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Synthesis, characterisation and biological aspects of copper(II) dithiocarbamate complexes, [Cu{S₂CNR(CH₂CH₂OH)}₂], (R = Me, Et, Pr and CH₂CH₂OH)

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1. Introduction

ABSTRACT

Cu(II) dithiocarbamates, $[Cu{S_2CNR(CH_2CH_2OH)}_2]$, R = Me (1), Et (2), Pr (3) and CH₂CH₂OH (4), have been prepared from HNR(CH₂CH₂OH) (R = Me, Et, Pr and CH₂CH₂OH), CS₂ and Cu(OAc)₂. Characterisation of the complexes were generally achieved by infrared and EPR spectroscopies and, in addition, for (2) and (3), by X-ray crystallography at 120 K. Complex (2) crystallises as a Cu–S linked dimer, in which the CH₂CH₂OH groups have a *cis* arrangement in each monomer but are *trans* to those in the other monomer partner. On the other hand complex (3) exists in the solid state in the form of two similar and independent centrosymmetric monomers. The weak antiferromagnetic coupling, present in similar complexes, was absent in complexes (1)–(3). The *in vitro* activity of (1)–(4) was investigated against colonies of *Candida albicans*, *Sthaphyloccocus aureus* and *Pseudomonas aeruginosa*. They all displayed MIC (minimal inhibitory concentration) values against *C. albicans* close to those found for Fluconazole. All complexes were inert towards Gram-negative or Gram-positive bacteria, *S. aureus* and *P. auruginosa*, respectively.

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Dithiocarbamate ligands, $[S_2CNR^1R^2]^-$, have found extensive use in coordination chemistry [1,2]. Their wide range of applications, e.g. in industry, agriculture and medicine, has generated a large collection of crystallographic data for their metal complexes [3]. The majority of the complexes studied have simple R¹ and R² groups, such as methyl, ethyl and phenyl. Complexes with dithiocarbamate ligands having functional substituted organic groups, such as R¹ and or R² equal to CH₂CH₂OH, are increasingly being studied, with crystal structures reported for a number of metal complexes including those of alkali metals [4] copper [5,6], nickel [7–9], zinc [10], mercury [11] and antimony [12,13]. Clearly the extra structural aspects generated by the functional groups [4–13] have encouraged interest in these compounds.

By far the best studied of the reported $[Cu{S_2CNR(CH_2CH_2-OH)}_2]$ compounds, where R = Me, Et and CH₂CH₂OH is the latter [14–26]. Very limited reports have been made on (1) and (2), [16]. Apart from informations on the synthesis, spectroscopy [14,15] and crystal structure of (4) [5,6], other areas of interest

* Corresponding author. E-mail address: delima.geraldo@gmail.com (G.M. de Lima). include thermolysis [16–19], uses in analytical chemistry [20–24], and interactions with NO and their biological applications [25,26]. It is apparent that biological studies of similar derivatives have not really attracted much attention. This has been so despite the possibility that the increased hydrophilicity of these compounds, over compounds not bearing hydroxyl groups, may have significant biological implications.

Following our general interest in the biological properties of metal complexes [27–30], we now report results on the anti-fungal and anti-bacterial properties of complexes (1)–(4), as well as their IR and EPR spectra. In addition, the crystal structures (2) and (3) are described.

2. Experimental

2.1. Chemistry

2.1.1. Materials and methods

All starting materials were purchased from Aldrich, Merck or Synth and used as received. Infrared spectra were recorded in the range of 4000–400 cm⁻¹ with samples in KBr pellets using a Perkin–Elmer 283B spectrometer. Carbon, hydrogen and nitrogen analyses were performed on a Perkin–Elmer PE-2400 CHN-analysis using tin sample-tubes.

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2.1.2. Synthesis of (1) (R = Me)

To a solution of HN(Me)(CH₂CH₂OH) (2.50 g, 0.017 mol) in cold ethyl ether at -10 °C, was successively added carbon disulfide (0.75 g, 0.017 mol) and a suspension of Cu(OAc)₂·H₂O (1.70 g, 0.009 mol) in cold ether. The reaction mixture was allowed to reach room temperature and after stirring for 2 h, the solid product was collected. The dark brown residue was re-crystallised from methanol. Yield 68%. Mp. 196.4–198.5 °C.

IR (ν/cm^{-1}): 1507 (ν_{C-N}) and 989 (ν_{CS}).

Analysis for $C_8H_{16}CuN_2O_2S_4$ found% (calc.%): C 32.3 (32.1), H 5.6 (5.3), N 8.9 (9.3).

