## **Chemical Science**

Cite this: Chem. Sci., 2012, 3, 778

www.rsc.org/chemicalscience



# Stimuli-responsive $Pd_2L_4$ metallosupramolecular cages: towards targeted cisplatin drug delivery<sup>†</sup>

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Received 10th November 2011, Accepted 18th November 2011 DOI: 10.1039/c2sc00899h

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<sub>4</sub><sup>-</sup> or SbF<sub>6</sub><sup>-</sup>). The cages have been fully characterised using <sup>1</sup>H, <sup>13</sup>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 <sup>1</sup>H 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<sup>1</sup> 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.<sup>2</sup> 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,<sup>3</sup> polymers and dendrimers,<sup>4</sup> organic macrocycles,<sup>5</sup> nanoparticles,<sup>6</sup> viruses<sup>7</sup> and carbon nanotubes<sup>8</sup> have all shown promise as drug delivery vehicles for platinum therapeutics.<sup>9</sup> These nanoscale materials are designed to exploit the enhanced permeability and retention (EPR)<sup>10</sup> 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.<sup>11</sup> These supramolecular architectures have been exploited for molecular recognition and encapsulation<sup>12</sup> of a wide variety of molecules and some have been shown to act as molecular reaction flasks,<sup>13</sup> and catalysts.<sup>14</sup> More recently the biological properties of these metallosupramolecular structures have also begun to emerge. Metallosupramolecular macrocycles<sup>15</sup> and helicates<sup>16</sup> have been found

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedures, <sup>1</sup>H, <sup>13</sup>C and DOSY NMR, and ESMS spectra, <sup>1</sup>H NMR stacked plots, MMFF calculations and crystallographic data. CCDC reference numbers 853226 and 853227. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc00899h

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.<sup>18</sup> 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<sup>20</sup> 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(1) ions.<sup>21</sup> Based on the work of McMorran/Steel,<sup>22</sup> Fujita<sup>23</sup> and others<sup>24</sup> we expected that 1 would self-assemble into a small molecular cage in the presence of Pd(II) ions.<sup>25,26</sup> 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)<sub>2</sub> (1 eq.) in acetonitrile or acetone (for X = BF<sub>4</sub><sup>-</sup> and SbF<sub>6</sub><sup>-</sup>, 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<sub>4</sub><sup>-</sup>, 95%; X = SbF<sub>6</sub><sup>-</sup>, 79%). The molecular cages **2** (X = BF<sub>4</sub><sup>-</sup> or SbF<sub>6</sub><sup>-</sup>) were characterised by <sup>1</sup>H, <sup>13</sup>C and DOSY NMR spectroscopy, elemental analysis, IR spectroscopy, HR-ESMS and the molecular structure of **2** (X = SbF<sub>6</sub><sup>-</sup>) 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<sub>4</sub>NCl (8 eq.) to form  $[Pd(L)_4]^{2+/-}$ . The cage, **2**, can be quantitatively reassembled by addition of acid (TsOH or CSA) or silver(1) ions, respectively. *Reagents and conditions*: (i) CD<sub>3</sub>CN or *d*<sub>6</sub>-DMSO, 1 h, 298 K; (ii) DMAP (8 eq.) or Bu<sub>4</sub>NCl (8 eq.); (iii) TsOH or CSA (8 eq.) or AgSbF<sub>6</sub> (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 <sup>1</sup>H NMR spectra (CD<sub>3</sub>CN, 298 K) of the cage complexes, **2** (X = BF<sub>4</sub><sup>-</sup> or SbF<sub>6</sub><sup>-</sup>), both show one set of sharp signals (Fig. 1b and ESI<sup>†</sup>). All the proton resonances in the <sup>1</sup>H NMR spectrum of **2** (X = BF<sub>4</sub><sup>-</sup>) 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<sub>a</sub> and H<sub>b</sub>,  $\Delta \delta = \sim 0.50$  ppm) either side of the coordinating nitrogen atoms. Furthermore, the cage complexes have been shown to be stable in both CD<sub>3</sub>CN and *d*<sub>6</sub>-DMSO solution for several months.

