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Theoretical study of geometry and molecular recognition mechanism of Casein Kinase 2α (CK2α) with the FMO-MP2 method

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1. Introduction

Casein Kinase 2 (CK2) is one of the serine threonine kinases and a ubiquitous heterotetrameric protein made up of two α catalytic subunits and two β regulatory subunits. Recently, it was reported that CK2 plays critical role in the progression of immunogenic renal injury [1].

In a previous study, we optimized the complex structure of CK2α and its ligand using the FMO-HF/3-21(+)G method [2] and analyzed the protein-ligand interactions. In the present study, to provide more reliable prediction, we performed the geometry optimization using FMO-MP2 /6-31(+)G, which considers electron correlation, and calculated the binding energy and residue-ligand interaction energies at the FMO-MP2/6-31G* level.

2. Method

2-1. Geometry optimization

Initial structure of the complex of CK2α and a known inhibitor (Fig. 1) was taken from the X-ray experiment. Missing hydrogen atoms were added using Sybyl6.91 and their positions were optimized with the tripos force field. The geometry optimization with FMO was performed on a truncated model complex consisting of amino acid residues and water molecules within 8Å from the ligand, in which the dangling bonds of extracted residues were capped with hydrogen atoms. All the ligand and protein atoms located within 2.0 van der Waals radii from the ligand atoms were optimized, while the other atoms were frozen at their experimental positions. The geometry optimization was performed at the FMO-MP2/6-31(+)G level and using one residue per fragment division.

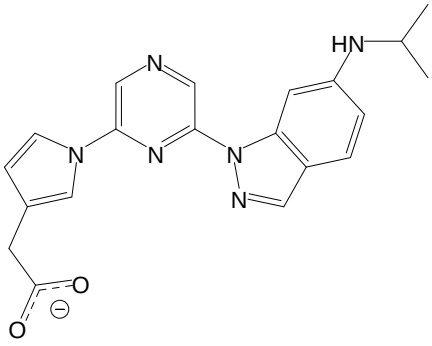


Fig. 1. The chemical structure of the ligand

2-2. Energy evaluation

All the energies were calculated with FMO-MP2/6-31G* at the optimized geometry described above. For the calculation of binding free energy, two residues per fragment division was used to obtain better accuracy, while one residue per fragment division was employed for the analysis of residue-ligand interactions.

3. Result and Discussion

3-1. Optimized geometries

The optimized structures obtained from FMO-MP2/6-31(+)G and FMO-HF/3-21(+)G calculations are compared with the experiment in Fig. 2. The RMS displacements (RMSD) of the non-hydrogen atoms of MP2 and HF structures are 0.61 and 0.75 Å, respectively. The MP2 geometry is in good agreement with the experiment, while indazol ring and isopropyl amine moieties in the HF geometry are largely deviated from the experiment. It is thought that because these groups do not have the hydrogen bond interaction which is important to fix the ligand conformation and are mainly stabilized by dispersion interactions, the geometry refined with HF has the relatively large conformational difference. HF optimizations give a reasonable complex

geometry when the ligand is tightly bound by hydrogen bonds and/or salt-bridges. The CK2α complex is not the case and the electron correlation (dispersion energy) should be considered.

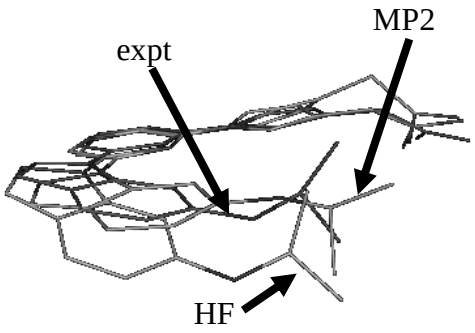
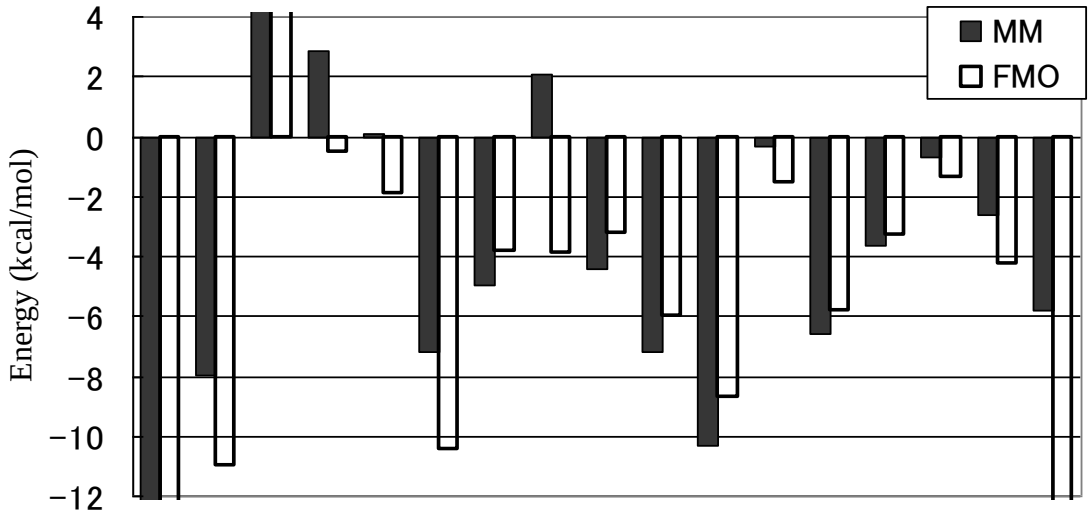


Fig. 2. Superposition of the experimental structure (expt) and the HF and MP2 optimized structures

3-2. The interaction energies between the amino acid residues of CK2 and its ligand

The residue-ligand interaction energies of FMO for selected residues are shown in Fig. 3, along with those of AMBER for comparison. One can see a number of attractive interactions; a salt-bridge (LYS68), a hydrogen bond (VAL116), and several vdW interactions (LEU45, VAL66, ASN118, MET163, ILE174). There are large differences in HIS115 and TRP176 energies between FMO and AMBER. HIS115 makes a CH-O bond with the ligand and TRP176 binds the ligand with electrostatic and polarization interactions. Both types of interactions are not well described by AMBER and quantum mechanical methods are needed to provide reliable estimation of these interactions.



4. Conclusion

The optimized geometry with FMO-MP2/6-31(+)G agreed well with the experiment, while that with HF/3-21(+)G did not. The result indicates that the electron correlation (dispersion) is indispensable to describe the complex structure. We revealed that the ligand is bound by a hydrogen bond, a salt-bridge and many vdW interactions. Among these important interactions, CH-O (HIS115) and large polarization (TRP176) interactions are not well described by AMBER.

[1] M. Yamada *et al.*, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 7736.
[2] D. G. Fedorov *et al.*, *J. Phys. Chem. A* **2007**, *111*, 6904.