Facile Synthesis of a Tadpole-Shaped Dendrimer Based on *N*-Alkylated Oligo(*p*-benzamide)

Yumiko Ito, Isao Washio, 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

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ABSTRACT: A novel, rapid, inexpensive, and highly accelerated approach for the synthesis of a tadpole-shaped dendrimer possessing monodisperse *N*-alkylated oligo(*p*-benzamide) as a rod block with a precise length and an amine-terminated dendritic block based on 3,5-diaminobenzoic acid has been developed. The *N*-alkylated oligo(*p*-benzamide)s were prepared by an rapid stepwise method using thionyl chloride as an activating agent and trifluoroacetamide as the protecting group for the end amine, in which the number of amide units dramatically propagated only through every deprotection and condensation. From this rod block, each generation of dendron rod molecules was formed divergently using 3,5-bis(trifluoroacetamido)benzoyl chloride as an AB_2 building block.

Introduction

Dendrimers are characterized by their perfect branching, monodispersity, and three-dimensional structure with a large number of reactive end groups. Therefore, they have received considerable attention as new polymeric materials for applications in areas such as molecular light harvesting, catalysts, liquid crystals, molecular encapsulation, and drug delivery systems.[1] However, the synthesis of dendrimers requires a tedious multistep procedure with repetitive protection−deprotection and purification processes, which interfere with their widespread use. To solve this problem, over the past several years, we have focused on the development of facile synthetic approaches to dendrimers[2] and reported the rapid syntheses of aromatic polyamide dendrimers via both divergent and convergent methods, where the total number of reactions decreased to half of that required in the conventional approaches. In the convergent method, we utilized a two-step method comprising the activation of carboxylic acids with thionyl chloride and condensation with an unprotected AB_2 building block possessing diamine moieties. In the divergent method, we employed a novel protected AB_2 building block, 3,5-(bistrifluoroacetamido)benzoyl chloride, which enables a reduction in the deprotection reaction time of amines by a transamidation reaction with hydrazine as well as one-pot condensation and deprotection reactions.[2d]

The development of an efficient approach to the synthesis of well-defined macromolecular architectures is also the central theme underlying a new strategy for the preparation of functional dendrimers. Recently, Stupp et al. reported the synthesis of dendron rod coils comprising a series of novel block structures containing dendritic, rod-like, and coil-like segments, which yield interesting hierarchiral self-assembled nanostructures.[3] The synthesis is based on the combination of a catalyzed esterfication reaction and silyl protection/deprotection chemistry. Lee et al. synthesized tree-shaped molecules with octa-*p*-phenylene as the stem segment and oligoether dendrons as the flexible head by using a sequence of the Suzuki coupling reaction of 4-trimethylsilylbiphenyl-4′-boronic acid with oligo-*p*-phenylene iodides.[4] Hammond et al. also reported an amphiphilic comb−dendritic block copolymer based on poly(γ-*n*-dodecyl-L-glutamate) as the hydrophobic comb block and a hydrophilic polyester dendron block modified with poly(ethylene glycol).[5] This comb−dendritic block copolymer was prepared from the polyester dendritic initiator, which initiated a ring-opening polymerization of the *N*-carboxyanhydride of γ-*n*-dodecyl-L-glutamate. Thus, the synthesis of dendrimers consisting of rod dendrons and monodisperse linear-rod segments is interesting to compare their hierarchiral self-assembled nanostructures to those of dendrimers from rod dendrons and coil-like segments.

In this paper, we report a facile synthesis of a monodisperse dendron rod block copolymer, termed as a tadpole-shaped dendrimer, possessing monodisperse *N*-alkylated oligo(*p*-benzamide) as a rod block with a precise length and an amine-terminated dendritic block based on 3,5-diaminobenzoic acid, where each block was prepared by fewer reaction steps using a protocol similar to that described above.

Experimental Section

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

Synthesis of Rod Blocks. *Preparation of AB Monomer (1″).* To the solution of 4-aminobenzoic acid (33.0 g, 200 mmol) in hexamethylphosphoric triamide (100 mL) was added butyl iodide (18.4 g, 100 mmol) under nitrogen. The reaction solution was stirred at 120 °C for 10 h, allowed to cool to 25 °C, and then was poured into water. The deposit was filtered, dissolved in MeOH (400 mL), and then reprecipitated with water (500 mL). The precipitate was collected and dissolved in EtOH (150 mL). To this solution was added potassium hydroxide (22.0 g, 392 mmol) under nitrogen, and the resultant solution was refluxed for 6 h. The reaction mixture was poured into water, and then the pH of the resulting solution was adjusted around 4.0 using HCl_{aq}. The precipitate was filtered, dried, and recrystallized from MeOH to give a slightly yellow crystal (77% yield calculated toward ethyl iodide); mp = 157 °C. IR (KBr, cm^{-1}): 1531, 1601 (Ar−H), 1662 (C=O), 2500−3300 (O−H), 2866, 2931, 2958 (C−H), and 3398 (N−H). ^1H NMR ($CDCl_3$, ppm, 25 °C): $\delta = 0.97$ (t, 3H), 1.44 (m, 2H), 1.63 (m, 2H), 3.18 (t, 2H), 6.55 (d, 2H), 7.92 (d, 2H). ^{13}C NMR (DMSO, 40 °C): $\delta = 13.6$, 19.7, 30.6, 42.0, 110.6, 116.7, 131.1, 152.7, and 167.5. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.33; H, 7.80; N, 7.14.

Preparation of Protected Monomer (2″). Trifluoroacetic anhydride (21.5 g, 102 mmol) was added to a solution of 4-(*N*-butylamino)benzoic acid (9.00 g, 46.6 mmol) in THF (72 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 3 h. Then, water (150 mL) was

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* Corresponding author: Tel +81-3-57342127; fax +81-3-57342127; e-mail ueda.m.ad@m.titech.ac.jp.

