cm³, 50 mol) in methanol was added dropwise in to a methanol solution of G2Den A (2.0 g, 10 mmol). Nitrogen gas was flushed, and the reaction solution was stirred at room temperature for 1 day. After the completion of reaction, the excess solvent and unreacted methylacrylate were removed by vacuum distillation to give a yellow oil like liquid product (3.0 g, 90% yield). (**G2.5Den A**) elemental analysis (FW 1931) (C₉₅H₁₇₉N₁₃O₂₅Si) Calculated C59.07, H9.34, N9.24; Observed C59.88, H9.60, N10.60; FTIR(neat) 3292, 3185, 2932, 2853, 2828, 1738, 1651, 1555, 1435, 1373, 1199, 1116, 1033 cm⁻¹.

Typical amidation reaction for dendron synthesis was as follows: A Michael addition product G2.5Den A (1.2 g, 2 mol) was dissolved in 40 cm³ methanol and hexamethylene diamine (3.0 g, 10 mol) in methanol was added dropwise under nitrogen atmosphere. Whole reaction mixture was stirred at room temperature for 1 day. After the completion of reaction, excess methanol and hexamethylene diamine were removed by vacuum distillation to give a yellow oil like viscous product (2.0 g, 90% yield). (**G3Den A**) elemental analysis (FW 2604) (C₁₃₅H₂₇₅N₂₉O₁₇Si) Calculated C62.24, H10.64, N15.59; Observed C61.46, H11.30, N16.10; FTIR(neat) 3351, 3291, 3185, 2930, 2858, 2022, 1642, 1550, 1450, 1377, 1319, 1124, 1059 cm⁻¹; UV-Vis (methanol) λ_{max} (ε) = 212 nm (3.18 X 10³ mol⁻¹cm²); ¹H-NMR (500MHz, CD₃OD) δ = 1.35-1.36 (s, 112 H), 1.49-1.54 (m, 56 H), 2.36-2.38 (t, 16 H), 2.55-2.60 (t, 28 H), 2.60-2.65 (t, 28 H), 2.70-2.71 (m, 6 H), 2.80-2.82 (t, 15 H), 3.14-3.20 (t, 14 H) ppm.

G2.5Den B elemental analysis (FW 5389) (C₂₇₀H₄₉₈N₄₂O₆₆) Calculated C60.17, H9.31, N10.91; Observed C59.88, H9.60, N10.60; FTIR(neat) 3293, 3082, 2931, 2856, 1737, 1649, 1553, 1461, 1439, 1366, 1257, 1200, 1176, 1124, 1036 cm⁻¹.

G3Den B elemental analysis (FW 2443) (C₁₂₈H₂₅₉N₂₉O₁₅) Calculated C62.91, H11.12, N16.93; Observed C63.05, H11.49, N17.34; FTIR(neat) 3329, 3275, 3069, 2919, 2849, 1647, 1597, 1555, 1464, 1365, 1124, 1063, 1009, 954 cm⁻¹; UV-Vis (methanol) λ_{max} (ε) = 206 nm (10.28 X 10⁶ mol⁻¹cm²); ¹H-NMR (500MHz, CD₃OD) δ = 1.35-1.36 (m, 56 H), 1.50-1.57 (m, 28 H), 2.31-2.33 (t, 8 H), 2.36-2.38 (t, 16 H), 2.43-2.44 (t, 8 H), 2.56-2.59 (t, 16 H), 2.67-2.69 (t,

