Mössbauer and Nuclear Magnetic Resonance Spectroscopic Studies on 'Myocrisin', 'Solganol', 'Auranofin',† and Related Gold(I) Thiolates

Ali K. H. Al-Sa'ady, Karen Moss, Charles A. McAuliffe, and R. V. ('Dick') Parish *
Department of Chemistry, The University of Manchester Institute of Science and Technology, Manchester M60 1QD

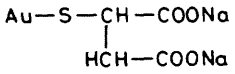
A large number of gold(I) thiolates, [Au(SR)], have been prepared in which the R group is an alkyl, aryl, carboxylic acid, amino acid, or heterocycle. Most are highly insoluble in all common solvents, but [Au(SC_6H_4R'-*p*)] (R' = Et, Pr^i, Bu^s, or Bu^t) dissolve in organic solvents. The ^1H and ^{13}C n.m.r. spectra of the soluble compounds show several sets of signals, which coalesce to single sets at high temperature, consistent with the presence of fluxional, possibly pentameric, polymeric rings. The ^{197}Au Mössbauer spectra are consistent with linear co-ordination of the gold by two sulphur ligands and, in agreement with the n.m.r. data, show broadening indicative of the presence of non-equivalent gold atoms. The therapeutic compounds appear to be structurally similar to the other gold(I) thiolates.

Gold(I) thiolates have been successfully used over many years in the treatment of rheumatoid arthritis;[1-3] some actually induce remission of the disease, rather than simply halting its progress, or alleviating symptoms. Curiously, however, many of these compounds are structurally very poorly characterised;[1-3] so much so that it is unlikely that their clinical use would now be sanctioned, were they currently undergoing trial.

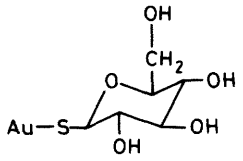
The thiolates are frequently formulated as simple monomers, [Au(SR)], *e.g.* (1)—(3) ['Krysolgan' = sodium (4-amino-2-mercaptobenzene-1-carboxylato-*S*)aurate(I)]. However, it is clear from the general chemistry of gold(I) that the metal is likely to be at least two-co-ordinate, and polymeric structures are probable. The manner and extent of polymerisation are difficult to establish, because most gold(I) thiolates are highly insoluble. Several of the gold-containing drugs are soluble in water, but owe their solubility to ionisation, which precludes accurate molecular weight measurements. Cryoscopic and gel-filtration data for aurothiomalic acid {[mercaptosuccinato(1−)-*S*]gold}, [Au{$SCH(CO_2H)CH_2CO_2H$}], and its sodium salt ('Myocrisin') suggest an average of six to eight units in the polymer.[2,4] None of the thiolates has been crystallised, but silver(I) cyclohexanethiolate has been shown to have a helical polymeric structure involving both two- and three-co-ordinate silver in 1 : 2 ratio.[5] The corresponding linear hexanethiolates exhibit degrees of association in solution from eight to 12.

The thiolate drugs are administered parenterally (by injection), and cause disastrous side effects when taken orally. In recent years, however, phosphine derivatives of the thiolates, such as 'Auranofin' (4), have been found to be effective when given orally.[6]

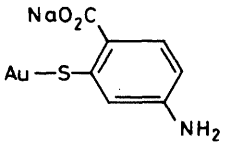
In an attempt to characterise the gold(I) thiolates more fully, we have prepared a wide range of compounds, and some phosphine derivatives, and examined them by ^{197}Au Mössbauer, ^1H and ^{13}C n.m.r. spectroscopy, comparing them with the drugs 'Myocrisin' (1), 'Solganol' (2), and 'Auranofin' (4). Some of the data have been presented in preliminary form.[7]



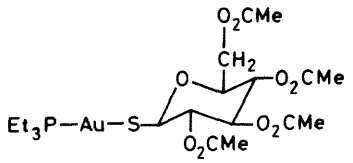
(1); 'Myocrisin'



(2); 'Solganol'



(3); 'Krysolgan'



(4); 'Auranofin'

Experimental

Far-infrared, ^1H, ^{13}C, and ^{31}P n.m.r. spectra were obtained with Beckman 720M, Perkin-Elmer R34 and R32, and Bruker WP80 spectrometers. Gold-197 Mössbauer spectra were measured with source (Au–Pt) and sample immersed in liquid helium as described previously;[8] isomer shift values are quoted relative to gold foil. Microanalytical data were obtained in this Department, and are given in Table 1. Molecular weights were determined isopiestically.

Gold(I) thiolates were obtained by two major routes representative examples of which are given.

Gold(I) *n-Butanethiolate.*—Sodium tetrachloroaurate(III) dihydrate (1.00 g, 2.51 mmol) was dissolved in ethanol (20 cm^3) and warmed to 50 °C. n-Butanethiol (0.68 g, 7.54 mmol)

† Disodium [mercaptosuccinato(3−)-*S*]aurate(I), (1-thio-β-D-glucopyranosato-*S*)gold(I), and (2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*)(triethylphosphine)gold(I) respectively.

Non-S.I. unit employed: mmHg = 133.3 Pa.

Table 1. Analytical data [a] (calculated values in parentheses)

