

Synthesis and Structure of Intramolecularly Hydrogen Bonded Dendrons

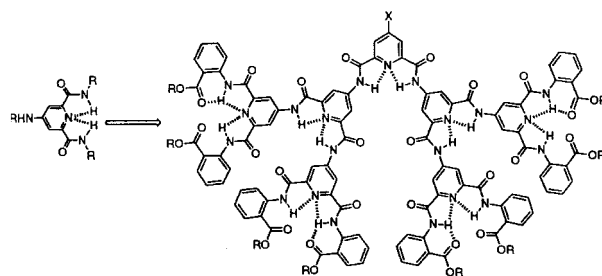
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ABSTRACT



A convenient synthesis of monodendrons whose conformation is restricted through the intervention of intramolecular hydrogen bonding and repulsive electrostatic interactions is described. X-ray crystal structure analysis of the second generation dendron shows the presence of a propeller-type secondary structure and indicates that the dendrons have assembled into a symmetrically interdigitated dimer in the solid state. ¹H NMR and IR spectral data are in agreement with the presence of intramolecular hydrogen bonding between the amides and the pyridine N throughout the dendron structure in solution.

Many recent studies suggest that, in the absence of attractive or repulsive secondary interactions between otherwise flexible dendritic subunits, many dendrimers are conformationally flexible, especially at lower generations.^{1,2} The development of strategies to restrict this conformational flexibility remains as an important goal, because future applications of these materials will rely on an ability to control their properties through their three-dimensional organization. Inter- and intramolecular self-assembly and self-organization are driven by the cooperative interplay of multiple molecular recognition processes such as hydrogen-bonding, van der Waals, electrostatic, and hydrophobic interactions.³ Although the development of secondary and tertiary structure relies

on the simultaneous action of all these recognition mechanisms, several laboratories have demonstrated that a single mechanism can be used to dominate the secondary structure of monodendrons and their supramolecular assemblies.⁴ For example, Percec described a series of monodendrons that maintain a flat-tapered, half-disk, conical or hemispherical shape depending on their substitution patterns and generation

(1) For a recent review of studies relevant to the conformational behavior of dendrimers, see: Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665.

(2) Phenylacetylene dendrimers maintain a "shape-persistent" structure in the absence of secondary interactions: (a) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (b) Pesak, D. J.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1636. (c) Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159. (d) Xu, Z.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537.

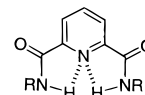
(3) (a) Buckingham, A. D. In *Principles of Molecular Recognition*; Buckingham, A. D., Legon, A. C., Roberts, S. M., Eds.; Chapman and Hall: New York, 1993; p 1. (b) *Molecular Design and Bioorganic Catalysis*; Wilcox, C. S., Hamilton, A. D., Eds.; North Atlantic Treaty Organization, Scientific Affairs Division; Kluwer Academic Publishers: Dordrecht, Boston, 1996. (c) Vögtle, F.; Alfter, F. *Supramolecular Chemistry: An Introduction*; Wiley: Chichester, New York, 1991. (d) Delaage, M. *Molecular Recognition Mechanisms*; VCH: New York, Paris, 1991. (e) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229. (f) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153.

(4) (a) Percec, V. *J. Macromol. Sci., Pure Appl. Chem.* **1996**, *A33*, 1479. (b) Percec, V.; Johansson, G.; Schlueter, D.; Ronda, J. C.; Ungar, G. I. *Macromol. Symp.* **1996**, *101*, 43. (c) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681. (d) Narayanan, V. V.; Newkome, G. R. *Top. Curr. Chem.* **1998**, *197*, 19. (e) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 885. (f) Emrick, T.; Fréchet, J. M. J. *Curr. Opin. Colloid Interface Sci.* **1999**, *4*, 15.

