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Multivalent Crown-ether Receptors Enable Allosteric Regulation of Anion Exchange in an Fe_4L_6 Tetrahedron

Larissa K. S. von Krbek,[‡] Derrick A. Roberts,[‡] Ben S. Pilgrim, Christoph A. Schalley,* Jonathan R. Nitschke*

Abstract: We report a strategy for regulating the rate of internally-bound anion exchange within an Fe_4L_6 metal-organic tetrahedron through external coordination of tripodal tris(alkylammonium) cations. The cage features three flexible 18-crown-6 receptors at each of its Fe^{II} vertices, facilitating strong tritopic interactions with tris(ammonium) cations to 'cap' the vertices of the tetrahedron. This capping mechanism restricts the flexibility of the cage framework, thereby reducing the rate of anion exchange within its central cavity by 20-fold. Thus, we demonstrate the first use of an externally-bound multivalent effector to allosterically control internal guest binding in a molecular cage.

Molecular containers exhibit a broad range of host-guest behaviors that render them useful for catalysis,[1] reactivity modulation,[2] sensing,[3] chemical sequestration,[4] separation,[5] and delivery.[6] The nature of host-guest interactions depends on factors that include the favorability of guest solvation, the shape and size of the container's inner cavity and the flexibility of its outer framework. This latter property can influence the rates of guest exchange, since a common mode of guest uptake and release involves squeezing through openings around the host framework.[7]

For self-assembled metal–organic "cage" molecules, the flexibility of the metal–ligand framework is fixed for each set of building blocks,[8] leading to fixed exchange rates for each guest–cage pair.[9] Designed mechanisms to change the rate of guest exchange in response to signals can enable stimuli-controlled guest capture and release.[10] For instance, Clever and co-workers harnessed light-mediated reactions to switch a Pd_2L_4 cage between flexible and rigid ligand configurations, thereby regulating the uptake and release of $B_{12}F_{12}^{2-}$.[11] The Mirkin group also prepared an allosterically regulated cage-like receptor capable of reversible drug encapsulation in response to anionic effectors.[12]

Here we demonstrate an alternative strategy for modulating cage flexibility by using multivalent effectors restrict the cage's conformational freedom. Multivalent interactions are promising in this context, as they can achieve high affinity through multi-point interactions.[13] However, the design of appropriate multivalent receptors is restricted by synthetic feasibility, especially when integrating them into sophisticated molecular architectures.[14] To circumvent this issue, we have developed a one-pot self-assembly strategy that conveniently incorporates multivalent receptors into a cage framework while avoiding pre-synthesis of complex building blocks. Fe_4L_6 tetrahedral cage **1** features three flexible benzo-18-crown-6 receptors at each of its four Fe^{II} vertices (Figure 1a). The geometry of **1** causes three crowns to converge at each *fac*-Fe^{II} vertex, grouping them into sets of *pseudo*-C_3-symmetric trivalent receptors while simultaneously generating the tetrahedral cage.

Cage **1** can bind guests in two ways: internal anion capture in its central cavity, and external capping of the vertex receptors by tripodal trisammonium cations. These two binding modes are allosterically linked[15] such that binding of an external guest influences the rate of internal anion exchange. We attribute this allostery not to a physical blockage of the cage portals, but rather to restriction of cage flexibility upon trivalent vertex capping. Depending on the size of the tris(ammonium) cation, anion exchange could be slowed by up to 20-fold.

Tetrahedron **1** was prepared as a PF_6^- inclusion complex, ($PF_6 \subset$ **1**), by the assembly of dialdehyde **A** (6 equiv) and 18-crown-6 aniline **B** (12 equiv) around iron(II) cations (4 equiv) and a PF_6^- internal template anion (1 equiv) (Figure 1a). NMR and ESI-MS analyses confirmed formation of the expected *T*-symmetric Fe_4L_6 complex (SI, Section S3). As with other tetrahedra derived from dialdehyde **A**,[16] cage **1** required an anion template to form. Attempts to prepare **1** using only triflimide (NTf_2^-), which is too large for the central cavity, failed to produce a discrete supramolecular species (SI, Figure S11).

We anticipated that the vertex receptors of **1** would bind tris(ammonium) cations, thereby 'capping' the tetrahedron. To test this hypothesis, we prepared tris(triflimide) salts of tris(2-aminoethylamine) **C** and tris(3-aminopropylamine) **D** (SI, Section S4). Molecular mechanics models of **C** bound to **1** indicated that vertex-capping was sterically feasible (Figure 1a), whereas an alternative face-blocking mode was deemed unlikely as it would require extreme distortion of the ligand framework (SI, Figure S16).

