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Communications to the Editor

Starburst Dendrimers. 4. Covalently Fixed Unimolecular Assemblages Reminiscent of Spheroidal Micelles

It has been stated that aqueous micelles are "stable, disjoint, cooperative, closed equilibrium colloidal aggregates"[1] that possess topological order (an inside and an outside) and may be more accurately thought of as dimensionally discordant fractals.[2,3] A variety of ingenious models has been proposed to explain certain of these aggregate structures, and they include those proposed by Menger,[4] Franses,[1] Hartley,[6] Wennerström and Lindman,[7] Ninham,[8] Butcher[2] and Dill,[5] to mention a few. "Unfortunately, there is no direct method available to date for unequivocal determination of micellar structures",[9] although it is known that micellar size, shape[10] and structure[11,12] can dramatically affect the kinetics and course of reactions occurring in these microdomains. Currently, there is some controversy over micellar structure[13] and possible perturbation effects caused by introduction of probe (guest) molecules into these aggregates. For this reason, it would be of interest to mimic the fundamental parameters (i.e., size, shape, topology, and chemical functionality) associated with these microenvironments in a "covalently fixed" model. In our quest for such models, we examined molecular architecture possessing regular dendritic branching with radial symmetry, which we refer to as "starburst dendrimers". Their successful synthesis and characterization has allowed us to demonstrate the *controlled occupation of microspace in three dimensions as a function of size, shape, and disposition of desired organic functionality.*[14] More recently, Newkome and co-workers[15] have reported related "treelike" structures called arborols and compared them to micellar organizations, albeit without size or shape documentation. In this Communication, we wish to compare the properties of a series of starburst dendrimers (poly(amido amines)) with important spheroidal micelle criteria to see if they are consistent with such parameters as size, shape, quantization of head groups (aggregation number), head-group functionality, and topology.

Examples of covalently fixing (stabilizing) aqueous micelles into nonequilibrating unimolecular assemblies remains rare[16] if not uncertain at this time.[17] Unlike micelles, related assemblages such as liposomes (vesicles) have been successfully stabilized by polymerization[18] of unsaturated amphiphiles to produce a wide variety of "membrane mimetic" systems.[9]

A series of three directional dendrimers [A-E, core, NH_3; repeating unit, $-CH_2CH_2C(O)NHCH_2CH_2N-$; Z = $-CO_2Me$ or $-NH_2$] with projected two-dimensional branching patterns and empirical formula as shown in Chart I was examined. Inspection of the unimolecular dendrimer structures shows that they mimic the topology and discrete aggregation numbers noted for multimolecular micellar assemblies in that the number of dendrimer head groups (Z) is quantized as a function of generation A–E. Accumulation of Z groups per generation is equal to $N_cN_r^{G-1}$, where N_c is the multiplicity of the initiator core, N_r is the repeating unit multiplicity, and G is the generation (i.e., A $\equiv$ Gen = 2 $\rightarrow$ E $\equiv$ Gen = 6 with Z = 6 and 96, respectively, as shown in Table I).

