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PAPER

Towards a monomeric structure of phenylboronic acid: The influence of *ortho*-alkoxy substituents on the crystal structure†

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The structures of three *ortho*-alkoxyphenylboronic acids (2-methoxy-, 2-ethoxy-, 2-isobutoxy-), and three di*ortho*-alkoxyphenylboronic acids (2,6-dimethoxy-, 2,6-diethoxy- and 2-isobutoxy-6-methoxy) were determined by single crystal X-ray diffraction. The study was undertaken with the intention of designing a novel boronic acid having a monomeric structure, which to date has been an unavailable building block for crystal engineering. This motif can be enhanced by involving two hydroxyl groups at the boron atom in intramolecular hydrogen bonds. Although monosubstituted systems form typical dimers in the crystal lattice, disubstituted species reveal a much bigger variety of possible interactions. Among the analyzed compounds, 2,6-dimethoxyphenylboronic acid and 2,6-diethoxyphenylboronic acid crystallize in two polymorphic forms each. The unprecedented packing with monomers as the dominant structural motif has been found in the crystal structure of 2-isobutoxy-6-methoxyphenylboronic acid and one of the polymorphs of both 2,6-dimethoxyphenylboronic acid and 2,6-diethoxyphenylboronic acid. This description of the molecular packing is also supported by the analysis of fingerprint 2-D plots based on the Hirshfeld surfaces. The variety of possible types of interactions either within a single moiety or between moieties in dimers were additionally analyzed on the basis of the interaction energies, which have been estimated by *ab initio* calculations at the MP2/6-31+G* and B3LYP/6-311+G** level of theory.

Introduction

For many years crystal engineering has been an extremely fast growing area of experimental chemistry leading to new materials with a controlled and understood nature. Design and understanding the crystal architecture still remains challenging, as this knowledge and experience impacts on the standard of life for each of us.[1,2] Phenylboronic acids are one of the class of molecular systems which have recently stimulated much interest, not only due to the Suzuki coupling reaction in organic chemistry,[3] but also due to their wide applications in catalysis, medicine and biology.[4] Great interest has been also paid to the supramolecular systems which can be formed by both covalent[5] bonds – *e.g.* covalent organic frameworks (COF), an emerging class of crystalline, porous materials composed of organic subunits,[6] as well as by hydrogen bonds.[7,8]

To date there are about 150 known diverse phenylboronic acid structures.[9] Five main factors play a crucial role in determining the crystal architecture: (i) the electron-deficiency of the boron center enabling dative bond formation,[10] (ii) the flexibility of the boronic group,[4,11] (iii) the presence of two hydroxyl groups in different conformations (*syn*,*syn*, *syn*,*anti* or *anti*,*anti*),[12–14] (iv) functional groups in the phenyl ring and last but not least (v) the presence of other components.[15–18] In addition to strong intermolecular hydrogen bonds in typical dimeric units and lateral hydrogen bonds connecting them,[11,19] there are many examples of weaker inter- and intramolecular bond formation determining the crystal architecture. Boronic acids are used as tools for self assembly in supramolecular chemistry,[20] but one of the building blocks has never been taken into account. This missing link is the monomer.

The architecture of phenylboronic acids is often compared with that of benzoic acids.[4,11] In the latter, breaking of the dimer motif is possible due to substitution in the *ortho* position by a group enabling intramolecular hydrogen bond formation. This can be done efficiently with the ethoxy substituent,[21,22] but surprisingly not with methoxy.[22,23] This simple, albeit nice idea inspired us to devise monomeric structures of phenylboronic

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† Electronic supplementary information (ESI) available. It contains a full list of bond lengths, bond angles and torsion angles of the experimentally studied systems (**1**)–(**6**). It also contains symmetry, absolute electronic energy at MP2/6−31+G* and B3LYP/6−311+G** (in Hartree) and Cartesian coordinates at MP2/6−31+G* and B3LYP/6−311+G** levels for the molecules studied. The detailed data relating to hydrogen bond energies estimated at two levels of theory (MP2/6−31+G* and B3LYP/6−311+G**) is also presented. See DOI: 10.1039/c2ce25657f

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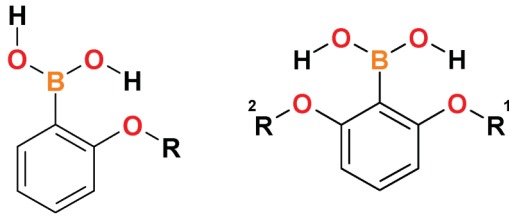
acids. Support for this work comes from a survey of crystal structures of mono *ortho*-substituted phenylboronic acids.[9] The vast majority of them, except fluoro-,[24] trifluoromethyl-[25] acetylphenyl-[26] or 2-methoxycarbonyl-[27] substituents, form an intramolecular hydrogen bond involving the hydroxyl group at boron and heteroatom(s) situated in the *ortho* position or in a side chain. To obtain a monomeric motif, two hydroxyl groups should be involved in intramolecular hydrogen bonds. In the crystal field they should be strong enough to overcome intermolecular hydrogen bond interactions. Obviously this may be achieved if the boronic group is coplanar with the phenyl fragment. In mono *ortho*-substituted systems this can be most effectively achieved for alkoxy-[28,29] and for phenylazo-substituents.[30] Importantly, the twist between the fragments is significantly smaller in the former case,[31] which make them very attractive.

The aim of this paper is to devise a monomer structure by systematic investigation of the influence of two *ortho* alkoxy groups in phenylboronic acid on their molecular and crystal structures. Comparison with reference systems containing one *ortho* alkoxy group and estimation of the hydrogen bond energies of the most common interactions observed in the crystal lattice is another goal of this paper. The experimentally investigated compounds are shown in Scheme 1.



(**1**): R=Me (**4**): R^1=R^2=Me

(**2**): R=Et (**5**): R^1=R^2=Et

(**3**): R=i-Bu (**6**): R^1=Me, R^2=i-Bu

Scheme 1 Structures of investigated compounds.

Results and discussion

Structures

Structural details for all the obtained systems are given in Tables 4 and 5 (later), whereas the plots representing thermal displacement ellipsoids together with the numbering scheme are collected in Fig. 11 (later).

A. 2-Alkoxyphenylboronic acids. The molecules of 2-methoxyphenylboronic acid (**1**), 2-ethoxyphenylboronic acid (**2**) and 2-isobutoxyphenylboronic acid (**3**) crystallize in a monoclinic system, with one molecule (**1** and **2**) or with two molecules (**3**) as the asymmetric part of the unit cell. In all three structures molecules form dimers, the most common motif observed in the structures of phenylboronic acids.[9,11] These dimers are either centrosymmetric ((**1**), (**2**)) or asymmetric – *i.e.* formed by two independent molecules (**3**). The boronic group in all cases shows a similar geometry with *syn* and *anti* conformation of hydroxyl groups (see Fig. 1). The group is always planar and almost coplanar with the phenyl ring fragment with only a slight twist of 4.11° (**1**), 7.41° (**2**) and 1.44° or 2.81° [two symmetrically independent molecules of (**3**)].

The hydrogen bonds in the dimers are rather strong with the O12–H12···O11 distance in the range of 1.92(2)–1.96(2) Å [O11···O12 is in the range of 2.752(1)–2.840(2) Å], see Table 1. This is comparable with the distances in other phenylboronic acids with polyoxaalkyl substituents at the *ortho*-position having been studied before,[29] but slightly longer than in the unsubstituted phenylboronic acid (O···O equals to 2.721 or 2.734 Å).[19,41] Due to the presence of the alkoxy group *ortho* to the boronic group, the hydroxyl group in the *anti* conformation plays not only the role of hydrogen bond acceptor, but is also an intramolecular hydrogen bond donor to the proximal oxygen atom. The intramolecular O–H···O bonds are somewhat shorter than the intermolecular ones and vary from 1.89(2) –1.94(2) Å (O···O distances in the range of 2.622(2) –2.664(1) Å), which might suggest that they are stronger. In fact the estimations of interaction energies do not support this view (see discussion below).