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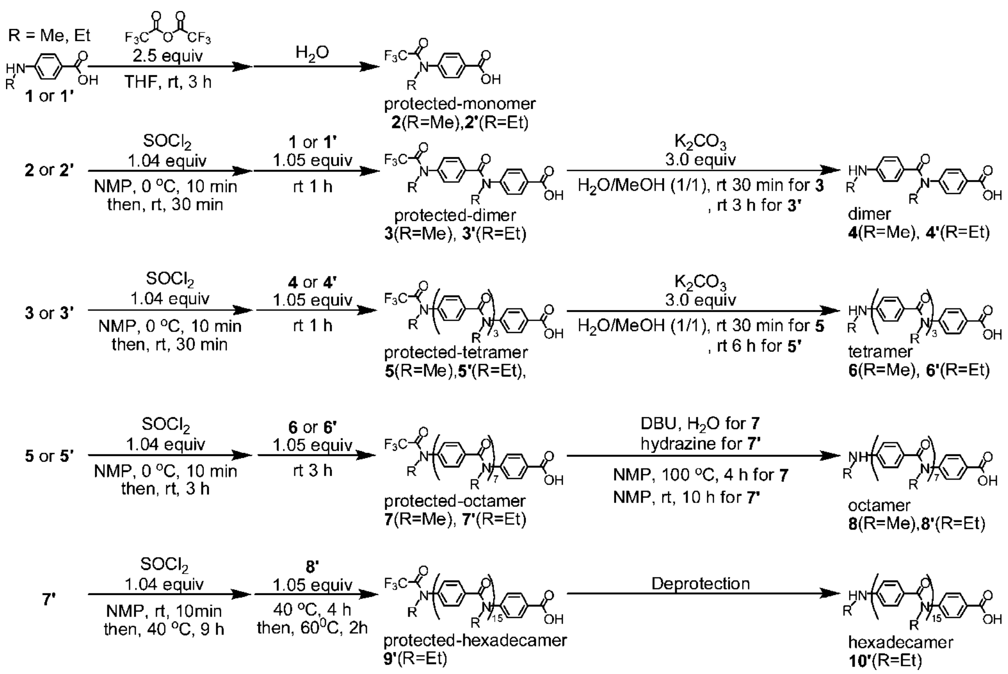
Scheme 1. Synthesis of Monodisperse *N*-Alkylated Oligo(*p*-benzamide)s



added, and stirring was continued for 6 h at the temperature. The reaction mixture was extracted with diethyl ether, and the organic layer was washed with water several times, dried over $MgSO_4$, and filtered. The filtrate was evaporated, and the residue was recrystallized from hexane at 50 °C to give a white crystal (85% yield); mp = 85–87 °C. IR (KBr, cm^{-1}): 1211 (C−F), 1512, 1608 (Ar−H), 1701 (C=O, 2500−3300 (O−H), and 2877, 2935, 2962 (C−H). ^1H NMR ($CDCl_3$, ppm, 25 °C): δ = 0.92 (t, 3H), 1.34 (m, 2H), 1.56 (m, 2H), 3.78 (t, 2H), 7.36 (d, 2H), 8.21 (d, 2H). ^{13}C NMR ($CDCl_3$, ppm, 25 °C): δ = 13.5, 19.8, 28.9, 51.7, 116.3 (q, J = 286.7 Hz), 128.6, 129.9, 131.5, 144.0, 117.3, 156.4 (q, J = 35.3 Hz), and 171.1. Anal. Calcd for $C_{13}N_{14}F_3NO_3$: C, 53.98; H, 4.88; N, 4.84. Found: C, 54.06; H, 4.87; N, 4.65.

Preparation of Protected Trimer (4″). Thionyl chloride (1.91 mL, 26.2 mmol) was added to a solution of protected monomer **2″** (7.29 g, 25.2 mmol) in NMP (30 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 30 min. To this solution, 4-(*N*-butylamino)benzoic acid, **1″** (4.87 g, 25.2 mmol), was added, and stirring was continued for 1 h at the temperature. Subsequently, the activation of terminal carboxylic acid using thionyl chloride (1.91 mL, 26.2 mmol) was performed again at 0 °C for 10 min, followed by 25 °C for 30 min. Then, the condensation of it with another **1″** (4.92 g, 25.5 mmol) was conducted at the temperature for 1 h. The reaction mixture was poured into dilute HCl, and the precipitate was filtered and dried. The crude product was purified by recrystallization from hexane/THF (v:v = 50:7) to give a white crystal (85% yield); mp = 112–113 °C. IR (KBr, cm^{-1}): 1207 (C−F), 1512, 1604 (Ar−H), 1651 (C=O(NH)), 1697 (C=O (trifluoroacetyl amide), C=O(OH)), 2500−3300 (O−H), and 2873, 2935, 2958 (C−H). ^1H NMR ($CDCl_3$, ppm, 25 °C): δ = 0.81–0.94 (m, 9H), 1.21–1.66 (m, 12H), 3.68 (t, 2H), 3.87 (t, 2H), 3.94 (t, 2H), 6.83 (d, 2H), 7.00 (d, 2H), 7.03 (d, 2H), 7.16 (d, 2H), 7.24 (d, 2H), 7.92 (d, 2H). 13C NMR ($CDCl_3$, ppm, 25 °C): δ = 13.39, 13.47, 13.49, 19.59, 19.88, 19.93, 28.72, 29.58, 29.73, 50.00, 51.26, 116.23 (q, J = 287.0 Hz), 126.78, 127.17, 127.53, 127.88, 129.47, 129.72, 130.79, 134.40, 136.31, 140.15, 144.18, 147.74, 156.21 (q, J = 35.3 Hz), 168.80 and 169.4 ppm. Anal. Calcd for $C_{35}H_{14}F_3N_3O_5$: C, 65.71; H, 6.30; N, 6.57. Found: C, 66.10; H, 6.39; N, 6.19.

