Oral Presentation 10

日時：2020 年 10 月 30 日 14:45-16:15
チャンネル：1

口頭発表10
『計算化学(分子計算)』
Computational Chemistry (Molecular Modeling)

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Advanced methods to predict properties of cyclic peptides: conformation analysis of peptides cyclized by non-amide bonds

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Keywords: Conformation analysis, Cyclic peptides

Drug discovery in middle sized molecules such as cyclic peptides is an attracting area as they have higher selectivity compared to small molecules and higher membrane permeability compared to antibodies. Since the properties depend on their conformation[1], we developed a "Ring Expansion Method"[2] for the generation of cyclic glycine conformers and an addition method of side chain conformers[3] to analyze the stable conformation exhaustively. In CBI annual meeting 2019, we reported these methods and calculation results for peptides cyclized by only the amide bond[4,5]. Recently, we expanded the scope of application to analyze conformations of peptides cyclized by non-amide bonds.

Our new conformation analysis methods are as follows.

(i) Generation of cyclic glycine conformers by "Ring Expansion Method", and addition of heavy atoms between N and CA atom in the main chain to generate non-amide bonds.

(ii) Substitution of a cyclic residue like the proline for a glycine residue and addition of a heavy atom whose position is uniquely determined (CB atom of the alanine or C atom of the N-methylated amide bond). These conformers are named "stem ring conformers".

(iii) Addition of side chain conformers to the stem ring conformers.

We analyzed the conformation for the peptide (YDYPGDYCYLY) cyclized by non-amide bonds (PDB ID: 5KGN). In this study, we analyzed residues of the ring part (YDYPGDYC).

The analysis time was less than 2 hours using 400 cores (Xeon E5-2660 (2.2 GHz)). The conformations of several stable conformers obtained were found to be similar to that of the experimentally observed one. The lowest RMSD between the PDB and obtained conformations is 1.79 Å, here these conformers are superposed on all heavy atoms (Figure 1). When these are superposed on backbone atoms, the lowest RMSD is 1.21 Å.

Our advanced methods achieved the conformation analysis of peptides cyclized by not only the amide bond but also non-amide bonds.

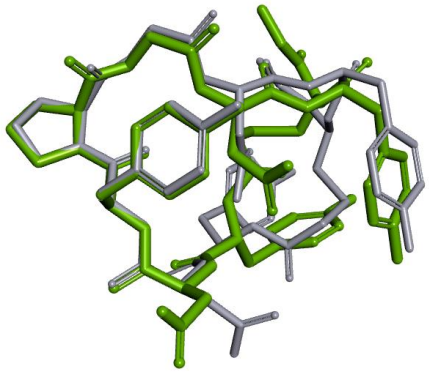

Figure 1: The closest conformer (green line) to the conformer reported in PDB (gray line). These conformers are superposed on all heavy atoms.

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O1-13

Enhanced conformational sampling of cyclic peptide Cyclorasin by coupled Nosé-Hoover equation

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Keywords: cyclic peptide, Cyclorasin, membrane permeability, enhanced conformational sampling, coupled Nosé-Hoover equation

The importance has been increasing in recent drug discovery to design cyclic peptides that have high affinity to target proteins for inhibition and high membrane permeability for drug delivery. The affinity is estimated by simulating the fluctuation around the protein-peptide complexes and by calculating the associated binding free energies, whereas the membrane permeability should rely on intrinsic flexibility of the cyclic peptides. To reveal the permeability in terms of atomistic viewpoints, we have attempted to fully obtain the structural ensembles of our target cyclic peptides by use of the coupled Nosé-Hoover equation (cNH) of our recent development [1,2].

The original Nosé-Hoover equation generates a canonical distribution at a predetermined static temperature. In cNH, in contrast, a physical system is simulated at nonequilibrium temperature that is fluctuating in a dynamic manner. This corresponds to a temperature replica exchange simulation with continuous temperatures by adopting continuous time development using a single replica. The dynamics are realized by coupling the physical system with a temperature system of small degrees of freedom, both of which are described by the Nosé-Hoover method. The desired distribution of the fluctuating temperature is achieved by the established formalism, allowing an enhanced conformational sampling and a reconstruction of the canonical distribution for the physical system at an arbitrary temperature.

