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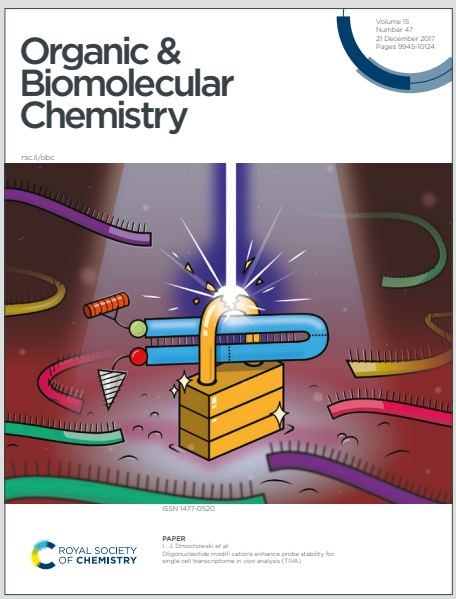

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Examination of pinanediol - boronic acid ester formation in aqueous media: relevance to the relative stability of trigonal and tetrahedral boronate esters

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Abstract

The interaction of pinanediol with 2-fluorophenylboronic and several other substituted phenylboronic acids was studied in 40% vol. aqueous acetonitrile by ^{1}H and ^{11}B NMR, potentiometric and spectrophotometric titrations at variable pH. The experimental results reveal a formation of a very stable trigonal ester ($K_{trig} \approx 2\times10^{4}$ M^{-1}) and a significantly less stable tetrahedral hydroxocomplex ($K_{tet} \approx 5\times10^{3}$ M^{-1}) in contrast to traditionally observed inverted order of stabilities $K_{trig} < K_{tet}$. Comparison of the crystal structure of trigonal ester isolated from aqueous acetonitrile with DFT simulated structure of the respective hydroxocomplex shows that the unusual order of stabilities $K_{trig} > K_{tet}$ is observed in spite of the existence of a usual strain release effect in the O-B-O angle considered responsible for the typically observed increased stability of the tetrahedral hydroxocomplex. A complementary study of stability of the six-membered cyclic boronate esters of chromotropic acid demonstrated the order $K_{trig} << K_{tet}$ although the strain was absent in these esters. Results for *m-, p*-substituted phenylboronic acids show that stability of both five- and six-membered trigonal esters formed with pinanediol and chromotropic acid, respectively, is insensitive to electronic effects but the electron accepting substituents stabilize the hydroxocomplexes. It follows from the whole set of results that K_{tet} can be much larger than K_{trig} in the absence of the strain, but with a sufficiently acidic diol, and that the presence of the strain does not necessarily make K_{tet} larger than K_{trig} for a low acidic diol with purely saturated hydrocarbon backbone. Thus, the electronic effects manifested in acidity of the diol appear to be more significant than the strain release effect in determining the K_{tet}/K_{trig} ratio.

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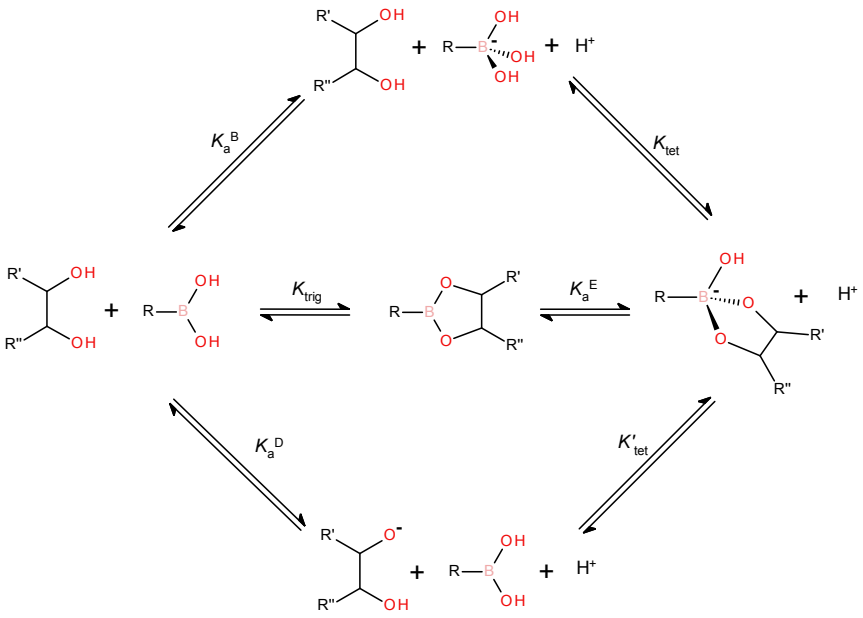
Introduction

The formation of boronic acid diol esters is important for molecular recognition of sugars,[1] self-assembly of stimuli responsive supramolecular structures [2,3,4,5] and as a type of bioorthogonal chemical reactions for bioconjugation.[6] The process is pH-dependent and generally is interpreted in terms of Scheme 1.[1,2] Typically $K_{tet} >> K_{trig}$ and therefore as a rule only formation of hydroxyboronate esters (hydroxocomplexes of boronic acid esters) shown at the right side of Scheme 1 is observed in water.



Scheme 1. The equilibria for boronate ester formation coupled with the equilibria for acid dissociation of the reaction components (water as the reaction component omitted)

The stability of boronate esters in neutral aqueous solutions is generally modest with observed formation constants (K_{obs}) rarely surpassing 10^3 M^{-1} for most often employed phenylboronic acid and common polyols such as sugars or sugar alcohols.[7,8] However the high stability under "physiological" conditions is very important especially for bioconjugation applications. Earlier the improved binding with K_{obs} above 10^4 M^{-1} was found with salicylhydroxamic acid as a ligand,[6b,9] and recently unprecedentedly high stability constants reaching the range 10^5-10^6 M^{-1} for boronate esters of pinanediol derivatives like **1** with *ortho*-substituted phenylboronic acids were reported. [10]

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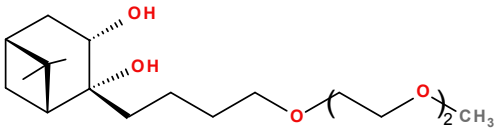
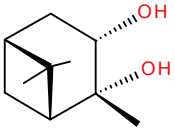
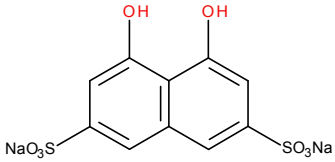


1



(−)-Pinanediol



Chromotropic acid

A traditional anionic tetrahedral hydroxyboronate ester structure was assigned to the complexes, but at the same time the stability of pinanediol esters decreased for boronic acids with electron acceptor substituents [10] in a contradiction with a large positive Hammett ρ constant reported for stability constants of hydroxyboronate esters with different diols.[8] This prompted us to undertake a deeper study of the thermodynamics of pinanediol – boronic acid interaction involving determination of equilibrium constants by three different techniques (potentiometric, UV-Vis and NMR titrations) in a wide range of pH together with X-Ray structural characterization of the esters isolated from the same reaction medium. The interaction with 2-fluorophenylboronic acid was studied in most details because it combined the high affinity with fast equilibration time.

