A Carbon-13 Nuclear Magnetic Resonance Study of Thiol-exchange Reactions of Gold(I) Thiomalate ('Myocrisin') including Applications to Cysteine Derivatives

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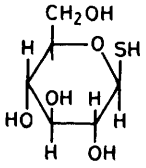
Reactions at pH 7 between gold(I) thiomalate and a variety of thiols with pK_{SH} values ranging from 7.6 (thioglucose) to 10.2 (mercaptoacetate) have been studied by ^{13}C n.m.r. spectroscopy. New species $[Au(SR)_n]^{1-n}$, where n appears to be less than 2, are formed and thiomalate is readily displaced, especially by thiols with low pK_{SH}. The latter are in fast exchange with Au^I on the n.m.r. time scale. Similar activation parameters have been derived for thiomalate, *N*-acetyl-L-cysteine, and mercaptoacetate exchange ($\Delta G^{\ddagger}$ 63 kJ mol^{-1}, $\Delta S^{\ddagger}$ −145 J K^{-1} mol^{-1}, E_A 22 kJ mol^{-1}) *via* a line-shape analysis of ^{13}C n.m.r. spectra at different temperatures. Thiol exchange rates increase at high pH, but at low pH 1 : 1 polymers are more stable than $[Au(SR)_n]^{1-n}$ species.

MUCH of the current interest in the biological chemistry of gold results from the clinical use of 1 : 1 gold(I) thiolate compounds such as aurothiomalate ('Myocrisin') and aurothioglucose ('Solganol') as antiarthritic agents.[1-3] We have recently demonstrated[4] that aurothiomalate has a variable oligomeric structure in solution, being highly dependent on ionic strength and pH. Bridging thiomalates provide two-co-ordination for Au^I. We now show by ^{13}C n.m.r. spectroscopy that the gold(I) in aurothiomalate will readily bind to further thiols (Table 1) forming $[Au(SR)_n]^{1-n}$ complexes ($n < 2$), and that displacement of thiomalate readily occurs. The rates and activation parameters for thiol-exchange reactions of these new species have been derived. In view of the abundance of thiols such as cysteine and glutathione (γ-glutamylcysteinylglycine) *in vivo*, these observations are likely to be of importance in understanding the molecular pharmacology of gold drugs.

TABLE 1

Thiols used in this study and their proton dissociation constants [a]

Thiol	Structural formula	pK_{SH} (I; T/K)	Ref.
Mercaptoacetic acid	HS–CH_2–CO_2H	10.2 (0.1; 293)	*b*
Thiomalic acid	HS–CH(–CH_2–CO_2H)–CO_2H	9.9 (1; 298)	*c*
N-Acetyl-L-cysteine	HS–CH_2–CH(–CO_2H)–NHCOMe	9.5 (0.3; 303)	*d*
Glutathione	γ-glu-cys-gly	8.9 [e] (0.2; 298)	*f*
2-Aminoethanethiol	HS–CH_2CH_2–NH_2	8.6	*g*
L-Cysteine	HS–CH_2–CH(–CO_2H)–NH_2	8.5 [e] (—; 296)	*h*
D-Penicillamine	HS–CMe_2–CH(–CO_2H)–NH_2	8.1 [e] (—; 298)	*f*
β-D-Thioglucose		7.6 (0.5; 303)	*i*
L-Cysteine methyl ester	HS–CH_2–CH(–CO_2Me)–NH_2	7.3 [e] (—; 298)	*f*

[a] All measurements in H_2O, except β-D-thioglucose (^2H_2O); I is ionic strength in mol dm^{-3}. [b] D. D. Perrin and J. G. Sayce, *J. Chem. Soc. A*, 1967, 82. [c] O. Mäkitie and A. Ilvonen, *Acta Chem. Scand.*, 1972, **26**, 847. [d] M. Friedman, J. F. Cavins, and J. S. Wall, *J. Am. Chem. Soc.*, 1965, **87**, 3672. [e] Refers to $R(NH_3^+)S^-$ as deprotonated species. [f] L. Flohe, W. Günzler, G. Jung, E. Schaich, and F. Schneider, *Z. Physiol. Chem.*, 1971, **352**, 159. [g] L. Flohe, E. Breitmaier, W. A. Günzler, W. Voelter, and G. Jung, *Z. Physiol. Chem.*, 1972, **353**, 1159, [h] R. E. Benesch and R. Benesch, *J. Am. Chem. Soc.*, 1955, **77**, 5877. [i] A. A. Isab, Ph.D. Thesis, University of London, 1978.

EXPERIMENTAL

Myocrisin, as [Au(tm)]·0.3glycerol·$2H_2O$,† was obtained from May and Baker Ltd. (Dagenham). 2-Aminoethanethiol hydrochloride and sodium mercaptoacetate were purchased from Aldrich Ltd.; other thiols were from Sigma Ltd.

