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Keywords: hydrogen bond, high pressure, DFT calculations

MS.73.3

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Determining Hydrogen Positions in Hydrogen Bonded Structures: A CSD Survey

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Although X-ray diffraction is not suitable for accurately determining the positions of hydrogen atoms in a crystal structure, an increasing number of publications are appearing in which the hydrogen positions are identified by this technique, and used to describe structure topology without first applying appropriate corrections. The consequences of this approach are of particular relevance when hydrogen-bond (H-bond) interactions are considered, due to their importance in chemical and biological systems. In some cases the use of neutron-normalized distances reduces the systematic errors that are measured for the hydrogen positions by X-ray diffraction, but those values do not take into account effects such as bond elongation and polarization that may be relevant for the stronger interactions. [2]

In this work crystal structures solved by neutron and X-ray diffraction have been retrieved from the Cambridge Structural Database (CSD) and H-bond geometrical descriptors (distances and angles) are pairwisely compared, confirming the expected results. Inclusion of neutron-normalized data into the analysis reveals that normalization fails to adequately correct for bond elongation and polarization when applied to H-bond interactions. Statistical analysis has been carried out and an empirical method is suggested to calculate the position of hydrogen atoms involved in hydrogen bonds. The method is based on the donor – acceptor distance and could easily be integrated into common structure refinement software packages.

The results presented offer an opportunity for discussing how to approach one of the main limitations of X-ray diffraction as applied to a major area of structural chemistry.

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Keywords: hydrogen_normalization, hydrogen_refinment, hydrogen_bond

MS.73.4

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Pharmaceutical cocrystals model drug-receptor interactions

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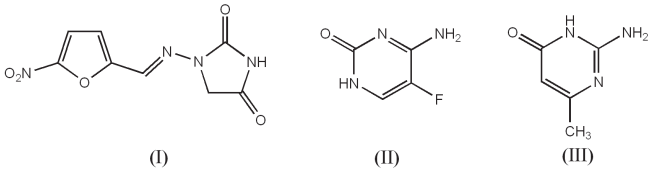
In order to study drug-receptor interactions, we cocrystallized active pharmaceutical ingredients with potential receptors. Since drug binding requires shape and property complementarity, both components have to adapt to each other for a successful recognition process. We focus on supramolecular complexes, which are held together by N–H···N and N–H···O hydrogen bonds, and investigate whether the molecular conformation or the tautomeric form changes during the complex formation.

Recently we reported a potential drug-receptor complex of nitrofurantoin (I) and 2,6-diacetaminopyridine [1]. Nitrofurantoin is not only used for the treatment of urinary tract infections, but also illegally applied as an animal food additive. The cocrystal structure confirmed a previous NMR study [2] and showed that derivatives of 2,6-diaminopyridine might serve as artificial receptors for nitrofurantoin by forming three hydrogen bonds. In the cocrystal, nitrofurantoin adopts a conformation, which is not favoured in the (pseudo)polymorphs of nitrofurantoin. However, calculations with *GAUSSIAN* [3] and our force-field program *MOMO* [4] showed that it is indeed the lower-energy conformer and explained the unusual preference of the higher-energy conformer in most of the nitrofurantoin structures.

We also obtained cocrystals of the systemic antifungal drug flucytosine (II), which inhibits RNA and DNA synthesis and is applied as a prodrug against liver tumors [5]. In the cocrystals, flucytosine is connected to its receptor by three hydrogen bonds similar to the Watson-Crick C–G base pair. Some of the receptor molecules selected for cocrystallization experiments are flexible and may undergo a conformational change in order to enable the desired hydrogen-bond interactions. In one case, the receptor adopts a conformation, whose calculated steric energy is more than 10 kJ/mol above the global minimum.

Furthermore, we cocrystallized the pyrimidin-4-one derivative 6-methylisocytosine (III) in order to study its tautomers. In the solid state, (III) shows no tautomeric predominance but in its cocrystal structures one tautomer can selectively be crystallized in the presence of a receptor which is complementary to it. Again the drug-receptor interaction resembles the hydrogen-bonding pattern within the Watson-Crick C–G base pair.



