et al. claim curvature. Clearly such curvature does not exist; neither therefore does the necessity to invoke kinetically significant triplet exciplex intermediacy.

It is also important to point out that aliphatic alcohols are much stronger bases than aromatic ketones.[5] It is therefore inconceivable that benzophenone ($\sim 10^{-2}$ mol L^{-1}) could compete with methanol (~ 25 mol L^{-1}) as an acceptor of a hydrogen bond from the naphthol triplet. What is to be anticipated, however, is that the H-abstraction process under consideration would be hindered by methanol hydrogen bonding. In agreement with this conclusion, the plot in Figure 1 yields a rate constant for H-abstraction of 2.2×10^7 L mol^{-1} which is 2 orders of magnitude smaller than the corresponding value for benzene, 3.2×10^9 L mol^{-1} s^{-1}.[2,6]

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Starburst Dendrimers. 3. The Importance of Branch Junction Symmetry in the Development of Topological Shell Molecules

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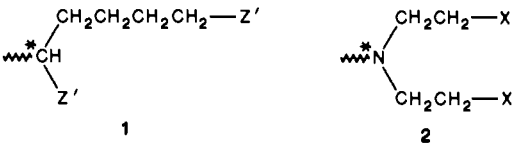
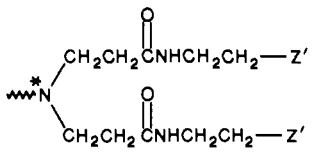
A theoretical report by Maciejewski[1] proposed that XRY_n type monomers (where $n = 2$) should lead to hollow, "shell-like" globular molecules if allowed to propagate to a cascade branched structure. The topology and dimensions of these proposed structures were of particular interest to us in that they appeared to be "covalently fixed" mimics of micelles yet they possessed unique hollow interiors usually associated with liposomes (vesicles).[2a-c] Denkewalter et al.[3] synthesized a series of lysine-derived globular structures which fit Maciejewski's criteria; however, they possessed unsymmetrical and unequal branch segments as illustrated by **1**.



1

2



3

Z' = NH_2, X = CO_2Me, * = branch juncture

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(2) (a) Calvin, M. *Acc. Chem. Res.* **1978**, *1*, 369. (b) Kunitake, T.; Okahata, Y.; Shimomura, M.; Yasunumi, S.; Takarabe, K. *J. Am. Chem. Soc.* **1981**, *103*, 5401. (c) Akimoto, A.; Dorn, K.; Gros, L.; Ringsdorf, H.; Schupp, H. *Agnew. Chem., Int. Ed. Engl.* **1981**, *20*, 90.
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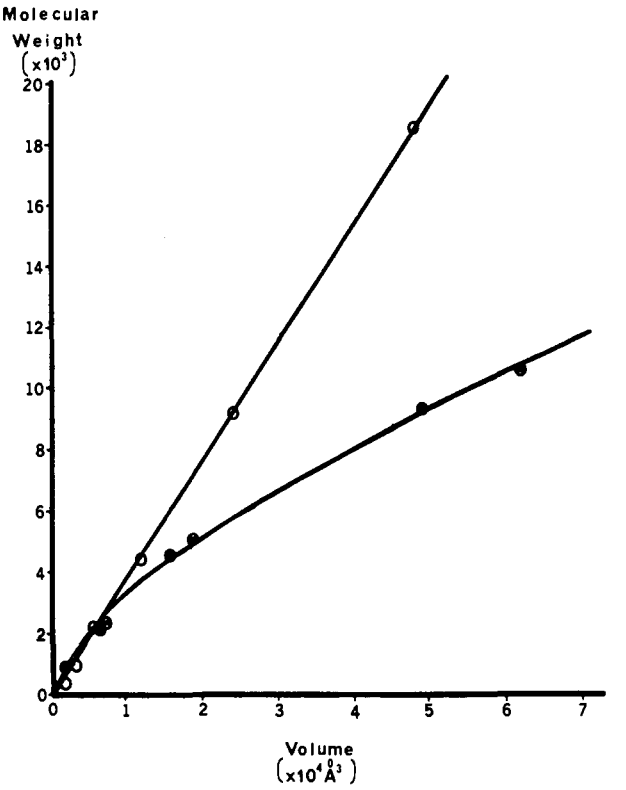

Figure 1. Comparison of the relationship between volume and molecular weight of Denkewalter cascade molecules (○) and starburst dendrimers: (●) ester-terminated dendrimers (**2**); (⊗) amine-terminated dendrimers (**3**).

