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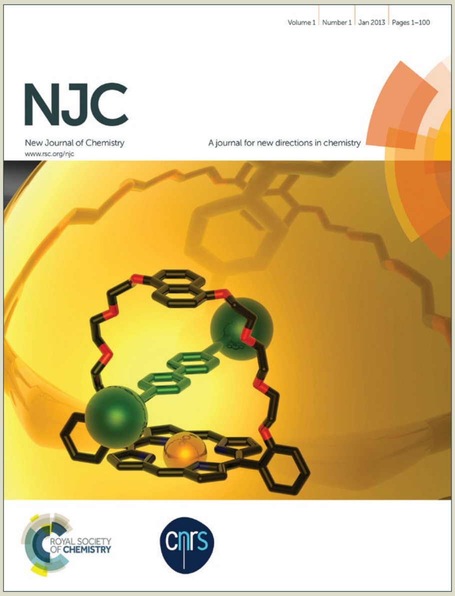

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LETTER

A Water Molecule in the Interior of a 1*H*-Pyrazole Cu^{2+} Metallocage.

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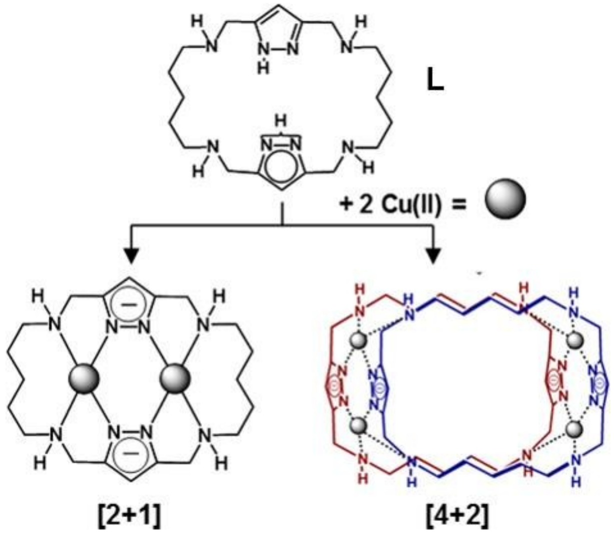
Water has great tendency to associate through hydrogen bonding with water molecules or other hydrogen bond donor or acceptor groups. Here the case of a water molecule encapsulated in the interior of a metallocage receptor is presented. Association of four copper(II) ions and two azamacrocyclic receptors in which two 1*H*-pyrazole units are connected by cadaverine diamines, leads to inclusion of a water molecule as proved by X-ray analysis and infrared spectroscopy. The included water molecule shows no hydrogen bonding with any component of the cage presenting only a weak hydrogen bond with an oxygen atom of a perchlorate counter-anion. The IR stretching vibrations predicted by DFT calculations agree with the experimental results.

Water "the solvent of life" is constituted by ensembles of single molecules linked by hydrogen bond interactions.[1] The unique properties of liquid and solid water result from the ability of water molecules to act simultaneously as double hydrogen bond donors and acceptors. Clusters of water molecules, identified either in the gas phase or confined in nanoscale spaces defined by the hydrophobic interiors of carbon nanotubes or self-assembled coordination cages, show also hydrogen bonding between them and with electronegative groups of the host structure. In this respect, several studies have been conducted on discrete hydrogen bond tetrameric, pentameric, hexameric, octameric, and decameric water clusters within various hosts.[2-14] A number of cases in which single water molecules are hydrogen bonded in the interior of a receptor ("water cryptates") has also been described.[15-18] However, the presence of an isolated water molecule without forming any hydrogen bond with other organic molecules, or coordination bonds to metals is very limited. The examples described regard those of a water molecule incorporated in a palladium metallocage,[19] and an elegant system in which chemical surgery was employed to introduce a water molecule within a hydrophobic fullerene buckyball.[20]

