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Synthesis of Aliphatic Polyamide Dendrimers Based on Facile Convergent Method

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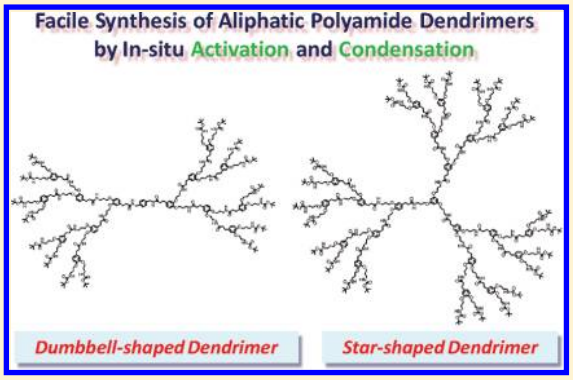
Supporting Information

ABSTRACT: A novel and rapid approach for the synthesis of aliphatic polyamide dendrimers, consisting of the 3,4-dialkoxyhydrocinnamamide structure as a repeating unit, has been developed. Aliphatic polyamide dendrons and dendrimers were easily prepared by a convergent approach involving activation of a carboxylic acid at the focal point using (2,3-dihydro-2-thioxo-3-benzoxazolyl)phosphonate (DBOP) as the activating agent, followed by condensation with an unprotected AB_2 building block. Dumbbell-shaped and star-shaped third generation dendrimers were prepared from the third generation dendron and core molecules containing two or three functional groups. All the above products could be purified only by precipitation, and their structures were confirmed by ^1H NMR, IR, and matrix-assisted laser desorption ionization time-of-flight mass (MALDI−TOF−MS) spectroscopies and elemental analysis.



INTRODUCTION

Dendrimers are hyperbranched and three-dimensional macromolecules with a well-defined core, backbone and multivalent periphery. Their characteristic structures give dendrimers specific characteristics such as a low viscosity in solution, numerous functionalization possibilities and accommodation of guest compounds. These specifities have encouraged the pursuit of new polymeric materials for applications in areas, such as catalysts,[1] liquid crystals,[2] photonic devices,[3] and drug delivery systems.[4−6] Although dendrimers have received much attention as new materials, their widespread uses were interfered because the synthesis of dendrimers requires a tedious multistep procedure with repetitive protection−deprotection and purification processes. To solve this problem, we have focused on the development of facile synthetic approaches of dendrimers, and reported the rapid syntheses of aromatic polyamide dendrimers via both divergent and convergent methods,[7−11] in which the total number of reactions decreased to half that required in the conventional approaches. Whereas a few aromatic polyamide dendrimers have been reported as functional materials, there are many reports on the development of aliphatic polyamide dendrimers[12,13] as the functional materials, such as polyamide amine (PAMAM) dendrimers, lysine dendrimers and airbol. These aliphatic polyamide dendrimers have been receiving attention especially as medical,[14−17] biological,[18,19] catalytic,[20] and encapsulation materials.[21,22] These aliphatic polyamide dendrimers were prepared by the repetitive conversion of the terminal groups or protection−deprotection, and purification processes, and a few papers were reported about the facile synthetic method of aliphatic polyamide dendrimers. Haridas et al. reported the time-efficient synthesis of peptide dendrimers using the 1,3-dipolar cycloaddition (Click) reaction.[23] Al-Hamra et al. reported peptide dendrimers with a petaaminecobalt(III) complex at the core as a facile synthetic method.[24] However, these methods still have the following problems: (i) the dendrimers synthesized by the former method contain a triazole unit and that could change the property of the dendrimers, and (ii) though the latter synthetic method succeeds to facilitate the purification steps, the number of reaction steps was still high and the protection−deprotection steps are still required. From this standpoint, it is important to develop a facile synthetic method of aliphatic polyamide dendrimers. In this article, we report the facile synthesis of a aliphatic polyamide dendrimer having the 3,4-dialkoxyhydrocinnamamide structure as a repeating unit based on the convergent method by extending the facile synthetic method of aromatic polyamide dendrimers.

EXPERIMENTAL SECTION

Materials. *N*-Methyl-2-pyrrolidinone (NMP) was distilled under reduced pressure over calcium hydride, and then stored under nitrogen. Triethylamine (TEA) was distilled over calcium hydride under nitrogen, and then stored under nitrogen. DBOP was supplied from KYOCERA Chemical Corporation and recrystallized from hexane, then stored under nitrogen in a refrigerator. Other reagents

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and solvents were obtained commercially and used as received unless otherwise noted.

Synthesis of Protected First Generation Dendrons (protected-G1-dendron). To a mixture of 3-bromopropyl-1-NHBoc (**1**, 9.00 g, 37.8 mmol), K_2CO_3 (7.84 g, 56.7 mmol) and molecular sieves (12 g) in DMF (25 mL) was added methyl 3,4-dihydroxyhydrocinnamate (2.47 g, 12.6 mmol) at room temperature under nitrogen. The reaction mixture was stirred at 60 °C overnight, cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (EtOAc)/ether = 1/1, and the organic phase was washed with water and brine. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography (methanol/EtOAc/hexane = 1/3/15). Recrystallization from methanol/water gave white solid (4.36 g, 68%). Mp: 83−84 °C. IR (KBr, cm^{-1}): 1172 (Ar−O−alkyl), 1689, 1728 (C═O, amide and carbamate), 2938, 2977 (Ar−H), 3379 (N−H, carbamate). ^1H NMR (MeOH-d_4, δ, ppm): 1.43 (s, 18H), 1.87−1.99 (m, 4H), 2.60 (t, 2H, ^3J = 7.7 Hz), 2.84 (t, 2H, ^3J = 7.7 Hz), 3.21−3.29 (m, 4H) 3.64 (s, 3H) 4.02 (m, 4H) 6.73 (dd, 1H, ^3J = 8.0, ^4J = 2.0), 6.82 (d, 1H, ^4J = 2.0) 6.86 (d, 1H, ^3J = 8.0). Anal. Calcd for $C_{26}H_{42}N_2O_8$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.96; H, 8.15; N, 5.45.

Synthesis of First Generation Dendrons (G1-dendron). A mixture of the compound **protected-G1-dendron** (4.05 g, 7.93 mmol) and KOH (0.620 g, 9.80 mmol) in methanol/water (45 mL/15 mL) was refluxed for 2 h. The reaction solution was cooled to room temperature and acidified with acetic acid. Then, the organic layer was diluted with dichloromethane (DCM) and washed with water three times, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The **G1-dendron** was obtained as white solid after the recrystallization from toluene/hexane (3.32 g, 84%). Mp: 102−103 °C. IR (KBr, cm^{-1}): 1172 (Ar−O−alkyl), 1704, 1735 (C═O, carbamate and carboxylic acid), 2938, 2977 (Ar−H), 3332 (N−H, carbamate). ^1H NMR (MeOH-d_4, δ, ppm): 1.43 (s, 18H), 1.87−2.01 (m, 4H), 2.60 (t, 2H, ^3J = 7.7 Hz), 2.84 (t, 2H, ^3J = 7.7 Hz), 3.21−3.29 (m, 4H) 4.02 (m, 4H) 6.75 (dd, 1H, ^3J = 8.0, ^4J = 2.0), 6.83−6.88 (m, 2H). Anal. Calcd for $C_{25}H_{40}N_2O_8$: C, 60.47; H, 8.12; N, 5.64. Found: C, 60.38; H, 8.09; N, 5.63.