Carbon-13 n.m.r. spectra were recorded on a JEOL FX60 spectrometer at 15 MHz using the glycerol CH_2 peak (g_2) as an internal reference. This occurs at 63.4 p.p.m. to high frequency of $SiMe_4$. Most spectra are the result of *ca.* 4 000 scans, with pulse interval 2 s, and 70° pulse angle. Solutions were routinely purged with N_2 to minimise air oxidation of thiols. pH Adjustments were made with 10 mol dm^{-3} Na[OD] or DCl. pH* indicates a pH meter reading in D_2O solution.

Spectra were simulated and rate constants calculated using a computer program (Trigen three) kindly supplied by Dr. J. S. Anderson (University College, London). The linewidths for CH–CH_2–S ^{13}C resonances in the fully formed Au_4S_7 type species were assumed to be the same as those of a 1.75 : 1 solution of thiomalate : Au^I where no free-ligand resonances are observed (7.0 Hz for b_2 and 3.0 Hz for b_1, CH_2 and CH respectively).

Activation energies were calculated from Arrhenius plots of ln k_r *versus* T^{-1} and free energies of activation from Eyring rate plots of ln (k_r/T) against T^{-1}.

As a guide to the likely effects of T_1 differences on peak areas, the T_1 values for CH and CH_2 ^{13}C nuclei were measured in a 0.4 : 1.2 mol dm^{-3} solution of gold(I)–thiomalate at pH* 7. Values were similar for free and bound thiomalate, *ca.* 0.5 s.

† The abbreviation used for thiomalate, $HSCH(CO_2^-)CH_2CO_2^-$, is Htm. The proton is therefore that on the thiol group, and the charges on the carboxylate groups are ignored in the formulations presented in this paper.

RESULTS AND DISCUSSION

Thiomalate Exchange.—Addition of thiomalic acid (Htm) to a solution of [Au(tm)] at a constant pH* 7 results in a high-field shift of the CH ^{13}C n.m.r. resonance and a smaller low-field shift of that for CH_2 (see Figure 6). Only one averaged set of resonances is observed until a Au : Htm ratio of 1 : 1.75 is reached. At this point, This suggests, as we have previously reported,[4] that a new species with empirical formula $[Au_4(tm)_7]^{3-}$ is formed, according to equation (1), and undergoes slow

$$4[Au(tm)] + 3Htm \rightleftharpoons [Au_4(tm)_7]^{3-} + 3H^+ \quad (1)$$

(mean lifetime >8 ms) exchange with Htm. [Au(tm)] itself, although formally a 1 : 1 complex, is polymeric both in the solid state [5] and in aqueous solution with

