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Structure of Copper Cimetidine Nitrate

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Abstract. [*N*-Cyano-*N'*-methyl-*N''*-(2-[(5-methyl-1*H*-imidazol-4-yl)methyl]thio)ethyl)guanidine]copper(II) nitrate, $[\text{Cu}(\text{NO}_3)_2(\text{C}_{10}\text{H}_{16}\text{N}_6\text{S})_2]$, $M_r = 692.22$, monoclinic, $P2_1/n$, $a = 11.597(3)$, $b = 10.555(1)$, $c = 12.256(1)$ Å, $\beta = 97.07(1)^\circ$, $V = 1488.8(4)$ Å³, $Z = 2$, $D_x = 1.54$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.927$ mm⁻¹, $F(000) = 718$, $T = 295 \pm 1$ K, $R = 0.024$ for 2215 observed diffractometer data. The Cu²⁺ ions lie at symmetry centres and are six-coordinated with a distorted octahedral geometry. The structure is characterized by infinite polymeric chains along [010], constructed from $[\text{Cu}(\text{cimetidine})_2]$ entities which are linked through *N*-cyano groups belonging to symmetry-related molecules. The interchain packing is assured by hydrogen bonds between O atoms from nitrate groups and N atoms from cimetidine.

Introduction. Cimetidine (CM) is an imidazole derivative used as an antihistamine H₂ receptor drug in the treatment of peptic ulcer. The X-ray structural study of the compound in several polymorphic crystalline forms has already been carried out by many authors (Hädicke, Frickel & Franke, 1978; Shibata, Kokubo, Morimoto, Morisaka, Ishida & Inoue, 1983; Párkányi, Kálmán, Hegedüs, Harsányi & Kreidl, 1984).

The structure determination of the title compound was undertaken as part of a continuing research project developed in the Department of Inorganic Chemistry involving the synthesis, structure and properties of metal complexes of cimetidine (Sancho, Borrás, Soto-Tuero, Esteban-Calderón, Martínez-Ripoll & García-Blanco, 1985; Sancho, Soto & Borrás, 1985). Also, it was of particular interest to confirm the

molecular structure of this complex previously established by spectroscopic techniques (Soto, Sancho & Borrás, 1985).

Experimental. Brown crystals were obtained from a mixture of aqueous solutions of Cu(NO₃)₂·3H₂O and cimetidine. Crystal 0.3 × 0.3 × 0.3 mm. Enraf–Nonius CAD-4 diffractometer. Lattice parameters from least-squares refinement of 25 medium-angle reflections. Lorentz and polarization corrections applied. No correction for absorption or extinction. Variation of standard reflections ±0.46%. $2^\circ \leq 2\theta \leq 50^\circ$. ω - 2θ scan. 2915 measured reflections ($-13 \leq h \leq 13$; $0 \leq k \leq 12$; $0 \leq l \leq 14$), 2215 observed [$I > 2.5\sigma(I)$]. Structure solved by direct methods (*MULTAN*11/84; Main, Germain & Woolfson, 1984), using the 262 highest *E* values; 17 non-H atoms found in first *E* map. Remaining non-H atoms were located from a subsequent Fourier synthesis. Full-matrix least-squares refinement of the model with isotropic temperature factors minimizing $\sum w(|F_o| - |F_c|)^2$ gave $R = 0.095$; $w = 1/\sigma^2(F)$. Inclusion of anisotropic temperature factors reduced *R* to 0.044. At this stage all H atoms were located from a difference map. *R* reduced to 0.024 ($wR = 0.031$) (245 variables) when refinement was carried out with inclusion of H atoms. All H atoms were given an isotropic temperature factor (*U*) of 0.05 Å², and this overall value was 0.0548 Å² in the last cycle. Max. and min. values in final difference density maps 0.32 and -0.25 e Å⁻³ respectively. $(\Delta/\sigma)_{\text{max}} = 0.07$, $S = 1.35$. Atomic scattering factors and corrections for anomalous dispersion taken from *International Tables for X-ray Crystallography* (1974). Calculations performed with *SHELX76* (Sheldrick, 1976), *PLUTO78* (Motherwell & Clegg, 1978) and *XANADU* (Roberts & Sheldrick, 1975).

