DALTON

Thiomalate complexes of gold(I): preparation, characterization and crystal structures of 1:2 gold to thiomalate complexes†

Daren J. LeBlanc,* Richard W. Smith, Zhixian Wang, Helen E. Howard-Lock and (the late) Colin J. L. Lock

Department of Chemistry, McMaster University, Hamilton, ON L8S 4M1, Canada

The preparation and characterization of 1:2 gold to thiomalate complexes, as ammonium salts, has been described. The crystal structures of both racemic and optically pure samples are described and compared. In each case, the gold atom is linearly co-ordinated to two ligand sulfur atoms. Bond lengths and angles are normal.

Several gold(I) thiol complexes have been used as drugs for the treatment of rheumatoid arthritis for more than half a century.[1] Despite this successful record of chrysotherapy (gold therapy), the mechanism of action of these drugs is still unknown and some of the drugs are surprisingly poorly characterized. With the exception of Sanochrysin® (gold sodium thiosulfate) and Auranofin® [triethylphosphinegold(I) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside], which are well characterized monomers with a 1:2 gold to ligand ratio, the structures of these drugs are not conclusively known. Most of the gold(I) thiolates have a gold to ligand ratio close to 1:1 and are believed to be polymeric with the sulfur atoms of the thiol groups linking pairs of gold atoms. The size of the polymers, and whether they exist as open chain or closed ring forms, is still an unsettled question.

Some specific structures that have been proposed for the gold drug Myochrysine® [disodium gold(I) sulfanylmalate(3−), gold sodium thiomalate], GST, are illustrated in Fig. 1. It has so far proven impossible to grow X-ray quality crystals of GST, or any of the 1:1 gold to thiol ligand complexes used medicinally. However, a closed-ring hexamer structure, of the type predicted for GST by Sadler[2] [Fig. 1(*a*)] has recently been found for the gold complex of the 2,4,6-tri(isopropyl)thiophenol ligand.[5] Two closed-ring tetrameric structures of gold complexes with non-polar thiol ligands have also been reported recently[6] and, a tetramer has been found to be the principal species present in the mass spectrum of Myochrysine.[7] The extended X-ray absorption fine structure (EXAFS) and wide angle X-ray scattering (WAXS) studies of Elder and co-workers[8] are, arguably, the most definitive studies into the structure of Myochrysine so far; their results are inconsistent with the closed-ring structure types and, instead, support the open chain polymer or oligomer structure.

Further complications to the structural characterization of Myochrysine are that it is known to be a mixture with varying chemical analyses[9] and, that it is a racemate, containing an equal amount of *R*- and *S*-thiomalate. In this paper, the preparation, characterization, and determination of the structure by X-ray crystallography, of 1:2 gold to thiomalate complexes, with both racemic and optically pure thiomalate, is described. Although such 1:2 complexes are not likely to be an important component of Myochrysine as administered, they are of interest because they are the simplest possible models for Myochrysine, and, they may be an important metabolite and active component *in vivo*.

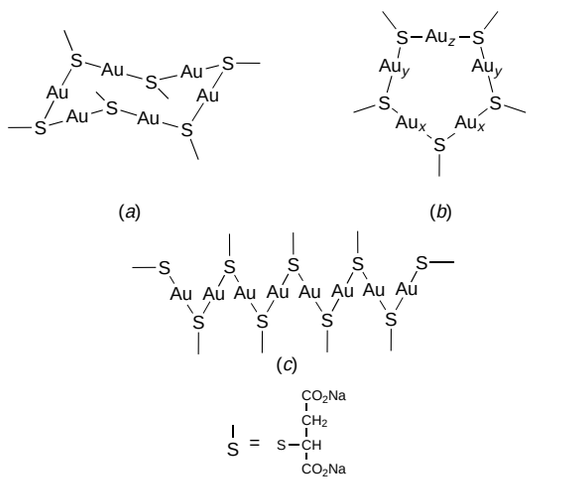

Fig. 1 Three postulated structures for gold sodium thiomalate (GST), (*a*) cyclic hexamer (Isab and Sadler,[2] 1981); (*b*) cyclic pentamer (Parish and co-workers,[3] 1984); (*c*) open chain octamer (Smith and co-workers,[4] 1988)

Early NMR experiments were interpreted as suggesting that 1:2 gold to thiomalate complexes cannot be prepared, even with large excesses of thiomalate.[10] However, the bis(thiomalate) anion was later identified, in solution, as a product of the reaction of thiomalic (sulfanylmalic) acid with gold iodide[11] and of the reaction of thiomalic acid with Myochrysine.[12] The complexes reported here, isolated as ammonium salts, are the first gold thiomalate complexes for which crystal structures have been determined. Although the bis(triphenylphosphoranylidene)ammonium bis(2-thiomalato-*S*)gold(I) complex was recently reported,[13] its structure was not determined crystallographically.

Results and Discussion

Syntheses

The preparation of thiomalic acid of high optical purity (as described in the Experimental section and SUP 57262) consisted of three distinct steps. The first step was a diazotisation reaction, that started with optically pure aspartic acid, to give bromosuccinic acid of the same absolute configuration as the aspartic acid starting material. The second step of the synthesis was an S_N2 substitution of the bromine atom with *O*-ethyl dithiocarbonate to give *O*-ethyl dithiocarbonatosuccinic acid of opposite absolute configuration. The third step was a base hydrolysis of the dithiocarbonate group to yield thiomalic acid without change of the absolute configuration. This procedure was based upon the methods of Holmberg,[14] with important modifications. This chiral synthesis was initially undertaken with the hope that an optically pure ligand would promote crys-

† Dedicated to the memory of Professor Sir Geoffrey Wilkinson on behalf of his friend and colleague Colin Lock.

