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Metal complexes of cimetidine. Synthesis, X-ray structure determination and semiempirical calculations on the [cimetidinatecopper(II)]$^+$ cation

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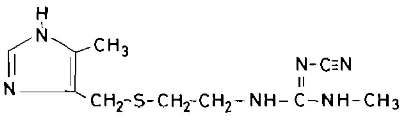
Abstract

The addition of a methanolic solution of cimetidine (**1**) to a methanolic solution of M^{2+} cations (M = Co, Ni, Cu, Zn) affords the cationic complexes $[M(\mathbf{1})_2]^{2+}$. In the case of M = Cu the addition of KOH in the reaction medium at 60 °C gives the $[Cu(\mathbf{2'})]^+$ cation, where **2'** is an anionic ligand resulting from deprotonation of a cimetidine molecule modified by methanolic solvolysis of the nitrilic function. The X-ray structure characterization of $[Cu(\mathbf{2'})]X \cdot 0.5H_2O$ has been performed for $X = ClO_4^-$ (**5**) and I^- (**6**). Compound **5** is monoclinic, space group $C2/c$ with $a = 20.732(8)$, $b = 7.471(3)$, $c = 23.734(5)$ Å, $\beta = 100.76(3)°$, $Z = 8$, $R = 0.034$, $R_w = 0.045$ for 1767 reflections with $I > 3\sigma(I)$. Compound **6** is monoclinic, space group $C2/c$ with $a = 20.736(3)$, $b = 7.426(3)$, $c = 22.786(2)$ Å, $\beta = 99.65(1)°$, $Z = 8$, $R = 0.029$, $R_w = 0.045$ for 2498 reflections with $I > 3\sigma(I)$. In both compounds the **2'** anion acts as a tetradentate ligand coiled around the almost square planar metal center. Quantomechanical semiempirical calculations (CNDO/2) have been carried out on simple models of **2'**, **5** and **6**.

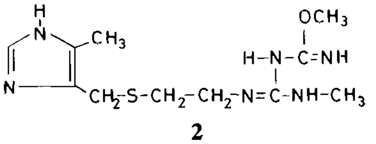
Introduction

The potent histamine H_2-receptor antagonist cimetidine (**1**), traded under the name TAGAMET* has been extensively used for the treatment of the peptic ulcer [1].



1

It is well known that copper, which is recognized to be an essential metallo-element in biochemical processes, is present in tissues and fluids and the amount of this metal correlates with many metabolic processes requiring metal ions. Although there are historical reports on the anti-ulcer activity of copper compounds in the treatment of peptic ulcer [2–4], there are as yet no modern-day uses of copper compounds in the treatment of this disease. It seemed to us a good idea, in performing anti-ulcer drug design in order to increase the pharmacological activity of several kinds of drugs, to synthesize and characterize copper complexes of some H_2-blockers belonging to the cimetidine family. The interaction of cimetidine with copper(II) has been previously studied by Greenaway *et al.* [5], who reported the X-ray structure of two complexes: the green $[Cu(\mathbf{1})_2](ClO_4)_2$ (**3**) and the blue $[Cu(\mathbf{2})ClO_4]ClO_4$ (**4**), where **2** is a cimetidine molecule, modified by methanolic solvolysis of the nitrilic function.



2

Moreover the structural isomerism in three $[Cu(\mathbf{1})_2]^{2+}$ complexes has been investigated (see ref. 6 and refs. therein). The cationic unit $[Cu(\mathbf{1})_2]^{2+}$ is an infinite polymer. The copper atom lies on a crystallographic centre of symmetry and displays a strongly distorted octahedral CuN_4S_2 environment.

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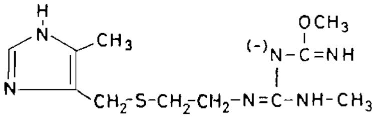
*Marketed by Smith, Kline and French, Philadelphia, PA.

0020-1693/91/$3.50

Two centrosymmetrically related cimetidine molecules are chelated through the N(imidazole) and S(thioether) atoms and two other centrosymmetrically related molecules are coordinated through the N(cyano) atom. The distortion is quite different from one complex to another and the infinite chains are characterized by different conformations of the cimetidine molecule, depending on the counterion and the presence of water molecules. The $[Cu(\mathbf{2})ClO_4]^+$ cationic unit is also an infinite polymer formed by bidentate perchlorate anions bridging, with a weak interaction, nearly square planar dicationic Cu(II) complexes of the neutral tetradentate methoxyimine ligand (**2**).

We report here the synthesis and X-ray structure of a new non-polymeric violet cationic complex of cimetidine of formula $[Cu(\mathbf{2'})]^+$, where **2'** is a deprotonated form of **2** [7], together with the synthesis and spectroscopical characterization of three complexes of general formula $[M(\mathbf{1})_2]^{2+}$ (M = Co, Ni, Zn).



