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Short communication

Synthesis, crystal structure and relevant antiproliferative activity against *Toxoplasma gondii* of a new binuclear Co(II) complex

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ABSTRACT

The crystal structure of [(HPClNOL)Co(-μ-Cl_2)Co(HPClNOL)]$(ClO_4)_2$ **1** (HPClNOL: 1-(bis-pyridin-2-ylmethyl-amino)-3-chloropropan-2-ol) revealed a distorted octahedral geometry around both Co(II) centers. The coordination plane comprised one tertiary amine, one alcohol in the protonated form and two chloride which link the two Co(II) centers, resulting in the binuclear arrangement. Two pyridine nitrogen atoms are coordinated and occupy the axial sites. Investigations in solid state and in solution (dimethylformamide) carried out by electronic spectroscopy suggest that the arrangement in the solid state changes in solution. Furthermore, ESI(+)-MS and conductivimetry studies indicated the formation of mononuclear species in solution in agreement with the lability of the chloride ligands. Complex **1** reduced the growth of *Toxoplasma gondii* infecting LLC-MK2 host cells. After treatment this complex reduced *T. gondii* growth by 55%, the ligand HPClNOL had no effect on parasite growth and sulfadiazine (SDZ), traditional terapeutic compound for this parasite, was effective only after 48 h of treatment. These results suggest the relevance of the cobalt ion on the anti-toxoplasma activity.

Cobalt is an essential element for life and it is less toxic than non-essential metals such as platinum. Cobalt is an integral component of cyanocobalamin (vitamin B12), and as such is essential for red blood cell formation and the maintenance of nerve tissue [ref]. Corrinoid metalloenzymes as vitamin B12 are widespread among prokaryotes and eukaryotes, catalyzing electron transfer, transmethylation and rearrangement reactions. Although not confirmed, cobalt may also function as an activating agent for various enzyme systems. Despite its versatile catalytic role, cobalt occurs in only 1% of structurally characterized proteins, significantly less than that of other trace metals such as zinc (9%), iron (8%) and manganese (6%) [1].

There are several recent reports that highlight the relevant properties of cobalt complexes as antitumoral compounds [2,3]. Furthermore, many other cobalt complexes have been found to possess pronounced biological activities, such as antiviral and antibacterial [4].

In the present study we report the synthesis, characterization and antiproliferative activity against an intracellular parasite of a new binuclear cobalt(II) complex, containing the ligand HPClNOL = 1-(bis-pyridin-2-ylmethyl-amino)-3-chloropropan-2-ol), which was previously described by us [5]. This ligand has been successfully employed in the syntheses of several coordination compounds by our group, which exhibit interesting biological properties, as antitumoral and antioxidant [6–8]. Recently, we report the cytotoxic effect on *Toxoplasma gondii* of a dinuclear iron(III) complex [Fe(HPClNOL)(SO4)2]-μ-oxo, which induces reduction of superoxide dismutase and catalase activities disturbing the parasite redox equilibrium, resulting in cystogenesis and parasite death [9]. This parasite causes toxoplasmosis a severe disease that affects individuals with compromised immune system, such as HIV and immunosuppressed organ transplanted patients.

Nowadays, the current treatment for toxoplasmosis involves the use of synergistic combinations of pyrimethamine and sulfadiazine (SDZ), which presents IC_{50} 600–700 mg/L [10]. Unfortunately, there are no large scale trials on the efficacy of new drugs to treat toxoplasmosis, a severe disease in individuals with compromised immune system, such as HIV patients and immunosuppressed organ transplanted patients.

Aiming to show that metallocompounds may be a good strategy for toxoplasmosis treatment, herein we report the synthesis, X-ray crystal structure, studies in solution and initial results of the antiproliferative activity against *T. gondii* of the first dinuclear Co(II) complex containing the ligand HPClNOL on its structure.

The binuclear cobalt(II) complex reported herein was prepared by the reaction between the ligand HPClNOL [5] (1 mmol, 290 mg) and cobalt(II) chloride dihydrate ($CoCl_2 \cdot 2H_2O$) (240 mg, 1 mmol), in isopropanol, which resulted in a blue solution. After, $LiClO_4$ (110 mg, 1 mmol) was added and the solution was heated for 2 h. After allowing the blue solution to stand for a few days a microcrystalline purple solid was filtered off and dried with ether. Yield: 580 mg (46%). m.p.: 230 °C.

