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An Extremely Stable Host–Guest Complex That Functions as a Fluorescence Probe for Calcium Ions

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In memory of Tong-Ing Ho

Abstract: Herein, we report a crown ether based molecular cage that forms extremely stable supramolecular complexes with dimethyldiazapyrenium (DMDAP) ions in CD_3CN through the collaboration of multiple weak C–H···O hydrogen bonds. The very strong binding affinity in this host–guest system allows the molecular cage to bleach the fluorescence signal of DMDAP substantially in equimolar solutions at concentrations as low as 1×10^{-5} M. Remarkably, a 1×10^{-5} M equimolar solution of the molecular cage and DMDAP is highly selective toward Ca^{2+} ions—relative to other biologically important Li^+, Na^+, K^+, and Mg^{2+} ions—and causes a substantial increase in the fluorescence intensity of the solution. As a result, this molecular cage/DMDAP complex behaves as a supramolecular fluorescence probe for the detection of Ca^{2+} ions in solution.

Keywords: calcium · fluorescence · host–guest systems · molecular cages · sensors · supramolecular chemistry

Introduction

Artificial optical sensors that respond selectively to biologically important metal ions (e.g., Li^+, Na^+, K^+, Mg^{2+}, and Ca^{2+}) have attracted much attention for their potential use in chemical and biological applications.[1] Because of the importance of ionic calcium in physiological processes,[2] chemosensors that display specificity toward Ca^{2+} ions are in particular demand.[3] Currently, most fluorescence detectors are prepared by covalently linking molecular receptors to fluorophores; signal processing is achieved through variation of the molecule's electronic nature[4] or of the chromophore's properties[3f,5] after association with the metal ion. Although indicator-displaceable ensembles[6] and cyclodextrin-based supramolecular host–guest systems[7] have been applied in many elegant supramolecular sensing complexes, 1:1 host–guest mixtures have yet to be applied as fluorescence probes in submillimolar concentrations for the detection of trace amounts of Ca^{2+} ions. Part of the difficulty in developing supramolecular host–guest complexes that operate as optical sensors at low concentrations is that a very strong binding affinity must exist between the host and guest species to avoid a strong background signal from the fluorescent, free species.[8] Herein, we report a crown ether based molecular cage[9] that forms extremely stable supramolecular complexes with dimethyldiazapyrenium (DMDAP) ions in CD_3CN through the collaboration of multiple weak C–H···O hydrogen bonds. The very strong binding affinity in this host–guest system allows the molecular cage to substantially bleach the fluorescence signal of DMDAP in equimolar solutions at concentrations as low as 1×10^{-5} M. Remarkably, a 1×10^{-5} M equimolar solution of the molecular cage and DMDAP is highly selective toward Ca^{2+} ions: the solution displays a substantial increase in its fluorescence intensity in the presence of Ca^{2+}, but much less so in the presence of Li^+, Na^+, K^+, or Mg^{2+} ions. As a result, this molecular cage/DMDAP complex behaves as a supramolecular fluorescence probe for the detection of Ca^{2+} ions in solution.

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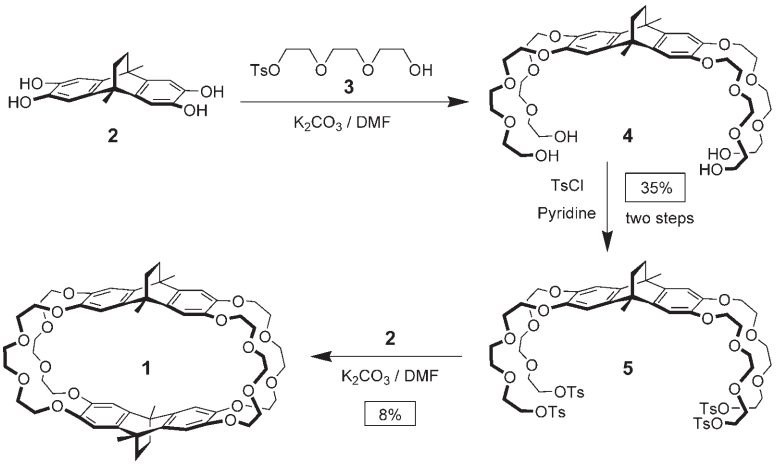
Results and Discussion

