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Competition Between Gold(I) Thiomalate 'Myocrisin' and Five-member and Six-member Heterocyclic Ligands

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Abstract

The interactions of gold(I) thiomalate ('Myocrisin') [Au(tm)] with imidazolidine-2-thione [Imt] (a five-member heterocyclic ligand) and 1,3-diazinane-2-thione [Diaz] (a six-member heterocyclic ligand) are studied in aqueous solution at pH* 7.20 using ^{13}C NMR spectroscopy. It is found that [Au(tm)] forms a 1:1 complex at tm–Au–R where R = Imt or Diaz. However, Imt binds more strongly to gold(I) than to Diaz as seen by ^{13}C NMR spectroscopy.

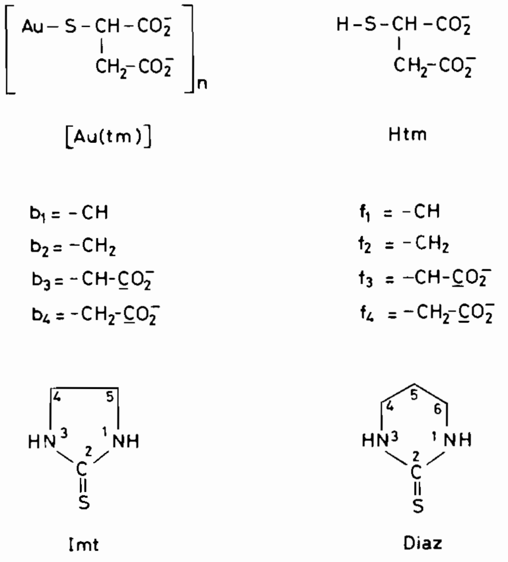
Introduction

The gold(I)–thiolate complexes have been used as antiarthritic drugs since 1929. These complexes are water-soluble but exist in powder form. The structures in solution have been determined by NMR spectroscopy. Both drugs, *i.e.* gold(I) thiomalate [Au(tm)] and gold(I) thioglucose [Au(tg)], exist as polymers in the solid state as well as in solution [1–3]. This polymerization occurs up to hexamers but can be dissociated in the presence of thiols, CN^- and thione-containing ligands, forming a tm–Au–ligand complex [4–7].

In the present paper, we report the relative binding strengths of a five-member ring heterocyclic ligand, imidazolidine-2-thione [Imt], and a six-member ring heterocyclic ligand, 1,3-diazinane-2-thione [Diaz], with [Au(tm)] in aqueous solution, as determined by ^{13}C NMR spectroscopy.

Experimental

[Au(tm)] was obtained from ICN K and K Laboratories, Plainview, New York. It was analyzed as [Au(tm)] 0.33 glycerol·H_2O [8, 9]. Imt and Diaz were synthesized as described in the literature [10, 11]. ^{13}C NMR spectra were measured at 50 MHz on a Varian XL-200 NMR spectrometer operating in the pulsed Fourier-transform mode. Carbon-13 chemical shifts were measured relative to the CH_2 resonances of internal glycerol (g_2), which occurs at 63.33 ppm from $SiMe_4$. The resonance assignments for [Au(tm)], Htm, Imt and Diaz are shown in Scheme 1.



Scheme 1.

pH* indicates an actual meter reading for D_2O solution with no correction for deuterium isotope effects [12].

Results

Figure 1a shows the ^{13}C NMR spectrum of [Au(tm)] in D_2O solution. The addition of Imt as a solid to the [Au(tm)] (0.300 mol dm^{-3}) D_2O solution at various equivalent molar ratios resulted in a higher field shift of the b_1 resonance, from 47.81 to 46.59 ppm, as shown in Fig. 1b to 1d. The b_2 resonance remains almost unshifted throughout the titration. The b_3 resonances were shifted from 181.98 ppm to 183.08 ppm, and the b_4 resonance from 179.44 to 180.10 ppm (Table I).