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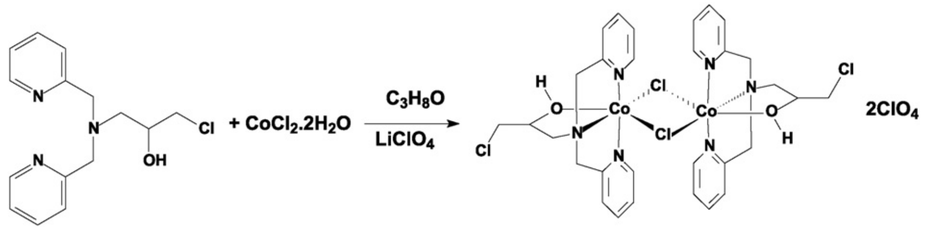

Scheme 1S. Synthesis of [(HPClNOL)Co(-μ-Cl_2)Co(HPClNOL)]$(ClO_4)_2$ 1.

Anal. Calcd. for $C_{30}H_{36}Cl_6Co_2N_6O_{10}$; MW = 971 g mol^{-1}: C, 37.10; H, 3.74; N, 8.85. Found: C, 37.47; H, 3.58; N, 8.85.

Scheme 1S presents the synthesis of the binuclear cobalt(II) complex.

The IR spectrum of the complex exhibits bands at 3033 (aromatic CH), 2950–2912 (aliphatic CH), 1608, 1570, 1477 and 1440 (ν CN and CC), 1118 and 1045(ν ClO_4^-) and at 767 cm^{-1} (δ C—H) (Fig. 1S). For the ligand, these bands are observed at 3085 and 3087 (aromatic CH), 2914–2849 (aliphatic CH), 1593, 1570, 1475 and 1435 (ν CN py and CC) and at 764 cm^{-1} (δ C—H). We noted intense bands in the range of 1118–1045 which are related to the perchlorate group, as indicated by X-ray diffraction studies. The cobalt(II) complex under investigation presents at least four absorption bands in the visible range, at 490 nm (98), 512 nm (109), 555 nm (84) and at 600 nm (66 dm^3 mol^{-1} cm^{-1}), which are attributed to d-d transition, typical for Co(II) complexes (Fig. 2S). When the spectrum was obtained using a suspension of the complex in nujol, only one absorption at 930 nm was observed, indicating distinct behavior in solution and in solid state. Three d-d-electronic transition on the visible range are expected for octahedral Co(II) complexes, but only two are observed, at 460 nm (^{4}T1g(F)➔ $^4T_2$g(F)) and at 950 nm (^{4}T1g(F) ➔ ^{4}T1g(P)) [11]. The presence of more transitions in solution indicates a highly distorted geometry around the Co(II) center, which is less distorted in solid state, presenting only one electronic transition at 930 nm which is attributed to ^{4}T1g ➔ ^{4}T2g. The complex **1** consists of two distorted octahedral Co(II) centers (distorted octahedral), each of them coordinated to one molecule of the tetradentade donor ligand HPClNOL, which exhibits a N3O donor environment. Each Co(II) center is further coordinated by two chlorides which act like bridges between the two Co(II) centers, resulting in a dinuclear complex. The coordination plane comprised the tertiary amine, one alcohol in the protonated form and two chloride. The axial positions are occupied by two pyridine nitrogen atoms. A perspective view of the cation is displayed in Fig. 1. The coordination behaviour of this ligand has been described already for Cu, Mn and Fe. With copper [5] and manganese [12], mononuclear complexes were isolated. With iron, both mono and dinuclear oxo-bridge complexes were reported [13–15].

The ESI(+)-MS data of complex **1** indicate the presence of peaks with *m/z* 313, 349, 385, 449, 771, 835 and 898, revealing mononuclear and dinuclear complexes in solution. The spectrum is presented in Fig. 2. The peaks in the range of 300–450 were ascribed as mononuclear Co(II) complexes and in the range of 700–900 they were ascribed to dinuclear Co(II) complexes. Based on the intensity of the signals in the range of 700–900 we suggest that under these conditions, the rupture of the dinuclear unit is taking place, rendering highly stable mononuclear complexes.The peak with *m/z* 313 is ascribed to the protonated ligand (H_2L^+), the peaks at *m/z* 349, 385 and 449 were ascribed to the complexes $[Co(L)]^+$, $[Co(HL)Cl]^+$ and $[Co(HL)ClO_4]^+$, respectively. The peaks with *m/z* 771, 835 and 898 are ascribed to: $[(HL)Co(\mu\text{-}Cl)_2Co(L)]^+$, $[(HL)Co(\mu\text{-}ClO_4)(\mu\text{-}Cl)Co(L)]^+$ and $[(HL)Co(\mu\text{-}ClO_4)_2Co(L)]^+$, respectively, based on the MS/MS data, which indicates that the species with *m/z* 898 yields the cation with *m/z* 797, ascribed as $[Co(L)_2(ClO_4)]^+$ (by the loss of a neutral $HClO_4$ molecule) and the species with *m/z* 449, by the loss of a neutral molecule of 449 Da, described as a neutral complex $[Co(L)(ClO_4)]$. The species with *m/z* 835 yields the cations with *m/z* 799 ($[Co(L)_2(ClO_4)]^+$) and 385 ($[Co(HL)Cl]^+$), by the loss of HCl and $[Co(L)(ClO_4)]$, respectively. The species with *m/z* 771 yields the cations with *m/z* 735 and with *m/z* 385, which were ascribed as $[(L)Co(\mu\text{-}Cl)Co(L)]^+$ and

