# Hydrogen-1 and Carbon-13 Nuclear Magnetic Resonance Studies of Gold(I) Thiomalate ('Myocrisin') in Aqueous Solution: Dependence of the Solution Structure on pH and Ionic Strength

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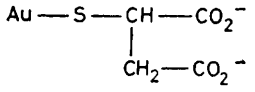
The conformation of thiomalate (mercaptosuccinate) in neutral aqueous solutions of the anti-arthritic drug aurothiomalate has been determined by analysis of $^{1}H-^{1}H$ and $^{1}H-^{13}C$ three-bond n.m.r. coupling constants. The results indicate the formation of a low molecular weight polymer with only sulphur co-ordination for $Au^{I}$. At high ionic strength additional $^{1}H$ and $^{13}C$ n.m.r. resonances appear and peaks broaden, consistent with the formation of higher molecular weight species with up to three different environments for thiomalate. Structural changes are accompanied by a new electronic absorption band at 340 nm. High molecular weight polymers are also formed at low pH, where the $^{1}H$ and $^{13}C$ resonances are severely broadened.

1 : 1 COMPLEXES of $Au^{I}$ with thiolates such as thiomalate (mercaptosuccinate) and glucothiose have been in clinical use for the treatment of rheumatoid arthritis for over forty years,[1-4] but little information is available about their structures either in the solid state or in solution, or about biologically relevant ligand-exchange reactions.

In this study we describe the use of $^{1}H$ and $^{13}C$ n.m.r. spectroscopy to monitor the environment of thiomalate in aqueous solutions of aurothiomalate † (see below, trade name 'Myocrisin'). We have used a combination



of $^{1}H-^{1}H$ and $^{13}C-^{1}H$ three-bond coupling constants to define fully the conformation of thiomalate in the lowest molecular weight species present in dilute solutions. Dramatic shifts and broadenings of both $^{1}H$ and $^{13}C$ resonances are observed in concentrated solutions or at high ionic strengths. These are related to changes in structure and the degree of polymerisation, which also show a marked pH dependence.

In subsequent papers[5] we shall describe the determination of kinetic and thermodynamic parameters for thiolate exchange reactions by n.m.r. methods. We have previously referred briefly to preliminary results of this work.[2,6]

## EXPERIMENTAL

*Materials.*—Disodium aurothiomalate (batches C12 and H1) were the gift of May & Baker Ltd. (Dagenham). Integration of the $^{1}H$ n.m.r. spectrum showed the presence of 0.3 mol of glycerol per mol of thiomalate. The patented manufacturing process[7] uses glycerol in the final purification step. A satisfactory analysis was obtained (Found: C, 13.4; H, 1.7; S, 6.4, Au, 43.5. $C_4H_3AuNa_2O_4S\cdot0.3C_3H_8O_3\cdot2H_2O$ requires C, 13.0; H, 1.6; S, 7.0; Au, 43.4%). Thiomalic acid (mercaptosuccinic acid) was purchased from Sigma Ltd. and all other salts were AnalaR grade.

*N.M.R. Measurements.*—100-MHz $^{1}H$ n.m.r. spectra were recorded on a JEOL JNM-MH100 spectrometer in CW mode, at 28 °C. Higher field measurements were made on a Varian HR220 machine [Physico Chemical Measurements Unit (P.C.M.U.), Harwell] or Bruker 270 [National Institute for Medical Research (N.I.M.R.), Mill Hill]. A JEOL FX-60 spectrometer was used for $^{13}C$ spectra, operating at 29 °C. Most $^{13}C$ spectra were obtained using 70° (14 μs) pulses and a resolution of 0.6 Hz per computer point, although for coupling constant measurements 0.12 Hz per computer point was used. $T_1$ values were measured by the 180°–τ–90° sequence, and spectrum simulation was carried out with a standard JEOL programme.

Air oxidation of thiomalate was minimised during the long $^{13}C$ n.m.r. accumulations by saturating the solutions (1—2 $cm^3$, 10-mm tubes) with $N_2$. Glycerol was used as a chemical-shift reference, although dioxan or $Bu^tOH$ was sometimes added. The $CH_2$ $^{13}C$ resonance of glycerol is 3.96 p.p.m. upfield of dioxan and 63.4 p.p.m. downfield from $SiMe_4$. Ionic references such as silapentanesulphonates were avoided because they affected the spectrum of aurothiomalate in common with other salts.

*pH Measurements.*—These were made on a Radiometer PHM 62 meter equipped with a combination electrode. Care was taken to remove black deposits which sometimes occurred at the porous plug and impaired the electrode performance (presumably arising from $Ag^+$–aurothiomalate reactions). Standardisations were made with $H_2O$ buffers. pH* Indicates a meter reading in $D_2O$ solution uncorrected for the deuterium isotope effect (pD = pH* + 0.4); NaOD (10 mol $dm^{-3}$) or DCl (10 mol $dm^{-3}$) was used for pH* adjustment.

*Electronic Absorption Spectroscopy.*—U.v.–visible spectra were measured on a Perkin-Elmer model 402 instrument at 18 °C using 1-cm cells.

*Laser Raman Spectroscopy.*—Spectra were obtained on the Cary 81 Krypton Ion Laser machine of the Intercollegiate Research Service at Imperial College at 23 °C using the yellow line at 5 682 Å. The solutions of aurothiomalate containing the appropriate salt were lyophilised.

