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ortho-(Aminomethyl)phenylboronic acids – synthesis, structure and sugar receptor activity

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A series of *ortho*-(aminomethyl)phenylboronic acids was synthesized and their structures were determined by single-crystal X-ray diffraction. The structures are stabilized by the inter- and intramolecular hydrogen bonds. The sugar-binding ability of these compounds was evaluated for D-glucose, D-fructose and D-galactose by the competition assay with Alizarin Red S (ARS). The results indicate that the sugar binding ability and selectivity towards sugars depend on the substituents in amino group.

Keywords: boronic acids; Mannich bases; molecular recognition; sugar receptors; crystal structure

Introduction

Arylboronic acids are systems that are attracting increasing scientific interest due to their new applications in organic synthesis, catalysis, supramolecular chemistry, biology and medicine.[1] This interest is essentially stimulated by their extensive use in organic chemistry as chemical building blocks and/or intermediates. Their wide application in biochemistry and medicinal chemistry is worth mentioning, and more recently they have become relevant to the field of material science.[2] In organic synthesis they are predominantly applied for the Suzuki cross-coupling reaction[3] and Petasis synthesis of α-amino acids.[4] These and many other applications have been recently reviewed by Cuthbertson.[5] From the medicinal chemistry point of view, the phenylboronic acid derivatives are used in anticancer therapy as boron neutron capture therapy (BNCT)[6] or as chemotherapeutic agents,[7] antibiotics,[8] enzyme inhibitors[9] or for the treatment of tumors.[10] Their unique feature of forming reversible covalent complexes with sugars[11] has been applied in the design of new saccharide sensors,[12] particularly focused on the measure of the blood glucose level of diabetic patients. Following work on molecular recognition,[2] boronic acids have also recently been employed as promising building blocks in crystal engineering in order to achieve predictably organized crystal materials.[13]

The detection of biologically important sugars (D-glucose, D-fructose, D-galactose and others) is one of the challenges in medicine and industry. Especially important is glucose determination due to the relation of its level in the body with various diseases. The possibility of a fast, quantitative and non-invasive determination of glucose allows, in addition to the diagnostic importance, avoidance of the risk of complications caused by improper levels. Its industrial application is related mainly to the monitoring of fermentation processes and to the determination of the enantiomeric purity of synthetic drugs.

Chemical receptors create a possibility of designing a sensor for each sugar, including enantiomers. Boronic acids $RB(OH)_2$ are a very important group of sugar receptors due to the strong covalent binding of sugar molecules, high stability and low toxicity.

The action of boronic acids as sugar receptors is based on their ability of fast and reversible ester formation with 1,2- and 1,3-diols.[11] In 1959 Lorand and Edwards stated that cyclic *cis*-diols, i.e. compounds containing a system of hydroxyl group present in sugars, form more stable cyclic ester than chain- and trans-diols.[14] Owing to the possibility of formation of boronate anion in basic media, several equilibrium reactions are possible (Scheme 1).[15]

To standardize quantitative determination of interaction of boronic acids with sugars, Springsteen and Wang[16] introduced the term of overall binding constant in the receptor–boronic acid system (K_{eq}; Scheme 2).

Equilibrium constant values depend on the structure of a sugar, and the differences are the basis of selective sugar determination. Fluorescent receptors are the most important ones from the point of view of their applications. The fluorescent method of detection is fast (sub-millisecond response time is typical), cheap (low-cost lasers or even LED systems) and sensitive (typical concentration of 10^{-6} M).

A variety of boronic acids can be used as sugar receptors. The proper structure of the receptor molecule involves the presence of one or several $B(OH)_2$ groups, their spatial arrangement in relation to other functional groups allowing binding selectively specific