Preparation of Trimer (5″). To a solution of protected-trimer **3′** (7.3 g, 11.4 mmol) in NMP (17 mL) was added hydrazine monohydrate (1.71 g, 34.2 mmol) at 25 °C under nitrogen. The reaction mixture was stirred at 50 °C for 3 h. The resulting solution was diluted with water, and the pH of the solution was adjusted around 4.0 using HCl_{aq}. The precipitate was filtered and dried at 60 °C under reduced pressure to give white glass (95% yield); mp = 174–176 °C. IR (KBr, cm^{-1}): 1512, 1604 (Ar−H), 1643 (C=O(NH)), 1716 (C=O(OH)), 2500−3300 (O−H), 2870, 2931, 2958 (C−H), and 3386 (N−H). ^1H NMR ($CDCl_3$, ppm, 25 °C): δ = 0.81–0.96 (m, 9H), 1.20–1.65 (m, 12H), 3.05 (t, 2H), 3.81 (t, 2H), 3.94 (t, 2H), 6.19 (d, 2H), 6.87 (d, 2H), 6.98 (d, 2H), 7.03 (d, 2H), 7.15 (d, 2H), 7.91 (d, 2H). ^{13}C NMR ($CDCl_3$, ppm, 25 °C): δ = 13.58, 13.70, 19.89, 19.92, 20.00, 29.54, 31.04, 42.87, 49.82, 50.18, 110.63, 121.95, 126.69, 127.06, 128.01, 129.15, 130.77, 130.92, 133.36, 145.54, 147.26, 149.82, 168.26, 169.90, and 170.78. Anal. Calcd for $C_{33}H_{41}N_3O_4$: C, 72.90; H, 7.60; N, 7.73. Found: C, 72.91; H, 7.65; N, 7.73.

Preparation of Protected Nonamer (7″). Thionyl chloride (65.0 uL, 0.895 mmol) was added to a solution of protected trimer **4″** (0.550 g, 0.860 mmol) in NMP (1.5 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, followed by 25 °C for 1 h. To this solution trimer **5″** (0.463 g, 0.852 mmol) was added, and stirring was continued for 3 h at the temperature. Subsequently, the activation of terminal carboxylic acid using thionyl chloride (65.0 uL, 0.895 mmol) was performed again at the temperature for 30 min. Then, the condensation of it with another **5″** (0.473 g, 0.869 mmol) was conducted at the temperature for 12 h. The reaction mixture was poured into dilute HCl, and the precipitate was filtered and dried. The crude product was dissolved in 2-butanone and reprecipitated with hexane. The precipitate was collected and dried at 100 °C under reduced pressure

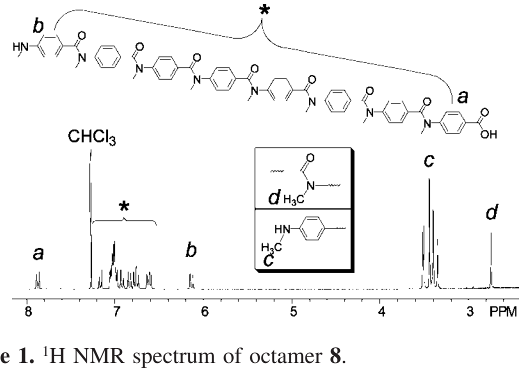


Figure 1. ^1H NMR spectrum of octamer **8**.

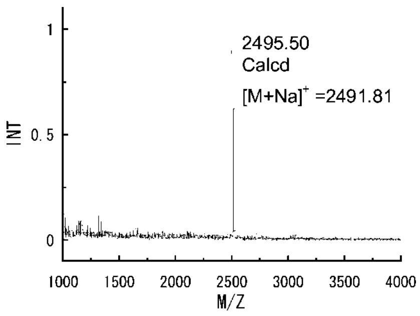


Figure 2. MALDI-TOF MS spectrum of protected hexadecamer **9′**.

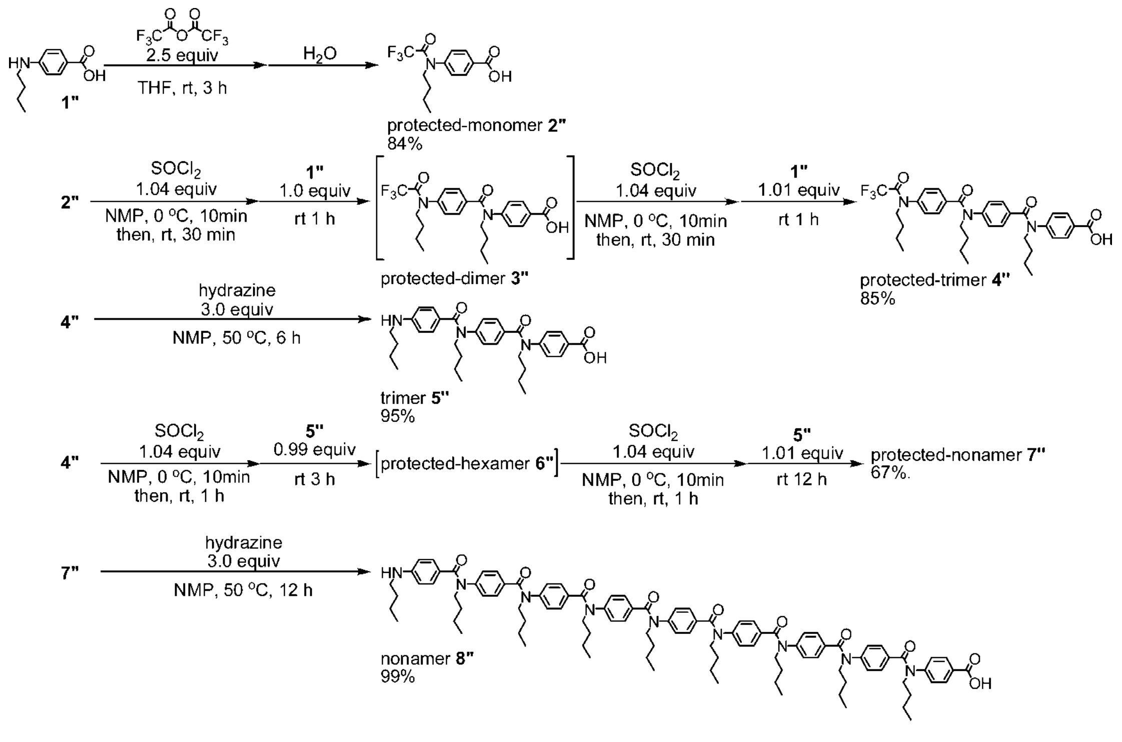
to give white solid (67% yield); mp = 212–214 °C. IR (KBr, cm^{-1}): 1215 (C−F), 1508, 1604 (Ar−H), 1651 (C═O(NH)), 1701 (C═O (trifluoroacetyl amide)), 1716 (C═O(OH)), and 2873, 2931, 2958 (C−H). ^{1}H NMR (CDCl$_3$, ppm, 25 °C): δ = 0.80–0.94 (m, 27H), 1.18–1.65 (m, 36H), 3.69 (t, 2H), 3.73–4.00 (m, 16H), 6.67–6.90 (m, 14H), 6.93–7.17 (m, 18H), 7.24 (d, 2H), 7.85 (d, 2H). Calcd: $[M]^+$ m/z = 1689.9. Found: MALDI-TOF-MS: $[M + H]^+$ = 1691.4, $[M + Na]^+$ = 1713.4, $[M - H + 2Na]^+$ = 1735.5 Anal. Calcd for $C_{101}H_{118}F_3N_9O_{11}$: C, 71.73; H, 7.03; N, 7.45. Found: C, 71.53; H, 7.08; N, 7.18.