Synthesis of AB_2 Building Blocks (AB_2). The **G1-dendron** (50.0 mg, 0.1 mmol) was dissolved in trifluoroacetic acid (TFA) (0.5 mL), and the reaction solution was stirred at room temperature for 1.5 h. The solvent was evaporated to dryness to give white sticky oil. The oil was washed with ether three times and dried under reduced pressure to give white stickly oil (51.1 mg, 97%). IR (NaCl, cm^{-1}): 1133 (Ar−O−Alkyl), 1203 (C−F), 1681 (C═O, carboxylate), 2700−3300 (N−H, ammonium), ^1H NMR (MeOH-d_4, δ, ppm): 2.08−2.24 (m, 4H), 2.58 (t, 2H, 3J = 7.6 Hz) 2.86 (t, 2H, ^3J = 7.6 Hz), 3.13−3.23 (m, 4H) 4.09−4.21 (m, 4H), 6.81 (dd, 4H, ^3J = 8.2 Hz, ^4J = 2.0 Hz), 6.59−6.82 (m, 9H) 7.16−7.29 (m, 2H) 6.65−6.85 (m, 9H). Anal. Calcd for $C_{19}H_{26}F_6N_2O_8$: C, 43.52; H, 5.00; N, 5.34. Found: C, 43.70; H, 4.91; N, 5.04.

Synthesis of Second Generation Dendrons (G2-dendron). To a solution of **G1-dendron** (1.49 g, 3.00 mmol) in NMP (4.8 mL) were added DBOP (1.00 g, 2.85 mmol) and TEA (0.4 mL, 2.85 mmol) under nitrogen. The reaction solution was stirred at room temperature for 1.5 h. Then, the reaction solution was added dropwise to a NMP (4.8 mL) solution of TEA (1.20 mL, 8.10 mmol) and AB_2 which was synthesized from 0.670 g (1.35 mmol) of **G1-dendron**, and the reaction solution was stirred at room temperature for 3 h. The reaction solution was diluted with EtOAc/ether = 1/1. The organic layer was washed with 1 M HCl (aq) and brine, and then dried with $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give pale yellow oil. The oil was diluted with acetone (18 mL), and hexane (54 mL) was added to the solution. The precipitate was collected and dried in vacuo at 40 °C to give white powder. (1.26 g, 75%) Mp: 74 −75 °C. IR (KBr, cm^{-1}): 1172 (Ar−O−alkyl), 1643, 1689 (C═O, carbamate, carboxylic acid and amide), 2931, 2969 (Ar−H), 3363 (N−H, carbamate and amide). ^1H NMR (THF-d_8, δ, ppm): 1.39 (s, 36H), 1.80−1.95 (m, 12H), 2.30−2.39 (m, 4H), 2.57 (t, 2H, J = 7.8 Hz) 2.79 (t, 6H, J = 7.8 Hz), 3.17−3.40 (m, 12H) 3.86−3.99 (m, 12H), 6.07−6.24 (m, 4H), 6.59−6.82 (m, 9H) 7.16−7.29 (m, 2H) 6.65−6.85 (m, 9H). Anal. Calcd for $C_{65}H_{100}N_6O_{18}$: C, 62.28; H, 8.04; N, 6.70. Found: C, 62.52; H, 8.12; N, 6.62. MALDI−TOF MS: Calcd: $[M]^+$ = 1274.7, Found: $[M + Na]^+$ = 1272.0.

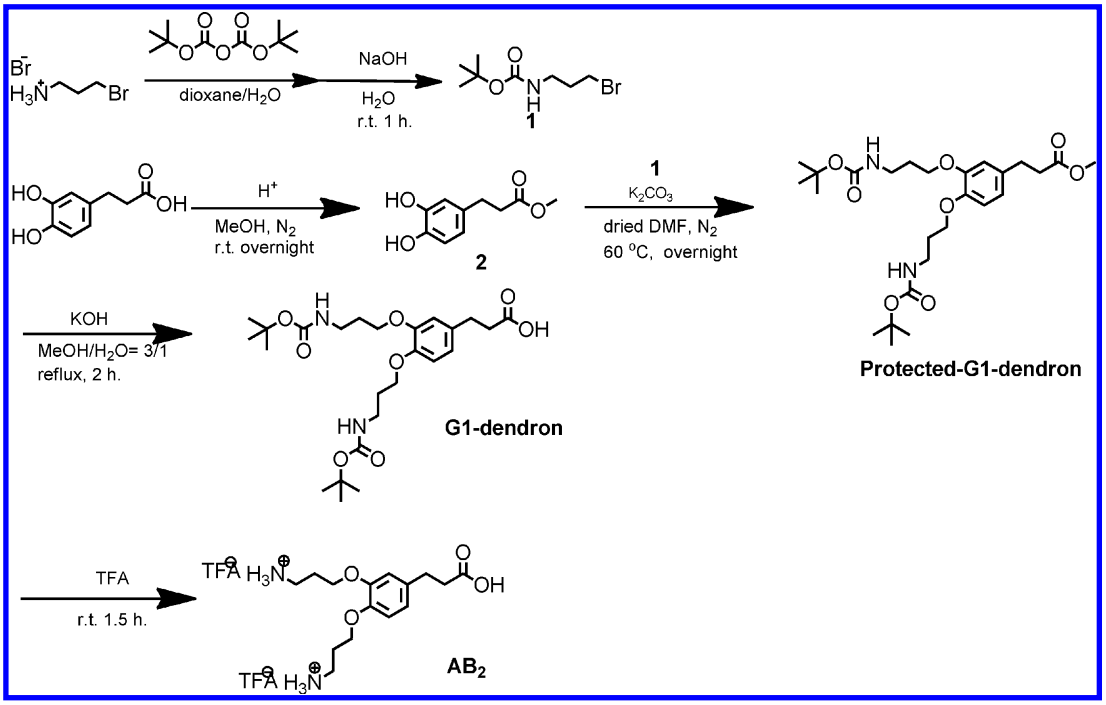
Synthesis of Third Generation Dendrons (G3-dendron). To a solution of **G2-dendron** (1.51 g, 1.20 mmol) in NMP (4.0 mL) were added DBOP (0.460 g, 1.20 mmol) and TEA (0.17 mL, 1.20 mmol) under nitrogen. The reaction solution was stirred at room temperature for 1.5 h. Then, the reaction solution was added dropwise to a NMP (4.5 mL) solution of TEA (1.50 mL, 10.8 mmol) and AB_2 which was synthesized from 0.274 g (0.552 mmol) of **G1-dendron**. The reaction solution was stirred at room temeperature for 3 h. The reaction solution was poured in water and acidified with 1 M HCl (aq). The precipitate was collected and dried. The crude product was dissolved in methanol (30 mL), diluted with acetone (60 mL), and then hexane (240 mL) was added to the solution. The precipitate was collected and dried in vacuo at 40 °C to give white powder (1.33 g, 87%). T_g: 45 °C. IR (KBr, cm^{-1}): 1172 (Ar−O−alkyl), 1650, 1697 (C═O, carbamate, carboxylic acid and amide), 2931, 2969 (Ar−H), 3347, 3402 (N−H, carbamate and amide). ^1H NMR (THF-d_8, δ, ppm): 1.39 (s, 72H), 1.78−1.95 (m, 28H), 2.31−2.41 (m, 12H), 2.49 (t, 2H, J = 7.8 Hz) 2.79 (t, 14H, J = 7.8 Hz), 3.17−3.40 (m, 28H) 3.79−4.01 (m, 28H), 6.13−6.25 (m, 8H), 6.59−6.82 (m, 21H) 7.16−7.29 (m, 6H) 6.65−6.85 (m, 9H). Anal. Calcd for $C_{145}H_{220}N_{14}O_{38}$: C, 62.93; H, 8.01; N, 7.09. Found: C, 63.26; H, 8.13; N, 6.98. MALDI−TOF MS: calcd $[M]^+$ = 2787.5; found $[M + Na]^+$ = 2787.6.