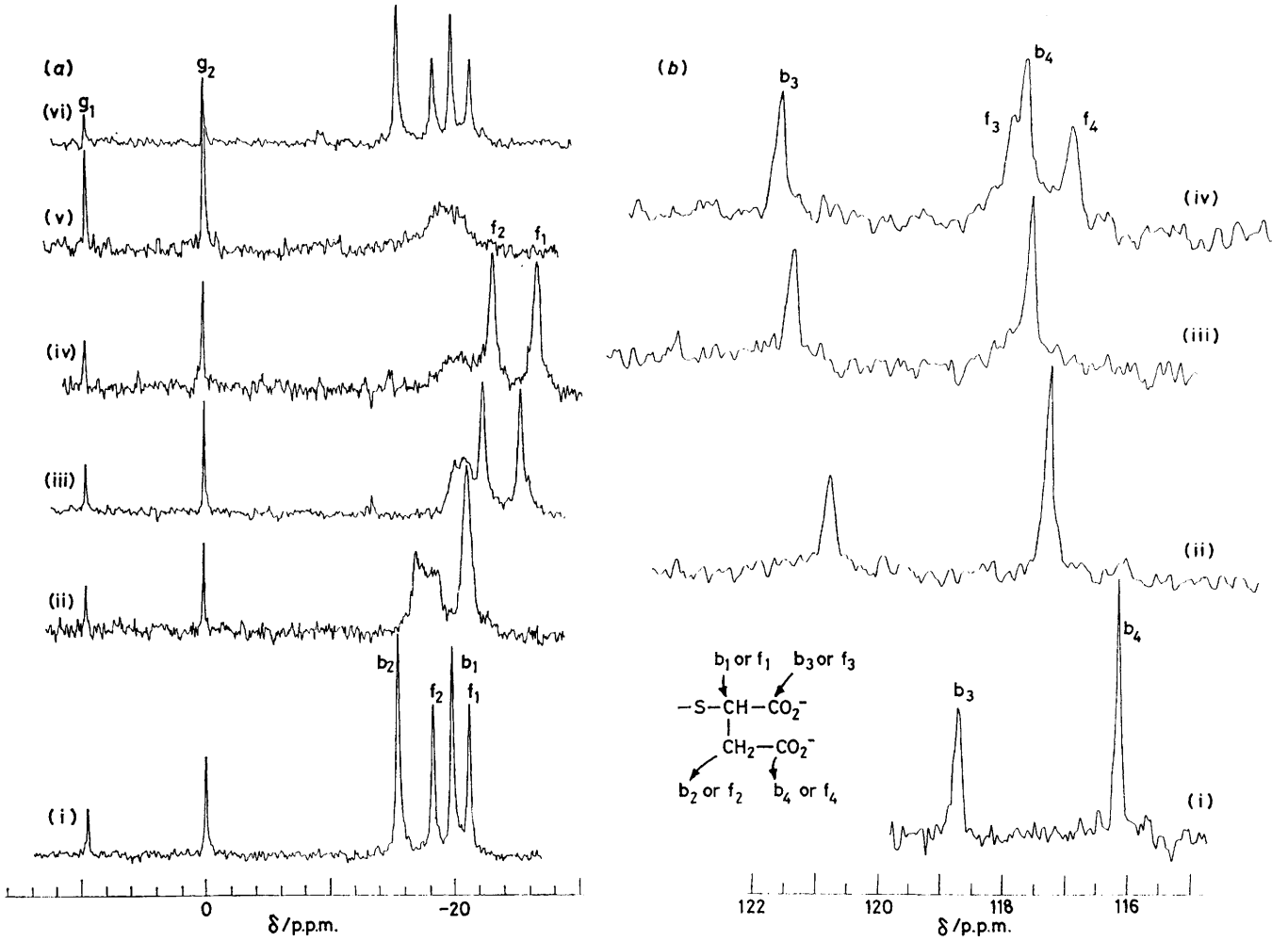


FIGURE 1 $\{^1H\}$-^{13}C n.m.r. spectra of a 0.4 mol dm^{-3} solution of aurothiomalate (*a*) (the CH,CH_2 region) with two molar equivalents of thiomalic acid added (total ratio Au^I:thiomalate, 1 : 3) at pH 7.0 (i), 6.2 (ii), 3.0 (iii), 1.3 (iv), 1.5 (v), and 7.1 (vi), except spectrum (v) which is aurothiomalate alone at pH 1.5. Spectrum (vi) results from reversing the pH of the solution used for (iv). The labels f_1 and b_1 refer to CH resonances of free and bound thiomalate, f_2 and b_2 similarly for CH_2. (*b*) The carboxylate region, pH* 7. Molar ratios of Au^I : thiomalate are 0.4 : 0.4 (i), 0.4 : 0.6 (ii), 0.4 : 0.8 (iii), and 0.4 : 1.2 (iv)

resonances for free Htm appear in the spectrum [Figure 1(*a*) (i)]. Similarly, averaged resonances are observed for the carboxylates, Figure 1(*b*), both undergoing shifts to low field. Carbon-13 n.m.r. resonances for free Htm carboxylate carbons are not noticeable until after a 1 : 2 ratio is reached. This can be attributed to spin–lattice relaxation effects under the pulsing conditions used. For [Au(tm)] alone, the T_1 values (*ca.* 0.15 s) for the CH,CH_2 resonances are more than ten times shorter that those (*ca.* 3 s) for the carboxylate resonances. bridging sulphur.[4] Since our original report,[6] Shaw [2] has suggested from n.m.r. shift considerations that the new species is the 1 : 2 complex $[Au(tm)_2]^-$ a linear species with S_2 co-ordination for Au^I. Although it is difficult to be confident about the interpretation of the intensities of ^{13}C resonances, free thiomalate CH and CH_2 resonances always appear in our spectra before a 1 : 2 ratio is reached, even under conditions of long pulse delays and gated decoupling (to remove nuclear Overhauser and relaxation effects). A cluster species such as

$[Au_4(tm)_7]^{3-}$ requires three-co-ordinate gold(I) analogous to known copper(I) species.[7-9] The copper(I) complexes $[Cu_5(\mu\text{-}SBu^t)_6]^-$ and $[Cu_5(\mu\text{-}SPh)_7]^{2-}$ are both based on the Cu_4S_6 unit found in $[Cu_4(thiourea)_6]^{4+}$. Recently, Bowmaker and Dobson [10] have described the isolation of $[Au(SR)_2]^-$ complexes, R = Me, Bu^t, or Ph, which can be recrystallised from *non-aqueous* solutions. The preparation of $K[Au(SC_6F_5)_2]$ had been reported previously.[9] However, there are still no reports of the isolation or crystallisation of 1 : 2 thiolate complexes from *aqueous* solutions, and it should be noted that most of the reactions described here are carried out at pH* 7 for physiological relevance.