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Table 1. Fractional coordinates ($\times 10^4$, S $\times 10^5$) and equivalent isotropic temperature factors (\AA^2) with *e.s.d.'s* in parentheses

$$B_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
Cu	$\frac{1}{2}$	0	0	2.1 (1)
S	66603 (6)	11561 (6)	8823 (5)	2.1 (1)
C(1)	6723 (2)	943 (2)	-1329 (2)	2.3 (2)
N(2)	5637 (1)	386 (2)	-1356 (1)	2.1 (2)
C(3)	5169 (2)	405 (2)	-2396 (2)	2.5 (2)
N(4)	5897 (2)	938 (2)	-3021 (2)	3.1 (2)
C(5)	6894 (2)	1307 (2)	-2364 (2)	2.9 (2)
C(6)	7862 (3)	1979 (4)	-2808 (3)	4.9 (3)
C(7)	7501 (2)	979 (2)	-269 (2)	2.5 (2)
C(8)	6242 (2)	2810 (2)	753 (2)	2.4 (2)
C(9)	7185 (2)	3652 (2)	1344 (2)	2.5 (2)
N(10)	6865 (2)	4987 (2)	1251 (2)	2.7 (2)
C(11)	6132 (2)	5570 (2)	1856 (2)	2.4 (2)
N(12)	5862 (2)	6794 (2)	1751 (2)	2.9 (2)
C(13)	6244 (2)	7489 (2)	987 (2)	2.6 (2)
N(14)	6488 (2)	8212 (2)	346 (2)	3.5 (3)
N(15)	5627 (2)	4913 (2)	2596 (2)	3.0 (2)
C(16)	4820 (3)	5505 (3)	3250 (3)	4.2 (3)
N	5730 (2)	1959 (2)	4205 (2)	3.2 (2)
O(1)	6124 (2)	967 (2)	4674 (1)	3.6 (3)
O(2)	5969 (2)	2216 (2)	3271 (1)	3.8 (3)
O(3)	5113 (3)	2654 (3)	4676 (2)	8.1 (3)

Table 2. Bond lengths (\AA), bond angles ($^\circ$) and relevant torsion angles ($^\circ$), with *e.s.d.'s* in parentheses

S—Cu	2.419 (1)	C(9)—C(8)	1.522 (3)
N(2)—Cu	1.942 (2)	N(10)—C(9)	1.459 (3)
N(14 ^{III})—Cu	2.558 (2)	C(11)—N(10)	1.343 (3)
C(7)—S	1.820 (2)	N(12)—C(11)	1.333 (3)
C(8)—S	1.813 (2)	N(15)—C(11)	1.333 (3)
N(2)—C(1)	1.388 (3)	C(13)—N(12)	1.309 (3)
C(5)—C(1)	1.362 (3)	N(14)—C(13)	1.155 (3)
C(7)—C(1)	1.489 (3)	C(16)—N(15)	1.448 (3)
C(3)—N(2)	1.323 (3)	O(1)—N	1.254 (3)
N(4)—C(3)	1.332 (3)	O(2)—N	1.240 (2)
C(5)—N(4)	1.382 (3)	O(3)—N	1.218 (3)
C(6)—C(5)	1.486 (3)		
N(2)—Cu—S	84.9 (1)	C(6)—C(5)—N(4)	122.4 (2)
N(14 ^{III})—Cu—S	79.3 (1)	C(1)—C(7)—S	110.8 (1)
N(14 ^{III})—Cu—N(2)	88.7 (1)	C(9)—C(8)—S	110.6 (2)
C(7)—S—Cu	94.3 (1)	N(10)—C(9)—C(8)	111.5 (2)
C(8)—S—Cu	104.9 (1)	C(11)—N(10)—C(9)	124.8 (2)
C(8)—S—C(7)	101.2 (1)	N(12)—C(11)—N(10)	123.2 (2)
C(5)—C(1)—N(2)	109.5 (2)	N(15)—C(11)—N(10)	119.9 (2)
C(7)—C(1)—N(2)	118.8 (2)	N(15)—C(11)—N(12)	116.9 (2)
C(7)—C(1)—C(5)	131.6 (2)	C(13)—N(12)—C(11)	121.0 (2)
C(1)—N(2)—Cu	120.6 (1)	N(14)—C(13)—N(12)	171.7 (3)
C(3)—N(2)—Cu	132.4 (2)	C(13 ^{II})—N(14 ^{III})—Cu	112.6 (2)
C(3)—N(2)—C(1)	106.2 (2)	C(16)—N(15)—C(11)	121.4 (2)
N(4)—C(3)—N(2)	110.4 (2)	O(2)—N—O(1)	119.8 (2)
C(5)—N(4)—C(3)	109.1 (2)	O(3)—N—O(1)	119.2 (2)
N(4)—C(5)—C(1)	104.8 (2)	O(3)—N—O(2)	121.1 (2)
C(6)—C(5)—C(1)	132.7 (2)		
C(5)—C(1)—C(7)—S	150.7 (3)		
N(2)—C(1)—C(7)—S	-33.8 (4)		
C(8)—S—C(7)—C(1)	-74.3 (3)		
C(7)—S—C(8)—C(9)	-86.2 (3)		
S—C(8)—C(9)—N(10)	180.0 (4)		
C(8)—C(9)—N(10)—C(11)	79.1 (3)		
C(9)—N(10)—C(11)—N(12)	180.0 (3)		
C(9)—N(10)—C(11)—N(15)	-1.0 (3)		
N(10)—C(11)—N(12)—C(13)	4.6 (4)		
N(10)—C(11)—N(15)—C(16)	-179.0 (3)		

