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^{11}B NMR Spectroscopy: Structural Analysis of the Acidity and Reactivity of Phenyl Boronic Acid−Diol Condensations

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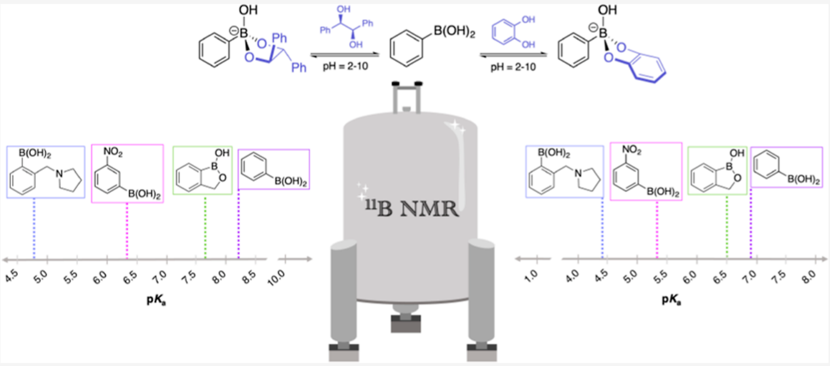

ABSTRACT: Phenyl boronic acids are valuable for medical diagnostics and biochemistry studies due to their ability to readily bind with carbohydrates in water. Incorporated in carbohydrates are 1,2-diols, which react with boronic acids through a reversible covalent condensation pathway. A wide variety of boronic acids have been employed for diol binding with differing substitution of the phenyl ring, with the goals of simplifying their synthesis and altering their thermodynamics of complexation. One method for monitoring their pK_a's and binding is ^{11}B NMR spectroscopy. Herein, we report a comprehensive study employing ^{11}B NMR spectroscopy to determine the pK_a of the most commonly used phenyl boronic acids and their binding with catechol or *d,l*-hydrobenzoin as prototypical diols. The chemical shift of the boronic acid transforming into the boronate ester was monitored at pHs ranging from 2 to 10. With each boronic acid, the results confirm (1) the necessity to use pHs above their pK_a's to induce complexation, (2) that the pK_a's change in the presence of diols, and (3) that ^{11}B NMR spectroscopy is a particularly convenient tool for monitoring these interconnected acidity and binding phenomena.

■ INTRODUCTION

Boronic acid−diol condensations have been widely used in sensors for biomedical applications. The ability for boronic acids to selectively bind with 1,2-diols, a common moiety in carbohydrates, is a valuable interaction used in the early detection of diseases like cancer and diabetes.[1] The tools to study this binding have evolved over the past century. In 1832, Jean Baptiste Biot discovered a change in optical rotation upon the addition of boric acid to tartaric acid.[2] After this work, it was not until 1959 for Lorand and Edwards[3] to first quantify binding affinities of phenyl boronic acids to polyols (saccharides, 1,2- and 1,3-diols) using pH depression. Since then, boronic acid−diol binding motifs have been incorporated into hydrogels, covalent organic frameworks, nanomaterials, polymers, and electrochemical- and chemosensors for carbohydrates, commonly studied using fluorescence or indicator displacement assays.[4−10] Additionally, the boronic acid−diol binding pair has been used as a building block for creating dynamic assemblies composed of gold nanoparticles.[11] Although boronic acid and diol binding have been employed in this wide range of applications, there is still a need for a simple characterization tool to study the key features that underlie the binding, such as the effects of structural changes that contribute to the condensation reaction at varying pH ranges.

The mechanistic pathways for boronic acid−diol condensation exemplify the importance of an understanding of boronic acid acidity and electronic effects from both the diol and boronic acid. A thermodynamic cycle with two different pathways exists that couples the diol binding with acid/base reactions (Scheme 1). In one leg of the cycle, a *sp*^{2}-hybridized boronic acid, $\boldsymbol{\alpha}$, possessing an empty p-orbital, undergoes hydroxylation by water, thereby generating hydronium, and $\boldsymbol{\beta}$ (hence the term "boronic acid"). This generates a sp^3 borate anion, $\boldsymbol{\beta}$, which dominates at pHs above the pK_a of the boronic

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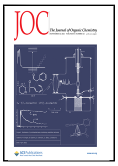

