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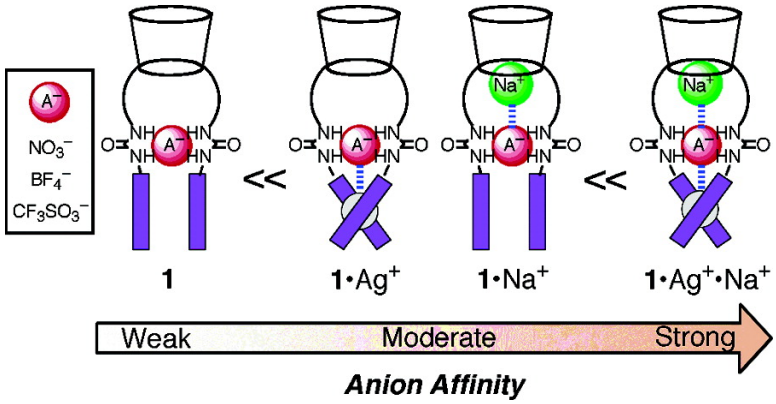

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Stepwise and Dramatic Enhancement of Anion Recognition with a Triple-Site Receptor Based on the Calix[4]arene Framework Using Two Different Cationic Effectors

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Abstract: Synthesis and binding behavior of a novel multi-responsive host **1**, in which two esters, two polyether moieties, two urea sites, and two bipyridine units as ion binding sites are arranged on the calix[4]arene skeleton, is reported. **1** recognizes Na^+ and Ag^+ simultaneously and quantitatively and captures an anionic guest. The ability of **1** to recognize anions, including $CF_3SO_3^-$ and BF_4^-, remarkably increases in a stepwise manner using Na^+ and Ag^+ as effectors. The enhancement of the K_a eventually reaches factors of 1500 and 2000 for NO_3^- and $CF_3SO_3^-$, respectively, in the presence of both Na^+ and Ag^+, compared to the free **1**. The regulation of binding of multiple ligands may be applicable to multistep cascade systems for the amplification of molecular events, and further studies in this field could provide insight applicable to more advanced molecular devices.

Introduction

The multistep regulation of molecular events by different effectors is an effective and significant means of fine-tuning allosteric and feedback regulation as well as cascade amplification in biological systems. Such regulation plays critical roles in many biological events.[1] The selection of effectors can provide a wide range of conditions optimal for sensing various ions and molecules by artificial receptors. Additionally, appropriate artificial receptors may serve as biomimetic models, molecular devices, and molecular logics.[2] Thus, while challenging, the construction of sophisticated molecular systems responsive to different external stimuli is potentially extremely useful. However, the design and synthesis of these molecules is difficult because different binding sites[3−5] must be introduced into the framework of host molecules and laborious synthetic procedures would be necessary for their production. Consequently, most responsive molecules prepared thus far utilize only one type of effector to modulate a single response.[2] Here, we report the synthesis and binding behavior of a novel multi-responsive host **1**, in which three different types of ion binding sites are arranged on the calix[4]arene skeleton. This molecule is capable of the effective and efficient multistep regulation of anion recognition by utilizing two different cationic guests.[6]

On the lower rim of the conical calix[4]arene framework, host **1** possesses two ester substituents and two polyether units

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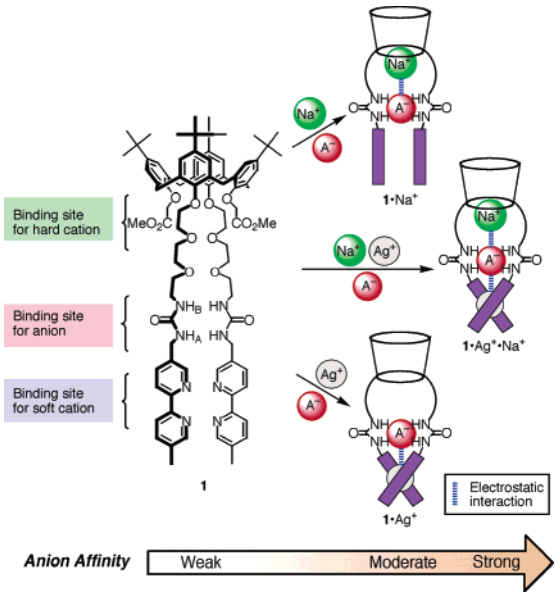


Figure 1. Anion recognition by host **1** is regulated by two different cationic effectors.

