Boron Heterocycles Bearing a Peripheral Resemblance to Naturally-Occurring Purines: Design, Syntheses, Structures, and Properties†

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Abstract: To test the design and initiate the development of a new class of boron-containing purine nucleoside and aglycon analogs, the benzo-fused boron heterocycles 1-hydroxy-1*H*-2,4,1-benzoxazaborine (**2**), 1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (**3**), and 3-amino-1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (**4**) were synthesized, and their structural properties and chemical reactivities were investigated. The heterocyclic peripheries of these targets possess heteroatom, hydrogen atom, and in-plane lone-pair electron loci specifically selected to match closely those of the pyrimidine ring portions of the naturally-occurring purines adenine, hypoxanthine, and guanine. According to ^{1}H and ^{11}B NMR spectral analyses, **2–4** are stable to facile *hydrolysis*, but not to facile *hydration*, which occurs in a 1,4-fashion to give zwitterionic adducts. In addition, these benzo-fused boron heterocycles form bis-methanol adducts simply upon warming in methanol solution. A single-crystal X-ray diffraction analysis of the bis-methanol adduct (**14**) derived from **3** confirmed it to be a zwitterion comprised of tetrahedral borate anion and formamidinium cation molecular fragments. From NMR-based solution structure determinations made of **2–4** and a series of substituted derivatives, the facile 1,4-hydration property appears to be endemic to the 2,4,1-oxaza- and diazaborine classes of boron heterocycles and is projected to imbue certain future imidazo[5,4-*e*]-fused members with the requisite aqueous solution structural features for "transition-state" analog inhibition of the enzyme adenosine deaminase (EC 3.5.4.4). This work underscores the attraction of employing boron-for-carbon replacement strategies in the design of new, potentially bioactive agents.

Introduction and Historical Context

In the design of new, potentially bioactive analogs of naturally-occurring substances,[1] the replacement of carbon for boron is not often considered, even though there is ample precedent that analogs prepared by this strategy can possess unique physicochemical and sometimes useful biochemical properties. A good example is the class of boronic acid-based inhibitors of protease enzymes which was developed in the early 1970s[2] and has since remained the subject of investigations.[3] Some members of this class are known to undergo reversible covalent attachment to a nucleophilic residue at an enzyme's active site, and while others may act simply as competitive inhibitors in their borate conjugate base form, in all cases successful inhibition can be attributed to the relative ease with which the boron atom undergoes interconversion between sp^2 and sp^3 hybridization states. While boron-for-carbon replacement analogs of certain amino acids and peptides are currently under development,[3,4] there appears to have been a long-standing reluctance to apply this analog design strategy to components of the nucleic acids.[5,6] This is perhaps due to the fact that the only successful such replacement produced a compound of limited hydrolytic stability and thus of no utility in enzymatic or biological assay systems. Over 30 years ago, Dewar's group reported the preparation of 1,2-dihydro-5-methyl-2-phenyl-5*H*-imidazo[4,5-*d*]-1,3,2-diazaborin-4(3*H*)-one (2-phenyl-6-hydroxy-7-methyl-2-boradihydropurine, **1**) but found this endocyclic boron-containing purine analog to be readily hydrolyzed in 95% aqueous ethanol at room temperature.[7] Almost parenthetically,[8] these investigators suggested that a strategy

† Presented in part: (a) Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *Abstracts of Papers*; 205th National Meeting of the American Chemical Society, Denver, CO, Spring, 1993; American Chemical Society: Washington, DC, 1993; ORGN 170. (b) Groziak, M. P.; Ganguly, A. D. *Abstracts*; 14th International Congress of Heterocyclic Chemistry, Antwerp, Belgium, 1993 1–6, Aug; Fourteenth International Congress of Heterocyclic Chemistry: Antwerp, Belgium 1993; OP-DA-12.

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(4) (a) Boron analogs of aspartic acid: Kinder, D. H.; Ames, M. M. *J. Org. Chem.* **1987**, *52*, 2452–2454. (b) Of acetylcholine: Spielvogel, B. F.; Ahmed, F. U.; McPhail, A. T. *J. Am. Chem. Soc.* **1986**, *108*, 3824–3825. (c) Egan, M. A.; Zoellner, R. W. *J. Org. Chem.* **1993**, *58*, 1719–1729 and references therein. (d) Of glycine: Spielvogel, B. F.; Das, M. K.; McPhail, A. T.; Onan, K. D.; Hall, I. H. *J. Am. Chem. Soc.* **1980**, *102*, 6343–6344.

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(6) The preparation of an endocyclic boron-containing pyrimidine analog is claimed in Maitra, A. *Indian J. Chem.* **1978**, *16B*, 85–86.

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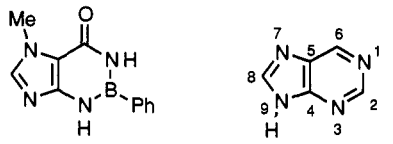

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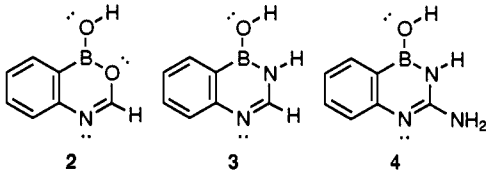
involving a boron-for-carbon replacement at the 6- rather than the 2-position (purine numbering system, shown above) of the bicyclic ring would afford boron-containing purine analogs of much greater hydrolytic stability.

To date, no one has prepared a purine analog fitting this description, even though several structures based upon a 6-boradihydropurine framework have been proposed as attractive synthetic targets for biomedical research.[9] As an early part of our program to develop just such boron-containing heterocycles into a new class of purine nucleoside and aglycon analogs, we felt it imperative to determine the hydrolytic stability, structural features, and chemical reactivities of those benzo-fused boron heterocycles possessing heteroatom peripheries representative of the ultimate imidazo-fused targets of interest.

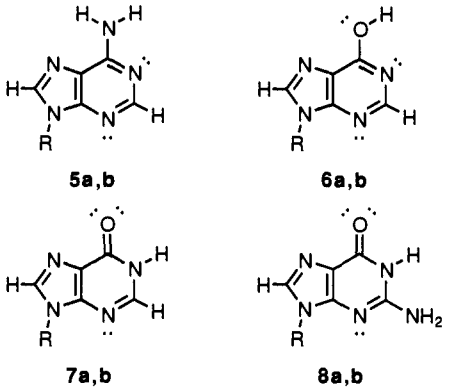
Design and Background

An examination of the heteroatom peripheries of the heretofore unknown boron heterocycles 1-hydroxy-1*H*-2,4,1-benzoxazaborine (**2**), 1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (**3**), and 3-amino-1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (**4**) will



2 3 4

reveal that they contain many of the same structural features (i.e., heteroatom, hydrogen atom, and in-plane lone-pair electron loci) found in the pyrimidine portions of the aglycon/nucleoside pairs adenine/adenosine (**5a,b**), hypoxanthine/inosine in both minor enol (**6a,b**) and major keto (**7a,b**) forms,[10] and guanine/guanosine (**8a,b**). The exact match between the 6-membered heterocyclic ring peripheral features of **2** and **6** is especially noteworthy, as it serves to highlight the fact that a boron–oxygen single bond is at least an isovalent if not also a reasonably isoelectronic and isosteric replacement moiety for an endocyclic carbon–nitrogen imine double bond located within a heteroaromatic ring. In addition to the "anchoring" of the boron atom to a ring junctional carbon atom, which should serve to suppress hydrolysis, the design of heterocycles **2–4** (as well as that of Dewar's postulated 6-boradihydropurines) features the boron atom located at the site of attachment of a π-electron-contributing heteroatom ring substituent. This latter feature is in accord with the tenets of the "topological charge stabilization" theory,[11] which predicts that it is precisely one of these sites which should best accommodate an electron-deficient boron heteroatom, because



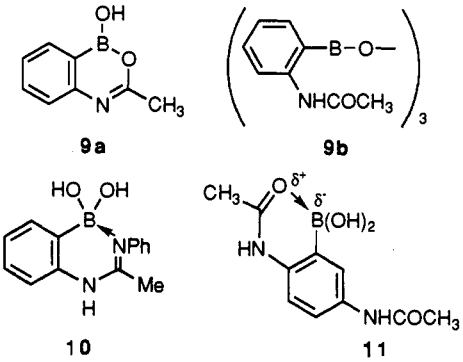
5a,b **6a,b**

7a,b **8a,b**

a, R = H; **b**, R = 1-β-D-ribofuranosyl

the least amount of Hückel π-electron charge is found to accumulate there in the corresponding isoelectronic hydrocarbon uniform reference frames.[12]

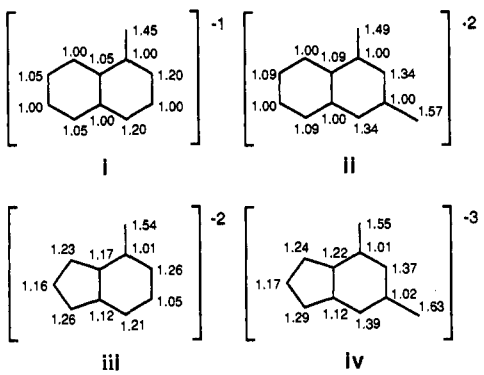
Even from the broad view of heterocycles **2–4** as simple intramolecular dehydration products of 2-(formamido)-, 2-(formamidino)-, and 2-(guanidino)phenylboronic acid, respectively, only a handful of compounds with similar heteroatom connectivity patterns are known. In 1960, Soloway reported the preparation of 2-(acetamido)phenylboronic acid which, according to limited characterization data, was formulated as either the bicyclic *B*-hydroxy monomeric structure **9a** or its trimeric (substituted boroxine) counterpart **9b**.[13] Included within a series of investiga-



9a **9b**

10 **11**

tions of organoboron compounds by Mikhailov's group[14] between 1976 and 1985 was the preparation and physicochemical analysis



i ii

iii iv

(7) (a) Chissick, S. S.; Dewar, M. J. S.; Maitlis, P. M. *J. Am. Chem. Soc.* **1959**, *81*, 6329–6330; (b) **1961**, *83*, 2708–2711.

