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Ligand substitution reactions and cytotoxic properties of $[Au(L)Cl_2]^+$ and $[AuCl_2(DMSO)_2]^+$ complexes (L = ethylenediamine and S-methyl-L-cysteine)

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ABSTRACT

We have studied the kinetics of the complex formation of gold(III) complexes, $[AuCl_2(en)]^+$ (dichlorido (ethylenediamine)aurate(III)-ion) and $[AuCl_2(SMC)]$ (dichlorido (S-methyl-L-cysteine)aurate(III)) with four biologically N-donor nucleophiles. It was shown that studied ligands have a high affinity for gold(III) complex, which may have important biological implications, since the interactions of Au(III) with DNA is thought to be responsible for the anti-tumour activity. The $[AuCl_2(SMC)]$ complex is more reactive than $[AuCl_2(en)]^+$. L-His reacts faster than the other N-donor nucleophiles in the reaction with $[AuCl_2(en)]^+$, but in the reaction with $[AuCl_2(SMC)]$ 5′-GMP is the best nucleophile. Gold(III) complexes are much more reactive than Pt(II) complexes with the same nucleophiles. The activation parameters for all studied reactions suggest an associative substitution mechanism. The cytotoxicity of gold(III) complexes, $[AuCl_2(en)]^+$, $[AuCl_2(SMC)]$ and $[AuCl_2(DMSO)_2]^+$ was evaluated in vitro against chronic lymphocytic leukemia cells, obtained from blood of patients with chronic lymphocytic leukemia (CLL). The $[AuCl_2(en)]^+$ complex show comparable cytotoxicity profiles compared to cisplatin.

1. Introduction

Metal complexes have been used for decades as drugs in medicine. For instance, cisplatin and the second generation of the complexes such as carboplatin and oxaliplatin are still the most widely used agents for the treatment of different types of cancer [1]. The success of cisplatin has aroused great interest in the study of metal complexes as possible application in medicine [2–5].

Gold(III) complexes have a long tradition in applications in medicine as drugs [6–10]. In particular, during the last 10–20 years, much interest has focused on gold(III) complexes [11–13]. Gold(III) complexes are square-planar d^8, isoelectronic and isostructural to Pt (II) complexes. Moreover, gold(III) compounds appear to be very good candidates for anticancer investigations. On the other hand, because of their reductive potential, gold(III) complexes are not very stable under physiological conditions [12]. Before there were not many reports in the literature describing the cytotoxic properties and in vivo anti-tumour effects of gold(III) complexes [14,15]. During the last years, much interest has focused on gold(III) complexes as a number of newly synthesized complexes [13]. The acceptable solution stability of these gold(III) complexes [16,17] facilitated extensive pharmacological investigation, both in vitro and in vivo [18–22].

However, compared to the corresponding Pt(II) complexes, ligand substitution reactions of gold(III) complexes [23–26] have not been extensively studied. Probably because of their poor kinetic and redox stabilities, there is a tendency for reduction Au(III) to Au(I) and disproportionation to colloid Au(0) [27].

Interest in the reactions of some biological N-donor nucleophiles with gold(III) complexes could be very important because there is evidence of direct interactions of gold(III) complexes with DNA [20,28,29].

We have performed and now report here a detailed study on the complex formation kinetics of some selected gold(III) complexes, *viz.* $[AuCl_2(en)]^+$, $[AuCl_2(SMC)]$, $[AuCl_2(DMSO)_2]^+$ and $[PtCl_2(NH_3)_2]$ (en is ethylenediamine, SMS is S-methyl-L-cysteine) with some biologically important molecules such as: 5′-GMP, inosine (INO), 5′-IMP and L-His. The reactions were studied in aqueous solutions at physiological pH (7.2), using stopped-flow technique. In addition, we evaluated and report here cytotoxic activity in vitro towards the chronic lymphocytic leukemia cells (CLL). It was envisaged that this study could throw more light on the interactions of gold(III) complexes with nitrogen-donor nucleophiles.

Fig. 1 shows the structures of the investigated complexes. The set of nucleophiles was selected because of their difference in nucleophilicity, steric hindrance, binding properties and biological relevance (structures are shown in Fig. 2).

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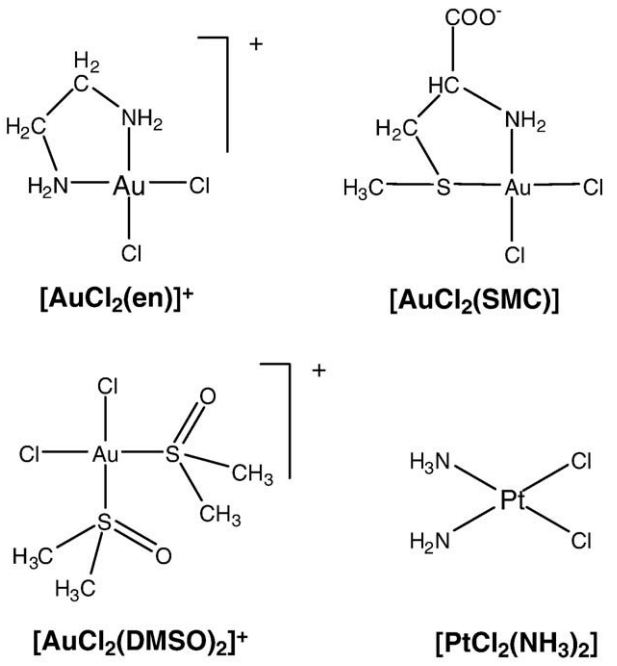

Fig. 1. Structures of the investigated complexes.

