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Synthesis and recognition behavior of multi-point receptors with binding sites for different metal ions

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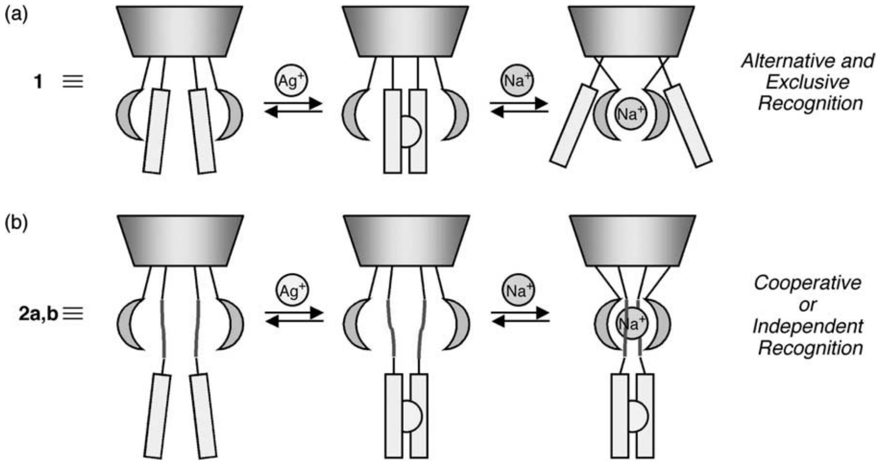
Abstract—Novel multi-point receptors which have a calix[4]arene skeleton, two esters, and two bipyridine moieties with a polyether chain were designed and synthesized. The host with shorter polyethers recognizes Na^+ and Ag^+ cooperatively, and the host with longer polyethers captures them independently.

A variety of functional molecules responsive to external stimuli play important roles in sense organs, nerves, enzymes, and transport of materials.[1] Hence, artificial molecules possessing such responsive properties have recently been investigated intensively.[2] These systems are interesting as biomimetic models, sensors, molecular devices, and molecular logics. To construct more sophisticated molecular devices, independent and cooperative responses to different kinds of stimuli are important and useful, although such multi-response is usually difficult to achieve because of a long-step synthetic route necessary for the preparation of these functional molecules.

Recently, we have reported multi-responsive host **1** based on a calix[4]arene with two ester and two bipyridine moieties.[3] This host recognizes Na^+ with the ester moieties, and Ag^+ with the bipyridine units to perform complete inhibition on Ag^+ binding with Na^+ (Scheme 1a). It is interesting and important to tune cooperative



Scheme 1. Schematic drawing of Ag^+ and Na^+ recognition by multi-responding hosts **2**. (a) Alternative and exclusive recognition, (b) Cooperative or independent recognition.

Keywords: Calixarene; Ag complex; Cooperative complexation; Ternary complex; Ion recognition.

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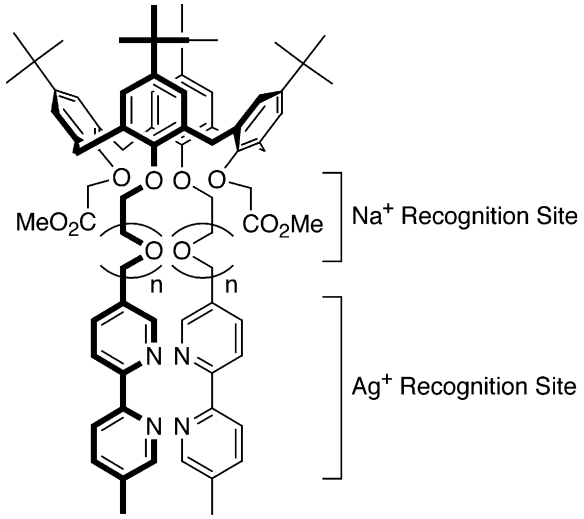


1 (n = 0)
2a (n = 1)
2b (n = 2)

