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Synthesis of Poly(benzyl ether) Dendrimer Containing Tetra(ethyleneoxide) at Core Using Click Chemistry

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The convergent synthetic strategy for the poly(benzyl ether) dendrimers having the tetraethyleneoxide at core via the copper-catalyzed 1,3-dipolar cycloaddition reaction between alkyne and azide was described. Tetraethyleneglycol diazide, designed to serve as the core in dendrimer, was stitched with the alkyne-functionalized poly(benzyl ether) dendrons by the click chemistry leading to the formation of triblock dendritic polymers in high yields. The absorption and emission of the dendrimers were investigated. The structure of the dendrimers was characterized with ¹H NMR, ¹³C NMR, and IR spectroscopies, mass spectra, and gel-permeation chromatography.

Keywords: 1,3-Dipolar cycloaddition; click chemistry; dendrimer; PEO

INTRODUCTION

Dendrimers are highly branched macromolecules, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies [1]. Generally, the reactions employed are high yielding without any side reactions. Well known processes, such as

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the Michael reaction, Williamson ether synthesis, amidations and reductions have been used extensively [2]. 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 [3]. This reaction is characterized by very high yields, mild and simple reaction conditions, oxygen and water tolerance, and ease of product isolation. It is highly chemoselective affording only the desired 1,2,3-triazole even in the presence of a large variety of other functional groups. This click chemistry is a modular approach that uses the most practical and reliable chemical transformations and is clearly a breakthrough in the synthesis of dendrimers and dendritic and polymer materials [4]. We have developed the fusion and stitching methods for the synthesis of symmetric and unsymmetric dendrimers and diblock codendrimers using click chemistry between an alkyne and an azide [5–7]. Overall, this method was found to be a straightforward strategy for the synthesis of triazole-based dendrimers. At this time, we are intrigued to obtain the functional dendrimers containing poly(ethyleneoxide) unit at core which could be utilized as solid-state electrolyte for fuel cells and DSSCs, electrochemical sensors, electrochromic devices, and so on. The convergent methodology in the synthesis of dendrimers installs the core in the final step and allows for a large degree of chemical diversity such that functional groups can be incorporated at nearly central position in the dendritic architecture. Taking advantage of these facts, herein we report the general and efficient strategy for the synthesis of Fréchet-type poly(benzyl ether) dendrimers having a tetra(ethyleneoxide) at core via click reaction between azide and alkyne.

EXPERIMENTAL

General Methods

^1H NMR spectra were recorded on a 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 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 μ m MIXED-C, refractive index detector) in THF solution. All chemicals were obtained from commercial sources and used as received.

General Procedure for the Synthesis of Dendrimers 3-Gm

A mixture of alkyne-functionalized poly(benzyl ether) dendrons **1-Dm** (0.27 mmol) and tetraethylene glycol diazide **2** (0.12 mmol) in DMF-H₂O (4:1, 1.2 mL) in the presence of 10 mol% CuSO₄ · 5H₂O with 20 mol% sodium ascorbate was stirred at 50°C for ~2.5 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. R_f 0.1 (EtOAc); 95% yield. A yellowish oil; IR: 3005, 2940, 2870, 1597, 1462, 1204, 1153, 1096, 1053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.54–3.55 (m, 8H), 3.77 (s, 12H), 3.82 (t, J = 4.8 Hz, 4H), 4.50 (t, J = 4.8 Hz, 4H), 4.53 (s, 4H), 4.66 (s, 4H), 6.37 (s, 2H), 6.50 (d, J = 1.7 Hz, 4H), 7.70 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 50.6, 55.7, 64.1, 69.8, 70.8, 70.9, 72.8, 100.1, 106.0, 124.1, 140.7, 145.3, 161.3; MS (FAB): m/z 657.0 [M⁺]; HRMS (FAB) Calcd for C₃₂H₄₄N₆O₉: 656.3170. Found: 657.3248 [M⁺ + H]. PDI: 1.01.

