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Homotropic negative allostery in alkali metal ion recognition by biscalix[4]arene-based receptor

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Abstract—A novel host which shows homotropic and negative allostery for alkali metal ion recognition is constructed by utilizing a biscalix[4]arene skeleton bearing biphenyls and ester moieties. As the ionic radius of the guest increases, recognition of the second guest is suppressed more effectively. A larger ion changes the structure of the first binding site more drastically to cause conformational change unfavorable for the guest binding of the second site.

Calix[4]arenes have been widely utilized as a basic skeleton for artificial receptors and sensors in supramolecular chemistry because they possess unique, three-dimensional structures, which are useful to arrange and assemble functional moieties.[1] Many host molecules which recognize cations, anions, and organic molecules have been constructed by introducing various functional groups onto the upper or lower rim of calix[4]arenes. Recently, cooperative regulation of molecular recognition has been intensively studied to modulate molecular functions via external stimulus.[2] Biscalix[4]arenes[3] would be a suitable framework for such cooperative systems since two recognition sites obviously exist and conformation of the binding sites can be mutually changed through an appropriate linker between two calixarene moieties. In this letter we report the synthesis and recognition ability of a novel biscalix[4]arene-based host with a homotropic[4] and remarkably negative allosteric effect on ion recognition, which plays a very important role in noncompetitive inhibition in the body (Fig. 1).[5]

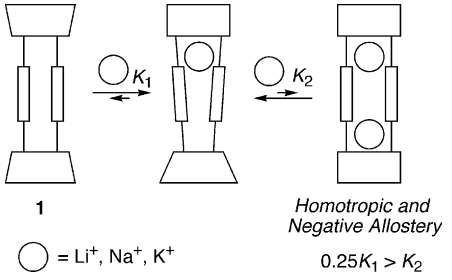

Figure 1. Artificial homotropic allosteric host **1**.

Bisbiphenyl biscalix[4]arenes **1a**,**b** were synthesized as shown in Scheme 1. Reaction of *p*-*t*-butylcalix[4]arene with 1.1 equiv of 4,4′-bis(bromomethyl)biphenyl in acetonitrile with K_2CO_3 afforded biscalix[4]arene **1a** in 21% yield. Treatment of compound **1a** with NaH and excess ethyl bromoacetate gave **1b** in 45% yield.

The ^{1}H NMR spectra of **1a**,**b** exhibit one singlet for the methylene protons adjacent to the biphenyl moieties, two singlets for the aromatic protons of calix[4]arenes, and one AB pattern for the methylene groups in the calixarene moiety.[6] The differences in the chemical shifts ($\Delta\delta$) in the AB system of **1a**,**b** are 1.02 and 1.50 ppm, respectively. Each ^{13}C NMR spectrum of **1a**,**b** shows one signal (at δ_C 31.9 and 31.8 ppm) for the bridging methylene moieties. Both spectra suggest that the molecules **1a**,**b** have D_{2h} symmetry, and the calix[4]arene units adopt a cone conformation.[1,7] The structure was also ascertained by IR, ESIMS, and elemental analysis.

The X-ray crystal structure of **1b** is shown in Figure 2.[8,9] In the solid state, the compound has a 2-fold axis through the cavity consisting of two calix[4]arenes and

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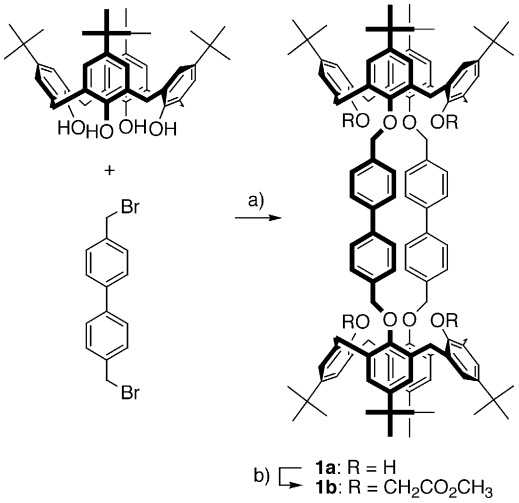

Scheme 1. Synthesis of hosts **1a**,**b**. Reagents: (a) K_2CO_3, CH_3CN, reflux, 21%; (b) $BrCH_2CO_2CH_3$, NaH, THF, reflux, 45%.

two biphenyl units. Each calix[4]arene moiety adopts a cone conformation, and the four phenyl rings intersect the plane of the four methylene groups at angles of 65°, 68°, 59°, and 71°. The two biphenyl moieties are not parallel, and the molecule has a twisted barrel-like structure. The distance between the oxygen atoms (O1–O3*) adjacent to the benzyl methylenes is 11.46 Å.

The complexation ability of these hosts toward alkali metal ions was evaluated by ^{1}H NMR titration experiments (toluene-d_8/CD_3CN, 6:5). No detectable spectral change was observed when Li^+ (added as $LiClO_4$), Na^+ and K^+ (added as MPF_6) were added to **1a**. The weak affinity of **1a** to the alkali metal ions is due to lack of an ester group, which interacts with alkali metal ions.[10]

