Analysing protein-osmolyte interactions by molecular dynamic simulations

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Abstract:

Amino acids are known to have profound effects as cosolvents on the thermodynamic stability of proteins and the inhibition of protein aggregation as well. However, the mechanistic insights into the molecular-level interactions are scarce. To illustrate the molecular mechanism of amino acid-induced (de)stabilization of proteins, the molecular dynamic (MD) simulations of two model proteins bovine pancreatic ribonuclease A (RNase A) and bovine milk alpha-lactalbumin (α-LA) were performed in the presence of four charged amino acids arginine (Arg), lysine (Lys), aspartate (Asp) and glutamate (Glu). As Arg has the side chain similar to that of guanidinium (Gdm), a chemical denaturant, MD simulations of the proteins were carried out in the presence of Gdm as well. RMSD and SASA derived from the simulations suggest that no major conformational changes are observed in the proteins during the simulations in the presence of any of the cosolvents. The density distribution functions and hydration fraction analysis reveals that the preferential interaction of the proteins with water increases upon the addition of amino acids; however, the extent of increase varies among the cosolvents. Among all the cosolvents, destabilizing cosolvents (Arg and Gdm) exhibit higher interaction compared to stabilizing amino acids (stAAs-Lys, Asp and Glu). The extent of interaction of amino acids with the proteins and the hydrational changes induced on the protein surface differ among the amino acids and the net outcome of these two effects might determine the stabilizing or destabilizing nature of the amino acid. Further, the interactions of these cosolvents with proteins at the residue-level are quantified. The inter-molecular interaction energies evaluated from the simulations show that the net protein-water interaction energies are higher than the net protein-cosolvent interaction energies. Moreover, the interaction sites and energies for Arg and Gdm are similar which could be attributed to the common guanidinium group in their side chains. All these

observations suggest that the preferential hydration or interaction could be the plausible mechanism of amino acid-induced protein stabilization or destabilization, respectively.