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Synthesis and Properties of a New Class of Polyether Dendritic Fragments: Useful Building Blocks for Functional Dendrimers

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Abstract: Polyether dendritic sectors **1** - **4** from the first to the fourth generations, respectively, were prepared by a convergent approach from readily available 4-*tert*-butylphenol, phloroglucinol and 1,3-dibromopropane. Using a three-step iterative synthetic sequence involving mono-*O*-alkylation of [Gn]-OH with excess 1,3-dibromopropane, bis-*O*-alkylation of the resulting compound with 5-benzyloxyresorcinol **5** followed by hydrogenolysis with palladium catalyst, [G(n+1)]-OH of the next higher generation could be prepared in good yields. These dendritic sectors have good solubility properties and are inert in both acidic and basic media, and do not show any redox behaviour from -2.0 to +1.9 V. Hence they are useful dendritic building blocks for the preparation of functional dendrimers.

FUNCTIONAL DENDRIMERS - INTRODUCTION

Research in dendrimer chemistry has undergone a transition after the initial efforts devoted to their synthesis and structural property investigations.[1] Emphasis in this area has recently switched to the exploration of the practical usefulness of functionalized dendritic molecules.[2] Hence, instead of looking at the global properties of dendrimers, research is now focused on the investigation of the change of photophysical/photochemical,[3] electrochemical,[4] optical,[5] biological[6] and catalytic properties[7] when simple functional unit (*e.g.* photo-active, redox-active or catalytic) is attached to a dendritic matrix. Hyperbranched dendritic molecules have thus become useful macromolecular models to study a wide variety of biological and nano-physical processes.

There are several ways by which dendritic fragments can be attached to simple organic moieties (Figure 1). One strategy is to attach the functionality into the interior of the dendrimer. In this situation, the functional group of interest is encapsulated inside a dendritic envelope and this provides a good opportunity for us to investigate the internal properties of dendrimers by observing the property change of the functional group. The alternative way is to append the functional group(s) on the exterior surface of the dendrimer. In this case, one can study the influence of the surface sector on the properties of the functional moiety. Moreover, if more than one functional

groups are attached onto the surface of a dendritic molecule, the resulting molecule will be an ideal model for studying the cooperativity or allosteric interactions between these functional units.

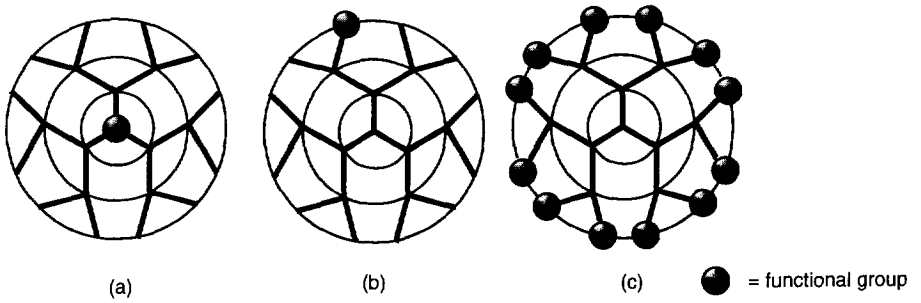


Figure 1. Functional dendrimers with (a) one functional moiety inside the interior, (b) one functional group on the surface and (c) multiple functional groups on the surface of a dendrimer.

Central to the successful preparation of functional dendrimers is the selection of an appropriate dendritic sector, which will inevitably affect the physico-chemical properties of the functional group of interest as well as the overall three-dimensional topology and physical properties of the dendrimer. Several important selection criteria are apparently crucial:

- The dendritic fragment should be stable and inert under the experiment of interest.
- It should possess a handle to which the functional unit can be anchored.
- The dendritic sector should have good solubility properties.
- The synthesis of the dendritic sector should be straightforward, high yielding and amenable to large scale preparation.
- The synthetic strategy should be versatile enough to allow easy modifications of the surface functionality, the linker and the branching unit.

Examination of the literature revealed a number of useful dendritic molecules. For examples, the polyamidoamine (PAMAM) dendrimer pioneered by Tomalia[1a,c] can be synthesized up to the tenth generation with molecular weight approaching 7 x 10^5 and a diameter of about 130Å. The polyester dendrimers developed independently by Miller[8] and Fréchet[9] can also be prepared very conveniently in grams scale with great efficiency. The slight drawback for these two class of dendrimers is that they are liable to acid or basic hydrolysis. Silane dendrimers are another exciting candidates because they are readily available in kilogram quantities.[10] However, because they are prepared by a divergent approach, structural defects will inevitably occur and this problem becomes more prominent with the higher generations.[11] The other problem is that there is no handle to which the desired functional unit can be attached to these silane dendrimers without invoking further functional group transformations. Other useful candidates were the polyether-amide hybrid dendrimers reported by Newkome[12]

but these sectors had been reported to interfere electrochemical redox process.[4a] Very recently, polyamine-based dendrimers become extremely popular following a breakthrough in their synthesis,[13] and they have been used in the construction of a number of interesting functional dendrimers.[14] In terms of chemical stability, hydrocarbon dendrimers[15] are probably the preferred choices but they usually have limited solubilities. The polyether based dendrimers developed by Fréchet[16] are another candidate because their synthetic strategy offers greater flexibility for preparing dendrimers with layer-block, sector block and surface specific dendritic envelopes, but it is questionable whether the benzylic linkages can survive under electrochemical redox conditions. Despite all these important developments, we believe there is still the need to explore new and useful dendritic fragments for novel applications. Recently we disclosed[17] the preparation of a new series of acid-base and redox stable polyether-based dendritic fragments up to the fourth generation. These dendritic derivatives are readily soluble in organic solvents and are valuable tools for the synthesis of custom-designed functional dendrimers. Report herein are the full experimental details as well as the stability and properties of these dendritic sectors.