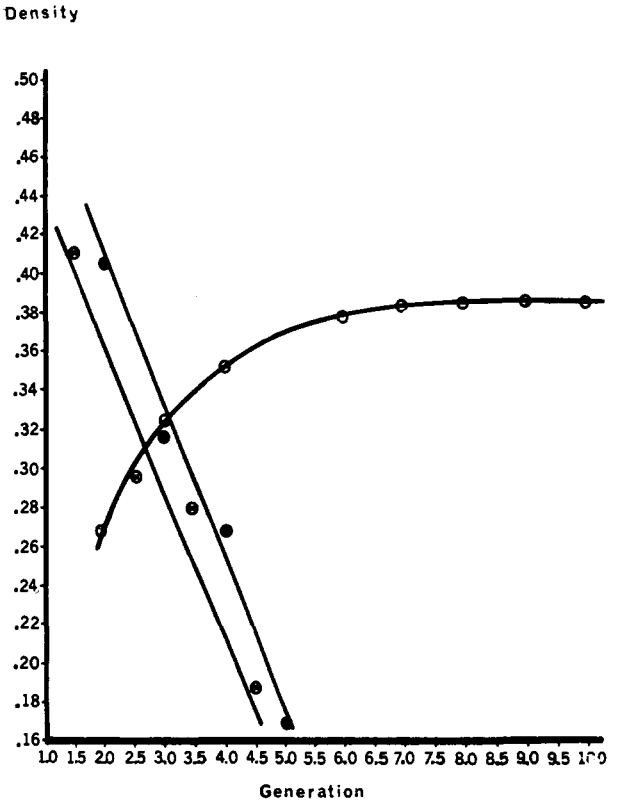

Figure 2. Concentration (amu/Å³) of polymer within solvent-filled microdomains of Denkewalter cascades (○) and starburst dendrimers: (⊗) ester family (**2**); (●) amine family (**3**).

Recently, we reported the synthesis[4a-e] of radially symmetrical three-directional molecules, coined "starburst dendrimers", with

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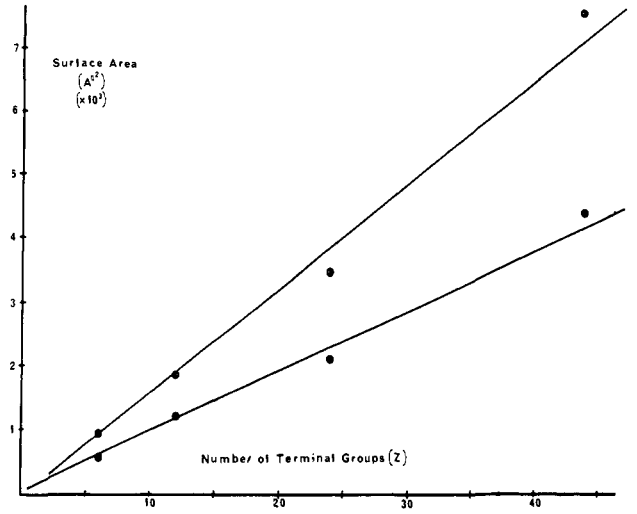

Figure 3. Dependence of starburst dendrimer surface areas on the number of surface groups: (⊗) amine-terminated dendrimers (**3**); (●) ester-terminated dendrimers (**2**).

