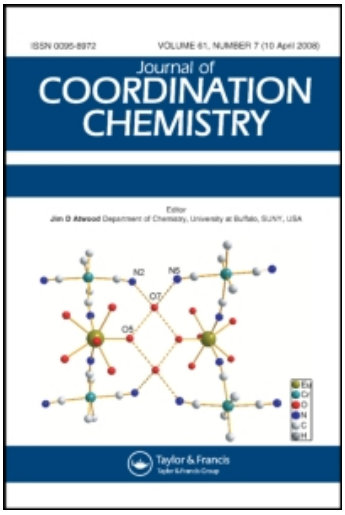

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SIMULTANEOUS REPLACEMENTS OF TRIETHYL PHOSPHINE AND TETRAACETYL THIOGLUCOSE LIGANDS FROM AURANOFIN (AN ANTIARTHRITIC DRUG) WITH SELENOCYANATE ^{13}C and ^{31}P NMR STUDIES

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SIMULTANEOUS REPLACEMENTS OF TRIETHYL PHOSPHINE AND TETRAACETYL THIOGLUCOSE LIGANDS FROM AURANOFIN (AN ANTIARTHRITIC DRUG) WITH SELENOCYANATE

^{13}C and ^{31}P NMR STUDIES

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The interaction of $SeCN^-$ with a new gold-based antiarthritic drug auranofin ($Et_3PAuSATg$, where $SATg^-$ = 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-glucopyranosato-*S*) in aqueous methanol has been studied by ^{13}C and ^{31}P NMR spectroscopy. It is observed that $SeCN^-$ releases both ligands (*i.e.*, $SATg^-$ and Et_3P) to form [ATgS-Au-CN]$^-$ and [Et_3P-Au-SeCN]. These newly generated species undergo further disproportionation and decomposition to generate species such as $[(Et_3P)_2Au]^+$, $[Au(CN)_2]^-$, Et_3PO and metallic selenium. The formation of $[(Et_3P)_2Au]^+$ and $[Au(CN)_2]^-$ is found to be much faster for Et_3PAuNO_3 than for $Et_3PAuSATg$ when reacted with $SeCN^-$. Exchange between unlabelled CN^- of $Au(CN)_2^-$ and labelled $Se^{13}CN^-$ was observed without selenium being precipitated from $Se^{13}CN^-$.

INTRODUCTION

Gold(I)-thiolate drugs have been used in the treatment of rheumatoid arthritis (RA) for over 60 years. Although they have been found to be very effective [1], the specific mechanism of action of these gold(I) drugs is unknown. The most commonly used gold(I) drugs are shown in Figure 1.

Characteristic of these gold drugs as well as other gold(I) complexes is the tendency of the gold(I) to coordinate two ligands in linear geometry [2-6].

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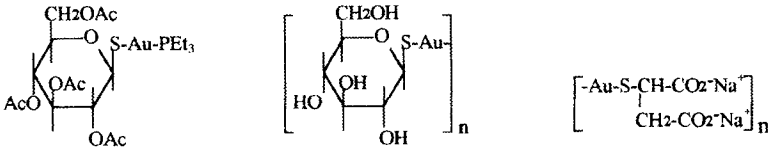


Auranofin Gold(I)-thioglucose Gold(I)-thiomalate

FIGURE 1 Structures of some gold(I) drugs.

Auranofin (1-thio-β-*D*-glucopyranose-2,3,4,6-tetraacetato-*S*)(triethylphosphine-)gold(I) is an orally active drug, while solganal (gold(I)thioglucose; AuStg) and myochrysine (gold(I)thiomalate; AuStm) are only active by injection [2-4]. Solganal and myochrysine are highly water soluble, whereas auranofin is sparingly soluble in water.

It is well known that unsymmetric linear gold(I) complexes are stable in solution [6-8], *e.g.*, auranofin which has phosphine and thiol ligands *trans* to each other [8]. However, if any of these ligands is replaced by CN^-, [Et_3P-Au-CN] or [TgAS-Au-CN]$^-$ complexes will be formed [9-12]. These newly generated complexes are unstable and disproportionate as shown in (*1*) and (*2*): [9-13].

$$[Et_3P\text{-Au-CN}] \rightleftharpoons 1/2[(Et_3P)_2Au]^+ + 1/2[Au(^{13}CN)_2]^- \qquad (1)$$

$$[ATgS\text{-Au-CN}]^- \rightleftharpoons 1/2[(ATgS)_2Au]^- + 1/2[Au(^{13}CN)_2]^- \qquad (2)$$

These disproportionations have been studied extensively using ^{13}C, ^{15}N and ^{31}P NMR spectroscopy [9, 10, 14, 15].

Exchange reactions of auranofin have been studied with various biologically available S-containing ligands, *e.g.*, bovine serum albumin (BSA), red blood cells, *etc.*, at physiological concentrations of drug and biomolecule [16-21]. When bovine serum albumin was reacted with auranofin, for example, it was observed that the thiosugar of auranofin was replaced and Et_3P-Au-BSA formed [17], which further underwent thiol exchange with cysteine and glutathione [20]. Displacement of phosphine ligand from auranofin was not observed.

Recently, we reported redox reactions of $(AuStm)_n$ with $SeCN^-$ in aqueous solution [22]. $(AuStm)_n$ initially formed a complex with $SeCN^-$, [tmS-Au-SeCN]$^-$, which eventually disproportionated by reducing gold(I) to metallic gold and oxidizing Stm^- to $(Stm)_2$. These redox reactions of [tmS-Au-SeCN]$^-$ have only been studied for polymeric gold(I)-thiolate complexes [22, 23]. In the present study, we report simultaneous replacements of both phosphine and thiolate ligands from Au^+ in auranofin in the presence of $SeCN^-$ in MeOH.