Preparation of Nonamer (8″). To a solution of protected nonamer **7″** (0.951 g, 0.562 mmol) in NMP (2.8 mL) was added hydrazine monohydrate (84.3 mg, 1.69 mmol) at 25 °C under nitrogen. The reaction mixture was stirred at 50 °C for 12 h. Then, the resultant solution was diluted with water, and the pH of the solution was adjusted around 4.0 using HCl_{aq}. The precipitate was filtered and dried under reduced pressure at 100 °C to give white solid (99% yield); mp = 95 °C. IR (KBr, cm^{-1}): 1508, 1604 (Ar−H), 1643 (C═O(NH)), 1716 (C═O(OH)), and 2870, 2931, 2958 (C−H). ^{1}H NMR (CDCl$_3$, 25 °C): δ = 0.74–0.97 (m, 27H), 1.15–1.66 (m, 36H), 3.09 (t, 2H), 3.70–3.99 (m, 16H), 6.34 (d, 2H), 6.60–6.83 (m, 14H), 6.90–7.17 (m, 18H), 7.67 (d, 2H). Calcd: $[M]^+$ m/z = 1593.9. Found: MALDI-TOF-MS: $[M + H]^+$ = 1593.0 $[M + Na]^+$ = 1614.9, $[M + 2Na - H]^+$ = 1636.8. Anal. Calcd for $C_{99}H_{119}N_9O_{10}$: C, 74.55; H, 7.52; N, 7.90. Found: C, 73.81; H, 7.46; N, 7.46.

Synthesis of Dendrimers. *Preparation of G1d-rod (13).* AB$_2$ building block **11** (0.236 g, 0.650 mmol) was added to a solution of nonamer **8″** (0.798 g, 0.500 mmol) in NMP (1.0 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 5 min and subsequently at 25 °C for 5 h. Then, water (ca. 5 cm^3) was added, and stirring was continued for 1 h at 50 °C. The resultant solution was treated with hydrazine monohydrate (0.200 g, 4.00 mmol) for another 12 h at the temperature. The reaction mixture was poured into 2 wt % of $NaHCO_{3aq}$. The precipitate was filtered and dispersed in water and then adjusted at pH ~7 using diluted HCl_{aq}. The resulting precipitate was collected and dried at 60 °C under reduced pressure to give white solid (98% yield); mp = 150 °C. IR (KBr, cm^{-1}): 1508, 1604 (Ar−H), 1647 (C═O(NH)), 1716 (C═O(OH)), 2870, 2931, 2958 (C−H), and 3375 (N−H). ^{1}H NMR (CDCl$_3$, ppm, 25 °C): δ = 0.78–0.96 (m, 27H), 1.18–1.65 (m, 36H), 3.71–3.99 (m, 18H), 5.84 (t, 1H), 5.90 (d, 2H), 6.64–6.88 (m, 16H), 6.92–7.18 (m, 18H), 7.83 (d, 2H). Calcd: $[M]^+$ m/z = 1728.0. Found: MALDI-TOF-MS: $[M + H]^+$ = 1729.0, $[M + Na]^+$ = 1751.0, $[M + 2Na - H]^+$ = 1773.0. Anal. Calcd for $C_{106}H_{120}N_{11}O_{11}0.60H_2O$: C, 72.49; H, 7.18; N, 8.77. Found: C, 72.49; H, 7.01 N, 8.79.

Preparation of G2d-rod (14). AB$_2$ building block **11** (0.236 g, 0.650 mmol) was added to a solution of G1d-rod **13** (0.432 g, 0.250 mmol) in NMP (1.0 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 5 min and subsequently at 25 °C for 5 h. Then, water (ca. 5 mg) was added, and stirring was continued for 1 h at 50 °C. The resultant solution was treated with hydrazine monohydrate (0.200 g, 4.00 mmol) for another 12 h at the temperature. The reaction mixture was poured into 2 wt % of $NaHCO_{3aq}$. The precipitate was filtered and dispersed in water and then adjusted at pH ~7 using diluted HCl_{aq}. The resulting precipitate was collected and dried at 60 °C under reduced pressure to give white solid (96% yield). IR (KBr, cm^{-1}): 1508, 1601 (Ar−H), 1643 (C═O(NH)), 1716 (C═O(OH)), 2870, 2931, 2958 (C−H), and 1543, 3375 (N−H). ^{1}H NMR (DMSO-d_6, ppm, 40 °C): δ = 0.70–0.87 (m, 27H), 1.08–1.54 (m, 36H), 3.65–3.90 (m, 18H), 6.02 (t, 2H), 6.30 (d, 4H), 6.78–7.17 (m, 34H), 7.39 (d, 2H), 7.75 (d, 2H), 8.06 (t, 1H), 9.70 (s, 2H). Calcd: $[M]^+$ m/z = 1997.0. Found: MALDI-TOF-MS: $[M + H]^+$ = 1997.0, $[M + Na]^+$ = 2018.7, $[M + 2Na - H]^+$ = 2040.0. Anal. Calcd for $C_{120}H_{137}N_{15}O_{13}$