Inspired by a jawlike ditopic [18]crown-6 (18C6) host that is capable of forming stable face-to-face complexes with diammonium ions through multiple N^+–H···O hydrogen bonds[10] and by the crown ether bis(*para*-phenylene)[34]crown-10 (BPP34C10), which forms a pseudorotaxane-like complex with DMDAP through aryl–aryl interactions and C–H···O hydrogen bonds,[11] we expected that the cage-like host **1** would form a very stable complex with DMDAP in solution, that is, one that would be stabilized through multiple weak C–H···O hydrogen bonds between the methyl and α-pyridinium protons of the DMDAP ion and the oxygen atoms of the triethylene glycol chains of molecular cage **1** (Figure 1).[12] In addition, we expected that the capture of DMDAP within molecular cage **1** would quench the fluorescence emission of the DMDAP ion through intermolecular, radiationless, energy-transfer[13] or charge-transfer[14] processes, and we hoped that the addition of a metal ion to this solution would cause the dissociation of the complex $[\mathbf{1}\supset\text{DMDAP}]^{2+}$ to release free DMDAP ions into solution with a concomitant increase in the fluorescence emission intensity of the mixture.

We synthesized molecular cage **1** from 2,3,6,7-tetrahydroxy-9,10-dimethyl-9,10-dihydro-9,10-ethanoanthracene (**2**)[15] in three steps (Scheme 1). The reaction of the biscatechol **2** with triethyleneglycol monotosylate (**3**) under basic conditions gave the tetraol **4**, which we then reacted with tosyl chloride to give the tetrakistosylate **5**. The [1+1] macrocyclization reaction of **5** and the biscatechol **2** gave the desired molecular cage **1** in 8% yield.



Scheme 1. Synthesis of molecular cage **1**.

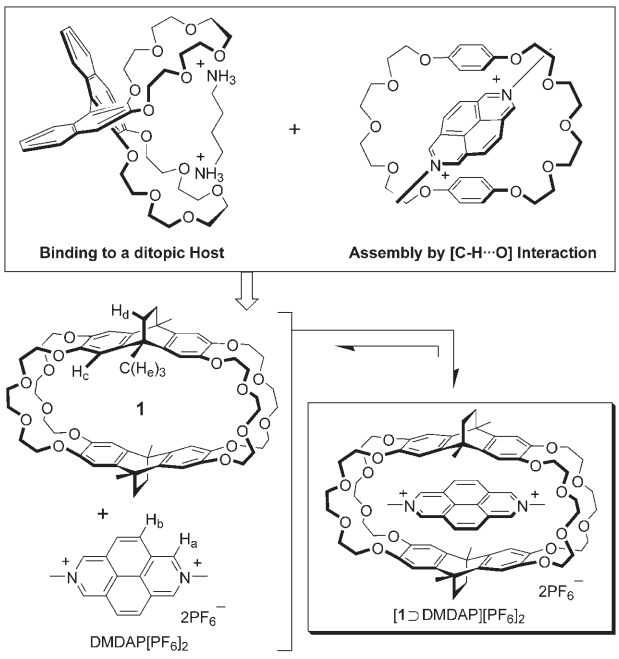


Figure 1. Design of molecular cage **1** for the complexation of DMDAP.

The ^{1}H NMR spectrum of an equimolar mixture of molecular cage **1** and $DMDAP[PF_6]_2$ in CD_3CN (4 mM) at room temperature displays significant changes in the chemical shifts of the protons of the complex relative to those of its free components (Figure 2). To confirm that the disappearance of the signals of the free species in the spectrum is due to complete complexation of both components, rather than being the result of fast rates of exchange in the complexation/decomplexation processes under these conditions, we used ^{1}H NMR spectroscopy to monitor a nonstoichiometric mixture of molecular cage **1** (4 mM) and $DMDAP[PF_6]_2$ (10 mM) in CD_3CN; we observed two sets of signals, which integrated in a 2:3 ratio, with the stronger absorption set corresponding to the signals of the free DMDAP ions (Figure 2d). This observation suggests that the binding stoichi-