EXPERIMENTAL

Chemicals

Auranofin was a gift from the Smith Kline and French Laboratories. $KSe^{13}CN$ was obtained from the Isotec Inc., Ohio, U.S.A. KSeCN, CD_3OD, D_2O, $NaAuCl_4$ and $K[Au(CN)_2]$ were obtained from Fluka Chemical Company. Tetra-2,3,4,6-*O*-acetyl-β-1-*D*-thioglucose was purchased from Aldrich Chemical Co.

Et_3PAuCl

Et_3PAuCl complex was prepared by the addition of triethylphosphine to an ethanolic solution of $NaAuCl_4$ as described in the literature [24].

^{13}C and ^{31}P NMR Spectroscopy

All measurements were made on a Varian XL-200 spectrometer at 297 K using 2 cm^3 of sample in a 10 mm tube. ^{13}C NMR spectra were measured at 50.30 MHz, and all measurements were made with coherent off-resonance ^1H decoupling, or with broad-band ^1H decoupling. Chemical shifts were measured relative to internal reference dioxane (67.80 ppm). All spectra were recorded using 20,000-30,000 scans.

^{31}P NMR spectra were obtained at 80.90 MHz using the same solutions as for ^{13}C NMR studies. Chemical Shifts were measured relative to internal reference TMP [25]. All spectra were recorded using 5000-10000 scans. Conditions were: 5.0 s delay time, 32 K data points, spectrum width 10,000 Hz, pulse width 5.0 μs, 10 mm multinuclear probe.

RESULTS AND DISCUSSION

Interaction of Auranofin with $SeCN^-$

Figure 2(A) shows the ^{31}P NMR spectrum of 0.05 mol dm^{-3} auronofin in CD_3OD (2.0 cm^3). When one equivalent of KSeCN was added as a solid to the auranofin solution, it partially dissolved. Therefore 0.1 cm^3 of D_2O was added to dissolve it completely. The solution was colourless and no change was observed after addition of $SeCN^-$. The ^{31}P NMR spectrum of the solution after 40 min is shown in Figure 2(B). The resonance due to auranofin is shifted slightly upfield and broad. Two additional resonances at 47.25 and 57.0 ppm are also observed in the spectrum and which are assigned to $[(Et_3P)_2Au]^+$ and Et_3PO species,

respectively, as in (*3*) to (*5*) [9, 10, 21] (where $ATgS^-$ = tetra-2,3,4,6-*O*-acetyl-*β*-1-*D*-thioglucose)

$$ATgS\text{-}Au\text{-}PEt_3 + SeCN^- \rightleftharpoons Et_3P\text{-}Au\text{-}SeCN + ATgS^- \quad (3)$$

$$Et_3P\text{-}Au\text{-}SeCN \rightleftharpoons 1/2\ [(Et_3P)_2Au]^+ + [Au(^{13}CN)_2]^- + Se(0) \quad (4)$$

$$ATgS\text{-}Au\text{-}PEt_3 + SeCN^- \rightleftharpoons [ATgS\text{-}Au\text{-}CN]^- + Se(0) + Et_3P{\downarrow}[O]Et_3PO \quad (5)$$

After 24 h the colour of the solution had changed to very light yellow. Figure 2(C) shows the ^{31}P NMR spectrum of the same solution after 29 h. The resonance due to auranofin had decreased in intensity while the resonance due to $[(Et_3P)_2Au]^+$ had increased. After 120 h the colour of solution was bright yellow and $[(Et_3P)_2Au]^+$ resonance was further increased in intensity and auranofin decreased. The chemical shifts of various resonances are given in Table I.

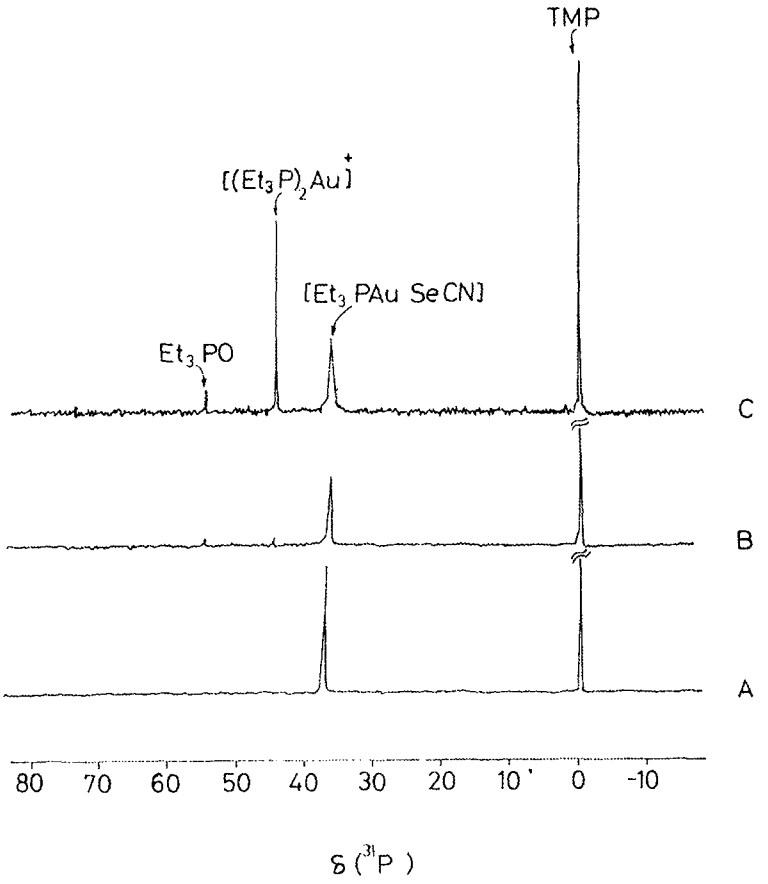


FIGURE 2 80.9 MHz ^1H noise decoupled ^{31}P NMR spectra in CD_3OD of auranofin:$SeCN^-$ (0.05 mol dm^{-3} (A) 1:0, (B) 1:1 after 40 min, (C) 1:1 after 29 h.

