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ANALYSIS OF CRYSTAL PACKING EFFECTS USING RELIBASE+

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It is widely accepted that X-ray crystal structures of proteins resemble the 'real' structure and fold present in a biological system. However, regions located at the protein surface are likely to undergo conformational changes due to interactions with neighboring molecules in the crystal environment. Such changes can for example comprise side chain flips, loop rearrangements, or even domain movements. Also, the binding of small ligands can be seriously affected by crystal packing effects, thus leading to artifact binding modes unlikely to represent the physiological situation. Moreover, small ligands can also mediate protein-protein contacts, thereby binding to exposed surface areas, which are unlikely to represent typical functional ligand binding sites. Such problems can only be avoided by careful examination of crystal packing effects when applying structural knowledge to rational drug design projects. The analysis of crystal packing can help to interpret unusual ligand binding modes, gross failures in docking calculations, and may also provide exclusion criteria delimiting the usability of a particular structure.
Relibase+, the successor to Manfred Hendlich's well-known ReLiBase, is a database search, retrieval and analysis system for 3D protein-ligand complex structures. Relibase+ covers all data available in the PDB. Recent developments in Relibase+ comprise the precalculation of the crystal-packing environment of all stored protein-ligand binding sites. This feature enables comprehensive analysis of crystal packing effects.

Keywords: CRYSTAL PACKING PROTEINS DATABASES

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A SEARCH FOR NEW TUMOR NECROSIS FACTOR-α SECRETION ENHANCEMENT AGENTS

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TNF-α is a cytokine produced mainly by activated monocyte/macrophages, and an attractive molecular target for the development of biological response modifiers (BRMs). Recently, a simple N-(1-adamantyl)phthalimide has been reported to enhance tumor necrosis factor-α (TNF-alpha) production in 12-O-tetradecanoylphorbol-13-acetate-stimulated human leukemia HL-60 cell line. We have previously reported the adamantylation of heterocyclic compounds by adamantyl cation attack [1]. In this way C-, N-, and N-amino-adamantylated compounds were obtained. The new and previously obtained adamantylated compounds were tested for their TNF-α production-enhancing properties. Tests were performed using murine melanoma cells that have been transduced with the gene for human TNF-α. This clone secretes TNF-alpha at constant rate, and because of this is found to be useful for testing the effect of various chemicals on TNF-α production. The most active of the tested compounds were 2-adamantylamino-6-methylpyridine and 2-adamantyloamino-4-methylpyrimidine [2]. The pyridine derivative show high TNF- α-induction activity and relatively low cytotoxicity. Till now the mechanism of TNF-α secretion is not known. Nevertheless, the structural and molecular modeling studies for 4 active compounds suggest that the differences in their biological activity may be caused by divergent cell membranes permeability. Conformational flexibility and lipophilic/electrophilic character of potential conformers may differentiate biological response of the discussed compounds.
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FROM POLYPEPTIDES TO PROTEIN PROPERTIES USING A CHARGE DENSITY APPROACH

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Third generation synchrotron and progress in protein crystallization [1] allows ultrahigh resolution protein crystallography (d < 0.8 Å) for which refinement enables Hydrogen locations. For some of the data sets tested [2,3], residual maps show without any doubt that the independent atom model is not valid to take into account all X ray data information. Therefore using transferability of electron density [4] we show that one can go a step further, by using a multipolar refinement with a charge density refinement program, MOPRO, specially designed for macromolecules and big systems like supra molecules [5]. The refinement strategy will be described and applied to the protein Aldose Reductase protein [1] (d_{min} = 0.64 Å). The resulting electrostatic potential calculated in the active site shows for the first time the electrostatic complementarity between the protein and ligand and therefore allows calculating the interactions. This leads to an electrostatic, not geometric, interpretation of the 'lock and key' mechanism. This result will be compared to order N DFT calculations [6] and a new strategy for drug design at the atomic level will be defined.
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HIRSHFELD SURFACES IN MOLECULAR AND IONIC CRYSTALS: APPLICATIONS TO CRYSTAL ENGINEERING AND COMPARISONS WITH BADER'S ATOMIC AND MOLECULAR VOLUMES

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Hirshfeld surfaces represent a new way of exploring interactions in molecular crystals using a novel partitioning of crystal space[1]. The surfaces encode information about all intermolecular interactions simultaneously, but sophisticated interactive graphics are required to extract the information most efficiently. To complement these methods we have devised a 2D mapping, which summarizes the nature and type of intermolecular interaction experienced by a molecule in the bulk, and presents it in a convenient graphical format. Applications relevant to crystal engineering will be presented. More recently, we have been applying Hirshfeld surfaces to ionic crystals, focusing on the shapes, radii and volumes that result for cations and anions, especially their relationship to existing ideas of cation vs anion size in simple ionic solids. Surprisingly, partitionings based on atomic electron densities yield Hirshfeld surfaces which are largely cubic or spherical, while partitionings using ionic electron densities yield a remarkably diverse range of shapes, especially for anions. We have compared the resulting information on cation/anion shape, size and net charge with the results obtained from ab initio crystal Hartree-Fock calculations on these materials via topological analysis based on Bader's quantum theory of atom in molecules, and the results suggest a possible link between Hirshfeld surfaces and Bader's virial surfaces.
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