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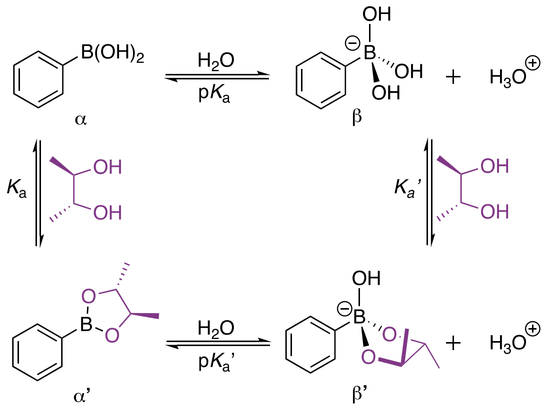
Scheme 1. Mechanistic Pathway to Form a Boronate Ester, *β′*, from a Boronic Acid, *α*[a]



[a] There are two mechanistic pathways, either going from ***α*** to the borate species ***β*** prior to exchanging with the 1,2-diol or ***α*** exchanging with a 1,2-diol forming a boronic ester, ***α′***, prior to forming ***β′***. The key for both mechanistic pathways is exceeding the pK_a of the boronic ester.

acid. In the presence of 1,2-diols, ***β*** is in equilibrium with boronate ester ***β′***. In this second pathway, the 1,2-diol binds with ***α*** creating a boronic ester ***α′***. Once ***α′*** is formed, it can also act as an acid via hydroxylation generating ***β′*** and releasing hydronium. Although both ***α′*** and ***β′*** have the diol bound, one of these species is more thermodynamically stable than the other, which is dictated by the pH of the solution and any strains introduced upon diol binding. It has been reported that creating a five-membered ring is less strained with an *sp*^{3} boron (***β′***) than an *sp*^{2} boron (***α′***).[12−15] Thus, the key to forming the more stable five-membered ring of the boronate ester ***β′*** in both pathways is to use a pH that exceeds the pK_a of the boronic ester. This is a critical feature that is sometimes overlooked in studies using boronic acids to bind carbohydrates and other diols in aqueous media. Further, the pK_a is thereby dependent not only upon the boronic acid but also upon the diol.

Sumerlin and co-workers[16] assessed six boronic acid derivatives (Figure 1) with varying electronic features to determine their binding affinities to fructose, glucose, and sorbitol using ultraviolet−visible (UV−vis) spectroscopy. The boronic acids spanned from a Wulff type,[17] a five-membered heterocycle,[14] and electron-deficient boronic acids.[18] Using a series of competitive binding assays, Sumerlin was able to determine the binding affinities of each boronic acid derivative with the desired saccharide. The significance of Sumerlin's work portrays the importance of considering the relative design of the boronic acid and the reactivity of the diol to shed light upon the structural feature requirements for exceeding the pK_a.

While indicator displacement assays are common methods for characterizing the boronic acid−diol condensation,[19−21] ^{11}B nuclear magnetic resonance (NMR) is relatively easy and provides the structural information needed to determine whether the boronic acid−diol condensation reaction has been achieved under the given conditions. Boron has two naturally occurring nuclei, ^{11}B and ^{10}B with a spin of 3/2 and 3, respectively. While both ^{11}B and ^{10}B are active nuclei for NMR spectroscopy, ^{11}B is more sensitive due to the lower quadrupole moment and being 80.10% naturally abundant.[22] ^{11}B NMR spectroscopy is commonly viewed as impractical due to needing adequate concentrations to observe signals and the need to use quartz NMR tubes to avoid a residual broad signal in the spectrum from borosilicate glass NMR tubes.[23,24] In our experience, we have found that ∼4 mg of the boronic acid is needed within 0.65 mL of deuterated solvent (with 1024 scans at 128 MHz).

