MAGNETIC PROPERTIES AND ANTIBACTERIAL ACTIVITY OF TETRANUCLEAR COPPER COMPLEXES BRIDGED BY OXO GROUP.

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ABSTRACT

A series of three tetranuclear Cu(II) complexes of general formula $[Cu_4OCl_6L4]$, where L is a Lewis Base ligand has been characterized through magnetic measurements and determination of antimicrobial activities.

This study include the following species $[Cu_4OCl_6)Cl(PhIm)_3](HPhIm) \bullet H_2O$ (1) where PhIm= 4-phenylimidazole, $[(Cu_4OCl_6)(PyNO)_4] \bullet 1/5(H_2O)$ (2) where PyNO= Pyridine-N-oxide and $[(Cu_4OCl_6)(MeIm)_4] \bullet 3(CH_3OH)$ (3) where MeIm = 2-methylimidazole.

The polynuclear cluster in the complexes contains a central oxygen atom tetrahedral coordinated to four copper(II) ions, each of which coordinates a monodentate L ligand. Each pair of copper atoms is bridged by on a chlorine ion, resulting a trigonal bipiramidal environment.

The variable temperature magnetic susceptibilies of these complexes were investigated in the temperature range 5-300K.

Satisfactory fits to the observed susceptibility data were obtained only for the complexes (1) and (3), by assuming isotropic magnetic exchange interactions and using the appropriate spin Hamiltonian and susceptibility equation giving the coupling constants $J_1 = 0.148 cm^{-1}$, $J_2 = -1.707 cm^{-1}$ for (1) and $J_1 = 0.522 cm^{-1}$, $J_2 = -5.32 cm^{-1}$ for (3).

The antimicrobial activities of these complexes have been screened in vitro against Gram positive and negative bacteria.

Keywords: Copper, magnetism, antibacterial activities.

INTRODUCTION

Copper (II) is probably the most extensive studied among the transition metal ions. This is due to their lability, their high affinity with different ligands and the wide variety of ligands geometries that can accommodate.

Due to their importance in biological processes and industrial application, copper(II) complexes synthesis and activity studies have been the focus from different perspectives.

Copper(II) complexes have found possible medical uses in the treatment of many diseases including cancer [1,2]. On the other hand, an increasing number on antibacterial activity studies in copper complexes have been reported [3,5].

Significant research from experimental and theoretical viewpoint have devoted to analyzing the polynuclear Cu(II) complexes with various bridges between the metal centers, matter in connection with their magnetic behaviour and design of new catalysts [6-8].

We report here the synthesis, magnetic properties and antibacterial activity of the $[(Cu_4OCl_6)Cl(PhIm)_3] \bullet (HPhIm) \bullet H_2O$ (1), $[(Cu_4OCl_6)(PyNO)_4] \bullet 1/5(H_2O)$ (2) and $[(Cu_4OCl_6)(MeIm)_4] \bullet 3(CH_3OH)$ (3), complexes which contains both µ4-bridging oxygen and µ –halogens in their structures.

Experimental section

All chemicals and reagents are commercially available and were used as received without further purification.

Synthesis

The copper (II) complexes were synthesized by the method previously reported [9]. A methanol solution of the organic ligand (1 mmol) was added with constant stirring to a solution containing copper chloride (1 mmol) in the same solvent. The resulting solution was refluxed for 45 min. Single crystals suitable for X-ray analysis were obtained by slow evaporation of the solution of the complexes in methanol.

C, H and N microanalyses were carried out with Fison Carlo Erba EA 1108.
Anal. Calcd for complex $Cu_4O_2C_{36}H_{31}N_8Cl_6$ (1): C, 38.95; H, 2.82; N, 10.09 Found C, 38.70; H, 2.78; N, 9.89.
Calcd. for complex $Cu_4O_{5.2}C_{20}H_{20.4}N_4Cl_6$ (2); C, 27.71; H, 2.37; N, 6.46 Found C, 27.69; H, 2.11; N, 6.25.

Calcd. for complex $Cu_4O_4C_{19}H_{36}N_8Cl_6$ (3); C, 25.15; H, 4.00; N, 12.34. Found C, 24.99; H, 3.87; N, 12.07.

Magnetic Measurement

The magnetic susceptibility of (1), (2) and (3) complexes were determined over the temperature range 5-300K by using a SQUID magnetometer (QUANTUM DESING MODEL MPMS-XL5 instrument) with a field of 0.1 T. The data were corrected to compensate for the diamagnetism of the constituent atoms using the Pascal's constant, and also corrected for the temperature independent paramagnetism 60 x10^{-6} cm-3mol^{-1} per copper (II).