It appeared that although the postulated tetrahedral boronate ester of pinanediol did exist in basic solutions, it was surprisingly less stable than the trigonal boronic acid ester ($K_{tet} < K_{trig}$) breaking seemingly universal tendency of higher stability of tetrahedral boronate esters usually attributed to the release of strain induced in the O-B-O angle of the trigonal five-membered cyclic ester.[1] However, the X-ray structures of two isolated pinanediol esters showed the existence of a usual strain, which in this case did not provide the expected large K_{tet}/K_{trig} ratio. It is worth noting that large reported K_{tet}/K_{trig} ratios [7,11,12] are obtained with polyols rather than with diols because only polyols give esters of sufficient stability allowing determination of both K_{trig} and K_{tet}. However polyols tend to form tridentate tetrahedral complexes [1,13] impossible for trigonal esters. This extra chelation evidently gives an extra stability to tetrahedral complexes in comparison with trigonal esters and contributes to high K_{tet}/K_{trig} ratios. In this respect pinanediol provides a unique example of an aliphatic diol which allows one a quantitative estimate of the K_{tet}/K_{trig} ratio free of the extra chelation effect.

To further discuss the role of strain in relative stabilities of trigonal and tetrahedral esters we measured also K_{tet}/K_{trig} ratios for a series of strain-free six-membered esters of chromotropic acid. A comparison of results obtained in this study with relevant literature data shows that the

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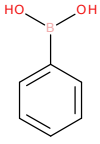
electronic effects manifested in the diol acidity are more important for the relative stability of trigonal and tetrahedral esters than the strain release effect.

An often discussed related phenomenon is the difference in acidities of a free boronic acid and its trigonal ester. It follows from the Scheme 1 that the ratio K_{tet}/K_{trig} must be equal to the ratio of the acidity constants K_a^E/K_a^B. This relationship is manifested in a shift in the observed pK_a of a boronic acid in the presence of added diol, which has been proved on many occasions experimentally.[1,7,11,12] At the molecular level the origin of both effects is the same because the same species are involved and throughout this paper only the interpretation of K_{tet}/K_{trig} ratio is discussed.

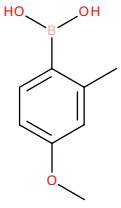
The relative stability of tetrahedral hydroxyboronate complexes and the respective trigonal cyclic boronic acid esters (K_{tet}/K_{trig} or K_a^E/K_a^B ratio) is one of the key aspects of thermodynamics of boronate ester formation. In a comprehensive review of different approaches to interpretation of this ratio it is concluded that analysis based on O-B-O angle contraction "is somewhat of a simplification", but it still plays the central role.[1a] In this paper we turn attention to the importance of diol acidity as a predominant factor.

Results and Discussion

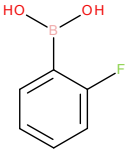
Reactions of pinanediol with boronic acids were studied under conditions similar to those employed in ref.10, namely in aqueous solutions containing 40% vol. MeCN at room temperature in the presence of 0.05 M appropriate buffer. Initially we attempted to study the interaction with 2-methyl-4-methoxyphenylboronic acid (MMPBA) which was reported as the most efficient reagent (K_{obs} = 3.3×10^5 M^{-1} for binding to **1**)[10], but the equilibration was very slow and therefore the most of the work was performed with 2-fluorophenylboronic acid (FPBA) possessing lower, but still a very large affinity (K_{obs} = 2.7×10^4 M^{-1} for binding to **1**)[10] and equilibrating within ca. 5 min.



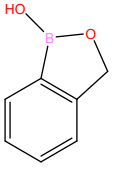
PBA



MMPBA



FPBA



benzoxaborole

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The signals in ^{1}H spectrum of both free pinanediol and its PBA (phenylboronic acid) ester were assigned by using the standard 2D technique (ESI, Figs. S1, S2). Figure 1 shows superposition of spectra of free components, pinanediol and FPBA (Fig.1a, b), and their 1:1 mixture, which is converted almost quantitatively into the ester (Fig.1c). Large complexation induced downfield shifts are observed for protons of pinanediol in positions 2 and 10 closest to the hydroxyl groups apparently due to the electron acceptor effect of the boronic acid. Also significant both upfield and downfield shifts are observed for distant protons in positions 5′ and 3′. All signals of aromatic protons of FPBA move slightly upfield. Noticeable shifts of sharp intense signals of methyl groups provide the most convenient way for the calculation of the observed association constant by integration of the signals of free and bound diol. From results shown in Fig. 1 we estimated $K_{obs} = 1.5\times10^4$ M^{-1} in a close agreement with the reported stability constant of FPBA ester of **1** under similar conditions (Ref. 10, see above). Similar spectral changes were observed in DMSO, where the disappearance of OH groups of both components is clearly seen (ESI, Fig.S3), and with other arylboronic acids in MeCN/water (ESI, Fig.S4).