2'

Two structure determinations were performed on $[Cu(\mathbf{2'})]X$ with two anions having different nucleophilic properties ($X = ClO_4^-$ (**5**), I^- (**6**)), with the hope of clarifying a disorder problem involving the coordinated sulfur atom and its neighbours (*vide infra*).

Experimental

Chemicals

Cimetidine (Sigma) and copper(II) perchlorate hexahydrate (Janssen) were used without further purification. All other chemicals were reagent grade.

Preparation of $[Cu(\mathbf{2'})]ClO_4 \cdot 0.5H_2O$ (5)

Compound **5** was prepared by adding a methanolic solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (30 ml, 0.001 mol) to a solution of cimetidine in the same solvent (20 ml, 0.001 mol). The resulting solution, upon heating at 60 °C in a water bath, assumed a green colour turning to blue after 35 min. A methanolic solution of KOH (5 ml, 0.056 g, 0.001 mol) was added and the mixture left in a water bath at 60 °C for 15 min until the solution became violet. After concentration to about 50% by rotary evaporation, the separated $KClO_4$ was filtered and the solution was left for 24 h. Violet crystals suitable for X-ray diffraction studies were collected by filtration. Yield 43%; m.p. 207 °C. *Anal.* Calc. for $C_{11}H_{20}ClCuN_6O_{5.5}S$: C, 29.01; H, 4.43; N, 18.45. Found: C, 29.41; H, 4.26; N, 18.96%.

Preparation of $[Cu(\mathbf{2'})]I \cdot 0.5H_2O$ (6)

A total of 0.453 g of **5** (0.001 mol) was dissolved in methanol (30 ml) and then a methanolic solution of KI (20 ml, 0.001 mol) was added. The resulting solution was warmed in a water bath at 60 °C. After about 5 h the solution was concentrated by rotary evaporation. The insoluble $KClO_4$ was eliminated by filtration and a microcrystalline bright violet compound was separated by adding ethanol. Crystals suitable for X-ray diffraction studies were obtained by slow evaporation of a methanolic solution of the compound. Yield 70%; m.p. 187 °C. *Anal.* Calc. for $C_{11}H_{20}CuIN_6O_{1.5}S$: C, 27.36; H, 4.18; N, 17.41. Found: C, 27.30; H, 4.24; N, 17.00%.

Preparation of $[M(\mathbf{1})_2](ClO_4)_2$ (M = Co, Ni, Zn)

The complexes were prepared by adding the methanolic solution of $M(ClO_4)_2 \cdot 6H_2O$ (30 ml, 0.001 mol) to a cimetidine methanolic solution (20 ml, 0.002 mol). The resulting solutions were heated for 4 h in a water bath at 60 °C and very insoluble solid compounds $[M(\mathbf{1})_2](ClO_4)_2$ were obtained and subsequently separated by filtration, washed with methanol and dried. The addition of a methanolic KOH solution in the same conditions used for obtaining compounds **5** and **6** afforded neither the $[M(\mathbf{2})ClO_4](ClO_4)$ nor the $[M(\mathbf{2'})](ClO_4)$ complexes, probably because the methanolysis is prevented by the very scarce solubility of the $[M(\mathbf{1})_2](ClO_4)_2$ compounds. In the case of copper either the larger solubility and/or a catalytic activity performed by the metal, as already postulated [5], can account for solvolysis. The list of the complexes studied, their analytical results, melting points and IR assignments are reported in Table 1.

Physical measurements

Carbon, hydrogen and nitrogen analyses were performed on a Perkin-Elmer 240B, C,H,N-analyser. Infrared spectra were recorded with a Brucker IFS-66 spectrophotometer on KBr plates. Diffuse reflectance electronic spectra were recorded on a Beckman Acta MIV spectrophotometer. Magnetic susceptibilities were measured by using a Bruker B-MB4 Faraday system equipped with a Cahn 1000 electrobalance. Electron spin resonance spectra were recorded on a Bruker ER220D-SRC X-band ESR spectrometer.

X-ray data collection and structure determination

Crystal data and other experimental details for compounds **5** and **6** are summarized in Table 2. The

TABLE 1. Analytical data and IR vibrational stretching frequencies (cm^{-1}) for the $[M(1)_2](ClO_4)_2$ compounds

	Colour	Melting point (°C)	Analysis (%)[a]			$\nu(C{\equiv}N)$
			C	H	N	
1	white	140	(47.59)	(6.39)	(33.30)	2177
M=Co	pink	243	30.81 (31.50)	4.28 (4.23)	22.12 (22.04)	2191
M=Ni	violet	273	30.98 (31.51)	4.29 (4.23)	22.50 (22.05)	2195
M=Zn	white		30.88 (31.24)	4.25 (4.19)	22.05 (21.85)	2206

[a] Calculated values in parentheses.