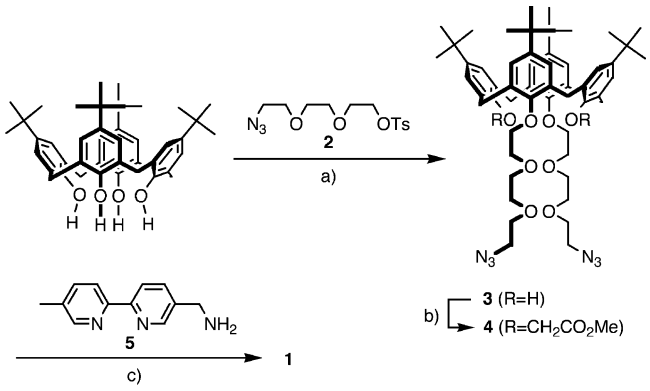
containing a urea group linked to a bipyridine moiety. The mechanism of the stepwise regulation of anion recognition is illustrated in Figure 1. The anion affinity of **1**, controlled by hydrogen bonding to the urea moieties, should be enhanced in a stepwise fashion due to the electrostatic interactions of the soft and hard cationic guests, which are bound by the bipyridine and ester units, respectively. Upon complexation of the bipyridine moieties with a cationic guest, a conformational change is expected to occur in **1** that brings the two urea moieties in close proximity, and this change is expected to favor anion binding.

Results and Discussion

The reaction of *p-tert*-butylcalix[4]arene with **2**[7] and K_2CO_3 yielded azide **3**. Treatment of **3** with methyl bromoacetate and NaH in THF gave **4**. The urea moieties were introduced by the reaction of **4** with amine **5**[8] in the presence of PPh_3 and CO_2 to give **1** with 78% efficiency (Scheme 1). Host **1** was characterized by ^1H and ^{13}C NMR, IR, and ESI mass spectra and elemental analysis.

To estimate the ability of **1** to recognize hard and soft metal ions, we carried out ^1H NMR, UV−vis titration experiments, and ESI-MS analysis. The ^1H NMR titration in $CDCl_3/CD_3CN$ (9:1) showed quantitative 1:1 complexation of **1** with Na^+ or Ag^+.[9−11] As the concentrations of Na^+ increased, the signals of free **1** decreased and new signals of **1**•Na^+ appeared. For Ag^+, however, signals with averaged chemical shifts between free **1** and **1**•Ag^+ were observed. Hence, the capture and release

Scheme 1. Synthesis of Host **1**[a]



[a] Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 79%; (b) $BrCH_2CO_2Me$, NaH, THF, reflux, 72%; (c) PPh_3, CO_2, toluene/DMF, rt, 78%.

of Na^+ and Ag^+ is slow and fast on the NMR time scale, respectively. Upon the addition of Na^+, the chemical shift of the protons in the ester groups[12] and polyether chains changed significantly, but those of the bipyridine units did not. In contrast, only the bipyridine protons were substantially changed by the presence of Ag^+. Noteworthy is that the NH protons of the urea moieties shifted upfield ($\Delta\delta = \delta_{\mathbf{1}\bullet Na^+} - \delta_{\mathbf{1}}$: H_A, −0.39 ppm; H_B, −0.34 ppm) and downfield ($\Delta\delta' = \delta_{\mathbf{1}\bullet Ag^+} - \delta_{\mathbf{1}}$: H_A, 0.79 ppm; H_B, 0.36 ppm) upon the addition of 1 equiv of Na^+ and Ag^+, respectively (Figure 2A, a−c). This opposite effect on the chemical shifts can be ascribed to weakening and strengthening intramolecular hydrogen bonding between the urea moieties. Inspection of the CPK models suggests that spatial orientation of the urea groups is suitable for interaction between the urea moieties of the free **1**. Similar hydrogen bonding is often observed when urea groups locate in close proximity.[4a,b,13] Intramolecular assembly of the two ester groups upon the complexation of **1** with Na^+ should be unfavorable due to the hydrogen bonding between the urea moieties. On the other hand, Ag^+ binding with the bipyridine units forces the urea groups to be close to each other and increases the strength of the hydrogen bonding.

