Planar Boron Heterocycles with Nucleic Acid-Like Hydrogen-Bonding Motifs†

Michael P. Groziak,*,‡,§ Liya Chen,§ Lin Yi,§ and Paul D. Robinson||

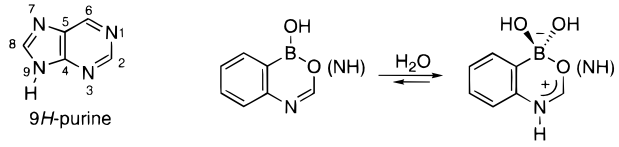
Contribution from the Department of Chemistry and Biochemistry and the Department of Geology, Southern Illinois University, Carbondale, Illinois 62901-4409

Received October 31, 1996. Revised Manuscript Received May 23, 1997⊗

Abstract: To promote the development of boron-containing purine analogues that exist in planar, non-zwitterionic dominant structural form in aqueous solution, rigorous solution and solid state structural analyses of 1-hydroxy-1*H*-2,3,1-benzoxazaborine (**1**), 1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborine (**2**), and related 2,3,1-benzodiheteraborines were undertaken. With the aid of isotope-enriched compounds, a multisolvent ^{1}H, ^{13}C, ^{11}B, and ^{15}N NMR spectroscopic analysis of **1** and **2** was conducted, providing structurally-diagnostic chemical shift data for all non-oxygen atoms that constitute their heterocyclic peripheries. In addition, single-crystal X-ray diffraction analyses of **1** and **2** were performed. In stark contrast to their 2,4,1 isomeric counterparts, the 2,3,1-benzoxaza- and benzodiazaborines exist in planar structural form in protic solution and in the solid state and display proton dissociative and associative tendencies reflective of the predominant Brønsted, yet still Lewis acidic-capable character of the B-OH group together with the basic one at the C4−N3 imine group. In the solid state, **1** and **2** display intermolecular hydrogen-bonding patterns not too dissimilar from the motifs of certain natural nucleic acid bases. Diazaborine **2** was shown by VT-NMR to undergo a triple hydrogen-bonding solution association with a 2′,3′,5′-tri-*O*-protected cytidine in a demonstration of one biomimetic potential held by a 1-hydroxy-2,3,1-diheteraborine periphery. In general, **1**, **2**, and related 1-hydroxy-2,3,1-benzodiheteraborine heterocycles were found to be characterized by an environment-dependent O1→N3 Brønsted prototropy and B−OH group Brønsted/Lewis acid ambidency so sensitive and subtle that certain past difficulties encountered in attempts to delineate their physicochemical properties now become readily appreciated.

Introduction and Background

A renewal of interest in the development of boron-containing analogues of biologically derived and/or active molecules is now emerging at a time when the synthetic methodologies for preparation and the analytical techniques for characterization of these often unique substances are more sophisticated than when, for instance, boroaromatic heterocycles were avidly studied in the 1950s and 1960s. Many have recognized an untapped potential value held by boron-containing compounds to biomedical and other types of investigations.[1] Some of the efforts in this laboratory directed toward the preparation of boron-based purine analogues bearing a boron atom at the 6-position are focused on 6-hydroxy-1,3,6-oxaza- and 4-hydroxy-1,3,4-diazaborines because they bear the closest peripheral resemblance to the pyrimidine ring portion of many naturally occurring purines. In an initial study of models of these types of purine mimics,[2] a susceptibility to facile 1,4-hydration in aqueous solution was demonstrated to be an endemic property of the 2,4,1-benzodiheteraborine subclasses of boron heterocycles, and it was suggested that the 1,4-hydrate-related structural features of the resultant zwitterions were particularly attractive as they are encouraging to the design of "transition-state" analogue inhibitors of adenosine deaminase, a purine nucleoside-utilizing enzyme. When viewed from the context of access to more broadly useful planar, uncharged boron mimics of the naturally occurring purine aglycons existent in aqueous solution, however, these same structural features are seen to be disadvantaging.



A relocation of the imine nitrogen atom at the position transannular to the boron center in these compounds should provide classes of boron heterocycles resistant at the least to 1,4-hydration. Accordingly, attention also is being given to the imine "inverted" isomeric 6-hydroxy-1,2,6-oxaza- and 3-hydroxy-1,2,3-diazaborines in a parallel research effort. To ensure the most rapid access to materials with which to examine hydration susceptibilities and to obtain compounds for proper direct comparisons to ones of the previous study, benzo-fused members (1-hydroxy-1*H*-2,3,1-benzoxazaborine (**1**) and 1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborines (**2**−**4**)) were selected as the subjects for the initial study of these diheteraborines related herein.

† Presented in part: (a) Groziak, M. P.; Yi, L.; Merrill, J. M.; Robinson, P. D. *Abstracts of Papers*, 209th National Meeting of the American Chemical Society, ORGN Division, Anaheim, CA, 1995; Abstr. 181. (b) Groziak, M. P.; Chen, L.; Yi, L.; Robinson, P. D. 25th National Medicinal Chemistry Symposium, 1996, Ann Arbor, MI, 1996; Abstr. 115.

‡ New address: SRI International, Pharmaceutical Discovery Division, 333 Ravenswood Avenue, Menlo Park, CA 94025-3493.

§ Department of Chemistry and Biochemistry.

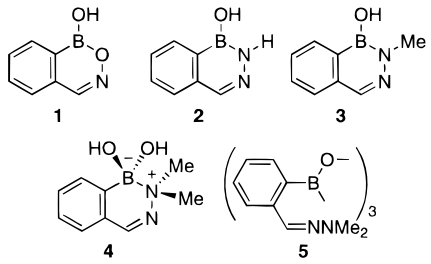
|| X-ray Crystallographer, Department of Geology.

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Reviews: (a) Morin, C. *Tetrahedron* **1994**, *50*, 12521−12569. (b) Goudgaon, N. M.; El-Kattan, G. F.; Schinazi, R. F. *Nucleosides Nucleotides* **1994**, *13*, 849−880. (c) Spielvogel, B. F.; Sood, A.; Shaw, B. R.; Hall, I. H. In *Current Topics in the Chemistry of Boron*; Kabalka, G. W., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1994; pp 193−198. (d) Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 950−984. (e) Terashima, M.; Ishikura, M. *Adv. Heterocycl. Chem.* **1989**, *46*, 143−167.

