Chemical and biological studies of antitumor dinuclear platinum(II) complexes binding covalently and non-covalently with DNA

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Cisplatin is one of the most effective antitumor agents. In an attempt to search for more active platinum complexes and to overcome cisplatin resistance, we have developed a dinuclear platinum(II) complex, $[\{cis\text{-Pt}(NH_3)_2\}_2(\mu\text{-pyrazolato})\ (\mu\text{-OH})](NO_3)_2$ (AMPZ). AMPZ reacts with 5'-GMP at pH 7 to gives AMPZ-$(GMP)_2$ with Pt-N7 bonds, and its reaction is extremely slow. For example, it took about 24hr and 90hr to finish the reaction at 330 and 310K, respectively when AMPZ($1x10^{-3}$ mol/l) was reacted with 5'-GMP($4x10^{-3}$ mol/l) in the phosphate buffer($1x10^{-3}$ mol/l, pH 7). On the other hand, CD spectra of DNA were changed at pH 7 immediately after the addition of AMPZ and the intact spectra of DNA were obtained by the addition of sodium chloride. Binding study by the equilibrium dialysis method showed that AMPZ bound to DNA(binding constant: 8×10^6 $(mol/l)^{-1}$) was removed by the addition of sodium chloride. These two experiments show that AMPZ can bind DNA in a non-covalent fashion. Viscosity change of DNA found in the presence of an intercalator, ethidium bromide was not observed in the presence of AMPZ. The inhibition of topoisomerase I activity was found in the presence of AMPZ(10 µmol/l) by agarose gel electrophoresis using Col E1 plasmid DNA. AMPZ induces apoptosis in the cisplatin-resistant tumor cell line, L1210.

Research on the effect of non-covalent interaction of AMPZ with DNA on its biological acitivities is expected to be of fundamental importance.

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A NMR spectroscopic analysis of the adduct between AMPZ and a 12-mer duplex oligonucletide is now undergoing.

Binding study by ultrafiltration   operated as promptly as possible   This finding suggests that AMPZ does not play a role as intercalator.

Which was operated as promptly as possible
the melting temeperature and
Proton-assisted substitution reaction of a hydroxo-bridged dinuclear platinum(II) complex capable of circumventing cisplatin-resistance.

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Cisplatin is one of the most effective antitumor agents. In an attempt to search for more active platinum(II) complexes and to overcome cisplatin resistance, we have developed a dinuclear platinum(II) complex, $[\{cis\text{-Pt}(NH_3)_2\}_2(\mu\text{-pyrazolato})(\mu\text{-hydroxo})]^{2+}$ (AMPZ). The substitution reaction of the μ-hydroxo dinuclear platinum(II) complex has been investigated in the presence of chloride ion as a nucleophile by HPLC, 1H-NMR and electronic spectral methods. In 0.2 mol/l sodium chloride the dinuclear complex did not react at neutral pH region within 60min, but reacted on the addition of hydroperchloric acid to give $[\{cis\text{-Pt}(NH_3)_2\}_2(\mu\text{-pyrazolato})(\mu\text{-Cl})]^{2+}$ as one of the intermediates and $[\{cis\text{-Pt}(NH_3)_2Cl\}_2(\mu\text{-pyrazolato})]^{+}$ as the final product.

On the other hand, an isosbestic point was found at 255nm in the electronic spectra of AMPZ in 0.1 mol/l hydroperchloric acid, which were measured periodically. The product in the mixture was estimated to be$[\{cis\text{-Pt}(NH_3)_2(OH_2)\}_2(\mu\text{-pyrazolato})]^{3+}$, the acid dissociation constant of which was determined 0.52 mol/l by photometric titration method.

Some of observed rate constants were determined and overall equilibrium reactions among the dinuclear platinum(II) complexes were proposed.

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