Synthesis of Diblock Codendrimers by Fusion of the Fréchet-Type and the PAMAM Dendrons

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Summary: Several diblock dendrimers were synthesized by fusion between the propargyl functionalized Fréchet-type polyether and the azide functionalized Tomalia-type PAMAM dendrons. This was based on the click chemistry protocol, the copper-catalyzed cycloaddition reaction between an alkyne and an azide. The diblock dendrimers were characterized by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and mass spectra as well as GPC analysis.

Keywords: 1,2,3-triazoles; click chemistry; cycloaddition; diblock dendrimers

Introduction

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.[1] Amphiphilic dendritic–linear block copolymers are believed to combine the advantageous properties of both linear and dendritic amphiphiles.[2–6] Dendritic–linear diblock copolymers have been synthesized by the stepwise preparation methods, which proceed in either a convergent or divergent strategy. The former involves the coupling of preformed linear polymers functionalized at one or both chain ends with reactive dendrons having a complementary functionality at their focal point.[7–10] The latter is that the dendritic segment is grown via a divergent strategy from a suitably end-functionalized linear polymer[11–13] or that reactive functionality at the focal point of dendrons can also serve as macromolecular initiators in the polymerization.[14]

Although the dendritic polymer amphiphiles possessing a hydrophilic dendritic component and a hydrophobic linear polymer (or vice versa) and the unimolecular dendritic amphiphiles are well-known,[1] relatively few diblock codendrimers have been reported. The diblock codendrimer composed of two different dendrons could function as polymeric amphiphiles, which have the advantages of linear-linear amphiphilic block copolymers, and promise superior performance. Since the concept of a codendrimer was established by Hawker and Fréchet,[15] several surface-modified block dendrimers was synthesized.[16] Recently an example of block codendrimer composed of two different monodendrons was reported which one block is the third-generation Fréchet-type poly(benzyl ether) monodendron and the other one is the third-generation aliphatic polyether monodendron.[17] A general strategy for the facile synthesis of diblock codendrimers from distinct component blocks, however, is still needed.[18] The convergent approach allows

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for a large degree of chemical diversity such that functional groups can be incorporated at nearly central position in the dendritic architecture. Recent solid chemistry used in the synthesis of dendrimers via the convergent and divergent approach is the click chemistry which is the copper-catalyzed 1,3-dipolar cycloaddition reaction between an alkyne and an azide.[19] Taking advantage of this fact, we present a general strategy for the convergent synthesis of the block codendrimers by fusion between the Fréchet-type polyether and the Tomalia-type PAMAM dendrons.

Experimental Part

Methods

^{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 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 5μm 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.

General Procedure for the Preparation of Diblock Codendrimers 3-Gmn

A mixture of propargyl-Fréchet dendrons **1-Dm** (0.11 mmol) and azido-PAMAM dendrons **2-Dn** (0.10 mmol) in THF- H_2O (4:1, 1 mL) in the presence of 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate was stirred at room temperature for ~4 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 to afford the desired product 3-Gmn.

3-G11

91% yield; IR 2952, 2840, 1734, 1598, 1457, 1434, 1203, 1153, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.03$–2.08 (m, 2H), 2.41–2.43 (m, 6H), 2.73 (t, $J = 6.8$ Hz, 4H), 3.67 (s, 6H), 3.78 (s, 6H), 4.35 (t, $J = 7.1$ Hz, 2H), 4.55 (s, 2H), 4.68 (s, 2H), 6.38 (t, $J = 2.2$ Hz, 1H), 6.52 (d, $J = 2.2$ Hz, 2H), 7.68 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.4$, 161.3, 145.3, 140.8, 123.4, 106.0, 100.2, 72.8, 64.1, 55.8, 52.0, 50.9, 49.6, 48.3, 32.9, 28.6; MS (FAB): $m/z =$ 479.2 [$M^+ + H$]; HRMS (FAB) calcd for $C_{23}H_{34}N_4O_7$: 478.2428. found: 479.2506 [$M^+ + H$]. PDI: 1.01.