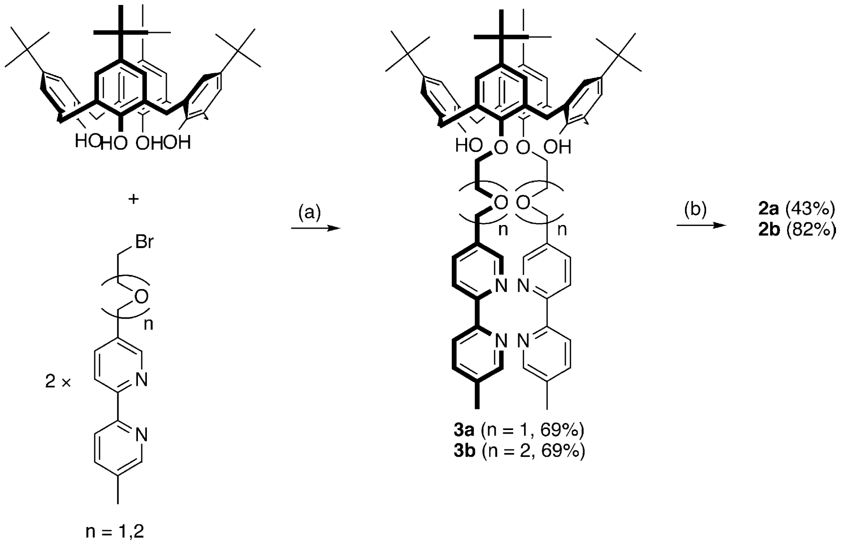
Chart 1.

regulation of ion recognition by using this type of functional calixarenes with different sites. In addition, simultaneous recognition of different metal ions is also a fascinating objective in terms of multi-point recognition and multi-metal-assisted reaction systems. We wish to report here the synthesis and unique binding behavior of novel multi-responding hosts **2** consisting of a calix[4]arene framework[4] with two ester and two bipyridine moieties as Na^+ and Ag^+ recognition sites, respectively (Chart 1). The bipyridine moieties are connected to the calixarene skeleton by a polyether chain, which works not only as a spacer to communicate with the hard-and-soft-ions-binding sites via conformational change upon the guest binding but also as a hard ion binding site.[5] Consequently, cooperativity on the ion recognition would be changed dramatically just by changing the length of the spacers in **2** (Scheme 1b).

Calix[4]arene derivatives **2** were synthesized by the method shown in Scheme 2. Reaction of 5-((2-bromoethoxy)methyl)-5′-methyl-2,2′-bipyridine (4.0 equiv) with *p*-*tert*-butylcalix[4]arene using K_2CO_3 as a base afforded precursor **3a**. Treatment of **3a** with methyl bromoacetate in THF containing NaH gave host **2a**. Compound **2b**, which has two longer polyether chains, was also obtained by similar procedures.

The structure of **2a**,**b** was characterized by ^1H, ^{13}C NMR, and ESIMS spectra.[6,7] In the ^1H NMR spectra of **2a**,**b**, a pair of doublets for the methylene groups of the calix[4]arene skeleton, four singlets for the Me-bpy, OCH_2-bpy, MeO, and OCH_2CO_2 protons, two singlets for the aromatic protons of the calix[4]arene and two singlets for the *tert*-butyl groups were observed. Differences in the chemical shifts ($\Delta\delta$) in the calix[4]arene methylenes of **2a**,**b** are 1.45 and 1.49 ppm, respectively. Each ^{13}C NMR spectrum of **2a**,**b** shows one signal at δ_C 31.4 ppm, which is assigned to the bridging methylene groups.[4,8] These results indicate a fixed cone conformation of the calix[4]arene skeleton in **2a**,**b**.

