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Octahedral $[Pd_6L_8]^{12+}$ Metallosupramolecular Cages: Synthesis, Structures and Guest Encapsulation Studies

Tae Y. Kim,[a] Lori Digal,[a] Michael G. Gardiner,[b] Nigel T. Lucas[a],* and James D. Crowley[a],*

Abstract: Four planar tripyridyl ligands ($\mathbf{L}_{\mathbf{tripy}}$), 1,3,5-tris(pyridin-3-ylethynyl)benzene **1a**, 1,3,5-tris[4-(3-pyridyl)phenyl]benzene **2a**, and the hexyloxy chain functionalized derivatives 1,3,5-tris[(3-hexyloxy-5-pyridyl)ethynyl]benzene **1b**, and 1,3,5-tris[4-(3-hexyloxy-5-pyridyl)phenyl]benzene **2b**, were synthesized and used to generate a family of $[Pd_6(\mathbf{L}_{\mathbf{tripy}})_8](BF_4)_{12}$ octahedral cages ($\mathbf{L}_{\mathbf{tripy}}$ = **1a-b** or **2a-b**). The ligands and cages were characterized using a combination of ^{1}H, ^{13}C and DOSY nuclear magnetic resonance (NMR) spectroscopy, high resolution electrospray mass spectrometry (HR-ESI-MS), infrared (IR) spectroscopy, elemental analysis, and in three cases, X-ray crystallography. The molecular recognition properties of the cages with neutral and anionic guests was examined, in dimethyl sulfoxide (DMSO), using NMR spectroscopy, mass spectrometry and molecular modelling. No binding was observed with simple aliphatic and aromatic guest molecules. However, anionic sulfonates were found to interact with the octahedral cages and the binding interaction was size selective. The smaller $[Pd_6(\mathbf{1a\text{-}b})_8]^{12+}$ cages were able to interact with three *p*-toluenesulfonate guest molecules while the larger $[Pd_6(\mathbf{2a\text{-}b})_8]^{12+}$ systems could host four of the anionic guest molecules. To probe the importance of the hydrophobic effect, a mixed water-DMSO (1:1) solvent system was used to reexamine the binding of the neutral organic guests adamantane, anthracene, pyrene and 1,8-naphthalimide within the cages. In this solvent system all the guests except adamantane were observed to bind within the cavities of the cages. NMR spectroscopy and molecular modelling indicated that the cages bind multiple copies of the individual guests (between 3-6 guest molecules per cage).

Introduction

Strategies for the synthesis of two- and three-dimensional metallosupramolecular architectures[1] are now well understood and a range of applications for these systems are beginning to emerge. The biological, [2] photophysical[3] and redox[4] properties of metallosupramolecular architectures have all been examined. However, it is the interesting host-guest chemistry[5] of these metallosupramolecular systems which show the most potential. Architectures with hollow cavities, such as capsules and cages, are of particular interest due to the tunable nature of the internal cavities. The molecular recognition properties of these systems have already been exploited to encapsulate drugs,[6] environmental pollutants[7] and reactive species.[8] Additionally, the cavities of these cages have been exploited as molecular reaction flasks[9] and for catalysis.[10]

While almost any labile metal ion in combination with a correctly encoded ligand system can be used for the generation of these metallo-cage systems,[1] square planar palladium(II) ions have been extensively used to generate metallosupramolecular architectures.[11] This is due to the favorable combination of kinetic lability but thermodynamic stability in the Pd^{II}−pyridine interaction, which allows the self-assembly process to proceed in high yields. In a pioneering discovery, McMorran and Steel,[12] showed that the combination of “naked” Pd^{II} ions and a dipyridyl ligands ($\mathbf{L}_{\mathbf{dipy}}$) could be used to assemble a $[Pd_2(\mathbf{L}_{\mathbf{dipy}})_4]^{4+}$ cage. Since that work, the host-guest properties of these small metallosupramolecular architectures[13] have been extensively examined. The $[Pd_2(\mathbf{L}_{\mathbf{dipy}})_4]^{4+}$ cages have been shown to bind a wide range of neutral organic[14] and inorganic[15] guests and anions[16] but due to their small size often they interact with only one or two guest molecules and this potentially limits the applications of these systems.

Several larger octahedral $[Pd_6L_8]^{12+}$ cage systems,[17] generated from “naked” Pd^{II} ions and pseudo-planar tripyridyl ligands (Figure 1), are known and some have been exploited as catalysts.[18] However, despite these systems displaying large accessible cavities, the molecular recognition properties of these $[Pd_6L_8]^{12+}$ cages have hardly been examined.[19] This is surprising given the rich host-guest chemistry displayed by the related $[M_6L_4]^{12+}$ (where M = Pd^{II} or Pt^{II}) octahedral cages. These water soluble octahedral cages are usually generated from ethylenediamine-capped palladium(II) or platinum(II) ‘corner pieces’ and planar tripyridyl ligands (Figure 1) forming a semi open $[M_6L_4]^{12+}$ system. Fujita and coworkers have shown that these cages can bind one to four guest molecules,[20] mainly by exploiting the hydrophobic effect, and can act as molecular reaction flasks.[9]

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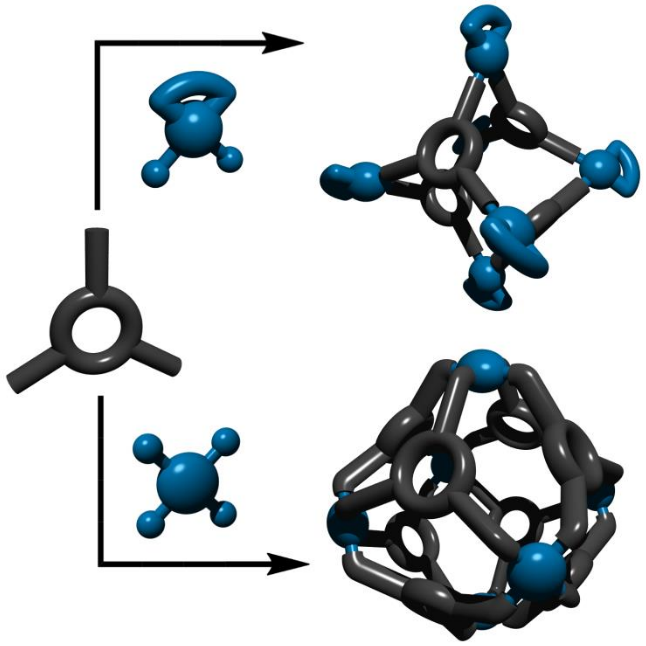