number. By attaching various functional groups to the focal point or periphery of these monodendrons, it was shown that different supramolecular interactions such as van der Waals, hydrogen bonds, hydrophobic and fluorophobic effects, and ion complexation by crown ethers could dominate the formation of supramolecular assemblies of these monodendrons in the liquid crystalline state.⁵ Zimmerman demonstrated the supramolecular construction of a nanometer-sized dendrimer by self-organization of functionalized monodendrons through *intermolecular* hydrogen-bonding interactions.⁶ *Intramolecular* hydrogen-bonding interactions between terminal amides are thought to be responsible for the rigidity of the outer shell of amidated poly(propylene imine) dendrimers.⁷ However, there are few examples wherein dendrimer conformation at each generational shell is restricted through intramolecular hydrogen bonding. Intramolecular hydrogen-bonding interactions have been exploited to improve the rigidity of an extended-core discotic liquid crystal.⁸ The goal of this paper is to describe the synthesis and structural characterization of monodendrons whose conformation is restricted through the intervention of *intramolecular* hydrogen-bonding and electrostatic interactions present in the AB₂ building block.

Pyridine-2,6-dicarboxamide derivatives exist in a conformation that places the amide NH groups in close proximity to the pyridine N due to intramolecular hydrogen bonding and repulsive electrostatic interactions between the amide oxygens.⁹ This conformational preference has been exploited to control the three-dimensional folding of molecular receptors¹⁰ and catenanes.¹¹ Moreover, Hamilton and co-workers demonstrated that linking two anthranilamides through a pyridine-2,6-dicarboxylic acid moiety produces a helical conformation in the resultant molecule that is stabilized by

several intramolecular hydrogen bonds.¹² The ability of these pyridine-2,6-dicarboxamide derivatives to coordinate to metals such as copper has also been utilized to create a rigid metallohelical complex that, in one case, experienced spontaneous resolution in the crystal lattice.¹³ On this basis, we constructed dendritic wedges using 4-aminopyridine-2,6-dicarboxamide as the branching AB₂ unit to preorganize the interior of the dendrons through intramolecular hydrogen-bonding interactions.



4-Chloropyridine-2,6-dicarbonyl chloride (**2**) was chosen as the branching monomer wherein convergent generational growth is accomplished using amide bond-forming reactions with the acid chlorides and focal point activation occurs by NaN₃ displacement of the 4-chloro group followed by hydrogenation. Initially, methyl esters were incorporated as terminal groups; however, beginning at the second generation, solubility was poor in all common organic solvents (THF, DMF, DMSO, EtOAc), except for chlorinated solvents such as CHCl₃ and CH₂Cl₂, which afforded only moderate solubility. Therefore, dodecyl ester groups were placed on the periphery to improve the solubility of the dendrons.

Monomer **2** was prepared by treating chelidamic acid (**1**) with neat POCl₃ at 100 °C (Scheme 1).¹⁴ The synthesis was initiated by exposing dodecyl anthranilate, prepared by transesterification of methyl anthranilate with dodecyl alcohol, to **2** in pyridine, which afforded the first-generation dendron [(C₁₂H₂₅O₂C)₂-[G1]-Cl] (**3a**). Displacement of the 4-chloro group with NaN₃ in DMF at 50 °C installed an azido group at the focal point, giving dendron [(C₁₂H₂₅O₂C)₂-[G1]-N₃] (**3b**). Hydrogenation over Pd–C in THF at 50 psi gave the amino dendron [(C₁₂H₂₅O₂C)₂-[G1]-NH₂] (**3c**) in quantitative yield, which was subsequently elaborated to the second-generation dendron [(C₁₂H₂₅O₂C)₄-[G2]-Cl] (**4a**) by reaction with **2** in pyridine. The solubility of **4a** was significantly enhanced in many solvents relative to the methyl ester analogue; however, in polar solvents such as DMSO and DMF, solubility was limited. Therefore, conversion of **4a** to the corresponding azide by displacement with NaN₃ was performed in THF–DMF (1:3) at 50 °C to maintain homogeneous conditions. Subsequent hydrogenation over Pd–C and reaction with **2** afforded the third-generation dendron [(C₁₂H₂₅O₂C)₈-[G3]-Cl] (**5a**). Repetition of the NaN₃ displacement–hydrogenation activation sequence afforded

(5) (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.

