456g Molecules Losing Space: an Entropy Calculation of Ache-Fas2 Association

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Due to their importance in molecular recognition, association free energy calculations have been the subject of many theoretical studies. In addition to enthalpic changes, the noncovalent binding of molecules is accompanied by a significant change in translational, rotational, vibrational, and solvent entropy. While enthalpic contributions to the free-energy can be accurately estimated using molecular force fields, entropic contributions to the free energy of binding are difficult to estimate because they require extensive sampling of phase space. In this study, we have calculated the entropic changes on binding of Fasciculin-2 to Acetylcholinesterase. In particular, by comparison with the Gibbs entropy formula, we have investigated the accuracy of the commonly invoked quasiharmonic approximation (QHA), and its sensitivity to the choice of reference structure used to eliminate translational and rotational motion. We propose a multiple-population decomposition of the simulation trajectory based on a principal component analysis(PCA) of the covariance matrix. By successively applying the original quasi-harmonic method to the separate populations, we can better satisfy the conditions necessary for QHA. Additionally, PCA provides a greater degree of physical insight into the entropic changes and their relationship to molecular structure and motion.