INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	Subrata Paul
Roll Number	:	10612224
Programme of Study	:	Ph.D.

Thesis Title: Molecular Dynamics Simulation Studies on Counteraction of Temperature-Induced and Urea-Conferred Protein Denaturation by Trehalose Molecules

Name of Thesis Supervisor	:	Dr. Sandip Paul
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SHORT ABSTRACT

The osmolyte, ”trehalose” often used in pharmaceutical, food, and biomedical applications to prepare glassy matrices for long-term storage of biological materials. It is also used naturally by several organisms to survive from external stresses (temperature change and/or dehydration and chemical denaturation). Despite its importance in bioprotection, how does trehalose stabilize proteins and counter the temperature-induced and urea-conferred protein denaturation is one of the unsolved problem in protein science. Exploring the molecular mechanism of stabilization and counteraction by trehalose by means of molecular dynamics (MD) computer simulations is the goal of the present thesis. To explore the underlying mechanism of protein stabilization by trehalose at low and high temperature and in presence of urea, we systematically investigated solvation characteristics of various functional groups comprising proteins by employing classical MD simulation technique. We started our investigations using neopentane as model hydrophobic group. We have found that trehalose dissolved the neopentane molecules at low temperature and this dissolvation in presence of trehalose is reduced when the temperature is high. Urea also destabilized the hydrophobic interactions between the neopentane molecules. Correlating with the urea conferred enhancement of hydration of neopentane and its counteraction by trehalose, we observed that trehalose and urea both were excluded from the neopentane surface and trehalose helped to increase the hydrophobic association of neopentane molecules slightly. An investigation of temperature dependence structural properties of NMA (the smallest amide that represents the solvent-exposed protein backbone) and hydrogen bonds with solution species showed the replacement of NMA-water hydrogen bonds by equal number of NMA-trehalose hydrogen bonds. Further, the analyses of hydrogen bond properties of NMA with the solution species in binary urea solution showed that large numbers of NMA-water hydrogen bonds were replaced by NMA-urea hydrogen bonds. On other hand, upon addition of trehalose to binary urea solution, hydrogen bond and preferential interaction parameter calculation indicated the modest decrease of urea density near to the NMA. Our simulation of peptide at high temperature and in presence of urea confirmed that trehalose can counteract the temperature-induced and urea-conferred protein denaturation. The calculations of translational diffusion coefficients indicated the trehalose induced slowing down of translational motion of all solution species. The reduction of water and trehalose dynamics is more significant in presence of trehalose. Hence, without excluding the importance of slowing down of solution species and its indirect effect on water structure, we conclude that trehalose’s ability to protect proteins at high temperature and in presence urea arises mainly due to the replacement of water molecules by trehalose molecules from the solvation shell of protein and supports water-replacement hypothesis.