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Lewis or Brønsted? A Rectification of the Acidic and Aromatic Nature of Boranol-Containing Naphthoid Heterocycles

M. Zain H. Kazmi,[#] Jason P. G. Rygus,[#] Hwee Ting Ang, Marco Paladino, Matthew A. Johnson, Michael J. Ferguson, and Dennis G. Hall*

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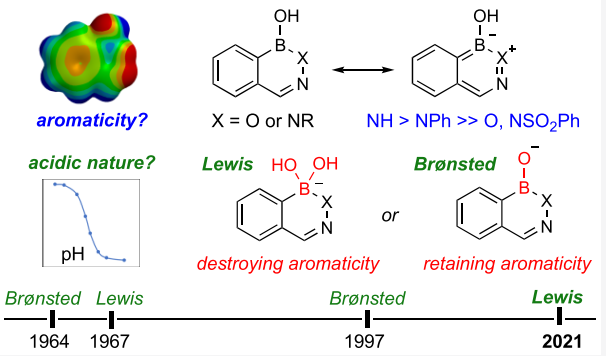
ABSTRACT: Boron-containing heterocycles are important in a variety of applications from drug discovery to materials science; therefore a clear understanding of their structure and reactivity is desirable to optimize these functions. Although the boranol (B−OH) unit of boronic acids behaves as a Lewis acid to form a tetravalent trihydroxyborate conjugate base, it has been proposed that pseudoaromatic hemiboronic acids may possess sufficient aromatic character to act as Brønsted acids and form a boron oxy conjugate base, thereby avoiding the disruption of ring aromaticity that would occur with a tetravalent boronate anion. Until now no firm evidence existed to ascertain the structure of the conjugate base and the aromatic character of the boron-containing ring of hemiboronic "naphthoid" isosteres. Here, these questions are addressed with a combination of experimental, spectroscopic, X-ray crystallographic, and computational studies of a series of model benzoxazaborine and benzodiazaborine naphthoids. Although these hemiboronic heterocycles are unambiguously shown to behave as Lewis acids in aqueous solutions, boraza derivatives possess partial aromaticity provided their nitrogen lone electron pair is sufficiently available to participate in extended delocalization. As demonstrated by dynamic exchange and crossover experiments, these heterocycles are stable in neutral aqueous medium, and their measured pK_a values are consistent with the ability of the endocyclic heteroatom substituent to stabilize a partial negative charge in the conjugate base. Altogether, this study corrects previous inaccuracies and provides conclusions regarding the properties of these compounds that are important toward the methodical application of hemiboronic and other boron heterocycles in catalysis, bioconjugation, and medicinal chemistry.



INTRODUCTION

Once viewed as a chemical curiosity, boron-containing heterocycles have taken a growing place in chemistry as remarkable compounds with various uses.[1] They display a wide range of properties and applications from functional luminescent materials and sensors to pharmaceutical drugs. The replacement of alkene C=C bonds with the isoelectronic and isosteric B−N/B−O bonds has been shown to significantly alter the photophysical and electronic properties of a molecule.[2,3] In drug discovery, the use of boron−heteroatom bonds is an emerging strategy to unveil novel bioisosteric pharmacophores with unique properties and opportunity to explore uncharted patent space.[4,5] For example, guided by new fundamental advances,[6] three cyclic nonaromatic hemiboronic acids were developed and commercialized as therapeutic agents in the past decade (Figure 1A).[7−9] These boranol (B−OH) compounds offer desirable *in vivo* properties as mild acids, with a unique ability to undergo reversible exchange of their boron−hydroxy bonds with alcohols and carboxylate groups on target biomolecules. Similarly, pseudoaromatic boron heterocycles display great potential, as demonstrated by recent developments in the use of 1,2-azaborine as an isosteric replacement of benzene rings in various preclinical candidates (Figure 1B).[10−12] Pseudoaromatic hemiboronic acids constitute another important and diverse subclass that has been studied for the past five decades. Among the most studied are the benzoxazaborine and benzodiazaborine scaffolds represented by compounds **1**−**3**, which are isosteric and isoelectronic to isoquinoline (e.g., **4**), along with the "inverted" naphthoids **5** and **6** and the phenanthroids **7** and **8**.[1] For example, 1-hydroxy-1,2-dihydro-2,3,1-benzodiazaborines have been proposed as components of molecules mimicking estrogen and other steroid hormones,[13] whereas *N*-sulfonyl derivatives were identified as potent inhibitors of bacterial NAD(P)H-dependent enoyl acyl carrier protein reductase[14,15]

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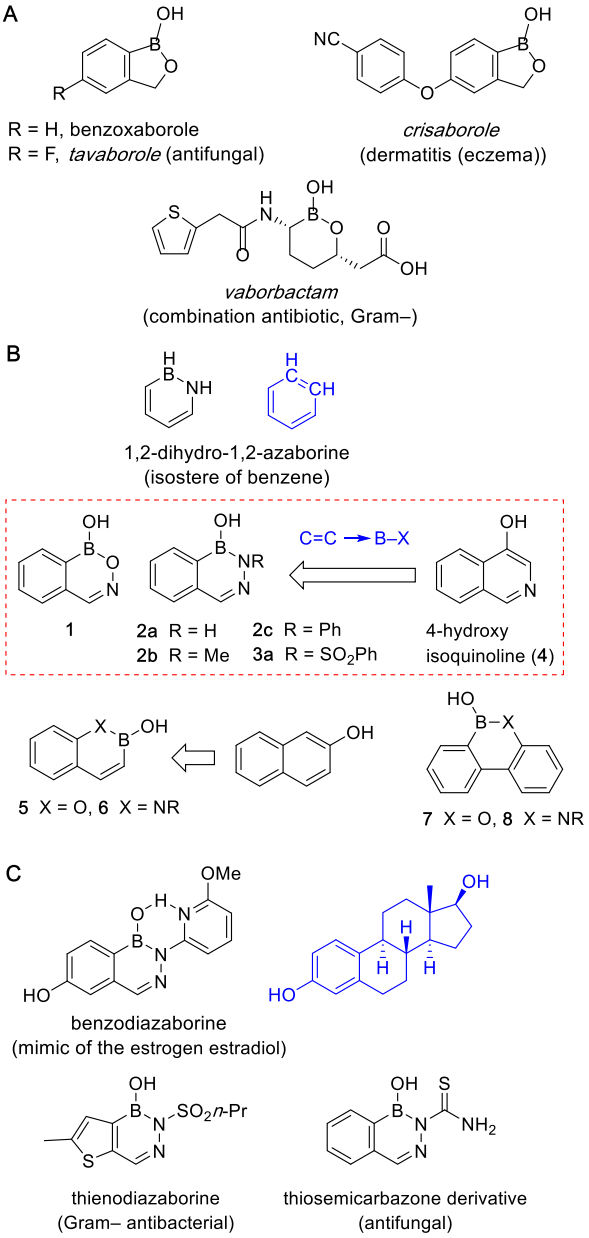

Figure 1. (A) Cyclic nonaromatic hemiboronic acid drugs. (B) Classes of pseudoaromatic boron heterocycles featuring C═C/B–X isosterism, with model compounds **1**, **2a–c**, and **3a** studied herein. (C) Examples of biologically relevant naphthoid hemiboronic acid heterocycles.

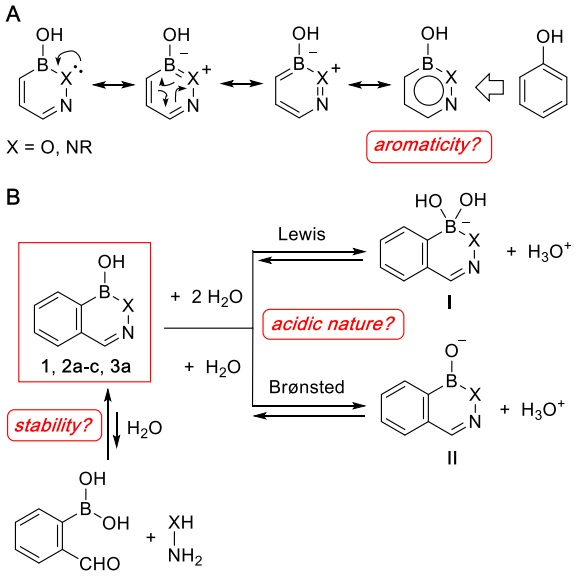

Figure 2. (A) Resonance and pseudoaromaticity in oxazaborine and diazaborine rings. (B) Questions of stability in aqueous medium and Lewis or Brønsted acidic nature addressed herein. (X = O, NR)

and the human neutrophil elastase (NHE) serine protease,[16] whereas thiosemicarbazone derivatives demonstrated antifungal activity (Figure 1C).[17]

Over the past 50 years, several important characteristics of these compounds' structural nature and properties have been the subject of debate and confusion. Taking into account the contribution of B_p–X_n resonance of the lone electron pairs from the endocyclic O or N atom into boron's vacant p orbital, the planar heterocyclic ring contains six delocalized π electrons and thus meets Hückel's rule (Figure 2A). Although the boron-containing rings of compounds **1–3** and **5–8** are isoelectronic and isosteric to phenol, claims pertaining to the extent of these compounds' aromatic character have varied widely. In part due to their pseudoaromaticity, their acidic nature has also been questioned, with reports claiming they act as Lewis acids and other reports suggesting Brønsted acidic behavior akin to alcohols (see Background section below). In the former, the corresponding conjugate base **I** disrupts the ring's putative aromatic character through forming a tetravalent hydroxyboryl structure similar to that of the borate anion and reminiscent of a ketone hydrate (Figure 2B).

This sort of indirect Brønsted acidity via boron's Lewis acidic behavior is well established for acyclic boronic acid derivatives. Indeed, although they can engage in hydrogen-bonding interactions in both the solid state and solution,[18,19] boronic acids form a tetravalent trihydroxyborate anion as their conjugate base in water.[20] In the case of Brønsted acidic behavior, the compounds would behave like alcohols and undergo deprotonation of the boranol (B–OH) unit to give a boron oxy anion **II** that may preserve the ring's pseudoaromatic character (Figure 2B).

No comprehensive studies exist to confirm the nature of the acidity of pseudoaromatic hemiboronic heterocycles in aqueous solutions, and without strong evidence such as X-ray crystallographic structures of the conjugate base of heterocycles **1–3** and **5–8**, this question remains unanswered. To exploit boron heterocycles to their full potential, it is critical to gain a definitive understanding of their aromatic character, their stability in water, and the acidic nature of the boranol unit (Figure 2B), especially in aqueous media relevant to biological applications. Herein, using benzoxaborine compound **1** and *N*-alkyl/aryl benzodiazaborines **2a–c** and *N*-sulfonyl derivative **3a** as models (Figure 1B), we address these questions with a combination of X-ray crystallographic, spectroscopic, and computational studies.