The dimers interact in the crystal lattice with other units by weak intermolecular interactions. In (**1**) C–H···O interactions (H···O distance of 2.687(2) Å) form infinite ribbons parallel to the ($\bar{1}$41) plane (Fig. 2a). These ribbons are further zipped by weak C^{π}–H···O and C–H···C^{π} interactions, while the layers of ribbons are joined by weak C^{π}–H···O and C^{π}···B interactions as shown in Fig. 2b. In (**2**) weak interactions lead to a 2-D

Table 1 The geometry of intra- and intermolecular interactions in crystals of 2-alkoxyphenylboronic acids [Å, °]

	H···A	D···A	D–H···A
1			
O12–H12···O11[a]	1.92(2)	2.781(1)	177(2)
O11–H11···O2[b]	1.94(2)	2.654(2)	140(2)
2			
O12–H12···O11[c]	1.89(2)	2.780(1)	169(2)
O11–H11···O2[b]	1.93(2)	2.664(1)	142(2)
3			
O12A–H12A···O11B[d]	1.96(2)	2.840(2)	139(1)
O11A–H11A···O2A[b]	1.89(2)	2.622(2)	141(2)
O12B–H12B···O11A[d]	1.87(2)	2.752(2)	168(2)
O11B–H11B···O2B[b]	1.95(2)	2.663(2)	143(2)

symmetry codes:[a] 1 − *x*, −*y*, 2 − *z*; [b] *x*, *y*, *z*; [c] 1 − *x*, 1 − *y*, 1 − *z*; [d] *x*, 1.5 − *y*, −0.5 + *z*

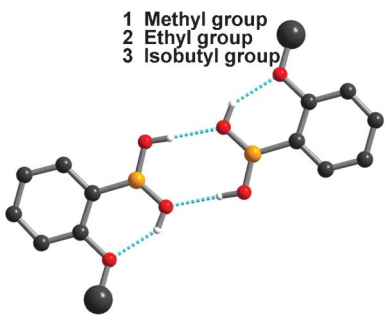


Fig. 1 Dimeric molecular motifs observed in the structures of (**1**), (**2**) and (**3**). In the case of (**1**) and (**2**) dimers are centrosymmetric while (**3**) is not. Bulky atoms represent the aliphatic chain: methyl-, ethyl- or isobutyl-.

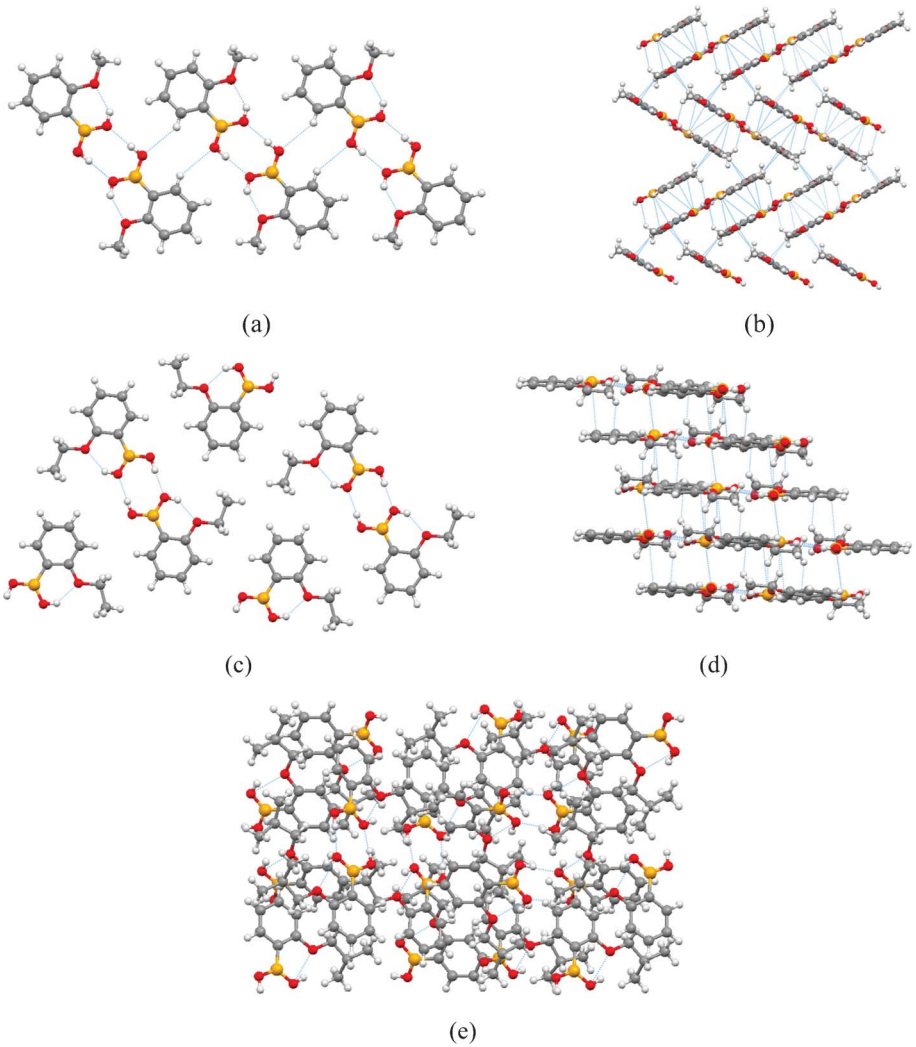


Fig. 2 a) Ribbon motif in the ($\bar{1}41$) plane in (**1**). b) The crystal packing along the [101] direction in (**1**). c) 2-D layer on ($10\bar{3}$) plane in (**2**). d) The crystal packing along the [010] direction in (**2**). e) The crystal packing along the [100] direction in (**3**).

structure, with molecules forming layers in the ($10\bar{3}$) plane. Within such layers, weak $C^{\pi}H\cdots O$, $B\cdots O$ or $B\cdots C^{\pi}$ interactions are present collecting the dimers together (Fig. 2c–d). In (**3**) the intermolecular interactions lead to complex 3-D structures involving both $CH\cdots C^{\pi}$, $C^{\pi}H\cdots B$ or $C^{\pi}\cdots B$ interactions (see Fig. 2e).

B. 2,6-Dialkoxyphenylboronic acids. 2,6-Dimethoxyphenylboronic acid forms two polymorphs. One of them crystallizes in tetragonal $P\bar{4}n2$ (**4A**) and the other one in the $C2/c$ space group (**4B**). The former consists of half of the molecule in an independent part of the unit cell, while the latter is composed of one-and-a-half molecules. Most importantly, the crystal packing is completely different in both cases. Polymorph I (**4A**) forms classic dimers, as shown in Fig. 3a. They have D_2 symmetry because they lay on three 2-fold axes. This forces the hydrogen atoms of the boronic group to be disordered. The hydrogen bonds in the dimers are even shorter than in (**1**)–(**3**) with the O11–H11$\cdots$O11′ and O11$\cdots$O11′ distances equal to 1.93(2) Å and 2.748(2) Å, respectively (see Table 2). The phenyl rings are twisted with respect to the boronic groups by 46.3° which disables the intramolecular hydrogen bond formation with methoxy groups at *ortho* positions. Instead, the dimers interact with the other pair of dimers and form infinite ribbons along the [001] direction with the distances O11–H11$\cdots$O11′ and O11$\cdots$O11′ equal to 2.00(2) Å and 2.729(2) Å, respectively. The ribbons interact further in the crystal lattice by weak $C^{\pi}H\cdots O$ interactions, which involve a *meta* phenyl hydrogen and methoxy group or a *para* phenyl hydrogen and hydroxyl groups of two other units. The latter is bifurcated as shown in Fig. 4a.

Polymorph II (**4B**) reveals a completely novel type of crystal packing. It consists of two kinds of molecules. One of them (**A**) displays two intramolecular hydrogen bonds between hydroxyl groups of a boronic fragment and the proximal methoxy groups (Fig. 3b). Notably, they are even shorter than in monosubstituted parent systems: the OH$\cdots$O distances are 1.90(3)–1.92(3) Å while the respective O$\cdots$O distances are 2.615(2)–2.621(2) Å, which suggests that they are more effective. Moreover, the boronic group is twisted with respect to the phenyl fragment by 6.9°, which is similar to the parent monosubstituted analogue. It should however be noted that one of the hydroxyl groups may serve as a hydrogen bond donor in an intermolecular hydrogen bond to a hydroxyl group of a molecule related by a center of