It is of interest to compare the ^{13}C n.m.r. shifts of [Au(tm)], $[Au(tm)_{1.75}]$, and thiomalate itself at pH* 7. The co-ordination shifts (p.p.m., positive to low field) for $[Au(tm)_{1.75}]$ compared to [Au(tm)] (given in parentheses) are $CHCO_2^-$ 1.39 (5.32), $CH_2CO_2^-$ 2.84 (2.77), $CHCO_2^-$ 3.44 (0.77), and $CH_2CO_2^-$ 0.52 (−0.81). The most striking features are the increase in shielding of the CH carbon in the cluster species, which probably reflects the increase in electron density on Au^I on co-ordination of further tm^- leading to a back donation into empty S *d* orbitals, and an equally large decrease in shielding at the adjacent carboxylate carbon. The latter has the largest co-ordination shift. Although this could be considered as possible evidence for carboxylate co-ordination, it seems more likely to arise from changes in the electronic distribution within the ligand as a result of S co-ordination only. Nevertheless, such large changes in electron density within the ligand, presumably including the S atoms, could have important biological consequences. For example, the redox potential of aurothiomalate may vary considerably with the average number of bound thiomalates, and experiments are in hand to test this.

pH Dependence.—The shifts of the ^{13}C resonances of thiomalic acid in a solution with molar ratio Au : tm = 1 : 1.75 are independent of pH in the range 7—12, indicating that all thiomalate is bound to Au^I in the ionised, tm^-, form. When the pH of a solution with molar ratio 1 : 3 is raised to 10.65, both CH (b_1 and f_1) and CH_2 (b_2 and f_2) peaks collapse to single averaged resonances, showing that exchange of thiomalate (tm^-) has now become rapid on the n.m.r. time scale. The broadness of the CH resonance compared to that of CH_2 is a consequence of the greater chemical-shift difference between b_1 and f_1 (2.33 p.p.m.) compared to b_2 and f_2 (0.26 p.p.m.) at this pH*. The calculated exchange rates are given in Table 2. There is a clear dependence on the amount of tm^- present. This increases about ten times from pH 8.6 to 10.6 and the observed exchange rate also increases by the same factor.

TABLE 2

Exchange rates for gold-bound thiomalate at various pH* values (Au^I : thiomalate, 1 : 3)

pH	k_r/s^{-1}
7.0	20
8.6	50
10.0	450

The high stability of the 1 : 1 Au : tm complex is evident when the pH* of the above solution containing a 1 : 3 molar ratio of Au : Htm is lowered. By pH* 4, all the excess of thiomalate has been ejected from the cluster species and gives separate resonances in the spectrum. The spectrum in acidic solution resembles that of [Au(tm)] alone with extra peaks for Htm, presumably broadened by exchange, Figure 1. This confirms the reversibility of equilibrium (1). The solution loses its yellowish colour around pH* 4, and increases in viscosity, as do solutions of [Au(tm)] alone.[4] The stability of the 1 : 1 complex is enhanced by the decreased charges on the ligands at low pH and possibly by Au–Au bonding.

Cysteine Derivatives: Exchange Rates and Activation Energies.—Addition of one equivalent of *N*-acetyl-L-

