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X-ray and Spectroscopic Studies of Cu(II) Complex with 2-Amino-1,3-thiazoline

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A compound of the type 2:1 2-amino-1,3-thiazoline hydrochloride–$CuCl_2$ was prepared and characterized by means of X-ray and spectroscopic measurements. Crystals of the complex $(ATH)_2CuCl_4$ (ATH^+ = 2-amino-1,3-thiazoline cation) are monoclinic, space group C2/c, with a *= 27.772(13) Å,* b *= 7.811(4) Å,* c *= 15.609(7) Å, β = 112.09(5)° and Z = 8. The structure was solved by the heavy atom technique and refined by full-matrix least-squares calculations to a final* R *= 0.042 for 2356 counter reflections. The crystal consists of a $CuCl_4^{2-}$ anion and two ATH^+ cations. There is no direct bonding between the metal atom and the ATH molecule. The $CuCl_4^{2-}$ ion shows a slight tetrahedral distortion with two large Cl–Cu–Cl angles (131.9 and 141.1(6)°). The Cu–Cl distances range from 2.221 to 2.271(1) Å. The ATH^+ cations are linked to $CuCl_4^{2-}$ units through hydrogen bonding involving the amino nitrogen atoms. Both 2-amino-1,3-thiazoline molecules have a similar conformation. This conformation is different from that of 2-amino-1,3-thiazoline hydrochloride. The spectroscopic studies have shown that in methanol solution the direct metal-2-amino-1,3-thiazoline bond is formed via heterocyclic nitrogen. The $Cu(AT)_2^{+2}$ complex is formed as a major species.*

Introduction

Gosálvez *et al.* [1–4] have reported that the compounds thiazoline-4-carboxylic acid (thiaproline) and 2-amino-1,3-thiazoline hydrochloride are both able to induce the restoration of 'contact inhibition' in tumour cells previously devoid of it [5]. Thiaproline was selected as a ligand possibly able to chelate a metal from a protein complex in the plasma membrane which could be the origin of contractile microfilaments [1, 6]. 2-Amino-1,3-thiazoline hydrochloride was selected as the only analog of thiaproline which is known to induce reverse transformation of tumour cells [7].

Recent potentiometric and IR studies of D. R. Williams *et al.* [8] suggest that the binding sites are the nitrogen donors for zinc, manganese, nickel and copper having some carboxylate involvement as appropriate. The nitrogens involved were suggested to be the secondary in thiaproline and the primary in 2-amino-1,3-thiazoline. Since the mechanism of anticancer action strongly depends on the metal-ligand binding we have undertaken the X-ray and spectroscopic studies of several metal complexes with thiaproline and 2-amino-1,3-thiazoline.

This paper reports the spectroscopic results and the X-ray structure of cupric complex with 2-amino-1,3-thiazoline.

Experimental

2-Amino-1,3-thiazoline hydrochloride was used as received from Trans World Chemicals, Washington, D.C. $CuCl_2$ was used as a metal ion source.

Yellow crystals of $(ATH)_2CuCl_4$ were prepared by crystallization from aqueous solution containing 1:2 molar ratio of $CuCl_2$ and 2-amino-1,3-thiazoline hydrochloride.

The solution studies were done for the 1:2 Cu^{2+} to ligand molar ratio with metal concentration of $5 \cdot 10^{-3}$ *M*.

EPR spectra were measured on a JEOL JES-ME-3X spectrometer in liquid nitrogen temperature at 9.13 GHz. The absorption spectra were recorded on a Beckman 5204 spectrophotometer.

Data of X-ray intensities were collected on a Syntex $P2_1$ computer controlled four-circle diffractometer equipped with a scintillation counter and graphite monochromator.

