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Self-Assembled Molecular Capsule Based on the Hydrogen-Bonding Interaction between Two Different Calix[4]arenes

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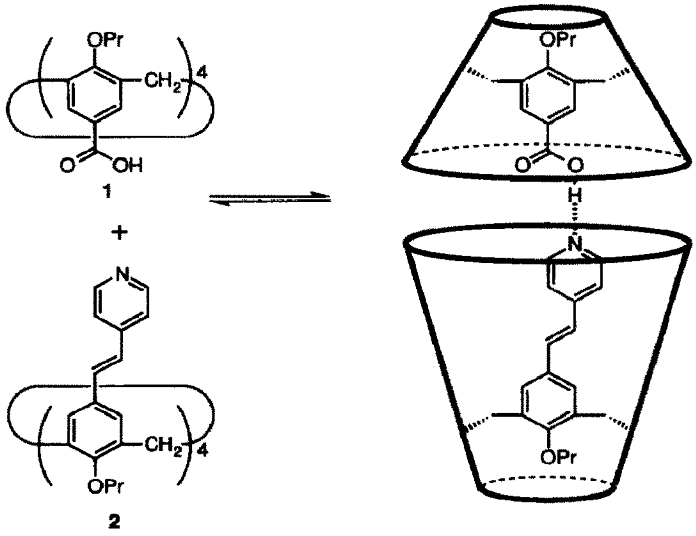
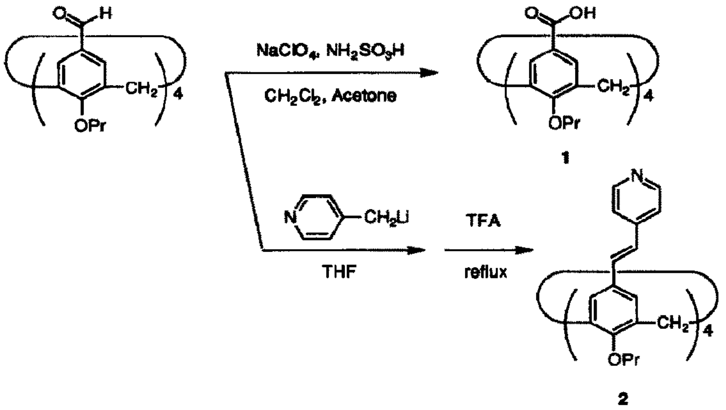
Abstract: Intermolecularly hydrogen-bonded molecular container constructed from two calix[4]arene derivatives having carboxylic acids (**1**) or pyridyl groups (**2**) on their upper rim was designed for the first time. The formation of a simple but very interesting self-assembled molecular capsule was confirmed by physical measurements: i.e., solubility, molecular weight, and fluorescence spectroscopy.

Cooperative action of multiple hydrogen-bonds plays the important role for molecular recognition in many biological systems: the typical, well-known examples are the assembly of DNA and the second structural feature of proteins.[1] In a similar way, the careful choice of complementary binding groups can operate the artificial molecular recognition through self-assembly of functional groups. Further developments in the understanding and control of artificial molecular recognition by self-assembly may be accomplished by taking well-designed hydrogen-bonding supramolecular aggregation into account. The survey of the past references taught us that the hydrogen-bonding interaction is utilized mainly for the construction of one-dimensional linear aggregates or two-dimensional planar aggregates.[2] In contrast, there are few precedents for three-dimensional architectural aggregates.[3] In a paper recently published, Rebek *et al.* demonstrated that the synthetic compound undergoes reversible dimerization with the aid of the hydrogen-bonding interaction to form a closed-shell cavity like a tennis ball microscopic analogy.[4] The same two molecules of this compound assemble to build a three-dimensional surface through a network of hydrogen-bonds. The creators of a molecular tennis ball think that it will act as a valuable basket for other compounds just as viruses slip into the cells and release their DNA.[5]

From the above-mentioned angles, we carefully examined the possibility of a more simple but more functional self-aggregation system with an inner cage. Recently, Kato *et al.*. demonstrated that COOH····N(pyridyl) interaction is so stable as to be applied as a hard segment in the liquid crystal.[6] It thus occurred to us that if two conformationally-mobile, cone-shaped calix[4]arenes with a hemisphere structure are stitched at the upper rim with the hydrogen-bonds between COOH and N(pyridyl), they may result in a self-assembled molecular capsule. Furthermore, if the stilbazole unit is used as a source of N(pyridyl), one may monitor the stitching process through fluorescence emission. These considerations in mind we synthesized conformationally-mobile, cone-shaped calix[4]arenes, **1** and **2**, and evaluated whether they really can form a self-assembled molecular capsule.



