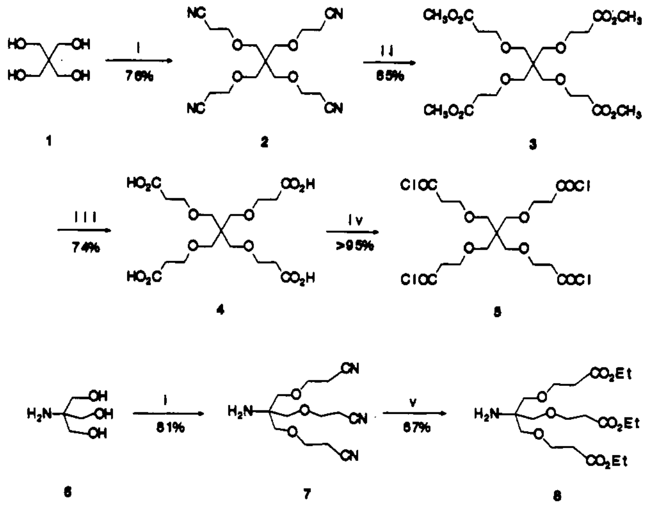
Symmetrical, Four-Directional, Poly(ether–amide) Cascade Polymers[1]

Since Vögtle et al.[2] reported the first synthesis of a "cascade" molecule over a decade ago, the field has attracted increasing attention[3–8] and importance.[9] The construction of high molecular weight, symmetrical, highly branched, and polyfunctional cascade polymers has expanded the meaning of supramolecular chemistry.[10] Appropriate selection of the cascade core, building blocks (monomers), and stepwise reiterative reactions defines the key properties of the types of cascade polymers (i.e., size, shape, and porosity, as well as internal and surface functionality). To date, major emphasis has been centered on the construction of these spherical cascades, although preliminary efforts to generate alternate shapes have been reported.[11]

Thus far, most cascades have been successfully synthesized with only a single type of internal functionality. Since few multi-internal-functionality cascades have yet been reported, we herein report a convenient way to synthesize a new series of difunctional global cascade molecules. These new polymers possess quaternary carbon branching points, maximized density of terminal functionality, equal bond distances between the surface terminal groups and cascade center, and the same chemical connection (–$CH_2OCH_2CH_2CONH$–) among all adjacent quaternary carbons, as well as have a symmetrical, three-dimensional, ball-shape structure.

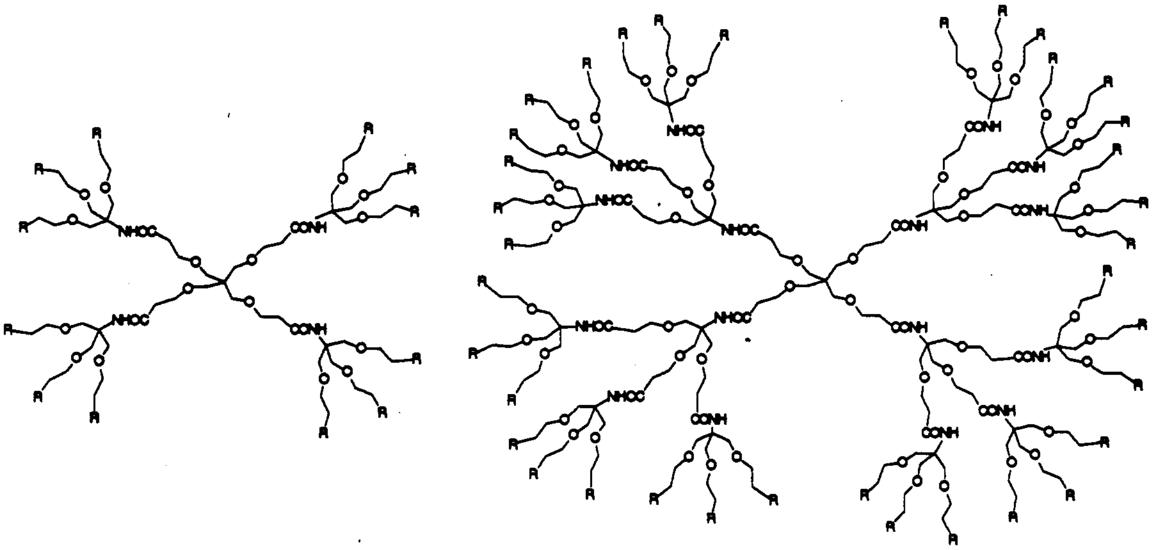
Available and inexpensive pentaerythritol (1) and tris(hydroxymethyl)aminomethane (Tris, 6) have been used to construct the core and key building block, respectively. In each case the terminal functional groups are adjacent to a quaternary carbon, which retards chemical reactivity due to a neopentyl substitution pattern,[12] and leads to the rapid onset of dense packing in the reiterative[7] process. Thus, polyhomologation is deemed essential to circumvent these limitations. On the basis of these constraints, a new cascade core and building block were synthesized (Scheme I). With use of Bruson's method,[13] treatment of 1 with 4.5 equiv of acrylonitrile, using KOH as catalyst, afforded (76%) tetrakis(cyanoethoxy)methyl]methane (2), as a white solid (mp 39–40 °C), which was supported by a new peak (^{13}C NMR) at 119.1 ppm and a spike (IR) at 2240 cm^{-1} for the $C{\equiv}N$. Nitrile 2, when refluxed in dry HCl saturated MeOH solution, gave (85%) tetrakis[((methoxycarbonyl)ethoxy)methyl]methane (3), as a yellowish oil [bp > 150 °C (2 mm)], which was indicated by a new peak (^{13}C NMR) at 51.2 ppm ($COOCH_3$) and disappearance of the peak at 119.1 ppm ($C{\equiv}N$). Hydrolysis of tetraester 3 with NaOH gave the tetrakis[(carboxyethoxy)methyl]methane (4), as a white solid (mp 94–96 °C), confirmed by a broad peak (^1H NMR) at 12.2 ppm ($COOH$) and a new signal (^{13}C NMR)

