Structure and Selectivity of a Small Dimeric Encapsulating Assembly

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Abstract: The binding selectivity of a dimeric molecular capsule in solution and its X-ray crystal structure in the solid state are reported. The capsule is a self-complementary bisglycoluril molecule, formed through a series of intermolecular hydrogen bonds. The dimeric host is capable of discriminating in $CDCl_3$ solution between methane and ethane as guests, and direct evidence for the selectivity is presented from ^1H NMR studies. The thermodynamic parameters for the encapsulation of methane, obtained from a VT ^1H NMR (500 mHz) study, are presented.

Keywords
dimerization · host–guest chemistry · hydrogen bonds · self-assembly · structure elucidation

We have been considering molecular self-complementarity as a means of assembly for functional supramolecular structures. The simplest systems are dimers that are drawn together by weak intermolecular forces into pseudospherical capsules.[1] The hydrogen-bonding sites along the edge of the monomers hold the dimeric forms together in the same way that stitches along the seam hold a baseball together. The capsules feature internal cavities for guests of appropriate sizes and shapes, and the encapsulated guests can be directly observed by NMR spectroscopy in solution.[1] We have also encountered disproportionation equilibria of related homodimers into heterodimers. The favored species in these disproportionations can, to some extent, be manipulated by the presence of suitable solvent guests.[2] Here we report the crystal structure of the smallest capsule **2** (Fig. 1) and give details concerning its binding selectivity. In this system the cavity is sufficiently reduced that selection between methane and ethane as guests is possible.

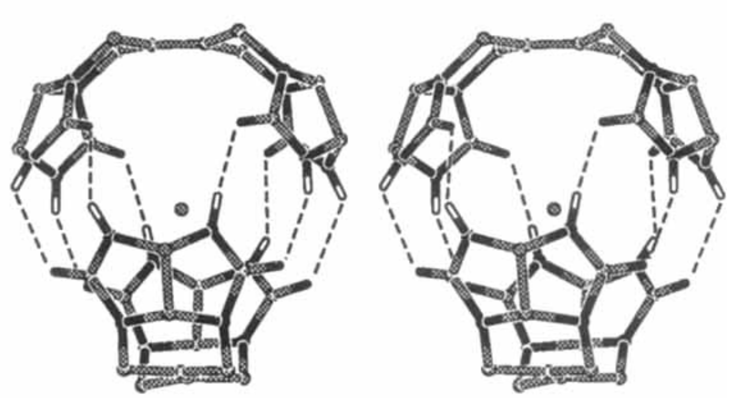
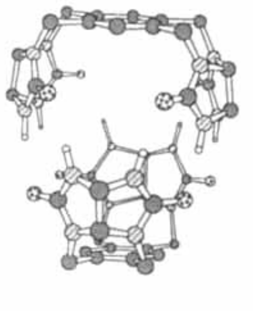


Fig. 1. Stereo representation of one of the capsules (ester groups omitted).

The capacity of these capsules is determined by the dimensions of the spacer between the glycoluril subunits (e.g., benzene in **1**), the conformations of the neighboring rings, and the geometry of the hydrogen bonds. The size of the spacer is the easiest to control, and we replaced the benzene in **1** with an ethylene in **2**. Tetramethylethylene tetrabromide **3** was used to alkylate the glycoluril diester **4** (Scheme 1). With potassium *tert*-



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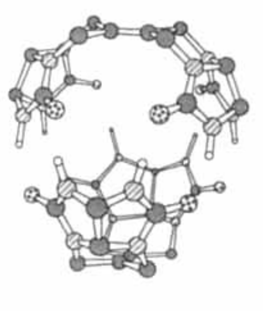

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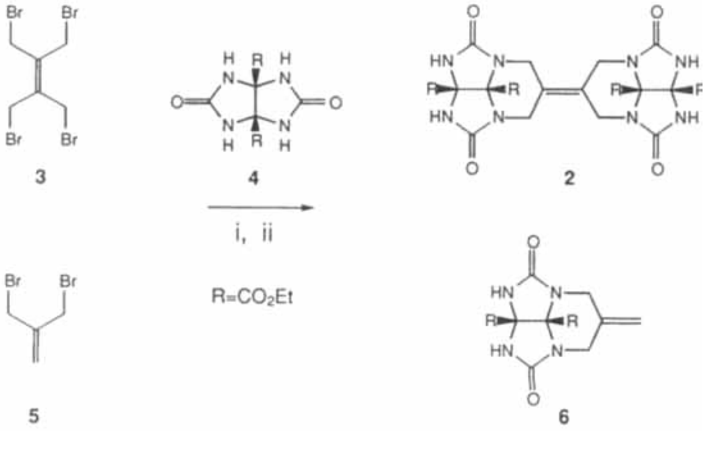

