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Substituent Effects and pH Profiles for Stability Constants of Arylboronic Acid Diol Esters

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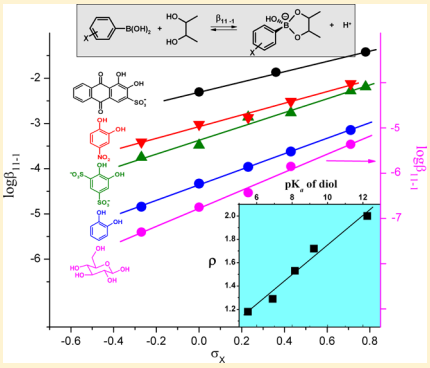
Supporting Information

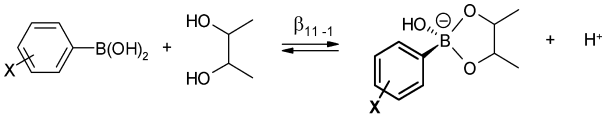
ABSTRACT: Stability constants of boronic acid diol esters in aqueous solution have been determined potentiometrically for a series of *meta*-, *para*-substituted phenylboronic acids and diols of variable acidity. The constants $\beta_{11\text{-}1}$ for reactions between neutral forms of reactants producing the anionic ester plus proton follow the Hammett equation with ρ depending on pK_a of diol and varying from 2.0 for glucose to 1.29 for 4-nitrocatechol. Observed stability constants (K_{obs}) measured by UV−vis and fluorometric titrations at variable pH for esters of 4,5-dihydroxy-1,3-benzenedisulfonate (Tiron) generally agree with those expected on the basis of $\beta_{11\text{-}1}$ values, but the direct fitting of K_{obs} vs pH profiles gives shifted pK_a values both for boronic acids and diol as a result of significant interdependence of fitting parameters. The subsituent effects on absorption and fluorescence spectra of Tiron arylboronate esters are characterized. The K_{obs} for Tiron determined by ^{11}B NMR titrations are approximately 1 order of magnitude smaller than those determined by UV−vis titrations under identical conditions. A general equation, which makes possible an estimate of $\beta_{11\text{-}1}$ for any pair of boronic acid and diol from their pK_a values, is proposed on the basis of established Brönsted-type correlation of Hammett parameters for $\beta_{11\text{-}1}$ with acidity of diols. The equation allows one to calculate stability constants expected only on basis of acid−base properties of the components, thus permitting more strict evaluation of contributions of additional factors such as steric or charge effects to the ester stability.



INTRODUCTION

Extensive use of boronic acid−diol complexation in recognition of saccharides and related molecules[1] stimulated studies aimed to deeper understanding of the nature of processes involved in boronate diol ester formation.[2−7] Most often, saccharide sensors are based on arylboronic acids and the principal reaction in aqueous solutions involves formation of a tetrahedral anionic ester as shown in Scheme 1.

Scheme 1



ArB(OH)$_2$ D(OH)$_2$ ArBOH(O)$_2$D$^-$

Surprisingly, a simple aspect of the substituent effect on the stability of arylboronic acid diol esters has not been analyzed yet quantitatively in spite of its importance for choosing an optimum boronic acid derivative. In recently reported studies with substituted arylboronic acids,[2a,3b,8] the quantitative analysis is limited to determination of the Hammett ρ constant for substituent effects on pK_a values, which confirm previously established correlations with ρ ranging from −2.0 to −2.1.[9] For this reason, our primary goal in this work was to determine ρ constants for diol ester formation with diols of variable acidity in order to obtain a comprehensive picture of electronic effects in this reaction. Structures of arylboronic acids and diols considered in this study are shown in Chart 1. The equilibrium constants were determined by potentiometric titrations, which give the most accurate values because measurements are performed in the absence of buffers and the fitting requires a minimum of adjustable parameters.

A more complex, but practically important, aspect is the interpretation of substituent effects on the observed equilibrium constants (K_{obs}) measured experimentally by, e.g., different types of spectroscopic titrations under given reaction conditions. These constants are pH-dependent because all components of the reaction, boronic acid, diol, and ester undergo acid dissociation processes. A serious concern was expressed regarding consistency of experimentally obtained and theoretically predicted pH profiles of observed equilibrium constants,[2a] and this prompted us to analyze this aspect in more details. We chose for this study as a model reaction the ester formation of substituted boronic acids with Tiron, a fluorescent diol freely soluble in water, which allows one determination of

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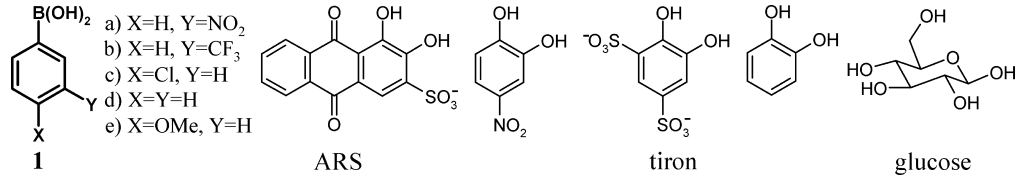
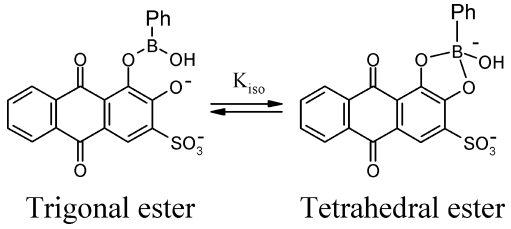
Chart 1



equilibrium constants both by spectrophotomery and fluorometry, two most popular techniques for study of boronic acid–diol equilibria and for development of optical saccharide sensors. The K_{obs} values were determined by both techniques and additionally by ^{11}B NMR with three boronic acids **1a**, **1d**, and **1e** in a wide interval of pH and were compared with those following from potentiometry.

These results allowed us to address another point of concern:[2a] the consistency of equilibrium constants determined by different experimental techniques. In principal, some variation in K_{obs} determined by different methods may be expected due to inevitable different systematic errors and often different experimental conditions employed for various techniques, but a strong discrepancy in K_{obs} found by different methods may indicate an erroneous reaction mechanism. It is worth noting in this respect that recently a strong discrepancy between equilibrium constants for ester formation of phenylboronic acid with alizarin red S (ARS) determined by fluorescence and ^{11}B NMR titrations was reported, and this led the authors to conclusion that the tetrahedral form of the ester in fact is a minor component coexisting in equilibrium with the major trigonal form, as shown in Scheme 2.[6]

Scheme 2



The results presented below demonstrate that pH profiles of K_{obs} determined by UV–vis and fluorometric titrations do show noticeable deviations from those predicted from potentiometric data, but nevertheless the equilibrium constants $\beta_{11\text{-}1}$ for the reaction in Scheme 1 calculated from spectroscopic results with independently determined pK_a values of diol and boronic acid agree very well with those determined potentiometrically. On the other hand, the values found from ^{11}B NMR titrations show significant deviations from those determined by other methods. Finally, a general equation, which allows one to estimate the $\beta_{11\text{-}1}$ values from pK_a of diol and boronic acid, is proposed on the basis of correlation data.

