

Convergent Synthesis of PAMAM Dendrimers Containing Tetra(ethyleneoxide) at Core Using Click Chemistry

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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 structures¹ and have served as functional objects in nanotechnology and nanoscience.² The two most widely studied dendrimer families are the Fréchet-type polyether and the Tomalia-type poly(amidoamine) (PAMAM) dendrimers.¹ PAMAM dendrimers are synthesized by the divergent approach. This methodology involves building the dendrimers from the core by an iterative synthetic procedure.³ The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.⁴ 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 (un)symmetrical dendrimers is the most attractive features of the convergent synthesis. Future applications of dendrimers rely on efficient and practical synthetic procedures.

Recent one of the solid chemistry is the click chemistry which is the copper-catalyzed 1,3-dipolar cycloaddition reaction between alkyne and azide developed by Sharpless and Tornøe.^{5,6} This reaction has many advantages: very high yields, mild and simple reaction conditions, oxygen and water tolerance, and easy isolation of product. This reaction is clearly a breakthrough in the synthesis of dendrimers⁷ and dendritic and polymer materials^{8,9} and click dendrimers provides a bridge between dendritic architectures and nanomaterials.¹⁰ We have developed the fusion and stitching methods for the synthesis of various dendrimers using click chemistry between an alkyne and an azide.^{11,12} Overall, this method was found to be a straightforward strategy for the synthesis of triazole-based dendrimers. Especially the stitching method of a core unit with dendrons will be indeed myriad ways to synthesize an ABA triblock copolymers which is dendritic-linear-dendritic triblock systems.¹³ A relatively few synthesis of an ABA triblock consisting of PAMAM as the A block with varying generations of PAMAM have been reported by the divergent synthetic method.¹⁴ Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and

core unit, herein we for the first time demonstrate a feasible route for the convergent synthesis of an ABA triblock consisting of PAMAM as the A block with varying generations of PAMAM and tetra(ethyleneoxide) unit as the B block.

Experimental Section

General. ¹H NMR and ¹³C NMR spectra were recorded on 500 MHz NMR spectrometers. Mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu and POSTECH. Flash chromatography was performed with 37-75 mm silica gel. 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.

General Procedure for the Synthesis of ABA Triblock Dendritic Compounds 3-Gm. A mixture of the alkyne-functionalized PAMAM dendrons **2-Dm** (0.22 mmol) and tetraethylene glycol diazide **1** (0.1 mmol) in THF-H₂O (4:1, 1.2 mL) in the presence of 10 mol % CuSO₄·5H₂O with 20 mol % sodium ascorbate was stirred at rt for ~4 h. The reaction mixture was poured into brine (30 mL) and the resulting solution was extracted with EtOAc (30 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product **3-Gm**.

Compound 3-G1: A yellowish oil; 97% yield; IR 2951, 2916, 2866, 1736, 1439, 1258, 1200, 1177, 1119, 1049 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.41 (t, *J* = 6.5 Hz, 8H), 2.71 (t, *J* = 6.4 Hz, 8H), 3.50 (m, 8H), 3.57 (s, 12H), 3.71 (s, 4H), 3.79 (t, *J* = 4.1 Hz, 4H), 4.45 (t, *J* = 3.9 Hz, 4H), 7.53 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 33.0, 48.9, 49.2, 50.5, 51.9, 69.9, 70.8, 70.9, 124.0, 144.7, 173.2; MS (FAB): *m/z* 699.5 [M⁺ + H]; HRMS (FAB) Calcd for C₃₀H₅₀N₈O₁₁: 698.3599. Found: 699.3674 [M⁺ + H]. PDI: 1.01.

Compound 3-G2: A yellowish oil; 97% yield; IR 2951, 2843, 1736, 1651, 1539, 1439, 1258, 1200, 1123, 1049 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.37-2.38 (m, 24H), 2.48 (m, 8H), 2.69-2.72 (m, 24H), 3.22 (m, 8H), 3.52 (m, 8H), 3.60 (s, 24H), 3.75 (s, 4H), 3.81 (m, 4H), 4.46 (m, 4H), 7.12 (m, 4H), 7.60 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 33.1, 34.0, 37.5, 47.9, 49.6, 49.7, 50.5, 52.0, 53.3, 69.8, 70.8, 70.9,

124.2, 143.9, 172.5, 173.4; MS (FAB): m/z 1499.53 [$M^+ + H$]; HRMS (FAB) Calcd for $C_{66}H_{114}N_{16}O_{23}$: 1498.8243. Found: 1499.8313 [$M^+ + H$]. PDI: 1.01.

