JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

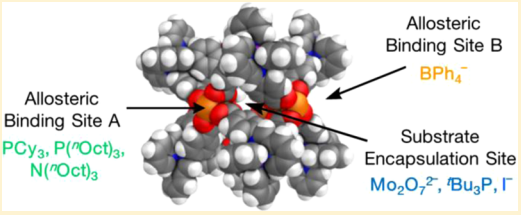
Two Distinct Allosteric Active Sites Regulate Guest Binding Within a $Fe_8Mo_{12}^{16+}$ Cubic Receptor

William J. Ramsay and Jonathan R. Nitschke*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom

Supporting Information

ABSTRACT: The binding of phosphine ligands to molybdenum sites on the faces of a supramolecular cube served to inhibit allosterically the encapsulation of a neutral or anionic guest. The edges of the cube also provided a distinct second allosteric site, where the binding of tetraphenylborate also allosterically inhibited anion binding in the cube's cavity. The two allosteric sites were shown to regulate the binding of an anionic guest either independently or in concert. The use of a tertiary amine as an allosteric effector also enabled a phosphine guest to be ejected from the cube's cavity into solution, to generate phosphine complexes with other metal ions.



INTRODUCTION

Communication between the constituents of a biological network is necessary to generate complex behavior. Moderating this communication is equivalent to carrying out logic operations, and such modulation thus enables a living system to process information.[1]

The replication of such signal transduction between molecular elements in abiological chemical networks is a difficult task to achieve, requiring methods to control signals that are passed between network elements.[2] Allosteric regulation has provided an effective means to achieve this goal. Allosteric effects function in a conceptually similar way to a logic gate, whereby the effects of a signal in one part of a system are modulated by another signal elsewhere. The promise of this type of control has stimulated efforts to develop artificial receptor systems that can be controlled by allosteric effects.[3] Cationic[4] and anionic[5] allosteric effectors are frequently used in contexts both homotropic,[6] where one ion influences the binding of an identical ion in a different site, and heterotropic,[7] where different ions are involved, because Coulombic interactions between ions facilitate these interactions. Fewer systems have been developed using neutral molecules as effectors in homotropic[8] or heterotropic[9] systems, suggesting the presence of additional design challenges.

The development of supramolecular metal−organic cages[10] with cavities to encapsulate guest molecules[11] has provided a platform for the investigation of allosteric regulation in synthetic systems.[12] More complex systems with more than one effector have been developed,[13] but synthetic supramolecular structures that possess multiple, independent allosteric binding sites that can be affected by a range of effectors and can influence the binding affinity of more than one type of substrate remain elusive. These characteristics are valuable, because they can allow complexity to be built up: the more information each logic element can process in a single operation, the fewer logic elements are required to accomplish a computation of a given complexity, and the more elaborate a response can emerge.

Herein we demonstrate multiple allosteric regulation of different substrates' binding within metallo-supramolecular host **1**[14] (Figure 1; Supporting Information Section 1.1). The ligation of neutral coordinating species to the exterior molybdenum sites at the centers of the faces of **1** exhibited a *trans* influence through the Mo−Mo quadruple bond,[15] which inhibited the binding of anionic or neutral encapsulated guests to the interior site. The clefts in the architecture of **1** also created a second allosteric binding site, which inhibited the binding of an anionic guest via a specific anionic effector, tetraphenylborate. The active sites are chemically distinct, yet display additive allosteric effects upon the binding of an anionic guest. The ejection of an encapsulated guest from the host by an allosteric effector was also used to control the guest's subsequent coordination to different metal centers in solution.

RESULTS AND DISCUSSION

Receptor **1** was prepared as previously described,[14] via subcomponent self-assembly[16] of tetrakis(*para*-aminobenzoato)-dimolybdenum(II) (6 equiv) and 2-formylpyridine (24 equiv) around iron(II) template ions (8 equiv). Cube **1** (Figure 1) consists of six metalloligands, which define the cube's faces, and eight Fe^{II} centers, which define the cube's vertices. The four-fold symmetry axes of the ligands and cube derive from the dimolybdenum(II) tetracarboxylate "paddle wheel" motif[17] at the ligands' cores and the cube's three-fold axes are provided by the *fac*-Fe^{II}(tris(pyridylimine)) centers. Each Mo_2 unit thus provides one free molybdenum axial binding site directed outward to the bulk solvent and one site oriented inward to the cavity of **1**.The arrangement of the ligands on the faces of the structure produced clefts at the edges of the cube. The distance

Received: February 20, 2014
Published: April 23, 2014

 © 2014 American Chemical Society dx.doi.org/10.1021/ja501809s | *J. Am. Chem. Soc.* 2014, 136, 7038−7043