Results and Discussions

1. Synthetic Strategy

Our polyether dendritic sectors **1** - **4** consist of four basic components: the handle, linker, branching juncture and surface group (Figure 2). The handle is a phenolic moiety which serves as the ligating site for its attachment to various functional units. The linker is a three-carbon alkyl chain which is flexible and long enough for the construction of dendrons of higher generations. In practice, any long chain alkyl groups can be chosen as the linking units to obtain dendritic sectors of different molecular dimensions. The branching juncture is a phloroglucinol unit which gives a branching multiplicity of three. The surface group selected is a 4-*tert*-butylphenoxy moiety for its distinctive ^{1}H-NMR signal of the *tert*-butyl group and excellent solubility property.

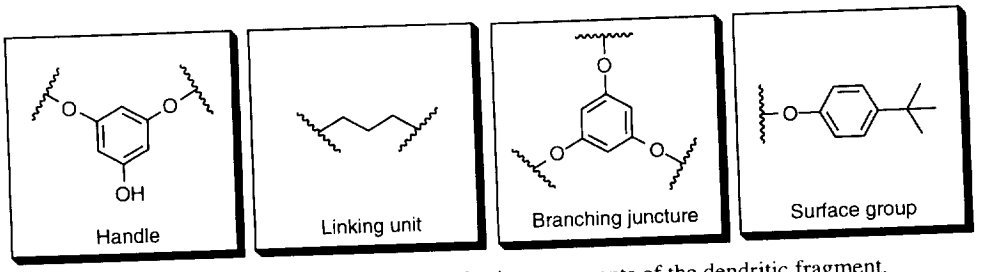


Figure 2. Diagram showing the four basic components of the dendritic fragment.

An iterative, convergent strategy[16] was employed to prepare this polyether dendritic series **1** - **4**. This method has the advantage over the divergent one in that the number of reactions in each step is restricted to a fixed small number irrespective of dendrimer generations. Therefore, completion of reactions in each step can be controlled and monitored and large excess of reagents is not required even in the preparation of higher generation

dendrimers. Moreover, even if imperfection does occur during the construction of dendrimer due to incomplete reaction, the defective dendrimer will generally differ greatly in polarity and size from the desired one. Thus,

