Strategies for developing pressure-dependent force fields

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Biochemical processes of a vast number of lifeforms are accommodated to extreme conditions such as deep oceanic water where high pressure has substantial impact on the molecular basis of biological function. This poses a challenge to computational modeling approaches since the applicability of conventional empirical molecular force fields is questionable. We here report the outline and preliminary results of our strategy towards developing pressure-dependent force fields for a number of important systems.

For instance, the peptide bond links two amino acids by rotatable bonds and is therefore the key element controlling protein conformations. Its amide group is moreover an important spectroscopic beacon for detecting environmental effects on protein folding. Hence, a detailed understanding of its electronic structure at high pressure is critically important not only to predict spectroscopic features but also to develop accurate pressure-sensitive force fields used for molecular dynamics simulations. We present results from high-level quantum-chemical calculations in the gas phase, with continuum dielectric solvation models, and in conjunction with the embedded cluster reference interaction site model (EC-RISM) [1-3] for simple model systems mimicking the protein backbone, N-methylacetamide (NMA) and Ac-Gly/Ala-NHMe. The results for both, the electronic energy surface and the solvent-mediated free energy surface challenge the applicability of established protein force fields for representing extreme environmental conditions. Unlike our experience with small osmolytes such as TMAO [1] or urea in water, a simple charge scaling procedure does not adequately represent the energetic pressure response such that a reparametrization of intramolecular dihedral force field terms will be necessary.

Similarly important is the accurate determination of the solvation free energy as a function of pressure. Since experimental reference data in this context are scarce we attempt to model the pressure dependent autoprotolysis of water for which measurements are available. [4] To this end, the EC-RISM formalism requires reasonable Lennard-Jones force field parameters for hydronium and hydroxide. We report progress by applying a differential evolutionary algorithm to optimize the radial distribution functions obtained from force field-based molecular dynamics simulations with respect to ab initio simulation data.

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