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Supramolecular Polymer Chemistry: Self-Assembling Dendrimers Using the DDA·AAD (GC-like) Hydrogen Bonding Motif

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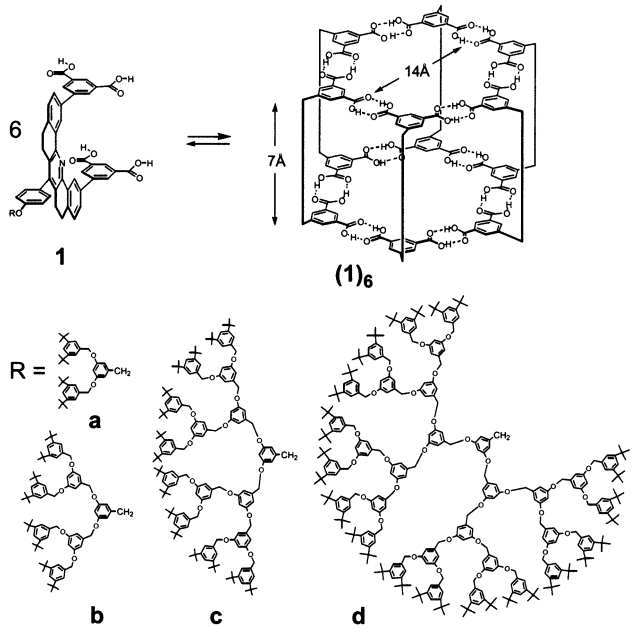
Abstract: Heterocyclic unit **2** containing complementary donor−donor−acceptor (DDA) and acceptor−acceptor−donor (AAD) hydrogen bonding arrays at an angle of about 60° was designed to self-assemble into a hexamer. To investigate whether this unit could self-assemble dendrimers, the 2,8-diamino-2-*N*-ethylpyrimido-(4,5-*b*)(1,8)naphthyridine-3*H*-4-one subunit was synthesized with a first (**2a**), second (**2b**), and third generation (**2c**) Fréchet-type dendron attached to the 8-amino group. The synthesis of **2a**−**c** was accomplished in 11 steps beginning with 2,6-diaminopyridine and the corresponding dendron bromide. Studies using ^{1}H NMR, size exclusion chromatography (SEC), and dynamic light scattering (DLS) support the cooperative formation of cyclic hexamers in apolar solvents. The stability of the self-assembled dendrimers is dependent on the size of the attached dendron, and mixing studies with **2a**−**c** indicate their usefulness in constructing dynamic combinatorial libraries.

Introduction

Engineering specific noncovalent interactions between preformed polymer molecules is emerging as a powerful strategy for modulating the next higher level of organizational complexity of macromolecules.[1] Beyond simply increasing the cohesive forces between polymers, such binding contacts may lead to specific higher-level architectures through programmed self-assembly. In turn these architectures may exhibit new properties unattainable by conventional methods. Hydrogen bonding is particularly useful in this regard because it is a strong and directional force that has been used to generate a variety of novel supramolecular structures through self-assembly.[2] For example, we recently reported a 34 kDa self-assembled dendrimer $(\mathbf{1d})_6$ formed by the specific pairing of 24 carboxylic acid groups at the core of **1** (Scheme 1).[3] This first example of a discrete aggregate of polymers had limitations, in particular, a low stability in even moderately competitive solvents such as tetrahydrofuran (THF). Furthermore, the information content in the isophthalic acid units was ambiguous with **1b**−**d** forming discrete hexamers, whereas **1a** formed oligo- and polymeric aggregates.[4]

Scheme 1



Our early investigations[5] of the stability of DNA base pairs and their heterocyclic analogues focused attention on the DDA·

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(1) For selected recent reviews see: (a) *Supramolecular Polymers*; Ciferri, A., Ed.; Marcel Dekker: NewYork, 2000. (b) Zimmerman, N.; Moore, J. S.; Zimmerman, S. C. *Chem. Ind.* (*London*) **1998**, 604−610. (c) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681−1712. (d) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071−4097. (e) Percec, V.; Cho, W. D.; Ungar, G.; Yeardley, D. J. P. *Angew. Chem., Intl. Ed.* **2000**, *39*, 1598−1602.

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AAD hydrogen-bonding motif found in the guanine−cytosine (G·C) base pair. This motif can form in only one way and exhibits an association constant (K_{assoc}) in chloroform[6] that is at least 10^2-fold higher than that of the benzoic acid dimer and the commonly used DAD·ADA motif.[5] Thus, we designed, synthesized, and studied **2a**[7] whose DDA and AAD hydrogen-bonding arrays are fixed at a 60° angle and serve, therefore, as an information code for cyclic assembly of a hexamer (Figure 1).[8,9] The strength of the DDA·AAD motif allowed hexamer $(\mathbf{2a})_6$ to form even in 15% aqueous THF.[7] Herein, we provide a detailed account of the synthesis and assembly studies of **2a** as well as its higher generation analogues **2b** and **2c**. Whereas experimental problems associated with the isophthalic acid based system prevented determination of the relative stability of the hexamers **1a**−**d**, studies with their heterocyclic counterparts **2a**−**c** allowed a relationship between dendrimer size and aggregate stability to be established. The results of the studies involving pairwise mixing of **2a**−**2c** indicate that **2** is a useful building block for creating supramolecular, dynamic combinatorial libraries.[10]

Results and Discussion

Synthesis. The synthesis of compounds **2a**−**c** followed the established synthetic route,[5b,7] with the minor modifications outlined below (Scheme 2). Thus, lithiation of **3** with BuLi followed by dimethylformamide (DMF) quench, aqueous work-up, and deprotection of the crude aldehyde **4** with lithium hydroxide (LiOH) gave **5** in a 62% yield without the need for column chromatography. Friedländer condensation of **5** with diethyl malonate afforded 7-amino-3-carbethoxy-1,8-naphthyridin-2(1*H*)-one (**6**) in a 92% yield.[5b] In the previously reported[7] conversion of **6** to BOC-protected **10**, the butanoyl protecting group in **7a** was found to give superior yields to the acetyl group. Increasing the protecting group chain length even more gives further improvements in yield. Thus, treatment of **6** with valeric anhydride in the presence of pyridine gave pentanoyl derivative **7b** in 93% yield. Naphthyridinones **7a** and **7b** react with $POCl_3$ to give gram quantities of chloronaphthyridines **8a** and **8b**. Protection of the amino group of **8a** and **8b** with $(BOC)_2O$ occurred in 75 and 97% yield, respectively, and chemoselective cleavage of the amide groups gave naphthyridine **10** in 82 and 93% yield, respectively (Scheme 2).

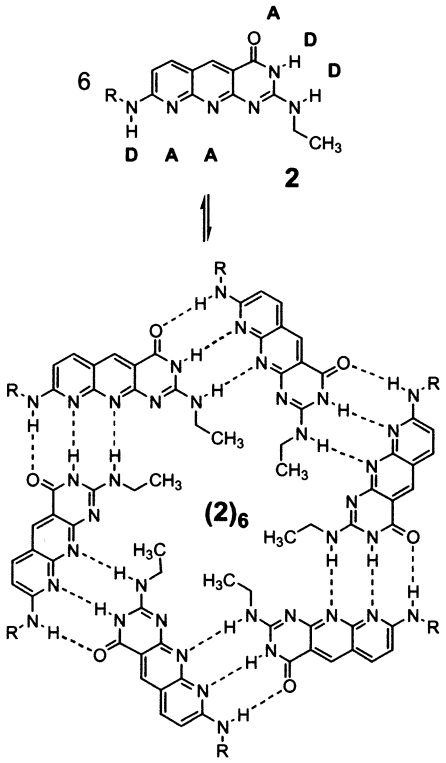

Figure 1. Self-assembling monomer **2** and the corresponding aggregate $(\mathbf{2})_6$: D, hydrogen bond donor; A, acceptor; R, G*n*, $n = 1-3$, **a**−**c** in Scheme 1.

The required dendron bromides **11a**−**c** were synthesized[3] by a convergent approach similar to that used by Fréchet.[11] Starting from methyl 3,5-dihydroxybenzoate and 3,5-di-*tert*-butylbenzyl bromide, dendron bromide **11a**−**c** were prepared in three, five, and seven total steps with overall yields of 47, 30, and 7%, respectively. *N*-Alkylation of **10** with the appropriate dendron bromide in the presence of potassium carbonate and 18-crown-6 produced compounds **12a** (80%), **12b** (47%), and **12c** (70%). The change in the 7-amino protecting group from pentanoyl to BOC was necessitated by the observation that alkylation of **8** was unselective, producing a mixture of the desired *N*-alkylated and undesired *O*-alkylated isomers. Beyond reducing the yield, the *O*-alkylation byproduct proved difficult to remove chromatographically. Changing the protecting group to BOC resulted in clean and regioselective *N*-alkylation of **10**. Chemoselective deprotection of **12** with trifluoroacetic acid (TFA) afforded amines **13a** (86%), **13b** (45%), and **13c** (64%) without affecting the ether groups of the dendrons. Finally, substitution and cyclization[12] of **13a**−**c** with *N*-ethyl guanidine, which was generated in situ from an excess of its sulfate salt and sodium hydride, afforded compounds **2a** (64%), **2b** (30%), and **2c** (64%), respectively (Scheme 2).

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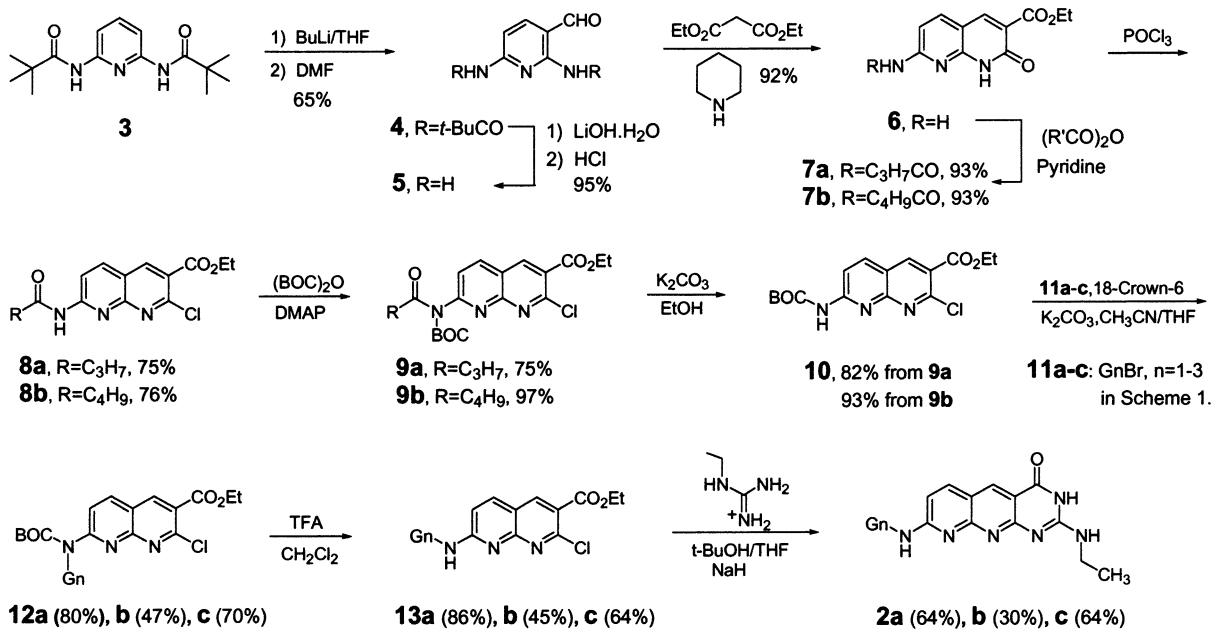
Scheme 2



Self-Assembly Studies. Establishing and characterizing solution assembly remains a challenging endeavor. Generally, no single method is sufficient to determine the solution structure of an aggregate, but a strong circumstantial case can be built by collecting data from several techniques. In the case of **2**, ^{1}H NMR, size exclusion chromatography (SEC), and dynamic light scattering (DLS) were used in conjunction with covalently synthesized size standards and analogues of **2** that serve as chemical shift standards.

