Reaction of Nitrogen and Sulphur Donor Ligands with the Antitumour Complex $[\{CuL(MeCO_2)\}_2]$ (HL = 2-formylpyridine thiosemicarbazone) and the Single-crystal X-Ray Structure of $[CuL(bipy)]ClO_4$ (bipy = 2,2'-bipyridyl) *

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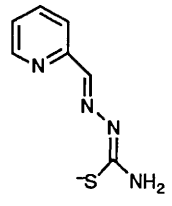
The preparation of N- and S-donor ligand adducts with CuL^+ (HL = 2-formylpyridine thiosemicarbazone) is described. The N-donors, 2,2'-bipyridyl (bipy), 1,10-phenanthroline (phen) and 4-dimethylaminopyridine (dmap) give the complexes $[CuL(bipy)]X$ (X = ClO_4 or PF_6), $[CuL(bipy)]_2SO_4 \cdot 8H_2O$, $[CuL(phen)]PF_6$ and $[CuL(dmap)_2]PF_6$, which have been characterized by physical and spectroscopic techniques. The structure of one of the complexes, $[CuL(bipy)]ClO_4$, has been determined by the single-crystal X-ray diffraction method: triclinic, space group $P\bar{1}$ with $a = 8.560(3)$, $b = 9.452(4)$, $c = 13.078(4)$ Å, $\alpha = 106.35(3)$, $\beta = 94.66(3)$, $\gamma = 95.27(3)°$ and $Z = 2$. The complex contains discrete $[CuL(bipy)]^+$ cations and ClO_4^- anions. The copper atom environment exhibits a distorted five-co-ordinate geometry. Three donor atoms (NNS) from L form a tricyclic ligating system with the remaining positions being occupied by bipy N atoms giving significantly different Cu–N distances of 1.986(4) and 2.179(4) Å. Pentafluoro-(pftp), pentachloro-(pctp) and 4-nitrothiophenolate (ntp) give S-donor complexes $[\{CuL(SR)\}_2] \cdot nH_2O$ (SR = pftp, $n = 4$; pctp, $n = 0$; ntp, $n = 6$). Thiolato co-ordination is proposed on the basis of spectroscopic evidence. With 2-mercaptobenzothiazole (Hmbt), 2-mercaptoimidazole (Hmi), 2-mercapto-1-methylimidazole (Hmmi) and 3-mercapto-4-methyl-1,2,4-triazole (Hmmt), either deprotonated ligand adducts of the type [CuL(A)] (A = mbt, mi or mmt) or neutral ligand adducts $[CuL(HA)_2]PF_6$ (HA = Hmmi or Hmi) are isolated. It is suggested that the thioamides co-ordinate *via* the imine nitrogen atom. The relevance of the results to proposed mechanisms for the antitumour activity of CuL^+ is discussed.

The copper complex $[\{CuL(MeCO_2)\}_2]$ (HL = 2-formylpyridine thiosemicarbazone) and related compounds have been shown to have marked antitumour activities, being more potent than the free ligands against Ehrlich cells injected into mice,[1-3] Sarcoma 180 ascites tumours[2] and Chinese hamster ovary cells.[4] Until recently, when we[5] and others[6] reported the first systematic characterization of the complexes formed with HL, including the single-crystal X-ray crystallographic structures of $[\{CuL(MeCO_2)\}_2]$[5,7] and the protonated ligand complex $[\{Cu(HL)(SO_4)\}_2]$,[5] most reports had described solution or *in vivo* experiments.

The exact mechanism by which such copper complexes exert their antitumour activity is not clear due to the large number of potential sites of action within the cell and the difficulties associated with monitoring and unequivocally assigning a reaction to a particular step. One of the proposed mechanisms is the interaction of the copper(II) drug with the thiol-containing enzyme, ribonucleoside diphosphate reductase (RDR), which is required for the synthesis of DNA precursors.[8,9] The CuL^+ species or HL (released by the reduction of CuL^+ with thiols) may displace the iron from the RDR metal binding site or CuL^+ may bind to a thiol group of the enzyme. Also it does appear that the drug can bind to intracellular thiols such as glutathione [*N*-(*N*-L-γ-glutamyl-L-cysteinyl)glycine] giving a thiolato complex with CuL^+.[10] This in turn is able to promote redox reactions with other thiols and oxygen to produce the disulphide along with $O_2^{\bullet -}$ and $OH^{\bullet}$ radicals which could be partly responsible for the observed cytotoxicity. A second possible mechanism involves the binding of the copper(II) drug to the nitrogen bases of DNA or RNA, thus hindering or blocking base replication. Antholine *et al.*[11] have studied the interaction of CuL^+ with ethylenediamine (en) in solution using ESR spectroscopy and deduced that adduct formation results. Generally however there has been little work published on the interactions of complexes containing tridentate monoanionic ligands with Lewis bases.

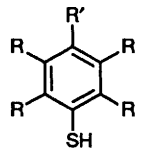


L

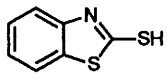
In order to provide a firmer chemical basis for the proposed antitumour action of the CuL^+ species, we have examined its reaction with a range of N-donor ligands [*viz.* 2,2'-bipyridyl (bipy), 1,10-phenanthroline (phen) and 4-dimethylaminopyridine (dmap)] as well as S and mixed S,N and S,O donors (see below), and show that in fact stable ternary copper(II) complexes can be isolated and characterized even with the thiolates. The single crystal X-ray structure of one of these adducts, $[CuL(bipy)]ClO_4$, is described.

