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Allosteric Receptor Based on Monodeoxycalix[4]arene Crown Ether

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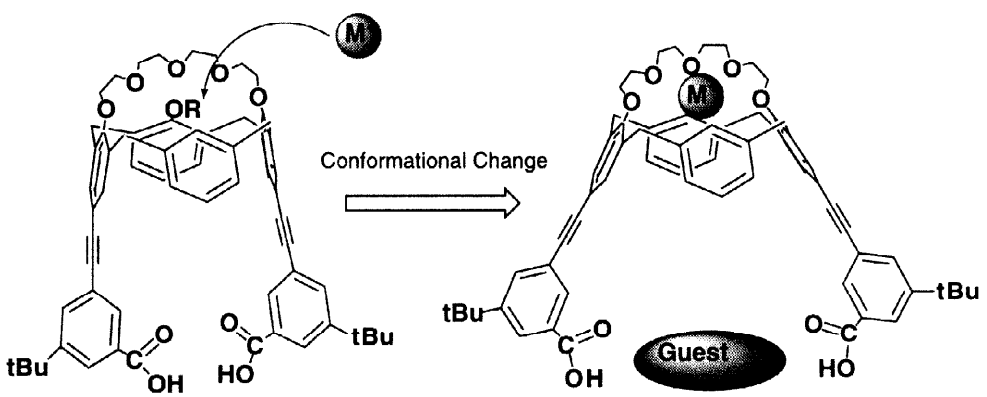
Abstract: A new allosteric host based on the monodeoxycalix[4]arene possessing two long arms as a guest binding portion was synthesized, and exhibited strong allosteric binding with neutral guest molecules. The allosteric binding of the host has been rationalized by molecular mechanics calculation.

Regulation of the catalytic activity of an enzyme by the binding of an effector on a remote position other than the active site can be frequently observed in biological systems. This type of regulation is known as the allosteric effect.[1] Most of the synthetic allosteric receptors reported so far contain two conformationally coupled binding sites.[2] Binding of an effector to a remote site causes a conformational change at the active site and alters the binding affinity to its substrate and, hence, it can regulate the activity of the enzyme.[3] It is of interest to mimick this phenomenon of regulating activity in a simple artificial organic molecule. Here, we demonstrate that a host based on the monodeoxycalix[4]arene[4] can exhibit an allosterically enhanced guest binding in the presence of excess amount of an appropriate alkali metal cation (Fig. 1).



1: R=CH_2CH_2OEt

Fugure 1. Schematic representation of alkali metal induced conformational change.

The synthesis of **1** is shown in scheme 1. Treatment of calix[4]arene **2**[5] with ethoxyethylbromide and potassium carbonate, followed by treatment with diethyl phosphite afforded a phosphate ester which was reductively cleaved (K/liquid NH_3, -78°C) to the deoxygenated derivative **3**.[6] Treatment of **3** with ICl followed by the introduction of trimethylsilylacetylene afforded the bis-acetylene **4** in good yield. Introduction of the bridging crown ether moiety into **4** and subsequent palladium(0) catalyzed coupling with the substituted iodobenzene **5** followed by ester hydrolysis furnished the desired host molecule **1**.

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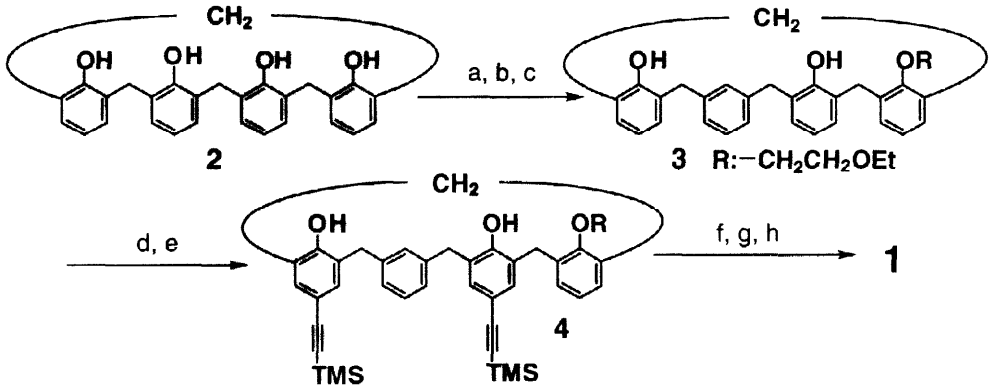
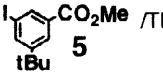


