Development of the Simulation Method for Evaluating the RNA Aptamer Modification against the Nuclease Digestion

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Abstract

Aptamers, consisting of usually 20-100 nucleotides (DNA or RNA) or sometimes small peptides, bind specifically to their target molecules like antibodies. Aptamer has a potential to be a novel promising bio-material for drugs, research reagents or *in vitro* diagnostics, although it was discovered almost 20 years ago. An RNA aptamer has one weak point against the RNA digestive enzymes. It is necessary to replace some nucleotides to 2'-*O*-methyl ones in the practical environment with natural RNase activities. But several replacements reduce its binding ability to the target in many cases. For the preparation of the degradation-resistant RNA aptamers, it is strongly desired to reduce time consuming and expensive experimental trial tests for all kinds of nucleic acid modifications.

In this study, the fragment molecular orbital (FMO) calculations were carried out in order to evaluate the effect of the systematic substitutions of the 2'-OH group at the sugar residue of each pyrimidine bases with 2'-O-Methyl group on the NF-kB aptamer. In general, the protein-ligand binding strength can be described by the sum of the inter-fragment interaction energies (IFIE) between protein and ligand. However, in the case of NF-kB in complex with its aptamer, the simple IFIE method could not be adopted, because many H_2O molecules make cross-bridges between protein and RNA.

In order to evaluate the binding energy including the effect of the bridging H_2O molecules, we proposed "the Supermolecule approach based on the FMO method" which could involve the hydration energy. This calculation approach also made it possible to evaluate the effect of each binding energy, including those of the bridging H_2O molecules, dehydration energy of each binding site, and the internal stabilization energies of the protein and ligand by themselves in before and after binding.

Keywords : aptamer, degradation resistance, NF-κB, fragment molecular orbital method (FMO method), Supermolecule approach, hydration energy