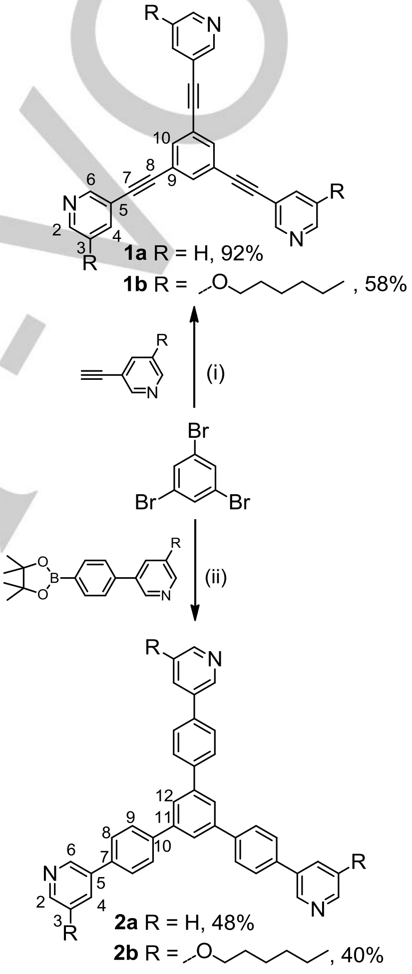
Figure 1. Cartoon representations of metallosupramolecular octahedral cage architectures. Top, semi-open Fujita-type $[M_6L_4]^{12+}$ cages and bottom, fully closed $[M_6L_8]^{12+}$ cages.

As part of our interest in the molecular recognition properties[21] of metallosupramolecular architectures,[22] herein we report the synthesis and characterization of four rigid, planar C_3 symmetric tripyridyl ligands (**L**$_{\mathbf{tripy}}$ = **1a-b** or **2a-b**) and the corresponding $[Pd_6(\mathbf{L}_{\mathbf{tripy}})_8]^{12+}$ cages (Figure 1 and Scheme 1). The tripyridyl systems feature two different linker units, either alkynyl or phenyl, to connect the coordinating pyridyl groups to the benzene core of the ligands. Therefore the ligands are different in length and this generates cages with altered portal and cavity sizes. This difference in portal and cavity sizes may play a role in host-guest binding interactions, potentially leading to differences in guest preference and the number of guest encapsulated. The molecular recognition properties of the cages with neutral organic and anionic guest molecules was examined using NMR spectroscopy, molecular modelling and mass spectrometry.

Results and Discussion

Synthesis of the ligands

The ligands 1,3,5-tris(pyridin-3-ylethynyl)benzene **1a**,[23] 1,3,5-tris[4-(3-pyridyl)phenyl]benzene **2a**[24] have been reported previously. However, we generated the ligands (**1a,b** and **2a,b**) from the commercially available 1,3,5-tribromobenzene core unit using either Sonogashira (**1a,b**) or Suzuki (**2a,b**) cross coupling conditions (Scheme 1 and Supporting Information). The ligands were isolated in moderate to good yields (40-92%) and the molecular formulations were confirmed via ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, high resolution electrospray mass spectrometry (HR-ESI-MS), infrared (IR) spectroscopy, and elemental analysis (Supporting Information).



Scheme 1. Synthesis of the four trigonal benzene core ligands. (i) $[PdCl_2(Ph_3P)_2]$, CuI, Et_3N, 40 °C. (ii) [PdCl$_2$(dppf)], K_2CO_3, toluene, EtOH, H_2O, 80 °C.

The molecular structures of the ligands **1b** and **2b** were unambiguously confirmed using X-ray crystallography (Figure 2 and Supporting Information). Both ligands **1b** and **2b** crystallized in the triclinic $P\bar{1}$ space group with the asymmetric unit consisting of one whole ligand. The X-ray diffraction data confirmed the expected bond connectivity, with three pyridyl units bound in the 1, 3 and 5 positions of the central benzene core unit. Each of the

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ligands adopts an essentially planar conformation in the solid state and engages in a number of hydrogen bond and π-π interactions (Supporting Information).

The ligand **1b** forms hydrogen-bonded dimers in the solid state involving interactions between a pyridyl nitrogen atom and a hydrogen atom of the benzene core ring (N3---C4 3.321(1) Å, N3---H4 2.40 Å) (Supporting Information). The hexyloxy chains on adjacent dimers interdigitate forming linear tapes. The linear tapes are involved in π-π stacking interactions (centroid-centroid distances 3.69-3.83 Å) (Supporting Information). The ligand **2b** forms slipped stacked supramolecular tapes through π-π interactions (centroid-centroid distance = 3.78 Å) (Supporting Information). The supramolecular tapes interact with adjacent tapes through dispersion interactions between head-to-tail packed hexyloxy chains (Supporting Information).