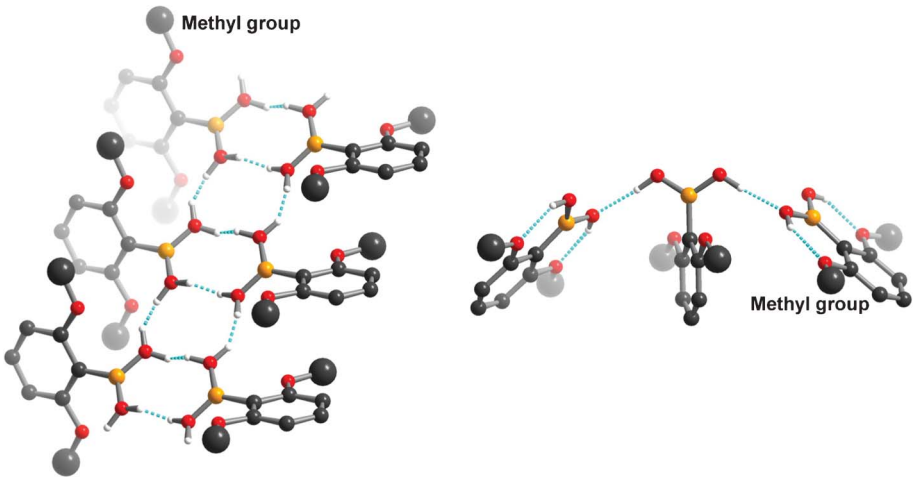


Fig. 3 Molecular structure of 2,6-dimethoxyphenylboronic acid: a) Polymorph I (**4A**). b) Polymorph II (**4B**).

inversion $(2 - x, -y, 1 - z)$; however, the O11A–H11A···O11A′ distance is rather long at 2.557(2) Å (the relevant O11A···O11A′ distance is 3.008 Å). The other molecule (**B**) lays on a 2-fold axis. In this case the ring is twisted by 60° with respect to the boronic group and the two hydroxyl hydrogen atoms are in *anti* conformations. They are donors of hydrogen bonds to one of hydroxyl groups of two adjacent (**A**) type molecules, forming rather unusual trimers, as shown in Fig. 3b. The respective O11B–H11B···O12A and O11B···O12A distances equal to 1.88(3) Å and 2.781(2) Å. The resulting packing along the $[1\bar{1}0]$ direction is shown in Fig. 4b. It is clear that monomers are the dominant motif while the dimers are not present in the structure at all.

Table 2 The geometry of intra- and intermolecular interactions in crystals of 2,6-dialkoxyphenylboronic acids [Å, °]

	H···A	D···A	D–H···A
4A			
O11–H11···O11′[a]	1.93(2)	2.748(2)	158(3)
O11–H11···O11′[b]	2.00(2) Å	2.729(2)	141(2)
4B			
O11A–H11A..O2A[c]	1.92(3)	2.621(2)	143(2)
O12A–H12A..O6A[c]	1.90(3)	2.615(2)	145(2)
O11B–H11B···O12A[d]	1.88(3)	2.781(2)	175(2)
5A			
O11–H11···O12[e]	1.79(2)	2.746(1)	165(2)
O12–H12···O11[f]	2.02(2)	2.727(1)	142(2)
5B			
O11A–H11A···O2A	1.91(2)	2.634 (2)	141(2)
O12A–H12A···O6A	1.95(2)	2.653(2)	139(2)
O11B–H11B···O2B	1.95(2)	2.651(2)	142(2)
O12B–H12B···O6B	1.90(2)	2.632(2)	144(2)
O11C–H11C···O2C	1.89(2)	2.632(3)	145(2)
O12C–H12C···O6C	1.91(3)	2.653(2)	144(3)
O11D–H11D···O2D	2.00(3)	2.657(2)	138(2)
O12D–H12D···O6D	1.91(2)	2.646(2)	142(2)
6			
O11–H11···O2	1.93(2)	2.640(1)	144(2)
O12–H12···O6	1.91(2)	2.635(1)	139(2)

symmetry codes:[a] $1.5 - y, 1.5 - x, 1.5 - z$; [b] $x, y, 1 + z$; [c] x, y, z; [d] $1.5 - x, 0.5 - y, 1 - z$; [e] $1.5 - x, -0.5 + y, 0.5 - z$; [f] $x, 1 + y, z$;

Also 2,6-diethoxyphenylboronic acid exists in two polymorphs which differ in volume of the unit cell, and most importantly, have totally different molecular interactions. Both systems crystallize in the monoclinic $P2_1/c$ space group. However, polymorph I (**5A**) consists of one molecule, while polymorph II (**5B**) comprises four independent molecules in the asymmetric part of the unit cell. The former forms an infinite ladder where the participating molecules are shifted with respect to each other along the 2_1 axis (Fig. 5a). This is not a very common motif in the structures of phenylboronic acids, although it has already been observed in 4-methoxyphenylboronic acid[15] and 1,2-ethynediylbis(4,1-phenylene)diboronic acid.[32] Again the boronic group is highly twisted with respect to the phenyl ring (by 51°), which disables intramolecular hydrogen bond formation. The intermolecular hydrogen bond lengths are somewhat shorter than those observed for monosubstituted species. The O11–H11···O12 distance between pairs of shifted units is 1.79(2) Å (the O11···O12 distance is 2.746(1) Å), while it is O12–H12···O11 2.02(2) Å between parallel units (the respective O12···O11 distance is 2.727(2) Å, see Table 2 for details). The crystal structure is further stabilized by weak CH···C^{π} or CH···B interactions. The packing is shown in Fig. 6a.

Polymorph II (**5B**) possesses quite different packing. All boronic groups are twisted with respect to phenyl rings by a much smaller extent (6.4°, 3.4°, 9.6° or 9.3° for A–D) and all hydroxy groups are in the *anti* conformation. The intramolecular O···O distances vary in a rather broad range (between 2.632(2)–2.657(2) Å, see Table 2), but again they are shorter than in the parent monosubstituted system. Importantly, solely intramolecular hydrogen bonds are observed! The molecules A and C and B and D form very similar layers in $(10\bar{1})$ planes, where the molecules and planes are joined by weak intermolecular $C^{\pi}H\cdots O$, CH···O or $C^{\pi}H\cdots B$ interactions only (see Fig. 6b–d). This is an even more striking packing motif than in 2,6-dimethoxyphenylboronic acid, polymorph II (**4B**), where there is no dimer formation at all!

Finally, a very similar pattern is observed in the crystal structure of 2-isobutoxy-6-methoxyphenylboronic acid (**6**) (Fig. 7). This molecule crystallizes as monoclinic $P2_1/n$ with

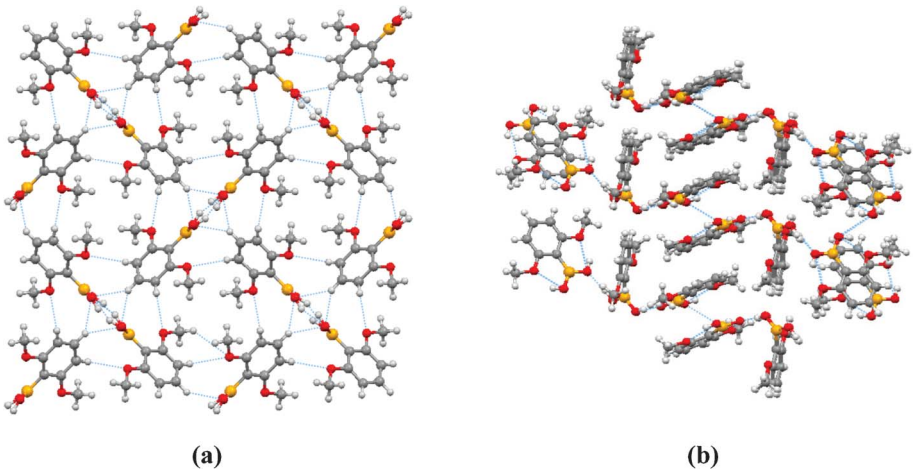


Fig. 4 a) The crystal packing along the [001] direction in (**4A**). b) The crystal packing along the [1$\bar{1}$0] direction in (**4B**).

one molecule in the asymmetric part of the unit cell. Again the boronic group is almost coplanar with the phenyl ring (the twist is 4.3°) and both hydrogen atoms at hydroxyl groups are in the *anti* conformation, which leads to intramolecular hydrogen bond formation. Despite the different bulkiness of the alkoxy groups, the O11···O6 and O12···O2 distances are very similar: 2.635(1) Å and 2.640(1) Å. The elongation in the latter case may be caused by a possible intermolecular interaction with another hydroxyl group of a molecule related by a center of inversion (the O···O distance is 2.911(1) Å). This might be the only significant intermolecular hydrogen bond interaction which contributes to the overall stability of the crystal structure. The other minor contributions again come from CH···C$^{\pi}$, CH···O or CH···B weak interactions.