RESULTS

Background. First prepared by Snyder and co-workers in 1958,[21] the properties and reactivity of 1-hydroxy-1*H*-2,3,1-benzoxazaborine (**1**), a borylated oxime, were further studied by Dewar and Dougherty in 1962, along with the diaza derivative **2a**.[22] Noting the compounds' exceptional stability through their resistance to strong aqueous acid and base,

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conditions that would normally destroy boronic acids, the authors concluded that the boron-containing ring of both **1** and **2a** is aromatic. Moreover, by infrared spectroscopy, the NH stretching band of solid **2a** appears at a relatively low frequency (3340 cm^{-1}) that is supportive of B_p-N_n resonance.[23] When **1** was treated with ethanolamine (toluene, Dean–Stark), Dewar also isolated a high-melting-point product suspected to be the adduct **9** (Figure 3A) where any

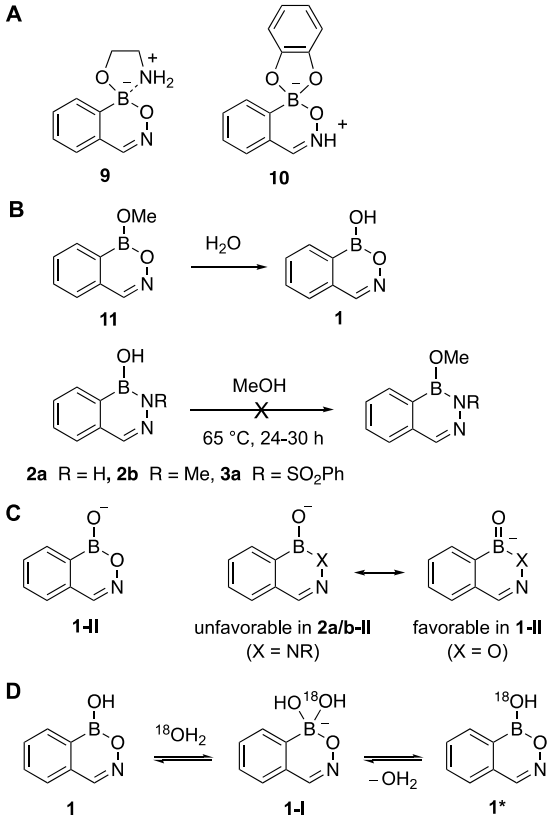

Figure 3. (A) Putative adducts of **1** reported in the 1960s.[23,27] (B–D) Previous studies on the reactivity (B–O bond exchange) and properties of heterocycles **1**–**3**.

ring aromaticity is temporarily destroyed, and, because **2a** failed to form a similar adduct, concluded that the heterocyclic ring of **1** is less aromatic than that of aza analogues **2**.[23] When examined by UV spectroscopy, compound **1** displayed a small bathochromic shift in alkaline solution. Because aromatic boronic acids and benzoxaborole show a small hypsochromic shift under similar conditions and were considered to be Lewis acids, it was concluded that **1** and **2a** must be Brønsted acids.[23] The advent of commercial NMR spectroscopy allowed a new and powerful means of examining the structure of the conjugate base by observing their ^{11}B chemicals shifts, which tend to be highly diagnostic of the hybridization and valence of boron. Whereas neutral trivalent boronic acid derivatives display ^{11}B chemical shifts in the range of 25–30 ppm, their anionic tetrahedral adducts with Lewis bases generally appear drastically upfield between 0 and 5 ppm. Thus, in 1967, Dewar and Jones reported the ^{11}B NMR analysis of **1** and **2a** under neutral (EtOH) and alkaline conditions (20% KOH in EtOH).[24] The resulting chemical shift of 5.0 ppm for the potassium salt of **1**, when compared to the shift of 30.0 ppm for its neutral form in EtOH, is supportive of a tetravalent Lewis base form **I** (cf. Figure 2B). With this new perspective of ^{11}B NMR spectroscopy, Dewar concurred that **1** had been mistakenly identified as a Brønsted acid (in previous UV spectrophotometric studies[23]) and is instead a Lewis acid. In contrast, **2a** was now decisively characterized as being aromatic and, to avoid the ionization of boron that would disrupt its aromatic stabilization, a Brønsted acid.[24] It is noteworthy that no data exist of trivalent boron oxy reference compounds in aqueous solution. Therefore, without such a comparator, the absence of a large upfield shift cannot be firmly associated with a Brønsted acidic behavior. The only available data for trivalent borate oxy salts are in the solid state or in organic solvent, and these species display chemical shifts around 15 ppm that are significantly distinct from tetravalent boronyl anions.[25,26] Subsequent to these NMR studies, Snyder and co-workers reported the isolation of an adduct between **1** and catechol with a composition corresponding to **10** (Figure 3A), in full support of the Lewis acidic character and the inferable lack of appreciable aromatic stabilization in the oxazaborine ring of **1**.[27]

In 1997, benefiting from new methods, Groziak and co-workers re-examined the acidic nature of heterocycles **1** and **2** as part of an elegant study to evaluate their suitability as mimics of nucleic acids.[28] Differences in the reactivity of the compounds were assessed. The methyl ether of **1**, derivative **11**, was found to readily hydrolyze to **1** upon exposure to water (Figure 3B). In contrast, **2a**, **2b**, and **3a** resisted their transformation into a B–OMe derivative when treated with anhydrous methanol even under forcing conditions (65 °C, 24 h). Exchange of the boranol hydroxy group was also studied by mass spectrometry in $^{18}OH_2$. In contradiction of the outcome of MeOH exchange experiments, diazaborines **2a** and **2b** were found to exchange their OH group much more readily than boryl oxime **1**. Ignoring this dichotomy, the authors suggested that the facile ^{18}O incorporation into the diazaborines **2** is indicative of their pronounced Lewis acid character compared to **1**. The compounds were also analyzed by NMR spectroscopy in solution. The authors corroborated the observations of Dewar,[24] confirming that heterocycles **1** and **3a** display a large upfield shift in alkaline solution (2.2 ppm in aqueous NaOH). No such upfield shift was observed for **2a** and **2b**; they both displayed resonances of ~26–27 ppm whether in neutral or alkaline solution. Using potentiometric measurements, **1** was found to be significantly more acidic (pK_a 4.8) compared to **2a**,**b** and **3a** (pK_a ~8).[28] Considering the ^{11}B NMR resonance of **2a** and **2b** provided no upfield shift in alkaline solutions, such near-neutral pK_a values are open to question. Surprisingly, the authors concluded that **1** is a Brønsted acid and ascribed the large upfield ^{11}B NMR shift of its conjugate base (~2 ppm) to the oxy anion structure, **1-II**, which was hypothesized to provide such an upfield ^{11}B resonance in spite of the lack of data for this type of trivalent boron oxy salt in aqueous solution (Figure 3C). This surprising assessment was deemed to best account for the sluggish ability of **1** to incorporate $^{18}OH_2$, as this ability to exchange the hydroxy group on the boranol unit was assumed to proceed through addition–elimination and full ionization into the Lewis base **1-I** that would temporarily disrupt ring aromaticity (Figure 3D). Finally, to support their claim that **2a** and **2b** also display Brønsted-type ionization despite the insensitivity of their ^{11}B NMR shift in alkaline solutions, the authors proposed that little or no delocalization of the oxyanion into boron can occur in the aza analogues due to the likelihood of electrostatic repulsion with the less

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electronegative N atom, which was thought to preclude the accumulation of charge on boron that would create an upfield shift (Figure 3C).

Although they reported X-ray crystallographic studies showing that the acid forms of **1** and **2** can engage in H-bonds in the solid state (with additional evidence by solution NMR studies), Groziak and co-workers did not report crystal structures of any conjugate bases yet concluded that "the B–OH moiety in both **1** and **2** is characterized by a predominant Brønsted acidity".[28] Recently, others have studied *N*-aryl[29,30] and *N*-acyl[31] derivatives of benzodiazaborines **2** for their stability in aqueous solutions, but the question of their conjugate base was not examined in detail.

Synthesis of Model Heterocycles and Spectroscopic Characteristics (NMR, MS). Model heterocycles **1**, **2a–c**, and **3a** were prepared according to literature procedures by condensation of the *ortho*-formyl arylboronic acid and hydroxylamine or hydrazines (see Supporting Information). Key ^{1}H and ^{11}B NMR resonances in acetone-d_6 are shown in Figure 4 along with the corresponding resonances for

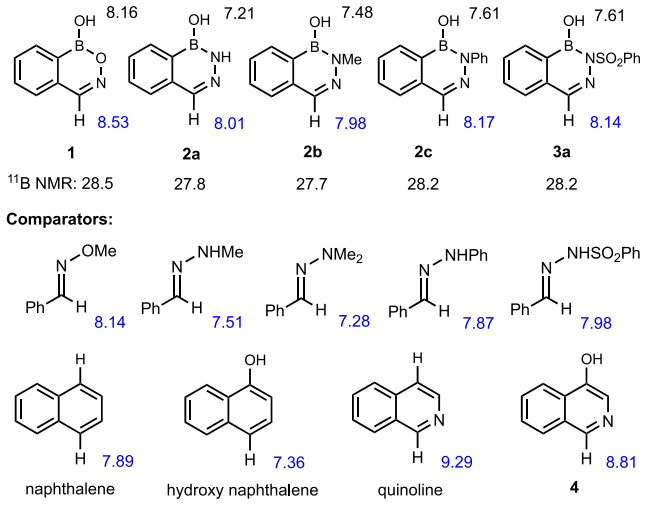


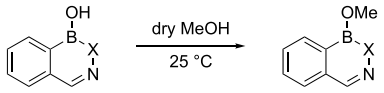
Figure 4. Select NMR spectroscopic data of heterocycles **1**, **2a–c**, and **3a** with comparators (all shifts in ppm; solvent: acetone-d_6).

comparator compounds. Although the ^{11}B NMR resonances show nearly no variance, the boranol proton resonances span a range of ~1 ppm, with **1** being the most deshielded and **2a** the least. Upon addition of a drop of D_2O, a precaution to suppress the formation of B–O–B anhydrides, the boranol resonance disappears, thus confirming the exchangeability of these protons. In the case of heterocycle **2a**, only ~20% of the NH proton exchanged. In agreement with this reluctance to exchange, previous ^{15}N NMR studies of **2a** likened this NH moiety to that of a secondary amide.[28]

The bivalent aldimine-like nitrogen atom of heterocycles **1–3** is not expected to be protonated in neutral aqueous solutions.[32] In support of this assertion, the chemical shift of the aldimine proton was found to be insensitive to an increase of pH. The aldimine resonance of all model compounds is significantly lower than that of the C=C/B–X isostere, 4-hydroxyquinoline (**4**); however it is more downfield compared to the acyclic oxime and hydrazone comparators. The effect is larger for **2a** and **2b**, but it is unclear whether these small differences can be attributed to the electron-withdrawing effect of boron or to the possible occurrence of ring anisotropy.

Mass spectrometric analysis of these compounds tends to provide B–O–B dehydration dimers; however, this phenomenon is typically observed in the gas phase or in anhydrous organic solvents.[31] Formation of these species is kinetically and entropically unfavorable in the presence of water and should not interfere in pK_a measurements and other structural studies in aqueous–organic media. For example, the dimer of **2c**, whose structure was resolved by X-ray diffraction analysis (see Figure S3), was found to break down in a CD_3CN solution upon addition of a small amount of water (see Figure S2).

