Electron Diffraction as a Tool for Hydrogen Atom Localization and Absolute Structure Determination of Nanocrystals Containing Organic Molecules

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Organic molecular crystals and metal organic frameworks (MOFs) are two families of materials, which often only form submicrometric crystals, whose structure cannot be characterized by conventional single-crystal x-ray diffraction techniques. During the last decade, 3D electron diffraction (3DED) developed to a method fully suitable for the structure solution of nanoscale materials.

Organic molecular crystals and MOFs pose specific problems for the structure analysis by 3DED. They often exhibit rather large mosaicity, they tend to contain disorder and on top of this they are very beam sensitive. Therefore, the determination of crystal structures of these materials is a challenging task. The problem of radiation damage may be mitigated by sample cooling, low dose techniques, distribution of the dose to a larger volume through crystal scanning in the case of rod-shaped or platelet crystals or combination of datasets from more crystals. In the most challenging cases, several or all of these approaches need to be combined. An important recent development has also been the advent of direct detection cameras, which enables acquisition of essentially noise free data. Without all these developments it would not be possible to solve a large portion of interesting materials. In our group, we develop software PETS [2], which in its current version 2.0 provides a complete data processing work flow and contains several advanced features specific for 3DED data like treatment of precession electron diffraction data, frame orientation refinement and correction for optical distortions. These advanced tools are vital for structure solution of beam sensitive materials as they significantly improve the quality of intensity extraction from the acquired data.

Fine structural details like localization of the hydrogen atoms [3] or/and determination the absolute structure of a chiral material [4] are very important for materials containing organic molecules. These features are of eminent interest for example for pharmaceutical industry. About 90% of the active pharmaceutical ingredients (APIs) are chiral molecules and determination of the absolute configuration is necessary for the drug approval. Determination of the position of protons, *i.e.* the ability to distinguish between salt and cocrystal, is also an important problem with potential impact on the patent protection of the drugs. Understanding the functionality of MOFs sometimes also requires the localization of hydrogen atoms as potential sites of catalytic activity. While hydrogen atoms can be located during the structure refinement using kinematical diffraction theory [3], application of the calculations involving dynamical diffraction theory (so called dynamical refinement) significantly increases the clarity of the residual potential due to hydrogen atoms in the difference potential maps and increases the number of detected hydrogen atoms as well as the accuracy of their position [3]. In case of the absolute structure determination, the kinematical approximation cannot distinguish between the opposite absolute structure models, while the dynamical refinement can determine the correct absolute structure thanks to the exploitation of multiple scattering effects, which are sensitive to the absolute structure. The absolute structure can be determined either by comparing the refinement quality indicators of the two mutually inverse absolute structure models [4] or through the determination of the 3DED-Flack parameter, a parameter analogical to the Flack parameter commonly used in single crystal x-ray diffraction.

The importance of the accurate extraction of the diffracted intensity with PETS 2.0 will be presented on an example of a MOF ICR-2 (space group $C2/c$, a = 30.1(1) Å, b = 17.3(1) Å, c = 9.41(2) Å, b = 94.9(3)°)

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, whose structure was solved and published in 2018 [5]. It was possible to locate only seven out of fifteen hydrogen atoms even when the dynamical refinement was used. After reprocessing of the data with the frame orientation refinement implemented in PETS 2.0 it was possible to locate 13 out of 15 hydrogens (both missing hydrogens were on methyl group). When only kinematical approximation is used for the refinement of the reprocessed data, only four hydrogen atoms can be located. Comparison of the difference potential maps is given in Figure 1.