(8) Footnote 5 in ref 7b.

(9) (a) Kliegel, W. *Pharm. Unserer Zeit* **1973**, *2*, 21–28. (b) Soloway, A. H. in *Radionuclide Applications in Neurology and Neurosurgery*; Wang, Y., Ed.; Thomas: Springfield, IL, 1970; pp 301–312. (c) Soloway, A. H. *Progress in Boron Chemistry*; Pergamon Press: New York, NY, 1964; pp 203–234.

(10) In aqueous solution, the keto (lactam) form of inosine (**7b**) was estimated to account for at least 85% of the solution structure(s): (a) Evans, F. E.; Sarma, R. H. *J. Mol. Biol.* **1974**, *89*, 249–253. In dimethyl sulfoxide solution, the population of **7b** was evaluated at 88–100%, and the percentage of the keto (lactam) form of hypoxanthine (**7a**) was suggested to be in this range as well: (b) Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4627–4636; (c) **1975**, *97*, 4636–4642.

(11) Gimarc, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 1979–1988.

(12) Hückel molecular orbital calculations reveal the following π electron charge density maps for the 1-substituted naphthalenide monoanion (**i**, 12 π electrons over 11 orbitals), 1,3-disubstituted naphthalenide dianion (**ii**, 14 π electrons over 12 orbitals), 4-substituted indenide dianion (**iii**, 12 π electrons over 10 orbitals), and 4,6-disubstituted indenide trianion (**iv**, 14 π electrons over 11 orbitals), the isoelectronic hydrocarbon uniform reference frames for the boron heterocycles **2**/**3** and **4**, and the naturally-occurring purines **5**/**6**/**7** and **8**, respectively.

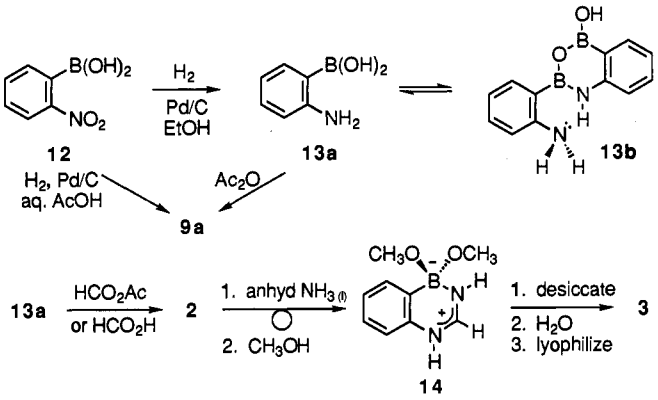
(13) Soloway, A. H. *J. Am. Chem. Soc.* **1960**, *82*, 2442–2444.

of 2-(N^3-phenylacetamidino)phenylboronic acid,[14f] formulated as the internally-chelated structure **10**. Finally, as part of their development of boron-based conjugating agents for carbohydrates, Cai and Keana reported the preparation of 2,5-bis(acetamido)-phenylboronic acid, which they represented as the weakly chelated structure **11**.[15] The structural formulae of **9–11** shown above have been reproduced exactly as the original investigators presented them. It should be noted that while certain 2-[(alkoxycarbonyl)amino]phenylboronic acids popularly utilized as components in Pd(0)-catalyzed cross-coupling reactions are most likely structurally related to **2**, these are commonly depicted as having no intramolecular interaction whatsoever between the boronic acid moiety and the ortho-substituent.[16]

Results and Discussion

Syntheses. We began by preparing Soloway's material **9** and then proceeded to prepare the adenine/hypoxanthine analogs oxazaborine **2** and diazaborine **3**. The synthesis of each of these is outlined in Scheme 1. 2-Nitrophenylboronic acid (**12**), obtained

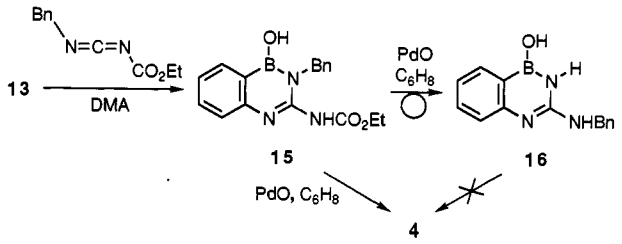
Scheme 1



in a 56% yield according to a modification of a literature method for low-temperature nitration of phenylboronic acid in Ac_2O solution,[17] was subjected to catalytic hydrogenation (H_2, Pd/C) on a Parr apparatus to give 2-aminophenylboronic acid (67% yield). This apparently unknown aminoboronic acid was found to exist as the monomer **13a** in $(CD_3)_2SO/D_2O$ solution but as the asymmetric didehydro dimer **13b** both in anhydrous aprotic solution and in the solid state by NMR and mass spectral and elemental microanalyses. Heterocycle **9** was prepared either by condensation of **13** and Ac_2O in refluxing dry 1,4-dioxane (quantitative) or by the Parr hydrogenation of **12** in aqueous acetic acid (73% yield), the latter as Soloway had reported.[13]

The synthesis of oxazaborine **2** from **13** was readily accomplished in one of two ways. The method of choice was the condensation of **13** and acetic formic anhydride[18] in cold, dry

Scheme 2



1,4-dioxane, which afforded **2** in quantitative yield. We found that heterocycle **2** could also be prepared by subjecting **13** to refluxing 97% formic acid, but this method gave **2** in only a 35% yield. For the preparation of diazaborine **3**, we reasoned that this heterocycle might be accessible via condensation of **2** and liquid NH_3 by a ring transformative S_N(ANRORC)[19] process. A residue was obtained after **2** was subjected to refluxing liquid NH_3 for 12 h, but we were unable to develop a workup procedure that permitted the direct isolation of **3**. This difficulty was circumvented by employing the following sequence of steps. This residue was first converted into a crystalline bis-methanol adduct (**14**) by simple recrystallization from absolute CH_3OH. Next, 1 equiv of CH_3OH was removed from this adduct by drying in an Abderhalden apparatus (110 °C, P_2O_5 desiccant, 12 h in vacuo). Finally, the resultant hygroscopic *B*-monomethoxy-2,4,1-diazaborine was readily hydrolyzed by dissolving in water, and lyophilization gave pure **3** in powder form. In this way, **3** was obtained from **2** in ca. 50% yield.

Several substituted derivatives (**18–21** in Table 5, *vide infra*) of heterocycles **2** and **3** needed for a ^{11}B NMR-based structural analysis study were prepared either by condensation of **13** and electrophilic reagents (Cl_3CCN, $(CF_3CO)_2O$) other than Ac_2O or HCO_2Ac or by S_N(ANRORC)-type ring transformation of **2** using nucleophilic ones ($PrNH_2$, NH_2NH_2) other than NH_3 (see Experimental Section). The mechanism of these S_N(ANRORC) ring transformations conducted on **2** may involve an initial attack of the nucleophile at either the C3 or the B1 ring atom positions.

For the preparation of the guanine analog **4**, we relied upon a carbodiimide-based synthetic strategy that had been developed for the synthesis of guanosine from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA-riboside).[20] As shown in Scheme 2, condensation of the aminophenylboronic acid **13** with 1-benzyl-3-(ethoxycarbonyl)carbodiimide[21] in anhydrous DMA solution directly afforded the di-*N*-protected 3-amino-2,4,1-benzodiazaborine **15** (79% yield). Attempted removal of the *N*-benzyl protecting group of **15** via catalytic transfer hydrogenolysis (Pd(II) oxide, 1,4-cyclohexadiene) directly afforded a rearrangement product characterized as **16** together with the desired target **4**. The presence of propitious water and/or the prolonged (17 h) exposure to elevated temperature (100 °C) may have contributed to the unexpected loss of the ethoxycarbonyl group from **15**. All attempts to effect a removal of the benzyl group of **16** to provide additional quantities of **4** were unsuccessful. As with **3**, both **16** and **4** were most readily isolated as their bis-methanol adducts, which were obtained in 47% and 16% yields, respectively.

Structures and Properties. ACE (alternating CI/EI) mass spectral analysis of Soloway's oxazaborine **9** revealed peaks due

(14) (a) Mikhailov, B. M.; Kuimova, M. E. *J. Organomet. Chem.* **1976**, *116*, 123–133. (b) Zolotarev, B. M.; Dorokhov, V. A.; Chizhov, O. S.; Lavrinovich, L. I.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 80–84. (c) Dorokhov, V. A.; Boldyreva, O. G.; Bochkareva, M. N.; Mikhailov, B. M. *Ibid.* **1979**, 174–180. (d) Dorokhov, V. A.; Bochkareva, M. N.; Boldyreva, O. G.; Rassadin, B. V.; Mikhailov, B. M. *Ibid.* **1979**, 411–418. (e) Vorontsova, L. G.; Chizhov, O. S.; Boldyreva, O. G.; Dorokhov, V. A.; Mikhailov, B. M. *Ibid.* **1985**, 329–332. (f) Boldyreva, O.; Dorokhov, V. A.; Mikhailov, B. M. *Ibid.* **1985**, 428–430.

(15) Cai, X. S.; Keana, J. F. W. *Bioconjugate Chem.* **1991**, *2*, 317–322.

(16) (a) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49–64. (b) Kalinin, V. N. *Synthesis* **1992**, 413–432. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (d) Fu, J.-M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665–1668. (e) Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679–6682. (f) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463–5466. (g) Cheng, W.; Snieckus, V. *Ibid.* **1987**, *28*, 5097–5098. (h) Sharp, M. J.; Cheng, W.; Snieckus, V. *Ibid.* **1987**, *28*, 5093–5096. (i) Thompson, W. J.; Guadino, J. *J. Org. Chem.* **1984**, *49*, 5237–5243. The recent study of Pd(0)-mediated cross-coupling chemistry involving a 2,1-benzoxaborine provides a nice exception to this practice: (j) Arcus, V. L.; Main, L.; Nicholson, B. K. *J. Organomet. Chem.* **1993**, *460*, 139–147.

