Stability of Peptides in Mixed Solvents

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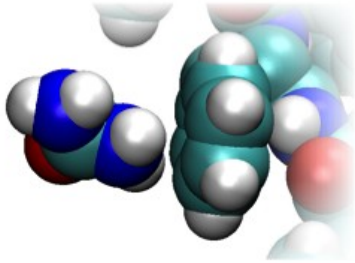
Small cosolutes like urea and trimethylamine-N-oxide (TMAO) have a decisive influence on the folding/unfolding equilibrium of proteins in solution. Urea, a 'denaturant' increases the solvent quality and renders an unfolded state more stable, while the 'osmolyte' TMAO increases the stability of the folded state. On the path towards a complete understanding of the underlying physical-chemical principles, we present insight by molecular simulations in combination with liquid state theories. Peptide stability in concentrated solutions of urea or TMAO is studied by a combination of the Gibbs adsorption equation, Kirkwood-Buff solvation theory, and molecular dynamics simulation results for pure urea/water mixtures and for peptide chains in these solvents. Different residue types and secondary structure motifs of the peptide are studied. Our results show that urea adsorbs at hydrophobic as well as hydrophilic peptide chains in all conformations, in accordance with experimental results. Simple thermodynamic arguments show that the indirect contribution to urea's denaturing capability is negligibly small, although urea strongly changes the water bulk properties as judged by the number of hydrogen bonds formed. We finally compare our results with simple models for the prediction of peptide stability in mixed solvents.



Exclusion of TMAO from polypeptides renders TMAO a stabilizer. Indirect effects contribute here to peptide stability, because TMAO-TMAO repulsion leads to nonideal solutions. Our simulations suggest that the exclusion of TMAO is caused by the simultaneous presence of a strong dipole moment and bulky hydrophobic groups.

REFERENCES

[1] Horinek, D., Netz R. R. "Can Simulations Quantitatively Predict Peptide Transfer Free Energies to Urea Solutions? Thermodynamic Concepts and Force Field Limitations", J. Phys. Chem. A **115**, 6125 (2011)