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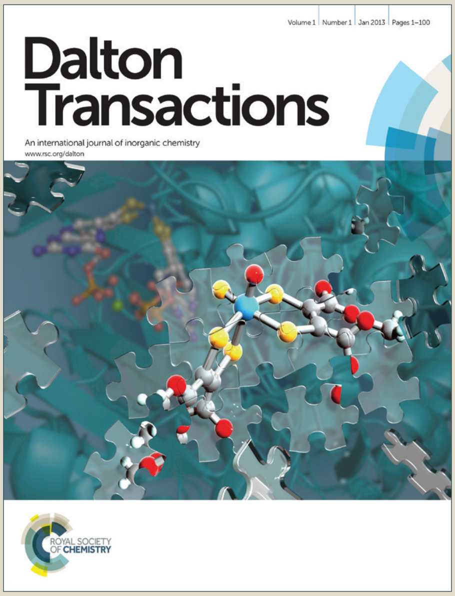

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ARTICLE

# “3 + 1 = 6 + 2” in Cu(II) Coordination Chemistry of 1*H*-Pyrazole aza cryptands

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A polyazamacrocycles formed by two tris(2-aminoethyl)amine units connected by 1*H*-pyrazole units shows unique of hexanuclear Cu(II) complexes by combination of two binuclear Cu(II) cryptand complexes through pyrazolate moieties belonging to both cryptands. The formation of these dimeric entities has been proved both in solution by potentiometric studies and mass spectroscopy and in the solid state by X-ray diffraction of crystals of three different batches of formulae $[Cu_6(H_{-3}\mathbf{L})_2(H_2O)_2](TsO)_6 \cdot 22H_2O$ (**2**), $[Cu_6(H_{-3}\mathbf{L})_2(NO_3)_2](NO_3)_4 \cdot 2H_2O$ (**3**) and $[Cu_6(H_{-3}\mathbf{L})_2Cl_2]Cl_4 \cdot (C_4H_5N_3O_2)_2 \cdot 14.35H_2O$ (**4**). The hexanuclear unit in **2** and **4** can be viewed like three magnetically independent binuclear complexes with $J$ = -366(3) $cm^{-1}$, g = 2.08(1) for **2** and $J$ = -360(3) $cm^{-1}$, g = 2.07(1) for **4.**

## Introduction

Cryptands are one of the classes of receptors most widely employed in metal coordination and/or supramolecular chemistry.[1,2] Among cryptands, polyaza macrocycles formed by condensation of tris(2-aminoethyl)amine units with aliphatic or aromatic spacers have received a particular attention in view of their ability to encapsulating metal ions, anions or neutral species. Cryptands reported in the literature operate alone, incorporating one or several guest species in its interior. However, it is not so frequent to find cryptands that besides encapsulating guest species can interconnect between them through coordinative bonds giving rise to particular metalla-cages. Several years ago some of us reported the synthesis of a cryptand containing 1*H*-pyrazole spacers (**L** in Figure 1) showing as this ligand was able to form binuclear Cu(II) complexes.[3] In such complexes the 1*H*-pyrazole unit and the amine groups of one of the bridges (see **1** in Figure 1) were free and ready to interact with a further metal ion and indeed we provided hints about the possible formation of trinuclear copper complexes. However, in spite of all these evidences no crystal structure supporting this point could be afforded. The particular and rich coordination chemistry of this small heterocycle may give rise to exo-binding modes and to association of more than one cryptand ligand in metal binding leading to the formation of multinuclear Cu(II) complexes.[4] Such complexes have raised a great interest as mimics of multicentric blue copper oxidases.[5] Herewith we report solution studies and three crystal structures of a nivel self-assembled dimeric hexanuclear cage which demonstrate that “3 Cu(II) + 1 ligand = 6 Cu(II) + 2 ligands” in pyrazole cryptand chemistry.

