ics: *PLATON* (Spek, 1990). Software used to prepare material for publication: *SHELXL*93.

The National Fund for Scientific Research (Belgium) is gratefully acknowledged for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AB1531). Services for accessing these data are described at the back of the journal.

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A Dinuclear Complex of the Thiopurine Drug Azathioprine: $[Cu_2Cl_4(\mu\text{-azathioprine})_2]$.4DMF

FU-CHUN ZHU, HELMUT W. SCHMALLE AND ERICH DUBLER

Institute of Inorganic Chemistry, University of Zürich, Winterthurerstraße 190, CH-8057 Zürich, Switzerland. E-mail: schmalle@aci.unizh.ch

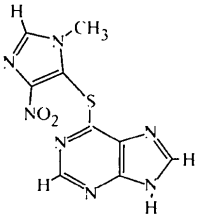
(*Received 3 November 1997; accepted 11 December 1997*)

Abstract

In the title centrosymmetric dinuclear complex, bis[μ-6-(1-methyl-4-nitro-5-imidazolylthio)-7*H*-purine-N^3:N^9]-bis[dichlorocopper(II)] tetrakis(dimethylformamide) solvate, $[Cu_2Cl_4(C_9H_7N_7O_2S)_2].4C_3H_7NO$, the two Cu atoms are each coordinated by two chloro and two N3:N9-bridging neutral azathioprine ligands. The coordination geometry of each Cu atom is strongly distorted square planar. The Cu···Cu distance within the dinuclear unit is 2.939 (2) Å. Azathioprine exhibits a conformation in which there is a *trans* arrangement of the C5—C6 and S6—C10 bonds with respect to C6—S6, and in which the imidazole substituent at S6 points away from the imidazole ring of the purine moiety. The imidazole plane is approximately perpendicular to the purine plane, with a corresponding dihedral angle of 72.1 (3)°.

Comment

Azathioprine, 6-(1-methyl-4-nitro-5-imidazolylthio)-9*H*-purine, (I), was first synthesized in the early 1960s and subsequently introduced as a slow-release prodrug for the antileukemic drug 6-mercaptopurine and as an immunosuppressant by Hitchings & Elion (Elion, 1989). In addition, azathioprine is currently used for the treatment of rheumatoid arthritis.

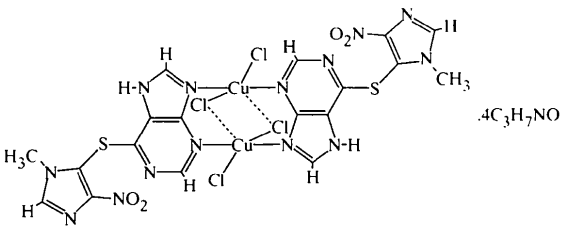


(I)

The investigation of the formation and structure of metal complexes of azathioprine and related purines is of much interest. First, considering the well known anticancer activity of the metal complex *cis*-$PtCl_2(NH_3)_2$ (Rosenberg *et al.*, 1969) and the fact that metal complexes containing ligands which have biological activity in their own right may exhibit a somewhat greater activity than does the free ligand (Kirschner *et al.*, 1966), the activity and/or selectivity of the purine drugs might be enhanced by metal complexation. Second, the copper dependence of rheumatoid arthritis and, therefore, of the corresponding drugs has received particular attention (Jackson *et al.*, 1981). Finally, we have proposed (Zhu *et al.*, 1998) that the embedding of drug molecules like azathioprine within the framework of a polynuclear mixed-ligand metal complex molecule could represent a new method for influencing the biological properties of purine drugs.