Scheme 2. Synthesis of Monodisperse *N*-Butylated Oligo(*p*-benzamide)s



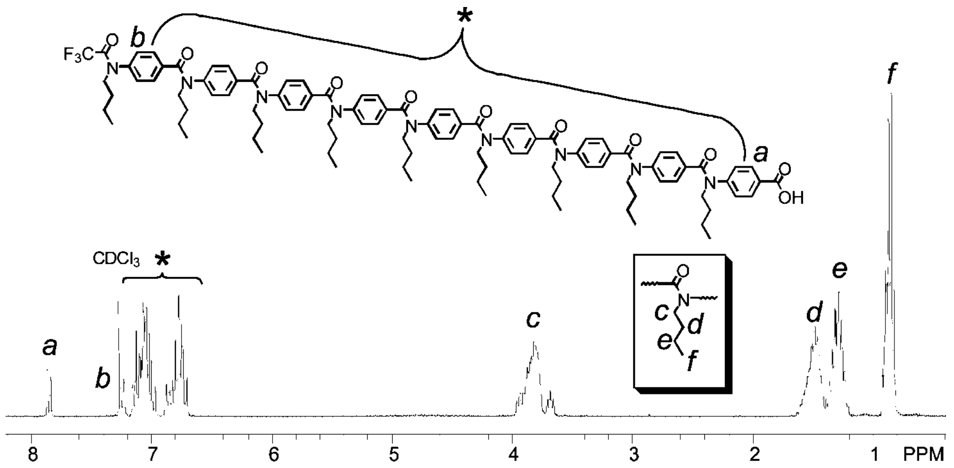


Figure 3. ^{1}H NMR spectrum of protected nonamer **7″**.

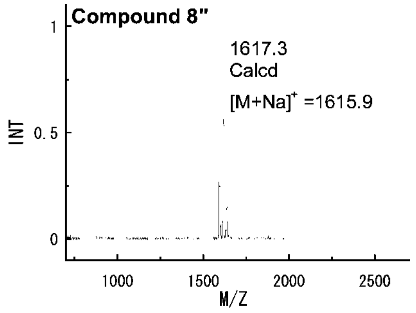


Figure 4. MALDI-TOF MS spectrum of nonamer **8″**.

0.65H$_2$0: C,70.86; H, 6.80; N, 10.35. Found: C, 70.86; H, 6.83; N, 10.37.

Preparation of G3d-rod (15). AB$_2$ building block **11** (0.236 g, 0.650 mmol) was added to a solution of G2d-rod **14** (0.252 g, 0.125 mmol) in NMP (1.0 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 5 min and subsequently at 25 °C for 5 h. Then, water (ca. 5 mg) was added and stirring was continued for 1 h at 50 °C. The resultant solution was treated with hydrazine monohydrate (0.200 g, 4.00 mmol) for another 12 h at the temperature. The reaction mixture was poured into 2 wt % of NaHCO$_{3aq}$. The precipitate was filtered and dispersed in water and then adjusted at pH ~7 using diluted HCl$_{aq}$. The resulting precipitate was collected and dried at 60 °C under reduced pressure to give white solid (96% yield). IR (KBr, cm^{-1}): 1508, 1601 (Ar−H), 1635 (C═O(NH)), 1716 (C═O(OH)), 2870, 2931, 2958 (C−H), and 1543, 3375 (N−H). ^{1}H NMR (DMSO-d_6, ppm, 40 °C): δ = 0.68–0.87 (m, 27H), 1.08–1.54 (m, 36H), 3.65–3.90 (m, 18H), 6.04 (t, 4H), 6.39 (d, 8H), 6.77–7.18 (m, 34H), 7.49 (d, 2H), 7.75 (d, 2H), 7.89 (d, 4H), 8.14 (t, 1H), 8.36 (t, 2H), 9.94 (s, 4H), 10.17 (s, 2H). Calcd: [M]$^+$ m/z = 2531.2. Found: MALDI-TOF-MS: [M + Na]$^+$ = 2553.5, [M + 2Na − H]$^+$ = 2575.5, [M + 3Na − 2H]$^+$ = 2598.3. Anal. Calcd for $C_{148}H_{161}N_{23}O_{17}$ 0.84 H$_2$O: C, 67.56; H, 6.16; N, 12.24. Found: C, 67.56; H, 6.39; N, 12.33.