3-G22

90% yield; IR 3307, 2952, 2926, 2846, 1736, 1664, 1531, 1436, 1258, 1199, 1176, 1046 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.07$ (m, 2H), 2.41 (t, $J = 6.5$ Hz, 12H), 2.52 (t, $J = 5.6$ Hz, 4H), 2.72 (t, $J = 6.6$ Hz, 8H), 2.82 (m, 6H), 3.25–3.28 (m, 4H), 3.65 (s, 12H), 3.78 (s, 12H), 4.39 (t, $J = 6.7$ Hz, 2H), 4.53 (s, 2H), 4.64 (s, 2H), 4.96 (s, 4H), 6.40 (t, $J = 1.8$ Hz, 2H), 6.52 (m, 1H), 6.56 (d, $J = 1.9$ Hz, 4H), 6.61 (d, $J = 1.8$ Hz, 2H), 6.96 (br s, 2H), 7.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.4$, 161.4, 160.4, 145.4, 140.8, 139.7, 123.4, 107.2, 105.7, 101.9, 100.4, 72.8, 70.4, 64.1, 55.8, 53.3, 52.1, 50.4, 50.1, 49.6, 48.3, 37.6, 33.1, 28.7; MS (FAB): $m/z = 1150.8$ [M^+]; HRMS (FAB) calcd for $C_{57}H_{82}N_8O_{17}$: 1150.5798. found: 1151.5876 [$M^+ + H$]. PDI: 1.02.

3-G12

84% yield; IR 3342, 2949, 2834, 1736, 1664, 1597, 1531, 1459, 1433, 1356, 1258, 1203, 1153, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.06$ (m, 2H), 2.37 (m, 4H), 2.40–2.43 (m, 10H), 2.53–2.54 (m, 6H), 2.72–2.74 (m, 10H), 3.28 (m, 4H), 3.66 (s, 12H), 3.78 (s, 6H), 4.39 (t, $J = 6.7$ Hz, 2H), 4.54 (s, 2H), 4.65 (s, 2H), 6.38 (m, 1H), 6.52 (m, 2H), 6.96 (br s, 2H), 7.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.5$, 161.3, 145.3, 140.7, 123.4, 106.0, 100.2, 72.9, 64.1, 55.8, 53.4, 52.1, 50.4, 50.1, 49.7, 48.3, 37.6, 33.1, 28.7; MS (FAB): $m/z = 879.3$ $[M^+ + H]$; HRMS (FAB) calcd for $C_{41}H_{66}N_8O_{13}$: 878.4749. found: 879.4828 $[M^+ + H]$. PDI: 1.04.

3-G21

92% yield; IR 2949, 2839, 1734, 1597, 1457, 1431, 1373, 1321, 1298, 1203, 1153, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.05$ (m, 2H), 2.41–2.43 (m, 6H), 2.73 (t, $J = 6.8$ Hz, 4H), 3.66 (s, 6H), 3.79 (s, 12H), 4.36 (t, $J = 7.1$ Hz, 2H), 4.55 (s, 2H), 4.67 (s, 2H), 4.97 (s, 4H), 6.41 (m, 2H), 6.53 (m, 1H), 6.57 (m, 4H), 6.62 (m, 2H), 7.77 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.1$, 161.4, 160.4, 145.3, 140.8, 139.6, 123.5, 107.1, 105.6, 101.8, 100.3, 72.7, 70.4, 64.1, 55.8, 52.1, 50.9, 49.5, 48.2, 32.5, 28.3; MS (FAB): $m/z = 751.2$ $[M^+ + H]$; HRMS (FAB) calcd for $C_{39}H_{50}N_4O_{11}$: 750.3476. found: 751.3554 $[M^+ + H]$. PDI: 1.01.

3-G31

94% yield; IR 2949, 2933, 2840, 1734, 1595, 1457, 1431, 1373, 1321, 1298, 1205, 1154, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.04$ (m, 2H), 2.39–2.42 (m, 6H), 2.72 (t, $J = 6.8$ Hz, 4H), 3.65 (s, 6H), 3.78 (s, 24H), 4.34 (t, $J = 7.1$ Hz, 2H), 4.55 (s, 2H), 4.68 (s, 2H), 4.96 (s, 4H), 4.97 (s, 8H), 6.40 (m, 4H), 6.52 (m, 1H), 6.55 (m, 2H), 6.57 (m, 8H), 6.62 (m, 2H), 6.67 (m, 4H), 7.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.4$, 161.4, 160.5, 160.4, 145.2, 140.9, 139.7, 139.6, 123.4, 107.1, 106.8, 105.7, 102.0, 101.8, 100.4, 72.7, 70.5, 70.4, 64.1, 60.8, 55.8, 52.0, 50.9, 49.5, 48.3, 32.8, 31.3, 28.6; MS (FAB): $m/z = 1294.8$ $[M^+]$; HRMS (FAB) calcd for $C_{71}H_{82}N_4O_{19}$: 1294.5573. found: 1295.5652 $[M^+ + H]$. PDI: 1.01.

