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Long-cavity $[Pd_2L_4]^{4+}$ cages and designer 1,8-naphthalimide sulfonate guests: rich variation in affinity and differentiated binding stoichiometry

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One of the most appealing features of $[Pd_2L_4]^{4+}$ cages is their well-defined cavities, giving binding affinity for specific guests. If seeking to bind larger and more complex guests, an attractive strategy is to lengthen the ligand backbone and therefore the inter-palladium(II) distance and cavity length. In comparison to large hollow $[Pd_nL_{2n}]^{2n+}$ polyhedra, this approach retains a well-ordered cavity environment. We report here a novel ligand, 1,3-*bis*(4-(4-ethynylpyridine)-phenyl)-adamantane, that has a hydrophobic *bis*(phenyl)adamantane core and forms $[Pd_2L_4]^{4+}$ cages with a large 19 Å inter-palladium(II) cavity length. This cage binds long designer anions: naphthalimide sulfonates at ≥ 15 Å in length, which consist of two distinct domains: a naphthalimide and a phenyl sulfonate. This binding derives from hydrogen bonding between the endohedral pyridyl protons of the cage and the phenyl sulfonate group, and π-hydrophobic interactions between the adamantane core and the naphthalimide unit. The strength of binding depends on the degree of electron deficiency of the naphthalimide, brought about by the nature of substituents on this moiety, with binding constants for monoanionic guests ranging from 400 to 1800 M^{-1}. The host/guest stoichiometry was found to be 1:2, *unless* the guest possessed a second sulfonate group, and was small enough to fit end-to-end within the cavity, in which case the stoichiometry was 1:1, and resulted in a high binding constant (for DMSO solvent) of 6100 M^{-1}. This work demonstrates the subtle interplay and potential between cages and guests that are both large and that both have distinct dual zones able to interact with each other, and offers a pathway to specific and tunable binding of large guests.

Introduction

Metallosupramolecular cages[1] possess a cavity which, much like the active site of enzymes, can bind specific guests. Such guest encapsulation has been used for functions including, the storage of reactive species and pollutants,[2] drug delivery[3] and biological diagnostics,[4] and serving as reaction vessels[5] and catalysts.[6] In order to fully realise the potential of these structures, it is essential that chemists continue to enhance their control and deepen their knowledge over these binding events, and develop new methodologies and systems to exploit them.

The first example of a quadruply-stranded $[Pd_2L_4]^{4+}$ helicate by McMorran and Steel[7] in 1998 continues to inspire metallosupramolecular chemists to this day. This is not only in respect to structural variations of the $[M_2L_4]^{n+}$ assembly, but also an exploration of how these alterations impact upon the molecular recognition characteristics of these assemblies. This first cage from McMorran and Steel used a 'small' *bis*-monodentate ligand, 1,4-bis(3-pyridyloxy)benzene, and thus had a small internal cavity, with a Pd^{2+}---Pd^{2+} distance of 7 to 9 Å (depending on size of the anion bound, Figure 1(i)), and bound a variety of mono-anionic species.[7-8] Most guests bound in similar cages following this report have been, relatively speaking, small. Since this time, however, there have been $[Pd_2L_4]^{4+}$ cages reported with longitudinal expansion of the ligand backbone, and concurrent lengthening of this cavity dimension. In contrast to the approach of creating large hollow $[Pd_nL_{2n}]^{2n+}$ polyhedra,[9] these cages have retained, in many cases, the guest specificity derived from tailored cavity environments, but with the capacity to bind guests of increasing size. At the same time, ligands have been designed with varying internal character, to exploit or explore different interaction types with guests. These interaction types have been generally hydrogen bonding between guests and acidic C-H protons on

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the coordinating heteroaromatic rings, or hydrophobic and/or π-π interactions between the ligand core and the guest.

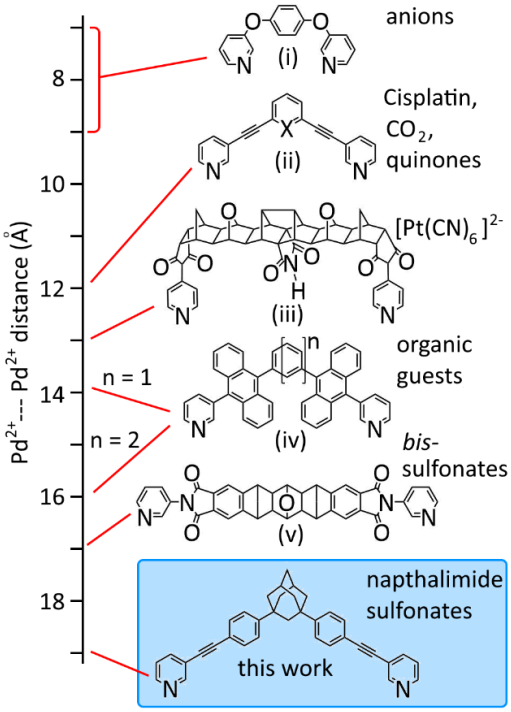

Figure 1 Exemplars of ligands from $[Pd_2L_2]^{4+}$ cages utilised for host guest chemistry, with the Pd^{2+}---Pd^{2+} distances of their cages, and some of their encapsulated guests. Numbering (i) – (v) cross references to discussion in the introduction, listed here is the corresponding author and first publication year: (i) Steel 1998, (ii) Crowley 2012, Lusby 2016, (iii) Clever and Pfeffer 2016, (iv) Yoshizawa 2013, 2015, (v) Shionoya 2009. X = N or CH. Solubilising elements and other substituent groups omitted for clarity.