(2) Groziak, M. P., Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597−7605.

S0002-7863(96)03784-5 CCC: $14.00



Historical Context and Specific Aims

While we were the first to access **4**,[3] the benzo-fused heterocycles **1**−**3** and certain derivatives were studied over 30 years ago by Dewar[4] and Snyder.[5] Thiophene-based versions of **1**−**3** have been examined quite extensively by Gronowitz,[6] and furan-[7] and even selenophene-based[8] versions of **1** and **2** have received some attention. Some of the more recent of these investigations likely were prompted in part by the discovery that certain *N*-aryl/alkylsulfonylated derivatives[9] of **2** possess good biocidal properties.[10] Even under all of this previous scrutiny, though, certain endemic properties of carbocycle- and heterocycle-fused 6-hydroxy-1,2,6-oxazaborines and 3-hydroxy-1,2,3-diazaborines closely related to the structural forms they adopt in various solution environments or in the solid state have for some reason remained elusive.[11] To finally gain a knowledge of these structural forms and thereby provide a firm basis for the expected development of imidazo-fused versions of **1** and **2** into nonhydrating boron mimics of the 2-aza-3-deazapurines,[12] then, it was apparent that a detailed reinvestigation of these and related heterocycles was in order. With the aid of isotope-enriched compounds, a multisolvent ^{1}H, ^{13}C, ^{11}B, and ^{15}N NMR spectroscopic survey of **1** and **2** was conducted to provide structurally diagnostic chemical shift data for all non-oxygen atoms that constitute their heterocyclic peripheries. In addition, single-crystal X-ray diffraction analyses of **1** and **2** were performed to define atom connectivity-related topographies and intermolecular hydrogen-bond associations in the solid state. Finally, the interactions of these heterocycles with certain reagents, solvents, and nucleosides bearing potential hydrogen-bonding complementarities were examined to assess properties of particular importance to those solution-based characteristics to be expected of the imidazo-fused versions under development.

Results and Discussion

Synthesis of Unlabeled Materials. Heterocycles **1**−**3** were prepared in unlabeled form from 2-formylbenzeneboronic acid via slightly modified literature procedures. Torssell had prepared the formylboronic acid precursor in low to moderate yield from 2-$MeC_6H_4B(OH)_2$ via hydrolysis of the α,α-dibromo derivative.[13] Snyder[5f] and Dewar[4c] had also used a variant of this approach, but Gronowitz had prepared it from the dioxolane of 2-BrC_6H_4CHO along a halogen-metal exchange route.[14] Although this latter method provided a more rapid access and an improved yield (57%), it was found to sometimes generate di- and triarylboronic acid byproducts that were difficult to remove. As Washburn et al.[15] had found the Grignard-based synthesis of $C_6H_5B(OH)_2$ to proceed without such complications, we decided to utilize an organomagnesium reagent in the Gronowitz approach. 2-Bromobenzaldehyde was converted to the dioxolane, which via the Grignard derivative (in THF, not Et_2O) gave the formylboronic acid in a 68% yield. Published procedures[4c,5f] were used to condense this aldehyde with NH_2-OH to afford **1** (99%) and with NH_2NH_2 and $MeNHNH_2$ to afford **2** (83%) and **3** (79%), respectively. Condensation with Me_2NNH_2 did not yield **4** directly but, instead, gave a tridehydro trimeric form (boroxin **5**[3]) from which **4** could be generated by mild hydrolysis (H_2O, 24 h, 25 °C). More forcing conditions (H_2O, 24 h, 100 °C) effected a deboronation in **5**, presumably via the intermediacy of **4**.

(3) Robinson, P. D.; Groziak, M. P.; Yi, L. *Acta Crystallogr.* **1996**, *C52*, 2826−2830. For a report describing related 1,1-dimethylhydrazones derived from 2-formylthiophene-3-boronic acid and 3-formylthiophene-2-boronic acid, see ref 6j.

(4) (a) Davis, F. A.; Dewar, M. J. S.; Jones, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 706−708. (b) Dewar, M. J. S.; Jones, R. *Ibid.* **1967**, *89*, 2408−2410. (c) Dewar, M. J. S.; Dougherty, R. C. *Ibid.* **1964**, *86*, 433−436. (d) Dewar, M. J. S.; Dougherty, R. C. *Ibid.* **1962**, *84*, 2648−2649.

(5) (a) Catlin, J. C; Snyder, H. R. *J. Org. Chem.* **1969**, *34*, 1660−1663. (b) Dunn, H. E.; Catlin, J. C.; Snyder, H. R. *Ibid.* **1968**, *33*, 4483−4486. (c) Haynes, R. R.; Snyder, H. R. *Ibid.* **1964**, *29*, 3229−3233. (d) Tschampel, P.; Snyder, H. R. *Ibid.* **1964**, *29*, 2168−2172. (e) Lennarz, W. J.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 2172−2175. (f) Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. *Ibid.* **1958**, *80*, 835−838.

(6) (a) Gronowitz, S.; Maltesson, A. *Acta Chem. Scand.* **1977**, *B31*, 765−767. (b) Gronowitz, S.; Roos, C.; Sandberg, E.; Clementi, S. *J. Heterocycl. Chem.* **1977**, *14*, 893−897. (c) Gronowitz, S.; Glennow, C. *Chem. Scr.* **1977**, *11*, 76−82. (d) Gronowitz, S.; Maltesson, A. *Acta Chem. Scand.* **1975**, *B29*, 461−467. (e) Gronowitz, S.; Maltesson, A. *Ibid.* **1975**, *B29*, 457−460. (f) Gronowitz, S.; Roos, C. *Ibid.* **1975**, *B29*, 990−998. (g) Gronowitz, S.; Toresson, C. *Chem. Scr.* **1972**, *2*, 143. (h) Gronowitz, S.; Dahlgren, T.; Namtvedt, J.; Roos, C.; Rosén, G; Sjöberg, B.; Forsgren, U. *Acta Pharm. Suecica* **1971**, *8*, 623−638. (i) Gronowitz, S.; Maltesson, A. *Acta Chem. Scand.* **1971**, *25*, 2435−2446. (j) Namtvedt, J. *Ibid.* **1968**, *22*, 1611−1622. (k) Namtvedt, J.; Gronowitz, S. *Ibid.* **1968**, *22*, 1373−1374. (l) Gronowitz, S.; Namtvedt, J. *Ibid.* **1967**, *21*, 2151−2166. (m) Gronowitz, S.; Bugge, A. *Ibid.* **1965**, *19*, 1271−1285.