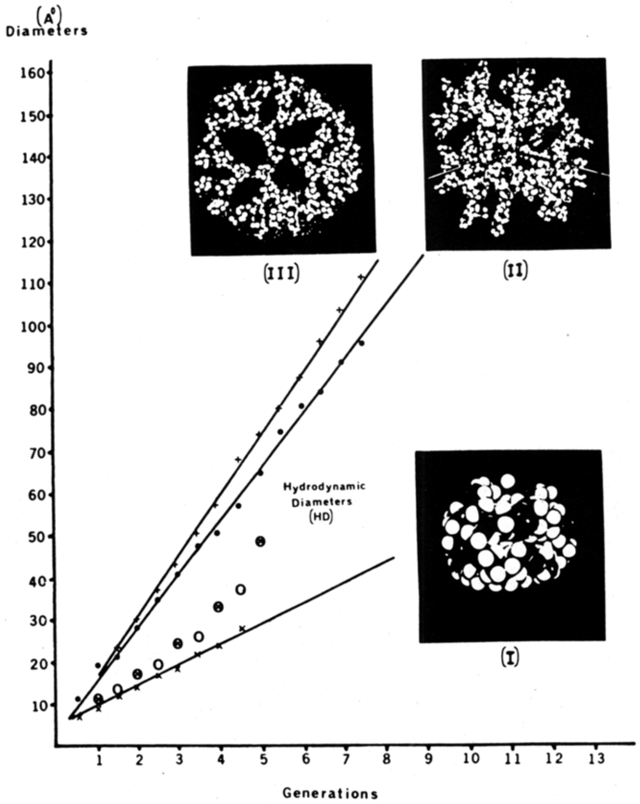

Figure 1. Comparison of starburst poly(amido amine) dendrimer hydrodynamic diameters (HD) vs. generation: (⊗) amine-terminated dendrimers, generations = 1–5; (○) carbomethoxy-terminated dendrimers, generations = 1.5–4.5. Comparison of CPK model measured diameters vs. generation: (×) form I, three-dimensional *contracted*, (●) form II, three-dimensional *extended*, (+) form III, two-dimensional *extended* (collapsed).

Scaled Corey–Pauling molecular models (Figure 1) were compared to hydrodynamic solution dimensions as well as electron microscopy measurements of individual dendrimer

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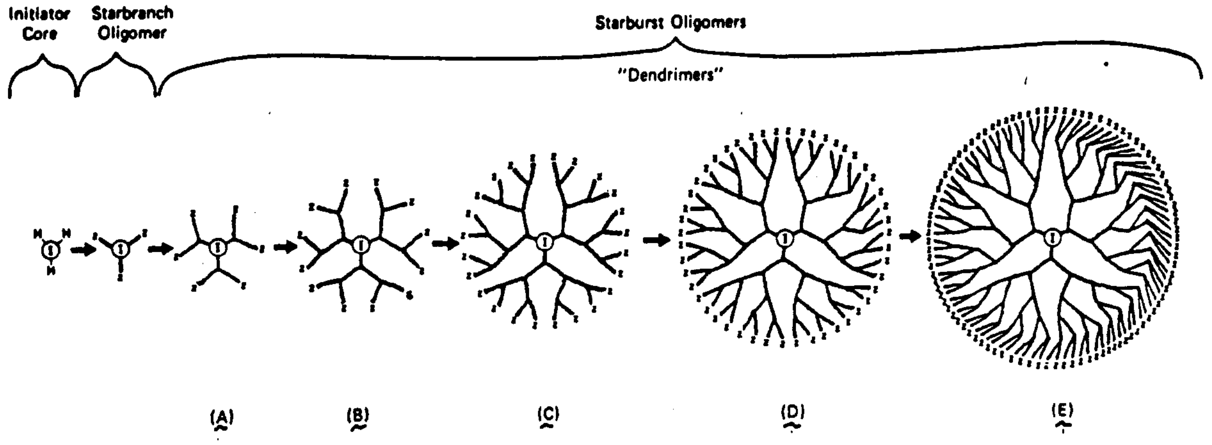
Chart I



$$N\left[(CH_2CH_2CONHCH_2CH_2N)_{\frac{N_r^G-1}{N_r-1}}(CH_2CH_2CONHCH_2CH_2\text{-}Z)_{\frac{N_r^G}{2}}\right]_3$$

Table I

Gen	Z	no. terminal groups	CPK model measd dendrimer diameters, Å I	II	III	hydrodynamic diameter, Å	$V_{HD} - V_I$ hollowness, Å^3
0.5	CO_2Me	3	8.0		9.6		
1.0	NH_2	3	9.6		20.0	11.4	311.6
1.5	CO_2Me	6	11.2	21.6	22.4	13.2	467.3
2.0	NH_2	6	12.8	28.8	29.6	17.0	1470.2
2.5	CO_2Me	12	16.0	35.2	34.4	19.6	1792.6
3.0	NH_2	12	17.6	41.6	43.2	24.4	4737.9
3.5	CO_2Me	24	22.4	48.0	49.6	25.8	3098.2
4.0	NH_2	24	24.5	51.2	57.6	33.2	11427.0
4.5	CO_2Me	48	28.1	57.6	68.0	37.6	16168.7
5.0	NH_2	48	30.5	65.6	73.6	49.2	47365.0
5.5	CO_2Me	96		75.2	80.0		
6.0	NH_2	96		81.6	86.4		
6.5	CO_2Me	192		84.8	96.0		
7.0	NH_2	192		91.2	104.0		
7.5	CO_2Me	384		96.0	111.2		
8.0	NH_2	384					

molecules. Molecular modeling measurements included both extended and contracted dendrimer forms. They are identified as (I) three-dimensional, *contracted* spherical; (II) three-dimensional *extended* spherical; (III) two-dimensional *extended* disk (Figure 1), and their dimensions are listed in Table I.