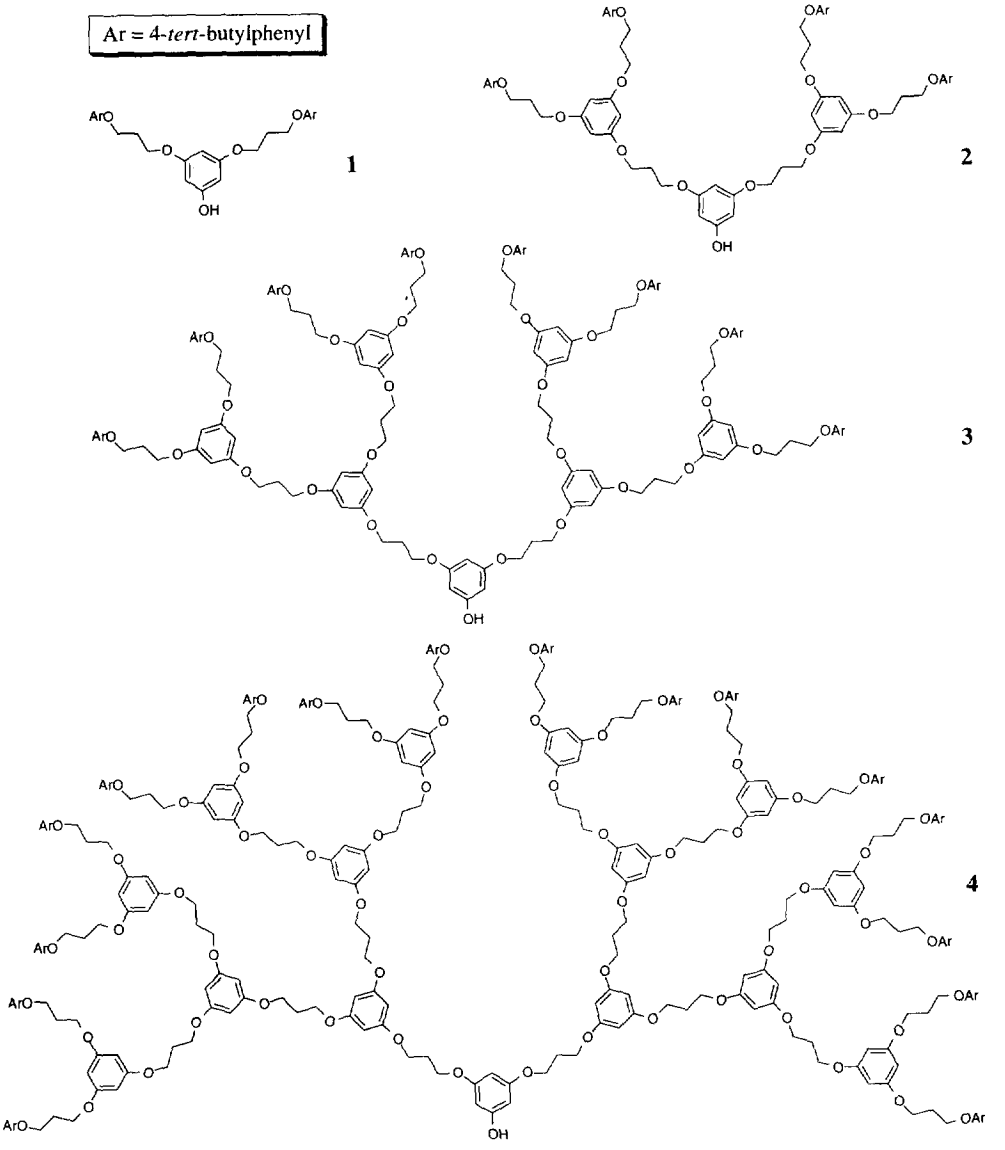


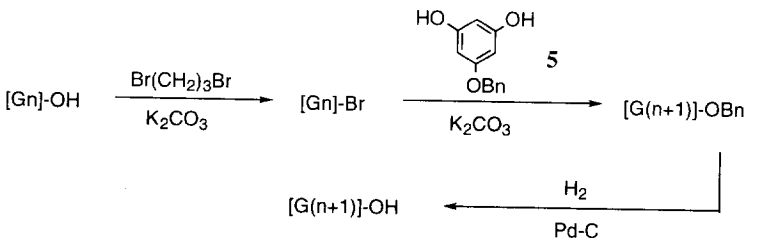
Figure 3. First to fourth generation polyether dendritic fragments **1** - **4** respectively.

removal of the defective species can be performed readily by various chromatography techniques. In the end, dendrimers synthesized by this approach normally have perfect monodispersity. In contrast, the divergent approach has been known to be a less reliable method for the preparation of monodisperse dendritic species,[11] especially for the higher generation dendrimers.

In the following discussions, the dendritic molecule of various generations will be designated using the notation [Gn]-f proposed by Fréchet,[16] in which [Gn] refers to the generation number (n = 0, 1, 2, 3 etc.) and f denotes the functional group located at the focal point. Since the synthetic method employed here is an iterative, stepwise process, it is essential that this sequence is short in terms of its number of steps, easy to operate and high yielding for each reaction cycle.

The principle steps involved in the preparation of the polyether-based dendritic fragments are (Scheme 1):

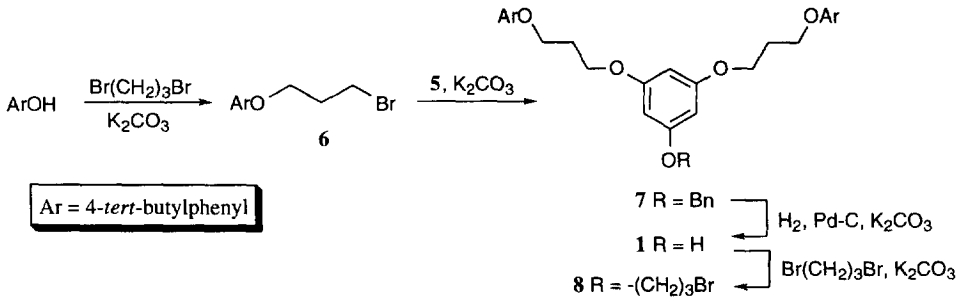
- Mono-*O*-alkylation of the phenolic compound [Gn]-OH with the linking unit, 1,3-dibromopropane, to generate the monobromide [Gn]-Br.
- Bis-*O*-alkylation of the branching juncture, 5-benzyloxyresorcinol[18] **5**, with the monobromide [Gn]-Br to give the benzylated ether of the next higher generation [G(n+1)]-OBn.
- Deprotection of the benzyl group by catalytic hydrogenolysis to yield [G(n+1)]-OH.



Scheme 1. The iterative synthetic sequence for the preparation of dendritic molecules **1** - **4**.

2. Assembly of the surface sector

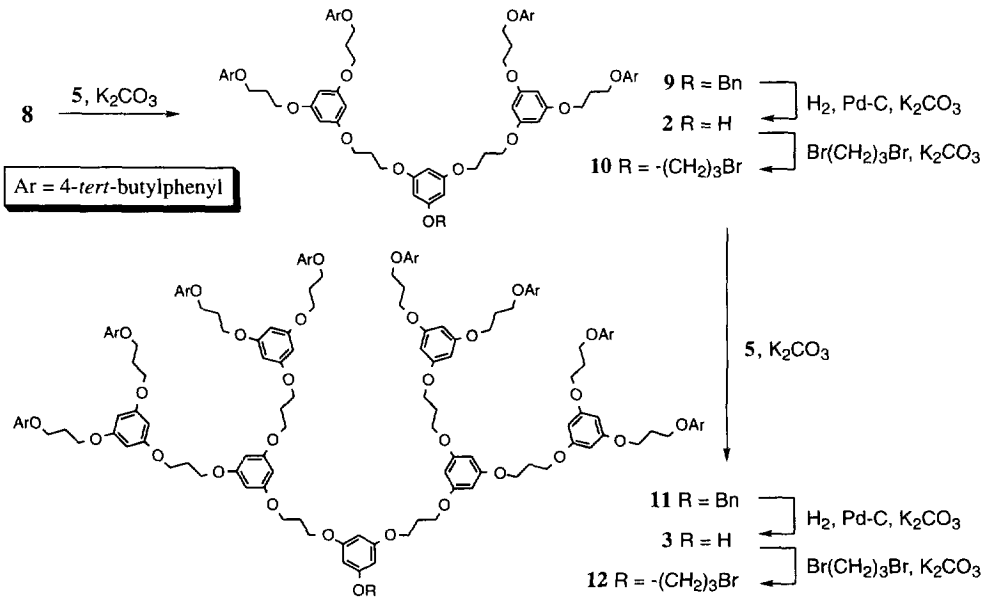
Treatment of 4-*tert*-butylphenol with 4.6 equivalent of 1,3-dibromopropane (K_2CO_3, acetone, 66°C, 20 h) gave the mono-*O*-alkylated product 3-bromo-1-(4-*tert*-butylphenoxy)propane **6** as an oil (92%) (b.p. 140°C/2.5 mm Hg) with little bis-*O*-alkylation contaminant (Scheme 2). Bis-*O*-alkylation (K_2CO_3, acetone, 66°C, 48 h) of 5-benzyloxy-resorcinol **5** with 2.1 equivalent of the monobromide **6** afforded the first generation C_2 symmetric benzyl ether **7**, [G1]-OBn, as an oil (80%). Upon hydrogenation using 10% palladium on carbon as catalyst (ethanol/EtOAc, powdered K_2CO_3), the benzyl ether **7** could be transformed into the phenol **1**, [G1]-OH, as a white solid (95%) (m.p. 92 - 93°C). It was discovered that addition of a small amount of powdered K_2CO_3 to the reaction mixture gave cleaner hydrogenolysis product.