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TABLE I. Positional Parameters and B_{eq} (Å)^2 Values for the non-H Atoms with e.s.d.s in Parentheses.

	x	y	z	B_{eq}
Cu	0.12560(2)	0.28171(7)	0.35125(4)	3.05(4)
Cl(1)	0.13987(5)	0.28448(20)	0.22047(9)	4.95(11)
Cl(2)	0.10180(5)	0.55339(16)	0.35237(9)	4.23(10)
Cl(3)	0.16799(6)	0.24707(17)	0.50601(9)	4.19(10)
Cl(4)	0.08037(5)	0.03317(16)	0.32968(8)	3.68(9)
S(1)	0.4631(1)	0.1997(2)	0.0224(1)	4.4(1)
S(2)	0.2582(1)	0.0918(2)	0.1404(1)	4.9(1)
N(1)	0.4848(2)	0.3132(8)	−0.1186(3)	5.4(5)
N(2)	0.5515(2)	0.2911(7)	0.0247(3)	4.7(4)
N(3)	0.1688(2)	0.1757(8)	0.0096(3)	4.5(4)
N(4)	0.2232(2)	0.3911(6)	0.0904(3)	4.9(4)
C(1)	0.5030(2)	0.2750(6)	−0.0308(3)	3.6(4)
C(2)	0.5657(2)	0.2324(9)	0.1189(4)	4.6(5)
C(3)	0.5156(2)	0.1981(10)	0.1338(4)	4.8(5)
C(4)	0.2116(2)	0.2308(6)	0.0732(3)	3.4(4)
C(5)	0.2744(4)	0.4292(14)	0.1581(7)	9.0(10)
C(6)	0.2945(3)	0.2672(14)	0.2107(6)	7.8(9)

$B_{eq} = 1/3\Sigma B_{ii}$

Positional Parameters and Isotropic Thermal Parameters (Å)^2 for the H atoms.

	x	y	z	B_{iso}
H(21)	0.589(2)	0.317(7)	0.165(4)	6.1(15)
H(22)	0.585(2)	0.132(7)	0.125(3)	5.2(14)
H(31)	0.514(2)	0.283(7)	0.171(4)	9.1(15)
H(32)	0.513(2)	0.098(7)	0.151(4)	9.8(15)
H(51)	0.290(2)	0.449(7)	0.123(4)	9.4(15)
H(52)	0.272(2)	0.524(7)	0.201(4)	11.2(14)
H(61)	0.284(2)	0.266(7)	0.264(4)	6.8(15)
H(62)	0.331(2)	0.249(7)	0.226(4)	12.9(15)
H(1)	0.502(2)	0.349(6)	−0.145(3)	2.3(10)
H(2)	0.450(2)	0.299(7)	−0.141(4)	7.9(16)
H(3)	0.168(2)	0.079(7)	0.011(3)	5.5(15)
H(4)	0.144(2)	0.237(7)	−0.037(4)	12.6(15)
HN(2)	0.574(2)	0.302(7)	0.004(4)	4.5(14)
HN(4)	0.202(2)	0.467(7)	0.063(4)	6.8(14)

Crystal Structure

The crystal structure analysis was carried out to establish possible involvement of AT ligand in metal ion coordination *via* its potential donor system, *i.e.* S, N heterocyclic or NH_2. The spectroscopic studies do not show clearly any interaction of cupric ion with AT within the available pH range (see below) and the recent work of Williams *et al.* [8] has suggested amino nitrogen as a main binding site of the AT molecule.

Structure Determination of $(ATH)_2CuCl_4$

Crystals of $(ATH)_2CuCl_4$ are monoclinic, space group $C2/c$, a = 27.772(13), b = 7.811(4), c = 15.609(7) Å, β = 112.09(5)°, V = 3137.5 Å^3, D_c = 1.74 g cm^{-3}, D_m = 1.75 g cm^{-3}, Z = 8, μ(MoK$_\alpha$, λ = 0.71069 Å) = 23.4 cm^{-1}.

Intensities from a crystal 0.12 × 0.15 × 0.15 mm were collected using graphite-monochromatized MoKα radiation on a Syntex P2_1 diffractometer with an θ–2θ scan. 2356 reflections with $I > 1.96\ \sigma(I)$ were used in the structure determination. The data were corrected for Lorentz and polarization effects only.