Antibacterial activity

Bacterial strains used in this study are property of the Molecular Bacteriology Laboratory collection (Universidad Diego Portales). *Staphylococcus aureus* AB68 *Streprococcus sp*. SJD1025, *Acinetobacter baumannii* PL9060, *Bacillus cereus* GCA250, *Citrobacter sp., Proteus vulgaris*, *Klebsiella pneumoniae* RYC492 and *Shigella flexnerii* strains were isolated from clinical samples while the Escherichia coli BL21 strain was obtained from Novagen Inc. and Escherichia coli DH5a strain was obtained from Gibco BRL.

Bacteria were grown in Mueller Hinton Agar (Difco) as Mueller Hinton broth (Difco) for 16 to 24 h at 37 ºC in an incubator.

The in vitro antibacterial activity of the complexes was tested using the paper disc diffusion method [10] and quantitative antibacterial activity was determined using minimum inhibitory concentration method (MIC) [11].

RESULTS AND DISCUSSION

In the complexes studied here, the copper (II) atoms are configured in a tetrahedron around the μ4-bridging central oxygen. Each one of the four copper atoms is bridged by μ2-halides. In the complexes the Cu_4OCl_6 nucleus is highly symmetric.

The major differences found in the complexes are due to the external ligands attached to copper: three PhIm ligands and one chloride ion in (1), four PyNO ligands in (2) and four MeIm ligands in (3). Figures 1 to 3 show individual ellipsoid plots of the three compounds.
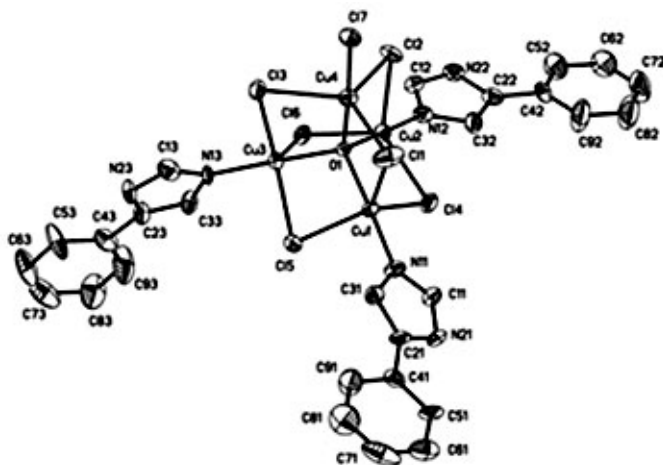

Figure 1: Molecular Structure of [Cu_4OCl_6)Cl (PhIm)$_3$] (HPhIm)•H_2O (1).
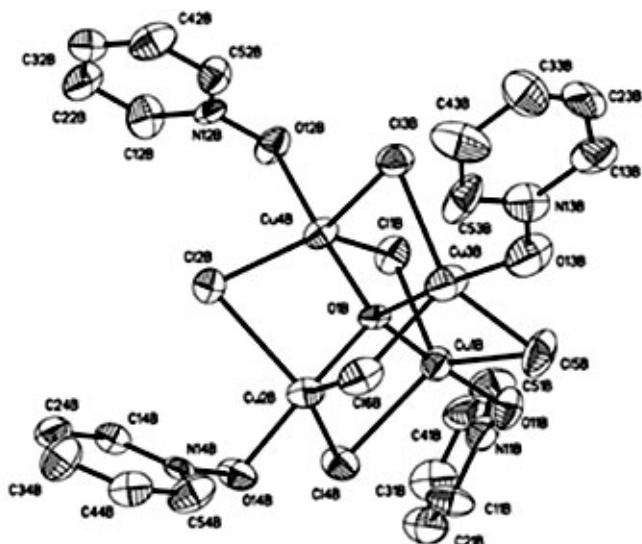
Figure 2: Molecular Structure of $[(Cu_4OCl_6)(PyNO)_4] \cdot 1/5(H_2O)$ (2).