TABLE I ^{13}C and ^{31}P NMR chemical shifts of the various species.†

Species	$\delta(^{31}P)$	$\delta(^{13}CN)$	*Ref.*
$Et_3PAuSATg$	36.25		8, 10
$Et_3PAu^{13}CN$	35.10	160.40	9, 10
$Et_3PAuSe^{13}CN$	37.36	113.10	This work
$[(Et_3P)_2Au]^+$	47.25		35, 36
Et_3PO	57.0		10, 20, 36
$Se^{13}CN^-$		119.58	22, 23
$[Au(^{13}CN)_2]^-$		152.23	11, 12, 13
$[ATgS\text{-}Au\text{-}^{13}CN]^-$		150.91	11, 12, 13
Et_3PAu^+	28.00		10, 29, 36

†$ATgS^-$ = tetra-2,3,4,6-*O*-acetyl-*β*-1-*D*-thioglucose.

Interaction of Auranofin with $Se^{13}CN^-$

In a second experiment, 0.05 mol dm^{-3} auranofin was prepared in 2.0 cm^3 of CD_3OD. One equivalent of $KSe^{13}CN$ was added as a solid and 0.1 cm^3 of D_2O was added to dissolve it completely. Figure 3(A) shows the ^{13}C NMR spectrum of the solution after 4 h; the chemical shifts of various resonances are given in Table I. Three intense resonances were observed in the low field region due to the labelled ^{13}CN group. Free $Se^{13}CN^-$ appeared at 119.58 ppm, with $^1J(^{77}Se\text{-}^{13}C)$ 269.7 Hz [23]. The $[Au(^{13}CN)_2]^-$ resonance was observed at 152.23 ppm, while the third intense resonance at 150.91 ppm is due to $[ATgS\text{-}Au\text{-}CN]^-$ as described in (*5*). After 10 h the free $Se^{13}CN^-$ resonance had decreased in intensity, while the other two had increased. After 23 h the colour of the solution was very light yellow and the ^{13}C NMR spectrum is shown in Figure 3(B).

These experiments involved a ^{31}P and ^{13}C NMR study of the interaction of auranofin with $SeCN^-$. As shown in Figure 2, the auranofin resonance shifted upfield and was broadened due to exchange reactions of thiol and phosphine by $SeCN^-$. After some time, a resonance due to $[(Et_3P)_2Au]^+$ appeared and increased in intensity, suggesting that the thiol ligand is exchanged with $SeCN^-$ to generate $Et_3PAuSeCN$ which then undergoes disproportionation to generate $[(Et_3P)_2Au]^+$. A resonance due to triethylphosphine oxide (Et_3PO) was also observed, which indicates that some of the Et_3P released from auranofin is oxidized in water [26] before it binds to $Et_3P\text{-}Au^+$ to form $[(Et_3P)_2Au]^+$.

Interaction of Et_3PAu^+ and $SeCN^-$

In order to understand the broadening and shift of the ^{31}P NMR resonance of auranofin on addition of $SeCN^-$ as described, the following experiment was carried out. A 0.05 mol dm^{-3} solution of Et_3PAuCl was prepared in 2.0 cm^3 of

CD_3OD. An aqueous solution (2.0 cm^3) of 0.05 mol dm^{-3} of $AgNO_3$ was added to it, resulting in the precipitation of AgCl. The ^{31}P NMR spectrum (Figure 4A) of the clear filtrate showed only one resonance at 28.00 ppm for Et_3PAuNO_3 as described in (*6*).

$$Et_3PAuCl + AgNO_3 \rightarrow Et_3PAuNO_3 + AgCl_{(s)} \qquad (6)$$

One equivalent of KSeCN was added as a solid to the above solution containing Et_3PAu^+ and its ^{31}P NMR spectrum recorded after 30 min is shown in Figure 4(B). Two resonances were observed in the spectrum; the $Et_3PAuSeCN$ resonances was very intense and resolved at 37.36 ppm (as described in (*7*), while the other resonance at 47.25 ppm due to $[(Et_3P)_2Au]^+$ was less intense.

$$Et_3PAu^+ + SeCN^- \rightarrow Et_3PAuSeCN \qquad (7)$$

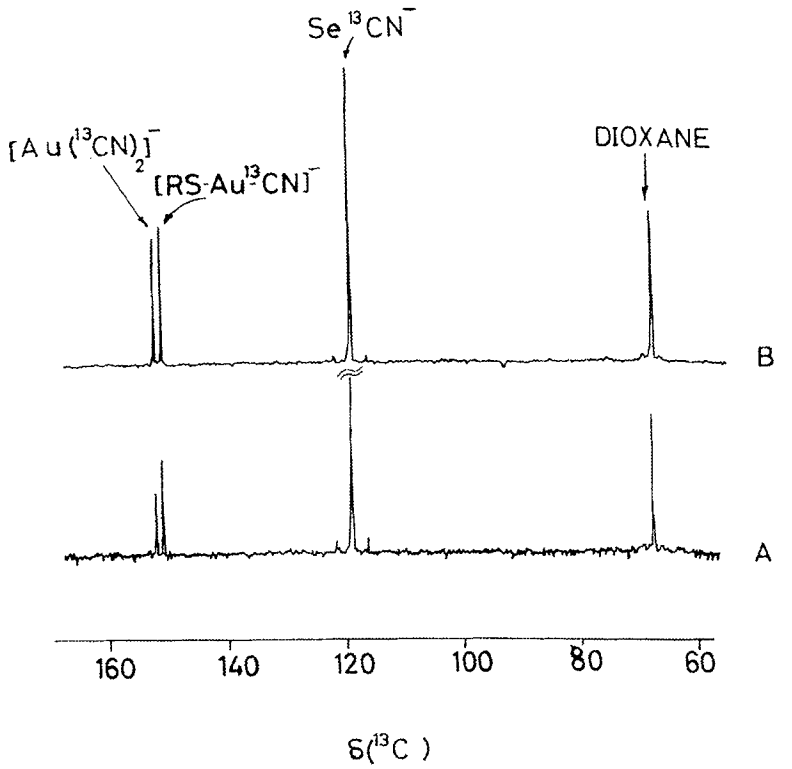


FIGURE 3 50.0 MHz ^1H noise decoupled ^{13}C NMR spectra in CD_3OD of auranofin:$Se^{13}CN^-$ (0.05 mol dm^{-3} at a 1:1 ratio after (A) 40 min, (B) 23 h.

