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Doubly bridged biscalix[4]arene for homotropic and heterotropic allosteric effects on ion recognition

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Abstract—A novel host, which shows homotropic and heterotropic allostery for Na^+ and Ag^+ recognition, is constructed by utilizing a biscalix[4]arene skeleton bearing bipyridine and ester moieties. The host binds two Na^+ ions, but the second binding to Na^+ is considerably suppressed by the first Na^+ ion bound in the other binding site.

Cooperative regulation of host–guest interactions plays a critical role to maintain homeostasis in metabolism, substrate transport, etc., because amounts of biologically important substrates in the body must be well controlled by various external stimuli.[1] Thus, artificial allosteric hosts have been investigated intensively.[2] Although these hosts exhibit effective positive and negative allosteric effects on guest recognition, most of them respond to only one effector. Multi-response, however, is inevitably important to construct sophisticated molecular devices and systems.[3] We report here the synthesis and functions of calix[4]arene[4] derivatives as an allosteric host responding to different effectors to show different binding behaviors. The framework of the hosts **1** is based on a biscalix[4]arene skeleton bridged by 2,2′-bipyridine moieties. The bridging units should be effective to capture soft metal ions. In addition, the ester or ether groups as a binding site for hard metal ions are introduced onto the lower rim of the calixarene unit.[5] The concept of the allosteric regulation employed here is shown in Figure 1. Two hard metal ions can interact with the host on the rim of the calixarene. In contrast, one soft metal ion is bound by the two bipyridine units if the complexation occurs. When two different effectors, a hard metal ion and a soft metal ion, modulate the affinity cooperatively, heterotropic allostery[6] is achieved. On the other hand, homotropic allostery[7] occurs if the same kind of effector, for example, hard metal ions, affects binding cooperatively.

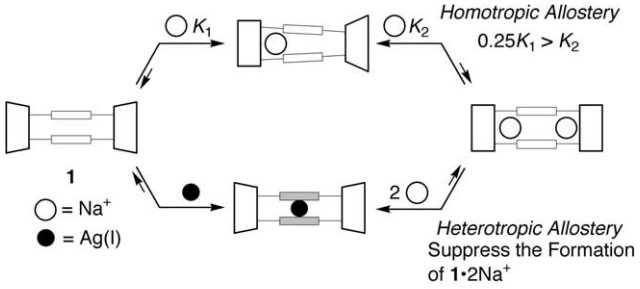

Figure 1. Artificial homotropic and heterotropic allosteric host **1**.

Biscalix[4]arene **1a**[8] was treated with methyl bromoacetate and NaH to give **1b** in 50% yield (Scheme 1). Reaction of **1a** with 2-methoxyethyl tosylate in the presence of NaH afforded **1c** in 45% yield. ^{1}H NMR spectroscopy supports the cone conformation of **1** because chemical shift differences of the benzylic methylene protons are 1.45 and 1.21 ppm for **1b** and **1c**, respectively.[4] The ^{13}C NMR spectra again indicate the conformation (δ 31.7 ppm in **1b**, 31.8 ppm in **1c** in $CDCl_3$).[9]

Finally, X-ray crystallography definitely confirms the molecular structure of **1b** and **1c**.[10] Host **1b** possesses a crystallographic center of symmetry between the two calix[4]arenes as shown in Figure 2.[11,12] Each calix[4]arene moiety adopts the pinched cone conformation,

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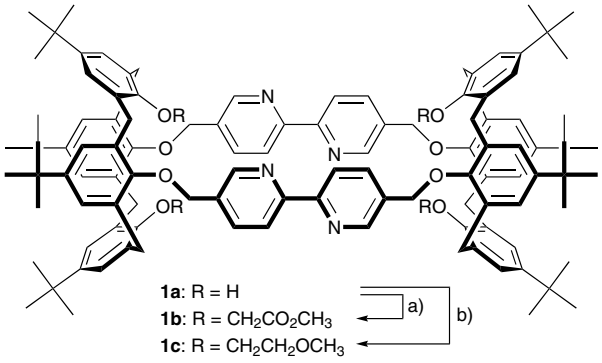