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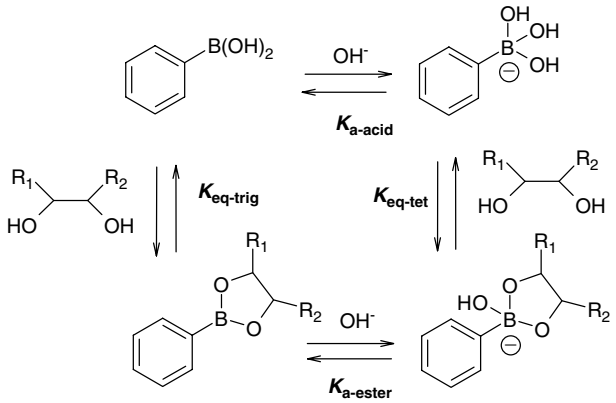
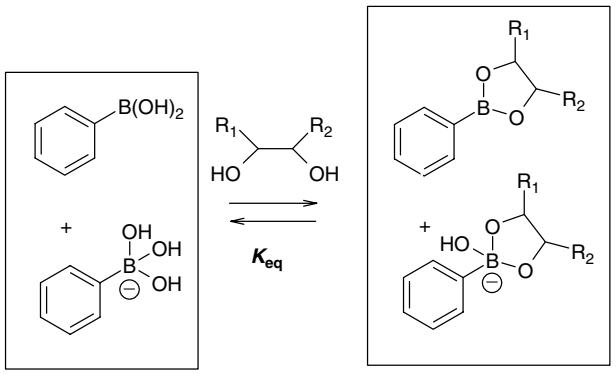
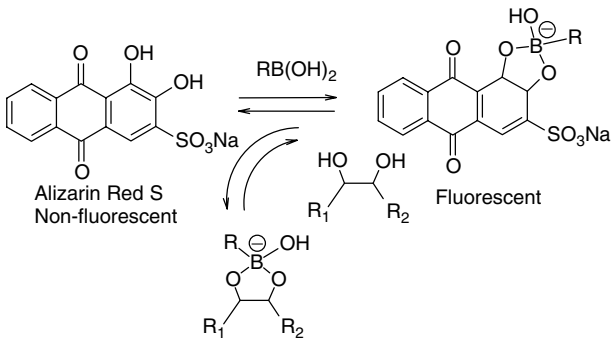


Scheme 1. Equilibrium in the boronic acid–diol system.



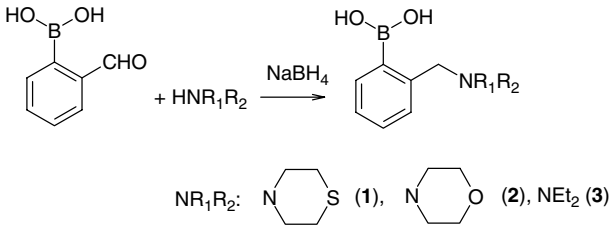
Scheme 2. Overall equilibrium in the boronic acid–diol system.



Scheme 3. Competitive binding of a boronic acid with ARS and a *cis*-diol.

sugar molecules and construction of chemical sensors sensitive to the particular sugar. The presence of fluorophores is not necessary to test their ability to bind sugars. The use of competition assays in which an equilibrium of two reactions allows determination of the association constant K_{eq} was described.[17] Among them, the use of Alizarin Red S (ARS) is the most common method (Scheme 3).[18]

This paper deals with synthesis and crystal structure determination of simple boronic acid receptors – *ortho*-aminomethylphenylboronic acids, followed by investigation of the influence of the amino group substituent on the sugar binding ability for the synthesized compounds.



Scheme 4. Synthesis of the compounds **1**–**3**.

