

Crystallographic Studies on Metal–Nucleotide Base Complexes. VI.* Dichloro-(6-thio-9-methylpurine)copper(II) Monohydrate

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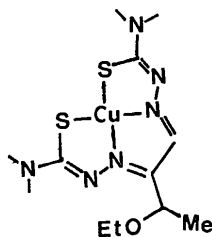
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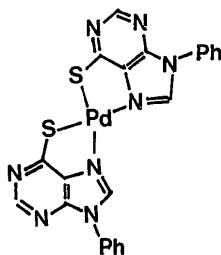
$[(C_6H_6N_4S)CuCl_2] \cdot H_2O$ crystallizes in space group $P2_1/c$ with $a=7.316$, $b=15.944$, $c=10.391$ Å, $\beta=117.50^\circ$. The structure determination is based on 2348 reflexions collected on a diffractometer with Mo $K\alpha$ radiation. The structure was solved by the Patterson method and refined by least-squares calculations to a final R of 0.037. The Cu coordination is square pyramidal (4+1). The thiopurine ligand is bidentate, binding at N(7) and S, Cu–N(7)=1.992, Cu–S=2.424 Å. The equatorial plane is completed by two Cl^- ions *trans* to S and N(7) respectively, Cu–Cl(1)=2.301, Cu–Cl(2)=2.244 Å. The complex units form centrosymmetrical dimers with the equatorial Cl(1) in one unit occupying the apical position in another, Cu–Cl(1)'=2.737 Å. The 'bite' of the ligand is reduced by 0.3 Å compared to the uncomplexed molecule.

Introduction

The anticarcinogenic activity of 6-thiopurine may be related to its metal-binding properties. The aliphatic antitumour agent, 2-keto-3-ethoxybutyaldehydebis-(thiosemicarbazone) is found to have enhanced activity in the presence of certain metal ions (Petering, Buskirk, Crim & Van Giessen, 1963). The Cu(II) complex of this ligand (I) (Taylor, Gabe, Glusker, Minkin & Patterson, 1966) has a geometry which is remarkably similar to that of a 6-thiopurinepalladium(II) complex, (II) (Heitner & Lippard, 1974).



(I)



(II)

In Cu(II) complexes of nucleoside analogues of hypoxanthine (Sletten, 1974), adenine (Sletten & Thorstensen, 1974; Sletten & Ruud, 1975) and guanine (Sletten & Fløgstad, to be published) the ligands have all been found to be monodentate. In these complexes the ligands are formally neutral, being coordinated at N(7). The various purine ligands form intramolecular hydrogen bonds to the coordination sphere through the substituent on C(6). To compare the difference in Cu binding properties between natural purines and 6-thiopurine, the present structure investigation was undertaken.

Experimental

90 mg of Sigma grade 6-thio-9-methylpurine was dissolved in 0.8 ml concentrated HCl and 1.2 ml H_2O . 2.4 ml 1M $CuCl_2$ were added and a brownish, amorphous precipitate was obtained. The precipitate was filtered, washed with slightly acidic water/methanol mixture, and redissolved in acidic 1:1 water/dioxane solution. After three weeks of slow evaporation at room temperature faintly coloured crystalline plates appeared.

Crystal data

$[(C_6H_6N_4S)CuCl_2] \cdot H_2O$, F.W. 318.7. Space group: monoclinic, $P2_1/c$; $a=7.316$ (3), $b=15.944$ (4), $c=10.391$ (2) Å, $\beta=117.50$ (2)°, $V=1075.2$ (7) Å³, $Z=4$, $F(000)=636$, $D_m=1.963$ (8), $D_x=1.969$ (5) g cm⁻³, $\lambda(Mo K\alpha)=0.71069$ Å, $\mu=27.6$ cm⁻¹.