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TABLE I. Chemical Shifts of [Au(tm)]:Imt at Various Molar Ratios. The pH* was 7.20 Throughout the Titration. The Values are Taken from Fig. 1, some of the Spectra are not Shown in Fig. 1

Spectrum	Imt:[Au(tm)]	b_3	b_4	C-2	b_2	b_1	C-4, 5
–	1:0	–	–	182.05	–	–	45.38
a	0:1	181.98	179.46	–	47.81	47.81	–
–	1:0.25	182.43	179.74	–	47.90	–	45.90
b	1:0.50	182.77	179.93	178.40	47.90	46.85	45.81
c	1:0.75	182.91	180.02	178.98	47.88	46.70	45.74
d	1:1	183.08	180.10	179.47	47.88	46.59	45.70

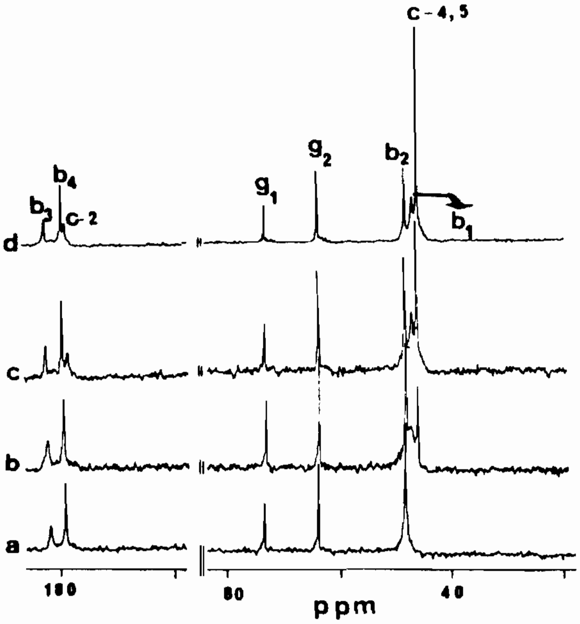

Fig. 1. The 50 MHz ^1H noise-decoupled ^{13}C NMR spectra of [Au(tm)]:Imt at various molar ratios (pH* 7.20 for all samples): (a) 0.300:0, (b) 0.300:0.150, (c) 0.300:0.225, (d) 0.300:0.300. g_1 and g_2 are the $-CH$ and $-CH_2$ resonances of glycerol, respectively.

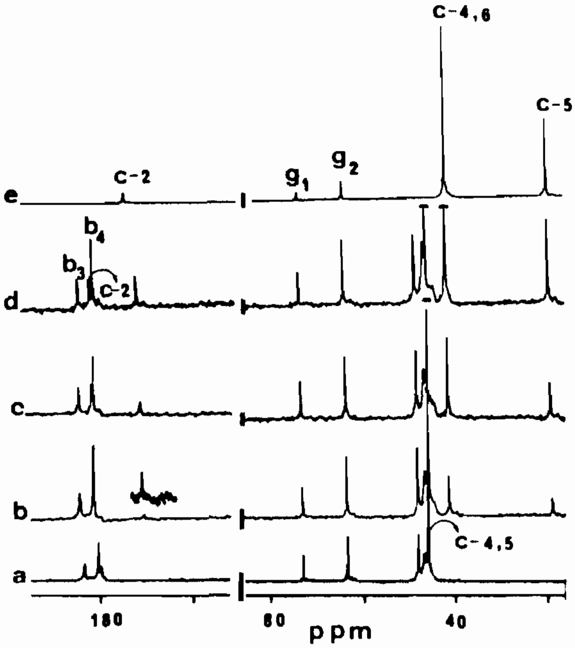

Fig. 2. The 50 MHz ^1H noise-decoupled ^{13}C NMR spectra of [Au(tm)]:Imt:Diaz at various molar ratios (pH* 7.20 for all samples): (a) 0.300:0.300:0, (b) 0.300:0.300:0.075, (c) 0.300:0.300:0.150, (d) 0.300:0.300:0.300, (e) 0:0:0.05.

