

클릭 화학에 의한 PEG 핵을 갖는 덴드리머의 합성

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Synthesis of Dendrimer with PEG Core by Click Chemistry

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초록: 선형 PEG단위를 덴드리머의 중심에 갖는 덴드리머의 합성을 위한 효율적인 연결 방법이 개발되었다. 합성 전략은 알카인과 아자이드기 사이의 반응을 구리(I)촉매의 존재하에서 진행하는 클릭화학을 이용하였다. 덴드리머의 핵으로 작용할 수 있는 단위체인 옥타(에틸렌글리콜)디아자이드와 도데카(에틸렌글리콜)디아자이드를 합성하였고, 이 두 화합물의 아자이드기는 덴드리머의 형성에 이용되었다. 두 디아자이드화합물을 알카인 덴드론과 클릭 반응을 통해서 덴드리머의 핵의 선형 길이가 다른 두 종류의 덴드리머 제조에 대한 수렴형 합성법을 완성하였다.

Abstract: Efficient stitching methods for the synthesis of Fréchet-type dendrimers with linear PEG units at a core were elaborated. The synthetic strategy involved an inexpensive 1,3-dipolar cycloaddition reaction between an alkyne and an azide in the presence of Cu(I) species which is known as the best example of click chemistry. The linear core building blocks, two diazido-PEG units, were chosen to serve as the azide functionalities for dendrimer growth via click reactions with the alkyne-dendrons. These two building blocks were employed together with the alkyne-functionalized Fréchet-type dendrons in a convergent strategy to synthesize two kinds of Fréchet-type dendrimers with different linear core units.

Keywords: alkyne, azide, click chemistry, dendrimers.

Introduction

Dendrons and dendrimers are the most intensely investigated subset of dendritic polymers. 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.¹ The amphiphilic dendrimer polymers consisting of both hydrophobic and hydrophilic regions in the same molecule appear as an important issue throughout the physical and life sciences and can be considered unimolecular micelles. Amphiphilic dendrimer polymers can be classified into dendritic-linear polymers possessing a hydrophilic dendritic component and a hydrophobic linear polymer (or vice versa)

and unimolecular dendritic amphiphiles.²

The building blocks of the linear-dendritic copolymers are only two, but they could be positioned in several distinct configurations due to the presence of multiple anchoring points in both of them. The characteristic feature is the attachment of two monodendrons to the extremities of a single linear chain. The variation of chain length and dendrimer size in this group also offers interesting macromolecular geometries.³ Recent 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.⁴ This reaction is characterized by mild and simple reaction conditions, reliable 1,4-regiospecific 1,2,3-triazole formations, and tolerance towards water as well as a wide range of functionalities, and is clearly a breakthrough in the synthesis of dendrimers^{5,6} and dendritic and polymer materials.⁷⁻¹⁶ We have developed the fusion and stitching methods for the synthesis of dendrimers and diblock

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codendrimers using click chemistry between an alkyne and an azide.¹⁷⁻²⁵ Taking advantage of this fact, herein we report the synthesis of Fréchet-type dendrimers with PEG core moieties by the stitching method of dendrons (Scheme 1). Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and core unit, the various dendritic-linear-dendritic materials could be obtained easily and shown the characteristic behaviors.

