Structural and magnetic properties of an asymmetric dicopper(II) anticancer drug analogue

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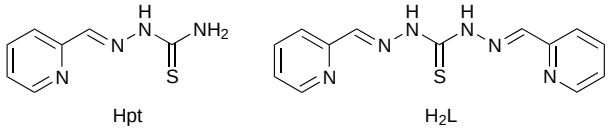
The single-crystal X-ray structure and variable temperature magnetic properties of the novel dicopper(II) anticancer drug analogue $[\{Cu_2(HL)(H_2PO_4)_2\}_2][NO_3]_2{\cdot}2H_2O$ [H_2L = bis(pyridine-2-aldehyde) thiocarbohydrazone] is determined; the complex shows a dimer of dimeric $\{Cu_2(HL)\}^{3+}$ units with dihydrogenphosphato and sulfur bridges between the inequivalent Cu^{II} centres, resulting in three antiferromagnetic exchange interactions: a dominant intradimer J of -109 to -116 cm^{-1}, and two weaker interdimer interactions.

Thiosemicarbazones have been extensively studied because of their biological properties. Cu^{II} is necessary for activity for kethoxal bis(thiosemicarbazone),[1] with the mode of action proposed to involve inhibition of DNA synthesis and oxidative phosphorylation,[2] and *N*-methylisatin-β-thiosemicarbazone can inactivate tumour viruses.[3] Attention has however focused on pyridine-2-aldehyde thiosemicarbazone (Hpt) and derivatives as the Cu^{II} complexes are more bioactive than the metal free ligands.[2,4] The metal-free 5-OH analogue underwent clinical trials as an anticancer drug but side effects such as disruption of iron metabolism prevented clinical use.[5] However, administration of a preformed metal complex may alleviate this. Adducts of $[Cu(pt)]^+$ with sulfur and nitrogen donors have been detected in biological fluids[6] with stable model thiolato complexes isolated from aqueous solution.[7] Crystallographic studies have revealed ternary nitrogen adduct formation,[7,8] complexation of dihydrogen phosphate[9] and pyrophosphate[10] and the system's remarkable ability to form complexes of both the anionic and neutral ligand.[11] The H_2L ligand may be considered as an extension of Hpt, now with a possible extra metal binding domain. Antiviral activity has been reported for 2-acetylpyridine thiocarbohydrazones[12] and H_2L is antifungal[13] and cytotoxic[14] but little chemical and no structural work has been carried out on the Cu–H_2L system. On the human leukemia cell line MOLT4 (at 10 μM), H_2L is more cytotoxic than Hpt, $Cu_2(HL)^{3+}$ and $Cu(pt)^+$ show equal activity whereas, surprisingly $Cu(HL)^+$ is the most cytotoxic.[14] Here we report the first crystallographic study of H_2L with Cu^{II}, $[\{Cu_2(HL)(H_2PO_4)_2\}_2][NO_3]_2{\cdot}2H_2O$, giving a dimer of dicopper(II) moieties with $H_2PO_4^-$ and weak sulfur bridges. Variable temperature magnetic studies reveal three antiferromagnetic exchange interactions involving superexchange pathways across the planar ligand, a three-atom $H_2PO_4^-$ bridge and direct $Cu^{II}\cdots Cu^{I}$ and/or out-of-plane (*via* S) interactions.



The starting nitrate complex, $[Cu_2L(NO_3)_2]{\cdot}3H_2O$ **1**, used in subsequent metathetical reactions with phosphate was prepared by addition of H_2L (0.616 g, 2.16 mmol) in hot ethanol (150 ml) to $Cu(NO_3)_2{\cdot}3H_2O$ (1.05 g, 4.34 mmol) in the same solvent (10 ml). After stirring for 1 h the product was filtered, washed with ethanol then dried *in vacuo* (913 mg, 72%). $[\{Cu_2(HL)(H_2PO_4)_2\}_2][NO_3]_2{\cdot}2H_2O$ **2** was prepared by dissolving **1** (157 mg, 0.267 mmol) and $NaH_2PO_4{\cdot}H_2O$ (37 mg, 0.268 mmol) in H_3PO_4 (2 ml, 2 M). Dark green crystals suitable for X-ray analysis were collected after 20 days (82 mg, 45%).

