Efficient Synthesis of First- and Second-Generation, Water-Soluble Dendronized Polymers

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ABSTRACT: The first and second generation neutral, water-soluble dendronized polymethacrylates **PG1** and **PG2**, respectively, carrying hydroxyl groups in the periphery are reported. The threefold branched repeating unit of the dendrons are synthesized on the multigram scale using gallic acid as the branching point and tri(oxyethylene) (TEG) units as the linker. All dendrons and their corresponding macromonomers carry either free or THP-protected hydroxyl groups in the periphery. **PG1** and **PG2** were obtained by radical polymerization in bulk, in DMF, as well as in aqueous solution. The polymerization of the hydroxyl-terminated G1 monomer **3b** proceeded at an exceptionally high rate in water. All polymers have high molar masses and are fully water-soluble. Their glass transition temperatures are in the range of −50 to −40 °C.

1. Introduction

Dendronized polymers are a novel class of branched polymers which carry dendrons at each repeat unit.[1] They are comprised of representatives which differ in dendron generation, nature of the backbone and branchwork, peripheral functional groups, and alike. Their unique structural characteristics[1a] and promising applications[2] have triggered intense research activity. Normally, dendronized polymers are synthesized via the macromonomer route even though they can also be accessed by the attach-to route or combined approaches. For a successful application of the former route, high concentrations of the polymerizable unit is essential. Many macromonomers employed so far are solid or crystalline, and highly concentrated polymerization media may therefore be difficult to achieve. Though liquid monomers tend to be more difficult to purify than solid ones, regarding the achievement of high concentrations they are often superior. Most dendronized polymers are soluble in organic solvents, which limits their usability for water-based applications.[3] A few charged dendronized polymers were reported to be water-soluble in certain pH ranges.[4] Charged polymers may, however, have disadvantages specifically for biomedical applications because the charges can provoke cell lysis and related unwanted effects. Oligo(oxyethylene)s (OEGs) and their derivatives are interesting water-soluble components. They were often found to be nontoxic and biocompatible in various applications, and it is therefore not surprising that OEG units were also used in dendrimers. In this latter connection, they were employed as the core, internal connectors, or surface groups.[5] OEG units have also been used for the construction of amphiphilic dendronized polymers.[6] Gallic acid derivatives with three OEG chains have been widely used whenever water-solubility mattered to more or less of a degree.[7] Though threefold branching units are known in dendrimer chemistry, there are surprisingly few reports in the literature combing the functionality and water-solubilizing power of threefold OEG substituted gallic acid derivatives for the synthesis of higher generation dendrimers.[8]

Here we report on the synthesis of non-charged, yet fully water-soluble first (G1) and second generation (G2) dendronized polymethacrylates, **PG1** and **PG2**, respectively (Figure 1). Their main structural features are (a) 3-fold branching units derived from gallic acid, (b) short OEG segments between the branching points, and (c) peripheral hydroxyl groups for further modifications.

2. Experimental Section

Materials. Monotosylated triethylene glycol (TEG−Ts) was synthesized similarly to the literature procedure[9] with the modifications that THF/water was used instead of DCM, NaOH/KI instead of NEt_3/KI, and no Ag_2O added. Azobis(isobutyronitrile) (AIBN) was recrystallized twice from methanol. Tetrahydrofuran (THF) was refluxed over lithium aluminum hydride (LAH) and dichloromethane (DCM) distilled from CaH_2 for drying. Other reagents and solvents were purchased at reagent grade and used without further purification. All reactions were run under a nitrogen atmosphere. Macherey-Nagel precoated TLC plates (silica gel 60 G/UV_{254}, 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Silica gel 60 M (Macherey-Nagel, 0.04−0.063 mm, 230−400 mesh) was used as the stationary phase for column chromatography.

Measurements. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 500 (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometers, and chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. High-resolution MALDI-TOF-MS analyses were performed by the MS service of the Laboratorium für Organizche Chemie, ETH Zürich, on IonSpec Ultra instruments. Elemental analyses were performed for the three key polymer samples (two **PG1** and one **PG2**) by the Mikrolabor of the Laboratorium für Organizche Chemie, ETH Zürich. The data do not strictly meet the calculated ones which are believed to be due to adhered water. Gel permeation chromatography (GPC) measurements were carried out by using a PL-GPC 220 instrument with a 2×PL-Gel Mix-B LS column set (2 × 30 cm) equipped with refractive index (RI), viscosity, and light scattering (LS; 15° and 90° angles) detectors, and LiBr (1 g L^{-1}) in DMF as the eluent at 45 °C. Universal calibration was performed with poly(methyl methacrylate) standards in the range of M_p = 2680 to 3 900 000 (Polymer Laboratories Ltd, UK). Differential scanning calorimetry (DSC) measurements were performed using the DSC Q1000 differential scanning calorimeter from TA Instruments in a temperature range of −80 ∼ +200 °C with a heating rate of 10 °C min^{-1}. Samples of a total weight ranging between 3 and 10 mg were closed into aluminum pans of 40 μL, covered by a holed cap, and analyzed under a nitrogen atmosphere. The glass transient temperature (T_g) was taken in the second heating

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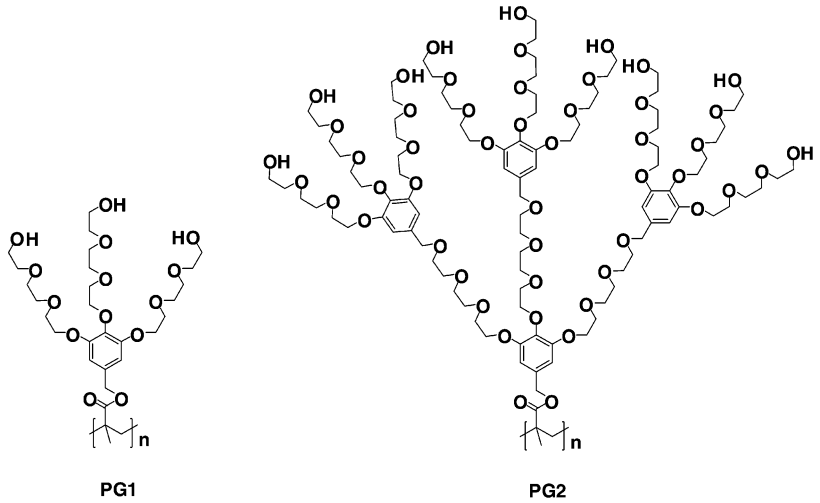


Figure 1. Chemical structures of the water-soluble dendronized polymers discussed in this study.

run. Dynamic light scattering (DLS) measurements were performed with a Zetasizer Nano (Malvern, UK) instrument using a light scattering apparatus equipped with a He−Ne (633 nm) laser. The measurements were made at the scattering angle of $\theta = 173°$ (backscattering detection). Solutions (0.1 wt %) of the dendronized polymers for DLS measurements were filtrated with a 0.45 μm filter prior to use.