(6) (a) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095. (b) Thiagarajan, P.; Zeng, F.; Ku, C. Y.; Zimmerman, S. C. *J. Mater. Chem.* **1997**, *7*, 1221. (c) Suarez, M.; Lehn, J.-M.; Zimmerman, S. C.; Skoulios, A.; Heinrich, B. *J. Am. Chem. Soc.* **1998**, *120*, 9526.

(7) (a) Stevelmans, S.; van Hest, J. C. M.; Jansen, J. F. G. A.; van Boxel, D. A. F. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 7398. (b) Put, E. J. H.; Clays, K.; Persoons, A.; Biemans, H. A. M.; Luyjckx, C. P. M.; Meijer, E. W. *Chem. Phys. Lett.* **1996**, *260*, 136. (c) Bosman, A. A. W.; Janssen, R. A. J.; Meijer, E. W. *Macromolecules* **1997**, *30*, 3606. (d) 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.

(8) (a) Palmans, A. R. A.; Vekemans, J. A. J. M.; Meijer, E. W. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 277. (b) Palmans, A. R. A.; Vekemans, J. A. J. M.; Fischer, H.; Hikmet, R. A.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 300. (c) Palmans, A. R. A.; Vekemans, J. A. J. M.; Havinga, E. E.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2648. (d) Palmans, A. R. A.; Vekemans, J. A. J. M.; Hikmet, R. A.; Fischer, H.; Meijer, E. W. *Adv. Mater.* **1998**, *10*, 873. (e) Langeveld-Voss, B. M. W.; Waterval, R. J. M.; Janssen, R. A. J.; Meijer, E. W. *Macromolecules* **1999**, *32*, 227.

(9) For X-ray crystal structures, see: (a) Newkome, G. R.; Fronczek, F. R.; Kohli, D. K. *Acta Crystallogr.* **1981**, *B37*, 2114. (b) Alcock, N. W.; Moore, P.; Reader, J. C.; Roe, S. M. *J. Chem. Soc., Dalton Trans.* **1988**, 2959. (c) Malone, J. F.; Murray, C. M.; Dolan, G. M.; Docherty, R.; Lavery, A. J. *Chem. Mater.* **1997**, *9*, 2983.

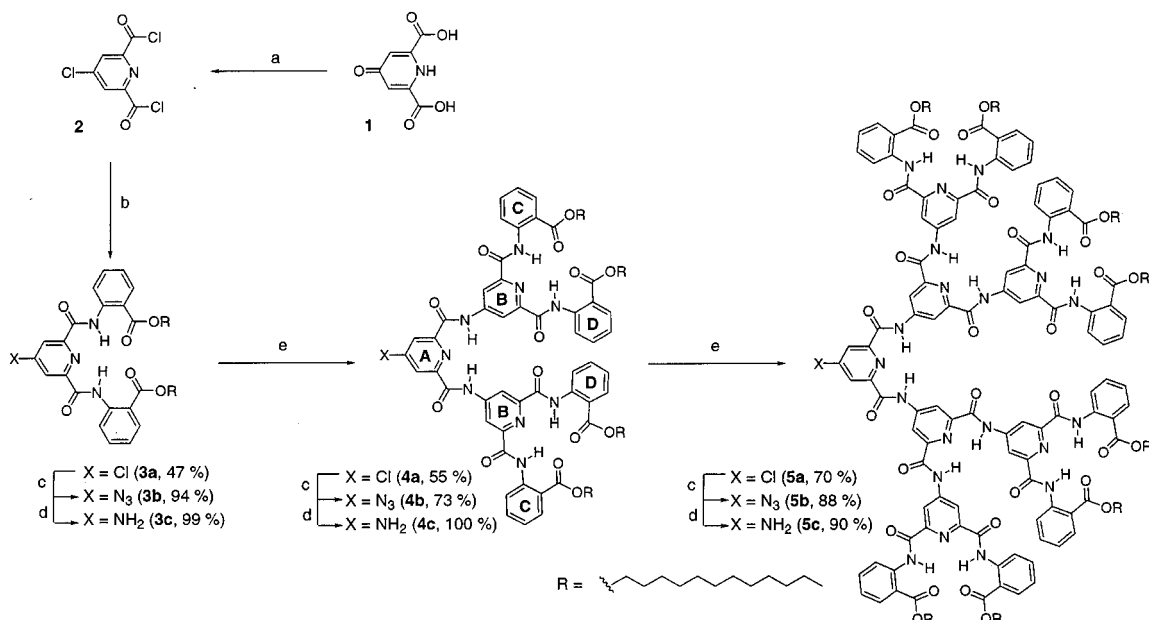
(10) (a) Hunter, C. A.; Purvis, D. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *6*, 792. (b) Crisp, G. T.; Jiang, Y.-L. *Tetrahedron* **1999**, *55*, 549.

