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¹³C AND ¹⁵N NMR STUDIES OF THE INTERACTION OF GOLD(I) THIOLATES WITH THIOUREA (¹³C AND ¹⁵N LABELLED)

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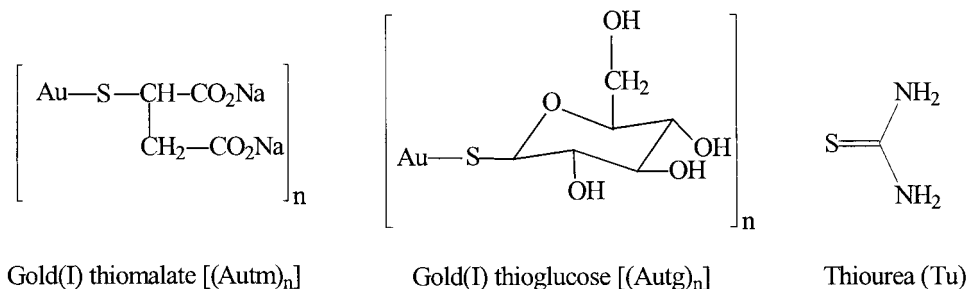
The interaction of gold(I) thiomalate [(Autm)_n] and gold(I) thioglucose [(Autg)_n] with thiourea (Tu) has been studied using ¹³C and ¹⁵N NMR spectroscopy. It is observed that thiourea binds to (Autm)_n to form a ternary complex, Tu–Au–tm. An upfield shift of 2.6 ppm in the >C=S resonance of Tu in ¹³C NMR and a downfield shift of 1.0 ppm in ¹⁵N NMR are indicative of gold(I) binding with Tu through sulfur only. In the case of (Autg)_n, the >C=S resonance of Tu remains unchanged throughout the titration, suggesting that Tu could not break the (Autg)_n polymer completely. Imidazolidine-2-thione (Imt) also shows a weak interaction towards (Autg)_n, similar to that of Tu.

Keywords: Gold(I) thiomalate; Gold(I) thioglucose; Thiourea; Thione; NMR

INTRODUCTION

Gold(I) thiolates [gold(I) thiomalate [(Autm)_n] (myocrisin) and gold(I) thioglucose [(Autg)_n] (solganol)] have been in clinical use for the treatment of rheumatoid arthritis for many years [1,2]. By various physical techniques, it has been established that gold(I) thiolate complexes exist as polymers in the solid state as well as in solution [3,4]. In the presence of other thiols, RSH, they undergo exchange reactions forming [Au(SR)₂][−] complexes [5,6]. With thiones, it is observed that (Autm)_n forms [$>C=S-Au-tm$] complexes [7,8], while there is no study describing the interaction of thiones with (Autg)_n. The present report describes the interaction of Tu with (Autm)_n and (Autg)_n in aqueous solution. To further study the interaction of (Autg)_n with thiones, its reaction with imidazolidine-2-thione (Imt) was examined. Although the interaction of Tu with (Autm)_n by ¹³C NMR has already been reported [9], we extend the study by using 5% ¹³C and ¹⁵N labelled thiourea to report ¹⁵N NMR chemical shifts and to observe changes in coupling constants (¹J_{C–N}) of Tu on its binding to (Autm)_n. The structures of (Autm)_n, (Autg)_n and Tu are shown in Scheme 1.

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SCHEME 1 Structures of gold(I) thiomalate, gold(I) thioglucose and thiourea.

EXPERIMENTAL

Chemicals

(Autm)_n and (Autg)_n were obtained from ICN K and K labs., New York. Thiourea, and D₂O were purchased from Fluka Chemical Co; 5% ¹³C enriched Tu was made by mixing 5% labelled with 95% unlabelled Tu by weight. Imt was prepared according to the published procedure [10].

NMR Measurements

¹³C NMR spectra were obtained on a Jeol JNM-LA 500 NMR spectrometer operating at a frequency of 125.65 MHz with ¹H broadband decoupling at 297 K. The acquisition conditions were: 32 k data points, 0.967 s acquisition time, 1.00 s pulse delay, 4.50 μs pulse width and an average of 10 000 accumulations. Chemical shifts are reported with respect to TMS. The pH of all solutions was around 7.0.

