Maximizing Coordination Capsule-Guest Polar Interactions in Apolar Solvents Reveals Significant Binding

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David P. August, Gary S. Nichol and Paul J. Lusby*

Abstract: Guest encapsulation underpins the functional properties of self-assembled capsules yet identifying systems capable of strongly binding small organic molecules in solution remains a challenge. Most coordination capsules rely on the hydrophobic effect to ensure effective solution-phase association. In contrast, we show that using non-interacting anions in apolar solvents can maximize favorable interactions between a cationic Pd_2L_4 host and charge-neutral guests resulting in a dramatic increase in binding strength. With quinone-type guests, association constants in excess of 10^8 M^{-1} were observed, comparable to the highest previously recorded for a metallosupramolecular capsule. Modulation of guests' optoelectronic properties was also observed, with encapsulation either changing or switching-on luminescence not present in the bulk-phase.

Supramolecular capsules appear at the forefront of research efforts because their propensity to partition whole molecules from the bulk-phase produces interesting properties ranging from sensing[1] through catalysis[2] to the stabilization of reactive species.[3] With coordination systems, binding charge neutral guests provides a notable challenge because of the competition with associated counter-anions or cations.[4] As a result, polar solvents are typically favored as these stabilize the counter-charged species outside of the cavity.[5] Certain solvents, such as water, can also provide a strong and universal driving-force for guest encapsulation through solvophobic desolvation pathways.[6] However, metallo-organic capsules often possess a mix of hydrophobic and hydrophilic regions—usually large apolar aromatic surfaces linked by polar coordination vertices—such that binding can be difficult to predict and also require a trade-off with possible favorable polar interactions.[7] Here we show that it is possible to attain significant binding, comparable with the strongest previously reported by a coordination capsule in water[5a,8]—almost 10^9 M^{-1} for a charge-neutral guest—by maximizing non-covalent interactions in apolar solvents.[9]

The system we selected to study was the Pd_2L_4 capsule, $\mathbf{1}^{4+}$ (Figure 1a), first reported by Hooley,[10] in anticipation that (a) the low charge would aid investigation in apolar solvents; (b) the strong Pd-pyridine interactions would ensure the integrity of the anion-free cavity; (c) it would be possible to better the modest binding (<20 M^{-1}) previously reported for various aromatic guests in DMSO.[10a] Molecular modelling also indicated that the *o*-pyridyl positions (H_a) are polarized by the Pd^{II} ions creating pockets of H-bond donors that can form complementary interactions with guests such as quinones (Figure 1b).[11] Promisingly, when excess naphthoquinone, $\mathbf{G^1}$, was added to $\mathbf{1}$·4OTf in CD_3CN, the ^1H NMR spectrum of the mixture showed significant changes when compared to the individual species (Figure 2). While the single set of host-guest signals indicated that the interaction was dynamic relative to the NMR timescale, it was notable that the inside cage resonances (H_a, H_e) and two of the guest (H_y, H_z) were most shifted. Also, whereas H_e, H_y and H_z all moved upfield due to mutual shielding by host and guest aromatic surfaces, H_a was downfield shifted, supporting the initial supposition that binding would be driven by multiple CH···O H-bonds.

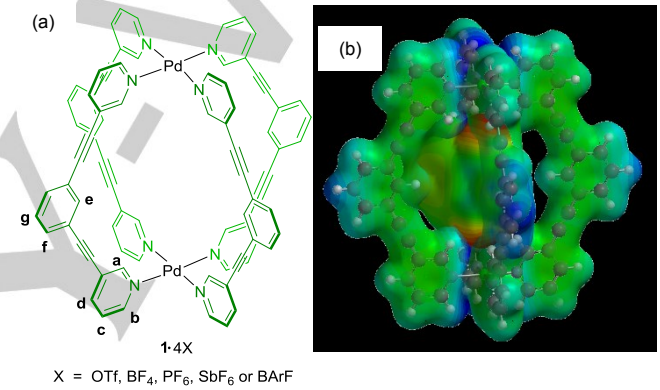

Figure 1. (a) Chemical structure of the $Pd_2L_4^{4+}$ cage, $\mathbf{1}^{4+}$; (b) Energy-minimised model of naphthoquinone $\mathbf{G^1}$ within the cavity of $\mathbf{1}^{4+}$ showing attractive electrostatic surface potentials between the electron deficient CH regions of the capsule (shown in blue) and electron-rich areas provided by the guest (shown in red).