^{1}H NMR Analysis. The ^{1}H NMR chemical shifts of the NH groups of **2a**−**c** (see Figure 2 for **2b**) recorded in different solvents are shown in Table 1. In each case the NH signals are sharp, downfield, and, in the case of **2a**, essentially insensitive to concentration in apolar solvents. All three compounds exhibit a small downfield shift in aromatic solvents, and there is a noticeable change in the NH shifts in moving to the third generation dendrimer (i.e., **2c**). The aromatic solvent effect is most likely a general solvent effect although stronger hydrogen bonding cannot be ruled out. It is notable that the spectra for **2a** and **2b** exhibit a relatively small dependence on solvent and dendrimer size and are nearly superimposable. Most importantly, the three NH signals are far downfield of analogous non-hydrogen-bonded NH protons such as those in **14** and **15**, and they appear in the same region as the corresponding NH groups in complexes **16·17** and **17·18** (Figure 3 and Table 1). These data indicate that the NH groups of **2** are engaged in strong hydrogen-bonding contacts.

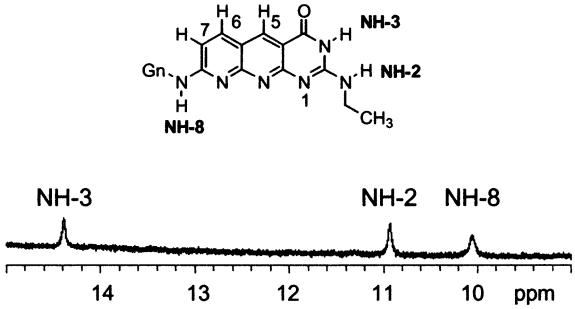


Figure 2. ^{1}H NMR signals of NH groups of **2b** in $CDCl_3$.

Table 1. ^{1}H NMR Chemical Shifts (ppm) of NH Groups in **2a**−**c** and Model Compounds **14**−**18**[a]

		proton obsd		
compd/complex	solvent	NH-2	NH-3	NH-8
2a	$CDCl_3$	10.89	13.96	10.33
	THF-d_8	11.00	14.04	10.48
	toluene-d_8	11.18	14.28	10.87
	dioxane-d_8	10.94	13.94	10.38
	10% DMSO-d_6/$CDCl_3$	10.66	13.89	10.26
	8% H_2O/THF-d_8	11.00	14.00	10.40
2b	$CDCl_3$	10.93	14.39	10.06
	THF-d_8	11.00	14.10	10.51
	toluene-d_8	11.21	14.31	10.84
2c	$CDCl_3$	10.91	14.34	10.11
	THF-d_8	11.15	14.39	10.29
	toluene-d_8	11.55	14.68	10.72
14	$CDCl_3$	5.04		
15	$CDCl_3$	4.80		
16·17a	$CDCl_3$	13.90[b] (**17a**)		
17a·18a	$CDCl_3$		13.27[b] (**18a**)	
17b·18b	$CDCl_3$	11.1 (**17b**)	13.3 (**18b**)	

[a] Not all NH protons were seen in complexes. Compound **14** was prepared from 7-amino-2,4-dimethyl-1,8-naphthyridine and **11a**. Compounds **15**−**18** were available from a previous study (see ref 3). [b] Value represents $\Delta\delta_{max}$ obtained by curve fitting 1:1 binding isotherms.

Two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY) was employed to probe structural details of aggregate (**2b**)$_6$ in solution. In the NOESY spectra of **2b** in $CDCl_3$ and toluene-d_8 (Figure 4), the cross-peaks from NH-8 to both NH-2 and NH-3 indicate their spatial proximity consistent with pairing of the DDA and AAD binding sites. In the structure of the monomer, the NH-8 to NH-3 distance based on molecular modeling (Macromodel) is >8.0 Å, which is much larger than the required distance to see a NOE correlation between the two protons.

Size Exclusion Chromatography Studies. Size exclusion chromatography with appropriate size comparisons is now established as a powerful method of determining the aggregation state of supramolecular assemblies.[2c,3,8b,13] Thus, whereas the ^{1}H NMR data indicated the formation of hydrogen bonds, SEC of **2a**−**c** provided molecular weight (MW) and size data

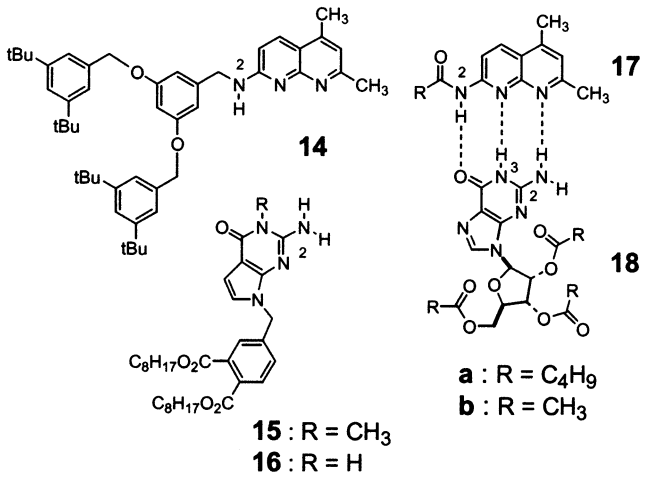
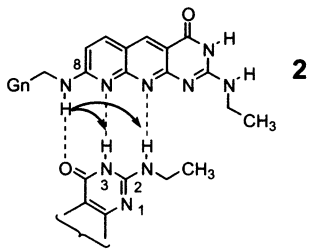


Figure 3. Structure of compounds **14**−**18**, analogues of **2**.



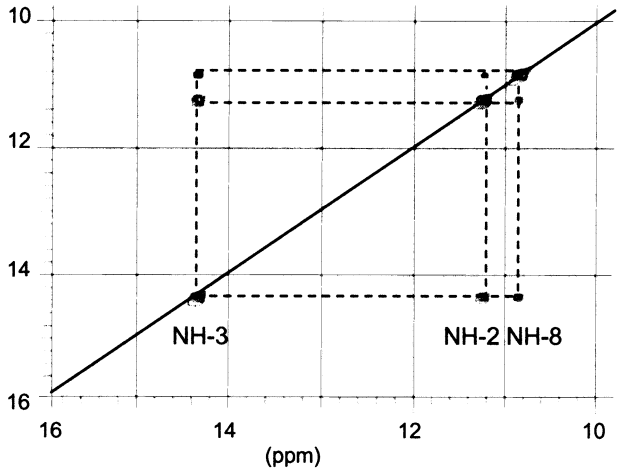


Figure 4. ^{1}H NMR NOESY of **2b** in toluene-d_8 (8.7 mM).

indicating their aggregation state in solution. As seen in Figure 5A, **2a**−**c** each gave a sharp and symmetrical peak in toluene with a polydispersity index (PDI) $M_W/M_n = 1.02$ that is in the range typically found for monodisperse, Fréchet-type dendrimers.[11,14] Concentration-independent SEC retention can be taken as prima fascia evidence in support of a discrete, closed (i.e., cyclic) aggregate.[15] As was reported for **2a**,[7] the polystyrene (PS) based molecular weights (MW_{PS}) of **2b** and **2c** in toluene changed minimally across a 10^3-fold dilution in SEC injection concentration (Figure 5B). These results indicate that **2b** and **2c** also form discrete, cyclic aggregates in toluene.

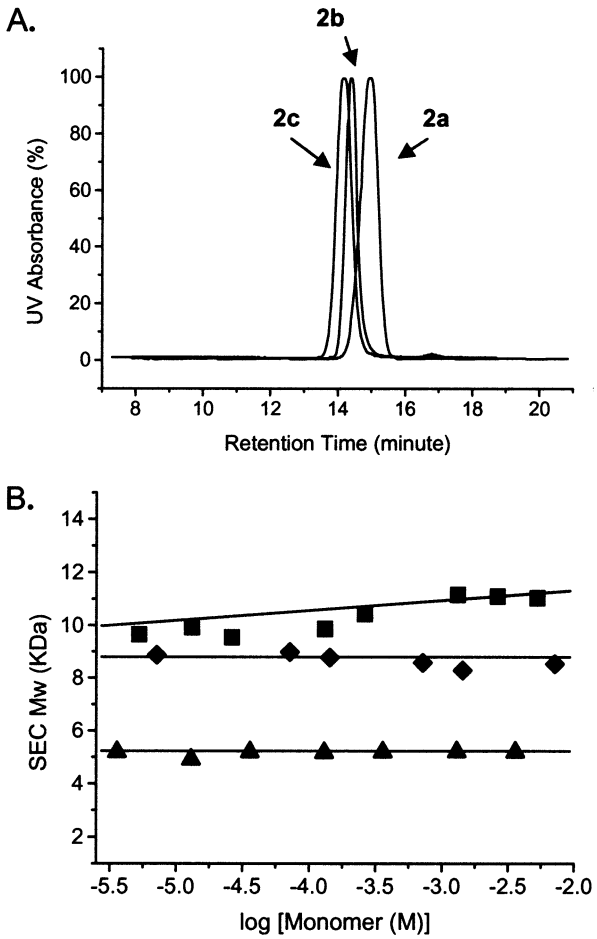


Figure 5. (A) SEC traces of **2a** (3.83 mM), **2b** (1.02 mM), and **2c** (4.47 mM) in toluene and (B) change in SEC derived MW with injected concentration of **2a** (▲), **2b** (◆), and **2c** (■) in toluene.

Table 2. Molecular Weight Determination by SEC

compd	calcd MW	MALDI	SEC (toluene)	SEC (THF)	calcd MW of hexamer
2a	782.49	784.4	5660[a]	4800[b]	4698
2b	1430.9	1430.4	8800[c]	8870[d]	8592
2c	2727.7	2730.3	11500[e]	2650[f]	16378

[a] 0.0036−3.6 mM. [b] 4.4 mM. [c] 0.007−7.0 mM. [d] 1.0−5.0 mM. [e] 0.7−4.4 mM. [f] 0.01−5.0 mM.

The nature of the aggregates formed by **2a**−**c** can be inferred from comparison of the SEC retention times to appropriate size standards. Thus, molecular weights were determined in both toluene and THF by SEC using PS standards for calibration (Table 2). The MW_{PS} values for **2a** and **2b** are ca. 25 and 2% larger than that calculated for the corresponding hexamers, whereas the MW_{PS} for **2c** is ca. 30% smaller than that calculated for the hexamer. The deviations from the theoretical MW calculated for hexamer can be explained by a low-density but rigid heterocyclic core holding six densely packed dendrons around a ca. 22.7 Å diameter disk. In **2a** the core dominates, whereas in **2c** the dendrons contain most of the mass. It is well-established that dendritic structures, being denser and more compact than linear polymers, give PS determined molecular weight values that underestimate their actual molecular weights, especially in the case of higher-generation dendrimers.[11,16]

Compound **19** was synthesized as a semirigid covalent size standard for proposed hexamer $(\mathbf{2a})_6$. As seen in Figure 6 the

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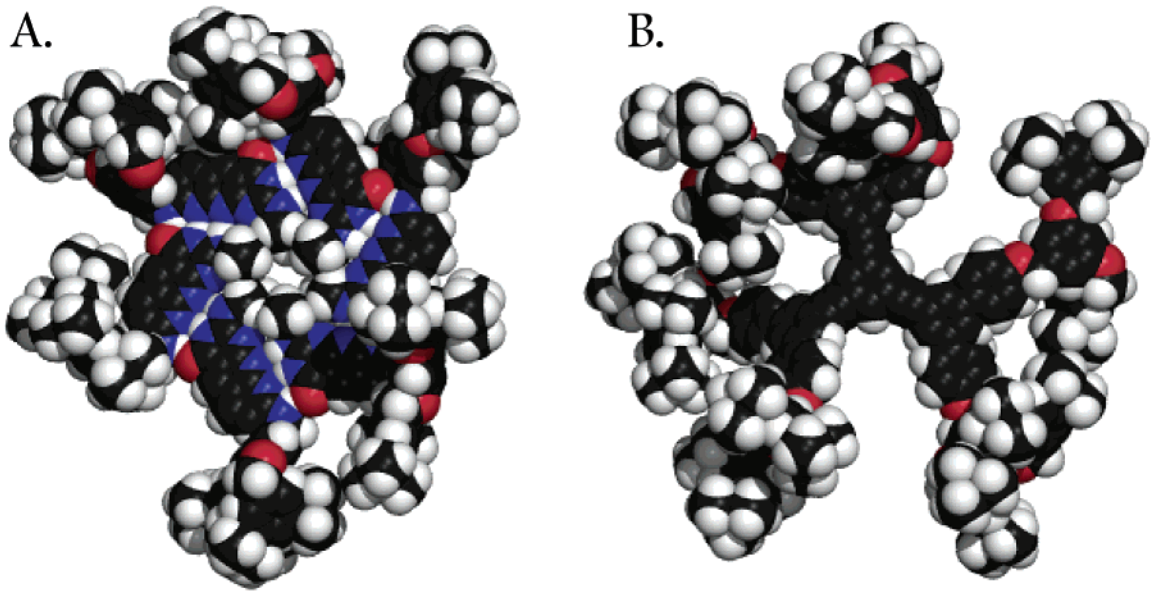
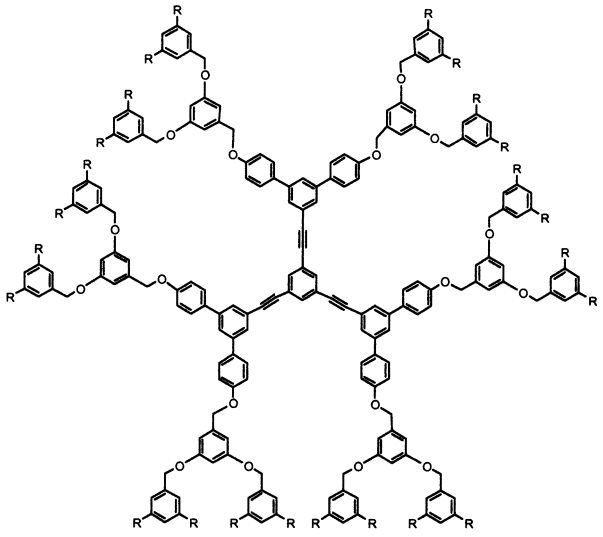


Figure 6. Molecular modeling of $(\mathbf{2a})_6$ (A) and **19** (B).