Diffusion-ordered NMR spectroscopy (DOSY)<sup>27</sup> provided additional support for the selective formation of the cages in



**Fig. 1** <sup>1</sup>H NMR spectra (CD<sub>3</sub>CN, 298 K) of (a) the ligand **1**, (b) the cage **2** (X = BF<sub>4</sub><sup>-</sup>), (c) the  $[2 \supset (cisplatin)_2](BF_4)_4$  host–guest adduct, and (d) the  $[2 \supset (cisplatin)_2](BF_4)_4$  host–guest adduct after the addition of DMAP (8 eq.).

CD<sub>3</sub>CN solution. <sup>1</sup>H DOSY spectra (CD<sub>3</sub>CN, 298K) were obtained for **1** and **2** (X = BF<sub>4</sub><sup>-</sup> or SbF<sub>6</sub><sup>-</sup>). 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<sup>†</sup>). All proton signals of the ligand **1** showed the same diffusion coefficient of  $8.07 \times 10^{-10}$  m<sup>2</sup> s<sup>-1</sup>, whereas diffusion coefficients of  $3.62 \times 10^{-10}$  m<sup>2</sup> s<sup>-1</sup> (X = BF<sub>4</sub><sup>-</sup>) or  $3.49 \times 10^{-10}$  m<sup>2</sup> s<sup>-1</sup> (X = SbF<sub>6</sub><sup>-</sup>) were obtained for **2** in CD<sub>3</sub>CN solution. The  $D_{\text{complex}}/D_{\text{ligand}}$  ratio of ~0.50 : 1 is consistent with the presence of the larger molecular cage species in solution (ESI<sup>†</sup>).

HR-ESMS experiments provided further evidence for the presence of the  $[Pd_2L_4](X)_4$  architecture in solution. The ESMS spectra (CH<sub>3</sub>CN) of **2** show isotopically resolved peaks consistent with the formulation  $[Pd_2(1)_4(BF_4)_n]^{(4-n)+}$  (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  $[Pd_2(1)_4(BF_4)_3]^+$  and  $[Pd_2(1)_4(BF_4)_2]^{2+}$  ions, respectively (ESI†). However, the cage architecture is not completely stable under the conditions of the ESMS experiments and prominent fragmentation peaks are also observed in the spectra (for example m/z = 687.0769, [Pd (1)<sub>2</sub>(OH)]<sup>+</sup>, 387.9998 [1 + Pd]<sup>+</sup>, 282.1049 [1 + H]<sup>+</sup>).

X-Ray crystallography confirmed unambiguously that **2** is a coordinatively saturated, quadruply stranded cage (Fig. 2). X-Ray quality crystals of **2** (X = SbF<sub>6</sub><sup>-</sup>) 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,<sup>22,23,24,26</sup> none of the SbF<sub>6</sub><sup>-</sup> 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<sub>2</sub>O) fill the void space and engage in hydrogen-bonding interactions with the central pyridine groups (ESI<sup>†</sup>).

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,<sup>28</sup> there are very few examples of the reversible stimuliresponsive disassembly/reassembly of metallosupramolecular cages reported in the literature.<sup>29,30</sup> 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<sub>3</sub>CN 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)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub> complex, **3a**, as judged by *in situ* <sup>1</sup>H NMR and ESMS experiments (ESI<sup>†</sup>). 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<sup>†</sup>).

The more biologically relevant chloride anion (Cl<sup>-</sup>) could also be used to induce the dissociation of **2**. Treatment of a  $d_6$ -DMSO solution of **2** with Bu<sub>4</sub>NCl (8 eq.) resulted in the quantitative disassembly of the cage and formation of tetrachloropalladate complex (NBu<sub>4</sub>)<sub>2</sub>[PdCl<sub>4</sub>], **3b** along with uncomplexed **1** (ESI<sup>†</sup>). Addition of an excess of  $AgSbF_6$  to the reaction mixture sequesters the  $Cl^-$  anions and releases the Pd(n) 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<sub>3</sub>CN, 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<sub>3</sub>CN provided more promising results. While cisplatin was essentially completely insoluble in CD<sub>3</sub>CN, simply adding 2 eq. of the guest to a solution of  $2(BF_4)_4$  in CD<sub>3</sub>CN, 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). <sup>1</sup>H NMR spectroscopy (CD<sub>3</sub>CN) of the resulting mixture further supported the postulate that the



