Organic LETTERS

Letter

pubs.acs.org/OrgLett

Negative Cooperativity in the Binding of Imidazolium and Viologen Ions to a Pillar[5]arene-Crown Ether Fused Host

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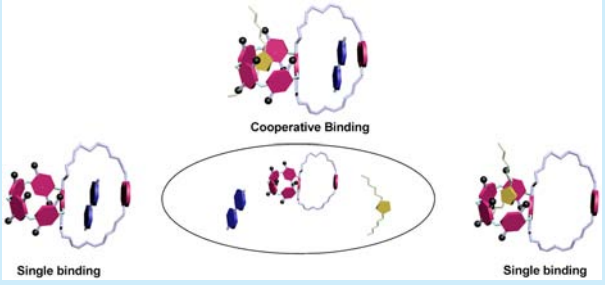
Supporting Information

ABSTRACT: A pillar[5]arene-crown ether fused bicyclic host **1** was found to be able to recognize an imidazolium ion **G1** by its pillar[5]arene subunit and a viologen ion **G2** by its crown ether receptor discriminatively. The simultaneous binding of **G1** and **G2** by **1** resulted in the formation of a three-component host–guest complex **G1**⊂**1**⊃**G2**. Negative heterotropic cooperative effects were displayed by **G1** and **G2** in their binding to **1** and were investigated by stepwise bindings of **G1** and **G2** to **1**.



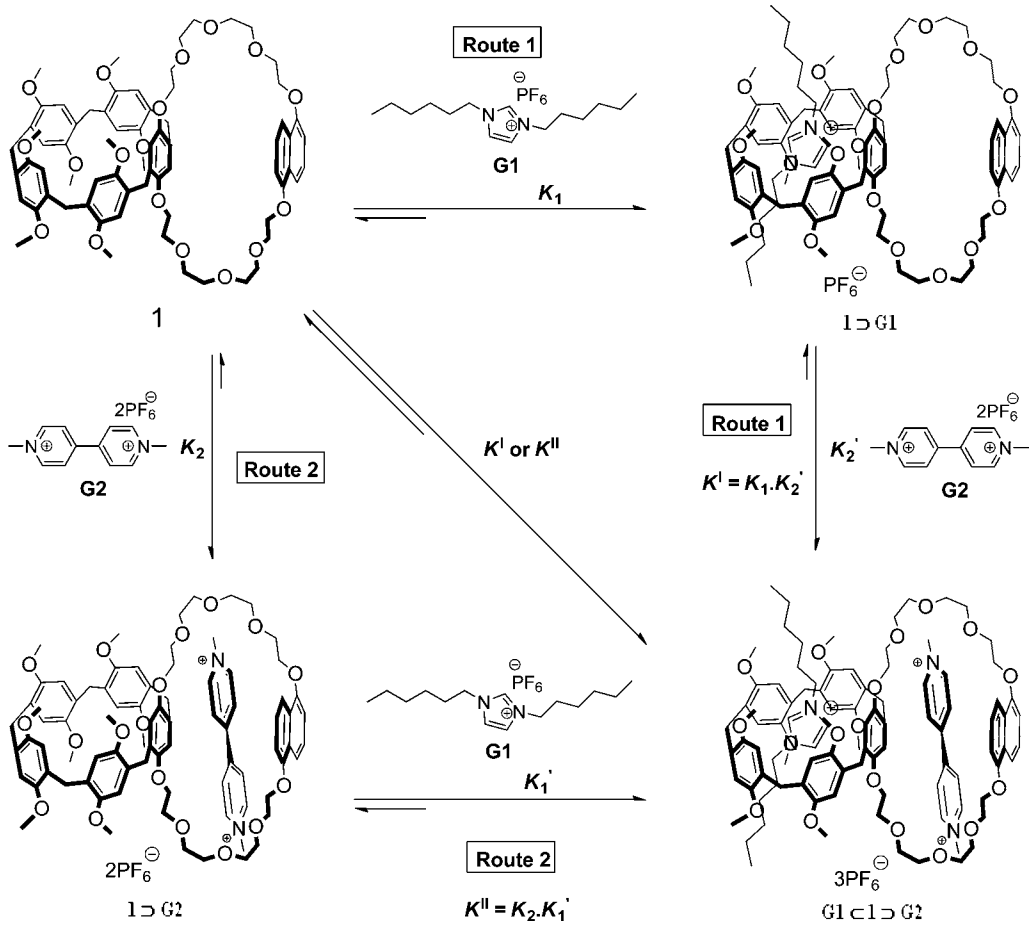
Cooperative interactions play a vital role in many natural processes, with examples including the formation of tobacco mosaic virus (TMV),[1] the allosteric oxygenation of hemoglobin,[2] and protein folding.[3] Cooperativity is crucial in nature without which the complex molecular systems required for life could not function.[4] Mimicking cooperativity chemically would advance our understanding of the cooperative interactions in nature's microscopic events. Therefore, the design and synthesis of well-defined artificial host systems that are capable of mimicking various cooperative binding processes in nature have been of great interest in the field of supramolecular chemistry. Macrocycles, such as crown ethers,[5] cyclodextrins,[6] calixarenes,[7] cucurbiturils,[8] cyclophanenes,[9] calixpyrroles,[10] and pillararenes,[11] have been used as artificial hosts to recognize various guest molecules of suitable shape, size, and electronic constitution through specific noncovalent interactions. It was reported that allosteric cooperativity has been achieved through the creation of multiple guest binding sites in a single macrocyclic host molecule.[12] In as early as 2003, Rowan, Nolte and co-workers developed a double-cavity porphyrin host which displayed very strong negative homotropic allosteric behavior toward viologen ions.[13] A cyclic dimer of a fused porphyrin zinc complex, developed by Aida and co-workers in 2005, bound two guest molecules in a cooperative way.[14] Recently, calix[4]pyrrole-based receptors were reported by Sessler and co-workers to bind ion pairs cooperatively.[15] We previously developed a pillar[5]arene-crown ether fused bicyclic host molecule **1** which can discriminatively bind a neutral guest molecule (1,4-dicyanobutane) by its pillar[5]-arene subunit and a viologen ion by its crown ether cavity simultaneously.[16] However, no cooperativity was displayed by the two guest molecules in their binding to **1**. We envisioned that the two guest species might display negative cooperativity in their binding to **1** if they were both positively charged; thus, we initiated an investigation on the binding behavior of two charged guest species imidazolium ion **G1**[17] and viologen ion **G2**[18] and found that the binding of the first guest electronically affected the second in its binding to the bicyclic host **1**, showing strong negative cooperativity.

