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# Synthesis of Poly(alkyl aryl ether) Dendrimers

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**Abstract:** Poly(alkyl aryl ether) dendrimers of up to four generations composed of a phloroglucinol core, branching components, and pentamethylene spacers are synthesized by a divergent growth methodology. A repetitive synthetic sequence of phenolic *O*-alkylation and *O*-benzyl deprotection reactions are adopted for the synthesis of these dendrimers. The peripheries of the dendrimers contain 6, 12, 24, and 48 phenolic hydroxyl groups, either in the protected or unprotected form, for the first, second, third, and fourth generations, respectively. Because of the presence of hydrophilic exterior and relatively hydrophobic interior regions, alkaline aqueous solutions of these dendrimers are able to solubilize an otherwise insoluble pyrene molecule and these supramolecular complexes precipitate upon neutralization of the aqueous solutions.

The particular class of hyperbranched macromolecules called dendrimers has grown into an active area of research among polymers during the last two decades.[1] The features such as molecular structure, architecture, topology, controllable growth, and the presence of endo- and exo-receptor properties among others have made these macromolecules intriguing and have contributed to the spectacular advances in the studies of a large number of dendrimers.[2] Such advances are also coupled intimately and critically with the ability to synthesize different kinds of dendrimers starting from a variety of monomers, depending on the desired purposes of the target dendrimers. While synthesis of nanometer-sized and monodispersed dendrimers with multi kilodaltons in molecular weights presents a formidable task, such challenges are also mitigated partly as a result of the necessity to have only a very few repetitive synthetic schemes for their successful synthesis. Among quite a few synthetic routes available at present[1,3] for the covalent synthesis of dendrimers, the most popular ones are the so-called "divergent"[1b] and "convergent"[3a] synthetic methodologies. With the aid of these and other methodologies, syntheses of a variety of dendrimers have been accomplished, starting from the respective monomers.[2] As much to the extent that each type of dendrimer possesses its own structural and molecular properties, identification of new monomers for dendrimer synthesis continues to be attractive. In our interest to synthesize new types of dendrimers, we report herein the synthesis of poly(alkyl aryl ether) dendrimers of up to four generations. These dendrimers possess inner polyalkylene segments radiating from symmetrically trifunctionalized benzenoid core and branching components. The trifunctional core and branching components of choice in these dendrimers are derived from phloroglucinol and the inner polyalkylene segment is composed of pentamethylene units. The presence of phloroglucinol unit offers the opportunity to have phenolic hydroxyl groups at the periphery, while the interior of these dendrimers are relatively lyophilic with the presence of the alkylene segments. The synthesis and structural characterization of these dendrimers, both with and without protecting groups on the phenolic hydroxyl groups, by adopting a divergent synthetic methodology, are described herein.

We have chosen the symmetrically functionalized phloroglucinol (1,3,5-trihydroxy benzene) as the core and branching component in the synthesis of poly(alkyl aryl ether) dendrimers. Phloroglucinol was used previously by Chow and co-workers[4] as the branching component of dendron derivatives. A convergent strategy was used to synthesize these dendrons composed of propylene spacers and phloroglucinol branching junctures and these dendrons were also end-capped with 4-*tert*-butylphenyl units. In our efforts to utilize phloroglucinol as the building block of dendrimers, we adopted a divergent growth methodology involving the reaction of bis-*O*-protected phloroglucinol with an alkyl halide in a repetitive sequence of *O*-alkylation, followed by *O*-deprotection.

Synthesis of the required phloroglucinol derivatives for forming dendrimers is presented in Scheme 1. The reaction of phloroglucinol (**1**) with an excess of 1,5-dibromopentane (4.5 molar equiv) afforded the tribromo derivative **2**, and in a divergent synthesis **2** forms as the core of dendrimers. Bis-*O*-benzyl phloroglucinol[5] **3** was

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10.1021/jo025844a CCC: $22.00 
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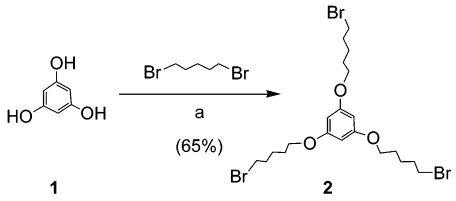
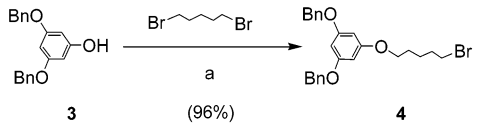
**SCHEME 1**[a]