* (2,2'-Bipyridine-κ^2N,N')(2-formylpyridine-κN thiosemicarbazonato-κ^2N^1,S) copper(II) perchlorate.

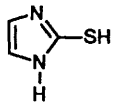
Supplementary data available: see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii–xxii.



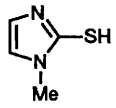
Hpftp R = R' = F
Hpctp R = R' = Cl
Hntp R = H, R' = NO_2



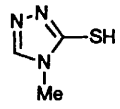
Hmbt



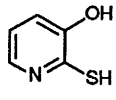
Hmi



Hmmi



Hmmt



H_2mp

Table 1 Colours, analytical and magnetic data

Complex	Colour	Analysis (%)[a] C	H	N	μ_{eff}[b]
$[CuL(bipy)]ClO_4$	Dark green	40.8 (41.0)	2.9 (3.0)	17.1[c] (16.9)	1.78
$[CuL(bipy)]PF_6$	Dark green	37.7 (37.5)	3.0 (2.8)	15.7 (15.5)	1.82
$[CuL(bipy)]_2SO_4·8H_2O$	Dark green	39.3 (39.3)	3.0 (4.4)	16.1 (16.2)	1.74
$[CuL(phen)]PF_6$	Dark green	40.8 (40.2)	2.6 (2.7)	14.5 (14.8)	1.78
$[CuL(dmap)_2]PF_6$	Green	39.6 (39.9)	4.2 (4.3)	17.7[d] (17.7)	2.19
$[\{CuL(pftp)\}_2]·4H_2O$	Brown	32.9 (32.7)	1.7 (2.3)	12.1[e] (11.7)	2.26
$[\{CuL(pctp)\}_2]$	Brown	29.9 (29.7)	1.2 (1.4)	10.7[f] (10.7)	1.87
$[\{CuL(ntp)\}_2]·6H_2O$	Dark brown	34.5 (34.6)	2.3 (3.8)	15.8 (15.5)	1.59
$[CuL(mbt)]·0.5H_2O$	Green	40.5 (40.2)	2.7 (2.9)	16.8 (16.8)	1.87
$[CuL(mi)]·2H_2O·EtOH$	Green	33.6 (34.0)	3.1 (4.7)	19.7 (19.8)	2.11
[CuL(mmt)]	Dark green	32.8 (32.8)	3.2 (3.3)	26.9 (26.8)	1.98
$[CuL(Hmmi)_2]PF_6·H_2O$	Green	28.3 (28.4)	3.4 (3.4)	17.2 (17.7)	2.30
$[CuL(Hmi)_2]PF_6·0.5H_2O$	Green	26.5 (26.2)	3.0 (2.7)	17.4 (18.8)	
$[Cu(Hmp)_2]$	Brown-green	37.7 (38.0)	2.6 (2.6)	9.1 (8.9)	2.03
[Cu(ntp)]	Orange	33.1 (33.2)	1.9 (1.9)	6.4 (6.6)	*g*

[a] Calculated values given in parentheses. [b] Measured at 293 K. [c] Cl 7.9 (7.1%). [d] F 18.0 (18.0%). [e] F 19.5 (19.9%). [f] Cl 33.4 (33.8%). [g] Diamagnetic.

Experimental

The ligand HL was synthesised following a published method [12] as was the complex $[\{CuL(MeCO_2)\}_2]$.[5] The thiols were purchased from Aldrich Chemical Co. All the complexes were dried under vacuum. Microanalyses were performed by the Microanalytical Laboratory, University of Otago and data are summarized in Table 1. Infrared spectra were recorded with a Philips Analytical SP3-300 spectrometer in Nujol mulls, electronic spectra with Shimadzu UV-160 or MPS 5000 instruments and ESR spectra (at 110 K) with a Varian E-104A spectrometer equipped with a Varian E-257 variable-temperature accessory. Spectral *g* values were calibrated with diphenylpicrylhydrazyl (dpph) as a standard. Conductance measurements were made on *ca.* 10^{-3} mol dm^{-3} solutions using a Philips PW9509 digital conductivity meter and a PW9510/60 cell. Magnetic susceptibilities were measured using the Faraday method on a Cahn model 7550 Millibalance with $Hg[Co(SCN)_4]$ as standard and diamagnetic corrections were made using Pascal's constants.

Preparation of the Copper Complexes.—$[CuL(bipy)]ClO_4$. To a solution of 2-formylpyridine thiosemicarbazone (250 mg, 1.39 mmol) in ethanol (40 cm^3) was added $Cu(ClO_4)_2·6H_2O$ (528 mg, 1.42 mmol) in water (10 cm^3). The resulting dark green solution was heated and bipy (240 mg, 1.54 mmol) in ethanol (5 cm^3) slowly added. After 5 min the solution was filtered and allowed to stand for 1 d. The product, which was obtained as dark green crystals, was washed with an ethanol–water mixture. Yield 539 mg (78%).

$[CuL(bipy)]PF_6$ *and* $[CuL(phen)]PF_6$. Either bipy (105 mg, 0.67 mmol) or phen (133 mg, 0.67 mmol), dissolved in hot water (10 cm^3), was added to $[\{CuL(MeCO_2)\}_2]$ (200 mg, 0.33 mmol) in water (40 cm^3), and the mixture heated under reflux for 2 h. The resulting green solutions were filtered while hot and NH_4PF_6 (110 mg, 0.67 mmol) in water (5 cm^3) immediately added. The dark green precipitates which separated were washed with hot water and diethyl ether. Yields: $[CuL(bipy)]PF_6$, 229 mg (64%); $[CuL(phen)]PF_6$, 228, mg (61%).

