ORGANIC LETTERS

2004
Vol. 6, No. 15
2547−2550

Dendrimers Based on a Three-Dimensionally Disposed AB_4 Monomer

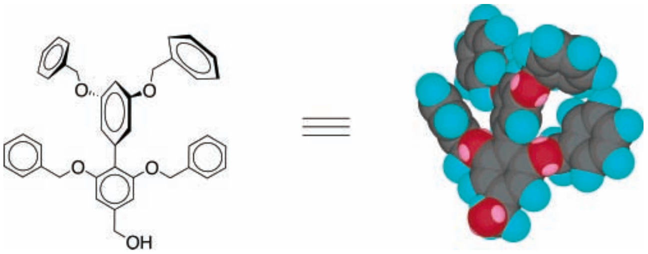
K. Natarajan Jayakumar, Pandi Bharathi, and S. Thayumanavan*

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

thai@chem.umass.edu

Received May 10, 2004

ABSTRACT



Design and synthesis of a novel class of dendrons based on an AB_4 monomer are described. These dendrons have been evaluated by using dendritic encapsulation of a redox active core. The electrochemical properties of symmetric ferrocene-cored dendrimers show that significant alterations in redox potential and heterogeneous electron-transfer rate constants could be achieved even at lower generations.

The study of dendrimers has been a topic of considerable interest in recent years for a variety of applications.[1] Syntheses of dendrimers are achieved by using AB_n monomers, where "n" represents the degree of branching. Most reported dendrimers are based on AB_2 or AB_3 building block units.[1,2] Understandably, increasing the magnitude of n results in a rapid assembly of high molecular weight dendrimers.[2] Herein, we wish to report on the dendrons and dendrimers based on a biaryl-based AB_4 monomer **5**.

The biaryl monomer design is based on our monomer design for uniformly functionalized amphiphilic dendrimers.[3] That molecular design is based on the twist that is commonly observed in biaryls, which should provide an interesting three-dimensional spatial disposition of the phenolic moieties with respect to the hydroxymethyl functionality in **5**. A space-filling model of a tetrabenzyl-substituted AB_4 monomer **7**, energy-minimized using MM2 calculations (shown in the abstract), supports the presumed spatial arrangement of the dendritic branches. We hypothesized that the three-dimensional disposition of the branches should provide dendritic microenvironments at the core of the dendrimer or the focal point of the dendrons at lower generations. Such features can be investigated by studying the effectiveness of these dendrimers in encapsulating electroactive units.[4] In this vein, we have unsymmetrically (monodendrons) and symmetrically (didendrons) attached dendrons based on the biaryl monomer **5** to ferrocene. Here, we report on the syntheses, characterization, and electrochemical studies of these dendrimers.

The AB_4 monomer **5** was synthesized from compounds **1** and **2**, as shown in Scheme 1. Compounds **1** and **2** were synthesized from 1-bromo-3,5-dimethoxybenzene and 4-bro-

---

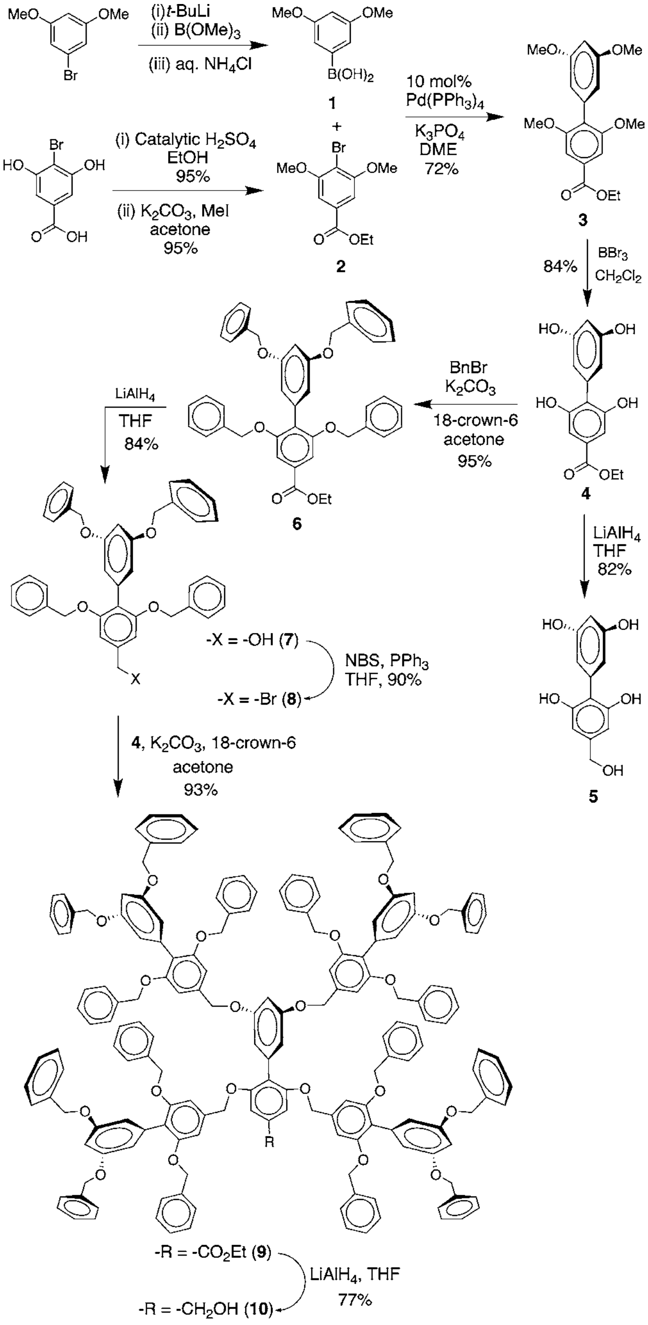
(1) (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons*: *Concepts*, *Syntheses*, *Applications*; Wiley-VCH: New York, 2001. (b) *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; John Wiley & Sons: New York, 2002. (c) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (d) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884. (e) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681. (f) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819.