Figure 4(C) shows the ^{31}P NMR spectrum of the same solution after 4 h. This time the resonance due to $[(Et_3P)_2Au]^+$ had increased in intensity according to (*4*) and that of $Et_3PAuSeCN$ had decreased in intensity, but even then was more intense than the $[(Et_3P)_2Au]^+$ resonance. Figure 4(D) shows the ^{31}P NMR spectrum of the same solution after 23 h. This time the resonance due to $[(Et_3P)_2Au]^+$ is very intense as compared to the $Et_3PAuSeCN$ resonance. Some

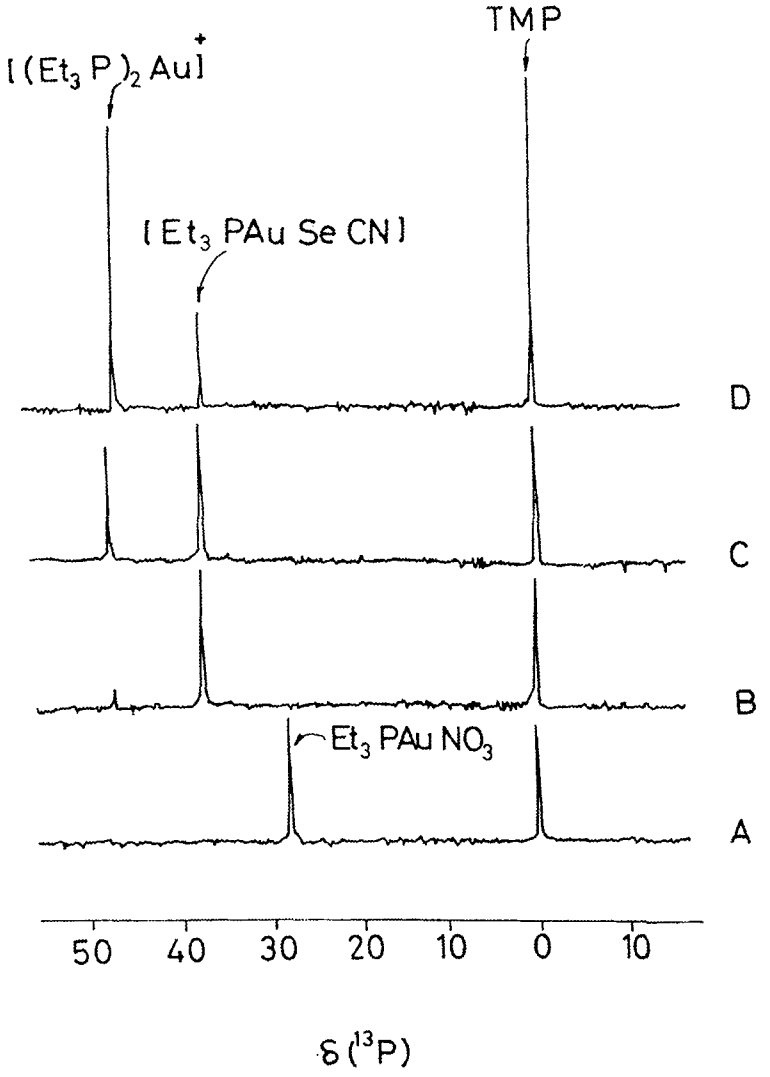


FIGURE 4 80.9 MHz ^1H noise decoupled ^{31}P NMR spectra in CD_3OD of Et_3PAuNO_3:$SeCN^-$ (0.05 mol dm^{-3}) (A) 1:0, (B) 1:1 after 30 min, (C) 1:1 after 4 h, (D) 1:1 after 23 h.

black metallic Se was observed in the solution. The disproportionation of $Et_3PAuSeCN$ is described in (*4*).

In this expt, $SeCN^-$ was added in a 1:1 ratio to Et_3PAuNO_3. Since NO_3^- is a weak ligand [27] it was completely replaced by $SeCN^-$ and the ^{31}P NMR resonance, observed at 37.36 ppm due to $Et_3PAuSeCN$, was very close to the ^{31}P NMR shift of auranofin. Due to the overlap of these two resonances ($Et_3PAuSeCN$ and auranofin) the auranofin resonance was broadened as shown in Figure 2. The $[(Et_3P)_2Au]^+$ resonance was also observed, and increased in intensity with time. Figure 5 shows the change in concentration of auranofin, $[(Et_3P)_2Au]^+$ and $Et_3PAuSeCN$ in auranofin:$SeCN^-$ and Et_3PAuNO_3:$SeCN^-$ systems. There is very slow decrease in auranofin concentration and increase in $[(Et_3P)_2Au]^+$ concentration, while in the Et_3PAuNO_3:$SeCN^-$ system there is very sharp decrease in $Et_3PAuSeCN$ and slow increase in $[(Et_3P)_2Au]^+$ concentrations.

