J. Am. Chem. Soc. **1998,** *120,* 819−820 819

Structural Rules Governing Self-Assembly Emerge from New Molecular Capsules

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Received September 24, 1997

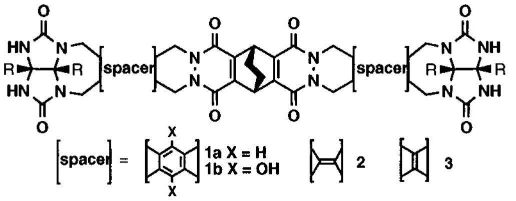
Structures such as **1** are self-complementary and dimerize because hydrogen-bond donors at the ends of the molecule are appropriately positioned for binding to the hydrogen-bond acceptors in the middle (Scheme 1). The overall dimensions of the dimeric assembly are determined by the size of the spacers between the glycolurils and the hinge. With spacers such as benzene **1a** or hydroquinone **1b**, dimerization in organic solvents leads to a pseudospherical capsule, the "softball" (Figure 2).[1] The present work was designed to test how much stress, in the form of structural change, could be incorporated into the system before its self-assembling properties broke down. We describe here two variants using an ethylene spacer; the synthesis, assembly properties, and encapsulation behavior of the "wiffle balls" **2** and **3** are discussed.

The syntheses of **2** and **3** were performed as shown in Schemes 2 and 3 (see the Supporting Information).[2, 3]

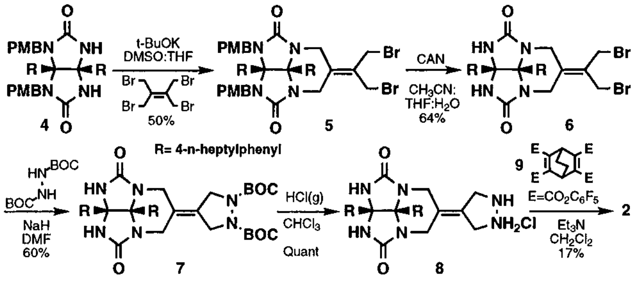
Monomer **2** features five- and six-membered rings on either end of the ethylene unit which make its spacer somewhat shorter and more rigid than that of **1**. The dimeric form, accordingly, has a smaller volume (245 Å,[3] compared with the 313 Å[3] in the "softball").[4] In compound **3**, the ethylene appears as the ring fusion between seven- and six-membered rings and the much-reduced dimensions lead to a dimeric capsule of only 187 Å[3].

The proton NMR signals of molecule **2** are sharp and well-defined in a variety of solvents (CD_2Cl_2, $CDCl_3$, C_6D_6, toluene-d_8), and considerable downfield shifts are observed for the NH resonances (CD_2Cl_2 $\delta = 7.59$ ppm, $CDCl_3$ $\delta = 7.69$ ppm, C_6D_6 $\delta = 8.48$ ppm, toluene-d_8 $\delta = 8.21$ ppm). The chemical shifts of these signals are independent of concentration and are characteristic of an ordered, extensively hydrogen-bonded system. The ease with which this molecule dimerizes in different solvents suggests a higher degree of preorganization in this system compared to that in the "softball" **1a·1a**. Nonetheless, in *p*-xylene-d_{10} it gives a broad spectrum, suggesting dynamic effects or the presence of higher order aggregates that form because the solvent is a poor guest for the dimer.

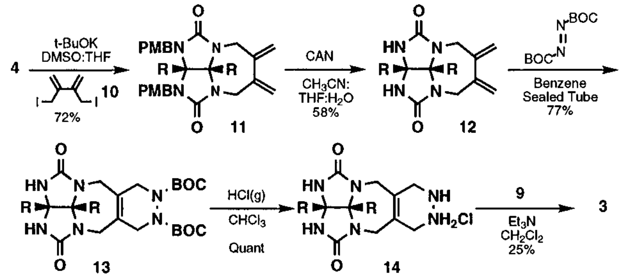
Scheme 1



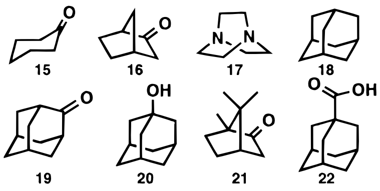
Scheme 2



Scheme 3



Scheme 4



Encapsulation experiments with **2** were performed in *p*-xylene-d_{10} using the molecules of Scheme 4. Addition of these guests results in the emergence of the sharp NMR signals of ordered, occupied capsular forms, but the ability of these guests to induce the capsular form at room temperature varied with their sizes, shapes, and functionalities. Separate signals were observed and integrated for guests inside the capsule and those in bulk solution; exchange is slow on the NMR time scale, though fast on the human time scale. Data obtained from the ^1H NMR spectra were used to calculate equilibrium association constants (K'_a) for various guests.[5, 6] Direct competition experiments[7, 8] gave the additional K'_a for different guests as reported in Table 1.

