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Synthesis of a Calix[5]arene Receptor Having Two Benzoic Acid Moieties

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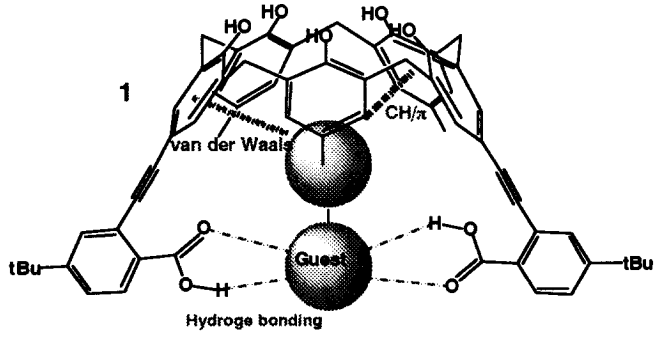
Abstract: **Synthesis and binding behavior of a calix[5]arene receptor possessing two benzoic acids are reported. Two water molecules were bound within the cavity by hydrogen bonding interaction between the two carboxylic acids of the receptor. It also binds 2-aminopyrimidine to form a complex in which the aromatic ring of the guest resides deeply within the cavity.** © 1999 Elsevier Science Ltd. All rights reserved.

Calix[5]arene is known to have an ideal cone shape in nonpolar solvents due to the cyclic hydrogen bonding array of its phenolic hydroxyl groups.[1] As part of our program to utilize the preorganized cone cavities of the small-size calix[n]arenes (n=4,5) for binding small organic guests, we have reported the synthesis of upper-rim functionalized calixarenes and their binding affinity towards nitrogen containing guest molecules.[2] In the continuous effort to understand the detailed mechanism of the guest binding, we have now succeeded the synthesis of calix[5]arene host (**1**). In this paper, we report on its binding of water and 2-aminopyrimidine. Water molecules play an important role in proteins. Some structurally modified proteins are known to be active in organic solvents.[3] The proteins are stabilized in organic solvents by intraprotein hydrogen bonded water molecules. Certain hydrogen bonds are critical to maintain the tertiary structure of the active site. Water molecules play an essential role of in reactions of proteins.[4]



Compound **1** was designed to have the polar functional group to a large cup-shaped cavity composed of five aromatic rings. The two benzoic acids on the upper-rim can grasp polar guest molecules to form hydrogen bonds and the aromatic cavity wall helps to bind the guests with van der Waals interactions.

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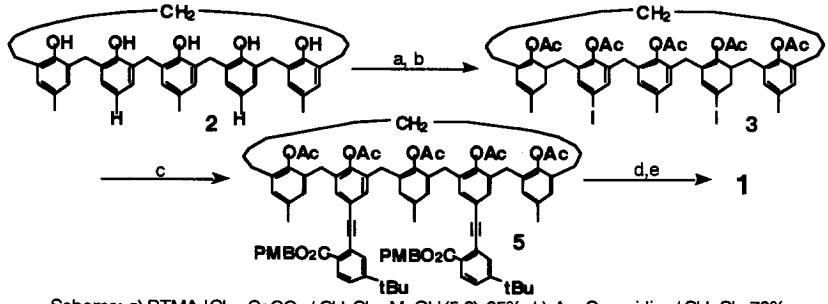
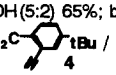
The synthesis of the host started from calix[5]arene **2**.[5] Treatment of **2** with BTMA-ICl_2 followed by protection of the hydroxyl groups afforded diiodocalix[5]arene **3**. Palladium mediated coupling reaction between **3** and **4**[6] gave protected receptor **5** in 68%. Deprotection of acetyl groups followed by BBr_3 treatment gave desired receptor **1**.