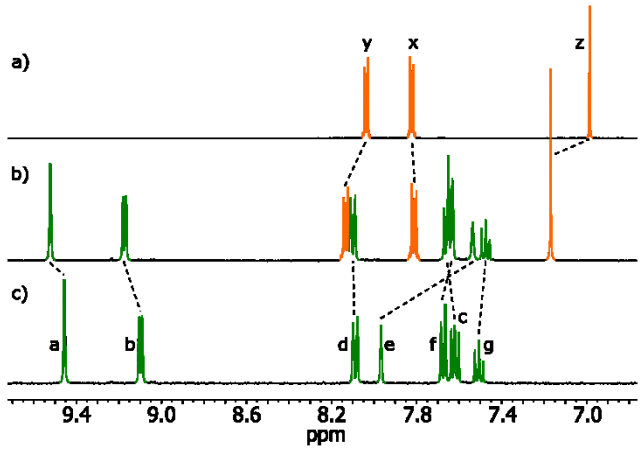

Figure 2. Partial ^1H NMR spectra (500 MHz, CD_3CN, 300 K) of a) naphthoquinone, $\mathbf{G^1}$, only; b) a mixture of $\mathbf{1}$·4OTf with excess $\mathbf{G^1}$; c) $\mathbf{1}$·4OTf only. The lettering refers to those shown in Figures 1 and 3.

We next sought to assess the strength of binding between $\mathbf{G^1}$ and $\mathbf{1}^{4+}$ (Table 1). Starting with $\mathbf{1}$·4OTf in CD_3CN, plotting the change in chemical shifts (Δδ) of the host when titrated with $\mathbf{G^1}$ produced multiple curves that fitted a 1:1 binding isotherm, which

[*] Mr. D. P. August, Dr. G. S. Nichol, Dr. P. J. Lusby
EaStCHEM School of Chemistry, Joseph Black Building, David Brewster Road, Edinburgh, UK, EH9 3FJ
E-mail: Paul.Lusby@ed.ac.uk

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Supporting information for this article (including synthetis, characterization data, X-ray analysis and details of titration experiments) is given via a link at the end of the document.

gave a global association constant, K_a, of 210 M^{-1} (Table 1, Entry 1; see Supporting Information for details). Encouraged that the affinity for **G¹** was ten-fold higher than the previous best guest,[10a] several different solvents were screened (Table 1, Entries 2-5), which indicated that apolar solvents promote better binding (Table 1, Entries 4-5). Surmising that even stronger binding was possibly being masked by tight ion-pairing, other capsule salts, **1**·4X, were then prepared either directly from the relevent Pd^{II} source (X^- = BF_4^-) or by adding excess NaX or KX to **1**·4OTf (X^- = PF_6^-, SbF_6^-, $BArF^-$ [BArF = $B(3,5\text{-}(CF_3)_2C_6H_3)_4^-$]).[12] Non-capsule salts were removed by exploiting the low solubility of **1**·4X in either methanol or water, while ^{19}F NMR spectroscopy confirmed anion metathesis. Interestingly, comparing the ^1H NMR spectra of **1**·4X (Figure S3, S27) indicates that the stronger coordinating anions, OTf^- and BF_4^- in particular, are likely to reside within the capsule's cavity, with internal signals H_a and H_e being notably deshielded by up to 0.2 ppm in the case of both **1**·4OTf and **1**·4BF_4.[13] The affinity of $\mathbf{1}^{4+}$ for the different anions was also qualitatively observed using ESI-MS; **1**·4OTf exhibited dominant 2+ and 3+ charge states with two and one associated anions, respectively, while the "naked" $\mathbf{1}^{4+}$ was the major ion with **1**·4BArF (Figures S28-32). Measuring the K_a for **G¹** with the additional ion-pair capsules **1**·4X in CD_3NO_2—the optimal solvent to balance solubility whilst maximizing favourable interactions—revealed that, as anticpated, replacing OTf^- with weaker interacting anions (Table 1, Entries 5-9) increases the binding strength, with a significant 25-fold increase in the case of $BArF^-$.