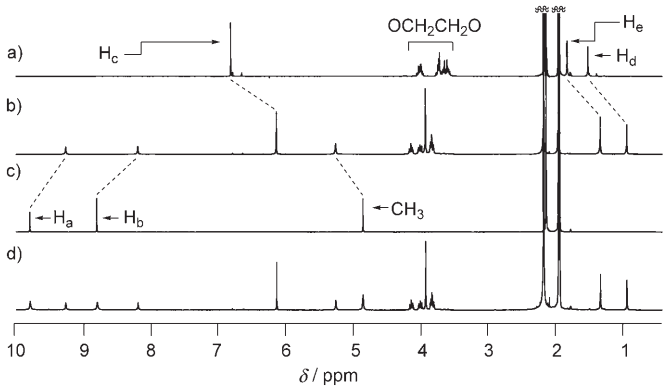


Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) molecular cage **1**, b) an equimolar mixture of **1** and $DMDAP[PF_6]_2$ (4 mM), c) $DMDAP[PF_6]_2$, and d) a mixture of **1** (4 mM) and $DMDAP[PF_6]_2$ (10 mM).

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ometry of the molecular cage **1** to DMDAP is 1:1 and that the exchange rates for their complexation and decomplexation are slow under these conditions.[16] We did not observe any signals of the free species in the ^{1}H NMR spectra upon diluting an equimolar mixtures of molecular cage **1** and DMDAP$[PF_6]_2$ from 1 mM to 10 μM (Figure 3), suggesting that the binding between molecular cage **1** and DMDAP is extremely tight.[17]

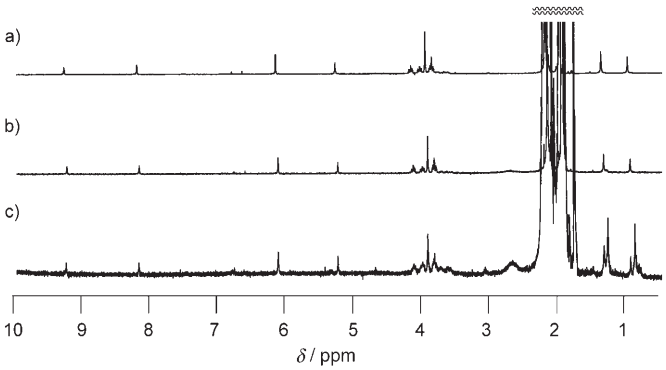

Figure 3. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of equimolar mixtures of **1** and DMDAP$[PF_6]_2$ at concentrations of a) 1, b) 0.1, and c) 0.01 mM.

The ^{1}H NMR spectra of the complex display a downfield shift for the signal of the protons of the methyl group of DMDAP and spreading of the protons of the ethylene glycol signals of molecular cage **1**; these features suggest the possible existence of C–H···O hydrogen bonds in the complex.[18] The upfield shifts of the signals of the aromatic protons of both **1** (from $\delta = 6.81$ to 6.14 ppm) and DMDAP (from $\delta = 9.79$ and 8.79 ppm to $\delta = 9.26$ and 8.19 ppm, respectively) suggest possible shielding between the aromatic rings of the two components in the complex. These results support our proposed molecular geometry for complex $[(\mathbf{1}\supset DMDAP)][PF_6]_2$ (Figure 1).

We grew single crystals suitable for X-ray crystallography through liquid diffusion of isopropyl ether into an equimolar solution of molecular cage **1** and DMDAP$[PF_6]_2$ in CH_3CN. The solid-state structure confirms the binding geometry in complex $[\mathbf{1}\supset DMDAP]^{2+}$ (Figure 4),[19] in which fourteen C–H···O hydrogen bonds formed between the methyl and α-pyridinium protons of DMDAP and the oxygen atoms on the ethylene glycol chains of molecular cage **1**. Although C–H···O hydrogen-bonding interactions are quite weak, the multiple copies of this weak interaction lead to a very stable complex $[\mathbf{1}\supset DMDAP]^{2+}$ in solution.

