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Facile Construction of Acid-base and Redox Stable Polyether-based Dendritic Fragments

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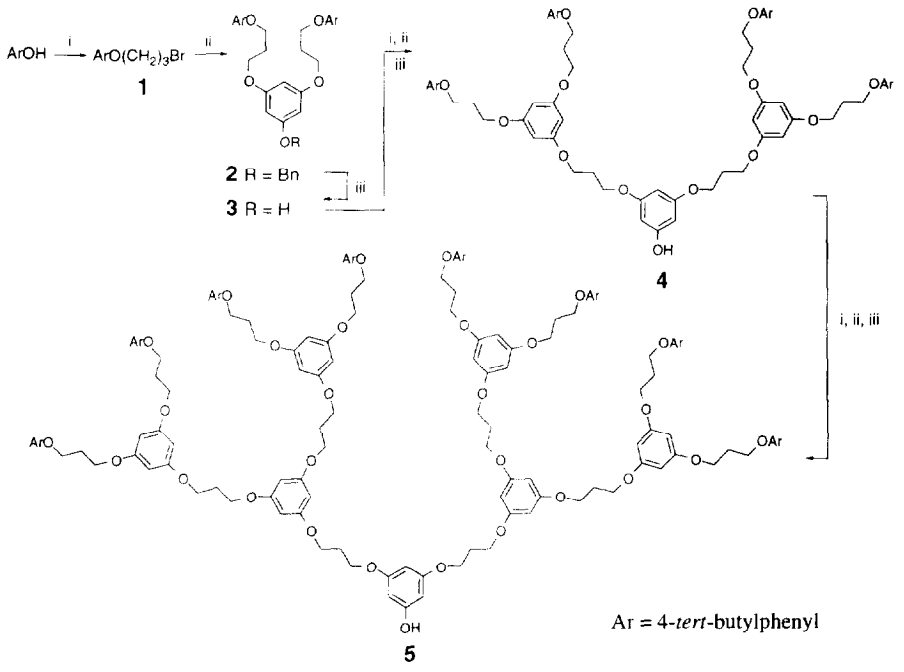
Abstract: Polyether-based dendritic fragments of up to the fourth generation can be synthesized in good yields from phloroglucinol and 1,3-dibromopropane. These dendritic fragments are stable in acid-base or redox conditions and can be linked to various functional core groups to form functional dendrimers which can be served as models to study the influence of the dendritic structure on the physical, chemical and electrochemical properties of the interior core.

Recent interest in dendrimer chemistry has sparked extensive investigations in their synthesis and structural property relationships. Initial research has centred on studying the global chemical and physical properties of this type of hyperbranched macromolecule.[1] Recently focus has switched to the investigations of the change of the physico-chemical properties of the interior core upon attachment to dendritic sectors. Several interesting phenomena have been observed and it appears that these dendritic molecules are excellent biological mimics of proteins and micelles.[2] In order to have a thorough understanding of the unusual properties of these hyperbranched molecules, it is necessary to have a selection of dendritic sectors of different generation, structure, connectivity and topology available for further study. Moreover, it is highly important that these dendritic sectors are stable and inert under a wide variety of experimental conditions (*e.g.* acid-base, redox, photochemical) such that they do not interfere the experiment of interest. One of the most commonly used dendritic fragments is Fréchet's polyether-based dendritic compound,[3] but it is questionable whether the benzylic ether linkages can survive under electrochemical redox conditions.[4] Silane dendrimers[5] are also good candidates but there is no handle to which one can attach functional units. Polyesters[6] or polyamides[7] are easy to synthesize but they are again relatively unstable in basic or acidic conditions. The other useful candidates are the amide-ester dendrimer reported by Newkome[8] and the polyamine-based dendrimer disclosed independently by Mülhaupt and de Brabander-van der Berg.[9] In this paper we report the facile construction of a new series of acid-basic and redox stable polyether-based dendritic sectors up to the fourth generation. These dendritic derivatives are readily soluble in organic solvents and has a phenolic functionality which can be used as the handle to attach to various functional units and thus create custom-designed functional dendrimers.