The crystal used for data collection was mounted along **b** and had dimensions 0.45 × 0.13 × 0.06 mm. Within the sphere of reflexion limited at $\sin \theta/\lambda=0.64$, 2348 unique reflexions were recorded. Of these, 537 were less than the threshold value of $2\sigma_c$, where σ_c is the estimated error due to counting statistics. The experimental procedure has been described elsewhere (Sletten, 1974). The usual corrections were carried out including absorption corrections. Accurate cell dimensions were obtained after data collection by determining 2θ settings for the Mo $K\alpha_1$ peak of 17 strong high-order reflexions by an ω -scan technique (Maartmann-Moe, 1974).

The structure was solved by the Patterson method. All non-hydrogen atoms were located, and refined anisotropically by full-matrix least-squares calculations to an R of 0.047 ($R = \sum ||F_o| - |F_c|| / \sum |F_o|$). All H atoms were located in a difference map and refined isotropically. The refinement converged at an R of 0.037. The final difference map shows the usual features observed in purine structures with a peak of

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Table 1. *The final atomic parameters*

(a) Non-hydrogen atoms. (Temperature parameters $\times 10^4$). Standard deviations are in parentheses. Anisotropic temperature factor = $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{23}klb^*c^* + 2U_{13}hla^*c^*)]$.

	X/c	Y/b	Z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{23}	U_{13}
Cu(1)	0.19140 (7)	0.55242 (3)	0.47329 (5)	387 (3)	289 (3)	317 (3)	-2 (2)	8 (2)	209 (2)
Cl(1)	0.22076 (14)	0.48267 (6)	0.67578 (10)	356 (5)	372 (5)	240 (4)	5 (4)	30 (4)	149 (4)
Cl(2)	0.17578 (17)	0.67954 (6)	0.56031 (11)	556 (7)	281 (5)	458 (6)	-61 (5)	-58 (5)	284 (5)
S(1)	0.21205 (17)	0.62225 (7)	0.27324 (12)	472 (6)	294 (5)	435 (6)	35 (5)	62 (5)	272 (5)
C(2)	0.2863 (6)	0.44457 (31)	0.0293 (4)	482 (25)	514 (27)	256 (20)	-12 (22)	-7 (21)	226 (19)
C(4)	0.2899 (6)	0.38196 (24)	0.2191 (4)	290 (20)	329 (21)	295 (20)	-18 (17)	39 (17)	158 (17)
C(5)	0.2656 (5)	0.45748 (24)	0.2726 (4)	273 (19)	340 (22)	269 (19)	3 (17)	-19 (16)	148 (16)
C(6)	0.2473 (6)	0.53228 (23)	0.2013 (4)	273 (19)	330 (22)	329 (20)	-18 (16)	25 (16)	157 (16)
C(8)	0.2743 (6)	0.36547 (27)	0.4219 (4)	346 (22)	383 (24)	270 (20)	-10 (18)	78 (18)	166 (18)
C(9)	0.3155 (9)	0.23202 (28)	0.3052 (6)	544 (32)	290 (25)	487 (30)	10 (23)	-7 (21)	239 (27)
N(1)	0.2570 (5)	0.52154 (23)	0.0750 (4)	410 (20)	397 (21)	285 (18)	19 (17)	107 (16)	179 (16)
N(3)	0.3025 (5)	0.37274 (21)	0.0942 (3)	476 (20)	398 (20)	277 (17)	4 (17)	-24 (15)	218 (16)
N(7)	0.2565 (5)	0.44702 (21)	0.3999 (3)	337 (17)	332 (17)	299 (16)	0 (15)	-4 (15)	196 (14)
N(9)	0.2950 (5)	0.32321 (19)	0.3155 (3)	334 (18)	290 (17)	303 (16)	-11 (15)	10 (14)	163 (14)
O(1)	0.2050 (7)	0.65180 (30)	-0.1066 (5)	880 (30)	442 (26)	474 (26)	46 (22)	28 (21)	407 (24)

Table 1 (cont.)

