A New Receptor Based on Calix[5]arene Analogue

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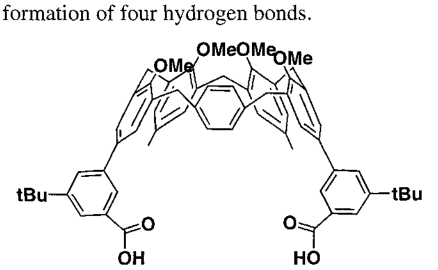
Abstract: Synthesis and the binding behavior for tetramethylether (**1**) of the calix[5]arene analogue are presented. In binding the guest molecules, an adjustment of the host structure to fit the guest shapes was predicted by molecular dynamics-molecular mechanics calculations.

Host-guest chemistry has been a rapidly growing and active research field in organic chemistry, and is essential to understand the relationship between the structure and the function of biological systems.[1] The development of artificial receptors for neutral molecules plays an important role in bio-organic chemistry.[2] The small organic receptors have several advantages, which are a manageable degree of structural complexities, flexibility and easily designed chemical properties.

We designed a flexible host molecule (**1**) based on calix[5]arene-type cyclic system including para-bridged benzene in a core structure. The core structure of the host is flexible because of its large cyclic system. In binding some amine guests such as 2-aminopyrimidine, 9-ethyladenine, and ethyleneurea, an adjustment of the structure of the flexible host would occur to attain the best complementarity with the guest shapes through the formation of four hydrogen bonds.



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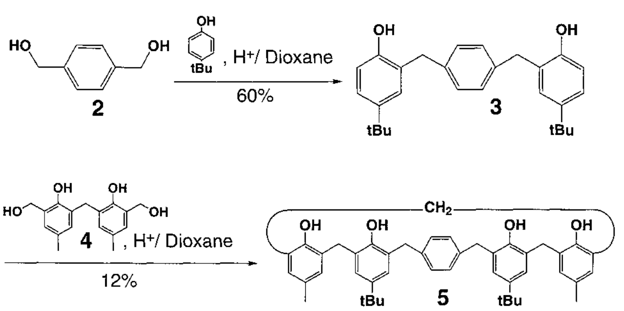
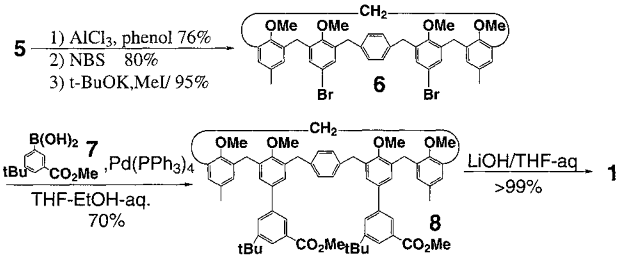
The synthesis of the flexible host molecule (**1**) is shown in schemes 1 and 2. The first stage of the synthesis is the construction of the core structure of the new calix[5]arene analogue (**5**). We selected a stepwise route similar to that developed by Böhmer et al.[3] Condensation of diol (**2**) with *t*-butylphenol under refluxing conditions gave **3** in good yield. Cyclization of **3** with **4** proceeded smoothly to give calix[5]arene analogue (**5**). The high flexibility of **5** is verified by the extremely low coalescence temperature (T_c<-90°C) of the bridging methylene chain as compared to that of the calix[5]arene itself (T_c= -2°C).[4]



Scheme 1

The second stage of the synthesis is an incorporation of the guest binding portion into **5**. Removal of the *t*-butyl groups under retro Friedel-Crafts conditions followed by bromination afforded dibromide, and successive protection of four hydroxyl groups gave tetramethylether (**6**). The incorporation of the guest binding portion was carried out by Suzuki's condition with boric acid (**7**)[5] to afford the coupling product (**8**) in 70% yield.[6] Hydrolysis of the ester furnished the target compound (**1**).



Scheme 2

The possibility of self-association of **1** was investigated over a wide range of concentration. From 10^{-3} to 10^{-2} M in CCl_4, the IR spectrum of hydroxyl and carbonyl groups of benzoic acid moieties in **1** did not change. No band attributable to the free OH and C=O was observed. Thus, the spectra suggested that two carboxyl groups of **1** form an intramolecular hydrogen bonding. The intermolecular hydrogen bonding, and hence the aggregation of **1** is negligible to an appreciable extent under the conditions employed for binding studies.