Guest recognition abilities of **2a** and **2b** were evaluated by ^1H NMR titration experiments ($CDCl_3/CD_3CN$, 9:1). First, we estimated the affinity of **2a** to Na^+ (added as sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, NaTFPB hereafter). As concentration of Na^+ increases, signal intensity of the free **2a** decreases and that of **2a**·Na^+ increases. This fact indicates that the rates for the Na^+ uptake and release are slow on the NMR timescale. Significant difference in the ^1H NMR chemical shifts between **2a** and **2a**·Na^+ was observed for the signals of ester, ethyleneoxy, and calixarene moieties, whereas little change was found in those for the bipyridine moiety. This indicates that the lower-rim ester and ether moieties mainly interact with Na^+. Upon the addition of 1 equiv of NaTFPB, free **2a** completely disappeared and **2a**·Na^+ was formed quantitatively. These results show that **2a** captures an Na^+ ion quantitatively and that the association constant K_a is too large



Scheme 2. Synthesis of hosts **2a**,**b**. (a) K_2CO_3, CH_3CN, reflux, (b) $BrCH_2CO_2Me$, NaH, THF, reflux.

to be determined. The complexation was also ascertained by ESIMS spectroscopy (*m*/*z* 1268.7 ([**2a**·Na]$^+$)).

High affinity of **2a** to the Ag$^+$ ion and the quantitative complexation was supported by ^{1}H NMR spectroscopy. Addition of $AgNO_3$ to a solution of **2a** resulted in changes in the ^{1}H NMR chemical shifts of **2a**, although no new signals appeared. This fact indicates that the equilibrium between the free **2a** and **2a**·Ag$^+$ complex is fast on the NMR time-scale. The chemical shifts of bipyridine signals changed significantly until 1 equiv Ag$^+$ ion was added. And then a different but slight spectral change was observed in the presence of excess Ag$^+$. These results suggest that **2a** captures an Ag$^+$ ion quantitatively with the bipyridine units when 1 equiv of Ag$^+$ was added. UV–vis titration and ESIMS spectroscopy (*m*/*z* 1353.7 ([**2a**·Ag]$^+$)) also confirmed this discrete complexation without formation of intermolecular oligomeric complexes.

Noteworthy is that the addition of Na$^+$ to **2a**·Ag$^+$ causes formation of the corresponding ternary complex **2a**·Ag$^+$·Na$^+$. As concentration of Na$^+$ increases, intensity of the signals for **2a**·Ag$^+$ decreases and that for **2a**·Ag$^+$·Na$^+$ increases. However, quantitative formation of **2a**·Ag$^+$·Na$^+$ was not achieved in the presence of 1 equiv of Na$^+$, and the molar ratio of **2a**·Ag$^+$:**2a**·Ag$^+$·Na$^+$ is 0.53:0.47 (Fig. 1). Complete formation of **2a**·Ag$^+$·Na$^+$ was achieved by the addition of 3 equiv of Na$^+$. These results clearly indicate that using **2a** enables heterotropic and negative cooperativity for recognition of Ag$^+$ and Na$^+$.

Host **2b**, which has two longer polyether chains, also recognizes Na$^+$ and Ag$^+$. ESIMS spectroscopy clearly indicates the formation of the ternary complex (*m*/*z* 688.5 [**2a**·Ag·Na]$^{2+}$; *m*/*z* 732.1 [**2b**·Ag·Na]$^{2+}$). Quantitative recognition of Na$^+$ and Ag$^+$ with **2b** was supported by spectroscopic methods (^{1}H NMR and UV–vis) employed as in the case of **2a**. The discrete 1:1 complex was produced without formation of oligomeric products by mixing **2b** and Ag$^+$ in a 1:1 ratio. The quantitative formation of an intramolecular complex is probably caused by the proximate location of the bipyridine units. In contrast to **2a**, the spectroscopic titrations showed that addition of 1 equiv of Na$^+$ to **2b**·Ag$^+$ resulted in quantitative formation of **2b**·Ag$^+$·Na$^+$ (Fig. 2). Consequently, **2b** works as a ditopic and noncooperative receptor for different metal ions. This simultaneous recognition of Ag$^+$ and Na$^+$ is probably due to less electrostatic repulsion between Na$^+$ and Ag$^+$ and to smaller conformational change upon the guest binding than that of **2a** because of the longer and more flexible spacers between the two guest recognition sites of **2b**.[9] Moreover, the larger Na$^+$-binding site of **2b** and more oxygen atoms in the polyether chains than in **2a** may enhance the Na$^+$ affinity.

