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

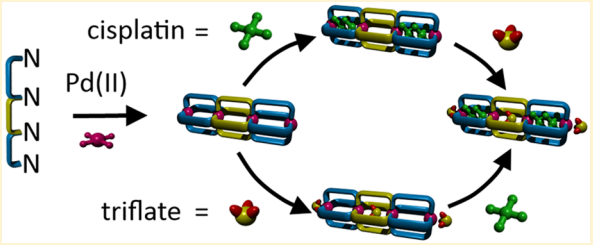
Multicavity $[Pd_nL_4]^{2n+}$ Cages with Controlled Segregated Binding of Different Guests

Dan Preston,[†] James E. M. Lewis,[†] and James D. Crowley*[,†]

[†]Department of Chemistry, University of Otago, P.O. Box 56, Dunedin, New Zealand

Supporting Information

ABSTRACT: Multicavity $[Pd_n(L)_4]^{2n+}$ metallosupramolecular cages based on long backboned ligands are an attractive approach to increasing molecular size without loss of the binding specificity conferred by small cavity $[Pd_2(L)_4]^{4+}$ assemblies. We herein report the synthesis of two double cavity polypyridyl $[Pd_3(L)_4]^{6+}$ cages that bind cisplatin $[Pt(NH_3)_2Cl_2]$ within their internal cavities and interact with triflate (TfO^-) on their exohedral faces. We also report the first example of a triple cavity $[Pd_4(L)_4]^{8+}$ cage. This cage differs in that the central cavity is phenyl-linked rather than having the pyridyl core as in the peripheral cavities. The difference in cavity character results in selective guest binding of cisplatin in the peripheral cavities, with triflate binding within the central cavity and on the exohedral faces of the peripheral palladium(II) ions. All the cavities could be simultaneously filled by introducing both cisplatin and triflate concurrently, providing the first example of a discrete metallosupramolecular architecture with segregated guest binding in different designed internal cavities. The ligands and cages were characterized by NMR spectroscopy, mass spectrometry, elemental analysis, and, in one case, X-ray crystallography.



INTRODUCTION

Using supramolecular interactions, nature is able to self-assemble massive and highly complex structures such as the DNA double helix and folded proteins with an extraordinary degree of fidelity and control. These structures exploit a wide range of molecular recognition events to carry out the processes essential for life. For example, molecular recognition events are responsible for controlling transcription or replication of DNA.[1] In a similar fashion molecular recognition events with proteins are exploited for molecular transport,[2] storage,[3] and catalysis,[4] as well as being used as a method of intramolecular communication and cellular regulation. Often these molecular recognition processes require the capacity to bind multiple guest molecules simultaneously.[5]

Since the inception of metallosupramolecular chemistry, workers have been inspired by nature to create discrete metal-containing architectures[6] of ever increasing complexity and size.[7] The cavities of these architectures have been exploited for molecular recognition and systems designed to bind a wide range of guests including reactive molecules and intermediates,[8] pollutants,[9] and drugs.[10] These impressive results have mostly been achieved using relatively small metallosupramolecular architectures that can only bind one guest molecule. Where the cage architecture has been large enough to encapsulate more than one guest molecule often the binding event remains homoleptic and multiple copies of the same guest are captured.[11]

In order to increase the sophistication and applications of these metallosupramolecular architectures, systems that are able to selectively bind multiple different guests molecules are required. This has been achieved in some examples and has enabled the use of metallosupramolecular architectures as molecular reaction flasks[12] and catalysts.[13] However, while these examples show the potential of these architectures the discovery of systems that are able to bind two (or more) different guest molecules is often carried out by trial-and-error rather than design.[14]

Indeed the design of metallosupramolecular architectures that are able to bind two (or more) different guests selectively is not simple. $[Pd_2(L)_4]^{4+}$ cages,[15] in particular those assembled using pyridyl ligands, have become one of the most common class of metallosupramolecular architectures and have been shown to display wide ranging molecular recognition properties.[16] These $[Pd_2(L)_4]^{4+}$ assemblies have been exploited for binding diverse guests, such as fullerenes,[17] radical initiators,[8b] metal complexes,[16f,18] and anions.[19] However, these $[Pd_2(L)_4]^{4+}$ systems are small and for the most part can only bind up to two guest molecules.[15,16] Fujita and co-workers have generated a series of related larger hollow $[Pd_n(L)_{2n}]^{2n+}$ complexes, where n equals 6, 12, 24, or 30, using bent bis-pyridine ligands and square planar Pd(II) ions (Figure 1a).[20] These larger $[Pd_n(L)_{2n}]^{2n+}$ species possess large cavities that could, in principle, be used to bind a large number of guest molecules. However, in practice, the parent unfunctionalized species have displayed rather limited molecular recognition properties presumably because they have large, undefined cavities with large portals that allow facile, rapid exchange of the

Received: November 20, 2016
Published: January 23, 2017

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

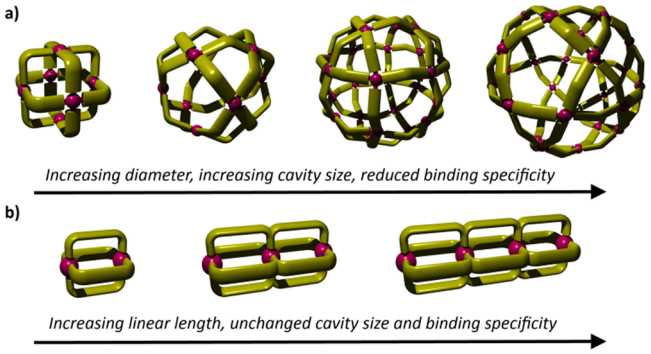


Figure 1. (a) Cartoon representation of the $[Pd_n(L)_{2n}]^{2n+}$ series of cages synthesized by Fujita and co-workers where n = 6, 12, 24, or 30 with increasing cavity size and (b) linearly extending cages with constant cavity size.

guest molecules from the internal space to the external environment. In contrast to the smaller $[Pd_2(L)_4]^{4+}$ systems there are no examples of the larger unfunctionalized $[Pd_n(L)_{2n}]^{2n+}$ species binding neutral guest molecules and only a few examples of binding anionic guests through strong ion−ion interactions.[21] In order to "turn on" guest binding in these larger systems the cavities have to be endo-functionalized with binding units that enhance molecular recognition events.[7a,22] Neutral organic guests such as nile red,[23] C_{60},[24] naphthalenediimide,[24] 1-pyrenecarboxaldehyde,[25] and even cationic cyclobis(paraquat-*p*-phenylene) macrocycles[26] have been bound with this endo-functionalized system. However, the endo-functionalization also reduces the size of the cavity.[27] Therefore, simply increasing the size of the cage cavity of the metallosupramolecular architecture does not automatically lead to systems that will bind more guest molecules. In most cases additional functionalization of the large single cavity is required to overcome the loss of multiple short-contact supramolecular interactions that are required for binding specificity.

An alternative approach to binding multiple different guest molecules selectively within a single metallosupramolecular architecture is to design systems that feature several smaller cavities within a larger self-assembled complex. These types of multicavity metallosupramolecular architectures remain rare. Lehn and co-workers reported heteroleptic copper(I) complexes with oligo-pyridyl ligands and hexaphenylhexaazatriphenylene to give double- and triple-cavity structures, capable of anion binding.[28] Bosnich and co-workers have generated self-assembled rectangles and trigonal prisms that display two or three molecular clefts capable of binding polyaromatic hydrocarbons[29] and planar metal complexes.[30] Several groups[31] have generated multicavity assemblies through interpenetration of discrete $[Pd_2(L)_4]^{4+}$ cages or other Pd(II) assemblies,[32] giving catenated, multicavity products. However, in most of these cases the multicavity metallosupramolecular architectures have only been shown to interact with multiple copies of the same guest molecule.