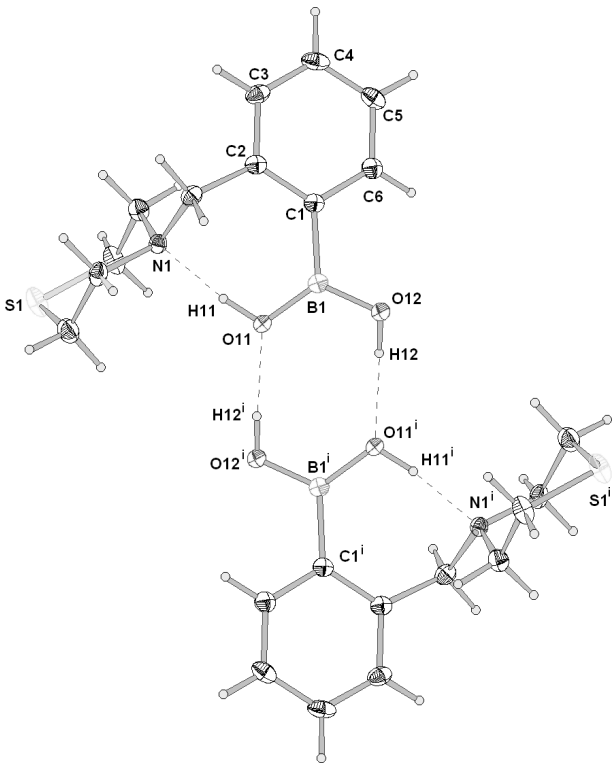


Figure 1. Dimeric interaction in **1**. The molecules are related by an inversion center (i: $1-x$, $1-y$, $2-z$), indicated by superscripts. The displacement ellipsoids are drawn at 50% probability level.

Results and Discussion

Synthesis

The compounds under investigation were synthesized by reductive amination reaction of *ortho*-formylphenylboronic acid with an appropriate secondary amine according to Scheme 4. This method was found to be the optimal way to obtain substituted aminomethyl derivatives of phenylboronic acid.[19]

Single crystal structures of 1 and 2

In the solid state, a dative bond N → B, essential for sugar receptor activity, is not observed at all. Instead, similarly to the recently synthesized *N*,*N*-diisopropyl-3-fluorobenzylamine-2-boronic acid and *N*,*N*-diisopropyl-5-trifluoromethylbenzylamine-2-boronic acid,[20] both structures **1** and **2** are stabilized by two kinds of hydrogen bonds, as shown in Figs 1 and 2. The asymmetric part of the unit cell is formed by one molecule in the case of the thiomorpholine derivative **1** and by three independent molecules (A, B and C) in the case of the morpholine derivative **2**.

