I-O Development of Techniques for Prediction of Conformations and Applications to Proteins and Organic Compounds

Various techniques of Prediction of Conformations have been developed in this decades including proteins and organic compounds. However, a prediction of protein 3D strcutures is still unsolved and difficult problem in the area of molecular biophysics. Therefore, the elucidation of the basic mechanism of protein folding is significant to develop a prediction method of protein 3D strcuture. Currently, we are treating simple spin model of the behabior of a protein and trying to understand the basic physics of protein folding. On the other hand, development of a modeling technique of organic compounds in terms of the interactions with a protein is also important especially in the field of drug design. We have developed a new method of QSAR (quantitative structure activity relationship) analysis which can be applied to modeling of drugs. Furthermore, we have applied our modeling techniques to the actual protein, human serum transferrin, and a organic photobase compounds.

I-O-1 Kinetics of a Finite One-Dimensional Spin System as a Model for Protein Folding

KIKUCHI, Takeshi
(IMS and Kurashiki Univ. Sci. Arts)

[*Biophys. Chem.* **85**, 93 (2000)]

Simple spin models were used to analyze the kinetic nature of lowest energy state formation of the spin systems as models of protein folding kinetics in the this work. The models employed in this work were based on the spin systems as models of biopolymers previously proposed for the analysis of the equilibrium nature of transition.[1)] In particular, the effect of frustrations on the kinetics was investigated with the Monte Calro simulations. The results showed that the kinetics of the present systems are characterized by the ratio of foldables (pathways on the energy landscape that leads to the lowest energy state) and the temperature dependence of the mean first passage time of fodables. These properties of the present spin model are corresponding to kinetic behavior of actural proteins. The important thing of the kinetics ofa zero frustration system is the passage from the Levinthal phase at higher temperature to the Arrhenius phase at lower temperature.

Reference

1) T. Kikuchi, *Biophys. Chem.* **65**, 109 (1997).

I-O-2 Molecular Modeling of Human Serum Transferrin for Rationalizing the Changes in Its Physicochemical Properties Induced by Iron Binding. Implication of the Mechanism of Binding to Its Receptor

YAJIMA, Hirofumi[1]; SAKAJIRI, Tetsuya[1]; KIKUCHI, Takeshi[2]; ISHII, Tadahiro[1]
([1]Sci. Univ. Tokyo; [2]IMS and Kurashiki Univ. Sci. Arts)

[*J. Protein Chem.* **19**, 215 (2000)]

In order to rationalize the resulting physicochemical properties of human serum-transferrin (Stf) and the Stf-receptor (TfR) recognition process, we have tried to predict the 3D structures of apo- and iron-loaded Stf using a homology modeling technique to study the changes in the structural characteristics that would take place upon the uptake of iron by Stf in solution. Therein, the crystal structures of both forms for ovotransferrin were used as templates for the Stf modeling. The modeled structure of Stf brought about a satisfactory interpretation for the tyoical physico-chemical properties such that (1) Stf has a negative electrophoretic mobility and its value increases with iron uptake, and (2) the radius of gyration (Rg) of Tf decreases with iron uptake. Moreover, in view of the findings from our capillary electrophoresis experiments, it is inferred that the connecting (bridge) and its neighboring region associated with a surface exposure of negative charge plays an important role in the Stf-receptor recognition process.

I-O-3 A CoMFA Analysis with Conformational Propensity: An Attempt to Analyze the SAR of a Set of Moleculas with Different Conformational Flexibility Using a 3D-QSAR Method

GOHDA, Keigo[1]; MORI, Ichiro[2]; OHTA, Daisaku[3]; KIKUCHI, Takeshi[4]
([1]Novartis Pharma; [2]GlaxoWelcome; [3]Osaka Pref. Univ; [4]IMS and Kurashiki Univ. Sci. Arts)

[*J. Comput. Aided Mol. Des.* **14**, 265 (2000)]

CoMFA analysis, a widely used 3D-QSAR method, has limitations to handle a set of SAR data containing diverse conformarional flexibility since it does not explicitly include the conforamtional entropic effects into the analysis. We presented in thi work an attempt to incorporate the confromational entropy effects of a molecule into a 3D-QSAR analysis. Our attempt is based on the assumption that the conformational entropic loss of a ligand upon making a ligand-receptor complex is small if the ligand in an unbound state has a conformational propensity to adopt an active conformation in a complex state. The conformational propensity is defined as the population ratio of active conformations to stable conformations. The active conformation is defined from the structure of a compound with a rigid structure with high activity. We applied the present method to 20 imidazoleglycerol phosphatase inhibitors with various conformational flexibility. The results show that our method improved the predictability compared with the stadard CoMFA

method.

I-O-4 Study on Photobase Generation from α-Aminoketones: Photocrosslinking of Epoxides with Carboxlic Acids

KURA, Hideaki[1]; OKA, Hidetaka[1]; BIRBAUM, Jean-Luvc[1]; KIKUCHI, Takeshi[2]
([1]Ciba Specialty Chem.; [2]IMS and Kurashiki Univ. Sci. Arts)

[*J. Photopolym. Sci. Technol.* **13**, 145 (2000)]

It was demonstrated that α-Aminoketones work effectively as photobase generators in epoxy-based compositions in this work. After irradiation they accelerate the thermal crosslinking reaction of phenol novolac epoxy resin with polyacrylate having carboxylic acid groups despite of their high latency before irradiated. The accelaration effect depends on the structure of the photogenerated amines. Conformational population of the α-aminoketones and the related compounds was also calculated based on the molecular mechanics. The results suggest that folded conformations contribute to the latency of the amine moiety. In the conformations, the bulky benzoyl group of the aminoketone sheilds the amino nitrogen from acidic species present in the composition. By irradiation, the benzoyl part is cleaved and the active tertiary amine base with small substituents is eventually liberated. The investigation using model amines supported the explanation. The compositions used for this study can be utilized in the base-catalyzed imaging application.