MS42 Solving Structures Through Combination of Reciprocal and Direct Space Methods

MS42-04

Structure of the active ingredient of Pepto-Bismol by 3D ED and STEM imaging

E. Svensson Grape [1], V. Rooth [1], M. Nero [1], T. Willhammar [1], A.K. Inge [1]

[1]Stockholm University - Stockholm (Sweden)

Abstract

Bismuth subsalicylate (BSS) is textbook[1] example of a metallodrug and has been used to treat upset stomachs for 120 years. It is the active ingredient of Pepto-Bismol, an over-the-counter medication and household brand name across North America and other countries. Tens of billions of doses have been consumed, and it remains as the most sold stomach remedy in countries such as the US. BSS is administered as a crystalline substance. Despite its history and current significance, the crystal structure has remained unknown due to small crystallite size, complexity of the structure, and disorder. At last, we reveal the crystal structure of BSS by 3D electron diffraction (3D ED), and disorder by scanning transmission electron microscopy (STEM).[2]

In order to solve the structure, 3D ED data were collected on 18 crystals of BSS which had a particularly high degree of order. Due to the low symmetry of the triclinic crystals individual datasets had low completeness. Select datasets were merged using hierarchical clustering analysis. All non-hydrogen atoms were then located in the crystal structure using the merged dataset.

The crystal structure of BSS is made of Bi_{3+} cations and bridging O^{2-} anions surrounded by organic salicylate anions ($Hsal^-$) in a 2D layered structure. All carboxylate groups coordinate to Bi_{3+} cations, while only half of the $Hsal^-$ anions also coordinate through the phenol group. The layered structure has been compared to that of a sugar wafer[3a] or an ice cream sandwich[3b], where the Bi^{3+} and O^{2-} ions form the inner filling and the $Hsal^-$ anions form the outer wafer or biscuit.

BSS crystals isolated from Pepto-Bismol appeared to have disorder. STEM imaging with integrated differential phase contrast (iDPC) was applied to visualize the disorder. In the ordered part of the crystal the stacked layers have the same orientation. However in the disordered parts neighbouring layers had opposite orientations. In some parts the layer orientation alternated periodically while in other parts the orientation appeared random.

Structure determination provides insight into some of the properties of BSS such as its poor solubility in water, which also may influence bioavailability. The disorder in the stacking of the layers indicates that crystals of BSS from different sources are somewhat different, which may be of interest for tuning the structure and properties of this compound.

References

[1] Inorganic Chemistry 7th ed., Oxford University Press 2018, Editted by Mark Weller, Tina Overton, Jonathan Rourke, and Fraser Armstrong.

[2] Svensson Grape, E., Rooth, V., Nero, M. et al. *Nature Commun.* **13**, 1984 (2022).

[3] a) *Nature* 604, **601** (2022), b) Kira Welter, *Chemistry World*, (April 25, 2022).

Fig. 1 Structure of BSS determined by 3D ED

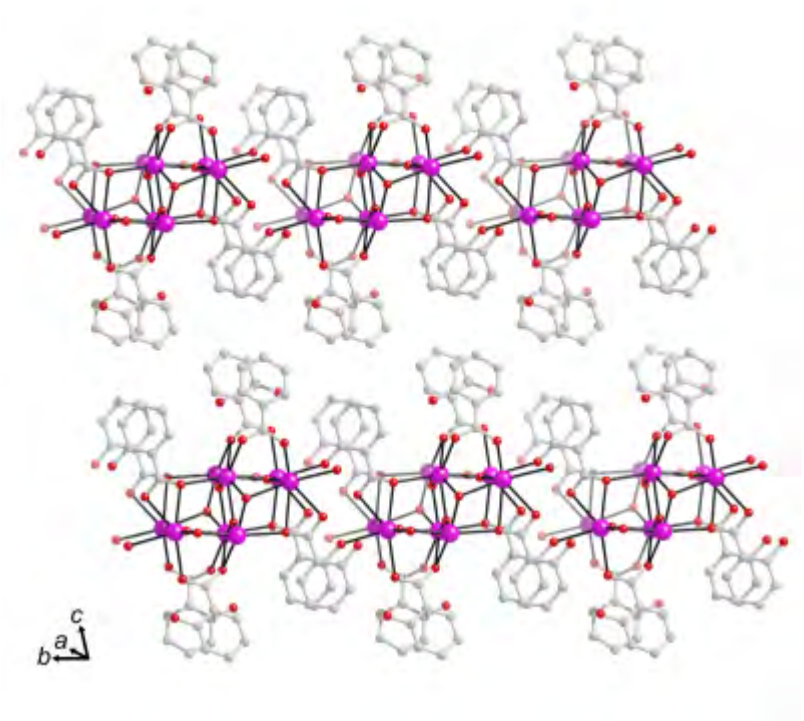

Fig. 2 iDPC STEM image of BSS with disorder