(7) (a) Florentin, D.; Fournié-Zaluski, M.-C.; Roques, B. P. *J. Chem. Res. (S)* **1977**, 158−159. (b) Florentin, D.; Roques, B. P.; Metzger, J.-M.; Colin, J.-P. *Bull. Soc. Chim. Fr.* **1974**, *11*, 2620−2622. (c) Roques, B.; Florentin, D. *J. Organomet. Chem.* **1972**, *46*, C38−C40. (d) Roques, B.; Florentin, D.; Juhasz, J.-P. *C. R. Acad. Sci. Paris, Sér. C* **1970**, *270*, 1898−1900. (e) Fournie-Zaluski, M. C.; Roques, B.; *C. R. Tetrahedron Lett.* **1970**, *56*, 4909−4912.

(8) Semard, D.; Paulmier, C.; Morel, J.; Pastour, P. *Int. J. Sulfur Chem., A* **1972**, *2*, 257−260.

(9) (a) Grassberger, M. A. *Liebigs Ann. Chem.* **1985**, 683−688. (b) Dallacker, V. F.; Both-Pollmann, E.-M.; Müllners, W. *Chem. Ztg.* **1984**, *108*, 287−288.

(10) (a) Bergler, H.; Wallner, P.; Ebeling, A.; Leitinger, B.; Fuchsbichler, S.; Aschauer, H.; Kollenz, G.; Högenauer, G.; Turnowsky, F. *J. Biol. Chem.* **1994**, *269*, 5493−5496. (b) Kater, M. M.; Koningstein, G. M.; Nijkamp, H. J. J.; Stuitje, A. R. *Plant Mol. Biol.* **1994**, *25*, 771−790. (c) Turnowsky, F.; Fuchs, K.; Jeschek, C.; Högenauer, G. *J. Bacteriol.* **1989**, *171*, 6555−6565. (d) Lam, C.; Turnowsky, Fr.; Högenauer, G.; Schuetze, E. *J. Antimicrob. Chemother.* **1987**, *20*, 37−45. (e) Grassberger, M. A.; Turnowsky, F.; Hildebrandt, J. *J. Med. Chem.* **1984**, *27*, 947−953. (f) Högenauer, G.; Woisetschläger, M. *Nature (London)* **1981**, *293*, 662−664. (g) Bailey, P. J.; Cousins, G.; Snow, G. A.; White, A. *J. Antimicrob. Agents Chemother.* **1980**, *17*, 549−553.

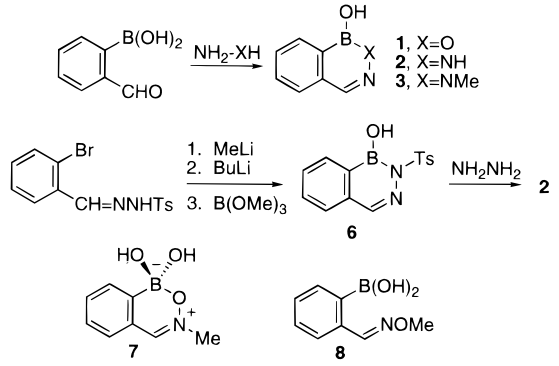
(11) Reviews: (a) Gronowitz, S. In *Lectures in Heterocyclic Chemistry*; (*J. Heterocycl. Chem.* **1976**, *13(S)*); HeteroCorporation: Orem, UT, 1976; Vol. 3, pp S17−S32. (b) Dewar, M. J. S. In *Progress in Boron Chemistry*; Steinberg, H., McCloskey, A. L., Eds.; Pergamon: London, 1964; Vol. 1, pp 235−263. (c) Dewar, M. J. S. In *Advances in Chemistry*, Vol. 42; Gould, R. F., Ed.; American Chemical Society: Washington, DC, 1964; pp 235−263. (d) Letsinger, R. L. In *Advances in Chemistry*, Vol. 42; Gould, R. F., Ed.; American Chemical Society: Washington, DC, 1974; pp 1−16. (e) Maitlis, P. M. *Chem. Rev.* **1962**, *62*, 223−245. (f) Fritsch, A. J. *Chem. Heterocycl. Compd.* **1977**, *30*, 381−440. (g) Ander, I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: Oxford, U.K., 1985; Vol. 1, pp 629−663. (h) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: Oxford, U.K., 1985; Vol. 4, pp 1000−1001. (i) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: Oxford, U.K., 1985; Vol. 4, pp 1029−1032. Also, see the discussion in the following: (j) Mikhailov, B. M.; Kuimova, M. E. *J. Organomet. Chem.* **1976**, *116*, 123−133.

(12) (a) Naguib, F. N. M.; Iltzsch, M. H.; el Kouni, M. M.; Panzica, R. P.; el Kouni, M. H. *Biochem. Pharmacol.* **1995**, *50*, 1685−1693. (b) Bussolari, J. C.; Ramesh, K.; Stoeckler, J. D.; Chen, S.-F.; Panzica, R. P. *J. Med. Chem.* **1993**, *36*, 4113−4120. (c) Ramesh, K.; Panzica, R. P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1769−1774.

(13) Torssell, K. *Arkiv Kemi* **1956**, *10*, 507−511.

(14) Gronowitz, S.; Hörnfeldt, A.-B.; Yang, Y.-H. *Chem. Scr.* **1986**, *26*, 311−344.

