MS30-03 | Absolute Configuration of Pharmaceutical Molecules Determined from a Nanocrystal by Electron Diffraction

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Crystallographic analysis plays an important role in the development and characterization of new pharmaceutical substances. An essential part of a complete structure analysis is determination of absolute configuration of chiral molecules. If an organic molecular crystal forms only micro- or nanocrystals, ab initio crystal structure determination becomes an extreme challenge. An important breakthrough in the structure analysis of micro- and nanocrystalline pharmaceutical materials has been made recently [1] by the employment of electron diffraction tomography (EDT) techniques, though the absolute structure determination has not been tackled yet. A limiting factor for structure determination of organic molecular crystals is the radiation damage. Ab initio structure determination by electron diffraction has so far been limited to compounds that maintain their crystallinity after a dose of 1 e^{-} $Å^{-2}$ or more. We present a complete structure analysis of a pharmaceutical cocrystal of sofosbuvir and L-proline, which is about one order of magnitude less stable. Data collection on multiple positions of a crystal and an advanced intensity integration procedure enabled us to solve the structure ab initio. We further show that dynamical diffraction effects are strong enough to permit unambiguous determination of the absolute structure of material composed of light scatterers [2].

[1] L. Palatinus, et al., Science 10.1126/science.aak9652 (2017); T. Gruene et al., Angew. Chem. Int. Ed. 10.1002/anie.201811318 (2018); C. G. Jones et al., ACS Cent. Sci. 10.1021/acscentsci.8b00760 (2018)
[2] Brázda et al., Science accepted (2019)