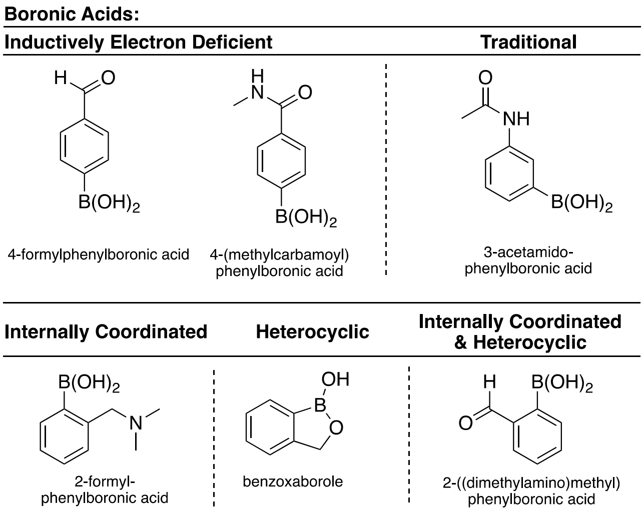
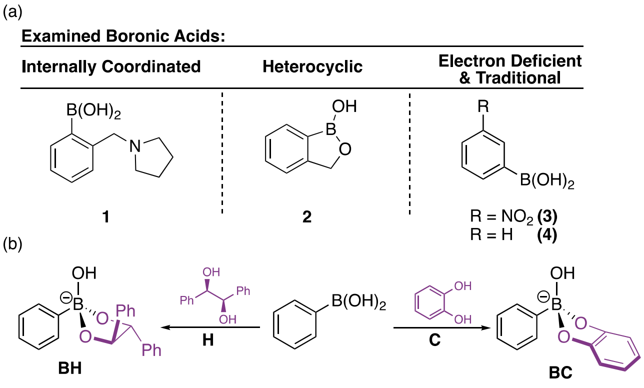


Figure 1. Different boronic acids used in Sumerlin's work.[16] Each exhibits different electronic behaviors that are attributed to modifying the pK_a.

Previous reports have used ^{11}B NMR spectroscopy to distinguish the *sp*^{2}-hybridized boronic acid and *sp*^{3}-hybridized borates and boronate esters.[12] Upon reaching the pK_a of a *sp*^{2}-hybridized boronic acid, the chemical shift moves upfield substantially due to shielding from the negative charge associated with the *sp*^{3}-hybridized species.[24] Thus, ^{11}B NMR spectroscopy is an extremely useful technique to determine the binding events associated with a given boronic acid and can be used to determine the pK_a of boronic acids when varying the pH.[25] While the chemical shifts have been widely documented, inconsistencies can be found within the literature when characterizing *sp*^{2} versus *sp*^{3}-hybridized boronic acid derivatives due to the complexity of ^{11}B NMR spectra. Thus, we saw a need to exemplify the benefits of ^{11}B NMR spectroscopy for measuring boronic acid binding and pK_a's, accentuating that it is a very simple tool for such studies, while also complementing the Sumerlin studies.

A set of commonly used boronic acids were employed for this study (Scheme 2a). The Wulff-type boronic acid, *ortho*-(pyrrolidinylmethyl)phenylboronic acid, **1**, has been widely postulated to exhibit an internal B−N coordination, that is, a dative bond.[26] Numerous examples have exemplified that Wulff-type boronic acids have a lower pK_a than traditional boronic acids due to the B−N bond.[24] However, we have shown that the B−N dative bond only exists in aprotic media,[27,28] while in protic media, the solvent (often water or methanol) is inserted between the N and B atoms, akin to a frustrated Lewis pair.[29] This structure also adequately explains the lowering of the pK_a of Wulff-type boronic acids relative to those lacking an *ortho*-(aminomethyl) group.[19] We also studied heterocyclic boronic acids, such as benzoxaboroles, as pioneered by the Hall research group,[30] **2**. The structures have been demonstrated to bind diols at neutral pH. Here, the appended *ortho*-(hydroxymethyl) group acts akin to the *ortho*-(aminomethyl) groups in the Wulff-type boronic acids.

Scheme 2. (a) Four Different Boronic Acids Used for the Structural Analysis; (b) with Each Boronic Acid, Either No Additive (Not Shown), Catechol, C, or *d,l*-Hydrobenzoin, H, Was Used to Examine the Structural Behavior, Where the Boronic Acid Forming the Boronate Ester with C Is Denoted as BC and with the H as BH



Additionally, an electron-withdrawing group in the meta position to the boronic acid moiety will lower the overall pK_a of the boronic acid species, as exemplified with (3-nitrophenyl)boronic acid, **3**.[31] Lastly, unsubstituted phenyl boronic acid, **4**, was also characterized and used as a reference to compare to these other boronic acids.