TABLE 2. Crystallographic data for compounds **5** and **6**

Compound	**5**	**6**
Formula	$C_{11}H_{19}ClCuO_5N_6S \cdot 0.5H_2O$	$C_{11}H_{19}CuION_6S \cdot 0.5H_2O$
Formula weight (amu)	455.37	482.83
Crystal system	monoclinic	monoclinic
Space group	$C2/c$	$C2/c$
a (Å)	20.732(8)	20.736(3)
b (Å)	7.471(3)	7.426(3)
c (Å)	23.734(5)	22.786(2)
β (°)	100.76(3)	99.65(1)
U (Å^3)	3611(4)	3459(2)
Z	8	8
$F(000)$	1872	1904
D_{calc} (g cm^{-3})	1.675	1.854
μ(Mo Kα) (cm^{-1})	15.09	31.59
Min. transmission factor	0.71	0.69
Scan mode	ω	ω
ω-scan width (°)	$1.1+0.35 \tan \theta$	$1.1+0.35 \tan \theta$
θ-range (°)	3–25	3–25
Octants of reciprocal space explored	$\pm h, +k, +l$	$\pm h, +k, +l$
Measured reflections	2898	3079
Unique observed reflections with $I>3\sigma(I)$	1767	2498
Final R and R_w indices[a]	0.034, 0.045	0.029, 0.045
No. variables	285	217
e.s.d.[b]	1.318	1.801

[a] $R=[\Sigma(F_o-k|F_c|)/\Sigma F_o]$, $R_w=[\Sigma w(F_o-k|F_c|)^2/\Sigma w F_o^2]^{1/2}$. [b] e.s.d. $=[\Sigma w(F_o-k|F_c|)^2/(N_{obs}-N_{var})]^{1/2}$, $w=1/(\sigma F_o))^2$, $\sigma(F_o)=[\sigma^2(I)+(0.04I)^2]^{1/2}/2F_o\text{Lp}$.

diffracted intensities were collected with variable scan speed on an Enraf-Nonius CAD-4 diffractometer at room temperature using graphite-monochromated Mo Kα radiation ($\lambda=0.71073$ Å). The calculations were performed on a PDP11/73 computer using the SDP-plus structure determination package [8]. All the reflections were corrected for Lorentz, polarization and absorption (empirical correction) [9] but not for extinction. Scattering factors for all the atomic species and anomalous dispersion corrections for atomic scattering factors of non-hydrogen atoms were taken from ref. 10. Both structures were solved by Patterson and Fourier methods and refined by full matrix least-squares, minimizing the function $\Sigma w(F_o-k|F_c|)^2$. Anisotropic thermal factors were refined for all the non-hydrogen atoms. All the hydrogen atoms were detected in a difference Fourier map, including also those bound to the disordered atoms, but they were introduced in the model at calculated positions and not refined. The final difference Fourier synthesis showed maximum residuals of 0.4 and 0.6 e/Å^3 for compounds **5** and **6**, respectively. The atomic coordinates of non-hydrogen atoms for **5** and **6** are listed in Tables 3 and 4, respectively.

TABLE 3. Positional parameters for compound **5** with e.s.d.s. in parentheses

Atom	*x*	*y*	*z*
Cu	−0.02833(2)	0.26017(9)	0.00215(2)
Cl	0.62877(6)	0.1412(2)	0.32828(5)
S(A)	−0.13772(9)	0.2837(3)	0.02179(9)
S(B)	−0.1266(1)	0.0859(4)	0.0048(1)
OW	0.500	−0.5446(7)	0.250
O(1)	0.6395(5)	0.319(1)	0.3186(5)
O(2)	0.5710(4)	0.121(1)	0.2834(3)
O(3)	0.6103(4)	0.167(1)	0.3795(3)
O(4)	0.6813(5)	0.012(1)	0.3396(5)
O(5)	0.6126(5)	0.118(2)	0.3811(3)
O(6)	0.6815(4)	0.064(1)	0.3176(5)
O(7)	0.5836(5)	0.045(1)	0.2901(3)
O(8)	0.6556(6)	0.299(2)	0.3119(5)
O(31)	0.1681(1)	0.3344(5)	0.0246(1)
N(1)	−0.0712(2)	0.2877(5)	−0.0780(1)
N(2)	−0.1018(2)	0.3518(5)	−0.1684(2)
N(3)	−0.0054(2)	0.1986(5)	0.0811(2)
N(4)	0.0670(2)	0.1617(6)	0.1680(2)
N(5)	0.1099(2)	0.2493(5)	0.0923(1)
N(6)	0.0598(2)	0.3165(6)	−0.0039(2)
C(1)	0.1316(3)	0.1631(8)	0.2040(2)
C(2)	0.0554(2)	0.2044(6)	0.1118(2)
C(3)	0.1093(2)	0.2975(6)	0.0392(2)
C(4)	−0.0581(2)	0.1446(8)	0.1108(2)
C(5A)	−0.1181(4)	0.090(1)	0.0690(4)
C(5B)	−0.1275(5)	0.200(2)	0.0707(5)
C(6)	−0.1756(2)	0.2006(7)	−0.0489(2)
C(7)	−0.1383(2)	0.2639(6)	−0.0933(2)
C(8)	−0.1579(2)	0.3031(6)	−0.1491(2)
C(9)	−0.2240(2)	0.3075(8)	−0.1878(2)
C(10)	−0.0514(2)	0.3417(7)	−0.1246(2)
C(31)	0.2265(2)	0.3127(7)	0.0677(2)