Compound 3-G2. R_f 0.15 (EtOAc); 96% yield; A yellowish oil; IR: 3009, 2940, 2839, 1597, 1458, 1204, 1153, 1092, 1053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.50–3.54 (m, 8H), 3.77 (s, 24H), 3.81 (t, J = 5.1 Hz, 4H), 4.48 (t, J = 5.0 Hz, 4H), 4.52 (s, 4H), 4.64 (s, 4H), 4.95 (s, 8H), 6.40 (t, J = 2.5 Hz, 4H), 6.52 (t, J = 2.0 Hz, 2H), 6.56 (d, J = 2.1 Hz, 8H), 6.60 (d, J = 2.0 Hz, 4H), 7.68 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 50.5, 55.8, 64.1, 69.8, 70.4, 70.8, 70.9, 72.7, 100.3, 101.8, 105.7, 107.2, 124.1, 139.6, 140.8, 145.3, 160.4, 161.4; MS (FAB): m/z 1200.57 [M⁺]; HRMS (FAB) Calcd for C₆₄H₇₆N₆O₁₇: 1200.5267 Found: 1201.5345 [M⁺ + H]. PDI: 1.01.

Compound 3-G3. R_f 0.2 (EtOAc); 97% yield; A yellowish oil; IR: 3013, 2940, 2839, 1597, 1458, 1204, 1153, 1053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.49–3.52 (m, 8H), 3.77 (s, 48H), 3.79 (t, J = 5.8 Hz, 4H), 4.46 (t, J = 5.0 Hz, 4H), 4.52 (s, 4H), 4.65 (s, 4H), 4.94 (s, 8H), 4.95 (s, 16H), 6.40 (t, J = 2.0 Hz, 8H), 6.52 (s, 2H), 6.55 (t, J = 2.1 Hz, 4H),

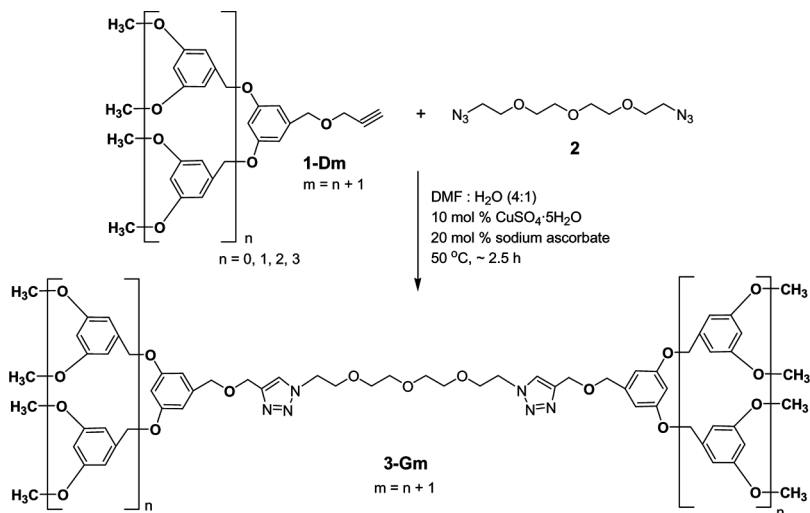
6.56 (d, $J = 2.1$ Hz, 16H), 6.60 (d, $J = 1.6$ Hz, 4H), 6.67(d, $J = 1.9$ Hz, 8H), 7.67 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 50.5, 55.8, 64.1, 69.8, 70.4, 70.5, 70.8, 70.9, 72.7, 100.4, 101.8, 102.0, 105.7, 106.9, 107.2, 124.2, 139.6, 139.7, 140.9, 145.3, 160.4, 160.5, 161.4; MS (MALDI): Calcd for $\text{C}_{128}\text{H}_{140}\text{N}_6\text{O}_{33}$: 2288.9461. Found: 2289.9343 $[\text{M}^+ + \text{H}]$, 2311.9053 $[\text{M}^+ + \text{Na}]$. PDI: 1.01.

Compound 3-G4. R_f 0.4 (EtOAc: dichloromethane = 2:1); 93% yield; A yellowish oil; IR 3013, 2940, 2839, 1593, 1458, 1204, 1150, 1049 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.47–3.49 (m, 8H), 3.75 (m, 100H), 4.42 (t, $J = 4.7$ Hz, 4H), 4.50 (s, 4H), 4.63 (s, 4H), 4.93 (s, 56H), 6.39 (m, 16H), 6.54–6.55 (m, 46H), 6.60 (m, 4H), 6.65 (m, 24H), 7.65 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 50.0, 55.3, 63.6, 69.3, 69.92, 69.98, 70.3, 70.4, 72.2, 99.9, 101.2, 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 $\text{C}_{256}\text{H}_{268}\text{N}_6\text{O}_{65}$: 4465.7850. Found: 4488.8603 $[\text{M}^+ + \text{Na}]$. PDI: 1.01.