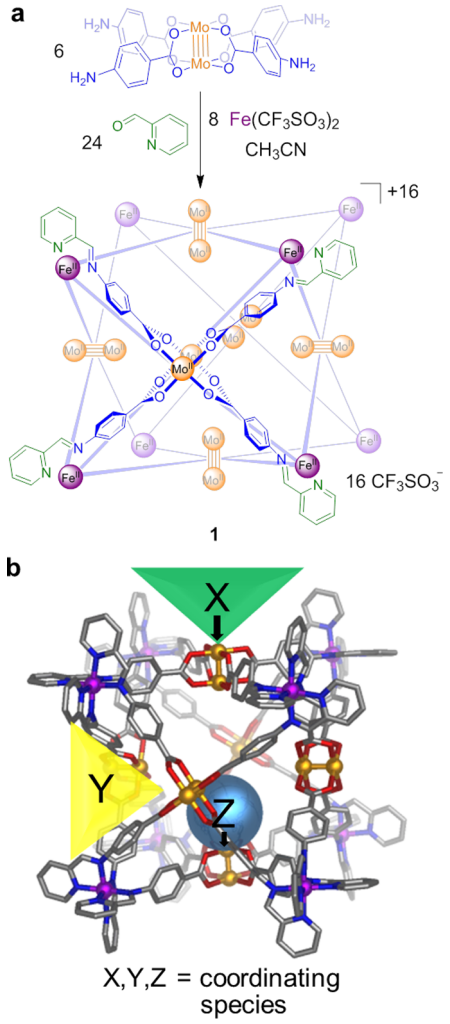


Figure 1. (a) The reaction of tetrakis(*para*-aminobenzoato)-dimolybdenum(II), 2-formylpyridine, and iron(II) triflate in acetonitrile produced host **1** ($Fe_8L_6(OTf)_{16}$); only one **L** environment is shown for clarity. (b) Schematic view of the X-ray structure[14] of **1**, showing the external allosteric regulation sites (**X** and **Y**) of the internally bound guest (**Z**).

between interior-facing molybdenum centers on parallel faces averaged 11.3 Å.

Regulation of Guest Binding via Two Allosteric Sites. An anionic guest, the tetra-*n*-butylammonium salt of dimolybdate ($TBA^+_2Mo_2O_7^{2-}$; Supporting Information Section 1.2.1), and a neutral guest, tri-*tert*-butylphosphine ($^tBu_3P$), were each found to axially coordinate to an interior molybdenum binding site of **1** (Supporting Information Sections 2 and 3, respectively); these species served as substrates to investigate allosteric regulation via external coordination.

When $Mo_2O_7^{2-}$ was titrated into a solution of **1** in CD_3CN, NMR spectra underwent changes consistent with interior $Mo_2O_7^{2-}$ binding (Figures S2 and S3). Additional signals were not observed in the ^1H NMR spectrum of the host–guest complex, reflecting rapid guest exchange between equivalent binding sites on the NMR time scale. The inward-facing host proton signals shifted downfield by only 0.04 ppm due to averaging across six sites during the exchange process. The perturbation of the chemical shift of H^2 is also expected to be minimized due to the substantial distance (estimated to be >4 Å based on triflate coordination to **1** observed in the X-ray crystal structure)[14] between H^2 and the closest coordinating dimolybdate oxygen. Job's Plot analysis confirmed a 1:1 binding stoichiometry (Figure S4), and a binding constant of $2.7 \pm 0.1 \times 10^5$ M^{-1} was obtained through UV–vis titration in acetonitrile (Figure S5).

Neutral $^tBu_3P$ was also observed to bind within **1**, as confirmed by ^{31}P, ^1H, ^{19}F, and DOSY NMR spectra (Figures S6–S10). When $Mo_2O_7^{2-}$ (1.0 equiv) was added to [$^tBu_3P\subset$**1**], dimolybdate was observed to completely displace the phosphine guest (Figure S11); we infer the stronger binding of $Mo_2O_7^{2-}$ within **1** to be a consequence of Coulombic attraction. Although $^tBu_3P$ appeared to be weakly coordinated to the exterior of **1** after it was competitively displaced from the cavity by $Mo_2O_7^{2-}$ (Figure S11), these guests' tandem behavior was not probed further due to the complexity of analyzing a system where $^tBu_3P$ can bind to both interior and exterior sites, potentially competing with the interior binding of $Mo_2O_7^{2-}$ and allosterically inhibiting its binding through two distinct mechanisms.

We next investigated the binding of tricyclohexylphosphine (PCy_3; Supporting Information Section 4) and tri-*n*-octylphosphine (TOP; Supporting Information Section 5) to **1**. In contrast with the cases of $Mo_2O_7^{2-}$ and $^tBu_3P$, however, ^{31}P, ^{19}F, ^1H and DOSY NMR spectra gave results more consistent with the binding of these phosphines to the exterior molybdenum sites of **1** (Figures S12–S21); models suggested that these larger phosphines would not fit within the cavity of **1**.

When $Mo_2O_7^{2-}$ was titrated into a solution of the PCy_3 or TOP adduct of **1** (Figures S22 and S24, respectively), UV–vis spectroscopy revealed the affinity of $Mo_2O_7^{2-}$ for **1** to have decreased to $3.0 \pm 0.7 \times 10^4$ M^{-1} for **1**·PCy_3 (Figure S23) and $1.4 \pm 0.4 \times 10^4$ M^{-1} for **1**·TOP (Figure S25); observations in the ^1H NMR titrations (Figures S22 and S24) were consistent with these results. These bulky phosphines thus serve to allosterically inhibit the binding of dimolybdate (Figure 2). We infer this inhibition to be a consequence of the *trans* effect across the Mo_2 unit.[15] Although spectroscopic evidence suggested that two bulky phosphines bound to the exterior of each equivalent of **1** (Figures S15 and S20), no further