Compound	%C	%H	%S	Other
[Au(SEt)]	9.3 (9.4)	1.9 (1.9)	12.4 (12.4)	
[Au(SPr^i)]	13.4 (13.2)	2.7 (2.6)		
[Au(SBu^n)]	16.8 (16.8)	3.5 (3.2)		
[Au{S(CH$_2$)$_2$NH$_2$}]	9.0 (8.8)	2.3 (2.2)	11.4 (11.7)	N, 4.8 (5.1)
[Au{S(CH$_2$)$_2$NH$_3$}]Cl	7.9 (7.8)	2.1 (2.3)		N, 3.9 (4.5); Cl, 10.5 (11.5)
[Au(SCH$_2$CO$_2$H)]	9.5 (8.3)	1.4 (1.1)	11.9 (11.1)	
[Au(SPh)]	23.5 (23.5)	1.7 (1.6)		
[Au(SC$_6$H$_4$Me-*p*)]	26.4 (26.3)	2.5 (2.2)	10.1 (10.1)	
[Au(SC$_6$H$_4$Et-*p*)]	28.8 (28.7)	3.0 (2.7)	9.5 (9.6)	Au, 59.5 (59.0)
[Au(SC$_6$H$_4$Pr^i-*p*)]	31.1 (31.0)	3.4 (3.2)	9.4 (9.2)	
[Au(SC$_6$H$_4$Bu^s-*p*)]	33.1 (33.1)	3.7 (3.6)	8.8 (8.8)	
[Au(SC$_6$H$_4$Bu^t-*p*)]	31.1 (31.0)	3.4 (3.2)	9.4 (9.2)	
[Au(SC$_{12}$H$_{25}$)]	35.9 (36.2)	6.5 (6.3)	8.3 (8.0)	
[Au(SC$_{18}$H$_{37}$)]	44.7 (44.8)	7.9 (7.7)	6.7 (6.6)	
[Au(SC$_6$H$_4$CO$_2$H-*o*)]	23.7 (24.0)	1.5 (1.4)	9.0 (9.1)	
[Au(C$_6$H$_4$NH$_2$-*o*)]	22.2 (22.4)	1.8 (1.8)		
[Au(SC$_6$H$_{11}$)]	23.3 (23.2)	3.5 (3.2)		
[Au{SCH$_2$CH(NH$_3$)CO$_2$}]	10.5 (10.4)	2.3 (2.0)		N, 4.8 (4.0)
[Au{SCH$_2$CH(NHCOCH$_3$)CO$_2$H}]	16.5 (16.7)	2.5 (2.2)	8.9 (8.9)	
[Au{SCH$_2$CH(NH$_2$)CO$_2$Et}]	14.3 (15.7)	3.1 (2.8)		Au, 49.2 (51.7)
[Au(glut)]·HCl [b]	21.9 (22.2)	3.4 (3.3)		N, 7.5 (7.8)
[Au{SC(Me)$_2$CH(NH$_3$)CO$_2$}]	17.1 (17.4)	3.2 (2.9)		
[Au(SC$_3$H$_4$NS)] (8)	11.1 (11.4)	1.4 (1.3)	19.2 (20.3)	N, 4.1 (4.4)
[Au(SC$_7$H$_5$N$_2$)] (9)	21.3 (24.3)	1.5 (1.5)	8.4 (9.3)	N, 6.6 (8.1)
[Au(SC$_7$H$_4$NO)] (10)	24.1 (24.2)	1.0 (1.2)		N, 3.7 (4.0)
[Au(SC$_7$H$_4$NS)] (11)	23.0 (23.1)	1.1 (1.1)		N, 3.8 (3.9)
[Au{SCH(C$_4$H$_3$S)CH$_2$COCF$_3$}]	21.8 (22.1)	0.8 (1.1)	15.4 (14.7)	F, 12.9 (13.1)
[Au(SC$_6$H$_4$Pr^i-*p*)(PMe$_2$Ph)]	40.9 (41.9)	4.3 (4.5)		P, 6.5 (6.4)
[Au(SC$_6$H$_4$Bu^t-*p*)(PMe$_2$Ph)]	42.9 (43.2)	4.9 (4.8)		P, 6.5 (6.2)
[Au(SC$_6$H$_4$Bu^s-*p*)(PMe$_2$Ph)]	43.4 (43.2)	5.1 (4.8)		P, 6.5 (6.2)
[Au(SC$_6$H$_4$Bu^t-*p*)(PEt$_3$)]	40.0 (40.0)	6.0 (5.8)		P, 6.8 (6.5)

[a] For structures of complexes (8)—(11) see Table 5. [b] glut = *N*-{1-[(carboxymethyl)carbamoyl]-2-mercaptoethyl}-L-glutamine.

was added dropwise, giving an immediate brown precipitate, which quickly became white. The solid was filtered off, washed with water, ethanol, and diethyl ether, and dried *in vacuo* over P_2O_5. Yield, 0.65 g (91%).

Gold(I) 2-*Thiazoline*-2-*thiolate*.—Sodium tetrachloroaurate(III) dihydrate (0.39 g, 1.00 mmol) was dissolved in ice-cold water (15 cm^3). Maintaining the temperature below 5 °C, bis(2-hydroxyethyl) sulphide (0.37 g, 3.00 mmol) in water (10 cm^3) was added dropwise. Decolourization of the solution occurred over 10 min. 2-Thiazoline-2-thiol (0.12 g, 1.01 mmol) in ethanol–water (2 : 1, 15 cm^3) was added dropwise. A lemon-yellow precipitate began to form after a few minutes, and the mixture was stirred for 1 h to complete the reaction, after which the solid was filtered off, washed, and dried as described above. Yield, 0.24 g (78%).

p-*Ethylthiophenol*.—*p*-Ethylaniline (15.1 g, 0.125 mol) was diazotized at 0 °C and the resulting solution added over 2 h to a warm (40—45 °C) solution of potassium *O*-ethyl dithiocarbonate (17.5 g) in water (22 cm^3). After a further 30 min, the separated red oil (*O*-*p*-ethylphenyl dithiocarbonate) was collected, and the residual aqueous layer extracted with diethyl ether (2 × 100 cm^3). The ether extracts were combined with the oil and washed with sodium hydroxide solution (10%, 100 cm^3), and then with water until the washings were neutral. The solution was dried (calcium chloride), the ether removed, and the residue dissolved in boiling ethanol (62 cm^3). Solid potassium hydroxide (21.8 g) was added at a rate to maintain steady ebullition, and the mixture refluxed until a sample was completely soluble in water (*ca.* 8 h). About 50 cm^3 of ethanol was distilled off, and the residue dissolved in the minimum amount of water (*ca.* 60 cm^3). The solution was extracted with diethyl ether (3 × 100 cm^3), and acidified to Congo Red (*ca.* 80 cm^3 of 3 mol dm^{-3} H_2SO_4). Zinc dust was added and the mixture steam distilled. The lower layer of the distillate was extracted with diethyl ether (3 × 100 cm^3). Ether was removed from the combined extracts, and the residue distilled under reduced pressure. Yield 64%.