Work by Crowley and co-workers with a tripyridyl ligand (Figure 1(ii)) has given a $[Pd_2L_4]^{4+}$ cage with a Pd^{2+}---Pd^{2+} distance of 12 Å, and this cage has been shown to bind the anticancer drug Cisplatin,[10] anions,[11] and, in the solid-state, CO_2.[12] In both cases, the key interaction between host and guest is hydrogen bonding between a hydrogen bond acceptor on the guest and the internally directed acidic proton of the coordinating pyridyl rings. Lusby and co-workers have also utilised this cage, and the analogue with a central phenyl linker[13] instead of pyridine (Figure 1(ii)) to bind quinones.[14] This binding event is similar to that utilised by Crowley and co-workers, with the two carbonyl groups of the quinone hydrogen bonding to the *endo*-pyridyl protons at both coordinative sites. They have exploited this binding to activate quinones as dienophiles for the Diels-Alder reaction, using the cage as a Diels-Alderase.[14b]

Clever and Pfeffer and co-workers used a [6]polynorbornane dipyridyl ligand to increase the distance between palladium(II) centres to 13 Å (Figure 1(iii)).[15] This allowed binding of a larger guest, $[Pt(CN)_6]^{2-}$, which possesses O_h symmetry. Encapsulation in the D_4 cage environment had the effect of enforcing desymmetrisation upon the bound species. Yoshizawa and co-workers have employed *bis*-pyridyl ligands with anthracene or acridinium panels linking to a central phenyl[16] or naphthalene[16c, 17] core (Figure 1(iv)) that give $[Pd_2L_4]^{4+}$ cages of 14 (phenyl) or 16 (naphthalene) Å in length. These hydrophobic cavities have proven excellent for binding a variety of guests, particularly organic aromatic molecules,[16a] including fullerenes. The acridinium-based cage also bound alkyl-BF_3^- anions through a combination of electrostatic attraction, hydrogen-bonding to the anion and π-hydrophobic interactions.[16c] A similar cavity length (Pd^{2+}---Pd^{2+} = 16 Å) in a cage reported by Bandi and Chand[18] from a dipyridyl ligand with a *bis*-amide linked *bis*-(phenyl)methylene also bound C_{60}. An even longer Pd^{2+}---Pd^{2+} distance in a $[Pd_2L_4]^{4+}$ cage used for host-guest chemistry was reported by Shionoya and co-workers (Figure 1(v)) with a norbornane-based ligand, with a 17 Å metal-to-metal span. This bound 1,1'-ferrocene-*bis*(sulfonate) in [D_3]acetonitrile with 1:1 stoichiometry, again utilising the internal hydrogen bonding sites on the pyridyl rings.[19] In a similar fashion, Shionoya, Clever and co-workers used this cage to bind a stoppered thread containing two sulfonate groups, forming a [2]pseudo-rotaxane that could be reversibly de-threaded by control of pH.[20]

There have certainly been larger $[Pd_2L_4]^{4+}$ cages developed, including a $[Pd_2L_4]^{4+}$ cage by Clever and co-workers with quinoline donors with a Pd^{2+}---Pd^{2+} distance of 18.8 Å.[21] In this work, the host-guest chemistry of an open 'bowl' $[Pd_2L_3(solvent)_2]^{4+}$ complex with C_{60} was explored. There has also been work by Severin and co-workers with dipyridyl ligands featuring *bis*-Fe(II) clathrochelate linkers that furnish cages of up to 3 nm in length.[22] Beves and co-workers have also reported a ligand with a *bis*-[Ru(terpy)$_2$] linker that gives a $[Pd_2L_4]^{4+}$ cage with a Pd^{2+}---Pd^{2+} distance of ~3.5 nm.[23] However, the host-guest behaviour of these systems has not been explored. Yoshizawa and co-workers, and Yoshizawa, Chand and co-workers have likewise reported 'long' $[Pd_2L_4]^{4+}$ cages (Pd^{2+}---Pd^{2+} = 28 Å) that have a 'peanut-shaped' internal space, using poly-anthracenyl ligands.[24] These bind fullerenes and other guests. They might be considered double-cavity systems with the cavities linked by a narrow aperture but have in fact bound covalently-linked *bis*-fullerene guests occupying both spheres of the 'peanut'. As with many other anthracenyl-based architectures reported by this group, the driving force for the host-guest interaction was again the π-rich environment provided by the polyaromatic panels.[25]

As part of our ongoing exploration of metallosupramolecular architectures[26] and molecular recognition,[6b, 27] we were interested in investigating the binding of long guests possessing different structural elements, within longitudinally-extended $[Pd_2L_4]^{4+}$ cages. In this regard, the length of the cage was not important in its own right, but rather in its ability to therefore contain spatially-separate domains. We sought to see whether a non-aromatic carbon- and hydrogen-rich core (adamantane)[28] could fulfil a similar role to anthracene in promoting encapsulation of hydrophobic guests, and in influencing binding affinities.[29] Furthermore, we hoped at the same time to exploit the internal hydrogen bonding event that has proven so fruitful in other systems. In other words, we sought to investigate the binding of large guests with more than one domain within multi-domain large cages that retained the tailored-cavity characteristics of smaller cages. In this respect, guests containing 1,8-naphthalimides are an excellent choice. 1,8-Naphthalimides are interesting molecules in their own right, being planar aromatic compounds, often with colorimetric, emissive and/or sensing properties,[30] and are used as fluorescent probes[31] and biological agents/drugs such as amonafide.[31-32] Some of us have an established interest in their chemistry,[33] including 1,8-

naphthalimide sulfonates.[34] 1,8-Naphthalimide sulfonates (Figure 2) have two domains: the anionic sulfonate group, potentially capable of hydrogen bonding to the *endo* acidic pyridyl protons of a $[Pd_2L_4]^{4+}$ cage,[35] and the naphthalimide moiety, with affinity for hydrophobic environments. While they do not occupy the same volume (~300 Å^3) as spherical guests such as C_{60} (~700 Å^3), they are comparatively long molecules to act as encapsulated guests, with a long axis of ≥ 15.5 Å between furthermost van der Waals surfaces.[36]

