6440 *J. Org. Chem.* **2001,** *66,* 6440−6452

Synthesis, Aggregation, and Chiroptical Properties of Chiral, Amphiphilic Dendrimers

Matthew J. Laufersweiler,[†] Jason M. Rohde,[†] Jean-Louis Chaumette,[†]
Dominique Sarazin,[‡] and Jon R. Parquette*,[†]

The Ohio State University, Department of Chemistry, Columbus, Ohio 43210, and
Institut Charles Sadron, Strasbourg, France

parquett@chemistry.ohio-state.edu

Received April 23, 2001

The syntheses of amphiphilic dendrimers based on 3,5-dihydroxybenzyl alcohol containing tri- or tetrafunctional chiral central cores and allyl ester termini are described. Water solubility is imparted to the dendrimers via a palladium-catalyzed deprotection of the peripheral allyl esters. This method affords complete deprotection of the carboxylate surface because, in contrast to the basic hydrolysis of methyl ester termini, the solubility of partially hydrolyzed intermediates is maintained throughout the course of the deprotection, thereby avoiding precipitation during the reaction. Chiroptical analysis indicates that the structure of the dendrimers collapses in water, resulting in an increased steric effect upon the central core that is manifested by lower optical rotatory power. However, contributions to the chiroptical properties from the dendron branch segments were not evident in water or organic media, suggesting that chiral substructures were not developing in the branch segments of the dendrimers. Multiangle light scattering studies revealed that the dendrimers experienced significant aggregation in aqueous media that decreased at higher generations. This behavior could be rationalized by a change in conformational preference from a disklike conformation at low generations to a more globular conformation at higher generations.

Introduction

In contrast to linear polymers, dendritic polymers are constructed with monomers containing multiple branching points. The presence of a branch at every stage of growth creates a structure that contains a large number of terminal groups and affords a globular shape at high molecular weights.[1] Due to this globular morphology, the terminal groups would be expected to reside near the surface of the polymer; however, the location of the terminal groups in relation to the central core has been the subject of recent debate and appears to be highly structure dependent.[2] For example, the presence of secondary interactions at the periphery such as hydrogen-bonding[3] and π-stacking[4] force the peripheral groups to reside at the periphery while in dendrimers containing flexible, noninteracting subunits, the end groups tend to fold back toward the dendrimer interior.[5] Percec has shown that amphiphilic polyaryl ether dendrimers containing perfluorinated or aliphatic terminal chains assemble into mesogenic phases that segregate the dendritic interior and the end groups in a manner that prevents backfolding.[6] Similarly, placement of polar end groups such as carboxylates on the periphery of an otherwise hydrophobic dendrimer creates a water-soluble, amphiphilic structure that superficially resembles the Hartley model of the micelle.[7] This structural model segregates the polar end groups from the nonpolar interior by surrounding the dendritic interior with a shell

---

[†] The Ohio State University.

[‡] Institut Charles Sadron.

(1) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules-Concepts-Synthesis-Perspectives*; VCH: New York, 1996.

(2) A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665.

(3) Bosman, A. W.; Bruining, M. J.; Kooijman, H.; Spek, A. L.; Janssen, R. A. J.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 8547.

(4) (a) Duan, R. G.; Miller, L. L.; Tomalia, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 10783. (b) Miller, L. L.; Hashimoto, T.; Tabakovic, I.; Swanson, D. R.; Tomalia, D. A. *Chem. Mater.* **1995**, *7*, 9.

(5) (a) Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Frechet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401. (b) Wooley, K. L.; Klug, C. A.; Tasaki, K.; Schaefer, J. *J. Am. Chem. Soc.* **1997**, *119*, 53. (c) De Backer, S.; Prinzie, Y.; Verheijen, W.; Smet, M.; Desmedt, K.; Dehaen, W.; De Schryver, F. C. *J. Phys. Chem. A* **1998**, *102*, 5451. (d) Gorman, C. B.; Hager, M. W.; Parkhurst, B. L.; Smith, J. C. *Macromolecules* **1998**, *31*, 815. (e) Topp, A.; Bauer, B. J.; Tomalia, D. A.; Amis, E. J. *Macromolecules* **1999**, *32*, 7232. (f) Kao, H.-M.; Stefanescu, A. D.; Wooley, K. L.; Schaefer, J. *Macromolecules* **2000**, *33*, 6214.

(6) (a) Percec, V.; Johansson, G.; Ungar, G.; Zhou, J. *J. Am. Chem. Soc.* **1996**, *118*, 9855. (b) Balagurusamy, V. S. K.; Ungar, G.; Percec, V.; Johansson, G. *J. Am. Chem. Soc.* **1997**, *119*, 1539. (c) Hudson, S. D.; Jung, H. T.; Percec, V.; Cho, W. D.; Johansson, G.; Ungar, G.; Balagurusamy, V. S. K. *Science* **1997**, *278*, 449. (d) Percec, V.; Cho, W. D.; Mosier, P. E.; Ungar, G.; Yeardley, D. J. P. *J. Am. Chem. Soc.* **1998**, *120*, 11061. (e) Percec, V.; Ahn, C. H.; Ungar, G.; Yeardley, D. J. P.; Moller, M.; Sheiko, S. S. *Nature* **1998**, *391*, 161. (f) Percec, V.; Ahn, C.-H.; Bera, T. K.; Ungar, G.; Yeardley, D. J. P. *Chem. Eur. J.* **1999**, *5*, 1070.

(7) (a) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Saunders: M. J.; Grossman, S. H. *Angew. Chem.* **1991**, *103*, 1207. (b) Hawker, C. J.; Wooley, K. L.; Frechet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287. (c) Kuzdzal, S. A.; Monnig, C. A.; Newkome, G. R.; Moorefield, C. N. *J. Am. Chem. Soc.* **1997**, *119*, 2255. (d) Zhang, H.; Dubin, P. L.; Kaplan, J.; Moorefield, C. N.; Newkome, G. R. *J. Phys. Chem. B* **1997**, *101*, 3494. (e) Krska, S. W.; Seyferth, D. *J. Am. Chem. Soc.* **1998**, *120*, 3604. (f) Pan, Y.; Ford, W. T. *J. Org. Chem.* **1999**, *64*, 8588. (g) Baars, M. W. P. L.; Kleppinger, R.; Koch, M. H. J.; Yeu, S.-L.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1285. (h) Pan, Y.; Ford, W. T. *Macromolecules* **2000**, *33*, 3731. (i) Kuzdzal, S. A.; Monnig, C. A.; Newkome, G. R.; Moorefield, C. N. *J. Chem. Soc., Chem. Commun.* **1994**, 2139. (j) Pesak, D. J.; Moore, J. S. *Macromolecules* **1997**, *30*, 6467. (k) Pesak, D. J.; Moore, J. S. *Tetrahedron* **1997**, 53, 15331. (l) Brettreich, M.; Burghardt, S.; Bottcher, C.; Bayerl, T.; Bayerl, S.; Hirsch, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1845. (m) Brettreich, M.; Hirsch, A. *Tetrahedron Lett.* **1998**, *39*, 2731. (m) Sebastian, R.-M.; Magro, G.; Caminade, A.-M.; Majoral, J.-P. *Tetrahedron* **2000**, *56*, 6269.

10.1021/jo010423z CCC: $20.00

of hydrophilic carboxylate end groups thereby obviating backfolding. This putative unimolecular micelle model of amphiphilic dendrimers in water is supported by several photophysical[8] and EPR[9] studies. Two-dimensional diffusion-ordered NMR spectroscopy (DOSY NMR) indicates that the hydrodynamic radii of amphiphilic dendrimers are highly dependent on environmental factors such as pH due to repulsions that occur between charged surface carboxylates.[10] Similarly, both theoretical[11] and experimental[12] studies suggest that the molecular dimensions of dendrimers expand in good solvents and collapse in poor solvents[13] because much of their inner volume is accessible to solvent.[14] Unlike micelles, however, the structure of an amphiphilic dendrimer is unimolecular and therefore stable to changes in pH, concentration, and the nature of the medium.

There has been considerable interest in dendrimers composed of chiral subunits because their well-defined structure and homogeneity permits studies to be undertaken that probe whether the local chirality of a subunit can be cooperatively transmitted to distal portions of the molecule.[15] However, several reports suggest that such cooperative transmission of asymmetry rarely occurs due to the conformational mobility of these systems.[16] Furthermore, these systems were studied in good solvents that afford a fully expanded conformation that likely exhibits backfolding and maximum flexibility. Our interest in studying chiral, amphiphilic dendrimers[17] stems from the potential of aqueous media to reduce backfolding and impose a hydrophobic effect that compresses the dendrimer into a more compact conformation to minimize interactions of the aqueous medium with the nonpolar interior. This solvent-induced compression should create a compact globular structure that is more structurally rigid, and hence, conformational order should be optimal in water.[18] Seebach observed a variation in the sign and shape of the CD spectra with dendrimer generation that occurred in a poor solvent, acetonitrile, but not in a good solvent such as dichloromethane.[19] Although this observation could not be explicitly rationalized, the origin of the chiroptical anomalies is likely due to a collapse of the dendrimer structure in acetonitrile that perturbs the conformational equilibria of the molecule. Similarly, we have observed conformational order in intramolecularly hydrogen-bonded dendrimers that was optimal in poor solvents.[20] Chiral, amphiphilic dendrimers may be useful as enantioselective phase-transfer catalysts in aqueous media especially if conformational order can be induced throughout the dendritic branches. The goal of this work is directed at developing a strategy to prepare amphiphilic dendrimers elaborated from a chiral, nonracemic central core and to explore the effect of aqueous media on the conformational and chiroptical properties of dendrimers constructed with highly flexible polyaryl ether branch units.

Results and Discussion

Synthesis. (1*R*,2*S*)-1-Phenyl-2-amino-1,3-propanediol, **1**, and 2,5-anhydro-D-mannitol, **4**,[21] were selected to be tri- and tetrafunctional chiral central core units, respectively. Polyfunctional cores **1** and **4** were acylated with 4-benzyloxybenzoyl chloride and subsequently hydrogenated, giving **3** and **6** to provide phenolic hydroxyls to simplify the convergent dendron attachment to the central cores by O-alkylation[22] (Scheme 1). Use of an acyl linkage to the central core posed potential selectivity issues in the final terminal ester hydrolysis that would be necessary to render the dendrimers amphiphilic; however, efforts to introduce other linkages were unsuccessful.

Since methyl esters can be readily cleaved by nonhydrolytic, dealkylative methods, we briefly investigated the selective hydrolyis of methyl ester terminated dendrimers. Accordingly, trialkylation of **3** with the first- ($(CH_3O_2C)_2$[G-1]-Br), second- ($(CH_3O_2C)_4$[G-2]-Br), or third-

---

[8] (a) Caminati, G.; Turro, N. J.; Tomalia, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 8515. (b) Gopidas, K. R.; Leheny, A. R.; Caminati, G.; Turro, N. J.; Tomalia, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 7335.

[9] (a) Ottaviani, M. F.; Cossu, E.; Turro, N. J.; Tomalia, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 4387. (b) Ottaviani, M. F.; Montalti, F.; Romanelli, M.; Turro, N. J.; Tomalia, D. A. *J. Phys. Chem.* **1996**, *100*, 11033.

[10] (a) Young, J. K.; Baker, G. R.; Newkome, G. R.; Morris, K. F.; Johnson, C. S., Jr. *Macromolecules* **1994**, *27*, 3464. (b) Newkome, G. R.; Young, J. K.; Baker, G. R.; Potter, R. L.; Audoly, L.; Cooper, D.; Weis, C. D.; Morris, K.; Johnson, C. S. J. *Macromolecules* **1993**, *26*, 2394.

[11] (a) Murat, M.; Grest, G. S. *Macromolecules* **1996**, *29*, 1278. (b) Welch, P.; Muthukumar, M. *Macromolecules* **1998**, *31*, 5892.

[12] (a) De Backer, S.; Prinzie, Y.; Verheijen, W.; Smet, M.; Desmedt, K.; Dehaen, W.; De Schryver, F. C. *J. Phys. Chem. A* **1998**, *102*, 5451. (b) Gitsov, I.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 3785. (c) Stechemesser, S.; Eimer, W. *Macromolecules* **1997**, *30*, 2204.

[13] We use the terms "good" and "poor" solvent to mean compatible or incompatible with the molecule in the usual polymer chemistry sense; see: Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, 1953 p 424.

[14] Naylor, A. M.; Goddard, W. A. I.; Kiefer, G. E.; Tomalia, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 2339.

[15] (a) For some reviews of chiral dendrimers, see: (a) Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Top. Curr. Chem.* **1998**, *197*, 125. (b) Peerlings, H. W. I.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1563. (c) Thomas, C. W.; Tor, Y. *Chirality* **1998**, *10*, 53.