$[CuL(bipy)]_2SO_4·8H_2O$. To $[\{CuL(MeCO_2)\}_2]$ (302 mg, 0.50 mmol) in water (30 cm^3) was added with heating bipy (158 mg, 1.01 mmol) in water–ethanol (1:1) (10 cm^3) followed by a solution of $Na_2MoS_4·3.5H_2O$ (178 mg, 0.53 mmol) in water (20 cm^3). The resulting green solution was stirred for 5 min, filtered and allowed to stand for a few hours. Crystals of the product were washed with water. Yield 80 mg (15%).

$[CuL(dmap)_2]PF_6$. To $[\{CuL(MeCO)_2\}_2]$ (302 mg, 0.50 mmol) in water (30 cm^3) was added dmap (350 mg, 2.86 mmol). The resulting solution was heated briefly and filtered and then NH_4PF_6 (170 mg, 1.04 mmol) in water (5 cm^3) was added. The product, which precipitated, was washed with water and diethyl ether. Yield 135 mg (26%).

$[\{CuL(pftp)\}_2]·4H_2O$, $[\{CuL(pctp)\}_2]$ *and* $[\{CuL(ntp)\}_2]·6H_2O$. To a filtered, hot solution of $[\{CuL(MeCO_2)\}_2]$ (200 mg, 0.33 mmol) in water (70 cm^3) was added dropwise a solution of the appropriate thiophenol [Hpftp (0.075 cm^3, 0.56 mmol), Hpctp (186 mg, 0.66 mmol) or Hntp (111 mg, 0.72 mmol)] dissolved in a solution of 0.1 mol dm^{-3} NaOH (7.5 cm^3) and methanol (10 cm^3). The resulting precipitates were immediately washed with water and diethyl ether. Yields: $[\{CuL(pftp)\}_2]·4H_2O$, 177 mg (66%); $[\{CuL(pctp)\}_2]$, 193 mg (56%); $[\{CuL(ntp)\}_2]·6H_2O$, 125 mg (42%).

[Cu(ntp)]. To a filtered solution of $[\{CuL(MeCO_2)\}_2]$ (200 mg, 0.33 mmol) in dimethyl sulphoxide (10 cm^3) was added Hntp (204 mg, 1.31 mmol) dissolved in ethanol (20 cm^3). The resulting dark red solution was heated under reflux in a nitrogen atmosphere for 0.5 h. The product, which was obtained as an orange precipitate, was washed with ethanol. Yield 36 mg (25%).

$[CuL(mbt)]·0.5H_2O$ *and* $[CuL(mi)]·2H_2O·EtOH$. To a filtered hot solution of $[\{CuL(MeCO_2)\}_2]$ (302 mg, 0.50 mmol) in water (150 cm^3) was added a solution of Hmbt (172 mg, 1.02 mmol) or Hmi (108 mg, 1.08 mmol) dissolved in ethanol (10 cm^3) containing Na (30 mg, 1.30 mmol). The reaction mixtures were warmed for 5 min. The resulting green precipitates were washed with water, ethanol and diethyl ether. Yields: $[CuL(mbt)]·0.5H_2O$, 222 mg (54%); $[CuL(mi)]·2H_2O·EtOH$, 186 mg (44%).

$[CuL(Hmmi)_2]PF_6·H_2O$ *and* $[CuL(Hmi)_2]PF_6·0.5H_2O$. To a warm solution of $[\{CuL(MeCO_2)\}_2]$ (200 mg, 0.33 mmol) in

Table 2 Fractional atomic coordinates ($\times 10^4$) for $[CuL(bipy)]ClO_4$ (standard deviations in parentheses)

Atom	X/a	Y/b	Z/c
Cu	313.1(7)	5 136.7(7)	7 830.6(5)
Cl	6 300(2)	−24(2)	7 452(1)
S	2 052(2)	3 458(2)	7 325(1)
O(1)	6 168(5)	−1 571(4)	6 976(4)
O(2)	7 896(5)	608(5)	7 678(4)
O(3)	5 466(5)	690(5)	6 777(4)
O(4)	5 600(6)	279(5)	8 452(4)
N(1)	−1 167(5)	6 324(5)	8 803(3)
N(3)	3 138(5)	5 305(5)	9 319(3)
N(2)	1 691(5)	5 787(5)	9 180(3)
N(4)	4 737(5)	3 628(5)	8 527(4)
N(11)	749(5)	6 932(4)	7 109(3)
N(12)	−1 252(5)	4 488(4)	6 533(3)
C(1)	−2 653(6)	6 562(6)	8 582(4)
C(2)	−3 398(6)	7 592(6)	9 281(4)
C(3)	−2 586(7)	8 434(6)	10 232(4)
C(4)	−1 033(7)	8 216(6)	10 480(4)
C(5)	−369(6)	7 141(6)	9 754(4)
C(6)	1 225(6)	6 771(6)	9 948(4)
C(7)	3 378(6)	4 211(6)	8 475(4)
C(10)	1 801(6)	8 152(6)	7 442(4)
C(11)	1 804(7)	9 306(6)	6 998(4)
C(12)	650(7)	9 227(6)	6 186(5)
C(13)	−432(7)	7 946(6)	5 809(4)
C(14)	−341(6)	6 826(6)	6 284(4)
C(15)	−1 440(6)	5 430(6)	5 944(4)
C(16)	−2 571(6)	5 081(6)	5 061(4)
C(17)	−3 530(6)	3 750(7)	4 794(4)
C(18)	−3 359(6)	2 789(6)	5 394(4)
C(19)	−2 215(7)	3 196(6)	6 262(4)