Here, we chose Cyclorasin 9A5 [3] and a derivative as target cyclic peptide systems. Cyclorasin inhibits Ras signaling by blocking Ras-effector protein interactions, which will have therapeutic benefits in cancer patients. A derivative, 9A54, achieved higher affinity than 9A5 after small modifications, which, however, resulted in lower membrane permeability [3]. To explain this controversial result from fully atomistic descriptions, we applied the cNH to sample the structural ensembles of both 9A5 and 9A54 in both explicit water and DMSO environments. The derived structures indicated minor but significant changes in the structural dynamics via the modification from 9A5 to 9A54, which is reasonably in agreement with the NMR experiment [4].

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O1-14

Development status of ABINIT-MP program in 2020

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Keywords: Fragment molecular orbital, FMO, ABINIT-MP, Interaction energy analysis

We have been developing the ABINIT-MP program [1] for about 20 years, and this system has been widely used in the fields of pharmaceutical chemistry and biophysics in Japan. The latest distribution package is the Open Version 1 Revision 22 (hereafter denoted as Rev.22) as of June 2020. In Rev. 22, the calculation of PIEDA in ABINIT-MP [2] is greatly accelerated by improving the loop structures; several bottlenecks of processing have been removed. Only the specified region can be calculated at the MP2 or MP3 levels [3] in a multilayer FMO (MFMO) framework [4]. Additionally, the frozen-domain (FD) [5] is supported for partial geometry optimizations.

From April 2020, the trial usage of Fugaku has been provided for ABINIT-MP, and a series of FMO calculations have been performed for several proteins related with COVID-19. With 3072 nodes of Fugaku, an FMO-MP3/cc-pVDZ job for a spike protein (consisting of 3.3 thousand amino acid residues) could be completed in only 3.4 h.

In the presentation, we will show the features of Rev. 22 and some demonstrative results.

[Acknowledgment] This work was supported by the following projects; a social and scientific priority issue #6 to be tackled by using post-K computer (Fugaku) operated by MEXT, Kaken-hi (16H04635), AMED/BINDS (JP19an010101113) and Rikkyo SFR. The trial usage of Fugaku was conducted by RIKEN R-CCS and MEXT under the special project against COVID-19 [6].

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O1-15

Development of multiscale FMO-DPD simulations for molecular design

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Keywords: FMO-DPD, Multiscale simulation, Dissipative particle dynamics, Reverse map

In the fields of drug design or materials science, control of molecular structures at an atomistic level is highly desired for the advancement of products, and pre-screening or understanding of molecular mechanism using computational chemistry has attracted much attention. In recent years, the prediction of meso-scale structures formed by molecular aggregates is important issue because meso-scale structure has a significant effect on various chemical and biological mechanisms. In order to predict meso-scale structures, simulations using coarse-grained models such as dissipative molecular dynamics (DPD) [1] are commonly used for handling long time-scale and large systems. The parameters that describe the interactions among particles are crucial for these simulations, and they are generally closely related to the so-called χ parameters that correlated with the affinities between components by the Flory-Huggins theory. However, it is well known that the evaluation of a reliable set of χ parameters is a difficult problem, and thus values based on experimental data or empirical values are generally used in DPD simulation. The parameter-dependent applications should have several limitations, and accurate evaluation of χ parameters is still a critical concern.

Our group has developed a new framework for calculating effective interaction parameters [2-4] between particles for meso-scale DPD simulations, based on nano-scale fragment molecular orbital (FMO) calculations [5] by using ABINIT-MP program [6]. In addition, the workflow of detailed FMO analyses of fully atomistic structure generated from meso-scale structure using the reverse map technology has been established recently. In other words, a series of the multiscale FMO-DPD simulation systems have been completed. In this presentation, we outline the frameworks of FMO-DPD and also the demonstrative applications [7-9].

[Acknowledgment] The present work was supported by MEXT as a social and scientific priority issue #6 to be tackled by using post-K computer (FS2020), AMED-BINDS (JP20am0101113), and Rikkyo SFR.

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