*Molecular Weight Measurements.*‡—The apparent diffusion coefficient was measured using a Spinco ultracentrifuge and the method of Yphantis[8] and equations of Williams *et al.*[9] The corrected molecular weight for aurothiomalate (0.015 mol $dm^{-3}$) in sodium phosphate buffer at pH 7.3 (ionic strength 0.05) increased from 2 467

† [Mercaptosuccinato(3—)-*S*]aurate(I).

‡ These were carried out by P. A. Charlwood (N.I.M.R.), and C. J. Danpure and D. A. Fyfe (Clinical Research Centre, Harrow).

to 2 642 when the NaCl concentration was increased from 0.5 to 1.0 mol $dm^{-3}$.

RESULTS AND DISCUSSION

In dilute (<0.3 mol $dm^{-3}$) aqueous solutions of aurothiomalate at neutral pH, one set of $^1H$ and $^{13}C$ n.m.r. resonances is observed for more than 95% of the thiomalate in solution. The remaining thiomalate is present as a minor species which increases in concentration at high ionic strengths and will be discussed later. The major species has the expected ABX type $^1H$ n.m.r. spectrum consisting of a triplet for CH and an eight-line pattern for the non-equivalent $CH_2$ protons (the CH carbon is an asymmetric centre), see Figure 1,

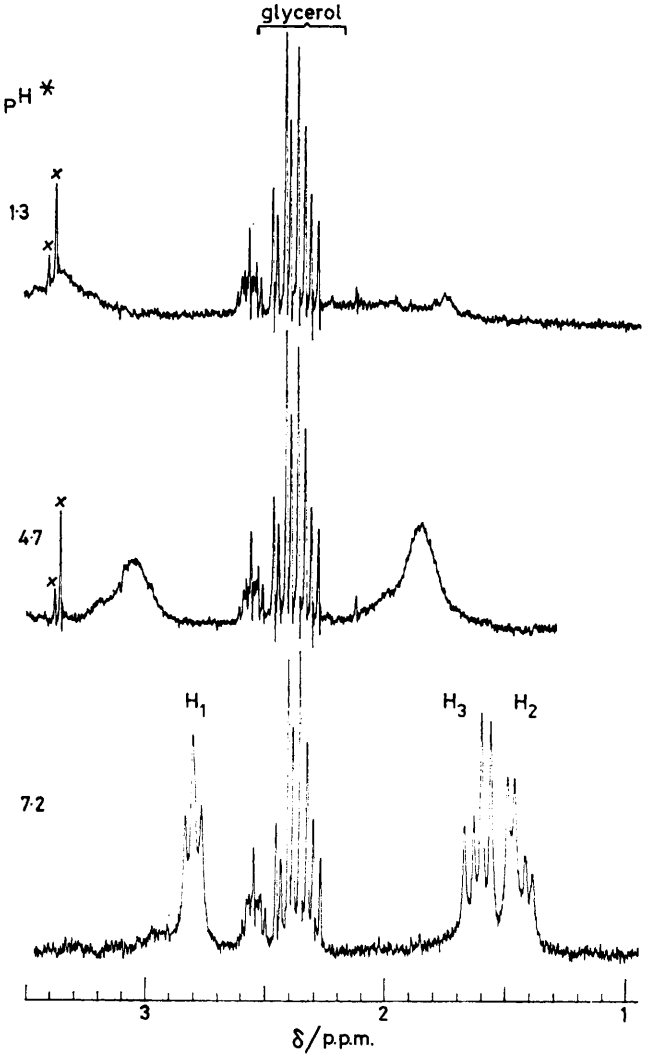



FIGURE 1 220-MHz $^1H$ n.m.r. spectra (δ p.p.m. relative to $Bu^tOH$) of a 0.3 mol $dm^{-3}$ solution of aurothiomalate at various pH* values. Peaks labelled *x* are spinning side-bands from HOD (not shown)

and four resonances in the $^{13}C$-{$^1H$} spectrum: A, D, K, and J in Figure 2. The chemical shifts of aurothiomalate and those of free thiomalate at pH* 7 are compared in Table 1. It can be seen that the largest co-ordination shift, 5.32 p.p.m. downfield, is for the *C*H carbon next to the sulphur atom.