Figure 5 provides a comparison of the emission spectra observed upon addition of molecular cage **1** to a solution of DMDAP$[PF_6]_2$ ($[\mathbf{1}] = [DMDAP[PF_6]_2] = 1\times10^{-5}$ M); it is clear that one equivalent of molecular cage **1** quenches the fluorescence of DMDAP substantially under these conditions. We monitored the fluorescence intensities of the supramolecular system in the presence of various metal ions. For Li^+, Na^+, K^+, and Mg^{2+} ions, the fluorescence changes

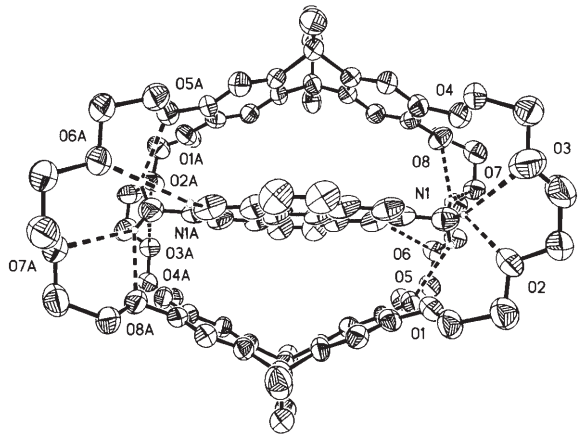

Figure 4. ORTEP plot of the solid state structure of $[\mathbf{1}\supset DMDAP]^{2+}$. The dashed lines indicate intracomplex C–H···O hydrogen bonds (see Supporting Information for the bond lengths and bond angles).

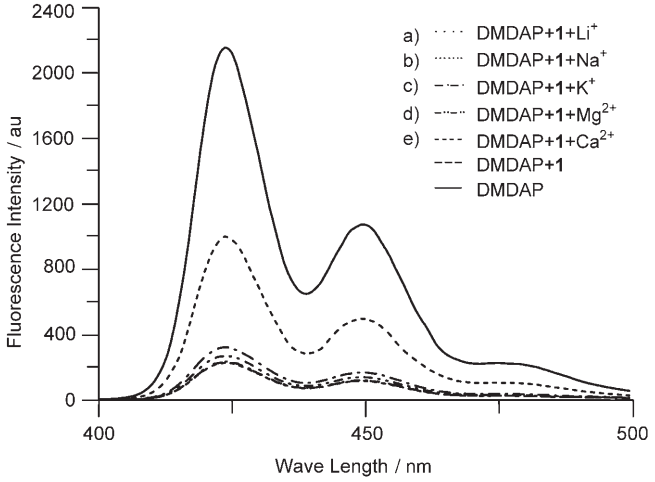

Figure 5. The corresponding fluorescence spectra (MeCN, 1×10^{-5} M, 298 K; excitation at 247 nm) of equimolar mixtures of **1**, DMDAP, and a) Li^+, b) Na^+, c) K^+, d) Mg^{2+}, and e) Ca^{2+}.

were much weaker than that observed for Ca^{2+} ions, suggesting that the interactions of the first four ions with molecular cage **1** are much weaker than those of the last one (Figure 5). The value of the fluorescence enhancement ratio $[(F-F_0)/F_0]$ after we had added one equivalent of Ca^{2+} ions to an equimolar mixture of molecular cage **1** and DMDAP-$[PF_6]_2$ (1×10^{-5} M) was at least ten times higher than those determined after the addition of the same amount of Li^+, Na^+, K^+, and Mg^{2+} ions in the same solution (Figure 6); this result suggests that this molecular cage/DMDAP complex displays good selectivity toward Ca^{2+} ions among this set of biologically important metal ions.[20]

The ^{1}H NMR spectrum of a 2:1 molar ratio mixture of molecular cage **1** and KPF_6 displayed a discernable shift in the signals of the ethylene glycol protons, but the shift seems to be quite different to the one in the spectrum of a mixture of **1** and Ca^{2+} (see Supporting Information); therefore, we suspected that the modes of complexation of mo-

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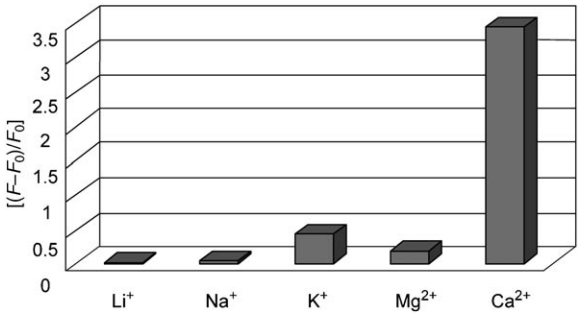