3-G32

93% yield; IR 3351, 2950, 2837, 1734, 1661, 1595, 1526, 1456, 1431, 1373, 1321, 1298, 1205, 1155, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.02$ (m, 2H), 2.33 (t, $J = 6.3$ Hz, 4H), 2.39–2.43 (m, 10H), 2.51 (t, $J = 5.9$ Hz, 4H), 2.70–2.75 (m, 12H), 3.24–3.28 (m, 4H), 3.64 (s, 12H), 3.78 (s, 24H), 4.37 (t, $J =$ 6.7 Hz, 2H), 4.54 (s, 2H), 4.66 (s, 2H), 4.96 (s, 4H), 4.97 (s, 8H), 6.40 (m, 4H), 6.52 (m, 1H), 6.55 (m, 2H), 6.57 (m, 8H), 6.62 (m, 2H), 6.67 (m, 4H), 6.93 (br s, 2H), 7.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.5$, 172.8, 161.4, 160.5, 160.4, 145.2, 140.9, 139.7, 139.5, 126.3, 107.1, 106.9, 105.7, 102.0, 101.8, 100.4, 72.8, 70.5, 70.4, 64.1, 55.8, 53.3, 52.0, 50.1, 49.6, 48.3, 37.6, 34.5, 33.1, 31.3, 28.6; MS (FAB): $m/z = 1695.1$ $[M^+]$; HRMS (FAB) calcd for $C_{89}H_{114}N_8O_{25}$: 1694.7895. found: 1695.7973 $[M^+ + H]$. PDI: 1.02.

3-G41

91% yield; IR 2955, 2932, 2871, 2837, 1731, 1595, 1456, 1431, 1373, 1321, 1298, 1205, 1154, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.02$ (m, 2H), 2.37–2.42 (m, 6H), 2.70 (t, $J = 6.8$ Hz, 4H), 3.63 (s, 6H), 3.76 (s, 48H), 4.32 (t, $J = 7.0$ Hz, 2H), 4.53 (s, 2H), 4.66 (s, 2H), 4.95 (s, 28H), 6.39 (m, 8H), 6.54–6.56 (m, 26H), 6.62 (m, 2H), 6.66 (m, 9H), 7.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.4$, 161.2, 161.0, 160.1, 145.0, 139.8, 139.2, 139.1, 125.9, 107.1, 106.4, 105.2, 105.0, 102.0, 101.6, 100.0, 72.3, 70.1, 70.0, 63.7, 60.3, 55.3, 51.5, 50.4, 49.1, 48.0, 32.4, 31.0, 28.2; MS (MALDI): m/z calcd for $C_{135}H_{146}N_4O_{35}$: 2382.9768. found: 2383.9597 $[M^+ + H]$, 2405.9877 $[M^+ + Na]$. PDI: 1.02.

3-G42

93% yield; IR 3340, 2955, 2932, 2871, 2837, 1735, 1664, 1597, 1530, 1456, 1431, 1373, 1348, 1321, 1298, 1260, 1204, 1154, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.04$ (m, 2H), 2.37 (t, $J = 6.4$ Hz, 4H), 2.40–2.43 (m, 10H), 2.51–2.57 (m, 4H), 2.72–2.78 (m, 12H), 3.28 (m, 4H), 3.66 (s, 12H), 3.76 (s, 48H), 4.38 (t, $J =$ 6.8 Hz, 2H),

4.53 (s, 2H), 4.65 (s, 2H), 4.95 (s, 28H), 6.38 (m, 8H), 6.54–6.57 (m, 26H), 6.63 (m, 2H), 6.65 (m, 9H), 6.96 (br s, 2H), 7.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.5$, 172.9, 161.4, 161.0, 160.3, 145.1, 140.5, 139.6, 139.4, 125.7, 107.1, 106.7, 106.0, 105.6, 102.1, 101.7, 100.4, 72.3, 70.3, 70.1, 64.0, 60.6, 55.5, 53.3, 52.0, 50.2, 49.6, 48.5, 37.8, 34.5, 33.1, 32.27, 29.2.