branching junctures as shown in **2** and **3**. These dendrimers are globular structures consisting of concentric tiers (generations) of β-(carbomethoxyethyl), **2**, or β-alanine, **3**, units symmetrically branched through their terminal nitrogens, thus introducing both multiplicity and segment replication (tier to tier), in a geometrically progressive fashion. More recent work by Newkome et al.[5a,b] produced cascade molecules which possess branch multiplicity adhering to a geometric progression, are symmetrically branched, but lack segment replication tier to tier. Although the branching pattern in the Denkewalter series (Figure 4, branching pattern A) follows a mathematical progression, that series differs from the present starburst dendrimers and Newkomes's molecules in that the latter two systems possess symmetry and equal segmented branch junctures as shown in Figure 4 (branching pattern B). Quite surprisingly, work by Aharoni et al.[6a] on the Denkewalter series showed that those macromolecules were dense, nondraining spheres exhibiting no evidence of shell-like topology or hollowness with hydrodynamic volumes that varied linearly with molecular weight (MW). This relationship, indicated by ○, can be seen in Figure 1 and curve fits to the equation MW = $0.383V$(hydrodynamic) (where V = volume). In contrast, hydrodynamic volumes ● and ⊗ for the symmetrical starburst dendrimer series[6b] (generations = 1–5) varied in an exponential fashion with molecular weight (radial accumulation of monomer units) for both the ester-terminated (X = CO_2Me) as well as the amine-terminated (Z = NH_2) families. The ester family (●) fits the equation MW = $6.84V_x$(hydrodynamic)$^{2/3}$ with a correlation coefficient of 0.997, whereas the amine family (⊗) fits the equation MW = $6.78V_z$(hydrodynamic)$^{2/3}$ with a correlation coefficient of 0.998. Densities computed from hydrodynamic dimensions and molecular weights (Figure 2) should be constant with increasing

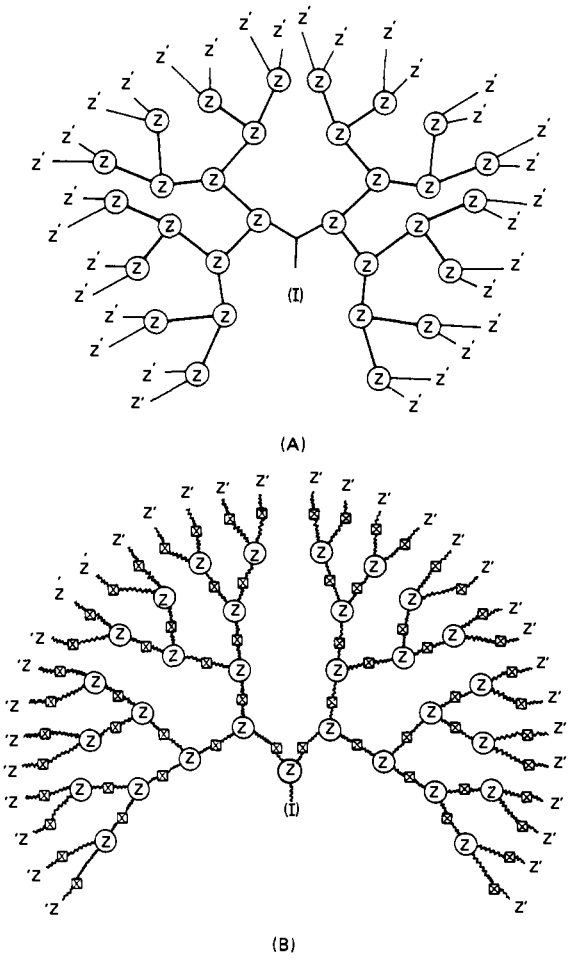

Figure 4. Unidirectional branching patterns for dendrimers possessing unsymmetrical branch junctures (A): Ⓩ = interior branch junctures * as designated in **1**; Z′ = NH_2. Symmetrical branch junctures (B): a crossed square = amide linkages derived from **2**; Ⓩ = branch junctures * as designated in **2** and **3**; Z′ = NH_2.

generation in the Denkewalter series (at the value 0.383 amu/Å^3, the slope in Figure 1).