Table 1. Association constants, K_a, for naphthoquinone, **G¹**, with various capsule ion-pairs, **1**·4X, in different solvents.[a]

	X	Solvent	K_a / M^{-1}	ΔG / kJ mol^{-1}
Entry 1	OTf	CD_3CN	210	13.2
Entry 2	OTf	CD_3OD	26	8.1
Entry 3	OTf	[D_8]THF	290	14.1
Entry 4	OTf	CD_2Cl_2	1800	18.7
Entry 5	OTf	CD_3NO_2	2000	18.8
Entry 6	BF_4	CD_3NO_2	6500	21.7
Entry 7	PF_6	CD_3NO_2	13000	23.5
Entry 8	SbF_6	CD_3NO_2	22000	24.8
Entry 9	BArF	CD_3NO_2	50000	26.8
Entry 10	BArF	CD_3OD	530	15.5
Entry 11	BArF	CD_3CN	1600	18.3
Entry 12	BArF	CD_2Cl_2	350000[b]	31.1

[a] Determined by ^1H NMR titration, errors are estimated to be <10%. [b] Competitive ^1H NMR titration with **G³**.

The affinity of **G¹** for **1**·4BArF has also been measured in different solvents (Table 1, Entries 9-12). This analysis was more complicated with CD_2Cl_2 as a solvent (Table 1, Entry 12) because of capsule signal broadening during the titration, indicating guest exchange was occurring close to the NMR timescale. In this case, K_a was determined using a competitive binding experiment with a stronger, slow exchange guest (see below and Supporting Information).[14] The trend of increased binding with **1**·4OTf in solvents of decreasing polarity (Table 1, Entries 1-4) was mirrored by **1**·4BArF (Table 1, Entries 9-12), however, the latter produced globally higher affinities, from a factor of ten in more polar solvents through to a greater than 100-fold increase in CD_2Cl_2. Overall, the combination of weakly interacting anions and a non-polar solvent dramatically increases the K_a between $\mathbf{1}^{4+}$ and **G¹** by 10^4 (Table 1, Entry 2 vs. Entry 1) thus indicating that a major contribution to the binding free energy are the polar CH···O H-bonds.

Using the optimized ion-pair and solvent combination (**1**·4BArF in CD_2Cl_2), different potential guests were explored (Figure 3). Notably, **G³⁻⁵** all showed slow in-out kinetics, which was most apparent with **G⁵** due to the reduction in capsule symmetry caused by the different benzo rings of the guest (Figure S35). Addition of sub-stoichiometric **G³⁻⁵** to **1**·4BArF also revealed that they were very tight binders as no free guest was detectable at concentrations above 50 μM.[15] Strong association was also evident by preservation of the inclusion complexes under ESI-MS conditions (Figures S57-59). Consequently, association constants were obtained using ^1H NMR competitive titration experiments; K_a for **G³** was measured using a large excess of the fast exchange guest **G²**, while **G⁴** was competed against **G³** (see Supporting Information). Attempts to obtain a binding constant for **G⁵** using competitive binding produced data of insufficient quality, however, the same experiment showed it was better than **G³**.