2.1.3. Synthesis of (2) (R = Et)

Prepared similarly using $HN(Et)(CH_2CH_2OH)$ (2.74 g, 0.02 mol), CS₂ (0.88 g, 0.02 mol) and Cu(OAc)₂·H₂O (1.99 g, 0.01 mol). Yield 68%. Mp. 171.1–171.9 °C.

IR (ν/cm^{-1}): 1499 (ν_{C-N}) and 985 (ν_{CS}).

Analysis for $C_{10}H_{20}CuN_2O_2S_4$ found% (calc.%): C 36.9 (36.6), H 6.5 (6.1), N 8.4 (8.5).

2.1.4. Synthesis of (3) (R = Pr)

Similarly prepared employing $HN(Pr)(CH_2CH_2OH)$ (2.45 g, 0.014 mol), $CS_2(0.62 \text{ g}, 0.014 \text{ mol})$ and $Cu(OAc)_2 \cdot H_2O$ (1.4 g, 0.007 mol). Yield 65%. Mp. 111.7–122.0 °C.

IR (ν/cm^{-1}): 1512 (ν_{C-N}) and 997 (ν_{C-S}).

Analysis for $C_{12}H_{24}CuN_2O_2S_4$ found% (calc.%): C 41.2 (40.5), H 7.1 (6.8), N 7.6 (7.9).

2.1.5. Synthesis of (4) $(R = CH_2CH_2OH)$

Prepared accordingly by reacting $HN(CH_2CH_2OH)_2$ (3.0 g, 0.03 mol), $CS_2(1.32 \text{ g}, 0.03 \text{ mol})$ and $Cu(OAc)_2$ (2.99 g, 0.015 mol). Yield 71%. Mp. 164.0–166.4 °C.

IR (v/cm^{-1}) : 1517 (v_{C-N}) and 993 (v_{C-S}) .

Analysis for $C_{10}H_{20}N_2S_4O_4Cu$ found% (calc.%): C 34.1 (33.4), H 5.8 (5.6), N 7.5 (7.8).

2.1.6. Electron paramagnetic resonance

Electron paramagnetic resonance spectra were recorded on a spectrometer constructed with a 500 mW klystron (Varian), a commercial cylindrical resonance cavity (Bruker), an electromagnet (Varian) with maximum field amplitude of 800 mT and a He flux cryosystem (Oxford) for low temperature measurements. Spectra were recorded as first-derivates using common 100 kHz field modulation. For *g* factor calibration, 1,1-diphenyl-2-picrylhydrazyl was used as the standard (g = 2.0037). Polycrystalline samples were measured as fine powders in cylindrical borosilicate tubes (Wilmad).

2.1.7. X-ray crystallography

Intensity data for $[Cu{S_2CNR(CH_2CH_2OH)}_2]$, R = Et (2) and Pr (3), were collected at 120 K with Mo K α radiation using the κ -goniostat Bruker–Nonius CCD camera of the EPSRC crystallographic service, based at the University of Southampton, UK. Data collection was carried using the program COLLECT [31] and data reduction and unit cell refinement were achieved with the COL-LECT and DENZO [32] programs. Corrections for absorption, by

Compound	(2) R = Et	(3) R = Pr
Empirical formula Formula weight Temperature, K	C ₁₀ H ₂₀ CuN ₂ O ₂ S ₄ 392.06 120(2) 0.71073	C ₁₂ H ₂₄ CuN ₂ O ₂ S ₄ 420.11 120(2) 0.71073
Wavelength, A Crystal system Space group Unit coll dimensions	Monoclinic P21/n	Triclinic P-1
a, Á	9.4925(2)	6.42860(10)
b, Å	10.9232(3)	11.5308(3)
с, Á	15.7429(4)	12.6699(4)
α, \circ β, \circ γ, \circ Volume Å3	90 102.2230(15) 90 1595.35(7)	92.0870(10) 97.863(2) 90.401(2) 929.66(4)
Z	4	2
Density (calculated), Mg/m ³ Absorption coefficient, mm^{-1} F(0 0 0)	1.632 1.890 812	1.501 1.628 438
Crystal size, m	$0.28 \times 0.16 \times 0.05$ 3.24-25.00	$0.10 \times 0.10 \times 0.01$ 3 20-27 48
Index ranges	$\begin{array}{l} -10 \leq h \leq 11 \\ -12 \leq k \leq 12 \\ -18 \leq l \leq 18 \end{array}$	$-8 \le h \le 8 \\ -14 \le k \le 14 \\ -16 \le l \le 16$
Reflections collected Independent reflections	18,609 2799 [<i>R</i> (int) = 0.0445]	14,004 4244 [<i>R</i> (int) = 0.0432]
Reflections obd. (>2sigma) Data completeness Absorption correction	2480 0.998 None	3662 0.993 None
Refinement method Data/restraints/parameters	Full-matrix least-squares on <i>F</i> ² 2799/0/185 1 053	Full-matrix least-squares on <i>F</i> ² 4244/0/197 1 108
Final <i>R</i> indices [<i>I</i> > 2sigma(<i>I</i>)]	$R_1 = 0.0525$ $wR_2 = 0.1442$	$R_1 = 0.0374$ $wR_2 = 0.0739$
R indices (all data)	$R_1 = 0.0584$ $wR_2 = 0.1495$ 2.247 and 0.641	$R_1 = 0.0482$ $wR_2 = 0.0796$ 0.275 and 0.266
Largest diff. peak and hole, e. Å ³	J.247 dild -0.041	002.0 – DIIb C (C.0