In 2002 McMorran and Steel,[33] building on their pioneering work on $[Pd_2(L)_4]^{4+}$ cages,[34] proposed that pseudolinear polypyridyl ligands could be exploited to generate tube-like metallosupramolecular architectures which feature multiple cavities of identical size and shape to that of the parent $[Pd_2(L)_4]^{4+}$ cage (Figure 1b).

Building on our own work with $[Pd_2(L)_4]^{4+}$ cages,[18c,19a,35] herein we report the synthesis of pseudolinear penta- and hexapyridyl ligands. These ligands are exploited to generate tube-like[36] double[37] and triple cavity metallosupramolecular architectures. Additionally, the molecular recognition properties of these multicavity architectures remain unchanged. We have previously reported a $[Pd_2(L)_4]^{4+}$ cage (**C1**) based on a 2,6-bis(pyridin-3-ylethynyl)pyridine ligand (**L1**), which binds two molecules of the anticancer drug cisplatin (diamminedichloroplatinum(II)) within the cavity.[18c] The double cavity systems (**C2**, **C2peg**, Scheme 1a) retain the molecular recognition properties of the parent cage but are able to bind twice as much of the guest. The corresponding triple cavity system (**C3peg**, Scheme 1a) contains two different types of cavity. The two terminal cavities are pyridyl lined like the parent **C1** cage, but the central cavity is different and is linked by a 1,3-disubstituted phenyl spacer unit. Titration experiments confirm that these two different cavities are able to selectively bind different guest molecules, demonstrating that these multicavity metallosupramolecular architectures are able to selectively encapsulate multiple different guest molecules in different pockets of the host architecture.

SYNTHESIS AND CHARACTERIZATION

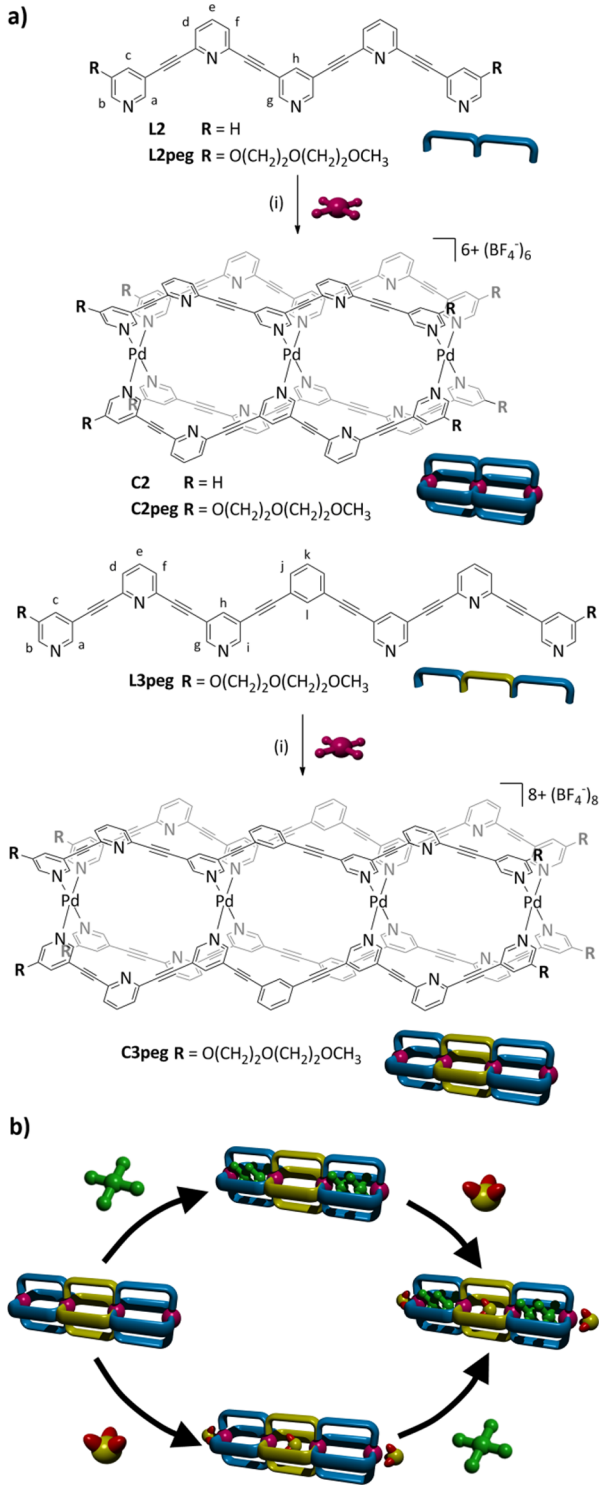
The polypyridyl ligands **L2**, **L2peg**, and **L3peg** (Scheme 1) were synthesized (yields of 71%, 49%, and 70% respectively) via sequential Sonogashira couplings (Supporting Information, Scheme S1.1) using methods analogous to those already reported.[18c,35d] Due to the low solubility of **L2** (and its **C2** cage, *vide infra*) the synthesis of the hexapyridyl analog without PEG solubilizing groups was not attempted. The composition of the ligands was confirmed using elemental analysis, high resolution electrospray ionization mass spectrometry (HR-ESMS), and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy (Supporting Information, Figures S1.1−1.12).

The cages (**C2**, **C2peg**, and **C3peg**) were assembled by heating d_6-DMSO solutions of $[Pd(CH_3CN)_4](BF_4)_2$ (3 or 4 equiv) and the corresponding ligand (**L2**, **L2peg**, or **L3peg** (4 equiv)) at 50−80 °C for 3−8 h (Scheme 1a). These conditions were different from those required for the formation of the parent $[Pd_2(L)_4]^{4+}$ cages (**C1** and **C1peg**[18c,35d]) which are instantaneously assembled at room temperature in acetonitrile, DMF, or DMSO. Presumably the highly coordinating DMSO solvent and the longer reaction times at elevated temperatures are required to facilitate the self-correction process and allow the formation of the tube-like systems. The cages (**C2**, **C2peg**, and **C3peg**) were characterized using ^{1}H, ^{13}C, and DOSY NMR spectroscopies, HR-ESMS, and elemental analysis (Supporting Information, Figures S1.13−1.21 and S2.1 and 2.2). The ^{1}H NMR spectra of the cages (**C2**, **C2peg**, and **C3peg**) display a single set of signals, all shifted downfield relative to the free ligand (Figure 2a and b, Supporting Information, Figures S1.13, 1.16, 1.19, and S2.1). The signals corresponding to those protons adjacent to the nitrogen atoms of the coordinating pyridyl rings were most significantly shifted ($\Delta\delta$ = 0.80−0.50 ppm for H_a, H_b, H_g, H_h, and H_i) (Figure 2a and b and Supporting Information, Figure S2.1).

^{1}H DOSY NMR spectra of the cages (**C2**, **C2peg**, and **C3peg**) were consistent with the formation of a single metallosupramolecular architecture in solution (Supporting Information, Figure S2.2 and Table S2.1). Comparison of the cage diffusion coefficients (D, × 10^{-10} m^2 s^{-1}) to those of the corresponding ligands (D_{L2} = 1.88, D_{L2peg} = 1.43, D_{L3peg} = 1.41, D_{C2} = 0.80, D_{C2peg} = 0.66, D_{C3peg} = 0.62) showed an approximately 2:1 ratio, consistent with results previously obtained for the parent $[Pd_2(L)_4]^{4+}$ cages (**C1** and

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

Scheme 1. (a) Synthesis of Multicavity Cages C2, C2peg, and C3peg;[a] (b) C3peg Exhibiting Selective Binding of Cisplatin in Peripheral Cavities (Top) and Triflate in the Central Cavity and Exohedral Faces (Bottom), with All Binding Sites Occupied in the Presence of Both Guests



[a]Conditions: (i) $[Pd(CH_3CN)_4](BF_4)_2$, d_6-DMSO, 50−80 °C, 3−8 h.