Supplementary data available (No. SUP 57262, 4 pp.): graphical summary of the chiral thiomalic acid synthesis, packing diagrams of compounds **1** and **2** and negative- and positive-ion electrospray ionization mass spectra for complex **1**. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1.

tallization of a 1:1 gold to thiomalate complex. Unfortunately, however, all attempts to crystallize such 1:1 complexes were unsuccessful.

The preparation, and isolation of crystalline samples, of pentammonium bis[(±)-thiomalato-*S*]gold(I) hydrate **1**, pentammonium bis(*R*-thiomalato-*S*)gold(I) hydrate **2**, and pentammonium bis(*S*-thiomalato-*S*)gold(I) hydrate **3** were successfully accomplished and their structures were determined by X-ray crystallography. The structure of an analogous complex of D-penicillamine will be reported elsewhere.[15] For discussion purposes, the preparation of diammonium thiomalato-*S*-gold(I) hydrate polymer, **4**, is also presented in the Experimental section.‡

The preparation of bulk quantities of reasonably pure samples of the 1:2 gold to thiomalate complexes proved to be a difficult task. For the type of preparation procedures used for the 1:1 complexes [*i.e.* addition of the reaction solution to a precipitating solvent, over a relatively short period of time (5–20 min)], the products invariably gave ESI mass spectra consistent with a tetrameric main component.§ Even when particularly forcing conditions were used (*i.e.* the gold starting complex added slowly to a stirring solution of a large excess of ligand), a pure 1:2 complex could not be isolated. However, bulk crystalline quantities of the 1:2 complexes were obtained by vapour diffusion of methanol into the reaction solution, which induced crystallization. It should be noted that the use of the ammonium counter ion appears to be crucial for obtaining crystalline products, as all crystallization attempts with sodium ions or the free acids resulted in amorphous products. The 1:1 complexes were not crystalline even with ammonium counter ions, however.

Crystal structures

The crystals of the 1:2 gold to thiomalate complexes were extremely unstable and quickly deteriorated upon removal from the mother-liquor. Therefore, it was necessary to load the crystals into Lindemann capillaries and collect data at low temperature.

Three different data sets were acquired for **1**, with no satisfactory space group determined from any of them. Since it was so difficult to get a suitable crystal loaded into a capillary without serious deterioration, a crystal with a dimension larger than the X-ray beam diameter was used to collect the data for the structure reported here; attempts to cut the crystals invariably made them unsuitable for data collection. The most satisfactory, though still problematic, structure for **1** was determined with the space group $Pna2_1$. Refinement indicated that racemic twinning occurred for this complex.

Although the chiral gold thiomalate structure reported here is of the *R*-thiomalate isomer [pentammonium bis(*R*-thiomalato-*S*)gold(I) hydrate, **2**], a previous crystal of the *S* isomer complex (**3**) was subjected to data collection at room temperature; about half a data set was collected before the crystal had decomposed to the point where data collection was pointless. However, a crude solution was obtained with the partial data set and it is consistent with the structure presented here, but with opposite absolute configuration.

The essential features of the structure of the anion for **1** and **2** are the same. In particular, although a racemic mixture was used, the anions found in the solid state for **1** contained only *R*,*R* or *S*,*S* ligands. This is not to say that the *R*,*S* species did not exist in solution, since ligand exchange for gold thiol complexes is known to be rapid;[10,16] rather, the crystal form found for **1** was the most thermodynamically favoured under the conditions of crystal growth. Interestingly, attempts to prepare an achiral solid complex of D- and L-penicillamine were unsuccessful; the crystals obtained had unit cells identical to the D-penicillamine complex.[15]

Table 1 Selected bond lengths (Å) and angles (°) for pentammonium bis[(±)-thiomalato-*S*]gold(I) hydrate **1** and pentammonium bis(*R*-thiomalato-*S*)gold(I) hydrate **2**

	1	**2**
Au–S	2.277(6)	2.284(4)
	2.251(6)	2.266(4)
S–C	1.79(3)	1.834(14)
	1.82(2)	1.818(12)
S–Au–S	178.8(2)	176.03(12)
Au–S–C	107.5(7)	106.5(4)
	108.5(7)	107.7(4)
C–S···S–C	79.45(99)	98.01(53)

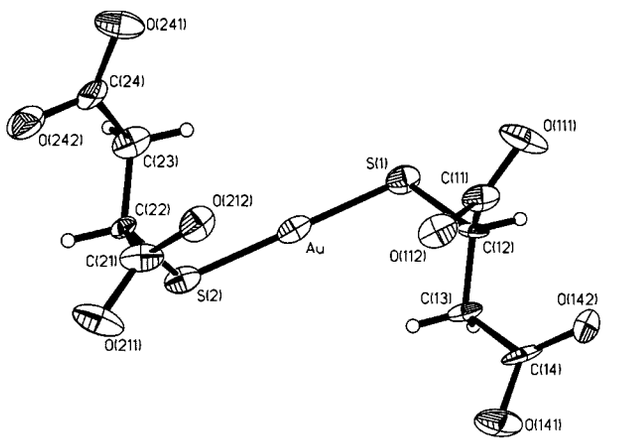

Fig. 2 The bis(*R*-thiomalato-*S*)gold(I) anion of complex **2** drawn with 50% probability displacement ellipsoids. Hydrogen atoms are drawn as spheres of arbitrary radius

The structure of the bis(*R*-thiomalato-*S*)gold(I) anion of **2** is shown in Fig. 2 and a summary of some of the more important bond lengths and angles of **1** and **2** are given in Table 1. In each case, the gold atoms were co-ordinated to two sulfur atoms from the two separate ligands and the Au–S bond lengths lay in the normal range for monomeric complexes of this type.[13,17] All other bond lengths and angles were normal.

