136. ^{1}H-NMR Spectroscopy of Gold Drugs. High-Resolution Studies of β-D-Thioglucosetetraacetate Phosphine Complexes of Au(I)

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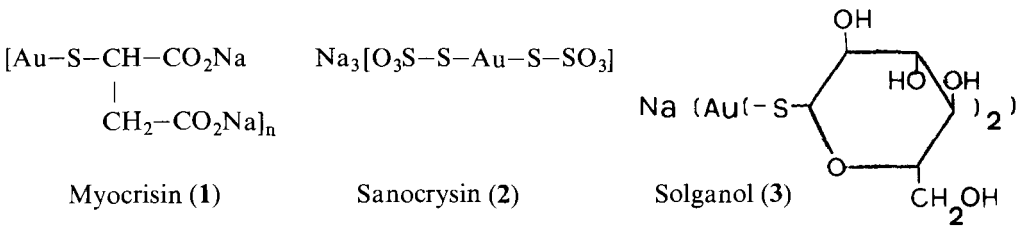
Summary

^{1}H-NMR data (11.74 Tesla) for the gold(I) complexes [R_3P-Au-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosido-S)] (R = Et, Cyclohexyl, C_6H_5, *p*-$CH_3OC_6H_4$) with sulfur coordination to gold, are reported. The resonances associated with the sugar protons have been assigned although these have similar chemical environments. The coordination chemical shifts, $\Delta\delta$, for the Au–S–C–*H* proton are ≈0.6 ppm, and support S-coordination to gold.

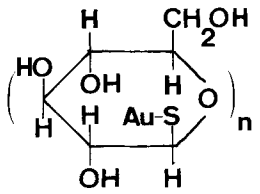
Introduction. – Gold complexes have been used in arthritis therapy for many years [1–3]. Amongst those currently in use are the compounds **1–3** with the thiolate ligands thiomalate, thiosulfate and thioglucose, respectively. All of these complexes contain several S-coordinated ligands although the exact coordination



Myocrisin (**1**) Sanocrysin (**2**) Solganol (**3**)

number and geometry is not always clear, *e.g.*, for **1** polymers are thought to be involved [2]. Even where the coordination chemistry is clear, the biochemistry with respect to the role of the gold remains uncertain [1–3]. Recently, the phosphine complex (2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosido-S)triethylphosphine-gold(I) (= auranofin, **4a** [4]), has been found to be a useful drug which can be taken orally. This linear gold(I) complex is monomeric and is thought to have a P–Au–S-arrangement of atoms. There is ample crystallographic support for such a geometry, *e.g.*, for **2** an S–Au–S angle of 176.5° has been found [5], and in [Au(C_6F_5) (PPh_3)] the C–Au–P angle is 178° [6].

The solution behavior of several gold drugs has been studied by ^{1}H-, ^{13}C- and ^{31}P-NMR spectroscopy [7–10]. Using ^{31}P-NMR, auranofin has been studied in terms of its possible interaction with albumin [7], and the same spectroscopic technique has been used to monitor the reactions of $[AuCl(PEt_3)]$ with glutathione [1] [8]. ^{13}C-NMR spectroscopy has shown that gold(I) thiomalate exchanges with a variety of thiols, and species of composition $Au(SR)_n^{1-n}$ were suggested.



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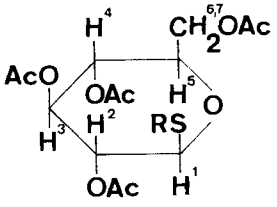

4a R = Au(PEt$_3$)
4b R = H

Although both these forms of NMR spectroscopy will continue to prove valuable, we have concerned ourselves with the ^{1}H-NMR characteristics of **4b** and its gold complexes, since this ligand is a component of both auranofin (**4a**) and solganol (**3**). Specifically, we were interested in determining the feasibility of using this method to monitor changes in the thioglucose due to coordination. This approach will allow us to develop a base of data concerned with *all* of the potential coordination sites of the sugar should the O-atoms eventually be involved. To this end we have measured ^{1}H-NMR spectra at 11.74 T (500 MHz), to overcome potential problems arising from the similarity of the sugar ^{1}H chemical shifts, and report here our model studies for the complexes [R_3P–Au-(2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosido-S)] (R = Et, **4a**; R = cyclohexyl(Cy), **5**; R = C_6H_5, **6**; R = *p*-$CH_3OC_6H_4$, **7**).

Experimental. – The β-D-thioglucose tetraacetate **4b** was obtained from *Aldrich* and used without further purification. $Na(AuCl_4) \cdot 2\,H_2O$ was purchased from *Johnson-Matthey* and used directly. A sample of auranofin (**4a**) was kindly provided by Dr. *B. Sutton* of *Smith Kline and French Philadelphia*, U.S.A. The complexes $[AuCl(PR_3)]$ with R = aryl, were prepared using the method described by *DeStefano & Burmeister* [11]. The thiolate-phosphine gold complexes were synthesized as described by *Schmidbaur et al.* [12]. Specifically:

$[AuCl(PR_3)]$ + β-D-thioglucose tetraacetate

$$\xrightarrow{CH_2Cl_2, NEt_3} [(PR_3)Au(\beta\text{-D-thioglucose tetraacetate-H})] + NEt_3 \cdot HCl$$

Typically the reactions were carried out using $\simeq$ 100 mg of gold complex and although the products were usually obtained in essentially quantitative yield, as judged by the ^{1}H- and ^{31}P-NMR, they sometimes proved difficult to crystallize. Thus for $P(CH_3OC_6H_4)_3$, the product is a colorless solid, whereas for PCy_3 an oil was obtained.

