05-Molecular Modelling and Design for Proteins and Drugs

An evident structural difference in the binding grooves of the two groups of antibodies is that a Tyr residue in one group, which is bound to the phosphonate-binding Tyr, is replaced by an Arg in the other group. This change can explain the differences in substrate inactivation and chemical modification. It also hints at possible dissimilarities in the water hydrolysis mechanism between the two groups of antibodies.

PS-05.01.12 MODELLING STUDY OF A NEUTRAL PHOSPHOLIPASE A\(1\) FROM THE VENOM OF AGASTRODON HAYLS PALLAS. By X.Q. Wang\(^1\), Z.J. Lin, National Laboratory of Biorneuromolecules, Institute of Biophysics, Academia Sinica, Beijing, China.

The neutral phospholipase A\(1\) (PLA\(1\)), isolated from Agastrosdon hayls pallus venom, has strong presynaptic neurotoxin activity and designated as agastrosdon A (ATX). The sequence of ATX (Kouloko\,K. et al. (1989)) has 196-203) is highly homologous to that of the toxic basic subunit of crototoxin. ATX has a tendency to associate with identical molecules to form dimer or higher aggregates from crystallization and M.W. determination (Jin,J. et al. (1991)). Chinese J. Biochem. Biophys. 9, 209-219).

Sequence alignment between ATX and non-toxic Crotalus atrox venom PLA\(1\) shows the identity of 50% at amino acids and presence of almost same residues involving subunit interaction. In order to study the possibility of dimerization from structure point of view, three dimensional models of both homologous and dimeric ATX have been graphically built using the X-ray structure of C. atrox venom PLA\(1\) and optimized by energy minimization technique with programs QUANTA and CHARMM. The result shows that the structure seems essentially similar to that of C. atrox venom PLA\(1\) (the r.m.s. deviation of corresponding C\(\alpha\) atoms is 1.65\(\AA\) except the fragment 81-89 in a loop region. The dimer-stabilization of ATX dimeric model are very similar to those of C. atrox venom PLA\(1\) except that the interaction between His34 and Gln is replaced by that between His34 and Asn. The energy calculation shows that the dimer's total energy and hydrogen bond energy are 241 and 41 kcal/mol respectively lower than twice of monomer's energies. These suggest that the C. atrox-like dimer is a more stable form than monomer. We plan to complete the modeling using molecular dynamics simulation method in next step. The definitive determination of the structure will be done by X-ray crystallography, which is currently underway.

PS-05.01.13 DISTANCE GEOMETRY AND MOLECULAR DYNAMICS CONFORMATIONAL SEARCH OF A CYCLIC PEPTIDE FOR PROTEIN DE NOVO DESIGN. Zhaowen Luo\(^2\), Luhua Lai, Xiaojie Xu, Department of Chemistry, Peking University, Beijing 100871, CHINA

A cyclic peptide, designed to act as topological template of the four-helix bundle, was investigated by distance geometry and molecular dynamics conformational search method. A sequence of the cyclic peptide is (Pro-Lys-Pro-Gly-Lys-Gly). Firstly, 100 conformations were generated by distance geometry with constraints for ring closure. Seven conformation clusters were classified according to their mutual rms. A representative conformation from the cluster with highest density was selected to