

Dopamine interaction with a polyamine cryptand of 1*H*-pyrazole in the absence and in the presence of Cu(II) ions. Crystal structure of [Cu₂(H₋₁L)](ClO₄)₃·2H₂O

Laurent Lamarque,^a Carlos Miranda,^a Pilar Navarro,^{*a} Francisco Escartí,^b Enrique García-España,^{*b} Julio Latorre^b and José A. Ramírez^{*b}

^a Instituto de Química Médica, Centro de Química Orgánica Manuel Lora Tamayo, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

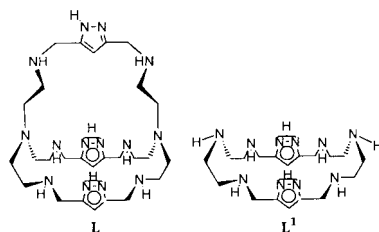
^b Departamento de Química Inorgànica, Facultat de Química, Universitat de València, C/Dr. Moliner 50, 46100 Burjassot, València, Spain. E-mail: enrique.garcia-es@uv.es

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The crystal structure of the binuclear Cu²⁺ complex [Cu₂(H₋₁L)](ClO₄)₃·2H₂O of the cryptand L = 1,4,7,8,11,14,17,20,21,24,29,32,33,36-tetradecaazapentacyclo[12.12.12.1^{6,9}.1^{19,22}.1^{31,34}]hentetraconta-6,9(41),19(40),21,31,34(39)-hexaene is presented; evidence for the formation in solution of binary L–dopamine and ternary Cu²⁺–L–dopamine complexes is presented.

Supramolecular chemistry has developed through the preparation of sophisticated molecular receptors which are able to discriminate and induce characteristic properties in given substrates.¹ Tridimensional cryptand-like receptors with appropriate arrangements of binding sites have yielded interesting patterns in many aspects of molecular recognition like metal ion or anion coordination chemistry.^{1,2} We have previously reported the synthesis, basicity and complexing properties of polyamine coronands of 1*H*-pyrazole able to form Zn²⁺ and Cu²⁺ pyrazolate salts.^{3,4} Herein we report on a polyamine cryptand of related structure.⁵ We advance the results of a study on its interaction with Cu²⁺ and on the formation of mixed complexes with the biologically relevant neurotransmitter dopamine.⁶

Ligand L was prepared as reported in ref. 5 by reacting 3,5-pyrazoledicarbaldehyde and tris(2-aminoethyl)amine in 3:2 molar ratio in MeOH, followed by reaction *in situ* with NaBH₄. Crystals of [Cu₂(H₋₁L)](ClO₄)₃·2H₂O **1** were prepared



mixing methanolic solutions of free L (57 mg, 0.1 mmol) and Cu(ClO₄)₂·6H₂O (74 mg, 0.2 mmol). Evaporation of the solution gave a blue solid that after re-dissolution in a minimum amount of hot water, gave crystals of [Cu₂(H₋₁L)](ClO₄)₃·2H₂O **1** suitable for X-ray diffraction analysis.[†] The crystal structure of **1** consists of [Cu₂(H₋₁L)]³⁺ cations, ClO₄⁻ anions and water molecules. The coordination geometry around each Cu²⁺ is square pyramidal, the base of the pyramid being formed by two secondary nitrogens of the bridge and two nitrogen atoms of two different pyrazolate moieties which act as exobidentate ligands. The axial positions are occupied by the bridgehead nitrogen atoms, with distortion being more pronounced in one of the two sites [Cu(1)–N(1) 2.29(2) Å, Cu(2)–N(6) 2.403(9) Å]. The Cu²⁺–L distances involving the sp² pyrazolate nitrogen atoms [Cu(1)–N(3) 1.90(1) Å, Cu(1)–N(9) 1.93(1) Å, Cu(2)–N(4) 1.92(1) Å, Cu(2)–N(8) 1.91(1) Å] are much shorter than those of the secondary nitrogen atoms

