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Hydrophobic metallo-supramolecular Pd_2L_4 Cages for zwitterionic guest encapsulation in organic solvents

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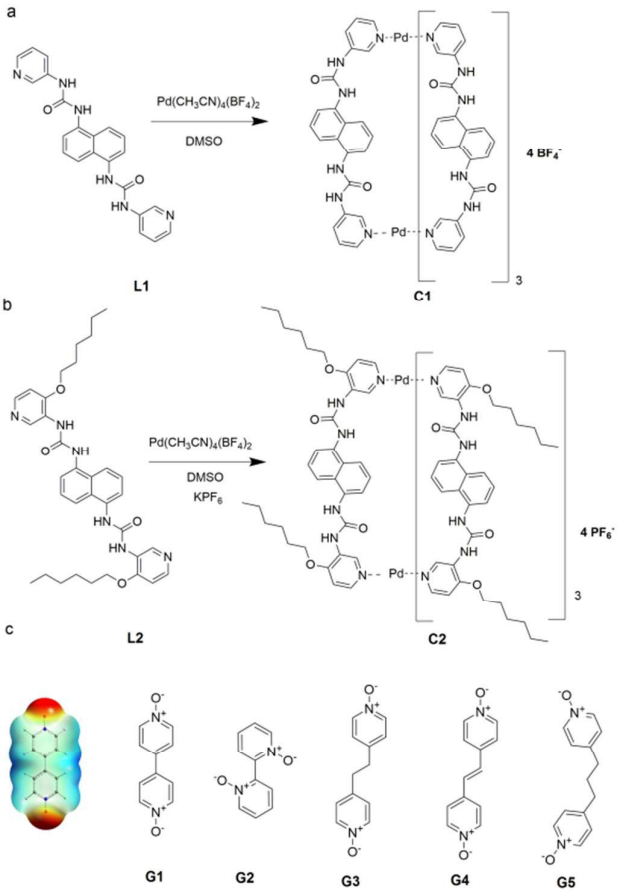
Hydrophobic metallosupramolecular cages are selectively encapsulating hydrophilic zwitterionic guests in organic solvents *via* synergetic multivalent recognition.

Compartmentalization is a basic feature of living systems, as most of the physiological processes occur in cells.[1] Molecular encapsulation is a fascinating domain. Crossing the solution/capsule barrier, interesting phenomena can be observed, relating new chemistry under confined conditions.[2]

Metallo-supramolecular cages have been proven to be particularly promising hosts for various guests and used for recognition and stabilization of reactive species, selective reactions, extractions, separations or catalysis.[3] The self-assembly of metal cations and pyridyl-based ligands has been employed as an effective method for the construction of a large variety of cages.[4] Hydrogen-bonding, anion templating, solvophobic effects have used to enhance the guest binding, with long-term views towards the dynamic self- adaptive cages and the control of their selectivity.[5]

Molecular encapsulation of hydrophilic guests in non-polar solvents is another challenging option, as they have large free hydration energies, and thus are difficult to extract from water. Lipidic or amphiphilic vesicles may be used for encapsulation.[6] Polytopic receptors have been used for the multivalent recognition of hydrophilic guests.[7] Examples of hydrophilic guests encapsulation are known, but the effective binding or extraction in organic solvents effects are rarely demonstrated with metallo-supramolecular cages.[8] Most of examples are related to hydrophobic guests, that are encapsulated in aqueous solutions or polar solvents.[3]

Herein we report a Pd_2L_4 hydrophobic cage able to encapsulate with a high binding affinity and selectivity hydrophilic zwitterionic guests in organic solvents.



Scheme 1 Synthesis of metallo-supramolecular cages a) **C1** and b) **C2**. c) (right) Five dipyridyl N,N'-dioxide guests used in this study and (left) a simulated electrostatic potential map of the 4,4'-dipyridyl N,N'-dioxide.

We first designed the ligand **L1**, containing two heteroditopic 3-ureidopyridil moieties, connected *via* a central naphthalene aromatic core center. 3-amino-pyridine, **1** was reacted with 1,5-diisocyanato-naphthalene, **2** to afford ligand **L1** (Scheme S1). Cage **C1** was obtained by simply heating overnight the

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Electronic Supplementary Information (ESI) available: synthetic procedures, NMR binding experiments, ESI-MS, X-ray data. See DOI: 10.1039/x0xx00000x