Table 1

Crystallographic data for complexes (2) (R = Et) and (3) (R = Pr).

comparison of the intensities of equivalent reflections, were applied using the program SADABS [33]. The structures were solved by direct methods using SHELXS-97 [34] and refined against F^2 with SHELXL-97 [35]. Hydrogen atoms were placed in calculated positions and refined as riding. The program ORTEP-3 for Windows [36] was used in the preparation of Figures and PLATON [37] in the calculation of molecular geometry. Crystal data and structure refinement details are listed in Table 1.

2.2. Anti-fungal activity

The standard method for anti-fungal susceptibility testing proposed by the NCCLS M27-A2 [38] was used for *in vitro* susceptibility tests. *Candida albicans* ATCC18804, stored in Sabouraud broth, was sub-cultured for testing in the same medium and grown at 35 °C for 24 h. An inoculum of 10^6 cells mL⁻¹ was prepared by a spectrophotometric method. Serial dilutions of the compounds dissolved in DMSO were prepared to provide final concentrations of 61.5–0.12 µg mL⁻¹. A 24 h old inoculum was added to each tube to provide a final concentration of 10^3 cells mL⁻¹. Minimum inhibitory concentration (MIC), the lowest concentration to give 100% inhibition of growth, was determined visually after incubation for 24 h at 35 °C. Tests using fluconazole as a negative control and DMSO as a positive control were carried out in parallel. All tests were performed in triplicate with full agreement between the results.

2.3. Anti-bacterial activity

The standard method for anti-bacterial susceptibility testing proposed by the NCCLS M7-A6 [39] was used for in vitro susceptibility tests. Pseudomonas aeruginosa ATCC 25853 and Sthaphyloccocus aureus ATCC 6538 stored in Müller-Hilton broth were sub-cultured for testing in the same medium and incubated at 37 °C for 24 h and 6 h, respectively. The bacterial cells of the two strains were suspended in Müller-Hilton broth to produce inocula of 10⁸ CFU mL⁻¹, determined by a spectrophotometric method. Serial dilutions of the compounds, previously dissolved in DMSO, were prepared in test tubes with Müller-Hilton broth to final concentrations of 270–1 μ g mL⁻¹ for *P. aeruginosa* and 160–0.6 μ g mL⁻¹ for *S. aureus*. An old inoculum of each strain was added to the tubes to obtain final concentrations of 10⁵ CFU. Minimum inhibitory concentration (MIC), the lowest concentration to give 100% inhibition of growth, were determined visually after incubation for 24 h at 37 °C. Tests using tetracycline as a negative control and DMSO as a positive control were carried out in parallel. All tests were performed in triplicate with full agreement between the results.

3. Results and discussion

3.1. General

All complexes were obtained from $Cu(OAc)_2$, CS_2 and $HNR(CH_2CH_2OH)$, see Eq. (1), as crystalline and stable brown-coloured solids, readily soluble in polar solvents such as ethanol, methanol and acetone.



Fig. 1. Complex (1) (R = Et) (a) atom numbering system and atom arrangements: only, O1a and O1aⁱ, of the pair of disordered OH sites, [O1a + O1c] and [O1a' + O1c'] are shown; probability ellipsoids are drawn at the 50% level and hydrogen atoms have been omitted for clarity; (b) packing of the molecules. Symmetry operations are shown in Table 2.

