

## EXAFS and WAXS Structure Determination for an Antiarthritic Drug, Sodium Gold(I) Thiomalate

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Several gold-based antiarthritic drugs are in widespread use.<sup>1</sup> However, their structures,<sup>2</sup> metabolism,<sup>3</sup> transport,<sup>4</sup> and modes of action<sup>5</sup> are not well understood. Since sodium gold(I) thiomalate (Myochrisin) and gold(I) thioglucose (Solganol) both are amorphous solids, attempts to determine their molecular structures by crystallography have been frustrated. Recently we<sup>6</sup> and Sadler,<sup>7</sup> independently, have used EXAFS (extended X-ray absorption fine structure) spectroscopy to specify the first details of the molecular structure of solid Myochrisin. We report here the use of the complementary technique, wide-angle X-ray scattering (WAXS), to elucidate the gold-sulfur framework of this molecule both in solution and in the solid state.

Myochrisin is an ideal candidate for structure studies using WAXS since it forms a noncrystalline solid and is very soluble in water (>1.0 M). We have measured the EXAFS spectra of Myochrisin both in solutions and as the solid. Using the curve-fitting approach of Hodgson and co-workers,<sup>8</sup> we are able to show that each gold atom is coordinated by two sulfur atoms at an Au-S distance of 2.30 Å in both solid and solution states.<sup>9</sup> The Fourier transform of the EXAFS from Myochrisin solid is given in Figure 1A. The single peak corresponds to two sulfur atoms bound to gold. Myochrisin contains gold/sulfur in an approximate 1/1 ratio, and for gold to be coordinated by two sulfur atoms requires bridging sulfur atoms. Although any such structure would be expected to require short gold-gold distances (from 3.2 to 4.6 Å depending on the Au-S-Au angle), no evidence of the Au-Au interaction is seen in Figure 1A. This inability of EXAFS to determine second-neighbor and further distances is well documented,<sup>10</sup> if distressing. Figure 1B shows the radial distribution function (RDF) obtained from wide-angle X-ray scattering (WAXS) data taken on a mineral oil mull of solid Myochrisin.<sup>11</sup> The solution (~1.0 M) RDF is nearly identical, indicating that the principal features arise from intramolecular aspects of the structure and not from contacts between molecules. The peak (1) at 2.30 Å can be assigned as the Au-S vector in agreement with the EXAFS curve fitting. In contrast to the EXAFS Fourier transform, the major peak (2) in the RDF corresponds to a

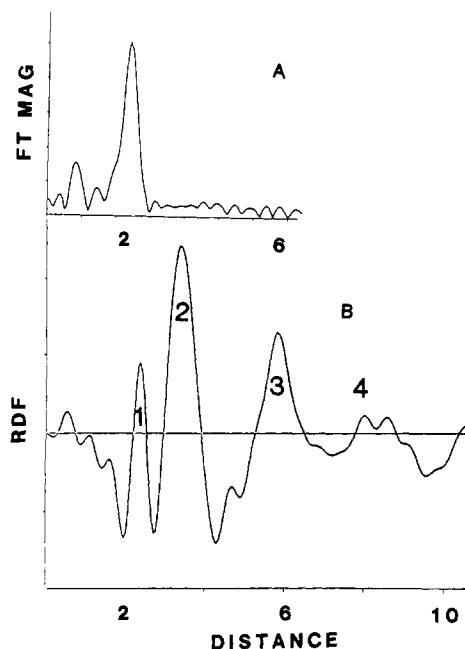


Figure 1. (A) EXAFS Fourier transform of myochrisin showing a single peak for the Au-S interaction and nothing at further distances. (B) The RDF calculated from X-ray scattering data measured at 11.915 keV. The horizontal line corresponds to an average electron density.

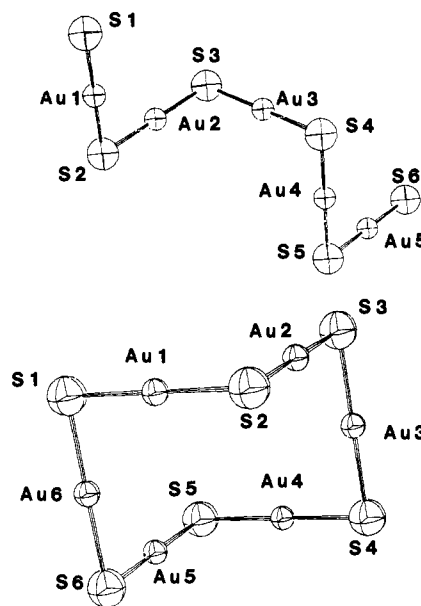


Figure 2. Possible frameworks of a hexameric cyclic structure and an open-chain pentamer for sodium gold(I) thiomalate.

second-neighbor distance of 3.35 Å. Given an Au-S-Au connectivity and an Au-S distance of 2.30 Å, this Au...Au distance depends solely on the Au-S-Au angle. For a distance of 3.35 Å that angle is 94° in close agreement with a previous result of 95° for [(Et<sub>3</sub>PAu)<sub>2</sub>S-thioglucose] nitrate.<sup>13</sup>

