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SYNTHESIS AND X-RAY CRYSTAL STRUCTURE OF A Cu^{II}–THEOPHYLLINE COMPLEX: [Cu(theo)₂(H₂O)₃]·2H₂O*

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Abstract—The complex [Cu^{II}(theo)₂(H₂O)₃]·2H₂O (theo = theophylline) was obtained from aqueous solution. The crystals belong to the monoclinic system, space group *P*2₁/*n*, and are reflection twins about the (001) face. The structure was solved using data from a twinned crystal and refined to final *R* and *R*_w values of 0.069 and 0.064, respectively. Copper has a square-pyramidal coordination with two theo molecules coordinating through N(7) at equatorial positions. The remaining sites are occupied by water molecules. O(6) of one of the theo molecules is at the other axial site at a longer distance of 3.18 Å. This could lead to an alternate (4+1+1) octahedral coordination geometry for Cu^{II}. The packing is stabilized by stacking interactions between the theophylline moieties at an average separation of 3.46 Å.

Several research groups have investigated the coordination of metal ions by oxopurines,¹ a major interest being the possibility of closing a chelate ring by binding of O(6) to a metal atom initially coordinated to the N(7) endocyclic site. Such a chelate was considered as an intermediate in a possible mechanism of action by antitumour drugs. Theophylline is a close analogue of guanine. This ligand has been shown to function both as an anion^{2–6} and as a neutral ligand,^{7,8} and in either case N(7) is the binding site to the metal ion. The only exception where it binds through N(9) is in theophyllinium trichloro theophylline platinate(II).⁹ N(7) is the preferred coordination site not only in guanosine, but also in ionosine and other 6-oxopurines.¹⁰ This site in guanosine is believed to be the primary target for platinum antitumour complexes in cellular DNA. One of the models postulated to explain this speci-

ficity is initial metal binding to N(7) followed by coordination to O(6) to form an N(7)/O(6) chelate. The exocyclic atom O(6) can take part in hydrogen bonding with the other ligands in the metal coordination sphere. In the absence of hydrogen bond donors, weak coordinating interactions with the residual coordination site on the metal may take place. Therefore, it is of interest to examine whether N(7)/O(6) chelation is observed in metal–theophylline complexes.

EXPERIMENTAL

Cu(NO₃)₂ and im (imidazole) aqueous solutions at 5 × 10^{−3} mol were mixed in the ratio 1:3 and kept aside for slow evaporation. Violet crystals of the composition [Cu(im)₃H₂O](NO₃)₂ were obtained after 2 weeks.

To the aqueous solution of the above complex, an equimolar solution of theo (5 × 10^{−3} mol) was added and the resulting mixture was allowed to evaporate at room temperature. After 2 weeks, dark green crystals separated which were filtered, washed with water and air dried.

Preliminary crystal data and density (measured by flotation using chloroform–bromoform) suggested the composition [Cu(im)₂(theo)(NO₃)]NO₃ or [Cu(im)(theo)(H₂O)₃](NO₃)₂·H₂O. Found: C,

* Listings of positional and thermal parameters of all atoms, bond distances and angles, possible hydrogen bonds and observed and calculated structure factors (15 pages) have been deposited at Cambridge Crystallographic Data Centre.

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33.0; H, 3.9; N, 21.2. Calc. for $\text{CuC}_{14}\text{H}_{24}\text{N}_8\text{O}_9$: C, 32.8; H, 4.7; N, 21.8%. These results do not agree with either of these formulae and suggested a binary complex, which was confirmed after structure solution. The complex has the molecular formula $[\text{Cu}(\text{theo})_2(\text{H}_2\text{O})_3] \cdot 2\text{H}_2\text{O}$.

Examination under the microscope suggested that the crystals were twinned.

