Self-Assembly of a Hydrogen-Bonded 2 + 3 Supramolecular Complex[1]

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We are designing and synthesizing three-dimensional supramolecular assemblies based on the pattern of hydrogen bonds present in the 1:1 complex between cyanuric acid and melamine (CA·M). We have previously shown that $hubM_3$ (Scheme I) organizes three melamine units into a geometry compatible with the CA·M lattice and forms a 1:3 complex with neohexyl cyanurate.[2] Here we report that $hubM_3$ reacts with the bis(cyanuric acid) $R(CA)_2$ (Scheme I) in $CHCl_3$ and forms a 2:3 complex, $(hubM_3)_2(R(CA)_2)_3$, that incorporates two layers of the CA·M lattice into a well-defined three-dimensional structure.[3,4]

We monitored the titration of $hubM_3$ in $CDCl_3$ with aliquots of $R(CA)_2$ by ^1H NMR spectroscopy (Figure 1). The spectrum of uncomplexed $hubM_3$ (bottom trace) has resonances that are broadened by self-association and restricted rotation around the amide and RNH–triazine bonds. At intermediate points in the titration, the spectrum shows resonances for $(hubM_3)_2(R(CA)_2)_3$ against a background of uncomplexed $hubM_3$. The complex appears to be predominantly a single conformation, and exchange between $(hubM_3)_2(R(CA)_2)_3$ and uncomplexed $hubM_3$ in solution is slow on the NMR time scale. Beyond the 2:3 stoichiometry, there is no further change in the spectrum. The $hubM_3$ units in $(hubM_3)_2(R(CA)_2)_3$ are chiral. From the ^1H NMR spectrum, we cannot tell whether the complex exists as a racemic mixture of *R,R* and *S,S* species or as a meso compound, *R,S*. The simplicity of the spectrum suggests, however, that only racemic or meso complexes are present, and not a mixture of the two.

Two features of Figure 1 support the assigned structure for $(hubM_3)_2(R(CA)_2)_3$: First, several equivalent protons of $hubM_3$ (g, g′; q, q′; and r, r′) and $R(CA)_2$ (w, w′ and x, x′) are diastereotopic in $(hubM_3)_2(R(CA)_2)_3$ and thus appear as separate resonances. Second, the two sets of imide NH protons (y, y′) of $R(CA)_2$ are in different hydrogen-bonding environments and thus appear as separate resonances in the complex, even though they are equivalent by symmetry in uncomplexed $R(CA)_2$. NOE studies also support our proposed structure. We observed several positive intermolecular NOEs between $hubM_3$ and $R(CA)_2$ that are consistent with a CPK model of the $(hubM_3)_2(R(CA)_2)_3$ complex (Scheme I). The NOEs between the imide NH protons (y, y′) of $R(CA)_2$ and the melamine NH protons (n, o, o′, p) of $hubM_3$ confirm the 3-fold nature of the hydrogen-bonded network.

Two other analytical methods support the 2:3 stoichiometry of $(hubM_3)_2(R(CA)_2)_3$. Vapor pressure osmometry (VPO) of the complex indicated MW ≈ 5300 (calcd for $(hubM_3)_2(R(CA)_2)_3$: 5519) over the concentration range 2–16 mM in $CHCl_3$ at 37 °C with a sucrose octaacetate standard.[5] Titration of $hubM_3$ (0.1 mM in CH_2Cl_2) with $R(CA)_2$ monitored by UV spectroscopy also indicated a 2:3 complex.[6]

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(2) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6409–6411.

(3) For other supramolecular assemblies, see: Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255 and references therein. Bryant, J.; Ericson, J.; Cram, D. *J. Am. Chem. Soc.* **1990**, *112*, 1255–1256. Etter, M. *Acc. Chem. Res.* **1990**, *23*, 120–126. Manka, J. S.; Lawrence, D. S. *J. Am. Chem. Soc.* **1990**, *112*, 2440–2442. Ashton, P.; Goodnow, T.; Kaifer, A.; Reddington, M.; Slawin, A.; Spencer, N.; Stoddart, J.; Vincent, C.; Williams, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1396–1399.

(4) All new compounds gave satisfactory ^1H NMR (500 MHz), ^{13}C NMR (125 MHz), and elemental analyses.

(5) The molecular weight of the complex estimated by using other standards was as follows ($MW_{complex}$, standard $MW_{standard}$): 5890, perbenzoyl β-cyclodextrin 3321; 5390, polystyrene 5050 (polydispersity = 1.05); 4430, *N,N′*-bis(*tert*-butyloxycarbonyl)gramicidin S 1342. We suggest that the gramicidin S derivative was associated in solution and, hence, unsuitable as a standard.

