Self-Assembly Mediated by the Donor−Donor−Acceptor·Acceptor−Acceptor−Donor (DDA·AAD) Hydrogen-Bonding Motif: Formation of a Robust Hexameric Aggregate

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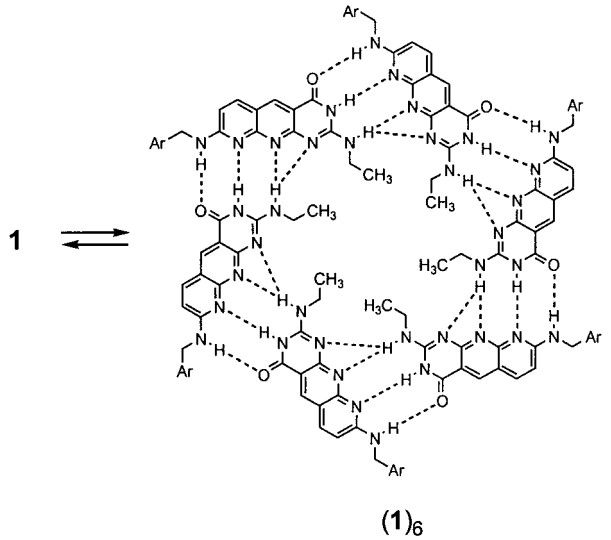
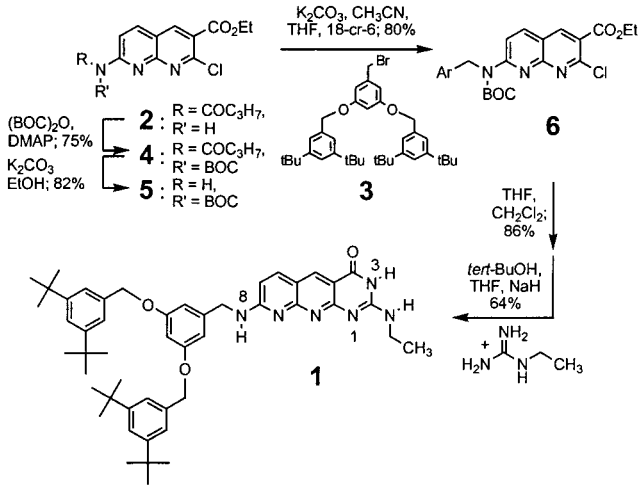
There is currently intense interest in hydrogen bond mediated self-assembly.[1] Considerable effort in this area has focused on discrete, cyclic assemblies containing between 3 and 10 molecules.[1,2] A few hydrogen-bonding motifs have dominated this work, including those found in the cyanuric acid−melamine system,[1a,2a] carboxylic acid[2b] or pyridone dimers,[2c,d] and 2-aminopyridine−carboxylic acid complexes.[2e] Despite the synthetic accessibility of compounds possessing these various functional groups, the hydrogen bonding contacts that they make have distinct drawbacks. First, the contacts are rather weak ($K_{assoc} \approx 100\ M^{-1}$ in $CDCl_3$).[3] Furthermore, at appropriate concentrations the closed assemblies are formed because they are enthalpically favored over polymeric ones, not because hydrogen-bonding specifically guides the formation of cyclic aggregates.

Herein we describe an especially stable, hexameric, disk-shaped aggregate $(\mathbf{1})_6$ containing 18 hydrogen bonds formed by the pairing of self-complementary DDA and AAD sites in **1**.[4] The information in the DDA·AAD hydrogen-bonding motif is unambiguous, dictating formation of a cyclic aggregate from **1**. Additionally, six (secondary) hydrogen bonds may be present in $(\mathbf{1})_6$ because the 2-NH group can serve as a long-range donor to



N-1.[3,5] Even without this auxiliary contact the DDA·AAD contacts in $(\mathbf{1})_6$ are likely to be at least 2 orders of magnitude stronger ($K_{assoc} \geq 10^4\ M^{-1}$ in $CDCl_3$) than those used in the cyclic aggregates described above.[3,5]

Scheme 1



The synthesis of **1** started with the chloronaphthyridine **2**[6] and a first generation dendron **3**, which was synthesized by a convergent approach similar to that used by Fréchet[7] (Scheme 1). The alkylation of **2** (R = COC_4H_9) with **3** produced both *O*- and *N*-alkylated regioisomers in an almost 1:1 ratio. Although the desired isomer was isolated in ca. 30% yield, a superior procedure used BOC derivative **5**, prepared via **4**. Deprotection of **6** and subsequent cyclization[8] with *N*-ethyl guanidine, generated in situ from sodium hydride and an excess of its sulfate salt, produced **1** in 55% yield.