(17) Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711–723.

(18) Krimen, L. I. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, 8–9.

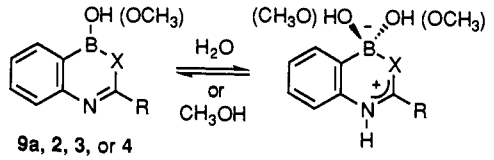
(19) Nucleophilic Substitution via Addition of a Nucleophile followed by Ring Opening and then Ring Closure. For reviews, see: (a) van der Plas, H. C. *Tetrahedron* **1985**, *41*, 237–281. (b) van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462–468.

(20) Groziak, M. P.; Townsend, L. B. *J. Org. Chem.* **1986**, *51*, 1277–1282.

(21) Groziak, M. P.; Townsend, L. B. In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; John Wiley and Sons, Inc.: New York, 1991; Vol. 4, pp 382–385.

to ions derived from the *B*-hydroxy monomer **9a** (*m/e* 161.1) and its B–O–B anhydro dimer (*m/e* 304.2), but not from the substituted boroxine **9b** (*m/e* 483.2). As this and other spectroscopic analyses of the compounds prepared in this study consistently provided evidence for the existence of benzo-fused oxaza- and diazaborine bicyclic ring structures, it is unlikely that appreciable amounts of trimeric species resembling **9b** are present either in the solid state or in solution.

All of the 2,4,1-oxaza- and diazaborines we studied exhibited chemical reactivity behavior consistent with the coexistence of a Lewis acidic site at the boron atom and a Lewis basic site at the N4 imine nitrogen atom. As a consequence, weakly nucleophilic species such as water and methanol were found to add readily and reversibly in a 1,4-fashion across the B1 and N4 atoms of **9a**, **2**, **3**, and **4** in a process that generates zwitterionic adducts and appears to be endemic to these classes of boron heterocycles. The first piece of evidence in support of this



9a, 2, 3, or 4

equilibrium came from a single-crystal X-ray diffraction analysis of the crystalline compound (**14**) obtained when crude **3** was recrystallized from absolute CH_3OH. This crystal structure determination of **14** (Figure 1 and Tables 1–4) revealed it to be

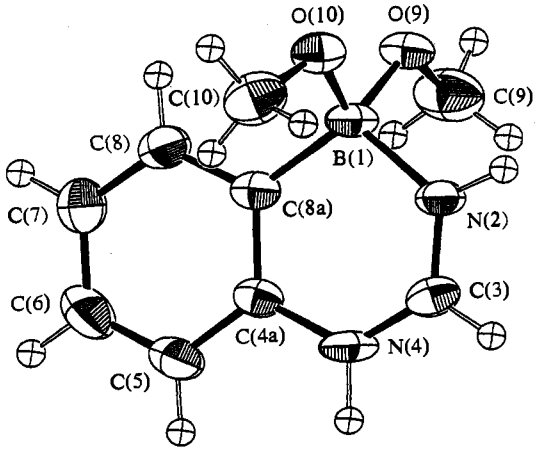


Figure 1. ORTEP drawing and atomic numbering scheme for $C_9H_{13}BN_2O_2$ (**14**).

a zwitterion possessing several interesting features. Tetracoordination at the boron atom shows it to possess a full negative charge, while the closeness of N2–C3 and C3–N4 bond lengths (1.293(4) and 1.319(4) Å, respectively) to each other and to those of the formamidinium fragment of *N,N,N',N'*-tetramethylformamidinium perchlorate (1.30(1) Å)[22] provides strong support for the positive charge delocalized over the N2–C3–N4 fragment. Both the endocyclic B–C and B–N bond lengths (1.602(5) and 1.581(4) Å, respectively) are in the normal range expected for borate anions of this type.[23] The heterocyclic ring's bond lengths and endocyclic angles compare well to Mikhailov's crystal structure determination of **17**,[14e] the structural formula of which is reproduced here exactly as originally formulated. From the perspective of facile 1,4-addition chemistry, compound **17** can be viewed as simply an acetic acid adduct of 1-butyl-1,2-dihydro-3-methyl-2-phenyl-2,4,1-benzodiazaborine and is more accurately

(22) Prick, P. A. J.; Beurskens, P. T. *Cryst. Struct. Commun.* **1979**, *8*, 293–298.

(23) Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; Oxford University Press: London, 1984.

Table 1. Summary of Crystallographic Data for $C_9H_{13}BN_2O_2$ (**14**): Crystal Data and Data Collection Parameters

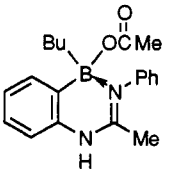
formula	$C_9H_{13}BN_2O_2$
formula weight, g mol^{-1}	192.02
crystal system	monoclinic
space group	$P2_1/c$
a, Å	6.735(9)
b, Å	20.488(9)
c, Å	7.194(4)
β, deg	100.52(7)
V, Å^3	976(2)
Z	4
ρ(calcd), g cm^{-3}	1.307
temp, °C	25
abs coeff, mm^{-1}	0.085
crystal dimens, mm	0.33 × 0.27 × 0.12
diffractometer	Rigaku AFC5S
radiation	Mo Kα (0.71069)
monochromator	graphite
method of structure soln	direct methods
refinement method	full-matrix least-squares
scan type	ω
2θ limit, deg	$3.5 \le 2\theta \le 50.0$
no. of reflcns measd	1935
no. of unique reflcns	1781
no. of reflcns used	937
R	4.1
R_w	4.8
goodness-of-fit	1.59

Table 2. Selected Bond Lengths (Å) for $C_9H_{13}BN_2O_2$ (**14**)

N(4)–C(3)	1.319(4)	C(5)–C(4a)	1.381(5)	C(8a)–C(4a)	1.398(4)
C(3)–N(2)	1.293(4)	B(1)–O(10)	1.446(4)	C(7)–C(8)	1.371(5)
B(1)–C(8a)	1.602(5)	O(10)–C(10)	1.413(4)	C(5)–C(6)	1.366(5)
C(8a)–C(8)	1.390(4)	N(4)–C(4a)	1.406(4)	B(1)–O(9)	1.470(4)
C(6)–C(7)	1.386(5)	N(2)–B(1)	1.581(4)	O(9)–C(9)	1.405(4)

Table 3. Bond Angles (deg) for $C_9H_{13}BN_2O_2$ (**14**)

N(4)–C(3)–N(2)	123.9(3)	N(4)–C(4a)–C(8a)	119.1(3)
N(4)–C(4a)–C(5)	118.6(3)	C(3)–N(4)–C(4a)	123.4(2)
C(3)–N(2)–B(1)	124.9(3)	N(2)–B(1)–C(8a)	106.4(2)
N(2)–B(1)–O(9)	107.6(3)	N(2)–B(1)–O(10)	109.4(3)
B(1)–C(8a)–C(8)	122.1(3)	B(1)–C(8a)–C(4a)	122.3(3)
C(8)–C(7)–C(6)	119.3(3)	C(7)–C(6)–C(5)	120.0(3)
C(6)–C(5)–C(4a)	119.8(3)	B(1)–O(9)–C(9)	116.9(2)
B(1)–O(10)–C(10)	117.1(3)	C(8a)–B(1)–O(10)	115.5(3)
C(8a)–C(8)–C(7)	123.0(3)	C(8a)–C(4a)–C(5)	122.3(3)
C(8)–C(8a)–C(4a)	115.6(3)	O(9)–B(1)–C(8a)	113.9(3)
O(9)–B(1)–O(10)	103.7(2)		



17

represented with a full B–N bond, a negative charge at the boron center, and a positive charge contained in a delocalized *N*-phenylacetamidinium cation fragment, all in concert with the structure shown above for **14**.

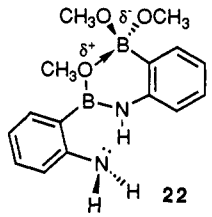
Further support for the ready interconversion of B_{sp^2}–OR and B_{sp^3}–$(OR)_2$ species came from the mass and NMR spectral analyses of **14**. The EI or CI mass spectra showed no parent ion peaks but instead revealed those derived from 1-methoxy-1,2-dihydro-2,4,1-benzodiazaborine (**14** less one CH_3OH) and from its hydrolysis product, the *B*-hydroxy compound **3**. By ^{1}H NMR, **14** spontaneously hydrolyzes to give **3** along with 2 equiv of free CH_3OH upon dissolution either in D_2O or $(CD_3)_2SO$, the latter mediated by trace moisture apparently introduced along with the crystalline sample. Thus, zwitterion **14** is stable predominantly in methanol solution or in the solid state.

