An Application of the Fragment Molecular Orbital Method to Molecular Simulation in the Drug Discovery Research

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Abstract

Recently, the number of known protein structures has grown exponentially. The use of protein structures in the drug discovery process is called structure-based drug design (SBDD) and is essential for rational drug design. SBDD analyzes the interaction between a protein and its ligands.

Kitaura and his co-workers developed the FMO method, which enables the *ab initio* calculation of large molecules, including proteins and nucleic acids, and their complexes. Nakano et al. incorporated an FMO program named ABINIT-MP in the Earth Simulator 2. FMO is expected to be useful tool for drug design. We examined three issues of SBDD by using large computer power of ES2. First is that interaction energies (IFIEs) between protein and ligand can be use to select the correct pose from a multiple of docking poses. Second is that the change of molecular interaction associated with dynamics of proten in water was traced by IFIEs. Last is application of the 6-31G* basis set to proteins, which have about 300 amino residues.

The prediction of docking pose is one of the important issues in SBDD. Eight complexes between LCK protein and its inhibitors were examined. For Five complexes, the correct pose is select by IFIEs. This result shows that IFIEs can be applied to the process of docking simulations.

To assess the change of molecular interaction, molecular dynamics (MD) simulations for three Gads-SH3 proteins: native, ligand mutation (I5*A), and protein mutation (W36A) were performed. After 10ns of MD, 18 trajectories were calculated by FMO. These results reveal that a single mutation influences the interaction of not only itself but also other residues, thereby providing the possibility of drug design considering the allosteric effect.

The interaction energy was calculated for complexes between LCK protein and its inhibitors with FMO/MP2/6-31G*. The interaction energies were well correlated with the IC_{50}, indicating the suitability of the FMO method.

KeyWords: Molecular interaction, Ab initio fragment molecular orbital (FMO) method, Molecular dynamics, Structure based drug design