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A Novel End-Reactive Dendron in the Accelerated Synthesis of Carboxylate-Terminated Dendritic Poly(Ether-Amides)

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A NOVEL END-REACTIVE DENDRON IN THE ACCELERATED SYNTHESIS OF CARBOXYLATE-TERMINATED DENDRITIC POLY(ETHER-AMIDES)

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ABSTRACT

A novel end-reactive AB_4 dendron with four phenolic coupling sites and a benzyl alcohol functionality at the focal point has been prepared by a chemoselective amidation process that requires no functional group protection. The usefulness of the end-reactive dendron for the accelerated synthesis of dendritic polymers has been demonstrated in the preparation of several poly(amide-ether) dendritic macromolecules with carboxylate chain-ends. The new dendritic polymers have been characterized by NMR and MALDI mass spectrometry, size exclusion chromatography, and thermal analysis methods.

INTRODUCTION

The preparation of synthetic globular macromolecules [1] that may act as carriers, catalysts, additives, or drug-delivery systems has attracted much attention

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recently. Both regular dendrimers [2, 3] with their precisely controlled molecular architecture and less regular, but more readily obtained, hyperbranched polymers [1, 4, 5] have been the object of numerous studies. In particular, dendritic macromolecules with carboxylic acid chain-ends have been prepared by several different routes because their anionic salts are water-soluble and behave as unimolecular micelles [1, 6-8]. Since their inner building blocks are frequently lipophilic, these unimolecular micelles may be used to carry normally water-insoluble molecules in water [8] suggesting applications in drug delivery, catalytic or tagging processes or, more generally, for water-borne chemistry.

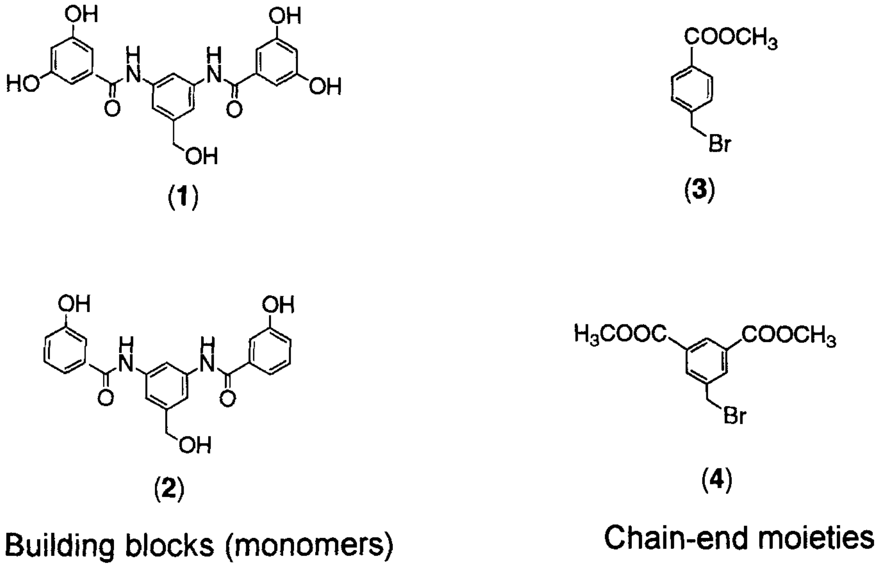
While hyperbranched polymers with degrees of branching [9] in the range of 0.45 to 0.60 are easily obtained by the polycondensation of AB_x monomers [5, 9] (in which x is usually 2 or 3) or through the self-condensing vinyl polymerization process we have described recently [4], more regular dendrimers with a degree of branching close to 1.0 are still best obtained by time-consuming multi-step syntheses if a pure product is expected. A very clever approach devised by Hult and coworkers [10] allows the preparation of a family of hyperbranched aliphatic polyesters said to have a very high degree of branching (e.g. 0.80) through the controlled stepwise addition of a monomer to a growing core moiety. The high degree of branching claimed for this process might be derived from the low of solubility of the monomer in the molten core to which it becomes bound. Since the effective concentration of dissolved monomer is kept low throughout the coupling process, the statistical self-condensation reactions of monomer that would lower the ultimate degree of branching may be suppressed. Unfortunately, this approach is currently limited to one family of monomers with both very specific solubility properties and a low propensity to transesterify. In addition, the lability of ester linkages precludes the ready use of this approach for the preparation of polymers with carboxylate chain-ends.

An alternate approach to the rapid synthesis of dendritic materials with a very high degree of branching involves the preparation of multifunctional branched monomers ("hypermonomers") or convergent dendrons with reactive chain-ends [11, 12] that can be assembled quickly into regular dendrimers [11] or polymerized to afford hyperbranched polymers. We first reported the use of such end-reactive dendritic molecules and hypermonomers in 1991, and have since used end-reactive dendrons to prepare a variety of dendrimers and hyperbranched polymers [12, 13]. The double-stage convergent approach [11] pioneered the use of large dendritic cores to prepare regular polyether dendrimers with molecular weights as high as 160,000. The versatility of this approach was further enhanced recently with the design of a family of end-functionalized dendrons that may be readily purified by crystallization [14]. We have also demonstrated the use of a two monomer approach that enables the growth of two generations through a "one pot synthesis" without intermediate purification steps [15]. A good illustration of an accelerated convergent approach is provided in the use of an AB_4 hypermonomer to prepare a fifth generation regular dendrimer in only three synthetic steps [13]. The group of Moore [16] has also reported a very fast growth method, the "double exponential" dendrimer growth approach which makes even more efficient use of the same accelerated growth concepts. Since the shape [17] and the unique viscosity properties [18-19] of dendrimers, both in solution [18] and in the melt, [19] are closely related to their molecular sizes, these accelerated synthesis techniques are important for the faster preparation of well-defined dendrimers and dendrons..

We now report the preparation of novel end-reactive branched monomers and dendrons for the rapid synthesis of dendritic polyamides. This approach makes use of a chemoselective amidation process with the diphenyl(2,3-dihydro-2-thioxo-3-benzoxazolyl)phosphonate (DBOP) reagent developed by Ueda *et al.* [20]. The advantage of this approach is that no functional group protection is required in contrast to most other stepwise syntheses.

RESULTS AND DISCUSSION

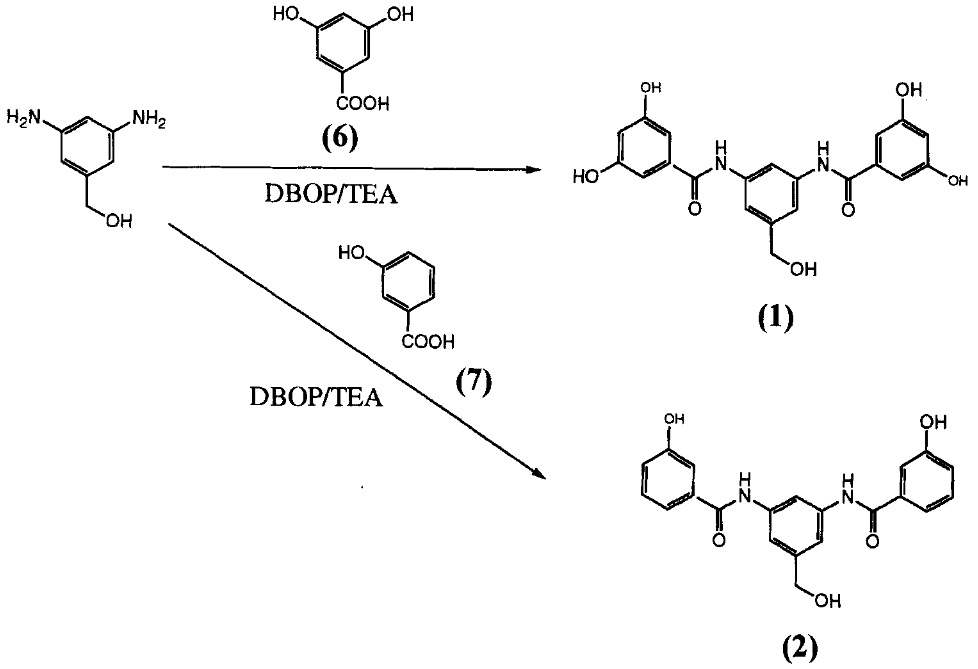
The various building blocks (monomers) and chain-end moieties used in this work are shown in Scheme I. Our primary targets included monomer **1** $(OH)_4$-[G-1]-OH with four reactive phenolic hydroxyl chain ends and a single benzyl alcohol focal point, as well as the analogous monomer **2** $(OH)_2$-[G-1]-OH with only two phenolic chain ends. Since the products obtained by Williamson syntheses involving these building blocks will be poly(ether amides) with a framework containing rigid amide bonds, their properties are expected to differ from those of the polyether dendrimers we have reported earlier [11, 21]. In order to obtain stable precursors of unimolecular micelles with carboxylate chain-ends, we also selected methyl 4-bromomethyl-benzoate (**3**) and the corresponding bromomethylated dimethyl ester of isophthalic acid (**4**) as the chain-end moieties. In both cases, the methyl ester groups are used as the latent ionic carboxylate end-groups since their removal should be possible under mild alkaline conditions without cleavage of the inner building blocks.