Scheme 2 Formation of the host–guest adduct  $[2 \supset (cisplatin)_2](BF_4)_4$ and subsequent release of the encapsulated cisplatin through disassembly of 2. *Reagents and conditions*: (i) sonication, 10 min, CD<sub>3</sub>CN, 298 K; (ii) DMAP (8 eq.) or Bu<sub>4</sub>NCl (8 eq.), CD<sub>3</sub>CN, 298 K.

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cisplatin was bound within the cavity of **2**. The internal proton of the cage (H<sub>a</sub>,  $\Delta \delta = \sim 0.11$  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<sub>b</sub>,  $\Delta \delta$ = ~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<sub>2</sub>(1)<sub>4</sub>(cisplatin)<sub>n</sub>(BF<sub>4</sub>)<sub>3</sub>]<sup>+</sup> (*m*/*z* = 1898.1980 and 2198.1578 for *n* = 1 and 2, respectively) and [Pd<sub>2</sub>(1)<sub>4</sub>(cisplatin)<sub>n</sub>(BF<sub>4</sub>)<sub>2</sub>]<sup>2+</sup> (*m*/*z* = 905.5928 and 1055.5713 for *n* = 1 and 2, respectively) ions being observed. In combination the <sup>1</sup>H NMR and HR-ESMS experiments strongly indicate that cisplatin and **2** form a [**2** $\supset$ (cisplatin)<sub>2</sub>](BF<sub>4</sub>)<sub>4</sub> host–guest complex in CD<sub>3</sub>CN.

Control experiments confirm the importance of the hydrogenbonding interaction between the cage and the amine ligands of the cisplatin guest. It was observed that on addition of small amounts of D<sub>2</sub>O to a solution of the  $[2 \supset (cisplatin)_2](BF_4)_4$  hostguest adduct in CD<sub>3</sub>CN the H<sub>a</sub> and H<sub>b</sub> 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<sup>+</sup>). No dissolution of cisplatin (2 eq.) in CD<sub>3</sub>CN was observed even after prolonged sonication in the presence of the Pd(II) cage derived from the 1,3-bis(pyridin-3-vlethvnyl)benzene) ligand, and the <sup>1</sup>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  $[2 \supset (cisplatin)_2]$ (BF<sub>4</sub>)<sub>4</sub> 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<sub>3</sub>CN:DMF solution of the host-guest adduct,  $[2 \supset (cisplatin)_2](BF_4)_4$ . 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 hydrogenbonding 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).<sup>29,33</sup> Treatment of a CD<sub>3</sub>CN solution of the  $[2 \supset (\text{cisplatin})_2](BF_4)_4$  host–guest adduct with either DMAP (8 eq.) or Bu<sub>4</sub>NCl (8 eq.) resulted in the quantitative disassembly of the cage and release of encapsulated guest cisplatin molecules as evidenced by *in situ* <sup>1</sup>H NMR and ESMS experiments (Fig. 1d and ESI<sup>†</sup>).



**Fig. 3** Labelled ORTEP views of the X-ray crystal structure of  $[2 \supset (\text{cisplatin})_2](BF_4)_4$ : (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  $[2 \supset [(cisplatin)_2](BF_4)_4$ 

	D…A/Å	D–H…A/Å	$D – H \cdots A /^{\circ}$	M…M/Å
NH <sub>3</sub> …N	2.867	1.989	161.13	
NH <sub>3</sub> …Cl	3.255	2.786	113.29	
NH <sub>3</sub> …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 stimuliresponsive manner by addition and subsequent removal of competing ligands (specifically DMAP and Cl<sup>-</sup>), 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 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  $[2 \supset (\text{cisplatin})_2]^{4+}$  to be internalised within cells and to examine their cytotoxic properties.