Binding of **C** to ($PF_6 \subset$ **1**) was studied by ^{1}H NMR titration. Increasing the relative concentration of **C** caused new signals corresponding to 'capped' vertices to appear, which were in slow

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exchange with signals of the 'uncapped' vertices (Figures 1b–d). Capping of each vertex was inferred to occur independently of its neighbors due to the large distance between them. Complete disappearance of the uncapped vertex signals occurred at a 4:1 molar ratio of **C** to ($PF_6 \subset$ **1**). Strong binding of one equivalent of **C** to each vertex of **1** to form the fully-capped species $\mathbf{C}_4$·($PF_6 \subset$ **1**) was confirmed by ^{1}H DOSY (Figure 1e) and ROESY (SI, Figures S24,S25) NMR. Additionally, the methylene ^{1}H signals of **C** were split into diastereotopic pairs when bound to **1**, indicating chiral induction by the nearby Δ or Λ Fe^{II} center (SI, Figure S19). Downfield shifts of up to $\Delta\delta$ = 1.04 (for H_e, Figure 1d) that followed binding of **C** are consistent with the positions of these protons with respect to nearby aromatic ring current fields (SI, Figure S18). Notably, we observed no evidence of amine exchange between **C** and aniline **B**, reflecting the low nucleophilicity of the protonated amines (Figure S40 and S41).

Low-temperature (233 K) ^{19}F NMR experiments revealed that vertex capping also alters the environment of the PF_6^- ion within cage **1** (SI, Section S6.2). This observation indicates mechanical coupling between the vertex receptors and the ligands that border the internal cavity of the cage.

We monitored the formation of capped tetrahedra by ^{19}F NMR to further elucidate the association of **C** to ($PF_6 \subset$ **1**). The speciation profile indicated stepwise association (Figure 2) that followed a hypergeometric distribution (SI, Figure S38b). Attempts to fit our data using Pauling's cooperativity model[17] did not indicate cooperative binding, further supporting our hypothesis that the vertex receptors operate independently. ESI-FTICR-MS titration data also supported this conclusion (SI, Section S6.1). Assuming non-cooperative association, we determined the intrinsic association constant[18] of **C** to one vertex receptor of ($PF_6 \subset$ **1**) to be on the order of 10^4 M^{-1} (SI, Section S6.2.2), consistent with strong, multivalent binding.

Larger trication **D** exhibited similar behavior to **C** (Figure 2f; SI, Sections S5.2, S6), albeit with smaller chemical shift changes between uncapped and fully-capped states, and no diastereotopic splitting of the methylene protons of **D**. These observations reflect the greater flexibility of **D**'s longer alkyl 'legs' compared to **C**, which allows **D** to bridge the crown ethers without restriction. The association constant determined from ^{19}F NMR titrations was within the same order of magnitude as that of **C**.

Mixed-cap NMR and MS experiments (SI, Section S7) showed that the receptors expressed no preference between **C** and **D**. Consequently, ($PF_6 \subset$ **1**) reversibly bound all possible cap combinations. Moreover, ^{1}H EXSY NMR allowed us to determine that the forward and backward exchange rate constants for the displacement of **C** by **D** at one site were approximately equal ($k \approx 0.7$ s^{-1}) for an equimolar mixture of **C** and **D**. The multivalent vertex–cap interaction thus engenders strong binding, reaching saturation at 1:1 cap/vertex stoichiometry, while maintaining reversibility.