The elemental analysis and FAB mass spectra (M + H = 783.5 for $C_{49}H_{62}N_6O_3$) were consistent with the proposed structure of **1**. The structure was further corroborated by ^{1}H NMR in DMSO-d_6 (60 °C), conditions in which **1** was expected to be monomeric due to the competitive nature of the solvent. Most importantly, the methylene of the *N*-ethyl group appears as a quintet indicating splitting by the neighboring methyl and 2-NH groups. Thus, the ethyl group is attached to N-2 and not N-3, as it would be in the regioisomeric product of the reaction between **6** (BOC-deprotected) with *N*-ethyl guanidine. All other signals in the spectrum are consistent with the assigned structure in the desired tautomeric form although other forms could not be ruled out.

The corresponding ^{1}H NMR spectra of **1** in THF-d_8, $CDCl_3$, and toluene-d_8 are very sharp and quite similar (Table 1). The slightly further downfield shifts in toluene might indicate stronger hydrogen bonding or a specific solvent effect. A COSY experiment allowed definitive assignment of all the protons of **1**. Of particular note are the chemical shifts of the NH groups which are far downfield of the analogous nonassociated NH groups in **7** and **8**, but in the region where NH groups appear in hydrogen-bonded complexes such as **10·9** and **10·11**. A NOESY spectrum

(1) For reviews see: (a) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37−44. (b) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (c) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229−2260. Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154−1196.

(2) For selected examples see: (a) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1215−1218. (b) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095−1098. (c) Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215−2217. (d) Boucher, E.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1995**, *60*, 1408−1412. (e) Yang, J.; Fan, E.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314−5415.

(3) Zimmerman, S. C.; Murray, T. J. *Philos. Trans. R. Soc. London, Ser. A* **1993**, *345*, 49−56 and references therein.

(4) During the course of this work a bicyclic system similar the tricyclic one described herein was reported by Lehn and Mascal: Marsh, A.; Silvestri, M.; Lehn, J.-M. *Chem. Commun.* **1996**, 1527−1528. Mascal, M.; Hext, N. M.; Warmuth, R.; Moore, M. H.; Turkenburg, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2204−2206.

(5) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008−2010. Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810−2819. Zimmerman, S. C.; Murray, T. J. *Tetrahedron Lett.* **1994**, 4077−4080.

(6) Fenlon, E. E.; Murray, T. J.; Baloga, M. H.; Zimmerman, S. C. *J. Org. Chem.* **1993**, *58*, 6625−6628.

(7) Hawker, C. J.; Wooley, K. L.; Frechet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, *21*, 1287−1297.

(8) Taylor, E. C.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 3618−3624.

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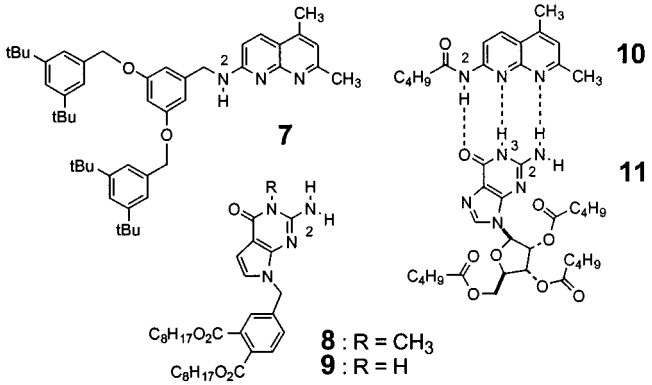
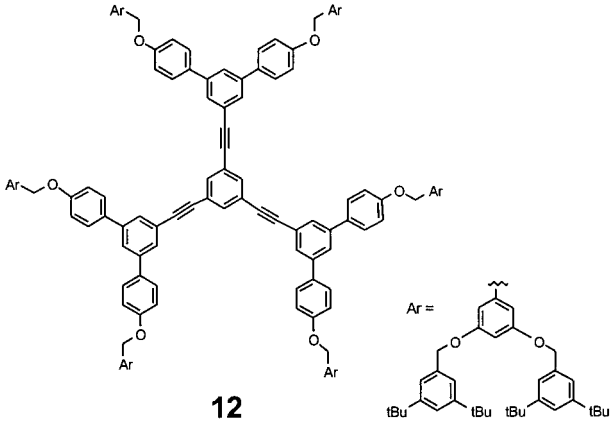
Table 1. ^{1}H NMR Chemical Shifts (ppm) of NH Groups in **1** and Model Compounds[a]