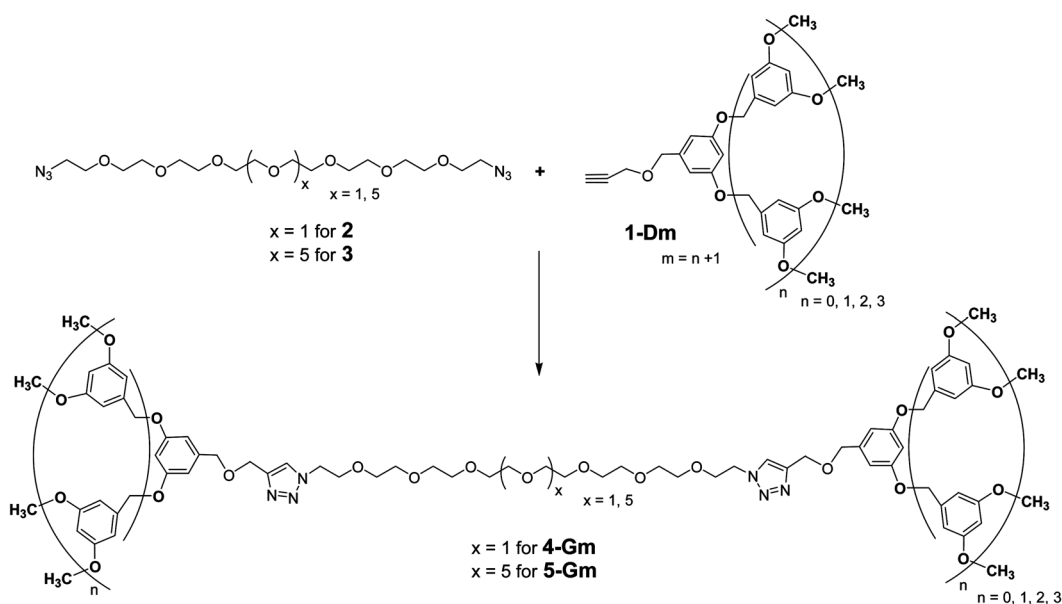
Experimental

¹H 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. ¹³C 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 μ m silica gel. Analytical thin layer chromatography was performed on silica plates with F₂₅₄ 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 μ m MIXED-C, refractive index detector) in THF solution.

Synthesis of Octa(ethylene glycol) Diazide 2. NaH (55%, 70 mg, 1.61 mmol) was treated to a solution of tetra(ethylene glycol) monoazide (211 mg, 0.96 mmol) in THF (6 mL) and stirred for 1 h, followed by adding a solution of azido tetra(ethylene glycol) tosylate (300 mg, 0.80 mmol) in THF (2 mL). The resulting mixture was stirred at rt for 10 h and treated with saturated ammonium chloride aqueous solution (20 mL). The resulting solution was extracted with methylene chloride (20 mL \times 4). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by column chromatography to afford the desired product **2** (236 mg, 70%). IR 3009, 2870, 2106, 1350, 1288, 1234, 1096 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃) δ 3.39 (t, $J=4.6$ Hz, 4H), 3.66 (m, 28H); ¹³C NMR (75 MHz, CDCl₃) δ 50.6, 69.9, 70.45, 70.51, 70.55, 70.59; MS (FAB): m/z 443.58 [$M^+ + \text{Na}$]; HRMS (FAB) Calcd for C₁₆H₃₂N₆O₇: 420.2332. Found: 421.2414 [$M^+ + \text{H}$], 443.2233 [$M^+ + \text{Na}$].

Synthesis of Dodeca(ethylene glycol) Diazide 3. NaH (55%, 104 mg, 2.39 mmol) was treated to a solution of tetra(ethylene glycol) monoazide (393 mg, 1.79 mmol) in THF (15 mL) and stirred for 1 h, followed by adding a solution of tetra(ethylene glycol) ditosylate (300 mg, 0.60 mmol) in THF (3 mL). The resulting mixture was stirred at rt for 12 h and treated with saturated ammonium chloride aqueous



Scheme 1. Synthesis of dendrimers by click reaction between bis-azido-PEG derivatives and alkyne-functionalized dendrons. *Reagents and conditions:* 10 mol% of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /20 mol% of sodium ascorbate, DMF/ H_2O (4:1), 50 $^\circ\text{C}$.

solution (30 mL). The resulting solution was extracted with methylene chloride (30 mL \times 4). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by column chromatography to afford the desired product **3** (217 mg, 61%). IR 3009, 2870, 2106, 1350, 1288, 1234, 1096 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.36 (t, $J=5.0$ Hz, 4H), 3.61-3.65 (m, 44H); ^{13}C NMR (75 MHz, CDCl_3) δ 51.1, 70.4, 70.9, 71.01, 71.04, 71.07; MS (FAB): m/z 597.24 [M^+]; HRMS (FAB) Calcd for $\text{C}_{24}\text{H}_{48}\text{N}_6\text{O}_{11}$: 596.3381. Found: 597.3455 [$\text{M}^+ + \text{H}$].

