Computer Simulation Studies on the Dynamics of Water and Polar Amino Acid Sidechains in Complex Cavities

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Abstract

The primary aim of this thesis is to use computer simulation studies to probe correlated motions for polar amino acid sidechains and water molecules inside an appropriate cavity to understand how they contribute to highly specific functions such as enzyme catalysis. For this purpose, the thesis has been organized in two parts as described below.

In the first part of this thesis, a hydrophobic pore has been computationally modeled based on a single walled carbon nanotube functionalized at the inner wall with an analogue of polar amino acid sidechain such as that of His, Asp, Glu, Ser and Thr. We have carried out classical molecular dynamics simulation to study the spontaneous filling and retention of water molecules inside the core of functionalized cabon nanotubes immersed in water. A seemingly counter-intuitive application of the FCNTs as a prototype of water storage devices is also explored.

In the second part, the well-known enzyme human carbonic anhydrase II has been studied where rotation of the sidechain of a histidine residue at the active site controls the formation of water mediated proton transfer paths in the rate determining step of catalysis. For this key sidechain rotation, within the frame work of transition path sampling simulation, an optimal reaction coordinate is determined using aimless shooting and half trajectory likelihood maximization along with a Bayesian information criterion. Finally, the relevance of such sidechain rotation in the steps of catalysis is assessed by calculating the free energy profile and rate constant of transition along this reaction coordinate.