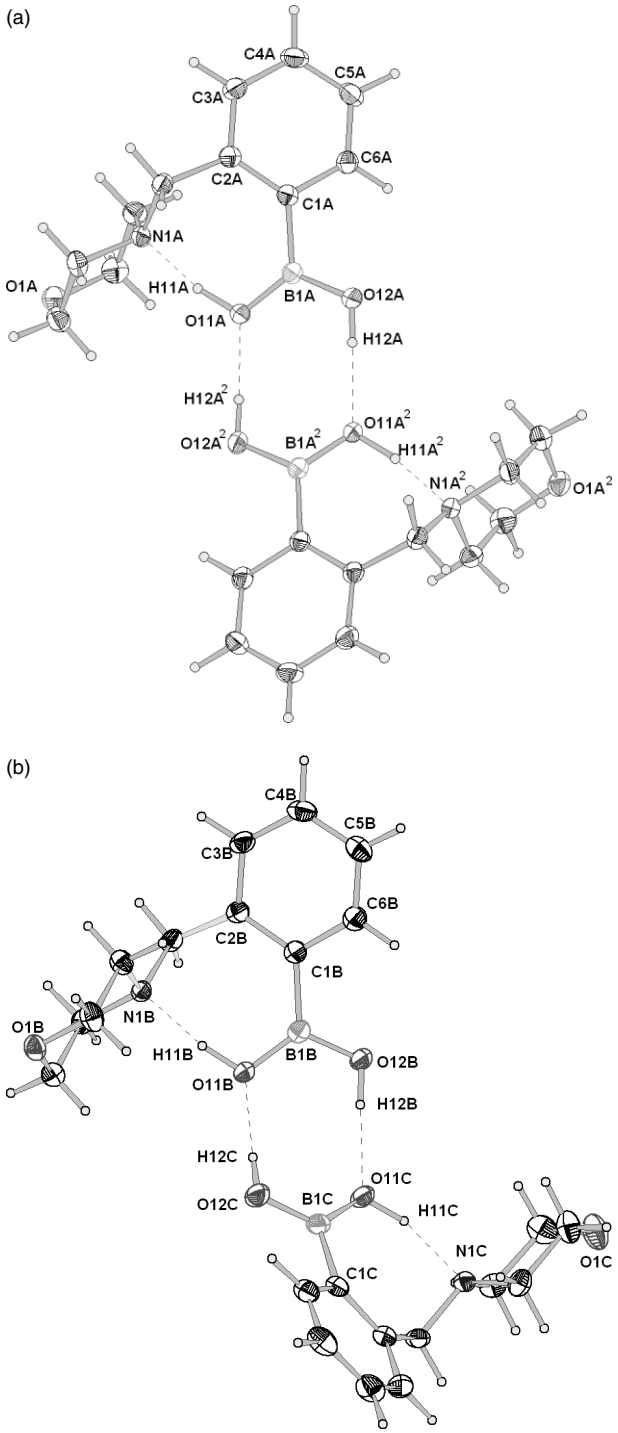


Figure 2. Dimeric interactions in **2** molecule: the dimer A–A (the molecules related by twofold axis; 2: $2-x, y, 1/2-z$), indicated by superscripts (a), the dimer B–C (b). The displacement ellipsoids are drawn at 50% probability level.

In both cases, one of the hydroxy groups at the boron atom forms an intramolecular hydrogen bond with a nitrogen atom of the morpholine or thiomorpholine fragment, respectively, whereas the other one is involved in an intermolecular hydrogen bond with a counter pairing molecule. This leads to the formation of a dimer, the basic structural motif observed in most crystal structures of boronic acids.[21,22] Despite the existing similarity between **1** and **2**, as might be expected, the latter system displays a more complicated structural pattern. In **1**, molecules form a centrosymmetric dimer, which implies that the phenyl rings are situated parallel to each other. The ring which was formed by hydrogen bonds is almost planar (with the mean deviation of atoms from the plane of 0.04 Å), whereas the distance between oxygen atoms, $d_{O\cdots O}$ is equal to 2.7223(11) Å. This is comparable with the distance in the parent phenylboronic acid where it is equal to 2.721 or 2.734 Å.[23,24] In order to maximize the intramolecular interaction between the OH group and the nitrogen atom at the thiomorpholine fragment, $B(OH)_2$ is twisted with respect to the phenyl ring by 24°. The O···N distance is equal to 2.5992(11) Å, and this is a little smaller than that observed in **2**. In contrast to this, none of the dimers observed in the morpholine derivative is centrosymmetric. Two molecules of A type (see Fig. 2) form a dimer and lie at the crystallographic twofold axis. The other two molecules (B and C, see Fig. 2) form another dimer, which is asymmetrical. In both cases, the molecules in the dimers are more distant than in **1**. In the former case, the O···O distance is equal to 2.7544(10) Å, whereas in the latter case it is equal to $d_{O\cdots O}$ = 2.7512(10) and 2.7408(10) Å. Unlike in **1**, the central rings in dimers formed by hydrogen bonds are folded (the mean deviation from the plane of the atoms is 0.088 Å for A-dimer or 0.1586 Å for B–C dimer), and the phenyl fragments are turned to each other by Θ = 29.3° or Θ = 80.7° in the dimers of A–A or B–C type, respectively. In the A–A type of the dimer the twist of the phenyl ring with respect to the $B(OH)_2$ group, Θ, is comparable to **1**. It is equal to 18.8°, which involves a similar O···N distance of 2.6109(10) Å, as in **1**. The B–C dimer demonstrates increased the flexibility of the molecular shape, and the twist angles Θ are equal to 18.6° or 27.9°, whereas the $d_{O\cdots N}$ distances are equal to 2.6063(10) and 2.6587(10) Å. This suggests that the molecule is flexible and therefore interactions in solution may appreciably stabilize the forms which enable sugar receptor activity.

Binding activity of boronic acids

The interaction of boronic acids **1**–**3** with monosaccharides was investigated by a competition binding assay with Alizarin Red S (ARS) as a reporter.[18] The example of fluorescence changes is presented in Fig. 3. In the first step, the ARS binds to the boronic acid and a significant increase of fluorescence intensity is observed [Fig. 3(a)]. When D-fructose is added to a mixture of ARS and receptor **1,** it causes a decrease of fluorescence intensity [Fig. 3(b)], which indicates that the complex between sugar and receptor is formed.

Using the competition assay, the interaction between receptor **1** and glucose and galactose was also investigated. The same method was applied to investigate the interaction of receptors **2** and **3** with fructose, glucose and galactose. Fluorescence spectra for the further investigated systems are similar.