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Keywords: drug-receptor interaction, pharmaceutical cocrystals, conformational change

MS.73.5

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Hydrogen bonding in amino acid racemates and a game of side-chain domino

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Racemates of amino acids without hydrogen-bonding functional groups in their side chains (hydrophobic amino acids) and complexes between L- and D-enantiomers of two such amino acids (quaziracemates) are known to choose between just two different

crystal packing arrangements, each with a unique type of hydrogen bonding pattern within a two-dimensional hydrophilic layer [1]. When side chains are linear, as in aminobutyric acid (Abu), norvaline (Nva), norleucine (Nle) and methionine (Met), steric conflict is limited, and the inherently most favorable pattern can form, where the two hydrogen-bonded sheets constituting a hydrophilic layer contain amino acids of both chiralities (thus called LD-LD layers). The unique property of these four racemates is that they display reversible first-order solid-solid transitions between two monoclinic forms in space groups $P2_1/c$ (α) and $C2/c$ (β). The crystal structures of two polymorphs of DL-Nva have now been determined [2], revealing details on the hydrogen bonding pattern, but also on side-chain conformations. In the low-temperature α-form (data collected at -90 °C) the n-propyl side chain is disordered over two positions, while in the higher temperature β-form (-70 °C) it has three alternative positions with refined occupancies 0.509:0.345:0.146. From an analysis of steric conflict, where the conformation of one side chain affects its neighbours in a domino-like fashion, it is possible to construct an idealized, ordered pattern that rationalizes this odd distribution. The presence of such conformational cascades has implications for the understanding of the dynamics of proteins during enzymatic reactions.

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Keywords: amino acids, phase transition, side-chain conformations

MS.74.1

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Combined X-ray Diffraction and Absorption Measurements of Active Catalysts

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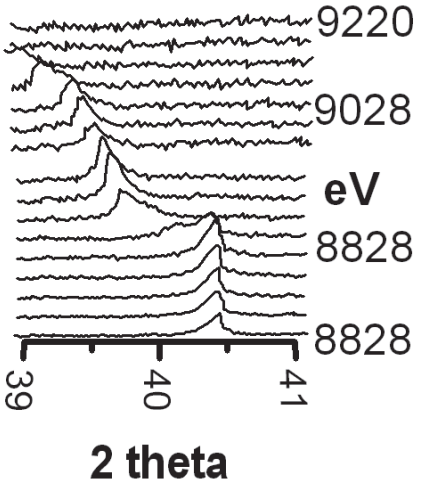
Combined X-ray diffraction (XRD) and X-ray absorption (XAS) has used effectively for 20 years [1]. At NSLS we have developed a new beam line for catalysis studies with combined XRD/XAS and *in situ* cells [2]. We have used the INEL curved linear detector as in the original experiments, but we have also used a Perkin Elmer amorphous silicon area detector and a silicon linear detector [3].

We will present expected and unexpected structural differences between the quantitatively analyzed XRD and XAS data. The most interesting was evidence for amorphous Cu metal in a CuO/Ceria catalyst. This is a remarkable demonstration between the measurement of long and short range order by the two techniques.

Experiments which combine two techniques can suffer from the compromises made to allow the combination. For instance, the XAS is measured at the most highly absorbing wavelength and consequently, the diffraction patters are difficult to correct for absorption. An obvious solution to this problem is moving away from the absorption edge when the diffraction is measured. However, this makes the time gap between XRD and XAS measurements larger.

On the other hand if there is sufficient flux and fast detectors, a diffraction pattern can be collected at each XAS point and the diffraction data can corrected for changing wavelength. The figure shows the raw time-resolved diffraction data at constant energy followed by measurement during a part of a single XAS scan of $CuFe_2O_4$ during CO reduction. Further analysis is in progress.



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Keywords: In situ, EXAFS, synchrotron

MS.74.2

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Modulation Enhanced Diffraction: a new tool for solving crystal structures and study solid-state kinetics

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When a system is perturbed by a periodic external stimulation, e.g. concentration, pH, light flux, pressure and temperature, for many materials the structural response is also periodic. Periodic perturbations are used frequently in spectroscopic investigations because they enhanced Sensitivity or Signal to Noise and introduce selectivity into experiments. This technique has been called Modulation Excitation Spectroscopy (MES) [1, 2].

We have adapted this methodology for diffraction and named it Modulation-Enhanced Diffraction (MED). First we present the theory that is developed to explain the kinematic diffraction response of a crystal when it is subjected to a periodically varying external perturbation [3]. We show that if a part the local electron density varies linearly with an external stimulus, the diffracted signal is not only a function of the stimulation frequency Ω, but also of its double 2Ω. These frequency components can provide selective access to partial diffraction contributions that are normally summed up in the interference pattern. MED simulations and experiments will be presented where a phasing process applied to partial diffraction terms allow to recover *directly* the substructure actively responding to the stimulus.

Second we have also combined MED with its spectroscopic analogue, MES. Our experimental results using *in situ* MES-MED will be presented. These data contain both the information responsible for structural transformation in the long range from diffraction, while the spectroscopic techniques yield detailed insights into local chemical