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Acta Cryst. (2011) A67, C163**LAFIRE: Automated refinement software for biomacromolecular crystallography**

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Biomacromolecular structure determination by X-ray crystallography involves many steps starting from data collection, data processing, phasing, model building, model completion, refinement and validation. Now most of these steps are highly automated because of recent advances in development of the methods and the softwares.

When incomplete model is obtained, refinement and structure completion process would be started. Currently, many refinement softwares are available such as *REFMAC*, *CNS*, *BUSTER-TNT*, *SHELXL* and *phenix.refine*. Each refinement software has advantage, users can choose the best one depending on the circumstance. However, manual process is still required to complete the refinement process because refinement softwares cannot build and even fit the model due to the convergence radius problem. In such cases, users are required to build and fit models into electron density using graphical software such as *Coot*.

LAFIRE has been developed to automate these manual steps. *LAFIRE* builds the missing residues and fits the ill-fitted residues into electron density map. Subsequently, *LAFIRE* starts refinement program such as *REFMAC* or *CNS*. These steps will be iterated to improve *R*-free factor.

Recently, some new features including (1)nucleic acid fitting, (2)ligand fitting and (3)*LAFIRE-FBDD*, have been added into *LAFIRE*. Graphical user interface (GUI) is also developed, so users can start the job, monitor the running status and check the result by using GUI.

(1)Nucleic acid is rather flexible compared to protein since nucleotide unit has six rotatable bonds in main chain. Therefore, fitting nucleic acid structure is more complicated than that of protein. Here, we made conformational restraints for nucleic acid structures based on deposited structures in PDB.

(2)Ligand fitting function finds all possible ligand positions (electron density blobs), and then fit the ligand model into the blobs.

(3)Fragment based drug design (FBDD) by crystallography is powerful method to find drug candidates, but requires many crystal structures to be analyzed. *LAFIRE-FBDD* has been developed to automate crystallographic investigation in FBDD. *LAFIRE-FBDD* gives refined structures with built ligand models for all collected datasets, based on apo structure of protein and possible ligand models. The resultant ligand structure in electron density map can also be viewed with GUI.

LAFIRE is distributed freely for academic use at our website: http://altair.sci.hokudai.ac.jp/g6/Research/Lafire_English.html

Keywords: refinement, biomacromolecule

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Acta Cryst. (2011) A67, C163**Hydrogen Bonds: the Toolkit**

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The hydrogen bond is a hugely valuable intermolecular interaction, in which interest continues at a high level. This interest covers both the fundamentals of the interaction (and indeed recently a further refinement of our definition of this interaction was issued), but also the widespread use of the hydrogen bond in attempting to control the self-assembly of molecular systems, in both the crystalline (for example in Crystal Engineering) and in non-crystalline forms. A goal of “Directed Assembly” of molecular materials with designed architectures or tunable properties using this ubiquitous yet challenging interaction seems always so close yet tantalisingly far away.

This presentation will attempt briefly to cover both aspects of the hydrogen bond tool-kit:

A discussion of the methods employed in the study of this interaction will be given, with particular reference to the combined use of diffraction experiments and computation, stressing modern approaches that attempt to understand hydrogen bonding and its evolution in increasingly complex molecular systems.

The use of hydrogen bonding as the glue to hold together molecules in predictable ways will also be discussed, with emphasis on the choice of relatively simple, robust hydrogen bonded supramolecular synthons, and attempts to use these not only to control the assembly of molecules and molecular complexes into predicted architectures but also to design into these systems some degree of structural; (and hence functional) tunability.

In addition, recent developments in the control of crystallization of hydrogen bonded systems will be mentioned briefly, with reference to isolation of elusive polymorphs and in the use of continuous crystallisation techniques for the manufacturing of molecular materials.

Keywords: hydrogen bonding, control of self-assembly, diffraction and computational methods

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Acta Cryst. (2011) A67, C163-C164**Strong Hydrogen bonds in crystals under high pressure**

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Although the hydrogen bonding (HB) is the most investigated interaction in molecular crystals, not much is known of HB at high pressure. Some crystallographic works [1] reported the characterization of structural features of strong HB systems under pressure. Very little is known from theoretical calculations, instead.

We have recently reported on the behavior of oxalic acid dihydrate (1) at high pressure [2], showing that the α form rapidly undergoes a transformation into a charge transfer crystal (C₂O₄²⁻(H₃O⁺)₂), produced by the proton shift occurring in the range 2-4 GPa. The β form, instead, is less keen on transformation and it remains a neutral crystal up to 10 GPa (theoretical prediction).

We have carried out further investigations [3] on other crystal species containing oxalic acid or oxalate anions, for example KHC₂O₄, K(HC₂O₄)(H₂C₂O₄)(H₂O)₂, (C₄N₂H₁₂)(HC₂O₄)₂. These studies show that structural motifs like that found in 1 α (COOH---OH₂) are more suited for pressure induced proton transfer, at variance from COOH-OCO systems (either charge assisted or neutral). This behavior is explained with theoretical considerations and supported by experimental work.

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Keywords: hydrogen bond, high pressure, DFT calculations

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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 pairwise 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.

[1] F.H. Allen, I.J. Bruno, *Acta Crystallogr.* **2010**, B66, 380-386. [2] T. Steiner, *J. Chem. Soc., Chem. Commun.* **1995**, 1331-1332.

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Pharmaceutical cocrystals model drug-receptor interactions

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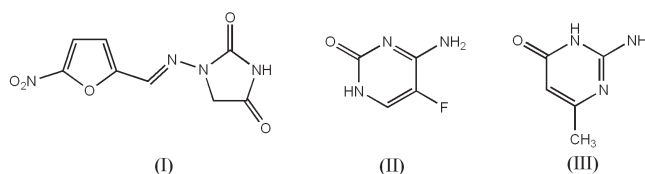
In order to study drug-receptor interactions, we cocrystallized active pharmaceutical ingredients with potential receptors. Since drug binding requires shape and property complementarity, both components have to adapt to each other for a successful recognition process. We focus on supramolecular complexes, 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

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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