Results and Discussion

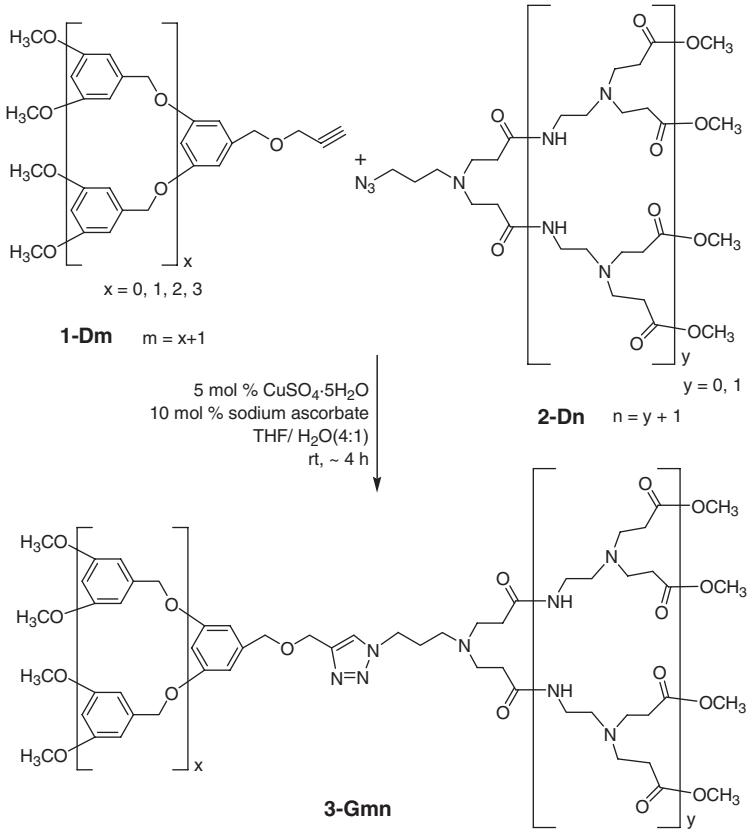
Stitching together different dendrons effectively and efficiently without any ensuing problems in isolation and purification is a major challenge. The clue was provided by the click chemistry which is developed by Sharpless and Tornøe.[19] This reaction has been used in the synthesis of dendrimers,[20] but an application in the synthesis of diblock codendrimer has been reported.[18] Taking these advantages, we are intrigued to utilize the click chemistry for the synthesis of componently differentiated diblock codendrimers.

The synthetic strategy for the diblock codendrimers **3-Gmn** utilized a convergent method using the propargyl-functionalized Fréchet-type dendrons **1-Dm** and the azide-functionalized PAMAM dendrons **2-Dn** (Scheme 1). The Fréchet-type alkyne-dendrons **1-Dm** ($m = 1 \sim 4$: generation of dendron) were prepared according to the reported procedure.[20i] The azido-PAMAM dendrons **2-Dn** ($n = 1 \sim 2$: generation of dendron) are synthesized by the divergent approach using azidopropyl amine as an azide focal point.[20m]

To demonstrate the effectiveness of the dipolar cycloaddition reactions of the alkyne-dendrons **1-Dm** and azido-dendrons **2-Dn** in the synthesis of diblock codendrimer, we have screened conditions using 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate in a 4:1 solvent ratio of THF to H_2O. It was found that the reaction of alkyne-dendron **1-D1** and azido-dendrons **2-D1** conducted for 1 h 50 min at room temperature afforded the desired product **3-G11** in 91% yield. The accelerated rate of reactions may potentially be explained by anchimeric assistance due to the amine part in the PAMAM dendrons **2-D1**.[20m] Given the success in the synthesis of first generation dendrimer **3-G11**, we expanded this reaction to get second generation dendrimers with 5 mol % $CuSO_47 \cdot 5H_2O$ with 10 mol % sodium ascorbate in a 4:1 solvent ratio of THF to H_2O. Reaction of **1-D2** with **2-D2** afforded the block dendrimers **3-G22** in 90% yield after 2 h 10 min. This result showed that the formation of triazole could be regarded as an efficient connector to construct the diblock codendrimers from two different dendron components.