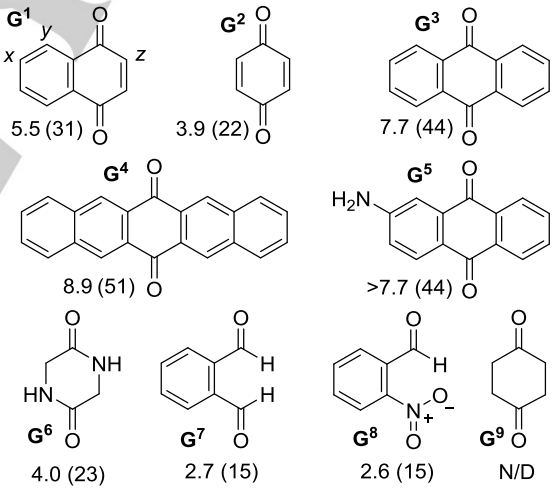

Figure 3. The log K_a values for selected molecules, with binding strength energies (kJ mol^{-1}) shown in parenthesis. Association constants measured in CD_2Cl_2 using **1**·4BArF, except **G⁶**, which was obtained in CD_3CN.

With the quinone series (**G¹**-**G⁵**), increasing the number of fused aromatic rings results in a significant increase in K_a. The difference between **G¹** vs. **G²** and **G²** vs. **G³** are fairly similar, with each additional aromatic ring adding about 10 kJ mol^{-1} to the binding strength.[16] These energetic contributions are likely a result of additional edge-to-face interactions (CH–π H-bonds[9a], see below), which is consistent with the significant shielding of H_e observed by ^1H NMR spectroscopy following host-guest complexation. With pentacenedione, **G⁴**, the extra two rings

produce a smaller increase, perhaps not unsurprisingly as these protrude further into the void between adjacent ligands. Nonetheless, the log K_a of 8.9 for **G⁴** is, as far as we are aware, comparable to the highest for a charge neutral guest inside a coordination capsule. The crystal structure of [**G⁴**⊂**1**]4OTf has also been obtained, using single crystals grown from CH_3CN and Et_2O (Figure 4).[17] The solid state structure confirms the solution binding model with the oxygen atoms of **G⁴** clearly located in the two pockets of four H_a atoms, with C—O distances ranging from 3.3 to 3.8 Å, indicating multiple CH···O H-bonds. Edge-to-face interactions between the extended aromatic surface of **G⁴** and the four H_e atoms are also apparent (see above). In addition to quinones, **1⁴⁺** also binds other guests with suitably disposed H-bond acceptor groups (e.g.**G⁶⁻⁸**). The log K_a of 4.0 for **G⁶** was measured in CD_3CN to alleviate problems of intermediate exchange; a comparison with **G¹** under similar conditions (Table 1, entry 11) is consistent with the better H-bond acceptor properties of amides vs. enones, not least considering **G⁶** lacks the additional benzo ring that adds 10 kJ mol^{-1} to the binding strength of **G¹**. A further interesting comparison can also be made to the classic tetraamide macrocycle reported by Hunter and co-workers,[18] which binds **G²**, **G⁶** and **G⁹**. Whereas the K_a for [**G²**⊂**1**]$^{4+}$ is an order of magnitude higher than the tetraamide macrocycle under similar conditions, and a solvent/anion adjusted value for [**G⁶**⊂**1**]$^{4+}$ would be at least comparable with the covalent host, in contrast **G⁹** shows no evidence of encapsulation inside **1⁴⁺**.[19] A molecular model of **G⁹** revealed that the preferred chair conformation results in only a marginally smaller distance between H-bond acceptor oxygen atoms in comparison to **G²** (Δ(O–O) = 0.1 Å). Instead, the lack of binding could possibly be due to the non-linear orientation of carbonyl groups, coupled to the relative rigidity of the metallosupramolecular framework, thus not allowing an optimal arrangement of H-bonding interactions with both sets of CH donor pockets.

