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Allosteric Modulation of Substrate Binding within a Tetracationic Molecular Receptor

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Supporting Information

ABSTRACT: The synthesis and recognition phenomena of a tetracationic molecular receptor that possesses a nanometer-sized molecular cavity are described. The host–guest properties of the molecular receptor can be tuned and modulated allosterically, where the association of a heterotropic effector at the periphery of the molecule serves to modulate its affinity for the globular, electron-rich guest that resides within its molecular cavity. This stimuli-responsive host–guest behavior was observed in both the solution phase and the crystalline solid state, and can be reversed with high fidelity by sequestration of the effector molecule.

The classical understanding of allostery[1] refers to the regulation of substrate binding by a biological receptor, where the association of a secondary effector molecule[2] serves to modulate its affinity for the substrate. These processes are governed by an intricate structure–function relationship[3] that allows for both the positive[4] and negative[5] regulation of biological activity, depending on the nature of the effector.[6] Although this representation of allostery is perhaps more synonymous with the proteins[7] present in Nature than with the abiotic synthetic receptors that reside under the umbrella of supramolecular chemistry, the two share a great deal of similarities,[8] particularly when stimuli-responsive host–guest systems are considered.[9]

The design and preparation of molecular hosts that are capable of encapsulating guests with high levels of selectivity has been a staple of supramolecular chemistry for nearly three decades.[10] The early carcerands[11] first demonstrated the propensity for synthetic receptors to encapsulate[12] permanently a wide range of guests—generally solvent and other small molecules—in the formation of carceplexes. In the years that followed, these prototypical "container compounds" have driven research toward increasingly sophisticated host–guest systems[13] that offer wide-ranging utility and applications.

Unlike coordination cages[14] and metal–organic frameworks,[15] a molecular host possesses an inherent ability to encapsulate guests, regardless of its relative speciation or assembly. While there is typically a high degree of complementarity between the host and guest of any given inclusion complex,[16] the vast majority of these systems remain unaffected by the application of an external stimulus, although the ability to induce a conformational change in the host so as to perturb its binding efficacy is known.[17] Nevertheless, the allosteric modulation of guest binding within synthetic systems remains a relatively rare occurrence.

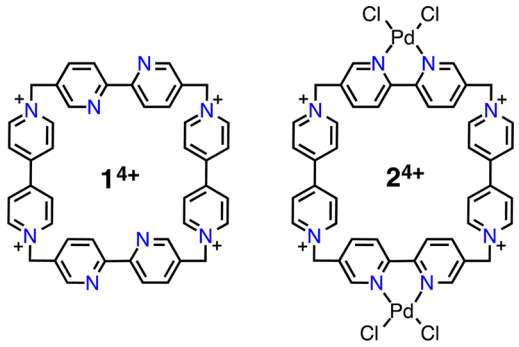

Figure 1. Structural formulas of the two hosts employed in this investigation.

In recent years, we have investigated extensively the inclusion and recognition properties of a series of polycationic cyclophanes[18] and cages,[19] the majority of which possess the ability to sequester polyaromatic hydrocarbons from both organic and aqueous media. Their ability to select for and bind guests is typically governed by the stereoelectronic properties of the receptor. In addition to their inclusion chemistry, polycationic cyclophanes have been shown[20] to form a variety of mechanically interlocked molecules, such as catenanes, rotaxanes, and artificial molecular machines.

Here we report the preparation of a tetracationic molecular receptor $\mathbf{1}^{4+}$ (Figure 1) that exhibits positive allosteric modulation of substrate (ferrocene, Fc) binding upon the application of a heterotropic effector ($PdCl_2$). This modulation is fully reversible, and guest binding can be both enhanced and diminished through the stepwise addition and removal of the effector.

The molecular receptor $\mathbf{1}^{4+}$ was designed such that it can interact independently with two orthogonal molecules and that the binding of a secondary effector, away from the active site, does not preclude the binding of the primary substrate. The square framework of $\mathbf{1}^{4+}$, which features mutually coplanar 4,4′-bipyridinium and 2,2′-bipyridine units, allows for its interaction

