

contrast, we propose that it is unnecessary to demonstrate that every event correlates with a resolution of better than 0.5 million years. We have anchored key stratigraphic levels (such as reflectors m1 to m4 and m6) to a precise chronology and report a similar number of events in both the margin and  $\delta^{18}\text{O}$  records, indicating that unconformities (sequence boundaries) correlate with glacioeustatic lowerings. By firmly dating the sequences and providing error estimates for these ages, we provide a template of Oligocene to Miocene sequences that will be compared with records from other margins.

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## Self-Assembling Dendrimers

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Hydrogen bond-mediated self-assembly is a powerful strategy for generating large structures from smaller subunits. The synthesis of molecules containing two isophthalic acid units covalently attached to a rigid aromatic spacer is described. By normal pairing of carboxylic acids into hydrogen-bonded dimers, these molecules self-assemble in organic solvents to form either a series of linear aggregates or a cyclic hexamer. These molecules were linked to the core of a family of polyether dendrimers, which caused the hexamer to be formed preferentially. The stability of the hexamer depended on the generation number of the dendrimer. The largest of these hydrogen-bonded macromolecular assemblies is roughly disk-shaped with a 9-nanometer diameter and a 2-nanometer thickness. Its size and molecular mass (34,000 daltons) are comparable to that of small proteins.

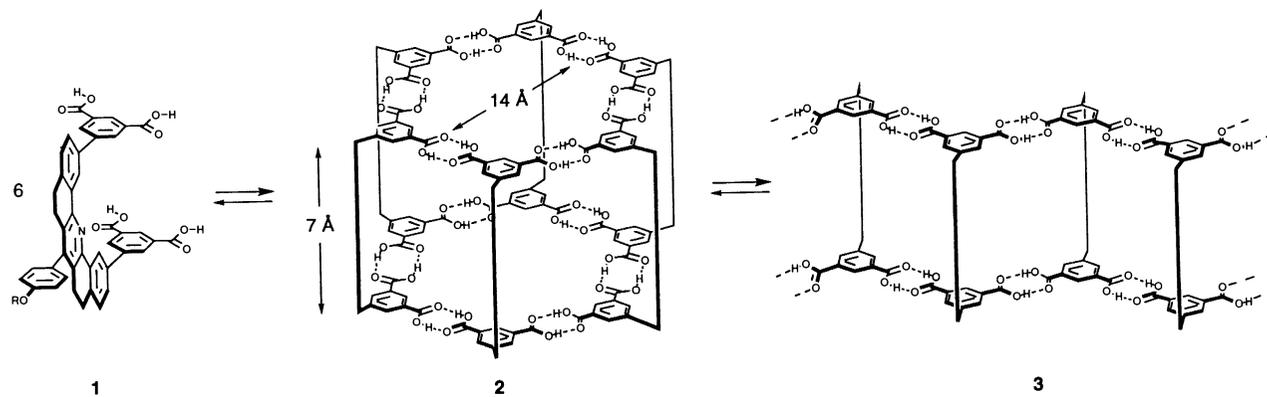
One of the hallmarks of biological organization is the noncovalent assembly of large structures from smaller subunits. The self-assembly strategy not only minimizes the energy invested in synthesis, it maximizes the accuracy with which the subunits can be produced, and therefore better guarantees the structural fidelity of the ultimate assembly. The same reasoning and principles have been applied recently to the construction of abiotic structures, where the chemical synthesis of compounds with nanometer dimensions remains a formidable challenge (1). Among the most notable nanoscale compounds synthesized to date are the dendrimers, a group of highly branched macromolecules

emanating from a central core to a periphery that becomes more dense with increasing generation number (2–5). A wide range of dendrimers have been prepared through iterative synthesis.

Dendrimers can be made in multigram quantities, and their large size and controllable peripheral functionality make them ideal building blocks for assembling larger nano- and mesoscopic structures in solution (2). For example, amphiphilic compounds wherein a hydrophobic dendrimer resides at one end of a hydrophilic polyethyleneoxide polymer aggregate in aqueous solution (4) and act as surfactants (6). Likewise, the hydrophobic linker in dumbbell-shaped arborols stack to form rod-shaped assemblies, resulting in gel formation in aqueous solution (7). Meijer and co-workers recently reported that dendritic block copolymers with amphiphilic character self-assemble to

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**Fig. 1.** Schematic representation of two possible hydrogen-bonded aggregates formed by **1**: cyclic hexamer **2** and linear oligomers **3**.

