Accurate Calculation of Conformational Free Energy Differences in Explicit Water: The Confinement-Solvation Free Energy Approach

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The calculation of the free energy of conformation is key to understand the function of biomolecules and has attracted significant interest in recent years. Here, I present a variant of the confinement method that was designed for use in the context of explicit solvent MD simulations. The new development involves an additional step in which the solvation free energy of the harmonically restrained conformers is accurately determined by multistage free energy perturbation simulations. As a test-case application, the newly introduced confinement/solvation free energy (CSF) approach is used to compute differences in free energy between conformers of the alanine dipeptide in explicit water. The results are in excellent agreement with reference calculations based on both converged molecular dynamics and umbrella sampling. I will show that the CSF method provides conformational free-energy differences with a statistical uncertainty below 0.1 kcal/mol at a moderate computational cost even with a full representation of the solvent. Last, the conformational equilibria of more complex biomolecules such as met-enkephalin (5 residues) and deca-alanine (10 residues) in explicit water are analyzed to generalize the applicability of the CSF strategy.

Keywords: free energy of conformation, confinement method, all-atom molecular dynamics, explicit water simulations, chemical accuracy