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Experimental and molecular modeling studies on the DNA-binding of diazacyclam-based acrocyclic copper complex

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ABSTRACT

The interaction of a new macrocyclic copper complex, $[CuL(NO_3)_2]$ in which L is 1,3,6,10,12,15-hexaaza tricyclo[13.3.1.1^{6,10}] eicosane was investigated in vitro under simulated physiological conditions by multi-spectroscopic techniques and molecular modeling study. The fluorescence spectroscopy and UV absorption spectroscopy indicated the complex interacted with ct-DNA in a groove binding mode while the binding constant of UV–vis and the number of binding sites were $1.0 \pm 0.2 \times 10^4$ L mol^{-1} and 1.01, respectively. The fluorometric studies showed that the reaction between the complex with ct-DNA is exothermic ($\Delta H = 14.85$ kJ mol^{-1}; $\Delta S = 109.54$ J mol^{-1} K^{-1}). Circular dichroism spectroscopy (CD) was employed to measure the conformational change of DNA in the presence of $[CuL(NO_3)_2]$ complex. Furthermore, the complex induces detectable changes in the viscosity of DNA. The molecular modeling results illustrated that the complex strongly binds to groove of DNA. Experimental and molecular modeling results showed that Cu(II) complex bound to DNA by a groove binding mode.

1. Introduction

Macrocyclic structures are extremely favorable for metal complexation and hence, a large number of macrocyclic ligands have been synthesized because of their importance in coordination chemistry. Among the various ligands, the cyclam (1,4,8,11-tetra aza cyclo tetra decane) is one of the most studied aza macrocycles [1]. In the last years, investigations into cyclam-derived ligands and their complexes have often been initiated by their use in medicine and biochemistry. For instance, it was proposed that cyclam based anti-HIV agents are more active in vivo in the form of metal ion complexes [2]. The macrocyclic ligands are generally preferred to open-chain ligands due to the higher thermodynamic and mainly kinetic stabilities of their complexes [3].

Among all transition metal complexes copper is the most studied metal ions. It exhibits considerable biochemical action either binding to proteins like albumins or binding to ligands forming complexes that interact with biomolecules such as nucleic acids [4–6]. The main interest in copper complexes is arising from their potential use as antiviral, anti-inflammatory and antitumor. For instance the copper complexes of NSAID Piroxicam that exert enhanced anti-cancer activity compared to the free ligand [7].

In the molecular biology, DNA as a carrier of genetic information is often a target for small molecules like metal drugs. Such drugs exhibit DNA-targeted pharmacological activity as they affect DNA replication, a major step in cell growth and cell division, and also they interfere with the transcription processes and protein synthesis [8]. Based on DNA binders, investigations of bioinorganic chemistry have only existed for about the last few decades with the serendipitous discovery of the antitumor activity of cisplatin drug [9].

The interactions of DNA with metal complexes have ranging from intercalation to covalent and groove binding. Thus the research on the mechanism of the interaction of complexes with DNA is important for the design of efficacious drug entities [10–12].

In our previous contributions to the field, we synthesized and characterized the macrocyclic copper complex, $[CuL(NO_3)_2]$ (Scheme 1) that L is 1,3,6,10,12,15-hexa aza tricyclo [13.3.1.1^{6,10}] eicosane [13]. Within this study, we focused on binding studies of this complex with calf thymus DNA (ct-DNA) using multiple spectroscopic techniques such as absorption spectroscopy, emission spectroscopy and circular dichroism study. Furthermore, we used dynamic viscosity measurements.

