**Application of the Fragment Molecular Orbital (FMO) Method to Drug Discovery. Focus on Kinase Inhibitors**

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The *ab initio* fragment molecular orbital (FMO) method for very large molecules has been developed by Kitaura and Nakano[1,2]. In the FMO method, a molecule or a cluster is divided into many fragments, and the MO calculations are performed in the fragments (monomers) and the fragment pairs (dimers). The results for the fragments (monomers) and the fragment pairs (dimers) are combined to obtain the total energy. The FMO method reproduces regular *ab initio* properties with good accuracy. In a protein, the fragmentation is carried out an amino acid residue as a unit; the results can be used to the interaction analysis between ligand and each amino acid residue.

The number of experimental protein 3D structure is recently growing exponentially by the development of protein expression systems and progress in instrumentation of structure determination. It is clear that protein structure information will contribute to many stages of drug discovery process. The analysis of protein structure based on the quantum chemical calculations is expected to an accurate estimation of interaction energies.

We applied the FMO method to the complexes of protein and inhibitor, which were solved by the diffraction data collected at SPring-8. The interaction energies calculated by the FMO method is well correlated with $IC_{50}$ value. Furthermore, the FMO calculations show that the CH/π hydrogen bonds[3] play an important role in the interaction between protein and inhibitor.

References

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3) M. Nishio, Topics in Stereochemistry, 25, 255-302 (2006)