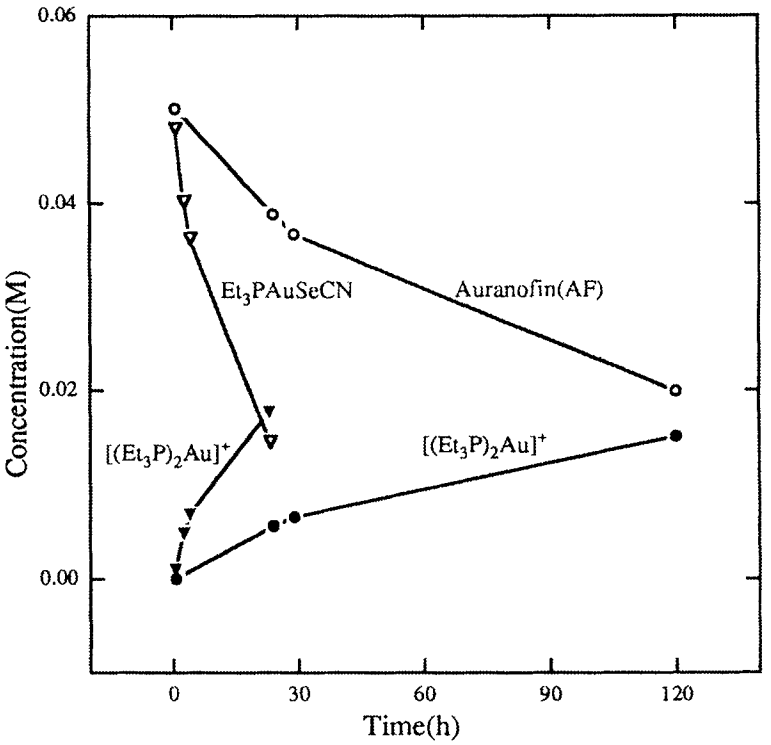


FIGURE 5 Change in concentration of auranofin and $[(Et_3P)_2Au]^+$ in auranofin:$SeCN^-$ (represented by open and closed circles). Change in concentration of $Et_3PAuSeCN$ and $[(Et_3P)_2Au]^+$ in Et_3PAuNO_3:$SeCN^-$ systems with time (represented by open and closed triangles).

Interaction of Et_3PAu^+ and $Se^{13}CN^-$

A solution of 0.05 mol dm^{-3} Et_3PAuNO_3 in 2.0 cm^3 of CD_3OD was prepared as described above. One equivalent of $KSe^{13}CN$ was added as a solid and its ^{13}C NMR spectrum was recorded after 4 h (Figure 6). Two intense resonances were observed in the low field region due to the labelled ^{13}CN group. The $Et_3PAuSe^{13}CN$ resonance was resolved at 113.10 ppm with $^1J(^{77}Se\text{-}^{13}C)$ 260.06 Hz, while the other resonance was resolved at 152.23 ppm due to $[Au(^{13}CN)_2]^-$. After 24 h (not shown in the figure) the $[Au(^{13}CN)_2]^-$ resonance had increased in intensity while that of $Et_3PAuSe^{13}CN$ had decreased as described in (*1*) and (*2*). Note that the resonance due to $Et_3PAu^{13}CN$, which is supposed to appear at 160.4 ppm [9, 10], was not observed, indicating that $Et_3PAuSe^{13}CN$ is an unstable species, and readily undergoes disproportiation as well as decomposition to generate $[(Et_3P)_2Au]^+$, $[Au(^{13}CN)_2]^-$ and metallic selenium as shown in (*4*).

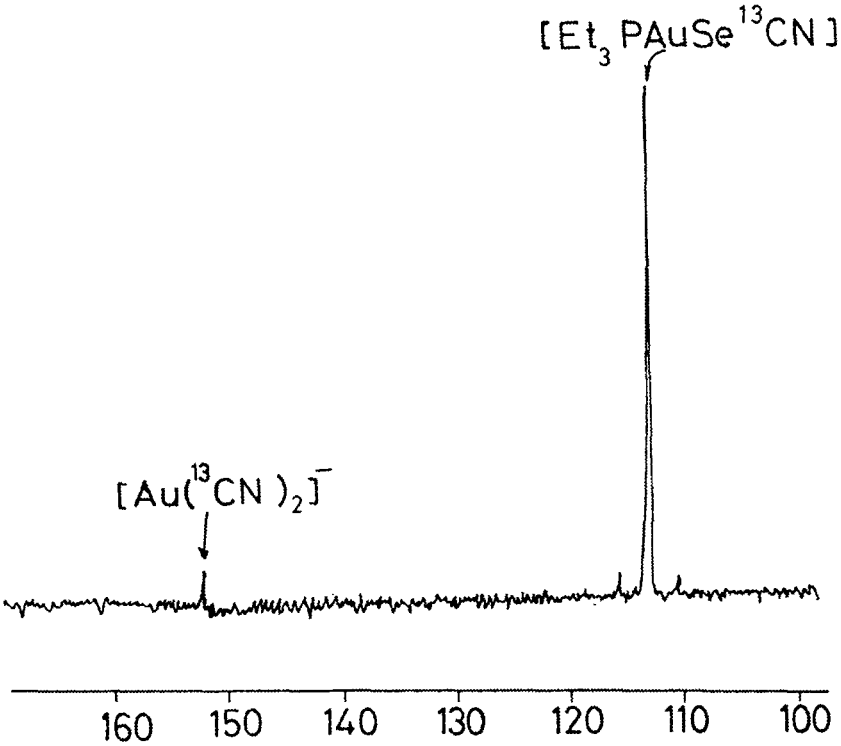


FIGURE 6 50.0 MHz ^1H noise decoupled ^{13}C NMR spectra in CD_3OD of Et_3PAuNO_3:$Se^{13}CN^-$ (0.05 mol dm^{-3} at a 1:1 ratio after 4 h.

