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EDGE ARTICLE

Stimuli-responsive Pd_2L_4 metallosupramolecular cages: towards targeted cisplatin drug delivery†

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Metallosupramolecular cages are an emerging, but as of yet relativity unexplored, drug delivery vector. Herein we show that discrete dipalladium(II) molecular cages of the formula $[Pd_2L_4](X)_4$ can be quantatively self-assembled from a simple tripyridyl ligand (2,6-bis(pyridin-3-ylethynyl)pyridine) and $[Pd(CH_3CN)_4](X)_2$ (X = BF_4^- or SbF_6^-). The cages have been fully characterised using ^1H, ^{13}C and DOSY NMR spectroscopy, elemental analysis, IR spectroscopy, and high resolution electrospray mass spectrometry (HR-ESMS). Additionally, the molecular structure of the $[Pd_2L_4](SbF_6)_4$ cage was confirmed unequivocally using X-ray diffraction. These $[Pd_2L_4](X)_4$ cages are stimuli-responsive and can be reversibly disassembled/reassembled upon the addition/removal of suitable competing ligands. The central cavities of the $[Pd_2L_4](X)_4$ cages are lined with four hydrogen bond accepting pyridine units which enable the encapsulation of two cisplatin molecules within the metallosupramolecular architecture through hydrogen bonding interactions between the cage and the amine ligands of the cisplatin guest. The structure of the $[Pd_2L_4 \supset (cisplatin)_2](BF_4)_4$ host–guest adduct has been confirmed by ^1H NMR spectroscopy, HR-ESMS and X-ray crystallography. Additionally we have demonstrated that the cage–cisplatin host–guest adduct can be quantatively disassembled upon the addition of a competing ligand, releasing the cisplatin guest. This is the first crystallographically characterised example of a discrete metallosupramolecular cage encapsulating an FDA-approved inorganic drug molecule. This host–guest chemistry could open the way to relatively unexplored methods of drug delivery, which circumvent the malicious side effects and drug resistance associated with cisplatin and other anticancer therapeutics.

Introduction

The serendipitous discovery[1] of the biological activity of cisplatin (*cis*-diamminedichloroplatinum(II), $(NH_3)_2PtCl_2$) revolutionised cancer chemotherapy. Cisplatin was approved for medical use by the US FDA in 1978, and has been used in the treatment of a variety of cancers, including ovarian, head and neck, bladder, cervical, melanoma and lymphomas. Most effectively it is used to treat testicular cancer where it cures over 90% of cases. However, the doses in which cisplatin can be administered are severely limited by the harsh side effects, which include nephrotoxicity (kidney damage), neurotoxicity (damage to the nervous system) and myelotoxicity (bone marrow suppression). The efficacy of cisplatin can also be diminished by intracellular degradation and resistance. These issues have led to the development of a vast number of cisplatin derivatives including carboplatin and oxaliplatin.[2] While these derivatives exhibit improved therapeutic properties compared to cisplatin, the issues associated with these platinum drugs remain. As such, considerable effort has been put into the development of drug delivery vectors that would alleviate these toxicity, degradation and resistance issues. Liposomes,[3] polymers and dendrimers,[4] organic macrocycles,[5] nanoparticles,[6] viruses[7] and carbon nanotubes[8] have all shown promise as drug delivery vehicles for platinum therapeutics.[9] These nanoscale materials are designed to exploit the enhanced permeability and retention (EPR)[10] effect to selectively accummulate within cancer cells. Metallosupramolecular cages are, as of yet, a relativity unexplored class of nanoscale drug delivery vector.

