Crystal Structure of the Antiarthritic Drug Gold Thiomalate (Myochrysine): A Double-Helical Geometry in the Solid State

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Gold(I) thiolate complexes have been used as therapeutic agents against rheumatoid arthritis for over 50 years.[1,2] The most prominent of these compounds are gold sodium thiomalate (Myochrysine, sodium aurothiomalate), gold thioglucose (Solganal, aurothioglucose), sodium aurothiopropanol sulfonate (Allochrysine), and more recently the orally administered compound auranofin (Ridaura), a thiosugar/phosphine complex of gold. Studies on aurothiomalate and aurothioglucose have been complicated by their uncertain solid state and solution structures: in fact, it has been mentioned repeatedly that these compounds have never been successfully crystallized.[1] In this paper we report the single-crystal X-ray structure determination of gold(I) thiomalate (Myochrysine).

At the outset, it was decided to apply the systematic crystallization techniques used for macromolecular samples[3] to the problem of obtaining suitable crystals of gold thiomalate. We were curious to see if those procedures, which were developed primarily for the crystallization of proteins and nucleic acids, would also work for small molecules. As anticipated, we found that Myochrysine was indeed very difficult to crystallize. Innumerable attempts using a wide range of precipitants and screens yielded essentially nothing. Eventually it was discovered that the use of cationic additives[4] proved to be decisive. After screening a large number of organic and inorganic cations, we found that gold sodium thiomalate could be successfully crystallized in the presence of cesium ions by vapor diffusion against 50% PEG 4000.[5]

Gold thiomalate crystallizes as a mixed sodium/cesium salt in the tetragonal space group $P\bar{4}b2$ (No. 117),[6a] with $a = 18.767(2)$ and $c = 4.798(2)$ Å. X-ray diffraction data were collected with Cu Kα radiation on a Siemens P4/RA diffractometer, equipped with a rotating-anode generator. The structure was solved using conventional heavy-atom techniques and refined to a present agreement factor of $R(F) = 7.1\%$.[6b] In the unit cell, the atoms are situated in positions such that the ratio of Au:S:Na:Cs is 2:2:2:1. To preserve charge balance, this requires that half of the thiomalate ligands in the crystal are monoprotonated, consistent with the fact that commercial Myochrysine is a mixture of monosodium and disodium salts.[7] We thus formulate the title compound as $Na_2CsAu_2(L)(LH)$, where L is the thiomalate ligand $[O_2C\text{-}CH_2\text{-}CH(S)\text{-}CO_2]^{3-}$.

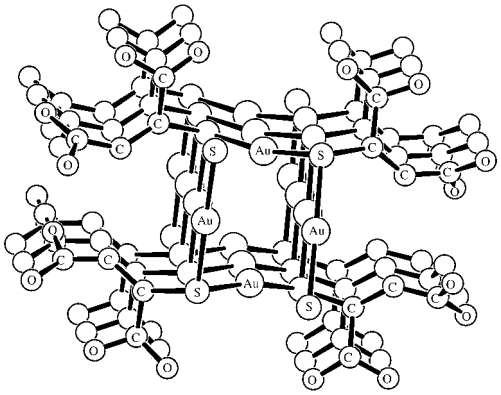

Figure 1. Top view of the main axis in gold(I) thiomalate, showing the approximate 4-fold helical symmetry of the structure.

Gold thiomalate is indeed polymeric in the solid state, as predicted by many previous investigators.[1,2,8] The main gold−sulfur backbone exists as two interpenetrating spirals, with approximate 4-fold helical symmetry. Figure 1 shows a top view, and Figure 2 a side view of the two intertwined helices; the −Au−S−Au−S− chain is linear at gold and bent at sulfur. Figure 3, which displays one turn of the helix, shows the conformations of the thiomalate ligands in more detail.