The C-2 resonance of Imt was shifted from 182.05 ppm to 179.49 ppm, a total shift of 2.55 ppm, at a 1:1 ratio of [Au(tm)]:Imt.

Figure 2a shows the spectrum of [Au(tm)]:Imt at a 1:1 ratio. When Diaz was added as a solid, the b_1 resonance shifted a little further high field from 46.59 to 46.05 ppm, as shown in Fig. 2b. Very small shifts were observed for the b_2, b_3, and b_4 resonances (see Table II).

The C-2 resonance of Imt, which was at 179.47 ppm at a 1:1 ratio, shifted toward a free position at 181.05 ppm when the 1:1:1 ratio was reached for [Au(tm)]:Imt:Diaz. The C-2 resonance of Diaz shifted from 173.29 ppm to 170.91 ppm, a total shift of 2.38 ppm, whereas a shift of 182.05 ppm to 181.05 ppm, a total shift of 1.00 ppm, was observed for Imt at a 1:1:1 ratio of [Au(tm)]:Imt:Diaz.

Figure 3a shows a ^{13}C NMR spectrum of Imt, and Fig. 3b shows a ^{13}C NMR spectrum of $[(Imt)_2Au]Cl \cdot H_2O$. The complex was prepared as described in the literature [13, 14]. The C-2 resonance of Imt shifted by 6.32 ppm after complexing with gold(I). Both spectra were recorded at pH* 7.20 in aqueous D_2O solutions.

Figure 4 shows the shift of the C-2 resonances of Imt and Diaz as a function of concentration. At a 1:1 ratio of [Au(tm)]:Imt a shift of 2.55 ppm was observed for the C-2 resonance. However, at the same ratio of [Au(tm)]:Diaz a shift of 2.05 ppm was observed for the C-2 resonance [7].

TABLE II. Chemical Shifts of [Au(tm)]:Imt:Diaz at Various Molar Ratios. The pH* of the Solution was 7.20 Throughout the Titration. The Values are Taken from Fig. 2, some of the Spectra are not Shown in Fig. 2

Spectrum	[Au(tm)]:Imt:Diaz ratio	b_3	b_4	C-2 Imt	b_2	b_1	C-4, 5 Imt	C-2 Diaz	C-4, 6 Diaz	C-5 Diaz
a	1:1:0	183.08	180.10	179.47	47.89	46.59	45.70	–	–	–
b	1:1:0.25	183.25	180.20	180.20	47.90	46.37	45.62	169.48	41.20	19.05
c	1:1:0.50	183.37	180.28	180.57	47.91	46.25	45.57	170.12	41.17	19.09
–	1:1:0.75	183.47	180.33	180.86	47.93	46.14	45.54	170.58	41.15	19.10
d	1:1:1	183.57	180.36	181.05	47.96	46.05	45.52	170.91	41.15	19.15
e	0:0:1	–	–	–	–	–	–	173.29	40.99	19.26
Fig. 3a	0:1:0	–	–	182.05	–	–	45.38	–	–	–
Fig. 3b	$[(Imt)_2Au]Cl \cdot H_2O$	–	–	175.73	–	–	46.07	–	–	–

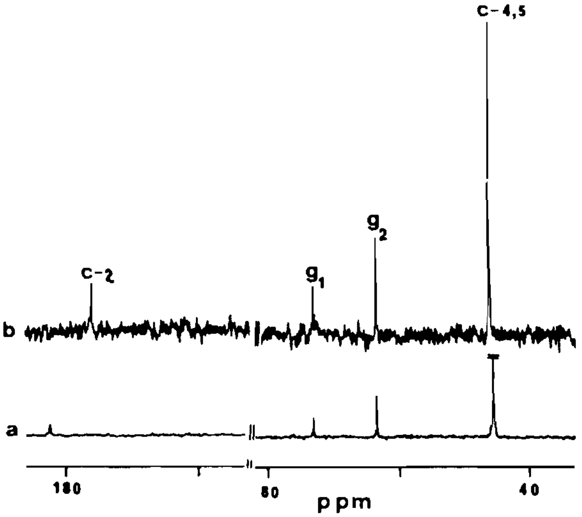

Fig. 3. (a) ^{13}C NMR spectrum of Imt ligand dissolved in D_2O at pH* 7.20, (b) ^{13}C NMR spectrum of $[(Imt)_2Au]Cl \cdot H_2O$ dissolved in D_2O at pH* 7.20.

