L.A.04

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Mutual Additive-Induced Polymorphism in Aspirin / Aspirin Anhydride Derivatives

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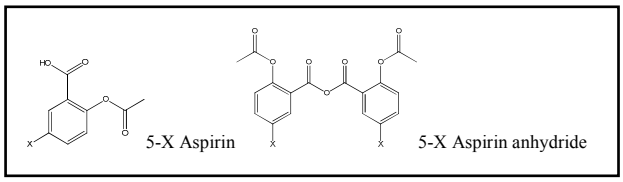
Polymorphism is the ability of compounds to crystallise in different arrangements, and it is a common phenomenon in various classes of chemical materials. To be able to control polymorphism is extremely important because different crystal forms can have different physicochemical properties. Aspirin is a unique drug: it is effective against pain, it has anti-pyretic and anti-inflammatory properties, and it is widely used during heart attacks or strokes. The structural chemistry of aspirin has been found to be unusual because it has a tendency to crystallise as an "intergrown" form, which contains domains of two polymorphs within a single crystal [1-3]. We have recently reported that the second polymorph of aspirin can be obtained in the presence of a specific additive, aspirin anhydride [4]. Aspirin anhydride is a common impurity, which can be produced during "standard" aspirin synthesis or during heating of aspirin in various aprotic organic solvents. Our further research has been focussed on aspirin derivatives, since we were interested to find other systems similar to aspirin. The presented research examines several aspirin derivatives (5-X-aspirin, where X = Cl, Br, I, Me) and the corresponding anhydrides. We have found that the aspirin derivatives also have a tendency to be polymorphic and that the polymorphism is dependent on the presence of aspirin anhydride impurities. In addition, we have found that the aspirin anhydrides display polymorphism, and that the polymorphism is dependent on the presence of aspirin during crystallisation. The broader significance of this work lies in the illustration of polymorph control induced by specific impurities that can be generated as by-products during synthesis or even during a common crystallisation procedure such as heating in organic solvents.



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Keywords: pharmaceuticals, polymorphism, additive

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MAX IV MX: Macromolecular Crystallography at the New MAX IV 3-GeV Storage Ring

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MAX IV is a new synchrotron radiation facility under construction in Lund, Sweden [1]. The new facility will include a linac working as a full energy injector, a 3 GeV storage ring with 528 m circumference, a 1.5 GeV storage ring with 96 m circumference and a short pulse facility using the linac for time-resolved experiments. Together these will provide optimal radiation sources for a wide spectrum and for a wide range of experimental techniques. The 3 GeV storage ring will have 20-fold symmetry and a horizontal emittance of well below 1 nmrad.

The funding of the beamlines are not yet secured but it is expected that the initial set of beamlines on the 3 GeV ring will include at least one macromolecular crystallography (MX) beamline.

The first MX beamline will be a multi-purpose high-throughput beamline that will be an ideal beamline for most MX experiments including e.g. challenging experiments with small crystals of large molecular complexes and membrane proteins. The beamline will be energy tunable with x-ray beam focus down to 10 μm, include a state-of-the-art experimental set-up with on-line UV/vis spectroscopy. The very small emittance of the MAX IV 3 GeV ring will give a very parallel beam suitable for the largest unit cells and for difficult crystals.

The MX microfocus beamline is suggested to focus down to 1 μm for the most challenging experiments with small and inhomogeneous crystals. The small focus size and small samples will put high demands on the experiment set-up and the beamline stability.

The MAX IV facility is also suggested to include other beamlines of interest for the life sciences e.g. x-ray absorption spectroscopy (XAS), small angle x-ray scattering (SAXS), infrared spectroscopy and imaging/tomography, as well as a nanofocusing beamline covering microscopy, spectroscopy, scattering, diffraction and imaging. Furthermore the short pulse facility will offer opportunities for time-resolved experiments. The number and types of beamlines in the first phase will depend on the available funding.

The construction of the MAX IV facility started on May 18th 2011 with beamline user operation starting in 2015/2016.

[1] http://www.maxlab.lu.se

Keywords: Synchrotron, Biocrystallography, Macromolecular

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Charge density study of phosphoglycolate monopotassium salt

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Phosphoglycolates are important compounds appearing in some metabolic pathways, such as photorespiration in plants, and DNA repair in bacteria [1]. Because of their importance we have performed charge density analysis of the title compound, and in this communication we report the preliminary analysis of its experimentally determined charge density.

The crystal structure of monopotassium phosphoglycolate was reported earlier by Lis [2] as part of a long study focused on elucidating the crystal chemistry and structure of organic phosphates. The aim of this paper is to push this work further by means of high resolution charge density study coupled with density functional theory (DFT) calculations.