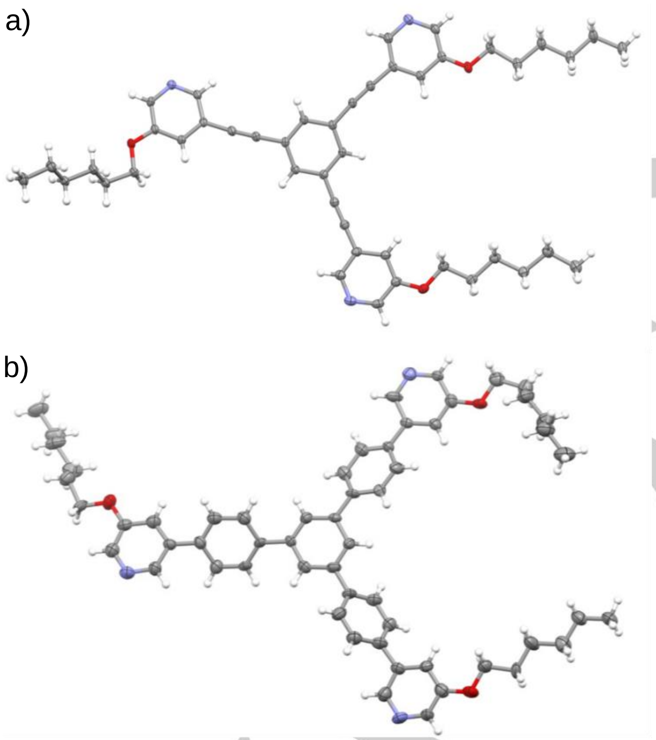

Figure 2. The molecular structures of ligands **1b** and **2b:** a) ORTEP[25] diagram of the X-ray crystal structure of **1b**, b) ORTEP[25] diagram of the X-ray crystal structure of **2b**. Ellipsoids are shown at the 50% probability level. Colours: Grey = carbon, white = hydrogen, red = oxygen, blue = nitrogen.

Synthesis of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages

The $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages were prepared by mixing $[Pd(CH_3CN)_4](BF_4)_2$ (6 equiv.) with one the ligands (either **1a** or **1b** or **2a** or **2b,** 8 equiv.) in dimethyl sulfoxide (DMSO) and heating at 50 °C for 2 h. The heating was essential for the formation of the cage system; simply leaving the components in DMSO solution at room temperature (RT) for 2 days did not lead to the clean formation of the octahedral architecture. This behavior is different to what was observed for related $[Pd_2L_4]^{4+}$ cages[21d-g, 21k] which assemble instantaneously at RT in either acetonitrile (CH_3CN) 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 larger octahedral cage systems. The $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages ($\mathbf{L_{tripy}}$ = **1a-b or 2a-b**) were characterized using a combination of ^1H NMR, DOSY, and HR-ESI-MS data (Figures 3-5 and Supporting Information).

The ^1H NMR spectra (Figure 3 and Supporting Information) of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages each show a single set of peaks shifted downfield relative to $\mathbf{L_{tripy}}$, consistent with complexation to palladium(II) ions (Figures 3 and Supporting Information). The sharp, uncomplicated signals observed in the ^1H NMR spectra of $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages are similar to what was previously observed for the formation of $[Pd_2L_4]^{4+}$[21d-g, 21k] and other palladium(II) based octahedral cages and are consistent with the formation of a complex with O_h symmetry in solution.[21e-g, 21k]

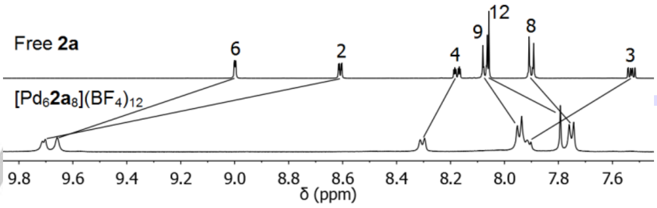

Figure 3. Stacked ^1H NMR spectra (500 MHz, 298 K) of the free ligand **2a** and $[Pd_6(\mathbf{2a})_8]^{12+}$ cage in $[D_6]$DMSO.

Further solution phase evidence for the formation of the desired discrete cage architectures was obtained from ^1H DOSY NMR spectroscopy (Figure 4 and Supporting Information). Each of the proton signals in the individual spectra of the $[Pd_6(\mathbf{L_{tripy}})_8]_{12+}$ cages (D = 0.5-0.6 × 10^{-10} m^2 s^{-1}) and the corresponding ligands (D = 1.7-2.0 × 10^{-10} m^2 s^{-1}) show the same diffusion coefficients (D), indicating that there is only one species present in solution and the ratio of the diffusion coefficients of the ligand and palladium cage in d_6-DMSO are approximately 3:1, consistent with the presence of the larger molecular cage species in solution. Additionally, a plot of log*D* against logMW for ligands and complexes gave a good linear fit (Figure 5).

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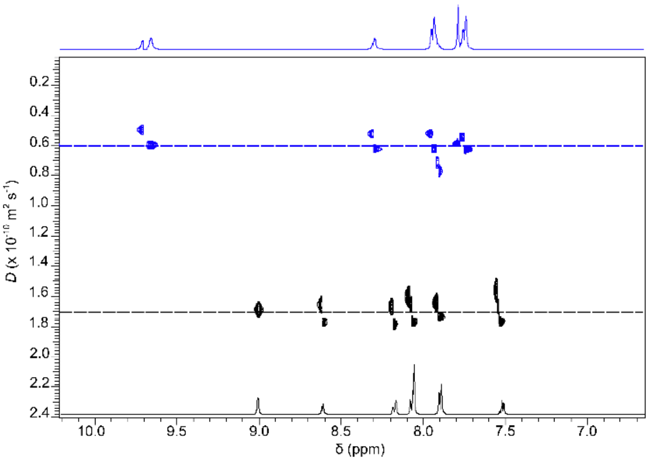

Figure 4. Overlaid ^1H DOSY NMR spectra (500 MHz, [D$_6$]DMSO, 298 *K*) of $[Pd_6(\mathbf{2a})_8]^{12+}$ cage (blue (top) trace) and free ligand **2a** (black (bottom) trace).

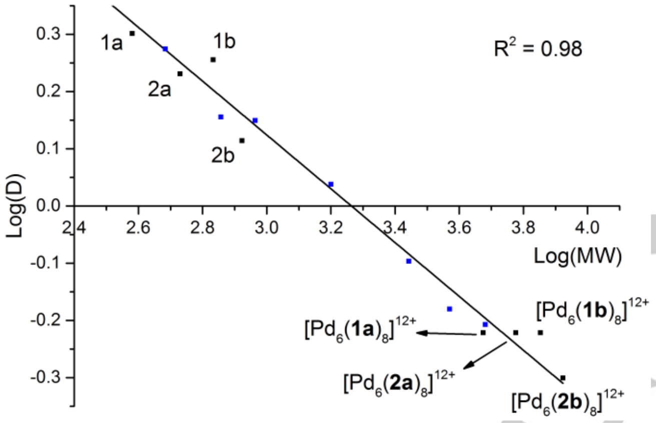

Figure 5. Plot of log(D) against log(MW) for reported ligands and cages ([D$_6$]DMSO, 298 *K*, 500 MHz) (black dots). The blue dots are previously reported ligands and $[Pd_2(\mathbf{L})_4]^{4+}$, $[Pd_3(\mathbf{L})_4]^{6+}$ and $[Pd_4(\mathbf{L})_4]^{8+}$ cages.[21a, 21c] Units D: x 10^{-10} m^2 s^{-1}, MW: g mol^{-1}.