Binding constants for the investigated systems were calculated according to the method described by Spingsteen and Wang.[25] The results are presented in Table 1.

All the investigated receptors bound the fructose in the strongest way, while the interactions with glucose were the weakest. The selectivity was the best for receptor **3**. Significant differences in sugar binding between receptors were observed: the compound with diethylamino group **3** bound all the investigated sugars in the strongest way. The differences between cyclic amines **1** and **2** were not so high.

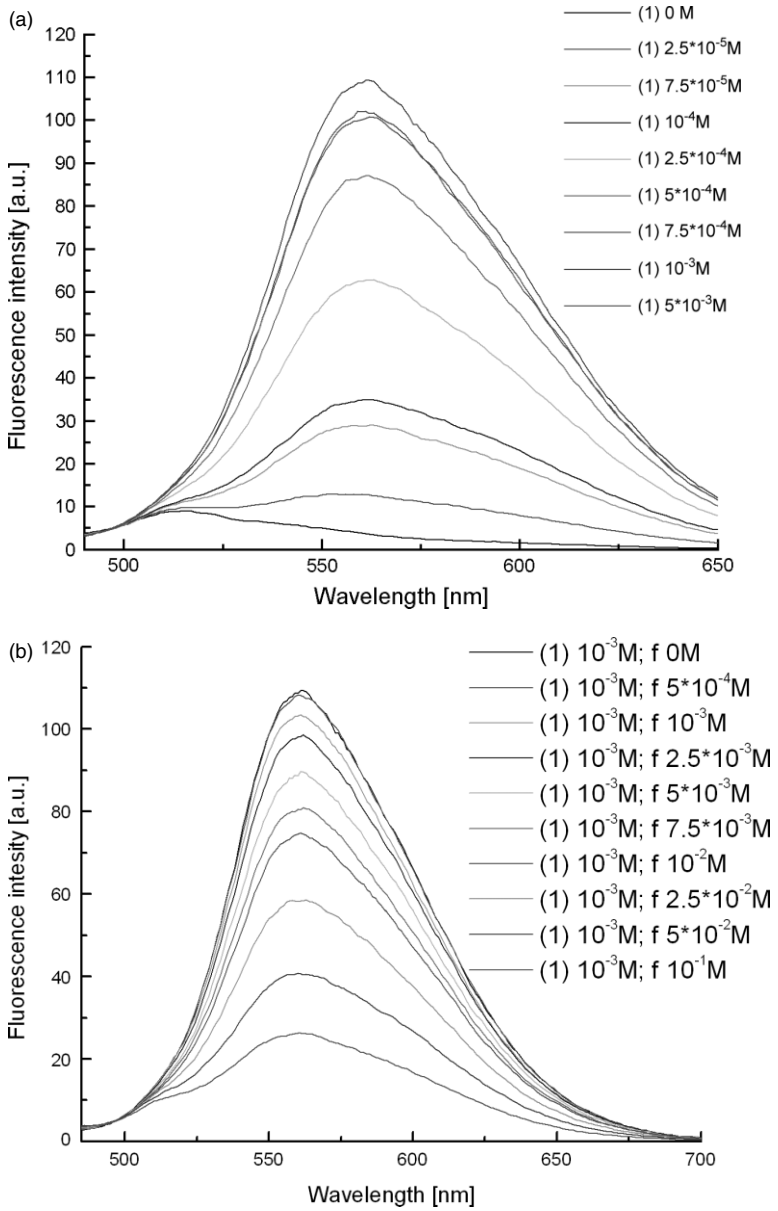


Figure 3. (a) Fluorescence spectral change of ARS (10^{-4} M) with different concentrations of receptor **1** in solution: methanol–0.1 M aqueous phosphate buffer pH = 7.4 (1 : 1, v/v), λ_{exc} = 455 nm; (b) fluorescence spectral change of ARS (10^{-4} M) and receptor **1** (10^{-3} M) with different concentrations of fructose (f) in solution: methanol–0.1 M aqueous phosphate buffer pH = 7.4 (1 : 1, v/v), λ_{exc} = 455 nm.