The structure was solved by the heavy-atom method and refined by full-matrix least-squares with anisotropic temperature factors for the non-H atoms. All the H atoms were located from the subsequent difference Fourier synthesis after the anisotropic refinement of the non-hydrogen atoms. The atomic-scattering factors were taken from International Tables for X-ray Crystallography 1974 [9]. Full-matrix least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms and

TABLE II. Anisotropic Thermal Parameters with e.s.d.s in Parentheses.[a]

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cu	3.35(3)	3.20(2)	2.59(2)	0.18(2)	0.78(2)	0.01(2)
Cl(1)	4.96(7)	6.39(8)	3.49(5)	0.58(6)	2.10(5)	0.15(5)
Cl(2)	4.66(6)	3.50(6)	4.53(6)	0.98(5)	0.84(5)	−0.31(5)
Cl(3)	4.99(7)	4.72(7)	2.86(5)	−0.35(5)	−0.00(5)	0.14(4)
Cl(4)	4.20(6)	3.31(5)	3.54(5)	−0.42(5)	0.38(4)	0.06(4)
S(1)	3.23(6)	6.62(8)	3.26(5)	0.27(6)	1.04(4)	0.44(5)
S(2)	4.32(7)	6.43(9)	4.06(6)	1.88(6)	0.23(5)	0.13(6)
N(1)	5.4(3)	7.6(3)	3.3(2)	−0.6(2)	1.4(2)	1.4(2)
N(2)	3.5(2)	6.8(3)	3.9(2)	−1.1(2)	1.0(2)	−0.1(2)
N(3)	3.7(2)	5.3(3)	4.5(2)	−0.2(2)	0.1(2)	−0.2(2)
N(4)	5.7(3)	3.9(2)	5.0(2)	−0.3(2)	2.3(2)	−0.3(2)
C(1)	3.7(2)	4.2(2)	3.1(2)	−0.1(2)	1.0(2)	−0.0(2)
C(2)	3.8(3)	6.5(4)	3.6(2)	0.4(3)	0.3(2)	−0.0(2)
C(3)	5.1(3)	6.3(4)	3.1(2)	0.4(3)	0.6(2)	0.6(3)
C(4)	3.2(2)	4.0(2)	3.0(2)	−0.0(2)	1.5(2)	−0.1(2)
C(5)	8.9(6)	9.7(6)	8.5(5)	−5.3(5)	5.2(5)	−5.0(5)
C(6)	5.2(4)	12.4(7)	5.6(4)	0.4(4)	−0.1(3)	−3.5(4)

[a] The temperature factor is of the form: $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

TABLE III. Bond Distances (Å) and Angles (°) with e.s.d.s in Parentheses.

Cu–Cl(1)	2.221(1)	Cl(1)–Cu–Cl(2)	98.87(6)
Cu–Cl(2)	2.225(1)	Cl(1)–Cu–Cl(3)	141.13(6)
Cu–Cl(3)	2.271(1)	Cl(1)–Cu–Cl(4)	98.76(6)
Cu–Cl(4)	2.267(1)	Cl(2)–Cu–Cl(3)	98.16(6)
		Cl(2)–Cu–Cl(4)	131.93(6)
		Cl(3)–Cu–Cl(4)	95.31(5)
S(1)–C(1)	1.720(6)	C(1)–S(1)–C(3)	91.9(3)
S(1)–C(3)	1.801(6)	C(1)–N(2)–C(2)	117.7(5)
C(1)–N(1)	1.304(7)	N(2)–C(2)–C(3)	107.2(5)
C(1)–N(2)	1.305(7)	S(1)–C(3)–C(2)	107.9(5)
C(2)–N(2)	1.446(7)	S(1)–C(1)–N(2)	113.8(4)
C(2)–C(3)	1.519(10)	N(2)–C(1)–N(1)	124.8(5)
		S(1)–C(1)–N(1)	121.3(4)
S(2)–C(4)	1.713(5)	C(4)–S(2)–C(6)	90.7(4)
S(2)–C(6)	1.807(10)	C(4)–N(4)–C(5)	116.7(6)
C(4)–N(3)	1.302(7)	N(4)–C(5)–C(6)	106.7(8)
C(4)–N(4)	1.295(7)	S(2)–C(6)–C(5)	107.4(7)
C(5)–N(4)	1.449(12)	S(2)–C(4)–N(3)	121.3(4)
C(5)–C(6)	1.498(15)	N(4)–C(4)–N(3)	124.2(5)
		S(2)–C(4)–N(4)	114.5(4)