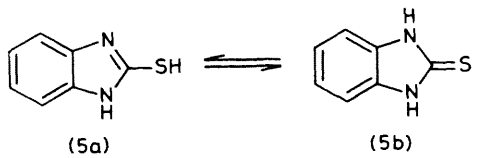
p-*s*-*Butylthiophenol*.—s-Butylbenzene (25.9 g, 0.33 mol) was added dropwise with stirring to chlorosulphonic acid (33 g, 1.0 mol). The resulting mixture was added to crushed ice (250 g) and rapidly extracted with carbon tetrachloride. The extract was washed with dilute sodium carbonate, the solvent removed, and the residue distilled under reduced pressure, to give *p*-s-butylbenzenesulphonyl chloride, boiling at 120—122 °C/10 mmHg.

Crushed ice (180 g) and concentrated sulphuric acid were maintained at −5 °C while the sulphonyl chloride was added dropwise with stirring (*ca.* 30 min). The mixture was stirred at 0 °C for a further 90 min, and then allowed to stand at room temperature for 4—5 h. Steam distillation gave *p*-s-butylthiophenol, which was dried over magnesium sulphate and distilled. Yield, 60%, b.p. 78—80 °C/0.8 mmHg.

p-Isopropylthiophenol was prepared analogously.

Results

Preparation.—Most of the gold(I) thiolates were prepared in high yield by addition of the appropriate thiol (RSH) to aqueous sodium tetrachloroaurate(III), either directly,[9] or with prior reduction to gold(I) using bis(2-hydroxyethyl) sulphide [10] [equations (i) and (ii)]. The latter method is particularly convenient when the product is insoluble in water, or when it is necessary to economise on the ligand.



(5a) (5b)

(6a) (6b)

R = $CH_2CH(NMe_3^+)CO_2^-$

$$[AuCl_4]^- + 3\ RSH \longrightarrow [Au(SR)] + RSSR + 3\ HCl + Cl^- \quad (i)$$

$$[AuCl_4]^- + 2\ (HOCH_2CH_2)_2S \xrightarrow{H_2O} [AuCl\{S(CH_2CH_2OH)_2\}] + (HOCH_2CH_2)_2SO + 2\ HCl + Cl^- \quad (iia)$$

$$[AuCl\{S(CH_2CH_2OH)_2\}] + RSH \longrightarrow [Au(SR)] + (HOCH_2CH_2)_2S + HCl \quad (iib)$$

When the first method was employed using 2-mercaptobenzimidazole (5), a blood-red solution rapidly formed, which slowly deposited a buff precipitate. Similar behaviour has been observed with compound (6),* and is probably due to preliminary co-ordination by the thione tautomers (5b) and (6b).[11]

When the second method was used with ethyl L-cysteinate, colloidal precipitates were obtained, which were very difficult to isolate. In this case, direct reaction of the ligand with $[Au(CN)_2]^-$ was more satisfactory. Attempts to repeat the reported preparation [12] of $Na[Au\{SCH_2CH(NH_3)CO_2\}Cl]\cdot 3H_2O$ gave only $[Au\{SCH_2CH(NH_3)CO_2\}]$. Difficulty was also experienced with D-penicillamine, which gave by the first method a product containing both gold(I) and gold(III); the pure gold(I) derivative was obtained by the second method.

Solution Studies.—Most of the gold(I) thiolates are extremely insoluble in all common solvents. However, the substituted aryl derivatives $[Au(SC_6H_4R'\text{-}p)]$ show increasing solubility as R′ increases in size.[13] Thus, for R′ = H, solubility is very low but, with non-polar solvents, increases along the series R′ = Me, Et, Pr^i, Bu^s, Bu^t, so that the t-butyl compound shows high solubility in all common solvents except alcohols and water. It was therefore possible to make detailed n.m.r. studies on several of these compounds.

The ^1H n.m.r. spectrum of $[Au(SC_6H_4Bu^t\text{-}p)]$ shows three strong signals in the methyl region, with approximate intensities 2 : 2 : 1 (Table 2, Figure). At ambient temperatures the three methyl groups of any one t-butyl group are expected to be equivalent, as was observed for the free thiol, $HSC_6H_4Bu^t\text{-}p$. The observation of multiple signals suggests either the presence of several different molecular species or of a single polymeric species containing non-equivalent t-butyl groups. The aromatic region was also complex, containing three pairs of doublets, also in *ca.* 2 : 2 : 1 ratio, showing similar chemical-shift differences to the methyl groups: *i.e.* the weaker signal

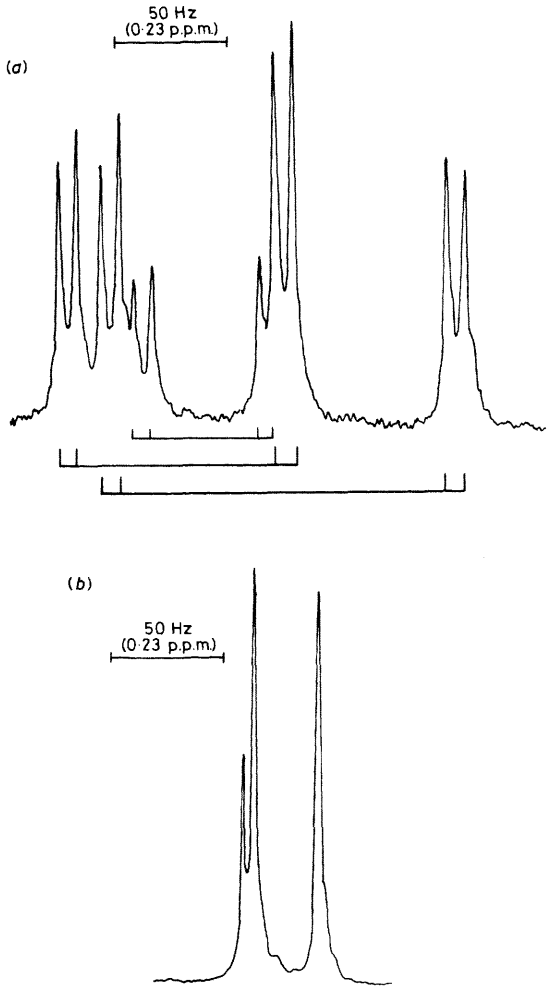


Figure. ^1H N.m.r. spectrum of $[Au(SC_6H_4Bu^t\text{-}p)]$ in (*a*) the aromatic region, and (*b*) the methyl region