General Procedure for the Preparation of Dendrimers 4-Gm from Alkyne-Dendrons 1-Dm and Octa(ethylene glycol) Diazide 2. A mixture of alkyne-dendrons **1-Dm** (0.22 mmol) and octa(ethylene glycol) diazide **2** (0.1 mmol) in DMF- H_2O (4:1, 2 mL) in the presence of 10 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with 20 mol% sodium ascorbate was stirred at 50 $^\circ\text{C}$ for \sim 1 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL \times 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product.

4-G1. A yellowish oil; 96% yield; IR 3001, 2870, 1597, 1466, 1204, 1150, 1096, 1057 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.57 (m, 28H), 3.74 (s, 12H), 3.83 (t, $J=4.6$ Hz, 4H), 4.51 (m, 8H), 4.64 (s, 4H), 6.34 (m, 2H), 6.49 (m, 4H), 7.73 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 50.1, 55.2, 63.5, 69.3, 70.3, 70.4, 72.2, 99.6, 105.4, 123.7, 140.2, 144.7, 160.7; MS (FAB): m/z 833.4 [$\text{M}^+ + \text{H}$]; HRMS (FAB) Calcd for $\text{C}_{40}\text{H}_{60}\text{N}_6\text{O}_{13}$: 832.4218. Found: 833.4301 [$\text{M}^+ + \text{H}$]. PDI: 1.01.

4-G2. A yellowish oil; 95% yield; IR 3001, 2870, 1597, 1458, 1204, 1150, 1096, 1057 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.58 (m, 28H), 3.77 (s, 24H), 3.85 (t, $J=4.6$ Hz, 4H), 4.53 (m, 8H), 4.65 (s, 4H), 4.95 (s, 8H), 6.39 (m, 4H), 6.53 (m, 2H), 6.56 (m, 8H), 6.61 (m, 4H), 7.73 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 50.1, 55.3, 63.5, 69.4, 69.9, 70.37, 70.44, 72.2, 99.8, 101.3, 105.1, 106.6, 123.7, 139.1, 140.3, 144.8, 159.9, 160.9; MS (FAB): m/z 1377.8 [$\text{M}^+ + \text{H}$]; HRMS (FAB) Calcd for $\text{C}_{72}\text{H}_{92}\text{N}_6\text{O}_{21}$: 1376.6316. Found: 1377.6387 [$\text{M}^+ + \text{H}$]. PDI: 1.01.

4-G3. A yellowish oil; 94% yield; IR 3009, 2870, 1597, 1458, 1204, 1150, 1096, 1049 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.58-3.59 (m, 28H), 3.78 (m, 52H), 4.51-4.54 (m, 8H), 4.67 (s, 4H), 4.97 (s, 24H), 6.41 (m, 8H), 6.57 (m, 22H), 6.62 (m, 4H), 6.68 (m, 8H), 7.74 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 50.2, 55.3, 63.6, 69.4, 69.9, 70.0, 70.39, 70.45, 72.2, 99.9, 101.3, 101.5, 105.2, 106.3, 106.6, 123.7, 139.1, 139.2, 140.4, 144.7, 159.9, 160.0, 160.9; MS (MALDI): Calcd for $\text{C}_{136}\text{H}_{156}\text{N}_6\text{O}_{37}$: 2465.0510. Found:

2466.1262 [$\text{M}^+ + \text{H}$], 2488.1074 [$\text{M}^+ + \text{Na}$]. PDI: 1.01.

