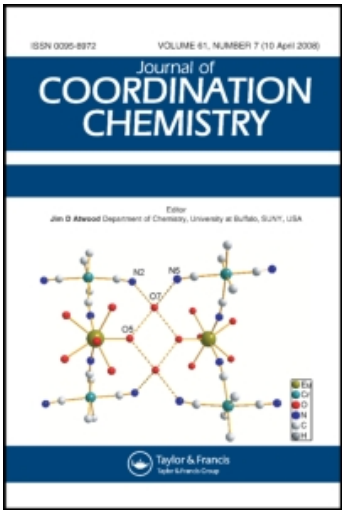

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COMPARATIVE ^{13}C NMR STUDIES OF COMPLEXATION OF IMIDAZOLIDINE-2-SELENONE AND ITS ANALOGOUS THIONE TO GOLD(I) THIOMALATE

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COMPARATIVE ^{13}C NMR STUDIES OF COMPLEXATION OF IMIDAZOLIDINE-2-SELENONE AND ITS ANALOGOUS THIONE TO GOLD(I) THIOMALATE

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The interaction of gold(I) thiomalate $(AuStm)_n$ (Myocrisin) with imidazolidine-2-selenone (SeImt) was studied in an aqueous solution at pH 7.40 using ^{13}C NMR spectroscopy. It was found that SeImt binds more strongly to $(AuStm)_n$ than imidazolidine-2-thione and its derivatives as determined by ^{13}C NMR spectroscopy. SeImt reacts differently with $Au(Stm)_2^-$, as compared to $(AuStm)_n$. With $(AuStm)_n$, SeImt forms a ternary complex of ImtSe-Au-Stm, releasing free Stm^- to solution. Redox reaction of gold(I) to metallic gold and free thiomalate (Stm^-) to disulfide $(Stm)_2$ occurs when $Au(Stm)_2^-$ reacts with SeImt.

Keywords: gold; selenone; thione; thiomalate; nm

INTRODUCTION

The exchange reactions of gold(I) drugs with thiols, CN^- and selenols have been reported in the literature.[1–4] These ligands upon exchange with $(AuStm)_n$ usually release Stm^- (thiomalte) as a free ligand forming $Au(SR)_2^-$,[5–7] $Au(CN)_2^-$,[8–9] or $Au(selenol)_2^-$,[10,11] type complexes. Thiones, on the other hand, do not release Stm^- as a free ligand; instead they form an asymmetric *bis* complex of the type C=S —Au—Stm.[12–14] To our knowledge no report has appeared in the literature on the interaction of selenone with any gold(I) complexes. Selenium-containing

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ligands, *e.g.*, selenols or selenones are expected to form more stable complexes with class B metal ions such as gold(I) because they are considered to be softer Lewis bases than sulfur.[15]

In the present study we report the interaction of SeImt with $(AuStm)_n$ and compare the analogous binding studies of the imidzolidine-2-thione (Imt) ligand with $(AuStm)_n$. The importance of studies of this nature is stressed because it has been reported that glutathione peroxidase is present in the human red blood cells which contain Se-H group[16] at a 2×10^{-6} M concentration. This glutathione peroxidase may react with gold(I)-thiolates causing side effects. The present study would indeed enhance our understanding of the reaction between gold(I) drugs and selenium-containing proteins and enzymes.[17,18]

EXPERIMENTAL

SeImt was prepared as described in the literature.[19] Gold(I) thiomalate $(AuStm)_n$ was obtained from ICN K & K Labs., Plainview, New York. The 99.7% D_2O, 40% NaOD in D_2O 35% DCl in D_2O, thiomalic acid (HStm) and KCN were obtained from Fluka Chemical Co.

NMR Measurements

^{13}C NMR spectra were measured at 50.30 MHz on a Varian XL-200 spectrometer operating in the pulsed Fourier transform mode. ^{13}C NMR measurements were carried out with coherent off-resonance ^1H decoupling or with broad-band ^1H decoupling. ^{13}C NMR chemical shifts were measured relative to internal reference dioxane at 67.40 ppm upfield from $SiMe_4$. All spectra are the result of 10,000–20,000 scans.