The last major peak (3) at 5.8 Å may be assigned to the next Au...Au interaction as follows: If the S-Au-S angle is assumed to be 180°, in agreement with many previous studies for two-coordinate gold(I),<sup>14</sup> then the torsional angle,  $\phi$ , which gives the orientation of Au(1)-S(2) relative to S(3)-Au(3) (as indicated in Figure 2) will determine the Au(1)...Au(3) distance. These

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(11) X-ray scattering experiments were performed in reflection geometry using the materials diffractometer on beam line IV-3 at the Stanford Synchrotron Radiation Laboratories following previously described techniques.<sup>12</sup> Calculations were performed at the University of Cincinnati using locally modified versions of the programs of the Bienenstock group. Myochrisin was purchased from Aldrich and used as received.

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Au(1)···Au(3) distances range from 5.0 Å in the cis configuration,  $\phi = 0^\circ$ , to 6.7 Å in the trans configuration,  $\phi = 180^\circ$ , with a value of 5.8 Å for  $\phi = 90^\circ$ . The peak (3) in the RDF at 5.8 Å strongly supports the choice of  $\phi = 90^\circ$ .

Two possible gold-sulfur frameworks for the Myochrisin structure are indicated in Figure 2. Of the possibilities for cyclic structures only the closed hexamer of Figure 2 can satisfy Au-S = 2.30 Å, Au(1)···Au(2) = 3.35 Å, and Au(1)···Au(3) = 5.8 Å. For instance, a closed tetramer would have Au(1)···Au(3) = 4.6 Å, whereas a pentamer would have 5.2 Å for that distance. A heptameric structure is quite irregular with a variety of Au(1)···Au(3) type distances from 4.6 to 6.4 Å. Although an octamer can be symmetric, the Au(1)···Au(3) type distance becomes 6.2 Å. The one difficulty with the closed hexamer is that the Au(1)···Au(4) distance is predicted to be 6.7 Å, where no excess density is found in the RDF. Although there is only one distance of the type Au(1)···Au(4) for two of the types assigned to peaks 2 and 3, the absence of a noticeable peak at 6.7 Å makes it unlikely that a closed structure occurs. The open structure, as in the pentamer of Figure 2, solves the Au(1)···Au(4) problem by turning out rather than in. That structure yields a distance of 8.1 Å in agreement with peak 4. The open-chain structure can be composed of any number of units and still give distances in accord with peaks

1-4 in the RDF. For an open structure one additional ligand is required to end the chain as indicated in Figure 2. Preparations of the drug frequently contain "excess" ligand<sup>15</sup> and could satisfy the formula Au<sub>n</sub>(ligand)<sub>n+1</sub>. The length of the chain is currently a matter of conjecture; however, the work of Sadler<sup>16</sup> would suggest a hexamer as most likely in solution.

The use of WAXS and EXAFS as complementary tools is very promising. EXAFS defines the first coordination sphere most precisely, while WAXS can give information over more extended distances. The paired techniques should be extremely useful for studying cluster species.

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## Additions and Corrections

**Molecular Mechanical Studies of Inclusion of Alkali Cations into Anisole Spherands** [*J. Am. Chem. Soc.* **1985**, *107*, 2212-2219]. PETER A. KOLLMAN,\* GEORGES WIPFF, and U. CHANDRA SINGH

Pages 2216 and 2217: The captions for Figures 3 and 4 were inadvertently reversed. Figure 3 corresponds to structure Li<sup>+</sup>/3b and Figure 4 to structure Li<sup>+</sup>/3a.

**Stereoselective Synthesis and Biological Activity of  $\beta$ - and  $\alpha$ -D-Arabinose 1,5-Diphosphate: Analogues of a Potent Metabolic Regulator** [*J. Am. Chem. Soc.* **1984**, *106*, 7851]. BRUCE E. MARYANOFF,\* ALLEN B. REITZ, GENE F. TUTWILER, STEPHEN J. BENKOVIC, PATRICIA A. BENKOVIC, and SIMON J. PILKIS

Page 7853: In the synthesis of known compound 5, "pyridine/HOAc" should read as "pyridine/Ac<sub>2</sub>O".

**Optimized Intermolecular Potential Functions for Amides and Peptides. Hydration of Amides** [*J. Am. Chem. Soc.* **1985**, *107*, 1489-1496]. WILLIAM L. JORGENSEN\* and CAROL J. SWENSON

Page 1495: The solute-water interaction energies in Table III for NMA and DMF are incorrect. The correct values are given below. No changes in the text are required.

atom	solute-water energy	
	NMA	DMF
N	-1.00	-0.87
C	-0.12	-0.84
O	-4.41	-4.68
H <sub>N</sub> trans	-3.80	
CH <sub>3</sub> cis	-0.34	-0.42
CH <sub>3</sub> trans		-0.38
CH <sub>3</sub> on C	-0.32	