[L12] A Linear Interaction Energy (LIE) model for Cavitand Host-Guest Binding Affinities

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Host-guest systems provide excellent models to explore molecular recognition in solution along with relevant technological applications from drug carriers to chemosensors. Here, we present a linear interaction energy (LIE) model to predict the binding affinity in host-guests with remarkable efficiency and predictive power. Using four host families including cucurbiturils, octa acids, and β-cyclodextrin, and a large set (49) of chemically-diverse guests, we demonstrate that binding-affinity predictions with a RMSE < 1.5 kcal/mol from experiments can be obtained with a few nanoseconds of Molecular Dynamics. The parameters of the LIE model are shown to be transferable among host-guest families and the quality of the predictions to be essentially force-field independent. Inclusion of the strain energy of the host in the bound state appears to be critically important to improve the quality of the predictions, particularly when the host and the guest have comparable sizes. The disruptive potential of the approach is demonstrated through the accurate prediction of the orthogonal selectivity of steroid guests to cucurbituril hosts. Unsuccesfull predictions for 28 additional highly-charged and bulky guests to cucurbit[7]uril indicate future directions for improvement.