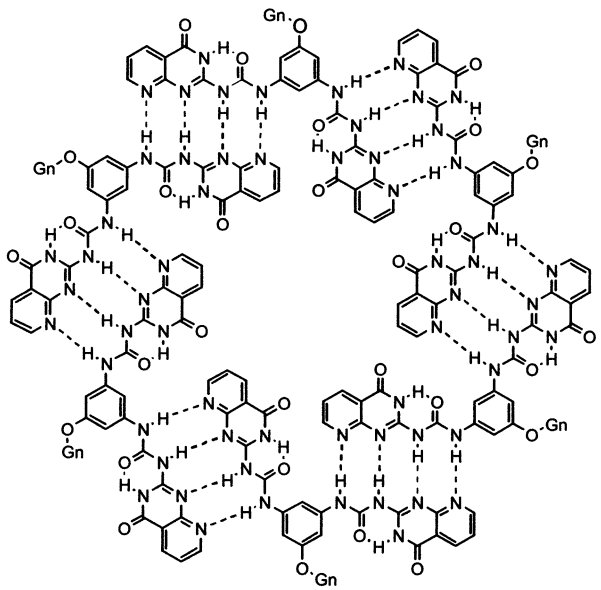
sizes of $(\mathbf{2a})_6$ and **19** obtained by molecular modeling are very similar. Indeed, the two compounds have identical SEC retention



19 : R = *tert*-Bu

times in both toluene and THF and coelute when co-injected. For compounds **2b** and **2c** comparisons were made to known hexamers **1b** and **1c** and to recently described hexamers $(\mathbf{20b})_6$ and $(\mathbf{20c})_6$.[15] Thus, the elution times followed the order **1c** > **20c** > **20b** > **2c** > **2b** > **2a** ≅ **19**, paralleling their modeled sizes, which, in turn, is consistent with ordering of the core diameters as determined by molecular modeling: $(\mathbf{1})_6$ (41.1 Å) > $(\mathbf{20})_6$ (30.6 Å) > $(\mathbf{2})_6$ (22.7 Å).

The SEC retention times are determined by the hydrodynamic volume of the aggregate or compound examined.[17] Thus, to put the comparison of retention times on a more quantitative footing, the radius of gyration (R_g) of size standard **19** and self-assembled dendrimers $(\mathbf{1c})_6$, $(\mathbf{20b},\mathbf{c})_6$, and $(\mathbf{2a}-\mathbf{c})_6$ were determined computationally (see Experimental Section for details). Both highly extended and folded-back conformations were examined to provide an indication of the uncertainty in the calculated R_g values. As seen in Figure 7, a reasonably linear correlation is seen between the calculated R_g values and the experimentally determined SEC retention times.



$(\mathbf{20})_6$

Dynamic Light Scattering. The aggregates formed by **1c** and **2a**−**c** were also studied by dynamic light scattering. In some runs a trace amount (ca. 0.1 wt %) of a very large particle was observed. Nonetheless, and consistent with the SEC results, all compounds gave a narrow polydispersity value (Table 3), indicating formation of a discrete aggregate in toluene solution. Most importantly, the relative magnitude of the hydrodynamic radii (R_h) measured by DLS correlated well with the observed by SEC retention times and the aggregate sizes determined by molecular modeling. Thus, the R_h values decreased in the order $(\mathbf{1c})_6$ > $(\mathbf{2c})_6$ > $(\mathbf{2b})_6$ > $(\mathbf{2a})_6$ ≅ **19** and were found to be within

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(17) Grubisic, Z.; Rempp, P.; Benoit, H. *Polym. Lett.* **1967**, *5*, 753−759.

Table 3. Hydrodynamic Radius (R_h) Determined by Dynamic Light Scattering

	19	$(\mathbf{2a})_6$	$(\mathbf{2b})_6$	$(\mathbf{2c})_6$	$(\mathbf{1c})_6$
calcd R_h[a] (nm)	1.78 ± 0.14	1.68 ± 0.08	1.88 ± 0.15	2.34 ± 0.12	3.24 ± 0.24
DLS R_h[b] (nm)	1.79	1.90	2.20	2.30	3.40
polydispersity (%)	12	13	15	14	15
MW (starburst)	4670	6000	9000	11000	40000
calcd MW	4098	4698	8592	16378	19200

[a] Determined by molecular modeling (see text and Experimental Section). Calcd $R_h = R_g\,(5/3)^{1/2}$ assuming a spherical, compact structure. [b] Average R_h from DLS on sample solutions of 5.0 mg/mL at 25 °C.

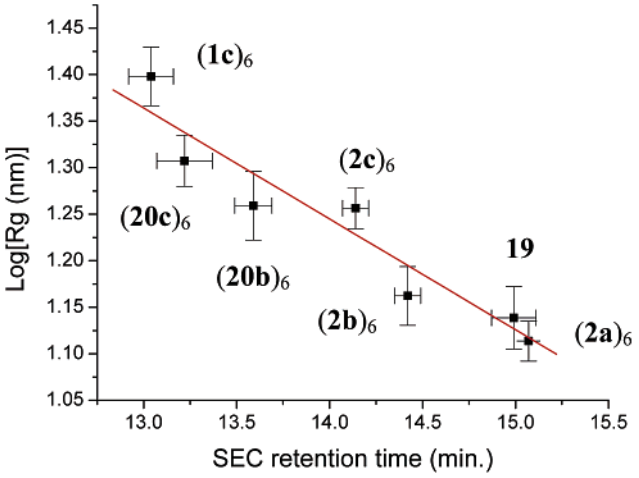

Figure 7. Correlation between SEC retention time and modeled size of covalent size standard **19** and self-assembled dendrimers $(\mathbf{1c})_6$, $(\mathbf{20b,c})_6$, and $(\mathbf{2a-c})_6$.

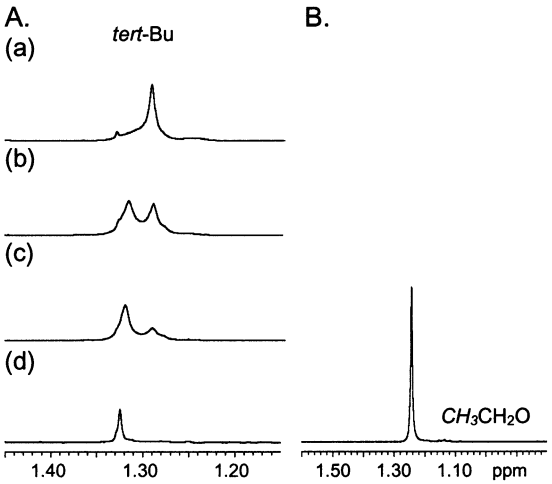

Figure 8. Upfield spectral regions from a representative ^{1}H NMR dilution study of the $(\mathbf{2b})_6$ in (A) $CDCl_3$ at (a) 0.588 mM, (b) 98.0 μM, (c) 16.3 μM, and (d) 2.72 μM and (B) $CDCl_3$/DMSO-d_6 = 1:1 (v/v) at 1.77 mM.

15% of the calculated R_h values[18] obtained from molecular modeling (Table 3). Although molecular weights could be derived from the DLS data by applying a starburst polymer model, these values deviated by approximately 50% in the case of **1c** and **2c**.

Both the SEC and DLS experiments are consistent with the formation of discrete, hexameric aggregates from **2**, but the data do not exclude the formation of pentamers or heptamers. Nonetheless, such structures cannot be made with conventional CPK models, and computational studies indicate that such aggregates, if formed, would have highly distorted hydrogen bonds.

Monomer−Hexamer Equilibrium. The SEC of compound **2c** in THF shows a single peak corresponding to monomer. At most concentrations of **2a** the SEC in THF shows a single sharp peak corresponding to hexamer, but at very high dilution some monomer is observed. For **2b** the SEC exhibits intermediate behavior with monomer and hexamer present at most concentrations; with the former increasing at the expense of the latter upon dilution. These data suggest that (1) the larger dendrons destabilize the hexamer and (2) the hexamer forms cooperatively with monomer and hexamer in slow exchange on the time scale of the SEC experiment (minutes).

Similar observations were made in the ^{1}H NMR of **2b** in chloroform-*d* ($CDCl_3$), THF-d_8, and benzene-d_6, with two sets of proton signals assigned to monomer and hexamer in slow exchange. For example, as shown in Figure 8A, the singlets at δ 1.28 and δ 1.33 ppm in $CDCl_3$ are assigned, respectively, to the *tert*-butyl groups of the hexamer and monomer of **2b**. As the concentration decreased from 1.0 mM to 1.0 μM, the relative peak ratio of hexamer to monomer also decreased. The same result is observed by increasing the temperature in a variable temperature (VT) ^{1}H NMR study in $CDCl_3$. Likewise, upon addition of a polar solvent (e.g., DMSO-d_6) to a solution of **2b** in $CDCl_3$, the hexamer peak decreases in intensity, being replaced by the monomer. As seen in Figure 8B, in a 1:1 (v/v) $CDCl_3$−DMSO-d_6 mixture a single sharp peak was observed for the monomer *tert*-butyl groups.

The slow exchange between monomer and hexameric aggregate observed in ^{1}H NMR spectra of **2b** allowed the effect of the solvent on the aggregation process to be studied more systematically. Thus, for **2b**, the concentrations which afford a 1:1 ratio of the monomer and hexamer *tert*-butyl peaks was $\sim 10^{-3}$ M in THF-d_8, $\sim 10^{-4}$ M in $CDCl_3$ and $\sim 10^{-6}$ M in benzene-d_6. These results and those described above indicate that the relative stability of the hexamer increases with decreasing solvent polarity: benzene-d_6 > $CDCl_3$ > THF-d_8 > DMSO-d_6.

^{1}H NMR dilution and VT studies were also carried out on **2a** and **2c** with similar results. For example, the *tert*-butyl region of the ^{1}H NMR spectra of **2a** shows a single *tert*-butyl singlet (hexamer) at a concentration greater than 0.1 mM in $CDCl_3$ but the presence of monomer at ca. 15 μM and below (Figure 9). All of these observations are consistent with a cooperative, cyclic aggregation process driven by hydrogen bonding. Thus, decreasing the concentration, increasing the temperature, or adding a competitive solvent destabilizes the hexamer, shifting the equilibrium toward monomer in solution.

Dependence of Hexamer Stability on Dendron Size. The well-separated *tert*-butyl signals seen for the monomer and hexamer in the ^{1}H NMR were used to provide semiquantitative data on the relative stability of the hexamers formed from **2a**−

(18) Trollsås, M.; Atthof, B.; Würsch, A.; Hedrick, J. L.; Pople, J. A.; Gast, A. P. *Macromolecules* **2000**, *33*, 6423−6438.