Syntheses. Methyl 3,4,5-Tris(2-(2-(2-hydroxyethoxy)ethoxy)-ethoxy)benzoate (2a). A mixture of methyl gallate (18.15 g, 98.57 mmol), TEG−Ts (120.00 g, 394.27 mmol), KI (12.62 g, 78.85 mmol), and K_2CO_3 (136.23 g, 985.70 mmol) in dried DMF was stirred at 80 °C over 24 h. After evaporation of DMF in vacuo, the residue was extracted with DCM. The organic phase was washed sequentially with $NaHCO_3$ and brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo. Purification by column chromatography with DCM/MeOH (15:1, v/v) afforded **2a** as a yellow oil (95.0 g, 83%). ^{1}H NMR ($CDCl_3$): $\delta = 3.07$ (s, 1H, OH), 3.59 (m, 6H, CH_2), 3.66 (m, 6H, CH_2), 3.71 (m, 12H, CH_2), 3.82 (t, 2H, CH_2), 3.87 (m, 7H, $CH_2 + CH_3$), 4.20 (t, 4H, CH_2), 4.26 (t, 2H, CH_2), 7.28 (s, 2H, CH). ^{13}C NMR ($CDCl_3$): $\delta = 52.39$, 61.68, 61.83, 68.87, 69.68, 70.45, 70.53, 70.68, 70.73, 70.94, 72.64, 72.81, 72.88, 109.02, 125.23, 142.46, 152.34, 166.72. HR-MS (MALDI): *m*/*z* 603.2633 $[M + Na]^+$.

Methyl 3,4,5-Tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)-ethoxy)ethoxy) ethoxy)benzoate (2b). 3,4-Dihydro-2*H*-pyran (DHP) (26.08 g, 310.01 mmol) and pyridinium toluenesulfonate (PPTS) (7.79 g, 31.00 mmol) were added to a solution of **2a** (30.00 g, 51.67 mmol) in dry DCM at −5 °C, and the mixture was stirred for another 6 h at room temp. After successive washing with aqueous $NaHCO_3$ solution and brine, the organic phase was dried over $MgSO_4$. Purification by column chromatography with hexane/ethyl acetate (1:5, v/v) afforded **2b** as a slightly yellow oil (38.50 g, 90%). ^{1}H NMR ($CDCl_3$): $\delta = 1.49$ (m, 6H, CH_2), 1.55 (m, 6H, CH_2), 1.68 (m, 3H, CH_2), 1.79 (m, 3H, CH_2), 3.47 (m, 3H, CH_2), 3.58 (m, 3H, CH_2), 3.66 (m, 12H, CH_2), 3.68 (m, 6H, CH_2), 3.78 (t, 2H, CH_2), 3.85 (m, 13H, CH_2), 4.18 (m, 6H, CH_2), 4.60 (s, 3H, CH), 7.27 (s, 2H, CH). ^{13}C NMR ($CDCl_3$): $\delta = 19.64$, 25.57, 30.71, 52.31, 62.37, 66.79, 69.00, 69.77, 70.69, 70.73, 70.83, 71.01, 72.58, 99.09, 109.15, 125.08, 142.71, 152.45, 166.73. HR-MS (MALDI): *m*/*z* 855.4363 $[M + Na]^+$.

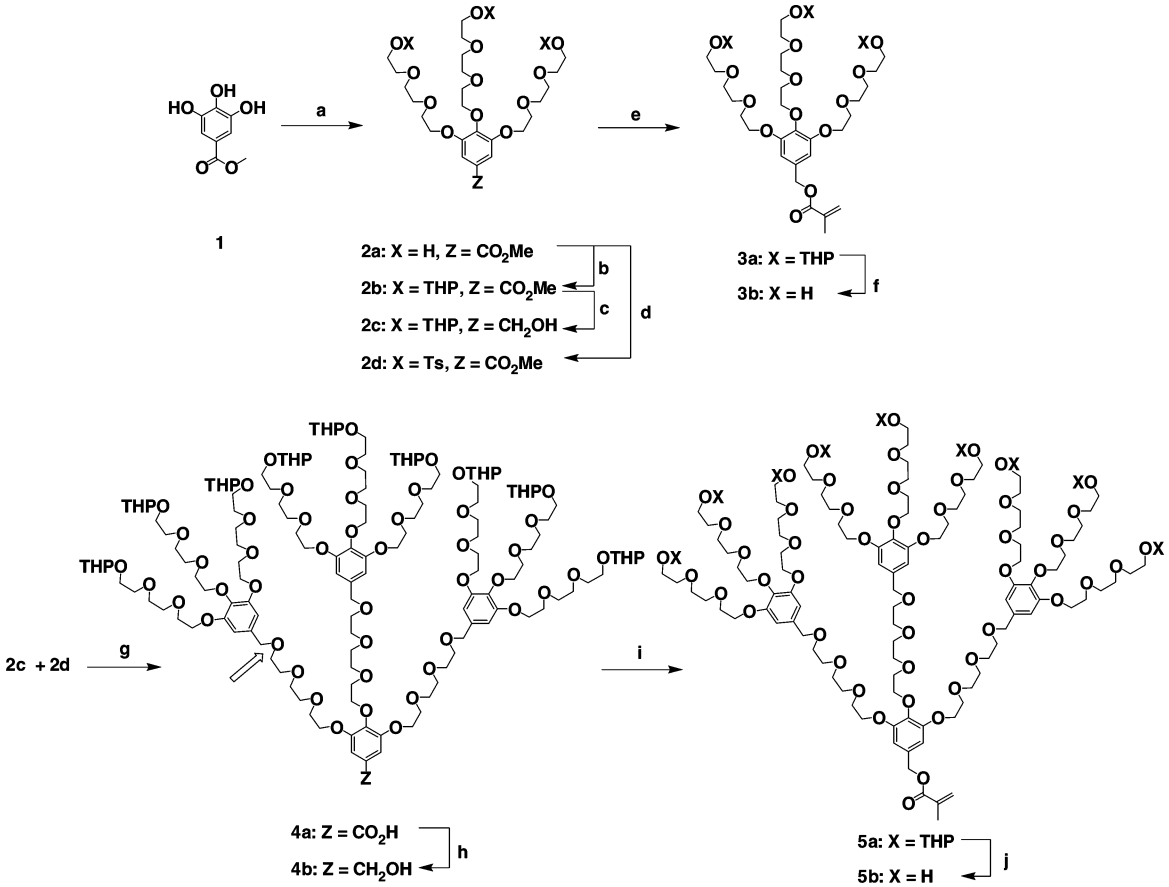
3,4,5-Tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy)ethoxy)-ethoxy)benzyl Alcohol (2c). LAH (2.60 g, 68.43 mmol) was added to a solution of **2b** (38.0 g, 45.62 mmol) in dry THF (300 mL) at −5 °C, the mixture was stirred for 30 min, warmed to room temp., and then stirred for another 3 h. The reaction was quenched by dropwise addition of water (15 mL), 10% NaOH (45 mL), and water (40 mL). The resulting precipitate was filtered, and THF was evaporated. The residue was dissolved in DCM and then washed with brine. After drying over $MgSO_4$, purification by column chromatography with DCM/MeOH (20:1, v/v) afforded **2c** (33.60 g, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (m, 6H, CH_2), 1.58 (m, 6H, CH_2), 1.68 (m, 3H, CH_2), 1.80 (m, 3H, CH_2), 3.47 (m, 3H, CH_2), 3.58 (m, 3H, CH_2), 3.65 (m, 12H, CH_2), 3.68 (m, 6H, CH_2), 3.76 (t, 2H, CH_2), 3.82 (m, 10H, CH_2), 4.11 (t, 2H, CH_2), 4.14 (t, 4H, CH_2), 4.54 (s, 2H, CH_2), 4.60 (t, 3H, CH), 6.60 (s, 2H, CH). ^{13}C NMR ($CDCl_3$): $\delta = 19.60$, 25.56, 30.69, 62.36, 65.30, 66.80, 69.03, 69.97, 70.68, 70.81, 70.85, 70.97, 72.42, 99.09, 106.74, 136.92, 137.91, 152.83. HR-MS (MALDI): *m*/*z* 827.4414 $[M + Na]^+$.

