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Unusually Stable Molecular Capsule Formation of a Tetraphenyleneurea Cavitand

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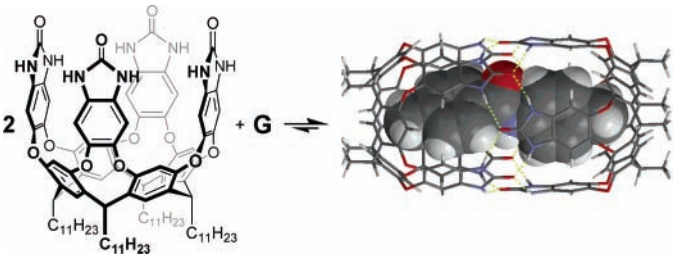
ABSTRACT



An unusually stable molecular capsule was formed by heating phenyleneurea-spanned resorcinarene cavitand with 4-methyl-*N*-*p*-tolylbenzamide. The molecular capsule behaved as a discrete molecular entity showing a cylindrical D_{4d} structure and showed no guest exchange in toluene-d_8 even at 100 °C.

Self-assembled molecular capsules held together by hydrogen bonds or metal−ligand interaction have attracted much interest.[1−3] The successful application of the complementary hydrogen-bonding theme was first introduced by the groups of Rebek and de Mendoza for self-assembling glycoluril-derived capsules such as "tennis balls" and "softballs".[4−10]

Cavitand **1** reported by Rebek and co-workers self-assembled to form a cylinder-shape capsule **1·1** by eight bifurcated hydrogen bonds between an imide hydrogen atom in a cavitand with two neighboring carbonyl oxygen atoms as shown in Figure 1.[11−23] Capsule **1·1** can accommodate various guests such as 4-methyl-*N*-*p*-tolylbenzamide **4** in a

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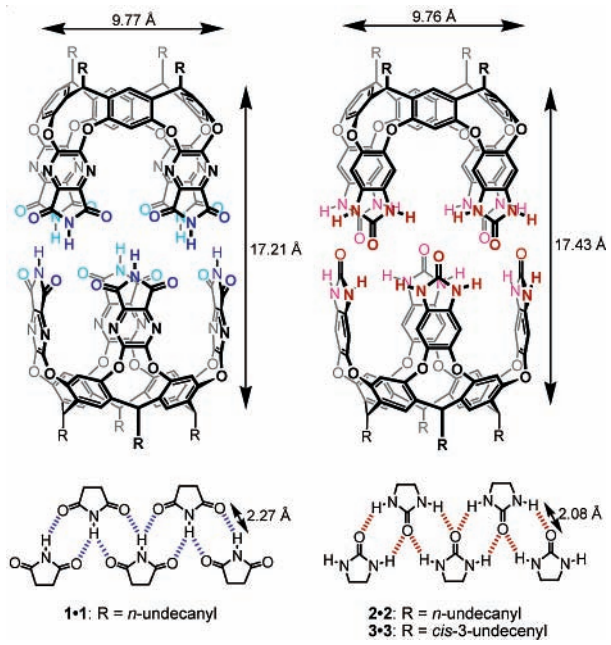

Figure 1. Hydrogen bonding modes of self-assembled pyrazinimide capsule **1·1** and phenyleneurea capsule **2·2**. The bond lengths were calculated from the energy-minimized structures (Spartan 04, V1.0.1, AM1 semiempirical).

nonpolar mesitylene-d_{12}. The inclusion complexes **G@1·1** show interesting guest-exchange phenomena and unprecedented isomerism.[11−23]

Phenyleneurea cavitands **2**, **3**, and other analogues were first reported by de Mendoza et al.[24] These cavitands aggregated, forming different self-organized structures such as vesicles or filaments, depending on the nature and length of the four alkyl feet. Cavitand **2** formed large reverse vesicles through side to side extensive stacking. In contrast, cavitand **3** formed dimeric capsules with carboxylic acids.

We report the observation of the unusually stable capsule formation of cavitand **2**. At elevated temperature guest molecules could template cavitand **2** to form a dimeric capsule **2·2** by reorganizing the intermolecular hydrogen bonds of the aggregate of cavitand **2**.