X-Ray analysis of **2**† shows the structure (Fig. 1) to be best described as a centrosymmetric dimer of dicopper(II) moieties with dihydrogenphosphato and weak sulfur bridges. Cu(1) has a square-pyramidal geometry with the monoanionic HL bound through pyridyl and imine nitrogens and sulfur. The coordination sphere is completed by phosphato oxygens O(11) and O(21). Cu(2) adopts a tetragonal '4 + 2' geometry with pyridyl, imine and deprotonated amide nitrogens from HL and phosphato oxygen in the plane. Much weaker axial interactions to O(11) and S(1A) 3.24 Å] are from symmetry related molecules. The dimeric $Cu_2(HL)^{3+}$ units are linked *via* three-atom phosphato [Cu(1)–O(21)–P(2)–O(1A)–Cu(2)] and one-atom sulfur bridges with adjacent dimers connected by the weak Cu(2)–O(11) interaction and a hydrogen-bonding network involving phosphato, water and nitrate oxygens and protonated amide [N(3)] nitrogen. Other metric parameters may be considered normal.[7–12] The two phosphate ions adopt different coordination modes, with P(2) chelating and P(1) being monodentate and P(2) binds through the keto oxygen [P(2)–O(1) 1.468(4) Å].

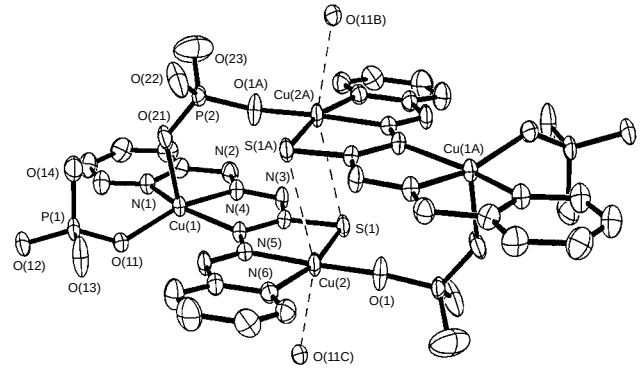


Fig. 1 Molecular structure of the dimeric dicopper(II) ion $[\{Cu_2(HL)(H_2PO_4)_2\}_2]^{2+}$ of **2**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): Cu(1)–N(1) 2.053(4), Cu(1)–N(2) 1.954(4), Cu(1)–N(4) 2.076(4), Cu(1)–O(11) 1.933(3), Cu(1)–O(21) 2.159(3), Cu(2)–N(5) 1.966(3), Cu(2)–N(6) 2.004(4), Cu(2)–O(1) 1.890(3), Cu(2)–S(1) 2.263(2), Cu(2)–O(11C) 2.860(4), Cu(2)–S(1A) 3.242(2), Cu(1)···Cu(2) 4.996, Cu(1)···Cu(2A) 5.076, Cu(2)···Cu(2A) 3.905, Cu(2)···Cu(2C) 3.797, Cu(1)···Cu(1A) 9.326; O(11)–Cu(1)–N(1) 95.4(2), N(4)–Cu(1)–O(11) 140.5(1), O(21)–Cu(1)–N(1) 97.4(2), O(21)–Cu(1)–O(11) 95.0(1), N(1)–Cu(1)–N(4) 155.1(1), N(2)–Cu(1)–O(11) 160.5(2), O(1)–Cu(2)–N(6) 92.8(2), S(1)–Cu(2)–O(1) 100.7(1), S(1)–Cu(2)–N(6) 165.4(1), S(1)–Cu(2)–N(5) 84.9(1), O(1)–Cu(2)–N(5) 171.9(2), O(11)–Cu(2)–S(1) 86.6(1), O(11)–Cu(2)–O(1) 107.4(1), O(11)–Cu(2)–N(5) 78.6(1), O(11)–Cu(2)–S(1A) 159.2(2), S(1A)–Cu(2)–S(1) 94.7(1), S(1A)–Cu(2)–O(1) 92.8(1).

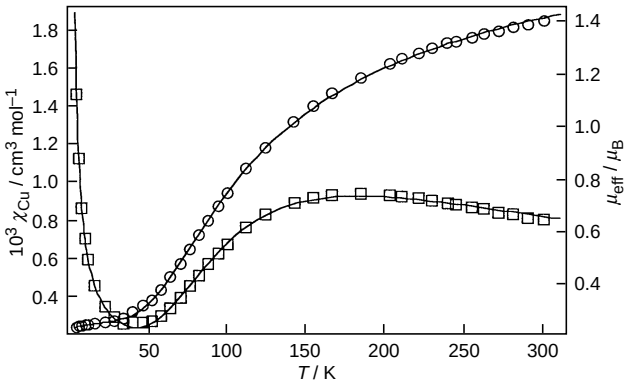
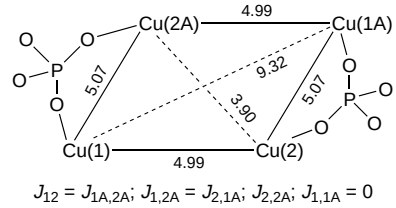


Fig. 2 Temperature dependence of χ_{Cu} and μ_{Cu} *vs.* T for [{Cu_2(HL)(H_2PO_4)$_2$}$_2$](NO_3)$_2$·2H_2O **2**. Solid lines represent the best fit calculated values.

