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Convergent synthesis of PAMAM dendrimers using click chemistry of azide-functionalized PAMAM dendrons

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Abstract—Azide-functionalized PAMAM dendrons containing an azidopropylamine focal point were synthesized by the divergent method and applied for the construction of symmetric PAMAM-like dendrimers containing 1,2,3-triazole rings as connectors via stitching with two different multi-terminal alkynes. The stitching method was based on the click chemistry protocol, i.e., the copper-catalyzed cycloaddition reaction between an alkyne and an azide.

1. Introduction

Organoazides are versatile intermediates in synthetic organic chemistry, because the azide group can subsequently be converted into several other types of substituent groups.[1] Azides are among the most stable 1,3-dipoles and generally can be stored for indefinite time without significant decomposition. Since the 1,3-dipolar cycloaddition of azides with alkynes was investigated by Huisgen et al.,[2] it has been attracted much attention because of the synthetic importance of the five-membered [1,2,3]-triazole heterocycles.[3] The traditional method for producing the triazoles by cycloaddition requires elevated temperature, typically in refluxing conditions and also provides a mixture of 1,4- and 1,5-disubstituted triazoles. Over the years, several efforts to control the 1,4- versus 1,5-regioselectivity have been reported.[4] Recently the click chemistry,[5] which is the Cu(I)-catalyzed Huisgen [2+3] dipolar cycloaddition reaction between an organic azide and a terminal alkyne, has found many applications[6] in combinatorial and organic chemistries, bioconjugations, and materials science. The reaction, characterized by very high yields, mild and simple reaction conditions, excellent oxygen and water tolerance, and simple product isolations, is highly chemoselective affording only the desired 1,2,3-triazole even in the presence of a large variety of other functional groups.

Dendrimers, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies, are highly branched and regular macromolecules with well-defined structures and have served as functional objects in nanotechnology and nanoscience.[7] The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.[8] The convergent methodology installs the core in the final step, enabling the incorporation of functionalities. It provides greater structural control than the divergent approach due to its relatively low number of coupling reactions at each growth step. The ability to prepare well-defined symmetrical dendrimers is the most attractive features of the convergent synthesis. By far the most widely used dendrimers prepared by convergent syntheses are the poly(benzyl ether)s, developed by Fréchet and Grayson,[8c] and the poly(arylethynyl)s developed by Moore and co-workers. On the other hand, PAMAM dendrimers are synthesized by the divergent approach. This methodology involves building the dendrimers from the core by an iterative synthetic procedure.[9] Although many methods for the convergent synthesis of various dendrimers were developed, a relatively few methods for PAMAM dendrimer have been reported in the literature.[10] Recent research emphasis seems to shift from the synthesis of novel dendrimers to their properties and potential applications, but future applications of dendrimers rely on efficient and practical synthetic procedures.[11]

Although there are several reports to synthesize triazole-mediated dendritic materials using click chemistry,[12] relatively few applications in PAMAM dendrimer synthesis

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have been reported.[13] Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and core unit, the various dendrimers having functional building block at core could be obtained easily and show the characteristic behaviors. Due to our interest in developing new functional dendrimers, we became involved in exploring efficient cycloaddition reactions that provide easy accesses to dendrimers. Herein, we present the synthesis of azide-functionalized poly(amidoamine) (PAMAM) dendrons **1-Dm** and their application to the convergent synthesis of poly(amidoamine) (PAMAM) dendrimers by reacting **1-Dm** with two different multi-terminal alkynes.

2. Results and discussion

The synthetic strategy for PAMAM dendrimers is schematically shown in Figure 1. PAMAM dendrons **1-Dm** (m=1–3: generation of dendron) are synthesized by the divergent approach using azidopropylamine as an azide focal point shown in Scheme 1. Although, we have screened with several Lewis acid-catalyzed Michael addition reactions to find the efficient condition in conjugate addition of free amine,[14] we utilized a standard PAMAM synthesis eventually furnishing us with the desired ester-terminated dendrons. This methodology involves typical stepwise and iterative two-step reaction sequences, consisting of amidation of methyl ester groups with a large excess of ethylenediamine (EDA) and Michael addition of primary amines with methyl acrylate (MA) to produce methyl ester terminal groups. The reaction of azidopropylamine and 3.5 equiv of MA in methanol gave dendron **1-D1** in 86% yield. For dendron **1-D2**, dendron **1-D1** was reacted with 20 equiv of EDA in methanol and then removal of methanol and excess EDA under vacuum produced the amine-terminated dendron, which was reacted with 7 equiv of MA in methanol to afford dendron **1-D2** in 91% yield. Dendron **1-D3** was obtained from **1-D2** by the consecutive amidation and Michael addition reactions in yield of 64%. The yield of high generation dendron (**1-D3**) is lower than those of low generation dendrons (**1-D1** and **1-D2**). The somewhat lower isolation yield of the former could be due to side reaction(s) between an azide group and the acrylate added in excess.[15] The structures of the dendrons **1-Dm** were confirmed by ^{1}H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB mass spectra. In the ^{1}H NMR spectra ($CDCl_3$) shown in Figure 2, the peaks of the amide protons (NH) were found at 6.96 ppm for **1-D2**, and at 6.99 and 7.61 ppm for **1-D3**, respectively. The IR spectra show the azide (N_3) at 2098 cm^{-1} and C=O of esters at 1739 cm^{-1} for **1-D1**, azide (N_3) at 2096 cm^{-1}, C=O of esters at 1737 cm^{-1}, and C=O of amides at 1667 cm^{-1} for **1-D2**, and azide (N_3) at 2096 cm^{-1}, C=O of esters at 1735 cm^{-1}, and C=O of amides at 1652 cm^{-1} for **1-D3**. Their FAB mass spectra exhibited very good correlation with the calculated molecular masses.

