Specific interactions between lactose repressor protein and DNA: classical MD and *ab initio* MO calculations

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Lactose repressor (LacR) protein controls the transcriptional mechanism of gene information from DNA to mRNA in a ligand-dependent manner. Although the ligand-binding to LacR was found to change the mechanism drastically, the effect of ligand-binding on the conformation of LacR-DNA complex has not been clarified at atomic and electronic levels. In our previous study [1], molecular simulations combined with classical molecular mechanics (MM) and *ab initio* fragment molecular orbital (FMO) methods were performed to elucidate the specific interactions between LacR monomer, DNA and ligand. In the present study, we investigated the change in conformation of the solvated complex of LacR dimer and DNA induced by the ligand-binding by molecular dynamics (MD) simulations.

The initial structure of the complex with LacR dimer, DNA and anti-inducer ONPF, which is defined as LacR-DNA-ONPF, was constructed based on the PDB structure (PDB ID: 1EFA). The structure of LacR-DNA without ligand was constructed by deleting ONPF, while that of LacR-DNA-IPTG with inducer IPTG was constructed by replacing ONPF by IPTG. These structures were optimized in water by the MM method based on AMBER99SB-ILDN and TIP3P force fields, and 100 ns MD simulations were performed to elucidate the conformational change of LacR-dimer+DNA complexes.

We first analyzed the time evolution in RMSD of Cα atoms of LacR during the MD simulation. In LacR-DNA and LacR-DNA-ONPF, the conformation of LacR dose not change significantly. In contrast, LacR in LacR-DNA-IPTG has large conformational change at 7.7 ns, indicating the remarkable effect of inducer IPTG on the LacR-DNA complex. To elucidate the effect, the structures of LacR-DNA-IPTG at 1.5 and 7.7 ns are compared in Figure 1. LacR dimer tilts 12.8 degree to the left relative to DNA at 7.7 ns. We furthermore investigated which parts of LacR are affected by the IPTG binding to find that the conformation of the α-helix including Asp149 and Asn125 residues is changed significantly. These residues contribute to the specific binding between LacR and IPTG. Therefore, it is elucidated that the information of IPTG binding transfers to the α-helix, leading to the change in its conformation. This change is expected to influence the conformation of the DNA-binding domain of LacR and the binding affinity between LacR and DNA. The specific interactions between LacR and DNA investigated by *ab initio* FMO calculations will be shown at the conference.

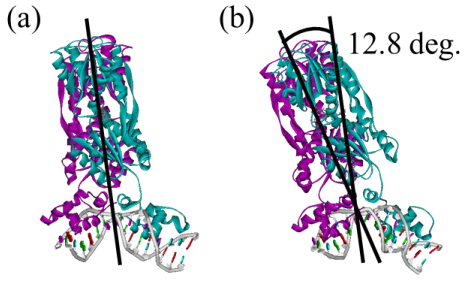

Fig. 1 Structure of LacR-DNA-IPTG at (a) 1.5 ns and (b) 7.7 ns of MD.

[1] T.Ohyama *et al., J. Comp. Chem.* 32, 1661(2011).