The Effect of Solvent on the Reaction of Sodium Tetrachloroaurate and 2-Mercaptosuccinic Acid

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Gold compounds remain among the few therapeutic agents which can produce a remission of the symptoms of rheumatoid arthritis [1–3]. The gold is usually given as a gold(I) sulphur compound and is distributed widely *in vivo*, occurring in almost all protein, cellular and tissue fractions examined so far. It is presumed that this distribution is caused by exchange reactions with naturally occurring thiol and disulphide groups. In the absence of any known specific mechanism of action of gold compounds, and in view of the wide distribution of the gold *in vivo*, it seemed of interest to try to understand the non-enzymatic chemistry of gold and sulphur. Many *in vivo* environments are more akin to non-aqueous solvents than to aqueous solutions and yet the effect of the solvent on the chemistry of gold has not been studied in much detail. As part of this problem we chose to study *in vitro* the reaction of 2-mercaptosuccinic acid (thiomalic acid) with sodium tetrachloroaurate in water, ethanol and acetonitrile. Thiomalic acid is the ligand used in the gold drug Myoccrysin (Sodium aurothiomalate).

In water, thiomalic acid and sodium tetrachloroaurate react to give a colourless to yellow solution with a spectrum characteristic of gold(I), and similar to that produced by the dissolution of sodium aurothiomalate in water. The colour of this solution can be varied from colourless to yellow by changes in pH or the addition of sodium chloride. This is due to a shift in the charge transfer band edge and an increase in intensity of a low energy shoulder at about 280 nm in the electronic spectrum. There is no evidence of a peak at about 330 nm which is characteristic of many gold(III) compounds [4]. Thus, it would seem that in water, thiomalate produces a ready reduction to gold(I).

However, in absolute ethanol, anhydrous sodium tetrachloroaurate and thiomalic acid solutions produced an immediate precipitate which on analysis proved to be sodium chloride. The electronic spectra of a 1/1 solution was similar to that of sodium tetrachloroaurate but the intensity was reduced to about 70% of the aqueous value. The spectra are similar to those noted before for equilibria between $AuCl_4^-$ and $AuCl_3^-OH^-$ [7] and $AuCl_4^-$ and $AuCl_3$ DMS [8] and are typical of a wide range of mono-substituted gold(III) chloride complexes [4]. Addition of Et_4NAuCl to the solution produced a precipitate of Et_4NAuCl_4, confirming the presence of gold(III).

Traces of water produced a decolouration of the solution with time and no further evidence of gold(III) could be obtained (Fig. 1). Spectroscopic and conductometric titrations of anhydrous solutions indicate 2:1 and 1:1 compounds and the presence of compounds with 1.5/1 and 1/2 acid to gold ratios. The results were dependent on the time taken for the titrations and may indicate the presence of polymeric species in solution. Solution infrared spectra indicate that the carboxylate groups are not involved in the bonding. Thus, by comparison which aqueous solution, gold(III) thiol species appear to be relatively stable in ethanol.

In acetonitrile, a 1/1 mixture produced an immediate white precipitate which analysed for Au thiomalate NaCl. The precipitate continued to form for some hours and initial and subsequent fractions of the precipitate gave similar analytical results. Replacement of sodium tetrachloroaurate with chloroauric acid produced the complex Au thiomalate HCl.

The solution remained yellow with a typical Au(III) spectra and the yield of the solid was about 30%. The complex is bonded through the sulphur and on dissolution in ethanol of gold(I) spectrum was observed.

The low affinity of the carboxylate groups for gold makes thiomalic acid a reasonable model for an isolated thiol in a protein system and the effect of solvent on the stability of gold(III) and on the solubility of the gold product in the reaction is quite marked. It arises partly from a competition between coordination.

$$RSH + AuCl_4 \longrightarrow RS\,AuCl_3 + Cl^-$$

and reduction,

$$RSH + AuCl_4 \longrightarrow Au(I)SR + RSSR + 3HCl + Cl^-$$

and partly from the ability of gold to form complex insoluble compounds of the type found in acetonitrile.