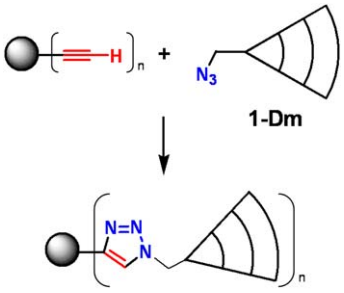


Figure 1. Synthetic strategy for PAMAM dendrimers linked by the triazole units.

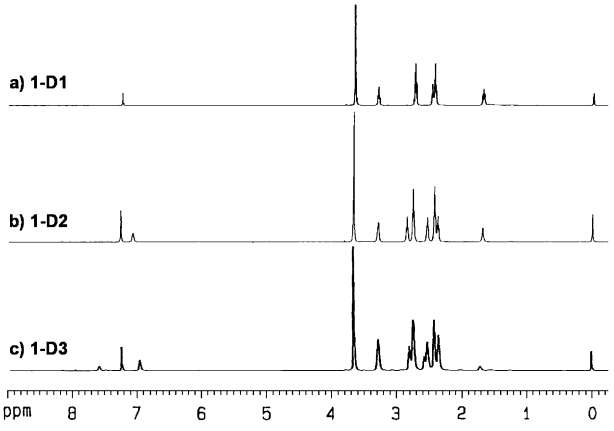
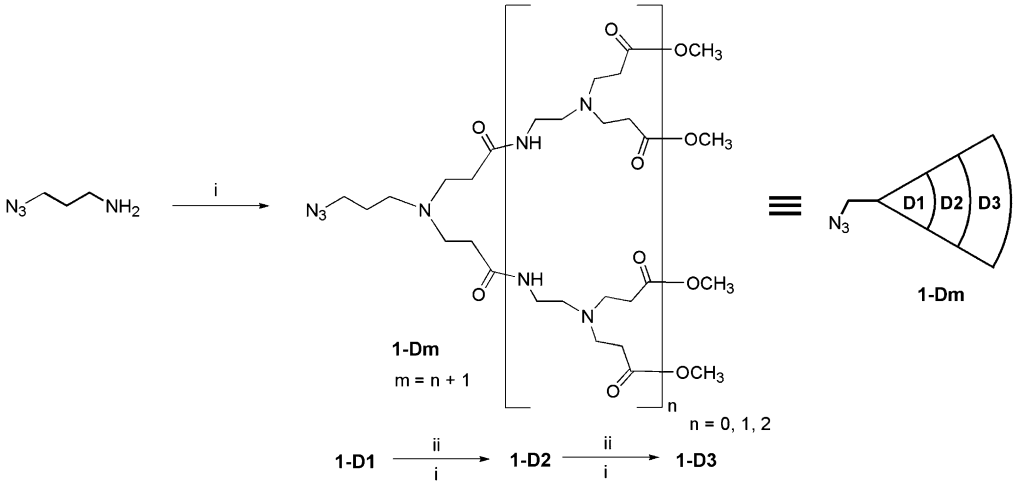
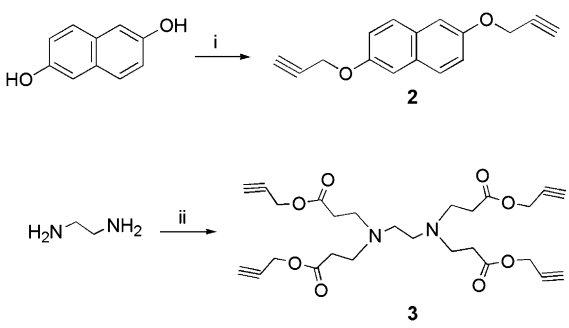


Figure 2. ^{1}H NMR spectra for dendrons (a) **1-D1**, (b) **1-D2**, and (c) **1-D3**.



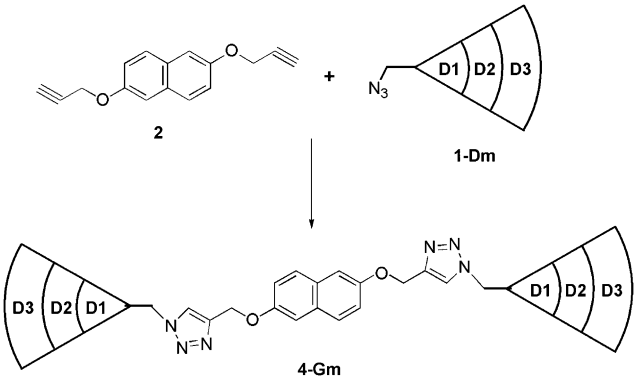
Scheme 1. Reagents and conditions: (i) methyl acrylate, MeOH, rt; (ii) ethylenediamine, MeOH, rt.

