Gold Complexes of L-Cysteine and D-Penicillamine

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The preparation of a range of gold-(I) and -(III) complexes of L-cysteine and D-penicillamine is described. In the presence of chloride, L-cysteine forms gold(I) complexes and D-penicillamine forms gold(III) complexes. In the presence of triphenylphosphine only gold(I) complexes are obtained. Ultraviolet–visible spectra are reported.

PERHAPS the best established use of heavy transition metals and their complexes in the treatment of disease is the use of gold complexes as anti-inflammatory drugs in rheumatoid arthritis.[1] The initial reason for their introduction was based on erroneous reasoning and even yet little is known of the *modus operandi*. It has been suggested [2] that it is the metal ion which is effective and different gold complexes have been used successfully. Chemically, it seems likely that gold will be involved with the sulphydryl or disulphide groups of proteins or enzymes,[3] many of which arise from cysteine or cystine residues. A range of gold(I) complexes with ligands containing SH or S^- groups is known, including those of thiomalic acid and thioglucose which are used commercially as drugs. One major drawback to gold therapy is that, in certain cases, toxic side-effects occur.[4] One method of dealing with these has been treatment of the patient with D-penicillamine [5] (β-mercaptovaline) which is a β-substituted dimethylcysteine. The efficiency of this treatment has been questioned.[6]

The difference in complexing behaviour of D-penicillamine and L-cysteine in biological systems has been utilised in the mobilisation of copper in the treatment of Wilson's disease [7] by D-penicillamine. D-Penicillamine is much more efficient in removing the excess of copper present in patients having Wilson's disease. Although the mechanism for this selective reaction is as yet unresolved, there are parallel differences in the chemistry of these ligands with first-row transition-metal ions.[8,9]

In this paper we examine the reactions of Au^0, Au^I, and Au^{III} with L-cysteine and D-penicillamine.

EXPERIMENTAL AND RESULTS

The ligand complexing species in each case appeared to be the monoanion.

Preparations.—*L-Cysteinatogold*(I). From a 1 : 1 10^{-2} mol dm^{-3} aqueous solution of L-cysteine and $K[Au(CN)_2]$,[10] a white solid precipitated {Found: C, 11.0; Au, 61.9; N, 4.2; S, 10.3. [Au(L-cys — H)] requires C, 11.3; Au, 62.2; N, 4.4; S, 10.0%}.

Sodium chloro(L-*cysteinato*)*aurate*(I) *trihydrate*. From a 5 : 1 10^{-2} mol dm^{-3} solution of L-cysteine hydrochloride and $Na[AuCl_4]$ in water, a pale yellow solid precipitated {Found: C, 9.0; H, 2.0; Cl, 8.2; Na, 5.0; S, 7.6. Na[Au(L-cys — H)Cl]·$3H_2O$ requires C, 8.4; H, 2.5; Cl, 8.2; Na, 5.4; S, 7.4%}.

Sodium chloro(D-*penicillaminato*)*aurate*(I) *dihydrate*. From a 1 : 2 10^{-2} mol dm^{-3} aqueous solution of D-penicillamine hydrochloride and $Na[AuCl_4]$, a pale yellow solid precipitated, the reaction being carried out under nitrogen {Found: C, 13.2; H, 2.2; Cl, 8.6; N, 3.1; Na, 5.0. Na[Au(D-pen — H)Cl]·$2H_2O$ requires C, 13.6; H, 2.1; Cl, 8.1; N, 3.2; Na, 5.2%}.

Bis(D-*penicillaminato*)*gold*. From a 5 : 1 10^{-2} mol dm^{-3} solution of D-penicillamine hydrochloride and $Na[AuCl_4]$ in ethanol, an orange-red solid precipitated {Found: C, 24.2; H, 3.9; N, 5.7; S, 12.8. $[Au(D\text{-pen} - H)_2]$ requires C, 24.3; H, 4.0; N, 5.7; S, 12.9%}.

L-*Cysteinato*(*triphenylphosphine*)*gold*(I) *dihydrochloride*. A 1 : 1 solution in cold ethanol of $[Au(PPh_3)Cl]$ [11] and D-penicillamine hydrochloride was made and excess of solvent removed *in vacuo* until a white precipitate appeared {Found: C, 38.5; H, 3.9; Cl, 12.3; N, 2.6; S, 4.6. $[Au(PPh_3)$(L-cys — H)]·2HCl requires C, 38.6; H, 3.1; Cl, 10.9; N, 2.1; S, 4.9%}.