Scheme 2. Assembly of the surface sector.

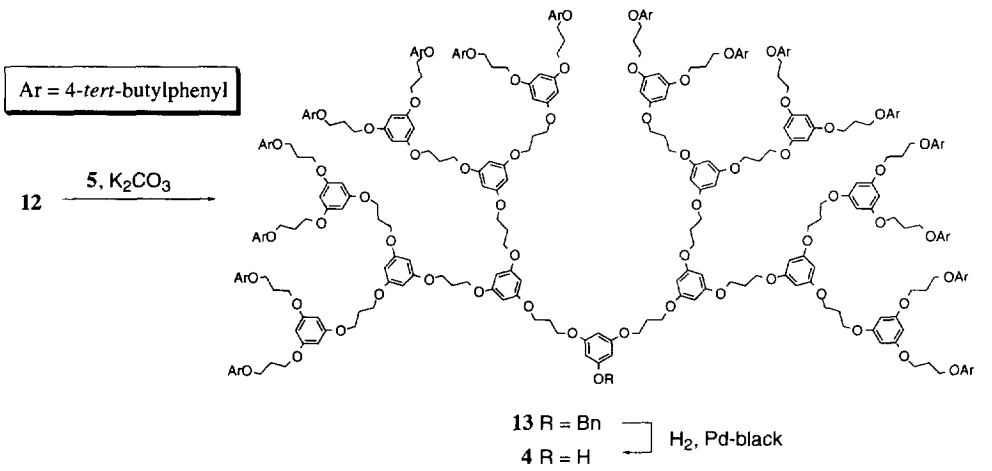
3. Synthesis of dendritic fragments of higher generations

Reaction of [G1]-OH **1** with 15 equiv. of 1,3-dibromopropane (K_2CO_3, acetone, 66°C) afforded the monobromide of the first generation [G1]-Br **8** in 93% yield as a white solid (m.p. 68 - 70°C). By repeating the above reaction sequence (Scheme 3), the second and third generation phenols [G2]-OH **2** and [G3]-OH **3**, could be obtained in overall yields of 70% and 66% from [G1]-OH **1** and [G2]-OH **2** respectively. Subsequent reaction of [G3]-OH **3** with 15 equiv. of 1,3-dibromopropane (K_2CO_3, acetone, 66°C) afforded [G3]-Br **12** in 90% yield.



Scheme 3. Assembly of the dendritic sectors of various generations.

Preparation of the phenol compound of the fourth generation **4** from [G3]-Br **12** was accomplished with slight modifications (Scheme 4). It was necessary to add a few drops of dimethylformamide (DMF) in acetone solution to effect a clean bis-*O*-alkylation of 5-benzyloxyresorcinol **5** with [G3]-Br **12**. By this method, [G4]-OBn **13** could be obtained in 72% yield. In the absence of DMF, the reaction proceeded very sluggishly. Dismantling of the benzyl group in [G4]-OBn by hydrogenation employing Pd black as the catalyst in EtOAc afforded [G4]-OH **4** in 74% yield. If 10% Pd/C was used instead, the hydrogenation reaction was again extremely slow. This may reflect that the benzyl group in the dendrimer of higher generations is less accessible to reaction due to increased steric crowding.



Scheme 4. Synthesis of the fourth generation dendritic sector.

The structural identities of these compounds are readily diagnosed by their ^{1}H-NMR spectra. Thus, the *tert*-butylphenoxy moiety has a characteristic singlet at δ 1.3 attributed to the *tert*-butyl group and a double doublet due to the aromatic protons from δ 7.3 to 6.7, while those of the branching phloroglucinol unit resonate at around δ 6.1. Although the benzyl group in [Gn]-OBn has the aromatic proton signals overlapping with those of the *tert*-butyl-phenol, the unique benzylic signal at δ 5.0 allows unambiguous identification of its existence. The alkyl branching units have their proton signals at two separate regions (δ 4.2 to 4.1 and δ 2.2 to 2.1). On the other hand, the methylene protons adjacent to the bromine atom in [Gn]-Br resonate at around δ 3.6. Since all the signals were non-overlapping, structural identification of all the dendritic fragments was greatly facilitated. The ^{1}H-NMR spectra of [G2]-Br **10** and [G3]-OBn **11** (Figure 4) shown on the next page exemplify the points described above.