The pillar[5]arene-crown ether fused bicyclic host **1** was synthesized as previously reported[16] in which the size of the naphthalene unit in the polyether chain prevents formation of a self-included *pseudo*[1]catenane through rotation of the 1,4-hydroquinone unit.[19] As shown in Scheme 1, thanks to their difference in size, shape, and mode of supramolecular interactions, guests **G1** and **G2** can selectively bind the pillar[5]arene and crown ether macrocyclic subunits of **1**. As previously reported, host **1** and guest **G2** formed a charge-transfer complex **1**⊃**G2** in acetone-d_6 through the host–guest interaction by threading guest **G2** into the crown ether ring of **1**.[16] The ^{1}H NMR spectra of host **1**, guest **G2**, and an equimolar mixture of **1** and **G2** in acetone-d_6 (5.0 mM) are shown in Figure 1. A Job plot (Figure S2) based on ^{1}H NMR data and MS (ESI) spectrum of the complex (Figure S3) demonstrated that host **1** and **G2** form a complex in a 1:1 ratio in acetone-d_6. The associate constant (K_2) of the complex **1**⊃**G2** in acetone-d_6 was determined to be 769.5 ± 73 M^{-1} by a ^{1}H NMR titration method (Supporting Information and Figures S4–S5). In this investigation, by following a very similar procedure, we prepared a host–guest complex of host **1**