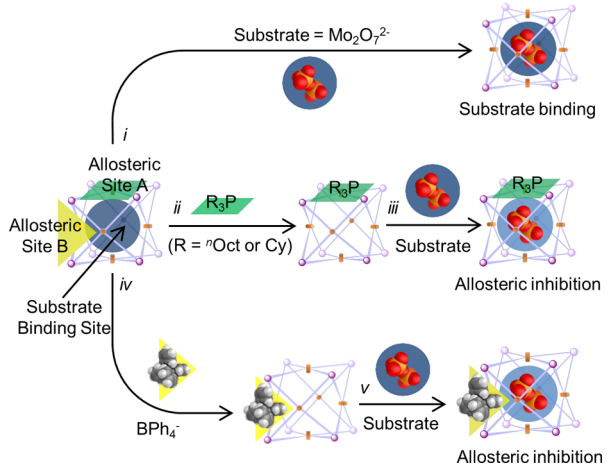


Figure 2. (i) The dimolybdate anion, $Mo_2O_7^{2-}$, was found to bind internally to **1** with high affinity, but when PCy_3 or TOP coordinated to an exterior molybdenum face (allosteric site A; ii) or BPh_4^- associated with the edge (allosteric site B; iv), the binding affinity of $Mo_2O_7^{2-}$ was found to decrease substantially (iii and v, respectively).

dx.doi.org/10.1021/ja501809s | J. Am. Chem. Soc. 2014, 136, 7038–7043

allosteric inhibition of $Mo_2O_7^{2-}$ binding by **1** was observed when more than one equivalent of phosphine was present.

Tetraphenylborate (BPh_4^-, introduced as the TBA salt; Supporting Information Section 1.2.2) was also observed to bind to **1**, but at a different site than any of the other coordinating species studied. Its binding also gave rise to allosteric inhibition of dimolybdate binding, independently of the phosphines' allosteric effects.

Evidence of BPh_4^- binding to **1** was provided by ^1H, ^{11}B and ^{19}F NMR (Figures S26–S31). All spectra were consistent with fast exchange on the NMR time scale, even at −40 °C (Figure S27). A NOESY spectrum allowed us to infer BPh_4^- to bind in a cleft along the cube edge of **1** (Figure 3a). Although **1** possesses 12 edges to serve as prospective BPh_4^- binding sites, a 1:1 binding stoichiometry was identified using a UV–vis Job's Plot (Figure S32). UV–vis titration provided a binding constant of 9.8 ± 0.7 × 10^4 M^{-1} (Supporting Information Section 7.1).

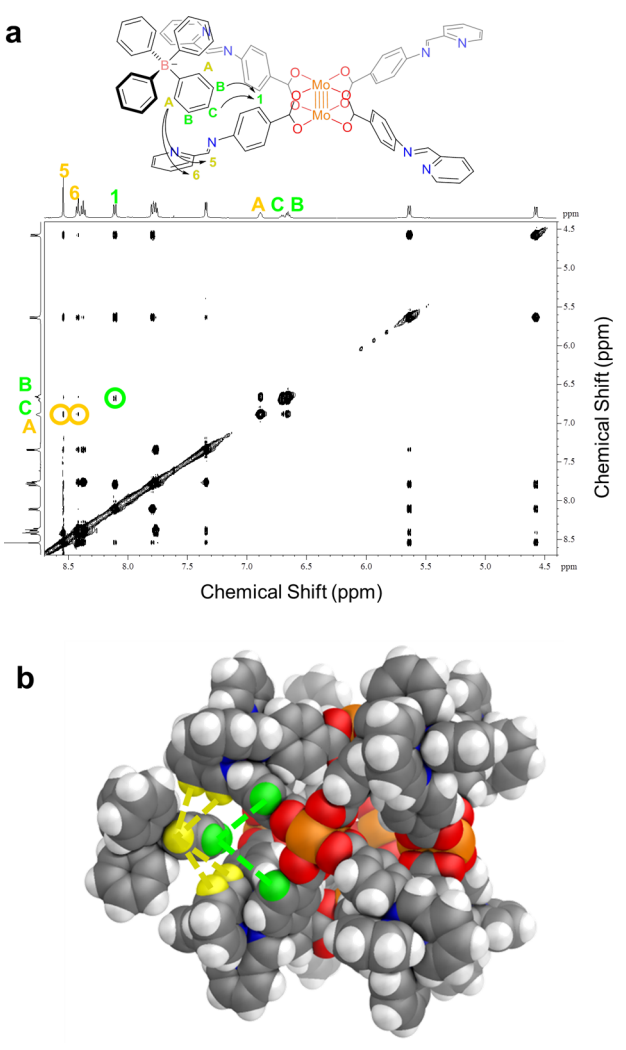


Figure 3. (a) Interaction between BPh_4^- and **1** was observed by NOESY NMR. Correlations between the *ortho* protons of BPh_4^- (H^A) with **1** (H^5 and H^6) are highlighted in yellow, and the correlations between the *meta* and *para* protons (H^B and H^C, respectively) with **1** (H^1) are highlighted in green. (b) Energy-minimized molecular model of BPh_4^- docked with the crystal structure of **1**.[14] Color scheme: dark gray, C; white, H; blue, N; purple, Fe; orange, Mo; red, O; pink, B.

The interaction between **1** and BPh_4^- appears, thus, to involve edge-to-face interactions between the electron-rich π-clouds of BPh_4^- and the host's electron deficient C–H groups,[18] which experienced ^1H NMR shielding as a result (Figures 3 and S27). Tetraphenylborate presented a particularly good size and charge match for **1**'s edge clefts, as little evidence of interaction was observed between **1** and either larger and less π-basic $B(C_6F_5)_4^-$ (Supporting Information Section 1.2.3; Figure S34) or neutral tetraphenylmethane (Figure S35).

