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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 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

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Pharmaceutical cocrystals model drug-receptor interactions

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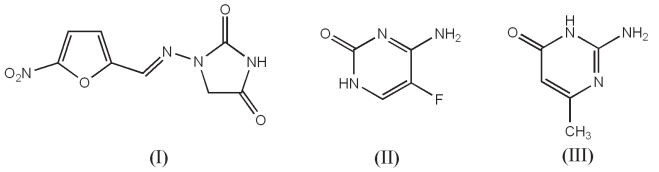
In order to study drug-receptor interactions, we cocrystallized active pharmaceutical ingredients with potential receptors. Since drug binding requires shape and property complementarity, both components have to adapt to each other for a successful recognition process. We focus on supramolecular complexes,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