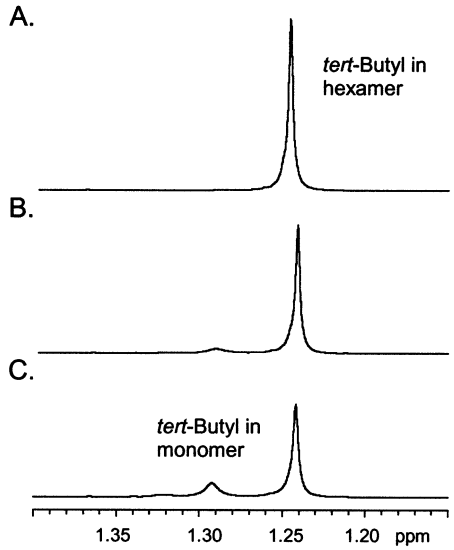

Figure 9. Upfield spectral region from a representative ^{1}H NMR dilution study of the $(\mathbf{2a})_6$ in $CDCl_3$ at (a) 6.90 mM, (b) 0.144 mM, and (c) 15.4 μM.

c. Thus, $CDCl_3$ solutions of **2a**−**c** were titrated with DMSO-d_6 until the hexamer signal was no longer visible. Figure 10 shows representative data for hexamer $(\mathbf{2a})_6$ whose *tert*-butyl and NH group signal intensity regularly decreases upon addition of DMSO-d_6 and then fully disappears at 35% (v/v) DMSO-d_6−$CDCl_3$. The same experiments were carried out for **2b** and **2c**, but in this case the amount of DMSO-d_6 required to fully dissociate the hexamer in $CDCl_3$ was 19 and 9% (v/v), respectively. These results, which are fully consistent with the SEC dilution studies (vide supra), indicate that the stability of the hexameric aggregates decreases with increasing dendrimer size: $(\mathbf{2a})_6 > (\mathbf{2b})_6 > (\mathbf{2c})_6$.

Cooperativity in the Cyclic Assembly Process. The observation that monomer and hexamer are in equilibrium, absent any obvious observation of the intermediate *n*-mers ($n = 2-5$), suggested strongly that a type of cooperativity is present in the cyclic assembly. To probe this aspect in more detail, the stability of hexamer $(\mathbf{2a})_6$ was compared to that of complex **17b·18b**, which utilizes the same DDA·AAD hydrogen bonding motif.[19] Because of the high K_{assoc} value for the **17·18** complex in $CDCl_3$ ($K_{assoc} > 10^4$ M^{-1}),[5] ^{1}H NMR dilution studies were carried out in 5% (v/v) DMSO-d_6−$CDCl_3$. At a concentration of 0.08 mM **17b·18b** was mostly dissociated, while NH proton signals of $(\mathbf{2a})_6$ showed a minimal upfield shift. Full dilution curves are shown in Figure 11, where it is seen that the half-dissociation point for **2a** ($[(\mathbf{2a})_6]_{1/2\ dissoc} = 0.125$ mM) comes at *lower concentration* than it does for **17b·18b** ($[\mathbf{17b{\cdot}18b}]_{1/2\ dissoc} = 0.725$ mM).

The cohesive force that stabilizes both species is the DDA·AAD hydrogen-bonding motif. The obvious, yet striking, conclusion that can be drawn from these data is that $(\mathbf{2a})_6$ is more stable than complex **17b·18b**, even though the former, being comprised of six molecules, requires a considerably higher loss in entropy. The greater stability of $(\mathbf{2a})_6$ may be attributable to two factors. First, there are subtle differences in the hydrogen bonding contacts used. As seen in Figure 12, N-1 in **2** provides a secondary hydrogen bonding interaction[5,6] that is not present in the **17b·18b** complex. In a related system the additional secondary hydrogen bond was found to contribute about 0.7 kcal mol^{-1}.[20] On the other hand, the N−H donor in **17b** is an amide group, whereas the corresponding N−H donor in **2** is an amine suggesting stronger primary hydrogen bonding in the complex. In short, no definitive conclusion can be drawn regarding the relative strength of the hydrogen bonding in the two systems, but the hexamer does contain six additional secondary hydrogen bonds.

The second factor that is certainly operating is a cooperativity originating in the cyclic assembly process. This same higher stability for a cyclic aggregate relative to an analogous complex was most clearly demonstrated for a trimerization process.[8a] Although the cooperativity manifests itself in the thermodynamics of assembly, its origin can best be thought of in terms of the kinetics of hexamer dissociation. Thus, upon breaking one set of DDA·AAD hydrogen bonds in $(\mathbf{2})_6$ the barrier to re-forming the hexamer is very low in comparison to the barrier to dissociating a molecule of **2** giving the pentamer.

Dynamic Combinatorial Library from 2a + 2c. The rapid and economical generation of large libraries of compounds continues to be a significant challenge to organic chemists. One approach that has attracted considerable attention recently uses a dynamic combinatorial library in which constituent members may interconvert.[10] Thus, an external stimulus may shift the equilibrating library toward one or a subset of members. Often the interconversion occurs through the breaking and formation of covalent bonds, but the library may also contain supramolecular complexes or assemblies that equilibrate through noncovalent exchange processes.[21]

As a logical extension of the research described above, the possibility of generating a dynamic library from **2** was investigated by mixing first- and third-generation dendritic monomers **2a** and **2c**. In toluene, **2a** and **2c** exhibit discrete, symmetrical SEC peaks with retention times of 15.1 and 14.2 min, respectively, but only one sharp peak with a retention time of 14.3 min was observed after equimolar amounts of **2a** and **2c** were mixed in solution for several hours before injection. The measured PDI (1.02) was comparable to the PDI of each individual hexamer. The kinetics of mixing, which were monitored by SEC, clearly show that the subunits in each aggregate $(\mathbf{2a})_6$ and $(\mathbf{2c})_6$ combine to generate new aggregates but these ultimately convert to a discrete structure (Figure 13). This recombination process was fully complete in about 16 min. This rapid mixing may seem inconsistent with the slow interconversion of monomer and hexamer, wherein monomers **2a** and **2b** do not exchange significantly with their respective hexamers $(\mathbf{2a})_6$ and $(\mathbf{2b})_6$ on the time scale of the SEC runs (ca. 16 min). However, the solvent in the two experiments is different, and the mechanism for exchange need not proceed through monomer. For example, the mixing of $(\mathbf{2a})_6$ and $(\mathbf{2c})_6$ might occur by an end-unit exchange between linear aggregates as opposed to a full dissociation−recombination.

(19) For a more quantitative treatment of cyclic vs linear aggregation see: Bielejewska, A. G.; Marjo, C. E.; Prins, L. J.; Timmerman, P.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2001**, *123*, 7518−7533.

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(21) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106−2110. Calama, M. C.; Hulst, R.; Fokkens, R.; Nibbering, N. M. M.; Timmerman, P.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 1021−1022. Hof, F.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4251−4252. Furlan, R. L. E.; Cousins, G. R. L.; Sanders, J. K. M. *Chem. Commun.* **2000**, 1761−1762. Cousins, G. R. L.; Furlan, R. L. E.; Ng, Y.-F.; Redman, J. E.; Sanders, J. K. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 423−428.

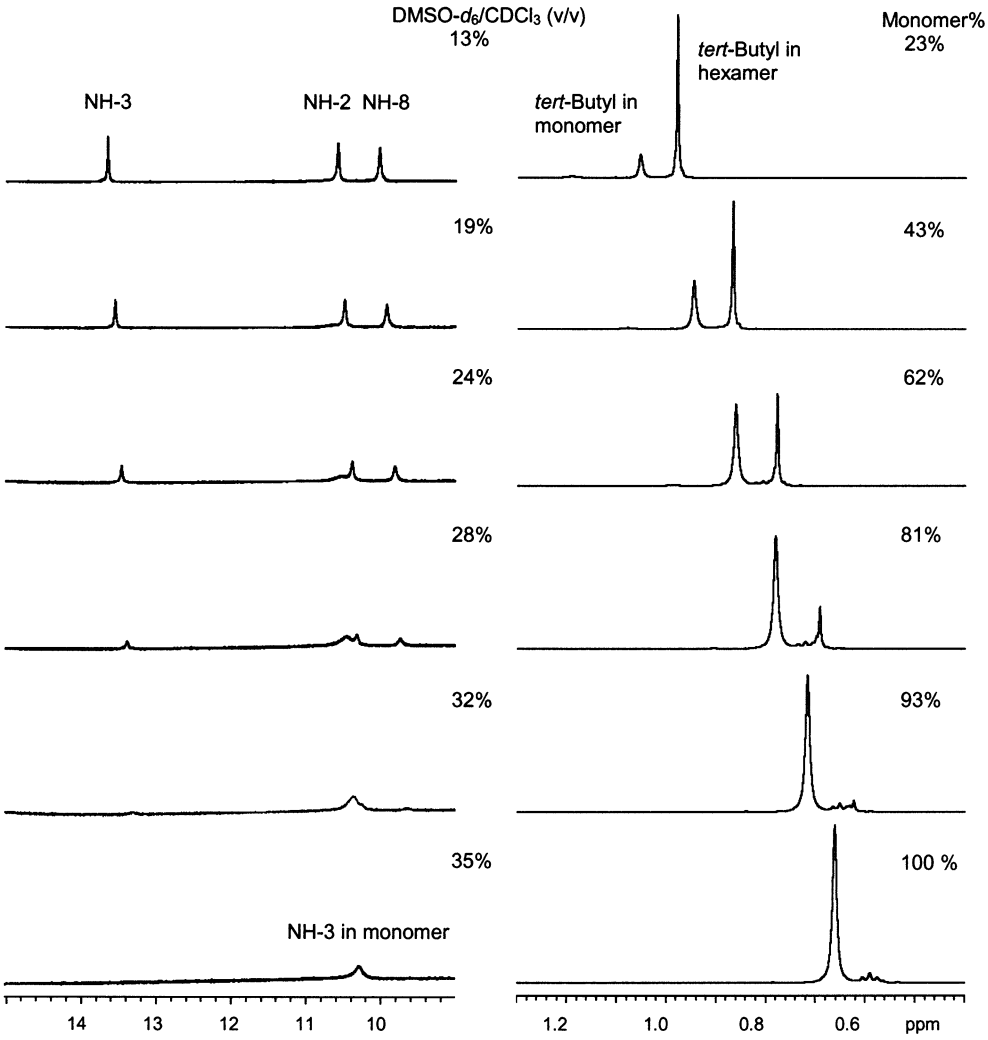


Figure 10. ^{1}H NMR titration of $(\mathbf{2a})_6$ in $CDCl_3$ by DMSO-d_6.

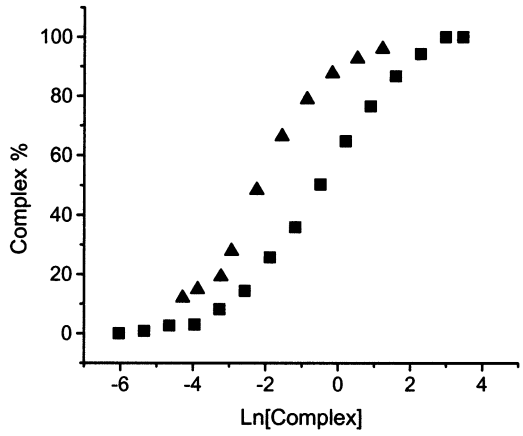


Figure 11. Stability comparison of $(\mathbf{2a})_6$ (▲) with G·C base-pair analogue **17b·18b** (■).

In addition to $(\mathbf{2a})_6$ and $(\mathbf{2c})_6$, monomers **2a** and **2c** can form 11 distinct hexameric aggregates (Figure 14). Thus, mixed hexamers $(\mathbf{2a})_1(\mathbf{2c})_5$ and $(\mathbf{2a})_5(\mathbf{2c})_1$ have a single structure possible, whereas $(\mathbf{2a})_2(\mathbf{2c})_4$ and $(\mathbf{2a})_4(\mathbf{2c})_2$ each have three different structures as does $(\mathbf{2a})_3(\mathbf{2c})_3$. The broadness of the SEC signal at intermediate mixing times (Figure 13) suggest that many, if not all, of these of aggregates are sampled but that ultimately a single aggregate is formed. Given the significantly

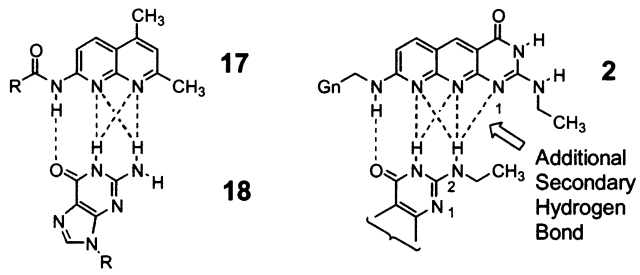


Figure 12. Comparison of hydrogen bonding contacts in complex **17·18** and $(\mathbf{2})_6$.

lower stability of $(\mathbf{2c})_6$, it is reasonable to hypothesize that the destabilizing steric interactions between the dendritic side chains can be minimized in the fully mixed and alternating $(\mathbf{2a2c})_3$ hexamer (see **21**).