The inward growth employed by the convergent synthesis is ideally suited for the attachment of diverse core moieties. As a result, building dendrimers via the convergent approach allows for the synthesis of symmetric dendrimers and for incorporation of specific functions into the dendrimer's interior. To efficiently connect the azide focal point PAMAM dendrons with core unit(s) via the convergent approach, we intended to use the click condition using Cu(I) species.[16] 2,6-Bis-prop-2-ynyloxynaphthalene **2** and *N*,*N*,*N*′,*N*′-tetra-(prop-2-ynyloxycarbonylethyl)-1,2-diaminoethane **3**, designed to present alkyne functionalities available for dendrimer growth via click reactions with the dendrons, were synthesized readily from the bis-propargylation of 2,6-dihydroxynaphthalene with propargyl bromide in the presence of a base and Michael addition of 1,2-diaminoethane with propargyl acrylate in yields of 87 and 95%, respectively (Scheme 2). The structures of these compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB mass spectra. The IR spectra show the terminal ≡C–H at 3277 cm^{-1} and C≡C triple bond at 2131 cm^{-1} for compound **2** and the terminal ≡C–H at 3290 cm^{-1}, C≡C triple bond at 2128 cm^{-1}, and C═O of esters at 1739 cm^{-1} for compound **3**.



Scheme 2. Reagents and conditions: (i) propargyl bromide, K_2CO_3, DMF, rt; (ii) propargyl acrylate, CH_3CN, rt.

To test the effectiveness of the dipolar cycloaddition reactions of the bis(alkynes) core **2** and azide-dendrons **1-Dm** (Scheme 3), we have screened several conditions using various Cu(I) sources in different solvents.[6,16] We have found that the reaction conducted under the conditions of 10 mol % of $CuSO_4 \cdot 5H_2O$ with 20 mol % of sodium ascorbate in a 4:1 solvent ratio of THF to H_2O for 2.5 h at room temperature afforded the desired product **4-G1** in yield of 99%. The generation and disappearance of the mono-triazole derivative were monitored by TLC runs of the reaction mixture. Given the success in the synthesis of first generation dendrimers, we expanded this reaction to get higher generation dendrimers with 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of THF to H_2O. Reactions of the core **2** with 2.1 equiv of **1-D2** and **1-D3** afforded the PAMAM dendrimers **4-G2** and **4-G3** in yields of 95 and 91%, respectively, after 4 and 6.5 h. For completion of the reaction between the dendritic azide and the alkynes, the higher generation dendron takes longer time than the lower generation dendron, which can be ascribed to the steric demand of the dendron. The symmetric PAMAM dendrimers were purified by column chromatography and the structures were confirmed by ^{1}H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB or MALDI mass spectra. From the ^{1}H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **4-Gm** were found at 4.36, 7.77, and 5.27 ppm for **4-G1**, 4.39, 7.85, and 5.26 ppm for **4-G2**, and 4.41, 7.93, and 5.26 ppm for **4-G3**, respectively (Fig. 3). As the dendrimer generation increased, the peaks of the methylene protons adjacent to the nitrogen of triazole and the triazole proton shifted gradually to down-field, which may be influenced by the dendritic microenvironment effect.[17] IR data also confirmed that neither alkyne (~3277 cm^{-1}) nor azide (~2098 cm^{-1}) residues remain in the final dendrimer. Their FAB mass spectra exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluant shows very low polydispersity values PDI=1.02 and 1.04 for **4-G1** and **4-G2**, respectively (Fig. 4). Unfortunately, GPC analysis of **4-G3** could not be performed due to their poor solubility and aggregation property in THF.



Scheme 3. Reagents and conditions: 10 mol % of $CuSO_4 \cdot 5H_2O$/20 mol % of sodium ascorbate, THF/H_2O (4:1), rt.

To probe the viability of our approach, we next turned our attention toward the construction of PAMAM dendrimers **5-Gm** with tetra(alkyne) **3** (Scheme 4). The reaction of the tetra(alkyne) **3** and 4.4 equiv of azide-dendrons **1-D1** in the presence of 0.1, 0.2, and 0.5 equiv of CuI with respect to the alkyne in THF (0.1 M) did not occur at room temperature. However, the reaction proceeded at 50 °C very efficiently to afford the desired product **5-G1** in isolated

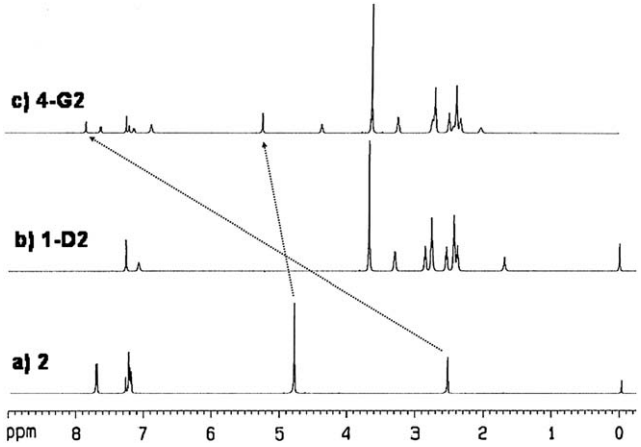


Figure 3. ^{1}H NMR spectra for (a) **2**, (b) **1-D2**, and (c) **4-G2**.