Table 4. Torsion Angles (deg) for $C_9H_{13}BN_2O_2$ (**14**)

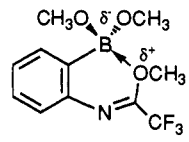
N(4)–C(3)–N(2)–B(1)	–0.8(5)	N(4)–C(4a)–C(8a)–B(1)	–0.1(4)
N(4)–C(4a)–C(8a)–C(8)	–180.0(3)	N(4)–C(4a)–C(5)–C(6)	–178.9(3)
C(3)–N(4)–C(4a)–C(8a)	–1.2(5)	C(3)–N(4)–C(4a)–C(5)	178.2(3)
C(3)–N(2)–B(1)–C(8a)	–0.3(4)	N(2)–B(1)–C(8a)–C(8)	–179.4(3)
N(2)–B(1)–C(8a)–C(4a)	0.7(4)	N(2)–B(1)–O(10)–C(10)	–69.5(3)
N(2)–B(1)–O(9)–C(9)	64.1(3)	N(2)–C(3)–N(4)–C(4a)	1.7(5)
C(8a)–B(1)–O(10)–C(10)	50.6(4)	C(8a)–B(1)–O(9)–C(9)	–53.6(4)
C(8a)–C(8)–C(7)–C(6)	0.9(6)	C(8a)–C(4a)–C(5)–C(6)	0.4(5)
C(8)–C(8a)–C(4a)–C(5)	0.7(5)	C(8)–C(7)–C(6)–C(5)	0.3(6)
C(7)–C(8)–C(8a)–B(1)	178.7(3)	C(7)–C(8)–C(8a)–C(4a)	–1.3(5)
C(7)–C(6)–C(5)–C(4a)	–0.9(5)	C(5)–C(4a)–C(8a)–B(1)	–179.4(3)
O(9)–B(1)–C(8a)–C(8)	–61.0(4)	O(9)–B(1)–C(8a)–C(4a)	119.1(3)
O(9)–B(1)–N(2)–C(3)	–122.8(3)	O(9)–B(1)–O(10)–C(10)	175.9(2)
O(10)–B(1)–C(8a)–C(8)	59.0(4)	O(10)–B(1)–C(8a)–C(4a)	–120.9(3)
O(10)–B(1)–N(2)–C(3)	125.2(3)	O(10)–B(1)–O(9)–C(9)	179.9(3)

The strongest evidence for the facile 1,4-hydration or methanol addition susceptibility of these heterocycles in solution phase came from a multisolvent ^{11}B NMR spectral study. The ^{11}B NMR chemical shift is quite sensitive to the identity of substituents attached to, as well as the amount of negative charge residing at, the boron center.[24] Within a series of compounds bearing a similar substitution pattern at the boron atom, its hybridization state may be deduced from the ^{11}B chemical shift values and an analysis of structure(s) present in solution performed. Solution structure determination by ^{11}B chemical shift measurement has been applied to many different types of boron-containing compounds,[24,25] including a number of boron heterocycles by Dewar,[26] to compounds related to **10** by Mikhailov,[14a,c,f] to **11** itself and related compounds by Keana,[15] and even to some of the boronic acid-based inhibitors of serine proteases as they exist in protein-bound form.[3c-g]

We measured the ^{11}B NMR chemical shift and line width for compounds **9a**, **2**, **3** (and **14**), **4**, their synthetic precursors (PhB-$(OH)_2$, **12**, and **13**), and some substituted derivatives (**18**–**21**) each separately in CH_3CN, CH_3OH, and H_2O solution. The results are presented in Table 5. Although the line widths were of limited utility, the chemical shifts were quite diagnostic of solution structure. For these compounds, a resonance at ca. 10 ppm on the $B(OCH_3)_3$ scale is indicative of a trigonal-planar substituted, sp^2 hybridized neutral boron atom, while one in the –15 to –20 ppm range is indicative of a tetrahedral substituted, sp^3 hybridized anionic borate center. It is clear from the data in Table 5 that while the acyclic boronic acid precursors PhB-$(OH)_2$ and **12** possess sp^2 hybridized neutral boron centers in all three solvents, almost all of the 2,4,1-oxaza- and diazaborines do so only in dry CH_3CN solution. Dissolution of these bicyclic heterocycles in either CH_3OH or in H_2O immediately produces sp^3 hybridized anionic borate centers characteristic of zwitterionic species. There is one exception to this trend and two intermediary chemical shift values which deserve comment. The chemical shift (8.4 ppm) of the 3-(trifluoromethyl)oxazaborine **20** in aqueous solution clearly indicates the existence of an sp^2 hybridized neutral boron center. Apparently, when **20** is dissolved in water it suffers a hydrolysis of the O2–C3 bond to afford 2-(trifluoroacetamido)phenylboronic acid in a process that may involve a simple ring opening of the zwitterionic hydrate but is no doubt made possible by the extreme electron-withdrawing ability of the trifluoromethyl moiety. The chemical shift (3.2 ppm) measured for one of the boron atoms of **13** in CH_3OH solution, and that (5.0 ppm) measured for **20** in the same solvent are consistent with solution structures **22** and **23**, respectively. Accordingly,



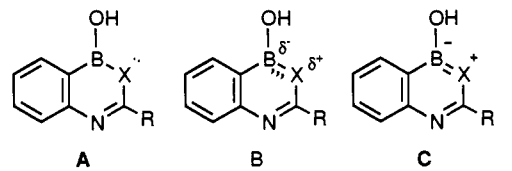
22



23

these two species represent the only true weak chelates uncovered in our study. In our view, the weakly chelated structure previously formulated for **11** should be amended to one of a fully zwitterionic bicyclic heterocycle, as the published ^{11}B NMR chemical shift for this compound in D_2O solution (–14.0 ppm on the $B(OCH_3)_3$ scale)[15] is clearly diagnostic of a full negative charge in residence at the boron center.

Depending upon the extent of α-heteroatom lone-pair electron delocalization into the boron empty p-orbital, 1,2,4-oxaza- and diazaborines in their uncharged *B*-monohydroxy form might be represented by structures **A**, **B**, or **C** shown below. Based upon



A **B** **C** **I**

the similarity between the ^{11}B NMR chemical shifts of the cyclic and acyclic boron-containing compounds of our study as well as of one conducted by Mikhailov,[14a] appreciable lone-pair electron delocalization for these types of boron heterocycles is unlikely, and thus their structures are best represented by structural formula **A**.[27] It should be noted, however, that a delocalized π-electron system is thought to impart benzene-like aromatic character to borazine ($B_3N_3H_6$).[28] Along another structural/electronic continuum, the hydration products of 1,2,4-oxaza- and diazaborines might be represented by structures **D**, **E**, or **F** (below), depending upon the degree of interaction (zero to full bond formation)

(24) (a) Kidd, R. G. In *NMR of Newly Accessible Nuclei*; Laszlo, P.; Ed.; Academic Press: New York, 1983; Vol. 2, pp 49–77. (b) Nöth, H.; Wrackmeyer, B. In *NMR Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; Springer-Verlag: Berlin, 1978; Vol. 14.

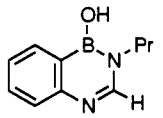
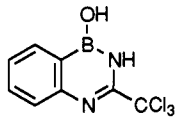
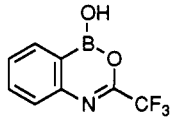
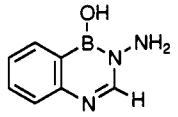
(25) ^{11}B NMR-based structure elucidation of phenylboronic acids complexed to α-amino acids: (a) Mohler, L. K.; Czarnik, A. W. *J. Am. Chem. Soc.* **1993**, *115*, 7037–7038. To ribonucleosides: (b) Paugam, M.-F.; Smith, B. D. *Tetrahedron Lett.* **1993**, *34*, 3723–3726. To glucopyranosides: (c) Morin, G. T.; Paugam, M.-F.; Smith, B. D. *Tetrahedron Lett.* **1993**, *34*, 7841–7844. To *cis*-diols: (d) Singhal, R. P.; De Silva, S. S. M. *Adv. Chromatogr.* **1992**, *31*, Chpt. 5, pp 293–336. (e) Singhal, R. P.; Ramamurthy, B.; Govindraj, N.; Sarwar, Y. *J. Chromatogr.* **1991**, *543*, 17–38. Structure elucidation of intermolecular aminoboranes: (f) Fisher, G. B.; Juarez-Brambila, J. J.; Goralski, C. T.; Wipke, W. T.; Singaram, B. *J. Am. Chem. Soc.* **1993**, *115*, 440–444. Of intramolecular aminoboranes: (g) Lauer, M.; Wulff, G. *J. Organomet. Chem.* **1983**, *256*, 1–9.

(26) Dewar, M. J. S.; Jones, R. *J. Am. Chem. Soc.* **1967**, *89*, 2408–2410. (b) Davis, F. A.; Dewar, M. J. S.; Jones, R. *Ibid.* **1968**, *90*, 706–708.

(27) Another example can be found in the 2,1-benzoxaborine described in ref 16j. Its ^{11}B NMR chemical shift at 11.2 ppm (converted to the $B(OCH_3)_3$ scale; presumably in $CDCl_3$ solution) and the X-ray-determined endocyclic B–O bond length of 1.378(3) Å are diagnostic of structural type **A**, not **B** or **C**.

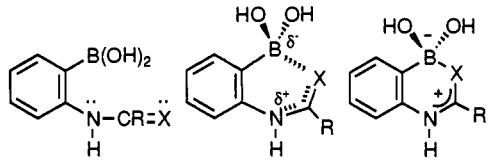
(28) Doering, J. P.; Gedanken, A.; Hitchcock, A. P.; Fischer, P.; Moore, J.; Olthoff, J. K.; Tossell, J.; Raghavachari, K.; Robin, M. B. *J. Am. Chem. Soc.* **1986**, *108*, 3602–3608.