and one of the stronger signals have very similar chemical shifts and the third is quite distinct (Figure). The aromatic protons form two chemically equivalent pairs, but the two protons in each pair are magnetically non-equivalent, which should give a second-order AA′BB′ pattern. However, the two very different *para* substituents (Bu^t and SAu) give quite different chemical shifts for the two pairs, resulting in an approximate AA′XX′ pattern of two doublets. When the temperature was raised to 120 °C the methyl signals coalesced to a sharp singlet. The aromatic region could not be observed, owing to the necessity to use chlorobenzene as solvent, but at 100 °C in 1,2-dichloroethane, both sets of signals were broadening and collapsing in similar fashion. The original spectrum was regained on cooling from either temperature, and the heating–cooling cycle could be repeated with similar results. Thus, some exchange process is occurring, which becomes rapid at 120 °C, and renders the organic groups equivalent on the n.m.r. time-scale. Since the ambient-temperature spectrum did not depend on the history of the sample or of the solution, it must correspond to either a single species, or an equilibrium mixture.

Similar behaviour was observed for the Bu^s, Pr^i, and Et derivatives. In each case, three major sets of resonances could be distinguished (or were overlapped) for each type of proton in both the alkyl and aromatic regions.

In the $^{13}C\text{-}\{^1H\}$ spectra, however, only one set of resonances

* ' Ergothioneine ' = [1-carboxy-2-(2-mercaptoimidazol-4-yl)ethyl]-trimethylammonium.

Table 2. ^{1}H N.m.r. spectra (δ/p.p.m.) of gold(I) thiolates

Compound	δ(C_6H_4) [a]		δ(CH_3)	δ(CH_2)	δ(CH)
[Au($SC_6H_4Bu^t$-*p*)]	6.94	7.63	1.18		
	7.29	7.73	1.30		
	7.32	7.56	1.32		
[Au($SC_6H_4Bu^s$-*p*)]	6.68	7.72	0.83 [b,c]	1.47 [b]	2.40 [b]
	7.16	7.68	1.10 [d]	1.56 [b]	2.57 [b]
	7.17	7.53	1.22 [b]		
[Au($SC_6H_4Pr^i$-*p*)]	6.89	7.70	1.18 [b]		2.62 [b]
	7.30	7.78			
	7.50	7.74			
[Au(SC_6H_4Et-*p*)]			1.20 [b]	2.50 [b]	
[Au($SC_6H_4Bu^t$-*p*)] + L [e,f]	7.09	7.40	1.22		
[Au($SC_6H_4Bu^t$-*p*)] + *ca.* ½L [e]	7.08	7.52	1.23		
[Au($SC_6H_4Bu^s$-*p*] + L [e]	7.4(m)		0.8(t)	1.53(m)	2.48(m)
			1.15(d)		
[Au($SC_6H_4Pr^i$-*p*) + L [e]	7.4(m)		1.19(d)		2.78(q)
[Au(SC_6H_4Et-*p*)] + L [e]	7.25(m)		1.10(t)	2.50(q)	

[a] Centroids of doublets. [b] Centroids of complex pattern. [c] Terminal methyl. [d] Approximate doublet. [e] L = PMe_2Ph. [f] Signals for thiolate only.

Table 3. ^{13}C-{^{1}H} N.m.r. spectra of gold(I) thiolates and free thiols

Compound	Solvent	Phenyl				Alkyl			
$HSC_6H_4Bu^t$-*p*	$CDCl_3$	148.8	129.6	128.9	126.0	34.1	31.1		
[Au($SC_6H_4Bu^t$-*p*)]	$CDCl_3$	150.1	133.6	132.5	125.9, 125.7	34.4	31.3		
	CH_2Cl_2	150.5	133.7	132.5	126.0	34.3	31.2		
$HSC_6H_4Bu^s$-*p*	$CDCl_3$	145.0	129.7	127.5	126.0	40.9	30.8	21.3	11.8
[Au($SC_6H_4Bu^s$-*p*)]	$CDCl_3$	146.7	133.8, 132.8	131.5, 131.3	127.7, 127.3	41.2	31.2	21.7	12.2
	CH_2Cl_2	147.1	133.9	132.7	127.9, 127.6	41.4	31.2	21.8	12.3
	CH_2Cl_2 *	146.4	131.8	130.0	127.1	40.8	30.7	21.7	12.0
[Au($SC_6H_4Pr^i$-*p*)]	$CDCl_3$	147.8	133.8, 132.7	131.3, 130.7	127.0, 126.7	33.6	23.9		

* At 200 K.

were observed for the alkyl groups (Table 3). The aromatic region showed four major absorptions, some of which appeared to be doubled, with separations of 0.1—1.0 p.p.m. Thus, the alkyl-group resonances do not show the non-equivalence demonstrated by the ^{1}H spectra, which is possibly attributable to the lower frequency employed (20.1 MHz *vs.* 220 MHz for ^{1}H). That is, with the lower frequency of observation, the system is showing high-temperature limit behaviour even at room temperature. The Bu^s derivative was examined at low temperature (200 K), whereupon the spectrum broadened slightly, but showed no further splitting. The phenyl resonances apparently show slight inequivalences at ambient temperature, which may represent non-equivalence for the two sides of the rings, or the beginnings of resolution into the different types of groups indicated by the ^{1}H spectra. This system is under further investigation.