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(1) (a) Meissner, R. S.; Rebek, Jr., J.; de Mendoza, J. *Science* **1995**, *270*, 1485−1488. (b) Kang, J.; Rebek, Jr., J. *Nature* **1996**, *382*, 239. (c) Conn, M. M.; Rebek, Jr., J. *Chem. Rev.* **1997**, *97*, 1647.

(2) Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 846.

(3) The compounds **2** and **3** were obtained together with their corresponding geometrical isomers (**2s**, **2w**, **3s**, **3w**), which were separated by chromatographic methods. Tokunaga, Y.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2656−2659.

(4) Results obtained from the GRASP program. Nicholls, A.; Sharp, K. A.; Honig, B. *Proteins* **1991**, *11*, 281.

(5) These values are derived from eq 1 and are apparent association constants, K'_a, because of the unknown resting state of **2** in the solvent (assumed to be aggregated); g = guest.

$$\mathbf{2}_{(\text{aggregate})} + \text{g} \rightleftharpoons \mathbf{2}\cdot\text{g}\cdot\mathbf{2} \quad K'_a = \frac{[\mathbf{2}\cdot\text{g}\cdot\mathbf{2}]}{[\mathbf{2}_{(\text{aggregate})}][\text{g}]} \qquad (1)$$

(6) The assumptions are (1) the amount of dimer (unfilled or filled with solvent) present before addition of the guest is negligible, (2) after addition of the guest, all of the host material not assembled into the capsule is in the aggregate state, and (3) the association of the guest with itself is negligible.

(7) The competition experiments were performed using a solution of **2** in *p*-xylene-d_{10} with 1 equiv of a guest (**2·g·2**) and addition of 1 equiv of another guest (g′).

$$\mathbf{2}\cdot\text{g}\cdot\mathbf{2} + \text{g}' \rightleftharpoons \mathbf{2}\cdot\text{g}'\cdot\mathbf{2} + \text{g} \quad K = \frac{[\mathbf{2}\cdot\text{g}'\cdot\mathbf{2}][\text{g}]}{[\mathbf{2}\cdot\text{g}\cdot\mathbf{2}][\text{g}']} = \frac{K''_a}{K'_a}$$

S0002-7863(97)03341-6 CCC: $15.00

Table 1. Inclusion of Guest Species in the Cavity of the Dimer **2·2**

guest	packing coefficient	K'_a (M^{-1})	$-\Delta G°$ (kcal mol^{-1})
15	0.43	1.7×10^{2} [b]	3.00
16	0.45	1.8×10^{3} [b]	4.38
17	0.47	5.0×10^{2} [b]	3.63
18	0.60	3.8×10^{3} [b]	4.83
19	0.61	5.2×10^{5} [b]	7.72
20	0.63	5.2×10^{5} [b]	7.72
21	0.68	9.1×10^{2} [a]	3.98
22	0.71	1.3×10^{2} [a]	2.85

[a] Calculated by encapsulation experiment. [b] Calculated by competition experiment.[7,8]

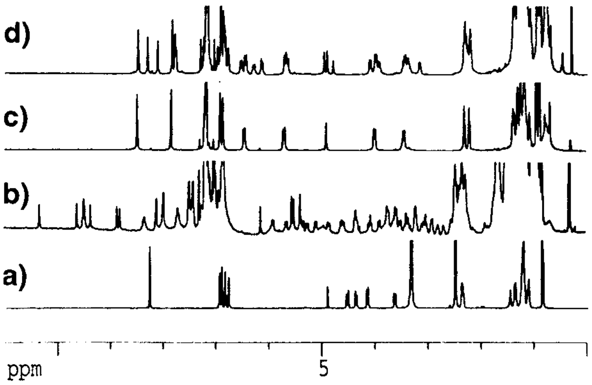
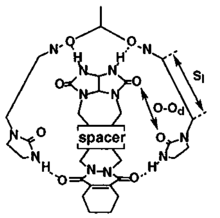


Figure 1. ^1H NMR spectra at 600 MHz of (a) **3** (2.3 mM) in DMSO-d_6 solvent. The signal at 3.3 ppm is H_2O. (b) **3** (5.4 mM) in benzene-d_6. (c) **2·2** (3.8 mM) in benzene-d_6. (d) Equimolar mixture of **2** and **3** (3.8 mM) in benzene-d_6.

From the table and the calculated values of the packing factor,[9] it appears that guests that occupy between 0.60 and 0.63 showed particular affinity for the cavity of **2·2**; the presence of the functional groups in the guests enhances their affinity. Compare, for example, adamantane (**18**) with 2-adamantanone (**19**): they are approximately equal in size and shape but their K'_a are very different, probably due to attractive interactions of the carbonyl of the guest with the hydrogen bonds that line the cavity of the host.