Symmetry code: (i) $1-x, -y, -z$ (see Fig. 1); (ii) $x, y-1, z$; (iii) $1-x, 1-y, -z$.

Discussion. Final atomic coordinates are in Table 1.* The overall geometry of the cation and the atomic numbering scheme are shown in Fig. 1. The Cu^{2+} ions lie at symmetry centres and are six-coordinated by two imidazole N atoms and two thioether S atoms belonging to different cimetidine molecules, and two cyano N atoms from neighbouring molecules. Bond lengths and angles are listed in Table 2.

The geometry of the coordination polyhedron can be considered as elongated [along Cu—N(14)] distorted octahedral, with the Cu—N(2) and Cu—S distances comparable with those found in related compounds containing imidazole and thioether groups (Prochaska *et al.*, 1981; Dagdigan, McKee & Reed, 1982) and the Cu—N(14) bond distance relatively long, N(14) being weakly bonded to Cu (Tomlinson, Hathaway, Billing & Nichols, 1969). However, since the Cu—S [2.419 (1) \AA] and Cu—N(14) [2.558 (2) \AA] distances are not very different, the octahedron can also be considered as compressed along the Cu—N(2) [1.942 (2) \AA] bond.

The most interesting difference between the previously determined structure of the copper cimetidine perchlorate complex (CCP) (Sancho, Borrás *et al.*, 1985; Greenaway, Brown, Dabrowiak, Thompson & Day, 1980) and the title compound is the type of distortion in the Cu^{II} coordination polyhedron. Thus, the S atom is more weakly bonded [Cu—S 2.790 (2) \AA] but N(14) is more strongly bonded [Cu—N(14) 2.042 (7) \AA] to the Cu atom in the perchlorate

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and equations of the mean planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42286 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

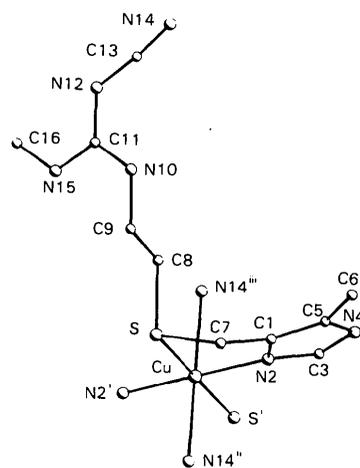


Fig. 1. Perspective view of the cimetidine molecule together with the Cu^{2+} environment showing atomic labelling. For symmetry code, see Table 2.

complex, resulting in an elongated tetragonally distorted octahedral geometry, probably due to different crystal packing.

