

Bigger, Better, and Biologically Relevant: An EFP-SAPT benchmarking study on the BFDdb database.

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Previously reported benchmark comparisons between the Effective Fragment Potential (EFP) method and the Symmetry-Adapted Perturbation Theory (SAPT) for the S22 and S66 sets of non-covalent interactions provided promising results for usage of EFP as an alternative to parameterized molecular mechanics models for obtaining accurate interaction energies. Here, in collaboration with the Sherrill Group at Georgia Tech, a benchmarking study was performed to examine the robustness of EFP in describing non-covalent interactions in the Biofragment Database (BFDdb). The BFDdb contains a large set of biomolecular fragments obtained from multiple high-resolution protein structures. Specifically, we examined EFP performance for dimers associated with the side chain - side chain interactions (SSI) and backbone-backbone interactions (BBI) that number 3380 and 100 dimers, respectively.

Accuracy of EFP was analyzed with respect to basis set employed for computing effective fragment potentials and type of interactions in the dimer. Potentials were generated using 6-31G*, 6-31+G*, 6-311+G(3df,2p), and mixed bases 6-31G*|6-31+G* and 6-31G*|6-31+G*|6-311+G(3df,2p). Mean absolute deviations (MAD) between the EFP and SAPT0/jun-cc-pVDZ calculations for EFP generated with different bases are within a range of 0.6-1.1 kcal/mol. Comparison of the EFP and SAPT energy components demonstrates the rigorousness of EFP in describing the nonpolar interactions found within the more hydrophobic regions of proteins and the challenges it faces in describing polar interactions typically found in the hydrophilic surfaces and pockets of globular proteins. Our results provide error bars for EFP when applied to interactions in proteins as well as recommendations for the most optimal use of the method.