Here we report two examples of a water molecule which is practically isolated in the interior of a metallocage; it only has a weak hydrogen bond contact with either a perchlorate anion or a water molecule placed outside the cage. The cage (Scheme 1) is formed by four Cu^{2+} ions and two macrocycles (**L**) constituted by pyrazole spacers connected through methylenic linkages to cadaverine diamines ([4+2] cage).[21]

1*H*-Pyrazole can behave in its neutral form as a hydrogen bond donor and acceptor while in its deprotonated form behaves as a double hydrogen bond acceptor. While the latter case has been exemplified for instance in the formation of hetero-double-stranded helical structures with different ammonium salts,[22] the former case is clearly illustrated in the crystal structure here presented of the $[H_2\mathbf{L}](ClO_4)_2$ salt (crystals **1**). The layered structure shown in Figure 1 is achieved by hydrogen bonding between the two protonated amine groups diagonally located in each macrocycle and the non-protonated amine groups of two other macrocycles, and by hydrogen bonding between the two pyrazole units which act as hydrogen bond donors and acceptors to analogous pyrazole fragments of two neighbour macrocycles. All the macrocycles adopt the chair conformation.



Scheme 1 [2+1] and [4+2] Cu^{2+} complexes of **1**.

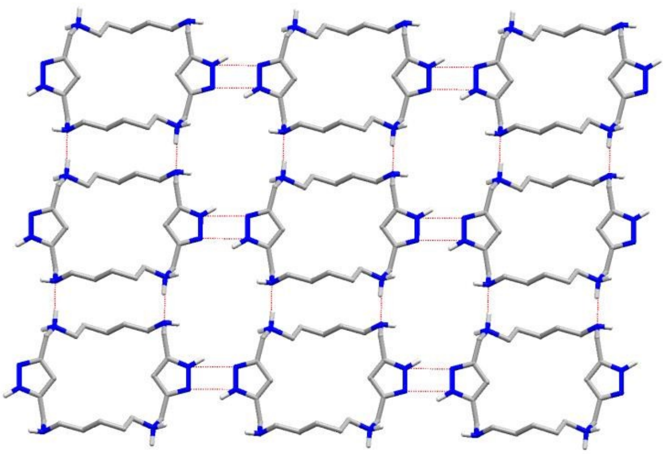


Fig. 1 Layer structure formed by [H$_2$**L**]$^{2+}$. Only relevant hydrogen atoms are shown.

First synthesis of the tetranuclear complexes curiously led to the empty [4+2] cage.[21] However, since the free space within the cage 80±6 Å^3 was enough to host molecules of size close to a water molecule 43±6 Å^3,[23] we have now performed further work aimed at achieving this inclusive behaviour.

In this work we have prepared new samples of metallocages which encapsulated water molecules and we show as the attainment of complexes of [2+1] or [4+2] stoichiometry (Scheme 1) is highly dependent on the initial concentration. Indeed, while we have obtained crystals containing mixtures of [4+2] metallocages and [2+1] binuclear complexes (crystals **2a** and **2b**, Figure 2) when evaporating solution of Cu(ClO$_4$)$_2$·6H$_2$O and **L** in 2:1 molar ratio with a concentration of **1** of 0.007 M, we have obtained only [4+2] metallocages (crystals **3**, Figure 3) when the concentration of **L** was 0.01 M. [2+1] Complexes alone were obtained for concentration of **L** below 0.004 M (crystals **4**, Figure 4) (Tables S1-S9, ESI†).

ESI mass spectrometry carried out on aqueous solutions containing Cu^{2+} and **L** in 2:1 mole ratio confirm these observations. Formation [4+2] dimeric cages was observed at concentrations of [**L**] ≥ 0.006 M by the appearance of a peak at m/z 1325 corresponding to the species ([Cu$_4$(H$_{-2}$**L**)$_2$](ClO$_4$)$_3$)$^+$. The monomer binuclear species was identified by a peak at m/z 613 which can be ascribed to the ([Cu$_2$(H$_{-2}$**L**)](ClO$_4$))$^+$ species (Fig. S6 ESI). However as evaporation was required to get the different crystals, the interconversion between the binuclear complexes and the metallocages should be kinetically hindered, which is reasonable since several coordination bonds need to be broken and reformed to achieve the interchange.