Methyl 3,4,5-Tris(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)-benzoate (2d). *p*-Tosyl chloride (TsCl) (15.76 g, 82.67 mmol) was added to a mixture of **2a** (8.00 g, 13.78 mmol), freshly prepared Ag_2O (14.37 g, 62.01 mmol), KI (13.23 g, 82.67 mmol) in dry DCM (200 mL) at 0 °C. The mixture was stirred for 30 min and then warmed to room temp, and stirring was continued for another 12 h at room temp. After washing with brine, the organic phase was dried over $MgSO_4$. Purification by column chromatography with DCM/MeOH (30:1, v/v) afforded **2d** (11.50 g, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 2.36$ (s, 9H, CH_3), 3.52 (m, 8H, CH_2), 3.61 (m, 12H, CH_2), 3.70 (t, 2H, CH_2), 3.77 (m, 4H, CH_2), 3.82 (s, 3H, CH_3), 4.08 (m, 10H, CH_2), 4.13 (t, 2H, CH_2), 7.23 (s, 2H, CH), 7.26 (d, 6H, CH), 7.72 (d, 6H, CH). ^{13}C NMR ($CDCl_3$): $\delta = 21.73$, 52.32, 61.80, 68.77, 68.80, 68.96, 69.40, 69.48, 69.51, 69.75, 70.38, 70.53, 70.74, 70.83, 70.86, 72.51, 109.03, 125.09, 128.04, 130.00, 133.02, 142.60, 145.00, 145.05, 152.41, 166.65. HR-MS (MALDI): *m*/*z* 1065.291 $[M + Na]^+$.

3,4,5-Tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy)ethoxy)-ethoxy)benzyl Methacrylate (3a). Methacryloyl chloride (MAC) (1.17 g, 11.18 mmol) was added dropwise to a mixture of **2c** (6.00 g, 7.45 mmol), TEA (3.01 g, 29.80 mmol), and DMAP (0.15 g) in dry DCM at 0 °C over 5 min. The mixture was stirred for another 4 h at room temp. After successive washing with aqueous $NaHCO_3$ solution and brine, the organic phase was dried over $MgSO_4$. Purification by column chromatography with DCM/MeOH (20:1, v/v) afforded **3a** (6.0 g, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.50$ (m, 6H, CH_2), 1.56 (m, 6H, CH_2), 1.69 (m, 3H, CH_2), 1.80 (m, 3H, CH_2), 1.95 (s, 3H, CH_3), 3.48 (m, 3H, CH_2), 3.60 (m, 3H, CH_2), 3.66 (m, 12H, CH_2), 3.70 (m, 6H, CH_2), 3.77 (t, 2H, CH_2), 3.84 (m,10H, CH_2), 4.13 (m, 6H, CH_2), 4.61 (t, 3H, CH), 5.05 (s, 2H, CH_2), 5.57 (m, 1H, CH_2), 6.13 (m, 1H, CH_2), 6.59 (s, 2H, CH). ^{13}C NMR ($CDCl_3$): $\delta = 18.32$, 19.45, 25.39, 30.53, 62.17, 66.36, 66.60, 68.89, 69.69, 70.50, 70.54, 70.63, 70.81, 72.29, 98.90, 107.88, 125.81, 136.15, 138.14, 152.64, 167.11. HR-MS (MALDI): *m*/*z* 895.4678 $[M + Na]^+$.

3,4,5-Tris(2-(2-(2-hydroxylethoxy)ethoxy)ethoxy)benzyl Methacrylate (3b). *p*-Toluenesulfonic acid (PTSA) (1.31 g, 6.87 mmol) was added to a solution of **3a** (4.00 g, 4.58 mmol) in MeOH (50 mL), and the mixture was stirred for 2 h at room temp. Then MeOH was evaporated under vacuum at room temp. The residue was dissolved in DCM and successively washed with aqueous $NaHCO_3$

Scheme 1. Synthesis of Dendrons (2 and 4) and Corresponding Macromonomers (3 and 5)[a]



[a] Reagents and conditions: (a) TEG-Ts, K_2CO_3, KI, DMF, 80 °C, 24 h (83%); (b) DHP, PPTS, DCM, −5 to 25 °C, 6 h (90%); (c) LAH, THF, −5 to 25 °C, 3.5 h (92%); (d) TsCl, Ag_2O, KI, DCM, 0 to 25 °C, 12.5 h (80%); (e) MAC, DMAP, TEA, DCM, 0 to 25 °C, 4 h (92%); (f) PTSA, MeOH, room temp, 2 h (82%); (g) KI, 15-crown-5, NaH, THF, room temp, 12 h (57%); (h) *N*-methylmorpholine, ethyl chloroformate, $NaBH_4$, THF, −15 to 25 °C (83%); (i) MAC, DMAP, TEA, DCM, 0 to 25 °C, 5 h (83%); (j) PPTS, MeOH, 50 °C, 10 h (88%). The arrow indicates the position that is cleaved during the focal point reduction with LAH (see text).

solution and brine. After drying over $MgSO_4$, purification by column chromatography with DCM/MeOH (10:1, v/v) afforded **3b** (2.30 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.93 (m, 3H, CH_3), 3.56 (m, 6H, CH_2), 3.64 (m, 6H, CH_2), 3.69 (m, 12H, CH_2), 3.78 (t, 2H, CH_2), 3.83 (t, 4H, CH_2), 4.16 (m, 6H, CH_2), 5.04 (s, 2H, CH_2), 5.56 (m, 1H, CH_2), 6.11 (m, 1H, CH_2), 6.58 (s, 2H, CH). ^{13}C NMR ($CDCl_3$): δ = 18.51, 61.60, 61.78, 66.53, 68.87, 69.74, 70.42, 70.47, 70.50, 70.61, 70.62, 70.92, 72.47, 72.78, 72.83, 107.81, 126.08, 131.81, 136.30, 138.19, 152.69, 167.32. HR-MS (MALDI): *m*/*z* 643.2947 [M + Na]$^+$.

