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Ring Structure and Aromatic Substituent Effects on the pK_a of the Benzoxaborole Pharmacophore

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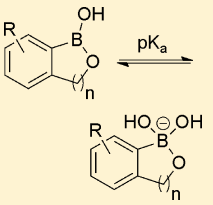
Supporting Information

ABSTRACT: In this work, we present an investigation into the physical properties of a unique class of aromatic boronic acids, the benzoxaboroles. Using spectrophotometric methods, the ionization constants of a family of substituted benzoxaboroles are determined. Heterocyclic ring modifications are examined to determine their effects on the ionization of the boronic acid moiety. It is also shown that the substituent effects about the aromatic ring follow a Hammett relationship with the compounds' measured pK_a values. Finally, these substituent effects are also shown to extend to the sugar binding properties of these compounds under physiologically relevant conditions. Combined, these data will inform medicinal chemists wishing to tailor the ionization and/or ability of this class of compound to bind diol-containing biomolecules.



KEYWORDS: *Benzoxaborole, oxaborole, benzoboroxole, benzoxaborin, boronic acid, diol binding, Hammett relationship, pK_a prediction*

Surrounding the recent FDA approval of the first boron-containing pharmaceutical, Velcade (bortezomib),[1] there has been great interest in the use of boronic acids for medicinal purposes.[2−6] In most cases, it has been determined that boronic acids form monodentate active-site complexes with enzyme nucleophiles (i.e., the serine −OH of proteases) mimicking the transition state. This is in contrast to the prevailing notion in the field of sugar recognition where the boron atom is involved in a covalent bidentate adduct with the cis-diols of the saccharide.[5,7−12] However, the worlds of diol binding and enzyme inhibition came firmly together with the report of the mechanism of action of the antifungal agent AN2690, a 5-fluoro-substituted benzoxaborole, upon the leucyl-tRNA synthetase (Leu-RS). The inhibitory complex was crystallized and was found to involve a tRNA adduct in the editing domain active site in which two B−O bonds are formed between the benzoxaborole and the 2′- and 3′-hydroxyls of the terminal ribose.[13]

Benzoxaborole (**1**) was first synthesized and characterized by Torssell[14] and was determined to be a very hydrolytically stable, water-soluble boronic acid.[15] Until recently, little attention has been paid to this remarkable class of boronic acids[16] as evidenced by the fact that a majority of the publications and patents involving **1** have been published since 2005. This increased interest is due to the excellent sugar-binding properties of **1** under physiological conditions as reported by the Hall group[17−19] and to extensive research into the medicinal properties of this class of compounds.[20−27] These recent developments have unveiled the benzoxaborole unit as an important boron-containing pharmacophore.

The structural difference between the simple aryl-boronic acids, that is, phenyl boronic acid (PBA), and the benzoxaboroles is the involvement of one of the boronic oxygens in the oxaborole heterocyclic ring system. The predominant physiochemical result of the incorporation of the oxaborole ring is the lowering of the boronic pK_a from 8.8 for PBA[28] to 7.3 for **1**. This difference in pK_a is believed to be due to ring strain induced upon the boron atom in its neutral, trigonal planar form when involved in this five-membered ring.[29] Ring strain is relieved upon ionization of the boronic acid since this transformation is accompanied by a change in conformation about boron to an anionic species with tetrahedral geometry. With this structural cause of pK_a depression, it was also questioned whether aromatic substitutions about the benzoxaborole ring would parallel the effects seen with analogous substitutions within the PBA family.