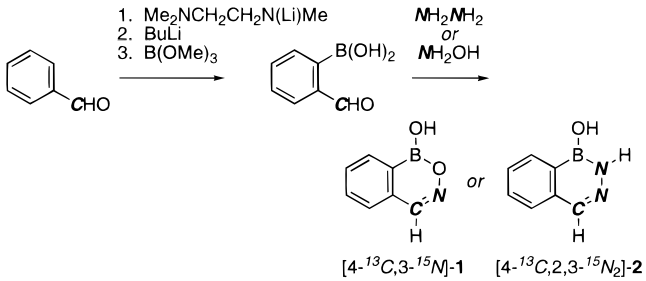
(15) Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. *Organic Syntheses*, 2nd ed.; John Wiley and Sons: New York, NY, 1963; Collect. Vol. IV, pp 68−72.

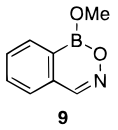


In an alternative approach to **2**, the dianion-based protocol of Sharp and Skinner[16] was applied to the *N*-tosylhydrazone of 2-bromobenzaldehyde to afford **6**, one of the known competent biocides,[10e] in an excellent (93%) yield. Precursor **6** was readily converted to **2** (65%) upon exposure to NH_2NH_2 in a transformation likely to be S_N(ANRORC)[17] in nature. The nitrone **7**[18] and oxime **8**[5b,19] desired as NMR reference compounds each were prepared according to their respective literature procedures.

Synthesis of Labeled Materials. Commercial [*formyl*-^{13}C]-PhCHO was selected as a likely convenient precursor to the doubly isotope-enriched [4-^{13}C,2-^{15}N]**1** and the triply isotope-enriched [4-^{13}C,2,3-$^{15}N_2$]**2** needed for ^{1}H, ^{13}C, and especially ^{15}N NMR spectroscopic analyses. Because no previous synthesis of 2-formylbenzeneboronic acid[4c,5f,13,14,19] had employed PhCHO as starting material, though, a new synthesis had to be developed. Guided by works of Comins and Brown[20] on low-temperature *ortho*-lithiation of the α-amino alkoxide derived from lithiated *N*,*N*,*N*′-trimethylethylenediamine and PhCHO, Snieckus et al.[21] on the synthesis of arylboronic acids via the directed lithiation of benzamides, and Washburn et al.[15] on the beneficial effect of low temperature and extended reaction time in the PhMgBr/$B(OMe)_3$-based preparation of $C_6H_5B(OH)_2$, a highly expedient one-step synthesis of the requisite labeled formylboronic acid was developed. The $B(OMe)_3$-mediated boronation of the BuLi-generated dianion derived from the PhCHO/MeN(Li)$CH_2CH_2NMe_2$ adduct was found to be highly temperature and time dependent, requiring a 24 h equilibration at −78 °C to effect a 50% conversion. The doubly isotope-enriched [4-^{13}C,2-^{15}N]**1** was prepared in a 90% yield by condensation of the resultant labeled formylboronic acid and [^{15}N]NH_2OH·HCl in warm pH 4−5 aqueous solution. The triply isotope-enriched [4-^{13}C,2,3-$^{15}N_2$]**2** was prepared in an 86% yield by a similar condensation employing [$^{15}N_2$]-NH_2NH_2·H_2SO_4 in aqueous EtOH containing NaOH.

Interconversions and Acidities. Although **6** had readily afforded **2** upon exposure to NH_2NH_2, it did not afford **1** when treated with NH_2OH. Oxazaborine **1**, which like **6** gave **2** (54%) upon treatment with NH_2NH_2, was found to give a low melting hygroscopic *B*-methoxy derivative (**9**) simply upon recrystallization from CH_3OH. Heterocycle **9** was stable in the solid state and in CD_3CN solution but reverted to **1** upon exposure to water. That this hydrolysis occurs via an addition−elimination route rather than via a demethylative S_N2 displacement was verified by establishing that ^{18}O isotope acquisition by **1** occurs upon hydrolysis in $H_2{}^{18}O$. Even under forcing conditions (anhydrous CH_3OH, 65 °C, 24−30 h), heterocycles **2**, **3**, and **6** resisted the formation of *B*-methoxy derivatives. By UV, neither **2** nor **3** is substantially affected by dissolution in CH_3CN, CH_3OH, or H_2O. An attempt to convert **9** to a *B*-amino derivative by exposing it to anhydrous NH_3 gave an extremely hygroscopic material suspected to be the desired material, but this was found to hydrolyze to **1** simply upon exposure to the atmosphere. Upon rigorous desiccation, **1** could be converted to an isolable, hygroscopic *B*−*O*−*B* anhydro dimer. Diazaborines **2** and **3** resisted such dehydration even though anhydro dimer ions were observed in their ACE mass spectra. The triphenylboroxin **5** was found to undergo methanolysis simply upon dissolution in absolute CH_3OH, affording a 2:1 mixture of mono- and dimethoxylated boronic acid derivatives, by ^{11}B NMR. Upon heating to effect dissolution in water, the *O*-methyl oxime **8** was found to undergo facile demethylation to **1**, by ^{1}H and ^{11}B NMR. Potentiometric measurement of the pH of aqueous solutions of **1**−**3** and **6** revealed a pK_a of *ca.* 4.8 for **1** and *ca.* 8 for each the three diazaborines.



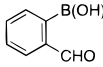
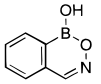
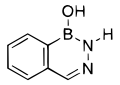
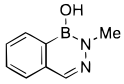
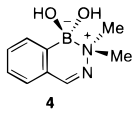
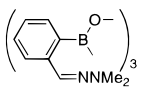
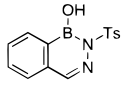
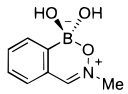
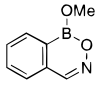


9

^{18}O Isotope Acquisition. Equilibration of **1** or **2** with excess $H_2{}^{18}O$ in CH_3CN solution at 69−75 °C for 12 h resulted in little or no ^{18}O isotope acquisition by the former heterocycle, but complete isotope acquisition by the latter one, as determined by low-resolution ACE-mass spectral analysis. Even when subjected to these conditions for 36 h, **1** was found to acquire a single ^{18}O atom only to a 50% extent. A careful scrutiny of the low-intensity (1%) $[2M - H_2O]^+$ peak pattern in the 274−280 *m/e* mass-spectral region of this material revealed the same single ^{18}O-atom content in the minor, possibly spectrometer-generated anhydro dimer species, thereby eliminating the possibility that the isotopic enrichment in **1** had origins in the hydrolysis of a 100% single-labeled anhydro dimer by propitious unenriched water during post-$H_2{}^{18}O$-equilibration handling. Diazaborine **2** was found to so readily exchange its O1 atom with that of $H_2{}^{18}O$ that the process occurred with reasonable facility ($t_{1/2}$ of *ca.* 4 h) even at 23 °C. A similar propensity toward ^{18}O isotope acquisition was noted for **3**, suggesting that the diazaborines, perhaps due to a weaker inherent Brønsted acidity (*vide infra*), display a more pronounced Lewis acidic character than does the oxazaborine **1**. The sluggish ^{18}O isotope acquisition by **1** could be overcome by equilibration in 2 N $Li^{18}OH/H_2{}^{18}O$ (23 °C, 1 h) followed by neutralization with HOAc, whereby a >50% acquisition was achieved. The diazaborines' reactivity was also enhanced in this manner in the order **3** ≫ **2** ∼ **6**.