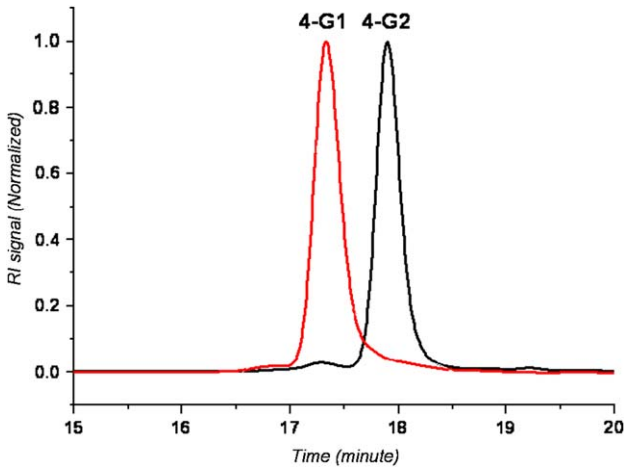
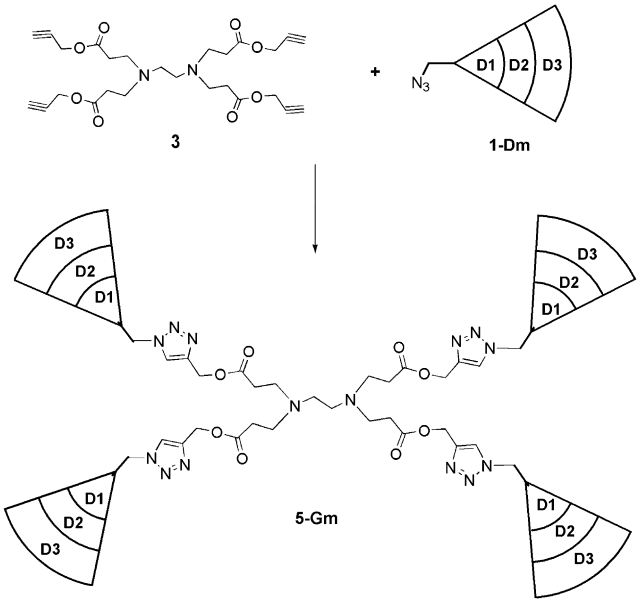


Figure 4. GPC diagrams of dendrimers **4-Gm** obtained from THF eluant.

yields of ~85% after 24 h irrespective of the amount of CuI used. We have found that the reaction conducted in 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O proceeded smoothly at room temperature and finished within 24 h at 60 °C providing the desired product **5-G1** in an isolated yield of 95%. The generation and disappearance of the mono, di, and tri-triazole derivatives were monitored by TLC runs of the reaction mixture. Based on these optimizations for the synthesis of the first generation dendrimer, we fixed conditions for higher generation dendrimers. It was observed that the reactions carried out with 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O at 60 °C proceeded quickly than those using CuI. Therefore, we tried to synthesize higher generation dendrimers with 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O (Scheme 4). The reactions of the tetra(alkyne) **3** and 4.4 equiv of azide-dendrons **1-D2** and **1-D3** afforded the



Scheme 4. Reagents and conditions: 20 mol % of $CuSO_4 \cdot 5H_2O$/40 mol % of sodium ascorbate, DMF/H_2O (4:1), 60 °C.

PAMAM dendrimers **5-G2** and **5-G3** in yields of 69 and 56%, respectively, after 30 and 38 h, which were separated by column chromatography. The low yields, in the absence of any side product(s) as observed by TLC, could be due to significant retention of the polar dendrimer in the silica column. To improve the isolated yield of dendrimers, we decided to use the membrane dialysis. The crude product was dissolved in methanol and dialyzed (cellulose membrane with molecular weight cut-off 1000) against methanol for 1 day to provide **5-G2** and **5-G3** in yields of 90 and 84%, respectively. For completion of the reaction between the dendritic azide and the alkyne, the higher generation dendron takes longer time than the lower generation dendron, which can be differentiated by the accessibility of azide group due to the steric hindrance (bulkiness) of dendron and spatial congestion of core region. This observation led us to imagine that the reaction between the dendritic azide and the core was kinetically controlled. This result showed that the formation of triazole could be regarded as a new connector to construct the symmetric PAMAM dendrimers from dendrons.