RESULTS AND DISCUSSION

Considering ester formation in a wide range of pH one needs to take into account deprotonation of boronic acid and diol as well as formation of two types of esters: neutral trigonal and anionic tetrahedral forms.[10] In dilute aqueous solutions employed in this study, formation of the trigonal ester with several exceptions[3] contributes insignificantly to the overall process and will be neglected in the subsequent analysis.[11] We will consider therefore three simultaneous processes: dissociation of arylboronic acid with the acid dissociation constant K_a^B (1), the first step of dissociation of diol with the acid dissociation constant K_a^D (2), and reaction of the ester formation (3) in accordance with Scheme 1 with the equilibrium constant $\beta_{11\text{-}1}$.

$$ArB(OH)_2 \rightleftarrows ArB(OH)_3^- + H^+ \quad (K_a^B) \tag{1}$$

$$D(OH)_2 \rightleftarrows D(OH)O^- + H^+ \quad (K_a^D) \tag{2}$$

Table 1. Equilibrium Constants for Diol Ester formation (Scheme 1) with *Meta*- or *Para*-Substituted Phenylboronic Acids in Water at 25 °C[a]

boronic acid			diol				
			ARS[b)]	4-nitrocatechol	Tiron	catechol	glucose
substituent	σ	pK_a^B	log $\beta_{11\text{-}1}$				
3-CO_2Me-5-NO_2	1.08	6.74	−1.074				
4-NO_2	0.78	7.23	−1.37		−2.19		
3-NO_2	0.71	7.27	−1.29	−2.12	−2.28	−3.15	−5.36
3-CF_3	0.43	7.94		−2.51	−2.77	−3.62	−5.85
4-$CONH_2$	0.36	8.18	−1.87				
4-Cl	0.23	8.26		−2.87	−2.86	−3.96	−6.43
H	0	8.90	−2.3	−3.02	−3.48	−4.33	−6.75
4-MeO	−0.27	9.24		−3.41	−3.75	−4.84	−7.30
pK_a^D			5.5	6.9	8.16	9.32	12.25
ρ		−2.0(1)	1.2(1)	1.29(9)	1.5(1)	1.72(3)	2.0(1)
ρ (K_{tet})			−0.89(4)	−0.7(2)	−0.49(8)	−0.3(1)	0.0(2)

[a]Errors in log $\beta_{11\text{-}1}$ are equal or less than ±0.03. [b)]From data reported in ref 12.

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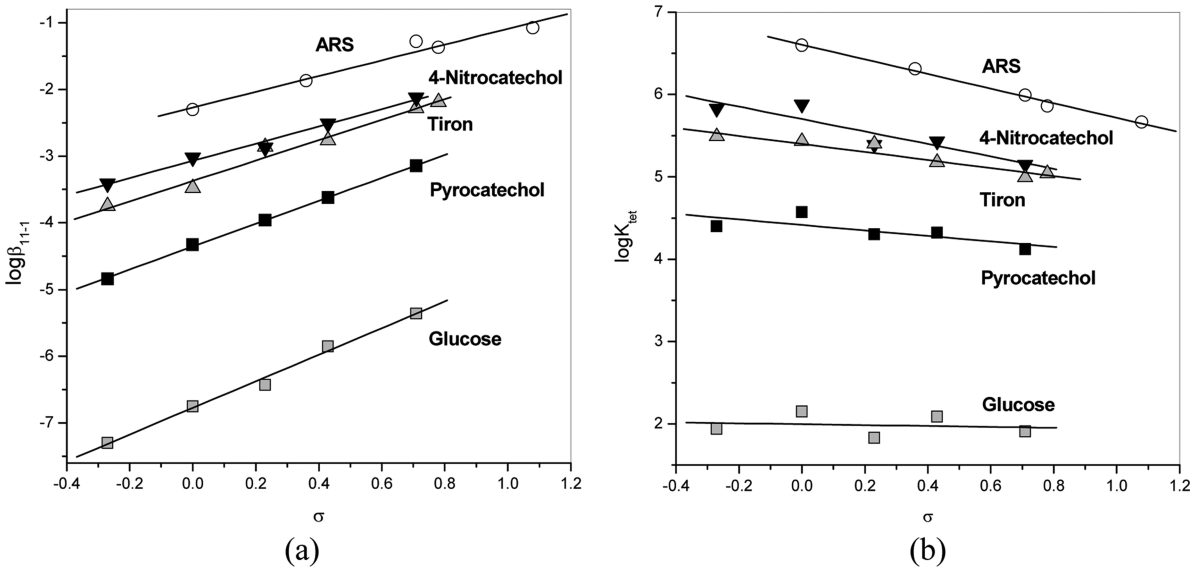

Figure 1. Hammett plots for log $\beta_{11\text{-}1}$ (a) and log K_{tet} (b) with different diols.

$$ArB(OH)_2 + D(OH)_2 \rightleftarrows ArBOH(O)_2D^- + H^+ \quad (\beta_{11\text{-}1}) \tag{3}$$

Another often employed equation for diol ester formation refers to the interaction of deprotonated boronic acid with neutral diol, reaction 4, with the equilibrium constant usually labeled as K_{tet} related to $\beta_{11\text{-}1}$ by eq 5.

$$ArB(OH)_3^- + D(OH)_2 = ArB(O)_2D(OH)^- \quad (K_{tet}) \tag{4}$$

$$K_{tet} = \beta_{11\text{-}1}/K_a^B \text{ or } \log K_{tet} = \log \beta_{11\text{-}1} + pK_a^B \tag{5}$$

The experimentally important parameter, which reflects the degree of ester formation under given conditions, is the so-called observed formation constant (K_{obs}) defined by eq 6 in terms of total concentrations of all components (the subscript "T" stands for total concentration that is the sum of concentrations of neutral and deprotonated forms of boronic acid and diol; since the tetrahedral ester is the sole reaction product its total concentration coincides with its equilibrium concentration).

$$K_{obs} = \frac{[ArB(O)_2D(OH)^-]}{[(ArB(OH)_2)]_T[D(OH)_2]_T} \tag{6}$$

Combining eq 6 with mass balance equations and expressions for respective dissociation constants one obtains eq 7, which predicts a bell-shaped profile of K_{obs} vs pH with the optimum pH and maximum K_{obs} corresponding to this pH given by eqs 8 and 9, respectively.

$$K_{obs} = \frac{\beta_{11\text{-}1}[H^+]}{(K_a^D + [H^+])(K_a^B + [H^+])} \tag{7}$$

$$pH_{opt} = (pK_a^D + pK_a^B)/2 \tag{8}$$

$$K_{obs}^{max} = (\beta_{11\text{-}1}/K_a^D)/(1 + (K_a^B/K_a^D)^{0.5})^2 \tag{9}$$

In the first step, the equilibrium constants for the whole set of arylboronic acids and diols were determined by potentiometric titrations. The results are collected in Table 1. Also included in Table 1 are $\beta_{11\text{-}1}$ values for ARS calculated by using eq 7 from K_{obs} at pH 7.5 reported in ref 12 for *meta*- and *para*-substituted phenylboronic acids.