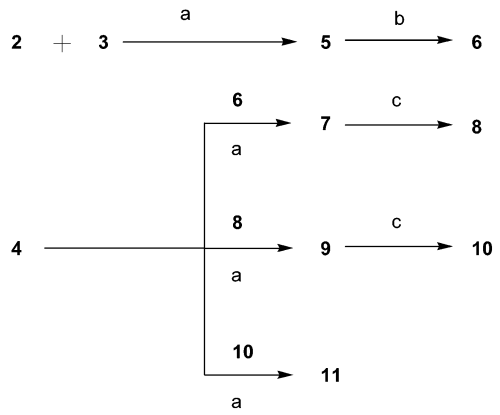

[a] Reagents and conditions: (a) $K_2CO_3$, DMF, 48 h.

**SCHEME 2**[a]




[a] Reagents and conditions: (a) $K_2CO_3$, 18-C-6, MeCN, reflux, 7 h.

**SCHEME 3**[a]




[a] Reagents and conditions: (a) $K_2CO_3$, 18-C-6, MeCN, reflux; (b) 10% Pd-C, $H_2$, EtOAc/MeOH (9:1); (c) 10% Pd-C, $C_6H_{12}$, THF, reflux.

obtained by the removal of a benzyl group from the corresponding tris-*O*-benzyl phloroglucinol[6] under transfer hydrogenation conditions. *O*-Alkylation of **3** with 1,5-dibromopentane afforded the phloroglucinol derivative **4** (Scheme 2). Synthesis of the first generation dendrimer **5** (**G-1**) (Scheme 3) involved alkylation of **3** with **2**, followed by deprotection of the peripheral *O*-benzyl groups by hydrogenolysis (10% Pd-C, $H_2$). These two reactions, namely, *O*-alkylation and *O*-benzyl deprotection, were used repetitively to generate the higher generation dendrimers (Scheme 3). The molecular structures of dendrimers **G-1** to **G-4** are given in Figures 1−3. The *O*-alkylation and *O*-benzyl deprotections are high-yielding reactions and all the dendrimers are stable for long periods of time in general. While the *O*-benzyl deprotection in **G-1** (**5**) is facile and complete deprotection could be achieved in ∼7 h to afford **6**, the higher generation dendrimers **G-2** (**7**) and **G-3** (**9**) required deprotection to be conducted for longer time at higher pressures (45 psi, Parr apparatus), to obtain the free −OH groups in **8** and **10**. Alternatively, the transfer hydrogenation was found to be more facile for the *O*-debenzylation and thus the transfer hydrogenation was conducted for *O*-debenzylations of dendrimers **7** and **9** to afford **8** and **10**. To ensure alkylations at multiple −OH groups, reactions of **6**, **8**, and **10** were conducted with bromide **4** in 1.3−1.4 molar excess per −OH functionality. While the progress of *O*-alkylation reactions could be monitored by TLC methods, that of *O*-benzyl deprotections were ascertained by $^1$H NMR spectroscopy after workup of the reaction mixture.