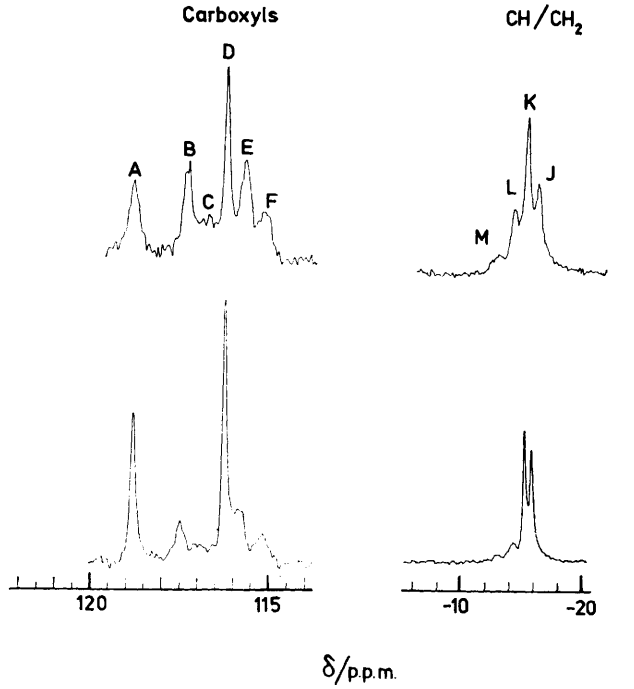



FIGURE 2 $^{13}C$-{$^1H$} n.m.r. spectrum (δ p.p.m. relative to glycerol) of 0.8 mol $dm^{-3}$ aurothiomalate at pH* 7, before (bottom) and after (top) the addition of $Na_2[SO_4]$ (1 mol $dm^{-3}$). For aurothiomalate alone, measured $T_1$ values were 0.15 (peak J, CH), 0.13 (K, $CH_2$), 4.4 (A, $CHCO_2^-$), and 3.0 s (D, $CH_2$-$CO_2^-$). They are approximately ten-fold smaller than those of thiomalate at this pH*

TABLE 1

Hydrogen-1 and carbon-13 n.m.r. shifts †

| | (*i*) Thiomalate | (*ii*) Aurothiomalate | Co-ordination shift (*ii*) − (*i*) |
|---|---|---|---|
| *C*H–COO⁻ | −21.15 | −15.83 | 5.32 |
| *C*$H_2$–COO⁻ | −18.27 | −15.50 | 2.77 |
| CH–*C*OO⁻ | 117.93 | 118.70 | 0.77 |
| $CH_2$–*C*OO⁻ | 116.95 | 116.14 | −0.81 |
| *C*H–COO⁻ | 2.29 | 2.88 | 0.59 |
| *C*$H_2$(2)–COO⁻ | 1.48 | 1.48 | 0.00 |
| *C*$H_2$(3)–COO⁻ | 1.15 | 1.64 | 0.49 |

† Recorded at pH* 7; $^{13}C$ shifts are relative to $CH_2$ group of glycerol, $^1H$ relative to $Bu^tOH$. A negative sign indicates a low-frequency (high-field) shift.

*Conformational Analysis.*—The conformation of thiomalate can be analysed in terms of the populations $p_I$, $p_{II}$, and $p_{III}$ of the three rotamers I, II, and III, Figure 3, using equations (1)—(7).

$$p_I = [J_{3,1} - J_g(HH)]/[J_t(HH) - J_g(HH)] \quad (1)$$

$$p_{II} = [J_{2,1} - J_g(HH)]/[J_t(HH) - J_g(HH)] \quad (2)$$

$$p_{III} = 1 - p_I - p_{II} \quad (3)$$

$$p_{II} = [J_{4,3} - J_g(CH)]/[J_t(CH) - J_g(CH)] \quad (4)$$

$$p_{III} = [J_{4,2} - J_g(CH)]/[J_t(CH) - J_g(CH)] \quad (5)$$

$$p_I = 1 - p_{II} - p_{III} \quad (6)$$

$$J_{5,1} = p_I J_g(CH) + p_{II} J_g(CH) + p_{III} J_t(CH) \quad (7)$$

These relate the rotamer populations, $p$, to the observed three-bond coupling constants $J_{3,1}$ *etc.* and *trans* and *gauche* $^1H-^1H$ and $^1H-^{13}C$ coupling constants $J_t(HH)$, $J_g(HH)$ and $J_t(CH)$, $J_g(CH)$. This combined approach [10,11] is necessary to eliminate the ambiguity in the assignment of $H_A$ and $H_B$ to $H^1$ and $H^2$.

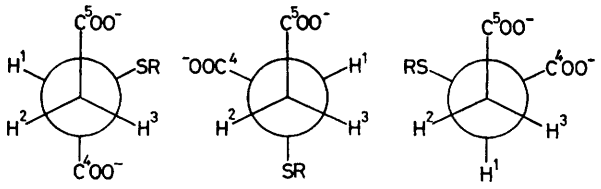



FIGURE 3 Rotamers I, II, and III: R = H, thiomalate; R = $Au^I$, aurothiomalate

To test this method we examined thiomalate itself at pH* 7 and pH* 1, since a conformational analysis using $^1H$ couplings alone has previously been reported by Leyden and Walters.[12] The $^1H$-coupled $^{13}C$ n.m.r. spectrum of the CH–$COO^-$ carbon of thiomalate at pH* 7 shows eight peaks of approximately equal intensity: a doublet ($^2J_{1.4}$ 5.2 Hz) of doublets ($^3J_{4.3}$ 4.1 Hz) of doublets ($^3J_{4.2}$ 2.6 Hz). For $CH_2COO^-$, a triplet ($^2J_{5.2} = {}^2J_{5.3}$ 6.0 Hz) of doublets ($^3J_{5.1}$ 2.3 Hz) was observed.

Solving equations (4), (5), and (6) with the values of $p$ of Leyden and Walters [12] we obtained $J_t(CH)$ 14.1 Hz and $J_g(CH)$ − 0.2 Hz, whereas interchange of $p_I$ and $p_{II}$ gave $J_g(CH) \gg J_t(CH)$. Since it was a reasonable assumption that $J_g(CH)$ would be much smaller than $J_t(CH)$ the previous assignment was confirmed. In addition, the value of $J_{5.1}$ calculated from equation (7) was in good agreement with that observed (2.3 and 2.2 Hz respectively). These values are listed in Table 2.