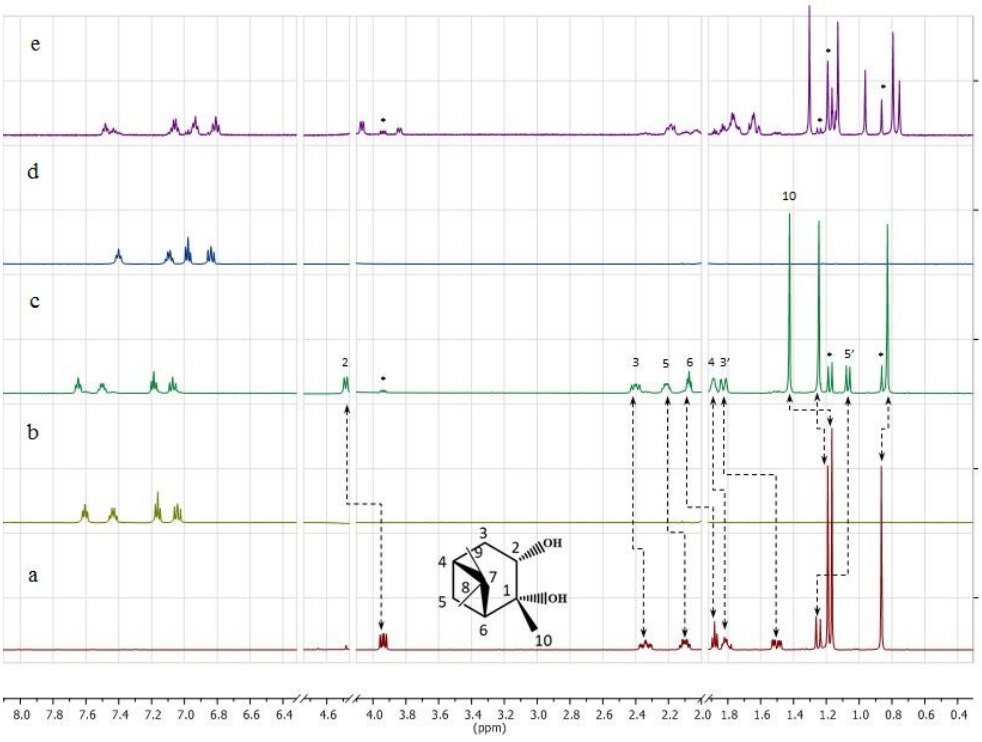

Figure 1. ^{1}H NMR spectra for free pinanediol (a), free FPBA (b), the equimolar mixture of 5 mM FPBA-pinanediol (c), FPBA in the presence of 1 equivalent of NaOH (d), the equimolar mixture of 5 mM FPBA-pinanediol in presence of 1 equivalent of NaOH (e) in 40% v/v MeCN-d_3/D_2O. Asterisks mark the signals of free pinanediol in spectra of FPBA-pinanediol mixtures.

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If the ester obtained under conditions of Fig. 1c would be the tetrahedral hydroxocomplex, the addition of base would not induce further changes in its NMR spectrum. However, as shown in Fig.1e, the addition of NaOH induces strong changes in the spectrum of the system. Signals of protons of free pinanediol become relatively more intense, signals which belong to the trigonal ester disappear completely and new signals apparently belonging to the tetrahedral hydroxocomplex are observed. Signals of aromatic protons move up-field and become close to those of the FPBA anion (Fig.1d). There are more signals than expected for a single reaction product indicating formation of a mixture of isomeric hydroxocomplexes. Since pinanediol is chiral and the formation of the tetrahedral boron by addition of hydroxide creates a new chiral center, a mixture of diastereomeric complexes can be produced. An estimate of K_{tet} by integration of signals in this spectrum was impossible due to the uncertainty in signal assignment, but a quantitative analysis of the ester formation in a basic solution turned out to be possible by using ^{11}B NMR results.

Figure 2a shows the ^{11}B NMR spectrum of free FPBA in a neutral solution with the signal at 27.95 ppm. In the presence of 1 molar equivalent of pinanediol two poorly resolved signals are observed attributable to the mixture of the trigonal ester with maximum at 29.28 ppm and a small amount of the free acid (Fig.2b). Addition of 1 molar equivalent of hydroxide to this mixture transforms the spectrum in that shown in Figure 2d with well resolved signals at 1.57 and 5.88 ppm. The signal at 1.57 ppm belongs to the free anion of FPBA (Fig. 2c). Integration of these signals gives K_{tet} = 4000 M^{-1}, approximately 4 times smaller than the given above K_{obs} in a neutral solution, which corresponds to K_{trig}.

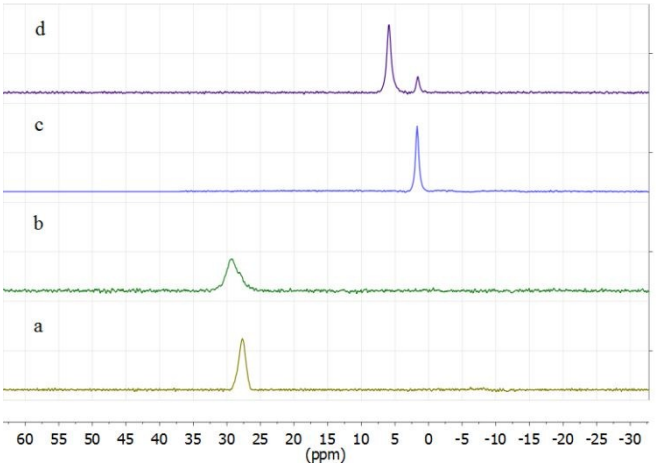

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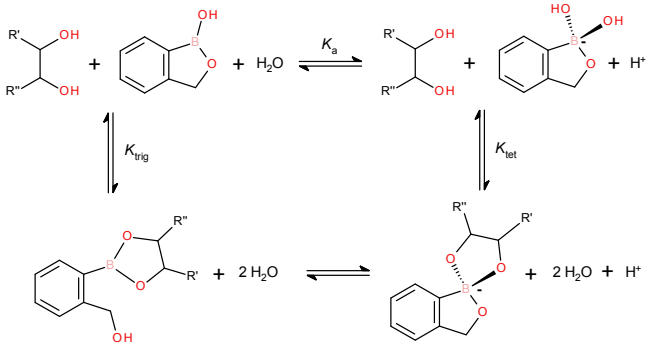
Figure 2. ^{11}B NMR spectra of free 5 mM FPBA (a), the equimolar mixture of FPBA-pinanediol without added base (b), FPBA in presence of 1 equivalent of NaOH (c), equimolar mixture of FPBA-pinanediol in the presence of 1 equivalent of NaOH (d) obtained in 40% v/v MeCN-d_3/D_2O.

In addition, monitoring the FPBA – pinanediol interaction by ^{19}F NMR, which showed well resolved peaks for free boronic acid and the respective ester both in neutral and basic solutions (ESI, Fig. S5), allowed us to estimate K_{trig} = 1.8×10^4 M^{-1} and K_{tet} = 4500 M^{-1} values in agreement with above results.

Additional useful information was obtained with benzoxaborole as a boronic acid. In this case formation of a trigonal ester seems impossible because this requires opening of a highly stable oxaborole ring,[14] Scheme 2.



Scheme 2. The equilibria for boronate ester formation with benzoxaborole.

Results shown in Figure 3a,b demonstrate that addition of benzoxaborole to pinanediol induces shifts of pinanediol proton signals resembling those observed with FPBA (cf. Fig.1a-c) indicating the ester formation. However, the integration of methyl signals gives in this case a small K_{trig} = 300 M^{-1} evidently due to unfavorable opening of the oxaborole ring manifested in the appearance of the signal at 4.7 ppm corresponding to *ortho*-CH_2OH group. [15] Formation of a trigonal nopoldiol (a pinanediol derivative) complex with benzoxaborol was reported recently by Di Wu et al. [16] Addition of hydroxide in this case leads to formation of the tetrahedral ester with a simple spectrum (Fig. 3c) and K_{tet}=1.4×10^4 M^{-1}. Studies by ^{11}B NMR confirm results obtained by ^{1}H NMR (ESI, Fig.S6).