In the presence of BPh_4^- (1.3 equiv), the association constant of $Mo_2O_7^{2-}$ was observed to decrease to 3.0 ± 0.7 × 10^4 M^{-1} (Supporting Information Section 7.4) via allosteric inhibition. Further increasing the concentration of BPh_4^- resulted in only marginally reduced binding affinities for $Mo_2O_7^{2-}$, consistent with the observed 1:1 binding stoichiometry of both guests with **1**; similar results were recorded in the ^1H NMR titrations (Figure S36).

We infer the allosteric inhibition by BPh_4^- of $Mo_2O_7^{2-}$ encapsulation within **1** to have occurred through electrostatic repulsion between the substrate and inhibitor through the framework of **1**. This idea was reinforced by the observation that BPh_4^- binding had no apparent effect upon $^tBu_3P$ binding by **1** (Figure S39), whereas spectroscopic evidence indicated $^tBu_3P$ encapsulation to be inhibited by the presence of either PCy_3 (Supporting Information Section 8.2), TOP (Supporting Information Section 8.3), or even excess $^tBu_3P$ (Supporting Information Section 4). The two allosteric effector sites identified within **1** thus modulated guest encapsulation through two chemically distinct mechanisms.

The two individual allosteric sites within **1** are able to independently act to inhibit the binding of $Mo_2O_7^{2-}$ within **1**, without interfering with each other (Supporting Information Section 9). As shown in Table 1, the presence of either TOP or PCy_3 together with BPh_4^- resulted in a combined inhibitory effect upon $Mo_2O_7^{2-}$.

Table 1. Association Constants for $Mo_2O_7^{2-}$ in 1 in the Presence of Different Allosteric Effectors

	allosteric effector			
	PCy_3	TOP	BPh_4^-	K_a (× 10^5 M^{-1})
equiv	0.0	0.0	0.0	2.7 ± 0.1
	1.1	0.0	0.0	0.30 ± 0.07
	0.0	1.0	0.0	0.14 ± 0.04
	0.0	0.0	1.3	0.30 ± 0.07
	1.1	0.0	1.0	0.11 ± 0.04
	0.0	1.0	1.0	0.08 ± 0.04

As halide anions have been shown previously to bind to the interior molybdenum sites of **1**,[14] we investigated the allosteric regulation of the most strongly coordinating halide, iodide (Supporting Information Section 10). The association constant of iodide, as determined by UV–vis spectroscopy, decreased from 4.1 ± 0.5 × 10^4 M^{-1} (in the absence of any allosteric effector) to 3.7 ± 0.3 × 10^4 M^{-1} in the presence of PCy_3 (1.1 equiv), 3.6 ± 0.3 × 10^4 M^{-1} in the presence of BPh_4^- (1.2 equiv), and 3.4 ± 0.3 × 10^4 M^{-1} in the presence of TOP (1.0 equiv) (Figures S47 and S49); ^1H NMR titrations were consistent with these results (Figures S46 and S48). The concerted action of the PCy_3 and BPh_4^- (1.1 equiv of PCy_3 and 1.0 equiv of BPh_4^-) weakened iodide binding strength to 3.0 ± 0.2 × 10^4 M^{-1}, and TOP and BPh_4^- (1.0 equiv of each)

dx.doi.org/10.1021/ja501809s | J. Am. Chem. Soc. 2014, 136, 7038–7043

together reduced iodide affinity to 2.6 ± 0.4 × 10^4 M^{-1}. We infer that $Mo_2O_7^{2-}$ was more responsive to allosteric inhibition than iodide because it is dianionic (incurring stronger Coulombic repulsion by BPh_4^-) and more strongly bound within the cavity of **1** (thus rendering changes in its binding strength more straightforward to quantify).

Allosteric Release of ^{t}Bu$_3$P and Its Subsequent Metal Coordination. Tri-*n*-octylamine (TOA) was also observed to allosterically inhibit the binding of ^{t}Bu$_3$P through exterior binding (Supporting Information Section 11), in similar fashion to TOP. Whereas ^{t}Bu$_3$P remained bound as [^{t}Bu$_3$P⊂**1**] in the presence of excess TOP (Figure S41), the addition of TOA resulted in quantitative expulsion of ^{t}Bu$_3$P, as confirmed by ^{1}H and ^{31}P NMR spectroscopy (Figures S54 and S55); two equivalents of TOA were required to eject the ^{t}Bu$_3$P.

As ^{t}Bu$_3$P can serve as a ligand to a variety of transition metals, we investigated how the TOA-mediated release of ^{t}Bu$_3$P from **1** might be used as in the context of signal transduction, whereby the addition of TOA would prompt the formation of a metal complex containing ^{t}Bu$_3$P (Figure 4).