Analysis of fingerprints based on the Hirshfeld surfaces

The ideal way to compare similar crystal structures is the analysis of interactions in the crystal lattice based on the Hirshfeld surfaces.[33] Internal (d_i) and external (d_e) distances between atoms serve to create a surface which can easily demonstrate differences between polymorphs and more generally the different packing motifs based on the fingerprints of selected interactions. The phenylboronic acid structures analyzed in this paper form dimers, ladders or even monomers. It is particularly interesting to link the type of the structural motif with a 2-D fingerprint plot based on the Hirshfeld surface analysis. Even disordered structures [H-disordered (**4A**), ethyl group disordered (**5A**)] were included in the investigations of the fingerprint plots, but these data should be treated with some care.

The comparison of the fingerprint plots for separate moieties present in the structures is presented in Fig. 8. It can be easily seen that, for the first three structures of phenyl boronic acid derivatives (see Fig. 8a–d), very sharp and symmetrical tails are formed. This results from strong intermolecular interactions between O–H···O atoms which are present in the dimers. The symmetrical shape of these plots also indicates that all oxygen atoms in the boronic groups are simultaneously donors and

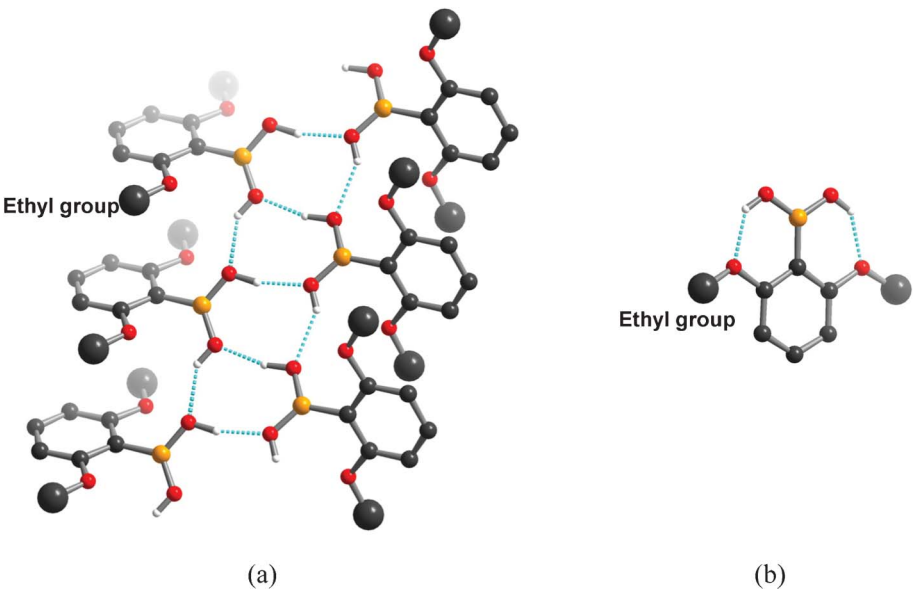


Fig. 5 Molecular structure of 2,6-diethoxyphenylboronic acid: a) Polymorph I (**5A**). b) Polymorph II (**5B**).

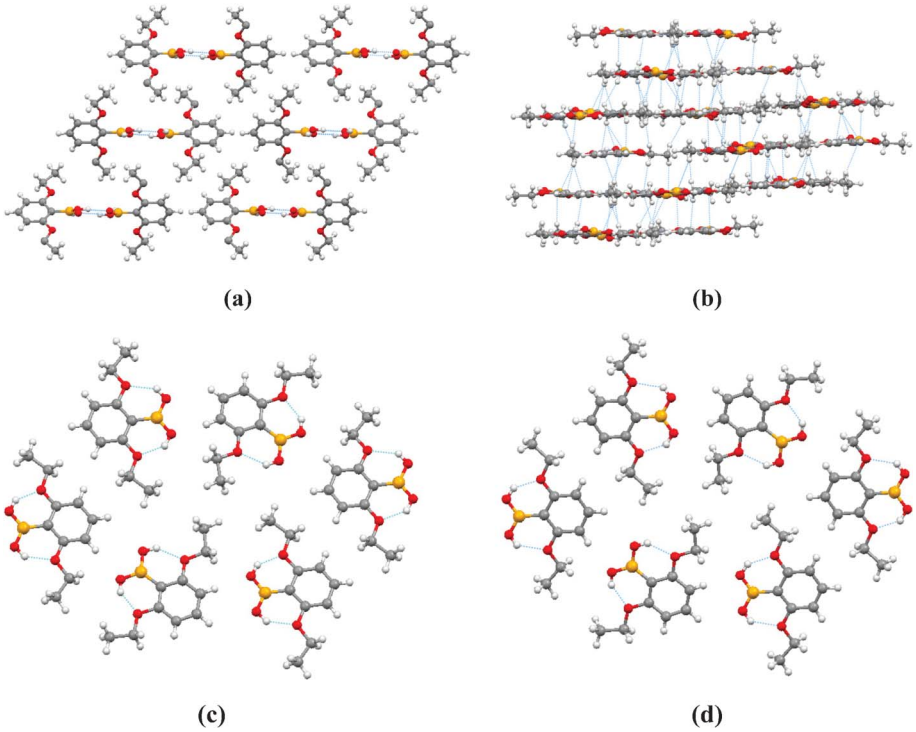


Fig. 6 a) The crystal packing along the [010] direction in (**5A**). b) The crystal packing along the [010] direction in (**5B**). c) 2-D layer in the (10$\bar{1}$) plane formed by molecules A and C. d) 2-D layer in the (10$\bar{1}$) plane formed by molecules B and D.

acceptors of hydrogen bonds. For the structure (**4A**) a somewhat strange but rather symmetrical fingerprint plot is observed (see Fig. 8e). The reason for this is the disorder of hydrogen atoms in hydroxyl groups, which is enforced by the special position in the P$\bar{4}$n2 space group. To get further insight into this fingerprint, we have artificially ordered all hydrogen atoms by doing a transformation to the *P*1 space group and by removing all redundant hydrogen atoms at hydroxyl groups. Fig. 8f presents the 2-D fingerprint for one of these tricky ordering cases. The picture now resembles the plots for (**1**), (**2**) or (**3**) with strong O–H contacts observed in the form of long and symmetrical tails. In this case (**4A**) the tails are slightly wider, and result from the polymeric hydrogen bonded structure where the O···H interactions are present along linearly-independent directions. For the next (**4B**) structure two 2-D fingerprints plots (Fig. 8g–h) can be obtained for each symmetry independent moiety in the crystal lattice. Here the plots are non-symmetrical with only one sharp tail representing a strong O–H···O contact present in the linear trimer. The asymmetrical nature of the plot is due to the fact that molecules in the trimer are either donors or acceptors of HB but cannot play both of these roles. For the structure (**5A**), due to disorder in the ethyl chain, two alternative fingerprint plots were prepared (i and j). In the plot (i) short H···H contacts can be observed (gray scattered spots for smaller d_e and d_i) which is due to intermolecular contact distances between ethyl chains which are too close, even in modeled ordered structure variant I. Both plots are symmetrical as all oxygen atoms of hydroxyl groups are simultaneously donors and acceptors of hydrogen bonds. It is noteworthy that these plots are rather similar to the one generated for the ordered structure (**4A**). Also in this case a broadening of the tails is clear. This is due to the formation of a ladder-type motif in the crystal lattice where the molecules form an infinite chain. Finally the last five 2-D plots (Fig. 8k–o) nicely illustrate the lack of any strong O···H interactions in the investigated structures for four molecules in (**5B**) and one molecule in (**6**), respectively. Thus these plots are characteristic of purely monomeric motifs in these types of structures.

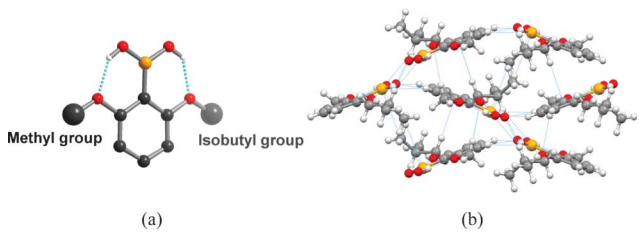


Fig. 7 a) Molecular structure of 2-isobutoxy-6-methoxyphenylboronic acid. b) Interactions in the crystal lattice - view along [001].

Calculations

What is the reason for the great variability of observed crystal structure types? The answer is given by the analysis of the interaction energies, most importantly in the case of hydrogen bonds.