TABLE 4. Positional parameters for compound **6** with e.s.d.s. in parentheses

Atom	*x*	*y*	*z*
I	0.62314(1)	0.13419(5)	0.33192(1)
Cu	−0.02947(2)	0.26013(8)	0.00257(2)
S(A)	−0.13804(6)	0.2760(2)	0.02668(6)
S(B)	−0.1256(1)	0.0786(3)	0.0083(1)
OW	0.500	−0.5804(6)	0.250
O(31)	0.1663(1)	0.3427(4)	0.0220(1)
N(1)	−0.0744(1)	0.2858(4)	−0.0797(1)
N(2)	−0.1080(2)	0.3398(5)	−0.1739(1)
N(3)	−0.0052(1)	0.1923(4)	0.0838(1)
N(4)	0.0671(2)	0.1557(5)	0.1729(1)
N(5)	0.1091(1)	0.2526(4)	0.0926(1)
N(6)	0.0579(1)	0.3187(5)	−0.0065(1)
C(1)	0.1318(2)	0.1630(7)	0.2090(2)
C(2)	0.0552(2)	0.2008(5)	0.1146(2)
C(3)	0.1075(2)	0.3023(5)	0.0378(2)
C(4)	−0.0567(2)	0.1348(6)	0.1166(2)
C(5A)	−0.1184(3)	0.0844(9)	0.0747(3)
C(5B)	−0.1257(4)	0.190(2)	0.0785(5)
C(6)	−0.1767(2)	0.1915(7)	−0.0451(2)
C(7)	−0.1413(2)	0.2537(5)	−0.0926(2)
C(8)	−0.1626(2)	0.2875(6)	−0.1511(2)
C(9)	−0.2287(2)	0.2813(8)	−0.1886(2)
C(10)	−0.0562(2)	0.3387(6)	−0.1296(2)
C(31)	0.2235(2)	0.3239(6)	0.0664(2)

Results and discussion

The crystal packing for the two isomorphous compounds **5** and **6** is determined by a pattern of short van der Waals interactions and hydrogen bonds, as reported in Table 5. Two conformers of the cation are present in the crystals of both compounds, differing only in the conformational parameters of the C(4)–C(5)–S–C(6) moiety. As a result such a part of the cation appears disordered in the solid state. Their relative occupancies in both compounds have been refined to the following values: isomer A 0.60, isomer B 0.40. Perspective views of the two isomers A and B of the $[\mathrm{Cu}(\mathbf{2}')]^{+}$ cation in **5** are reported in Figs. 1 and 2, respectively, and are representative also for the numbering scheme in **6**. The **2′** ligand displays a coiled conformation around the copper atom resulting, upon coordination to the metal center, in one six-membered and two five-membered rings fused together. The coordination about the copper atom is essentially square planar, slightly distorted toward pyramidal if we consider as donor atom, beside N(1), N(3) and N(6) the sulfur atom belonging to isomer A, S(A), whereas the distortion is tetrahedral considering the sulfur atom of isomer B, S(B). The way in which the **2′** ligand coordinates to the metal center is the same as that observed for the neutral ligand in the polymeric $[\mathrm{Cu}(\mathbf{2})\mathrm{ClO_4}]^{+}$ cation, but in the present case the cations are discrete units. The shortest Cu...Cu distance is 3.778(1) Å in **5** and 3.775(1) Å in **6**. Individual bond lengths and angles within the $[\mathrm{Cu}(\mathbf{2}')]^{+}$ cation are in most cases statistically coincident within three e.s.d.s for both compounds **5** and **6**. The six-membered ring is planar and also the O(31), C(31), N(4) and C(1) atoms are only slightly displaced from this plane (deviations from the 'best' plane are the following: compound **5**: O(31) 0.072(3), C(31) 0.158(5), N(4) −0.042(4), C(1) −0.048(6) Å; compound **6**: O(31) 0.074(3), C(31) 0.135(5), N(4) −0.042(4), C(1) −0.075(5) Å). The Cu–N(3) and Cu–N(6) bonds have essentially the same length, thus showing that the sulfur *trans*-influence is comparable to that of nitrogen. The presence of a −1 net charge on the anionic ligand seems to affect these distances which are significantly shorter in complexes **5** and **6** (1.902(3) and 1.906(3) Å in **5**; 1.904(2) and 1.908(2) Å in **6** versus 1.954(5) and 1.944(6) Å in **4** respectively).

