

# A mixed-valence iron complex of the antitumour drug 6-mercaptopurine: tris(6-mercaptopurine)iron(II) tetrachloroferrate(III) chloride

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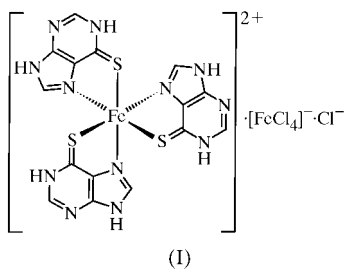
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Single crystals of the title complex, tris(1,6-dihydro-9H-purine-6-thione-*N*<sup>7</sup>,*S*)iron(II) tetrachloroferrate(III) chloride,  $[\text{Fe}(\text{C}_5\text{H}_4\text{N}_4\text{S})_3][\text{FeCl}_4]\text{Cl}$ , were grown on the surface of solid 6-mercaptopurine monohydrate pellets in a solution of iron(III) chloride. The solution of the hexagonal structure required the application of twin refinement techniques. All the component ions lie on threefold rotation axes. The complex contains distorted octahedral  $[\text{Fe}(\text{C}_5\text{H}_4\text{N}_4\text{S})_3]^{2+}$  cations with three N7/S6-chelating neutral 6-mercaptopurine ligands, tetrahedral  $[\text{FeCl}_4]^-$  anions with a mean Fe–Cl distance of 2.189 (1) Å, and free chloride ions.

## Comment

6-Mercaptopurine (6-MP), the synthetic thio analogue of the naturally occurring purine derivative hypoxanthine, is a clinical agent routinely administered for the therapy of human leukaemia. 6-MP is converted intracellularly to the corresponding ribonucleotide, which inhibits purine biosynthesis (Elion, 1989). Metal complexes of 6-MP and related drugs are of special interest in view of their possibly enhanced therapeutic effect with respect to the free base, which may also be a consequence of the protection of the molecule from enzymatic



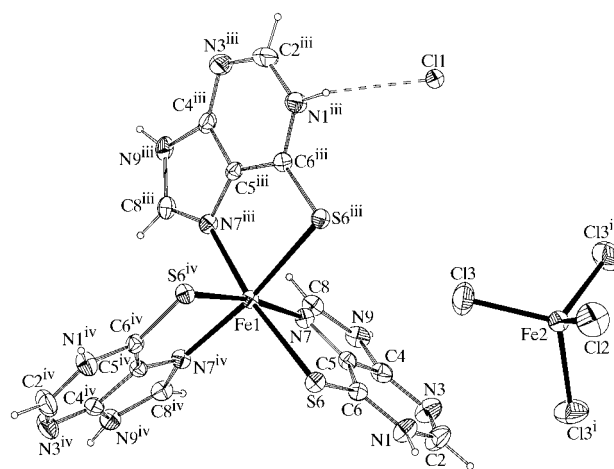
biological degradation by metal complexation. Metal complexes of drug molecules could, in addition, be used as slow-release drugs (Farrell, 1989). Preliminary investigations

by UV spectroscopy of the enzymatic degradation of 6-MP in aqueous solutions by xanthine oxidase, supported by catalase, show a significant decrease of the decomposition reaction rate of 6-MP in the form of the title iron complex, (I), compared with the corresponding rate of the free ligand.

A review of metal complexes of sulfur-containing purine derivatives has recently been given by Dubler (1996). It has been shown that, depending on the protonation status of the ligand and on the hardness or softness of the corresponding metal atom, 6-MP variously coordinates in a monodentate manner through S6, N7 or N3, chelates through N7/S6 and/or bridges two metal atoms through S6, S6/N7 or N1/N7. As part of a program elucidating the coordination properties of oxo- and thiopurines (Zhu *et al.*, 1998), we present here the synthesis and structure of the title complex, (I).

There are three building units in the structure (Fig. 1): octahedral  $[\text{Fe}(\text{C}_5\text{H}_4\text{N}_4\text{S})_3]^{2+}$  cations with three N7/S6-chelating neutral 6-MP ligands, tetrahedral  $[\text{FeCl}_4]^-$  anions and free chloride anions. The  $\text{FeN}_3\text{S}_3$  octahedron is significantly distorted, with octahedral angles ranging from 83.39 (5) to 95.44 (5)°. The neutral 6-MP ligand is protonated at N1 and N9, but not at the coordinating N7 atom.