(b) Hydrogen atoms (parameters $\times 10^3$). Isotropic temperature factor = $\exp[-8\pi^2 U \sin^2 \theta / \lambda^2]$

	X/a	Y/b	Z/c	U
H(1)	230 (7)	559 (3)	22 (5)	50 (15)
H(2)	285 (5)	445 (3)	-56 (4)	29 (10)
H(8)	286 (6)	339 (3)	487 (4)	40 (13)
H(11)	205 (8)	690 (3)	-85 (5)	44 (19)
H(12)	204 (8)	646 (3)	-163 (5)	29 (16)
H(91)	428 (8)	217 (3)	286 (5)	69 (16)
H(92)	366 (9)	208 (4)	403 (7)	118 (24)
H(93)	207 (7)	217 (3)	235 (5)	53 (16)

residual electron density ($0.3 \text{ e } \text{\AA}^{-3}$) located on the C(4)-C(5) bond. In the region between the equatorial Cl^- ions positive and negative peaks of about $0.4 \text{ e } \text{\AA}^{-3}$ are found.

Atomic parameters are listed in Table 1.* Scattering factors and computer programs are those mentioned elsewhere (Sletten, 1974).

Results and discussion

Cu has square pyramidal (4 + 1) coordination (Fig. 1). The complex units are linked pairwise *via* a bridging Cl^- ion which is equatorial in one unit and apical in the centrosymmetrically related one. The four equatorial ligands S, N(7), Cl(1), Cl(2) are coplanar, the Cu^{2+} ion being displaced 0.17 \AA out of plane towards the fifth ligand, Cl(1'). The Cu-Cl(1) bond (2.301 \AA) *trans* to S is significantly longer than the Cu-Cl(2) bond (2.244 \AA) *trans* to N(7). The weak apical interaction, Cu-Cl(1'), may explain the elongation in the bridging equatorial bond. Cu-N(7) (1.992 \AA) is of the same length as found in related Cu^+ -purine complexes. The appreciable directional change in the coordinating orbital on N(7) does not seem to reduce the covalent character of the bond.

The complex is formally an adduct of copper(II) chloride and 6-thiopurine. The sum of the ionic radius of Cu^{2+} (0.72 \AA) and the van der Waals radius of S (1.80 \AA) is only 0.1 \AA longer than the Cu-S length of 2.424 \AA . In a corresponding CuCl_2 adduct of bis-(*N,N*-dimethylacetamido)thioether, $\text{CuCl}_2 \cdot \text{C}_8\text{H}_{16}\text{N}_2\text{O}_2\text{S}$, the Cu^{2+} ion has a square pyramidal coordination with Cu-S = $2.410 (5) \text{ \AA}$ (Coetzer, 1970). Thus the thioether S shows the same metal-binding properties as the thione S. An attempt to crystallize an inner complex of Cu(II)-thiopurine, analogous to the Pd(II) complex, has not been successful so far. In related five-membered chelates Cu-S lengths have been found in the range 1.85 - 2.24 \AA (Bryan & Knopf, 1961; Walter & Holst, 1969). The $\text{Cu}(\text{NS})_2$ chelates referred to above are *trans* isomers even though the *cis* isomers are expected to be slightly more stable (Heitner & Lippard, 1974).

The molecular dimensions of complexed and uncomplexed 6-thiopurines show that in the complex the C=S length is significantly increased with a correspond-

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30997 (16 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Hydrogen-bond distances and angles*

	Position of acceptor atom	Distances (\AA)		Angle ($^\circ$)
		$D \cdots A$	$H \cdots A$	$D-H \cdots A$
N(1)-H(1) \cdots O	x, y, z	2.713 (6)	1.93 (4)	172 (4)
O-H(11) \cdots Cl(2)	$x, \frac{1}{2}-y, z-\frac{1}{2}$	3.260 (5)	2.63 (6)	164 (2)
O-H(12) \cdots Cl(2)	$x, y, z-1$	3.396 (6)	2.83 (6)	164 (2)
C(2)-H(2) \cdots Cl(1)	$x, y, z-1$	3.531 (5)	2.67 (4)	165 (3)
C(9)-H(92) \cdots N(3)	$x, \frac{1}{2}-y, \frac{1}{2}+z$	3.476 (7)	2.58 (7)	151 (4)

ing shortening of the adjacent bonds N(1)–C(6) and C(5)–C(6) (Sletten, Sletten & Jensen, 1969; Sletten & Nygjerd, 1973). The ligand bond angles within the chelate ring, $\angle C(5)–C(6)–S$ and $\angle C(6)–C(5)–N(7)$, are reduced by about 7° and 5° respectively. The 'bite' distance $S \cdots N(7)$ is shortened from 3.342 in 6-thiopurine to 3.041 in the Cu complex and 3.06 (1) Å in the Pd complex. In the corresponding 'inner' complex of Cu the Cu–S bond is expected to be appreciably shorter