#### Acknowledgements

We thank Dr David McMorran and Dr Paul Donnelly for useful discussions. Mr James Wright is thanked for obtaining the ESMS data for the  $[2 \supset (cisplatin)_2](BF_4)_4$  host-guest adduct. The Department of Chemistry, University of Otago, provided financial support for this work. E. L. G. thanks the University of Otago, Division of Health Sciences and the Otago Medical Research Foundation for providing a summer scholarship (2010–11).

#### Notes and references

- B. Rosenberg, *Nature*, 1965, **205**, 698–699; B. Rosenberg, L. VanCamp, J. E. Trosko and V. H. Mansour, *Nature*, 1969, **222**, 385–386.
- N. J. Wheate, S. Walker, G. E. Craig and R. Oun, *Dalton Trans.*, 2010, **39**, 8113–8127; E. R. Jamieson and S. J. Lippard, *Chem. Rev.*, 1999, **99**, 2467–2498; J. Reedijk, *Eur. J. Inorg. Chem.*, 2009, 1303– 1312.
- 3 J. Meerum Terwogt, G. Groenewegen, D. Pluim, M. Maliepaard, M. Tibben, A. Huisman, W. ten Bokkel Huinink, M. Schot, H. Welbank, E. Voest, J. Beijnen and J. Schellens, *Cancer Chemother. Pharmacol.*, 2002, **49**, 201–210; M. S. Newman, G. T. Colbern, P. K. Working, C. Engbers and M. A. Amantea, *Cancer Chemother. Pharmacol.*, 1999, **43**, 1–7; C. Lu, R. Perez-Soler, B. Piperdi, G. L. Walsh, S. G. Swisher, W. R. Smythe, H. J. Shin, J. Y. Ro, L. Feng, M. Truong, A. Yalamanchili, G. Lopez-Berestein, W. K. Hong, A. R. Khokhar and D. M. Shin, *J. Clin. Oncol.*, 2005, **23**, 3495–3501; V. Chupin, A. I. P. M. de Kroon and B. de Kruijff, *J. Am. Chem. Soc.*, 2004, **126**, 13816– 13821; S. Khiati, D. Luvino, K. Oumzil, B. Chauffert, M. Camplo and P. Barthélémy, *ACS Nano*, 2011, **5**, 8649–8655; S. C. White, P. Lorigan, G. P. Margison, J. M. Margison, F. Martin, N. Thatcher, H. Anderson and M. Ranson, *Br. J. Cancer*, 2006, **95**, 822–828.
- 4 J. M. Rademaker-Lakhai, C. Terret, S. B. Howell, C. M. Baud, R. F. de Boer, D. Pluim, J. H. Beijnen, J. H. M. Schellens and J.-P. Droz, *Clin. Cancer Res.*, 2004, **10**, 3386–3395; M. Campone, J. Rademaker-Lakhai, J. Bennouna, S. Howell, D. Nowotnik, J. Beijnen and J. Schellens, *Cancer Chemother. Pharmacol.*, 2007, **60**, 523–533.
- A. M. Krause-Heuer, N. J. Wheate, M. J. Tilby, D. G. Pearson, C. J. Ottley and J. R. Aldrich-Wright, *Inorg. Chem.*, 2008, 47, 6880–6888; S. Walker, R. Oun, F. J. McInnes and N. J. Wheate, *Isr. J. Chem.*, 2011, 51, 616–624; N. J. Wheate, *J. Inorg. Biochem.*, 2008, 102, 2060–2066; N. J. Wheate, D. P. Buck, A. I. Day and J. G. Collins, *Dalton Trans.*, 2006, 451–458; N. J. Wheate, A. I. Day, R. J. Blanch, A. P. Arnold, C. Cullinane and J. G. Collins, *Chem. Commun.*, 2004, 1424–1425; N. J. Wheate, R. I. Taleb, A. M. Krause-Heuer, R. L. Cook, S. Wang, V. J. Higgins and J. R. Aldrich-Wright, *Dalton Trans.*, 2007, 5055– 5064.
- 6 S. Dhar, W. L. Daniel, D. A. Giljohann, C. A. Mirkin and
  S. J. Lippard, J. Am. Chem. Soc., 2009, 131, 14652–14653;
  S. D. Brown, P. Nativo, J.-A. Smith, D. Stirling, P. R. Edwards,