The structures of the PAMAM dendrimers were also confirmed by ^1H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB and MALDI mass spectra. From the ^1H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **5-Gm** were found at 4.35, 7.77, and 5.18 ppm for **5-G1**, 4.37, 7.79, and 5.16 ppm for **5-G2**, and 4.36, 7.71, and 5.16 ppm for **5-G3**, respectively (Fig. 5). There are no characteristic differences in their chemical shifts according to the dendrimer generations, which may have same chemical environments in the tetra-branched core system compared to the bis-branched core. The IR spectra show the disappearance of the acetylene peak at ~3290 cm^{-1} and the azide peak at ~2096 cm^{-1} in the final dendrimer (Fig. 6) while the ^1H NMR revealed no alkyne peak at around δ 2.47 ppm. Their FAB and MALDI mass spectra exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluant shows very low polydispersity values PDI=1.02 for **5-G1**, which means no signs of products with defects that would arise from incomplete coupling (Fig. 7). Unfortunately, GPC analysis for **5-G2** and **5-G3** could not be performed due to their poor solubility and aggregation property in THF.

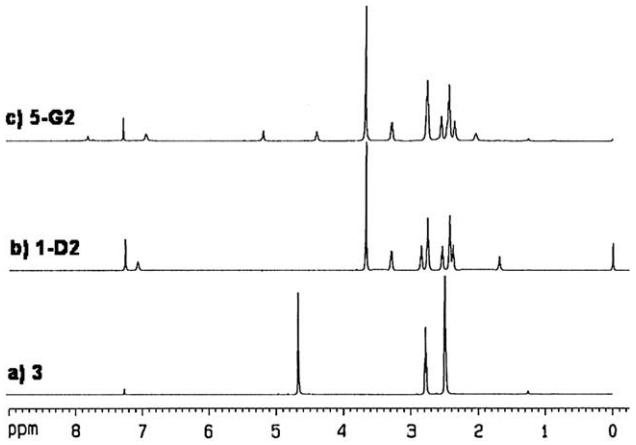


Figure 5. ^1H NMR spectra for (a) **3**, (b) **1-D2**, and (c) **5-G2**.

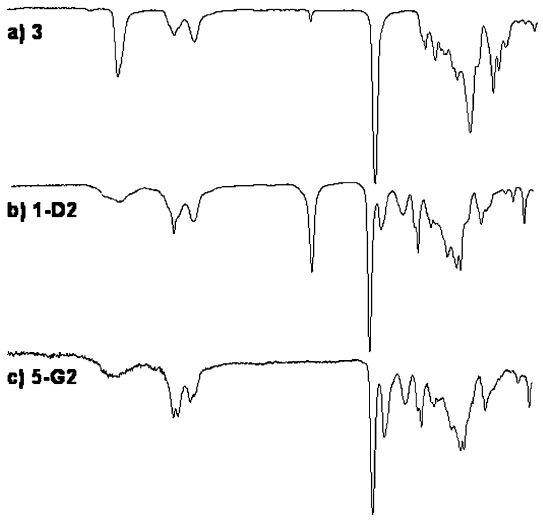


Figure 6. IR spectra for (a) **3**, (b) **1-D2**, and (c) **5-G2**.

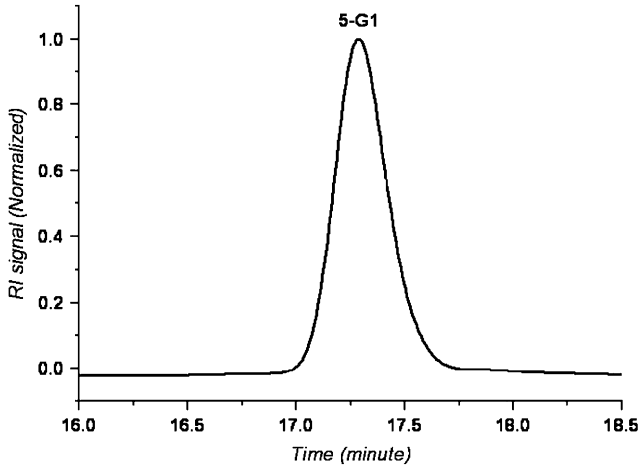


Figure 7. GPC diagrams of dendrimers **5-G1** obtained from THF eluant.

3. Conclusion

We have demonstrated that the azide-functionalized PAMAM dendrons are synthesized by the divergent approach using azidopropylamine as an azide focal point and that click reactions between the bis- or tetra-terminal alkynes and the azide-functionalized PAMAM dendrons lead to the formation of symmetric PAMAM dendrimers in high yields. This method can be applied for the fast synthesis of PAMAM-like dendrimers with different lengths (spacers) at core and may then provide an insight into designing various symmetrical dendrimers with the functional cores. We are currently working toward the synthesis of various functional dendrimers using this strategy for tailored applications.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; d of d, doublet of a doublet; m, multiplet; br, broad. ^{13}C NMR spectra were proton decoupled and recorded on a 75 or 125 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. FAB and MALDI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu or Daejeon and POSTECH. Flash chromatography was performed with 37–75 μm silica gel. Analytical thin layer chromatography was performed on silica plates with F-254 indicator and the visualization was accomplished by UV lamp or using an iodine chamber. Polydispersity (PDI) of dendrimers was determined by gel-permeation chromatography (GPC) analysis relative to polystyrene calibration (Agilent 1100 series GPC, Plgel 5 μm MIXED-C, refractive index detector) in THF solution. All chemicals were obtained from commercial sources and used as received, unless otherwise mentioned. THF was distilled over Na/Ph_2CO ketyl.