compd or complex	solvent	proton observed NH-2	NH-3	NH-8	concn (% hexamer)[b]
1	$CDCl_3$	10.89	13.96	10.33	0.3−13 mM (80)
	THF-d_8	11.00	14.04	10.48	90 μM to 10 mM (70)
	toluene-d_8	11.18	14.28	10.87	35 μM to 14 mM (70)
	CD_2Cl_2	10.86	13.94	10.32	4.2 mM (100)
	dioxane-d_8	10.94	13.94	10.38	4.8 mM (100)
	10% DMSO-d_6/$CDCl_3$	10.66	13.89	10.26	2.4 to 16 mM (70)
	8% H_2O/THF-d_8	11.00	14.00	10.40	6 mM (70)
8	$CDCl_3$	4.80			
7	$CDCl_3$	5.04			
9·10	$CDCl_3$	13.90[c] (**10**)			
10·11	$CDCl_3$		13.27[c] (**11**)		

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





of **1** in toluene-d_8 shows a strong cross-peak between the 8-NH and 3-NH groups that is also consistent with the pairing shown in $(\mathbf{1})_6$. Whereas the methylene groups of the benzylic ether groups resonate as singlets in DMSO-d_6, they appear as AB quartets in the less polar solvents of Table 1. Molecular modeling suggests that the methyl groups in the center of $(\mathbf{1})_6$ alternate up and down out of the plane of **1** so that the assembly has S_6 symmetry and all methylene protons are diastereotopic.

To determine the structure of the aggregate, molecular weight determinations were carried out by using size exclusion chromatography (SEC) calibrated with polystyrene standards. In either chloroform or dichloromethane, **1** interacts strongly with the matrix of the SEC column, and is fully retained. This absorption is attributed to the polar hydrogen-bonding sites interacting with the column matrix. The same SEC retention is observed for **7** in toluene and in dichloromethane. In pure toluene the aggregate of **1** is not adsorbed and its SEC peak is sharp and symmetrical; and the elution time is independent of the injection concentration (from 10 mM to 4 μM). It is estimated that ≥90% of the injected sample is eluted as determined by UV analysis of the collected peak. The aggregate has a polystyrene equivalent molecular weight between 5660 and 6050 Da, a value that is 20−29% higher than that calculated for a hexamer (4698 Da) and 3−10% higher than that calculated for a heptamer (5481 Da). Because of the uncertainties in using polystyrene as a standard, dendrimer **12** was prepared as a covalent analogue of $(\mathbf{1})_6$.[2c,9] Molecular modeling suggests a very similar size for **12** and $(\mathbf{1})_6$. Indeed, these compounds exhibit identical SEC elution times in toluene. Combined with the fact that a heptamer cannot be constructed with CPK models, the SEC results suggest formation of a hexameric aggregate from **1**.

The stability of the aggregate was further investigated by ^{1}H NMR experiments in various solvents (Table 1). The results of a dilution experiment in toluene-d_8 mirrored the SEC results with a stable aggregate present from 0.25 to 14 mM. Heating a solution of **1** in toluene-d_8 to 90 °C did not significantly alter the ^{1}H NMR spectra. Most strikingly, the aggregate persists across a broad concentration range in apolar solvents, and remains the predominant species at millimolar concentrations in 8% v/v aqueous THF and 10% DMSO−chloroform. Our previously reported[2b] hexameric aggregate fully dissociated in THF,[10] and the cyclic hexamer was favored over linear oligomeric aggregates only when peripheral steric interactions prevented formation of the latter.[11] The present results confirm the utility of the DDA·AAD hydrogen-bonding motif. Its superior stability and unambiguous information content make it an outstanding element for supramolecular construction.

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Supporting Information Available: Synthetic schemes and characterization data for compound **12** (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(9) The synthesis of **12** is described in the Supporting Information.

(10) A referee asked for a quantitative comparison of the thermodynamic stability of the two hexameric aggregates. Despite significant effort we have been unable to determine a K_6 value for **1** in solvents where monomer and hexamer coexist.

(11) Peripheral crowding was used in Whitesides' rosette assembly: Mathias J. P.; Simanek E. E.; Whitesides G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4326−4340.