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RESEARCH ARTICLE

A reduced symmetry heterobimetallic $[PdPtL_4]^{4+}$ cage: assembly, guest binding and stimulus-induced switching

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Abstract: As part of efforts to enhance the applications of self-assembled metallosupramolecular architectures (MSAs) there is considerable current interest in the development of lower symmetry heterometallic systems. Herein we report a strategy that enables the quantitative assembly of a reduced symmetry heterobimetallic $[PdPtL_4]^{4+}$ cage **C**. We anticipated that the presence of two different metal ions (Pd(II) and Pt(II)) with differing labilities could enable the cage to be "opened" and "closed" selectively at one end upon treatment with suitable stimuli. Combining an inert platinum(II) tetrapyridylaldehyde complex with a suitably substituted pyridylamine and Pd(II) ions led to the assembly of **C**. ^{1}H and DOSY nuclear magnetic resonance spectroscopy (NMR) and electrospray ionization mass spectrometry (ESIMS) data were consistent with the quantitative formation of the cage and the heterobimetallic structure was confirmed using single crystal X-ray crystallography. The cage **C** was shown to bind quinone guest molecules. The structure of the host-guest adduct with a 2,6-diaminoanthraquinone (**G**) guest molecule was determined using X-ray crystallography. Additionally, the system was shown to be stimuli responsive and could be opened and closed on demand. Addition of N,N'-dimethylaminopyridine (DMAP) to the cage **C** resulted in the formation of the "open-cage" $\mathbf{[Pt(L)_4]^{2+}}$ compound and $\mathbf{[Pd(DMAP)_4]^{2+}}$ complex. This new type of stimulus-induced cage opening is similar to a flower blossoming/blooming. This process could then be reversed, with the reformation of **C**, upon the addition of *p*-toluenesulfonic acid (TsOH). When DMAP was added to the host-guest adduct, $[\mathbf{C}\sqsubset\mathbf{G}]^{4+}$, the guest was released from **C.** The host-guest adduct was subsequently restored upon addition of TsOH.

Introduction

Over the past three decades, there has been considerable interest in self-assembled metallosupramolecular architectures (MSAs). The general principles for the synthesis of high symmetry assemblies[1] are now well understood and a range of interesting applications of MSAs are emerging.[2] To further enhance these nascent applications, there has been an up-surge in efforts to develop lower symmetry cage systems, especially those that utilize two different metals with dissimilar coordination properties.[3]

Homometallic M_2L_4 cage-like systems (where M is a square planar metal ion, commonly palladium(II)) are one of the most studied sub-classes of MSAs (Figure 1).[4] Since the early work of McMorran and Steel,[5] there have been many $[Pd_2L_4]^{4+}$ cages synthesized, ranging in size from small to large.[4, 6] The molecular recognition properties of the $[Pd_2L_4]^{4+}$ cages have been extensively examined, with systems that can bind both neutral[7] and anionic[8] guests, including drugs[9] and pollutants,[10] reported. Additionally, the redox,[11] photophysical,[12] biological,[12e, 13] and catalytic[14] properties of these types of cages have also been explored and others have developed switchable systems that can either change shape or release guest molecules on demand.[9, 15] For the most part, these results have been achieved using high symmetry $[Pd_2L_4]^{4+}$ cages. Related $[Pt_2L_4]^{4+}$ systems are known but are far less common, presumably because the relatively inert nature[16] of Pt(II) (in comparison to the more labile Pd(II)) makes the self-assembly process more difficult.[17]

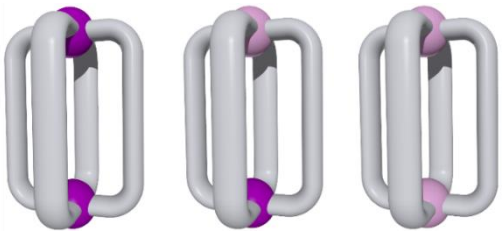

Figure 1. Cartoon representations of homometallic $[Pd_2L_4]^{4+}$ (right) and $[Pt_2L_4]^{4+}$ (left) cages. A lower symmetry heterobimetallic $[PdPtL_4]^{4+}$ cage (center). Colors: palladium(II) = purple, platinum(II) = pink, grey = semi rigid di-monodentate linker ligand.