Compound **1** with a cone conformation was prepared according to the literature.[7] Compound **2** with a cone conformation was synthesized from tetra-formyl-O-propylcalix[4]arene according to scheme 1. The products were identified by IR, ^{1}H NMR spectral evidence and elemental analysis.[8]



Scheme 1. Synthetic routes of 1 and 2

Firstly, we tested the hypothesis by the solubility. Compound **2** is very soluble in chloroform whereas compound **1** is scarcely soluble in it.[9] When **2** was added to a chloroform solution containing the **1** precipitate, **1** was solubilized into the chloroform solution. The concentration of **1** (determined by ^{1}H NMR spectroscopy) was always equivalent to the concentration of added **2** (Fig. 1), indicating that **1** and **2** always form a 1:1 aggregate.

The COOH····N(pyridyl) interaction between **1** and **2** may be detectable by ^{1}H NMR spectroscopy (250 MHz). In $CDCl_3$ at 25 °C, however, we could not observe any significant change in the chemical shift and the peak for the COOH protons was broadened. The situation could not be improved even at - 50 °C. To find direct evidence for dimerization we estimated the molecular weight by vapor pressure osmometry in $CHCl_3$ at 40 °C. The result (MW 1820 ± 110) was consistent with the desired molecular weight for the dimer (MW 1774.1) formed from **1** (MW 768.8) and **2** (MW 1005.3).

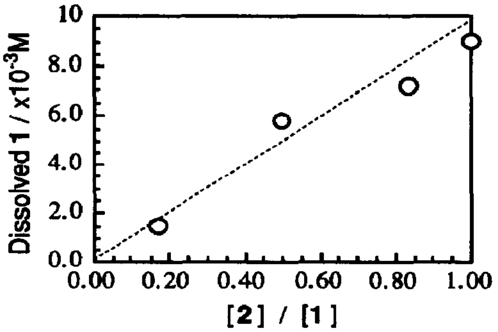


Fig. 1. Solubility of **1** in $CDCl_3$ at 25°C : **1** (1.00 x 10^{-2} M when totally dissolved) was maintained constant.

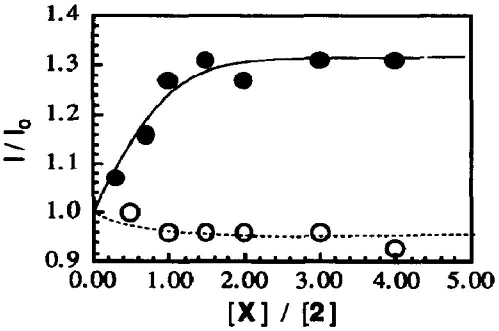


Fig. 2. Plots of the fluorescence intensity emitted from **2** in THF solvent at 25°C : [**2**] = 1.67 x 10^{-5} M (constant) ; excitation wave -length, 315 nm ; emission wavelength, 415 nm ; O, [X] = [**1**] ; O, [X] = [*p* - methoxybenzoic acid] / 4.

The foregoing two experimental data support the view that **1** and **2** are self-assembled to a dimeric molecular capsule with an inner cage. Here, to explore a possible change in physical phenomena induced upon dimerization we measured the fluorescence spectra arising from the stilbazole units in **2**. As shown in Fig. 2, the fluorescence intensity of **2** was scarcely affected or only slightly decreased by the addition of *p*-methoxybenzoic acid. On the other hand, the fluorescence intensity increased with increasing **1** concentration and was saturated at the high concentration. The break-point appears at [**1**]/[**2**] = 1.0. In this experiment we employed tetrahydrofuran (THF) instead of chloroform to homogeneously solubilize **1**. The break-point in Fig. 2 indicates that even in THF which can act as a hydrogen-bond acceptor, **1** and **2** tend to form a 1:1 aggregate. This preference for the formation of the dimeric capsule is accounted for by the basicity of N(pyridyl) stronger as a hydrogen-bond acceptor than that of O (THF) and the entropy term favorable because of complementary preorganization.

On the other hand, it is not so easy to account for why the fluorescence intensity increases in the presence of **1**.[10] It is known that cone-calix[4]arenes enjoy C_{2v} - C_{2v} interconversion in solution.[11] This thermal vibratory interconversion in **2** may be suppressed by the formation of the multiple hydrogen-bonds with another calix[4]arene. If this is the case, one can expect that the fluorescence increase is due to the so-called "rigidification effect".[12]

In conclusion, we have shown that a simple but very interesting self-assembled, multi-hydrogen-bonding molecular capsule can be constructed from hemisphere calix[4]arene with hydrogen-bond donors and that with hydrogen-bond acceptors. We are continuously testing whether this capsule can include guest molecules in solution and in the solid state. We believe that the present paper shows the self-assembly of two calix[4]arenes has several unique potentials for the non-covalent chemirecognics system as a useful nano-scale container.

We owe Mr. Takashi Komori (Shinkai Chemirecognics Project, ERATO, Research Development Corporation of Japan) for the synthesis of **2**.

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9. We estimated the solubility of **1** in $CDCl_3$ from the ^{1}H NMR spectrum in the presence of naphthalene as an internal reference.
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