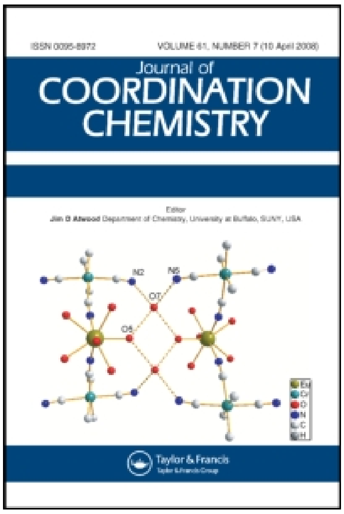

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Exchange Reactions of Aurothiomalate with 3-Selenopropionate in Aqueous Solution

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NOTE

EXCHANGE REACTIONS OF AUROTHIOMALATE WITH 3-SELENOPROPIONATE IN AQUEOUS SOLUTION

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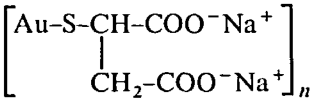
elenol such as 3-selenopropionate react with aurothiomalate in aqueous solution at pH 8.3 to give Au(3-elenopropionate)$^-_3$ bis complex ejecting thiomalate as a free ligand as observed by ^{13}C nmr spec-oscopy.

Keywords: Gold, myocrisin, 3-selenopropionic acid, exchange

NTRODUCTION

t has been well established[1] that the antiarthritic drug disodium aurothiomalate Myocrisin' (I) in the presence of other thiols undergoes exchange reactions; the hiomalate ligand is ejected from the drug, forming the $Au(SR)_2^-$ complex, where RS$^-$ = thiols such as glutathione, penicillamine, cysteine *etc.*

The complexation of (I) by selenium is also important since selenium is present, as . selenoate anion, at the active site of gluthathione peroxidase.[2] Since selenium is a ofter in a Lewis base sense than sulfur, it would be expected to form a more stable omplex with class B metal ions such as gold(I).[3] In this paper, we present the result f ^{13}C n.m.r. studies of the binding of disodium aurothiomalate (I) with 3-seleno-ropionate (II).

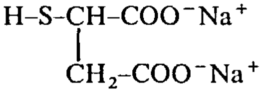


$$\left[\begin{array}{l}\text{Au–S–CH–COO}^-\text{Na}^+\\ \qquad\quad|\\ \qquad\quad\text{CH}_2\text{–COO}^-\text{Na}^+\end{array}\right]_n$$

(I)

$^-OOC–CH_2–CH_2–Se^-$

(II)



$$\begin{array}{l}\text{H–S–CH–COO}^-\text{Na}^+\\ \qquad\quad|\\ \qquad\quad\text{CH}_2\text{–COO}^-\text{Na}^+\end{array}$$

(III)

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EXPERIMENTAL

(I) was obtained from ICN K and K Labs, and analyzed as $C_4H_3O_4SNa_2Au.O.$-$33C_3H_8O_3.H_2O$. Glycerol forms an adduct with (I) as reported earlier.[1] 3,3′-Diselenodipropionic acid was prepared as described in the literature[4] and reduced to (II) as reported recently.[5] The g_2 resonance of glycerol which occurred at 63.33 ppm from $SiMe_4$ was used as an internal reference in the nmr measurements.

RESULTS AND DISCUSSION

The Figure (B) shows the effects of successive additions of (II) in the high field region of the ^{13}C-$\{^1H\}$ nmr spectrum of 0.0476 M (I) in D_2O at pH 8.3 (the pH is the actual meter reading and not corrected for deuterium isotope effects). The b_1 is shifted from 47.78 ppm to 43.68 ppm, whereas the b_2 resonance which at 47.78 ppm remains unshifted. Up to a ratio of Au(I):(III):(II) of 1:1:0.5, no free thiomalate f_2 and f_1 resonances appeared. However, when the concentration of (II) reached 1:1:2 (Au:(III):(II)), all the thiomalate was ejected (Fig. 1E) and the m_1 and m_2 resonances bound to gold(I) appeared with the correct ratio.

We selected pH 8.3 instead of physiological pH because at a ratio of Au(I):(III):(II) of 1:1:0.5, yellow precipitates occurred which dissolved only at pH 8.3. This may be due to 1:1 Au:selenopropionate polymerization. Gold(I) usually polymerizes with thiols at a 1:1 ratio.[1]

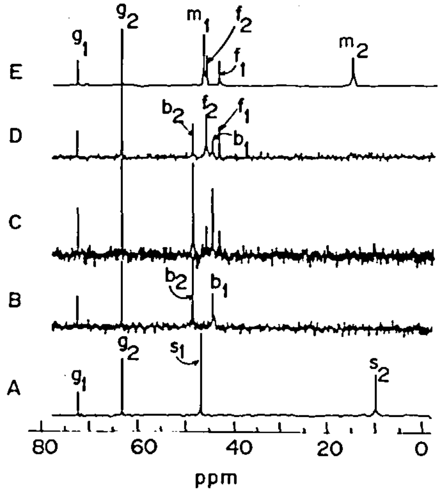

FIGURE 1 High-field region of the 90 MHz ^1H noise-decoupled ^{13}C nmr spectrum of (I) and (II) in D_2O; pH 8.3, 22°C. The concentrations (mole ratios) of Au(I):(III):(II) from A to E are: A, 0:0:1; B, 1:1:0.5; C, 1:1:1; D, 1:1:1.5; E, 1:1:2. Resonance assignments: g_1 = –CH and g_2 = $-CH_2$ of glycerol; b_1 = –CH and b_2 = $-CH_2$ of bound thiomalate to gold(I); f_1 = –CH and f_2 = $-CH_2$ of free thiomalate; s_1 = $-CH_2-CO_2^-$ and s_2 = $-CH_2$-Se– for free selenopropionate; m_1 = $-CH_2-CO_2^-$ and m_2 = $-CH_2$-Se– for selenopropionate bound to gold(I).

The m_1 and m_2 resonances do not appear under conditions referring to Fig. 1B to D indicating intermediate exchange rates with gold(I); as soon as the gold(I):(II) ratio reached 1:2, the m_1 and m_2 resonances did appear (forming the $Au(RSe)_2^-$ complex and ejecting (III) as a free ligand).

The m_2 resonance in Fig. 1E remains broad and indicates intermediate exchange with gold(I). The half line-width was 35 Hz. Figure 1A shows the ^{13}C-$\{^1H\}$ nmr spectrum of 0.0476 M, freshly prepared, (II) in aqueous solution at pH 8.3 for comparison. The m_2 resonance of (II) is shifted by 4.573 ppm to lower field when it forms a bis complex with gold(I), which indicates that selenium is shielded when gold(I) is bonded to it. The m_1 resonance remains virtually unshifted.

By analogy with recent findings for exchange reactions of various selenols with $CH_3Hg(II)$ it is shown that log k_f for selenols are higher than their analogous thiol compounds.[5] Hg(II) is isoelectronic with gold(I) and therefore it is expected that a selenol will form a more stable complex with gold(I) than a comparable thiol.

The results presented here indicate that gold(I) has a high affinity towards Se–H containing ligands. Glutathione peroxidase is present in red blood cells at the 2×10^{-6} M level[6] and therefore gold drugs entering red blood cells are expected to bind to selenol-containing enzymes along with glutathione. This would presumably affect their ability to protect cells from peroxidative damage.[7,8]

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