Figure 6. Fluorescence enhancement ratio profiles of a solution of **1** and DMDAP (1×10^{-5} M in MeCN) in the presence of equimolar selected metal ions. Excitation was performed at 247 nm; emission was monitored at 423 nm.

lecular cage **1** to these two types of ions may be different. We grew single crystals suitable for X-ray crystallography through liquid diffusion of isopropyl ether into 1:2 molar ratio solutions of molecular cage **1** and $Ca(ClO_4)_2$ or KPF_6 in CH_3CN. The solid-state structures reveal that the complexation of molecular cage **1** with Ca^{2+} ions utilized only one of the triethylene glycol chains of each crown ether moiety[21] (Figure 7), whereas the complex formed with the two K^+ ions involved the cooperation of all of the triethylene glycol loops[22] (i.e., each K^+ ion was bound to all eight oxygen atoms of each crown ether unit; Figure 7). Because the complexation geometries of the molecular cage **1** to these metal ions involve either one or two triethylene glycol chains, it is not evident why **1** has a much stronger binding affinity toward Ca^{2+} ions than toward Li^+, Na^+, K^+, or Mg^{2+} ions; presumably it results from a combination of effects including the size of the pseudocrown ether's cavity and the charge densities, sizes, and coordination numbers of the cations.[3f,23]

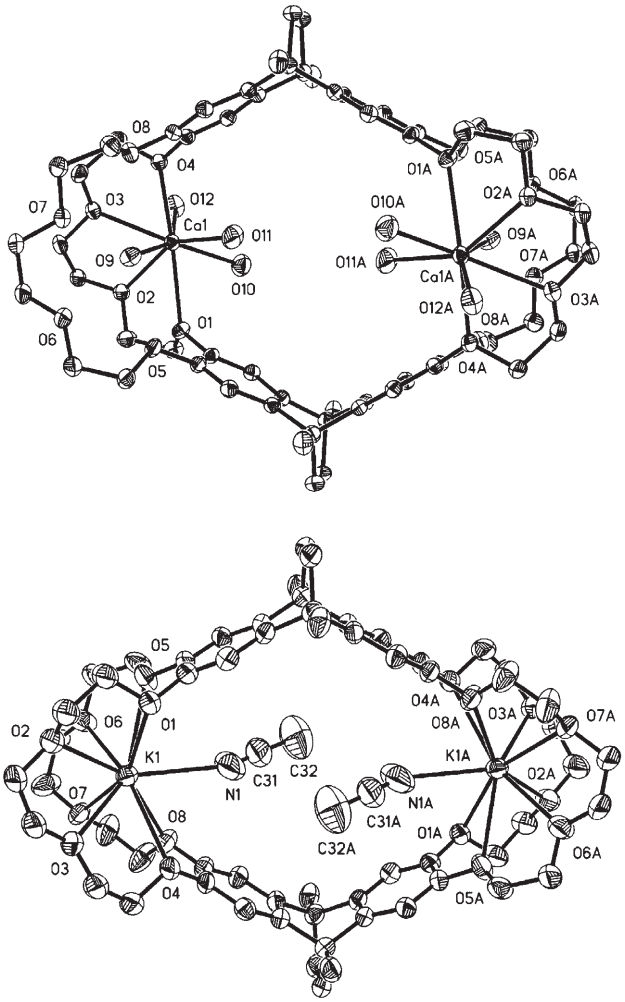

Figure 7. ORTEP plots of the solid state structures of $[\mathbf{1}\supset Ca_2]^{4+}\cdot 8H_2O$ (top) and $[\mathbf{1}\supset K_2]^{2+}\cdot 2MeCN$ (bottom).

