

Self-Assembly Through Hydrogen Bonding: Preparation of a Supramolecular Aggregate Composed of Ten Molecules**

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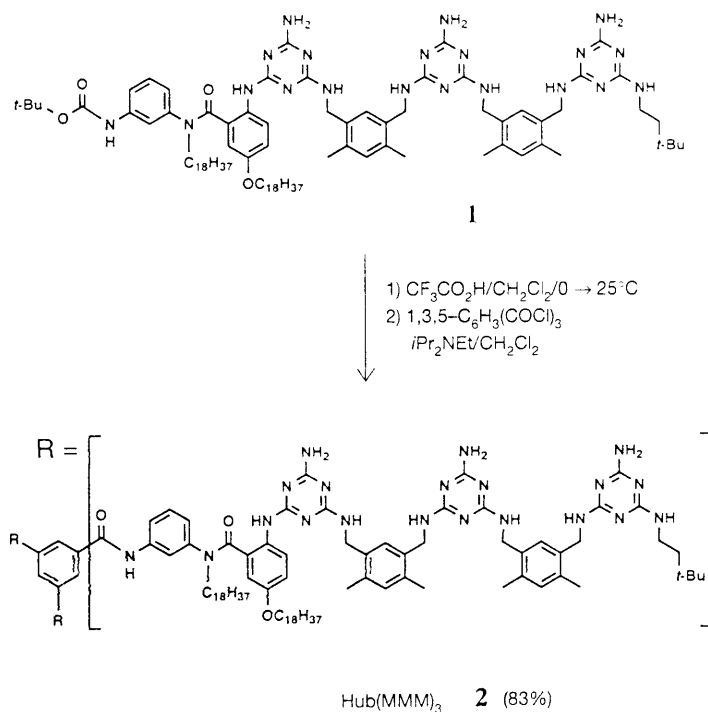
Learning how to control the association of many molecules into single, highly-structured supramolecular aggregates is a current objective in molecular self-assembly.^[1-5] In this communication we report the self-assembly of a supramolecular aggregate based on a compound containing

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nine melamine rings (M) that we have called Hub(MMM)₃ (2). This molecule associates with nine equivalents of neohexylisocyanurate (neohex(CA) 3) to form a hydrogen-bonded supramolecular aggregate of composition Hub(MMM)₃ · 9neohex(CA) (4). This aggregate is composed of ten molecules in three parallel CA₃ · M₃ "rosettes",^[6] and is stabilized by 54 hydrogen bonds.

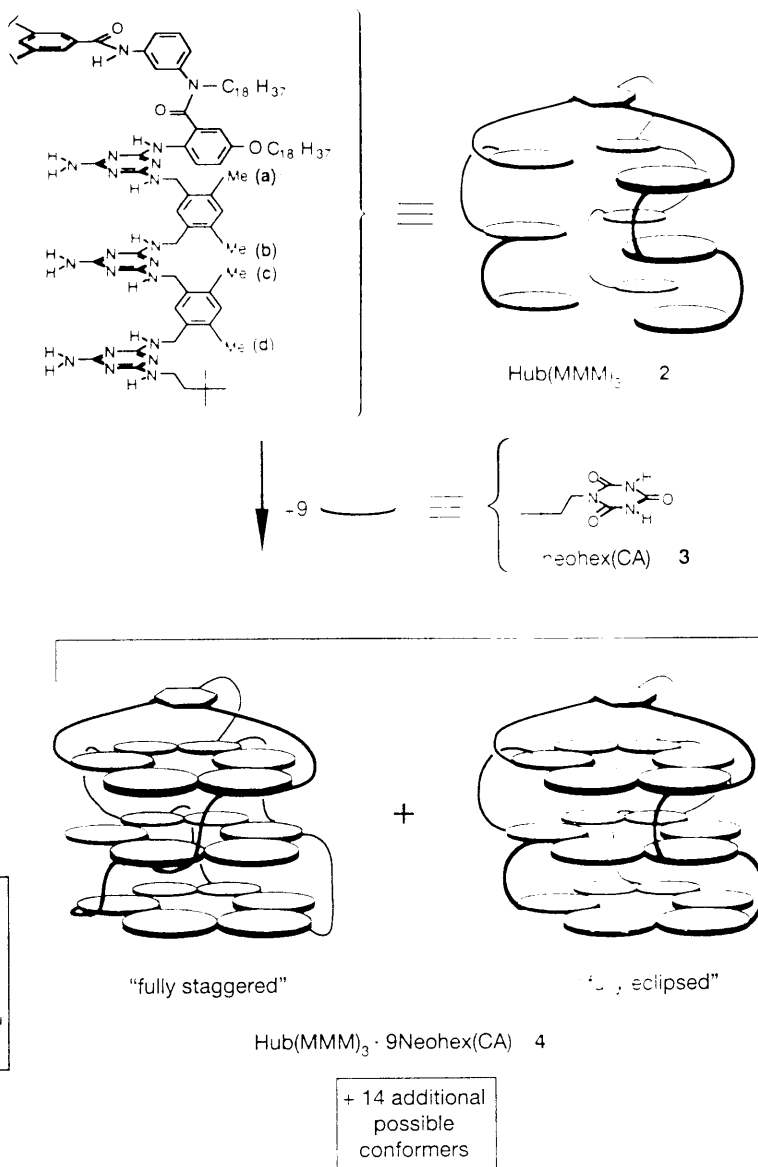
The nonamelamine derivative 2 was synthesized by using the procedure shown in Scheme 1. This synthesis extends a strategy we have described previously.^[2, 7] The *m*-xylyl spacers between adjacent melamine rings in each arm of 2 match those we have used in aggregates based on two parallel CA₃ · M₃ rosettes.^[3, 8]