Mass spectra (HR-ESI-MS) of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages, under pseudo cold-spray conditions, in DMSO–CH$_3$CN solution displayed a series of isotopically resolved peaks due to $[Pd_6(\mathbf{L_{tripy}})_8]^{(12\text{-}n)+}$ $(BF_4^-)_n$ ions, where n = 3-10, along with small peaks due to fragmentation of the cage (Figure 6 and Supporting Information). For example, ions at *m/z* = 511.332 $[Pd_6(\mathbf{2a})_8(BF_4)_2]^{10+}$, 577.705 $[Pd_6(\mathbf{2a})_8(BF_4)_3]^{9+}$, 660.788 $[Pd_6(\mathbf{2a})_8(BF_4)_4]^{8+}$, 767.756 $[Pd_6(\mathbf{2a})_8(BF_4)_5]^{7+}$, 910.213 $[Pd_6(\mathbf{2a})_8(BF_4)_6]^{6+}$, 1109.656 $[Pd_6(\mathbf{2a})_8(BF_4)_7]^{5+}$, 1408.820 $[Pd_6(\mathbf{2a})_8(BF_4)_8]^{4+}$ were observed for the $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ octahedral cage (Figure 6).

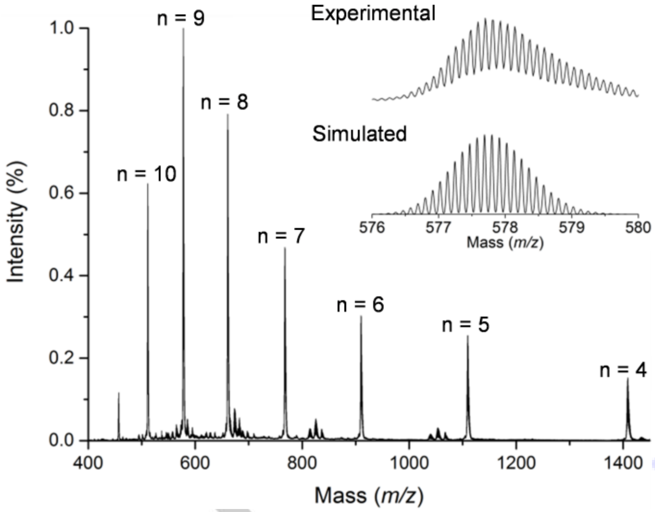

Figure 6. HR-ESI-TOF mass spectrum of $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ showing signals due to $[Pd_6(\mathbf{2a})_8(BF_4)_{12\text{-}n}]^{n+}$, n = 4 – 10. Inset: comparison of experimental (top) and simulated (bottom) spectra for the signal of $[Pd_6(\mathbf{2a})_8(BF_4)_3]^{9+}$ (*m/z* = 577.705).

The molecular structure of the $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ octahedral cage was confirmed using X-ray crystallography (Figure 5 and Supporting Information). A single crystal of $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ was grown by vapour diffusion of ether into a DMSO solution of the cage. The crystals were small and diffraction was modest thus the X-ray data was collected at the Australian Synchrotron. The cage crystallized in the trigonal $P\bar{3}$ space group with the asymmetric unit containing one Pd atom, one complete ligand and a third of a second ligand on a threefold axis. The BF_4^- anions and co-crystallized solvent (DMSO and diethyl ether) were too disordered to be located; their presence was accounted for using the SQUEEZE program (voids totalled ~7800 Å^3/cell and 1866 e$^-$/cell) Each **2a** ligand coordinates to three Pd^{II} ions, in a monodentate fashion, generating the expected $[Pd_6(\mathbf{2a})_8]^{12+}$ cage architecture. The N$_{py}$-Pd bond lengths of $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ are similar to those observed in other $[Pd(py)_4]^{2+}$ moieties of similar metallosupramolecular architectures (~2.0 Å). The cage displays a large central cavity with 2.5 nm between the diametrically opposed Pd^{II} ions (Pd1---Pd1′ 25.596(3) Å) and 1.8 nm between axial and equatorial Pd^{II} ions (Pd1---Pd1″ 18.119(3) Å) metal centres. The coordinated pyridyl units and the benzene core rings are almost perpendicular to each other (89°). The phenylene linkers have greater rotational freedom and are found twisted ~46° relative to the plane of the pyridyl units. The 12 portals into the internal cavity between the ligands, forming at the edges of the octahedral cage, are 7.1 Å at the widest point. These openings should allow relatively easy access to the internal cavity of the cage for small guest molecules. The portals are large enough for

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the small molecules (DMSO solvent molecules 4.6 Å at the widest point; BF_4^- counterions 2.0 Å across) and small organic guest molecules to freely move in and out of the internal cavity. The $[Pd_6(\mathbf{2a})_8]^{12+}$ cages laterally pack with a hexagonal arrangement displaying edge-to-face interactions between hydrogen atoms of a pyridyl unit of one ligand interacting with a benzene core ring of another ligand (hydrogen-centroid distance = 2.847 Å, carbon-centroid distance 3.579 Å, see Supporting Information), and pack vertically with a slipped face-to-face π-π stacking interaction between two benzene core rings (centroid-centroid distance 3.680 Å) and four edge-to-face interactions between two ligands (hydrogen-centroid distance = 3.121 Å, carbon-centroid distance 4.027 Å, see Supporting Information).