TABLE 5. Selected bond distances (Å) and angles (°) for compounds **5** and **6** with e.s.d.s. in parentheses

	5	**6**
Cu–N(1)	1.954(3)	1.957(2)
Cu–N(3)	1.902(3)	1.904(2)
Cu–N(6)	1.906(3)	1.908(2)
Cu–S(A)	2.405(2)	2.408(1)
Cu–S(B)	2.429(2)	2.429(2)
N(1)–C(10)	1.314(5)	1.316(4)
C(10)–N(2)	1.333(5)	1.345(4)
N(2)–C(8)	1.377(5)	1.380(4)
C(8)–C(9)	1.500(5)	1.488(4)
C(8)–C(7)	1.343(6)	1.357(4)
C(7)–N(1)	1.382(4)	1.390(3)
C(7)–C(6)	1.495(6)	1.478(4)
C(6)–S(A)	1.824(5)	1.809(3)
C(6)–S(B)	1.705(5)	1.695(4)
S(A)–C(5A)	1.831(10)	1.800(6)
S(B)–C(5B)	1.782(15)	1.802(10)
C(5A)–C(4)	1.497(11)	1.509(7)
C(5B)–C(4)	1.622(14)	1.598(11)
C(4)–N(3)	1.464(5)	1.465(4)
N(3)–C(2)	1.332(5)	1.331(3)
C(2)–N(5)	1.343(5)	1.354(3)
N(5)–C(3)	1.308(5)	1.299(4)
C(3)–N(6)	1.314(5)	1.319(4)
C(3)–O(31)	1.356(4)	1.361(3)
O(31)–C(31)	1.441(5)	1.430(4)
C(2)–N(4)	1.350(5)	1.352(4)
N(4)–C(1)	1.448(5)	1.453(4)
N(1)–Cu–S(A)	84.6(1)	84.31(7)
N(1)–Cu–S(B)	81.3(1)	80.92(8)
N(3)–Cu–S(A)	84.1(1)	84.01(7)
N(3)–Cu–S(B)	84.4(1)	83.47(8)
N(1)–Cu–N((6)	99.9(1)	100.5(1)
N(3)–Cu–N(6)	93.5(1)	93.7(1)
N(1)–Cu–N(3)	165.7(1)	164.4(1)
N(6)–Cu–S(A)	161.8(1)	162.7(1)
N(6)–Cu–S(B)	160.2(1)	159.3(1)
Cu–N(1)–C(7)	119.7(3)	118.9(2)
N(1)–C(7)–C(6)	118.9(3)	119.9(2)
C(7)–C(6)–S(A)	110.5(3)	110.7(2)
C(7)–C(6)–S(B)	111.8(3)	110.7(2)
C(6)–S(A)–Cu	93.2(2)	93.8(1)
C(6)–S(B)–Cu	95.5(2)	96.1(1)
Cu–S(A)–C(5A)	87.2(3)	88.5(2)
Cu–S(B)–C(5B)	85.0(4)	85.1(3)
S(A)–C(5A)–C(4)	104.5(6)	105.7(4)
S(B)–C(5B)–C(4)	104.0(7)	103.3(6)
C(5A)–C(4)–N(3)	111.1(5)	111.3(3)
C(5B)–C(4)–N(3)	107.9(6)	108.1(4)
C(4)–N(3)–Cu	117.9(2)	118.5(2)
C(4)–N(3)–C(2)	117.4(3)	116.6(2)
Cu–N(3)–C(2)	124.6(3)	124.8(2)
N(3)–C(2)–N(5)	126.2(4)	125.6(2)
N(3)–C(2)–N(4)	120.6(4)	120.3(2)
N(4)–C(2)–N(5)	113.2(3)	114.1(2)
C(2)–N(5)–C(3)	122.9(3)	123.2(2)
N(5)–C(3)–N(6)	130.1(4)	130.7(2)
N(5)–C(3)–O(31)	117.0(3)	116.0(2)
N(6)–C(3)–O(31)	112.8(4)	113.3(2)
C(3)–N(6)–Cu	122.5(3)	122.0(2)
C(1)–N(4)–C(2)	123.9(4)	123.1(3)
C(3)–O(31)–C(31)	118.2(3)	117.6(2)
N(1)–C(7)–C(8)	109.6(4)	109.0(2)
C(7)–C(8)–N(2)	105.5(3)	105.6(2)
C(8)–N(2)–C(10)	108.3(3)	108.5(2)
N(2)–C(10)–N(1)	110.5(3)	110.1(2)
C(10)–N(1)–C(7)	106.1(3)	106.8(2)
OW...O(1)″	3.21(3)	
OW...O(2)	2.93(2)	
OW...N(4)‴	3.017(4)	2.987(3)
OW...HN(4)‴	2.198(3)	2.163(3)
O(1)...HW	2.29(3)	
O(2)...HW	1.76(2)	
O(2)...N(2)′	2.92(2)	
O(2)...HN(2)′	2.02(2)	
O(31)...HN(6)	2.335(3)	2.358(2)
I...HN(2)′		2.645(1)