During the last two decades there has been a plethora of research carried out on the self-assembly of defined 2- and 3-D metallosupramolecular structures.[11] These supramolecular architectures have been exploited for molecular recognition and encapsulation[12] of a wide variety of molecules and some have been shown to act as molecular reaction flasks,[13] and catalysts.[14] More recently the biological properties of these metallosupramolecular structures have also begun to emerge. Metallosupramolecular macrocycles[15] and helicates[16] have been found

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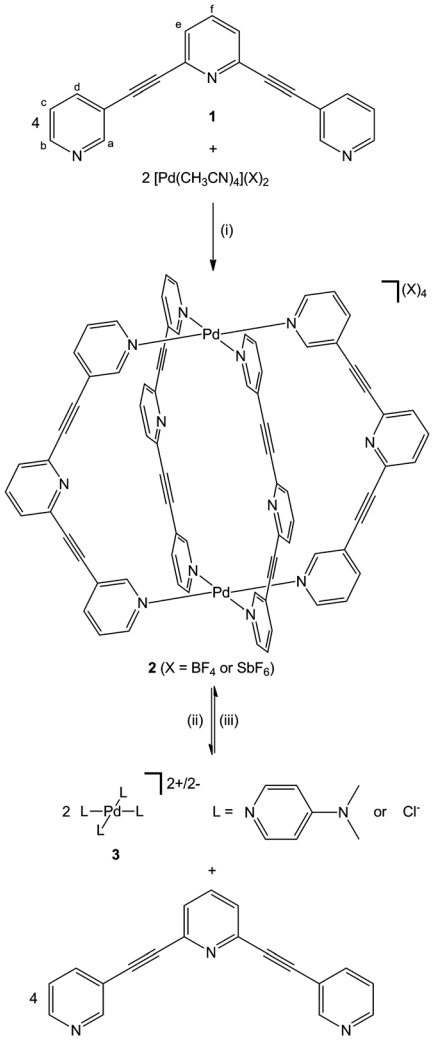
to interact with DNA, while other architectures have been shown to be cytotoxic to cancer cells and bacteria.[17] The molecular recognition properties coupled with the promising biological activity of metallosupramolecular cages suggests that these compounds could potentially act as drug delivery vectors. Indeed, Therrien and co-workers have recently reported the synthesis of a family of trigonal-prismatic hexaruthenium "Trojan horse" cages that are capable of binding a variety of hydrophobic guest molecules, including platinum and palladium acetylacetate complexes, within their molecular cavity.[18] The guest complexes by themselves were biologically inactive due to their insolubility in aqueous media. The cage and host–guest complexes however, both of which are water-soluble, were shown to possess some cytotoxic activity.[18] Further studies on this system, entailing the use of fluorescence microscopy to monitor the *in vivo* release of fluorescent pyrene-based guest molecules (whose fluoresence is suppressed when encapsulated within the Trojan horse), have shown that the water-soluble metallosupramolecular cages are capable of being internalised by cancerous cells, and subsequently broken down to release the hydrophobic guest molecules which would otherwise have been unable to enter the cells.[19]

Inspired by this and building on our expertise in metallosupramolecular structures[20] we have designed and synthesised a simple stimuli-responsive $[Pd_2L_4](X)_4$ cage molecule that is able to bind two molecules of cisplatin within its cavity. Furthermore, we have shown that the cage–cisplatin host–guest adduct can be broken down upon the addition of competitive ligands, thereby releasing the cisplatin molecules. This potentially paves the way for the exploitation of stimuli-responsive metallosupramolecular cages as targeted supramolecular cisplatin delivery systems.

Results and discussion

We have previously reported the synthesis of the tripyridyl ligand **1** (2,6-bis(pyridin-3-ylethynyl)pyridine), using a Sonogashira coupling of 2,6-diethynylpyridine with 3-iodopyridine, and demonstrated that it forms coordination polymers in the presence of Ag(I) ions.[21] Based on the work of McMorran/Steel,[22] Fujita[23] and others[24] we expected that **1** would self-assemble into a small molecular cage in the presence of Pd(II) ions.[25,26] Molecular modelling (ESI†) indicated that the cavity of the cage would be large enough to accomodate a variety of molecules (including cisplatin) and the presence of the central pyridine moiety within the ligand/cage provides a hydrogen-bond acceptor site that should enhance the host–guest chemistry of the species.