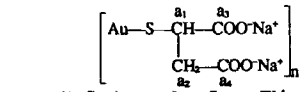
pH Measurements

All pH measurements were made at 22°C with a Fisher Accument pH meter (model 620) equipped with a Fischer microprobe combination pH electrode. The term pH* is used to indicate the actual meter reading for D_2O solutions without any correction for deutrium isotope effects.

Resonance Assignments

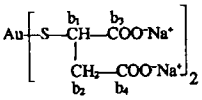
Resonance assignments of various gold(I) complexes and ligands is given in Scheme I.

Resonance assignments of various gold(I) complexes and ligands



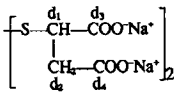
(AuStm)$_n$ where **Stm$^-$ = Thiomalate**

—*C*H=a_1, —*C*H$_2$=a_2, —*C*H—*C*O$_2^-$=a_3, —*C*H$_2$—*C*O$_2^-$=a_4



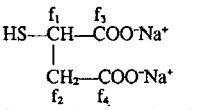
Au(Stm)$^-_2$

—*C*H=b_1, —*C*H$_2$=b_2, —*C*H—*C*O$_2^-$=b_3, —*C*H$_2$—*C*O$_2^-$=b_4



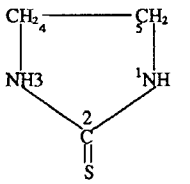
(Stm)$_2$ (Thiomalic disulfide)

—*C*H=d_1, —*C*H$_2$=d_2, —*C*H—*C*O$_2^-$=d_3, —*C*H$_2$—*C*O$_2^-$=d_4

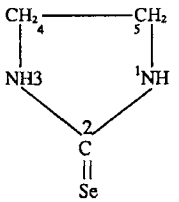


HStm (Thiomalic acid)

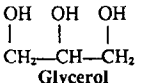
—*C*H=f_1, —*C*H$_2$=f_2, —*C*H—*C*O$_2^-$=f_3, —*C*H$_2$—*C*O$_2^-$=f_4



Imidazolidine-2-thione (Imt)



Imidazolidine-2-selenone (SeImt)