RESULTS AND DISCUSSION

The synthetic strategy for Fréchet-type poly(benzyl ether) dendrimers having a tetra(ethyleneoxide) at core, linked by the triazole units, utilized a convergent method using the alkyne-functionalized Fréchet-type poly(benzyl ether) dendrons **1-Dm** and tetraethylene glycol diazide **2** (Scheme 1). The propargyl-functionalized Fréchet-type poly(benzyl ether) dendrons **1-Dm** ($m = 1 \sim 4$: generation of dendron) were synthesized by the propargylation of the corresponding dendritic benzyl alcohols with propargyl bromide [5e]. Compound **2** was prepared from the mesylation reaction of tetraethylene glycol with methanesulfonyl chloride in the presence of triethylamine and the subsequent azidation with sodium azide. To efficiently connect the propargylfocal point Fréchet-type dendrons with tetraethylene glycol diazide **2**, the synthetic approach selected is based on the click condition using Cu (I) species [3].

The efficiency of the click reaction between the alkyne-dendrons and bis(azides) was evaluated by performing the model coupling reactions between alkyne-dendron **1-D1** and compound **2**. Click reaction was carried out in a 4:1 solvent ratio of DMF to H_2O using 5 mol% $\text{CuSO}_4 \cdot \text{H}_2\text{O}$ 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 **2** and 2.2 equiv of alkyne-dendron **1-D1** afforded the desired product **3-G1** in a yield of 94% after 2.5 h at 50°C which was separated by column chromatography.



SCHEME 1 Synthesis of dendrimers via click reaction.

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 **2** and 2.2 equiv of alkyne-dendrons **1-D2** and **1-D3** afforded the dendrimers **3-G2** and **3-G3** in yields of 96 and 97%, respectively, after 1.5 h

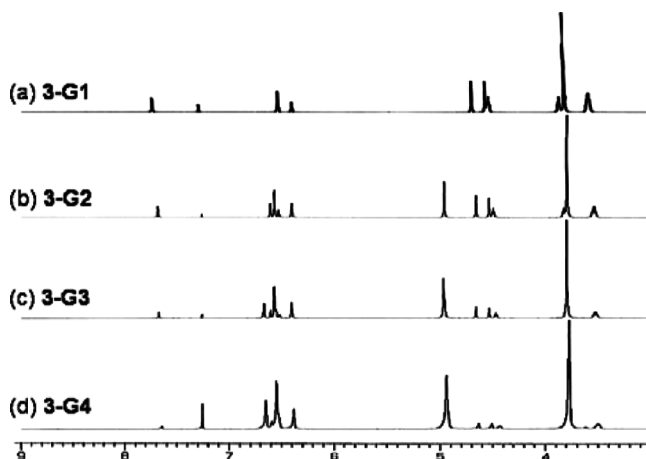


FIGURE 1 ¹H-NMR spectra for (a) **3-G1**, (b) **3-G2**, (c) **3-G3**, and (d) **3-G4**.

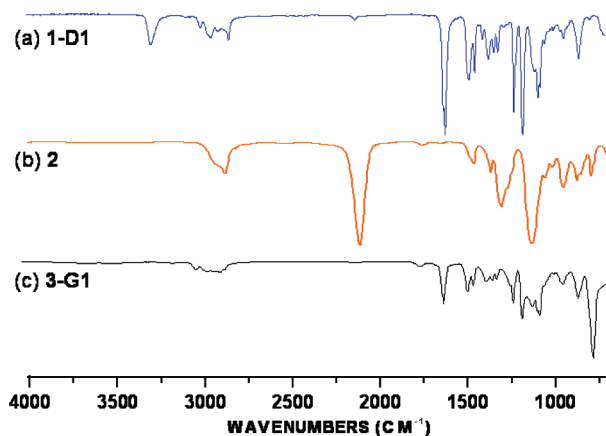


FIGURE 2 IR spectra for (a) **1-D1**, (b) **2**, and (c) **3-G1**.

and 45 min at 50°C. Finally, reaction of tetraethylene glycol diazide **2** and 2.2 equiv of alkyne-dendron **1-D4** gave the dendrimer **3-G4** in a yield of 93% after 30 min at 50°C. 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 tetraethyleneoxide with the dendrons. Therefore this approach may provide new methodological insight for synthesis of triblock dendritic polymers [2b] and would greatly contribute to researches on the application side.

