Two-Directional Cascade Polymer Synthesis: Effects of Core Variation[1]

George R. Newkome,* Xiaofeng Lin, Chen Yaxiong,[2] and Gregory H. Escamilla

Center for Molecular Design and Recognition, Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received December 29, 1992

A series of two-directional arborols possessing spirane or biphenyl cores has been prepared in order to evaluate steric parameters in molecular packing necessary for aggregation. The core molecules were prepared by known procedures and structurally confirmed by ^1H and ^{13}C NMR spectra. The resultant arborols failed to aggregate in an aqueous environment supporting the computationally generated picture depicting the molecular interactions during the initial stages of gelation.

Introduction

Newkome and co-workers have recently reported[3-6] a series of two-directional, dumb-bell shaped cascade arborols, which consist of two spheres with hydrophilic surfaces connected by a lipophilic framework. These were abbreviated as [*m*]-*n*-[*p*] arborols, where *m* and *p* designate the number of surface or terminal hydroxyl groups for each sphere and *n* denotes the number of carbon atoms in the connecting hydrocarbon bridge.[7] The chemical and physical properties of these dumb-bell shaped arborols can be easily manipulated by variation of (a) the length and composition of the bridging backbone moiety and (b) the size, shape, and surface functionality of the terminal cascade spheres.

In general, the connecting linkage between the hydrophilic terminal spheres has been limited to flexible lipophilic moieties, which should be compressed in aqueous solution reducing the lipophilic interface to the hydrophilic medium (Figure 1). Experiments have demonstrated[6] a unique relationship between the length (and steric demands) of the lipophilic linkage unit to the hydrophilic sphere size whereby at predictable ratios these arborols stack one upon another forming highly ordered structures resulting in the formation of thermally reversible aqueous gels. In the [6]-*n*-[6] arborol series, when the carbon atom number for the alkane bridge is between 8 and 13 ($8 \leq n \leq 13$), a gel will be formed at concentrations as low as 1.0 wt %. Since the saturated chain in the backbone of these arborols is flexible, as shown in Figure 2, stacking in an orthogonal array is energetically favored—maximizing both lipophilic–lipophilic and hydrophilic–hydrophilic interactions. Inclusion of a central acetylenic moiety gave rise to [6]-$(CH_2)_n$—≡—$(CH_2)_n$-[6] arborols,[5] which also

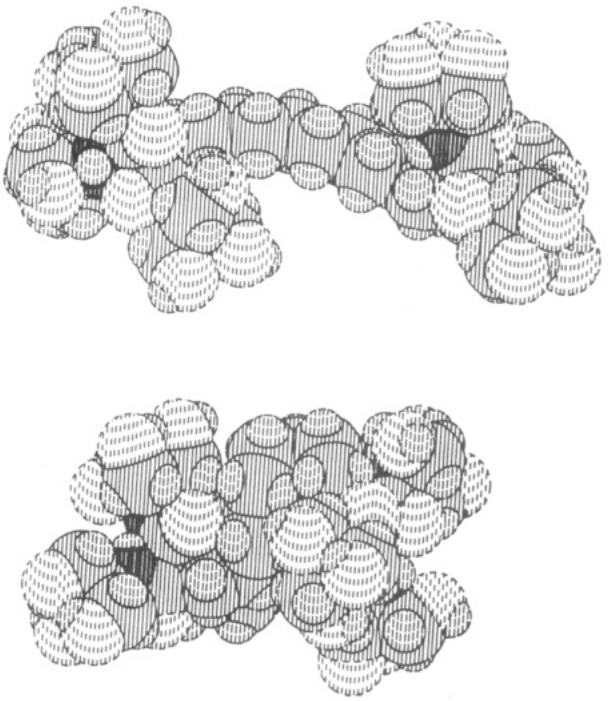


Figure 1. Extended (top) and compressed (bottom) structures of the [9]-10-[9] arborol.

stacked but in an highly ordered helical array, suggesting that the introduction of rigidity or interactive internal functionality plays a critical role in the aggregation process. Since little is known about the nature of the interactions within the lipophilic region of these two-directional arborols, we herein report the incorporation of rigid linear backbones comprised of either biphenyls or spiranes, in order to gain insight into the effect of core shape and thickness, as related to the assembly process.

A. Biphenyl Series. During our early studies in this field, *p*-bis(chloromethyl)benzene was treated with ethyl sodiomethanetricarboxylate[8] to afford a hexaester, which upon reaction with tris(hydroxymethyl)aminomethane (hereafter known as Tris) readily gave the [9]-$CH_2C_6H_4$-CH_2-[9] arborol. Dissolution of this simple arborol in water (D_2O) for spectral studies never gave any indication of gelation.[9] We later showed[6] that it takes greater than eight (8) carbon atoms between the spherical hydrophilic

(1) Cascade Polymer Series. 27. For the previous article in this series, see: Newkome, G. R.; Weis, C. D.; Lin, X.; Fronczek, F. R. *Acta Crystallogr.*, in press.

(2) Visiting Scholar, 1987–1989.

(3) Newkome, G. R.; Baker, G. R.; Saunders, M. J.; Russo, P. S.; Gupta, V. K.; Yao, Z.-q.; Miller, J. E.; Bouillon, K. *J. Chem. Soc., Chem. Commun.* **1986**, 752.

(4) Baker, G. R. Ph.D. Dissertation, Louisiana State University, 1989, p 63.

(5) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Behera, R. K.; Escamilla, G. H.; Saunders, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *104*, 901.

(6) Newkome, G. R.; Baker, G. R.; Arai, S.; Saunders, M. J.; Russo, P. S.; Theriot, K. J.; Moorefield, C. N.; Miller, J. E.; Lieux, T. R.; Murray, M. E.; Phillips, B.; Pascal, L. *J. Am. Chem. Soc.* **1990**, *112*, 8458.

(7) For a systematic nomenclature for cascade polymers see: Newkome, G. R.; Baker, G. R.; Young, J. K.; Traynham, J. G. *Polym. Sci.: Part A. Polym. Chem.* **1993**, *31*, 641.

(8) Newkome, G. R.; Baker, G. R. *Org. Prep. Proc. Int.* **1986**, *18*, 117.

(9) Hanson, P. G. University of South Florida, unpublished results.

0022-3263/93/1958-3123$04.00/0

Figure 2. Orthogonal stacking of the [9]-10-[9] arborol in which each arborol component is shaded differently for clarity.

end groups in the two-directional alkane arborol series prior to the onset of gelation. Therefore, the corresponding 4,4′-bis(bromomethyl)biphenyl would afford the desired bridging distance with 10 carbon atoms.