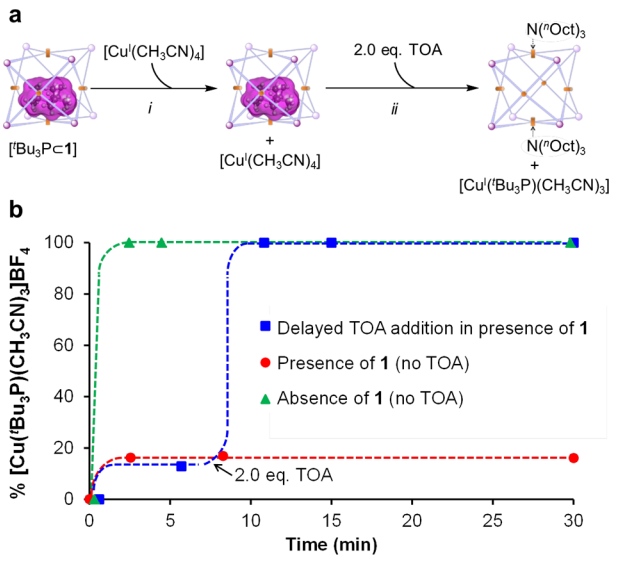


Figure 4. (a) When 1.0 equiv of [Cu^I(CH$_3$CN)$_4$] was added to a solution of [^{t}Bu$_3$P⊂**1**] (i), NMR spectra identified minimal reaction of ^{t}Bu$_3$P with Cu^I. When 2.0 equiv of TOA was added to this solution, ejection of ^{t}Bu$_3$P and production of [Cu^I(^{t}Bu$_3$P)(CH$_3$CN)$_3$] was observed (ii). (b) These results are shown graphically: formation of [Cu(^{t}Bu$_3$P)(CH$_3$CN)$_3$]BF$_4$ in the absence of **1**, in the presence of **1** (with no TOA added) and the experiment in which the addition of TOA was delayed. The delayed addition of TOA at t = 7 min triggered the release of ^{t}Bu$_3$P and thus its reaction with [Cu(CH$_3$CN)$_4$]BF$_4$. The dashed lines indicate the inferred reaction progression.

It has been shown that a solution of ^{t}Bu$_3$P in CD$_3$CN reacts quantitatively with an equimolar solution of [Cu(CH$_3$CN)$_4$]-BF$_4$ to form [Cu(^{t}Bu$_3$P)(CH$_3$CN)$_3$]BF$_4$[19] (Figures S56 and S57). In a control experiment, when ^{t}Bu$_3$P (1.0 equiv) was encapsulated within **1** and [Cu(CH$_3$CN)$_4$]BF$_4$ (1.0 equiv) was added, only 13% conversion to [Cu(^{t}Bu$_3$P)(CH$_3$CN)$_3$]BF$_4$ was observed by ^{1}H NMR spectroscopy (Figure S58; Figure 4). Upon addition of TOA (2.0 equiv) to an equimolar solution of [^{t}Bu$_3$P⊂**1**] and [Cu(CH$_3$CN)$_4$]BF$_4$, quantitative formation of [Cu(^{t}Bu$_3$P)(CH$_3$CN)$_3$]BF$_4$ was observed, as confirmed by ^{1}H and ^{31}P NMR spectroscopy (Figures S59 and S60).

Host **1** was also observed to prevent reaction between encapsulated ^{t}Bu$_3$P and Pd(C$_6$H$_5$CN)$_2$Cl$_2$ in solution (Figure S61). In the absence of **1**, the reaction of 1.0 equiv of ^{t}Bu$_3$P with 0.5 equiv of Pd^{II} (in a coordinating solvent) proceeds rapidly to generate several different square-planar Pd^{II} complexes,[20] confirmed via ^{1}H and ^{31}P NMR spectroscopy (Figures S62–S65). Upon addition of TOA (3.0 equiv) to a solution of [^{t}Bu$_3$P⊂**1**] (1.0 equiv) and Pd(C$_6$H$_5$CN)$_2$Cl$_2$ (0.5 equiv), release of the encapsulated phosphine with concomitant formation of several Pd^{II}(^{t}Bu$_3$P)$_n$ species was confirmed by ^{1}H and ^{31}P NMR (Figures S66 and S67).

CONCLUSIONS

In conclusion, we have shown that an externally binding guest, such as PCy$_3$, TOP, or BPh_4^-, can allosterically reduce the binding affinity of an internally bound anionic guest. The trialkylphosphines that coordinate to the exterior of **1** at molybdenum allosterically inhibit the binding of interior guests, whether they be neutral or negative. As a result of electrostatic repulsion, anionic guest encapsulation can also be allosterically inhibited by BPh_4^-. As the two allosteric active sites act independently of each other, they provide parallel modes of modulating the binding of $Mo_2O_7^{2-}$ or iodide. The effector TOA also brought about allosteric release of ^{t}Bu$_3$P from **1**; the released ^{t}Bu$_3$P could then go on to react with metal ions in solution, highlighting the use of functional container molecules such as **1** in the context of signal transduction.[21] Future work will investigate the use of such signaling to up- and down-regulate the rates of metal-catalyzed reactions.