The temperature dependence of magnetic susceptibility and moment, per Cu^{II}, for **2** is shown in Fig. 2. A maximum in χ at *ca*. 180 K is clearly indicative of medium strength antiferromagnetic exchange occurring. The rapid increase in χ at low temperature is due to monomer impurity. Use of a simple dinuclear Bleaney–Bowers model[15] ($-2\,JS_1S_2$ Hamiltonian) did not precisely reproduce the shape of the susceptibility in the region of χ_{max} but did yield an approximate J_{12} value of *ca*. -105 cm^{-1}, albeit with a low g value of 1.98 and a large interdimer θ parameter (in T–θ) of -25 K. Excellent fits could be obtained when the tetranuclear model of Hatfield[16] was employed. The rhomboidal framework of the dimer of dimers is shown in Fig. 3 together with the J labels. The value of the long Cu(1)···Cu(1A) parameter $J_{1,1A}$ was set at zero and the other parameters were varied widely for best-fit. It was found that two parameter sets gave equally excellent fits *i.e.* set A: $g = 2.00 \pm 0.02$, $N_\alpha = (60 \pm 3) \times 10^{-6}$ cm^3 mol^{-1}, $J_{2,2A} = -75.4 \pm 0.2$ cm^{-1}, $J_{1,2} = -116.6 \pm 0.2$ cm^{-1}, $J_{1,2A} = -16.8 \pm 0.2$ cm^{-1}, % monomer 1.7 ± 0.1. This fit is shown in Fig. 2. Set B: $g = 2.00 \pm 0.02$, $J_{2,2A} = -46.0 \pm 0.5$ cm^{-1}, $J_{1,2} = -109.5 \pm 0.2$ cm^{-1}, $J_{1,2A} = -47.9 \pm 0.2$ cm^{-1}, % monomer 1.7 ± 0.1. Thus the dominant coupling, $J_{1,2}$, remains virtually constant in both fits and occurs across the planar thiocarbohydrazonato moiety. It involves superexchange pathways in the *x*–*y* plane such as a two-atom *trans*-Cu–N–N–Cu pathway and three- or four-atom pathways Cu–S–C–N–Cu or Cu–S–C–N–N–Cu. The value of $J_{1,2}$ is similar to that of a structurally related carbohydrazonato dinuclear analogue, reported recently[17] having $J = -106.6$ cm^{-1} (there is a factor of two error in J in ref. 17). The size of the 'edge' and 'short-diagonal' parameters $J_{1,2A}$ and $J_{2,2A}$ could not be identified unambiguously. When using set B, but with $J_{2,2A}$ set at zero or slightly positive, {as anticipated from a previous study[18] on a related S-bridged complex [CuCl(S_2CNEt)]$_4$} much poorer fits were obtained, with the calculated and observed curves crossing each other in the region of χ_{max}. Thus it appears that the Cu(2)S(1)-Cu(2A)S(1A) pathways yield stronger antiferromagnetic coupling (minimum of -46 cm^{-1}) than do related Cu(SR)CuCl or Cu(SR)Cu(SR) pathways[18] in [CuCl(S_2CNEt)]$_4$ and [Cu(S_2CNEt)$_2$]$_2$. The antiferromagnetic coupling across the three-atom $H_2PO_4^-$ bridge, with J of at least -16.8 cm^{-1}, is weak as anticipated and involves axial–equatorial d-orbital overlap, respectively on Cu(1) and Cu(2A). The uncertainties and correlation in the $J_{1,2A}$ parameters may also be influenced by the weak axial interaction Cu(2)–O(11) and Cu(2)–S occurring between teramers, although these are expected to be very weak. In this regard, the visible spectra of solid and H_3PO_4 solutions of **2** are nearly identical.



$J_{12} = J_{1A,2A}$; $J_{1,2A} = J_{2,1A}$; $J_{2,2A}$; $J_{1,1A} = 0$

Fig. 3 Rhomboidal framework for the Cu^{II} centres of **2** showing distances (Å) together with the J labels.

The X-band ESR spectrum of a neat powder of **2** at 298 K shows a broad, symmetrical signal at $g = 2.1$. At 77 K this signal is resolved into a typical axial lineshape ($g_\parallel = 2.19$, $A_\parallel = 184.6$ gauss, $g_\perp = 2.00$) probably due to the monomer impurity (*vide supra*). Triplet state lines due to $Cu^{II}\cdots Cu^{I}$ interactions[19] are evident as weak broad lines at 'half-field' (1500 G) and 3700 G. The same spectrum is observed in frozen 2 M H_3PO_4 solution, with evidence for a weaker monomer lineshape ($g_\parallel = 2.33$, $A_\parallel = 175$ G, $g_\perp = 2.06$) superimposed.