There is a growing number of lower symmetry $[Pd_2L_4]^{4+}$ cages that have either been generated with lower symmetry ligands[18] or with two or more different types of ligands[19] incorporated into the cage architecture. Several discrete heterometallic $[Pd_XM_XL_Y]$ structures[3] (where M = Ti(IV),[20] Zn(II),[21] Fe(II),[6b, 22] Fe(III),[23] Ru(II),[6e, 24] Ir(III),[25] Al(III)[26] Zr(IV),[27] and lanthanide ions (Ln)[28] have been reported but there are very few $[Pd_XPt_XL_Y]$ systems[29] and, thus far, to the best of our knowledge, there have been no reports of a reduced symmetry heterobimetallic $[PdPtL_4]^{4+}$ cage system (Figure 1 center).

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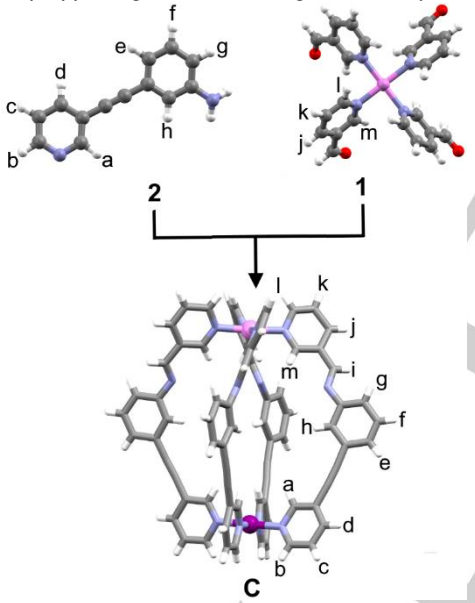
Herein we describe a method for the quantitative assembly of a heterobimetallic $[PdPtL_4]^{4+}$ cage. Additionally, we examine the stimuli responsiveness, as well as guest binding and release of this cage.

Results and Discussion

Inspired by the subcomponent self-assembly method[1f, 30] and dynamic covalent cage systems,[31] we have devised an approach to a reduced symmetry heterobimetallic $[PdPtL_4]^{4+}$ cage. We reasoned that combining an inert platinum(II) tetrapyridylaldehyde complex[32] with a suitably substituted pyridylamine and a labile Pd(II) complex should lead to the assembly of a heterometallic $[PdPtL_4]^{4+}$ cage through the reversible formation of imine and Pd-pyridyl bonds (Scheme 1).

The relatively inert platinum(II) complex [Pt(3-pyridylcarboxyaldehyde)$_4$](BF$_4$)$_2$ (**1**) was synthesized in good yield (95%) by heating 3-pyridylcarboxyaldehyde (4 equiv.), [Pt(DMSO)$_2$Cl$_2$] (1 equiv.) and AgBF$_4$ (3 equiv.) in acetonitrile at 60 °C for 20 h (Supporting Information, Scheme 1, Scheme S1, Figures S1-S3). 3-[2-(3-Pyridinyl)ethynyl]benzenamine (**2**) was synthesized in modest yield (43%) using a Sonogashira coupling between the commercially available 3-ethynylpyridine and 3-iodoaniline (Supporting Information, Figures S4-S5).



Scheme 1. Synthesis of the $[PdPtL_4](BF_4)_4$ cage (**C**): (i) **1** (1 eq.), **2** (4 eq.), and $[Pd(CH_3CN)_4](BF_4)_2$ (1 eq.), [D$_6$]DMSO, RT, 1 h. The ball and stick structures **1** (one possible conformation) and **2** are SPARTAN'16® models, whereas the stick model of **C** is the molecular structure determined by X-ray diffraction analysis: selected bond lengths (Å) Pt1-N4 = 2.08(3), Pt1-N9 = 2.08(4), Pt1-N3 = 2.04(4), Pt1-N12 = 2.02(3), Pd1-N10 = 2.01(2), Pd1-N7 = 2.04(3), Pd1-N1 = 2.03(3), Pd1-N6 = 2.00(2), Pt1-Pd1 = 11.52(2). Color: pink = platinum, purple = palladium, light blue = nitrogen, red = oxygen, grey = carbon, white = hydrogen. Solvent molecules and counterions were omitted for clarity.

