Macromolecules **2005,** *38,* 2237−2246

Facile Synthesis of Polyamide Dendrimers from Unprotected AB_2 Building Blocks: Dumbbell-Shaped Dendrimer, Star-Shaped Dendrimer, and Dendrimer with a Carboxylic Acid at the Core

Isao Washio, Yuji Shibasaki, and Mitsuru Ueda*

Department of Organic and Polymeric Materials, Graduate School of Science and Engineering,
Tokyo Institute of Technology, 2-12-1, O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Received October 18, 2004; Revised Manuscript Received December 27, 2004

ABSTRACT: A fast, inexpensive, and highly efficient synthesis of aromatic polyamide dendrimers, without the need for protection and deprotection steps, has been developed. Dendrons and various types of polyamide dendrimers were easily prepared by a convergent approach involving activation of a carboxylic acid at the focal point using a small excess of thionyl chloride as the activating agent, followed by condensation with an unprotected AB_2 building block, 3,5-bis(4-aminophenoxy)benzoic acid. A third generation dendrimer with a molecular weight of 8197 Da was prepared in a high yield, using 1,3,5-tris-[*N*-(4-aminophenyl)]benzenetricarboxamide as a core molecule. A dendrimer with a carboxylic acid group at its core (molecular weight: 10 700 Da) could be prepared from the third generation dendron with 3,5-bis(3,5-diaminobenzoylamino)benzoic acid as the core molecule. All the above products purified only by precipitation revealed a high purity, assessed using matrix assisted laser desorption ionization time-of-flight mass spectroscopy spectra.

Introduction

Dendrimers are well-defined, highly branched, three-dimensional molecules with a large number of reactive end groups. Dendrimers are therefore receiving interest as new polymeric materials for applications in areas such as molecular light harvesting,[1] catalysts,[2] liquid crystals,[3] molecular encapsulation,[4] and drug-delivery systems.[5]

Synthesis of dendrimers via a divergent[6] or convergent[7] route involves reiterative growth strategies that require a tedious multistep procedure with repetitive protection−deprotection and purification processes in each generation of the dendrimer syntheses. Several groups have reported shortening the time for these syntheses by diminishing the number of steps.[8] The first method called "double-stage" implies the grafting of dendrons to the surface of small dendrimers called "hypercores". However, the total number of reactions used to obtain the dendron and the hypercore is the same as for the simple step-by-step synthesis of the final dendrimer. The second method is the "double-exponential growth" method, which involves the bidirectional growth of the dendron (periphery and focal point). This method is effective for the rapid synthesis of high-generation dendrimers, but it has been practiced only for middle-sized dendrons, leading, for instance, to a fourth generation dendron in seven steps (instead of the eight steps in a classical method). The third method uses hypermonomers, such as AB_4 or AB_8, instead of the AB_2 or AB_3 monomers classically used in dendrimer chemistry. This strategy rapidly increases the number of end groups, but it does not decrease the number of steps needed to obtain one generation. Finally, the fourth method, called "orthogonal coupling strategy", involves convergent growth with two different monomers. This type of "orthogonal system" implies a set of completely independent protecting groups. Therefore, the total number of reactions is decreased to half of that for a conventional method. However, this strategy generally requires complicated reaction systems to perform the quantitative coupling reaction in the presence of different types of functional groups, especially for dendrimers having the same repeat unit of the linkage.[9]

Rannard et al. recently reported a one-pot multiple-addition convergent synthesis of polycarbonate dendrimers, in which the second generation dendrimer was obtained by sequential activation of an alcohol unit with 1,1-carbonyldiimidazole and an AB_2 triol.[10a] Similarly, a rapid synthesis of polyamide dendrimers from two kinds of building blocks, dialkylenetriamines and succinic anhydride, was reported; however, this method has not been applied to the AB_2 monomer.[10b]

Although various synthetic methods have been developed to prepare dendrimers containing amide functions, they have problems such as poor yield and tedious multisynthetic steps.[9,10b,11] The efficient synthesis of polyamide dendrimers has been shown to be difficult due to poor solubility and high water absorption. Recently, we reported the rapid synthesis of a perfectly branched third generation polyamide dendrimer by the convergent method without repetitive protection−deprotection procedures.[12] This synthesis involved the direct condensation of a carboxylic acid and an unprotected AB_2 building block, 3,5-bis(4-aminophenoxy)-benzoic acid, using the condensing agent diphenyl (2,3-dihydro-2-thioxo-3-benzoxazolyl)phosphonate (DBOP). DBOP is very useful for producing amides and esters from carboxylic acids and amines or phenols in quantitative yields;[13] however, DBOP is an expensive reagent, especially for industrial large-scale synthetic use. Therefore, the discovery of a substitute for DBOP is important to expand the scope of dendrimer syntheses.

Thionyl chloride, an inexpensive, commercially available reagent, is well-known as an activating agent for the preparation of amides as well as acid chlorides from carboxylic acids.[14] The authors previously reported that thionyl chloride is effective for polyamide[15a] and poly-

---

* Corresponding author. E-mail mueda@polymer.titech.ac.jp.

10.1021/ma0478456 CCC: $30.25

ester[15b] syntheses in amide solvents such as hexamethylphosphoric triamide and *N*-methyl-2-pyrrolidinone (NMP). Following these syntheses, difficult purification procedures are not necessary because the only byproducts are gases such as SO_2 and HCl. These findings prompted the development of a facile synthesis of polyamide dendrimer from an unprotected AB_2 building block. The authors made a brief report of the successful synthesis of a dumbbell-shaped polyamide G3 dendrimer, using thionyl chloride as a versatile and common activating reagent for carboxylic acids, which did not require tedious purification steps such as column chromatography.[16]

This paper presents a detailed polyamide dendrimer synthesis using thionyl chloride and its application to the synthesis of a star-shaped dendrimer and a dendrimer with a carboxylic acid at its core.

Experimental Section

Measurement. Infrared (IR) spectra were recorded on a Horiba FT-720 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-300 spectrometer at ^{1}H, 300 MHz and ^{13}C, 75 MHz, respectively. Deuterated dimethyl sulfoxide (DMSO-d_6) was used as a solvent with tetramethylsilane as an internal standard. Matrix-assisted laser desorption ionization with time-of-flight (MALDI−TOF) mass 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 agent.

Materials. *N*-Methyl-2-pyrrolidinone (NMP) was distilled under reduced pressure over calcium hydride and then stored under nitrogen. Thionyl chloride was distilled under nitrogen over triphenyl phosphite and then stored at 0 °C under nitrogen. The other reagents and solvents were obtained commercially and used as received.

G1 Dendron (4). To a solution of dendron **3** (4.880 g, 14.51 mmol) in 25 mL of NMP, 3.0 equiv of acetyl chloride (4.556 g, 58.04 mmol) to **3** was added at 0 °C and stirred for 3 h. The reaction mixture was poured into water, and the precipitate was collected and dried. The precipitate was redissolved in NMP, and the solution was reprecipitated with water. The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 98% (5.978 g). IR (KBr): ν (cm^{-1}) = 2700−3700 (−OH, st), 3294 (N−H, st), 1697 (C=O(OH), st), 1658 (C=O(N−H), st), 1597, 1504 (phenyl, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.03 (s, 6H), 6.82 (t, 1H), 7.01−7.08 (m, 6H), 7.61 (d, 4H), 9.90 (s, 2H). ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$): δ (ppm) = 23.9, 111.1, 111.7, 120.2, 120.8, 133.7, 136.1, 150.5, 159.2, 166.1, 168.2. Anal. Calcd for $C_{23}H_{20}N_2O_6$: C, 65.71%; H, 4.79%; N, 6.66%. Found: C, 65.59%; H, 4.93%; N, 6.71%.

G2 Dendron (5). 1.04 equiv of thionyl chloride (0.705 mL, 9.665 mmol) to **4** were added to a solution of **4** (3.907 g, 9.293 mmol) in 20 mL of NMP at 0 °C under nitrogen and stirred for 15 min at that temperature and for 15 min at room temperature. Then, 0.48 equiv of **3** (1.488 g, 4.425 mmol) to **4** was added to the solution, and the reaction was carried out for 4 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was redissolved in NMP and diluted with methanol, and the resulting solution was reprecipitated with water (MeOH/H_2O 1/1 in volume ratio). The precipitate was collected and dried in vacuo at 160 °C to give a white solid. The yield was 92% (4.646 g). IR (KBr): ν (cm^{-1}) = 2700−3700 (−OH, st), 3417 (N−H, st), 1666 (C=O(N−H), st), 1589, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.03 (s, 12H), 6.70 (t, 2H), 6.89 (t, 1H), 7.01−7.13 (m, 14H), 7.28 (d, 4H), 7.60 (d, 8H), 7.76 (d, 4H), 9.87 (s, 4H), 10.22 (s, 2H). ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$): δ (ppm) = 23.8, 109.8, 111.1, 111.5, 111.8, 119.7, 119.9, 120.7, 122.4, 133.7, 135.3, 135.8, 137.7, 150.7, 151.2, 158.7, 159.0, 164.0, 166.0, 168.1. Calcd: $[M]^+$ m/z = 1141.1. Found: MALDI−TOF−MS: $[M + H]^+$ = 1141.3, $[M + Na]^+$ = 1163.0, $[M + K]^+$ = 1179.3. Anal. Calcd for $C_{65}H_{52}N_6O_{14}\cdot 0.30H_2O$: C, 68.09%; H, 4.62%; N, 7.33%. Found: C, 67.96%; H, 4.71%; N, 7.46%.