A cocrystal of EMPAgliflozin and L-prolin (composition $C_{28}H_{35}ClNO_9$, space group $P2_1$, a = 19.5(1) Å, b = 5.50(2) Å, c = 13.3(1) Å, b = 108.4(3)°) is a beam sensitive chiral material (Figure 2). Its structure was solved after the application of the advanced data processing options in PETS 2.0. The absolute structure was determined using dynamical refinement. The use of both R-factor difference and 3DED-Flack parameter will be discussed [8].
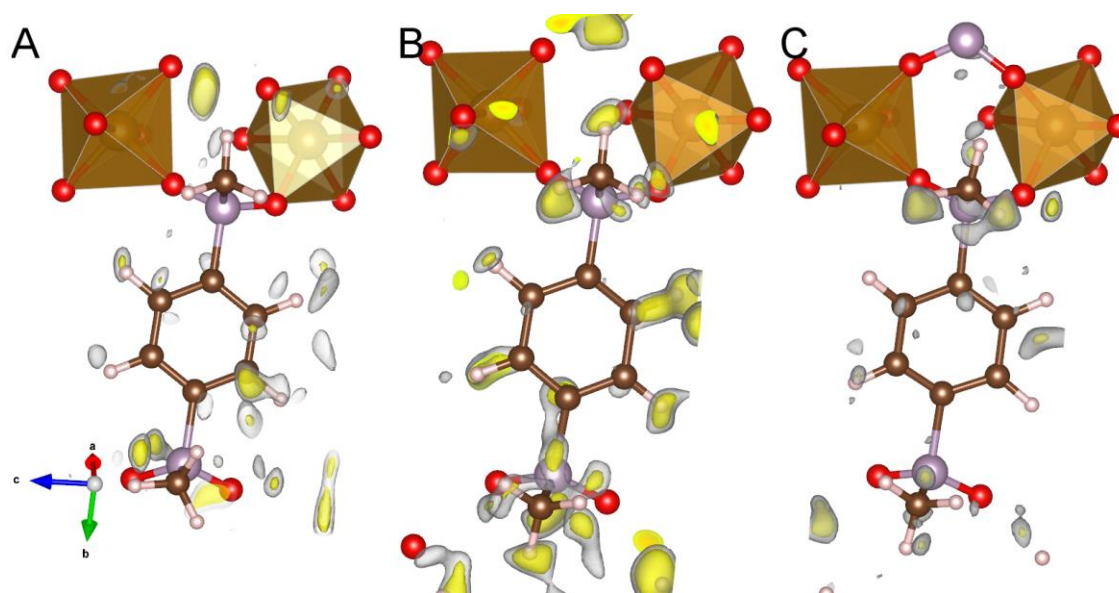

Figure 1. Difference potential maps at 2.0 sigma (grey) and 2.5 sigma (yellow) of ICR-2. Dynamically refined data processed without frame orientation refinement (A), dynamically refined data processed with frame orientation refinement (B), kinematically refined data processed with frame orientation refinement (C).
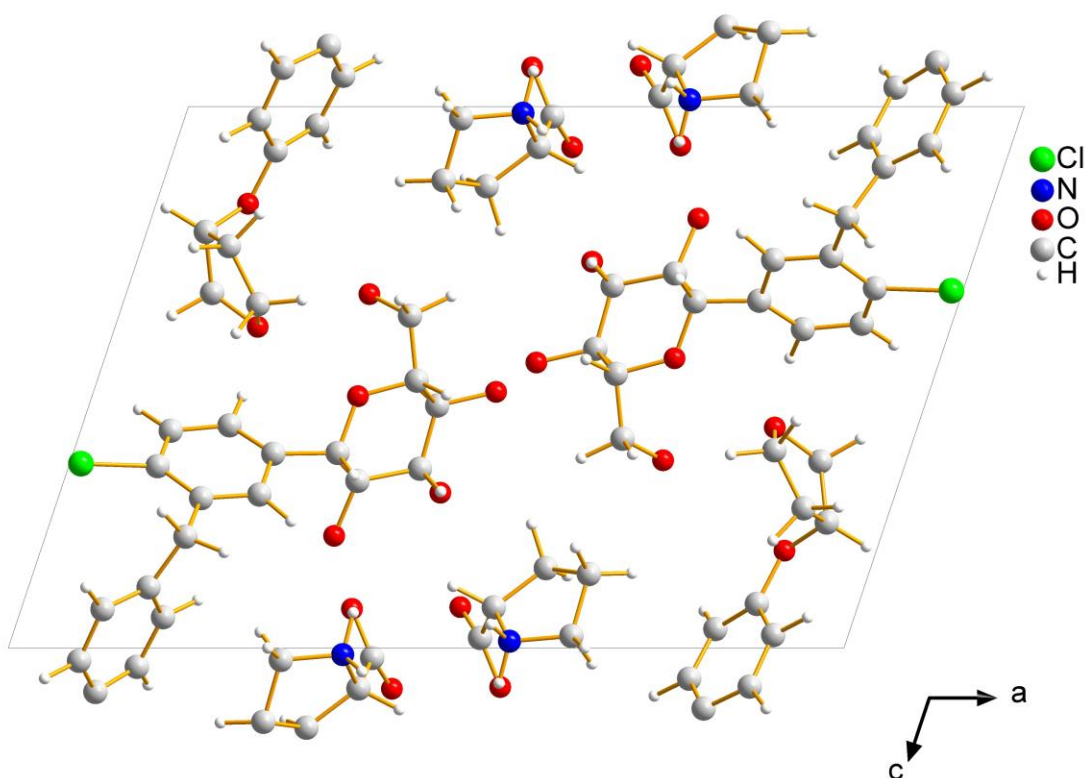
Figure 2. Structure of EMPAgliflozin L-prolin cocrystal.

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[6] This research was supported by the Czech Science Foundation, project number 20-04408S.
[7] The crystallographic part was supported by the project No. LO1603 under the Ministry of Education, Youth and Sports National sustainability programme I of Czech Republic.
[8] The authors thank Zentiva k.s. and The Parc (https://www.theparc.eu/) for providing the samples.