With intrinsic viscosity measurements (η), hydrodynamic diameters were determined in MeOH for both ester- and amine-terminated dendrimers; generations = 1.0–5.0 (Table I).[19] Plotting these values as a function of generation gave a linear relationship for generation = 1.0–3.5; however, noticeable upward (extended) deviation becomes apparent for generations = 4.0, 4.5, and 5.0. In comparison to the model measured, three-dimensional *contracted* (I) and three-dimensional *extended* (II) forms, these solution dimensions fall in an intermediate range with an apparent upward drift toward the extended form (II) as a function of generation. This suggests that the dendrimers are either becoming more effectively engorged (extended) by solvent or we are observing a sterically induced hollowness (extension) effect upon the topology, as proposed by de Gennes[20] and Maciejewski.[21] Preliminary evidence[22] suggests that the latter is occurring and steric interaction of the terminal Z groups is beginning to introduce hollowness to the advanced generations = 4.0, 4.5, 5.0, etc., which will ultimately reach a limit.[23] Plotting dendrimer surface areas (from hydrodynamic diameters, Table I) for each of the Z = $-CO_2Me$ (○) and Z = $-NH_2$ (⊗) series (Figure 1) against the quantized number of surface groups per generation gave linear relationships with correlation coefficients of 0.9971 and 0.9977, respectively.[19,22] The slopes, which are the individual terminal group (Z) surface areas, were 150 Å^2 (Z = $-NH_2$) and 92 Å^2 (Z = $-CO_2Me$), respectively. This indicates the dendrimers expand as a function of generation to maintain a constant terminal group surface area in each series. This introduces hollowness that can be estimated by [hydrodynamic volume (V_{HD}) − three dimension *contracted*, (V_I)], namely, ($V_{HD} - V_I$), as shown in Table I. Although this unique property is more characteristic for liposomes (vesicles) or "swollen micelles", it should be noted that these hydrodynamic diameters are much smaller and fall well within the traditional dimensions (30–60 Å) reported for classical aqueous micelles.[9]

Further dimension and shape corroboration of the dendrimer–micelle analogy was obtained by direct observation of individual dendrimer molecules via several electronmicroscopy techniques. Initial efforts to directly observe dendrimers (generations = 1.0–5.0 where Z = $-NH_2$ or $-CO_2Me$) were futile. A generation = 5.0 dendrimer (Z = NH_2) was examined by use of carbon and platinum–carbon shadowing techniques and found to be quite monodisperse with 85% of the particles measuring 42 ± 10 Å (see Figure 2) out of a total count of 127 particles.

