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## Molecular Dynamics Simulation for Hydroxylation of Camphor by Cytochrome P450

○Abdul Rajjak Shaikh<sup>1</sup>, Hideyuki Tsuboi<sup>1</sup>, Michihisa Koyama<sup>1</sup>,  
Nozomu Hatakeyama<sup>1</sup>, Akira Endou<sup>1</sup>, Hiromitsu Takaba<sup>1</sup>, Momoji Kubo<sup>1</sup>,  
Carlos A. Del Carpio<sup>1</sup>, Ewa Broclawik<sup>2</sup>, Akira Miyamoto<sup>1,3</sup>

<sup>1</sup>Grad. Sch. Eng., Tohoku Univ. (6-6-11-1302 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)

<sup>2</sup>Pol. Acad. Sci., Poland (ul. Niezapominajek 8, 30-239 Kraków)

<sup>3</sup>NICHe, Tohoku Univ. (6-6-10 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)

### 【Introduction】

Cytochrome P450 enzymes are ubiquitous hemo-proteins that are involved in the metabolism of very diverse compounds, such as steroids, fatty acids, and alkaloids. These monooxygenases play an important role in many bioregulatory functions, which includes biosynthesis of hormones or detoxification of xenobiotics. Cytochrome P450cam (CYP101) is a heme-containing monooxygenase from the soil bacterium *Pseudomonas putida* that catalyzes the 5-exo hydroxylation of camphor. In present study we observe the hydroxylation of Camphor by P450cam using molecular dynamics simulation.

### 【Method】

P450cam crystal structure (3CPP) was obtained from protein data bank<sup>1</sup>. Oxygen was inserted to Fe atom of heme group to mimic the Compound I model. Hydrogen's were added to all amino acids. Water molecules in crystal structure are used in calculation. Molecular dynamics simulation was carried out using our in-house program NEW-RYUDO with chemical reaction extension function included in it. MD simulation was carried out for 500000 steps with step size of 0.1 fs and temperature 298 K.

### 【Results and Discussion】

Metabolism of camphor by P450cam has been the subject of many experimental and computational studies. A generally accepted mechanism for Camphor hydroxylation by P450cam involves the initial H atom abstraction from a C-H bond of the substrate, followed by the recombination of the resultant radical species to form the hydroxylated product. During MD simulation, formation of O-H bond and breaking of C-H bond was observed. At 3600 fs, the C-H bond break and O-H bond forms (Fig. 1). This might be the transition state where distance between C-H was 1.8 Å and O-H was 1.4 Å. After this step hydrogen was totally abstracted by O atom. In second step, radical carbon of Camphor recombines with O to produce a 5-exo-hydroxy camphor. In this new approach, we simulated the dynamic movement of C-H bond breaking and O-H bond formation and later C-O bond formation. We attempt to carry rate of reaction for this hydroxylation reaction. These results were later compared with experimental findings. More detailed results will be presented in conference.

### 【Results and Discussion】

1) R. Raag, T. L. Poulos. Biochemistry, 1989, 28, 7586.

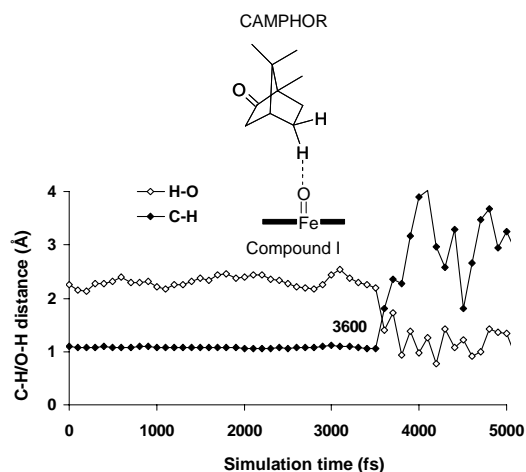


Fig. 1: Graph of C-H/O-H distance versus simulation time.