The platinum(II) complex, **1**, $[Pd(CH_3CN)_4](BF_4)_2$ and **2** were then combined in [D$_6$]DMSO at room temperature (RT) and the reaction monitored using ^{1}H NMR spectroscopy (Scheme 1, Figure 1 and Supporting Information, Figures S6-S8). Within 1 h, the signals (Figure 1a and c) of the platinum(II) aldehyde complex (**1**) and amine **2** had completely disappeared and were replaced by a new series of resonances (Figure 1b). Diagnostic of cage formation, the aldehyde and amine resonances of **1** and **2**, respectively, were replaced by a signal (H_i, δ = 8.95 ppm) consistent with imine formation and the α-pyridyl peaks (H_a and H_b) were shifted downfield, relative to **2**, indicating coordination to the Pd(II) ion. The new set of peaks were also different to those observed for the free ligand **L** (Figure 1d and Supporting Information, Figures S9-10). ^{1}H DOSY NMR spectrum of the reaction mixture revealed that all the new resonances have the same diffusion coefficient ($D_C = 1.22 \times 10^{-10}$ m^2 s^{-1}) suggesting clean formation of one product (Supporting Information, Figure S11 and Table S1). Furthermore, this diffusion coefficient was different to those found for **1** and **2** and consistent with the formation of a larger architecture (Supporting Information, Table S1). Electrospray ionization mass spectrometry (ESIMS) data obtained from the solution of the reaction mixture also supported the formation of the cage **C**. The major peak observed at *m*/*z* = 358.5741 was consistent with the formulation $[PdPtL_4]^{4+}$ and the observed isotope pattern matched that calculated for this 4+ ion (Supporting Information, Figure S8).

The cage **C** was isolated as a colorless solid in 87% yield from the [D$_6$]DMSO solution of the reaction mixture by addition of excess ethyl acetate. The colorless solid was dissolved in nitromethane and diethyl ether was vapor-diffused into the solution to provide colorless crystals of quality suitable for single crystal X-ray diffraction analysis. The molecular structure determined from the X-ray data (Supporting Information, Table S2 Figure S14) is given in Scheme 1 and provides confirmation for the formation of the reduced symmetry $[PdPtL_4](BF_4)_4$ cage, **C**. As expected, the four bridging ligands are oriented so that the cage has different coordination environments at each end. At one end the Pd(II) ion is coordinated to the four pyridyl alkyne groups of the bridging ligands while the Pt(II) ion is bound to four pyridylimines (Scheme 1 and Supporting Information). The metal-pyridyl bond distances are consistent with those observed in related molecules and the Pd-Pt distance (11.52 Å) is similar to those found in related homometallic pyridyl alkyne-type cages.[7d, 8a, 9-10, 12b, 12e, 13b, 13f, 14c, 17f, 33] The cage **C** adopts a slight helical twist and the cavity contains a BF_4^- anion (positioned towards the pyridyl alkyne end) and a nitromethane molecule (found close to the pyridylimine end). Both guests form hydrogen bonds to the acidic α-pyridyl hydrogen atoms (Supporting Information, Figure S14).

Having confirmed the formation of the reduced symmetry heterometallic cage **C**, we next examined the host-guest (HG) chemistry of the system. Homobimetallic $[Pd_2L_4]^{4+}$ cages have been shown previously to bind a variety of neutral and anionic guest molecules. Lusby and co-workers,[7d, 14c] and others[8a] have reported that benzoquinone (**BQ**) will bind within the cavity of homobimetallic $[Pd_2L_4]^{4+}$ cages through hydrogen bonding interactions between the carbonyl groups of the guest and the acidic α-pyridyl hydrogen atoms of the coordinated pyridyl group of the host. However, the same authors also showed the HG interaction with neutral guests is weakened by competition with anions and solvents.[7d] As the solid state structure of **C** showed a BF_4^- anion bound within the cavity of the cage, we first examined this interaction in solution using ^{19}F NMR spectroscopy ([D$_6$]DMSO, 298 K). The NMR data suggested that the BF_4^- anions were, at least weakly, interacting with the cage, presumably in a similar fashion to that observed in the X-ray structure, because the resonance due to the BF_4^- anions of **C** was shifted (Δδ = 0.2 ppm) relative to that of $NaBF_4$ (Supporting Information, Figure S15).