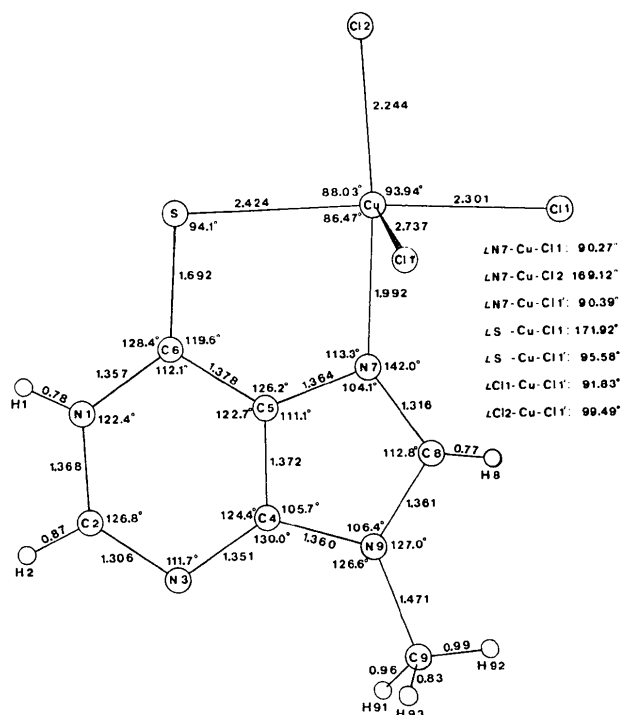


Fig. 1. Interatomic distances and angles in the complex unit. The σ 's in bond lengths are: Cu–S(Cl) 0.001 Å, Cu–N 0.004 Å, C–C(N)(S) 0.004–0.006 Å, H–C(N)(O) 0.04–0.06 Å. The σ 's for angles at the copper atom are in the range 0.04–0.1°, for other angles involving only non-hydrogen atoms the range is 0.2–0.4°, and for those involving hydrogens 1–8°.

than in the adduct, while the Cu–N(7) length remains relatively constant. Consequently, the strain in the chelate ring would increase, leaving a monodentate coordination, analogous to that of the natural purine ligands, equally favourable.

The purine ring is not strictly planar. However, the deviations from the least-squares plane are within one $\sigma_{r.m.s.} = 0.018$ Å. The substituents S and C(9) are displaced 0.026 and 0.052 Å from the least-squares plane. The often observed bend around C(4)–C(5) in purines (Sletten & Jensen, 1969) is not pronounced in the ligand, and may have been offset by the chelation.

The crystal packing is shown in a stereo drawing viewed along **a** (Fig. 2). The complex units are linked in ribbons running parallel to **c**. The bridging water molecule is hydrogen-bonded to the base at N(1) and to Cl(2) in two different units related by a *c*-glide (see Table 2). The interaction $Cl(1) \cdots H(2)–C(2)$ may also be characterized as a hydrogen bond, the distance being 3.531 (1) Å and the angle at H(2), $165(3)^\circ$. Between the ribbons there exists a region occupied mostly by hydrophobic groups. However, a very weak polar interaction may be present between N(3) and the methyl group, $C(9)–H(92) \cdots N(3) = 3.476(7)$ Å, and the angle at H(92), $151(4)^\circ$. In the direction of **b** the molecular layers are connected pairwise *via* the very weak dimer bridge, $Cu \cdots Cl(1') = 2.737(1)$ Å. Alternate layers of purine rings are separated by 2.93 and 3.34 Å respectively. However, there is virtually no overlap between adjacent layers.