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butoxide as the base in DMSO (1 h, 25°), the alkylation gave a 1:1 mixture of two isomers: the *trans*, S-shaped isomer (not shown) and the *cis*, C-shaped **2**. The latter could be obtained by crystallization from a CH_2Cl_2/CH_3OH solvent mixture.

Results and Discussion

In $CDCl_3$ solution the spectrum of the crystalline isomer **2** showed the spectroscopic characteristics of the dimeric form: the N–H chemical shift in the ^1H NMR spectrum appeared at $\delta = 9.12$ and the NH stretching band in the IR spectrum appeared at 3217 cm^{-1}. These spectra are independent of concentration. In contrast, the model compound **6** shows an upfield signal at $\delta = 5.83$ and an NH stretching band at 3442 cm^{-1}. High-resolution mass spectroscopic analysis of a sample of **2** showed a $[M + H]^+$ peak at 1297.4375, in agreement with the calculated value of 1296.4274 for the mass of the dimer.

Structure: For X-ray crystallographic analysis, single crystals of **2** were obtained by slow evaporation of a 4:1 CH_2Cl_2/CH_3OH solution. The compound crystallized in the centrosymmetric monoclinic space group *C*2/c with 16 molecules per unit cell and two molecules in an asymmetric unit. The structure showed that the alkylation reaction had taken the expected course, leading to the six-membered rings with the exocyclic ethylene spacer shown in **2** rather than to seven-membered rings with an endocyclic double bond at their fusion. Furthermore, the unit cell contained 8 intermolecular hydrogen-bonded dimeric assemblies, each held together by 8 hydrogen bonds in the range 2.78–2.94 Å (163–167°), as expected from NMR and MacroModel[3] modeling studies.

Two types of dimer exist; both possess C_2 symmetry,[4] but they are crystallographically distinct from each other (Fig. 2). That is, each type of dimer is formed by a crystallographically unique monomer related to its pair by the twofold axis. In one case, however, the twofold axis passes diagonally through the center of the cavity without intersecting any atom or bond in the dimer, and in the second case, it intersects the dimer through the double bonds. Even though the capsules are crystallographically distinct, they are structurally superimposable to within 1%.

The crystal lattice has an overall layered arrangement. The ester groups of the capsules interpenetrate and are directed towards the interlayer space so as to maximize packing efficiency. There is a highly disordered species in the lattice (probably CH_2Cl_2) accomodated within hydrophobic channels formed by four neighboring rows of dimers. However, this disorder could not be resolved. In addition, both dimers contain a low-occupancy disordered guest species at the centers of the cavities. It was not possible to determine the identity of this species. We believe that the species in the cavities are methanol molecules that hydrogen-bond to the π faces of the carbonyl oxygens of the glycoluril units from the inside.[5] If this is the case, there are 8 possible positions for the oxygen atom to occupy. Molecular modeling of the dimer containing a methanol molecule inside suggests such bonding is favorable, and places the methyl group of the methanol at the center of the cavity. In accord with this positioning of the guest, we were able to refine a carbon atom on the twofold axis at the center of the dimer, but the positions of the oxygen atom could not be located.