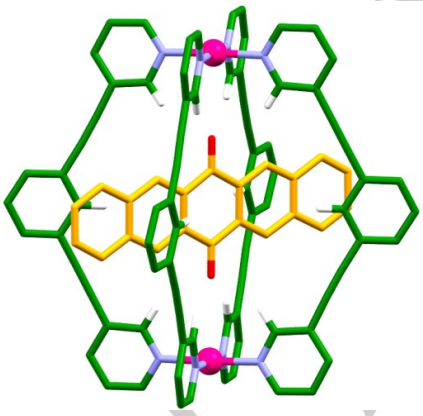

Figure 4. X-ray crystal structure of [**G⁴**⊂**1**]4OTf (counteranions, solvent and non-interacting H atoms omitted for clarity). Color code: carbon of **1⁴⁺**, green; carbon of **G⁴**, orange; hydrogen, white; nitrogen, blue; oxygen, red; palladium, magenta.

The optoelectronic properties of guests **G⁴⁻⁵** are modulated upon encapsulation within **1**$^{4+}$. With **G⁵** both the λ_{max} of the absorption and emission spectra are redshifted with respect to the free guest, by 70 and 34 nm, respectively (see Figures S66), a possible consequence of the LUMO being stabilized by H-bonding to the capsule. Similar yet even more dramatic effects are seen with **G⁴**. Whereas both **1**·4BArF and **G⁴** are virtually colorless to the naked eye under ambient lighting, [**G⁴**⊂**1**]4BarF is clearly yellow (Figure 5a, left). When held under a UV lamp, the difference is even more stark, with [**G⁴**⊂**1**]4BarF showing strong emission whereas **G⁴** alone shows little (Figure 5a, right). The switch-on emission of the host-guest complex has also been confirmed spectroscopically, both by titrating **1**·4BarF into **G⁴** (Figure 5b) and also **G⁴** into **1**·4BarF (Figure S63-64). In both cases, the emission intensity increases until a 1:1 ratio of **1**·4BarF and **G⁴** is reached, where after it remains constant, strongly indicating that that the luminescence is due to the formation of [**G⁴**⊂**1**]4BarF. While many coordination cages have been shown to quench the emission of guests, due to heavy-atom effects and/or charge-transfer processes, those that either maintain or even enhance the optoelectronic properties of the encapsulated species are rare.[20] In the case of [**G⁴**⊂**1**]4BarF, we likely attribute the increase in fluorescence with respect to the free guest due to preventing the formation of weakly-emissive aggregates.[20a]

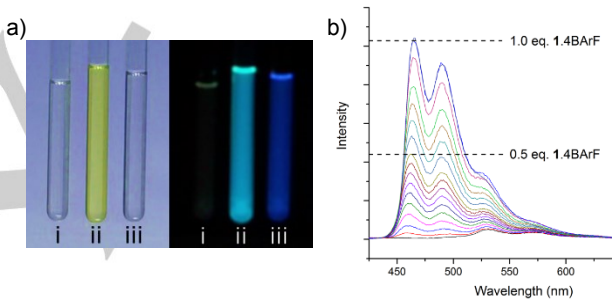

Figure 5. a) Images of 100 μM CD_2Cl_2 solutions of i) **G⁴**; ii) [**G⁴**⊂**1**]4BarF; iii) **1**·BarF under ambient lighting (left) and under a 365 nm UV lamp (right); b) Fluorescence titration of **1**·4BArF into 100 μM of **G⁴** in CH_2Cl_2 with excitation at 412 nm (isosbestic point of **G⁴** and [**G⁴** ⊂ **1**]4BarF). A quantum yield enhancement factor of 15.6 was calculated from the relative peak intensities of **G⁴** and [**G⁴**⊂**1**]4BarF. No further increase in emission intensity was observed upon addition of excess **1**·4BArF.

In conclusion, we have shown that minimizing the competitive interactions between a charged cationic cage and its associated anions can lead to a dramatic increase in the strength of charge-neutral guest binding in apolar solvents, giving association constants comparable to the highest previously observed for a metallosupramolecular capsule system. We are currently investigating how such electronic manipulation of guest molecules can be exploited for various applications.

