Tuning the DNA Cleavage Activity of Fe$^{III}$Zn$^{II}$ Complexes by Addition of Pyrene Motifs

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Introduction: Purple acid phosphatases (PAPs) are a group of metallohydrolases that contain a heterovalent dinuclear Fe$^{III}$M$^{II}$ center (M$^{II}$ = Fe, Mn, Zn) in the active site, and which are able to catalyze the hydrolysis of a variety of phosphoric acid esters and anhydrides. Recently, we had demonstrated the DNA cleavage ability of Fe$^{III}$Zn$^{II}$ complexes using the unsymmetrical donor ligand 2-[N-bis-(2 pyridylmethyl)-aminomethyl]-4-methyl-6-[N'-(2-pyridylmethyl)(2-hydroxybenzyl) aminomethyl]phenol (H$_2$L-R) that mimics the active site of red kidney bean PAP. To improve this ability, the complex ligand was specifically altered by the addition of a pyrene motif that tightly binds to the DNA structure, facilitating the nucleophilic attack of a phosphodiester bond. Herein, we report the strong enhancement of DNA cleavage activity promoted by [Fe$^{III}$-(µ-OH)Zn$^{II}$L-Pyrene] (2) compared to its parent complex without the pyrene motif [Fe$^{III}$-(µ-OH)Zn$^{II}$L-H] (1).

Material and methods: The ability of 1 and 2 to cleave DNA was examined following the conversion of supercoiled form of pBSK-II plasmid into its cleaved forms using agarose gel electrophoresis. Results: the addition of pyrene motif in the complex ligand does not alter the mechanism of strand scission in terms of catalytic pathway or DNA groove binding preference. The efficiency of cleavage, on the other hand, was strongly enhanced. While 1 yielded ~10% of cleaved DNA after 16 h of reaction at 50 ºC, 2 completely (100%) fragmented the intact form of plasmid DNA under the same conditions. In addition, the complex 2 can significantly generates double-strand breaks which were not observed for 1. The rate of the DNA cleavage process ($k_{obs}$) for 2 is ~140-fold higher than 1. Conclusions: the addition of pyrene motifs seems to be an interesting strategy to enhance the cleavage of DNA by synthetic nucleases without changing the mechanism of strand breakage process.

Keywords: DNA cleavage, metal complexes, pyrene

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