Synthesis of Water-Soluble, Ester-Terminated Dendrons and Dendrimers Containing Internal PEG Linkages

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ABSTRACT: Dendrimers up to three generations, possessing internal PEG units within the branching framework, were synthesized by a convergent approach via the reaction of amine-based dendrons **6**, **9**, and **11** with 6,6-bis(4-chlorocarbonyl-2-oxabutyl)-4,8-dioxaundecane-1,11-dicarbonyl chloride. These new constructs were fully characterized, shown to exhibit good solubilities in organic as well as aqueous solvents, and demonstrated to solubilize lithium triflate salts in nonaqueous environments, such as chloroform.

Introduction

During this past decade, the syntheses, characterization, and applications of dendrimers have been introduced into diverse fields of research.[1,2] These highly branched, 3-dimensional, globular macromolecules have shown promising utility in molecular electronic devices, such as light-emitting diodes,[3,4] molecular antennae,[5,6] light-harvesting systems,[7,8] drug delivery systems,[9,10] chemical sensors,[11] receptors in molecular recognition processes,[12,13] enhanced binding or sensor effects,[14,15] and luminescent materials,[16−19] to mention but a few.

Poly(ethylene glycol)s (PEGs) and their derivatives are important biocompatible materials that exhibit a wide range of solubilities[20,21] and are generally nontoxic.[22] Hence, their use as drug carriers,[9,23,24] anchors for biological receptors,[25] and metal ion binding for ion transport[26] is well documented. In tethered, bilayer membrane systems, where they are employed as hydrophilic linkers, PEG units act as the integral component of an ion channel switch biosensor.[27] Further, ether-, ester-, and amine-based linear polymers with short PEG units in the presence of inorganic salts have potential applications in high-energy density batteries, electrochemical cells, and electrochromic devices.[28−31]

For dendritic architectures incorporating the PEG moiety, the most common attachment of PEG moieties is onto their surface in order to instill aqueous solubility in general, to water-insoluble species. In that dendrimers have three structural regions in which a PEG unit can be introduced, namely, the core,[32−42] internal connective moieties,[43−47] and surface groups,[9,36,48−82] the former and latter attachments predominate due to the ease of instillation. Also, dendrons have been focally PEGed.[38,83−89] Gitsov et al.[32,36] reported linear−dendritic block copolymers using large PEG components, as the internal core as well as surface unit(s), and studied their properties; a review by Gitsov[90] has recently appeared. Diederich et al. utilized a series of dendroclefts[53,60,64] and heme proteins[50,59,61,68,70,91,92] possessing 1 → 3 *C*-branched monomers capped with small, surface PEGed subunits and then studied their unique properties such as their selective recognition of monosaccharides. Phthalocyanines[65,93] and related benzoporphyrins[77] as well as metalloclusters[94] have also been made readily water-soluble by the attachment of small PEG units. Nierengarten recently reviewed[79] examples of dendritic encapsulation, which is, in part, based on related PEGed surfaces. The highly stable PEG-functionalized saturated hydrocarbon-type dendrimers act as electrolyte materials and were shown to improve the efficiency[95,96] of a lithium rocking chair battery. More recently, Itoh et al.[44,97] studied the ionic conductivity of hyperbranched PEG derivatives in the presence of lithium metal salts [$LiCF_3SO_3$ and $Li(CF_3SO_2)_2N$] to determine their effectiveness as polymer electrolytes. Only three examples of PEG units being used as noncore, internal linkages have appeared, to the best of our knowledge: functionalization of tetrathiafulvalene (TTF),[43,46] hyperbranched Fréchet-type materials,[47,97,98] and in the solid-phase peptide synthesis of multimeric cyclo-(RGD*t*E)-peptides.[45]

Our interest in the design and application of dendrimers led us to synthesize a series of useful PEGed dendrons and dendrimers, which utilize a combination of (1) amide connectivity affording minimal internal hydrolytic cleavage in that most PEGed dendrimers possess the more labile ester connectivity, (2) 1 → 3 *C*-branching motif, and (3) a noncore, internal PEG linkage, derived from commercially available triethylene glycol. Incorporation of PEG functionality within the dendritic framework is also envisioned to enhance the dendrimers potential to facilitate the transport of alkali metal species such as is required of polymer electrolytes in solid-state batteries.

Experimental Section

General Remarks. Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. All of chemicals were purchased from Aldrich Co. except for the tetradirectional core,

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Behera's amine, and its nitro precursor.[99] Tetrahydrofuran (THF) was dried by refluxing over benzophenone/Na under N_2. Dichloromethane was dried over CaH_2. All other commercially available solvents were used without further purification. Column chromatography was conducted using silica gel (60−200 mesh) from Fisher Scientific with the stipulated solvent mixture. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, except where noted, and are recorded at 250 and 52 MHz, respectively. The NMR spectra of selected samples dissolved in formic acid were obtained without a lock signal and were shimmed on the FID. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded on an ATI Mattson Genesis Series FTIR spectrometer. Mass spectral data were obtained using an Esquire electron ionization mass spectrometer (ESI) and are reported as (assignment, relative intensity); ESI samples were typically prepared in MeOH/H_2O/TFA (70:30:01) for positive ion mode or Me_2CHOH/H_2O/NH_3 (70:30:1) for negative ion mode and matrix-assisted laser desorption ionization time-of-flight (MALDI−TOF) mass spectrometer. Differential scanning calorimetry (DSC) data were obtained using a TA DSC 2910 using scanning rates of 10 °C/min.

