Developments of the Computational Technique to Predict the Binding Enthalpy for Protein–Inhibitor Complex

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Abstract

Although recent advances in Japanese original software make it now possible to carry out the quantum chemical calculations of the protein-inhibitor interaction energy, it is still very difficult to calculate the quantum chemical binding free energy ($\Delta G = \Delta H - T\Delta S$), which is directly concerned with the pharmacological activity of inhibitor. However, there is a possibility that the binding enthalpy term (ΔH) can be calculated with quantum chemical calculation. The aim of the project is developments of the computational technique for the prediction of the binding enthalpy for the protein–inhibitor complex with the quantum chemical calculation on the Earth Simulator in order to utilize it for SBDD (Structure Based Drug Design). In fiscal year 2009, we designed the computational technique using DIEM (Difference mean Interaction Energy Matrix) which was defined by the subtraction the interaction energy matrix for hydrated protein from that for hydrated protein–inhibitor complex and the subtraction the interaction energy matrix for hydrated inhibitor from that for pure water. Using DIEM, it is possible to make the molecular system to calculate quantum chemically small. The Fragment molecular orbital (FMO) method is carried out in order to evaluate the inter-fragment interaction energies (IFIE). Here, we apply the DIEM method for the HIV1 protease-inhibitor complex. We analyze the decomposition of the binding enthalpy into six components, which are intra-protein, protein-inhibitor, protein-water, intra-inhibitor, inhibitor-waters, and inter-water molecules, and discuss the binding mechanism of protein and inhibitor. All FMO calculations for protein systems were carried out by using the program ABINIT-MP on the Earth Simulator in JAMSTEC.

Keywords: binding enthalpy, Fragment molecular orbital (FMO) method, SBDD, interaction energy matrix