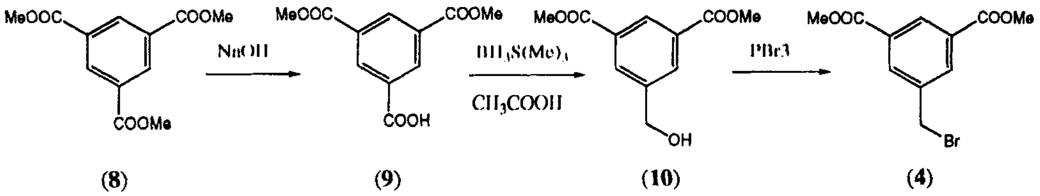
Building blocks (monomers)

Chain-end moieties

Scheme I



Scheme II



Scheme III

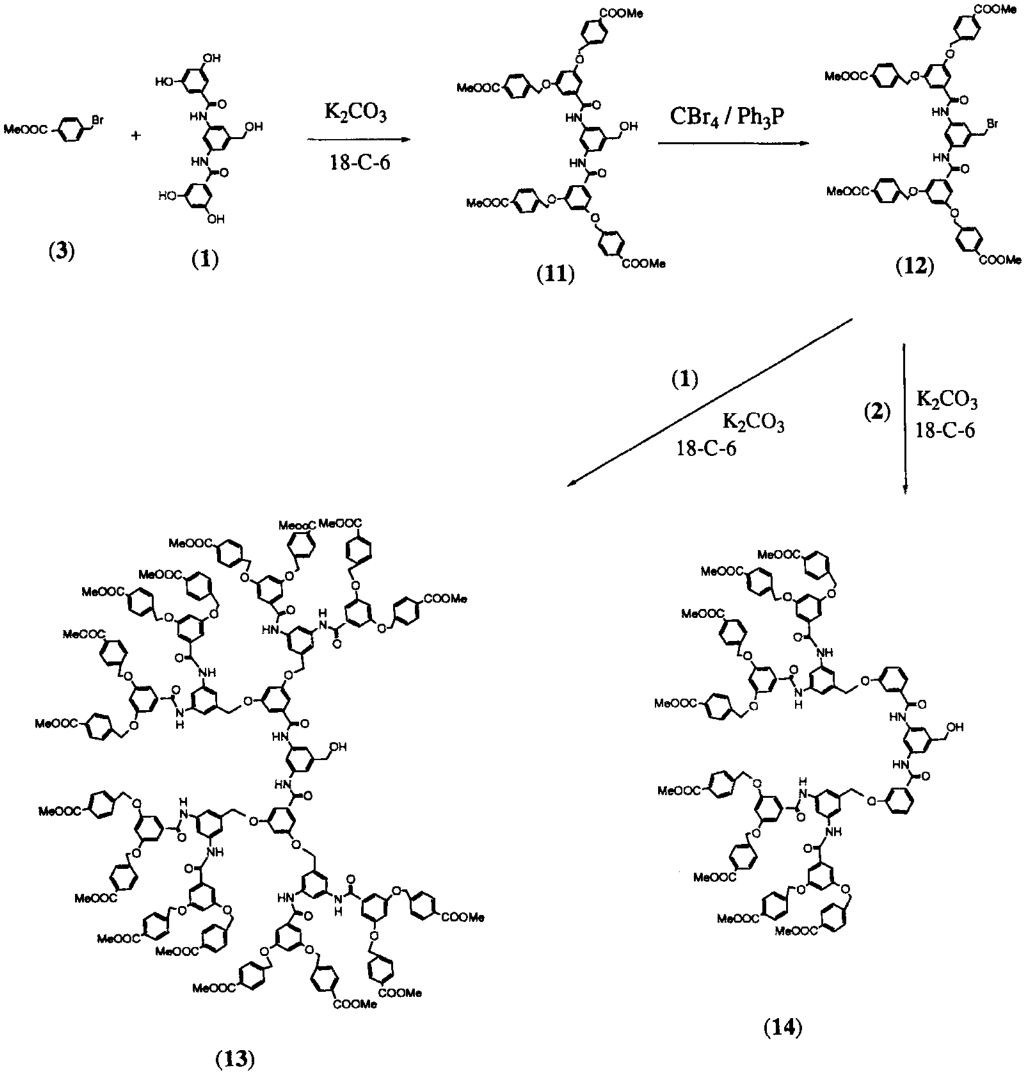
Preparation of the Building Blocks and End-Reactive Moieties

Scheme II outlines the preparation of monomers **1** and **2** from commercially available 3,5-diaminobenzyl alcohol and 3,5-dihydroxybenzoic acid (**6**) or 3-hydroxybenzoic acid (**7**). As mentioned earlier, the amidation reaction can be carried out in chemoselective fashion [20] without any need to protect the benzyl alcohol group of the starting material. The preparation of **1** requires that a slight excess (2.2 equiv.) of the activating agent DBOP be used with 4 equiv. of triethylamine also present to maintain neutrality. This procedure affords monomers **1** and **2** in yields of 80 and 60%, respectively. Monomer **1** is insoluble in solvents such as acetone or THF and, once precipitated from its solution in N-methylpyrrolidone (NMP), it is best purified by soxhlet extraction with ethyl acetate.