Chelating cimetidine may be considered as comprising three parts: 4,5-disubstituted imidazole, cyano-guanidine derivative and cysteamine.

The imidazole ring is planar [mean plane defined by C(1), N(2), C(3), N(4) and C(5)], and the methyl group deviates from this plane by only 0.054 (4) Å. The bond angles and distances in this ring are similar to those found in CCP and show some degree of electronic delocalization.

The methyl and cyano groups [C(16) and C(13)—N(14)] may be considered to be in the mean plane of the guanidine [C(11), N(10), N(12), N(15)] [deviations from the plane are: 0.018 (4) Å for C(16), 0.102 (2) Å for C(13) and 0.214 (2) Å for N(14)]. The N—C bond distances [C(11)—N(10), C(11)—N(12) and C(11)—N(15)] have equivalent values due to the delocalization of the double bond. This effect has also been observed in all cimetidine forms and derivatives. However, the two bond angles N(10)—C(11)—N(12) and N(12)—C(11)—N(15) show values approximately equal to those found in conformer *A* of cimetidine (Párkányi, Kálmán, Hegedüs, Harsányi & Kreidl, 1984), although the same angles for CCP correspond to conformer *Z*.

The S—C bond distances in the cysteamine part are similar to those found in CCP and in cimetidine forms. Nevertheless, the bond angles about the four-atom chain [C(7)—S—C(8)—C(9)] show significant differences from those found in these structures, since this chain possesses great flexibility. The overall shape of the title compound may be defined by the relevant torsion angles (Table 2), in particular by the rotation

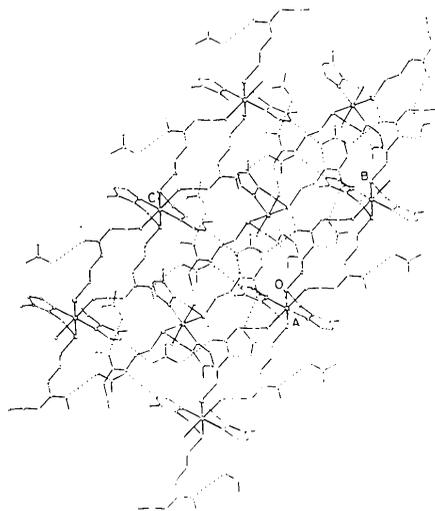


Fig. 2. Hydrogen-bonding scheme and molecular packing viewed down *a*, showing three chains parallel to [010].

Table 3. *Hydrogen bonds with e.s.d.'s in parentheses*

X—H...Y	X...Y (Å)	X—H (Å)	H...Y (Å)	∠X—H...Y (°)
N(4)—H(4)...O(1 ^b)	2.869 (3)	0.84 (3)	2.06 (3)	163 (3)
N(10)—H(10)...O(1 ^c)	2.906 (3)	0.84 (3)	2.14 (3)	152 (3)
N(15)—H(15)...O(2)	2.977 (2)	0.85 (3)	2.14 (3)	169 (2)

Symmetry code: (iv) *x*, *y*, *z*—1; (v) $\frac{1}{2}$ —*x*, $\frac{1}{2}$ +*y*, $\frac{1}{2}$ —*z*.

about bonds S—C(8), C(8)—C(9) and C(9)—N(10) and by the dihedral angles between the mean planes of the imidazole ring and the guanidine group [89.6 (4)°].

The different values for these angles found in the literature and in the present work show also the great variety of molecular shapes for cimetidine. The structure is characterized by infinite polymeric chains along [010], constructed from [Cu(CM)₂] entities which are linked through the N-cyano groups belonging to symmetry-related molecules (Fig. 2). The interchain packing is assured by hydrogen bonds between O atoms from nitrate groups and N atoms from cimetidine (Table 3). These nitrate groups show one shorter N—O bond that corresponds to the O(3) oxygen atom not involved in the hydrogen bonds.

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