(11) Leigh, D. A.; Murphy, A.; Smart, J. P.; Deleuze, M. S.; Zerbetto, F. *J. Am. Chem. Soc.* **1998**, *120*, 6458.

(12) (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587. (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529.

(13) (a) Kawamoto, T.; Hammes, B. S.; Haggerty, B.; Yap, G. P. A.; Rheingold, A. L.; Borovik, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 285. (b) Yu, Q.; Baroni, T. E.; Liable-Sands, L.; Rheingold, A. L.; Borovic, A. S. *Tetrahedron Lett.* **1998**, *39*, 6831.

(14) Bhattacharya, S.; Snehalatha, K.; George, S. K. *J. Org. Chem.* **1998**, *63*, 27.

Scheme 1^a

^a Key: (a) POCl_3 ; (b) dodecyl anthranilate, pyridine, DMAP; (c) NaN_3 , THF/DMF; (d) $\text{H}_2/\text{Pd}-\text{C}$, THF/ CH_3OH ; (e) **2**, pyridine, DMAP.

the third-generation dendritic amine **5c**. Characterization with regard to molecular weight, structure, and dispersity was accomplished by FAB (**3a–c**) or MALDI-TOF (**4a–c**, **5a–c**; see Supporting Information) MS, NMR, and SEC analysis, respectively. Molecular weights determined by MS were consistent with the expected structures, and SEC indicated the monodispersity of all the dendrons.

A clear, monoclinic crystal with a $P2_1/c$ space group was obtained for the second-generation dendron **4a** ($\text{R} = \text{Me}$) by crystallization from CH_2Cl_2 .¹⁵ X-ray diffraction showed that the asymmetric unit was a dimer composed of two virtually identical, interdigitated monodendrons with two associated molecules of CH_2Cl_2 (Figure 1).¹⁶ The dimeric

with the corresponding B and C rings of the second dendron; however, the focal A ring of one dendron is sandwiched between the adjacent terminal D rings of the other dendron, resulting in a structure containing approximate D_2 symmetry. Both monodendrons display all six of the expected bifurcated hydrogen bonds between the amide NH's and the pyridine N, having pyN...H bond distances ranging from 2.13 to 2.23 Å. Additionally, two of the four terminal ester carbonyl oxygens participate in additional hydrogen bonds with the outer shell amide NH's. This network of hydrogen bonds serves to restrict the branches of each monodendron to a cisoid conformation, and due to pairwise steric interactions between adjacent aryl subunits, the dendron assumes an overall propeller shape (Figure 2). The unit cell contains both

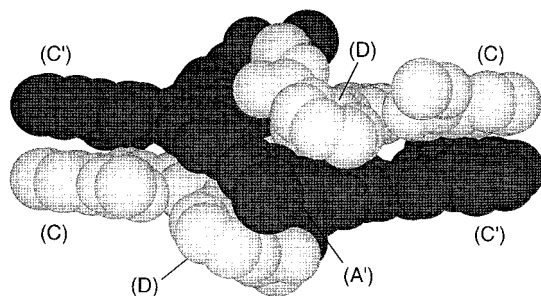


Figure 1. CPK depiction of the asymmetric unit of the X-ray structure of **4a** ($\text{R} = \text{Me}$).

