Notes

Complexation of Gold(I) Thiomalate ('Myocrisin') with 1,3-Diazinane-2-thione in Aqueous Solution followed by ^{13}C Nuclear Magnetic Resonance Spectroscopy

Anvarhusein A. Isab
Department of Chemistry, University of Petroleum and Minerals, Dhahran, Saudi Arabia 31261

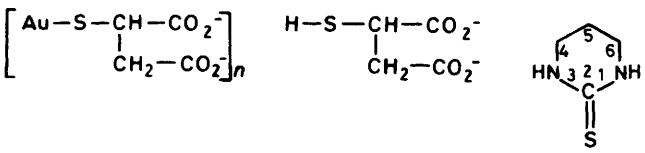
The interaction of gold(I) thiomalate ('Myocrisin'; an anti-arthritic drug) [Au(tm)] with 1,3-diazinane-2-thione (L) has been studied in aqueous solution at pH* 7.2 by using ^{13}C n.m.r. spectroscopy. It is found that [Au(tm)] forms a 1:1 complex of tm–Au–L. In the presence of excess thiomalate, L is displaced as a free ligand in solution suggesting that a thiol binds to gold(I) more strongly than does a thione.

Current interest in the biological chemistry of gold arises largely from the clinical use of gold(I) thiomalate ('Myocrisin'), [Au(tm)],† and gold(I) thioglucose ('Solganol') as anti-arthritic drugs.[1–3] These gold(I) thiolate drugs are known to exist as polymers in the solid state as well as in solution as identified by extended *X*-ray absorption-fine structure, Mössbauer spectroscopy, gel-permeation chromatography, and n.m.r. spectroscopy.[4–7]

I report here a study of the interaction of [Au(tm)] with 1,3-diazinane-2-thione (L) in aqueous solution using ^{13}C n.m.r. spectroscopy. It is shown that [Au(tm)] forms a tm–Au–L complex at pH* 7.2. However, L is displaced when excess tm is added to the tm–Au–L system.

Experimental

[Au(tm)] was obtained from K and K Laboratories, Plainview, New York. It was analyzed as [Au(tm)]·0.33glycerol·H_2O.[7–10] 1,3-Diazinane-2-thione (L) was synthesized as described in the literature.[11,12] ^{13}C N.m.r. spectra were measured at 90.5 MHz on a Bruker WM-360 spectrometer operating in the pulsed Fourier-transform mode. Carbon-13 chemical shifts were measured relative to the CH_2 resonance of internal glycerol (g_2) which occurs at 63.33 p.p.m. from $SiMe_4$. The resonance assignments for [Au(tm)], Htm, and L are shown below.



[Au(tm)] Htm L

b_1 = –*C*H f_1 = –*C*H
b_2 = –*C*H_2 f_2 = –*C*H_2
b_3 = –CH–*C*O_2^- f_3 = –CH–*C*O_2^-
b_4 = –CH_2–*C*O_2^- f_4 = –CH_2–*C*O_2^-

pH* indicates the actual meter readings for D_2O solutions with no correction for deuterium isotope effects.[13]

† The abbreviation used for thiomalate, $HSCH(CO_2^-)CH_2CO_2^-$, is Htm. The proton is therefore that on the thiol group, and the charges on the carboxylate group are ignored in the formulations presented throughout.

Results

Figure 1(*a*) shows the ^{13}C n.m.r. spectrum of [Au(tm)] in D_2O solution. Addition of L as a solid to the [Au(tm)] (0.376 mol dm^{-3}) D_2O solution at various equivalent molar ratios resulted in a higher-field shift of the b_1 resonance from 47.86 to 45.93 p.p.m. (see Figure 1). The b_2 resonance remains almost unshifted throughout the titration. The b_3 resonance was shifted