Scheme 1. Synthesis of Hub(MMM)₃ (2).

A homogeneous solution of Hub(MMM)₃ · 9neohex(CA) (4) was prepared by mixing one equivalent of 2 and nine equivalents of 3 in chloroform (Scheme 2). We have enumerated at least 16 different geometrical conformers as being possibilities for 4.^[9] We believe that the aggregate exists initially as a mixture of the many available conformers on mixing the two different components. The conversion of this mixture to a single supramolecular aggregate of composition 4 occurs over about 48 h at room temperature (or 1 min at reflux) in chloroform, as judged by ¹H NMR spectroscopy.

The supramolecular aggregate 4 was characterized by ¹H NMR spectroscopy (COSY, NOE, and NOESY experiments), gel permeation chromatography (GPC), and vapor pressure osmometry (VPO). The ¹H NMR spectrum of 4 (Fig. 1a) shows a sharp set of resonances that can be assigned to a single conformer of the supramolecular aggregate. These sharp resonances contrast with the broad, poorly-defined resonances observed in the spectrum obtained from uncomplexed 2 in CDCl₃ (Fig. 1c); the broadening of the resonances in this spectrum may reflect hindered rotation about amide bonds in 2 and/or self-association of 2. Even in a strong hydrogen-bonding solvent such as dimethylsulfoxide (DMSO), however, there is little detail in the ¹H NMR



Scheme 2. Self-assembly of Hub(MMM)₃ · 9neohex(CA) (4). The conformational isomers shown are just two of at least 16 possibilities.

spectrum of 2. The spectrum in Figure 1b shows the aggregate immediately after mixing the components 2 and 3. The progression from a mixture of conformers (Fig. 1b) to a single conformer (Fig. 1a) is clear in these ¹H NMR spectra. The observation of discrete resonances for the different conformers confirms that exchange between them is slow on the NMR time scale. The six resonances with equal intensities (●, in Fig. 1a) between δ = 14 and 16 correspond to three sets of the two unsymmetrical hydrogen-bonded isocyanurate protons seen in each CA₃ · M₃ rosette in 4. The observation of four discrete singlets (∇, Fig. 1a) between δ = 1.8 and 2.1 for the four methyl substituents [(a)–(d), Scheme 2] provides further support for the proposed structure of 4. Cooling the sample has no effect on the signals observed in the ¹H NMR spectrum. This feature strengthens the inference that the resonances observed at 298 K in Figure 1a belong to a single conformer and not to a rapidly-equilibrating mixture of conformations.^[10] Nuclear Overhauser effects between the imide protons on the isocyanurate molecules (3) and those of the melamine rings in 2 confirm the geometry of the hydrogen-bonded regions, and are

consistent with the structure that we propose for **4**. We do not see NOE interactions between protons in adjacent $CA \cdot M_3$ rosettes. This feature means that we cannot deduce, unambiguously, which of the possible conformational isomers is the thermodynamically preferred (observed) one.