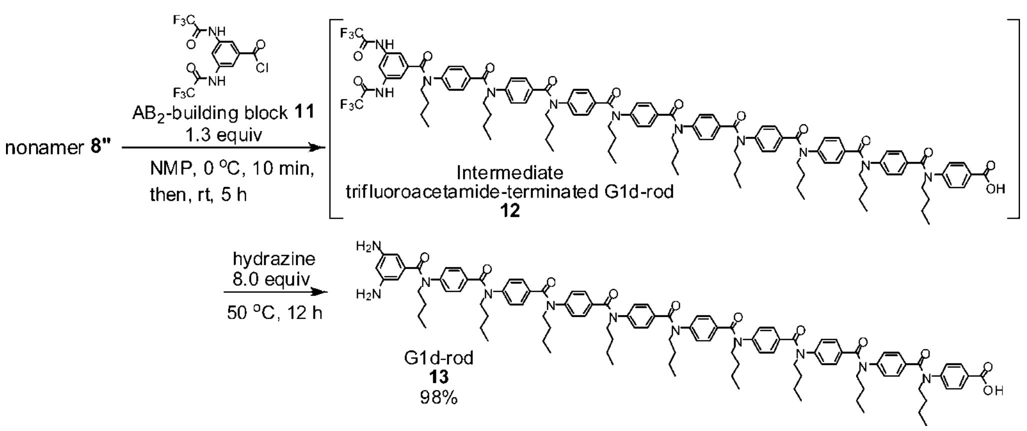
Preparation of G4d-rod (16). AB$_2$ building block **11** (0.236 g, 0.65 mmol) was added to a solution of G3d-rod **15** (0.158 g, 0.0625 mmol) in NMP (1.0 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 5 min and subsequently at 25 °C for 5 h. Then, water (ca. 5 mg) was added, and stirring was continued for 1 h at 50 °C. The resultant solution was treated with hydrazine monohydrate (0.200 g, 4.00 mmol) for another 12 h at the temperature. The reaction mixture was poured into 2 wt % of NaHCO$_{3aq}$. The precipitate was filtered and dispersed in water and then adjusted at pH ~7 using diluted HCl$_{aq}$. The resulting precipitate was collected and dried at 60 °C under reduced pressure to give white solid (97% yield). To obtain the validation of formation and isolation of the desired molecule using MALDI-TOF MS spectroscopy, the intermediate, trifluoroacetamide-terminated G4d-rod (CF$_3$-G4d-rod) was separately isolated and analyzed instead of amine-terminated G4d-rod **16**. IR (KBr, cm^{-1}): 1512, 1601 (Ar−H), 1628 (C═O(NH)), 2870, 2931, 2958 (C−H), and 1543, 3355 (N−H). ^{1}H NMR (DMSO-d_6, ppm, 40 °C): δ = 0.68–0.87 (m, 27H), 1.06–1.54 (m, 36H), 3.64–3.91 (m, 18H), 6.04 (t, 8H), 6.40 (d, 16H), 6.77–7.19 (m, 34H), 7.51 (d, 2H), 7.75 (d, 2H), 7.97 (d, 12H), 8.22 (t, 1H), 8.38 (t, 4H), 8.49 (t, 2H), 9.98 (s, 8H), 10.30 (s, 2H), 10.40 (s, 4H). Anal. Calcd for $C_{204}H_{209}N_{39}O_{25}$ 12.08H$_2$O: C, 64.06; H, 6.14; N, 14.28. Found: C, 63.72; H, 5.80; N, 13.98. Calcd for CF$_3$-G4d-rod: [M]$^+$ m/z = 5140.3. Found: MALDI-TOF-MS: [M + Na]$^+$ = 5162.8, [M + 2Na − H]$^+$ = 5184.8, [M + 3Na − 2H]$^+$ = 5206.8.

Measurements. Infrared 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 300 and 75 MHz, respectively. Deuterated chloroform (CDCl$_3$) and deuterated dimethyl sulfoxide (DMSO-d_6) were 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 or 2,5-dihydroxybenzoic acid (DHBA) as a matrix, tetrahydrofuran (THF) or chloroform as a solvent, and sodium trifluoroacetate as an additive agent.

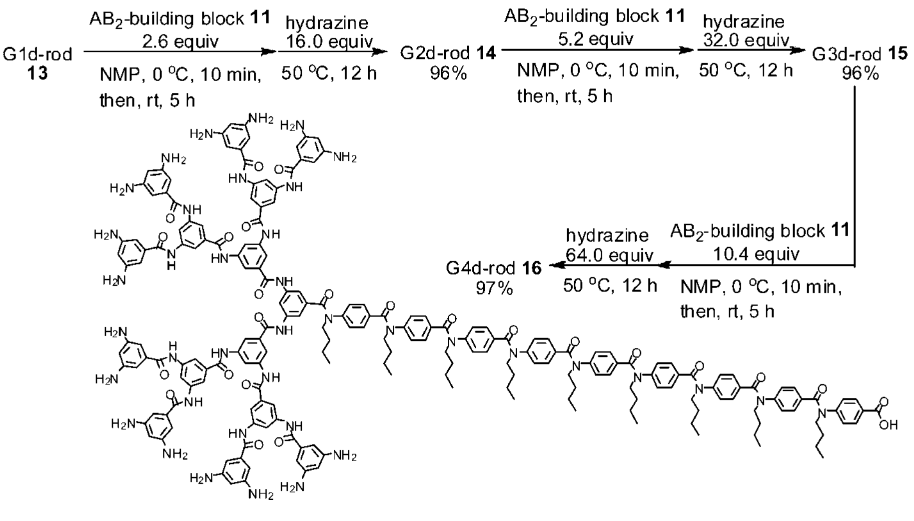
Results and Discussion

Synthesis of Rod Blocks. To synthesize rod blocks with precise lengths, 4-(N-alkylamino)benzoic acid **1** (methyl), **1′** (ethyl), and **1″** (butyl) were selected as unprotected AB monomers and synthesized according to the literature.[6] As we previously reported,[2d] a trifluoroacetamide group has high stability under acidic conditions and outstanding ability as a leaving group that enables the selective deprotection by hydrolysis under mild conditions or a transamidation with hydrazine. Thus, the AB monomer **1** was first protected with excess trifluoroacetic anhydride to produce the protected monomer **2** in 94% yield after recrystallization from *i*-PrOH (Scheme 1). The coupling reaction was carried out by the two-step method involving the activation of the carboxylic acid of a protected AB compound using thionyl chloride, followed by condensation with an unprotected AB compound. The protected dimer **3** was successfully prepared from **2** (protected) and **1** (unprotected) in 93% yield. The end trifluoroacetamide group was easily hydrolyzed by K$_2$CO$_3$ in H$_2$O/MeOH at room temperature for 30 min to yield the unprotected dimer **4** in a quantitative yield. Then, the carboxylic acid of **3** was activated using thionyl chloride and reacted with **4** to yield the protected tetramer **5** in one pot. The resulting protected tetramer **5** was quantitatively converted to the unprotected tetramer **6** by selective hydrolysis

Scheme 3. Synthesis of G1d-rod 13



Scheme 4. Synthesis of Dendron Rod Molecules



of the end group using K_2CO_3. We performed the reactions in the same manner using protected and unprotected tetramers to synthesize the protected octamer **7**. Since **7** was insoluble in H_2O/MeOH even under alkaline conditions, the hydrolysis of the end amide group in **7** was carried out in NMP using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) as a base with a small amount of water at 100 °C.