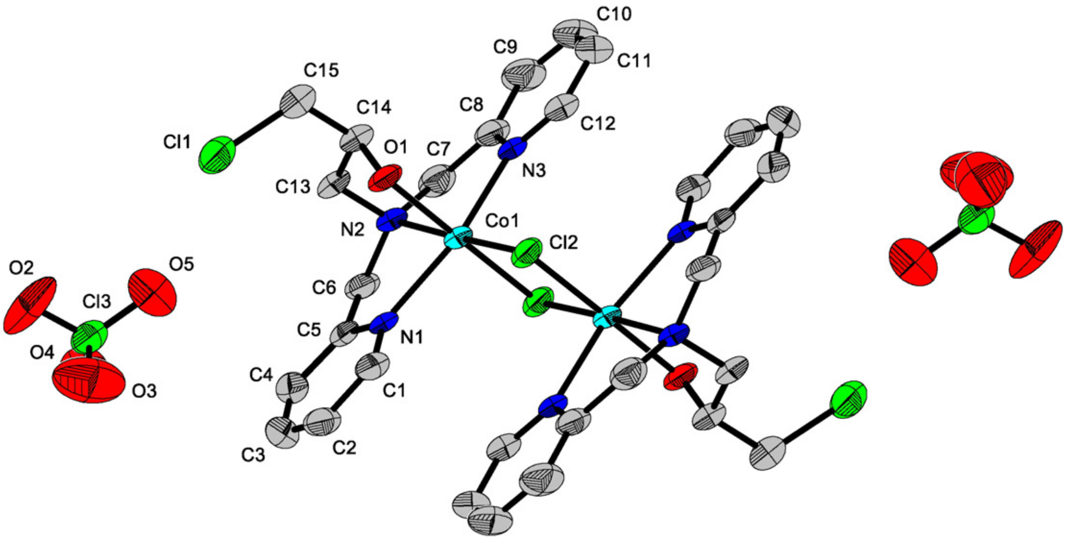

Fig. 1. ORTEP plot and labelling scheme of the complex **1**, thermal ellipsoid plot at 50% probability level. The other atoms from the asymmetric unit was generated by −x + 1, −y + 1, −z + 1 symmetry [11]. Selected bonds (A°) and angles (°).Co(1)–Co(1)#1 3.1257(10), Co(1)–N(3) 2.072(3), Co(1)–N(1) 2.074(3), Co(1)-O(1) 2.115(2), Co(1)–N(2) 2.275(3), Co(1)–Cl(2)# 2.5645(11), Cl(2)–Co(1) 2.5280(12), Co(1)–Cl(2)–Co(1)#1 75.72(3), N(3)–Co(1)–N(1) 155.89(12), N(3)–Co(1)–O(1) 97.79(10), N(1)–Co(1)–O(1) 87.34(10), N(3)–Co(1)–N(2) 79.18(11), N(1)–Co(1)–N(2) 76.97(11), O(1)–Co(1)–N(2) 93.98(10), N(3)–Co(1)–Cl(2) 100.99(9), N(1)–Co(1)–Cl(2) 103.02(9), O(1)–Co(1)–Cl(2) 82.83(7), N(2)–Co(1)–Cl(2) 176.81(7), N(3)–Co(1)–Cl(2)#1 79.14(8), N(1)–Co(1)–Cl(2)#1 92.84(8), O(1)–Co(1)–Cl(2)#1 92.84(8), O(1)–Co(1)–Cl(2)#1 172.64(7), N(2)–Co(1)–Cl(2)#1 78.90(7), Cl(2)–Co(1)–Cl(2)#1 104.28(3). See Tables 1S, 2S, 3S and Fig. 3S.