Compound 3-G3: A yellowish oil; 93% yield; IR 2951, 2835, 1736, 1651, 1543, 1439, 1258, 1200, 1126, 1045 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, $J = 6.3$ Hz, 24H), 2.40 (t, $J = 5.7$ Hz, 32H), 2.51 (t, $J = 5.7$ Hz, 16H), 2.56 (m, 8H), 2.73 (t, $J = 6.6$ Hz, 40H), 2.79 (m, 16H), 3.25-3.26 (m, 24H), 3.57 (m, 8H), 3.64 (s, 48H), 3.81 (s, 4H), 3.85 (t, $J = 5.2$ Hz, 4H), 4.50 (t, $J = 5.0$ Hz, 4H), 7.04 (t, $J = 4.8$ Hz, 8H), 7.65 (s, 2H), 7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5, 33.4, 66.7, 37.0, 37.2, 47.2, 49.1, 49.7, 49.9, 51.4, 52.3, 52.7, 69.3, 70.3, 123.6, 143.3, 172.0, 172.1, 172.8; MS (MALDI): Calcd for $C_{138}H_{242}N_{32}O_{47}$: 3099.7530. Found: 3122.4824 [$M^+ + Na$]. PDI: 1.01.

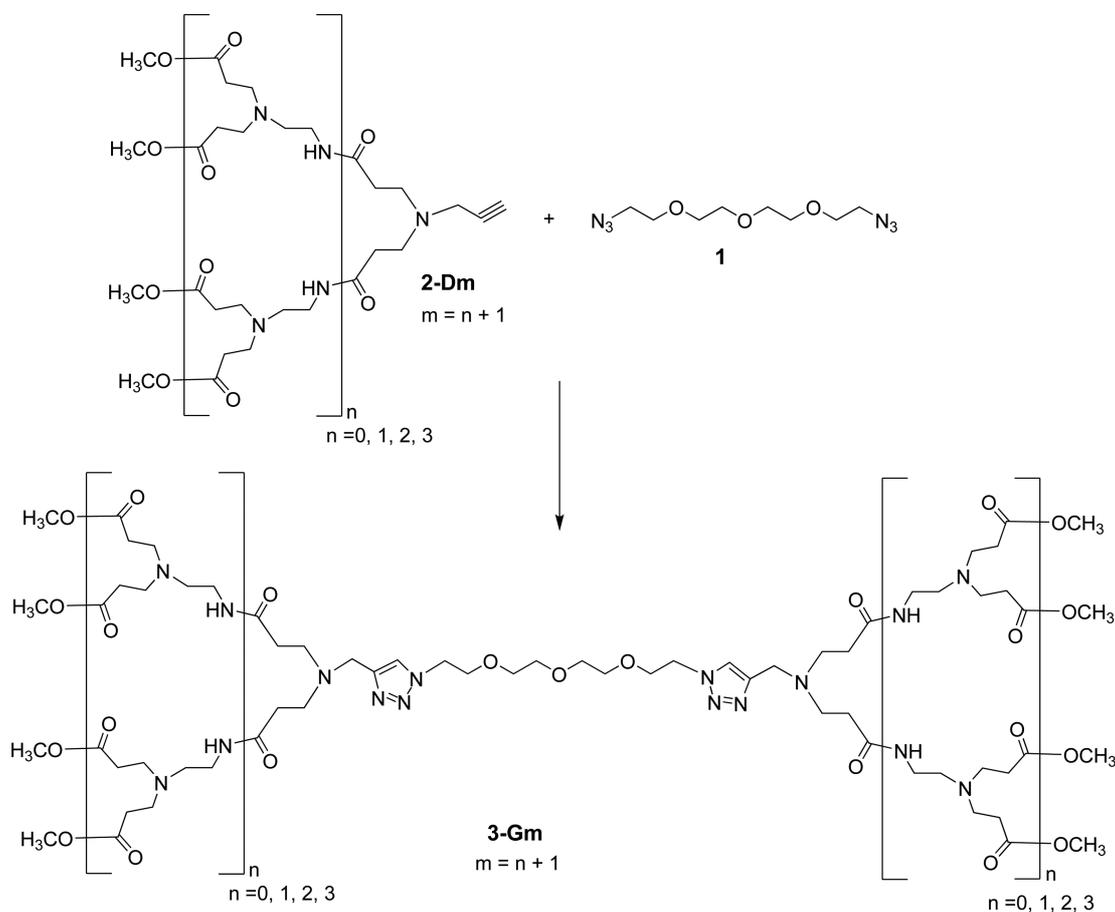
Compound 3-G4: A yellowish oil; 90% yield; IR 2951, 2832, 1736, 1647, 1543, 1439, 1258, 1200, 1126, 1045 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, $J = 5.7$ Hz, 56H), 2.41 (t, $J = 6.5$ Hz, 64H), 2.51-2.54 (m, 56H), 2.72-2.78 (m, 120H), 3.25-3.27 (m, 56H), 3.59-3.61 (m, 8H), 3.65 (s, 96H), 3.81 (s, 4H), 3.87 (t, $J = 5.4$ Hz, 4H), 4.52 (t, $J = 4.7$ Hz, 4H), 7.07 (m, 16H), 7.64 (m, 8H), 7.67 (s, 2H), 7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5, 33.3, 33.6, 36.9, 37.2, 47.1, 49.0, 49.6, 49.8, 51.4, 52.3, 52.7, 69.2, 70.2, 123.6, 143.1, 172.0, 172.06, 172.15, 172.8; MS (MALDI):