C1peg[18c,35d]). The diffusion coefficient of **C3peg** is smaller than those observed for **C2** and **C2peg** consistent with the larger size of the triple cavity cage, and a plot of log(D) against log(M_W) for ligands and complexes gave a good linear fit (Supporting Information, Figure S2.2).

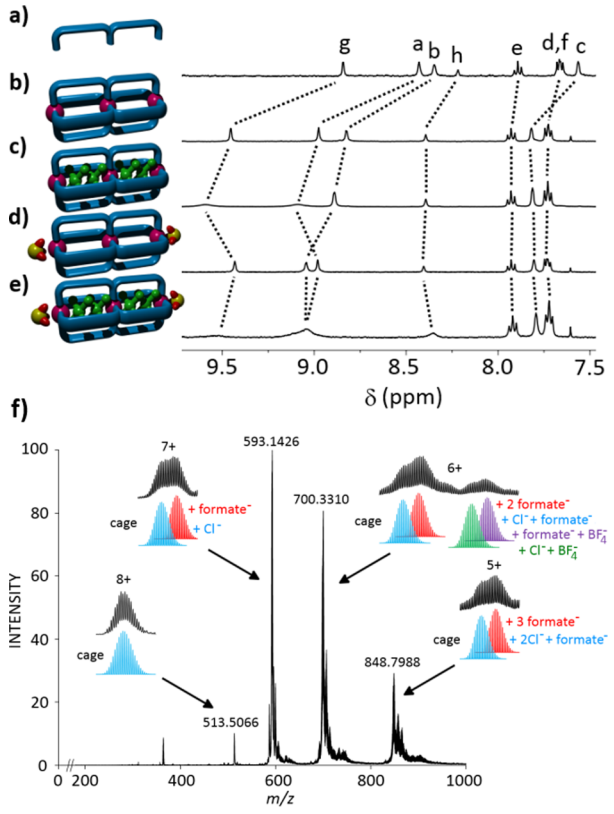


Figure 2. Partial ^{1}H NMR spectra (CD_3CN, 298 K, 400 MHz) of (a) **L2peg**, (b) **C2peg**, (c) (cisplatin)$_4$⊂**C2peg**, (d) (triflate)$_2$⊂**C2peg**, (e) (cisplatin)$_4$(triflate)$_2$⊂**C2peg**, and (f) partial HR-ESI mass spectrum (DMSO/CH_3CN) of **C3peg**, showing observed isotopic distributions in black above and calculated distributions in color below.

HR-ESMS, under pseudocoldspray conditions,[38] provided further support for the formation of the tube-like cages (Figure 2f, Supporting Information, Figures S1.15, 1.18, and 1.21). While the spectra were complicated by varied types and number of anions (formate (HCO_2^-), chloride (Cl^-), and tetrafluoroborate (BF_4^-)), associated under mass spectrometry conditions, a series of isotopically resolved peaks consistent with the presence of the polycationic complexes $[Pd_3($**L2** or **L2peg**$)_4(X)_{6-n}]^{n+}$ and $[Pd_4($**L3peg**$)_4(X)_{8-n}]^{n+}$ (where X = HCO_2^-, Cl^-, or BF_4^- and n = 6, 5, or 4) were observed and deconvoluted (Supporting Information, Figure S1.15).

Additionally, X-ray diffraction-quality crystals were also obtained of **C2** through vapor diffusion of diethyl ether into a DMF solution of the cage. The structure was solved in the triclinic space group $P\bar{1}$. This revealed the anticipated discrete structure with four ligands joined together by three palladium(II) ions giving the desired $[Pd_3(L)_4]^{6+}$ assembly architecture with pseudo-D_{4h} symmetry (Figure 3, Supporting Information, Figures S3.1 and S3.2 and Tables S3.1 and S3.3). Crystallographically the two cavities of the assembly are related by symmetry through a center of inversion through Pd2 and are therefore identical. Two molecules of DMF were found within each of the cavities. The oxygen atoms of the solvent molecules are engaging in quadfurcated hydrogen bonding to the internally directed H_a and H_g hydrogen atoms of the cage. The individual cavities are of similar dimensions to the parent system **C1**,[18] with the distance between the nearest palladium-

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

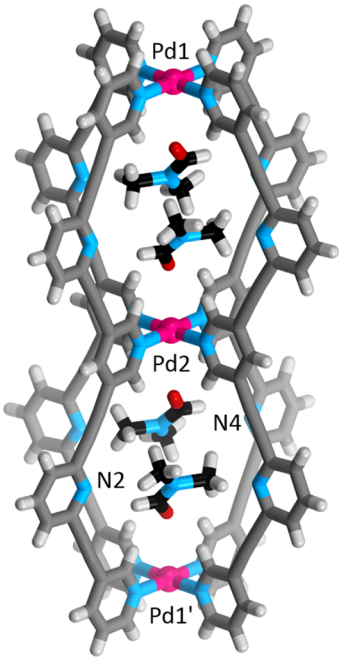


Figure 3. Tube representation of the crystal structure of $(DMF)_4$⊂**C2**. Counterions omitted for clarity. Colors: Cage carbon, gray; DMF carbon, black; hydrogen, white; nitrogen, blue; palladium, magenta. Bond lengths/interatomic distances (Å): Pd1−N1 2.005(5), Pd2−N3 2.004(5), Pd1′−N5 2.009(5), N2---N4′ 10.72(1), Pd1---Pd2 11.7530(6), Pd1---Pd1′ 23.506(1).

(II) ions (Pd1---Pd2) being 11.75 Å, and the distance between opposing endohedral pyridyl nitrogen atoms being 10.72 (N2---N4) and 10.77 Å (N42---N44). The distance between the terminal (ter) palladium(II) ions (Pd1---Pd1′) was thus found to be double that between the central and terminal ions, at 23.51 Å.

Thus, the dicavity cages **C2** and **C2peg** (SPARTAN16, MMFF, Supporting Information, Figure S3.3) are 2.3 and 2.4 nm in length (Pd_{ter}---Pd_{ter} distance), and while we could not confirm the molecular structure of the **C3peg** cage using crystallography, molecular modeling (SPARTAN16, MMFF, Supporting Information, Figure S3.3) indicated that the tricavity system was approximately 3.5 nm in length (Pd_{ter}---Pd_{ter} distance), similar to what would be predicted from the solid state structures of **C1** and **C2**.

■ HOST−GUEST CHEMISTRY

With the structures of these multicavity architectures confirmed we examined the molecular recognition properties of these new systems. The host−guest behavior of the parent $[Pd_2(L)_4]^{4+}$ cage **C1** (generated from 2,6-bis(pyridin-3-ylethynyl)pyridine ligand **L1**) is somewhat limited due to the small size of the cavity. However, we[18c,35a,d,g,h] and others[39] have shown that **C1** and related systems will bind two molecules of cisplatin within the central cavity. We have also shown that **C1** will encapsulate certain anions (nitrate, NO_3^-; mesylate, MsO^-) but not others (toslyate, TsO^-; triflate, TfO^-; hexafluoroantimonate, SbF_6^-).[19a] Hooley et al.[19b,40] and Lusby and co-workers[41] have shown that related cages $\mathbf{C1}_{phenyl}$ that have a central 1,3-disubstituted phenyl spacer unit rather that a 2,6-substituted pyridyl core are able to bind both neutral organic and anionic (TfO^-) guest molecules. Thus, we have used cisplatin and triflate guests to examine the host−guest behavior of the multicavity cages (**C2**, **C2peg**, and **C3peg**).

