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Citation for published version:

Digital Object Identifier (DOI):
10.1002/anie.201608229

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Angewandte Chemie International Edition

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

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 Pd4L4 cage and charge-neutral guests resulting in a dramatic increase in binding strength. With quinone-type guests, association constants in excess of 10^9 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 through catalysis to the stabilization of reactive species. With coordination systems, binding charge-neutral guests provides a notable challenge because of the competition with associated counter-ions or cations. As a result, polar solvents are typically favored as these stabilize the counter-charged species outside of the cavity. Certain solvents, such as water, can also provide a strong and universal driving-force for guest encapsulation through solvophobic desolvation pathways. 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. Here we show that it is possible to attain significant binding, comparable with the strongest previously reported by a coordination capsule in water—the largest in terms of the cavity volume—almost 10^9 M^-1 for a charge-neutral guest—by maximizing non-covalent interactions in apolar solvents.

The system we selected to study was the Pd4L4 capsule, 1**(a), first reported by Hooley, 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. Molecular modelling also indicated that the o-pyridyl positions (H_a) are polarized by the Pd^0 ions creating pockets of H-bond donors that can form complementary interactions with guests such as quinones (Figure 1b). Promisingly, when excess naphthoquinone, G1, was added to 1·4OTf in CD3CN, 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_b) and two of the guest (H_a, H_b) were most shifted. Also, whereas H_a, H_b and H_c all moved upfield due to mutual shielding by host and guest aromatic surfaces, H_c 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 Pd4_L4 cage, 1**: (b) Energy-minimised model of naphthoquinone G1 within the cavity of 1**: 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 1](https://via.placeholder.com/150)

Figure 2. Partial 1H NMR spectra (500 MHz, CD3CN, 300 K) of a) naphthoquinone, G1, only; b) a mixture of 1·4OTf with excess G1; c) 1·4OTf only. The lettering refers to those shown in Figures 1 and 3.

We next sought to assess the strength of binding between G1 and 1**(Table 1). Starting with 1·4OTf in CD3CN, plotting the change in chemical shifts (Δδ) of the host when titrated with G1 produced multiple curves that fitted a 1:1 binding isotherm, which
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Increasing 

The affinity of 

was determined using a competitive binding experiment with 

a strong, 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 CD2Cl2. Overall, the 

combination of weakly interacting anions and a non-polar solvent 

dramatically increases the 

between 1\(^+\) and 

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 CD2Cl2), different potential guests were explored 

(figure 3). Notably, 

all showed slow in-out kinetics, which was most apparent with 

due to the reduction in capsule symmetry caused by the different benzo rings of the guest (Figure S35). Addition of sub-stoichiometric 

G\(^5\) to 1-4BArF also revealed that they were very tight binders as no free guest was detectable at concentrations above 50 \(\mu M\).\(^{19}\) Strong association was also evident by preservation of 

the inclusion complexes under ESI-MS conditions (Figures S57-59). Consequently, association constants were obtained using 

\(^1\)H NMR competitive titration experiments; \(K_a\) for 

was measured using a large excess of the fast exchange guest 

\(G^3\), while 

\(G^4\) was competed against 

(see Supporting Information). Attempts to obtain a binding constant for 

\(G^4\) using competitive binding produced data of insufficient quality, 

however, the same experiment showed it was better than \(G^3\).

Figure 3. The log \(K_a\) values for selected molecules, with binding strength 

energies (kJ mol\(^{-1}\)) shown in parenthesis. Association constants measured in 

CD2Cl2 using 1-4BArF, except 

which was obtained in CD3CN.

With the quinone series (\(G^1\)-\(G^3\)), increasing the number of fused aromatic rings results in a significant increase in 

\(K_a\). The difference between 

\(G^1\) vs. \(G^2\) and \(G^2\) vs. \(G^3\) 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···H-bonds\(^{20}\), see below), which is consistent with the significant shielding of 

\(H_a\) observed by 

\(^1\)H NMR spectroscopy following host-guest complexation. With pentacenedione, 

\(G^4\), the extra two rings

Table 1. Association constants, \(K_a\), for naphthoquinone, \(G^1\), with various 

capsule ion-pairs, 1-4X, in different solvents.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Solvent</th>
<th>(K_a) / M(^{-1})</th>
<th>(\Delta G) / kJ mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>OTf</td>
<td>CD3CN</td>
<td>200</td>
<td>13.2</td>
</tr>
<tr>
<td>Entry 2</td>
<td>OTf</td>
<td>CD3OD</td>
<td>26</td>
<td>8.1</td>
</tr>
<tr>
<td>Entry 3</td>
<td>OTf</td>
<td>DMSO</td>
<td>290</td>
<td>14.1</td>
</tr>
<tr>
<td>Entry 4</td>
<td>OTf</td>
<td>CD2Cl2</td>
<td>1800</td>
<td>18.7</td>
</tr>
<tr>
<td>Entry 5</td>
<td>OTf</td>
<td>CD3NO2</td>
<td>2000</td>
<td>18.8</td>
</tr>
<tr>
<td>Entry 6</td>
<td>BF3</td>
<td>CD3NO2</td>
<td>6500</td>
<td>21.7</td>
</tr>
<tr>
<td>Entry 7</td>
<td>BF3</td>
<td>CD3NO2</td>
<td>13000</td>
<td>23.5</td>
</tr>
<tr>
<td>Entry 8</td>
<td>BF3</td>
<td>CD3NO2</td>
<td>22000</td>
<td>24.8</td>
</tr>
<tr>
<td>Entry 9</td>
<td>BArF</td>
<td>CD3NO2</td>
<td>50000</td>
<td>26.8</td>
</tr>
<tr>
<td>Entry 10</td>
<td>BArF</td>
<td>CD3OD</td>
<td>530</td>
<td>15.5</td>
</tr>
<tr>
<td>Entry 11</td>
<td>BArF</td>
<td>CD3CN</td>
<td>1600</td>
<td>18.3</td>
</tr>
<tr>
<td>Entry 12</td>
<td>BArF</td>
<td>CD3CN</td>
<td>350000(^b)</td>
<td>31.1</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR titration, errors are estimated to be <10%. \(^b\) Competitive \(^1\)H NMR titration with \(G^1\).

