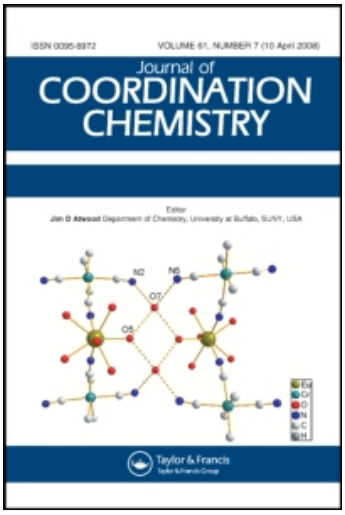

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Anvarhusein A. Isab[a]; Abdul Rahman A. Al-Arfaj[a]; M. Naseem Akhtar[a]
[a] Department of Chemistry, King Fahd University of Petroleum and Minerals, Dhahran, Saudi Arabia

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THE REDOX REACTION OF GOLD(I)-THIOMALATE IN THE PRESENCE OF SELENOUREA

ANVARHUSEIN A. ISAB,* ABDUL RAHMAN A. AL-ARFAJ and M. NASEEM AKHTAR

Department of Chemistry, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

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The interaction of thiourea (TU) and selenourea (SeU) with aurothiomalate (Autm) has been studied by ^{13}C NMR spectroscopy. At a 1:1 ratio of TU:Autm, TU binds to Autm forming a ternary TU-Au-tm complex. However, in the presence of SeU at various mol ratios, some of the thiomalate (Htm) was ejected from Autm as a free ligand, oxidized to tm_2, and gold(I) was reduced to metallic gold. This redox reaction is observed only in the presence of SeU which may be acting as a catalyst.

KEYWORDS: gold, thiomalic acid, urea, selenourea, nmr

INTRODUCTION

Gold(I)-thiomalate (Autm) has been used as an anti-arthritic drug since 1929.[1–3] The drug has an oligomeric structure.[4–6] The interaction of Autm with various ligands, *e.g.*, CN^-,[7,8] disulfides,[9] thiols,[10,11] thiones,[12,13] bovine serum albumin[14] and human red blood cells[15] has been reported in the literature. Most of these ligands, except CN^-, contain a thiol or thione which acts as a binding sites for gold(I).

In the presence of excess thiol (RSH) or CN^-, Htm of Autm is ejected to form $Au(SR)_2^-$.[10,11] However, in the presence of thiones, it forms only a ternary complex of the type >C=S-Autm.[12,13]

Although much work has been done on the complexation of Autm with sulfur-containing ligands, very little is known about the interaction of selenol- or selenone-containing ligands with gold(I). However, it has recently been reported that Autm and gold(I) thioglucose inhibit glutathione peroxidase present in human red bloods cells (which contains selenoate as an active binding site).[16,17] We have recently reported the exchange reaction of Autm with 3-selenopropionate ($^-O_2C-CH_2-CH_2-Se^-$) in aqueous solution.[18]

Since there is very little information available regarding the interaction of selenol- or selenone-containing ligands with gold(I), it should be of interest to study the interaction of Autm with selenium-containing ligands such as selenourea (SeU).

* Author for correspondence.

In this paper, we report the interactions of thiourea (TU) and selenourea (SeU) with Autm in an aqueous solution, as followed by ^{13}C NMR spectroscopy. While both ligands were found to bind to Autm it has been shown that SeU binds to Autm more strongly than TU.

EXPERIMENTAL

Chemicals

Autm was obtained from ICN K and K Laboratories, Plainview, New York. It was analyzed as Autm.0.33glycerol.H_2O.[10,11,19] Thiourea and selenourea were obtained from Fluka Chemical Co. and were used without purification.