Keywords: Host-guest • coordination capsule • self-assembly • non-coordinating anions • quinone

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[13] For anions such as OTf and BF_4, it is likely that strong coulombic attraction is supplemented by a well defined secondary coordination sphere that involves mutiple *o*-pyridyl CH···O or CH···F H-bonds. For the X-ray structure of a similar primary and secondary coordination sphere, see a) C. Bianchini, J. Filippi, A. Lavacchi, W. Oberhauser, *Eur. J. Inorg. Chem.* **2011**, 1797-1805. With **1**·4OTf and **1**·4BF_4, it is anticipated that, in solution, two anions interact with the external *o*-pyridyl pokets (noticeable shifts of H_b in the ^{1}H NMR spectra are observed, Figure S27), however, it is suspected that both the coulombic repulsion and size limitation of the capsules cavity means that only one of the internal *o*-pyrdyl sites is occupied at any one time. Similar anion binding within capsules has been observed in the solid state, see ref [9a] and also, b) J. E. M. Lewis, J. D. Crowley, *Supramol. Chem.* **2014**, *26*, 173-181.

[14] While the errors associated with binding constants determined by competitive titration experiments are likely to be greater than 10%, such uncertainty is offset by the significant difference in K_a values, see Figure S38.

[15] At concentrations less than 50 μM, $\mathbf{1}^{4+}$ starts to disassemble, see Figure S33.

[16] A slightly larger increase in the binding strength is observed between the first and second additional benzo groups (9 vs. 12 kJ mol^{-1}), possibly indicating that for $\mathbf{G^2}$ there is free rotation of the guest in the cavity around the C_2 axis that connects both CO groups. With $\mathbf{G^1}$ the additional CH-π interactions would be partially offset by the loss in entropy caused by the lack of rotation for this larger guest, hence the subsequent difference between $\mathbf{G^1}$ and $\mathbf{G^3}$ is larger.

[17] CCDC 1492902 [$\mathbf{G^4}$ ⊂ **1**]4OTf contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

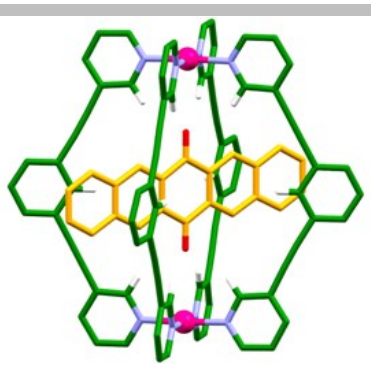
[18] H. Adams, F.J. Carver, C. A. Hunter, N. J. Osborne, *Chem. Conmmun.* **1996**, 2529-2530.

[19] While small changes to the ^{1}H NMR signals of $\mathbf{1}^{4+}$ signals were observed upon titration with $\mathbf{G^9}$, attempts to fit this data to a 1:1 binding model gave a meaningless K_a value (0.1 ± 96 M^{-1}). We attribute the small changes to other possible, weak binding modes, such as interactions with the exteral *o*-pyridyl H-bond donors.

[20] a) K. Ono, J. K. Klosterman, M. Yoshizawa, K. Sekiguchi, T. Tahara, M. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 12526–12527; b) P. P. Neelakandan, A. Jiménez, J. R. Nitschke, *Chem. Sci.* **2014**, *5*, 908-915; c) M. Yamashina, M. M. Sartin, Y. Sei, M. Akita, S.Takeuchi, T.Tahara, M. Yoshizawa, *J. Am. Chem. Soc.* **2015**, *137*, 9266−9269.

COMMUNICATION

A combination of apolar solvents and weakly interacting anions have been used to maximize the non-covalent interactions between a simple Pd_2L_4 host and various charge-neutral guest molecules, giving association constants comparable with the highest previously reported for a coordination capsule. Modulation of the guest's optoelectronic properties, notably either changing or switching-on luminescence not present in the bulk-phase, was also observed.



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