4.2. Synthesis of azide-functionalized-PAMAM dendron 1-Dm

4.2.1. Synthesis of azide-functionalized-PAMAM dendron 1-D1. A solution of azidopropylamine (3.0 g, 30 mmol) in methanol (25 mL) was added dropwise to a stirred solution of methyl acrylate (6.5 g, 75 mmol) in methanol (25 mL) over a period of 1 h in an ice-water bath. The resulting solution was stirred for 30 min in an ice-water bath and then allowed to warm to room temperature and stirred for further 48 h. The volatiles were removed under reduced pressure using a rotary evaporator and vacuum. The residue was purified by column chromatography (EtOAc/*n*-hexane, 1:1) to afford the desired product (7.02 g, 86%). Dendron **1-D1**: a colorless oil; 86% yield; IR 2954, 2825, 2098, 1739, 1437, 1256, 1198, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.69 (quint, J=6.6 Hz, 2H), 2.44 (t, J=6.9 Hz, 4H), 2.48 (t, J=6.6 Hz, 2H), 2.74 (t, J=6.9 Hz, 4H), 3.31 (t, J=6.6 Hz, 2H), 3.67 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.33, 51.94, 50.95, 49.67, 49.58, 32.94, 27.06; FABMS: m/z=273 [M^++H], 202; HRMS (FAB) calcd for $C_{11}H_{20}N_4O_4$: 272.1485; found: 273.1563 [M^++H].

4.2.2. Synthesis of azide-functionalized-PAMAM dendron 1-D2. A solution of ester **1-D1** (3.8 g, 14 mmol) in methanol (100 mL) was added dropwise to a stirred solution of 1,2-diaminoethane (21 g, 0.35 mol) in methanol (100 mL) over a period of 1 h in an ice-water bath. The resulting solution was allowed to warm to room temperature and stirred for further 7 days at room temperature at which time no methyl ester was detectable by NMR spectroscopy. The solvent was removed under reduced pressure using a rotary evaporator maintaining the temperature not higher than 40 °C and then the excess 1,2-diaminoethane was removed using an azeotropic mixture of toluene and methanol (9:1). The remaining toluene was removed by azeotropic distillation using methanol and finally kept under vacuum to provide the amino-terminated product (4.55 g, 99%) as a colorless oil. A solution of the previously prepared amino-terminated product (3.15 g, 9.6 mmol) in methanol (50 mL) was added dropwise to a stirred solution of methyl acrylate (5.84 g, 67.2 mmol) in methanol (50 mL) over a period of

1 h in an ice-water bath. The resulting solution was stirred for 30 min in an ice-water bath and then allowed to warm to room temperature and stirred for further 60 h. The volatiles were removed under reduced pressure using a rotary evaporator and vacuum. The residue was purified by column chromatography (EtOAc/methanol, 10:1) to afford the desired product (5.9 g, 91%). Dendron **1-D2**: a colorless gum; 91% yield; IR 3295, 2952, 2828, 2096, 1737, 1667, 1531, 1436, 1257, 1196, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.70 (quint, J=6.6 Hz, 2H), 2.36 (t, J=6.57 Hz, 4H), 2.43 (t, J=6.54 Hz, 8H), 2.49–2.54 (m, 6H), 2.75 (t, J=6.51 Hz, 12H), 3.25–3.33 (m, 6H), 3.67 (s, 12H), 6.96 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.12, 172.33, 53.08, 51.72, 50.26, 49.87, 49.46, 49.34, 37.22, 33.92, 32.79, 26.46; FABMS: m/z=674 [M^++2H], 672 [M^+]; HRMS (FAB) calcd for $C_{29}H_{52}N_8O_{10}$: 672.3806; found: 673.3885 [M^++H].

4.2.3. Synthesis of azide-functionalized-PAMAM dendron 1-D3. Dendron **1-D3** was synthesized from **1-D2** (3.5 g, 5.2 mmol) using same method as successive amidation of methyl ester groups with a large excess of ethylenediamine (EDA) and Michael addition of primary amines with methyl acrylate (MA) in yield of 64–70% and the spectroscopic data are as follows. Dendron **1-D3**: a colorless gum; 64% yield; IR 3304, 2952, 2825, 2096, 1735, 1652, 1540, 1437, 1256, 1196, 1177 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.71 (quint, J=6.8 Hz, 2H), 2.37 (m, 12H), 2.43 (t, J=6.5 Hz, 16H), 2.54 (t, J=5.7 Hz, 10H), 2.59 (m, 4H), 2.76 (t, J=6.5 Hz, 20H), 2.81 (t, J=6.5 Hz, 8H), 3.29 (m, 14H), 3.67 (s, 24H), 6.99 (br s, 4H), 7.61 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.39, 172.69, 172.63, 53.27, 52.87, 51.99, 50.36, 50.19, 49.75, 49.56, 49.45, 37.87, 37.48, 34.12, 33.04, 26.64; FABMS: m/z=1474 [M^++H]; HRMS (FAB) calcd for $C_{65}H_{116}N_{16}O_{22}$: 1472.8450; found: 1473.8528 [M^++H].