Interactions of $[Au(CN)_2]^-$, $Se^{13}CN^-$ and $ATgS^-$

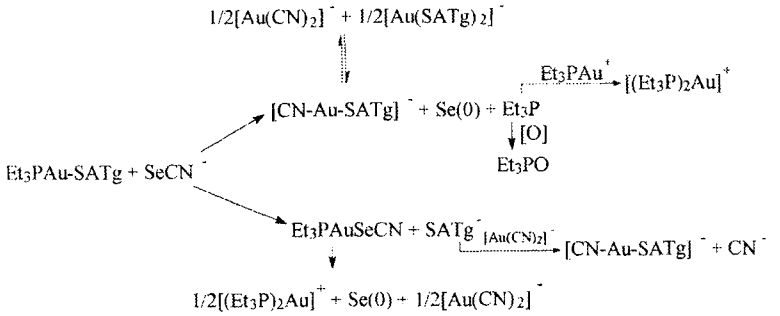
In order to assign the resonance at 150.91 in Figure 3, the following experiment was carried out. A 0.05 mol dm^{-3} $K[Au(CN)_2]$ solution was prepared in CD_3OD (2.0 cm^3) and D_2O (0.3 cm^3). Figure 7(A) shows the ^{13}C NMR spectrum of this solution. The $[Au(CN)_2]^-$ resonance was resolved at 152.17 ppm [12, 13]. One equivalent of $KSe^{13}CN$ was added as a solid and the ^{13}C NMR is shown in Figure 7(B) after 40 min. Two very intense resonances were resolved in the low field region due to labelled ^{13}CN groups. Free $Se^{13}CN^-$ was resolved at 119.58 ppm with $^1J(^{77}Se\text{-}^{13}C)$ 269.7 Hz, while $[Au(^{13}CN)_2]^-$ was resolved at 152.17 ppm. Figure 7(C) shows the ^{13}C NMR spectrum of the same solution after 2.5 h. This time the $[Au(^{13}CN)_2]^-$ resonance had increased and the free $Se^{13}CN^-$ resonance had decreased in intensity. After 23 h the $[Au(^{13}CN)_2]^-$ resonance (not shown in Figure) was further increased and the free $Se^{13}CN^-$ resonance was further decreased. Fast exchange of 'CN' between $[Au(CN)_2]^-$ and $Se^{13}CN^-$ was observed at 1:1 mol equivalents. Figure 8 shows the change in concentration of $Se^{13}CN^-$ and $[Au(^{13}CN)_2]^-$ with respect to time.

$$[Au(^{13}CN)(CN)]^- + Se^{13}CN^- \rightarrow [Au(^{13}CN)(^{13}CN)]^- + SeCN^- \qquad (8)$$

At this stage one equivalent of tetra-2,3,4,6-*O*-acetyl-*β*-*D*-thioglucose ($ATgS^-$) was added as a solid to the solution. Figure 7(D) shows the ^{13}C NMR spectrum after 4 h. This time three resonances were resolved, two of them due to $[Au(^{13}CN)_2]^-$ and free $Se^{13}CN^-$, but a new resonance at 151.02 ppm was assigned to $[ATgS\text{-}Au\text{-}^{13}CN]^-$ as described in (*9*) [13].

$$[Au(^{13}CN)_2]^- + SATg^- \rightarrow [ATgS\text{-}Au\text{-}^{13}CN]^- + {}^{13}CN^- \qquad (9)$$

Figure 9 shows changes in concentrations of free $Se^{13}CN^-$, $[Au(^{13}CN)_2]^-$ and $[ATgS\text{-}Au^{13}CN]^{-1}$ with time. The generation of all species described in the experiments can be explained through the reactions in Scheme 1.