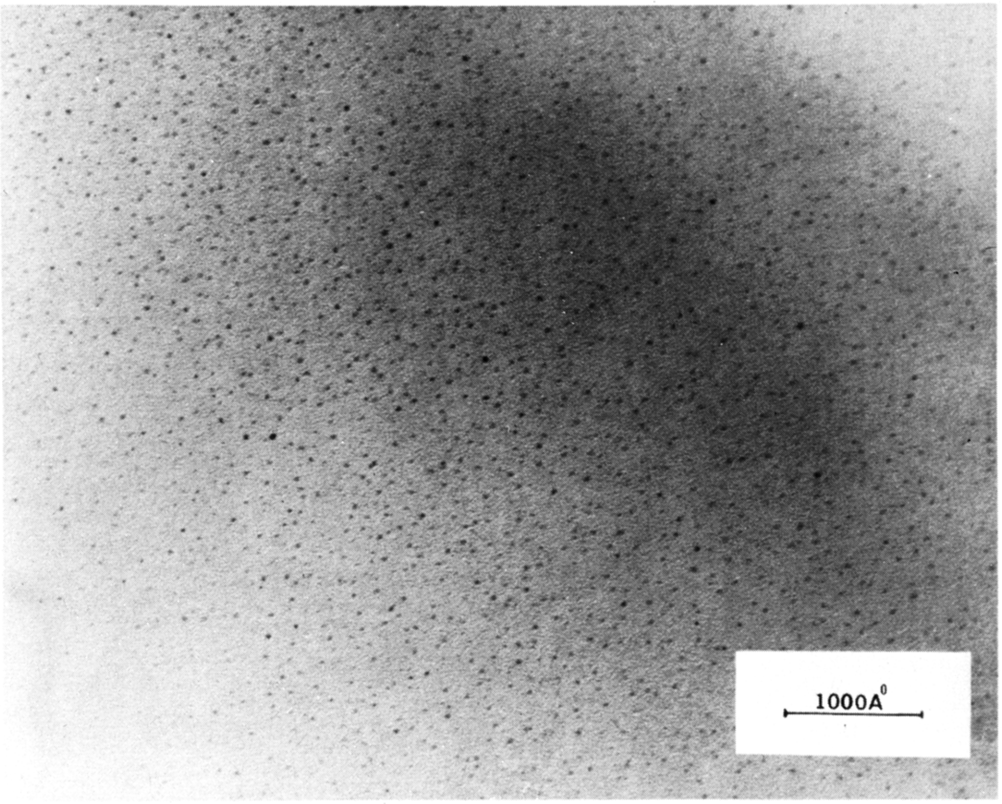


Figure 2. Electron micrograph of individual dendrimer molecules. Initiator core is NH_3; repeating unit is $-CH_2CH_2C(O)NHCH_2CH_2N<$; terminal group Z is $-NH_2$.

This dimension is relatively close to the hydrodynamic diameter of 49.2 Å, determined in MeOH, and falls well within the dimensional range predicted by CPK models for three-dimensional *extended* (II, 65.6 Å) and *contracted* (I, 30.5 Å) forms. In an effort to mimic the microenvironment of a micelle derived from an anionic amphiphile, a generation = 4.5 ($Z = -CO_2CH_3$) was carefully hydrolyzed with stoichiometric amounts of group I (1)[26] metal hydroxides to give hygroscopic white products possessing surface groups ($Z = CO_2^-M^+$, where $M = Na^+, K^+, Cs^+$, or Rb^+). For example, generation = 4.5 ($Z = -CO_2CH_3$) in MeOH was treated with a stoichiometric amount of 2.5 M NaOH at 25 °C for 4–8 h to give a viscous oil upon devolatilization. Dissolution in MeOH and precipitation with Et_2O gave a 98% yield of fine off-white powder. IR (KBr) 3350, 3240, 3190, 2920, 2810, 1640, 1560, 1400 cm^{-1}. NMR (D_2O) δ 3.32 (90 H, CONCH_2), 2.84 (276 H, CH_2N), 2.54 (186 H, COCH_2). Anal. Calcd for $C_{369}H_{577}O_{141}N_{91}Na_{48}\cdot 24H_2O$: C, 43.3; H, 6.44; N, 12.6. Found: C, 43.6; H, 6.51; N, 12.4. It was anticipated that the anionically charged surface of these dendrimers might force these arrays into extended forms such as II or III. Examination of the dendrimer (generation = 4.5; $Z = CO_2^-Na^+$) by CTEM very surprisingly revealed that individual dendrimer molecules could be observed directly without resorting to heavy-metal staining or shadowing techniques. A particle size count of the spheroids showed that they were highly monodisperse with 86% of the particles measuring 88 ± 10 Å out of a total count of 47 particles.[14d] Measurements (CPK model) obtained for the two-dimensional collapsed form (III) corrected for the coordinated sodium atoms compared favorably with a predicted dendrimer diameter of $\cong$78 Å.

The topological distinction that a micelle possesses an inside and outside, as described by Wennerström and Lindman,[7] has been demonstrated for the dendrimer model. Our earlier work[14c] has shown that chemical shifts of carbons in the interior of the dendrimers are largely insensitive to substitutions on the terminal portions of the dendrimer. It is believed that the concentric symmetry of dendrimers leads to anisotropic homogeneity around the interior. Consistent with this topology, relaxation times (T_1), as measured by the inversion recovery method, indicate that the interior carbons of the dendrimer are considerably less mobile than the exterior carbons. ^{13}C spin-lattice relaxation times for a variety of probe guest molecules (i.e., substituted benzoic acids) were determined according to the techniques of Menger[24] et al. for characterizing micelles. Dramatically decreased T_1 values for the probe molecules included in the dendrimer interiors vs. those in the bulk phase were observed.[25] This probe molecule behavior completely parallels that observed for micellar systems.