Ethyl [2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy]acetate (1). To the stirred solution of triethylene glycol (20 g, 133 mmol) and BF_3·THF (2 drops) in CH_2Cl_2 under N_2 was added dropwise ethyl diazoacetate (15.4 g, 133 mmol) in CH_2Cl_2 (50 mL) over 1 h. After stirring at 20 °C for 12 h, the organic phase was washed with water (50 mL, 2×), dried ($MgSO_4$), filtered, and evaporated in vacuo to give (70%) **1** as a colorless oil: 21.4 g; R_f 0.41 [SiO_2: EtOAc/hexane (1:1)]. ^{1}H NMR δ 1.12 (t, 3H, CH_3, J = 7.2 Hz), 3.22 (t, 2H, HOCH_2, J = 5.4 Hz), 3.43−3.57 (m, 10H), 3.98 (s, 2H, OCH_2CO), 4.05 (q, 2H, OCH_2CH$_3$, J = 7.2 Hz). ^{13}C NMR δ 13.91 (*C*H$_3$), 60.50 (O*C*H$_2$CH$_3$), 61.25 (HO*C*H$_2$), 68.32−72.35, 170.20 (*C*O$_2$). IR 3500 (OH), 1751 (C=O), 1127 cm^{-1} (C−O). FAB-MS: m/z = 258.9 (M + H$^+$); calcd m/z = 259.2 (M + H$^+$).

Ethyl [2-[2-(2-Mesyloxyethoxy)ethoxy]ethoxy]acetate (2). To the stirred solution of ester **1** (10 g, 42 mmol), Et_3N (4.30 g, 43 mmol), and toluene (50 mL) was added dropwise a solution of mesyl chloride (4.85 g, 43 mmol) in toluene (10 mL) for 30 min at −10 °C. The mixture was stirred for 3 h at 25 °C then concentrated in vacuo to give a residue, which was column chromatographed eluting with EtOAc/ CH_2Cl_2 (20:80) to give (90%) mesylate **2** as a viscous oil: 12.0 g; R_f = 0.34. ^{1}H NMR δ 1.15 (t, 3H, OCH$_2$CH_3, J = 7.2 Hz), 2.96 (s, 3H, SO$_2$CH_3), 3.54−3.59 (m, 10H), 3.64 (t, 2H, MsOCH_2, J = 4.5 Hz), 4.00 (s, 2H, OCH_2CO), 4.09 (q, 2H, OCH_2CH$_3$, J = 7.2 Hz). ^{13}C NMR δ 13.94 (OCH$_2$*C*H$_3$), 37.31 (SO$_2$*C*H$_3$), 60.48 (O*C*H$_2$CH$_3$), 68.29−70.51, 170.10 (*C*O$_2$); IR 1750 (C=O), 1174 cm^{-1} (C−O). FAB-MS: m/z = 336.9 (M + Na$^+$); calcd m/z = 337.3 (M + Na$^+$).

Ethyl [2-[2-(2-Azidoethoxy)ethoxy]ethoxy]acetate (3). A stirred mixture of **2** (10 g, 32 mmol) and excess NaN_3 (3X) in dry DMF (200 mL) was maintained at 60 °C for 3 h. The mixture was filtered, concentrated in vacuo, and column chromatographed (SiO_2) eluting with an EtOAc/hexane mixture (1:1) to give (95%) the desired azide **3** as a yellow oil: 7.90 g; R_f = 0.55. ^{1}H NMR δ 0.95 (t, 3H, OCH$_2$CH_3, J = 7.2 Hz), 3.06 (t, 2H, N$_3$CH_2, J = 4.2 Hz), 3.33 (m, 10*H*), 3.81 (s, 2H, CH_2CO), 3.87 (q, 2H, OCH_2CH$_3$, J = 7.2 Hz). ^{13}C NMR δ 13.19 (*C*H$_3$), 49.66 (N$_3$*C*H$_2$), 59.65 (CH$_3$*C*H$_2$O), 67.51−69.75, 169.47 (*C*O$_2$). IR 2108 (N$_3$), 1751 (C=O), 1125 cm^{-1} (C−O). ESI-MS m/z = 336.9 (M + Na$^+$), calcd m/z = 337.3 (M + Na$^+$).

[2-[2-(2-Azidoethoxy)ethoxy]ethoxy]acetic Acid (4). Ester **3** (5 g, 19.1 mmol) was hydrolyzed in aqueous KOH at 20 °C for 6 h. The resultant solution was neutralized with 10% aqueous HCl and then concentrated in vacuo to give an oil, which was extracted with THF, filtered, and evaporated in vacuo to give (96%) the pure acid **4** as a colorless oil: 4.3 g. ^{1}H NMR δ 3.26 (t, 2H, N$_3$CH_2, J = 4.5 Hz), 3.57 (m, 10H), 4.01 (s, 2H, OCH_2CO), 10.66 (s, 1H, CO$_2$*H*). ^{13}C NMR δ 50.31 (N$_3$*C*H$_2$), 68.02−70.71, 173.54 (*C*O$_2$). IR 3450 (CO$_2$H), 2108 (N$_3$), 1743 (C=O), 1123 cm^{-1} (C−O). ESI-MS m/z = 234 (M + H$^+$), calcd m/z = 234.22 (M + H$^+$).