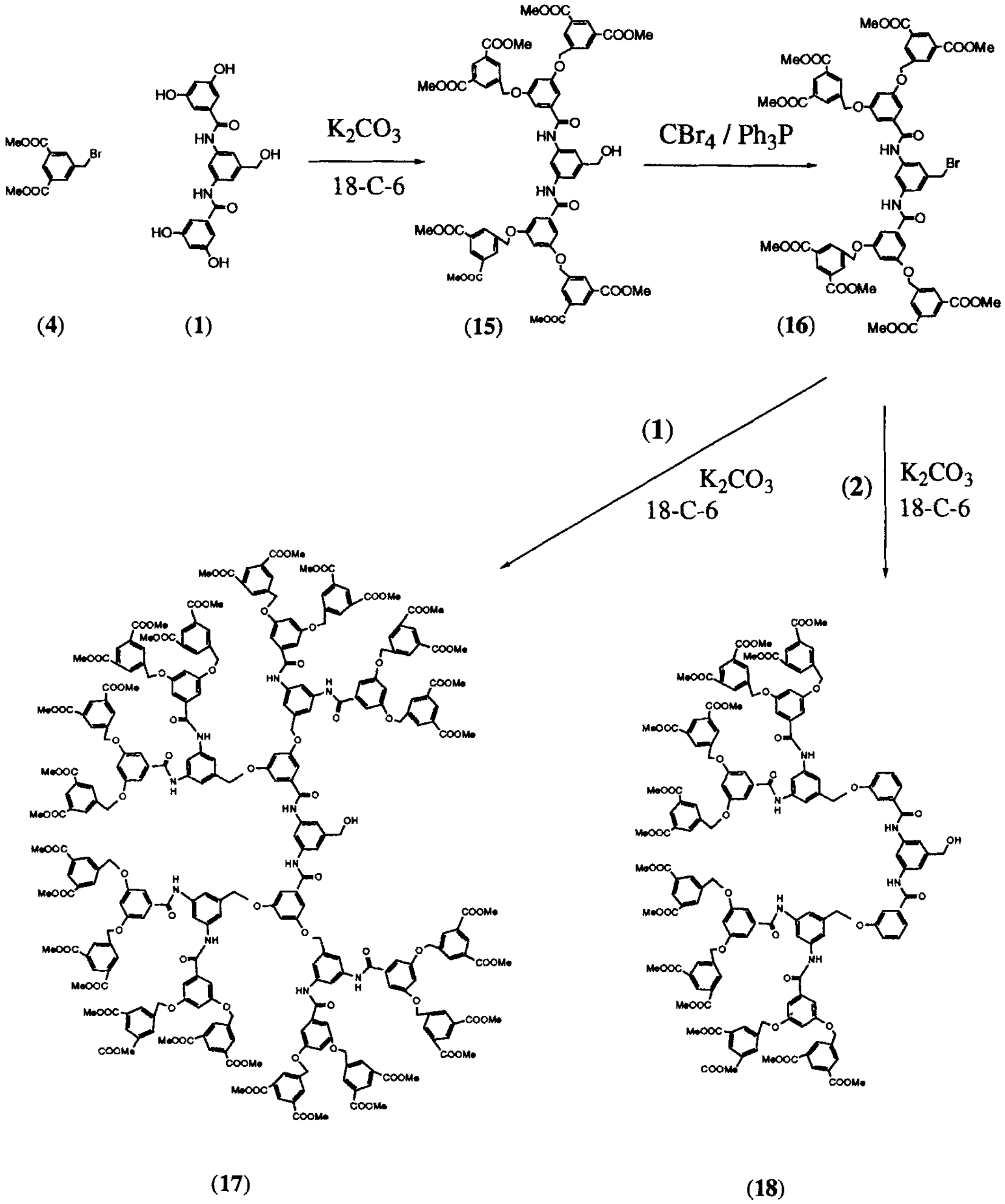
The end-reactive moiety **3** is available commercially while dimethyl 5-(bromomethyl)-isophthalate, **4**, is readily prepared as shown in Scheme III. Reaction of trimethyl 1,3,5-benzenetricarboxylate (**8**) with one equivalent of sodium hydroxide gave the corresponding monoacid (**9**) in 78% yield after recrystallization from water. Reduction of the free acid to the corresponding benzyl alcohol (**10**) is effected in 76% yield using borane-methyl sulfide complex. Finally, bromination of the benzylic alcohol group with phosphorus tribromide affords the desired dimethyl 5-(bromomethyl)-isophthalate (**4**) in 72% yield after purification.

Preparation of End-Reactive Generation Three and Four Dendrons

Scheme IV details the synthetic route used to prepare generation four and generation three dendrons with sixteen (**13**) and eight (**14**) reactive ester chain-ends respectively, while Scheme V shows the preparation of analogous but more highly end-functionalized dendrons with thirty two (**17**) and sixteen (**18**) chain-ends. For both families the same convergent synthesis [21] was applied using either the monofunctional or the difunctional end-reactive moieties **3** and **4** in the first growth step.


MeOOC
Br
+
HO
OH
HN
O
OH
(3)
(1)
K_2CO_3
18-C-6
COOMe
MeOOC
(11)
CBr_4 / Ph_3P
(12)
(1)
K_2CO_3
18-C-6
(2)
K_2CO_3
18-C-6
(13)
(14)

Scheme IV



Scheme V

For all of these syntheses, the solubility of both starting materials and products became an important issue. The presence of strongly hydrogen-bonding amide linkages in our target molecules drastically restricts the choice of solvents. For example, the lack of solubility of starting material **1** in acetone or THF, the solvents of choice in classical [21] convergent syntheses of polyether dendrimers, led us to use NMP instead. The coupling reaction of **1** and **3**, which occurs readily in NMP in the presence of potassium carbonate and 18-crown-6, affords a product that has a somewhat enhanced solubility when compared to **1** as a result of the introduction of ester end-groups. The next synthetic step involves activation of the focal point group of **11** by reaction with carbon tetrabromide in the presence of triphenylphosphine to afford the desired bromide **12**. Both generation four (**13**) and generation three (**14**) dendrons can be prepared directly from **12** by reaction with the appropriate branched monomer. Formation of **13** required both the use of a slight excess (4.8 equiv.) of **12** under rigorously dry conditions, and careful purification of the crude product by flash chromatography to remove partly functionalized dendrons. Dendrimer **14**, which is less sterically crowded than **13** could be obtained in higher yield, due in part to its limited solubility in THF which allowed facile purification by recrystallization.

The more highly end-functionalized dendrimers **17** and **18** were more elusive and obtained in lower overall yields than **13** and **14** both as a result of difficulties encountered in the search for appropriate solvents and because extensive purification by flash chromatography or fractional precipitation was necessary.

Characterization of the Dendrimers

NMR spectroscopy proved to be essential for the characterization of the various dendrimers with alternating internal amide and ether linkages. Figure 1 shows the ^{1}H NMR spectra of the alcohol and bromide dendrons **11** and **12**. As expected, the resonances for the focal point benzylic methylene of these dendrons near 4.50 ppm and 4.70 ppm for the alcohol and bromide, respectively, allow their facile identification. The transformation of **11** into the corresponding fourth generation dendron **13** is accompanied by some broadening of signals (Figure 2a). The focal point benzylic methylene is seen at 4.48 ppm with two additional layers of benzyl ether methylene groups observed at 5.17 and 5.23 ppm. The amide signal of **11** observed at 10.20 ppm is replaced by signals at 10.24 and 10.30 ppm for the NH groups of **13**.

Much additional structural information can be obtained from the ^{13}C NMR spectra of the various dendrons (Figure 2b) since all of the C atoms of the structures can be assigned even in the case of the fourth generation dendrimer **13**.