3,4,5-Tris(2-(2-(2-(3,4,5-tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy) ethoxy)ethoxy)benzyloxy)ethoxy)ethoxy)ethoxy)-benzoic Acid (4a). Compound **2d** (2.94 g, 2.82 mmol) in dry THF (50 mL) was added dropwise to a mixture of **2c** (7.50 g, 9.32 mmol), KI (0.27 g, 1.69 mmol), 15-crown-5 (2.06 g, 9.35 mmol), and NaH (0.67 g, 27.90 mmol) in dry THF (200 mL). The mixture was stirred for 12 h at room temp. MeOH was added to quench excess NaH, and solvent was evaporated. The residue was dissolved in DCM and successively washed with aqueous $NaHCO_3$ solution and brine. After drying over $MgSO_4$, purification by column chromatography with DCM/MeOH (15:1, v/v) afforded **4a** (4.70 g, 57%) as a slightly yellow oil. ^{1}H NMR (CD_2Cl_2): δ = 1.53 (m, 36H, CH_2), 1.68 (m, 9H, CH_2), 1.80 (m, 9H, CH_2), 3.47 (m, 9H, CH_2), 3.55−3.71 (m, 87H, CH_2), 3.76 (t, 8H, CH_2), 3.84 (m, 34H, CH_2), 4.09−4.18 (m, 24H, CH_2), 4.42 (s, 6H, CH_2), 4.60 (t, 9H, CH), 6.59 (s, 6H, CH), 7.31 (s, 2H, CH). ^{13}C NMR (CD_2Cl_2): δ = 19.70, 25.63, 30.76, 62.24, 66.75, 68.78, 68.86, 69.63, 69.68, 69.73, 69.87, 70.47, 70.57, 70.65, 70.71, 70.79, 70.86, 72.41, 72.42, 72.52, 73.20, 99.05, 106.79, 106.82, 109.01, 125.41, 134.19, 137.60, 142.42, 152.38, 152.70, 167.32. HR-MS (MALDI): *m*/*z* 2948.557 [M + Na]$^+$.

3,4,5-Tris(2-(2-(2-(3,4,5-tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy) ethoxy)ethoxy)benzyloxy)ethoxy)ethoxy)ethoxy)-benzyl Alcohol (4b). *N*-Methylmorpholine (0.58 g, 5.72 mmol) and ethyl chloroformate (0.62 g, 5.72 mmol) were added sequentially to a solution of **4a** (4.20 g, 1.43 mmol) in dry THF (100 mL) at −15 °C, and the mixture was stirred for 1 h. Then $NaBH_4$ (0.43 g, 11.44 mmol) was added at −5 °C, and the reaction mixture was stirred for another 2 h. Water was added to quench the reaction, and THF was evaporated. The residue was dissolved in DCM and then successively washed with aqueous $NaHCO_3$ solution and brine. After drying over $MgSO_4$, purification by column chromatography with DCM/MeOH (20:1, v/v) afforded **4b** (3.46 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.53 (m, 36H, CH_2), 1.68 (m, 9H, CH_2), 1.80 (m, 9H, CH_2), 3.47 (m, 9H, CH_2), 3.52−3.69 (m, 87H, CH_2), 3.76 (t, 8H, CH_2), 3.83 (m, 34H, CH_2), 4.09−4.20 (m, 24H, CH_2), 4.43 (s, 6H, CH_2), 4.53 (s, 2H, CH_2), 4.59 (t, 9H, CH), 6.59 (s, 6H, CH), 6.61 (s, 2H, CH). ^{13}C NMR (CD_2Cl_2): δ = 19.58, 25.50, 30.64, 59.12, 61.94, 62.11, 64.74, 66.27, 66.61, 68.36, 68.70, 68.91, 69.52, 69.72, 69.76, 70.45, 70.53, 70.57, 70.74, 72.30, 73.04, 98.93, 105.93, 106.72, 131.00, 134.05, 137.27, 152.58. HR-MS (MALDI): *m*/*z* 2934.5879 [M + Na]$^+$.

3,4,5-Tris(2-(2-(2-(3,4,5-tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy) ethoxy)ethoxy)benzyl)ethoxy)ethoxy)ethoxy)benzyl Methacrylate (5a). MAC (0.70 g, 6.69 mmol) was added dropwise to a mixture of **4b** (3.90 g, 1.34 mmol), TEA (0.68 g, 6.69 mmol), and DMAP (0.15 g) in dry DCM (100 mL) at 0 °C over 5 min. The mixture was stirred for 5 h at room temp before MeOH (2 mL) was added. After successive washing with aqueous $NaHCO_3$ solution and brine, the organic phase was dried over $MgSO_4$. Purification by column chromatography with ethyl acetate/MeOH

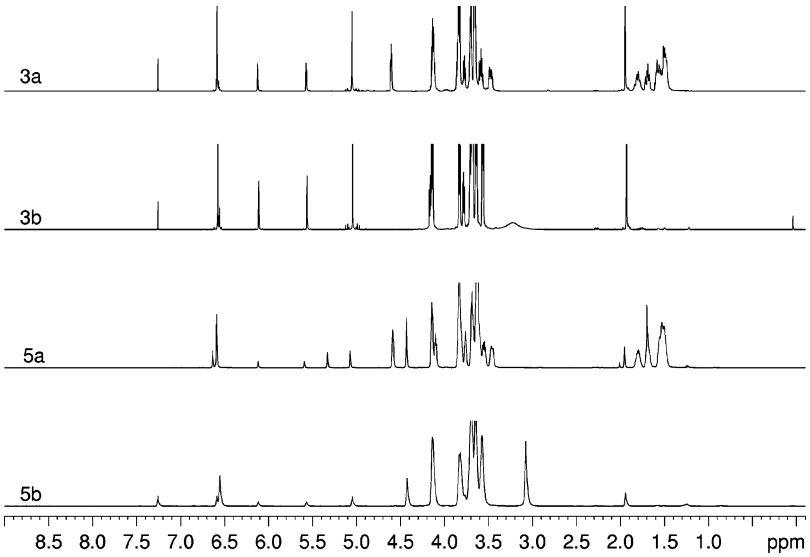


Figure 2. ^{1}H NMR spectra of **3a** (in $CDCl_3$), **3b** (in $CDCl_3$), **5a** (in CD_2Cl_2), and **5b** (in $CDCl_3$) at room temperature.