[16] (a) Seebach, D.; Lapierre, J. M.; Skobridis, K.; Greiveldinger, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 440. (b) Seebach, D.; Lapierre, J. M.; Greiveldinger, G.; Skobridis, K. *Helv. Chim. Acta* **1994**, *77*, 1673. (c) Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **1998**, *573*, 3. (d) Chen, Y.-M.; Chen, C.-F.; Xi, F. *Chirality* **1998**, *10*, 661. (e) Peerlings, H. W. I.; Trimbach, D. C.; Meijer, E. W. *Chem. Commun.* **1998**, 497. (f) Peerlings, H. W. I.; Struijk, M. P.; Meijer, E. W. *Chirality* **1998**, *10*, 46. (g) McElhanon, J. R.; McGrath, D. V. *J. Am. Chem. Soc.* **1998**, *120*, 1647. (h) Junge, D. M.; McGrath, D. V. *Tetrahedron Lett.* **1998**, *39*, 1701. (i) McGrath, D. V.; Wu, M.-J.; Chaudhry, U. *Tetrahedron Lett.* **1996**, *37*, 6077. (j) McElhanon, J. R.; Wu, M.-J.; Escobar, M.; McGrath, D. V. *Macromolecules* **1996**, *29*, 8979. (k) Chang, H.-T.; Chen, C.-T.; Kondo, T.; Siuzdak, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 182. (l) Kress, J.; Rosner, A.; Hirsch, A. *Chem. Eur. J.* **2000**, *6*, 247. (m) Chow, H.-F.; Mak, C. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 91. (n) Chow, H.-F.; Mak, C. C. *Pure Appl. Chem.* **1997**, *69*, 483. (o) Mak, C. C.; Chow, H.-F. *Chem. Commun.* **1996**, 1185. (p) Chow, H.-F.; Mak, C. C. *Tetrahedron Lett.* **1996**, *37*, 5935. (q) Lartigue, M.-L.; Caminade, A.-M.; Majoral, J. P. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2697. (r) Issberner, J.; Boehme, M.; Grimme, S.; Nieger, M.; Paulus, W.; Vögtle, F. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2223. (s) Newkome, G. R.; Lin, X.; Weis, C. D. *Tetrahedron*: *Asymmetry* **1991**, *2*, 957. (t) Jansen, J. F. G. A.; Peerlings, H. W. I.; de Brabander-Van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1206. (u) Jansen, J.; de Brabander-Van den Berg, E. M. M.; Meijer, E. W. *Recl. Trav. Chim. Pays-Bas.* **1995**, *114*, 225. (v) Murer, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2116. (w) Murer, P. K.; Lapierre, J. M.; Greiveldinger, G.; Seebach, D. *Helv. Chim. Acta* **1997**, *80*, 1648.

[17] For an example of a water-soluble dendrimer containing peripheral glucose units, see: (a) Schmitzer, A.; Perez, E.; Rico-Lattes, I.; Lattes, A. *Tetrahedron Lett.* **1999**, *40*, 2947. (b) Schmitzer, A.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Rosca, S. *Langmuir* **1999**, *15*, 4397.

[18] Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, 2nd ed.; John Wiley and Sons: New York, 1980.

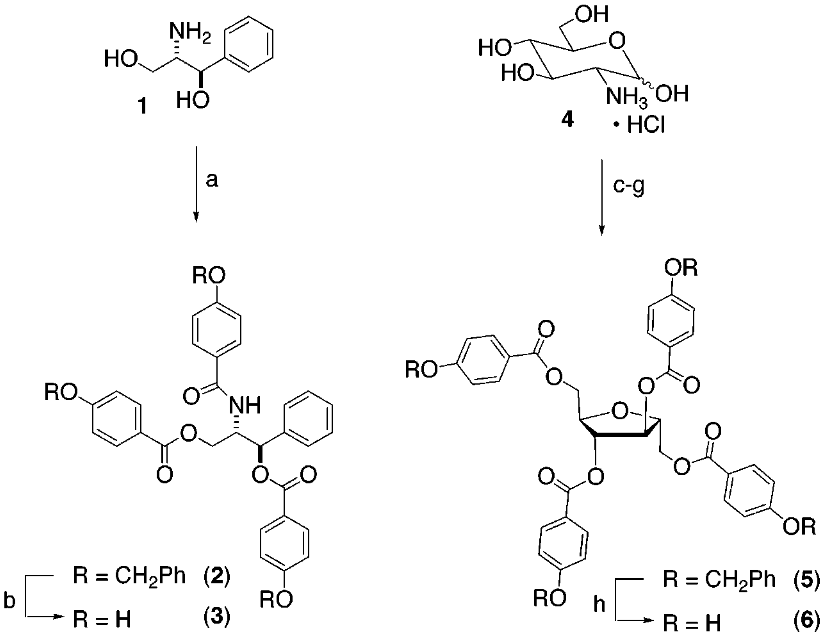
[19] Murer, P.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 603.

[20] Recker, J.; Tomcik, D. J.; Parquette, J. R. *J. Am. Chem. Soc.* **2000**, *122*, 10298.

[21] The preparation of this compound was adapted from the following report: Horton, D.; Philips, K. D. *Carbohydr. Res.* **1973**, *30*, 367.

[22] Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

Scheme 1. Synthesis of Tri- and Tetrafunctional Central Cores[a]



[a] Key: (a) 4-$BnOC_6H_4COCl$, DMAP, pyr, 64%; (b) H_2/Raney Ni CH_3OH/EtOAc, 52%; (c) $NaNO_2$−HOAc, 0 °C; (d) $NaBH_4$, H_2O, pH <8; (e) Ac_2O, pyr, DMAP, 51% from **4**; (f) $NaOCH_3$, CH_3OH, 81%; (g) 4-$BnOC_6H_4COCl$, DMAP, pyr, 85%; (h) H_2/Pd−C CH_3OH/EtOAc, 100%.

generation $(CH_3O_2C)_8$[G-3]-Br) Fréchet-type dendritic wedge using K_2CO_3/18-C-6 in THF/DMF (4:1) at 70 °C provided the first-, second-, and third-generation dendrimers.[23] Conversion of dendrimers with methyl esters on the periphery to the corresponding carboxylic acids required selective hydrolysis of the peripheral groups in the presence of the core benzoate linkages. Therefore, basic hydrolysis of the third-generation dendrimer was investigated first because the increased steric encumbrance of the internal ester linkages was expected to decrease the rate of hydrolysis relative to the terminal esters. However, exposure to a stoichiometric amount of KOH in THF/water at 60 °C resulted in cleavage of the ester linkages to the core leaving only the amide intact as determined by electrospray mass spectrometry. Dealkylative hydrolysis using NaCN in HMPA at 70 °C promoted hydrolysis of the methyl ester termini without core hydrolysis affording **16b** in 90% yield. However, ^1H NMR analysis indicated that only ca. 90% of the methyl esters had been hydrolyzed. This was, in part, a consequence of the decreasing solubility of the carboxylate-terminated dendrimer in HMPA as the hydrolysis proceeded. Efforts to extend the reaction time to afford complete hydrolysis led ultimately to decomposition, possibly due to cleavage of the benzyl ether linkages present in the dendrons.

To exhaustively deprotect the peripheral esters, a method capable of maintaining the solubility of the dendrimer throughout hydrolysis was necessary to avoid precipitation of partially hydrolyzed intermediates. Therefore, we turned to preparation of the allyl ester-terminated dendrimers as precursors since allyl esters can be readily deprotected using catalytic Pd(0) and $HCO_2H/(C_4H_9)_3N$,[24] thereby circumventing the possibility of core hydrolysis or degradation of the benzyl linkages. Further, since the tributylammonium carboxylate salts generated in this process tend to be soluble in THF, this method should prevent precipitation from occurring during hydrolysis. Accordingly, synthesis of the allyl ester-terminated dendron bromides was accomplished by bis-alkylation of 3,5-dihydroxybenzyl alcohol with methyl 4-bromomethyl benzoate[7b] followed by transesterification of the methyl esters with allyl alcohol/sodium allyloxide in THF (Scheme 2). Conversion of the dendritic benzyl alcohols to the corresponding bromides was carried out using phosphorus tribromide for each generation and was found to be superior to PPh_3/CBr_4, which afforded unreproducible yields. Synthesis of the second- and third-generation bromides proceeded by repetition of the alkylation and bromination steps.

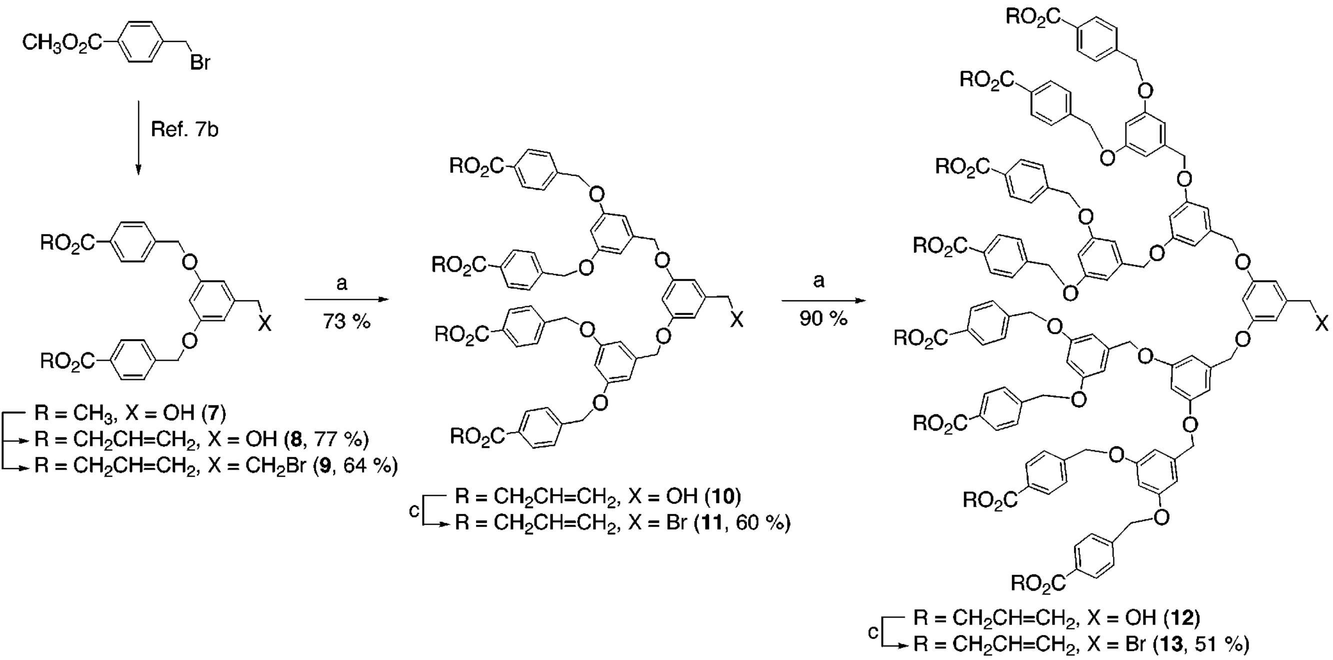
Trialkylation of the central core, **3**, with the first- ($(allylO_2C)_2$[G-1]-Br, **9**), second- ($(allylO_2C)_4$[G-2]-Br, **11**), and third-generation ($(allylO_2C)_8$[G-3]-Br, **13**) dendron monobromides was accomplished using K_2CO_3/18-C-6 in THF/DMF (3:1) at 70 °C. Purification over silica gel afforded monodisperse dendrimers with molecular weights of 1937 (**14a**, 63%), 3714 (**15a**, 74%), and 7267 (**16a**, 99%) with 6, 12, and 24 terminal allyl esters, respectively (Figure 1). The six protons ortho to the hydroxyl group of the benzoate linkage to the central aminodiol core were observed as a multiplet at 6.9 ppm in the ^1H NMR spectrum of all three dendrimers and were clearly distinguishable from the multiple resonances of the dendritic wedge even in the third-generation dendrimer **16a**. Integration of the areas of these protons and the peripheral allyl esters confirmed that complete alkylation of the central core had occurred for each generation. Tetrafunctional dendrimers **17a**−**19a** were prepared in an analogous fashion to **14a**−**16a** affording after purification over silica gel dendrimers with molecular weights of 2526 (**17a**, 72%), 4897 (**18a**, 72%), and 9638 (**19a**, 38%) with 8, 16, and 32 terminal allyl esters, respectively (Figure 2). Proton NMR was also useful in ascertaining

---

(23) (a) Chaumette, J.-L.; Laufersweiler, M. J.; Parquette, J. R. *J. Org. Chem.* **1998**, *63*, 9399. (b) Rohde, J. M.; Parquette, J. R. *Tetrahedron Lett.* **1998**, *39*, 9161.

(24) Hayakawa, Y.; Wakabayashi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 1691.

Scheme 2. Synthesis of Allyl Ester Terminated Dendritic Wedges[a]



[a] Reagents: (a) K_2CO_3, 18-C-6, 3,5-dihydroxybenzyl alcohol, acetone, reflux; (b) allyl alcohol, Na^0 (cat.) THF; (c) PBr_3, toluene, 0 °C.

that complete alkylation of **6** with the dendrons had occurred. The magnetic equivalence of the C-2,5 methine and C-1,6 methylene protons of the core caused these resonances to be observed in **17a**–**19a** as a singlet (or slightly broadened singlet) (6H) at 4.6 ppm and the C-3,4 methine protons to also be observed as a broad singlet at 5.7 ppm. These eight core protons were clearly distinguishable from the resonances arising from the wedges even in the third generation dendrimer **19a**. Integration of the respective areas of these protons and the peripheral allyl esters confirmed that complete alkylation of the central core had occurred for each generation.

All the dendrimers were obtained as white solids or glasses that were readily soluble in aprotic solvents such as CH_2Cl_2, acetone, ethyl acetate, and THF but were completely insoluble in methanol. MALDI-TOF mass spectrometry revealed molecular masses for **14a**–**15a** and **17a**–**19a** consistent with the expected structures; however, it was not possible to observe ions for third-generation dendrimer **16a** using several matrixes (Table 1). However, SEC analysis revealed the expected increase in M_w with generation for all dendrimers and the polydispersity values (M_w/M_n) were close to unity, indicating the high purity of these materials.