Binding studies of the host molecule with 9-ethyladenine were carried out by ^{1}H-NMR spectroscopic titration method. To a solution of the guest molecule in $CDCl_3$ was added the solution of the host (**1**) in the same solvent. The complexation induced shifts of NH were monitored. The chemical shift of the NH in the guest molecule moved to downfield when the host solution was added. Characteristic saturation of the chemical shift movement was clearly observed. Thus the host binds the guest by the hydrogen bonding interaction. A stoichiometry of the complex was determined by Job's plot for the complexation induced chemical shifts of NH protons, and found to be 1 : 1 (guest : host). The association constant determined by a non-linear least squares curve fitting program using Gauss-Newton algorithm.[7] Association constants and stoichiometries for the complexes with several guests were determined by the same procedure, and listed in Table 1.

Table 1. Stoichiometries and association constants of host-guest complexes

Guest	Stoichiometry	Association constant (M^{-1})
9-ethyladenine	1:1	2050±150
ethyleneurea	1:1	1050±140
2-aminopyrimidine	1:1	580± 50

Although these guests have different size and shape, the association constants do not change extensively, suggesting some adjustment of the host structure to have four hydrogen bonds with each guest. In order to assess the plausible geometry of these complexes, molecular modeling studies were performed. Molecular mechanics calculation has been extensively used for the prediction of the most probable structures of supramolecular complexes.[8] The 600 initial geometries of the complexes were sampled at every 0.1ps for 60ps during the stochastic dynamics simulation. Modeling study of these complexes was performed with AMBER* force field using GB/SA chloroform solvation model.[9] The resulting structures were then optimized using MULTIC routine in MacroModel V 4.0.[10] The most stable structures of the complexes are shown in figure 1. They all have four hydrogen bonds between the two carboxylic acids and the amine guests. Worthy to note is the coexistence of Hoogsteen (carboxylic acid, N6 and N7 of the guest) and Watson-Click type (carboxylic acid, N6 and N1 of the guest) hydrogen bondings between the **1** and 9-ethyladenine. In all these structures, one of the free anisole rings inclines so as to bury its methoxyl group into the cavity of the host in order to quench the vacant host space. The experimental support of these predicted complex structures was given from the ^{1}H-NMR chemical shift of the methoxyl signals. When twenty equivalents of the host was added to the guest solution, the methoxyl signal exhibited up-field shift of 0.12 ppm. Therefore the up-field shift should be close to 2.4 ppm in the 1:1 complex. This large up-field shift of the signal is a supporting evidence of the buried methoxyl conformation.

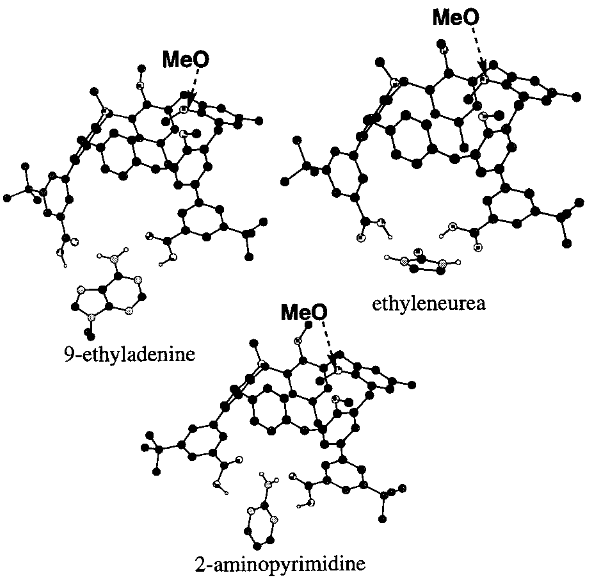


Figure 1. Most stable structures of the host-guest complexes; buried OMe group is shown by the arrow

In summary, we have succeeded in the synthesis of an artificial receptor having calix[5]arene analogue as a core structure, and shown that the synthetic receptor can form strong complexes with a variety of the amine guests through an adjustment of their structures.

Acknowledgments

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References and Notes

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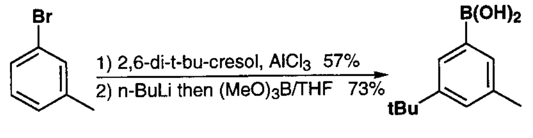
5) Phenylboric acid derivative (**7**) was synthesized by the following scheme.



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