The starburst dendrimers, in contrast, exhibited a steady decrease in density within each family approaching values of ≃0.18–0.16 amu/Å^3 for generations = 4.5 (ester terminated, **2**) and 5.0 (amine terminated, **3**), as per Figure 4 (pattern B). Comparing the hydrodynamic surface areas of the symmetrical dendrimers against the number of terminal groups (generations) showed that the surface area varied linearly within each family (Figure 3). *Quite remarkably, the dendrimers appear to expand three-dimensionally in order to maintain a constant terminal group surface area as the number of X* or *Z groups accumulates per generation.* From the slopes in Figure 3, it was found that the ester groups (**2**, X = CO_2Me) required 93 Å^2/X group whereas the amino groups (**3**) required 150 Å^2/Z groups. These data indicate that the branched form (**3**) is inducing more hollowness per generation than branch form **2**. This suggests that terminal groups with greater steric bulk may enhance the degree of hollowness per generation by steric interaction at the dendrimer surface. A comparison (Figure 4) of the Denkewalter cascade branching scheme (pattern A) with the starburst dendrimer (pattern B) suggests that a combination of steric bulk and packing inefficiency may be key parameters to this induced hollowness in pattern B, whereas the packing efficiency (staggering of surface groups) of pattern A leads to little or no hollowness in the development of its globular structure. It also follows that since the maximum possible radial dimensions of pattern B are increasing in a linear fashion per generation, whereas the number of surface groups is increasing exponentially, a so called "starburst limited" generation should ultimately be reached. According to deGennes[7]

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(6) (a) Aharoni, S. M.; Crosby; C. R., III; Walsh, E. K. *Macromolecules* **1982**, *15*, 1093–1098. (b) The hydrodynamic dimensions compared in this study were derived from intrinsic viscosity measurements as reported in ref. 4c. Dimensions calculated according to the Hester–Michell relationship (i.e.: Hester, R. D.; Michell, P. H. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 1727–1738) were used to determine hydrodynamic surface areas and volumes for the respective dendrimer generations.

branching ideality and stoichiometry should be diminished at this generation due to unique packing-induced steric interactions. Preliminary evidence has shown that this may indeed occur.[8]

In conclusion, the synthesis of topological shell molecules has been demonstrated and substantiated by physical measurements. Their development is dramatically affected by the branch juncture symmetry and presumably results from inefficient surface packing. These novel entities should be of immense interest in that their hollowness is reminiscent of a covalently fixed liposome yet their dimensions, shape, and topology are very much like that of a micelle. This latter analogy has been examined in our laboratory and will be reported shortly.[9]

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Synthesis of (−)-Vindoline

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We report a chirospecific synthesis of (−)-vindoline ((−)-**1**),[1] the most abundant alkaloid isolated from *Catharanthus roseus*, a highly oxygenated indoline which is part of the potent oncolytic agent vinblastine.[2,3] Several syntheses of (±)-**1** have been reported,[4] all of which use linear sequences beginning with 6-methoxytryptamine, or a similar compound, and construct upon it the remaining carbon framework of **1**. Recently, we reported a convergent route to vindoline in which tetrahydroquinolinate **2**, the E-ring precursor of **1**, was synthesized in enantiomerically pure form from L-aspartic acid.[5] Coupling **2** with 6-methoxytryptophyl bromide (**3**), itself prepared from *p*-cresol,[6] gave **4**, which was converted to quinolizine **5**α/**5**β (1/3.9) by using an α-amino acid decarbonylation iminium ion cyclization. Subsequent transformation of this mixture to (−)-**1** was to proceed via the precedented thionium ion promoted skeletal rearrangement to generate **8** from **7**.[4c] However, an intervening reversible Mannich reaction in the execution of this step led to racemic **8**[5] (see route A, Scheme I).