Table 3 Bond distances (Å) and angles (°) for $[CuL(bipy)]ClO_4$ (standard deviations in parentheses)

Cu–N(1)	2.050(4)	N(2)–C(6)	1.281(6)
Cu–N(2)	1.950(4)	N(3)–C(7)	1.328(6)
Cu–S	2.275(2)	N(4)–C(7)	1.337(6)
Cu–N(11)	2.179(4)	C(1)–C(2)	1.377(7)
Cu–N(12)	1.986(4)	C(2)–C(3)	1.365(7)
S–C(7)	1.739(5)	C(3)–C(4)	1.391(7)
N(1)–C(1)	1.335(6)	C(4)–C(5)	1.380(7)
N(1)–C(5)	1.354(6)	C(5)–C(6)	1.460(7)
N(2)–N(3)	1.374(5)		
N(1)–Cu–N(2)	80.3(2)	C(1)–N(1)–C(5)	118.0(4)
N(1)–Cu–S	156.9(1)	N(1)–C(1)–C(2)	122.7(5)
N(1)–Cu–N(12)	95.1(2)	C(1)–C(2)–C(3)	119.3(5)
N(1)–Cu–N(11)	90.7(2)	C(2)–C(3)–C(4)	119.2(5)
N(2)–Cu–S	84.1(1)	C(3)–C(4)–C(5)	118.6(5)
N(2)–Cu–N(12)	174.9(2)	C(4)–C(5)–N(1)	122.2(5)
N(2)–Cu–N(11)	104.0(2)	C(4)–C(5)–C(6)	123.4(5)
S–Cu–N(12)	99.5(1)	N(1)–C(5)–C(6)	114.4(4)
S–Cu–N(11)	109.6(1)	C(5)–C(6)–N(2)	115.9(4)
N(11)–Cu–N(12)	78.2(2)	C(6)–N(2)–N(3)	119.7(4)
Cu–N(1)–C(1)	130.2(3)	N(2)–N(3)–C(7)	111.6(4)
Cu–N(1)–C(5)	110.9(3)	N(3)–C(7)–N(4)	117.0(4)
Cu–N(2)–N(3)	123.6(3)	N(3)–C(7)–S	125.2(4)
Cu–N(2)–C(6)	116.7(3)	N(4)–C(7)–S	117.7(4)
Cu–S–C(7)	94.6(2)		

water (70 cm^3) was slowly added solid Hmmi (239 mg, 2.09 mmol) or Hmi (200 mg, 2.00 mmol). The resulting solutions were warmed briefly and NH_4PF_6 (114 mg, 0.70 mmol) in water (5 cm^3) was added. The precipitates which formed were washed with water and diethyl ether. Yields: $[CuL(Hmmi)_2]PF_6 \cdot H_2O$, 213 mg (51%); $[CuL(Hmi)_2]PF_6 \cdot 0.5H_2O$, 185 mg (47%).

[CuL(mmt)]. The preceding procedure was followed using Hmmt (260 mg, 2.26 mmol) however the product precipitated immediately upon the addition of Hmmt to the $[\{CuL(MeCO_2)\}_2]$ solution. Yield 109 mg (45%).

$[Cu(Hmp)_2]$. Solid H_2mp (86 mg, 0.68 mmol) was slowly added to a solution of $[\{CuL(MeCO_2)\}_2]$ (200 mg, 0.33 mmol) in a water (60 cm^3)–methanol (230 cm^3) mixture. The product, which was obtained as a fine powder, was washed with water, ethanol and diethyl ether. Yield 93 mg (87%).

Crystal Structure of (2,2′-Bipyridyl)(2-formylpyridine thiosemicarbazonato)copper(II) Perchlorate $[CuL(bipy)]ClO_4$.—*Crystal data.* $C_{17}H_{15}ClCuN_6O_4S$, M = 498.4, triclinic, space group $P\bar{1}$, a = 8.560(3), b = 9.452(4), c = 13.078(4) Å, α = 106.35(3), β = 94.66(3), γ = 95.27(3)°, U = 1004.7(7) $Å^3$ (by least-squares refinement of the angular settings of 18 reflections, λ = 0.710 69 Å), Z = 2, D_c = 1.65 g cm^{-3}. Dark green crystals, 0.10 × 0.10 × 0.54 mm, μ(Mo-Kα) = 12.90 cm^{-1}, $F(000)$ = 502.

Data collection and processing. Nicolet R3M four-circle diffractometer at 153 K. ω–2θ Scan with graphite-monochromated Mo-Kα radiation, θ range 2–22.5°, scan width 1.6°, scan speed 3.91° min^{-1}, 2710 unique data measured, (0 to $+h$, $-k$ to $+k$, $-l$ to $+l$) data corrected for Lorentz and polarization effects; empirical absorption corrections applied (maximum and minimum values 0.818 and 0.752 respectively); no corrections were applied for crystal decay since the variation in intensity for the three standards was only 0.6%.