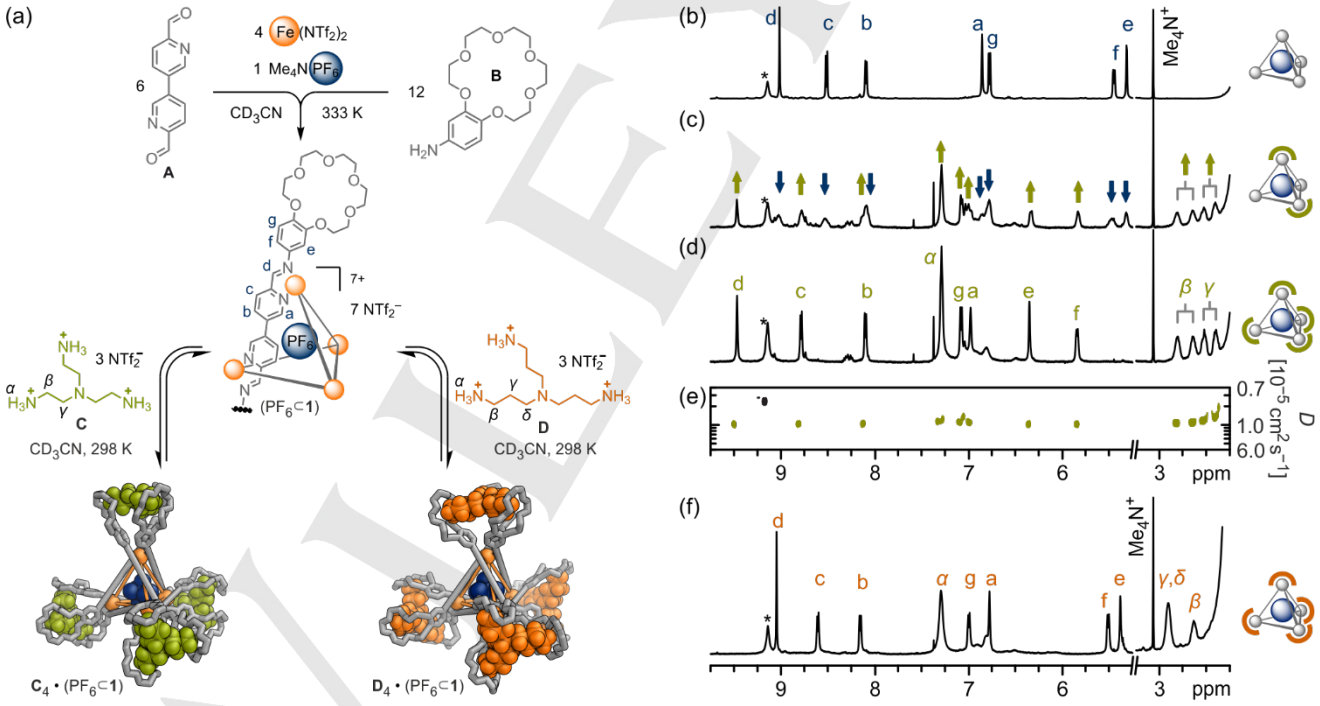

Figure 1. (a) Synthesis of tetrahedral cage ($PF_6 \subset$ **1**) and trivalent cation 'capping' of vertex receptors. (b–d) ^{1}H NMR spectra (500 MHz, 298 K, CD_3CN) of the stepwise addition of **C** (0, 2, 4 equiv.) to ($PF_6 \subset$ **1**). (e) ^{1}H DOSY of $\mathbf{C}_4$•($PF_6 \subset$ **1**). Asterisks denote signals which do not belong to the cage framework, as can be seen in the DOSY. (f) ^{1}H NMR spectrum of a 4:1 mixture of **D** to ($PF_6 \subset$ **1**).

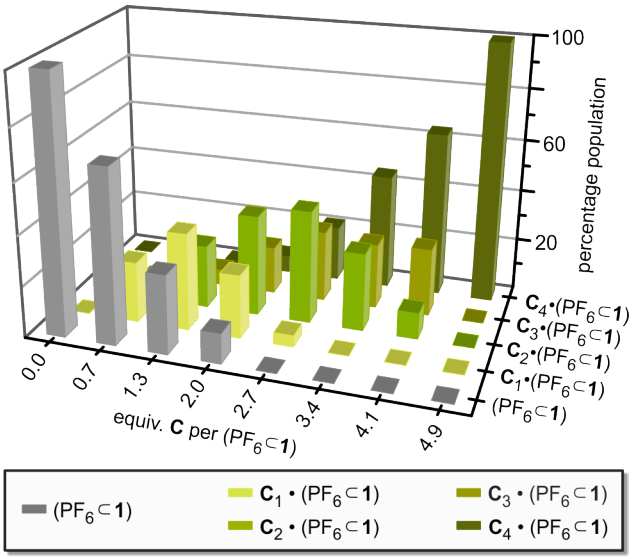

Figure 2. Speciation profile for the association of **C** to (PF_6 ⊂ **1**) derived from a low temperature (233 K) ^{19}F NMR titration of **C** into (PF_6 ⊂ **1**) (SI, Figure S36).

Coupling between the external vertex receptors of (PF_6 ⊂ **1**) and its internal cavity, revealed by ^{19}F NMR, prompted us to explore how caps **C** and **D** influence the rate of internal anion exchange. Using NMR and MS (SI, Section S8), we found that ReO_4^- displaced PF_6^- from **1**, reflecting its better size and shape complementarity for the tetrahedral cavity. The addition of Bu_4NReO_4 (1.3 equiv) to (PF_6 ⊂ **1**) caused a new set of signals corresponding to (ReO_4 ⊂ **1**) to appear in the ^{1}H NMR spectrum (SI, Figure S46), indicating anionic guest exchange to be slow on the ^{1}H NMR timescale. Guest exchange reached equilibrium after 19 h, achieving a maximum (ReO_4 ⊂ **1**) proportion of ≈45 mol%. In separate experiments, capped cages **C_4**·(PF_6 ⊂ **1**) and **D_4**·(PF_6 ⊂ **1**) also underwent anion exchange with ReO_4^- to reach a similar equilibrium distribution of (ReO_4 ⊂ **1**) and (PF_6 ⊂ **1**).