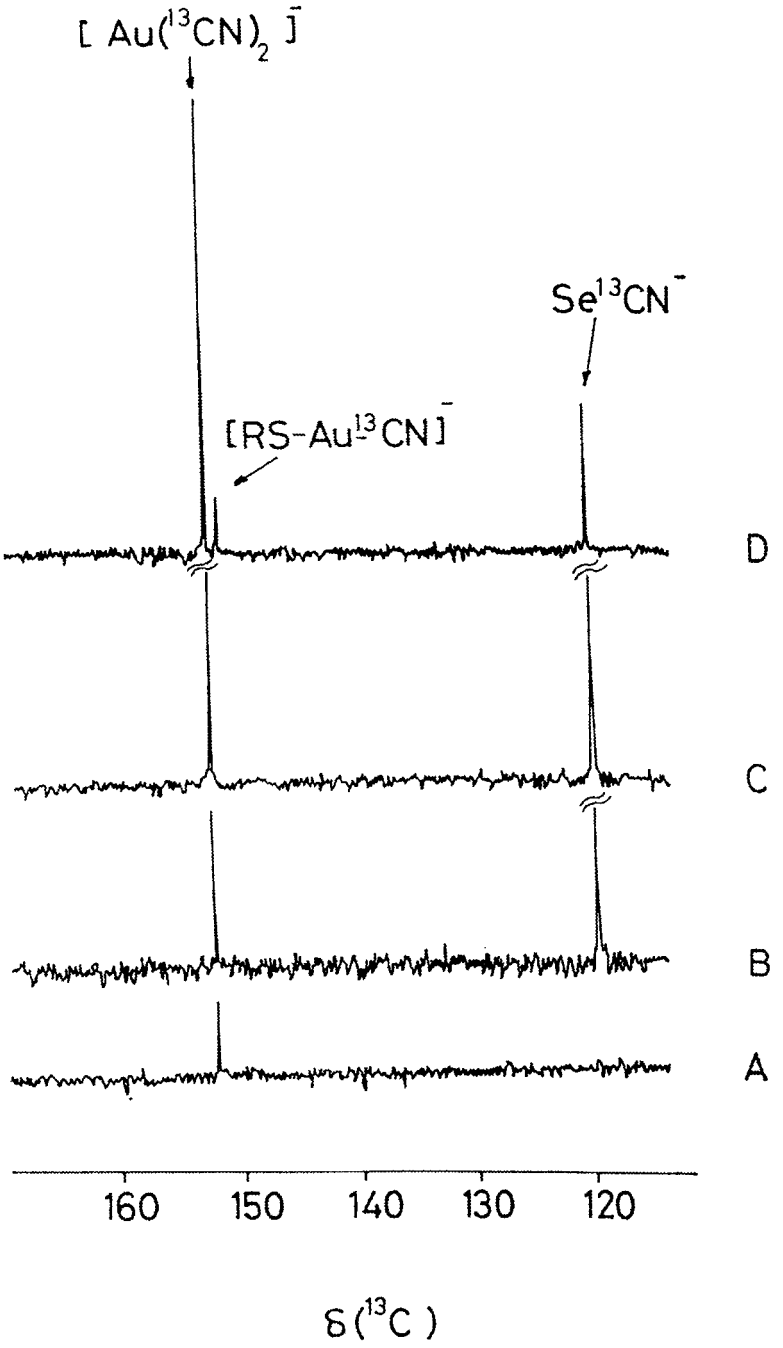


FIGURE 7 50.0 MHz ^1H noise decoupled ^{13}C NMR spectra in CD_3OD of $[Au(CN)_2]^-$: $Se^{13}CN^-$: $ATgS^-$ (0.05 mol dm^{-3}) (A) 1:0:0, (B) 1:1:0 after 40 min, (C) 1:1:0 after 2.5 h, (D) 1:1:1 after 4 h, $ATgS^-$ = tetra-2,3,4,6-*O*-acetyl-*β*-1-*D*-thioglucose.

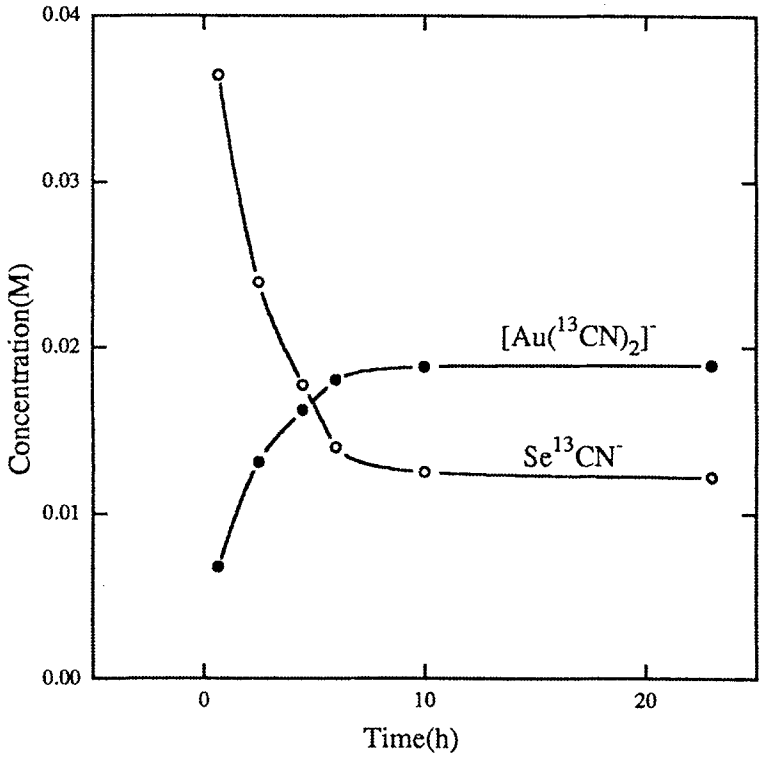


FIGURE 8 Change in concentration of $Se^{13}CN^-$ and $[Au(^{13}CN)_2]^-$ with time in the $[Au(CN-)_2]^-$:$Se^{13}CN^-$ system.

The present study shows interesting interactions of $SeCN^-$ with auranofin. Gold(I) is bonded to two different ligands in auranofin as compared to gold(I)-thiolates as shown in Figure 1. Since the gold(I) is blocked on both sides in auranofin, exchange reaction chemistry of these two forms of drug with $SeCN^-$ is very different.

Shaw and co-workers [17] have studied extensively the interaction of acetylated and deacetylated auranofin with BSA in aqueous buffer solutions. In their studies, the thiol was replaced by BSA immediately and most of the Et_3P remained bound to Au^+. Bryan *et al.* [28] studied the interaction of auranofin with HCl (50% MeOH/water) and they observed the formation of Et_3PAuCl. Since the present study was carried out in MeOH/D_2O (~95:5 v/v), the exchange reaction of auranofin with $SeCN^-$ is somewhat different that similar studies carried out in aqueous solution.

Equilibrium constants for R_3PAuCN complexes [9, 10] have been studied as a function of concentration, ionic strength, *etc.*, in MeOH. The complexes are

unstable and disproportionate as described in (*1*). This disproportionation is due to the larger formation constant (log $\beta = \sim 36$) [29] for $[Au(CN)_2]^-$.

In the present study we have shown that $Et_3PAuSeCN$ and $[AtgS\text{-}Au\text{-}SeCN]^-$ can be generated in methanolic aqueous solution, similar to a previous study in which we demonstrated that $[tmS\text{-}Au\text{-}SeCN]^-$ can be formed when $(AuStm)_n$ reacts with $SeCN^-$. However, $[tmS\text{-}Au\text{-}SeCN]^-$ was unstable in aqueous solution and disproportionated to give $[Au(tm)_2]^-$, $[Au(CN)_2]^-$ and metallic selenium [22]. Similar observations [23] were made when the gold(I)-captopril complex was reacted with $SeCN^-$. Contrary to the stability of $R_3PAuSeCN$ and R_3PAuCN complexes in solution, it is now reported [30] that $R_3PAuSCN$ complexes are stable and no disproportionation of these complexes is observed. This observation shows that $SeCN^-$ is unstable and reacts to give metallic selenium. This leaves CN^- to react with gold(I) to form $[Au(CN)_2]^-$, consequently, the *trans* ligand such as phosphine or thiolate in R_3PAuCN and $[tmS\text{-}Au\text{-}CN]^-$ will form *bis*(phosphine)gold(I) or *bis*(thiolate)gold(I). However,

