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Fluoro-substituted 2-formylphenylboronic acids: Structures, properties and tautomeric equilibria

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ABSTRACT

Four isomeric fluoro-2-formylphenylboronic acids were synthesized and characterized by ^{1}H, ^{13}C, ^{19}F and ^{17}O NMR. Molecular and crystal structure of two compounds was determined by single crystal XRD method. pK_a values of all the isomers have been determined by spectrophotometric method and compared with the results for the corresponding benzoxaboroles as well as fluoro- and formylphenylboronic acids. Tautomeric equilibrium with cyclic benzoxaborole form was investigated. The influence of position of fluorine substituents on the properties of investigated compounds is discussed.

1. Introduction

Arylboronic acids and their derivatives have attracted increasing interest because of their new applications in organic synthesis, catalysis, supramolecular chemistry, and material engineering, as well as in biology and medicine [1–4]. The presence of substituents in phenylboronic acid molecule has great influence on the molecular and crystal structure, and, consequently, on their properties [5]. 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. Results of the systematic NMR studies of fluorinated phenylboronic acids revealed a close correlation between their structure and spectroscopic properties [6]. The influence of the position of fluorine atom on the structures, spectral characteristics and biological activity has been investigated for fluorobenzoxaboroles [7,8].

The affinity of boronic compounds towards polyols is crucial in the most important applications of these compounds, *i.e.* in medicine and materials chemistry. Recently, a review on boronate affinity materials for separation and molecular recognition was published [9]. The key problem is the preparation of materials that would be able to bind at a relatively low pH, which minimizes the risk of labile biomolecules' degradation. Boronic ligands with electron withdrawing groups, benzoxaboroles as well as heterocyclic boronic acids have been found to be the most prospective receptors. Fluorine-substituted compounds exhibit higher acidity (lower pK_a) compared with their non-fluorinated analogs.

The compounds under investigation are four isomeric fluoro-2-formylphenylboronic acids (**1–4**) with fluorine substituent at various positions. These compounds are of potential applications due to the presence of two functional groups: fluorine atom that enhances acidity of the compounds, and formyl group of a high synthetic versatility [10–13]. Three of the investigated isomers have been previously used in asymmetric Suzuki-Miyaura coupling with further transformation of the formyl group [12]. Two of them have been used to obtain axially chiral monophosphine oxides [14]. Some of them were also used for spectroscopic analysis of the enantiopurity of chiral diacids [15] and diols [16]. The 3-fluoro-isomer (**1**) was used for the functionalization of protein amino

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groups to investigate the interactions with sugars [17]. Only one compound, namely 3-fluoro-2-formylphenylboronic acid (**1**), was previously characterized in crystal state and in solution. It was found, that it exists in equilibrium with its cyclic tautomer: hydroxybenzoxaborole [18].

The aim of this work is to investigate how the position of fluorine atom in 2-formylphenylboronic acids (**1–4**) influences their structures, spectral properties as well as acidity.

2. Results and discussion

The compounds investigated in the present paper are shown in Chart 1.

2.1. Synthesis

The compounds **1–4** were synthesized from the corresponding bromobenzaldehydes in two-step reactions with overall yield of over 78% according to Scheme 1.

2.2. Molecular and crystal structures

The present paper describes molecular and crystal structures of the compounds **2** (Fig. 1a) and **4** (Fig. 1b). Molecular structure of the compounds with the atomic numbering and ring labeling schemes are presented in Fig. 1.

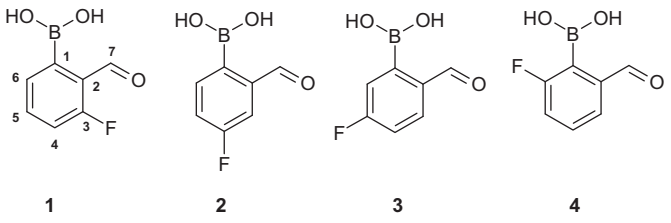
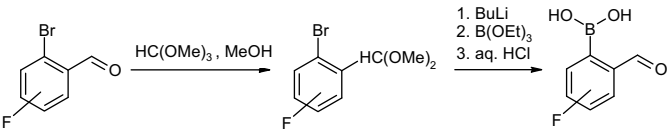


Chart 1. Boronic acids under investigation with numbering of carbon atoms.



Scheme 1. Synthesis of fluorinated 2-formylphenylboronic acids.