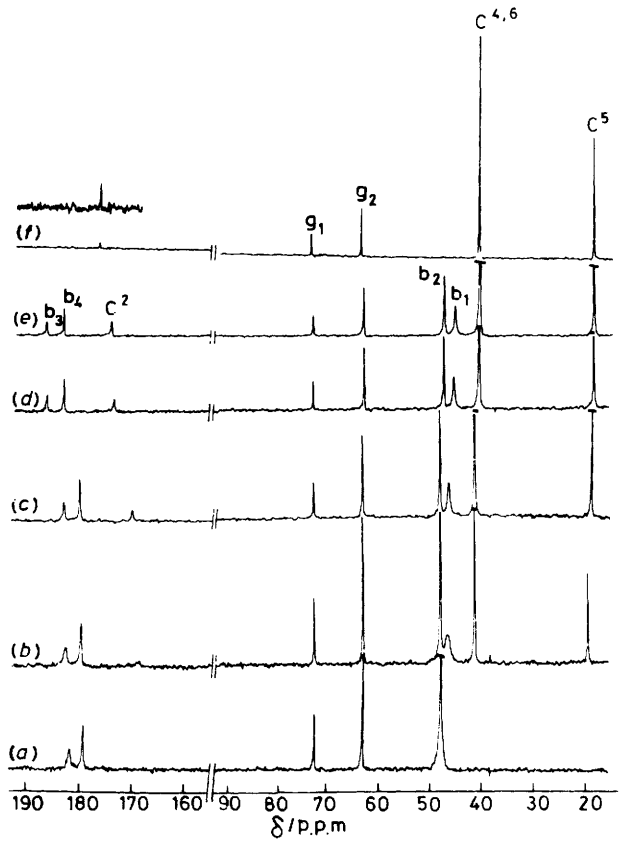


Figure 1. The 90.5-MHz ^1H noise-decoupled ^{13}C n.m.r. spectra of [Au(tm)]–L at various molar ratios (pH* 7.2 for all samples): (*a*) 0.376:0, (*b*) 0.376:0.094, (*c*) 0.376:0.188, (*d*) 0.376:0.282, (*e*) 0.376:0.376, and (*f*) 0:0.05; g_1 and g_2 are the *C*H and *C*H_2 resonances of glycerol respectively

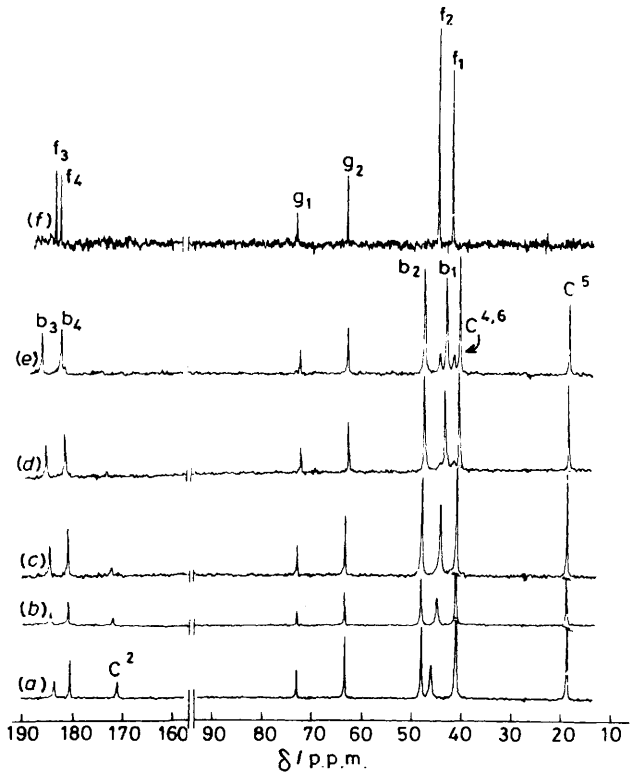


Figure 2. The 90.5-MHz ^1H noise-decoupled ^{13}C n.m.r. spectra of [Au(tm)]–L–tm at pH* 7.2, at molar ratios of (*a*) 0.376:0.376:0, (*b*) 0.376:0.376:0.094, (*c*) 0.376:0.376:0.188, (*d*) 0.376:0.376:0.282, (*e*) 0.376:0.376:0.376, and (*f*) 0:0:0.10

from 181.98 to 183.64 p.p.m. and the b_4 resonance from 179.44 to 180.39 p.p.m.

The C^2 resonance shifted to low field (toward the free ligand position) from 168.44 to 173.44 p.p.m. as the concentration of L increased. The chemical shift of the $C^{4,6}$ resonance at 40.96 p.p.m. and the C^5 resonance at 19.24 p.p.m. remained unshifted in the presence of [Au(tm)]. The pH* of the [Au(tm)] solution was 7.2 and this remained unchanged throughout the addition of L in the titration.

L was soluble in D_2O until a 1:1 ratio of [Au(tm)]:L was reached. As soon as the concentration of L was increased beyond this ratio, the excess L precipitated out in the aqueous solution. It is sparingly soluble in water.

Figure 2(*a*) shows the spectrum of another freshly prepared [Au(tm)]–L (1:1, 0.376 mol dm^{-3}) D_2O solution. Figure 2(*b*)–(*e*) shows the effect of adding solid tm to [Au(tm)]–L (1:1 ratio) in D_2O solution. The b_2 resonance shifted further upfield until a [Au(tm)]:L:tm ratio of 1:1:0.75 was reached. The chemical shifts are similar to those described in previous studies.[8-9] Further addition of tm to the above ratio resulted in the appearance of f_1, f_2, f_3, and f_4 resonances. It is worth noting here that the C^2 resonance shifted to low field and became almost unobservable when a 1:1:1 [Au(tm)]:L:tm ratio was obtained. At this point, L precipitated out in the solution.