All the products were purified only by recrystallization or precipitation in almost quantitative yields and characterized by ^{1}H NMR. The ^{1}H NMR spectrum of the octamer **8** showed doublets at 7.87 and 6.13 ppm, integrated to two protons each. These signals are denoted as a and b, respectively, in Figure 1. The MALDI-TOF MS spectrum of **8** only shows signals attributed to the presumable MSs, indicating the formation and isolation of the desired octamer (Supporting Information). However, because of the poor solubility of **7** in NMP, it was difficult to synthesize the protected hexadecamer. Nevertheless, this synthetic approach for monodisperse oligoamides is highly attractive since the number of amide units dramatically propagated only through every deprotection and condensation.

In the case of using 4-(*N*-ethylamino)benzoic acid **1′** as an another unprotected AB monomer, the overall synthetic route was almost similar to that in the case of using the AB monomer **1**. The resulting protected octamer **7′** had good solubility in NMP as we expected; therefore, it could be reacted with octamer **8′** via a two-step method to provide the protected hexadecamer **9′** in 82% yield. However, protected hexadecamer **9′** could not be converted to hexadecamer **10′** due to the poor solubility of the former in NMP. Figure 2 shows the MALDI-TOF MS spectrum of protected hexadecamer **9′**, which supports its formation.

Thus, we finally applied this approach to the preparation of monodisperse oligoamides with a butyl group in the side chain with better expected solubility in NMP (Scheme 2). In this case, the resulting oligoamides have low crystallinity and low melting points due to the relatively long alkyl side chain, leading to difficulties in their purification by recrystallization or reprecipitation. Therefore, to reduce the number of purification steps, a one-pot multiple addition condensation reaction was applied. The protected monomer **2″** was obtained from the reaction of AB monomer **1″** and excess trifluoroacetic anhydride. **2″** was converted into the corresponding acid chloride by adding 1.04 equiv of thionyl chloride to it at 0 °C for 10 min and then at room temperature for 30 min in NMP. Then, the following condensation with **1″** at room temperature for 1 h yielded the corresponding protected dimer **3″** in situ almost quantitatively. To this solution, another 1.04 equiv of thionyl chloride was added; subsequently, **1″** was added in one pot to afford the protected trimer **4″** in 85% yield after recrystallization from hexane/THF. **4″** was then successfully deprotected by a transamidation reaction with hydrazine at 50 °C for 6 h to yield the trimer **5″** in 95% yield. In a similar manner, the protected nonamer **7″** was synthesized by the repetition activation of the carboxylic acid of a protected AB compound using thionyl chloride and sequential condensation with **5″**. The yield of the protected nonamer after reprecipitation with 2-butanone/hexane was 67%. The relatively low yield probably resulted from the incomplete condensation of the protected hexamer **6″** with **5″**

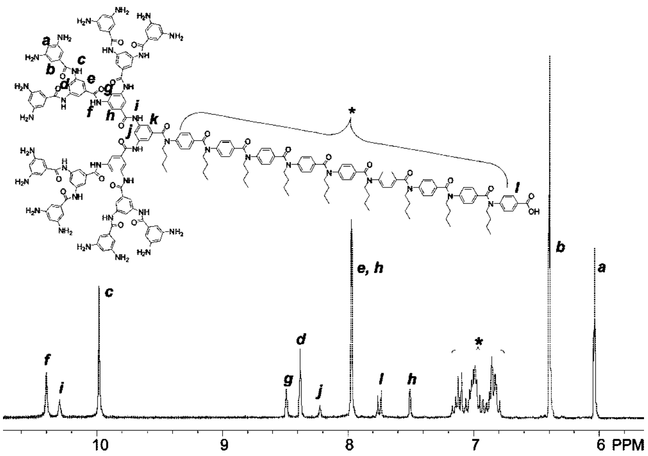


Figure 5. ^{1}H NMR spectrum of G4d-rod **16**.

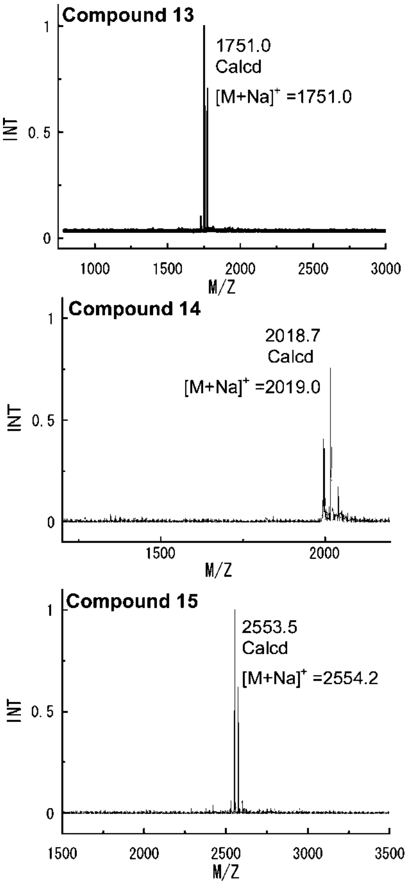


Figure 6. MALDI-TOF MS spectra of dendron rod **13**, **14**, and **15**.

