05-Molecular Modelling and Design for Proteins and Drugs

Comparative modelling can be envisaged as two steps. The first is to solve the inverse folding problem: to define all those sequences that can adopt a particular fold. Operationally this is more usefully posed as defining whether a new sequence belongs to any of the known folds. It involves projecting restraints from a three-dimensional X-ray structure onto a one-dimensional sequence. For this step we have calculated amino acid substitution tables in terms of local structural, environmental parameters, which can be used to generate sequence templates for secondary structures, structural motifs, and tertiary folds. The second step is to use the sequence, together with the knowledge that the protein belongs to a family of known fold, to construct a model. This form of protein modelling and prediction involves placing constraints from a known fold on a related protein sequence. The two steps require similar knowledge of the structures of protein families, and this knowledge can be expressed as rules that relate both local and global three-dimensional structure to patterns in the sequence of amino acids in a polypeptide chain. The method is comparative but exploits a broader knowledge-base of non-homologous protein structures.

MS-05.01.04 DESIGN STRATEGY FOR PROTEIN STABILITY: STABLE LOCAL CONFORMATION IN CONSISTENCY WITH THE GLOBAL CONFORMATION. By K. Ishikawa, S. Kimura, K. Morikawa, S. Kanaya and T. Nakamura, Protein Engineering Research Institute, 6-2-3 Furuego, Suita Osaka, Japan.

Various mechanisms of the protein stability have so far been studied, and several strategies to enhance the stability are now proposed. We have recently made lots of mutant proteins of ribonuclease H1 from Escherichia coli (E.coli RNase H1; 17.6kDa), and studied the conformational stability and their crystal structures. As a result, several of the mutant proteins obtained remarkable thermal stability, due to only very local amino acid replacements. For example, Ly95-Gly is considered to stabilize the local left-handed α-helical conformation by a G-Y rescue (S. Kimura et al., J. Biol. Chem., 1992, 267, 22014-22017). His92-Pro may stabilize the short turn structure (K. Ishikawa et al., Protein Eng., 1993, 6, 85-91). Val74-Leu fills the cavity in the hydrophobic core (K. Ishikawa et al., Biochemistry, 1993, in press). All three mechanisms are localized, and the characteristic features of individual amino acids contribute the increase of the thermal stability. Analyses of the crystal structures of the wild-type and mutant proteins of E.coli RNase H1 less than 1.8Å resolution reveal that the global conformation of all those mutant proteins deviate very little from that of the wild-type protein. It means that these local structural changes can be permitted and even suitable for the original global conformation. The additivity of the mutations was confirmed (S. Kimura et al., J. Biol. Chem., 1992, 257, 21535-21542), and the structural analysis of the associated protein from Thermus thermophilus show that these local mechanisms are used in the thermostable protein (K. Ishikawa et al., J. Mol. Biol., 1993, 230, 529-542).


Over the past few years, the number of chemical agents with K channel opening properties has greatly expanded. They are separated into distinct chemical classes typically exemplified by cromakalim (a benzylate), penciclidine (a pyridylalkylic-cyclopropanone), diacidoxide (a benzenesulphonamide), nicardipin (a pyridazin-nitro compound), nitrendipin (a pyridazin-4-derivative) and RP 49356 (a pyridazine thionoformamide). For the three best studied K channel openers, the rank order of potency for vascular smooth muscle relaxation was found to be cromakalim > nicardipine > diacidoxide whereas for their activity on neural secreting cells, the order was diacidoxide > penciclidine > cromakalim. Now we are at Thermus thermophilus, and the present work tries to evaluate the level of structural analogy between these three classes of compounds by using crystallographic and NMR data. A systematic search was performed with STaaS (Thermus, Associates Inc., St Louis, Missouri, USA) starting from the X-ray conformation of penciclidine optimized by the 'Hessian force field method', using energy minimization. The analysis of the search process exhibits four interesting low energy conformations. The four selected geometries have been optimized using the geomorphological method (HOMA 5.0) and have been compared in terms of total energy calculation: the lowest energy conformation is actually the one found in crystal. A comparative study was undertaken on conformational and spectroscopical properties of penciclidine, diacidoxide and cromakalim, highlighting the modifications which could be related to...
05-Molecular Modelling and Design for Proteins and Drugs

Hydrogen bonding and metal binding to nitrogen-containing heterocycles has been studied in this way. Heterocycles are often used as ligands in drug design. In this study, the authors investigated the binding of heterocyclic compounds to metal ions, focusing on the role of hydrogen bonding and metal coordination in the stability of the complex. The results indicate that the heterocyclic compounds can form stable complexes with metal ions, and the type of hydrogen bonding and metal coordination can significantly influence the stability of the complex. The findings suggest potential applications in the design of new drugs and materials.

Supported by grant GM 44360 from the National Institutes of Health.


The directional preferences for binding of functional groups to different molecules are studied by use of the Cambridge Structural Database (CSD). Data on intermolecular interactions to a selected functional group and large numbers of small-

molecule crystal structures are analysed. These are analysed in a statistical manner by use of the CSD. The results presented here suggest some directions in which the functional groups are preferentially oriented.

Supported by grant GM 44360 from the National Institutes of Health.