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Applying Ultra Accelerated Quantum Chemical Molecular Dynamics techniques for studying the role of NADPH in Dihydrofolate reductase.

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【Introduction】

Ultra accelerated quantum chemical molecular dynamics methods can describe the interactions for a large systems like Dihydrofolate reductase (DHFR), which catalyses the NADPH-dependent reduction of dihydrofolate to Tetrahydrofolate. Till now the study has been focused on experimental determination of binding site, but we successfully investigated the reduction of dihydrofolic acid using quantum chemical molecular dynamics. Tetrahydrofolate is essential for the biosynthesis of purines, thymidylate and several amino acids. Fig.1 shows initial structure of system. It shows the hydrogen from NADPH, which was transferred to the nitrogen of dihydrofolic acid during MD simulation. The nitrogen shown in the figure is associated with a double bond, which is reduced during this reaction.

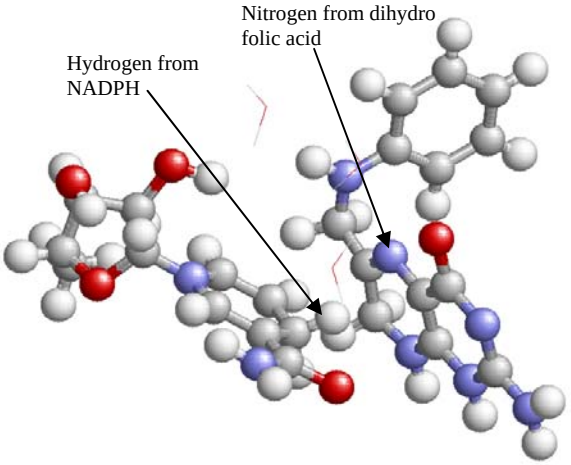

Fig 1. NADPH and Dihydrofolic acid in DHFR site (initial structure)

【Method】

Quantum chemical molecular dynamic simulation method, which is 10 million times faster than conventional ab initio method, was used in our calculation. We used a combination of MD simulation with quantum chemical methods in the form of Colors-New Ryudo combination. Prior to this simulation, the DHFR-NADPH-Dihydrofolic acid complex was subjected to a single point quantum chemical calculation by Colors program. This combination of Colors and New-Ryudo was repeated for a number of times to get the desired stability and accuracy of results.

【Results and Discussion】

In Fig.2, the graph plotted between Nitrogen – hydrogen distance and time shows that there is a possibility of hydrogen transfer from Nicotinamide Adenine Dinucleotide Phosphate (Reduced form) and dihydrofolic acid. This hydrogen is involved in the reduction of double bond associated with the nitrogen. We confirmed the role of NADPH in the reduction of Dihydrofolic acid into tetrahydrofolic acid. Also, we confirmed that our QC MD program could successfully calculate such biological interactions.

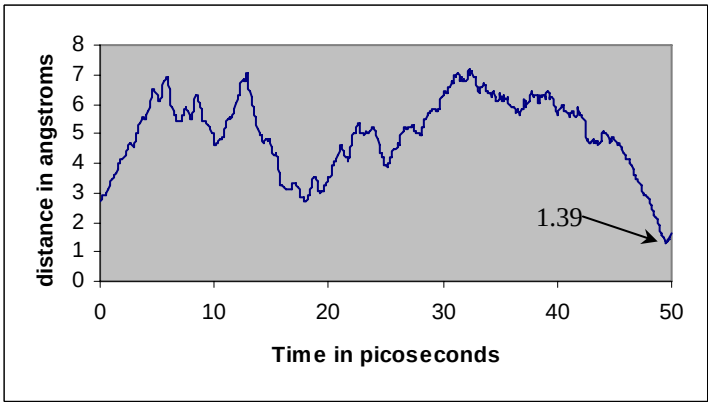

Fig.2 Plot showing distance between N and H with