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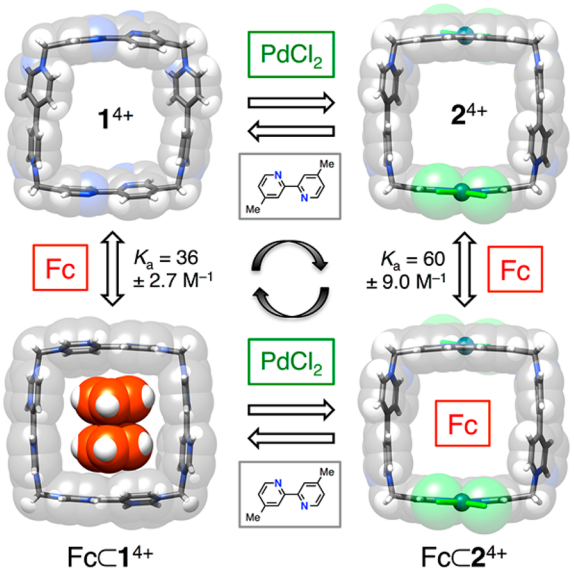

Figure 2. Allosteric modulation of guest binding, relevant equilibria, and additional reversible processes that occur between the species $\mathbf{1}^{4+}$, Fc⊂$\mathbf{1}^{4+}$, $\mathbf{2}^{4+}$, and Fc⊂$\mathbf{2}^{4+}$ in MeCN solution. Illustrations of the tetracationic cyclophanes and their corresponding inclusion complexes are based on their solid-state X-ray crystal (super)structures.

with globular, electron-rich guests within the molecular cavity in addition to its coordination to metal centers.

The molecular square **1**·4PF_6 was synthesized (see the Supporting Information (SI)) in 35% yield and characterized from its ^{1}H and ^{13}C NMR spectra, both of which are in support of a single, high-symmetry species existing in the solution phase. Additional evidence for the formation of $\mathbf{1}^{4+}$ was obtained by high-resolution mass spectrometry (HRMS), where the species $[M - PF_6]^+$ and $[M - 2PF_6]^{2+}$ were detected in the gas phase at m/z = 1111.1988 and 483.1183, respectively.

Diffusion of *i*-Pr_2O vapors into a MeCN solution of **1**·4PF_6 afforded crystals after 1 week that were analyzed by single-crystal X-ray diffraction (XRD) methods. The solid-state structure (Figure 2) shows that the molecular cavity of $\mathbf{1}^{4+}$ measures 1.07 × 1.09 nm and has an accessible window of ∼1.17 nm^2. As such, it has the spatial requirements necessary to accommodate globular, electron-rich guests such as Fc. The formation of the host–guest inclusion complex Fc⊂$\mathbf{1}^{4+}$ was confirmed by ^{1}H NMR spectroscopy (Figure 3). On the addition of 1 equiv of Fc to a solution of **1**·4PF_6 in CD_3CN, the Fc-H proton resonance shifted upfield from 4.16 to 4.02 ppm, indicative of guest encapsulation. Likewise, the bipyridinium α-H and β-H protons of the host were mutually shielded upon guest encapsulation, suggesting that the cyclopentadienyl rings of Fc and the 4,4′-bipyridinium units of the host are orientated coplanar with respect to one another and interact through π–π interactions. This conclusion was further supported by 2D nuclear Overhauser effect spectroscopy, where through-space correlations were identified between the α-H and β-H bipyridinium protons of the host and the cyclopentadienyl protons of the guest—such through-space correlations can only transpire if these two aromatic units are mutually coplanar.

^{1}H NMR titration was carried out to assess the strength of interaction between $\mathbf{1}^{4+}$ and Fc in CD_3CN solution, where an association constant (K_a) of 36.0 ± 2.7 M^{-1} for the inclusion complex Fc⊂**1**·4PF_6 was determined. The strength of Fc binding is therefore weak and suggests fast exchange on the ^{1}H NMR time scale.

The observation of a charge-transfer (CT) band centered at 452 nm in the UV–vis absorption spectrum of Fc⊂$\mathbf{1}^{4+}$ confirmed the formation of the host–guest inclusion complex. The relative intensity of this CT band reflects the weak association between the two components and is in agreement with the low binding constant determined by ^{1}H NMR spectroscopy.

The Fc⊂$\mathbf{1}^{4+}$ inclusion complex (Figure 2) was also analyzed in the crystalline solid state, but owing to a significant amount of both molecular and crystallographic disorder, it was not possible to deduce clearly the orientation of Fc within the host. In comparison with the solid-state structure of $\mathbf{1}^{4+}$, the tetracationic framework in Fc⊂$\mathbf{1}^{4+}$ displays a structural distortion in which the cavity, measuring 1.07 × 1.07 nm, is decreased in area from 1.17 to 1.14 nm^2. While this constriction of $\mathbf{1}^{4+}$ may be subtle, it does indicate that even a minor structural perturbation can enhance the embrace of an intracavity guest. Although it is not possible to define the exact orientation of the guest, aromatic interactions between the encapsulated Fc and the tetracationic host are observed, with centroid separations between neighboring π-systems measuring 3.68 Å.