Scheme 1. Synthesis of the hosts **1b**,**c**. (a) $BrCH_2CO_2CH_3$, NaH, THF, reflux, 50%; (b) $TsOCH_2CH_2OCH_3$, NaH, THF, reflux, 45%.

and each of the recognition sites for alkali metals consists of two esters on the lower rim. The distance between the oxygen atoms (O2–O4*) adjacent to the picolyl methylenes is 10.86 Å. The two bipyridine moieties locate parallel, and the distance between the bipyridine planes is 7.4 Å.

Binding affinity of **1a**–**c** to alkali metal cations was evaluated by ^{1}H NMR spectroscopy (Fig. 3). $NaPF_6$ or KPF_6 caused no detectable spectral changes in **1a** and **1c** probably due to the lack of ester groups as a binding site for alkali metal ions. In contrast, $NaPF_6$ resulted in drastic ^{1}H NMR spectral changes in **1b**, which has ester groups. In the presence of 0.5 equiv of $NaPF_6$ ([**1b**] = 2.00 mM, [Na^+] = 1.00 mM) a new set of signals assigned to an Na^+ complex of **1b** was observed. A different Na^+ complex, assigned to **1b**·2Na^+, however, is formed by the addition of equimolar Na^+ (2.00 mM), and the addition of 2 equiv of Na^+ (4.00 mM) causes complete formation of **1b**·2Na^+. This fact suggests that the association constants K_1 and K_2 are too large to be determined by ^{1}H NMR titration.

The ratio of $0.25K_1/K_2$, however, is roughly estimated to be ca. 6 from the ratios of [**1b**·Na^+] to [**1b**·2Na^+] in the ^{1}H NMR spectra. The correction factor of 0.25 is the statistical preference of the first over the second binding.[13] The $0.25K_1/K_2$ value shows that the binding to the

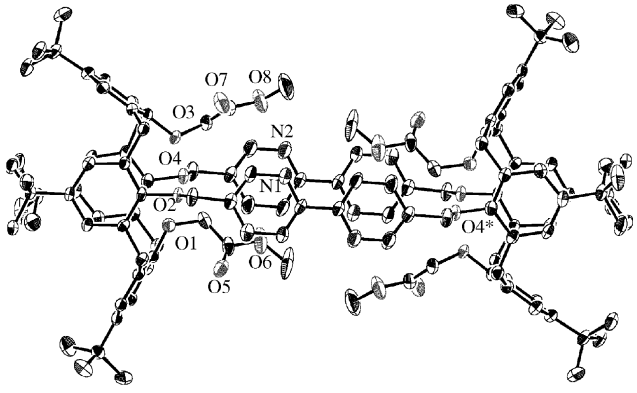

Figure 2. ORTEP drawing of **1b**. Hydrogen atoms, solvent molecules, and disordered atoms were omitted for clarity. Thermal ellipsoids were drawn at 50% probability level.

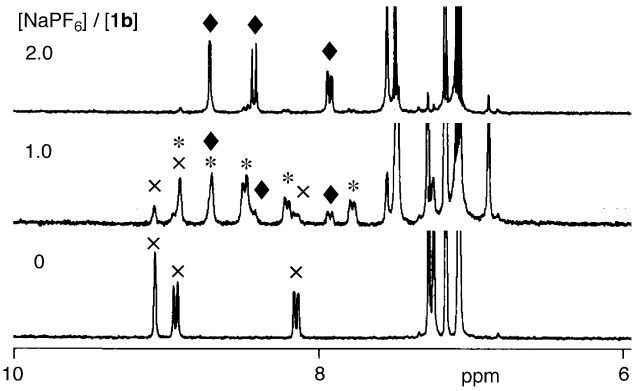

Figure 3. ^{1}H NMR spectral changes of **1b** by the addition of $NaPF_6$ (300 MHz, Toluene-d_8–CD_3CN = 6:5, [**1b**] = 2.00×10^{-3} M). The signals of **1b**, **1b**·Na^+, **1b**·2Na^+ are indicated by ×, ∗, ◆, respectively.