28 H), 2.70-2.73 (m, 28 H), 2.77-2.82 (m, 6 H), 3.04-3.06 (t, 15 H), 3.14-3.15 (m, 14 H) ppm.

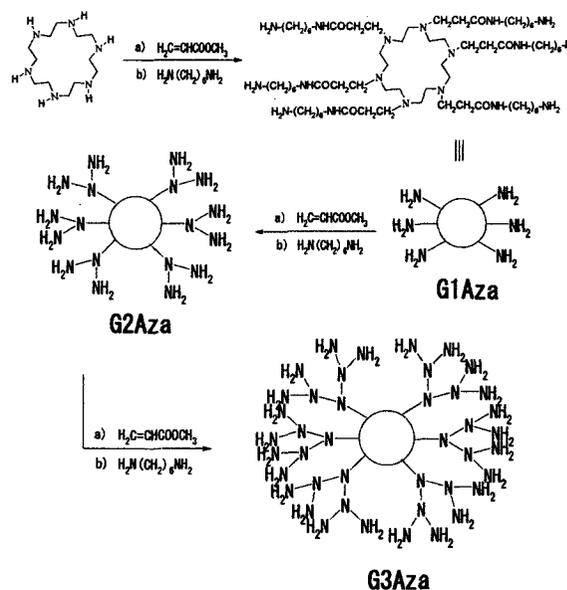
2.3. Measurements

Fourier transform infrared absorption spectra were recorded using a Bio-Rad FTS575C FT-IR spectrometer by sandwiching the liquid sample between calcium fluoride windows. Elemental analysis was performed on a LECO CHN 900C CHN analyzer. UV-Visible absorption spectra were recorded on a Shimadzu UV 2200 spectrometer. Solutions were prepared by dissolving samples (1mg/cm³) in methanol. NMR spectra were recorded on a JEOL LNCM3500 for samples (1mg/cm³) dissolved in a deuterated methanol. All the measurements were carried out at 25 °C.

3. RESULTS AND DISCUSSION

3.1. Synthesis of azacrown core-containing dendrimer:

Michael addition was used for the synthesis of the half-generation dendrimer. In this reaction, a slight excess of methylacrylate (10 mol%) was used for the alkylation step. However, for the synthesis of the integral generation, a very large excess of hexamethylene diamine (20 ~ 40 times in mol) was necessary to prevent bridging and gelation of dendrimers. Excess reagents and solvents were removed under vacuum (1mm Hg) at a temperature below 50 °C to avoid crossreactions. The typical synthetic procedure has been presented for (G2.5Aza and G3Aza) in experimental section, and similar procedure was followed for other dendrimers. The general synthesis scheme has been presented in Scheme 1.



Scheme 1: Scheme for synthesis of azacrown core-containing PAMAM dendrimers with hexamethylene spacers and amine terminal groups.

The progress of reaction of an azacrown core with methylacrylate in Michael addition and hexamethylene diamine in amidation reaction was monitored by infrared and UV-visible absorption spectra of reaction mixture to

confirm the completion of reaction. Comparative infrared absorption spectra of G2.5Aza and G3Aza were presented in Fig. 1. G2.5Aza shows an ester C=O stretching band at 1736 cm^{-1} [5,12]. However, G3Aza indicated amide I and II at 1643 and 1555 cm^{-1} [5,6,12]. The infrared spectrum of G3Aza also exhibited a band at 3304 cm^{-1} by NH_2 stretching mode, confirming that the terminal groups of dendrimer are primary amine. It also shows the other characteristic bands of amide A (3196 cm^{-1}), amide B (3096 cm^{-1}), and amide III (1319 cm^{-1}), confirming the predominant amide linkage in the dendrimer[5,6]. In addition, there were additional bands of CH_2 stretching modes (2942 , 2859 cm^{-1}), and a CH_2 bending mode (1456 cm^{-1})[5,6,12].

UV-visible absorption spectra of azacrown core PAMAM dendrimers show that the maximum absorption band (λ_{max}) value increases from 204 nm to 210 nm as the generation increases (from G1 to G3). Similarly its extinction coefficient (ϵ) value also

increases from 1.03×10^9 to $9.34 \times 10^9\text{ mol}^{-1}\text{cm}^2$. Elemental analysis is an important tool for the determination of molar mass of dendrimer during the synthesis. The elemental analysis data for dendrimers were in well agreement with theoretical values. In addition, the terminal groups have been estimated by potentiometric titration with 0.1 N HCl solution, corresponded to theoretical values. The results of elemental analysis and UV-visible absorption (λ_{max} and ϵ) with titration have been presented in Table I. Finally the dendrimer structure was confirmed by NMR spectra. All proton signals appeared in $\delta = 1.31$ to 3.26 ppm . They present the amide CONH proton peak ($\delta = 3.2\text{ ppm}$) and NH_2 characteristics peaks ($\delta = 2.39$ to 2.41 ppm) for amide and amine groups[7,12,13]. Predominantly ethylene (CH_2) protons ($\delta = 1.30$ to 1.46 ppm) and all signals match well with the structure of G3Aza dendrimer.