The *O*-benzylated dendrimers **5**, **7**, **9**, and **11** are oils, whereas the *O*-debenzylated dendrimer **6** is a solid and **8** and **10** exist as foamy solids. In the *O*-benzylated form, all the dendrimers are soluble in common organic solvents, thereby routine column chromatographic purifications could be performed, including the **G-4** dendrimer **11**. The corresponding *O*-debenzylated dendrimers are soluble in $Me_2CO$, MeCN, THF, MeOH, DMF, and DMSO and are insoluble in nonpolar organic solvents such as $Et_2O$, $CH_2Cl_2$, PhMe, and hexane. Consistent with increasing molecular weights, the relative retention times of poly(alkyl aryl ether) dendrimers in gel permeation chromatography (GPC) were found to lower with increasing generations, reflecting the evolution of more compact structures as the dendrimer generations advance. Structural elucidations of dendrimers **G-1** to **G-4** were performed by $^1$H and $^{13}$C NMR spectroscopy, elemental analysis, and mass spectrometry. The $^1$H NMR chemical shifts of the inner phloroglucinol units in **5**, **7**, **9**, and **11** in $CDCl_3$ appear as a single peak and the peripheral phloroglucinol units resonate as a pair of singlets: one singlet is twice as much as the other singlet. While the $^1$H NMR spectrum of **5** exhibited sharp peaks for all types of protons, dendrimers **7**, **9**, and **11** have shown peaks relatively broad in $CDCl_3$, most likely due to an aggregation in this solvent. In an attempt to resolve the peaks, the spectrum was also recorded in DMSO-$d_6$ solution. Although the peaks were still broad at room temperature, a refined spectrum was observed at higher temperatures. The *O*-debenzylated dendrimers **6**, **8**, and **10** have shown two resonances for the phloroglucinol units in $CD_3COCD_3$, one corresponding to the protons of inner region and the other, a broad singlet, corresponding to the protons of peripheral region. The resonances of the pentamethylene segment could also be observed distinctly, though as broad signals for the higher generation dendrimers. Similarly, $^{13}$C NMR spectra of all the dendrimers exhibited distinct resonances corresponding to the C (quat) and CH (methine) of phloroglucinol, apart from resonances for the benzylic units in the case of *O*-benzylated dendrimers and pentamethylene linkers. Much difference in the chemical shift values could not be observed between the *O*-benzylated and the *O*-debenzylated dendrimers. However, the signals in the $^{13}$C NMR spectrum were relatively weaker for the higher generation dendrimer **11**, when compared to the dendrimers **5**−**10**. The mass spectrometric analysis for dendrimers **5**−**8** has exhibited the expected molecular ion peak, either as $[M + H]^+$ or Na or K adducts. Elemental analysis was performed for all the *O*-benzylated dendrimers. While C and H values were in agreement for **5**, **7**, and **9**, reliable values could not be obtained for **G-4** (**11**), most likely due to entrapment of "guest molecules" in the interior of the dendrimer. Also, elemental analysis on *O*-debenzylated dendrimers **6**, **8**, and **10** could not be performed as a result of the association of solvent

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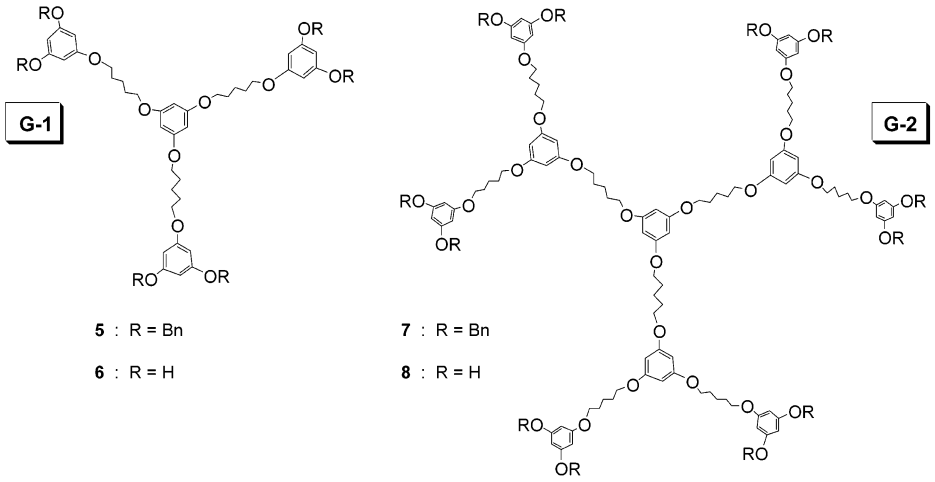


**FIGURE 1.** Molecular structures of the first generation (**G-1**) and the second generation (**G-2**) poly(alkyl aryl ether) dendrimers.