To avoid this racemization, a modified hexahydroindoloquinolizine was needed for the skeletal rearrangement. An attractive alternative substrate would be one in which the carbon α to the C-15 carbonyl is nucleophilic and would inhibit delocalization of the N_b lone pair of electrons into the carbonyl. This strategy, as opposed to that of route A, reverses the role of C-14 (electrophile to nucleophile) and C-2 (nucleophile to electrophile) during the skeletal rearrangement and makes the C-15 oxo function much less likely to participate in the racemizing reverse Mannich reaction. Methodology for applying this concept followed from a recent report describing the synthesis of hexahydropyrrolidino[2,3-*d*]carbazoles from tetrahydro-β-carbolines.[7] Since these transformations are initiated by intramolecular attack of a stabilized anion onto the electron-deficient C-2 of a chloroindolenine, β-keto ester **11**α was the ideal substrate. As applied to vindoline synthesis, it provides a stabilized anion as well as the functionality for extension to **1**.

Attempts to synthesize **11**α via a Claisen condensation of **5**α with methyl lithioacetate failed due to facile lactam formation that generated **6** in high yield. Successful synthesis of **11**α was effected via an intramolecular condensation followed by lactam methanolysis. This strategy avoided the problems of bringing an external nucleophile into the congested environment of the ester and protected the indole nitrogen during Dieckmann cyclization. The two-step protocol commenced with acetylation of **5**α (400 mol % KH, DMF, 0 °C, 20 min, 400 mol % Ac_2O; 55%, 85% based on recovered **5**α followed by Dieckmann condensation (225 mol % LDA/THF, −78 °C, 30 min; 0 °C, 15 min). Lactam **10**α was not isolated but was opened in situ (1000 mol % 1 M NaOMe/MeOH, 23 °C, 1 h) to **11**α (73% yield after chromatography on silica gel deactivated with TEA[8]). Exposing **11**α to silica gel without TEA yielded a small amount of **11**β believed to be formed by an acid-catalyzed reversible Mannich reaction. Epimer **5**β was not transformed to **11**β; rather, it was converted to **5**α by equilibration to an easily separable 3.6/1 mixture of **5**α/**5**β (TFA[8], Δx, 2 h, 91%).[5] β-Keto ester **11**α is the desired epimer for subsequent rearrangement, since its C-3 stereochemistry provides the correct C-19 stereochemistry in **12**.[9] Thus conversion of **11**α to **12** was accomplished in 75% yield with one recycle (90 mol % *t*-BuOCl,[10] CH_2Cl_2, 0 °C, 5 min/300 mol % DBU,[8] 0 °C, 20 min). The order of addition of *t*-BuOCl and DBU was crucial to the success of the reaction, since simultaneous addition of the reagents gave a small amount of **13** and mostly material bis chlorinated at C-14 of the chloroindolenine.

To test the configurational integrity of the transformation **11**α to **12**, **12** was converted to the known vindoline degradation product **17**.[1,4b] With $NaCNBH_3$ (800 mol %)/(TFA/MeOH, 1/10), 23 °C,[4c] imine **12** was rapidly isomerized to the more polar enamine, which was slowly reduced to **14**. N-Methylation of **14** with aqueous H_2CO (1000 mol %)/$NaCNBH_3$ (300 mol %)/(HOAc/CH_3CN, 1/10), 23 °C,[11] generated **15** in 85% yield from **12**. Hydrogenation of the E-ring double bond using H_2 (50 psi)/MeOH/HOAc gave **16**, which was subsequently decarbomethoxylated[12] (LiCl (1000 mol %)/Me_2SO/H_2O/ 150 °C, 25 min) to **17**. The optical rotation of **15** was the same as the reported value, within experimental error; however, unambiguous proof of

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(9) The mechanism postulated for the transformation of **11**α to **12** follows from the discussion given in ref 7. After chloroindolenine formation, the anion of the β-keto ester attacks the imine carbon, C-2. Subsequent Wagner–Meerwein rearrangement of the C-2–C-3 bond to C-12 (vindoline numbering) with concomitant chloride expulsion gives **12**. Since Wagner–Meerwein rearrangements proceed with retention of stereochemistry at the migrating carbon, the C-3 stereochemistry in **11**α determines the configuration at C-19 of **12**.
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