[Cu(1)–N(2) 2.11(1) Å, Cu(1)–N(10) 2.06(1) Å, Cu(2)–N(5) 2.08(1) Å, Cu(2)–N(7) 2.11(2) Å]. The Cu(1)···Cu(2) distance is 3.960(3) Å. Similar coordination features were observed in the crystal structure of the binuclear complex [Cu₂(H₋₂L¹)](ClO₄)₂, in which L¹ is the coronand ligand that constitutes the base of cryptand L,³ and in several crystal structures of pyrazole containing ligands.⁷ Interestingly, we have observed that Cu²⁺ leads to the ready deprotonation of the two pyrazole fragments involved in the coordination, without requiring any addition of base (*vide infra*). However, the pyrazole in the non-coordinating bridge of L (see Fig. 1) does not deprotonate, and lies to one side of the macrocyclic cavity. One of the nitrogen atoms of the aliphatic chains is protonated and hydrogen bonded to a water molecule [N(11)···O(1) 2.79(2) Å] placed at one side of the macrocyclic cavity and further connected to the sp² nitrogen of the pyrazole group through an additional hydrogen bond [N(12)···O(1) 3.12(2) Å]. The distances of the water molecule to the non-protonated nitrogen atom of the bridge and to the other pyrazole nitrogen are much longer (5.38 and 3.79 Å, respectively). The other water molecule, which is located completely outside of the cavity, is hydrogen bonded to N(10) [N(10)···O(2) 2.98(2) Å].

The coordination arrangement keeps both Cu²⁺ metal ions close to one face of the cage [the elevation of the Cu atoms over the mean plane defined by the nitrogen donors of the base of the square pyramid are 0.142(7) and 0.272(7) Å for Cu(1) and

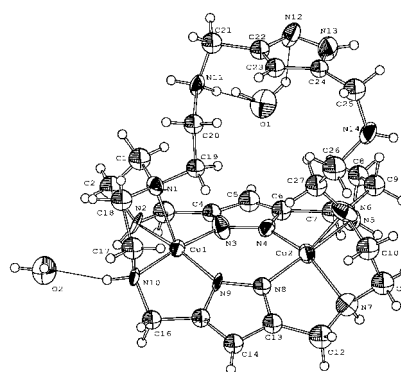
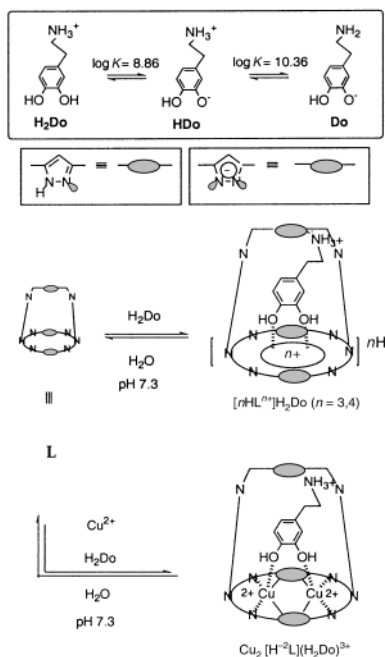


Fig. 1 ORTEP drawing of the [Cu₂(H₋₁L)]³⁺ complex cation also showing the hydrogen bonds to the water molecules. Selected distances (Å) and angles (°): Cu(1)–N(3) 1.90(1), Cu(1)–N(9) 1.93(1), Cu(1)–N(10) 2.06(1), Cu(1)–N(2) 2.11(1), Cu(1)–N(1) 2.29(2), Cu(1)–Cu(2) 3.96(3), Cu(2)–N(8) 1.91(1), Cu(2)–N(4) 1.92(1), Cu(2)–N(5) 2.08(1), Cu(2)–N(7) 2.11(2), Cu(2)–N(6) 2.403(9), O(1)–N(11) 2.79(2), O(1)–N(12) 3.12(3), O(2)–N(10) 2.98(2); N(10)–Cu(1)–N(2) 103.7(5), N(2)–Cu(1)–N(3) 81.4(6), N(3)–Cu(1)–N(9) 94.7(6), N(9)–Cu(1)–N(10) 79.6(6), N(1)–Cu(1)–N(2) 82.0(5), N(10)–Cu(1)–N(1) 81.4(5), N(3)–Cu(1)–N(1) 102.9(6), N(9)–Cu(1)–N(1) 111.3(5), N(8)–Cu(2)–N(4) 94.6(5), N(4)–Cu(2)–N(5) 80.2(6), N(5)–Cu(2)–N(7) 101.4(7), N(8)–Cu(2)–N(7) 81.4(6), N(4)–Cu(2)–N(6) 123.7(6), N(5)–Cu(2)–N(6) 81.1(4), N(7)–Cu(2)–N(6) 81.7(5), N(8)–Cu(2)–N(6) 105.6(5).



Scheme 1

Cu(2), respectively] leaving enough free room within the cavity to allow the encapsulation of further substrates as exogenous ligands. Owing to the biological relevance that ternary Cu^{2+} -dopamine complexes have in enzyme mimicking and neurotransmitter regulation, we have preliminarily studied this system.

pH-Metric analysis shows that free L displays up to six protonation steps in the pH range 2.5–10.5 with pK_a values in the range 9.5–5.2.⁸ This makes this compound highly charged in solution at physiological pH and a promising receptor for encapsulating anionic or polar substrates.