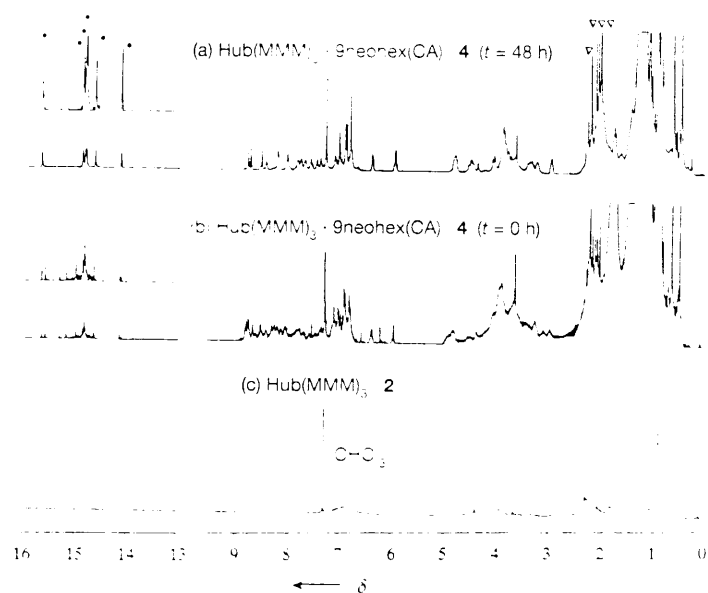


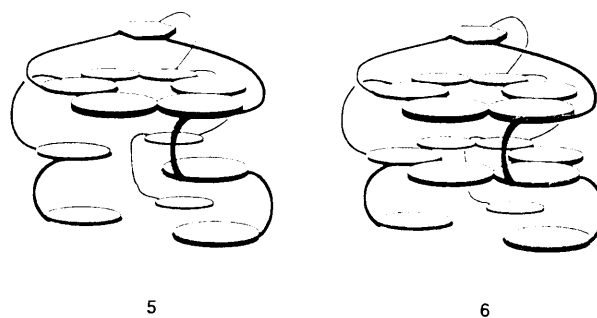
Fig. 1. ^1H NMR spectra (500 MHz, CDCl_3) of **4** (a) after equilibration and (b) on initial mixing of the components. The spectrum of uncomplexed **2** is shown in (c).

Retention times and shapes of the peaks for **4** (hatched) in CHCl_3 and CH_2Cl_2 as the eluent are consistent with observations from other self-assembled aggregates (Fig. 2). In each trace, *p*-xylene (shaded peak) was used as an internal standard. The trace in CH_2Cl_2 shows a single peak for the aggregate. The trace in CHCl_3 shows a much broader peak for the aggregate with a larger degree of "tailing" toward longer retention time. In each case, the peaks for the aggregate have sharp leading edges. This feature indicates that the solutions do not contain stable self-assembled or associated supramolecular aggregates that are larger than **4**. The tailing

in these traces is a consequence of dissociation of the aggregate that occurs during the analysis by GPC, and more tailing is seen in CHCl_3 than in CH_2Cl_2 . This difference indicates that the stability of **4** is lower in CHCl_3 , the stronger hydrogen-bonding solvent, than it is in CH_2Cl_2 .^[11] Although dissociation occurs during analysis of **4**, the GPC results establish that the dissociation is slow and indicate, therefore, that **4** is surprisingly stable.

The molecular weight *m* for **4** has been obtained by VPO in chloroform, using four different molecular weight standards.^[12] Each standard gives an observed *m* that is within 15% of the calculated value of **4** (6.435 kDa). Observed molecular weights of **4** are 5.6 kDa (standard: *N,N'*-bis-*tert*-butoxycarbonyl-gramicidin S), 6.4 kDa (sucrose octaacetate), 6.5 kDa (polystyrene), 7.5 kDa (perbenzoyl- β -cyclodextrin).

Addition of only three equivalents of **3** to one equivalent of **2** leads to formation of only fully assembled **4**; excess **2** remains uncomplexed. We do not observe any intermediates (such as $\text{Hub}(\text{MMM})_3 \cdot 3\text{neohex}(\text{CA})$ —the single layer aggregate **5**—or $\text{Hub}(\text{MMM})_3 \cdot 6\text{neohex}(\text{CA})$ —the double layer aggregate **6**) on the pathway between **2** and **4**. This observation indicates that the self-assembly of **4** displays positive cooperativity.