Synthesis of Dendron 5. To the stirred solution of acid **4** (560 mg, 2 mmol), DCC (496 mg, 2 mmol), and HOBT (325 mg, 2 mmol), Behera's amine[100,101] (1 g, 2 mmol) was added; the mixture was stirred at 25 °C for 15 h. After filtration, the solvent was evaporated in vacuo to give a viscous oil, which was column chromatographed (SiO_2) eluting with 95% CH_2Cl_2/EtOAc to give (92%) pure azide **5** as a viscous oil: 1.4 g. ^{1}H NMR δ 1.32 (s, 27H, CH_3), 1.87 (t, 6H, CH_2CH$_2$CO, J = 8.4 Hz), 2.09 (t, 6H, CH_2CO, J = 8.4 Hz), 3.28 (t, 2H, N$_3$CH_2, J = 4.5 Hz), 3.58−3.59 (m, 10H), 3.78 (s, 2H, OCH_2CO) 6.40 (s, 1H, N*H*). ^{13}C NMR δ 28.18 (*C*H$_3$), 29.69, 29.78 (*C*H$_2$CH$_2$-CO), 50.74 (N$_3$*C*H$_2$), 57.28 (NH*C*), 70.16−71.33, 80.54 (*C*Me$_3$), 169.09 (*C*ONH), 172.53 (*C*O$_2$). IR 2106 (N$_3$), 1726 (C=O), 1677 (C=O), 1153 cm^{-1} (C−O). FAB-MS m/z = 632 (M + H$^+$), calcd m/z = 631.77 (M + H$^+$).

Synthesis of Dendron 6. A suspension of azide **5** (3 g, 4.7 mmol) in EtOH (30 mL) with 10% Pd−C under 60 psi of hydrogen at 20 °C was stirred for 16 h and then carefully filtered to remove the catalyst (*caution: pyrophoric*) and concentrated in vacuo to give a viscous liquid, which was column chromatographed (SiO_2) eluting with EtOAc → 10% MeOH/EtOAc to afford (94%) amine **6**: 2.7 g. ^{1}H NMR δ 1.30 (s, 27H, CH_3), 1.84 (t, 6H, CH_2CH$_2$O, J = 6.6 Hz), 2.07 (t, 6H, CH_2O, J = 6.6 Hz), 3.04 (t, 2H, H$_2$NCH_2, J = 4.5 Hz), 3.57−3.79 (m, 10H), 3.84 (s, 2H, CH_2CO), 5.21 (s, 1H, N*H*), 6.56 (s, 2H, NH_2). ^{13}C NMR δ 27.94 (*C*H$_3$), 29.50, 29.56 (*C*H$_2$*C*H$_2$CO), 39.92 (H$_2$N*C*H$_2$), 57.24 (NH*C*), 67.86−70.57, 80.49 (*C*Me$_3$), 169.37 (*C*ONH), 172.52 (*C*O$_2$). IR 3371 (NH$_2$), 1726 (C=O), 1661 (C=O), 1153 cm^{-1} (C−O). FAB-MS m/z = 606 (M + H$^+$), calcd m/z = 605.77 (M + H$^+$).

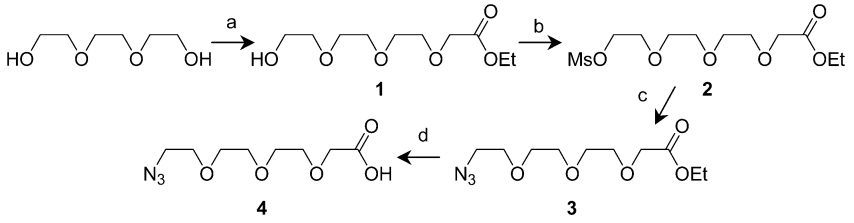
Synthesis of Dendron 7. To the stirred solution of azide **5** (3 g, 4.7 mmol), HCO_2H was added and then stirred for 6 h at 25 °C. The excess reagent was evaporated in vacuo, then toluene was added, and again evaporated in vacuo to remove the last traces of formic acid to afford (95%) the pure triacid **7**: 2.08 g. ^{1}H NMR δ 2.03 (t, 6H, CH_2CH$_2$O, J = 6.3 Hz), 2.26 (t, 6H, CH_2O, J = 6.3 Hz), 3.18 (t, 2H, N$_3$CH_2, J = 4.5 Hz), 3.62−3.66 (m, 10H), 3.87 (s, 2H, CH_2CO), 6.56 (s, 1H, N*H*), 9.54 (s, 3H, CO$_2$*H*). ^{13}C NMR δ 28.15 (*C*H$_2$CO), 29.22 (*C*H$_2$-CH$_2$CO), 50.06 (N$_3$*C*H$_2$), 56.60 (NH*C*), 69.32−70.41, 168.86 (*C*ONH), 174.50 (*C*O$_2$H). IR 3358 (CO$_2$H), 2110 (N$_3$), 1716 (C=O), 1668 (C=O), 1104 cm^{-1} (C−O). FAB-MS m/z = 463 (M + H$^+$), calcd m/z = 463.45 (M + H$^+$).