As such we set out to synthesise the Pd(II) cage complex **2**. Simply stirring the tripyridyl ligand **1** (2 eq.) with $[Pd(CH_3CN)_4](X)_2$ (1 eq.) in acetonitrile or acetone (for X = BF_4^- and SbF_6^-, respectively) led to quantitative formation of the cage complex **2** (Scheme 1). Vapour diffusion of diethyl ether into the crude solutions of the complexes provided the cages as pale yellow solids in good isolated yields (for X = BF_4^-, 95%; X = SbF_6^-, 79%). The molecular cages **2** (X = BF_4^- or SbF_6^-) were characterised by ^{1}H, ^{13}C and DOSY NMR spectroscopy, elemental analysis, IR spectroscopy, HR-ESMS and the molecular structure of **2** (X = SbF_6^-) was confirmed unequivocally by X-ray crystallography. Pleasingly, despite the presence of the third



Scheme 1 Self-assembly and stimuli-responsive dis- and re-assembly of the cage architecture **2**. Disassembly of **2** is achieved *via* the addition of DMAP or Bu_4NCl (8 eq.) to form $[Pd(L)_4]^{2+/-}$. The cage, **2**, can be quantitatively reassembled by addition of acid (TsOH or CSA) or silver(I) ions, respectively. *Reagents and conditions*: (i) CD_3CN or d_6-DMSO, 1 h, 298 K; (ii) DMAP (8 eq.) or Bu_4NCl (8 eq.); (iii) TsOH or CSA (8 eq.) or $AgSbF_6$ (excess).

potentially coordinating pyridyl unit within the ligand, the formation of **2** is quantitative. It is presumed that the lack of any coordination interaction at this site is due to steric effects.

The ^{1}H NMR spectra (CD_3CN, 298 K) of the cage complexes, **2** (X = BF_4^- or SbF_6^-), both show one set of sharp signals (Fig. 1b and ESI†). All the proton resonances in the ^{1}H NMR spectrum of **2** (X = BF_4^-) are shifted downfield compared to the corresponding resonances in the "free" ligand, **1**, (Fig. 1a) due to the electron withdrawing effect of the palladium(II) ions. The most significant downfield shifts are observed for the protons (H_a and H_b, $\Delta\delta$ = ~0.50 ppm) either side of the coordinating nitrogen atoms. Furthermore, the cage complexes have been shown to be stable in both CD_3CN and d_6-DMSO solution for several months.

Diffusion-ordered NMR spectroscopy (DOSY)[27] provided additional support for the selective formation of the cages in

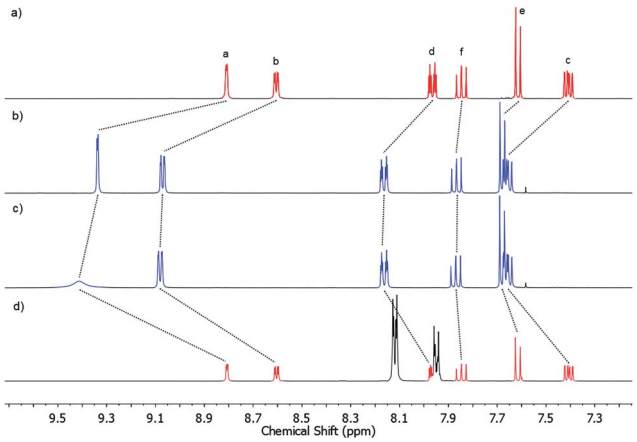


Fig. 1 ^{1}H NMR spectra (CD_3CN, 298 K) of (a) the ligand **1**, (b) the cage **2** (X = BF_4^-), (c) the [**2**⊃(cisplatin)$_2$](BF$_4$)$_4$ host–guest adduct, and (d) the [**2**⊃(cisplatin)$_2$](BF$_4$)$_4$ host–guest adduct after the addition of DMAP (8 eq.).