D-*Penicillaminato*(*triphenylphosphine*)*gold*(I) *dihydrochloride*. This was prepared as above but with D-penicillamine in place of L-cysteine {Found: C, 40.5; H, 4.2; Cl, 11.0; N, 1.8; S, 5.0. $[Au(PPh_3)$(D-pen — H)]·2HCl requires C, 40.5; H, 3.7; Cl, 10.4; N, 2.0; S, 4.7%}.

D-*Penicillaminato*(*triphenylphosphine*)*gold*(I) *dihydrate*. This was prepared as above but using $[Au(PPh_3)(NO_3)]$ and D-penicillamine as starting materials and water–ethanol mixture as solvent {Found: C, 42.7; H, 4.4; N, 2.6; S, 5.2. $[Au(PPh_3)$(D-pen — H)]·$2H_2O$ requires C, 42.9; H, 4.2; N, 2.1; S, 5.0%}.

Carbon, hydrogen, nitrogen, chlorine, and sulphur were carried out by standard microanalytical techniques, and sodium and gold by atomic absorption. The c.d. and u.v.–visible spectra were run as KCl discs and, in certain cases, coated as ethanol smears on silica discs to check that no reaction had taken place with KCl. The u.v.–visible spectra were run on a Pye-Unicam SP 1800 spectrophotometer and the c.d. spectra on an instrument designed in this laboratory and described previously.[12]

Reactions in Solution.—*Starting with gold*(0).—Colloidal gold reacted with 10^{-2} mol dm^{-3} L-cysteine hydrochloride and D-penicillamine hydrochloride in aqueous solution in

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the presence of oxygen. After 1 week at room temperature the c.d. spectra of the solutions gave Cotton effects at 370 and 300 nm for the L-cysteine solution and 510 and 400 nm for the D-penicillamine solution. In the absence of oxygen no reaction occurred.

Starting with gold(I). Using a 10^{-2} mol dm^{-3} solution of $K[Au(CN)_2]$ in dilute hydrochloric acid (pH 3.5), the addition of a five-fold excess of D-penicillamine hydrochloride gave, after 1 d, a solution showing Cotton effects at 370(−) and 300(+) nm. The same experiment but at pH 9.4 resulted in a different c.d. spectrum with Cotton effects at 510(+) and 430(−) nm. The latter experiment carried out under nitrogen gave Cotton effects at 370(−) and 300(+) nm. Under acid conditions, L-cysteine gave the relatively insoluble complex [Au(L-cys − H)]. In alkaline solution a solution was obtained which gave the same c.d. spectrum as a solution of [Au(L-cys − H)]. Myocrisin, a commercial, optically inactive, gold(I) complex of thiomalic acid used in the treatment of rheumatoid arthritis, at pH 8 gave Cotton effects at 510(+) and 440(−) nm in the presence of a five-fold excess of D-penicillamine and at 370(−) and 300(+) nm in a five-fold excess of L-cysteine.

Starting with gold(III). Using 10^{-2} mol dm^{-3} solutions of $Na[AuCl_4]\cdot 2H_2O$ in water, the addition of equimolar amounts of D-penicillamine resulted in the precipitation of a pale yellow salt which decomposed rapidly to Au^0. In the presence of nitrogen, a gold(I) complex, Na[Au(D-pen − H)Cl]·$2H_2O$ was isolated. Using a five-fold excess of D-penicillamine, stable solutions were obtained which showed Cotton effects at 530(−), 488(+), and 405(−) nm. With 1 : 1 L-cysteine in dilute acid solution, a transient red colour was observed in solution and a brown film of Au^0 formed. Addition, in acid solution, of excess of L-cysteine gave the solid [Au(L-cys − H)] (see above). In alkali, stable solutions were obtained using a 1 : 2 ratio of Au^{III} to L-cysteine. These gave Cotton effects at 392(−) and 335(+) nm. Using excess of L-cysteine in solutions at pH 2—11, *ca.* 40% of the L-cysteine present was converted into L-cystine. Manometry showed that oxygen was consumed quantitatively in the reaction according to equation (1). In the absence of oxygen, only trace amounts of L-cystine were produced.

$$4\ \text{L-cysteine} + O_2 \longrightarrow 2\ \text{L-cystine} + 2H_2O \quad (1)$$