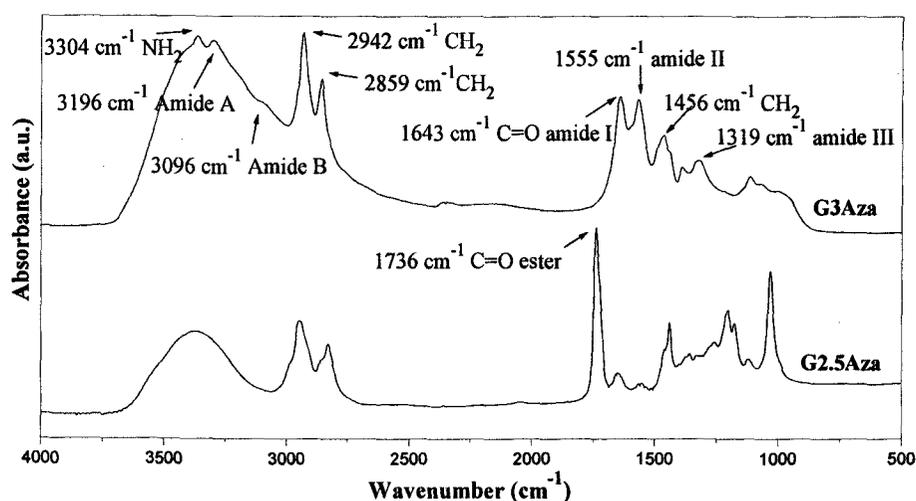


Fig. 1 Comparative infrared spectra of G2.5Aza and G3Aza

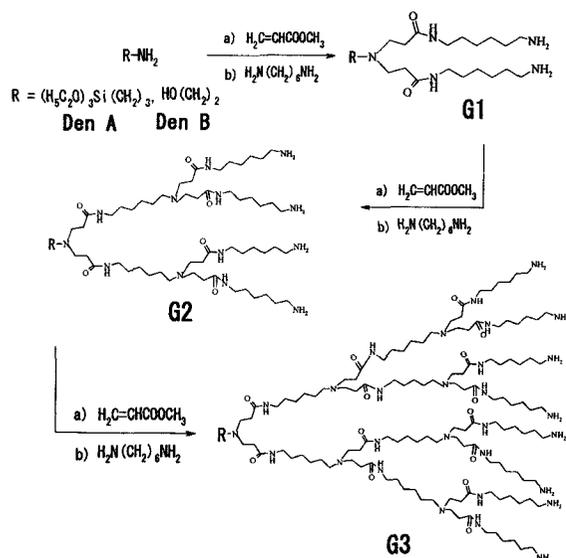
Table I: Elemental analysis data, UV-visible spectra and primary amine number of azacrown core dendrimers and siloxy and hydroxy focal point dendrons containing long alkyl chain spacers

Dendrimer /dendron	Elemental analysis						UV-Vis ^{d)} λ_{max}	ϵ	NH_2 group ^{e)}
	Calculated			Observed					
	C wt%	H wt%	N wt%	Cwt %	Hwt %	Nwt %	nm	$\text{mol}^{-1}\text{cm}^2$	
G1Aza ^{a)}	61.93	10.86	19.69	59.45	11.80	18.84	204	1.03×10^9	5.99
G2Aza	62.89	10.73	17.70	60.37	11.26	17.50	207	6.15×10^9	12.10
G3Aza	62.91	11.12	16.93	63.05	11.49	17.34	210	9.34×10^9	24.12
G1DenA ^{b)}	57.71	10.58	12.46	55.30	11.05	12.55	206	9.40×10^2	-f)
G2DenA	60.88	10.62	14.65	58.19	11.12	14.90	209	2.10×10^3	-f)
G3DenA	62.24	10.64	15.59	61.46	11.30	16.10	212	3.18×10^3	-f)
G1DenB ^{c)}	59.82	10.79	17.44	57.30	11.40	18.84	204	1.17×10^6	1.98
G2DenB	62.13	10.71	16.82	58.31	10.73	15.78	205	8.56×10^6	3.95
G3DenB	62.87	10.68	16.62	60.48	11.04	17.84	206	10.28×10^6	7.98