(10:1, v/v) afforded **5a** (3.30 g, 83%) as a colorless oil. ^{1}H NMR (CD_2Cl_2): δ = 1.53 (m, 36H, CH_2), 1.68 (m, 9H, CH_2), 1.80 (m, 9H, CH_2), 1.95 (s, 3H, CH_3), 3.47 (m, 9H, CH_2), 3.53−3.70 (m, 87H, CH_2), 3.76 (t, 8H, CH_2), 3.83 (m, 34H, CH_2), 4.09−4.14 (m, 24H, CH_2), 4.43 (s, 6H, CH_2), 4.59 (t, 9H, CH), 5.07 (s, 2H, CH_2), 5.60 (s, 1H, CH_2), 6.12 (s, 1H, CH_2), 6.60 (s, 6H, CH), 6.64 (s, 2H, CH). ^{13}C NMR (CD_2Cl_2): δ = 18.27, 19.73, 25.64, 30.78, 62.25, 66.45, 66.74, 68.81, 68.86, 69.65, 69.81, 69.86, 70.59, 70.67, 70.71, 70.88, 72.44, 73.20, 99.06, 106.79, 107.47, 125.57, 131.86, 134.16, 136.54, 137.62, 138.20, 152.72, 152.78, 167.07. HR-MS (MALDI): *m*/*z* $[M + Na]^+$.

3,4,5-Tris(2-(2-(2-(3,4,5-tris(2-(2-(2-hydroxylethoxy)ethoxy)-ethoxy)benzyl-oxy)ethoxy)ethoxy)ethoxy)benzyl Methacrylate (5b). PPTS (65.2 mg, 0.26 mmol) was added to a solution of **5a** (0.43 g, 0.14 mmol) in MeOH (20 mL), and the mixture was stirred for 10 h at 50 °C. Then MeOH was evaporated in vacuum at room temp, and the residue was extracted with DCM. The DCM phase was washed with brine three times. Removal of the solvent afforded **5b** (0.28 g, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.94 (s, 3H, CH_3), 3.57−3.70 (m, 96H, CH_2), 3.82 (m, 24H, CH_2), 4.14 (m, 24H, CH_2), 4.43 (s, 6H, CH_2), 5.05 (s, 2H, CH_2), 5.57(s, 1H, CH_2), 6.12 (s, 1H, CH_2), 6.55 (s, 6H, CH), 6.59 (s, 2H, CH). ^{13}C NMR ($CDCl_3$): δ = 18.50, 61.76, 61.80, 66.53, 68.84, 69.03, 69.54, 69.86, 70.53, 70.63, 70.68, 70.76, 70.81, 70.95, 72.49, 72.83, 72.94, 73.34, 107.12, 108.06, 126.05, 131.72, 134.09, 136.32, 137.68, 138.49, 152.66, 152.79, 167.31. HR-MS (MALDI): *m*/*z* 2247.093 $[M + Na]^+$.

General Procedure for Polymerization in DMF Solution (A). The required amounts of the monomer and AIBN (0.5 wt % to the monomer) were dissolved in DMF inside a Schlenk tube. The solution was thoroughly deoxygenated by several freeze−pump−thaw cycles and then stirred at 60 °C for the desired time. After cooling to room temp, the THP protected polymer was dissolved in DCM and purified by column chromatography with DCM as the eluent, while the hydroxyl group covered polymers were dissolved in water, and the aqueous phase was washed with DCM before to lyophilization.

General Procedure for Polymerization in Bulk (B). The required amounts of the monomer and AIBN (0.5 wt % to the monomer) were added to a Schlenk tube. The mixture was thoroughly deoxygenated by several freeze−pump−thaw cycles and then stirred at 60 °C for the desired time. After cooling to room temp, the THP protected polymer was dissolved in DCM and purified by silica gel column chromatography with DCM as the eluent, while the hydroxyl group covered polymer was dissolved in water. The aqueous phase was washed with DCM and then lyophilized.

General Procedure for Polymerization in Aqueous Solution (C). The required amounts of the monomer and 4,4′-azobis(4-cyanovaleric acid) (ACVA) (0.7 wt % to the monomer) were dissolved in water inside a Schlenk tube. The solution was thoroughly deoxygenated by several freeze−pump−thaw cycles and then stirred at 60 °C for desired time. After cooling to room temp, the polymer was dissolved in water and the aqueous phase washed with DCM prior to lyophilization.

Poly(3,4,5-tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy)-ethoxy)ethoxy) benzyl methacrylate) (THP−G1). Route 1: According to general procedure A from **3a** (0.6 g), AIBN (3 mg), and DMF (0.4 mL), polymerization for 19 h yielded **THP−PG1** as a colorless gel (0.40 g, 67%). ^{1}H NMR (CD_2Cl_2): δ = 0.88 (br, 2H, CH_3), 1.09 (br, 1H, CH_3), 1.50−1.54 (m, 12H, CH_2), 1.67−1.72 (m, 3H, CH_2), 1.77−1.79 (m, 3H, CH_2), 3.43−3.47 (m, 3H, CH_2), 3.50−3.63 (m, 21H, CH_2), 3.74−3.84 (m, 12H, CH_2), 4.06 (br, 6H, CH_2), 4.57−4.59 (m, 3H, CH), 4.80 (br, 2H, CH_2), 6.52 (br, 2H, CH). ^{13}C NMR ($CDCl_3$): δ = 19.62, 22.91, 25.62, 30.72, 45.40, 53.59, 62.16, 62.22, 65.93, 66.74, 66.76, 68.94, 69.81, 70.62, 70.70, 70.76, 70.84, 72.42, 96.27, 98.94, 98.99, 100.91, 107.01, 138.04, 144.22, 152.77. Route 2: According to general procedure B from **3a** (0.6 g) and AIBN (3 mg), polymerization for 3 h yielded **THP−PG1** as a colorless gel (0.42 g, 70%). The identical spectral data as in route 1 were obtained.

Poly(3,4,5-tris(2-(2-(2-(3,4,5-tris(2-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy) ethoxy) ethoxy)ethoxy)benzyl)ethoxy)ethoxy)ethoxy)-benzyl methacrylate) (THP−PG2). According to general procedure A from **5a** (0.19 g) and AIBN (1.0 mg), polymerization for 3 h yielded **THP−PG2** as a colorless gel (0.12 g, 64%). ^{1}H NMR (CD_2Cl_2): δ =1.49 (br, 36H, CH_2), 1.65 (br, 9H, CH_2), 1.77 (br, 9H, CH_2), 3.34−3.77 (m, 138H, CH_2), 4.06 (br, 24H, CH_2), 4.38 (br, 8H, CH_2), 4.56 (br, 9H, CH), 6.53 (br, 8H, CH). ^{13}C NMR (CD_2Cl_2): δ = 19.66, 25.65, 29.82, 30.75, 62.05, 66.70, 68.89, 69.67, 69.84, 70.56, 70.61, 70.67, 70.84, 72.47, 73.14, 98.90, 106.56, 134.12, 137.62, 152.72. The signals of the polymer backbone were so broad that they disappeared in the baseline.