CD_3CN solution. ^{1}H DOSY spectra (CD_3CN, 298K) were obtained for **1** and **2** (X = BF_4^- or SbF_6^-). Each of the proton signals in the individual spectra show the same diffusion coefficients (*D*), indicating that there is only one species present in solution (ESI†). All proton signals of the ligand **1** showed the same diffusion coefficient of 8.07×10^{-10} m^2 s^{-1}, whereas diffusion coefficients of 3.62×10^{-10} m^2 s^{-1} (X = BF_4^-) or 3.49×10^{-10} m^2 s^{-1} (X = SbF_6^-) were obtained for **2** in CD_3CN solution. The $D_{complex}/D_{ligand}$ ratio of ~0.50 : 1 is consistent with the presence of the larger molecular cage species in solution (ESI†).

HR-ESMS experiments provided further evidence for the presence of the $[Pd_2L_4](X)_4$ architecture in solution. The ESMS spectra (CH_3CN) of **2** show isotopically resolved peaks consistent with the formulation $[Pd_2(\mathbf{1})_4(BF_4)_n]^{(4-n)+}$ (n = 2–3) along with peaks due to fragmentation of the cage structure. For **2** (X = BF_4^-) the cage signals were observed in the mass spectrum at *m*/*z* = 1598.1482 and 756.0795, indicative of $[Pd_2(\mathbf{1})_4(BF_4)_3]^+$ and $[Pd_2(\mathbf{1})_4(BF_4)_2]^{2+}$ ions, respectively (ESI†). However, the cage architecture is not completely stable under the conditions of the ESMS experiments and prominent fragmentation peaks are also oberved in the spectra (for example *m*/*z* = 687.0769, [Pd(**1**)$_2$(OH)]$^+$, 387.9998 [**1** + Pd]$^+$, 282.1049 [**1** + H]$^+$).

X-Ray crystallography confirmed unambiguously that **2** is a coordinatively saturated, quadruply stranded cage (Fig. 2). X-Ray quality crystals of **2** (X = SbF_6^-) were grown by vapour diffusion of methanol (MeOH) into an acetone solution of the complex. Each Pd(II) ion is coordinated to four pyridyl donors in the expected square-planar fashion, generating the lantern shaped cage architecture with a central cavity lined by pyridyl units. Unlike what has been observed in related systems,[22,23,24,26] none of the SbF_6^- counterions were found to bind in the cage's central cavity, presumably because these counterions are too large to fit within the cage. However, the cage cavity was not empty; multiple disordered solvent molecules (MeOH and H_2O) fill the void space and engage in hydrogen-bonding interactions with the central pyridine groups (ESI†).

Having confirmed the self-assembly of **2** we set out to examine if the cage complexes could be reversibly disassembled and reassembled in response to stimuli. Somewhat surprisingly,

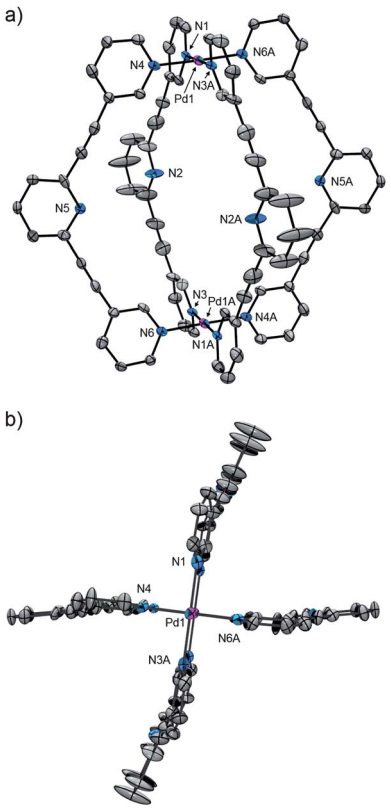


Fig. 2 Labelled ORTEP representations of the molecular structure of the cage **2** (X = SbF_6^-); (a) side view, and (b) top-down view. The hydrogen atoms, solvent molecules and SbF_6^- anions are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd1–N1 2.021, Pd1–N3A 2.027, Pd1–N4 2.027, Pd1–N6A 2.016, Pd1···Pd1A 11.497, N2···N2A 11.053, N5···N5A 10.996; N1–Pd1–N4 88.81, N4–Pd1–N3A 91.30, N3A Pd1–N6A 88.40, N6A–Pd1–N1 91.49.