Conclusion

Compound **2** was designed with complementary DDA and AAD hydrogen-bonding arrays fixed at a ca. 60° angle, thus serving as an information code for cyclic assembly of a hexamer. Extensive ^{1}H NMR, SEC, and DLS studies on **2a**−**c** and various related compounds indicate that these compounds self-assemble cooperatively into stable hexameric aggregates in apolar organic solvents. The equilibrium is shifted from hexamer to monomer

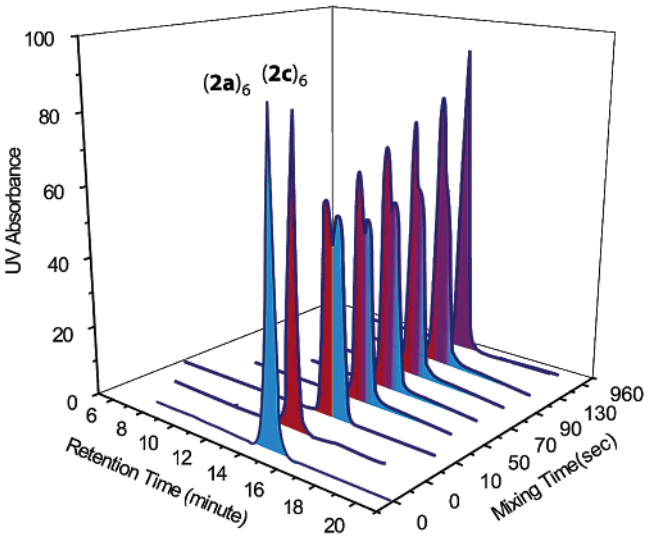
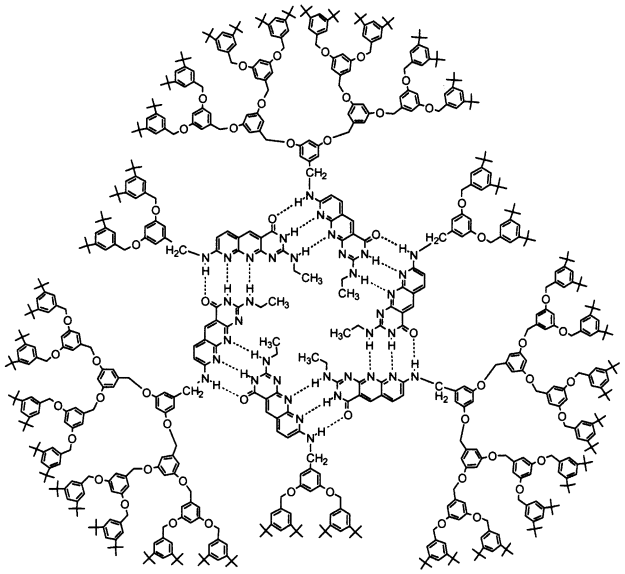


Figure 13. Mixing of $(\mathbf{2a})_6$ with $(\mathbf{2c})_6$ monitored by SEC in toluene (UV detector, 390 nm).

by increasing the temperature, adding polar solvents, or reducing the concentration. The ^{1}H NMR titration and SEC studies demonstrate that the first generation dendritic monomer **2a** forms the most stable hexamer, with the stability of hexamers decreasing upon increasing the dendron size: $(\mathbf{2c})_6 < (\mathbf{2b})_6 < (\mathbf{2a})_6$.



21

A library of hexameric aggregates was obtained by recombination of subunits within a mixture of preformed hexamers $(\mathbf{2a})_6$ and $(\mathbf{2c})_6$. The dynamic nature of the supramolecular assemblies is apparent, as the mixture appears to change over time ultimately producing a hexamer with first- and third-generation dendrons alternating. Given that there are at least 13 possible structures in the mixture, it is striking that a single, discrete aggregate is self-selected. This use of steric hindrance to direct the formation of a specific mixed aggregate should prove to be particularly useful for creating nanoscale assemblies with novel functions.

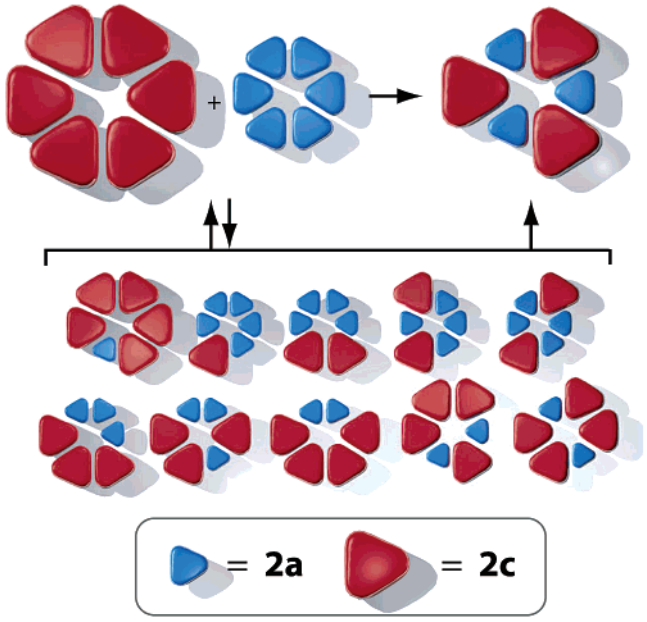


Figure 14. Possible mixed aggregates formed from mixing of $(\mathbf{2a})_6$ and $(\mathbf{2c})_6$.

Experimental Section

General Methods. The following solvents were freshly distilled under N_2 prior to use: tetrahydrofuran from sodium and benzophenone; acetonitrile (CH_3CN) and triethylamine from calcium hydride. Dry *tert*-butyl alcohol was obtained by storing the reagent grade *tert*-butyl alcohol over molecular sieves overnight. All other solvents and reagents were of reagent grade quality from Aldrich and used without further purification. All reactions were run under a nitrogen atmosphere unless otherwise noted.

Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica gel coated plastic sheets (Merck) with F254 indicator. Flash chromatography was performed on Merck 40−63 μm silica gel.[22] Preparative size exclusion chromatography was performed on polystyrene Bio-Beads S−X Beads (Bio-Rad: 400−14 000) in toluene. Melting points were determined on a Thomas-Hoover melting point apparatus without calibration.

Nuclear magnetic resonance (NMR) spectra were recorded on Varian Unity U-400 (400 MHz), Varian Unity U-500 (500 MHz), Varian Unity Inova 500 NB, or Varian Unity Inova (Keck) 750 (750 MHz) instruments in chloroform-*d* ($CDCl_3$) unless otherwise noted. Chemical shifts are reported in parts per million (ppm) with referencing to the solvent used, and coupling constants are reported in hertz (Hz). Elemental analyses were performed by the Microanalysis Lab at the University of Illinois School of Chemical Sciences. Mass spectra (MS) were obtained on a Micromass ZAB−SE (FAB) mass spectrometer and a PerSeptive Biosystems Voyager-DE-STR (MALDI-TOF) mass spectrometer.

The dendron bromides **11a**−**c** were synthesized[3] by a convergent approach similar to that used by Fréchet.[11] For the ^{1}H NMR assignments of the dendron units in **2, 12**, and **13**, the protons of the nonfused phenyl rings were given a prime (′), and their number increases proceeding from the core to the phenyl rings bearing *tert*-butyl groups.

Ethyl 7-butanoylamino-1,8-naphthyridin-2(1*H*)-one-3-carboxylate (**7a**) was synthesized by using a procedure similar to that was used to make **7b**.

2,6-Diaminopyridine-3-carboxaldehyde (5). This is a modification of the previously reported procedure.[5b] To a stirred suspension of 10 g (36 mmol) of protected pyridine **3** in 160 mL of THF was added dropwise 60 mL of BuLi (2.2 mol/ L in hexane), maintaining the

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

internal temperature < −50 °C. The solid dissolved upon complete addition. The flask was placed in a refrigerator (0 °C) overnight to yield a yellow solid. The yellow suspension was stirred at 0 °C for 1 h, cooled to −78 °C, and quenched with a solution of 8.5 mL (110 mmol) of freshly distilled DMF in 20 mL of THF. The flask was removed from the cooling bath, warmed to room temperature, and placed in a 30 °C water bath. The resulting yellow solution was poured onto 150 mL of ice water. The aqueous layer was extracted with 3 × 100 mL of dichloromethane (CH_2Cl_2). The combined organic layers were evaporated in vacuo. The resulting yellow oil was redissolved in 250 mL of CH_2Cl_2, and the solution was washed with 5% (w/w) aqueous HCl and then saturated aqueous sodium bicarbonate ($NaHCO_3$). The organic layer was dried over sodium sulfate (Na_2SO_4), and the solvent was removed in vacuo. The product was recrystallized from petroleum ether−ethyl acetate (PE−EtOAc) to afford 7.1 g (65%) of **4** as a light yellow solid: mp 138−140 °C.

To a warm light yellow solution of 7.1 g (23.3 mmol) of **4** in 100 mL of methanol (MeOH) was added in one portion 2.0 g (47.6 mmol) of $LiOH·H_2O$, and the resulting mixture was heated to reflux for 1 h. The resulting yellow solution was cooled to room temperature and neutralized with concentrated aqueous HCl to pH = 6. The solvent was evaporated in vacuo, and the solid was collected by vacuum filtration. The solid was suspended in 80 mL of Et_2O and filtered. The crude solid was recrystallized using EtOAc to give 3.05 g (95%) of **5** as yellow powder, which was identical to that described previously.[5b]

Ethyl 7-Pentanoylamino-1,8-naphthyridin-2(1*H*)-one-3-carboxylate (7b). A suspension of **6** (2.6 g, 11.2 mmol), 10 mL of valeric anhydride, and 5 mL of pyridine was heated to reflux for 24 h, during which time the granular solid disappeared forming a homogeneous brown solution which deposited silver and platelike crystals. The suspension was cooled to room temperature, diluted with petroleum ether (30 mL), stirred, and filtered. The yellowish plates were collected, suspended in 50 mL of dichloromethane, and filtered. Recrystallization of crude product from DMF produced 3.3 g (93%) of product as a yellow needles: mp 321−322 °C. ^{1}H NMR (DMSO-d_6): δ 12.17 (s, 1H, NH), 10.67 (s, 1H, NH), 8.44 (s, 1H, H-4), 8.19 (d, J = 8.6, 1H, H-5), 7.98 (d, J = 8.5, 1H, H-6), 4.25 (q, J = 7.1, 2H, O*CH*$_2$CH$_3$), 2.46 (t, J = 7.7, 2H, $CH_3CH_2CH_2$*CH*$_2$CO), 1.55 (pentet, J = 7.5, 2H, CH_3CH_2*CH*$_2$CH$_2$CO), 1.30−1.26 (m, 5H, CH_3*CH*$_2$CH$_2$CH$_2$CO + OCH$_2$*CH*$_3$), 0.87 (t, J = 7.4, 3H, *CH*$_3$CH$_2$CH$_2$CH$_2$CO); ^{13}C NMR (DMSO-d_6): δ 173.8, 164.7, 160.4, 155.5, 150.7, 143.5, 140.9, 121.8, 109.8, 106.1, 61.2, 36.5, 27.6, 22.3, 14.8, 14.3. MS (EI, 70 eV): *m*/*z* 317.2 (36, M^+), 233.1 (52), 188.1 (32), 161.1(100). HRMS (EI). Calcd for $C_{16}H_{19}N_3O_4$: 317.1375. Found: 317.1372. Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.27; H, 5.89; N, 13.12.