first Na^+ ion inhibits binding to the second Na^+ ion. Since the distances (ca. 10 Å) between the Na^+ recognition sites are ca. 5 times longer than the sum of the ionic radii of the two Na^+ ions (1.90 Å), electrostatic repulsion should not affect the Na^+ affinity. Thus, conformational change induced by the binding to the first Na^+ suppresses the binding affinity of the ester groups to Na^+ as a second guest. Namely, this homotropic negative allostery on Na^+ is finely achieved by the fact that information on the first Na^+ binding is transferred by way of the bipyridine linkers to cause unfavorable conformational change for Na^+ binding of the other binding site.

Complexes **1b**·Na^+ and **1b**·2Na^+ have been also characterized by ESI-MS spectrometry. The spectrum of an equimolar mixture of **1b** and $NaPF_6$ shows a peak at m/z 1968.1 of the complex [**1b**·Na]$^+$. A signal for [**1b**·2Na]$^{2+}$ was observed at m/z 995.7 in the case of **1b**:Na^+ = 1:2.

UV–vis titration experiment shows that the bipyridine moieties of **1b** bind to the Ag^+ ion as a soft metal guest to give the corresponding 1:1 complex (Fig. 4). ^{1}H NMR and ESI-MS also support the 1:1 stoichiometry. In ^{1}H NMR titration (toluene-d_8–CD_3CN = 6:5) significant changes were observed in aromatic, CH_2–bpy, and CH_2CO_2 methylene protons up to 1 equiv of Ag^+ (2.00 mM). These results indicate that the complexation between Ag^+ and the two bipyridine moieties of **1b** takes place. The accurate association constant K_a between **1b** and Ag^+ is too large to be determined by using these spectroscopic methods. The hosts **1a** and **1c** also show high affinity to Ag^+ ion.

Heterotropic allostery was observed in Na^+ recognition by using **1b** as a host and Ag^+ as an effector. As shown in Figure 5, when 1 equiv of $NaPF_6$ (2.00 mM) was added to **1b**·Ag^+, a white precipitate (probably $NaNO_3$) appeared and ^{1}H NMR spectral change was not observed probably due to formation of the salt. As shown in Figure 5, the addition of 3 equiv of $NaPF_6$ (6.00 mM) resulted in the formation of **1b**·2Na^+, but a small amount of **1b**·Ag^+ still remained, and the ratio of

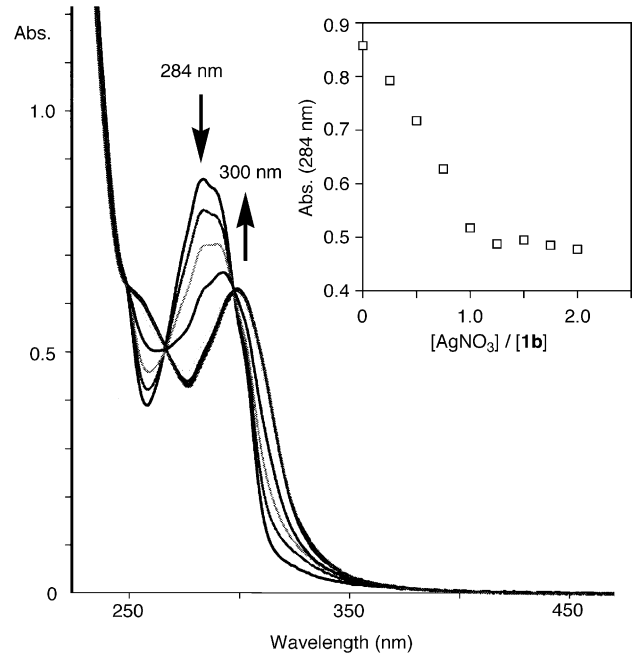

Figure 4. UV–vis spectral changes of **1b** by the addition of $AgNO_3$ (CH_3CN–$CH_2ClCH_2Cl = 1{:}40$, $[\mathbf{1b}] = 1.75 \times 10^{-5}$ M).