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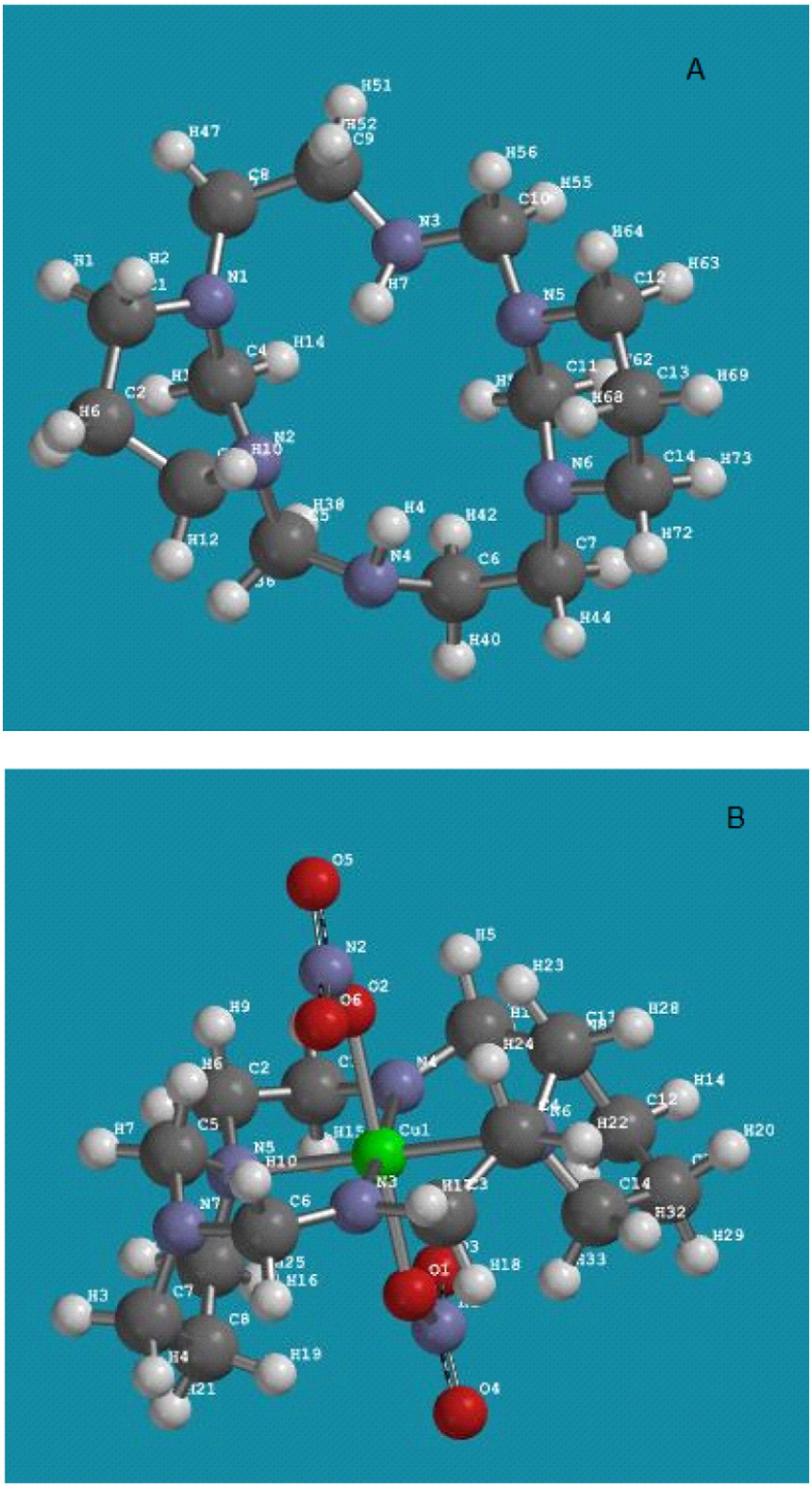

Scheme 1. Chemical structure of (A) L; 1,3,6,10,12,15 hexa aza tricyclo [13.3.1.1] eicosane and (B) $[CuL(NO_3)_2]$.

2. Material and Methods

2.1. Materials

$[CuL(NO_3)_2]$ in which L is 1,3,6,10,12,15-hexaaza tricyclo[13.3.1.1^{6,10}] eicosane was prepared according to described method in recent paper [13]. For this purpose, 20 mmol (2.34 g) of *N*-(2-aminoethyl)-1,3-diaminopropane (AEPD) was added to 10 mmol (2.41 g) of $[CuL(NO_3)_2]$ in 25 mL EtOH, then the mixture was treated with aqueous formaldehyde (36%, 5 mL). The final mixture was irradiated in microwave oven for 10 min with power 1000 W under reflux condition and solvent and excess formaldehyde were removed by a rotary evaporator and the residue was recrystallized from H_2O. Finally, violet crystals were obtained [13].

The suitable crystals for X-ray diffraction were obtained from the solution after standing for 6 days. Commercially pure chemicals such as Tris–HCl (Sigma Co., Madrid, Spain) and highly polymerized calf