A common feature of most coordinating purine bases is a slight non-planarity in the pseudo-aromatic ring system. Small deviations from planarity also occur in (I), where the maximum distances of an atom from the best plane through the nine purine ring atoms are  $-0.029$  (2) Å for N9 and 0.025 (2) Å for N7. The S6...N7 'bite distance' of the chelating 6-MP ligand is 3.179 (2) Å, compared with the corresponding distance of 3.342 (1) Å for the non-coordinating molecule in 6-mercaptopurine monohydrate (Sletten *et al.*, 1969). This fact is in agreement with the observation that the decrease of the bite distance is more pronounced the smaller the metal atom is. The distance varies from about 3.32 Å in  $\text{Cd}^{\text{II}}$  complexes to 3.04 Å in  $\text{Cu}^{\text{II}}$  complexes (Dubler & Gyr, 1988).

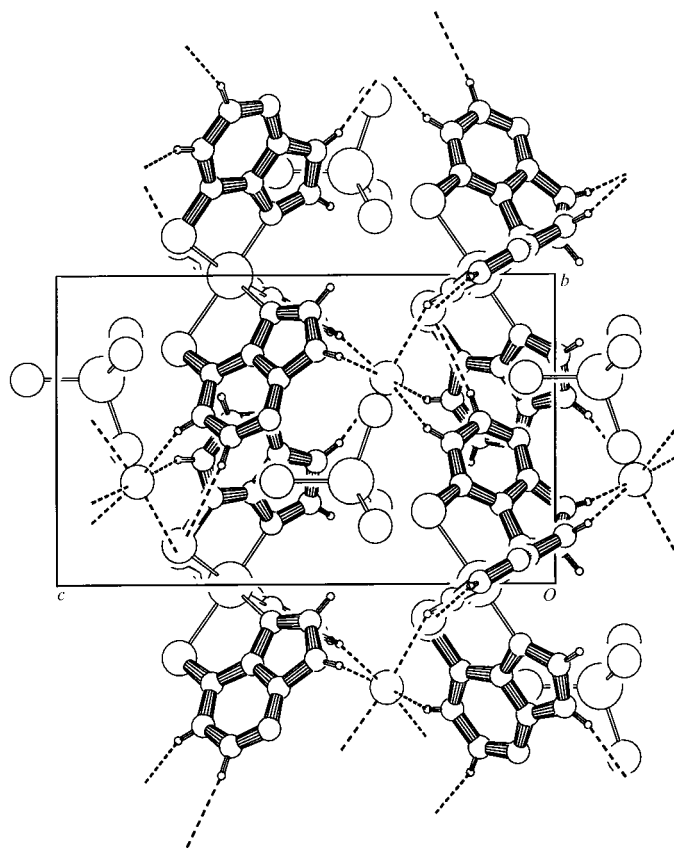


**Figure 1**

A PLATON (Spek, 1990) displacement ellipsoid plot of (I) at the 50% probability level with the atom-numbering scheme. H atoms are drawn as small spheres of arbitrary radii [symmetry codes: (i)  $1 - y, x - y, z$ ; (ii)  $1 - x + y, 1 - x, z$ ; (iii)  $-y, x - y, z$ ; (iv)  $-x + y, -x, z$ ].

The  $[\text{Fe}(\text{C}_5\text{H}_4\text{N}_4\text{S})_3]^{2+}$  cations are separated from each other by the  $[\text{FeCl}_4]^-$  anions, and there is no evidence of stacking interactions between the purine planes. The mean Fe—Cl distance in the  $[\text{Fe}^{\text{III}}\text{Cl}_4]^-$  anion is 2.189 (1) Å. This distance clearly indicates the  $\text{Fe}^{\text{III}}$  oxidation state of the central atom, since for a tetrahedral  $[\text{Fe}^{\text{II}}\text{Cl}_4]^{2-}$  anion, the expected mean bonding distance is about 2.30 Å (Pelizzi *et al.*, 1977).