^{1}H NMR experiments indicated that the double cavity systems (**C2** and **C2peg**) retain the cisplatin binding ability of the parent cages. While cisplatin was essentially completely insoluble in CD_3CN, addition of cisplatin to CD_3CN solutions of one of the double cavity cages (**C2** and **C2peg**) resulted in dissolution of the cisplatin, providing strong evidence that the cisplatin guest molecule is taken up by and complexed within the cages (Scheme 1b). ^{1}H NMR spectroscopy (CD_3CN) of the resulting mixtures further supported the postulate that the cisplatin was bound within the double cavity cages. The addition of cisplatin to **C2** or **C2peg** in CD_3CN brought about downfield shifts and broadening of the proton resonance due to the internally directed protons *ortho* to the coordinating nitrogen atoms (H_a and H_h for **C2** and H_a and H_g for **C2peg**) (Figure 2c, Supporting Information, Figure s4.1). For the cisplatin⊂**C2peg** host−guest adduct the H_a and H_g proton resonances were shifted by 0.10 and 0.15 ppm, respectively, while all the other proton resonances of the host cage were essential unaffected by the presence of cisplatin in solution indicating that the cisplatin guest molecules are bound within the cavities of the host. Unfortunately, the effective insolubility of cisplatin in CD_3CN precluded the use of a mole ratio titration[29a,35d,42] to confirm the encapsulation of four cisplatin molecules. However, given that it is well established[18c,35d,h] that the parent cages can bind two molecules of cisplatin and the X-ray structure (Figure 3) of **C2** contains four molecules of DMF, it is presumed that the host−guest adducts formed are $(cisplatin)_4$⊂**C2** and $(cisplatin)_4$⊂**C2peg** respectively (Figure 2).

The interaction of the anionic guest TfO^- with the more soluble **C2peg** cage in CD_3CN was also examined using NMR spectroscopy (Supporting Information, Figures s4.2 and S4.3). The introduction of $[NBu_4]OTf$ (2 equiv) to a CD_3CN solution of the cage at 298 K resulted in a downfield shift of the cage's exohedral proton H_b ($\Delta\delta$ = 0.13 ppm, Figure 2d, Supporting Information, Figure s4.2), indicative of interactions with the TfO^- guests on the exterior faces of the cage. No other notable shifts in the ^{1}H NMR spectrum were observed. Importantly, there were no shifts in the endohedral H_a and H_g protons which indicated that there was no encapsulation of the TfO^- anions in the internal cavities. Complexation-induced shifts were also observed in the ^{19}F NMR spectra (Supporting Information, Figure S4.3). The fluorine resonance of the TfO^- anions was shifted downfield from the chemical shift of "free" TfO^- due to the interaction with the cage. At the same time the chemical shift of the BF_4^- anions was shifted upfield (relative to its position in the **C2peg** complex spectrum) as it is displaced from the cage. These data are consistent with the TfO^- anions displacing associated BF_4^- anions from the outside face of the cage. A titration of $[NBu_4]OTf$ into a CD_3CN solution of the **C2peg** cage in CD_3CN was monitored via ^{1}H and ^{19}F NMR spectroscopies. Examining the shifts in the peaks belonging to H_b, $F_{triflate}$ and F_{BF4} using the mole-ratio method confirmed 1:2 binding between the cage and TfO^- anions (Supporting Information, Figure s4.4). Curve fitting the titration data using the 2:1 binding models (Supporting Information, Figures s4.4 and S4.5, www.supramolecular.org) suggested that the binding constants for the host−guest interaction were K_1 = 4800 ± 400 and K_2 = 20 ± 10 M^{-1},[43] values similar to those of related host−guest systems.[35d,44] These NMR experiments indicated that the **C2peg** cage binds two TfO^- anions on the outside

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

faces of the dicavity architecture. This behavior is similar to that observed with the parent **C1** cage and TfO^- anions.[19a] The lack of interaction between the TfO^- anions, and the central cavities of the cage can be attributed to the unfavorable lone pair−lone pair interactions between the lone pairs of electrons of the internally facing nitrogen atoms of the pyridyl linkers lining the cavities with the lone pairs of the fluorine atoms of the CF_3 group.[19a]

NMR experiments also confirmed that the **C2peg** cage can interact with both cisplatin and TfO^- guests simultaneously in CD_3CN. Addition of cisplatin (10 equiv) and triflate (2 equiv) to a solution of the cage in CD_3CN brought about downfield shifts of H_a, H_b, and H_g, confirming interaction with both guests concurrently (Figure 2e) forming a [(cisplatin)$_4$(triflate)$_2$⊂**C2peg**]$^{4+}$ host−guest adduct where cisplatin fills the cavities and TfO^- anions bind on the terminal faces of the metallo-tube. We have previously observed the formation of a similar adduct between cisplatin, MsO^- and the **C1peg** cage.[35d]

The design of the tricavity **C3peg** system offers the potential for simultaneously binding two different guests selectively in the different cavities of the cage. While the size of the cavities in the **C3peg** system are all identical, the two terminal cavities are lined with pyridyl units whereas the central cavity contains phenyl moieties (Scheme 1). The ^{1}H NMR spectrum of a mixture of cisplatin and **C3peg** in CD_3CN at room temperature was consistent with selective binding of cisplatin in the terminal cavities of the cage. Addition of cisplatin to **C3peg** resulted in downfield shifts of the internally directed α-pyridyl protons of the peripheral cavities only (Figure 4a and b, $\Delta\delta(H_a)$ = 0.07 ppm, $\Delta\delta(H_g)$ = 0.09 ppm). There were no shifts in the peaks pertaining to the protons internally directed into the central cavity (H_i and H_l), indicating that cisplatin guests were not encapsulated in this cavity. These finding are consistent with our previous results with the parent cages **C1** and **C1**$_{phenyl}$ which had shown that encapsulation within the cages' cavity is dependent on the key hydrogen−bonding interaction between the amines of the two bound cisplatin molecules and the noncoordinating pyridyl nitrogen atoms within the cage architecture.[18c]

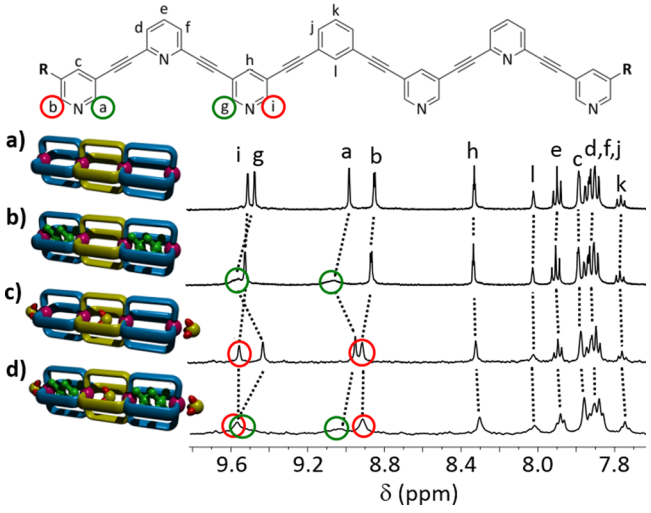


Figure 4. Partial ^{1}H NMR spectra (CD_3CN, 298 K, 400 MHz) of (a) **C3peg**, (b) (cisplatin)$_4$⊂**C3peg**, (c) (triflate)$_3$⊂**C3peg**, and (d) (triflate)$_3$(cisplatin)$_4$⊂**C3peg**.