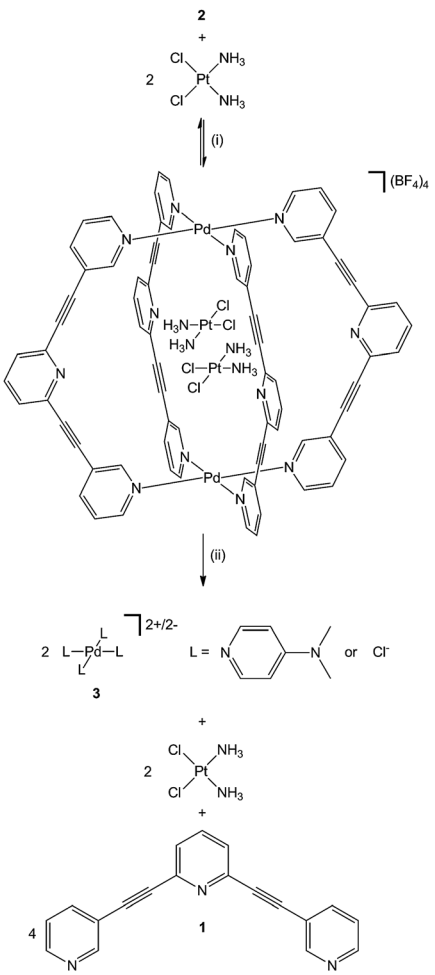
despite the considerable interest in synthetic molecular machines,[28] there are very few examples of the reversible stimuli-responsive disassembly/reassembly of metallosupramolecular cages reported in the literature.[29,30] This property is particularly desirable in the context of drug delivery as it would potentially enable the targeted release of an encapsulated drug from the metallosupramolecular cages at the site within the body where it is most needed.

In the first instance this was investigated using 4-dimethylaminopyridine (DMAP) as a competing ligand to displace **1**.[31] The addition of DMAP (8 eq.) to either a CD_3CN or d_6-DMSO solution of **2** led to the complete disassembly of the molecular cage and formation of the free ligand **1** along with the [Pd(DMAP)$_4$](BF$_4$)$_2$ complex, **3a**, as judged by *in situ* ^{1}H NMR and ESMS experiments (ESI†). The addition of either *p*-toluenesulfonic acid (TsOH) or (+)-camphor-10-sulfonic acid (CSA) to the reaction mixtures led to the selective protonation of the DMAP ligands and quantitative reassembly of the cage **2** (ESI†).

The more biologically relevant chloride anion (Cl^-) could also be used to induce the dissociation of **2**. Treatment of a d_6-DMSO solution of **2** with Bu_4NCl (8 eq.) resulted in the quantitative disassembly of the cage and formation of tetrachloropalladate complex $(NBu_4)_2[PdCl_4]$, **3b** along with uncomplexed **1** (ESI†).

Addition of an excess of $AgSbF_6$ to the reaction mixture sequesters the Cl^- anions and releases the Pd(II) ions. This cleanly and quantitativity regenerates the cage complex **2**.

