

Role of Non-Covalent Interactions in Carbonic Anhydrase I—Topiramate Complex Based on QM/MM approach

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Streszczenie

Carbonic anhydrase (CA) I with a Topiramate (TPM) complex was investigated on the basis of a Quantum Mechanics/Molecular Mechanics (QM/MM) approach. The QM part was treated using Density Functional Theory (DFT) while the MM was simulated using Amberff14SB and GAFF force fields. In addition, the TIP3P model was applied to reproduce the polar environment influence on the studied complex. Next, three snapshots (after 5 ps, 10 ps, and 15 ps of the simulation time) were taken from the obtained trajectory to provide an insight into the non-covalent interactions present between the ligand and binding pocket of the protein. Our special attention was devoted to the binding site rearrangement, which is known in the literature concerning the complex. This part of the computations was performed using ω B97X functional with Grimme D3 dispersion corrections as well as a Becke–Johnson damping function (D3-BJ). Two basis sets were applied: def2-SVP (for larger models) and def2-TZVPD (for smaller models), respectively. In order to detect and describe non-covalent interactions between amino acids of the binding pocket and the ligand, Independent Gradient Model based on Hirshfeld partitioning (IGMH), Interaction Region Indicator (IRI), Quantum Theory of Atoms in Molecules (QTAIM) and Natural Bond Orbitals (NBO) methods were employed. Finally, Symmetry-Adapted Perturbation Theory (SAPT) was applied for energy decomposition between the ligand and protein. It was found that during the simulation time, the ligand position in the binding site was preserved. Nonetheless, amino acids interacting with TPM were exchanging during the simulation, thus showing the binding site reorganization. The energy partitioning revealed that dispersion and electrostatics are decisive factors that are responsible for the complex stability.

Słowa kluczowe

Carbonic anhydrase I, Topiramate (TPM), non-covalent interactions, QM/MM. DFT, IGMH, IRI, QTAIM, NBO, SAPT

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