The v(C–S) and v(C–N) were observed in the ranges of 980– 1000 and 1490–1520 cm⁻¹, respectively, for all complexes. The values of the v(C–S) indicate a bidentate chelating form of the ligand towards the metal cation [40], according to the X-ray results. The infrared spectra of (2), which display an extra intermolecular Cu–S interaction, does not show any difference if compared to the spectra of (3) in the region of v(C–S) and v(C–N) absorption.

3.2. Crystallographic determination

The structures of $[Cu{S_2CNR(CH_2CH_2OH)}_2]$, R = Et (2) and Pr (3), were determined by X-ray crystallography using data collected at 120 K.

Generally $[Cu{S_2CNR^1R^2}_2]$, displays two distinct structural arrangements: (a) a square planar monomer, arising from chelating dithiocarbamate ligands and (b) a 5-coordinate dimer, resulting from square planar monomers linking by mutual inter-dimer Cu—S coordination. However a less common infinite polymeric chain has





Fig. 2. Complex **(3)** (R = Pr): (a) atom arrangement and numbering scheme for Molecule A:Molecule B is numbered similarly with suffix b in place of a; probability ellipsoids are drawn at the 50% level and hydrogen atoms as spheres of arbitrary radius; (b) a view of the O–H···O hydrogen bonding arrangements and formation of the cyclic tetramers. Symmetry operations are listed in Table 3.

been also described in the literature [40]. Structures (a) and (b) were determined in this study: complex (2) was isolated as a dimer, see Fig. 1, while (3) had the monomeric structure, see Fig. 2.

It is notable that very recently a monomeric form of **(4)** $R = CH_2CH_2OH)$ [6] has been reported in contrast to the dimeric form known for some years [5]. The new crystallographic determination revealed a distorted square planar geometry comprising the CuS_4 environment. In both cases, the crystals used in the structural determinations, based on data collected at 298 K, were grown from methanol solutions: from the scant synthetic and crystal growth details in the two articles, it is impossible to ascertain any differences in the procedures used to obtain the different crystals.

Generally the steric bulk of the organic groups on nitrogen is an important factor, with smaller groups leading to dimers [40–45], in contrast to the bulkier units providing monomers [40,46–53]. With bulk intermediate, the form can be solvent dependent, as with $[Cu{S_2CNR^1R^2}_2]$ (R¹, R² = Bu₂), for which recrystallisation from EtOH/CHCl₃ or CHCl₃/petroleum ether led to formation of monomeric [40,46] and dimeric forms [46,55], respectively. Also both monomeric and dimeric forms of [R¹, R² = Pr, CH₂(Pr-cyclo)] and [R¹, R² = cyclo-(CH₂)₆] were found within the same crystal [46,48].

In this study, complex (**2**) was isolated in the dimeric form, the asymmetric unit being composed of one molecule, Fig. 2, and as such is similar to that found for dimeric (**4**) [5]. Disorder is apparent in one of the 2-hydroxyethyl groups in each of the monomeric units making up the dimer: two almost equally populated sites, O1a and O1c, were found: only one each of these sites, O1a is



Fig. 3. EPR spectra for the complexes (black solid lines) measured at room temperature with microwave frequency of 9.39 GHz. Calculated spectra based on the electronic Zeeman interaction of isolated Cu(II) ions are shown as coloured lines.

indicated in Fig. 2a. Within each of the monomeric units, the 2-hydroxyethyl groups are in a *cis* arrangement. Both these groups have a *trans* relationship to the 2-hydroxy groups in the other monomeric unit.

Complex (3) was isolated as a centrosymmetric monomeric species, with the asymmetric unit consisting of two similar but independent fragments, each containing one dithiocarbarmate ligand and a copper ion, Fig. 3. In each of the centrosymmetric molecules of (3), Mol.A and Mol.B, the 2-hydroxyethyl groups are in a *trans* arrangement, which has also been observed in other unsymmetrical substituted monomeric compounds, *e.g.*, $[Cu{S_2CNR^1R^2}_2]$ (R¹, R² = MePh) [50].

Selected geometric parameters for (**2**) and (**3**) are shown in Tables 2 and 3, respectively. The dithiocarbamate ligands are slightly asymmetrically bonded to Cu, with the basal Cu—S bond lengths in the regions found for other copper dithiolates.

As generally found for dimeric copper(II) dithiocarbamates, the bridging S atom in (2) is involved with the longest Cu—S basal bond length. The length of the bridging Cu—S bond and the Cu…Cu separation in copper dithiolate dimers vary with the organic groups on nitrogen groups, see Table 4. The closest Cu…Cu distance in monomeric (3) was calculated to be 9.3206(2) Å compared to the Cu—Cu distances in dimers being between 3.4 and 3.9 Å.