(2) (a) Dukeson, D. R.; Ungar, G.; Balagurusamy, V. S. K.; Percec, V.; Johansson, G. A.; Glodde, M. *J. Am. Chem. Soc.* **2003**, *125*, 15974. (b) Elemans, J. A. A. W.; Boerakker, M. J.; Holder, S. J.; Rowan, A. E.; Cho, W.-D.; Percec, V.; Nolte, R. J. M. *Proc. Natl. Acad. Sci.* **2002**, *99*, 5093. (c) Ohta, M.; Fréchet, J. M. J. *J. Macromol. Sci., Pure Appl. Chem.* **1997**, *A34*, 2025. (d) Scott, D. A.; Krülle, T. M.; Finn, M.; Fleet, G. W. J. *Tetrahedron Lett.* **2000**, *41*, 3959.

(3) Bharathi, P.; Zhao, H.; Thayumanavan, S. *Org. Lett.* **2001**, *3*, 1961.

10.1021/ol049147b CCC: $27.50

Scheme 1. Synthesis of AB$_4$ Monomer and Dendrons



mo-3,5-dihydroxybenzoic acid, respectively. The former bromoarene was synthesized from the commercially available 3,5-dimethoxybenzoic acid, using a previously reported procedure.[5] This bromoarene was then subjected to a bromine−lithium exchange followed by treatment with trimethyl borate and hydrolysis to obtain the aryl boronic acid **1**. Compound **2** was synthesized from 4-bromo-3,5-dihydroxybenzoic acid, by converting the acid to an ester followed by methylation of the phenolic groups. A key step in the synthesis of target monomer is the aryl−aryl bond-forming reaction to obtain **3**. Since Suzuki coupling has been reported to give reasonably good yields of hindered biaryls, we have utilized this reaction for aryl−aryl coupling.[6] The biaryl compound **3** was synthesized by the palladium-catalyzed coupling of the boronic acid **1** and the bromoarene **2** in anhydrous DME in the presence of potassium phosphate in 72% yield. We also attempted Stille coupling reaction conditions for the synthesis of **3**. This methodology afforded the desired product in only about 45% yield. Demethylation of **3** with BBr$_3$ resulted in the tetraphenolic compound **4** in 84% yield. Lithium aluminum hydride reduction of the ester **4** afforded the target AB$_4$ monomer **5** in 82% yield.

The assembly of dendrons from the AB$_4$ monomer was achieved by using the protocols developed for AB$_2$ arylalkyl ethers.[7] Monomer **5** was treated with slightly more than 4 equiv of benzyl bromide in the presence of K$_2$CO$_3$ and 18-crown-6 to afford the first generation monodendron **7**. However, the yield was only about 50% and the product was accompanied by a few unidentified less polar compounds. To circumvent this complication, we attempted the alkylation of ester **4** with benzyl bromide, where the product **6** was obtained in 95% yield. Compound **6** was then reduced with LAH to afford the first generation alcohol **7** in 84% yield. The alcohol **7** was converted to bromide **8** upon treatment with NBS/PPh$_3$. Reaction of **4** with slightly more than 4 equiv of bromomethyl compound **8** followed by reduction with LAH afforded the second generation dendron **10** in 71% overall yield.