Synthesis of Predendron 8. To a stirred solution of 4-(2-carboxyethyl])-4-nitroheptanedioic acid[102,103] (530 mg, 1.91 mmol), HOBT (780 mg, 5.7 mmol), and DCC (1.2 g, 5.7 mmol) in THF at 25 °C, amine **6** (3.5 g, 5.7 mmol) was added. After 48 h, the mixture was filtered, and then the solvent was removed in vacuo to give the crude dendron, which was column chromatographed (SiO_2) eluting with hexane to remove the excess DCC and then 10% MeOH in CH_2Cl_2 to afford (70%) the desired predendron **8**: 2.7 g. ^{1}H NMR δ 1.33 (s, 81H, CH_3), 1.88 (t, 24H, CH_2CH$_2$CO, J = 7.2 Hz), 2.10 (t, 24H, CH_2CO, J = 7.2 Hz), 3.31 (t, 2H, NHCH_2, J = 4.8 Hz), 3.41−3.58 (m, 30H), 3.84 (s, 6H, CH_2CO), 6.42 (s, 3H, N*H*), 6.72 (s, 3H, N*H*CH$_2$). ^{13}C NMR δ 28.04 (*C*H$_3$), 29.59, 29.70 (*C*H$_2$*C*H$_2$CO), 30.36, 30.78 (*C*H$_2$*C*H$_2$CO), 39.36 (NH*C*H$_2$), 57.18 (NH*C*), 69.77−70.81, 80.49 (*C*Me$_3$), 92.80 (O$_2$N*C*), 169.22 (*C*ONH), 171.04 (*C*ONH), 172.46 (*C*O$_2$). IR 1726 (C=O), 1670 (C=O), 1153 cm^{-1} (C−O). MALDI−TOF m/z = 2056.2 (M + Na$^+$); calcd m/z = 2059.23 (M + Na$^+$)

Synthesis of Dendron 9. The predendron **8** (1 g, 490 μmol) was reduced (H_2, Raney Ni, 60 psi, EtOH, 50 °C), in a procedure similar to that of **6**, to give (80%) the corresponding amine **9** as a pale yellow liquid: 780 mg. ^{1}H NMR δ 1.24 (t, 24H, CH_2CH$_2$CO, J = 6.9 Hz), 1.43 (s, 81H, CH_3), 1.97 (t, 18H, CH_2CO, J = 7.5 Hz), 2.20 (t, 6H, CH_2CO, J = 7.5 Hz), 3.41 (t, 6H, NHCH_2, J = 4.8 Hz), 3.53−3.69 (m, 30H), 3.97 (s, 6H, CH_2-CO), 6.51 (s, 8H, N*H*, NH_2). ^{13}C NMR δ 27.90 (*C*H$_3$), 29.43, 29.54 (*C*H$_2$*C*H$_2$CO), 30.52, 34.72 (*C*H$_2$*C*H$_2$CO), 39.10 (NH*C*H$_2$), 57.02 (NH*C*), 57.96 (H$_2$N*C*), 69.71−70.77, 80.33 (*C*Me$_3$), 169.02 (*C*ONH), 172.27 (*C*ONH), 173.25 (*C*O$_2$). IR 3333 (NH$_2$), 1728 (C=O), 1672 (C=O), 1153 cm^{-1} (C−O). MALDI−TOF m/z = 2030.34 (M + Na$^+$), calcd m/z = 2030.55 (M + Na$^+$).

Synthesis of Azide 10. To the stirred solution of **7** (1 g, 2.16 mmol), EDC (1.24 g, 6.4 mmol), and HOBT (880 mg, 6.4 mmol), amine **6** (3.9 g, 6.4 mmol) was added in DMF at 25 °C.

Scheme 1. Synthesis of Key Extenders 3 and 4[a]



[a] (a) $N_2CHCO_2CH_2CH_3$, BF_3·THF, 20 °C, 12 h; (b) CH_3SO_2Cl, toluene, Et_3N, 6 h; (c) excess NaN_3, dry DMF, 60 °C, 3 h; (d) KOH, H_2O, THF, 20 °C, 6 h.

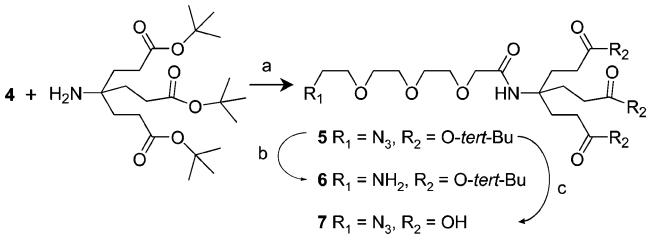
After 15 h, the residue was filtered and the solution evaporated in vacuo to afford the crude product, which was column chromatographed eluting with 10% MeOH in $CHCl_3$ to give (65%) pure azide **10**: 3.12 g. ^{1}H NMR δ 1.31 (s, 81H, CH_3), 1.88 (br m, 24H, CH_2CH$_2$CO), 2.08 (br, 24H, CH_2CO), 3.27 (t, 6H, H$_2$NCH_2, J = 4.5 Hz), 3.41 (t, 2H, N$_3$CH_2, J = 4.5 Hz), 352−3.57 (m, 40H), 3.80 (s, 8H, OCH_2CO), 6.41 (s, 3H, NH), 6.43 (t, 3H, NHCH$_2$, J = 6 Hz), 6.45 (s, 1H, NHC). ^{13}C NMR δ 27.82 (*C*H$_3$), 28.05, 29.39 (*C*H$_2$*C*H$_2$CO), 30.31, 30.68 (*C*H$_2$*C*H$_2$-CO), 39.09 (NH*C*H$_2$), 50.42 (N$_3$*C*H$_2$), 56.98 (NH*C*), 57.68 (NH*C*), 69.64−70.80, 80.26 (*C*Me$_3$), 168.92 (*C*ONH), 169.06 (*C*ONH), 172 0.23 (*C*ONH), 172.51 (*C*O$_2$). IR 3335 (NH), 2106 (N$_3$), 1726 (C═O), 1673 (C═O), 1152 cm^{-1} (C−O). MALDI−TOF m/z = 2245.76 (M + Na$^+$), calcd m/z = 2245.76 (M + Na$^+$).

