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A practical procedure to calculate intermolecular interactions including statistical information between a protein and a large ligand

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We investigated the method to compute intermolecular interactions around the binding site in the system composed of the histone deacetylase SIRT2[1], a nonstandard cyclic peptide (S2iL5[2]) and solvent, especially in view of the influence of water molecules.

First, we performed 1 μs molecular dynamics (MD) simulation in the system and obtained an equilibrium time region corresponding to local fluctuations of SIRT2 from the MD trajectory. In this region, we selected the water molecules whose RMSF values were as small as those of SIRT2. These water molecules were considered to be less fluctuated and thus *stable*. In order to include the statistical information in one typical structure, we averaged the structures of the complex with the *stable* water molecules in the region and then optimized the obtained structure by the molecular mechanics method. Next, we investigated the conformation of the binding sites and calculated the intermolecular interaction energy by the fragment molecular orbital (FMO[3]) method. We found that the optimized structure reproduced the binding site that had been frequently caused in the trajectory although the structure without the stable water molecules did not. We also found that the interaction energy between SIRT2 and each residue of S2iL5 with the stable water molecules were different from that without the stable water molecules by about 20 kcal/mol in the maximum. This indicates that it is important for the intermolecular interaction by the quantum mechanical method to determine the structure of the system including the stable water molecules.

A series of techniques presented here is considered to be a practical procedure to include statistical information in the intermolecular interactions by quantum mechanical method, relating the quantum mechanical method and the classical MD simulation.

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