In contrast, treatment of a room temperature CD_3CN solution of **C3peg** with 3 equiv of [NBu_4]OTf resulted in a downfield shift in the triflate peak in the ^{19}F spectrum ($\Delta\delta$(F) = 0.3 ppm, Supporting Information, Figure S4.8) compared to free [$N(Bu)_4$](OTf). The chemical shift of the fluorine peak pertaining to BF_4^- shifted upfield from that of the free host ($\Delta\delta$(F) = 0.3 ppm), suggesting displacement of BF_4^- by triflate. The corresponding ^{1}H NMR spectrum showed no shifts of the peaks belonging to internal protons of the terminal cavities H_a and H_g (Figure 4c, and Supporting Information, Figure S4.9). However, shifts of protons on the outside face (H_b) and inside the central cavity (H_i) of the tricavity cage were observed ($\Delta\delta(H_b)$ = 0.13 ppm, $\Delta\delta(H_i)$ = 0.05 ppm, Figure 4c, and Supporting Information, Figure S4.9). These results indicate selective encapsulation of the triflate anions within the central cavity and interaction with exohedral faces of the terminal palladium(II) ions, with no encapsulation in the outer cavities. Titration of triflate into a solution of the cage in CD_3CN using the mole-ratio method and ^{1}H and ^{19}F NMR spectroscopies (Supporting Information, Figure S4.10), monitoring the change in chemical shift of H_b, H_i, $F_{triflate}$, and F_{BF4} indicated that three triflate guests interacted with each cage, suggesting that two anions interact with the terminal faces of the tube in a similar fashion to what was observed with **C2peg** while the third guest is contained in the central cavity.[45] This postulate is consistent with the smaller downfield shift of proton H_i, as only one palladium(II) metal ion and associated H_i protons can interact with the sulfonate group at one time.

When excess cisplatin and triflate are simultaneously introduced to a CD_3CN solution containing the tricavity cage, downfield shifts of H_a, H_b, H_g, and H_l are observed indicative of guests binding in each of the cage cavities and on the outside faces of the architecture. These results are consistent with the formation of a [(cisplatin)$_4$(triflate)$_3$⊂**C3peg**]$^{5+}$ host−guest adduct and suggested that **C3peg** was able to concurrently bind two distinct guests selectively within the different cavities of the host architecture (Figure 4d).

To obtain further insight into the guest selectivity of the different cage cavities DFT calculations (gas phase, B3LYP with the LANL2DZ basis set for palladium atoms and the 6-31G(d) basis set for all other atoms, Supporting Information, section 5. Computations) were carried out to determine the minimized energies for the "empty" cages ($(CH_3CN)_2$⊂**C1** and $(CH_3CN)_2$⊂**C1**$_{phenyl}$) and the guest containing cages ((triflate)(CH_3CN)⊂**C1**, (triflate)(CH_3CN)⊂**C1**$_{phenyl}$, (cisplatin)$_2$⊂**C1**), and (cisplatin)$_2$⊂**C1**$_{phenyl}$). The energy of guest binding (ΔE) for each cage system was then calculated using Hess's Law (products − reactants, equation S1, Supporting Information). The calculation showed that the host−guest interaction of cisplatin with the **C1** cage was 30.8 kJ mol^{-1} more favorable than with the **C1**$_{phenyl}$ cage. Conversely, host−guest interaction of triflate with the **C1**$_{phenyl}$ cage was 61.1 kJ mol^{-1} more favorable than the same interaction with the **C1** cage (Supporting Information, Figure S5.1). Furthermore, the results of the calculations were completely consistent with the observed experimental binding selectivities. In the case of the cisplatin−cage adducts, the reasons for the observed binding selectivity is obvious. The **C1**$_{phenyl}$ cage is missing the four important central pyridyl----NH_3 hydrogen bonding interactions that are observed in the all solid state structures of the various (cisplatin)$_2$⊂**C1** adducts.[18c,35h,39] The reasons why triflate prefers to bind in the **C1**$_{phenyl}$ cage appear

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

to be more subtle. However, we have previously attributed this to unfavorable lone pair−lone pair interactions between the lone pairs of electrons of the internally facing nitrogen atoms of the pyridyl linkers lining the cavities with the lone pairs of the fluorine atoms of the CF_3 group and sulfonate oxygen atoms.[19a] Electrostatic potential maps of the calculated triflate cage adducts provide additional support for this postulate (Supporting Information, Figure S5.2).

CONCLUSIONS

A series of pseudolinear penta- and hexapyridyl ligands (**L2**, **L2peg**, and **L3peg**) were synthesized and combined with Pd(II) ions to create multicavity tube-like extended cages. The pentapyridyl ligands (**L2** and **L2peg**) gave the double cavity cages **C2** and **C2peg** which feature pyridyl cores within the cage cavities. These systems retained the molecular recognition properties of the parent **C1** and **C1peg** cages and were shown to encapsulate four molecules of cisplatin within the two cavities and bind two triflate anions on the terminal exterior faces of the host. The hexapyridyl ligand **L3peg** was used to form the first example of a multicavity cage of this sort with three cavities, **C3peg**. Additionally, the central cavity differed from the peripheries in that it had a phenyl spacer unit. This gave rise to two distinct cavity environments which could be exploited to give selective guest binding. It was shown using NMR experiments that only the peripheral pyridyl-core cavities bound cisplatin, while triflate guests could be bound within the phenyl lined central cavity and on the terminal exohedral faces of the assembly. No interaction of cisplatin with the central cavity or triflate with the peripheral cavities was observed. Thus, the multiple binding sites within the tricavity cage could engage in simultaneous segregated guest binding of the cisplatin and triflate guests.

To the best of our knowledge this is the first example of a discrete metallosupramolecular structure with differentiated internal cavities and the capacity for internal discrimination of guests between cavity types.[46] Assemblies with the capacity to concurrently bind more than one guest have been reported previously only for single-cavity systems where the guests are bound in the same cavity space,[12b−d,f,14a,c,18a,47] or for catenated coordination cages with pockets capable of differentiated anion/anion or anion/neutral guest binding.[31d,e,j]

Here we have shown that ligand design can be exploited to generate metallosupramolecular hosts with multiple discrete binding sites that can be used for selected encapsulation of different guests. While the current tricavity system is only a proof-of-principle design the ability to sequester different guests within segregated compartments of a single discrete metallosupramolecular structure could be highly advantageous in numerous potential applications, including dual guest (drug) delivery, and controllable enzyme-like multicomponent reactions and catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11982.

Experimental details, ^1H, ^{13}C and DOSY NMR and ESMS spectral information (PDF)

X-ray crystallography data (CIF)

Molecular modeling files (XYZ, XYZ)

AUTHOR INFORMATION

Corresponding Author

*jcrowley@chemistry.otago.ac.nz

ORCID

James D. Crowley: 0000-0002-3364-2267

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

D.P. and J.E.M.L. thank the University of Otago for PhD scholarships. The authors thank the Department of Chemistry, University of Otago for additional funding. The authors acknowledge the contribution of the NeSI high performance computing facilities to the results of this research. New Zealand's national facilities are provided by the New Zealand eScience Infrastructure and funded jointly by NeSI's collaborator institutions and through the Ministry of Business, Innovation & Employment's Research Infrastructure program.

REFERENCES

(1) (a) Myers, L. C.; Kornberg, R. D. *Annu. Rev. Biochem.* **2000**, *69*, 729−749. (b) Weigel, C.; Schmidt, A.; Ruckert, B.; Lurz, R.; Messer, W. *EMBO J.* **1997**, *16* (21), 6574−6583.

(2) Schechter, A. N. *Blood* **2008**, *112* (10), 3927−3938.