Experimental

Synthesis

o-*(Thiomorpholinomethyl)phenylboronic acid (**1**)*

Thiomorpholine (1.02 g, 6.6 mmol) was added to the solution of *o*-formylphenylboronic acid (0.98 g, 6.6 mmol) in methanol (30 ml). The reaction mixture was stirred at room temperature overnight under argon. Sodium borohydride (0.37 g, 9.8 mmol) was added slowly and the solution was stirred for an additional 2 h. After this time, the mixture was poured into iced-water (30 ml), 1 M HCl (13 ml) was added dropwise and left to stir for about 30 min. The oatmeal precipitate, which was formed, was removed by vacuum filtration to afford the desired product **1** (1.03 g, 66%).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.60 [4H, t, CH_2], 2.71 [4H, t, CH_2], 3.65 [2H, s, CH_2], 7.15 [1H, m, C_6H_4], 7.36 [2H, m, C_6H_4], 7.93 [1H, m, C_6H_4], 7.49 ppm [2H, s, OH]. ^{13}C{^{1}H} NMR (100.1 MHz, $CDCl_3$) δ: 27.4 [S-*C*H_2], 53.8 [N-*C*H_2], 64.8 [Ar-*C*H_2]; 126.3, 127.7, 130.2, 131.0, 136.5, 140.5 ppm [Ar*C*]. ^{11}B NMR (128.3 MHz, $CDCl_3$) δ: 30.0 ppm. Analysis calculated for $C_{11}H_{16}BNO_2S$: C 55.73, H 6.80, N 5.91; found: C 55.46, H 6.68, N 5.89.

o-*(Morpholinomethyl)phenylboronic acid (**2**)*

Morpholine (0.92 g, 6.6 mmol) was added to the solution of *o*-formylphenylboronic acid (0.98 g, 6.6 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature overnight under argon. Sodium borohydride (0.37 g, 9.8 mmol) was added slowly and the solution was stirred for an additional 2 h. After this time the mixture was poured into iced-water (30 ml), and 1 M HCl (15 ml) was added dropwise and left to stir for about 30 min. The solution was extracted with $CHCl_3$ (2 × 20 ml) and the organic

Table 1. Binding constants (K_{eq}) of ARS and sugars with receptors **1–3** in methanol–0.1 M aqueous phosphate buffer pH = 7.4 (1 : 1, v/v) solution

	$K_{eq}/(M^{-1})$		
Diol	**1**	**2**	**3**
Alizarin Red S	720 ± 40	2900 ± 120	7513 ± 550[a]
D-fructose	55 ± 4	120 ± 30	1073 ± 19[b]
D-galactose	5.7 ± 0, 8	100 ± 20	108 ± 10
D-glucose	2.4 ± 0, 9	13 ± 5	26 ± 4

[a] Ref. 26: 8110 ± 95 (in THF-phosphate buffer).
[b] Ref. 26: 1640 ± 330 (in THF-phosphate buffer).

layer was evaporated to about 25% of the volume. The remaining solution was treated with hexane, resulting in the formation of a white solid (0.72 g, 49%) of compound **2**.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.56 [4H, t, CH_2], 3.65 [2H, s, CH_2], 3.74 [4H, t, CH_2], 7.19 [1H, m, C_6H_4], 7.35 [2H, m, C_6H_4], 7.94 [1H, m, C_6H_4], 8.70 ppm [2H, s, OH]. ^{13}C{^{1}H} NMR (100.1 MHz, $CDCl_3$) δ: 52.3 [N-CH_2], 64.5 [Ar-CH_2], 66.4 [O-CH_2]; 127.7, 130.2, 13.7, 136.5, 140.1 ppm [Ar*C*]. ^{11}B NMR (128.3 MHz, $CDCl_3$) δ: 30.0 ppm. Analysis calculated for $C_{11}H_{16}BNO_3$: C 59.76, H 7.29, N 6.33; found: C 59.72, H 7.14, N 6.34.

