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Refinement of Crystal Structures Using Partial Geometry Optimization and Electron Density Calculations Based on the Fragment Molecular Orbital Method.

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The *ab initio* fragment molecular orbital (FMO) method was applied to refine X-ray crystal structures of protein–ligand complex using ABINIT-MP/BioStation program package [1]. Partial geometry optimization surrounding a ligand and electron density calculations were performed at the MP2/6-31G* level for complex between human estrogen receptor α and 17β-estradiol (PDB ID: 3ERE) [2]. Members of hydrogen bond network were optimized: ligand, Glu353, Arg394, Phe404, His524 and a water molecule. In addition to the inter-fragment interaction energy (IFIE), the configuration analysis for fragment interaction (CAFI) was performed to analyze charge transfer interactions on the basis of optimal hydrogen bond network structures. Strong charge transfer interaction between the ligand and Glu353 was observed through a “shared proton” with long OH distance of ligand (1.07 Å) and short ligand - Glu353 hydrogen bond distance (1.42 Å). Such findings are consistent with the existence of considerable experimental electron density [3] between them. Three protonation states of His524 (HIE, HID, HIP) were also considered for the calculations. Based on the optimized structure, strength of interaction, and electron density map, we concluded His524 is most likely deprotonated HIE conformation.

[1] ABINIT-MP/BioStation download site; http://www.ciss.iis.u-tokyo.ac.jp/dl/index.php.
[2] Fukuzawa, K., Watanabe, N., Watanabe, C., Okiyama, Y., Tanaka, S., and Mochizuki, Y., in preparation.
[3] EDS electron density server (http://eds.bmc.uu.se/eds).

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