In agreement with previously reported results,[2a,8,9] the values of pK_a^B follow the Hammett eq 10 with $\rho = -2.0 \pm 0.1$ (pK_a^H is pK_a^B for unsubstituted phenylboronic acid **1d**). The Hammett plots for log $\beta_{11\text{-}1}$, eq 11, for all diols are shown in Figure 1a, and the ρ values are collected in Table 1.

$$pK_a^B = \rho\sigma + pK_a^H \tag{10}$$

$$\log \beta_{11\text{-}1} = \rho\sigma + \log \beta_{11\text{-}1}^H \tag{11}$$

Evidently, ρ values become progressively smaller for more acidic diols. This is an expected trend because the absolute value of ρ reflects the degree of negative charge development on the boronate group in the ester and more acidic diols donate smaller negative charge. The ρ for glucose coincides by absolute value in limits of experimental errors with ρ for pK_a^B but have the opposite sign. In accordance with eq 5, this means that K_{tet} for glucose should be independent of the substituent. Indeed, the respective correlation shown in Figure 1b gives $\rho = -0.05 \pm 0.2$ for K_{tet} and glucose. With more acidic diols larger by absolute values negative ρ listed in Table 1 are observed (Figure 1b).

The equilibrium constants listed in Table 1 allow one to predict the pH profiles for K_{obs} with different combinations of boronic acids and diols by using eq 7. Figure 2 illustrates such profiles for two extreme cases: the most acidic diol ARS and the least acidic diol glucose. Several points are worth noting in this analysis.

A sharp pH-optimum is observed only when pK_a values of boronic acid and diol are sufficiently close to each other, as is the case for **1a** and ARS ($\Delta pK_a = 1.8$). With a larger difference in pK_a one observes a flat region around theoretically predicted pH_{opt} where K_{obs} remains practically constant. For weakly acidic diols with pK_a above 12 like glucose one observes a "saturation" rather than a "bell-shaped" plot. It follows from eq 7 that when $K_a^D \ll [H^+]$, a condition which is fulfilled for glucose at pH < 11, the expression for K_{obs} takes the form of eq 12, which predicts an increase in K_{obs} on increase in pH (decrease in $[H^+]$) until the limiting value $\beta_{11\text{-}1}/K_a^B = K_{tet}$. Actually, the optimum pH predicted from eq 8 is lower than 11 for all

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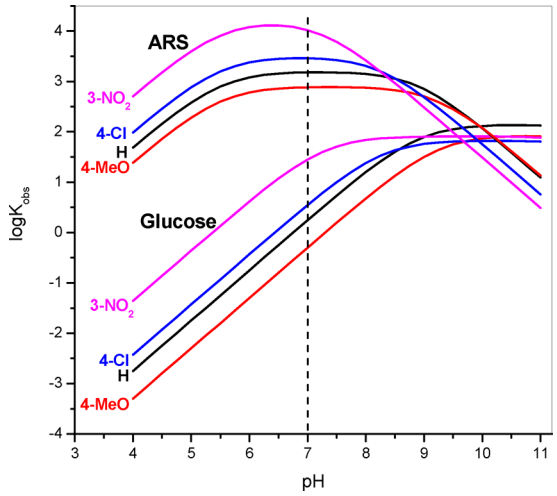

Figure 2. Simulated pH profiles calculated with eq 7 and parameters given in Table 1 for observed diol ester formation constants with different substituted phenylboronic acids and two diols: ARS and glucose.

boronic acids, e.g., pH_{opt} = 9.8 for **1a**, but since the optimum range is flat it looks like saturation.

$$K_{obs} = \beta_{11\text{-}1}/(K_a^B + [H^+]) \quad (12)$$

The maximum values of K_{obs} for ARS increase by more than 1 order of magnitude on going from less acidic **1e** to most acidic **1a**, but for glucose they remain practically constant for all boronic acids. This result can be predicted on the basis of eq 9. In the case of ARS, the ratio $K_a^B/K_a^D \ll 1$ and $K_{obs}^{max} = \beta_{11\text{-}1}/K_a^D$ which for a given diol varies as $\beta_{11\text{-}1}$ for different boronic acids. It can be shown that $\beta_{11\text{-}1}/K_a^D = K'_{tet}$ where K'_{tet} is the equilibrium constant for the reaction 13 between neutral boronic acid and diol monoanion. Indeed, these forms of reactants are predominant at pH around pH_{opt} for ARS. In the case of glucose, $K_a^B/K_a^D \gg 1$ and $K_{obs}^{max} = \beta_{11\text{-}1}/K_a^B = K_{tet}$, which is independent of the substituent (see above). The same result follows also from eq 12 at $[H^+] \ll K_a^B$, which corresponds to the pH region when K_{obs} reaches its maximum value.

$$ArB(OH)_2 + D(OH)O^- = ArB(O)_2D(OH)^- \quad (K'_{tet}) \quad (13)$$

Under neutral solutions at pH ~7 K_{obs} increases on going from **1e** to **1a** to approximately the same extent for both diols (see data along the vertical dashed line in Figure 2) although for different reasons. For ARS this is the variation in $K_{obs}^{max} \approx K'_{tet}$, but for glucose this is the effect of shifting to the left of the pH profiles for larger values of K_a^B with constant $K_{obs}^{max} = K_{tet}$.

We shall consider next the results of spectrophotometric and fluorometric titrations of Tiron by substituted phenylboronic acids. For these experiments, besides unsubstituted phenylboronic acid **1d**, two other acids **1a** and **1d** with substituents possessing extreme electron-acceptor (3-nitro) and electron-donor (4-methoxy) properties were selected to cover a maximum interval of the strength of boronic acids. Figures 1S and 2S (Supporting Information) show the absorption and emission spectra of Tiron at variable pH. In the absorption spectra deprotonation of Tiron is manifested in disappearance of the maximum at 291 nm and appearance of two more intense maxima at 260 and 307 nm with three isosbestic points at 244, 280, and 293 nm. In the emission spectra of Tiron recorded with excitation at the isosbestic point at 293 nm deprotonation induces the shift of the emission maximum at 339 nm to approximately 3 times less intense maximum at 369 nm. Figure 3 shows the pH profiles of absorption at 308 nm

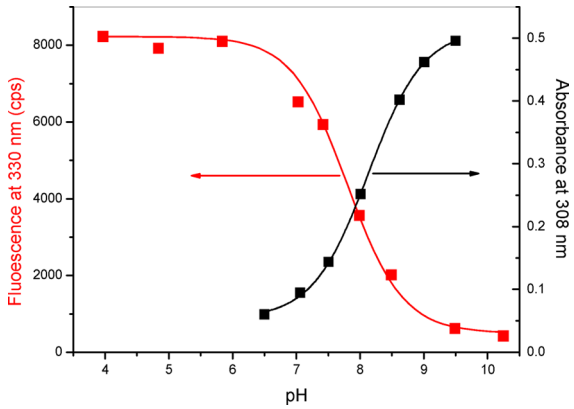

Figure 3. Fluorometric (red squares) and spectrophotometric (black squares) pH−titration plots for Tiron.

and emission at 330 nm from which one can calculate the pK_a^D values 8.12 ± 0.04 and 7.82 ± 0.02 respectively. The "spectrophotometric" pK_a^D coincides with that determined potentiometrically (Table 1), but the "fluorometric" pK_a^D is 0.3 units lower. A reduced pK_a found fluorometrically may reflect higher acidity of the excited state of a fluorophore as compared with its ground state.[13] A similar and even more pronounced effect exists also for ARS. It has pK_a^D = 5.5 determined spectrophotometrically,[14] but fluorescence titration data[2b,15] point to pK_a^D = 4.[2a]

Figure 4a shows the course of spectrophotometric titration of Tiron by phenylboronic acid at pH 7.3 at wavelengths above 280 nm where there is no interference with absorption of phenylboronic acid. The complexation-induced shift in the spectrum resembles that induced by deprotonation as one may expect for formation of an anionic ester, Scheme 1. Absorption spectra of esters obtained with differently substituted boronic acids are shown in Figure 3S (Supporting Information). They all have similar absorption maxima at 302 nm and also similar molar absorptivities about 6000 M^{-1} cm^{-1}.