We were unable to generate X-ray quality single crystals of either of the smaller octahedral cages $[Pd_6(\mathbf{1a})_8](BF_4)_{12}$ or $[Pd_6(\mathbf{1b})_8](BF_4)_{12}$. To provide an estimate of the size of those cage systems we exploited MMFF molecular modeling (SPARTAN16, MMFF, Supporting Information). The $[Pd_6(\mathbf{2a})_8]^{12+}$ cage was also modelled and the dimensions compared to the X-ray diffraction data. The calculated cage dimensions (Pd---Pd1' 25.048 verses 25.596(3) Å and Pd1---Pd1'' 17.010-17.877 verses 18.119(3)Å) were in good agreement with the crystallographic data, a strong indication the MMFF models could be used to effectively estimate the size of the smaller octahedral cages. The modelling indicated that the $[Pd_6(\mathbf{1a})_8](BF_4)_{12}$ cage was smaller than the $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ system, as expected, the diametrically opposed Pd^{II} ions were separated by 2.1 nm (Pd1---Pd1' 21.090 Å) and axial and equatorial Pd^{II} ions were approximately 1.45 nm apart (Pd1---Pd1'' 14.114-15.063 Å) meaning the alkyne linked cages have a smaller internal cavity than the aryl linked systems (Supporting Information).

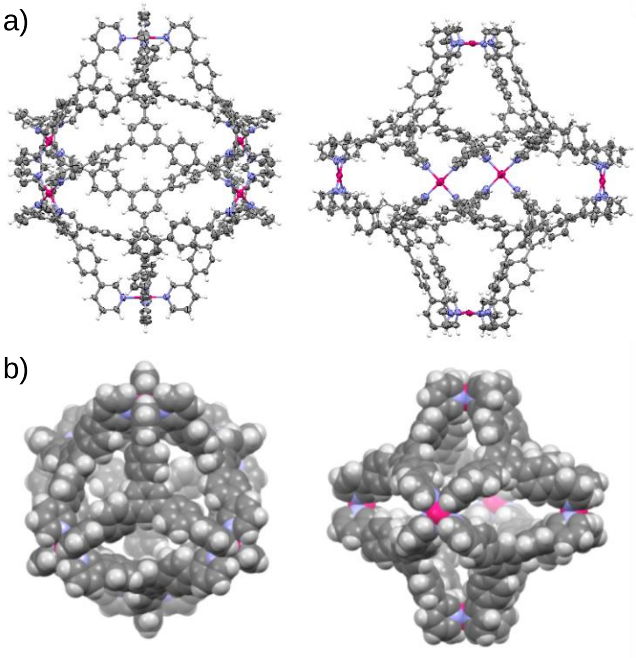

Figure 7. The molecular structure of the $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ shown as a) two ORTEP[25] diagrams and b) two space filling representations (anions and solvents molecules were not located). Ellipsoids are shown at the 50% probability level. Colours: Grey = carbon, white = hydrogen, magenta = palladium, blue = nitrogen. Bond lengths/interatomic distances (Å): Pd1-N1 2.05(2), Pd1-N3 2.067(9), Pd1-N5 2.07(1), Pd1-N7 2.056(9), Pd1---Pd1' 25.596(3), Pd1---Pd1'' 18.079(3).

Guest encapsulation studies

Having confirmed the formation of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages, we set out to examine the molecular recognition properties for these large metallosupramolecular hosts. The cages only showed appreciable solubility in DMSO and dimethylformamide (DMF); therefore, the host-guest studies were carried out in these media. Initially, we choose to examine the neutral organic molecules adamantane, anthracene, and pyrene, as guests (Figure 6). These molecules had previously been shown to bind within related $[Pd_2(\mathbf{L_{dipy}})_4]^{4+}$ cages,[14d, 14e, 14g] $[Pd_6(\mathbf{L})_4]^{12+}$ cages[9g-i] and $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages,[19b] and it was reasoned that the guests should interact with our $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages through either dispersion (adamantane) forces or π-π interactions (anthracene, and pyrene). The binding interaction was examined using ^1H NMR spectroscopy ([D$_6$]DMSO, 298 K) with one of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages (1 equiv.) mixed with one of the guests (10 equiv.). Somewhat surprisingly, none of the aliphatic or aromatic compounds showed any signs of encapsulation when added to a DMSO solution of $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cage systems. No complexation induced shifts (CIS) for the proton resonances for either the

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guests or the host cages were observed indicating that the organic molecules were not interacting with the octahedral cages (Supporting Information). All of the guests were small enough that they should readily fit through the portals of the host cages. However, to preclude any size-based kinetic exclusion, the binding experiments were repeated at 80 °C. Again no CIS of either the host or guest molecules were observed suggesting that the organic molecules simply do not interact with the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages in neat DMSO. An additional guest, 1,8-naphthalimide (Figure 6) was chosen to examine this further. 1,8-Naphthalimide features aromatic units that should be able to interact with the host cages via π-π and dispersion interactions and it also contains amide units that could hydrogen bond to the $[Pd(py)_4]^{2+}$ binding sites of the octahedral hosts. Again, ^1H NMR spectroscopy ([D$_6$]DMSO, 298 *K*) was used to evaluate guest binding (Supporting Information). As was observed with the hydrocarbon guests, no CIS for the proton resonances of the 1,8-naphthalimide or the host cages were observed indicating that the neutral guest was not interacting with the octahedral cages (Supporting Information). While the lack of binding observed for these guest molecules was initially puzzling, the binding of BF_4^-,[16d, 16f, 16g, 16k, 21d, 26] DMF[21a, 21c] and DMSO,[21d] through hydrogen bonding and ion-ion interactions, has been observed in related metallosupramolecular architectures that feature the $[Pd(py)_4]^{2+}$ motif. Thus we presume that the DMSO or DMF solvent and the BF_4^- counter anions, in the absence of the hydrophobic effect, are out competing the aliphatic or aromatic compounds and occupy the cage cavity. ^{19}F NMR spectroscopy of the cages provided some support for this postulate (Supporting Information). ^{19}F NMR spectroscopy (either CD_3CN or *d*$_6$-DMSO, 298 K) of the each of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages revealed one broad signal at δ = –150 ppm (Supporting Information) which is shifted upfield by (~ 2 ppm) compared to the position of the BF_4^- ions of $NaBF_4$ in CD_3CN (Supporting Information), consistent with the complexation of the anions within the cage. In [D$_6$]DMSO similar results are observed, however, the CIS of the BF_4^- ions is smaller (0.3 ppm) presumably reflecting competition between the DMSO solvent molecules and the BF_4^- counter anions for binding sites with the cage.