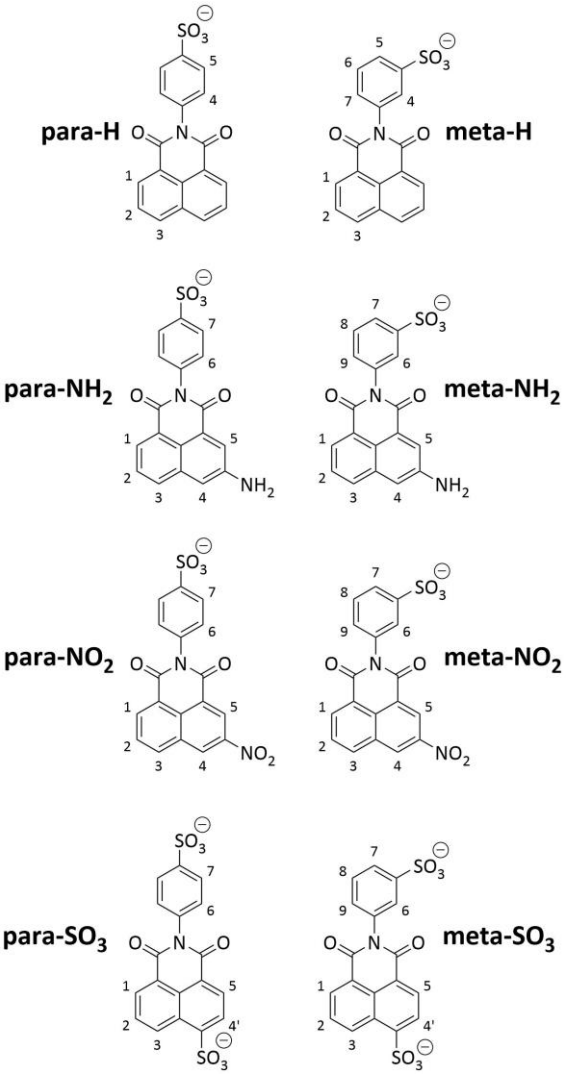

Figure 2 The 1,8-naphthalimide sulfonates utilised as guests in this study. Monoanionic guests were isolated as tetramethylammonium salts, dianionic guests as dipotassium salts.

We report here a new dipyridyl ligand, 1,3-*bis*(4-(4-ethynylpyridine)-phenyl)-adamantane (**L**) (Figure 1 bottom, Figure 3 top). In combination with Pd^{2+} metal salts (BF_4^- and NO_3^-) this ligand forms a $[Pd_2L_4]^{4+}$ cage with a ~19 Å Pd^{2+}---Pd^{2+} distance. This cage binds our designer 1,8-naphthalimide sulfonate anions, through a combination of hydrogen bonding between the sulfonate group and the *endo*-pyridyl proton, and π-solvophobic interactions between the naphthalimide subunit of guests and the adamantane core and phenyl rings of the ligand. Through alterations in the position and nature of substituents and thus in guest size and character, the strength and stoichiometry of binding can be influenced. This has allowed us to accurately map out the recognition character of the cage.

Results and discussion

Synthesis

Ligand synthesis was facile: a Sonogashira coupling between 1,3-*bis*(4-iodophenyl)-adamantane[37] and 3-ethynylpyridine (ESI†), accomplished in 59% yield. The ligand **L**, (Figure 3 *top*) showed the expected number of environments in the ^{1}H NMR spectrum (ESI†, Figure 4a), chiefly the five separate adamantane environments, related to environments g, i and j, and the splitting of the h environment into an AB quartet (h' being closer to the proton environment g than h). The ligand was also characterised via ^{13}C NMR and IR spectroscopies, high resolution electrospray ionisation mass spectrometry (HR-ESI-MS) and X-ray crystallography (Figure 3, ESI†).

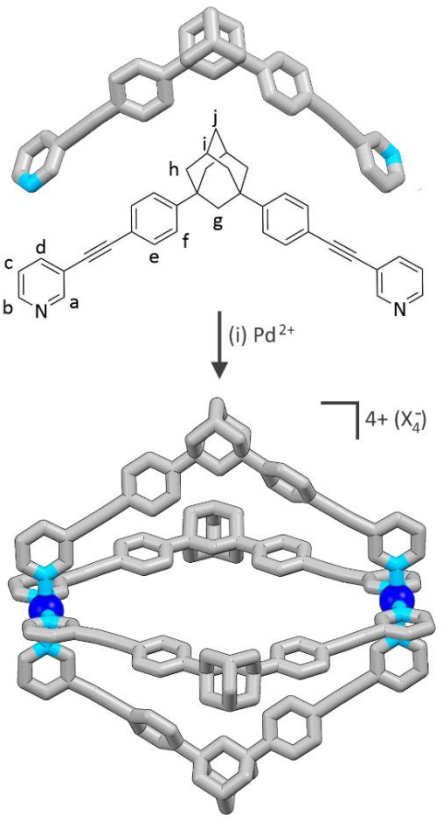

Figure 3 Synthetic scheme. Conditions: (i) either $[Pd(CH_3CN)_4](BF_4)_2$ or $Pd(NO_3)_2{\cdot}2H_2O$, DMSO. The $[Pd_2L_4]^{4+}$ cage (**C**) thus formed is shown in tube form as the crystal structure obtained for the $[Pd_2L_4](NO_3)_4$ cage, hydrogen atoms, counterions and solvent omitted for clarity. Colours: carbon grey, nitrogen light blue, palladium dark blue.

The combination of **L** with Pd^{2+} salts (either $[Pd(CH_3CN)_4](BF_4)_2$ or $Pd(NO_3)_2{\cdot}2H_2O$) in a 4:2 ratio in $[D_6]$DMSO resulted in a ^{1}H NMR spectrum with a single set of ligand environments, with the resonances associated with the pyridyl ring (H_a and H_b) being shifted downfield ($\Delta\delta$ = 0.66 – 0.75 ppm), consistent with complexation (Figure 4a and b). The degree of the shift downfield was (very) slightly larger for the NO_3^- counterion compared to BF_4^-. HR-ESI-MS confirmed the 4:2 ratio of ligand to metal ion (for example for $\mathbf{C}(BF_4)_4$, *m/z* = 543.6986, $[Pd_2L_4]^{4+}$, other data in ESI†).