The course of fluorometric titration of Tiron at the same pH 7.3 by phenylboronic acid is shown in Figure 4b. The emission maximum shifts to longer wavelengths as in the case of deprotonation, but the fluorescence intensity increases rather than decreases. Figure 5 shows emission spectra of esters obtained with substituted boronic acids together with spectra of neutral and deprotonated forms of Tiron. In contrast to absorption spectra, the emission spectra are very sensitive to the substituent with electron accepting substituents inducing the quenching effect. Such behavior is often observed for organic fluorophores.[13]

Insets in parts a and b of Figure 4 show the titration profiles for spectrophotomeric and fluorometric data at a single wavelength which fit very well to a theoretical equation for 1:1 binding isotherm. The K_{obs} calculated from such fittings at various pH are summarized in Table S1 (Supporting Information), and the results of spetrophotometric titrations are shown graphically in Figure 6. The spectrophotometric and fluorometric results agreed well between each other, but the

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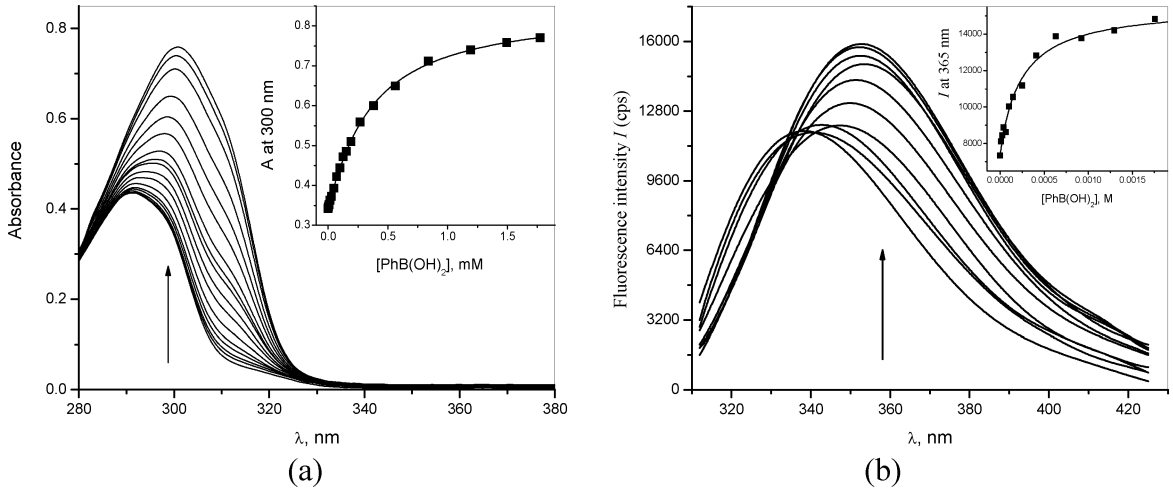

Figure 4. Spectrophotometric (a) and fluorometric (b) titrations of Tiron with **1d** at pH 7.3 (0.05 M MOPS buffer, 0.1 mM (a) and 0.03 mM (b) Tiron, excitation at 290 nm).

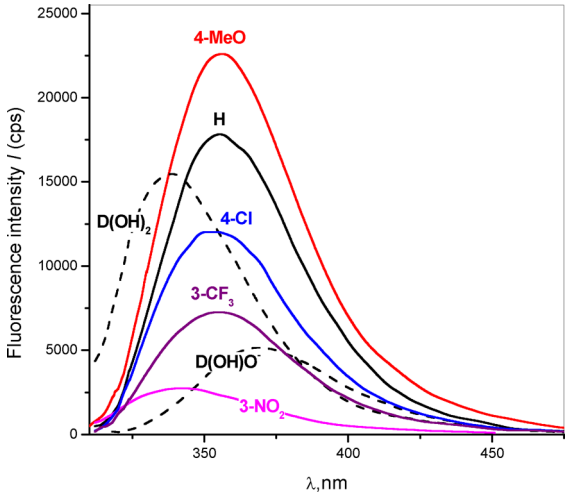

Figure 5. Emission spectra of neutral ($D(OH)_2$) and monoanionic ($D(OH)O^-$) forms of Tiron (dashed lines) and Tiron esters of substituted phenylboronic acids (excitation at 290 nm).

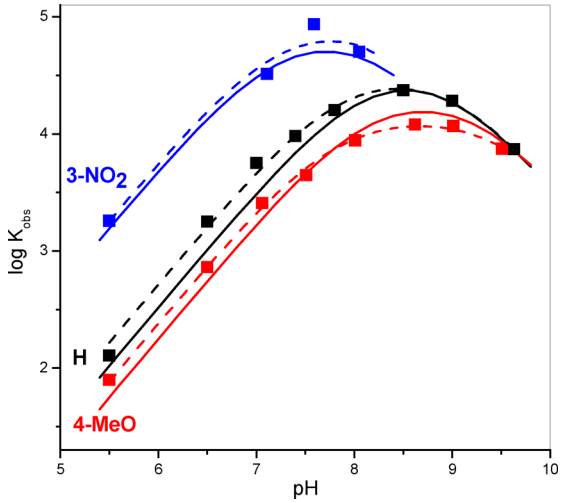

Figure 6. pH profiles of spectrophotometrically measured observed equilibrium constants for ester formation of Tiron with **1a**, **1d**, and **1e**. Solid lines are theoretically calculated profiles with parameters determined by potentiometric titrations given in Table 1; dashed lines are the best fit curves to eq 7.

former were more reproducible and were used in further analysis. The solid lines are profiles calculated with eq 7 and equilibrium constants determined by potentiometric titrations. Evidently, the spectrophotometric results pass very closely but do not follow exactly the profiles predicted from potentiometric data.

If one applies eq 7 to spectroscopic results to calculate $\beta_{11\text{-}1}$ from K_{obs} at each pH value with pK_a^D and pK_a^B determined potentiometrically and then takes the average for each boronic acid one obtains log $\beta_{11\text{-}1}$ = −2.21(4), −3.40(4), and −3.80(5) for **1a**, **1d**, and **1e**, respectively. These values in limits of errors coincide with those determined potentiometrically (see Table 1). On the other hand, one may fit the pH profiles of K_{obs} directly to the eq 7 and obtain all parameters from the spectroscopic data only. The fitting is shown as dashed lines in Figure 5 and gives the following set of parameters: log $\beta_{11\text{-}1}$ = −2.2(1), −3.28(4), and −3.61(2); pK_a^D = 8.2(3); 7.9(1) and 7.79(5); pK_a^B = 7.3(3), 9.0(2), and 9.5(1) for **1a**, **1d**, and **1e**, respectively. For **1a**, spectroscopic results are very close to potentiometric, but for two other acids one observes that the fitting requires lower pK_a values for Tiron and higher pK_a values for boronic acids than those found potentiometrically. The difference cannot be attributed to some sort of a buffer effect because pK_a of Tiron determined spectrophotometrically in the same buffer which was used in titrations with boronic acids coincided with that determined potentiometrically (see above) and because K_{obs} were independent of buffer concentration in the range 5−50 mM. A possible reason for discrepancy is a significant interdependence of parameters of eq 7 so that iterations during the fitting procedure find a minimum with smaller $\beta_{11\text{-}1}$ values "compensated" by shifted pK_a. Such interdependence should be smaller for interactions between boronic acids and diols with larger differences in their pK_a values because in these cases the optimum region is wider and pK_a values are determined essentially independently from each other. Obviously, the best way to obtain $\beta_{11\text{-}1}$ values from spectroscopic titrations is to apply eq 7 with fixed pK_a values determined independently.