Synthesis of Dumbbell-Shaped Third Generation Dendrimers (DS-G3-dendrimer). To a solution of **G3-dendron** (0.274 g, 0.100 mmol) in NMP (0.6 mL) were added DBOP (38.3 g, 0.100 mmol) and TEA (14.0 μL, 0.100 mmol) under nitrogen. The reaction solution was stirred at room temperature for 1.5 h. Then, the reaction solution was added dropwise to a solution of *p*-xylylenediamine (6.26 mg, 0.0460 mmol) in NMP (0.6 mL), and the reaction solution was stirred at room temperature for 6 h. The reaction solution was poured in 1 wt % $NaHCO_3$ (aq). The precipitate was collected and dried. The crude product was dissolved in DMF (1.2 mL) and diluted with MeOH (6.0 mL), and then acetone (24 mL) and hexane (12 mL) were added to the solution. The precipitate was collected and dried in vacuo at 40 °C to give white powder (0.174 g, 75%). T_g: 52 °C. IR (KBr, cm^{-1}): 1172 (Ar−O−alkyl), 1643, 1697 (C═O, carbamate and amide), 2931, 2969 (Ar−H), 3309, 3347 (N−H, carbamate and amide). ^1H NMR (DMSO-d_6, δ, ppm): 1.37 (s, 144H), 1.71−1.92 (m, 56H), 2.25−2.46 (m, 28H), 2.66−2.82 (m, 28H), 3.02−3.16 (m, 32H) 3.16−3.26 (m, 24H, overlapped with H_2O), 3.81−4.00 (m, 56H), 4.22 (d, 4H, ^3J = 5.8 Hz), 6.50−6.89 (m, 58H), 7.11 (s, 4H), 7.69−7.91 (m, 12H), 8.17 (t, 2H, ^3J = 5.8 Hz). Anal. Calcd for $C_{294}H_{448}N_{30}O_{74}$: C, 63.52; H, 8.01; N, 7.46. Found: C, 63.39; H, 8.02; N, 7.36. MALDI−TOF MS: calcd $[M]^+$ = 5653.2; found $[M + Na]^+$ = 5653.3.

Synthesis of Protected Three Functional Core (Protected-3-core). To a mixture of **1** (1.43 g, 6.00 mmol), K_2CO_3 (1.24 g, 9.00 mmol), and molecular sieves (2 g) in DMF (2 mL) was added phloroglucinol (0.126 g, 1.00 mmol) at room temperature under nitrogen. The reaction mixture was stirred at 60 °C overnight, cooled to room temperature and filtered. The filtrate was diluted with EtOAc/ether = 1/1, and the organic phase was washed with water and brine. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography (methanol/EtOAc/hexane =1/3/15). Recrystallization from methanol/water two times gave white solid (0.155 g, 26%). Mp: 109−110 °C. IR (KBr, cm^{-1}): 1164 (Ar−O−alkyl), 1689 (C═O, carbamate), 2977 (Ar−H), 3370 (N−H, carbamate). ^1H NMR (DMSO-d_6, δ, ppm): 1.38 (s, 27H), 1.75−1.85 (m, 6H), 3.02−3.10 (m, 6H) 3.92 (t, 6H, ^3J = 6.6) 6.05 (s, 3H), 6.60−6.80 (brs, 3H). Anal. Calcd for $C_{26}H_{42}N_2O_8$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.09; H, 8.34; N, 7.07.

Synthesis of the Three Functional Core (3-core). The **protected-3-core** (60.0 mg, 0.1 mmol) was dissolved in TFA (1 mL), and the reaction solution was stirred at room temperature for 1.5 h. The solvent was evaporated to dryness to give a white sticky oil. The oil was washed with ether three times and dried under reduced pressure to give white stickly oil (62.1 mg, 97%). IR (NaCl, cm^{-1}):

Scheme 1. Synthesis of G1-dendron and AB_2



1172 (Ar−O−Alkyl), 1203 (C−F), 1681 (C═O, carboxylate), 2500−3300 (N−H, ammonium), ^{1}H NMR (DMSO-d_6, δ, ppm): 1.94−2.07 (m, 6H), 2.89−3.03 (m, 6H) 4.02 (t, 6H, ^3J = 6.3 Hz), 6.14 (s, 3H). Anal. Calcd for $C_{21}H_{30}F_9N_3O_9$: C, 39.44; H, 4.73; N, 6.57. Found: C, 39.18; H, 4.64; N, 6.75.

Synthesis of Star-Shaped Third Generation Dendrimers (SS-G3-dendrimer). To a solution of **G3-dendron** (0.554 g, 0.200 mmol) in NMP (0.7 mL) were added DBOP (76.6 g, 0.200 mmol) and TEA (27.9 μL, 0.200 mmol) under nitrogen. The reaction solution was stirred at room temperature for 3 h. Then, the reaction solution was added dropwise to a NMP (0.3 mL) solution of TEA (72 μL, 0.513 mmol) and **3-core** which was synthesized from 0.034 g (0.057 mmol) of **protected-3-core**, and the reaction solution was stirred at room temperature for 1 day. The reaction solution was poured in 1 wt % $NaHCO_3$ (aq). The precipitate was collected and dried. The crude product was dissolved in DMF (2.4 mL) and diluted with methanol (73 mL), and then water (12 mL) was added to the solution. The precipitate was dissolved again in DMF (1.2 mL) and diluted with methanol (37 mL), and then water (6 mL) was added to the solution. The precipitate was collected and dried in vacuo at 40 °C to give white powder (0.200 g, 41%). T_g: 48 °C. IR (KBr, cm^{-1}): 1168 (Ar−O−alkyl), 1643, 1689 (C═O, carbamate and amide), 2931, 2973 (Ar−H), 3100−3600 (N−H, carbamate and amide). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.36 (s, 216H), 1.72−1.89 (m, 90H), 2.28−2.39 (m, 42H), 2.65−2.80 (m, 42H), 3.03−3.15 (m, 48H) 3.16−3.26 (m, 44H, overlapped with H_2O), 3.84−4.01 (m, 90H), 6.06 (s, 3H), 6.55−6.84 (m, 87H), 7.72−7.84 (m, 21H). Anal. Calcd for $C_{450}H_{681}N_{45}O_{114}$ 4.75 H_2O: C, 62.64; H, 8.06; N, 7.31. Found: C, 62.82; H, 7.92; N, 7.13. MALDI−TOF MS: calcd $[M]^+$ = 8539.9; found $[M + Na]^+$ = 8562.07

Measurements. ^{1}H NMR spectra were recorded in deuterated methanol (MeOH-d_4), tetrahydrofuran (THF-d_8) or dimethyl sulfoxide (DMSO-d_6) on a BRUKER DPX-300 spectrometer at 300 MHz. Infrared spectra were recorded on a Horiba FT-720 spectrophotometer. Matrix-assisted laser desorption ionization with time-of-flight (MALDI−TOF) MS spectra were recorded on a Kratos Kompact MALDI instrument operated in linear detection mode to generate positive ion spectra using dithranol as a matrix, THF as a solvent, and sodium trifluoroacetate as an additive.

