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Simulations of the folding/unfolding of biomolecules under solvent, and pressure perturbations[1]

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Proteins exhibit marginal stability, determined by the balance of many competing effects. This stability can be perturbed by changes in temperature, pH, pressure, and other solvent conditions. Osmolytes are small organic compounds that modulate the conformational equilibrium, folded (F) and unfolded (U), of proteins as cosolvents. Protecting osmolytes such as trimethylamine N-oxide (TMAO), glycerol, and sugars that push the equilibrium toward F play a crucial role in maintaining the function of intracellular proteins in extreme environmental conditions. Urea is a denaturing osmolyte that shifts the equilibrium toward U. We will describe calculations of the reversible folding/unfolding equilibrium, under various solution conditions that include urea, high pressure, and different charge states of the Trp-cage miniprotein. The folding/unfolding equilibrium is studied using all-atom Replica exchange MD simulations. For urea, the simulations capture the experimentally observed linear dependence of unfolding free energy on urea concentration. We find that the denaturation is driven by favorable direct interaction of urea with the protein through both electrostatic and van der Waals forces and quantify their contribution. Though the magnitude of direct electrostatic interaction of urea is larger than van der Waals, the difference between unfolded and folded ensembles is dominated by the van der Waals interaction. We also find that hydrogen bonding of urea to the peptide backbone does not play a dominant role in denaturation. The unfolded ensemble sampled depends on urea concentration, with greater urea concentration favoring conformations with greater solvent exposure.

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