MS25 3D electron diffraction for structure solution of organics and proteins

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Absolute structure of pharmaceutical salts of vilanterol using 3D ED – from Earth to the Space Station and back

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Abstract

Crystallographic analysis plays an important role in the development and characterization of new pharmaceutical substances. An essential part of a complete structure analysis is the determination of absolute configuration of chiral molecules. We showed that 3D electron diffraction (3D ED) can determine the absolute configuration of the pharmaceutical molecules [1] by the so-called dynamical refinement – a structure refinement against 3D ED data taking into account the dynamical diffraction theory [2]. This contribution will review the tedious but finally successful journey towards the determination of the absolute configuration of a pharmaceutical molecule vilanterol (Figure 1).

Two different salts were prepared in this project. The first material was a salt of vilanterol with triphenylacetic acid. It was grown at the International Space Station with the aim to obtain crystals large enough for using synchrotron radiation for structure solution and absolute structure determination. Unfortunately, the quality of the crystals turned out to be insufficient even for structure solution. We therefore embarked the project and decided to attempt the absolute structure determination by 3D ED. The crystals grown in microgravity [3] turned out to be more than sufficiently large for the application of 3D ED. The structure could be solved and refined. However, the combination of the poor crystallinity of the material and the fact that the symmetry of the structure (space group $P2_1$) was very close to $P2_1/n$ symmetry did not allow us to draw a clear conclusion on the absolute configuration. Therefore, a new salt was prepared in laboratory. This time the 1,5-naphtalene disulfonic acid was chosen instead of triphenylacetic acid. The size of the crystals was again too small for the synchrotron experiments. The material crystallized in space group *P*1 and again the structure was very strongly pseudocentrosymmetric. However, better quality of the crystals allowed us to determine the absolute structure of the material and thus the absolute configuration of vilanterol, which demonstrates that 3D ED can substantially speed up the pharmaceutical research even for very challenging materials and make it more cost effective.

References

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[3] Patent US 2021/0300861 A1.

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Figure 1 Vilanterol