

Synthesis and Crystal Structure of a Dinuclear Copper(II) Complex with a Novel Tetrapyrazolyl Macrocycle

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A novel 30-membered macrocycle containing four endocyclic, neutral pyrazole groups, binds two Cu^{II} ions, where a flexible propylene spacer separates the Cu^{II} ions by 7.14 Å; the crystal structure of the mixed-anion complex [Cu₂(L)Cl₂(EtOH)₂](NO₃)₂ shows that each Cu^{II} ion is bound in a square-pyramidal N₄X chromophore.

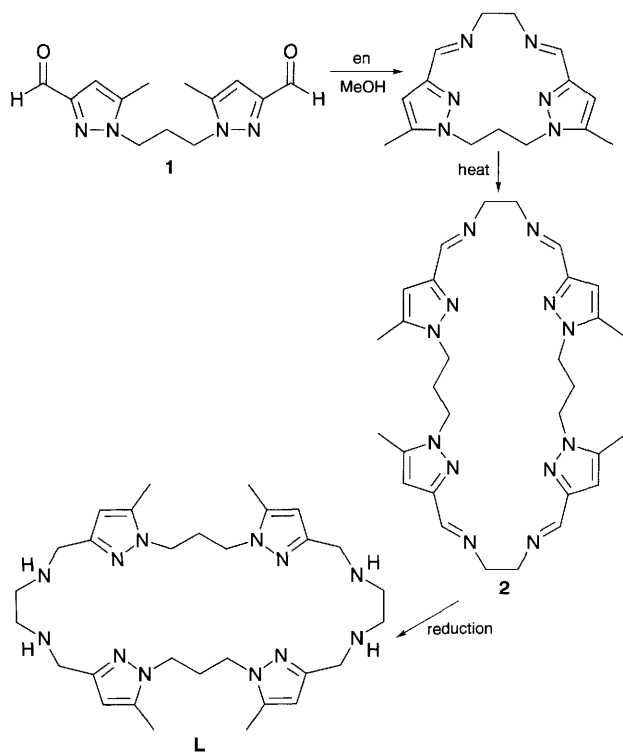
Macrocyclic receptors able to bind two Cu^{II} ions have become of increasing interest as mimics for the active site of copper proteins such as haemocyanin, tyrosinase and dopamine-β-hydroxylase.¹ Usually, aliphatic aza-crown macrocycles are used as rigid ligands for model compounds, capable of coordinating two copper ions in close proximity.² Also, chelating pyrazolyl ligands have been used successfully to obtain structural model compounds for the type-3 site of copper proteins.³ Dinuclear copper(II) complexes have been obtained by the self-assembly of two tris(pyrazolyl)borate copper(I) fragments with dioxygen in solution.⁴ Up to now, only a few macrocycles containing neutral heterocyclic sp² N donors endocyclic bound in the macrocyclic ring, have been reported.⁵ These considerations led us to preorganise four pyrazole donor groups in a semi-rigid macrocycle **L**,† a novel ligand capable of encapsulating two copper(II) ions at moderate distance. A space-filling model of **L** showed that Cu–Cu distances could be expected in a range of 4 to 7 Å, depending on the conformation of **L**. This would make **L** a suitable ligand to model the dinuclear type-3 site in copper proteins.

The synthesis of the 30-membered tetrapyrazolyl macrocycle **L** (Scheme 1) was based on the procedure of Tarrago *et al.*⁶ The macrocyclization reaction proceeds by a Schiff base condensation under dilute conditions between the 1,3-di(3'-formyl-5'-methyl-1'-pyrazolyl)propane precursor **1** and ethylenediamine. Contrary to the observation of Tarrago, who reported only the (1 + 1) 15-membered macrocycle containing two pyrazole groups, we observed the subsequent formation of the thermodynamically

more stable (2 + 2) tetraimine macrocycle **2**. After *in situ* reduction of **2** with NaBH₄, the tetraimine pyrazolyl macrocycle **L** was obtained. **L** was characterized by ¹H and ¹³C NMR, IR and FAB-MS, confirming the (2 + 2) ring size of **L**.‡

The addition of 2 equiv. of Cu(NO₃)₂ to a solution of **L** yields the dinuclear copper(II) complex **3**§. Analysis agrees with a mixed-anion composition with formula [Cu₂(L)Cl₂(EtOH)₂](NO₃)₂.¶ Spectroscopic data§ and X-ray analysis|| showed the high symmetry of the pyrazolyl macrocyclic complex and the presence of two copper(II) ions in **3**. The presence of chloride was due to the unexpected coordination of NaCl during the workup of **L**. This was proved by NMR and elemental analysis.** However, NaCl is only weakly bound to **L** and can be removed by washing a CH₂Cl₂ solution of **L** with H₂O.

