^{13}C Nuclear Magnetic Resonance Detection of Thiol Exchange on Gold(I): Significance in Chemotherapy

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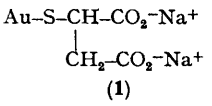
Summary Thiols such as *N*-acetyl-L-cysteine react with aurothiomalate in aqueous solution at pH 7 to give $Au_4(SR)_7^{3-}$ clusters which undergo fast exchange with RS^- but not RSH.

DISODIUM AUROTHIOMALATE ('Myocrisin') (**1**) is used clinically for the treatment of rheumatoid arthritis. Information on thiol exchange reactions at the $5d^{10}$ Au^I ion is of prime importance when a molecular basis of pharmacological action is considered[1] because of the *in vivo* abundance of free thiols such as cysteine and glutathione. Hitherto there has been little reported work in this area.

The Figure shows the effect of successive additions of thiomalic acid (tm-SH) on the high field region of the ^{13}C-{^1H} n.m.r. spectrum of 0·4 M (**1**) in D_2O at pH* 7 (meter reading, maintained with 10 M NaOD). [(**1**) was actually

obtained as the glycerol adduct and analysed satisfactorily (C, H, Au) as $C_4H_3O_4SNa_2Au\cdot 0{\cdot}3C_3H_8O_3\cdot 1H_2O$]. Up to a ratio Au : thiomalate of 1 : 1·75 all the thiomalate is in fast exchange on the n.m.r. time-scale, but beyond this free tm-SH peaks appear and increase in intensity. This suggests (i) the existence of a stable species with empirical formula† $Au_4(tm\text{-}S)^{3-}$ (mean lifetime > 8 ms), and (ii) that $Au(tm\text{-}S)_2^-$ does not form.



(1)

By analogy with recent findings for crystalline Cu^I-thiolates,[2] an Au_4S_7 cluster could have a structure based on a tetrahedron of trigonally planar co-ordinated Au^I ions located at the centres of opposite faces of a $(\mu_2 tm\text{-}S)_6$ octahedron with one additional (fluxional) terminal $tm\text{-}S^-$. Although isolation of the 1 : 2 complex $K[Au(SC_6F_6)_2]$ has been reported,[3] the observation that $Au(tm\text{-}S)_2^-$ does not form parallels the behaviour of Cu^I, $3d^{10}$, and Ag^I, $4d^{10}$, in solution.[4]

Fast exchange of bound ($tm\text{-}S^-$) and free thiomalate (tm-SH) is observed only when deprotonation is complete at pH* 11 ($pK_{SH} = 9{\cdot}9$ at $\mu = 1$[5]). On lowering the pH*, thiomalic acid appears to be ejected from the cluster, and at pH* 1 the spectrum resembles that of (1) itself together with peaks from free excess of thiomalic acid.

Addition of *N*-acetyl-L-cysteine (NAcC-SH) or mercaptoacetic acid, to 0·24—0·4 M solutions‡ of (1) at pH* 7 results in the displacement of some of the co-ordinated thiomalate. Separate resonances are observed for free and bound thiomalate and added thiol.

Thus integration shows that the ratio of bound $NAcC\text{-}S^-$: $tm\text{-}S^-$ increases from 1·3 : 1 after the addition of 1 equiv. of NAcC-SH to 3·1 : 1 in the presence of 2 equiv. Moreover, as with tm-SH, a ratio of bound thiol to Au^I of 1·75 : 1 is established, indicative of an $Au_4(SR)_7^{3-}$ species, which may now contain mixed thiols, in slow exchange with RSH. Addition of L-cysteine methyl ester, aminoethanethiol, penicillamine, or glutathione (γ-Glu-Cys-Gly) which all have amino-groups and lower pK_{SH} values, also leads to release of thiomalate, but only one set of (selectively broadened) resonances is observed for the added thiol. When 1 equiv. of γ-Glu-Cys-Gly is added, for example, one third of the thiomalate is released, and the Cys peaks are the most broadened and shifted ($CH_2 > CH$), indicative of an intermediate exchange rate.

If thiol exchange and displacement reactions such as these take place *in vivo*, the active species may not be a monomeric 1 : 1 Au^I thiomalate complex. Indeed, release of thiomalate may account for some of the toxic side-effects often encountered with this drug.

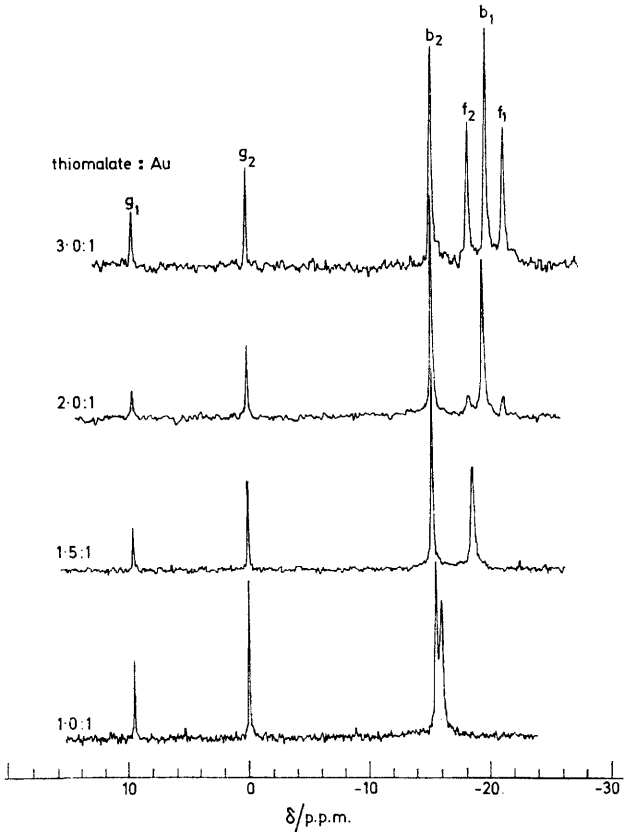


FIGURE. High-field region of the 15 MHz ^1H noise-decoupled ^{13}C n.m.r. spectrum of 0·4 M (1) in D_2O, pH* 7·2, 28 °C (2 s pulse interval, 14 μs pulse, 1500—6000 scans). Peak assignments: g_1 and g_2, CH and CH_2 (glycerol); b_1 and b_2, CH and CH_2 (bound thiomalate); and f_1 and f_2, CH and CH_2 (free thiomalate). Similar sets of peaks are seen in the CO_2^- region.

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† For simplicity, the negative charges on the carboxy groups of thiomalate are not included.

‡ In some experiments the 0·24 M solutions of (1) in H_2O marketed for clinical use were employed.

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[5] O. Mäkitie and A. Ilvonen, *Acta Chem. Scand.*, 1972, **26**, 847.