For ^{11}B NMR titrations of **1a**, **1d**, and **1e** by Tiron we chose pH 5.5 where K_{obs} are sufficiently small to be measured reliably

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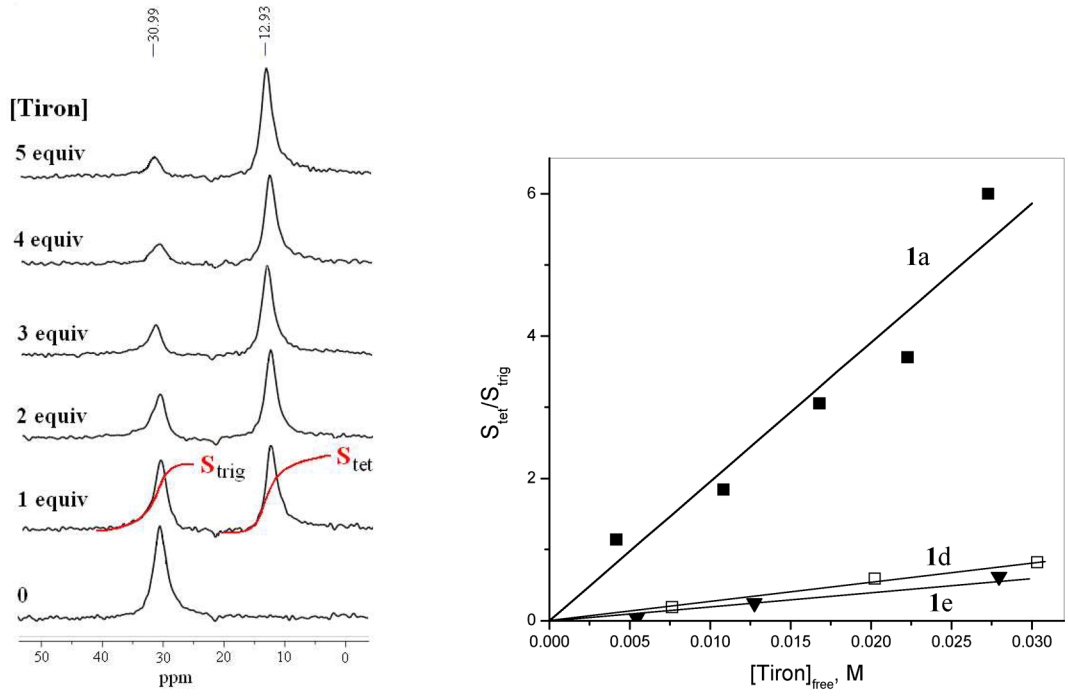

Figure 7. (a) ^{11}B NMR titration of 0.01 M **1a** by Tiron at pH 5.5. (b) Plots of S_{tet}/S_{trig} vs free Tiron concentration for **1a**, **1d**, and **1e**.

by this technique requiring high concentrations of components. A typical course of titration is illustrated in Figure 7 for **1a**. In the absence of Tiron a single signal at 31.0 ppm corresponding to neutral trigonal form of the acid is observed. Additions of Tiron induce appearance and subsequent growth of a new signal at 12.9 ppm corresponding to the tetrahedral boronate ester with simultaneous relative decrease in intensity of the peak at 31.0 ppm. For **1d** and **1e** the respective signals were observed at 31.8 and 31.6 ppm for free acids and 13.4 and 13.5 ppm for the esters. The ratio of the integrated areas of the signals (S_{tet}/S_{trig}) equals the ratio of concentrations of the ester and free boronic acid which allows one to calculate the concentrations of all components at equilibrium from the mass balance equation and finally to calculate the K_{obs} in accordance with eq 14.

$$S_{tet}/S_{trig} = [\text{ester}]/[\text{free boronic acid}] = K_{obs}[\text{free diol}] \quad (14)$$

The plot of S_{tet}/S_{trig} vs free Tiron concentration is shown in Figure 7b. It has a slope K_{obs} = 190 M^{-1}, which is, however, 1 order of magnitude smaller than the value expected from potentiometric and spectrophotometric results for this pH (see Figure 6). Since NMR titrations were performed in D_2O and a solvent isotope effect could be involved the titrations of Tiron with all three acids were repeated spectrophotometrically in D_2O at the same experimental pH and buffer composition including total buffer concentration as in case of NMR titrations. The results are shown in Table 2 (K_{obs} for **1d** and **1e** were determined from the same NMR titration procedure as described above for **1a**, see Figure 7b). The spectrophotometrically determined constants are just ca. 10% smaller than those determined in H_2O, but in all cases the ^{11}B NMR titration gives much lower K_{obs} values with the largest difference observed for **1a**. Another difference in conditions is a higher range of concentrations of boronic acid and Tiron (10−50 mM) in ^{11}B NMR titrations than that in spectrophotometric titrations (0.1−5 mM), which may alter the activity coefficients and lead to a some degree of formation of higher aggregates,[3a] but these effects hardly can be such significant taking into account equal total 0.05 M buffer concentration in both experiments.

Table 2. Observed Ester Formation Constants in D_2O at pH 5.5 Measured by Spectrophotometric and ^{11}B NMR Titrations

	K_{obs}, M^{-1}	
boronic acid	UV−vis	^{11}B NMR
1a	1600 ± 100	190 ± 20
1d	110 ± 8	27 ± 5
1e	70 ± 7	21 ± 6

A low K_{obs} value calculated from NMR data is a result of too small integration area of the signal belonging to the tetrahedral ester. For a similar reaction of phenylboronic acid **1d** with ARS it was suggested that this is due to the fact that the tetrahedral ester is a minor form of the product, which is in equilibrium with the trigonal major form nonresolved in ^{11}B spectrum with the free boronic acid (Scheme 2).[6] The results in Figure 7 do not fit to this model, however. If the reaction product exists as a mixture of several isomers of the same stoichiometry, the K_{obs} measured by spectrophotometric titration is the sum of formation constants for all isomers, and it refers to conversion of starting material to the sum of concentrations of all isomers.[16] With K_{obs} = 1600 M^{-1} for **1a** already addition of the first equivalent of Tiron (0.01 M) must convert the boronic acid into the mixture of esters nearly quantitatively, and the ratio S_{tet}/S_{trig} should be close to K_{iso} and remain constant on further increase in Tiron concentration, but it rises proportionally to added Tiron. In any case, since S_{tet}/S_{trig} reaches 6 (Figure 7b) the fraction of the tetrahedral isomer must be

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above 85% and the trigonal isomer must be a minor component, which cannot affect significantly the titration results. It seems difficult to propose any chemically sound reaction scheme which can explain anomalously low K_{obs} determined by ^{11}B NMR titration in this case. Integration of ^{11}B NMR signals was often employed for determination of stability constants for boronic acid diol ester and in several occasions the results were confirmed by determination of equilibrium constant by other experimental techniques.[17−19] In all cases, the interaction was studied with carbohydrates or aliphatic diols and often involved boric or methylboronic rather than arylboronic acids, which give more narrow signals. Possible problem with an arylboronic acid and an aromatic diol may consist in quaqrupolar interactions of ^{11}B nucleus and aromatic rings leading to strong signal broadening and a lack of proportionality between the signal areas and concentrations of respective species.