Glycerol

—CH=g_1 and —CH$_2$=g_2

Scheme 1

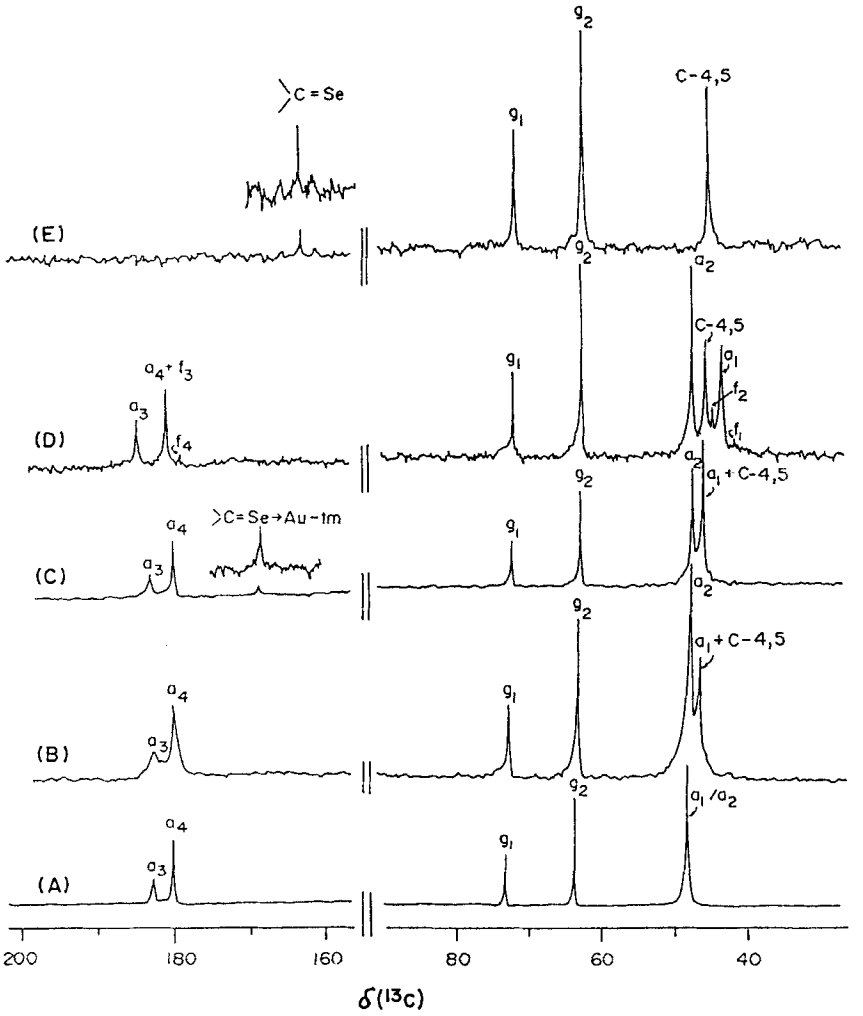


FIGURE 1 50 MHz ^{1}H noise-decoupled ^{13}C NMR spectra of 0.20 M $(AuStm)_n$:SeImt at pH* 7.40 at various mol ratios: (A) 1.00:0.00; (B) 1.00:0.25; (C)1.00:0.50; (D) 1.00:0.75; (E) 0.00:1.00.

RESULTS AND DISCUSSION

Figure 1A shows the ^{13}C NMR spectrum of 0.20 M $(AuStm)_n$ in 2.0 cm^3 D_2O solution at pH* 7.40. N_2 gas was bubbled through the solution. The a_2 and a_1 resonances of $(AuStm)_n$ appeared at 47.81 ppm, a_3 and a_4 resonances were observed at 181.98 and 179.46 ppm, respectively

TABLE I ^{13}C NMR Chemical Shifts (ppm) for $(AuStm)_n$: SeImt at various Mol Ratios. The pH* of the Solution was 7.40 Throughout the Titration. Notations are Taken from Figure 1

Spectrum	$Au(Stm)_n$:SeImt	a_3	a_4	f_3	f_4	C-2	a_2	a_1	f_2	f_1	C-4,5
1A	1:0.00	181.98	179.46				47.81	47.81			
1B	1:0.25	182.57	179.91				47.79	46.51			46.51
1C	1:0.50	183.28	180.26			168.92	47.84	46.51			46.51
1D	1:0.75	184.84	181.07	181.07	180.39	*	48.06	44.08	45.42	42.17	46.23
1E	0:1.00					162.97					46.21
	HStm			181.41	180.39				45.11	42.17	

*The resonance was not observed.

(Table I). When 0.050 M equivalent of SeImt was added as a solid to the $(AuStm)_n$ solution, the solution remained pale yellow. The a_1 resonance shifted to 46.51 ppm, and the C-4,5 resonance of SeImt overlapped with the a_1 resonance. No significant shift was observed in the other resonances. The C-2 resonance of SeImt was not observed at this stage, although a slight broadening of the other resonances was observed. When a further 0.05 M (0.10 M total) of SeImt was added to the $(AuStm)_n$ solution, the solution became colourless. The a_1 resonance increased in intensity because of the overlapping C-4,5 resonance. At this point, the C-2 resonance of SeImt was observed at 168.92 ppm. There was no significant chemical shift change observed in the other resonances. When 0.15 M (total) of SeImt was added to the $(AuStm)_n$, the solution remained colourless. However, during the overnight run, a precipitate was observed in the NMR tube. The a_1 resonance was shifted further upfield as noted in Table I and free thiomalate (HStm) resonances (f_1, f_2, f_3 and f_4) were also observed in the spectrum.

The chemical shifts of free and bound SeImt to $(AuStm)_n$ are given in Table I. The C-2 resonance of SeImt was not observed at the 1:0.75 mol ratio of $(AuStm)_n$: SeImt. Further titration was discontinued because of precipitation at this mol ratio.