Deprotection of the allyl esters of **14a**–**19a** was effected by exposure to 2.5 mol % $Pd_2(dba)_3CHCl_3$/25 mol % PPh_3 and $HCO_2H/(C_4H_9)_3N$ in THF at 55 °C for 12 h (Figures 1 and 2).[24] In all cases, homogeneity was maintained throughout the course of the deprotection, ultimately affording the poly-tributylammonium salt of the dendrimers. The tributylammonium salts of **14b**–**19b** were sufficiently soluble in organic media such that CH_2Cl_2 solutions of the crude salts could be washed with water to remove the excess tributylammonium formate used in the deprotection. Subsequent exchange of the tributylammonium counterion for sodium by washing the organic layer with aqueous sodium bicarbonate imparted water solubility to the dendrimers so that washing with CH_2Cl_2 separated the PPh_3 from the dendrimers. The dendrimers were finally isolated by adjusting the pH of the aqueous solution to 2–3, causing precipitation to occur and thereby permitting isolation of the dendrimers by filtration. This procedure afforded dendrimers from **14a**–**16a** with 6 $(HO_2C)_6$[G-1] (**14b**), 12 $(HO_2C)_{12}$[G-2] (**15b**), and 24 $(HO_2C)_{24}$[G-3] (**16b**) terminal acids in 90%, 66%, and 81% yields, respectively. Similarly, deprotection of **17a**–**19a** afforded dendrimers with 8 $(HO_2C)_8$[G-1] (**17b**), 16 $(HO_2C)_{16}$[G-2] (**18b**), and 32 $(HO_2C)_{32}$[G-3] (**19b**) terminal acids in 70%, 92%, and 62% yields, respectively.

Rigorous characterization of carboxylic acid terminated dendrimers was hampered by the propensity of these materials to aggregate in organic and aqueous solution.[25] ^1H and ^{13}C NMR analysis indicated that all of the allyl esters had been hydrolyzed without core hydrolysis; however, the proton resonances became significantly broadened with increasing generation in acetone-d_6 and to a lesser degree in DMSO-d_6. In D_2O (pH 9, Na_2DPO_4), extreme broadening was observed at all generations resulting in indecipherable spectra. Increasing the temperature from 22 to 70 °C in any of these solvents only slightly reduced the broadening in the spectra. Similarly, GPC analysis revealed broad, ill-defined peaks presumably due to the aggregation that occurred in the carrier solvent, THF. Polystyrene-equivalent molecular weights were significantly higher than the calculated molecular weights and some displayed varying amounts of an extremely broadened peak at very high molecular weight in the range of 18 000–45 000 Da. Negative-ion electrospray mass spectrometry in basic water (water/2-propanol, $(C_2H_5)_3N$) showed a peak at $m/e = 1696$ for **14b**; $m/e = 3236$ for **15b**; $m/e = 2206$ for **17b**; and $m/4e = 1066$ for **18b**, verifying that the deprotection protocol proceeded without core hydrolysis or cleavage of the benzylic linkages (Table 1). However, we have been unable to

---

[25] Aggregation of dendrimers with hydrophilic carboxylate termini has been observed previously in organic solvents, see ref 7j,k.

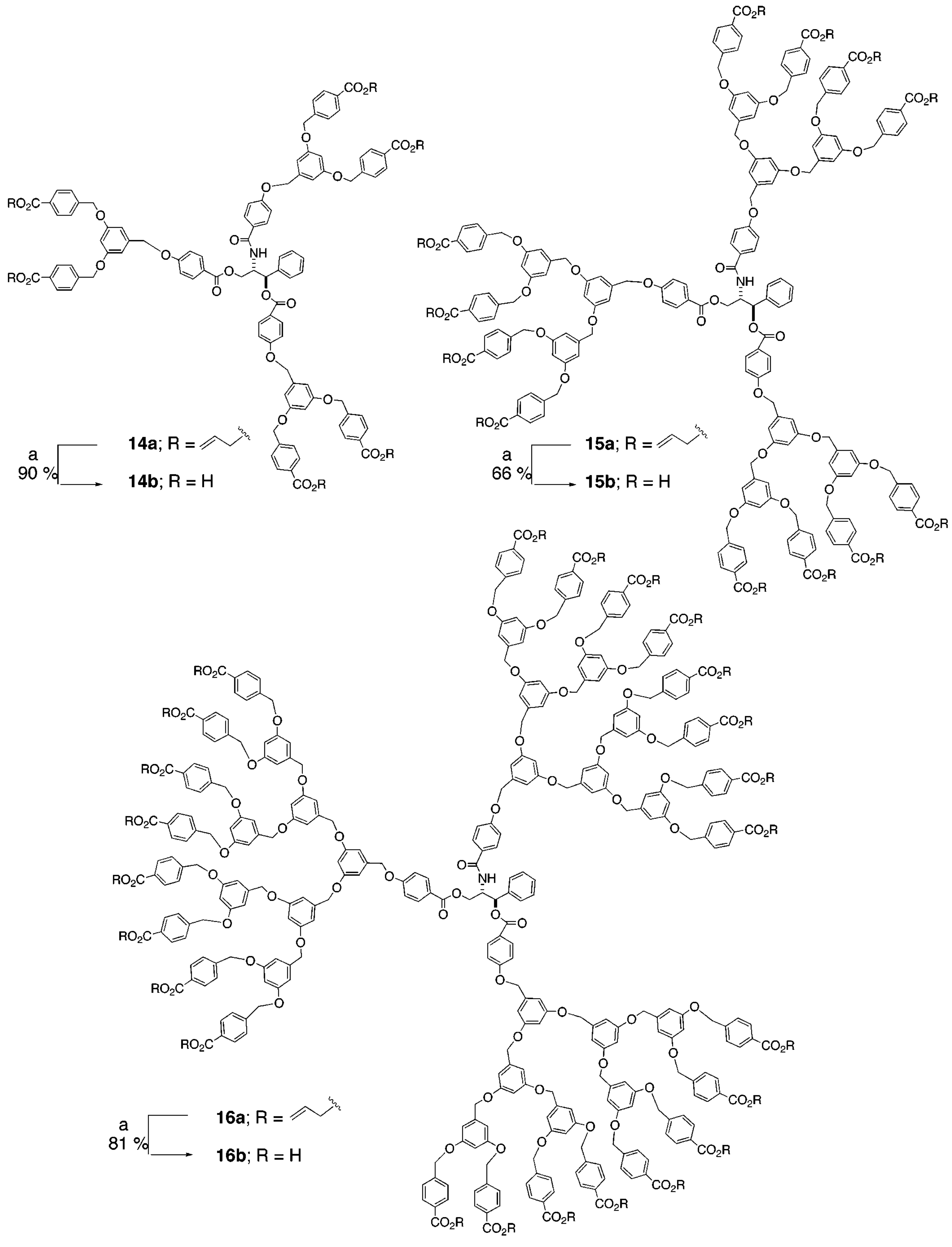
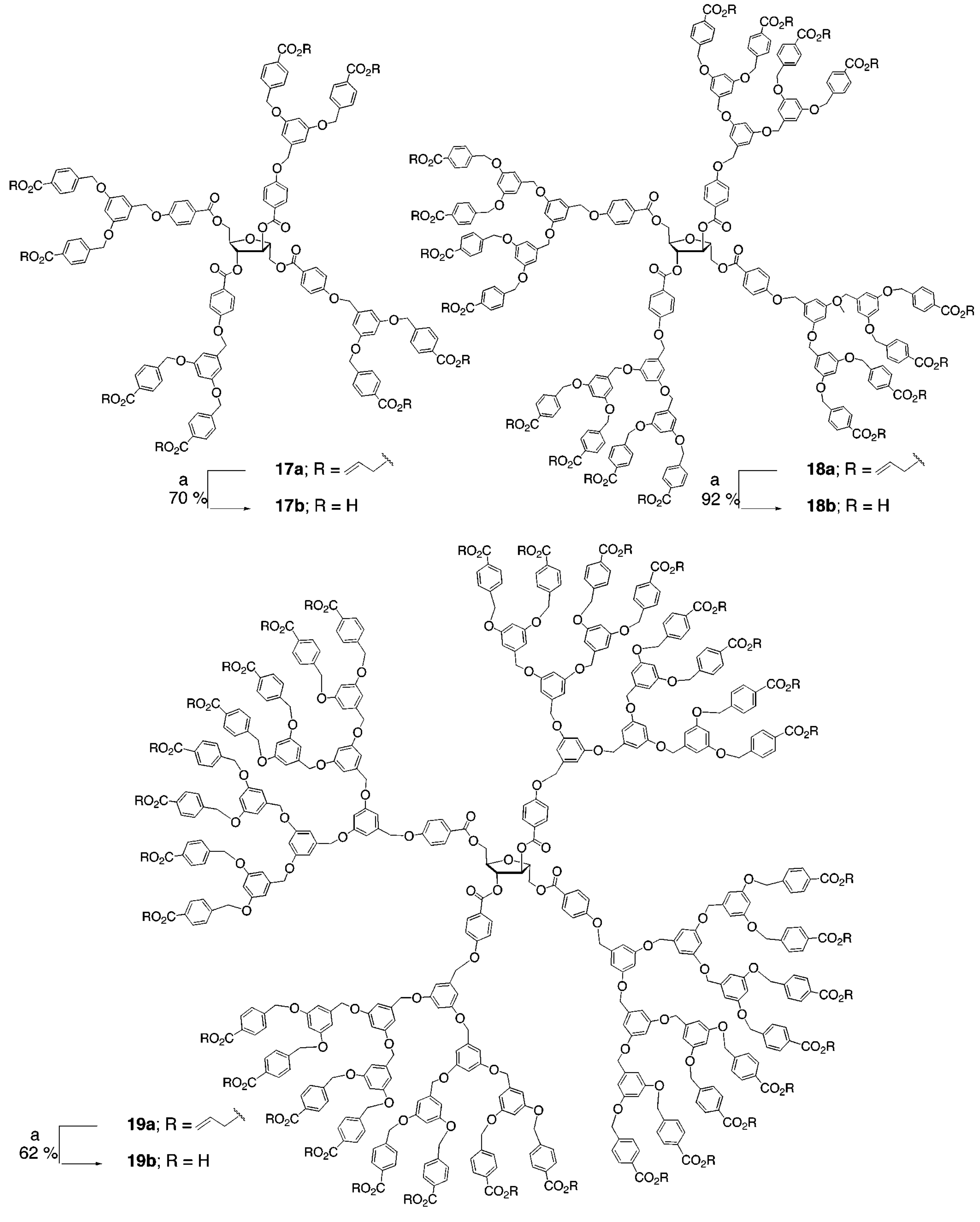


Figure 1. Trifunctional amphiphilic dendrimers: (a) 2.5 mol % $Pd_2(dba)_3CHCl_3$/25 mol % PPh_3, 1.2 M $HCO_2H/(C_4H_9)_3N$ (1:1) in THF, 55 °C.



17a; R =

17b; R = H

18a; R =

18b; R = H

19a; R =

19b; R = H

Figure 2. Tetrafunctional amphiphilic dendrimers: (a) 2.5 mol % $Pd_2(dba)_3CHCl_3$/25 mol % PPh_3, 1.2 M $HCO_2H/(C_4H_9)_3N$ (1:1) in THF, 55 °C.

observe distinct ions with dendrimers **16b** and **19b**, possibly as a consequence of the aggregation.

Differential Scanning Calorimetry. The glass transition temperatures of trifunctional dendrimers **14a/b**–**16a/b** and the corresponding methyl ester analogues were measured by differential scanning calorimetry (DSC) (Table 1). Interestingly, whereas all the allyl ester terminated dendrimers (**14a**–**16a**) and $(MeO_2C)_6$-[G1]

Table 1. GPC,[a] MS,[b] and DSC Data for Tri- and Tetrafunctional Dendrimers 14−19

dendrimer	*M* (calcd)	M_w (SEC)	M_n (SEC)	*M* (ms)	T_g (°C)	T_m (°C)
(MeO$_2$C)$_6$−[G1]	1782	1941	1865	1783 (MH)		+64
(MeO$_2$C)$_{12}$−[G2]	3402	3540	3405	3426 (M + Na)	+67	
(MeO$_2$C)$_{24}$−[G3]	6643	5671	5492	6683 (M + K)	+45	
(allylO$_2$C)$_6$−[G1] (**14a**)	1937	2477	2426	1964 (M + Na)		+45
(allylO$_2$C)$_{12}$−[G2] (**15a**)	3714	3422	3174	3738 (M + Na)		+45
(allylO$_2$C)$_{24}$−[G3] (**16a**)	7267	6399	6089			+43
(HO$_2$C)$_6$−[G1] (**14b**)	1697	2560	2504	1696 (M − H)	+133	
(HO$_2$C)$_{12}$−[G2] (**15b**)	3235	6455	5799	3234 (M − H)	+123	
(HO$_2$C)$_{24}$−[G3] (**16b**)	6306	14 928	5373		+132	
(allylO$_2$C)$_8$−[G1] (**17a**)	2524	2407	2095	2547 (M + Na)		
(allylO$_2$C)$_{16}$−[G2] (**18a**)	4893	4951	4711	4916 (M + Na)		
(allylO$_2$C)$_{32}$−[G3] (**19a**)	9638	9614	9264	4842 (M + 2Na)		
(HO$_2$C)$_8$−[G1] (**17b**)	2208	2819	2576	2206 (M − H)		
(HO$_2$C)$_{16}$−[G2] (**18b**)	4261	7781	6238	1066 (M − 4H)		
(HO$_2$C)$_{32}$−[G3] (**19b**)	8366	9144	6147			

[a] Molecular weights determined by comparison to polystyrene standards. [b] Determined by MALDI-TOF MS; **14b**−**19b** determined by negative-ion electrospray MS.