Circular dichroism and electronic spectra of the solid gold complexes

Complex	Cotton effect (λ/nm)	U.v.–visible spectra (λ/nm)
[Au(L-cys − H)]	410(+), 380(−), 338(+), 288(+)	240, 330, 350
Na[Au(L-cys − H)Cl]·$3H_2O$	380(−), 335(+), 260(−)	370
Na[Au(D-pen − H)Cl]·$2H_2O$	390(+), 300(−)	370, 290
[Au(PPh_3)(L-cys − H)]·2HCl	370(−), 330(+), 295(−)	360, 290, 262, 268, 276 340, 260
[Au(PPh_3)(D-pen − H)]·2HCl	370(+), 205(+)	370, 300, 262, 268, 276, 240
[Au(PPh_3)(D-pen − H)]·$2H_2O$		
[Au(D-pen − H)$_2$]	515(−), 475(+), 440(+), 360(+)	480, 400, 340, 274
$Na[AuCl_4]$ [a]		480, 410, 312
[Au(py)Cl_3] [b]		470, 360, 320, 260
Na_2[Au(tmal)] [c]		360, 320, 260, 230

[a] D. H. Brown and W. E. Smith, *J.C.S. Dalton*, 1976, 848. [b] Prepared as in C. Renz, *Z. anorg. Chem.*, 1103, **36**, 100. [c] tmal = Thiomalate.

DISCUSSION

One major problem that arises in discussing the chemistry of gold complexes is the oxidation state of the gold present. Magnetic measurements are unsatisfactory since gold(I), a d^{10} ion, and gold(III), a d^8 ion, are both diamagnetic. Ultraviolet–visible spectral measurements are difficult to interpret, since they generally consist of relatively intense overlapping charge-transfer bands in the u.v. which tail towards the visible, with a few shoulders or weak peaks in the blue region. However, using optically active ligands, well defined Cotton effects are generally observed in the c.d. spectra. When these can be related to compounds of known stoicheiometry reasonable assignments of oxidation states can be made. In this work, the gold(I) complexes containing at least one sulphur ligand showed Cotton effects at <400 nm, whereas the one gold(III) complex showed at least three Cotton effects at >400 nm. The u.v.–visible spectra of two non-optically active gold(III) complexes are included in the Table. A single-crystal study of $Na[AuCl_4]$ showed absorption peaks (above 400 nm) at 410 and 480 nm. In a KCl disc, the complex [Au(py)Cl_3] (py = pyridine) gave a peak at 480 nm. Thus, in the solutions used, the presence of gold(I) complexes was assumed if the Cotton effects observed were at <450 nm and if Cotton effects were observed at >450 nm gold(III) complexes were thought to be present. Further information on the oxidation state of gold in the penicillamine complex was obtained using ^{197}Au Mössbauer spectroscopy. The observed shift of 3.01 mm s^{-1} and a splitting of 3.74 mm s^{-1} are typical of gold(III)–sulphur complexes.[13]

From their spectra, the phosphine complexes are likely to contain Au^I. [Other gold(I) phosphine complexes have been previously reported.[11,12]] The solid obtained using [Au(PPh_3)Cl] and the ligand hydrochloride contained two chloride ions. When [Au(PPh_3)(NO_3)] and D-penicillamine are used the complex [Au(PPh_3)(D-pen − H)]·$2H_2O$ is obtained. This has the same u.v.–visible and c.d. spectra as the chloride species, suggesting that the chloride ions in the latter are not complexed to the gold and that the species are linear gold(I) complexes of the form $\geq$P–Au–S–. The u.v.–visible and c.d. spectra of [Au(L-cys − H)] and its analysis suggest a gold(I) complex, which again is probably linear.

The two complexes Na[Au(L-cys − H)Cl] and Na[Au(D-pen − H)Cl], from their analyses and u.v.–visible

[13] J. S. Charlton and D. I. Nichols, *J. Chem. Soc.* (*A*), 1970, 1484; T. Cranshaw, unpublished work.

and c.d. spectra, appear to contain Au^{I}. The L-cysteinato-complex dissolves completely in water to give a solution which has the same u.v.–visible and c.d. spectra as [Au(L-cys — H)]. The D-penicillaminato-complex, on the other hand, partly dissolved in water to give a solution whose c.d. spectrum suggests the presence of Au^{III}. The residue was confirmed by analysis to be gold metal. It is possible that disproportionation of the gold(I) complex took place to give Au^{0} and a gold(III) D-penicillaminato-complex. The structures of gold(I) complexes containing one thiol group are probably polymeric. A recent study [14] has suggested that Au^{I} forms clusters with thiomalic acid in solution. However, little is known of the structures of gold(I) complexes with thiols, although S-bridging is likely in some cases.

