An EXAFS Study of Gold Co-ordination in the Anti-arthritic Drugs Myocrisin and Solganol

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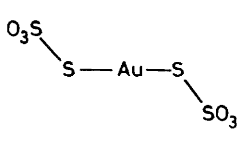
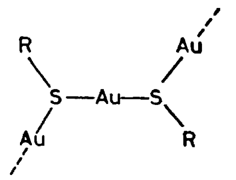
Summary Analysis of the fine structure on the L_{III} X-ray absorption edge of Au using calculated phase shifts shows that in disodium thiomalato-*S*-gold(I) ('Myocrisin') and thioglucopyranosyl-*S*-gold(I) ('Solganol') the gold(I) atom is bonded to two (bridging) S atoms 2·37 Å away; EXAFS spectra are compared with that of $Na_3Au(S_2O_3)_2$, a compound of known structure.

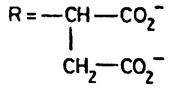
Disodium thiomalato-*S*-gold(I), 'Myocrisin', and thioglucopyranosyl-*S*-gold(I), 'Solganol', have been in clinical use for the treatment of the difficult cases of rheumatoid arthritis for nearly fifty years (chrysotherapy). However, these drugs have never been crystallised, and their structures are unknown. We have recently argued[1] that they are polymeric and contain linear AuS_2 co-ordination, and have now confirmed this by analysis of the extended X-ray absorption fine structure (EXAFS) of the L_{III} absorption edge of Au using synchrotron radiation. The technique is ideally suited to the determination of co-ordination numbers and accurate metal–ligand bond distances in amorphous metal compounds, particularly if a related compound of known structure is available.[2] In this work, EXAFS spectra of the gold drugs are compared with that of $Na_3Au(S_2O_3)_2$ which contains a linear AuS_2 unit.[3] The environment of Au^I is similar in all three compounds, but the Au–S distance in the gold drugs (2·37 Å) is 0·04 Å longer than in the thiosulphate complex.



(1)



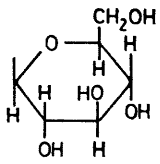
(2) R =



$$\text{R} = -\underset{\displaystyle CH_2-CO_2^-}{\underset{|}{CH}}-CO_2^-$$

(3)

R =



EXAFS spectra of the complexes were measured at ambient temperature on solid samples *ca* 1 mm thick which had been diluted about five times (w/w) with boron nitride. The EMBL synchrotron radiation EXAFS system at Hamburg was used.† Since the Au K edge is of high energy, spectra were obtained from L_{III}, which was *ca* three times as intense as L_I. The monochromator was that developed by Hart, Bordas, and co-workers[4] and stems parasitic reflections and harmonics (in this case $\lambda < 1$ Å).

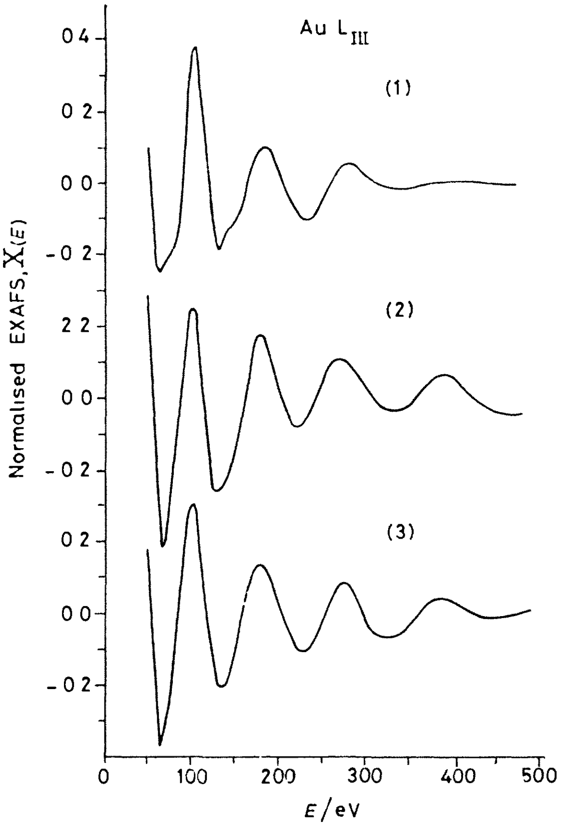


FIGURE 1 Normalised Au L_{III} EXAFS spectra of (**1**) trisodium gold(I) bisthiosulphate, (**2**) Myocrisin, and (**3**) Solganol. The backgrounds have been subtracted by standard procedures and the white lines removed. Best fits to these spectra were obtained by taking the energy zero 5.5 eV below the point of inflection of the appropriate absorption edge.