structure displays extensive face-to-face π -stacking interactions; all seven rings in **4a** are paired in stacked arrangements having closest edge-to-edge distances varying from 3.47 to 3.83 Å. Rings B and C of the first dendron are π -stacked

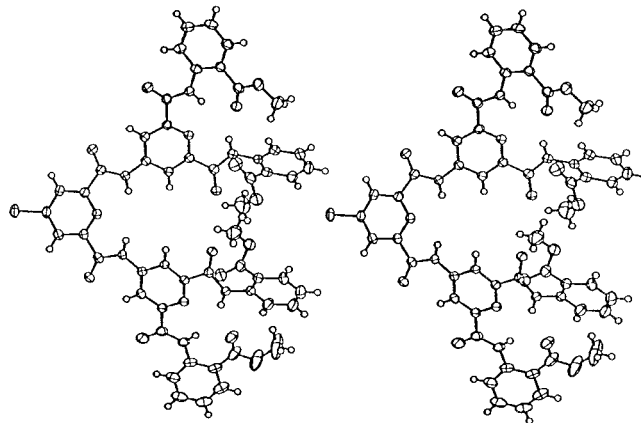


Figure 2. ORTEP diagram in stereo of an isolated monodendron drawn at the 50% probability level.

right- and left-handed propeller conformations. This conformational preference contrasts with the Fréchet-type polyaryl ether dendrons, which adopt a planar disklike conformation in the solid state.¹⁷ Since crystallization is a kinetically controlled process, this X-ray structure does not necessarily represent the energy minimum of the system.

¹H NMR and IR spectral data are in good agreement with the presence of intramolecular hydrogen-bonding between the amides and the pyridine N throughout the dendron structure in solution (see the Supporting Information). The proton NMR spectra display a unique downfield resonance for each set of the amide N–H's corresponding to a given generational shell. For example, the amide N–H groups exhibit a single, sharp low-field resonance at 12.75 ppm for the first-generation dendron **3a**, two slightly broadened resonances (12.23 and 11.16 ppm) for the second-generation species **4a**, and three slightly broadened resonances (12.46, 11.51, and 11.22 ppm) for the third-generation dendron **5a**. It is noteworthy that even in DMSO/CDCl₃ (1:3) at 50 °C the N–H resonances in **5a** do not experience significant upfield shifts relative to **3a–c** and **4a–c** in CDCl₃, suggesting that the intramolecular H bonds are quite robust. The infrared spectra in CDCl₃ (10 mM)¹⁸ of **3a–c**, **4a–c**, and **5a–c** exhibited broad N–H stretching bands at 3234–3374 cm⁻¹ characteristic of hydrogen-bonded N–H groups, but no peaks were observed in the free N–H stretching region (3400–3500 cm⁻¹).^{19,20}

The ¹³C and ¹H NMR spectra of **3a–c** and **4a–c** were well-resolved in CDCl₃ at ambient temperature; however, the proton NMR spectrum of **5a** in CDCl₃ (10 mM) was extremely broadened and structureless even at 50 °C. Dilution to 1 mM in CDCl₃ did not improve the spectrum. Despite the excellent solubility of **5a** in toluene, recording the spectrum in toluene-*d*₈ further increased the complexity of the spectrum, which did not improve upon heating to 90 °C. Interestingly, the spectral resolution improved dramatically in a mixture of DMSO-*d*₆ and CDCl₃ (1:3, 10 mM)²¹ at 50 °C (see the Supporting Information). Similar behavior was observed for **5b,c**.