While vertex capping did not change the position of the anion host–guest equilibrium, the kinetics of guest exchange were impacted by the size of the cap. For uncapped (PF_6 ⊂ **1**) and **D_4**·(PF_6 ⊂ **1**), PF_6-to-ReO_4 exchange reached a limit of ≈45% within 19 h (Figure 3; SI, Figures S46,S48). **C_4**·(PF_6 ⊂ **1**), by contrast, underwent guest exchange 20 times more slowly than (PF_6 ⊂ **1**) and **D_4**·(PF_6 ⊂ **1**). We propose that vertex-capping of (PF_6 ⊂ **1**) by cation **C**, with its shorter alkyl 'legs', restricts the flexibility of the cage framework by rigidly tethering together the ends of the ligands (Section S8.4). Conversely, the similar guest exchange rates for **D_4**·(PF_6 ⊂ **1**) and uncapped (PF_6 ⊂ **1**) indicated that the longer and more flexible 'legs' of **D** allowed cage **1** to retain the same degree of flexibility exhibited by its uncapped state. Putative interactions between the trications and ReO_4^- do not account for the observed differences in exchange rates (Section S8.5). Thus, we conclude that expansion of the apertures to enable guest exchange[7] is unchanged by **D** and slowed by **C**.

In conclusion, we have demonstrated a new approach for modulating the rate of internal anion exchange within a self-assembled cage complex using a multivalent allosteric effector that exhibits high binding affinity and facile reversibility. The coordination-driven self-assembly approach employed in this work provides a convenient one-pot route for incorporating multivalent receptors into a metallocage complex, adding to the growing suite of metal–templated synthesis strategies.[19] Our approach is modular and we envisage that the trivalent crown-ether receptors reported herein could be incorporated readily into other metallosupramolecular architectures, enabling further exploration of multivalent binding modes to control the host–guest behavior of molecular containers.

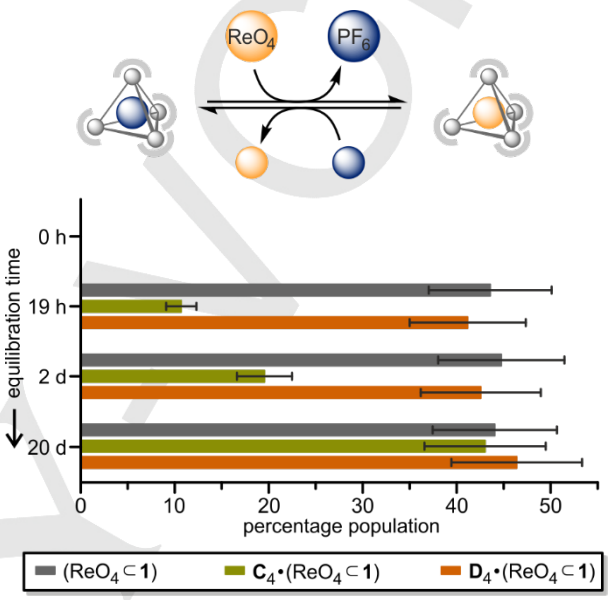

Figure 3. Time-dependent population changes of (ReO_4 ⊂ **1**), **C_4**·(ReO_4 ⊂ **1**), and **D_4**·(ReO_4 ⊂ **1**) (gray, green, orange) following hexafluorophosphate-to-perrhenate guest exchange, determined by ^{1}H NMR (SI, Figures S46–S50).

Acknowledgements

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Keywords: cage compounds • host-guest systems • self-assembly • multivalency • allostery

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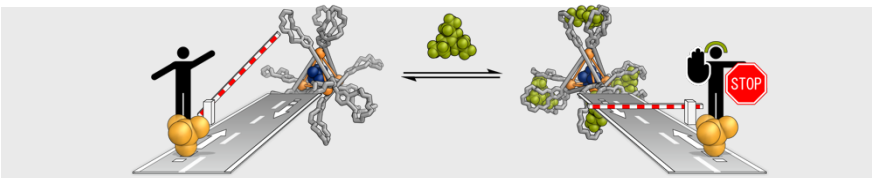

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Multivalent Crown-ether Receptors Enable Allosteric Regulation of Anion Exchange in an Fe_4L_6 Tetrahedron

Multivalent metal-organic cage receptors were prepared in a single step via subcomponent self-assembly. A tetrahedral metal-organic cage was functionalized with four trivalent receptors. These multivalent receptors in turn changed the guest exchange behavior of the cage cavity. Guest exchange kinetics were allosterically regulated by multivalent effectors binding to the receptors on the cage vertices.