Conclusion

We have demonstrated that the presence of multiple C–H···O hydrogen-bonding interactions can lead to the formation of an extremely stable supramolecular complex between molecular cage **1** and $DMDAP[PF_6]_2$. The strong binding affinity between these two species allows this complex to act as a fluorescence probe under dilute conditions (1×10^{-5} M), in which Ca^{2+} ions respond highly selectively with respect to Li^+, Na^+, K^+, and Mg^{2+} ions. This result suggests that supramolecular host–guest complexes can be used as efficient optical probes for detecting analytes at low concentrations, as long as the binding affinity between the host and guest is sufficiently strong, yet labile.

Experimental Section

General: All glassware, stirrer bars, syringes, and needles were either oven- or flame-dried prior to use. All reagents, unless otherwise indicated, were obtained from commercial sources. Anhydrous CH_2Cl_2 and MeCN were obtained by distillation from CaH_2 under N_2. Reactions were conducted under N_2 or Ar atmospheres. Thin-layer chromatography (TLC) was performed on Merck 0.25 mm silica gel (Merck Art. 5715). Column chromatography was undertaken over Kieselgel 60 (Merck, 70–230 mesh). Melting points are determined by Fargo MP-2D melting point apparatus. Fluorescence spectra were recorded on Hitachi F-4500. In NMR spectra, the deuterated solvent was used as the lock, while either the solvent's residual protons or TMS was employed as the internal standard. Chemical shifts are reported in parts per million (ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (mutiplet), and br (broad).

X-ray crystallographic analysis: CCDC-294241, CCDC-294242, and CCDC-294243 contain the supplementary crystallographic data for $[\mathbf{1}\supset DMDAP][PF_6]_2\cdot H_2O$, $[\mathbf{1}\supset K_2][PF_6]_2\cdot 4MeCN$, and $[(\mathbf{1}\supset Ca_2)\text{-}[ClO_4]_4\cdot 8H_2O\cdot 2CH_2Cl_2$, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Tetraol 4: A mixture of K_2CO_3 (13 g, 94.2 mmol), **2** (2.6 g, 8.6 mmol), and **3** (11.7 g, 38.5 mmol) in CH_3CN (150 mL) was heated under reflux for 48 h. The crude product obtained after evaporation of the organic solvent was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL); the organic layer was collected, dried ($MgSO_4$), and concentrated to afford a

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yellow liquid (4.2 g). This crude material was used directly in the next reaction without purification.

Tetrakistosylate 5: A solution of TsCl (4.9 g, 25.7 mmol) in CH_2Cl_2 (25 mL) was added over 10 min to a solution of tetraol **4** (4.2 g, 5.0 mmol) and triethylamine (3.6 mL, 25.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was slowly warmed to room temperature, stirred for a further 12 h, and then partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL). The organic layer was separated, dried ($MgSO_4$), concentrated, and purified (SiO_2; EtOAc/hexane, 7:3) to afford the tetrakistosylate **5** as a pale-yellow liquid (2.5 g, 35 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$ (s, 4H), 1.83 (s, 6H), 2.40 (s, 12H), 3.55–3.80 (m, 32H), 4.00–4.15 (m, 16H), 6.85 (s, 4H), 7.29 (d, $J = 8$ Hz, 8H), 7.76 ppm (d, $J = 8$ Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.0$, 21.9, 36.4, 41.4, 68.7, 69.3, 69.6, 70.0, 70.6, 70.7, 109.1, 127.5, 129.4, 132.4, 139.7, 144.2, 145.9 ppm; HR-MS (FAB): m/z calcd for $C_{70}H_{91}O_{24}S_4$: 1443.4783 $[M+H]^+$; found: 1443.4794.

Molecular cage 1: K_2CO_3 (5.3 g, 38.4 mmol) was added to a solution of biscatechol **2** (276 mg, 0.93 mmol) and tetrakistosylate **5** (1.3 g, 0.93 mmol) in CH_3CN (100 mL) at room temperature. The mixture was heated under reflux for 12 days and then the organic solvent was evaporated under reduced pressure. The crude product was partitioned between CH_2Cl_2 (250 mL) and H_2O (250 mL) and then the organic layer was collected, dried ($MgSO_4$), and concentrated to give a yellow solid, which was purified (SiO_2; MeOH/CH_2Cl_2, 5:95) to afford the molecular cage **1** as a white solid (78 mg, 8 %). M.p. >288 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.50$ (s, 8H), 1.77 (s, 12H), 3.60–3.90 (m, 32H), 3.95–4.10 (m, 16H), 6.72 ppm (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 19.0, 36.3, 41.3, 69.8, 69.9, 71.0, 108.3, 139.5, 145.7 ppm; HR-MS (FAB): m/z calcd for $C_{60}H_{77}O_{16}$: 1053.5212 $[M+H]^+$; found: 1053.5216.