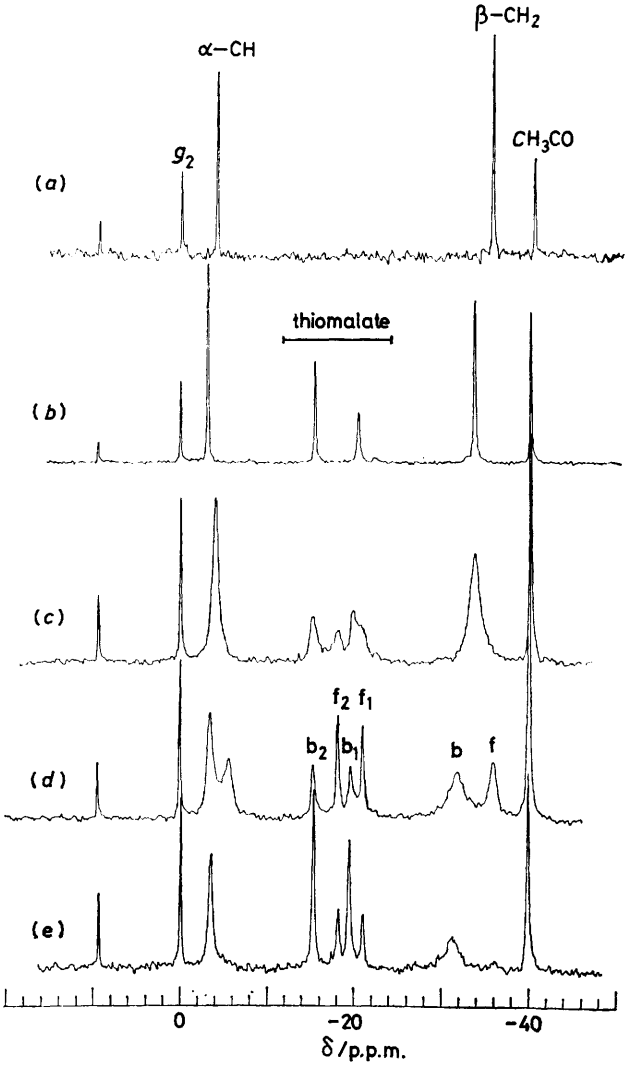


FIGURE 2 $^{13}C\{^1H\}$ n.m.r. spectra of [Au(tm)] : *N*-acetyl-L-cysteine solutions at various molar ratios showing bound and free thiols, and the increase in exchange rates at high pH. [Au(tm)] : [acysS] = 0 : 0.4, pH* 10.0 (*a*); 0.4 : 0.8, 10.0 (*b*); 0.4 : 0.8, 8.6 (*c*); 0.4 : 0.8, 7.0 (*d*); 0.4 : 0.4, 7.1 (*e*)

cysteine (acys) to a 0.4 mol dm^{-3} solution of [Au(tm)] at pH* 7 results in the displacement of *ca.* 25% of the bound thiomalate. The remaining bound thiomalate has ^{13}C resonances with chemical shifts similar to those of the $[Au(tm)_{1.75}]$ (cluster) species described above, Figure 2. Only one set of resonances is present for acys; both the CH and CH_2–SH resonances are broadened. It is notable again that although the ratio of Au^I : total RSH in this solution is 1 : 2, resonances for free RSH are observed indicating that, under these conditions, bis(thiolate) complexes $[Au(tm)_{2-x}(acysS)_x]^-$ ($x = 0$, 1, or 2), which may contain mixed thiolates do not have enormously greater stability than polymeric 1 : 1 complexes or cluster species. On addition of a second equivalent of acys, further displacement of Htm occurs and resonances for bound and free acysS are now present in the spectrum. Consideration of peak areas suggests that the gold acysS species has an empirical formula $[Au(acysS)_{1.6}]$, see Table 3. At higher pH*, coalescence of resonances due to both free and bound thiomalate and *N*-acetylcysteine is observed, Figure 2. This is partly a result of the shift of the resonances of the free ligand towards those of the bound ligand as RSH ionises, and partly due to the increase in exchange rate with an increase in RS^- concentration.

As shown in Figure 3, coalescence of both thiomalate and *N*-acetyl-L-cysteine CH and CH_2 resonances is also observed at high temperature. The thiol exchange rates were calculated from line-shape analyses, and activation parameters from Arrhenius and Eyring (straight-line) plots. These are listed in Table 4, where it can be seen that the kinetic behaviour of these two thiolates is almost identical, the highly negative entropy of activation indicating an associative transition state. This would involve an increase in gold(I) co-ordination number from three to four in a cluster species or two to three in a linear 1 : 2 species. Similar activation parameters are obtained for mercaptoacetate (Table 5) which

TABLE 3

Equilibrium data for [Au(tm)] in the presence of other thiols at pH 7 (300 K) calculated from the areas of ^{13}C resonances. All concentrations in mol dm^{-3}

Thiol	[Au(tm)] : [added thiol]	Bound thiomalate	Bound added thiol	Total bound thiol
Thiomalic acid	0.4 : 0.4	0.69		0.69
	0.4 : 0.6	0.72		0.72
	0.4 : 0.8	0.70		0.70
	0.4 : 1.2	0.75		0.75
N-Acetyl-L-cysteine	0.4 : 0.4	0.28	0.37	0.65
	0.4 : 0.6	0.20	0.43	0.63
	0.4 : 0.8	0.15	0.46	0.61
	0.4 : 1.2	0.13	0.53	0.66
	0.4 : 1.2 (254 K)	0.13	0.53	0.66
Mercaptoacetic acid	0.3 : 0.45	0.21	0.30	0.51
	0.3 : 0.6	0.18	0.31	0.49
	0.3 : 0.9	0.15	0.36	0.51