The metal centres in the [2+1] and [4+2] complexes present in crystals **2** have essentially square planar geometry as denoted by the red colour of the crystals and of their solutions. The coordination sphere of each metal ion is completed by two secondary amines and by two nitrogen atoms of a pyrazolate ring which behaves as a bis(monodentate) or exo(bidentate) ligand. In the cages, the amine groups and pyrazolate nitrogen atoms involved in the coordination to each metal ion belong to the two different macrocycles that conform the cage (Scheme 1, Figure 2). While in the cage two Cu^{2+} have a water molecule occupying distorted axial position, in the [2+1] complexes perchlorate anions occupy such positions.

The UV-Vis spectra of the solutions present two bands centred at around 410 nm and 530 nm that can be assigned to d-d transitions in the square planar Cu^{2+} pyrazolate complex as shown by time dependent DFT (TDDFT) (Fig. S2-S3, ESI†).

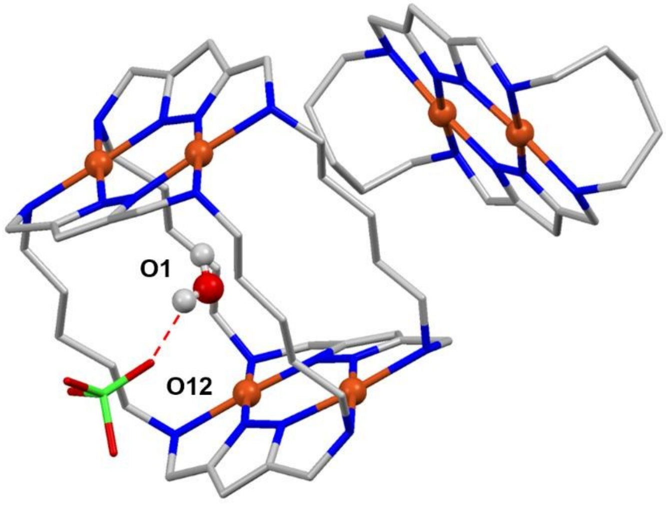


Fig. 2 Stick drawing showing the coexistence of [2+1] units and [4+2] units with an encapsulated water molecule represented with balls in crystals **2a**. Water molecules and perchlorate anions in distorted axial positions are not shown. The hydrogen bond between the water molecule and the perchlorate anion is represented by a red dotted line.

Interestingly, the cage structures [4+2] contain an encapsulated water molecule that is neither interacting with other water molecules nor connected to hydrogen bonding donor or acceptor groups of the cage. The only possible contact is an O-H••O weak hydrogen bond with a perchlorate counter-anion (distance O1-O12 = 2.957 Å) (Table S3, ESI†). As a matter of fact, the water molecule is slightly displaced from the centre of the cage towards the perchlorate counter-anion.

Additional information about the geometry of the system formed by the cage and the unique water molecule was derived from calculations using the B3LYP and M06-2X functionals without imposing symmetry restrictions (see ESI† for computational details).[24] The optimized geometry of the system at the B3LYP/6-31G** level is shown in Figure S4. The water molecule remains inside the box, with the plane passing through the oxygen and hydrogen atoms almost parallel to the shorter faces and perpendicular to the larger faces of the box. This behaviour is reproduced in all the optimizations performed with both functionals. According to the calculations no hydrogen bonds are formed between the water molecules and the nitrogen atoms present at the upper and lower sides. To exclude the possibility that the initial geometry used for the optimization influenced the final result, further computations were performed using the B3LYP functional and employing as starting point a geometry in which the water molecule was at bonding distance of one of the Cu^{2+} ions at one side of the cage.