Scheme 1. a) K_2CO_3, $EtO(CH_2)_2Br$/ toluene 54%; b) $(EtO)_2POH$, Et_3N/ toluene-CCl_4 (3:1) 90%; c) K/ NH_3-THF (1:1) 76%; d) ICl/ $CHCl_3$ 80%;d) ICl/ $CHCl_3$ 80%; e) $Pd(PPh_3)_4$, CuI, TMS−≡ /THF 92%; f) $Ts(OCH_2CH_2)_4OTs$, Cs_2CO_3/ MeCN 61%; g) $Pd(PPh_3)_4$, CuI,  /THF 70%; h) LiOH/MeOH-aq. 92%

In order to evaluate the binding ability of **1** toward the alkali metal cations, solid-liquid extraction experiments were carried out at 27°C.[7] By alkali metal picrate extraction, the association constants of **1** with Na^+ and K^+ were determined to be $8.9X10^4$ and $1.9X10^5$ $dm^3 \cdot mol^{-1}$, respectively, by UV spectroscopy. The stoichiometry of the host-metal complex is confirmed to be in a ratio of 1:1 by the ^{1}H-NMR spectrum of the complex. The results indicate that the concentration of alkali metal-free host is negligible in the presence of excess alkali metal picrate.

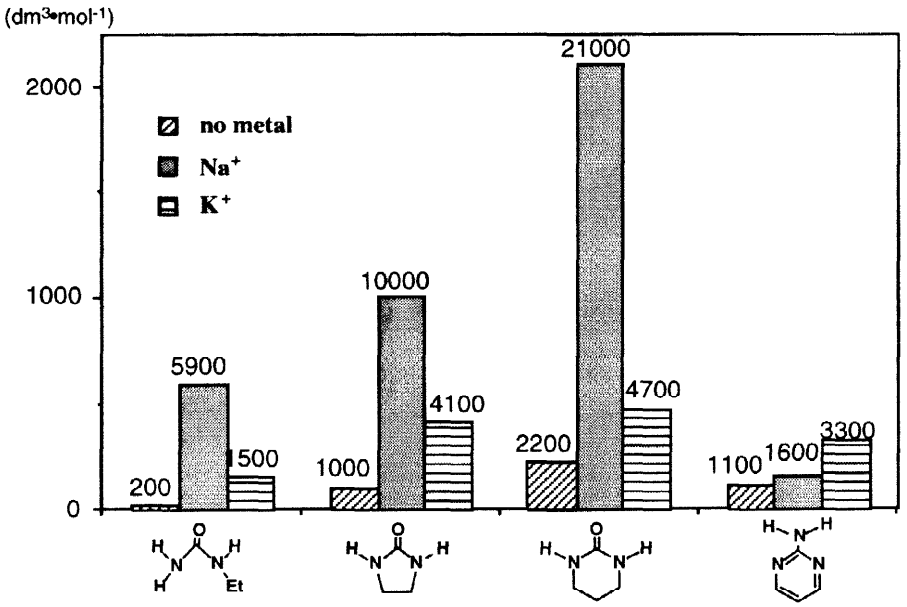


Figure 2. Association constants of **1** in the absence and presence of alkali metals in $CDCl_3$ at 27 °C. Estimated errors are less than ±10%.