X-ray data collection

The unit cell parameters and other crystal data are reported in Table 1. Preliminary oscillation and Weissenberg photographs revealed systematic absences corresponding to the monoclinic space group $P2_1/n$, and also gave an indication that the crystals were reflection twins about the (001) face. There was no crystal devoid of twinning in the entire crop. It was also not possible to separate the twinned crystal and obtain a single crystal for X-ray intensity measurement. Hence the data collection was proceeded with a twinned crystal measuring about $0.45 \times 0.28 \times 0.07$ mm. The ω - 2θ scan method was used with a scan speed of 3° min^{-1} and a scan width of $0.75 + 0.45 \tan \theta$ in the range $0 \leq 2\theta \leq 50^\circ$.

The intensities of two standard reflections were

monitored after every 50 min during the data collection. They did not show any systematic variation over the duration of the experiment. Intensity data were collected for the major component of the twinned crystal. However, reflections with $h = 0$ coincide for the two reciprocal lattices. There is again coincidence for $h = 4$ and its multiples. These reflections could not be separated during the data collection. A total of 3197 reflections were measured.

The intensity data were corrected for Lorentz and polarization effects but not for absorption.

Structure solution and refinement

The structure was solved by the heavy atom method and completed by a series of three-dimensional Fourier and difference Fourier maps. Isotropic refinement converged at an R index of 0.15. At this stage, the data were analysed for the effects of twinning and, as expected, large differences between observed and calculated structure factors were seen for reflections with $h = 0, 4$ and their multiples.

Figure 1 shows the interpenetrating reciprocal lattices for the twinned crystal and it can be seen that there is some coincidental overlap from both

Table 1. Crystal data

Formula	$\text{Cu C}_{14}\text{H}_{24}\text{N}_8\text{O}_9$
M	511.54
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	13.895(3)
b (Å)	11.977(2)
c (Å)	12.437(3)
β (°)	97.83(2)
V (Å ³)	2050.69
Z	4
D_m (g cm ⁻³)	1.63
D_c (g cm ⁻³)	1.65
$F(000)$	1060
μ (cm ⁻¹)	11.22
λ (Å)	0.7107
Crystal dimensions	$0.45 \times 0.28 \times 0.07$
2θ range (°)	0–50
Scan mode	ω - 2θ
Scan speed (° min ⁻¹)	3
Scan width ($\Delta\theta$)	$0.75 + 0.45 \tan \theta$
No. of reflections measured	3197
No. of reflections used ($I \geq 3\sigma(I)$)	1083
$R = \Sigma(F_o - F_c) / \Sigma F_o $	0.069
$R_w^a = [\Sigma w(F_o - F_c)^2 / \Sigma w F_o^2]^{1/2}$	0.064

^aWeighting scheme, $w = a/[\sigma^2(F_o) + b(F_o)^2]$, $a = 1$, $b = 0.00004$.

RESULTS

Description of the structure

The coordination sphere. The molecular structure with the atom labelling scheme is shown in Fig. 2. Selected bond distances and angles are given in Table 2. The copper ion has square-pyramidal geometry. Two theophylline molecules coordinate through N(7) at equatorial positions [Cu—N_{av} = 1.98(1) Å]. The remaining two equatorial sites are occupied by water molecules O(W1) and O(W2) [Cu—O = 1.98(1) Å]. O(W3) occupies the axial position [Cu—O(W3) = 2.28(1) Å]. Copper also has O(6) of theo(1) on the other axial site at a longer distance of 3.18(1) Å, which if included would lead to an alternate (4+1+1) octahedral geometry.

The two theophylline moieties are directed *trans* to each other at an angle of 161.5°. The other *trans* angle is 176.1°. The angle O(6)—Cu—O(W3) is 158.3°. The *cis* angles in the coordination plane range from 88.1° to 91.8°. The angles between the Cu—O(W3) bond and the bonds from copper to the atoms in the square plane range from 91.2° to 102.8°. The angle between the Cu—O(6) bond and the normal to the square plane is 76.7°. The copper atom is 0.185 Å off the square plane. Both the purine rings are planar. The methyl carbons C(1) and C(3) are out of the purine plane by 0.10 and 0.07 Å in molecule A and 0.03 and 0.01 Å in molecule B. Molecule B corresponds to the primed theophylline moiety. The exocyclic oxygen atoms O(2) and O(4)