NMR Measurements

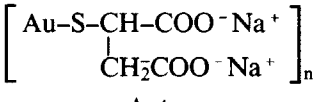
^{13}C NMR spectra were measured at 50.03 MHz on a Varian XL-200 spectrometer operating in the pulsed Fourier transform mode. The ^{13}C NMR measurements were made with coherent off-resonance ^1H decoupling or with broad-band ^1H decoupling. ^{13}C NMR chemical shifts were measured relative to the CH_2 resonance of internal glycerol (g_2) which occurs at 63.33 ppm relative to $SiMe_4$.

pH Measurements

All pH measurements were made at 24°C with a Fisher Accumet pH meter (model 620) equipped with a Fisher microprobe combination pH electrode. The term PH^* is used to indicate the actual meter reading for D_2O solutions with no correction for deuterium isotope effects.

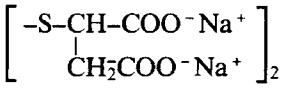
Explanation of Resonance Assignments

The ^{13}C NMR resonance assignments of gold(I)-thiomalate(Autm) and thiomalic disulfide (tm_2) are as follows:



Autm

$-CH = b_1$, $-CH_2 = b_2$, $-CH\text{-}CO_2^- = b_3$ and $-CH_2\text{-}CO_2^- = b_4$



tm_2 (thiomalic disulfide)

$-CH = d_1$, $-CH_2 = d_2$, $-CH\text{-}CO_2^- = d_3$ and $-CH_2 - CO_2^- = d_4$
$-CH = g_1$ and $-CH_2 = g_2$ for glycerol as internal reference.

RESULTS AND DISCUSSION

Figure 1A shows the ^{13}C NMR spectrum of Autm in D_2O solution at pH* 7.40. The solution of Autm was a pale yellow colour. Addition of TU as a solid to the Autm (0.30M, D_2O) solution at various mol ratios resulted in a higher field shift of the b_1 resonance from 47.81 to 46.50 ppm as shown in Fig 1B to 1E. The solution became colourless as soon as TU was added. The b_2 resonance remained almost unshifted throughout the titration. The b_3 resonance shifted from 181.98 ppm to 183.08 ppm and the b_4 resonance shifted from 179.44 to 181.22 ppm (see Table 1). The thione