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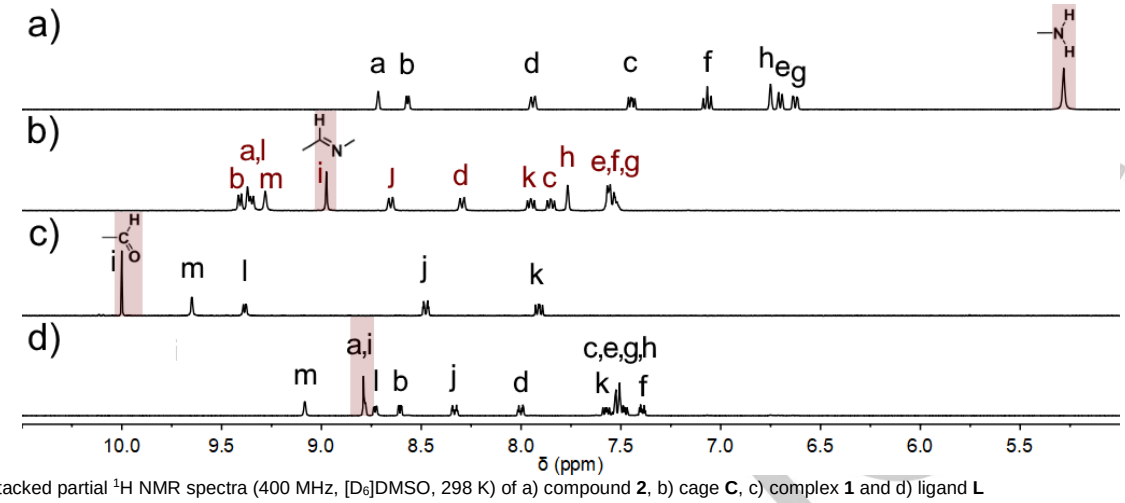

Figure 1. Stacked partial ^{1}H NMR spectra (400 MHz, [D$_6$]DMSO, 298 K) of a) compound **2**, b) cage **C**, c) complex **1** and d) ligand **L**

Nevertheless, since the Pd-Pt distance (11.52 Å) of **C** was similar to the Pd-Pd distances found in homometallic pyridyl alkyne-type cages,[7d, 8a, 9-10, 12b, 12e, 13b, 13f, 14c, 17f, 33] we decided to investigate HG interactions between **C** and selected neutral guest molecules that had been found to bind within $[Pd_2L_4]^{4+}$ cages. In the first instance we examined the interaction of **BQ** with the cage **C** using ^{1}H NMR spectroscopy ([D$_6$]DMSO, 298 K). Upon titration of **BQ** into a [D$_6$]DMSO solution of **C** very modest complexation induced shifts (CIS) of the protons (H$_a$, H$_b$, H$_m$, H$_l$ and H$_i$) of **C** were observed (Δδ = 0.04 – 0.13 ppm, in the presence of 50 equiv. of guest). This indicated that **BQ** does interact with **C**, albeit weakly. Fitting the titration data to a 1:1 binding model using Bindfit (supramolecular.org)[34] gave a binding constant (K) of 23.3 ± 0.8 M^{-1} for the $[\mathbf{C}\subset\mathbf{BQ}]^{4+}$ interaction (Supporting Information, Figures S16-S19). Presumably, the modest binding interaction was caused by competition with the BF_4^- anions and DMSO solvent molecules.