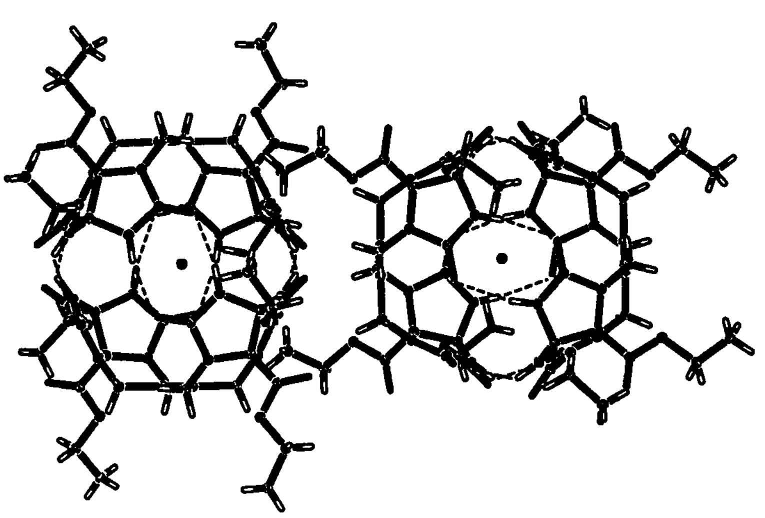

Fig. 2. Structure of the two crystallographically different dimers of compound **2**.

Binding: Dimer **1** can accommodate CD_2Cl_2, and direct evidence of encapsulated CD_2Cl_2 in $CDCl_3$ solution was recently obtained by ^{13}C NMR.[2] In contrast, the spectrum of **2** in $CDCl_3$ shows no changes when CD_2Cl_2 is present. Apparently, the reduced volume of **2** can no longer accommodate this guest.

Further evidence of the smaller capacity of **2** was provided by its selectivity for methane vs. ethane. When a $CDCl_3$ solution of **2**[6] is treated with commercially available pure methane, two new signals are immediately observed. The encapsulated methane appears at $\delta = -0.44$, and a new NH signal appears at $\delta = 8.95$. Furthermore, integration of the two signals indicates a 1:1 ratio of guest to host, in agreement with the presence of a new dimer containing a methane molecule within its interior. Through integration of the ^1H NMR (500 MHz) signals of free and bound methane and "empty"[7] and occupied dimer, the inclusion constant $K_{inc}^{273K} = 3.8\,M^{-1}$ was calculated. The thermodynamic parameters for the encapsulation process were determined by VT ^1H NMR (500 MHz). A van't Hoff plot of the data ($R\ln K_a$ vs. T^{-1}) resulted in the typical straight line (Fig. 3). Values for $\Delta H^{273K} = 5.7\,kcal\,mol^{-1}$ and $\Delta S^{273K} = 18\,cal\,mol^{-1}$ were obtained, and $\Delta G^{273K} = -0.7\,kcal\,mol^{-1}$ was calculated. The entropy-driven nature of this process is peculiar for association phenomena but is consistent with observations elsewhere[8] on related systems.

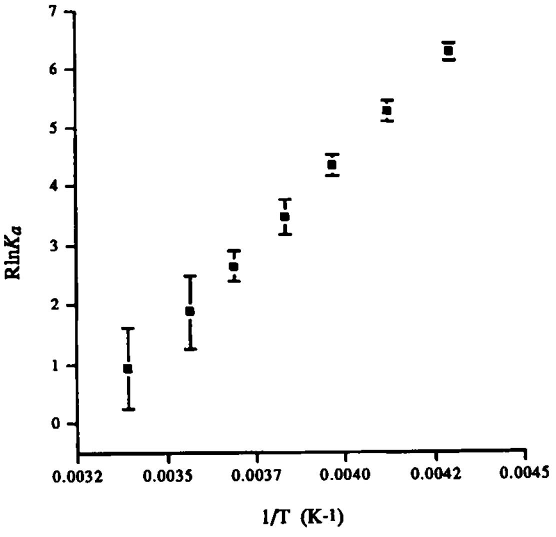

Fig. 3. van't Hoff plot for the encapsulation of methane by dimer **2** in $CDCl_3$ for the temperature range 298–233 K, determined by ^1H NMR (500 mHz).

In contrast to the binding of methane by dimer **2**, when a solution of the latter is treated with commercially pure ethane gas, no encapsulation is observed even after 48 h. Treatment with a mixture of methane and ethane produces only the characteristic encapsulated-methane ^1H NMR signal at $\delta = -0.44$.

Conclusion

We have demonstrated that the structure of the dimeric assembly in the solid state is that of a spherical capsule held together at the seam by eight hydrogen bonds. Moreover, the presence of a disordered guest inside its cavity is evidence that these species encapsulate guests in the solid state as well as in solution. While methane is encapsulated with modest affinity, encapsulated ethane is never observed. We interpret this selectivity as a consequence of host-to-guest size match. The cavity in the dimer is sufficiently small to exclude the larger ethane molecule.