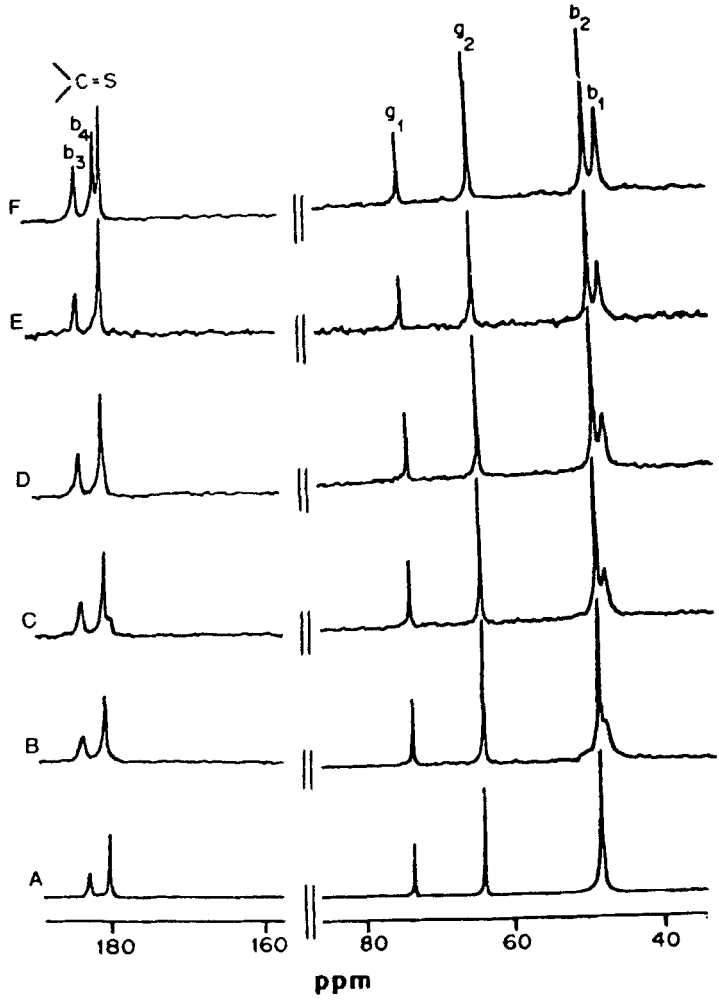


Figure 1 50 MHz ^1H noise-decoupled ^{13}C NMR spectra of Autm:TU at various mol ratios (pH* is 7.4 for all samples): (A) 0.300:0 M, (B) 0.300:0.075 M, (C) 0.300:0.150 M, (D) 0.300:0.225 M, (E) 0.300:0.300 M and (F) 0.300:0.600 M.

Table 1 ^{13}C NMR chemical shifts of Autm: thiourea (TU) at various mol ratios. The pH* was 7.40 throughout the titration. The values are taken from Fig. 1; some of the spectra are not shown in the figure.

Spectrum	Autm:TU	b_3	b_4	b_2	b_1	C of TU
–	0:1					182.64
A	1:0	181.98	179.46	47.81	47.81	
B	1:0.25	182.65	179.85	47.86	47.00	[a]
C	1:0.50	183.02	180.09	47.87	46.79	179.27
D	1:0.75	183.23	180.22	47.85	46.58	179.88
E	1:1	183.37	180.30	47.86	46.50	180.30
F	1:2	183.62	180.41	47.82	46.13	181.22

[a] The resonance is too small to detect or may be overlapped with other resonances.

carbon resonance of TU moved from free chemical shifts of 182.64 ppm to 180.30 ppm at a 1:1 ratio of Autm:TU and to 181.22 ppm at a 1:2 ratio of Autm:TU.

Figure 2A shows a ^{13}C NMR spectrum of a Autm:SeU solution (0.30:0.075 M) at a 1:0.25 ratio in D_2O. SeU was added as a solid to the Autm solution and pH* was kept at 7.40 throughout the titration. The solution was kept under an N_2 atmosphere and became colourless after the first addition of SeU. The b_2 resonance remained unshifted whereas the b_1 resonance shifted to a higher field of 46.99 ppm. The selenone resonance of SeU appeared at 169.44 ppm. Figure 2B shows the spectrum of Autm: SeU at a 1:0.5 ratio. The b_2 resonance is shifted further upfield, whereas the b_1 resonance remains unshifted. At this ratio some metallic gold appears in the NMR tube. The two disulfide resonances b_1 and b_2 of thiomalate appear at 54.42 (54.42 and 54.07 as a doublet) and 41.11 ppm, respectively. The selenone resonance of SeU shifts toward a free position at 171.15 ppm. The b_3 and b_4 resonances appear at 183.33 and 180.28 ppm respectively (See Table 2). As concentrations of SeU are increased, the disulfides of free thiomalate resonances increase in intensity and the amount of metallic gold also increases in the NMR tube. There is no sign of metallic selenium in the NMR tube. Beyond a ratio of 1:1 (Autm:SeU), colourless precipitates appear.

Autm in the presence of 1 equivalent of thiones (>C=S) forms ternary tm-Au←S=C< complexes. However, in the presence of thiols, Htm of Autm is ejected, forming $Au(SR)_2^-$.[11]

Table 2 ^{13}C NMR chemical shifts of Autm: selenourea (SeU) at various mol ratios. The pH* was 7.40 throughout the titration. The values are taken from Fig. 2; some of the spectra are not shown in the figure.

Spectrum	Autm:SeU	b_3	b_4	b_2	b_1	d_2	d_1	C of SeU
	0:1							176.55
	1:0	181.98	179.46	47.81	47.81			
A	1:0.25	182.74	179.93	47.87	46.99			169.94
B	1:0.50	183.33	180.28	47.84	46.61	41.13	54.42 54.07	171.15
C	1:0.75	183.72	180.47	47.82	46.10	41.11	54.41 54.05	172.68
D	1:1	183.92	180.60	47.85	45.96	41.13	54.42 54.07	173.43