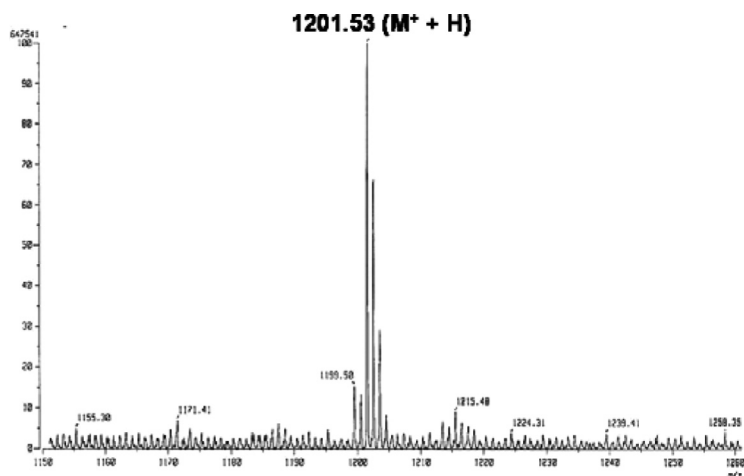


FIGURE 3 FAB mass spectrum of dendrimer **3-G2**.

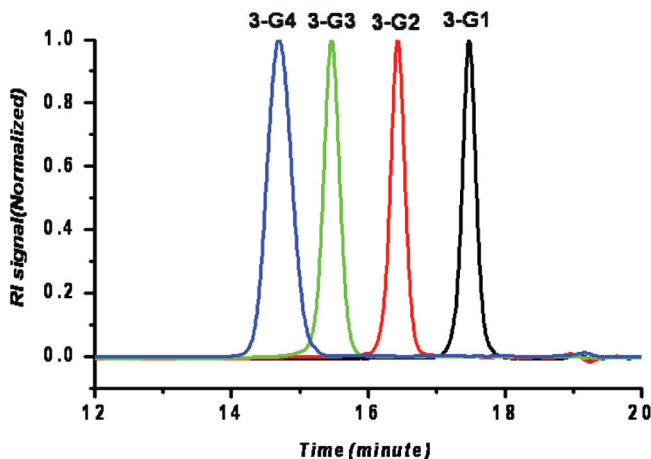


FIGURE 4 GPC diagrams of dendrimers **3-Gm** obtained from THF eluent.

The structures of the dendrimers **3-Gm** were confirmed by ^1H NMR, ^{13}C NMR, and IR spectroscopy. From the ^1H NMR spectra (CDCl_3), the peaks of the triazole proton in dendrimers **3-Gm** were found at 7.70 ppm for **3-G1**, 7.68 ppm for **3-G2**, 7.67 ppm for **3-G3**, and 7.65 ppm for **3-G4**, respectively (Fig. 1). The peaks of the methylene protons adjacent to the nitrogen of triazole in dendrimers **3-Gn** were found at 4.50 ppm for **3-G1**, 4.48 ppm for **3-G2**, 4.46 ppm for **3-G3**, and 4.42 ppm for **3-G4**, respectively. As the dendrimer generation increased, the peaks of the triazole proton and the methylene protons adjacent to the nitrogen of triazole shifted gradually to up-field which may be influenced by the dendritic microenvironment effect [8]. IR data also confirmed that neither alkyne ($\sim 3285\text{ cm}^{-1}$) nor azide ($\sim 2093\text{ cm}^{-1}$) residues remain in the final dendrimer (Fig. 2). 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 (Fig. 3). Analysis of the dendrimers by gel-permeation chromatography (GPC) shows very low polydispersity values, $\text{PDI} = 1.01$ for all dendrimers (Fig. 4).

CONCLUSION

We have successfully synthesized a series of triblock dendritic polymers by copper-catalyzed 1,3-dipolar click chemistry between azide

and alkyne. The tetraethyleneglycol diazide building block, designed to serve as the core in dendrimer, was stitched together with the propargyl-functionalized Fréchet-type poly(benzyl ether) dendrons leading to the formation of Fréchet-type poly(benzyl ether) dendrimers having the tetraethyleneoxide at core 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 connector to construct the diblock and/or triblock dendritic polymers from dendrons and linear compound. This strategy may then provide an insight into designing various amphiphilic dendritic materials. The synthesis and applications of the block dendritic polymers with specific structures and properties will now become part of the ongoing research efforts in our laboratories.

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