Encapsulation of Small Molecules by a Cavitand Porphyrin Self-Assembled via Quadruple Hydrogen Bonds
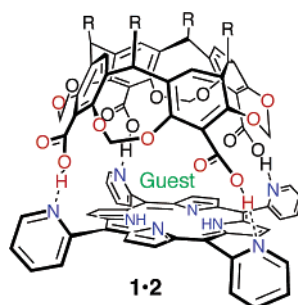
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ABSTRACT

1·2

A new and stable quadruple hydrogen-bonded capsule, tetracarboxylcavitand·*meso*-tetra(2-pyridyl)porphyrin (1·2) has been synthesized and spectroscopically characterized. 1·2 can encapsulate small molecules of various size from methane to cyclopentane. The guest and host exchange rates were evaluated by EXSY.

Molecular capsules are attracting interest with regard to their applications as guest molecule storage flasks, separation tools, sensors, and catalysts for specific chemical reactions.[1] A variety of capsule-like compounds have been reported,[1] including covalently linked compounds[2] and compounds that are self-assembled by metal coordination[3] or hydrogen bonding.[4] Recently, we reported the synthesis of a new capsule molecule, which we have designated "cavitand-porphyrin" (H₂**CP**). This compound has a small cavity created by the combination of a cavitand and a porphyrin with two flexible covalent ether linkages and can reversibly encapsulate single hydrocarbon molecules smaller than propane.[5]

Keys requirements for efficient reversible encapsulation of guest molecules are (1) retention of a "closed" form of the capsule on an appropriate time scale and (2) opening of the capsule by thermal or other physical stimuli to allow guest exchange. In this context, self-assembled systems are simpler than covalent-linked systems but are quite challenging to develop for encapsulation applications because reversible encapsulation has two inconsistent requisites in capsule stability and flexibility.

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Here, we describe a stable self-assembled cavitand-porphyrin formed with four hydrogen bonds without template guest molecules and report reversible binding of small organic molecules.

Tetracarboxylcavitand (**1**)[6] and *meso*-tetra(2-pyridyl)porphyrin (**2**)[7] are appropriate components for formation of a self-assembled capsule through quadruple hydrogen bonding as a result of considerations of convergence and relative separation of functional groups and symmetry (Figure 1).
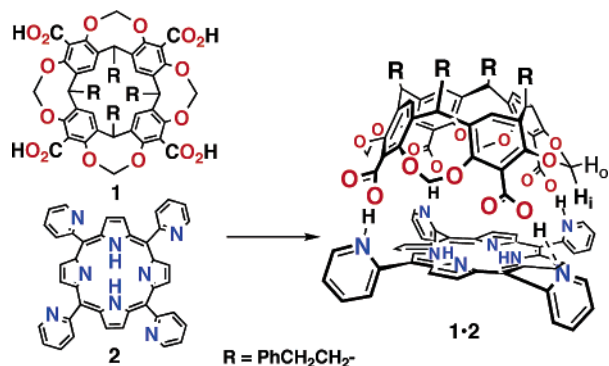
**Figure 1.** Tetracarboxylcavitand·tetra(2-pyridyl)porphyrin (**1·2**).

The capsule formation of **1·2** was examined by ^{1}H NMR in 1,1,2,2-tetrachloroethane-d_2 (Figure 2). Upon addition of
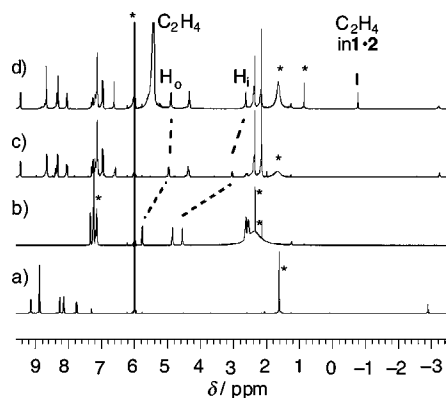
Figure 2. ^{1}H NMR spectra of (a) **2**, (b) **1** with 1% DMSO-d_6, (c) **1·2**, (d) **1·2** with ethylene in 1,1,2,2-tetrachloroethane-d_2 at 298 K. H_o and H_i indicate outer and inner protons of -OCH$_2$O-, respectively. * denotes the signals of 1,1,2,2-tetrachloroethane, H$_2$O, toluene, DMSO, and ethane originating from recrystallization of **1**, solvents, or ethylene gas. For spectrum (b), DMSO-d_6 was added for the dissolution of **1**.