¹⁵N NMR spectra were recorded at 50.55 MHz, using ¹H broad band decoupling or DEPT 135° pulse sequences. Conditions were 0.721 s acquisition time, 2.50 s pulse delay, 22.00 μs pulse width and an average of 20 000 accumulations. A 2.1 M NH₄¹⁵NO₃ solution in D₂O was used as external reference; this lies at 375.1 ppm relative to pure CH₃NO₂ (380.2 ppm) [11].

RESULTS AND DISCUSSION

Interaction of Thiourea with (Autm)_n

¹³C NMR Spectroscopy

Figure 1(a) shows the ¹³C NMR of 0.05 M (Autm)_n and Fig. 1(b) that of Tu in D₂O at pH 7.0. The >C=S resonance of Tu remained unshifted when its spectra were recorded pH 3.5 and 11.0. In ¹H NMR, the resonance of NH₂ protons was not observed at any of the abovementioned pH values, because of exchange with D₂O. When 0.5 equivalents of Tu were added to 0.20 M (Autm)_n, the b₁ resonance of (Autm)_n shifted upfield and broadened, while b₃ and b₄ shifted downfield. The b₂ resonance remained almost unshifted throughout the titration. The solution of (Autm)_n was of a pale yellow colour and turned colourless after addition of Tu. An upfield shift was observed in

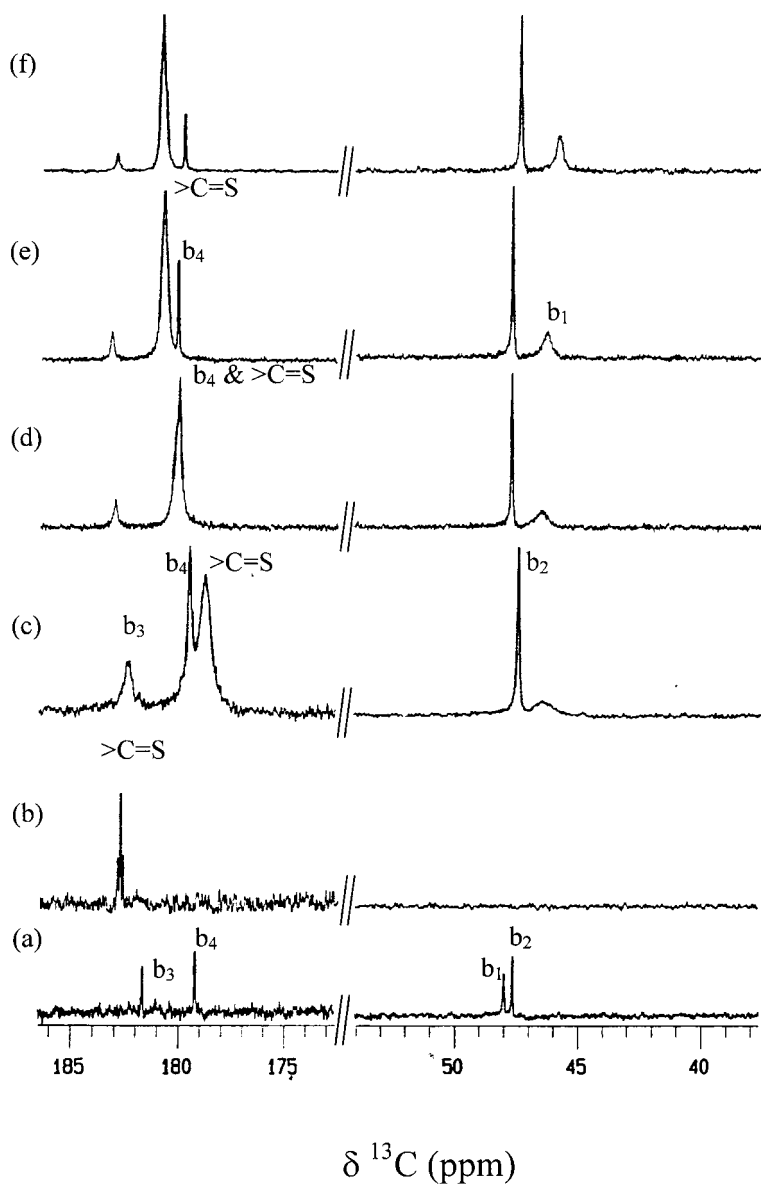


FIGURE 1 125.65 MHz $^{13}\text{C}\{^1\text{H}\}$ spectra of 0.20 M $(\text{Autm})_n:\text{Tu}$ at various mol ratios in D_2O : (a) 1:0; (b) 0:1; (c) 1:0.5; (d) 1:1; (e) 1:1.5; (f) 1:2.