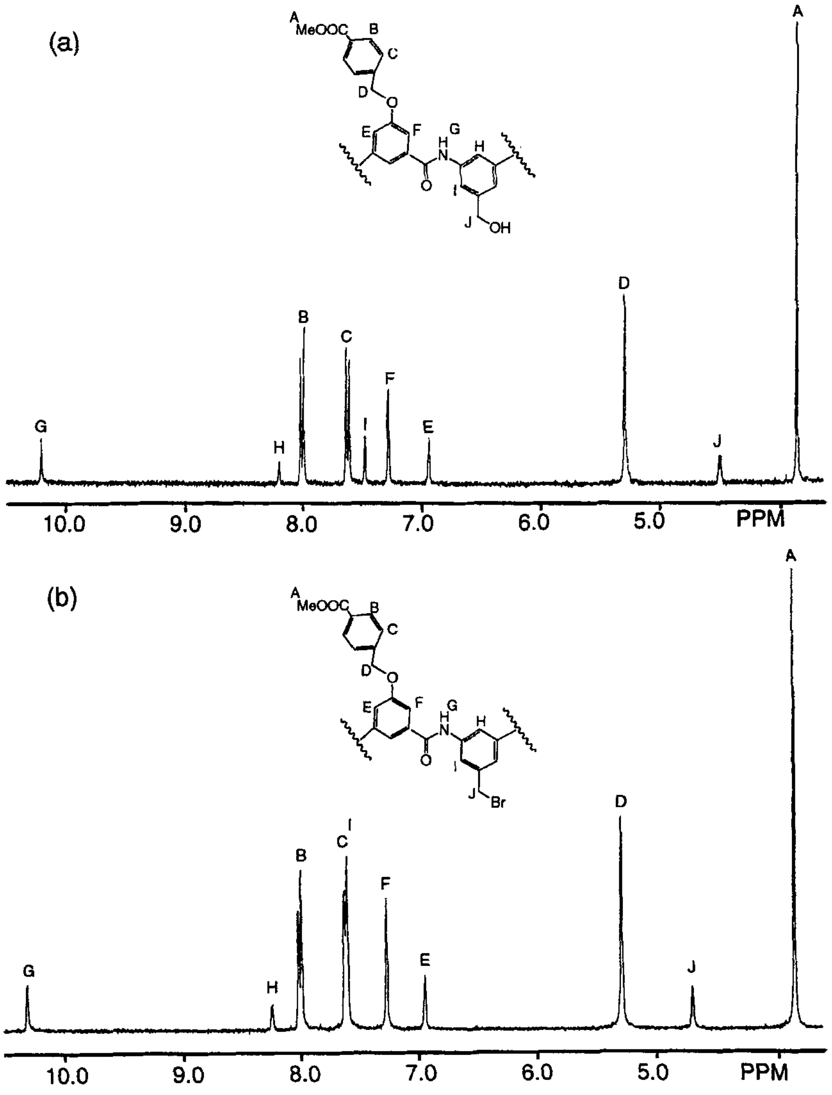


Figure 1. ^{1}H NMR spectra of the second generation dendrimers: (a) (MeOOC)$_4$-[G-2]-OH (**11**) and (b) MeOOC)$_4$-[G-2]-Br (**12**).

As expected, the ^{1}H NMR spectra of **15** and **16** in DMSO-d$_6$ are quite similar to those of **11** and **12** except for the resonances characteristic of the 1,3,5 substituted aromatic rings of the end groups with signals at 8.30 and 8.40 ppm. In the case of **17** and **18**, NMR spectrometry was less useful due to significant broadening of the signals.

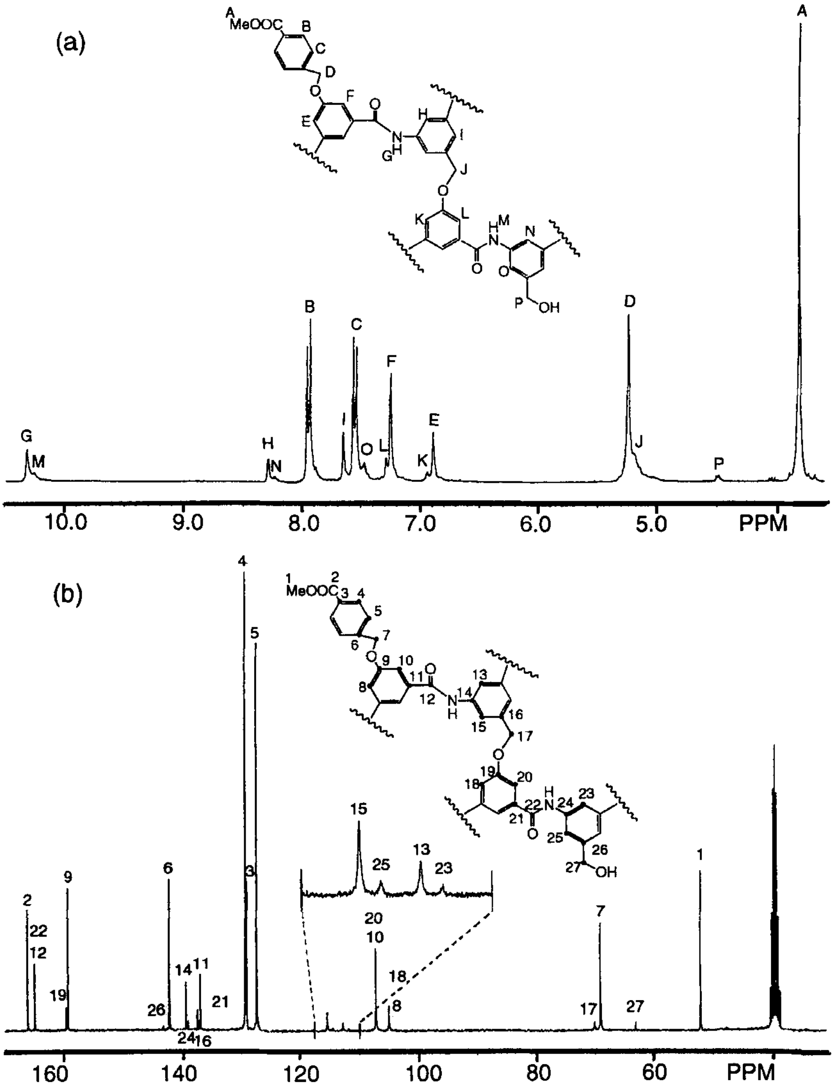


Figure 2. ^1H NMR (a) and 13C NMR (b) spectra of the fourth generation dendrimer $(MeOOC)_{16}$-[G-4]-OH (**13**).

Table 1 provides a comparison of theoretical molecular weights with those measured by size exclusion chromatography (SEC) and MALDI mass spectrometry. Although the SEC data is relative, since calibration was effected using polystyrene standards, the data is useful in confirming the low polydispersity of the dendrimers. In all cases, excellent agreement was obtained between theoretical

TABLE 1. Theoretical Molecular Weights of the Poly(ether-amide) Dendritic Macromolecules as Compared to the Molecualr Weights Determined by SEC and MALDI

Structure	Compound	Polymer yield (%)	SEC				MALDI
			Theoretical	M_w	M_n	M_w/M_n	M/Z
(**13**)	$(MeOOC)_{16}$-[G-4]-OH	55	4350	4127	3964	1.04	4371.5
(**14**)	$(MeOOC)_8$-[G-3]-OH	73	2346	1936	1980	1.02	2364.8
(**17**)	$(MeOOC)_{32}$-[G-4]-OH	30	5279	5217	4831	1.08	5321.8
(**18**)	$(MeOOC)_{16}$-[G-3]-OH	40	2813	-	-	-	-