RESULTS AND DISCUSSION

Synthesis of G1-dendron and AB_2. Scheme 1 shows the synthetic route for **G1-dendron** and **AB_2**. 3-Bromo-propyl-1-NHBoc (**1**) was prepared according to a previous paper.[25] Methyl 3,4-dihydroxyhydrocinnamate (**2**) was prepared by the Fischer esterification of 3,4-dihydroxyhydrocinnamic acid with methanol.[26] **2** was reacted with **1** in the presence of K_2CO_3 and molecular sieves to yield a protected **G1-dendron** (**Protected-G1-dendron**), which was converted into the **G1-dendron** by the hydrolysis of the methyl ester group of **Protected-G1-dendron**. **Protected-G1-dendron** and **G1-dendron** were characterized by ^{1}H NMR and IR spectorcopy and elemental analysis. The ^{1}H NMR spectrum of **G1-dendron** is shown in Figure 1. All signals are well assigned to the corresponding

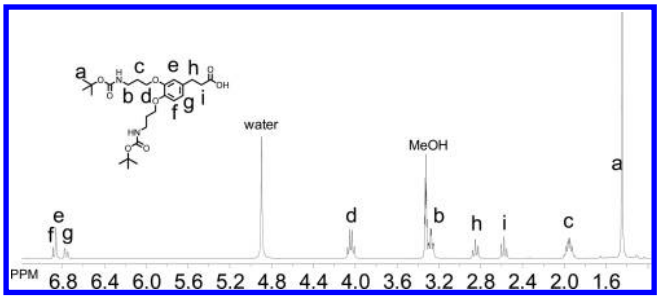


Figure 1. ^{1}H NMR spectrum of **G1-dendron**.

structure. The *N-tert*-Boc group of **G1-dendron** was deprotected using TFA to afford the **AB_2**. **AB_2** was also characterized by ^{1}H NMR and IR spectroscopies and elemental analysis.

Synthesis of G2-dendron and G3-dendron. As described in the Introduction, we previously developed a facile synthetic method of aromatic polyamide dendrimers using DBOP as the condensing agent.[7] In this method, coupling reactions for synthesis of the dendrons were conducted by a two-step method consisting of (1) activation of a carboxylic

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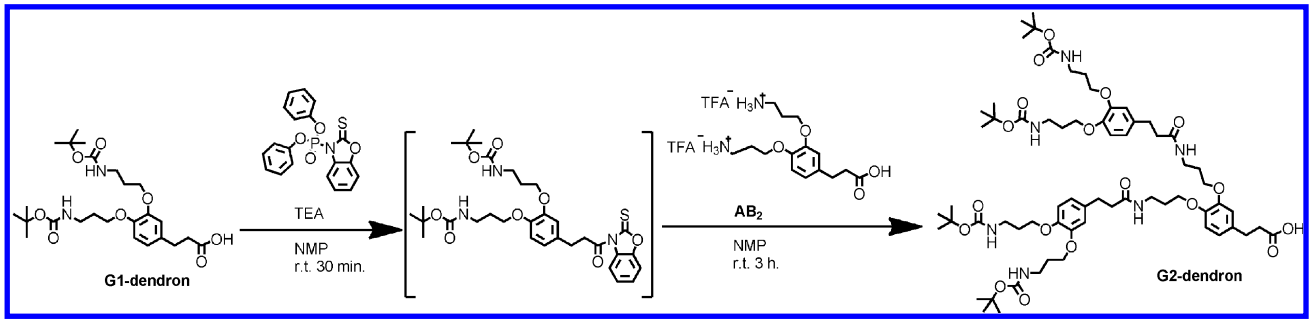
Scheme 2. Synthesis of G2-dendron



acid by DBOP, i.e., generation of an active amide, and (2) condensation of this active amide with an amino group by addition of the AB_2 building block.

We then prepared **G2-dendron** following the procedure described above (Scheme 2). **G1-dendron** was activated with a 0.98 equiv of DBOP in the presence of TEA in NMP at room temperature for 30 min, and then reacted with $\mathbf{AB_2}$ in the presence of TEA in NMP at room temperature for 3 h.

However, the MALDI−TOF MS spectrum of the isolated products showed strong signals corresponding to not only **G2-dendron,** but also higher molecular weight byproducts which were not observed in the synthesis of the aromatic polyamide dendrimers (Figure 2).

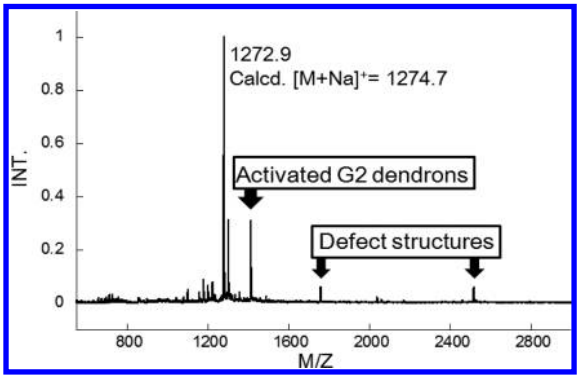


Figure 2. MALDI−TOF MS spectrum of **G2 dendron**.

The possible reasons for the presence of higher molecular weight products are (1) the presence of remaining DBOP in the condensation step, and (2) an undesired side reaction of the active amide with the aliphatic carboxyl group of $\mathbf{AB_2}$. Thus, the molar ratio of DBOP to the substrate was decreased from 0.98 equiv to 0.93 equiv and the activation time was extended from 30 min to 1.5 h However, the signals of the higher molecular weight products still remained. The following model reactions were then carried out to confirm the reactivity of aliphatic carboxyl group to the active amide (Scheme 3). The reaction conditions are noted in the Supporting Information, and the ^{1}H NMR spectra of the model compounds are shown in Figure S1, Supporting Information.

The active amide of hydrocinnamic acid (**HyC−Act**) was synthesized by the reaction of hydrocinnamic acid (**HyC−OH**) with DBOP. When a solution of 4-methoxyhydrocinnamic acid (**MeO−HyC−OH**), 2-ethylhexylamine (**2-EHA**), and TEA were added to a solution of **HyC−Act**, *N*-(2-ethylhexyl)-3-phenylpropanamide (**HyC−Amide**) (79%) and *N*-(2-ethylhexyl)-3-(4-metoxyphenyl)propanamide (**MeO−HyC−Amide**) (21%) were obtained as products (Scheme 3a). On the other hand, only **HyC−Amide** was obtained as the expected product when benzoic acid was used instead of **MeO−HyC−OH** (Scheme 3b). This result is probably due to the higher nucleophilicity of the aliphatic carboxylate anion than the aromatic carboxylate anion. In the former reaction (Scheme 3a), the **MeO−HyC−OH** anion reacted with **HyC−Act** to form the acid anhydride together with the formation of **HyC−Amide** from **HyC−Act** and **2-EHA**. The mixed acid anhydride reacted with **2-EHA** to yield **HyC−Amide** and **MeO−HyC−Amide** (Scheme 4). The formation of the acid anhydride was investigated by the reaction of **HCy-Act** with **MeO−HyC−OH** in the presence of TEA. After removal of **MeO−HyC−OH,** the product was characterized by ^{1}H NMR and IR spectroscopies. The ^{1}H NMR spectrum in $CDCl_3$ showed a decrease in the signal at 8.1 ppm which corresponded to the active amide and appearance of the signal at 3.8 ppm, which was due to the methyl ether group of **MeO−HyC−OH**. The IR spectrum of the product showed peaks at 1727 and 1812 cm^{-1} which corresponded to the C═O stretching of the active amide and acid anhydride, respectively. These results clearly indicated the formation of the acid anhydride.

