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Commentary Open Acces

Crystal Structures of New Ivermectin Pseudopolymorphs

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ABSTRACT

Ivermectin is a macrocyclic lactone developed in the 1980's as a multitarget drug. In the present study it was performed an analysis of crystal structure of new pseudopolymorphs of ivermectin using X-ray diffraction and quantum chemical methods.

Keywords:

Ivermectin; Pseudopolymorph; Crystal structure analysis

Commentary

New pseudopolymorphs of ivermectin (IVM), a potential anti-COVID-19 drug [1,2], were prepared [3]. The crystal structure for three pseudopolymorphic crystalline forms of IVM has been determined using single-crystal X-ray crystallographic analysis. It is well known that the semisynthetic substance of IVM represents a mixture of two macrocyclic compounds ivermectin-B1a and ivermectin-B1b in molar ratio 80:20 [4]. Thus, a solid solution of these two components as a single crystal structure was obtained during crystallization. Despite the fact that there are two components of IVM in crystals, this investigation will further focus on the main component of IVM, namely ivermectin-B1a. The molecular conformation of IVM in crystals has been compared with the conformation of isolated molecules modeled by DFT calculations [5]. It turned out the molecular conformation in the Free State is close to the one in the crystals. It is known that many molecules of macrocyclic compounds are characterized by the fact that the function of distribution of the electrostatic potential has considerable extrema [6]; this allows the molecules to form supramolecular adducts with ions and polar molecules. However, for the IVM molecule, the electrostatic potential obtained from the DFT calculation of the distribution of electron density does not contain significant extrema. This is also the case for other macrocyclic molecules [7]. For this reason, molecules of IVM can form inclusion compounds with polar molecules mostly due to the formation of hydrogen bonds.

In order to get an additional quantitative picture of the intermolecular interactions of the crystal structure of IVM, calculation of interaction energies was performed in CrystalExplorer 17 [8] by assessing the electrostatic, polarization, dispersion and exchange-repulsion terms that together form the total interaction energy. Calculations of the lattice energy indicate that interactions between IVM and solvents play a minor role; the main contribution to energy is made by the interactions between the molecules of IVM itself, which form a framework in the crystal structure by means of intermolecular hydrogen bonds. Notably lower contribution in the stabilization of this IVM crystal structure is provided by interaction between IVM and solvent molecules, and even here electrostatic interactions and dispersion interactions provide similar contribution, and only in the pair connected by a hydrogen bond the electrostatic components are the dominant ones. Thus, it has been hypothesized that IVM forms two types of the frameworks: monoclinic (space group I2) with a small volume of voids, and orthorhombic (space group P212121) where volume of voids is significantly larger than in the monoclinic case. In a solvent with relatively small molecules (ethanol), IVM forms monoclinic crystal structure. When crystallized from solvents with larger molecules, like gamma, valerolactone and methyl tert-butyl ether, IVM forms orthorhombic crystal structure with two independent molecules of IVM in the asymmetric unit. Interactions between IVM and molecules of solvents were evaluated using Hirshfeld surface analysis and two-dimensional fingerprint plots of these Hirshfeld surfaces.

Thermal analysis of the new pseudopolymorphs of IVM was performed by differential scanning calorimetry and thermogravimetric analysis. The peculiarities of the crystal structures explain the thermal analysis data.

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