Hydrogen bonds

D–H		A	D····A	A····H	<DHA
N(1)–H(1)	0.79(5) Å	$Cl(4)_i$	3.278(7) Å	2.53(5) Å	159(5)°
N(3)–H(4)	0.92(6)	$Cl(2)_{ii}$	3.245(6)	2.35(6)	164(5)
N(4)–HN(4)	0.82(6)	$Cl(3)_{ii}$	3.249(5)	2.46(6)	160(5)

i: 0.5 + x, 0.5 − y, z − 0.5; ii: x, 1 − y, z − 0.5

(continued overleaf)

TABLE III. *(continued)* Bond Lengths and Angles involving H Atoms.

N(1)–H(1)	0.79(5)	H(1)–N(1)–H(2)	127(5)
N(1)–H(2)	0.89(7)	C(1)–N(1)–H(1)	124(3)
N(2)–HN(2)	0.81(6)	C(1)–N(1)–H(2)	109(4)
C(2)–H(21)	1.01(6)	C(1)–N(2)–HN(2)	120(4)
C(2)–H(22)	0.93(6)	C(2)–N(2)–HN(2)	119(4)
C(3)–H(31)	0.90(6)	H(21)–C(2)–H(22)	107(5)
C(3)–H(32)	0.84(6)	C(3)–C(2)–H(21)	112(3)
		C(3)–C(2)–H(22)	111(3)
		H(31)–C(3)–H(32)	117(6)
		C(2)–C(3)–H(31)	105(4)
		C(2)–C(3)–H(32)	114(4)
N(3)–H(3)	0.76(5)	H(3)–N(3)–H(4)	122(6)
N(3)–H(4)	0.92(6)	C(4)–N(3)–H(3)	109(4)
N(4)–HN(4)	0.82(6)	C(4)–N(3)–H(4)	129(4)
C(5)–H(51)	0.83(6)	C(4)–N(4)–HN(4)	121(4)
C(5)–H(52)	1.02(6)	C(5)–N(4)–HN(4)	122(4)
C(6)–H(61)	0.98(6)	H(51)–C(5)–H(52)	119(5)
C(6)–H(62)	0.96(7)	C(6)–C(5)–H(51)	110(4)
		C(6)–C(5)–H(52)	111(3)
		H(61)–C(6)–H(62)	115(5)
		C(5)–C(6)–H(61)	108(4)
		C(5)–C(6)–H(62)	113(4)

