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A Molecular Cage That Selectively Complexes Three Different Guests in Solution

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ABSTRACT

A system based on a molecular cage, in which bisdiazonium, bispyridinium, and anthraquinone guests can be complexed to the host sequentially through the application of suitable stimuli, is reported.

One way to develop a molecular switch is to activate a competing guest in a designed host−guest system through the addition or removal of electrons,[1] photons,[2] or ions[3] to create detectable spectroscopic changes between the two different guest-complexed states. Molecular machines[4] exhibiting stepwise molecular motions and a molecular logic gate[5] that perform complicated functions may be developed from host molecules that can interact with a number of exchangeable guests. Most artificial guest-exchanging systems developed to date, however, feature a single host molecule that switches between only two different types of guests; we are unaware of any previous host−guest systems that allow the host to sequentially complex three or more different types of guests through in situ operation. This lack of precedent is not surprising because it is difficult to balance the stabilization energies of the three guests in their complexation to the host to create clean and clear switching and because of possible interference of the stimuli (e.g., buildup of counterions) when exchanging one complexed guest for another. Previously, we demonstrated that a mixture of bispyridinium ion- and quinone-based threading components and the molecular cage **1** undergoes a new type of molecular motion in solution, powered through the addition and removal of K^+ ions and [2,2,2]cryptand units, in which the rodlike components penetrate the molecular cage alternately through its different faces.[6] We suspected that the addition of a stronger-binding third guest component to this system,

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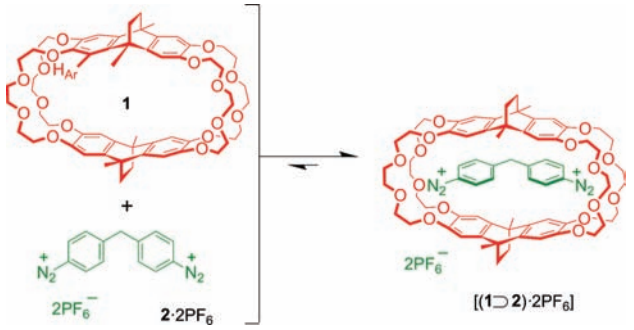
Scheme 1



together with judicious choice of the stimulation method, might allow the development of a unique three-guest complexation system. Herein, we report a system based on the molecular cage **1** in which bisdiazonium, bispyridinium, and anthraquinone guests can be complexed to the host sequentially through the application of suitable stimuli.

Because diazonium ions form complexes with small crown ethers {e.g., [18]crown-6 (18C6) and [21]crown-7 (21C7)} with high affinity,[7] we suspected that the bisdiazonium salt **2**·2PF_6 might bind the molecular cage **1** tightly in low-polarity solvents (Scheme 1). The slow rates of exchange for the complexation/decomplexation processes and the 1:1 binding stoichiometry for the complex formed between the molecular cage **1** and **2**·2PF_6 were manifested by two sets of signals—corresponding to the free and complexed $\mathbf{2}^{2+}$ ions, which integrated in a 1:1 ratio—in the ^{1}H NMR spectrum of a nonstoichiometric mixture of the molecular cage **1** (4 mM) and **2**·2PF_6 (8 mM) in $CDCl_3/CD_3CN$ (1:1).[8] The extremely large upfield shift for the signal for the methylene protons of the bisdiazonium ion $\mathbf{2}^{2+}$ (from δ 4.5 to 1.2) and the lesser (albeit, still large) upfield shifts of the aromatic protons of each component suggested that the aromatic rings of this host and guest may have been involved in significant π-stacking in their complex under these conditions. We grew single crystals suitable for X-ray crystallography through liquid diffusion of isopropyl ether into an equimolar CH_3CN solution of the molecular cage **1** and **2**·2PF_6.[9] Two sets of aromatic stacking interactions between the catechol rings of the DB24C8 motif of the molecular cage **1** and the phenylene rings of the thread component **2**·2PF_6, with the centroid···centroid distances and mean interplanar separations of 4.09, 3.28 and 4.11, 3.34 Å, respectively, are identified in the solid state structure of the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ (Figure 1).

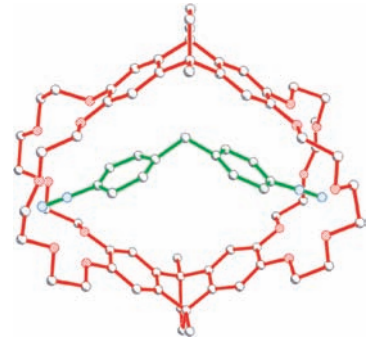


Figure 1. Ball-and-stick representation of the solid state structure $(\mathbf{1}\supset\mathbf{2})^{2+}$. Color code: C, gray; O, red; N, blue.