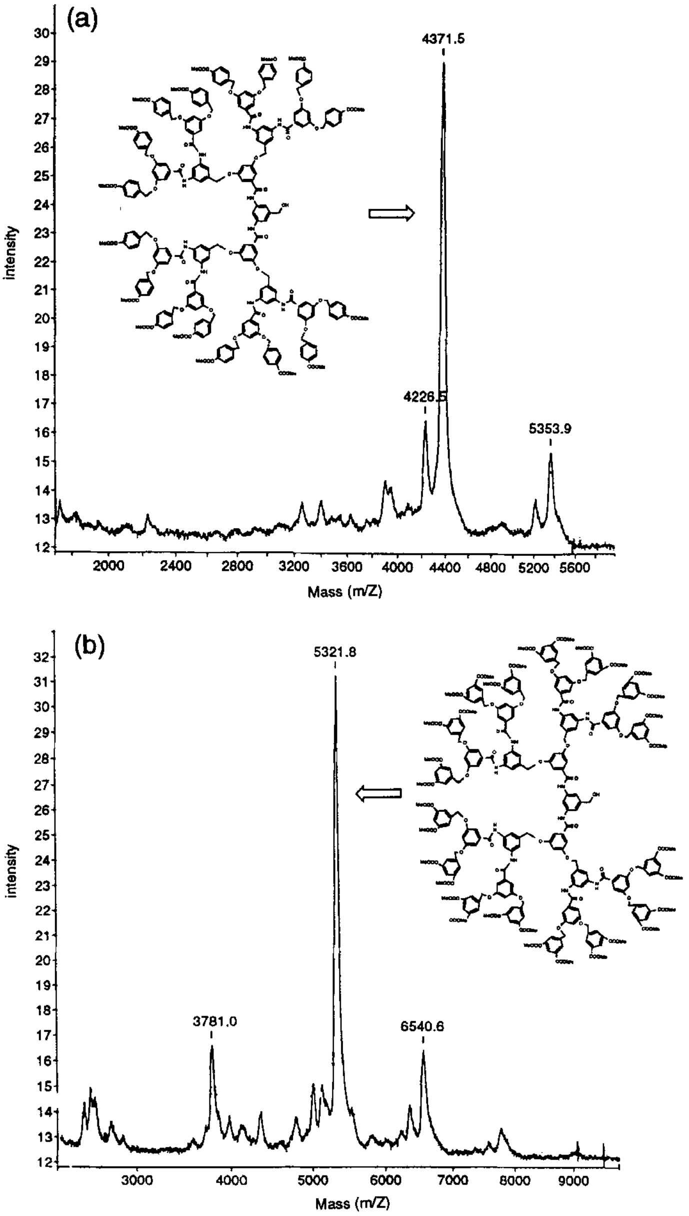


Figure 3. MALDI-TOF spectra of the fourth generation dendrimers: (a) $(MeOOC)_{16}$-[G-4]-OH (**13**) and (b) $(MeOOC)_{32}$-[G-4]-OH (**17**).

TABLE 2. Glass Transition Temperatures and Decomposition Temperatures for the Poly(amide-ether) Dendritic Macromolecules

Structure	Compound	DSC	TGA
		T_g (°C)	T_d (°C)
(13)	$(MeOOC)_{16}$-[G-4]-OH	107.5	373.4
(14)	$(MeOOC)_8$-[G-3]-OH	107.3	373.6
(17)	$(MeOOC)_{32}$-[G-4]-OH	120.7	379.9
(18)	$(MeOOC)_{16}$-[G-3]-OH	119.2	384.5

molecular weights and the molecular weights measured by MALDI. The third generation dendrimer **18** was not analyzed due to its low solubility in THF.

Figure 3 shows the MALDI spectra of **13** and **17**. The spectrum of **13** shows the expected signal for the pure compound with a sodium cation (theory: 4,373; found: 4,371.5). Several smaller peaks are also seen including one at 5,354 which might result from a side-reaction that leads to the coupling of one additional generation two bromide dendron (compound **12**). No peaks at higher mass are observed while a small peak at 4,226 might well correspond to the loss of one of the methyl 4-oxymethylbenzoate chain-ends. The MALDI spectrum of **17** shows a main signal at 5,322 corresponding to the potassium adduct of the desired structure. Smaller peaks also reflect the occurrence of side-reactions, some of which likely involve the loss of a chain-end unit with coupling of additional G-2 bromide dendrons. Overall, these spectra confirm that the desired products have been obtained with an excellent level of purity, at least when compared to typical synthetic macromolecules. Clearly, the solubility problems encountered during the syntheses make complete purification of the product very difficult and hence the exceedingly high levels of purity we have reported for other dendrimers [14, 21] cannot be matched here.

Table 2 outlines glass transition and thermogravimetric data for the various dendrimers. The influence of the chain-end moieties described in our earlier work [22] is clearly seen in the DSC data. Both **13** and **14** with the same methyl 4-oxymethylbenzoate terminal group have similar T_g values (ca. 107°C). This value is considerably higher than the value of 60°C observed for polyether dendrimers with the same terminal groups, a finding that is not unexpected in view of the presence of more rigid H-bonding amide groups in dendrimers **13** and **14**. The higher T_g values (ca. 120°C) recorded for **17** and **18** reflect the additional rigidity introduced by the 1,3,5-trisubstituted end units. Overall, these T_g values are consistent with the partly aromatic structures of these dendrimers since they are intermediate between the T_g values of aliphatic and wholly aromatic polyamides.

EXPERIMENTAL

General Directions

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet IR/44 spectrometer as KBr pellets. ^1H-NMR spectra were recorded using solutions in DMSO-d_6 on a Bruker WM 300 (300 mhz) spectrometer with the solvent proton signal as standard. ^{13}C-NMR spectra were recorded at 75 MHz on a Bruker WM 300 spectrometer with DMSO-d_6, as the solvent with the solvent carbon signal as internal standard. Analytical TLC was performed on commercial Merck plates coated with silica gel GF_{254} (0.25 mm thick). Silica for flash chromatography was Merck Kieselgel 60 (230-400 mesh). Size-exclusion chromatography was carried out on a chromatograph connected to a Milton Roy RefractoMonitor IV refractive index detector, and data analysis was performed with software from Viscotek Corp. Three 5-μm PL-Gel GPC columns connected in series in order of increasing pore size (500 Å, 1000Å, mixed bed C) were used with THF as solvent; calibration was performed with sixteen polystyrene standards; results of the GPC analyses are given in Table 1. MALDI mass spectrometry was carried out using a Finnigan MAT instrument equipped with a 337 nm nitrogen laser. Sample preparation was performed as follows: (i) 1-2 mg of sample was dissolved in 1 ml of solvent (THF for $(MeOOC)_{16}$-[G-4]-OH and $(MeOOC)_{32}$-[G-4]-OH and acetone for $(MeOOC)_8$-[G-3]-OH); (ii) 5 μl of analyte solution was combined with 20 μl of matrix solution (2M indoleacrylic acid in THF) or acetone in the case of $(MeOOC)_8$-[G-3]-OH) and 0.1 μl of this solution was spotted onto a sample plate via automatic pipette and allowed to dry over a period of 10 minutes. Results of the MALDI analyses are given in Table 2. The glass transition temperature for each sample was measured by differential scanning calorimetry using a Mettler DSC 30 low-temperature cell coupled to a TC10A-TA processor. Heating rates were 10K/min. and T_g was taken as the midpoint of the inflection tangent. The decomposition temperatures of the dendrimers were measured by thermogravimetry using a Seiko Instruments TG/DTA 220 Thermogravimetric Analyzer. Heating rates were 20 K/min. Elemental analyses were performed by MHW laboratories, Phoenix, AZ.

Preparation of 1: $(HO)_4$-[G-1]-OH

A mixture of 3,5-diamino benzoyl alcohol dihydrochloride (**5**) (4.222 g, 20 mmol), 3,5-dihydroxybenzoic acid (**6**) (6.165 g, 40 mmol) and distilled triethylamine (11.2 ml, 80 mmol) in dry NMP (50 ml) was stirred until a homogeneous solution was obtained. Recrystallized DBOP (16.868g, 44 mmol) was then added, and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into 1% aqueous $NaHCO_3$ and the precipitate was filtered and dried under vacuum at 45°C. The dried sample was purified by extraction from EtOAc in a Soxhlet extractor to give (**1**) as a light brown powder: yield 80%; IR: (cm^{-1}) 3300-2800, 1654, 1602, 1553, 1464, 1340 and 1006. NMR; (DMSO-d_6) δ_H: 4.46 (2H, d), 5.22 (lH, tr), 6.40 (2H, s), 6.78 (4H, s), 7.43 (2H, s), 8.10 (1H, s), 9.54 (4H, s), 10.08 (2H, s) δ_C (DMSO-d_6) 63.03, 105.31, 105.81, 111.39, 114.03, 137.17, 139.05, 142.98, 158.25, 165.64.