Commonly used 1,2-diols, *d*,*l*-hydrobenzoin, **H**, and catechol, **C**, were combined in excess with each boronic acid to form the respective boronate esters **BH** or **BC** (Scheme 2b). Given that the binding constants of these diols are in the vicinity of 10^3 M^{-1} in water/methanol mixtures, using the boronic acids at [40 mM] and the diols at [80 mM] ensured >95% complexation. The diol, **H**, was chosen due to previous literature that demonstrated the preference of *d*,*l*-hydrobenzoin over the *meso*-hydrobenzoin isomer.[32] These diols were also examined due to their extensive use and utility in forming reconfigurable assembly systems in polymer and materials science.[33−37]

■ RESULTS AND DISCUSSION

^{11}B NMR spectroscopy was used to follow the transformation of the sp^2-hybridized boronic acid into the tetrahedral, sp^3-hybridized, boronate ester (Figures S1−S24). For the boronic acids, **1** through **4**, three experiments were performed to determine the pK_a of the boronic acids: (1) no additive (changing only the pH), (2) addition of **C**, and (3) addition of **H**. The pH ranged from 2 to 10. We used the methanol/water (3:1) solvent system, and the pH was altered using hydrochloric acid or sodium hydroxide. Due to a lower solubility in water, **4** was used in a methanol/water 9:1 ratio. ^{1}H NMR spectra were taken prior to each ^{11}B NMR experiment to avoid the use of the toxic internal standard BF_3:OEt_2; and instead, trimethylsilane was used as the internal standard.[38]

In acidic media (pH ≅ 2), the boronic acids **1** through **4** are sp^2-hybridized boron species with a chemical shift ranging from approximately 27 to 33 ppm. However, upon the addition of base, the chemical shifts move upfield approximately between 4 and 10 ppm, depending upon the boronic acid, indicative of forming a sp^3-hybridized borate $\boldsymbol{\beta}$ (Figure 2a). Upon addition of either **H** or **C**, the individual chemical shift for each boronic acid is the same in the acidic media, showing that no significant formation of boronate ester $\boldsymbol{\beta'}$ occurs (i.e., comparing Figure 2b,c to 2a). However, under basic conditions (pH ≅ 9−10), the chemical shifts again move downfield in the presence of **H** or **C**, now between 7.5 and 13.0 ppm. For each boronic acid in the presence of **H**, the chemical shifts are different than without **H**, indicative of forming **BH** boronate esters $\boldsymbol{\beta'}$ (Figure 2b, bottom panel). Similar results are found for the ^{11}B NMR analysis of **1** through **4** with the addition of **C**; that is, at high pHs, binding occurs to create **BC** ($\boldsymbol{\beta'}$ species). This conclusion is indicated by the fact that the chemical shifts of the dominate species are all different than with no additive or with the addition of **H** (Figure 2c, bottom panel).