B. Venugopal, D. J. Flint, J. A. Plumb, D. Graham and N. J. Wheate, J. Am. Chem. Soc., 2010, 132, 4678–4684.

- 7 Z. Yang, X. Wang, H. Diao, J. Zhang, H. Li, H. Sun and Z. Guo, *Chem. Commun.*, 2007, 3453–3455.
- 8 R. P. Feazell, N. Nakayama-Ratchford, H. Dai and S. J. Lippard, J. Am. Chem. Soc., 2007, 129, 8438–8439; S. Dhar, Z. Liu, J. R. Thomale, H. Dai and S. J. Lippard, J. Am. Chem. Soc., 2008, 130, 11467–11476.
- 9 B. W. Harper, A. M. Krause-Heuer, M. P. Grant, M. Manohar, K. B. Garbutcheon-Singh and J. R. Aldrich-Wright, *Chem. Eur. J.*, 2010, **16**, 7064–7077; K. S. Lovejoy and S. J. Lippard, *Dalton Trans.*, 2009, 10651–10659; C. Sanchez-Cano and M. J. Hannon, *Dalton Trans.*, 2009, 10702–10711.
- 10 Y. Matsumura and H. Maeda, Cancer Res., 1986, 46, 6387-6392.
- R. Chakrabarty, P. S. Mukherjee and P. J. Stang, *Chem. Rev.*, 2011, 111, 6810–6918; C. R. K. Glasson, L. F. Lindoy and G. V. Meehan, *Coord. Chem. Rev.*, 2008, 252, 940–963; M. D. Ward, *Chem. Commun.*, 2009, 4487–4499; S. J. Dalgarno, N. P. Power and J. L. Atwood, *Coord. Chem. Rev.*, 2008, 252, 825–841; M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, 38, 371–380; B. J. Holliday and C. A. Mirkin, *Angew. Chem., Int. Ed.*, 2001, 40, 2022–2043; D. L. Caulder and K. N. Raymond, *Acc. Chem. Res.*, 1999, 32, 975–982; P. J. Lusby, *Annu. Rep. Prog. Chem., Sect. A, Inorg. Chem.*, 2010, 106, 319–339.
- B. Breiner, J. K. Clegg and J. R. Nitschke, *Chem. Sci.*, 2011, **2**, 51–56;
  M. Yoshizawa and M. Fujita, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 609–618;
  J. K. Klosterman, Y. Yamauchi and M. Fujita, *Chem. Soc. Rev.*, 2009, **38**, 1714–1725;
  M. D. Pluth and K. N. Raymond, *Chem. Soc. Rev.*, 2007, **36**, 161–171;
  Y.-F. Han, H. Li and G.-X. Jin, *Chem. Commun.*, 2010, **46**, 6879–6890;
  J. D. Crowley and B. Bosnich, *Eur. J. Inorg. Chem.*, 2005, 2015–2025;
  V. Maurizot, M. Yoshizawa, M. Kawano and M. Fujita, *Dalton Trans.*, 2006, 2750–2756.
- 13 M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew Chem., Int. Ed.*, 2009, **48**, 3418–3438.
- M. J. Wiester, P. A. Ulmann and C. A. Mirkin, *Angew Chem., Int. Ed.*, 2011, **50**, 114–137; H. J. Yoon, J. Kuwabara, J.-H. Kim and C. A. Mirkin, *Science*, 2010, **330**, 66–69; C. J. Hastings, M. D. Pluth, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2010, **132**, 6938–6940; M. D. Pluth, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2009, **42**, 1650–1659.
- 15 D. Schilter, J. K. Clegg, M. M. Harding and L. M. Rendina, *Dalton Trans.*, 2010, **39**, 239–247; D. Schilter, T. Urathamakul, J. L. Beck, M. J. Hannon and L. M. Rendina, *Dalton Trans.*, 2010, **39**, 11263–11271; N. P. E. Barry, N. H. Abd Karim, R. Vilar and B. Therrien, *Dalton Trans.*, 2009, 10717–10719; R. Kieltyka, P. Englebienne, J. Fakhoury, C. Atutexier, N. Moitessier and H. F. Sleiman, *J. Am. Chem. Soc.*, 2008, **130**, 10040–10041; M. Mounir, J. Lorenzo, M. Ferrer, M. J. Prieto, O. Rossell, F. X. Avilès and V. Moreno, *J. Inorg. Biochem.*, 2007, **101**, 660–666.
- 16 L. Cardo, V. Sadovnikova, S. Phongtongpasuk, N. J. Hodges and M. J. Hannon, Chem. Commun., 2011, 47, 6575-6577; C. Ducani, A. Leczkowska, N. J. Hodges and M. J. Hannon, Angew. Chem., Int. Ed., 2010, 49, 8942-8945; D. R. Boer, J. M. C. A. Kerckhoffs, Y. Parajo, M. Pascu, I. Uson, P. Lincoln, M. J. Hannon and M. Coll, Angew. Chem., Int. Ed., 2010, 49, 2336-2339; L. Cardo and M. J. Hannon, Inorg. Chim. Acta, 2009, 362, 784-792; A. Oleksi, A. G. Blanco, R. Boer, I. Usón, J. Aymamí, A. Rodger, M. J. Hannon and M. Coll, Angew. Chem. Int. Ed., 2006, 45, 1227-1231; A. Oleksi, A. G. Blanco, R. Boer, I. Uson, J. Aymami, A. Rodger, M. J. Hannon and M. Coll, Angew. Chem., Int. Ed., 2006, 45, 1227-1231; C. Uerpmann, J. Malina, M. Pascu, G. J. Clarkson, V. Moreno, A. Rodger, A. Grandas and M. J. Hannon, *Chem. Eur. J.*, 2005, **11**, 1750–1756; E. Moldrheim, M. J. Hannon, I. Meistermann, A. Rodger and E. Sletten, JBIC, J. Biol. Inorg. Chem., 2002, 7, 770-780; I. Meistermann, V. Moreno, M. J. Prieto, E. Moldrheim, E. Sletten, S. Khalid, P. M. Rodger, J. C. Peberdy, C. J. Isaac, A. Rodger and M. J. Hannon, Proc. Natl. Acad. Sci. U. S. A., 2002, 99, 5069-5074; I. Meistermann, V. Moreno, M. J. Prieto, E. Moldrheim, E. Sletten, S. Khalid, P. M. Rodger, J. C. Peberdy, C. J. Isaac, A. Rodger and M. J. Hannon, Proc. Natl. Acad. Sci. U. S. A., 2002, 99, 5069-5074; M. J. Hannon, V. Moreno, M. J. Prieto, E. Moldrheim, E. Sletten, I. Meistermann, C. J. Isaac, K. J. Sanders and A. Rodger, Angew. Chem. Int. Ed., 2001, 40, 880-884.

