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## Cubane-like tetranuclear Cu(II) complexes bearing a $Cu_4O_4$ core: crystal structure, magnetic properties, DFT calculations and phenoxazinone synthase like activity

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In the present work, two new copper complexes **3a** and **3b** with  $Cu_4O_4$  cubane core are reported. Both complexes are obtained by means of the *in situ* conversion of the imine functionality of a Schiff's base ligand **1a** [(*E*)-4-chloro-2-((thiazol-2-ylimino)methyl)phenol] and **1b** [(*E*)-4-bromo-2-((thiazol-2-ylimino)methyl)phenol)] into an amino alcohol **2a** (4-chloro-2-(hydroxy(thiazol-2-ylamino)methyl)phenol) and **2b** (4-bromo-2-(hydroxy(thiazol-2-ylamino)methyl)phenol), respectively. The ligand transformation may be metal assisted and the generated ligands show an interesting mode of coordination, in which the alkoxo-O atom binds in a  $\mu^3$ -manner connecting simultaneously three copper centers and forming a  $Cu_4O_4$  cubane core. First analysis of single crystal X-ray diffraction studies reveals that both molecules possess a [4+2] cubane-type core, and low temperature magnetic measurements show antiferromagnetic behaviour, in agreement with DFT calculations. However, the best fit and DFT calculations point out three pairs of coupling constants, more coherent with a [2+2+2] situation, in accordance with fine analysis of structural data. Finally, phenoxazinone synthase activity have been measured for both molecules, finding  $k_{cat} = 86.3 h^{-1}$  for the chloride derivative copper(II) complex in methanol, whereas the bromide derivative copper(II) complex displays  $k_{cat} = 3.4026 \times 10^2 h^{-1}$  and 10.289 x  $10^2 h^{-1}$  in methanol and DMSO, respectively.

#### Introduction

High nuclearity transition metal complexes have attracted the scientific community owing to the diversity of their structural features and potential application in a high number of fields, both in material and biological sciences, such as molecular magnetism,<sup>1</sup> bioinorganic chemistry<sup>2</sup> (as mimics for multicentred metal-containing active sites) and catalysis.<sup>3</sup> Among them, tetranuclear Cu(II) complexes with cubane core draw special attention due to their magnetic properties,<sup>4</sup> as well as because they represent model system for metalloenzymes.<sup>5</sup>

The magnetochemistry of the  $Cu_4O_4$  cubane core with hydroxo, alkoxo and phenoxo bridges has been explored under experimental and theoretical approaches.<sup>6</sup> Inherent structural complexity in  $Cu_4O_4$  cubanes is manifested by two different classifications proposed by R. Mergehenn et. al.<sup>7</sup> and Ruiz et. al.6b depending on the relative values of the measured Cu-O or Cu-Cu, respectively, in-core distances. The first proposal classified the Cu<sub>4</sub>O<sub>4</sub> core as Type I (four long Cu-O distances between two dinuclear subunits) and Type II (long Cu-O distances within each dinuclear subunit). The second one is based on the Cu-Cu distances and distinguishes three categories: 1) [2+4] with two short and four long distances, 2) [4+2] four short and two long and 3) [6+0] six similar Cu-Cu distances. With these various types of structures no simple magneto-structural correlation is available since small changes in the structure carry significant changes in the magnetic behaviour.

Polynuclear copper systems are also found in biological system in the form of oxidase enzymes.<sup>8</sup> This type of metalloenzymes developed by nature can activate molecular oxygen to undergo spin forbidden interactions with organic substrates towards biochemical oxidation processes.<sup>9</sup> For instance, multicopper oxidases catalyze the reduction of molecular oxygen through a four-electron oxidation process by a reducing substrate. Among them, phenoxazinone synthase (PHS)<sup>10</sup> catalyses the oxidative coupling of two molecules of a substituted 2-aminophenol to the phenoxazinone

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Electronic Supplementary Information (ESI) available: Crystal refinement parameters (Table S1), selected bond lengths and angles (Table S2), change in spectral pattern (Figure S1), rate vs substrate concentration and Lineweaver-Burk plots (Figure S2),  $\chi$ T vs T dependence (Figure S5), and Cartesian coordinates of the theoretical calculated model structures (Table S3). See DOI: 10.1039/x0xx00000x

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chromophore at the final step in the biosynthesis of the potent antineoplastic agent actinomycin D. Unlike other oxidase enzymes, which catalyse only one-electron oxidation processes, this is a six-electron oxidation process, actually a combination of three consecutive two-electron oxidations. PHS exists as two oligomeric forms: a less active dimer and a highly active hexamer. Structure of hexameric PHS, as determined by single crystal X-ray diffraction<sup>11</sup> confirms the presence of five Cu(II) centres in a unit cell. Like other Cu oxidases, hexameric PHS possesses three copper binding motifs: one type 1 (blue), one type 2 (normal), and one binuclear type 3 centers. Thus the active site of hexameric PHS contains a tetranuclear Cu<sub>4</sub> motif and a fifth copper atom remains bound at a loop, establishing interactions between the subunits that stabilizes the hexamer and hence renders an additional structural role. However, there are a limited number<sup>12</sup> of model systems screened for phenoxazinone synthase activity. Therefore, the synthesis and study of polynuclear Cu(II) complexes may enable the exploration of the PHS activity unveiling a more clear redox mechanism and thus allowing to develop biomimetic catalysis strategies for new oxidation processes.