4-G4. A yellowish oil; 94% yield; IR 3001, 2878, 1597, 1458, 1204, 1150, 1049 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.56-3.58 (m, 28H), 3.76 (m, 100H), 4.48 (t, 4H), 4.53 (s, 4H), 4.66 (s, 4H), 4.95 (s, 56H), 6.39 (m, 16H), 6.56 (m, 46H), 6.62 (m, 4H), 6.67 (m, 24H), 7.71 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 50.1, 55.3, 63.6, 69.4, 69.92, 69.98, 70.39, 70.46, 72.2, 99.9, 101.3, 101.5, 101.6, 105.2, 106.4, 106.7, 123.7, 139.1, 139.2, 139.3, 140.4, 144.8, 159.9, 160.0, 160.9; MS (MALDI): Calcd for $\text{C}_{264}\text{H}_{284}\text{N}_6\text{O}_{69}$: 4641.8899. Found: 4683.8348 [$\text{M}^+ + \text{K}$]. PDI: 1.01.

General Procedure for the Preparation of Dendrimers 5-Gm from Alkyne-Dendrons 1-Dm and Dodeca(ethylene glycol) Diazide 3. A mixture of alkyne-dendrons **1-Dm** (0.22 mmol) and dodeca(ethylene glycol) diazide **3** (0.1 mmol) in DMF- H_2O (4:1, 2 mL) in the presence of 10 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with 20 mol% sodium ascorbate was stirred at 50 $^\circ\text{C}$ for \sim 3 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL \times 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product.

5-G1. A yellowish oil; 92% yield; IR 3001, 2870, 1597, 1466, 1219, 1150, 1096 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.59-3.61 (m, 40H), 3.77 (s, 12H), 3.85 (t, $J=5.0$ Hz, 4H), 4.52 (m, 8H), 4.66 (s, 4H), 6.36 (m, 2H), 6.50 (m, 4H), 7.74 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 50.6, 55.7, 64.0, 69.8, 70.8, 70.9, 72.7, 100.1, 105.9, 124.2, 140.7, 145.2, 161.3; MS (FAB): m/z 1009.9 [$\text{M}^+ + \text{H}$]; HRMS (FAB) Calcd for $\text{C}_{48}\text{H}_{76}\text{N}_6\text{O}_{17}$: 1008.5267. Found: 1009.5342 [$\text{M}^+ + \text{H}$]. PDI: 1.01.

5-G2. A yellowish oil; 94% yield; IR 2870, 1597, 1458, 1211, 1150, 1096, 1057 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.57-3.59 (m, 40H), 3.76 (s, 20H), 3.84 (t, $J=4.9$ Hz, 4H), 4.51 (m, 8H), 4.64 (s, 4H), 4.94 (s, 8H), 6.38 (m, 4H), 6.51 (m, 2H), 6.55 (m, 8H), 6.60 (m, 4H), 7.72 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 50.6, 55.8, 64.0, 69.9, 70.4, 70.85, 70.93, 72.7, 100.3, 101.8, 105.6, 107.1, 124.3, 139.7, 140.8, 145.2, 160.4, 161.4; MS (FAB): m/z 1553.5 [$\text{M}^+ + \text{H}$]; HRMS (FAB) Calcd for $\text{C}_{80}\text{H}_{108}\text{N}_6\text{O}_{25}$: 1552.7364. Found: 1553.7437 [$\text{M}^+ + \text{H}$]. PDI: 1.01.

5-G3. A yellowish oil; 96% yield; IR 3001, 2870, 1597, 1458, 1204, 1150, 1096, 1049 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.59-3.61 (m, 40H), 3.78 (s, 48H), 3.86 (t, $J=4.9$ Hz, 4H), 4.51 (t, $J=5.0$ Hz, 4H), 4.54 (s, 4H), 4.67 (s, 4H), 4.97 (s, 24H), 6.41 (m, 8H), 6.53 (m, 2H), 6.57 (m, 20H), 6.62 (m, 4H), 6.68 (m, 8H), 7.72 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 50.1, 55.3, 63.6, 69.4, 69.9, 70.0, 70.4,