Behavior and Stability in Hydroxylic Solvents. The possibility for heterocycles **1–3** to exchange their boranol hydroxy group in aqueous medium may provide more information about the nature of their acidic character and the extent of their aromatic stabilization. We first set out to reexamine $^{18}OH_2$ exchange experiments described by Groziak and co-workers with heterocycles **1** and **2a**,**b**[28] as well as extending these investigations to model compounds **2c** and **3a**. The heterocycles, dissolved in anhydrous CH_3CN, were exposed to $^{18}OH_2$ for several hours and analyzed by ESI-TOF mass spectrometry. Due to the large imprecision caused by the occurrence of reverse hydrolysis from adventitious $^{16}OH_2$ in the chamber, these experiments were found to be unreliable. Similar issues may have affected the interpretation of exchange experiments performed by Groziak and co-workers. Instead, we examined the ability of hemiboronic acids **1–3** to undergo methanolysis to form the corresponding methyl hemiboronic esters. To this end, the model heterocycles were incubated in dry methanol for 0.5–24 h at ambient temperature, and the extent of BOH-to-BOCH$_3$ exchange was analyzed by ^{1}H NMR spectroscopy. Additionally, heterocycles **1–3** were dissolved in CD_3CN along with 5 equiv of dry methanol to monitor the extent of exchange in a polar aprotic solvent (Figure 5).



Compound	% Exchange 30 min	24 h	5 equiv. MeOH in CD_3CN[a]
1 X = O	38	46	56
2a X = NH	50	54	45
2b X = NMe	<5	<5	<5
2c X = NPh	<5 (42% conversion)[b]	<5 (40% conversion)[b]	<5
3a X = NSO_2Ph	<5 (53% conversion)[b]	<5 (50% conversion)[b]	<5

[a]Substrate and 5 equiv. MeOH mixed in CD_3CN solution.
[b]Reaction with methanol for **2c** and **3a** leads to B–N bond cleavage and opening of the boron-containing ring rather than direct B–OH/B–OMe exchange to give the product shown above. For details, see SI.

Figure 5. Exchange of heterocycles **1**, **2a–c**, and **3a** with methanol.

Under these conditions, heterocycles **1** and **2a** showed moderate boranol exchange to the corresponding methyl esters. The equilibrium between the corresponding acids and esters was relatively unchanged after the first 30 min and showed comparable exchange in either neat methanol or acetonitrile. Addition of D_2O to these mixtures was found to promote rapid hydrolysis of the methyl esters of **1** and **2a** to re-form the corresponding B–OD hemiboronic acids. In contrast, *N*-alkyl heterocycle **2b** was inert to methanol exchange. Rather than direct BOH-to-BOCH$_3$ exchange, heterocycles **2c** and **3a** behaved differently and appeared to undergo significant B–N

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bond cleavage in methanol, a process that was not reversed upon addition of D_2O (see Supporting Information).

In principle, in aqueous solution these boron heterocycles can break down to their starting materials via hydrolysis of both the internal B−X and C═N bonds (Figure 6A). The fact

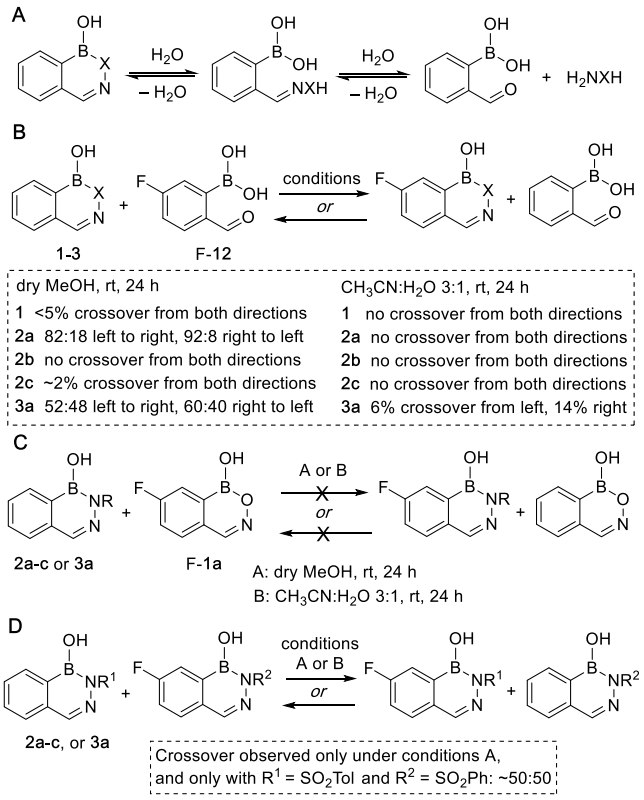

Figure 6. (A) Possible hydrolytic equilibrium between compounds **1**−**3** and their *o*-formyl arylboronic acid precursor. (B−D) Behavior and stability of compounds **1**, **2a**−**c**, and **3a** via exchange and crossover experiments in hydroxylic solvents (see Supporting Information for full details).

that these components are not observed by NMR spectroscopy cannot rule out a dynamic equilibrium that strongly favors the heterocyclic products. Therefore, to assess their stability in water, a series of crossover experiments were set up between each of the five compounds **1**, **2a**−**c**, and **3a** and a distinct benzaldehyde containing an *ortho*-boronyl substituent, **12** (Figure 6B). These experiments, which were performed from both directions in either dry methanol or H_2O/CH_3CN for 24 h, revealed that the *N*-sulfonylated derivative **3a** is the most prone to exchange in either solvent medium. The labile nature of **3a** is consistent with observations by Bane and co-workers on similar *N*-acyl analogues, which were shown to be in equilibrium with their open form in aqueous solution.[31] Interestingly, **3a** demonstrated less crossover in aqueous acetonitrile compared to methanol, where virtually complete equilibration was observed. Use of buffered H_2O/CH_3CN (pH 6.9) did not change this outcome, and additional control experiments confirmed the distinct ability of methanol to promote the breakdown of *N*-sulfonyl heterocycles (see Discussion and Supporting Information). Hydrazine-derived heterocycle **2a** showed a small amount of crossover in methanol but was unreactive in acetonitrile/water, whereas compounds **1**, **2b**, and **2c** showed no significant crossover in either medium.

These experiments were corroborated by another series of crossover experiments between sets of heterocycles made with different 2-formyl arylboronic acids and heteroatom components (Figure 6C). These experiments were performed starting from both directions. Consistent with the benzaldehyde exchange experiments, crossover could be observed only when two distinct *N*-sulfonyl heterocycles are employed in dry methanol (Figure 6D and Supporting Information). Overall, these experiments demonstrate the stability of heterocycles **1** and **2a**−**c** in aqueous media, thus confirming their suitability for applications in medicinal chemistry and chemical biology.

pK_a Measurements. The pK_a values of all model heterocycles were measured in buffered 1:1 H_2O/CH_3CN solvent mixtures by way of ^{11}B NMR titration, a method that has proven reliable for similar hemiboronic and boronic acids.[6,33,34] Use of mixed aqueous organic solvent was necessary to ensure all model heterocycles provide homogeneous solutions across a wide range of pH. The pK_a's of **1**, **2c**,**d**, and **3a** were also validated by the UV method and provided similar values (see Supporting Information). Benzoxaborole was chosen as a standard because its pK_a in water was previously reported using two methods (^{11}B NMR spectroscopy and UV spectrophotometry).[33,35] As they are slightly soluble in water, the pK_a's of benzoxaborole and oxime **1** were also measured in water to provide an estimate of the effect of the cosolvent. The resulting values point to an increase of ca. 1.5−2.0 units in the mixed 1:1 H_2O/CH_3CN system compared to water alone (Table 1).

Table 1. ^{11}B NMR Chemical Shifts and pK_a of Heterocycles 1, 2a−d, and 3a in Aqueous Media[a]

compound	δ acid (ppm)	δ conj. base (ppm)	pK_a
benzoxaborole	32.8	8.5	9.2[b]
1	27.7	2.5	7.1[c]
2a	27.8	–[d]	>14
2b	27.5	–[d]	>14
2c	28.0	1.2	12.2
2d (R = C_6H_4-4-SO_2Me)	28.8	1.6	9.4
3a	28.4	1.6	5.5

[a]Measured by ^{11}B NMR titration in 1:1 H_2O/CH_3CN (phosphate buffer, referenced to CD_3CN). [b]7.4 in H_2O with 3−4% DMSO. [c]5.5 in H_2O with 3−4% DMSO. [d]A negligible change in the chemical shift was observed up to a very high pH: **2a**: 27.0 ppm at pH 13.4; **2b**: 27.1 ppm at pH 13.6.

Titration of **1** and **3a** afforded well-defined curves transitioning from a downfield resonance at low pH to the expected upfield resonance of the corresponding conjugate base (see Table 1 and Figures S68, S70). Because **3a** is slightly labile in aqueous solvent (cf. Figure 6), its aldehyde precursor, *o*-formylphenylboronic acid (pK_a 7.3, water),[36] was examined at high pH and it yielded a distinct ^{11}B NMR resonance, confirming that the measured pK_a is truly that of **3a** (see Figure S79). As noted by Groziak,[28] even at pH 13.6 no downfield shifts were observed for **2a** and **2b** that could be unambiguously attributed to the conjugate base. In our hands, back-titration of a high-pH sample to a neutral pH and analysis by both ^{1}H and ^{11}B NMR spectroscopy reproduced these findings and confirmed that **2a** and **2b**

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sustained these conditions unchanged. Consequently, the pK_a of **2a** and **2b** cannot be determined in aqueous medium (H_2O/CH_3CN, 1:1), and they were assessed a value of >14. The ^{1}H NMR spectra of **2a**,**b** show broader resonances in this solvent mixture at high pH (pH > 12), and the UV absorption spectra undergo some changes (see Supporting Information). Because there is little variation in the ^{11}B NMR resonance (<1 ppm), this behavior may be attributable to the intractable dimerization (reversible B−O−B anhydride formation) observed with related heterocycles.[37] Remarkably, it was found possible to isolate the tetramethylammonium salt of the conjugate bases of **2a** and **2b** as hygroscopic solids from organic solvent (toluene/methanol),[38] and these anionic species display upfield ^{11}B NMR chemical shifts (DMSO-d_6: 1.3 ppm for **2a**, 2.4 ppm for **2b**), in full agreement with a Lewis basic structure (i.e., **2a-I**/**2b-I**) (see Supporting Information). Consistent with their predicted high pK_a, according to ^{1}H and ^{11}B NMR these anionic species cleanly revert to their acid form **2a** and **2b** when exposed to a pH 13.5 solution (H_2O/CH_3CN, 1:1) (see Figures S88, S89). Moreover, because the hydrazone NH resonance of **2a-I** is observable, it is implausible that heterocycle **2a** displays Brønsted acidity through deprotonation of its NH group.