Synthesis of the Second-Generation Dendron 11. Azide **10** (2 g, 890 μmol) was converted to its corresponding amine **11** by reduction with 10% Pd/C at 60 psi at 25 °C, as noted above. After 24 h, the mixture was filtered through the Celite to remove the catalyst (*caution*: *pyrophoric*), and then the solvent was removed in vacuo to give (94%) the pure amine **11**: 1.85 g. ^{1}H NMR δ 1.36 (s, 81H, CH_3), 1.99 (br m, 24H, CH_2CH$_2$-CO), 2.20 (br m, 24H, CH_2CO), 3.41 (br m, 8H, NHCH_2, CH_2N$_3$), 3.49−3.69 (m, 40H), 3.94 (s, 8H, OCH_2CO), 6.52 (s, 3H, NH), 7.31 (s, 5H, NHCH$_2$, H_2NCH$_2$), 7.44 (s, 1H, NHC). ^{13}C NMR δ 28.01 (*C*H$_3$), 29.53, 29.67 (*C*H$_2$*C*H$_2$CO), 30.55, 31.23 (*C*H$_2$*C*H$_2$CO), 39.22 (NH*C*H$_2$), 39.63 (NH$_2$*C*H$_2$), 57.15 (NH*C*), 58.19 (NH*C*), 69.53−70.92, 80.46 (*C*Me$_3$), 169.15 (*C*ONH), 170.08 (*C*ONH), 172 0.39 (*C*ONH), 173.60 (*C*O$_2$). IR 3334 (NH$_2$), 1724 (C═O), 1670 (C═O), 1153 cm^{-1} (C−O). MALDI−TOF m/z = 2218.40 (M + Na$^+$), calcd m/z = 2218.34 (M + Na$^+$).

Synthesis of First-Generation Dendrimer 12. General Procedure. To a stirred solution of amine **6** (2.5 g, 4.13 mmol) and NEt_3 (2 g, 19.6 mmol) in dry CH_2Cl_2 was added tetraacid chloride[104] (500 mg, 1.0 mmol), prepared from the corresponding tetraacid[105] in CH_2Cl_2 added dropwise. The mixture was stirred for 30 min at 0 °C and then for 6 h at 25 °C. The mixture was washed sequentially with 10% cold HCl, water, and saturated brine solution, then dried ($MgSO_4$), and evaporated in vacuo to give the crude product, which was column chromatographed (SiO_2) eluting with 7% MeOH in CH_2Cl_2 to afford (83%) the pure dendrimer **12** as a viscous oil: 2.2 g. ^{1}H NMR δ 1.44 (s, 108 H, CH_3), 1.98 (t, 24H, CH_2CH$_2$CO, J = 8.7 Hz), 2.21 (t, 24H, CH_2CO, J = 8.7 Hz), 2.44 (t, 8H, OCH$_2$CH_2-CO, J = 6.0 Hz), 3.31 (s, 8H, OCH_2), 3.45 (t, 8H, OCH_2CH$_2$-CO, J = 4.8 Hz), 3.56 (t, 8H, NHCH_2, J = 4.8 Hz), 3.66−3.68 (m, 40H), 3.93 (s, 8H, OCH_2CO), 6.47 (s, 4H, NH), 6.83 (t, 4H, NHCH$_2$, J = 2.0 Hz). ^{13}C NMR δ 27.71 (*C*H$_3$), 29.26, 29.40 (*C*H$_2$*C*H$_2$CO), 36.34 (*C*H$_2$CO), 38.92 (NH*C*H$_2$), 45.12 (4°*C*), 56.85 (NH*C*), 67.04 (O*C*H$_2$CH$_2$), 68.80 (*C*H$_2$OCH$_2$), 69.57−70.67, 80.04 (*C*Me$_3$), 168.80 (*C*ONH), 171.07 (*C*ONH), 172.03 (*C*O$_2$). IR 3342 (NH), 1724 (C═O), 1672 (C═O), 1153 cm^{-1} (C−O). MALDI−TOF m/z = 2792.35 (M + Na$^+$), calcd m/z = 2794.50 (M + Na$^+$).