Structure analysis and refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique. A difference electron-density synthesis revealed all hydrogen-atom positions and these were included in the calculations; those for the pyridine and bipyridyl rings and on C(6) were fixed with a C–H length of 1.08 Å. All non-hydrogen atoms were refined assuming anisotropic thermal motion. At convergence R = 0.041 and R' = 0.041 for the 287 variables and 2065 data for which $F > 3\sigma(F)$. The weight w is defined as $2.8766/(\sigma^2F + 0.000\,166F^2)$ with σF being obtained from counting statistics. Computations employed the MULTAN 80[13] and SHELX 76[14] programs. Fractional atomic coordinates are given in Table 2 and selected bond lengths and angles in Table 3.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters, and remaining bond lengths and angles.

Results and Discussion

Nitrogen Donor Ligand Adducts.—Ternary complexes $[CuL(bipy)]^+$, $[CuL(phen)]^+$ and $[CuL(dmap)_2]^+$ were prepared by addition of the appropriate Lewis base to an aqueous solution of the CuL^+ moiety and generally precipitated as green solids upon addition of NH_4PF_6. Analytical data are summarized in Table 1. Physicochemical studies (presented below) suggest that all the complexes are five-co-ordinate cationic species as found for $[CuL(bipy)]ClO_4$. Attempts to prepare an analogous complex with MoS_4^{2-} as the co-anion resulted in the formation of $[CuL(bipy)]_2SO_4 \cdot 8H_2O$, the sulphate apparently having arisen from the thiomolybdate ion. The product contained no Mo but displayed IR bands, at 995 and 615 cm^{-1}, indicative of sulphate.

Crystal Structure of $[CuL(bipy)]ClO_4$.—Crystals of the complex $[CuL(bipy)]ClO_4$ contain discrete five-co-ordinate $[CuL(bipy)]^+$ cations and ClO_4^- anions. A view of the cation is shown in Fig. 1 and selected bond lengths and angles are given in Table 3. The N_4S co-ordination environment around the copper(II) atom arises from the approximately planar 2-formylpyridine thiosemicarbazonato ligand [binding *via* the thiolato S, the N(1) of the pyridine ring, and the imine nitrogen N(2)], and the bipy [co-ordinating *via* its two nitrogens, N(11) and N(12)]. There is no sixth ligand approach to the copper within 4.0 Å and no unusual features in either the bond lengths or angles for L,[5] bipy[15–18] or the ClO_4^- ion are observed.

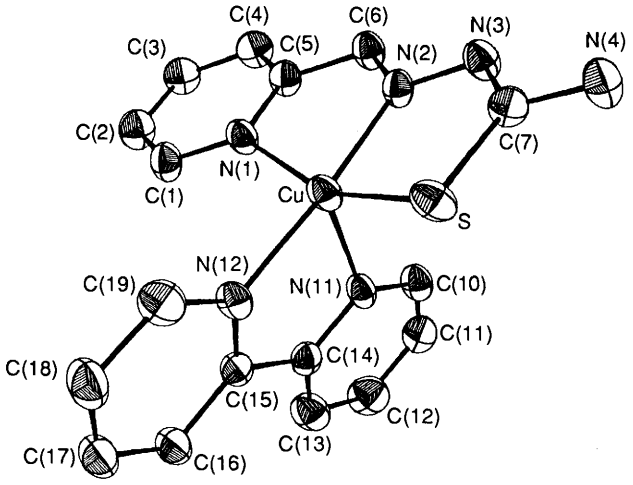


Fig. 1 The structure of the cationic species $[CuL(bipy)]^+$ in the compound $[CuL(bipy)]ClO_4$ showing the numbering system used. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are numbered according to the atoms to which they are attached

Table 4 Electronic spectral and molar conductivity data

Complex	Absorption maxima (nm)[a] S→Cu	d–d	Λ^b/S cm^2 mol^{-1}
$[CuL(bipy)]ClO_4$	415	650, 860	21, 65[c]
$[CuL(bipy)]PF_6$	419	647, 850(sh)	19, 145[d]
$[CuL(bipy)]_2SO_4·8H_2O$	415	670, 890	33
$[CuL(phen)]PF_6$	397	590(sh), 937	30, 153[d]
$[CuL(dmap)_2]PF_6$	400(sh)	635	22
$[\{CuL(pftp)\}_2]·4H_2O$	440	659	14
$[\{CuL(pctp)\}_2]$	426	*e*	9
$[\{CuL(ntp)\}_2]·6H_2O$	426(sh)	*e*	6
$[CuL(mbt)]·0.5H_2O$	420	*e*	8
$[CuL(mi)]·2H_2O·EtOH$	420	*e*	3
[CuL(mmt)]	423	635	—
$[CuL(Hmmi)_2]PF_6·H_2O$	410(sh)	680	23, 67[c]
$[CuL(Hmi)_2]PF_6·0.5H_2O$	420	680	24
$[Cu(Hmp)_2]$	420(sh)	*e*	0

[a] Nujol-mull transmittance spectra. [b] In dimethyl sulphoxide. [c] In nitromethane. [d] In acetone. [e] Obscured by S→Cu c.t. absorption.