Figure 2A shows the ^{13}C NMR spectrum of 0.20 M $(AuStm)_n$: 0.180 M HStm in 2.0 cm^3 of D_2O at pH* 7.40. Since $(AuStm)_n$ itself contains about 10% free Stm^- as a free ligand,[20,21] the actual species would be $Au(Stm)_2^-$. The b_1, b_2, b_3 and b_4 resonances due to $Au(Stm)_2^-$ appeared in the spectrum; the chemical shifts of these resonances are given in Table II. No f_2 and f_1 resonances due to free Stm^- appeared in the spectrum. When 0.10 M equivalent of SeImt was added to the above solution, the d_1, d_2, d_3 and d_4 resonances which are due to the thiomalic disulfide $(Stm)_2$ appeared in the spectrum as shown in Figure 2B. The chemical shifts of these resonances are given in Table II. The C-4,5 resonance of SeImt also appeared at 46.48 ppm. Some metallic gold appeared in the NMR tube. When further 0.10 M (0.20 M total) SeImt was added to the above solution, the disulfide resonance of $(Stm)_2$ increased in intensity compared to the g_2 resonance of glycerol as shown in Figure 2C. It is to be noted that there is no C-2 resonance of SeImt observed in Figure 2B or 2C. After reaching the ratio of 1:1 ($Au(Stm)_2^-$: SeImt), solid KCN of 1 and 2 mol equivalent were added to the above solution. As shown in Figure 2D and 2E, the b_2 and d_2 resonances decreased and increased in intensity, respectively. The $Au(CN)_2^-$ resonance was also observed at 154.04 ppm.[8,9]

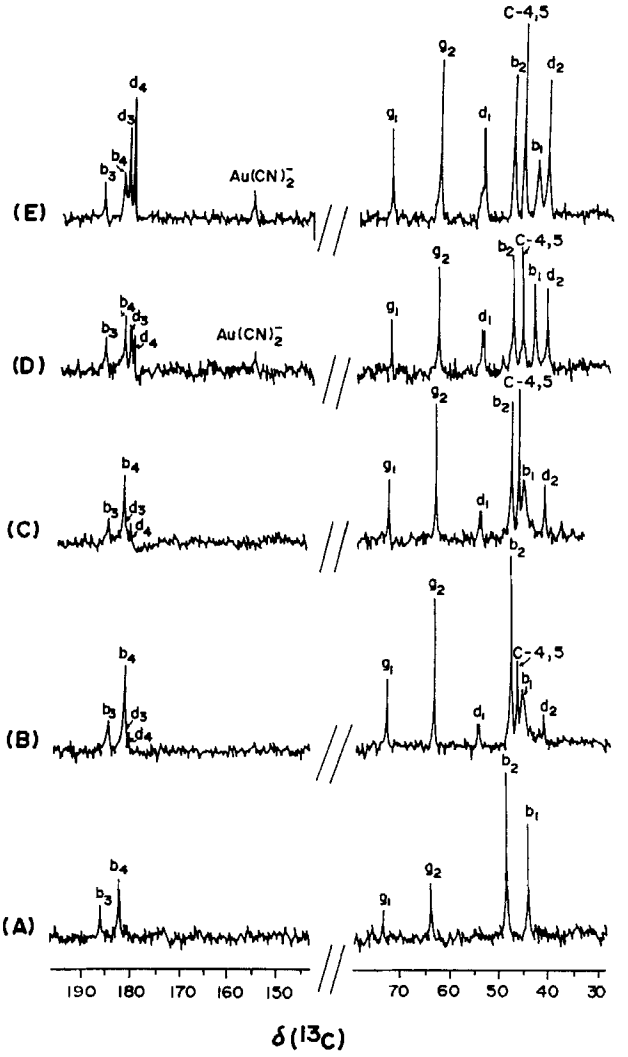


FIGURE 2 50 MHz ^1H noise-decoupled ^{13}C NMR spectra of 0.20 M $(AuStm)_n$:HStm: SeImt: KCN (pH* 7.40) at various molar ratios: (A) 1.00: 0.90 : 0.00 : 0.00; (B) 1.00:0.90:0.50:0.00; (C) 1.00: 0.90:1.00:0.00; (D) 1.00:0.90: 1.00:1.00; (E) 1.00:0.90:1.00:2.00.