The ^1H NMR titration isotherms for Na^+ and Ag^+ reach plateaus upon the addition of 1 equiv of the metal ions. In the UV−vis absorption spectrum of **1**, bathochromic shift caused by Ag^+ clearly indicates the interaction of the bipyridines with Ag^+ (**1**, λ_{max} = 291 nm; **1**•Ag^+, λ_{max} = 301 nm; $CHCl_3/CH_3CN$ (9:1)). The UV−vis titration using this absorption supports the 1:1 stoichiometry for the quantitative complexation of **1** with Ag^+. However, **1**•Na^+ exhibited the same λ_{max} at 291 nm as the free **1**. These results support the model wherein **1** quantitatively captures Na^+ with the ester and polyether groups

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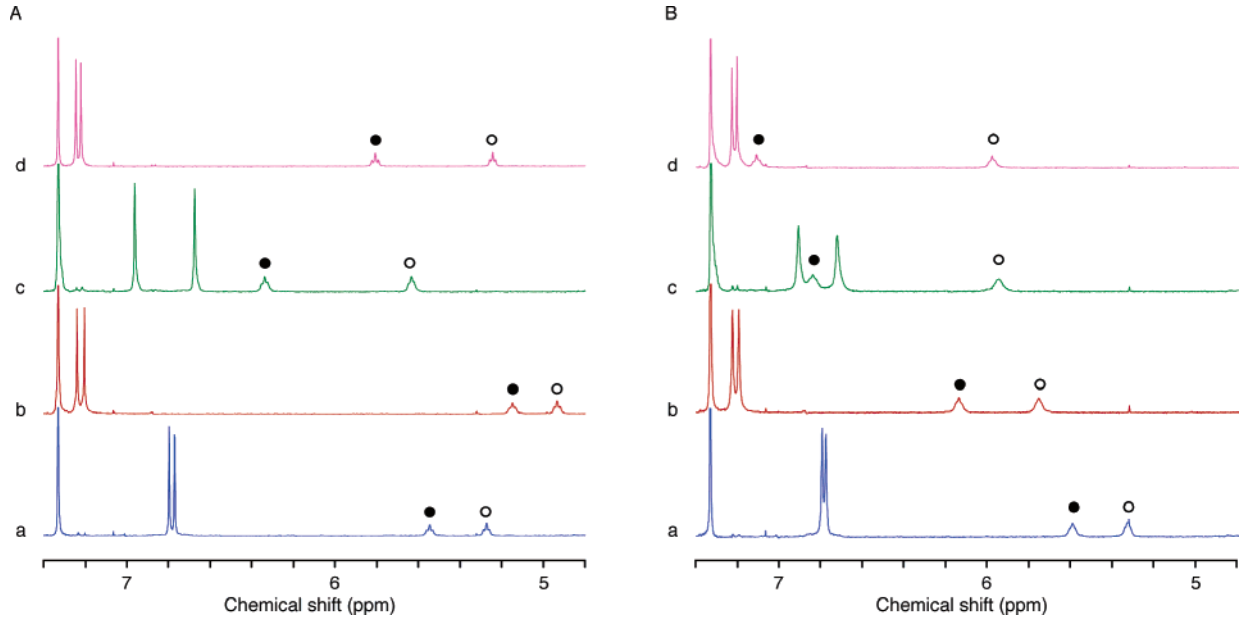

Figure 2. The 400 MHz ^{1}H NMR spectra of (a) **1**, (b) **1**•Na^+, (c) **1**•Ag^+, and (d) **1**•Ag^+•Na^+ in $CDCl_3/CD_3CN$ (9:1), (A) without anionic guest and (B) with 1.25 equiv of *n*-$Bu_4N^+NO_3^-$, [**1**] = [AgTFPB] = [NaTFPB] = 2.0×10^{-3} M. The signals of urea protons H_A and H_B are denoted by filled and open circles, respectively.

and Ag^+ with the bipyridine moieties.[14] The ESI mass spectra of **1** in the presence of Na^+ and Ag^+ also confirmed the 1:1 stoichiometry.