In contrast to **2**, the smaller **3** was not easily characterized, and some difficulties were encountered in distinguishing **3** from **3w** (**3s** has doubled NMR signal patterns since its two ends are different). Neither shows the characteristic downfield shifts of the NH signals associated with dimerization, and dilution experiments using **3**, **3w**, or **3s** in chloroform-*d* and dichloromethane-d_2 showed that their NH signals were all concentration dependent. Thus, none of the isomers gave capsules in these solvents; rather they existed as largely monomeric species. In solvents such as benzene-d_6 and toluene-d_8 only one of the isomers (**3** or **3w**) was soluble, and the ^1H NMR spectra exhibited unprecedented complexity (Figure 1a,b). The isomer **3** (identified ultimately by the heterodimerization experiments described below) forms an ordered aggregate of yet unknown structure. The ^1H COSY spectrum in toluene-d_8 reveals 8 different NH resonances, the lowest at 10.3 ppm, and 16 different methylene resonances: therefore, the complex is at least a dimer. Dilution experiments in benzene-d_6 and toluene-d_8 showed concentration-independent behavior from 12.2 to 1.8 mM. A variable-temperature experiment showed that the complex is stable up to 330 K. From 350 to 380 K, it was basically a single species. This complex can be dissociated by adding chloroform-*d*. After addition of 14% chloroform-*d*, the aggregate breaks up to give a simplified spectrum with the NH and CH_2 signals broadened.



Capsule	O-O_d (Å)	S_l (Å)
3•3	3.1	3.3
3•2	3.5	-
2•2	3.7	4.2
1•1	4.3	4.9

Figure 2. Schematic representation of the capsular dimers and the intermolecular glycoluril carbonyl distances (O−O_d), and spacer length (S_1).[11]

Dilution of a solution of **3** in chloroform-*d* with benzene-d_6 caused the NH and the CH_2 signals to move downfield, which might indicate a conformational change induced by whatever nucleation process is underway. A parallel dilution experiment using **3w** showed an upfield shift for the NH signal; however, the CH_2 signals remained constant.

The similarities between **2** and **3** suggested that a *hybrid* structure could be formed. This heterodimer would necessarily have a cavity shape and size (210 $Å^3$) which is intermediate between the parent homodimers. A one-to-one mixture of **2** and **3** was prepared and analyzed in different solvents (CD_2Cl_2, $CDCl_3$, C_6D_6, toluene-d_8, *p*-xylene-d_{10}). Only in benzene-d_6 was the heterodimer observed: the spectrum showed the signals corresponding to **2·2** and two new sets of signals with the one-to-one intensity corresponding to the heterodimer **2·3** (Figure 1d).[10]

Why does **3** form a heterodimer but not a homodimer? Molecular modeling studies[11] show that in the homodimer **3·3** the intermolecular O−O_d distance between glycoluril carbonyls is quite short (3.1 Å) and some repulsion between the two oxygens can be expected (Figure 2). This distance in the hetereodimer **2·3** is increased to 3.5 Å while that in the homodimer **2·2** is large enough (3.7 Å) that repulsion between oxygens is negligible. Accordingly, there are subtle, often unpredictable, effects that can dramatically change the assembly information contained within similar systems.

In summary, the structural diversity available with congeners of the softball provides useful information for the further development of capsules and self-assembly in general. The use of two different spacers in the subunit can lead to dimers with dissymmetric *cavities* and we will report on these in the sequel.

Acknowledgment. We thank the Skaggs Research Foundation and the National Institutes of Health for support. We also thank Dr. Tomas Szabo for advice on the synthesis of protected glycolurils. Administración de Fomento Económico of Puerto Rico provided fellowship support to J.M.R. The Ministerio de Educación y Cultura of Spain provided fellowship support to T.M.

Supporting Information Available: Procedures and spectral data for all compounds (33 pages). See any current masthead page for ordering and Internet access instructions.

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(8) All of these spectra are in *p*-xylene-d_{10} solution. Some signals of the guest inside are impossible to observe because they coincide with the *p*-xylene-d_{10} or *n*-heptyl signals. When **21** and **22** were used as guests, it was possible to observe clearly the guest outside and inside of the dimer, the signals of which were easily integrated. The reliable K'_a for **21** was then used to calculate constants for the rest of the guests **15**−**20** by competition experiments.

(9) Garel, L.; Dutasta, J.; Collet, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1169.

(10) (a) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255. (b) Valdés, C.; Spitz, U. P.; Toledo, L. M.; Kubik, S. W.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 12733. (c) Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489.

(11) Molecular modeling was performed using MACROMODEL 5.5 (MM2* force field). These distances were obtained from the energy-minimized structures of the corresponding dimers. Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.