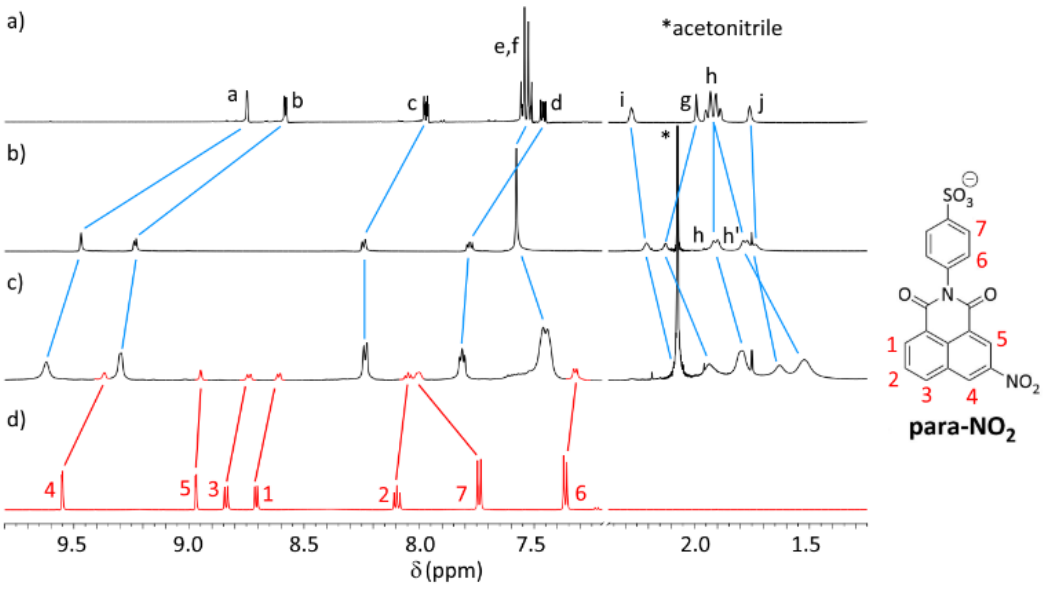

Figure 4 Partial stacked ^{1}H NMR spectra (600 MHz, [D_6]DMSO, 298 K, **C** = 2.5 mM) of a) **L**, b) **C**$(BF_4)_4$, c) **C**$(BF_4)_4$ + 1eq. **para-NO₂**, and d) **para-NO₂**.

Vapour diffusion of diethyl ether into a DMSO/DMF solution of the NO_3^- cage gave crystals suitable for X-ray diffraction, the solution from which ($P2_1/c$) revealed a $[Pd_2L_4]^{4+}$ cage (**C**, Figure 3 *bottom*), with a Pd^{2+}---Pd^{2+} distance of 18.957(1) Å. The cage has four portals, each of which is lined with the adamantane cores of two of the ligands, with the protons g and h' directed into the cavity or towards the portals (ESI†). The structure obtained from crystals of the BF_4^- cage revealed a similar structure in the same spacegroup with essentially the same cell dimensions (ESI†). In both, cages interacted with anions on the exohedral face of the $Pd(py)_4$ units of the cage through C-H---anion hydrogen bonding, with each anion hydrogen bonding to two cages. In the structure for **C**$(BF_4)_4$, there was also internal encapsulation in a similar manner. However, solution phase analysis of the BF_4^- cage through ^{19}F NMR spectroscopy indicated that this anion interacted weakly at best in [D_6]DMSO (δ = -148.1 ppm, compared with -148.2 ppm for tetrabutylammonium BF_4, ESI†). The isolated yields were 71% for **C**$(BF_4)_4$ and 82% for **C**$(NO_3)_4$.

The eight guests investigated in this study were all 1,8-naphthalimide sulfonates (Figure 2). The sulfonate groups were all on a phenyl ring attached to the naphthalimide at the N1 position. The substitution of the sulfonate group was either in the *para* or *meta* position. The naphthalimide moieties were further substituted with either –H, -NH_2 or –NO_2 groups in a *meta* position to the imide carbonyl substitution, or in the *para* position with –SO_3^- groups: for example *para*-substituted with respect to the phenyl-sulfonate, nitro group on the naphthalimide: **para-NO₂**. The monoanionic guests were generated as $[N(CH_3)_4]^+$ salts. **Para-H** and **meta-H** were converted to these salts from previously reported pyridinium salts,[34b] while **para-NO₂** and **meta-NO₂** were synthesised in analogous fashion. **Para-NH₂** and **meta-NH₂** were synthesised via hydrogenation under a H_2 atmosphere with palladium on carbon from the pyridinium nitro precursors. Using similar procedures to those above, **para-SO₃** and **meta-SO₃** were synthesised as dipotassium salts (ESI†). The yields at the final stage for all guests were 54 – 96%.

The ^{1}H NMR spectroscopic chemical shifts of the naphthalimide unit of the guests were considered to give insight into the electronic effects of the various substitutions (ESI†). Relative to the unsubstituted guests (**para-H** and **meta-H**), the amino-substituted guests had chemical shifts ([D_6]DMSO) further upfield indicating that these guests were more electron rich ($\Delta\delta H_{1,2,3}$ = -0.27 – -0.43 ppm). The inductively and mesomerically withdrawing nitro group brought about downfield shifts across the entire naphthalene moiety (for $H_{1,2,3}$, Δδ = 0.18 – 0.33 ppm compared to the unsubstituted guests). The protons *ortho* to the substitution, H_4 and H_5, were downfield from those in the amino substituted guests (Δδ = 0.56 – 1.43 ppm), also due to hydrogen bonding between them and the nitro group. Sulfonate substitution induced downfield shifts in the ^{1}H NMR spectra localised to the location of substitution ($\Delta\delta H_{3,4'}$), in keeping with the effect of the sulfonate being primarily electron withdrawing in a localised fashion. As expected, this suggests that the electron deficiency of the naphthalimide functionalities is ordered: -NH_2 < -H < -SO_3^- < -NO_2.

Host-guest chemistry

Model guests

The cage used for an exploration of host-guest chemistry was **C**$(BF_4)_4$. Before exploring the recognition between the cage and the 1,8-naphthalimide sulfonates, we sought a basic understanding of how the different components of the guests (phenylsulfonate and naphthalimide) interacted with the cage. To this end we used tetramethylammonium para-toluenesulfonate (**para-Ts**) and the four naphthalic anhydrides, 1,8-naphthalic-anhydride, 3-amino-1,8-naphthalic-anhydride, 3-nitro-1,8-naphthalic-anhydride and 4-sulfonate-1,8-naphthalic-anhydride, as model guests in ^{1}H NMR spectroscopic studies. A brief summary of the findings from these model studies is given here (spectroscopic details in the ESI†).