Syntheses of unsymmetrical and symmetrical ferrocene-cored dendrimers are shown in Scheme 2. Ferrocene was chosen as the redox active core mainly because of its simple and well-studied one-electron redox feature. Benzylferrocene carboxylate (**11**) and benzylferrocene-1,1′-dicarboxylate (**12**) were synthesized as the control for the unsymmetrical and symmetrical dendrimers, respectively. Compounds **11** and **12** were synthesized by the EDC/DMAP mediated coupling of benzyl alcohol with ferrocenecarboxylic acid and 1,1′-ferrocenedicarboxylic acid, respectively. Unfortunately, the same reaction conditions afforded poor yield of the desired product in the reaction with the dendritic alcohol **7**. Therefore, we employed fluorocarbonylferrocene or ferrocenyl-1,1′-diacid fluoride[8] as the electrophilic species. Reaction of fluorocarbonylferrocene with the dendritic alcohols **7** and **10** in the presence of DMAP resulted in the unsymmetrical dendrons **13** and **14** in 88% and 75% yields, respectively, as shown in Scheme 2. Similarly, treatment of **7** and **10** with ferrocenyl-1,1′-diacid fluoride afforded symmetrical den-

---

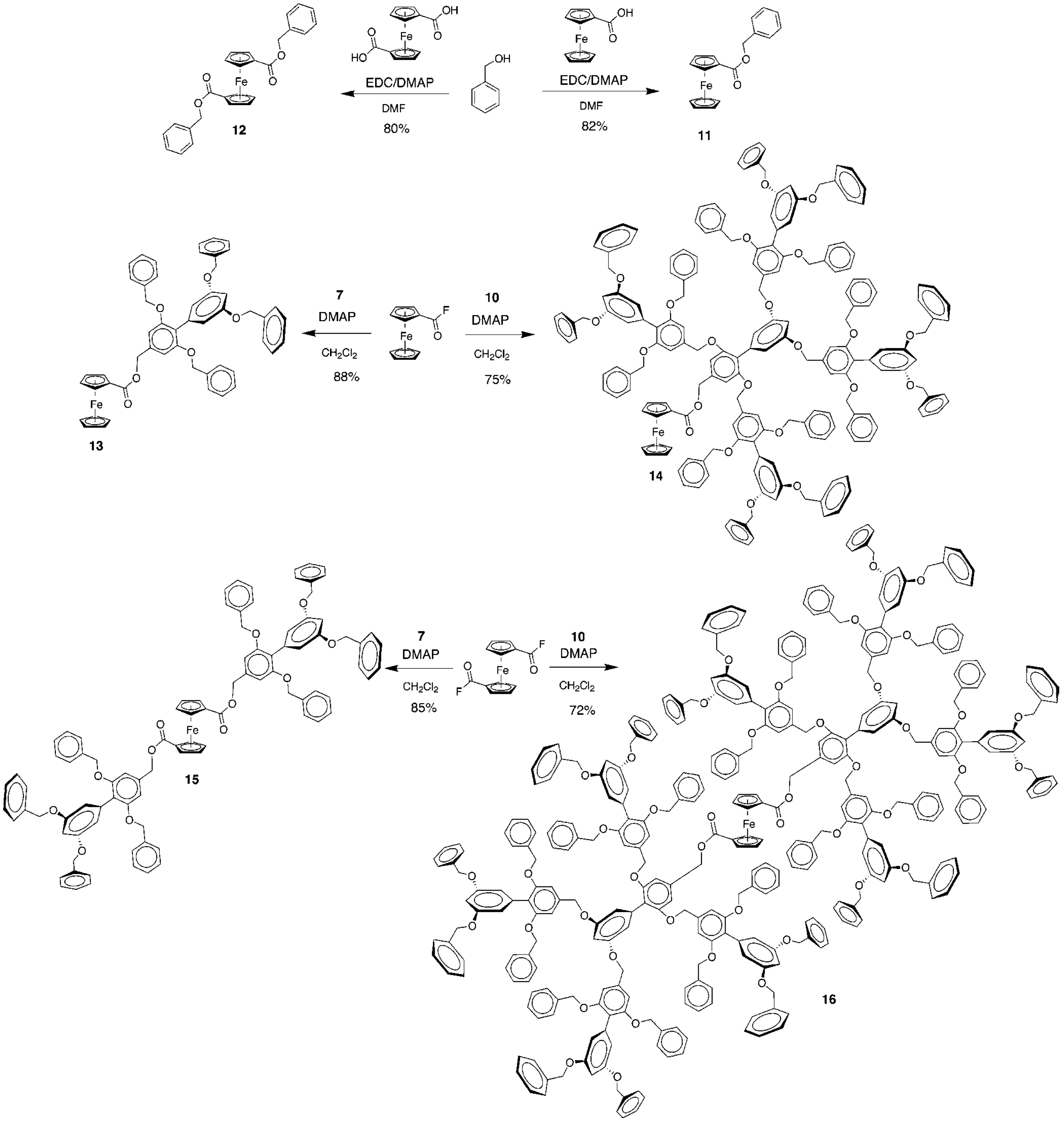
(4) (a) Diederich, F.; Felber, B. *Proc. Natl. Acad. Sci.* **2002**, *99*, 4778. (b) Dandliker, P. J.; Diederich, F.; Gisselbrecht, J. P.; Louati, A.; Gross, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2725. (c) Jiang, D. L.; Aida, T. *Chem. Commun.* **1996**, 1523. (d) Gorman, C. B.; Smith, J. C.; Hager, M. W.; Parkhurst, B. L.; Sierzputowska-Gracz, H.; Haney, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 9958. (e) Chasse, T. L.; Sachdeva, R.; Li, Q.; Li, Z.; Petrie, R. J.; Gorman, C. B. *J. Am. Chem. Soc.* **2003**, *125*, 8250. (f) Cardona, C. M.; Mendoza, S.; Kaifer, A. E. *Chem. Soc. Rev.* **2000**, *29*, 37. (g) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74. (h) Newkome, G. R.; Güther, R.; Moorefield, C. N.; Cardullo, F.; Echegoyen, L.; Pérez-Cordero, E.; Luftmann, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2023. (i) Balzani, V.; Campagna, S.; Denti, G.; Juris, A.; Serroni, S.; Venturi, M. *Acc. Chem. Res.* **1998**, *31*, 26.