Synthesis of Second-Generation Mono-PEG Extended Dendrimer 13. The second-generation dendrimer was prepared using the amine **9** (8.1 g, 4.03 mmol) and tetraacyl chloride (500 mg, 1.0 mmol), following the above general procedure. Purification was accomplished by chromatography eluting with 5% MeOH in CH_2Cl_2 to afford (70%) the pure dendrimer **13** as a waxy semisolid: 5.8 g. ^{1}H NMR δ 1.33 (s, 324 H, CH_3), 1.88 (t, 96H, CH_2CH$_2$CO, J = 7.5 Hz), 2.16 (t, 96H, CH_2CO, J = 7.5 Hz), 2.78 (t, 8H, OCH$_2$CH_2, J = 3.9 Hz), 3.28 (s, 8H, CH_2O), 3.33 (s, 8H, OCH_2), 3.42 (t, 8H, OCH_2CH$_2$-CO, J = 3.9 Hz), 3.54 (t, 24H, NHCH_2, J = 6.0 Hz), 3.59 (m, 120H), 3.82 (s, 24H, OCH_2CO), 6.38 (s, 12H, NH), 6.81 (s, 4H, NHCH$_2$), 6.92 (s, 4H, NH). ^{13}C NMR δ 28.05 (*C*H$_3$), 29.60, 29.77 (*C*H$_2$*C*H$_2$CO), 30.5, 30.72 (*C*H$_2$*C*H$_2$CO), 37.47 (*C*H$_2$CO), 39.29 (NH*C*H$_2$), 45.33 (4°*C*), 57.17 (NH*C*), 57.71 (NH*C*), 66.19 (*C*H$_2$-OCH$_2$), 67.80 (CH$_2$OCH$_2$), 69.75−70.97, 80.48 (*C*Me$_3$), 169.00 (*C*ONH), 172.41 (*C*ONH), 173.29 (*C*ONH), 173.36 (*C*O$_2$); IR 3331 (NH), 1726 (C═O), 1669 (C═O), 1153 cm^{-1} (C−O). MALDI−TOF m/z = 8406.10 (M + Na$^+$), calcd m/z = 8405.59 (M + Na$^+$).

Scheme 2. Construction of Extended Dendrons 6 and 7[a]



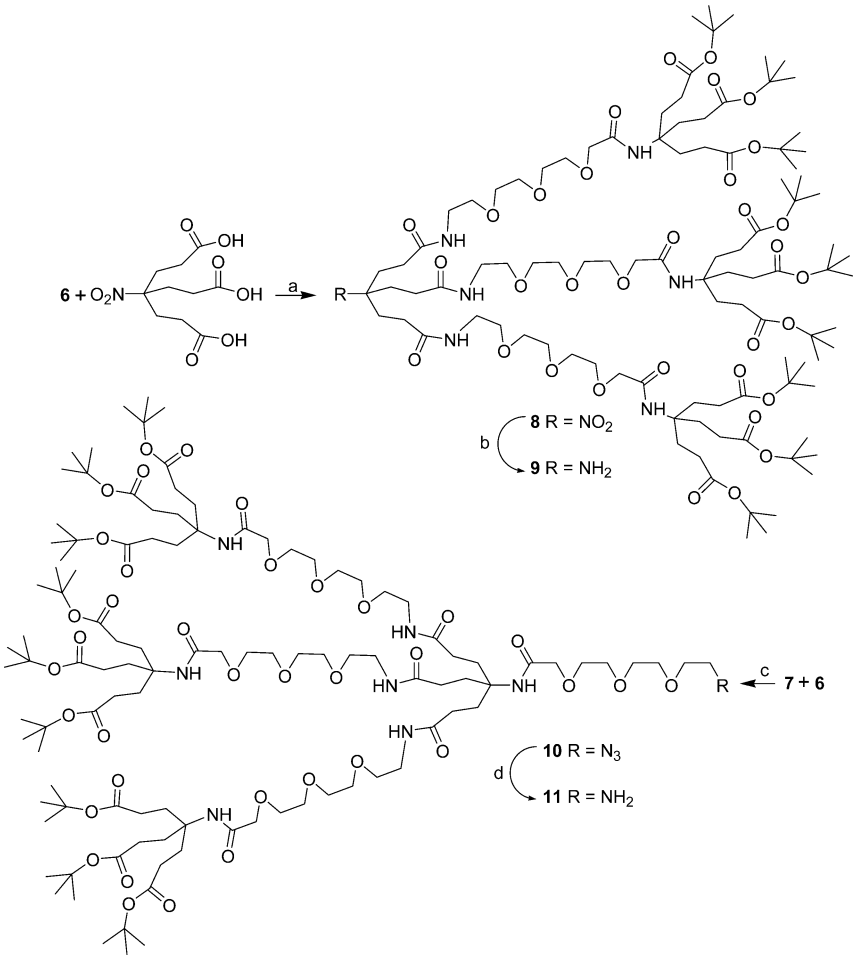
[a] (a) DCC, 1-HOBT, THF, 25 °C, 15 h; (b) EtOH, 10% Pd/C, H_2 (60 psi), 20 °C, 16 h; (c) HCO_2H, 25 °C, 6 h.