## Results and Discussion

### Synthesis of the Complexes and X-Ray Diffraction Studies

Macrocycle **L** was obtained as previously reported by [2+3] condensation of tris(2-aminoethyl)amine with 3,5-pyrazoledicarbaldehyde in methanol followed by in situ reduction with sodium borohydride.[3] By slow evaporation of a methanol:water solution of $Cu(ClO_4)_2 \cdot 6H_2O$ and **L** in 2:1 molar ratio at pH = 9 we have obtained a new batch of crystals of the binuclear complex **1** (Figure 1 middle and Figure S1). Each Cu(II) has a square pyramidal coordination ($\tau$ = 0.16)[6] formed by two nitrogen atoms of two different pyrazolate anions which behave as bis(monodentate) ligands, by two contiguous nitrogen atoms to the pyrazolate moieties and by a bridgehead nitrogen which occupies the elongated axial position. Magnetic susceptibility measurements show that both Cu(II) atoms are strongly coupled with $J$ = -310(5) $cm^{-1}$ and g = 2.08(1) (see ESI). As observed in this structure and in the one previously described by some of us,[3] one of the bridges with two secondary amine groups and one neutral *1H*-pyrazole moiety is still available for additional coordination. However, here the secondary amine groups of the free bridge are non-protonated while the previous structure had one protonated amine group with a water molecule partly filling the free cavity. Therefore, we proceeded to mix in 3:1 molar ratio an aqueous solution of $Cu(ClO_4)_2 \cdot 6H_2O$ with an aqueous solution of L acidified to pH ca. 2 with p-toluensulfonic acid (TsOH). Slow evaporation of the resulting solution brought to pH 6 with NaOH gave crystals of $[Cu_6(H_{-3}\mathbf{L})_2\ (H_2O)_2](TsO)_6 \cdot 22H_2O$ **(2).** suitable for X-ray analysis.

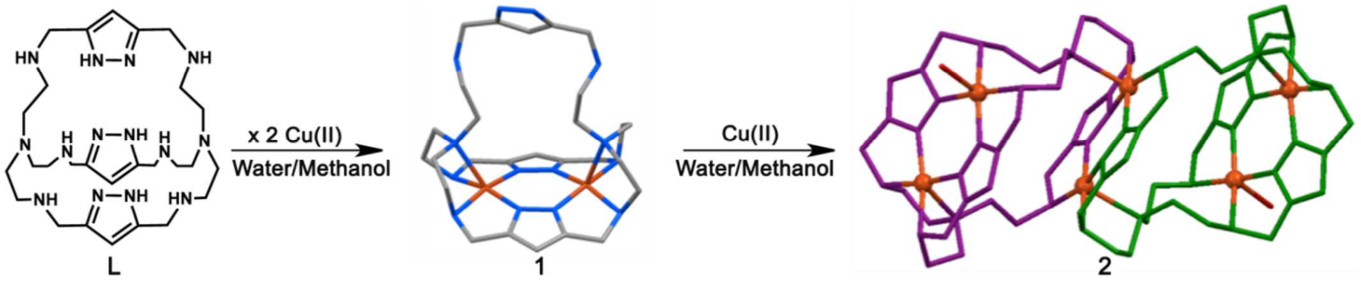

Figure 1. Synthesis of the hexanuclear Cu(II) complex **2**. In violet and green the two different cryptand units.

The structure consists of two binuclear Cu(II) cryptand complexes self-assembled by two metal ions giving a 6:2 Cu(II):**L** overall stoichiometry. The hexanuclear complex is composed by three binuclear units (Figures 1 right and 2a, 2b). The structure presents an inversion centre being the three non-equivalent Cu(II) atoms pentacoordinated. Cu(1) atoms placed in the top and bottom binuclear units of the cage keep the same coordination pattern than the copper atoms in the binuclear complex **1**, being coordinated by two pyrazolate nitrogens (N3, N9), the two contiguous secondary amines (N2, N10) and by the tertiary amine group N1, which occupies the elongated axial position of the square pyramid ($\tau = 0.182$) (Figure 2). The Cu(II) atom is placed 0.16 Å above the plane of the nitrogen atoms.

