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. In this communication we report the self-assembly of a supramolecular aggregate based on a compound containing

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[**] This work was supported by the National Science Foundation (Grants CHE-91-22331 to G. M. W. and DMR-89-20481 to the Harvard University Materials Research Laboratory). NMR instrumentation was supported by the National Science Foundation Grant CHE-88-14019 and the National Institutes of Health Grant 1 S10 RR 4876. Mass spectrometry was performed by Dr. A. Tyler, The Harvard University Mass-Spectrometry Facility was supported by the National Science Foundation Grant CHE-90-20443 and The National Institutes of Health Grant 1 S10 RR 06716-01. J. P. M. was an SERC NATO Postdoctoral Fellow, 1991–1993.
nine melamine rings (M) that we have called Hub(MMI)$_3$ (2). This molecule associates with nine equivalents of neohexylisocyanurate (neohex(CA) 3) to form a hydrogen-bonded supramolecular aggregate of composition Hub-(MMI)$_3$·9neohex(CA) (4). This aggregate is composed of ten molecules in three parallel CA$_3$·M$_3$ "rosettes" and is stabilized by 54 hydrogen bonds.

The homogenous solution of Hub(MMI)$_3$·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. 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 $^1$H NMR spectroscopy.

The supramolecular aggregate 4 was characterized by $^1$H NMR spectroscopy (COSY, NOE, and NOESY experiments), gel permeation chromatography (GPC), and vapor pressure osmometry (VPO). The $^1$H 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 CDCl$_3$ (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 $^1$H NMR 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 of 4 (Fig. 1b) to a single conformer (Fig. 1a) is clear in the $^1$H 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 (a, in Fig. 1a) between $\delta = 1.8$ and 2.1 for the four methyl substituents (a)–(d) in 4. The observation of four discrete singlets (v, Fig. 1a) between $\delta = 1.8$ and 2.1 for the four methyl substituents (a)–(d) in 4. Scheme 2 provides further support for the proposed structure of 4. Cooling the sample has no effect on the signals observed in the $^1$H 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. 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 CH₃M rosettes. This feature means that we cannot deduce, unambiguously, which of the possible conformational isomers is the thermodynamically preferred (observed one.

![Diagram of rosettes](image)

Retention times and shapes of the peaks for 4 (hatched in CHCl₃ and CH₂Cl₂ 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 CH₂Cl₂ shows a single peak for the aggregate. The trace in CHCl₃ 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

![Diagram of retention times](image)

in these traces is a consequence of dissociation of the aggregate that occurs during the analysis by GPC, and more tailing is seen in CHCl₃ than in CH₂Cl₂. This difference indicates that the stability of 4 is lower in CHCl₃, the stronger hydrogen-bonding solvent, than it is in CH₂Cl₂. 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. 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: X-β-histroy-butyroxy-carbonyl-gramicidin S), 6.4 kDa (sucrose octaacetate), 6.3 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 Hub(MIM)₃·3nheex(CA)—the single layer aggregate 5 or Hub(MIM)₄·3nheex(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.

![Diagram of self-assembly](image)

Experimental Procedure

Hub(MIM)₄·3nheex(CA) (2). Tributyrinic acid (2.5 mL) was added dropwise to a solution of 1.451 mg, 0.09 mmol in CH₂Cl₂ (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 Na₂CO₃ (5% solution, 25 mL). The organic extract was washed with aqueous Na₂CO₃ (5% solution, 25 mL), brine (2 × 25 mL), dried over MgSO₄, filtered, and concentrated in vacuo to give 402 mg (0.27 mmol, 95% yield) of the deprotected amine as a white foam (high-resolution FAB-MS: m/z calculated for C₃H₁₈N₂O₂ (M + H)⁺ 1454.0920, found 1454.0949). This amine (399 mg, 0.27 mmol) was dissolved in CH₂Cl₂ (10 mL) and diisopropylethylamine (DIPEA) (0.19 mL) and the solution was cooled to 0 °C. 1,3,5-Benzene tricarboxylic chloride (242 mg, 0.99 mmol) was added and the solution was allowed to warm to 25 °C. After 90 min, the reaction mixture was diluted with CH₂Cl₂ (25 mL) and washed with aqueous Na₂CO₃ (5% solution, 20 mL), brine (2 × 25 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography related with a solution of 3.5% NH₄OH MeOH in CH₂Cl₂ (5:95 v/v) to give 342 mg (0.057 mmol, 83%), two steps of the product (2) as a white solid, correct elemental analysis.

Received: July 12, 1993 [Z 6207H E]
German version: Angew. Chem. 1993, 105, 1848
In principle, there are 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), unit can lie in eclipsed or staggered conformations, resulting in a total of at least 16 discrete conformers.

Supramolecular aggregates based on a single CA^-M_3 rotor are 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. Waaijers, J. P. Mathijs, E. E. Simanek, G. M. Whitesides, unpublished results.

The traces from 4 in the GPC are significantly broader than those of previously reported double-layer aggregates, such as that between the hexamethylenedecyramide (Hub)MM and six equivalent of methoxyisocyanurate. Hub(MMM), 6-methoxycarbonyl (MOCA). 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.

Chloroform was Aldrich HPLC grade. No attempt was made to monitor its moisture content during analysis by VPO.