(5) Dol, G. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **1998**, 359.

(6) (a) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(7) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

Scheme 2. Synthesis of Symmetrical and Unsymmetrical Ferrocene-Cored Dendrimers



drimers **15** and **16** in 85% and 72% yields, respectively (Scheme 2). All dendrimers were characterized by ^{1}H NMR, ^{13}C NMR, and MALDI-ToF spectrometry. The dendrimers were also analyzed with GPC as an additional check for purity.

Electrochemical measurements were performed with 0.2 M tetrabutylammonium hexafluorophosphate as a supporting electrolyte in CH_2Cl_2. Electrochemical data for compounds **11**−**16** are given in Table 1. Half-wave potentials ($E_{1/2}$) were measured relative to Fc/Fc$^+$, using square wave voltammetry. Experimental cyclic voltammograms were simulated by using Digisim to determine diffusion coefficients (D_o) and heterogeneous electron-transfer rate constants (k^0) (see Figure 1).

Diffusion coefficients, estimated by using the Randles−Sevcik equation $\{i_P = (2.69 \times 10^5)ACD^{1/2}v^{1/2}\}$, were used as the starting point for the simulation. The $E_{1/2}$ and the k^0 values are shown in Table 1. The redox potentials of the unsymmetrical dendrons **13** and **14** are essentially unchanged compared to those of the control ferrocene carboxylic ester **11**. This suggests that the difference between the stability

Table 1. Electrochemical Data for Dendrimers[a]

compd	$E_{1/2}$[b] (mV)	D_0 (10^{-6} cm^2/s)	hydrodynamic radius[c] (nm)	k^0 (10^{-4} cm/s)
		unsymmetrical dendrimers		
11	264	4.5 ± 0.5	1.08	46 ± 7
13	264	2.0 ± 0.1	2.43	31 ± 7
14	268	1.0 ± 0.1	5.11	21 ± 2
		symmetrical dendrimers		
12	496	5.5 ± 2.5	0.88	45 ± 14
15	508	1.4 ± 0.1	3.47	28 ± 5
16	528	irr.	irr.	7 ± 0[d]

[a] Carried out with 0.2 M $TBA^+PF_6^-$ in CH_2Cl_2 at 25 °C. See the Supporting Information for other experimental details. [b] Half-wave potentials ($E_{1/2}$) were measured relative to Fc/Fc$^+$, using square wave voltammetry. [c] Determined by using the Stokes–Einstein equation. [d] k^0 for **16** was approximated by inputting the D_0 value of **15**.