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ligand **L1** and $Pd(CH_3CN)_4(BF_4)_2$ in 2:1 molar ratio, at 70 °C in DMSO (Scheme 1a). Unfortunately, further host-guest investigations were hindered by the poor solubility of **C1** in solvents other than DMSO. In order to improve the solubility in the organic solvents, we next synthetized the hexyl-modified ligand **L2**: 4-hydroxy-3-nitropyridine, **3** was reacted with PCl_5 in 1,2-dichlo-roethane, followed by addition of 1-hexanol, **4** to afford the 4-(hexyloxy)-3-nitropyridine, **5** which after hydrogenation with Pd/C gave the corresponding 4-(hexyloxy) pyridin-3-amine, **6**.[7f] Compound **6** was then reacted with 1,5-diisocyanato-naphthalene, **2** to afford ligand **L2** (Scheme S2). The reaction of **L2** with 0.5 equiv. of $Pd(CH_3CN)_4(BF_4)_2$ at 70 °C overnight, in DMSO led to the formation of the cage **C2**, precipitating as a $Pd_2\mathbf{L2}_4(PF_6)_4$ brown solid from saturated KPF_6 aqueous solution (Scheme 1b). The cage **C2** is soluble in most common polar solvents such as acetonitrile, acetone or methanol. ^{1}H-NMR spectrum of the cage **C2** at room temperature indicated the highly symmetric structure of the cage in solution (Fig. S1).

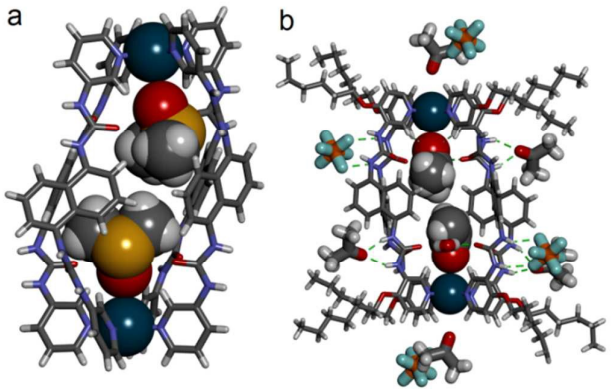

Fig. 1. X-ray crystal structures in stick representation of a) **C1** encapsulating two DMSO molecules in CPK representation; counter-anions and solvent molecules have been omitted for clarity and of b) **C2** encapsulating two acetone molecules in CPK representation; external counter-anions and solvent acetone molecules in stick representation. The Pd^{2+} cations are shown as blue spheres.

Vapor diffusion of ethyl acetate into an acetonitrile/DMSO solution of **C1** gave single-crystals, suitable for X-ray diffraction analysis (Fig. 1a). The distorted array of ligands **L1** rendered two planes of the square-planar $Pd(Py)_4^{2+}$ not parallel to each other. Two DMSO molecules are encapsulated in the cavity, with the oxygen atoms coordinating the Pd^{2+} and the methyl groups residing in the hydrophobic central part of the cage.

Evaporation of an acetone solution of **C2** afforded single-crystals suitable for X-ray diffraction analysis (Fig. 1b). Oppositely to **C1**, two $Pd(Py)_4^{2+}$ panels are parallel-displaced in **C2**. Two acetone molecules are encapsulated inside the cage, with the oxygen atom coordinating to the metal ion. The encapsulated DMSO (**C1**) and acetone (**C2**) guests are not H-bonded to urea-groups. Their carbonyl groups point towards the interior of the cavity and are hydrogen bond to H_a of the pyridyl group ($d_{H\cdot O}$=2.24 Å). It is known that carbonyl, sulfoxide or amide (C=O, S=O) groups have been shown to H-bond to the alpha-pyridyl protons of Pd_2L_4 cages as have been shown for DMSO by Crowley et al.[9] The H-bond formation can be clearly observed in solution by ^{1}H-NMR spectroscopy, from the shielded shifts of the H_a protons of the **C2** in *d6*-acetone, when compared with their spectral signals recorded in the more polar CD_3CN (Fig. S1). Several counter-anions and acetone molecules are H-bonded to externally oriented NH moieties of urea groups or coordinated to Pd^{2+} cations.

The good solubility of the cage **C2** in common solvents allowed us to explore the possible guest binding property within its cavity. Inspired by Custelcean work,[10] we presumed that the pre-organization of four ureido-ligands around the square-coordinated Pd^{2+} cations would be selectively favoured by the synergetic encapsulation of anionic guests *via* multiple urea H-bonding.