4.3. Synthesis of multi(alkynes) core 2 and 3

4.3.1. Synthesis of 2,6-bis-prop-2-ynyloxynaphthalene 2. A solution of 2,6-dihydroxynaphthalene (0.25 g, 1.56 mmol) and propargyl bromide (0.52 g, 4.68 mmol) in DMF (20 mL) in the presence of K_2CO_3 (0.54 g, 3.9 mmol) was stirred at room temperature for 12 h. The reaction mixture was added to EtOAc (50 mL) and the resulting solution was washed with brine (20 mL×3). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by recrystallization (EtOAc/*n*-hexane system) and column chromatography (EtOAc/*n*-hexane, 1:4) to afford the desired product **2** (0.32 g, 87%). IR 3277, 2964, 2924, 2853, 2131, 1604, 1508, 1399, 1229, 1168, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.55 (t, J=2.1 Hz, 2H), 4.80 (d, J=2.1 Hz, 4H), 7.19–7.22 (m, 4H), 7.69 (d, J=8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=154.72, 130.35, 128.92, 119.59, 108.29, 79.01, 75.99, 56.37; FABMS: m/z=236 [M^+], 197; HRMS (FAB) calcd for $C_{16}H_{12}O_2$: 236.0837; found: 237.0916 [M^++H].

4.3.2. Synthesis of *N,N,N′,N′*-tetra(prop-2-ynyloxycarbonylethyl)-1,2-diaminoethane 3. A solution of propargyl acrylate (458 mg, 4.16 mmol) in CH_3CN (5 mL) was added dropwise to a stirred solution of 1,2-diaminoethane (50 mg, 0.83 mol) in CH_3CN (5 mL) over a period of 5 min in an ice-water bath. The resulting solution was allowed to warm to room temperature and stirred for further 23 h at room temperature. The volatiles were removed under reduced pressure using a rotary evaporator and vacuum. The residue was purified by column chromatography (EtOAc/*n*-hexane, 2:3) to afford the desired product (395 mg, 95%). IR 3290, 2950, 2827, 2128, 1739, 1166, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.46–2.49 (m, 16H), 2.77 (t, J=6.9 Hz, 8H), 4.67 (d, J=2.3 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.00, 78.12, 75.40, 52.69, 52.30, 50.02, 33.01; FABMS: m/z=501 [M^++H], 403, 264, 250; HRMS (FAB) calcd for $C_{26}H_{32}N_2O_8$: 500.2159; found: 501.2237 [M^++H].

4.4. Synthesis of PAMAM-like dendrimers 4-Gm from azide-PAMAM dendrons 1-Dm and bis(alkynes) core 2

General procedure: A mixture of azido-dendrons **1-Dm** (0.21 mmol) and 2,6-bis-prop-2-ynyloxynaphthalene **2** (0.10 mmol) in THF/H_2O (4:1, 1 mL) in the presence of 10 mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate was stirred at room temperature for ~7 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL×3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/methanol system or methanol) to afford the desired product.

4.4.1. Compound 4-G1. Yield 99%; IR 3142, 2954, 2845, 1735, 1604, 1436, 1226, 1167, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.08 (m, 4H), 2.41 (m, 12H), 2.73 (m, 8H), 3.63 (s, 12H), 4.36 (t, J=6.7 Hz, 4H), 5.27 (s, 4H), 7.14 (d, J=8.8 Hz, 2H), 7.20 (d, J=1.7 Hz, 2H), 7.62 (d, J=8.8 Hz, 2H), 7.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.65, 154.83, 143.84, 129.76, 128.32, 123.28, 119.14, 107.51, 62.06, 51.59, 50.35, 49.01, 47.82, 32.85; FABMS: m/z=782 [M^++2H]; HRMS (FAB) calcd for $C_{38}H_{52}N_8O_{10}$: 780.3806; found: 781.3885 [M^++H]. PDI=1.02.

4.4.2. Compound 4-G2. Yield 93%; IR 3318, 2952, 2827, 1736, 1666, 1604, 1531, 1436, 1225, 1198, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.03 (m, 4H), 2.33 (m, 8H), 2.39 (t, J=6.6 Hz, 16H), 2.44 (m, 4H), 2.50 (t, J=5.8 Hz, 8H), 2.71 (t, J=6.6 Hz, 16H), 2.74 (m, 8H), 3.23–3.27 (m, 8H), 3.64 (s, 24H), 4.39 (t, J=6.8 Hz, 4H), 5.26 (s, 4H), 6.89 (br s, 4H), 7.15 (dd, J=8.8, 2.2 Hz, 2H), 7.22 (d, J=2.2 Hz, 2H), 7.64 (d, J=8.8 Hz, 2H), 7.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.87, 172.14, 154.77, 143.71, 129.63, 128.20, 123.18, 119.02, 107.22, 61.85, 52.71, 51.48, 49.70, 49.44, 49.01, 47.81, 36.96, 33.77, 32.50; FABMS: m/z=1582 [M^++2H]; HRMS (FAB) calcd for $C_{74}H_{116}N_{16}O_{22}$: 1580.8450; found: 1581.8528 [M^++H]. PDI=1.04.