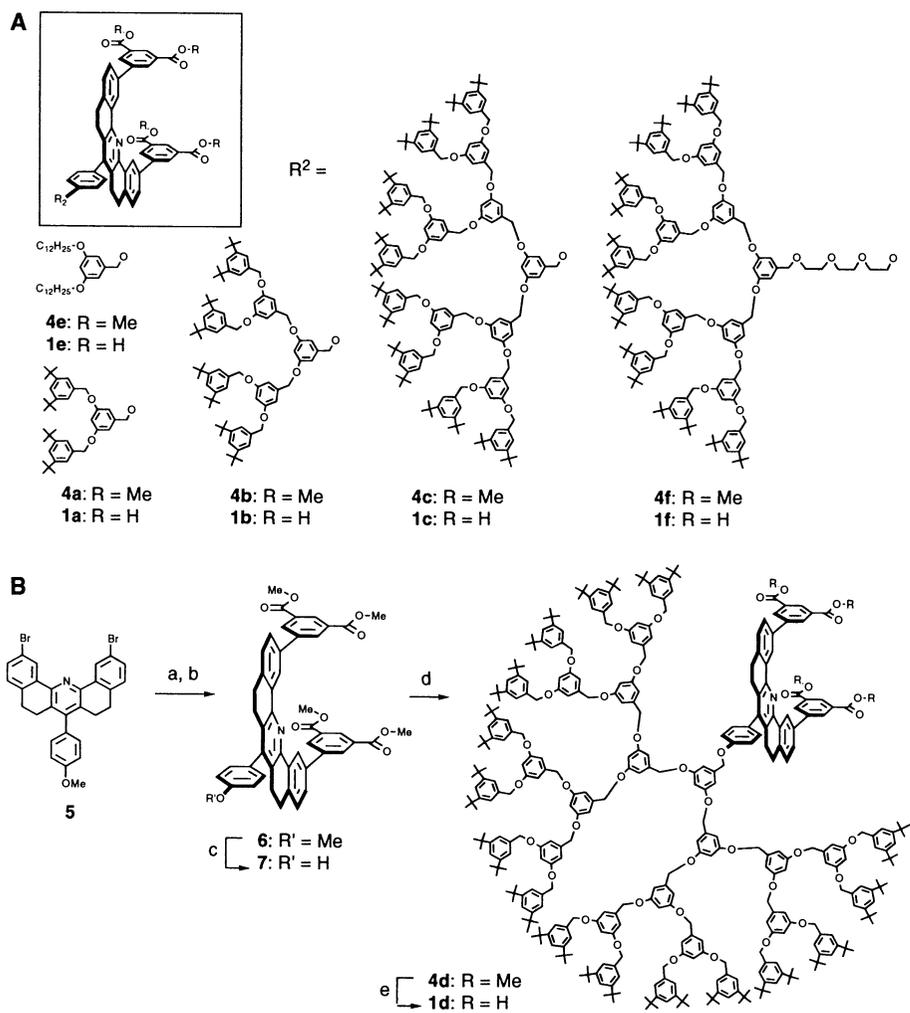
form both micellar and vesicular superstructures (8). We report that compound **1** (Fig. 1) self-assembles through hydrogen bonding to form a hexameric, dendritic aggregate whose stability varies in a generation-dependent manner (9).

By virtue of its two rigidly held isophthalic acid units, **1** was designed to form the cyclic, hydrogen-bonded hexamer **2**, which contains a significant internal void space (Fig. 1). Alternatively, a variety of polymeric aggregates might form (such as