After relaxation the minimum energy geometry shows the water molecule in the centre of the cage supporting its ability to host a water molecule (Fig S5).

Crystals **3** contain a mixture of empty and water-filled metallocages (Figure 3). The water molecule placed in the interior of the cage is in two symmetry related positions with half occupancy. In contrast with the metallocages found in crystals **2**, in this crystal structure a long range interaction (distance O2-O1 = 2.836 Å) was found with another water molecule placed in the exterior of the cage.

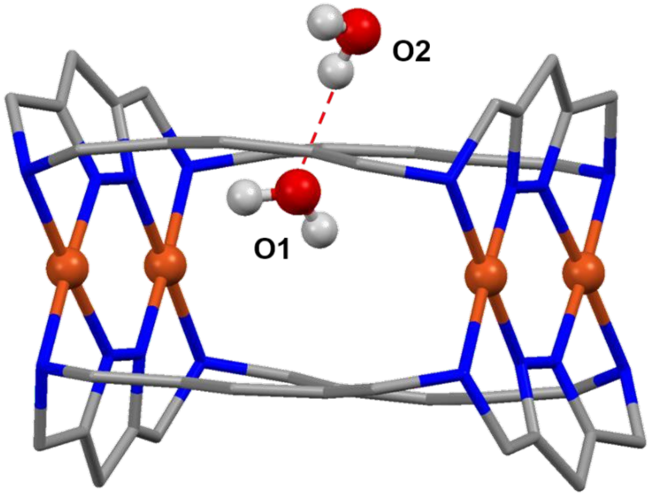


Fig. 3 Ball and stick drawing showing a [4+2] unit with an encapsulated water molecule placed in the middle of the cavity in crystal **3**. Hydrogens omitted. Hydrogen bond is represented by red dotted line.

Crystals **4** consists of two slightly different types of [2+1] complexes, perchlorate counter anions and lattice water molecules. In one of the types of [2+1] complexes the binuclear subunits are interconnected through perchlorate anions, which occupy the strongly distorted axial position of a square pyramid, and behave as bis(monodentate) bridging ligands forming a zigzag 1-D coordination polymer (Fig. 4). In the second type of [2+1] complexes, the binuclear subunits are isolated and do not present any axial ligand. All the macrocycles are in the chair conformation.

The spectroscopic properties of the isolated water molecule are very interesting. The IR spectrum of crystals **2** (Fig. 5) shows, apart from a broad band centred at around 3450 cm^{-1} that should correspond to the outer water molecules and other ones at about 3250 and 3260 cm^{-1} which correspond to the symmetric and asymmetric stretching vibration modes of the NH groups, a small sharp band at 3855 cm^{-1} . This band as it is indicated in the very few literature precedents about similar systems,[19,20] can be attributed to the H-O stretching vibration of the encapsulated water molecule.

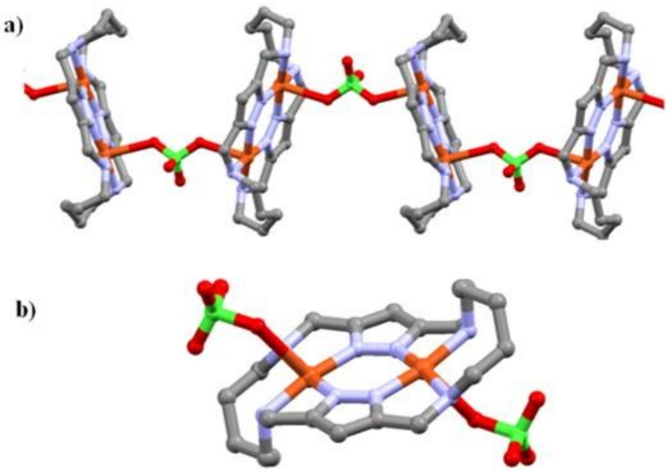


Fig. 4. (a) Chain-like structures formed by $[Cu_2(H_{-2}\mathbf{L})]^{2+}$ and ClO_4^- bridging ligands in crystal **4**. (b) View of the $[Cu_2(H_{-2}\mathbf{L})(ClO_4)_2]$ neutral complexes.