Titration of **para-Ts** into a solution of **C**$(BF_4)_4$ brought about small shifts in the cage architecture, and only for the resonance associated with the endohedral pyridyl proton, H_a. These shifts were to a downfield position, consistent with hydrogen bonding between the

sulfonate group and these protons.[11] The guest was therefore encapsulated. The protons from the ligand core did not undergo significant spectral shifts, showing that **para-Ts** did not interact with the *bis*(phenyl)adamantane linker. Assuming a 1:2 binding model (in line with larger, more strongly binding guests, see below),[38] a non-cooperative binding constant of K_{11} = 76 ± 2 M^{-1} was determined.[39] 1:2 binding with **para-Ts** (and with 2-naphthalene-sulfonate, see **nap-SO$_3$** below) has previously been observed in $[Pd_2L_4]^{4+}$ systems of sufficient size.[40]

Only one of the naphthalic anhydrides interacted with the cage and gave a ^{1}H NMR spectrum with altered chemical shifts from 'free' host or guest. Unsurprisingly, this was the anionic, sulfonate-containing 4-sulfonate-1,8-naphthalic-anhydride, **nap-SO$_3$**. Shifts downfield for the resonance of the H_a proton of the cage indicated a hydrogen bonding event (and internal encapsulation), as did downfield shifting of the 3 and 4' proton environments of the guest. In contrast, the nitro-containing **nap-NO$_2$** did not interact with the cage, presumably because it is a less effective hydrogen bonding group, especially in DMSO solvent. With **nap-SO$_3$**, the chemical shifts of the other guest environments and the *bis*(phenyl)adamantane core moved upfield, indicative of π-hydrophobic interactions. These shifts were small (Δδ = 0.05 – 0.06 ppm over 10 equivalents): molecular modelling indicates poor surface overlap between the naphthalimide moiety and the ligand core during this hydrogen bonding event (ESI†). Again assuming 1:2 host/guest binding stoichiometry, non-cooperative binding was calculated at K_{11} = 176 ± 7 M^{-1},[39] higher than that of **para-Ts**. Hence, while in DMSO there was not sufficient energetic favourability for interaction between naphthalic anhydrides and the cage, when tethered to an anionic hydrogen bonding acceptor, interaction occurs and leads to enhanced overall affinity.

Mono-anionic guests

One equivalent of each guest and **C**$(BF_4)_4$ were combined in a DMSO/DMF solvent mix, and mass spectral data obtained for the samples. In all cases, the 3+ species obtained for **C** with the guest was of greater intensity than other 3+ peaks (such as $[Pd_2\mathbf{L}_4 + BF_4]^{3+}$ for example), suggesting affinity between host and the guests (for example, [**para-NO$_2$**⊂**C**]$^{3+}$, *m/z* = 857.2724) (ESI†).

In the ^{1}H NMR spectra ([D_6]DMSO) of the combination of 1 equivalent of each guest with the host ([C] = 2.5 mM), there were spectral shifts in the resonances of the host architecture (Figure 4, ESI†).[41] One of these was of the internally directed proton from the coordinating pyridine ring (H_a), which moved to higher chemical shift upon introduction of a guest, indicating a hydrogen bonding event on the interior of the cage (with the guest **para-NO$_2$**, Δδ(H_a) = 0.15 ppm). The second set of significant shifts were to further upfield frequencies, for the e/f resonances of the phenyl rings of the cage (with **para-NO$_2$**, Δδ($H_{e/f}$) = -0.13 ppm), and from the adamantane core, particularly the g resonance from the proton directly orientated into the cage cavity (with **para-NO$_2$**, Δδ(H_a) = -0.19 ppm), and the h' resonance from the methylene proton likewise internally positioned (with **para-NO$_2$**, Δδ(H_a) = -0.25 ppm). These shifts suggest interaction between the aromatic surface of the guests and the hydrophobic elements of the cage. The size of the shifts of the cage architecture depended on the guest, with the order being -NO_2 > -H ≈ -NH_2. The trend saw (relatively) electron deficient 1,8-naphthalimide sulfonates inducing larger shifts in the cage than electron-rich guests.

Mole ratio titrations[38a] of the mono-anionic guests were carried out using ^{1}H NMR spectroscopy, as while some of the 1,8-naphthalimide sulfonates described herein are weakly emissive in DMSO, unfortunately preliminary investigations revealed that even small amounts of Pd^{2+} (either as part of a cage or free in solution) quenched the fluorescence, meaning fluorescence could not be used to quantify host-guest interaction**.** Titration of guests into a 1.25 mM [D_6]DMSO solution of **C** and monitoring with ^{1}H NMR spectroscopy revealed that there was a 1:2 host-guest ratio in the adducts formed (ESI†). The capacity for 1:2 binding was corroborated through X-ray crystallography. Vapour diffusion of diethyl ether into a DMF solution of **C**$(BF_4)_4$ and 2 equivalents of **para-NO$_2$** gave crystals suitable for X-ray diffraction. The solution from one of these ($P2_1/c$) revealed a structure with two (symmetry equivalent) guests encapsulated (Figure 5). The sulfonate of each guest was hydrogen bonding to the H_a *endo* protons of the coordinated pyridyl rings (O---H-C: 2.41 – 2.53 Å). The naphthalimide section of the guest lay against the hydrophobic diphenyl-adamantane core of a ligand backbone. The nitro group was orientated out of the cage environment. Interestingly, the cell dimensions and packing were very similar to those of the 'empty' cage structures, suggesting a strong preference for this lattice arrangement. Efforts to crystallise other mono-anionic guests with either **C**$(BF_4)_4$ or **C**$(NO_3)_4$ gave crystals only of the respective cages. It is possible that in solution, two adamantane units 'squeeze' together around the naphthalimide during the binding event.