The supramolecular approach to synthesize polynuclear metal complexes is undoubtedly the most rational way. This has been aesthetically developed by M. Fujita et. al.<sup>13</sup> by the use of several strategies in designing the ligand *e.g.*, the donor atoms position and orientation that forbids coordination to the same metal or the use of suitable ancillary ligands (N<sub>3</sub><sup>-</sup>. SCN<sup>-</sup>, RCOO<sup>-</sup> etc.). However, the designed assembly strategy suffers from certain limitations as it can make incorrect predictions and, more importantly, it limits the horizons of the new molecular architecture.

Polynuclear metal complexes with improved magnetic properties were not obtained by designed assembly. In 1993 the first single molecule magnets  $[Mn_{12}O_{12}(O_2CR)_{16}(H_2O)_4]$  (R = Me or Ph) were made by accident from reaction involving permanganate and a Mn(III) triangle.<sup>14</sup> From then on, this approach gained popularity as it proved to be successful in obtaining large assemblies of metal ions in a variety of structures. This new approach is known as serendipitous assembly and can result in the formation of structures that cannot be imagined at synthetic level. Metal assisted serendipity is reported by S. P. Perlepes et. al. in a number of cases.<sup>15</sup> The ligand is transformed in situ and coordinates the metal producing an unexpected complex. In the presence of a base, a ketone is transformed into a hemiketal or gem-diol and an alkoxo-bridged complex is formed.<sup>15a-b</sup> Metal-assisted in situ conversion of oxime into carboxylic acid functionality is also known.15a

In the present work we report two new copper complexes bearing a  $Cu_4O_4$  cubane core with an antiferromagnetic behaviour and some phenoxazinone synthase activity. Both complexes are obtained by means of the *in situ* conversion of the imine functionality of a Schiff's base pro-ligand into an amino alcohol, presumably with metal assisted ligand transformation.

#### **Results and discussion**

#### Synthetic procedure.

Both pro-ligands 1a,b [X: Cl (a), Br (b)] were synthesized in a similar way by condensation of 2-aminothiazole with the corresponding salicylaldehydes (Scheme 1) in moderate yields. The resulting products were purified in silicagel column with 25-30% DCM/hexane mixture as eluent. The Schiff base proligands were characterized by spectroscopic techniques, one of them (1a) being also characterized by single crystal X-ray diffraction. In order to get high-nuclearity copper complexes 3, the complexation reaction was performed with equimolecular amounts of  $Cu(ClO_4)_2$ , the corresponding pro-ligand and a base (Et<sub>3</sub>N), used to deprotonate the phenolic hydroxyl groups. The reaction mixture was refluxed for 5 h and a green solid was separated. On analysing the single crystal X-ray diffraction data of the collected crystals, it turned out that the Schiff's base changed in situ into the chiral amino alcohol 2 through water addition to the imine bond (Scheme 1).



**Scheme 1.** Synthesis of the pro-ligand **1**, its Cu(II)-assisted *in situ* transformation into the protonated ligand **2** (=LH<sub>2</sub>) and complex **3** (=Cu<sub>4</sub>L<sub>4</sub>) formation.

#### Molecular Structure of 1a, 3a and 3b.

Single crystal X-ray diffraction studies were performed on **1a**, **3a** and **3b**. NMR and mass spectra were also coherent with the crystal structure determined for the Schiff base ligand **1a**, in which the imine bond (C7-N6) distance (Figure 1) is 1.293 Å, which supports its double bond nature.

Both complexes, **3a** (X=Cl) and **3b** (X=Br), contain the heteronuclear  $Cu_4O_4$  cubane-like structural motif and crystallize in the triclinic P-1 space group together with two DMF and two water molecules, therefore having the molecular formulas **3a**·2DMSO·2H<sub>2</sub>O and **3b**·2DMSO·2H<sub>2</sub>O. Molecular structures and the atom numbering scheme around the metal centres for both complexes are given in Figure 1. Crystal data and refinement parameters (Table S1), as well as bond lengths and angles around the metal centres (Table S2) are given in the ESI. The  $Cu_4O_4$  core consists of four alkoxo-bridged Cu(II) centres approximately arranged in a cuboid geometry of an alternating array of Cu and O atoms that occupy the corners of the cube (Figure 2). This structure could alternatively be seen as two interpenetrated  $Cu_4$  and  $O_4$  tetrahedrons.



**Figure 1.** Molecular structure of **1a** (top), **3a** (middle) and **3b** (bottom). Anisotropic displacement parameters are a 50% probability; hydrogen atoms and solvent molecules are omitted for **3a** and **3b** for clarity.

The chiral amino alcohol ligand **2**, formed *in situ* from Schiff's base pro-ligand **1**, behaves as a bideprotonated tridentate ligand with the alkoxo-O atom acting as a  $\mu^3$  donor, since it bridges three Cu(II) atoms at once in the cubane structure. Beyond the cubane structure, thiazol-N and phenoxide-O atoms collectively provide an additional NO donor environment for each copper ion. In both complexes, namely **3a** and **3b**, each Cu(II) centre is penta-coordinated showing an apparent (4+1) square pyramidal geometry. For a penta-

coordinated system, the *trigonality index*  $(\tau)^{16}$  is given by the relation  $\tau = (\alpha - \beta)/60$ , where  $\alpha$  and  $\beta$  are the two largest angles in the pyramid. Therefore, strictly speaking, for a square pyramid  $\tau = 0$ , and for a trigonal bipyramid  $\tau = 1$ . The obtained  $\tau$  values for the Cu centres (Table 1) indicate that the metal environment can be described as square pyramidal with a little distortion towards a trigonal bipyramidal geometry in both cases. Slight distortion between copper centres and the plane of the coordinated atoms around them could be attributed to the restrictions imposed by the tridentate ligands. The basal plane of each Cu(II) ion is coordinated by one thiazole nitrogen, one phenoxide-oxygen and two alkoxo-oxygen, whereas the axial position is occupied by a third alkoxooxygen. Observed Cu-N bond distances in the basal planes lie in the normal range of 1.965-1.983 Å. The equatorial Cu-O bonds at each Cu centre are shorter (ranging 1.897-1.995 Å) than the axial Cu-O bond (in the range 2.375-2.409 Å),<sup>17</sup> performing a final (4+1) coordination environment, which is at the origin of the high distortion observed for these structures. Similar trends in the axial and equatorial bond lengths in  $\mathsf{Cu}_4\mathsf{O}_4$ cubane cores have also been reported earlier.  $^{\ensuremath{^{18}}}$  The phenolic C-O distances in the complexes are slightly shorter (Table 1) than the ideal value of 1.35-1.37 Å, as expected for a coordinated catechol that could feature some semiquinonoid contribution.