As shown in Table 1, the C–S···S–C torsional angles in these complexes were relatively close to 90°. The analogous torsion angles in other complexes of this type range from 20.8°[17c] to 180°.[17a] If dπ–dπ bonding was present, as has been suggested for complexes of this type,[17b,18] the extent of this interaction would be maximized if one sulfur atom was involved in $d_{yz}\pi$–$d_{yz}\pi$ bonding and the other was involved in $d_{xz}\pi$–$d_{xz}\pi$ bonding, when the C–S–Au planes should be roughly at right angles to each other. The extent of this multiple bonding is probably small, however, considering the large variations from 90° observed for the torsion angles of some of the complexes. Therefore, the strength of the π–π interactions appears to be of the same magnitude as packing forces in the solid state. The fact that both the racemic and the optically pure gold thiomalate complexes packed in such a way as to have torsional angles within 10° of 90°, however, suggests that dπ–dπ bonding for gold thiomalate complexes could be considerable.

For both of the structures reported here, there was evidence of disorder for some of the ammonium ions and the waters of hydration. An examination of the packing (SUP 57262) of the compounds showed why there were disorder problems. For **1**, the anions packed in the *a* direction, one on top of the other, but steric interactions of the ligands prevented close approach

‡ The characterization of this complex, and commercial Myochrysine, by electrospray ionization (ESI) mass spectrometry, was reported in a preliminary communication.[7]

§ As reported previously,[7] a tetramer has been found to be the principal component in the ESI mass spectra of 1:1 gold to thiomalate complexes.

of the S–Au–S cores so that the shortest Au · · · Au distance was about 4.2 Å. All ammonium ions were involved in hydrogen bonding to carboxylate groups, but the hydrogen bonding to the water molecule was less, and its position was not so well defined. Compound **2** had fairly well defined hydrogen bonding patterns between ammonium ions and carboxylate groups, arranged to form a channel around the three-fold axes at $x,y\ \frac{1}{3},\frac{2}{3}$ and $\frac{2}{3},\frac{1}{3}$; the N(5) ammonium cations, which were positioned on these axes, were involved in the weakest hydrogen bonding and were the most disordered. The S–Au–S cores were arranged around the 6_2 axis at the origin and left a fairly large channel. The distances across the channel were about 7.5 Å (Au · · · Au) and 7.8 Å (S · · · S). The water molecules sat in this channel and had very weak hydrogen bonding interactions (if any) to define their positions and thus showed disorder.

Experimental

Commercially available chemicals were used without further purification, with the exception of solvent deoxygenation. Solvents were deoxygenated before use by vacuum filtration through 0.22 μm pore size millipore filters, followed by saturation with dry nitrogen. All of the gold complex preparations were performed with deoxygenated solvents, under an atmosphere of nitrogen and with precautions taken to exclude light. Gold was analyzed gravimetrically, by complete combustion of an accurately weighed sample, followed by weight determination of the gold residue. Carbon, hydrogen, nitrogen and sulfur were analyzed by Guelph Chemical Laboratories, Guelph, ON, Canada. Infrared spectra were recorded on a Bio Rad FTS-40 Fourier-transform spectrometer, solid samples were prepared as KBr pellets (1–5% w/w) for the 4000–400 cm^{-1} region or as Nujol mulls between polyethylene plates for the 500–100 cm^{-1} region. Raman spectra were recorded on a ISA/Jobin-Yvon Mole S-3000 triple spectrograph system. The 514.5 nm line of a Spectra Physics model 2016 Ar^+ ion laser was used for excitation of the samples. Spectra were recorded at ambient temperature on neat, powdered samples which were loaded into glass capillaries. Proton and ^{13}C spectra were recorded on a Bruker AC-200 Fourier-transform spectrometer operating at 200.13 MHz for ^1H and 50.33 MHz for ^{13}C. Samples were dissolved in D_2O or $(CD_3)_2CO$. Tetramethylsilane was used as an internal reference for $(CD_3)_2CO$ solutions and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as an external reference for D_2O solutions. Chemical ionization (CI), with ammonia as the reagent gas and electron impact (EI) mass spectra were recorded on a VG Analytical ZAB-E double focussing mass spectrometer. Low-resolution spectra were recorded for routine sample analysis. Pneumatically assisted electrospray ionization (ESI) mass spectrometry was performed with CH_3CN–H_2O (50:50) as the mobile phase at a flow rate of 15 μl min^{-1}, with use of a Brownlee microgradient syringe pump. Samples were dissolved in CH_3CN–H_2O (50:50) plus NH_4OH, at a concentration sufficient to give a good signal to noise ratio, and were introduced by flow injection. Full scan ESI experiments were performed with a Fisons platform quadrupole instrument. Optical activities ($[\alpha]_D$), were measured with a Perkin-Elmer 241 MV polarimeter and $\lambda = 589$ nm radiation (sodium D line). Melting points were measured on a Gallenkamp capillary tube melting point apparatus and were uncorrected. Chloro(tetrahydrothiophene)gold(I) was prepared by the method of Uson *et al.*[19]

