Stability and Charge Transfer in Cadmium Substituted Zinc Finger Structures in XPA

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Xeroderma Pigmentosum Group A (XPA) preferentially binds to damaged DNA and is an essential component of Nucleotide Excision Repair (NER). The zinc finger structure of XPA consists of an active site composed of four cysteines tetrahedrally bound to a zinc dication. Metallic substitutions of zinc by cadmium, cobalt or nickel inactivate this protein, and that has been associated with the carcinogenicity of these metals. In the case of cadmium in particular, reduction of the metal center has been observed experimentally. In a previous investigation, a simplified model led to the suggestion that reduction is accompanied by a structural change, causing the first coordination sphere of the metal to be exposed to surrounding water molecules, otherwise the reduction seems to be thermodynamically unfavorable.

In this investigation, a larger model was used to represent the zinc finger motif. Optimized structures obtained with various semi-empirical methods were compared to experimental data to select an appropriate method for obtaining initial geometries. Further semi-empirical calculations were used to assess several protonation states of XPA. Then DFT calculations were used to compare the relative energy of the different protonation states, electron affinities, and solvent effects for this system. These calculations shed light on the reduction of cadmium in the substituted metal center of XPA, and elucidate the loss of activity of the protein due to zinc displacement by cadmium.

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