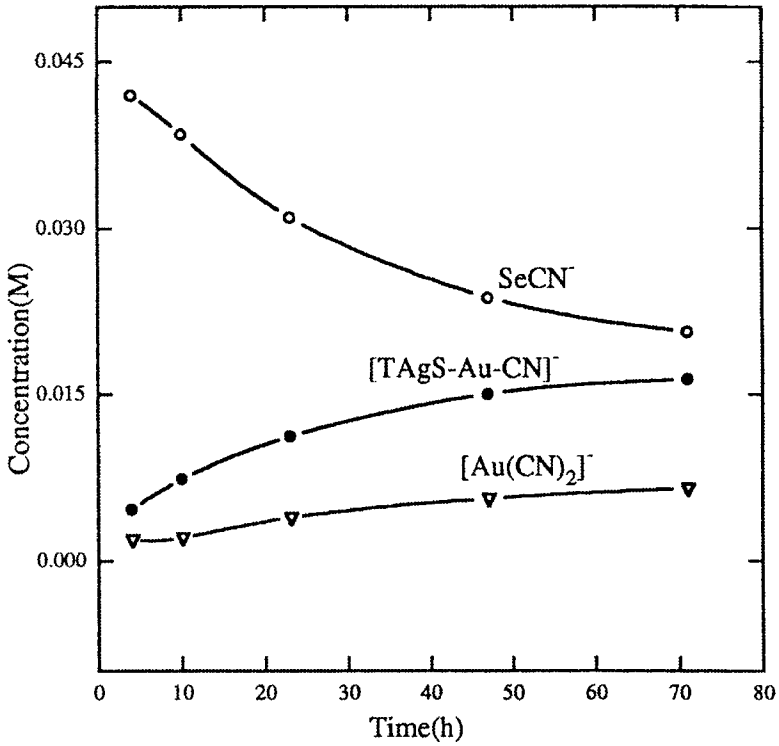


FIGURE 9 Change in concentrations of $Se^{13}CN^-$, $[TAgS\text{-}Au\text{-}^{13}CN]^-$ and $[Au(^{13}CN)_2]^-$ with time in the auranofin:$Se^{13}CN^-$ system.

unlike selenide ligands, selenols form stable gold(I)-selenoate complexes such as Au(Se-cysteine)$_2^-$ and Au(3-selenoproportionate)$_2^-$ in aqueous solution [31, 32].

The generation of $[(Et_3P)_2Au]^+$ measured by ^{31}P NMR spectroscopy in two different experiments is shown in Figure 5. When $Et_3PAuSATg$ (auranofin) was reacted with $SeCN^-$, 30% (0.015 mol dm^{-3}) of $[(Et_3P)_2Au]^+$ was generated after 120 h. However, the same amount of $[(Et_3P)_2Au]^+$ was generated within 27 h when Et_3PAu^+ was reacted with $SeCN^-$. Similarly, ^{13}C NMR studies show the generation of $[Au(CN)_2]^-$ is much faster for Et_3PAu^+ as compared to auranofin. This indicates that once $Et_3PAuSeCN$ or $[ATgS\text{-}Au\text{-}CN]^-$ was generated, the disproportion of both species would be much faster. However, in the case of auranofin, $SeCN^-$ has to compete with $ATgS^-$ and Et_3P, and therefore the reaction is much slower.

Figure 8 shows the exchange reaction between unlabelled CN^- of $[Au(CN)_2]^-$ and labelled $Se^{13}CN^-$. Since the labelled $^{13}CN^-$ of $Se^{13}CN^-$ is incorporated in $[Au(CN)_2]^-$, the intensity of $Se^{13}CN^-$ decreases and the intensity of $[Au(^{13}CN)_2]^-$ increases. However, the actual equilibrium concentration of $[Au(CN)_2]^-$ remains constant; if there were exchange between free and bound CN^-, the chemical shift of $[Au(CN)_2]^-$ should move toward free $^{13}CN^-$ at about 113 ppm [11, 33], and the $[Au(CN)_2]^-$ resonance should broaden. Appearance of a single sharp resonance at 152.0 ppm indicates that $^{13}CN^-$ of $Se^{13}CN^-$ is exchanging with $[Au(CN)_2]^-$ without selenium being precipitated. This is the first example as far as we know which demonstrates that CN^- can be exchanged with $Se^{13}CN^-$.

The formation of $[RS\text{-}Au^{13}CN]^-$ has already been reported by partially displacing cyanide from $[Au(^{13}CN)_2]^-$ with thiols such as cysteine and glutathione in aqueous solution [12, 13]. Similarly, the insoluble Au(I)-cysteine polymer was prepared [34] by reaction (*10*).

$$[Au(CN)_2]^- + cysH + H^+ \rightarrow 1/n\,[Au\text{-}cys] + 2HCN \qquad (10)$$

This displacement of CN^- with thiols from $[Au(^{13}CN)_2]^-$ is possible, although the formation constant is less than for $Au(CN)_2^-$ and therefore even though [RS-$Au^{13}CN$] species can be generated in solution, they always disproportionate as described in (*2*).

Previous studies have shown that during exchange reactions of auranofin with different biological ligands [16, 17] only the gold-thiol bond undergoes cleavage. In this study it is observed that $SeCN^-$ causes the cleavage of both gold-thiol and gold-phosphine bonds, and results in the generation of $[ATgS\text{-}Au\text{-}^{13}CN]^-$ and $[Et_3P\text{-}Au\text{-}Se^{13}CN]$, which further undergo redox and decomposition reactions to produce $[(R_3P)_2Au]^+$, $[Au(^{13}CN)_2]^-$, metallic selenium and Et_3PO.

The chemical basis for the metabolism of metallodrugs is intrinsically different than that for organic drugs. Metallodrugs undergo ligand-exchange and metal-centred redox reactions. The results presented here show that gold(I) is extremely susceptible to ligand exchange and that the ligands and the metal ion may have independent metabolic fates [1-4, 35, 36].

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