The single-crystal X-ray structure of **3** (Fig. 1) shows **L** with two copper(II) ions, each bound in a distorted square pyramidal fashion. Each copper ion is equatorially coordinated at 2.05 and 2.01 Å by secondary amine donors of the ethylenediamine spacer and one pyrazole at 2.03 Å. The last equatorial position is occupied by a chloride anion at 2.25 Å. Each copper ion is axially coordinated at 2.48 Å by a second pyrazole. An EtOH molecule is weakly bound to each copper ion in an axial position at a long distance of 2.83 Å. Two nitrate anions are connected by a hydrogen bridge (O...O = 2.82 Å) to both EtOH molecules.



Scheme 1

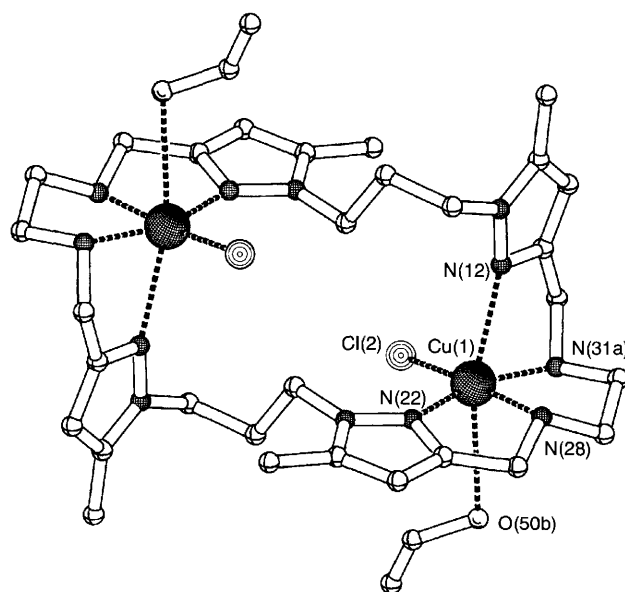


Fig. 1 Structure of the cation [Cu₂(L)Cl₂(EtOH)₂]²⁺. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Cu(1)–Cl(2) 2.252(4), Cu(1)–N(12a) 2.484(7), Cu(1)–N(22) 2.030(8), Cu(1)–N(28) 2.014(6), Cu(1)–N(31a) 2.046(7), Cu(1)–O(50b) 2.832(7), Cu(1)–Cu(1a) 7.137(10); N(12a)–Cu(1)–Cl(2) 90.75(16), N(12a)–Cu(1)–N(22) 111.9(2), N(12a)–Cu(1)–N(28) 94.0(2), N(12a)–Cu(1)–N(31) 75.1(2), N(22)–Cu(1)–Cl(2) 102.44(18), N(22)–Cu(1)–N(28) 79.9(3), N(22)–Cu(1)–N(31) 162.1(2), N(28)–Cu(1)–Cl(2) 173.5(2), N(28)–Cu(1)–N(31) 83.3(3), N(31)–Cu(1)–Cl(2) 93.65(19).

The Cu^{II}–Cu^{II} distance is long (7.14 Å), which is not surprising when no bridging ligand between the two copper ions is present. In the observed conformation of **L**, the Cu–Cu and Cl–Cl distances are maximal, probably to reduce electrostatic repulsions. The equatorial planes of the Cu ions are parallel to each other in a 'stairway' conformation, which precludes direct interaction of the magnetic $d_{x^2-y^2}$ orbitals of the copper ions. Indeed, frozen solution EPR (77K; X-band; MeOH–EtOH = 9 : 1) of **3** agrees with a mononuclear N₄O–Cu^{II} site, indicating that no magnetic interaction occurs between the copper ions of **3** in solution. However, preliminary experiments show that **3** reacts with 2 equiv. of NaOH (MeOH, room temp.). The EPR spectrum (frozen glass, 77 K) of the formed blue product shows, besides a monomeric signal of **3**, a triplet EPR signal indicative of a dinuclear Cu^{II} species. Although the triple spectrum is not well resolved, an H_{\min} signal at $g = 4.28$ ('half-field') and a HX_2-HY_2 signal at $g = 1.87$ is observed. The full characterisation of this dinuclear Cu^{II} species is currently under investigation.

Complex **3** is the first example of a structurally characterised macrocycle containing neutral endocyclic pyrazole donors, capable of coordinating the two metal ions. Although the Cu^{II}–Cu^{II} distance found in the X-ray structure is large, the molecule appears to be flexible enough to allow bridging of small molecules, such as hydroxide anions. Further studies of **3** with externally added substrates (imidazolate, acetate), linking both Cu^{II} ions are in progress.

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Footnotes

† Named using the IUPAC-approved system for phane nomenclature: 1,5,10,13,18,22,27,30,35,36,37,38-dodecaaza-(6,17,23,34-tetra-methyl)pentacyclo[30.2.1.1^{5,8}.1^{5,18}.1^{22,25}]octatricontane-6,8(36),15(37),16,23,25(38),32(35),33-octaene.