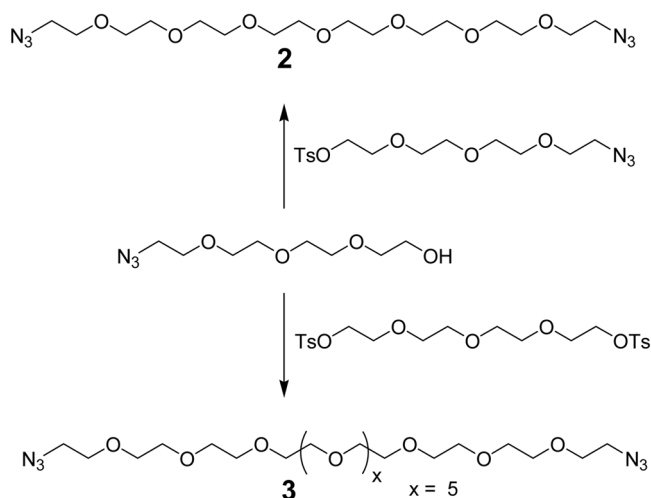
70.5, 72.2, 100.0, 101.4, 101.6, 105.2, 106.4, 106.7, 123.7, 139.2, 139.3, 140.4, 144.8, 159.9, 160.1, 161.0; MS (MALDI): Calcd for $C_{144}H_{172}N_6O_{41}$: 2641.1559. Found: 2642.1659 [$M^+ + H$], 2664.1309 [$M^+ + Na$]. PDI: 1.01.

5-G4. A yellowish oil; 94% yield; IR 3001, 2878, 1597, 1458, 1204, 1150, 1096, 1049 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 3.58-3.61 (m, 40H), 3.77 (s, 96H), 3.84 (t, $J=4.7$ Hz, 4H), 4.50 (t, $J=4.8$ Hz, 4H), 4.54 (s, 4H), 4.66 (s, 4H), 4.96 (s, 56H), 6.40 (m, 16H), 6.56 (m, 46H), 6.63 (m, 4H), 6.67 (m, 24H), 7.72 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.1, 55.3, 63.6, 69.4, 69.92, 69.99, 70.41, 70.47, 72.2, 99.9, 101.3, 101.6, 105.2, 106.4, 106.7, 123.8, 139.1, 139.2, 139.3, 140.4, 144.8, 159.9, 160.0, 160.9; MS (MALDI): Calcd for $C_{272}H_{300}N_6O_{73}$: 4817.9947. Found: 4841.9676 [$M^+ + Na$]. PDI: 1.02.

Results and Discussion

The synthetic strategy for Fréchet-type dendrimers with PEG units at core, linked by the triazole units, utilized a convergent method using the alkyne-functionalized Fréchet-type dendrons and the diazido-PEG units (Scheme 1). To efficiently connect the alkyne focal point Fréchet-type dendrons with the diazido-PEG units, the synthetic approach selected is based on the click chemistry between an alkyne and an azide in the presence of Cu (I) species.^{26,27} The alkyne focal point Fréchet-type dendrons **1-Dm** ($m=1\sim 4$: generation of dendron) are synthesized by the propargylation of the corresponding dendritic benzyl alcohols with propargyl bromide.¹⁹ The diazido-PEG compound **2** and **3** were prepared from the O-alkylation reaction of monoazido-tetra(ethylene glycol) with the tosylated monoazido-tetra(ethylene glycol) and the O-alkylation reaction of monoazido-tetra(ethylene glycol) with tetra(ethylene glycol) ditosylate, respectively (Scheme 2).

To investigate the effectiveness of the click reaction between octa(ethylene glycol) diazide **2** and alkyne-dendron **1-D1** (Scheme 1), we have screened with several conditions using various Cu(I) sources in different solvents.²⁷ We have found that the reaction conducted from the condition of 5 mol% of $CuSO_4 \cdot 5H_2O$ with 10 mol% of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O for 1 h at 50 °C provided the desired product **4-G1** in yield of 96%. The disappearance of diazido-PEG compound **2** as well as generation and disappearance of the mono-triazole derivative were monitored by TLC runs of the reaction mixture. The dendrimer **4-G1** was purified by column chromatography and the structure of dendrimer was confirmed by 1H and ^{13}C NMR spectroscopy, IR