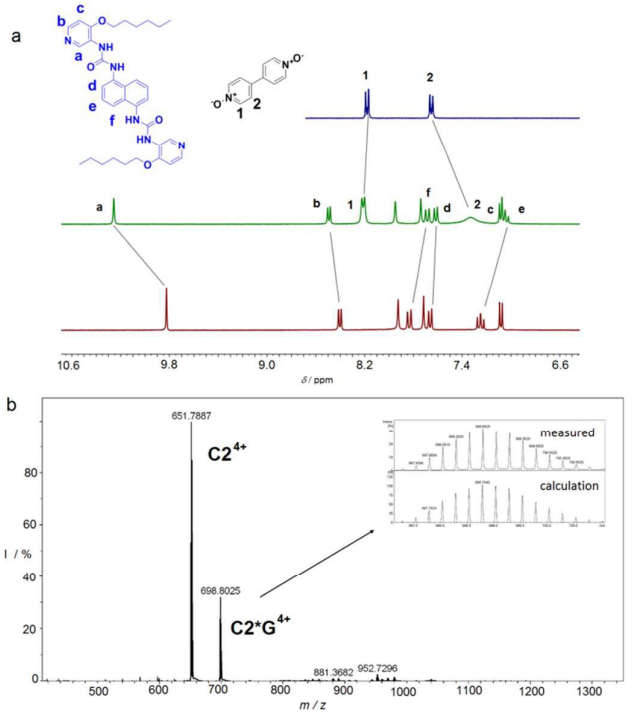

Fig. 2 a) Partial ^{1}H NMR spectra (300 MHz, CD_3CN, 298 K) of 4,4'-dipyridyl N,N'-dioxide guest (blue), **C2**· 4,4'-dipyridyl N,N'-dioxide (green) and **C2**· capsule; b) ESI mass spectrum of **C2**· 4,4'-dipyridyl N,N'-dioxide.

Insignificant shifts upon anion binding were observed in ^{1}H-NMR spectra after the addition of common hydrophilic or hydrophobic anions such as sulfate, phosphate or perchlorate, triflate and tetrafluoroborate. This is very surprising as the $Pd_2L_4^{4+}$ cage is highly charged and has had urea units installed in order to bind anions. It is known that the vast majority of Pd_2L_4 cages bind the anions.[11] The only example of a Pd_2L_4cage that does not encapsulate anions is reported by Crowley et al.[12] in which electrostatic repulsions the cage's central groups and the anions are the major force preventing the binding of the anion. A similar mechanism is possible in the present case: the lone pairs on the urea carbonyls point into the cage cavity and presumably causing repulsion that prevent anion binding with the cavity. The stereochemical spatial disposition (relative distance, geometry, etc.) of the four urea groups around the anions is not favourable for an efficient binding via N-H H-bonding of the anions.

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The addition of nitrate anion induces a broadening of the spectrum, reminiscent with fast host-guest exchanges on the NMR time scale, followed by the formation of a precipitate after the addition of second equivalent of nitrate (Fig. S2). Insignificant shifts in ^{1}H-NMR spectrum upon nitrate anion binding are reminiscent with the formation of a insoluble P_2L_4 NO_3^- host-guest adduct. The addition of the chloride anion induces cage decomposition and precipitation generating free ligand as precipitate (Fig S18) and $[Pd(CH_3CN)_4Cl_4]^{2-}$ (Fig S19) present in solution in CD_3CN as previously observed.[13]

Then, aromatic substrates (i.e. naphthalene, anthracene, pyrene, coumarin, 4.4'-bispyridine), and aliphatic hydrocarbons (i.e. cyclohexane, dodecane-1,12-diol or undecane-1,11-diamine) (Scheme S3) were selected as potential guests. None of these hydrophobic molecules were encapsulated, reminiscent with non-favourable hydrophobic interactions in the central region of the cage (see ESI). The lack of observed binding in the present experiments in CH_3CN would appear to be due to the absence of the hydrophobic effect, contrary to previously successful experiments by Yoshiazawa et al. using anthracene based Pd_2L_4 cages in aqueous CH_3CN or CH_3OH as the solvent mixtures.[14]

