X-Ray Crystal Structure of Sodium Bis(N-methylhydantoinato)gold(1) Tetrahydrate; a Linear, Planar Complex of Pharmacological Interest Stabilised by Two Nitrogen Ligands

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Summary The complex formed, in alkaline aqueous solutions, between N-methylhydantoin and Au^{III} has been shown by X-ray crystallography to be a linear, planar Au^{I} complex, the first Au^{I} complex stabilised by two nitrogen ligands.

Following the successful introduction of gold(I) thioglucose for the treatment of rheumatoid arthritis ('chrysotherapy') in 1929, an intensive search was made for other stable, preferably water-soluble, gold complexes of improved activity and reduced toxicity.¹ Most of these were Au^I thiolates, including aurothiomalate ('Myocrisin') which is still in wide clinical use today, but a curious exception was the tetrasuccinimidogold(III) complex (1). The preparation of (1) was reported by Kharasch and Isbell² and, in the animal trials of Block,³ was well absorbed and very effective against micro-organism-induced arthritis.



However, Tyabji and Gibson were unable to isolate such a complex, and doubted its existence in view of the steric interactions between 1,3-dicarbonyl groups.⁴ In the light of this controversy we have examined reactions of $[Au^{III}-Cl_4]^-$ with a series of related hydantoins in aqueous solution and have demonstrated that a readily isolable, stable, white crystalline complex, which was initially thought to be a bis(hydantoinato)dihydroxygold(III) complex, is a linear, planar bis(*N*-methylhydantoinato)gold(I) complex. This is the first structure to be reported in which Au^I is coordinated to nitrogen ligands⁵ only.

Sodium bis(1-methylhydantoinato)gold tetrahydrate was prepared in 45-60% yield by dissolving 10 mmol of 1methylhydantoin (Aldrich) in water (10 ml), adjusting the pH to 11.7-12 (2 M NaOH)[†] and adding 2.5 mmol of solid $NaAuCl_4 \cdot 2H_2O$. After shaking, the bright yellow solution became pale yellow (30 min) and eventually colourless, giving a good yield of white needles after standing in the dark at room temperature (17 °C) for 4-5 days. The crystals were filtered off and washed with ice-cold water, acetone, and diethyl ether. The crystallisation can be hastened by dropwise addition of 2 M NaOH with stirring, but deposits of metallic Au appear if it is added too quickly or before the solution becomes colourless. The complex was characterised by a variety of methods.[‡] It is stable in air. but darkens after exposure to light for several hours, is very soluble in methanol, and solutions in pH 7 buffer are stable for more than three days.



FIGURE. The crystal structure of sodium bis(N-methylhydan-toinato)gold· $4H_2O$. ---, hydrogen bonds; oxygen atoms of the four water molecules are numbered; \bigcirc , Na atoms.

Crystal data: $[C_8H_{10}AuN_4O_4]Na\cdot 4H_2O$, M = 518, triclinic, $a = 6\cdot 111(1)$, $b = 13\cdot 378(2)$, $c = 10\cdot 174(2)$ Å, $\alpha = 81\cdot 98(2)$, $\beta = 103\cdot 90(2)$, $\gamma = 99\cdot 37(2)^\circ$, space group $P\bar{1}$

 \uparrow A pK_a of 9.54 was measured for 1-methylhydantoin in D₂O by ¹H n.m.r. methods, therefore it is almost all in the N⁻ form at this pH.