Scheme 2. Synthesis of octa(ethylene glycol) diazide **2** and dodeca(ethylene glycol) diazide **3**. *Reagents and conditions:* NaH, THF, rt.

spectroscopy, and FAB mass spectra. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers with 5 mol% of $CuSO_4 \cdot 5H_2O$ with 10 mol% of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O . Reactions of the diazido-PEG compound **2** with 2.2 equiv of **1-D2** and **1-D3** afforded the dendrimers **4-G2** and **4-G3** in yields of 95 and 94%, respectively, after 1 h, which were separated by column chromatography. In case of **1-D4**, the dendritic-linear-dendritic material **4-G4** was obtained in 94% yield after 1 h. This comparative efficiency of the click methodology is emphasized by the synthesis of the dendritic-linear-dendritic materials. Therefore this approach may provide new methodological insight into introduction of various linear functional cores and would greatly contribute to researches on the application side.

Structural characterization of the dendrimers **4-Gm** with 1H NMR, ^{13}C NMR, and IR spectroscopy showed no defects due to incomplete reaction. 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 **4-Gm** were found at 4.51, 7.73, and 4.51 ppm for **4-G1**, 4.53, 7.73, and 4.53 ppm for **4-G2**, 4.51, 7.74, and 4.54 ppm for **4-G3**, and 4.48, 7.71, and 4.53 ppm for **4-G4**, respectively (Figure 1). Analysis of the dendrimers by mass spectrometry as well as by gel permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling (Figure 2). As expected, the obtained dendrimer possessed a very well-defined molecular structure

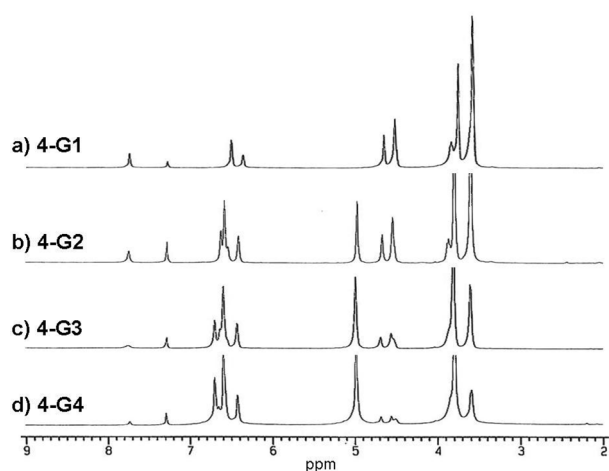


Figure 1. ^1H NMR spectra for a) 4-G1; b) 4-G2; c) 4-G3; d) 4-G4.

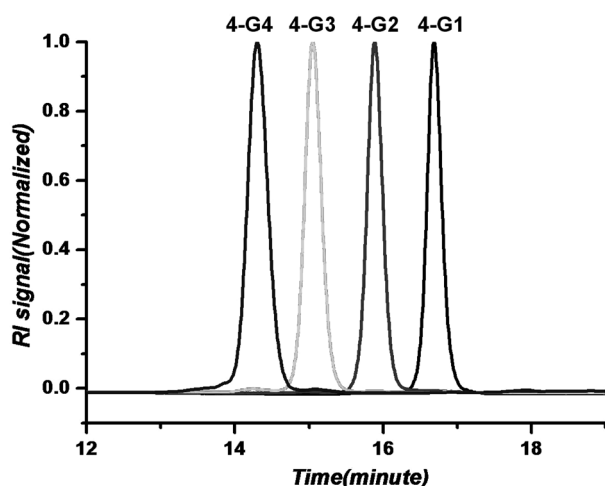


Figure 2. GPC diagrams of dendrimers 4-Gm obtained from THF eluent.