Inspired by these results, we decided to combine synergetic bonding effects to enhance the guest recognition.[5] N-oxide-pyridines, with a relatively poor solubility in organic solvents, are the class of hydrophilic polarized molecules able to combine H-bonding and stacking hydrophobic interactions (Scheme 1). Indeed, upon addition of 4,4'-dipyridyl-N,N'-dioxide, **G1** to a CD_3CN solution of **C2**, significant shifts of the aromatic protons the encapsulated host as well as the guest were observed in ^{1}H-NMR spectrum (Fig. 3). H_a has the most distinguished 0.43 ppm downfield shift by due to the CH···O H-bond, as previously reported or to Pd^{2+} coordination as observed in the crystal structures.[8b,12,13] Furthermore, no shifts upon guest binding were observed for the N-H urea protons, reminiscent with their orientation outside the cavity. The H_1 and H_2 protons of the guest are upfield and respectively downfield shifted, thanks to the H-bonding to the carbonyl group and their CH-π interactions with the aromatic region of the cage. ESI-MS spectrum shows peaks corresponding to [**C2**+guest]$^{4+}$ (30% intensity) and to [**C2**]$^{4+}$ (Fig. 2b). Binding strength of 4,4'-dipyridyl-N,N'-dioxide guest was quantified by fluorescence titration. The addition of guest to a CD_3CN solution of **C2**, resulted in quenching of fluorescence of the host (Fig.3). The 1:1 binding affinity was determined to be 5×10^4 by non-linear least squares fit of the fluorescence intensities, which is considerably high for a hydrophilic guest in organic solvents (Fig. S8). The release of the encapsulated guest can be realized by the addition of water to the host-guest CD_3CN solution (Fig. S8). Supplementary experiments confirm the perfect fit between 4,4'-dipyridyl-N,N'-dioxide guest and the **C2** host cage. Non-oxidated 4,4'-bipyridine, and 2,2'-dipyridyl-N,N'-dioxide, **G2** show any interaction with the host cage under same conditions, emphasizing the importance the N→O group in the guest binding and the regioselectivity of the encapsulation (Fig. S7). Longer 4,4'-bis(pyridine-oxide), **G3**, **G4** guests didn't result in the interactions with the **C2** host cage (Scheme 1).

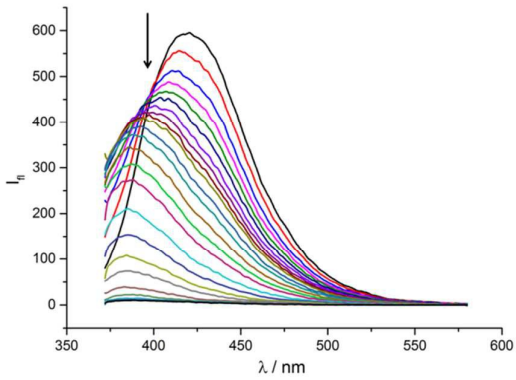

Fig. 3 Emission spectra (λ_{ex} = 352 nm) of **C2** (2.5×10^{-5} M) upon titration with 4,4'-dipyridyl N,N'-dioxide in CH_3CN; arrow indicates spectral change.

Interestingly, the addition of flexible 4,4'-(propane-1,3-diyl)bis (pyridine-oxide), **G5** results in the shift of N-H protons from urea, probably interacting outside the cavity. Similar studies for the encapsulation of molecular guests with both correct size and electronic complementarity have been reported.[15]

In conclusion, we want to highlight the selective strong binding of highly hydrophilic 4,4'-dipyridyl N,N'-dioxide guest by a hydrophobic Pd_2L_4 cage in CH_3CN. It is based on the relative constitutional stability of host-guest system, through synergetic coordination, H-bonding and hydrophobic interactions. Singular recognition events led to unpredicted non-encapsulation of anions or of hydrophobic aromatic guests. A next step could involve the ligands of different dimensionality and flexibility undergoing adaptive cage construction for multiple guest encapsulation.

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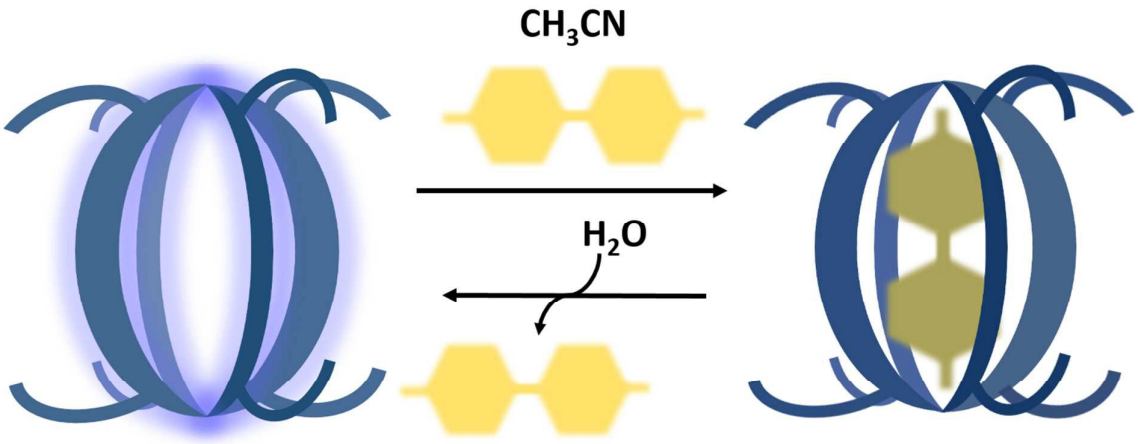

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