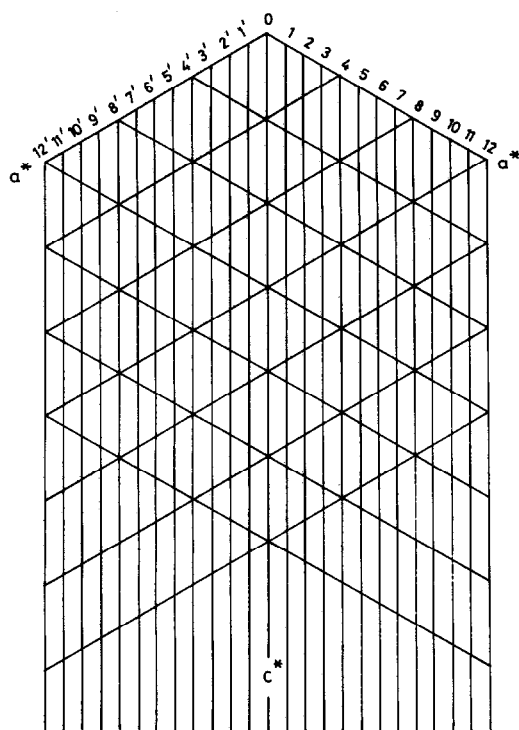


Fig. 1. Interpenetrating reciprocal lattices of the twinned crystal.

halves for reflections with $h = 4$ and its multiples. The first layer Weissenberg photograph was scanned in a microdensitometer and its optical density values were measured. The integrated intensities of a few peaks (intense spot and its weak twin component spot) were measured and these helped to obtain an average value of the ratio of strong : weak components. Using this value, the zero layer reflections okl were corrected. Reflection with h indices 4, 8 and 12 could not be corrected in this manner and hence a total of 251 reflections were eliminated from the data set, leaving 1083 reflections with $I \geq 3\sigma(I)$. A similar procedure was adopted by Cameron and Maguire¹¹ and also by Behm.¹² Using the remaining 1083 reflections, three cycles of isotropic refinement brought down the R value to 0.086. Allowance for anisotropic motion was given to all non-hydrogen atoms and the contributions from hydrogen atoms from their calculated positions were included in further least-squares refinement, leading to $R = 0.069$.

The neutral scattering factors for copper atom were taken from International Tables.¹³ The scattering factors for all other atoms are available in the program SHELX 76.¹⁴ Anomalous dispersion correction was applied to the scattering factors of all the non-hydrogen atoms.¹⁵

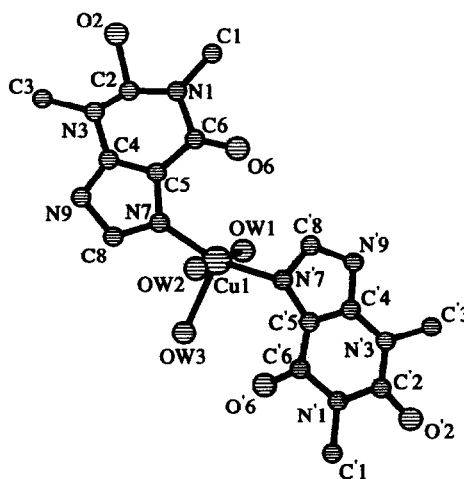


Fig. 2. A perspective view of the molecule with atom numbering scheme.

Table 2. Coordination parameters with their ESD values in parentheses

Distances (Å)			
Cu—N(7)	1.98(1)	Cu—N'(7)	1.98(1)
Cu—O(W1)	1.99(1)	Cu—O(W2)	1.97(1)
Cu—O(W3)	2.28(1)		
Angles (°)			
N(7)—Cu—N'(7)	162(1)	N(7)—Cu—O(W1)	92(1)
N(7)—Cu—O(W2)	90(1)	N(7)—Cu—O(W3)	95(1)
N'(7)—Cu—O(W1)	89(1)	N'(7)—Cu—O(W2)	88(1)
N'(7)—Cu—O(W3)	103(1)	O(W1)—Cu—O(W2)	176(1)
O(W1)—Cu—O(W3)	92(1)	O(W2)—Cu—O(W3)	91(1)

are 0.07 and 0.04 Å off the purine plane in A and 0.01 and 0.02 Å in B. The dihedral angle between the imidazole and pyrimidine rings is 2.30° and 1.83° in A and B, respectively. The dihedral angles between the equatorial plane and the theophylline rings are 81.71° and 86.34° for A and B, respectively.