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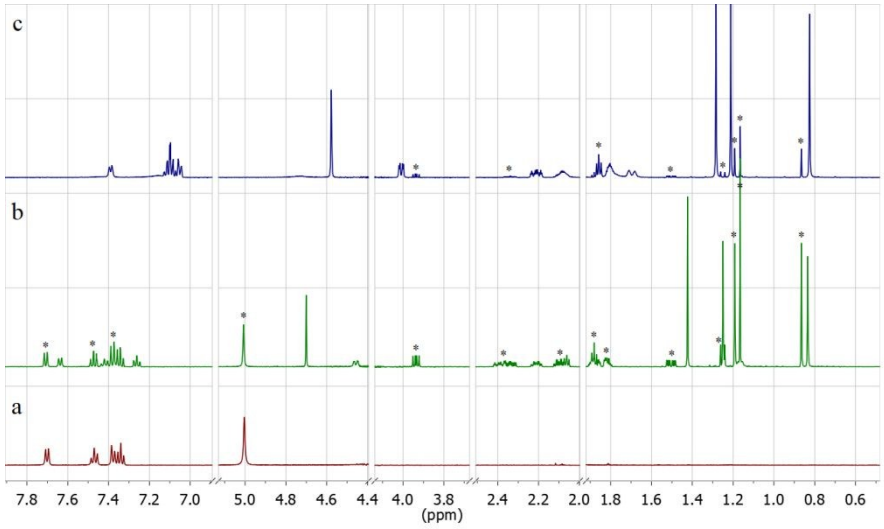

Figure 3. ^{1}H NMR spectra for free 5 mM benzoxaborole (a), the equimolar mixture of benzoxaborole-pinanediol without added base (b) and in presence of 1 equivalent of NaOH (c) in 40% v/v MeCN-d_3/D_2O. Asterisks mark the signals of free pinanediol and free benzoxaborole in spectra of benzoxaborole-pinanediol mixtures.

The predominant formation of the trigonal ester with FPBA was confirmed by the potentiometric titration. The interaction of a polyol with a boronic acid typically shifts the titration curve of the acid to lower pH values as a result of consumption of hydroxide ions for the formation of the tetrahedral hydroxocomplex. As one can see from Figure 4, the addition of pinanediol shifts the titration profile of FPBA in the opposite direction, to higher pH values, which reflects a higher stability of the neutral trigonal ester. To be sure that this was not an effect of a high content of organic co-solvent, the titration of FPBA in the same conditions was performed also with mannitol and a "normal" behavior was observed (Figure 4). Fitting of titration curves with Hyperquad program allowed us to calculate pK_a = 9.3 for FPBA, logK_{tet} = 3.93 for mannitol (lit.[17] logK_{tet} = 3.36 in water with PBA), $K_{trig} = 2.0\times10^4$ M^{-1} and $K_{tet} = 6.2\times10^3$ M^{-1} for pinanediol in agreement with NMR results. It is worth noting that an increased apparent pK_a 9.7 for the FPBA in the presence of pinanediol is observed in line with $K_{trig}/K_{tet} > 1$.

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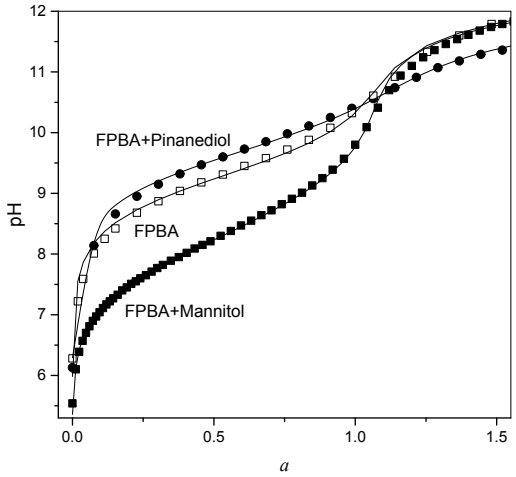

Figure 4. Potentiometric titration of FPBA (open squares) and 1:1 mixtures of FPBA with pinanediol (solid circles) or mannitol (solid squares) in 40% vol MeCN; *a* is the number of mole equivalents of NaOH. Solid lines are the fitting curves generated by HYPERQUAD.

Interaction of FPBA with pinanediol is accompanied by a noticeable change in the UV-Vis spectrum of the boronic acid, which allows one a fast and simple determination of the equilibrium constant under variable conditions. Figure 5 illustrates the course of the spectrophotometric titration of FPBA with pinanediol characterized by an increase in the absorbance in the range 260-290 nm. The results fit very well to the respective theoretical equation 1 (see Experimental Section), as shown in the inset in the Figure 5, with K_{obs} = $(1.9\pm0.1)\times10^4$ M^{-1}.

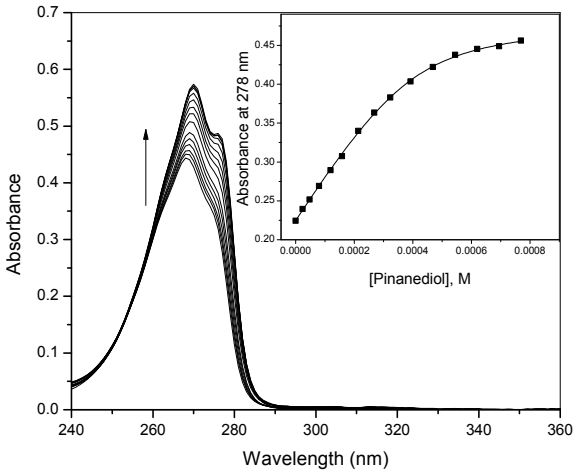

Figure 5. Spectrophotometric titration of 0.4 mM FPBA by pinanediol in 40% vol MeCN at pH 7. Arrow shows the direction of spectral changes induced by increased pinanediol concentrations. Inset shows the titration profile at a single wavelength and its fitting to the equation (1).

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Spectrophotometric titrations at variable pH showed that K_{obs} remained constant in the range of pH 5-8 and started to decrease at pH above 9 in agreement with lower stability of the tetrahedral anionic ester.

All values of K_{trig} and K_{tet} for pinanediol determined by different techniques in 40% vol MeCN are collected in Table 1.

Table 1. Stability constants (M^{-1}) of boronic acid esters of pinanediol in 40% vol aqueous MeCN; relative errors less or equal ±20%. Entries 5 through 13 show substituents in PBA.

