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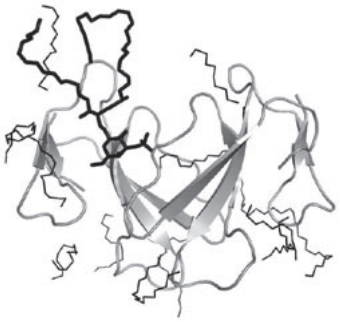
Glycosphingolipid-facilitated membrane insertion and pore formation of cobra cardiotoxin

Jyung-Hurng Liu[1,2], Chia-Hui Wang[3], Shao-Chen Lee[3], Chwan-Deng Hsiao[2], Wen-guey Wu[3]
[1]National Chung Hsing University, Biotechnology Center, 250, Kuo Kuang Rd., Taichung, Taiwan, 40227, Taiwan, [2]Academia Sinica, Taipei, Taiwan 115, Taiwan, [3]National Tsinghua University, Hsinchu, Taiwan 30013, Taiwan, E-mail：jhliu@nchu.edu.tw

Cobra cardiotoxins, a family of basic polypeptides having lipid- and heparin-binding capacities, induce severe tissue necrosis and systolic heart arrest in snakebite victims. Recent studies showed that CTX A3, the major cardiotoxin from Taiwan cobra venom, binds sulfatide in the outer leaflet of the plasma membrane, and consequently sulfatide mediates CTX A3-induced membrane leakage and CTX A3 internalization into mitochondria. Sulfatide is a glycosphingolipid with 3'-sulfated galactose headgroup. Here we describe the crystal structure of a CTX A3/sulfatide complex in a membrane-like environment at 2.3-Å resolution. CTX A3 recognizes both the headgroup and the ceramide interfacial region of sulfatide and induces a lipid conformational change that may play a key role in CTX A3 oligomerization and cellular internalization.



Keywords: pore-forming toxins, protein-lipid interactions, protein-lipid crystal structure

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Crystals, cocrystals & supramolecular synthesis

V R Pedireddi
National Chemical Laboratory, Solid State & Supramolecular Structural Chemistry Lab, Division of Organic Chemistry, Dr. Homi Bhabha Road, Pune, Maharashtra, 411008, India, E-mail：vr.pedireddi@ncl.res.in

Crystals of solid entities (for example, diamonds, pearls and so on) with alluring features are quite attractive objects for the entire humankind, perhaps, due to their extraordinary physical properties like morphology, glittering, stability, etc. For structural chemists, however, not just the external geometry but the internal arrangement of the constituents (molecules in organic crystals) is of great concern. Thus, the efforts toward understanding of nature of intermolecular interactions between the molecules in the crystals, indeed, lead to the creation of new solids consisting of different types of compounds within a crystal lattice, often referred as cocrystals, and the process is broadly termed as supramolecular synthesis. Although efficacy of several functional groups to yield exotic supramolecular assemblies have been demonstrated, the targeted synthesis of a desired ensemble is still beyond realization, perhaps due to the overwhelming importance given only to the mere recognition features. In this direction, we have made systematic exploration of supramolecular synthesis of cocrystals of different types of carboxylic acids and aza-donor compounds and have observed that in addition to the recognition patterns between the functional groups, other features like pKa, non-ambient conditions, etc., would also play a crucial role in the ultimate geometry of the resultant assemblies and these exotic features would be discussed in this presentation.

Keywords: cocrystals, supramolecular synthesis and molecular recognition, pKa and non-ambient conditions

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Anchoring spots mapping on protein surfaces: Application in docking and peptide inhibitor design

Miriam Eisenstein[1], Avraham Ben-Shimon[2]
[1]Weizmann Institute of Science, Chemical Research Support, Department of Chemical Research Support, Rehovot, Israel, 76100, Israel, [2]Weizmann Institute of Science, Department of Structural Biology, Rehovot, 76100, Israel, E-mail：miriam.eisenstein@weizmann.ac.il

The currently accepted model of molecular recognition processes includes at least two steps: formation of an encounter complex dominated by the energetic contribution of hot-spots, and an induced-fit step in which additional structural rearrangements occur. Hot spot residues tend to form anchoring spots which consist of a protruding anchor residue that packs tightly in a pocket on the surface of the binding partner. In addition, hot spot residues are often evolutionarily conserved and located at the core of the binding interface. The prediction of anchoring spots can contribute significantly in protein-protein and protein-peptide docking, protein engineering, peptide inhibitor design, and advance our understanding of molecular recognition processes. We developed a procedure for predicting anchoring spots that employs an empirical scoring function designed for the specific task of mapping anchoring spots in the context of protein-protein interactions. Through adequate account of the solvation and dielectric shielding effects, the anchor residue is treated as a fragment attached to a hypothetical protein. We tested the procedure on 20 proteins whose structures in complex and in the unbound state are resolved and experimental alanine mutation energies of interface residues are known. The entire surfaces of the unbound proteins were explored showing that (1) correct anchoring pockets are identified and accurate anchoring spots are predicted despite the structural rearrangements that occur upon complex formation; (2) the ranks of the correct anchoring spots are high, <40 for 18 of the 20 test cases, and the calculated energies are in line with the alanine mutation data; (3) anchoring spots involving amino acids R, E, D, Y, W and H are predicted more accurately than others.

Keywords: hot spots, protein docking, protein interactions

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Crystal structure and theoretical calculations of *N*-(2,2-diphenylacetyl)-*N*'-(naphthalen-1yl)thiourea

Hakan Arslan[1,2], Demet S Mansuroglu[3], Don VanDerveer[4], Gun Binzet[1], Nevzat Kulcu[1]
[1]Mersin University, Chemistry, Faculty of Arts and Science, Department of Chemistry, Ciftlikkoy Campus, Mersin, 33343, Turkey, [2]Fayetteville State University, Department of Natural Sciences, Fayetteville, NC 28301, USA, [3]Mersin University, Faculty of Pharmacy, Department of Chemistry, 33169-Mersin, Turkey, [4]Clemson University, Department of Chemistry, Clemson, SC 29634, USA, E-mail：arslanh@mersin.edu.tr

Thiourea derivatives have been the subject of special attention in recent years because it has been shown that they have antitumor