Ethyl 2-Chloro-7-butanoylamino-1,8-naphthyridine-3-carboxylate (8a). Using the published procedure,[5b] an analytically pure sample was obtained by column chromatography over silica gel (1−3% MeOH−CH_2Cl_2) followed by recrystallization from EtOAc−heptane (10% (v/v)) as short, white needles, mp: 202−204 °C. ^{1}H NMR: δ 9.72 (s, 1H, NH), 8.67 (m, 2H, H-4, H-5), 8.27 (d, J = 8.8, 1H, H-6), 4.44 (q, J = 7.0, 2H, O*CH*$_2$CH$_3$), 2.55 (t, J = 7.5, 2H, *CH*$_2$CH$_2$CH$_3$), 1.74 (sextet, J = 7.4, 2H, CH$_2$*CH*$_2$CH$_3$), 1.43 (t, J = 7.0, 3H, OCH$_2$*CH*$_3$), 0.95 (t, J = 7.3, 3H, CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR: δ 173.2, 164.0, 156.5, 154.7, 151.5, 141.6, 139.8, 123.9, 118.2, 116.8, 62.2, 39.5, 18.4, 14.1, 13.6. Anal. Calcd for $C_{15}H_{16}N_3O_3Cl$: C, 55.99; H, 5.01; N, 13.06; Cl, 11.02. Found: C, 55.91; H, 4.95; N, 12.89; Cl, 11.20.

Ethyl 2-Chloro-7-pentanoylamino-1,8-naphthyridine-3-carboxylate (8b). Using the published procedure,[5b] reaction of **7b** (2.69 g, 8.5 mmol) with 25 mL of $POCl_3$ afforded 2.17 g (76%) of the desired product as light yellow flakelike crystals after recrystallized from DMF/H_2O: mp 192−193 °C. ^{1}H NMR ($CDCl_3$): δ 8.83 (brs, 1H, NH), 8.65 (s, 1H, H-4), 8.64 (d, J = 9.0, 1H, H-5), 8.27 (d, J = 9.0, 1H, H-6), 4.47 (q, J = 7.1, 2H, O*CH*$_2$CH$_3$), 2.53 (t, J = 7.4, 2H, $CH_3CH_2CH_2$*CH*$_2$-CO), 1.74 (pentet, J = 7.5, 2H, CH_3CH_2*CH*$_2$CH$_2$CO), 1.45 (t, J = 7.2, 3H, OCH$_2$*CH*$_3$), 1.42 (m, 2H, CH_3*CH*$_2$CH$_2$CH$_2$CO), 0.95 (t, J = 7.3, 3H, *CH*$_3$CH$_2$CH$_2$CH$_2$CO); ^{1}H NMR (DMSO-d_6): δ 11.25 (s, 1H, NH), 8.92 (s, 1H, H-4), 8.58 (d, J = 9.1, 1H, H-5), 8.48 (d, J = 9.1, 1H, H-6), 4.38 (q, J = 7.1, 2H, O*CH*$_2$CH$_3$), 2.49 (t, J = 7.8, 2H, CH_3CH_2-CH_2*CH*$_2$CO), 1.59 (pentet, J = 7.5, 2H, CH_3CH_2*CH*$_2$CH$_2$CO), 1.36 (t, J = 7.0, 3H, OCH$_2$*CH*$_3$), 1.33 (m, 2H, CH_3*CH*$_2$CH$_2$CH$_2$CO), 0.87 (t, J = 7.3, 3H, *CH*$_3$CH$_2$CH$_2$CH$_2$CO); ^{13}C NMR (DMSO-d_6): δ 174.2, 164.4, 157.4, 155.3, 150.1, 143.0, 141.2, 123.6, 118.8, 116.6, 62.5, 36.7, 27.4, 22.4, 14.6, 13.4. MS (EI, 70 eV): *m*/*z* 335.1 (20, M^+), 306.1 (48), 293.1 (27), 251.1 (100), 206.1 (58). MS (FAB): 336.0 ($M + H)^+$. HRMS (FAB). Calcd for $C_{16}H_{19}ClN_3O_3$: 336.1115. Found: 336.1115. Anal. Calcd for $C_{16}H_{18}ClN_3O_3$: C, 57.23; H, 5.40; N, 12.51; Cl, 10.56. Found: C, 56.93; H, 5.31; N, 12.25; Cl, 10.45.

2-Chloro-3-carbethoxy-7-amino-*N*-*tert*-BOC-*N*-butanoyl-1,8-naphthyridine (9a). To a suspension of 7.4 g (23 mmol) of **8a** in 170 mL of reagent grade dichloromethane were added 5.43 g (24.9 mmol) of BOC-anhydride followed by 0.54 g (4.4 mmol) of 4-*N*,*N*-(dimethylamino)pyridine (DMAP). After the addition of DMAP all solid dissolved to result in a brown solution. The solution was stirred at room temperature for 4 h at which time a TLC indicated complete consumption of **8a**. Then the brown solution was diluted with 100 mL of dichloromethane and 20 mL of ethyl acetate and passed through a 50 mL plug of silica gel eluting with 10% EtOAc−CH_2Cl_2. The fractions containing product were combined and the solvent was removed under vacuum. The resulting brown oil was chromatographed over 250 mL of silica gel (10% PE-CH_2Cl_2 to 10% EtOAc−CH_2Cl_2). The fractions containing the product were combined, and the resulting yellow oil was crystallized from a mixture of hexane and a small amount of ethyl acetate to afford 8.0 g (75%) of the desired **9a** as a white solid. An analytically pure sample of **9a** was obtained by second recrystallization from the same solvent: mp 113−115 °C. ^{1}H NMR: δ 8.67 (s, 1H, H-4), 8.29 (d, J = 8.5, 1H, H-5), 7.46 (d, J = 8.5, 1H, H-6), 4.46 (q, J = 7.0, 2H, O*CH*$_2$CH$_3$), 2.95 (t, J = 7.2, 2H, *CH*$_2$CH$_2$CH$_3$), 1.73 (m, J = 7.3, 2H, CH$_2$*CH*$_2$CH$_3$), 1.41 (t, J = 7.0, 3H, OCH$_2$*CH*$_3$), 1.34 (s, 9H, *tert*-Bu), 0.97 (t, J = 7.5, 3H, CH$_2$CH$_2$*CH*$_3$); ^{13}C NMR: δ 175.8, 163.9, 157.1, 154.8, 151.4, 151.2, 141.4, 138.9, 126.3, 123.4, 119.6, 84.3, 62.4, 39.6, 27.7, 18.0, 14.1, 13.6. Anal. Calcd for $C_{20}H_{24}N_3O_5Cl$: C, 56.94; H, 5.73; N, 9.96; Cl, 8.40. Found: C, 56.90; H, 5.72; N, 9.76; Cl, 8.48.

2-Chloro-3-carbethoxy-7-amino-*N*-*tert*-BOC-*N*-pentanoyl-1,8-naphthyridine (9b). Using the procedure described for **9a**, a suspension of 2.79 g (8.31 mmol) of **8b**, 2.0 g (9.15 mmol) of BOC-anhydride, and 0.22 g (1.8 mmol) of DMAP afforded a crude brown oil, which was purified by column chromatography over silica gel (5−10% EtOAc−CH_2Cl_2) to afford 3.52 g (97%) of **9b** as white needles: mp 104−106 °C. ^{1}H NMR: δ 8.70 (s, 1H, H-4), 8.30 (d, J = 8.5, 1H, H-5), 7.48 (d, J = 8.4, 1H, H-6), 4.49 (q, J = 7.2, 2H, O*CH*$_2$CH$_3$), 3.00 (t, J = 7.6, 2H, $CH_3CH_2CH_2$*CH*$_2$CO), 1.70 (m, 2H, CH_3CH_2*CH*$_2$-CH_2CO), 1.46 (t, J = 7.2, 3H, OCH$_2$*CH*$_3$), 1.42 (m, 2H, CH_3*CH*$_2$CH$_2$-CH_2CO), 0.94 (t, J = 7.3, 3H, *CH*$_3$CH$_2$CH$_2$CH$_2$CO). ^{13}C NMR: δ 176.0, 164.0, 157.2, 154.8, 151.2, 141.4, 138.9, 127.5, 126.4, 123.5, 119.6, 84.3, 62.5, 37.6, 27.8, 26.6, 22.2, 14.2, 13.9. MS (FAB): 436.1 ($M + H)^+$. HRMS (FAB). Calcd for $C_{21}H_{27}ClN_3O_5$: 436.1639. Found: 436.1640. Anal. Calcd for $C_{21}H_{26}ClN_3O_5$: C, 57.86; H, 6.01; N, 9.64; Cl, 8.13. Found: C, 57.73; H, 6.05; N, 9.51; Cl, 8.41.

2-Chloro-3-carbethoxy-7-amino-*N*-*tert*-BOC-1,8-naphthyridine (10). A suspension of 3.52 g (8.08 mmol) of **9b**, 2.23 g (16.2 mmol) of potassium carbonate in a mixture of 30 mL of reagent grade dichloromethane, and 40 mL of reagent grade ethanol was stirred for 3 h at room temperature. An additional 2.23 g (16.2 mmol) of potassium carbonate were added. The suspension became yellow over time and was stirred at room temperature for 24 h at which time TLC showed complete consumption of **9b**. The suspension was filtered to give a yellow solid and the solvent removed from the filtrate under vacuum retaining the residue. The yellow solid was partitioned between 80 mL

of dichloromethane and 60 mL of water. The organic layer was combined with the retained residue and washed with 100 mL of a solution prepared by saturation with sodium bicarbonate and addition of 1 mL of glacial acetic acid. The collected organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (5−10% EtOAc−CH_2Cl_2) to afford 2.40 g (93%) of the desired product as white needle crystals: mp 125−126 °C. ^{1}H NMR: δ 8.63 (s, 1H, H-4), 8.42 (d (br), 1H, H-5), 8.20 (d, J = 9.2, 1H, H-6), 7.78 (s, 1H, NH), 4.46 (q, J = 7.4, 2H, OCH_2CH$_3$), 1.55 (s, 9H, *tert*-Bu), 1.44 (t, J = 7.1, 3H, OCH$_2$$CH_3$); ^{13}C NMR: δ 168.5, 156.4, 154.9, 151.8, 151.6, 141.6, 139.4, 123.6, 117.6, 114.4, 82.5, 62.6, 28.1, 14.2. MS (FAB): 352.10 (M + H)$^+$. HRMS (FAB). Calcd for $C_{16}H_{19}ClN_3O_4$: 352.1064. Found: 352.1062. Anal. Calcd for $C_{16}H_{18}N_3O_4Cl$: C, 54.63; H, 5.16; N, 11.94; Cl, 10.08. Found: C, 54.45; H, 5.13; N, 11.80; Cl, 10.32.

2-Chloro-3-carbethoxy-7-amino-*N*-*tert*-BOC-*N*-(3′,5′-bis(3″,5″-di-(*tert*-butyl)benzyloxy)benzyl)-1,8-naphthyridine (12a). A suspension of 3.66 g (10.4 mmol) of chloronaphthyridine **10**, 5.8 g (9.7 mmol) of **11a**, 9.8 g (71 mmol) of potassium carbonate, and 136 mg (0.6 mmol) of 18-crown-6 in a mixture of 60 mL of THF and 110 mL of acetonitrile was heated to reflux for 4 h at which time TLC indicated consumption of starting materials. The resulting yellow suspension was cooled to room temperature, and the solvent was removed at reduced pressure. The resulting yellow residue was partitioned between 200 mL of water and 260 mL of dichloromethane. The organic layer was washed with 200 mL of water and dried over Na_2SO_4, and the solvent was removed in vacuo. The resulting yellowish solid was recrystallized from heptane−toluene to afford 6.8 g (80%) of **12a** as a white solid. An analytically pure sample of **12a** was obtained by preparative thin-layer chromatography over silica gel (30% petroleum ether−dichloromethane to dichloromethane to 10% ethyl acetate−dichloromethane): mp 210−211 °C. ^{1}H NMR: δ 8.60 (s, 1H, H-4), 8.28 (d, J = 8.8, 1H, H-5), 8.09 (d, J = 8.8, 1H, H-6), 7.38 (t, J = 1.5, 2H, H-4″), 7.24 (d, J = 1.5, 4H, H-2″, H-6″), 6.67 (d, J = 2.1, 2H, H-2′, H-6′), 6.53 (t, J = 2.1, 1H, H-4′), 5.48 (s, 2H, NCH_2Ar), 4.94 (s, 4H, OCH_2Ar), 4.45 (q, J = 7.1, 2H, OCH_2CH$_3$), 1.48 (s, 9H, *tert*-BuO), 1.44 (t, J = 7.1, 3H, OCH$_2$$CH_3$), 1.32 (s, 36H, *tert*-Bu); ^{13}C NMR: δ 164.2, 164.0, 158.8, 154.7, 153.9, 151.1, 150.9, 141.3, 140.9, 137.5, 135.8, 123.9, 122.2, 121.1, 119.8, 117.6, 106.6, 100.5, 82.9, 70.8, 62.1, 49.4, 34.8, 31.4, 28.0, 14.1. Anal. Calcd for $C_{53}H_{68}N_3O_6Cl$: C, 72.45; H, 7.80; N, 4.78; Cl, 4.04. Found: C, 72.65; H, 7.88; N, 4.61; Cl, 4.21.