G3 Dendron (6). Compound **5** (2.062 g, 1.807 mmol) was placed in a two-necked flask and heated at 150 °C under reduced pressure for 4 h. Into the flask cooled in a water bath, 7.5 mL of NMP and 1.10 equiv of thionyl chloride (0.145 mL, 1.988 mmol) to **5** were added under nitrogen. The reaction mixture was stirred for 10 min at that temperature and 50 min at room temperature. Then, 0.48 equiv of **3** (0.2894 g, 0.8605 mmol) to **5** was added to the solution, and the reaction was performed for 5 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was redissolved in NMP, and this was reprecipitated with 1,4-dioxane. The precipitate was collected and dried in vacuo at 160 °C to give a white solid. The yield was 94% (2.089 g). IR (KBr): ν (cm^{-1}) = 3421 (N−H, st), 1658 (C=O(N−H), st), 1589, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.02 (s, 24H), 6.69 (t, 4H), 6.77 (t, 2H), 6.91 (t, 1H), 7.01−7.13 (m, 30H), 7.27 (d, 8H), 7.32 (d, 4H), 7.60 (d,16H), 7.75 (d, 12H), 9.88 (s, 8H), 10.22 (s, 4H), 10.25 (s, 2H). Calcd: $[M]^+$ m/z = 2582.6. Found: MALDI−TOF-MS: $[M + Na]^+$ = 2606.3. Anal. Calcd for $C_{149}H_{116}N_{14}O_{30}\cdot 0.34H_2O$: C, 69.13%; H, 4.54%; N, 7.58%. Found: C, 69.29%; H, 4.70%; N, 7.59%.

Dumbbell-Shaped G3 Dendrimer (7). Compound **6** (0.4833 g, 0.1828 mmol) was placed in a two-necked flask and dried at 150 °C under the reduced pressure for 6 h. Into the flask cooled with a water bath, 1.7 mL of NMP and 1.50 equiv of thionyl chloride (20.00 μL, 0.2742 mmol) to **6** were added under nitrogen. The reaction mixture was stirred for 10 min at that temperature and 50 min at room temperature. Then, 0.5 equiv of 4,4′-oxydianiline (0.017 85 g, 0.08917 mmol) to **6** was added to the solution, and the reaction was performed for 6 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was dissolved in DMF, and this was reprecipitated with THF. The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 74% (0.3517 g). IR (KBr): ν (cm^{-1}) = 3421 (N−H, st), 1654 (C=O(N−H), st), 1608, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.01 (s, 48H), 6.68 (t, 8H), 6.75 (m, 6H), 6.95 (d, 4H), 6.99−7.13 (m, 56H), 7.26 (d, 16H), 7.31 (d, 12H), 7.59 (d, 32H), 7.68 (d, 4H), 7.74 (d, 24H), 9.87 (s, 16H), 10.18 (s, 2H), 10.21 (s, 8H), 10.23 (s, 4H). Calcd: $[M]^+$ m/z = 5329.4. Found: MALDI−TOF-MS: $[M + Na]^+$ = 5354.3. Anal. Calcd for $C_{310}H_{240}N_{30}O_{59}\cdot 13.95H_2O$: C, 66.72%; H, 4.84%; N, 7.53%. Found: C, 66.66%; H, 4.78%; N, 7.50%.

Star-Shaped G1 Dendrimer (9). 1.04 equiv of thionyl chloride (30.00 μL, 0.4113 mmol) to **4** was added to a solution of **4** (0.1663 g, 0.3955 mmol) in 1 mL of NMP at 0 °C under nitrogen and stirred for 15 min at that temperature and for 15 min at room temperature. Then, 0.32 equiv of **8** (0.060 30 g, 0.1255 mmol) to **4** was added to the solution, and the reaction was carried out for 5 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was redissolved in NMP and diluted with methanol, and the resulting solution was reprecipitated with water (MeOH/H_2O 4/1 in volume ratio). The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 86% (0.1822 g). IR (KBr): ν (cm^{-1}) = 3298 (N−H, st), 1664 (C=O(N−H), st), 1608, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.03 (s, 18H), 6.71 (s, 3H), 7.06 (d, 12H), 7.29 (d, 6H), 7.74 (q, 4H), 8.68 (s, 3H), 9.89 (s, 6H), 10.20 (s, 3H), 10.48 (s, 3H). Calcd: $[M]^+$ m/z = 1687.7. Found: MALDI−TOF-MS: $[M + Na]^+$ = 1710.7. Anal. Calcd for $C_{96}H_{78}N_{12}O_{18}\cdot 2.09H_2O$: C, 66.83%; H, 4.80%; N, 9.74%. Found: C, 66.79%; H, 4.76%; N, 9.73%.

Star-Shaped G2 Dendrimer (10). Compound **5** (0.2844 g, 0.2493 mmol) was placed in a two-necked flask and heated at 150 °C under reduced pressure for 5 h. Into the flask cooled in a water bath, 1 mL of NMP and 1.10 equiv of thionyl chloride (20.00 μL, 0.2742 mmol) to **5** were added under

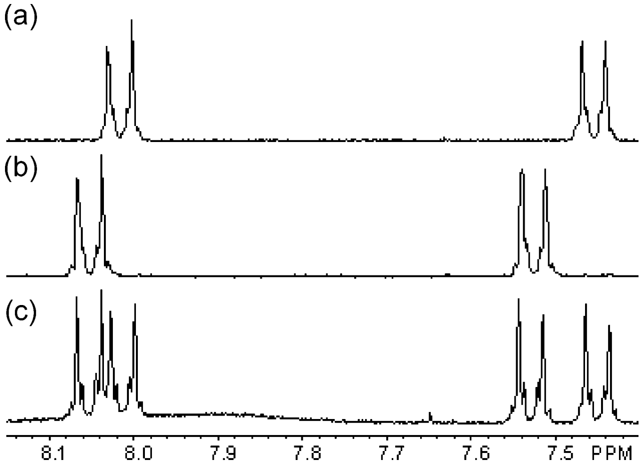
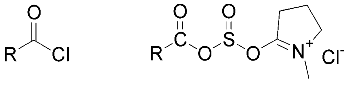


Figure 1. ^{1}H NMR spectra of reaction solutions (a) before activation and (b) after activation using 1.1 equiv of thionyl chloride and (c) after activation using 0.5 equiv of thionyl chloride.



1 **2**

Figure 2. Suggested active intermediates.

nitrogen. The reaction mixture was stirred for 10 min at that temperature and 50 min at room temperature. Then, 0.32 equiv of **8** (0.038 00 g, 0.079 13 mmol) to **5** was added to the solution, and the reaction was performed for 6 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was redissolved in NMP, and this was reprecipitated with EtOH. The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 81% (0.2483 g). IR (KBr): ν (cm^{-1}) = 3298 (N–H, st), 1664 (C=O(N–H), st), 1606, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.02 (s, 36H), 6.69 (t, 6H), 6.78 (t, 3H), 7.04 (d, 24H), 7.10 (d, 12H), 7.27 (d, 12H), 7.32 (d, 6H), 7.60 (d, 24H), 7.69–7.80 (m, 24H), 8.67 (s, 3H), 9.89 (s, 12H), 10.21 (s, 3H), 10.23 (s, 6H), 10.48 (s, 3H). Calcd: [M]$^+$ *m/z* = 3873.3. Found: MALDI–TOF-MS: [M + Na]$^+$ = 3849.9. Anal. Calcd for $C_{222}H_{174}N_{24}O_{42}\cdot 5.48H_2O$: C, 67.53%; H, 4.72%; N, 8.51%. Found: C, 67.45%; H, 4.65%; N, 8.59%.

Star-Shaped G3 Dendrimer (11). Compound **6** (0.4721 g, 0.1828 mmol) was placed in a two-necked flask and dried at 150 °C under the reduced pressure for 6 h. Into the flask cooled with a water bath, 1.7 mL of NMP and 1.50 equiv of thionyl chloride (20.00 μL, 0.2742 mmol) to **6** were added under nitrogen. The reaction mixture was stirred for 10 min at that temperature and 50 min at room temperature. Then, 0.32 equiv of **8** (0.027 90 g, 0.058 03 mmol) to **6** was added to the solution, and the reaction was performed for 8 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was dissolved in DMF, and this was reprecipitated with THF. The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 78% (0.3711 g). IR (KBr): ν (cm^{-1}) = 3303 (N–H, st), 1664 (C=O(N–H), st), 1606, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.02 (s, 72H), 6.70 (t, 12H), 6.76 (t, 9H), 6.96–7.12 (m, 84H), 7.30 (d, 24H), 7.36 (d, 12H), 7.39 (d, 6H), 7.57 (d, 48H), 7.68–7.79 (d, 48H), 8.67 (s, 3H), 9.61 (s, 24H), 10.01 (s, 14H), 10.04 (s, 6H), 10.26 (s, 3H). Calcd: [M]$^+$ *m/z* = 8174.3. Found: MALDI–TOF-MS: [M + Na]$^+$ = 8197.8. Anal. Calcd for $C_{474}H_{366}N_{48}O_{90}\cdot 6.42H_2O$: C, 68.68%; H, 4.61%; N, 8.11%. Found: C, 68.84%; H, 4.77%; N, 8.13%.

