as the experimental. Potential energy map of the phase transition between form I and II is also evaluated to demonstrate the dynamical behaviors of aspirin polymorph. It is indicated that activation energy required for the polymorphic transition is small enough to be able to overcome the energy barrier at room temperature.

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Keywords: drug polymorphism, crystal structure analysis, phase transitions

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Effects of initial conformations of small ligands on computational docking accuracies

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Computational ligand docking is one of the most important techniques of Structure-Based Drug Design, which makes the most of 3D-structures of drug target proteins determined by experimental studies, such as NMR or crystallographic analyses for the drug discovery and development. In this study, the effects of initial conformations of ligands on computational docking were investigated, and appropriate settings of conditions for computational docking were determined. Five types of initial conformations were prepared, and docking calculations were carried out by using each conformation as inputs. Furthermore, several settings of docking parameters were used (default, accurate, high throughput, etc), and robust settings for various initial structures were investigated. GOLD and eHiTS were used as docking software, and structurally known protein-ligand complexes were used as test set. Root mean square deviations between computational and experimental structures (RMSD) were adopted for criteria for evaluations, and the docking pose with RMSD < 2.0 Å were defined as “reasonable poses”. When at least one of the generated poses by a docking trial was reasonable, the trial was defined as “success”, and when the top ranked pose, i.e. the pose with the lowest binding free energy, was reasonable, the trial was defined as “top pose success”. The search abilities of docking were evaluated by “success rate” and “top pose success rate”. As the results, bad initial conformations, which were much different from crystal ligand structures, cause the worst success rate and the worst top pose success rate in all initial conformations. Comparing GOLD and eHiTS, eHiTS was better than GOLD to obtain reasonable poses regardless of rankings, but GOLD was better to obtain reasonable top poses.

Keywords: computer-aided drug design, conformational analysis, protein-ligand complexes

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Trypanosoma cruzi DHOD structure-based design of 5-halogen and 5-alkyl orotate derivatives

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Trypanosoma cruzi (*T. cruzi*) is the pathogen of Chagas’ disease and affects approximately 16 to 18 million people in Latin America. *T. cruzi* produces succinate as the main end product of respiration, even though it uses the TCA cycle and the aerobic respiratory chain. Fumarate reductase (FRD), which catalyzes the last step in succinate fermentation, is the key enzyme in the energy metabolism and a promising drug target for some parasites such as Ascaris suum, Leishmania donovani and *T. cruzi*, because human hosts do not possess FRD. It has been noted that FRD in mitochondria and glycosomes of T. brucei and *T. cruzi* uses NADH as the electron donor. On the other hand, we identified a novel type of FRD in the cytoplasm of T. cruzi that uses dihydroorotate as the electron donor, and characterized this enzyme as the dihydroorotate dehydrogenase (DHOD). Since DHOD is the fourth enzyme of de novo pyrimidine biosynthetic pathway, the enzyme may play an important role not only in succinate fermentation but also in de novo pyrimidine biosynthesis. In this study, we have determined the first complete set of structures of TcDHOD in the native form and in complexes with all physiological substrates and products. In addition, we found a parasite-specific pocket near the 5th carbon of the bound orotate. In order to design specific inhibitors, 5-halogen (Cl, Br and I) and 5-alkyl (vinyl and 3,3-dimethyl-but-1-enyl) orotate derivatives, whose substituent groups were aimed for filling the pocket, were synthesized and the structures of DHOD complexed with these compounds were also determined.

Keywords: *trypanosoma cruzi*, energy metabolism, fumarate reductase, dihydroorotate dehydrogenase, drug design, parasite

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First principles study of composition fluctuation and residual strain in InGaN/GaN MQW

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The quantitative relations between mechanical properties and the composition fluctuation in InGaN films are studied theoretically. In the ternary alloy InGaN, the indium composition has been known to show spatial inhomogeneity in various growth conditions. This composition fluctuation has been considered to form the quantum disk structures in InGaN quantum wells those influence the spontaneous emission rate in light emitting devices. To investigate the mechanical properties of the structures theoretically, a new method based on first principles calculation was used in this study. The simulation models of InGaN films contain triangular pillar-shaped cells, where the composition ratio, the strain and the stress in the each cell follow an equation of state which has been determined by ab initio electronic structure calculations. The quantitative