Anal. Calcd for $C_{21}H_{18}O_7N_2$: C,61.46; H, 4.42; N, 6.82.
Found: C, 61.39; H, 4.58; N, 6.75

Preparation of 2: $(m\text{-}0H)_2$-[G-1]-0H

A mixture of 3,5-diaminobenzyl alcohol dihydrochloride (**5**) (4.222 g, 20 mmol), 3-hydroxybenzoic acid (**7**) (5.525 g, 40 mmol), and distilled triethylamine (11.2 ml, 80 mmol) in dry NMP (50 ml) was stirred until homogeneous. Recrystallized DBOP (16.868 g, 44 mmol) was added and the reaction mixture was stirred at room temperature for 4 hours. After pouring into 1% aqueous $NaHCO_3$, the precipitate was purified by extraction from EtOAc in a Soxhlet extractor to give compound **2**. The dried sample was purified affording a light brown powder in 70% yield. IR (cm^{-1}): 3300-2900, 1660, 1584, 1551, 1489, 1452, 1423, 1294, 1236 and 1053; NMR, δ_H(DMSO-d_6) 4.48 (2H,d), 5.24 (lH, t), 6.97 (2H, d), 7.30(2H, t), 7.34 (2H, d), 7.36 (2H, ABq), 7.47 (2H, *d*), 8.15 (lH, s), 9.72 (2H, s), 10.18 (2H, s); δ_C(DMSO-d6) 63.01, 111.44, 114.13, 114.59, 118.19, 118.41, 129.34, 136.42, 139.09, 143.10, 157.31, 165.48.

Anal. Calcd for $C_{21}H_{18}O_5N_2$: C, 66.66; H, 4.80; N, 7.41.
Found: C, 66.40; H, 5.01; N, 7.31%

Preparation of 4: Dimethyl 5-bromomethyl-isophthalate

The trimethyl ester (**8**) (50.44 g, 200 mmol) was dissolved in methanol (500 ml) and the solution was stirred at reflux while 1 equiv. NaOH (8 g, 200 mmol in 100 ml of methanol) was added dropwise. After stirring at reflux for 6 hours, the methanol was evaporated and the mixture was extracted between water and ether (3X) to remove the unreacted trimethyl ester. The water layer was col-lected and acidified with conc. HCl (16.8 ml, 200 mmol) to afford a white precip-itate, and the slurry was extracted with ethyl acetate (3X). The ethyl acetate layers were collected and concentrated. The dried sample was then purified by recrystallization from water to afford the desired monoacid (**9**) as a white fine crystalline powder in 78% yield. Monoacid **9** (22.82 g, 100 mmol) was then dissolved in THF(100 ml) and borane-methyl sulfide complex (55 ml of 2.0 M solution in THF, 110 mmol) was added dropwise. The solution was stirred at reflux for 3 hours, cooled, then quenched with a mixture of water and acetic acid. The THF was evaporated to leave a slurry which was dissolved and neutralized with saturated aqueous sodium carbonate at reflux. Upon cooling to room temperature, a precipitate was formed. The precipitate was recrystallized from water to give the mono-alcohol (**10**) as a white cotton-like crystalline material in 76% yield. Monoalcohol **10** (21.42 g, 100 mmol) was then dissolved in 100 ml of THF and a THF solution of phosphorus tribromide (3.78 ml, 40 mmol in 10 ml of THF) was added dropwise to the ice-cold solution. The solution was stirred at r.t. overnight and concentrated by evaporation. The reaction mixture was extracted between water and CH_2Cl_2 (3X) and the CH_2Cl_2 phases were concentrated and dried. The dried sample was purified by flash chromatography eluting with 19:1 CH_2Cl_2/methanol to give dimethyl 5-bromomethyl-isophthalate (**4**) as a white powder in 72% yield.

IR (cm^{-1}): 1721, 1456, 1434, 1336, 1275, 1245, 1212, 1127, 1106 and 1000; NMR δ_H ($CDCl_3$) 3.96 (6H, s), 4.55 (2H, s), 8.26 (2H, d), 8.62 (1H, t); δ_C ($CDCl_3$) 31.37, 52.41, 130.43, 131.21, 134.08, 138.72, 165.57.

Anal. Calcd for $C_{11}H_{11}O_4Br$: C,46.02; H, 3.86.

Found: C, 46.17; H, 3.94%

Preparation of 11: $(MeOOC)_4$-[G-2]-0H

Monomer **1** (2.05 g,5 mmol), compound **3** (5.04 g,22 mmol), K_2CO_3 (3.46 g, 25 mmol) and 18-crown-6 were mixed in 50 ml of NMP and the solution was stirred at 45°C for 24 hours, then poured into water. The precipitate was filtered, washed with water and dried. The sample was recrystallized from THF/CH_2Cl_2 mixture. The yield was 76%.

IR (cm^{-1}): 1718, 1675, 1653, 1593, 1540, 1281, 1111 and 1060. NMR, δ_H (DMSO-d6) 3.86 (12H, s), 4.49 (2H, d), 5.29 (8H, s), 6.93 (2H, s), 7.27 (4H, d), 7.46 (2H, s), 7.60 (8H, d), 7.99 (8H, d), 8.19 (1H, s), 10.20 (2H. s); δ_C (DMSO-d6) 52.13, 62.91, 68.90, 104.66, 107.01, 111.59, 114.31, 127.50, 129.03, 129.35, 136.93, 138.87, 142.28, 143.20, 159.17, 164.56, 165.97

Anal. Calcd for $C_{57}H_{50}O_{15}N_2$: C, 68.25; H, 5.03; N, 2.79.

Found: C, 67.99; H, 5.30; N, 2.79%

Preparation of 12: $(MeOOC)_4$-[G-2]-Br

A mixture of **11** $(MeOOC)_4$[G-2]-OH (5.18 g, 5.7 mmol), carbon tetrabromide(2.03 g, 7.75 mmol) and triphenylphosphine (2.57 g, 7.75 mmol) in THF (100 ml) was stirred at r.t. under nitrogen. A white precipitate formed and THF(100 ml), carbon tetrabromide (1.36 g, 5.17 mmol) and triphenylphosphine (1.72 g, 5.17 mmol) were added and stirred at r.t. then at 40°C until the starting material disappeared, as confirmed by TLC(ethyl acetate/THF 9:1). The reaction was stopped by adding water and the reaction mixture was extracted between water and CH_2Cl_2 (3X) the CH_2Cl_2 layers were dried over MgSO4 and evaporated to dryness. The crude product was dissolved in small amount of THF and the solution was stored at -20°C until the solid product formed. After drying *in vacuo*, the yield was 73%.

IR (cm^{-1}): 1721, 1679, 1594, 14,37, 1282, 1162, 1111 and 1060. NMR, δ_H (DMSO-d6) 3.86 (8H, s), 4.70 (2H, s), 5.29 (8H, s), 6.94 (2H, s), 7.27 (4H, s), 7.60 (10H, d), 8.00 (8H, d), 8.23 (1H, s), 10.30 (2H, s); δ_C (DMSO-d6) 34.71, 52.12, 68.91, 104.92, 107.05, 112.95, 116.92, 127.50, 129.03, 129.35, 136.73, 138.35, 139.39, 142.26, 159.18, 164.72, 165.96

Anal. Calcd for $Cr_{57}H_{49}O_{14}N_2Br$: C, 64.23; H, 4.63, N, 2.63.

Found: C, 64,42; H, 4.66; N, 2.62%

Preparation of 13: $(MeOOC)_{16}$-[G-4]-0H

A mixture of monomer **1** (82 mg, 0.2 mmol), $(MeOOC)_4$-[G-2]-OH (**12**) (852 mg, 0.8 mmol), K_2CO_3 (138 mg, 1 mmol) and 18-crown-6 (26.4 mg, 0.1 mmol) in NMP (8 ml) and THF (8 ml) was stirred under nitrogen at 47°C for 60 hours. During the reaction, an excess of (**12**) (85 mg, 0.08 mmol), K_2CO_3 (69 mg, 0.5 mmol) and 18-crown-6 (13 mg, 0.05 mmol)) was added. The reaction mixture was poured into water and the precipitate was filtered and dried under vacuum. The crude compound was purified by flash chromatography eluting with 9:1:1 ethyl acetate/THF/methanol to give a brown powder in 55% yield.

