

Improving Density Functional Tight Binding Predictions of Free Energy Surfaces for Peptide Condensation Reactions in Solution. M. P. Krooblawd and N. Goldman, Physical and Life Sciences Directorate, Lawrence Livermore National Laboratory, Livermore, CA 94550.

Introduction: Formation of oligopeptides in aqueous solution is thought to be an important precursor to prebiotic materials synthesis. Simple amino acid reactants, such as glycine, could have been present in Archaean oceans or brought to Earth by comets. The temperature and pressure conditions present at submarine thermal vents or during cometary impact could have facilitated oligopeptide formation, but can be difficult to model and analyze experimentally.

First principles molecular dynamics using highly accurate density functional theory (DFT) is a common tool for predicting chemistry, but the accessible time and space scales are often orders of magnitude beyond the resolution of experiments. Semi-empirical methods such as density functional tight binding (DFTB) offer up to a thousand-fold reduction in required CPU hours and can approach experimental scales, but standard DFTB parameter sets lack good transferability. Force matching the pairwise repulsive energy term in DFTB to short DFT trajectories can improve the former's accuracy for chemistry that is fast relative to DFT simulation times (< 10 ps), but the effects on slow chemistry and the free energy surface are not well-known.

We present a force matching approach to increase the accuracy of DFTB free energy surfaces in order to study slow peptide condensation reactions. Accelerated sampling techniques are combined with path collective variables to generate the reference DFT data set and validate fitted DFTB potentials without *a priori* knowledge of transition states. Accuracy of force-matched DFTB free energy surfaces is assessed for diglycine formation in explicit solvent. Improved accuracy in free energy differences compared to a standard DFTB parameterization is demonstrated. Extension of the approach to model glycine oligomerization chemistry at different reactive conditions is also discussed.

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