Table 5. ^{11}B NMR Chemical Shift and Line Width Data for Boron-Containing Compounds[a]

compound	solvent: CH_3CN	CH_3OH	H_2O
phenylboronic acid	10.4 (97)	10.2 (109)	10.2 (225)[b]
2-nitrophenylboronic acid (**12**)	10.8 (104)	10.5 (80)	10.3 (216)
2-aminophenylboronic acid (**13**)	12.2 (88[c]), 10.6 (77[c])	10.2 (277), 3.2 (252)	8.3 (116)
9a	*d*	−12.4 (114)	−14.5 (280)
2	8.8 (70)	−13.1 (120)	−13.9 (176)
3	11.9 (79)[e]	−17.3 (74)[f]	−20.2 (66)
4	*d*	−16.8 (74)	−19.2 (83)
 **18**	11.0 (106)	−15.5 (65)	−19.0 (101)
 **19**	10.5 (176)	−16.7 (88)	−17.2 (271)
 **20**	8.7 (186)	5.0 (220)	8.4 (229)
 **21**	*d*	−16.3 (56)	−18.7 (69)

[a] Chemical shifts in ppm downfield (positive) or upfield (negative) of neat external $B(OCH_3)_3$ (δ = 0.0); line widths in Hz in parentheses. [b] For comparison, phenylborate anion generated in 10% aqueous NaOH solution displayed a ^{11}B signal at −16.3 ppm (90-Hz line width). [c] Estimated. [d] Insufficient solubility for detection of signal. [e] At 50 °C. [f] For crystalline **14**. In freshly prepared CH_3OH solution, powdery anhydrous **3** displayed a ^{11}B signal at −18.3 ppm (39-Hz line width) that is indicative of a "hemiacetal"-like zwitterionic species possessing both OH and OCH_3 substituents at an anionic boron center.

between the boron center and the X-heteroatom of the ortho side chain. Structural type **E** has precedence in the solid-state structure

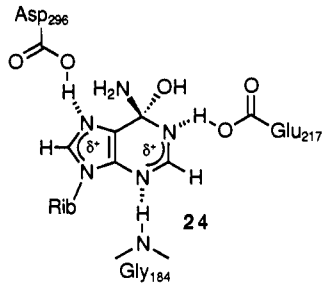


D **E** **F**

of 4-carboxy-2-nitrophenylboronic acid,[29] but the only two instances of this type uncovered in the present study both involved the weak chelation of a methoxyl group into a aryl borate diester (**22** and **23**). Except for the one apparent example of structural type **D** (**20** in H_2O solution), the hydrated versions of our boron heterocycles can all be best represented as structural type **F**.

Enzymatic Relevance and Conclusions

It should be possible to extend the development of boron-based enzyme inhibitors from the serine protease arena to that of the purine-utilizing metabolic or catabolic enzymes. Adenosine deaminase (ADnase, EC 3.5.4.4) is a hydrolytic enzyme that catalyzes the conversion of adenosine to inosine and even of adenine to hypoxanthine in vivo. According to numerous biochemical investigations,[30] as well as two recent crystal structure determinations of ADnase complexed to competitive inhibitors,[31] the mechanism of action of this enzyme is known to be of A_N+D_N type and to involve primarily the production and stabilization of the enzyme-bound tetrahedral intermediate (6*R*)-6-amino-6-hydroxy-1,6-dihydro-9-(β-D-ribofuranosyl)purine (**24**), shown below accepting hydrogen bonds from the three active site residues identified by the crystal structure determinations as being of prime importance to the binding and activation of the substrate(s). From



24

the viewpoint of developing a boron-based inhibitor of ADnase,

(29) Soundararajan, S.; Duesler, E. N.; Hageman, J. H. *Acta Crystallogr.* **1993**, *C49*, 690–693.

(30) (a) Dzingeleski, G. D.; Wolfenden, R. *Biochemistry* **1993**, *32*, 9143–9147. (b) Grosshans, J.; Wolfenden, R. *Biochim. Biophys. Acta* **1993**, *1161*, 28–32. (c) Kati, W. M.; Acheson, S. A.; Wolfenden, R. *Biochemistry* **1992**, *31*, 7356–7366. (d) Kati, W. M.; Wolfenden, R. *Biochemistry* **1989**, *28*, 7919–7927. (e) Kati, W. M.; Wolfenden, R. *Science* **1989**, *243*, 1591–1593. (f) Philips, A. V.; Coleman, M. S.; Maskos, K.; Barkley, M. D. *Biochemistry* **1989**, *28*, 2040–2050. (g) Jones, W.; Kurz, L. C.; Wolfenden, R. *Biochemistry* **1989**, *28*, 1242–1247. (h) Kurz, L. C.; Frieden, C. *Biochemistry* **1987**, *26*, 8450–8457. (i) Weiss, P. M.; Cook, P. F.; Hermes, J. D.; Cleland, W. W. *Biochemistry* **1987**, *26*, 7378–7384. (j) Frick, L.; Wolfenden, R.; Smal, E.; Baker, D. C. *Biochemistry* **1986**, *25*, 1616–1621.

(31) The structure of ADnase complexed to a single diastereomer of the 1,6-hydrate of 9-(β-D-ribofuranosyl)purine: (a) Wilson, D. K.; Rudolph, F. B.; Quiocho, F. A. *Science* **1991**, *252*, 1278–1284. (b) Sharff, A. J.; Wilson, D. K.; Chang, Z.; Quiocho, F. A. *J. Mol. Biol.* **1992**, *226*, 917–921. ADnase complexed to 1-deazaadenosine: (c) Wilson, D. K.; Quiocho, F. A. *Biochemistry* **1993**, *32*, 1689–1694.

the most striking feature of solid-state **14** reported herein is that the topology of its 6-membered heterocyclic ring periphery *almost exactly* matches that of the putative ADnase-bound tetrahedral intermediate for this enzymatic reaction.[32]

The reactivity and structural properties elucidated herein for the benzo-fused 2,4,1-oxaza- and diazaborines provide very strong support for the design and pursuit of imidazo[5,4-*e*]-fused derivatives as Dewar-type 6-boradihydropurine nucleoside and aglycon "transition-state" analog inhibitors of the hydrolytic enzyme ADnase. The topology of the heterocyclic peripheries of the 2,4,1-oxaza- and diazaborines **2–4** makes them exceedingly attractive potential replacements for the pyrimidine ring portion of naturally-occurring purine aglycon/nucleoside pairs adenine/adenosine, hypoxanthine/inosine, and guanine/guanosine, and underscores the broader, mostly untapped potential of employing endocyclic B—O/B—N for C=N/C=C moiety replacement strategies in other drug design efforts involving the manipulation of (hetero)aromatic rings of drugs or natural products.

Experimental Section

General Procedures and Materials. Melting points were determined on a Thomas-Hoover UniMelt capillary apparatus and are uncorrected. Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA) using Merck silica gel-60 PF254 as adsorbant; column chromatography was performed using Merck silica gel-60 (200–430 ASTM); and ascending preparative-layer chromatography was performed on 2-mm silica gel-GF plates from Analtech. Visualizations were done with short-wave (254 nm) UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 or a VXR-500 spectrometer on solutions as dilute as practical in order to ensure the predominance of monomeric species. These spectra were recorded using tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonic acid, sodium salt (DSS), (δ = 0.0 for ^{1}H), dioxane (δ = 66.5 for ^{13}C), or $(CD_3)_2SO$ (δ = 39.5 for ^{13}C) as internal reference. Heterocycles **2**, **3**, and **4** were obtained in at least 98% purity by ^{1}H NMR spectral analysis. Heterocycles **18–21** were characterized solely on the basis of their multinuclear NMR and low-resolution mass spectral characteristics. Signals for those carbons directly attached to a boron atom were unobservable in the ^{13}C NMR spectra due to strong quadrupolar line-broadening. ^{11}B NMR spectra were recorded without field frequency lock using nondeuterated solvents on the VXR-300 instrument at 96.2 MHz using neat $B(OMe)_3$ (δ = 0.0) as external reference. Resonances observed upfield of the reference signal were assigned negative values. Conversion of the ^{11}B chemical shift values reported herein to the $Et_2O{\cdot}BF_3$ scale is accomplished by addition of 18.1 ppm.[24a] Lyophilizations were conducted on a Labconco Lypho-Lock 4.5-L benchtop freeze-drier. Acetic formic anhydride was prepared according to a literature procedure[18] and was stored at 4 °C. 1-Benzyl-3-(ethoxycarbonyl)carbodiimide was prepared according to a literature procedure[21] and was used immediately. Phenylboronic acid, white fuming nitric acid, 98% anhydrous hydrazine, propylamine, trichloroacetonitrile, trifluoroacetic anhydride, 1,4-cyclohexadiene, and 10% palladium on charcoal were purchased from the Aldrich Chemical Co. Palladium (II) oxide monohydrate was obtained from Alfa. Methanol-d_4 (99%) was purchased from Isotec, Inc. 1,4-Dioxane was dried by distillation from sodium under argon using benzophenone ketyl as indicator, DMF and DMA were dried by distillation from CaH_2 under argon, and methanol was dried by distillation from in situ-generated magnesium methoxide. Hydrogenations were performed on a Parr hydrogenation apparatus. UV spectra were recorded on a Shimadzu UV-160U spectrophotometer. Elemental microanalyses were performed by Tom McCarthy and his staff at the University of Illinois, and mass spectral analyses were obtained from Richard Milberg and his staff of the Mass Spectrometry Facility, also at the University of Illinois.

2-Nitrophenylboronic Acid (12). This material was prepared according to the method of Seaman and Johnson,[17] modified to employ 2.9 equiv of white fuming nitric acid. The crude product thus obtained was first dried in vacuo and then purified by radial chromatography (2% CH_3OH/CH_2Cl_2 as eluent). Recrystallization from water routinely afforded pure **12** in ca. 56% yield as pale yellow crystals: mp 168–169 °C (lit.[17] mp 139.2–140.8 °C); ^{1}H NMR ($(CD_3)_2SO$) δ 8.20 (s, exchanges with D_2O, 2H, $B(OH)_2$), 8.14 (d, J = 8.4 Hz, 1H, H3), 7.75 (pseudo t, J_{app} = 8.7 Hz, 1H, H6), 7.58 (m, 2H, H4 and H5); ^{13}C NMR ($(CD_3)_2SO$) δ 150.0, 134.2, 132.4, 129.2, 122.6.