General Procedure for Deprotection of THP from Dendronized Polymers (D). The corresponding THP-protected polymer was dissolved in a mixture of THF, water, and AcOH (2:1:4), and the solution was stirred for 3 days at room temp. After removal of the solvent in vacuo, the deprotected polymer was dissolved in water and lyophilized.

Poly(3,4,5-tris(2-(2-(2-hydroxylethoxy)ethoxy)ethoxy)benzyl methacrylate) (PG1). Route 1: According to general procedure C from **3b** (0.33 g), ACVA (2.3 mg) and water (0.25 mL), polymerization 3 h yielded **PG1** as a colorless gel (0.26 g, 78%). ^{1}H NMR (D_2O): δ = 0.70−0.93 (m, 3H, CH_3), 1.96−1.99 (m,

Table 1. Conditions and Results for the Polymerization of Macromonomers 3a, 3b, 5a, and 5b

	polymerization conditions[a]					GPC[b]			
entry	monomer	solvent	[monomer] (mol L^{-1})	time (h)	yield (%)	M_n $\times 10^{-6}$	DP $\times 10^{-3}$	PDI	T_g[b] (°C)
1	**3a**	DMF	0.71	19	67	0.88	1.41	2.31	−47.1
2	**3a**	bulk	1.26	3.0	70	1.94	3.12	4.86	−46.5
3	**3b**	DMF	1.07	5.0	80	0.98	1.58	6.40	−48.1
4	**3b**	H_2O	0.49	3.0	78	5.81	9.37	2.93	−44.0
5	**5a**	bulk	0.37	3.0	64	0.30	0.13	2.40	−39.8
6	**5a**	bulk	0.37	15	68	0.29	0.13	4.52	−41.1
7	**5b**	H_2O	0.26	12	–[c]	–[c]	–[c]	–[c]	–[c]

[a] Polymerization was carried out at 60 °C. [b] All GPC and T_g measurements were done for the hydroxyl-terminated polymers (see text). [c] No polymer formed.

2H, CH_2), 3.25−3.27 (m, 3H, OH), 3.48−3.74 (m, 30H, CH_2), 4.07 (br, 6H, CH_2), 4.80 (br, 2H, CH_2), 6.62 (br, 2H, CH). The carbon signals were so broad that they disappeared in the baseline. Elemental analysis (%) calcd for $(C_{29}H_{48}O_{14})_n$ $(620.69)_n$: C, 56.12; H, 7.79. Found: C, 54.84; H, 7.80. Route 2: According to general procedure D from **THP−PG1** (0.40 g), AcOH (16 mL), THF (8 mL), and water (4 mL) was yielding **PG1** as a colorless gel (0.25 g, 88%). The identical spectral data as in route 1 were obtained. Elemental analysis (%) calcd for $(C_{29}H_{48}O_{14})_n$ $(620.69)_n$: C, 56.12; H, 7.79. Found: C, 54.37; H, 7.78.

Poly(3,4,5-tris(2-(2-(2-(3,4,5-tris(2-(2-(2-hydroxylethoxy)ethoxy)-ethoxy) benzyloxy)ethoxy)ethoxy)ethoxy)benzyl methacrylate) (PG2). According to general procedure D from **THP−PG2** (0.34 g), AcOH (12 mL), THF (6 mL), and water (3 mL) was yielding **PG2** as a colorless oil (0.20 g, 80%). ^{1}H NMR (D_2O): δ = 3.58−3.78 (m, 120H, CH_2), 4.06 (br, 24H, CH_2), 4.37 (br, 6H, CH_2), 6.62 (br, 8H, CH). The proton signals of backbone and carbon signals were so broad that they disappeared in the baseline. Elemental analysis (%) calcd for $(C_{104}H_{174}O_{50})_n$ $(2224.49)_n$: C, 56.15; H, 7.88. Found: C, 55.03; H, 7.93.

3. Results and Discussion

Synthesis of Dendrons and Macromonomers. The synthesis procedures for dendrons and macromonomers are delineated in Scheme 1. Methyl gallate was reacted with monotosylated triethylene glycol (TEG−Ts) according to established procedures[10] to give the hydroxyl-terminated branching unit **2a**. The TEG−Ts used for this transformation were prepared according to a statistic reaction and the formation of the ditosylated TEG therefore a necessary side reaction. This unwanted product is typically obtained in approximately 30% yield.[11] In order to suppress its formation as far as possible, the coupling reaction was done in the presence of 1 equiv of KI per TEG. This way the content of ditosylated TEG in the raw product mixture could be reproducibly reduced to 5−10%. In the next step, the hydroxyl groups of **2a** were THP-protected to give **2b** in order to allow to specifically addressing the focal point hydroxyl group generated in just one step ahead. The reduction of **2b** to give **2c** with a focal alcohol group was first attempted with $NaBH_4$ and LiCl and then directly with $LiBH_4$.In neither case a reaction was observed. Therefore, lithium aluminum hydride (LAH), which normally renders workup more complicated, was applied and furnished the product **2c** with excellent yield (∼92%). To the alcohol function of **2c**, methacryloyl chloride (MAC) was added to give the THP-protected G1 macromonomer **3a**. This monomer was either directly employed into polymerization reactions or after deprotection with PTSA to **3b**. This latter monomer has a significantly decreased molar mass which is a means to increase the concentration of its polymerizable unit in the polymerization mixture. This way the formation of higher molar mass product was to be expected. Also, **3b** had the advantage that the polymerization could be tried in water which is important for environmental and cost considerations.

Two different routes for the synthesis of G2 dendron **4a** were designed and compared in their efficiency (Scheme 1). In the first, the ether synthesis was attempted by trying to react the tosylated benzylic focal point methylene group of **2c** (not shown) with the three terminal hydroxyl groups of **2a**. In the second, the focal point alcohol of **2c** was used to replace the peripheral tosylates of **2d**. The first route unfortunately failed because tosylation of THP-protected G1 alcohol **2c** under broadly varied basic conditions led to deprotection.[12] The second route was successful when done with NaH as the base in the presence of the catalyst KI/15-crown-5. Under these conditions, product **4a** was obtained in a yield of 57%. It is necessary to point out here, however, that it was not the expected G2 focal point ester which was obtained as the product of this etherification reaction but rather its saponified analogue **4a**. The saponification had obviously taken place in parallel. Nonbasic etherification conditions (with Ag_2O/KI)[12] were also tried but found to be unsuccessful. On the basis of the experience for the reduction of G1 ester **2b**, LAH was also tried for the reduction of G2 acid **4a** to give G2 alcohol **4b**. Although it was conducted at 0 °C, LAH not only reduced the focal carboxyl group but also cleaved the three equivalent benzyl ether linkages connecting the first and second generation and could therefore not be used. This cleavage gave G1 alcohols from **2a** and **2c**. Fortunately, the protocol from Kokotos[14] proved successful. It allowed the use of much milder conditions. The reduction was conducted in two steps by first preparing the mixed anhydride of acid **4a** and ethyl chloroformate, which in the second step was then reduced directly by excess $NaBH_4$. This protocol afforded the targeted G2 alcohol **4b** in a yield of 83%. Finally, THP-protected G2 macromonomer **5a** was obtained by reacting **4b** with MAC. **5a** was deprotected first by PTSA to afford the unprotected G2 macromonomer **5b**, but purification became tedious as **5b** tends strongly to stick inside the silica gel column. In order to avoid column chromatography for the purification, the deprotection was then performed with PPTS as it can be removed by extraction with water. The overall yield for **5b** from **2a** is around 25%.