Scheme: a) BTMA-ICl_2, $CaCO_3$/ CH_2Cl_2 -MeOH(5:2) 65%; b) Ac_2O, pyridine/ CH_2Cl_2 70%;
c) $Pd(PPh_3)_4$, CuI, n-$BuNH_2$,  / THF 68%;
d) LiOH/ MeOH-THF-H_2O 85% ;
e) BBr_3/ CH_2Cl_2 80%.

All the ^{1}H-NMR signals of **1** in $CDCl_3$ were easily assigned except for the sharp singlet appeared at 4.65 ppm (Fig. 1). The signal disappeared when a small amount of D_2O was added to the solution. The signal of a trace amount of water in $CDCl_3$ usually appears at ca. 1.6 ppm.[7] Judging from the chemical shift and its signal intensity, the 4.65 ppm singnal should be due to the two water molecules bound within the host cavity of **1** by hydrogen bonds. The two bound water molecules are not equivalent because the singlet split into the two broad signals at below –10 °C. To gain the information about the structure of this complex, differential ROE experiments were carried out. The irradiation of the 4.65 ppm signal caused the negative ROEs at several protons; Ha,b,e: -7 %, Hc,d: -10 %, Hf: -18 %. The negative ROEs suggest[8] that the bound and unbound water molecures are exchanging to each other. Actually, in this case a broad

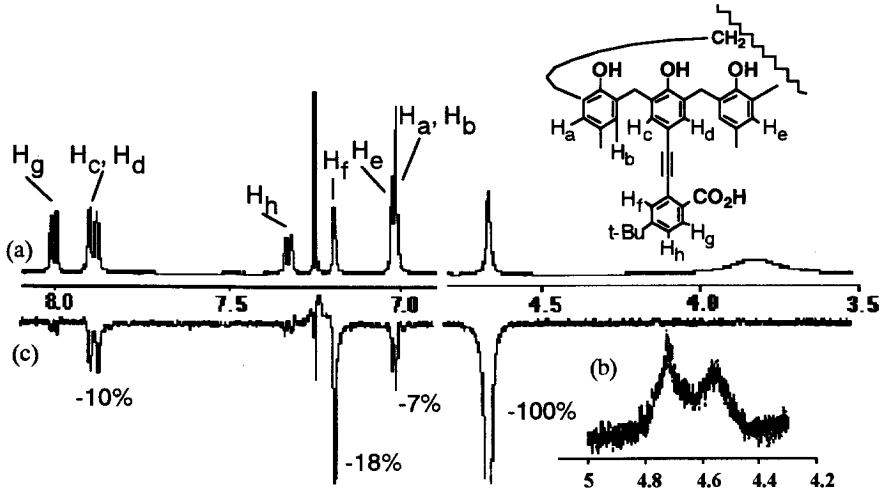


Figure 1. ^{1}H-NMR (a) at R.T. (b) at -10 °C and (c) ROE spectra of **1**•$2H_2O$ complex.

^{1}H-NMR signal of the unbound water molecules appeared at ca. 2.2 ppm suggesting a slow exchange process.

With the aid of molecular mechanics calculation (MacroModel[9] V.6.0 using MMFF force field) we selected some of the plausible structures which meet the distance criteria of the ROE experiment. Two representative structures, symmetric and asymmetric, are shown in Figure 2. The asymmetric structure is lower in steric energy than the symmetric one. In the former structure (Figure 2a) both of the water molecules are trapped between the two carboxyl groups. One of the protons of the deeper bound water molecule has close contacts to aromatic protons (Hd, He). A proton of the deeper bound water molecule in the symmetric structure (Figure 2b) is closer to the cavity aromatic protons. Of course the structures obtained by the molecular mechanics calculation are motionless in nature, and the actual picture of the complex has freedom of movements of the bound water molecules within the cavity, which may explain the ROE result of the other protons.

