SNBNCBS THESIS COLLOQUIUM

Azadi Ka Amrit Mahotsav

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Thesis Title

Microscopic studies on biomolecular complexes

Thesis Abstract

Studying biomolecular complexes is important for their applications in gene cloning, protein expression, drug design, sensors and detection of diseases. Biomolecular complexes are of two major kinds: (i) complexes of biomolecule with another biomolecule and (ii) complexes of biomolecule with inorganic surface. Although, several experimental and theoretical studies are performed on the biomolecular complexes, a microscopic understanding at the interface of two biomolecules or at the interface of biomolecules and inorganic surfaces is still unclear. In this thesis, we have considered biomolecular complexes of both types. We consider an important class of biomolecular complex, namely, restriction endonucleases and DNA. REs protect bacterial cells against bacteriophage infection by cleaving the viral DNA into fragments. The cleavage by the REs occur in presence of Mg2+, but not in presence of Ca2+, although the proteins binds to DNA in presence of both metal ions. In order to understand the metal ion specificity in EcoRV, we calculate the changes in conformational free energy and entropy of DNA base pair steps and dihedral angles of protein residues in Mg2+ ion bound EcoRV-DNA (Mg2+-EcoRV-DNA) complex compared to those in Ca2+ bound EcoRV-DNA (Ca2+-EcoRV-DNA) complex using all-atom Molecular Dynamics (MD) trajectories of the complexes. We find that the base pairs in cleavage region are highly disordered in Ca2+-EcoRV-DNA compared to Mg2+-EcoRV-DNA. One of the acidic residues ASP90, co-ordinating to the metal ion in the vicinity of the cleavage site, is conformationally destabilized and disordered.

Previous studies suggest that water plays important role in the DNA cleavage activity by the REs. We extend our calculations on EcoRI to investigate the role of water molecules in cofactor sensitivity in DNA recognition and cleavage. We consider four complexes, EcoRI-DNA, Mg2+-EcoRI-DNA, Ca2+-EcoRI-DNA and Mg2+-EcoRI-DNA(M) where the second base pair in the recognition sequence in Mg2+-EcoRI-DNA is mutated. We observe that the number of hydrogen bonds (HBs) around the scissile phosphate group decreases compared to those for the other phosphate groups in all the complexes. The number of HBs at the cleavage phosphate group is smaller in Mg2+-EcoRI-DNA and mutated complexes compared to those of the other complexes. Hence, the HB network in the scissile phosphate group is less strong in Mg2+-EcoRI-DNA and mutated complexes. This indicates that the probability of attacking the scissile phosphate group by a water molecule is more in these complexes compared to the other complexes. Among these two complexes, however, the conformational stability is higher in the Mg2+-EcoRI-DNA than Mg2+-EcoRI-DNA(M). Thus, Mg2+-EcoRI-DNA is having the maximum efficiency in cleavage activity.

Next, we consider a couple of nano-bio complexes. We investigate the interactions of ZnO nanoparticle (ZnONP) with ATP, ADP and AMP using density functional theory (DFT) based quantum chemical calculations. Interactions of ZnONP with ATP, ADP and AMP are important to understand how the metal oxide nanoparticles affect the cellular energy transfer reactions. We establish chelation of the metal oxide surface involving Zn-O bond through ZnONP phosphate CT and Zn-N bond via adenine ZnONP CT and additional O-H---O non-classical bonds with ZnO nano-cluster with phosphate groups in all the nano-bio complexes. DFT-calculated Raman spectra strongly support presence of these bonds in these nano-bio complexes.

ZnO is extensively used in non-enzymatic glucose biosensors for the detection of glucose concentrations in human blood. To understand the binding mechanism of glucose with four common surfaces, , , (0001) and respectively of ZnO, and examining the most preferable surface for glucose adsorption in aqueous solution, we carry out molecular dynamics (MD) simulations enhanced by umbrella sampling. We observe that layered character of the water molecules formed above the surfaces affects the closer approach of glucose to the surfaces that weakens the binding. The glucose density of 0.478 gm/cc is found to be maximum near the surface of () compared to the other surfaces. Potential of mean force (PMF) calculations show that glucose molecules on () surface shows strongest adsorption of adsorption free energy -3.814 kJ/mol. Thus, the interactions between glucose and the surfaces are observed to be highly specific to the surface.

Conclusion

Our studies pave the way for better understanding how the interface between biomolecules behaves. Moreover, the nano-bio interface in our studies may help in designing ZnO based sensors.

Publication List

- "Microscopic insight to specificity of metal ion cofactor in DNA cleavage by restriction endonuclease EcoRV", **Sasthi** Charan Mandal, Lakshmi Maganti, Manas Mondal, Jaydeb Chakrabarti, *Biopolymers* e23396 (2020).
- "Quantum chemical studies on chelation in nano-bio conjugate between ZnO nanoparticle and cellular energy carrier molecules", Mausumi Ray,[⊥] **Sasthi Charan Mandal**,[⊥] Jaydeb Chakrabarti ([⊥] These authors contributed equally to this work), (under review).
- "Theoretical studies on interactions of glucose with hydrated ZnO surfaces", **Sasthi Charan Mandal**, Jaydeb Chakrabarti, *Manuscript in preparation*.
- "Role of hydration in DNA recognition and cleavage by EcoRI", **Sasthi Charan Mandal**, Jaydeb Chakrabarti, *Manuscript in preparation*.