Figure 2. Schematic Cu-O bond lengths (a) and Cu-O-Cu bond angles (b) of the cubane  $Cu_4O_4$  core for  $3a \cdot 2DMF \cdot 2H_2O$ .

**Table 1.** Trigonality index ( $\tau$ ) of the Cu atoms in the cubane core for each complex.

	3a·2DMF·2H <sub>2</sub> O	3b·2DMF·2H <sub>2</sub> O				
Cu1	0.003	0.010				
Cu2	0.019	0.053				
Cu3	0.026	0.030				
Cu4	0.022	0.010				

Each  $Cu_4O_4$  cubane exhibits both chiralities for the ligand **2**, two *R* and two *S* configurations, per cubane. Therefore, around each cubane, the ligands are arranged as *RSRS* making achiral the whole structure and, hence, the crystal.

Furthermore, analysis of the  $Cu_4O_4$  cubane core reveals that there are two short (Cu2-Cu3 and Cu3-Cu4 in **3a**, and Cu1-Cu4 and Cu3-Cu4 in **3b**), two medium (Cu1-Cu2 and Cu1-Cu4 in **3a**, and Cu1-Cu2 and Cu2-Cu3 in **3b**), and two long (Cu1-Cu3 and Cu2-Cu4 for both complexes) intermetallic distances (Table 2) which, therefore, more properly falls within a [2+2+2]  $Cu_4O_4$ 

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cubane structure category, beyond the classification of Ruiz et. al.<sup>6a</sup> It is noteworthy that complex **3b** has interchanged Cu2-Cu3 and Cu1-Cu4 from short to medium distances with respect to complex **3a** (Table 2). Both complexes, however, present roughly the same long distances Cu1-Cu3 and Cu2-Cu4.

Table 2. Non-bonding Cu…Cu distances (	(Å)	in the	C <sub>4</sub> O <sub>4</sub> core.
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	8	, , ,
	3a-2DMSO-2H <sub>2</sub> O	3b·2DMSO·2H <sub>2</sub> O
Cu1…Cu2	3.195	3.196
Cu1…Cu3	3.244	3.257
Cu1…Cu4	3.201	3.170
Cu2…Cu3	3.179	3.203
Cu2…Cu4	3.251	3.258
Cu3…Cu4	3.169	3.171

#### Electronic spectra of 3.

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Electronic absorption spectra of complexes **3a** and **3b** are, as expected, quite similar (Figure 3). Complex **3a** shows one intraligand transition at 313 nm, whereas complex **3b** displays two shoulders of intraligand nature at 310 and 345 nm. Another important feature in their absorption spectra is the phenolate to Cu(II) LMCT transition, which takes place at 406 and 410 nm for complex **3a** and **3b**, respectively. Furthermore, d-d transition bands are observed, respectively, at 700 and 678 nm for complexes **3a** and **3b**.



Electrochemistry of 3a and 3b.

Cyclic voltammograms (CV) and differential pulse voltammograms (DPV) were measured for complexes 3a and 3b at ambient temperature in DMF and DMSO medium, respectively, using tetraethylammonium perchlorate (TEAP) as supporting electrolyte. The measured potentials were referenced versus the ferrocenium/ferrocene (FcH<sup>++</sup>/FcH) redox couple. Both complexes show one guasi-reversible peak on cathodic scan (Figure 4). Complex 3a shows this reductive peak at -1.3 V, whereas complex 3b has the same peak at -1.0 V. This can be assigned to a Cu<sup>II</sup>/Cu<sup>I</sup> reduction process. Higher inductive -I effect of Cl over Br at the para position of the -OH group in the phenyl ring, restricts the reduction of Cu(II) to  $\mbox{Cu(I)}$  in case of  ${\bf 3a.}$  Scanning on the anodic side, a peak appeared at 0.5 V and 0.7 V, respectively, for complexes 3a and 3b, which can be attributed to the oxidation of the phenolic hydroxyl group to a phenoxyl radical.



**Figure 4.** Cyclic voltammogram of a 1 mM solution of complexes **3** with 0.1 M TEAP as supporting electrolyte. a) Complex **3a** in DMF (working electrode: Pt; sweep rate: 100 mV/s). b) Complex **3b** in DMSO (working electrode: glassy carbon; sweep rate: 20 mV/s).

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## Oxidation of 2-aminophenol and determination of the rate of formation of the phenoxazinone chromophore.

