ELSEVIER

Journal of Inorganic Biochemistry 88 (2002) 44–52

JOURNAL OF Inorganic Biochemistry

www.elsevier.com/locate/jinorgbio

^{13}C, ^{31}P and ^{15}N NMR studies of the ligand exchange reactions of auranofin and chloro(triethylphosphine)gold(I) with thiourea

Saeed Ahmad, Anvarhusein A. Isab*

Department of Chemistry, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

Received 13 February 2001; received in revised form 25 June 2001; accepted 27 June 2001

Abstract

The interaction of thiourea (Tu) with auranofin ($Et_3PAuSATg$) and its analogue, Et_3PAuCl has been studied using ^{13}C, ^{31}P and ^{15}N NMR spectroscopy. It is observed that Tu is able to replace both the ligands, Et_3P and $SATg^-$ simultaneously from gold(I) in auranofin, forming $[Et_3P\text{-}Au\text{-}Tu]^+$ and Tu-Au-SATg complexes. However, no separate resonances for these species were observed either due to their rapid exchange with auranofin and thus giving only the average resonances or because the chemical shifts of either two species are same so that they cannot be resolved. The displaced $SATg^-$ is oxidized to its disulfide, $(SATg)_2$. However, some of the displaced Et_3P is oxidized to Et_3PO while the remaining reacts with Tu to form Et_3P-Tu species, characterized by δ ^{31}P of 1.0 ppm, assigned after an independent reaction between Et_3P and Tu. In an experiment using a 0.05 M solution of auranofin, the Et_3PO resonance appeared in auranofin spectrum after 4 days of addition of 1.0 equivalent of Tu, showing that the reaction is slow. A resonance for free Et_3P is also detected in ^{31}P NMR on the addition of CN^-. It is also observed that Tu reacts with Et_3PAuCl to form $[Et_3P\text{-}Au\text{-}Tu]^+$ via displacement of Cl^-, consistent with an upfield shift of 6.2 ppm in >C=S resonance of Tu in ^{13}C NMR. In ^{15}N NMR, a smaller downfield, instead of an upfield shift, in NH_2 resonance of Tu on its addition to auranofin and Et_3PAuCl indicates that it is not binding to gold(I) through nitrogen.

Keywords: Auranofin; Chloro(triethylphosphine)gold(I); Thiourea; Cyanide; NMR

1. Introduction

Gold-based drugs have been successfully used for the treatment of rheumatoid arthritis over many years [1–3]. The structures of some important gold drugs are shown in Fig. 1. Auranofin ($Et_3PAuSATg$, where $SATg^-$ is 2,3,4,6-tetra-*o*-acetyl-1-thio-β-D-glucopyranosato-*S*) and Et_3PAuCl are monomers while myocrisin and solganol are polymeric in nature (by sulfur bridging) [4]. Since gold(I) is extremely labile, these gold(I) complexes after their administration, undergo several ligand exchange reactions in the body with biofluids, cells and proteins [5–8].

Despite the strong binding of both triethylphosphine and thioglucose ligand to gold(I), auranofin undergoes facile thiol exchange reactions [8,9]. Auranofin ($Et_3PAuSATg$) reacts rapidly with mercaptalbumin (AlbSH) via a ligand exchange reaction to form AlbS-Au-PEt_3 with gold binding to Cys-34. The albumin–gold–phosphine complex is stable if isolated from displaced thiol. If $ATgS^-$ remains in solution or is replaced with other thiols the Et_3P is displaced and is oxidized to Et_3PO [8–11]. When Cl^-, a low affinity ligand for gold(I) is substituted for $SATg^-$, no Et_3PO is formed [8–11]. The preferred ligands for R_3PAu^+ would be; $R_3P{\sim}CN^- > RS^- \gg C{=}S > R_2S$ [12]. Most studies of the exchange reactions of auranofin deal with thiols and cyanide [8,10,13,14]. To learn about the role of thiones like thiourea on the reactions of gold drugs, we undertook an investigation of the interaction of thiourea (Tu) (5% ^{13}C and ^{15}N labelled) with auranofin and Et_3PAuCl in methanol using ^{13}C, ^{31}P and ^{15}N NMR spectroscopy. We selected thiourea since ergothionine, which is present in red blood cells at a 0.15–0.60 mM concentration level, has a thione binding site similar to thiourea [13].

2. Experimental

2.1. Materials

Auranofin was a generous gift from Smith Kline and

*Corresponding author. Fax: +966-3-860-4277.
E-mail address: aisab@kfupm.edu.sa (A.A. Isab).

0162-0134/02/$ – see front matter
PII: S0162-0134(01)00305-1