(16) Sharp, J. T.; Skinner, C. E. D. *Tetrahedron Lett.* **1986**, *27*, 869−872.
(17) van der Plas, H. C. *Khim. Geterotsikl. Soedin.* **1994**, 1649−1668.
(18) Kliegel, W.; Nanninga, D. *J. Organomet. Chem.* **1983**, *247*, 247−252.
(19) Scouten, W. H.; Liu, X.-C.; Khangin, N.; Mullica, D. F.; Sappenfield, E. L. *J. Chem. Crystallogr.* **1994**, *24*, 621−626. Experimental details of preparation and characterization contained therein are strikingly similar to those found in refs 5b,d.
(20) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078−1083.
(21) (a) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, 5093−5096. (b) Sharp, M. J.; Snieckus, V. *Ibid.* **1985**, 5997−5600. (c) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron* **1985**, *39*, 1955−1962.

Table 1. ^{1}H, ^{13}C, ^{11}B, and ^{15}N NMR Data for Boron-Containing Compounds, (δ in ppm, coupling constants in Hz)

compd	solvent	O*H*[a]	N*H*	C*H*O/H4	*C*HO/C4	$^{1}J_{CHO/C4-H}$	B1[b]	N2[b]	$^{1}J_{N2-H}$	N3[b]	$^{1}J_{N3-C4}$
	CD_3CN	6.66		10.05	197.0	176.9	29.9 (90)				
	$(CD_3)_2SO$	8.25		10.13	194.2	175.9	−				
	CD_3OD			6.00	105.1	168.5	30.9 (187)				
	D_2O			9.93	197.1	177.5	30.3 (211)				
	aq NaOH						7.1 (105)				
 **1**	CD_3CN	6.78		8.45	151.2	177.6	28.8 (99)			−12.1 (4)	3.5
	$(CD_3)_2SO$	9.42		8.65	150.0	178.5	−			−11.6 (1)	4.4
	CD_3OD[c]			8.49	151.2	178.4	24.6 (125)			−33.6 (40)	−
	D_2O			8.45	150.3	180.8	18.7 (125)[d]			−35.4 (70)	−
	aq NaOH						2.2 (71)				
 **2**	CD_3CN	6.00	8.95[e]	7.98	140.5	178.1	28.2 (87)	−216.3 (29)	90.8	−54.9 (8)	5.3
	$(CD_3)_2SO$	8.20	9.96[f]	8.00	138.5	177.3	−	−212.0 (1)	90.9	−52.0 (4)	8.6
	CD_3OD			8.02	141.7	178.2	27.7 (138)	−222.6 (76)		−68.8 (38)	−
	D_2O			8.07	139.7	175.8	27.5 (100)	−219.1 (33)		−71.2 (8)	8.8
	aq NaOH						26.9 (319)				
 **3**	CD_3CN	6.22		7.98	138.8		28.0 (83)				
	$(CD_3)_2SO$	8.54		8.00	137.4		−				
	CD_3OD			7.92	139.4		27.4 (152)				
	D_2O			8.02			26.8 (111)				
	aq NaOH						26.2 (326)				
 **4**	H_2O			8.25			3.9 (123)				
 **5**	CD_3CN			8.53, 8.10[g]	162.0		28.9 (102), 4.8 (103)[g]				
	$(CD_3)_2SO$			8.47, 8.28[g]	160.9		−				
	CD_3OD			8.14, 7.41[g]	140.4		26.6 (121), 5.8 (38)[h]				
 **6**	aq NaOH						1.4 (166)				
 **7**	D_2O			8.49	150.7		4.3 (126)				
	aq NaOH						4.0 (130), 2.0 (75)				
 **9**	CD_3CN						32.6 (103)				
	CD_3OD			8.49	151.2						

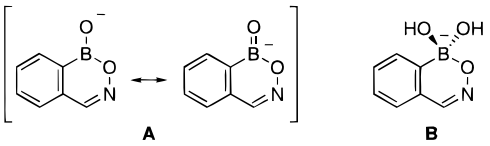
[a] Acquisition of ^{2}H upon addition of D_2O, $t_{1/2}$ of <1 min at 23 °C. [b] Line widths in Hz shown in parentheses. [c] Verified as **1** and not **9** by a comparison of the ^{11}B NMR chemical shift values. [d] Highly variable and temperature dependent. Other values at room temperature, 14.9 (140 Hz), 13.0 (134 Hz), and 6.8 ppm (115 Hz). Values at 70 °C, 19.7 (277 Hz) and 15.2 ppm (130 Hz). [e] Acquisition of ^{2}H upon addition of D_2O, $t_{1/2}$ 40 min at 23 °C; $^{2}J_{N3-NH}$ and $^{4}J_{H4-NH}$, 6.6 and 8.6 Hz, respectively. [f] Acquisition of ^{2}H upon addition of D_2O, $t_{1/2}$ of 4 h at 23 °C; $^{2}J_{N3-NH}$ and $^{4}J_{H4-NH}$, 7.5 and 7.5 Hz, respectively. [g] Integration ratio 1:2. [h] Integration ratio 2:1.