The ^{1}H spectra showed little dependence on concentration suggesting the presence of a single polymeric species rather than an equilibrium mixture of different species. Chromatographic analysis [t.l.c. and high-performance liquid chromatography (h.p.l.c.)] showed the presence of only a single component, although slight ' tailing ' was observed, consistent with a polymeric species. The molar absorption coefficient for u.v. absorption was also independent of concentration. Molecular-weight measurements, although somewhat unreproducible, suggested a degree of association of four to five (Table 4).

On addition of one molar equivalent of dimethylphenylphosphine to a solution of [Au($SC_6H_4Bu^t$-*p*)], the n.m.r. spectra (^{1}H and ^{13}C) were those expected for the simple mononuclear adduct [Au($SC_6H_4Bu^t$-*p*)(PMe_2Ph)], and the spectra were unaffected by cooling the solution. With *ca.* 0.5 molar equivalent of the phosphine, only a single set of signals was seen for the thiolate groups, slightly shifted from the positions for the equimolar mixture, suggesting rapid phosphine exchange between the adduct and the thiolate. On cooling to 190 K, this spectrum resembled that of the superposition of the individual spectra of the thiolate and of the phosphine derivative at the same temperature. Similar behaviour was found for the other aromatic thiolates.

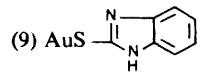
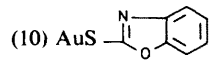
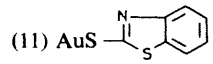
Table 4. Molecular weights

Compound	Formula weight	Experimental *M*
[Au($SC_6H_4Bu^t$-*p*)]	362	1 490, 1 650, 2 000 *
[Au($SC_6H_4Bu^s$-*p*)]	362	1 430, 1 570
[Au($SC_6H_4Pr^i$-*p*)]	348	1 640, 1 752
[Au($SC_6H_4Bu^t$-*p*)(PMe_2Ph)]	500	452
[Au($SC_6H_4Bu^s$-*p*)(PMe_2Ph)]	500	571
[Au($SC_6H_4Pr^i$-*p*)(PMe_2Ph)]	486	524
[Au($SC_6H_4Bu^t$-*p*)(PEt_3)]	581	513

* By gel permeation chromatography (g.p.c.) (*vs.* silicones).

Solid-state Studies.—Infrared spectra in the ' fingerprint ' region showed absorptions characteristic of the thiol groups, and served only to demonstrate the absence of S–H groups and the maintaining, by the amino-acid derivatives, of the zwitterionic form. In the far-i.r. all the gold(I) thiolates showed a

Table 5. Gold–sulphur stretching frequencies

Compound	$\tilde{\nu}$(Au–S)/cm^{-1}
[Au(SEt)]	324
[Au(SPr^{i})]	320
[Au(SBu^{n})]	332
[Au(SBu^{t})]	346
[Au($SC_{12}H_{25}$)]	330
[Au(SCH_2CO_2H)]	320
[Au{$S(CH_2)_2NH_3$}]Cl	325
[Au{$SCH_2CH(NH_3)CO_2$}]	322
[Au{$SCH_2CH(NHCOCH_3)CO_2H$}]	330
[Au(glut)]·HCl *	334
Ca[Au{$SCH(CO_2)CH_2CO_2$}]	325
Ba[Au{$SCH(CO_2)CH_2CO_2$}]	326
[Au(SC_6H_5)]	310
[Au(SC_6H_4Me-*p*)]	346
[Au(SC_6H_{11})]	302
(8) AuS 	330
(9) AuS 	318
(10) AuS 	340
(11) AuS 	340

* See footnote *b* of Table 1.

weak, broad resonance at 310—340 cm^{-1} (Table 5). This frequency is similar to that (342 cm^{-1}) reported [14] as ν(Au–S) for $[NBu_4][Au(SMe)_2]$. {The same report suggests 244 cm^{-1} as ν(Au–S) for $[Au(SBu^{t})_2]^-$, which seems very low; however, bands were also found in the region 300—320 cm^{-1}, and it is likely that this assignment is incorrect.} The low intensity of the Au–S stretching bands in [Au(SR)] is probably a result of of the polymeric structures, which give rise to small dipole moments for the Au–S–Au linkages.

No band corresponding to ν(Au–Cl) was observed in the far-i.r. spectrum of the sample prepared by Brown's [12] procedure for $Na[Au\{SCH_2CH(NH_3)CO_2\}Cl]\cdot 3H_2O$. The spectrum of this material was identical to that of [Au{$SCH_2CH(NH_3)CO_2$}].

The ^{197}Au Mössbauer spectra of the gold(I) thiolates give narrow ranges of parameters, with isomer shifts (i.s.) of 2.3—3.2 mm s^{-1} (relative to metallic gold), and quadrupole splittings (q.s.) of 6.0—7.0 mm s^{-1} (Table 6). These values lie well within the range characteristic of two-co-ordination,[15] and are similar to those for compounds known to involve linear co-ordination of gold(I) by two sulphur-donor ligands (Table 6). [The i.s. value observed here for $Na_3[Au(S_2O_3)_2]\cdot 3H_2O$ is very different from the literature value,[16] but is more in keeping with the known S–Au–S co-ordination.] The parameters vary systematically with the nature of the group attached to the sulphur atom, becoming more positive as the group becomes less electronegative (Table 7), suggesting that all the compounds have related structures.

No three-co-ordinate gold(I) compounds involving sulphur ligands have been reported, but extrapolation of the data for phosphine complexes [8,17–20] indicates that the i.s. would be expected to decrease by *ca.* 1 mm s^{-1}, and that the q.s. would be approximately unaltered. Even allowing for the slight broadening of the spectra (discussed below), the presence of doublets with an i.s. of 1.5—2.0 mm s^{-1} can definitely be discounted.