Similarly, at pH* 1 we again obtained reasonable values of $J_g(CH)$ (0.5 Hz) and $J_t(CH)$ (12.6 Hz) using the reported populations. However, the spectrum could only be simulated if the reported value of $\delta(H^2) - \delta(H^3)$ of 16.5 Hz was corrected to 9.9 Hz. The calculated value of $J_{5.1}$ (3.4 Hz) compared well with that observed (3.0 Hz).

Thus the most populated rotamer at pH* 7 is I (Figure 3), in which the negatively charged carboxylate groups are *trans*, whereas at pH* 1 there is a slight preference for II, Table 2. We then examined conformational changes induced by $Au^I$ co-ordination.

The carboxyl region of a $^1H$-coupled $^{13}C$ n.m.r. spectrum of aurothiomalate is shown in Figure 4. It was necessary to use a concentrated solution to obtain a reasonable signal-to-noise ratio, although a greater amount of the minor species is now present. Using the above values of $J_g(HH)$ and $J_t(HH)$, with $H_A$ assigned to $H^2$ and $H_B$ to $H^3$, gave $p_I = 0.49$, $p_{II} = 0.3$, and $p_{III} = 0.21$. These lead to reasonable values of $J_g(CH)$ 0.6 Hz, and $J_t(CH)$ 14.0 Hz. Interchange of $p_I$ and $p_{II}$, on the other hand, gives $J_g(CH) \gg J_t(CH)$ which is unacceptable.

TABLE 2

Two- and three-bond $^{13}C-^1H$ and $^1H-^1H$ coupling constants (Hz) and rotamer populations for thiomalic acid and disodium aurothiomalate

| | $HSCH(CO_2H)CH_2CO_2H$ | | $Na_2[AuSCH(CO_2)CH_2CO_2]$ |
|---|---|---|---|
| pH* | 7.0 | 1.0 | 7.2 |
| $^3J$ $C^4-H^2$ | 2.6 | 3.5 | 3.4 |
| $C^4-H^3$ | 4.1 | 6.1 | 4.6 |
| $C^5-H^1$ | 2.3 | 3.0 | 2.2 |
| $^3J$ $H^1-H^2$ | 6.0 | 8.6 | 6.4 |
| $H^1-H^3$ | 9.6 | 6.1 | 8.6 |
| $H^2-H^3$ | −15.6 | −17.4 | −16.0 |
| $J_t(CH)$ [a] | 14.1 | 12.6 | 14.0 |
| $J_g(CH)$ [b] | −0.2 | 0.5 | 0.6 |
| $^2J$ $C^4-H^1$ | 5.2 | 5.8 | 4.9 |
| $C^5-H^2$ | 6.0 | 6.8 | 6.2 |
| $C^5-H^3$ | 6.0 | 6.8 | 5.8 |
| $p_I$ | 0.57 [c] | 0.28 [c] | 0.49 |
| | (0.55) [d] | (0.32) | (0.45) |
| $p_{II}$ | 0.26 [c] | 0.47 [c] | 0.30 |
| | (0.28) | (0.44) | (0.32) |
| $p_{III}$ | 0.17 [c] | 0.25 [c] | 0.21 |
| | (0.17) | (0.24) | (0.23) |

[a] Average, 13.5 Hz. [b] Average, 0.3 Hz. [c] Calculated from $^1H$ data (see ref. 11). A $\delta(H^2) - \delta(H^3)$ value of 16.5 Hz instead of 9.9 Hz reported was used at pH* 1. [d] The rotamer populations in parentheses are based on the average values of $J_t(CH)$ and $J_g(CH)$.

We can conclude therefore that $Au^I$ co-ordination causes little change in the conformation of thiomalate

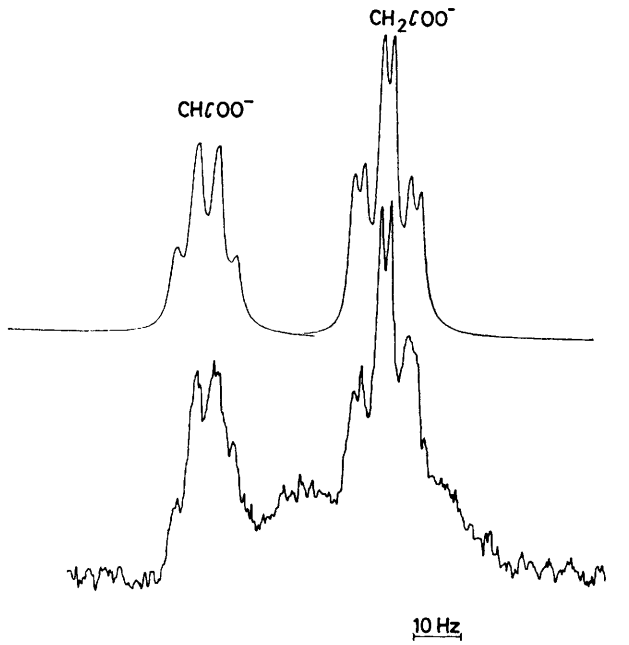


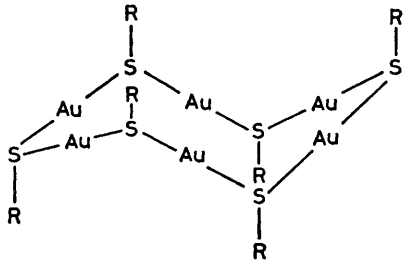

FIGURE 4 $^{13}C$ n.m.r. spectrum of the carboxylate region of a 0.8 mol $dm^{-3}$ solution of aurothiomalate at pH* 7. Gated $^1H$ noise decoupling was used to retain the nuclear Overhauser enhancement; the spectrum is the result of 12 000 scans with a pulse interval 12.0 s, 250 Hz sweep width, and 4 K computer points. The simulated spectrum is shown at the top

at pH* 7. This implies that the ligand does not chelate *via* $S^-$ and $COO^-$. Gold(I) shows a strong preference for linear co-ordination in most of its complexes; [13] linear

positions cannot be spanned with five- or six-membered rings.