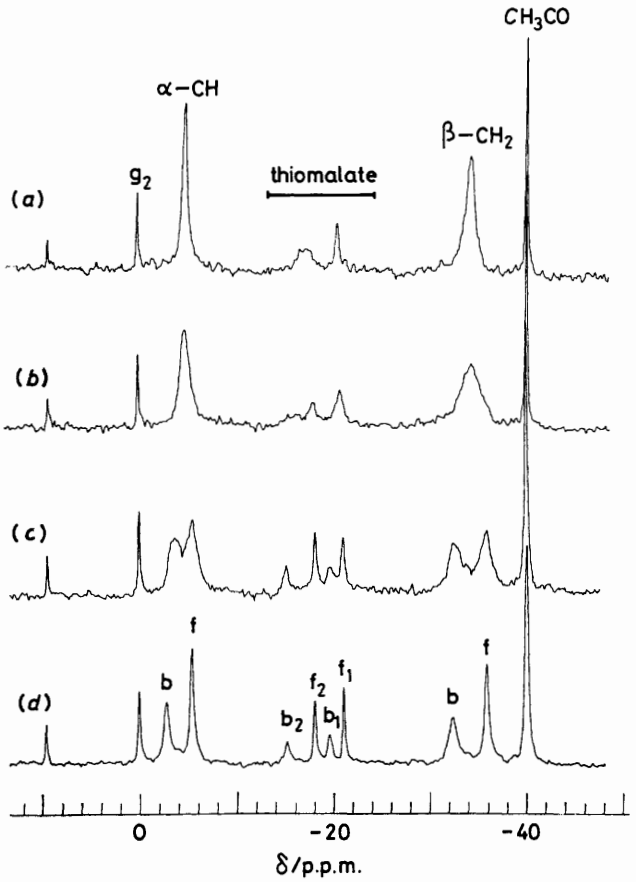


FIGURE 3 Temperature dependence of the ^{13}C-{^1H} n.m.r. spectrum of a solution of [Au(tm)] : *N*-acetyl-L-cysteine, 0.4 : 1.2 mol dm^{-3} at pH* 7, T = 348 (*a*), 323 (*b*), 290 (*c*), and 255 K (*d*)

TABLE 4

Thiol exchange rates and activation parameters for gold-bound thiolates in 1 : 3(0.4 : 1.2 mol dm^{-3}) [Au(tm)] : *N*-acetyl-L-cysteine solutions, pH* 7

	k_r/s^{-1}	
T/K	Thiomalate	*N*-Acetyl-L-cysteine
254	8	19
270	16	36
300	30	66
323	68	178
348	126	293

Thiol	$\Delta H^‡$/ kJ mol^{-1}	$\Delta G^‡$/ kJ mol^{-1}	$\Delta S^‡$/J K^{-1} mol^{-1}	E_A/kJ mol^{-1}
Thiomalic acid	18.8	64.4	−151	21.3
N-Acetyl-L-cysteine	18.8	62.8	−141	21.3

TABLE 5

Thiol exchange rates and activation parameters for gold-bound thiolates in 1 : 3 (0.3 : 0.9 mol dm^{-3}) [Au(tm)] : mercaptoacetate solutions, pH* 7

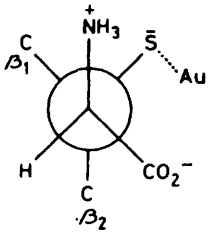
	k_r/s^{-1}	
T/K	Thiomalate	Mercaptoacetate
300	10	60
318	50	120
343	120	200

Thiol	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta G^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	E_A/kJ mol^{-1}
Mercaptoacetic acid	20.9	63.1	−141	23.0

tends to support the possible existence of 1 : 2 species since the co-ordinated thiols are further apart than in a cluster species of the $[Au_4(SR)_7]^{3-}$ type and the interaction of charged side chains would have less effect on the stability of the transition state. The activation free energy found here is comparable with that observed by Bach and Weibel [11] for exchange in the [HgMe(SPh)]–[HgMe(CN)] system.

For all of the above thiols with $pK_{SH} > 9$, resonances for free and bound thiolate are observable, but for the others studied only averaged resonances were seen, although thiomalate is still in slow exchange in these solutions. Thus the ^{13}C resonances of cys C_α and C_β of cysteine methyl ester and glutathione were shifted to low field and broadened in the presence of [Au(tm)]. Typical spectra for glutathione are shown in Figure 4. The shift changes, Table 6, confirm that Au^I binds exclusively to sulphur and that no co-ordination to the glutamyl or glycyl carboxylates occurs.

A precipitate appears on addition of L-cysteine (cys) to aqueous solutions of [Au(tm)] at pH* 7. This redissolves at high pH; *ca.* pH 9.5 at a molar ratio [Au(tm)] : cys of 1 : 1, and as low as pH 7.8 at a ratio of 1 : 2. The precipitate may be the 1 : 1 gold(I) cysteine complex



which has been previously described [12] and is known to be highly insoluble. However, the difference in solubility behaviour at different tm : cys ratios suggests that mixed Au^I–tm–cys species may exist.