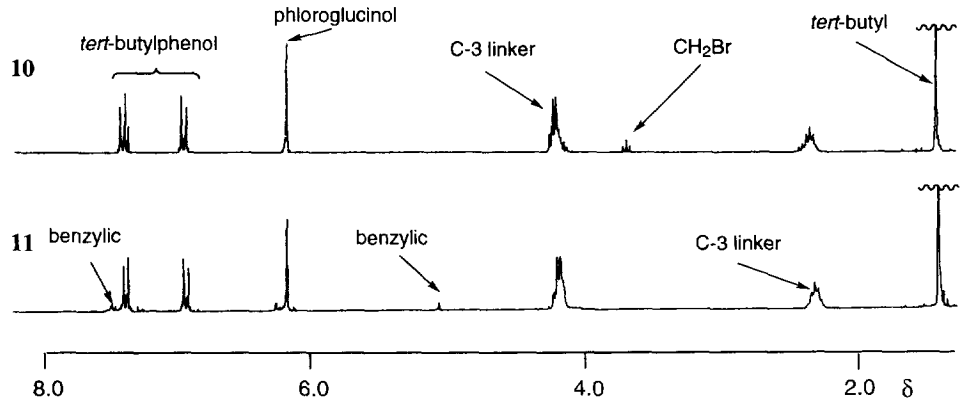


Figure 4. ^{1}H-NMR spectra of [G2]-Br **10** and [G3]-OBn **11**.

^{13}C-NMR spectroscopy is another useful technique to determine the purity and to detect structural defects of the dendritic fragments. In general, any defective dendrimer will be unsymmetrical and additional carbon signals will be observed. On the contrary, perfect dendrimer will have very sharp and simple signals because of its symmetrical structure. In addition, ^{13}C-NMR data provide information regarding to the dendrimer generation. To illustrate this point, the ^{13}C NMR spectra of [Gn]-OBn (n = 1 to 4) are shown on the next page (Figure 5). As can be observed, the higher the dendrimer generation, the smaller the relative intensities of the benzyl ether carbon signals at the focal point to those of the signals resulting from the surface 4-*tert*-butylphenoxy moieties. This is because the focal point/surface carbon ratio decreases with increasing generation.

In addition to ^{1}H and ^{13}C-NMR data, mass spectra data provide unequivocal proof of their identities. Hence, the dendritic phenols **1** - **4** showed molecular ions at 506 (M^{+}), 1219.9 ($M + H^{+}$), 2645.4 ($M + H^{+}$) and 5492 (M^{+}) respectively. Thus, one needs a combination of ^{1}H and ^{13}C-NMR and mass spectral techniques to confirm the structure of these dendritic species.

The iterative synthetic steps described above are both easy to operate and can be performed on a large scale with good yields. The major side reaction in the first step is elimination (< 5%) of the resulting monobromo compound [Gn]-Br. Although the side product allyl compound has an R_f value closed to the desired product, it is unreactive towards 5-benzyloxyresorcinol **5** and hence does not interfere the subsequent reaction. The second step behaves well throughout various generations, giving the bis-*O*-alkylation compound [Gn]-OBn as the major product with only a small amount of mono-*O*-alkylation product. Anyhow, these two compounds can be easily separated by column chromatography due to their large difference in polarity. The slightly problematic reaction in this synthetic sequence is the last step, namely catalytic hydrogenation. The reaction is rather sluggish for the higher generation benzyl ethers and occasionally an undesirable product of unknown identity is formed. This by-product has an R_f value very close to that of the desired [Gn]-OH and thus complete separation of them by column

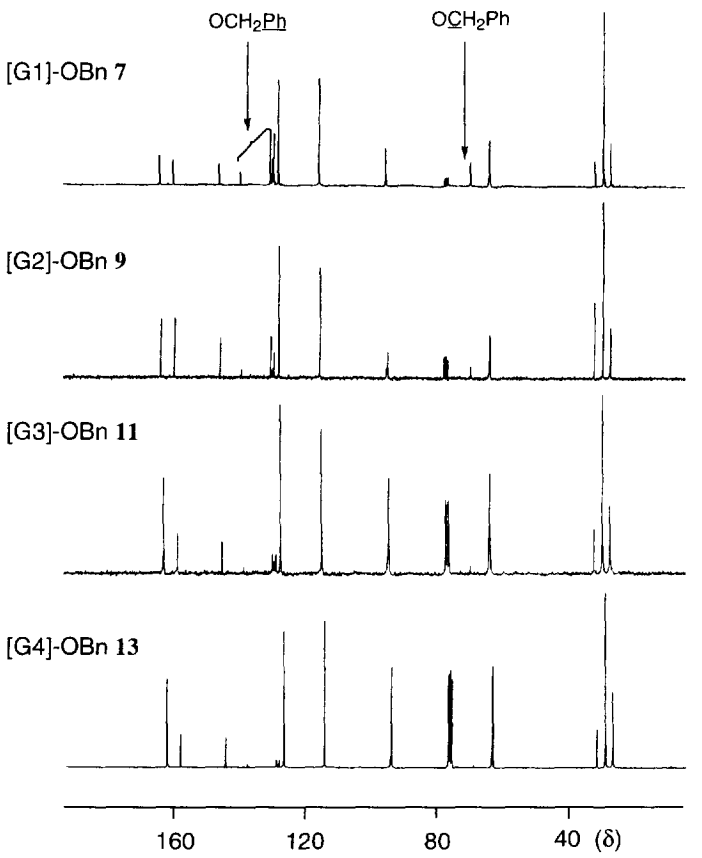


Figure 5. ^{13}C-NMR spectra of [Gn]-OBn.

chromatography is difficult. Fortunately, the formation of this product can be suppressed to <5% by addition of a small amount of powdered K_2CO_3 to the reaction mixture.

4. Properties and stability of dendritic sectors

The lower generation dendritic sectors are crystalline solids and show physical properties similar to those of simple organic ethers. The higher generation hyperbranched benzyl ethers and phenols are glassy substances and are readily soluble in organic solvents such as acetone, ethyl acetate, tetrahhydrofuran, dichloromethane or chloroform, although they are sparingly soluble in hexane or methanol.