Percec et al. have reported that polyaryl ether dendrimers with perhydrogenated or perfluorinated alkyl termini aggregate in such a way that segregation occurs between the

dendritic wedge and the termini.⁵ The broadening observed in the proton NMR spectrum of **5a** may be due to aggregation occurring that segregates the polar dendritic interior from the nonpolar terminal aliphatic chains. Aggregates that sequester the polar interior from the solvent would be stabilized in relatively nonpolar solvents such as toluene that interact well with the nonpolar termini but poorly with the interior.²² Polar solvents such as DMSO that interact favorably with the interior could be expected to dissociate the aggregate and simplify the spectra, which is observed. Meijer has observed a similar solvent dependence in the aggregation of an intramolecularly H-bonded discotic molecule containing aliphatic terminal groups;^{8b} this behavior was also evident in stilbenoid and phenylacetylene dendrimers reported by Meier²³ and Moore,^{2b} respectively. The propensity of the dendrons to aggregate increases with molecular weight. For example, while **3c** (mol wt 757) and **4c** (mol wt 1659) do not exhibit a tendency to aggregate in CDCl₃, reaction of trimesic acid trichloride with the first-generation dendron **3c** affords a dendrimer (mol wt 2427) that aggregates in CDCl₃.²⁴ The exact nature of this aggregation is currently under investigation.

In conclusion, we have described a convenient strategy to prepare monodendrons based on an AB₂ subunit with a conformational preference that is directed by intramolecular hydrogen bonding and repulsive electrostatic interactions. These hydrogen-bonded dendritic networks offer a new scaffold for designing intramolecularly ordered macromolecules. We are currently constructing these dendrons with chiral, nonracemic terminal groups so that circular dichroism can be used to gain information concerning the conformation of these materials in solution.

Acknowledgment. We thank Dr. Judith Gallucci for the X-ray structure determination of **4a** (R = Me). This work was supported by The Ohio State University and the National Science Foundation CAREER program (Grant No. CHE 98-75458). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Supporting Information Available: Experimental procedures and analytical data for **2a–c**, **3a–c**, **4a–c**, and **5a–c**, ¹H NMR spectra of **5a** in CDCl₃ and DMSO-*d*₆/CDCl₃ (1:3) at elevated temperatures, ORTEP diagrams in stereo of the asymmetric unit, unit cell, and isolated dendrons of **4a**, and tables of X-ray structural data for **4a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) For an example of a heterocyclic dendrimer that aggregates in solution see: (a) Kraft, A. Osterod, F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1019. (b) Osterod, F. Kraft, A. *Chem. Commun.* **1997**, 1435. (c) Kraft, A. *Liebigs Ann./Recl.* **1997**, 1463. (d) Kraft, A. *Chem. Commun.* **1996**, 2103. (d) Kraft, A. *Chem. Commun.* **1996**, 77.

(23) Meier, H.; Lehmann, M. *Angew. Chem., Int. Ed.* **1998**, 37, 643.

(24) Similar broadening was observed in the ¹H NMR spectrum in CDCl₃; however, in 1:1 CDCl₃/DMSO-*d*₆ the spectrum was well-resolved. Tomcik, D.; Parquette, J. R. Unpublished results.

(15) Compound **4a** (R = C₁₂H₂₅) was obtained as a waxy solid for which high-quality crystals could not be obtained. However, the methyl ester derivative was a crystalline solid rather than a wax.

(16) General crystallographic information: *T* = 173(1) K; *P*2₁/*c*, *a* = 13.5199(2) Å, *b* = 29.2090(4) Å, *c* = 27.1316(4) Å; β = 90.135(1)°; *V* = 10 714.3(3) Å³; *Z* = 8; 18 847 unique data; *R*_w = 0.063; GOF = 1.060.

(17) For an X-ray structure of a second-generation poly(aryl ether) dendron, see: Karakaya, B.; Claussen, W.; Gessler, K.; Saenger, W.; Schlüter, A.-D. *J. Am. Chem. Soc.* **1997**, 119, 3296.

(18) Decreasing the concentration of **5a** in CDCl₃ from 10 to 1 mM produced no change in the IR spectrum, supporting the presence of intramolecular hydrogen bonds.

(19) (a) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, 115, 4228. (b) Gellman, S. H.; Dado, G. P.; Liang, G.-L.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, 113, 1164.

(20) Amino dendron **2c** exhibited an N–H stretch at 3479 cm⁻¹ due to the free NH₂ function.

(21) This solvent mixture was necessary due to the poor solubility of **5a** in pure DMSO.