While the hydroxyl groups in (2) and (3) have little influence on the geometries at Cu, they do have major impacts on the packing of the molecules and do lead to packing difference with compounds $[Cu{S_2CNR^1R^2}_2]$, having unsubstituted alkyl groups. Unfortunately, the disorder of one HO group in (2) prevents a readily describable account of the hydrogen bonding arrangements of

Table	2
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Selected crystallographic parameters (Å, °) for complex (2) (R = Et).

Cu1—32A C34—014		2.7950(13)		52A-Cul	2		2.7950(15)
C3A-01C ^a		1.220(14)			C3D-011)		1.500(8)
S1A-Cu1-S2B		160 07(5))		S1A-Cu1			101 21(5)
S2B-Cu1-S1B		76.92(5)			S1A-Cu1	-S2A		76.75(4)
S2B-Cu1-S2A		102.41(5))		S1B-Cu1	-S2A		172.31(5)
S1A-Cu1-S2A ⁱ		101.04(5))		S2B—Cu1	—S2A ⁱ		98.89(4)
S1B—Cu1—S2A ⁱ		95.07(5)			S2A—Cu1	—S2A ⁱ		92.60(4)
Cu1—S2A—Cu1 ⁱ		87.40(4)						
01A-C3A-01C		106.6(12))		01A-C3/	A—C2A		116.8(7)
01C ^a —C3A—C2A		112.5(12))		01BC3E	3—C2B		114.5(5)
(b) Hydrogen bonding p	arameters	ation		DU	11 A	Л	٨	
D−n···A	Symmetry oper	ation		D-n	n·…∧	D	·A	D—⊓…A
O1A—H1A···S2A				0.84	2.75	3.4	63(14)	144
01B—H1B···01B	1 - x, 2 - y, 1 -	- Z		0.84	2.13	2.9	21(9)	157
CZA-HZAZ···SZA				0.99	2.59	3.00	52(5) 85(5)	109
C2B-H2B····52B	$1/2 + \chi 2/2$	$1/2 \pm 7$		0.99	2.58	3.00	85(5) 27(6)	111
C_{2D} H_{12D} $C_{1\Delta}$ H_{12D} $C_{1\Delta}$	1/2 + x, 3/2 - y	1/2 + 2		0.99	2.65	3.0	57(0) 69(5)	175
C4R = H4R1 = S1R				0.99	2.57	3.0	32(6)	105
C5B-H5B201A	$x_{1} - 1 + y_{2} z_{3}$			0.98	2.52	3.4	68(16)	149
(c) C–H···. π interaction								
C—H···Cg			H…Cg	H _{perp}	Г	C—H· · ·Cg	C···Cg	С—Н, π
C5B—H5B3····Cg2	1/2 - x, $-1/2 + y$, $1/2 - y$	z	2.90	2.708	21.09	139	3.695(7)	70
-								
(d) $\pi \cdots \pi$ interactions								
$Cg(I) \cdots Cg(J)$		Cg···Cg		α	β	CgI _{perp}	CgJ _{perp}	Slippage
$Cg(1) \cdot \cdot \cdot Cg(1^{i})$	1 - x, 2 - y, -z	3.7322(18)	0.00	42.73	2.742	2.741	2.533
$Cg(1) \cdots Cg(2^{i})$	1 - x, 2 - y, -z	3.9384(18)	20.39	34.93	41.90	2.931	3.229
$Cg(2) \cdots Cg(1^{i})$	1 - x, 2 - y, -z	3.9384(18)	20.39	41.90	34.93	3.229	2.931
(e) Cu $\cdots \pi$ interactions								
				Cg(1)····C	'u	Cu-Perp		β
Cg(1)····Cu	1 - x, 2 - y,	-z		3.274		2.744		33.06
	, - ,,	11						

Cg(2) is the centroid of the ring defined by Cu1B, S1B, C1B, S2B; Gamma is the angle at H between the vectors H...Cg and H_{perp}. C-H, π is an estimate of the significance of the interaction.

Cg(1) and Cg(2) are the centroids of the rings defined by Cu1, S1A, C1A, S2A; and Cu1, S1B, C1B, S2B, respectively Alpha is the dihedral angle between planes I and J and is identically zero because the overlapping rings are related to one another by unit cell translation. Beta is the angle between $Cg(I) \cdots Cg(J)$ and CgI_{perp} where CgI_{perp} is the perpendicular from Cg(I) to ring J. Slippage is the distance between Cg(J) and perpendicular projection of <math>Cg(I) on ring J.