1 into the solution of **2**, the signals of **2** decrease in intensity without shifting and new sharp signals appear at different

positions. When [**1**]:[**2**] = 1:1, only signals assignable to the associated **1·2** remain as a result of the disappearance of the free components. Interestingly, signals arising from eight protons of four methylene-bridge rims (O-CH$_2$-O) in **1·2** appear as two upfield-shifted doublets ($\Delta\delta = -0.81$ and -1.50 ppm from those of free **1**), whereas only small changes are observed for the remaining signals ($\Delta\delta < 0.5$ ppm). These shifts originate from the large anisotropic effect of the porphyrin ring current.[5] Consequently, these properties and the symmetry considerations suggest that the cavitand is located above the porphyrin plane and provides a capped structure with respect to the porphyrin. Formation of the capsule was also characterized by ESI-MS at $m/z = 1748.8$ [**1·2** + H] $^+$ (Figure 3).[8]
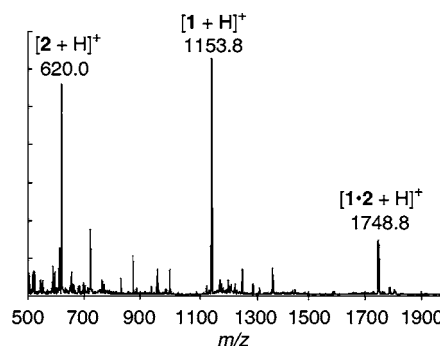
Figure 3. ESI-MS spectra of **1·2** (20 μM) in 1,1,2,2-tetrachloroethane/acetonitrile/formic acid.

The stability of associated **1·2** was examined by a ^{1}H NMR dilution experiment at 298 K. The spectrum remains virtually unaltered upon dilution of the solution to a concentration of 0.1 mM, indicating the existence of a very strong interaction between the two components. No signals of free **1** and **2** appeared. Thus, the capsule **1·2** is thermodynamically stable despite being assembled solely by quadruple hydrogen bonds and without template guests.[9] This result indicates the existence of strong hydrogen-bonding interaction between the pyridyl and the carboxyl groups as previously assumed.

Encapsulation of ethylene in **1·2** was examined (Figure 2d). Upon exposure of ethylene gas to a C$_2$D$_2$Cl$_4$ solution of **1·2**, a new proton signal appears at $\delta = -0.80$ ppm, which disappears upon exposure to argon. This signal is assigned to the protons of the encapsulated ethylene molecule. The large upfield shift ($\Delta\delta = -6.19$ ppm) from the free ethylene signal ($\delta = 5.39$ ppm) is rationalized by the anisotropic effect arising from both the cavitand and porphyrin aromatic ring systems.[5] The stoichiometry shows one encapsulated ethylene molecule per equivalent of **1·2**. The perfect separation of the signals corresponding to free and encapsulated guest protons indicates that the guest exchange rate in **1·2** with the guest in the bulk solvent phase is slower than the ^{1}H NMR time scale.

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(8) Except the peak for **1·2**, each component gives its peak at $m/z =$ 620.0 [**2** + Na]$^+$ and $m/z =$ 1153.8 [**1** + H]$^+$.

(9) There is a posibility of existing water molecules in the capsule.

Encapsulation of other small guests in **1·2** is also observed (Figure S1, Table S1, Supporting Information). Methane, acetylene, ethylene, ethane, propane, and other small organic molecules are encapsulated by **1·2** and give rise to new signals upfield from those of the protons of the free guests.[10] On the other hand, molecules such as benzene that are larger than cyclopentane were not encapsulated, as judged by the absence of upfield-shifted signals.[11] Thus, guest sizes equivalent to cyclopentane and chloroform appear to be the largest acceptable molecules for encapsulation. Each equivalent proton(s) of a given encapsulated guest appeared as a single and sharp signal, indicating that the encapsulated guests in the cavity of **1·2** are generally capable of free rotation.
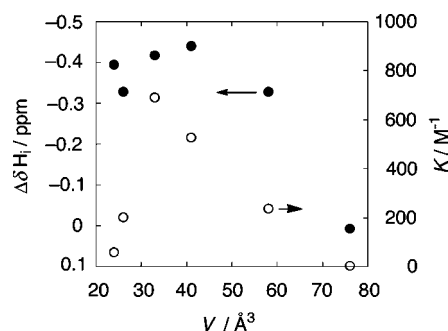
To evaluate guest size selectivity for encapsulation, we determined the 1:1 association constants K of hydrocarbons. K values (M^{-1}, at 298 K) depend on guest sizes as follows: methane (56 ± 13) < acetylene (202 ± 14) < ethylene (690 ± 16) > ethane (527 ± 73) > propane (236 ± 22) > 2-methylpropane (<3). The K value ratio of saturated hydrocarbons into H_2**CP** is methane:ethane:propane:2-methylpropane = 9:1:0:0.[5] The value ratio of saturated hydrocarbons into **1·2** is methane:ethane:propane 2-methylpropane = 0.1:1:0.4:~0. The highest affinity was observed for methane in H_2**CP**, and for ethane in **1·2**, H_2**CP** exhibits higher guest size selectivity than **1·2** for smaller guests as a result of its cavity size. On the other hand, **1·2** can encapsulate guests of various sizes ranging widely from methane to cyclopentane as a result of both its larger cavity size and its flexibility provided by the four hydrogen bonds of the host capsule. The absolute values of association constants cannot be compared simply in these systems because of the different solvent conditions employed ($CDCl_3$ vs $C_2D_2Cl_4$).