4.4.3. Compound 4-G3. Yield 91%; IR 3308, 2954, 2828, 1735, 1659, 1647, 1604, 1544, 1437, 1227, 1196, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.05 (m, 4H), 2.35 (m, 24H), 2.41 (t, J=6.4 Hz, 32H), 2.53–2.54 (m, 20H), 2.57 (m, 8H), 2.74 (t, J=6.5 Hz, 40H), 2.78 (m, 16H), 3.27 (m, 24H), 3.66 (s, 48H), 4.41 (t, J=6.5 Hz, 4H), 5.26 (s, 4H), 7.00 (br s, 8H), 7.16 (d, J=8.8 Hz, 2H), 7.26 (d, J=2.2 Hz, 2H), 7.55 (br s, 4H), 7.66 (d, J=8.8 Hz,

2H), 7.93 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.45, 172.83, 172.72, 155.46, 144.27, 130.28, 128.82, 123.87, 119.63, 107.86, 62.46, 53.34, 52.97, 52.05, 50.21, 49.66, 48.56, 37.98, 37.60, 34.22, 33.11; MS (MALDI) *m/z* calcd for $C_{146}H_{244}N_{32}O_{46}$: 3181.7738; found: 3181.9377 [M^+].

4.5. Synthesis of PAMAM-like dendrimers 5-Gm from azide-PAMAM dendrons 1-Dm and tetra(alkynes) core 3

General procedure: A mixture of azido-dendrons **1-Dm** (0.05 mmol) and tetra(prop-2-ynyloxycarbonylethyl)-1,2-diaminoethane **3** (0.01 mmol) in DMF/H_2O (4:1, 0.5 mL) in the presence of 20 mol % of $CuSO_4\cdot 5H_2O$ with 40 mol % of sodium ascorbate was stirred at 60 °C for ~38 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with CH_2Cl_2 (20 mL×3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/methanol system or methanol). On the other hand, the membrane dialysis for **5-G2** and **5-G3** was also carried out. The crude product was dissolved in methanol and dialyzed (regenerated cellulose membrane, Spectra/Por MWCO, 1000, Spectrum Laboratories Inc., The Netherlands) against methanol for 1 day. The retentate was evaporated, and the residue was dried in a vacuum to provide **5-G2** and **5-G3** in yields of 90 and 84%, respectively.

4.5.1. Compound 5-G1. Yield 95%; IR 2953, 2923, 2849, 1735, 1661, 1536, 1437, 1252, 1199, 1176, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.03–2.07 (m, 8H), 2.40–2.44 (m, 36H), 2.71–2.75 (m, 24H), 3.66 (s, 24H), 4.35 (t, *J*=7.0 Hz, 8H), 5.18 (s, 8H), 7.77 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.78, 171.89, 142.25, 124.13, 57.60, 51.50, 50.23, 49.38, 48.92, 47.80, 32.22, 27.92; FABMS: *m/z*=1590 [M^++H]; HRMS (FAB) calcd for $C_{70}H_{112}N_{18}O_{24}$: 1588.8097; found: 1589.8175 [M^++H]. PDI=1.02.

4.5.2. Compound 5-G2. Yield 90%; IR 2952, 2921, 2851, 1735, 1662, 1533, 1436, 1252, 1199, 1176, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.01 (m, 8H), 2.32–2.36 (m, 12H), 2.41 (t, *J*=6.6 Hz, 48H), 2.51–2.52 (m, 24H), 2.73 (t, *J*=6.7 Hz, 56H), 3.25–3.30 (m, 16H), 3.65 (s, 48H), 4.37 (t, *J*=6.7 Hz, 8H), 5.16 (s, 8H), 6.93 (br s, 8H), 7.79 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.42, 172.69, 172.58, 143.03, 124.41, 58.05, 53.34, 52.60, 52.02, 50.53, 50.34, 50.17, 50.04, 49.64, 48.38, 37.57, 36.86, 34.37, 34.20, 33.09, 31.81, 28.57; HRMS (MALDI) calcd for $C_{142}H_{240}N_{34}O_{48}$: 3189.7384; found: 3191.6426 [M^+], 3214.1877 [M^++Na].

4.5.3. Compound 5-G3. Yield 84%; IR 3302, 2952, 2827, 1736, 1661, 1649, 1540, 1437, 1257, 1198, 1177, 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.01 (m, 8H), 2.34 (m, 36H), 2.40–2.41 (m, 96H), 2.57 (m, 48H), 2.73–2.73 (m, 120H), 3.26 (m, 48H), 3.65 (s, 96H), 4.37 (m, 8H), 5.16 (s, 8H), 6.92 (br s, 16H), 7.71 (s, 4H), 7.78 (br s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.40, 172.78, 172.68, 172.57, 143.03, 124.40, 58.07, 53.35, 52.87, 52.57, 52.02, 50.55, 50.35, 50.16, 50.03, 49.64, 49.28, 48.38, 37.57, 34.38, 34.21, 33.40, 33.09, 32.72, 28.61; MS (MALDI) *m/z* calcd for $C_{286}H_{496}N_{66}O_{96}$: 6391.5959; found: 6415.7686 [M^++Na].

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