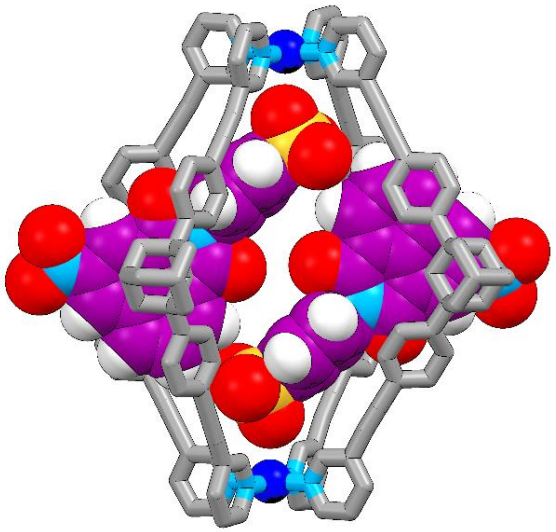

Figure 5 Depiction of the X-ray crystal structure of [(p**ara-NO$_2$**)$_2$⊂**C**]$^{2+}$, with the cage shown in tube style and the guests in spacefilling style. Some hydrogen atoms and counterions omitted for clarity. Colours: carbon grey for the cage and purple for the guests, nitrogen light blue, oxygen red, palladium dark blue, sulphur orange.

The binding mode in all cases was best described as non-cooperative (ESI†). The highest constant obtained was with **para-NO$_2$**, K_{11} = 1800 ± 300 M^{-1}, and the lowest was **meta-NH$_2$**, 360 ± 30 M^{-1} (Table 1). K_{12} in the non-cooperative system is one quarter of K_{11}: hence in these large cavities with large spatial separation between bound anionic guests, no negative cooperativity appears to be present. The overall trend in binding constants was in agreement with the complexation

induced shifts from ^{1}H NMR spectroscopic data: -NO_2 > -H > -NH_2. While there were nominal differences between the constants for *para*- and *meta*- guests (*para* having higher affinities), these were within calculated errors.

It is clear from these data that although the majority of 1,8-naphthalic anhydride model compounds did not interact with the cage, when connected to the phenylsulfonate domain in the guests the chemical character of the 1,8-naphthalimides strongly influenced the overall binding affinity.

Table 1 Host/guest stoichiometries and non-cooperative binding constants for guests with **C**$(BF_4)_4$ in this study. Studies carried out via ^{1}H NMR titrations, in [D_6]DMSO, 298 K, with [**C**] = 1.25 mM. Binding constants are expressed as K_{11}, the second binding event, K_{12} (where applicable) is one quarter of K_{11}.

GUEST	HOST:GUEST RATIO	K_{11} (M^{-1})
para-Ts	1:2	76 ± 2
nap-SO_3	1:2	176 ± 7
para-H	1:2	800 ± 200
meta-H	1:2	670 ± 80
para-NH_2	1:2	420 ± 50
meta-NH_2	1:2	360 ± 30
para-NO_2	1:2	1800 ± 300
meta-NO_2	1:2	1400 ± 400
para-SO_3	1:2	3700 ± 500
meta-SO_3	1:1	6100 ± 900

We attribute this to the presence of electron withdrawing groups strengthening interactions with the adamantane core. It would perhaps be plausible that for –NO_2 guests the nitro group hydrogen bonds to the Pd(py)$_4$ protons at the opposite end from the sulfonate, but given the 1:2 binding stoichiometry, the fact that **nap-NO_2** shows no interaction of this sort, and that the guest resonances 4 and 5 move upfield upon encapsulation (Figure 4), indicating π-alkyl interactions rather than hydrogen bonding, this is less likely than the effect of nitro substitution being to tune the electronic character of the naphthalimide. We turned to DFT calculations (BP86, def2-SVP) for additional corroboration of this, comparing ΔE of [**para-NO_2⊂C**]$^{3+}$ (with the -NO_2 group hydrogen bonding to the Pd(py)$_4$ protons) with [(DMSO)(**para-NO_2**)⊂**C**]$^{3+}$ (-NO_2 group not binding, with DMSO hydrogen bonding), finding this second mode more enthalpically favoured (ESI†).

Dianionic guests

We next investigated the interaction between the *bis*-sulfonate dianions (**para-SO_3** and **meta-SO_3**) and the cage. In contrast to the earlier guests, the charge balance for the dianions was made up by two potassium cations. However, introduction of a large excess of KBF_4 into a solution of the cage resulted in effectively no ^{1}H NMR spectral shifts, indicating that the identity of the cation with the guests was not important. Analysis through HR-ESI-MS of 1:1 solutions of the cage and *bis*-sulfonate guests (DMSO/DMF) showed association between the host and the guests. For example, for [**meta-SO_3⊂C**]$^{2+}$, *m/z* = 1303.3753 (ESI†).