Cavitand **2** was directly prepared as reported by de Mendoza,[24] and the intermediates, i.e., the corresponding octanitro cavitand and octaamino cavitand reported by Rebek[23,25−27] were similarly prepared by the method reported by Cram et al.[28]

At room temperature, cavitand **2** was barely soluble in CH_2Cl_2, $CHCl_3$, toluene, or mesitylene but reasonably soluble in DMF or DMSO, as reported by de Mendoza.[24] However, at elevated temperature it became soluble in these nonpolar solvents and then stayed in homogeneous solution at room temperature.

The encapsulation studies of cavitand **2** and 4-methyl-*N*-*p*-tolylbenzamide **4** were performed in mesitylene as devised by Rebek.[12,13] A mixture of cavitand **2** and guest **4** in mesitylene remained as a heterogeneous mixture at room temperature even after 5 days, but at above 100 °C the mixture was slowly homogenized. The encapsulation complex **4@2·2** was prepared by heating the mixture under reflux until it became homogeneous and then removing the solvent by vacuum distillation at 70 °C. The solid residue was dried at 100 °C under vacuum. The solid complex **4@2·2** is then soluble in $CDCl_3$, DMSO-d_6, or toluene-d_8 at room temperature.

An equimolar mixture of cavitand **2** and guest **4** (1.67 mM: 1.67 mM) in mesitylene gave a soluble complex in a relatively short period (30 min at 170 °C), but incomplete encapsulation was observed by ^{1}H NMR spectroscopy, which showed three different chemical shifts of the N−H of urea moieties for cavitand **2** (10.35, 10.36, and 10.40 ppm). The chemical shift of the N−H of cavitand **2** was a good indicator of whether the encapsulation complex **4@2·2** was formed completely or partially: the chemical shift of **2·2** in toluene-d_8 was observed at 10.35 ppm.

A complete encapsulated complex **4@2·2** was prepared from a mixture of cavitand **2** and guest **4** (1.67 mM:6 mM, respectively) in mesitylene by heating under reflux for 30 min. The ^{1}H NMR spectrum of **4@2·2** in toluene-d_8 at 100 °C showed the chemical shifts for guest **4** at 5.41 (d, H_c), 5.20 (d, H_e), 3.29 (d, H_b), 3.14 (d, H_f), −2.33 (s, H_g), and −2.41 (s, H_a) ppm (Figure 2 and Table 1). Like the isomorphous cavitand **1·1**,[11] the large upfield chemical shifts of encapsulated guest **4** in capsule **2·2** are observed up to 4.50 ppm for the methyl group (H_a, 2.09 ppm) of free **4** in the ^{1}H NMR spectrum as a result of the shielding by aromatic ring current of capsule **2·2**. Compared to the chemical shifts ($\Delta\delta_1$) for **4** in **1·1**, those ($\Delta\delta_2$) in **2·2** are slightly smaller ($\Delta\Delta\delta$ = 0.40, 0.37 for H_a and H_g, respectively), which is consistent with the molecular dimensions (17.21 vs 17.43 Å through the long C_4 axis of **1·1** and **2·2**, respectively) calculated using semiempirical AM1.

The two different chemical shifts of the N−H of urea moieties for cavitand **2** (10.40 and 10.36 ppm) confirm that

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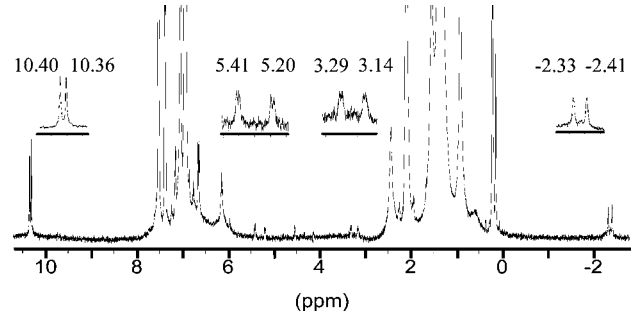
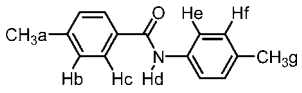


Figure 2. ^{1}H NMR spectrum of encapsulation complex 4-methyl-*N*-*p*-tolylbenzamide@**2·2** in toluene-d_8 at 100 °C.

two chemically nonequivalent methyl groups of guest **4** occupy each cavitand of the dimeric capsule and the guest's head-to-tail rotation is tightly restricted on the ^{1}H NMR time scale even at 100 °C.