The orange solid [Au(D-pen — $H)_2$], from its u.v.–visible, c.d., and Mössbauer spectra and analysis, appears to contain Au^{III}. The i.r. spectrum of the solid gave two peaks in the carboxylate region at 1 710 and 1 585 cm^{-1}, suggesting that one carboxylate is either complexed or ionised and the other un-ionised. The ionised carboxylate, plus the two sulphide groups, could balance the charge of the gold(III) ion. The change in frequency of the NH_2 modes from 3 380 and 3 280 cm^{-1} in the free ligand to 3 220 cm^{-1} in the complex suggests that the NH_2 groups are also complexed. The structure therefore could be square planar with co-ordinated sulphur and nitrogens. The position of the ionised carboxyl group is unclear; perhaps in the solid state it occupies a fifth co-ordination site in a neighbouring ion giving a polymeric species. No stable gold(III)–L-cysteine complex was isolated, although a transient red colour obtained on mixing L-cysteine with $Na[AuCl_4]$ could be indicative of an unstable complex in solution.

The oxidation of metallic gold with atmospheric oxygen in the presence of a stabilising ligand is well known and is the basis of the extraction of gold from its ores. The different properties of L-cysteine and D-penicillamine towards gold are exemplified by the different products from their reactions with Au^{0}, namely Au^{I} with cysteine and Au^{III} with penicillamine. Similar results arise from their reactions with $K[Au(CN)_2]$ in the presence of oxygen.

The commercial product myocrisin, used extensively as an anti-inflammatory agent in the treatment of rheumatoid arthritis, is a gold(I) thiomalato-complex. When this was added to excess of D-penicillamine at approximately blood pH a gold(III) complex was formed. Since a significant amount of gold in blood is complexed to albumin, either directly or as a gold(I) thiomalate adduct,[15] it would be expected that the treatment of patients suffering from gold toxicity with high doses of D-penicillamine would result in a redistribution of gold in the body. Unless the excess of D-penicillamine is maintained, decomposition of the complex would be expected and gold(0) deposits and other gold complexes would be formed. However, in the presence of excess of D-penicillamine the complex is surprisingly stable. Naturally occurring compounds like alanine, fructose, and tartaric acid, which reduce the tetrachloroaurate(III) ion rapidly, have no effect on the penicillamine complex.

Starting with Au^{III}, a stable solution of a gold(III) D-penicillaminato-complex was obtained only in the presence of an excess of D-penicillamine. At a *ca.* 1 : 1 ratio of the components, solids were obtained which in air were reduced to Au^{0}. Thus, in the presence of excess of ligand, oxygen is necessary for the oxidation of Au^{I} to the stable [Au^{III}(D-pen — $H)_2$] complex, whereas under other conditions, notably the presence of less ligand, oxygen is apparently involved in the reduction of gold. This latter reaction produces several organic products such as dipenicillamine and so the reduction products could result from the decomposition of an unstable monosubstituted gold complex.

L-Cysteine reacts quite differently, in that a gold(I) complex is the stable species formed and, in the presence of excess of L-cysteine, oxygen is consumed in the oxidation of L-cysteine to L-cystine.

Since the reactions of L-cysteine with other metal ions [8,9] are different from those of D-penicillamine, it is not surprising that they also differ with gold, but the ability to produce different stable valence states under a range of experimental conditions is a particularly clear-cut example of the differences between these ligands. The reason for this difference could, for example, be due to steric effects, to a difference in bond character affecting the formation of dioxygen intermediates, or to differences in the ' hardness ' of the sulphur caused by the electron-donating groups of penicillamine. A recent study of a complex formed between copper and penicillamine,[16] however, indicates how complicated the present system may be and so a detailed analysis will require further studies. Nevertheless, it is clear that the use of penicillamine to remove gold or the combination of gold and penicillamine therapies could produce *in vivo* gold(III) complexes which may well be potentially more toxic than the gold(I) species used as drugs.

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