	Boronic acid	K_{trig}	K_{tet}	**Method**
1	FPBA	2.0×10^4	6.2×10^3	Pot
2	FPBA	1.9×10^4		UV
3	FPBA	1.5×10^4	4.0×10^3	NMR
4	benzoxaborole	3.0×10^2	1.4×10^4	NMR
5	4-MeO	4.6×10^3		NMR
6	4-Cl	1.5×10^3		NMR
7	3-NO_2	2.4×10^3		NMR
8	H (PBA)	1.0×10^4		NMR
9	2-Me-4-MeO	2.1×10^5		NMR
10	3-CF_3	6.5×10^3		NMR
11	2-Formyl	1.3×10^4		UV
12	2-F-5-MeO	2.8×10^4		UV
13	2-CN	3.3×10^4		UV

Results with *meta*- and *para*-substituted phenylboronic acids are shown as a plot of logK_{trig} vs. the Hammett substituent constant in Fig. 6. It gives a small negative slope $\rho = -0.3\pm0.5$ not distinguishable from zero in limits of uncertainty. This observation qualitatively agrees with reported[18] results on stability of trigonal esters of substituted phenylboronic acids with 4-*tert*-butylcatechol in chloroform also shown in Fig.6 in Hammett coordinates with $\rho = -0.9\pm0.3$. Small values of ρ indicate a minor contribution of electronic effects in stability of trigonal esters.

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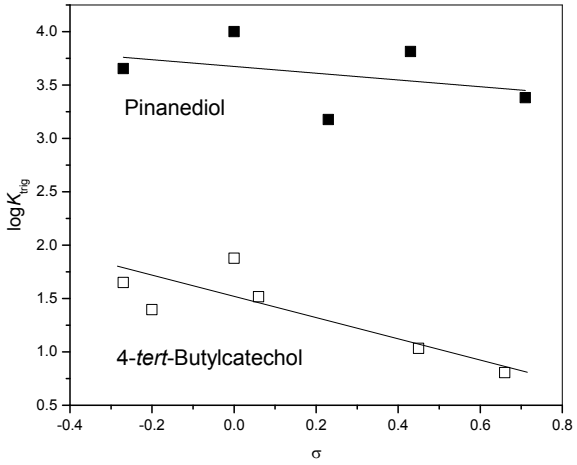

Figure 6. Hammett correlations of stability constants for trigonal esters of *meta*- and *para*-substituted phenylboronic acids with pinanediol in 40% aqueous MaCN (solid squares, this paper) and with 4-*tert*-butylcatechol in $CDCl_3$ (open squares, Ref. [18]).

Another conclusion which follows from inspection of Table 1 is a significant stabilizing effect of *ortho*-substituents in phenylboronic acid. Thus the incorporation of *ortho*- CHO, -F and –CN groups in PBA increases K_{trig} by factors 1.3, 1.5-2 and 3.3 respectively (cf. entries 8, 11, 1-3 and 13). Particularly strong effect is observed with *ortho*-Me group, which improves binding by the factor of 45 (entries 5 and 9). This stabilizing *ortho*-effect reported also in Ref. 10 is opposite to usually observed steric hindrance effects [19] and its origin is unclear. In a hope to observe a structural manifestation of this effect we prepared and characterized by single crystal X-ray diffraction the pinanediol esters with FPBA and MMPBA.

The esters were isolated from 40% vol aqueous MeCN under the same conditions which were used in equilibrium studies employing high concentrations of both components. Their crystal structures (Fig. 7, see also ESI, Figs. S15 and S16) confirm formation of neutral trigonal esters and closely resemble reported earlier crystal structure of the pinanediol ester of unsubstituted PBA.[20] In the FPBA ester **2** O-B-O angle is 114.72°, sum of the bond angles around B is 360.0°, the phenyl ring is practically coplanar to the dioxaborolane ring with the interplanar tilt angle 2.57° (the respective values for the PBA ester are 114.25°, 360° and 1.96°). In the MMPBA ester **3** the O-B-O angle is 113.07°, the sum of the bond angles around B is 360.0° and the tilt angle between the rings 8.85°. Structures of the dioxaborolane ring and the pinanediol moiety in all three esters are practically identical. So the structures of esters by themselves do not demonstrate any unusual features due to the presence of an *ortho*-substituent,

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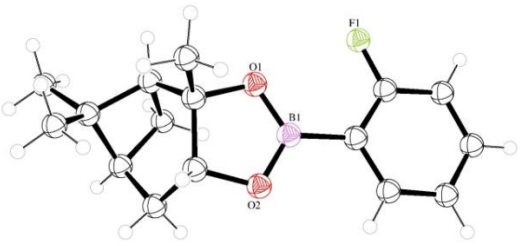
in particular 2-Me group. On the other hand, the presence of *ortho*-substituents in phenylboronic acids typically creates a large distortion in coplanarity between the aryl ring and the BO_2 plane inducing tilt angles up to 75°.[21] For instance, the presence of 2-Me group in 2-methyl-4-methoxycarbonylphenylboronic acid induces the tilt angle of 42.92°. [22] (ESI, Fig. S17). However in the ester **3** the tilt angle is only 8.85° and a plausible reason for this is the contraction of the O-B-O angle during formation of the ester, which moves the O3 atom further from the 2-Me group reducing the steric repulsion. We suppose therefore that the stabilizing effect of the 2-Me group is observed because the strain created in the cyclic ester is compensated by the release of the strain initially created by the *ortho*-methyl group in the free boronic acid.



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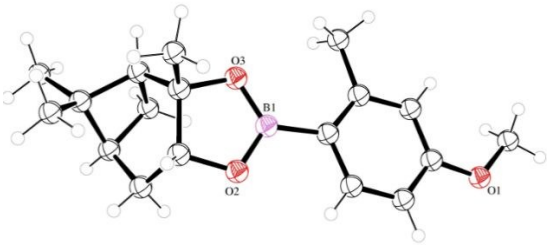

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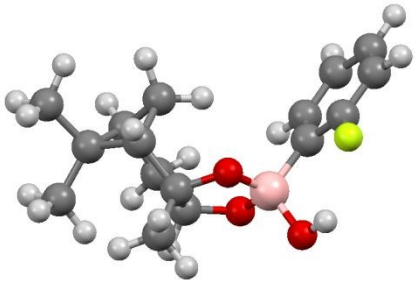

4

Figure 7. Crystal structures of pinanediol esters of FPBA (**2**) and MMPBA (**3**) and the simulated structure of the hydroxocomplex of FPBA ester (**4**). In structures **2** and **3** non-H atoms are represented by 50% probability ellipsoids and H atoms are shown as small circles of arbitrary size.

