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. Nevertheless, there is still room for improvement in SBDD. First, the interaction energies are calculated using molecular mechanics, which is not reliable. Second, the simulations of the interactions between the protein and ligand are performed in a vacuum, which differs from biological environments. We applied the *ab initio* fragment molecular orbital (FMO) method to examine these two points.

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 and used it to analyze the interaction of the influenza hemagglutinin antigen–antibody system.

ABINIT-MP was used to examine two systems in the Earth Simulator. The interaction energy was calculated for complexes between LCK protein and its inhibitors. The interaction energies were well correlated with the IC_{50}, indicating the suitability of the FMO method. In addition, the interactions between SH3 protein and ligand peptides including water molecules were also simulated. The effect of changing the number of water molecules around the SH3 protein and peptide on the interaction energies between SH3 protein and peptide was examined. The interaction energies were saturated when water molecules were within 8 Å of the SH3 protein and ligand, suggesting the importance of water in the protein and ligand interaction.

Keywords： Molecular interaction, Ab initio fragment molecular orbital (FMO) method, Solvent effect, Structure based drug design