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The influence of fluorine position on the properties of fluorobenzoxaboroles

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ABSTRACT

5-Fluoro-2,1-benzoxaborol-1(3H)-ol, a potent antifungal drug also known as Tavaborole or AN2690, has been compared with its three isomers in terms of its activity against several fungi as well as pK_a and multinuclear NMR characterization. The molecular and crystal structure of 6-fluoro-2,1-benzoxaborol-1(3H)-ol was determined and compared with that of AN2690.

1. Introduction

Benzoxaboroles are important organoboron compounds due to their specific properties and wide applications. The benzoxaborole structural motif has been applied for medicinal purposes [1] such as HIV entry inhibitors [2–4], antiprotozoal drugs [5], antibacterial or antifungal agents [6,7] as well as a potential drug delivery scaffold [8]. Their applications in biotechnology and therapeutic treatments was recently reviewed [9].

5-Fluoro-substituted benzoxaborole (**1**, Chart 1), is a FDA-approved drug KERYDIN™ (Tavaborole), the first oxaborole antifungal dedicated for the topical treatment of onychomycosis of the toenails [10]. The mechanism of its antifungal activity is based on the interaction with the active site of enzyme, which results in inhibition of LeuRS and blocking the protein synthesis [11,12]. The history of these investigations and mechanism of action have been recently described [9].

Our recent research on the structures and properties of organoboron compounds was focused on the characterization of fluoro-substituted phenylboronic compounds. Generally, introduction of fluorine atoms increases the acidic character of the boronic center. It was found that cyclic boronic esters with fluorine atom at the *ortho* position display higher acidity in comparison with other monosubstituted isomers. Increasing the number of fluorine substituents does not simply result in rise of the acceptor number for these compounds [13], and the overall Lewis acidity of equally fluorinated diol phenylboronates is significantly affected by the structure of the diol [14]. The number and position of the fluorine substituents has also a substantial influence on the crystal structure of phenylboronates [15]. In case of fluorinated acids, introduction of *ortho*-fluorine atom weakens the intermolecular hydrogen bond [16,17]. Moreover, results of the systematic NMR studies of fluorinated phenylboronic acids revealed a close correlation between their structure and spectroscopic properties [18].

Tomsho et al. [19] showed that the substituents in benzene ring of benzoxaboroles follow a Hammett relationship with the pK_a values. Moreover, these substituents' effects are also related to the polyols binding properties of these compounds under physiologically relevant conditions. The presence of fluorine substituent as well as its position are crucial from the point of view of the antifungal activity [20,21].

The compounds under investigation are four isomeric benzoxaboroles with fluorine substituent in benzene ring at various positions. The aim of this work is to compare their properties:

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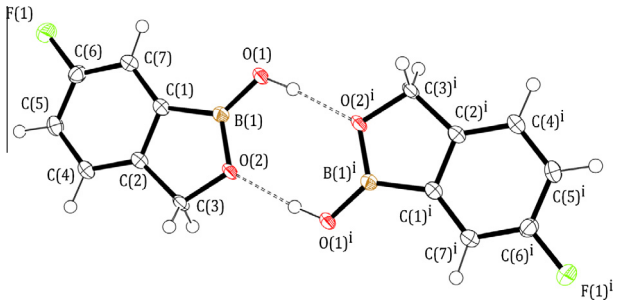

Fig. 1. Molecular structure of **2** from single crystal X-ray diffraction (XRD) data. Ellipsoids corresponding to anisotropic thermal displacement parameters (ADP's) drawn at the 50% probability level. Hydrogen atoms (refined isotropically) are shown with an arbitrary radius. Second molecule (labels with superscript *i*) generated by $1 - x$, $-y$, $1 - z$ symmetry operation.

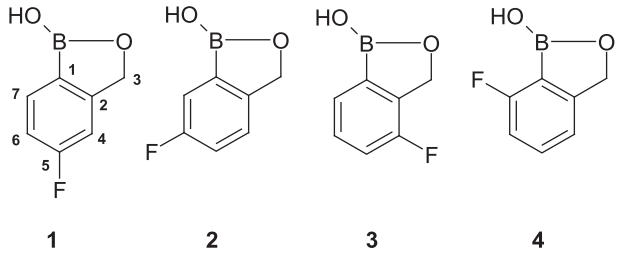

Chart 1. Benzoxaboroles under investigation.