^a O1C is the alternative site to O1A of the hydroxyl oxygen atom.

ⁱ Symmetry operation: i = -x + 1, -y + 2, -z.

the hydroxyl groups. However it is clear that the $O-H\cdots O$ hydrogen bonds link molecules, see Table 2. In addition to the $O-H\cdots O$ hydrogen bonds, molecules are also linked by $C-H\cdots S$, and $C-H-\pi$ and other intermolecular interactions, see Table 2. Packing of molecules of (2) is shown in Figs. 2b.

A much simpler picture can be drawn for (**3**), see Fig. 3b. Here, the molecules, with *trans* 2-hydroxyethyl groups, are linked into cyclic tetrameric arrays by $O-H\cdots O$ hydrogen bonds, see Table 3. Further contacts between the monomers are engendered by $C-H\cdots S$ and $C-H\cdots \pi$ intermolecular interactions leading to a three dimensional arrangement.

3.3. EPR spectra and magnetic properties

Fig. 3 shows the first-derivative EPR spectra (black lines) for compounds **(1)–(4)** as polycrystalline samples measured at room temperature in X-band (9.39 GHz). The spectra exhibit axial symmetric EPR lines with half widths ranging from 1.0 to 3.5 mT. In Fig. 3 the colour lines correspond to calculated Cu(II) EPR spectra

based only on the electron Zeeman interaction. The calculations reveal that all Cu(II) centres have nearly axial g tensors. The spin Hamiltonian parameters are listed in Table 5.

The EPR spectra are typical for isolated Cu(II) with $S = \frac{1}{2}$ and the EPR lines are due to the allowed $\Delta m_s = \pm 1$ transitions. EPR transitions, corresponding to coupled Cu(II) ions at half-field (transitions $\Delta m_s = \pm 2$ of a spin triplet), were not observed. From Fig. 4 and Table 5 one may infer that the EPR spectra of compounds (1)-(3) present very similar spin Hamiltonian parameters. The medium g values $\langle g \rangle$ of these compounds are about 2.050 and the parallel values greater than the perpendicular values, i.e. $g_{\parallel} > g > g_{e}$, where g_{e} (=2.0023) is the g factor of the free electron. According to the literature if $g_{\parallel} > g_{\perp}$ it implies in a distortion of the complex by elongation in z [54]. Therefore the obtained results for complexes (1)–(3) are consistent with a distorted octahedral or square pyramidal symmetry for which it is expected the ground state to be the d_{x2-y2} orbital. It is consistent with the X-ray results obtained for complexes (2) and (3). The medium g factors of all compounds and also the axial components are within the ranges found for

Table 3

Selected crystallographic parameters (Å, $^{\circ}$) for complex (3) (R = Pr).

(a) Bond angle and lengths Molecule A				Molecu	ıle B		
Cu1A—S2A		2 2891(7)		Cu1B—	-\$2B		2 2757(6)
Cu1A–S2A ⁱ		2.2891(7)		Cu1B-	S2B ⁱⁱ		2.2757(6)
Cu1A–S1A ⁱ		2.3105(6)		Cu1B-	 S1B		2.3172(6)
Cu1A–S1A		2.3105(6)		Cu1B-	S1B ⁱⁱ		2.3172(6)
S1A–C1A		1.733(3)		S1B-C	1B		1.728(2)
S2A–C1A		1.726(3)		S2B-C	1B		1.726(2)
S2A—Cu1A—S2A ⁱ		180		S2B-C	u1B—S2B ⁱⁱ		180
S2A—Cu1A—S1A ⁱ		102.25(2)		S2B—C	u1B—S1B ⁱⁱ		102.07(2)
S2A ⁱ —Cu1A—S1A ⁱ		77.75(2)		S2B ⁱⁱ —0	Cu1B—S1B ⁱⁱ		77.93(2)
S2A–Cu1A–S1A		77.75(2)		S2B-C	u1B—S1B		77.93(2)
S2A ⁱ —Cu1A—S1A		102.25(2)		S2B ⁱⁱ —0	Cu1B—S1B		102.07(2)
S1A ⁱ —Cu1A—S1A		180		S1B—C	u1B—S1B ⁱⁱ		180
(b) Undrogon bonding param	actors)						
D_HA	Symmetry on	eration	р_н	Н	Δ	D A	D_HA
D-II···A	Symmetry op	cration	D-11	11	n -	Dirin	D=11N
01A—H01A…01B	-x, $1 - y$, $1 -$	Ζ	0.84	1.87		2.705(3)	175
01B—H01B···01A			0.84	1.90		2.704(3)	160
C2A—H2A2···S2A			0.99	2.72		3.053(3)	100
C2B-H2B1···S2B			0.99	2.56		3.075(3)	112
C3B-H3B2···SIA	-x, 1-y, 1-	Ζ	0.99	2.86		3.760(3)	152
C4A—H4A2···SIA			0.99	2.61		3.051(2)	107
	1		0.99	2.04		3.043(2)	104
C4B—H4B1···S2B	-1 + x, y, z		0.99	2.87		3.825(3)	162
(c) .C–H···. π interactions							
C—H.·Cg		H∴Cg	H _{perp}	γ	C—H· · · Cg	C···Cg	С—Н, π
C3B-H3B2-Cg1	-x, $1 - y$, $1 - z$	2.83	2.702	17.07	178	3.816(3)	75
C3B—H3B2—Cg2	1 + x, -1 + y, z	2.83	2.702	17.07	178	3.816(3)	75
C6A-H6A3-Cg3		2.02	2 000	10.15	100	2 500(2)	50
•	-x, 1 - y, -z	2.92	2.800	16.15	126	3.380(3)	52