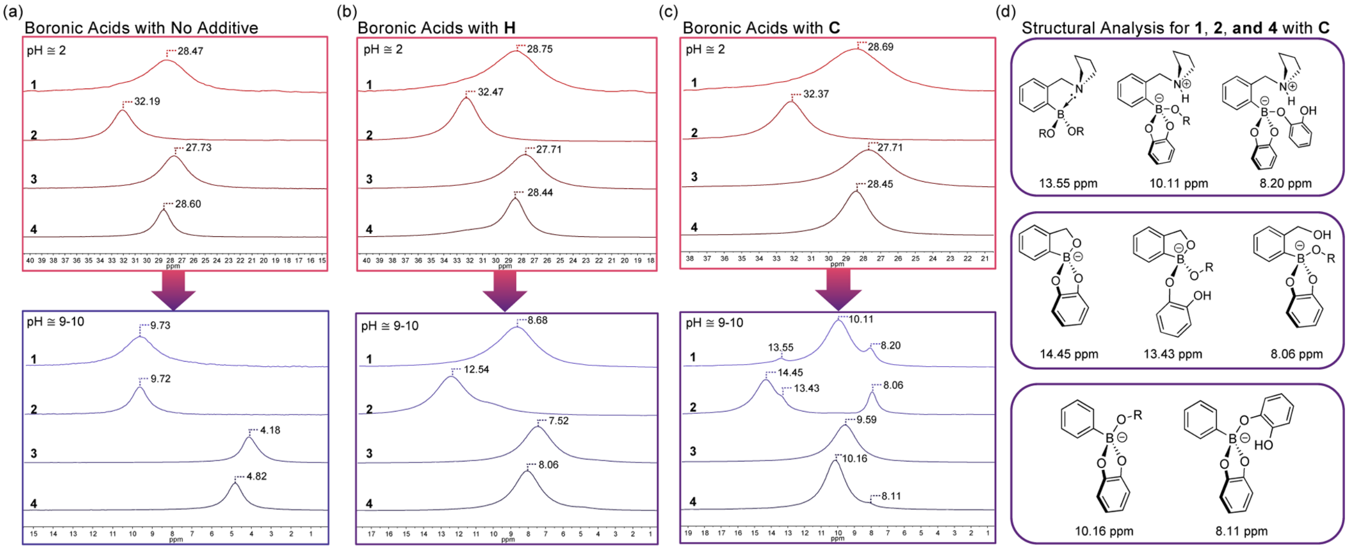


Figure 2. (a) Chemical shifts of the boronic acids **1** through **4** with no additives at a pH ≅ 2 and 9−10. (b) Chemical shifts of the boronic acids **1** through **4** (40 mM) with **H** in excess (80 mM) at pH ≅ 2 and 9−10. (c) Chemical shifts of the boronic acids **1** through **4** (40 mM) with **C** in excess (80 mM) at a pH ≅ 2 and 9−10. (d) ^{11}B NMR spectroscopy analysis of **1**, **2**, and **4** with **C** in excess (80 mM) under the basic condition (pH ≅ 9−10).

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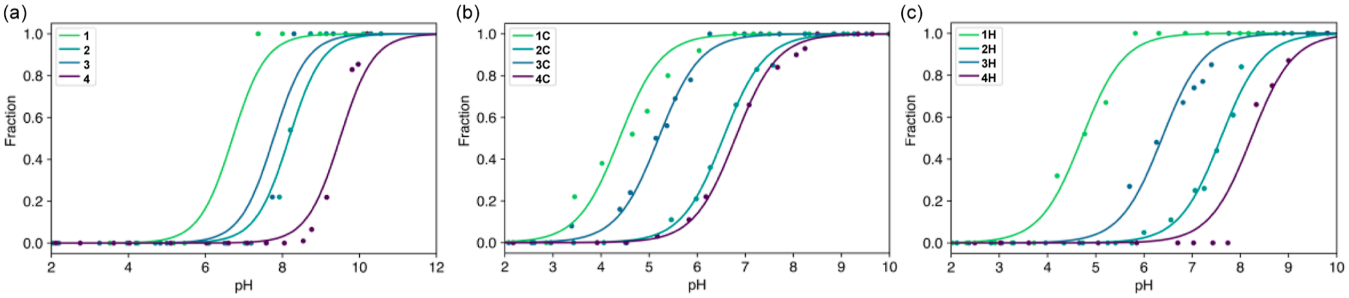


Figure 3. Henderson−Hasselbach sigmoidal analysis: (a) mole fraction vs the pH using ^{11}B NMR of **1**−**4** ([40 mM], solvent: MeOH-d_4/D_2O (3:1)) with no additive. The inflection is representative of the boronic acid derivative transforming into the borate. (b) Mole fraction vs pH using **1**−**4** ([40 mM], solvent: MeOH-d_4/D_2O (3:1)) with **C** [80 mM]. The inflection is representative of the boronic acid derivative transforming into the boronate ester. (c) Mole fraction vs pH using **1**−**4** ([40 mM], solvent: MeOH-d_4/D_2O (3:1)) with **H** [80 mM]. The inflection is representative of the boronic acid derivative transforming into the boronate ester.