Calcd for $C_{282}H_{498}N_{64}O_{95}$: 6301.6105. Found: 6324.7052 [$M^+ + Na$]. PDI: 1.03.

Results and Discussion

The characteristics of the convergent synthesis are ideal for the synthesis of dendritic-linear-dendritic triblock systems. However, most dendritic materials including PAMAM were synthesized by the divergent method. Meanwhile there is the limitation for construction of dendritic-linear-dendritic triblock systems incorporated with PAMAM units,¹⁵ the stitching method of a core unit with dendrons using click chemistry would be one of best in synthesis of an ABA triblock systems. To construct the dendritic-linear-dendritic triblock systems, consisting of PAMAM as the dendritic block and tetra(ethyleneoxide) unit as the linear block, the tetra(ethyleneoxide) diazide **1** was designed to serve as the linear block and the azide functionalities for dendrimer growth *via* click reactions with the alkyne-dendrons. Compound **1** was prepared from the mesylation reaction of tetraethylene glycol with methanesulfonyl chloride in the presence of triethylamine and the subsequent azidation with sodium azide.

The synthetic strategy for PAMAM dendrimers with a tetra(ethyleneoxide) unit at core, linked by the triazole units,



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

utilized a convergent method using the alkyne-functionalized PAMAM dendrons **2-Dm** and the tetraethylene glycol diazide **1** (Scheme 1). The propargyl-functionalized PAMAM dendrons **2-Dm** ($m = 1-4$: generation of dendron) were synthesized by the divergent approach using propargylamine as an alkyne-focal point.^{12d} To efficiently connect the propargyl focal point dendrons with compound **1**, the synthetic approach selected is based on the click condition using Cu(I) species.¹⁶

The efficiency of the click reaction between the alkyne-dendrons and bis(azides) was evaluated by performing the model coupling reactions between alkyne-dendron **2-D1** and compound **1**. Click reaction was carried out in a 4:1 solvent ratio of THF to H₂O using 5 mol % CuSO₄·5H₂O with 10 mol % sodium ascorbate with respect to alkyne as the *in situ* reducing agent to generate the active Cu(I) species. The reaction of tetraethylene glycol diazide **1** and 2.2 equiv of alkyne-dendron **2-D1** afforded the desired product **3-G1** in a yield of 97% after 1 h at rt which was separated by column chromatography. The disappearance of bis(azides) as well as 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 dendrimer, therefore we expanded this reaction to get higher-generation dendrimers. The reactions of tetraethylene glycol diazide **1** and 2.2 equiv of alkyne-dendrons **2-D2** and **2-D3** afforded the dendrimers **3-G2** and **3-G3** in yields of 97 and 93%, respectively, after 1.5 and 2.5 h at rt. Finally, reaction of tetraethylene glycol diazide **1** and 2.2 equiv of dendron **2-D4** gave the dendrimer **3-G4** in a yield of 90% after 4 h at rt. For completion of the reaction between the dendritic acetylene and the core, the higher generation dendron takes longer time than the lower generation dendron which can be differentiated by the accessibility of acetylide due to the steric hindrance (bulkiness) of dendron and spatial congestion of core region. This result showed that the formation of triazole ring from an azide and an alkyne can be regarded as a new connector to stitch a tetra(ethyleneoxide) with the dendrons. Therefore this approach may provide new methodological insight for synthesis of triblock dendritic polymers¹⁵ and