Having successfully demonstrated the stimuli-responsive disassembly and reassembly of **2**, its host–guest chemistry with cisplatin was investigated. The host–guest studies were somewhat hampered by the modest solubilities of both **2** and the cisplatin guest. The cages, **2** (X = BF_4^- or SbF_6^-), were only soluble in CH_3CN, DMF and DMSO, while the cisplatin guest displayed extremely modest solubility in all the common organic solvents. Initial host–guest studies in d_6-DMSO solution were unsurprisingly unsuccessful as DMSO is well known to disrupt the formation of hydrogen-bonding interactions. Changing solvent to CD_3CN provided more promising results. While cisplatin was essentially completely insoluble in CD_3CN, simply adding 2 eq. of the guest to a solution of $\mathbf{2}(BF_4)_4$ in CD_3CN, followed by sonication (10 min), led to the almost complete dissolution of the cisplatin, providing strong evidence that the cisplatin guest molecule is taken up by and complexed within **2** (Scheme 2). ^{1}H NMR spectroscopy (CD_3CN) of the resulting mixture further supported the postulate that the cisplatin was bound within the cavity of **2**. The internal proton of the cage (H_a, $\Delta\delta$ = ~0.11 ppm) is broadened and shifted downfield which is indicative of guest binding within the molecular cage. One of the external protons of the cage (H_b, $\Delta\delta$ = ~0.05 ppm) is also slightly downfield shifted, while all the other proton resonances are unaffected by the presence of cisplatin in solution. Further evidence for the formation of the host–guest adduct was obtained from HR-ESMS experiments, with signals for $[Pd_2(\mathbf{1})_4(\text{cisplatin})_n(BF_4)_3]^+$ (m/z = 1898.1980 and 2198.1578 for n = 1 and 2, respectively) and $[Pd_2(\mathbf{1})_4(\text{cisplatin})_n(BF_4)_2]^{2+}$ (m/z = 905.5928 and 1055.5713 for n = 1 and 2, respectively) ions being observed. In combination the ^{1}H NMR and HR-ESMS experiments strongly indicate that cisplatin and **2** form a $[\mathbf{2}\supset(\text{cisplatin})_2](BF_4)_4$ host–guest complex in CD_3CN.



Scheme 2 Formation of the host–guest adduct $[\mathbf{2}\supset(\text{cisplatin})_2](BF_4)_4$ and subsequent release of the encapsulated cisplatin through disassembly of **2**. *Reagents and conditions*: (i) sonication, 10 min, CD_3CN, 298 K; (ii) DMAP (8 eq.) or Bu_4NCl (8 eq.), CD_3CN, 298 K.

Control experiments confirm the importance of the hydrogen-bonding interaction between the cage and the amine ligands of the cisplatin guest. It was observed that on addition of small amounts of D_2O to a solution of the $[\mathbf{2}\supset(\text{cisplatin})_2](BF_4)_4$ host–guest adduct in CD_3CN the H_a and H_b proton signals of the cage sharpen and shift upfield, indicating evacuation of cisplatin from the cavity of **2**. Furthermore, we have synthesised the related Pd (II) cage complex (by mixing $[Pd(CH_3CN)_4](BF_4)_2$ with 1,3-bis (pyridin-3-ylethynyl)benzene) which has a central benzene unit in place of the pyridine core of **2** (ESI†). No dissolution of cisplatin (2 eq.) in CD_3CN was observed even after prolonged sonication in the presence of the Pd(II) cage derived from the 1,3-bis(pyridin-3-ylethynyl)benzene) ligand, and the ^{1}H NMR signals of the cage showed no shifts from their orginal positions. The lack of any observable interaction between cisplatin and the cage derived from 1,3-bis(pyridin-3-ylethynyl)benzene) highlights the necessity for the presence of a hydrogen-bond acceptor within the cage cavity.

The exact nature of the host–guest adduct $[\mathbf{2}\supset(\text{cisplatin})_2](BF_4)_4$ was determined by X-ray crystallography (Fig. 3). X-Ray quality crystals were grown by diffusion of diethyl ether vapour into a 1 : 1 CH_3CN:DMF solution of the host–guest adduct, $[\mathbf{2}\supset(\text{cisplatin})_2](BF_4)_4$. As expected the structure shows two cisplatin molecules bound within the cavity of **2**. The guest molecules interact with the cage *via* hydrogen-bonding interactions (N–H···N and C–H···Cl) (Table 1). There are strong hydrogen-bonding interactions between the amine ligands of the cisplatin guest and the central pyridine moiety of the cage. Additionally the acidic C–H protons of the coordinated pyridines which point into the cage cavity engage in a hydrogen-bonding interaction with the chloride ligands of the cisplatin guests. The guest molecules are further stabilised within the cavity by hydrogen bonding to each other (N–H···Cl). Furthermore, the platinum(II) ions of the cisplatin molecules are aligned, suggesting the presence of a metal–metal interaction (Pt···Pt 3.321 Å).[32]

Finally, it was shown that the cisplatin guests could be released from the host–guest adduct by addition of a competing ligand to disassemble the cage (Scheme 2).[29,33] Treatment of a CD_3CN solution of the $[\mathbf{2}\supset(\text{cisplatin})_2](BF_4)_4$ host–guest adduct with either DMAP (8 eq.) or Bu_4NCl (8 eq.) resulted in the quantitative disassembly of the cage and release of encapsulated guest cisplatin molecules as evidenced by *in situ* ^{1}H NMR and ESMS experiments (Fig. 1d and ESI†).