The dendritic phenols **1** - **4** are stable in either 1 M HCl or NaOH aqueous THF solution at 25°C for 16 h without decomposition. In addition, their solution do not show any observable redox pattern in cyclic

voltammetry experiment (scanning potential from 1.9 to -2.0 V in CH_2Cl_2, sweep rate 100 mVs^{-1}, supporting electrolyte $Bu_4N^+BF_4^-$, Ag reference electrode, platinum working and counter electrodes).

With the increasing demand of functional dendrimers for novel applications, there is a definite need to discover new and novel dendritic fragments with special properties. Because of their stability and inertness, the polyether dendritic sectors reported here should be useful building blocks for the synthesis of functionalized dendrimers. Moreover, surface functionality other than 4-*tert*-butylphenol can also be used. For examples, we have employed 3,5-dimethylphenol and 3,5-dimethoxyphenol as the surface groups and carry out the same iterative synthetic sequence to prepare dendrimers up to the third generation. These two new dendritic fragments have slightly different polarity but very similar solubility properties to the series reported here.

EXPERIMENTAL SECTION

Melting points were measured on a Reichert Microscope apparatus and are uncorrected. Brüker WM 250 spectrometer was used to obtain ^1H (250 MHz) and ^{13}C (62.9 MHz) NMR spectra unless otherwise stated. ^1H (500 MHz) NMR spectra were acquired on a Brüker ARX 500 spectrometer. Coupling constants were reported in Hertz. IR spectra were recorded on a Nicolet 205 FT-IR spectrometer as film on KBr disc. Mass spectra were obtained on a Bruker APEX 47e FTMS by fast atom bombardment (FAB), electron ionization (EI) or electrospray ionization (ESI) technique. The reported molecular mass (*m/z*) are monoisotopic mass based on ^1H, ^{13}C, ^{14}N, ^{16}O and ^{79}Br. Elemental analyses were carried out at MEDAC Ltd., Middlesex, United Kingdom. Unless otherwise stated, all chemicals were purchased from commercial suppliers and used without further purification.

3-Bromo-1-(4-*tert*-butylphenoxy)propane 6. A mixture of 4-*tert*-butylphenol (20 g, 0.13 mol), 1,3-dibromopropane (60 cm^3, 0.60 mol) and potassium carbonate (35 g, 0.26 mol) in acetone (250 cm^3) was refluxed for 20 h. The mixture was cooled and filtered. After concentration of the filtrate on a rotary evaporator, the crude compound was distilled under reduced pressure to give 3-bromo-1-(4-*tert*-butylphenoxy)propane **6** (32 g, 92%) as a colorless oil, b.p. 140°C/2.5 mmHg. R_f 0.22 (hexane/Et_2O = 60/1); δ_H ($CDCl_3$) 1.32 (9 H, s), 2.32 (2 H, quin, *J* 6.1), 3.62 (2 H, t, *J* 6.4), 4.10 (2 H, t, *J* 5.8), 6.87 (2 H, d, *J* 8.8), 7.33 (2 H, d, *J* 8.8); δ_C ($CDCl_3$) 29.7, 31.4, 32.4, 33.8, 65.1, 113.9, 126.0, 143.2, 156.3.

General procedure for the synthesis of [Gn]-OBn. A mixture of the bromide [G(n-1)]-Br (2 equiv.), 5-benzyloxyresorcinol[18] **5** (1 equiv.) and potassium carbonate (4 equiv.) was refluxed in acetone. The reaction time required was 48, 32 and 72 h for the preparation of [G1]-OBn, [G2]-OBn and [G3]-OBn respectively. For the preparation of the monobenzylated compound of fourth generation [G4]-OBn **13**, the mixture was refluxed in acetone with a few drops of DMF as co-solvent for 35 h. The reaction mixture was cooled and filtered. After concentration of the filtrate on a rotary evaporator, the crude product was purified as described in the following text.

[G1]-OBn 7. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 100/3) afforded [G1]-OBn **7** (80%) as a colorless oil. R_f 0.13 (hexane/EtOAc = 100/4); υ_{max} (film)/cm^{-1} 2961, 1600, 1513; δ_H ($CDCl_3$) 1.29 (18 H, s), 2.21 (4 H, quin, *J* 6.1), 4.09 (4 H, t, *J* 6.0), 4.11 (4 H, t, *J* 5.9), 4.99 (2 H, s), 6.11 (1 H, t, *J* 2.1), 6.17 (2 H, d, *J* 2.0), 6.84 (4 H, d, *J* 8.8), 7.29 (4 H, d, *J* 8.8), 7.25 - 7.32 (5 H, m); δ_C ($CDCl_3$) 29.3, 31.5, 33.9, 64.4, 64.6, 69.9, 94.7, 114.1, 126.0, 127.3, 127.7, 128.4, 137.0, 143.3, 156.6, 160.7, 160.8; *m/z* (EI) 596 (M^+, 5%), 91 ($C_7H_7^+$, 100). (Found: C, 78.60; H, 8.07. $C_{39}H_{48}O_5$ requires C, 78.49; H, 8.27%).

[G2]-OBn 9. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 20/3 gradient to 5/1) afforded [G2]-OBn **9** (81%) as white glassy substance. R_f 0.27 (hexane/EtOAc = 100/15); υ_{max} (film)/cm^{-1} 2963, 1601, 1514; δ_H ($CDCl_3$) 1.28 (36 H, s), 2.17 - 2.22 (12 H, m), 4.05 - 4.12 (24 H, m), 4.97 (2 H, s), 6.09 (7 H, br s), 6.17 (2 H, d, *J* 2.0), 6.84 (8 H, d, *J* 8.8), 7.28 (8 H, d, *J* 8.8), 7.31 - 7.38 (5 H, m); δ_C ($CDCl_3$) 29.2, 31.4, 33.8, 64.2, 64.4, 69.8, 94.1, 94.3, 113.9, 126.0, 127.3, 127.7, 128.3, 136.8, 143.1, 156.5, 160.6; *m/z* (FAB) 1309.8 (M + H^+, 3%). (Found: C, 75.85; H, 8.05. $C_{83}H_{104}O_{13}$ requires C, 76.12; H, 8.00%).