The strength of the intramolecular hydrogen bond can be estimated using a simple homodesmotic reaction (see eqn (1) and (2)). This is a theoretical approach,[34] where on the right side of the reaction scheme one of the compounds contains two molecular fragments interacting with each other, whereas on its left side the fragments are separated. Benzene has been added to fulfill homodesmotic reaction requirements. This kind of theoretical approach has been extremely fruitful in the estimation

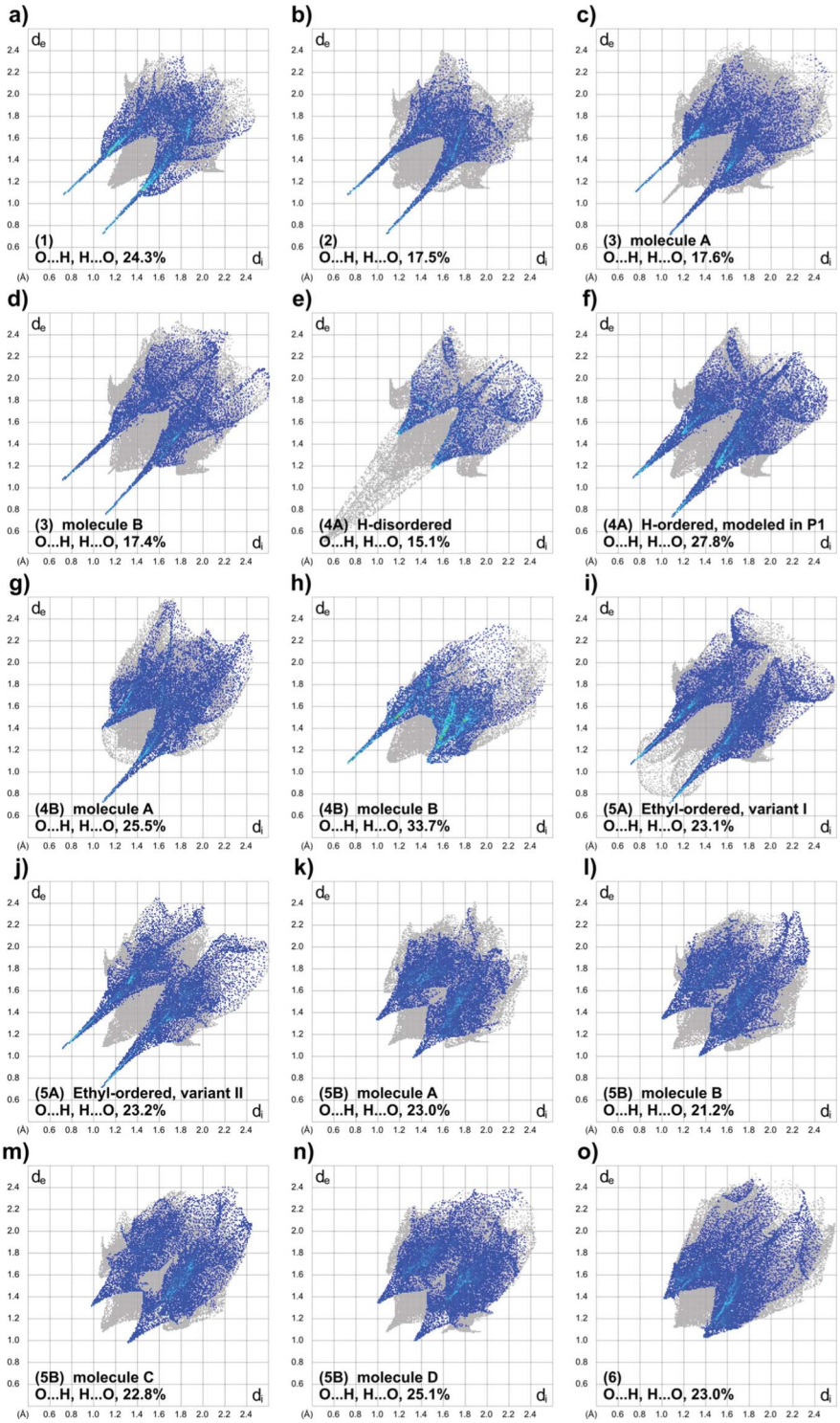
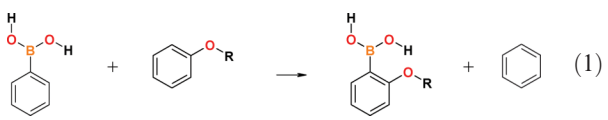


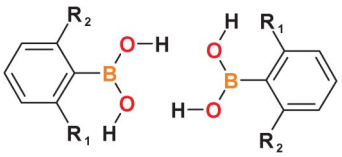
Fig. 8 Fingerprint plots visualizing d_e and d_i for O and H atoms (including reciprocal ones) generated for structures a) (**1**). b) (**2**). c) (**3**) molecule **A**. d) (**3**) molecule **B**. e) (**4A**) H-disordered molecule. f) (**4A**) H-ordered molecule modelled in *P*1 space group based on $P\bar{4}n2$ structure. g) (**4B**) molecule **A**. h) (**4B**) molecule **B**. i) (**5A**) ethyl-ordered variant I. j) (**5A**) ethyl-ordered variant II. k) (**5B**) molecule **A**. l) (**5B**) molecule **B**. m) (**5B**) molecule **C**. n) (**5B**) molecule **D**. o) (**6**). On each plot the percentage contribution of O and H distances is given.

of many subtle energetic effects in physical organic chemistry,[35] like aromatic stabilization energies[36] or substituent effect stabilization energies.[37] Most recently it was used to analyze substituent effects on intramolecular hydrogen bond or dative bond formation in imino- and aminomethylphenylboronic acids.[38]



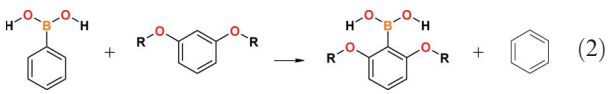
(1)

Table 3 The energies of intramolecular hydrogen bonds in phenylboronic dimers [given in kcal mol^{-1}]. The symmetry refers to the most stable conformation (optimal) at B3LYP/6−311+G** level. The values optimised at MP2/6−31+G* are given in brackets



System	Symm.	Energy	System	Symm.	Energy
R_1 = H, R_2 = H	C_i	8.6 [11.9][a]	R_1 = OC_2H_5, R_2 = H	C_{2h}	9.6 [14.8][b]
R_1 = OCH_3, R_2 = H	C_{2h}	9.6 [14.7][b]	R_1 = OCH_3, R_2 = OCH_3	C_i	8.5
			R_1 = OC_2H_5, R_2 = OC_2H_5	C_i	8.7

[a] 13.5 kcal mol^{-1} if not corrected for ZPE. [b] Value not corrected for ZPE.



(2)

The energy of the intramolecular hydrogen bond in 2-methoxy- or 2-ethoxyphenylboronic acid is virtually independent of the alkane chain length, being 3.8 kcal mol^{-1} in both cases (at B3LYP/6-311+G** level) or 5.4–5.7 kcal mol^{-1}, respectively (at MP2/6-31+G* level), based on eqn (1)). Interestingly, the introduction of a second methoxy- (or ethoxy-) group at the *ortho* position does not double the interaction energy value. Instead, it seems to cause a negative synergism. The resulting energy values are 5.6 at kcal mol^{-1} (at B3LYP/6-311+G** level) or 7.4 or 8.3 kcal mol^{-1} (at MP2/6-31+G* level), respectively, in 2,6-dimethoxy- or 2,6-diethoxyphenylboronic acid. This result might be attributed, at least in part, to repulsive steric interactions between the hydrogen atom of the hydroxyl group and hydrogen atom(s) in *ortho* position(s) in the benzene ring of phenylboronic acid. This effect leads to a twist of the boronic group in respect to the phenyl fragment and to the elongation of the C–B bond. If planarity of reference compounds is enforced then the estimated energy values rise up to 5.9 kcal mol^{-1} (at B3LYP/6-311+G** level) or 8.2 or 9.2 kcal mol^{-1} (at MP2/6-31+G* level) for 2,6-dimethoxy- or 2,6-diethoxyphenylboronic acid, respectively.[39] Based on these data it is safe to conclude that the energy of a single intramolecular hydrogen bond in *ortho*-alkoxyphenyl boronic acid is approximately 4-5 kcal mol^{-1} at this level of theory.