- V. Vajpayee, Y. J. Yang, S. C. Kang, H. Kim, I. S. Kim, M. Wang, P. J. Stang and K.-W. Chi, *Chem. Commun.*, 2011, 47, 5184–5186; V. Vajpayee, Y. H. Song, Y. J. Yang, S. C. Kang, H. Kim, I. S. Kim, M. Wang, P. J. Stang and K.-W. Chi, *Organometallics*, 2011, 30, 3242–3245; N. P. E. Barry, F. Edafe and B. Therrien, *Dalton Trans.*, 2011, 40, 7172–7180; N. P. E. Barry, O. Zava, J. Furrer, P. J. Dyson and B. Therrien, *Dalton Trans.*, 2010, 39, 5272–5277; N. P. E. Barry, O. Zava, P. J. Dyson and B. Therrien, *Aust. J. Chem.*, 2010, 63, 1529–1537; N. P. E. Barry, F. Edafe, P. J. Dyson and B. Therrien, *Dalton Trans.*, 2010, 39, 2816–2820; B. Therrien, *Eur. J. Inorg. Chem.*, 2009, 2445–2453; D. K. Orsa, G. K. Haynes, S. K. Pramanik, M. O. Iwunze, G. E. Greco, J. A. Krause, D. M. Ho, A. L. Williams, D. A. Hill and S. K. Mandal, *Inorg. Chem. Commun.*, 2007, 10, 821–824.
- 18 B. Therrien, G. Süss-Fink, P. Govindaswamy, A. K. Renfrew and P. J. Dyson, *Angew. Chem., Int. Ed.*, 2008, **47**, 3773–3776.
- A. Pitto-Barry, N. P. E. Barry, O. Zava, R. Deschenaux and B. Therrien, *Chem.-Asian J.*, 2011, **6**, 1595–1603; A. Pitto-Barry, N. P. E. Barry, O. Zava, R. Deschenaux, P. J. Dyson and B. Therrien, *Chem.-Eur. J.*, 2011, **17**, 1966–1971; N. P. E. Barry, O. Zava, P. J. Dyson and B. Therrien, *Chem.-Eur. J.*, 2011, **17**, 9669–9677; O. Zava, J. Mattsson, B. Therrien and P. J. Dyson, *Chem.-Eur. J.*, 2010, **16**, 1428–1431; J. Mattsson, O. Zava, A. K. Renfrew, Y. Sei, K. Yamaguchi, P. J. Dyson and B. Therrien, *Dalton Trans.*, 2010, **39**, 8248–8255.
- S. O. Scott, E. L. Gavey, S. J. Lind, K. C. Gordon and J. D. Crowley, *Dalton Trans.*, 2011, **40**, 12117–12124; K. J. Kilpin, U. S. D. Paul, A.-L. Lee and J. D. Crowley, *Chem. Commun.*, 2011, **47**, 328–330; M. L. Gower and J. D. Crowley, *Dalton Trans.*, 2010, **39**, 2371– 2378; J. D. Crowley and E. Gavey, *Dalton Trans.*, 2010, **39**, 4035– 4037; J. D. Crowley, A. J. Goshe and B. Bosnich, *Chem. Commun.*, 2003, 2824–2825; A. J. Goshe, J. D. Crowley and B. Bosnich, *Helv. Chim. Acta*, 2001, **84**, 2971–2985.
- 21 K. J. Kilpin, M. L. Gower, S. G. Telfer, G. B. Jameson and J. D. Crowley, *Inorg. Chem.*, 2011, **50**, 1123–1134.
- 22 D. A. McMorran and P. J. Steel, Angew. Chem., Int. Ed., 1998, 37, 3295–3297.