Addition of 2 equiv of $PdCl_2(MeCN)_2$ to a MeCN solution of **1**·4PF_6 afforded the palladated congener **2**·4PF_6 in quantitative yield. Analysis by ^{1}H NMR spectroscopy in CD_3CN (Figure 3) revealed the presence of a single, high-symmetry species in which the expected coordination-induced shifts of the 2,2′-bipyridine resonances were observed. The successful metalation was also observed by HRMS, where the species $[M - 2PF_6]^{2+}$ was detected at m/z = 658.9579. Furthermore, the UV–vis absorption spectrum (see the SI) of $\mathbf{2}^{4+}$ illustrates the presence of the palladated 2,2′-bipyridine units with the appearance of new absorbances at 310 and 319 nm. There is also additional evidence for the separation of 4,4′-bipyridinium and 2,2′-bipyridine absorbances,[21] which appear as a single, broad absorbance in the UV–vis absorption spectrum of $\mathbf{1}^{4+}$.

Single crystals of **2**·4PF_6, which were grown by diffusing *i*-Pr_2O vapors into a MeCN solution of the molecular square, were analyzed by XRD. The solid-state structure of $\mathbf{2}^{4+}$ (Figure 2) displays an increased level of distortion when compared with

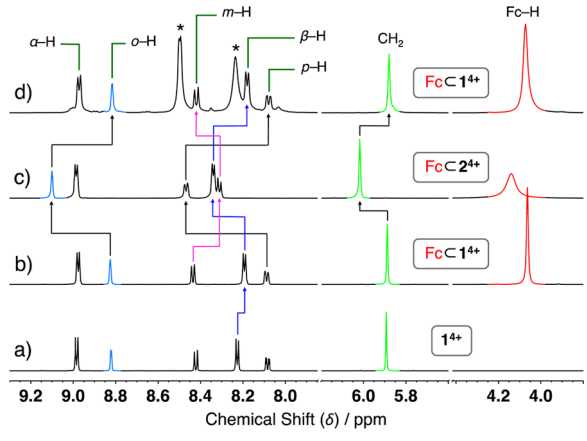

Figure 3. ^{1}H NMR spectra (298 K, 500 MHz, CD_3CN) illustrating the chemically induced, reversible allosteric modulation under investigation. Treatment of $\mathbf{1}^{4+}$ (a) with Fc affords the host–guest inclusion complex Fc⊂$\mathbf{1}^{4+}$ (b). Addition of the heterotopic effector $PdCl_2(MeCN)_2$ to this dynamic system generates the host–guest inclusion complex Fc⊂$\mathbf{2}^{4+}$ (c), in which the binding affinity for Fc is enhanced. This process can be reversed through sequestration of the $PdCl_2$ effector by 4,4′-dimethyl-2,2′-bipyridine, where the source of allosteric modulation is removed and the host–guest inclusion complex Fc⊂$\mathbf{1}^{4+}$ (d) is regenerated.

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both $\mathbf{1}^{4+}$ and Fc⊂$\mathbf{1}^{4+}$. The molecular cavity of $\mathbf{2}^{4+}$ measures 1.06 × 1.07 nm and has an accessible binding window of ∼1.13 nm^2. Although this distortion may appear insignificant, this molecular constriction leads to a 0.3 Å decrease in the separation between the coplanar bipyridinium units that, when considered in terms of $\pi-\pi$ interactions, could be advantageous for the formation of an inclusion complex. The tetracationic framework of $\mathbf{2}^{4+}$ is also rigidified, and the torsional angles are considerably reduced (see the SI), which may, in turn, lower the entropic cost of Fc encapsulation. It was predicted that these structural perturbations, coupled with the increased electron deficiency of the tetracationic cyclophane, would enhance its ability to form inclusion complexes.