the $>\text{C}=\text{S}$ resonance of Tu. A decrease in upfield shift in the $>\text{C}=\text{S}$ resonance of Tu was observed on further additions to $(\text{Autm})_n$ solution (Fig. 1(b)–(e)), showing exchange between free and bound Tu. The observed chemical shifts of various resonance are summarized in Table I. Because of the overlap of Tu resonances with b_4 , the coupling constants could not be obtained by ^{13}C NMR. However, the $^1J(\text{C}-\text{N})$ values were obtained using ^{15}N NMR spectroscopy.

TABLE I ^{13}C NMR chemical shift changes (ppm) with and without addition of Tu to $(\text{Autm})_n$ solution in D_2O

$(\text{Autm})_n : \text{Tu}$	b_1	b_2	b_3	b_4	$>\text{C}=\text{S}$
1:0	48.01	47.66	181.70	179.24	
0:1					182.75
1:0.5	46.77	47.80	182.71	179.89	179.19
1:1	46.61	47.80	183.08	180.11	180.11
1:1.5	46.37	47.80	183.30	180.21	180.86
1:2	46.24	47.81	183.40	180.26	181.28

^{15}N NMR Spectroscopy

Figure 2(a) shows the ^{15}N NMR spectrum of thiourea in H_2O at pH 7.0 (using D_2O as a deuterium lock and NH_4NO_3 as an external standard). There is a doublet for the Tu nitrogen at 107.7 ppm. When 0.5 equivalents of Tu were added to $(\text{Autm})_n$ solution, the resonance shifted downfield by 1.2 ppm. On further additions of Tu this resonance became sharper and shifted slightly upfield, indicating rapid exchange between free and bound Tu (Figs. 2(b)–(e)). Changes in ^{15}N chemical shifts to Tu resonance and coupling constant are given in Table II.

Gold(I) is found in AuS_2 coordination environments for various types of gold(I) thiolate complexes [1,2,12]. When excess thiol such as cysteine and glutathione are added to $[\text{Au}(\text{SR})_n]$ polymers, they usually eject RS^- groups forming $[\text{Au}(\text{thiolate})_2]^-$ species [2,6]. However, when thiones such as ergothionine [13], Imt [7] and Diaz (1,3-diazinane-2-thione) [7,8] are added to $(\text{Autm})_n$ solution, a ternary complex of the type $[\text{>C}=\text{S}-\text{Au}-\text{tm}]$ is usually formed without ejecting thiomalate. In the present study, on addition of Tu to $(\text{Autm})_n$, no free thiomalate resonances were observed in ^{13}C NMR (even at a ratio of 1:2 of $(\text{Autm})_n : \text{Tu}$), suggesting that it binds only as a thione ligand.

In ^{15}N NMR a downfield shift of 1.0 ppm in Tu resonances indicates the binding of Tu to gold(I). However, it does not give information about the nature of different species. This shift is too small to show the binding of Tu to gold(I) via nitrogen, since direct bonding through nitrogen should involve an upfield shift of at least 50 ppm in the NH_2 resonance of Tu as observed in Pt(II) complexes [14,15]. This confirms that Tu is bonded to gold(I) via sulfur alone. In ^{15}N NMR no separate resonance for free Tu was detected and this result provides no clear evidence about whether Tu forms a ternary complex, $[\text{Tu}-\text{Au}-\text{tm}]$, or a bis complex, $[\text{Au}(\text{Tu})_2]^+$. However, ^{15}N NMR is useful in providing coupling constants for this interaction.