The  $[\text{Fe}(\text{C}_5\text{H}_4\text{N}_4\text{S})_3]^{2+}$  cations and the free  $\text{Cl}^-$  anions are connected through a network of hydrogen bonds of the N—H...Cl type, where the  $\text{Cl}^-$  anion acts as a six-coordinate acceptor. In addition, weak interactions of the C—H...S type are observed (Table 2 and Fig. 2).



**Figure 2**  
A PLUTON (Spek, 1991) packing diagram for (I) showing the hydrogen-bonding interactions between the 6-MP ligands and the  $\text{Cl}^-$  ion.

## Experimental

A solution of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (270 mg, 1 mmol) in ethanol (20 ml) and 1 N HCl (1 ml) was overlaid on a solid pill of  $6\text{-MP} \cdot \text{H}_2\text{O}$  and stored at a temperature of 333 K in a closed vessel. After 2 d, red-brown hexagonal prismatic crystals of (I) suitable for X-ray analysis had grown on the surface of the pill. Crystals of the same composition were also synthesized by heating a solution of  $6\text{-MP} \cdot \text{H}_2\text{O}$  (681 mg, 4 mmol) and  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (1081 mg, 4 mmol) in 1 N HCl (2 ml) and ethanol (100 ml). The reaction mixture was filtered and kept at a temperature of 333 K for crystallization. Within a few hours, a red-brown microcrystalline product, (I), was separated from the solution.

## Crystal data

$[\text{Fe}(\text{C}_5\text{H}_4\text{N}_4\text{S})_3][\text{FeCl}_4]\text{Cl}$   
 $M_r = 745.50$   
 Trigonal,  $P6_3$   
 $a = 10.3499$  (6) Å  
 $b = 10.3499$  (6) Å  
 $c = 14.6652$  (11) Å  
 $\alpha = 90.00^\circ$   
 $V = 1360.48$  (15) Å<sup>3</sup>  
 $Z = 2$   
 $D_x = 1.820$  Mg m<sup>-3</sup>  
 Mo  $K\alpha$  radiation  
 Cell parameters from 7998 reflections  
 $\theta = 3.60\text{--}30.35^\circ$   
 $\mu = 1.820$  mm<sup>-1</sup>  
 $T = 173$  (1) K  
 Prism, red-brown  
 $0.28 \times 0.25 \times 0.24$  mm

## Data collection

Stoe IPDS diffractometer  
 $\varphi$  rotation scans  
 Absorption correction: numerical (Coppens *et al.*, 1965)  
 $T_{\text{min}} = 0.630$ ,  $T_{\text{max}} = 0.669$   
 16 156 measured reflections  
 1411 independent reflections (plus 1306 Friedel-related reflections)  
 2484 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.031$   
 $\theta_{\text{max}} = 30.35^\circ$   
 $h = -12 \rightarrow 14$   
 $k = -14 \rightarrow 14$   
 $l = -20 \rightarrow 20$   
 50 to 200 standard reflections every image  
 frequency: 3.5 min  
 intensity decay: none

## Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.021$   
 $wR(F^2) = 0.038$   
 $S = 1.098$   
 2717 reflections  
 114 parameters  
 H-atom parameters constrained  
 $w = 1/[\sigma^2(F_o^2) + (0.01P)^2]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\text{max}} < 0.001$   
 $\Delta\rho_{\text{max}} = 0.26$  e Å<sup>-3</sup>  
 $\Delta\rho_{\text{min}} = -0.24$  e Å<sup>-3</sup>  
 Extinction correction: SHELXL97 (Sheldrick, 1997)  
 Extinction coefficient: 0.0107 (4)  
 Absolute structure: Flack (1983)  
 Flack parameter =  $-0.05$  (2)