Received: April 24, 2015
Published: May 27, 2015

DOI: 10.1021/acs.orglett.5b01209
Org. Lett. 2015, 17, 2940–2943

Scheme 1. Stepwise Bindings of Guests G1 and G2 by Host 1



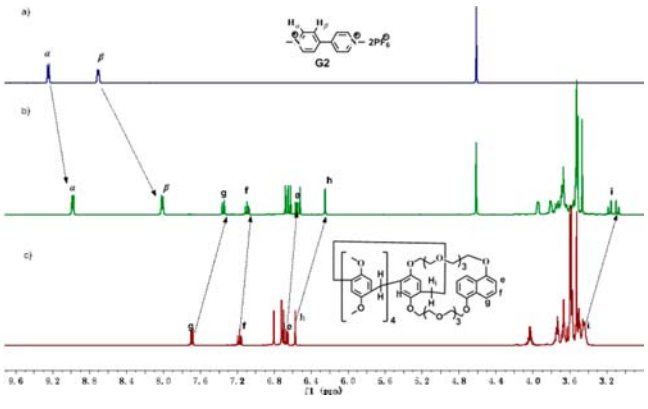


Figure 1. ^{1}H NMR spectra (400 MHz, acetone-d_6): (a) Free **G2** (5.0 mM); (b) **1** (5.0 mM) + **G2** (5.0 mM); (c) Free **1** (5.0 mM).

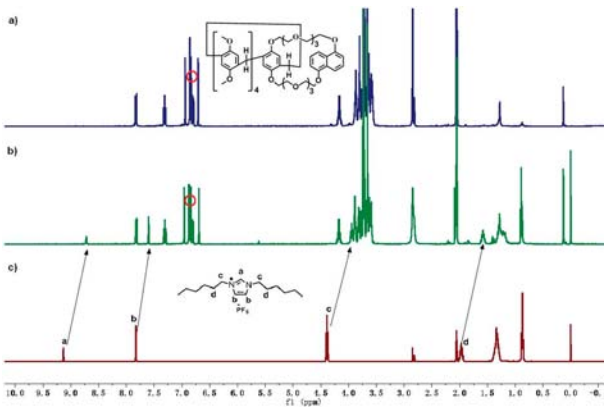


Figure 2. ^{1}H NMR spectra (400 MHz, acetone-d_6): (a) Free **1** (5.0 mM); (b) **1** (5.0 mM) + **G1** (5.0 mM); (c) Free **G1** (5.0 mM).

with guest **G1** by mixing **1** and **G1** in 1:1 molar ratio in acetone-d_6 (5.0 mM). In the ^{1}H NMR spectra (shown in Figure 2), although there were no obvious changes in chemical shifts for the naphthalene proton signals of host **1**, splitting of the proton signals of the hydroquinone units in the pillar[5]arene scaffold of host **1**, as well as upfield shifts (−0.38, −0.21, −0.42, and −0.35 ppm) for proton signals of H_a, H_b, H_c, and H_d of **G1**, caused by the shielding effect of the tubular cyclophane, were observed, suggesting the formation of a threaded host−guest complex **1⊃G1** by the pillar[5]arene subunit of **1** and **G1**. Addition of excess **G1** to the acetone-d_6 solution of complex **1⊃G1** caused no change in chemical shifts for the naphthalene proton signals of the crown ether subunit of host **1**, so excess **G1** did not lead to the binding of a second **G1** by the crown ether subunit of **1**. The 2D NOESY spectrum (Figure S6) showed the NOE correlations between the proton signals of **G1** (H_a and H_b, H_c and H_d) and the pillar[5]arene methoxy protons of **1**, supporting the assignment of a threaded structure **1⊃G1**. There is no host−guest interaction between the crown ether subunit of host **1** and **G1** since no NOE correlations were observed between the proton signals of **G1** and the protons of crown ether in **1**. A Job plot (Figure S7) based on ^{1}H NMR data proved that host **1** and **G1** form a complex in a 1:1 ratio.

DOI: 10.1021/acs.orglett.5b01209
Org. Lett. 2015, 17, 2940−2943

The associate constant (K_1) of the complex **1⊃G1** in acetone-d_6 was determined to be 50.9 ± 4.9 M^{-1} with a ^{1}H NMR titration method (Supporting Information and Figures S8−S9).