EXPERIMENTAL METHODS

General. All reagents were purchased from commercial sources and used as received. The solvents were purchased from Sigma-Aldrich; prior to use, diethyl ether and tetrahydrofuran were distilled over sodium, acetonitrile was distilled over calcium hydride, and diglyme and DMF were purchased as anhydrous solvents and used as received. NMR spectra were recorded on Bruker Avance DRX-400, Bruker Avance 500 BB ATM, or Bruker Avance 500 Cryo spectrometers. Chemical shifts for ^{1}H, ^{11}B, ^{13}C, ^{19}F and ^{31}P{^{1}H} are reported in ppm on the δ scale; ^{1}H and ^{13}C were referenced to the residual solvent peak, ^{11}B was referenced to BF$_3$·Et$_2$O at 0 ppm in CDCl$_3$, ^{31}P{^{1}H} was referenced to 85% H$_3$PO$_4$ at 0 ppm in D$_2$O, and ^{19}F was referenced to C$_6$F$_6$ in CD$_3$CN at −164.9 ppm. Coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to describe signal multiplicity for ^{1}H, ^{13}C, and ^{31}P{^{1}H} NMR spectra: s: singlet, d: doublet, t: triplet, m: multiplet, br: broad. DOSY experiments were performed on a Bruker Avance 500 BB ATM spectrometer. Maximum gradient strength was 6.57 G/cmA. The standard Bruker pulse program, ledbpgp2s, employing a stimulated echo and longitudinal eddy-current delay (LED) using bipolar gradient pulses for diffusion using 2 spoil gradients was utilized. Rectangular gradients were used with a total duration of 1.5 ms. Gradient recovery delays were 500–950 μs. Diffusion times were 100 ms. Individual rows of the quasi-2D diffusion databases were phased and baseline corrected. Elemental analyses were obtained on an Exeter Analytical CE-440 Elemental Analyzer. Electronic absorbance spectra were measured in dry acetonitrile with a PerkinElmer Lambda 750 UV–vis NIR spectrometer. Infrared absorbance spectra were measured on a PerkinElmer Frontier IR spectrometer (HeNe 633 nm, <0.4 mW) with Nujol mull on NaCl plates; the following abbreviations were used to describe the wavenumber peaks: s: strong, m: medium, w: weak, sh: sharp, and br: broad. Unless otherwise stated, all reactions were performed under nitrogen.

Synthesis of 1. Host **1** was prepared according to the previously reported method.[14]

dx.doi.org/10.1021/ja501809s | J. Am. Chem. Soc. 2014, 136, 7038–7043

Procedure for ^{1}H, ^{19}F, $^{31}P\{^{1}H\}$, ^{11}B and DOSY NMR Titrations. *General Host–Guest Complexes.* A 0.5 or 0.6 mL solution of **1** ($5.2–5.4 \times 10^{-4}$ M) in CD_3CN was added to a sealed, nitrogen-filled NMR tube, which was titrated with a nitrogen filled, concentrated solution of guest in CD_3CN ($3.0–3.2 \times 10^{-2}$ M). The total change in concentration of the host was 8.5–9.1% over the course of the titration, and the error involved was assumed to be negligible. Upon each addition, the solution was manually stirred for 5 min before acquiring the spectrum, which was sufficient time for equilibrium to be reached between the host and guest.

Allosteric Experiments.

(a) A 0.5 or 0.6 mL solution of **1** ($5.2–5.4 \times 10^{-4}$ M) in CD_3CN was added to a sealed, nitrogen-filled NMR tube, to which was added 1.0 equiv of tri-*tert*-butylphosphine ($^{t}Bu_3P$) or tetra-*n*-butylammonium dimolybdate ($TBA^{+}_2Mo_2O_7^{2-}$) or iodide and the host–guest complex was allowed 5 min to equilibrate. This solution was then titrated with a nitrogen-filled, solution of tetra-*n*-butylammonium tetraphenylborate ($TBA^{+}BPh_4^{-}$), tricyclohexylphosphine (PCy_3), tri-*n*-octylphosphine (TOP) or tri-*n*-octylamine (TOA) in CD_3CN ($3.0–3.2 \times 10^{-2}$ M). The total change in concentration of the host was 4.0–8.5% over the course of the titration, and the error involved was assumed to be negligible. Upon each addition, the solution was manually stirred for 5 min before acquiring the spectrum, which was sufficient for equilibrium to be reached between the host and guest.

(b) A 0.5 or 0.6 mL solution of **1** ($5.2–5.4 \times 10^{-4}$ M) in CD_3CN was added to a sealed, nitrogen-filled NMR tube, to which was added a stoichiometric amount of BPh_4^{-}, PCy_3, or TOP, and the complex was allowed 5 min to equilibrate. This solution was then titrated with a nitrogen-filled, concentrated solution of $Mo_2O_7^{2-}$ or iodide in CD_3CN ($3.0–3.2 \times 10^{-2}$ M). The total change in concentration of the host was 8.5–9.1% over the course of the titration, and the error involved was assumed to be negligible. Upon each addition, the solution was manually stirred for 5 min before acquiring the spectrum, which was sufficient for equilibrium to be reached between the host and guest.

Cumulative Allosteric Experiments. A 0.5 or 0.6 mL solution of **1** ($5.2–5.4 \times 10^{-4}$ M) in CD_3CN was added to a sealed, nitrogen-filled NMR tube, to which was added 1.0 equiv of TOP or 1.0 equiv of PCy_3 and 1.0 equiv of BPh_4^{-}, and the complex was allowed 5 min to equilibrate. This solution was then titrated with a nitrogen-filled, concentrated solution of $Mo_2O_7^{2-}$ or iodide in CD_3CN ($3.0–3.2 \times 10^{-2}$ M). The total change in concentration of the host was 8.5–9.1% over the course of the titration, and the error involved was assumed to be negligible. Upon each addition, the solution was manually stirred for 5 min before acquiring the spectrum, which was sufficient for equilibrium to be reached between the host and guest.