With respect to the host, the ^1H NMR signals of the peripheral protons of the cavitand moiety undergo an upfield shift upon encapsulation of hydrocarbons. In particular, a remarkable upfield shift is observed for the inner protons (H_i, Figure 1) of the cavitand -OCH_2O- segment, which is located close to the porphyrin plane. These signals provide a sensitive marker of the cavity shape. The magnitude of the shifts also shows an inverse correlation with volumes of the guest molecules (Figure 4). A concomitant decrease in the porphyrin anisotropic effect accompanies this movement. These results suggest that encapsulation occurs by an "induced-fit" type of complexation. Upon entry of a small guest molecule, the capsule size contracts in size as a result of flexibility of the host hydrogen bonds, to optimize the van der Waals contacts between the host and guest. However, molecules requiring a larger capsule size than the original cavity cannot be encapsulated.

The cavity of **1·2** is larger than the cavity of H_2**CP**,[5] which has the smallest cavity reported thus far for small guests

Figure 4. ^1H NMR chemical shift difference $\Delta\delta$ H_i (●) and binding constant K (○) versus guest molecular volume V. Guest: methane, acetylene, ethylene, ethane, propane, 2-methylpropane. $\Delta\delta$ H_i = (H_i of guest encapsulated **1·2**) − (H_i of free **1·2**).

including hydrocarbons. The cavity of **1·2** is almost the same size as the cavities of other host compounds such as cryptophane-A,[2a] glycoluril self-assembled tennis ball capsule,[4a] and benzene-capped cavitand.[2b] Thus, **1·2** is capable of encapsulating various guests ranging in size of methane to cyclopentane[10] as a result of its larger cavity and the flexibility imparted as a result of self-assembly.

We evaluated host and guest exchange rates by EXSY for the **1·2**/ethylene system. The observed guest exchange rate $k_{C_2H_4,obs}$ is 0.6 s^{-1}. On the other hand, the host exchange process of free porphyrin **2** with **1·2** was not evaluated by EXSY under the same conditions, and the exchange rate could be <0.06 s^{-1}.[12] This indicates that the guest exchange rate is faster than that of the host. In addition, a molecular modeling study indicates that the guest cannot escape through the portal without some extent of hydrogen bond cleavage. On the basis of these results, it is expected that the guest exchange could proceed if the partial dissociation of hydrogen bonds occurs to yield a half-opened capsule.[13]

In conclusion, a new stable capsule-shaped host (**1·2**) was successfully prepared at room temperature by self-assembly via quadruple hydrogen bonds without template guests. Host **1·2** can reversibly encapsulate various small guest molecules ranging in size from methane to THF as a result of the flexibility of the capsule, is very stable host, and has fewer hydrogen bonds than any of the previously reported self-assembled systems. Further investigations of applications of **1·2** are presently underway in our laboratory.

(10) Following guests are incorporated to the cavity: 2-methyl-propane, cyclopentane, methanol, ethanol, 2-propanol, furan, tetrahydrofuran, 1,3-oxirane, 1,3-oxirane-2-one, 1,3,5-trioxirane, dichloromethane, chloroform, dimethyl sulfide, dimethyl sulfoxide, acetonitrile, propionitrile, fumaronitrile, and acetone.

(11) Cyclohexane, 1-propanol, dimethyl sulfone, 2-butanone, and ethyl acetate were also not encapsulataed in **1·2**.

(12) Host exchange rate (k) was roughly estimated by following theoretical equations with 2D NMR integration limit, T_1, and mixing time (t_m). $I_{AA}(t_m) = 1/2\{1 + \exp(-2kt_m)\} \exp(-t_m/T_1)I_0$; $I_{AB}(t_m) = 1/2\{1 - \exp(-2kt_m)\} \exp(-t_m/T_1)I_0$. I_{AA} is the intensity of the diagonal peak, I_{AB} is the intensity of the cross-peak, and I_0 is the initial intensity of the diagonal peak.

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Supporting Information Available: Experimental details and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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