Preparation of [AuCl(PCy$_3$)]. Solid $PCy_3 \cdot CS_2$ (360 mg, 1.0 mmol) was added to a solution of $Na[AuCl_4] \cdot 2\,H_2O$ (199 mg, 0.5 mmol) in 20 ml EtOH. The dark suspension which results was warmed to 50° and maintained at this temperature for 45 min. The colorless filtrate was removed and the remaining solid washed successively with H_2O, EtOH and Et_2O. The product as a colorless solid was then collected (0.195 g, 76%) and shown to be pure by ^{31}P-NMR. ^{1}H- and ^{31}P-NMR spectra were measured as $CDCl_3$-solutions using a *Nicolet* spectrometer operating at 500 MHz for ^{1}H and 202 MHz for ^{31}P. Routinely, 45° pulses were employed with acquisition times of 1–2 sec. ^{31}P chemical shifts are relative to external H_3PO_4; ^{1}H chemical shifts relative to TMS.

Results and Discussion. – ^{1}H-NMR data for the gold complexes, as well as for the protonated ligand are shown in the *Table* and the following points are worth mentioning: 1) High-field ^{1}H-NMR spectroscopy when combined with ^{1}H{^{1}H}-experiments allows for a complete assignment of all of the ring sugar protons in

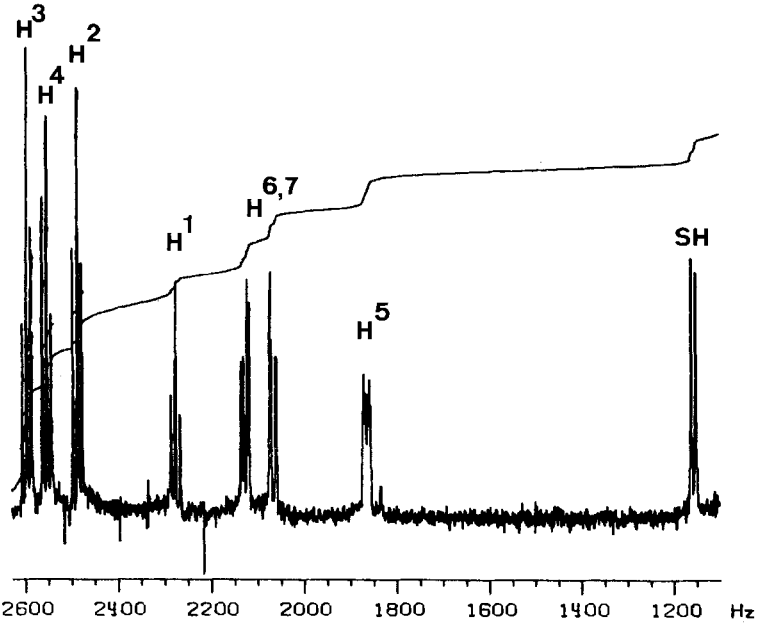

Fig. 1. *^{1}H-NMR Resonances of the Sugar Protons of* **4b** (Note that a) H^1, the proton adjacent to the SH-group, appears at about 2270 Hz and b) that the SH proton couples to H^1)

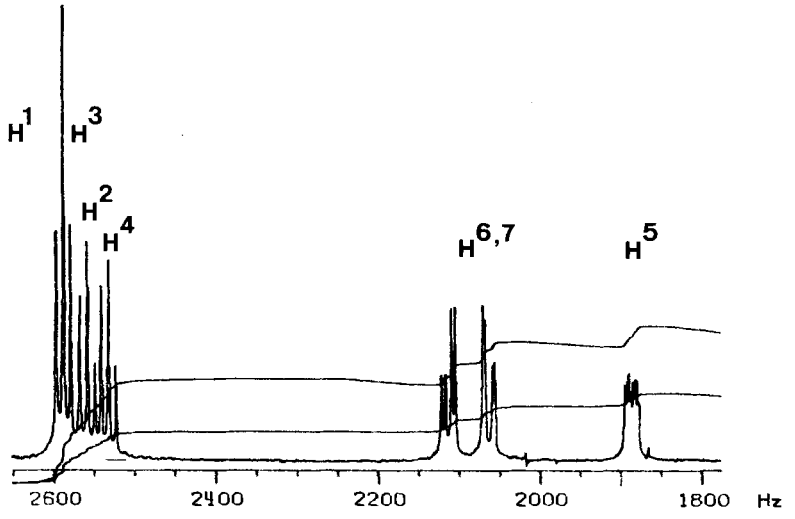

Fig. 2. *^{1}H-NMR Resonances of the Sugar Ring Protons of* **6** (The resonances for H^1 and H^3 overlap)