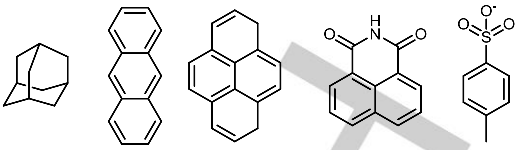

Figure 6. Neutral and anionic molecules examined as potential guest molecules.

The combined results suggested that even combinations of hydrogen bonding, π-π and dispersion interactions are not enough in order to achieve effective binding in the competitive DMSO solvent environment with these $[Pd_6(\mathbf{L})_4]^{12+}$ cages. This highlights the importance of both the hydrophobic effect[9, 14d, 14e, 14g, 19b, 20] and anion binding[14a] when designing cationic metallo-hosts. Anionic sulfonates have been shown to bind in other palladium(II) based metallosupramolecular architectures[16b, 16c, 16h-k, 21a, 21c, 21f, 27] via a combination of hydrogen bonding and ion-ion interactions. The presence of ion-ion interactions should further enhance any potential guest binding within the octahedral $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages. Therefore, we explored the used of *p*-toluenesulfonate (TsO^-) as guest. Addition of NaOTs into a *d*$_6$-DMSO solution of one of the cages (either $[Pd_6(\mathbf{1a\text{-}1b})_8]^{12+}$ or $[Pd_6(\mathbf{2a\text{-}2b})_8]^{12+}$) led to CIS of the both the guest and the host (Supporting Information). When the cages were mixed with 1 equiv. of the TsO^- guest, appreciable (0.10-0.15 ppm) shifts of the endohdral H_6 proton of the respective cage systems were observed. In the presence of 10 equiv. of TsO^- the H_6 proton resonance was shifted even further downfield (0.30-0.50 ppm). This provided strong evidence for endohedral TsO^- binding within the cavities of the cages. However, there was evidence for guest interaction with the exohedral face of the cages as well with smaller CIS observed (0.02-0.06 ppm) for the H_2 proton resonance of the respective cage systems. The collected data suggest that ion assisted hydrogen bonding interactions are essential for guest interaction with the octahedral cages in the highly DMSO polar solvent environment.

There are 12 potential guest binding sites, involving endohedral or exohedral interaction with the $[Pd(py)_4]^{2+}$ units of the cages. To gain insight in the stoichiometry of the host-guest interaction mole-ratio method[28] NMR titrations were carried out. Following the change in chemical shift of the H_6 proton resonance of the cages, mole-ratio titrations indicated that the smaller $[Pd_6(\mathbf{1a\text{-}1b})_8]^{12+}$ cages interact with three TsO^- guest molecules, while the larger $[Pd_6(\mathbf{2a\text{-}2b})_8]^{12+}$ systems were interacting with four TsO^- anions (Figure 7 and Supporting Information).[29] Thus there is clearly a size selectivity for the guest binding interaction with the different cages. Molecular modelling (SPARTAN16, MMFF, Supporting Information) of the TsO⁻/cage host-guest adducts suggests that the cages can accommodate three ($[Pd_6(\mathbf{1a\text{-}b})_8]^{12+}$ cages) or four ($[Pd_6(\mathbf{2a\text{-}b})_8]^{12+}$ cages) guest without any obvious steric impediment (Supporting Information, Figure S41). The volumes of the ($[Pd_6(\mathbf{1a\text{-}b})_8]^{12+}$ and $[Pd_6(\mathbf{2a\text{-}b})_8]^{12+}$ cages were estimated to be 1500 and 1900 Å^3, respectively (Supporting Information Figure S40). The volume of the TsO⁻ guest molecule was calculated to be 154 Å^3 (SPARTAN16, Supporting Information). Therefore the three TsO⁻ guest occupy 30.8% of the $[Pd_6(\mathbf{1a\text{-}b})_8]^{12+}$ cage cavities while four TsO⁻ fill 32.4% of the $[Pd_6(\mathbf{2a\text{-}b})_8]^{12+}$ cages. While these values are self-consistent they are less than the 55% expected from Rebek's rule.[30] This deviation from the Rebek rule is presumably caused by repulsive anion-anion interactions between the bound guest molecules.

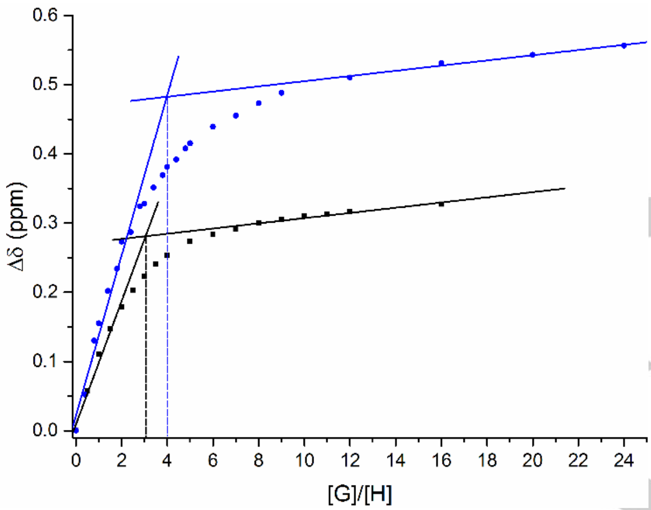

Figure 7. Mole-ratio titration plots (500 MHz, d_6-DMSO, 298 K)[28] showing the ^{1}H chemical shift change of the internally directed proton H_6 of the $[Pd_6(\mathbf{2a})_8]^{12+}$ (blue data) and $[Pd_6(\mathbf{1a})_8]^{12+}$ (black data) cages with increasing equiv. of TsO⁻ guest (from 0 to 22 equiv.). [Host] = 1.07 mM.