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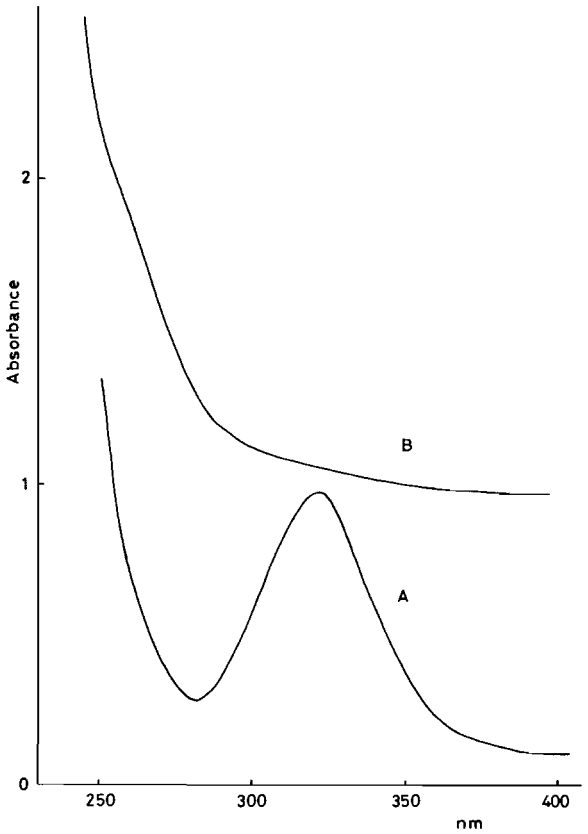

Fig. 1. Spectra of an ethanolic solution of 2×10^{-3} molar sodium tetrachloroaurate containing a two-fold molar excess of thiomalic acid and a trace of water. Spectrum A, taken immediately the solution was prepared, is typical of the gold(III) solutions and spectrum B, taken after one week, is typical of the gold(I) solutions. The baseline of B has been offset by 0.9 absorbance units. Allowing for some variation in peak position, the spectra are similar in form to those found in aqueous and acetonitrile environments.

The production of gold(III) from gold(I) is well within the compass of mamalian systems and stable gold(III) complexes of penicillamine [5] and BAL [6] have been characterised *in vitro*. Thus the solvent environment may be a key feature in determining the presence or absence of gold(III). Further, aggregates of gold sulphur compounds have been detected *in vivo* and although insoluble gold(I) cysteinate may be a good model for these compounds, the difference between the water and ethanol soluble acetonitrile insoluble complex reported here and sodium aurothiomalate which is water soluble and ethanol and acetonitrile insoluble suggests that complexes which are soluble in water could still act as storage forms for gold in lipid environments. Thus, from a chemical view-point, it is clear that the chemistry of gold in lipids cannot be predicted from our present, largely water based, knowledge of gold chemistry and much requires to be done *in vitro* before *in vivo* effects can be understood.

References

1 D. T. Walz, M. J. Di Martino and B. M. Sutton in 'Anti-inflammatory Agents', Ed. Whitehouse, Academic Press, 1974, Vol. 1, p. 217.
2 F. Shaw, *Inorganic Perspectives in Biochemistry and Medicine, 2*, 287 (1979).
3 D. H. Brown and W. E. Smith, *Chem. Soc Reviews*, 9, 217 (1980).
4 D. H. Brown, G. C. McKinlay and W. E. Smith, *Inorg. Chim Acta, 32*, 117 (1979).
5 D. H. Brown, G. C McKinlay and W. E. Smith, *J. Chem. Soc. Dalton*, 199 (1978).
6 D. H. Brown, G. C. McKinlay and W. E. Smith, *J Inorg. Biochem., 10*, 275 (1979).