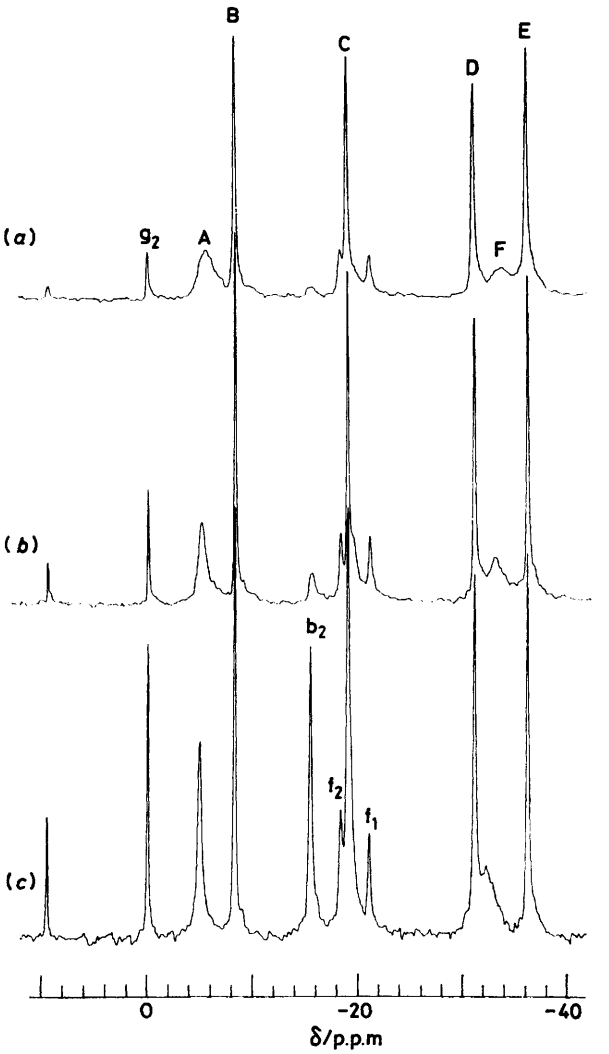


FIGURE 4 ^{13}C-{^1H} n.m.r. spectra of [Au(tm)]–glutathione solutions, pH* 7, at molar ratios [Au(tm)] : [glut] of 0.24 : 0.72 (*a*), 0.24 : 0.48 (*b*), and 0.24 : 0.24 (*c*). Glutathione peaks are labelled: A, cys-C_α, B, glu-C_α; C, gly-C_α; D, glu-C_γ; E, glu-C_β; and F, cys-C_β

A notable feature of the shifts of the ^{13}C resonances of D-penicillamine (D-pen, 3-mercaptovaline) in the presence of [Au(tm)] (Figure 5) is the contrasting behaviour of the two β-CH_3 groups. At an [Au(tm)] : D-pen molar ratio of 1 : 0.5 one CH_3 resonance (with the larger exchange broadening) has shifted by 5.04 p.p.m. and the other by only 0.26 p.p.m. compared to the free ligand. The shift for the α-C resonance is 1.95 and for the β-C 4.32 p.p.m. Clearly, co-ordinated D-pen has a strongly preferred conformation in which one CH_3 group (*e.g.*

TABLE 6

Carbon-13 chemical-shift changes † for 0.24 mol dm^{-3} glutathione (glut) in the presence of aurothiomalate at pH* 7.0

[Au(tm)] : glut	gly CO_2^-	glu CO_2^-	glu CONH	cys CONH	cys C_α	cys C_β	glu C_α	gly C_α	glu C_γ	glu C_β
1 : 1	0.13	0.13	0.19	0.59	2.01	5.12	0	0	0	0
1 : 2	0.07	0.07	0.19	0.52	1.88	3.90	0	0	0	0
1 : 3	0.07	0.07	0.13	0.46	1.75	3.38	0	0	0	0

† In p.p.m. to low field of free glut at pH* 7.