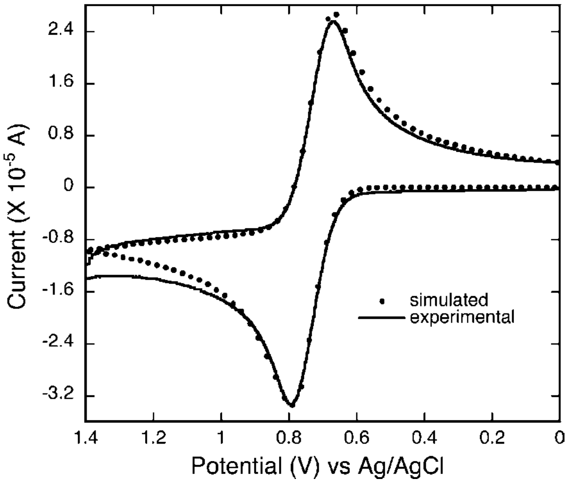


Figure 1. A typical experimental CV and the simulation (compound **13**).

of ferrocene and the ferrocenium species is similar in **11**, **13**, and **14**. These unsymmetrical monodendrons exhibit steady, but small decreases in the electron-transfer rate constants. Compared to the control molecule **11**, with $k^0 = 4.6 \times 10^{-3}$ cm/s, the biaryl dendrons **13** and **14** exhibit k^0 of 3.1×10^{-3} and 2.1×10^{-3} cm/s, respectively.

Interestingly, the symmetrical biaryl dendrimers **15** and **16** exhibit a different behavior. These molecules exhibit a steady increase in the redox potential of 508 and 528 mV, respectively, compared to the 496 mV for the control molecule **12**. With respect to electron-transfer rate constants, compound **15** exhibits a slight decrease in k^0 relative to **12**, while the second generation dendrimer **16** exhibits a large attenuation in the rate. Also, compound **16** exhibits a significant decrease in the reversibility of the electrochemical reactions, especially at higher scan rates.

The rate of electron transfer decreases steadily and slowly in the case of monodendrons **13** and **14**. This could be attributed to the steric inhibition of electron transfer. In the symmetrical dendrimer **15** also, a decrease in the electron-transfer rate was observed. A larger decrease accompanied by irreversibility in the cyclic voltammogram was observed with the dendrimer **16**. This suggests that ferrocene is reasonably well-encapsulated in the second generation dendrimer.[9] The fact that the monodendrons do not provide sufficient encapsulation to vary the microenvironment of the ferrocene at the focal point is not surprising, because one side of the ferrocene unit is likely to be significantly exposed to the bulk solvent. However, it is noteworthy that even the first generation symmetrical dendrimer **15** was able to provide a sufficiently different microenvironment for the ferrocene at the core that there is a change in the redox potential.[9] The observed increase in potential suggests that the ferrocenium ion is less stabilized in the first generation dendrimer. The destabilization is understandably enhanced in the second generation. Alterations in the microenvironment of ferrocene are likely to be due to encapsulation by the dendritic backbone. Since the polarity of the backbone should be less than that of the solvent electrolyte, it is not surprising that the more charged ferrocenium species is less stabilized. Three-dimensional shielding of the electroactive species seems to be necessary for altering the redox potential of the ferrocene core. The fact that the first generation symmetrical dendrimer affords a noticeable alteration in the redox potential provides supporting evidence for the presumed three-dimensional arrangement of the branches in these biaryl dendrimers. Investigations in the area of encapsulating catalysts to achieve substrate selectivity are part of the ongoing efforts in our laboratories with these dendrimers.

Acknowledgment. We are grateful to National Science Foundation for a CAREER award.

Supporting Information Available: Synthetic procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049147B

---

(8) Galow, T. H.; Rodrigo, J.; Cleary, K.; Cooke, G.; Rotello, V. M. *J. Org. Chem.* **1999**, *64*, 3745.

(9) Compare these results to a rather insensitive behavior of arylalkyl ether dendrimers based on the AB_2 monomer, 3,5-dihydroxybenzyl alcohol: (a) Toba, R.; Quintela, J. M.; Peinador, C.; Román, E.; Kaifer, A. E. *Chem. Commun.* **2001**, 857. (b) Smith, D. K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1563. For related reports, see: (c) Stone, D. L.; Smith, D. K.; McGrail, P. T. *J. Am. Chem. Soc.* **2002**, *124*, 856. (d) Cardona, C. M.; Kaifer, A. E. *J. Am. Chem. Soc.* **1998**, *120*, 4023. (e) Ong, W.; Kaifer, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 9358.