IR (cm^{-1}) 1722, 1675, 1593,1437, 1282, 1160, 1110 and 1060. NMR, δ_H(DMSO-d6) 3.81 (48H, s), 4.49 (2H, d), 5.20-5.23 (40H, m), 6.89 (8H, s), 6.93 (2H, br), 7.25 (16H, s), 7.29 (4H, s), 7.47 (2H, s), 7.55 (32H, d), 7.65 (8H, s), 7.94 (32H, d), 8.24 (lH, br), 8.29 (4H, s), 10.24 (2H, br), 10.30 (8H, s); δ_C (DMSO-d6) 51.97, 62.95, 68.90, 69.92, 104.83, 107.01, 111.70, 112.68, 114.48, 115.39, 127.34, 129.00, 129.26, 136.81, 137.33, 138.90, 139.29, 142.23, 144.02, 159.17, 159.46, 164.75, 165.95.

Anal. Calcd for $C_{249}H_{210}O_{63}N_{10}$: C, 68.74; H, 4.87; N, 3.22.
Found: C, 68.59; H, 5.03; N, 3.20 %

Preparation of 14: (MeOOC)$_8$-[G-3]-OH

A mixture of **2** (189 mg, 0.5 mmol), **12** (1065 mg, 1 mmol), K_2CO_3 (207 mg, 1.5 mmol) and 18-crown-6 (40 mg, 0.15 mmol) in NMP (6 ml) and THF (6 ml) was stirred under nitrogen at 47°C for 24 hours. During the reaction, **12** (106.5 mg, 1 mmol), K_2CO_3 (69 mg, 0.5 mmol) and 18-crown-6 (13 mg, 0.05 mmol)) were added. The reaction mixture was poured into water and the precipitate was filtered, dried under vacuum, and reprecipitated from THF. The yield was 73% after purification.

IR (cm^{-1}): 1721, 1675, 1593, 1544, 1439, 1416, 1282, 1159, 1110 and l060. NMR, δ_H (DMSO-d6) 3,85(24H, s), 4.49 (2H, d), 5.19 (4H, s), 5.28 (16H, s), 6.93 (4H, br), 7.23-7.27 (10H, br), 7.45, 7.48, 7.57, 7.60, 7.64 (26H, m), 7.98 (16H, d), 8.21 (lH, s), 8.28 (2H, s), 10.26 (2H, s), 10.30 (4H, s); δ_C (DMSO-d6) 52.10, 63.00, 68.89, 104.89, 107.04, 111.59, 112.60, 114.20, 115.17, 127.48, 129.01, 129.33, 136.32, 136.82, 137.48, 138.97, 139.29, 142.24, 143.20, 158.25, 159.16, 164.71, 164.98, 165.95.

Anal. Calcd for $C_{135}H_{112}O_{33}N_6$: C, 69.10; H, 4.81; N, 3.58
Found: C, 68.92; H, 4.93; N, 3.52

Preparation of 15: (MeOOC)-[G-2]-OH

Monomer **1** (1640 mg, 4 mmol), **4** (5051 mg, 17.6 mmol), K_2CO_3 (3345 mg, 25 mmol) and 18-crown-6 (661 mg, 2.5 mmol) were mixed in 60 ml of NMP. The solution was stirred at 45°C for 24 hours and poured into water. The precipitate was filtered, washed with water and dried. The sample was recrystallized from THF/CH_2Cl_2 mixture. The yield was 69% IR (cm^{-1})1726, 1594, 1544, 1435, 1334, 1249, 1207, 1164, 1112 and 1061; NMR, δ_H(DMSO-d6) 3.90 (24H, s), 4.50 (2H, d), 5.38 (5.38, s), 6.96 (2H, s), 7.30 (4H, d), 7.48 (2H, s), 8.20 (1H, s), 8.30 (8H, s), 8.44 (4H, s), 10.23 (2H, s); δ_C (DMSO-d6) 52.51, 63.11, 66.99, 104.35, 107.16, 111.50, 114.31, 128.94, 130.45, 138.75, 136.93, 138.75, 143.20, 159.07, 164.49, 165.18

Anal. Calcd for $C_{65}H_{58}O_{23}N_2$: C,63.20; H, 4.73; N, 2.27.
Found: C, 63.47; H, 4.98; N, 2.16 %

Preparation of 16: $(MeOOC)_8$-[G-22]-Br

A mixture of **15** (3085 mg, 2.5 mmol), carbon tetrabromide (655.7 mg, 2.5 mmol) and triphenylphosphine (829.1g, 2.5 mmol) in NMP (20 ml) and THF (40 ml) was stirred at r.t. under nitrogen for 20 hours. During the reaction, additional carbon tetrabromide (328 mg, 1.25 mmol) and triphenylphosphine (415 mg, 1.25 mmol) were added to the solution. The reaction was stopped by adding water and the reaction mixture was concentrated then poured into water and the precipitate was washed with methanol. After reprecipitation from THF- CH_2Cl_2 and vacuum drying the yield was 72%.

IR (cm^{-1}):1726, 1593, 1543, 1436, 1332, 1249, 1208, 1163, 1111 and 1061. NMR, δ_H (DMSO-d6) 3.90 (24H, s), 4.70 (2H, s), 5.39 (5.38, s), 6.97 (2H, s), 7.30 (4H, d), 7.48 (2H, s), 8.25 (1H, s), 8.30 (8H, s), 8.44 (4H, s), 10.33 (2H, s); δ_C (DMSO-d6): 34.71, 52.52, 68.35, 104.60, 107.20, 112.92, 116.95, 128.93, 130.44, 132.15, 136.90, 138.72, 139.49, 159.07, 164.66, 165.17

Anal. Calcd for $C_{65}H_{57}O_{22}N_2Br$: C, 60.14; H, 4.43; N, 2.16.
Found: C, 60.38; H, 4.56; N, 2.16 %

Preparation of 17: $(MeOOC)_{32}$-[G-4]-0H

A mixture of **1** (24.6 mg, 0.06 mmol), **16** (311.5 mg, 0.24 mmol), K_2CO_3 (498 mg, 0.36 mmol) and 18-crown-6 (8.5 mg, 0.036 mmol) in NMP (2 ml) and THF (2 ml) was stirred under nitrogen at 47°C for 60 hours. During the reaction, additional **16** (155.7 mg, 0.12 mmol), K_2CO_3 (50 mg, 0.36 mmol) and 18-crown-6 (8.5 mg, 0.036 mmol) were added. The reaction mixture was poured into water, and the precipitate was filtered and dried under vacuum. The crude compound was purified by fractional precipitation (THF/Hexanes). As a result of difficulties in purification the final yield was 30%.

IR (cm^{-1}) 1727, 1593, 1544, 1436, 1333, 1249, 1208, 1161 and 1060. NMR δ_H(DMSO-d6) 3.84 (96H, s), 4.48-4.50 (2H, br), 5.15-5.40 (24H, m), 6.88 (10H, m), 7.26 (20H, br), 7.60-7.50(10H, m), 8.00-8.50 (53H, m), 10.2-10.3(10H, m); δ_C (DMSO-d6) 52.33, 68.28, 104.60, 107.12, 115.20, 128.79, 130,29, 131.86, 136.78, 138.50, 139.21, 158.96, 164.53, 165.04

Anal. Calcd for $C_{281}H_{242}O_{95}N_{10}$: C, 63.93; H, 4.62; N, 2.65.
Found: C, 63.66; H, 4.90; N, 2.59%

Preparation of 18: (MeOOC)16[G-3]-0H

A mixture of **2** (26.5 mg, 0.07 mmol), **16** (181.7 mg, 0.14 mmol), K_2CO_3 (24.2 mg, 0.175 mmol) and 18-crown-6 (4.6 mg, 0.0175 mmol) in NMP (2 ml) and THF (2 ml) was stirred under nitrogen at 47°C for 24 hours. During the reaction, additional **16** (90.9 mg, 0.07 mmol), K_2CO_3 (24.2 mg, 0.175 mmol) and 18-crown-6 (4.6 mg, 0.0175 mmol) were added. The reaction mixture was poured into water and the precipitate was washed with methanol, filtered and dried under vacuum. The crude compound was purified by fractional precipitation from THF/Hexanes. The final yield was 40%.