In an effort to achieve a stronger HG interaction, we examined some larger quinone guests including anthraquinone, 2,6-diaminoanthraquinone (**G**) and 6,13-pentacenequinone. However, the limited solubility of these compounds in [D$_6$]DMSO restricted our studies to **G**. Addition of **G** (1 equiv.) to the cage **C** in [D$_6$]DMSO resulted in a substantial change in the resonances of the cage as indicated by the ^{1}H NMR spectrum of the mixture (Figure 2b). The resonances of the cage **C** were shifted and doubled upon addition of **G** to the solution. In addition, peaks due to free cage **C**, as well as free and bound **G**, could all be discerned. The data suggested that **G** is bound within **C** and the exchange between free and bound states is slow on the NMR timescale. Due to the slow exchange (both inter- and intra-molecular) the **C** and **G** peaks of the **C⊂G** host-guest adduct were doubled. The low symmetry of the cage coupled with the slow exchange led to the number of host-guest signals doubling. When **G** is bound it removes the four-fold symmetry of the cage as the amino groups of **G** are nearer to two of the metal bound pyridyl units but the other two pyridyl units are near a hydrogen on the guest (*vide infra*, Scheme 2). The integration of the bound host and guest signals suggested that one **G** molecule was interacting with **C**. Upon titration of more **G** into the solution the peaks due to the free cage eventually disappear leaving only the signals due to the **C⊂G** host-guest adduct and the excess free **G** (Supporting Information, Figure S21). ESIMS data obtained on the 1:1 mixture of **C** and **G** in [D$_6$]DMSO provided additional support for the formation of the **C⊂G** host-guest adduct (Supporting Information, Figure S20). While a series of peaks due to the empty cage with different numbers of counterions was observed, two peaks consistent with **C** forming a 1:1 host-guest adduct with **G** (Supporting Information) were also present (*m/z* = 418.0981 ($[\mathbf{C}\subset\mathbf{G}]^{4+}$) and 566.4655 ($[\mathbf{C}\subset\mathbf{G}(BF_4)]^{3+}$), respectively). Using a 1:1 binding model, we were able to estimate the binding constant (K) to be 2900 ± 300 M^{-1} for the system (Supporting Information, Figures S21-S22). Vapor diffusion of ethylacetate into a 1:1 mixture of **C** and **G** in DMSO provided small single crystals that could be used for X-ray diffraction analysis. While the intensity of diffraction was weak and there was some positional disorder in the cage unit, the cationic cage and the presence of the guest **G** (and the anions) could clearly be observed confirming the formation of a 1:1 host-guest adduct (Scheme 2 and Supporting Information, Figure S23). As was observed in related $[Pd_2L_4]^{4+}\subset$quinone host-guest adducts,[7d, 14b] there are hydrogen bonding interactions between the carbonyl groups of the guest and the acidic α-pyridyl hydrogen atoms of the coordinated pyridyl group of the cage (Scheme 2 and Supporting Information, Figure S23).

Having confirmed that **C** would act as a host for guest molecules, we next examined if the presence of two different metal ions (Pd(II) and Pt(II)) with differing labilities could be exploited to “open” and “close” the cage selectively at one end upon treatment with a suitable stimulus. We postulated that addition of N,N'-dimethylaminopyridine (DMAP) to the reduced symmetry $[PdPtL_4](BF_4)_4$ cage **C** should remove the more labile Pd(II) ions from the cage while leaving the more inert Pt(II) ions coordinated to the four ligands **L**. This would lead to the cage opening in a similar way to a flower blossoming/blooming. Several switchable $[Pd_2L_4]^{4+}$ cages are known and a range of different stimuli have been used to generate switching.[9, 15] In most cases, the stimulus results in complete decomposition of the cage or rearrangement into new metallosupramolecular architectures. Here, we chose to use DMAP as a competitive ligand for Pd(II) as we[9] and others[35] have previously shown that addition of this very basic ligand will remove Pd(II) from metallosupramolecular architectures as $[Pd(DMAP)_4]^{2+}$ with release of the free ligands. Furthermore, this process is completely reversible, and addition of acid to the $[Pd(DMAP)_4]^{2+}$:ligand mixtures that are produced results in protonation and dissociation of the more basic DMAP ligands with reformation of the initial metallosupramolecular architectures.

