DNA Hydrolysis and Oxidative Cleavage by Metal-Binding Peptides Tethered to Rhodium Intercalators†

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Abstract:

With the goal of developing artificial nucleases for DNA hydrolysis, metal-coordinating peptides have been tethered to a DNA-intercalating rhodium complex to deliver metal ions to the sugar-phosphate backbone. The intercalator, $[Rh(phi)_2bpy']Cl_3$ [phi = 9,10-phenanthrenequinone diimine; bpy' = 4-(butyric acid)-4'-methyl-2,2'-bipyridine], provides DNA binding affinity, and a metal-binding peptide contributes reactivity. This strategy for DNA hydrolysis is a general one, and zinc(II)-promoted cleavage has been demonstrated for two widely different tethered metallopeptides. An intercalator coupled with a de novo-designed α-helix containing two histidine residues has been demonstrated to cleave both supercoiled plasmid and linear DNA substrates. Mutation of this peptide confirms that the two histidine residues are essential for Zn^{2+} binding and cleavage. Zinc(II)-promoted cleavage of supercoiled plasmid has also been demonstrated with an intercalator-peptide conjugate containing acidic residues and modeled after the active site of the *Bam*HI endonuclease. Other redox-active metals, such as copper, have been delivered to DNA with our intercalator-peptide conjugates to effect oxidative chemistry. Copper cleavage experiments and photocleavage experiments with $[Rh(phi)_2bpy']^{3+}$ complement the hydrolysis studies and provide structural information about the interactions between the tethered metallopeptides and DNA. Variation of the rhodium intercalator was also explored, but with a mismatch-specific intercalator, no site-specific hydrolysis was found. These experiments, in which the peptide, the metal cation, and the intercalator components of the conjugate are each varied, illustrate some of the issues involved in creating an artificial nuclease with DNA intercalators and metallopeptides.