Formation of the host−guest inclusion complex Fc⊂$\mathbf{2}^{4+}$ was established by ^{1}H NMR spectroscopy (Figure 3). The addition of 1 equiv of Fc to a solution of $\mathbf{2}\cdot 4PF_6$ in CD_3CN solution led to shifts in the Ar-H resonances of the tetracationic framework that were similar to those observed for Fc⊂$\mathbf{1}^{4+}$, indicating that the relative orientation of Fc in both $\mathbf{1}^{4+}$ and $\mathbf{2}^{4+}$ is the same, in spite of the palladation. Although the mode of Fc interaction and its relative orientation within both $\mathbf{1}^{4+}$ and $\mathbf{2}^{4+}$ are consistent for both Fc⊂$\mathbf{1}^{4+}$ and Fc⊂$\mathbf{2}^{4+}$ inclusion complexes, the observed changes in the chemical shifts of the Fc-H protons are quite different. While the resonance for the Fc-H protons in Fc⊂$\mathbf{1}^{4+}$ is well-defined, the corresponding signal for the Fc-H protons in Fc⊂$\mathbf{2}^{4+}$ is broadened significantly, suggesting slower host−guest exchange on the ^{1}H NMR time scale. In spite of this observation, coalescence of the signal for the Fc-H protons was not observed, even when the sample was cooled to −40 °C. ^{1}H NMR titration was used to determine $K_a = 60.0 \pm 9.0\ M^{-1}$ for the binding of Fc by $\mathbf{2}\cdot 4PF_6$ in CD_3CN solution (see the SI). This ∼2-fold increase in K_a (when compared to that of Fc⊂$\mathbf{1}^{4+}$) can be related to the structural modulation that is observed between $\mathbf{1}^{4+}$ and $\mathbf{2}^{4+}$ in the solid state, in addition to the increased electron deficiency of the palladated host.

The UV−vis absorption spectrum of Fc⊂$\mathbf{2}^{4+}$ provides a great deal of structural information in relation to the nature of the host−guest interaction. First, the CT band that arises from Fc encapsulation, centered on 437 nm, is of greater intensity than that for Fc⊂$\mathbf{1}^{4+}$ and is significantly more pronounced. This observation is consistent with the conclusions reached by ^{1}H NMR spectroscopy and provides qualitative evidence that $\mathbf{2}^{4+}$ forms a more stable inclusion complex with Fc than does $\mathbf{1}^{4+}$. A closer examination of these absorption spectra confirms that the cyclopentadienyl rings of Fc within Fc⊂$\mathbf{2}^{4+}$ are arranged coplanar with the 4,4′-bipyridinium units of the host and that the two interact through $\pi-\pi$ interactions (see the SI). Whereas the absorption band of the palladated 2,2′-bipyridine unit remains unaffected by Fc encapsulation, the absorption band of the 4,4′-bipyridinium unit becomes red-shifted,[21] an observation that is consistent with the two components interacting through face-to-face aromatic interactions.

To support the notion of positive allosteric modulation, an equilibrated sample of Fc⊂$\mathbf{1}^{4+}$ in CD_3CN was treated with 2 equiv of $PdCl_2(MeCN)_2$ to immediately afford the inclusion complex Fc⊂$\mathbf{2}^{4+}$ and to concomitantly enhance the binding of Fc, as observed by ^{1}H NMR spectroscopy (Figure 3). Here, the heterotropic effector $PdCl_2$ associates well away from the molecular cavity of Fc⊂$\mathbf{1}^{4+}$ and serves to alter the stereoelectronic properties of the host and, as a result of positive modulation, enhance the binding of the Fc substrate by the receptor. It is worth noting that the ^{1}H NMR spectrum of Fc⊂$\mathbf{2}^{4+}$ acquired by this route is identical to the spectrum obtained upon the treatment of $\mathbf{2}^{4+}$ with Fc.

We infer that the association of the effector to Fc⊂$\mathbf{1}^{4+}$ induces structural perturbations where the tetracationic framework is both constricted and rigidified, while the torsional angles are decreased (see the SI). It is believed that these structural changes are the primary source of the allosteric modulation and are responsible for the enhancement of Fc binding by the host. This positive allosteric modulation can be subsequently and quantitatively reversed by the addition of the sequestering agent 4,4′-dimethyl-2,2′-bipyridine, which acts to chelate the $PdCl_2$ from Fc⊂$\mathbf{2}^{4+}$ and return the dynamic system to Fc⊂$\mathbf{1}^{4+}$, where guest binding is diminished. This conclusion was supported by ^{1}H NMR spectroscopy (Figure 3), in which the diagnostic Fc-H proton was used as a probe.

Through a series of solution-phase experiments and a thorough examination of the crystalline solid state, we have developed a dynamic host−guest system that operates under allosteric control. The ability to modulate quantitatively and reversibly the binding affinity of a receptor for its substrate has implications for the selective encapsulation and separation of guests, and anticipates their application in areas such as cargo delivery and toxin sequestration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08656.

Experimental details and characterization data (PDF)
X-ray data for $\mathbf{1}\cdot 4PF_6(MeCN)_6$ (CIF)
X-ray data for $\mathbf{2}\cdot 4PF_6(DMSO)_4$ (CIF)
X-ray data for Fc⊂$\mathbf{1}\cdot 4PF_6$ (CIF)

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Notes

The authors declare no competing financial interest.

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