The coordination environment around the other two metal ions at the top and bottom binuclear units (Cu2) is somewhat different since while the donor atoms at the equatorial planes remain to be two pyrazolate nitrogens and two adjacent secondary amines, the axial position is now occupied by a water molecule coming from the bulk (Figure 2). In this case, the copper atoms do not show any elevation above the donor atoms of the equatorial plane of the square pyramid ($\tau = 0.18$). The third type of non-equivalent copper atoms are placed in the middle of the cage (Cu(3)). The square pyramidal coordination ($\tau = 0.17$) is completed in this case by the tertiary amine group N6 at the elongated axial position and, similarly to the other two kinds of copper sites, by two pyrazolate nitrogen atoms and two contiguous amines at the equatorial planes. Previous work on a [1+1] condensation, pyrazole macrocycle supports the exo coordination exhibited by the Cu(II) atoms as the most stable binding mode in constrained systems where an endo orientation is not feasible.[7] In this structure there are also a large number of water molecules that form an extensive hydrogen bond network with the tosylate anions groups, the NH groups of the macrocycles and the axially coordinated water molecules. Since the water molecule hydrogen bond network does not affect the coordination of the metal and the self-assembling of the cage we are not going to discuss further this point.

Similar crystal structures of formulae $[\mathrm{Cu_6(H_{-3}\mathbf{L})_2(NO_3)_2}](\mathrm{NO_3})_4{\bullet}2\mathrm{H_2O}$ (**3**) and $[\mathrm{Cu_6(H_{-3}\mathbf{L})_2Cl_2}]\mathrm{Cl_4}{\bullet}(\mathrm{C_4H_5N_3O_2})_2{\bullet}14.35\mathrm{H_2O}$ (**4**) were obtained by reaction of $\mathrm{Cu(NO_3)_2}{\bullet}5\mathrm{H_2O}$ or $\mathrm{CuCl_2}{\bullet}2\mathrm{H_2O}$ with **L** in methanol followed by slow evaporation. The crystal structures are analogous to **2** with the difference of having monodentate chloride or nitrate ligands instead of water molecules at the axial positions of Cu(2) (see Figures 2c and 2d, S2 and S3 in the ESI).

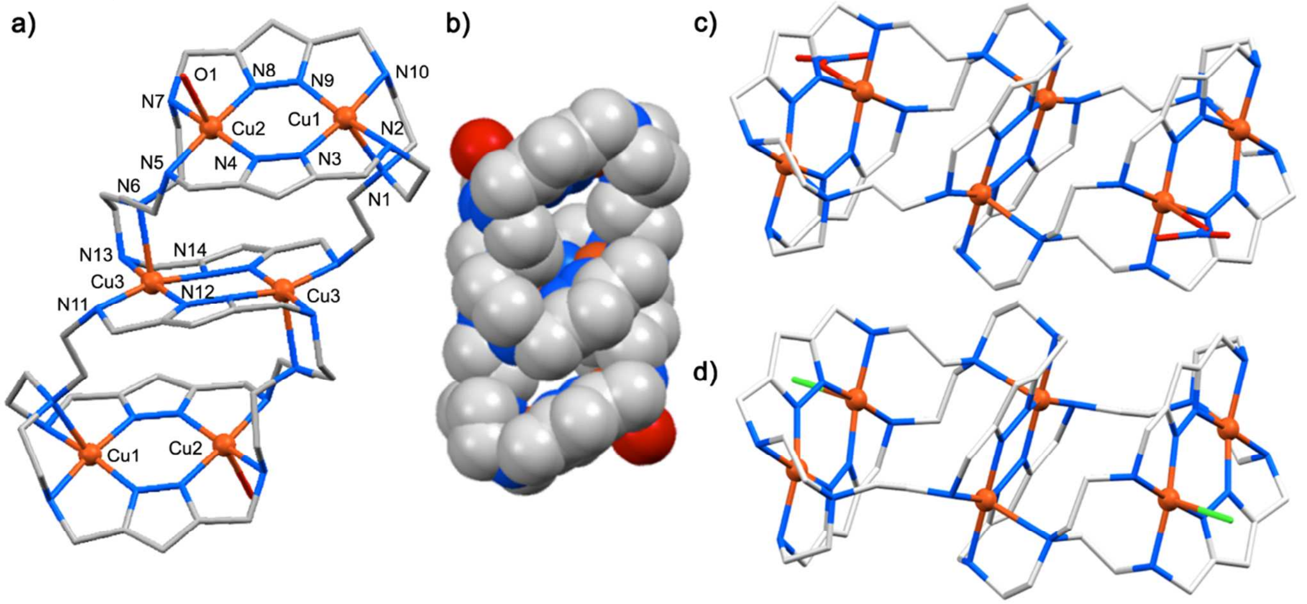

Figure 2. a) Stick view of Complex **2**.b) Space filling view of complex **2**.c) Stick view of Complex **3**.d) Stick view ofComplex **4.**