Previously, we demonstrated the slow rates of exchange of the components in the complex formed between the bispyridinium salt **3**·2PF_6 and the molecular cage **1**. After observing strong binding between the bisdiazonium ion $\mathbf{2}^{2+}$ and the molecular cage **1**, we used ^{1}H NMR spectroscopy to monitor the competition of an equimolar (4 mM) mixture of **1**, $\mathbf{2}^{2+}$, and $\mathbf{3}^{2+}$ in $CDCl_3/CD_3CN$ (1:1). As expected, the tighter binding of the bisdiazonium ion $\mathbf{2}^{2+}$ to the molecular cage **1** resulted in the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ predominating in solution, with the $\mathbf{3}^{2+}$ ion being uncomplexed under these conditions. Our attempts to dissociate the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ in solution by adding 21C7, which has a high affinity for diazonium ions, failed to provide clean switching, even at a large excess of 21C7. Thus, the binding of the bispyridinium ion $\mathbf{3}^{2+}$ to the molecular cage **1** was not sufficiently strong to replace the guest $\mathbf{2}^{2+}$ in the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ under these conditions. Because stronger [C−H···O] hydrogen bonding between the α-protons of the bispyridinium ion $\mathbf{3}^{2+}$ and the oxygen atoms of the triethylene glycol chains of the molecular cage **1** would enhance their complexation, we synthesized the threadlike bispyridinium salt **4**·2PF_6 as a more suitable guest for the molecular cage **1**; i.e., the electron-withdrawing alkyne units would enhance the [C−H···O] hydrogen bonding interactions.[10]

As anticipated, the addition of an excess of 21C7 (15 equiv) to the equimolar (4 mM) mixture of **1**, **2**·2PF_6, and **4**·2PF_6 in $CDCl_3/CD_3CN$ (1:1) dissociated the formerly tightly binding complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ completely, allowing the pseudorotaxane $(\mathbf{1}\supset\mathbf{4})^{2+}$ to form (Scheme 2), based on analyses of ^{1}H NMR spectra. The addition of Na^+ or K^+ ions to the solution failed to restore the system to its original binding status, possibly because these metal ions possess insufficient binding selectivity toward 21C7 over the crown ether motifs in the molecular cage **1**.[11] Therefore, we turned our attention to using a dipropargylammonium cation to

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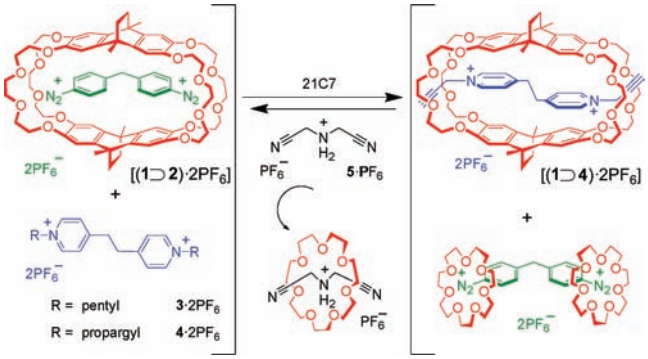
(8) We determined the association constant (K_a) for the complex formed from these two species to be 2.9×10^8 M^{-1}, through ^{1}H NMR spectroscopic competition experiments using 1,2-bis(methylpyridinium)ethane as the competing reagent. Using an isothermal titration calorimetry (ITC)-based competition experiment, we determined the binding constant between the molecular cage **1** and 1,2-bis(methylpyridinium)ethane in $CHCl_3/CH_3CN$ (1:1) to be 1.8×10^8 M^{-1}.

(9) Crystal data for $[(1\supset2)\cdot3MeCN\cdot2PF_6]$: $[C_{79}H_{95}O_{16}N_7][PF_6]_2$; M_r = 1688.56; triclinic; space group $P\bar{1}$; a = 14.3156(7); b = 15.2385(8); c = 21.0682(11) Å; V = 4174.1(4) Å^3; ρ_{calcd} = 1.344 g cm^{-3}; μ(Mo Kα) = 0.147 mm^{-1}; T = 295(2) K; orange cube; 18 962 independent measured reflections; F2 refinement; R_1 = 0.1193; wR_2 = 0.2629.