IR (cm^{-1}): 1726, 1680, 1593, 1543, 1436, 1333, 1249, 1207, 1163 and 1060.

NMR, δ_H (DMSO-d6): 3.88 (24H, s), 4.48 (2H, d), 5.19 (4H, s), 5.34 (16H, s), 6.95 (4H, s), 7.20-7.35 (10H, br), 7.40-7.70 (12H, m), 8.20-8.35 (19H, m), 8.40 (8H, s), 10.25 (2H, s), 10.30 (4H, s);

δ_C (DMSO-d6): 52.41, 62.91, 68.33, 69.58, 104.68, 107.18, 111.55, 112.50, 113.95,115.10, 117.86, 120.15, 128.87, 129.47, 130.38, 132.04, 136.28, 136.85, 137.41, 138.62, 139.24, 143.15, 158.22, 159.02, 164.58, 164.91, 165.95.

CONCLUSION

We have demonstrated the preparation of a novel family of dendrimers based on amide-ether linkages. The construction of these dendrons takes advantage of an accelerated protocol in which a branched monomer capable of anchoring four dendrons at once is used. A drawback of this family of dendrimers is their limited solubility that makes product purification difficult. The dendrimers with carboxylate ester end-groups are useful functionalized moieties that may serve as precursors for a family of dendritic structures with free carboxylate end-groups collectively known as “unimolecular micelles”.

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REFERENCES

[1] J. M. J. Fréchet and C. J .Hawker, *"Synthesis and Properties of Dendrimers and Hyperbranched Polymers"* in "Comprehensive Polymer Science, 2nd Suppl.", S. L. Aggarwal and S. Russo, Eds., Pergamon, 1996, 71.

[2] D. A. Tomalia, H. Baker, J. Dewald, M. Hall, F. Kallos, S. Martin, J. Roeck, J. Ryder, and P. Smith, *Polym. J.*, *17*, 117 (1985); G. R. Newkome, Z.-Q. Yao, G. R. Baker, and V. K. Gupta, *J. Org. Chem.*, *50*, 2003 (1985); D. A. Tomalia, A. M. Naylor, and W. A. Goddard, *Angew Chem. Int. Ed. Engl.*, *29*, 138 (1990); J. S. Moore and Z. Xu, *Macromolecules, 24*, 5893 (1991); G. R. Newkome, C. N. Moorefield, and G. R. Baker, *Aldrich. Acta*, *25*, 31 (1992); T. M. Miller, T. X. Neenan, R. Zayas, and H. E. Bair, *J. Am. Chem. Soc.*, *114*, 1018 (1992); A. Morikawa, M. Kakimoto,Y.Imai, *Polymer J., 24*, 573 (1992); *Ibid., Macromolecules, 26*, 6324 (1993); E. M. M. De Brabander-van den Berg, A. Nijenhuis, M. Mure, J. Keulen, R. Reintjens, B. Vandenbooren, B. Bosman, R. de Raat, T. Frijns, S. v. d. Wal, M. Castelijns, J. Put, and E. W. Meijer, *Macromol. Symp.*, *77*, 51 (1994).

[3] J. M. J. Fréchet, *Science*, *263*, 1710 (1994).

[4] J. M. J. Fréchet, M. Hemni, I . Gitsov, S. Aoshima, M. Leduc, and R. B. Grubbs, *Science*, *269*, 1080 (1995).

[5] B. I. Voit, *Acta Polym., 46*, 87 (1995).

[6] D. A. Tomalia, V. Berry, M. Hall, and D. M. Hedstrand, *Macromolecules*, *20*, 1164 (1987); Y. H. Kim and O. W. Webster, *J. Am. Chem. Soc.*, *112*, 4592 (1990).

[7] G. R. Newkome, C. N. Moorefield, G. R. Baker, M. J. Saunders, and S. H. Grossman, *Angew. Chem. Int. Ed. Engl.*, *30*, 1178 (1991); G. R. Newkome, J. K. Young, G. R. Baker, R. L. Potter, L. Audoly, D. Cooper, C. D. Weis, K. Morris, and C. S. Johnson, Jr., *Macromolecules*, *26*, 2394 (1993).

[8] C. J. Hawker, K. L. Wooley, and J. M. J. Fréchet, *J. Chem. Soc., Perkin Trans 1*, 1287 (1993).

[9] C. J. Hawker, R. Lee, and J. M. J. Fréchet, *J. Am. Chem. Soc.*, *113*, 4583 (1991); K. E. Uhrich, C. J. Hawker, J. M. J. Fréchet, and S. R. Turner, *Macromolecules, 25*, 4583 (1992); K. L. Wooley, C. J. Hawker, R. Lee,

J. M. J. Fréchet, *Polymer J.*, *26*, 187 (1994); K. L. Wooley, C. J. Hawker, and J. M. J. Fréchet, *Polymer*, *35*, 4489 (1994).

[10] M. Johansson, E. Malmstrom, and A. Hult, *J. Polym. Sci., Polym. Chem.*, *31*, 619 (1993).

[11] K. L. Wooley, C. J. Hawker, and J. M. J. Fréchet, *J. Am. Chem. Soc.*, *113*, 4252 (1991).

[12] J. M. J. Fréchet, I. Gitsov, R. B. Grubbs, C. J. Hawker, M. Henmi, M. Leduc, E. Sanford, and K. Yui, *Polym. Mat. Sci. Eng.*, *73*, 271 (1995).

[13] K. L. Wooley, C. J. Hawker, and J. M. J. Fréchet, *Angew. Chem. Int. Ed. Engl.*, *33*, 82 (1994).

[14] J. W. Leon, M. Kawa, and J. M. J. Fréchet, *J. Am. Chem. Soc.*, *118*, 8847 (1996).

[15] R. Spindler and J. M. J. Fréchet, *J. Chem. Soc. Perkin I*, 913 (1993).

[16] T. Kawaguchi, K. L. Walker, C. L. Wilkins, and J. S. Moore, *J. Am. Chem. Soc.*, *117*, 2159 (1995).

[17] P. M. Saville, P. A. Reynolds, J. W. White, C. J. Hawker, J. M. J. Fréchet, K. L. Wooley, J. Penfeld, and J. R. P. Webster, *J. Phys. Chem.*, *99*, 8283 (1995); C. J. Hawker, K. L. Wooley, and J. M. J. Fréchet, *J. Am. Chem. Soc.*, *115*, 4375 (1993); P. M. Saville, J. W. White, C. J. Hawker, K. L. Wooley, and J. M. J. Fréchet, *J. Phys. Chem.*, *97*, 293 (1993); A. M. Naylor, W. A. Goddard, G. E. Kiefer, and D. A. Tomalia, *J. Am. Chem. Soc.*, *111*, 2339 (1989).

[18] T. H. Mourey, S. R. Turner, M. Rubinstein, J. M. J. Fréchet, C. J. Hawker, and K. L. Wooley, *Macromolecules*, *25*, 2401 (1992).

[19] C. J. Hawker, P. J. Farrington, M. E. Mackay, K. L. Wooley, J. M. J. Fréchet, *J. Am. Chem. Soc.*, *117*, 4409 (1995).

[20] M. Ueda, A. Kameyama, and K. Hashimoto, *Macromolecules*, *21*, 19 (1988); M. Ueda, T. Morosumi, M. Kakuta, and R. Sato, *Polymer J.*, *22*, 733 (1990).

[21] C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, *112*, 7638 (1990); C. J. Hawker and J. M. J. Fréchet, *J. Chem. Soc. Chem. Commun.*, 1010 (1990).

[22] K. L. Wooley, C. J. Hawker, J. M. Pochan, and J. M. J. Fréchet, *Macromolecules*, *26*, 1514 (1993).