For further analysis of substituent effects in diol ester formation we looked for possible Brönsted-type correlation of the parameters of Hammett eq 11 with pK_a^D. As one can see from Figure 8 both ρ and $\log\beta_{11\text{-}1}^H$ are linear functions of pK_a^D in accordance with eqs 15 and 16.

$$\rho = 0.5 \pm 0.1 + (0.13 \pm 0.01)pK_a^D \quad (15)$$

$$\log \beta_{11\text{-}1}^H = 1.7 \pm 0.6 - (0.67 \pm 0.07)pK_a^D \quad (16)$$

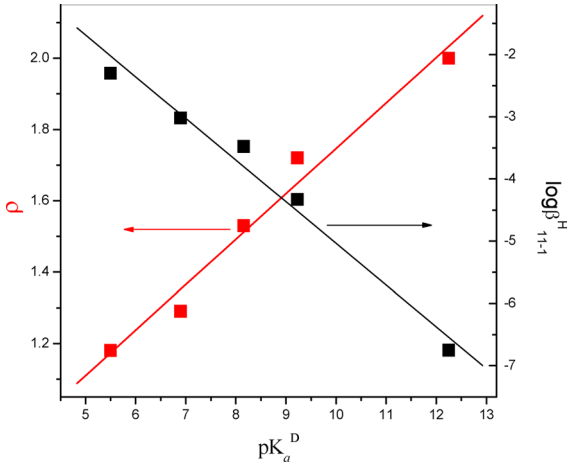

Figure 8. Correlation of parameters of the Hammett equation for ester formation constants with pK_a of diol.

Obviously, the presence of glucose on the same correlation line with aromatic diols is fortuitous because it interacts with boronic acids in its minor furanose form[20] while the reported pK_a refers to its major pyranose form. However, this fortunate situation allows one to elaborate a general equation, which predicts $\beta_{11\text{-}1}$ for any pair of diol including glucose and boronic acid just from their pK_a values. Combining eqs 10, 11 with 15, 16 and rounding parameters in accordance with their standard errors one obtains eq 17.

$$\log \beta_{11\text{-}1} = 3.9 - 0.25pK_a^B - 0.1pK_a^D - 0.065pK_a^BpK_a^D \quad (17)$$

The inset in Figure 9 shows the correlation between logarithms of experimental ($\beta_{11\text{-}1}^{exp}$) and calculated ($\beta_{11\text{-}1}^{calc}$) stability constants for all boronic acids and diols listed in Table 1, which follows eq 18 with correlation coefficient 0.98554 and

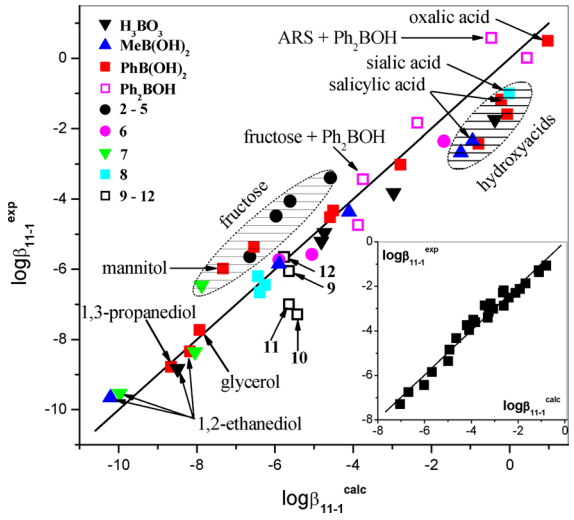

Figure 9. Correlation between logarithms of experimentally determined and calculated with eq 17 equilibrium constants of ester formation of different boronic acids and diols (Table 3 and Chart 2). Points for mannitol and glycerol are statistically corrected by −0.7 and −0.3, respectively. Solid line corresponds to $\log \beta_{11\text{-}1}^{exp} = \log \beta_{11\text{-}1}^{calc}$. Inset shows the correlation of all data from Table 1.

standard deviation 0.3 roughly corresponding to the precision of eq 17 expected from standard errors in its parameters.

$$\log \beta_{11\text{-}1}^{exp} = (1.00 \pm 0.03)\log \beta_{11\text{-}1}^{calc} + (-0.05 \pm 0.1) \quad (18)$$

In order to see the limits of validity of eq 17 and its possible applications to analysis of experimental data we have compared calculated and experimental equilibrium constants for an additional set of 45 reactions between different types of boronic acids and diols (Table 3 and Chart 2) for which pK_a^B and pK_a^D values are available together with $\beta_{11\text{-}1}$ or K_{obs} at a given pH so that $\beta_{11\text{-}1}$ can be calculated with eq 7.

The results are shown graphically in Figure 9, where the solid line corresponds to $\beta_{11\text{-}1}^{exp} = \beta_{11\text{-}1}^{calc}$. Evidently, the validity of eq 17 is not limited to substituted phenylboronic acids: data for benzoboroxole (**6**), methylboronic, diphenylborinic, and boric acids are also close to predicted values. The equation predicts satisfactorily stability constants in a very wide range of $\beta_{11\text{-}1}$ from ca. 10^{-10} to 1 and for diols ranging in their acidity by ca. 14 orders of magnitude from 1,3-propanediol to oxalic acid.

Data for fructose esters with different boronic acids clearly show nearly constant systematic upward deviation by more than 1 order of magnitude (points encircled with an ellipse above the solid line in Figure 9), which can be attributed to a constant additional binding contribution from the third hydroxyl group of the sugar molecule. Notably, the point for fructose and Ph_2BOH to be incapable of binding the third hydroxyl lays on the line corresponding to stability constants predicted for diols. Data for hydroxy acids (points encircled with an ellipse below the solid line in Figure 9) also show nearly constant, but downward, deviation probably due to steric effects.[3b] Polyols like glycerol or mannitol form much more stable complexes than simple aliphatic diols (Table 2, lines 18−21). The eq 17 within the limits of its precision correctly predicts $\beta_{11\text{-}1}$ for 1,2-ethanediol and 1,3-propanediol with smaller stability constant for the latter due to its larger pK_a. Experimental $\beta_{11\text{-}1}$ for a polyol requires statistical correction before it can be compared with the calculated value valid for a