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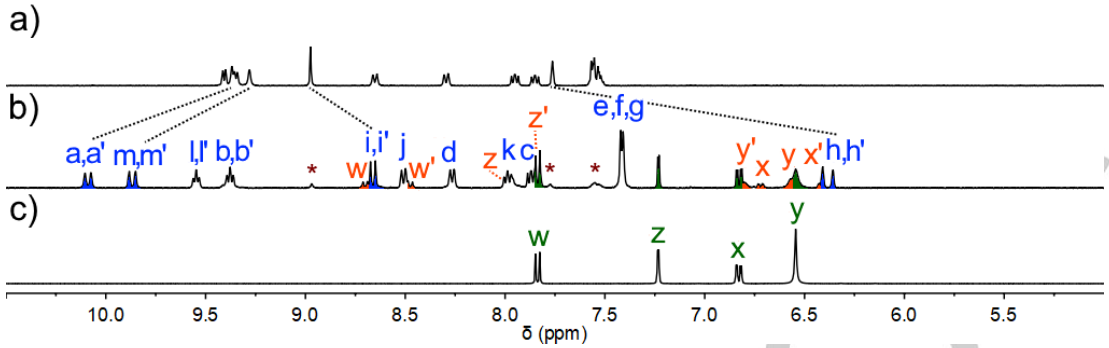
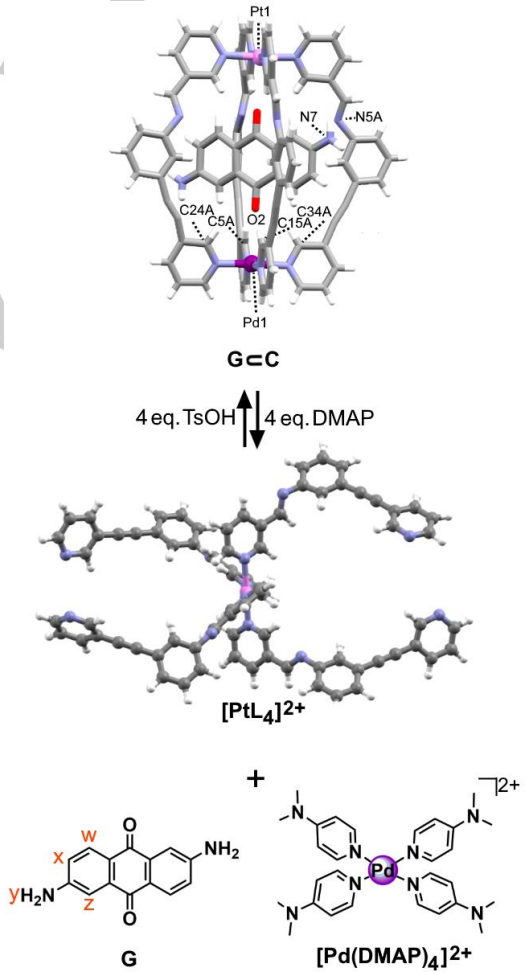


Figure 2. Stacked partial ^{1}H NMR spectra (400 MHz, [D$_6$]DMSO, 298 K) of a) cage **C**, b) **G⊂C** complex at a 1:1 ratio, and c) 2,6-diaminoanthraquinone (**G**). Proton peak labels: blue; **C** of **G⊂C** complex, orange; **G** of **G⊂C** complex, green; **G**. The prime symbols on host and guest proton labels of the **C⊂G** host-guest adduct indicate the doubling of these resonances due to desymmetrization caused by the lower symmetry of **C** and slow guest exchange (both inter- and intra-molecular exchange).

Initially, we titrated DMAP into a [D$_6$]DMSO solution of **C** and monitored the reaction using ^{1}H NMR spectroscopy (Supporting Information, Figures S24 and S25). As the amount of DMAP was increased (from 0-5 equiv.), the resonances for **C** slowly decreased and two new sets of peaks appeared. One set of peaks was consistent with the formation of **[Pd(DMAP)$_4$]$^{2+}$**, as expected, and the other set of peaks was assigned to the complex, **[Pt(L)$_4$]$^{2+}$**. No signals were observed for free **L**. 2D COSY and NOESY NMR spectra enabled the full assignments to be made for [Pt(L)$_4$]$^{2+}$ and the observed chemical shifts for the pyridyl proton resonances were consistent with one pyridyl(imine) unit of **L** being complexed to the Pt(II) ion while the second pyridyl(alkyne) unit was not coordinated. ESIMS data obtained on the 1:4 mixture of **C** and DMAP in [D$_6$]DMSO provided additional support for the formation of **[Pt(L)$_4$]$^{2+}$** (*m/z* = 664.2042) and **[Pd(DMAP)$_4$]$^{2+}$** (*m/z* = 297.0913) (Supporting Information, Figure S26).