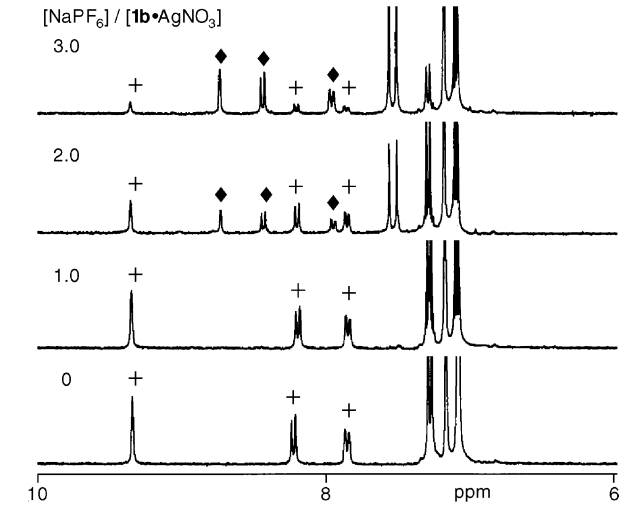

Figure 5. ^{1}H NMR spectral changes of **1b**·$AgNO_3$ by the addition of $NaPF_6$ (300 MHz, Toluene-d_8–$CD_3CN = 6{:}5$, $[\mathbf{1b}] = [AgNO_3] = 2.00 \times 10^{-3}$ M). The signals of **1b**·Ag^+ and **1b**·$2Na^+$ are indicated by + and ◆, respectively.

[**1b**·$2Na^+$] to [**1b**·Ag^+] is 1:0.175. The complete formation of **1b**·$2Na^+$ occurred by the addition of 2 equiv of $NaPF_6$ to free **1b**. This fact suggests that the formation of **1b**·$2Na^+$ is suppressed by the complexation of **1b** with Ag^+. The formation of the $Ag(bpy)_2$ complex alters the conformation of the calix[4]arene moieties to lower the affinity to the Na^+ ion. Consequently, this host **1b** exhibits a homotropic and a heterotropic negative allostery on ion recognition of Na^+ when Na^+ and Ag^+ ions are used as an effector, respectively.

In summary, the biscalix[4]arene bearing two bipyridine bridges works as a host, which shows homotropic and heterotropic allosteric ion recognition. In biscalix[4]arene **1b**, the recognition of Na^+ is suppressed by two kinds of effectors, the first Na^+, and Ag^+. Our current efforts are focused on the synthesis of host recognizing and releasing organic molecules responding to different kinds of external stimuli, and further attempts to extend this system to construct nano-capsules are under investigation.

Acknowledgements

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11. Crystal data for **1b**·H_2O·$2CHCl_3$·$1.5CH_2Cl_2$:$C_{127.5}H_{151}Cl_9N_4O_{17}$, $M = 2330.57$, triclinic, space group $P\bar{1}$, $a = 10.9957(18)$, $b = 13.365(2)$, $c = 22.225(2)$ Å, $\alpha = 79.348(5)$, $\beta = 87.2339(17)$, $\gamma = 80.2685(15)°$, $V = 3163.2(8)$ Å^3, $Z = 1$, $D_{calcd} = 1.223$ g cm^{-1}, μ(Mo-Kα) = 0.262 mm^{-1}, crystal size = $0.3 \times 0.2 \times 0.08$ mm^3, reflections collected 20114, unique 10702 ($R_{int} = 0.0418$), $R1 = 0.0807$ ($I > 2\sigma(I)$), $wR2 = 0.2171$ (all data), GOF (F^2) = 1.023. The intensity data were collected on a Rigaku Mercury CCD diffractometer with Mo-Kα radiation,

$\lambda = 0.71069$ Å, $T = 123$ K. CCDC 224544 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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