The spectra of all the gold(I) thiolates are slightly asymmetric: the higher-velocity line is somewhat broadened in every case, but the areas of the two lines were always very similar. Several experiments were carried out to eliminate sample thickness, instrumental, and other effects as the cause of broadening: (*a*) the data reported in Table 6 for 'Myocrisin' refer to a sample of thickness 200 mg (Au) cm^{-2}; a thinner sample (50 mg cm^{-2}) gave similar i.s. and q.s. values (2.99 and 6.55 mm s^{-1}) and narrower lines, as expected, but showed similar asymmetry (linewidths 1.89 and 2.27 mm s^{-1}). (*b*) Asymmetric spectra can be observed when a sample has a non-random alignment of crystallites. In the case of ^{197}Au, the extreme intensity ratios for samples oriented with the principal axis of the electric-field gradient parallel or perpendicular to the γ-ray direction are smaller than for many other isotopes, owing to the mixed multipolarity of the nuclear transition (M1/E2), and are 0.83 and 1.14.[21] The observed ratios lie within these limits. However, when a sample of 'Myocrisin' was ground with alumina to remove any preferential alignment, the asymmetry in linewidth was unaffected, and the areas remained equivalent (to 7%). (*c*) In view of the linear co-ordination postulated, asymmetry of the recoil-free fraction (Goldanskii–Karyagin effect) is a possible cause of asymmetry. This effect, however, usually results in unequal areas for the two peaks of a doublet, and was not seen for any of the non-polymeric compounds. (*d*) Finally, non-linearity of the velocity scale was considered. This seemed unlikely, since the iron-foil calibration spectra, which cover the velocity range concerned, showed no significant asymmetry. Three compounds were chosen which have absorption peaks in similar positions to the broadened peak of the thiolates (6.6—6.8 mm s^{-1}): $Na_3[Au(S_2O_3)_2]\cdot 3H_2O$, [{Au($S_2CNEt_2$)}$_2$], and [AuCl($AsPh_3$)]. As shown in Table 6, these compounds all gave much more symmetrical spectra than the thiolates and, in particular, the high-velocity peaks showed no significant broadening. The asymmetry observed for the thiolates thus seems to be related to their polymeric structures, and indicates the superposition of two or more doublets with similar but non-equivalent parameters.

The broadening of only one line of the doublet results from the systematic variation of i.s. and q.s. with ligand, which has a slope of approximately 1 : 2.[15] For a given increase in q.s., therefore, the upper- and lower-velocity lines move by *ca.* $+\frac{1}{2}$q.s. and $-\frac{1}{2}$q.s. respectively, while the spectrum as a whole moves to higher velocity by *ca.* $\frac{1}{2}$q.s. The low-velocity lines of the superimposed doublets thus have closely similar positions, while the higher-velocity lines are more separated.

The gold(I) derivatives of 2-mercapto-2-(2-thienyl)ethyl trifluoromethyl ketone, $HSCH(C_4H_3S)CH_2COCF_3$, give a similar spectrum to those of the other thiolates. This suggests that only the thiolate sulphur atom is involved in co-ordination.

The Mössbauer spectra of the phosphine derivatives [Au(SR)(PR′$_3$)] show much higher values of i.s. and q.s. (Table 6), consistent with the expected linear P–Au–S co-ordination. This structure has been confirmed by *X*-ray crystal structure determination of 'Auranofin'.[22]

Discussion

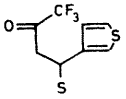
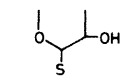
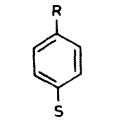
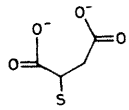
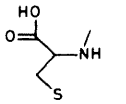
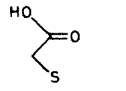
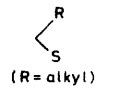
The gold(I) thiolates appear, from the similarity of their Mössbauer spectra, all to have closely related, polymeric structures. Most are very insoluble in the common solvents, but the n.m.r. spectra of the *p*-substituted benzene thiolates show the presence of three major types of thiol group. Similar observations have been made from the n.m.r. spectra of 'Myocrisin' in aqueous solution at high ionic strength.[23,24]

Table 6. ^{197}Au Mössbauer spectroscopic data (4.2 K)