^{1}H NMR spectral change upon the addition of Na^+ to **1**•Ag^+ indicates the quantitative formation of the ternary complex **1**•Ag^+•Na^+ (Figure 2Ad), and this spectrum did not change in the presence of excess Na^+. The presence of this ternary complex was also confirmed by ESI-MS (*m*/*z* 817.4, [**1**•Ag•Na]$^{2+}$). Furthermore, addition of 1 equiv of Na^+ and Ag^+ to **1**•Ag^+ and **1**•Na^+, respectively, gave the same ^{1}H NMR and UV−vis spectra, which could not be changed even in the presence of excess amount of additional cations, Ag^+ and Na^+. These results clearly indicate that **1**•Ag^+•Na^+ is a very stable complex. Thus, **1** captures Na^+ and Ag^+ simultaneously and quantitatively with the appropriate binding sites.[15]

In contrast to these cations, the anion affinity of **1** is considerably weaker. ^{1}H NMR spectroscopy ($CDCl_3/CD_3CN$ (9:1)) determined the association constants logK_a (K_a in M^{-1}) of NO_3^- and $CF_3SO_3^-$ to be 1.88 and 1.4, respectively (Table 1), by analyzing the small downfield shifts of the urea protons H_A (Figures 2 and 3a). These changes indicate anion binding through relatively weak hydrogen bonding with the urea groups (Figure 2). As no spectral change was observed for **1** and BF_4^-, there seems to be no affinity worth mentioning. The very low affinity for the anions is partly due to the structural flexibility of the urea moieties. In addition, the intramolecular hydrogen bonding between the carbonyl and NH groups in the urea (vide supra) well rationalizes the low anion binding strength. The anion affinities, however, were tremendously enhanced in the presence of Na^+ and/or Ag^+. Significant downfield shift of the urea protons, H_A and H_B (Figure 2b,c), demonstrates the

Table 1. Association Constants logK_a (K_a in M^{-1}) for the Hosts and Anionic Guests[a]

host	NO_3^-	$CF_3SO_3^-$	BF_4^-
1	1.88 ± 0.03	1.4 ± 0.2	*b*
1•Ag^+	3.31 ± 0.07 (30)[c]	3.40 ± 0.07 (100)[c]	*b*
1•Na^+	3.82 ± 0.15 (90)[c]	3.32 ± 0.11 (80)[c]	3.46 ± 0.11
1•Ag^+•Na^+	5.07 ± 0.17 (1500)[c]	4.7 ± 0.2 (2000)[c]	4.28 ± 0.11

[a] Determined by ^{1}H NMR (400 MHz, $CDCl_3/CD_3CN$ (9:1), [host] = 2.0×10^{-3} M). [b] Not determined due to small chemical shift change. [c] Values in parentheses are relative anion affinities (K_a for **1**•Ag^+, **1**•Na^+, or **1**•Ag^+•Na^+ over K_a for **1**).

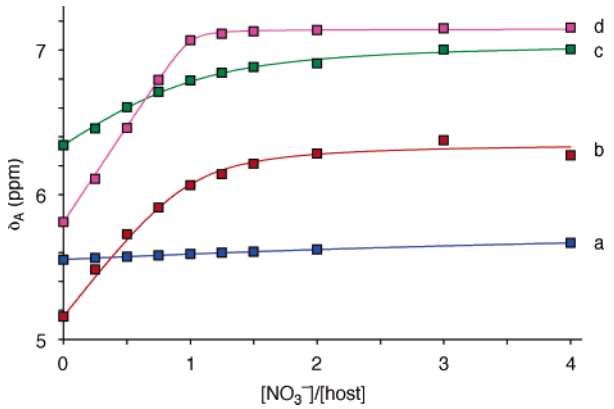

Figure 3. Chemical shift changes of H_A by the addition of *n*-$Bu_4N^+NO_3^-$: (a) **1**, (b) **1**•Na^+, (c) **1**•Ag^+, and (d) **1**•Ag^+•Na^+.

effective hydrogen bonding with the anions, although the other protons did not change significantly. Both the urea protons shifted downfield considerably when NO_3^- was added to **1**•Na^+. In the case of **1**•Ag^+, however, the NO_3^- anion caused larger and smaller downfield shifts of the H_A and H_B protons, respectively. Hence, the NO_3^- anion probably locates closer to H_A than to H_B due to stronger hydrogen bonding. Analysis of the downfield shift provided the K_a (**1**•Na^+, logK_a = 3.82;

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1•Ag^+, logK_a = 3.31), which is enhanced dramatically by either Na^+ or Ag^+ (Figure 3b,c and Table 1). **1**•Na^+ exhibited a higher affinity for NO_3^- and BF_4^- than did **1**•Ag^+. The different binding behavior is rationalized by the difference in strength of the hydrogen bonds between the urea units of **1**, **1**•Na^+, **1**•Ag^+, and **1**•Ag^+•Na^+. As the intramolecular hydrogen bonds of the urea moieties in the hosts are weaker, the affinity of the urea moieties for anions is higher.