The structure of diblock codendrimers was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and 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 **3-Gmn** were found at 4.35, 7.68, and 4.68 ppm for **3-G11** and 4.39, 7.72, and 4.64 ppm for **3-G22**, respectively (Figure 1). As the dendrimer generation increased, the peaks of the methylene protons adjacent to the nitrogen of triazole and the triazole proton shifted gradually to downfield, which may be influenced by the PAMAM dendritic microenvironment effect.[21] IR data also confirmed that neither alkyne (~ 3285 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 (Figure 2). Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluent shows polydispersity values PDI = 1.01 and 1.02 for **3-G11** and **3-G22**, respectively.

To probe the viability of our approach, we next turned our attention toward the construction of unsymmetrical diblock codendrimers, which are differentiated from the symmetrical ones by the generation of dendrons. Click reactions were carried out in a 4:1 solvent ratio of THF to H_2O using 5 mol % $CuSO_4 \cdot 5H_2O$ with 10 mol % sodium ascorbate as the in situ reducing agent to



Scheme 1.
Synthesis of diblock codendrimers.

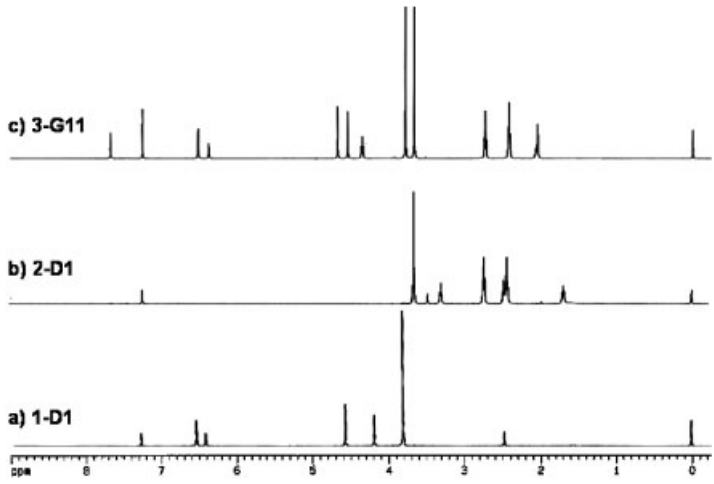


Figure 1.
^{1}H-NMR spectra for (a) **1-D1**, (b) **2-D1**, and (c) **3-G11**.

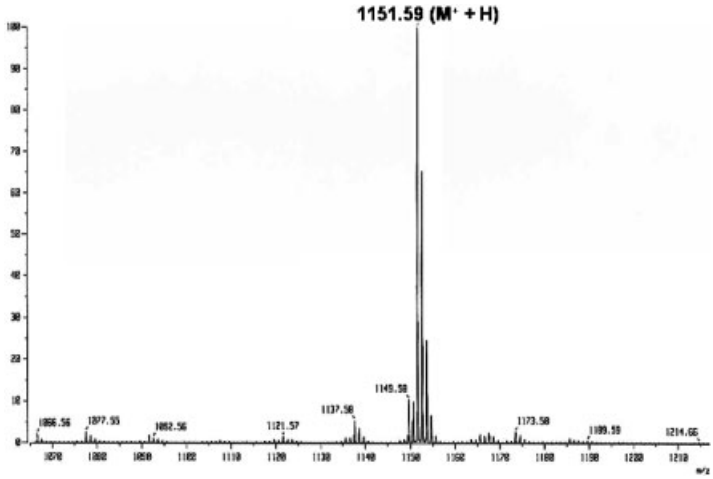


Figure 2.
Mass spectrum of dendrimer **3-G22**.

generate the active Cu(I) species. The reaction of alkyne-focal dendron **1-D1** with **2-D2** afforded the unsymmetrical diblock codendrimers **3-G12** in 84% yield after 2 h. Next, it was proven that the reaction of second generation **1-D2** with azido-dendron **2-D1** provided the unsymmetrical diblock codendrimers **3-G21** in 92% yield after 2 h. It was also found that the reactions of third generation alkyne-focal dendron **1-D3** with **2-D1** and **2-D2** gave the unsymmetrical diblock codendrimers **3-G31** and **3-G32** in yields of 94% and 93%, respectively, after 2.5 h. Finally we have investigated the reactions based on the fourth generation Fréchet-type alkyne-dendron **1-D4**. The reactions of alkyne-focal dendron **1-D4** with azido-dendrons **2-D1** and **2-D2** afforded the unsymmetrical diblock codendrimers **3-G41** and **3-G42** in yields of 91% and 93%, after 3.5 h, respectively. For completion of the reaction between the dendrons, the higher