Synthesis of Second-Generation Bis-PEG Extended Dendrimer 14. The second-generation dendrimer can be prepared via amine **11** (1.75 g, 790 μmol) and tetraacyl chloride (100 mg, 200 μmol) using the general procedure. The residual solid was column chromatographed (SiO_2) eluting with 5% MeOH in CH_2Cl_2 to give (63%) the pure dendrimer **14** as a waxy solid: 1.1 g. ^{1}H NMR δ 1.29 (s, 324H, CH_3), 1.84 (t, 96H, CH_2CH$_2$CO, J = 8.4 Hz), 2.06 (t, 96H, CH_2CO, J = 8.4 Hz), 2.29 (t, 8H, OCH$_2$CH_2, J = 4.8 Hz), 3.26 (t, 8H, OCH_2, J = 4.8 Hz), 3.39 (t, 32H, NHCH_2, NHCH_2 J = 5.1 Hz), 3.50−3.55 (br m, 160H), 3.78 (s, 32H, OCH_2CO), 6.37 (s, 16H, NH, NH), 6.69 (br m, 16H, NHCH$_2$). ^{13}C NMR δ 27.90 (*C*H$_3$), 29.44, 29.58 (*C*H$_2$*C*H$_2$CO), 30.40, 30.85 (*C*H$_2$*C*H$_2$CO), 36.46 (*C*H$_2$CO), 39.13 (NH*C*H$_2$), 45.38 (*C*), 57.04, 57.76 (2 NH*C*), 67.26, 68.97 (2 CH$_2$OCH$_2$), 69.61−70.78, 80.32 (*C*Me$_3$), 168.95, 169.35, 171.25, 172.28 (4 *C*ONH), 172.95 (*C*O$_2$); IR 3334 (NH), 1724 (C═O), 1670 (C═O), 1153 cm^{-1} (C−O). MALDI−TOF m/z = 9115.98 (M + Na$^+$), calcd m/z = 9120.36 (M + Na$^+$).

Results and Discussion

The treatment (Scheme 1) of triethylene glycol with ethyl diazoacetate in the presence of BF_3·Et_2O gave the monoester **1**, which with mesyl chloride in the presence of Et_3N, followed by NaN_3 in DMF at 60 °C gave (95%) the desired azidoester **3**, which was supported (^{1}H NMR) by the upfield shift (3.64−3.06 ppm) for the ω-CH_2 triplet upon substitution. Ester **3** was then saponified to give (96%) the azidoacid **4**, which was identical to a sample generated in four steps from chlorotriethylene glycol.[106] Both ester **3** and acid **4** were used as the simple PEG connectors between branching points within a dendrimer framework. Treatment (Scheme 2) of the azidoacid **4** with Behera's amine[100,101] under peptide coupling conditions[107,108] afforded (92%) the PEG-

Scheme 3. Synthesis of Dendrons 9 and 11[a]



[a] (a) DCC, 1-HOBT, dry THF, 25 °C, 24 h; (b) H_2 (60 psi), Raney Ni, EtOH, 50 °C, 12 h; (c) EDC, 1-HOBT, anhydrous DMF, amine **6**, 25 °C, 24 h; (d) EtOH, 10% Pd/C, H_2 (60 psi), 25 °C, 24 h.

extended branched amide **5**, which was supported by the 3:1 integration (^{1}H NMR) of the triplet (1.87 ppm) for the α-CH_2CO$_2$R to the singlet for the α-OCH_2CON as well as the MS peak at *m*/*z* 632 for the desired parent ion.

Deprotection of **5** with formic acid at 25 °C quantitatively generated the corresponding triacid **7**, evidenced by the absence of the *tert*-butyl resonances and appearance of a peak at 9.54 ppm for the carboxylic acid, whereas subjecting **5** to reductive conditions using Pd on carbon gave (94%) the desired amine **6**, which was spectrally (^{1}H and ^{13}C NMR) similar to the azide except for the shift noted for the N$_3$CH_2− to H$_2$NCH_2− conversion; the mass spectral data showed a peak at *m*/*z* 606 for the M + H$^+$, further supporting the assignment.

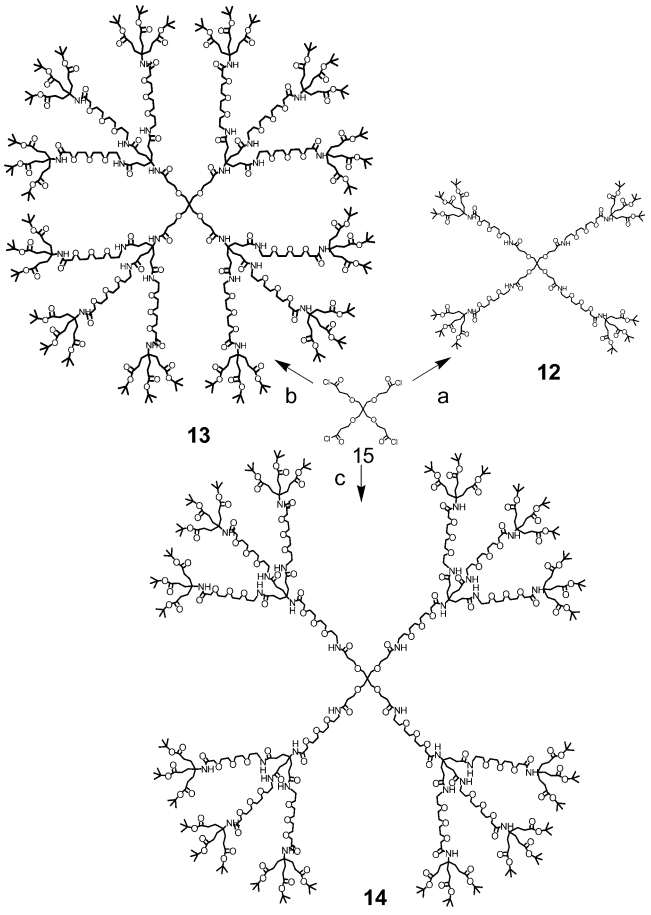
The PEG-extended dendron **9** was constructed (Scheme 3) by initially treating 4-(2-carboxyethyl)-4-nitroheptanedioic acid[101−103] with amine **6** under typical amidation conditions to give (70%) the second-generation predendron **8**, which was chromatographed to remove the excess DCC and urea byproducts. The ^{13}C NMR spectral data revealed peaks at 57.31, 57.96, and 80.67 ppm for the three different quaternary centers representing the two branching carbons and intact termini; the three carbonyl groups (169.33, 172.54, and 172.58 ppm) as well as MALDI−TOF MS peak at 2056.2 (M + Na)$^+$ support the successful amidation. Reduction of the focal nitro substituent was accomplished using T1 Raney nickel to afford (80%) the corresponding amine **9**, which was supported by the shift (^{13}C NMR) for the O$_2$N*C* to H$_2$N*C* conversion (92.8−57.9 ppm) and the MS peak at 2030.34 (M + Na)$^+$.