Procedure for UV–vis Titrations. A solution of **1** (either empty or with stoichiometric proportions of appropriate allosteric effectors; $2.3–2.7 \times 10^{-6}$ M) in a nitrogen-filled UV–vis cuvette was titrated with a nitrogen-filled solution of the same concentration of **1** and excess substrate such that the concentration of the host (or host-coordination complex) remained constant with each addition of substrate. Upon each addition, the solution was manually stirred for 2 min before acquiring the UV–vis spectrum.

Procedure for Job's Plots:[22] A series of solutions containing **1** and guest were prepared such that the sum of the total guest and **1** concentration remained constant ($2.3–2.7 \times 10^{-6}$ M). The mole fraction of the guest was varied from 0.1 to 1.0. The corrected absorbance (mole fraction * absorbance at 435 nm) at 435 nm was plotted against the molar fraction of the guest solution.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Preparative procedures and characterization data for the interaction of **1** with $Mo_2O_7^{2-}$, $^{t}Bu_3P$, BPh_4^{-}, PCy_3, TOP, and TOA; characterization data for allosteric inhibition, cumulative allosteric inhibition, and metal coordination complexes with Cu^{I} and Pd^{II} resulting from [$^{t}Bu_3P\subset$**1**]. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jrn34@cam.ac.uk

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Marie Curie Academic-Industrial Initial Training Network on Dynamic Molecular Nanostructures (DYNAMOL).

■ REFERENCES

(1) Ray, D.; Foy, J. T.; Hughes, R. P.; Aprahamian, I. *Nat. Chem.* **2012**, *4*, 757.

(2) (a) de Silva, P. A.; Gunaratne, N. H. Q.; McCoy, C. P. *Nature* **1993**, *364*, 42. (b) Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D. *J. Am. Chem. Soc.* **1992**, *114*, 193.

(3) (a) Kremer, C.; Lützen, A. *Chem.—Eur. J.* **2013**, *19*, 6162. (b) Kovbasyuk, L.; Krämer, R. *Chem. Rev.* **2004**, *104*, 3161.

(4) (a) Tatsuya, N.; Tadashi, I.; Takahiro, S.; Naomichi, F. *Tetrahedron Lett.* **1990**, *31*, 3919. (b) Kobuke, Y.; Kokubo, K.; Munakata, M. *J. Am. Chem. Soc.* **1995**, *117*, 12751. (c) Katoh, A.; Kudo, H.; Saito, R. *J. Supramol. Chem.* **2002**, *2*, 79. (d) Beer, P. D.; Rothin, A. S. *J. Chem. Soc., Chem. Commun.* **1988**, 52. (e) Baylies, C. J.; Harding, L. P.; Jeffery, J. C.; Riis-Johannessen, T.; Rice, C. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4515. (f) Brunet, E.; Juanes, O.; Mata, María; José, de l.; Rodríguez-Ubis, Juan C. *Eur. J. Org. Chem.* **2000**, *2000*, 1913.

(5) (a) Chrisstoffels, L. A. J.; de Jong, F.; Reinhoudt, D. N. *Chem.—Eur. J.* **2000**, *6*, 1376. (b) Uppadine, L. H.; Keene, F. R.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2188. (c) Amendola, V.; Boiocchi, M.; Colasson, B.; Fabbrizzi, L.; Rodriguez Douton, M.-J.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6920. (d) Schneider, H.-J.; Werner, F. *J. Chem. Soc., Chem. Commun.* **1992**, 490. (e) Tobey, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2003**, *125*, 10963. (f) Bondy, C. R.; Gale, P. A.; Loeb, S. J. *J. Supramol. Chem.* **2002**, *2*, 93. (g) Willans, C. E.; Anderson, K. M.; Potts, L. C.; Steed, J. W. *Org. Biomol. Chem.* **2009**, *7*, 2756. (h) Kubik, S. *J. Am. Chem. Soc.* **1999**, *121*, 5846. (i) Nielsen, K. A.; Cho, W.-S.; Sarova, G. H.; Petersen, B. M.; Bond, A. D.; Becher, J.; Jensen, F.; Guldi, D. M.; Sessler, J. L.; Jeppesen, J. O. *Angew. Chem.* **2006**, *118*, 7002.

(6) (a) Rebek, J.; Costello, T.; Marshall, L.; Wattley, R.; Gadwood, R. C.; Onan, K. *J. Am. Chem. Soc.* **1985**, *107*, 7481. (b) Sessler, J. L.; Tomat, E.; Lynch, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 4184. (c) Yagi, S.; Hyodo, Y.; Hirose, M.; Nakazumi, H.; Sakurai, Y.; Ajayaghosh, A. *Org. Lett.* **2007**, *9*, 1999. (d) Thordarson, P.; Bijsterveld, E. J. A.; Elemans, J. A. A. W.; Kasák, P.; Nolte, R. J. M.; Rowan, A. E. *J. Am. Chem. Soc.* **2003**, *125*, 1186. (e) Huang, W.-H.; Liu, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2006**, *128*, 14744.

(7) (a) Sijbesma, R. P.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1991**, *113*, 6695. (b) Ayabe, M.; Ikeda, A.; Shinkai, S.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2002**, 1032. (c) Kubo, Y.; Murai, Y.; Yamanaka, J.-i.; Tokita, S.; Ishimaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6019.