(3) Theil, E. C. *Annu. Rev. Biochem.* **1987**, *56*, 289−315.

(4) Hedstrom, L. *Chem. Rev.* **2002**, *102* (12), 4501−4523.

(5) Neves, S. R.; Ram, P. T.; Iyengar, R. *Science* **2002**, *296* (5573), 1636−1639.

(6) For some recent reviews of the area, see: (a) Cook, T. R.; Stang, P. J. *Chem. Rev.* **2015**, *115* (15), 7001−7045. (b) Castilla, A. M.; Ramsay, W. J.; Nitschke, J. R. *Acc. Chem. Res.* **2014**, *47* (7), 2063−2073. (c) Ronson, T. K.; Zarra, S.; Black, S. P.; Nitschke, J. R. *Chem. Commun.* **2013**, *49* (25), 2476−2490. (d) Young, N. J.; Hay, B. P. *Chem. Commun.* **2013**, *49* (14), 1354−1379. (e) Nakamura, T.; Ube, H.; Shionoya, M. *Chem. Lett.* **2013**, *42* (4), 328−334. (f) Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurney, R. T. *Angew. Chem., Int. Ed.* **2011**, *50* (40), 9260−9327. (g) Cook, T. R.; Vajpayee, V.; Lee, M. H.; Stang, P. J.; Chi, K.-W. *Acc. Chem. Res.* **2013**, *46* (11), 2464−2474. (h) Chakrabarty, R.; Mukherjee, P. S.; Stang, P. J. *Chem. Rev.* **2011**, *111* (11), 6810−6918. (i) Li, H.; Yao, Z.-J.; Liu, D.; Jin, G.-X. *Coord. Chem. Rev.* **2015**, *293*−*294*, 139−157. (j) Han, Y.-F.; Li, H.; Jin, G.-X. *Chem. Commun.* **2010**, *46* (37), 6879−6890. (k) Ward, M. D. *Chem. Commun.* **2009**, *30*, 4487−4499. (l) Glasson, C. R. K.; Lindoy, L. F.; Meehan, G. V. *Coord. Chem. Rev.* **2008**, *252* (8-9), 940−963.

(7) (a) Harris, K.; Fujita, D.; Fujita, M. *Chem. Commun.* **2013**, *49* (60), 6703−6712. (b) Wang, W.; Wang, Y.-X.; Yang, H.-B. *Chem. Soc. Rev.* **2016**, *45* (9), 2656−2693. (c) Stang, P. J.; Whiteford, J. A.; Fechtenkotter, A.; Olenyuk, B. *Nature* **1999**, *398* (6730), 796−9. (d) Olenyuk, B.; Levin, M. D.; Whiteford, J. A.; Shield, J. E.; Stang, P. J. *J. Am. Chem. Soc.* **1999**, *121* (44), 10434−10435.

(8) (a) Mal, P.; Breiner, B.; Rissanen, K.; Nitschke, J. R. *Science* **2009**, *324* (5935), 1697−1699. (b) Yamashina, M.; Sei, Y.; Akita, M.; Yoshizawa, M. *Nat. Commun.* **2014**, *5*, 4662−4668. (c) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122* (26), 6311−6312. (d) Taylor, C. G. P.; Piper, J. R.; Ward, M. D. *Chem. Commun.* **2016**, *52* (37), 6225−6228.

(9) (a) Riddell, I. A.; Smulders, M. M. J.; Clegg, J. K.; Nitschke, J. R. *Chem. Commun.* **2011**, *47* (1), 457−459. (b) Mochizuki, M.; Inoue, T.; Yamanishi, K.; Koike, S.; Kondo, M.; Zhang, L.; Aoki, H. *Dalton Trans.* **2014**, *43* (48), 17924−17927. (c) Tripathy, D.; Pal, A. K.; Hanan, G. S.; Chand, D. K. *Dalton Trans.* **2012**, *41* (37), 11273−11275.

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

(d) Chand, D. K.; Biradha, K.; Fujita, M. *Chem. Commun.* **2001**, *17*, 1652−1653. (e) Peinador, C.; Pia, E.; Blanco, V.; Garcia, M. D.; Quintela, J. M. *Org. Lett.* **2010**, *12* (7), 1380−1383. (f) Alvarino, C.; Pia, E.; Garcia, M. D.; Blanco, V.; Fernandez, A.; Peinador, C.; Quintela, J. M. *Chem. - Eur. J.* **2013**, *19* (45), 15329−15335. (g) Blanco, V.; Garcia, M. D.; Terenzi, A.; Pia, E.; Fernandez-Mato, A.; Peinador, C.; Quintela, J. M. *Chem. - Eur. J.* **2010**, *16* (41), 12373−12380.

(10) (a) Therrien, B.; Süss-Fink, G.; Govindaswamy, P.; Renfrew, A. K.; Dyson, P. J. *Angew. Chem., Int. Ed.* **2008**, *47* (20), 3773−3776. (b) Yi, J. W.; Barry, N. P. E.; Furrer, M. A.; Zava, O.; Dyson, P. J.; Therrien, B.; Kim, B. H. *Bioconjugate Chem.* **2012**, *23* (3), 461−471. (c) Zheng, Y.-R.; Suntharalingam, K.; Johnstone, T. C.; Lippard, S. J. *Chem. Sci.* **2015**, *6* (2), 1189−1193. (d) Cullen, W.; Turega, S.; Hunter, C. A.; Ward, M. D. *Chem. Sci.* **2015**, *6* (1), 625−631.

(11) (a) Riddell, I. A.; Smulders, M. M. J.; Clegg, J. K.; Hristova, Y. R.; Breiner, B.; Thoburn, J. D.; Nitschke, J. R. *Nat. Chem.* **2012**, *4* (9), 751−756. (b) Chepelin, O.; Ujma, J.; Wu, X.; Slawin, A. M. Z.; Pitak, M. B.; Coles, S. J.; Michel, J.; Jones, A. C.; Barran, P. E.; Lusby, P. J. *J. Am. Chem. Soc.* **2012**, *134* (47), 19334−19337. (c) Yamauchi, Y.; Yoshizawa, M.; Akita, M.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132* (3), 960−966. (d) Yamauchi, Y.; Yoshizawa, M.; Akita, M.; Fujita, M. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (26), 10435−10437. (e) Ono, K.; Yoshizawa, M.; Kato, T.; Watanabe, K.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46* (11), 1803−1806. (f) Yoshizawa, M.; Ono, K.; Kumazawa, K.; Kato, T.; Fujita, M. *J. Am. Chem. Soc.* **2005**, *127* (31), 10800−10801. (g) Yoshizawa, M.; Miyagi, S.; Kawano, M.; Ishiguro, K.; Fujita, M. *J. Am. Chem. Soc.* **2004**, *126* (30), 9172−9173. (h) Sun, W.-Y.; Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **2002**, *124* (39), 11570−11571. (i) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **2002**, *124* (45), 13576−13582. (j) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature* **1995**, *378* (6556), 469−471.

(12) (a) Murase, T.; Nishijima, Y.; Fujita, M. *J. Am. Chem. Soc.* **2012**, *134* (1), 162−164. (b) Horiuchi, S.; Murase, T.; Fujita, M. *Chem. - Asian J.* **2011**, *6* (7), 1839−1847. (c) Murase, T.; Horiuchi, S.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132* (9), 2866−2867. (d) Nishioka, Y.; Yamaguchi, T.; Kawano, M.; Fujita, M. *J. Am. Chem. Soc.* **2008**, *130* (26), 8160−8161. (e) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129* (22), 7000−7001. (f) Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M. *J. Am. Chem. Soc.* **2003**, *125* (11), 3243−3247.