Compound	I.s.[a] /mm s^{-1}	Q.s. [a]/mm s^{-1}	Line-widths [b]/mm s^{-1}	
[Au(SEt)]	2.99	6.48	1.99	2.16
[Au(SPr^{i})]	3.09	6.81	2.00	2.17
[Au(SBu^{n})]	3.08	6.69	1.95	2.21
[Au(SBu^{t})] [c]	2.9	6.7	2.2	2.2
[Au(SC_6H_{11})]	2.85	6.50	1.81	2.21
[Au($SC_{12}H_{25}$)]	3.15	6.79	1.90	2.11
[Au($SC_{18}H_{37}$)]	3.05	6.64	1.97	2.16
[Au(SC_6H_5)]	2.71	6.24	1.92	2.01
[Au(SC_6H_4Me-*p*)]	2.70	6.24	1.89	2.15
[Au(SC_6H_4Et-*p*)]	2.64	6.16	1.72	2.18
[Au(SC_6H_4Pr^{i}-*p*)]	2.72	6.24	1.69	2.41
[Au(SC_6H_4Bu^{s}-*p*)]	2.59	6.21	1.85	2.33
[Au(SC_6H_4Bu^{t}-*p*)]	2.65	6.21	2.07	2.44
[Au($SC_6H_4NH_2$-*o*)] [d]	2.8	6.5	1.6	2.2
[Au($SC_6H_4CO_2H$-*p*)]	2.69	6.50	2.03	2.60
[Au(SCH_2CO_2H)]	2.98	6.71	2.02	2.23
[Au{$S(CH_2)_2NH_3$}]Cl	2.86	6.48	1.88	2.04
[Au{$SCH_2CH(NH_3)CO_2$}]Cl	2.87	6.47	2.12	2.36
[Au{$SCH_2CH(NHCOCH_3)CO_2H$}]	2.97	6.51	1.90	2.18
[Au{$SCH_2CH(NH_2)CO_2Et$}]	3.18	7.00	1.80	3.17
[Au{$SCH(CO_2Na)CH_2CO_2Na$}]·H_2O·½$C_3H_8O_3$ ('Myocrisin')	2.91	6.53	2.12	2.56
	2.8 [e]	6.5 [e]		
[Au{$SCH(CO_2Na)CH_2CO_2Na$}]·$2H_2O$	2.82	6.47	2.27	2.78
	2.60 [f]	6.48 [f]	2.03 [f]	2.58 [f]
[Au{SCH(O)CH(CH_2OH)(CHOH)$_2$CHOH}] ('Solganol')	2.57	6.19	2.08	2.53
	2.5 [e]	6.1 [e]		
Ca[Au{$SCH(CO_2)CH_2CO_2$}]	2.51	6.52	2.15	2.88
Ba[Au{$SCH(CO_2)CH_2CO_2$}]	2.75	6.43	2.03	2.61
[Au(glut)]·HCl [g]	2.86	6.43	1.91	2.12
[Au(SC_3H_4NS)]	2.47	6.50	1.85	2.53
[Au($SC_7H_5N_2$)] [c,h]	2.4	6.5	4.3	3.0
[Au(SC_7H_4NO)]	2.29	6.44	2.11	2.23
[Au(SC_7H_4NS)]	2.51	6.21	1.90	2.30
[Au{$SCH(C_4H_3S)CH_2COCF_3$}]	2.32	6.01	1.92	2.21
$Na_3[Au(S_2O_3)_2]\cdot 3H_2O$	3.13	7.01	1.97	1.90
	1.93 [i]	7.08 [i]		
Na[Au{$SCMe_2CH(NH_3)CO_2$}]Cl·$2H_2O$ [j]	2.63	6.63	2.17	1.98
[{Au(S_2CNEt_2)}$_2$]	2.89 [k]	6.04 [k]	2.00 [k]	2.09 [k]
	2.89 [l]	6.02 [l]		
[{Au($S_2CNPr^{n}_2$)}$_2$]	3.00 [l]	6.39 [l]		
[{Au($S_2CNBu^{n}_2$)}$_2$]	2.84 [l]	5.94 [l]		
[{Au($S_2COC_8H_{17}$)}$_2$]	2.64 [l]	6.16 [l]		
$[PPh_4]_2[Au(CS_3)]$	3.13 [l]	6.43 [l]		
$[PPh_4]_2[Au_2(WS_4)_2]$	2.08 [l]	5.58 [l]		
$[AsPh_4]_2[Au_2(WS_4)_2]$	2.32 [l]	5.71 [l]		
[Au{$S_2P(OR)_2$}]	2.18 [l]	6.09 [l]		
$[Au(SPPh_3)_2]PF_6$	2.46 [m]	6.82 [m]		
[Au{S=CNH(CH_2)$_2$NH}$_2$]PF_6	2.77 [m]	7.49 [m]		
$[Au(SMe_2)_2]PF_6$	3.43 [m]	7.56 [m]		
[Au(PEt_3)(atg)] [n] ('Auranofin')	4.80	8.77	1.95	2.05
	4.7 [e]	8.8 [e]		
[AuCl($AsPh_3$)]	3.12	7.08	1.92	1.94
[Au(SC_6H_4Bu^{t}-*p*)(PMe_2Ph)]	4.43	8.09	2.00	1.96
[Au(SC_6H_4Bu^{s}-*p*)(PMe_2Ph)]	4.57	8.18	2.01	2.11
[Au(SC_6H_4Pr^{i}-*p*)(PMe_2Ph)]	4.55	8.13	1.90	2.21
[Au(SBu^{n})(PPh_3)]	4.82	8.87	1.95	2.05

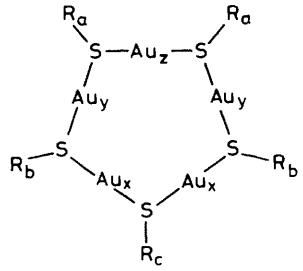
[a] ±0.03 mm s^{-1}. [b] ±0.06 mm s^{-1}. [c] ±0.1 (i.s., q.s.) or 0.2 (linewidth) mm s^{-1}. [d] Contains metallic gold. [e] D. T. Hill, B. M. Sutton, P. J. Sadler, G. H. M. Calis, and J. M. Trooster, 'Abstracts of Papers,' 179th Nat. Meeting Am. Chem. Soc., Houston, 1980; Abstr. MEDI 16. [f] On Al_2O_3. [g] See footnote *b* of Table 1. [h] Contains a gold(III) component, i.s. = 4.07 mm s^{-1}, q.s. = 6.04 mm s^{-1}. [i] Ref. 16. [j] Contains a gold(III) component, i.s. = 3.59 mm s^{-1}, q.s. = 6.61 mm s^{-1}. [k] R. V. Parish and J. D. Rush, unpublished work. [l] M. P. A. Viegers, Ph.D. Thesis, University of Nijmegen, The Netherlands, 1976. [m] P. G. Jones, A. G. Maddock, M. J. Mays, M. M. Muir, and A. F. Williams, *J. Chem. Soc., Dalton Trans.*, 1977, 1434. [n] atg = 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosate-*S*.