The cryptand heterocyclophane L displays high affinity for Cu^{2+} forming in aqueous solution very stable binuclear complexes of stoichiometries $[\text{Cu}_2\text{L}]^{4+}$, $[\text{Cu}_2\text{H}_{-1}\text{L}]^{3+}$ and $[\text{Cu}_2\text{H}_{-2}\text{L}]^{2+}$,⁹ at a molar ratio $\text{Cu}^{2+}:\text{L} = 2:1$, which are the only species over a wide pH range ($[\text{Cu}_2\text{L}]^{4+}$ from pH 3 to 5, $[\text{Cu}_2\text{H}_{-1}\text{L}]^{3+}$ from pH 5.5 to 8 and $[\text{Cu}_2\text{H}_{-2}\text{L}]^{2+}$ above pH 8.5). Taking into account that in the crystal structure of **1**, the two pyrazole groups involved in the coordination of Cu^{2+} are deprotonated and that the constant of the equilibrium $[\text{Cu}_2\text{L}]^{4+} = [\text{Cu}_2\text{H}_{-1}\text{L}]^{3+} + \text{H}^+$ is $\log K = -5.37$, Cu^{2+} coordination to L induces a decrease of more than six pH units in the protonation constant of pyrazole with respect to the free heterocycle. A similar behaviour has also been observed in the system $\text{Cu}^{2+}\text{-L}^{10}$ and in a related system containing two 1,4,7-triazacyclononane units linked by a 3,5-pyrazole bridge.⁷

The interaction of L with dopamine (Do) has been analysed in the pH range 2.5–9.0 with 1:1 dopamine:receptor species being detected with degrees of protonation varying between 7 and 1. Around physiological pH, the magnitude of the interaction reaches values close to 5 logarithm units ($K_{\text{app}} = \Sigma[\text{DoH}_{i+j}\text{L}]/\Sigma[\text{H}_j\text{Do}]\Sigma[\text{H}_i\text{L}] = 10^5$;¹¹ therefore, the neurotransmitter forms a remarkably stable complex with the receptor. UV studies confirm this interaction. UV spectra of solutions containing a constant amount of L and variable amounts of dopamine at pH 7 show an increase in absorptivity and eventual saturation of an absorption band centred at 214 nm. Fitting of the absorbance vs. $[\text{Do}]/[\text{L}]$ plots confirms the 1.1 Do:L stoichiometry and allows an estimation of an affinity constant of ca. 5 logarithmic units, in agreement with the pH-metric studies. Molecular models suggest the possibility of a partial inclusion of the dopamine molecule in the cavity of the receptor and its stabilisation by a variety of intermolecular forces such as electrostatic and/or hydrogen bonding interactions (Scheme 1).

Finally, we comment on the formation of ternary complexes $\text{Cu}^{2+}\text{-L-dopamine}$ of stoichiometry $[\text{Cu}_2\text{H}_2\text{LDo}]^{5+}$, $[\text{Cu}_2\text{HLDo}]^{4+}$, $[\text{Cu}_2\text{LDo}]^{3+}$ and $[\text{Cu}_2\text{H}_{-1}\text{LDo}]^{3+}$ which, taking into account the pH range of their formation, can be formulated formally as deriving from the following equilibria: $\text{H}_2\text{Do}^+ + [\text{Cu}_2\text{L}]^{4+} = [\text{Cu}_2\text{H}_2\text{LDo}]^{5+}$, $\log K = 3.7$; $\text{H}_2\text{Do}^+ + [\text{Cu}_2\text{H}_{-1}\text{L}]^{3+} = [\text{Cu}_2\text{HLDo}]^{4+}$, $\log K = 4.0$; $\text{H}_2\text{Do}^+ + [\text{Cu}_2\text{H}_{-2}\text{L}]^{2+} = [\text{Cu}_2\text{LDo}]^{3+}$, $\log K = 3.7$; $\text{HDo} + [\text{Cu}_2\text{H}_{-1}\text{L}]^{3+} = [\text{Cu}_2\text{H}_{-1}\text{LDo}]^{2+}$, $\log K = 4.0$.

The formation of the ternary complexes implies breaking of the Cu–N axial bonds and their replacement by strong Cu–phenolate bonds¹² as suggested by modelling of the system. An interaction of the ammonium group of dopamine with the sp^2 bond of the pyrazole moiety might also contribute to the final stabilisation of the complexes (Scheme 1).