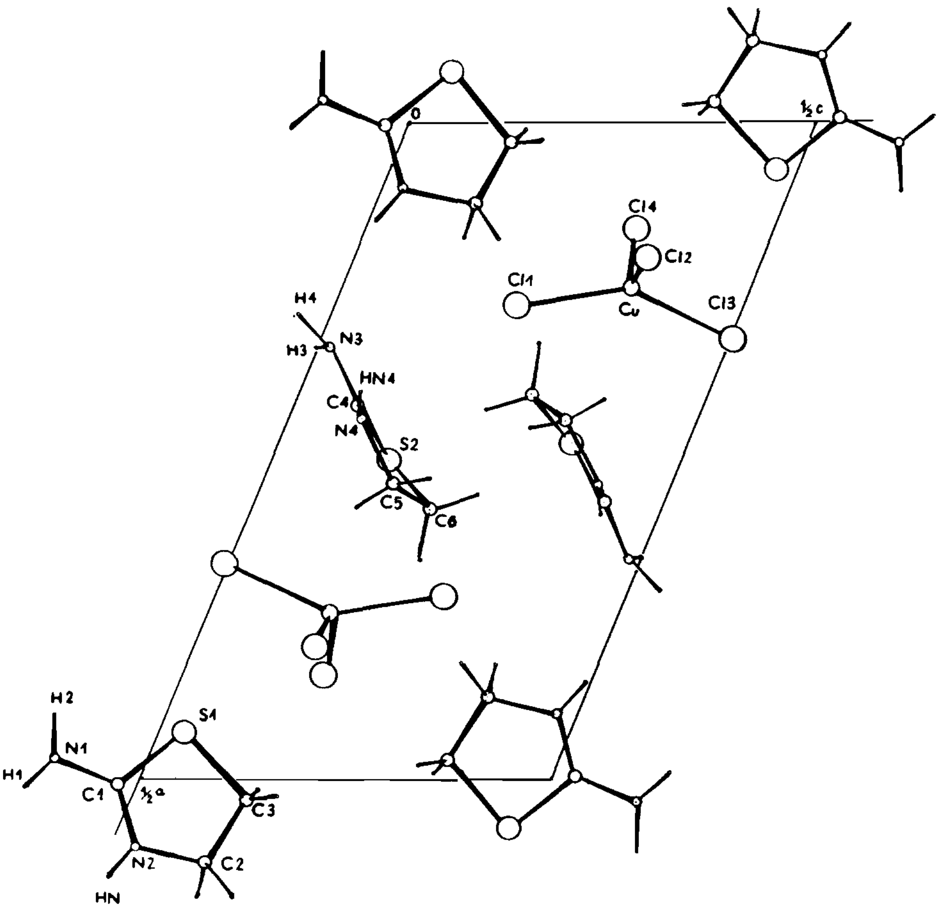

Fig. 1. A fragment of the crystal structure viewed down *b* with the numbering system used.

TABLE IV. Least-Squares Planes. Deviations (Å) of Relevant Atoms from the Planes and their e.s.d.s are given in Parentheses.

Plane 1 through N(1), C(1), S(1), N(2)
$0.2766\ X - 0.9372\ Y - 0.2124\ Z - 1.9900 = 0$
N(1) −0.003(6), C(1) 0.005(5), S(1) 0.000(2), N(2) −0.002(5), C(2) 0.095(7), C(3) −0.108(7)

Plane 2 through C(2), C(3), S(1)
$0.1647\ X - 0.9823\ Y - 0.0896\ Z - 0.5359 = 0$
N(2) −0.303(5), C(1) −0.275(5), N(1) −0.453(6)

Plane 3 through N(3), C(4), S(2), N(4)
$0.7416\ X + 0.0088\ Y - 0.6708\ Z - 3.3516 = 0$
N(3) 0.003(5), C(4) −0.006(5), S(2) 0.000(2), N(4) 0.002(5), C(5) 0.109(10), C(6) −0.229(9)

Plane 4 through C(5), C(6), S(2)
$0.9028\ X - 0.0776\ Y - 0.4230\ Z - 4.8160 = 0$
N(4) −0.489(6), C(4) −0.486(5), N(3) −0.799(5)

Plane 5 through Cu, Cl(1), Cl(2)
$-0.8223\ X - 0.2548\ Y - 0.5089\ Z + 4.3187 = 0$
Cl(3) −1.291(1), Cl(4) 1.582(1)

Plane 6 through Cu, Cl(3), Cl(4)
$0.8641\ X - 0.4767\ Y - 0.1614\ Z + 0.6366 = 0$
Cl(1) 1.301(2), Cl(2) −1.591(2)

Interplanar angles (°)
1–2 9.9; 3–4 17.7; 5–6 59.5

isotropic temperature factors for all hydrogen atoms converged at $R = 0.042$ and $R_w = 0.043$. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/\sigma 2\ F$.

All calculations were performed on a Nova 1200 computer with the Syntex XTL structure determination system. Final positional and thermal parameters are given in Tables I–II. The calculated bond lengths and angles are shown in Table III. Figure 1 shows a fragment of the crystal structure viewed down b and indicates the numbering system used.

Description of the Structure

The crystal structure consists of a tetrachlorocuprate anion and two protonated 2-amino-1,3-thiazoline cations held together by a combination of ionic and hydrogen-bonded contacts.