both the thiol and many of its complexes. The double-resonance experiments started from the readily recognizable *ABX*-pattern for H^5–H^7, after which all of the ring protons were readily traced. 2) The proton H^1 closest to the S-atom experiences a moderate downfield shift of $\simeq 0.6$ ppm on complexation, consistent S-coordination. 3) The remaining ^{1}H-signals in the complexed thiolate, including the acetate CH_3-resonances, do not significantly change their position relative to the ligand **4b**. All four acetate CH_3-resonances are well-resolved. 4) The CH_2-resonances (H^6 and H^7) are non-equivalent. 5) In the thiol the exchange of the S–H proton is slow in $CHCl_3$ $J(H_1\text{–C–S–H}) = 10$ Hz. 6) The substituent R in the phosphine ligand does not strongly influence any of the ^{1}H-NMR parameters of the complexed thiolate.

Point 1 is of value in that it might now prove useful to consider ^{1}H-NMR studies of the reaction of gold drugs with various biologically pertinent molecules. *Figures 1* and *2* clearly show that almost all of the protons in both the thiol and

Table. *^{1}H-NMR Data for the Complexes*[a])

Compound	H^1	H^2	H^3	H^4	H^5	$H^{6,7}$	OAc
β-D-thioglucose$(OAc)_4$[b]) (**4b**)	4.540	4.960	5.179	5.090	3.717	{4.249 / 4.129}	{1.995, 2.010 / 2.068, 2.081}
						$^2J = 12.5$	
	(10)	(10)	(10)	(10)	(10)	{$^3J = 2.5$ / $^3J(H^1, H^5) = 10$)}	
Et_3P–Au–β-D-thioglucose$(OAc)_4$(Auranofin[c]) (**4a**)	5.139	4.948	{complex 5.08}		3.692	{4.070 / 4.212}	{1.952, 1.980 / 2.022, 2.046}
	(10)		H^3 lower field than H^4			$^3J = 2.5$ $^2J = 12$	
Cy_3P–Au–β-D-thioglucose$(OAc)_4$ (**5**)	5.153	5.016	5.128	5.048	3.710	{4.084 / 4.229}	{1.970, 2.001 / 2.059, 2.071}
	(9)	(9)	(9)	(9)	(10)	{$^3J = 2.5$ / $^2J = 12$}	
Ph_3P–Au–β-D-thioglucose$(OAc)_4$[d]) (**6**)	5.180	5.060	5.153	5.112	3.77	{4.134 / 4.226}	{1.900, 1.982 / 2.029, 2.057}
	(9)	(10)	($\simeq$10)	(10)		{$^3J = 2.5$ / $^2J = 11$}	
$(p\text{-}CH_3OC_6H_4)_3P$–Au-thioglucose$(OAc)_4$[e]) (**7**)	5.148	5.034	5.146	5.098	3.75	{4.106 / 4.196}	{1.886, 1.955 / 1.992, 2.032}
	(9)	(9)	(9)	(10)		{$^3J = 2.5$ / $^2J = 12$}	

[a]) In $CDCl_3$ at r.t. Values in parenthesis are $^3J(H,H)$. When only one value is given this implies equivalent coupling constants. Coupling constants are ± 1 Hz.

[b]) $\delta(SH) = 2.314$, $^3J(H,H) \simeq 10$.

[c]) $\delta(^{31}P) = 37.3$, $\delta(CH_2) = 1.822$, $\delta(CH_3) = 1.194$.

[d]) Assigned by analogy with **5**.

[e]) Aromatic protons: 6.96 and 7.45, CH_3O at 3.82.

complex give well-resolved resonances. In the Ph_3P-complex, H^1 and H^3 have similar chemical shifts although $^1H\{^1H\}$-experiments allow the correct assignment. Regrettably, for the commercial complex auranofin (**4a**) there is appreciable overlap, indeed the spectrum has considerable second – order character – nevertheless an assignment is possible[1]).

Knowing the chemical shift of H^1 in the complexes should prove a useful empirical tool in studies where exchange of thiol is possible [7–10]. The high-field position of H^1 in the protonated ligand, $\delta = 4.450$, relative to its value in the complexed thiolate, $\delta = 5.139$–5.180, will facilitate its recognition if the thioglucose is set free.

Point 3 is logical in that sites remote from coordination are not expected to experience large changes, as is point 4 since we are studying chiral molecules. In connection with this nonequivalence of the CH_2-protons, we note that, in all cases, the low-field half of the $H^6, H^7 AB$ spin system shows a larger coupling to H^5, $\simeq 5$ Hz, than does the higher-field proton. The geminal coupling constant $^2J(H^6, H^7)$ $\simeq 12$ Hz is constant throughout our series, as are all of the vicinal coupling constants associated with the sugar moiety ($^3J(H,H) \simeq 9$–10 Hz). The absence of changes in the chemical shift data as a function of the tertiary phosphine suggests that either the *trans*-influences of these ligands are very similar or that the thioglucose protons are insensitive to these differences.

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[1]) This seems a candidate for 2-D NMR spectroscopy.