- 23 D. K. Chand, K. Biradha and M. Fujita, Chem. Commun., 2001, 1652–1653.
- N. Kishi, Z. Li, K. Yoza, M. Akita and M. Yoshizawa, J. Am. Chem. Soc., 2011, 133, 11438–11441; G. H. Clever, W. Kawamura and M. Shionoya, Inorg. Chem., 2011, 50, 4689–4691; G. H. Clever, S. Tashiro and M. Shionoya, J. Am. Chem. Soc., 2010, 132, 9973– 9975; G. H. Clever and M. Shionoya, Chem.–Eur. J., 2010, 16, 11792– 11796; G. H. Clever, S. Tashiro and M. Shionoya, Angew. Chem., Int. Ed., 2009, 48, 7010–7012; M. Fukuda, R. Sekiya and R. Kuroda, Angew. Chem., Int. Ed., 2008, 47, 706–710; R. Sekiya and R. Kuroda, Chem. Commun., 2011; N. L. S. Yue, D. J. Eisler, M. C. Jennings and R. J. Puddephatt, Inorg. Chem., 2004, 43, 7671–7681.
- 25 During the course of our work on **2** a related family of metallosupramolecular cages have been reported by Hooley and co-workers, see ref. 26.
- 26 P. Liao, B. W. Langloss, A. M. Johnson, E. R. Knudsen, F. S. Tham, R. R. Julian and R. J. Hooley, *Chem. Commun.*, 2010, 46, 4932–4934; A. M. Johnson and R. J. Hooley, *Inorg. Chem.*, 2011, 50, 4671–4673; A. M. Johnson, O. Moshe, A. S. Gamboa, B. W. Langloss, J. F. K. Limtiaco, C. K. Larive and R. J. Hooley, *Inorg. Chem.*, 2011, 50, 9430–9442.
- 27 S. V. Kharlamov and S. K. Latypov, *Russ. Chem. Rev.*, 2010, **79**, 635–653; A. Pastor and E. Martinez-Viviente, *Coord. Chem. Rev.*, 2008, **252**, 2314–2345.
- 28 M. W. Ambrogio, C. R. Thomas, Y.-L. Zhao, J. I. Zink and J. F. Stoddart, Acc. Chem. Res., 2011, 44, 903–913; K. K. Coti, M. E. Belowich, M. Liong, M. W. Ambrogio, Y. A. Lau, H. A. Khatib, J. I. Zink, N. M. Khashab and J. F. Stoddart, Nanoscale, 2009, 1, 16–39; K. Konstas, S. J. Langford and M. J. Latter, Int. J. Mol. Sci., 2010, 11, 2453–2472; G. Vives and J. M. Tour, Acc. Chem. Res., 2009, 42, 473–487; J. D. Crowley, E. R. Kay and D. A. Leigh, Intell. Mater., 2008, 1–47; E. R. Kay, D. A. Leigh and F. Zerbetto, Angew. Chem., Int. Ed., 2007, 46, 72– 191; W. R. Browne and B. L. Feringa, Nat. Nanotechnol., 2006, 1, 25–35.
- 29 I. A. Riddell, M. M. J. Smulders, J. K. Clegg and J. R. Nitschke, *Chem. Commun.*, 2011, **47**, 457–459; P. Mal, D. Schultz, K. Beyeh, K. Rissanen and J. R. Nitschke, *Angew. Chem., Int. Ed.*, 2008, **47**, 8297–8301.