Cg(1)–Cg(4) are the centroids of the rings defined by Cu1A, S1A, C1A, S2A; Cu1A, S1Aⁱ, C1Aⁱ, S2Aⁱ; Cu1B, S1B, C1B, S2B; Cu1B, S1Bⁱⁱ, C1Bⁱⁱ, S2Bⁱⁱ, respectively: Gamma is the angle at H between the vectors H \cdots Cg and H_{perp}. C–H, π is an estimate of the significance of the interaction.

ⁱ Symmetry operation: i = -x - 1, -y + 2, -z + 1.

ⁱⁱ Symmetry operation: ii = -x, -y + 1, -z.

analogous compounds, which ranges between 2.044 and 2.050, respectively [55,56]. The calculated g_{\parallel} values for complexes (1)– (3), which are between 2.02 and 2.10, indicate a strong covalent bonding between the Cu²⁺ and sulfur ions [57]. The compounds $[Cu{S_2CNR^1R^2}_2]$ (R¹R² = simple alkyl) investigated in a previous work [58,59] display very similar EPR spectra such as in (1)-(3). In those compounds the Cu-Cu distances varied between 3.4 and 7.6 Å and a weak antiferromagnetic coupling was observed. The latter was not the case for the four compounds investigated in this work. Compound (4), $[Cu{S_2CNR(CH_2CH_2OH)}_2]$ (R = CH₂CH₂OH), behaves somewhat differently. Although the medium g value $\langle g \rangle$ is similar to that of the other complexes, the parallel and perpendicular g values are inverted. It might be a consequence of the geometry at the Cu(II) centre which in view of the crystallographic determination [6], is not symmetrical as in the case of (3). This subtle deviation of the square planar geometry might transform d_{72} orbital in the ground state. EPR measurements at low temperatures (down to 10 K) do not modify significantly the line shape and spin Hamiltonian parameters of any of the investigated compounds.

Table 5

Spin Hamiltonian parameters for complexes (1)–(4), g factors and g_{\parallel} and g_{\perp} , the full width at half maximum in units of mT and the medium $\langle g \rangle$ which is $\langle g \rangle = 1/3$ $(g_{\parallel} + 2g_{\perp})$.

$[Cu{S_2CNR(CH_2CH_2OH)}_2]$	g_{\parallel}	g_{\perp} }	$\Delta H_{pp} (mT)$	$\langle g \rangle$
(1) (R = Me)	2.099(1)	2.032(1)	2.0	2.054
(2) (R = Et) (2) (R - Pr)	2.072(1) 2.101(1)	2.032(1)	3.5	2.045
(3) (R = CH_2CH_2OH)	2.025(1)	2.0565(5)	1.0	2.075

3.4. Pharmacological results

It was expected that the presence of CH₂CH₂OH, a more hydrophilic group, could increase biologic activity. However, only complexes (**3**) and (**4**) displayed biocidal activity. The best results were found towards *C. albicans*. The MIC values 26.5×10^{-3} and 36.3×10^{-3} mmol L⁻¹ respectively, are close to that of the control drug Fluconazole 32.9×10^{-3} mmol L⁻¹, see Table 6. In the

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Bridging Cu-S bond lengths and Cu-Cu separations in dimeric copper dithiocarbamates.