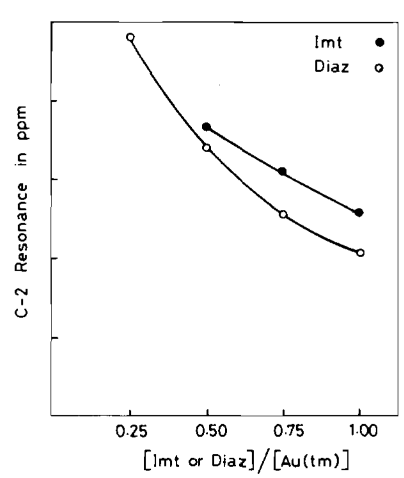

Fig. 4. Shift of the C-2 resonances of Imt (●) and Diaz (○) after binding with [Au(tm)] as a function of concentration. The [Au(tm)]:Diaz data are taken from ref. 7.

Discussion

Mössbauer and EXAFS data have established that gold(I) thiolates such as thiomalate (Htm), thioglucose (Htg), cysteine and glutathione have AuS_2 coordination environments formed by bridging of the thiolate ligands between two gold(I) ions to form oligomers, $[Au(thiolate)]_n$ [4, 15]. When excess thiols are added to $[Au(tm)]_n$ polymers, they usually eject Htm by forming $[Au(thiolate)_2]^-$ species [5].

In the present study, it is shown that thiones behave differently after addition to $[Au(tm)]_n$ solution. Ratios up to 1:1 of thione:$[Au(tm)]_n$ were reached; no Htm resonances were detected, confirming the formation of a bis complex [thione–Au–tm].

The C-2 resonances of Imt shift more than the C-2 resonances of Diaz, as shown in Fig. 3. This is in contrast with the other complexes of Imt and Diaz: e.g., the C-2 resonance was shifted by a 9.67-ppm high field after complexing for [(Diaz)AuCN] but by 7.81 ppm for [(Imt)AuCN]. This is probably due to the hydrophilic character and size of the ligand [16]. Similar effects have been observed for $[(Imt)_2HgCl_2]$, which has a chemical shift difference of 6.99 ppm for the C-2 resonance, compared to 7.33 ppm for $[(Diaz)_2HgCl_2]$ [17]. These spectra are recorded in DMSO/acetone solvents. However, the present study is carried out at pH* 7.20 in aqueous solution. It should be noted that the $[(Imt)_2Au]Cl \cdot H_2O$ complex is water-soluble, while $[(Diaz)_2AuCl]$ is water-insoluble. Also, Au–Cl absorption, which is usually found in the region of 310–320 cm^{-1}, was observed for the $[(Diaz)_2AuCl]$ complex. However, this Au–Cl absorption was not found in the $[(Imt)_2Au]Cl \cdot H_2O$ complex. This shows that $[(Diaz)_2AuCl]$ may be a three-coordinated neutral or a complex polymeric in nature [14].

Both ligands exist as thione form in the solid state as well as in solution as identified by the various groups. After complexing with various metal ions, they still exist in the thione forms [18–21]. In the present study both ligands act as monodentate ligands and bind to $[\mathrm{Au(tm)}]_n$ by forming a water-soluble complex such as L—Au—tm where L = Imt or Diaz.

Conclusions

The five-member ring heterocyclic ligand Imt binds to [Au(tm)] more strongly than does the six-member ring Diaz in aqueous solution.

The C-2 resonance of Imt is shifted the most when gold(I) forms a bis complex such as $[\mathrm{Au(Imt)_2}]\mathrm{Cl}\cdot\mathrm{H_2O}$. However, when one of the Imt is substituted by Htm, then the C-2 resonance is shifted toward the free Imt ligand.

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