Interaction of Thiourea and Imidazolidine-2-thione with $(\text{Autg})_n$

As shown in Fig. 3, the ^{13}C NMR spectrum of $(\text{Autg})_n$ consists of very broad resonances. Intense signals in the spectrum are assigned to aurothioglucose, while the broad peaks are due to some impurity [16,17]. When 0.5 equivalents of Tu were added, the solution remained yellow (in the case of $(\text{Autm})_n$ the solution became colourless). It is observed that peaks due to $(\text{Autg})_n$ became sharp and intense, while the impurity peaks remained broad. There was no shift in the $>\text{C}=\text{S}$ resonance of Tu (Fig. 3(c)). On addition of further equivalents of Tu, the positions of $(\text{Autg})_n$ resonances were also found to be unchanged (Fig. 3(d)–(e)). The $>\text{C}=\text{S}$ resonance of

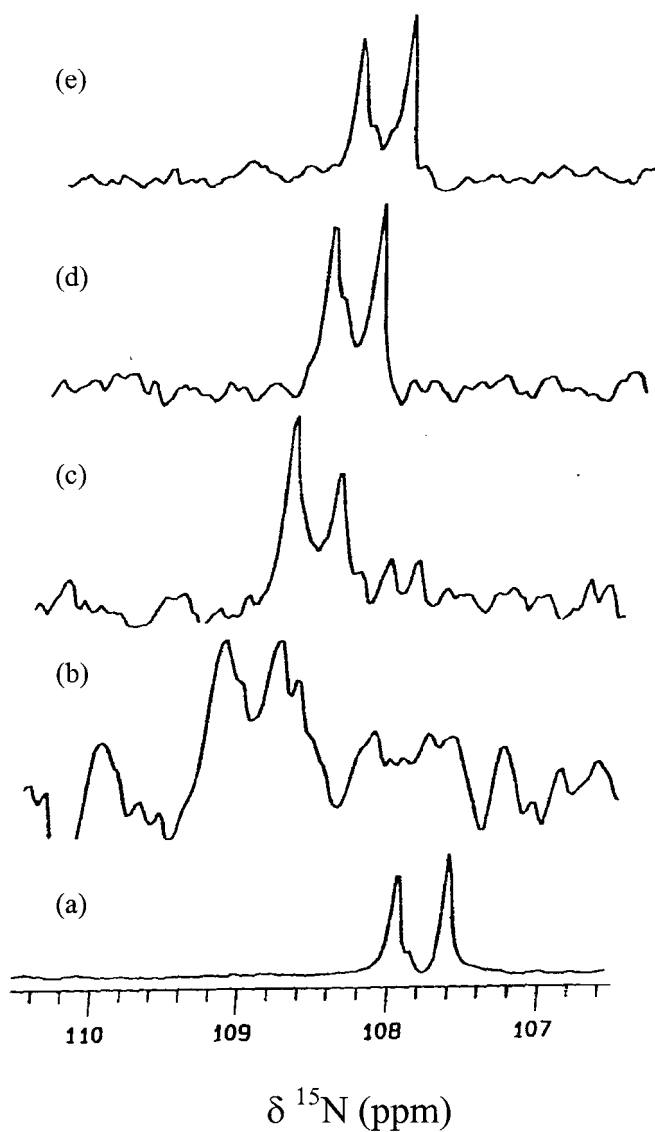


FIGURE 2 50.55 MHz $^{15}\text{N}\{^1\text{H}\}$ NMR spectra of 0.20 M $(\text{Autm})_n$: Tu at various mol ratios in H_2O : (a) 0 : 1; (b) 1 : 0.5; (c) 1 : 1; (d) 1 : 1.5; (e) 1 : 2.

TABLE II ^{15}N NMR chemical shift changes in Tu resonances on addition of $(\text{Autm})_n$ solution in H_2O

$(\text{Autm})_n$: Tu	$\delta^{15}\text{N}$	$^1J_{\text{C-N}}$ (Hz)
0 : 1	107.71	16.7
1 : 0.5	109.15	17.7
1 : 1	108.70	15.0
1 : 1.5	108.51	15.0
1 : 2	108.39	14.0