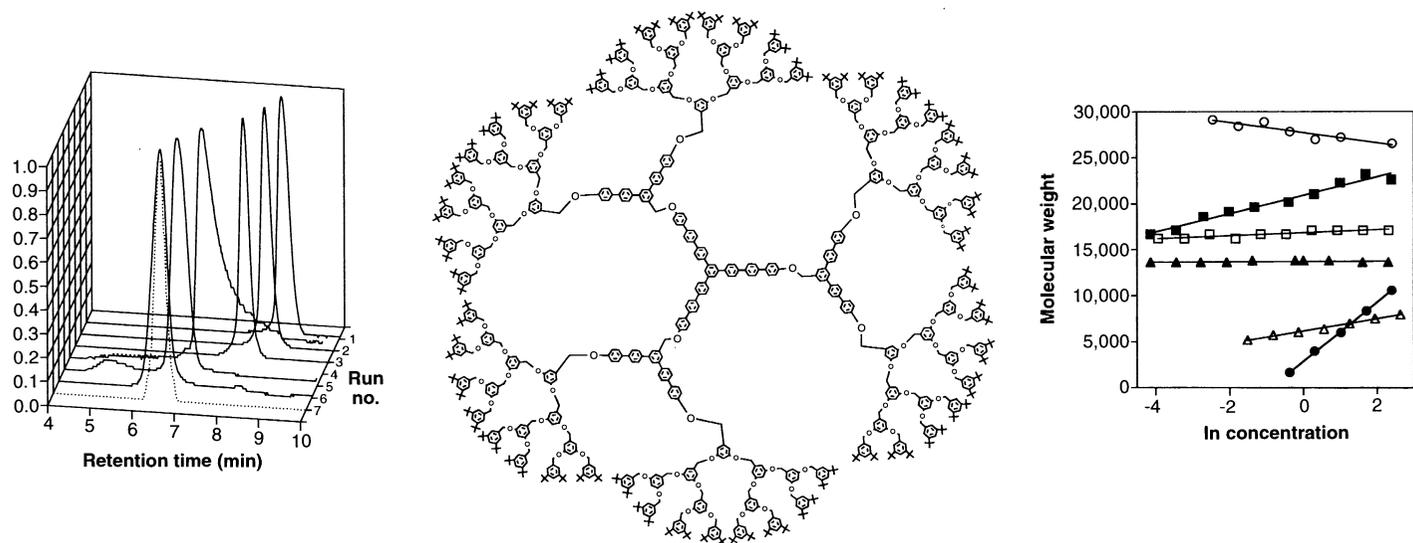
**3**), but these were expected to be enthalpically disfavored. The synthesis of the target molecules **1a** to **1d** was achieved by the convergent pathway illustrated for **1d** (Fig. 2B). Multigram quantities of **5** were available by a previously described route (10). Conversion to the bis-boronic acid and palladium-mediated coupling with dimethyl 5-iodoisophthalate afforded **6**, which was demethylated to **7** (11). This key intermediate was alkylated with a variety of benzylic bromides, including four generations of dendritic bromides constructed by a convergent approach similar to that used by Fréchet and co-workers (12). Di(*tert*)butyl groups residing on the surface of these polyphenylether dendrimers were chosen to render higher solubility to **1a** to **1d** in apolar organic solvents. These solvents were expected to compete weakly for the hydrogen bonding sites in solution studies.

The aggregation behavior of **1a** to **1d** and **4a** to **4d** was examined by size exclusion chromatography (SEC), vapor pressure osmometry (VPO), and laser light scattering (LLS). The aggregation of the acids in  $\text{CDCl}_3$  was clearly evident by the peak broadness in the  $^1\text{H}$  nuclear magnetic resonance (NMR) spectra. For the second-through the fourth-generation tetraacids (**1b** to **1d**), the signals corresponding to the protons of the aromatic spacer unit were too broad to be observed. When the more polar solvents dimethyl sulfoxide- $d_6$  (DMSO- $d_6$ ) or tetrahydrofuran- $d_8$  (THF- $d_8$ ) were used, the spectra of each tetraacid became sharp and well resolved and were in full agreement with assigned structures. These solvents are competitive with carboxylic acid dimer formation, and it was assumed that the compounds are monomeric in them. To test qualitatively the stability of the aggregate in chloroform solution, we titrated a  $\text{CDCl}_3$  solution of **1c** separately with DMSO- $d_6$  and with THF- $d_8$  at  $50^\circ\text{C}$ . The  $^1\text{H}$  NMR spectra were completely resolved when  $\sim 23\%$  (v/v) of DMSO- $d_6$  or  $64\%$  (v/v) of THF- $d_8$  was present.