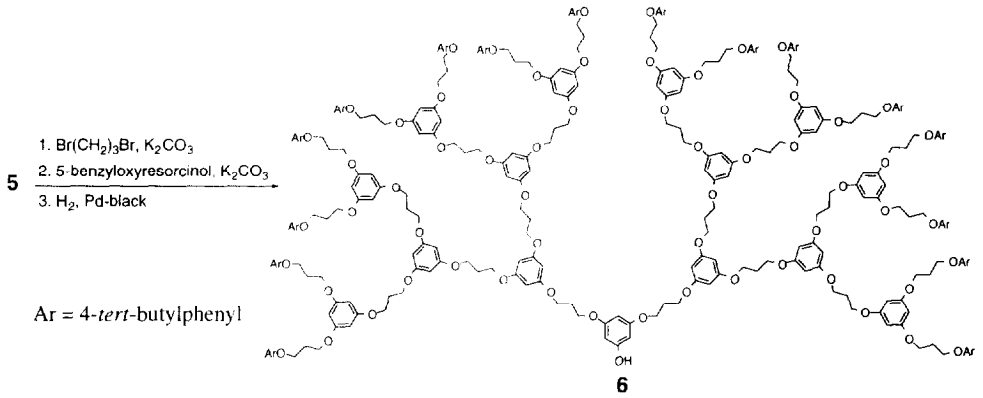
An iterative, convergent strategy[10] was used to synthesize these polyether dendritic sectors. Treatment of 4-*tert*-butylphenol with 4.6 equivalent of 1,3-dibromopropane (K_2CO_3, acetone, 66°C, 20 h) gave the mono-*O*-alkylated product **1**[11] as an oil (92%) (b.p. 140 °C/2.5 mm Hg) with little di-*O*-alkylated contaminant. Bis-*O*-alkylation (K_2CO_3, acetone, 66 °C, 48 h) of 5-benzyloxyresorcinol[12] with 2.1 equivalent of the monobromide **1** afforded the first generation C_2 symmetric benzyl ether **2**,[11] [G-1]-OBn,[13] as an oil (80%). Upon hydrogenation using 10% palladium on carbon as catalyst (ethanol/ethyl acetate, powdered K_2CO_3), the benzyl ether



Reagents: i. $Br(CH_2)_3Br$, K_2CO_3; ii. 5-benzyloxyresorcinol, K_2CO_3; iii. H_2, Pd-C, K_2CO_3

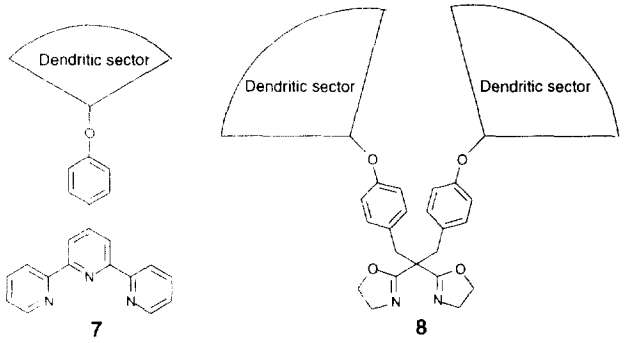
2 could be transformed into the phenol **3**,[11] [G-1]-OH, as a white solid (95%) (m.p. 92 - 93°C). Addition of a small amount of powdered K_2CO_3 to the reaction gave cleaner hydrogenolysis product. By repeating the above reaction sequence, the second and third generation phenols **4** and **5**,[11] could be obtained in overall yields of 70% and 46% respectively from **3**. For the fourth generation phenol **6**,[11] [G-4]-OH, (22% overall yield from **3**), the hydrogenation reaction had to be performed by using Pd-black as the catalyst since the reaction was extremely slow with 10% palladium on carbon. This preparative method can be performed on large scale with little difficulties and thus 10 to 50 g quantities of the dendritic fragments could be readily synthesized.

One of the advantages of our synthesis is that, like many other convergent approaches, any defective side products in the reaction sequence can be easily detected and eliminated. Thus, a very small amount of the mono-*O*-alkylated and *C*-alkylated side-products from 5-benzyloxyresorcinol are separable from the desired bis-



O-alkylated compound by column chromatography.[14] These hyperbranched benzyl ethers and phenols are readily soluble in organic solvents such as acetone, ethyl acetate, tetrahydrofuran, dichloromethane or chloroform and thus facilitate the study of their solution chemistry, although they are sparingly soluble in hexane or methanol. The fourth generation phenol **6** has a nominal molecular weight of 5493 and a calculated average distance[15] of 22 Å between the surface *tert*-butyl groups and the central phenolic moiety. As expected, these dendritic sectors are stable in either HCl (1M) or NaOH (1M) aqueous THF solution at 25°C for 16 h without decomposition. In addition, solutions of the dendritic phenols **3** - **6** do not show any observable redox pattern in cyclic voltammetry[16] and hence they will not interfere electrochemical studies.