G4 Dendron (13). Compound **6** (0.5956 g, 0.2285 mmol) was placed in a two-necked flask and dried at 150 °C under the reduced pressure for 5 h. Into the flask cooled with a water bath, 2.1 mL of NMP and 1.20 equiv of thionyl chloride (20.00 μL, 0.2742 mmol) to **6** were added under nitrogen. The reaction mixture was stirred for 10 min at that temperature and 50 min at room temperature. Then, 0.47 equiv of **3** (0.036 60 g, 0.1088 mmol) to **6** was added to the solution, and the reaction was performed for 6 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was dissolved in DMF, and this was reprecipitated with THF. The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 80% (0.4778 g). IR (KBr): ν (cm^{-1}) = 3263 (N–H, st), 1662 (C=O(N–H), st), 1604, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) = 2.01 (s, 48H), 6.68 (t, 8H), 6.72–6.78 (m, 6H), 6.91 (t, 1H), 6.99–7.12 (m, 62H), 7.26 (d, 16H), 7.31 (d, 12H), 7.59 (d, 32H), 7.69–7.79 (m, 28H), 9.88 (s, 16H), 10.21 (s, 8H), 10.23 (s, 4H), 10.25 (s, 2H). Calcd: [M]$^+$ *m/z* = 5465.5. Found: MALDI–TOF-MS: [M + Na]$^+$ = 5489.4. Anal. Calcd for $C_{317}H_{244}N_{30}O_{62}\cdot 8.55H_2O$: C, 67.75%; H, 4.68%; N, 7.48%. Found: C, 67.68%; H, 4.61%; N, 7.53%.

Dendrimer with a Carboxylic Acid at the Core (14). Compound **6** (0.5956 g, 0.2285 mmol) was placed in a two-necked flask and dried at 150 °C under the reduced pressure for 6 h. Into the flask cooled with a water bath, 2.2 mL of NMP and 1.20 equiv of thionyl chloride (20.00 μL, 0.2742 mmol) to **6** were added under nitrogen. The reaction mixture was stirred for 10 min at that temperature and 50 min at room temperature. Then, 0.24 equiv of **12** (0.023 43 g, 0.055 73 mmol) to **6** was added to the solution, and the reaction was performed for 12 h at room temperature. The reaction mixture was poured into water, and the precipitate was collected and dried. The

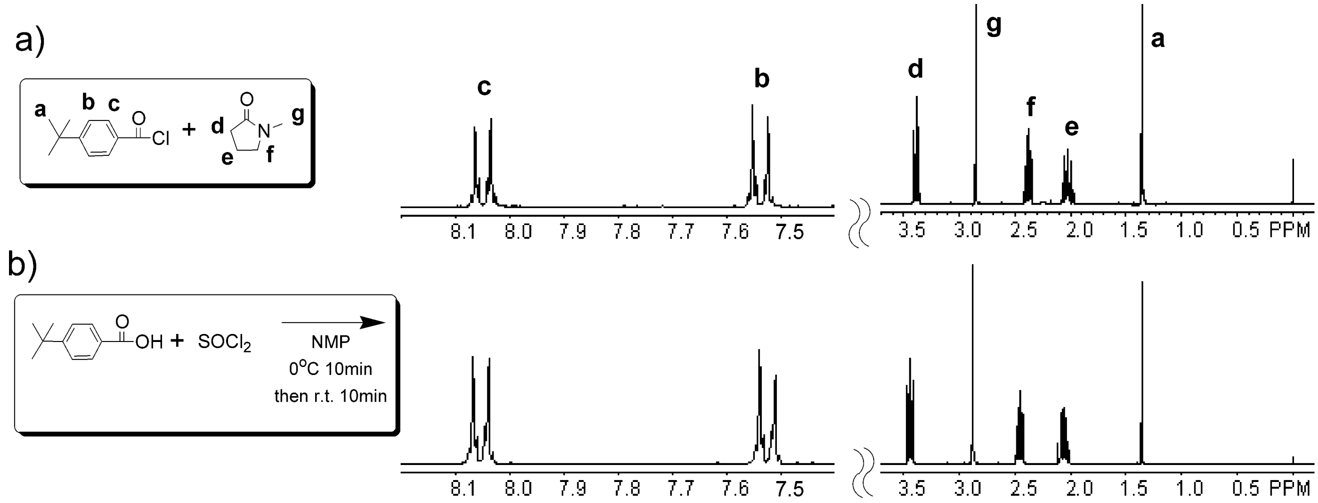


Figure 3. ^{1}H NMR spectra of (a) mixture of 4-*tert*-butylbenzoyl chloride and NMP and (b) reaction solution of 4-*tert*-butylbenzoic acid and thionyl chloride in NMP.

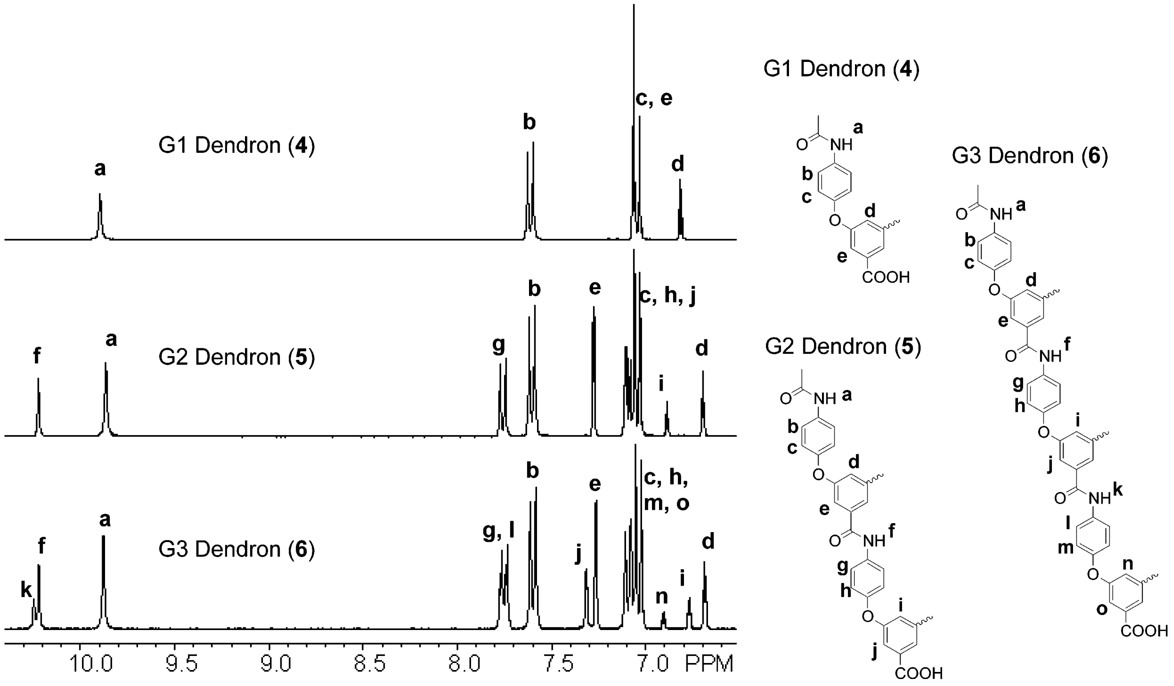
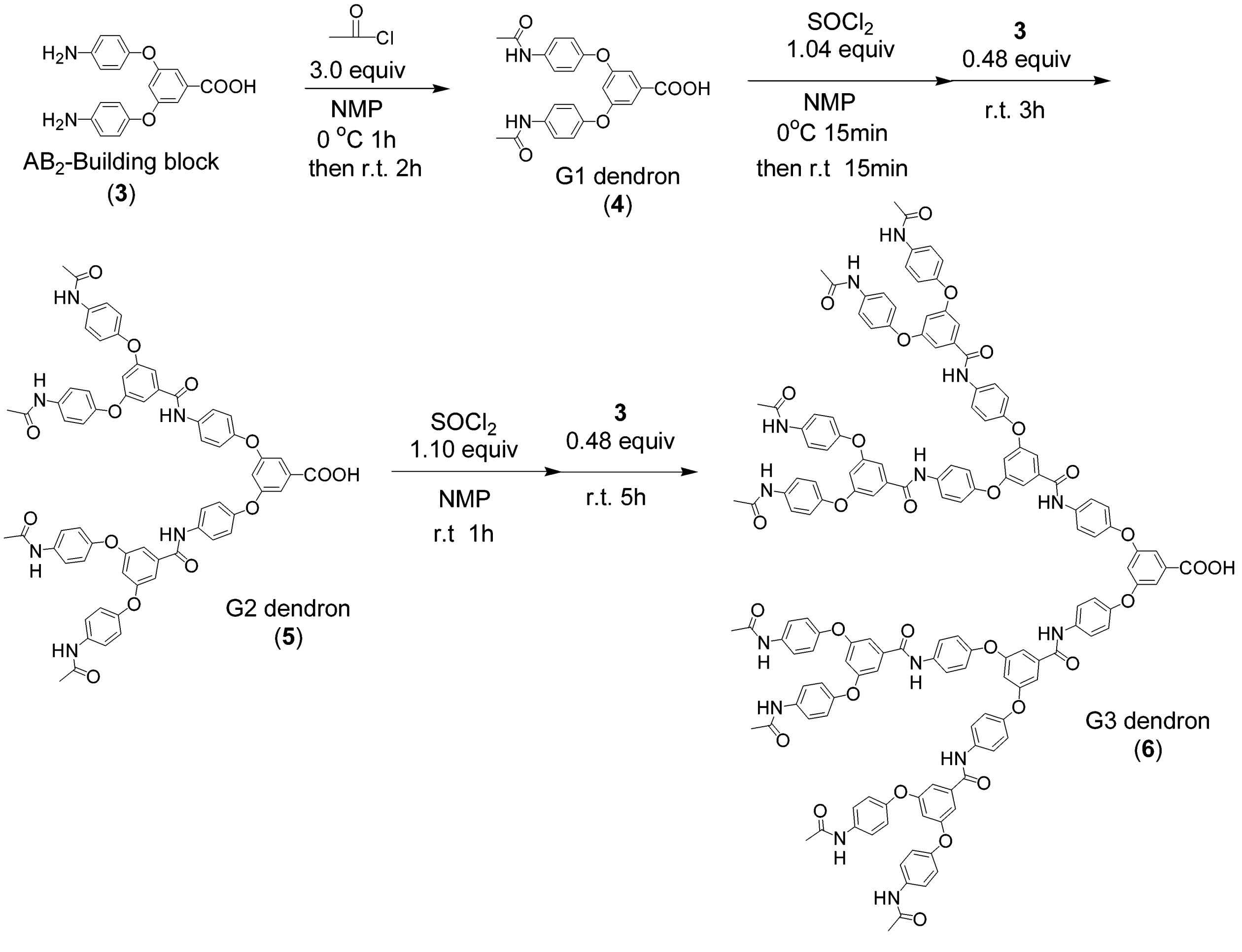