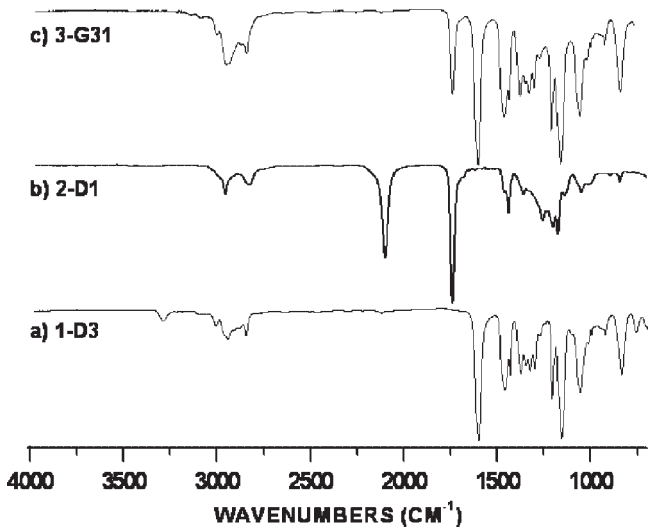


Figure 3.
IR spectra for (a) **1-D3**, (b) **2-D1**, and (c) **3-G31**.

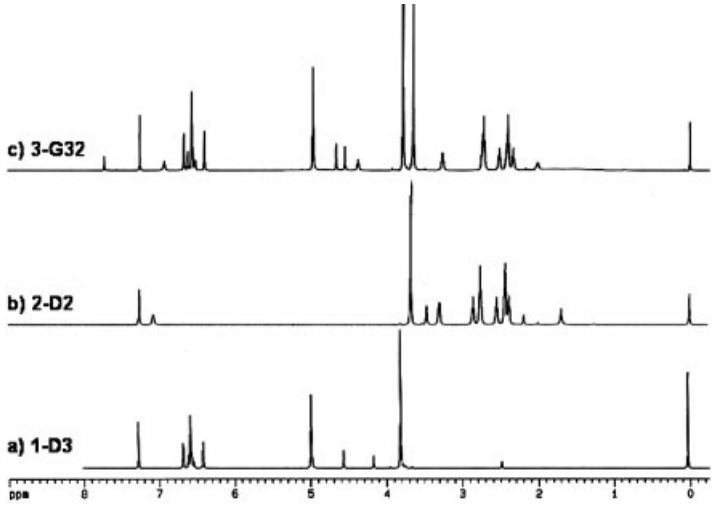


Figure 4.
^{1}H-NMR spectra for (a) **1-D3**, (b) **2-D2**, and (c) **3-G32**.

generation dendron takes longer time than the lower generation dendron, which can be ascribed to the steric demand of the dendron. This result also showed that the click chemistry is found to be an efficient method for the synthesis of unsymmetric diblock codendrimers using the different generations of dendrons. The diblock unsymmetric dendrimers were purified by column chromatography and the structures were also characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectra, and gel-permeation chromatography (GPC). The IR spectra shows the disappearance of the acetylene peak at $\sim$ 3285 cm^{-1} and the azide peak at $\sim$ 2098 cm^{-1} in the final dendrimer (Figure 3) while the ^{1}H NMR revealed the triazole proton peak at around δ 7.66$\sim$7.73 ppm and no alkyne peak at around δ 2.46 ppm (Figure 4). Their mass spectra exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluent shows very low polydispersity values.

Conclusions

We have demonstrated the facile synthesis of diblock codendrimers from distinctly different component blocks by fusion between the Fréchet-type polyether and the Tomalia-type PAMAM dendrons based on the copper-catalyzed cycloaddition reaction between an alkyne and an azide. Furthermore, the coupling using different generation dendrons afforded the size- and component-differenciated diblock codendrimers. This method may provide an insight into designing various diblock dendrimers such as amphiphilic dendrimers. We are currently studying about the aggregation behavior of these codendrimer and working toward synthesis of various functional dendrimers using this strategy for tailored applications for life sciences such as drug and gene delivery.

Acknowledgements: This research was supported by the University IT Research Center (ITRC) Project of the Ministry of Information and Communication (J.W.L) and the National Research Laboratory (NRL) program of KOSEF (S.H.J). We also thank the Korean Ministry of Education (BK 21 Program) for graduate studentships.

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