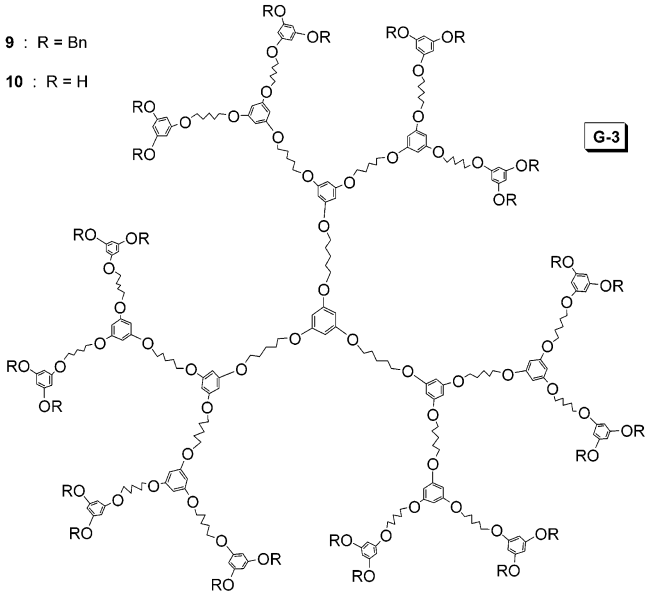


**FIGURE 2.** Molecular structure of the third generation (**G-3**) poly(alkyl aryl ether) dendrimers.

molecules. Thus, in combination with GPC, $^{1}$H and $^{13}$C NMR spectroscopy, mass spectrometric methods, and elemental composition analyses, the identities and the structural homogeneities of dendrimers **5**−**11** were confirmed.

To test the ability of hydroxyl terminated dendrimers **6**, **8**, and **10** as hosts, we have conducted solubilization experiments. An aqueous insoluble molecule, namely, pyrene, was admixed with an aqueous alkaline solution of dendrimer **6**, **8**, and **10** (pH ∼10.5) and the suspension was shaken at 25 °C for 24 h. The extent of pyrene solubilization was then checked by UV−vis absorption spectroscopy, after filtration of the above suspension. The results of these experiments are given in Table 1. The saturation concentration of pyrene in water is $8 \times 10^{-7}$ M,[7] while that in dendrimer solutions of **6**, **8**, and **10** was found to be 5, 8, and 24 times higher, which reflect the effective strength of pyrene solubilization as the dendrimer generations advance. The values of free energies of transfer ($\Delta G_{tr}$) of pyrene from water to the aqueous solutions of dendrimers are also given in Table 1. It is clear from this analysis that the dendrimer containing aqueous solutions solubilize pyrene. Further, there exists a linearity of aqueous solubility of pyrene with the concentration of the dendrimer, indicating that the solubilzation of pyrene is *not* due to any on-set of aggregation in dendrimer-containing solutions. These observations agree with that reported by Fréchet and coworkers[8] on the pyrene solubilization in a carboxyl-terminated poly(benzyl aryl ether) dendrimer. Because the dendrimers **6**, **8**, and **10** are insoluble in neutral aqueous medium, conversion to the phenoxide form is necessary for their solubility in an aqueous solution. The direct effect of such phenoxide formation at the periphery would be the "elongation" of the molecule resulting from the repulsive interactions between adjacent arms within the dendrimer molecule. These molecular features should thus allow the maximum extent of interaction of the pyrene molecules with complementary hydrophobic surfaces arising from the alkylene segments and the aromatic regions of the dendrimer. We have also tested the possibility of precipitating the pyrene−dendrimer supramolecular complex upon neutralization. The precipitation of the above supramolecular complex was observed upon neutralizing the alkaline solution of the pyrene-containing dendrimer solutions. These experiments open up possibilities to explore the transport properties of aqueous solutions of these dendrimers.

In conclusion, a two-step iterative procedure involving *O*-alkylation and *O*-benzyl group deprotection reactions has been found to be suitable for the synthesis of new poly(alkyl aryl ether) dendrimers, composed of phloroglucinol core, branching components, and pentamethylene linker units. The synthesis involving these two reactions is also found to be facile and dendrimers of up to four generations have been synthesized by using this iterative procedure. Although the pentamethylene linker has been chosen to construct these dendrimers, the reactions are amenable for incorporating other alkylene linkers. Within the currently known varieties of dendrimers, "completely" polyether dendrimers[3a] and den-