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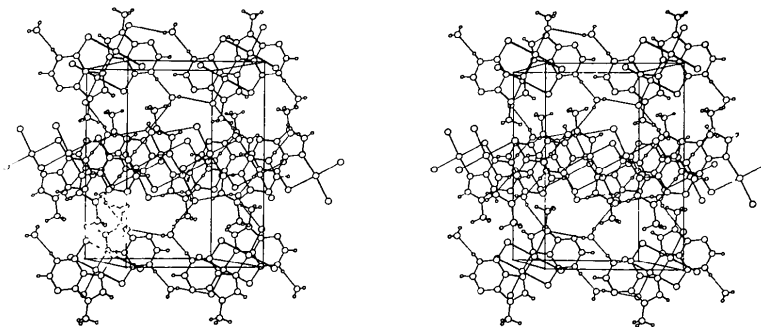


Fig. 2. Stereoscopic drawing of the crystal packing viewed along **a**, with **c** parallel to the interocular line. The drawing was made by *ORTEP* (Johnson, 1970).

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A Neutron Diffraction Study of L-Cysteine

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The orthorhombic form of L-cysteine, $C_3H_7NO_2S$, crystallizes in space group $P2_12_12_1$ with four molecules in a unit cell of dimensions $a = 8.116$ (3), $b = 12.185$ (4), and $c = 5.426$ (2) Å. A three-dimensional neutron diffraction study has provided a more precise description of the hydrogen bonds than was possible in the X-ray experiment. In addition, the neutron study has confirmed that the disordered thiol group is involved in two short contacts, one to oxygen and the other to sulphur. The disorder can be modeled as involving only the hydrogen of the thiol group, or as involving both hydrogen and sulphur. Parameters resulting from both models are presented.

Introduction

There has been some discussion in the literature as to whether sulphur can act as a donor in hydrogen bonding (Srinivasan & Chacko, 1967; Hamilton & Ibers, 1968; Paul, 1974). In our X-ray study of orthorhombic L-cysteine (Kerr & Ashmore, 1973) we found that the sulphur atom was involved in two short intermolecular contacts, one with oxygen and one with a symmetry-related sulphur; but we were not able to locate the thiol hydrogen in difference maps. The present study is part of a series of precision neutron diffraction studies of amino acids and peptides being carried out at Brookhaven National Laboratory.*

Experimental

Neutron diffraction data were collected at room temperature on a computer-controlled four-circle diffractometer at the Brookhaven High Flux Beam Reactor using the multi-spectrometer control system (Beaucage, Kelley, Ophir, Rankowitz, Spinrad & van Norton, 1966). In all, 1960 reflections with $\sin \theta/\lambda \leq 0.680$ were

measured at a neutron wavelength of 1.012 Å using a θ - 2θ step can. A fixed scan range of 3.0° and a step increment of 0.06° were used for low-angle data ($\sin \theta/\lambda \leq 0.494$). For the high-angle data the scan range was determined by the expression $\Delta 2\theta = 1.0^\circ (1.1 + 8.8 \tan \theta)$ and the step increment was adjusted to give about 40 steps per reflection. In order to minimize the occurrence of simultaneous reflections, the crystal was oriented with its c axis about 5° from the axis of the goniometer (Young, 1969). The unit-cell constants shown in Table 1 and the orientation matrix were determined by least-squares refinement of setting angles of 25 high-angle reflections. Two standards, measured after every 60 reflections, showed maximum deviations of less than 2.5% from their mean values. Background corrections were made using a method that defines the peak by two points that minimize $\sigma(I)/I$ (Lehmann & Larsen, 1974).

Squared structure amplitudes were defined as $F_o^2 = I \sin 2\theta$ and corrected for absorption using Gaussian numerical integration with the crystal shape defined by eight rational planes. The linear absorption coefficient was calculated assuming the incoherent scattering cross section for hydrogen to be 40 barn and using the value of (μ/ρ) for C, N, O, S tabulated in *International Tables for X-ray Crystallography* (1968). Resulting transmission factors were in the range 0.76 to 0.88.

* This paper is regarded as part XVI in the series *Precision Neutron Diffraction Determination of Protein and Nucleic Acid Components*.