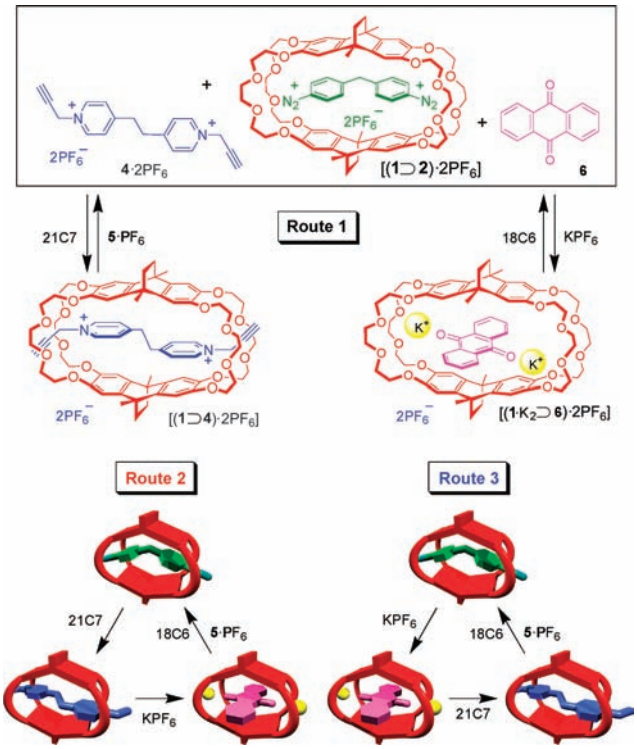
(10) Using ITC competition experiments, we determined the association constants for the interactions of the molecular cage **1** with the threadlike salts **3**·2PF_6 and **4**·2PF_6 in $CHCl_3/CH_3CN$ (1:1) to be 2.9×10^5 and 1.7×10^6 M^{-1}, respectively.

(11) The binding selectivities of 21C7 and 24C8 ($K_{21C7\supset M+}/K_{24C8\supset M+}$) toward either the Na^+ or K^+ ion in MeOH at 298 K are less than 10. See: (a) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600–606. (b) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 475–479. (c) Inoue, Y.; Liu, Y.; Tong, L.-H.; Ouchi, M.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1947–1950.

Scheme 2



Scheme 3



disrupt the complex formed between 21C7 and $\mathbf{2}^{2+}$ based on the knowledge that dipropargylammonium tetrafluoroborate forms a strong pseudorotaxane complex with 21C7.[12] To increase the binding affinity of the dipropargylammonium cation toward 21C7, so that the system could be disrupted more efficiently, we synthesized the threadlike salt **5**·PF_6, which possesses electron-withdrawing cyano groups appended to the NH_2^+ adjacent methylene units. As expected, addition of the bis(cyanomethyl)ammonium salt **5**·PF_6 into the mixture of the molecular cage **1**, the bisdiazonium salt **2**·$2PF_6$, the bis(*N*-propargylpyridinium) salt **4**·$2PF_6$, and 21C7

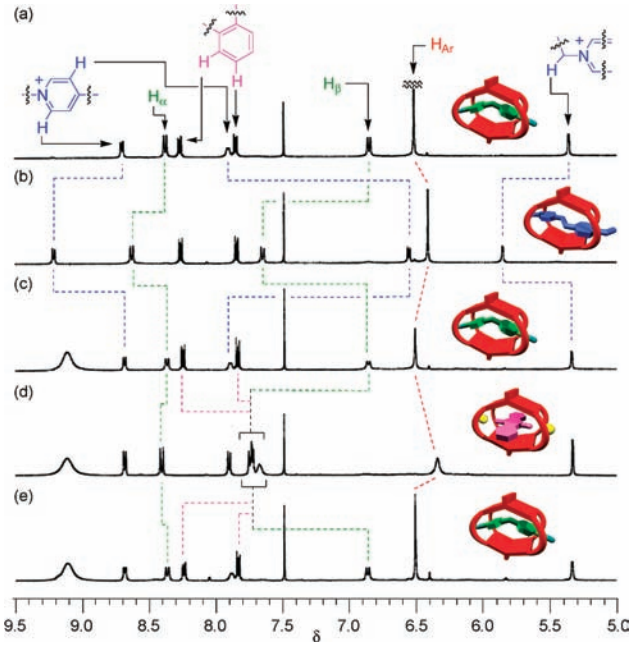


Figure 2. Partial ^{1}H NMR spectra [400 MHz, $CDCl_3/CD_3CN$ (1:1), 298 K] of (a) an equimolar mixture of the molecular cage **1**, the bisdiazonium salt **2**·$2PF_6$, the bis(*N*-propargylpyridinium) salt **4**·$2PF_6$, and anthraquinone (4 mM), (b) the mixture obtained after adding 21C7 (15 equiv) to the solution in (a), (c) the mixture obtained after adding the bis(cyanomethyl)ammonium salt **5**·PF_6 (16 equiv) to the solution in (b), (d) the mixture obtained after adding KPF_6 (8 equiv) to the solution in (c), and (e) the mixture obtained after adding 18C6 (12 equiv) to the solution in (d).