The affinity of 

for 1-4BArF has also been measured in 

different solvents (Table 1, Entries 9-12). This analysis was more 

complicated with CD2Cl2 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,
produce a smaller increase, perhaps not unsurprisingly as these protrude further into the void between adjacent ligands. Nonetheless, the log $K_d$ of 8.9 for $G^4$ is, as far as we are aware, comparable to the highest for a charge neutral guest inside a coordination capsule. The crystal structure of [G$^4$⊂1]4OTf has also been obtained, using single crystals grown from CH$_3$CN and Et$_2$O (Figure 4).$^{[17]}$ The solid state structure confirms the solution binding model with the oxygen atoms of $G^4$ clearly located in the two pockets of four $H_4$ 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 $G^4$ and the four $H_4$ atoms are also apparent (see above). In addition to quinones, $1^+\text{r}$ also binds other guests with suitably disposed H-bond acceptor groups (e.g. $G^6$). The log $K_d$ of 4.0 for $G^6$ was measured in CD$_3$CN to alleviate problems of intermediate exchange; a comparison with $G^1$ under similar conditions (Table 1, entry 11) is consistent with the better H-bond acceptor properties of amides vs. enones, not least considering $G^6$ lacks the additional benzo ring that adds 10 kJ mol$^{-1}$ to the binding strength of $G^1$. A further interesting comparison can also be made to the classic tetraamide macrocycle reported by Hunter and co-workers,$^{[18]}$ which binds $G^2$, $G^3$ and $G^3$. Whereas the $K_d$ for [G$^3$⊂1]$^{2+}$ is an order of magnitude higher than the tetraamide macrocycle under similar conditions, and a solvent/anion adjusted value for [G$^6$⊂1]$^{4+}$ would be at least comparable with the covalent host, in contrast $G^2$ shows no evidence of encapsulation inside $1^+$.$^{[19]}$ A molecular model of $G^3$ revealed that the preferred chair conformation results in only a marginally smaller distance between H-bond acceptor oxygen atoms in comparison to $G^2$ ($\Delta(O-O)=0.1$ 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.

The optoelectronic properties of guests $G^4$ and $G^6$ are modulated upon encapsulation within $1^+$. With $G^3$ both the $\lambda_{\text{max}}$ 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 $G^4$. Whereas both 1·4BarF and $G^4$ are virtually colorless to the naked eye under ambient lighting, [G$^4$⊂1]4BarF is clearly yellow (Figure 5a, left). When held under a UV lamp, the difference is even more stark, with [G$^4$⊂1]4BarF showing strong emission whereas $G^4$ alone shows little (Figure 5a, right). The switch-on emission of the host-guest complex has also been confirmed spectrosopically, both by titrating 1·4BarF into $G^4$ (Figure 5b) and also $G^4$ into 1·4BarF (Figure S63-64). In both cases, the emission intensity increases until a 1:1 ratio of 1·4BarF and $G^4$ is reached, where after it remains constant, strongly indicating that the luminescence is due to the formation of [G$^4$⊂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 [G$^4$⊂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$_3$Cl$_2$ solutions of i) $G^4$; ii) [G$^4$⊂1]4BarF; iii) 1·4BarF under ambient lighting (left) and under a 365 nm UV lamp (right); b) Fluorescence titration of 1·4BarF into 100 µM of $G^4$ in CH$_3$Cl$_2$, with excitation at 412 nm (isosbestic point of $G^4$ and [G$^4$⊂1]4BarF). A quantum yield enhancement factor of 15.6 was calculated from the relative peak intensities of $G^4$ and [G$^4$⊂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

For examples of metal ion polarised CH–H bonding, see a) A. J. Metherell, W. Cullen, A. Stephenson, C. A. Hunter, M. D. Ward, Dalton Trans. 2014, 43, 71–84. For examples of similar host-guest interactions in coordinations cages, see refs 4a, 5a and 8.


For anions such as OTF − and BF4 −, it is likely that strong coulombic attraction is supplemented by a well defined secondary coordination sphere which involves multiple o-π-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. 2015, 17, 197–2005. With 1·4OTF and 1·BF4 −, it is anticipated that, in solution, two anions interact with the external o-π-pyridyl (noticeable shifts of δH in the 1H 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-π-pyridyl sites is occupied at any one time. Similar anion binding within capsules has been observed in the solid state, see ref [b] and also, b) J. E. M. Lewis, J. D. Crowley, Supramol. Chem. 2014, 26, 173–181.

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 Ks values, see Figure S38. At concentrations less than 50 µM, 1+ starts to disassemble, see Figure S33.

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 G1 there is free rotation of the guest in the cavity around the C6 axis that connects both CO groups. With G2 the additional CH···S 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 G1 and G2 is larger.

CCDC 1492902 (G1) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request.cif.


While small changes to the 1H NMR signals of 14+ signals were observed upon titration with G1+, attempts to fit this data to a 1:1 binding model gave a meaningless Ks value (0.1 ± 96 M−1). We attribute these small changes to other possible, weak binding modes, such as interactions with the external o-π-pyridyl H-bond donors.

A combination of apolar solvents and weakly interacting anions have been used to maximize the non-covalent interactions between a simple \( \text{Pd}_2\text{L}_4 \) 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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