Experimental Section

Materials and Methods: NMR spectra were recorded on Bruker AC250, Varian XL300, and Varian VXR500 spectrometers with the solvents as the internal lock and internal reference (^1H NMR: $CDCl_3$, $\delta = 7.26$; CD_2Cl_2, $\delta = 5.32$). Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. Deuterated solvents and were purchased from Cambridge Isotope Labs. Anhydrous DMSO was obtained from Aldrich and used without purification.

Bisglycoluril 2: This compound was obtained in 25% overall yield according to the procedure described in ref. [2]. Single crystals were obtained by slow evaporation of a solution of **2** in 1:4 methanol/methylene chloride solvent mixture.

X-Ray Diffraction Studies [9]: A crystal of about 0.4 × 0.4 × 0.2 mm was mounted on a fiber embedded in a matrix of Paraton N. Data were collected at -66°C on a Siemens CCD diffractometer (equipped with an automated 3 circle goniometer and a solid state generator) with graphite-monochromated $Mo_{K\alpha}$ radiation (0.710690 Å) by the ω scan method operating under the program SMART [10]. A total of 15 frames at 30 s measured at 0.3° increments of ω at three different values of 2θ and ϕ were collected, and after least squares, a preliminary unit cell was obtained. For data collection, three sets of frames of 30 s exposure were collected. Data were collected in three distinct shells. For the first shell, 606 frames were collected with values of $\phi = 0°$ and $\omega = -26°$; for the second shell, 435 were collected with $\phi = 88°$ and $\omega = -21°$, and for the third shell values of $\phi = 180°$ and $\omega = -23°$ were used to collect 230 frames. When data collection was complete, the first 50 frames of the first shell were collected once more to correct for any crystal decay, but no anomalies were observed. The data were integrated with the program SAINT [11]. The integrated intensities of the three shells were merged into one reflection file. The data were filtered to reject outliers based on the agreement of the intensity of the reflection and the average of the symmetry equivalents to which the reflection belongs. Of a total of 21890 reflections collected ($2\theta_{max} = 46.6°$), 8384 were unique ($R_{int} = 0.069$); equivalent reflections were merged.

The space group was found to be monoclinic $C2/c$ (based on systematic absences of hkl: $h+k \neq 2n$ and h0l: $l \neq 2n$, statistical analysis of intensity distribution, and the successful solution and refinement of the structure). The unit cell dimensions were $a = 22.176(1)$ Å, $b = 22.156(1)$ Å, $c = 25.849(2)$ Å, $\beta = 102.961(7)°$, $V = 12376(1)$ Å^3 with $Z = 16$. The structure was solved with the direct methods program Sir92 of the TeXsan [12] crystallographic package. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 4155 reflections ($I > 3\sigma(I)$) and 851 variables gave a final $R = 0.072$ ($1/\sigma^2$) and $R_w = 0.075$. The residual density was refined for carbon atoms with fixed position and temperature factors.

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[4] The centers of both dimers sit on the twofold axis, but these axes are offset from each other by rotations about the other two crystallographic axes.

[5] Molecular modeling suggests that the dimer with a methanol molecule inside is highly favored, since methanol can form strong hydrogen bonds to the carbonyl oxygen. Inspection of the NMR spectra of the crystals did not indicate the presence of considerable amounts of solvent of crystallization. Other work in this group indicates that guests that hydrogen-bond from the inside are readily encapsulated: R. S. Meissner, J. Rebek, Jr., J. de Mendoza, *Science* **1995**, *270*, 1485.

[6] Even though compound **2** was purified by chromatography with a methanol/methylene chloride solvent mixture as eluant, inspection of the ^1H NMR spectrum of the pure dimer does not indicate the presence of methanol inside its cavity.

[7] It is difficult to determine spectroscopically whether these dimers are truly empty or occupied by atmospheric gases. We tried to determine the affinity for water of dimer **2** by ^1H NMR titration methods, but were unable to observe a signal corresponding to included water.

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[9] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1220-16. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: Int. code +(1223)336-033; e-mail: teched@chemcrys.cam.ac.uk).

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