SEC has become a widely used tech-



**Fig. 2.** (A) Structures of dendritic monomers **1a** to **1f**. (B) Synthesis of fourth-generation dendritic tetraacid **1d**. (a) *N*-butyl lithium, THF, followed by  $\text{B}(\text{OMe})_3$  (Me, methyl). (b) Dimethyl 5-iodoisophthalate,  $\text{Pd}(\text{PPh}_3)_4$  (Ph, phenyl); 65% yield, two steps. (c)  $\text{BBr}_3$ , 80% yield. (d)  $\text{K}_2\text{CO}_3$ , fourth-generation dendritic bromide; 65% yield. (e)  $\text{KOH}$ ,  $\text{H}_2\text{O}$ , THF; 94% yield.



**Fig. 3 (left).** Stacked SEC traces of **4a** (run 1), **4b** (run 2), **4c** (run 3), **1a** (run 4), **1b** (run 5), **1c** (run 6), and **8** (run 7, dotted line) normalized with arbitrary intensity units. Performed on a Waters Ultrastaygel HR3 column (MW range 500 to 30,000) in  $\text{CH}_2\text{Cl}_2$ . **Fig. 4 (middle).** Structure of dendrimer **8**, covalent analog of  $(1c)_6$ . **Fig. 5 (right).** SEC-determined

molecular weights of **1a** ( $\Delta$ ), **1b** ( $\blacktriangle$ ), **1c** ( $\square$ ), **1d** ( $\circ$ ), **1e** ( $\bullet$ ), and **1f** ( $\blacksquare$ ) as a function of injection concentration. All runs were performed in  $\text{CH}_2\text{Cl}_2$  except **1d** (toluene). An HR3 column was used to measure **1a**, **1b**, and **1e**; all other compounds were measured on an HR5E column (see Table 1 for details).

nique for characterizing macromolecular systems (13), and for studying organic supramolecular assemblies in particular (14). This technique is especially useful in the present study because of the large differences in hydrodynamic radii between the different monomers and between the monomers and their putative aggregates. Furthermore, the tetraesters **4a** to **4d** serve as excellent standards because they have nearly identical structures to the corresponding tetraacids **1a** to **1d**, but they should not aggregate. With  $\text{CH}_2\text{Cl}_2$  as the eluent, tetraacids **1a** to **1d** and tetraesters **4a** to **4d** showed two well-separated peaks, the tetraacids eluting earlier (Fig. 3) (15, 16). In contrast, the retention times of tetraacids **1a** to **1d** and their analogous esters **4a** to **4d** were nearly identical when THF was used as the eluent.

The experimental molecular weights (MWs) of **1a** to **1d** and **4a** to **4d** were determined from their SEC retention times; polystyrene (PS) standards were used for calibration (Table 1). For the tetraesters, the experimental values in both  $\text{CH}_2\text{Cl}_2$  and THF match the theoretical values well. The experimental MWs for acids **1a** to **1d** in  $\text{CH}_2\text{Cl}_2$  are within 20% of those calculated for hexameric aggregates, whereas in THF they are close to the monomer MWs. This result suggests that each of the tetraacids **1a** to **1d** forms hexameric aggregate **2** in  $\text{CH}_2\text{Cl}_2$  but is monomeric in THF, as was indicated by the  $^1\text{H}$  NMR studies.

The assignment of the aggregation state of **1a** to **1d** as hexamer is based on the appropriateness of the PS standards for calibration. Specifically, it is assumed that if an aggregate  $(1a \text{ to } 1d)_6$  and a PS standard

have the same radius of gyration, they will have comparable MWs (17). In spite of the close agreement between the calculated MWs for **4a** to **4d** and those determined by SEC, it was desirable to have a unimolecular analog of hexameric aggregate **2**. Thus, dendrimer **8** (Fig. 4) was synthesized (11) as a model of the hexameric aggregate formed by **1c**. The former has a MW of 16,932, which is near that of  $(1c)_6$  (MW of 19,062), but more importantly, molecular modeling suggested that the two structures have similar sizes and shapes. As seen in Fig. 3, the SEC retention times of **1c** and **8** are nearly identical. Indeed, the SEC peak for **1c** is only slightly broader than that for **8**, sug-

gesting formation of a discrete, hexameric aggregate with high stability.

