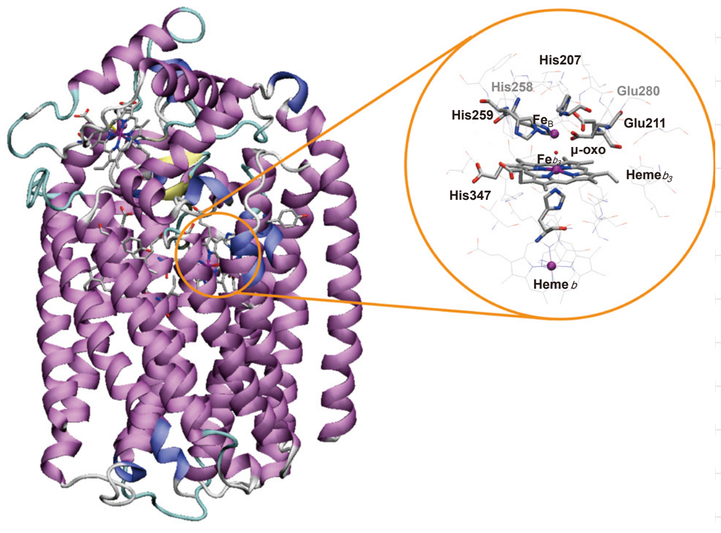
Biological Sciences on PACS-CS/T2K

QM/MM Studies on Reaction Mechanisms

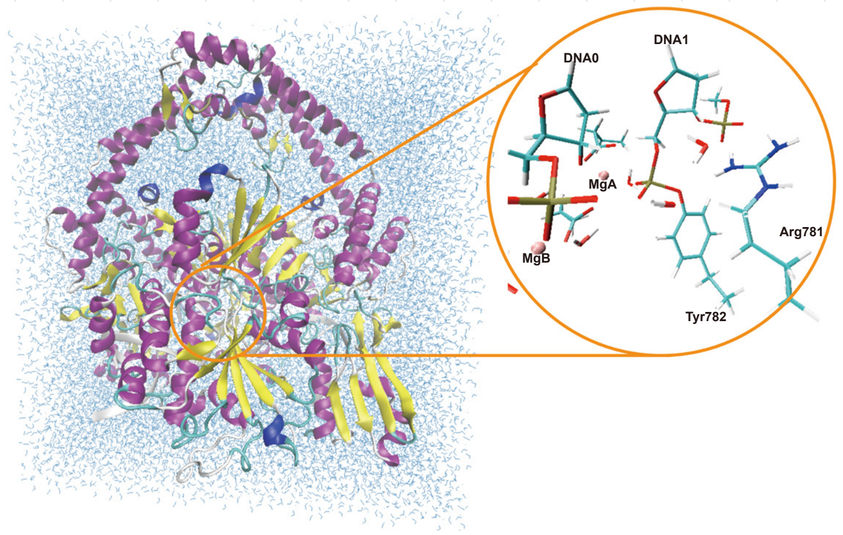
Nitric Oxide Reductase (NOR)



Nitric oxide reductase (NOR) is a transmembrane protein which catalyzes a reduction of nitric oxide (NO) to nitrous oxide (N2O). This step is critical for the denitrification process in the anaerobic respiration: NO3- -> NO2- -> NO -> N2O -> N2. In 2010, first x-ray crystal structure of NOR was reported at atomic resolution (2.7Å). It was revealed that catalytic site is constituted by non-heme iron FeB and heme b3 and the overall structure of NOR has many similarities to cytochrome oxidase (COX), in consistent with the evolutionary relatedness. The reaction mechanism of NOR is, however, not fully elucidated. Three reaction mechanisms have been proposed, the cis-FeB, cis-heme b3 and trans mechanisms.

We have been investigating the reaction mechanism by using the quantum mechanical/ molecular mechanical (QM/MM) method. Geometrical structures and the energies in the intermediate states were examined to elucidate the enzyme catalytic mechanism.