2-Aminophenylboronic Acid (13). A mixture of **12** (1.00 g, 5.99 mmol) and 10% Pd/C (100 mg) in absolute ethanol (55 mL) was shaken under 45 psi of H_2 for 15 h. The solution was filtered, and the filtrate was rotary evaporated in vacuo to give a brown oil. Recrystallizaton of this residue from MeOH–H_2O afforded 550 mg (67% of a monomer) of pure product as dark yellow crystals: mp 166–166.5 °C. According to ^{1}H and ^{13}C NMR spectral analyses, **13** exists as a monomer in D_2O or $(CD_3)_2SO/D_2O$ solution but as a didehydro dimer in dry $(CD_3)_2SO$ solution.

Didehydro dimer 13b: ^{1}H NMR ($(CD_3)_2SO$) δ 9.01 (s, exchanges with D_2O, 1H, NH or OH), 8.51 (s, exchanges with D_2O, 1H, NH or OH), 7.77–7.70 (m, 2H, ArH), 7.43 (pseudo t, J_{app} = 8.4 Hz, 1H, ArH), 7.24 (d, J = 8.1 Hz, 1H, ArH), 7.13 (pseudo t, J_{app} = 7.7 Hz, 1H, ArH), 6.95 (pseudo t, J_{app} = 7.4 Hz, 1H, ArH), 6.63 (d, J = 8.1 Hz, 1H, ArH), 6.55 (pseudo t, J_{app} = 7.2 Hz, 1H, ArH), 5.90 (s, exchanges with D_2O, 2H, NH_2); ^{13}C NMR ($(CD_3)_2SO$) δ 154.7, 150.7, 135.2, 133.5, 132.5, 131.5, 119.9, 116.5, 115.0, 114.8; low-resolution ACE (alternating CI/EI) mass spectrum, EI *m/e* 252.1 (100, $(M + CH_3OH - H_2O)^+$), 238.1 (47, M^+); CI (CH_4) *m/e* 253.1 (97, $(MH^+ + CH_3OH - H_2O)$), 239.1 (43, MH^+). Anal. Calcd for $C_{12}H_{12}B_2N_2O_2$ (**13b**): C, 60.60; H, 5.09; B, 9.09; N, 11.78. Found: C, 60.51; H, 5.31; B, 9.26; N, 11.36.

Monomer 13a: ^{1}H NMR ($(CD_3)_2SO/D_2O$) δ 7.52 (d, J = 7.2 Hz, 1H, ArH), 7.12 (pseudo t, J_{app} = 7.7 Hz, 1H, ArH), 6.58–6.52 (m, 2H, ArH); ^{13}C NMR ($(CD_3)_2SO/D_2O$) δ 154.8, 136.6, 132.3, 116.3, 115.4.

1-Hydroxy-3-methyl-1*H*-2,4,1-benzoxazaborine (9a). From 12. A mixture of **12** (1.00 g, 5.99 mmol) and 10% Pd/C (100 mg) in 70 mL of 50% aqueous HOAc was shaken under 45 psi of H_2 at room temperaturefor 15 h. The mixture was filtered, and the catalyst was washed with fresh 50% aqueous HOAc. The combined solutions were rotary evaporated, and traces of HOAc were removed by repeated coevaporation with water. The residue was dried in vacuo to afford 705 mg (73%) of **9a** as a white solid: mp 293–294 °C (lit.[13] mp 296–298 °C). According to ^{1}H and ^{13}C NMR spectral analyses, **9a** exists in *B*-monohydroxy form in dry $(CD_3)_2SO$ solution but in zwitterionic hydrate form in D_2O solution: ^{1}H NMR ($(CD_3)_2SO$) δ 11.80 (s, exchanges with D_2O, 1H, OH), 7.58 (d, J = 6.2 Hz, 1H, H5), 7.43 (d, J = 8.1 Hz, 1H, H8), 7.24 (pseudo t, J_{app} = 7.7 Hz, 1H, H7), 7.09 (pseudo t, J_{app} = 7.3 Hz, 1H, H6), 2.10 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2SO$) δ 168.8, 133.0, 127.9, 124.3, 115.9, 22.3 (CH_3); ^{1}H NMR (D_2O) δ 7.53 (pseudo t, J_{app} = 7.7 Hz, 1H, H5), 7.35 (pseudo t, J = 7.8 Hz, 1H, H6), 7.31 (pseudo t, J = 7.5 Hz, 1H, H7), 7.04 (pseudo t, J_{app} = 7.5 Hz, 1H, H8), 2.37 (s, 3H, CH_3); ^{13}C NMR (D_2O) δ 170.3, 135.8, 131.4, 128.0, 126.8, 115.6, 20.9 (CH_3); UV, λ_{max} (nm) ($\epsilon \times 10^4$) (pH 1) 248 (1.1), 207 (2.0), (pH 7) 247 (1.4), 203 (3.6), (pH 11) 249 (1.1), 216 (0.8); low-resolution ACE mass spectrum, EI *m/e* 304.2 (33, $(2M - H_2O)^+$), 161.1 (71, M^+); CI (CH_4) *m/e* 305.2 (28, $(2M - H_2O) + H^+$), 162.1 (79, MH^+). Anal. Calcd for $C_8H_8BNO_2$: C, 59.69; H, 5.01; B, 6.72; N, 8.70. Found: C, 59.42; H, 5.13; B, 6.53; N, 8.36.

From 13. A mixture of **13** (500 mg, 3.65 mmol) and 4 mL of Ac_2O in dry dioxane (20 mL) under argon was heated at 60 °C for 17 h. The volatiles were removed by rotary evaporation in vacuo, and the solid obtained was twice coevaporated to dryness with water (10 mL). The filtrate was rotary evaporated in vacuo and the residue pumped dry to afford 587 mg (100%) of **9** as a pale yellow powder: ^{1}H NMR ($(CD_3)_2SO$) identical to that listed above.

1-Hydroxy-1*H*-2,4,1-benzoxazaborine (2). From 13 and Acetic Formic Anhydride. A mixture of **13** (1.06 g, 7.73 mmol of monomer) and 4 mL of acetic formic anhydride[18] in dry dioxane (20 mL) under argon was stirred at 11 °C for 12 h. Volatiles were removed by rotary evaporation in vacuo, and the resulting solid was thrice coevaporated to dryness with water (10 mL) to afford, after drying in vacuo, 1.143 g (100%) of pure **2** as an off-white powder: mp 257.5–259 °C. By NMR, this compound was found to exist in dihydroxy zwitterionic hydrate form in D_2O solution: ^{1}H NMR (D_2O) δ 8.26 (s, 1H, H3), 7.56 (d of d, J = 7.0, 1.8 Hz, 1H, H5), 7.38 (d of pseudo t, J = 7.5, 1.9 Hz, 1H, H6), 7.35 (d of pseudo t, J = 7.2, 1.4 Hz, 1H, H7), 7.11 (d of d, J = 6.8, 1.8 Hz, 1H, H8); ^{13}C NMR (D_2O) δ 160.1, 134.9, 131.7, 128.2, 127.4, 116.4; IR

(32) Since ADnase has as strong an affinity for the heterocycle adenine as for the nucleoside adenosine,[33] we examined the ability of **2** and **3** to inhibit the enzymatic conversion of adenosine to inosine. The procedure employed was that described in: Agasimundin, Y. S.; Oakes, F. T.; Kostuba, L. J.; Leonard, N. J. *J. Org. Chem.* **1985**, *50*, 2468–2474. Neither **2** nor **3** showed competitive inhibitory activity (K_i values > 500 μM), suggesting that the imidazole ring of the natural substrate(s) contributes much to their ability to bind to the ADnase active site. We thank Ms. Christina Olivetti for conducting these enzymatic evaluations.

(33) Ogawa, T.; Aikawa, Y.; Aikawa, T. *Comput. Biochem. Physiol.* **1987**, *88B*, 91–100.

(KBr) 3448 (broad O—H stretch), 1643 (C=N stretch) cm^{-1}; UV, λ_{max} (nm) ($\epsilon \times 10^4$) (CH_3CN) 250 (0.9), 211 (1.6), (H_2O) 251 (1.0), 206 (2.2); low-resolution ACE mass spectrum, EI *m/e* 276.0 (48, $(2M - H_2O)^+$), 147.0 (100, M^+); CI (CH_4) *m/e* 277.0 (32, $(2M - H_2O) + H^+$), 148.0 (100, MH^+); high-resolution EI mass spectrum *m/e* 147.0492 ($C_7H_6BNO_2$ (M^+) requires 147.0492).

From 13 and Formic Acid. A solution of **13** (213 mg, 1.56 mmol of monomer) in 30 mL of 97% HCO_2H was heated at reflux for 13 h. After rotary evaporation and repeated coevaporations with water, the solid thus obtained was purified by ascending preparative TLC (30% MeOH/CH_2Cl_2 as eluent) to afford 80 mg (35%) of **2** as an off-white powder: ^1H NMR (D_2O) identical to that listed above.

Bis-methanol Adduct of 1,2-Dihydro-1-hydroxy-2,4,1-benzodiazaborine (14). A solution of **2** (500 mg, 3.40 mmol, dried in an Abderhalden apparatus at 110 °C over P_2O_5 in vacuo overnight) in 125 mL of liquid NH_3 was allowed to reflux at −33 °C under argon for 12 h. The volatiles were allowed to evaporate first under a stream of argon and then in vacuo. The off-white powdery residue was dissolved in anhydrous MeOH by gentle warming. Slow evaporation of this solution gave 327 mg (50%) of pure crystalline bis-methanol adduct **14**: mp 209–212 °C; ^1H NMR (CD_3OD) δ 7.95 (s, 1H, H3), 7.54 (d of d, *J* = 7.5, 1.5 Hz, 1H, H5), 7.23 (d of pseudo t, *J* = 7.6, 1.7 Hz, 1H, H7) 7.14 (d of pseudo t, *J* = 7.3, 1.2 Hz, 1H, H6), 6.96 (d of d, *J* = 7.3, 0.7 Hz, 1H, H8), 3.35 (s, 6H, two OCH_3); ^{13}C NMR (CD_3OD) δ 150.8, 140.3, 133.4, 128.3, 125.8, 116.3, 49.0 (OCH_3).