Preparation of chiral thiomalic acid

Bromosuccinic acid. L-Aspartic acid {*S*-(+)-aspartic acid, $[\alpha]_D^{24} = +24.6°$, $c = 2$, 6 M HCl} (27.3 g, 0.206 mol) and sodium bromide (72.9 g, 0.612 mol) were dissolved in 2 M HBr (250 cm^3) with magnetic stirring. The solution was cooled to less than −5 °C with an ice–salt mixture and pulverized sodium nitrite (22 g) was added in small portions over a period of approximately 4 h, with the temperature maintained at or below −5 °C. After a further 20 min, sulfuric acid (9 M, 20 cm^3) was added and the acidic solution was extracted with diethyl ether (4 × 100 cm^3). The diethyl ether was evaporated at reduced pressure to leave a colourless solid product which was recrystallized from water and yielded, after drying in an evacuated desiccator, *S*-(−)-bromosuccinic acid (33.1 g, 0.168 mol, 81.6%), m.p. 175–178 °C (lit.[14a] 177–178 °C), $[\alpha]_D^{25} = -61.4°$, $c = 1.03$, ethanol (lit.[14a] −65.0°, $c = 6.01$, ethanol). *R*-(+)-Bromosuccinic acid (yield 83.2%, m.p. 174–178 °C, $[\alpha]_D^{25} = +64.3°$, $c = 1.14$, ethanol) was prepared in the same way but starting from D-aspartic acid {*R*-(−)-aspartic acid, $[\alpha]_D^{20} = -24°$, $c = 2.3$, 6 M HCl}. The crystal structure of *R*-(+)-bromosuccinic acid has been reported previously.[20] The compounds showed: $\delta_H(D_2O)$ 3.22 (2 H, m, CH_2) and 4.70 (1 H, m, CHBr), ($J_{AX} \approx J_{BX} \approx 7$, $J_{AB} \approx 17$ Hz); $\delta_C(D_2O)$ 41.9, 42.1 (CH_2 and CHBr) and 175.5, 176.4 (2 CO_2H); EI mass spectra: *m/z* (%) 178 $[M-H_2O]^+$ (50), 152 $[M - CO_2]^+$ (45), 133 $[M - H - CO_2 - H_2O]^+$ (5), 106 $[M - 2H - 2CO_2]^+$ (15), 99 $[M - HBr - H_2O]^+$ (10), 80 $[HBr]^+$ (45) and 73 (100); CI mass spectra: *m/z* (%) 214 $[M + NH_4]^+$ (85), 152 $[M - CO_2]^+$ (10) and 134 $[M + NH_4 - HBr]^+$ (100); negative-ion ESI mass spectra: *m/z* (%) 195 $[M - H]^-$ (100) and 151 $[M - H - CO_2]^-$ (5).

***O*-Ethyl dithiocarbonatosuccinic acid.** *Synthesis.* *S*-(−)-Bromosuccinic acid (31.7 g, 0.161 mol) was dissolved in distilled water (1500 cm^3) with stirring and neutralized with potassium hydroxide. Potassium *O*-ethyl dithiocarbonate (25.8 g, 0.161 mol) was added and the solution was left stirring. After 18 h, strontium chloride ($SrCl_2 \cdot 6H_2O$) (85.9 g, 0.322 mol) was added with continuous stirring. The strontium chloride dissolved within $\frac{1}{2}$ h, but, the precipitation of another colourless solid soon began. Stirring was continued for a further 24 h and the precipitate was collected by filtration (wet weight 175.4 g). The precipitate was suspended in distilled water (200 cm^3) and dissolved by addition of concentrated hydrochloric acid dropwise to pH ≈ 2. The acid solution was extracted with diethyl ether (3 × 100 cm^3), and the solvent removed by evaporation at reduced pressure to leave a light yellow solid, *R*-(+)-*O*-ethyl dithiocarbonatosuccinic acid (27.6 g, 0.101 mol, 79.5%), m.p. 128–130 °C, $[\alpha]_D^{25} = +75.6°$, $c = 0.508$, ethanol. *S*-(−)-*O*-Ethyl dithiocarbonatosuccinic acid (yield 79.2%, m.p. 129–131 °C, $[\alpha]_D^{25} = -72.4°$, $c = 1.14$, ethanol) was prepared in the same way but starting from *R*-(+)-bromosuccinic acid.

Purification. *R*-(+)-*O*-Ethyl dithiocarbonatosuccinic acid (23.3 g, 0.0978 mol) was suspended in distilled water (200 cm^3), with stirring, and dissolved by addition of sodium bicarbonate in small portions to pH ≈ 7. *R*-(+)-α-Methylbenzylamine (11.9 g, 0.0981 mol), dissolved in a solution of sulfuric acid (3.3 M, 30 cm^3, 0.098 mol of H_2SO_4), was added dropwise with stirring continued. Within 5 min, a very thick colourless suspension resulted. In order to keep the suspension stirring, it was diluted with distilled water (400 cm^3). The suspension was stirred for 1 h and then filtered and washed with cold distilled water (wet weight 38.8 g). The salt was suspended in distilled water (200 cm^3), with magnetic stirring, and dissolved by addition of concentrated hydrochloric acid dropwise to pH ≈ 2. The acid solution was extracted with diethyl ether (3 × 100 cm^3), and the solvent removed by evaporation at reduced pressure to leave purified *R*-(+)-*O*-ethyl dithiocarbonatosuccinic acid (14.6 g, 0.0613 mol, 62.5%), $[\alpha]_D^{25} = +79.8°$, $c = 1.14$, ethanol. *S*-(−)-*O*-Ethyl dithiocarbonatosuccinic acid was purified the same way but with use of *S*-(−)-α-methylbenzylamine (yield 63.1%), $[\alpha]_D^{25} = -79.3°$, $c = 0.442$, ethanol.