To avoid the formation of the acid anhydride, the **HyC−Act** solution was added dropwise to a solution of **MeO−HyC−OH** and **2-EHA** and TEA in NMP. This procedure successfully reduced the formation of **MeO−HyC−Amide** to 2% (Scheme 5).

On the basis of these model reactions, the second and third generation dendrons (**G2-dendron**, **G3-dendron**) were prepared as shown in Scheme 6. The solution of the activated **G1-dendron** or **G2-dendron** was added dropwise to the solution of $\mathbf{AB_2}$ and TEA in NMP. **G2-dendron** and **G3-dendron** were simply purified by reprecipitation in 75 and 87% yields, respectively.

The formations of **G2-dendron** and **G3-dendron** were confirmed by ^{1}H NMR and IR spectroscopies, elemental analysis, and MALDI−TOF MS spectroscopy. The^{1}H NMR spectrum of **G2-dendron** is shown in Figure S2, Supporting Information. The IR spectrum of **G3-dendron** showed strong absorptions at 3401, 3347, 1697, and 1650 cm^{-1} due to the characteristic N−H and C═O stretchings of the carbamate and amide groups, respectively. Furthermore, the characteristic ether stretching was observed at 1172 cm^{-1}. The ^{1}H NMR spectrum of **G3-dendron** showed signals corresponding to the carbamate protons (A) at 6.13−6.25 ppm, amide protons (B and C) at 7.28−7.41 ppm, aromatic protons (e, f, g, m, n, o, u, v, w) at 6.61−6.79 ppm, and *tert*-butyl protons of the end unit (a) at 1.39 ppm, respectively (Figure 3).

Furthermore, the MALDI−TOF MS spectra of the **G2-dendron** and **G3-dendron** showed peaks observed at M/Z ([M + Na]$^+$) = 1272.0 and 2787.6 and well agreed with the

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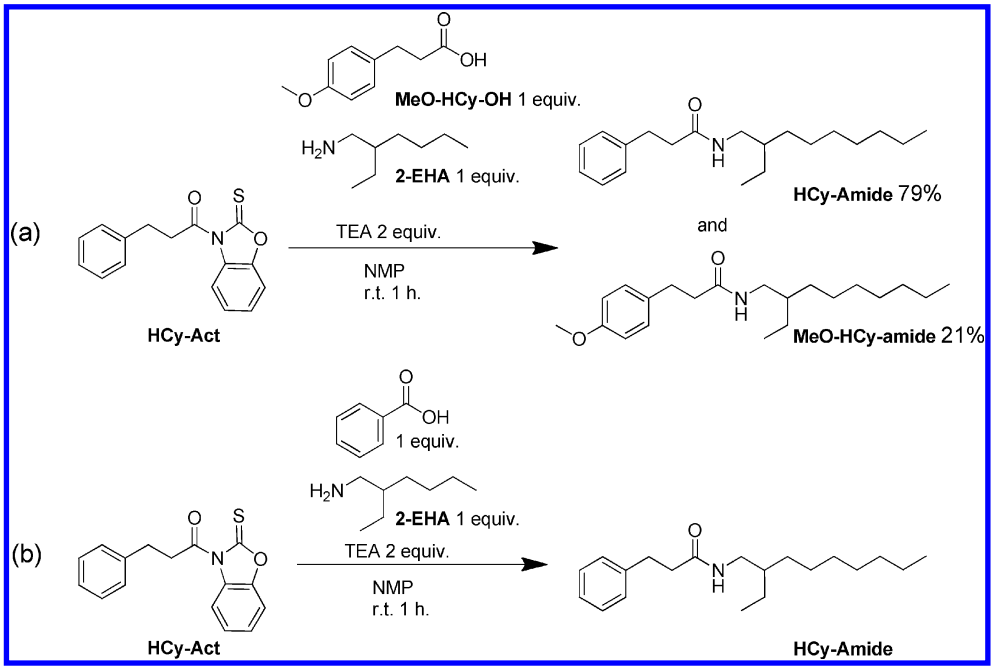
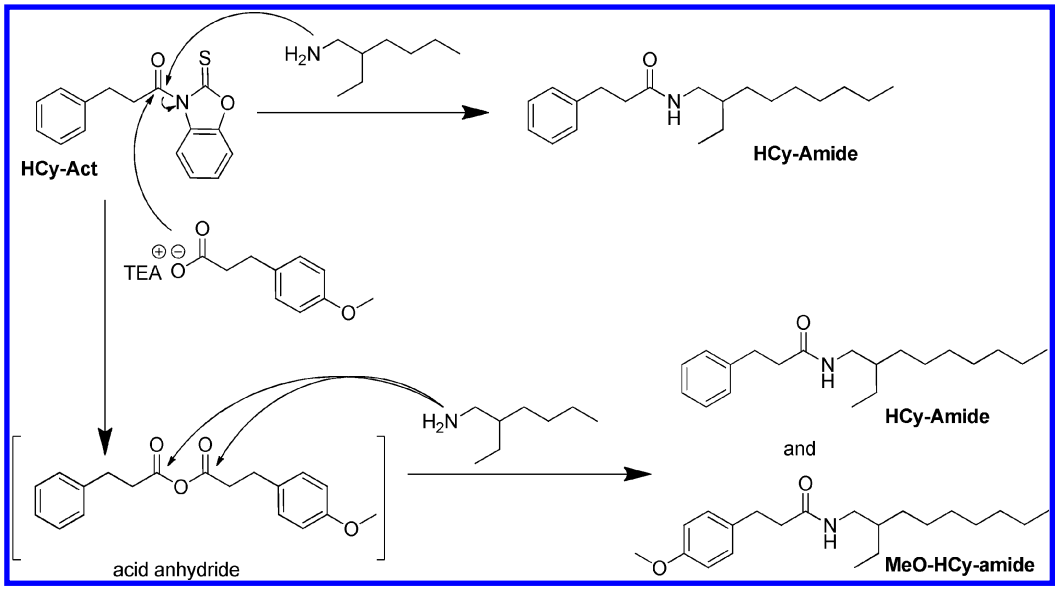
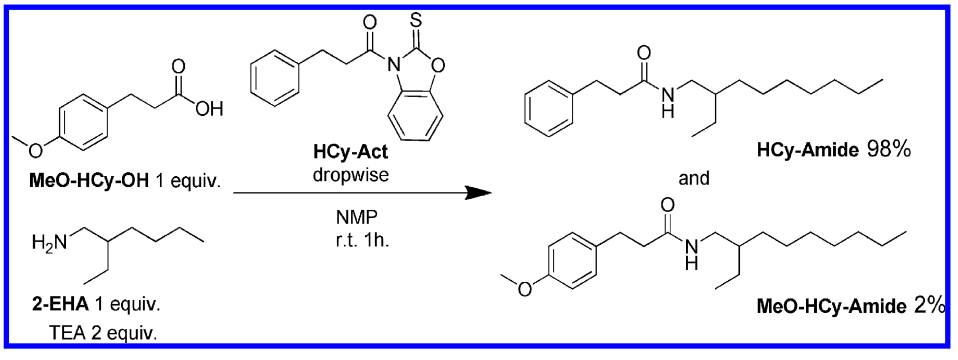
Scheme 3. Model Reaction 1