Mössabaur, NMR and EXAFS data have established that gold(I) thiolates such as $(AuStm)_n$, gold(I) thioglucose, gold(I) cysteine and gold(I) glutathione have AuS_2 coordination environments formed by bridging of the thiolate ligands between two gold(I) ions to form oligomers *e.g.*,

TABLE II ^{13}C NMR Chemical Shifts in ppm of $(AuStm)_n$: HStm: SeImt: KCN at Various Mol Ratios. The pH* of the Solution was 7.40 Throughout the Titration. Notations are taken from Figure 2

Spectrum	b_1	b_2	b_3	b_4	C-4,5	d_1	d_2	d_3	d_4	$Au(CN)_2^-$
2A	43.28	47.71	184.65	180.76						
2B	45.37	47.91	183.57	180.31	46.48	54.17 54.52	41.15	180.01	179.27	
2C	45.31	47.99	183.85	180.45	46.41	54.15 54.52	41.18	180.03	179.27	
2D	43.62	48.14	185.03	181.07	46.12	54.17 54.53	41.18	180.04	179.27	154.02
2E	43.21	48.61	185.22	181.13	46.12	54.12 54.52	41.22	180.04	179.27	154.04

{(Au-thiolate)$_n$}.[1-4,22-26] When excess thiols are added to the $(AuStm)_n$ polymer, they usually release HStm to form Au(thiolate)$_2^-$ species.[5-7]

We have recently reported that when thiones are added to $(AuStm)_n$, they usually form >C=S—Au—Stm-type, asymmetric *bis* complexes without releasing Stm^- as a free ligand.[12-14] Also, we have demonstrated that when ergothionine (ErSH), which is present in human red blood cells at 2 mM concentration,[27] is added to $(AuStm)_n$, it also forms a ErS—Au—Stm type complex without releasing HStm as a free ligand.[14] However, in the present study it is shown that SeImt behaves differently to Imt and analogous thione ligands; it releases Stm^- as free ligand at a 1:0.75 ratio of $(AuStm)_n$:SeImt. This observation indicates that SeImt binds to $(AuStm)_n$ more strongly than all thiones reported in the literature.[12-14] As noted in Table III, the C-2 chemical shift difference between the free thione and the complex $(AuStm)_n$:Imt at a 0.5:1 ratio is 3.65 ppm[13], whereas that for $(AuStm)_n$:SeImt at the same ratio is 5.95 ppm. These chemical shift differences between Imt and SeImt bound to $(AuStm)_n$ also support our conclusion that SeImt binds to $(AuStm)_n$ more strongly than Imt.

The a_1 resonance of $(AuStm)_n$ shifts by 1.11 ppm at a 1:0.75 ratio of $(AuStm)_n$:Imt whereas for SeImt at the same ratio it is shifted by 3.73 ppm. Thus the electron withdrawal effect for SeImt is much greater than

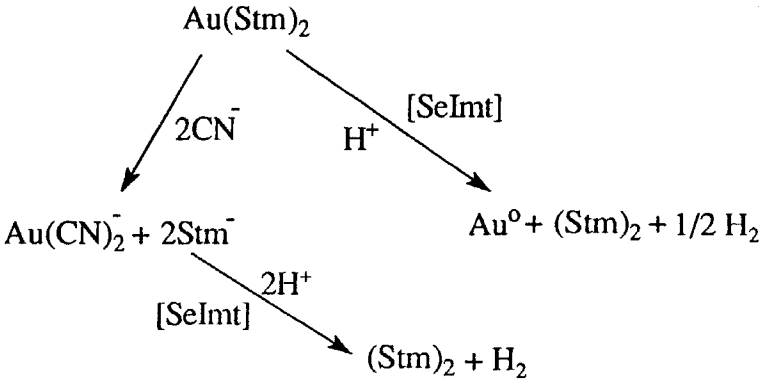
TABLE III ^{13}C NMR Chemical Shift Difference ($\triangle$) of the C-2 Resonance Between the Free Ligand and Complex at a 1.0:0.50 ratio of $(AuStm)_n$:Ligand at pH* 7.40

Complex	Δ	Reference
$(AuStm)_n$:Ergothionine	3.92 ppm	14
$(AuStm)_n$:Imidazolidine-2-thione	3.65 ppm	13
$(AuStm)_n$:1,3-Diazinane-2-thione	3.40 ppm	13
$(AuStm)_n$:Imidazolidine-2-selone	5.95 ppm	This work

that for Imt when it binds to $(AuStm)_n$. The C-4,5 resonance of SeImt did not shift much during the titration which indicates that the NH group of the ligand is not involved in binding to gold(I).