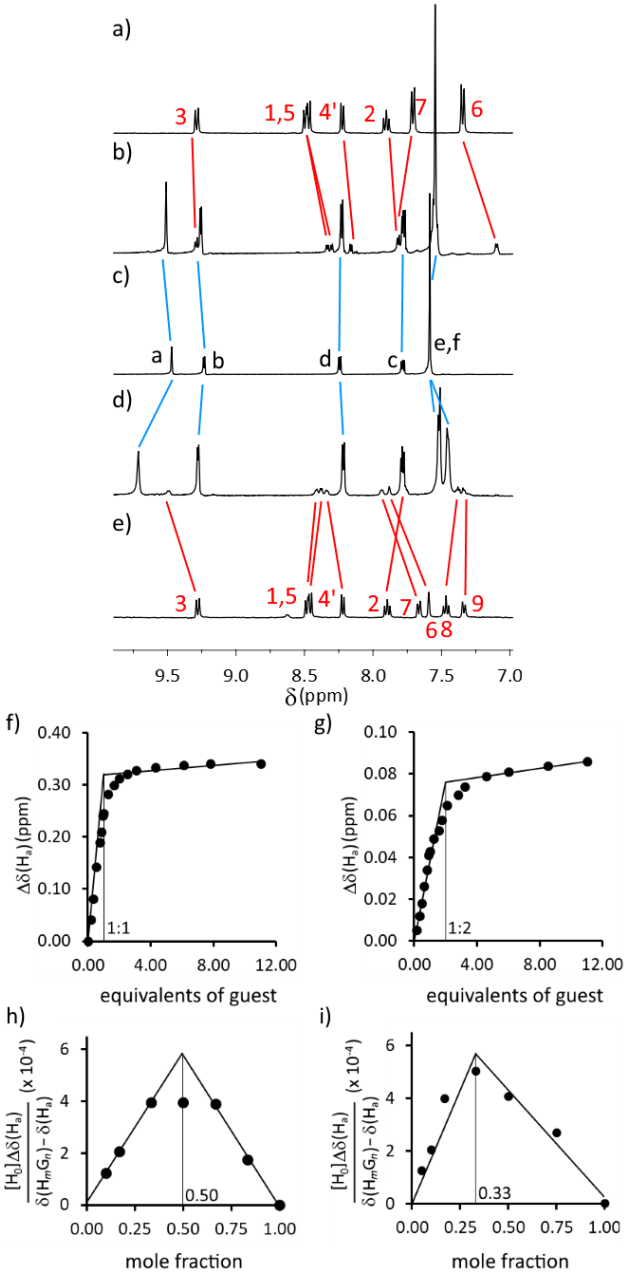

Figure 6 *Above:* partial stacked ^{1}H NMR spectra (600 MHz, [D_6]DMSO, 298 K, **C** = 1.25 mM) of a) **para-SO_3**, b) 1:1 **C**$(BF_4)_4$ and **para-SO_3**, c) **C**$(BF_4)_4$, d) 1:1 **C**$(BF_4)_4$ and **meta-SO_3**, and e) **meta-SO_3**. *Below:* plots of mole-ratio titrations (600 MHz, [D_6]DMSO, 298 K, [**C**] = 1.25 mM) for f) **meta-SO_3** and g) **para-SO_3**, and Job plots (600 MHz, [D_6]DMSO, 298 K, [system total] = 2.5 mM) for h) **meta-SO_3** and i) **para-SO_3**.

Introduction of 1 equivalent of the guests into a 1.25 mM [D_6]DMSO solution of **C**$(BF_4)_4$ brought about, as with the monoanionic guests, downfield shifting of the H_a resonance in the ^{1}H NMR spectra, and upfield shifting of the resonances pertaining to proton environments e/f, g and h'. At higher concentrations, combinations of hosts with dianionic guests were prone to precipitation. The spectral shifts were far more pronounced for **meta-SO_3**, (for example Δδ(H_a) = 0.25 ppm at 1:2 eq, compared with 0.05 ppm for **para-SO_3**, Figure 6). Thus, of

all the guests screened, only the *meta* variant of the *bis*-sulfonates brought about larger shifts than the *para* guest: for all others the *para* guest induced larger shifts. At 0.5 equivalents of **meta-SO$_3$**, the H_a resonance was broadened and slightly split into two (ESI†). This was not observed with any other guests. A similar observation has been made by Shionoya and co-workers in [D_3]acetonitrile with a $[Pd_2L_4]^{4+}$ cage and 1,1'-ferrocene-*bis*(sulfonate),[19] and like them we attribute this to exchange for this guest close to being slow on the ^{1}H NMR timescale.

Of particular interest were differences in the directionality of chemical shift changes for the guests themselves. With **para-SO$_3$**, the shifts of the proton resonances proximal to the sulfonate on the naphthalimide moiety were either effectively unchanged (H_3) or moved upfield -0.06 ppm ($H_{4'}$) (Figure 6, 1:2 eq.). With **meta-SO$_3$** however, these resonances moved significantly downfield ($\Delta\delta(H_3)$ = 0.22 ppm, $\Delta\delta(H_{4'})$ = 0.13 ppm, Figure 6, 1:2 eq.) consistent with the interaction between cage and the naphthalimide now being predominantly a hydrogen bonding event between the sulfonate and the internal Pd(py)$_4$ protons of the cage.

Titration of the dianionic guests into 1.25 mM solutions of **C**$(BF_4)_4$ using the mole ratio method[38a] clearly suggested a 1:2 host/guest ratio for **para-SO$_3$** (Figure 6g, ESI†). Due to the different substitution pattern from the monoanionic guests, **para-SO$_3$** is the largest of the guests in this study, with a length between van der Waals surfaces of 15.5 Å (compared with 14.6 Å for **meta-SO$_3$**). Molecular modelling of a 1:1 adduct of **C** with para-SO_3 with the two sulfonates spanning the ends of the cage showed that the guest is too large for the end-to-end binding mode (ESI†). The near-zero or upfield movement of the chemical shifts for peaks 3 and 4' respectively of the guest suggest that it is the phenylsulfonate rather than the sulfonate on the naphthalimide which is predominantly involved in hydrogen bonding. However, as these shifts are small in magnitude, an alternative reversed binding mode which in tandem gives time-averaged shifts cannot be entirely discounted. We note that hydrogen bonding through the phenylsulfonate allows greater overlap of the π-surface of the naphthalimide of the guest with the *bis*(phenyl)adamantane core (models in ESI†). The binding constant for **para-SO$_3$** was best described as non-cooperative, with K_{11} = 3700 ± 500 M^{-1} (ESI†).[39] This is higher than that for **para-NO$_2$** despite the greater electron deficiency of the naphthalimide for this latter guest (1800 ± 300 M^{-1}). Plausibly this is due to greater electrostatic attraction between the cage and the dianionic guest.

For **meta-SO$_3$**, inspection of the H_a and H_h resonances in a mole ratio titration was fully consistent with a 1:1 adduct. For the e/f, and g resonances this was less clear, but still indicated less than 1:2 equivalency (Figure 6f, ESI†). To corroborate that the two *bis*-sulfonates had different binding stoichiometries, we also used the Job method.[42] A mole fraction different from 0.5 for **meta-SO$_3$** would indicate that the 1:1 ratio was incorrect. There has been doubt cast over the use of the Job method for stoichiometric determination for 1:2 supramolecular systems in recent years,[38b, 39b, 43] but of all the 1:2 guests, **para-SO$_3$** was the most suited to this analysis, due to its higher binding constant (see below). The Job plots for these two guests (Figure 6h and i, details in ESI†) indicated 1:1 binding for **meta-SO$_3$** (mole fraction 0.5), and 1:2 binding for **para-SO$_3$** (mole fraction 0.33).

