Spectroscopic studies on the interaction between poly-phosphane gold(I) complexes and dihydrofolate reductase: an interplay with nicotinamide adenine dinucleotide cofactor.

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Abstract

A class of gold (I) phosphane complexes have been identified as inhibitors of dihydrofolate reductase (DHFR), an enzyme that catalyzes the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF), using NADPH as a coenzyme [1]. Since DHFR does not contain seleno-cysteines either cysteines in the active site, which are the most favorable sites of attack of Au(I) moieties, exploiting the nature of the interaction at the base of these effects could add new insights about the mechanisms by which these compounds exert their action. In this work, the interactions of bis and tris(4- or 2-benzoic-diphenyl)phosphane acid gold(I) chloride compounds [((4-COOH Ph)$Ph_2P)_3$AuCl], [((4-COOH Ph)$Ph_2P)_3$AuTf], Tf = triflate, [((2-COOH Ph)$Ph_2P)_3$AuCl], [(4COOHPh-$Ph_2P)_2$AuCl], [(2COOHPh-Ph2P)$_2$AuCl], and [$(PPh_3)_2$AuCl] with DHFR from *E. coli* have been studied by emission spectroscopy and spectrophotometric assay. By elucidating the energetic aspects of the binding event, we have attempted to dissect the role played by the phosphine/protein interactions, in the gold (I) phosphane complexes inhibitory activity. The effect of the carboxylic polar group in one phenyl ring of the triphenyl-phosphine and the interplay with the cofactor NADPH have been investigated. By analyzing the temperature dependence of the dissociation constants obtained by quenching of Trp fluorescence, through the van't Hoff equation, the enthalpy and entropy contributions to the energetics of binding have been evaluated. In this study, the presence of the carboxylic group in the phenyl ring of [((4-COOH Ph)$Ph_2P)_3$AuCl] did not produce a higher affinity for the enzyme, neither a stronger inhibition; nevertheless, an exothermic enthalpy change and a positive entropic contribution ($\Delta H° = -5.04 \pm 0.08$ kcal/mol and $\Delta S° = 7.34 \pm 0.005$ cal/mol·K) was associated to its interaction with the enzyme. The negative enthalpy value can be associated with hydrogen bonds and van der Waals forces occurring between the functional groups of the gold complex and DHFR. The increase of entropy is mainly due to the hydrophobic effect, related to the increase of the degree of freedom of the water molecules released from the solvation shells of both protein and gold complexes [2]. The not covalent binding between the enzyme and the gold complex yields an enzyme fluorescence quenching, the inhibition of its activity and a hyperchromic effect of the intrinsic complex fluorescence.

References:

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