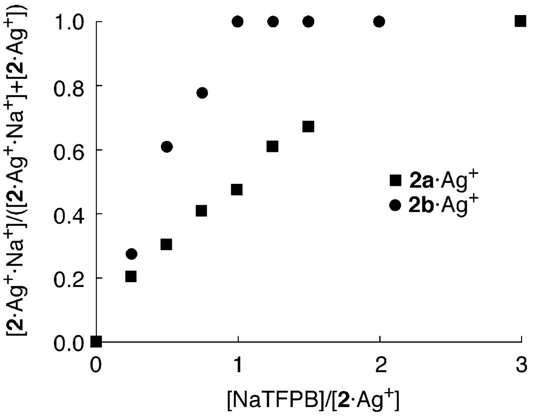


Figure 2. Formation of ternary complex **2**·Ag$^+$·Na$^+$.

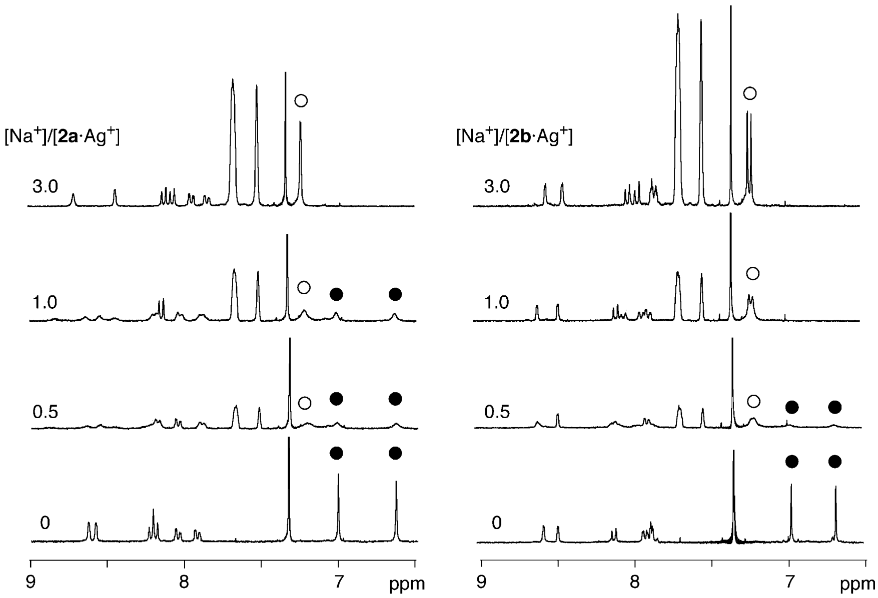


Figure 1. ^{1}H NMR spectral changes of **2**·Ag$^+$ by the addition of NaTFPB (300 MHz, $CDCl_3/CD_3CN$ (9:1), [**2**] = [$AgNO_3$] = 2.0×10^{-3} M). Signals of **2**·Ag$^+$ and **2**·Ag$^+$·Na$^+$ are denoted as filled and open circles.

In conclusion, we have designed and synthesized novel multi-recognition hosts **2a**,**b**, which bear a calix[4]arene skeleton, two esters and two bipyridine moieties with a polyether chain. Host **2a** with the shorter spacers recognizes Na^+ and Ag^+ cooperatively, and host **2b** with the longer spacers captures them independently. Our current efforts are focused on the construction of a novel multi-responsive host, which recognizes organic molecules, and further attempts to extend this strategy to construct nano-molecular systems are now under investigation.