Addition of *p*-toluenesulfonic acid (TsOH, 4 equiv.) to the 1:4 mixture of **C** and DMAP in [D$_6$]DMSO led to the protonation/dissociation of the DMAP ligands and reformation of the heterobimetallic cage **C**, confirming that the stimulus induced opening of the cage is completely reversible (Supporting Information, Figure S24). Having demonstrated that **C** was able to open and close on demand, we then examined if this could be used to release and then rebind guest molecules (Scheme 2). The [**C⊂G**]$^{4+}$ host-guest adduct was generated by adding 1 equiv. of **G** to a [D$_6$]DMSO solution of **C** (1 equiv.). The resulting host-guest complex was then treated with DMAP (4 equiv.) and the reaction monitored using ^{1}H NMR spectroscopy (Figure 3). The ^{1}H NMR spectrum (Figure 3b) showed that addition of the DMAP resulted in the formation of **[Pt(L)$_4$]$^{2+}$** and **[Pd(DMAP)$_4$]$^{2+}$** with liberation of the guest **G** (Scheme 2). In a process that paralleled that observed with the empty cage **C**, addition of TsOH (4 equiv.) to the mixture resulted in protonation/dissociation of the DMAP ligands on Pd(II) with accompanying reformation of the cage **C** and, importantly, reuptake of the guest **G** to form the [**C⊂G**]$^{4+}$ host-guest adduct.



Scheme 2. Reversible release and re-binding of **G** from **C** by the addition of 4 eq. TsOH and 4 eq. DMAP, respectively. The ball and stick structure of **[PtL$_4$]$^{2+}$** (one possible conformation) is a SPARTAN'16® model. The stick model of **G⊂C** is the solid-state X-ray crystal structure (distances (Å): Pt1-Pd1 = 11.7310(8), N7-N5A = 3.67(2), N7-N2B = 3.84(2), O2-C24A = 3.43(1), O2-C15A = 3.34(1), O2-C5A = 3.464(9), O2-C34A = 3.35(1)). Color: pink = platinum, purple = palladium, light blue = nitrogen, red = oxygen, grey = carbon, white = hydrogen. Solvent molecules and counterions are omitted for clarity.

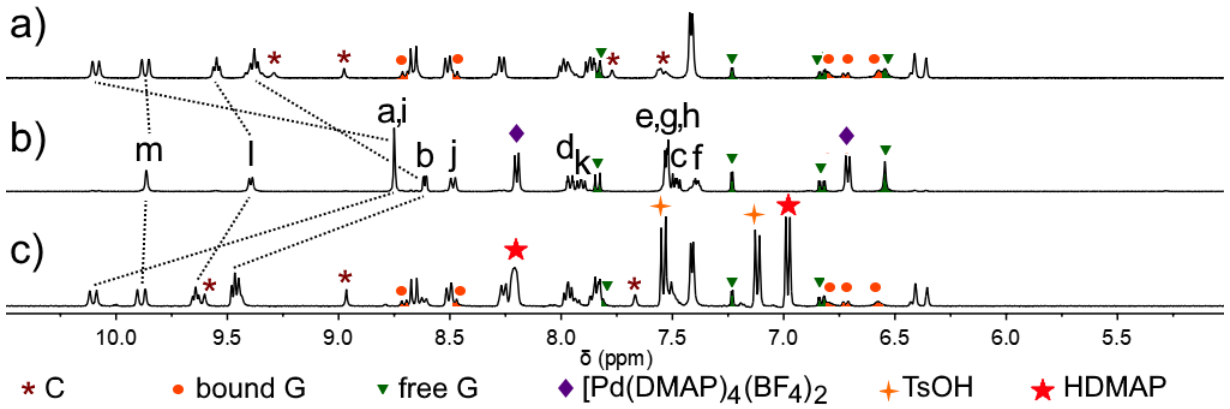


Figure 3. Stacked partial ^{1}H NMR spectra (400 MHz, [D$_6$]DMSO, 298 K) of a) **G⊂C** at a 1:1 ratio, b) open Pt complex with the addition of DMAP, and c) reformation of the cage into **G⊂C** with the addition of TsOH.

