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Glycosphingolipid-facilitated membrane insertion and pore formation of cobra cardiotoxin

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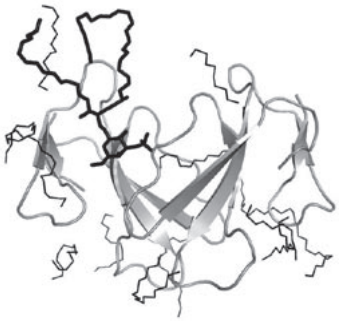
Cobra cardiotoxins, a family of basic polypeptides having lipid- and heparin-binding capacities, induce severe tissue necrosis and systolic heart arrest in snakebite victims. Recent studies showed that CTX A3, the major cardiotoxin from Taiwan cobra venom, binds sulfatide in the outer leaflet of the 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

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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

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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

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

bioactivities, antifungal bioactivities and inhibitor activities against viruses. In the past few years, we have pursued investigations on the new thiourea derivatives. As a continuation of these studies, *N*-(2,2-diphenylacetyl)-*N'*-(naphthalen-1yl)-thiourea (PANT) has been synthesized and characterized by elemental analysis, IR spectroscopy and ^{1}H-NMR spectroscopy. The crystal and molecular structure of the title compound has been determined from single crystal X-ray diffraction data. It crystallizes in the triclinic space group *P*-1, *Z* = 2 with *a* = 10.284(2) Å, *b* = 10.790(2) Å, *c* = 11.305(2) Å, α= 64.92(3) °, β= 89.88(3) °, γ= 62.99(3) °, *V* = 983.7(3) Å^3 and *Dcalc* = 1.339 Mg/m^3. The molecular structure, vibrational frequencies and infrared intensities of PANT were calculated by the Hartree-Fock and Density Functional Theory methods (BLYP and B3LYP) using 6-31G(d) basis set. The calculated geometric parameters were compared to the corresponding X-ray structure of the title compound. We obtained 22 stable conformers for the title compound; however the Conformer 1 is approximately 9.53 kcal/mol more stable than the Conformer 22. The comparison of the theoretical and experimental geometry of the title compound shows that the X-ray parameters fairly well reproduce the geometry of the Conformer 17. The harmonic vibrations computed of this compound by the B3LYP/6-31G(d) method are in a good agreement with the observed IR spectral data. Theoretical vibrational spectra of the title compound were interpreted by means of PEDs using VEDA 4 program. A general better performance of the investigated methods was calculated by PAVF 1.0 program.

Keywords: crystal structure, *ab-initio* calculations, thiourea derivatives

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Molecular complex formation of medicinal cationic surfactants with aromatic compounds

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Some aromatic drugs (4-chlro-m-cresol of germicide, flopropione of antispasmodic agent, etc) make molecular complexes with quaternary ammonium halides such as hexadecyltrimethylammonium bromide (abbreviated as CTAB). The structures of the complex crystals have been analyzed by X-rays.[1] They were shown to be very similar to each other. Moreover, we confirmed that these surfactant complexes had new characteristics. If an aromatic drug is a water insoluble drug, the dissolution rate is increase. If it easily takes oxygen damage, it is kept out to oxygenate. The complexes can control of the vaporization of drugs by heat treatment, too.[2, 3] We recently studied molecular complex formation between surfactant of different type in cationic surfactants, medicinal surfactants such as 1-hexadecylpyridinium bromide (abbreviated as CPB), benzyl(hexadecyl) dimethylammonium chloride (abbreviated as BCDAC), and aromatic compounds containing drugs (hydroquinone of treatment of skin pigmentation, etc). After many trials, we obtained complexes above fifteen, three of which were suitable for X-ray analysis. The three complexes, CPB/guaiacol, CPB/9-anthracenecarboxylic acid, and BCDAC/hydroquinone were obtained from alcohol or aqueous solutions. Their crystal structures were similar to that observed in the quaternary ammonium surfactant complexes. Therefore, these complexes will show the similar characteristics to those of the quaternary ammonium complexes.

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Keywords: molecular complex, surfactant, stabilization of drug

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Chiral recognition in cholamide crystals: Four-location model for hydrogen and stereogenic carbon

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A four-location model for enantioselective inclusion of secondary aliphatic and aromatic alcohols with steroidal acids and their derivatives is presented. In principle, two kinds of disordered structures of guest components may be observed in a concave cavity at least. The one is that a stereogenic carbon of the guest is disordered with a substituent, such as a hydrogen. The other is that the stereogenic carbon is almost fixed while two neighboring substituents, such as a hydrogen and a methyl group, are disordered. For example, cholamide accommodates 2-methyl-3-hexanol (**1**) and 2,2-dimethyl-3-hexanol (**2**) into its channels. (*S*)-isomer of **1** is separated in less than 20% ee, while that of **2** in more than 98% ee. Crystallographic studies brought us a profound insight for such one methyl group effect in chiral recognition. It was confirmed that the inclusion crystal of **1** exhibits a disordered structure of hydrogen around a stereogenic carbon, while that of **2** a definite structure. Such a difference requires a chirality recognition model which explains selective locations of the forth substituent, hydrogen, together with chiral carbon. Employment of a four-location model resulted in a successful interpretation for the chirality recognition. Moreover, cholamide includes various 1-phenylethanol derivatives. Among them, (*S*)-isomers of ortho-substituted 1-phenylethanols showed higher enantioselectivity than those of para-substituted ones. X-ray crystallographic analysis clarified that the former has a definite structure in the channels, while the latter has a disordered structure between hydrogen and methyl group. The four-location model enabled us to explain these experimental results for enantioresolution.

Keywords: chiral recognition, inclusion compounds, alcohols

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Protein intrinsic disorder predicted with conditional random fields

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A large fraction of eukaryotic proteins harbour significant intervals of disordered residues which allow the protein to adopt multiple, alternate conformations (Dunker, et al., 2002). Frequently, such proteins have important biological functions in the cell, such as in