R-(+)-*O*-Ethyl dithiocarbonatosuccinic acid (14.3 g, 0.0600 mol), from the above purification step, was dissolved in warm 0.01 M hydrochloric acid (50 cm^3) and, after cooling to room temperature, was placed in a refrigerator (≈7 °C) and left for 12 h. The precipitate which formed was filtered and washed with ice-cold distilled water (50 cm^3) to leave purified *R*-(+)-*O*-ethyl

dithiocarbonatosuccinic acid (12.478 g, 0.0524 mol, 87.3%), m.p. 128–130 °C (lit.[14c] 130–131 °C), $[\alpha]_D^{25} = +81.7°$, $c = 2.19$, ethanol, +102.3°, $c = 0.44$, ethyl acetate (lit.[14c] +82.8°, $c = 5.20$, ethanol, +101.4°, $c =$ 5.06, ethyl acetate). Similarly, for *S*-(−)-*O*-ethyl dithiocarbonatosuccinic acid (yield 78.0%), $[\alpha]_D^{25} = -79.9°$, $c = 0.584$, ethanol, −102.1°, $c = 0.476$, ethyl acetate (lit.[14c] −101.6°, $c = 5.48$, ethyl acetate). The compounds showed: $\delta_H[(CD_3)_2CO]$ 1.43 (3 H, t, $J = 7$, CH_3CH_2O), 3.06 (2 H, m, CH_2), 4.75 (2 H, q, $J = 7$, CH_3CH_2O) and 4.76 [1 H, m, CH(S), $J_{AX} \approx J_{BX} \approx 7$, $J_{AB} \approx 16$ Hz]; $\delta_C[(CD_3)_2CO]$ 13.8 (CH_3CH_2O), 36.6 (HO_2CCH_2CHS), 48.1 (HO_2CCH_2CHS), 71.6 (CH_3CH_2O), 170.8, 171.9 (2 CO_2H) and 223.0 [SC(S)O]; EI mass spectra: *m/z* (%) 238 $[M]^+$ (10), 220 $[M - H_2O]^+$ (5), 117 $[M - CH_3CH_2OCS_2]^+$ (55) and 104 (100); CI mass spectra: *m/z* (%) 256 $[M + NH_4]^+$ (100); negative-ion ESI mass spectra: *m/z* (%) 237 $[M - H]^-$ (100).

Thiomalic acid. *R*-(+)-*O*-Ethyl dithiocarbonatosuccinic acid (11.0 g, 0.0462 mol) was dissolved in concentrated ammonium hydroxide (20 cm^3), under an atmosphere of nitrogen, and stirred for 1 h. The solution was transferred to a separatory funnel and the xantho–amide was extracted with diethyl ether (4 × 50 cm^3). The water layer was acidified by slow addition of concentrated hydrochloric acid to pH ≈ 2, with stirring, and the acidified solution was extracted with diethyl ether (4 × 50 cm^3). The diethyl ether solution was dried over sodium sulfate and the solvent removed at reduced pressure to leave crude *R*-(+)-thiomalic acid (4.79 g), $[\alpha]_D^{21} = +54.1°$, $c = 0.443$, ethanol. The solid was dissolved in warm ethyl acetate (35 cm^3) and allowed to cool to room temperature. The solution was placed in a refrigerator (≈7 °C) for 1 h and a freezer (≈−10 °C) for 12 h. The colourless precipitate was recovered by filtration and washed with ice-cold ethyl acetate (20 cm^3) to yield purified *R*-(+)-thiomalic acid (2.63 g, 0.0175 mol, 37.9%), m.p. 149–151 °C (lit.[14b] 151–152 °C), $[\alpha]_D^{24} = +63.2°$, $c = 0.564$, ethanol, +77.4°, $c = 0.443$, ethyl acetate (lit.[14b] +64.4°, $c = 5.02$, ethanol, +76.5°, $c = 5.10$, ethyl acetate). *S*-(−)-Thiomalic acid (yield 35.5%), m.p. 149–151 °C (lit.[14b] 152–153 °C), $[\alpha]_D^{24} = -62.5°$, $c = 0.530$, ethanol, −78.6°, $c = 0.440$, ethyl acetate (lit.[14b] −64.8°, $c = 5.14$, ethanol, −76.5°, $c = 5.02$, ethyl acetate) was prepared in the same way but starting from *S*-(−)-*O*-ethyl dithiocarbonatosuccinic acid. The compounds showed: $\tilde{\nu}_{max}/cm^{-1}$ 2560 (S–H) and 552 (C–S); $\delta_H(D_2O)$ 2.88 (2 H, m, CH_2) and 3.72 [1 H, m, C*H*(SH), $J_{AX} \approx J_{BX} \approx 7$, $J_{AB} \approx 17$ Hz]; $\delta_C(D_2O)$ 38.5 [CH(SH)], 42.0 (CH_2), 177.3 [CH(SH)CO_2H] and 179.1 (CH_2CO_2H); EI mass spectra: *m/z* (%) 132 $[M - H_2O]^+$ (95) and 104 $[M - 2H - CO_2]^+$ (100); CI mass spectra: *m/z* (%) 168 $[M + NH_4]^+$ (100); negative-ion ESI mass spectra: *m/z* (%) 149 $[M - H]^-$ (100) and 115 $[M - H - H_2S]^-$ (55).