When both Na^+ and Ag^+ are added, the effect on anion recognition is even more profound. As assessed by regression analysis, logK_a for NO_3^- was 5.07 (Figure 3d and Table 1). The K_a values of **1**•Ag^+, **1**•Na^+, and **1**•Ag^+•Na^+ toward NO_3^- are 30, 90, and 1500 times larger than those of **1**, respectively. The formation of the quaternary complex **1**•Ag^+•Na^+•NO_3^- was confirmed by ESI mass spectrometry (*m*/*z* 1969.8, [**1**•Ag•Na•NO_3]$^+$). Interestingly, the ternary complex **1**•Ag^+•Na^+ strongly captures $CF_3SO_3^-$ and BF_4^-, which, in general, are difficult substrates for artificial anion receptors.[16] These form 1:1 host−guest complexes with a large K_a. For $CF_3SO_3^-$ recognition, the affinity increases by a factor of 2000, compared to that of free **1**. This large stepwise enhancement can be reasonably ascribed to the electrostatic interactions between the anions and cations and the fixation of the two anion binding sites, thus reducing the conformational freedom of the urea units. Molecular modeling for **1**•Ag^+•Na^+•BF_4^- suggests that distances for Na^+−BF_4^- and Ag^+−BF_4^- are 6−7 Å, which are expected to produce a favorable electrostatic interaction for simultaneous cation−anion recognition.[17] To our knowledge, this is the first description of a multi-responsive anion receptor that is regulated stepwise by different cationic effectors.

Conclusion

In conclusion, **1** recognizes Na^+ and Ag^+ simultaneously and independently and captures an anionic guest. The ability of **1** to recognize anions, including $CF_3SO_3^-$ and BF_4^-, remarkably increases in a stepwise manner using Na^+ and Ag^+ as effectors. The regulation of binding of multiple ligands may be applicable to multistep cascade systems for the amplification of molecular events, and further studies in this field could provide insight applicable to more advanced molecular devices. We are currently investigating the ability of molecules, such as **1**, to facilitate the stepwise regulation of molecular recognition of ion pairs, charged organic molecules, and zwitter ions, such as amino acids.

Experimental Section

General Methods. All chemicals were reagent grade and used without further purification. Tetrahydrofuran (THF) and toluene were distilled over sodium benzophenone ketyl under argon atmosphere. *N*,*N*-Dimethylformamide (DMF) was distilled over calcium hydride and stored over molecular sieves. Column chromatography was performed with Kanto Chemical silica gel 60N (spherical, neutral). Gel permeation chromatography (GPC) was performed by LC-908W with JAI gel 1H + 2H columns (Japan Analytical Industry) with chloroform as eluent. Melting points were determined on a Yanaco melting point apparatus and not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE600 spectrometer (600 and 150 MHz, respectively) or a Bruker ARX400 spectrometer (400 and 100 MHz, respectively) using tetramethylsilane as an internal standard. ESI mass spectra were recorded on an Applied Biosystems Qstar/Pulsar *i* spectrometer. UV−vis spectra were recorded on a JASCO Ubest V-560 or a V-570 spectrometer. Elemental analyses were performed at Chemical Analysis Center, University of Tsukuba.