Scheme I[a]



[a] Reagents and conditions: (i) $CH_2{=}CHCN$, KOH, *p*-dioxane, 25 °C, 24 h; (ii) MeOH, dry HCl, reflux, 2 h; (iii) 3 N NaOH, 70 °C, 24 h; (iv) $SOCl_2$, CH_2Cl_2, reflux, 1 h; (v) EtOH, dry HCl, reflux, 3 h.

Chart I



9 R=$CO_2CH_2CH_3$
10 R=CN
11 R=COOH

12 R=$CO_2CH_2CH_3$
13 R=CN
14 R=COOH
15 R=$CONHC(CH_2OCH_2CH_2CO_2CH_2CH_3)_3$
16 R=$CONHC(CH_2OCH_2CH_2CO_2H)_3$
17 R=$CONHC[CH_2OCH_2CH_2CONHC(CH_2OCH_2CH_2CO_2CH_2CH_3)_3]_3$

0024-9297/91/2224-1443$02.50/0

at 173.0 ppm (*C*OOH), as well as the disappearance of the peak at 51.2 ppm. Acid **4** was treated with redistilled $SOCl_2$ in CH_2Cl_2 to afford (>95%) the reactive tetrakis[((chlorocarboxy)ethoxy)methyl]methane (**5**), which was characterized by the signal (^{13}C NMR) at 34.7 ppm (CH_2COOH) shifting to low field 47.2 ppm (CH_2COCl), and disappearance of the broad peak (^1H NMR) at 12.2 ppm.

The pivotal building module **8** was prepared in two steps from *Tris*; similar careful treatment of **6** with 3.25 equiv of acrylonitrile at 25 °C afforded (81%) tris[(cyanoethoxy)methyl]aminomethane (**7**), as a yellowish oil [bp > 150 °C (2 mm)], which was supported by an absorption (^{13}C NMR) at 117.5 ppm and in the IR a spike at 2239 cm^{-1} ($C{\equiv}N$). Nitrile **7**, when refluxed in dry HCl saturated EtOH solution, afforded (67%) the corresponding triethyl ester **8**[14] as a yellowish oil [bp > 150 °C (2 mm)], which was characterized by new signals (^{13}C NMR) at 59.9 ppm (CH_2CH_3) and 13.8 ppm (CH_3).

Treatment[15] of the core **5** with amine **8** gave (52%) the [12]-ester **9** (fw = 2038.3; Chart I), which was identified (^{13}C NMR) by new peaks at 59.7 and 69.1 ppm due to the internal amide moieties.[16] Ester **9** was hydrolyzed with NaOH in methanol–water at 25 °C to give (84%) the [12]-acid **11** (fw = 1701.7),[17] which is viscous oil due to its hygroscopic properties. Alternatively, treatment of the core **5** with amine **7** generated (65%) the related [12]-nitrile **10** (fw = 1473.6), which showed new peaks (^{13}C NMR) at 118.2 ($C{\equiv}N$), 59.8, and 69.5 ppm indicative of new tier formation.

Subsequent cascade generation was synthesized using a peptide formation procedure.[18] Reaction of acid **11** in tetrahydrofuran (THF) at 5 °C with amine **8**, 1-hydroxybenzotriazole, and dicyclohexylcarbodiimide (DCC) gave (37%) the [36]-ester **12** (fw = 6543.3). Similarly, reaction of **11** with **7** gave (41%) the related [36]-nitrile **13** (fw = 4849.3). By the two-step reiterative reactions, hydrolysis of [36]-ester **12** gave the [36]-acid **14** (fw = 5533.4).[17] Treatment of the [36]-acid **14** with amine **8** gave the resultant [108]-ester **15** (fw = 20 057.9). Similarly, the [108]-ester **15** was transformed to the [108]-acid **16** (fw = 17 028.0),[17] and its subsequent reaction with amine **8** afforded the next tiered [324]-ester **17** possessing a molecular weight of 60 604. In light of the size differences between each tier, size-exclusion chromatography was used to isolate and purify the cascades.[19]

All the nitrile and ester cascade polymers are soluble in CH_2Cl_2, and all the carboxylic acid cascade polymers are slightly soluble in water and in THF. All the cascade molecules showed nearly identical, yet assignable NMR patterns; only the relative peak intensities vary from tier to tier. At the third tier, the peak (^{13}C NMR δ 45.4 ppm) for the central core carbon becomes insignificant. The 40–60% yields at each step, easy characterization, and inexpensive starting materials make this a viable route to large homogeneous spherical polymers. Research is continuing on this series of cascades in order to delineate their porosity, molecular inclusion characteristics, and dense packing limits.

Acknowledgment. This research was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (Grant DMR-86-00929 and 89-06792).

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Received November 26, 1990
Revised Manuscript Received January 29, 1991