Pentammonium bis(thiomalato-*S*)gold(I) hydrate, 1 (±)-, 2 (*R*)- and 3 (*S*)-thiomalato compounds

Chloro(tetrahydrothiophene)gold(I) (200 mg, 0.62 mmol) was added, while stirring with use of a glass rod, in small portions over the course of about 5 min, to a solution of thiomalic acid (300 mg, 2.0 mmol) in methanol (2 cm^3). A clear solution, with a slight brown tinge, resulted. Upon dropwise addition of concentrated ammonium hydroxide a colourless precipitate began to appear. A total of 2 cm^3 of NH_4OH was added and the mixture was stirred until all solid material dissolved (with the exception of a small amount of insoluble impurity). The solution was gravity filtered and subjected to vapor diffusion of methanol for 5 d. The resulting colourless, crystalline product was collected by filtration, washed with methanol (50 cm^3) and diethyl ether (50 cm^3) to leave pentammonium bis[(±)-thiomalato-*S*]gold(I) hydrate **1** (260 mg, 70%), m.p. 160–165 °C (decomp.) (Found; C, 15.9; H, 4.1; Au, 33.5; N, 12.0; S, 10.6. $C_8H_{26}AuN_5O_8S_2 \cdot H_2O$ requires C, 16.0; H, 4.7; Au, 32.9, N, 11.7; S, 10.7%); $\tilde{\nu}_{max}/cm^{-1}$ 595 (C–S) and 367 (Au–S); $\delta_H(D_2O)$ 2.64 (2 H, m, CH_2) and 3.82 [1 H, m, CH(S), $J_{AX} \approx 7$, $J_{BX} \approx 9$, $J_{AB} \approx 15$ Hz]; $\delta_C(D_2O)$ 46.3 (CHS), 49.7 (CH_2) and 181.9, 183.1 (2 CO_2^-); negative-ion ESI mass spectrum: *m/z* (%) 841 $[Au_2(tma)_3H_6]^{1-}$ (10), 495 $[Au_1(tma)_2H_4]^{1-}$ (100), 379 $[Au_1(tma)_1S_1H_3]^{1-}$ (20), 345 $[Au_1(tma)_1H_1]^{1-}$ (10), 247 $[Au_1(tma)_2H_3]^{2-}$ (10) and 149 $[(tma)H_2]^{1-}$ (60); positive-ion ESI mass spectrum: *m/z* (%) 843 $[Au_2(tma)_3H_8]^{1+}$ (30) and 497 $[Au_1(tma)_2H_6]^{1+}$ (100); tma = thiomalate trianion = $[SCH(CO_2)CH_2CO_2]^{3-}$. Pentammonium bis(*R*-thiomalato-*S*)gold(I)-hydrate **2** and pentammonium bis(*S*-thiomalato-*S*)gold(I) hydrate **3** were prepared by use of the same procedure but starting with the appropriate isomer of thiomalic acid; their physical characterization was consistent with that reported above for compound **1**.

Diammonium (±) thiomalato-*S*-gold(I) hydrate polymer, 4

Racemic thiomalic acid (220 mg, 1.5 mmol) was added, in small portions over the course of about 10 min, to a suspension of chloro(tetrahydrothiophene)gold(I) (500 mg, 1.6 mmol), in acetone (10 cm^3), with continuous stirring. The resultant clear, colourless solution was stirred for 10 min. Concentrated ammonium hydroxide was added dropwise. After several drops a significant amount of colourless precipitate began to appear. A total of 2 cm^3 of concentrated ammonium hydroxide was added and the suspension was stirred for a further 10 min. Upon removal of most of the acetone under reduced pressure, a clear solution, with a slight yellow tinge and a small amount of suspended impurities, resulted. The solution was gravity filtered, with concentrated ammonium hydroxide (1 cm^3) used for rinsing, into vigorously stirred absolute ethanol (100 cm^3). The resulting suspension was stirred for 20 min. The colourless precipitate was collected by filtration with a fine fritted Buchner funnel, washed with absolute ethanol (3 × 50 cm^3), methanol (3 × 50 cm^3) and diethyl ether (3 × 50 cm^3). The solid was dissolved in distilled water (3 cm^3), and the resultant solution was gravity filtered, with distilled water (1 cm^3) used for rinsing, into vigorously stirred absolute ethanol (100 cm^3). The colourless precipitate was collected by filtration with a fine fritted Buchner funnel, washed with absolute ethanol (3 × 50 cm^3), methanol (3 × 50 cm^3) and diethyl ether (3 × 50 cm^3) and dried in an evacuated desiccator for 12 h to give diammonium thiomalato-*S*-gold(I) hydrate polymer **4** (420 mg, 70%, assuming one water of hydration), m.p. 180–190 °C (decomp.) (Found C, 12.2; H, 3.1; Au, 49.3; N, 7.4; S, 8.1. $C_4H_{11}AuN_2O_4S \cdot H_2O$ requires C, 12.1; H, 3.3; Au, 49.5; N, 7.0; S, 8.1%); $\delta_H(D_2O)$ 2.79 (2 H, m, CH_2) and 4.10 [1 H, m, CH(S), $J_{AX} \approx 8$, $J_{BX} \approx 7$, $J_{AB} \approx 16$ Hz]; $\delta_C(D_2O)$ 49.7, 49.9 [CH_2 and CH(S)] and 181.1, 183.6 (2 CO_2^-); negative-ion ESI mass spectrum: *m/z* 1383, 691, 460 $[Au_4(tma)_4H_8 - 1,$ 2 or 3 $H]^{1-,\ 2-\text{ or }3-}$, 1267, 633, 422 $[Au_4(tma)_3S_1H_7 - 1,$ 2 or 3 $H]^{1-,\ 2-\text{ or }3-}$, 1151, 575 $[Au_4(tma)_2S_2H_6 - 1$ or 2 $H]^{1-\text{ or }2-}$, 1035, 517 $[Au_4(tma)_1S_3H_5 - 1$ or 2 $H]^{1-\text{ or }2-}$, 919 $[Au_4S_4H_4 - 1\ H]^{1-}$, 1233 $[Au_4(tma)_3H_6 - 2\ H]^{1-}$, 1117 $[Au_4(tma)_2S_1H_5 - 2\ H]^{1-}$, 1001 $[Au_4(tma)_1S_2H_4 - 2\ H]^{1-}$, 885 $[Au_4S_3H_3 - 2\ H]^{1-}$, 495 $[Au_1(tma)_2H_4]^{1-}$, 345 $[Au_1(tma)_1H_2 - 1\ H]^{1-}$, 149 $[(tma)H_2]^{1-}$ and 115 $[(tma)H_2 - H_2S]^{1-}$; positive-ion ESI mass spectrum: *m/z* 1402 $[Au_4(tma)_4H_8 + 1\ NH_4]^{1+}$, 1385 $[Au_4(tma)_4H_8 + 1\ H]^{1+}$ and 1367 $[Au_4(tma)_4H_8 + 1\ H - H_2O]^{1+}$. The analogous chiral compounds were prepared in the same way but starting with either *R*- or *S*-thiomalic acid instead of racemic thiomalic acid; their physical characterization was consistent with that reported above for polymer **4**.