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Table 3. Calculated with eq 17 and Experimentally Determined Equilibrium Constants for Ester Formation between Selected Boronic Acids and Diols[a]

	boronic acid	diol	pK_a^B	pK_a^D	log β_{11-1} calcd	log β_{11-1} expt	ref
1	H_3BO_3	1,2-ethanediol	8.98	14.8	−8.44	−8.83	18a
2	H_3BO_3	4-methylcatechol	8.98	9.39	−4.77	−5.20	21
3	H_3BO_3	catechol	8.98	9.27	−4.68	−4.96	
4	H_3BO_3	4-nitrocatechol	8.98	6.69	−2.92	−3.82	
5	H_3BO_3	tartaric acid	8.98	2.89	−0.32	−1.74	
6	$MeB(OH)_2$	salicylic acid	10.4	2.83	−0.90	−2.35	18c
7	$MeB(OH)_2$	mandelic acid	10.4	3.22	−1.20	−2.68	
8	$MeB(OH)_2$	4-nitrocatechol	10.4	6.69	−4.05	−4.37	
9	$MeB(OH)_2$	catechol	10.4	9.27	−5.85	−5.80	
10	$MeB(OH)_2$	1,2-ethanediol	10.4	14.8	−10.15	−9.66	
11	$PhB(OH)_2$	4-methylcatechol	8.72	9.39	−4.54	−4.52	21
12	$PhB(OH)_2$	catechol	8.72	9.27	−4.46	−4.33	
13	$PhB(OH)_2$	4-nitrocatechol	8.72	6.69	−2.74	−3.02	
14	$PhB(OH)_2$	lactic acid	8.72	3.7	−0.75	−2.43	
15	$PhB(OH)_2$	malonic acid	8.72	2.59	−0.007	−1.58	
16	$PhB(OH)_2$	oxalic acid	8.72	1.04	1.03	0.51	
17	$PhB(OH)_2$	salicylic acid	8.72	2.83	−0.17	−1.17	34
18	$PhB(OH)_2$	mannitol	8.72	13.5	−7.28	−5.28	21
19	$PhB(OH)_2$	1,2-ethanediol	8.72	14.8	−8.13	−8.34	18a
20	$PhB(OH)_2$	1,3-propanediol	8.72	15.5	−8.61	−8.78	22
21	$PhB(OH)_2$	glycerol	8.72	14.4	−7.88	−7.43	
22	$PhB(OH)_2$	fructose	8.9	12.03	−6.49	−5.36	23
23	Ph_2BOH	ARS	6.2	5.5	−0.42	0.58	24
24	Ph_2BOH	catechol	6.2	9.27	−2.31	−1.83	
25	Ph_2BOH	lactic acid	6.2	3.7	0.49	0.015	
26	Ph_2BOH	fructose	6.2	12.03	−3.70	−3.44	
27	Ph_2BOH	glucose	6.2	12.28	−3.83	−4.74	
28	**2**	fructose	8.35	12.03	−5.92	−4.48	
29	**3**	fructose	8.0	12.03	−5.56	−4.06	
30	**4**	fructose	9.0	12.03	−6.59	−5.64	
31	**5**	fructose	7.0	12.03	−4.53	−3.40	
32	**6**	glucose	7.34[b]	12.28	−5.00	−5.58	25
33	**6**	methyl α-D-glucopyranoside	7.34[b]	13.71	−5.85	−5.73	
34	**6**	ARS[c]	7.7	6.0	−1.63	−2.36	26
35	**7**	glucose[d]	10.2	12.25	−7.83	−8.35	27
36	**7**	fluctose[d]	10.2	12.03	−8.00	−6.45	
37	**7**	1,2-ethanediol[d]	10.2	14.8	−9.92	−9.54	
38	**8**	sialic acid	8.6	2.6	0.037	−1.00	19
39	**8**	glucose	8.6	12.28	−6.34	−6.67	
40	**8**	mannose	8.6	12.08	−6.21	−6.44	
41	**8**	galactose	8.6	12.35	−6.39	−6.20	
42	**9**	glucose	7.9	12.28	−5.59	−6.05	28
43	**10**	glucose	7.7	12.25	−5.36	−7.29	
44	**11**	glucose	7.9	12.25	−5.59	−6.99	
45	**12**	glucose	8.0	12.25	−5.71	−5.65	29

[a] pK_a^B are taken from cited references; pK_a^D are taken either from cited references or from refs 30−33. β_{11-1} given in entries 1−18 are reported values, and in other cases they are calculated from K_{obs} reported at a given pH by using eq 7 or from K_{tet} with eq 5. [b] From ref 8. [c] 4% v/v DMSO. [d] MeOH−H_2O (1:2, w/w).

diol of the respective acidity. Such corrected values are shown in Figure 9 from which one observes good agreement for glycerol. The corrected point for mannitol appears together with points for fructose, which reflects the possibility of formation of the third ester bond with this long chain polyol in a manner analogous to fructose.

It was proposed that boronic acids possessing positively charged substituents in the *ortho*-position to boronate group such as **9** and **12** form exceptionally stable diol esters due to electrostatic interaction with the boronate group.[28,29] As it is evident from Figure 9, stability constants for these compounds are just in line with expected from their acidity, but isomeric compounds **10** and **11** for some unclear reasons have lower affinities than expected and this makes an impression of an extra-stability of *ortho*-isomers. The above examples illustrate the utility of eq 17 for analysis of possible factors contributing to stability of boronic acid esters above what is expected simply from acid−base properties of boronic acid and diol.

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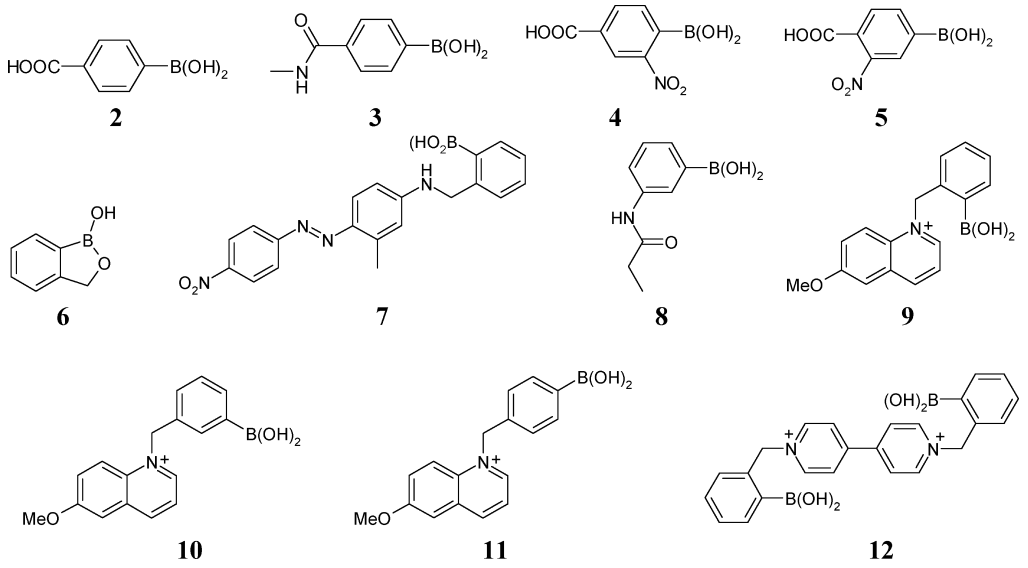
Chart 2