These results could be explained by the existence of the monomer (A) or dimer (B). However, the ion is very

$H_2O$–Au–SR (A)  RS–Au • • • Au–SR (B)



(C)

'soft' on either the Edwards α parameter scale [14] or the Klopman $\sigma_p$ scale: [15] $Hg^{II} > Au^{I} > Au^{III} >$ $Ag^{I} > Cu^{I} > Cd^{II}$, and has a very low affinity for *O*-bonded ligands. The only known examples are with a phosphine as *trans* ligand, *e.g.* $CH_3COO$–Au–$PPh_3$.[13] In addition we would have expected a bound water molecule to be readily substituted by S of *N*-acetylmethionine or N of histidine, but we have not been able to detect any binding of these to aurothiomalate by $^1H$ n.m.r. Gold–gold bonding is often observed in crystals of gold(I) complexes, although it is normally stabilised by bridging ligands. Unfortunately in the Raman spectrum the signal-to-noise ratio around 185 $cm^{-1}$, the region in which Au–Au stretching is expected,[16] was too low to be useful. Aurothiomalate did give a band at 340 $cm^{-1}$, confirming Au–S bonding.[13]

Thiolate S atoms are good bridging groups and it seems more likely that $Au^{I}$ attains linear co-ordination *via* polymeric structures such as the hexamer (C). Models show that small rings bring the negatively charged carboxylate groups into close proximity. This is electrostatically unfavourable and there may be a rapid interchange (on the n.m.r. time scale) between rings and chains.

*Influence of ionic strength.* A single set of aurothiomalate $^1H$ and $^{13}C$ n.m.r. resonances is observed for 0.2 mol $dm^{-3}$ solutions. Spectral changes occur as the concentration is increased to 0.4, 0.6, and 0.8 mol $dm^{-3}$. The proton resonance of $H^2$ shifts slightly to low field and broadens and a new broader CH peak appears, 0.1 p.p.m. to lower field of the original resonance. New carboxyl peaks B, C, E, and F appear in the $^{13}C$ spectrum, Figure 2, together with new $CH/CH_2$ peaks M and L. A slight shift of peak J to high field is observed. In the single-resonance $^{13}C$ n.m.r. spectrum, L is a doublet (*i.e.* CH) and its increase in intensity parallels the decrease in intensity of the doublet associated with peak J (more clearly observed with added salts). It was not

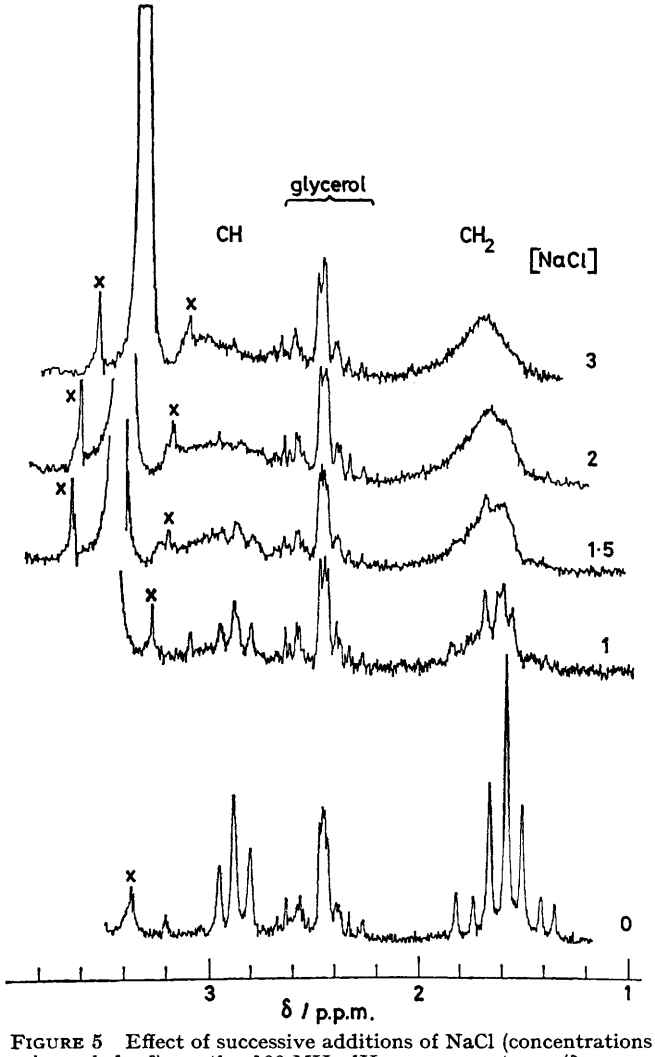



FIGURE 5 Effect of successive additions of NaCl (concentrations in mol $dm^{-3}$) on the 100-MHz $^1H$ n.m.r. spectrum (δ p.p.m. relative to $Bu^tOH$) of a 0.2 mol $dm^{-3}$ solution of aurothiomalate at pH* 7. Peaks labelled *x* are spinning side-bands. The HOD peak moves to higher field with increase in NaCl concentration