Catalytic behaviour of complex 3a was studied in MeOH, whereas complex 3b was screened in both MeOH and DMSO solutions. In MeOH the absorbance was monitored at 430 nm ( $\epsilon$  = 9095 M-1cm-1),<sup>19</sup> whereas for DMSO was followed at 435 nm ( $\epsilon$  = 23200 M-1cm-1).<sup>20</sup> Time dependent spectral profiles \_ for the catalytic study on complex 3a is shown in Figure S7, whereas for complex 3b the same is displayed in Figure 5 (in DMSO solvent) and Figure S9 (in MeOH solvent), respectively. The same experiment performed without catalyst under identical conditions did not show any significant growth of the band at the respective positions. For the kinetic study the initial rate method was followed. To determine the dependence of rate with the substrate (2-aminophenol, OAPH) concentration, a solution of a fixed concentration  $(1 \times 10^{-5} \text{ M})$ of complex 3 used as catalyst was treated with increasing concentrations of the substrate (from 20 to 200 eq) in a pseudofirst order environment under aerobic condition at 25 °C. For a particular catalyst-substrate mixture, time scans at the highest band position of the 2-aminophenoxazine-3-one chromophore were performed for 25 minutes. A linear regression was followed to determine the initial rate from the slope of the plot of the absorbance versus time. Plots of initial rate versus concentration of the substrate for 3a (in MeOH) are shown in Figure S8a, and those of 3b in Figure 6a (in DMSO) and Figure S10a (in MeOH). In both cases, a rate saturation kinetics is followed.



Figure 5. Change in the spectral pattern for complex 3b after addition of OAPH up to 4.5 h in DMSO.

The dependency of the saturation rate with the concentration of the substrate can be treated with a Michaelis–Menten approach by means of a Lineweaver–Burk plot (Figure S&b for **3a**, and Figure 6b for **3b** in DMSO and Figure S10b for **3b** in MeOH), which enables the calculation of all the kinetic parameters such as  $K_m$ ,  $V_{max}$  and  $k_{cat}$  (Table3). The turn-over number (TON) of the complex was calculated by dividing the value of  $V_{max}$  by the complex concentration.

**Table 3.** Kinetic parameters for the oxidation of 2-amino-phenol catalyzed by **3a** and **3b**.

	3a·2DMSO·2H <sub>2</sub> O	3b·2DMSO·2H <sub>2</sub> O	
Solvent	MeOH	MeOH	DMSO
V <sub>max</sub> (M·h⁻¹)	8.63x10 <sup>-4</sup>	3.40x10 <sup>-3</sup>	10.29x10 <sup>-3</sup>
K <sub>m</sub> (M)	18.28x10 <sup>-3</sup>	1.44x10 <sup>-2</sup>	4.16x10 <sup>-3</sup>
k <sub>cat</sub> (h⁻¹)	86.3	340.26	1028.9



**Figure 6.** a) Rate vs substrate concentration plot for the oxidation of 2-aminophenol in DMSO catalysed by **3b** at 25  $^{\circ}$ C. b) Lineweaver-Burk plot for the corresponding oxidation of 2-aminophenol.

Catalytic investigations with copper based model complexes for the oxidation of 2-amino phenol to phenoxazinone chromophore are very rare. Moreover, the catalytic turn over rate has not been determined in many of such studies.<sup>12</sup> In comparison to the available literature, the molecules under investigation in the present study show good to efficient catalytic activity for the aforementioned reaction.  $k_{cat}$  for **3a** is 86.3 h<sup>-1</sup> in methanol, whereas for **3b** the values are 340.26 h<sup>-1</sup> and 1028.9 h<sup>-1</sup> in methanol and dimethyl sulphoxide respectively. In past few years A. Panja et. al. have made

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significant contribution towards the detailed kinetic study of the PHS catalysis with manganese<sup>21</sup> and cobalt<sup>22</sup> based model systems. M. R. Maurya et. al reported<sup>23</sup> a copper complex for the PHS activity with  $k_{cat}$  values 29.7 and 131.5 h<sup>-1</sup> in solution and after anchoring onto a chloromethylated polystyrene surface, respectively. However, from the current kinetic study the molecules in the present study can be considered as efficient catalysts for this purpose. The higher rate of **3b** over **3a** may be explained on the basis of the above mentioned higher -I effect of -Cl over -Br at the *para* position of the -OH group in the phenyl ring, which restricts the metal to undergo reduction to Cu(I). Since the mechanism requires the reduction of Cu(II) to Cu(I) in the intermediate steps, the bromo derivative with relative lower -I effect shows more catalytic efficiency.

#### Magnetic Susceptibility Measurements.

Variable-temperature magnetic susceptibility measurements were carried out in the temperature range of 2-250 K in an applied magnetic field of 1 kOe on polycrystalline samples of  $3a \cdot 2DMF \cdot 2H_2O$  (complex 3a) and  $3b \cdot 2DMF \cdot 2H_2O$  (complex 3b) with a SQUID magnetometer. The temperature dependence of the molar susceptibility ( $\chi$ ) and the product of the susceptibility and the temperature ( $\chi$ T) for both complexes are displayed in Figure 7 (complex 3b) and Figure S11 (complex 3a, in the ESI).



**Figure 7.** Temperature dependence of  $\chi$  (o experimental data, — best fit) and  $\chi$ T (o experimental data, — best fit) for complex **3b**:  $J_1 = -40.6 \text{ cm}^{-1}$ ,  $J'_1 = -16.3 \text{ cm}^{-1}$ ,  $J_2 = +5.0 \text{ cm}^{-1}$ , g =2.17, TIP = 60 10<sup>-6</sup> per Cu,  $\rho = 0.096$  with  $R_{\chi T} = 8.9 \text{ 10}^{-5}$  and  $R_{\chi} =$ 3.1 10<sup>-3</sup>.