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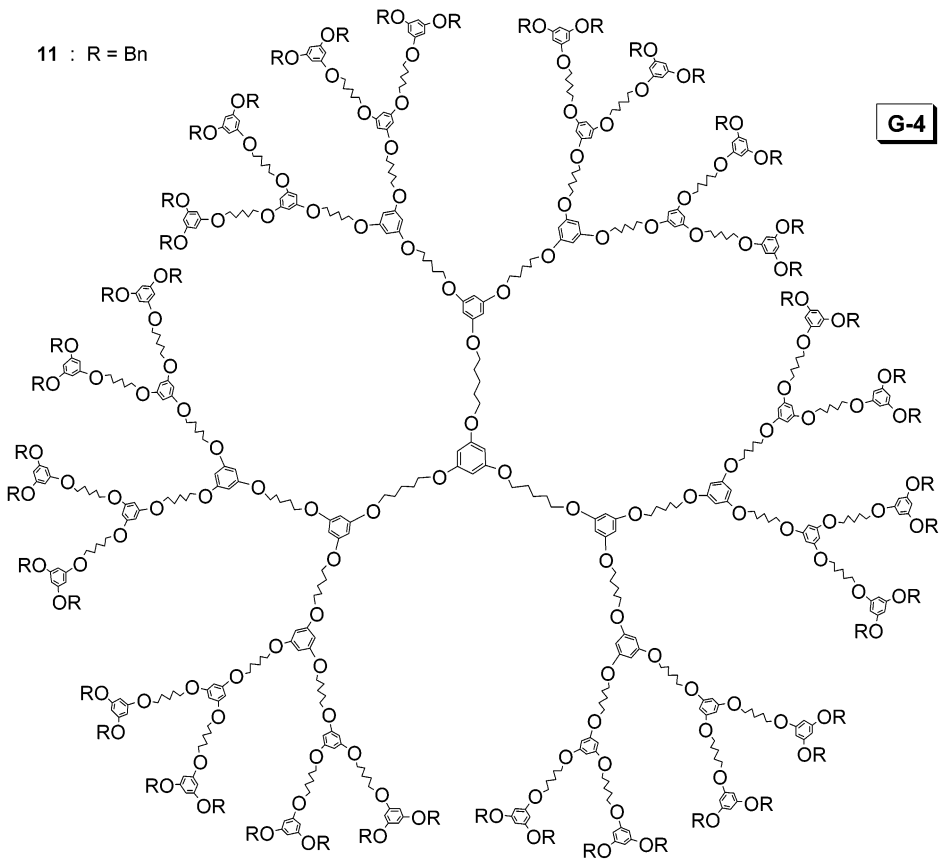


**FIGURE 3.** Molecular structure of the fourth generation (**G-4**) poly(alkyl aryl ether) dendrimer.

**TABLE 1. Solubility and $\Delta G_{tr}$ of Pyrene in Aqueous Solutions of Dendrimers 6, 8, and 10**

| aq soln of dendrimer (100 $\mu$M) | pyrene ($\mu$M)[a] | $\Delta G_{tr}$ (cal/mol)[b] |
|---|---|---|
| 6 | 4.2 | −982 |
| 8 | 6.3 | −1222 |
| 10 | 18.8 | −1781 |

[a] A solution of known concentration of **6**, **8**, and **10** at pH ~10.5 (0.05 N NaOH) was added with pyrene (5 mg) and with stirring for 24 h at 25 °C; the solution was filtered (0.2 $\mu$m filter) and the amount of solubilized pyrene was determined by its absorption at 335 nm. [b] The free energy of transfer ($\Delta G_{tr}$) was calculated from the equation $\Delta G_{tr} = -RT \ln(C_s/C_w)$, where $C_s$ and $C_w$ are the solubilities of the pyrene in the aqueous dendrimeric solution and in water.

drons[4,9] are still small in number[10] and the most well-studied among these is the Fréchet's poly(benzyl aryl ether)[3a] dendrimers. The dendrimers reported herein thus represent a new type within the class of polyether dendrimers. Moderate stabilities of alkyl aryl ether linkages toward acidic and basic environments, as well as the presence of hydrophilic exterior and lyophilic interior, should impart specific attributes arising due to these molecular features in the poly(alkyl aryl ether) dendrimers reported herein. An assessment of the supramolecular properties of hydroxyl-terminated dendrimers **6**, **8**, and **10** shows that aqueous solutions of these dendrimers indeed solubilize an otherwise insoluble pyrene molecule due to the existence of a hydrophilic−hydrophobic balance within the dendrimer molecules.

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**Supporting Information Available:** General methods of experimental details, synthesis of **2**−**11**, $^1$H NMR spectrum of dendrimer **9** (**G3-(OBn)$_{24}$**) and GPC profiles of the **G1-(OBn)$_6$** (**5**), **G2-(OBn)$_{12}$** (**7**), **G3-(OBn)$_{24}$** (**9**), and **G4-(OBn)$_{48}$** (**11**) dendrimers. This material is available free of charge via the Internet at http://pubs.acs.org.

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