To further elucidate the role of the oxaborole ring on the boronic pK_a, samples of two related heterocycles, 2-(2-hydroxyethyl) benzene boronic acid cyclic monoester (benzoxaborin, **2**) and 3,3-*gem*-dimethyl-benzoxaborole (**3**), were obtained for study. To address the question of aromatic ring substitutions, a family of aryl-substituted benzoxaboroles (**4**−**9**) was collected (Figure 1). A spectral method for the determination of the ionization constants of these compounds was developed after a modification of the method of Soundararajan, et al.[30] For comparison purposes, a meta-

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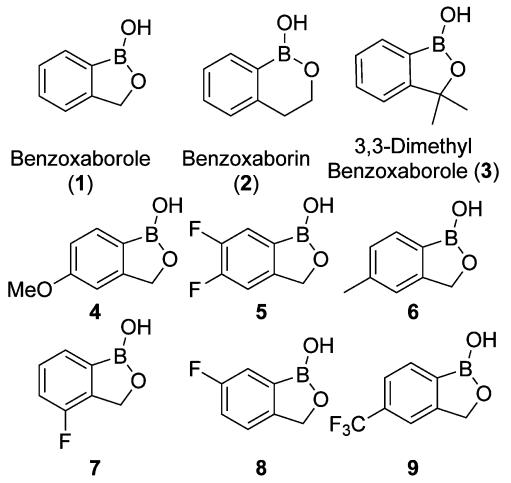
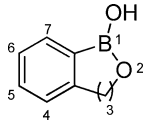


Figure 1. Compound structures and names.

analysis of the published ionizations of PBAs in water was assembled. Finally, the binding constants of several key benzoxaboroles to adenosine monophosphate (AMP, to mimic the terminus of a tRNA) were determined to investigate whether the sugar-binding properties of these compounds might be affected by aromatic substitutions as well. For instance, this information might lead to a better understanding of the contributing factors involved in the complexation of biomolecules to benzoxaborole drugs such as AN2690.

For the spectrophotometric determination of ionization constants, all compounds were initially screened by UV/vis spectral scans in aqueous 0.1 M HCl and NaOH solutions to check the solubility at extremes of pH, determine optimal compound concentrations, and confirm the presence of useful spectral changes. The absorption, spectral difference, and pK_a plots for each compound at each pH are included in the Supporting Information. The results of the pK_a determinations are summarized in Table 1 and Figures 2 and 3. All of the

Table 1. Data Summary



compd	3-position	aqueous pK_a
benzoxaborole (**1**)	$-CH_2-$	7.34 ± 0.02
benzoxaborin (**2**)	$-CH_2-CH_2-$	8.40 ± 0.03
3,3-*gem*-dimethyl (**3**)	$-C(CH_3)_2-$	8.32 ± 0.03

compounds exhibited spectra that passed through a common isosbestic point, which indicates a smooth transition from one species to another across the entire pH range included in the pK_a analyses. In addition, the measured pK_a values of **1** (7.3) and **2** (8.4) by this method match well with the published data (7.2 and 8.4, respectively) as determined by ^{11}B NMR titration experiments.[18]

Examination of the results for benzoxaborole (**1**), benzoxaborin (**2**), and the 3,3-*gem*-dimethyl benzoxaborole (**3**) compounds reveals that the pK_a of **2** (8.4) falls nearer to that of PBA (8.8) than to that of **1**. This is consistent with the idea that the ring strain in the 5-membered oxaborole ring distorts the geometry about the boron atom leading to a more favorable ionization and a lowered pK_a. The 6-membered ring of the

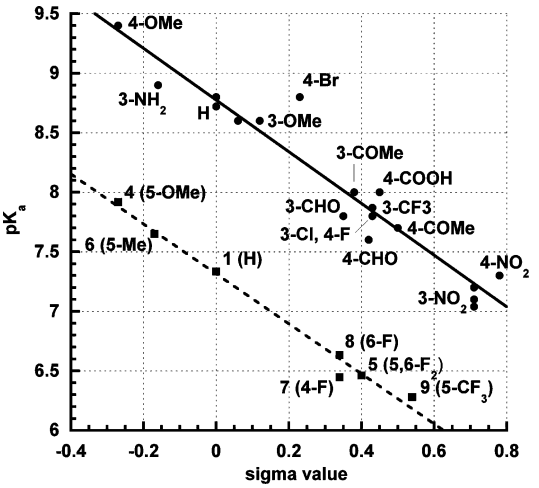


Figure 2. Hammett analyses of the relationship between substituent σ values and the ionization of benzoxaboroles (■) or the published pK_a values for a family of PBAs (●) in aqueous solution.