Drying in an Abderhalden apparatus (110 °C over P_2O_5 in vacuo) liberated 1 equiv of CH_3OH and gave the moisture-sensitive 1,2-dihydro-1-methoxy-2,4,1-benzodiazaborine: IR (KBr) 3589 (sharp N—H stretch), 1648 (C=N stretch) cm^{-1}; low-resolution ACE mass spectrum, EI *m/e* 160.1 (100, M^+), 146.1 (7, $(M - CH_3OH + H_2O)^+$); CI (CH_4) *m/e* 161.1 (100, (MH^+), 147.1 (5, $(M - CH_3OH + H_2O) + H^+$). Anal. Calcd for $C_8H_9BN_2O$: C, 60.06; H, 5.67; N, 17.51; B, 6.76. Found: C, 60.04; H, 5.64; N, 17.60; B, 6.83.

Dissolution of crystalline **14** in $(CD_3)_2SO$ spontaneously afforded **3** along with 2 equiv of CH_3OH: ^1H NMR ($(CD_3)_2SO$) δ 9.16 (bd, exchanges with D_2O, 1H, NH), 8.64 (s, exchanges with D_2O, 1H, OH), 8.06 (d of d, 1H, *J* = 7.6, 1.1 Hz, H5), 7.82 (d, *J* = 5.2 Hz, collapses to a singlet upon addition of D_2O, 1H, H3), 7.57 (d of pseudo t, J_{app} = 7.6, 1.6 Hz, 1H, H7), 7.46 (d, *J* = 8.3, 1H, H8), 7.26 (d of pseudo t, J_{app} = 7.3, 1.2 Hz, 1H, H6), 4.20 (q, *J* = 5.2 Hz, 2H, two CH_3OH), 3.26 (d, *J* = 5.2 Hz, 6H, two CH_3OH). Desiccation of this $(CD_3)_2SO$ solution with 4-Å molecular sieves completely removed the CH_3OH by ^1H NMR.

Dissolution of crystalline **14** in D_2O spontaneously afforded the zwitterionic hydrate of **3** along with 2 equiv of CH_3OH: ^1H NMR (D_2O) δ 7.89 (s, 1H, H3), 7.62 (d of d, *J* = 7.3, 1.4 Hz, 1H, H5), 7.32 (d of pseudo t, *J* = 7.6, 1.7 Hz, 1H, H7), 7.24 (d of pseudo t, *J* = 7.3, 1.3 Hz, 1H, H6), 7.03 (d of d, *J* = 7.8, 1.0 Hz, 1H, H8), 3.34 (s, 6H, two CH_3OH); ^{13}C NMR (D_2O) δ 148.4, 137.0, 131.5, 127.5, 125.1, 115.4, 48.8 (CH_3OH).

1,2-Dihydro-1-hydroxy-2,4,1-benzodiazaborine (3). Crystalline **14** (300 mg, 1.56 mmol) was powdered and dried at 110 °C over P_2O_5 in vacuo in an Abderhalden apparatus for 12 h and then was dissolved in 100 mL of H_2O. The aqueous solution was suction filtered and then was reduced to ca. 50% of its volume by rotary evaporation at room temperature in vacuo to remove trace CH_3OH. The solution was then lyophilized to afford, after drying in vacuo, 282 mg (wet, greater than quantitative yield) of **3** as a white fluffy solid: mp 234–260 °C dec. The ^1H NMR ($(CD_3)_2SO$) spectrum was identical to that of **14** in $(CD_3)_2SO$ solution (vide supra) but without the signals assigned to free CH_3OH: UV, λ_{max} (nm) ($\epsilon \times 10^4$) (CH_3CN) 257 (0.7), 212 (2.1), (H_2O) 256 (0.7), 208 (1.4); low-resolution CI mass spectrum *m/e* 147.1 (100, MH^+); high-resolution EI mass spectrum *m/e* 146.0644 ($C_7H_7BN_2O$ (M^+) requires 146.0651).

2-Benzyl-3-((ethoxycarbonyl)amino)-1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (15). A solution of **13** (predried at 110 °C over P_2O_5 overnight, 1.085 g, 7.92 mmol) in 35 mL of anhydrous *N,N*-dimethylacetamide under argon was treated with 1-benzyl-3-(ethoxycarbonyl)-carbodiimide[21] (3.183 g, 13.26 mmol, 1.67 equiv) and stirred for 48 h at room temperature. The reaction mixture was rotary evaporated to dryness in vacuo, and the residue was purified by radial chromatography using 7% CH_3OH/CH_2Cl_2 as the eluent. The oily product obtained was triturated with methanol, and the resulting powder was dried in vacuo to afford 2.115 g (72%) of bis-methanol adduct of **15** as white crystals: mp 133–135 °C; ^1H NMR (CD_3OD) δ 7.47 (d, *J* = 6.6 Hz, 1H, H5), 7.33–7.27 (m, 5H, C_6H_5), 7.23 (pseudo t, J_{app} = 7.8 Hz, 1H, H7), 7.14 (pseudo t, J_{app} = 7.4 Hz, 1H, H6), 6.99 (d, *J* = 7.8 Hz, 1H, H8), 4.80 (s, 2H, $C_6H_5CH_2$), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.34 (s, 6H, two OCH_3), 1.22 (t, *J* = 7.2 Hz, 3H, CH_3); ^1H NMR ($(CD_3)_2SO$) δ 12.33 (s, exchanges with D_2O, 1H, NH), 9.84 (s, exchanges with D_2O, 1H, OH), 8.01 (d, *J* = 7.8 Hz, 1H, H5), 7.60 (pseudo t, J_{app} = 7.8 Hz, 1H, H6), 7.33 (d, *J* = 8.1 Hz, 1H, H8), 7.35–7.26 (m, 5H, C_6H_5), 7.22 (pseudo t, J_{app} = 8.1 Hz, 1H, H7), 5.05 (s, 2H, $PhCH_2$), 4.10 (q, *J* = 4.8 Hz, 1H, CH_3OH), 4.04 (d, *J* = 6.9 Hz, 2H, CH_2O), 3.17 (d, *J* = 4.8 Hz, 3H, CH_3OH), 1.17 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($(CD_3)_2SO$) δ 163.4, 156.5, 142.5, 139.4, 133.2, 132.4, 128.1, 126.9, 126.4, 122.9, 116.1, 60.4, 48.6 (CH_3OH), 44.1, 14.5; ^{11}B NMR (CH_3OH) δ −14.6 (111-Hz line width); low-resolution ACE mass spectrum, EI *m/e* 337.2 (100, M^+); CI *m/e* 338.3 (30, MH^+); high-resolution CI mass spectrum *m/e* 338.1679 ($C_{18}H_{21}BN_3O_3$ (MH^+) requires 338.1676). Anal. Calcd for $C_{19}H_{24}BN_3O_4$ (bis-methanol adduct): C, 61.81; H, 6.55; B, 2.93; N, 11.38. Found: C, 61.98; H, 6.60; B, 2.49; N, 11.70.

3-Amino-1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (4). To a mixture of **15** (250 mg, 0.74 mmol) and $PdO \cdot H_2O$ (300 mg, 2.14 mmol) was added 3.5 mL of dry DMF, and the resulting suspension was heated to 100 °C. To this hot suspension was added 2 mL of 1,4-cyclohexadiene, and the reaction mixture was heated at reflux for 17 h, with an additional 1 mL of 1,4-cyclohexadiene introduced after the first hour. The catalyst was then removed by filtration and washed with a small amount of methanol, and the combined solutions were rotary evaporated in vacuo to an oil. Recrystallization from CH_3OH gave 103 mg (47%) of the bis-methanol adduct of **16** as white crystals: mp 183–186 °C after shrinkage at 60–65 °C; ^1H NMR ($(CD_3)_2SO$) δ 8.35 (s, exchanges with D_2O, 1H, OH), 7.81 (d, *J* = 7.2 Hz, 1H, H5), 7.75 (s, exchanges with D_2O, 1H, NH), 7.4–7.2 (m, 6H, C_6H_5 and H7), 7.07 (d, *J* = 8.1 Hz, 1H, H8), 6.89 (pseudo t, J_{app} = 7.2 Hz, 1H, H6), 6.53 (t, *J* = 4.2 Hz, exchanges with D_2O, 1H, CH_2NH), 4.52 (d, *J* = 4.2 Hz, collapses to a singlet upon addition of D_2O, 2H, $PhCH_2$), 4.11 (q, *J* = 5.3 Hz, 2H, two CH_3OH), 3.16 (d, *J* = 5.3 Hz, 6H, two CH_3OH); ^{11}B NMR (CH_3OH) δ -16.6 (99-Hz line width); low-resolution ACE mass spectrum, EI *m/e* 265.1 (89, M^+); CI *m/e* 266.1 (100, MH^+).