Neutral azathioprine is found as its 9*H* tautomer in the crystal structure of azathioprine (Acharya, 1984) and of azathioprine.$2H_2O$ (Cook & Bugg, 1975). By deprotonation or tautomerization of azathioprine, all four N atoms of the purine ring become potential coordination sites for metal ions. Two different coordination modes have already been established for azathioprine by X-ray crystallography: monodentate binding of the neu-

tral ligand *via* N3 in the dimeric complex $[Rh^{II}_2$(azathioprine)$_2(\mu$-$Ac^-)_4]$.4DMAA (Chifotides *et al.*, 1992) and N3:N9 bridging as well as N9:N7 bridging of the monodeprotonated anionic ligand in the octanuclear complex $[\{Cu_4$(azathioprine$^-)_2(THD^-)_5(OH^-)\}_2]$.$2CH_3CN$ (Zhu *et al.*, 1998). We report here the synthesis and structure of a new dinuclear copper(II) complex, $[Cu_2Cl_4(\mu$-azathioprine$)_2]$.4DMF, (II).



(II)

A drawing of this centrosymmetric complex is presented in Fig. 1. A coordination scheme of neutral azathioprine ligands connecting two Cu atoms [interatomic distance 2.939 (2) Å] by N3:N9 bridging is found in this structure. In contrast to the octanuclear complex described above, the N7 atom is not coordinated but bears an H atom. Each Cu^{II} atom, which is coordinated by an N3 and an N9 atom from two different azathioprine molecules and by two Cl atoms, exhibits a strongly distorted square-planar coordination geometry with corresponding bonding distances of 1.985 (6) (N9), 2.008 (6) (N3), 2.241 (3) (Cl2) and 2.280 (3) Å (Cl1). An additional, weak interaction with an internuclear distance of 2.789 (3) Å is observed between Cu1 and $Cl1^i$ [symmetry code: (i) $1-x$, $-y$, $-z$]. If this weak bridging interaction of Cl1 is considered to represent a chemical bond, the copper(II) coordination sphere may also be described as a (4+1) distorted square pyramid. However, we do not classify this $Cu1\cdots Cl1^i$ interaction as a true chemical bond. A typical μ-Cl bridge is expected to be approximately symmetrical, as for example in the $[Cu_2Cl_6]^{2-}$ unit (Textor *et al.*, 1974), with Cu—Cl distances of 2.292 (2) and 2.321 (2) Å. Therefore, the $Cu\cdots Cl1^i$ interaction has been shown by dashed lines in the scheme above and in Fig. 1.

There is no interaction between the S and Cu^{II} atoms. A strong N7—H7$\cdots$O1*A* hydrogen bond with an N$\cdots$O distance of 2.602 (9) Å is formed between the dinuclear complex and one of the solvent molecules. There is only a very weak hydrogen bond between the complex and the second solvent molecule. This fact might be responsible for the instability of the crystals in air. The imidazole ring attached at the S atom of the 6-mercaptopurine unit prevents the coordinated purine moiety from establishing inter- or intramolecular base-stacking interactions.

There are no unusual features of the bond distances and angles within the azathioprine molecule. The C6—S6 bond length of 1.769 (8) Å indicates slight double-bond character. A *trans* arrangement of the C5—C6 and S6—C10 bonds with respect to C6—S6 is observed. This leads to a conformational arrangement in which the imidazole substituent at S6 points away from the purine moiety. The interplanar angles found are 14.2 (5)° between the purine (N1—C2—N3—C4—C5—C6—N7—C8—N9) and sulfur planes (C6—S6—C10), 72.1 (3)° between the purine and imidazole planes (C10—N11—C12—N13—C14), 70.0 (3)° between the sulfur and imidazole planes, and 6.4 (2)° between the imidazole plane and the nitro group (O11—N15—O12). Similar conformations of azathioprine have been found in all corresponding crystal structures reported to date (Zhu *et al.*, 1998).