Discussion

Gold(I) is found in AuS_2 co-ordination environments for the various types of gold(I) thiolate complexes.[6,14-17]

The addition of L to a [Au(tm)] solution does not release tm and only shifts in the b_1 and b_2 resonances are seen. If tm had been displaced, then f_1 and f_2 resonances would have been observed. From the results presented here (as shown in Figure 1), it can be concluded that [Au(tm)] forms a bis complex: $>C{=}S + \frac{1}{n}[Au(tm)]_n \longrightarrow >C{=}S{-}Au(tm)$.

Recently, we have reported the synthesis, ^{13}C n.m.r., and *X*-ray structural studies of various *N*-alkylated imidazolidine-2-thione–gold(I)–halide complexes.[18-21] It was found that the complexes were linear, and that the gold(I) always bonded to these ligands *via* the thione group. The complex $Au(L)_2Cl$ has also been synthesised as a white crystal.[18] The ^{13}C n.m.r. chemical shift difference of the C^2 resonance between the free ligand and the $Au(L)_2Cl$ complex was found to be +8.22† p.p.m. whereas for $Au(L)_2Br$ it was +7.08 p.p.m. (measured in 50:50 v/v Me_2SO–[$^2H_6$]acetone). These values are considerably higher than that (+2.08 p.p.m. in D_2O) found in the L–Au–tm system. Two factors contribute to this large difference: the solvent and the substitution of one of the L ligands by tm.

The high-field shifts of the b_2 resonance (see Figure 1) in the presence of L are small compared to that of excess tm itself (see Figure 2), which suggests that L breaks the [Au(tm)] polymer and forms a complex of L–Au–tm. However, that this L can be displaced in the presence of excess tm indicates that gold(I) binds to –SH in preference to C=S.

We are currently studying the complexation of [Au(tm)] and gold(I) thioglucose with *N*-alkylated and *N,N'*-alkylated imidazolidine-2-thione ligands, their biological activities, and also their interactions with biologically important thiols and with trialkylphosphine ligands.

Acknowledgements

This research was supported by the University of Petroleum and Minerals, Dhahran, Saudi Arabia and carried out in Professor D. L. Rabenstein's research laboratory at the University of Alberta, Edmonton, Canada. The author is grateful to Professor Rabenstein for providing the facilities and for helpful discussions.

References

1 P. J. Sadler, *Struct. Bonding (Berlin)*, 1976, **29**, 171; *Gold Bull.*, 1976, **9**, 110.
2 C. F. Shaw, *Inorg. Perspect. Biol. Med.*, 1979, **2**, 287.
3 D. H. Brown and W. E. Smith, *Chem. Soc. Rev.*, 1980, **9**, 217.
4 M. A. Mazid, M. T. Razi, P. J. Sadler, G. N. Greaves, S. J. Gurman, M. H. J. Koch, and J. C. Phillips, *J. Chem. Soc., Chem. Commun.*, 1980, 1261.
5 D. T. Hill, B. M. Sutton, A. A. Isab, M. T. Razi, P. J. Sadler, J. M. Trooster, and J. M. Calis, *Inorg. Chem.*, 1983, **22**, 2936.
6 C. F. Shaw, G. Schmitz, H. O. Thompson, and P. Witkiewics, *J. Inorg. Biochem.*, 1979, **10**, 317.
7 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1981, 1657.
8 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Chem. Commun.*, 1976, 1051.
9 A. A. Isab and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, 1982, 135.
10 G. M. Otiko, M. T. Razi, P. J. Sadler, A. A. Isab, and D. L. Rabenstein, *J. Inorg. Biochem.*, 1983, **19**, 227.
11 G. D. Thorn, *Can. J. Chem.*, 1955, **33**, 1278.
12 L. Maier, *Helv. Chim. Acta*, 1970, **53**, 1417.
13 P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188.
14 C. F. Shaw, J. Eldridge, and M. P. Canaro, *J. Inorg. Biochem.*, 1981, **14**, 267.
15 M. C. Grootveld, M. T. Razi, and P. J. Sadler, *Clin. Rheumatol.*, 1984, **3** (suppl. 1), 5.
16 C. F. Shaw, N. A. Schaffer, R. C. Elder, M. K. Eidness, J. M. Trooster, and G. H. M. Calis, *J. Am. Chem. Soc.*, 1984, **106**, 3511.
17 C. J. Danpure, *Biochem. Pharm.*, 1976, **25**, 2343.
18 A. A. Isab and M. S. Hussain, *Polyhedron*, 1985, **4**, 1683.
19 M. S. Hussain and A. A. Isab, *Transition Met. Chem.*, 1984, **9**, 398.
20 M. S. Hussain and A. A. Isab, *J. Coord. Chem.*, 1985, **14**, 17.
21 M. S. Hussain and A. A. Isab, *Transition Met. Chem.*, 1985, **10**, 178.

† The positive shift indicates a high-field shift of resonance.

Received 29*th April* 1985; *Paper* 5/691