The host **1** can bind a number of nitrogen containing neutral guests irrespective of the presence or absence of alkali metal cations. The complexation induced shifts of N-H proton in the guest were monitored by ^{1}H-NMR spectroscopy. The N-H proton shifted down-field when a solution of the host **1** was added. The binding phenomena should thus arise from hydrogen bonding between the two carboxylic acids of the host

and N-H of the guest. Stoichiometry of the complexes as analyzed by Job's plot using the complexation induced chemical shifts of N-H, was found to be always 1:1 and that of the ternary complexes (alkali metal cation-**1**-guest) as 1:1:1. The association constants of the neutral guest binding process were determined by the ^{1}H-NMR titration method with use of a non-linear least squares curve fitting procedure[8] (Fig.2).

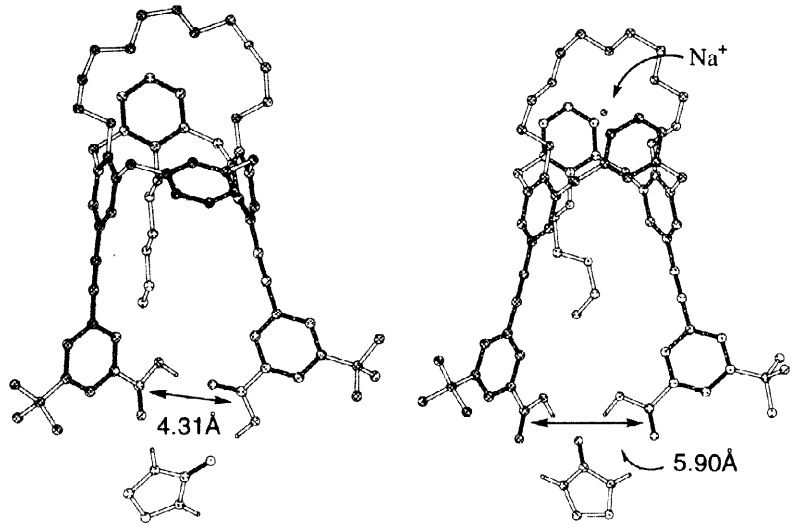


Figure 3. Calculated structures of the complexes in the absence and in the presence of the alkali metal.

The host **1** can bind both the cyclic and acyclic monoalkylsubstituted ureas efficiently. The binding constant of the free host to the acyclic guest is smaller than those to the cyclic guests. Whereas the cyclic guests have two N-H groups fixed in syn arrangement to the carbonyl groups, the acyclic urea has only one, due to the N-alkyl group prefering to have a syn orientation to the carbonyl.[9] This might be one of the reasons for the small association constant of the acyclic guest. When alkali metal cations are added, the association constants of the urea guests increased significantly. Sodium ions give larger enhancement factors than potassium ions. The enhancement factor of Na^+ is larger in the binding of the acyclic urea (by 29 times) than that of the cyclic ureas (ethylene urea, by 10; propylene urea, by 10). On the other hand, a reverse order of the enhancement factors of Na^+ and K^+ was observed in the binding of 2-aminopyrimidine. In order to explain these positive allosteric effects for the guest binding in the presence of the alkali metal ions, molecular mechanics calculations of both the binary and ternary complexes were carried out using the molecular modeling system, MacroModel V.6.0.[10] The global energy minimum structures of these complexes were determined by the modified Merck force field[11] with the aid of the low mode conformational search algorithm (Fig.3)[12]. In the metal free complex, one of the two secondary amide moieties of the urea guest was bound by two carboxylic acids, which are linked by one hydrogen bond to each other, reflecting a short distance between the two carboxylic acid moieties. However, in the presence of an appropriate alkaline metal cation, the lower rim crown ether changes conformation so as to have a prefered arrangement for the binding of the cation. As a result of this conformational change of the polyoxyethylene chain, the two distal benzene rings carrying ether oxygene tilt inward to each other, and hence, the two carboxyl groups move away from each other by breaking the intramolecular hydrogen bond between them. This cost in energy is well compensated by the increase of favorable attractive H-bonding interaction between the host and guest. Urea binding occurs

to the two carboxylic arms with four points of hydrogen bonding. Hence, the alteration of the guest binding affinity of the host is regulated by the structural change induced by the 1:1 binding of a metal cation.

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