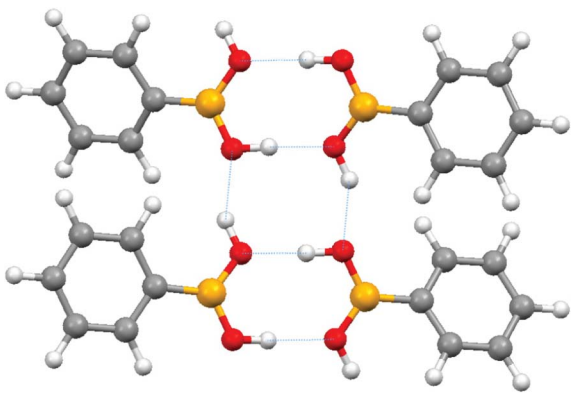


Fig. 9 The phenylboronic acid tetramer optimised from 2,6-di-methoxyphenylboronic acid, polymorph I.

The energies of intermolecular hydrogen bonds were calculated by comparison of the energies of dimers of phenylboronic acid, 2-methoxyphenylboronic acid, 2-ethoxyphenylboronic acid, 2,6-dimethoxyphenylboronic acid and 2,6-diethoxyphenylboronic acid with their fully-optimised monomeric fragments, taking into account basis-set superposition error (for details see the experimental part and the ESI†). The resulting energies are given in Table 3.

It is clear that the energies of hydrogen bonds vary over a very small range: 8.5–9.6 kcal mol^{-1} (at B3LYP/6-−311+G**) and do not depend on the length of the alkyl chain. The value of the interaction energy in the parent phenylboronic acid is consistent with the value estimated earlier by Rodriguez-Cuamatzi *et al.*,[40] and more recently by our group.[19] Smaller values of interaction energies in the case of di-*ortho*-substituted systems can be attributed to repulsive interactions between lone pairs at oxygens of the hydroxy groups involved in intermolecular hydrogen bonds and the oxygen of the *ortho*-alkoxy group. This is accompanied by lowering the formal symmetry from C_{2h} (*ortho*-alkoxyphenylboronic acid dimer) to C_i. So the intermolecular interaction energy is *ca.* 4–5 kcal mol^{-1} *per* hydrogen bond.

In the structure of phenylboronic acids one more important interaction has to be taken into account. The dimers interact

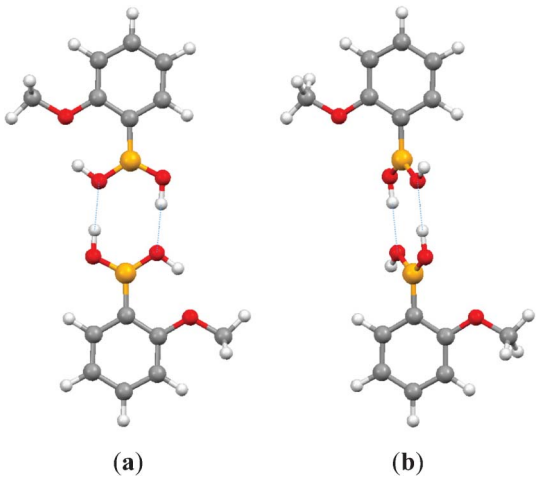


Fig. 10 Two kinds of *ortho*-methoxyphenylboronic acid dimers (a) with two intramolecular hydrogen bonds, (b) with two repulsive interactions between proximal oxygen atoms.

with the neighbouring dimeric units in the crystal lattice. One of the possibilities is that the dimer interacts with four other dimeric units which are twisted with respect to the given unit. This kind of motif has been observed in the structure of the parent phenylboronic acid[11,19,41] Another basic arrangement is noticed if a dimer interacts with another two dimers which are situated parallel to each other. Infinite ribbons are formed in this way. This kind of structure is observed *e.g.* in the case of 2,6-dimethoxyphenylboronic acid, polymorph I discussed in this report (see Fig. 3). Starting from the experimental data of this system we have optimised the tetramer having C_2 symmetry at the B3LYP/6−311+G** level. To avoid unwanted possible interactions involving methoxy groups, they were replaced by hydrogen atoms as shown in Fig. 9.

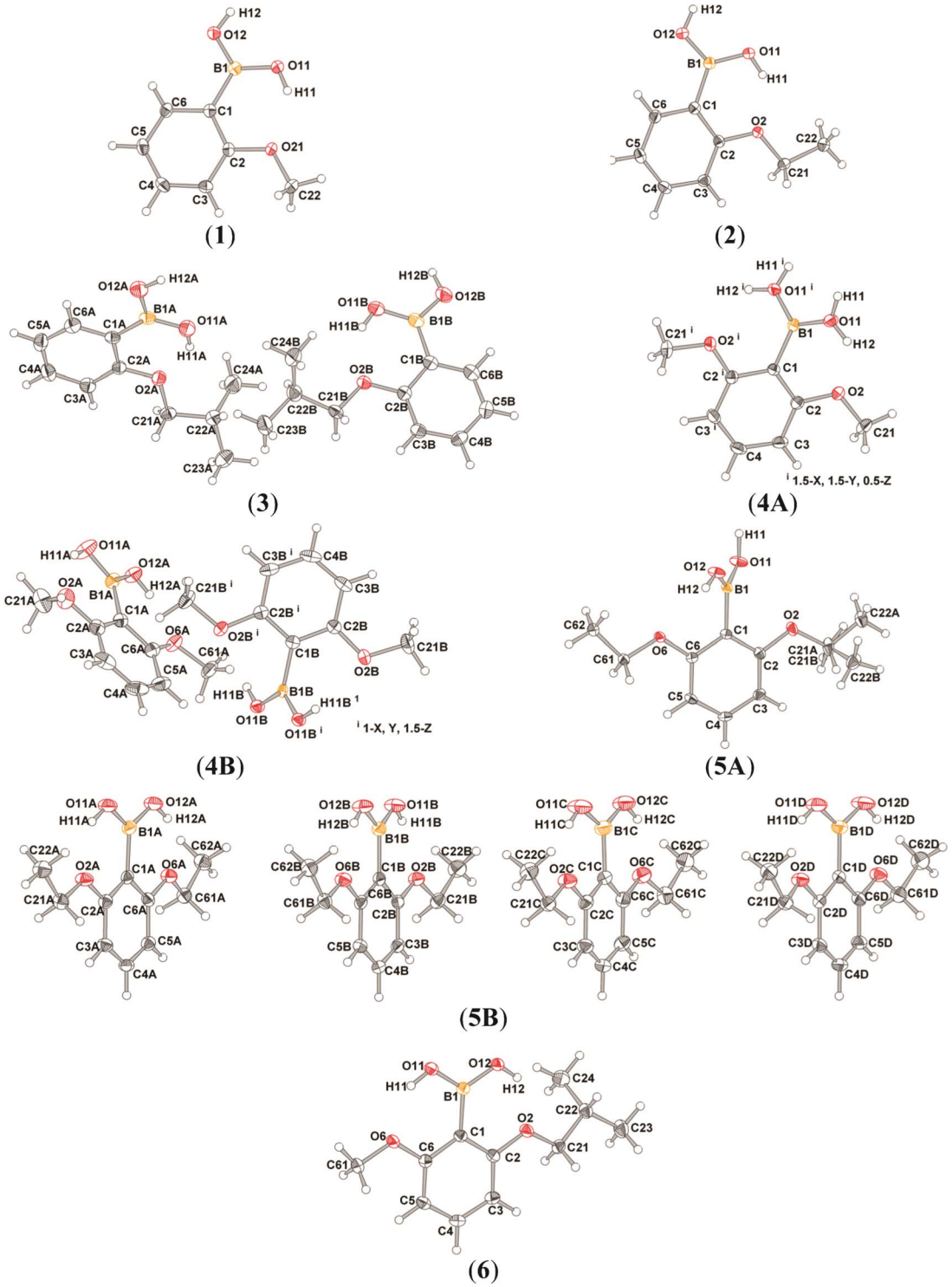


Fig. 11 Thermal ellipsoid plot of all moieties in structures (**1**), (**2**), (**3**), (**4A**), (**4B**), (**5A**), (**5B**) and (**6**). All plots are on the same scale and present ADPs at the 50% probability level.