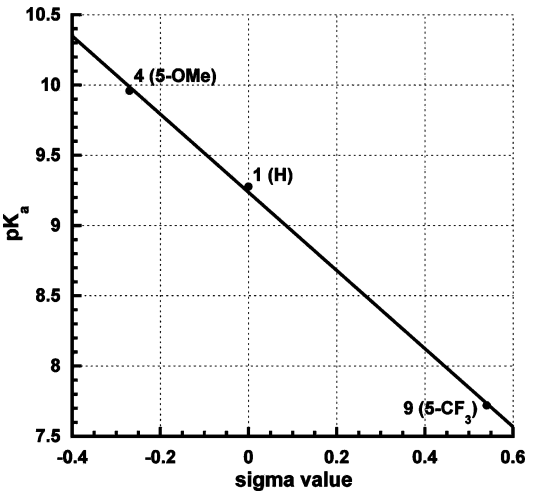


Figure 3. Hammett analysis of the ionization of benzoxaboroles in 50% aqueous ethanol solution.

benzoxaborin does not induce this distortion and therefore results in a higher pK_a. The ~0.5 pK_a unit difference between **2** and PBA may be explained by the reduced flexibility of the intramolecular monoboronic ester, which prevents optimal B–O (lone pair) conjugation in **2** and consequently increases the boron atom's electronic deficiency. It was also determined that as the steric bulk is increased at the 3-position, on the 5-membered ring, from $-CH_2-$ to $-C(CH_3)_2-$, the pK_a increases from 7.3 for **1** to 8.3 for **3**. This is likely a result of the *gem*-dimethyl effect,[31] which likely increases the bond angle about boron, alleviating the bond distortion and disfavoring ionization. Taken together, these results indicate that any deviation from the unsubstituted oxaborole ring system, by either ring expansion or substitution, would act to significantly increase compound pK_a.

To elucidate the role of aryl substitutions on benzoxaborole pK_a, a Hammett analysis of the data was completed. The experimentally determined pK_a values, obtained in both aqueous and ethanolic solution, were plotted against available σ_m and σ_p values.[32] As can be seen in Figures 2 (■ data) and **3**, an excellent correlation was found for all compounds included in this study. The ρ value for the ionization of the

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benzoxaboroles in aqueous solution was determined to be −2.10 (Figure 2, ■ data). This value is nearly identical to the −2.17 value determined by a meta-analysis (Figure 2, ● data) of the published ionizations of PBAs in water.[28,33−35] This similarity in ρ values between the benzoxaborole and the PBA families indicates that the oxaborole ring has essentially no electronic effects on the system.

Next, the data obtained in ethanolic solution were examined. These data were obtained to address two concerns. First was the practical experimental concern that the compounds to be studied might be insoluble in a pure aqueous solution. Second, and more theoretically, the effect of solvent composition on the pK_a of **1** was unknown. It was thought that the incorporation of a large amount of a less polar solvent could inform us as to what occurs within an enzyme active site. Thus, the pK_a values for **1**, **4**, and **9** (chosen to cover the range of σ values) were determined in 50% aqueous ethanol. There is an across the board increase in pK_a measurements in this solvent system when compared to a purely aqueous system (Table 1). Also, the resultant ρ value obtained from the Hammett analysis was −2.78 (Figure 3). The ethanolic/aqueous ratio of the two ρ values (−2.78/−2.10) was calculated to be 1.32 and may be compared with the 1.46 ratio reported for the ionization of benzoic acids in similar solvent systems.[36] These results indicate that ionization in a less polar environment is disfavored, likely due to lesser solvent stabilization of the resultant anion. Additionally, the electronic effects of aryl substitutions are more pronounced as evidenced by the larger magnitude of the ρ value in ethanolic vs aqueous conditions.