There are two independent gold atoms in the unit cell. One of them is essentially linear [S−Au_1−S = 178.9(5)°], while the other one is significantly distorted from linearity [S−Au_2−S = 169.4(4)°]. The reason for this distortion is not immediately apparent, but it may simply have to do with crystal packing effects. Both Au−S distances are essentially equivalent [Au_1−S = 2.289(8) Å, Au_2−S = 2.285(7) Å] and agree rather well with earlier EXAFS-derived measurements (2.30 Å[9] and 2.37 Å[10]). The Au−S−Au angle, 99.2(3)°, is also in reasonably good agreement with previous estimates (94°).[9]

Various models have been proposed over the years for the solid-state structure of gold thiomalate, including a cyclic tetramer,[8a] cyclic pentamer,[11] cyclic hexamer,[9,12] open-chain pentamer,[9] open-chain hexamer,[2] and open-chain octamer.[13] Perhaps the most detailed structural analysis previously carried out was the EXAFS/WAXS (wide-angle X-ray scattering) analysis of Elder and co-

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(3) Ducruix, A.; Giegé, R. *Crystallization of Nucleic Acids and Proteins*; Oxford University Press: Oxford, U.K., 1992.

(4) See page 157 of ref 3.

(5) The technique used was hanging drop vapor diffusion.[3] Typically, 1 mL of 50% PEG 4000 (poly(ethylene glycol), MW 4000) was placed in the reservoir, and the hanging drop contained 2 μL of 2 M gold sodium thiomalate (Aldrich, lot no. 11214-DG), 2 μL of 2 M CsCl, and 2 μL of 50% PEG 4000. Tiny colorless crystals in the form of thin square tiles or, more commonly, stubby needles appeared in about 2 weeks, which were allowed to grow slowly over a 2 mo period to a size adequate for X-ray data collection. The crystal used in the X-ray analysis had dimensions 0.12 × 0.12 × 0.04 mm.

(6) (a) The thiomalate ligand, as it appears in commercial sodium aurothiomalate, exists in its racemic form (for a discussion, see: Kean, W. F.; Lock, C. J. L.; Howard-Lock, H. E. *Lancet* **1991**, *338*, 1565). This explains why both (*R*)-thiomalate and (*S*)-thiomalate ligands were found in this structure determination. (b) Programs used in this structural analysis were DIFABS for the absorption correction and SHELXL for the least-squares refinement.

(7) Commercial Myochrysine is a variable mixture of the monosodium [NaAu(LH)] and disodium [Na_2Au(L)] salts, where L is the thiomalate ligand $[O_2C\text{-}CH_2\text{-}CH(S)\text{-}CO_2]^{3-}$ (*Merck Index*, 12th ed.; Merck & Co.: Rahway, NJ, 1996; p 4538. *Physicians' Desk Reference*, 52nd ed.; Medical Economics Co.: New Jersey, 1998; p 1706). In addition, recent electrospray ionization (ESI) mass spectral investigations by Lock and co-workers (ref 8a) on the commercial product uncovered ample evidence for the presence of both L^{3-} and LH^{2-} ligands, coordinated to Au_4 tetrameric clusters. In the present structure determination, it was not possible to distinguish between the L^{3-} and LH^{2-} ligands, which are equivalent crystallographically.

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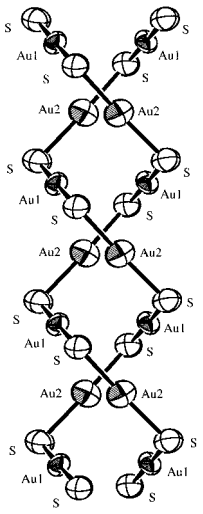

Figure 2. Side view of the gold−sulfur double helix. The closest interstrand Au···Au distance in this diagram is 3.227(5) Å. This particular diagram shows a left-handed double helix (i.e., both strands define a left-handed screw). The molecules pack in such a way as to form an equal number of left-handed and right-handed helices in the unit cell. The left-handed helix shown here is formed exclusively with the (*S*)-thiomalate ligand (see Figure 3), while the right-handed helix (not shown) contains only thiomalate ligands in the (*R*) absolute configuration.