The value of the  $\chi$ T at 250 K is 1.6 cm<sup>3</sup>mol<sup>-1</sup>K for complex **3a** and 1.52 for complex **3b**. These values are just slightly higher than those expected for four uncoupled S = 1/2 spins ( $\chi$ T = 1.5 cm<sup>3</sup>mol<sup>-1</sup>K with g = 2.0). For both complexes, upon cooling, the  $\chi$ T value decreases continuously for both complexes from room temperature to 2 K indicating the predominance of

antiferromagnetic (AF) interactions, which was confirmed for **3b**·2DMF·2H<sub>2</sub>O by the presence of a maximum at 24 K for the  $\chi$  vs T curve. The increasing  $\chi$  value at low temperature could indicate the presence of paramagnetic impurities coming from monomeric complexes. For **3a**·2DMF·2H<sub>2</sub>O, the susceptibility increases continuously upon cooling suggesting the presence of a higher amount of paramagnetic impurities that mask the expected decrease.

We first tried to fit the magnetic data of complex **3b** using two different coupling constants,  $J_1$  and  $J_2$ , logically corresponding to the 4 shortest Cu-Cu distances (1-2, 1-4, 2-3, 3-4:  $J_1$ ) and 2 longest (1-3, 2-4:  $J_2$ ), according to the classification from Ruiz et al.<sup>6b</sup> The exchange pathways with the orientation of the orbitals are represented in Figure 8 (a) for  $J_1$  and (b) for  $J_2$ . Therefore, the magnetic susceptibility could be fitted according to equation **(1)**:

$$\chi_{exp} = (1 - \rho) \cdot \chi_{cubane} + \rho \cdot \chi_{s=\frac{1}{2}} + TIP$$
 (1)

where  $\chi_{s=\frac{1}{2}}$  is the susceptibility of a S=1/2 impurity,  $\rho$  is the amount of these impurity, *TIP* is the temperature independent paramagnetism and  $\chi_{cubane}$  results from the full diagonalization of the matrix arising from the spin Hamiltonian (2):

$$\mathbf{H} = -J_{1} \cdot \left( \hat{S}_{Cu1} \cdot \hat{S}_{Cu2} + \hat{S}_{Cu2} \cdot \hat{S}_{Cu3} + \hat{S}_{Cu1} \cdot \hat{S}_{Cu4} + \hat{S}_{Cu3} \cdot \hat{S}_{Cu4} \right) - J_{2} \cdot \left( \hat{S}_{Cu1} \cdot \hat{S}_{Cu3} + \hat{S}_{Cu2} \cdot \hat{S}_{Cu4} \right) \quad (2)$$

The best fit leads to  $J_1 = -26.9 \text{ cm}^{-1}$ ,  $J_2 = -20.0 \text{ cm}^{-1}$ , g = 2.22, TIP = 60 10<sup>-6</sup> per Cu,  $\rho = 0.095$  with  $R_{\chi T} = 1.5 10^{-4}$  and  $R_{\chi} = 8.7 10^{-3}$ 



**Figure 8**: Relative orientation of the Cu orbitals involved in the exchange pathway in 3a and 3b

As had been done for hydroxo- and alkoxo-bridged dinuclear complexes,<sup>24</sup> a great effort has been made to find magnetostructural correlations for the Cu<sub>4</sub>O<sub>4</sub> core.<sup>6c,25</sup> The  $J_1$  coupling constant corresponds to the shortest Cu-Cu distances with three short (~1.97 Å) and one long (~2.40 Å) Cu-O distances. In this case the overlap of the orbitals of the two coppers that are involved in the exchange pathway appears only in one bridge (scheme 2a).

For Tercero et *al.*, this leads to weak ferro or antiferro coupling, the sign of the coupling being correlated with the exchange pathway displaying the shortest Cu-O distances.<sup>6c</sup> For complex **3a**, the pathway displaying the shortest Cu-O distances is associated with a Cu-O-Cu angle of *ca*. 108.9°. This value is larger than 104° which is considered as the boundary between ferromagnetic (angle < 104°) and antiferromagnetic

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coupling. The  $J_1$  = -26.9 cm<sup>-1</sup> value extracted from the fit is in agreement with this correlation.

For  $J_2$ , none of the bridges show the possibility of an overlap of the orbitals containing the unpaired electrons. This configuration should lead to a weak ferromagnetic (F)  $^{6c,26}$  coupling instead of the antiferromagnetic (AF) coupling that is deduced from the fitting process.

However, a ferromagnetic behaviour naturally arises on considering a three-*J* isotropic spin Hamiltonian, which (as indicated by DFT calculations, see below) describes better this Cu<sub>4</sub> cubane-like system that could, indeed, be considered as belonging to a [2+2+2] class: with Cu1-Cu3 and Cu2-Cu4 being the longest distances ( $J_2$ ), Cu<sub>1</sub>-Cu<sub>2</sub> and Cu<sub>1</sub>-Cu<sub>4</sub> medium distances ( $J_1$ ) and Cu2-Cu3 and Cu3-Cu4 shortest distances ( $J'_1$ ).