### Solution Studies

In order to know if this interesting structural organization is preserved in solution we carried out potentiometric and UV-Vis studies in water as well as HRMS studies. The potentiometric titrations showed that for 3:1 Cu(II):**L** molar ratio, in addition to different mono- and binuclear species, there was above pH 5 formation of a complex of Cu(II):H:**L** 3:-3:1 stoichiometry (see ESI, Table S2 and Figs. S4). The appearance of a precipitate above pH 8 prevented to get reliable data at those basic pH values. Formation of 3:1 Cu(II):**L** complexes was also supported by the UV-Vis spectra of solutions containing Cu(II) and **L** in molar ratio 3:1 recorded at variable pH. The spectra present two bands in the visible region centred at 569 nm and 800 nm. A plot of the absorbance at 569 nm versus pH shows two breaks in correspondence with the formation of bi- and trinuclear species (Figure S4). However, to decide whether these species are monomers or dimers just from potentiometric data or UV-Vis is rather cumbersome, particularly if the overall concentration of the reactants cannot be varied in a large extent. Therefore, we complemented the study by recording mass spectra. Spectra of 3:1 Cu(II):**L** aqueous solutions at pH 7 in NaTsO show peaks at 673.8025, 738.4707, 802.4633, 867.7989 and 1097.2093 m/z that can be assigned to the species $[Cu_6(H_{-3}\mathbf{L})_2(TsO)_3]^{3+}$, $[NaCu_6(H_{-3}\mathbf{L})_2(TsO)_4]^{3+}$, $[Na_2Cu_6(H_{-3}\mathbf{L})_2(TsO)_5]^{3+}$, $[Na_3Cu_6(H_{-3}\mathbf{L})_2(TsO)_6]^{3+}$ and $[Cu_6(H_{-3}\mathbf{L})_2(TsO)_4]^{2+}$, respectively (Figure 4 and Figure S5), clearly supporting that the hexanuclear Cu(II) complexes are also formed in solution.

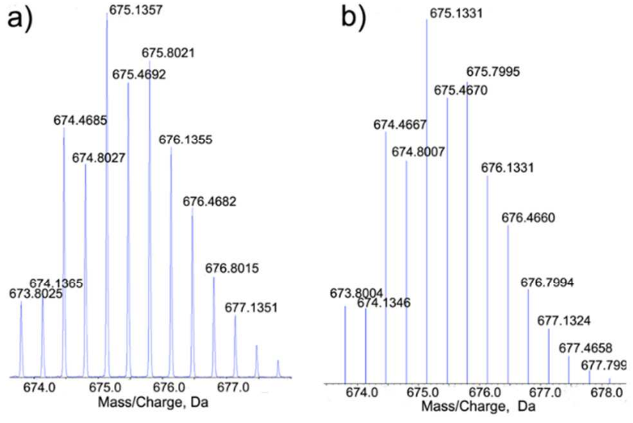

Figure 3. Experimental (a) and calculated (b) HRMS spectra of the $[Cu_6(H_{-3}\mathbf{L})_2(TsO)_3]^{3+}$ species.

### Magnetic Behaviour

The magnetic behaviour of the hexanuclear dimers **2** and **4** was analysed to understand the connections between the different metal centres. The temperature dependence of the $\chi_M$T product for **2** and **4** [$\chi_M$ is the magnetic susceptibility per six Cu(II) ions] are shown in Figures 4 and S7, respectively. $\chi_M$T at room temperature is equal to 1.10 and 1.15 cm$^3$ mol$^{-1}$ K (for **2** and **4** respectively), a value which is much smaller than that expected for six uncoupled Cu(II) ions (ca. 2.43 cm$^3$ mol$^{-1}$ K with g =2.08). Upon cooling, this value decreases very quickly, and it practically vanishes at 50 K. This plot is indicative of a strong antiferromagnetic coupling leading to a low-lying singlet spin state. The $\chi_M$ curve is also typical for a strong antiferromagnetic coupling because of the occurrence of a rounded maximum about 300 K.