Given the fact that host **1** binds guests **G1** and **G2** selectively in its pillar[5]arene and crown ether submacrocyclic units, the simultaneous binding of guests **G1** and **G2** by host **1** was thus examined in acetone-d_6. The ^{1}H NMR spectra of **1**, **G1**, **G2**, **1⊃G1**, **1⊃G2**, and an equimolar mixture of **1**, **G1**, and **G2** in acetone-d_6 (5.0 mM) are shown in Figure 3. Besides the upfield

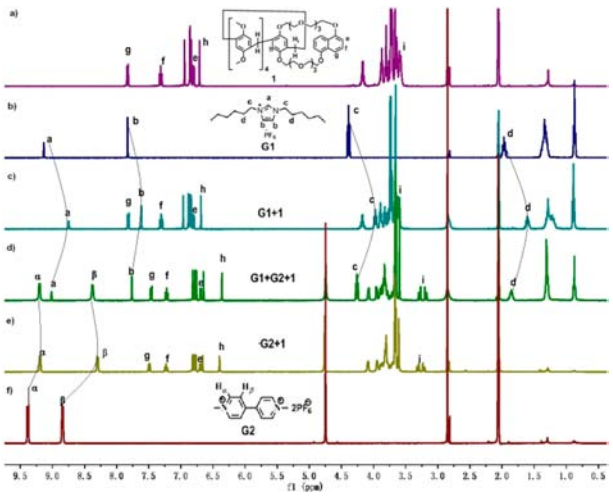


Figure 3. ^{1}H NMR spectra (400 MHz, acetone-d_6): (a) Free **1** (5.0 mM); (b) Free **G1** (5.0 mM); (c) **1** (5.0 mM) + **G1** (5.0 mM); (d) **1** (5.0 mM) + **G1** (5.0 mM) + **G2** (5.0 mM); (e) **1** (5.0 mM) + **G2** (5.0 mM); (f) Free **G2** (5.0 mM).

shifts for proton signals of **G1** (H_a, H_b, H_c, and H_d), and α- and β-pyridinium proton signals of **G2**, upfield shifts are also observed for the signals of naphthalene protons (H_e, H_f, and H_g), proton (H_h) of the hydroquinone unit of the crown ether, and the protons (H_i) of pillar[5]arene bridging methylene groups connected to the crown ether hydroquinone unit in host **1**, suggesting the formation of a 1:1:1 host−guest complex **G1⊂1⊃G2** from host **1** and the two guests. The 2D NMR ROESY spectrum of a mixture of **1**, **G1**, and **G2** in acetone-d_6 showed correlations between the methylene proton signals of **G1** with the methoxyl proton signals of the pillar[5]arene subunit of **1**, as well as correlations between the pyridinium proton signals of **G2** with those of the crown ether subunit of **1**. This result provided additional evidence for the formation of a host−guest complex **G1⊂1⊃G2** (Figure S14). The obvious smaller change of chemical shifts for proton signals in the ^{1}H NMR spectrum of complex **G1⊂1⊃G2**, compared with the corresponding change of the chemical shifts in the ^{1}H NMR spectra of either **1⊃G1** or **1⊃G2** (Figure 3), implied weakened binding of **G1** and **G2** by host **1** in **G1⊂1⊃G2** than those in either **1⊃G1** or **1⊃G2**. Hence, there seemed to be a negative cooperative effect of the guests **G1** and **G2** toward each other in their binding to **1**, possibly due to repulsive Coulombic interactions between the two positively charged guests.

As the two binding pockets of host **1** can selectively complex **G1** and **G2**, the binding cooperativity of **G1** and **G2** to **1** was then assessed by two stepwise bindings (Scheme 1), and the stepwise association constants and the overall binding constants for the two binding routes could be expressed by eqs 1 and 2.

$$\mathbf{1} + \mathbf{G1} \overset{K_1}{\rightleftharpoons} \mathbf{1}\supset\mathbf{G1} \underset{\mathbf{G2}}{\overset{K_2'}{\rightleftharpoons}} \mathbf{G1}\subset\mathbf{1}\supset\mathbf{G2} \quad K^{\mathrm{I}} = K_1 \cdot K_2' \tag{1}$$

$$\mathbf{1} + \mathbf{G2} \overset{K_2}{\rightleftharpoons} \mathbf{1}\supset\mathbf{G2} \underset{\mathbf{G1}}{\overset{K_1'}{\rightleftharpoons}} \mathbf{G1}\subset\mathbf{1}\supset\mathbf{G2} \quad K^{\mathrm{II}} = K_2 \cdot K_1' \tag{2}$$