Table 4 Crystal data and structure refinement for: 2-methoxyphenylboronic acid (**1**), 2-ethoxyphenylboronic acid (**2**) and 2-isobutoxyphenylboronic acid (**3**)

Compound	(**1**)	(**2**)	(**3**)
Empirical formula	$C_7H_9BO_3$	$C_8H_{11}BO_3$	$C_{10}H_{15}BO_3$
Formula weight	151.95	165.98	194.03
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$
Unit cell dimensions			
a [Å]	7.718 (1)	5.418 (1)	12.909(2)
b [Å]	14.454 (1)	14.812 (3)	12.984(2)
c [Å]	7.284 (1)	10.728 (2)	18.437(3)
β [°]	113.43 (1)	103.29 (3)	134.64(3)
Volume V [Å^3]	745.5 (1)	837.9 (3)	2198.9 (8)
Z [molecules/cell]	4	4	8
$D_{calculated}$ [Mg m^{-3}]	1.354	1.316	1.173
Absorption coefficient μ/mm^{-1}	0.102	0.097	0.083
θ range for data collection [°]	2.82–27.16	3.90–25.49	3.11–25.50
Limiting indices	$-9 <= h <= 9$	$-6 <= h <= 5$	$-15 <= h <= 15$
	$-18 <= k <= 18$	$-17 <= k <= 17$	$-13 <= k <= 15$
	$-9 <= l <= 9$	$-12 <= l <= 12$	$-22 <= l <= 22$
Reflections collected/unique	7983/1610	6271/1551	16 486/4084
Data/parameters	1610/136	1551/153	4084/374
Goodness of Fit	1.045	1.091	1.003
Final R index ($I > 2\sigma$)	0.0381	0.0341	0.0399
wR^2	0.1163	0.0908	0.0809
Largest diff. peak and hole [Å^{-3}]	0.253 and −0.323	0.217 and −0.275	0.189 and −0.167

Based on the energies of a tetramer and two neighbouring dimers (BSSE corrected) we have estimated the energy of interaction between the dimers as 8.5 kcal mol^{-1}, which equates to around 4 kcal mol^{-1} per hydrogen bond. Yet another estimation based on pairs of phenylboronic acids not involved in the dimers (left and right pair of the acids) led to the value of 18.1 kcal mol^{-1}, which gives 4.5 kcal mol^{-1} of energy *per* hydrogen bond forming the dimer. This is fully consistent with the data presented above.

Finally, it is instructive to compare the energies of two symmetric *ortho*-methoxy (or *ortho*-ethoxy) phenylboronic acid dimers, where one of them has hydroxyl groups at *ortho*-positions enabling or disabling intramolecular hydrogen bond formation, as shown in Fig. 10. Although the interaction energies within the dimers are comparable (8.3 kcal mol^{-1} *versus* 9.6 kcal mol^{-1}), the (**b**) unit is less stable by 13.9 kcal mol^{-1} than (**a**), both for *ortho*-methoxy or *ortho*-ethoxy phenylboronic acid dimers. The reason is not only the stabilization effect of two intramolecular hydrogen bonds in (**a**) (2 × 4–5 kcal mol^{-1}) but also two unfavourable repulsive interactions between lone pairs at proximal oxygen atoms in (**b**). To minimize the latter effect, the phenyl ring twists with respect to the boronic group by 50.9° (2-methoxyphenylboronic acid dimer) or 51.4° (2-ethoxyphenylboronic acid dimer, (**b**) type), exactly as in the structure of 2,6-dimethoxyphenylboronic acid, polymorph I, where the angle between the mean planes of the boronic group and the phenyl ring is 46.3°.

Table 5 Crystal data and structure refinement for: 2,6-dimethoxyphenylboronic acid, polymorph I (**4A**), 2,6-dimethoxyphenylboronic acid, polymorph II (**4B**), 2,6-diethoxyphenylboronic acid, polymorph I (**5A**), 2,6-diethoxyphenylboronic acid, polymorph II (**5B**) and 2-isobutoxy-6-methoxyphenylboronic acid (**6**)

Compound	(**4A**)	(**4B**)	(**5A**)	(**5B**)	(**6**)
Empirical formula	$C_8H_{11}BO_4$	$C_8H_{11}BO_4$	$C_{10}H_{15}BO_4$	$C_{10}H_{15}BO_4$	$C_{11}H_{17}BO_4$
Formula weight	181.98	181.98	210.03	210.03	224.06
Space group	$P\bar{4}n2$	$C2/c$	$P2_1/n$	$P2_1/c$	$P2_1/n$
Unit cell dimensions					
a [Å]	13.376 (1)	14.405(1)	15.188(2)	20.081(1)	7.571 (1)
b [Å]	13.376 (1)	8.471(1)	5.0173(5)	15.533(1)	14.670 (2)
c [Å]	5.033 (1)	22.271(1)	15.737(2)	15.096(1)	10.660 (2)
β [°]		98.17(1)	117.18(2)	109.72(1)	91.73(1)
Volume V [Å^3]	900.5(1)	2690.1(3)	1066.8(2)	4432.5(3)	1183.5(3)
Z [molecules/cell]	4	12	4	16	4
$D_{calculated}$ [Mg m^{-3}]	1.342	1.348	1.308	1.259	1.257
Absorption coefficient μ/mm^{-1}	0.105	0.105	0.098	0.094	0.093
θ range for data collection [°]	3.05–25.48	2.88–25.50	2.91–27.50	3.15–25.50	3.35–25.50
Limiting indices	$-16 <= h <= 15$	$-17 <= h <= 17$	$-19 <= h <= 17$ 0	$-21 <= h <= 24$	$-9 <= h <= 9$
	$-16 <= k <= 16$	$-10 <= k <= 10$	$<= k <= 6$ 0	$-18 <= k <= 18$	$-16 <= k <= 17$
	$-6 <= l <= 6$	$-26 <= l <= 26$	$<= l <= 20$	$-18 <= l <= 18$	$-12 <= l <= 12$
Reflections collected/unique	6907/847	10 471/2496	2447/2447	34 808/8231	8321/2182
Data/parameters	847/89	2496/245	2447/154	8231/781	2181/214
Goodness of Fit	1.017	0.991	1.102	1.036	1.106
Final R index (I > 2σ)	0.0232	0.0430	0.0426	0.0452	0.0415
wR^2	0.0565	0.0667	0.1372	0.0917	0.1102
Largest diff. peak and hole [Å^{-3}]	0.225 and −0.103	0.186 and −0.140	0.391 and −0.229	0.286 and −0.210	0.249 and −0.226

It is fair to note that the energy values of the most important interactions observed in the crystal lattices of *ortho*-alkoxyphenylboronic acids are very similar. All kinds of hydrogen bonds have energies around 4–5 kcal mol^{-1} *per* interaction. The repulsive interactions between oxygen lone pairs are significantly weaker and their influence is reduced by conformational adjustments of the molecules or their dimers in the crystal lattice. Therefore the competition between intra- and intermolecular interactions in the crystal lattices is very efficient and explains why many diverse structures may be formed. Even small structural effects, like *e.g.* change of solvent or thermodynamic conditions may easily influence the crystal packing.

Conclusions

In this report we have studied crystal structures of three 2-alkoxy-substituted phenylboronic acids and three 2,6-dialkoxy-substituted phenylboronic acids with methoxy, ethoxy or isobutoxy groups. The former species served as reference structures for the latter ones. The molecules in monosubstituted derivatives (**1**)–(**3**) interact with each other by intermolecular hydrogen bonds to form dimers, the most common motif of phenylboronic acids. The participating molecules are stabilized by intramolecular hydrogen bonds involving hydroxyl groups in the *anti* position and the alkoxy group in the proximal position. A much wider variety of possible types of interactions has been found in the disubstituted species. Two of them: 2,6-dimethoxyphenylboronic acid and 2,6-diethoxyphenylboronic acid form two polymorphs each. In three crystal structures we have found unprecedented packing, where the predominant motifs are monomers. In 2,6-diethoxyphenylboronic acid, polymorph II (**5B**) the molecular environment disables any other types of intermolecular interactions, except very weak ones. In the structure of 2,6-dimethoxyphenylboronic acid, polymorph II (**4B**), one of the independent molecules form monomers while the other one plays the role of a bridge which links two monomers. Yet another molecule: 2-isobutoxy-6-methoxyphenylboronic acid shows peculiar crystal packing with only monomers present in the crystal lattice. The remaining polymorphs of 2,6-dimethoxyphenylboronic acid or 2,6-diethoxyphenylboronic acid form dimers (**4A**) or ladders (**5A**) respectively – a rather uncommon molecular motif in phenylboronic acids, but already known. Different structural motifs present in the solid state were illustrated and described by analysis of the fingerprints based on the Hirshfeld surfaces. Four types of plots are associated with the presented structures. For the dimeric motif, the characteristic tails are long and sharp. For both the polymeric ladder or ribbon type of motifs, a slight broadening of these long tails is observed. For the purely monomeric structures there are only short and wide peaks. All of these three types of plots are symmetric. A non-symmetrical type of fingerprint plot has been found only for the trimer motif, where oxygen atoms of hydroxyl groups can play the role of hydrogen bond donor or acceptor.