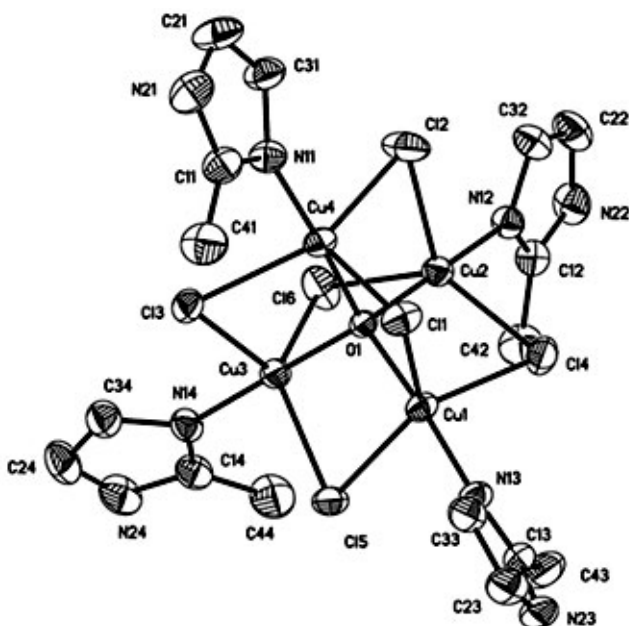**Figure 3**: Molecular Structure of $[(Cu_4OCl_6)(MeIm)_4] \cdot 3(CH_3OH)$ (3).

In all three structures the four copper atoms bound to O1 define an almost perfect tetrahedron while each chlorine atom coordinates to two different Cu_i, Cu_j centers, laying at the bisectors of the corresponding Cu_i-O1-Cu_j angles. The symmetry of this almost tetrahedral arrangement C_{3v}, where the axe 3 is defined by the Cu4 - O1 distance and the vertical plane by the Cu4, O1 and Cu1 atoms in the case of (1). The Cl6 array thus conformed defines a nearly perfect octahedron centered at, though beyond bonding distance to, the central oxygen O1 and interpenetrating the copper tetrahedron. The slight deviation of each core from a regular geometry is responsible of the different magnetic properties of each compound, as we shall try to demonstrate below. The detailed discussion of the X-ray crystal structures, data collection, structure solution, and refinement of these complexes can be found in reference [12].

The coordination geometry around each metal center is a irregular bi-pyramid, where the percentage trigonal distortions from the square pyramidal geometry of the atomic arrangement around the four Cu (II) atoms are t ranging between 74-87 % for (1), 62-85 % for (2) and 69-82 % for (3) [13].

The complexes were characterized on the bases of magnetic measurement. Variable temperature (5-300K) magnetic susceptibility data were collected for a polycrystalline sample of compounds (1), (2) and (3) in a 0.1T field.

The magnetic properties of the tetrameric complexes under the form of the χ_{MT} product versus T plots (cM being molar magnetic susceptibility per tetrameric molecule and T the absolute temperature) are shown in Fig. (4).
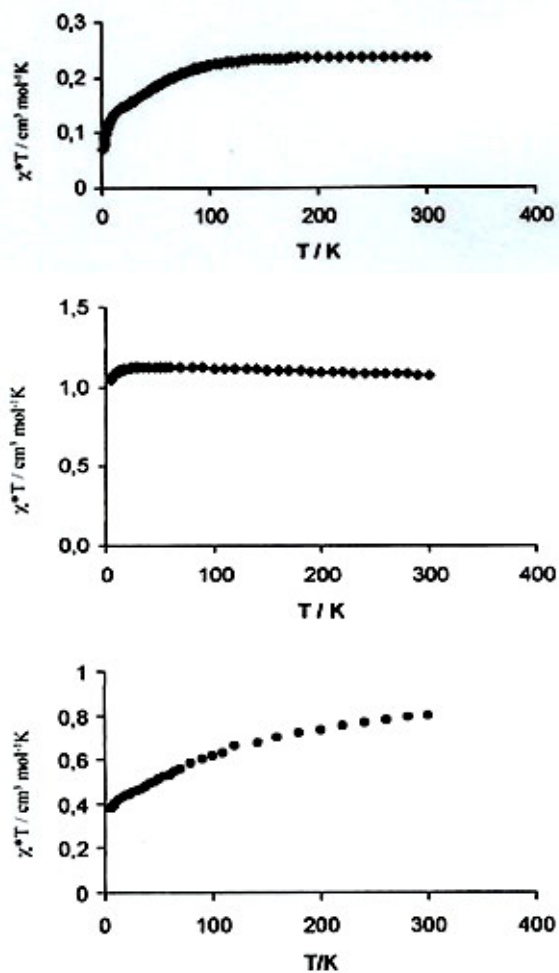

Figure 4: Temperature dependence of the χ_{MT} product for (1), (2) and (3) complexes.

For the complex $[(Cu_4OCl_6)Cl(PhIm)_3] \cdot (HPhIm)H_2O$ (1), the data values in the 40-300K range are indeed well-fitted by a Curie-Weiss law, C= 0.25 and q= -16.94K.

