KN29.29
Acta Cryst. (2005). A**61**, C7
Molecular Recognition Principles in Protein-Ligand Interactions as a Prerequisite for the Design of Specific and Selective Leads
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In order to bind to a protein, a ligand has to exhibit correct shape and interaction properties complementary to the residues exposed towards the binding pocket of a target protein. Since protein-ligand binding is a process of mutual molecular recognition, rational drug design is greatly concerned with understanding the principles of molecular recognition. The statistical analysis of geometries of protein-ligand complexes provides a powerful tool to retrieve and correlate information about recognition patterns with respect to protein binding. To efficiently access such data, we have developed Relibase [1,2] as a database system particularly tailored to handle protein-ligand related problems, e.g. the induced adaptation of proteins upon ligand binding, the role of water in the binding process, the mapping of hot-spots of ligand binding or analyzing the versatile molecular recognition properties of functional groups.

The function of proteins is almost invariably linked with the specific recognition of substrates and ligands in well-defined binding pockets. In consequence, proteins of related function should share comparable recognition properties exposed to these pockets. Cavbase has been developed as new module for Relibase that stores protein cavities in terms of simple surface-exposed physicochemical properties [3]. These descriptors allow for fast retrieval of proteins with functional relationships independent of a particular sequence or fold homology. The approach also allows to detect unexpected cross-reactivity of ligands among unrelated proteins. Via the alignment of binding pockets across protein family members, the consensus pattern representative for individual protein families can be extracted and mutually compared. By decomposing binding pockets into elementary sub-pocket motifs the analysis of preferred ligand occupants can be achieved.

Mapping preferred interaction sites in binding pockets in terms of knowledge-based approaches such as SuperStar [4] or DrugScore [5,6] “hot spots” of ligand binding can be elucidated. Such information can be translated in a protein-based pharmacophore hypothesis and serves as guideline for ligand docking and virtual screening [7].

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Keywords: protein-ligand interactions, molecular recognition, drug discovery

KN30.29
Acta Cryst. (2005). A**61**, C7
Structural Studies of Macromolecular Complexes: Cytochrome b_6f
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Seeing protein complexes in states relevant to their biological function is one of the challenges of macromolecular crystallography. The integral-membrane cytochrome b_6f complex carries out electron and proton transfer reactions in the photosynthetic membrane of oxygen-evolving photosynthetic organisms, and is the electronic connection between photosystems II and I. The 220-kDa dimeric b_6f complex consists of a total of 16 subunits and 14 chromophores. The 3.0-Å crystal structure [1] was solved by isomorphous replacement and anomalous scattering, with reference to previously determined structures of the extrinsic domains of two subunits. Dimer formation creates two central cavities with access to electron transfer sites for exchange of the lipid-soluble substrate. The most significant finding was an unexpected and novel heme group, bound to the protein by a single thioether bond. Motion of one extrinsic domain between electron-transfer sites within the b_6f complex is suggested by the overall organization of subunits.

Preparation of pure, monodisperse complex and its crystallization required a significant period of testing poorly diffracting crystals to optimize purification and crystallization protocols. In general, crystals of complexes are frequently quite small or imperfect. A synchrotron X-ray beam that can be tailored to the size of a small crystal or to a region of a crystal is optimal for such samples. The GM/CA Collaborative Access Team has developed dual undulator beamlines at the Advanced Photon Source to deliver small X-ray beams and the goniometry to orient and visualize small samples [2].

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Keywords: membrane protein complexes, synchrotron radiation applied to biomedical sciences, photosynthetic proteins

KN31.29
Acta Cryst. (2005). A**61**, C7
Metal-Organic Frameworks: Assembly and Crystal Dynamics of Functional Materials
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Many efforts have been made for the design and synthesis of metal-organic frameworks (MOFs) having specific topologies and functions. MOFs containing pores and channels of controllable sizes and shapes can be applied to adsorption and separation processes, ion exchange, catalysis, and sensor technology. An exciting, yet little explored area is the transformation of the structures in the solid state by the input of external stimuli. Retaining single crystallinity even after chemical reaction is relevant to the development of certain devices. We have assembled porous metal-organic frameworks by various synthetic strategies such as 1D-, 2D-, and 3D- network construction from the pre-designed metal and organic molecular building blocks. Some exhibit simultaneously permanent porosity, high H_2 gas sorption capacity, thermal stability, and selective guest binding property. In particular, certain solids respond to the external stimuli, and change their colors and luminescence. In addition, some solids have flexible frameworks and undergo structural transformations, with retention of the single crystallinity, via shrinkage and swelling, sliding, or rotational motion of the molecular components.[1-4]

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Keywords: metal-organic frameworks, crystal dynamics, structure transformation

KN32.29
Acta Cryst. (2005). A**61**, C7-C8
Nano Structures Studied by Convergent Beam Electron Diffraction
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Lattice defect and interface analyses by using the large angle technique [1] of convergent-beam electron diffraction are reviewed. The large angle convergent-beam electron diffraction (LACBED) enables us to obtain real- and reciprocal-space information of lattice defects and interfaces.

The technique can determine the shift vector of a stacking fault and the Burgers vector of a dislocation much more reliably than the traditional electron-microscope-image method can. Screw and edge dislocations can be distinguished easily by the technique [2]. The angular change at a twin boundary can be determined with an accuracy of less than 0.1 degree, while a better accuracy than 1 degree is not possible in ordinary or spot electron diffraction.