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

|                           |             |          |             |
|---------------------------|-------------|----------|-------------|
| Fe2—Cl2                   | 2.1878 (11) | N7—C5    | 1.371 (3)   |
| Fe2—Cl3                   | 2.1892 (7)  | C8—N9    | 1.345 (3)   |
| Fe1—N7                    | 2.1638 (19) | N1—C6    | 1.363 (3)   |
| Fe1—S6                    | 2.5908 (6)  | N1—C2    | 1.364 (3)   |
| S6—C6                     | 1.686 (2)   | C6—C5    | 1.398 (3)   |
| N3—C2                     | 1.307 (3)   | N9—C4    | 1.371 (3)   |
| N3—C4                     | 1.335 (4)   | C5—C4    | 1.380 (3)   |
| N7—C8                     | 1.318 (3)   |          |             |
| Cl2—Fe2—Cl3               | 109.11 (3)  | C6—N1—C2 | 123.7 (2)   |
| Cl3 <sup>i</sup> —Fe2—Cl3 | 109.83 (2)  | N1—C6—C5 | 112.0 (2)   |
| N7—Fe1—N7 <sup>ii</sup>   | 91.66 (7)   | N1—C6—S6 | 125.13 (17) |
| N7—Fe1—S6 <sup>ii</sup>   | 95.44 (5)   | C5—C6—S6 | 122.85 (19) |
| N7—Fe1—S6                 | 83.39 (5)   | C8—N9—C4 | 107.62 (18) |
| N7 <sup>ii</sup> —Fe1—S6  | 171.45 (6)  | N7—C5—C4 | 111.59 (19) |
| S6 <sup>ii</sup> —Fe1—S6  | 90.122 (19) | N7—C5—C6 | 128.2 (2)   |
| C6—S6—Fe1                 | 93.51 (8)   | C4—C5—C6 | 120.2 (2)   |
| C2—N3—C4                  | 112.1 (2)   | N3—C4—N9 | 129.4 (2)   |
| C8—N7—C5                  | 103.72 (19) | N3—C4—C5 | 126.5 (2)   |
| C8—N7—Fe1                 | 144.36 (17) | N9—C4—C5 | 104.1 (2)   |
| C5—N7—Fe1                 | 111.92 (13) | N3—C2—N1 | 125.5 (2)   |
| N7—C8—N9                  | 112.9 (2)   |          |             |

Symmetry codes: (i)  $1 - y, x - y, z$ ; (ii)  $-y, x - y, z$ .

**Table 2**  
Hydrogen-bonding geometry (Å, °).

| $D\text{—}H \cdots A$                     | $D\text{—}H$ | $H \cdots A$ | $D \cdots A$ | $D\text{—}H \cdots A$ |
|---|--------------|--------------|--------------|-----------------------|
| N1—H1 <sup>i</sup> ...Cl1 <sup>i</sup>    | 0.88         | 2.48         | 3.273 (2)    | 150                   |
| N9—H9 <sup>ii</sup> ...Cl1 <sup>ii</sup>  | 0.88         | 2.38         | 3.231 (2)    | 164                   |
| C2—H2 <sup>iii</sup> ...S6 <sup>iii</sup> | 0.95         | 2.78         | 3.693 (3)    | 161                   |

Symmetry codes: (i)  $x - y - 1, x - 1, \frac{1}{2} + z$ ; (ii)  $x - 1, y - 1, z$ ; (iii)  $-1 - x + y, -1 - x, z$ .

The structure had been refined previously (Gyr, 1991) with *SHELX76* (Sheldrick, 1976) on  $F_o$  based on room-temperature measurements (three different crystals were used), with relatively bad  $R$  values of about 0.08. Improvement of refinement techniques (e.g. *SHELXL97*) and the possibility of user-friendly twin refinements with *SHELXL97* (Sheldrick, 1997; Herbst-Irmer & Sheldrick, 1998) led us to remeasure one of the example crystals at 173 (1) K with an image-plate detector system (Stoe IPDS) in order to resolve this old problem structure. Repeating the refinement of the known model with the new data set showed the same result ( $R1 = 0.09$ ,  $wR2 = 0.143$ , based on  $F_o^2$  using all unique reflections). Application of the twin matrix (010, 100, 00 $\bar{1}$ ) led to a remarkable improvement of the final  $R$  values, as shown in the *Experimental* section; the twinning ratio was 0.286:0.714. The positions of the H atoms were determined from difference electron-density maps, but they were finally calculated after each cycle of refinement using a riding model.

Data collection: *IPDS* (Stoe & Cie, 1999); cell refinement: *IPDS*; data reduction: *XRED* in *IPDS*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1990) and *PLUTON* (Spek, 1991); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1395). Services for accessing these data are described at the back of the journal.

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