Compound	Bridging Cu—S bond length, Å	d (Cu⊷Cu) Å	T (K)	Ref.
(2) (R = Et)	2.793(13)	3.5552(8)	120	This study
(4) $(R = CH_2CH_2OH))$	2.773(4)	3.451(2)	293	[5]
$[Cu{S_2CNR^1R^2}_2] (R^1, R^2 = Pr_2)$	2.740(1)	3.418	295	[40,41]
$[Cu{S_2CNR^1R^2}_2] (R^1, R^2 = Et_2)$	2.844(1)	3.572	295	[42,43]
$[Cu{S_2CNR^1R^2}_2] R^1, R^2 = (2-pyridinyl)]$	3.230(3)		295	[44]
$[Cu{S_2CNR^1R^2}_2] (R^1, R^2 = allyl_2)$	2.888(2)		295	[45]
$[Cu{S_2CNR^1R^2}_2] (R^1, R^2 = Bu_2)$	2.902(1)	3.783(1)	295	[52]

Table 6

Minimal inhibitory concentrations (MIC) for complexes (1)–(4), and starting materials towards *C. albicans*, *S. aureus* and *P. aeruginosa*.

[Cu{S ₂ CNR(CH ₂ CH ₂ OH)} ₂]	MIC 10^{-3} mmol L^{-1}				
	C. albicans	cans S. aureus P. aerugir			
(1) (R = Me)	-	-	-		
(2) (R = Et)	-	-	-		
(3) (R = Pr)	26.5	17.7	-		
$(4) (R = CH_2CH_2OH)$	36.3	>187	-		
Tetracycline	-	2.2	>96.7		
Fluconazole	32.9	-	-		
$[Cu(OAc)_2] \cdot 2H_2O$	-	-	-		

presence of the Gram-negative *S. Aureus* both complexes showed smaller activity than tetracycline and were inert against Gram-po-sitive *P. auruginosa* bacteria.

In view of the structures one should not expect great differences between complexes (1-3), in terms of structure-reactivity relationship. However, complexes (1) and (2) are inactive towards the microorganisms used in this study. On the other hand, compound (3) is more effective against *C. albicans* than (4) or fluconazole. One should expect that the CH₂CH₂OH group, should enhance biocidal activity, and complex (4), [Cu{S₂CN(CH₂CH₂OH)}₂] the more efficient. However our results show another reality. Complex (3), [Cu{S₂CNR(CH₂CH₂OH)}₂] which possesses the less polar R group (propyl) is more active than complex (4). We believe it just confirms the importance of liposolubility in the drug-cell interaction. Even though, it is not an easy task to explain the biocidal activities of metallic complexes such as (1)-(4) frustrating any attempt to establish a mechanism of action. The anti-fungal activity might be explained by new interaction of the Cu-based complexes with the cytoplasmatic membrane. Such interactions with other rich electronic donor centres, amino-acids, proteins, nucleosides, carbohydrates and steroids can increase lipid-solubility assisting the complexes to cross the cell membrane [60]. In spite of the low activity towards C. Albicans, the use of metal-based compounds might represent an alternative therapeutic route to overcome resistance of the most used drugs such as fluconazole, amphotericin, among others [60].

4. Conclusions

Complexes $[Cu{S_2CNR(CH_2CH_2OH)}_2]$, R = Me (1), Et (2), Pr (3) and CH₂CH₂OH (4), have been prepared and characterised. The infrared results confirmed the bidentate coordination form of the ligand. The EPR spectra of (1)-(3) were consistent with a square pyramidal or square planar geometry with the ground state being the orbital d_{x2-v2} . Compound (4) has been studied previously by X-ray [5,6]. The inversion in the g values found in our study can only be justified if compound (4) has been crystallised as a distorted square planar molecule, as found previously [6]. Complex (2) crystallises as a dimer linked by intermolecular Cu-S bonds, and (3) exists in the solid state in the form of two similar and independent centrosymmetric monomers. The in vitro activity of (1)-(4) was investigated against colonies of C. albicans, S. aureus and P. aeruginosa. The biocidal results of (3) and (4) against C. albicans, in terms of MIC (Minimal Inhibitory Concentration), were quite promising. All complexes were inert in the presence of P. aeruginosa.

Supplementary data

Crystallographic data are available on request from: Cambridge Crystallographic Data Centre on quoting the deposition numbers CCDC 754825 and 754826 for complexes (**2**) and (**3**), respectively.

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