[G3]-OBn 11. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 5/1) afforded [G3]-OBn **11** (84%) as white glassy substance. R_f 0.26 (hexane/EtOAc = 40/9); υ_{max} (film)/cm^{-1} 2959, 2875, 1600, 1514; δ_H ($CDCl_3$) 1.28 (72 H, s), 2.14 - 2.21 (28 H, m), 4.05 - 4.12 (56 H, m), 4.96 (2 H, s), 6.09 (19 H, br s), 6.17 (2 H, d, *J* 2.0), 6.83 (16 H, d, *J* 8.8), 7.27 (16 H, d, *J* 8.8), 7.30 - 7.37 (5 H, m); δ_C ($CDCl_3$) 29.3, 31.5, 34.0, 64.4, 64.6, 70.0, 94.2, 94.5, 114.0, 126.1, 127.5, 127.9, 128.5, 136.9, 143.4, 156.6, 160.7. (Found: C, 75.25; H, 7.96. $C_{171}H_{216}O_{29}$ requires C, 75.08; H, 7.96%).

[G4]-OBn 13. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 70/15 gradient to 50/11) afforded [G4]-OBn (72%) **13** as white glassy substance. R_f 0.29 (hexane/EtOAc = 4/1); υ_{max} (film)/cm^{-1} 2962, 2878, 1601, 1514; δ_H ($CDCl_3$) 1.27 (144 H, s), 2.16 - 2.21 (60 H, m), 4.02 - 4.14 (120 H, m), 4.95 (2 H, s), 6.07 (43 H, br s), 6.15 (2 H, d, *J* 2.0), 6.82 (32 H, d, *J* 8.8), 7.27 (32 H, d, *J* 8.8), 7.33 - 7.41 (5 H, m); δ_C ($CDCl_3$) 29.3, 29.4, 31.5, 34.0, 64.5, 64.6, 70.1, 94.4, 114.1, 126.2, 127.5, 127.9, 128.5, 137.0, 143.4, 156.6, 160.8. (Found: C, 74.90; H, 8.06. $C_{347}H_{440}O_{61}$ requires C, 74.60; H, 7.93%).

General procedure for the synthesis of [Gn]-OH. A suspension of [Gn]-OBn (n = 1 to 3), 10% palladium on charcoal (15% by weight) and potassium carbonate (0.5 g) in ethanol/EtOAc (3:1) mixture was stirred under hydrogen at room temperature. For the synthesis of [G4]-OH, EtOAc and Pd black were used as the solvent and catalyst respectively. The reaction was monitored by TLC until all starting materials had been used up. The reaction mixture was then filtered through Celite. After concentration of the filtrate on a rotary evaporator, the crude product was purified as described in the following text.

[G1]-OH 1. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 10/1 gradient to 6/1) afforded [G1]-OH **1** (95%) as a white crystalline solid, m.p. 92 - 93°C. R_f 0.22 (hexane/ethyl acetate = 5/1); υ_{max} (film)/cm^{-1} 3418, 2961, 2871, 1608, 1514; δ_H (500 MHz, $CDCl_3$) 1.29 (18 H, s), 2.21 (4 H, quin, *J* 6.1), 4.09 (4 H, t, *J* 6.2), 4.11 (4 H, t, *J* 6.0), 4.92 (1 H, s), 6.00 (2 H, d, *J* 2.0), 6.07 (1 H, t, *J* 2.0), 6.85 (4 H, d,

J 8.7), 7.30 (4 H, d, *J* 8.7); δ_C ($CDCl_3$) 29.2, 31.5, 33.9, 64.5, 94.3, 95.0, 114.1, 126.1, 143.4, 156.4, 157.4, 160.8; *m/z* (EI) 506 (M^+, 34%), 357 (M^+ - $C_{10}H_{13}O$, 55), 167 ($C_9H_{11}O_3^+$, 100). (Found: C, 75.78; H, 8.41. $C_{32}H_{42}O_5$ requires C, 75.86; H, 8.35%).

[G2]-OH 2. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 4/1) afforded [G2]-OH **2** (91%) as white glassy substance. R_f 0.23 (hexane/EtOAc = 4/1); υ_{max} (film)/cm^{-1} 3422, 2961, 1601, 1514; δ_H ($CDCl_3$) 1.29 (36 H, s), 2.21 (12 H, quin, *J* 6.1), 4.04 - 4.14 (24 H, m), 5.02 (1 H, s), 6.00 (2 H, d, *J* 2.0), 6.08 (7 H, br s), 6.84 (8 H, d, *J* 8.8), 7.29 (8 H, d, *J* 8.8); δ_C ($CDCl_3$) 29.2, 31.4, 33.8, 64.3, 64.5, 94.2, 94.9, 113.9, 126.0, 143.2, 156.4, 157.7, 160.6; *m/z* (FAB) 1219.9 (M + H^+, 24%). (Found: C, 74.58; H, 8.15. $C_{76}H_{98}O_{13}$ requires C, 74.85; H, 8.10%).