In the case of **2c**, the observed high-pH transition appeared to result from a slower exchange, as both resonances were observed around the transition point, eventually becoming a single upfield resonance above pH 13 (see Supporting Information, Section 7.4). Addition of KOH to a solution of **2c** in CD_3CN also provided the same ^{11}B NMR resonance. When performed in toluene, the conjugate base crashes out after 5 min of stirring, and the isolated solid was added to a pH 13.8 1:1 solution of H_2O/CH_3CN, providing a resonance at 1.3 ppm identical to that observed in the titration. Furthermore, a back-titration followed by ^{1}H and ^{11}B NMR analysis confirmed that the observed transition is a true, reversible ionization equilibrium (see Figure S81). To further support the validity of the pK_a of **2c**, another *N*-aryl derivative was prepared with a strong electron-withdrawing substituent that could depress the pK_a. In the event, the 4-methylsulfonyl derivative **2d** provided a typical titration curve with a single averaged resonance around a transition point corresponding to a pK_a of 9.4 (see Figure S69). A decrease of ∼2.5 units compared to **2c** is commensurate with the effect of *para*-sulfonyl substitution on the pK_a of phenol.[39]

X-ray Crystallographic Structural Analysis of Acids and Conjugate Bases. Single-crystal X-ray diffraction analysis can provide unequivocal insight on the solid-state structure of the hemiboronic acids **1**−**3** and their corresponding conjugate bases. Structural data such as the bond length of key bonds can provide invaluable information on bond orders and the extent of π electron delocalization in the neutral acid species. X-ray crystal structures of heterocycles **1** and **2a** were reported and thoroughly discussed by Groziak and coworkers.[28] Salient details of these planar boron heterocycles include bond lengths for the B−C, external B−O, and internal B−X bonds of 1.533(6) and 1.530(3), 1.350(6) and 1.371(3), and 1.388(6) and 1.432(3) Å, respectively, for **1** and **2a**. Both compounds display a planar trivalent boron atom, though **2a** shows significant distortion of the C−B−OH angle (128.1°, vs 122.5° for **1**) and consequently also for the HO−B−N/O angle (116.7°, vs 118.0° for **1**) and for the C−B−N/O angle (115.2°, vs 119.4° for **1**). Both compounds show intermolecular H-bonding motifs between the boranol hydrogen and the imino nitrogen atoms, whereas the NH unit of **2a** enables dimerization via additional NH/BOH H-bonding interactions.[28] We successfully analyzed monocrystals of **2c** and **3a** (see Supporting Information), and some particular features of the resulting structures are worth mentioning. The *N*-phenyl unit of **2c** shows a tilt of ∼30° relative to the planar borazaheterocycle, while the structure of **3a** displays a short (2.15 Å) hydrogen bond between the BOH unit and one of the two sulfonamide oxygens.

No crystal structures of any of the conjugate bases of heterocycles **1**−**3** had been reported to date. To form suitable crystals of the conjugate bases, a modified procedure for the preparation of potassium trihydroxy borate salts of boronic acids was employed.[40] The resulting potassium salts of heterocycles **1**−**3** were subjected to various recrystallization attempts. To our delight, X-ray-quality crystals were obtained and successfully analyzed for the salts of **1**, **2d**, and **3a**, which unambiguously revealed their Lewis basic structure: form **I**. ORTEP representations of **1-I**, **2d-I**, and **3a-I** are shown in Figure 7, clearly showing the tetravalent dihydroxy-substituted

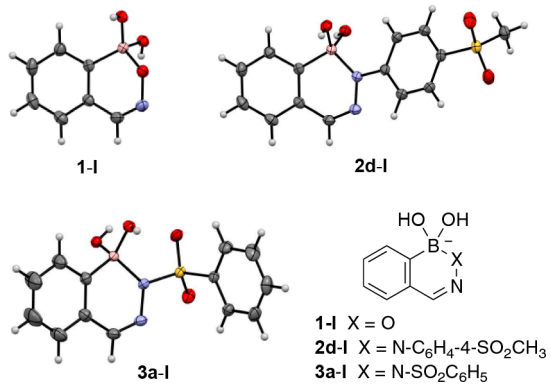

Figure 7. ORTEP representations of the Lewis conjugate bases of **1**, **2d**, and **3a**: **1-I**, **2d-I**, and **3a-I**. Note: the countercation and bound solvent molecules were omitted for clarity.

boron atom. Moreover, ^{11}B NMR analysis of isolated crystals of **3a-I** in H_2O/CH_3CN showed the same upfield resonance of ∼2 ppm obtained in the pK_a titration, which provides strong evidence that form **I** also represents the conjugate base structure in solution. Compared to the crystal structure of **1**, **1-I** shows significant lengthening of the C−B bond (1.533(6) to 1.613(3) Å) and especially of the internal B−O bond (1.388(6) to 1.537(3) Å). Such a lengthening of the internal B−O bond provides strong support for the olefinic character of this bond in heterocycle **1**, through extensive B_p−O_n resonance. The structure of **3a-I** shows a similar lengthening of the C−B and B−N bonds (Å): **3a**: C−B: 1.540(3), B−N: 1.461(3); **3a-I**: C−B: 1.6084(18), B−N 1.6218(16).

It was not possible to form high-quality crystals of the putative conjugate bases of **2a**−**c** under the same reaction and recrystallization conditions. We succeeded, however, in making and resolving the structures of adducts of 1,3-diols under basic conditions for these three heterocycles. The resulting single-crystal X-ray diffraction structures of adducts **13**−**15** shown in Figure 8 represent the first reported examples of derivatives of **2a**−**c** with a tetravalent boron atom (^{11}B NMR δ (CD_3CN) **13**: −0.3 ppm, **14**: 1.0 ppm, **15**: − 0.9 ppm). Like **1-I** and **3a-I** (*vide supra*), a substantial lengthening of both C−B and B−N bonds accompanies a change a rehybridization of boron from

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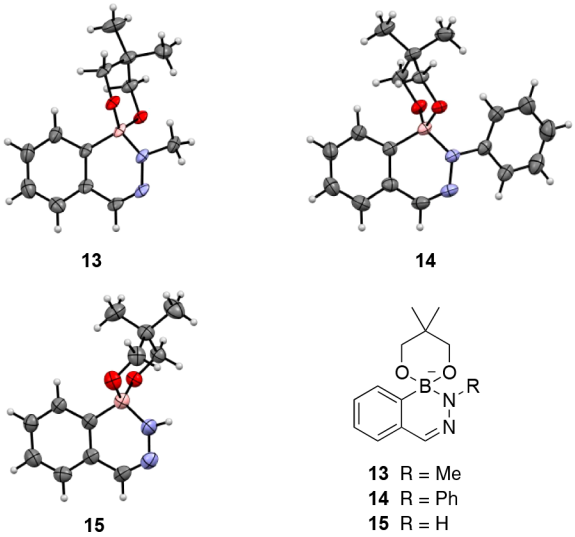


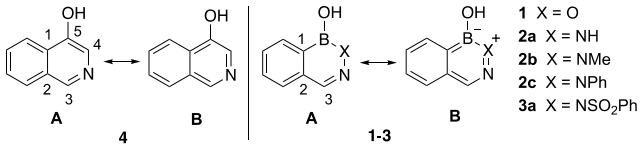
Figure 8. ORTEP representations of the tetravalent adducts **13**−**15** of neopentyl glycol with **2a**−**c**. Note: the tetrabutylammonium countercation was omitted for clarity.

sp^2 to sp^3 (Å), e.g., **2c**: C−B: 1.551(2); B−N: 1.445(2); **14**: C−B: 1.6339(16); B−N: 1.5783(13). Unlike **14**, and consistent with the high pK_a of **2a** and **2b**, adducts **13** and **15** are not stable in aqueous conditions and revert to their acid form even upon exposure to a pH 13.5 H_2O/CH_3CN (1:1) solution (see Table S2 and Figure S90).

Computational Studies. Density functional theory (DFT) calculations of the ground-state equilibrium geometry and molecular orbitals of model heterocycles **1**, **2a**−**c**, and **3a** were performed in the gas phase using the ωB97X-D functional with the 6-31G* basis set.[41] Because it is lower or comparable in energy (see Supporting Information), the *syn* conformers with the boranol O−H bond synperiplanar with the endocyclic B−X bond was employed. For comparative purposes, the corresponding C=C isostere, 4-hydroxyisoquinoline (**4**), was also calculated. Some key properties are shown in Table 2 along with a representation of limit resonance forms with alternate single and double bonds. The calculated structures are in excellent agreement with the crystal structures of **1** and **2a** described above. For example, key bond lengths for both compounds such as the B−C, external B−O, and internal B−X bonds differ by no more than 0.01 Å. Whereas key bond angle values are identical within 1° for heterocycle **1**, there is substantial disagreement for **2a**: C−B−OH: 128.1° vs 121.9° (calcd); HO−B−N: 116.7° vs 123.3° (calcd); and for the C−B−N angle: 115.2° vs 114.8° (calcd). The discrepancy is likely due to the dimeric structure of **2a**, in its crystal lattice, which imposes substantial distortion of the orientation of the B−OH bond to accommodate the geometry of this hydrogen-bonded dimer. Such restrictions do not exist in the computed monomer. It is also noteworthy that the calculated ground-state structure of **3a** displays the same internal BOH---(O)S hydrogen bond observed in the crystallographic structure (*vide supra*).

As the parent B−X/C=C isostere, the aromatic naphthoid compound **4** displays bond orders (Lowdin) that support the existence of a highly delocalized structure represented by a hybrid of both resonance limit forms **4A** and **4B**. For example, all of the bond orders in the azacycle of **4** are fractional, ranging between 1.23 and 1.76, which reflects a substantial contribution from limit form **4B** with alternating single and double bonds. By comparison, bond orders of all B−X isosteres **1**−**3** hint at a relatively small contribution of resonance form **B**. This observation is corroborated by the much shorter C^1-C^5 bond length in **4** compared to the crystallographic and calculated C^1−B bond lengths of **1**−**3**, which are indicative of a single-bond character. In contrast, the B−N bond orders for **2a** and **2b** (1.323, 1.276) show that this bond is a reasonably good isoelectronic mimic of the alkene bond of **4** (1.528). The B−O

Table 2. Key Properties for DFT-Optimized Structures of Model Heterocycles 1−3 and the Parent C=C/B−N Isostere, 4-Hydroxyisoquinoline 4 (ωB97X-D/6-31G*, Gas Phase)



property[a]	4 (B = C^5, X = C^4)	1	2a	2b	2c	3a
bond length C^1−B (Å)	1.422 (C^1-C^5)	1.542	1.542	1.540	1.541	1.546
bond length B−OH (Å)	1.357 (C^5−OH)	1.360	1.373	1.374	1.368	1.351
bond length B−X (Å)	1.375 ($C^5=C^4$)	1.381	1.429	1.432	1.443	1.465
bond length X−N (Å)	1.356 (C^4−N)	1.390	1.366	1.366	1.373	1.377
bond order C^1−B	1.231	1.041	1.056	1.062	1.057	1.043
bond order B−OH	1.280	1.512	1.456	1.452	1.472	1.551
bond order B−X	1.528	1.357	1.325	1.276	1.232	1.172
bond order X−N	1.461	1.217	1.319	1.293	1.263	1.251
bond order N=C^3	1.765	2.004	1.931	1.914	1.929	1.951
bond order C^2-C^3	1.273	1.127	1.153	1.158	1.150	1.138
atomic charge B	0.323 (C5)	1.136	1.014	1.029	1.038	1.05
atomic charge C^1	−0.085	−0.390	−0.372	−0.371	−0.372	−0.367
atomic charge OH	−0.697	−0.895	−0.889	−0.889	−0.892	−0.894
atomic charge X	−0.104	−0.569	−0.678	−0.497	−0.498	−0.750
atomic charge N=C	−0.439	−0.093	−0.244	−0.249	−0.248	−0.266

[a]Lowdin bond orders and charges.