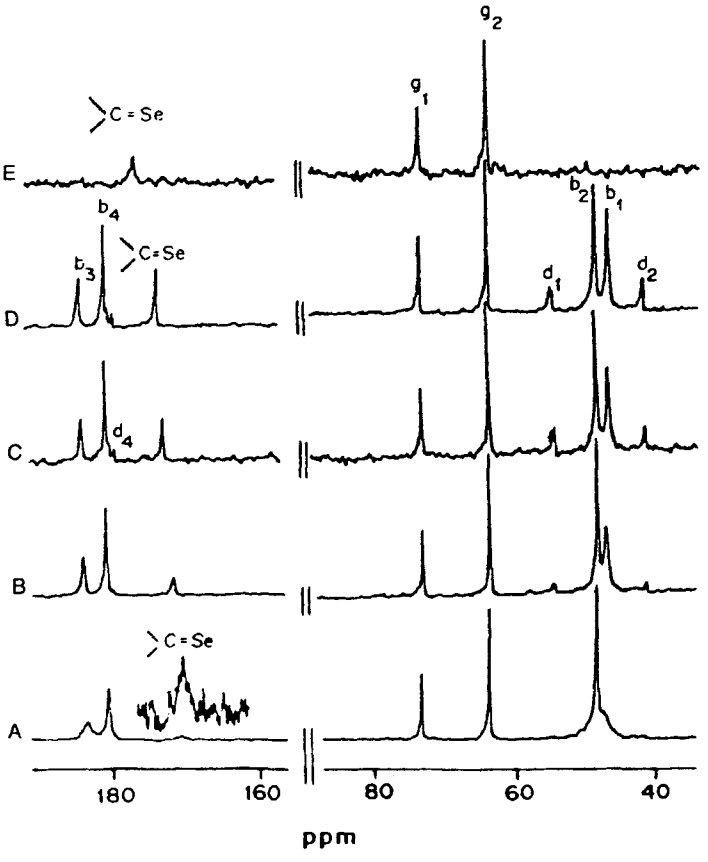


Figure 2 50 MHz ^1H noise-decoupled ^{13}C NMR spectra of Autm:SeU at various mol ratios (pH* is 7.4 for all samples): (A) 0.300:0.075 M, (B) 0.300:0.150 M, (C) 0.300:0.225 M, (D) 0.300:0.300 M and (E) 0:0.300 M.

In this study it has been shown that even in the presence of 1:2 Autm:TU, no free Htm resonances appear, indicating that it only forms tm-Au-TU complex and excess TU is in fast exchange with bound TU. In the presence of SeU, some Htm is ejected as the free ligand in solution, and is consequently oxidized to $(tm)_2$ as gold(I) is reduced to metallic gold.

We have recently reported[18] the exchange reaction of Autm with 3-selenopropionate using ^{13}C NMR spectroscopy. At a 1:2 ratio of Autm:3-selenopropionate, 3-selenopropionate binds to gold(I) ejecting thiomalate (Htm) as a free ligand in aqueous solution to form $Au(SeR)_2^-$. In this case, the thiomalate which was released from Autm remained in the thiol form and was not oxidised to the disulfide.

The results presented here are the first examples which clearly demonstrate that a redox reaction of Autm takes place, mediated by SeU. Only metallic gold appeared in the NMR tube and no free selenium metal was formed. However, in

the presence of other ligands such as CN^- or thiols, Htm was ejected as a free ligand but always remained in the thiol (Htm) form and never oxidised to disulfide.[7,8,10,11]

Goddard *et al.*[20,21] have determined the stability constants of metal complexes of selenourea as well as of thiourea. They reported that the order of affinity towards a 'class b' metal like Hg(II) is Se>S>>O. We have also found, while studying the binding of Hg^{+2} with *L*-methionine and *D,L*-selenomethionine, that the ^{13}C NMR chemical shift of the methyl resonance was shifted by 3.56 ppm in the presence of *L*-methionine.[22] However, it shifted by 9.29 ppm in the presence of *D,L*-selenomethionine.[23] Log K_f values of $CH_3Hg(II)$ for *L*-methionine and *D,L*-selenomethionine were reported to be 1.94 and 3.73, respectively, in an acidic