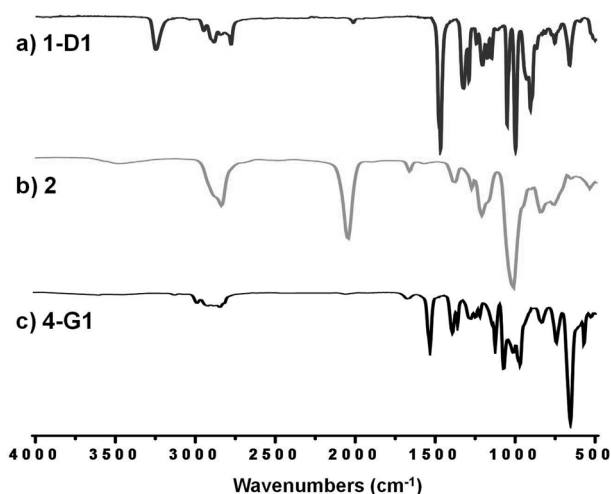


Figure 3. FTIR spectra for a) 1-D1; b) 2; c) 4-G1.

with very low polydispersity values ($\text{PDI} = 1.01$). The IR spectra shows the disappearance of the acetylene peak at $\sim 3277\text{ cm}^{-1}$ and the azide peak at $\sim 2106\text{ cm}^{-1}$ in the final dendrimer (Figure 3) while the ^1H NMR revealed no peak for the methylene protons adjacent to the azide at around δ 3.39 ppm (Figure 1).

Encouraged by this successful proof of concept, we decided to apply this methodology into the synthesis of another dendritic-linear-dendritic material so that we next turned our attention toward the click reaction between the alkyne-dendrons **1-D1** and dodeca(ethylene glycol) diazide **3** (Scheme 1). Based on optimizations for the synthesis of the Fréchet-type dendrimers **4-Gm**, click reactions for the construction of dendritic polymers **5-Gm** were carried out in a 4:1 solvent ratio of DMF to H_2O using 5 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with 10 mol% sodium ascorbate with respect to alkyne. Reaction of the di(azides) **3** and 2.2 equiv of alkyne-dendron **1-D1**, conducted for 2 h at 50°C , afforded the desired product **5-G1** in yield of 92%. The disappearance of di(azides) **3** as well as generation and disappearance of the mono-triazole derivative were also monitored by TLC runs of the reaction mixture. The linear-dendritic copolymer **5-G1** was purified by column chromatography and the structure of **5-G1** was confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB mass spectra. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers with 5 mol% of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with 10 mol% of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O . Reactions of the di(azides) **3** with 2.2 equiv of **1-D2** and **1-D3** afforded the dendrimers **5-G2** and **5-G3** in yields of 94 and 96%, respectively, after 2 h, which were separated by column chromatography. In case of **1-D4**, the dendritic-linear-dendritic material **5-G4** was obtained in 94% yield after 3 h. Therefore, the formation of regiospecific 1,4-disubstituted triazoles via copper(I)-catalyzed [2+3]-dipolar cycloaddition reaction between an alkyne and an azide can be regarded as a new and efficient methodology to construct the dendritic-linear-dendritic materials with the tailor-made core unit. We are now investigating for the linear-dendritic copolymers with the size (length and generation) and the polarity of the blocks.

The structures of the dendrimers **5-Gm** were confirmed by ^1H NMR, ^{13}C NMR, and IR spectroscopy. 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 4.51, 7.74, and 4.52 ppm

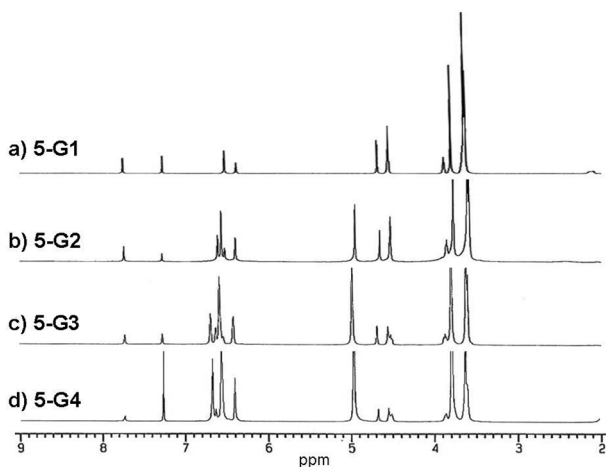


Figure 4. ^1H NMR spectra for a) **5-G1**; b) **5-G2**; c) **5-G3**; d) **5-G4**.