Interestingly, upon analyzing the ^{11}B NMR spectra of **1**, **2**, and **4** **BC** species under basic conditions, small additional peaks were found. With **1**, the resonance at 10.11 ppm is the dominate species corresponding to bound catechol with solvent insertion (either water or methanol) between the N and B atoms. However, peaks at 13.55 and 8.20 ppm are also present. The 13.55 ppm resonance corresponds with previous reports demonstrating a very small extent of B−N dative bond formation, which seems to only occur with catechol (Figure 2d).[28] The 8.20 ppm resonance has been previously assigned to the coordination of a second catechol in place of the inserted solvent.[28] The binding with **2** is less widely understood as the reactivity of this boronic acid has been less studied. Three different species were found within the basic media: 14.45 (major), 13.43 (tiny), and 8.06 ppm (minor) (Figure 2c). The species at 14.45 ppm is undoubtedly catechol bound with an intramolecular five-membered ring (analogous to a B−N dative bond), and we hypothesize that the 13.43 ppm resonance is addition of a second catechol as found for **1**. However, the peak located at 8.06 ppm is highly suggestive of O−B bond breaking within the five-membered ring (Figure 2d) because the resonance moved upfield, whereas the 5-membered ring species are typically downfield. With compound **3**, only one species was found, with a resonance at 9.59 ppm (Figure 2c). Lastly, compound **4** shows two peaks under basic media with **C** at 10.16 (major) and 8.11 (minor) ppm. These can be attributed to one and two catechols' binding to the boron, respectively (Figure 2d). A take-home lesson is that catechol, due to its lower acidity than methanol, or water, or the intramolecular alcohol in **2**, has some tendency to bind to a second equivalent, displacing the associated solvent or intramolecular alcohol of **2**.

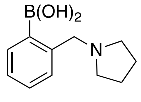
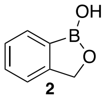
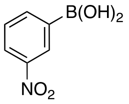
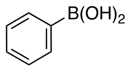
Using the Henderson−Hasselbach equation,

$$\mathrm{pH} = \mathrm{p}K_a + \log_{10}\left(\frac{[\mathrm{A}^-]}{[\mathrm{HA}]}\right) \tag{1}$$

the pK_a can be determined by measuring the pH and concentration of the conjugate base, A^-, and acid, HA. While the ratio of [A^-] to [HA] is based on concentrations, it can be related to the fraction of the sp^2-hybridized boronic acid and the sp^3-hybridized boronate ester, respectively. Thus, the fraction between the sp^2 and sp^3 boron species was determined by integrating the respective signals in the ^{11}B NMR spectra. The pH was altered incrementally for each boronic acid **1** through **4** [40 mM] with no additive and with the addition of twofold excess **C** and **H** (Figures S1−S24). Then, the fraction between the sp^2 and sp^3 boron species was plotted against the varied pH's (Figure 3a−c). The distinct sigmoidal curves, indicative of the Henderson−Hasselbach equation, gave rise to the pK_a's (Table 1).

Note that in a few of the NMR-pH titrations, the chemical shifts were reasonably unresponsive to the change in pH until near the pK_a values, when a large jump occurs. This behavior occurred for those studies where the ^{11}B NMR resonances became very broad as the pH was varied, sometimes approaching the baseline. This can be attributed to the

Table 1. pK_a's of the Boronic Acids with No Additive, C, and H Compared with Literature Values[16,28,30,31,40−42] (Many with Different Diols)[b]

Boronic Acid	p*Ka*: No Additive	C	H	Literature Values
 1	6.7	4.4	4.7	5.3[15] 6.5[27] 6.7[38]
 2	8.2	6.5	7.6	7.3[29] 7.2[39] 7.15[15]
 3	7.8	5.2	6.4	7.1[38] 7.0[30,40]
 4[a]	9.5	6.8	8.2	8.8[38] 8.7[30] 8.5[15]

[a]The solvent system used 9:1 MeOH/water. [b]pK_a determination: reference 15 no additive, acidic buffer soln. [0.1 M], and titrated with dilute NaOH. Reference 27 no additive, 75% methanolic soln. with HEPES. Reference 29 aq. HCl and NaOH [0.1 M]. Absorption differences were monitored via UV−vis. Reference 30 via titration with standard base. Reference 38 ARS [9 × 10^{-6} M] with 20% free boronic acid. Titrated in [0.1 M] phosphate buffer with sugar keeping [boronic acid] and [ARS] constant. Spectral differences were measured using fluorescence. Reference 39 average pK_a determined by (1) **2** [0.05 M] with the addition of base (0.025 M NaOH, 0.015 M NaCl in water). Potentiometric studies determined the pK_a = 7.2. (2) ^{11}B NMR (10% D_2O in H_2O, **2** [16 mM] in 0.10 M phosphate buffer). Reference 40 diol = 4-isopropyltropolone with 10% acetonitrile in acidic soln.

