Pairwise Additivity of Energy Components for Protein-Ligand Binding Events

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Abstract:
An energy expansion (binding energy decomposition into n-body interaction terms for $n \geq 2$) to express the receptor-ligand binding energy for the fragmented HIV II protease-Indinavir system is described to address the role of cooperativity in ligand binding. The outcome of this energy expansion is compared to the total receptor-ligand binding energy at the Hartree-Fock, density functional theory, and semiempirical levels of theory. We find that the sum of the pairwise interaction energies approximates the total binding energy to ~82% for HF and to >95% for both the M06-L density functional and PM6-DH2 semiempirical method. Thus we conclude that the two-body terms represent a good approximation to the total binding energy of the system, which points to pairwise additivity in the present case. This basic principle of pairwise additivity is utilized in fragment-based drug design approaches and our results support its continued use. The present results can also aid in the validation of non-bonded terms contained within common force fields and in the correction of systematic errors in physics-based score functions.