NMR Solution Structures. Data from extensive multisolvent ^{1}H, ^{13}C, ^{11}B, and ^{15}N NMR spectroscopic analyses of **1**−**4** and related compounds are shown in Table 1.[22] The upfield chemical shifts for the CHO group proton and carbon resonances of 2-formylbenzeneboronic acid when in CD_3OD solution are clear indications that this solvent readily adds to the aldehyde to produce a methoxylated borophthalide species.[5d] In every other combination of compound and neutral solvent, however, no other such addition to a C═O or C═N moiety was revealed. Thus, importantly, heterocycles **1**−**3** maintain the integrity of their C4−N3 imine unit in every solvent examined, a conclusion corroborated by the observation of a large (175−180 Hz) $^{1}J_{C4-H}$ coupling constant in every case. The B−OH group proton chemical shift in **1**−**3** and even for 2-formylbenzeneboronic acid itself experiences a large (1.6−2.7 ppm) downfield displacement upon transfer from CD_3CN to $(CD_3)_2SO$, no doubt caused by the greater hydrogen-bond accepting ability of the latter solvent. This effect is more pronounced in **1** than in **2**, indicating that the oxazaborine is the more Brønsted acidic. In a finding somewhat related to that noted previously for a furo[3,2-*d*][1,2,3]-diazaborine,[7a] the N2−H group proton chemical shift in **2** shows a similar (1.0 ppm) displacement as it too acts a hydrogen-bond donor to solvent $(CD_3)_2SO$. That the N2−H group of **2** can donate a hydrogen bond is further documented by the results of the X-ray crystal structure determination (*vide infra*) of this heterocycle. However, a comparison of the $t_{1/2}$ values for deuterium exchange from D_2O into this group in the two polar aprotic solvents reveals this process to be significantly faster in CD_3CN, suggesting that the H2 atom in **2** exchanges *not* as a direct result of Brønsted acid behavior on the part of the N2−H unit, but rather as an indirect consequence of a 1,2-addition of D_2O to the 2,3,1-diazaborine ring *via* a 1,2-zwitterion like **4**. The retarded rate of such a hydration of **2** when in $(CD_3)_2SO$

(22) The expected utility of ^{15}N and ^{11}B solution NMR spectroscopic analyses to the solution structure elucidation of boron heterocycles similar to **1** and **2** was recognized in at least one prior investigation. See ref 7b.

containing D_2O is likely a result of the rendering of the B1 atom less electron-deficient by the partial ionization of the Brønsted acidic B−OH group. This interpretation gains support from the results of experiments that revealed **2** to be susceptible to ^{18}O isotope acquisition from $H_2{}^{18}O$ even at room temperature under neutral conditions. An elimination−addition pathway for H2 deuterium exchange in **2** is indirectly rendered doubtful by the finding that **3** acquires an ^{18}O isotope from $H_2{}^{18}O$ under neutral conditions with at least equal facility to that of **2**. Besides this, the non-zwitterionic B═N moiety of the putative intermediate along such a pathway has no known precedent.[23]

Except for the fact that they were consistently smaller for species in CH_3CN solution, the ^{11}B line widths were found to be of little diagnostic utility. On the other hand, the ^{11}B chemical shifts were quite diagnostic of the amount of charge at, and to a *limited* degree, the hybridization state of the boron center in the heterocycle solution species. No signals ever were obtained from $(CD_3)_2SO$ solutions of these compounds,[24] but the chemical shift values of **1**−**3** in all other neutral solvents save for **1** in H_2O were found to be in the 25−30 ppm range characteristic of the trigonal-planar substituted sp^2-hybridized neutral boron centers of CBO_2 or CB(O)N molecular fragments. The intermediate ^{11}B chemical shift value of 18.7 ppm for **1** in H_2O shows an increase in electron density near this center, but not nearly to the extent indicated by the δ value of **1** or **6** in aqueous NaOH or of **4** or **7** in H_2O. The upfield ^{11}B chemical shift of **1** in H_2O is best explained by the presence of species **A**, the product of a proton dissociation from the B−OH group acting in Brønsted acid fashion, rather than by that of **B**, the



A **B**

hydration product of the B−OH group acting in Lewis acid fashion. In **A**,[25] a species properly viewed as a B−O for C═N isoelectronic replacement analogue of the conjugate base of phthalazin-1(2*H*)-one,[26] the delocalization of charge from the oxyanion onto the boron center in a π-bond-forming fashion accounts for both the observed upfield shifted ^{11}B signal for **1** in water and for the sluggishness of ^{18}O isotope acquisition from $H_2{}^{18}O$ by **1** in CH_3CN. Moreover, a Brønsted-type ionization of **1** to produce **A** in water is consistent with the observation that the 300 nm "boroaromatic" diagnostic absorption in the UV spectrum of **1** observed in CH_3CN, $(CH_3)_2SO$, and CH_3OH is absent for **1** in aqueous solution.

According to the NMR data, the integrity of the diheteraborine ring and, surprisingly, the electronic environment of the boron center as measured by ^{11}B NMR chemical shifts in **2** or **3** remain largely unaffected under high-pH conditions despite the fact that their aqueous pK_a value of *ca.* 8 together with their ready dissolution in alkali are clearly suggestive of ionization in this environment. The best explanation for this seemingly contradictory set of findings is that both **2** and **3** *do* indeed form Brønsted conjugate bases in a strongly alkaline medium, but

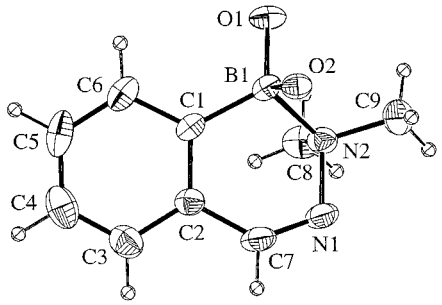


Figure 1. ORTEP diagram and atomic numbering scheme for one of the 1,2-dihydro-2,3,1-benzodiazaborines formed by intramolecular chelation in bis(8-B-4)-1,3,5-tris[2-[(dimethylhydrazono)methyl]phenyl]-boroxin (**5**).[3]

there is little or no oxyanion charge delocalized onto the boron center. By electrostatic repulsion, the presence of the adjacent p-electron-rich, sp^2-hybridized nitrogen center in the diazaborine conjugate bases may preclude such charge accumulation by the boron atom. Thus, we conclude that the ^{11}B NMR chemical shift value of **2** and **3** is insensitive to their Brønsted-type ionization in alkali, in contrast to the great sensitivity of this shift for **1** even in neutral aqueous solution. Interestingly, this 6-hydroxy-1,2,6-oxazaborine exhibits a ^{11}B NMR chemical shift value diagnostic of species **B** in alkaline solution, and the 3-hydroxy-1,2,3-diazaborine **6** also adopts such a Lewis acid conjugate base form in this medium.[27]