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Notes and References

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† *Crystal data*: $C_{13}H_{17}Cu_2N_7O_{12}P_2S$, $M = 684.4$, dark green crystal, 0.15 × 0.1 × 0.1 mm, triclinic, space group $P\bar{1}$, $a = 8.604(2)$, $b = 10.719(2)$, $c = 14.268(3)$ Å, $\alpha = 109.57(3)$, $\beta = 90.11(3)$, $\gamma = 110.62(3)°$, $U = 1149.6(4)$ Å^3, $D_c = 1.977$ g cm^{-3}, $Z = 2$, $F(000) = 688$, μ(Mo-Kα) = 2.157 mm^{-1}; $R = 0.041$, $R_w = 0.122$ using 3150 unique reflections with $I > 4\sigma(I)$. CCDC 182/711.

1 *Inorganic and Nutritional Aspects of Cancer*, ed. G. N. Schrauzer, Plenum, New York, 1978.
2 J. R. Sorenson and W. M. Willingham, *Trace Elements Med.*, 1986, **3**, 139.
3 W. C. Kaska, C. Carrano, J. Michalowski, J. Jackson and W. Levinson, *Bioinorg. Chem.*, 1978, **8**, 225; W. Rohde, R. Shafer, J. Idriss and W. Levinson, *J. Inorg. Biochem.*, 1979, **10**, 183.
4 W. E. Antholine, P. Gunn and L. E. Hopwood, *Int. J. Radiat. Oncology Biol. Phys.*, 1981, **7**, 491; L. A. Saryan and E. A. Petering, *J. Med. Chem.*, 1979, **22**, 1218; E. W. Ainscough, A. M. Brodie, R. Cresswell, J. D. Ranford and J. M. Waters, submitted.
5 R. C. DeConti, B. R. Toftness, K. C. Agrawal, R. Tomchick, J. A. Mead, J. R. Bertino, A. C. Sartorelli and W. A. Creasey, *Cancer Res.*, 1972, **32**, 1455.
6 W. E. Antholine and F. Taketa, *J. Inorg. Biochem.*, 1982, **16**, 145.
7 E. W. Ainscough, A. M. Brodie, J. D. Ranford and J. M. Waters, *J. Chem. Soc., Dalton Trans.*, 1991, 1737.
8 E. W. Ainscough, E. N. Baker, A. M. Brodie, R. J. Cresswell, J. D. Ranford and J. M. Waters, *Inorg. Chim. Acta*, 1990, **172**, 185.
9 E. W. Ainscough, A. M. Brodie, J. D. Ranford and J. M. Waters, *J. Chem. Soc., Dalton Trans.*, 1997, 1251.
10 E. W. Ainscough, A. M. Brodie, J. D. Ranford, J. M. Waters and K. S. Murray, *Inorg. Chim. Acta*, 1992, **197**, 107.
11 E. W. Ainscough, A. M. Brodie, J. D. Ranford and J. M. Waters, *J. Chem. Soc., Dalton Trans.*, 1991, 2125; A. G. Bingham, H. Bögge, A. Müller, E. W. Ainscough and A. M. Brodie, *J. Chem. Soc., Dalton Trans.*, 1987, 493; C. F. Bell and C. R. Theocharis, *Acta Crystallogr., Sect. C*, 1987, **43**, 26; J. Garcia-Tojal, M. K. Urtiaga, R. Cortés, L. Lezama, M. I. Arriortua and T. Rojo, *J. Chem. Soc., Dalton Trans.*, 1994, 2233.
12 T. A. Blumenkopf, J. A. Harrington, C. S. Koble, D. D. Bankston, R. W. Morrison, Jr., E. C. Bigham, V. L. Styles and T. Spector, *J. Med. Chem.*, 1992, **35**, 2306.
13 B. G. Choi, *Yakhak Hoechi*, 1986, **30**, 79.
14 K. O. Lian, Y. C. Long, J. D. Ranford and X. Wang, unpublished work.
15 B. Bleaney and K. D. Bowers, *Proc. R. Soc. London, Ser. A*, 1952, **214**, 451.
16 W. E. Hatfield and G. W. Inman, Jr., *Inorg. Chem.*, 1969, **8**, 1376.
17 A. Bacchi, A. Bonini, M. Carcelli, F. Ferraro, E. Leporati, C. Pelizzi and G. Pelizzi, *J. Chem. Soc., Dalton Trans.*, 1996, 2699.
18 P. D. W. Boyd and R. C. Martin, *J. Chem. Soc., Dalton Trans.*, 1977, 105.
19 T. D. Smith and J. R. Pilbrow, *Coord. Chem. Rev.*, 1974, **13**, 173.

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