The experiments described above indicate that **1a** is nominally a hexamer; however, unexpectedly, its SEC retention time was variable and the peak was significantly broader than that for **1c** and **1b**, with extensive tailing. This observation was more consistent with the formation of a nondiscrete or low-stability aggregate. One possible explanation is that the larger dendritic substituents cannot be accommodated in linear aggregates such as **3**, thus favoring hexamer **2** (18). The SEC peak shape for **3** should depend on concentration and show tailing from the terminal carboxylic acid

**Table 1.** Molecular weight determination. The SEC values were obtained on a Waters Ultrastaygel HR3 column (MW range 500 to 30,000) in  $\text{CH}_2\text{Cl}_2$  or THF. The VPO measurements were made at  $35^\circ\text{C}$  in  $\text{CHCl}_3$  with benzil as standard by means of a Gonotec Osmomat 070-SA osmometer. LLS was performed with a dual-angle laser ( $15^\circ$  and  $90^\circ$ ) PD2000 detector. The  $dn/dc$  values were measured off-line on a Wyatt Optilab 903 interferometric refractometer. FAB mass spectrometry was performed on a VG ZAB-SE instrument. No aggregates were detected.

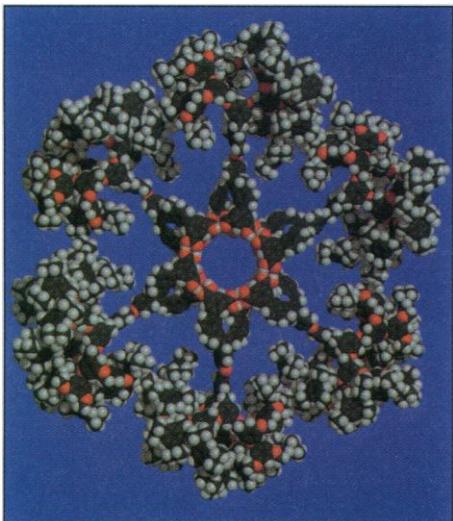
Compound	SEC				VPO $M_n$	LLS		FAB mass spec
	Theory*	Experiment		$M_w$		$dn/dc$		
		$\text{CH}_2\text{Cl}_2$	THF					
<b>4a</b>	1,285.6	1,570	1450				1,286.5	
<b>1a</b>	7,377.6	7,960 <sup>†</sup>	1340				1,230.6	
<b>4b</b>	1,935.0	2,280	2190		2,310	0.187	1,935.5	
<b>1b</b>	11,273.9	13,600	2130		39,500	0.189	1,879.9	
<b>4c</b>	3,232.9	3,500	3390	3,400	3,510	0.192	3,233.3	
<b>1c</b>	19,060.9	18,500	3410	15,600	49,600	0.175	3,198.0 <sup>‡</sup>	
<b>4d</b>	5,828.6	5,030	5160		5,800		5,831.9 <sup>§</sup>	
<b>1d</b>	34,610.9	28,300 <sup>  </sup>	4790		83,900			
<b>8</b>	16,932	16,200			18,600			

\*Exact masses of most abundant isotope. For **1a** to **1d**, values are for hexamers (six times exact mass of most abundant isotope of monomer). <sup>†</sup>Value was concentration-dependent; a 10 mM injection concentration was used. Other runs represent the average of multiple runs at different concentrations. <sup>‡</sup>Ion is  $\text{M} + \text{Na}^+$ . <sup>§</sup>Determined by MALDI. <sup>||</sup>Measured in toluene on a Waters Styragel HR5E column (MW range  $2 \times 10^3$  to  $4 \times 10^6$ ).

groups. Indeed, molecular modeling showed adjacent dendrimer attachment sites in cyclic hexamer **2** to be  $\sim 2.2$  nm apart and to diverge, whereas they are within  $\sim 1.5$  nm and parallel in linear, polymeric aggregate **3**. This latter distance is too small to accommodate the second- to fourth-generation dendrimers in **1b** to **1d**. To further explore this marked steering effect induced by remote substituents, we synthesized compounds **1e** and **1f** (Fig. 2).