[G3]-OH 3. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 4/1) afforded [G3]-OH **3** (83%) as white glassy substance. R_f 0.26 (hexane/EtOAc = 3/1); υ_{max} (film)/cm^{-1} 3422, 2960, 1601, 1514; δ_H ($CDCl_3$) 1.28 (72 H, s), 2.16 - 2.22 (28 H, m), 4.03 - 4.12 (56 H, m), 5.34 (1 H, br s), 5.98 (2 H, d, *J* 1.8), 6.08 (19 H, s), 6.84 (16 H, d, *J* 8.8), 7.28 (16 H, d, *J* 8.8); δ_C ($CDCl_3$) 29.4, 31.5, 34.0, 64.6, 64.7, 64.8, 94.5, 95.1, 114.2, 126.2, 143.5, 156.7, 157.6, 160.8; *m/z* (FAB) 2645.4 (M + H^+, 1%). (Found: C, 74.17; H, 7.94. $C_{164}H_{210}O_{29}$ requires C, 74.46; H, 8.00%).

[G4]-OH 4. Flash chromatography of the crude product on silica gel (hexane/EtOAc = 100/22 gradient to 4/1) afforded [G4]-OH **4** (73%) as white glassy substance. R_f 0.18 (hexane/EtOAc = 4/1); υ_{max} (film)/cm^{-1} 3423, 2962, 2878, 1600, 1514; δ_H ($CDCl_3$, OH not detected) 1.28 (144 H, s), 2.16 - 2.22 (60 H, m), 4.03 - 4.11 (120 H, m), 5.96 (2 H, d, *J* 2.0), 6.08 (43 H, br s), 6.83 (32 H, d, *J* 8.8), 7.27 (32 H, d, *J* 8.8); δ_C ($CDCl_3$) 29.3, 29.4, 31.5, 34.0, 64.6, 64.7, 94.5, 95.0, 114.2, 126.2, 143.5, 156.7, 157.6, 160.8; *m/z* (ESI) 5492 (M^+, 100%). (Found: C, 74.17; H, 8.01. $C_{340}H_{434}O_{61}$ requires C,74.29; H, 7.96%).

General procedure for the synthesis of [Gn]-Br. A mixture of the phenol [Gn]-OH (1 equiv.), 1,3-dibromopropane (15 equiv.) and potassium carbonate (2.5 equiv.) in acetone was heated to reflux. The reaction time required was 8, 16 and 24 h for the preparation of [G1]-Br, [G2]-Br and [G3]-Br respectively. The reaction mixture was cooled, filtered and evaporated *in vacuo* to remove excess 1,3-dibromopropane. The crude product was then purified as described in the following text.

[G1]-Br 8. Flash chromatography of the crude compound on silica gel (hexane gradient to hexane/Et_2O = 50/3) afforded [G1]-Br **8** (95%) as a white crystalline solid, m.p. 68 - 70°C. R_f 0.13 (hexane/Et_2O = 10/1); υ_{max} (film)/cm^{-1} 2961, 2871, 1600, 1514; δ_H (500 MHz, $CDCl_3$) 1.29 (18 H, s), 2.22 (4 H, quin, *J* 6.1), 2.28 (2 H, quin, *J* 6.1), 3.58 (2 H, t, *J* 6.5), 4.04 (2 H, t, *J* 5.8), 4.10 (4 H, t, *J* 6.1), 4.12 (4 H, t, *J* 6.0), 6.08 (2 H, d, *J* 2.0), 6.10 (1 H, t, *J* 2.0), 6.85 (4 H, d, *J* 8.8), 7.29 (4 H, d, *J* 8.8); δ_C ($CDCl_3$) 29.4, 30.0, 31.5, 32.4, 34.0, 64.3, 64.6, 65.4, 94.2, 114.0, 126.2, 143.4, 156.6, 160.5, 160.8; *m/z* (EI) 626 (M^+, 13%). (Found: C, 67.44; H, 7.64. $C_{35}H_{47}O_5Br$ requires C, 66.98; H, 7.55%).

[G2]-Br 10. Flash chromatography of the crude compound on silica gel (hexane gradient to hexane/EtOAc = 6/1) afforded [G2]-Br **10** (95%) as white glassy substance. R_f 0.29 (hexane/EtOAc = 20/3); υ_{max} (film)/cm^{-1} 2962, 2878, 1601, 1514; δ_H (500 MHz, $CDCl_3$) 1.28 (36 H, s), 2.19 - 2.29 (14 H, m), 3.56 (2 H, t, *J* 6.4),

4.00 - 4.13 (26 H, m), 6.09 (9 H, br s), 6.84 (8 H, d, *J* 8.9), 7.29 (8 H, d, *J* 8.9); δ_C ($CDCl_3$) 29.3, 29.8, 31.5, 32.4, 34.0, 64.4, 64.6, 65.4, 94.3, 114.0, 126.2, 143.4, 156.6, 160.7; *m/z* (FAB) 1339.5 (*M* + H^+, 7%). (Found: C, 70.59; H, 7.88. $C_{79}H_{103}O_{13}Br$ requires C, 70.78; H, 7.74%).

[G3]-Br 12. Flash chromatography of the crude compound on silica gel (hexane gradient to hexane/EtOAc = 4/1) afforded [G3]-Br (90%) as white glassy substance. R_f 0.15 (hexane/EtOAc = 5/1); υ_{max} (film)/cm^{-1} 2960, 2877, 1604, 1514; δ_H ($CDCl_3$) 1.28 (72 H, s), 2.17 - 2.27 (30 H, m), 3.54 (2 H, t, *J* 6.5), 3.99 - 4.12 (58 H, m), 6.08 (21 H, br s), 6.83 (16 H, d, *J* 8.8), 7.28 (16 H, d, *J* 8.9); δ_C ($CDCl_3$) 29.3, 29.4, 29.7, 31.5, 32.4, 34.0, 64.6, 64.7, 65.5, 94.3, 114.1, 126.2, 143.5, 156.7, 160.8; *m/z* (ESI) 2764.6 (*M* + H^+, 43%). (Found: C, 72.66; H, 7.87. $C_{167}H_{215}O_{29}Br$ requires C, 72.50; H, 7.83%).

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