The varieties of possible types of interactions were analyzed by interaction energies, which have been estimated to be very similar for both intra- and intermolecular hydrogen bonds in the studied systems. From this point of view they are highly competitive and molecules are "at the edge". Hence many diverse structures can be formed and small structural or environmental effects may efficiently influence the crystal packing. For this reason we expect that these kinds of systems will be commonly used as important building blocks to obtain new types of structures in supramolecular chemistry and/or crystal engineering. Their flexibility towards diverse interactions and variability towards various structure formation may also have an immense practical importance, as *ortho*- substituted aryl monoboronic acids are commonly used in sugar recognition.[42,43] Boron is often called "the least boring element" by its aficionados.[44] We expect that the same applies to *ortho*-alkoxyboronic (or di-*ortho*-alkoxyboronic acids) in the boronic acids family.

Experimental

Synthesis of 5

a) 1,3-Diethoxybenzene. To a mixture of 35.73 g (0.324 mol) of resorcinol, 4.20 g (0.013 mol) of TBAB and 28.50 g (0.710 mol) of NaOH in 250 ml of water, 105.90 g (0.972 mol) of ethyl bromide was added. The mixture was refluxed with stirring for 5 h. After cooling, the organic layer was separated, washed with 1 M aq. NaOH and finally several times with water to obtain neutral pH. Volatiles were evaporated under vacuum to obtain 32.84 g (0.20 mol, 61.7%) of crude 1,3-diethoxybenzene, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (m, 1H), 6.44 (m, 3H), 3.94 (q, 4H), 1.36 (t, 6H).

b) 2,6-Diethoxyphenylboronic acid (**5**). The reaction was carried out under an argon atmosphere. To a solution of 32.84 g (0.20 mol) of 1,3-diethoxybenzene in 170 ml of ether placed in 3-necked vessel equipped with CO_2/acetone bath, magnetic stirrer, dropping funnel and thermometer, 23.9 g (31 ml, 0.206 mol) of TMEDA was added. The mixture was cooled down to −20 °C. n-Butyllithium (10 M, 20 ml, 0.20 mol) was dropped-in while keeping the temperature below −10 °C. After 1 h of stirring at that temperature, the mixture was cooled down to −65 °C and 30.07 g of triethyl borate (35 ml, 0.206 mol) was dropped-in while keeping the temperature below −60 °C. The mixture was left overnight at RT, cooled down to −20 °C, and hydrolyzed with 1.5 M aq. H_2SO_4. The aqueous layer was extracted with 2 × 60 ml of ether. The organic phases were combined and about 3/4 of the volume of the solvent removed under reduced pressure. Water (50 ml) was added to the remaining liquid and evaporation was continued for an additional half an hour. The yellowish solid was filtered-off and dried in air to obtain 20.0 g (48.7%) of the product. ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 7.36 (m, 1H), 6.70 (m, 2H), 4.16 (q, 4H), 1.42 (t, 6H). ^{11}B NMR (128.3 MHz, acetone-d_6) δ (ppm): 35.0.

2-Methoxyphenylboronic acid (**1**), 2-ethoxyphenylboronic acid (**2**), 2-isobutoxyphenylboronic acid (**3**), 2,6-dimethoxyphenylboronic acid (**4**) and 2-isobutoxy-6-methoxyphenylboronic acid (**6**) were obtained from Aldrich.

Crystallization

The crystallizations were performed by slow evaporation from methanol, ethanol, methanol/water, ethanol/water or hexane solutions. Suitable crystals for X-ray diffraction experiment were obtained from ethanol solutions. In the case of 2,6-diethoxyphenylboronic acid, two distinct types of single crystals were obtained. They differed in morphology (*i.e.* long needle (**5A**) and prism (**5B**)) and were found to be two polymorphs. In turn, the

crystallization from hexane solution was successful only in one case *i.e.* 2,6-dimethoxyphenylboronic acid. Its structural analysis revealed a second polymorph of the acid (**4B**).

X-ray diffraction

The X-ray measurements of 2-methoxyphenylboronic acid (**1**), 2-ethoxyphenylboronic acid (**2**) 2-isobutoxyphenylboronic acid (**3**), 2,6-dimethoxyphenylboronic acid, polymorph I (**4A**), 2,6-dimethoxyphenylboronic acid, polymorph II (**4B**), 2,6-diethoxyphenylboronic acid, polymorph I (**5A**), 2,6-diethoxyphenylboronic acid, polymorph II (**5B**) and 2-isobutoxy-6-methoxyphenylboronic acid (**6**) were performed at 100 (2) K on a KUMA CCD k-axis diffractometer with graphite-monochromated Mo Kα radiation (0.71073 Å) (see Fig. 11 for thermal ellipsoid plots). The crystals of (**1**), (**2**), (**3**), (**4A**), (**4B**), (**5A**), (**5B**) and (**6**) were positioned 62.25 mm from the KM4CCD camera; 1920 frames were measured at 0.8° intervals on a counting time of 2s, 748 frames were measured at 0.8° intervals with a counting time of 25s, 748 frames were measured at 0.8° intervals with a counting time of 20s, 748 frames were measured at 0.8° intervals with a counting time of 25s, 1200 frames were measured at 0.5° intervals with a counting time of 25s, 1200 frames were measured at 0.5° intervals with a counting time of 15s, 856 frames were measured at 0.7° intervals with a counting time of 25s, and 664 frames were measured at 0.9° intervals with a counting time of 3s, respectively for (**1**)–(**6**). Data collection, cell refinement and data reduction were carried out with the KUMA Diffraction programs: CrysAlis CCD and CrysAlis RED.[45] The data were corrected for Lorentz and polarization effects, but no absorption correction was applied. The structure was solved by direct methods[46] and refined by using SHELXL.[47] The refinement was based on F^2 for all reflections except for those with very negative F^2. The weighted R factor, wR and all goodness-of-fit S values are based on F^2. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from a difference map and were refined isotropically. The atomic scattering factors were taken from the International Tables.[48] Crystal structure and structural refinement are specified in Tables 4–5. In the case of 2,6-dimethoxyphenylboronic acid, polymorph I (**4A**) the hydrogen atoms forming the dimers were disordered due to their position on a 2-fold axis. In the case of 2,6-diethoxyphenylboronic acid the crystals of (**5A**) were twinned by reticular pseudomerohedry with a twin obliquity of 2.29(1)°. During data reduction two twin components were included with the ratio yielding 0.49 : 0.51. After the final HKLF 5 refinement the twinning effect was included in the reflection file and the final HKLF 4 refinement based on the merged data were carried out. The structure of (**5A**) is disordered with one of the ethyl chains occupying two alternative sites with 50% occupancy each. A full list of bond lengths, bond angles and torsion angles is given in Tables 1–9 in the ESI.† Analysis of fingerprints based on the Hirshfeld surfaces was performed with the CrystalExplorer program.[49] The presenting the packing were generated with Mercury (ver. 2.3).[50] The other were prepared with use of Diamond program (ver. 2.1c).[51]

Calculations

All systems for estimation of intramolecular hydrogen bond energies in 2-methoxyphenylboronic acid, 2-ethoxyphenylboronic acid, 2,6-dimethoxyphenylboronic acid and 2,6-diethoxyphenylboronic acid as well as the intermolecular hydrogen bond energies in their homodimers, and the parent phenylboronic acid dimer, were initially optimised at MP2/6−31+G* level of theory[52] starting from the most stable conformers (see the ESI† for details). Due to convergence problems in the case of the latter systems (except for dimers of phenylboronic acid, 2-methoxyphenylboronic acid 2-ethoxyphenylboronic acid) all systems were also optimised at the B3LYP/6−311+G** level of theory. The structures so obtained corresponded to real minima on the potential energy surfaces as checked by frequency calculations at corresponding levels of theory MP2/6−31+G* or B3LYP/6−311+G**, respectively. The energy values (except two cases, see Table 3) were corrected for vibrational zero point energy correction (ZPE). Although the estimated values of hydrogen bond energies (corrected by basis-set superposition error (BSSE) in the case of intermolecular interactions) were slightly larger at MP2/6-31+G* as compared with B3LYP/6−311+G** level, their relative values fit each other almost perfectly. The correlation coefficient for the dependence between the energies estimated at two levels of theory is equal $R = 0.9886$ (see Fig. S1 and Fig. S2 in the ESI†).

Acknowledgements

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