The χ_{MT} product remains constant during cooling from room temperature to 150 K and it decreases slowly at lower temperature reaching minimum value of 0.114 cm^3 mol^{-1} K.

At 300K, χ_{MT} is 0.235 cm-3 mol^{-1} K which corresponds to an effective magnetic moment (meff) of 1.37 MB. This value is smaller than the expected for four independent copper (II) ions (meff= 3.46 MB).

For the complex $[(Cu_4OCl_6)(PyNO)_4] \cdot 1/5(H_2O)$ (2) the data obey the Curie –Weiss law and a least-squares calculation of C and q (the Curie Weiss constant) using measurements in the whole temperature range resulted in C=1.084 cm^3 mol^{-1} and q= 1.20K. The low positive value

of q is indicative of a weak ferromagnetic interaction between tetrameric compounds. In this case, the χ_{MT} product decreases slowly from 1.078 to 1.066 cm-3 mol^{-1} K between 300 and 6 K.

For the complex $[(Cu_4OCl_6)(MeIm)_4] \cdot 3(CH_3OH)$ (3) the magnetic susceptibility data obey the Curie-Weiss law, using measurements in the 45-300 temperature range resulted in C= 0.905 cm^3 mol^{-1} and θ= -44.14 K. The negative value of θ is indicative of an antiferromagnetic interaction between complexes.

The χ_{MT} product at 300K is equal to 0.800 cm-3 mol^{-1} K, this value is lower than the theoretical value for four uncoupled copper (II) ions, and gradually decreases to 0.376 cm-3 mol^{-1} K at 6 K.

The tetrameric copper complexes have been classified in three classes in relation to the existence of a maximum in the temperature dependence of the effective magnetic moment [14,15]. In class I, the magnetic moments decrease monotonically with decreasing temperature, and in class II and class III, the magnetic moment passes through a maximum and then decreases at lower temperatures. (Class II complexes have a strong maximum, while class III complexes have a slight maximum in the m vs T curve).

In the complexes described in this paper the distortion from the idealized tetrahedral geometry permits us to describe the cluster in the C3v symmetry group.

The Cu-Cu distances can be classified in two groups: a group of short distances, and a second group of the large distance.

For the complex (1) the short distances are Cu(1)-Cu(2)= 3.066 Å, Cu(1)- Cu(3)= 3.094 Å, Cu (2)-Cu(4)= 3.118 Å, and large distances are Cu(1)-Cu(4)= 3.127 Å, Cu(2)-Cu(3)= 3.156 Å, and Cu(3)-Cu(4)= 3.140 Å.

For the complex (3) the short distances are Cu(1)-Cu(2)= 3.114Å, Cu(2)- Cu(4)= 3.094 Å, Cu (1)-Cu(3)= 3.115 Å, and large distances are Cu(1)-Cu(3)= 3.138 Å , Cu(3)-Cu(4)= 3.143 Å, and Cu(1)-Cu(4)= 3.135 Å.

The magnetic susceptibility under C3v symmetry is given by the expression derived from the Heisenberg spin operator $\hat{H} = -\sum_i J_i \hat{S}_i \hat{S}_i$, the exchange integral J is negative for antiferromagnetic interaction and positive for ferromagnetic interaction [16].

$$\chi_m = \frac{N\beta^2 g^2}{kT} \frac{\{0 + 4\exp[-(3J_1 + J_2)/2kT] + 2\exp[-2J_2/kT]\}}{\{5 + 6\exp[-(3J_1 + J_2)/2kT] + 3\exp[-2J_2/kT] + 2\exp[-3(J_1 + J_2)/2kT]\}}$$

In this equation J_1 and J_2 correspond to exchange constants associated to short and long distances respectively. The C3v coupling is shown in scheme 1
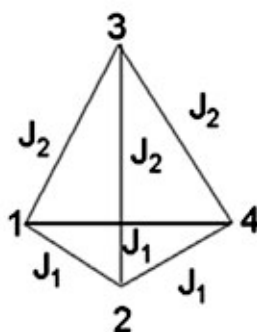
Scheme1