The preparation of 4,4′-dimethylbiphenyl (**1**) followed the novel procedure of Taylor et al.,[10] in which *cis*-1,4-dichloro-2-butene was treated with (4-methylphenyl)-magnesium bromide. Biphenyl **1** was isolated (75%) and characterized (^{1}H NMR) by the singlet at δ 2.34 for the methyl groups and the two doublets at δ 7.17 and 7.45 for the aryl hydrogens. Treatment of **1** with *N*-bromosuccinimide and AIBN, as initiator, in methyl formate afforded (52%) the desired bromomethyl derivative **2**.[11] The singlet (^{1}H NMR) at δ 4.47 and the peak (^{13}C NMR) at δ 33.1 (shifted from 20.9 for **1**) confirmed the presence of the CH_2Br moieties.

The related 3,3′,5,5′-tetramethylbiphenyl[12] was prepared (66%) by the Co(I)-catalyzed coupling of the Grignard reagent prepared from 3,5-dimethylbromobenzene. Subsequent free-radical bromination of this tetrasubstituted biphenyl, using the method of Offermann and Vögtle,[13] gave (70%) 3,3′,5,5′-tetrakis(bromomethyl)biphenyl (**5**), which was characterized by its ^{1}H NMR spectrum showing singlets at δ 4.52, 7.43, and 7.51 for the methylene, para, and ortho hydrogens, respectively.

The nonahydroxyl-coated spheres were prepared in the usual manner via treatment of the bromomethyl derivatives **2** and **5** with triethyl methanetricarboxylate in DMF–benzene solutions at ca. 50 °C using anhydrous K_2CO_3 as base followed by reaction with Tris. Conversion to the polyester was confirmed (^{1}H NMR) by the loss of the unique CH_2Br moiety and appearance of a singlet at δ 3.44–3.55 for the new arylmethylenes. Treatment of these hexa- (**3**) and dodecaesters (**6**) with excess Tris in Me_2SO at 45–50 °C afforded the corresponding two-directional arborols (**4** and **7**, respectively) via an initial, rapid transesterification, followed by rearrangement to the hexa- and dodecaamides.[6] Loss of the classic ester signals (^{1}H and ^{13}C NMR) and the appearance (^{13}C NMR) of peaks at δ 60.6 for the CH_2OH moieties support the conversion. In general, the combustion analysis data for these arborols were unacceptable due to their highly hygroscopic nature. Thus, treatment of these arborols with acetic anhydride with a catalytic amount of pyridine gave (>95%) the corresponding acetates, which possessed the appropriate methyl signal (δ 2.10, ^{1}H NMR) and elemental analysis data (±0.4%). Subsequent transesterification with NaOMe in anhydrous MeOH regenerated (>90%) the respective arborol; there were no indications of amide hydrolysis under these reaction conditions.

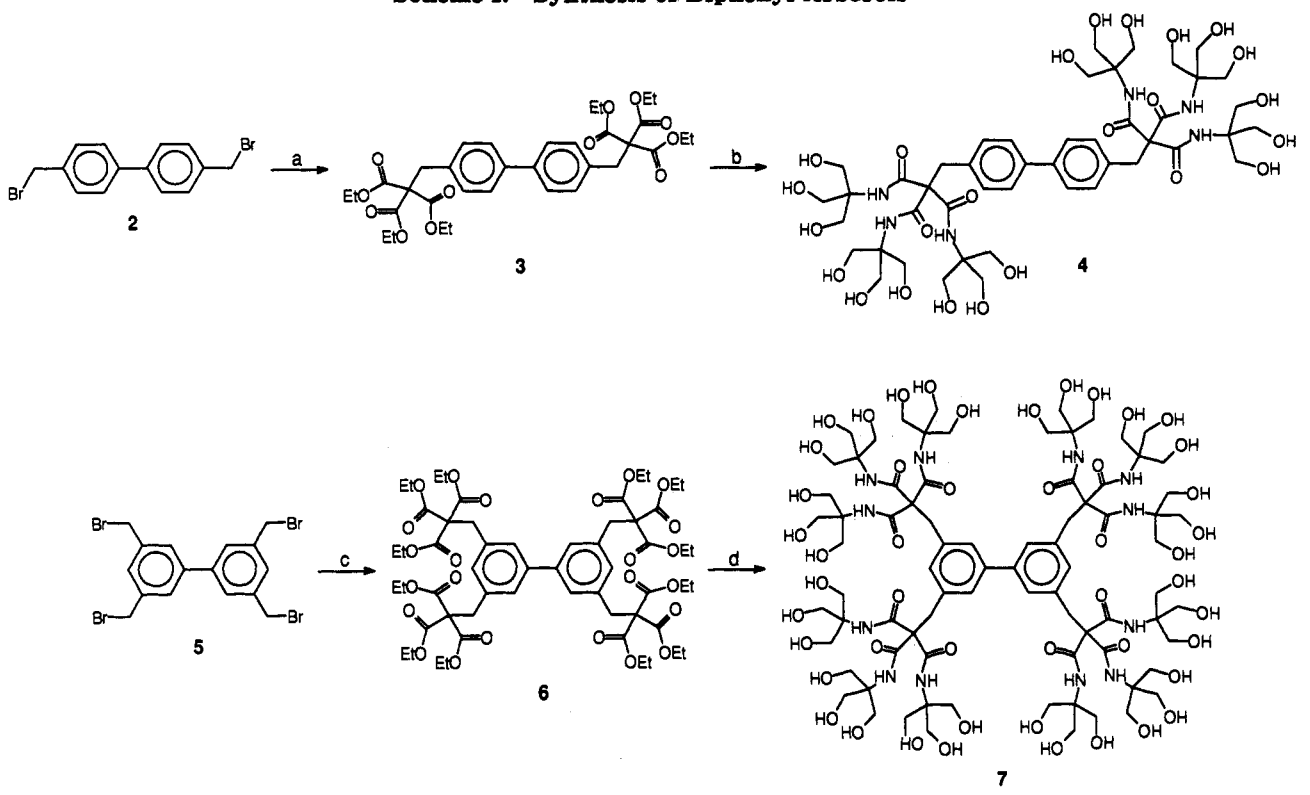
B. Spirane Series. In 1900, Baeyer[14] created the first spirane, described as bicyclic hydrocarbons, which were connected by a single carbon. Due to the tetrahedral nature of the spiro-linked carbon, the two ring planes are nearly perpendicular with respect to each other. Although these spiranes have attracted[15] considerable attention from a synthetic[16,17] standpoint, their preparation via an intramolecular alkylation has been the most successful of the diverse procedures used for their construction.[18]