Experimental

$[Cu_2Cl_4(\mu$-azathioprine$)_2]$.4DMF was synthesized by mixing azathioprine (Sigma) in DMF and anhydrous $CuCl_2$ in DMF in a molar ratio of 1:2. After slow evaporation of the mixture

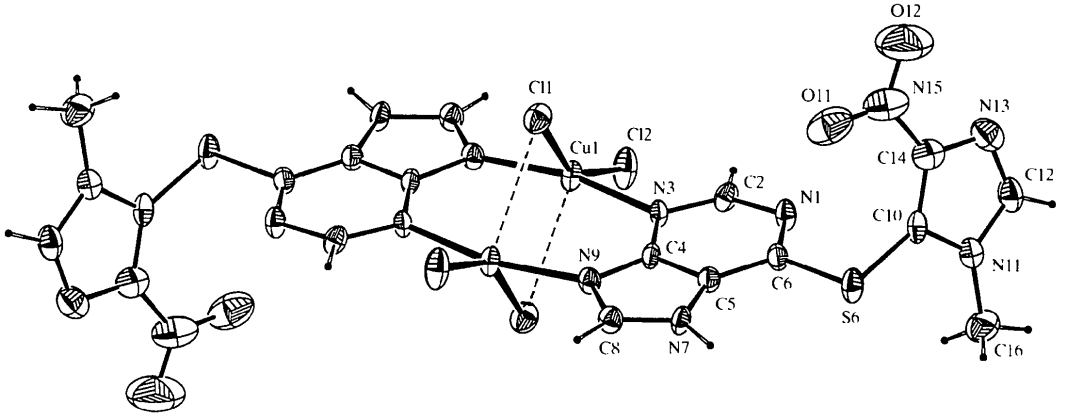


Fig. 1. Drawing of $[Cu_2Cl_4(\mu$-azathioprine$)_2]$.4DMF with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are shown as small circles of arbitrary radii and the solvent molecules have been omitted for clarity.

at 333 K, a small amount of tiny green crystals of the title compound and some blue amorphous precipitate appeared within two days. The crystals decompose in air or when recrystallized from DMF. The data crystal was protected in a glass capillary together with a drop of mother liquor immediately after separation from the solution.

Crystal data

$[Cu_2Cl_4(C_9H_7N_7O_2S)_2].4C_3H_7NO$
$M_r = 1115.82$
Monoclinic
$P2_1/c$
$a = 11.739\,(2)$ Å
$b = 10.092\,(2)$ Å
$c = 20.652\,(4)$ Å
$\beta = 99.53\,(3)°$
$V = 2412.9\,(8)$ Å^3
$Z = 2$
$D_x = 1.536$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 5.3$–$10.8°$
$\mu = 1.253$ mm^{-1}
$T = 296\,(2)$ K
Irregular fragment
0.1 × 0.1 × 0.1 mm
Green