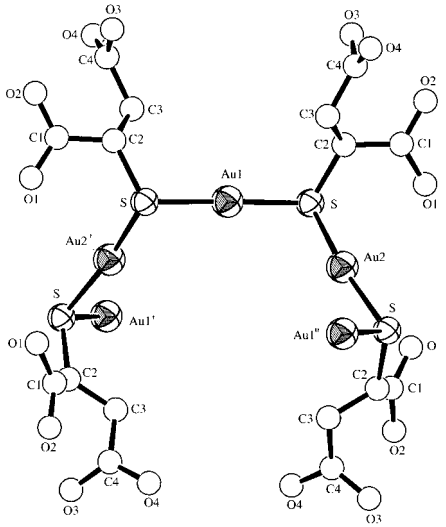

Figure 3. A single turn of one of the helices, showing the thiomalate ligands in more detail. Note that the main backbone of the thiomalate ligand, $C_1-C_2-C_3-C_4$, is in a gauche conformation, while the S and C_4 atoms are in a trans orientation with respect to the C_2-C_3 bond. Nonbonding Au···Au distances within the helix are the following: Au1···Au2 = 3.485(2) Å, Au1···Au1′ = 5.780(4) Å, Au2···Au2′ = 6.170(3) Å.

workers,[2,9] who based their models partly on an observed Au···Au vector of 3.35 Å. In the present work, we find two close Au···Au vectors: an intrastrand $Au_1\cdots Au_2$ distance of 3.485(2) Å (which corresponds to the Au_1-S-Au_2 angle of 99.2°) and an interstrand separation of $Au_1\cdots Au_1' = 3.227(5)$ Å, which represents the closest distance between gold atoms on the opposite strands shown in Figure 2. Interestingly, the average between these two numbers (3.227 + 3.485)/2 = 3.356 Å, agrees exceedingly well with the 3.35 Å peak found in the EXAFS/WAXS work, which probably represents an unresolved composite of these two vectors. The other major Au···Au peak found in the EXAFS/WAXS work, 5.8 Å,[2,9] is probably also a composite of other Au···Au vectors we find in the present X-ray analysis (5.780, 6.170 Å; see Figure 3). It is remarkable that this earlier work, which proposed an open-chain hexameric structure of a helical nature,[14] essentially predicted a portion of one of the two strands we find in the present analysis.

The structure of gold thiomalate described here is reminiscent of the structure of a polymeric silver thiolate $(AgSR)_n$ reported by Dance and co-workers many years ago, which also involves intertwined, double-stranded metal/sulfur chains.[15] Interestingly, the S−Ag−S angles in $(AgSR)_n$ also show a rather large spread of values [169.2(4)° − 177.7(5)°], and the average angle at sulfur (Ag−S−Ag = 95°) is similar to what we find here. The main difference is that in the silver case the repeating unit of the polymeric chain is octameric, $(AgSR)_8$, while in our case it is tetrameric. In the $(AgSR)_n$ paper,[15] the authors speculate on how the polymeric −Ag−S−Ag−S− strands could rearrange themselves into $(AgSR)_8$ rings when the compound is dissolved. They suggest an intriguing "crossover" mechanism by which the intertwined silver/sulfur chains exchange Ag−S bonds in a concerted fashion to give rise to octameric rings in solution.[15] Whether or not a similar mechanism happens with the double-stranded gold/sulfur chains in Myochrysine upon dissolution is unclear, as it is not known if the structure of gold thiomalate in solution is cyclic.

Thus, one remaining issue is whether the structure of gold thiomalate we find in the crystal is representative of its geometry in solution. Most investigators agree that some degree of oligomerization still persists in the dissolved state,[12,16] and there is convincing ^1H and ^{13}C NMR evidence[12] that low molecular weight polymers can be found in solution. One report, based on gel-exclusion chromatographic measurements, estimated a molecular mass of about 10 000 Da in aqueous media.[17] A WAXS/DAS (differential anomalous scattering) analysis by Elder and Eidsness[2] showed virtually the same radial distribution function for Myochrysine in solution and in a solid-state mull, strongly implying that the solid-state chain structure is maintained in solution. In fact, they also find that the related compound gold thioglucose (Solganol) has a very similar WAXS spectrum as well, again implying an analogous structure.[2] We therefore suggest that the intertwined spiral structure we find for gold thiomalate in the solid state, or a portion thereof (short double helical fragments), may in fact be the species that exists in solution.

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Supporting Information Available: Tables summarizing the results of the X-ray structural analysis (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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