A series of rigid spirocyclobutane-based backbones was synthesized (Scheme II) via Rice's[19] and Buchta's procedures.[20] Tetrakis(bromomethyl)methane (**8**) was prepared from pentaerythritol by the general procedure of Herzog.[21] Thus, treatment of pentaerythritol with benzenesulfonyl chloride at <40 °C gave the tetrakis[[(benzenesulfonyl)oxy]methyl]methane, which was refluxed with a solution of NaBr to afford (51%) tetrabromide **8**. Alkylation of tetrabromide **8** with diethyl malonate under base conditions yielded (56%) the bicyclic spiroester **9**, whose structure was confirmed (^{13}C NMR) by the appearance of peaks at δ 32.5 and 47.7 attributed to the two different quaternary carbons (*C*-4 and *C*-2, *C*-6) as well as signals at δ 170.8, 60.9, and 13.5 for the *C*=O, CH_2CH_3, and CH_3, respectively. The ^{1}H NMR spectrum of **9** showed a typical ethyl pattern [(δ 4.22, q); (δ 1.26, t)] and a singlet at δ 2.60 indicative of a ring methylene moiety.

Reduction of ester **9** with $LiAlH_4$ in dry tetrahydrofuran afforded (65%) alcohol **10**, which was treated with tosyl chloride in dry pyridine to give (95%) the bicyclic spiro tosylate **11**. Alkylation of tosylate **11** with diethyl malonate, pretreated with Na metal, afforded (78%) the spiroester **12**. The ^{1}H NMR spectrum of ester **12** was

(10) Taylor, L. F.; Bennett, S. G.; Heinz, K. J.; Lashley, L. K. *J. Org. Chem.* **1981**, *46*, 2194.
(11) Reynolds, D. D.; Dunham, K. R. U.S. Pat. 2,789,971; *Chem. Abstr.* **1957**, 14814b.
(12) Castro, C. E.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1958**, *80*, 2325.
(13) Offermann, W.; Vögtle, F. *Synthesis* **1977**, 272.
(14) Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3771.
(15) Dolbier, W. R., Jr. *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; Vol. 3, pp 1–66.
(16) Marshall, J. A.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 192. Marshall, J. A.; Brady, S. F. *J. Org. Chem.* **1970**, *35*, 4068.
(17) Krapcho, A. P. *Synthesis* **1974**, 383.
(18) Buchta, E.; Merk, W. *Naturwissenschaften* **1963**, *50*, 441. Buchta, E.; Geibel, K. *Liebigs Ann. Chem.* **1961**, *683*, 36.
(19) Rice, L. M.; Grogan, C. H. *J. Org. Chem.* **1961**, *26*, 54.
(20) Buchta, E. von; Merk, W. *Liebigs Ann. Chem.* **1966**, *694*, 1. Naemura, K.; Furutani, A.; *J. Chem. Soc., Perkin Trans. 1* **1990**, 3215; *J. Chem. Res., Synop.* **1992**, 174; *J. Chem. Res., Miniprint* **1992**, 1301.
(21) Herzog, H. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 753.

Scheme I. Synthesis of Biphenyl Arborols[a]



[a] Key: (a) $HC(CO_2Et)_3$, anhyd K_2CO_3, DMF/C_6H_6, 45–50 °C, 88 h; (b) Tris, anhyd K_2CO_3, anhyd Me_2SO, 40–45 °C, 160 h; (c) $HC(CO_2Et)_3$, anhyd K_2CO_3, DMF, 40 °C, 113 h; (d) Tris, anhyd K_2CO_3, anhyd Me_2SO, 45–50 °C, 96 h.

similar to that of **9** except for the additional signal at δ 1.92 assigned to the additional unique methylene groups. Repetition of the above reaction sequence gave the six-ring spiroester **15**, whose structure was confirmed (^1H NMR) by the peaks at δ 2.40, 1.87, and 1.79 assigned to the three different methylene groups in the spiro rings. This spirane possesses an 11-carbon atom equivalent, rigid connecting bridge between the quaternary points of terminal sphere attachment.

The desired two-directional arborols were constructed by treatment of the corresponding spiroesters (**9**, **12**, and **15**) with slightly more than 4 equiv of Tris in the presence of anhydrous K_2CO_3 in dry Me_2SO at 25 °C for 72 h. Successful amidations were indicated (^{13}C NMR) by the downfield shifts (from ca. δ 170 to ca. δ 173) for the C=O groups and disappearance of the peaks for the ester moieties. The IR spectra of all three arborols exhibited a similar pattern, especially for the new amide carbonyl stretch (ca. 1650 cm^{-1}) and the broad OH stretch at about 3330 cm^{-1}. Again, in view of the hygroscopic nature of these arborols, elemental analyses were difficult to obtain; thus, the corresponding acetates were prepared. Arborols **16–18** were each refluxed for 10 h with excess Ac_2O in the presence of a catalytic amount of pyridine and then column chromatographed to afford the corresponding analytically pure acetates (**19–21**) possessing satisfactory elemental analyses (±0.4%). Their structures were confirmed (^{13}C NMR) by the new peak at δ 20.5 for the acetyl methyl groups. These acetates were saponified with K_2CO_3 in EtOH to regenerate the corresponding **16–18**, which were identical in all respects to the original arborols.