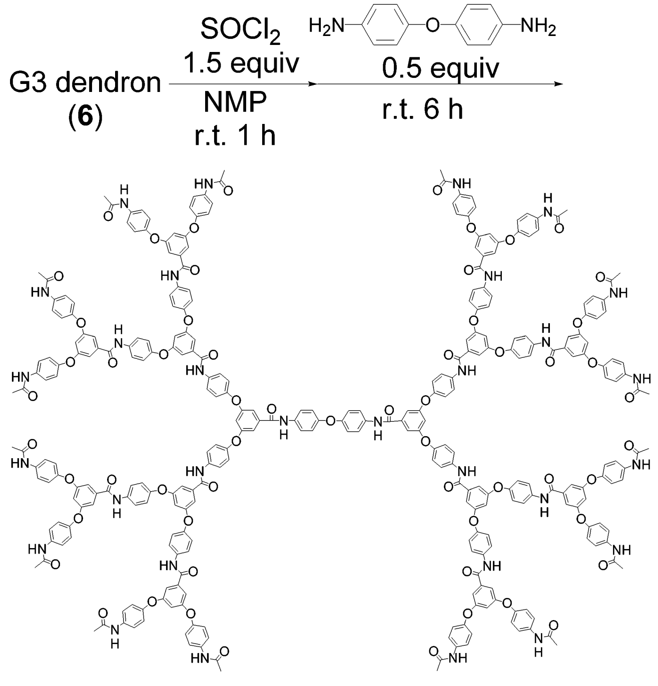
Figure 4. ^{1}H NMR spectra of each dendron.

Scheme 1. Synthesis of Dendrons



crude product was dissolved in DMF, and this was reprecipitated with THF. The precipitate was collected and dried in vacuo at 120 °C to give a white solid. The yield was 76% (0.4532 g). IR (KBr): ν (cm^{-1}) = 3290 (N–H, st), 1658 (C=O(N–H), st), 1604, 1504 (phenyl ring, st). ^{1}H NMR (300 MHz, (CD$_3$)$_2$SO): δ (ppm) = 2.00 (s, 96H), 6.67 (t, 16H), 6.68–6.72 (m, 12H), 6.96–7.12 (m, 112H), 7.26 (d, 32H), 7.33 (d, 16H), 7.42 (d, 8H), 7.58 (d, 64H), 7.68–7.79 (m, 48H), 8.00 (b, 4H), 8.06 (b, 2H), 8.48 (b, 2H), 8.58 (b, 1H), 9.86 (s, 32H), 10.19 (s, 16H), 10.21 (s, 8H), 10.45 (b, 6H). Calcd: [M]$^+$ m/z = 10 678.7.

Scheme 2. Synthesis of Dumbbell-Shaped G3 Dendrimer



Dumbbell-shaped G3 dendrimer (**7**)

Found: MALDI−TOF-MS: $[M + Na]^+ = 10\,700.2$. Anal. Calcd for $C_{617}H_{476}N_{62}O_{120}\cdot 9.00H_2O$: C, 68.36%; H, 4.59%; N, 8.01%. Found: C, 68.16%; H, 4.72%; N, 8.02%.

Results and Discussion

Model Reactions. The coupling reaction for dendron and dendrimer synthesis was carried out by a two-step method involving (1) activation of carboxylic acids with thionyl chloride and (2) condensation with an unprotected AB_2 building block. To determine the reaction conditions for step 1 and step 2, the reactions of 4-*tert*-butylbenzoic acid with thionyl chloride, and the active intermediate with *p*-phenoxy aniline, were investigated in advance.

The activation of 4-*tert*-butylbenzoic acid with thionyl chloride was carried out in NMP at 0 °C for 10 min. Figure 1 shows the ^{1}H NMR spectra (in $CDCl_3$) of (a) 4-*tert*-butylbenzoic acid in NMP, (b) 4-*tert*-butylbenzoic acid activated with 1.1 equiv of thionyl chloride in NMP, and (c) 4-*tert*-butylbenzoic acid activated with 0.5 equiv of thionyl chloride in NMP. When 1.1 equiv of thionyl chloride to the carboxylic acid was employed, the two aromatic signals corresponding to 4-*tert*-butylbenzoic acid were shifted entirely from 7.45 and 8.02 ppm to 7.53 and 8.05 ppm, respectively (Figure 1b). On the other hand, signals that can be assigned to the active intermediate and the starting material were both observed in an almost equivalent integration ratio when the reaction was conducted with 0.5 equiv of thionyl chloride (Figure 1c). These results clearly indicate that the activation of carboxylic acid proceeds quantitatively with thionyl chloride in NMP at 0 °C for 10 min.

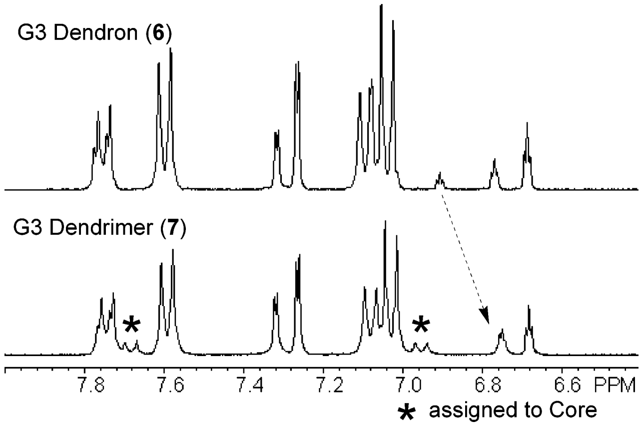


Figure 5. ^{1}H NMR spectra of the G3 dendron **6** and G3 dendrimer **7**.

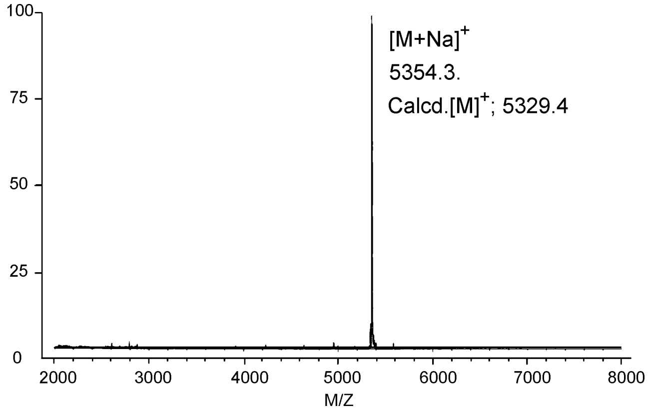


Figure 6. MALDI−TOF-MS spectrum of **7**.