Symmetry codes: $' = \frac{1}{2}-x, \frac{1}{2}-y, -z$; $'' = x, y-1, z$; $''' = \frac{1}{2}+x, y-\frac{1}{2}, z$.

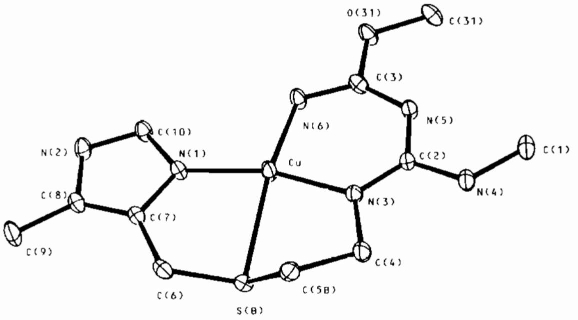


Fig. 1. ORTEP drawing of the $[Cu(\mathbf{2'})]^+$ cation (conformer A). Thermal ellipsoids are drawn at 30% probability.

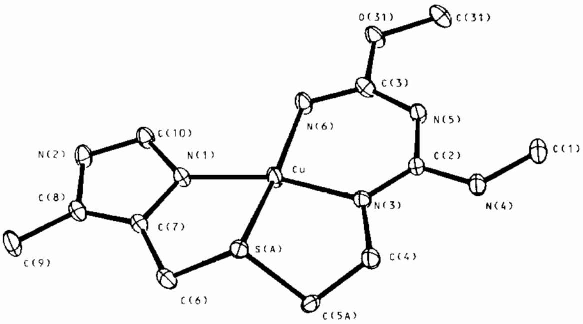


Fig. 2. ORTEP drawing of the $[Cu(\mathbf{2'})]^+$ cation (conformer B). Thermal ellipsoids are drawn at 30% probability.

The distribution of the bond distances and angles within the six-membered ring is in keeping with a partial delocalization along the N(6), C(3), N(5), C(2), N(3) fragment, with an extension to the O(31) and N(4) atoms, favoured by the planarity of the whole moiety. The puckering of the five-membered chelated rings is described by the torsion angles reported in Table 6. The C(4)–C(5B) and C(6)–S(B) distances are quite anomalous and probably affected by the disorder involving the C(6)–S–C(5)–C(4) moiety. The imidazolic ring is planar with bond distances and angles comparable with those found in the previously reported cimetidine complexes. In compound **5** the ClO_4^- anion appears disordered in the solid state, the model of disorder consisting of two interpenetrating tetrahedra with the unique chlorine atom in the center; the two sets of perchlorate oxygens have been refined with a population parameter of 0.5.

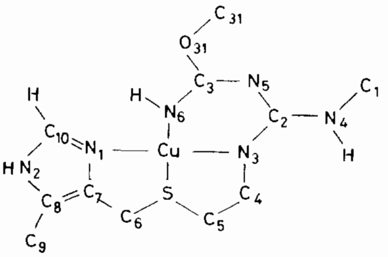
In agreement with the X-ray results, reflectance measurements show that the Cu(II) atoms in the present complexes exhibit a strong planar character (λ_{max} (nm) 560) [11], and the magnetic susceptibility is consistent with this coordination geometry (μ_{eff} 2.20 BM, $g = 2.08$). From visible spectra we can also suggest that the planar arrangement of the Cu(II) atom is retained in solution.