C. Observations. Both series of arborols were highly hygroscopic white solids, which decomposed when heated above 100 °C. Dissolution of these arborols was conducted by addition of ca. 20 mg of each (**4**, **7**, **16–18**) in ca. 400 μL of water at 90 °C and then cooling to 25 °C and allowing the solutions to stand undisturbed. Under these conditions, none of these rigid arborols formed any visible aqueous gels as readily demonstrated in our previous studies.[6]

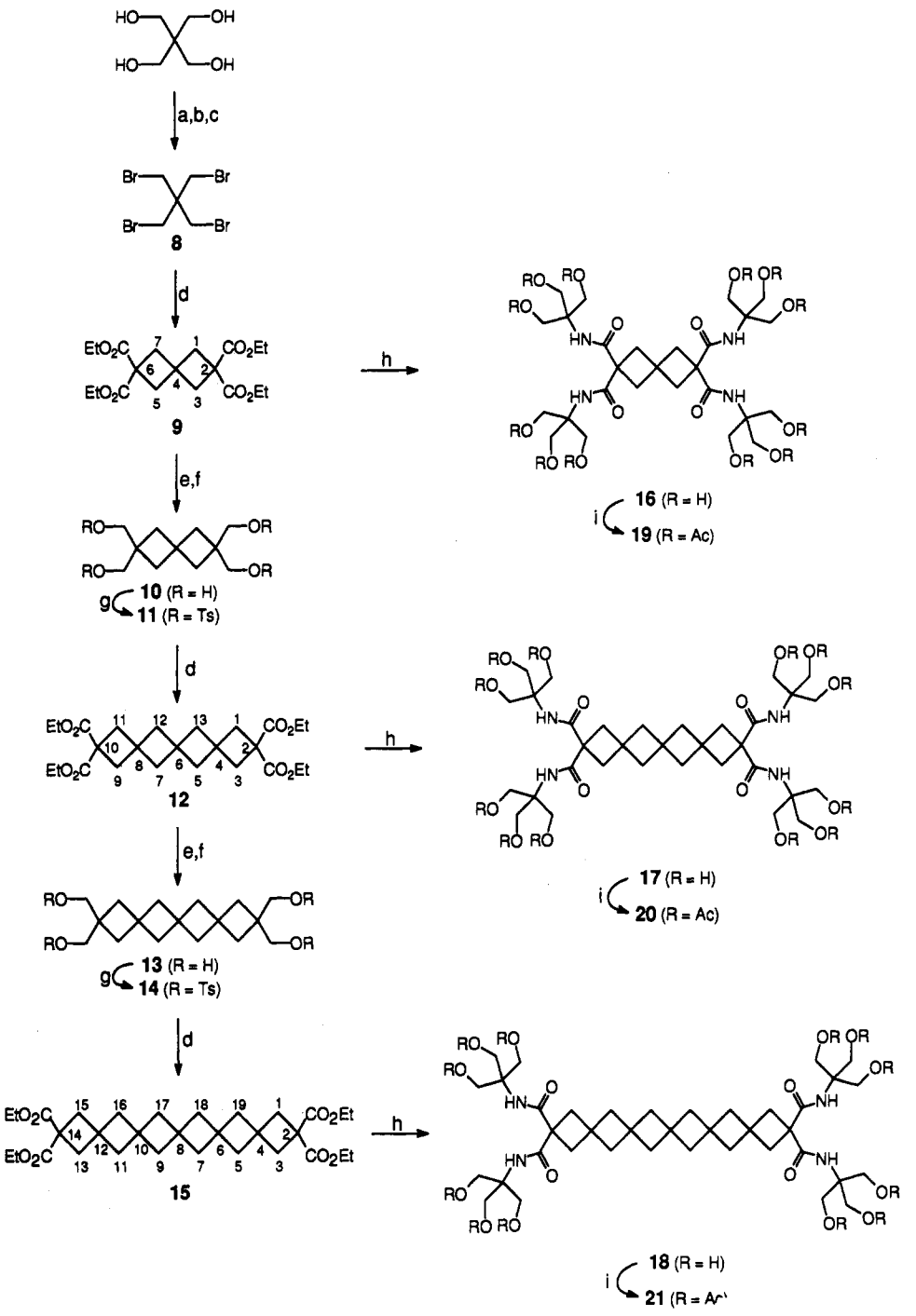
In comparing the biphenyl and spirane arborols to that of the gel-forming alkane arborols prepared earlier, some conclusions can be made based upon observations and the calculated values[22] (Table I) for these and related arborols. These calculated values represent several measures that can be used to compare the various synthesized, or planned, backbones. There appear to be three size parameters that have an influence on the gelation phenomenon: the length of the backbone, the diameter of the backbone, and the size of the terminal spheres. The length of the backbone was measured from branch point to branch point; in **15** (Scheme II), this would be from C2 to C14. The diameter of the backbone was obtained using a computed Connolly surface[23] measuring from the center of the backbone outward perpendicular to the long axis of the backbone to the edge of the surface and doubling this value. The surface area and the volume of the end spheres were calculated using an unattached end group. The values for surface area and volume for the nine and six terminal groups were used for each [9]-*n*-[9] and [6]-*n*-[6] system, respectively. The diameter of the backbone, overall surface area, and the volume of the terminal sphere provide a pivotal insight to their steric demands.

The spiranes are more sterically demanding than the related alkane series as evidenced by comparison of the

(22) The results published were generated using the programs CHARMm and QUANTA. These programs have been developed by Molecular Simulations, Inc. Karplus, M.; Kushick, J. N. *Macromolecules* **1981**, *14*, 325.

(23) Connolly, M. L. *Science* **1983**, *221*, 709.

Scheme II. Synthesis of Spirane Arborols



[a] Key: (a) anhyd pyr, $PhSO_2Cl$, 40 °C, 1 h; (b) HCl, H_2O, MeOH; (c) diethylene glycol, NaBr, 140–150 °C, 10 h; (d) $CH_2(CO_2Et)_2$, Na, xylene, reflux, 12 h; (e) $LiAlH_4$, anhyd THF, reflux, 10 h; (f) H_2O, NaOH; (g) TsCl, anhyd pyr, 36 h; (h) Tris, anhyd K_2CO_3, anhyd Me_2SO, 25 °C, 72 h; (i) pyr, Ac_2O.

backbone diameters; the spirane 18 (Figure 3, bottom) was determined to be about 0.8 Å larger than the related alkane spacer. This greater size does not allow the separate spirane units to approach close enough to maximize the hydrophilic and hydrophobic interactions, critical for aggregation. Another factor is the spirane's shorter length compared to the related alkane core. From our previous studies,[5] there appeared to be a range of spacer length to dumb-bell size in which gelation, or best fit, is favored. A similar pattern is seen in the biphenyl series of arborols. The biphenyl (Figure 3, top) has a backbone diameter approximately 0.6 Å larger than the corresponding alkane spacer. Again, the increased steric demand of the biphenyl prevents the units from aggregation; furthermore, the biphenyl core tends to be slightly shorter than the comparable alkane spacer.