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scan
Absorption correction: none
4885 measured reflections
4745 independent reflections
2003 reflections with $I > 2\sigma(I)$
$R_{int} = 0.058$
$\theta_{max} = 26°$
$h = -14 \rightarrow 14$
$k = 0 \rightarrow 12$
$l = 0 \rightarrow 25$
3 standard reflections
every 400 reflections
intensity decay: 0.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.077$
$wR(F^2) = 0.124$
$S = 1.223$
4743 reflections
293 parameters
H atoms riding (see below)
$w = 1/[\sigma^2(F_o^2) + (0.0497P)^2 + 0.7303P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.029$
$\Delta\rho_{max} = 0.480$ e Å^{-3}
$\Delta\rho_{min} = -0.477$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0002 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Cu1—N9^i	1.985 (6)	C5—N7	1.372 (10)
Cu1—N3	2.008 (6)	C5—C6	1.373 (10)
Cu1—Cl2	2.241 (3)	N7—C8	1.333 (10)
Cu1—Cl1	2.280 (3)	C8—N9	1.332 (10)
Cu1···Cu1^i	2.939 (2)	C10—N11	1.365 (10)
S6—C10	1.748 (9)	C10—C14	1.360 (12)
S6—C6	1.769 (8)	N11—C12	1.347 (11)
N1—C2	1.330 (9)	N11—C16	1.431 (10)
N1—C6	1.350 (9)	C12—N13	1.275 (12)
C2—N3	1.314 (9)	N13—C14	1.353 (12)
N3—C4	1.345 (9)	C14—N15	1.421 (14)
C4—N9	1.374 (9)	N15—O12	1.190 (12)
C4—C5	1.395 (10)	N15—O11	1.228 (12)
N9^i—Cu1—N3	165.6 (3)	C5—C6—S6	119.2 (6)
N9^i—Cu1—Cl2	94.8 (2)	C8—N7—C5	106.3 (7)
N3—Cu1—Cl2	95.6 (2)	N7—C8—N9	113.1 (8)
N9^i—Cu1—Cl1	87.7 (2)	C8—N9—C4	105.4 (7)
N3—Cu1—Cl1	88.5 (2)	C8—N9—Cu1^i	129.6 (6)
Cl2—Cu1—Cl1	148.70 (11)	C4—N9—Cu1^i	124.9 (5)
C10—S6—C6	99.6 (4)	N11—C10—C14	104.9 (8)
C2—N1—C6	117.2 (7)	N11—C10—S6	120.4 (7)
N3—C2—N1	128.8 (8)	C14—C10—S6	134.6 (8)
C2—N3—C4	113.6 (7)	C12—N11—C10	104.9 (8)
C2—N3—Cu1	126.0 (6)	C12—N11—C16	127.5 (9)
C4—N3—Cu1	120.3 (5)	C10—N11—C16	127.6 (8)
N3—C4—N9	128.7 (7)	N13—C12—N11	115.2 (9)
N3—C4—C5	123.0 (7)	C12—N13—C14	103.3 (9)
N9—C4—C5	108.2 (7)	N13—C14—C10	111.7 (9)
N7—C5—C6	134.9 (8)	N13—C14—N15	123.3 (11)
N7—C5—C4	106.9 (7)	C10—C14—N15	124.9 (11)
C6—C5—C4	118.1 (8)	O12—N15—O11	122.9 (13)
N1—C6—C5	119.3 (7)	O12—N15—C14	118.0 (13)
N1—C6—S6	121.5 (6)	O11—N15—C14	119.0 (11)

Symmetry code: (i) $1 - x, -y, -z$.

Of the two crystallographically independent solvent molecules, one was disordered and was refined with two positions, *B*1 and *B*2, for each of C2*B*, C4*B* and C5*B*, and with a final site-occupation ratio of *B*1/*B*2 = 0.511 (12)/0.489 (12). The *PART* instruction of *SHELXL*93 (Sheldrick, 1993) was employed to define the disordered atoms. The three H atoms of the purine moiety (H2, H7 and H8) and H12 of the imidazole substituent could be refined freely with isotropic displacement parameters. The positional parameters of all methyl H atoms and of the H atom attached to the carbonyl group of DMF were calculated. They were refined with constrained bond lengths of 0.96 and 0.93 Å, respectively. Their displacement parameters were fixed at values of 1.5 and 1.2 times, respectively, the equivalent isotropic displacement parameters of the attached C atom. A trial analytical absorption correction was applied using six indexed but irregularly grown faces. However, as no improvements in the refinement parameters or standard uncertainties were obtained, the absorption correction was discarded. The elevated values of the *R* factors most probably result from the fact that the very small data crystal was mounted in a glass capillary together with mother liquor and only gave a limited set of significant intensities.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Data reduction: *MolEN* (Fair, 1990). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93. Molecular graphics: *PLATON* (Spek, 1990). Software used to prepare material for publication: *SHELXL*93.