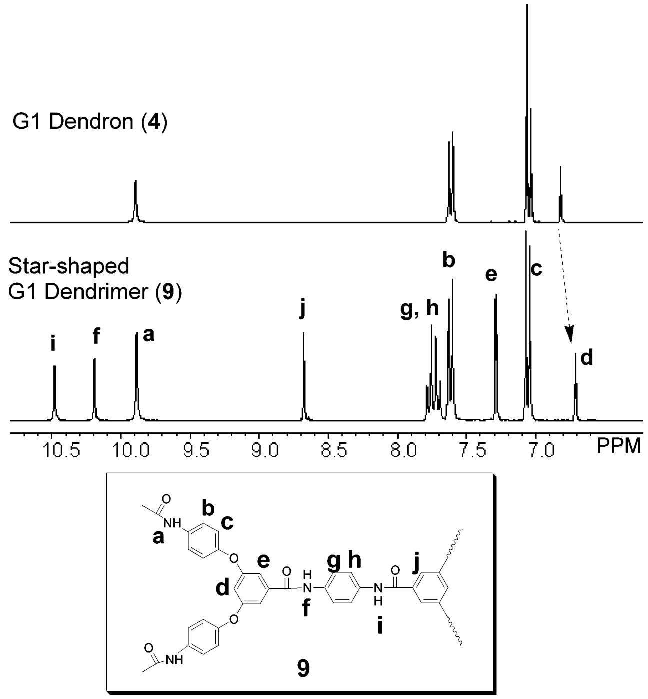
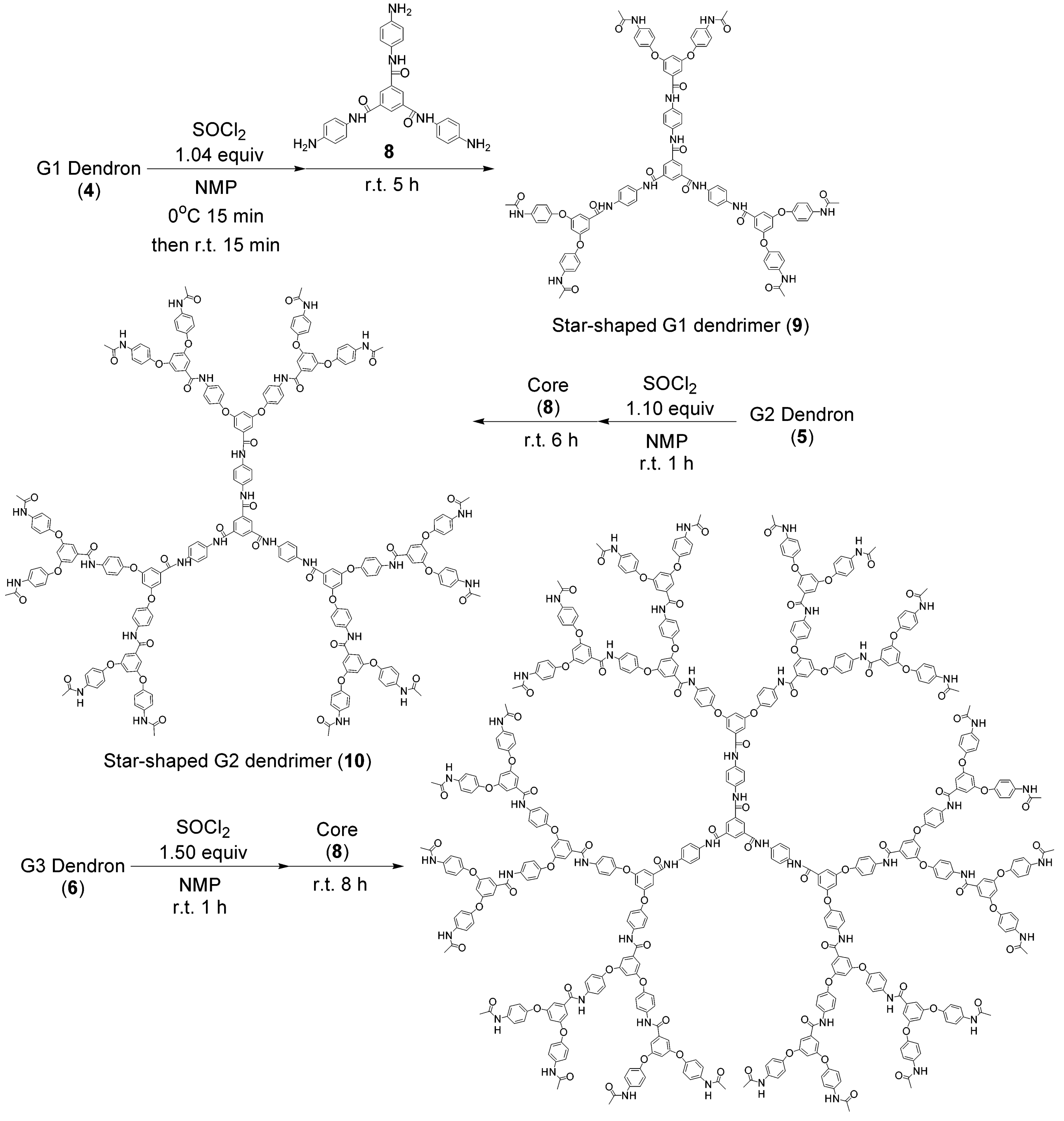


Figure 7. ^{1}H NMR spectrum of the star-shaped G1 dendrimer **9**.

The intermediate from the reaction of carboxylic acid with thionyl chloride in amide solvents was believed to be an acid chloride **1**[15a] or a complex **2**,[17] as shown in Figure 2. The ^{1}H NMR spectrum of the intermediate in Figure 1b shows exact agreement with that of 4-*tert*-butylbenzoyl chloride with NMP, indicating that the active intermediate in this reaction is the acid chloride (Figure 3).

The condensation of the active intermediate with *p*-phenoxyaniline was then investigated. The condensation was performed after the activation of 4-*tert*-butylbenzoic acid with 1.1 equiv of thionyl chloride in NMP

Scheme 3. Syntheses of Star-Shaped Dendrimers from G1–G3 Dendrons



at 0 °C for 10 min. Small signals corresponding to 4-*tert*-butylbenzoyl chloride still remained in the ^{1}H NMR spectrum after the reaction had proceeded for 10 min, and these then completely disappeared after 1 h. The amount of thionyl chloride should be decreased to avoid unfavorable side reactions, such as self-condensation between the AB$_2$ building blocks. The condensation still occurred quantitatively with 1.04 equiv of thionyl chloride. On the basis of the results obtained above, the dendron and dendrimer synthesis were then carried out.

Synthesis of Dendrons. An AB$_2$ building block should contain one carboxylic and two amino groups for the convergent synthesis of a polyamide dendrimer using thionyl chloride. Therefore, 3,5-bis(4-aminophenoxy)benzoic acid (**3**)[18] was selected as an unprotected AB$_2$ building block. The syntheses of G1, G2, and G3 dendrons are shown in Scheme 1. The AB$_2$ building block **3** was reacted with acetyl chloride to give the G1 dendron **4** in a 98% yield after precipitation in water. The G2 (**5**) and G3 (**6**) dendrons were prepared by the two-step method as described above. The activation time of the carboxylic acid, and the time for condensation, was independently set depending on the dendron, as shown in Scheme 1. For the G3 dendron synthesis, 2.0 equiv of thionyl chloride to G2 dendron was required. It was assumed that thionyl chloride decomposed during the activation because of the hygroscopic nature of the amides in the G2 dendron. When the same reaction was

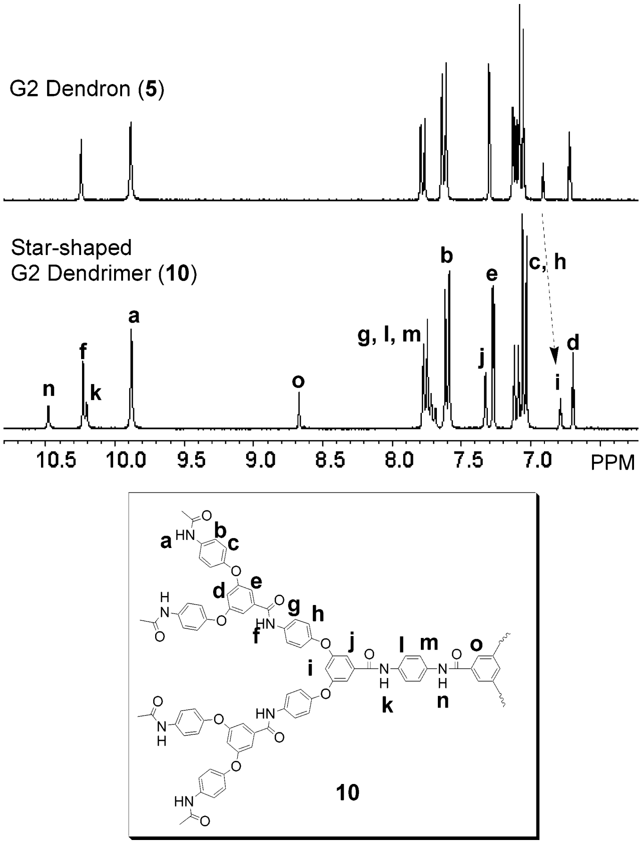


Figure 8. ^{1}H NMR spectrum of the star-shaped G2 dendrimer **10**.