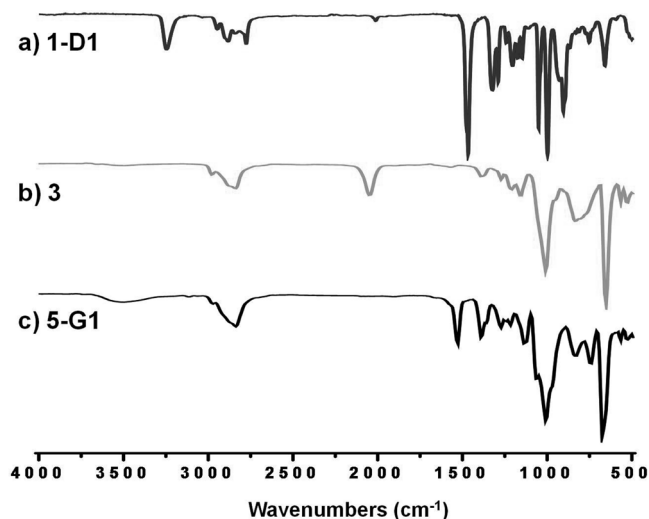


Figure 5. FTIR spectra for a) **1-D1**; b) **3**; c) **5-G1**.

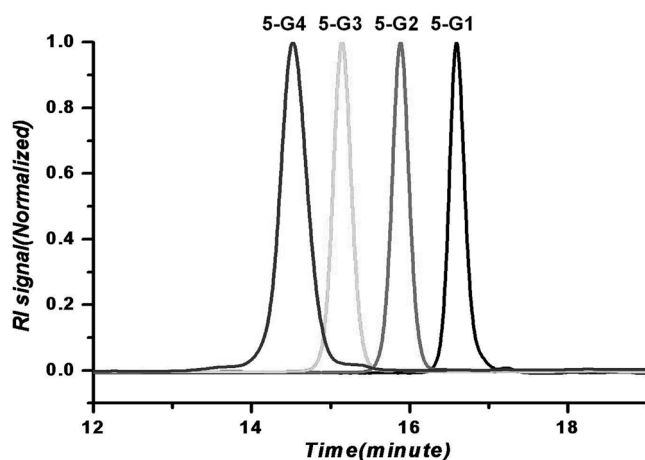


Figure 6. GPC diagrams of dendrimers **5-Gm** obtained from THF eluent.

for **5-G1**, 4.51, 7.72, and 4.51 ppm for **5-G2**, 4.51, 7.72, and 4.54 ppm for **5-G3**, and 4.50, 7.72, and 4.54 ppm for **5-G4**, respectively (Figure 4). IR data also confirmed that neither alkyne ($\sim 3277\text{ cm}^{-1}$) nor azide ($\sim 2106\text{ cm}^{-1}$) residues remain in the final dendrimer (Figure 5). Analysis of the dendrimers by mass spectrometry as well as by GPC provides no signs of products with defects that would arise from incomplete coupling (Figure 6). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01-1.02).

Conclusions

We have demonstrated general, fast, and efficient stitching methods for the synthesis of Fréchet-type dendrimers with linear PEG units at a core. The stitching method was based on the click chemistry protocol between an alkyne and an azide. The linear core building blocks, two diazido-PEG units, were chosen to serve as the core in dendrimer, were stitched together with the alkyne-functionalized Fréchet-type dendrons in a convergent strategy to lead to the formation of two kinds of dendritic-linear-dendritic materials with different linear core units, respectively, in high yields. Therefore, the formation of regiospecific 1,4-disubstituted triazoles via copper(I)-catalyzed [2+3]-dipolar cycloaddition reaction between an alkyne and an azide can be regarded as a new and efficient methodology to construct the dendritic-linear-dendritic materials with the tailor-made core unit. The synthesis and applications of the linear-dendritic copolymers with the size (length and generation) and the polarity of the blocks will now become part of the ongoing research efforts in our laboratories.

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