The mother liquor from the above crystallization was purified using preparative TLC (1:3:6 $NH_4OH/MeOH/CH_2Cl_2$) to afford a colorless oil which, upon recrystallization from methanol, gave 24 mg (16%) of the bis-methanol adduct of 4 as white crystals: mp > 280 °C; ^1H NMR (CD_3OD) δ 7.35 (d, *J* = 7.2 Hz, 1H, H5), 7.04 (pseudo t, J_{app} = 6.9 Hz, 1H, H7), 6.89 (pseudo t, J_{app} = 7.2 Hz, 1H, H6), 6.68 (d, *J* = 6.9 Hz, 1H, H8), 3.25 (s, 6H, two OCH_3); ^{13}C NMR (CD_3OD) δ 155.8, 141.6, 132.9, 128.2, 123.6, 115.0, 48.7; ^1H NMR ($(CD_3)_2SO$) δ 8.31 (bs, exchanges with D_2O, 1H, NH), 7.81 (s, exchanges with D_2O, 1H, OH), 7.79 (d, *J* = 7.8 Hz, 1H, H5), 7.32 (pseudo t, J_{app} = 8.4 Hz, 1H, H7), 7.00 (d, *J* = 8.4 Hz, 1H, H8), 6.87 (pseudo t, J_{app} = 7.2 Hz, 1H, H6), 5.90 (bs, exchanges with D_2O, 2H, NH_2), 4.05 (q, *J* = 4.8 Hz, 2H, two CH_3OH), 3.10 (d, *J* = 4.8 Hz, 6H, two CH_3OH). This crystalline bis-methanol adduct, upon Abderhalden drying (P_2O_5, 110 °C), dissolution in H_2O, and lyophilization, gave **4** as a fluffy white solid: mp > 280 °C; ^1H NMR ($(CD_3)_2SO$) identical to that above but without the signals due to CH_3OH; ^1H NMR (D_2O) δ 7.54 (d, *J* = 7.2 Hz, 1H, H5), 7.24 (pseudo t, J_{app} = 7.7 Hz, 1H, H7), 7.10 (pseudo t, J_{app} = 7.4 Hz, 1H, H6), 6.87 (d, *J* = 7.8 Hz, 1H, H8); ^{13}C NMR (D_2O) δ 152.6, 138.7, 131.0, 128.0, 123.2, 114.3; UV, λ_{max} (nm) ($\epsilon \times 10^4$) (H_2O) 242 (1.0), 202 (2.4); low-resolution CI (CH_4) mass spectrum *m/e* 120.0 (53, $MH^+ - CN_3H_2$), 176.1 (20, MH^+); high-resolution CI mass spectrum *m/e* 176.0994 ($C_8H_{11}BN_3O$ (MH^+) requires 176.0995).

1,2-Dihydro-1-hydroxy-2-propyl-2,4,1-benzodiazaborine (18). A solution of **2** (predried at 110 °C over P_2O_5 overnight, 320 mg, 2.18 mmol) in 20 mL of 1-propylamine was heated at reflux for 7 h. The solvent was removed by rotary evaporation in vacuo, and the residue was recrystallized from MeOH to afford 86 mg (17%) of **18** as a white crystalline bis-methanol adduct: mp 205–207 °C with shrinkage at 100–110 °C; ^1H NMR ($(CD_3)_2SO$) δ 8.96 (s, exchanges with D_2O, 1H, OH), 8.13 (pseudo t, J_{app} = 7.1 Hz, 1H, H5), 7.90 (s, 1H, H3), 7.58 (pseudo t, J_{app} = 7.5 Hz, 1H, H7), 7.46 (d, *J* = 8.1 Hz, 1H, H8), 7.27 (pseudo t, J_{app} = 7.2 Hz, 1H, H6), 4.11 (q, *J* = 5.0 Hz, 2H, two CH_3OH), 3.62 (t, *J* = 7.1 Hz, 2H, CH_2), 3.17 (d, *J* = 5.0 Hz, 6H, two CH_3OH), 1.73–1.60 (m, 2H, CH_2), 0.87 (t, *J* = 7.2 Hz, 3H, CH_3); ^1H NMR (CD_3OD) δ 8.02 (s, 1H, H3), 7.48 (d of d, *J* = 7.5, 1.5 Hz, 1H, H5), 7.22 (d of pseudo t, *J* = 7.7, 1.7 Hz, 1H, H7), 7.13 (d of pseudo t, *J* = 7.4, 1.2 Hz, 1H, H6), 6.95 (d, *J* = 7.8 Hz, 1H, H8), 3.35 (s, 6H, two OCH_3), 3.31 (t, *J* = 1.5 Hz, 2H, CH_2), 1.84–1.72 (m, 2H, CH_2), 0.99 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 151.8, 140.9, 133.4, 128.4, 125.6, 116.0, 50.7, 49.3, 25.3, 11.9; low-resolution ACE mass spectrum, EI *m/e* 202.1 (100, M), CI (CH_4) *m/e* 203.1 (100, MH^+). Desiccation of these crystals

in vacuo over P_2O_5 at 60 °C, followed by dissolution in H_2O (50mL) and lyophilization, gave **18** as a fluffy white solid: ^1H NMR ($(CD_3)_2SO$) identical to that listed above for the bis-methanol adduct in $(CD_3)_2SO$ solution but without the signals assigned to CH_3OH.

1,2-Dihydro-1-hydroxy-3-(trichloromethyl)-2,4,1-benzodiazaborine (19). A suspension of 204 mg (1.49 mmol) of **13** in 15 mL of trichloroacetonitrile was heated at reflux overnight. The solvent was rotary evaporated in vacuo to afford 340 mg (87%) of **19** as a brown solid: mp 155–158 °C with shrinkage at 75 °C; ^1H NMR ($(CD_3)_2SO$) δ 9.64 (s, exchanges with D_2O, 1H, NH), 8.90 (s, exchanges with D_2O, 1H, OH), 8.14 (d, J = 7.2 Hz, 1H, H5), 7.71 (pseudo t, J_{app} = 7.5 Hz, 1H, H7), 7.63 (d, J = 7.5 Hz, 1H, H8), 7.44 (pseudo t, J_{app} = 7.4 Hz, 1H, H6); ^{13}C NMR ($(CD_3)_2SO$) δ 151.1, 150.8, 132.5, 131.5, 128.0, 126.0, 95.3; low-resolution ACE mass spectrum, EI *m/e* 262.0 (35, M^+), 227.0 (100, M – Cl^-); CI *m/e* 263.0 (78, MH^+), 227.0 (100, MH^+ – HCl).

1-Hydroxy-3-(trifluoromethyl)-1*H*-2,4,1-benzoxazaborine (20). A solution of **13** (500 mg, 3.65 mmol of monomer) in 20 mL of anhydrous 1,4-dioxane was cooled in an ice bath and was treated with 2.5 mL (17.7 mmol, 4.85 equiv) of trifluoroacetic anhydride. The solution was stirred at 0 °C for 30 min and then at room temperature for 3 h. The solvent was removed by rotary evaporation in vacuo at 30 °C, and the residue was treated with water (3 × 5 mL) and evaporated in vacuo at 30 °C to give 785 mg (100%) of **20** as a pale yellow solid: mp 256–258 °C; ^1H NMR ($(CD_3)_2SO$) δ 11.68 (s, exchanges with D_2O, 1H, OH), 8.13 (d, J = 7.5 Hz, 1H, H5), 7.85 (d, J = 6.9 Hz, 1H, H8), 7.50 (pseudo t, J_{app} = 7.5 Hz, 1H, H6), 7.23 (pseudo t, J_{app} = 6.6 Hz, 1H, H7); ^1H NMR (D_2O) δ 7.80 (d, J = 7.5 Hz, 1H, H5), 7.54 (pseudo t, J_{app} = 7.8 Hz, 1H, H7), 7.38 (pseudo t, J_{app} = 7.5 Hz, 1H, H6), 7.27 (d, J = 7.8 Hz, 1H, H8); ^{13}C NMR (D_2O) δ 162.7 (q, $^2J_{C-F}$ = 36 Hz, C3), 135.9, 134.8, 132.4, 128.7, 123.2, 116.3 (q, $^1J_{C-F}$ = 278 Hz, CF_3); low-resolution ACE mass spectrum, EI *m/e* 412.0 (48, 2M – H_2O), 215.0 (100, M), CI *m/e* 413.1 (46, 2M – H_2O + 1), 216.1 (100, MH^+).

2-Amino-1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (21). A suspension of **2** (231 mg, 1.57 mmol) in 15 mL of 98% anhydrous hydrazine under argon was stirred at room temperature for 24 h. The suspension was slowly poured into 300 mL of ice-cold acetone, and the mixture was stirred for 30 min at 0 °C. The solution was reduced in volume to 50 mL by rotary evaporation in vacuo, and the resulting white suspension was treated with 300 mL of anhydrous diethyl ether. After being stirred for 30 min, the suspension was suction filtered to give 210 mg of a white powder. This was recrystallized from MeOH to afford 180 mg (55%) of the bis-methanol adduct of **21** as pale yellow crystals: mp 183–186 °C; ^1H NMR (CD_3OD) δ 8.13 (s, 1H, H2), 7.49 (d, J = 7.2 Hz, 1H, H5), 7.22 (pseudo t, J_{app} = 7.5 Hz, 1H, H7), 7.14 (pseudo t, J_{app} = 7.2 Hz, 1H, H6), 6.97 (d, J = 7.8 Hz, 1H, H8), 3.35 (s, 6H, two OCH_3); ^{13}C NMR (CD_3OD) δ 151.5, 141.0, 133.4, 128.7, 125.7, 116.3, 49.9. This crystalline bis-methanol adduct, upon Abderhalden drying (P_2O_5, 110 °C), dissolution in H_2O, and lyophilization, gave **21** as a fluffy white solid: ^1H NMR ($(CD_3)_2SO$) δ 9.02 (s, exchanges with D_2O, 1H, OH), 8.09 (d, J = 7.5 Hz, 1H, H8), 7.95 (s, 1H, H3), 7.57 (pseudo t, J_{app} = 7.5 Hz, 1H, H6 or H7), 7.47 (d, J = 7.8 Hz, 1H, H5), 7.27 (pseudo t, J_{app} = 7.5 Hz, 1H, H6 or H7), 5.25 (bs, exchanges with D_2O, 2H, NH_2); low-resolution ACE mass spectrum, EI *m/e* 161.1 (100, M^+); CI (*m/e*) 162.1 (100, MH^+).

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Supplementary Material Available: ^{11}B NMR spectral plots of phenylboronic acid, **12**, **13**, **9a**, **2–4**, and **18-21** in CH_3CN, CH_3OH, and H_2O solution; ^1H NMR spectral plots of **2** in D_2O, **3** in $(CD_3)_2SO$, and **4** in CD_3OD solution; positional and thermal parameters for **14** (14 pages); listing of observed and calculated structure factors for **14** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.