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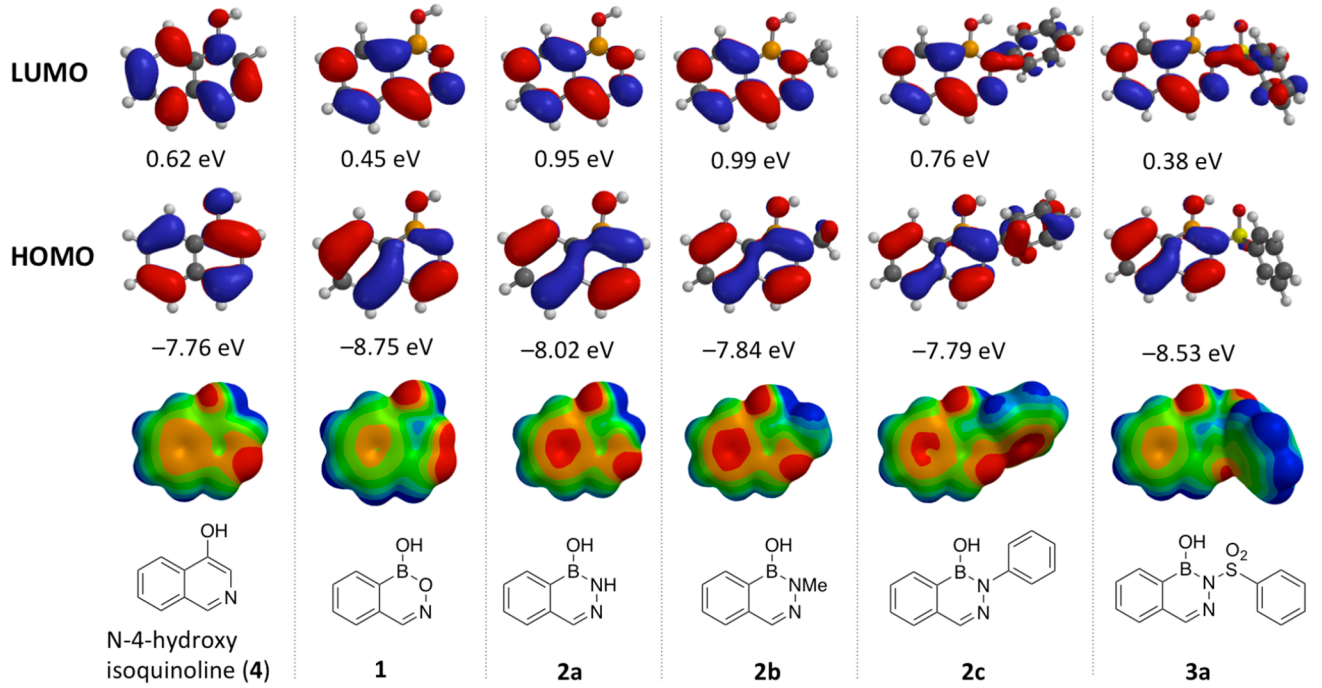

Figure 9. Frontier molecular orbitals, energies, and electrostatic potential maps for model boron heterocycles **1**−**3** and the parent isostere **4** (ωB97X-D/6-31G*, gas phase). The *syn* conformer with the boranol O−H bond synperiplanar with the endocyclic B−O/N bond was employed.

bond of **1** is an even better model, as indicated by its higher bond order (1.357) and its shorter bond length, which is nearly identical to that of the C^4═C^5 bond in **4**. However, a number of indicators present significant differences between the borylated oxime **1** and its aza congeners **2**. Whereas compound **1** shows nearly no extended conjugation (e.g., C^1−B and C^3═N bond orders of 1.04 and 2.00), the boraza derivatives show increased delocalization of their π electrons, as indicated by the higher C^1−B and lower C^3═N bond orders (optimal for **2b** with 1.062 and 1.914, respectively). Owing to boron's vacant p orbital, resonance of the hydroxy group of heterocycles **1**−**3** leads to a substantially higher B−(OH) bond order compared to the corresponding C^5−(OH) bond of **4** (∼1.5 vs 1.28), and, in all cases it is higher than the endocyclic B−X bond order. Finally, it is noteworthy that the boron atom appears to be significantly more electron-deficient in **1** compared to the aza analogues **2**, which corroborates its relatively lower pK_a. Considering the higher B−X bond order in **1**, this is suggestive that the electrophilicity of the boron atom is largely attributable to the inductive sigma effect of the endocyclic, highly electronegative O atom.

Ground-state geometries and molecular orbitals of the corresponding conjugate bases **I** of **1**−**3** were also computed (see Table S1). Lengths of key bonds for theoretical structures **1-I** and **3a-I** compare closely, within 0.005−0.015 Å, to those from the above crystallographic structures. As observed in the solid-state structures, compared to the respective acids the computed structures of conjugate bases show a large increase of the B−X bond lengths that is indicative of the loss of of B_p−X_n resonance (see Table S3). Reaction energies were computed for conjugate base formation using single-point calculation of equilibrium geometries at a higher level of theory (ωB97XV/6-311+G(2df,2p)[6-311G*]). A linear relationship was observed between the pK_a and the computed reaction energies for *N*-alkyl/aryl heterocycles **2a**−**d**, which suggests a pK_a around 14 for **2a** and **2b** (see Supporting Information). Heterocycles **1** and **3a**, which are electronically distinct from **2a**−**d**, did not provide a good fit in this correlation.

Calculated frontier molecular orbitals and electrostatic potential maps of compounds **1**, **2a**−**c**, and **3a** are shown in Figure 9. Unlike isoquinoline **4** and compounds **2a**−**c**, the electrostatic potential maps of **1** and **3a** depict no or little ring current in the heterocyclic ring. Moreover, the shapes of molecular orbitals (MOs) of all model heterocycles are significantly different compared to **4**, whose MOs show good symmetry across both rings. The highest occupied molecular orbital (HOMO) of **2a** and **2b**, however, shows partial conjugation of the B−N bond with the benzenoid ring as depicted with larger density in the C^1−B bond. In contrast, the HOMO of compounds **1**, **2c**, and **3a**, which contain a less basic *O*- or *N*-aryl/sulfonyl atom, is interrupted between the C^1 and B atoms. Calculated MO energies revealed that both **1** and **3a** have significantly lower-lying lowest unoccupied molecular orbitals (LUMOs) than the other boron heterocycles, which is consistent with their higher acidity.

Based on the above crystallographic structures and calculations, boron heterocycles **1**−**3** appear to be valid isoelectronic and isosteric analogues of isoquinoline **4**. However, based on calculated bond orders and MOs, only the boraza compounds **2a**−**c** display a small degree of extended conjugation across rings, represented by resonance limit form **B**, that is suggestive of a partial aromatic character. To better assess the aromatic character of heterocycles **1**−**3**, nucleus independent chemical shift (NICS) calculations were performed.[42] For both NICS(0) and NICS(1) indexes, negative values are indicative of aromatic character; however, the former computes the average shielding at the center of the ring and includes the contribution of the σ-framework, including substituents, whereas the latter measures shielding 1 Å above the ring where π contributions are dominant. The resulting NICS(0) and NICS(1) values for the boroheterocyclic ring (***B***) of compounds **1**−**3** are significantly lower than

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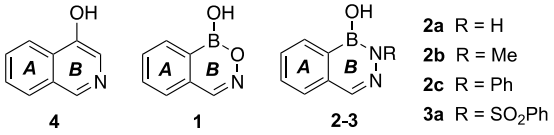
that of the corresponding ring in isoquinoline **4** (Table 3), and, while highest in **2a** and **2b**, they are substantially lower than

Table 3. Nucleus-Independent Chemical Shift Calculations for Heterocycles 1−3 and 4 (GIAO-B3LYP/6-311+G(2d,p))



ring	4	1	2a	2b	2c	3a
A						
NICS(0)	−7.95	−7.41	−7.67	−7.66	−7.47	−7.59
NICS(1)	−10.28	−10.25	−10.47	−10.45	−10.23	−10.46
B						
NICS(0)	−7.87	0.79	−1.33	−1.91	−0.81	−1.34
NICS(1)	−9.95	−2.75	−4.35	−4.86	−3.75	−3.88

that of 1,2-azaborine and 1,2-oxaborine.[43] Together the DFT and NICS calculations support the idea that the oxazaborine ring of **1** possesses nearly no aromatic character, while **2a**, **2b**, and **2c** retain to a small degree the ring aromaticity of the parent C═C isostere, isoquinoline **4**.

DISCUSSION

The aromatic character, the acidic nature (Brønsted vs Lewis), and the pK_a of individual hemiboronic heterocycles **1−3** are strongly linked (cf. Table 1). Whether their conjugate base is represented by form **I** or **II**, ionization is expected to affect the electron distribution around the pseudoaromatic heterocycle. Empirical observations based on chemical stability and UV spectrophotometry made in decades-old pioneering studies can provide a misleading assessment of the aromatic character of these boron heterocycles. The analysis of aromatic stabilization in pseudoaromatic heterocycles is a notorious challenge that often requires a multipronged approach. The combination of DFT and NICS calculations presented herein converges into a reasonably consistent picture. Thus, according to calculated bond orders, electrostatic potential maps, the shape of their HOMO, and NICS values, only the boraza heterocycles **2a** and **2b** retain a significant degree of the aromaticity of the parent isoquinoline B−X/C═C isostere **4**. A comparison of the five model heterocycles highlights the importance of the availability of lone electron pairs on the O or N heteroatom. According to estimated bond orders and the values of bond lengths obtained experimentally and by DFT calculations, the endocyclic B−O unit of heterocycle **1** serves as an effective isoelectronic and isosteric mimic of a C═C bond, one that is slightly better than the B−N bond in **2a** and **2b**. However, likely because of its high electronegativity, the O atom does not appear to allow an effective delocalization of its π electrons within the rest of the pseudoaromatic system. As a result, there is little contribution from the extended resonance form **B** (cf. Table 2) necessary for developing significant aromatic character. The superior ability of a nitrogen vs an oxygen atom to participate in pseudoaromatic delocalization was also established in other boron heterocycles.[43,44] In this regard, compared to **2a−c**, the boraza heterocycle **3a** contains a sulfonyl-conjugated nitrogen lone electron pair that is relatively less available to delocalize into the diazaboryl heterocycle. This qualitative assessment is corroborated by the pK_a measurements obtained from ^{11}B NMR titrations. The hemiboronic oxime **1** has a measured pK_a of 5.5 (in water), which is significantly lower than that of a normal boronic acid (8−9) and even that of benzoxaborole (7.4). Being nonaromatic, compared to **2a−c** there is little penalty for its ionization into a conjugate base that would break π-conjugation. Conversely, owing to their partial aromatic character, the boraza heterocycles **2a−c** have pK_a's well above that of boronic acids. For reasons mentioned above, the *N*-sulfonyl derivative **3a** behaves much like heterocycle **1**. When measured in 1:1 H_2O/CH_3CN, it displays a lower pK_a than **1** (5.5 vs 7.1). Collectively, the measured order of pK_a's, **3a** < **1** < **2c** < **2a,b**, correlates with the anion-stabilizing ability of the X group on the B−X unit that is consistent with the pK_a's of the corresponding protic acids: H_2NSO_2Ph (pK_a 10) < H_2O (pK_a 15.7) < H_2NPh (pK_a 25) < H_2NR (pK_a ∼40). Whereas ^{11}B NMR is of no help in predicting acidity, the ^{1}H B−OH resonances of heterocycles **1** and **2** (cf. Figure 4) match well with the above rankings, except for **3a**, which is biased by an internal H-bond (*vide supra*). The DFT-computed ground-state structures can also help rationalize the pK_a's of heterocycles **1−3**. In this regard, the calculated positive charge on boron is far greater in **1** than **2a−c**; however it is also much higher than **3a** despite their similarly low pK_a's (cf. Table 2). LUMO energy levels appear to correlate better with the measured acidity. Indeed, heterocycles **1** and **3a** display similar LUMO energy levels that are significantly lower than that of **2a−c** (cf. Figure 9). Likewise, the HOMO energy level of the corresponding Lewis conjugate bases correlates neatly with their expected order of basicity based on the measured pK_a's of their acid forms (see Table S3).