The authors thank the Swiss National Science Foundation for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1050). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1998). C**54**, 776–779

Aquabis(3-methyl-4-octanoyl-1-phenyl-5-pyrazolonato-*O*,*O*′)zinc(II) and Bis(ethanol-*O*)bis(3-methyl-1-phenyl-4-stearoyl-5-pyrazolonato-*O*,*O*′)cadmium(II)

WULFHARD MICKLER, ANNETT REICH, STEFAN SAWUSCH, UWE SCHILDE AND ERHARD UHLEMANN

Universität Potsdam, Institut für Anorganische Chemie und Didaktik der Chemie, Postfach 601553, Am Neuen Palais 10, D-14415 Potsdam, Germany. E-mail: us@conrad.chem.uni-potsdam.de

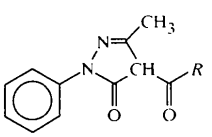
(*Received 17 June 1997; accepted 11 December 1997*)

Abstract

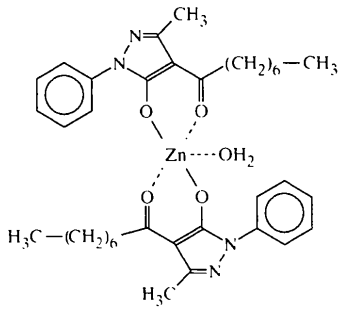
The structures of the zinc and cadmium complexes of 4-acyl-3-methyl-1-phenyl-5-pyrazolones, [Zn-$(C_{18}H_{23}N_2O_2)_2(H_2O)$] and [$Cd(C_{28}H_{43}N_2O_2)_2(C_2H_6O)_2$], show remarkable differences. In the case of zinc, the coordination number is five and a square-pyramidal structure was found, which is realized by the coordination of one molecule of water in the apical position. The coordination polyhedron is significantly distorted towards a trigonal-bipyramidal arrangement. The cadmium compound contains two coordinated ethanol molecules and is octahedral.

Comment

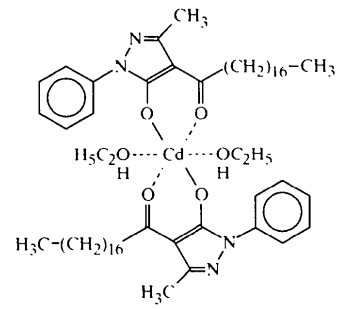
4-Acyl-3-methyl-1-phenyl-5-pyrazolones are useful agents for the extraction of metals (Jensen, 1959*a*,*b*; Zolotov & Kuzmin, 1977).



Long-chain 4-acyl-3-methyl-1-phenyl-5-pyrazolones can be used likewise as carriers in the liquid membrane permeation of copper (Mickler *et al.*, 1991; Kümmel *et al.*, 1996), as well as in the competing permeation of nickel, zinc and cadmium (Mickler *et al.*, 1996). In this case, zinc is selected before cadmium and nickel, even though the stability constants of complexes with 4-acyl-5-pyrazolones show the reverse sequence (Friedrich *et al.*, 1989). In order to clarify any influences of structural parameters on this behaviour, the molecular structures of the zinc and cadmium complexes with long-chain 4-acyl-3-methyl-1-phenyl-5-pyrazolones, *i.e.* (1) and (2), respectively, were determined.



(1)



(2)

In the zinc complex, (1), the central atom displays square-pyramidal coordination, strongly distorted towards trigonal-bipyramidal coordination (Fig. 1). Characteristic of the distortion are the angles about the Zn atom: 161.1 (2) (O11—Zn—O21), 152.2 (2) (O12—Zn—O22), 104.3 (2) (O12—Zn—O3) and 103.5 (2)° (O22—Zn—O3). The Zn—O bond lengths were found to range from 1.970 (3) to 2.061 (4) Å. The C—O and C—C bond lengths within the chelate rings are nearly equal, indicating delocalized π electrons. Both chelate rings are folded about the O donor atoms, by angles of 20.5 (3) and 17.6 (3)°. The planes formed by the chelate and pyrazolone rings are nearly parallel to each other. The double bonds N12═C14 [1.312 (6) Å] and N22═C24 [1.312 (6) Å] are characteristic of the pyrazolone ring. The planes of the phenyl rings are slightly twisted with respect to the pyrazolone planes [charac-