 $^{^{+}}$ M.p. 216—218 °C; satisfactory C, H, N, and Au analyses for [(1-methylhydantoin)₂gold]⁻ Na⁺·4H₂O (C₈H₁₈AuN₄NaO₈); ¹H n.m.r.: δ (D₂O) 4·00 (s, CH₂) and 2·95 (s, Me) (addition of *ca*. 1 equiv. of NaOD causes an almost immediate deuterium exchange of CH₂ protons which was not observed for the free ligand); molar conductance in water or methanol: 92 Ω^{-1} cm² mol⁻¹ for 10⁻³ M solutions (indicative of a 1:1 electrolyte); i.r. spectrum (CSI disc) shows the presence of H-bonded H₂O (strong, broad band at *ca*. 3415 cm⁻¹), and two strong, broad absorptions at 1680 and 1655 cm⁻¹ implying that carbonyl groups are also involved in H-bonding (medium and strong shoulders are present at 1725 and 1700 cm⁻¹, respectively) and a weak band at 430 cm⁻¹ probably due to an Au–N stretch (a laser-Raman spectrum could not be obtained owing to fluorescence problems); Mössbauer measurements gave an isomer shift of 2·19 mm s⁻¹ and quadrupole splitting of 7·95 mm s⁻¹, confirming that the complex contains Au¹ and not Au¹¹¹, and suggesting that the ligand is a strong *m*-acceptor.

confirmed by structure analysis, Z = 2. 1705 reflections significantly above background were measured on an Enraf-Nonius CAD-4 diffractometer with $Mo-K_{\alpha}$ radiation. The structure was refined to $R \ 0.043.$ §

The crystal structure has approximate A-face centering, with two half-weight gold atoms in the asymmetric unit positioned on centres of symmetry at (0,0,0) and $(0,\frac{1}{2},\frac{1}{2})$, thus making the bis(N-methylhydantoinato)gold anions centro-symmetric, necessarily making the N-Au-N angle 180°. The average Au-N distance is 1.94 Å compared with 2.07 Å in chloro(piperidine)gold.⁵ The anions participate in a complex network of hydrogen bonds and electrostatic interactions with the sodium ions and water molecules (Figure). A noteworthy feature of the structure is the (asymmetric) bridging of all pairs of carbonyl oxygen atoms by hydrogen-bonding to water molecules.

This is only the third structure to be reported of an Au^I complex crystallised form aqueous solution, the others being $K[Au(CN)_2]^6$ and $Na_3[Au(S_2O_3)_2] \cdot 2H_2O.^7$ The chemistry of Au is dominated⁸ by the high thermodynamic stability of elemental Au, and Au^I (5d¹⁰) complexes readily disproportionate unless stabilised by a ligand with strong π -acceptor properties. On either the Klopman σ_p , or the Edwards α parameter scale, Au^I is a very 'soft' metal ion.9 The existence of stable 1,3-dicarbonylimido complexes may be dependent on the distinct co-planar relationship around the Au^I ion, allowing the carbonyl π^* -orbitals to participate in back-bonding.

Substituted hydantoin complexes are more stable than those of hydantoin itself, or succinimide, and 1:3 Au^{III} complexes of the type $Na[AuX_3L]$ can be isolated for X = (2b), L = OH^-, and X = (2c), L = Cl^-. Since a 1:2 Au^I complex can also be isolated with (2b), the 1:3 complexes may be key intermediates in the reduction pathway to Au^I.

Sodium bis(N-methylhydantoinato)gold has a low toxicity in *in vitro* cell tests ¶ and is currently on animal antiinflammatory trials. It is possible that the supposed AuIII tetrasuccinimido complex tested by Block was actually the 1:2 Au^I complex. This would explain why its antiinflammatory behaviour is similar to that of Au^I thiolates. We expect the imido ligands to be labile in vivo, since their quantitative stepwise release can be observed by 1H n.m.r. spectroscopy on addition of N-acetyl-L-methionine (known to S-bond¹⁰) to aqueous solutions of the complex. Sulphides are themselves readily displaced by thiolates, and thiol exchange reactions are thought to play a prominent part in the molecular pharmacology of gold drugs.¹¹ The ease of imido ligand release makes these Au^I complexes attractive as starting materials for the preparation of other Au^I complexes, or for inserting Au^I into proteins and enzymes; work along these lines is in progress.

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§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

¶ A dose of 60 μ g ml⁻¹ reduced the survival of mouse L-cell colonies to 50 %.

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