disrupted the complex formed between the $\mathbf{2}^{2+}$ dication and 21C7. The released $\mathbf{2}^{2+}$ dication displaced the $\mathbf{4}^{2+}$ dication from its complex with **1** and resulted in the restoration of the original signals of the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ and the uncomplexed threadlike salt **4**·$2PF_6$ in the ^{1}H NMR spectra (see the Supporting Information).[13] Thus, exchange of the bisdiazonium and bispyridinium guests in their complexation with the molecular cage **1** can be achieved in solution through the addition and removal of 21C7.

After confirming that exchange of the bisdiazonium dication $\mathbf{2}^{2+}$ by anthraquinone was possible in solution through the addition and removal of K^+ ions (see the Supporting Information), consistent with the situation that we reported previously for the bispyridinium salt **3**·$2PF_6$ and anthraquinone,[6] we examined the possibility of controlling the guest selectivity in a mixture of three different types of guests and the molecular cage **1** (Scheme 3). The ^{1}H NMR spectra in Figure 2 reveal that an equimolar (4 mM) mixture of the molecular cage **1**, the bisdiazonium salt **2**·$2PF_6$, the bis(*N*-propargylpyridinium) salt **4**·$2PF_6$, and anthraquinone featured the highly selective formation of the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$, which was then dissociated completely to give the [2]pseudorotaxane $(\mathbf{1}\supset\mathbf{4})^{2+}$ as the predominant cage-complexed species after the addition of an excess of 21C7. Subsequent addition of the bis(cyanomethyl)ammonium salt **5**·PF_6 into this solution gave a spectrum similar to that obtained from the original mixture, suggesting that exchange between the bisdiazonium salt **2**·$2PF_6$ and the bis(*N*-prop-

(12) Hsu, C.-C.; Chen, N.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7475–7478.

(13) Under the same conditions, the addition of dipropargylammonium tetrafluoroborate to the solution did not result in clean or efficient switching.

argylpyridinium) salt **4**•2PF_6 could be performed successfully without interference from the anthraquinone guest. The ^{1}H NMR spectrum in Figure 2d reveals that the $(\mathbf{1}\supset\mathbf{2})^{2+}$ complex in this solution dissociated when we added KPF_6. The upfield shifts of the signals of the aromatic protons of anthraquinone, the appearance of signals corresponding to the free bisdiazonium dication $\mathbf{2}^{2+}$, and the unaffected signals for the free bis(*N*-propargylpyridinium) salt **4**•2PF_6 all suggested that anthraquinone was the guest complexed by the molecular cage **1** under these conditions. Using 18C6 to remove the K^+ ions from the complex $(\mathbf{1}\cdot K_2\supset\mathbf{6})^{2+}$ allowed the original $(\mathbf{1}\supset\mathbf{2})^{2+}$ complex to be restored in the solution, as evidenced by the ^{1}H NMR spectrum in Figure 2e appearing similar to that of the original host−guest mixture in the absence of any additives. Therefore, switching between the bisdiazonium ion $\mathbf{2}^{2+}$ and anthraquinone as guests in the complexation of the molecular cage **1** can be achieved, even in the presence of the bis(*N*-propargylpyridinium) salt **4**•2PF_6.

Having demonstrated the ability to selectively control the complexation of the molecular cage **1** to one of three guests in solution, we examined the possibility of reversing the order of complexation for the bis(*N*-propargylpyridinium) dication and anthraquinone. Addition of KPF_6 to an equimolar (4 mM) mixture of the molecular cage **1** and the three guests resulted in dissociation of the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$ and formation of the pseudorotaxane-like complex $(\mathbf{1}\cdot K_2\supset\mathbf{6})^{2+}$, which we then switched back to its original state through the subsequent addition of 18C6. Predominant formation of the [2]pseudorotaxane-like complex $(\mathbf{1}\supset\mathbf{4})^{2+}$ was then achieved by adding 21C7 to this solution; addition of the bis(cyanomethyl)ammonium salt **5**•PF_6 resulted in $\mathbf{2}^{2+}$ being restored as the guest complexed within the cavity of the molecular cage **1**. Therefore, in this system, starting from the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$, we may select at will the guest that we wish to complex with the molecular cage **1**, depending on our choice of operating reagent (Scheme 3, route 1).

