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Urea's action on the hydrophobic interaction in physical and biophysical systems

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For more than a century, urea has been commonly used as an agent for denaturing proteins. However, the mechanism behind its denaturing power is still not well understood. The mechanism of denaturation of proteins by urea is explored using all-atom microseconds molecular dynamics simulations of hen lysozyme generated on BlueGene/L. Accumulation of urea around lysozyme shows that water molecules are expelled from the first hydration shell of the protein. We observe a two stage penetration of the protein, with urea penetrating the hydrophobic core before water, forming a "dry globule." The direct dispersion interaction between urea and the protein backbone and sidechains is stronger than for water, which gives rise to the intrusion of urea into the protein interior and also to urea's preferential binding to all regions of the protein. This is augmented by preferential hydrogen bond formation between the urea carbonyl and the backbone amides which contributes to the breaking of intra-backbone hydrogen bonds. Our study supports the "direct interaction mechanism" whereby urea has a stronger dispersion interaction with protein than water. We also show by molecular dynamics simulations that a 7 M aqueous urea solution unfolds a chain of purely hydrophobic groups which otherwise adopts a compact structure in pure water. The unfolding process arises due to a weakening of hydrophobic interactions between the polymer groups. Again the action of urea is found to be direct, through its preferential binding to the polymer or plates. It is, therefore, acting like a surfactant capable of forming hydrogen bonds with the solvent. The preferential binding and the consequent weakened hydrophobic interactions are driven by enthalpy and are related to the difference in the strength of the attractive dispersion interactions of urea and water with the polymer chain or plate. We also show that the indirect mechanism, in which urea acts as a chaotrope, is not a likely cause of urea's action as a denaturant. These findings suggest that, in denaturing proteins, urea (and perhaps other denaturants) forms stronger attractive dispersion interactions with the protein side chains and backbone than does water and, therefore, is able to dissolve the core hydrophobic region.