Table 2. Chiroptical[a] Data for 14−19

compd	$[\alpha]^{22}_{365}$[b]	$[\Phi]^{22}_{365}$[c]
(allylO$_2$C)$_6$−[G1] (**14a**)	141.5	2743
(allylO$_2$C)$_{12}$−[G2] (**15a**)	57.0	2118
(allylO$_2$C)$_{24}$−[G3] (**16a**)	20.4	1483
(HO$_2$C)$_6$−[G1] (**14b**)	11.3	192.9
(HO$_2$C)$_{12}$−[G2] (**15b**)	6.3	203.9
(HO$_2$C)$_{24}$−[G3] (**16b**)	5.2	328.2
(allylO$_2$C)$_8$−[G1] (**17a**)	−65.1	−1644
(allylO$_2$C)$_{16}$−[G2] (**18a**)	−26.7	−1307
(allylO$_2$C)$_{32}$−[G3] (**19a**)	−10.8	−1041
(HO$_2$C)$_8$−[G1] (**17b**)	−41.4	−916
(HO$_2$C)$_{16}$−[G2] (**18b**)	−18.8	−800
(HO$_2$C)$_{32}$−[G3] (**19b**)	−11.0	−918

[a] Rotations measured in CHCl$_3$ for **14a**−**19a**; **14b**−**19b** in THF. [b] Specific rotations in 10^{-1} deg cm^2 g^{-1}. [c] Molar rotations in 10^{-1} deg cm^2 mol^{-1}.

exhibited melting transitions (T_m), (MeO$_2$C)$_{12}$-[G2], (MeO$_2$C)$_{24}$-[G3], and the acid-terminated dendrimers (**14b**−**16b**) displayed glass transitions (T_g). Glass transition temperatures of dendrimeric molecules have been previously shown to increase with increasing polarity of the terminal groups because of the large proportion of end-groups in these systems.[26] The significantly increased glass transition temperatures for the acid-terminated dendrimers relative to the corresponding methyl esters are consistent with these reports.

Chiroptical Properties. The allyl ester-terminated dendrimers (**14a**−**16a**) exhibited positive molar rotations in CHCl$_3$ that decreased going from the first- to the third-generation dendrimers (Table 2). Similarly, the molar rotations in CHCl$_3$ of tetrafunctional dendrimers **17a**−**19a** became less negative going from the first- to the third-generation dendrimer. We have previously observed this behavior with the methyl ester dendrimers derived from this central core and allyl ester dendrimers derived from 2,5-anhydro-D-mannitol.[23] By comparison to a series of model compounds, this effect was correlated with a change in conformational equilibrium brought about by the increase in steric congestion developing around the central core as the dendrimers increased in size.[23]

In contrast to the ORD curves observed in THF or CHCl$_3$, the value of the rotations of acid-terminated dendrimers **14b**−**19b** in water were extremely fluxional and difficult to reproduce within the first hour following dissolution in the aqueous buffer (Figures 3 and 4). However, the ORD curves became stable when measured after equilibrating for 1 h following dissolution. Interestingly, both series of dendrimers exhibited rotations that varied in sign and magnitude as a function of generation. Although deviations of the dendrimer optical activity with generation from that of the chiral central core suggest the presence of chiral substructures within the achiral dendritic branches,[27] the dynamic nature of the rotation values and the broadening observed in the ^{1}H NMR spectra also suggest that the chiroptical variation arises from aggregation that occurs in water and reaches

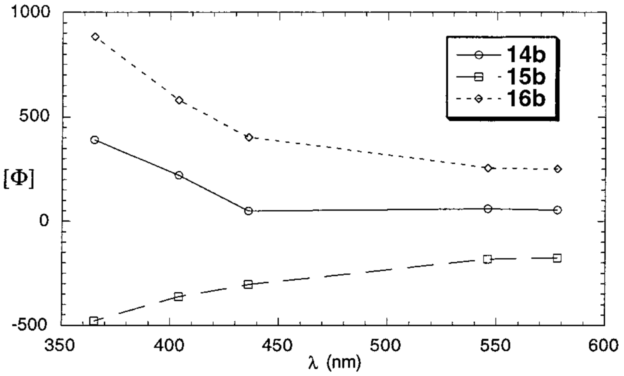


Figure 3. Molar rotations of **14b**−**16b** in water (pH 9, 5% phosphate).

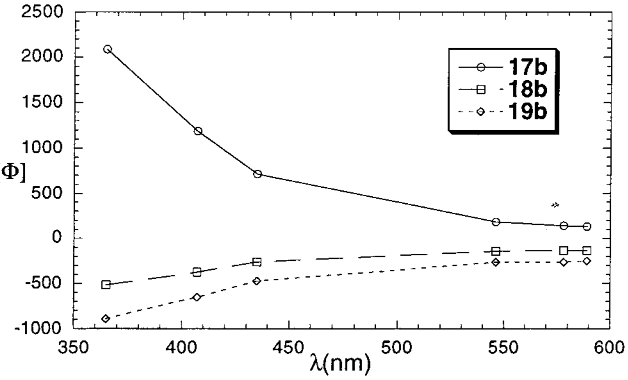


Figure 4. Molar rotations of **17b**−**19b** in water (pH 9, 5% NaHCO$_3$).

---

(26) (a) Wooley, K. L.; Hawker, C. J.; Pochan, J. M.; Frechet, J. M. J. *Macromolecules* **1993**, *26*, 1514. (b) Hawker, C. J.; Frechet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2459.

(27) For a discussion of the relationship of optical activity to conformation in linear polymers, see: (a) Farina, M. *Top. Stereochem.* **1987**, 171. (b) Pino, P.; Salvadori, P.; Chiellini, E.; Luisi, P. L. *Pure Appl. Chem.* **1968**, *16*, 469.

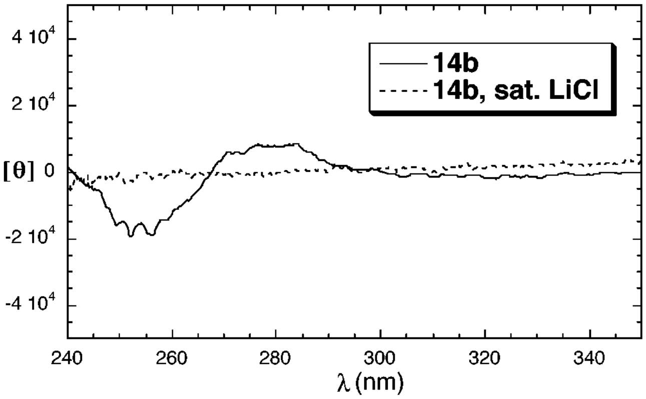


Figure 5. CD of **14b** in water (pH 9).

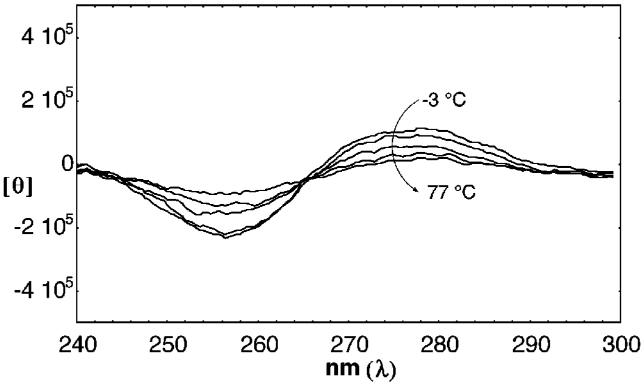


Figure 6. CD of **17b** in water (pH 9) as a function of temperature.

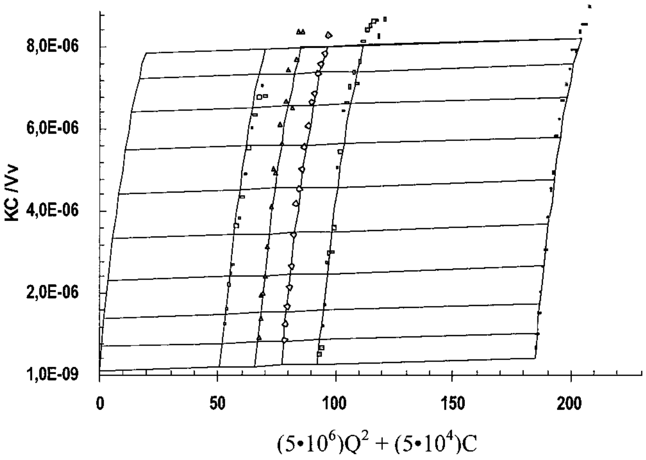


Figure 7. Zimm plot of **14b** in water with buffer at pH = 9. $M_w = 9.1\ 10^6$ g mol^{-1}, $\langle R_G \rangle_Z = 911$ nm, $A_2 = 4.5\ 10^{-5}$ cm^3 mol g^{-2}. V_v is the excess Raleigh ratio for the vertically polarized incident beam detected through a vertically positioned analyzer placed before the photomultiplier. C = concentration of the solution; K = the optical constant; Q = wave vector (Å^{-1}).

a state of equilibrium within 1 h for each of the dendrimers. Changes in aggregation state can give rise to large variations in optical rotatory power.[28] The simultaneous presence of several different equilibrating aggregation states likely contributes significantly to the dynamic optical rotatory behavior that is observed in water. Multiangle light scattering studies (vide infra) support this interpretation of the chiroptical variation with dendrimer generation.

In aqueous solution, the first-generation dendrimer **14b** exhibited a weak excitonically coupled[29] Cotton effect centered at 264 nm (Figure 5); however, the second- (**15b**) and third-generation (**16b**) dendrimers did not exhibit any observable Cotton effects. This is in contrast to the CD spectra recorded in $CHCl_3$ for the methyl ester derivatives that displayed excitonically coupled Cotton effects at this wavelength for all generations.[23] The intensity of CD observed for **14b** in water was also decreased by an order of magnitude in water relative to the CD of the corresponding methyl ester measured in $CHCl_3$. To increase the extent of the hydrophobic effect, the CD spectrum was recorded for the dendrimers in aqueous media saturated with LiCl. However, this destroyed the Cotton effect observed for **14b** resulting in flat lines for **14b**−**16b**. A decrease in the amplitude of this Cotton effect with increasing generation was previously observed for the methyl ester derivatives in $CHCl_3$ and was correlated with an increasing steric effect that perturbed the conformational equilibrium of the chiral central core.[23] The low intensity of the Cotton effect at 264 nm observed for **14b** and the lack of any CD observed for **15b** and **16b** are also consistent with a solvent-induced structural collapse that increases the effective steric bulk of the dendritic wedges.

Neither the allyl ester or the acid-terminated tetrafunctional dendrimers **17a/b**−**19a/b** exhibited any detectable CD in $CHCl_3$ or THF, respectively, in the range of 230−350 nm. Although the second- (**18b**) and third-generation (**19b**) dendrimers did not show any Cotton effects in aqueous solution, the first-generation dendrimer, **17b**, exhibited an excitonically coupled Cotton effect at 264 nm similar to the curve seen for **14b** (Figure 6). It is noteworthy that even the central core **6** did not exhibit a Cotton effect in aqueous medium. The CD curve was also sensitive to temperature becoming maximal at −3 °C and smoothly decreasing upon heating to 77 °C. Similar to **14b**, saturating the solution with LiCl resulted in a loss of the Cotton effect at 264 nm and did not change the spectra of **18b** or **19b**. The transition at 264 nm is due to a $\pi \rightarrow \pi^*$ transition (^1L_a) associated with the 4-alkoxylbenzoate linkages connecting the central core to the dendritic wedges. Therefore, we conclude that the variations of the optical rotations and CD spectra of **14b**−**19b** in water reflect a solvent induced aggregation of the dendrimers that is accompanied by a shift in conformational state that increases the steric effect of the dendritic wedges on the central core rather than to the presence of chiral conformations present in the dendritic branches.

Light Scattering Studies. Multiangle laser light scattering (MALLS) was used to determine the degree of aggregation that occurs when the carboxylic acid terminated dendrimers were dissolved in aqueous media. Solutions were prepared by dissolving the dendrimers in aqueous buffer (glycine/NaOH; pH 9) and the static light scattering measurements were carried out using a Sematech instrument equipped with a He−Ne laser.

The MALLS measurements confirmed that the acid-terminated dendrimers were significantly aggregated in aqueous media (Tables 3 and 4). The molecular dimen-

---

(28) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 1076.