Furthermore, one can readily alter the hydrophobic character of the interior by utilizing more hydrophobic amines such as 1,6-diaminohexane, 1,3-diaminopropane, or 1,2-diaminopropane in place of 1,2-diaminoethane to more closely mimic an aqueous micelle. Likewise, the terminal surface groups (Z) can be converted to a wide variety of polar moieties (e.g., hydroxyl, quaternary amine, carboxylic, etc.). In conclusion, these dendrimers should offer unique micellar/liposome-like microenvironmental effects. Examination of parameters such as compartmentalization, preorientation, cage, localization, solubilization, polarity, and surface group/counterion-ion effects should be of considerable interest to organic chemists in their quest for novel catalysis and specificity media.

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(19) Hydrodynamic dimensions compared in this study were derived from intrinsic viscosity measurements reported in ref 14c. The Mark–Houwink coefficients were low (i.e., 0.19–0.20), thus supporting tight spheroidal structures. Dimensions calculated according to the Hester–Mitchell relationship (i.e., Hester, R. D.; Mitchell, P. H. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 1727) were used to determine hydrodynamic surface areas and volumes for the respective dendrimer generations.

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(23) Given a starburst dendrimer with repeating units of constant length, it is evident that exponential accumulation of terminal groups (Z) as a function of generation will eventually congest the surface to a point where ideality of the starburst branching will be diminished. This generation is referred to as the "starburst limit" (see ref 20). An account of this dendrimer behavior is forthcoming; Tomalia, D. A.; Hedstrand, D.; Meier, D., unpublished results.

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(25) This strongly supports the proposed micelle-like topology: Kiefer, G.; Tomalia, D. A., unpublished results.

(26) In this paper the periodic group notation in parentheses is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Groups IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the p-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the new numbering: e.g., III → 3 and 13.)

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Conformational Calculations on Poly(di-*n*-hexylsilane)

Substituted poly(di-*n*-alkylsilanes) have recently been the object of considerable attention[1–11] because of the applications potential embodied in their UV absorption characteristics. Alkyl-substituted polysilanes absorb at about 300–325 nm in solution,[1,2] the transition being attributed to a σ-bonded transition of the backbone silicon atoms. Films of poly(di-*n*-hexylsilane) (PDHS), on the other hand, show an absorption at 370–380 nm at room temperature.[2] Above 41 °C, the films absorb at the more typical 316-nm wavelength. Spectroscopic and X-ray diffraction studies[2,3,6,7] indicate that PDHS at room temperature is highly crystalline and that the backbone is in an all-trans, planar zigzag conformation. The long-wavelength absorption was attributed to the all-trans conformation, and the shift to shorter wavelength absorption was associated with a change in conformation, to either a conformationally disordered backbone structure or to an alternative regular conformation.[2,3,6,7]

X-ray diffraction studies[2,3,6,7] at room and elevated temperatures indicate that the structural transition is reversible on the time scale of the diffraction exposures (about 3 h). At room temperature, the structure is unusually well developed for a polymer, having sharp reflections out to 1.5 Å. Above the transition at 41 °C, the pattern consists of a single sharp diffraction maximum at about 13.5 Å. In fiber patterns, this reflection occurs on the zero layer and shows no significant broadening or elongation, even after prolonged periods above the transition temperature. Upon cooling to room temperature, the sample regains its remarkably well-ordered structure and remains highly oriented. These observations suggest a conformational change far less extensive than those typically associated with a melting phenomenon. Consideration of the severe steric crowding of the polymer due to the hexyl substituents on every backbone silicon atom further suggests a chain stiffness not readily amenable to major changes in the torsion angles. In order to elucidate the nature of the observed conformational transition, and thereby to provide information about the polymer conformation above the transition, semiempirical conformational energy calculations were undertaken for PDHS.

Full relaxation empirical force field calculations, as contained in the MM2 program, have recently been reported[10] for PDHS. Only all-trans, all-gauche, and trans–gauche backbone conformations were examined. A methylene group potential was used to describe the side chains, which were fixed in an all-trans conformation. The