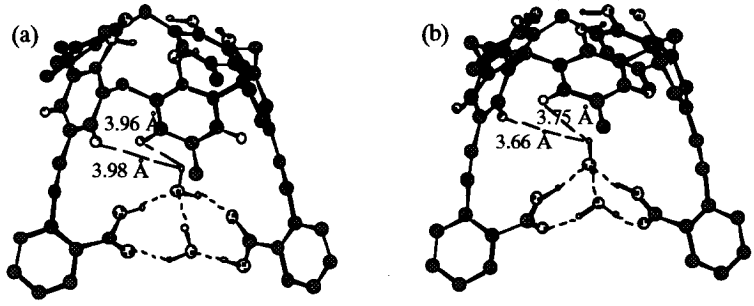


Figure 2. Calculated (a) asymmetric and (b) symmetric structures of **1**•2H_2O complex.

As a basic guest molecule, 2-aminopyrimidine was selected. The N-H signal of the guest was shifted down-field when **1** was added to the guest solution. A 1:1 stoichiometry of the complex was confirmed by Job's plot. The association constant of the complex was determined to be 8900±1700 M^{-1} by a non-linear regression analysis.[10] The association constant should be greater if anhydrous solvent was used. [11] On the other hand the two aromatic signals of the guest shifted up-field. The similar analysis disclosed the complexation induced shift (CIS) of the aromatic protons (H4: -2.36(4), H5: -1.56(3) ppm)

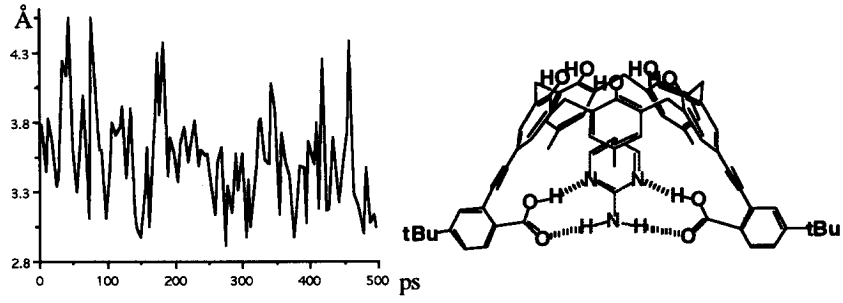


Figure 3. Histry of the distances between the centroid of the 5-membered ring composed of five phenolic oxygens of **1** and C_5 of the guest.

of the bound guest. From the CIS values of the guest, it was suggested that the pyrimidine ring, and especially the less polar portion of it, resided deeply in the cone cavity of the host.

To get the information about the precise structure of the complex in solution we selected a combination of the molecular dynamics calculation and chemical shift simulation. [12] Since the guest can move within the cavity, the molecular dynamics simulation was carried out using the stochastic dynamic treatment at 300 K with AMBER* force field. [9] As found by the trajectory of 500 ps simulation (Fig. 3), the guest is moving rapidly within the cavity, though roughly keeping the hydrogen bondings with the host. The averaged induced shifts of the guest protons were estimated[12] using 100 structures monitored at every 5 ps during the simulation period. Although the magnitude of the calculated CIS values (Δδ: H4: -3.00, H5: -1.80) are larger to some extent than the observed ones, the above mentioned arrangement of the guest is confirmed by these calculations. Thus, molecular dynamics simulation analysis has proven very efficient in reproducing the structure and the movement of the supramolecular complex. From this analysis it is concluded that the receptor (**1**) binds the amine guest by the hydrogen bonds and van der Waals interactions cooperatively.

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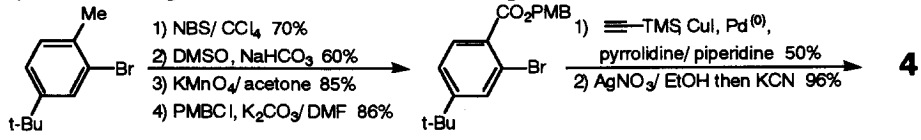
6) The synthesis of the segment **4** was carried out as the following scheme.



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