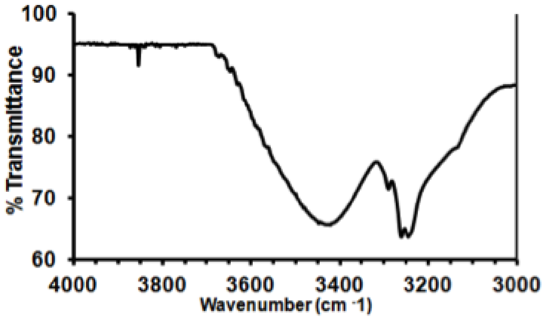


Fig. 5 IR spectrum (3000-4000 cm^{-1} range) of crystal **3**

The IR spectrum calculated at M06-02X/6-311G(2d,p) level, (Fig. S7) gives further support to this assignment.

Another relevant point is the stability of the water molecule retained in the hydrophobic environment originated by the pentamethylenic chains of the cage interior. Differential scanning calorimetry of **3** shows a broad peak that indicates that the loss of water molecules starts already at room temperature with a maximum midpoint at around 35 °C, this implies a slight stabilisation of about -100 J/g (Fig. S8).

The theoretical stabilization energy ΔE was computed as the difference between the energy of the complete system (box with the water molecule inside), and the sum of the energies of the box and one isolated molecule of water. The more negative ΔE is the more stabilized is the complete system with respect to the isolated molecules. In all cases the computed ΔE is negative, but |ΔE| is small with a value of 10 kcal/mol so, while the formation of the complete system is predicted to be favourable, its dissociation energy will be small.

Since the [4+2] cage dissociates at acidic pH when the amine groups become protonated, the capture of the water molecule may be controlled by three inputs, temperature, pH and concentration. As far as we know, this is the first time in which such a situation has been reported and affords important conceptual and practical developments in chemical and biological sciences.

Experimental

Synthesis of L.

The synthesis of **L** was achieved following the procedure reported in ref (21). mp. 181–183 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ(ppm) 5.98 (s, 2 H), 3.80 (s, 8 H), 2.65 (t, 8 H), 1.47 (m, 8 H), 1.26 (m, 8 H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 147.55, 102.43, 48.38, 45.93, 28.58, 26.48. Calcd. for $C_{20}H_{36}N_8$: C, 61.82, H, 9.34, N, 28.84; found C, 61.7, H, 9.4, N, 28.5.ESI-MS (MeOH): m/z (%) = 411 (100) [**L** + Na]$^+$. 389 (62) [**L** + H]$^+$.

Syntheses of the complexes.

$[H_2\mathbf{L}](ClO_4)_2$ (**1**). A solution of **L** (10 mg, 0.024 mmol) in 2 mL of water acidified with $HClO_4$ to pH 7 was slowly evaporated to obtain single crystals in 75% yield. Calcd. for $C_{20}H_{38}Cl_2N_8O_8$: C, 40.80, H, 6.52, N, 19.04; found: C, 41.1, H, 7.2, N, 19.2.

Complex 2a. $((H_2O@[Cu_4(H_{-2}L)_2(ClO_4)_2])[Cu_2(H_{-2}\mathbf{L})((ClO_4)_2](ClO_4)_2$

$\cdot 5.5H_2O$). A solution of **L** (12.6 mg, 0.03 mmol) in 3.5 mL of water was brought to pH 2 with a few drops of a concentrated $HClO_4$ solution. Then an aqueous solution of $Cu(ClO_4)_2\cdot 6H_2O$ (0.06 mmol, 0.5 mL) was added and the pH adjusted to 6 with NaOH. Small red crystals were formed after slow evaporation. Yield. 65%. Calcd. for $C_{60}H_{114}Cl_6Cu_6N_{24}O_{30.5}$: C, 32.05, H, 5.11, N, 14.96; found: C, 32.3, H, 5.5, N, 15.2.