Yet, the use of spin Hamiltonian (3) leads to a better fit for the magnetic susceptibility of complex 3b (Figure 7) with a positive value (ferromagnetic coupling) for  $J_2$ :  $J_1 = -40.6 \text{ cm}^{-1}$ ,  $J'_1 = -16.3 \text{ cm}^{-1}$ ,  $J_2 = +5.0 \text{ cm}^{-1}$ , g = 2.17, TIP = 60  $10^{-6}$  per Cu,  $\rho = 0.096$  with  $R_{\chi T} = 8.9 \, 10^{-5}$  and  $R_{\chi} = 3.1 \, 10^{-3}$ .

$$\mathbf{H} = -J_{1} \cdot \left( \hat{S}_{Cu1} \cdot \hat{S}_{Cu2} + \hat{S}_{Cu1} \cdot \hat{S}_{Cu4} \right) - J_{1}' \left( \hat{S}_{Cu2} \cdot \hat{S}_{Cu3} + \hat{S}_{Cu3} \cdot \hat{S}_{Cu4} \right) - J_{2} \cdot \left( \hat{S}_{Cu1} \cdot \hat{S}_{Cu3} + \hat{S}_{Cu2} \cdot \hat{S}_{Cu4} \right)$$
(3)

Since the geometry is quite similar in both complexes, we used the same three-*J* isotropic spin Hamiltonian for complex **3a**, for which the best fit (see Figure S3 in the ESI) was obtained for  $J_1$ = -36.4 cm<sup>-1</sup>,  $J'_1$  = -8.0 cm<sup>-1</sup>,  $J_2$  = +6.7 cm<sup>-1</sup>, g = 2.23, TIP = 60 10<sup>-6</sup> per Cu,  $\rho$  = 0.23 with  $R_{\chi T}$  = 9 10<sup>-5</sup> and  $R_{\chi}$  = 6.7 10<sup>-3</sup>. As expected, the values of the magnetic coupling constants are rather similar in both complexes, also taking into account the uncertainty caused by the higher amount of paramagnetic impurity calculated for complex **3a**.

#### Theoretical DFT calculations.

In order to confirm the magnetic behaviour found in complexes **3a** and **3b**, density functional theory (DFT) calculations were performed. For the sake of reducing the computational cost, models (namely **3a-model** and **3b-model**) built from the corresponding crystal structures by changing O-

containing molecular fragments by MeO and N ones by NH<sub>3</sub> were used (Figure 9). Solvent molecules were discarded (as usual) in the calculations.<sup>27</sup> The approach used to determine the exchange coupling constants for polynuclear complexes has been described in detail elsewhere.<sup>6b,26</sup> Each Cu(II) cation has two basal and one apical oxygen atom belonging to the  $Cu_4O_4$  cubane scaffold. Since the magnetic orbitals are positioned at the basal copper plane, the apical oxygen breaks the magnetic pathway, but the remaining two basal oxygen atoms are connected to one apical and one basal copper atom. Therefore, for each Cu-Cu pair, there are two basal-basal exchange pathways that allow transmitting the magnetic interaction (Figure 9). Nevertheless, the magnetic superexchange is broken for Cu1-Cu3 and Cu2-Cu4 pairs that present just two axial-basal oxygen bridges. Therefore, we expect a F (ferromagnetic) behaviour for these two magnetic pathways (represented by  $J_4$  and  $J_5$  respectively, see Figure 9) due to the orthogonality of the interacting magnetic orbitals.<sup>28</sup> To calculate  $nJ_i$  exchange coupling constants in a polynuclear complex, at least n + 1 energy calculations on different spin configurations must be performed, that correspond to singledeterminant Kohn–Sham solutions.<sup>29b</sup> Therefore, since strictly both complexes are not symmetric, eight calculations for the eight possible broken-symmetry spin states (i.e. a single quintuplet (high spin, + + + + HS, situation), four triplets (medium spin, - + + + MS1, + - + + MS2, + + - + MS3 and + + + -MS4) and three singlets (low spin, + + - - LS1, + - + - LS2 and + -- + LS3)) are convenient (seven calculations are mandatory always including the HS configuration) to be performed in order to obtain the values of the six possible exchange pathways for each complex (Figure 9). The corresponding values for the  $J_i$  constant set were obtained by a least-square fit-process from the energy (without spin projection)<sup>29a</sup> found for the above mentioned spin configurations (see SI).

As mentioned before, it should be pointed out that a [4+2] classification could not be a good approach. Instead, it seems more appropriate to talk about [2+2+2] cubanes with short, medium and long distances (Figure 9), and there arise the pairing of the coupling constant values.

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Figure 9. Left to right and up to down: Distance pairing, theoretical J values, spin densities (for the lowest-energy brokensymmetry state), available magnetic pathways for each Cu(II) ion, the J scheme used in the calculations, the axial-axial Cu1-Cu3 or Cu2-Cu4 ferromagnetic interaction, and the J vs theta ( $\vartheta$ ) correlation.

Calculated coupling constants are in the order of magnitude and same sign of those obtained experimentally and, therefore, three different pairs of values were found. From calculations, it is also possible to assign which value correspond to each Cu-Cu pair (Figure 9). One could erroneously infer that there is a correlation between intermetallic distances and magnetic exchange coupling values but this is not true: for example, the highest antiferromagnetic (AF) values correspond to medium distances in complex 3b, where J values are quite different. On the other hand, in complex **3a**, J values are almost the same for a medium and a short distance. Short distances correlate, apparently, with small AF values and, therefore, long distances should exhibit the highest AF values in both cases. Nevertheless they actually correspond to ferromagnetic ones, as predicted above by the

axial-axial relationship between the metallic centres, following the order medium < short < long. Thus, distances should never be used as the key parameter to establish any magnetostructural correlation. Although the analysis of the magnetostructural data for Cu<sub>4</sub>O<sub>4</sub> cubane complexes has allowed the understanding of the main structural factors that govern the magnetic exchange coupling in this type of system, 6d,23a no simple magneto-structural correlations could be established for them. This means that it is not only a question of long and short Cu-Cu distances, but other parameters apply influencing the magnetic behaviour towards a more complex situation. Thus, since they are actually angles the parameters closely related to an effective orbital overlap (through the oxygen atoms of the cubane scaffold), which in turn is related to an enhanced AF behaviour, maybe some correlation could be **Dalton Transactions Accepted Manu** 

found between the Cu-O-Cu angles ( $\vartheta$ ) for the basal-basal exchange pathways and the calculated negative (AF) *J* values. Yet, Figure 9 shows a fair correlation for these two variables. In this context, the AF coupling increases with the  $\vartheta$  value. Ferromagnetic values are out of this plot since they are not correlated: the reason for the F behaviour encountered is not the angle value (about 96-97°), but the absence of magnetic exchange for Cu1-Cu3 and Cu2-Cu4 owing to the presence of just axial pathways between these metallic centres. Thus, the small angle values exhibited are due to the parallel disposition of both neighbour axial coordinations (Figure 9).

