Concerning the nature of the gold-containing anti-arthritic drug, myochrysine

Helen E. Howard-Lock, Daren J. LeBlanc, Colin J. L. Lock,* Richard W. Smith and Zhixian Wang

Laboratories for Inorganic Medicine, Departments of Chemistry and Pathology, McMaster University, ABB-266A, Hamilton, ON, L8S 4M1, Canada

An ammonium analogue of the main component of the anti-arthritic drug myochrysine, disodium thiomalato-*S*-aurate(I) polymer, is examined by both positive- and negative-ion electrospray ionization (ESI) mass spectrometry; the principal peaks are those of a tetrameric species; subsequent examination of a drug sample by the same technique showed that the principal peaks were also those of a tetrameric species.

The gold complex, disodium thiomalato-*S*-aurate(I) polymer **1**, is one of the components of the drug marketed in Canada as myochrysine. The drug, as marketed, is a mixture.[1] It is generally agreed that the main component is a polymer, but there is no consensus on the degree of polymerization, and various models have been proposed that include a cyclic hexamer,[2] cyclic pentamer,[3] open-chain polymer based on a tetrameric repeat unit[4] and open chain octamer.[5] We have synthesized an ammonium salt analogue of the main component of myochrysine, diammonium thiomalato-*S*-aurate(I) **2**, and examined it by electrospray ionization mass spectrometry, with spectra obtained at varying cone voltages. High cone voltages can cause extensive dissociation of ions formed in the electrospray process, which could yield ambiguous results for the molecular mass determination of a compound unless full studies, with variation of the cone voltage, are undertaken. The spectra discussed here represent the optimum cone voltage corresponding to formation and detection of the molecular species in both positive- and negative-ion ESI.

The positive-ion spectrum of **2** is shown in Fig. 1(*a*). The spectrum was very clean and showed significant peaks at *m/z* 1385 and 1402. These *m/z* values corresponded to $Au_4L_4H_9^+$ (*P*) and (*P* + NH_3) {L is the ligand anion $[O_2CCH(S)CH_2CO_2]^{3-}$}. The anion spectrum was more complicated, and showed peaks that corresponded to $[Au_4L_{4-n}S_nH_{7-n}]^-$ (*n* = 0–4) [Fig. 1(*b*)]. Although we are not certain, we think the cleavage of the C–S bond, and the resultant loss of the organic fragment, occurred in the mass spectrometer. Peaks from some of the corresponding doubly, triply and quadruply charged tetrameric anions were seen at *m/z* 691, 633, 575, 460 and 345.

As a result of these studies we examined a sample of commercial myochrysine. The cation spectrum was more complicated than that of the ammonium salt because of the presence of sodium ions, but a peak corresponding to the tetrameric parent ion $Au_4L_4Na_9^+$ was observed (*m/z* 1583), together with the doubly charged $Au_4L_4Na_{10}^{2+}$ and monomer peaks $AuL_2Na_6^+$ and $AuL_2Na_5H^+$.

The anion spectrum [Fig. 1(*c*)] was complex and did not show a tetramer parent peak, although very weak, poorly resolved peaks that corresponded to $Au_4L_3SNa_{6-n}H_n^-$ (*n* = 1–4), $Au_4L_2S_2Na_{5-n}H_n^-$ (*n* = 0–3), $Au_4LS_3Na_{4-n}H_n^-$ (*n* = 0–3) and $Au_4S_4Na_{3-n}H_n^-$ (*n* = 0–2) were observed. In addition, peaks were observed that corresponded to the doubly charged anions $Au_4L_4Na_{6-n}H_n^{2-}$ (*n* = 1–5), $Au_4L_3SNa_{5-n}H_n^{2-}$, (*n* = 0–4), $Au_4L_2S_2Na_{4-n}H_n^{2-}$ (*n* = 0–2). Peaks were also observed for the triply charged anions $Au_4L_4Na_{5-n}H_n^{3-}$ (*n* = 1–4). Similar results have been obtained for the corresponding silver salt, which suggested that the principal anion was $Ag_4L_4^{8-}$. Nomiya *et al.* also suggested, on the basis of molecular mass determinations in solution, that there was further association to give higher polymer species.[6] This may be occurring in the gold samples as well. The anion spectrum of myochrysine showed a series of peaks at *m/z ca.* 1000, separated by about 7 mass units. These peaks, although poorly resolved, corresponded to the triply charged octameric anions $[(Au_4L_4)_2]Na_{13-n}H_n^{3-}$ (*n* = 0–5).