Acknowledgements

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6. Compound **2a**: pale yellow glassy solid, mp 84–87 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (s, 18H), 1.13 (s, 18H), 2.37 (s, 6H), 3.16 (d, $J = 12.7$ Hz, 4H), 3.70 (s, 6H), 4.10 (t, $J = 5.6$ Hz, 4H), 4.28 (t, $J = 5.6$ Hz, 4H), 4.61 (d, $J = 12.7$ Hz, 4H), 4.65 (s, 4H), 4.67 (s, 4H), 6.73 (s, 4H), 6.85 (s, 4H), 7.60 (dd, $J = 8.2$, 1.6 Hz, 2H), 7.80 (dd, $J = 8.1$, 1.9 Hz, 2H), 8.26 (d, $J = 8.2$ Hz, 2H), 8.32 (d, $J = 8.1$ Hz, 2H), 8.48 (d, $J = 1.6$ Hz, 2H), 8.63 (d, $J = 1.9$ Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 18.34 (q), 31.31 (q), 31.36 (d), 31.48 (q), 33.78 (s), 33.88 (s), 51.51 (q), 70.31 (t × 2), 71.33 (t), 72.82 (t), 120.44 (d), 120.60 (d), 125.17 (d), 125.28 (d), 133.08 (s), 133.33 (s), 133.92 (s × 2), 136.25 (d), 137.46 (d), 144.87 (s), 145.08 (s), 148.35 (d), 149.57 (d), 152.56 (s), 153.48 (s), 153.70 (s), 155.48 (s), 170.58 (s). ESIMS observed *m/z* 1267.7 ($[M + Na]^+$), calcd for $C_{78}H_{92}N_4O_{10}Na$ *m/z* 1267.7. Anal. Calcd for **2a**·H_2O: C, 74.14; H, 7.50; N, 4.43. Found: C, 73.90; H, 7.28; N, 4.30.
7. Compound **2b**: pale yellow glassy solid, mp 66–68 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (s, 18H), 1.10 (s, 18H), 2.38 (s, 6H), 3.16 (d, $J = 12.8$ Hz, 4H), 3.67 (t, $J = 4.7$ Hz, 4H), 3.727 (t, $J = 4.7$ Hz, 4H), 3.731 (s, 6H), 3.97 (t, $J = 5.6$ Hz, 4H), 4.15 (t, $J = 5.6$ Hz, 4H), 4.61 (s, 4H), 4.65 (d, $J = 12.8$ Hz, 4H), 4.77 (s, 4H), 6.72 (s, 4H), 6.82 (s, 4H), 7.61 (dd, $J = 8.1$, 1.5 Hz, 2H), 7.77 (dd, $J = 8.1$, 1.9 Hz, 2H), 8.26 (d, $J = 8.1$ Hz, 2H), 8.31 (d, $J = 8.1$ Hz, 2H), 8.49 (d, $J = 1.5$ Hz, 2H), 8.60 (d, $J = 1.9$ Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) 18.31 (q), 31.33 (q), 31.35 (q + d), 33.73 (s), 33.79 (s), 51.37 (q), 69.82 (t), 70.29 (t), 70.51 (t), 70.60 (t), 71.09 (t), 73.02 (t), 120.43 (d), 120.53 (d), 124.92 (d), 125.37 (d), 133.30 (s), 133.37 (s), 133.44 (s), 133.61 (s), 136.33 (d), 137.37 (d), 144.66 (s), 145.02 (s), 148.47 (d), 149.58 (d), 152.88 (s), 153.31 (s), 153.43 (s), 155.67 (s), 170.89 (s). ESIMS observed *m/z* 1355.8 ($[M + Na]^+$), calcd for $C_{82}H_{100}N_4O_{12}Na$ *m/z* 1355.7. Anal. Calcd for **2b**·3.5H_2O: C, 70.51; H, 7.72; N, 4.01. Found: C, 70.46; H, 7.34; N, 3.81.
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