

Abstract Submitted  
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**Direct Osmolyte-Macromolecule Interactions Confer Entropic Stability to Folded States**<sup>1</sup> FRANCISCO RODRIGUEZ-ROPERO, NICO F.A. VAN DER VEGT, Tech Univ Darmstadt — Protective osmolytes are chemical compounds that shift the (bio)macromolecule folding/unfolding equilibrium toward the folded state under osmotic stresses. Traditionally it has been considered that osmolytes are depleted from the macromolecule first solvation shell, leading to entropic stabilization of the folded state. Recent theoretical and experimental studies suggest that protective osmolytes may directly interact with the macromolecule. As an exemplary and experimentally well-characterized system, we herein discuss poly(N-isopropylacrylamide) (PNiPAM) in water whose folding/unfolding equilibrium shifts toward the folded state in the presence of urea. Based on Molecular Dynamics simulations we show that urea preferentially accumulates in the first solvation shell of PNiPAM driven by attractive van der Waals dispersion forces leading to the formation of urea clouds around the polymer. Solvation thermodynamics analysis of the folded and unfolded states discards direct urea/macromolecule interactions as driving force of the folding mechanism. Our data shows that entropic penalization of unfolded polymer chains upon increasing urea concentration drives the collapse of the polymer chain.

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