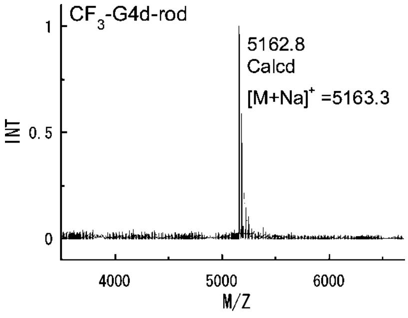


Figure 7. MALDI-TOF MS spectrum of CF$_3$-G4d-rod.

due to the heterogeneous reaction system. Finally, the nonamer **8″** was quantitatively obtained by a transamidation of **7″** with hydrazine at 50 °C for 12 h. Despite their moderate solubility in NMP (in weight percent), it was difficult to use **7″** and **8″** in the subsequent reaction because sufficient concentrations of their solutions (in mole percent) were not achieved due to their relatively high molecular weights resulting from the butyl group in their side chains.

The ^{1}H NMR spectrum of **7″** shows two doublets at 7.24 and 7.85 ppm, integrated to two protons each. These signals are denoted by a and b, respectively, in Figure 3. The MALDI-TOF MS spectrum of **7″** (Supporting Information) and **8″** (Figure 4) indicate their molecular weights $[M + Na]^+$ to be 1713 and 1616.9 Da, which are close to the calculated molecular weights of 1714 and 1614.9 Da, respectively. These findings clearly indicate the formation of the desired molecules.

Synthesis of Dendrimers. The dendron block was prepared by a divergent approach from the secondary amine group of the *N*-butylated nona(*p*-benzamide) **8″**. As reported previously,[2d] the condensation and deprotection reactions of these growth processes can be performed in one pot using 3,5-bis(trifluoroacetamido)benzoyl chloride **11** as an AB$_2$ building block. The reaction of **8″** with a slight excess of **11** quantitatively yields the intermediate, trifluoroactamide-terminated G1d-rod (first generation dendron coupled with rod block) molecule **12** in situ. After the hydrolysis of the acid chloride group of the unconverted-excess AB$_2$ building block, **12** was converted to the amine-terminated G1d-rod **13** by a transamidation reaction with excess hydrazine. Since all the byproducts in the resulting final solution are soluble in alkaline water, G1d-rod **13** can be purified simply by precipitation in NaHCO$_{3aq}$ in a quantitative yield (Scheme 3).

The larger amine-terminated rod dendron molecules were synthesized using a similar protocol and isolated in excellent yields after precipitation in alkaline water (Scheme 4). Finally, G4d-rod **16** was successfully obtained simply through a four-step process from **8″**.

Characterization of Dendrimers. The structures of the dendrimers were characterized by IR and ^{1}H NMR spectroscopies and elemental analyses. The IR spectrum of **16** showed strong absorptions at 3355 and 1628 cm^{-1}, characteristic of the N−H and C═O stretchings of the amino and amide carbonyl groups, respectively. The ^{1}H NMR spectrum of **16** showed signals corresponding to the amide protons (c, f, and i) at 9.98, 10.30, and 10.40 ppm and aromatic protons (a and b) of the end unit at 6.04 and 6.40 ppm, respectively (Figure 5).

The MALI-TOF MS spectra of **13**, **14**, and **15** indicate their molecular weights $[M + Na]^+$ to be 1751.0, 2018.7, and 2553.5 Da, which are close to the calculated molecular weights of 1751.0, 2019.0, and 2554.2 Da, respectively (Figure 6). The G4d-rod could not be analyzed by the MALDI-TOF MS spectrum probably because of strong intermolecular interactions between the terminated amines and dendrimers. Therefore, the intermediate, trifluoroacetamide-terminated G4d-rod (CF$_3$-G4d-rod), which was expected to show weak interactions, was analyzed by MALDI-TOF MS spectroscopy (Figure 7). The spectrum exhibited the desired signals at *m/z* $[M + Na]^+$ 5162.8, $[M - H + 2Na]^+$ 5184.8, $[M - 2H + 3Na]^+$ 5206.8, and $[M - 3H + 4Na]^+$ 5228.5 Da. These findings clearly indicate the formation of the desired dendrimers.

The thermal property of **8″** and dendrimers **13**, **14**, **15**, and **16** were measured by DSC analysis. **8″** and **13** exhibited the melting point at 95 and 150 °C in the first scan and the glass transition temperature (T_g) at 90 and 105 °C in the second and third scans, respectively. On the other hand, no melting points and T_gs of **14**, **15**, and **16** were observed.

Conclusions

We have developed a facile synthesis of a tadpole-shaped dendrimer possessing *N*-butylated nona(*p*-benzamide) as a rod block with a precise length and dendritic block based on 3,5-diaminobenzoic acid. In this method, the monodisperse *N*-alkylated oligoamides (R = methyl, ethyl, butyl) were prepared by an accelerated approach using thionyl chloride as an activating agent and trifluoroacetamide as a protecting group. Using the resulting nonamer **8″** as a core molecule, the dendritic block was successfully prepared in excellent yields by a divergent approach using a two-step method with the AB_2 building block **11**. Finally, the fourth-generation tadpole-shaped dendrimer **16** was obtained via this efficient route. This novel structure is particularly attractive as a building block of a self-assembly because the strong hydrogen bonding between the polyamide dendritic blocks and interaction of alkyl pendant groups between the rod blocks would enhance the stability of the resulting self-assembled architectures. Furthermore, since the rod moiety has an exact length and the oligomers/polymers of *N*-alkyl-*p*-benzamide show a helical conformation as reported by Yokozawa et al.,[7] this dendron rod block molecule has a very persistent precise structure that would enable the direct application of the theory relating the molecular geometric shape to the final self-assembling form.[5] Modifying the functionalities either at the periphery or the focal point of this novel tadpole dendrimer would increase its promising applications for the fabrication of self-assembled architectures.

Supporting Information Available: Experimental procedures and characterization of *N*-alkylated oligo(*p*-benzamide)s. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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