2. Materials and methods

2.1. Chemicals and solutions

The nucleophiles INO, 5′-IMP, 5′-GMP and L-His were obtained from Acros Organics and Fluka. Nucleophile stock solutions were prepared shortly before use by dissolving the chemicals in purified water. The ligands en, SMC and DMSO as well as Hepes buffer (N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid) were obtained from Aldrich. Starting potassium-tetrachloridoaurate(III) compound, $K[AuCl_4]$, was purchased from ABCR GmbH & Co. KG, 98 %, while cisplatin, *cis*-diamminedichloroplatinum(II), *cis*-$[Pt(NH_3)_2Cl_2]$, was purchased from Aldrich. 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.

For the cytotoxicity determination further chemicals were bused: fetal bovine serum (FBS), growth medium RPMI 1640, penicillin G, streptomycin; (3-(4,5)-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium-bromide (MTT), phosphate-buffered saline (PBS); dimethyl sulphoxide (DMSO), histopaque 1077, trypan blue staining (all from Sigma Chemicals, Germany); 96 well plates (Sarstedt, Germany) and Haemaccel (Theraselect Gmbh, Germany).

2.2. Synthesis of complexes

The compound $[AuCl_2(en)]Cl\cdot 2H_2O$ was prepared according to the published procedure [30]. $[AuCl_2(DMSO)_2]Cl$, was synthesized by dissolving $KAuCl_4$ (0.2 g, 0.53 mM) in 5 mL 0.05 M HCl in the dark.

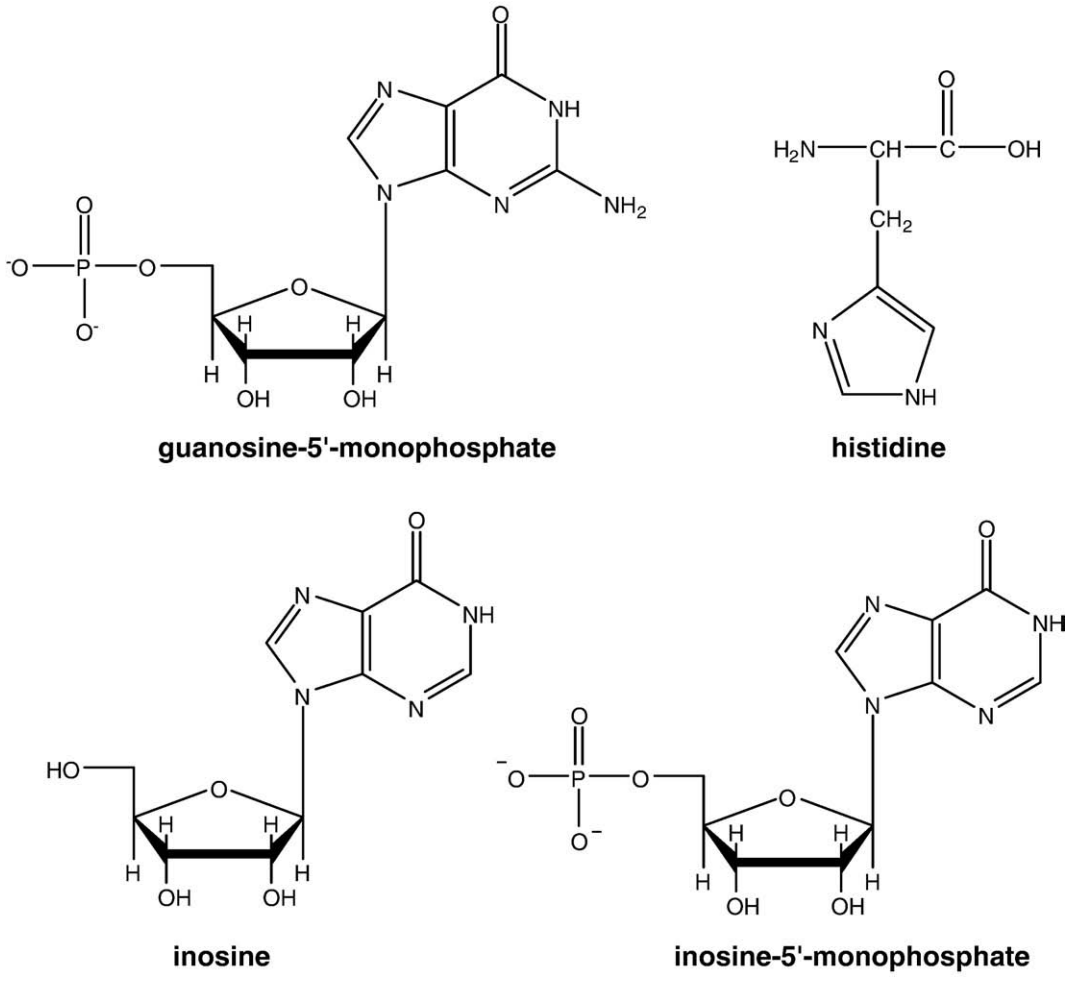

Fig. 2. Structures of studied nucleophiles.