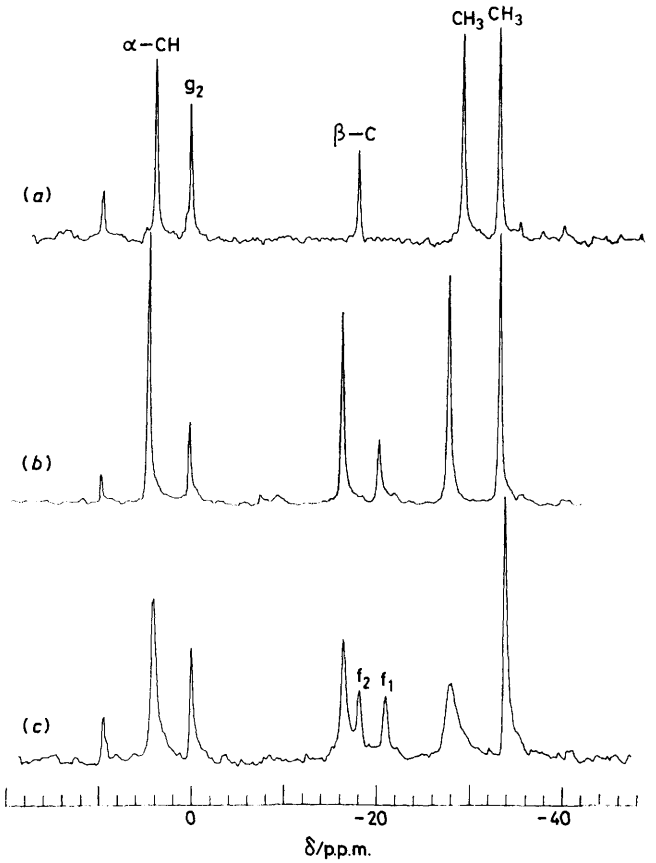


FIGURE 5 ^{13}C-{^1H} n.m.r. spectra of D-penicillamine (*a*, pH* 9.0), and [Au(tm)] (0.3 mol dm^{-3}) in the presence of D-penicillamine (0.75 mol dm^{-3}) at pH* 7 (*c*) and 9.1 (*b*). Note the differential shifts and broadenings of the two CH_3 peaks of penicillamine

β_2-CH_3) is much nearer to Au than the other. Hydrogen-bonding interactions (*e.g.* $NH_3^+ \cdots S^-$) may help to stabilise such a structure. Restricted β-C–S rotation may be more likely to occur in an $[Au_4(SR)_6]^{2-}$-type cluster species than in $[Au(SR)_2]^-$. We have previously observed differential rotamer populations for aurothiomalate itself [4] where the shift pattern for the two CH_2 protons resembles that of the CH_3 groups here. Weak $Au^{-}O_2C$ interactions could also stabilise the conformation and cannot be ruled out.

Relative Stabilities of $[Au(SR)_n]^{1-n}$ *Complexes.*—A consideration of the intensities of the ^{13}C resonances of thiomalate displaced from [Au(tm)] in the presence of two equivalents of added thiol at pH* 7 gave the following order of binding strength: cysteine methyl ester ≈ D-penicillamine > β-D-thioglucose > *N*-acetylcysteine > glutathione ≈ thiomalate ≈ mercaptoacetate. This parallels the pK_a order, see Table 1. We note the use of D-penicillamine to reverse toxicity due to gold drugs. The most strongly bound thiols are those with the lowest pK_a values.

Figure 6 shows the shifts of the ^{13}C resonances of gold-bound thiomalate as a function of the concentration of added thiol. The pattern of shifts is similar in all cases: a small shift of the CH_2 resonance of thiomalate to low field and a larger shift of up to *ca.* 4 p.p.m. to high field for the S–*C*H resonance. The breakdown of [Au(tm)] polymers therefore occurs by a similar route in all cases with the remaining bound thiomalate being present in $[Au(SR)_n]^{1-n}$ complexes similar to $[Au(tm)_{1.75}]$, although they may be mixed thiolate species.

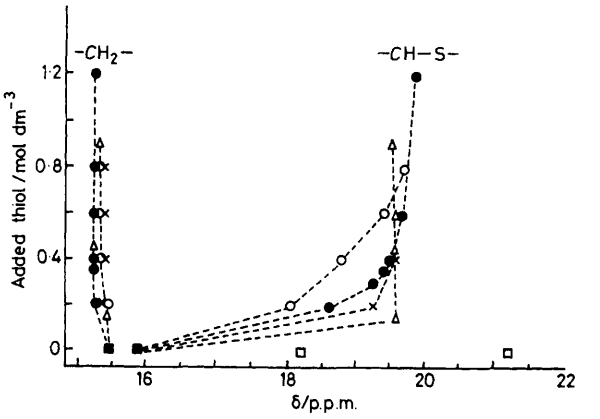


FIGURE 6 Shifts of gold-bound thiomalate ^{13}C n.m.r. resonances of [Au(tm)] (0.4 mol dm^{-3}, except 0.3 mol dm^{-3} with mercaptoacetate) on addition of other thiols at pH 7: [Au(tm)] (■) thiomalate (□) (both alone at pH 7), thiomalate (●), β-D-thioglucose (○), *N*-acetyl-L-cysteine (×), and mercaptoacetate (△)

Conclusions.—Thiols such as cysteine and glutathione are available *in vivo*, and it is clear from this work that, once injected, [Au(tm)] will rapidly react with further thiols or thiolates to form $[Au(SR)_n]^{1-n}$ complexes. The thermodynamic stability of these is such that gold will seek out those thiol groups with the lowest pK_a values. Thiomalate displacement is facile, which may account for some of the toxic side effects of the drug. In view of the ease of thiol-exchange reactions it is perhaps not surprising that gold distribution in the body after drug treatment is very widespread. The chemistry of gold(I) in thiolate solutions is clearly very complicated, with the possible existence of polymers, oligomers, clusters, and perhaps bis(thiolate) and mixed thiolate species. Gold(I) may be a good thiol-transporting agent. Nuclear magnetic resonance methods are now available for observing resonances from thiols in intact cells,[13] and the exciting possibility arises of studying gold thiolate exchange reactions directly. Experiments along these lines are now in progress.

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