Normalised EXAFS spectra for $Na_3Au(S_2O_3)_2 \cdot 2H_2O$, (**1**), disodium thiomalato-*S*-gold(I) $2H_2O \cdot \frac{1}{3}$(glycerol), (**2**), and thioglucopyranosyl-*S*-gold(I) H_2O, (**3**),‡ are shown in Figure 1. All three have similar amplitudes and periodicity suggesting that the local environments of Au are also similar. For (**1**) this is known from the *X*-ray crystal structure[3] to be two sulphurs at 2.28 Å (S–Au–S = 177°). However, at low energies, the spectrum of (**1**) exhibits shoulders on each of the first two maxima. These are absent for (**2**) and (**3**), and appear to arise from the beating of an intermolecular Au shell with an intramolecular S shell. The small difference in EXAFS periodicity apparent in Figure 1 for (**1**) compared with that for (**2**) and (**3**) arises from a small change in Au–S bond distance.

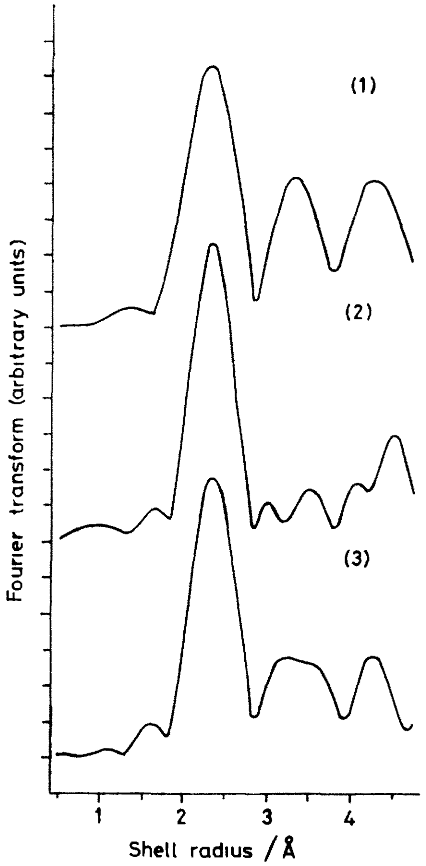


FIGURE 2 Fourier transforms of the EXAFS spectra shown in Figure 1. A Gaussian window function centred at 167 eV was used along with S back scattering parameters. Note the similar amplitudes and radial positions (2.3—2.4 Å) of the peaks due to the first co-ordination shell (S_2).

Fourier transforms (FT) of these spectra are shown in Figure 2. They incorporate calculated phase shifts for an excited Au atom surrounded by S and Au atoms. The shifts were obtained using a 'muffin-tin' calculation,[5] modified for Au atoms to include relativistic corrections.[6] This is an extension of the *ab initio* technique described previously[7] and is applied here for the first time to EXAFS spectra from L_{III} edges. Transitions of the excited photoelectron from an initial p state to both s and d states are allowed. However, calculated matrix elements indicate[8] that, certainly for Au, p to s transitions do not make significant contributions to the absorption cross-section, as others have also noted.[9] Accordingly, only $l = 2$ phase shifts were used.

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† During data collection the parent storage ring DORIS ran close to 4.5 GeV with about 20 mA of positron beam.

‡ Compound (**1**) was synthesised by the published procedure (ref. 3), (**2**) was from May and Baker Ltd., and (**3**) from the Shering Corporation. All compounds had satisfactory elemental analyses.

The first peak in the FT spectrum of (**1**) yields an Au–S bond length of 2·33 Å, in good agreement with the reported value determined by *X*-ray crystallography (2·28 Å). This demonstrates the success of the *ab initio* approach for analysis of L_{III} edge EXAFS. Discrepancies of *ca.* 0·05 Å are also commonly encountered in EXAFS analysis of K edges.[10] The second peak is at 3·33 Å, and clearly arises from the second shell sulphurs of thiosulphate and intermolecular gold; in the crystal structure there are 2 S atoms at 3·41 Å and 1 Au atom at 3·3 Å. Similarly the third FT peak at 4·26 Å corresponds to the intermolecular Au–S contact of 3·9 Å in the crystal. The remainder of the atoms around Au are light (H, C, O, and Na) and make little contribution to the fine structure.

It is clear from Figure 2 that the first co-ordination shell is the same in (**1**), (**2**), and (**3**). Curve fitting for (**2**) and (**3**) yields an Au–S bond distance of 2·37 Å and a co-ordination number of 2. Since (**2**) and (**3**) are 1 : 1 complexes, they must be polymeric with bridging thiolate sulphurs. As expected, because of the atomic composition of the ligands, the FT peaks beyond the first are quite different for (**1**), (**2**), and (**3**). The Au–Au contacts in (**2**) and (**3**) appear to be less than 3·6 Å, but further refinement is required to clarify this. In view of the possible existence of chains of varying length, chain folding, and ring formation, the co-ordination geometries of all the Au atoms in each of these compounds may not be identical. The simplicity of the EXAFS spectra, Figure 1, may be an indication of this, in agreement with the interpretation of the broadened asymmetrical doublets seen in Mossbauer spectra.[11] Also, three environments for thiomalate can be detected by ^{13}C n.m.r. measurements on concentrated aqueous solutions of (**2**).[1,12] Ultracentrifuge measurements[13] and Sephadex chromatography[14] suggest that the drug is also polymeric in solution. High molecular weight species may be more readily taken up by macrophages in which Au is thought to inhibit enzymes responsible for joint destruction. However, thiolate exchange reactions are also facile.[15]

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