Crystal structure determination of complex 1

The crystal used for data collection was surrounded by inert oil immediately after removal from the mother-liquor, sealed in a Lindemann glass capillary tube and transferred to the cooling gas stream of the diffractomer.

Crystal data and data collection parameters. $[NH_4]_5[Au(C_4H_3O_4S)_2] \cdot H_2O$, $M = 599.44$, orthorhombic, $a = 8.4196(14)$, $b = 10.112(2)$, $c = 23.593(3)$ Å, $U = 2008.7(6)$ $Å^3$ (by least

squares refinement on diffractometer angles from 43 centred reflections, $10.02° \leqslant 2\theta \leqslant 25.00°$), $T = 213(2)$ K, space group $Pna2_1$ (no. 33), graphite-monochromated Mo-Kα radiation, $\lambda = 0.710\,73$ Å, $Z = 4$, $D_c = 1.982$, $D_m = 1.96(2)$, $F(000) = 1176$, colourless plate with dimensions $0.6 \times 0.4 \times 0.1$ mm, μ(Mo-Kα) = 7.580 mm^{-1}, semiempirical absorption correction based on ψ scans, transmission factors 0.011–0.035; Siemens *P*4 diffractometer with low-temperature attachment, ω–2θ scans, data collection range $3.46 \leqslant 2\theta \leqslant 50.0°$, $-1 \leqslant h \leqslant 10$, $-1 \leqslant k \leqslant 12$, $-28 \leqslant l \leqslant 28$, three standard reflections showed no significant variation in intensity; 4233 reflections measured, 3522 unique ($R_{int} = 0.0742$) which were used in all calculations.

Structure solution and refinement. The structure was solved by direct methods and subsequent Fourier-difference techniques, and refined anisotropically, by full-matrix least squares, on F^2 (SHELXTL program package[21]). Hydrogen atoms were added at calculated positions and allowed to ride on the atoms to which they were attached. Their isotropic displacement parameters (*U*) were set to 1.2 times the U_{eq} of the atom to which they were attached. Hydrogen atoms were not added to the ammonium counter cations or the waters of hydration. A Flack[22] parameter of 0.5 in the late stages of refinement suggested that racemic twinning had occurred for this sample; when the racemic twinning was taken into account, the residuals improved significantly. The final refined value of the Flack[22] parameter [0.5(3)] indicates that the twinning domains are present in approximately equal proportions. The weighting scheme was $w^{-1} = \sigma^2(F^2) + (aP^2)$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$ and $a = 0.1506$ (as suggested by the refinement program, XL). The final $wR(F^2)$ was 0.230, with conventional $R(F)$ 0.1084 for 3521 reflections (*R* factors defined in ref. 21), 227 parameters and 1 restraint (floating origin), $S = 1.013$, maximum $\Delta/\sigma = -0.003$, maximum $\Delta\rho = 2.102$ e $Å^{-3}$ within 1.2 Å of the gold atom.

Crystal structure determination of complex 2

The crystal used for data collection was surrounded by inert oil immediately after removal from the mother-liquor, sealed in a Lindemann glass capillary tube and transferred to the cooling gas stream of the diffractometer.

Crystal data and data collection parameters. $[NH_4]_5[Au(C_4H_3O_4S)_2]\cdot H_2O$, $M = 599.44$, hexagonal, $a = b = 16.292(2)$, $c = 13.574(3)$ Å, $U = 3120.3(9)$ $Å^3$ (by least squares refinement on diffractometer angles from 25 centred reflections, $14.62° \leqslant 2\theta \leqslant 28.66°$), $T = 153(2)$ K, space group $P6_2$ (no. 171), graphite-monochromated Ag-Kα radiation, $\lambda = 0.560\,86$ Å, $Z = 6$, $D_c = 1.914$, $D_m = 2.05(5)$, $F(000) = 1764$, colourless plate with dimensions $0.35 \times 0.30 \times 0.12$ mm, μ(Ag-Kα) = 3.987 mm^{-1}, semiempirical absorption correction based on ψ scans, transmission factors 0.633–1.000; Siemens *P*3 diffractometer with low-temperature attachment, ω–2θ scans, data collection range $3.94 \leqslant 2\theta \leqslant 40.1°$, $-1 \leqslant h \leqslant 17$, $-1 \leqslant k \leqslant 17$, $-16 \leqslant l \leqslant 16$, three standard reflections showed no significant variation in intensity; 5334 reflections measured, 3957 unique ($R_{int} = 0.0375$) which were used in all calculations.

