Comparative Analysis of Enhanced Sampling and Direct Molecular Dynamics for Binding Free Energies

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The precise determination of thermodynamic equilibrium constants for dissolved diatomic molecules is investigated using a model interatomic potential. We establish a rigorous comparison between unbiased “brute-force” molecular dynamics (quantities are obtained directly by simulating sufficiently large molecular systems) and enhanced sampling techniques, specifically Metadynamics [1] and Umbrella Integration [2]. A consistent thermodynamic framework is applied to convert the potential of mean force into standard binding free energies, incorporating necessary entropic corrections for radial collective variables. The study focuses on the accuracy and convergence of these methods across a range of temperatures. We observe excellent quantitative agreement between the biased and unbiased approaches, with relative errors in the determination of the equilibrium constant being equal $1\% \pm 0.3\%$. This was achieved by performing sufficiently lengthy calculations and by systematically analyzing sources of uncertainty, including thermostat artifacts and the definition of the bound state. Thus we validate a robust pipeline for predicting chemical equilibrium in complex solvents with high precision.

[1] Laio A and Parrinello M 2002 *Proceedings of the National Academy of Sciences* **99** 12562–12566

[2] Kästner J and Thiel W 2006 *The Journal of chemical physics* **124**