It follows from eq 17 that higher acidity (lower pK_a) of both boronic acid and diol is favorable for ester stability expressed in terms of $\beta_{11\text{-}1}$ in accordance with previous qualitative observations.[34] This trend seems logical because in the reaction 3 ester formation is accompanied by deprotonation favored by higher acidity of both components. Obviously, considering ester stability in terms of K_{tet} or K'_{tet} one will find different trends. These constants under certain conditions represent the observed stability constants (see above discussion of the Figure 2), but generally K_{obs} is a complex pH-dependent parameter, which in principle can be predicted combining eqs 7 and 17. A simpler and still useful picture can be obtained for maximum values of K_{obs}, which can be reached experimentally at the optimum pH for a given pair of boronic acid and diol. An estimate of K_{obs}^{max} can be done with eq 19 obtained combining eqs 9 and 17.

$$\log K_{obs}^{max} = 3.9 - 0.25pK_a^B + 0.9pK_a^D - 0.065pK_a^B pK_a^D - 2\log(1 + (K_a^B/K_a^D)^{0.5}) \quad (19)$$

The results predicted by eq 19 are shown graphically in Figure 10, which covers the range of pK_a from 5 to 11 for boronic acids and from 2 to 15 for diols. It follows from this analysis that the largest possible K_{obs} is about 10^5 M^{-1}, and it can be reached by combination of boronic acid and diol each with pK_a about 5 at pH 5 in accordance with eq 8. Among experimentally studied systems the closest one to this is the reaction between $Ph_2B(OH)$ and ARS (Table 3, line 23) for which log K_{obs} = 5.2 at pH 7.0 was reported.[24] This is even higher than predicted log K_{obs} = 4.9 from eq 19, which would be observed at pH 5.85. The respective point on the plot in Figure 9 indeed shows a significant positive deviation for $\beta_{11\text{-}1}$ probably resulting from hydrophobic or stacking interactions of one of phenyl rings of the diphenylborinic acid with ARS.

As it follows from Figure 10 for each boronic acid there is an optimum diol with pK_a^D close to, but not exactly matching, pK_a^B of the given acid. For example, the largest possible log K_{obs}^{max} = 4.0 for phenylboronic acid (pK_a^B = 8.9) would be observed with a diol possessing pK_a^D = 8.3 at pH 8.6 (cf. log K_{obs} = 4.38 for **1d** and Tiron at pH 8.5, Figure 6 and Table 1S, Supporting Information). On the other hand, for a given diol K_{obs}^{max} increases monotonically on decrease in pK_a^B for diols with pK_a^D below 8 and is rather insensitive to pK_a^B for less acidic diols. One should take into account of course that with stronger boronic acids K_{obs}^{max} is reached at lower pH.

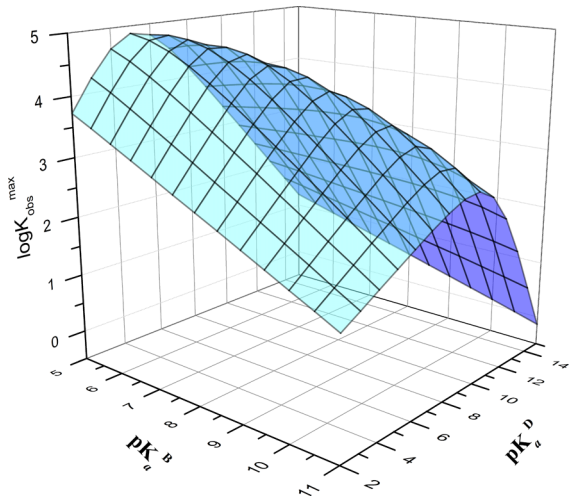


Figure 10. Logarithms of K_{obs}^{max} values corresponding to the optimum pH for different pairs of boronic acids and diols in accordance with eq 19.

■ CONCLUSIONS

Hammett- and Brönsted-type correlation relationships obtained in this work for stability constants of boronic acid diol esters allowed us to propose an equation which made it possible to calculate the stability constants from pK_a values of boronic acids and diols with an uncertainty of ±0.3 logarithmic units in a range of stability constants covering 11 orders of magnitude. Calculated in this way, stability constants take into account only acid−base properties of both components mostly determined by electronic effects, and their comparison with experimentally measured values allows one to see more clearly possible contributions from other factors, such as additional bond formation, charge, or steric effects.

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Observed pH-dependent stability constants measured by UV−vis and fluorometric titrations agree well with those predicted on basis of potentiometric titrations but preferably should be analyzed by using independently determined pK_a as fixed parameters. The spectral changes induced in a chromogenic diol by complexation with arylboronic acids resemble those induced by deprotonation. Changes in UV−vis spectra are rather insensitive to the substituent in the arylboronic acid, but the fluorescence can either increase or decrease on complexation depending on the type of the substituent. ^{11}B NMR titrations may give undervalued observed stability constants for interactions between arylboronic acids and catechols, which not always can be interpreted in terms of Scheme 2 developed for interactions of arylboronic acids with ARS.[6,26]

EXPERIMENTAL SECTION

General Experimental Methods. Commercially available substituted phenylboronic acids, catechols, glucose, components of buffer solutions (CHES, MOPS, MES), and D_2O (99.9% D) were used as supplied. All titration experiments were performed at 25 °C and ionic strength 0.05 M created either by buffer or NaCl.

Potentiometry. Potentiometric titrations were performed in a 25-mL thermostated cell kept under nitrogen at 25 ± 0.1 °C with 0.05 M NaCl as background electrolyte. Depending on solubility, 2−5 mM solutions of boronic acids in the presence of 2−10 mM catechols or 0.1 M glucose were employed. The pK_a values of all components were determined independently by potentiometric titrations in the same conditions and were used as fixed parameters in the fitting of results for the boronics acid−diol mixtures. Experimental details and procedure for the electrode calibration were the same as in ref 35. The program Hyperquad 2003[36] was used to calculate all equilibrium constants.

Spectrophotometric and Fluorometric Titrations. To a 0.1 mM solution of Tiron (0.03 mM for fluorometric titrations) 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 boronic acid in the same buffer were added, and the mixture was incubated for 3 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 constant of the ester formation (K_{obs}) was calculated from the absorbance or fluorescence intensity (A) vs concentration of boronic acid (B) profiles at several wavelengths by nonlinear least-squares fitting to the eq 20, and the results were averaged. In eq 20, subscript T stands for total concentration, A_0 is the initial absorbance or fluorescence intensity of Tiron (D) measured in the absence of B, and $\Delta\varepsilon$ is the difference in molar absorptivities or respective proportionality coefficients for fluorescence between the ester and free D.

$$A = A_0 + 0.5\Delta\varepsilon[[D]_T + [B]_T + 1/K_{obs} - (([D]_T + [B]_T + 1/K_{obs})^2 - 4[D]_T[B]_T)^{0.5}] \quad (20)$$

^{11}B NMR titrations. ^{11}B NMR spectra were recorded in D_2O at 128.3 MHz with $Et_2O{\cdot}BF_3$ in $CDCl_3$ as the external standard 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 scans were taken for each sample. To 0.01 M solution of a boronic acid in 0.05 M MES buffer in D_2O at pH 5.5 (uncorrected pH reading) portions of concentrated Tiron solution prepared in the same buffer and adjusted to the same pH were added, and the spectra were recorded as described above.

ASSOCIATED CONTENT

Supporting Information

[UV−vis absorption and fluorescence spectra of Tiron at variable pH; UV−vis absorption spectra of Tiron esters of substituted phenylboronic acids; spectroscopically determined observed stability constants of Tiron esters of substituted phenylboronic acids at variable pH] This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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