Additionally, we attempted to obtain further information on the stoichiometry of the host-guest interaction from electrospray ionization mass spectrometry experiments of the host-guest mixtures. The $[Pd_6(\mathbf{L_{tripy}})_8{\supset}(TsO^-)_n]^{12\text{-}n}$ adducts were generated by adding a [D$_6$]DMSO solution of the TsO⁻ guest to a [D$_6$]DMSO solution of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages at RT. A range of host-guest adducts we observed in the mass spectra of $[Pd_6(\mathbf{L_{tripy}})_8{\supset}(TsO^-)_n]^{12\text{-}n}$ (n = 5-9) with higher stoichiometries than those observed for the mole ratio titrations. This suggests that the host-guest interaction is strong and that in addition to the observing tight endohedral bound guests, the presumably weaker association of TsO⁻ with the exohedral binding sites on the exterior surface of the octahedral cages can be detected under the conditions of the mass spectral analysis.

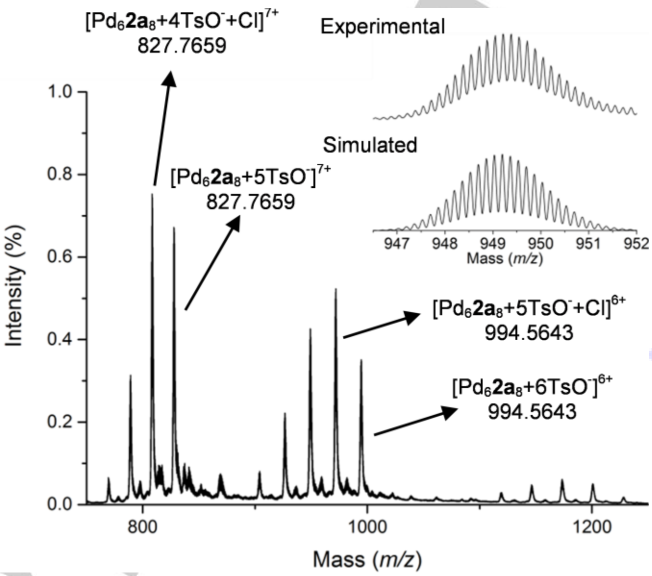

Figure 8. HR-ESI-TOF mass spectrum of $[Pd_6(\mathbf{2a})_8{\supset}(TsO^-)_n]^{12\text{-}n}$ showing host-guest adduct signals with varying numbers of guest molecules associated. Inset: comparison of experimental (top) and simulated (bottom) spectra for the signal of $[Pd_6(\mathbf{2a})_8{\supset}(TsO^-)_6]^{6+}$ (Experimental *m/z* 949.2144; Simulated *m/z* 949.1967).

To further probe the importance of the hydrophobic effect on guest binding we examined the use of mixed water-DMSO solvent systems for host-guest studies. Preliminary experiments showed that the $[Pd_6(\mathbf{1a})_8]^{12+}$ and $[Pd_6(\mathbf{2a})_8]^{12+}$ cages were soluble in a 1:1 mixture of D_2O and [D$_6$]DMSO therefore we used this solvent system to re-examine binding of the neutral organic molecules adamantane, anthracene, pyrene and 1,8-naphthalimide within the cage cavities (Supporting Information).

The binding interaction was examined using ^{1}H NMR spectroscopy ([D$_6$]DMSO/D_2O 1:1, 298 K) with one of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages (1 equiv.) mixed with one of the guests (10 equiv.). When 10 equiv. of the guests (anthracene, pyrene, and 1,8-naphthalimide) were added to the cages in 1:1 [D$_6$]DMSO /D_2O, suspensions were obtained indicating that the guest molecules were not completely soluble at higher concentrations in this solvent mixture. These suspensions were stirred at RT for 16 hours then centrifuged and the solution decanted and analyzed using ^{1}H NMR spectroscopy. Unlike what was observed in neat [D$_6$]DMSO solvent, the anthracene, pyrene, and 1,8-naphthalimide guest molecules displayed CIS for their proton resonances indicative of guest binding (Supporting Information). As observed previously in neat [D$_6$]DMSO, no CIS were observed

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with the adamantane guest suggesting a combination of π-π interactions and the hydrophobic effect were required for guest uptake.

In addition to the CIS of the guest molecules, several proton resonances of the $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ cages shifted in the presence the guest molecules. The endohdral H_6 proton of each cage undergoes a small (0.05-0.17 ppm) shift, while the proton resonances of the trisubstituted benzene spacer units (either H_{10} in **1a** or H_{12} in **2a**) shift upfield between 0.10-0.25 ppm consistent with a π-π interaction (Supporting Information). The proton resonances of the disubstituted phenyl linker (H_8 and H_9) of the $[Pd_6(\mathbf{2a})_8]^{12+}$ cage also show upfield shifts of 0.10-0.15 ppm. While the planar organic guest molecules could potentially bind on the outside faces of the cages the exohedral H_2 protons of each cage display only very small CIS (0.01-0.05 ppm) indicating that the guest binding is predominantly within the cage cavity as would be expected on entropic grounds.