For the prediction of pK_a values, the equations obtained from the Hammett analyses (Figures 2 and 3) may be used in combination with the readily available σ values. The equations for the PBAs (aqueous), benzoxaboroles (aqueous), and benzoxaboroles (ethanolic) follow respectively.

$$pK_a = 8.74 - 2.17*\sigma \quad (1)$$

$$pK_a = 7.31 - 2.10*\sigma \quad (2)$$

$$pK_a = 9.24 - 2.78*\sigma \quad (3)$$

On a more speculative note, it is now possible to estimate pK_a values of the benzoxaborin and 3,3-*gem*-dimethyl benzoxaborole compound families. Given that these compounds yielded pK_a values between that of PBA and benzoxaborole and that the Hammett analyses of the PBA and benzoxaborole compound families yielded nearly identical ρ values (Figure 2, slopes of −2.17 and −2.10, respectively), it is reasonable to assume that the ρ values of the benzoxaborin and 3,3-*gem*-dimethyl benzoxaborole compound families are similar. Therefore, the equations that may be used to *estimate* the pK_a values of these compounds, respectively, are as follows:

$$pK_a = 8.40 - 2.14*\sigma \quad (4)$$

$$pK_a = 8.32 - 2.14*\sigma \quad (5)$$

Finally, it remained to be seen if the aromatic substitutions about the benzoxaborole might affect sugar binding in addition to compound ionization. This was accomplished by assessing the binding of benzoxaboroles **1**, **4**, and **9** to AMP, a close mimic to the tRNA terminus, utilizing a spectrophotometric competition experiment developed by Wang et al.[37] In these experiments, a three-component mixture of benzoxaborole, indicator (ARS), and saccharide (AMP) is prepared. UV absorbances are taken as saccharide concentrations are varied. From these data, and previously determined benzoxaborole-ARS binding constants (K_{ARS}), the binding constants between the benzoxaborole and the saccharide (K_{AMP}) may be calculated. Thus, it was found that the binding between the substituted benzoxaboroles and the AMP also follows a Hammett type relationship, Figure 4, under these conditions

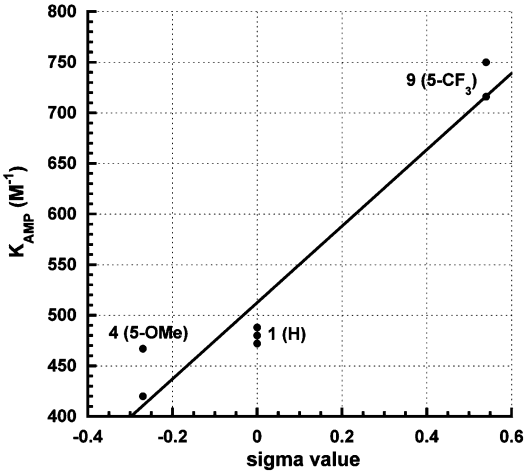

Figure 4. Hammett analysis of the relationship between substituent σ values vs benzoxaborole-AMP binding constants (K_{AMP}) at pH 7.4 in phosphate buffer.

(pH = 7.4, phosphate buffer). Examination of the data reveals that as the substituent σ value increases, along with decreasing pK_a, the binding to AMP increases. This indicates that both phenomena are due to enhanced stability of the anionic tetrahedral products as aided by removal of electron density about boron. These relationships, as determined under physiologically relevant conditions, should prove useful to the medicinal chemist working with these compounds.

In conclusion, the spectrophotometric method for the determination of benzoxaborole ionization constants developed and utilized in this study is preferable to ^{11}B NMR titration methods due to the lower amount of compound needed for analysis and faster determinations made on readily available equipment. From the examination of the results obtained for compounds **1**−**3**, medicinal chemists should take note that the oxaborole ring system seems to be a privileged structure for the lowering of aryl-boronic acid pK_a. However, aryl ring substitutions provide a ready and predictable means for the tailoring of compound pK_a and sugar-binding strength.