As in most other known structures with $CuCl_4^{2-}$ anions [10, 11], the coordination polyhedron around the Cu is approximately a flattened tetrahedron, since two Cl–Cu–Cl angles [131.9, 141.1(6)°] are greater than tetrahedral, while the others are smaller. The Cu–Cl distances range from 2.221 to 2.271(1) Å. The deformation from the tetrahedral geometry can be expressed by the dihedral angle between Cu, Cl(1), Cl(2) and Cu, Cl(3), Cl(4) planes equal to 59.5° in the studied compound (Table IV).

All bond distances and angles of both protonated 2-amino-1,3-thiazoline molecules fall into the expected range. The exocyclic bonds C(1)–N(1) and C(4)–N(3) are short (1.304, 1.302(7) Å) and their lengths are comparable to those of endocyclic C(1)–N(2) and C(4)–N(4) bonds (1.305 and 1.295(7) Å). The endocyclic S–C(sp^2) and S–C(sp^3) distances range from 1.713 to 1.720(6) and from 1.801(6) to 1.807(10) Å, respectively. These bond distances and angles in the 2-amino-1,3-thiazoline cations indicate extensive electron delocalization in the part of the molecule including N(exo)–CS–N-(endo) atoms. This distribution of bond lengths is in good agreement with values obtained from the structure determination of 2-amino-1,3-thiazoline hydrochloride [12] and other aminothiazoline structures [13, 14].

The two independent ATH molecules are very similar in their geometry and conformation. The thiazoline rings are not planar, with carbon atoms situated on opposite sides of the NCSN planes at 0.095, −0.108(7) Å and 0.109, −0.229(10) Å, respectively.

This conformation is different from that of the 2-amino-1,3-thiazoline hydrochloride [12], where the thiazoline ring has an envelope-like conformation. Therefore effects of the packing forces may be responsible for the actual conformation found in the various aminothiazoline ligands.

Spectroscopic Methods in Solution

EPR and Absorption Spectra of the Cu(II)–AT System

The EPR spectrum of the powder sample obtained from yellow crystals gives three g values; $g_1 = 2.365$, $g_2 = 2.147$ and $g_3 = 2.038$. These values correspond well to the distorted tetrahedral environment around the cupric ion found by X-ray (see above). The crystals dissolved in water give poorly resolved spectra and the pH variation up to 5.5 does not improve or change these spectra. At pH ~ 6 precipitation occurs and the ligand decomposition could be observed. The absorption spectrum of the Cu(II)–AT system in aqueous solutions up to pH ~ 6 does not show any shift of the d–d transition with pH and in all studied samples the d–d band was centered at 800 nm ($\epsilon = 12\ M^{-1}\ cm^{-1}$). The latter value corresponds well to cupric aquoion species [15].

In the UV region, besides the free ligand transitions at 208 ($\epsilon \sim 14000\ M^{-1}\ cm^{-1}$) and 230 nm ($\epsilon \sim 8000\ M^{-1}\ cm^{-1}$), absorption at 300 nm ($\epsilon = 200\ M^{-1}\ cm^{-1}$) is observed. The latter band may be assigned as the $Cl^- \rightarrow Cu(II)$ charge transfer transition which suggests some amount of cupric ion bound to Cl^- ion [16].

The EPR spectra of the frozen methanol solution of the yellow crystals are well resolved and they indicate the presence of two cupric species. Both species have axial g and A tensors. One of them, with $g_\parallel = 2.449$ and $A_\parallel = 12.36$ mK, corresponds to solvated cupric ion and the other one to cupric ion with chlorides in its coordination sphere. The absorption spectra of these solutions with the d–d band at 860 nm does not indicate any direct involvement of AT in metal ion binding. The two other transitions at 410 ($\epsilon = 40\ M^{-1}\ cm^{-1}$) and 285 nm ($\epsilon = 600\ M^{-1}\ cm^{-1}$) are most likely the $Cl \rightarrow Cu(II)$ charge transfer transitions of the different species present in solution [16–20]. The latter result indicates that methanol molecules are less competitive for chloride ion binding to metal ion than those of water (see above).