The self-assembly of *ten* molecules into a single *supramolecular aggregate* (**4**) that is stabilized by *fifty four* hydrogen bonds demonstrates further the potential of molecular self-assembly as a strategy for the preparation of well-defined chemical nanostructures. In particular, these results illustrate that parallel hydrogen-bonded $CA_3 \cdot M_3$ rosettes are a structural motif that is well-suited to the preparation of large, structurally complex supramolecular aggregates.

Experimental Procedure

$\text{Hub}(\text{MMM})_3$ (**2**). Trifluoroacetic acid (2.5 mL) was added dropwise to a solution of **1** (451 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 2 h. This solution was diluted with toluene (20 mL) and concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and aqueous Na_2CO_3 (5% solution, 25 mL). The organic extract was washed with aqueous Na_2CO_3 (5% solution, 25 mL), brine (2×25 mL), dried over MgSO_4 , filtered, and concentrated in vacuo to give 402 mg (0.276 mmol, 95%) of the deprotected amine as a white foam [high-resolution FAB-MS: *m/z* calcd for $\text{C}_{84}\text{H}_{113}\text{N}_5\text{O}_2$: $([M + \text{H}]^+)$ 1454.0920, found: 1454.0959]. This amine (399 mg, 0.274 mmol) was dissolved in CH_2Cl_2 (10 mL) and di-isopropylethylamine (DIPEA) (0.19 mL) and the solution was cooled to 0 °C. 1,3,5-Benzene tricarboxyl chloride (24.2 mg, 0.0913 mmol) was added and the solution was allowed to warm to 25 °C. After 90 mins, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with aqueous Na_2CO_3 (5% solution, 20 mL), brine (2×35 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography (eluted with a solution of 7.5% NH_4OH MeOH in CH_2Cl_2 [7.5:92.5 v/v]) to give 342 mg (0.0757 mmol, 83%, two steps) of the product (**2**) as a white solid; correct elemental analysis.

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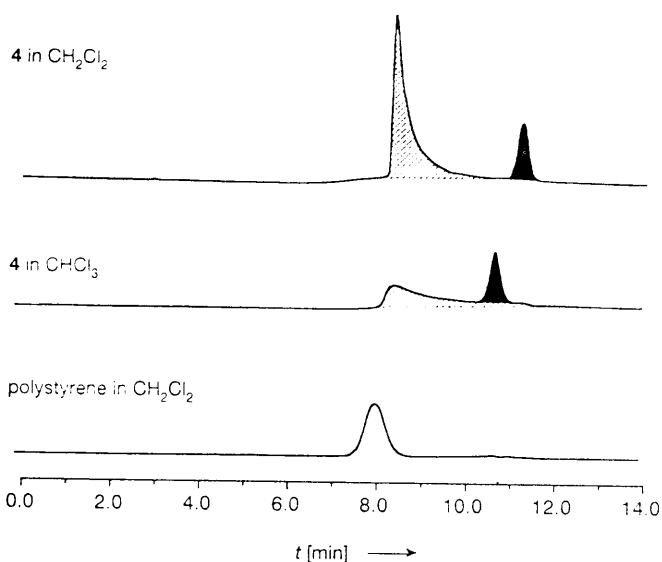


Fig. 2. Top and middle: Gel permeation chromatograms of **4** (hatched peaks). The shaded peaks are *p*-xylene, which is used as an internal standard. Bottom: Gel permeation chromatogram of polystyrene (PS) (F.W. 5050).

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- [9] In principle, there are at least four conformations in which the linker arm can join the uppermost melamine ring in **4** to the central benzene “hub” [2]. Additionally, adjacent melamine rings in each arm of the Hub(MMM)₃ unit can lie in eclipsed or staggered conformations, resulting in a total of at least 16 discrete conformers.
- [10] Supramolecular aggregates based on a single CA₃ · M₃ rosette often exist as mixtures of different geometrical isomers. The exchange between these structures can be slowed to reveal the separate isomers by ¹H-NMR at temperatures below ambient; M. Wazeer, J. P. Mathias, E. E. Simanek, G. M. Whitesides, unpublished results.
- [11] The traces from **4** in the GPC are significantly broader than those of previously reported double-layer aggregates, such as that between the hexamelamine derivative Hub(MM)₃ and six equivalent of neoheptylisonocyanurate, Hub(MM)₃ · 6neohep(CA). The reduction in stability for **4** suggested by this observation places this aggregate close to the lower limit of stability that can be observed successfully by GPC.
- [12] Chloroform was Aldrich HPLC grade. No attempt was made to monitor its moisture content during analysis by VPO.