The proton resonances of the all the guest molecules within the cages were very broad at 298 *K* (Supporting Information). However, heating the host-guest mixtures to 353 *K* sharpens the resonances of the 1,8-naphthalimide (in both host cages) and the pyrene in the smaller cage to allow the host-guest stoichiometry to be estimated from integration of the guest resonances. Unfortunately, the proton resonances of anthracene guest molecules (in both host cages) remained too broad to allow reliable integration, and as such we were not able to estimate the host-guest stoichiometry for these systems. The smaller $[Pd_6(\mathbf{1a})_8]^{12+}$ cage was found to bind four 1,8-naphthalimide guests in $[D_6]$DMSO/D_2O 1:1, while the larger $[Pd_6(\mathbf{2a})_8]^{12+}$ cage interacted with six 1,8-naphthalimides. Three pyrene guest were found to bind with the smaller $[Pd_6(\mathbf{1a})_8]^{12+}$ cage, and the larger $[Pd_6(\mathbf{2a})_8]^{12+}$ cage was found to encapsulate five pyrene guest. Using the cage cavity volume calculated above and volumes for each guest molecule calculated in SPARTAN16 (Supporting Information), it was found that the four 1,8-naphthalimide guests occupy 50.6% of the $[Pd_6(\mathbf{1a})_8]^{12+}$ cage cavities while six 1,8-naphthalimide fill 59.7% of the $[Pd_6(\mathbf{2a})_8]^{12+}$ cage. Similarly, three pyrene fill 44% of the $[Pd_6(\mathbf{1a})_8]^{12+}$ cage cavity, while five pyrene occupy 59% of the $[Pd_6(\mathbf{2a})_8]^{12+}$ cage. The values for these neutral organic guest are consistent with the 55% expected from Rebek's rule.[30] Therefore we used the cage and guest volumes to estimate host-guest stoichiometry for the pyrene (with the larger cage) and anthracene host-guest adducts. Four pyrene guest molecules would occupy 46% of the larger cage, while five would fill 58%; thus it is likely that the either four or five guests bind in the $[Pd_6(\mathbf{2a})_8]^{12+}$ cage. The volume of anthracene was calculated to be 200 Å^3 (SPARTAN16). Therefore four guests would occupy 53.3% of the smaller cage and five guest molecules would fill 52.6% of the larger cage.

Conclusions

Four planar *C₃* symmetric tripyridyl ligands ($\mathbf{L_{tripy}}$ = **1a-b** and **2a-b**) were synthesized and used to assemble a family of $[Pd_6(\mathbf{L_{tripy}})_8](BF_4)_{12}$ octahedral cages. The ligands and cages were characterized using a combination of ^{1}H, ^{13}C and DOSY NMR spectroscopy, HR-ESI-MS, IR spectroscopy, and elemental analysis. Additionally, the solid state structures of two of the ligands (**1b** and **2b**) and the $[Pd_6(\mathbf{2a})_8](BF_4)_{12}$ cage were determined using X-ray crystallography. The molecular recognition properties of the cages with neutral and anionic guests was examined, in $[D_6]$DMSO and $[D_7]$DMF, using NMR spectroscopy, mass spectrometry and molecular modelling. No binding was observed with simple aliphatic and aromatic guest molecules or aromatic molecules featuring hydrogen bond acceptors units. However, anionic sulfonates were found to interact with the octahedral cages and the binding interaction was size selective. The smaller $[Pd_6(\mathbf{1a\text{-}b})_8]^{12+}$ cages were able to interact with three guest molecules while the larger $[Pd_6(\mathbf{2a\text{-}b})_8]^{12+}$ systems could host four guest molecules.

The molecular recognition properties of the cages with neutral guests were examined, in 1:1 $[D_6]$DMSO/D_2O mixtures to examine the importance of the hydrophobic effect. In this solvent mixture the anthracene, pyrene, and 1,8-naphthalimide guest molecules were all observed to bind with the cavity of the cages, while the adamantane guest still showed no interaction with the cationic hosts. These results strongly indicate that a combination of π-π interactions and the hydrophobic effect were required for the uptake of neutral guests. NMR spectroscopy and molecular modelling indicated that the cages bound multiple copies of the individual aromatic guests (between 3-6 guest molecules per cage).

The reported cage $[Pd_6(\mathbf{L_{tripy}})_8]^{12+}$ systems clearly display relativity large central cavities that can be used to encapsulate multiple guest molecules. The ability to bind multiple guest molecules could potentially be exploited for catalysis and drug delivery. However, the limited guest binding ability of the reported systems, in the absence of water, highlights the importance of both the hydrophobic effect,[9, 14d, 14e, 14g, 19b, 20] and competitive anion binding[14a] when designing cationic metallo-hosts.

Therefore, to improve the host-guest capabilities of these $[Pd_6(\mathbf{L}_{\mathbf{tripy}})_8](BF_4)_{12}$ octahedral cages and enable the binding of a wider range of guest molecules, we are now targeting systems decorated with water solubilizing groups and that contain larger, less competitive anions. Efforts in these directions will be reported in due course.

Experimental Section

Experimental Details including synthetic procedures and characterisation, NMR and MS spectral data, X-ray data (CCDC #: 1531037-1531039) and MMFF molecular models are available free of charge in the supplementary information.

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Keywords: metallosupramolecular architectures • molecular recognition • palladium(II) • cages • host-guest chemistry

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[29] Due to the high host-guest ratios observed (3:1 and 4:1) we are unable to curve fit the titration data and obtain binding constant data for the tosylate adducts as too many variables need to be fitted. We have attempted to gain some insight into the host-guest association constants by carrying out ^{1}H NMR titrations (d_6-DMSO) with larger di- and tetra-sulfonate guests, including sunset yellow, tartrazine, bis(p-sulfonatophenyl)phenylphosphine gold(I) chloride dipotassium and 5,10,15,20-tetraphenyl-21H,23H-porphine-p,p′,p″,p‴-tetrasulfonic acid tetrasodium hydrate. Unfortunately, while CIS were observed at low host-guest ratios, indicative of guest binding, precipitation of the H-G adduct is observed, in each case, once a 1:1 ratio was obtained in the titration.

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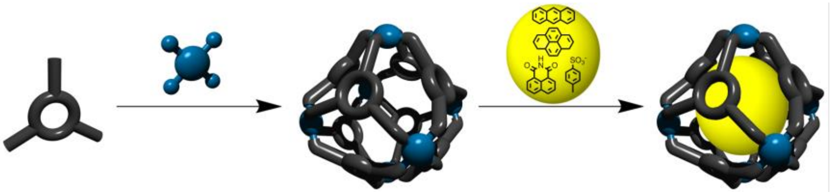

A combined effort: A series of octahedral cages of varying cavity sizes were synthesized with Pd^{II} and trigonal tripyridyl ligands. In dimethyl sulfoxide (DMSO) solution the cages only encapsulated anionic guests whereas in a 1:1 D_2O:DMSO solvent mixture neutral aromatic guests could be bound with the cage cavity via a combination of π-π stacking, dispersion forces and the hydrophobic effect.

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