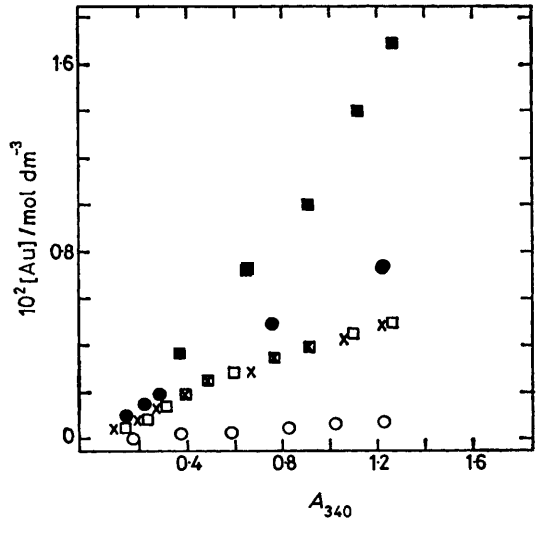



FIGURE 6 The variation of the absorbance at 340 nm with increase in aurothiomalate and added salt concentration: ■ no added salt, ● 1 mol $dm^{-3}$ NaCl, × 1 mol $dm^{-3}$ $Na_2[SO_4]$, □ 1 mol $dm^{-3}$ $Na[ClO_4]$, ○ 5 mol $dm^{-3}$ NaCl

possible to assign peak M. These results suggest that up to three different environments are possible for thiomalate.

As shown in Figures 2 and 5, similar spectral effects are induced by the addition of alkali-metal salts, including NaF, NaCl, NaI, $Na[ClO_4]$, $Na[NO_3]$, $Na_3[PO_4]$, CsCl, and CsI. Salts containing divalent or trivalent cations (*e.g.* $Ca^{2+}$, $Mg^{2+}$, or $Ln^{3+}$) cause precipitation, presumably because they cross-link carboxylate groups. A 5 mmol $dm^{-3}$ solution of aurothiomalate gives sharp $^1H$ n.m.r. resonances even in the presence of 1 mol $dm^{-3}$ NaCl, and the broadening in the $^1H$ n.m.r. spectrum of a 0.8 mol $dm^{-3}$ solution of aurothiomalate containing 3 mol $dm^{-3}$ NaCl is reversed immediately on dilution of the sample 100 times. These observations point to a reversible intermolecular association process at high ionic strengths. Curiously, the species are in relatively slow exchange ($<10\ s^{-1}$) on the n.m.r. time scale.

The association process can also be followed by electronic absorption spectroscopy. The solutions become a deeper yellow in the presence of salts. A new band appears at 340 nm, and its intensity increases approximately linearly with ionic strength, Figure 6. Its intensity ($\varepsilon > 4\,000\ dm^3\ mol^{-1}\ cm^{-1}$) suggests that it may be a charge-transfer band, perhaps due to $AuS_3$ centres. The possibility that $Au^{3+}$ is formed cannot be ruled out completely, although the n.m.r. dilution experiments seem to argue against this.

The six peaks in the carboxyl region of the $^{13}C$ n.m.r. spectrum of aurothiomalate at high ionic strength (Figure 7) collapse to two peaks, with intermediate shifts of 118.3 and 116.1 p.p.m., at 70 °C. This was reversible on cooling. Some of the broadening at 29 °C may therefore arise from chemical exchange of thiomalate between its three different environments.

A curious *phase separation* was observed for solutions of aurothiomalate containing NaCl (but not $Na_2[SO_4]$)