The very high stability of the trigonal esters of pinanediol can be attributed to well preorganized rigid structure of the diol. However, such preorganization must be equally favorable for stability of the respective tetrahedral complex and therefore cannot explain the "inverted" order $K_{tet} < K_{trig}$. The "normal" relationship $K_{tet} > K_{trig}$ is usually explained by the release of strain in the O-B-O angle of trigonal esters, too small for still sp^2 boron atom and more appropriate for sp^3 boron in tetrahedral esters. This concept fails in the case of pinanediol. Figure 7 shows the minimized structure of the hydroxo complex of FPBA **4** generated by adding OH^- anion to the

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respective neutral ester **2**. It has the O-B-O angle 104.81° within the range 102-105° found in crystal structures of many tetrahedral anionic esters, [23] while the O-B-O angle in **2** is close to the typical for trigonal esters value of 113°.[24] So the strain release occurs in pinanediol esters to the same degree as in esters of other diols. No intramolecular short contacts potentially producing repulsive interactions and reducing stability were identified in the calculated structure **4**. The closest to the boronic acid aromatic ring proton of a CH bond in the pinane backbone is at 3.48 Å from the ring centroid. Incidentally, one may note that reported O-B-O angles in tetrahedral complexes (102-105°)[23] are smaller than the tetrahedral angle 109.5° to the same extent as O-B-O angles of trigonal esters (112-114°)[24] are smaller than the trigonal angle 120° and this additionally makes questionable whether the strain release really contributes to higher stability of tetrahedral esters.

An indirect evidence in favor of the strain release hypothesis comes from studies of complexation with 1,3-diols. In six-membered cyclic esters formed with 1,3-diols the difference in stabilities between trigonal and tetrahedral esters should be small or even absent because they are expected to have unstrained O-B-O angles 120° and 109° respectively.[25a] The relevant experimental results are scarce, however. For 1,3-propanediol in water only tetrahedral hydroxocomplexes were reported with PBA and boric acid,[17] although an increase in pK_a of PBA in the presence of 1,3-propanediol indicative of greater stability of the trigonal ester was reported.[7] A very low stability of these esters may create some uncertainty in experimental measurements. For more stable esters of substituted aliphatic 1,3-diols such as 2,4-pentanediol indeed both trigonal and tetrahedral complexes of boric acid were detected with K_{trig} only 3-5 times smaller than K_{tet} and with inverted relationship $K_{trig} > K_{tet}$ for 2-methyl-2,4-pentanediol.[26]

In case of aromatic 1,3-diols formation of both trigonal and tetrahedral complexes was reported for chromotropic acid.[27] To get more details on this system we measured K_{trig} and K_{tet} for chromotropic acid and a series of substituted phenylboronic acids by spectrophotometric titrations as illustrated in Figures S7 and S8 (ESI). Chromotropic acid with pK_a^D = 5.33 is more acidic than PBA with pK_a^B = 8.8 and therefore the experimentally measured association constant (K_{obs}) at pH 7 corresponds to interaction of the deprotonated diol with neutral boronic acid i.e. $K_{obs} = K'_{tet}$ (Scheme 1). At pH 1 both boronic acid and diol are neutral species and $K_{obs} = K_{trig}$. The values of K_{obs} determined spectrophotometrically at pH 7 and pH 1 for several substituted phenylboronic acids are shown in Fig. 8 in coordinates of the Hammett equation.

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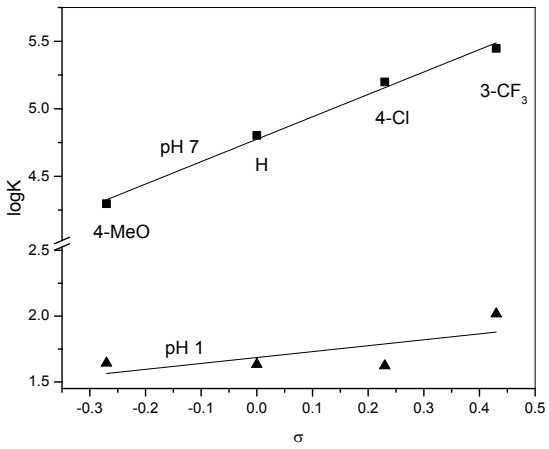
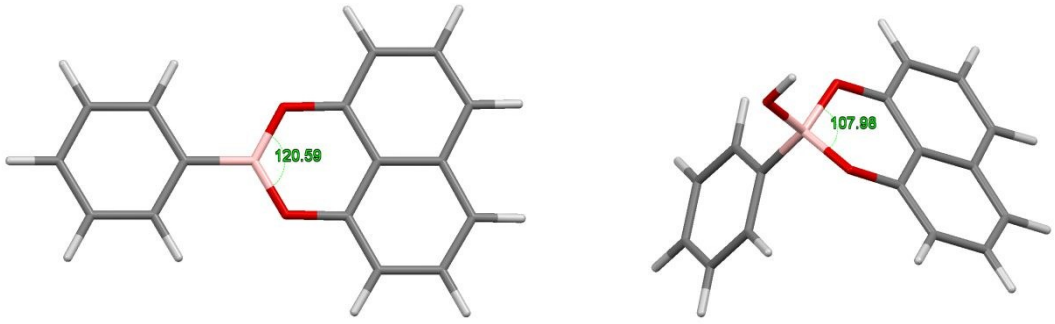


Figure 8. Hammett plots for formation constants of substituted phenylboronic acid esters with chromotropic acid at pH 7 (squares) and pH 1 (triangles).

The large positive slope ρ = 1.7±0.1 of the plot at pH 7 agrees with the formation of an anionic ester and a small slope ρ = 0.4±0.3 at pH 1 agrees with results for pinanediol confirming week electronic effects in the formation of the trigonal ester. For PBA logK'_{tet} = 4.80 and logK_{trig} =1.63. As follows from Scheme 1, log K_{tet} = log K'_{tet} + pK_a^B – pK_a^D = 8.2. Evidently, the stability of anionic tetrahedral complex with chromotropic acid is by several orders of magnitude higher than that of neutral trigonal ester, but this cannot be attributed to the strain effect because O-B-O angles in each ester (**5** and **6**, Fig. 9) allow the formation of unstrained cycles. Therefore the relationship K_{tet} >> K_{trig} in this case should be attributed to the stabilization of the negatively charged tetrahedral ester by the electron acceptor effect of the acidic aromatic 1,3-diol. Such acceptor effect is absent for aliphatic 1,3-diols and they form trigonal and tetrahedral esters of similar stability.[26]



5 **6**

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Figure 9. Simulated structures of PBA trigonal ester (**5**) and tetrahedral hydroxocomplex (**6**) with chromotropic acid.

It follows from the whole set of results that K_{trig} can be much smaller than K_{tet} in the absence of strain, but with a sufficiently acidic diol, and that the presence of strain does not make K_{tet} larger than K_{trig} with a low acidic diol incapable of formation of tridentate tetrahedral complexes. The role of tridentate binding can be seen e. g. from comparison of $\log(K_{tet}/K_{trig})$ = 5.2 for PBA and fructose, with predominantly tridentate binding, and $\log(K_{tet}/K_{trig})$ = 2.6 for PBA and glucose,[12] with predominantly bidentate binding. On the other hand, it is well known that stability of tetrahedral boronate hydroxocomplexes increases when both the boronic acid and diol become more acidic.[8,28] In quantitative terms $\log K_{tet}$ was found to correlate with pK_a of diol linearly with the slope -0.7 for PBA.[8] There are no quantitative data of this sort for trigonal esters, but semi-quantitative results of Roy and Brown [29] show that the increased acidity of diols is not favorable for K_{trig}. Thus comparing an aliphatic 1,2-diol with pK_a about 15 and a sugar with pK_a about 12 one should expect for the latter an increased by ca. 2 orders of magnitude K_{tet} but unchanged or even decreased K_{trig} and therefore a significantly increased K_{tet}/K_{trig} not related to the strain releasing effect. Further increase in diol acidity for catechol leads to even much higher K_{tet} value with no indication of detectable trigonal ester formation,[17] meaning very large K_{tet}/K_{trig} ratio.

