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Comparative ^{13}C and ^{31}P NMR studies of the ligand exchange reactions of auranofin with ergothionine, imidazolidine-2-thione and diazinane-2-thione

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Abstract

The interaction of auranofin ($Et_3PAuSATg$) with ergothionine (ErS), imidazolidine-2-thione (Imt) and diazinane-2-thione (Diaz) has been studied using ^{13}C and ^{31}P NMR spectroscopy. It is observed that these thiones are able to replace both Et_3P and $SATg^-$ ligands simultaneously from gold(I) in auranofin forming >C=S–Au–SATg and $[Et_3P–Au–S=C<]^+$ type complexes. 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 thiones to form $Et_3P–S=C<$ species characterized by δ ^{31}P NMR of 1.0–1.5 ppm. The Et_3PO resonance appeared in the ^{31}P NMR spectrum, after 10 days of the addition of ErS, after 19 days of the addition of Imt and after 6 days of the addition of Diaz, to auranofin solution showing that the thiones react with auranofin very slowly.

Keywords: Gold(I); Auranofin; Ergothionine; Imidazolidine-2-thione; Diazinane-2-thione; NMR

1. Introduction

Chrysotherapy has been widely accepted for the treatment of rheumatoid arthritis for many years [1–3]. Gold drugs after their administration undergo several ligand exchange reactions in the body with biofluids, cells and proteins [4–8]. Gold(I) thiolates, (Gold(I), thiomalate and thioglucose) being polymers cannot enter red blood cells (RBCs) [9,10], while auranofin being monomeric does enter into RBCs immediately after its absorption and binds to glutathione (GSH) and hemoglobin (Hb) [11,12]. The RBCs, which contain thiol and thione ligands, e.g., Hb, GSH and ergothionine (ErS), can form stable complexes with gold drugs [13–15]. The concentrations of Hb and GSH in RBCs are 4 and 2.5 mM, respectively, while that of ErS is 0.15–0.60 mM [14]. GSH and Hb have SH group as their binding site and are more reactive than ErS, which exists in thione (ErS) I–thiol (ErSH) II equilibrium as given in Eq. (1). The thione form is predominant in the solid state and at physiological pH [15,16].

In order to gain an insight into the mechanism of action of gold drugs with intracellular ligands, it is important to assess independently the chemical reactivities of these ligands towards gold(I) complexes. Therefore, in this study we investigated the interaction of auranofin with ErS and its analogous thiones, Imt and Diaz, using ^{13}C and ^{31}P NMR spectroscopy. Recently, we have reported the results of ^{13}C, ^{31}P and ^{15}N NMR investigation of interaction of auranofin with thiourea (Tu) showing a simultaneous replacement of both the thiol and phosphine ligands from auranofin [17]. The structures of auranofin and the thiones under study are shown in Fig. 1.

2. Experimental

2.1. Materials

Auranofin was a generous gift from Smith Kline and French Laboratories (Philadelphia, PA). ErS, CD_3OD and D_2O were purchased from Fluka. Imt and Diaz were prepared according to the literature procedure [18,19].

2.2. ^{13}C NMR Spectroscopy

^{13}C NMR spectra were obtained on a Jeol JNM-LA 500 NMR spectrometer, operating at a frequency of 125.65 MHz with ^1H broadband decoupling at 297 K. The spectral conditions were: 32k data points, 0.967 s acquisition time, 1.00 s pulse delay, 4.50 μs pulse width and with an average 10 000 accumulations. The chemical shifts were

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