Conclusion

Herein we have developed a method that enables the quantitative assembly of a reduced symmetry, heterobimetallic $[PdPtL_4]^{4+}$ cage **C**. Combining an inert platinum(II) tetrapyridylaldehyde complex with a suitably substituted pyridylamine and Pd(II) ions led to the assembly of the heterobimetallic $[PdPtL_4]^{4+}$ cage through the reversible formation of imine and relatively labile Pd-pyridyl bonds. ^{1}H and DOSY NMR and ESI-mass spectra were consistent of the quantitative formation of the cage and the heterobimetallic structure was confirmed using X-ray crystallography. The heterobimetallic $[PdPtL_4]^{4+}$ cage displayed a similarly sized cavity to known homometallic $[Pd_2L_4]^{4+}$ cages. Like the known $[Pd_2L_4]^{4+}$ cages, **C** was shown to bind quinone guest molecules using ^{1}H NMR spectroscopy. The larger 2,6-diaminoanthraquinone (**G**) interacted with the cage quite strongly ($K = 2900 \pm 300\ M^{-1}$) and the host-guest adduct could be detected using ESIMS. The structure of the $[\mathbf{C}\subset\mathbf{G}]^{4+}$ host-guest adduct was also determined using X-ray crystallography.

Importantly, the deliberate design of the cage with inert Pt(II)-pyridyl donor bonds at one end and relatively labile Pd(II)-pyridyl donor bonds at the other end enabled the cage to be opened and closed reversibly and in a controlled manner. This new type of stimulus-induced cage opening can be viewed as similar to the blossoming/blooming of a flower and is distinct from the mechanisms observed in previously reported homometallic stimuli-responsive cages. The stimuli-responsive behavior of **C** was achieved by sequential addition of the basic ligand DMAP, followed by the acid TsOH. Thus, the addition of 4 equivalents of DMAP to **C** resulted in cage opening through removal of the relatively labile Pd(II) ion from the cage as $\mathbf{[Pd(DMAP)_4]^{2+}}$ and formation of the $\mathbf{[Pt(L)_4]^{2+}}$ "open-cage". Subsequent addition of TsOH to the mixture then resulted in protonation/dissociation of the DMAP ligands from $[Pd(DMAP)_4]^{2+}$ and reformation of **C**. When this process was carried out on the host-guest adduct, $[\mathbf{C}\subset\mathbf{G}]^{4+}$, DMAP addition resulted in the formation of $\mathbf{[Pt(L)_4]^{2+}}$ and $\mathbf{[Pd(DMAP)_4]^{2+}}$ with release of the guest **G**. Upon addition of TsOH to this reaction mixture, the host-guest adduct, $[\mathbf{C}\subset\mathbf{G}]^{4+}$, was restored.

These new stimuli responsive, reduced symmetry heterobimetallic $[PdPtL_4]^{4+}$ cages could find use in drug delivery systems and/or switchable catalysis. They may also offer different photophysical and biological properties when compared to the related higher symmetry $[Pd_2L_4]^{4+}$ and $[Pt_2L_4]^{4+}$ cages. We are currently examining these properties and attempting to extend the methodology to other (larger) heterobimetallic metallosupramolecular architectures.

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Keywords: metallosupramolecular architectures • cages • stimuli responsive • host-guest • heterometallic

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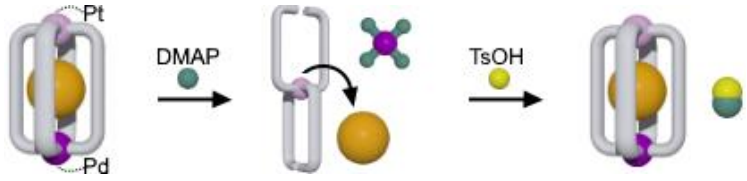

Insert text for Table of Contents here. A method for the quantative assembly of the heterobimetallic cage, $[PdPtL_4]^{4+}$, is described. The cage is shown to interact with quinone guest molecules in a 1:1 fashion. The cage can be selectively and reversibly opened then re-closed at the Pd(II) end by the sequential addition of base then acid. Guest molecules can be reversibly released/bound during this process.

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