Conclusions

Pinanediol forms highly stable trigonal boronic acid esters, but less stable tetrahedral hydroxocomplexes with arylboronic acids in aqueous media. Stability constants of trigonal esters with *meta* and *para*-substituted phenylboronic acids demonstrate the Hammett plot with small negative slope, not distinguishable from zero in limits of uncertainty. This indicates that the electronic effects of substituents in the boronic acid are insignificant for stability of trigonal esters.

An unusual feature of pinanediol complexation is a strongly enhanced stability with phenylboronic acids bearing the *ortho*-substituents particularly the methyl group. Comparison of crystal structures of the esters **2** and **3** of such acids with that of the ester of unsubstituted phenylboronic acid does not reveal any structural differences which might be responsible for this effect, but a possible explanation is that the strain induced by O-B-O angle contraction is

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compensated by the relieve of strain created by the *ortho*-methyl group in the free boronic acid.

Inspection of crystal structures **2** and **3** together with the simulated structure **4** of the hydroxocomplex of **2** reveals typical for 5-membered cyclic trigonal esters strain in O-B-O angle, which can be relieved by the addition of hydroxide anion to boron atom to the same degree as is characteristic for other five-membered boronate esters, but this does not lead to the "normal" relationship $K_{tet} > K_{trig}$. On the other hand, the relationship $K_{tet} >> K_{trig}$ is observed for strain free six-membered boronic acid esters with an aromatic 1,3-diol chromotropic acid due to stabilization of the anionic tetrahedral complex by the electron accepting diol. In general, results of this study and relevant literature data show that the stability of trigonal esters is essentially independent of electronic effects, but the stability of tetrahedral hydroxocomplexes increases significantly for more electron accepting diols. From this point of view the "inversion" in relative stabilities of the trigonal ester and the tetrahedral hydroxocomplex of pinanediol, $K_{tet} < K_{trig}$, is observed because this diol lacks the electron acceptor power for an extra stabilization of the tetrahedral hydroxocomplex.

Experimental section

General Experimental Methods. Commercially available pinanediol, substituted phenylboronic acids and components of buffer solutions (CHES, MOPS, MES) were used as supplied. All titration experiments were performed at 25°C and ionic strength 0.05 M created either by buffer or NaCl. All spectroscopic and potentiometric titrations were performed with completely equilibrated solutions incubated at 25°C for at least 1 h before starting the titration experiment and making at least 5 min intervals between additions of a titrant aliquots to the mixtures of pinanediol and the respective boronic acid.

Pinanediol ester of FPBA (2); (4S,6R,7aS)-2-(2-fluorophenyl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole. (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol (85 mg, 0.5 mmol) in 4 mL of acetonitrile was added to a solution of 2-fluorophenylboronic acid (70 mg, 0.50 mmol) in 6 mL of water, the mixture was stirred about 1 h at room temperature and the white precipitate was collected by filtration and washed with water to give the ester **2** (92 mg) in 67% yield; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.69 – 7.65 (m, 1H), 7.56 (dddd, J = 9.3, 7.6, 5.7, 1.9 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.16 (dd, J = 13.3, 4.6 Hz, 1H), 4.53 (dd, J = 8.7, 1.8 Hz, 1H), 2.38 (ddt, J = 13.6, 8.7, 2.3 Hz, 1H), 2.25 – 2.20 (m, 1H), 2.08 (t, J = 5.5 Hz, 1H), 1.90 (tt, J

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= 5.9, 3.0 Hz, 1H), 1.82 (ddd, *J* = 14.5, 3.3, 1.9 Hz, 1H), 1.43 (s, 3H), 1.27 (s, 3H), 1.06 (d, *J* = 10.8 Hz, 1H), 0.86 (s, 3H); **^{13}C**{1H} **NMR** (101 MHz, DMSO-d_6) δ 166.8 (d, J = 249.5 Hz), 137.0 (d, *J* = 8.0 Hz), 134.4 (d, *J* = 8.7 Hz), 124.6 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 23.4 Hz), 86.3, 77.6, 51.2, 38.2, 35.4, 28.7, 27.3, 26.5, 24.1; **^{11}B NMR** (160 MHz, DMSO- d_6) δ 28.94; **HRMS** (ESI-TOF) for $C_{16}H_{21}BFO_2$ $[M+H]^+$ *calcd.*: 275.1613; *found*: 275.1619; for $C_{16}H_{24}BFNO_2$ $[M+NH_4]^+$ *calc.*: 292.1879; *found*: 292.1889; **Anal.** for $C_{16}H_{20}BFO_2$ *calcd.*: C, 70.10; H, 7.35; *found*: C, 70.49; H, 7.47.

Pinanediol ester of MeMPBA (3); (3aR,4R,6R,7aS)-2-(4-methoxy-2-methylphenyl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole. (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol (85 mg, 0.50 mmol) in 4 mL of acetonitrile was added to a solution of 4-methoxy-2-methylphenylboronic acid (83 mg, 0.50 mmol) in 6 mL of water, the mixture was stirred about 1 h at room temperature and the white precipitate was collected by filtration and washed with water to give the ester **3** (118 mg) in 79% yield; **^{1}H NMR** (500 MHz, DMSO- d_6) δ 7.59 (d, *J* = 8.1 Hz, 1H), 6.74 (dd, *J* = 8.4, 5.4 Hz, 2H), 4.47 (dd, *J* = 8.7, 1.9 Hz, 1H), 3.75 (s, 3H), 2.43 (s, 3H), 2.41 – 2.35 (m, 1H), 2.23 – 2.18 (m, 1H), 2.06 (t, *J* = 5.5 Hz, 1H), 1.89 (tt, *J* = 5.8, 3.0 Hz, 1H), 1.81 (ddd, *J* = 14.5, 3.2, 2.0 Hz, 1H), 1.41 (s, 3H), 1.27 (s, 3H), 1.06 (d, *J* = 10.7 Hz, 1H), 0.86 (s, 3H); **^{13}C**{1H} **NMR** (75 MHz, DMSO- d_6) δ 161.9, 146.8, 138.0, 115.8, 110.9, 85.6, 77.3, 55.3, 51.4, 38.2, 35.8, 28.9, 27.3, 26.5, 24.1, 22.6; **^{11}B NMR** (160 MHz, DMSO-d_6) δ 30.00; **HRMS** (ESI-TOF) for $C_{18}H_{26}BO_3$ $[M+H]^+$ *calcd.*: 301.1970; *found*: 301.1938; **Anal.** for $C_{18}H_{25}BO_3$ *calcd.*: C, 72.02; H, 8.39; *found*: C, 72.61; H, 8.21.