The crystal packing is illustrated in Fig. 3, which is a projection of the unit cell down the *a*-axis. There is intramolecular hydrogen bonding between the exocyclic oxygen O(6) and the coordinated water O(W3). O(W3) donates a proton to O(6) [O(W3)⋯O(6) = 2.69 Å]. O(6) of theo accepts a proton from lattice water O(W4) [O(W4)⋯O(6) = 2.89 Å]. The two lattice water molecules O(4) and O(5) are also hydrogen bonded [O(W4)⋯O(W5) = 2.75 Å]. The coordinated water O(W2) forms hydrogen bonds with the atoms N(9) and N'(9) of symmetry related molecules [O(W2)⋯N(9) = 2.82 Å; O(W2)⋯N'(9) = 2.74 Å]. O(W3) and the lattice water O(W5) are also involved in hydrogen bonding [O(W3)⋯O(W5) =

2.72 Å]. The packing is further stabilized by stacking interactions between the theophylline moieties at an average separation of 3.46 Å and an angle of 18.2°.

DISCUSSION

In the present structure, theo acts as a uninegative anion coordinating through N(7). This site is the primary binding site and is very common among metal–theo complexes. Marzilli, Kistenmacher and co-workers²⁻⁶ confirmed N(7) as the primary binding site and noticed that O(6) is generally hydrogen bonded with other ligands in the metal coordination sphere. However, a significant direct interaction [Cu—O(6) = 2.92 Å] was observed in the (*N*-3,4-benzo - salicylidene - *N',N'* - dimethylethylenediamine)(theo)Cu^{II} complex.⁵ This distance was comparatively longer than the Cu—N(7) distance of 1.95 Å. The presence of the 6-oxo group near the relatively open axial position of the primary coordination sphere and the absence of any coor-

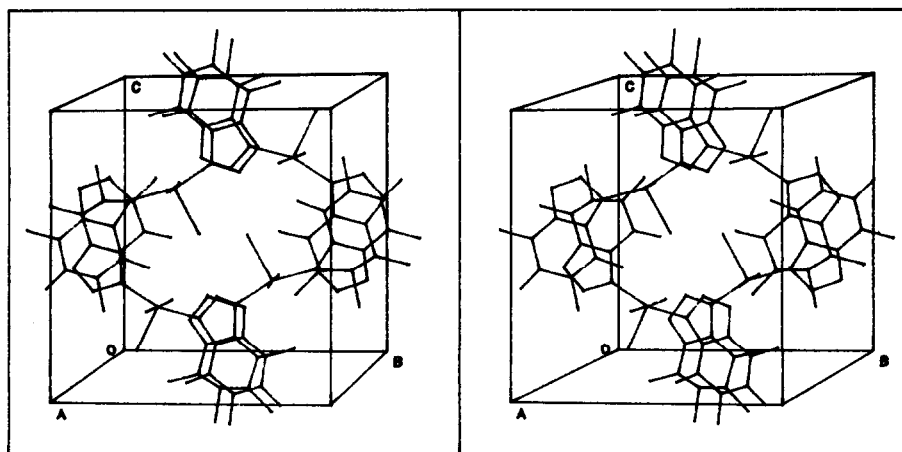


Fig. 3. A stereoscopic view of the packing of the molecules in the unit cell.