‡ *Synthesis* of **L**·2H₂O: 4.00 g (15.37 mmol) of 1,3-di(3'-formyl-5'-methyl-1'-pyrazol)propane **1**⁶ was dissolved in 500 ml dry MeOH at reflux under a dry N₂ atmosphere. Ethylenediamine (1 equiv.) in 100 ml dry MeOH was added dropwise over 30 min. After 3 h at reflux, NaBH₄ (50% excess) was added and the clear yellow solution was heated under reflux for 4 h. The MeOH was evaporated off, 100 ml of 1 mol dm⁻³ HCl was added, the mixture washed with CH₂Cl₂ and basified with concentrated ammonia until pH ≥ 9. The pale-yellow H₂O layer was extracted with CH₂Cl₂ and the organic layer was dried over Na₂SO₄ for 20 min. After vapour diffusion of Et₂O, the bis(aqua) complex of **L** was obtained as an off-white solid and dried *in vacuo*. Yield 2.04 g (3.46 mmol); 45%. δ_H (200 MHz, CDCl₃): 2.13 [s, 12 H, (5)Pz-CH₃], 2.24 (m, 4 H, PzCH₂CH₂CH₂Pz), 2.79 (s, 8 H, NCH₂CH₂N), 3.70 [s, 8 H, (3)PzCH₂N], 3.95 (t, 8 H, PzCH₂CH₂CH₂Pz), 5.88 [s, 4H, (4)PzH]. FAB-MS (35 eV, VG Autospec HRMS, glycerol matrix): m/z 577.7 (M⁺ + 1, 40%). Satisfactory elemental analysis was obtained. No chloride detected (see also footnote **).

§ *Synthesis and spectroscopic data* of **3**: 25 ml of a hot EtOH solution containing 0.42 mmol Cu(NO₃)₂ was added dropwise to a solution of 0.21 mmol **L** in 45 ml hot EtOH. After cooling and filtering, light blue crystals appeared after slow evaporation of the solvent. The crystals were filtered off, washed with EtOH and dried in air (48% yield). IR (KBr disk) ν/cm^{-1} : 1549 (Pz-CN); $\delta(N-H)$ shifts from 1575 to 1633 cm^{-1} upon coordination. EPR (Jeol Esprit 330, X-band, frozen solution, MeOH–EtOH = 9 : 1): axial spectrum with $g_{\perp} = 2.06$, $g_{\parallel} = 2.22$; $A_{\parallel} = 178$ Gauss. Ligand-field (powder, diffuse reflectance): $\lambda = 698$ nm (ν 14.330 cm^{-1}). Satisfactory elemental analysis was obtained.

|| *Crystal data* for complex **3**: C₃₀H₄₈Cl₂Cu₂N₁₂·2NO₃·2C₂H₅OH, triclinic, space group P $\bar{1}$ (no. 2), $a = 11.120(10)$, $b = 8.523(7)$, $c = 14.36(2)$ Å, $\alpha = 90.43(8)$, $\beta = 120.24(5)$, $\gamma = 103.76(9)^{\circ}$, $V = 1129(2)$ Å³, $Z = 1$, $D_c = 1.455(3)$ g cm⁻³, $F(000) = 516.00$. A single crystal of **3**, suitable for X-ray diffraction studies, was mounted in a glass capillary tube. Intensities were measured at room temperature with graphite-monochromated radiation $\mu(Mo-K\alpha) = 11.2$ cm⁻¹, using an ω -scan ($2.2 \leq 2\theta \leq 27.5^{\circ}$) on an Enraf-Nonius CAD-4 diffractometer. 2383 Unique reflections with $I > 2\sigma(I)$ were used in the refinement. Absorption correction was not applied. The structure was solved by direct methods using the XTAL package.⁷ Following refinement of the non-hydrogen atoms using anisotropic thermal parameters, the hydrogen atoms were placed idealized positions (C–H 0.96 Å, C–C–H 109° or 120°). Refinement converged at $R = 0.055$, $R_w = 0.055$, $S = 2.39$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

** Initially, **L** was isolated as a bis-NaCl adduct with composition **L**·2NaCl·MeOH. NMR (JNM-FX 200, CDCl₃), ¹H (200 MHz): σ 2.14 [s, 12H, (5)Pz-CH₃], 2.22 [m, 4H, PzCH₂CH₂CH₂Pz], 3.01 (s, 8H, NCH₂CH₂N), 3.90 [s, 8H, (3)PzCH₂N], 3.92 (t, 8H, PzCH₂CH₂CH₂Pz), 6.08 [s, 4H, (4)PzH]. IR KBr disk ν/cm^{-1} : 1551 (Pz-CN); $\delta(N-H)$ shifted from 1575 to 1633 cm^{-1} . Satisfactory elemental analysis was obtained.

¶ Complexation of **L** with Cu(ClO₄)₂ yielded crystals of similar mixed anion composition: [Cu₂(L)Cl₂(EtOH)₂](ClO₄)₂. X-Ray structure determination proved the molecular structure, the coordination geometry around both Cu^{II} ions and the conformation of **L** to be the same as in **3**: independent of the non-coordinating anion. Owing to a different orientation of the non-coordinating ClO₄⁻ anions, a different crystal packing with space group P2₁/c ($R = 0.082$) resulted.

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