The observed recognition patterns and crystal structure suggest interesting developments of this receptor in the fields of medicinal chemistry and enzyme mimicking.

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Notes and references

† Crystal data for **1**: $\text{C}_{27}\text{H}_{51}\text{N}_{14}\text{O}_{14}\text{Cl}_3\text{Cu}_2$, $M = 1029.25$, monoclinic, space group $C2/c$, $a = 44.667(5)$, $b = 9.124(5)$, $c = 20.050(5)$ Å, $\beta = 97.687(5)$, $V = 8098(5)$ Å³, $Z = 4$, 6579 reflections collected of which 3411 were independent ($R_{\text{int}} = 0.1348$), $D_c = 1.687$ Mg m^{-3} , $R(R_w) = 0.0625(0.1621)$. CCDC 182/1674.

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- Potentiometry was carried out in 0.15 mol dm^{-3} NaCl at 298.1 K using concentrations of L, Cu^{2+} and dopamine in the range $1\text{--}3 \times 10^{-3}$ mol dm^{-3} . The program HYPERQUAD (A. Sabatini, A. Vacca and P. Gans, *Coord. Chem. Rev.*, 1992, **120**, 389) was used to derive the values of the protonation and stability constants. Protonation constants of L under the same experimental conditions: $\log K_{\text{H}_1\text{L}/\text{H}_1\text{L}} = 9.54(2)$, $\log K_{\text{H}_2\text{L}/\text{H}_1\text{L}} = 8.71(1)$; $\log K_{\text{H}_3\text{L}/\text{H}_2\text{L}} = 7.72(2)$; $\log K_{\text{H}_4\text{L}/\text{H}_3\text{L}} = 6.55(3)$, $\log K_{\text{H}_5\text{L}/\text{H}_4\text{L}} = 6.51(3)$, $\log K_{\text{H}_6\text{L}/\text{H}_5\text{L}} = 5.23(3)$. Protonation constants of dopamine (Do), see Scheme 1): $\log K_{\text{HDo}/\text{Do}} = 10.36(1)$, $\log K_{\text{H}_2\text{Do}/\text{HDo}} = 8.86(1)$.
- At a molar ratio of 2:1 the species $[\text{Cu}_2\text{HL}]^{5+}$, $[\text{Cu}_2\text{L}]^{4+}$, $[\text{Cu}_2\text{H}_{-1}\text{L}]^{3+}$ and $[\text{Cu}_2\text{H}_{-2}\text{L}]^{2+}$ are found in solution with stability constants: $2\text{Cu}^{2+} + \text{H}^+ + \text{L} = [\text{Cu}_2\text{HL}]^{5+}$, $\log K = 38.73(7)$; $2\text{Cu}^{2+} + \text{L} = [\text{Cu}_2\text{L}]^{4+}$, $\log K = 36.61(3)$; $2\text{Cu}^{2+} + \text{L} = [\text{Cu}_2\text{H}_{-1}\text{L}]^{3+} + \text{H}^+$, $\log K = 31.39(3)$; $2\text{Cu}^{2+} + \text{L} = [\text{Cu}_2\text{H}_{-2}\text{L}]^{2+} + 2\text{H}^+$, $\log K = 24.24(4)$.
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- Potentiometric titrations indicate that between pH 3 and 9.5 the formation of the species H_jDoL with $j = 1\text{--}7$: $\text{Do} + \text{H}^+ + \text{L} = \text{HDoL}^+$, $\log K = 16.19(2)$; $\text{Do} + 2\text{H}^+ + \text{L} = \text{H}_2\text{DoL}^{2+}$, $\log K = 25.72(2)$; $\text{Do} + 3\text{H}^+ + \text{L} = \text{H}_3\text{DoL}^{3+}$, $\log K = 34.57(2)$; $\text{Do} + 4\text{H}^+ + \text{L} = \text{H}_4\text{DoL}^{4+}$, $\log K = 43.04(2)$; $\text{Do} + 5\text{H}^+ + \text{L} = \text{H}_5\text{DoL}^{5+}$, $\log K = 50.39(2)$; $\text{Do} + 6\text{H}^+ + \text{L} = \text{H}_6\text{DoL}^{6+}$, $\log K = 57.08(2)$; $\text{Do} + 7\text{H}^+ + \text{L} = \text{H}_7\text{DoL}^{7+}$, $\log K = 63.40(2)$. Conditional constants defined as $K_{\text{app}} = \Sigma[\text{DoH}_{i+j}\text{L}]/\Sigma[\text{H}_j\text{Do}]\Sigma[\text{H}_i\text{L}]$ range from 2 to 5.5 logarithmic units in the pH range studied.
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