The stability of all aggregates was analyzed by SEC as a function of the injected sample concentration. The retention times were recorded and converted to average MWs, which were then plotted against the natural logarithm of the injected concentration (Fig. 5). For **1a**, the average MW decreased with decreasing concentration, and the peak broadened. When the injected concentration was lower than 0.22 mM, the signal was too broad to monitor. The same response was observed with **1e** where the even greater concentration dependence is consistent with the smaller size of the 3,5-(didodecyloxy)benzyl group. For **1b** and **1c**, the retention time (MW) and sharpness of the peak remained essentially unchanged across the entire concentration range, providing additional evidence for a discrete aggregate of high stability. A large dendrimer alone is not enough to guarantee selective formation of **2**, because **1f**, a close analog of **1c**, gives a broad SEC peak and the MW was dependent on concentration (Fig. 5). Presumably the flexible triethylene glycol linker in **1f** allows a greater separation between the dendrimers in polymeric aggregates such as **3**.

Weight-average MWs ( $M_w$ ) were also determined by means of a dual-angle LLS



**Fig. 6.** Representation of one possible conformation of  $(1d)_6$  created with MacroModel. Molecular dynamics minimization was performed separately on the hexameric core and dendrimer substituents.

detector and a differential refractometer detector coupled to SEC (Table 1). All covalently linked dendrimers gave experimental  $M_w$  values close to the corresponding theoretical values. However, for tetraacids **1b** to **1d**, the MWs determined by light scattering were more than two times greater than expected for hexameric aggregates. Although we cannot rule out higher order aggregates, the SEC data, and particularly the comparison results with **8**, do not support such large structures. The origin of the high  $M_w$  values from LLS is not yet known, but there have been several reports of unexpectedly high MW measurements obtained for proteins and polysaccharides with various light-scattering methods, including multi-angle and low-angle LLS detection coupled to SEC (19). In these cases, the high  $M_w$  values were attributed to the presence of small quantities of higher MW aggregates or impurities.

Finally, the number average MW ( $M_n$ ) of **1c**, **4c**, and **9** (the third-generation dendritic bromide, which was used to convert **7** to **4c**; Fig. 2) was determined by VPO. With benzil as the standard, the  $M_n$  values measured for **1c**, **4c**, and **9** were 15,600, 3390, and 1700 g/mol, respectively, which agree reasonably well with their respective calculated values of 19,062 (hexamer), 3233, and 2554 g/mol (Table 1). Benzil is generally used as a standard because of its high purity and favorable solute behavior. When **9** and **4c** were used as standards, the  $M_n$  of **1c** was determined to be 23,400 and 14,800 g/mol, respectively, values which again are in the range expected for a hexamer.

The experiments described above show that hydrogen bond-mediated self-organization can be used to form mesomolecular dendritic assemblies with high stabilities and discrete structures. A molecular modeling study of  $(1d)_6$  showed a roughly disk-shaped aggregate with a 2-nm thickness and a 9-nm diameter (Fig. 6). The two cyclic arrays of isophthalic acid units within  $(1d)_6$  are  $\pi$ -stacked on one another in an off-set arrangement, which creates an overall helical arrangement of the spacer groups. Several peripheral aromatic rings on adjacent dendrimers are in close contact, suggesting that the overall stability of the assembly benefits from van der Waals interactions. Thus, the pronounced generation-dependent stability of  $(1a$  to  $1f)_6$  may originate in the subtle interplay between the favorable hydrogen bonding and van der Waals contacts and the unfavorable steric repulsion between proximal dendrimers in competing aggregates. Larger nanoscopic assemblies might be made wherein functional groups within the interior void could complex sizable molecules or catalyze chemical reactions.

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- Because of its high MW, **1d** was examined in toluene on an SEC column with a higher MW range. This precluded many direct comparisons with **1a** to **1c**.
- For example, Hawker and Fréchet reported that PS is a reasonable standard for small dendrimers (similar to **4a** to **4d**), but it underestimates the MW of dendrimers with higher generation numbers [C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.* **112**, 7638 (1990)]. Assemblies **1a** to **1d** are not expected to exhibit similar SEC behavior to dense dendrimers of high-generation number. The radius of gyration of each aggregate **1a** to **1d** determined with PS as the standard was close to the aggregate radius determined by molecular modeling. A similar finding was reported by Moore and co-workers for covalent dendrimers (5).
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