The phenolic functionality now can serve as a handle for it to attach to various core groups. Thus, the dendritic phenols **3** - **6** can be attached to a polypyridine moiety to give dendritic terpyridine ligands of the general structure **7** in good yields, which can then be transformed into the corresponding $Fe(\mathbf{7})_2^{2+}$ complexes[17] and allow us to investigate the redox behavior of the iron(II) ion upon ligand dendritification. Similarly these dendritic sectors have also been attached to a catalytic bis-(oxazoline) unit[18] to generate catalytic dendrimers of the general structure **8**. The results of these studies will be reported in due course.



7 **8**

Finally, it should be noted that by changing the surface group of the dendrimer, one can fine tune the physico-chemical properties of the resulting functional dendrimers. In our hands, we have successfully modified these dendritic wedges by changing the surface 4-*tert*-butylphenyl groups to 3,5-dimethoxyphenyl moieties and created a new series of dendrimer with significantly different physical properties.

In summary, we disclosed here the facile synthesis of a new series of acid-base and redox stable polyether dendritic fragments which can be linked to various functional core groups and then to study the influence of the dendritic sectors on the physico-chemical properties of the resulting functional dendrimers.

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11. All compounds give satisfactory ^{1}H and ^{13}C NMR spectral data and elemental analysis (C, H ± 0.4% within calculated values). Selected NMR data (δ, 250 MHz for ^{1}H-NMR and 62.5 MHz for ^{13}C-NMR in $CDCl_3$): **3**: ^{1}H-NMR: 7.30 (d, *J* = 8.7 Hz, 4 H), 6.85 (d, *J* = 8.7 Hz, 4 H), 6.07 (t, *J* = 2.0 Hz, 1 H), 6.00 (d, *J* = 2.0 Hz, 2 H), 4.92 (br s, 1 H), 4.11 (t, *J* = 6.0 Hz, 4 H), 4.09 (t, *J* = 6.2 Hz, 4 H), 2.21 (quin, *J* = 6.1 Hz, 4 H), 1.29 (s, 18 H). ^{13}C-NMR: 160.8, 157.4, 156.4, 143.4, 126.1, 114.1, 95.0, 94.3, 64.5, 33.9, 31.5, 29.2. *m/z* (EI) 506 (M^+, 34%). **4**: ^{1}H-NMR: 7.29 (d, *J* = 8.8 Hz, 8 H), 6.84 (d, *J* = 8.8 Hz, 8 H), 6.08 (br s, 7 H), 6.00 (d, *J* = 2.0 Hz, 2 H), 5.02 (br s, 1 H), 4.14 - 4.04 (m, 24 H), 2.21 (quin, *J* = 6.1 Hz, 12 H), 1.29 (s, 36 H). ^{13}C-NMR: 160.6, 157.7, 156.4, 143.2, 126.0, 113.9, 94.9, 94.2, 64.5, 64.3, 33.8, 31.4, 29.2. *m/z* (FAB) 1219.9 (M^+ + H, 24%). **5**: ^{1}H-NMR: 7.28 (d, *J* = 8.8 Hz, 16 H), 6.84 (d, *J* = 8.8 Hz, 16 H), 6.08 (s, 19 H), 5.98 (d, *J* = 1.8 Hz, 2 H), 5.34 (br s, 1 H), 4.12 - 4.03 (m, 56 H), 2.22 - 2.16 (m, 28 H), 1.28 (s, 72 H). ^{13}C-NMR: 160.8, 157.6, 156.7, 143.5, 126.2, 114.2, 95.1, 94.5, 64.8, 64.7, 64.6, 34.0, 31.5, 29.4. *m/z* (FAB) 2645.4 (M^+ + H, 1%). **6**: ^{1}H-NMR (OH not observed): 7.27 (d, *J* = 8.8 Hz, 32 H), 6.83 (d, *J* = 8.8 Hz, 32 H), 6.08 (br s, 43 H), 5.96 (d, *J* = 2.0 Hz, 2 H), 4.12 - 4.03 (m, 120 H), 2.22 - 2.16 (m, 60 H), 1.28 (s, 144 H). ^{13}C-NMR: 160.8, 157.6, 156.7, 143.5, 126.2, 114.2, 95.0, 94.5, 64.7, 64.6, 34.0, 31.5, 29.4, 29.3. *m/z* (ESI) 5492 (M^+, 100%).
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13. The shorthand notation described by Fréchet is used here. For details see reference 10.
14. The mono-*O*-alkylated ($R_f \approx 0.3$), *C*-alkylated ($R_f \approx 0.4$) and bis-*O*-alkylated ($R_f \approx 0.6$) are readily separable on silica gel eluting with hexane-ethyl acetate (3: 1) mixture.
15. Molecular modeling was performed on a Macintosh® Quadra 650 machine by using the Alchemy® Software (version 3.02) purchased from Tripos Associates, Inc., St. Louis, Missouri, USA.
16. Experimental conditions: 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.
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