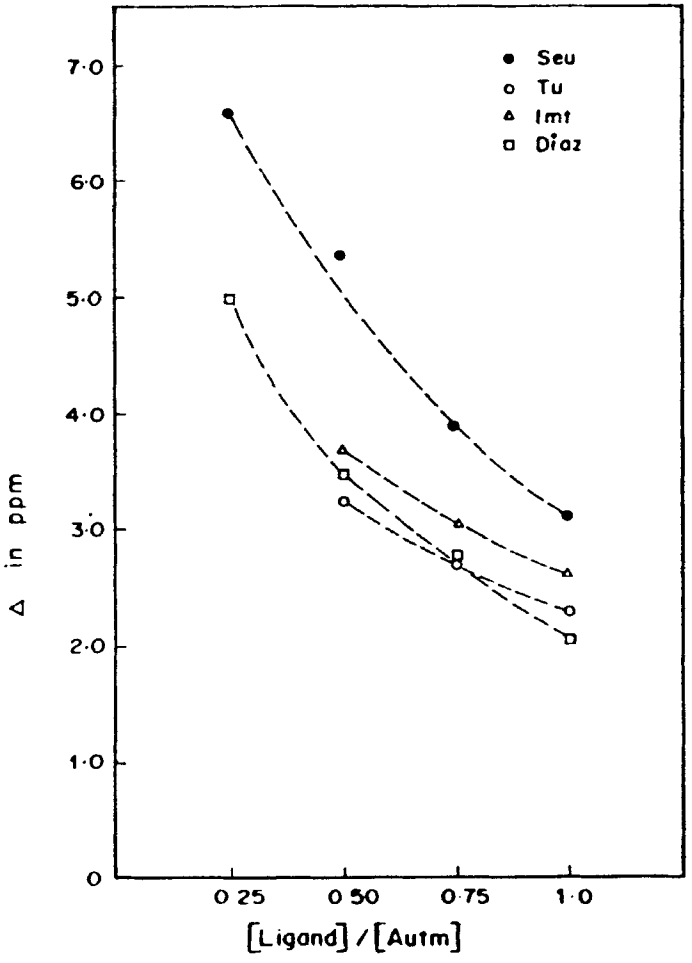


Figure 3 ^{13}C NMR chemical shift differences (in ppm) between free and bound ligand after binding with Autm as a function of concentration. Imidazolidine-2-thione (Imt) and diazinane-2-thione (Diaz) data are taken from refs. 13 and 12, respectively.

aqueous solution.[24,25] Since Au(I) is isoelectronic with Hg(II) it is not surprising that gold(I) binds more strongly to selenourea than to thiourea.

TU and SeU also reacts with Autm; the b_1 resonance is shifted by 1.68 ppm and 1.85 ppm, respectively, at a 1:1 ratio of TU:Autm and SeU:Autm (see Tables 1 and 2). As shown in Figure 3, the selenone resonance of SeU shifted more, as compared to the thione resonance, at a 1:1 ratio of Autm:thione (where thione = thiourea, imidazolidine-2-thione and 1,3-diazinine-2-thione).[12,13]

The formation constants for SeU and Au(I) have not been reported in the literature. However the formation constants for the $CH_3Hg(II)$-selenol complexes were found to be 0.1 to 1.2 log K units larger than corresponding thiol complexes.[26] These data along with X-ray structural results suggest that Hg-Se binding is stronger than in the analogus Hg-S complex.[27–29] Since Hg(II) is isoelectronic with gold(I), it can be concluded that gold(I) binds to SeU more strongly than to TU. This conclusion is based on the following three factors:

(i) the b_1 resonance of Autm shifts more in the presence of SeU as compared to TU,
(ii) tm^- is ejected from Autm only in the presence of SeU and not in the presence of TU, and
(iii) the ^{13}C NMR resonance of >C=Se shifts more than that of >C=S after binding with gold(I).

Acknowledgements

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