

Proton-linked bi- and tri-metallic gold cyanide complexes observed by ESI-MS spectrometry

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Abstract

Electrospray ionization spectra of potential cyanide-containing gold-drug metabolites revealed additional, weak, unanticipated peaks at approximately twice the mass of the gold(I) and gold(III) cyanide complexes. The exact masses correspond to proton-linked bimetallic complexes, $[\text{H}\{\text{Au}(\text{CN})_m\}_2]^-$, ($m = 2,4$). Further investigation revealed a total of 12 examples, including trimetallic complexes, $[\text{H}_2\{\text{Au}(\text{CN})_m\}_3]^-$; mixed species with two complexes, $[\text{H}\{\text{Au}(\text{CN})_2\}\{\text{Au}(\text{CN})_4\}]^-$; and thiolato species, $[\text{H}\{(\text{RS})\text{Au}(\text{CN})_3\}_2]^-$. *trans*- $[\text{AuX}_2(\text{CN})_2\text{Cl}_2]^-$ and *trans*- $[\text{AuX}_2(\text{CN})_2\text{Br}_2]^-$ generated $^{35}\text{Cl}/^{37}\text{Cl}$ and $^{79}\text{Br}/^{81}\text{Br}$ isotopic patterns for the protonated bi- and tri-metallic analogues which were in good agreement with the presence of four or six halide ligands, respectively. Concentration-dependent studies demonstrated that the signals are independent of the solution concentrations of mono-metallic precursors, suggesting formation in the gas phase during or following droplet desolvation.

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1. Introduction

Gold-based anti-arthritis drugs have been used for nearly eight decades [1–3] and are considered to be disease-modifying drugs, as opposed to palliative treatments. One of the known metabolites is aurocyanide ($[\text{Au}(\text{CN})_2]^-$), which has been detected in blood and urine of patients using three different drugs: myochrysin (gold sodium thiomalate), solgonal (gold thioglucose) and auranofin (2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranosato-*S*-(triethylphosphine)gold(I)) [4,5]. Evidence for the conversion of gold(I) to gold(III) has been reported in mice [6] and men [7]. The enzyme myeloperoxidase has been implicated in both processes [8–10] and this has led to the hypothesis that aurocyanide ($[\text{Au}(\text{CN})_4]^-$) might also be a metabolite [10]. A variety of gold(III) complexes show very promising anti-tumor activity [11], but are subject to poten-

tial reduction to gold(I), giving impetus to studies of the mechanisms of the biological reduction mechanisms.

While studying the reduction of auricyanide by thiols, mass spectra revealed negative-ion peaks resulting from complexes containing two or three gold ions, which could not be accounted for by a ligand exchange of thiolate for cyanide (P.M. Yangyuoru, J.W. Webb, C.F. Shaw III, this issue). The masses of these peaks correspond to formation of bi- and tri-metallic complexes, $[\text{H}_n\{\text{Au}(\text{CN})_m\}_{n+1}]^-$. It was therefore interesting to investigate these species further because such proton-linked clusters have not been documented yet in the solution chemistry of gold nor, to our knowledge, in ESI-MS spectra of other metal cyanides.

2. Experimental

Reagents were obtained as follows: reduced glutathione from Sigma–Aldrich; cysteine, Sigma Chemical Company; cysteine methyl ester (Lot # A016240201), *N*-acetylcysteine (Lot # A018477901) and formic acid (Lot # A019673801) from Acros Organics; HPLC-grade acetonitrile (ACN,

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Lot # 054754) from Fisher Chemicals Company. $\text{K}[\text{Au}(\text{CN})_2\text{Cl}_2]$ was prepared by the method of Canumalla et al. [10], $\lambda_{\text{max}} = 217, 287 \text{ nm}$ (lit 217, 287 nm), $m/z = 319.0, 321.0, 323.0$; $\nu_{\text{CN}} = 2175 \text{ cm}^{-1}$. $\text{K}[\text{Au}(\text{CN})_2\text{Br}_2]$ was a generous gift of Dr. Anna Cannumalla.

2.1. ESI-mass spectrometry

ESI-mass spectra were recorded on a Hewlett Packard (Agilent) LC-MS (Series 1100 LC-MSD with a UV-vis diode array detector) set in the negative ion mode with 40 V fragmentation voltage, 3500 V capillary voltage; 10 L/min N_2 flow at 25 psi; ionization temperature 250 °C. Samples (10.0 μL of 0.1–100 mM concentration of gold complex) were injected into the ESI chamber. The flow rate was set at 0.400 mL/min. Mobile phase solvents were typically (A) 0.1% formic acid in nanopure water and (B) 0.1% formic acid in acetonitrile (ACN). Unless otherwise indicated, a mobile phase composition of 50% A and 50% B was used throughout this research. Solvent composition and spray parameters were fixed for most of the analyses. Using the auto sampler, the delay time between mixing and the first spectrum was typically 3 min.