Scheme 4. Reaction of HCy-Act with 2-EHA under the Presence of MeO−HCy−OH



Scheme 5. Model Reaction 2



calculated masses (1274.7 and 2787.5), together with minor peaks which could be assigned to the partially deprotected dendrons (Figure 4 and Figure 5). The deprotection probably occurred during the measurement. Moreover, no signals

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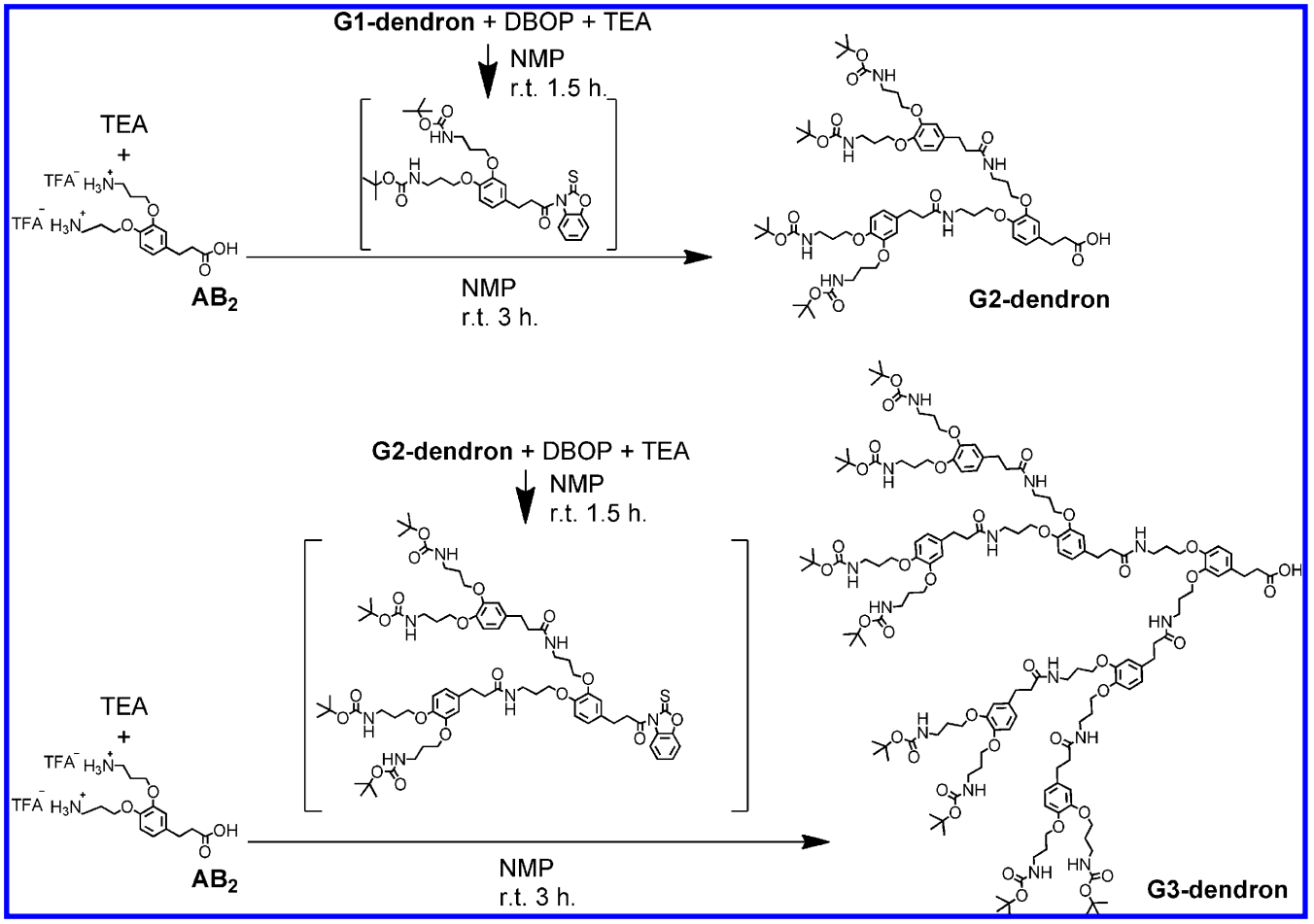
Scheme 6. Synthesis of G2-dendron and G3-dendron



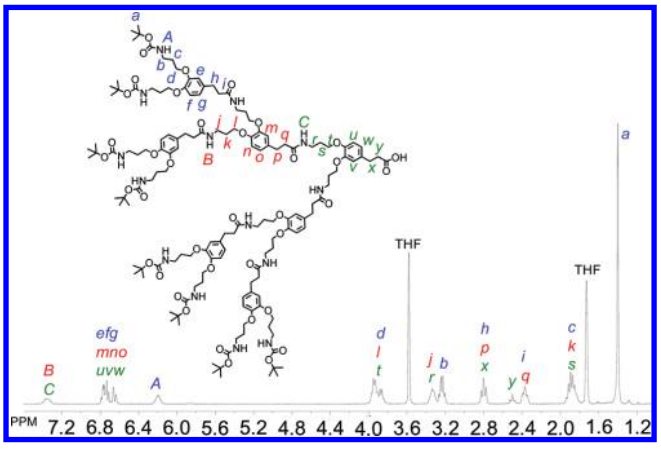


Figure 3. ^{1}H NMR spectrum of **G3-dendron**.

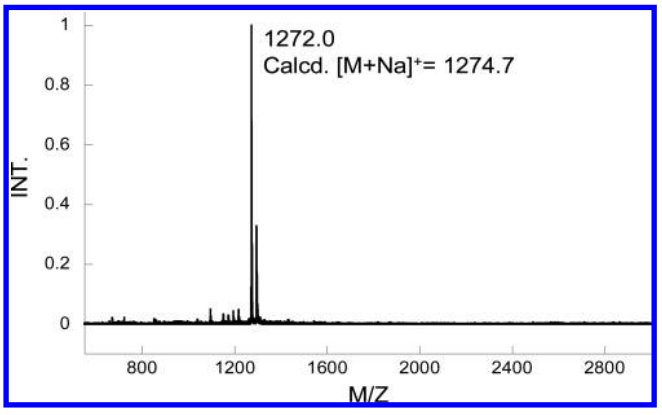


Figure 4. MALDI–TOF MS spectrum of **G2-dendron**.

derived from dendrons having lower or higher molecular weights were observed in Figure 4 and Figure 5.

Synthesis of Dumbbell-Shaped Dendrimers. Dumbbell-shaped dendrimers (**DS-G3-dendrimer**) were synthesized by a procedure similar to the dendron synthesis (Scheme 7). The activated **G3-dendron** was added dropwise to a solution of *p*-xylylenediamine in NMP. **DS-G3-dendrimer** was purified by reprecipitation in 75% yield. **DS-G3-dendrimer** was characterized by ^{1}H NMR (Figure 6) and IR spectroscopies, elemental analysis, and MALDI–TOF MS spectroscopy. The IR spectrum of **DS-G3-dendrimer** showed strong absorptions at 3347, 3309, 1697, and 1643 cm^{-1} due to the characteristic N–H and C=O stretchings of the carbamate and amide groups, respectively. Furthermore, the characteristic ether stretching was observed at 1172 cm^{-1}.