Diazide 3. Anhydrous potassium carbonate (1.106 g, 8.00 mmol) was added to a solution of *p-tert*-butylcalix[4]arene (1.298 g, 2.00 mmol) in acetonitrile (26 mL), and the mixture was refluxed for 30 min under N_2. After the addition of 2-(2-(2-azidoethoxy)ethoxy)-ethyl tosylate (**2**)[7] (1.582 g, 4.00 mmol) in acetonitrile (10 mL), the mixture was refluxed for 24 h under N_2. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Water (40 mL) was added to the residue and extracted with chloroform (30 mL × 3). The organic layers were collected and dried over anhydrous magnesium sulfate. After removal of the solvent, the mixture was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 15:1 then 5:1) to give **3** (1.520 g, 1.58 mmol, 79%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 18H), 1.29 (s, 18H), 3.28 (d, J = 13.0 Hz, 4H), 3.29 (t, J = 5.1 Hz, 4H), 3.67 (t, J = 5.1 Hz, 4H), 3.74 (t, J = 4.6 Hz, 4H), 3.84 (t, J = 4.6 Hz, 4H), 3.96 (t, J = 4.7 Hz, 4H), 4.15 (t, J = 4.7 Hz, 4H), 4.36 (d, J = 13.0 Hz, 4H), 6.75 (s, 4H), 7.05 (s, 4H), 7.11 (s, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 31.0 (CH_3), 31.4 (CH_2), 31.7 (CH_3), 33.76, 33.83 (C), 50.6, 70.0 (×2), 70.8, 71.1, 75.3 (CH_2), 125.0, 125.4 (CH), 127.8, 132.5, 141.2, 146.7, 149.8, 150.6 (C); IR (KBr) ν 2113 cm^{-1} (s, N_3); ESI-MS observed *m*/*z* 985.6 ([M + Na]$^+$). Anal. Calcd for $C_{56}H_{78}N_6O_8$: C, 69.83; H, 8.16; N, 8.72. Found: C, 69.63; H, 7.89; N, 8.71.

Diester 4. Sodium hydride (60% in oil, 632 mg, 15.8 mmol) was added to a solution of diazide **3** (1.50 g, 1.56 mmol) in THF (50 mL), and the mixture was refluxed for 60 min under N_2. After the addition of ethyl bromoacetate (7.5 mL, 79 mmol), the solution was refluxed for 24 h under N_2. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Water (30 mL) was added to the residue and extracted with chloroform (25 mL × 3), and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the mixture was purified by column chromatography (SiO_2, hexane/$CHCl_3$ (1:3) then $CHCl_3$) and subsequent recrystallization from methanol to give **4** (1.254 g, 1.132 mmol, 72%) as a colorless solid: mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 18H), 1.12 (s, 18H), 3.15 (d, J = 12.8 Hz, 4H), 3.34 (t, J = 5.2 Hz, 4H), 3.64−3.71 (m, 12H), 3.78 (s, 6H), 3.94 (t, J = 5.4 Hz, 4H), 4.12 (t, J = 5.4 Hz, 4H), 4.66 (d, J = 12.8 Hz), 4.79 (s, 4H), 6.70 (s, 4H), 6.84 (s, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 31.09, 31.13 (CH_3), 31.13 (CH_2), 33.45, 33.54 (C), 50.3 (CH_2), 51.0 (CH_3), 69.7, 70.0, 70.2, 70.4, 70.8, 72.8 (CH_2), 124.6, 125.1 (CH), 133.1, 133.4, 144.3, 144.7, 152.7, 153.0, 170.6 (C); IR (KBr) ν 2105 cm^{-1} (s, N_3); ESI-MS observed *m*/*z* 1129.6 ([M + Na]$^+$). Anal. Calcd for $C_{62}H_{86}N_6O_{12}$: C, 67.25; H, 7.83; N, 7.59. Found: C, 66.97; H, 7.82; N, 7.55.