Quantomechanical semiempirical calculations

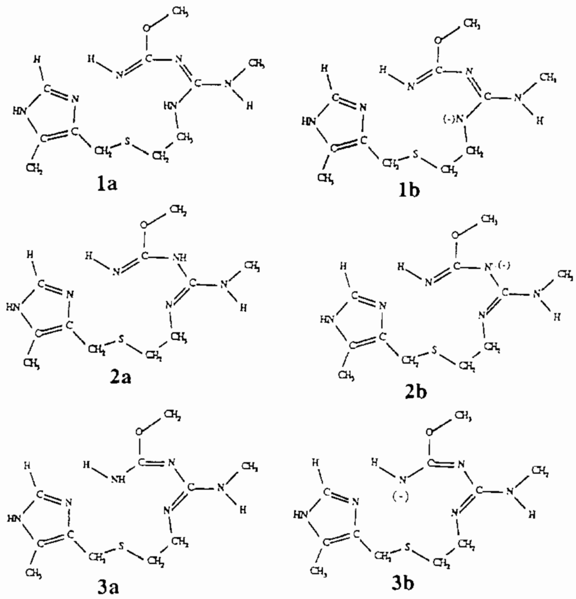
Quantomechanical semiempirical calculations have been performed on simple models of the ligand **2′** and of the complexes **5** and **6**, in order to get an insight into a detailed electronic arrangement and the net atomic charges. A sketch of complex [Cu(**2′**)]$^+$ with the atom labelling is given below.

TABLE 6. Selected torsion angles for compounds **5** and **6**

	5	**6**
Cu–N(1)–C(7)–C(6)	−5.7	−3.3
N(1)–C(7)–C(6)–S(A)	32.2	29.9
N(1)–C(7)–C(6)–S(B)	−24.2	−26.7
C(7)–C(6)–S(A)–Cu	−35.3	−34.2
C(7)–C(6)–S(B)–Cu	33.5	34.9
C(6)–S(A)–Cu–N(1)	25.9	25.9
C(6)–S(B)–Cu–N(1)	−28.4	−29.0
S(A)–Cu–N(1)–C(7)	−15.7	−16.8
S(B)–Cu–N(1)–C(7)	22.1	21.0
Cu–S(A)–C(5A)–C(4)	56.3	54.2
Cu–S(B)–C(5B)–C(4)	−59.9	−60.5
S(A)–C(5A)–C(4)–N(3)	−56.2	−53.9
S(B)–C(5B)–C(4)–N(3)	57.5	57.3
C(5A)–C(4)–N(3)–Cu	18.9	17.8
C(5B)–C(4)–N(3)–Cu	−14.0	−13.9
C(4)–N(3)–Cu–S(A)	16.7	15.8
C(4)–N(3)–Cu–S(B)	−21.1	−22.0
N(3)–Cu–S(A)–C(5A)	−37.8	−36.5
N(3)–Cu–S(B)–C(5B)	43.7	43.9
Cu–N(3)–C(2)–N(5)	−1.9	−2.5
N(3)–C(2)–N(5)–C(3)	1.4	0.6
C(2)–N(5)–C(3)–N(6)	1.7	1.8
N(5)–C(3)–N(6)–Cu	−3.8	−1.8
C(3)–N(6)–Cu–N(3)	2.5	0.0
N(5)–C(3)–O(31)–C(31)	1.9	1.0
N(5)–C(2)–N(4)–C(1)	−0.2	0.3



In principle three tautomeric forms (represented in Fig. 3: **1a**, **2a**, **3a**) can be hypothesized for **2** (i.e. for the neutral ligand obtained from cimetidine after methanolysis), to which three anionic forms (reported in Fig. 3: **1b**, **2b**, **3b**, respectively) correspond. The X-ray structure determination carried out by Greenaway *et al.* [5] showed that in **4**, among the various forms conceivable for the ligand, the one represented as **2a** has the major contribution. On the other hand the geometrical features of the ligand **2′** in complexes **5** and **6** are in keeping with a partial delocalization over the moiety included between N(3) and N(6). For the calculation of the net atomic charges the quantomechanical semiempirical method CNDO/2 [12] has been chosen, with some modifications allowing us to include the copper atom in the calculation, because it represented a good compromise between the accuracy of the calculation and a reasonable computational effort. The following models



1a **1b**

2a **2b**

3a **3b**

Fig. 3. Tautomeric forms for ligands **2** and **2′**.

were built using the atomic coordinates obtained from our X-ray analysis:

(i) an anionic model of the ligand **2**′;

(ii) three neutral models of the ligand (corresponding to the three tautomeric forms conceivable for the neutral ligand) adding a hydrogen atom (called HX) to the nitrogen atom bearing a −1 net charge in the three limit formulae, respectively;

(iii) a model of the $[Cu(\mathbf{2}')]^+$ cation;

(iv) a model of compounds **5** and **6** including as a counterion a Cl^- anion and replacing the methyl group of the imidazolic moiety by a hydrogen atom, because of computational limits. The latter substitution seemed reasonable, as we checked from a comparison between the net atomic charges for a neutral model of the ligand with and without the methyl group: none was significantly affected by the substitution of the methyl group.