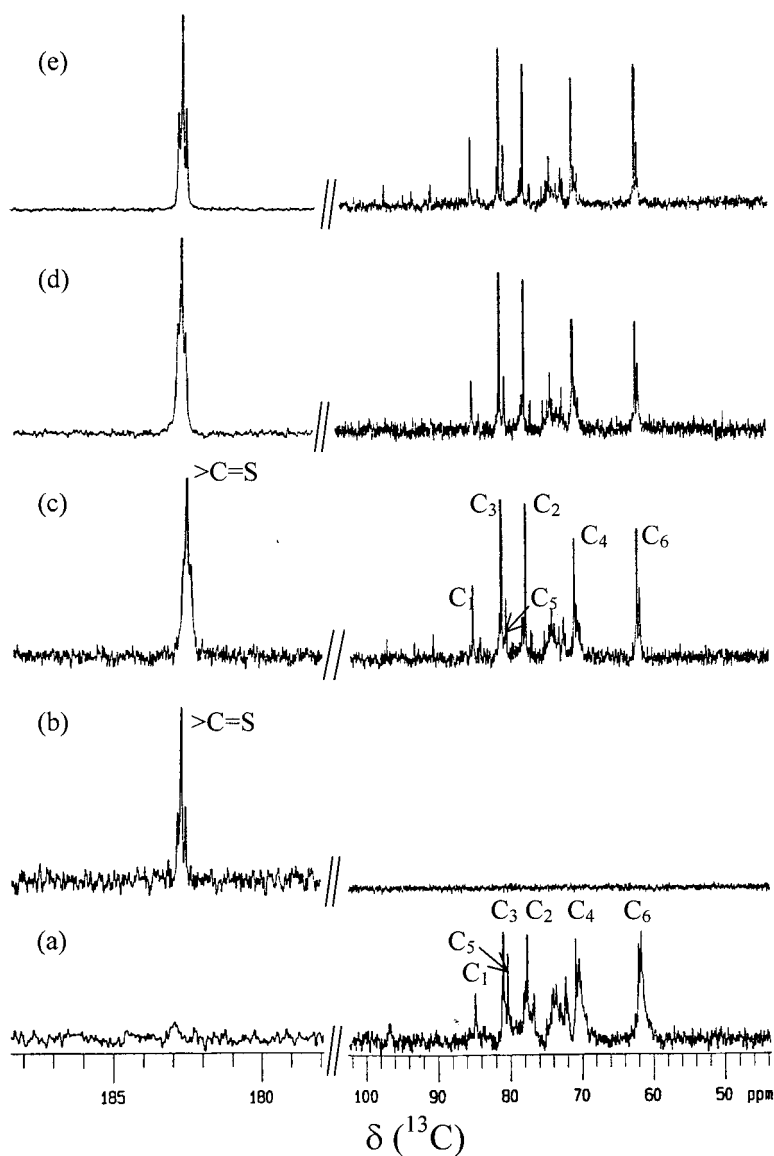


FIGURE 3 125.65 MHz $^{13}\text{C}\{^1\text{H}\}$ spectra of 0.10 M $(\text{Autg})_n$:Tu at various mol ratios in D_2O : (a) 1:0; (b) 0:1; (c) 1:0.5; (d) 1:1; (e) 1:2.

Tu remained almost unshifted throughout the titration. Similarly, in ^{15}N NMR, the Tu resonance at 107 ppm was not affected by its addition to $(\text{Autg})_n$. These observations show that Tu does not disrupt the $(\text{Autg})_n$ polymer completely and that there is only a weak interaction between thiourea and $(\text{Autg})_n$.

To further confirm the observation that thiones bind to $(\text{Autg})_n$ weakly, the interaction of $(\text{Autg})_n$ with Imt was investigated. It was found that the C-2 resonance of Imt remained unshifted on addition of various equivalents to $(\text{Autg})_n$. Thus $(\text{Autg})_n$

polymer does not undergo exchange reactions with thione ligands, completely. On the other hand, reactions of thiol [16] and CN^- [17] result in the loss of polymeric structure, leading to the formation of $[\text{Au}(\text{SR})_2]^-$ and $[\text{Au}(\text{CN})_2]^-$ (or $[\text{tg-Au-CN}]^-$) species, respectively. From this study it can be concluded that although both gold thiolate drugs are polymeric in nature, their reactivities towards thiones are different. It seems that the Au-S bond in $(\text{Autg})_n$ is stronger than that in $(\text{Autm})_n$.

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