o-*(Diethylaminomethyl)phenylboronic acid (**3**)*

Diethylamine (0.48 g, 6.6 mmol) was added to the solution of *o*-formylphenylboronic acid (0.98 g, 6.6 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature overnight under argon. Sodium borohydride (0.37 g, 9.8 mmol) was added slowly and the solution was stirred for an additional 2 h. After this time the mixture was poured into iced-water (30 ml), 1 M HCl (15 ml) was added dropwise and left to stir for about 30 min. The solution was extracted with $CHCl_3$ (3 × 15 ml) and the organic layer was evaporated to about 25% of the volume. The remaining solution was treated with hexanes resulting in the formation of a white solid. The resultant solid was recrystallized from warm hexane to give compound **3** as white, thin crystals (0.41 g, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07 [6H, t, CH_3], 2.60 [4H, q, CH_2], 3.70 [2H, s, CH_2], 7.19 [1H, m, C_6H_4], 7.33 [2H, m, C_6H_4], 7.93 [1H, m, C_6H_4], 8.83 ppm [2H, s, OH]. ^{13}C{^{1}H} NMR (100.1 MHz, $CDCl_3$) δ: 10.2 [CH_3], 45.0 [N-CH_2], 59.7 [Ar-CH_2]; 127.2, 130.1, 130.4, 136.4, 141.9 ppm [Ar*C*].

X-ray crystallography

The X-ray measurement of **1** and **2** was performed at 100(2) K on a KUMA CCD *k*-axis diffractometer with graphite-monochromated Mo K_α radiation (0.71073 Å). The crystals were positioned at 62.25 mm from the KM4CCD camera. In both cases 1875 frames were measured at 0.4° intervals with a counting time of 10 s. Data reduction and analysis were carried out using the Kuma Diffraction programs. The data were corrected for Lorentz and polarization effects but no absorption correction was applied. The structure was solved by direct methods[26] and refined by using SHELXL.[27] 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, whereas the H-atoms were found from the differential map of electron density and their positions were refined isotropically. The atomic scattering factors were taken from the International Tables.[28] **(1)** $C_{11}H_{16}BNO_2S$, colorless crystal, 0.3 × 0.2 × 0.2 mm, formula weight M = 237.12, orthorhombic, space group Pbca, a = 10.6653(3) Å, b = 12.3875(3) Å, c = 18.4214(5) Å, V = 2433.8(1) Å^3, Z = 8, D_x = 1.294 mg m^{-3}, $F(000)$ = 1008, absorption coefficient μ = 0.250 mm^{-1} The collected data range was 2.75 < Θ < 27.98 deg. (−14 ≤ h ≤ 14, −16 ≤ k ≤ 16, −24 ≤ l ≤ 23), 26 291 reflections collected, 2934 [R(int) = 0.0239] unique reflections, goodness-of-fit on F^2 = 0.934, final R = 0.0287, wR^2 = 0.0718 [for all 2297 $F_o > 4\sigma(F_o)$], R = 0.0388, wR^2 = 0.0739 (for all data), weight = $1/[\sigma^2(F_o^2) + (0.0453P)^2 + 0.53P]$ where $P = (F_o^2 + 2F_c^2)/3$; maximum and minimum difference electron densities were 0.335 and −0.278 e. Å^{-3}. **(2)** $C_{11}H_{16}BNO_3$, colorless crystal, 0.35 × 0.2 × 0.2 mm, formula weight M = 221.06, monoclinic, space group C2/c, a = 42.4537(11) Å, b = 9.5038(2) Å, c = 18.9198(5) Å, β = 112.14(1)°, V = 7070.9(3) Å^3, Z = 24, D_x = 1.246 mg m^{-3}, $F(000)$ = 2832, absorption coefficient μ = 0.088 mm^{-1} The collected data range was 2.65 < Θ < 28.00 deg. (−55 ≤ h ≤ 55, −12 ≤ k ≤ 12, −24 ≤ l ≤ 24), 40 053 reflections collected, 8437 [R(int) = 0.0236] unique reflections, goodness-of-fit on F^2 = 0.914, final R = 0.0333, wR^2 = 0.0776 [for all 5945 $F_o > 4\sigma(F_o)$], R = 0.0501, wR^2 = 0.0809 (for all data), weight = $1/[\sigma^2(F_o^2) + (0.0526P)^2 + 0.00P]$ where $P = (F_o^2 + 2F_c^2)/3$, maximum and minimum difference electron densities were 0.255 and −0.236 e Å^{-3}. Selected bond lengths, bond angles and torsion angles are given in Table 2, whereas parameters describing hydrogen bond interactions are given in Table 3.