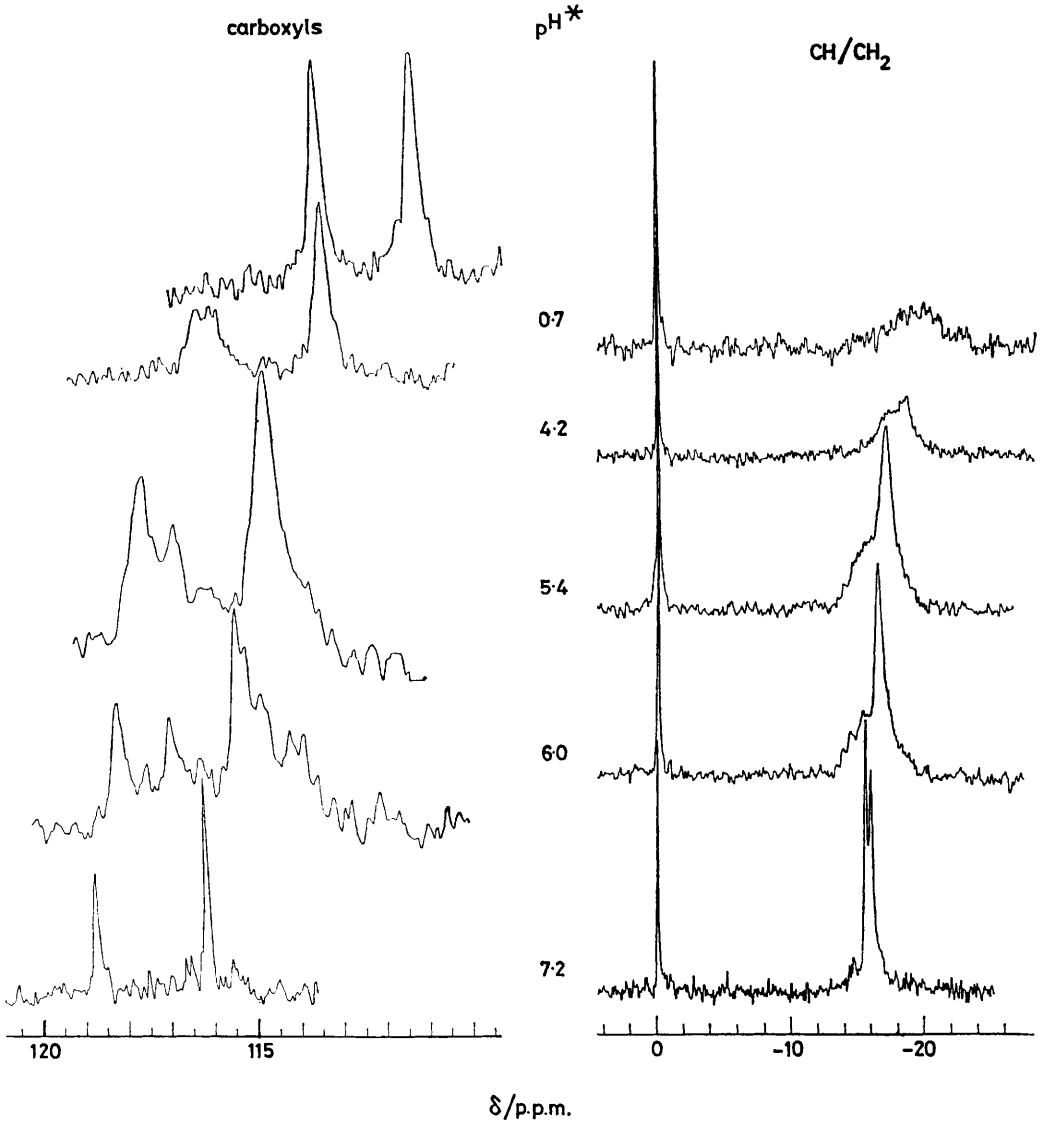
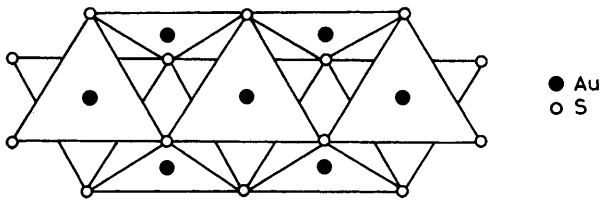



FIGURE 7 $^{13}C$-{$^1H$} n.m.r. spectra of a 0.4 mol $dm^{-3}$ solution of aurothiomalate at various pH* values

which had stood for a few hours at 8 °C. A deep yellow, viscous lower layer separated from a pale yellow upper layer. This was reversed by warming to ambient temperature.

The effects of salts on the n.m.r. and electronic absorption spectra of aurothiomalate seem to be independent of added anion, and therefore a specific association with $Au^I$ can be ruled out. The existence of up to three thiomalate environments seems more likely to arise from different polymer configurations. The molecular weight estimation indicates an increase in molecular weight with increasing salt concentration, although such measurements involve several assumptions. The effect of the cation may be to neutralise charges on the thiomalate carboxylates allowing closer approach of Au ions; besides chains and rings, a tube structure such as (D) may be possible. Here each $Au^I$ is surrounded by three bridging thiolate S atoms. Perhaps an inversion of such a structure, so that the carboxylate groups point inwards, could lead to a phase separation. As expected if the carboxylate groups play a major role in determining the structure of the polymeric gold(I) thiomalate, there is a strong pH dependence of the solution structure.




(D)

Other workers have noted that the structure of gold(I) thiolates are dominated by steric and electronic effects of the ligands,[17,18] and gold(I) thiomalate increases in molecular weight with a decrease in pH.

*pH dependence.* A dramatic broadening of both the $^1H$ and $^{13}C$ n.m.r. resonances of aurothiomalate occurs on lowering the pH, see Figures 1 and 7. There is a notable change in colour and viscosity of the solution: pH* $\geqslant$ 7, pale yellow; pH* 7—4.2, deeper yellow; pH* $<$ 4.2, pale yellow, viscous. The variations with pH* of the chemical shifts of the $^{13}C$ n.m.r. peaks in a 1.2 mol $dm^{-3}$ solution of thiomalate are compared to those of a 0.8 mol $dm^{-3}$ solution of aurothiomalate in Figure 8. The reported $pK_a$ values for thiomalic acid are 9.9 (SH), 4.4 ($CH_2CO_2H$), and 3.2 ($CHCO_2H$).[19] Although n.m.r. shifts associated with SH titration between pH* 9 and 11 are absent for aurothiomalate, confirming $S^-$ co-ordination, similar shifts occur between pH* 2 and 6 suggesting that the carboxyl groups are titrating normally and are not co-ordinated to Au. However, two differences are apparent. First, more than two carboxylate $^{13}C$ resonances are present in the spectrum of aurothiomalate from *ca.* pH* 6 to 4 (over which range the solution is deeper in colour), and secondly aurothiomalate continues to titrate below pH* 2. The latter may be attributable to protonation of co-ordinated $S^-$.