To prove that exchange between the bis(*N*-propargylpyridinium) dication and anthraquinone as guests within the molecular cage **1** did not have to proceed through the formation of the complex $(\mathbf{1}\supset\mathbf{2})^{2+}$, we added K^+ ions to the solution of the [2]pseudorotaxane-like complex $(\mathbf{1}\supset\mathbf{4})^{2+}$ prepared from 21C7 (15 equiv) and an equimolar mixture (4 mM) of the molecular cage **1**, the bisdiazonium salt **2**•2PF_6, the bis(*N*-propargylpyridinium) salt **4**•2PF_6, and anthraquinone. The resulting ^{1}H NMR spectrum revealed (Figure 3) that anthraquinone replaced the bis(*N*-propargylpyridinium) dication $\mathbf{4}^{2+}$ within the cavity of the molecular cage **1**. In this case, direct exchange of the guest complexed by the molecular cage **1** proceeded in the following order: bisdiazonium dication → bis(*N*-propargylpyridinium) dication → anthraquinone. The reverse exchange process could be performed through the sequential addition of 18C6 and the bis(cyanomethyl)ammonium salt **5**•PF_6 (Scheme 3, route 2).

We found that the direct exchange of these three guests could also be achieved by adding K^+ ions prior to 21C7, allowing the guests to be exchanged in the order: bisdiazonium dication → anthraquinone → bis(*N*-propargylpyridinium) dication (Scheme 3, route 3). In this case, however, a large excess of 21C7 was required in the final step, i.e., to eliminate interference from the bisdiazonium dication $\mathbf{2}^{2+}$ and K^+ ions. Note that our ability to select the guest that

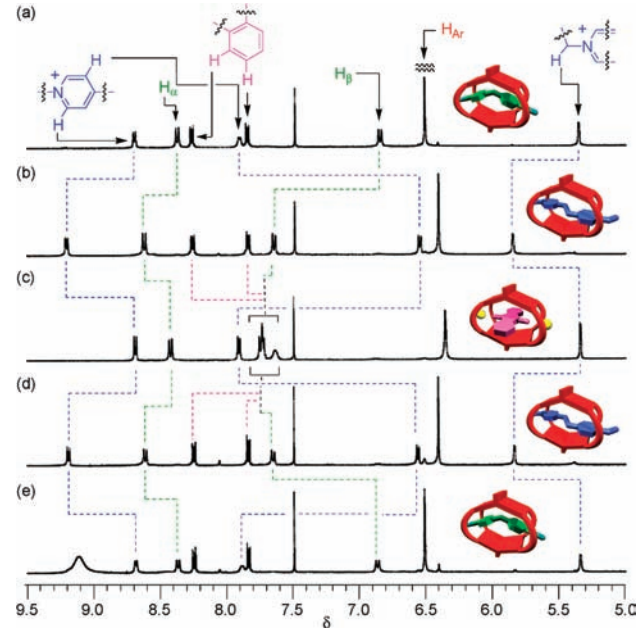


Figure 3. Partial ^{1}H NMR spectra [400 MHz, $CDCl_3/CD_3CN$ (1:1), 298 K] of (a) an equimolar (4 mM) mixture of the molecular cage **1**, the bisdiazonium salt **2**•2PF_6, the bis(*N*-propargylpyridinium) salt **4**•2PF_6, and anthraquinone, (b) the mixture obtained after adding 21C7 (15 equiv) to the solution in (a), (c) the mixture obtained after adding KPF_6 (15 equiv) to the solution in (b), (d) the mixture obtained after adding 18C6 (18 equiv) to the solution in (c), and (e) the mixture obtained after adding the bis(cyanomethyl)ammonium salt **5**•PF_6 (16 equiv) to the solution in (d).

complexes with the molecular cage **1** is dependent merely upon the order of addition of 21C7 and K^+ ions. This situation arises because these two species themselves form a strong complex. If these operating reagents did not interact with each other, then we would have been able to perform direct switching along only one pathway because the coexistence of the two independent operating reagents in solution would have resulted in the same complex. Subsequent addition of the bis(cyanomethyl)ammonium salt **5**•PF_6 and 18C6 into this solution restored the system back to its original $(\mathbf{1}\supset\mathbf{2})^{2+}$ complex.

We have demonstrated a unique host/guest complexation system, in which the molecular cage **1** can be coaxed to selectively complex one of three different guests through the addition of appropriate operating agents (i.e., in situ control). The multiple stages of these switching processes are remarkably clean and clearly identifiable (^{1}H NMR spectroscopy), suggesting that the thermodynamic parameters dictating these host/guest complexes were agreeably balanced.

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Supporting Information Available: Synthetic procedures, characterization data, and association constants for the guests. This material is available free of charge via the Internet at http://pubs.acs.org.

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