Fluorescence measurements

A Jasco FP-750 fluorometer was used for fluorescence studies. Titrations were conducted in methanol −0.1 M aqueous phosphate buffer pH = 7.4 (1 : 1, v/v) solutions.

Chemicals

Saccharides were purchased from Fluka assay >98.0% (HPLC, sum of enantiomers). *o*-Formylphenylboronic acid was synthesized in the reaction of *o*-bromobenzaldehyde dimethylacetal with butyllithium and triethyl borate according to common method.[5] Other chemicals were purchased from Aldrich and used without further purification.

Table 2. Selected bond length (Å), bond angles (deg) and torsion angles (deg) in **1** and **2**. The values for three independent molecules in **2** are denoted by A, B and C

	1	**2A**	**2B**	**2C**
B(1)–O(11)	1.3659(14)	1.3603(13)	1.3599(13)	1.3563(13)
B(1)–O(12)	1.3590(14)	1.3575(12)	1.3632(13)	1.3716(14)
B(1)–C(1)	1.5859(15)	1.5910(15)	1.5843(15)	1.5797(15)
O(12)–B(1)–O(11)	119.5(1)	120.1(1)	119.5(1)	119.8(1)
O(12)–B(1)–C(1)	117.6(1)	116.3(1)	116.8(1)	117.7(1)
O(11)–B(1)–C(1)	122.8(1)	123.6(1)	123.6(1)	122.4(1)
O(12)–B(1)–C(1)–C(6)	22.6(1)	18.1(1)	−17.0(1)	−26.6(1)
O(11)–B(1)–C(1)–C(6)	−153.2(1)	−160.1(1)	159.3(1)	150.1(1)
O(12)–B(1)–C(1)–C(2)	−160.1(1)	−162.5(1)	163.8(1)	155.9(1)
O(11)–B(1)–C(1)–C(2)	24.2(2)	19.3(2)	−19.9(2)	−27.4(2)
B(1)–C(1)–C(2)–C(3)	−176.2(1)	−178.9(1)	178.0(1)	175.6(1)
B(1)–C(1)–C(2)–C(7)	7.0(2)	4.6(2)	−6.7(2)	−6.1(2)

Table 3. Selected parameters describing hydrogen bond interactions in **1** and **2**. The values for three independent molecules in **2** are denoted by A, B and C. The distances given in (Å), the angles given in degrees. The molecules of **1** are related in the dimer by an inversion center (i: $1-x, 1-y, 2-z$). In **2** the molecules of A type are related by twofold axes in the dimer (2: $2-x, y, 1/2-z$), whereas the molecules of B and C type form an asymetric dimer

	1	2A	2B	2C
O12···O11	2.7223(11)	2.7544(10)	2.7512(10)	2.7408(10)
H12···O11	1.90(2)	1.84(2)	1.85(1)	1.88(1)
O11···N1	2.5992(11)	2.6109(10)	2.6063(10)	2.6587(10)
H11···N1	1.70(2)	1.59(2)	1.62(1)	1.72(1)
O12–H12···O11	173(2)	178(1)	176(1)	175(1)
O11–H11···N1	168(2)	167(1)	168(1)	165(1)

Conclusions

ortho-(Aminomethyl)phenylboronic acids can be synthesized in high yield by reductive amination of *o*-formylphenylboronic acid. In the solid state, a dative bond N → B is not observed, while intramolecular hydrogen bond is formed. Competition assay with ARS allows easy determination of sugar binding activity of these compounds. The investigated compounds reveal differences in sugar binding and selectivity, depending on the substituents on nitrogen atom. This is promising for further systematic investigations of the influence of substituents both in amino group and benzene ring on sugar binding activity, which is in progress. The structures of two phenylboronic acids, determined by single crystal X-ray diffraction, show an importance of hydrogen bond interactions in the solid state, which on the one hand stabilize the molecules by an intramolecular OH···N interaction, and on the other lead to a dimer formation.

Supplementary material

Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 671 579 (**1**) and 671 580 (**2**). Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).

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