At first sight, modelling the magnetic properties of **2** and **4** appears as quite complicated because of the coexistence of different exchange pathways within the hexanuclear Cu(II) unit and the occurrence of three crystallographically independent Cu(II) ions. Figure 4 shows these features and eqn (1) the corresponding Hamiltonian.

$$H = -J_{12}(S_{1a}S_{2a} + S_{1b}S_{2b}) - J_{13}(S_{1a}S_{3a} + S_{1b}S_{3b}) - J_{23}(S_{2b}S_{3a} + S_{2a}S_{3b}) - J_{33}S_{3a}S_{3b} \quad (1)$$

Although Cu(1), Cu(2) and Cu(3) are crystallographically independent, all of them are five-coordinated in pyramidal square coordination with similar structural parameters. So, we can assume $J_{12} = J_{33}$ (magnetic coupling through double pyrazolato bridge in the equatorial plane) and $J_{13} = J_{23}$ (magnetic coupling through the N-C-C-N fragment in apical position).

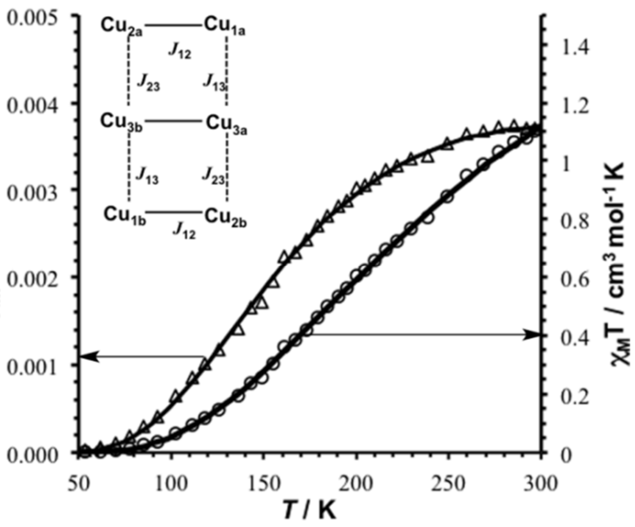

Figure 4. Thermal dependence of $\chi_M$ and $\chi_M$T for **4**. Solid line is the theoretical curve using the best-fit parameters. Scheme of magnetic coupling in complex **4**.

Because of the magnetic orbital is a $d_{x^2-y^2}$ type orbital mainly located in the equatorial plane of the metal atom [the x and y axes being roughly defined by the short equatorial bonds corresponding to the copper-pyrazole bonds], the magnetic coupling between two Cu(II) ions through double pyrazole bridges is expected to be very large, while those through the pathway provided by the large axial bonding (through N-C-C-N fragment) are expected to have very little relevance because of the low unpaired electron density along de $d_{z^2}$ orbital (that is $J_{13} = J_{23} \approx 0$). In this sense, the hexanuclear unit in **2** and **4** can be viewed like three magnetically independent dinuclear complexes,[8] and following this description their magnetic data were analysed by using the spin Hamiltonian H = -*J* S1•S2, from which the following susceptibility equation can be derived [Equation (2)]:

$$\chi_M = (2N\beta^2 g^2/kT)[3 + \exp(-J/kT)]^{-1} \qquad (2)$$

Where N, g, $\beta$ and $k$ have their usual meanings and $J$ is the exchange coupling parameter ($J = J_{12} = J_{33}$). Best-fit parameters are: $J$ = -366(3) cm$^{-1}$, g = 2.08(1) for **2** and $J$ = -360(3) cm$^{-1}$, g = 2.07(1) for **4**. The theoretical curve matches well the magnetic data in the whole temperature range. These values of $J$ lies within the range of those previously reported for other double pyrazole-bridged Cu(II) complexes[9] and they are larger than the analogous triazolate-Cu(II) systems.[10]