^{1}H NMR titration was used to evaluate the negative cooperative binding effect displayed by **G1** and **G2** in their binding to **1** in acetone-d_6 (5.0 mM) through two routes shown in Scheme 1. In Route 1, whose binding is defined by eq 1, host **1** binds **G1** in its pillar[5]arene cavity first with an association constant (K_1) of 50.9 ± 4.9 M^{-1} (described above). Under the condition that the pillar[5]arene cavity of host **1** was fully saturated by **G1** (complex **1⊃G1**, $[M_{G1}]/[M_1]$ = 60), the association constant (K_2') for the upcoming binding of **G2** by the crown ether cavity of **1⊃G1** was determined to be 114.5 ± 11 M^{-1} (Supporting Information and Figures S10−S11), much smaller than that for the binding of **G2** by free host **1** (Figure 4), which means that binding of **G2** is hindered by the presence

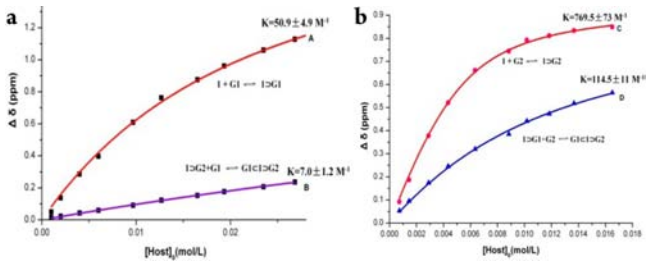


Figure 4. (a) Binding constants between host **1** and guest **G1** in the absence and the presence of guest **G2**; (b) binding constants between host **1** and guest **G2** in the absence and the presence of guest **G1**, determined by ^{1}H NMR titration.

of **G1**, clear evidence of negative cooperativity. The overall binding constant ($K^{\mathrm{I}} = K_1 \cdot K_2'$) for the product **G1⊂1⊃G2** determined by eq 1 is *ca.* 5839 M^{-2}. Similarly, for bindings defined by eq 2 (Route 2 in Scheme 1), the association constant (K_1') for the upcoming binding of **G1** by the pillar[5]arene cavity of **1⊃G2** was determined to be 7.0 ± 1.3 M^{-1} under the condition that the crown ether cavity of host **1** was fully saturated by **G2** (complex **1⊃G2**, $[M_{G2}]/[M_1]$ = 16, which is the highest ratio due the limited solubility of **G2** in acetone-d_6) (Supporting Information and Figures S12−S13), showing $K_1' \ll K_1$ (Figure 4), clear evidence that binding of **G1** and **G2** by host **1** has negative cooperativity. The overall binding constant ($K^{\mathrm{II}} = K_2 \cdot K_1'$) for the product **G1⊂1⊃G2** expressed by eq 2 is *ca.* 5386 M^{-2}. Theoretically, the overall binding constants of the two routes for formation of the product **G1⊂1⊃G2** should be the same, i.e., $K^{\mathrm{I}} = K^{\mathrm{II}}$, which is quite consistent with what we found: K^{I} and K^{II} obtained experimentally with NMR titration methods were actually very close (5839 and 5386 M^{-1}, respectively).

In conclusion, we have shown that the pillar[5]arene-crown ether fused bicyclic host **1** is able to bind an imidazolium ion **G1** and a bipyridinium ion **G2** discriminately with its two submacrocyclic receptor units. Guests **G1** and **G2** were found to display a negative cooperative effect in their binding to host **1**, which was mainly due to the repulsive Coulombic interactions between the two positively charged guests. The cooperativity in binding of **G1** and **G2** by **1** was assessed by two stepwise bindings, where the overall binding constants of the two routes obtained experimentally with NMR titration

DOI: 10.1021/acs.orglett.5b01209
Org. Lett. 2015, 17, 2940−2943

methods were found to be very close, consistent with the thermodynamic property of cooperativity.

■ ASSOCIATED CONTENT

Supporting Information

General methods, titration protocol, Job plots, determination of the association constants. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01209.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21371177, 21071053, 21002031), Shanghai Commission for Science and Technology (12DZ1100901), and the "Strategic Priority Research Program" of the Chinese Academy of Sciences (XDA01020304) for generous financial support.

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DOI: 10.1021/acs.orglett.5b01209
Org. Lett. 2015, 17, 2940−2943