Understanding molecular binding with the fragment molecular orbital method

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Quantum-chemical calculations of large molecular systems such as proteins, DNA, or nanomaterials can be efficiently done with the fragment molecular orbital (FMO) method [1]. This is accomplished by performing electrostatically embedded calculations of fragments and their pairs. On a single PC node with 40 cores, for a protein (Fig. 1) with 3214 atoms, an FMO-MP2/PCM calculation takes 16 hours, but an FMO-DFTB/PCM calculation takes only 7 minutes, performed with the freely distributed GAMESS program. FMO can be used for geometry optimization, transition state search, MD, and Hessian calculations.

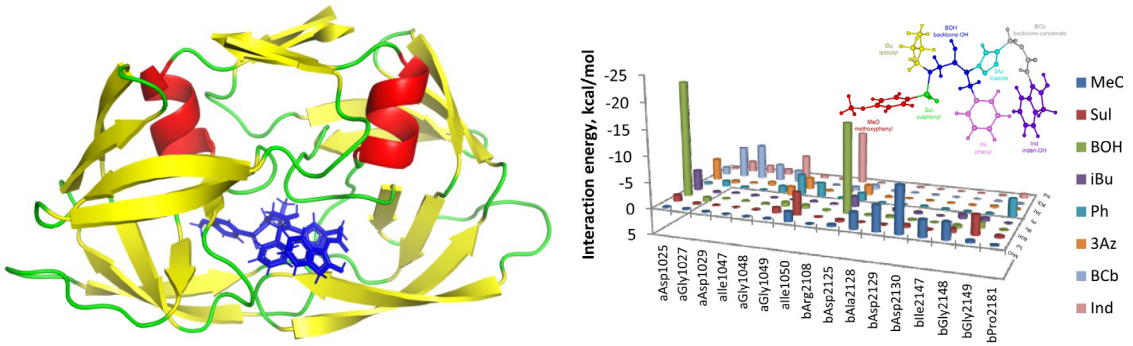

Fig. 1. Interactions of functional groups in the AB-2 ligand with amino acid residues of the HIV protease (PDB: 2hc0), computed with FMO-DFTB3/PA/PCM.

A summary of the FMO methodology will be followed by applications of interfragment interaction analyses. At the DFTB level, an analysis can be done for functional groups, providing a quantitative measure of the importance of fragments in macromolecules to molecular binding so that hotspots can be identified, aiding drug discovery and material design (e.g., zeolites and nanomaterials). Interactions can also be visualized in 3D space using the non-covalent interaction index [2].

[1] Analyzing many-body charge transfer effects with the fragment molecular orbital method. D. G. Fedorov, J. Comput. Chem. 46 (2025) e70128.
[2] D. G. Fedorov, D. Inostroza, B. Courbiere, F. Guegan, J. Contreras-García, S. Mori, J. Chem. Theory Comput. 21 (2025) 4435-4446.