The net atomic charges for the different models, relative to significant atoms are reported in Table 7. From an analysis of the results of our calculations we can point out that not necessarily the most basic sites of the isolated anionic ligand correspond to the donor atoms observed in the complex; the arrangement of the ligand about the copper atom is therefore determined also by geometric constraints deriving from the need of obtaining suitable-size rings containing the copper atom. We can suggest that the isolated anionic ligand bears its negative charge delocalized over the three nitrogen atoms N(3), N(5) and N(6) and consequently the two double bonds are delocalized along the N(3)–C(2)–N(5)–C(3)–N(6) moiety. We can then observe that all the three tautomers of the neutral model show that the HX atom added to the anionic ligand, independently of its location, bears the highest positive charge, always higher than that on HN(2) and HN(6), i.e. HX is the most deshielded or the most 'acidic' proton. While a general shift toward lower values of the net charge on all atoms is observed when passing from the three neutral models of the ligand to the anionic one, only few atoms significantly change their net charge values when passing from the models without Cu^{2+} to those where Cu^{2+} is present. The only atoms involved in significant changes (a general shift of their net charges toward higher values) are in all cases C(7), N(1), C(10), S, C(4), N(3), C(2), C(3), N(6) and HN(6), i.e. those involved in coordination to the metal and their next neighbours. Moreover, as expected, upon coordination, N(5) changes its partial charge less than the donor atoms N(1), N(3), N(6) and S.

We can conclude that the double bond arrangement in **2**′ cannot be completely described by only one of the limit structures reported in Fig. 3 but is better represented by a combination of structures **3b** (with a greater weight) and **1b** (with smaller weight), in agreement with the short distance found between atoms C(3) and N(5) (1.308(5) and 1.299(4) Å). We finally observe that the C(3)–O(31) and C(2)–N(4) bond lengths are also shorter than typical single bonds and that the molecular moieties containing them are strictly planar. These bonds therefore show a partial double bond character due to a certain amount of delocalization of lone pairs of N(4) and O(31), supported by the π electron distribution on

TABLE 7. Net atomic charges obtained by CNDO/2 calculations

Atom	Neutral model			Anionic ligand (**2**′)	$[Cu(\mathbf{2}')]^+$ cation	$[Cu(\mathbf{2}')]X$ complex
	1	**2**	**3**			
HN(4)	0.122	0.123	0.118			
HN(6)	0.037	0.042	0.170			
HN(2)	0.147	0.145	0.146			
HX	0.437	0.384	0.377			
S	−0.036	−0.036	−0.040	−0.035	0.133	0.109
C(8)				−0.014	0.079	0.019
C(7)				0.008	0.073	0.107
N(1)				−0.177	0.000	0.007
C(10)				0.051	0.180	0.209
N(2)				−0.074	0.007	0.026
N(3)				−0.364	−0.087	−0.093
C(2)				0.194	0.317	0.309
N(4)				−0.167	−0.105	−0.115
C(1)				−0.063	−0.008	−0.016
N(5)				−0.380	−0.268	−0.276
C(3)				0.237	0.384	0.385
N(6)				−0.460	−0.132	−0.122

the portion of the chain included between N(3) and N(6).

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References

1 G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E. Parson, H. D. Prain and G. R. White, *J. Med. Chem., 20* (1977) 901.

2 J. R. J. Sorenson, *Biology of Copper Complexes,* Humana, Clifton, NJ, 1987.

3 J. R. J. Sorenson, *Inflammatory Diseases and Copper,* Humana, Clifton, NJ, 1980.

4 H. H. A. Dollwet and J. R. J. Sorenson, *Trace Elements Med., 2* (1985) 80.

5 F. T. Greenaway, L. M. Brown, J. C. Dabrowiak, M. R. Thompson and V. M. Day, *J. Am. Chem. Soc., 102* (1980) 7784.

6 L. Soto, J. P. Legros and A. Sancho, *Polyhedron, 7* (1988) 307.

7 A. M. Bianucci, F. Demartin, M. L. Ganadu, L. Naldini and A. Panzanelli, *Chimica dei Sistemi e dei Processi Biologici, Meet., Modena, Jan. 19, 1987,* Abstract P16.

8 B. A. Frenz and Associates, *S. D. P. Structure Determinations Package Plus,* Version 1.0, Enraf-Nonius, Delft, The Netherlands, 1980.

9 A. C. T. North, D. C. Phillips and F. S. Mathews, *Acta Crystallogr., Sect. A, 24* (1968) 351.

10 *International Tables for X-Ray Crystallography,* Vol. 4, Kynoch Press, Birmingham, U.K., 1974.

11 F. Demartin, M. Manassero, L. Naldini, A. Panzanelli and M. A. Zoroddu, *Inorg. Chim. Acta, 171* (1990) 229.

12 M. Rajzmann and P. Francois, *Quantum Chemistry program Exchange,* No. 382, Indiana University.