a) Azacrown core containing long alkyl chain spacer PAMAM dendrimers. b) Siloxane focal core functional long alkyl chain spacer dendron. c) Hydroxy focal core functional long alkyl chain spacer dendrons. d) in methanol ($1\text{ mg}/\text{cm}^3$), e) Obtained from titration with a 0.1 N HCl solution. f) Cannot be obtained as acid.

3.2. Synthesis of siloxane and hydroxy focal point dendrons:

Synthesis of functional long alkyl chain spacer PAMAM dendrons is a two-step process involving exhaustive Michael addition of suitable amine (3-aminopropyltriethoxysilane for siloxane and 2-amino ethanol for hydroxy) with methylacrylate and exhaustive amidation of resulting esters with large excess of hexamethylenediamine to obtain the functional dendrons. The complete reaction scheme has been presented in Scheme 2.



Scheme 2: Synthetic scheme for functional dendrons with siloxane and hydroxy focal points and long alkyl chain spacers.

The functional dendrons obtained were isolated as amorphous pale yellow viscous liquid, and the viscosity and color of product increased as generation increased from G1 to G3. Progress of reaction was monitored by infrared, UV-visible absorption and elemental analysis techniques. The ester terminated product formed deep blue color by mixing with $CuSO_4$ solution, whereas amine terminated product gives a deep purple colored solution by mixing with it[4]. An half-generation product presents the infrared absorption band (1738 cm^{-1}) of ester $C=O$ stretching mode[5] whereas an integer product shows a band at 1642 cm^{-1} for $CONH$ stretching mode[5]. UV-visible λ_{max} as well as extinction coefficient value increases as generation increases. The results of elemental analysis and spectroscopic data of functional dendrons have been presented in Table I. Finally, the constituted structures of dendrons were confirmed by NMR spectra. The characteristic amide peak appeared at $\delta = 3.20$ ppm, primary amine NH_2 $\delta = 2.38$ ppm, spacer CH_2 $\delta = 1.36$ ppm [4,11,12].

Conducting both the alkylation and amidation steps at lower temperatures (i.e. 25 to 50 °C) are important[4]. Higher temperatures (i.e. >80 °C) are detrious to ideal starburst branching due to not only intramolecular cyclization but also retro-Michael reaction, dendron bridging, crosslinking reaction and gelation[4,12]. It has been found that the reaction could be reversed in the first generation at high temperatures (i.e. >100 to 120 °C)

either in presence or absence of diamine, and hence the reactions were proceeded below 50 °C [4,11,12].

Dendron and dendrimer analysis by titrimetry was supportable. Titration of full generations (G1, G2 and G3) with 0.1 N HCl presents that the equivalents of acid required were in close agreement with the theoretical values calculated for terminal primary amines (see Table I). The distinctive endpoints exhibited by these polyamines are quite different from those observed for other poly(ethyleneimine)[4,13]. Barucci et. al [13] have shown that PAMAM exhibits unique titration character.

3.3. Conclusions

We reported the synthesis of new class of topological macomolecules with functional core or focal point and with long alkyl chain spacers. Azacrown core-containing dendrimers are useful in encapsulating guest molecules like metal nanoparticle, vitamin A, fullerene, etc. Siloxane functional focal point dendrons are useful in metal nanoparticle synthesis for various applications, while hydroxy functional focal point dendrons are useful in formation of block copolymers.

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