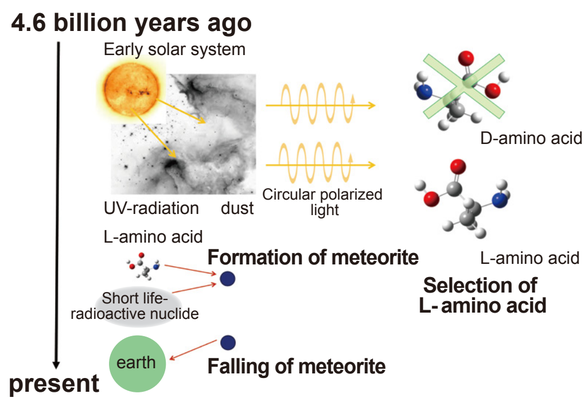
Type II DNA Topoisomerase (topo II)

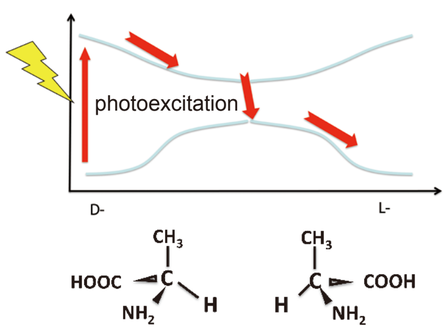


DNA topoisomerase is a DNA-binding enzyme which catalyzes interconversions of the different topological forms of DNA. This enzyme forms a covalent intermediate in which catalytic tyrosine residue is covalently bonded to the DNA backbone phosphate, after and before cleavage and religation reactions. Accumulation of this intermediate is lethal to cell. In fact, several drugs acting on DNA topoisomerase lead to an accumulation of this intermediate. Thus detailed understanding of DNA religation reaction, which is needed to resolve the covalent bond, is helpful for designing drugs acting on this enzyme.

Recently, the crystal structure of the covalent intermediate of yeast topo II in complexed with single DNA was solved at 3.0Å resolution, as shown in Figure. Using the x-ray crystal structure as the initial coordinate, we performed MD (molecular dynamics) simulations and QM/MM calculations. We revealed a detailed reaction mechanism of the DNA religation reaction in topo II.

Investigation of the Early Solar System Based on the Photo-induced Chirality Formation of Amino Acids





The naturally-occurring amino acids in terrestrial life are all the levorotatory (L-) form, none of the D-form. The cause for its selectivity still remains a big mystery. One of the possible scenarios is that the chiral induction of amino acids is originated from meteorites during the formation of the early solar systems [1]. In order to validate the hypothesis, we have investigated the mechanisms of photo-induced chirality formation by using the TDDFT method. Circular dichroism and UV- absorbance spectrum are calculated for amino acids and plausible chiral induction mechanisms are discussed.

Theoretical Prediction of 3D Structure of Yeast Prion Sup35 in Amyloid Fibrils

Prions are infectious proteins, where self-propagating amyloid conformations of proteins are transmitted. The Sup35 protein is the best-characterized prion in yeast [2], which functions as a translation termination factor. It has been shown in vitro that the N-terminal portion of Sup35 (1–123) forms the core structure of amyloid fibrils. For the amyloid fibrils of Sup35 on the basis of experimental studies, several structural models such as beta-helix, beta-solenoid and in-register model have been proposed. The beta-helix model is a nanotube in which beta-sheets are aligned along the fiber axis with a pitch of 4.7 Å [3]. However, due to the difficulty of their inherent noncrystalline and insoluble nature, the detailed structure of the amyloid fibril for Sup35 remains unclear at the atomic level.

We have investigated on the validity of several amyloid models for yeast prion Sup35 by using molecular modeling and molecular dynamics (MD) simulations in combination with experimental approaches.

[1] J. R. Cronin et. al., Science 275, 951 (1997); M. H. Engel et. al., Nature 389, 265 (1997).

[2] Hideki Taguchi and Shigeko Kawai-Noma, “Amyloid oligomers: diffuse oligomer-based transmission of yeast prions”, FEBS 277 1359-1368 (2010).
[3] Kishimoto, A. et al., “beta-Helix is a likely core structure of yeast prion Sup35 amyloid fibers”. Biochem Biophys Res Commun 315, 739-745 (2004).