The stereochemistry around the copper(II) atom is intermediate between square-pyramidal (*SPY*) and trigonal-bipyramidal (*TBPY*) geometries. Consideration of the distortion from an idealized *TBPY* geometry illustrates this point. Assuming N(2) and N(12) to be the 'axial' donors, an angle of 174.9(2)° is subtended at the Cu^{II}, which is near to the theoretical value of 180°. The angles between these two 'axial' donors and the three 'equatorial' donors, S, N(1) and N(11), range from 78.2(2)° for N(11)–Cu–N(12) to 104.0(2)° for N(2)–Cu–N(11) although the other angles are closer to the expected 90°. The three 'equatorial' angles of N(1)–Cu–S [156.9(1)°], S–Cu–N(11) [109.6(1)°] and N(1)–Cu–N(11) [90.7(2)°] show the most marked differences from the ideal value of 120°. A similar comparison can be made for an idealized *SPY* geometry assuming N(11) to be the 'apical' donor and S, N(2), N(1) and N(12) to form the 'basal' plane.

One of the reasons for the deviations from an idealized stereochemistry is the restricted bite angles imposed by both the L and bipy ligands. In other complexes involving HL or L co-ordinated to copper,[5] the bite angles around the metal [namely N(1)–Cu–N(2) and N(2)–Cu–S] are limited to 80–85°. Similarly the bite angle N(11)–Cu–N(12) of 78.2(2)° for bipy may be considered normal when compared with an average value of 77° cited in the literature.[15–17] The Cu–N(bipy) bond lengths at 1.986(4) and 2.179(4) Å are significantly different as has been observed in other cases where the chelate links 'axial' and 'equatorial' positions [mean Cu–N(bipy) 'equatorial' 2.034 Å, mean Cu–N(bipy) 'axial' 2.179 Å].[15–17] The two pyridine rings of bipy are inclined at an angle of 4.8° to one another *via* a twist around the C(14)–C(15) bond. Similar observations have been made previously.[15–17]

The hydrogen atoms on N(4), the terminal amino group of L, form two hydrogen-bonding contacts. One is to N(3) of an L ligand co-ordinated in an adjacent molecule [N(4)···N(3′) 3.082 Å] and the other weaker contact is to a perchlorate oxygen [N(4)···O(3) 3.208 Å]. No other contacts of significance appear to be present. These results may be contrasted with the extensive hydrogen-bonding scheme involving the co-ordinated sulphate anion in the protonated ligand complex $[\{Cu(HL)(SO_4)\}_2]$.[5]

Physicochemical Studies in the N-Donor Ligand Adducts.—The ternary complexes, $[CuL(bipy)]X$ (X = ClO_4 or PF_6), $[CuL(phen)]PF_6$ and $[CuL(dmap)_2]PF_6$, all show molar conductivities approaching, or equal to, values expected[19] for 1:1 electrolytes (Table 4) indicating that their ionic nature is retained in solution as well as in the solid state. Their electronic spectra (Table 4) exhibit a strong absorption band near 400 nm which is assigned to a S→Cu^{II} ligand-to-metal charge-transfer (l.m.c.t) transition.[5] For the bipy and phen complexes the d–d absorptions are observed as two weaker bands in the ranges 600–650 and 850–940 nm which is not inconsistent,[20] when coupled with the X-ray structural data above, with a distorted trigonal-bipyramidal structure for these chelate CuL^+ ternary complexes. For $[CuL(dmap)_2]PF_6$ only one d–d absorption is observed near 600 nm which is more consistent with the '4 + 1' co-ordination geometry around the Cu^{II} as found in $[\{CuL(MeCO_2)\}_2]$ and $[\{Cu(HL)(SO_4)\}_2]$.[5] Presumably the constraints imposed on the co-ordination sphere by the chelates (bipy and phen) no longer apply when they are replaced by two monodentate dmap ligands. The magnetic moments (Table 1) and the ESR spectral data (Table 5 and Fig. 2) for the complexes are normal for monomeric copper(II) compounds with a $d_{x^2-y^2}$ ground state.

Sulphur Donor Ligand Adducts.—Deprotonated, sterically bulky thiols, containing electron-withdrawing substituents, react in aqueous solution with $[\{CuL(MeCO_2)\}_2]$ to give brown complexes, formulated as $[\{CuL(SR)\}_2]$ [SR = pentafluorothiophenolate (pftp), pentachlorothiophenolate (pctp) or 4-nitrothiophenolate (ntp)] on the basis of analytical (Table 1) and physicochemical (Tables 4 and 5) data. The isolation of stable thiolato complexes of copper(II) is unexpected since thiols usually reduce Cu^{II} to Cu^I with concomitant formation of the appropriate disulphide. Attempts to form stable copper(II)–thiolate bonds as models for Type 1 blue copper proteins[22] have in the main been limited to a few complexes containing tetradentate nitrogen-donor macrocyclic ligands,[23–27] *e.g.* $[CuL'(o\text{-}SC_6H_4CO_2)]·H_2O$ (L′ = *rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane).[23] As well as using the macrocycles which result in more negative Cu^{II}–Cu^I redox potentials, reactions are often carried out at low temperatures using electron-withdrawing substituents on aromatic thiophenols to give a more positive potential to the RSSR–RS^- couple. Unfortunately, in the present study, attempts to grow crystals of the $[\{CuL(SR)\}_2]$ complexes have not been successful.

Excess of thiol causes the reduction of CuL^+ to copper(I). For example, addition of 4-nitrothiophenol (Hntp) to a dimethyl sulphoxide solution of $[\{CuL(MeCO_2)\}_2]$ immediately gives a red solution, which, if left to stand in air, turns green and the disulphide of Hntp crystallizes out. However, if the initial reaction mixture is refluxed under dinitrogen an orange copper(I) complex, [Cu(ntp)], is obtained.