These observations coupled with known physical results[24] for the biphenyl spacer suggest that a phenanthrene or pyrene[25] backbone (Figure 3, middle) would reduce the inherent nonplanar steric issues. Comparison of the

(24) Crystal data: Trotter, J. *Acta Crystallogr.* **1961**, *14*, 1135. Fischer-Hjalmars, I. *Tetrahedron* **1963**, *19*, 1805. Gas phase data: Almenningen, A.; Bastiansen, O. *Kgl. Norske Vid. Selsk. Skr.* **1959**, No. 4.

(25) Hazell, A. C.; Lomborg, J. G. *Acta Crystallogr.* **1972**, *B28*, 1059. Hazell, A. C.; Larson, F. K.; Lehmann, M. S. *Acta Crystallogr.* **1972**, *B28*, 2977. Camerman, A.; Trotter, J. *Acta Crystallogr.* **1965**, *18*, 636. Gramaccioli, C. M.; Filippini, G. *Acta Crystallogr.* **1983**, *A39*, 784.

Table I

arborol	backbone: length (Å)	backbone: min diam[a] (Å)	backbone: predicted gap (Å)	hydrophilic sphere: surface area (Å²)	hydrophilic sphere: vol (Å³)	minimized[b] (kcal/mol)	gel formation (yes/no)
[6]-8-[6][c]	11.52	4.8	4.69	265	254.4	−72.30	yes[d]
[6]-10-[6][c]	14.01	4.8	4.77	265	254.4	−333.50	yes
[6]-11-[6][c]	15.03	4.8	4.23	265	254.4	−283.49	yes
[6]-12-[6][c]	16.57	4.8	4.58	265	254.4	−64.82	yes
[6]-14-[6][c]	19.09	4.8	4.01	265	254.4	−58.82	yes[b]
[9]-8-[9][c]	11.69	4.8	3.78	356	985.1	−6.36	no
[9]-10-[9][c]	13.91	4.8	4.18	356	985.1	−540.95	yes
[9]-11-[9][c]	14.99	4.8	4.29	356	985.1	−531.78	yes
[6]-3-C≡C-3-[6]	11.21	3.8	4.47	265	254.4	−24.15[e]	yes
[6]-4-C≡C-4-[6]	13.73	3.8	3.41	265	254.4	−52.46[e]	yes
[6]-5-C≡C-5-[6]	15.81	3.8	3.74	265	254.4	−67.66[e]	yes
[6]-6-C≡C-6-[6][f]	18.81	3.8	3.94	265	254.4	−61.81[e]	yes
cis-[6]-4-CH=CH-4-[6][g]	10.14	4.2	6.81	265	254.4	−355.80	yes
trans-[6]-4-CH=CH-4-[6][g]	13.27	4.2	4.93	265	254.4	−338.05	yes
trans-[6]-6-CH=CH-6-[6][g]	18.77	4.2	4.05	265	254.4	−313.00	yes
spirane 18[h]	11.18	5.6	5.32	265	254.4	807.04	no
[9]-1-(2,7-phen)-1-[9]	12.27	3.8	4.02	356	985.1	−118.27	yes[i]
biphenyl 4[h]	11.99	5.4	5.58	356	985.1	328.97	no
[9]-1-(2,7-pyrene)-1-[9]	11.95	3.8	4.46	356	985.1	−260.59	yes[i]

[a] These values were obtained by generating a Connolly surface for the desired backbone. Doubling the measurement from the center of this backbone out to the edge of its surface provided the reported diameter. [b] These values were obtained from minimization of a stack containing four arborol molecules. The initial geometry oriented adjacent arborols in an orthogonal fashion with intermolecular (backbone) separations initially set at 4 Å (a typical value for these systems). After an initial minimization, a repetitive procedure was employed: the gap between arborol backbones was measured, the intermolecular spacing was slightly reduced, and this resulting arrangement was again minimized. This process was halted when no change in calculated energy was observed between iterations. This procedure avoided an observed tendency of the force field to terminate in a local energy minima and not the desired minimum intermolecular spacing. Other relevant backbone dimensions reported in Table I were obtained from this minimized arrangement. [c] Reference 6. [d] Minimal gelation. [e] Low values are apparently an artifact of the parameters used for the alkyne moiety. [f] Reference 5. [g] Moorefield, C. N., unpublished results. [h] This work. [i] Predicted based on these data.

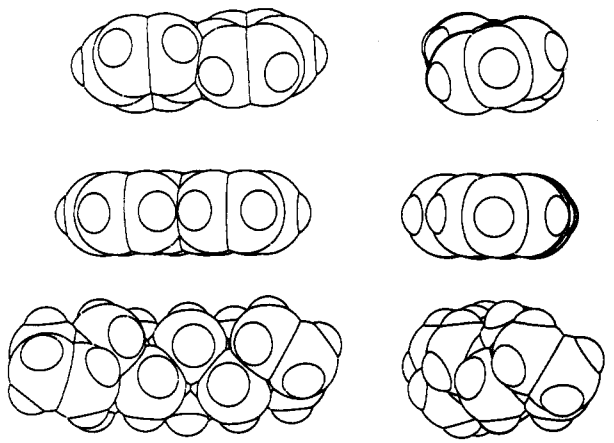


Figure 3. Comparative cross-sections and related end-views of biphenyl (top), phenanthrene (middle), and spirane (bottom) connecting linkages pictorially showing their molecular thickness.

biphenyl and phenanthrene spacers via molecular modeling helps to visualize these inherent differences. When the arborol is viewed down the long axis, the surface presented by the biphenyl has a circular cross-section, whereas the phenanthrene spacer has an oval cross-section with a major axis (diameter) of ca. 8 Å and a minor axis (diameter) of ca. 4 Å. This reduction in the symmetry of the spacer's surface would allow a closer approach along the minor axis of the phenanthrene. The length of the phenanthrene (ca. 12.3 Å) is longer than the [9]-8-[9] alkane arborol, which does not gel, but shorter than the [9]-10-[9] arborol, which does gel. The use of such spacers as phenanthrene (or pyrene) would permit confirmation of the prediction that [9]-1-(2,7-phen)-1-[9] should gel, thus affording further insight to the relationship of the length and diameter of the spacer in these two-directional arborols. Such an understanding would be a great aid in designing arborols for utilitarian purposes.