## Conclusions

Summarising all these data, it can be concluded that formation of unique [6+2] pyrazole cages is achieved both in the solid state as well as in milimolar Cu(II) aqueous solutions when cryptand **L** and Cu(II) are mixed in the 3:1 mole ratio

## Experimental Section.

The cryptand **L** was prepared as previously reported.[3a,3c] 3,5-Pyrazoledicarbaldehyde (0.228 g, 6 mmol) was dissolved in warm methanol (120 mL) and added drop wise during 2 h under an argon atmosphere to a stirred solution of tris(2-aminoethyl)amine (0.292 g, 2 mmol) in methanol (80 mL). After stirring overnight at room temperature, sodium borohydride (228 mg, 6 mmol) was added portion wise, and after 2 h the solvent was evaporated to dryness under reduced pressure. The residue was directly recrystallized from water (15 mL).

Yield (0.380 g, 65%); mp 245 °C. NMR (400 MHz, $CD_3OD$) $^1$H δ: 5.85 (s, 3 H, H4), 3.72 (s, 12 H, H6), 2.80-2.83 (m, 12 H, HR), 2.68-2.71 (m, 12 H). $^{13}$C δ: 147.92 (br s, C3,5), 103.28 (C4), 52.86 (Cβ), 48.54 (Cα), 46.47 (C6). FAB-MS (m/z, %): 569 $[M + H]^+$ (60), 307 (17), 154 (100), 136 (83). Anal. Calcd (%) for $C_{27}H_{48}N_{14}$, $H_2O$ (586.8): C, 55.27; H, 8.59; N, 33.42. Found: C, 55.42; H, 8.91; N, 33.70.

### Synthesis of the metal complexes.

**$[Cu_2(H_{-2}L)](ClO_4)_2$•$2H_2O$ (1).** $Cu(ClO_4)_2$ $6H_2O$ (12.6 mg, 34 mmol) dissolved in water were added to a solution of **L** (10 mg, 17 mmol) at pH=4. The pH was corrected until 8 with concentrated solutions of perchloric acid and NaOH.

After 2 h, a blue solution had formed. A slow evaporation of the solution in a vessel afforded the formation of blue crystals suitable for X-ray diffraction in 90% yield. Anal. Calcd.for $C_{27}H_{50}Cl_2Cu_2N_{14}O_{10}$: C, 34.98; H, 5.44; N, 21.16. Found: C, 34.9; H, 5.5; N, 21.1.

**$[Cu_6(H_{-3}L)_2(H_2O)_2](TsO)_6$•$22H_2O$ (2).** A solution of $Cu(ClO_4)_2$•$6H_2O$ (18.9 mg, 51 mmol) in water (2 mL) was added with stirring to a solution of **L** (10 mg, 17 mmol) in 2 mL in water acidified with p-toluenesulfonic acid until pH = 2. Finally, the pH was adjusted to 6 with a 0.1M NaOH solution. The blue solution formed by means of a slowly evaporation at room temperature, affords blue crystals in 95% yield. Anal. Calcd. for $C_{96}H_{182}Cu_6N_{28}O_{43}S_6$: C, 38.59; H, 6.42; N, 13.13, S,6.42. Found: C, 38.7; H, 6.2; N, 13.1, S, 6.5.

**$[Cu_6(H_{-3}L)_2(NO_3)_2](NO_3)_4$ •$2H_2O$ (3).** A solution of $Cu(NO_3)_2$•$3H_2O$ (12.32 mg, 51 mmol) in water (2 mL) was added with stirring to a solution of **L** (10 mg, 17 mmol) in 2 mL of water at pH =7. After 2 h, the pH was adjusted to 6 with a solution 0.1M of NaOH. The blue solution affords blue crystals of **3** after one month in 75% yield. Anal. Calcd. for $C_{54}H_{94}Cu_6N_{34}O_{20}$: C, 33.81; H, 4.94; N, 24.84. Found: C, 33.7; H, 5.0; N, 24.7.

**$[Cu_6(H_{-3}L)_2(Cl)_2]Cl_4$•$14.35H_2O$•$(C_4H_5N_3O)_2$ (4).** A solution of $CuCl_2$•$2H_2O$ (51 mmol) in 2 ml of in methanol was added to a solution of 2 ml that contains **L** in methanol (10 mg, 17 mmol).