Table 7. Variation of Mössbauer parameters with nature of the thiolate ligand

Thiolate type	Average i.s./mm s^{-1}	Average q.s./mm s^{-1}
	2.3	6.0
 (Solganol)	2.6	6.2
	2.7	6.3
	2.8	6.4
	2.9	6.5
	3.0	6.7
 (R = alkyl)	3.1	6.7

The implied non-equivalence of gold atoms occurs also in the solids, as is evidenced by the asymmetry of the Mössbauer spectra; the resolution is not sufficient to define the number of sites. For ' Myocrisin ' and its corresponding acid form, $[\{Au[SCH(CO_2H)CH_2CO_2H]\}_n]$, the Mössbauer spectra of the solid and of frozen aqueous solutions are identical, showing that the structures are similar in the two phases.[25] The parameters of the spectra are consistent with two-co-ordination, and do not indicate any significant fraction of gold atoms with higher co-ordination; the structures are therefore not analogous to that of $[\{Ag(SC_6H_{11})\}_n]$.[5,*] For compounds of stoicheiometry $[\{Au(SR)\}_n]$, two-co-ordination of all the gold atoms can only be achieved by cyclisation, unless the R group contains ligand sites. For the simple alkyl and aryl compounds, no such sites exist. For ' Myocrisin ', ' Solganol ', ' Krysolgan ', and the amino-acid derivatives, carboxylic acid and/or amino-groups are potentially available. However, *O*- and *N*-donor ligands are not normally strongly bound to gold(I), which is a ' soft ' Lewis acid, and would readily be displaced in favour of the ' softer ' bridging sulphur atoms of

* *Note added in proof.* The data of ref. 5 have been reinterpreted in terms of a puckered dodecameric ring structure involving two-co-ordinate silver(I),$[\{Ag(SC_6H_{11})\}_{12}]$, which may be stabilised by some cross-linking giving three-co-ordination (I. G. Dance, *Inorg. Chim. Acta*, 1977, **25**, L17).



(7)

the thiolate. Such ligands could possibly be implicated in the exchange processes shown by the n.m.r. spectra.[26] The simplest cyclic structure which will give three non-equivalent thiolate and gold sites is a pentamer (7), with which the molecular-weight data are not inconsistent. Since the sulphur atoms each have one lone pair, their stereochemistry is effectively tetrahedral, and the ring will be non-planar; the substituents R_a, R_b, and R_c are non-equivalent, as are the gold atoms Au_x, Au_y, and Au_z. The size of the ring cannot be defined, but the n.m.r. intensity ratios require it to be odd-membered. On the evidence available, it is likely that a single (polymeric) species is the major component, but we cannot rigorously exclude a rapidly exchanging equilibrium mixture of polymers.

The high-temperature ^1H n.m.r. spectra (220 MHz) of the arenethiolates show that apparent equivalence of the organic groups is readily achieved by a rapid exchange process. The ^{13}C spectra appear to show rapid exchange even at room temperature (at 20.1 MHz). For 'Myocrisin' and 'Solganol', the mercaptosuccinate or 1-thioglucoside ligands all appear equivalent at room temperature,[23,27] implying rapid exchange in these cases also. When a 'Myocrisin' solution is acidified, or other monovalent cations are added, the spectra broaden and, at high ionic strength, resolve into three sets of signals.[23,24] Here, exchange is presumably slowed by intermolecular interactions between cations and carboxylate groups, and the final structure of the spectra is not dissimilar from those of the arenethiolates. The exchange process is probably intramolecular; flexing of the rings would be expected, and would be rendered more facile by inversion at the sulphur atoms. There appears to be little concentration dependence of the coalescence temperatures, which supports an intramolecular process, but we cannot exclude intermolecular exchange. The latter certainly occurs with the linear oligomers obtained by the addition of the free thiol.[25]

An interesting aspect of the gold(I) thiolates is the wide variation in solubility with the nature of the thiol group. When the organic group is a simple alkyl or phenyl group, the compounds are extremely insoluble, even when the alkyl chain is long (*e.g.* $n\text{-}C_{18}H_{37}$). The introduction of large substituents on the phenyl group induces solubility in organic solvents, while carboxyl groups in aliphatic derivatives lead to aqueous solubility of the sodium salts (*e.g.* ' Myocrisin '). The highly polar zwitterionic forms of the amino-acid derivatives (*e.g.* cysteine) have very low aqueous solubilities around pH 7, but dissolve readily in acidic or basic media, where the charges on the alkylammonium or carboxyl ions are neutralised. We earlier attributed these trends to control of the degree of polymerisation by intramolecular interaction between the substituents.[7] Thus, the zwitterionic amino-acid form could lead to strong electrostatic or hydrogen-bonding interactions between groups bound to adjacent gold atoms, resulting in an opening of the Au–S–Au bond angles, and an increase in size of the polymer. On the other hand, adjacent groups of similar

charge, *e.g.* the carboxylate groups in ' Myocrisin ', could reduce the size of the polymer by repulsive interactions. However, phenomena of this type cannot explain the solubility trend of the aromatic derivatives $[\{Au(SC_6H_4R'\text{-}p)\}_n]$: for $R' = H$, the thiolate is quite insoluble whereas, for $R' = Bu^t$ solubility is extremely high. Since the substituents are *para* to the sulphur atom, there can be no steric effect on the bond angle at sulphur. It thus seems more likely that the factor controlling solubility in these cases (and possibly the others also) is intermolecular interaction between adjacent polymer units in the solid (in addition, of course, to their interaction with the solvent). Such intermolecular interactions must depend on the size and polarity of the substituents. It is likely also that the insolubility of salts of aurothiomalic acid with di- and tri-valent cations is also due to the association of adjacent polymer units with the cations, a form of cationic cross-linking.*

It is apparent that there is no fundamental difference between the therapeutically active compounds and the other gold(I) thiolates. Differences in clinical efficacy therefore depend, in part, on the ease of absorption in the body which will, in turn, depend on the solubility of the thiolates and their interactions with the other ligands present *in vivo*. Gold in the blood stream is associated principally with albumin,[28] which contains a free thiol group, but it is not yet known with certainty whether the original thiol ligand is still present. However, it seems likely that an important factor in assimilation of the drugs is the opening of the polymer ring by interaction with thiol groups *in vivo* (cysteine, glutathione, albumin *etc.*), which may require that the biological thiol should have a stronger interaction with gold(I) than that in the administered thiolate.

* *Note added in proof.* It has recently been observed that (3-methylpentane-3-thiolato)silver(I) has a twisted double-strand chain structure in the solid which breaks into octameric cyclic units in solution (I. G. Dance, L. J. Fitzpatrick, A. D. Rae, and M. L. Scudder, *Inorg. Chem.*, 1983, **22**, 3785). Similar chain/ring behaviour may occur in the gold(I) thiolates.

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