(13) (a) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48* (19), 3418−3438. (b) Yoshizawa, M.; Fujita, M. *Bull. Chem. Soc. Jpn.* **2010**, *83* (6), 609−618. (c) Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *Chem. Rev.* **2015**, *115* (9), 3012−3035. (d) Cullen, W.; Misuraca, M. C.; Hunter, C. A.; Williams, N. H.; Ward, M. D. *Nat. Chem.* **2016**, *8* (3), 231−236.

(14) (a) Leenders, S. H. A. M.; Becker, R.; Kumpulainen, T.; de Bruin, B.; Sawada, T.; Kato, T.; Fujita, M.; Reek, J. N. H. *Chem. - Eur. J.* **2016**, *22* (43), 15468−15474. (b) Yamashina, M.; Sartin, M. M.; Sei, Y.; Akita, M.; Takeuchi, S.; Tahara, T.; Yoshizawa, M. *J. Am. Chem. Soc.* **2015**, *137* (29), 9266−9269. (c) Murase, T.; Otsuka, K.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132* (23), 7864−7865.

(15) (a) Han, M.; Engelhard, D. M.; Clever, G. H. *Chem. Soc. Rev.* **2014**, *43* (6), 1848−60. (b) Schmidt, A.; Casini, A.; Kühn, F. E. *Coord. Chem. Rev.* **2014**, *275* (0), 19−36.

(16) (a) Ahmedova, A.; Momekova, D.; Yamashina, M.; Shestakova, P.; Momekov, G.; Akita, M.; Yoshizawa, M. *Chem. - Asian J.* **2016**, *11* (4), 474−477. (b) Kishi, N.; Li, Z.; Sei, Y.; Akita, M.; Yoza, K.; Siegel, J. S.; Yoshizawa, M. *Chem. - Eur. J.* **2013**, *19* (20), 6313−6320. (c) Kishi, N.; Li, Z.; Yoza, K.; Akita, M.; Yoshizawa, M. *J. Am. Chem. Soc.* **2011**, *133* (30), 11438−11441. (d) Clever, G. H.; Tashiro, S.; Shionoya, M. *J. Am. Chem. Soc.* **2010**, *132* (29), 9973−9975. (e) Clever, G. H.; Shionoya, M. *Chem. - Eur. J.* **2010**, *16* (39), 11792−11796. (f) Clever, G. H.; Tashiro, S.; Shionoya, M. *Angew. Chem., Int. Ed.* **2009**, *48* (38), 7010−7012.

(17) Kishi, N.; Akita, M.; Kamiya, M.; Hayashi, S.; Hsu, H.-F.; Yoshizawa, M. *J. Am. Chem. Soc.* **2013**, *135* (35), 12976−12979.

(18) (a) Clever, G. H.; Kawamura, W.; Tashiro, S.; Shiro, M.; Shionoya, M. *Angew. Chem., Int. Ed.* **2012**, *51* (11), 2606−2609. (b) Johnstone, M. D.; Schwarze, E. K.; Ahrens, J.; Schwarzer, D.; Holstein, J. J.; Dittrich, B.; Pfeffer, F. M.; Clever, G. H. *Chem. - Eur. J.* **2016**, *22* (31), 10791−5. (c) Lewis, J. E. M.; Gavey, E. L.; Cameron, S. A.; Crowley, J. D. *Chem. Sci.* **2012**, *3* (3), 778−784.

(19) (a) Lewis, J. E. M.; Crowley, J. D. *Supramol. Chem.* **2014**, *26* (3−4), 173−181. (b) Liao, P.; Langloss, B. W.; Johnson, A. M.; Knudsen, E. R.; Tham, F. S.; Julian, R. R.; Hooley, R. J. *Chem. Commun.* **2010**, *46* (27), 4932−4934. (c) Kim, T. Y.; Lucas, N. T.; Crowley, J. D. *Supramol. Chem.* **2015**, *27* (11−12), 734−745.

(20) (a) Suzuki, K.; Tominaga, M.; Kawano, M.; Fujita, M. *Chem. Commun.* **2009**, *13*, 1638−1640. (b) Tominaga, M.; Suzuki, K.; Kawano, M.; Kusukawa, T.; Ozeki, T.; Sakamoto, S.; Yamaguchi, K.; Fujita, M. *Angew. Chem., Int. Ed.* **2004**, *43* (42), 5621−5625. (c) Sun, Q.-F.; Iwasa, J.; Ogawa, D.; Ishido, Y.; Sato, S.; Ozeki, T.; Sei, Y.; Yamaguchi, K.; Fujita, M. *Science* **2010**, *328* (5982), 1144−1147. (d) Fujita, D.; Ueda, Y.; Sato, S.; Yokoyama, H.; Mizuno, N.; Kumasaka, T.; Fujita, M. *Chem.* **2016**, *1* (1), 91−101.

(21) (a) Cookson, N. J.; Henkelis, J. J.; Ansell, R. J.; Fishwick, C. W. G.; Hardie, M. J.; Fisher, J. *Dalton Trans.* **2014**, *43* (15), 5657−5661. (b) Kikuchi, T.; Murase, T.; Sato, S.; Fujita, M. *Supramol. Chem.* **2008**, *20* (1−2), 81−94. (c) Hiraoka, S.; Harano, K.; Shiro, M.; Ozawa, Y.; Yasuda, N.; Toriumi, K.; Shionoya, M. *Angew. Chem., Int. Ed.* **2006**, *45* (39), 6488−6491.

(22) Sato, S.; Iida, J.; Suzuki, K.; Kawano, M.; Ozeki, T.; Fujita, M. *Science* **2006**, *313* (5791), 1273−6.

(23) Suzuki, K.; Iida, J.; Sato, S.; Kawano, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2008**, *47* (31), 5780−2.

(24) Suzuki, K.; Takao, K.; Sato, S.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132* (8), 2544−2545.

(25) Murase, T.; Sato, S.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46* (27), 5133−5136.

(26) Bruns, C. J.; Fujita, D.; Hoshino, M.; Sato, S.; Stoddart, J. F.; Fujita, M. *J. Am. Chem. Soc.* **2014**, *136* (34), 12027−12034.

(27) The large cavities of these cages have also been used for other purposes including generating monodisperse polymers and nanoparticles and the encapsulation of large covalently linked guests such as the 8.6 kDA protein ubiquitin; see; (a) Murase, T.; Sato, S.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46* (7), 1083−1085. (b) Suzuki, K.; Sato, S.; Fujita, M. *Nat. Chem.* **2010**, *2* (1), 25−29. (c) Fujita, D.; Suzuki, K.; Sato, S.; Yagi-Utsumi, M.; Yamaguchi, Y.; Mizuno, N.; Kumasaka, T.; Takata, M.; Noda, M.; Uchiyama, S.; Kato, K.; Fujita, M. *Nat. Commun.* **2012**, *3*, 1093.

(28) (a) Baxter, P.; Lehn, J. M.; DeCian, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32* (1), 69. (b) Baxter, P. N. W.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Chem. - Eur. J.* **1999**, *5* (1), 113−120.

(29) (a) Crowley, J. D.; Goshe, A. J.; Bosnich, B. *Chem. Commun.* **2003**, *22*, 2824−2825. (b) Goshe, A. J.; Bosnich, B. *Synlett* **2001**, *2001* (SpecialIssue), 941−944.

(30) Crowley, J. D.; Steele, I. M.; Bosnich, B. *Eur. J. Inorg. Chem.* **2005**, *2005*, 3907−3917.