Upon transfer from an aprotic to a protic solvent, the ^{15}N chemical shift in oxazaborine **1** undergoes a moderate (22.5 ppm) upfield displacement reflective of a protophilic association with solvent. This same solvent effect is noted for diazaborine **2** but to a lesser extent ($\Delta\delta$ 16.5 ppm) that is suggestive of a slightly lower basicity. Despite its juxtaposition with the ^{11}B quadrupolar nucleus, the ^{15}N NMR signal from the N2 atom of [4-^{13}C,2,3-$^{15}N_2$]**2** was observed and was found to be in a chemical shift range (δ 217 ± 5 ppm) typical of an amide-type nitrogen in all four neutral solvents. That this nitrogen in **2** is truly amide-like in character is further supported by the 91 Hz $^1J_{N2-H}$ coupling constant magnitude for this heterocycle found in the two aprotic solutions.

X-ray Crystal Structures. An X-ray crystallographic analysis of **5**, the tridehydro form of **4** which exists in the solid state and in aprotic solution, was conducted and the details have been reported elsewhere.[3] In a solid state structure likely to be found similar to those of earlier-reported imine derivatives of 2-formylbenzeneboronic acid,[5b] crystalline **5** is the first triaryl-substituted boroxin[28] found to display two B_3O_3-ring chelations. These occur on opposite faces of the boroxin ring and assemble 1,1,2,2-tetrasubstituted 1,2-dihydro-2,3,1-benzodiazaborine moieties of relevance to the discussion of the heterocycles of the present work. An ORTEP representation of one of these is shown in Figure 1. In an alleviation of eclipsing interactions, each of the chelation-derived diazaborine heterocyclic fragments in crystalline **5** displays a severe twist at the B−N site of ring saturation that places the four substituents at these two heteroatoms into near-perfect axial and equatorial positionings (select

(23) See for example the MNDO study described in the following: Sporzynski, A.; Szatylowicz, H. *J. Organomet. Chem.* **1994**, *470*, 31−33.

(24) Facile aggregate formation in this medium provides one explanation for this phenomenon.

(25) A B═O containing resonance structural representation of **7**-H_2O similar to that depicted for **A** can be found in ref 17.

(26) An insight into the reason why diazaborines like **2** and **3** do not readily dissociate in Brønsted fashion as does **1** to form **A** can be gained by the realization that the resultant anions are species properly viewed as B−N for C═C isoelectronic replacement analogues of the conjugate bases of isoquinolin-4(3*H*)-ones (*i.e.*, enolate anions).

(27) **Note Added in Proof:** By X-ray crystallographic analysis of the enzyme−inhibitor complexes, it has recently been shown that **6**-like thieno-fused and benzo-fused 1,2,3-diazaborine antibacterial agents condense with NAD^+ to form species **B**-like bisubstrate analogue inhibitors of *Escherichia coli* enoyl reductase: Baldock, C.; Rafferty, J. B.; Sedelnikova, S. E.; Baker, P. J.; Stuitje, A. R.; Slabas, A. R.; Hawkes, T. R.; Rice, D. W. *Science* **1996**, *274*, 2107−2110.

(28) (a) Brock, C. P.; Minton, R. P.; Niedenzu, K. *Acta Crystallogr.* **1987**, *C43*, 1775−1779. (b) Yalpani, M.; Boese, R. *Chem. Ber.* **1983**, *116*, 3347−3358. (c) Köster, R.; Angermund, K.; Sporzynski, A.; Serwatowski, J. *Chem. Ber.* **1986**, *119*, 1931−1952.

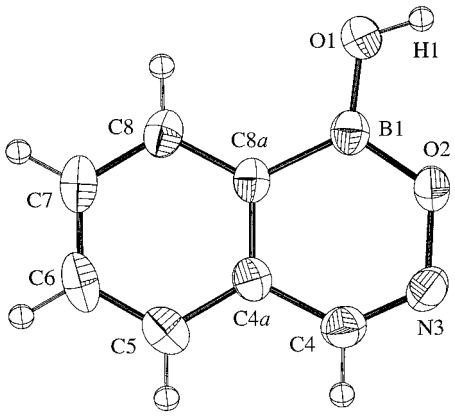


Figure 2. ORTEP diagram and atomic numbering scheme for 1-hydroxy-1*H*-2,3,1-benzoxazaborine, $C_7H_6BNO_2$ (**1**).

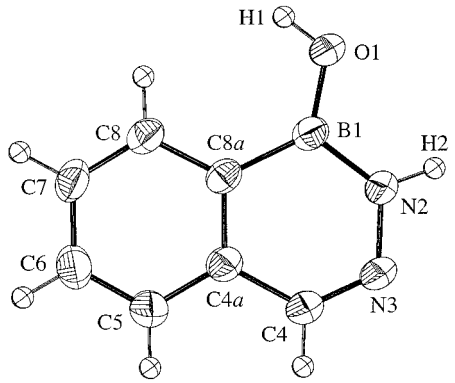


Figure 3. ORTEP diagram and atomic numbering scheme for 1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborine, $C_7H_7BN_2O$ (**2**).

Table 2. Selected Crystal Data and Structure Refinement for $C_7H_6BNO_2$ (**1**) and $C_7H_7BN_2O$ (**2**)

	1	**2**
formula	$C_7H_6BNO_2$	$C_7H_7BN_2O$
fw, g mol^{-1}	146.94	145.96
crystal system	orthorhombic	monoclinic
space group	*Fdd*2	$P2_1/c$
color	colorless	colorless
a, Å	11.2028(15)	7.791(2)
b, Å	30.390(8)	7.2907(10)
c, Å	8.1221(17)	12.3990(16)
β, deg		96.33(2)
V, Å^3	2765.2(10)	700.0(2)
ρ(calcd), g·cm^{-3}	1.4119(5)	1.3850(4)
Z	16	4
R	0.040	0.041
R_w	0.031	0.029
goodness-of-fit	2.40	2.29

O−B−N−C dihedral angle values of −170.2(4)° and −174.4(4)°). The 1,2-zwitterionic molecular fragment shown in Figure 1 is a reasonable model for the aqueous solution structure of **4**. If for the minor 1,2-hydrate aqueous solution form of **2** or **3** as well, it provides an insight into the structure of the Lewis conjugate bases derived from these through which ^{18}O isotope acquisition from $H_2{}^{18}O$ occurs.