Table 3. Structural parameters in some metal-theophylline complexes

Complex ^a	Coordination geometry	M—N(7) (Å)	M—O(6) (Å)	M—N(7)—C(5)	M—N(7)—C(8)	Intra molecular hydrogen bonding
1	Square-planar	2.004(13)	—	130(1)	124(1)	None
2	Square-planar	1.969(7)	3.340(8)	127.5(6)	128.6(6)	None
3	Open-clamshell	2.211(3)	2.278(2)	104.6(2)	154.2(2)	None
4	Square-pyramidal	1.956(3)	2.919(3)	117.8(2)	138.9(2)	None
5	Square-pyramidal	1.978(10)	3.182(11)	124.2(9)	129.2(9)	None
		1.984(10)	3.711(10)	137.9(9)	117.2(9)	OH ₂ (ax)···
6	Square-planar	1.986(1)	3.730(1)	138.0(1)	118.9(1)	N—H(eq)···O(6)
7	Square-pyramidal	2.000(3)	3.739(3)	136.1(2)	117.0(2)	N—H(eq)···O(6) OH ₂ (ax)···O(6)
8	Square-pyramidal	2.007(3)	3.683(3)	135.9(3)	120.2(3)	N—H(eq)···O(6)
9	Square-pyramidal	2.006(3)	3.834(3)	136.5(2)	118.8(2)	OH ₂ (eq)···O(6)
		1.965(3)	3.278(8)	127.9(2)	127.2(2)	None

^a1, Chlorobis(theo)Cu^{II};¹⁷ 2, *N*-salicylidene-*N,N'*-dimethylethylenediamine-(theo)Cu^{II};⁶ 3, bis(*N*⁵-cyclopentadienyl)(theo)Ti^{III};¹⁶ 4, *N*,3-4-benzosalicylidene-*N,N'*-dimethylethylenediamine(theo)Cu^{II};⁵ 5, present study: [Cu(theo)₂(H₂O)₃]·2H₂O; 6, *N*-salicylidene-*N'*-methylthylenediamine(theo)(aquo)Cu^{II};⁴ 7, bis(theo)(diethylenetriamine)Cu^{II};³ 9, [nitrate bis(aquo) bis(theo)Cu^{II}]⁺.

minated potential hydrogen bond donor on the Schiff base in this complex have apparently prompted the formation of a Cu—O(6) bond. Cozak *et al.*¹⁶ have reported a very unusual balanced N(7)/O(6) chelation in (μ^5 -C₅H₅)₂(theo)Ti, where Ti—N(7) and Ti—O(6) are 2.21 and 2.28 Å, respectively, the two distances being nearly equal. It has been suggested that chelate formation in this case is favoured since the Van der Waals profile of the titanocene unit makes it difficult for theo to coordinate in a unidentate manner, because of steric hindrance with the groups at C(6) and N(3). This is relieved by bidentate coordination through N(7) and O(6). In another structure,¹⁷ Cu(theo)₂Cl₂, where theo is a neutral ligand, a Cu···O(6) distance of 3.44 Å was attributed to a weak Cu···O interaction. The absence of intramolecular interligand hydrogen bonds and the presence of the O(6) exocyclic atom close to the relative open positions in the primary coordination sphere have apparently influenced this interaction.

The present structure represents another instance of a weak Cu—O(6) interaction in a 6-oxopurine complex. Here, O(6) occupies the second axial site which is relatively open due to the absence of a hydrogen donor ligand, in the presence of which interligand-hydrogen bond formation would have taken place. Although the Cu—O(6) distance is significantly longer than is observed for occupation of the axial position by water or small anions, this

distance is considerably shorter than the Cu···O(6) distance (average 3.75 Å) in structures where O(6) is involved in interligand hydrogen bonding. It may also be noted that in the present structure, the 6-oxo group of the other theo moiety is involved in the hydrogen bonding and the Cu···O(6) distance is 3.71 Å. The stereochemical changes that bring O(6) on to the open axial position are evidenced by the disymmetry in the exocyclic bond angles at N(7). While the Cu—N(7)—C(5) and Cu—N(7)—C(8) angles are 124.2° and 129.2°, respectively for theo(A), an opposite disymmetry is observed for theo(B), where the angles are 137.9° and 117.2°, respectively. Table 3 gives the comparative structural parameters for theo complexes.

Thus, it is observed that the overall environment of the coordination sites play a determining role in the formation of the chelate ring in these complexes of theophylline. The fact that N(7)/O(6) chelation is rare and not normally observed suggests that this bonding mode is not favoured under less restricted conditions.

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