Potentiometry. Potentiometric titrations were performed in a 25 mL thermostated cell kept under nitrogen at 25.0 ± 0.1 °C with 0.05 M NaCl as background electrolyte; 2.0 mM aqueous solutions (40% vol MeCN) of pinanediol in the presence of equimolar amount of FPBA were employed. The pK_a value of FPBA was determined independently by potentiometric titrations in the same conditions and was used as a fixed parameter in the fitting of results for the polyol−FPBA mixtures. Experimental details and procedure for the electrode calibration were the same as in ref.[30] The program Hyperquad 2008[31] was used to calculate all equilibrium constants.

^{11}B NMR measurements. ^{11}B NMR spectra were recorded in quartz tubes at 128.3 MHz with $Et_2O{\cdot}BF_3$ in $CDCl_3$ as the external standard using the instrumental parameters similar to those employed previously.[8] Spectra were obtained using a 4.9 μs and 90° pulse, 50 ms FID acquisition time, and 0 s acquisition delay. The sweep width was set to 87.2 ppm. Two thousand

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scans were taken for each sample. A solution of a boronic acid was prepared in D_2O and mixed with pinanediol solution in MeCN-d_3 and buffer or base solution in D_2O to obtain 5 – 10 mM total boronic acid in final 40% v/v MeCN-d_3/D_2O solution.

Spectrophotometric Titrations. To a 0.40 mM aqueous solution (40% vol MeCN) of FPBA in an appropriate 0.05 M buffer (MES, MOPS, or CHES in order of increasing pH from 5.5 to 9.5) portions of concentrated solution of pinanediol in the same buffer were added, and the mixture was incubated for 8 min after each addition before recording the spectrum. In an independent experiment, it was established that the system equilibrates completely during this incubation period. The observed equilibrium constants of the ester formation (K_{obs}) were calculated from the absorbance (A) vs concentration of pinanediol (L) profiles at several wavelengths by nonlinear least squares fitting to the equation (1), and the results were averaged. In equation (1), subscript T stands for total concentration, A_0 is the initial absorbance of the boronic acid B measured in the absence of L, and $\Delta\varepsilon$ is the difference in molar absorptivities between the ester and free boronic acid.

$$A = A_0 + 0.5\Delta\varepsilon\{[L]_T + [B]_T + 1/K_{obs} - (([L]_T + [B]_T + 1/K_{obs})^2 - 4[L]_T[B]_T)^{0.5}\} \quad (1)$$

Calculation method. Structural optimization was performed at DFT level using a dispersion corrected B3LYP-D3 functional [32] and 6-311+G(d,p)) basis set as is implemented in Gaussian 09.[33] At same time, frequency calculations were performed and no imaginary frequencies were detected in all cases. The calculations were performed in water with the Polarizable Continuum Model (PCM) method of solvation.[34]

X-ray Crystallography. Crystals of the boronate esters suitable for X-ray diffraction were grown by slow evaporation from water-acetonitrile solution. Crystals **2** and **3** were studied with Oxford Diffraction Gemini "A" diffractometer with a CCD area detector ($\lambda_{MoK\alpha}$ = 0.71073 Å, monochromator: graphite) source equipped with a sealed tube X-ray source. Unit cell constants were determined with a set of 15/3 narrow frame/runs (1° in ω) scans. A data sets consisted of 417/5 and 168/4 frames/runs of intensity data collected for **2** and **3** respectively with a frame width of 1° in ω, and a crystal-to-detector distance of 55.00 mm. The double pass method of scanning was used to exclude any noise. The collected frames were integrated by using an orientation matrix determined from the narrow frame scans.

CrysAlisPro and CrysAlis RED software packages[35] were used for data collection and data integration. Analysis of the integrated data did not reveal any decay. Final cell constants

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were determined by a global refinement of 3520 and 6510 reflections ($\theta < 26$ °) for **2** and **3** respectively. Collected data were corrected for absorbance by using Analytical numeric absorption correction[36] using a multifaceted crystal model based on expressions upon the Laue symmetry using equivalent reflections.

Structure solution and refinement were carried out with the SHELXS-2014 and SHELXL-2014 packages;[37] WinGX v2014.1 software was used to prepare material for publication.[38]

Full-matrix least-squares refinement was carried out by minimising $(Fo^2 - Fc^2)^2$. All non-hydrogen atoms were refined anisotropically.

The crystallographic data for **2** and **3** compounds reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1902042 and 1902043. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).

Conflicts of interest

There are no conflicts to declare.

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Electronic supplementary information (ESI) available: COSY spectra of (-)-pinanediol and their 1:1 mixture with phenylboronic acid, ^{1}H NMR spectra of pinanediol, 2-Fluorophenylboronic acid and their 1:1 mixture in DMSO, ^{11}B NMR spectra of mixtures of benzoxaborole and pinanediol, spectrophotometric titrations of chromotropic acid by phenylboronic acid at selected pH values as well as ^{1}H, ^{13}C and ^{11}B NMR spectra, crystallographic data and CIF files of newly synthesized compounds are presented.

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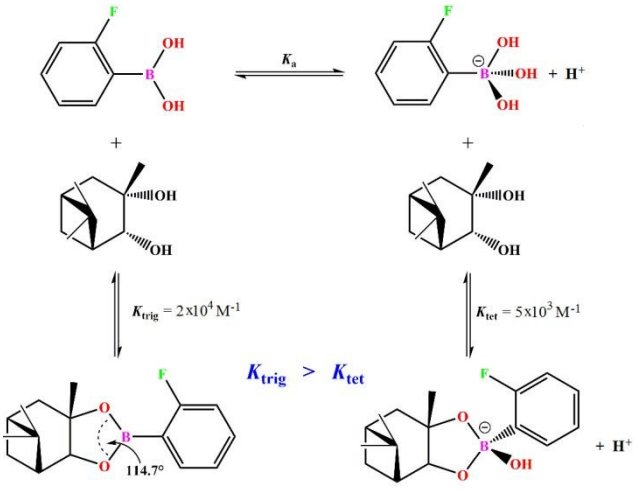

The "inverted" order of stabilities $K_{trig} > K_{tet}$ is observed for pinanediol boronate esters in spite of the existence of a usual strain release effect in the O-B-O angle of the cyclic diol ester.