(29) (a) *Circular Dichroism: Principles and Applications*; Nakanishi, K. L., Berova, N., Woody, R., Eds.; VCH: New York, 1994. (b) Harada, N.; Nakanishi, K. O. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

Table 3. Molecular Dimensions in Water (pH = 9.0) by MALLS

dendrimer	concentration ($\times 10^{-3}$ g/mL)	M_w (g/mol)	$\langle R_G \rangle^a$ (nm)	$A_2{}^b$ (mol·mL·g$^{-2)}$	$\rho_V{}^c$	$\rangle$QR$\langle^d$	THF dn/dc^e mL·g^{-1}	water (pH = 9) dn/dc mL·g^{-1}
G1(CO_2H)$_6$ (**14b**)	3.69	9.1 10^6	911	4.5 10^{-5}	0.04	4 ... 11	0.184	0.228
G2(CO_2H)$_{12}$ (**15b**)	3.62	1.9 10^6	539	−2.5 10^{-4}	0.015	2.4...7	0.182	0.227
G3(CO_2H)$_{24}$ (**16b**)	2.63	3.5 10^5	395	5.3 10^{-3}	0.06	1.8...5	0.187	0.230
G1(CO_2H)$_8$ (**17b**)	3.40	1.6 10^7	480	−1.3 10^{-4}	0.02	2...6	0.122	0.173
G2(CO_2H)$_{16}$ (**18b**)	1.22	1.9 10^5	217	5.4 10^{-3}	0.07	0.9...2.8	0.160	0.201
G3(CO_2H)$_{32}$ (**19b**)	0.91	4.6 10^5	352	1.6 10^{-3}	0.023	1.6...4.5	0.150	0.196

[a] Radius of gyration. [b] Second virial coefficient. [c] Depolarization ratio. [d] Scattering windows: QR < 1 (Guinier domain) and QR > 1 (asymptotic domain). [e] dn/dc = refractive index increment.

Table 4. Molecular Dimensions in Water (pH = 9.0) by MALLS

dendrimer	porod slope small Q (shape)	porod slope high Q (shape)	b^a (Å)	M_L g (mol Å)$^{-1}$	$N_{aggr}{}^b$	starlike fit: no. of branches
G1(CO_2H)$_6$ (**14b**)	−2 disc	−1 rod	2700	75	5360	6
G2(CO_2H)$_{12}$ (**15b**)	−2 disc	−2 disc	2040	42	587	4
G3(CO_2H)$_{24}$ (**16b**)	−1.1 rod	−1.1 rod			55	2
G1(CO_2H)$_8$ (**17b**)	−3 aggregated	−2.2 branched	2000	280	6900	10
G2(CO_2H)$_{16}$ (**18b**)	−1 rod	−0.3 globular			45	5
G3(CO_2H)$_{32}$ (**19b**)	−1 rod	−0.33 globular			55	8

[a] Persistence length. [b] Degree of aggregation.

sions of the aggregates were determined from a Zimm plot[30] as shown in Figure 7 for **14b** as an example. The linearity of the lines indicate low polydispersity and the validity of the extrapolation for the mean weight molecular weight (M_w) determination. The extent of aggregation was highly dependent on dendrimer generation and the branching multiplicity of the central core, each of which altered the conformational preference of the dendrimers. First-generation dendrimers **14b** and **17b** developed very high molecular weight aggregates in water displaying aggregation numbers (N_{agg}) of 5360 ($M_w = 9.1 \times 10^6$) and 6900 ($M_w = 1.6 \times 10^7$), respectively. The molecular dimensions (M_w, N_{agg}, and $\langle R_g \rangle$) decreased for each generational step up to the third generation for both series of dendrimers. Although the aggregation number (N_{agg}) of the trifunctional dendrimers (**14b**−**16b**) decreased by a factor of 10 for each generational step, the tetrafunctional series (**17b**−**19b**) experienced a 150-fold decrease in N_{agg} upon going from the first to the second generation, and only a small change in aggregation number occurred upon increasing to the third generation. The value of the second virial coefficient, A_2, generally increased in value at higher dendrimer generation for both dendrimer series. This indicates that the dendrimer-solvent interaction becomes more favorable at higher generations as would be expected for a more globular conformation.

The shape of the aggregates was estimated by measuring the fractal dimensions (D) at large scattering windows (QR > 1) in the asymptotic regime as shown for **14b** in Figure 8 as an example.[31] The trifunctional first- and second-generation dendrimers, **14b** and **15b**, exhibited a fractal dimension of 2, suggesting that the aggregates resembled a smooth two-dimensional shape such as a disk morphology. At the third generation (**16b**), D decreased to 1.1, which is characteristic of a smooth rodlike morphology. The tetrafunctional first-generation dendrimer **17b** had $D = 3$, indicating that a highly irrregular three-dimensional aggregate was formed consistent with the high molecular weight of the aggregate. The fractal D value decreased to 1 for the second- (**18b**) and third-generation (**19b**) dendrimers in contrast to the trifunctional series, which remained disklike at the second generation. AFM images obtained for **17b**−**19b** showed that aggregates of **17b** exhibited spherical shapes while fiberlike aggregates were formed for **18b**−**19b** in agreement with the MALLS studies (Figure 9).

The flexibility of polyaryl ether dendritic branches likely affords dendrimers that exhibit highly dynamic structural morphologies. Accordingly, the observed decrease in the degree of aggregation (N_{agg}) with increasing dendrimer generation can be rationalized by considering a conformational equilibrium interconverting two limiting dendrimer conformations such as a disklike shape at one extreme and a globular shape at the other (Figure 10). If this conformational equilibrium favors the disklike shape with a large hydrophobic surface exposed to solvent, as would be expected at lower dendrimer generation, aggregation would occur to minimize unfavorable interactions with the aqueous phase. At higher generations, the position of the conformational equilibrium shifts in the direction of the globular morphologies exposing the hydrophilic carboxylates to solvent thereby segregating the hydrophobic interior segments of the dendrimer from the aqueous phase. Consequently, the degree of aggregation would decrease at higher generations because the need to avoid the unfavorable interactions of the solvent with the hydrophobic dendrimer interior would decrease. That the tetrafunctional dendrimers experienced a more pronounced decrease in the

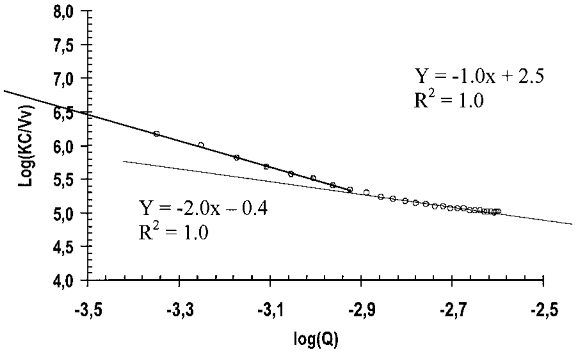


Figure 8. Porod slope or fractal determination of **14b** in water with buffer at pH = 9 ($c = 3.7\ 10^{-3}$ g/mL).

---

(30) Zimm, B. H. *J. Chem. Phys.* **1948**, *16*, 1093.

(31) Higgins, J. S.; Benoit, H. C. *Polymers and Neutron Scattering*; Oxford Science: Oxford, 1994.

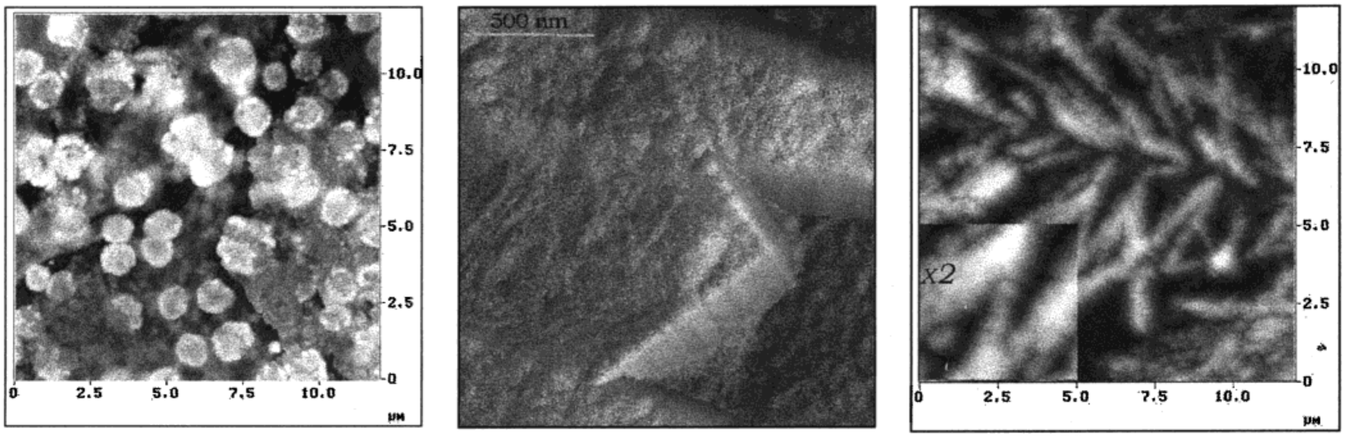


Figure 9. Atomic force micrographs (AFM) for G1$(CO_2H)_8$, **17b** (left); G2$(CO_2H)_{16}$, **18b** (middle); and G3$(CO_2H)_{32}$, **19b** (right). AFM films were prepared by dissolving the dendrimers in water (pH = 9) and then allowing them to dry slowly in an inert atmosphere at 80 °C for 24 h. The films were then washed with distilled water and dried again at 80 °C for 24 h affording crack-free wafers. The wafers were then scanned in contact mode using a cantilever spring constant of 0.58 N m^{-1}. The *z* scale representation is achieved by using a gray scale for which a lower value of *z* is indicated by darker gray and, conversely, lighter gray indicates a higher *z* value. These images show that the aggregation of **18b** and **19b** form rodlike structures resembling a linear necklace of spherical particles, whereas **17b** forms a more globular aggregate.

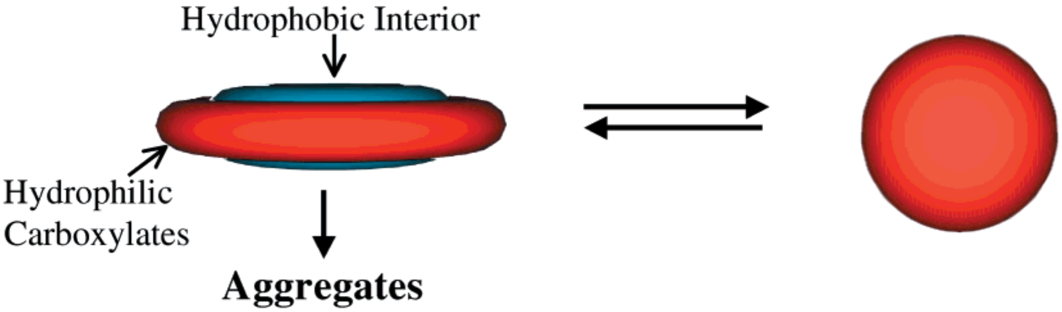


Figure 10. Notional depiction of generation-dependent dynamic conformational equilibrium of amphiphilic dendrimers in water interconverting between disklike and spherical morphologies.

degree of aggregation upon progressing from the first to second generations than observed in the trifunctional series is consistent with this interpretation since a higher core multiplicity would be expected to create a more globular shape at lower generations.

Conclusions

A convenient strategy to prepare chiral, amphiphilic dendrimers displaying peripheral carboxylates has been described. A palladium-catalyzed deprotection of the peripheral allyl esters circumvents precipitation of partially hydrolyzed intermediates, thereby permitting access to homogeneous amphiphilic dendrimers. Chiroptical analysis of these materials in aqueous media revealed that the dendrimer structures experience a structural collapse that increases the effective steric bulk of the dendritic wedges. However, the associated increase in structural rigidity does not create stable chiral substructures in the achiral dendritic branches as evidenced by circular dichroism. Further, to avoid interactions with the aqueous media, the dendrimers experience a generation dependent aggregation that can be rationalized by a change in conformational equilibria that accompanies the increase in dendrimer generation.

Experimental Section

General Methods. Melting points were determined in open capillaries and are uncorrected. Elemental analyses were carried out at Atlantic Microlab, Inc., Norcross, GA. Infrared spectra were recorded on a Perkin-Elmer model 1600 instrument. ^1H NMR spectra were recorded at 300, 400, or 500 MHz and ^{13}C NMR spectra at 75, 100, or 125 MHz on a Bruker AC-300, AC-400, or AC-500 instrument as indicated. EI or FAB mass spectra were recorded at The Ohio State University Chemical Instrument Center. MALDI-TOF spectrometry was performed with a Kratos Kompact III spectrometer using indoleacrylic acid as the matrix in tetrahydrofuran (THF). Electrospray mass spectrometry was performed on a PE Sciex API300 triple quadrupole mass spectrometer, with negative ion electrospray at a concentration of 2 mg/mL in a 10% NH_4OH solution in 1:1 H_2O/*i*-PrOH. Ultraviolet spectroscopy was performed on a Hewlett-Packard 8452 A diode array spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Optical rotations were performed in chloroform, THF or 5% aqueous sodium phosphate solution (pH 9.0). Concentrations are given in g/100 mL. Circular dichroism measurements were performed on a JASCO J-500C spectrapolarimeter. Gel permeation chromatography (gpc) was carried out using a Waters 6000A pump, a Waters 410 differential refractometer detector, and three divinylbenzene columns arranged in series (10^3, 10^4, and 10^5 Å). All runs were carried out using THF as the carrier solvent at 40 °C. All reactions were performed under an argon or nitrogen atmosphere. Dimethylformamide (DMF) was dried by distillation from barium oxide; THF was distilled from sodium/benzophenone ketyl; acetone was distilled from $CaSO_4$ and dichloromethane was distilled from calcium hydride. Chromatographic separations were performed on silica gel 60 (230−400 mesh, 60 Å) using the indicated solvents.