The addition of NaOH to the methanol solution containing dissolved $(ATH)_2CuCl_4$ crystals leads to considerable variation of EPR and absorption spectra. An increase in solution basicity leads to a shift of the d–d band from 860 ($\epsilon = 58\ M^{-1}\ cm^{-1}$) to 615 nm ($\epsilon = 88\ M^{-1}\ cm^{-1}$) (or to 675 nm in 1:1 Cu:AT molar ratio solutions). This considerable increase in the d–d transition energy indicates the direct involvement of the AT molecule in cupric ion binding *via* nitrogen donors. At least two such donors are needed to shift the d–d band to 615 nm (the 675 nm band suggests that nitrogen is bound to the Cu(II) ion in a major species formed in the 1:1 molar ratio solutions) [15, 26]. The UV absorption spectrum of a free ligand is limited to a single band at 220 nm ($\epsilon \sim 5600\ M^{-1}\ cm^{-1}$) which is almost insensitive on a protonation state of the thiazoline molecule *i.e.* transition of ATH to AT changes the ϵ value only slightly. Also the formation of the metal–nitrogen bond seen in the d–d region does not affect the intraligand transitions distinctly. The addition of NaOH also causes the appearance of the EPR spectrum of the new species and its intensity increases with amount of added base. The EPR parameters of this spectrum are $g_\parallel = 2.366$, $g_\perp = 2.080$, $A_\parallel = 14.58$ mK. When the intensity of the latter spectrum reaches about 70% of the total copper(II) spectrum (Fig. 2), precipitation occurs similar to that observed for aqueous solutions. Thus the use of methanol solutions permits the observation of the formation of the direct Cu(II)–AT bond *via* a nitrogen donor with formation of $Cu(AT)_2^{+2}$ complex species.

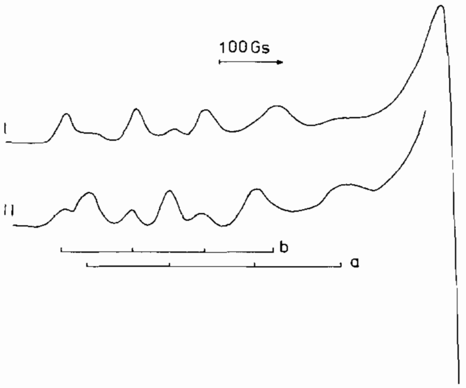

Fig. 2. EPR spectra of methanol solutions containing Cu^{2+} and AT with different amounts of base added: I (90 mmol/dcm^3), II (300 mmol/dcm^3). Two overlapped spectra correspond to complexed (a) $CuAT^{2+}$ and solvated (b) cupric ion.

Conclusions

Though the X-ray study of the 2-amino-1,3-thiazoline complex with the cupric ion does not indicate any direct involvement of the ligand donors in metal ion binding, its accurate performance, including hydrogen atom fitting (see above) permits conclusions to be made about possible coordination sites in the thiazoline molecule. The strong delocalization of the ring double bond over the $N–C–NH_2$ fragment excludes the primary nitrogen (NH_2) as a protonation site by hydrochloride proton. This delocalization process, however, makes the heterocyclic nitrogen capable of accepting such a proton (see above). Thus the pK value of 8.4 found for 2-amino-1,3-thiazoline is most likely to correspond to the protonation of the secondary and not the primary nitrogen as was assumed in the potentiometric studies, at least in its major tautomeric form. The relatively high value of pK indicates that ring nitrogen is a considerably basic site. This explains why in the aqueous solutions in the available pH range up to pH $\cong$ 6.0 no nitrogen involvement in metal binding is seen by spectroscopy. The use of methanol solvent, however, permits the observation of direct Cu(II)-2-amino-1,3-thiazoline binding. The formation of $Cu(AT)_2^{+2}$ complex ion with two nitrogens bound to the cupric ion is observed before the decomposition of the ligand.

The presence of a protonation site at heterocyclic nitrogen indicates that this site would be a major binding site after deprotonation for metal ions like Cu^{2+}, Zn^{2+}, Ni^{2+}, Cd^{2+} in the proper pH range. As can be seen from the results presented in this paper the amino nitrogen does not seem to play an important role in the direct binding of the metal center. Also the sulfur donor does not bind the cupric ion though in some cases thioether sulfur may be a binding site of Cu^{2+} [21–23].