First results indicate that both approaches produce comparable results. Testing different multipole models generally shows, that phosphorus has a higher positive Bader charge than in hydrogen methylphosphates of calcium and lithium (unpublished results) and in aminomethylphosphonic acid [3], that is approximately +3.9 e with regard to ~+ 3.5 e in those compounds.

This is confirmed by the DFT Bader charge of ~+3.7 e in the present compound; in the phosphonates the charge was ~+3.4 e. This difference may be attributed to the presence of an additional oxygen atom in the phosphate group. In the experimental approach the carboxylic O and O(H) oxygen atoms show almost equal charges of 0.92 and 0.97 e respectively, which is not supported by the DFT results - higher on the average by ~0.3 e for these atoms. The phosphate O(H) atom displays a lower or slightly lower charge than the other phosphate oxygen atoms. This is consistent with previous findings [3].
The respective values are -1.43 e for O(H) and -1.46 – 1.67 e for the remaining oxygen atoms in the experimental approach.

The reported topological properties are comparable to those of hydrogen methylphosphonates of calcium and lithium with P-O ρ_c values being near 1.55 e·Å^{-3} and P-O(H) near 1.31 e·Å^{-3}. Interestingly the value of ρ_c of P-O(C) bonds is also near to 1.30 e·Å^{-3} as in the P-O(H) bonds.

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Keywords: charge density, phosphoglycolate, phosphorus

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A novel high-throughput approach for purification and reconstitution of large multi-protein complexes
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Proteins are both building blocks and molecular motors for virtually all cellular functions. To perform and regulate complex cellular processes, proteins form interacting heterogeneous assemblies (henceforth referred to as multi-protein complexes or MPCs) whose components exchange continuously during the process. As a result of the transient nature of their interactions, monomeric and multimeric components of MPCs typically have low binding affinities, making their recovery almost impossible during purification. Therefore assembly of MPCs often requires expression and purification of individual (monomeric and multimeric) components in a form (mono-dispersed and properly folded) conducive to reconstitution; furthermore, individual constituents of such large MPCs are frequently insoluble in the absence of the associated components. Thus, identifying conditions leading to MPC reconstitution represents a highly desirable goal in structural biology. To this end we have developed novel solubilization and purification protocols that have allowed us to: 1) solubilize individual monomeric and multimeric components of MPCs; 2) reconstitute (using previously solubilized components), fully active (and stoichiometric) MPCs. Such techniques work equally well on cytosolic and membrane proteins. Despite the intrinsic difficulties that MPCs represent to the field of structural biology, it is crucial to tackle these structural giants since we will only begin to comprehend their biology when the structures of the whole machines have been determined.

Keywords: Biochemistry, Protein, Complex

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Crystallization of a serpin with a insulin-sensitizing function
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Serpins (serine protease inhibitors) are proteins with a molecular mass of about 50 kDa that inhibit chymotrypsin-like serine proteases via the formation of a covalent complex with the target protease. We purified and crystallized SERPINA12, that acts as an adipokine with insulin-sensitizing effects. It could be found in visceral adipose tissue of a rat model of type 2 diabetes. Sequence identity shared with α-1-antitrypsin (41%) suggests a putative serpin function but its molecular target remains to be identified.

To confirm and further analyze the predicted serpin function we intend to determine the three-dimensional structure of the serpin. Thus, His-tagged protein was produced in *Escherichia coli* and purified by Ni-affinity chromatography and size exclusion chromatography. High-troughput screening crystallization trials were prepared in a nanoliter scale with a MicroSys pipetting system using the sitting-drop technique. First diffracting crystals were observed with polyethylene glycol of a molecular weight of 3350 as the precipitant. Crystallization conditions were improved in hanging-drop setups to yield two different crystal forms (space groups $P2_1$ or C2) with similar habitus. C2 crystals show the highest diffraction limit (2.08 Å) and gave rise to a complete dataset collected at BESSY beamline 14.1 at Helmholtz-Zentrum Berlin (Germany).

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Keywords: protein, crystallization

L.A.09

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Crystal structure of bacteriophage T4 fibre protein gp37
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Some viruses and bacteriophages attach to their host cell via specialised fibre proteins, like adenovirus, reovirus and tailed bacteriophages. The bacteriophage T4 short and long fibre proteins, the T5 L-shaped fibres and T7 fibre all have the same basic architecture: they are trimeric and contain an N-terminal phage attachment domain, a long, thin, but stable shaft domain and a more globular C-terminal cell attachment domain. Our goal is to determine the structures of these proteins and thus to make an inventory of stable trimeric folds present in nature.