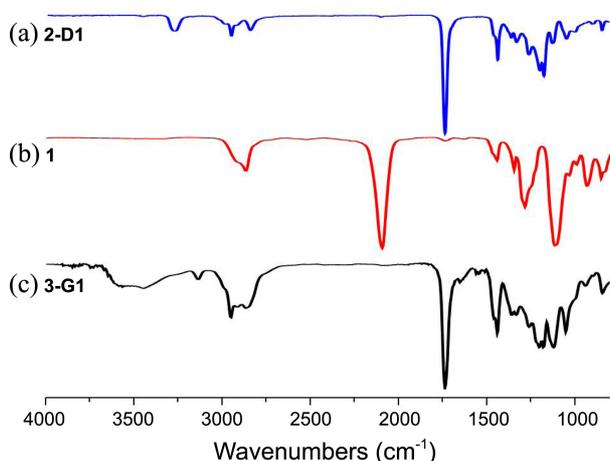


Figure 1. IR spectra for (a) **2-D1**, (b) **1**, and (c) **3-G1**.

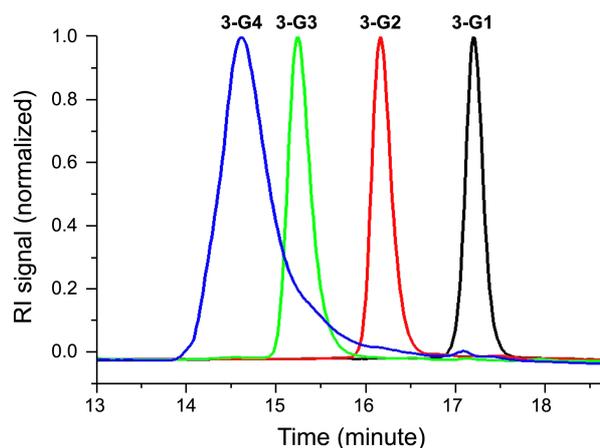


Figure 2. GPC diagrams of dendrimers **3-Gm** obtained from THF eluent.

would greatly contribute to researches on the application side.

The structures of the dendrimers **3-Gm** were confirmed by ¹H NMR, ¹³C NMR, and IR spectroscopy. From the ¹H NMR spectra (CDCl₃), the peaks of the triazole proton, the methylene protons adjacent to the nitrogen of triazole, and the methylene protons adjacent to the carbon of triazole in dendrimers **3-Gm** were found at 7.53, 4.45, and 3.71 ppm for **3-G1**, 7.60, 4.46, and 3.75 ppm for **3-G2**, 7.65, 4.50, and 3.81 ppm for **3-G3**, and 7.67, 4.52, and 3.81 ppm for **3-G4**, respectively. As the dendrimer generation increased, the peaks of the investigated protons shifted gradually to down-field which may be influenced by the dendritic microenvironment effect. IR data also confirmed that neither alkyne (~3277 cm⁻¹) nor azide (~2093 cm⁻¹) residues remain in the final dendrimer (Figure 1). Analysis of the dendrimers by FAB or MALDI-TOF mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling. Their FAB or MALDI mass spectra for dendrimer exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) shows very low polydispersity values, PDI = 1.01-1.03 for all dendrimers (Figure 2).

In summary, we have demonstrated for the first time the convergent synthesis of an ABA triblock consisting of PAMAM as the A block with varying generations of PAMAM and tetra(ethyleneoxide) unit as the B block. Click reactions between tetra(ethyleneoxide) diazide core and the propargyl-functionalized PAMAM dendrons lead to the formation of symmetric ABA triblock dendritic materials in high yields. This method can be applied for the fast synthesis of ABA triblock dendritic materials with different lengths (spacers) at core and may then provide an insight into designing various symmetrical dendrimers such as amphiphilic dendrimers. We are currently working towards synthesis of various functional dendrimers using this strategy for various applications.

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