The result of this fit, which is displayed as the solid lines in figure 5 yields values of J_1= 0.15 cm^{-1}, J_2= -1.71 cm^{-1} for (1) and J_1= -0.52 cm^{-1} and J_2= -5.3 cm^{-1} for (3) with an agreement factor of R= 3.08 X 10^{-4} for (1) and R= 1.10 X10^{-4} for (3) (R=: $\Sigma[(X_m)_{obs}-(X_m)calc]2/ \Sigma [(X_m)_{obs}]^2)$.
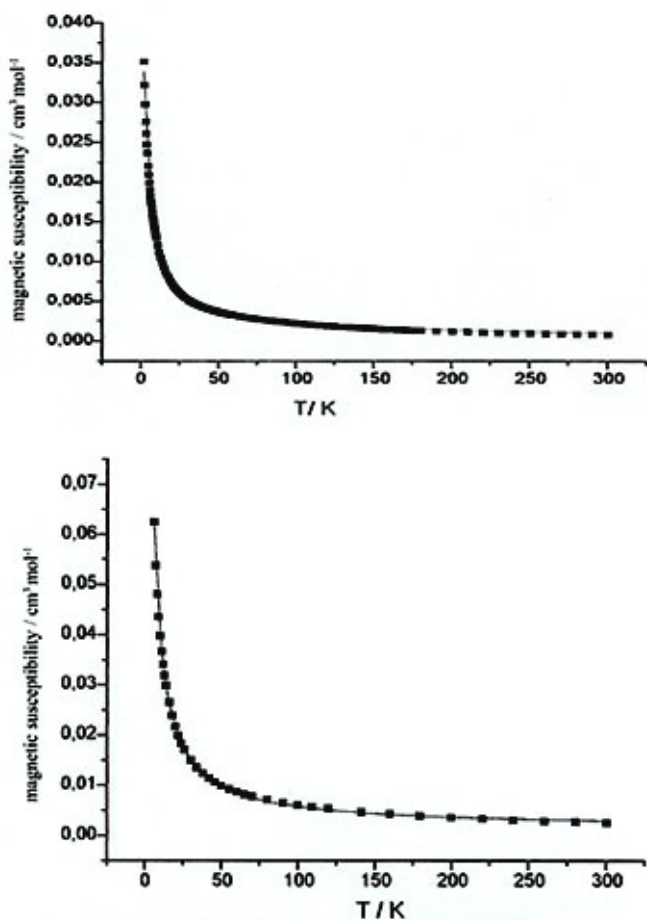

Figure 5: Temperature dependence of the magnetic susceptibility for (1) and (3). The solid lines correspond to the best fit with the model described in the text.

The Table 1 shows the antimicrobial activities of tetranuclear copper complexes synthesized in this work.

TABLE 1. Antibacterial activity of copper complexes

Bacteria	MIC (µg/mL)*		
	[Cu₄OCl₆(Phim)₄](HPhim)₄H₂O (1)	[Cu₄OCl₆(Py-NO)₄]¹/₂(H₂O) (2)	[Cu₄OCl₆(MeIm)₄]3CH₃OH (3)
Staphylococcus aureus AB68	80	>1000	>1000
Streptococcus sp. SJD1025	125	>1000	>1000
Bacillus sp. UDP1	75	>1000	>1000
Bacillus cereus GCA250	31.3	>1000	>1000
Acinetobacter baumannii PL9060	70	250	125
Escherichia coli BL21	62.5	75	75
Escherichia coli MC4100	62.5	75	70
Klebsiella pneumoniae RYC492	70	62.5	62.5
Citrobacter sp.	125	125	250
Salmonella enterica Tiphymurium LT2	250	125	125
Shigella flexnerii	250	500	500

* Number of assays = 3

The complex (1) shows antibacterial activity against all bacteria tested, β. *cereus* is the most sensitive strain against this complex within Gram positive bacteria studied. The complexes (2) and (3) presented activity against Gram negative bacteria only. From Gram negative bacteria tested, *E. coli* and *K. pneumoniae* presented a greater sensitivity to three copper complexes and *S. flexnerii* presented a smaller sensitivity.

Under the same conditions the free ligands (4-phenilimidazole, 2-methylimidazole and pyridine-N-oxide) and DMSO were inactive.

Although no satisfactory results were obtained for the compound (2), we believe that the model used here provide the appropriate description of the magnetic properties of the copper (II) complexes. This model retains the know structural features and also accurate reproduce the data

In conclusion, we can indicate that the polynuclear copper complexes studied here have weak Cu-Cu magnetic interactions, as seen by the calculated 2J values, and the lack maximum in the curve χT vs T.

The complexes showed antibacterial activity mainly over Gram negative bacteria, with exception of the complex (1) that showed activity against both Gram positive and Gram negative bacteria. The difference in the antibacterial activity of copper complexes studied in this work probably is associated to ligand type and its space distribution around the complex core, since the core of the three complexes has a similar structure.

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