As shown in Figure 2, $Au(Stm)_2^-$ reacts differently with SeImt than with $(AuStm)_n$. When both sites of gold(I) are blocked by Stm^-, SeImt replaces Stm^- which is oxidized to disulfide and some metallic gold appears in the NMR tube. This observation indicates that SeImt acts as a catalyst for a redox reaction to give metallic gold and $(Stm)_2$. This observation of binding of $Au(Stm)_n$ and $Au(Stm)_2^-$ to SeImt is similar to our latest report of $SeCN^-$ binding to these complexes.[28] $SeCN^-$ binds to $Au(Stm)_n$ forming the tmS-Au-$SeCN^-$ complex, which eventually disproportionates to give $(Stm)_2$, metallic gold, metallic selenium and $Au(CN)_2^-$ species. However, $Au(Stm)_2^-$ reacts differently with KSeCN. Since Au(I) is blocked by Stm^- from both sides, $SeCN^-$ does not form a tmS-Au-$SeCN^-$ complex; instead a redox reaction of gold(I) to metallic gold and Stm^- to $(Stm)_2$ occurs.

This redox reaction is not observed when $(AuStm)_n$ reacts with SeImt. In this case formation of the ternary complex of ImtSe-Au-Stm was observed and some free Stm^- was released to solution which remained in the thiol (Stm^-) form and did not oxidize to disulfide $(Stm)_2$. The redox reaction is considered to take place with reduction of H^+ ions to H_2. This redox reaction was promoted when CN^- was added to the solution as shown in Figure 2. Since the formation constant in log units of $Au(CN)_2^-$ is 38.8,[31] CN^- binds to gold(I) leaving HStm as a free ligand which is oxidized to $(Stm)_2$. Reactions of $Au(Stm)_2^-$ with H^+ and CN^- catalyzed by SeImt can be explained as shown below.



Recently we studied[30] the interaction of $(AuStm)_n$ with selenourea. Selenourea reacted as a catalyst similar to SeImt by reducing gold(I) to metallic gold and oxidizing thiomalate to disulfide. Selenourea has an $-NH_2$ group which must be supporting 'Se' to act as a catalyst. This conclusion was based on our previous experiments of redox reactions of $AuCl_4^-$ with *L*-methionine and *N*-acetyl-*L*-methionine.[31] It was observed that when the $-NH_2$ group was blocked with an acetyl group the rate of redox reaction of gold(III) to gold(I) and oxidation of $-S-CH_3$ to $O=S-CH_3$ (*i.e.*, methionine to sulfoxide) was reduced considerably. In SeImt, the —NH group is a secondary amine and therefore not expected to be involved in the redox reaction.

We have studied the formation constants between methionine (Met) and selenomethionine (SeMet) with $CH_3Hg(II)$ in acidic aquous solution.[32] Log K_f for Met was found to be 1.94 whereas for SeMet it was reported to be 3.73. Also, we studied ^{13}C NMR spectroscopy of $Met:Hg^{2+}$ and $SeMet:Hg^{2+}$ at a 1:1 ratio in acidic aquous solution. the methyl resonance for Met shifted by 3.56 ppm; however, for SeMet complex it was shifted by 9.29 ppm.[33]

Both these studies indicate that the selenium-containing ligand binds to Hg^{2+} (isoelectronic with gold(I)) more strongly than analogous sulfur-containing ligands. A similar observation was made for $PdCl_2$ where it was found that $PdCl_2$ binds more strongly to SeMet compared to Met.[34]

Recently, Arnold *et al.*,[35] studied formation constants of $CH_3Hg(II)$ with thiols and analogous selenols. They reported that the formation constants for selenol-containing ligands are much higher than for analogous thiols. Formation constants ($\log K_f$) of selenocysteine, cysteine, selenopenicillamine and penicillamine are 17.38, 16.67, 17.40 and 16.94 respectively. The formation constant for $CH_3HgSeCN$ is larger than for CH_3HgSCN.[36] Structural data suggests that Hg-Se binding in $CH_3HgSeCH_2CH(NH_2)CO_2H_2O$ ($CH_3Hg(II)$-selenocysteineate) is stronger than Hg-S binding in the analogous cysteine complex.[37] These studies support the fact that selenium-containing ligands bind more strongly to class B metal ions than analogous sulfur-containing ligands.[15]

The present study indicates that selenium-containing ligands bind more strongly to gold(I) drugs than analogous sulfur-containing ligands. If the gold drug enters red blood cells, it is expected to bind glutathione peroxidase, consequently causing side effects of the drug.

Acknowledgements

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