Table 5 ESR spectral results for the complexes

Complex	$g_\perp$	$g_\parallel$	$10^4 A_\parallel$/cm^{-1}	$\alpha^{2\,a}$	State[b]
[CuL(bipy)]ClO_4	2.026 (g_1)	2.068 (g_2), 2.168 (g_3)			Solid
[CuL(bipy)]PF_6	2.032 (g_1)	2.058 (g_2), 2.177 (g_3)	181	0.75	Solid
	2.061	2.181			dmso
[CuL(phen)]PF_6	2.013 (g_1)	2.089 (g_2), 2.179 (g_3)			Solid
[CuL(dmap)$_2$]PF_6	2.063	2.195	173	0.74	Water[c]
[{CuL(pftp)}$_2$]·4H_2O	2.026	2.110			Solid
	2.043	2.151	175	0.69	dmf
[{CuL(pctp)}$_2$]	2.028	2.121			Solid
	2.051	2.150	171	0.69	dmf
	2.038	2.149	176	0.69	EtOH[c]
[{CuL(ntp)}$_2$]·6H_2O		2.077 (g_{iso})			Solid
	2.053	2.151	170[d]	0.69	dmf
[CuL(mbt)]·0.5H_2O	2.029	2.159			Solid
	2.049	2.178	188	0.76	dmf
[CuL(mmt)]	2.035	2.192			Solid
	2.055	2.176	185	0.75	dmf
[CuL(Hmmi)$_2$]PF_6·H_2O		2.078 (g_{iso})			Solid
	2.054	2.195	177[e]	0.75	Water[c]

[a] $\alpha^2 = (A_\parallel/0.036) + (g_\parallel - 2) + (3/7\,(g_\perp - 2) + 0.04$.[21] [b] dmf = Dimethylformamide. [c] Containing 10% (v/v) dmso. [d] Second species present: $g_\parallel$ = 2.187, $A_\parallel$ = 183 × 10^{-4} cm^{-1}. [e] Second species present: $g_\parallel$ = 2.154, $A_\parallel$ = 179 × 10^{-4} cm^{-1}.

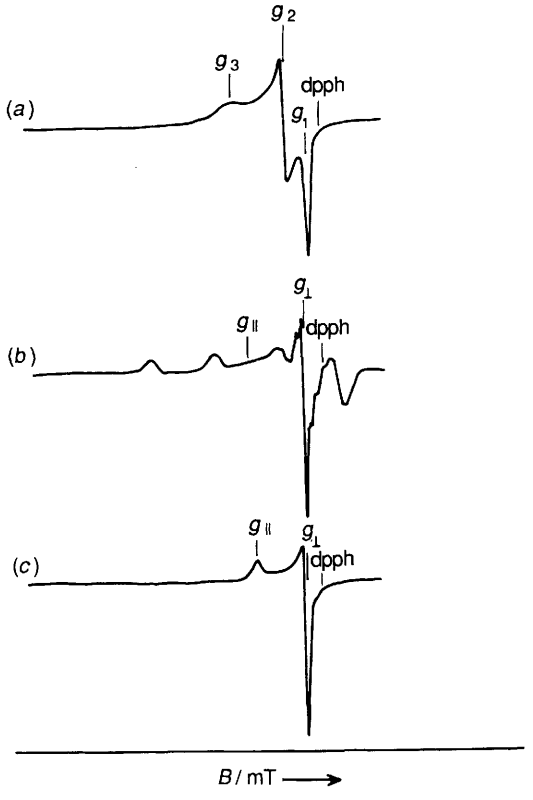


Fig. 2 ESR spectra at 100 K of (*a*) [CuL(bipy)]ClO_4 as a solid, (*b*) [{CuL(pctp)}$_2$] in EtOH–dmso (9:1 v/v) and (*c*) [{CuL(pctp)}$_2$] as a solid

Physicochemical Studies on the S-Donor Ligand Adducts.—The thiolato ligand complexes, [{CuL(SR)}$_2$] (SR = pftp, pctp or ntp) have molar conductivities in dimethyl sulphoxide (Table 4) well below the values expected (50–70 S cm^2 mol^{-1})[19] for 1:1 electrolytes which points to thiolate co-ordination. Further evidence for thiolate co-ordination comes from electronic spectral measurements (Table 4). The complexes are all brown, rather than green as observed for the N-donor ligand adducts, the result of a broad absorption, assignable to a S→Cu^{II} l.m.c.t.,[5,28] centred in the range 400–420 nm and tailing into the visible. The broadness of the band can be explained by the presence of two different, negatively charged, S-donors, co-ordinated in the plane, giving rise to two S→Cu^{II} l.m.c.t. transitions of different energies. Weakly bound axial thiolates do not give intense l.m.c.t. bands in this region.[27] The two components are actually observed [at 395 and 420(sh) nm] only in the case of [{CuL(pctp)}$_2$], dissolved in acetone.