All new compounds were synthesized on the multigram scale with satisfying to excellent yields. They were characterized by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. The typical ^{1}H NMR spectra of **3a**, **3b**, **5a**, and **5b** are shown in Figure 2 to illustrate the high purities achieved.

Polymerizations. All polymerizations were done under conventional radical conditions using AIBN or ACVA as initiators at 60 °C. THP-protected monomers **3a** and **5a** were polymerized either in DMF solution or in bulk and the hydroxyl monomers **3b** in DMF solution and aqueous solution. The corresponding polymers **THP−PG1** and **THP−PG2** as well as **PG1**, respectively, were obtained as colorless, very soft or sticky solids. But there is no polymer detected from the

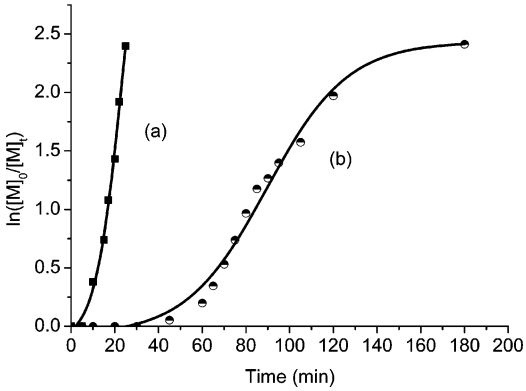


Figure 3. Kinetic plots of the polymerization of **3b** at 50 °C in D_2O (a) and DMF-d_6 (b) ([**3b**] = 0.60 mol L^{-1}, [AIBN] = 11.5 mmol L^{-1}, [ACVA] = 9.4 mmol L^{-1}).

polymerization of **5b** either in DMF or water. Therefore, **PG2** was obtained via deprotection from the corresponding THP-protected polymer **THP−PG2**. The conditions and molar masses are compiled in Table 1. The molar masses of **PG1** and **PG2** were determined by GPC referenced to PMMA standards using UV, RI, and viscometer detection and DMF (LiBr) as the eluent. Those of **THP−PG1** and **THP−PG2** could not be determined by this method despite their good solubility in solvents such as THF, CH_2Cl_2, $CHCl_3$, or DMF. In DMF, no signals were observed both with RI and UV detection. The same was observed when chloroform was used as the eluent. A possible explanation could be a partial deprotection of the polymers on the column which could lead to aggregation and sticking of the polymer on the support inside the GPC columns. Thus, prior to the GPC measurements, polymers **THP−PG1** and **THP−PG2** were deprotected into **PG1** and **PG2** with acetic acid in a mixed solvent of THF/water at room temperature.

From Table 1, the following conclusions can be drawn: (1) The polymerization yields are normally in the range of 60−80%, irrespective of whether protected or unprotected monomers are used. (2) **PG1** and **PG2** are obtained in high molar masses. Bulk polymerization affords **PG1** with much high molar masses (entry 2) than from DMF solution (entries 1 and 3). Although generally concentrated solutions of macromonomers are essential to achieve high-molar mass polymers, extremely high-molar mass **PG1** is obtained even when the somewhat less concentrated aqueous solution of **3b** (entry 4) is used instead of concentrated DMF (entry 3). To our knowledge, this is the first example for the synthesis of a dendronized polymer in aqueous solution. (3) The molar mass of **PG2** (entries 5 and 6) is lower compared to those of **PG1** as is typical for the macromonomer route. Reducing the molar mass of the macromonomer **5a** prior to polymerization by deprotecting it to **5b** led to even worse results. It is believed that insufficient purity is the reason for this, because column chromatography could not be employed.

Interestingly, the radical polymerization of **3b** in aqueous solution went much faster than in DMF and is, in fact, the fastest observed in our laboratory. Therefore, the polymerization kinetics was investigated in some detail by directly monitoring the reaction progress by ^{1}H NMR spectroscopy. Nitrogen-flushed NMR tubes with (i) DMF-d_6 and (ii) deuterium oxide solutions of the macromonomer were placed in the spectrometer and heated to 50 °C [(i): **3b** (0.2 g, 0.32 mmol), AIBN (1 mg), DMF-d_6 (0.35 mL). (ii): **3b** (0.2 g, 0.32 mmol), ACVA (1.4 mg), D_2O (0.35 mL)]. At defined intervals, spectra were recorded. The conversions were determined by integration of the vinylic monomer signals at $\delta = 6.11$ versus the signal of the OCH_2 groups of both monomer and polymer at $\delta = 4.14$. The results are plotted in Figure 3, where $[M]_0$ and $[M]_t$ refer to the concentrations of monomer **3b** at the beginning and at time t of the polymerization. Curve a is almost linear and has a steep slope. The conversion reaches 85% in less than 30 min. In contrast, curve b is "S"-shaped, which is an indication for a typical radical polymerization with an induction period at the beginning followed by an auto-acceleration. Three hours were needed to reach a conversion of approximately 85%. These considerable rate differences may be caused by a preorganization in aqueous medium in which the polymerizable units are oriented favorable for polymerization. Though this interpretation is speculative at the present time, a similar observation was described by Ito and Percec.[15]

PG1 and **PG2** are well-soluble in water and polar organic solvents, such as DMF and DMSO. The hydrodynamic diameter (D_h) of both polymers in DMF and water were determined by DLS measurements. For **PG1** ($M_n = 9.8 \times 10^5$) in DMF, D_h = 61.5 nm was determined, which is nearly the same as that in water (D_h = 60.0 nm), while for **PG2** ($M_n = 2.9 \times 10^5$) in DMF, D_h = 43.4 nm was found, which is slightly larger than that in water (D_h = 34.8 nm). This suggests that **PG1** shows similar solubility in water and DMF, while **PG2** is better soluble in water than in DMF. The T_g values given in Table 1 are the lowest so far observed for dendronized polymers. Typically, these values are in the range of 55−80 °C.[16]

