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Redox and ligand exchange reactions of potential gold(I) and gold(III)-cyanide metabolites under biomimetic conditions

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Abstract

Biomimetic pathways for the oxidation of $[Au(CN)_2]^-$, a gold metabolite, and further cyanation of the gold(III) products to form $Au(CN)_4^-$ were investigated using ^{13}C NMR and UV–Visible spectroscopic methods. Hypochlorite ion, an oxidant released during the oxidative burst of immune cells, was employed. The reaction generates mixed dicyanoaurate(III) complexes, *trans*-$[Au(CN)_2X_2]^-$, where X^- represents equilibrating hydroxide and chloride ligands, and establishes the chemical feasibility of dicyanoaurate oxidation by OCl^- to gold(III) species. This oxidation reaction suggests a new procedure for synthesis of $H[Au(CN)_2Cl_2]$. Reaction of *trans*-$[Au(CN)_2X_2]^-$ ($X^-=Cl^-$ and Br^-) or $[AuCl_4]^-$ with HCN in aqueous solution at pH 7.4 leads directly to $[Au(CN)_4]^-$ without detection of the anticipated $[Au(CN)_xX_{4-x}]^-$intermediates, which is attributed to the *cis*- and *trans*-accelerating effects of the cyanides. The reduction of $[Au(CN)_4]^-$ by glutathione and other thiols is a complex, pH-dependent process that proceeds through two intermediates and ultimately generates $[Au(CN)_2]^-$. These studies provide further insight into the possible mechanisms of an immunogenically generated gold(I)/gold(III) redox cycle in vivo.

Keywords: Aurocyanide; Auricyanide; Hypochlorite; Cis effects; Trans effects; Gold; Biological redox reactions

1. Introduction

Gold(I) drugs have been used for the treatment of rheumatoid arthritis since the 1920s despite the fact that their exact mechanism of action remains unknown [1–5]. Other gold complexes show activity against HIV [6] and malaria [7]. Two recent advances in understanding the metabolism of gold in vivo may provide insight into the generation of the pharmacologically active species. First, the gold(I) drugs and/or their metabolites react in vivo with cyanide, resulting in the formation of dicyanoaurate(I), $[Au(CN)_2]^-$ [1,2,8]. The cyanide is generated from thiocyanate and hypochlorite, OCl^-, during the oxidative burst of macrophages and other immune cells, and for some patients even larger amounts are absorbed from tobacco smoke. The $[Au(CN)_2]^-$ ion has been identified as a common metabolite of the gold(I) drugs in the blood and urine of chrysotherapy patients [6,9]. As a result of the two tightly bound cyanide ligands, $[Au(CN)_2]^-$ is relatively unreactive towards ligand exchange reactions with other gold binding ligands. Recent equilibrium and Mössbauer studies indicate non-covalent association of intact $[Au(CN)_2]^-$ ions with the transport protein, serum albumin, to form albumin–$[Au(CN)_2]_n^-$ adducts [10–12]. The binding is labile and easily reversible ($K_1=5.5\times10^4$ M^{-1}; $K_2=7.0\times10^3$ M^{-1}) [10,12] explaining the presence of significant amounts of $[Au(CN)_2]^-$ in body fluids of chrysotherapy patients. Second, although gold(I) is the primary oxidation state found in vivo [13], there is immunological evidence for the generation of gold(III) metabolites [14–16]. Biomimetic studies indicate that the oxidation of gold(I) thiomalate and gold(I) thioglucose [10,17] by OCl^-, which is released when cells are induced to undergo the oxidative burst at inflammed sites, is rapid and thermodynamically feasible resulting in the formation of gold(III) species. These studies have been extended to the second generation gold(I) drug, auranofin [18]. Since OCl^- is involved in

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