The ESR spectra (Table 5 and Fig. 2) for the [{CuL(SR)}$_2$] complexes also provide evidence for thiolato-adduct formation. The parameters, from spectra recorded in frozen dimethylformamide solution ($g_\parallel \approx 2.15$, $A_\parallel \approx 170 \times 10^{-4}$ cm^{-1}, and $g_\perp \approx 2.05$), may be compared with the values for the parent complex [{CuL(MeCO$_2$)}$_2$] [$g_\parallel$ = 2.198, $A_\parallel$ = 191 × 10^{-4} cm^{-1} and $g_\perp$ = 2.071 in frozen dmso (dimethyl sulphoxide)[5]], where an N_2SO in-plane donor set exists arising from the co-ordinated L ligand and dmso. {Evidence has been presented[5] suggesting that the dimer dissociates into a [CuL(dmso)]$^+$ species.} The lower $g_\parallel$ and $A_\parallel$ values observed for the thiolato-adducts point to the formation of an in-plane 'N_2S_2' donor set with the thiolate replacing the O-donor. If the data are plotted on a Blumberg–Peisach plot[29–31] of $g_\parallel$ *versus* $A_\parallel$ the points fall close to the 'N_2S_2' delineator. Moreover, although comparison of the α^2 covalency parameter[21] must be made with caution for 'N_2S_2' donor sets, and as well co-ordination geometries may vary, it is noted that the value of 0.69 calculated for the thiolato-complexes is consistently lower than that found (0.75) for the N-donor ligand adducts. The introduction of a thiolate ligand into the co-ordination sphere is expected to increase the overall covalent character of the metal–ligand bonding system and hence give α^2 values nearer to 0.5.[21]

The present ESR study gives a firmer chemical basis for the nature of the proposed thiol–CuL^+ interaction[32] in Ehrlich ascites tumour cells,[33] red cell components[10] and cat and human haemoglobins.[34] For instance CuL^+ is readily taken up by Ehrlich cells since it forms cellular adducts.[33] The ESR spectral parameters of the CuL^+ cellular adduct, which could be modelled by the addition of CuL^+ to excess of glutathione or to cat haemoglobin which has several reactive thiols, suggested an 'N_2S_2' in-plane donor set. The parameters are very similar to those found for the isolated thiolate adducts of CuL^+ characterized in this study thus substantiating the conclusions of previous workers.[32]

Dimeric structures are proposed for the [{CuL(SR)}$_2$] (SR = pftp, pctp or ntp) complexes in the solid state with the monomeric units being bridged by two thiolato ligands. The copper atoms are five-co-ordinate with three in-plane donor atoms (NNS) coming from L and the fourth from the bridging SR^- ion. The fifth co-ordination position is occupied by a

less strongly bound sulphur from the second bridging SR^- ion. Dimeric, rather than monomeric, structures are preferred by analogy with the structures found by X-ray diffraction methods for $[\{CuL(MeCO_2)\}_2]$ and $[\{Cu(HL)(SO_4)\}_2]$[5] and the known propensity of thiolates to act as bridging ligands.[35] On the other hand dimeric structures allow a ready pathway for disulphide formation and reduction to copper(I). The magnetic moments of the complexes (Table 1) are in general near to spin-only values at room temperature and the ESR spectra do not show a signal corresponding with the forbidden $\Delta_m = 2$ transition. This is not inconsistent with the copper(II) centres being only very weakly antiferromagnetically coupled as has been found for $[\{CuL(MeCO_2)\}_2]$.[36]

Reaction of S,N *and* S,O *Donor Ligands with* $[\{CuL(MeCO_2)\}_2]$.—An important feature of heterocyclic thioamide ligands such as 2-mercaptobenzothiazole (Hmbt), 2-mercaptoimidazole (Hmi), 2-mercapto-1-methylimidazole (Hmmi) and 3-mercapto-4-methyl-1,2,4-triazole (Hmmt) is their thione to thiol tautomerism and their ability to co-ordinate *via* N or S atoms or both.[37] The reactions of these ligands with $[\{CuL(MeCO_2)\}_2]$ produces either deprotonated ligand complexes *viz.* [CuL(A)] (A = mbt, mi or mmt) or neutral ligand complexes *viz.* $[CuL(HA)_2]PF_6$ (HA = Hmmi or Hmi) depending on the reaction conditions (see Experimental section). The compounds are all green solids which suggests but does not prove that the in-plane donor set is 'N_3S' with the thioamides co-ordinating *via* the N atom rather than the exocyclic S atom. The l.m.c.t. absorptions observed near 420 nm in the electronic spectra are not as broad as for the thiolate adducts and the ESR spectral parameters (Table 5) favour N-donor co-ordination.

The reaction of 2-mercaptopyridin-3-ol (H_2mp) with $[\{CuL(MeCO_2)\}_2]$ affords a brown-green complex which on the basis of analytical and IR evidence is formulated as $[Cu(Hmp)_2]$. The ESR spectrum of this complex has been discussed previously,[31] the parameters pointing to an 'S_2O_2' in-plane donor set.

Conclusion

Stable Lewis-base adducts of CuL^+ with N- and S-donor ligands have been isolated and characterized thus substantiating earlier proposals for their formation in solution or *in vivo*. The remarkable stability of the copper(II) state relative to copper(I) when the metal is co-ordinated to the 2-formylpyridine thiosemicarbazonato ligand is exemplified by the isolation of the thiolate adducts and also an iodo complex.[5] As for copper(II)–macrocycle complexes, an important feature in providing a kinetic barrier to reduction must be the steric constraint provided by the presence of the rigid planar structure around the copper(II) demanded by the binding of the 2-formylpyridine thiosemicarbazonato ligand. The half-wave reduction potential in aqueous solution for CuL^+ is only 0.002 V lower than the value of 0.120 V exhibited by the more flexible $[Cu(bipy)_2]^{2+}$ complex but more positive than the −0.080 V found for $[Cu(terpy)]^{2+}$ (terpy = 2,2′:6′,2″-terpyridyl).[11] However, although terpy also generates a rigid tricyclic ring system around the metal, it does not provide a soft S-donor atom.

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