After 2 h, a water solution of cytosine was added and the stirring kept for further 2 h. The formed precipitate was removed by filtration. The blue solution affords blue crystals of **4** after one month in 75% yield. Anal. Calcd. for $C_{62}H_{128.7}Cl_6Cu_6N_{34}O_{16.35}$: C, 33.75; H, 5.88; N, 21.59; Found: C, 34.6; H, 5.4; N, 22.1.

### Electromotive Force Measurements.

The potentiometric titrations were carried out at 298.1±0.1 K using NaCl 0.15 M as supporting electrolyte. The experimental procedure (burette, potentiometer, cell, stirrer, microcomputer, etc.) has been fully described elsewhere.[11] The acquisition of the emf data was performed with the computer program PASAT.[12] The reference electrode was an Ag/AgCl electrode in saturated KCl solution. The glass electrode was calibrated as an hydrogen-ion concentration probe by titration of previously standardized amounts of HCl with $CO_2$-free NaOH solutions and determining the equivalent point by the Gran's method,[13] which gives the standard potential, Eº', and the ionic product of water (pKw = 13.73(1)).

The computer program HYPERQUAD[14] was used to fit the protonation and stability constants. Solutions containing the ligand salts with concentrations ranging from 1 x $10^{-3}$ to 5 x $10^{-3}$ M and with Cu(II):**L** molar ratios varying from 3:1 to 1:2 were titrated with NaOH . The different titration curves for each ligand were treated as separated curves without significant variations in the values of the stability constants. Finally, the sets of data were merged together and treated simultaneously to give the final stability constants.

### Spectroscopic Measurements.

UV-Vis spectra of the complexes in 3:1 Cu(II):**L** molar ratio (2 x $10^{-3}$ M) were recorded in an Agilent 8453 spectrometer UV−Vis spectra at 293.15 K.

### NMR Measurements.

Bruker Advance DPX 400 MHz spectrometer operating at 399.95 MHz for $^1$H and at 100.58 MHz for $^{13}$C. TMS was used as a reference standard.

### Spectrometric Measurements.

HR-ESI mass spectra of crystals of compound **2** dissolved in water/methanol (50/50 vol/vol) were acquired in the positive ion mode using a Triple TOF 5600 hybrid quadrupole time-of-flight (TOF) mass spectrometer (Figures S5a-e). $N_2$ was used as a curtain and nebulizing gas. The experiments were performed at a voltage of 5300 V and GS1 and GS2 (35 psi) ion source gas at 723.15 K. The ABSCIEX Peak View software was used for the analysis of the data.

### Magnetic Susceptibility Measurements

Magnetic susceptibility measurements of polycrystalline samples were measured over the temperature range 2-300 K with a Quantum Design SQUID magnetometer using an applied magnetic field of 1 T. Diamagnetic corrections of the constituents atoms were estimated from Pascal's constants and a value of $60 \times 10^{-6}$ $cm^3 \bullet mol^{-1}$ was used for the temperature-independent paramagnetism of each Cu(II) ion.

### X-Ray Analysis

Single crystals of **1**, **2**, **3** and **4** were measured in an Enraf Nonius KappaCCD using MoKα radiation ($\lambda$ = 0.71073 Å at 293 K (**1-3**) and 120 K (**4**). Structures were solved by direct methods using SIR97[15] and refined by full-matrix least-squares on all $F^2$ using SHELXL97[16] with the Olex2[17] suite. Molecular drawings were produced with MERCURY

Cifs of **1-4** are deposited in CCDC with numbers 983271-983274. These data can be obtained free of charge from The CCDC via www.ccdc.cam.ac.uk/data_request/cif.

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Electronic Supplementary Information (ESI) available: [Text figures, tables, physical measurements, CIF files and X-ray crystallographic data.]. See DOI: 10.1039/b000000x/

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# “3 + 1 = 6 + 2” in Cu(II) Coordination Chemistry of 1H-Pyrazole aza cryptands.

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We report the first example of a cryptand able to form 6+2 Cu(II)-ligand dimeric hexanuclear complexes, both in the solid state and in aqueous solution, by simply combining the metal and the ligand in 3:1 molar ratio.