2-Chloro-3-carbethoxy-7-amino-*N*-(3′,5′-bis-(3″,5″-di-*tert*-butyl)-benzyloxy)benzyl-1,8-naphthyridine (13a). To a clear solution of 1.3 g (1.5 mmol) of **12a** in 50 mL of reagent grade dichloromethane were added 0.8 mL of trifluoroacetic acid. The solution was stirred overnight at room temperature at which time it became pale yellow. The solution was washed with 40 mL of a saturated aqueous solution of sodium bicarbonate, collected, and dried over Na_2SO_4, and the solvent was removed at reduced pressure. The resulting yellowish solid was recrystallized from heptane−toluene to afford 1 g (86%) of the desired **13a** as a white solid. An analytically pure sample of **13a** was obtained by column chromatography over silica gel (1−5% methanol−chloroform): mp 229−231 °C. ^{1}H NMR: δ 8.44 (s, 1H, H-4), 7.77 (d, J = 8.8, 1H, H-5), 7.42 (t, J = 1.7, 2H, H-4″), 7.27 (d, J = 1.7, 4H, H-2″, H-6″), 6.72 (d, J = 8.8, 1H, H-6), 6.68 (d, J = 2.1, 2H, H-2′, H-6′), 6.53 (t, J = 2.1, 1H, H-4′), 4.82 (d, J = 5.6, 2H, NCH_2-Ar), 4.98 (s, 4H, OCH_2Ar), 4.42 (q, J = 7.0, 2H, OCH_2CH$_3$), 1.43 (t, J = 7.1, 3H, OCH$_2$$CH_3$), 1.34 (s, 36H, *tert*-Bu); ^{13}C NMR: (THF) δ 164.8, 161.9, 161.5, 158.6, 151.4, 150.9, 142.3, 141.9, 137.7, 137.6, 122.9, 122.4, 120.3, 116.3, 115.7, 107.8, 101.3, 71.3, 61.8, 46.0, 35.4, 31.8, 14.6. Anal. Calcd for $C_{48}H_{60}N_3O_4Cl$: C, 74.06; H, 7.77; N, 5.40; Cl, 4.55. Found: C, 74.19; H, 7.89; N, 5.42; Cl, 4.73.

2,8-Diamino-2-*N*-ethyl-8-*N*-(3′,5′-bis(3″,5″-di-*tert*-butyl)benzyloxy)-benzylpyrimido(4,5-*b*)(1,8)naphthyridine-3*H*-4-one (2a). To a mixture of 40 mL of THF and 40 mL of *tert*-butyl alcohol were added 0.52 g (13 mmol) of sodium hydride as a 60% (w/w) suspension in oil and the mixture was heated to reflux for 10 min at which time hydrogen gas evolution ceased. To the resulting turbid mixture was added 2 g (7.35 mmol) of bis(*N*-ethyl guanidinium) sulfate and the mixture was heated to reflux for 20 min. The resulting turbid solution was separated from the insoluble salts by pipet and added to 1.7 g (2.2 mmol) of **13a** and then sealed into a glass tube. The resulting yellow mixture was heated in a 160 °C oil bath for 24 h. All the initial **13a** dissolved after ca. 20 min, and a new solid formed after ca. 12 h. The resulting yellow suspension was cooled to room temperature, and the solvent was removed in vacuo. The resulting yellow residue was partitioned between 150 mL of dichloromethane and 120 mL of a saturated aqueous solution of sodium bicarbonate and 2 mL of a 6 N aqueous solution of hydrochloric acid. The collected organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The product was further purified by column chromatography over silica gel (5% methanol−dichloromethane to 10% methanol−dichloromethane) followed by preparative size exclusion chromatography in toluene over S−X beads (Bio-Rad; 400−14 000 Da) to afford 1.1 g (64%) of the desired **2a** as a yellow solid: mp 218−220 °C. ^{1}H NMR (DMSO-d_6): δ 10.75 (br, 1H, NH-3), 8.50 (s, 1H, H-5), 8.02 (br s, 1H, NH-8), 7.93 (br d, 1H, H-7), 7.33 (t, J = 1.7, 2H, H-4″), 7.24 (d, J = 1.7, 4H, H-2″, H-6″), 6.76 (d, J = 8.0, 1H, H-6), 6.68 (d, J = 1.9, 2H, H-2′, H-6′), 6.61 (t, 1H, H-4′), 6.50 (br s, 1H, NH-2), 5.01 (s, 4H, OCH_2Ar), 4.63 (d, J = 5.1, 2H, 8-N-CH_2), 3.40 (quintet, J = 5.9, 2H, 2-N-CH_2), 1.27 (s, 36H, *tert*-Bu), 1.16 (t, J = 7.1, 3H, NCH$_2$$CH_3$); ^{1}H NMR (deacidified $CDCl_3$): δ 13.95 (s, 1H, NH-3), 10.89 (s, 1H, NH-2), 10.33 (s, 1H, NH-8), 8.21 (s, 1H, H-5), 7.33 (s br, 2H, H-4″), 7.28 (d, J = 8.7, 1H, H-6), 7.20 (br s, 4H, H-2″, H-6″), 6.76 (d, J = 8.7, 1H, H-7), 6.68 (d, J = 1.9, 2H, H-2′, H-6′), 6.61 (t, J = 1.9, 1H, H-4′), 4.93 (AB q, J = 11, 4H, OCH_2Ar), 4.72 (br d, J = 10.9, 1H, 8-N-CH_2), 4.42 (br d, J = 13.8, 1H, 8-N-CH_2), 4.33 (br s,1H, 2-N-CH_2), 4.19 (br s, 1H, 2-N-CH_2), 1.47 (br, 3H, NCH$_2$$CH_3$), 1.26 (s, 36H, *tert*-Bu); ^{13}C NMR: δ 165.4, 162.6, 162.4, 160.5, 160.0, 154.2, 150.9, 141.4, 139.1, 137.6, 135.6, 122.3, 122.2, 113.4, 109.6, 107.1, 105.7, 100.6, 70.9, 46.6, 35.4, 34.8, 31.4, 16.6; IR (deacidified $CHCl_3$): 1688. MS (MALDI): 784.4 (M + H)$^+$. MS (FAB): 783.5 (M)$^+$. Anal. Calcd for $C_{49}H_{62}N_6O_3$: C, 75.16; H, 7.98; N, 10.73. Found: C, 75.16; H, 7.79; N, 10.77.

2-Chloro-3-carbethoxy-7-amino-*N*-*tert*-BOC-*N*-(3′,5′-bis(3″,5″-bis(3‴,5‴-di(*tert*-butyl)benzyloxy)benzyloxy)benzyl)-1,8-naphthyridine (12b). Using the procedure described for **12a**, a suspension of 0.352 g (1.0 mmol) of chloronaphthyridine **10**, 1.255 g (1.0 mmol) of **11b** (G2-Br), 0.966 g of potassium carbonate, and 14 mg of 18-crown-6 in a mixture of 6 mL of THF and 11 mL of acetonitrile afforded yellowish oil, which was purified twice by column chromatography (CH_2Cl_2−hexane = 2:1) to give 0.72 g of **12b** (47%). ^{1}H NMR: δ 8.58 (s, 1H, H-4), 8.26 (d, J = 9.0, 1H, H-5), 8.05 (d, J = 9.0, 1H, H-6), 7.40 (t, J = 1.7, 4H, H-4‴), 7.27 (d, J = 1.7, 8H, H-2‴, H-6‴), 6.69 (d, J = 2.4, 4H, H-2″, H-6″), 6.62 (t, 2H, H-4″), 6.60 (d, 2H, H-2′, H-6′), 6.49 (t, 1H, H-4′), 5.46 (s, 2H, NCH$_2$), 4.98 (s, 8H, Ar‴CH$_2$OAr″), 4.93 (s, 4H, Ar″CH$_2$OAr′), 4.44 (q, J = 7.0, 2H, OCH_2-CH$_3$), 1.43 (s, 9H, *tert*-BuO), 1.42(t, J = 7.0, 3H, OCH$_2$$CH_3$), 1.33(s, 72H, *tert*-Bu); ^{13}C NMR: δ 164.0, 160.2, 160.1, 159.7, 154.6, 153.7, 151.0, 150.9, 141.3, 141.0, 139.0, 137.5, 135.5, 123.8, 122.2, 122.1, 117.5, 106.4, 106.2, 106.1, 101.3, 100.5, 82.8, 70.9, 69.9, 62.0, 34.7, 31.3, 27.9, 14.1; MS (MALDI): *m*/*z* 1527.65 (M + H)$^+$; MS (FAB): *m*/*z* 1528.0 (M + H)$^+$. Anal. Calcd for $C_{97}H_{124}ClN_3O_{10}$: C, 76.27; H, 8.18; N, 2.75. Found: C, 76.69; H, 8.54; N, 2.31.

2-Chloro-3-carbethoxy-7-amino-*N*-(3′,5′-bis(3″,5″-bis(3‴,5‴-di-*tert*-butyl)benzyloxy)benzyloxy)benzyl-1,8-naphthyridine (13b). Using the procedure described for **13a**, a solution of 0.72 g of **12b** in 20 mL of reagent grade CH_2Cl_2 and 0.5 mL of trifluoroacetic acid afforded yellowish oil, which was purified by column chromatography (2% MeOH−$CHCl_3$) to give 0.30 g (45%) of **13b**. ^{1}H NMR: δ 8.44 (s, 1H, H-4), 7.76 (d, J = 9.2, 1H, H-5), 7.40 (t, J = 1.6, 4H, H-4‴), 7.27 (d, J = 1.7, 8H, H-2‴, H-6‴), 6.71 (d, J = 2.4, 4H, H-2″, H-6″), 6.67

(d, J = 9.0, 1H, H-6), 6.64 (t, J = 2.3, 2H, H-4″), 6.63 (d, J = 2.5, 2H, H-2′, H-6′), 6.58 (t, J = 2.2, 1H, H-4′), 4.99 (s, 8H, OCH_2″Ar), 4.98 (s, 4H, OCH_2′Ar), 4.78 (s, 2H, 8-N-CH_2), 4.43 (q, J = 7.1, 2H, OCH_2CH$_3$), 1.43 (t, J = 7.1, 3H, OCH$_2$$CH_3$), 1.33 (s, 72H, *tert*-Bu); ^{13}C NMR: δ 167.9, 160.7, 160.5, 151.3, 141.7, 139.1, 135.8, 124.9, 122.6, 122.2, 106.7, 106.6, 101.7, 101.4, 70.4, 57.8, 35.1, 31.7, 14.4; MS (MALDI): 1426.79 (M + H)$^+$. Anal. Calcd for $C_{92}H_{116}ClN_3O_8$: C, 77.41; H, 8.19; N, 2.94. Found: C, 77.37; H, 8.35; N, 2.76.