Structure solution and refinement. The structure was solved by direct methods and subsequent Fourier-difference techniques, and refined anisotropically, by full-matrix least squares, on F^2 (SHELXTL program package[21]). Hydrogen atoms were added at calculated positions and allowed to ride on the atoms to which they were attached. Their isotropic displacement parameters (*U*) were set to 1.2 times the U_{eq} of the atom to which they were attached. Hydrogen atoms were not added to the ammonium counter cations or the water of hydration. The weighting scheme was $w^{-1} = \sigma^2(F^2) + (aP^2)$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$ and $a = 0.0476$ (as suggested by the refinement program, XL). Final $wR(F^2)$ was 0.1066, with conventional $R(F)$ 0.0654 for 3957 reflections (*R* factors defined in ref. 21), 234 parameters and 1 restraint (floating origin), $S = 1.011$, maximum $\Delta/\sigma = -0.001$, maximum $\Delta\rho = 1.415$ e $Å^{-3}$ in the solvent region. The absolute configuration was confirmed by refinement of the Flack[22] parameter to 0.01(2).

CCDC reference number 186/587.

Acknowledgements

Thankful acknowledgement is hereby extended to the Natural Sciences and Engineering Research Council of Canada for financial support of this work and to Dr. James F. Britten for collecting the X-ray crystallographic data. Thanks also to Dr. Carol A. Kingsmill and the Ontario Ministry of Agriculture, Food and Rural Affairs for the use of their Fisons Quattro II mass spectrometer and to Mr. Blake LeBlanc for translating, from Swedish, ref. 14(*b*).

References

1 S. L. Best and P. J. Sadler, *Gold Bull.*, 1996, **29**, 87; S. P. Fricker, *Gold Bull.*, 1996, **29**, 57; P. J. Sadler and R. E. Sue, *Met. Based Drugs*, 1994, **1**, 107; R. V. Parish, *Interdiscip. Sci. Rev.*, 1992, **17**, 221; P. J. Sadler, *Adv. Inorg. Chem.*, 1991, **36**, 1; E. W. Smith and J. Reglinski, *Perspect. Bioinorg. Chem.*, 1991, **1**, 183; W. F. Kean, *Baillière's Clinical Rheumatology*, 1990, **4**, 219.
2 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1981, 1657.
3 A. K. H. Al-Sa'ady, K. Moss, C. A. McAuliffe and R. V. Parish, *J. Chem. Soc., Dalton Trans.*, 1984, 1609.
4 J. Reglinski, S. Hoey and W. E. Smith, *Inorg. Chim. Acta*, 1988, 261; W. E. Smith, J. Reglinski, S. Hoey, D. H. Brown and R. D. Sturrock, *Inorg. Chem.*, 1990, **29**, 5190.
5 I. Schröter and J. Strähle, *Chem. Ber.*, 1991, **124**, 2161; D. J. LeBlanc and C. J. L. Lock, *Acta Crystallogr., Sect. C*, in the press.
6 W. Wojnowski, B. Becker, J. Sabmannshausen, E. M. Peters, K. Peters and H. G. von Schnering, *Z. Anorg. Allg. Chem.*, 1994, **620**, 1417; P. J. Bonasi, D. E. Gindelberger and J. Arnold, *Inorg. Chem.*, 1993, **32**, 5126.
7 H. E. Howard-Lock, D. J. LeBlanc, C. J. L. Lock, R. W. Smith and Z. Wang, *Chem. Commun.*, 1996, 1391.
8 R. C. Elder and M. K. Eidsness, *Chem. Rev.*, 1987, **87**, 1027; R. C. Elder, K. Ludwig, J. N. Cooper and M. K. Eidsness, *J. Am. Chem. Soc.*, 1985, **107**, 5024.
9 D. A. Harvey, H. E. Howard-Lock and C. J. L. Lock, *Can. Chem. News*, 1988, **40**, 19.
10 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Chem. Commun.*, 1976, 1051.
11 M. Hagar, B.Sc. Thesis, McMaster University, 1981.
12 G. G. Graham, J. R. Bales, M. C. Grootveld and P. J. Sadler, *J. Inorg. Biochem.*, 1985, **25**, 163.
13 J. Vicente, M.-T. Chicote, P. González-Herrero and P. G. Jones, *J. Chem. Soc., Dalton Trans.*, 1994, 3183.
14 (*a*) B. Holmberg, *Ber. Dtsch. Chem. Ges.*, 1927, **60**, 2198; (*b*) B. Holmberg, *Ark. Kemi, Mineral. Geol.*, 1916, **6**, 1; (*c*) B. Holmberg, *Ber. Dtsch. Chem. Ges.*, 1914, **47**, 167.
15 D. J. LeBlanc, J. F. Britten, Z. Wang, H. E. Howard-Lock and C. J. L. Lock, *Acta Crystallogr., Sect. C*, in the press.
16 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1982, 135.
17 (*a*) R. Usón, A. Laguna, J. Jiménez, M. P. Gómez, A. Sainz and P. G. Jones, *J. Chem. Soc., Dalton Trans.*, 1990, 3457; (*b*) P. A. Bates and J. M. Waters, *Acta Crystallogr., Sect. C*, 1985, **41**, 862; (*c*) P. G. Jones, J. J. Guy and G. M. Sheldrick, *Acta Crystallogr., Sect. B*, 1976, **32** 3321; (*d*) H. Ruben, A. Zalkin, M. O. Falten and D. H. Templeton, *Inorg. Chem.*, 1974, **13**, 1836.
18 M. G. B. Drew and M. J. Riedl, *J. Chem. Soc., Dalton Trans.*, 1973, 52.
19 R. Uson, A. Laguna and M. Laguna, *Inorg. Synth.*, 1989, **26**, 85.
20 J. F. Britten, H. E. Howard-Lock, D. J. LeBlanc and C. J. L. Lock, *Acta Crystallogr., Sect. C*, 1993, **49**, 1222.
21 SHELXTL, Version 5.03, Program package for the solution and refinement of crystal structures, Siemens Analytical X-ray Instruments Inc., Madison, WI, 1994.
22 H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876.

Received 4*th February* 1997; *Paper* 7/00827I