Complex 2b. ($(H_2O@[Cu_4(H_{-2}\mathbf{L})_2(ClO_4)_2])[Cu_2(H_{-2}\mathbf{L})(ClO_4)](ClO_4)_3\cdot 4H_2O$). Working under argon, a solution of $Cu(ClO_4)_2\cdot 6H_2O$ in water (1 mL, 0.06 mmol) was added with stirring to a solution of the polyamine **L** (12.6 mg, 0.03 mmol) in 4 mL of MeOH. After 2 h, a red solution was formed. On slow evaporation at room temperature red crystals evolved in 75% yield. Calcd. for $C_{60}H_{112}Cl_6Cu_6N_{24}O_{29}$: C, 32.42, H, 5.08, N, 15.18; found: C, 31.8, H, 5.3, N, 15.3.

Complex 3. ($(H_2O@[Cu_4(H_{-2}\mathbf{L})_2(ClO_4)_2])\ [Cu_4(H_{-2}\mathbf{L})_2(ClO_4)_2]\ (ClO_4)_4\cdot 7H_2O$). A solution of L (12.6 mg, 0.03 mmol) in 2.5 mL of water was brought to pH 2 with a few drops of a concentrated $HClO_4$ solution. Then an aqueous solution of $Cu(ClO_4)_2\cdot 6H_2O$ (0.06 mmol, 0.5 mL) was added and the pH adjusted to 6 with NaOH. Red crystals suitable for X-ray analysis were formed after slow evaporation. Yield. 80%. Calcd. for $C_{40}H_{76}Cl_4Cu_4N_{16}O_{20}$: C, 32.17, H, 5.13, N, 15.01; found: C, 32.4, H, 5.4, N, 15.3.

Complex 4. ($[Cu_2(H_{-2}\mathbf{L})](ClO_4)_2\cdot H_2O$). **L** (10 mg, 0.024 mmol) was dissolved in 5 mL of a 1 M $HClO_4$ aqueous solution. Then the pH was adjusted to 7 with NaOH and an aqueous solution of $Cu(ClO_4)_2\cdot 6H_2O$ (0.048 mmol, 0.437 mL) was added. The pH was adjusted to 7 with NaOH. Prismatic red crystals suitable for X-ray analysis appeared after slow evaporation. Yield: 80%. Calcd. for $C_{40}H_{72}Cl_4Cu_4N_{16}O_{18}$: C, 32.96, H, 4.98, N, 15.38; found C, 32.9, H, 5.0, N, 15.3.

Acknowledgements

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Notes and references

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Electronic Supplementary Information (ESI) available: Details of measurements, synthesis, computational calculations, figures and tables are available. CCDC reference numbers 892312, 892315, 892316, 1468807 and 1468808. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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A Water Molecule in the Interior of a 1*H*-Pyrazole Cu^{2+} Metallocage.

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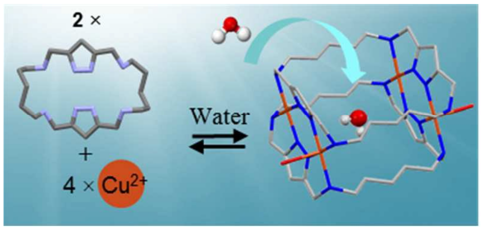

Association of four Cu^{2+} ions and two aza-macrocyclic receptors in which two *1H*-pyrazole are connected by cadaverine diamines, leads to the inclusion in the cage of a single water molecule which does not present hydrogen bonds wityh any donor or acceptor group of the metallocage.