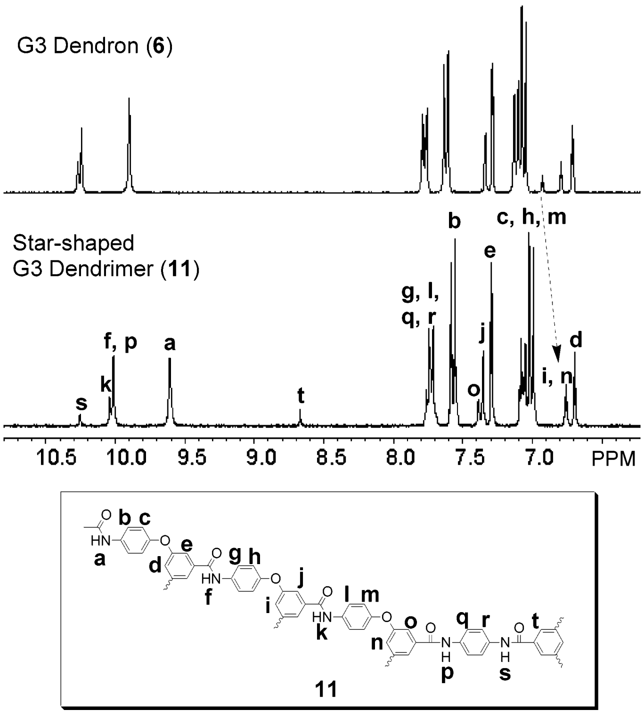


Figure 9. ^{1}H NMR spectrum of the star-shaped G3 dendrimer **11**.

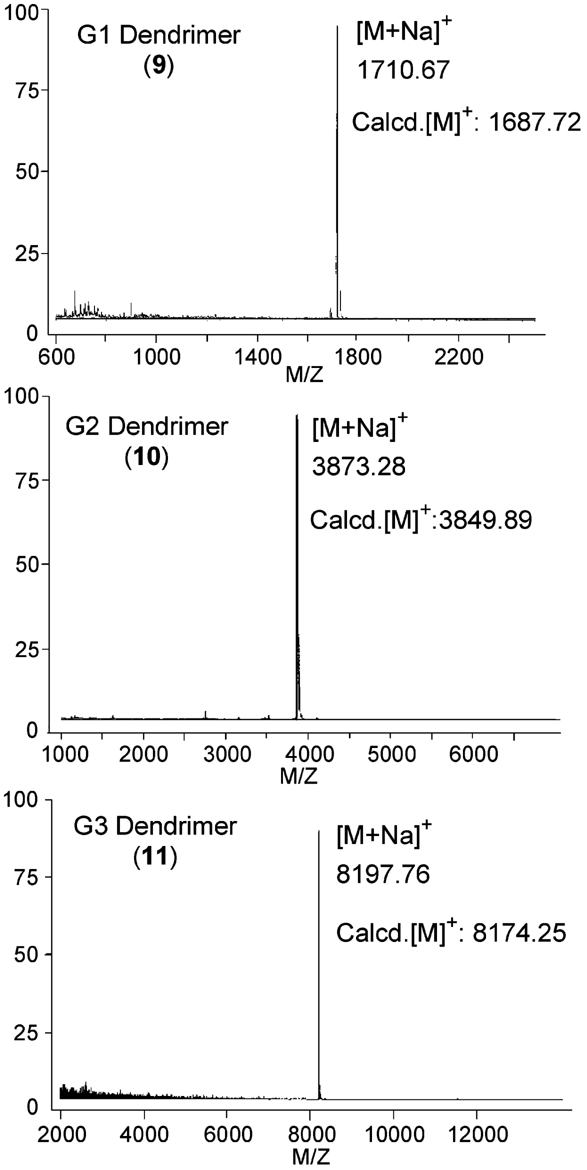
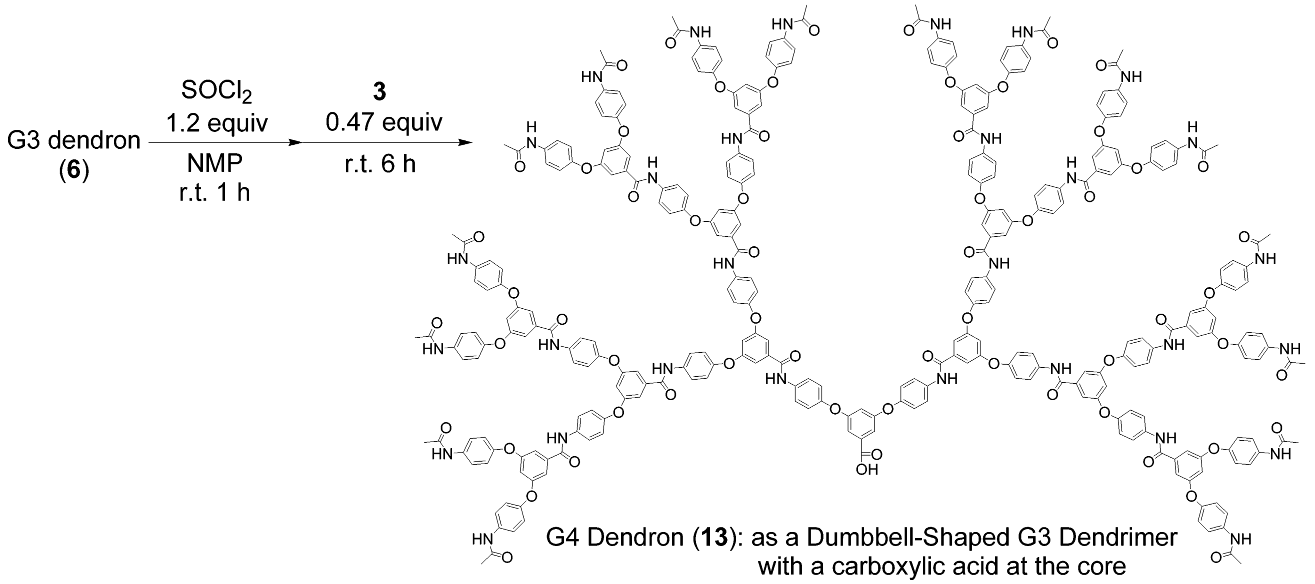


Figure 10. MALDI−TOF−MS spectra of star-shaped G1−G3 dendrimers.

conducted using water-free **5,** which was dried at 150 °C for 6 h under reduced pressure, 1.1 equiv of thionyl chloride was sufficient to obtain **6**. Each dendron was purified simply by reprecipitation to remove the parent dendrons. G2 and G3 dendrons were isolated by reprecipitation with MeOH/water and 1,4-dioxane in 92% and 94% yields, respectively. The elemental analysis revealed a slight contamination of water in these dendrons, even after the dehydration procedure at high temperature under reduced pressure. Thus, accurate yields of G2 and G3 were determined by elemental analysis.

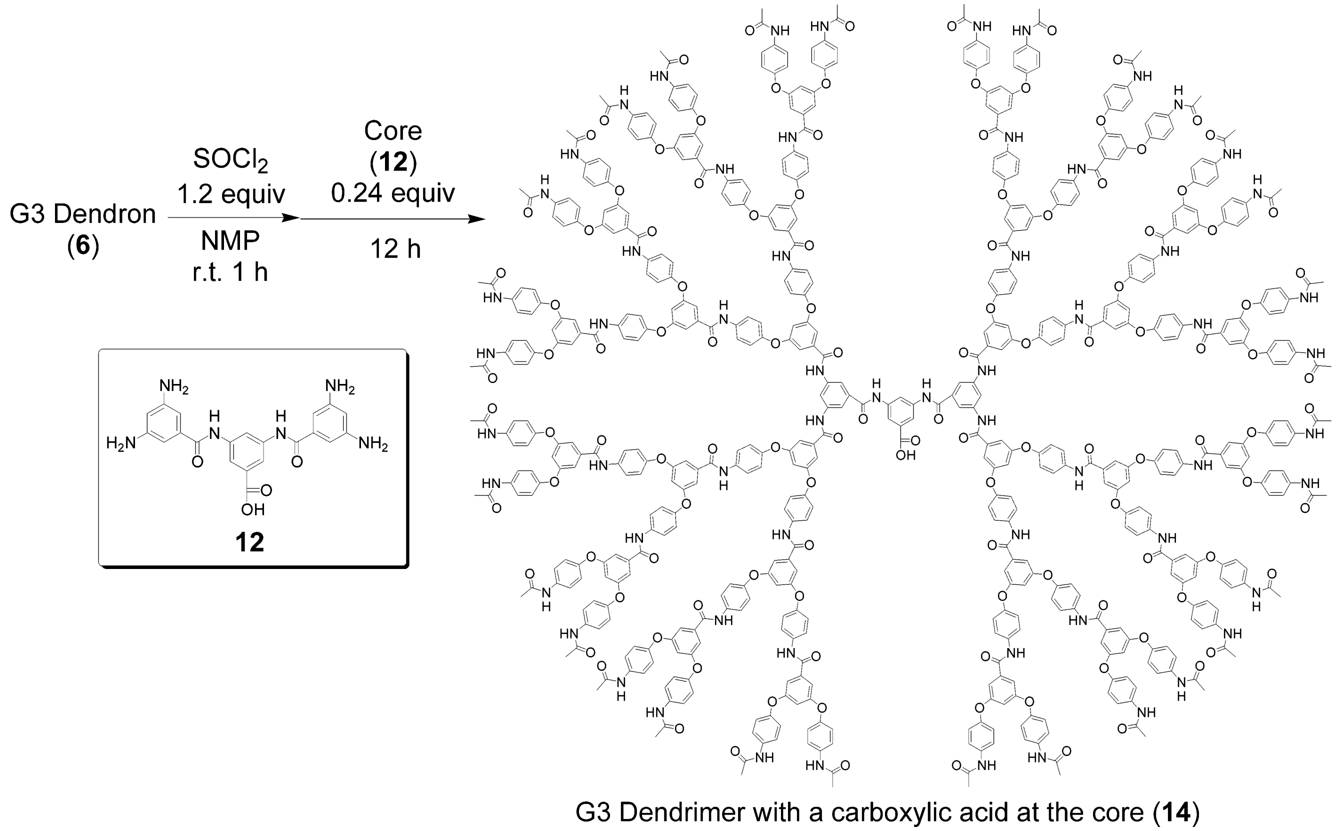
Characterization of Dendrons. The structure of **4** was characterized by IR spectroscopy, ^{1}H NMR spectroscopy, and elemental analyses. The IR spectrum of **4** showed strong absorptions at 1697 and 1658 cm^{-1}, characteristic of the C=O stretching of carboxyl acid and amide groups, respectively. ^{1}H NMR spectra of all dendrons show signals corresponding to amide protons (*a, f, k*) and aromatic protons of the *para*-position of a carbonyl moiety (*d, i, n*) at 9.8−10.4 and 6.6−7.0 ppm, respectively (Figure 4). The ^{1}H NMR spectrum of the G3 dendron **6** shows three signals at 6.69, 6.77, and 6.91 ppm, integrated as 4 protons, 2 protons, and 1 proton, respectively. These signals are assigned to *d, i,* and *n* in Figure 4, respectively, and these indicate the satisfactory formation of the desired dendrons. The MALDI−TOF−MS spectra of **5** and **6** indicate their molecular weight [M + Na]$^+$ to be 1163.0 and 2606.3 Da, which