(8) (a) Ebmeyer, F.; Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1148. (b) Takeuchi, M.; Imada, T.; Shinkai, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2096. (c) Chang, S.-Y.; Jang, H.-Y.; Jeong, K.-S. *Chem.—Eur. J.* **2004**, *10*, 4358. (d) Lustenberger, P.; Welti, R.; Diederich, F. *Helv. Chim. Acta* **1998**, *81*, 2190.

(9) (a) Sato, H.; Tashiro, K.; Shinmori, H.; Osuka, A.; Murata, Y.; Komatsu, K.; Aida, T. *J. Am. Chem. Soc.* **2005**, *127*, 13086. (b) Heo, J.; Mirkin, C. A. *Angew. Chem.* **2006**, *118*, 955.
(10) (a) Ward, M. D. *Chem. Commun.* **2009**, 4487. (b) Jin, P.; Dalgarno, S. J.; Atwood, J. L. *Coord. Chem. Rev.* **2010**, *254*, 1760. (c) Chakrabarty, R.; Mukherjee, P. S.; Stang, P. J. *Chem. Rev.* **2011**, *111*, 6810. (d) Albrecht, M.; Shang, Y.; Rhyssen, T.; Stubenrauch, J.; Winkler, H. D. F.; Schalley, C. A. *Eur. J. Org. Chem.* **2012**, *2012*, 2422. (e) Fontenot, S. A.; Cangelosi, V. M.; Pitt, M. A. W.; Sather, A. C.; Zakharov, L. N.; Berryman, O. B.; Johnson, D. W. *Dalton Trans.* **2011**, *40*, 12125. (f) Weilandt, T.; Kiehne, U.; Bunzen, J.; Schnakenburg, G.; Lützen, A. *Chem.—Eur. J.* **2010**, *16*, 2418. (g) Arora, H.; Cano, J.; Lloret, F.; Mukherjee, R. *Dalton Trans.* **2011**, *40*, 10055.
(11) (a) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418. (b) Smulders, M. M. J.; Zarra, S.; Nitschke, J. R. *J. Am. Chem. Soc.* **2013**, *135*, 7039. (c) Mugridge, J. S.; Szigethy, G.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 16256. (d) Custelcean, R.; Bonnesen, P. V.; Duncan, N. C.; Zhang, X.; Watson, L. A.; Van Berkel, G.; Parson, W. B.; Hay, B. P. *J. Am. Chem. Soc.* **2012**, *134*, 8525. (e) Frischmann, P. D.; Mehr, S. H. M.; Patrick, B. O.; Lelj, F.; MacLachlan, M. J. *Inorg. Chem.* **2012**, *51*, 3443. (f) Chung, M.-K.; Severin, K.; Lee, S. J.; Waters, M. L.; Gagne, M. R. *Chem. Sci.* **2011**, *2*, 744. (g) Samanta, S. K.; Schmittel, M. *Org. Biomol. Chem.* **2013**, *11*, 3108.
(12) (a) Freye, S.; Hey, J.; Torras-Galán, A.; Stalke, D.; Herbst-Irmer, R.; John, M.; Clever, G. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 2191. (b) Park, J. S.; Le Derf, F.; Bejger, C. M.; Lynch, V. M.; Sessler, J. L.; Nielsen, K. A.; Johnsen, C.; Jeppesen, J. O. *Chem.—Eur. J.* **2010**, *16*, 848. (c) Yoon, H. J.; Kuwabara, J.; Kim, J.-H.; Mirkin, C. A. *Science* **2010**, *330*, 66.
(13) (a) Rudkevich, D. M.; Brzozka, Z.; Palys, M.; Visser, H. C.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 467. (b) Cooper, J. B.; Drew, M. G. B.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2000**, 2721. (c) Le Gac, S.; Marrot, J.; Reinaud, O.; Jabin, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3123. (d) Jayawickramarajah, J.; Tagore, D. M.; Tsou, L. K.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7583. (e) Oliveri, C. G.; Gianneschi, N. C.; Nguyen, S. T.; Mirkin, C. A.; Stern, C. L.; Wawrzak, Z.; Pink, M. *J. Am. Chem. Soc.* **2006**, *128*, 16286.
(14) Ramsay, W. J.; Ronson, T. K.; Clegg, J. K.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 13439.
(15) Chifotides, H. T.; Catalan, K. V.; Dunbar, K. R. *Inorg. Chem.* **2003**, *42*, 8739.
(16) Ronson, T. K.; Zarra, S.; Black, S. P.; Nitschke, J. R. *Chem. Commun.* **2013**, *49*, 2476.
(17) Cotton, F. A.; Murillo, C. A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*; Springer Science and Business Media, Inc.: New York, 2005.
(18) Chifotides, H. T.; Giles, I. D.; Dunbar, K. R. *J. Am. Chem. Soc.* **2013**, *135*, 3039.
(19) Goel, R. G.; Beauchamp, A. L. *Inorg. Chem.* **1983**, *22*, 395.
(20) Goel, R. G.; Montemayor, R. *Inorg. Chem.* **1977**, *16*, 2183.
(21) (a) Vargas Jentzsch, A.; Hennig, A.; Mareda, J.; Matile, S. *Acc. Chem. Res.* **2013**, *46*, 2791. (b) Gale, P. A.; Pérez-Tomás, R.; Quesada, R. *Acc. Chem. Res.* **2013**, *46*, 2801.
(22) Maity, D.; Govindaraju, T. *Chem. Commun.* **2010**, *46*, 4499.