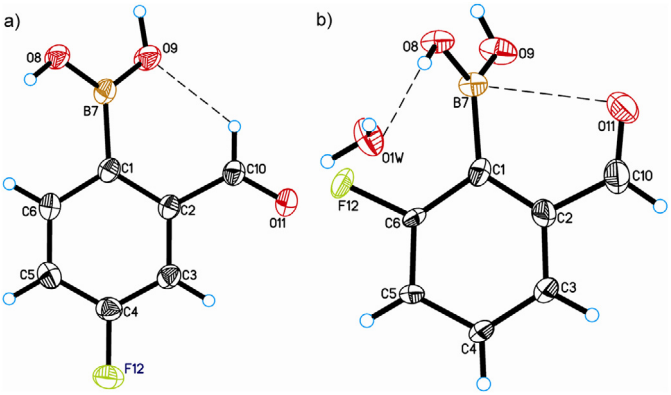


Fig. 1. Molecular structures of compounds **2** (a) and **4** (b) showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius (hydrogen bonds and B···O interactions are represented by dashed lines).

The crystal data and refinement parameters are summarized in Table 1.

Single-crystal X-ray diffraction measurements show that compounds **2** and **4** crystallize in the monoclinic *C*2/c (**2**) and $P2_1/c$ (**4**) space groups with one molecule in the asymmetric unit (Fig. 1, Table 1). The bond lengths and valence angles characterizing the geometry of the phenylboronic acid moiety in compounds **2** and **4** are consistent with the geometric parameters observed for formylphenylboronic acids [19]. The comparison of the crystal structure of compounds **2** and **4** with the known crystal structure of 3-fluoro-2-formylphenylboronic acid (**1**) (triclinic *P*-1 space group) [18], shows that in all cases the boronic moiety ($B(OH)_2$) has *syn-anti* conformation and makes angle of 10.3(1)°, 44.6(1), and 74.7(2)° with the mean plane of the phenyl ring, in compounds **1**, **2**, and **4**, respectively. As a consequence, differences in the crystals packing of mono fluoro substituted 2-formylphenylboronic acids are observed. In the crystals of compound **2**, the intermolecular C10–H10···O9 hydrogen bond is observed and molecules are linked into inversion $R_2^2(8)$ dimers by pairs of O9–H9···O8 hydrogen bonds which is typical of many phenylboronic acids (Table 2 and Fig. 2a). Centrosymmetric $R_2^2(8)$ dimers are also observed in the crystals of compound **1**, however one of the hydroxyl group is engaged in intramolecular O—H···O hydrogen bond with the formyl group. In the crystal packing of **2**, the neighbouring dimers are linked by O8–H8···O11 hydrogen bond to produce 2D-layers along the *c*-axis (Table 2 and Fig. 3a). Adjacent layers are interwoven and interact by C6–H6···O11 hydrogen bond and π–π interactions (*Cg*···*Cg* = 3.754(1) Å; Cg is the centroid of the benzene ring C1–C6; interplanar distances = 3.489(2) Å; slippage 1.385(2) Å), to form a double layers along the *b*-axis (Table 2, Fig. 3b). The neighbouring layers are linked by C—H···F (C3–H3···F12 and C5–H5···F12) hydrogen bonds to form a three-dimensional framework structure (Table 2, Fig. 3b). Similar crystal packing is observed in the crystals of 3-formylboronic acid [19]. In the crystal packing of **1**, centrosymmetric dimers are linked *via* weak C—H···O hydrogen bonds and π–π interactions into columns along the *c*-axis.

Table 1
Crystal data and structure refinement for the compounds **2** and **4**.

Compound	**2**	**4**
Chemical formula	$C_7H_6BFO_3$	$C_7H_6BFO_3{\cdot}H_2O$
FW/g mol^{-1}	167.93	185.94
Crystal system	monoclinic	monoclinic
Space group	C_2/c	$P2_1/c$
a/Å	30.045(6)	7.540(9)
b/Å	3.754(6)	8.180(9)
c/Å	13.516(9)	14.096(9)
β/°	90.39(1)	99.16(1)
V/Å^3	1524.2(2)	858.3(2)
Z	8	4
T/K	295(2)	295(2)
λ_{Cu}/Å	1.54184	1.54184
ρ_{calc}/g cm^{-3}	1.464	1.439
μ/mm^{-1}	1.094	1.114
F(000)	688	384
2θ range for data collection/°	5.89–67.50	5.94–67.39
Completeness 2θ/%	99.0	99.0
Reflections collected	7101	4172
Reflections unique	1371[R_{int} = 0.0484]	1534[R_{int} = 0.0331]
Data/restraints/parameters	1371/0/115	1534/15/186
Goodness-of-fit on F^2	1.056	1.102
Final R_1 value ($I > 2\sigma(I)$)	0.0463	0.0842
Final wR_2 value ($I > 2\sigma(I)$)	0.1347	0.2136
Final R_1 value (all data)	0.0571	0.0974
Final wR_2 value (all data)	0.1493	0.2259
CCDC number	1439278	1439279