This study also puts to rest the question of the structure of the conjugate base of heterocycles **1−3** that remained unsettled for several decades. All of the heterocycles studied here were confidently determined to act as Lewis acids in aqueous solutions to afford a conjugate base of structural form **I** characterized by a tetravalent dihydroxylated boron atom. The results of ^{11}B NMR titrations in alkaline solutions are unequivocal; the presence of upfield species at 0−5 ppm cannot be attributed to a Brønsted basic form **II**. Likewise, this study corrects previous conclusions made in the literature and confirms that the absence of such upfield resonances with *N*-alkyl heterocycles **2a,b** at high aqueous pH are simply due to pK_a values that are significantly above the normal range for boronic acid derivatives. This conclusion is supported by the relatively high pK_a of 12.2 (1:1 H_2O/CH_3CN) measured for the *N*-phenyl heterocycle **2c**, which is expected to lie a few units lower than the *N*-alkyl derivatives **2a,b**. Moreover, conjugate bases **2a-I** and **2b-I** are observable by NMR spectroscopy, as their tetramethylammonium salts in dry DMSO, and they predictably revert to their acid form even in pH 13.5 aqueous conditions.

The structures of conjugate bases **1-I**, **2d-I**, and **3a-I** obtained by X-ray crystallography, which were shown by ^{11}B NMR to exist also in aqueous solution, provide indisputable evidence of Lewis acidity. No such crystal structures could be obtained for **2a−c**; indeed difficulties in crystallizing these conjugate bases underpins their higher pK_a. On the other hand, due to the entropic advantage of intramolecularity, anionic adducts with diols form more easily and were successfully crystallized. Thus, the structure of dialkoxy adducts **13−15** of **2a−c** confirms that the partial aromatic character of heterocycles **2** can be disrupted to form an anionic tetravalent dialkoxyboronyl species consistent with Lewis acidic behavior.

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The reactivity of heterocycles **1**, **2b**, and **3a** with methanol is consistent with the higher Lewis acidity of **1** and **3a** and the partial aromaticity of **2b**. The contradictory result of **2a**, which exchanges its hydroxy group with methanol despite showing a high pK_a and computed aromaticity similar with **2b**, may be rationalized without invoking the association−dissociation mechanism and the corresponding anionic tetrahedral boron intermediate. It can be proposed that H-bonding participation of the N−H bond of **2a** could help mediate a concerted exchange of the B−O bonds without a formal ionization of the boron atom (Figure 10A). This type of proton-transfer

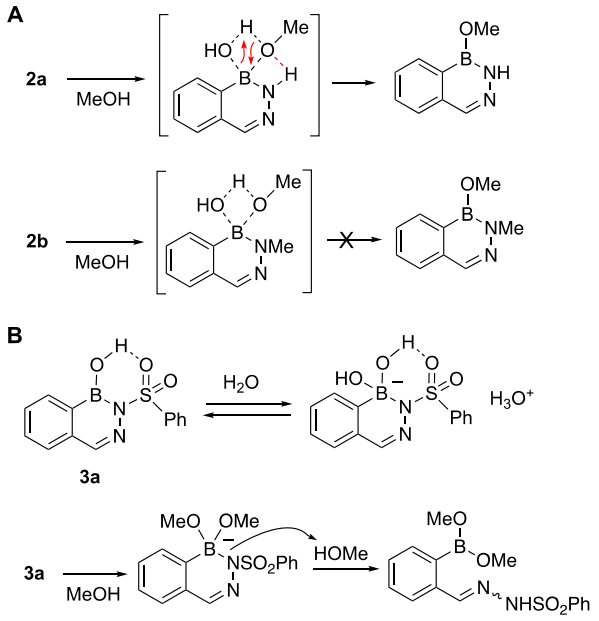

Figure 10. (A) Proposed rationalization for the behavior of heterocycles **2a** in methanol and (B) for the different reactivity of **3a** with water and methanol.

mechanism was shown to be kinetically plausible in the related esterification of high-pK_a boronic acids with aliphatic diols at neutral pH.[45] In contrast, *N*-methylated derivative **2b** lacks the requisite H-bond donor to promote a concerted mechanism and is unlikely to undergo a stepwise mechanism through an anionic tetrahedral boron intermediate due to its high pK_a. The higher propensity of **3a** to break down in methanol, as seen in both the methanol exchange (Figure 5) and aldehyde crossover experiments (Figure 6), may originate from the strong internal B−OH---O=S hydrogen bond observed in the solid state of both **3a** and its conjugate base. In aqueous solution, this H-bond is maintained in both the trigonal and tetrahedral boron environments, bestowing increased stability to heterocycle **3a**. A transient exchange with methanol, facilitated by the relatively high acidity of **3a**, eliminates this stabilizing internal H-bond and would facilitate hydrolysis of the B−N bond (Figure 10B). While heterocycles **2c** and **3a** both appear to undergo B−N bond cleavage in methanol, the increased crossover observed with **3a** may be due to its lower pK_a and the stronger electron-withdrawing effect of the sulfonyl moiety that promotes the prerequisite hydrazone C=N bond cleavage. Altogether, the contrasting results of heterocycles **1**, **2a**−**c**, and **3a** in methanol exchange and aldehyde crossover experiments clearly indicate that acidity alone does not predict the behavior or stability of these hemiboronic acids in methanol.

While this study answers long-standing fundamentally important questions, it raises new ones too. Even when considering their lack of aromatic stabilization, it is surprising that benzoxaborine **1** and **3a** display such unusually low pK_a's (high acidity), and its origin is intriguing. Both compounds have pK_a's lower than that of benzoxaborole. Relief of angle strain from the rehybridization of boron from sp^2 to sp^3, a factor that was invoked to explain the relatively low pK_a of benzoxaborole,[6] is not dominant with **1**. Compared to benzoxaborole and acyclic oxime and hydrazone analogues, bond angles around the heterocyclic ring of **1** do not appear to suffer from large deviations. A more plausible explanation entails that when freed of its double-bond character with boron, the internal O atom of conjugate base **1-I** can benefit from the stabilization of its partial negative charge by the inductive effect of the neighboring N atom and through resonance with the C=N unit. As related above, this view is consistent with the difference of protic acidity between alcohols (pK_a ∼16) and benzophenone oxime (pK_a ∼11). As demonstrated in a recent report by Raines and co-workers, stereoelectronic factors can play an important role in the reactivity and stability of tetravalent boronate intermediates.[46] Thus, it is also possible that *exo* n_O−$\sigma^*_{B-O/N}$ and *endo* $n_{O/N}$−σ^*_{B-OH} interactions contribute to the differences in stability between conjugate bases **I**. Specifically, charge stabilization via donation of antiperiplanar lone pairs from the $B(OH)_2$ unit is expected to be more important with the lower-energy σ^* of the electron-poor endocyclic B−O bond of **1-I** compared to the more electron-rich B−N bond in **2a-I**. To assess the potential contribution of secondary orbital interactions to the relative stability of **1-I** and **2a-I**, we performed a natural bonding orbital (NBO) analysis.[47] Taking into account the *exo* n_O−$\sigma^*_{B-O/N}$ overlap from both exocyclic oxygen atoms on the optimized geometries (ωB97XD/6-31G(d)), second-order perturbation energies (E^2) are more beneficial in **1-I** by 2.6 kcal/mol (Figure 11 and Supporting Information for additional data). However, the larger *exo* n_O−σ^*_{B-O} interactions are counterbalanced by the stronger donor effect of N (despite having only a single lone pair) in the *endo* n_N-σ^*_{B-OH} interactions (1.5 kcal/mol favoring **2a-I**), which results in no net advantage for either structure (only 1.1 kcal/mol favoring **1-I**). Thus although stabilizing secondary orbital interactions do exist in these boronate conjugate bases, they are unlikely to exhibit a significant influence on the relative acidity of heterocycles **1**−**3**.

Overall, the substantially higher Lewis acidity of heterocycles **1** and **3a** compared to **2a**−**c** can be rationalized by a combination of anion-stabilizing inductive effect from the B−X heteroatom and its substituent in conjugate bases **1-I** and **3a-I** and the larger loss of aromatic stabilization energy in **2a**−**c** relative to **1** and **3a**.