Conclusion

Results from modeling studies suggest that a pyrene or phenanthrene spacer should gel, based upon a comparison of the various steric parameters of these two systems with known gel-forming systems. In addition, the proposed pyrene and phenanthrene arborols have steric energies for an aggregate of four molecules, which are comparable to the other gel-forming systems, as calculated from the CHARMm force field. Using the energy calculations of an aggregation consisting of four (4) orthogonally stacked arborols (see Figure 1), it appears that there is a correlation between the steric energies of greater than −50 kcal/mol and their tendency to gel in aqueous medium. A positive steric energy value would be a fairly good predictor that the subunits preclude the close intermolecular approach necessary for gel formation. A larger library of two-direction cascade polymers needs to be prepared to test this observation and better understand the relationship of the steric parameters. Studies are in progress to probe the relevant relationships and to take chemical advantage of the lipophilic inner region within the resultant rodlike aggregate.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra (IR) were obtained on a Perkin-Elmer 621 grating infrared spectrometer. Mass spectra data were determined at the mass spectroscopy laboratory of Florida State University. NMR spectra were obtained in $CDCl_3$ solution, unless otherwise indicated. Elemental analyses were determined from M-H-W Laboratories (Phoenix, AZ).

Reagents. Solvents were purified by simple distillation, unless indicated otherwise. *N,N*-Dimethylformamide (DMF) was purified by the previous method[26,27] to ensure the absence of cyanide ion. Dimethyl sulfoxide (Me_2SO) was dried and stored over 3A

molecular sieves. Benzene was washed with concentrated H_2SO_4 and then water, dried ($CaCl_2$), distilled over metallic sodium, and stored over 3A molecular sieves. Pyridine was dried over KOH pellets, distilled, and stored over KOH. Tetrahydrofuran (THF) was refluxed over metallic sodium and then distilled from benzophenone ketyl immediately prior to use. Diethyl ether was refluxed over $LiAlH_4$ and then distilled immediately prior to use. Triethyl methanetricarboxylate,[28] 4,4'-dimethylbiphenyl (1),[10] 4,4'-(bromomethyl)biphenyl (2),[11] 3,3',5,5'-tetramethylbiphenyl,[12] and 3,3',5,5'-tetrakis(bromomethyl)biphenyl[13] were prepared via literature procedures.

A. Biphenyl Series. General Method A for Ester Formation. Diethyl α,α,α',α'-Tetrakis(ethoxycarbonyl)-4,4'-biphenyldipropanoate (3). A stirred DMF–benzene (20 mL; 3:2) solution of 4,4'-bis(bromomethyl)biphenyl (2) [mp 170–172 °C (C_6H_{12}) (lit.[11] mp 169.5–171.5 °C); 204 mg, 600 μmol], triethyl methanetricarboxylate (500 mg, 2.15 mmol), and anhydrous K_2CO_3 (300 mg, 2.17 mmol) was heated at 45–50 °C for 88 h. After cooling, the solution was filtered and concentrated in vacuo to give a residue, which was dissolved in benzene (40 mL). This benzene solution was washed sequentially with water (2 × 30 mL), aqueous NaOH (7.5%; 3 × 15 mL), and water (2 × 30 mL), dried ($MgSO_4$), and then concentrated in vacuo to give a light yellow oil, which solidified up standing overnight. The crude product was column chromatographed (SiO_2) eluting with EtOAc/C_6H_{12} (4:1) to afford (73%) the hexaester **3** as a colorless waxy solid: 282 mg; mp 79–80 °C; ^1H NMR δ 1.21 (t, CH_3, J = 7.1 Hz, 18 H), 3.55 (s, CH_2, 4 H), 4.21 (q, OCH_2, J = 7.1 Hz, 12 H), 7.39 (m, ArH, 8 H); ^{13}C NMR δ 13.4 (CH_3), 38.0 (CH_2), 61.8 (OCH_2), 66.6 (CCO), 126.3 (C2), 130.9 (C3), 134.6 (C4), 139.4 (C1), 166.5 (C=O). Anal. Calcd for $C_{34}H_{42}O_{12}$: C, 63.54; H, 6.59. Found: C, 63.33; H, 6.55.

General Method B for Amide Formation. N,N'-Bis[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-α,α,α',α'-tetrakis-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]-4,4'-biphenyldipropanamide (4). A mixture of hexaester **3** (116 mg, 180 μmol), Tris (144 mg, 1.19 mmol), and anhydrous K_2CO_3 (149 mg, 1.08 mmol) in anhydrous Me_2SO (20 mL) was stirred at 40–45 °C for 160 h. After filtration, the solution was concentrated in vacuo to give a residual oil, which was precipitated twice with H_2O/acetone to give (37.5%) arborol **4** as a white solid: 72 mg; ^{13}C NMR (Me_2SO-d_6) 34.6 ($ArCH_2$), 60.7 (CH_2O), 62.5 (CCH_2), 68.4 (CCCO), 126.5, 129.7, 131.3, 138.7 (C_{Ar}), 170.5 (C=O). Acetate. Anal. Calcd for $C_{46}H_{72}N_6O_{24}$: C, 50.55; H, 6.59; N, 7.69. Found: C, 50.46; H, 6.63; N, 7.65.

General Method C for Acetate Formation. A stirred mixture of the arborol (1 mmol), Ac_2O (10 mL), and pyridine (1 drop) was refluxed for 10 h. After removal of excess Ac_2O in vacuo, the residue was dissolved in $CHCl_3$ (20 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) then water (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude polyacetate, which was column chromatographed (SiO_2) eluting with EtOAc/petroleum ether (2:1) to afford (≈90%) the desired acetate: ^1H NMR δ ca. 2.10 (s, CH_3); ^{13}C NMR δ ca. 20.3 (CH_3), 62.2 (CH_2-OAc); IR (neat) 1740, 1670 cm^{-1}.

General Method D for Hydrolysis of Acetates. A stirred mixture of the polyacetate (500 μmol), NaOMe (1 mmol), and dry MeOH (5 mL) was refluxed for 10 h. The solvent was removed in vacuo to give a residual oil, which was acidified with aqueous acetic acid, concentrated in vacuo, and precipitated twice with H_2O/acetone to give (ca. 80–90%) the regenerated arborol as a white solid upon drying in vacuo.