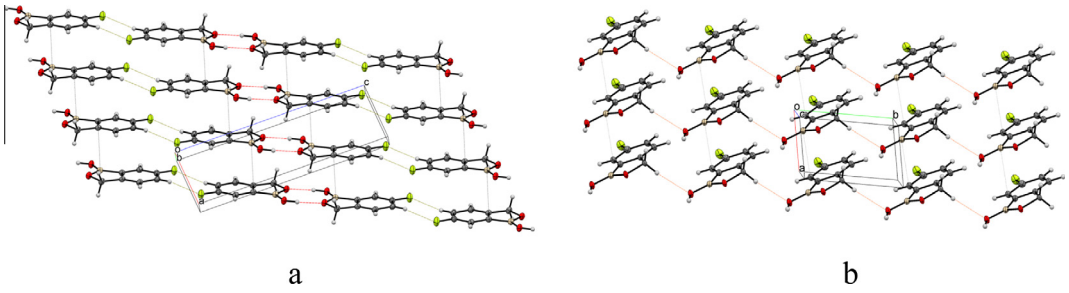

Fig. 2. Crystal packing pattern in the solid-state structure of **2**: along the *b*-axis with the O–H···O hydrogen bonds and C–H···F interactions (a), along the *c*-axis with the C–H···O interactions (b).

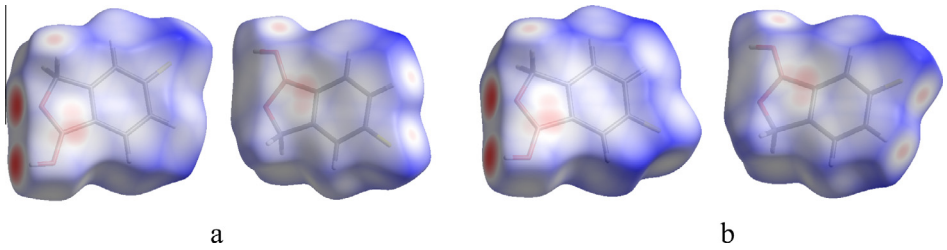

Fig. 3. Visualization of Hirshfeld surface attributed to **1** (a) and **2** (b) solid-state structures; the shortest contacts in the crystal bulk (colored red) are associated with hydrogen bonds (strong O–H···O, weak C–H···F and C–H···O), wherein interactions perpendicular to molecule plane may be ascribed to weak $\pi\cdots\pi$ stacking interactions.

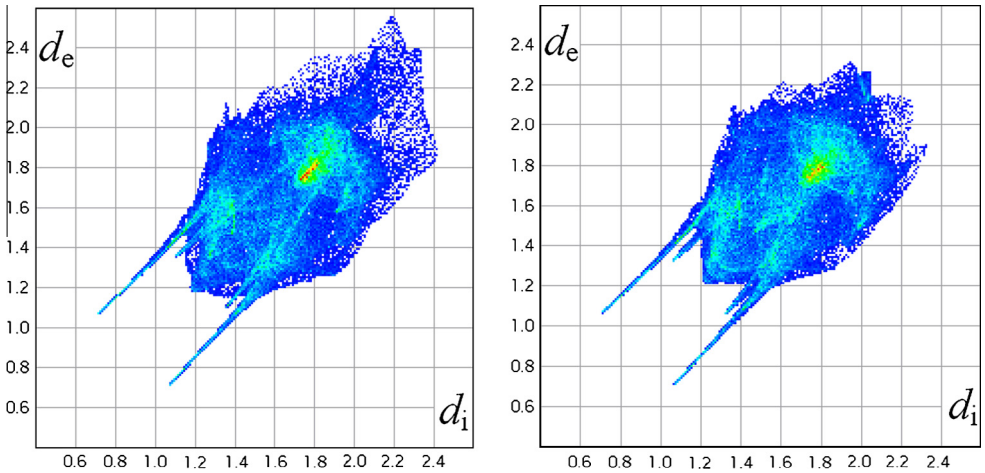

Fig. 4. Two-dimensional fingerprint plot attributed to **1** (left) and **2** (right) solid-state structures, presenting combination of distances external (d_e, in Å) and internal (d_i, in Å) to the Hirshfeld surface; the shortest contacts in the crystal bulk are associated with O–H···O and C–H···F hydrogen bonds (indicated by pairs of long sharp spikes).