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chemical exchange rate between the boronic acid and diol approaching that of the NMR spectrometer, leading to a loss of a signal to integrate (Figure 3a–c).

The pK_a's of the boronic acids **1** through **4** with no additives are higher than when **C** or **H** is present. This can be attributed to the thermodynamic sync that is made when forming a boronate ester (Scheme 2). When considering the pathway involving the intermediacy of $\boldsymbol{\alpha}'$, the bound diol influences the electrophilicity of the B-atom and therefore affects the hydroxylation that releases hydronium, that is, the acidity reaction. Moreover, when considering the pathway with the intermediacy of $\boldsymbol{\beta}$, the binding of the diol pulls the equilibrium toward $\boldsymbol{\beta}'$, and therefore, this equilibrium is coupled to the pK_a values. Additionally, for each of the four boronic acids, the pK_a measured was lower when using **C** compared to **H**. Because **C** binds with boronic acids better than **H**,[33] the reasoning just presented about pathways involving $\boldsymbol{\alpha}'$ or $\boldsymbol{\beta}$ nicely explains why the pK_a associated with the binding of **C** is lower. Thus, the lesson is that in the presence of **C** or **H** (or any another diol, or sugar), these pK_a values (or others reported in the literature) are not distinctly for either structures $\boldsymbol{\alpha}$ or $\boldsymbol{\alpha}'$.

As a comparison, Table 1 lists pK_a values reported elsewhere in the literature, and in refs 15272930, and 38–40, we list the conditions in these studies as the table footnote. Many of the literature values (Table 1) previously reported for **1** through **4** vary from one another and from the experimental findings reported herein. However, refs 15 and 38 use an analogue of **1**, 2-((dimethylamino)methyl)phenyl boronic acid instead of **1**. Additionally, with the exception of refs 38 and 40, all pK_a's were determined with no diol present and in an aqueous environment that varied from pure water (DI, Milli-Q, or unspecified) to different mixtures of methanol– or acetonitrile–water mixtures. References 38 and 40 used the diols alizarin and 4-isopropyltropolone, respectively, in aqueous conditions. The varying pK_a values reflect the different solvent systems, different diols, and possibly even differences in the methods used (albeit, of course, this should not affect a thermodynamic value).

The pK_a's listed in Table 1 derived from our ^{11}B NMR titrations are for solutions with large proportions of methanol. It is well documented that in lower dielectric media, pK_a values tend to increase relative to pure water.[39] The literature values for compound **4**, all hovering around 8.7, have been taken as an example. Yet, in 90% methanol, we measured a value of 9.5. Similarly, for compound **3**, the literature values for water are near 7.0, but in 75% methanol, we found a value of 7.8. Thus, for the other values in our table (with added **C** and **H**), we may expect the pK_a values in pure water to be around 0.7 to 0.8 pK_a units lower.

SUMMARY

^{11}B NMR spectroscopy was used to analyze four commonly used boronic acids with two different diols. The spectra accentuate the need to use a pH that exceeds the apparent pK_a of the boronic acid when in the presence of a diol in order for the diol to bind. When using catechol as a guest, small extents of a second guest association are found. We also analyzed the chemical shifts of a *sp*^{2}-hybridized boron, and *sp*^{3} boron species, to determine the pK_a using a Henderson–Hasselbach-like analysis, and compared the values to the literature. Critically important, the pK_a values are influenced by the binding of the diols. This experimental study acts as a reference guide for using boronic acid diol condensations and ^{11}B NMR spectroscopy and for determining the necessary pH needed to form a desired boronate ester.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01514.

> ^{11}B NMR-pH analysis and experimental overview, ^{11}B NMR pK_a analysis, pK_a determination for **1–4**, and equilibrium concentration calculations (PDF)

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Author Contributions

S.A.V. wrote the initial draft of the paper, while E.V.A., J.R.H., H.M.P., and S.D. provided edits to the draft. J.R.H. wrote the Henderson–Hasselbach script used to determine the pK_a of the spectra. H.M.P. helped develop the experimental protocol. S.D. took the ^{11}B NMR spectra of **1–4** without buffer. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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