Acknowledgements

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[17] If we assume that the observation of no free species in the ^{1}H NMR spectrum of the equimolar mixture of molecular cage **1** and DMDAP$[PF_6]_2$ at 10 μM concentration suggests that the free species presented in the solution are less than 5 %, then the binding constant (K_a) between molecular cage **1** and DMDAP$[PF_6]_2$ may be estimated to be as high as $3.8\times10^7\,\text{M}^{-1}$.

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[19] Crystal data for $[\mathbf{1}\supset\text{DMDAP}][PF_6]_2\cdot H_2O$: $M_r = 1595.5$, triclinic, space group $P\bar{1}$, $a = 11.9376(10)$, $b = 13.7324(12)$, $c = 14.8477(14)$ Å, $\alpha = 65.109(4)$, $\beta = 72.059(4)$, $\gamma = 79.729(6)°$ $V = 2097.2(3)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.263\,\text{g cm}^{-3}$, $\mu(\text{Mo}_{K\alpha}) = 0.141\,\text{cm}^{-1}$, $T = 295$ K, orange red plates; 7312 independent measured reflections, F^2 refinement, $R_1 = 0.1338$, $wR_2 = 0.2919$.

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[20] For practical usage, calcium sensors, which only operate in non-aqueous solvents may need further modification in order to operate in water.

[21] Crystal data for $[\mathbf{1}\supset Ca_2][ClO_4]_4\cdot 8H_2O\cdot 2CH_2Cl_2$: $M_r=1845.2$, triclinic, space group $P\hat{1}$, $a=9.0650(1)$, $b=14.1963(1)$, $c=17.2977(2)$ Å, $\alpha=101.5440(5)$, $\beta=91.7530(5)$, $\gamma=108.3000(5)°$ $V=2060.23(4)$ Å^3, $Z=1$, $\rho_{calcd}=1.487\,g\,cm^{-3}$, $\mu(Mo_{K\alpha})=0.489\,cm^{-1}$, $T=295$ K, colorless plates; 9416 independent measured reflections, F^2 refinement, $R_1=0.0665$, $wR_2=0.1975$. A triethylene glycol ligand adopting a crown ether like conformation while complexing with a Ca^{2+} center, with water and other ligands in a pentagonal bipyramidal geometry, has been observed previously. See: a) R. D. Rogers, A. H. Bond, *Acta Crystallogr. Sect. C* **1992**, *48*, 1782–1785; b) G. Hundal, M. Martinez-Ripoll, M. S. Hundal, N. S. Poonia, *Acta Crystallogr. Sect. C* **1996**, *52*, 789–792.

[22] Crystal data for $[\mathbf{1}\supset K_2][PF_6]_2\cdot 4CH_3CN$: $M_r=1585.56$, monoclinic, space group $P2_1/n$, $a=14.2301(4)$, $b=13.6183(4)$, $c=21.8428(7)$ Å, $\beta=98.336(2)°$, $V=4188.2(2)$ Å^3, $Z=2$, $\rho_{calcd}=1.257\,g\,cm^{-3}$, $\mu(Mo_{K\alpha})=0.237\,cm^{-1}$, $T=295$ K, colorless plates; 7367 independent measured reflections, F^2 refinement, $R_1=0.0907$, $wR_2=0.2359$. The solid state structure of a related diester crown ether complexing with KPF_6 also reveals a centered K^+ ion bound through ion–dipole interactions to all eight ether oxygen atoms of the crown ether; see: H. W. Gibson, H. Wang, K. Bonrad, J. W. Jones, C. Slebodnick, L. N. Zackharov, A. L. Rheingold, B. Habenicht, P. Lobue, A. E. Ratliff, *Org. Biomol. Chem.* **2005**, *3*, 2114–2121.

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