Host 1. A solution of diester **4** (410.5 mg, 0.371 mmol) and triphenylphosphine (272.2 mg, 1.038 mmol) in dry toluene (5.5 mL) was stirred at room temperature for 24 h under CO_2 atmosphere. To the mixture was added a solution of 5-aminomethyl-5′-methyl-2,2′-bipyridine (**5**)[8] (184.6 mg, 0.927 mmol) in DMF (4.0 mL), and stirring was continued for further 24 h at room temperature. After the removal of the solvent, the residue was purified by GPC ($CHCl_3$) and recrystallized from $CHCl_3$/Et_2O to give **1** (436.8 mg, 0.290 mmol, 78%) as a pale yellow solid: mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 18H), 1.07 (s, 18H), 2.37 (s 6H), 3.10 (d, J = 12.8 Hz, 4H), 3.35 (dt, J = 5.2, 4.4 Hz, 4H), 3.50 (t, J = 4.4 Hz, 4H), 3.57−3.59 (m, 4H), 3.63−3.65 (m, 4H), 3.71 (s, 6H), 3.92 (t, J = 5.8 Hz, 4H), 4.08 (t, J = 5.8 Hz, 4H), 4.37 (d, J = 5.8 Hz, 4H), 4.54 (d, J = 12.8 Hz, 4H), 4.71 (s, 4H), 5.34 (t, J = 5.2 Hz, 2H), 5.55 (t, J = 5.8 Hz, 2H), 6.74 (s, 4H), 6.76 (s, 4H), 7.58 (dd, J = 8.4, 1.7 Hz, 2H), 7.72 (d, J = 8.2, 2.1 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 8.24 (d, J =

(16) (a) Fochi, F.; Jacopozzi, P.; Wegelius, E.; Rissanen, K.; Cozzini, P.; Marastoni, E.; Fisicaro, E.; Manini, P.; Fokkens, R.; Dalcanale, E. *J. Am. Chem. Soc.* **2001**, *123*, 7539−7552. (b) Hayashida, O.; Shivanyuk, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 3423−3426.

(17) Molecular mechanics calculations (MM2 force field) were carried out using ChemOffice Ultra version 5.0 package, CambridgeSoft.

8.2 Hz, 2H), 8.46 (d, J = 1.7 Hz, 2H), 8.55 (d, J = 2.1 Hz, 2H); ^{13}C NMR (150 Hz, $CDCl_3$) δ 18.2 (CH_3), 31.30 (CH_2), 31.30, 31.35 (CH_3), 33.8 (C, ×2), 40.1, 41.4 (CH_2), 51.5 (CH_3), 70.11, 70.15, 70.3, 70.8, 71.1, 72.8 (CH_2), 120.4, 120.5, 125.1, 125.3 (CH), 133.1, 133.4, 133.5, 135.3 (C), 136.1, 137.3 (CH), 144.9, 145.2 (C), 148.3, 149.4 (CH), 152.6, 153.3, 153.4, 154.9, 158.7, 171.2 (C); IR (KBr) ν 1760 cm^{-1} (s, C=O); ESI-MS observed m/z 1527.8 ($[M + Na]^+$). Anal. Calcd for $C_{88}H_{112}N_8O_{14}\cdot 0.4CHCl_3$: C, 68.34; H, 7.29; N, 7.21. Found: C, 68.48; H, 7.13; N, 6.96.

Spectrophotometric Titration. Sample solutions containing **1** (2×10^{-5} M), NaTFPB[10,18] (2×10^{-5} M, if necessary), and varying amounts of AgTFPB[11] ($0-8 \times 10^{-5}$ M) in chloroform/acetonitrile (9:1, 4 mL) were prepared. Spectra were recorded at ambient temperature in a 10 mm path-length quartz cell.

^{1}H NMR Titration (cation binding). Sample solutions containing **1** (2×10^{-3} M), MTFPB (M = Na or Ag; 2×10^{-3} M, if necessary), and varying amounts of MTFPB (M = Na, Ag; $0-8 \times 10^{-3}$ M) in $CDCl_3/CD_3CN$ (9:1, 0.5 mL) were prepared. ^{1}H NMR spectra (400 MHz) were recorded at 300 K.

^{1}H NMR Titration (anion binding). Sample solutions containing **1** (2×10^{-3} M), MTFPB (M = Na and/or Ag; 2×10^{-3} M, if necessary), and varying amounts of n-Bu_4NX (X = NO_3, BF_4, CF_3SO_3; $0-8 \times 10^{-3}$ M) in $CDCl_3/CD_3CN$ (9:1, 0.5 mL) were prepared. ^{1}H NMR spectra (400 MHz) were recorded at 300 K. Chemical shift of H_A was used for nonlinear least squares regression.

(18) The preparation described in ref 10 was modified by substituting 1-bromo-3,5-bis(trifluoromethyl)benzene.

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Supporting Information Available: Complexation studies of **1**, 2D NMR spectra (**1**, **1**•Ag^+, and **1**•Na^+), and X-ray crystallographic analysis of **4** in pdf and cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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