The ^{1}H NMR spectrum of **DS-G3-dendrimer** showed signals corresponding to the amide protons (B, C and D) at 7.69–7.91 and 8.17 ppm, aromatic protons of the core (*) at 7.11 ppm, carbamate and aromatic protons (A, e, f, g, m, n, o, u, v and w) at 6.50–6.89 ppm, benzyl protons of the core (z) at 4.22 ppm, and *tert*-butyl protons of the end unit (a) at 1.37 ppm. Furthermore, the MALDI–TOF MS spectrum of **DS-G3-dendrimer** showed a peak observed at *M*/*Z* ([M + Na]$^+$) =

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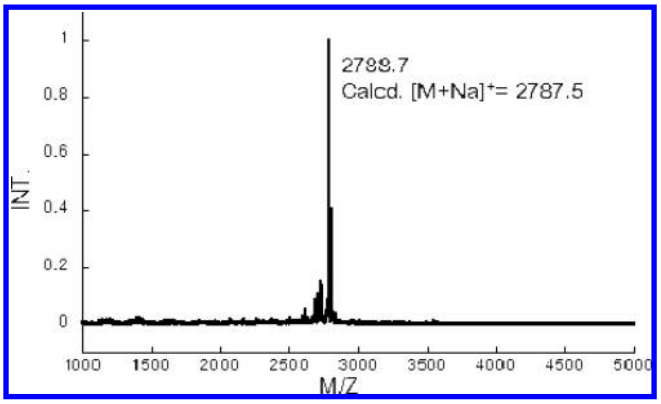


Figure 5. MALDI−TOF MS spectrum of **G3-dendron**.

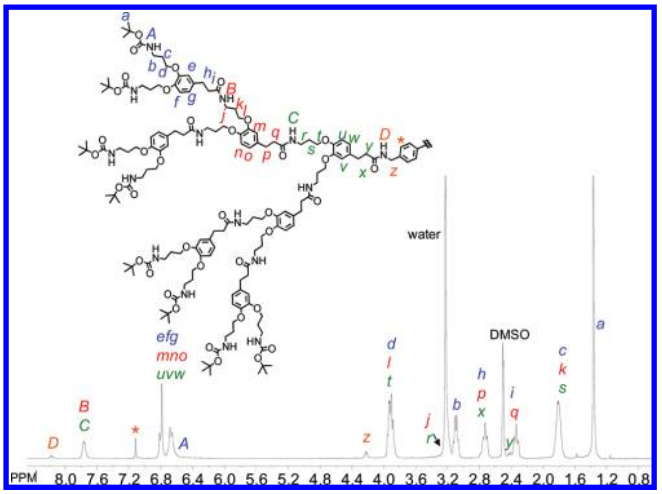


Figure 6. ^{1}H NMR spectrum of **DS-G3-dendrimer**.

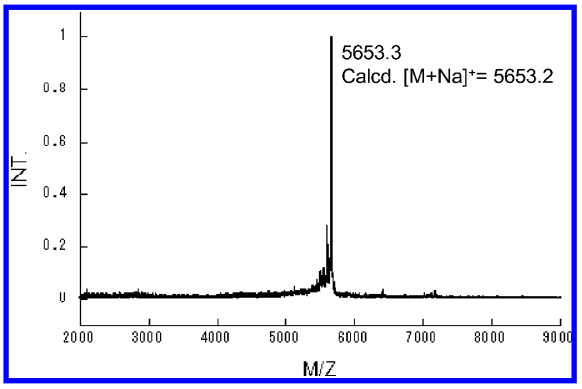


Figure 7. MALDI−TOF mass spectrum of **DS-G3-dendrimer**.

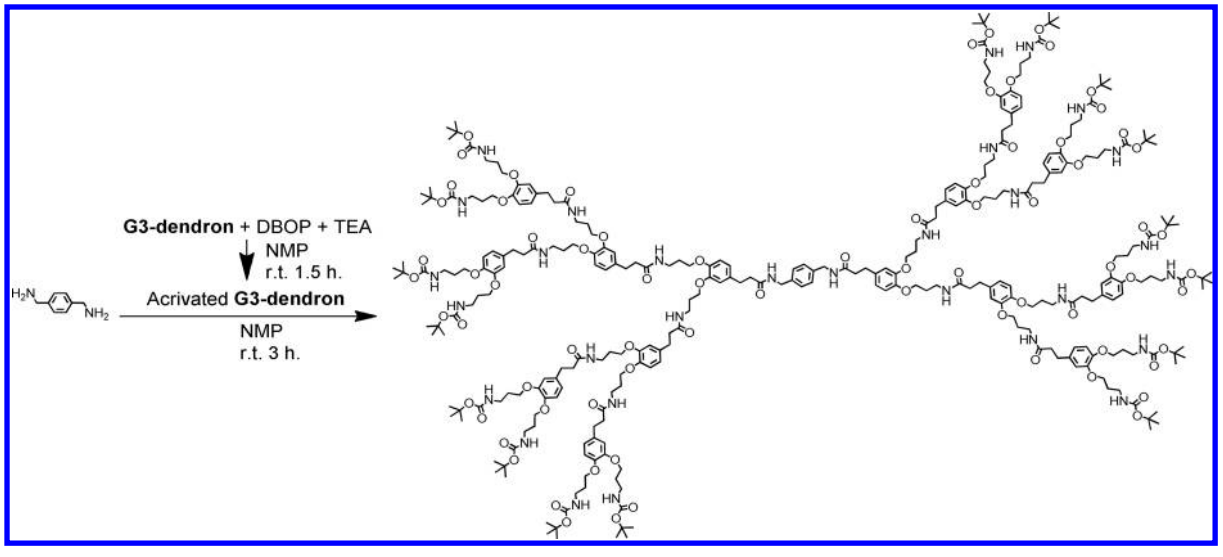
5653.3, which well agreed with the calculated mass (5653.2), together with minor peaks which could be assignable to partially deprotected dendrimers, probably obtained during the measurement (Figure 7). Moreover, no extra signals derived from dendrons having defect structures were observed in Figure 7.

Synthesis of Star-Shaped Dendrimers. A coupling reaction of **G3-dendrons** with a trifunctional core molecule (**3-core**) was performed to obtain star-shaped dendrimers (**SS-G3-dendrimer**) (Scheme 8).

Activation and condensation reactions were conducted using similar conditions for the synthesis of the **SS-G3-dendrimer**. The activated **G3-dendron** was added dropwise to a solution of TEA and **3-core** in NMP. **SS-G3-dendrimer** was purified by reprecipitation in 41% yield. **SS-G3-dendrimer** was characterized by ^{1}H NMR (Figure 8) and IR spectroscopies, elemental analysis, and MALDI−TOF MS spectroscopy. The IR spectrum of **SS-G3-dendrimer** showed strong absorptions at 3600−3100, 1689, and 1643 cm^{-1} due to the characteristic N−H and C═O stretchings of the carbamate and amide groups, respectively. Furthermore, the characteristic ether stretching was observed at 1168 cm^{-1} (see Figure S3 in Supporting Information). The ^{1}H NMR spectrum of **SS-G3-dendron** showed signals corresponding to the amide protons (B, C and D) at 7.72−7.84 and ppm, carbamate and aromatic protons (A, e, f, g, m, n, o, u, v and w) at 6.55−6.89 ppm, aroatic protons of the core (∗) at 6.06 ppm, and *tert*-butyl protons of the end unit (a) at 1.36 ppm.