2,5-Anhydro-[α]-D-mannitol.[21] A. 1,3,4,6-Tetra-*O*-acetyl-2,5-anhydro-D-mannitol. A solution of D-glucosamine hydrochloride (10 g, 0.05 mol) in water (116 mL) was stirred for 5 h at room temperature to attain mutarotational equilibrium. The solution was cooled to 0 °C, and sodium nitrite (9.6 g, 0.14 mol) was added followed by the dropwise addition of glacial acetic acid (5.6 g, 5.3 mL, 0.09 mol). After being stirred at 0 °C for 2 h, the solution was allowed to warm to ambient temperature. After the mixture was sparged with nitrogen for 30 min, the solvent was removed by lyophilization. Methanol (75 mL) was repeatedly added to and evaporated from the solid residue until the insoluble salts in the solution became sufficiently granular to remove by filtration. The filtercake was then washed with methanol (2 × 10 mL), and the combined methanol fractions were concentrated in vacuo giving a yellow oil. The yellow oil was dissolved in water (116 mL), and sodium borohydride (1.75 g, 0.05 mol) was added slowly at 0 °C maintaining the pH at 8 by the addition of several portions of dry ice. After the solution was stirred for an additional 1 h at 0 °C, the solution was brought to pH 7 with acetic acid and the water was removed by lyophilization. Borate salts were converted to trimethylborate by repeatedly adding methanol (3 × 75 mL) to the residue and then concentrating in vacuo to evaporate the methanol−trimethyl borate azeotrope. Further desalting was achieved by dissolving the residue in methanol (75 mL) and adding IR-120 Amberlite H$^+$ resin. Removal of the resin by filtration followed by evaporation of the methanol afforded a yellow oil that was dispersed in dry pyridine (50 mL), cooled to 0 °C, and treated with excess acetic anhydride (46.2 g, 50 mL, 0.43 mol). After the mixture was stirred at ambient temperature for 24 h, methanol (50 mL) was added dropwise at 0 °C, and then the mixture was concentrated in vacuo. The resultant oil was partitioned between water (50 mL) and dichloromethane (50 mL), and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with a 1.2 M HCl (50 mL), 5% NaHCO$_3$ (50 mL), and saturated NaCl (50 mL) and then dried over Mg$_2$SO$_4$ and concentrated. Chromatography over silica gel (1:1/ ethyl acetate/hexanes) afforded 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-D-mannitol as a yellow oil (8.46 g, 0.026 mol, 51%):[32] ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.03 (bd, 2.35 Hz, 2H), 4.12 (bm, 6H), 1.97 (s, 12H).

B. 2,5-Anhydro-D-mannitol. To a solution of the 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-D-mannitol from part A (3.66 g, 11.0 mmol) in dry methanol (30 mL) was added 1 M NaOMe in methanol (1 mL). After 24 h at room temperature, the solution was neutralized with Amberlite IR 120 H$^+$ resin (10 g), which was then removed by filtration. Evaporation of the methanol in vacuo afforded 2,5-anhydro-D-mannitol. To remove the last traces of methanol, pyridine (5 × 20 mL) was repeatedly added to the solid and evaporated in vacuo affording 2,5-anhydro-D-mannitol as a white solid (1.46 g, 8.9 mmol, 81%).

1,3,4,6-Tetra-*O*-(4-benzyloxybenzoyl)-2,5-anhydro-D-mannitol (5). A stirred suspension of 4-benzyloxybenzoic acid (6.45 g, 28.3 mmol) in dichloromethane (25 mL) was charged with oxalyl chloride (3.66 mL, 5.33 g, 41.9 mmol) and DMF (5 drops). After the mixture was stirred for 24 h at ambient temperature, the solvent was removed in vacuo affording a light yellow solid. A mixture of 2,5-anhydro-D-mannitol (0.58 g, 3.53 mmol) and DMAP (43 mg, 0.35 mmol) in pyridine (10 mL) was added, and the resulting solution was heated at 50 °C for 24 h. The reaction was then cooled to room temperature and concentrated. The resultant solid was dissolved in dichloromethane (40 mL) and washed with a 1.2 N aqueous hydrochloric acid (50 mL) and 5% aqueous sodium bicarbonate (50 mL). The organic layer was then dried over Mg$_2$SO$_4$ and concentrated to a brown solid. Purification by flash chromatography (SiO$_2$) with 0−2.5% diethyl ether/dichloromethane afforded **5** (3.0 g, 2.98 mmol, 85%) as a white solid: ^{1}H NMR (200 MHz, CDCl$_3$) δ 4.65 (bm, 6H), 5.05 (s, 4H), 5.1 (s, 4H), 5.7 (bs, 2H), 6.9 (d, J = 8.7 Hz, 4H), 6.95 (d, J = 8.7 Hz, 4H), 7.4 (bs, 20H), 7.92 (d, J = 8.7 Hz, 4H), 8.05 (d, J = 8.7 Hz, 4H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ 63.8, 70.1, 70.2, 79.5, 82.1, 114.5, 114.6, 122.4, 127.4, 128.2, 128.6, 131.9, 132.0, 136.0, 136.2, 162.6, 163.0, 165.3, 165.9; IR (neat) 1715, 1605 cm^{-1}; HRMS for C$_{62}$H$_{53}$O$_{13}$ (FAB) (MH) calcd 1005.35, obsd 1005.60. Anal. Calcd for C$_{62}$H$_{52}$O$_{13}$: C, 74.09; H, 5.21. Found: C, 73.95; H, 5.16.

1,3,4,6-Tetra-*O*-(4-hydroxybenzoyl)-2,5-anhydro-D-mannitol (6). 1,3,4,6-Tetra-*O*-(4-benzyloxybenzoyl)-2,5-anhydro-D-mannitol, **5** (1.29 g, 1.28 mmol), was dispersed in 100 mL of methanol/ethyl acetate (1:1). The solution was degassed by sparging with argon for 5 min, charged with Pd/C (0.23 g), and then hydrogenated at 50 psi. After 24 h, the reaction mixture was filtered through a short plug of Celite and the resultant filtrate was concentrated, affording **6** (0.83 g, 1.28 mmol, 100%) as a white solid: mp = 131−134 °C (CH$_3$OH/EtOAc); ^{1}H NMR (250 MHz, acetone-d_6) δ 4.67 (m, 6H), 5.78 (bd, J = 2.0 Hz, 2H), 6.86 (d, J = 8.8 Hz, 4H), 6.92 (d, J = 8.8 Hz, 4H), 7.94 (d, J = 8.5 Hz 4H), 7.95 (d, J = 8.5 Hz, 4H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ 64.2, 80.1, 82.3, 115.8, 115.9, 121.3, 121.9, 132.4, 132.6, 162.5, 162.8; IR (neat) 3448, 1694, 1609 cm^{-1}; HRMS for C$_{34}$H$_{28}$O$_{13}$ (FAB) (MH) calcd 645.1608, obsd 645.1610.

(AllylO$_2$C)$_2$[G1]-OH (8). Allyl alcohol (1.5 mL) was treated with sodium metal (50 mg, 2.2 mmol) and was allowed to stir for ca. 5 min until all the sodium metal was consumed. This solution was added to (CH$_3$O$_2$C)$_2$[G1]-OH (**7**)[7b] (10.43 g, 24 mmol) in 1:1 THF/allyl alcohol (80 mL) and was then heated to 50 °C. After 24 h, the solvents were evaporated in vacuo, and the residue was dissolved in dichloromethane (80 mL) and washed with 1.2 N aqueous HCl (80 mL). The organic layer was dried over Mg$_2$SO$_4$ and evaporated to dryness. Purification by flash chromatography (SiO$_2$) with (0−5%) diethyl ether/dichloromethane afforded **8** (9.04 g, 18.5 mmol, 77%) as a pale yellow oil: ^{1}HNMR (300 MHz, CDCl$_3$) δ 4.61 (s, 2H), 4.81 (dt, J = 1.3, 5.6 Hz, 4H), 5.07 (s. 4H), 5.29 (dd, J = 1.3, 10.4 Hz, 2H), 5.39 (dd, J = 1.3, 16.1, Hz, 2H), 5.97−6.08 (m, 2H), 6.49 (t, J = 2.2 Hz, 1H), 6.60 (d, J = 2.2 Hz, 2H), 7.47 (d, J = 8.3 Hz, 4H), 8.06 (d, J = 8.3 Hz, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 65.0, 65.5, 69.25, 101.3, 105.7, 118.2, 126.8, 129.8, 132.1, 142.0, 143.7, 159.7, 165.9; IR (CHCl$_3$) 3504, 1714, 1596 cm^{-1}; HRMS for C$_{29}$H$_{28}$O$_7$ (EI) (M$^+$) calcd 488.1835, obsd 488.1853.

(AllylO$_2$C)$_2$[G1]-Br (9). Phosphorus tribromide (1.48 g, 0.52 mL, 5.5 mmol) was added dropwise to a stirred solution of **8** (8.58 g, 17.6 mmols) in toluene (40 mL) at 0 °C. The mixture was allowed to warm to room temperature over 2 h. The solvent was then evaporated in vacuo, and the yellow residue was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were dried over Mg$_2$SO$_4$ and evaporated to dryness. Purification by flash chromatography (SiO$_2$) with 5% diethyl ether/dichloromethane afforded **9** (6.19 g, 11.3 mmol, 64%) as a white solid: mp = 79−81 °C ((C$_2$H$_5$)$_2$O, CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.40 (s, 2H), 4.83 (dt, J = 1.6, 5.6 Hz, 4H), 5.09 (s, 4H), 5.29 (dq, J = 1.6, 10.4 Hz, 2H), 5.41 (dq, J = 1.6, 17.2 Hz, 2H), 5.95−6.14 (m, 2H), 6.51 (t, J = 2.2 Hz, 1H), 6.63 (d, J = 2.2 Hz, 2H), 7.48 (d, J = 8.4 Hz, 4H), 8.08 (d, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 33.3, 65.5, 69.3, 102.1, 108.2, 118.2, 126.9, 129.8, 132.1, 139.9, 141.7, 159.7, 165.8; IR (CHC;$_3$) 3024, 1718, 1596. cm^{-1}; HRMS for C$_{29}$H$_{27}$BrO$_6$ (EI) (M) calcd 550.1035, obsd 550.0976. Anal. Calcd for C$_{29}$H$_{27}$BrO$_6$; C, 63.17; H, 4.94. Found: C, 63.52; H, 5.04.

(AllylO$_2$C)$_4$[G2]-OH (10). Compound **9** (6.19 g, 11.25 mmol), 3,5-dihydroxybenzyl alcohol (0.7 g, 5.0 mmol), finely powdered potassium carbonate (3.52 g, 25.5 mmol), and 18-crown-6 (0.13 g, 0.5 mmol) were suspended in 25 mL of dry acetone. The mixture was heated at reflux for 18 h, at which time the solvent was removed in vacuo and the resultant residue was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were dried over Mg$_2$SO$_4$ and then evaporated to dryness. Purification via flash chromatography (SiO$_2$) with (0−5%) diethyl ether/dichloromethane afforded **10** (4.42 g, 4.08 mmol, 73%) as a clear glass: ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.58 (s, 2H), 4.80 (dt, J = 1.4, 5.6 Hz, 8H), 4.94 (s, 4H), 5.07 (s, 8H), 5.24 (dq, J = 1.54, 10.53 Hz, 4H), 5.39 (dq, J = 1.54, 17.25

---

[32] Kozlowski, J. S.; Marzabadi, C. H.; Rath, N. P.; Spilling, C. D. *Carbohydr. Res.* **1997**, *300*, 301.

Hz, 4H), 5.95−6.12 (m, 4H), 6.44 (t, J = 2.1 Hz, 1H), 6.51 (t, J = 2.1 Hz, 2H), 6.54 (d, J = 2.1 Hz, 2H), 6.63 (d, J = 2.1 Hz, 4H), 7.44 (d, J = 8.4 Hz, 8H), 8.03 (d, J = 8.4 Hz, 8H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 64.9, 65.5, 69.3, 69.6, 101.0, 101.5, 105.5, 106.3, 118.2, 126.9, 129.6, 129.8, 132.1, 139.5, 141.9, 143.7, 159.8, 165.8; MS for $C_{65}H_{60}O_{15}$ (MALDI-TOF) (MH) calcd 1081.2, obsd 1081.0; IR (neat) 3512, 1720, 1597 cm^{-1}. Anal. Calcd for $C_{65}H_{60}O_{15}$; C, 72.21; H, 5.59. Found: C, 72.31; H, 5.64.