2,8-Diamino-2-*N*-ethyl-(8-*N*-(3′,5′-bis(3″,5″-bis(3‴,5‴-di-*tert*-butyl)benzyloxy)benzyloxy)benzyl)pyrimido(4,5-*b*)(1,8)naphthyridine-3*H*-4-one (2b). Using the procedure described for **2a**, in a glass sealed tube placed in a 160 °C oil bath, the reaction of 0.3 g (0.21 mmol) of **13b** with *N*-ethylguanidine which was generated by refluxing a solution of 0.2 g (0.735 mmol) of bis(*N*-ethylguanidinium) sulfate and 52 mg (1.3 mmol) of sodium hydride in a mixture of 4 mL of dry THF and 4 mL of dry *tert*-butyl alcohol afforded yellowish residue, which was purified by column chromatography (2−5% MeOH−CH_2Cl_2), followed by preparative size exclusion chromatography in toluene over S−X beads (Bio-Rad: 400−14 000 Da) to afford 80 mg of **2b** (30%) as a yellow solid: mp 138−140 °C. ^{1}H NMR: δ (deacidified $CDCl_3$) 14.40 (s, 1H, NH-3), 10.90 (s, 1H, NH-2), 10.10 (s, 1H, NH-8), 8.65 (s, 1H, H-5), 7.72 (d, J = 8.7, 1H, H-6), 7.39 (t, 4H, H-4‴), 7.24 (d, 8H, H-2‴, H-6‴), 7.18 (d, J = 8.7, 1H, H-7), 6.71 (d, 4H, H-2″, H-6″), 6.62 (t, 2H, H-4″), 6.56 (d, 2H, H-2′, H-6′), 6.54 (t, 1H, H-4′), 5.00 (s, 12H, -CH_2OAr), 4.60 (s, br, 2H, 8-N-CH_2), 4.16 (s, br, 2H, 2-N-CH_2), 1.45 (br, 3H, NCH$_2$$CH_3$), 1.29 (s, 72H, *tert*-Bu); ^{13}C NMR: δ 172.8, 160.9, 160.6, 151.3, 139.2, 138.8, 135.9, 125.1, 122.6, 118.1, 106.8, 105.9, 101.8, 97.2, 71.3, 54.3, 35.1, 31.8, 29.3, 16.2; MS (MALDI): 1430.4 (M)$^+$; MS (FAB): 1431.8 (M + H)$^+$. Anal. Calcd for $C_{93}H_{118}N_6O_7$: C, 78.00; H, 8.31; N, 5.87. Found: C, 77.81; H, 8.41; N, 5.56.

2-Chloro-3-carbethoxy-7-amino-*N*-*tert*-BOC-*N*-(3′,5′-bis(3″,5″-bis(3‴,5‴-bis(3⁗,5⁗-di-*tert*-butyl)benzyloxy)benzyloxy)benzyloxy)-benzyl-1,8-naphthyridine (12c). Using the procedure described for **12b**, reaction of **11c** (G3-Br, 1.22 g, 0.5 mmol) with **10** (0.183 g, 0.5 mmol) in the presence of potassium carbonate and 18-crown-6 in CH_3-CN/THF afforded 0.95 g (70%) of **12c** as yellow oil. ^{1}H NMR: δ 8.54 (s, 1H, H-4), 8.24 (d, J = 9.0, 1H, H-5), 8.03 (d, J = 9.2, 1H, H-6), 7.39 (t, J = 1.8, 8H, H-4⁗), 7.27 (d, J = 1.9, 16H, H-2⁗, H-6⁗), 6.72 (d, J = 2.1, 8H, H-2‴, H-6‴), 6.66 (d, J = 2.2, 4H, H-2″, H-6″), 6.64 (t, J = 2.2, 4H, H-4‴), 6.60 (d, J = 2.2, 2H, H-2′, H-6′), 6.57 (t, J = 2.2, 2H, H-4″), 6.51 (t, J = 2.3, 1H, H-4′), 5.44 (s, 2H, NCH_2-Ar′), 5.00 (s, 16H, OCH_2Ar⁗), 4.97 (s, 8H, OCH_2Ar‴), 4.92 (s, 4H, OCH_2Ar″), 4.40 (q, J = 7.2, 2H, COOCH_2CH$_3$), 1.41 (s, 9H, *tert*-butyl), 1.38 (t, J = 7.1, 3H, COOCH$_2$$CH_3$), 1.32(s, 144H, *tert*-Bu); ^{13}C NMR: δ 164.4, 160.7, 160.4, 160.1, 159.1, 154.9, 151.4, 151.3, 141.7, 139.6, 139.2, 137.9, 135.9, 122.6, 122.5, 122.4, 119.9, 117.9, 106.7, 106.6, 101.8, 71.2, 70.3, 62.3, 57.8, 35.1, 31.7, 28.3, 14.4; MS (MALDI): 2847.92 (M + Na)$^+$; MS (FAB): 2725.8 (M − BOC)$^+$. Anal. Calcd for $C_{185}H_{236}ClN_3O_{18}$: C, 78.47; H, 8.51; N, 1.29. Found: C, 78.65; H, 8.42; N, 1.49.

2-Chloro-3-carbethoxy-7-amino-*N*-(3′,5′-bis(3″,5″-bis(3‴,5‴-bis(3⁗,5⁗-di-*tert*-butyl)benzyloxy)benzyloxy)benzyl-1,8-naphthyridine (13c). Using the procedure described for **13b**, a solution of 2.26 g of **12c** (0.8 mmol) and 0.5 mL of trifluoroacetic acid (TFA) in 30 mL of CH_2Cl_2 afforded 1.40 g (64%) of **13c** as a pale yellow solid: mp 108−111 °C. ^{1}H NMR: δ 8.40 (s, 1H, H-4), 7.71 (d, J = 9.2, 1H, H-5), 7.39 (t, J = 1.9, 8H, H-4⁗), 7.27 (d, J = 1.9, 16H, H-6⁗, H-2⁗), 6.72 (d, J = 2.2, 8H, H-6‴, H-2‴), 6.67 (d, J = 2.2, 4H, H-6″, H-2″), 6.64 (t, J = 2.2, 4H, H-4‴), 6.59 (t, J = 2.2, 2H, H-4″), 6.58 (d, J = 2.2, 2H, H-6′, H-2′), 6.57 (t, J = 2.2, 1H, H-4′), 6.55 (d, J = 8.9, 1H, H-6), 4.98 (s, 16H, OCH_2Ar⁗), 4.97 (s, 8H, OCH_2Ar‴), 4.95 (s, 4H, OCH_2Ar″), 4.95 (d, 2H, NCH_2Ar), 4.72 (s, br, 1H, *NH*CH$_2$Ar′), 4.40 (q, J = 7.1, 2H, COOCH_2CH$_3$), 1.41 (t, J = 7.1, 3H, COOCH$_2$$CH_3$), 1.32 (s, 144H, *tert*-Bu); ^{13}C NMR: δ 164.7, 160.7, 160.5, 160.4, 151.3, 141.6, 139.3, 139.2, 135.9, 122.6, 122.5, 120.4, 115.6, 106.7, 106.6, 101.9, 101.8, 71.3, 61.9, 57.8, 35.1, 31.7, 14.4; MS (MALDI): 2724.83; MS (FAB): 2725.0 (M + H)$^+$.

2,8-Diamino-2-*N*-ethyl-(8-*N*-(3′,5′-bis(3″,5″-bis(3‴,5‴-bis(3⁗,5⁗-di-*tert*-butyl)benzyloxy)benzyloxy)benzyloxy)benzyl)pyrimido(4,5-*b*)(1,8)naphthyridine-3*H*-4-one (2c). Using the procedure described for **2b**, 0.8 g of **13c** (0.29 mmol) was used to react with *N*-ethylguanidinium generated from 0.27 g of bis(*N*-ethylguanidinium) sulfate and sodium hydride to give 0.51 g (64%) of **2c** as a yellow solid: mp 120−122 °C. ^{1}H NMR (deacidified $CDCl_3$): δ 14.40 (s, 1H, NH-3), 10.90 (s, 1H, NH-2), 10.10 (s, 1H, NH-8), 8.64 (s, 1H, H-5), 7.68 (brs, 1H, H-6), 7.38 (brs, 8H, H-4⁗), 7.34 (brs, 8H, H-2⁗, H-6⁗), 7.22 (d, J = 2.5, 16H, H-2⁗, H-6⁗), 7.17 (brs, 1H, H-7), 6.70 (brs, 4H, H-4″), 6.68 (brs, 1H, H-2″, H-6″), 6.63 (brs, 2H, H-2′, H-6′), 6.60 (brs, 2H, H-4″), 6.55 (brs, 1H, H-4′), 5.0 (brs, 26H, −OCH_2Ar), 4.80 (d, br, 2H, −CH_2N-8), 4.55 (d, br, 2H, −CH_2N-2), 1.43 (br, 3H, −NCH$_2$$CH_3$), 1.31 (s, 144H, *tert*-Bu); ^{13}C NMR: δ 160.6, 160.4, 157.7, 151.3, 151.2, 139.2, 135.9, 122.6, 122.5, 122.4, 106.7, 101.7, 71.2, 57.8, 35.1, 31.7, 31.4, 16.8; MS (MADLI): 2730.34 (M + H)$^+$. Anal. Calcd for $C_{181}H_{230}N_6O_{15}$: C, 79.64; H, 8.49; N, 3.08. Found: C, 79.67; H, 8.54; N, 3.04.

Size Exclusion Chromatography. Analytical SEC was performed on a Hitachi SEC system including a Model L-6000 HPLC pump, Model L-4000H UV detector, Model D-2520 GPC integrator, and a Waters 410 differential refractometer. Two Waters Styragel HR3 (7.8 × 300 mm; effective molecular weight range, 500−30 000) SEC columns were connected in series. The flow rate was 1 mL/min unless otherwise noted.

Dynamic Light Scattering. Performed on a DynaPro-MS/X from Protein Solutions, Inc., (Charlottesville, VA) equipped with He−Ne Laser (10 mW) operating at 632.8 nm. All samples are measured at 90° scattering angle. Solutions were prepared in HPLC grade toluene (Sigma, 99.8% pure) and were filtered with 0.2 μm Nylon filter from Millipore.

The autocorrelation function of the intensity was analyzed by the method of cumulants analysis to obtain the average diffusion coefficient, D, of the particles and the polydispersity. The hydrodynamic diameter, D_h, was calculated by means of the Stokes−Einstein equation ($D_h = k_BT/3\pi\eta D$, where k_BT is the thermal energy and η is the viscosity of the continuous phase).

Molecular Modeling. Modeling was performed using Macromodel and Cerius^2 (Accelrys) on a Silicon Graphics workstation. The radius of gyration (R_g) of all models was calculated by Cerius^2. The DREIDING2.21 force field was used with the energy of monomers and covalent standard **19** minimized first. The intramolecular hydrogen bond in monomer **20** was preformed. Six molecules of monomers were then arranged to form the corresponding hexamer containing 18 primary hydrogen bonds for **2**, 24 for both **1** and **20**. The threshold for a primary hydrogen bond was set to a 2.1 Å.[9] The energy was minimized with the resulting hexamers each maintaining all of the initial hydrogen bonds. During the entire simulated annealing process of the dynamics simulation, the hexamer core was held fixed while leaving the dendron substituents to change conformation. Both extended and extensively folded back (compact) starting structures were generated by manual bond rotations. With both starting structures dynamics simulations were performed 10 times with a heating cycle from 300 to 1000 K with increments of 50 K in 1000 steps (1 step = 1 fs). The overall process generated 20 frames of minimized structures for each starting compound structure. A separate value for the radius of gyration (R_g) of the extended and compact structures was taken as an average of these 20 minimized structures.

^{1}H NMR Dilution and Titration Study. Chloroform-*d* was deacidified by running through a column of activated basic aluminum oxide. DMSO-d_6 was used without further purification. NMR tubes and microsyringes were dried in oven and cooled under nitrogen.

Dilution Studies. A stock solution of sample with known concentration was prepared in a chosen solvent ($CDCl_3$, 5% or 10% of DMSO-

d_6 in $CDCl_3$ (v/v)), and a ^1H NMR spectrum was recorded. The temperature was maintained at 20 °C. Half of the sample was removed and replaced by solvent. After sufficient mixing, the spectrum was recorded for the second sample whose concentration is half of the first sample. This procedure was repeated until the sample was too dilute to give a detectable spectrum (4 h at 750 MHz). For **2a**, the ratio of hexamers to monomers was calculated on the basis of the integration values of two sets of *tert*-butyl proton signals under the assumption of slow exchange between hexamers and monomers on the NMR time scale. For complex **17·18**, the observed chemical shifts represent the weighted average of the free and complexed monomers due to their fast exchange on the NMR time scale. The ratio of complexed species could be calculated by the following equation: complex % $= \Delta\delta/\Delta\delta_{max}$, while $\Delta\delta = \delta - \delta_{monomer}$ and $\Delta\delta_{max} = \Delta\delta_{complex} - \Delta\delta_{monomer}$.

Titration Studies. ^1H NMR spectrum of 0.65 mL of stock solution of **2** in deacidified $CDCl_3$ was recorded. The temperature was maintained at 20 °C. Then 0.01 mL (0.05 mL for **2a**) of DMSO-d_6 was added to the solution. After sufficient mixing, the ^1H NMR spectrum was recorded. This procedure was repeated until no hexamer signal could be observed in the spectrum. Once again, the ratio of hexamers to monomers was calculated on the basis of the integration values of two sets of *tert*-butyl proton signals under the assumption of slow exchange between hexamers and monomers on an NMR time scale.

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