As with many of the monoanionic guests, attempts to crystallise the adduct from **C**$(BF_4)_4$ or **C**$(NO_3)_4$ resulted in crystallisation of only the respective cages. We reasoned that this packing could be disrupted by changing to a larger anion, which could not link cages together through exohedral hydrogen bonding in the same fashion with the same cell dimensions as BF_4^- or NO_3^-. We therefore generated a DMF solution of **C**$(SbF_6)_4$ *in situ* from the 4:2:4 combination of **L**/$[Pd(CH_3CN)_2Cl_2]$/$AgSbF_6$ and removal of precipitated AgCl through centrifugation. This was combined with 2 equivalents of **meta-SO$_3$** in DMF. Vapour diffusion of diethyl ether into this solution resulted in the formation of colourless crystals. The diffraction data obtained from one of these provided a solution ($P\bar{1}$) which revealed the structure of [(**meta-SO$_3$**)⊂C](**meta-SO$_3$**) with assorted DMF solvent molecules. One of the **meta-SO$_3$** guests lay outside the cavity, with the phenylsulfonate group hydrogen bonding to two exohedral Pd(py)$_4$ centres. The other lay within the cavity, with each of sulfonate groups hydrogen bonding to the respective internally directed C-H pyridyl protons at each end of the cavity (Figure 7, Pd^{2+}---Pd^{2+} = 19.2 Å). This structure clearly demonstrates that the guest can occupy the cavity in a 1:1 stoichiometry, in agreement with the solution-phase data. The binding constant for the 1:1 adduct was calculated to be K = 6100 ± 900 M^{-1}.[39] This is over an order of magnitude greater than the (1:2) binding constants for the weakest of the monoanionic guests. The affinity of cages for guests is strongly dependent on solvent, with polar DMSO significantly lowering binding constants.[14a] For 1:2 host/guest systems, binding constants in DMSO for encapsulated guests (including sulfonates) have been reported to 5000 M^{-1} for both $[Pd_2L_4]^{4+}$ cages[44] and a $[Pd_6L_8]^{12+}$ cage.[45] Clever and co-workers have reported a 1:1 adduct between a *bis*-sulfonate and a $[Pd_2L_4]^{4+}$ cage with K = 5200 M^{-1}. Hence [**meta-SO$_3$**⊂C]$^{2+}$ has a binding constant at the upper end of those reported in competitive DMSO solvent.

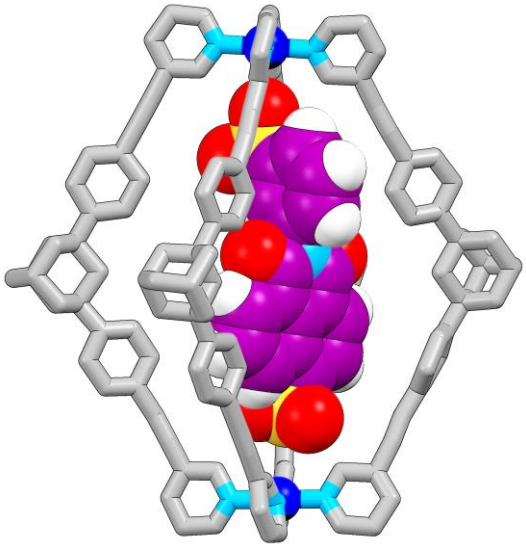

Figure 7 Depiction of the X-ray crystal structure of [**meta-SO$_3$**⊂**C**]$^{2+}$, with the cage shown in tube style and the guests in spacefilling style. Some hydrogen atoms and the *exo*-bound **meta-SO$_3$** anion omitted for clarity. Colours: carbon grey for the cage and purple for the guest, nitrogen light blue, oxygen red, palladium dark blue, sulphur orange.

Conclusions

A new dipyridyl ligand with a *bis*(phenyl)adamantane core has been synthesised. The combination of this ligand with Pd^{2+} gives a $[Pd_2L_4]^{4+}$ cage with a large ~19 Å Pd^{2+}---Pd^{2+} distance. This allowed binding of designer 1,8-naphthalimide sulfonate guests which are comparatively long for encapsulation in $[M_2L_4]^{n+}$ cages. To the best of our knowledge, molecules of this sort have not yet been explored as guests in this type of system. As noted in the introduction, naphthalimides have potential for many applications including as biological agents and probes. While the binding of these guests in DMSO fulfils no immediate function, future iterations will explore moving the system into other solvent systems. This will allow us to investigate the effects of encapsulation upon the multiple photophysical/sensing and cytotoxic properties of these compounds. In a more general sense, other guests with these two types of domain (hydrogen bonding and aromatic) would presumably interact with similar trends to those explored here.

By systematic investigation of these dual-domain guests through rational alteration of the position and character of their functional groups, we have been able to map out the molecular recognition behaviour of the cage with a good degree of insight. Generally speaking, and for all mono-anionic guests, these bound in a 1:2 host/guest ratio, with the sulfonate group hydrogen bonding to the internally directed pyridyl protons of the cage. The naphthalimide unit of the guests bound against the phenyl adamantane core of the cage ligands. The more electron deficient these naphthalimide moieties were, the stronger the binding affinity. The substitution position of the phenylsulfonate did not lead to significant changes in binding affinity for these guests, but became important for the *bis*-sulfonates. The two *bis*-sulfonate guests bound either in 1:2 or 1:1 fashion, depending on whether the guest size was such that it could fit end-to-end within the cavity. The **meta-SO_3** *bis*-sulfonate guest fit within the cavity, and its 1:1 binding constant was 6100 ± 900 M^{-1}, at the upper end of those reported in DMSO. The **para-SO_3** guest was less than an angstrom longer than **meta-SO_3**, but this slight increase in length was sufficient to switch binding stoichiometries.

Hence, variations in the size and electronic character of the guests allowed access to adducts with different binding stoichiometries and large differences in binding affinity. These results strongly show that 1) cages with more than one clearly defined domain can be matched to dual-domain guests. This is possible, even in this case with large guests with significant spatial separation between the sulfonate and naphthalimide, because of the length of the cage. Thus, 2) long-cavity $[Pd_2L_4]^{4+}$ cages, even those with open portals, can be highly sensitive to variations in guest structure and character, perhaps even more so than their small cavity cousins. In addition to reinforcing the importance of the ligand backbone in the molecular recognition properties of these structures, we anticipate that this report will encourage chemists to target specific binding of large guests within long $[Pd_2L_4]^{4+}$ cages and gain finely tuned control of adducts that possess dual domains.

Conflicts of interest

There are no conflicts to declare.

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