- 30 K. Harano, S. Hiraoka and M. Shionoya, J. Am. Chem. Soc., 2007, 129, 5300–5301; P. J. Lusby, P. Müller, S. J. Pike and A. M. Z. Slawin, J. Am. Chem. Soc., 2009, 131, 16398–16400.
- 31 A similar DMAP/pyridine switching system has been used to develop a [2]rotaxane molecular shuttle in which a palladium coordinated to a tridentate 2,6-pyridine dicarboxamido macrocycle can be translocated reversibly between 4-dimethylaminopyridine (DMAP) and pyridine (PY) derived stations via the addition and removal of a proton, see: J. D. Crowley, D. A. Leigh, P. J. Lusby, R. T. McBurney, L.-E. Perret-Aebi, C. Petzold, A. M. Z. Slawin and M.D. Symes, J. Am. Chem. Soc., 2007, 129, 15085–15090.
- 32 Pt…Pt interactions have been observed to stabilise host-guest adducts in other systems, see: M. Yoshizawa, K. Ono, K. Kumazawa, T. Kato

and M. Fujita, J. Am. Chem. Soc., 2005, **127**, 10800–10801; J. D. Crowley, I. M. Steele and B. Bosnich, *Inorg. Chem.*, 2005, **44**, 2989–2991; J. D. Crowley, I. M. Steele and B. Bosnich, *Eur. J. Inorg. Chem.*, 2005, 3907–3917; J. D. Crowley, A. J. Goshe, I. M. Steele and B. Bosnich, *Chem.–Eur. J.*, 2004, **10**, 1944–1955; J. D. Crowley, A. J. Goshe and B. Bosnich, *Chem. Commun.*, 2003, 392–393; A. J. Goshe, I. M. Steele and B. Bosnich, *J. Am. Chem. Soc.*, 2003, **125**, 444–451.

33 Stimuli responsive guest release from metallosupramolecular architectures has been demonstrated previously, see: M. Yoshizawa, K. Kumazawa and M. Fujita, J. Am. Chem. Soc., 2005, 127, 13456– 13457; W.-Y. Sun, T. Kusukawa and M. Fujita, J. Am. Chem. Soc., 2002, 124, 11570–11571; F. Ibukuro, T. Kusukawa and M. Fujita, J. Am. Chem. Soc., 1998, 120, 8561–8562.