2.2. $[\{\text{Au}(\text{CN})_m\}_{n+1}\text{H}_n]^-$

Solutions typically containing 2.00 mM $[\text{Au}(\text{CN})_m]^-$ ($m = 2, 4$) in nanopure water were analyzed by ESI mass spectrometry over the range 100–1000 m/z . To study the possibility of the formation of mixed clusters, solutions containing both 1.00 mM $[\text{Au}(\text{CN})_4]^-$ and 1.00 mM $[\text{Au}(\text{CN})_2]^-$ in nanopure water were analyzed by ESI-MS. Apart from nanopure water, studies were also conducted in acetonitrile + 0.1% HCOOH solvent medium.

2.3. $[\text{Au}(\text{CN})_m]^-$ and $[\text{H}_3\text{O}^+]$ concentration-dependence studies

Varying concentrations (1.00, 2.00, 4.00, 5.00, 50.0 and 100 mM) of only $[\text{Au}(\text{CN})_4]^-$ or equimolar mixtures of $[\text{Au}(\text{CN})_4]^-$ and $[\text{Au}(\text{CN})_2]^-$ in nanopure water were analyzed. Studies were done in the acetonitrile + 0.1% HCOOH medium and compared to identical studies in nanopure water to determine whether the formation of the protonated clusters is affected by the solvent and the $[\text{H}_3\text{O}^+]$ concentration.

2.4. $[\text{H}_n\{\text{Au}(\text{CN})_2\text{X}_2\}_{n+1}]^-$

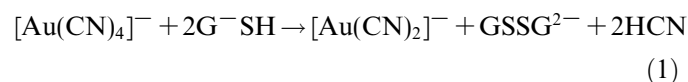
Aqueous solutions ranging from 2.3 to 22.8 mM of $\text{K}[\text{Au}(\text{CN})_2\text{Br}_2]$ and $\text{K}[\text{Au}(\text{CN})_2\text{Cl}_2]$ were examined. The chloride complex was used to study the effect of the fragmentation voltage (0–120 V in 20 V steps) on the intensity of the bi- and tri-metallic species and the extent of reductive elimination of X_2 from the anionic complexes.

2.5. $[\text{H}_n\{\text{Au}(\text{SR})(\text{CN})_3\}_{n+1}]^-$

An extensive library of ESI-MS spectra obtained during examination of the auricyanide reduction (P.M. Yangyuru, M.S. Thesis, Illinois State University, 2007) was scanned for bi- and tri-metallic thiolate-substituted complexes. Only bi-metallic complexes with $\text{RS}^- = \text{cysteine}$ or *O*-methyl-cysteine were noted.

3. Results

While studying the reduction of auricyanide by thiols, Eq. (1):



several ESI mass spectra revealed peaks of previously unrecognized complexes containing two or three gold ions. Fig. 1, for example, exhibits peaks corresponding to the reactants (GSH^- , $m/z = 306.0$ and $[\text{Au}(\text{CN})_4]^-$, $m/z = 301.0$), two intermediates ($[\text{Au}(\text{SGH})(\text{CN})_3]^-$, $m/z = 581.0$ and $[\text{Au}(\text{SCy-Gly})(\text{CN})_3]^-$, $m/z = 452.0$) and a trace of the product ($[\text{Au}(\text{CN})_2]^-$, $m/z = 249.0$). There is an additional peak at $m/z = 603.0$, approximately twice the mass of aurocyanide, but a dimer would have a mass of 602.0 and a net -2 charge, and would therefore have an m/z value of 301.0, indistinguishable from the monomeric complex. Nor did this peak correspond to any of the possible reactants or intermediates containing a thiolate ligand in the complex. The observed m/z of 603.0 can be accounted for by a proton linking two $[\text{Au}(\text{CN})_4]^-$ ions to form a bimetallic cluster with a net -1 charge, as detected by ESI-MS. The following protonation reaction, Eq. (2), was therefore suggested to generate the cluster $[\text{H}\{\text{Au}(\text{CN})_4\}_2]^-$:



If the postulated complex and its formation are correctly defined, it should form independently of the glutathione-derived species involved in the overall auricyanide reduction reaction, Eq (1).

ESI mass spectra of $[\text{Au}(\text{CN})_4]^-$ obtained before the reduction process also exhibited, upon reexamination, minor peaks corresponding to the bi-metallic complex, $[\{\text{Au}(\text{CN})_4\}_2\text{H}]^-$ (Fig. 2).

Two additional proton-linked clusters were observed in ESI mass spectra of pure $\text{K}[\text{Au}(\text{CN})_2]$ in nanopure water (Fig. 3). In addition to $[\text{Au}(\text{CN})_2]^-$ ($m/z = 249.0$), a bimetallic gold cluster, $[\text{H}\{\text{Au}(\text{CN})_2\}_2]^-$ ($m/z = 498.9$), analogous to the bimetallic gold(III) species, was present. In addition, a peak at $m/z = 749.2$ resulting from the formation of $[\text{H}_2\{\text{Au}(\text{CN})_2\}_3]^-$ was observed. The protonation reactions for $[\text{Au}(\text{CN})_2]^-$ (Eqs. (3) and (4)) correspond to peaks observed at $m/z = 498.9$ and 749.2, respectively:

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