DFT calculations also revealed that, as expected, the main spin density is located at the metal ions since they are the magnetic centres, the rest of spin density being delocalized towards the directly attached O and N atoms. Since the spin density is quite similar in both complexes, Figure 8 depicts that of complex **3b**-**model** as an example along with a table indicating the most relevant atoms supporting a non-negligible spin density value (in electrons) for both complexes.

#### Conclusions

Serendipitous assembly of four copper atoms have been successfully achieved from the condensation of a Schiff base with  $Cu(ClO_4)_2$ . *In situ* transformation of an imine functionality into an amino alcohol leads to the formation of a tetranuclear  $Cu_4O_4$  cubane-like scaffold. Single crystal X-ray diffraction analysis reveals a [4+2] cubane-type structure. However a fine analysis points towards a [2+2+2] cubane core which is supported by the best fitting of the low temperature magnetic susceptibility data and DFT calculations carried out on models from the crystal structures. A fair magneto-structural correlation could be stablished between the calculated *J* values and the  $\vartheta$  angle (Cu-O-Cu). From the spin density it could be pointed out the AF nature of the magnetic interaction in these kinds of complexes.

Both complexes have close structural features to those of naturally occurring multicopper oxidase phenoxiazinone synthase. Evaluation of the catalytic activity of both complexes have been performed and reported here through the kinetic parameters. According to a recent review article by A. Mukherjee et. al.<sup>30</sup> there is only one reported  $Cu_4O_4$  cubane showing phenoxiazinone synthase-like activity.

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#### Experimental

#### Materials and Physical Measurements.

2-Aminothiazole, 5-bromo- and 5-chloro-salicylaldehyde were purchased from Sigma Aldrich whereas triethylamine was procured from Rankem. All solvents were A.R. grade and used as received for synthetic work. HPLC grade MeOH, MeCN, DMF, DMSO and DCM were used for spectroscopic and electrochemical studies. All the solvents were purchased from Spectrochem.  $Cu(ClO_4)_2$  was prepared according to the published procedure.<sup>31</sup> Tetraethylammonium perchlorate (TEAP), used for the electrochemical studies, was prepared according to the literature.<sup>32</sup> Caution! Perchlorate salts of metal ions are potentially explosive, only a small amount of the materials should be handled with care. Infrared spectra (IR) were recorded on model IR prestige 21, SHIMADZU Corporation (Japan) from 400 to 4000 cm<sup>-1</sup> in KBr pellet. UV/VIS spectra were recorded in PERKIN-ELMER (LAMBDA-750) UV/VIS/NIR spectrophotometer. <sup>1</sup>H-NMR spectra of ligand were recorded using a JEOL JNM-ECZ 400S/L1 400 MHz NMR spectrometer. ESI-MS analysis data were obtained by using JEOL JMS-700 spectrometer. Cyclic voltammogram was recorded in CHI6003E Potentiostat in a typical three electrode system: Pt or glassy carbon working electrode, Ag/AgCl reference electrode and Pt wire counter electrode. The ferrocene/ferrocenium couple was observed at  $E^0$  ( $\Delta Ep$ ) = 0.4 V (100 mV) under these experimental conditions. TEAP was used as supporting electrolyte.

Magnetic measurements were carried out with a MPMS 5 Quantum Design Magnetometer with an applied field of 1 kOe. The independence of the susceptibility value with regard to the applied field was checked at room temperature. The susceptibility data were corrected for the sample holder and the diamagnetic contributions as calculated from Pascal's constants tables.

#### Synthesis of the ligands.

(E)-4-Chloro-2-((thiazol-2-ylimino)methyl)phenol) (1a). А mixture of 2 aminothiazole (15.0 g, 15 mmol) and 5-chlorosalicylaldehyde (4.69 g, 15 mmol) was dissolved in 60 mL methanol and the reaction mixture was refluxed for 24 h under nitrogen atmosphere. A brown coloured solid was obtained that was then filtered under vacuum and washed with (2mL × 3) methanol. The crude solid was purified in Silica gel column (100-200 mesh). Pure yellow crystalline solid was obtained by evaporating the fraction eluted by DCM/hexane 1:3 mixture. The yield was 1.434 g (40%) based on the starting material. M.P.: 125 °C. Elemental analysis calculated for C<sub>10</sub>H<sub>7</sub>N<sub>2</sub>SOCI : % C 52.05, H 2.03, N 11.28; Found % : C 50.02, H 2.33, N 11.88. ESI-MS: *m/z* 239 (M+1); <sup>1</sup>H NMR (δ, ppm) (d<sub>6</sub>-DMSO): 7.92 (m, 5H), 9.14 (s, 1H); 12.30 (s,1H); FTIR (KBr, cm <sup>1</sup>): 3218 (w, broad, OH ), 1628 (v<sub>C=N</sub>), 2974 (v<sub>Ar-C-H</sub> ) ,1515 (v<sub>Ar-</sub> c=c).