Diethyl α,α,α',α',α'',α'',α''',α'''-Octakis(ethoxycarbonyl)-biphenyl-3,3',5,5'-tetrapropanoate (6). A stirred mixture of tetrabromide **5** [mp 203–206 °C (lit.[13] mp 206–208 °C); 50 mg, 950 μmol], triethyl methanetricarboxylate (182 mg, 780 μmol), and anhydrous K_2CO_3 (84 mg, 607 μmol) in anhydrous DMF (50 mL) was heated at 40 °C for 113 h. After workup (method A), the crude product (90 mg) was column chromatographed (SiO_2) eluting with EtOAc/C_6H_{12} (2:3) to afford (43%) dodecaester **6** as a colorless oil: 46 mg; ^1H NMR δ 1.12 (t, CH_3, J = 7.1 Hz, 36 H), 3.44 (s, CH_2, 8 H), 4.13 (q, OCH_2, J = 7.1 Hz, 24 H), 7.09, 7.19 (m, ArH, 6 H); ^{13}C NMR δ 13.6 (CH_3), 38.6 (CH_2), 62.0 (OCH_2), 66.8 (CC=O), 128.3 (C2), 131.5 (C4), 135.8 (C3), 140.4 (C1), 166.6 (C=O). Anal. Calcd for $C_{56}H_{74}O_{24}$: C, 59.46; H, 6.59. Found: C, 59.41; H, 6.69.

N,N',N'',N'''-Tetrakis[2-hydroxy-1,1-bis(hydroxy-1,1-bis-(hydroxymethyl)ethyl]-α,α,α',α',α'',α'',α''',α'''-octakis[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]biphenyl-3,3',5,5'-tetrapropanamide (7). A mixture of dodecaester **6** (111 mg, 98 μmol), Tris (158 mg, 1.307 mmol), and anhydrous K_2CO_3 (166 mg, 1.2 mmol) in dry Me_2SO (18 mL) was stirred at 45–50 °C for 96 h. After workup (method B), arborol **7** was isolated (55%) as a highly hygroscopic, light yellow solid: 109 mg; ^1H NMR (D_2O + 1% dioxane) δ 45.5 ($ArCH_2$), 60.6 (CH_2O), 62.6 (CCH_2), 69.6 (CC=O), 126.2, 128.6, 138.8, 141.2 (ArC), 169.6 (C=O). Acetate (method C). Anal. Calcd for $C_{80}H_{134}N_{12}O_{45}$: C, 48.44; H, 6.76; N, 8.48. Found: C, 48.61; H, 6.74; N, 8.53.

Spirane Series. Tetraethyl spiro[3.3]heptane-2,2,6,6-tetracarboxylate (9) was prepared (56%) from tetrakis-(bromomethyl)methane (**8**) [mp 155–157 °C (lit.[21] mp 156.5–158 °C)] with diethyl malonate: bp 168 °C (0.5 mm) [lit.[20] bp 163 °C (0.03 mm)]; ^1H NMR (Me_2SO-d_6) δ 1.26 (t, J = 7.1 Hz, CH_2CH_3, 12 H), 2.60 (s, $^4CCH_2^4C$, 8 H), 4.22 (q, J = 7.1 Hz, CO_2CH_2, 8 H); ^{13}C NMR (Me_2SO-d_6) δ 13.5 (CH_2CH_3), 32.5 (C4), 40.7 (C1,3,5,7), 47.7 (C2,6), 60.9 (CH_2CH_3), 170.8 (C=O).

2,2,6,6-Tetrakis(hydroxymethyl)spiro[3.3]heptane (10), obtained (65%) by the reduction of the tetraester **9** [mp 186–188 °C (EtOH) (lit.[20] mp 185–186 °C)], was esterified to give (95%) the crystalline tetratosylate **11**: mp 120–122 °C (PrOH; lit.[20] mp 121–122 °C).

Tetraethyl trispiro[3.1.1.3.1.1]tridecane-2,2,10,10-tetracarboxylate (12) was prepared (78%) by treatment of tetratosylate **11** with diethyl malonate by a known procedure:[20] bp 190 °C (0.7 mm) [lit.[20] bp 176–179 °C (0.01 mm)]; ^1H NMR δ 1.20 (t, J = 7.1 Hz, CH_2CH_3, 12 H), 1.92 (s, $^4CCH_2^4C$, 8 H), 2.51 (s, $CH_2^4CCO_2$, 8 H), 4.20 (q, J = 7.1 Hz, OCH_2, 8 H); ^{13}C NMR δ 13.8 (CH_2CH_3), 33.2 (C6), 33.7 (C4,8), 41.3 (C5,7,12,13), 47.5 (C1,3,9,11), 48.7 (C2,10), 61.1 (CH_2CH_3), 171.9 (C=O).

Tetraethyl pentaspiro[3.1.1.1.1.3.1.1.1.1]nonadecane-2,2,-14,14-tetracarboxylate (15) was prepared (67%) via a known procedure[20] from diethyl malonate and tosylate **14** (75%; mp 110–112 °C (PrOH) (lit.[20] mp 110–111.5 °C)], which was obtained from the corresponding tetraol **13** [80%; mp 223.5–225 °C (EtOH; lit.[20] mp 224–225.5 °C)]: bp >220 °C (0.5 mm) [lit.[20] bp 221–226 °C (0.01 mm)]; ^1H NMR δ 1.13 (t, J = 7.0 Hz, CH_2CH_3, 12 H), 1.79 (s, 7,9,17,18-CH_2, 8 H), 1.87 (s, 5,11,16,19-CH_2, 8 H), 2.40 (s, 1,3,13,15-CH_2, 8 H), 4.08 (q, J = 7.0 Hz, CH_2CH_3, 8 H); ^{13}C NMR δ 13.6 (CH_3), 33.7 (C6,7,8,9,10,17,18), 34.2 (C5,11,16,19), 41.3 (C4,-12), 47.5 (C1,3,13,15), 48.7 (C2,14), 60.8 (CH_2CH_3), 171.7 (C=O)].