The S–C(1) bond is distinctly shorter than S–C(3) (Table III) which suggests some π character in the S–C(1) bond. It may also decrease the ability of the sulfur donor to bind the metal ion.

The possible involvement of the heterocyclic nitrogen as a major binding site for metal ions makes 2-amino-1,3-thiazoline very similar as a ligand to the thiaproline molecule. In the latter case the ring nitrogen plays a major role in metal binding though carboxylate involvement is also likely [8, 24, 25]. This similarity in metal ion binding may indicate that the ring nitrogen of both ligands and their possible chemical analogues could play a critical therapeutic role as inducers of reverse transformation, *i.e.* it may be responsible for the binding of a metal ion to a protein complex in the plasma membrane.

References

1 M. Gosálvez, Abstract, *Proc. AACR New Orleans, 20,* 17 (1979).

2 M. Gosálvez, C. Vivero and I. Alvarez, *Biochem. Soc. Trans., 7,* 191 (1979).

3 M. Gosálvez, *Abstract, AACR San Diego, 528,* 132 (1980).

4 A. Brugarolas and M. Gosálvez, *Lancet,* January, 68 (1980).

5 T. Puck, *Proc. Natl. Acad. Sci., 74,* 4491 (1977).

6 M. Gosálvez, L. Pecci and C. Vivero, *Biochem. Soc. Trans., 6,* 659 (1978).

7 J. Diaz-Gil and M. Gosálvez, 72nd Meeting AACR, Washington, D.C. (1981).

8 Z. X. Huang, P. M. May, D. R. Williams, and M. Gosálvez, *Inorg. Chim. Acta, 56,* 41 (1981).

9 International Tables for X-ray Crystallography, Vol. IV, Kynoch Press, Birmingham (1974).

10 H. J. Buser and G. W. Watt, *Acta Cryst., B35,* 91 (1979).

11 M. R. Caira, G. V. Fazakerley, P. W. Linder and L. R. Nassimbeni, *Acta Cryst., B30,* 1660 (1974).

12 B. M. Vedavathi and K. Vijayan, *Acta Cryst., B37,* 475 (1981).

13 R. Balhy and J. P. Mornon, *Acta Cryst., B29,* 1157 (1973).

14 C. Cohen-Addad and M. P. Viollet, *Cryst. Struct. Commun., 7,* 341 (1978).

15 G. Formicka-Kozłowska, H. Kozłowski and B. Jeżowska-Trzebiatowska, *Inorg. Chim. Acta, 25,* 1 (1977).

16 J. Sykora, E. Harvath and I. Gažo, *Z. Chem., 18,* 346 (1978).

17 R. D. Braun, *Fresenius Z. Anal. Chem., 285,* 47 (1977).

18 D. J. Miller, *Inorg. Nucl. Chem. Lett., 14,* 255 (1978).

19 J. R. Ferraro, *J. Coord. Chem., 5,* 101 (1976).

20 D. Abdelaziz, A. Therr-Sorrel, R. Perret, B. Chaillot and J. Guerchais, *Bull. Soc. Chim. Fr., 3,* 535 (1975).

21 H. Kozłowski and T. Kowalik, *Inorg. Chim. Acta, 34,* L231 (1978).

22 V. M. Miskowski, J. A. Thich, R. Solomon and H. J. Schugar, *J. Am. Chem. Soc., 98,* 8344 (1976).

23 A. C. Braithwaite, C. E. F. Richard and T. H. Waters, *J. Chem. Soc. Dalton Trans.,* 1817 (1975).

24 T. Tatarowski and H. Kozłowski, unpublished results.

25 F. Bigoli, M. Lanfranchi, E. Leporati and M. A. Pellinghelli, *Cryst. Struct. Commun., 9,* 1255 (1980).

26 G. Formicka-Kozłowska, H. Kozłowski, I. Z. Siemion, K. Sobczyk and E. Nawrocka, *J. Inorg. Biochem., 15,* 201 (1981).