Scheme 4. Synthesis of the G4 Dendron 13



G4 Dendron (**13**): as a Dumbbell-Shaped G3 Dendrimer with a carboxylic acid at the core

Scheme 5. Synthesis of the G3 Dendrimer with a Carboxylic Acid at the Core (14)

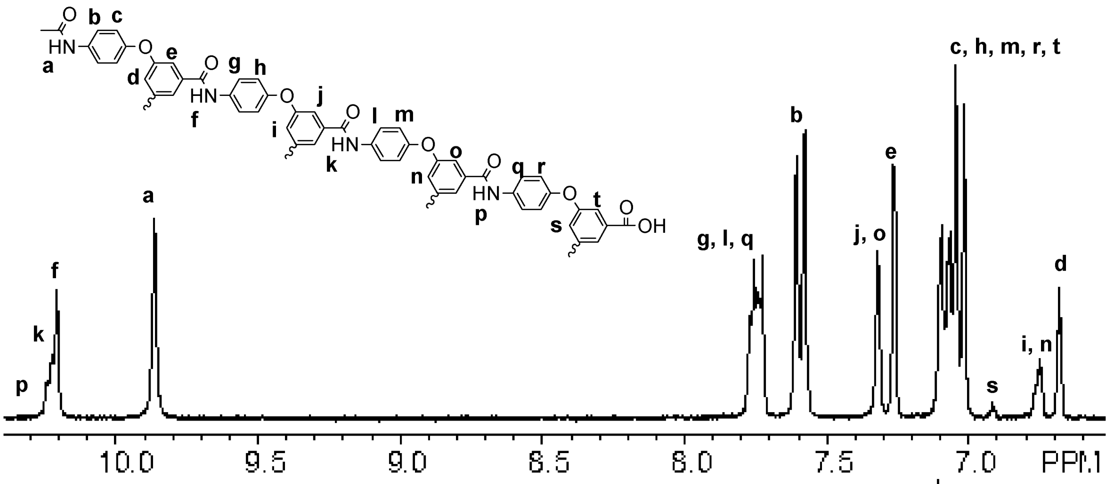


G3 Dendrimer with a carboxylic acid at the core (**14**)

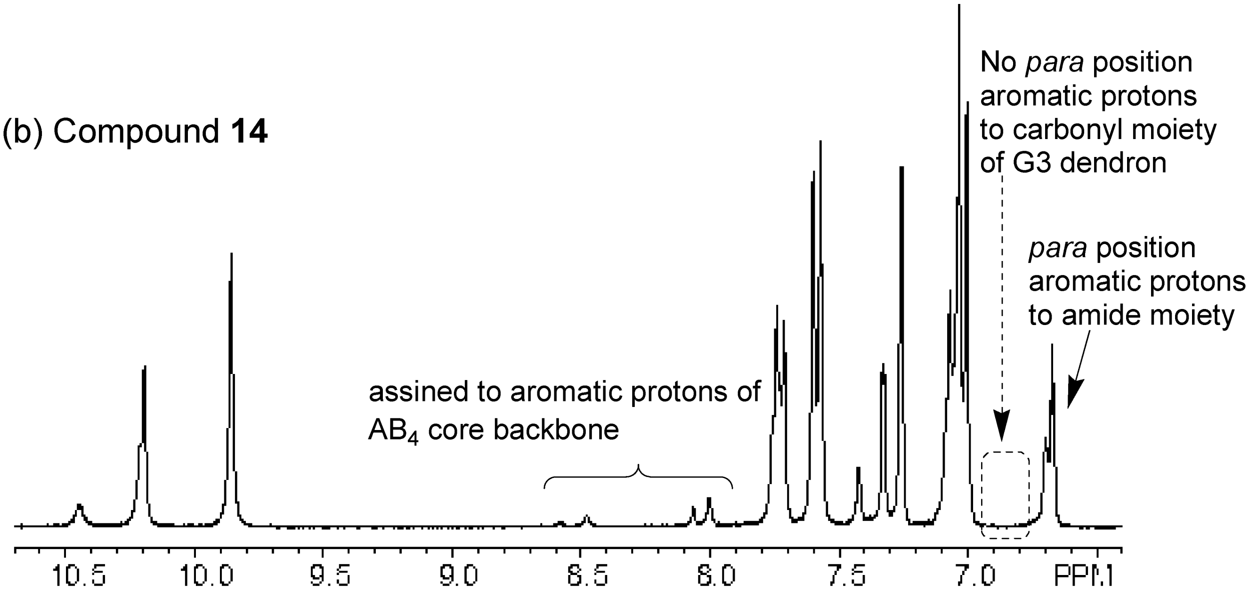
are close to the calculated molecular weights of 1164.3 and 2605.6 Da, respectively. These findings clearly indicate the formation of the desired dendrons.

Dumbbell-Shaped Dendrimer Synthesis. The dumbbell-shaped dendrimer (**7**) was synthesized from **6** and 4,4′-oxydianiline (Scheme 2). The reaction of **6** with 4,4′-oxydianiline was performed using 1.50 equiv of thionyl chloride with respect to the G3 dendron. The reaction mixture was poured into water, and the precipitate was collected and dried. The crude product was dissolved in *N*,*N*-dimethylformamide (DMF), and the resulting solution was reprecipitated with THF, resulting in a dendrimer **7** with 74% yield. This value was also calculated on the basis of water contamination determined by elemental analysis. IR, ^{1}H NMR, MALDI–TOF-MS, and elemental analyses were performed for the characterization of **7**. In the ^{1}H NMR spectrum (Figure 5), the signals assigned to the protons of the *para*-position to the carboxylic acid in compound **6** shift from 6.91 to 6.75 ppm after the coupling reaction, indicating the formation and isolation of the G3 dendrimer. Figure 6 shows the MALDI–TOF–MS spectrum of the G3 polyamide dendrimer **7** (calculated molecular weight 5329.39 Da). Signals representing the starting materials and incompletely substituted products are not observed, and only one signal is observed

(a) Compound **13**



(b) Compound **14**



No *para* position aromatic protons to carbonyl moiety of G3 dendron

para position aromatic protons to amide moiety

assined to aromatic protons of AB_4 core backbone

Figure 11. ^{1}H NMR spectra of dendrimers **13** and **14**.

at M/Z ([M + Na]$^+$) 5354.3 Da, which is assigned to the target molecule.

Synthesis of Star-Shaped Dendrimer. A coupling reaction of G1, G2, and G3 dendrons with a trifunctional core molecule was performed to obtain star-shaped dendrimers. To reduce the steric hindrance, 1,3,5-tris(*N*-(4-aminophenyl))benzenetricarboxamide (**8**) was selected as a core molecule and prepared according to the literature procedure.[9] Syntheses of star-shaped dendrimers are shown in Scheme 3. Each activation and condensation reaction was conducted using similar conditions as used for the synthesis of dumbbell-shaped dendrimers. Small excess amounts of each dendron to the core molecule were used, and the condensation time was prolonged enough to finish these reactions because the removal of defect molecules should be more difficult compared with that of dendrons. The isolation and purification of dendrimers G1 (**9**), G2 (**10**), and G3 (**11**) were performed by reprecipitation with solvents, similar for those of the dendrons, MeOH/water, EtOH, and tetrahydrofuran (THF) in 86%, 81%, and 78% yields, respectively. The structures of all dendrimers are characterized by IR, ^{1}H NMR, MALDI−TOF-MS, and elemental analyses. The complete formation and isolation of the dendrimers were confirmed in the same manner as that for the dendrons (**5** and **6**) and the dumbbell-shaped dendrimer **7**. The *para*-position aromatic protons to the carboxylic acid of each dendron completely disappeared, and the corresponding protons to the newly formed amide units in star-shaped dendrimers appeared in higher fields, as shown in Figures 7−9. Each MALDI−TOF-MS spectra for G1, G2, and G3 show a single signal at *m/z* ([M + Na]$^+$) 1710.7, 3849.9, and 8197.8 Da, respectively (Figure 10).

