Oxidative Cleavage of Plasmid DNA by Dicopper(II) Complex with 1,3,5-Triaminocyclohexane Derivatives

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Oxidative or hydrolytic cleavage of double strand DNA is one of the essential factors for the development of antitumor reagents and artificial nucleases. It is well known that metal complexes of iron, copper and zinc have DNA cleavage ability and the dinuclear complexes cleave DNA more specifically than mononuclear ones due to the cooperativity of two neighboring metal ions. We have synthesized a dicopper complex, $[Cu_2(Phtach)(OH)(OAc)](OTf)_2$ (**1**, Figure 1), in which two *cis,cis*-1,3,5-triaminocyclohexane (TACH) moieties are linked by isophtalaldehyde, maintaining the dinuclear core in aqueous solutions.

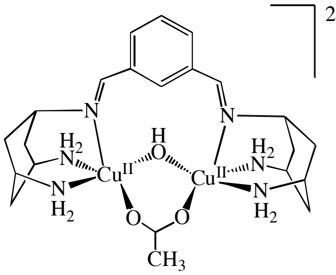

Figure 1. Structure of **1**.

The synthesis of **1** was achieved by using $Cu(OTf)_2$ instead of $Cu(BF_4)_2$ reported in the literature. **1** was identified by IR spectroscopy, elemental analysis, and X-ray diffraction. The structure of **1** is the same as that of $[Cu_2(Phtach)(OH)(OAc)](BF_4)_2$ except for the counter ion. A solution of **1** at pH 7.4 (20 mM HEPES buffer, 30 mM NaCl) showed an absorption band at 621 nm ($\varepsilon = 150\ M^{-1}\ cm^{-1}$) assignable to d-d transition of copper(II) ion. The reaction of **1** with hydrogen peroxide afforded new band at 354 nm ($\varepsilon = 3500\ M^{-1}\ cm^{-1}$) and red-shift of the d-d transition band to 650 nm. This indicates that transiently generated (μ-peroxo)dicopper(II) species hydroxylated the benzene moiety in the complex, converting it to the corresponding phenolate. In the cleavage of plasmid DNA pBR322 by **1** in the presence of hydrogen peroxide as an oxidant, Form I (supercoiled) disappeared in 10 minutes and Form II (nicked) and III (linear) were observed in the electrophoresis. These results suggest that **1** forms a dinuclear species bridged by phenolate and hydroxide ions and the replacement of the hydroxide ion with hydroperoxide ion resulted in the high oxidative ability of the complex, leading to the efficient scission of the plasmid DNA.

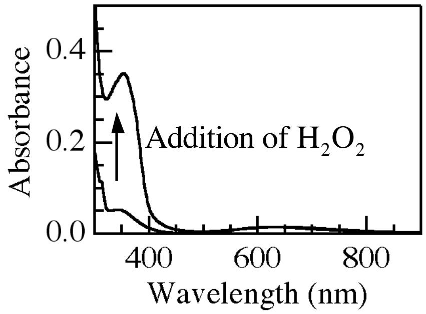

Figure 2. UV-vis spectra for the reaction of **1** with H_2O_2.