Cytotoxicity of gold(III) Complexes on A549 Human Lung Carcinoma Epithelial Cell Line

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Abstract: We have studied the kinetics of the complex formation of gold(III) complexes, $[Au(en)Cl_2]^+$ (dichlorido(ethylendiamine)aurate(III)-ion) $[Au(dach)Cl_2]$ (dichloride(1,2-diaminocyclohexane)aurate(III)-ion) and $[Au(bipy)Cl_2]^+$ (dichlorido(2,2'-bipyridyl)aurate(III)-ion) with guanosine5'-monophosphate (5'-GMP). It was shown that 5'-GMP have a high affinity for gold(III) complex, which may have important biological implications, since the interactions of Au(III) with DNA are thought to be responsible for the anti-tumor activity. The $[Au(bipy)Cl_2]^+$ complex is more reactive than $[Au(en)Cl_2]^+$ or $[Au(dach)Cl_2]^+$. The activation parameters for all studied reactions suggest an associative substitution mechanism. The cytotoxicity of gold(III) complexes was tested on A549 human lung carcinoma epithelial cell line and was evaluated by cytotoxic (MTT and LDH test) and apoptotic assays. The results showed that all tested gold(III) complexes displayed cytotoxic effect on A549 cells. Among the tested gold (III) complexes, AuBIPY showed the best cytotoxic effects.

Keywords: gold(III), complexes, DNA, kinetics, cytotoxic, A549 human lung carcinoma epithelial cell line.

INTRODUCTION

In recent years, great interest has been focused on gold(III) complexes as cytotoxic and anticancer drug [1-2]. To design a metal-based applicable anticancer drug, however, is quite challenging. Presently, platinum drugs are playing a major role in established medical treatments of cancer [3-4]. Gold(III) complexes are square-planar d^8, isoelectronic and isostructural to Pt(II) complexes. Generally speaking, gold(III) complexes are not very stable under physiological conditions because of their high reduction potential and fast hydrolysis rate. Therefore, selection of a suitable ligand to stabilize the complex becomes a foremost challenge in the design of gold(III) with one or more multidentate ligand to enhance the stability of the complex. However, Au(III) is coordinated by at list two chelating nitrogen donors which lower the reduction potential of metal center and thereby stabilize the complex. The acceptable solution stability of these gold(III) complexes [5-6], facilitated extensive pharmacological investigation, both in vitro and in vivo [7-10].

We have performed and now report here a detailed study on the complex formation kinetics of some selected gold(III) complexes, *viz.* $[Au(en)Cl_2]^+$, $[Au(dach)Cl_2]$, $[Au(bipy)Cl_2]^+$ with 5'-GMP. We choose 5'-GMP because it is the fragment of DNA, and it seems that DNA is the primary target for the gold(III) complexes. The reactions were studied in aqueous solutions at physiological pH (7.2), using stopped-flow technique.

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In addition, we evaluated and report here *in vitro* cytotoxic activity of these complexes on A549 human lung carcinoma epithelial cell line. A549 cells are i*n vitro* most usually used cancer cell line for research in the field of testing cytotoxicity and metabolism of new synthesized complexes towards human lung carcinoma epithelial cells [11].

It was envisaged that this study could throw more light on the interactions of gold(III) complexes with nitrogen-donor nucleophiles suggesting these complexes as potentaily new therapeutic agents in the treatment of lung carcinoma.

2. EXPERIMENTAL

2.1. Chemicals

The nucleophile guanosine-5'-monophosphate sodium salt hydrate, (5'-GMP) was obtained from Acros Organics. Nucleophile stock solutions were prepared shortly before use, by dissolving the chemicals in purified water. The ligands 2,2'-bipyridyl (bipy) and (1R,2R)-1,2-diaminocyclohexane (dach), ethylenediamine (en) were obtained from Acros Organics. Starting complex potassium tetrachloridoaurate(III), $K[AuCl_4]$, was purchased from ABCR GmbH & Co. KG, 98%. All the other chemicals were of the highest purity commercially available and were used without further purification. Ultra pure water was used in all experiments.

The solutions of complexes and ligands were prepared in 25 mM Hepes buffer (pH = 7.20). The reactions of bifunctional complexes were studied in the presence of 20 mM NaCl, to prevent the hydrolysis of complexes.

Cisplatin (*cis*-diamminedichloroplatinum(II), *cis*-[Pt(NH3)2Cl2]), was purchased from Sigma-Aldrich.

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