The double PEG-extended **11** was obtained in two steps from azide **7** with amine **6** using the same amidation procedure, except using EDC, to give (65%) the heptaamide intermediate **10**; catalytic reduction using Pd/C at 60 psi hydrogen then transformed (94%) the azide moiety to the corresponding amine **11**. The ^{13}C NMR data confirm this structure: 169.15, 170.08, and 172.39 ppm for the three different amide carbons and the expected shift for the N$_3$CH_2 to H$_2$NCH_2 (50.4−39.6 ppm) conversion as well as the observed mass peak for the parent ion 2218.34 (M + Na$^+$).

Treatment of 4.4 equiv of amine **6** and tetraacyl chloride[109] **15** in the presence of Et$_3$N afforded the desired polyester **12** (Scheme 4). The ^{13}C NMR spectrum of dodecaester **12** showed peaks at 45.12 ppm for the core quaternary carbon and peaks at 168.80, 171.07, and 172.03 ppm for the three distinct carbonyl groups as well as the MALDI−TOF MS showed a peak at 2792.35 (M + Na$^+$), supporting dendrimer formation.

When amine **9** was subjected to the same procedure, pure dendrimer **13** was isolated (70%) and characterized (^{13}C NMR) by the peaks (45.33, 57.17, and 57.71 ppm) for the three different quaternary centers representing one central and two branching carbons as well as the presence of four different carbonyl groups (169.00, 172.41, 173.29, and 173.36 ppm); the peak (MALDI−

Scheme 4. Synthesis of Dendrimers 12−14[a]



[a] (a) Et_3N, CH_2Cl_2, amine **6**; (b) Et_3N, CH_2Cl_2, amine **9**; (c) Et_3N, CH_2Cl_2, amine **11**.

TOF MS) at 8406.1 ($M + Na^+$) confirms the formation of the four new internal amide connections. The related second-generation dendrimer **14** was assembled (63%) from the bis-PEG-extended amine **11** using the same procedure; its ^{13}C NMR spectral data showed peaks for five carbonyl (168.95, 169.35, 171.25, 172.28, 172.95 ppm) groups, and its MALDI−TOF MS showed a peak for molecular ion at 9115.98 ($M + Na^+$), supporting the formation of the desired dendrimer **14**.

Dendrimers **12**−**14** are waxy solids and the differential scanning calorimetry (DSC) data of the dendrimers **12** through **14** (T_g = 5.9, 2.6, and −5.8 °C, respectively) revealed a gradual decrease in the glass transition temperature (T_g) with increasing dendrimer generation; all are soluble in most common organic solvents (i.e., Et_2O, $CHCl_3$, hexane, DMF, MeOH, and EtOH) as well as in aqueous solution. These dendrimers were also shown to solubilize lithium metal salts in organic media. To exclude trace amounts of encapsulated water associated with the ethereal oxygen atoms of triethylene glycol units, the dendrimers were dried in vacuo for extended periods of time. Upon addition of lithium triflate to $CHCl_3$ solutions of dendrimers **12**−**14**, lithium triflate readily dissolved, whereas the triflate salt was notably insoluble in $CHCl_3$ without added dendrimer. The ^{13}C NMR spectrum of the dendrimer−Li salt complex showed broadened peaks for ethylene glycol units and a quartet peak for the CF_3 group.

Conclusion

Monomer **4** was prepared in four steps from triethylene glycol. The first-generation dendron was prepared by the coupling reaction of the acid **4** and Behera's amine to produce **5**, which was reduced to give amino building block **6**. The second (**9**) and third (**10**) generation dendrons were prepared using similar coupling conditions. The first−third generation dendrimers were synthesized from monomers **6**, **9**, and **11**, respectively, using a tetraacyl chloride, as the core, via a convergent approach. These materials are soluble in organic solvents as well as in aqueous solvents. Dissolution of lithium triflate in $CHCl_3$ was shown with added dendrimer.

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