(31) (a) Frank, M.; Ahrens, J.; Bejenke, I.; Krick, M.; Schwarzer, D.; Clever, G. H. *J. Am. Chem. Soc.* **2016**, *138* (26), 8279−87. (b) Frank, M.; Hey, J.; Balcioglu, I.; Chen, Y.-S.; Stalke, D.; Suenobu, T.; Fukuzumi, S.; Frauendorf, H.; Clever, G. H. *Angew. Chem., Int. Ed.* **2013**, *52* (38), 10102−10106. (c) Zhu, R.; Luebben, J.; Dittrich, B.; Clever, G. H. *Angew. Chem., Int. Ed.* **2015**, *54* (9), 2796−2800. (d) Loeffler, S.; Luebben, J.; Krause, L.; Stalke, D.; Dittrich, B.; Clever, G. H. *J. Am. Chem. Soc.* **2015**, *137* (3), 1060−1063. (e) Freye, S.; Michel, R.; Stalke, D.; Pawliczek, M.; Frauendorf, H.; Clever, G. H. *J. Am. Chem. Soc.* **2013**, *135* (23), 8476−8479. (f) Frank, M.; Johnstone, M. D.; Clever, G. H. *Chem. - Eur. J.* **2016**, *22* (40), 14104−14125. (g) Fukuda, M.; Sekiya, R.; Kuroda, R. *Angew. Chem., Int. Ed.* **2008**, *47* (4), 706−10. (h) Sekiya, R.; Fukuda, M.; Kuroda, R. *J. Am. Chem. Soc.* **2012**, *134* (26), 10987−10997. (i) Sekiya, R.; Kuroda, R. *Chem. Commun.* **2011**, *47* (45), 12346−12348. (j) Li, Y.-H.; Jiang, J.-J.; Fan,

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386

Y.-Z.; Wei, Z.-W.; Chen, C.-X.; Yu, H.-J.; Zheng, S.-P.; Fenske, D.; Su, C.-Y.; Barboiu, M. *Chem. Commun.* **2016**, *52* (56), 8745−8.
(32) (a) Fujita, M.; Fujita, N.; Ogura, K.; Yamaguchi, K. *Nature* **1999**, *400* (6739), 52−55. (b) Yamauchi, Y.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2008**, *130* (18), 5832−5833. (c) Bar, A. K.; Raghothama, S.; Moon, D.; Mukherjee, P. S. *Chem. - Eur. J.* **2012**, *18* (11), 3199−3209. (d) Samanta, D.; Mukherjee, P. S. *J. Am. Chem. Soc.* **2014**, *136* (49), 17006−17009.
(33) McMorran, D. A.; Steel, P. J. *Supramol. Chem.* **2002**, *14* (1), 79−85.
(34) McMorran, D. A.; Steel, P. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3295−3297.
(35) (a) Preston, D.; McNeill, S. M.; Lewis, J. E. M.; Giles, G. I.; Crowley, J. D. *Dalton Trans.* **2016**, *45* (19), 8050−8060. (b) Preston, D.; Barnsley, J. E.; Gordon, K. C.; Crowley, J. D. *J. Am. Chem. Soc.* **2016**, *138*, 10578. (c) Elliott, A. B. S.; Lewis, J. E. M.; van der Salm, H.; McAdam, C. J.; Crowley, J. D.; Gordon, K. C. *Inorg. Chem.* **2016**, *55* (7), 3440−3447. (d) Preston, D.; Fox-Charles, A.; Lo, W. K. C.; Crowley, J. D. *Chem. Commun.* **2015**, *51* (43), 9042−9045. (e) McNeill, S. M.; Preston, D.; Lewis, J. E. M.; Robert, A.; Knerr-Rupp, K.; Graham, D. O.; Wright, J. R.; Giles, G. I.; Crowley, J. D. *Dalton Trans.* **2015**, *44* (24), 11129−11136. (f) Kim, T. Y.; Lucas, N. T.; Crowley, J. D. *Supramol. Chem.* **2015**, *27* (11−12), 734−745. (g) Lewis, J. E. M.; Elliott, A. B. S.; McAdam, C. J.; Gordon, K. C.; Crowley, J. D. *Chem. Sci.* **2014**, *5* (5), 1833−1843. (h) Lewis, J. E. M.; McAdam, C. J.; Gardiner, M. G.; Crowley, J. D. *Chem. Commun.* **2013**, *49* (33), 3398−3400.
(36) For some selected recent examples, see: (a) Aoyagi, M.; Biradha, K.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121* (32), 7457−7458. (b) Tashiro, S.; Tominaga, M.; Kusukawa, T.; Kawano, M.; Sakamoto, S.; Yamaguchi, K.; Fujita, M. *Angew. Chem., Int. Ed.* **2003**, *42* (28), 3267−3270. (c) Yamaguchi, T.; Tashiro, S.; Tominaga, M.; Kawano, M.; Ozeki, T.; Fujita, M. *J. Am. Chem. Soc.* **2004**, *126* (35), 10818−10819.
(37) During the course of our work developing these systems two other groups have reported similar "double-decker" $[Pd_3(L)_4]^{4+}$ cages; see: (a) Bandi, S.; Pal, A. K.; Hanan, G. S.; Chand, D. K. *Chem. - Eur. J.* **2014**, *20* (41), 13122−13126. (b) Bandi, S.; Samantray, S.; Chakravarthy, R. D.; Pal, A. K.; Hanan, G. S.; Chand, D. K. *Eur. J. Inorg. Chem.* **2016**, *2016*, 2816−2827. (c) Johnstone, M. D.; Schwarze, E. K.; Clever, G. H.; Pfeffer, F. M. *Chem. - Eur. J.* **2015**, *21* (10), 3948−3955.
(38) (a) Sakamoto, S.; Fujita, M.; Kim, K.; Yamaguchi, K. *Tetrahedron* **2000**, *56* (7), 955−964. (b) Sakamoto, S.; Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *Org. Lett.* **2001**, *3* (11), 1601−1604.
(39) Schmidt, A.; Molano, V.; Hollering, M.; Poethig, A.; Casini, A.; Kuhn, F. E. *Chem. - Eur. J.* **2016**, *22* (7), 2253−2256.
(40) Johnson, A. M.; Moshe, O.; Gamboa, A. S.; Langloss, B. W.; Limtiaco, J. F. K.; Larive, C. K.; Hooley, R. J. *Inorg. Chem.* **2011**, *50* (19), 9430−9442.
(41) August, D. P.; Nichol, G. S.; Lusby, P. J. *Angew. Chem., Int. Ed.* **2016**, *55* (48), 15022−15026.
(42) Meyer, A. S., Jr.; Ayres, G. H. *J. Am. Chem. Soc.* **1957**, *79*, 49−53.
(43) (a) www.supramolecular.org (accessed 10th October 2016). (b) Brynn Hibbert, D.; Thordarson, P. *Chem. Commun.* **2016**, *52* (87), 12792−12805.
(44) Bloch, W. M.; Abe, Y.; Holstein, J. J.; Wandtke, C. M.; Dittrich, B.; Clever, G. H. *J. Am. Chem. Soc.* **2016**, *138* (41), 13750−13755.
(45) A calculation of binding constants was precluded by the presence of different binding sites within **C3peg** for triflate and the number of variables that would need to be fitted.
(46) Systems which bind different guests within the central cavity and on the ousitde faces of the architecture are known; see: (a) Rizzuto, F. J.; Wu, W.-Y.; Ronson, T. K.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2016**, *55* (28), 7958−7962. (b) Ramsay, W. J.; Nitschke, J. R. *J. Am. Chem. Soc.* **2014**, *136* (19), 7038−7043.
(47) Kusukawa, T.; Nakai, T.; Okano, T.; Fujita, M. *Chem. Lett.* **2003**, *32* (3), 284−285.

DOI: 10.1021/jacs.6b11982
J. Am. Chem. Soc. 2017, 139, 2379−2386