The capsular complex **4**@**2·2** was unusually inert in nonpolar solvents such as toluene-d_8. No guest exchange with the solvent molecule was observed in toluene-d_8 at 100 °C for 24 h. However, in polar solvents such as DMSO-d_6 the guest **4** in capsular complex **4**@**2·2** escaped rapidly at room temperature.

Table 1. Comparison of ^{1}H NMR Chemical Shifts (ppm) of 4-Methyl-*N*-*p*-tolylbenzamide **4** and Encapsulation Complexes **4**@**1·1** and **4**@**2·2** in Toluene-d_8[a]



	protons						
	H_a	H_b	H_c	H_d	H_e	H_f	H_g
free **4**	2.09	6.96(d)	7.54(d)	*d*	7.40(d)	6.92(d)	2.12
4@1·1[b]	−2.81	*c*	*c*	*c*	*c*	*c*	−2.70
$\Delta\delta_1$	4.90						4.82
4@2·2	−2.41	3.29(d)	5.41(d)	4.54	5.20(d)	3.14(d)	−2.33
$\Delta\delta_2$	4.50	3.67	2.13		2.20	3.78	4.45
$\Delta\Delta\delta$	0.40						0.37

[a] $\Delta\delta_1 = \delta$ of free **4** − δ of **4**@**1·1**, $\Delta\delta_2 = \delta$ of free **4** − δ of **4**@**2·2**. $\Delta\Delta\delta = \Delta\delta_1 - \Delta\delta_2$. [b] In mesitylene-$d_{12}$ at 295 K.[11] [c] Not reported. [d] Obscured with solvent peak.

Capsular complexes with smaller guests such as *p*-xylene were prepared by heating cavitand **2** in *p*-xylene. In the toluene-d_8, *p*-xylene escaped rapidly as a result of the dynamic equilibrium with toluene-d_8 by mass law ($t_{1/2} = 37$ min at 50 °C).

It is obvious that the hydrogen bonding mode in the self-assembly **2·2** is superior to that in **1·1**, which has been already observed by de Mendoza.[24] For molecular capsule **2·2**, two sets of lone pair electrons in the sp^2 hybridized carbonyl oxygen complementarily hydrogen bond with two adjacent H-N protons, which consumes all of the potential hydrogen bond donors and acceptors. However, in the self-assembly **1·1** only one set of lone pair electrons of the carbonyl oxygen hydrogen bonds to the adjacent H−N proton, as shown in Figure 1.

The unusual stability of capsule **4**@**2·2** in toluene-d_8 without exchanging guest **4** with solvent even at 100 °C suggests that, in addition to the exceptional tight hydrogen bond between two cavitands **2**, van der Waals interaction between guest **4** and capsule **2·2** and the dipolar attraction or hydrogen bond between the amide group of guest **4** and the urea groups of the capsule **2·2** are efficiently operating.

However, in polar solvents such as DMSO-d_6 the guest **4** in capsular complex **4**@**2·2** escaped rapidly at room temperature. The polar DMSO-d_6 molecules compete for the hydrogen bond acceptors in the dimeric capsule **2·2**, which weakens the stability of capsule **2·2** and allows the fast escape of guest **4** and/or the fast exchange of guest **4** with solvent. The observed vase conformation of **2** in DMSO-d_6 confirms that cavitand **2** still exists as a dimeric capsule DMSO-d_6@**2·2** because monomeric cavitand **4** could only exist as rectangular kite conformation as a result of the repulsion between adjacent urea groups.[28]

In summary, the solvent- and/or guest-assisted molecular capsule formations **G**@**2·2** were observed and characterized by heating a mixture of cavitand **2** and guests in a nonpolar solvent at the elevated temperature.

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Supporting Information Available: Synthetic procedures, encapsulation experiments, molecular modeling, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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