■ EXPERIMENTAL PROCEDURES

2-(Hydroxymethyl) benzene boronic acid cyclic monoester (benzoxaborole, **1**) was purchased from Lancaster Synthesis, Inc.; 2-(2-hydroxyethyl) benzene boronic acid cyclic monoester (benzoxaborin, **2**) and 3,3-*gem*-dimethyl-benzoxaborole (**3**) were provided by Scynexis, Inc.; substituted benzoxaboroles [−OMe (**4**), 5-F-6-F (**5**), 5-Me (**6**), 4-F (**7**), 6-F (**8**), and 5-CF_3 (**9**)][23] were provided by Anacor Pharmaceuticals, Inc. Common solvents and reagents were obtained from commercial sources and were of the highest available purity.

Buffer stock solutions of 500 mM were prepared and adjusted to the final pH as follows: acetic acid−sodium acetate (pH = 4.0, 4.5, and 5.0), MES (pH = 5.5, 6.0, and 6.5), HEPES (pH = 7.0, 7.5, and 8.0), and CHES (pH = 8.6, 9.0, 9.5, and 10.0). Analyte compound stock solutions were prepared at 200 mM in DMSO. Aqueous solutions for spectroscopic analysis consisted of 50 mM buffer or 100 mM HCl or

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NaOH, 1% v/v DMSO, and 0.1−1.0 mM compound in ddH_2O at each pH. Ethanolic solutions for spectroscopic analysis were as above but also included 50% v/v anhydrous ethanol. Solutions were placed into 1 mL quartz cuvettes, and UV/visible spectral scans were taken from 240 to 340 nm (1 nm resolution) utilizing a Cary 100 Bio UV/vis spectrophotometer. The final solution pH was determined by measuring the pH of mock solutions (5 mL, lacking only compounds) on a Radiometer pH meter calibrated against aqueous buffer solutions using a combination electrode without correction for liquid junction potentials.

Data analysis included normalization of the raw scans ($Abs_{340\ nm}$ = 0) followed by calculation of the spectral difference between the acid spectra and the spectra obtained at every other pH. The wavelengths of maximum positive and negative deviations were determined graphically, and the absolute values of the absorbance difference at the chosen wavelengths were summed. The total absorbance difference was then plotted vs pH, and the data were fit to eq 6 to obtain the pK_a.

$$\text{absorbance total} = \frac{\varepsilon_{HA} - \varepsilon_{A-}*[10(pH - pK_a)]}{1 + 10(pH - pK_a)}*[S_t] \quad (6)$$

where ε_{HA} and ε_{A-} are the extinction coefficients of the acid and base forms of the compound, respectively, and $[S_t]$ is the total compound concentration. When using absorbance differences, the ε_{HA} and ε_{A-} are simply the minima and maxima of the curve.

All K_{AMP} values were obtained by Alizarin Red S (ARS) competitive experiments as developed by Springsteen and Wang.[37] Prepared were the following solutions: solution A − 0.144 mM ARS in 0.1 M phosphate solution, pH 7.4; solution B − 15 mM **1**, **4**, or **9** in solution A. Solutions A and B were mixed such that final [benzoxaborole] = 1.2−4.0 mM. UV absorbance measurements were taken from 450 to 460 nm to obtain maximum absorbance and plotted vs [benzoxaborole]. Multiple experiments were carried out to determine an average value of K_{ARS} for each compound. To obtain the binding constant with AMP in the three-component assay, prepared were the following solutions: solution C − solution B with **1**, **4**, or **9** was diluted with solution A such that [benzoxaborole] = 10 mM; solution D − 250 mM AMP in each solution C. Respective solutions C and D were mixed such that final [AMP] = 100−200 mM. UV absorbance measurements were taken from 450 to 460 nm to obtain maximum absorbance and plotted as described previously.[18]

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details and characterization of **2** and **3**; each compound's spectra and the subsequent pK_a determination plots; equations for the three-component, ARS method of binding constant determination; and binding constant determination example data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

J.W.T. and S.J.B. designed the research, J.W.T. determined all compound pK_a values and prepared the manuscript, A.P. determined the binding constants, J.W.T. analyzed the data, and D.G.H. and S.J.B. provided manuscript revisions.

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■ ABBREVIATIONS

PBA, phenyl boronic acid; AMP, adenosine monophosphate; ARS, Alizarin Red S

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