The relatively low aromatic character of naphthoids **1**−**3** is equally intriguing. Based on their pK_a and computational data, heterocycles **2a** and **2b** appear to be the most resonance-stabilized among all five model compounds, yet they retain only to a small degree the aromatic character of the parent isoquinoline **4**. This determination does not seem to arise from a deficiency in the π bond character of the B−X bond, which shows good mimicry of an alkene. Rather, it is likely to be caused by the poor ability of Csp^2−Csp^2 π bonds to delocalize into boron. Even in the most favorable case of **2a**,**b**, a C−B

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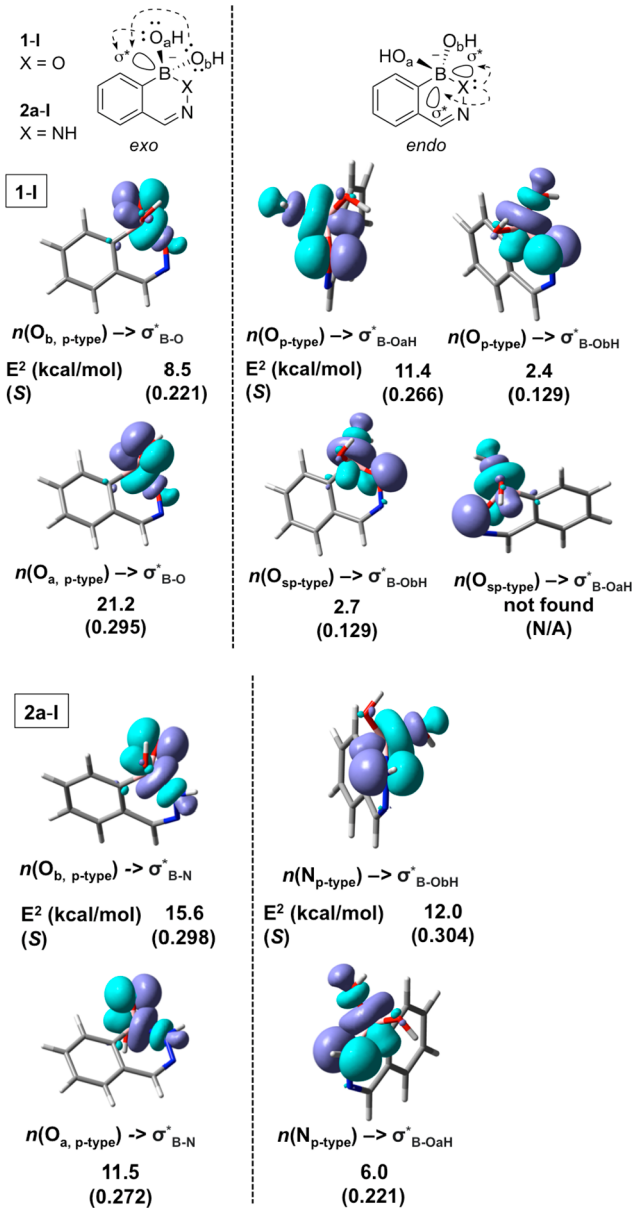

Figure 11. Stereoelectronic stabilization of conjugate bases assessed by NBO analysis of key overlapping orbitals in **1-I** and **2a-I** with second-order perturbation energies (E^2) and the "pre-orthogonal" NBO (PNBO) overlap matrix integral (S) (O_a: front-facing oxygen, O_b: back oxygen).

bond order of 1.06 does not compare well with the corresponding C−C bond order of 1.23 in isoquinoline **4**, which is reflective of a significant contribution from resonance forms with alternating single and double bonds (cf. **B**, Table 2). Finally, although this study firmly establishes the large preference for tetravalent conjugate bases (form **I**), the reason for its preference over the boron oxy form (**II**) is still lingering. It can be addressed in a preliminary manner through DFT calculations in a water solvation model that compares compounds **1**, **2a**, and **16** with the isoatomic compensation of a water molecule. The benzoxaborine **16** was selected for its nonaromatic character and its unstrained structure. Although this estimation ignores entropic contributions (expected to favor form **II**), the huge preference for the tetravalent boronate anion form **I** is evident in all three examples (Figure 12A).

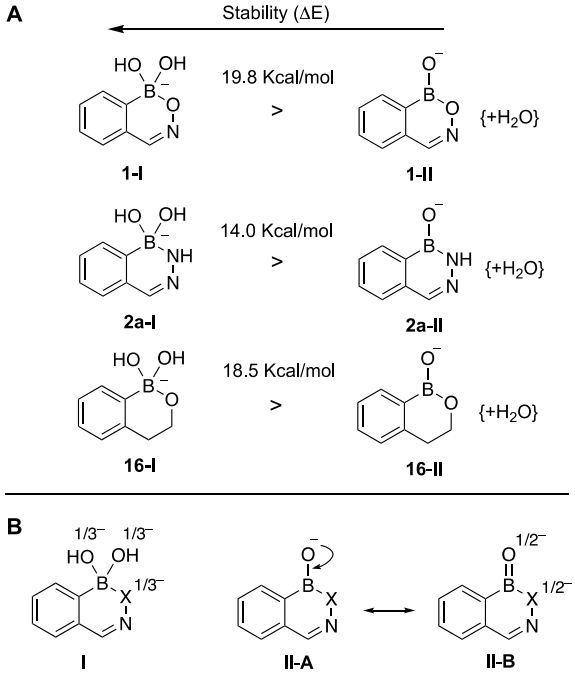

Figure 12. (A) Comparison of energies for tetravalent boronate form **I** and boron oxy form **II** (ωB97X-D/6-31G*, water C-PCM continuum solvent model, values not entropy-corrected). (B) Rationalization of the preference for Lewis bases **I**.

This preference is reduced by roughly 6 kcal/mol in the case of compound **2a**. This difference may be attributable to the small aromatic character of this heterocycle, which disfavors structure **I** yet clearly not enough to favor the boron oxy form **II**. It is noteworthy that the amido Brønsted base from deprotonation of the NH group was found to be even less stable than **2a-II** according to DFT calculations (see Supporting Information). Although the calculated B−O bond order values of ∼2.0 are supportive of substantial charge stabilization via resonance form **II-B** (Figure 12B), a simple explanation to rationalize the preference of structure **I** resides in the thermodynamic advantage of an additional σ B−O bond over a π B−O bond and the sharing of the negative charge between three electronegative heteroatoms instead of just two such atoms in form **II**.

CONCLUSION

This comprehensive study of naphthoid hemiboronic acid heterocycles **1**−**3** rectifies a number of incorrect conclusions and ambiguous results reported in the literature regarding the acidic nature and aromatic character of these B−X/C═C isosteric compounds (Figure 13). The evidence obtained herein, using a combination of experimental, spectroscopic, X-ray crystallographic, and computational studies of model boranol-containing benzoxa- and benzodiazaborines confirms the Lewis acidic nature of these compounds in aqueous conditions. Particularly compelling is the X-ray crystallographic elucidation of several conjugate bases or tetrahedral adducts that clearly highlights their Lewis basic structure and the resulting disruption of electronic delocalization within the boroheterocyclic ring. Unlike the highly acidic benzoxaborine **1** and *N*-sulfonyl benzodiazaborine **3a**, which display no evidence of heterocyclic ring aromaticity, boraza derivatives

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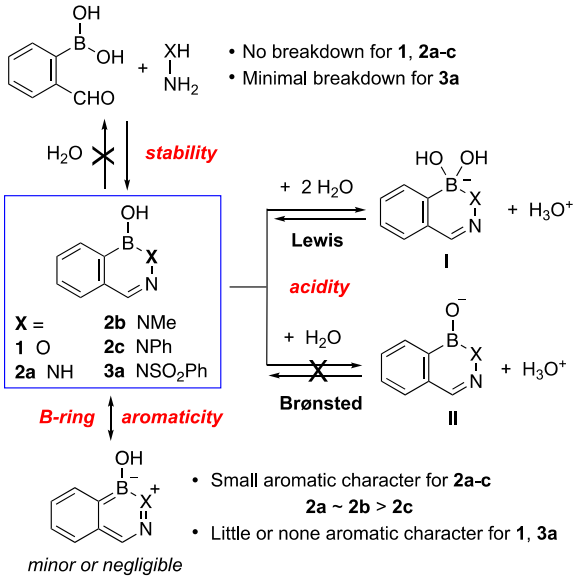

Figure 13. Summary of key conclusions for model naphthoid compounds **1**, **2a–c**, and **3a**.

2a–c with a basic nitrogen atom demonstrate an unusually high pK_a for a class of hemiboronic acids that is in agreement with a small aromatic character. As demonstrated by dynamic exchange and crossover experiments, most of these naphthoid heterocycles are stable in neutral aqueous medium, and they offer different and predictable boron configurations (ionized tetravalent or neutral trivalent) at biological pH that can be useful in drug discovery applications. Moreover, heterocycles **1** and **2a** can undergo reversible exchange of their boranol group with alcohols that makes these scaffolds attractive in the design of covalent ligands for biomolecules or for catalyzing reactions of alcohol substrates. On the other hand, the stability of *N*-alkyl and *N*-aryl scaffolds represented by **2b**,**c** along with the ability to modify their nitrogen atom substituent is appealing for applications in bioconjugation. Altogether not only does this study resolve inaccuracies and ambiguities reported in the literature in the past five decades, it also provides new conclusions that are important toward the methodical application of boron heterocycles in catalysis, medicinal chemistry, and chemical biology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02462.

Experimental details, analytical data, and spectral reproductions for all new compounds; details of all mechanistic and computational studies (PDF)

Accession Codes

CCDC 2065164–2065171 and 2081825 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Dennis G. Hall − *Department of Chemistry, University of Alberta, Centennial Centre for Interdisciplinary Science, Edmonton, AB T6G 2G2, Canada;* orcid.org/0000-0001-8555-6400; Phone: 1-780-492-3141; Email: dennis.hall@ualberta.ca

Authors

M. Zain H. Kazmi − *Department of Chemistry, University of Alberta, Centennial Centre for Interdisciplinary Science, Edmonton, AB T6G 2G2, Canada*

Jason P. G. Rygus − *Department of Chemistry, University of Alberta, Centennial Centre for Interdisciplinary Science, Edmonton, AB T6G 2G2, Canada*

Hwee Ting Ang − *Department of Chemistry, University of Alberta, Centennial Centre for Interdisciplinary Science, Edmonton, AB T6G 2G2, Canada*

Marco Paladino − *Department of Chemistry, University of Alberta, Centennial Centre for Interdisciplinary Science, Edmonton, AB T6G 2G2, Canada*

Matthew A. Johnson − *Department of Chemistry, University of Alberta, Centennial Centre for Interdisciplinary Science, Edmonton, AB T6G 2G2, Canada*

Michael J. Ferguson − *X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, AB T6G 2G2, Canada;* orcid.org/0000-0002-5221-4401