4. Conclusions

The two representatives **PG1** and **PG2** of a new kind of dendronized polymer were synthesized. The structural characteristic which sets them apart from all other known representatives of this class of comb polymers is the triethyleneoxy segment between the 3-fold, gallic acid-based branching unit which, together with the peripheral hydroxyl groups, not only mediates the polymers full water-solubility but also allows their synthesis to be performed in aqueous medium. The water-solubility of the **PG1** and **PG2**, which are noncharged, opens access to applications not yet within reach for dendronized polymers. This includes biomineralization, drug delivery, and the entire complex of protein resistant materials.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds and polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Schlüter, A. D.; Rabe, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 864−883. (b) Zhang, A.; Shu, L.; Bo, Z.; Schlüter, A. D. *Macromol. Chem. Phys.* **2003**, *204*, 328−339. (c) Zhang, A. *Prog. Chem.* **2005**, *17*, 157−171. (d) Frauenrath, H. *Prog. Polym. Sci.* **2005**, *30*, 325−384. (e) Schlüter, A. D. *Top. Curr. Chem.* **2005**, *245*, 151−191.

(2) (a) Pogantsch, A.; Wenzl, F. P.; List, E. W. J.; Leising, G.; Grimsdale, A. C.; Müllen, K. *Adv. Mater.* **2002**, *14*, 1061−1064. (b) Luo, J.; Liu, S.; Haller, M.; Liu, L.; Ma, H.; Jen, A. K.-Y. *Adv. Mater.* **2002**, *14*, 1763−1768. (c) Liang, C. O.; Helms, B.; Hawker, C. J.; Fréchet, J. M. J. *Chem. Commun.* **2003**, 2524−2525. (d) Suijkerbuijk, B. M. J. M.; Shu, L.; Gebbink, R. J. M. K.; Schlüter, A. D.; van Koten, G. *Organometallics* **2003**, *22*, 4175−4177. (e) Deng, G.-J.; Yi, B.; Huang, Y.-Y.; Tang, W.-J.; He, Y.-M.; Fan, Q.-H. *Adv. Synth. Catal.* **2004**, *46*, 1440−1444. (f) Zhang, Y.; Chen, Y.; Niu, H.; Gao, M. *Small* **2006**, *2*, 1314−1319. (g) Li, B.; Fu, Y.; Han, Y.; Bo, Z. *Macromol. Rapid Commun.* **2006**, *27*, 1355−1361.

(3) (a) Lee, C. C.; Grayson, S. M.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 3563−3578. (b) Lee, C. C.; Fréchet, J. M. J. *Macromolecules* **2006**, *39*, 476−481.

(4) (a) Böttcher, C.; Schade, B.; Ecker, C.; Rabe, J. P.; Shu, L.; Schlüter, A. D. *Chem.—Eur. J.* **2005**, *11*, 2923−2928. (b) Cheng, C.; Schmidt, M.; Zhang, A.; Schlüter, A. D. *Macromolecules* **2007**, *40*, 220−227.
(5) Li, J.-G.; Meng, C.; Zhang, X.-Q.; Zhang, L.; Zhang, A. *Prog. Chem.* **2006**, *18*, 1157−1180.
(6) (a) Bo, Z.; Rabe, J. P.; Schlüter, A. D. *Angew. Chem., Int. Ed.* **1999**, *38*, 2370−2372. (b) Bo, Z.; Zhang, C.; Severin, N.; Rabe, J. P.; Schlüter, A. D. *Macromolecules*, **33**, 2688−2694.
(7) For preferential localization of guest molecules: Baars, M. W. P. L.; Kleppinger, R.; Koch, M. H. J.; Yeu S.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2000**, 39, 1285−1288. For amphiphilic rotaxanes: Jeppesen, J. O.; Perkins, J.; Becher, J.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 3547−3550. For rendering chitosan water-solubility for medical applications: Meunier, S. J.; Wu, Q.; Wang, S.-N.; Roy, R. *Can. J. Chem.* **1997**, *75*, 1472−1482. Sashiwa, H.; Shigemasa, Y.; Roy, R. *Macromolecules* **2001**, *34*, 3905−3909. As cavitand receptors: Middel, O.; Verboom, W.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2002**, 2587−2597. For nanoparticle modification with fluorescence probes: Chen, C.-T.; Pawar, V. D.; Munot, Y. S.; Chen, C.-C.; Hus, C.-J. *Chem. Commun.* **2005**, 2483−2485.
(8) For examples, see (a) Müller, S.; Schlüter, A. D. *Chem.—Eur. J.* **2005**, *11*, 5589−5610. (b) Percec, V.; Rudick, J. G; Peterca, M.; Staley, S. R.; Wagner, M.; Obata, M.; Mitchell, C. M.; Cho, W.-D.; Balagurusamy, V. S. K.; Lowe, J. N.; Glodde, M.; Weichold, O.; Chung, K. J.; Ghionni, N.; Magonov, S. N.; Heiney, P. A. *Chem.—Eur. J.* **2006**, *12*, 5731−5746.
(9) (a) Loiseau, F. A.; Hii, K. K.; Hill, A. M. *J. Org. Chem.* **2004**, *69*, 639−647. (b) Ahmed, S. A.; Tanaka, M. *J. Org. Chem.* **2006**, *71*, 9884−9886.
(10) Gibson, H. W.; Lee, S.-H.; Engen, P. T.; Lecavalier, P.; Sze, J.; Shen, Y. X.; Bheda, M. *J. Org. Chem.* **1993**, *58*, 3748−3756.
(11) Svedhem, S.; Hollander, C.; Shi, J.; Konradsson, P.; Liedberg, B.; Svensson, S. C. T. *J. Org. Chem.* **2001**, *66*, 4494−4503.
(12) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 4770−4772.
(13) (a) Bouzide, A.; LeBerre, N.; Sauvé, G. *Tetrahedron Lett.* **2001**, *42*, 8781−8783. (b) Peng, X.-X.; Lu, H.-Y.; Han, T.; Chen, C.-F. *Org. Lett.* **2007**, *9*, 895−898.
(14) (a) Kokotos, G. *Synthesis* **1990**, 299−301. (b) Loukas, V.; Noula, C.; Kokotos, G. *J. Pept. Sci.* **2003**, *9*, 312−319.
(15) (a) Ito, K.; Tomi, Y.; Kawaguchi, S. *Macromolecules* **1992**, *25*, 1534−1538. (b) Percec, V.; Ahn, C.-H.; Barboiu, B. *J. Am. Chem. Soc.* **1997**, *119*, 12978−12979.
(16) (a) Zhang, A.; Zhang, B.; Wächtersbach, E.; Schmidt, M.; Schlüter, A. D. *Chem.—Eur. J.* **2003**, *9*, 6083−6092. (b) Zhang, A.; Okrasa, L.; Pakula, T.; Schlüter, A. D. *J. Am. Chem. Soc.* **2004**, *126*, 6658−6666.

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