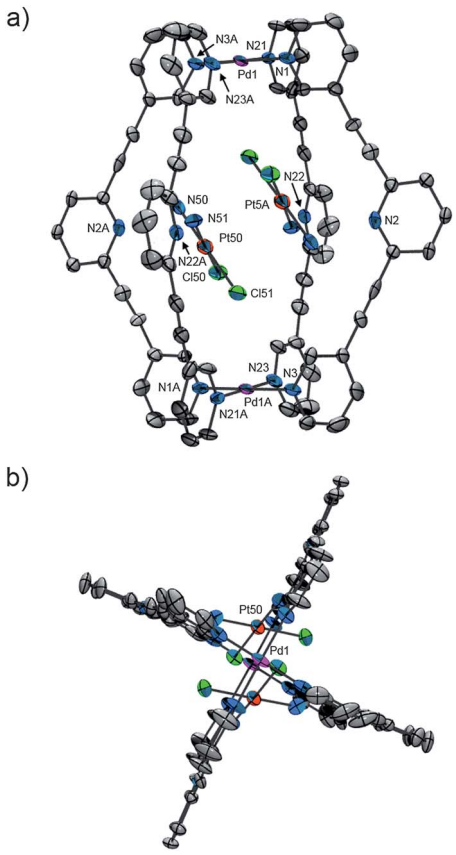


Fig. 3 Labelled ORTEP views of the X-ray crystal structure of [**2**⊃(cisplatin)$_2$](BF$_4$)$_4$: (a) side-view and (b) top-down view. The hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°); Pd1–N1 2.035, Pd1–N3A 2.019, Pd1–N21 2.019, Pd1–N23A 2.034, Pd1···Pd1A 11.669, N2···N2A 10.965, N22···N22A 10.709, N50···N2 2.867, N51···N22A 3.122, Pt50···Pt5A 3.321; N1–Pd1–N23A 89.40, N23A–Pd1–N3A 90.02, N3A–Pd1–N21 89.77, N21–Pd1–N1 90.81.

Table 1 Bond lengths and angles for supramolecular interactions present in the solid-state structure of [**2**⊃[(cisplatin)$_2$](BF$_4$)$_4$

	D···A/Å	D–H···A/Å	D–H···A/°	M···M/Å
NH$_3$···N	2.867	1.989	161.13	
NH$_3$···Cl	3.255	2.786	113.29	
NH$_3$···Cl	3.287	2.396	166.41	
CH···Cl	3.345	2.437	126.81	
Pt···Pt				3.321

Conclusions

We have shown that a quadruply-stranded dipalladium(II) cage complex **2** will self-assemble from the tripyridyl ligand **1** and Pd (II) ions in quantitative yield. The cage complex **2** can be reversibly disassembled/reassembled in a controlled stimuli-responsive manner by addition and subsequent removal of competing ligands (specifically DMAP and Cl$^-$), and this mechanism can be utilised for the controlled release of encapsulated guest molecules. Additionally, we have demonstrated that **2** can bind two molecules of cisplatin within its molecular cavity. This encapsulation is stabilised through a variety of supramolecular interactions. Release of the cisplatin molecules *via* the aforementioned stimuli-response mechanism was also successfully demonstrated. This proof-of-principle study suggests that discrete 3D metallosupramolecular cages have great potential as stimuli-responsive vectors for targeted and controlled drug delivery.

Future work will be focussed on increasing the stability of the cage and host–guest adducts under aqueous/biologically relevant conditions. Biological studies are currently underway to investigate the ability of **2** and [**2**⊃(cisplatin)$_2$]$^{4+}$ to be internalised within cells and to examine their cytotoxic properties.

Acknowledgements

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