(AllylO$_2$C)$_4$[G2]-Br (11). (AllylO$_2$C)$_4$[G2]-OH (**10**) (4.67 g, 4.3 mmol) was treated with PBr$_3$ (0.4 g, 0.14 mL, 1.5 mmol) in toluene (14 mL) at 0 °C as described for **9**. Purification by flash chromatography (SiO$_2$) with 5% diethyl ether/dichloromethane afforded **11** (2.91 g, 2.54 mmol, 60%) as a clear glass: ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.39 (s, 2H), 4.82 (dt, J = 1.4, 5.6 Hz, 8H), 4.96 (s, 4H), 5.10 (s, 8H), 5.30 (dq, J = 1.6, 10.5, Hz, 4H), 5.42 (dq, J = 1.6, 17.2, Hz, 4H), 5.98−6.11 (m, 4H), 6.48 (t, J = 2.2 Hz, 1H), 6.54 (t, J = 2.2 Hz, 2H), 6.59 (d, J = 2.2 Hz, 2H), 6.65 (d, J = 2.2 Hz, 4H), 7.48 (d, J = 8.4 Hz, 8H), 8.07 (d, J = 8.4 Hz, 8H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 33.5, 65.5, 69.3, 69.8, 101.6, 102.1, 106.4, 108.1, 118.2, 126.9, 129.7, 129.8, 130.2, 132.1, 139.2, 139.7, 141.9, 159.8, 165.8; IR (CHCl$_3$) 1717, 1597 cm^{-1}; MS for $C_{65}H_{59}BrO_{14}Na$ (MALDI-TOF) (M + Na) calcd 1167.08, obsd 1167.92

(AllylO$_2$C)$_8$[G3]-OH (12). (AllylO$_2$C)$_4$[G2]-Br (**11**) (2.86 g, 2.4 mmol) was converted to (allylO$_2$C)$_8$[G3]-OH (**12**) using 3,5-dihydroxybenzyl alcohol (0.15 g, 1.1 mmol), potassium carbonate (0.76 g, 5.5 mmol) and 18-crown-6 (0.029 g, 0.11 mmol) in 10 mL of dry acetone as described for **10**. Purification via flash chromatography (SiO$_2$) with (0−5%) diethyl ether/dichloromethane afforded **12** (2.26 g, 1.0 mmol, 90%) as a clear glass: ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.59 (s, 2H), 4.8 (dt, J = 1.29, 6.84 Hz, 16 H), 4.9 (s, 12 H), 5.1 (s, 16 H), 5.28 (dq, J = 1.28, 9.15 Hz, 8 H), 5.40 (dq, J = 1.28, 17.1 Hz, 8 H), 5.95−6.05 (m, 8H), 6.49−6.65 (m, 21 H), 7.43 (d, J = 8.3 Hz, 16 H), 8.03 (d, J = 8.3 Hz, 16 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 65.5, 69.3, 69.7, 101.1, 106.4, 118.2, 126.8, 129.4, 129.8, 132.1, 139.3, 141.9, 159.8, 165.8; IR (neat) 3462, 1715, 1597 cm^{-1}; MS for $C_{137}H_{124}O_{31}$ (MH) (MALDI-TOF) calcd 2264.8, obsd 2263.2. Anal. Calcd for $C_{137}H_{124}O_{31}$: C, 72.6; H, 5.51. Found: C, 72.39; H, 5.60.

(AllylO$_2$C)$_8$[G3]-Br (13). (AllylO$_2$C)$_8$[G3]-OH (**12**) (2.1 g, 0.92 mmol) was converted to (allylO$_2$C)$_8$[G3]-Br (**13**) by treatment with PBr$_3$ (0.8 g, 28.2 μL, 0.31 mmol) in toluene (5 mL) at 0 °C as described for **9**. Purification by flash chromatography (SiO$_2$) with 5% diethyl ether/dichloromethane afforded **13** (1.1 g, 0.47 mmol, 51%) as a white solid: mp = 53−56 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.38 (s, 2H), 4.81 (bd, J = 5.6 Hz, 16H), 4.95 (bs, 12 H), 5.10 (bs, 16 H), 5.30 (dd, J = 2.3, 10.52 Hz, 8 H), 5.4 (dd, J = 1.4, 16.7 Hz, 8 H), 5.98−6.87 (m, 8 H), 6.51−6.66 (m, 21 H), 7.45 (d, J = 8.3 Hz, 16H), 8.05 (d, J = 8.3 Hz, 16H); ^{13}C NMR (75 MHz, CDCl$_3$) 32.7, 65.5, 69.3, 69.7, 102.1, 106.3, 118.2, 126.8, 129.6, 129.8, 132.0, 139.3, 141.9, 159.9, 165.8; IR (CHCl$_3$) 1720, 1596 cm^{-1}; MS for $C_{137}H_{123}O_{30}Br$ (MH) (MALDI-TOF) calcd 2327.7, obsd 2328.3. Anal. Calcd for $C_{137}H_{123}O_{30}Br$: C, 70.64; H, 5.32. Found: C, 70.73; H, 5.29.

A. General Procedure for Allyl Ester Dendrimer Synthesis. Central core **3** or **6** (100 mol %), finely powdered potassium carbonate (excess), 18-crown-6 (20 mol %), and dendron monobromide (**9**, **11**, or **13**) were suspended in THF/DMF (3:1) (0.2 M in **3** or **6**) and heated at 65 °C. After 18 h, the solvents were removed in vacuo, and the resultant residue was partitioned between water and dichloromethane. The aqueous layer was extracted three times with dichloromethane, and the combined organic layers were dried over Mg$_2$SO$_4$ and evaporated to dryness. Final purification was achieved by flash chromatography (SiO$_2$) as indicated below.

B. General Procedure for Deprotection of Allyl Ester Terminated Dendrimers. Pd$_2$(dba)$_3$·CHCl$_3$ (25.8 mg, 0.025 mmol) and triphenylphosphine (65 mg, 0.25 mmol) were mixed in THF (1 mL) and stirred at ambient temperature until the solution became bright yellow and homogeneous (ca. 5 min). To a solution of the allyl ester terminated dendrimer (100 mol %) in THF was added a portion of the aforementioned solution corresponding to 5 mol % Pd followed by a preformed 1.2 M solution of N(Bu)$_3$/HCO$_2$H (1:1) in THF (4 equiv/allyl ester). The mixture was then heated to 55 °C for 12 h, and the solvent was removed in vacuo. The oily residue was dissolved in CH$_2$Cl$_2$ (10 mL) and washed with water (10 mL). The CH$_2$Cl$_2$ layer was concentrated in vacuo, and the resultant yellow solid was dissolved in 20 mL of 5% aqueous NaHCO$_3$ and washed with 20 mL of diethyl ether. The aqueous layer was diluted to 50 mL with water and acidified with concentrated hydrochloric acid to pH 2, causing a precipitate to form that was filtered, washed with two portions of deionized water, and dried for at least 12 h in a vacuum desiccator over P$_2$O$_5$. The dried solid was dissolved in 3 mL of THF, and to this solution was added 1 mL of chlorotrimethylsilane. The solution was allowed to stir for 15 min and was then poured into 6 mL of deionized water resulting in a white precipitate. The water was decanted, and the white solid was dried for at least 12 h in a vacuum desiccator over P$_2$O$_5$.

(AllylO$_2$C)$_6$[G1] Dendrimer 14a. (AllylO$_2$C)$_2$[G1]-Br (**9**) (0.35 g, 0.63 mmol), **3** (0.1 g, 0.19 mmol), K$_2$CO$_3$ (0.15 g, 1.1 mmol), and 18-crown-6 (0.01 g, 0.038 mmol) were reacted in THF/DMF (6 mL/2 mL) following general procedure A. Purification by flash chromatography (SiO$_2$) with 5−10% diethyl ether/dichloromethane afforded dendrimer **14a** (0.23 g, 0.12 mmol, 63%) as a white solid: mp = 66−71 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.25 (dd, J = 5.3, 11.3 Hz, 1H), 4.50 (dd, J = 2.5, 11.3 Hz, 1H), 4.81 (d, J = 5.5 Hz, 12H), 4.96−5.1 (m, 19H), 5.27 (d, J = 10.5 Hz, 6H), 5.38 (d, J = 17.2 Hz, 6H), 5.94−6.13 (m, 6H), 6.34 (d, J = 8.6 Hz, 1H), 6.53−6.64 (m, 9H), 6.83−6.96 (m, 7H), 7.35−7.54 (m, 17H), 7.65 (d, J = 8.6 Hz, 2H), 7.96−8.08 (m, 16H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 52.0, 63.0, 65.5, 69.35, 69.7, 69.8, 75.0, 101.6, 101.7, 106.3, 106.4, 114.5, 118.2, 122.2, 126.0, 126.9, 127.2, 128.7, 128.8, 129.7, 129.8, 129.9, 131.7, 131.8, 132.1, 138.8, 139.0, 141.8, 159.8, 162.5, 165.8, 166.0; IR (neat) 1719, 1605 cm^{-1}; UV (CHCl$_3$) λ_{max} 248 (ϵ = 113 301), 264 (ϵ = 71 223) nm; $[\phi]^{23}_{578}$ (c 0.6, CHCl$_3$) 537; MS for $C_{117}H_{103}NO_{26}Na$ (M + Na) (MALDI-TOF) calcd 1962, obsd 1964. Anal. Calcd for $C_{117}H_{103}NO_{26}$: C, 72.47; H, 5.35; N, 0.72. Found: C, 72.31; H, 5.36; N, 0.75.

(HO$_2$C)$_6$[G1] Dendrimer 14b. Following procedure B for allyl ester deprotection, (allylO$_2$C)$_6$[G1] dendrimer **14a** (95 mg, 0.05 mmol) in 2 mL of THF was converted to (HO$_2$C)$_6$[G1] **14b** using 0.18 mL of the Pd(0) solution and 1 mL of the 1.2 M solution of N(Bu)$_3$/HCO$_2$H in THF. This afforded **14b** as a white solid (77 mg, 0.045 mmol, 90%): mp= 147 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.19 (br s, 1H), 4.34 (br s, 1H), 4.90 (bm, 1H), 5.04−5.26 (m, 18H), 6.14 (d, J = 6.65 Hz, 1H), 6.63−6.73 (m, 9H), 7.00−7.10 (m, 6H), 7.27−7.35 (m, 3H), 7.44 (d, J = 7.8 Hz, 2H), 7.50−7.53 (m, 12 H), 7.70 (d, J = 8.6 Hz, 2H), 7.84−7.87 (m, 2H), 7.93 (d, J = 8.1 Hz, 12 H), 8.02 (d, J = 8.6 Hz, 2H), 8.58 (d, J = 7.85 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) 52.0, 63.3, 67.0, 68.7, 69.1, 69.3, 74.9, 101.2, 101.3, 106.7, 106.8, 114.2, 114.7, 121.8, 126.7, 127.0, 127.3, 128.2, 128.4, 129.1, 129.4, 130.1, 131.3, 131.6, 137.9, 138.9, 139.2, 141.9, 159.4, 160.5, 162.3, 164.5, 165.0, 166.4, 167.0; IR (KBr) 3422, 3058, 1695, 1594 cm^{-1}; MS for $C_{99}H_{78}NO_{26}$ (negative ion electrospray) (M − H) calcd 1697, obsd 1696; UV (0.6 M aq NaHCO$_3$) λ_{max} 238 nm (ϵ = 104 830).

(AllylO$_2$C)$_{12}$[G2] Dendrimer 15a. (AllylO$_2$C)$_4$[G2]-Br (**11**) (0.715 g, 0.625 mmol), **3** (0.1 g, 0.19 mmol), K$_2$CO$_3$ (0.15 g, 1.1 mmol), and 18-crown-6 (0.01 g, 0.14 mmol, 0.0378 mmol) were reacted in THF/DMF (6 mL/2 mL) following general procedure A. Purification by flash chromatography (SiO$_2$) with 5% diethyl ether/dichloromethane afforded **15a** (0.52 g, 0.14 mmol, 74%) as a white solid: mp = 69−74 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.23 (br m, 1H), 4.5 (br m, 1H), 4.8 (bs, 24 H), 4.9−5.15 (m, 42 H), 5.25 (d, J = 10.32, 12 H), 5.97−6.03 (m, 12H), 6.32 (d, J = 8.3 Hz, 1H), 6.50−6.63 (m, 27H), 6.81−6.97 (m, 6H), 7.26−7.48 (m, 29H), 7.60 (d, J = 8.4 Hz, 2H), 7.94−8.05 (m, 28H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 65.5, 69.2, 69.7, 83.4, 83.8, 101.5, 106, 114.5, 118.2, 126.9, 129.7, 132, 139.3, 141.9, 159.7, 159.9, 165.8; IR (CHCl$_3$) 1720, 1598 cm^{-1}; MS for $C_{225}H_{199}NO_{50}Na$ (M + Na) (MALDI-TOF) calcd 3737.3, obsd 3737.9; UV (CHCl$_3$) λ_{max} 246 (ϵ = 183 945), 276 (ϵ = 55 211)nm; $[\phi]^{23}_{578}$ (c 0.6, CHCl$_3$) 439. Anal. Calcd for $C_{225}H_{199}NO_{50}$: C, 72.71; H, 5.40; N, 0.38. Found: C, 72.57; H, 5.41; N, 0.28.