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c02462

Author Contributions

#M.Z.H.K. and J.P.G.R. contributed equally to the work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wang, B. J.; Groziak, M. P. Recent Advances in the Chemistry of Boron Heterocycles. *Adv. Heterocycl. Chem.* **2016**, *118*, 47–90.
(2) Giustra, X.; Liu, S.-Y. The State of the Art in Azaborine Chemistry: New Synthetic Methods and Applications. *J. Am. Chem. Soc.* **2018**, *140*, 1184–1194.
(3) Wang, X.-Y.; Wang, J.-Y.; Pei, J. BN Heterosuperbenzenes: Synthesis and Properties. *Chem. - Eur. J.* **2015**, *21*, 3528–3539.
(4) Santos Fernandes, G. F.; Denny, W. A.; Dos Santos, J. L. Boron in Drug Design: Recent Advances in the Development of New Therapeutic Agents. *Eur. J. Med. Chem.* **2019**, *179*, 791–804.
(5) Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y.-K.; Hernandez, V.; Xia, Y. Therapeutic potential of boron-containing compounds. *Future Med. Chem.* **2009**, *1*, 1275–1288.
(6) Dowlut, M.; Hall, D. G. An Improved Class of Sugar-Binding Boronic Acids, Soluble and Capable of Complexing Glycosides in Neutral Water. *J. Am. Chem. Soc.* **2006**, *128*, 4226–4227.
(7) Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, M.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. Discovery of a New Boron-containing Antifungal Agent, 5-Fluoro-1,3-

dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), for the Potential Treatment of Onychomycosis. *J. Med. Chem.* **2006**, *49*, 4447−4450.
(8) Akama, T.; Baker, S. J.; Zhang, Y.-K.; Hernandez, V.; Zhou, H.; Sanders, V.; Freund, Y.; Kimura, R.; Maples, K. R.; Plattner, J. J. Discovery and Structure-Activity Study of a Novel Benzoxaborole Anti-Inflammatory Agent (AN2728) for the Potential Topical Treatment of Psoriasis and Atopic Dermatitis. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2129−2132.
(9) Hecker, S. J.; Reddy, K. R.; Totrov, M.; Hirst, G. C.; Lomovskaya, O.; Griffith, D. C.; King, P.; Tsivkovski, R.; Sun, D.; Sabet, M.; Tarazi, Z.; Clifton, M. C.; Atkins, K.; Raymond, A.; Potts, K. T.; Abendroth, J.; Boyer, S. H.; Loutit, J. S.; Morgan, E. E.; Durso, S.; Dudley, M. N. Discovery of a Cyclic Boronic Acid β-Lactamase Inhibitor (RPX7009) with Utility vs Class A Serine Carbapenemases. *J. Med. Chem.* **2015**, *58*, 3682−3692.
(10) Zhao, P.; Nettleton, D. O.; Karki, R. G.; Zécri, F. J.; Liu, S.-Y. Medicinal Chemistry Profiling of Monocyclic 1,2-Azaborines. *ChemMedChem* **2017**, *12*, 358−361.
(11) Rombouts, F. J. R.; Tovar, F.; Austin, N.; Tresadern, G.; Trabanco, A. A. Benzazaborinines as Novel Bioisosteric Replacements of Naphthalene: Propranolol as an Example. *J. Med. Chem.* **2015**, *58*, 9287−9295.
(12) Davies, G. H. M.; Mukhtar, A.; Saeednia, B.; Sherafat, F.; Kelly, C. B.; Molander, G. M. Azaborininones: Synthesis and Structural Analysis of a Carbonyl-Containing Class of Azaborines. *J. Org. Chem.* **2017**, *82*, 5380−5390.
(13) Robinson, P. D.; Groziak, M. P. A boron-containing Estrogen Mimic. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *C55*, 1701−1704.
(14) Baldock, C.; Rafferty, J. B.; Sedelnikova, S. E.; Baker, P. J.; Stuitje, A. R.; Slabas, A. R.; Hawkes, T. R.; Rice, D. W. A Mechanism of Drug Action Revealed by Structural Studies of Enoyl Reductase. *Science* **1996**, *274*, 2107−2110.
(15) Baldock, C.; de Boer, G.-J.; Rafferty, J. B.; Stuitje, A. R.; Rice, D. W. The Mechanism of Action of Diazaborines. *Biochem. Pharmacol.* **1998**, *55*, 1541−1550.
(16) António, J. P. M.; Gonçalves, L. M.; Guedes, R. C.; Moreira, R.; Gois, P. M. P. Diazaborines as New Inhibitors of Human Neutrophil Elastase. *ACS Omega* **2018**, *3*, 7418−7423.
(17) Hicks, J. W.; Kylea, C. B.; Vogels, C. M.; Wheaton, S. L.; Baerlocher, F. J.; Decken, A.; Westcott, S. A. Synthesis, Characterization, and Antifungal Activity of Boron-Containing. *Chem. Biodiversity* **2008**, *5*, 2415−2422.
(18) Hall, D. G. In *Boronic Acids: Preparation and Application in Organic Synthesis, Medicine, and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Chapter 1, pp 1−133 and references therein.
(19) Martínez-Aguirre, M. A.; Yatsimirsky, A. K. Brønsted versus Lewis Acid Type Anion Recognition by Arylboronic Acids. *J. Org. Chem.* **2015**, *80*, 4985−4993.
(20) Lorand, J. P.; Edwards, J. O. Polyol Complexes and Structure of the Benzeneboronate Ion. *J. Org. Chem.* **1959**, *24*, 769−774.
(21) Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. Synthesis of Aromatic Boronic Acids. Aldehydo Boronic Acids and a Boronic Acid Analog of Tyrosine. *J. Am. Chem. Soc.* **1958**, *80*, 835−838.
(22) Dewar, M. J. S.; Dougherty, R. C. Boron-Containing Analogs of Isoquinoline. *J. Am. Chem. Soc.* **1962**, *84*, 2648−6249.
(23) Dewar, M. J. S.; Dougherty, R. C. New Heteroaromatic Compounds. XX. Derivatives of 4,3-Borazaroisoquinoline. *J. Am. Chem. Soc.* **1964**, *86*, 433−436.
(24) Dewar, M. J. S.; Jones, R. New Heteroaromatic Compounds. XXV. Studies of Salt Formation in Boron Oxyacids by ^{11}B Nuclear Magnetic Resonance. *J. Am. Chem. Soc.* **1967**, *89*, 2408−2410.
(25) Kroeker, S.; Stebbins, J. F. Three-Coordinated Boron-11 Chemical Shifts in Borates. *Inorg. Chem.* **2001**, *40*, 6239−6246.
(26) Fujdala, K. L.; Oliver, A. G.; Hollander, F. J.; Tilley, T. D. Tris(tert-butoxy)siloxy Derivatives of Boron, Including the Boronous Acid HOB[OSi(OtBu)$_3$]$_2$ and the Metal (Siloxy)boryloxide Complex Cp$_2$Zr(Me)OB[OSi(OtBu)$_3$]$_2$: A Remarkable Crystal Structure with 18 Independent Molecules in Its Asymmetric Unit. *Inorg. Chem.* **2003**, *42*, 1140−1150.
(27) Dunn, H. E.; Catlin, J. C.; Snyder, H. R. Arylboronic Acids. Imino Derivatives from *o*-Formylbenzeneboronic Acid. *J. Org. Chem.* **1968**, *33*, 4483−4486.
(28) Groziak, M. P.; Chen, L.; Yi, L.; Robinson, P. D. Planar Boron Heterocycles with Nucleic Acid-Like Hydrogen-Bonding Motifs. *J. Am. Chem. Soc.* **1997**, *119*, 7817−7826.
(29) Dilek, O.; Lei, Z.; Mukherjee, K.; Bane, S. Rapid Formation of a Stable Boron−Nitrogen Heterocycle in Dilute, Neutral Aqueous Solution for Bioorthogonal Coupling Reactions. *Chem. Commun.* **2015**, *51*, 16992−16995.
(30) Stress, C. J.; Schmidt, P. J.; Gillingham, D. G. Comparison of Boron-Assisted Oxime and Hydrazone Formations Leads to the Discovery of a Fluorogenic Variant. *Org. Biomol. Chem.* **2016**, *14*, 5529−5533.
(31) Gu, H.; Chio, T. I.; Lei, Z.; Staples, R. J.; Hirschi, J. S.; Bane, S. Formation of Hydrazones and Stabilized Boron−Nitrogen Heterocycles in Aqueous Solution from Carbohydrazides and Ortho Formylphenylboronic Acids. *Org. Biomol. Chem.* **2017**, *15*, 7543−7548.
(32) Kalia, J.; Raines, R. T. Hydrolytic Stability of Hydrazones and Oximes. *Angew. Chem., Int. Ed.* **2008**, *47*, 7523−7526.
(33) Bérubé, M.; Dowlut, M.; Hall, D. G. Benzoboroxoles as Efficient Glycopyranoside-Binding Agents in Physiological Conditions: Structure and Selectivity of Complex Formation. *J. Org. Chem.* **2008**, *73*, 6471−6479.
(34) Bhangu, J.; Whittal, R. M.; Hall, D. G. Design, Synthesis and Structure of a Frustrated Benzoxaborole and its Applications in the Complexation of Amines, Amino Acids, and Protein Modification. *Org. Biomol. Chem.* **2020**, *18*, 3492−3500.
(35) Tomsho, J. W.; Pal, A.; Hall, D. G.; Benkovic, S. J. Ring Structure and Aromatic Substituent Effects on the pKa of the Benzoxaborole Pharmacophore. *ACS Med. Chem. Lett.* **2012**, *3*, 48−52.
(36) Kowalska, K.; Adamczyk-Wozniak; Gajowiec, P.; Gierczyk, B.; Kaczorowska, E.; Popenda, L.; Schroeder, G.; Sikorski, A.; Sporzynski, A. Fluoro-substituted 2-Formylphenylboronic acids: Structures, Properties and Tautomeric Equilibria. *J. Fluorine Chem.* **2016**, *187*, 1−8.
(37) Harris, K. D. M.; Kariuki, B. M.; Lambropoulos, C.; Philp, D.; Robinson, J. M. A. A New Hydrogen Bonding Motif Based on 10-Hydroxy-10,9-Borazaphenanthrene. *Tetrahedron* **1997**, *53*, 8599−8612.
(38) Mikhailov, B. M.; Kuimova, M. E. Organoboron Compounds. CCCXVIII. On the Problem of the Aromatic Character of Boron Heterocyclic Compounds. *J. Organomet. Chem.* **1976**, *116*, 123−133.
(39) Zhang, S.; Baker, J.; Pulay, P. A Reliable and Efficient First Principles-Based Method for Predicting pKa Values. 2. Organic Acids. *J. Phys. Chem. A* **2010**, *114*, 432−442.
(40) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. Aryl Trihydroxyborates: Easily Isolated Discrete Species Convenient for Direct Application in Coupling Reactions. *Org. Lett.* **2006**, *8*, 4071−4074.
(41) Shao, Y.; et al. Advances in molecular quantum chemistry contained in the Q-Chem 4 program package. *Mol. Phys.* **2015**, *113*, 184−215.
(42) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. V. R. Nucleus-Independent Chemical Shifts (NICS) as an Aromaticity Criterion. *Chem. Rev.* **2005**, *105*, 3842−3888.
(43) Yruegas, S.; Patterson, D. C.; Martin, C. D. Oxygen Insertion Into Boroles as a Route to 1,2-Oxaborines. *Chem. Commun.* **2016**, *52*, 6658−6661.
(44) Chen, J.; Bajko, Z.; Kampf, J. W.; Ashe, A. J., III. 1,2-Dihydro-1,2-oxaborine: A Boron-Oxygen Heterocycle Isoelectronic with Benzene. *Organometallics* **2007**, *26*, 1563−1564.
(45) Eisuke Watanabe, E.; Miyamoto, C.; Tanaka, A.; Iizuka, K.; Iwatsuki, S.; Inamo, M.; Takagi, H. D.; Ishihara, K. Relative Kinetic

Reactivity of Boronic Acid and Boronate Ion Towards Tiron, 2,2′-Biphenol, and Propylene Glycol. *Dalton Trans.* **2013**, *42*, 8446−8453.
(46) Graham, B. J.; Windsor, I. W.; Gold, B.; Raines, R. T. Boronic Acid with High Oxidative Stability and Utility in Biological Contexts. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2013691118.
(47) Glendening, E. D.; et al. *NBO 6.0*; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 2013.

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This paper was published on June 24, 2021. The compound number in the second column header of Table 2 was incorrect. This has been updated and the paper was re-posted on June 28, 2021.

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