# Molecular dynamics and molecular orbital simulations on specific interactions between Aryl hydrocarbon receptor and dioxin congeners

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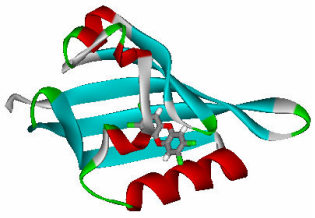
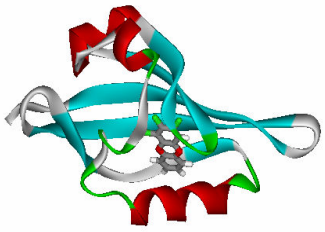
Aryl hydrocarbon receptor (AhR) binds specifically a diverse spectrum of chemicals as a ligand and regulates expression of genes in a ligand-dependent manner. However, the structure of AhR and the recognition mechanism between AhR and ligands have not been clarified yet. In the present study, we obtained stable structures of the solvated complex with rat AhR and dioxin congeners and investigated the specific interactions between AhR and the congeners by using *ab initio* fragment molecular orbital (FMO) method.

We first constructed several model structures for the ligand binding domain of AhR by using homology modeling. Solvating water molecules were added around the AhR structure, and their positions were optimized by a classical AMBER-MM method. As for the protonation state of His residues in AhR, we assigned the state based on the pKa value around His and determined the most stable state by the *ab initio* FMO calculations. The model structures of the complexes with AhR and the congeners were obtained by using the protein-ligand docking program Autodock4.2 and classical AMBER-MM method. In addition, the stable conformations of the congeners were widely searched by classical AMBER-MD simulations. Finally, the specific interactions between AhR and the congeners were investigated by the *ab initio* FMO method.

Figure 1 shows the optimized structures of the solvated AhR-TCDD and AhR-TrCDD complexes..The positions of the congeners in the ligand-binding pocket of AhR differ considerably. It seems to come from the difference in the positions of chlorine atoms of TCDD and TrCDD. To elucidate the binding affinity between AhR and the congeners, the binding energies as well as the binding free energies between AhR and congener were investigated by the FMO method. The results will be discussed in comparison to the toxicity observed by experiments in the poster.



(a) ratAhR-TCDD



(b) ratAhR-TrCDD

Fig. 1 Optimized structures of AhR-congener complexes

This work was partially supported by the Toyoaki Scholarship Foundation.

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