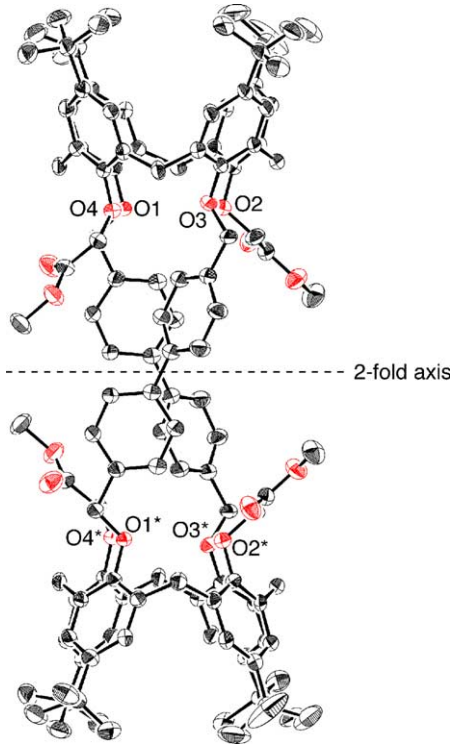

Figure 2. ORTEP drawing of **1b**. Hydrogen atoms, solvent molecules, and disordered atoms were omitted for clarity. Thermal ellipsoids were drawn at 50% probability level.

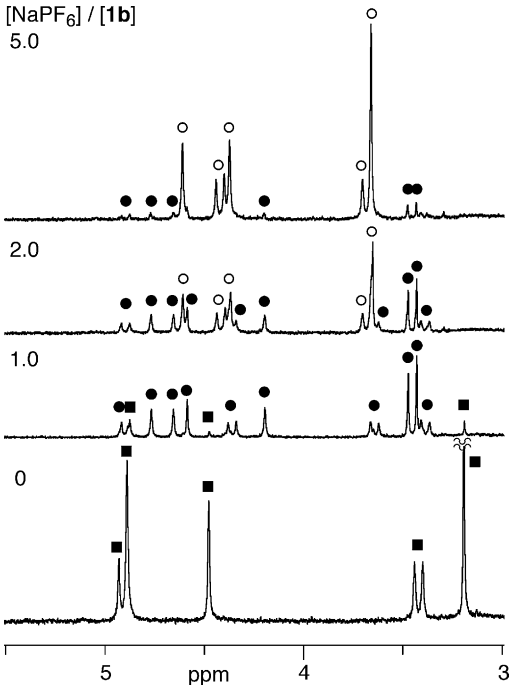

Figure 3. ^{1}H NMR spectral changes of **1b** by the addition of $NaPF_6$ (300 MHz, toluene-d_8/CD_3CN (6:5), [**1b**] = 5.0×10^{-4}M). The signals of **1b**, **1b**·Na, **1b**·2Na were indicated by filled squares, filled circles, and open circles, respectively.

In contrast, $NaPF_6$ caused drastic changes in the ^{1}H NMR spectra of **1b** (Fig. 3). As Na^+ increases, signal intensity of free **1b** decreases, but two sets of the signals for **1b**·Na and **1b**·2Na increase. The patterns of the signals suggest that **1b**·2Na possesses two equivalent calix[4]arene moieties containing an Na^+ ion. On the other hand, in **1b**·Na, there are two kinds of calix[4]arene units that is a free one and an Na^+ complex, because two sets of signals assigned to the free and complex units are obtained. These facts show that the exchange of the free Na^+ and the captured Na^+ ions in **1b**·Na is slow on the NMR timescale. ESIMS spectroscopy also supports the existence of these complexes (*m*/*z* 1964.4 ([**1b** + Na]$^+$), 993.9 ([**1b** + 2Na]$^{2+}$)).

Recognition of two Li^+ ions with host **1b** is also observed by the ^{1}H NMR titration. However, **1b** can bind only one K^+ ion because the ^{1}H NMR signals of **1b**·2K were not observed even in the presence of 5 equiv of K^+.

The association constants K_1 and K_2 were estimated by nonlinear least-squares regression by calculating the concentrations of **1b** and the metal complexes from the ^{1}H NMR measurement (Table 1). The ratios of $0.25K_1/K_2$ for Li^+ and Na^+ are 6.8 and >18, respectively. The correction factor of 0.25 is the statistical preference of the first binding over the second.[11] If the $0.25K_1/K_2$ value is larger than 1, the binding to the first ion inhibits

Table 1. Association constants[a] of host **1b** and alkali metal ions obtained from the results of ^{1}H NMR titration experiments

Guest	K_1/M^{-1}	K_2/M^{-1}	$0.25K_1/K_2$
Li^{+b}	7300 ± 280	270 ± 9	6.8
Na^{+c}	$>1\times10^5$	5600 ± 270	>18
K^{+c}	700 ± 13	—	—

[a] In toluene-d_8/CD_3CN (6:5), [**1b**] = 5.0×10^{-4}M.
[b] Added as ClO_4^- salt.
[c] Added as PF_6^- salt.

binding to the second ion. In the case of K^+, an extremely large value of $0.25K_1/K_2$ was estimated although the accurate value could not be determined due to the very low population of **1b**·2K, which is not detected in the NMR spectra. Combination of electrostatic repulsion between the two bound metal ions and conformational change of **1b** induced by the recognition of the first ion may contribute the decrease of the binding affinity to the second guest. As the ionic radius of the guest increases, the value of $0.25K_1/K_2$ increases. Probably a larger ion changes the structure of the first binding site more drastically to cause conformational change unfavorable for the guest binding of the second site.

In conclusion, we have synthesized a novel homotropic allosteric host **1b** by connecting two calix[4]arene units with two rigid biphenyl bridges. The host shows negative allostery for the recognition of alkali metal ions, and the binding to the first guest reduces the affinity to the second guest more effectively as the ionic radius of the guest increases. Our current efforts are focused on construction of host molecules which can capture and release organic molecules. Further attempts to extend this system to molecular devices such as a molecular transport system responding to external stimuli are also under investigation.

Acknowledgements

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