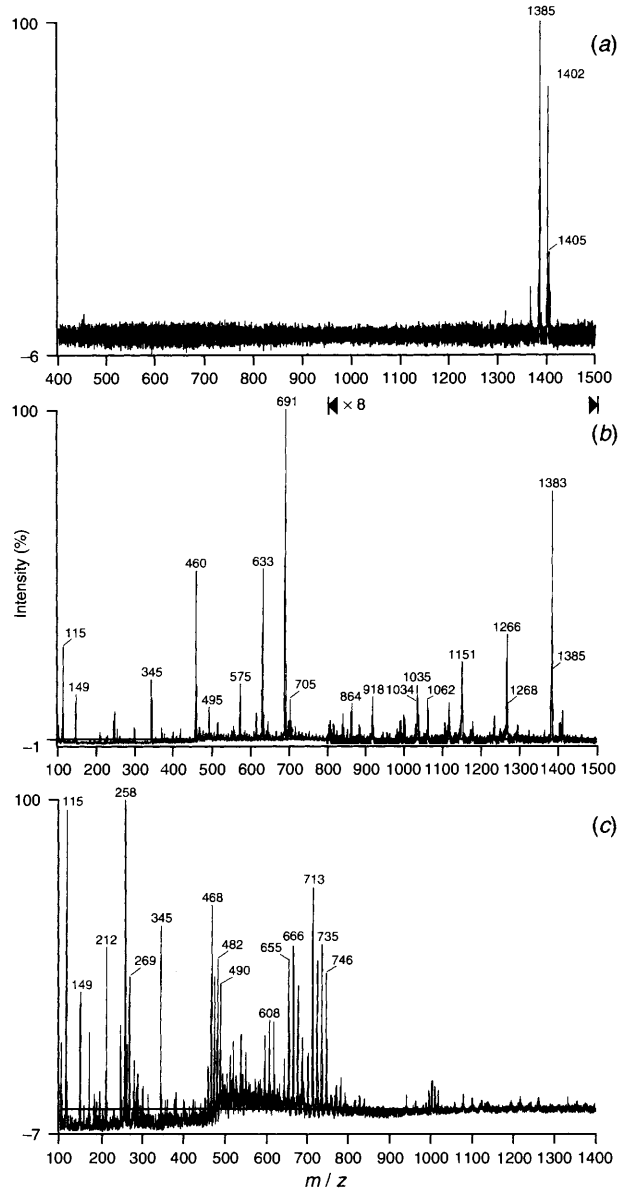

Fig. 1 ESI mass spectra of (*a*) **2**, positive ion, (*b*) **2**, negative ion, (*c*) **1**, negative ion. Spectra were obtained on a Fisons Platform quadrupole mass spectrometer. Samples were injected as 50:50 water–methyl cyanide solutions, plus ammonia. The cone voltage was 35 V, and spectra were obtained in 15 scans.

The results obtained here are in contrast to those of Elder *et al.*[4] that suggested that the principal component of myochrysine was an open-chain polymer based on a tetrameric repeat unit. Our results showed that the principal species in the mass spectrometer was a tetramer, or some multiple thereof, and, to satisfy valence requirements, it was cyclic with the thiol ligands bridging pairs of gold atoms. Stable cyclic tetramers of this type, Au_4R_4, where R = $SC(SiMe_3)_3^-$ [7] or $(Bu^tO)_3SiS^-$,[8] have been prepared as solids and characterized by single-crystal X-ray diffraction. These molecules had a near planar, square Au_4S_4 core, with almost rectilinear S–Au–S systems and Au–S–Au angles slightly greater than 90°. It is possible that the cyclic tetramer was formed in the mass spectrometer, although the insensitivity of the presence of tetrameric fragments in the spectra to cone voltage variations, and the results of collisional activation MS/MS studies of fragments, which also showed only tetrameric fragments, suggested the cyclic tetramer existed in the injected solution. Resolution of this dichotomy will have to await further experiments.

The characterization of monomeric $(NH_4)_5[AuL_2]$[9] suggests that in myochrysine an equilibrium of the type $4AuL_2^{5-} \rightleftarrows Au_4L_4^{8-} + 4L^{3-}$, (the tetramer may be a cyclic polymer or the repeat unit in a higher polymer) where the equilibrium lies well to the right, may exist, in addition to intermediate condensation products, which might explain the variation in analytical results that have been observed for the drug.[10]

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