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(*E*)-4-bromo-2-((thiazol-2-ylimino)methyl)phenol (1b). 1b was obtained in a similar way as 1a using 2-aminothiazole and 5-bromo-salicylaldehyde. The yield was 1.889 g (45.5%) based on the starting material. M.P.: 125 °C. Elemental analysis calculated for  $C_{10}H_7N_2SOBr$ : % C 42.40, H 2.47, N 9.89; Found % : C 41.02, H 2.82, N 10.08. ESI-MS: m/z 283 (M<sup>+</sup>); FTIR (KBr, cm<sup>-1</sup>): 3116 (w, broad, OH), 2914 (w, broad, C-H), 1595 (s, sharp, C =N), 1556 (m, sharp,  $C_{ar}$ –O), 1132 (s,C-N). <sup>1</sup>H NMR ( $\delta$ , ppm) (500MHz, CDCl<sub>3</sub>) : 12.27 (s, Ar-OH), 9.15 (s, 1H,C=N), 7.70-7.26 (m, 7H,Ar-H), 6.95-6.94 (2H, thiazole).

#### Synthesis of metal complex [Cu<sub>4</sub>(L)<sub>4</sub>] (3).

**3a.** To a methanolic solution (40 mL) of ligand **1a** (0.952 g, 4 mmol), Et<sub>3</sub>N (0.404 g, 4 mmol) was added on stirring followed by 5 mL methanolic solution of Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O (1.476 g, 4 mmol). Colour of the solution changed immediately from yellow to dark green. A green precipitate separated out slowly. The reaction mixture was allowed to reflux for 5 h. The green solid was filtered under vacuum and washed with cold methanol (2 mL × 3). Slow evaporation of a DMSO solution of the complex afforded X-ray quality single crystal in a couple of days. Crude yield: 60.0% (0.737 g). Elemental analysis calculated for C<sub>44</sub>H<sub>44</sub>N<sub>8</sub>O<sub>12</sub>S<sub>6</sub>Cl<sub>4</sub>Cu<sub>4</sub>: % C 36.07, H 3.03, N 7.65; Found % : C 36.49, H 3.44, N 7.19. Selected IR bands (cm<sup>-1</sup>) (Cu<sub>4</sub>L<sub>4</sub>): 3170 ( $\nu_{N-H}$ ), 2952 (Ar- $\nu_{C-H}$ ), 1628 ( $\nu_{C=N}$ ), 1508 ( $\nu_{Ar-C=C}$ ). UV/vis (DMF):  $\lambda_{max}$ /nm ( $\varepsilon$ /M<sup>-1</sup> cm<sup>-1</sup>) : 274<sub>sh</sub>(10946), 313 ( 7415), 404 ( 3820), 700 (125).

**3b**. The procedure is the same than that of **3a**. Yield: 0.795 g (56.5%). Elemental analysis calculated for  $C_{44}H_{44}N_8O_{12}S_6Br_4Cu_4$ : % C 32.16, H 2.70, N 6.82; Found % : C 32.52, H 2.52, N 7.12.IR (KBr,v/cm<sup>-1</sup>): 3093 ( $\nu_{N-H}$ ), 2951 (Ar- $\nu_{C-H}$ ), 1604 ( $\nu_{C=N}$ ),  $\lambda_{max}/nm$  ( $\epsilon/M^{-1}$  cm<sup>-1</sup>): 258 (49795), 310 (15582), 345 (6573), 410 (3830), 678 (301).

## Procedure for the oxidation of 2-amino phenol and determination of the rate of formation of phenoxazinone chromophore.

In this kinetic investigation 2 mL of a methanol solution  $(1 \times 10^{-5} \text{ M})$  of complex **3** was prepared in a quartz cell and treated with 100 eq of 2-amino phenol (OAPH) substrate solution  $(1 \times 10^{-3} \text{ M})$ . The reaction was then followed at 25 °C by UV-Vis spectral scan at 5 min intervals up to 1 h (for complex **3a**) or 4.5 h (for complex **3b**). The concentration of the phenoxazinone chromophore was calculated on the basis of its molar extinction coefficient (in methanol<sup>19</sup>  $\epsilon_{430}$  = 9095 M<sup>-1</sup> cm<sup>-1</sup> and in DMSO<sup>20</sup>  $\epsilon_{435}$  = 23200 M<sup>-1</sup> cm<sup>-1</sup>).

## X-ray Crystallographic Data Collection and Refinement of the Structure.

X-ray quality single crystals of complexes **3** were obtained by evaporation of DMSO solutions. For both complexes a suitable crystal was selected and mounted in Fomblin film on a micromount, and data were collected on a GV1000, Atlas diffractometer and on a SuperNova, Dual, Cu at zero, Atlas diffractometer, for **3a**·2DMSO·2H<sub>2</sub>O and **3b**·2DMSO·2H<sub>2</sub>O, respectively. Using Olex2,<sup>33</sup> the structure was solved with the olex2.solve structure solution program<sup>34</sup> using Charge Flipping and refined with the SHELXL<sup>35</sup> refinement package employing Least Squares minimisation. The crystal data collection and refinement parameters are given in the ESI (Table S1).

#### Computational Details.

Quantum chemical calculations were run with the GAUSSIAN09 suite of programs<sup>36</sup> using the hybrid B3LYP exchange-correlation functional.<sup>37</sup> The triple- $\zeta$  quality basis set (TZV) proposed by Ahlrichs and co-workers has been used for all atoms.<sup>38</sup> A quadratic convergence method has been employed in the self-consistent-field process.<sup>39</sup>

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Two tetranuclear copper complexes with Cu<sub>4</sub>O<sub>4</sub> cubane core exhibiting phenoxazinone synthase like activity are reported. Low temperature magnetic susceptibility measurements display antiferromagnetic interaction which has been explained theoretically by DFT calculation.



23x13mm (300 x 300 DPI)