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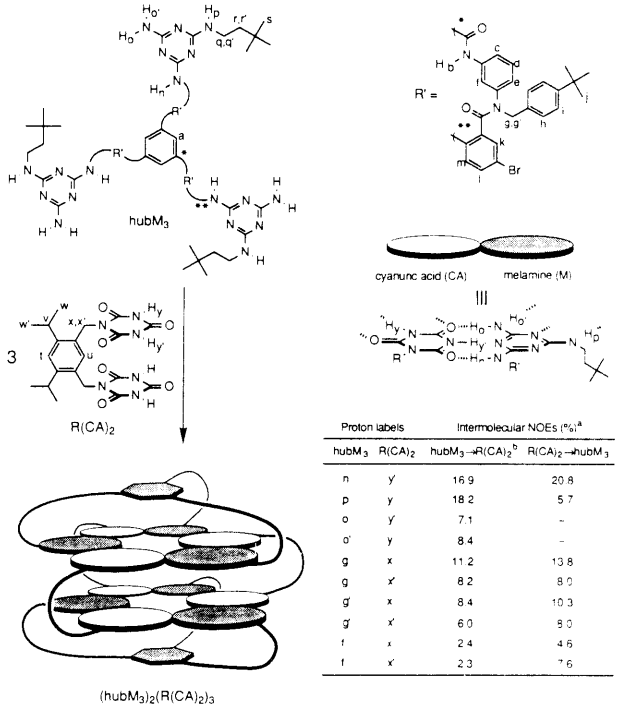
Scheme I. Self-Assembly of $hubM_3$ with $R(CA)_2$ To Give a Supramolecular 2:3 Complex



Proton labels		Intermolecular NOEs (%)[a]	
$hubM_3$	$R(CA)_2$	$hubM_3 \rightarrow R(CA)_2$[b]	$R(CA)_2 \rightarrow hubM_3$
n	y'	16.9	20.8
p	y	18.2	5.7
o	y'	7.1	–
o'	y	8.4	–
g	x	11.2	13.8
g	x'	8.2	8.0
g'	x	8.4	10.3
g'	x'	6.0	8.0
f	x	2.4	4.6
f	x'	2.3	7.6

[a] Intermolecular NOEs between $hubM_3$ and $R(CA)_2$ in the 2:3 complex are given in the table. The complex (10 mM) in $CDCl_3$ was degassed with five freeze–pump–thaw cycles, and the NOE difference spectra were taken at 500 MHz with a presaturation time of 3.0 s. [b] $hubM_3 \rightarrow R(CA)_2$ represents irradiation of the proton on $hubM_3$ and observation of an NOE at the proton of $R(CA)_2$.

Formation of the $(hubM_3)_2(R(CA)_2)_3$ complex is an unfavorable process entropically: five particles combine into a single particle; the spokes of $hubM_3$ are constrained to one conformation. The complex is stable only because the enthalpy gained by forming the 36 hydrogen bonds in the complex is large enough to compensate for the entropic factor.

(6) UV data: uncomplexed $hubM_3$ λ_{max} = 269 nm (ϵ = 94 050 M^{-1} cm^{-1}); $(hubM_3)_2(R(CA)_2)_3$ λ_{max} = 255 nm (ϵ = 100 200 M^{-1} cm^{-1}).

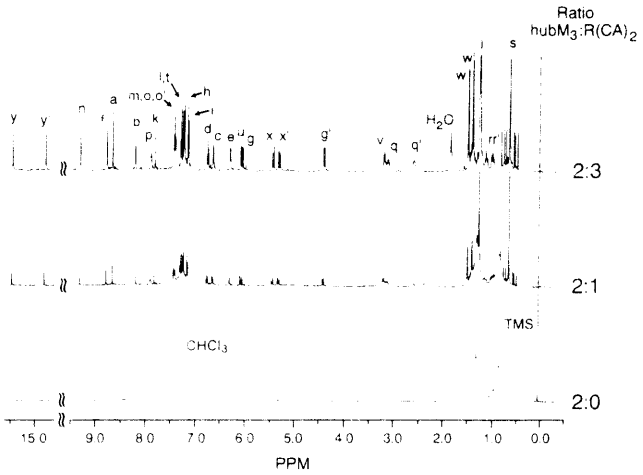


Figure 1. ^1H NMR titration of $hubM_3$ (500 MHz, 10 mM in $CDCl_3$) with $R(CA)_2$. The peak assignments are shown at the top of the figure. We believe that the small peaks in the base line of the upper spectrum correspond to conformational isomers of the 2:3 complex. These minor peaks are not impurities in either of the individual components. $R(CA)_2$ alone is too insoluble to give a detectable spectrum at saturation (<0.1 mM) in $CDCl_3$ at the instrument gain used here.

This procedure points the way to the synthesis of large molecular assemblies by a process based on self-assembly of stable hydrogen-bonding networks, rather than formation of covalent bonds. In that sense, its strategy is more closely modeled on the principles that determine secondary and tertiary structure in proteins and nucleic acids than on the methods used in classical organic synthesis. Future papers will describe the synthesis of structures more complex than $(hubM_3)_2(R(CA)_2)_3$.

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