N,N',N'',N'''-Tetrakis[2-hydroxy-1,1-bis(hydroxymethyl)-ethyl]spiro[3.3]heptane-2,2,6,6-tetracarboxamide (16). A mixture of Tris (1.26 g, 10.4 mmol), tetraester **9** (1.0 g, 2.6 mmol), and anhydrous K_2CO_3 (1.66 g, 12 mmol) in dry Me_2SO (5 mL) was stirred at 25 °C for 72 h. After standard workup (method B), arborol **16** was isolated (67%) as a white solid: 1.2 g; mp 100–140 °C dec; ^1H NMR (D_2O) δ 2.32 (s, $^4CCH_2^4C$, 8 H), 3.96 (s, CH_2OH, 24 H); ^{13}C NMR δ (Me_2SO-d_6) 31.8 (C4), 40.2 (C1,3,5,7), 51.4 (C2,6), 60.5 (CONHC), 62.5 (CH_2OH), 172.7 (CONH); IR (KBr) 3360, 2960, 2890, 1660, 1370, 1050 cm^{-1}. Acetate (method C): colorless oil; bp >200 °C (1 mm); ^1H NMR δ 2.10 (s, CH_3, 36 H), 2.49 (s, $^4CCH_2^4C$, 8 H), 4.40 (s, $^4CCH_2O$, 24 H), 6.68 (s, CONH, 4 H); ^{13}C NMR δ 20.3 (CH_3), 32.1 (C4), 41.7 (C1,3,5,7), 50.8 (C2,6), 58.0 (CONHC), 62.2 (CH_2OAc), 170.5 (CH_3CO), 171.9 (CONH); IR (neat) 1740, 1670 cm^{-1}. Anal. Calcd for $C_{51}H_{72}O_{28}$: C, 51.51; H, 6.10; N, 4.71. Found: C, 51.67; H, 6.19; N, 4.70.

A mixture of dodecaacetate **19** (300 mg, 250 μmol) and $NaOCH_3$ (30 mg, 550 μmol) in dry MeOH (5 mL) was refluxed for 10 h. After workup (method D), **16** was regenerated: 150 mg (87%).

N,N',N'',N'''-Tetrakis[2-hydroxy-1,1-bis(hydroxymethyl)-ethyl]trispiro[3.1.1.3.1.1]tridecane-2,2,10,10-tetracarboxamide (17) was prepared (method B) from a stirred mixture of tetraester **12** (800 mg, 1.72 mmol), Tris (833 mg, 6.88 mmol), and anhydrous K_2CO_3 (1.04 g, 7.5 mmol) in Me_2SO (5 mL) at 25 °C

(26) Trisler, J. C.; Feasier, B. F.; Wu, S.-M. *Tetrahedron Lett.* **1974**, 687.
(27) Newkome, G. R.; Robinson, J. M. *Tetrahedron Lett.* **1974**, 691.
(28) Lund, H.; Voigt, A. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 594.

for 72 h. After standard workup, **17** was isolated (60%) as a hygroscopic white solid: 200 mg; mp 108–150 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.21 (m, $^4°CCH_2{}^4°C$, 16 H), 4.02 (s, CH_2OH, 24 H), 6.45 (bs, CONH, 4 H); ^{13}C NMR (Me_2SO-d_6) δ 33.4 (C4,6,8), 40.4 (C5,7,12,13), 47.5 (C1,3,9,11), 51.8 (C2,10), 60.4 ($CONHCCH_2$), 62.6 (CH_2OH), 172.8 (CONH); IR (KBr) 3363, 2959, 1653, 1375, 1049 cm^{-1}.

Acetate **20** (method C): mp 115–116.5 °C; ^{1}NMR δ 1.97 (s, $^4°CCH_2{}^4°C$, 8 H), 2.09 (s, CH_3, 36 H), 2.44 (s, $CH_2{}^4°CCO$, 8 H), 4.40 (s, $^4°CCH_2O$, 24 H), 6.62 (s, CONH, 4 H); ^{13}C NMR δ 20.5 (CH_3), 33.2 (C6), 33.3 (C4,8), 42.3 (C5,7,12,13), 47.5 (C1,3,9,11), 51.4 (C2,10), 57.9 (CONHC), 62.3 (CH_2OAc), 170.6 (CH_3CO_2), 172.4 (CONH); IR (neat) 1738, 1670 cm^{-1}. Anal. Calcd for $C_{57}H_{80}N_4O_{28}$: C, 53.94; H, 6.35; N, 4.41. Found: C, 54.09; H, 6.36; N, 4.42.

A mixture of acetate **20** (500 mg) and NaOMe in absolute MeOH was refluxed for 10 h and then worked up (method D) to give (92%) the desired arborol **17**.

***N,N',N'',N'''*-Tetrakis[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]pentaspiro[3.1.1.1.1.3.1.1.1.1]nonadecane-2,2,14,14-tetracarboxamide (18)** was prepared (method B) by treatment of a stirred mixture of Tris (445 mg, 3.67 mmol), tetraester **15** (500 mg, 920 μmol), and anhydrous K_2CO_3 (550 mg, 3.98 mmol) in Me_2SO (5 mL) at 25 °C for 72 h. After workup, **18** was isolated as a white hygroscopic solid: 130 mg; mp 103–143 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.25 (m, $^4°CCH_2{}^4°C$, 24 H), 3.96 (s, CH_2OH, 24 H), 6.78 (bs, CONH, 4 H); ^{13}C NMR δ (Me_2SO-d_6) 33.1 (C6,8,10), 33.9 (C7,9,17,18), 34.4 (C4,12), 40.5 (C5,11,16,19), 47.7 (C1,3,13,15), 51.9 (C2,14), 60.5 ($CONHCCH_2$), 62.5 (CH_2OH), 172.8 (CONH); IR (KBr) 3360, 2965, 1661, 1380, 1050 cm^{-1}.

Acetate **21** (method C): mp 50–52 °C; ^{1}H NMR δ 1.96 (m, $^4°CCH_2{}^4°C$, 16 H), 2.10 (s, CH_3, 36 H), 2.46 (s, $CH_2{}^4°CCO$, 8 H), 4.44 (s, $^4°CCH_2O$), 6.02 (s, NH, 4 H); ^{13}C NMR δ 20.5 (CH_3), 33.2 (C4,6-10,12,17,18), 42.4 (C5,11,16,19), 47.7 (C1,3,13,15), 51.5 (C2,14), 57.9 (CONHC), 62.6 (CH_2O), 170.6 (CH_3CO), 170.7 (CONH); IR (neat) 1738, 1671 cm^{-1}. Anal. Calcd for $C_{63}H_{88}N_4O_{28}$: C, 56.07; H, 6.57; N, 4.15. Found: C, 55.89; H, 6.70; N, 4.12.

The arborol **18** was regenerated (90%) from **21** via Method D.

Gel–Solution-Phase Transition. Aqueous solutions of arborols **4**, **7**, and **16–18** (2–8 wt %) were prepared with the use of water from a three-stage Millipore R/Q water purifier. The solutions were heated to 90 °C and then cooled to 25 °C and allowed to stand undisturbed for 8 h. No gelation was visible even under prolonged time frames (up to 72 h).

Acknowledgment. This research was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (Grants DMR 89-06792; 92-17331).