The extreme broadening of $^{13}C$ and $^1H$ n.m.r. resonances of aurothiomalate at low pH and the high viscosity of solutions suggests that a very high molecular weight polymer is formed. The titration is reversible

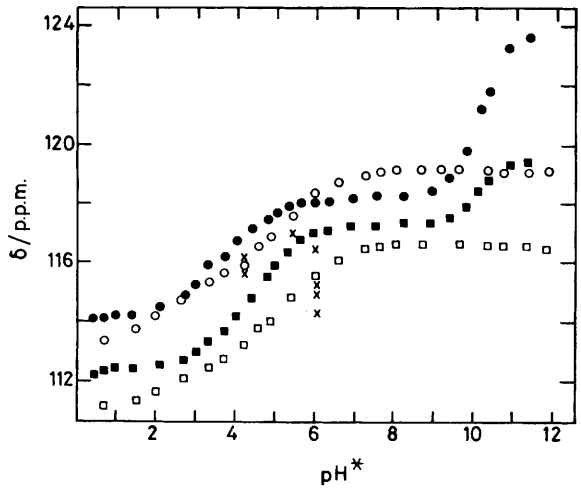



FIGURE 8 Variation of the $^{13}C$ n.m.r. chemical shifts of the carboxyl resonances of thiomalic acid (● $CHCOO^-$, ■ $CH_2COO^-$) and aurothiomalate (○ $CHCOO^-$, □ $CH_2COO^-$) with pH*. The extra peaks which appear in spectra of aurothiomalate between pH* 7 and 4 are labelled × (see Figure 7)

except that on return to pH* 7 the increase in ionic strength due to the addition of DCl (or $DNO_3$) and NaOD leads to a spectrum which resembles that in the presence of added salts.

*Conclusions.*—The structure of aurothiomalate in aqueous solution seems to be determined by the effective charges on the carboxylate groups. At low ionic strength the conformation of co-ordinated thiomalate is similar to that of free thiomalate, and binding to $Au^I$ is *via* S only. At high ionic strength, neutralisation of carboxylate charges by added cations allows the polymeric structure to become more compact and three types of co-ordinated thiomalate are now present. Specific structural changes also occur on lowering the pH and a very high molecular weight polymer is formed in strongly acidic solutions. We have demonstrated the advantage of $^{13}C$ over $^1H$ n.m.r. in studying these structural changes in solution, although its insensitivity does not allow the use of biologically meaningful drug concentrations (μmol $dm^{-3}$).

The polymerisation of aurothiomalate may be important in its biological activity. It is taken up by macrophages, cells which engulf high molecular weight species. However, as we shall describe further elsewhere, thiolate uptake and exchange by aurothiomalate is facile.[20,21]

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REFERENCES

[1] D. T. Walz, M. J. DiMartino, and B. M. Sutton in 'Anti-Inflammatory Agents,' Academic Press, New York, 1974, vol. 1, p. 217.
[2] P. J. Sadler, *Struct. and Bonding*, 1976, **29**, 171.
[3] C. F. Shaw, *Inorg. Perspect. Biol. Med.*, 1979, **2**, 287.
[4] D. H. Brown and W. E. Smith, *Chem. Soc. Rev.*, 1980, **9**, 217.
[5] A. A. Isab and P. J. Sadler, in preparation.
[6] P. J. Sadler, *Gold Bull.*, 1976, **9**, 110.
[7] M. Delepine, U.S.P. 1,994,213/1935.
[8] D. A. Yphantis, *Ann. N.Y. Acad. Sci.*, 1960, **88**, 586.
[9] J. W. Williams, K. E. van Holde, R. L. Baldwin, and H. Fujita, *Chem. Rev.*, 1958, **58**, 715.
[10] P. E. Hansen, J. Feeney, and G. C. K. Roberts, *J. Magn. Reson.*, 1975, **17**, 249.
[11] J. Feeney, P. E. Hansen, and G. C. K. Roberts, *J. Chem. Soc., Chem. Commun.*, 1974, 465.
[12] D. E. Leyden and D. B. Walters, *Spectrochim. Acta*, 1969, **A25**, 1869.
[13] R. J. Puddephatt, 'The Chemistry of Gold,' Elsevier, Amsterdam, 1978.
[14] (*a*) J. O. Edwards, *J. Am. Chem. Soc.*, 1954, **76**, 1540; (*b*) L. H. Skibsted and J. Bjerrum, *Acta Chem. Scand.*, 1977, **A31**, 155.
[15] G. Klopman, *J. Am. Chem. Soc.*, 1968, **90**, 223.
[16] F. J. Farrell and T. G. Spiro, *Inorg. Chem.*, 1971, **10**, 1606.
[17] S. Åkerström, *Ark. Kemi*, 1965, **24**, 505.
[18] S.-H. Hong, A. Olin, and R. Hesse, *Acta Chem. Scand.*, 1975, **A29**, 583.
[19] O. Mäkitie and A. Ilvonen, *Acta Chem. Scand.*, 1972, **26**, 847.
[20] A. A. Isab and P. J. Sadler, *J. Chem. Soc., Chem. Commun.*, 1976, 1051.
[21] A. A. Isab, Ph.D. Thesis, University of London, 1978.