Furthermore, the MALDI−TOF MS spectrum of **SS-G3-dendrimer** showed a peak observed at M/Z ([M + Na]$^+$) = 8562.1, which well agreed with the calculated mass (8561.9), together with minor peaks which could be assignable to

Scheme 7. Synthesis of DS-G3-dendrimer



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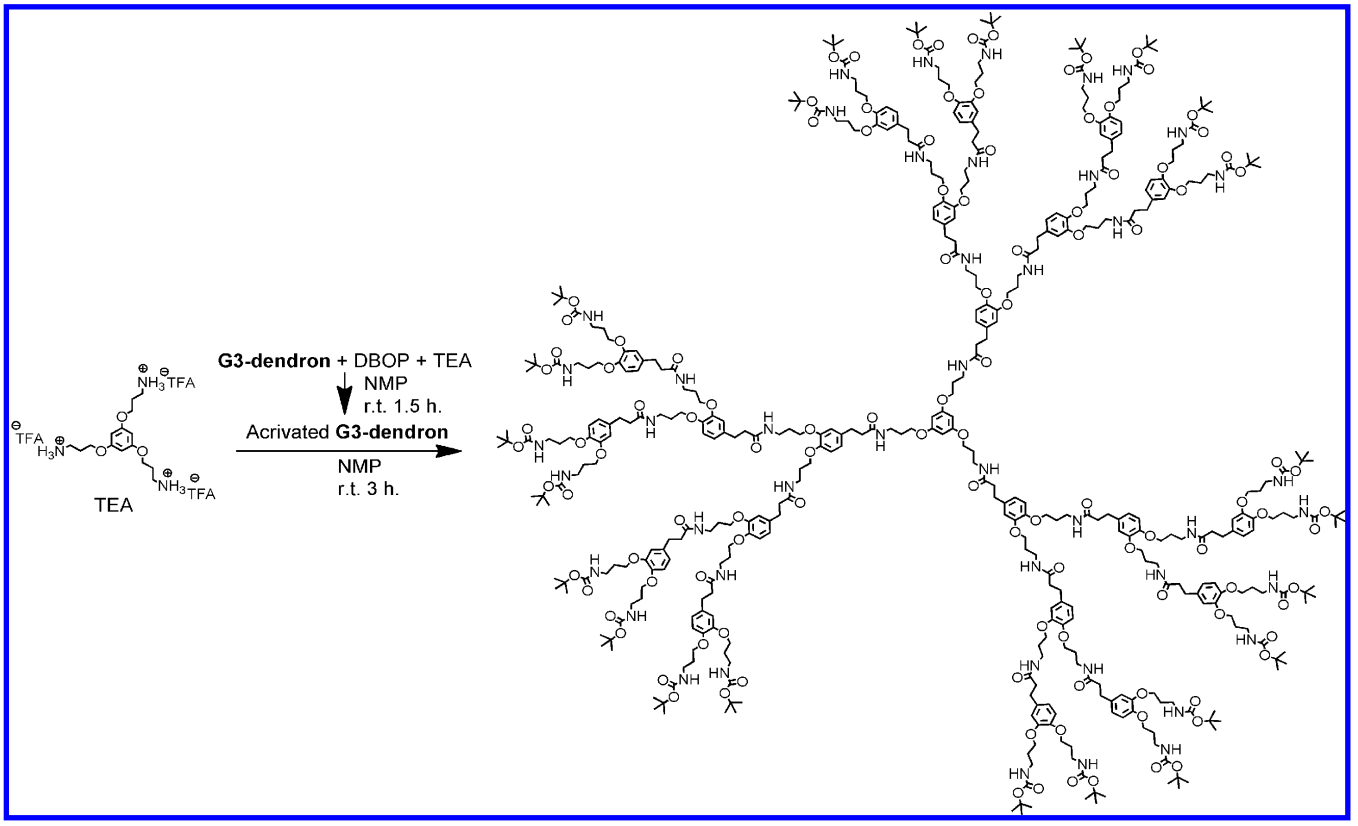
Scheme 8. Synthesis of SS-G3-dendrimer



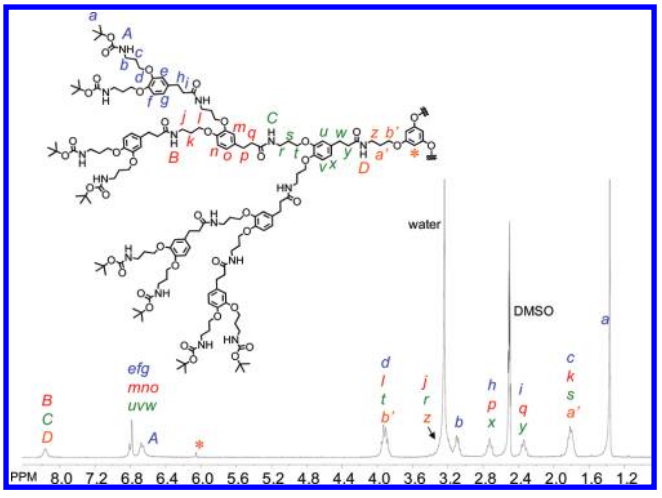


Figure 8. ^{1}H NMR spectrum of **SS-G3-dendrimer**.

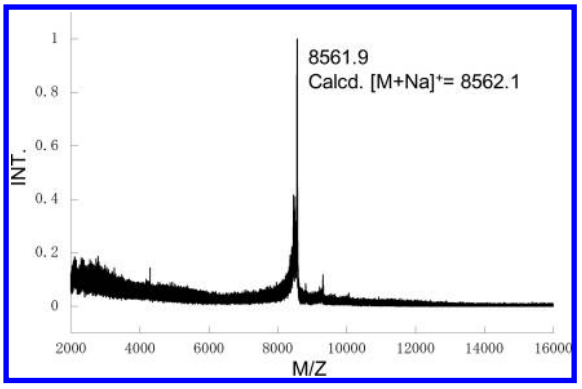


Figure 9. MALDI−TOF spectrum of **SS-G3-dendrimer**.

partially deprotected dendrimers (Figure 9). Moreover, no extra signals derived from dendrons having defect structures were observed in Figure 9.

In summary, we successfully developed a facile synthetic method of aliphatic polyamide dendrimers. To synthesize dendrons and dendrimers without byproducts, it was necessary that the solution of the activated dendrons was added dropwise to that of **AB$_2$** or core molecules. Thus, the addition order of reagents is very important. On the basis of these findings, we succeeded in synthesizing **DS-G3-dendrimer** and **SS-G3-dendrimer**.

■ CONCLUSIONS

We have developed a facile synthetic method of aliphatic polyamide dendrons and dendrimers based on a convergent approach, which consists of the direct condensation of a carboxylic acid and unprotected AB$_2$ building block using DBOP as the condensing agent. By this method, each of the dendrons and dendrimers was purified only by extraction and/or reprecipitation. The MALDI−TOF MS spectra supported the expected formation of each dendron and dendrimer. This novel convergent route for the aliphatic polyamide dendrimers is attractive both for use in the laboratory and industry, since it could be extended to the synthesis of other aliphatic dendrimers, such as polyamide amine dendrimers and lysine dendrimers, which have already been used as functional materials in many fields.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures of model reactions. ^{1}H NMR spectra of model compounds and **G2-dendron**, and the IR spectrum of **SS-G3-dendrimer**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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