$(HO_2C)_{12}$[G2] Dendrimer 15b. Following procedure B for allyl ester deprotection, $(allylO_2C)_{12}$[G2] dendrimer **15a** (210 mg, 0.056 mmol) in 2 mL of THF was converted to $(HO_2C)_{12}$-[G1] **15b** using 0.18 mL of the Pd(0) solution and 1 mL of the 1.2 M solution of $N(Bu)_3/HCO_2H$ in THF. This afforded **15b** as a white solid (119 mg, 0.036 mmol, 66%): mp = 151 °C dec; ^1H NMR (500 MHz, DMSO-d_6) δ 4.15 (br s, 1H), 4.35 (br s, 1H), 4.80 (bm, 1H), 4.99 (br s, 24H), 5.12 (br s, 18H), 6.16 (d, J = 6.05 Hz, 1H), 6.61 (br s, 9H), 6.68 (br s, 19H), 6.98−7.05 (m, 5H), 7.24−7.53 (m, 30H), 7.70 (d, J = 8.3 Hz, 1H), 7.82−8.01 (m, 28H), 8.56 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 67.0, 68.7, 69.1, 69.3, 101.1, 106.6, 114.2, 114.7, 121.8, 126.7, 127.3, 128.4, 129.1, 129.4, 130.1, 131.3, 138.7, 139.4, 141.9, 159.3, 159.4, 167.1; IR (KBr) 3425, 3047, 1690, 1592 cm^{-1}; UV (0.6 M aq $NaHCO_3$) λ_{max} 222 nm (ϵ = 130 583); MS for $C_{189}H_{150}NO_{50}$ (M − H) (negative ion electrospray) calcd 32354, obsd 3234.

$(AllylO_2C)_{24}$[G3] Dendrimer 16a. $(AllylO_2C)_8$[G3]-Br (**13**) (0.800 g, 0.343 mmol), **3** (53 mg, 0.101 mmol), K_2CO_3 (70 mg, 0.505 mmol), and 18-crown-6 (3 mg, 0.010 mmol) were reacted in THF/DMF (3 mL/1 mL) following general procedure A. Purification by flash chromatography (SiO_2) with 5% diethyl ether/dichloromethane afforded **16a** (0.75 g, 0.100 mmol 99%) as a white solid: mp = 65−70 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (br s, 1H), 4.5 (br s, 1H), 4.79−5.01 (m, 139H), 5.24−5.40 (m, 48H), 5.97−6.02 (m, 24H), 6.34 (br s, 1H), 6.56−6.63 (m, 63H), 6.83−6.91 (m, 7H), 7.31−7.42 (m, 53H), 7.65 (br s, 2H), 7.91−8.01 (m, 54H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.4, 69.3, 69.7, 101, 106, 118, 126.8, 126.9, 129.6, 129.7, 132, 139.3, 141.9, 159.7, 159.9, 165.7; IR (neat) 1720, 1597 cm^{-1}; UV ($CHCl_3$) λ_{max} 246 (ϵ = 426 624), 276 (ϵ = 130 299) nm; $[\phi]^{23}{}_{578}$ (c 0.6, $CHCl_3$) 291. Anal. Calcd for $C_{441}H_{391}NO_{98}$; C, 72.83; H, 5.42; N, 0.19. Found: C, 72.57; H, 5.40; N, 0.27.

$(HO_2C)_{24}$[G3] Dendrimer 16b. Following procedure B for allyl ester deprotection, $(allylO_2C)_{24}$[G3] dendrimer **16a** (200 mg, 0.027 mmol) in 2 mL of THF was converted to $(HO_2C)_{24}$-[G2] **16b** using 55 μL of the Pd(0) solution and 1 mL of the 1.2 M solution of $N(Bu)_3/HCO_2H$ in THF. This afforded **16b** as a white solid (136 mg, 0.022 mmol, 81%): mp = 152 °C dec; ^1H NMR (500 MHz, DMSO-d_6) δ 4.12 (br s, 1H), 4.50 (br s, 1H), 4.94 (br s, 31 H), 5.07 (br s, 60H), 6.15 (br s, 1H), 6.58−7.10 (m, 69H), 7.4−7.6 (m, 53H), 7.89 (bs, 53H); ^{13}C NMR (125 MHz, DMSO-d_6) 67.0, 68.7, 69.0, 101.0, 106.6, 127, 128.7, 129, 130, 131.4, 131.5, 132, 139.4, 141.8, 159.3, 159.4, 167; IR (KBr) 3419, 3066, 1692, 1598 cm^{-1}; UV (0.6 M aq $NaHCO_3$) λ_{max} 230 nm (ϵ = 305 340).

$(AllylO_2C)_8$[G1] Dendrimer 17a. $(AllylO_2C)_2$[G1]-Br (**9**) (0.980 g, 1.78 mmol), **6** (0.255 g, 0.396 mmol), K_2CO_3 (0.44 g, 3.2 mmol), and 18-crown-6 (0.021 g, 0.079 mmol) were reacted in THF/DMF (3 mL/1 mL) following general procedure A. Purification by flash chromatography (SiO_2) with 5−10% diethyl ether/dichloromethane afforded **17a** (0.710 g, 0.281 mmol, 72%) as a white solid: mp = 63−65 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.67 (bs, 6H), 4.81 (bd, 16H), 5.02 (m, 24H), 5.28 (dd, J = 10.3, 1.3 Hz, 8H), 5.39 (dd, J = 15.8, 1.3 Hz, 8H), 5.67 (bs, 2H), 6.04 (m, 8H), 6.50 (t, J = 2.4 Hz, 4H), 6.62 (bs, 8H), 6.86 (d, J = 8.92 Hz, 4H), 6.93 (d, J = 9.0 Hz, 4H), 7.45 (m, 16H). 7.9−8.1 (m, 24H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 65.6, 69.4, 69.4, 69.8, 101.8, 106.4, 114.5, 114.6, 118.2, 121.7, 122.5, 126.9, 128.5, 128.9, 129.7, 129.9, 131.9, 132.0, 132.2, 138.7, 138.8, 141.9, 159.9, 162.4, 162.8, 165.2, 165.9; IR (neat) 1718, 1604. cm^{-1}; MS for $C_{150}H_{132}O_{37}Na$ (MALDI-TOF) (M + Na) calcd 2547, obsd 2547. Anal. Calcd for $C_{150}H_{132}O_{37}$: C, 71.31; H, 5.27. Found: C, 71.55; H, 5.32.

$(HO_2C)_8$[G1] Dendrimer 17b. Following procedure B for allyl ester deprotection, $(allylO_2C)_8$[G1] dendrimer **17a** (0.40 g, 0.16 mmol) in 3 mL of 1.2 M solution of $(C_4H_9)_3N/HCO_2H$ (1:1) in THF was converted to $(HO_2C)_8$[G1] **17b** using 0.32 mL of the Pd(0) solution. This afforded **17b** as white solid (0.25 g, 0.11 mmol, 70%): mp = 130 °C dec; ^1H NMR (250 MHz, DMSO-d_6) δ 4.58−4.69 (m, 6H), 5.09−5.13 (m, 24H), 5.66 (br s, 2H), 6.65−6.73 (m, 12H), 6.99 (d, J = 8.8 Hz, 4H), 7.12 (d, J = 8.9 Hz, 4H), 7.52 (m, 16H), 7.94 (m, 24H), 12.98 (br s, 8H); ^{13}C NMR (62.5 MHz, DMSO-d_6) 68.5, 68.8, 106.7, 114.7, 121.3, 121.8, 127.3, 127.4, 129.4, 130.1, 131.4, 138.8, 141.9, 159.4, 162.5, 165.1, 167.1; IR (neat) 1713, 1601 cm^{-1}; UV (THF) λ_{max} 234 nm (ϵ = 151 639); UV (0.1M Na_2HPO_4) λ_{max} 210 nm (ϵ = 208 813); MS for $C_{126}H_{99}O_{37}$ (M − H) (negative ion electrospray) calcd 2206.2, obsd 2206.4.

$(AllylO_2C)_{16}$[G2] Dendrimer 18a. $(AllylO_2C)_4$[G2]-Br (**11**) (0.220 g, 0.192 mmol), **6** (28.8 mg, 0.0447 mmol), K_2CO_3 (49 mg, 0.358 mmol), and 18-crown-6 (2.36 mg, 0.0089 mmol) were reacted in THF/DMF (3 mL/1 mL) following general procedure A. Purification by flash chromatography (SiO_2) with 5−10% diethyl ether/dichloromethane afforded **18a** (157 mg, 0.032 mmol, 72%) as a glass: ^1H NMR (250 MHz, $CDCl_3$) δ 4.68 (bs, 6H), 4.81 (bd, J = 4.6 Hz, 24H), 4.90 (bd, J = 6.1 Hz, 8H), 4.95−5.09 (m, 56H), 5.28(d, J = 10.5 Hz, 16H), 5.40 (d, J = 17.4 Hz, 16H), 5.69 (s, 2H), 6.05 (bm, 16H), 6.52 (bs, 12 H), 6.65 (bs, 24H), 6.86 (d, J = 8.9 Hz, 4H), 6.95 (d, J = 8.9 Hz, 4H), 7.45 (m, 32H), 7.95−8.06 (m, 40H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 65.5, 69.3, 103.9, 104.0, 106.3, 106.6, 118.2, 126.9, 129.7, 129.9, 132.3 (mult carbons), 138.5, 139.3, 141.9, 159.8, 160.0, 162.8, 165.8; IR (neat) 1721, 1598 cm^{-1}; MS for $C_{294}H_{260}O_{69}Na$ (MALDI-TOF) (M + Na) calcd 4916, obsd 4916. Anal. Calcd for $C_{294}H_{260}O_{69}$: C, 72.11; H, 5.35. Found: C, 72.20; H, 5.37.

$(HO_2C)_{16}$[G2] Dendrimer 18b. Following procedure B for allyl ester deprotection, $(allylO_2C)_{16}$[G2] dendrimer **18a** (0.16 g, 0.033 mmol) in 1 mL of 1.2 M solution of $(C_4H_9)_3N/HCO_2H$ (1:1) in THF was converted to $(HO_2C)_{16}$[G2] **18b** using 65 μL of the Pd(0) solution. This afforded **18b** as white solid (0.13 g, 0.030 mmol, 92%): mp = 120 °C dec; ^1H NMR (500 MHz, DMSO-d_6) δ 4.58−4.69 (m, 6H), 4.88−5.17 (br m, 56H), 5.66 (br s, 2H), 6.55−6.62 (br m, 36H), 6.99 (br s, 4H), 7.12 (br s, 4H), 7.43 (br s, 32H), 7.85 (br s, 40H), 12.84 (br s, 16H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 66.7, 104.6, 125.3, 127.4, 128.1, 139.9, 157.4, 165.0; IR (neat) 3271, 1713, 1596 cm^{-1}; UV (THF) λ_{max} 232 nm (ϵ = 366 638); UV (0.1 M Na_2HPO_4) λ_{max} 210 nm (ϵ = 494 468); MS for $C_{246}H_{200}O_{69}$ (M − 4H) (negative ion electrospray) calcd 1065, obsd 1066 (m/4e).

$(AllylO_2C)_{32}$[G3] Dendrimer 19a. $(AllylO_2C)_8$[G3]-Br (**13**) (0.350 g, 0.150 mmol), **6** (23 mg, 0.036 mmol), K_2CO_3 (40 mg, 0.286 mmol), and 18-crown-6 (1.9 mg, 0.0072 mmol) were reacted in THF/DMF (3 mL/1 mL) following general procedure A. Purification by flash chromatography (SiO_2) with 5−10% diethyl ether/dichloromethane afforded **19b** (0.130 g, 0.0135 mmol, 38%) as a glass: ^1H NMR (200 MHz, $CDCl_3$) δ 4.60 (s, ca. 6H), 4.69−5.06 (m, 184H), 5.26 (d, J = 9.6 Hz, 32H), 5.37 (d, J = 17.1 Hz, 32H), 5.69 (bs, ca. 2H), 6.05 (m, 32H), 6.48−6.65 (m, 84 H), 6.8 (bd, ca. 4H), 6.9 (bd, ca. 4H), 7.33−7.48 (m, 64 H), 7.91−8.13 (m, 72H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.5, 65.6, 69.3, 69.6, 101.5, 106.4, 118.2, 126.9, 127.1, 129.6, 129.7, 129.8, 132.1, 138.4, 139.3, 139.4, 141.9, 159.8, 165.7, 165.8; IR (neat) 1719, 1597 cm^{-1}; MS for $C_{582}H_{516}O_{133}Na_2$ (MALDI-TOF) (M + 2Na) calcd (m/2e) 4842, obsd 4842. Anal. Calcd for $C_{582}H_{516}O_{133}$: C, 72.53; H, 5.59. Found: C, 72.24; H, 5.59.

$(HO_2C)_{32}$[G3] Dendrimer 19b. Following procedure B for allyl ester deprotection, $(allylO_2C)_{32}$[G3] dendrimer **19a** (90 mg, 9.3×10^{-3} mmol) in 0.5 mL of 1.2 M solution of $(C_4H_9)_3N/HCO_2H$ (1:1) in THF was converted to $(HO_2C)_{32}$[G3] **19b** using 65 μL of the Pd(0) solution. This afforded **19b** as white solid (48 mg, 5.74×10^{-3} mmol, 62%): mp = 120 °C dec; ^1H NMR (500 MHz, DMSO-d_6) δ 4.63 (barely visible br s, 6H), 4.93−5.06 (br m, 121H), 5.66 (barely visible br s, 1H), 6.62 (br s, 84H), 6.99 (barely visible br s, 4H), 7.12 (barely visible br s, 4H), 7.43 (br s, 64H), 7.85 (br s, 72H), 12.83 (br s, 32H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 66.7, 104.6, 125.3, 127.4, 128.1, 139.9, 157.4, 165.0; IR (neat) 3307, 1719, 1596 cm^{-1}; UV (THF) λ_{max} 234 nm (ϵ = 739 065); UV (0.1 M Na_2HPO_4) λ_{max} 208 nm (ϵ = 609 682).

Acknowledgment. This work was supported by the National Science Foundation CAREER program (CHE-98-75458), and acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

JO010423Z