Synthesis of a Dendrimer with a Carboxylic Acid Group at the Core. Finally, the syntheses of dendrimers with a carboxylic acid at the core (Schemes 4 and 5) were performed. The AB_2 building block **3** and 3,5-bis(3,5-diaminobenzoylamino)benzoic acid (**12**) were selected as the AB_2 and AB_4 type core molecules. The AB_4 type core molecule **12** was prepared according to the literature procedure.[9] The resulting compounds, **13** and **14,** were expected to be dumbbell-shaped and larger spherical shaped dendrimers, respectively. Coupling reactions of **3** and **12** with the G3 dendron were conducted by using 1.2 equiv of thionyl chloride to G3 dendron (**6**) to avoid self-condensation of these core molecules. In contrast, the synthesis of the star-shaped G3 dendrimer **11** was performed by using 1.5 equiv of thionyl chloride to **6** because the core molecule **8**

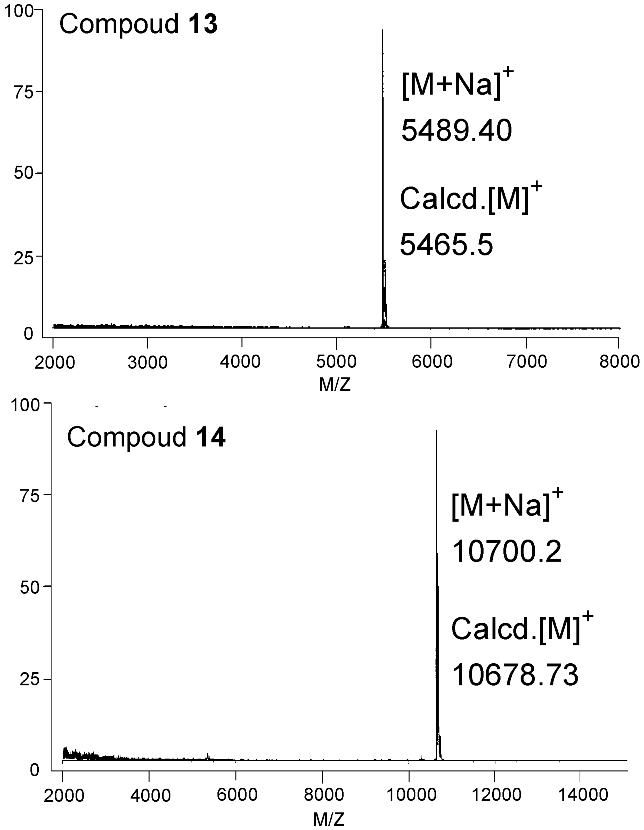


Figure 12. MALDI−TOF−MS spectra of dendrimers **13** and **14**.

possesses no ability for self-condensation. When the AB_4 type core **12** was used, the condensation time required to complete the coupling reaction was 12 h. Compounds **13** and **14** were purified by reprecipitation with THF in yields of 80% and 76%, respectively. Examination of the ^1H NMR spectra (Figure 11) shows the *para*-position aromatic protons of each carbonyl moiety observed to be different between **13** and **14**. The ^1H NMR spectrum of compound **13** shows the *para*-position aromatic proton for carboxylic acid, at the focal point of the G3 dendron, to have shifted from 6.91 to 6.75 ppm, and three signals at 6.68, 6.72−6.78, and 6.91 ppm are integrated as 8 protons, 6 protons, and 1 proton, respectively. On the other hand, all *para*-position aromatic protons of the amide moiety of **14** are observed at 6.64−6.72 ppm and are integrated as 28 protons. These results arise from the differences of the core structure. The MALDI−TOF−MS spectrum was used to confirm the formation and isolation of **13** and **14**. The spectra of **13** and **14** showed the single signal ($[M + Na]^+$) at 5489.4 and 10 700.2 Da, respectively, as shown in Figure 12. Although the core **12** possessing four amino groups and one carboxylic acid were used, the peaks from the incompletely substituted product and the product derived from self-condensation were not detected. The elemental analysis of **14** shows deviation between calculated and experimental values as seen in dendrons **5** and **6**. This contaminant was identified to be water by ^1H NMR spectroscopy measured in dehydrated DMSO-d_6. The water content was 7.0 H_2O/**14** calculated from ^1H NMR spectrum, while elemental analysis data indicate good agreement as **14** contains 9.0 H_2O.

Conclusion

In conclusion, we have demonstrated a simple and highly efficient convergent approach without protection and deprotection steps for the synthesis of aromatic polyamide dendrimers using the inexpensive reagent thionyl chloride. This strategy allows the synthesis of dumbbell-shaped dendrimers, star-shaped dendrimers, and dendrimers with a carboxylic acid at the core, without the use of an additional reagent, forepart from thionyl chloride, NMP, and common solvents. In this method, the purification of each dendron and dendrimers requires only precipitation and allows for the large-scale and facile synthesis of dendrimers. The MALDI−TOF−MS spectra provided evidential support for the formation and isolation of the target products.

References and Notes

(1) Jiang, D.-L.; Aida, T. *Nature (London)* **1997**, *388*, 454−456.
(2) Knapen, J. W. J.; van der Made, A. W.; de Wilde, J. C.; van Leeuwen, P. W. N. M.; Wijkens, P.; Grove, D. M.; van Koten, G. *Nature (London)* **1994**, *372*, 659−653.
(3) (a) Ponomarenko, S. A.; Rebrov, E. A.; Bobrovsky, A. Y.; Boiko, N. I.; Muzafarov, A. M.; Shibaev, V. P. *Liq. Cryst.* **1996**, *21*, 1−12. (b) Busson, P.; Ihre, H.; Hult, A. *J. Am. Chem. Soc.* **1998**, *120*, 9070−9071.
(4) (a) Jansen, J. F. G. A.; de Brabander van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226−1229. (b) Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, *19*, 2459−2469.
(5) (a) Haensler, J.; Szoka, F. C., Jr. *Bioconjugate Chem.* **1993**, *4*, 372−379. (b) Tang, M.; Redemann, C, T.; Szoka, F. C., Jr. *Bioconjugate Chem.* **1996**, *7*, 703−714. (c) Malik, N.; Wiwattanapatapee, R.; Klopsch, R.; Lorenz, K.; Frey, H.; Weener, J. W.; Meijer, E. W.; Paulus, W.; Duncan, R. *J. Controlled Release* **2000**, *65*, 133−148.
(6) (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138−175. (b) Newkome, G. R.; Moorefield, C. N.; Baker, G. R. *Aldrichim. Acta* **1992**, *25*, 31−38.
(7) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.
(8) For reviews, see for example: (a) *Dendrimers and Dendrons: Concepts, Syntheses, Application;* Newkome, G. R., Moorfield, C. N., Vögtle, F., Eds.; Wiley-VCH: Weinheim, Germany, 2001. (b) *Dendrimer and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; John Wiley & Sons: West Sussex, UK, 2001. (c) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819−3868.
(9) For polyamide dendrimer, see: Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules* **2000**, *33*, 3202−3211.
(10) (a) Rannard, S. P.; Davis, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 11729−11730. (b) Rannard, S.; Davis, N.; McFarland, H. *Polym. Int.* **2000**, *49*, 1002−1006.
(11) (a) Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1990**, *2*, 346−349. (b) Bayliff, P. M.; Feast, W. J.; Parker, D. *Polym. Bull. (Berlin)* **1992**, *29*, 265−270. (c) Backson, S. C. E.; Bayliff, P. M.; Feast, W. J.; Kenwright, A. M.; Parker, D.; Richards, R. W. *Macromol. Symp.* **1994**, *77*, 1−10. (d) Romagnoli, B.; Ashton, P. R.; Harwood, L. M.; Philp, D.; Price, D. W.; Smith, M. H.; Hayes, W. *Tetrahedron* **2003**, *59*, 3975−3988.
(12) Okazaki, M.; Washio, I.; Shibasaki, Y.; Ueda, M. *J. Am. Chem. Soc.* **2003**, *125*, 8120−8121.
(13) (a) Ueda, M.; Kameyama, A.; Hashimoto, K. *Macromolecules* **1988**, *21*, 19−24. (b) Okazaki, M.; Hayakawa, T.; Ueda, M.; Takeuchi, K.; Asai, M. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *38*, 78−85.
(14) Normant, J. F.; Deshayes, H. *Bull. Soc. Chim. Fr.* **1972**, 2854−2859.
(15) (a) Ueda, M.; Aoyama, S.; Konno, M.; Imai, Y. *Makromol. Chem.* **1978**, *179*, 2089−2091. (b) Imai, Y.; Aoyama, S.; Nguyen, T. Q.; Ueda, M. *Makromol. Chem. Rapid Commun.* **1980**, *1*, 655−668.
(16) Washio, I.; Shibasaki, Y.; Ueda, M. *Org. Lett.* **2003**, *5*, 4159−4161.
(17) Higashi, F.; Nishi, T. *J. Polym. Sci., Part A: Polym. Chem.* **1986**, *24*, 701−706.
(18) Yang, G.; Jikei, M.; Kakimoto, M. *Macromolecules* **1998**, *31*, 5964−5966.

MA0478456