Crystal structure determinations of **1** and **2** were also obtained, and selected data from these analyses are shown in Figures 2 and 3 and are collected in Tables 2−5. Structures for comparison with and contrast to **1** include 4-ethyl-1-hydroxy-3-(4-hydroxyphenyl)-1*H*-2,1-benzoxaborine (**10**)[29] and 2-formylbenzeneboronic acid and its *O*-methyl oxime **8**, both of which have been found to exist in planar, seven-membered ring intramolecularly hydrogen-bonded form.[19] For comparison with that of **2**, the crystal structure determination[30] of 6,7-dihydro-7-hydroxy-6-methylthieno[2,3-*d*][1,2,3]diazaborine (**11**, a thiophene analogue of **3**), is of particular interest. Finally, for both

(29) Arcus, V. L.; Main, L.; Nicholson, B. K. *J. Organomet. Chem.* **1993**, *460*, 139−147.

Table 3. Selected Bond Lengths (Å) for $C_7H_6BNO_2$ (**1**) and $C_7H_7BN_2O$ (**2**)

	1	**2**
H(1)−O(1)	0.86(4)	0.87(2)
O(1)−B(1)	1.350(6)	1.371(3)
B(1)−C(8a)	1.533(6)	1.530(3)
B(1)−O/N(2)	1.388(6)	1.432(3)
O/N(2)−N(3)	1.419(6)	1.373(2)
N(3)−C(4)	1.283(5)	1.291(3)
C(4)−C(4a)	1.452(6)	1.445(3)
C(4a)−C(5)	1.406(6)	1.401(3)
C(4a)−C(8a)	1.394(7)	1.406(3)
C(5)−C(6)	1.372(7)	1.370(3)
C(6)−C(7)	1.393(8)	1.389(3)
C(7)−C(8)	1.380(6)	1.375(3)
C(8)−C(8a)	1.395(6)	1.405(3)

Table 4. Selected Bond Angles (deg) for $C_7H_6BNO_2$ (**1**) and $C_7H_7BN_2O$ (**2**)

	1	**2**
O(1)−B(1)−C(8a)	122.5(4)	128.08(18)
O(1)−B(1)−O/N(2)	118.0(4)	116.68(18)
B(1)−O(1)−H(1)	118(3)	114.9(15)
O/N(2)−B(1)−C(8a)	119.4(5)	115.24(17)
O/N(2)−N(3)−C(4)	117.3(4)	116.74(15)
N(3)−C(4)−C(4a)	127.8(4)	126.80(19)
N(3)−C(4)−H(4)	116	117
N(3)−O/N(2)−B(1)	121.9(3)	125.62(15)
C(4)−C(4a)−C(5)	121.1(4)	120.68(18)
C(4)−C(4a)−C(8a)	117.7(4)	118.62(19)
C(4a)−C(4)−H(4)	116.13	117
C(4a)−C(5)−C(6)	118.9(5)	120.07(19)
C(4a)−C(8a)−B(1)	115.9(4)	116.70(17)
C(4a)−C(8a)−C(8)	118.2(4)	117.44(19)
C(5)−C(4a)−C(8a)	121.2(4)	120.69(18)
C(5)−C(6)−C(7)	120.8(4)	120.2(2)
C(6)−C(7)−C(8)	119.9(4)	120.20(19)
C(7)−C(8)−C(8a)	121.0(5)	121.35(19)
C(8)−C(8a)−B(1)	125.9(5)	125.86(18)

Table 5. Selected Torsion Angles (deg) for $C_7H_6BNO_2$ (**1**) and $C_7H_7BN_2O$ (**2**)

	1	**2**
O(1)−B(1)−C(8a)−C(4a)	−176.3(4)	−174.3(2)
O(1)−B(1)−C(8a)−C(8)	2.1(8)	6.4(3)
O(1)−B(1)−O/N(2)−N(3)	177.4(4)	174.46(17)
B(1)−O/N(2)−N(3)−C(4)	−0.3(6)	1.7(3)
O/N(2)−B(1)−C(8a)−C(4a)	3.1(7)	5.6(3)
O/N(2)−B(1)−C(8a)−C(8)	−178.5(5)	−173.66(19)
O/N(2)−N(3)−C(4)−C(4a)	1.7(7)	2.2(3)
N(3)−C(4)−C(4a)−C(5)	180.0(15)	177.4(2)
N(3)−C(4)−C(4a)−C(8a)	−0.5(7)	−1.5(4)
C(4)−C(4a)−C(5)−C(6)	179.7(5)	−176.1(2)
C(4)−C(4a)−C(8a)−B(1)	−1.9(6)	−2.6(3)
C(4)−C(4a)−C(8a)−C(8)	179.5(4)	176.7(2)
C(4a)−C(5)−C(6)−C(7)	0.6(8)	−0.6(3)
C(5)−C(4a)−C(8a)−B(1)	177.7(4)	178.5(2)
C(5)−C(4a)−C(8a)−C(8)	−0.9(7)	−2.1(3)
C(5)−C(6)−C(7)−C(8)	−0.6(8)	−2.1(4)
C(6)−C(7)−C(8)−C(8a)	−0.1(10)	2.7(3)
C(7)−C(8)−C(8a)−B(1)	−177.5(5)	178.7(2)
C(7)−C(8)−C(8a)−C(4a)	0.9(8)	−0.6(3)
C(8a)−B(1)−O/N(2)−N(3)	−2.1(7)	−5.5(3)
C(8a)−C(4a)−C(5)−C(6)	0.2(7)	2.7(3)
H(1)−O(1)−B(1)−C(8a)	170(4)	6.1(17)
H(1)−O(1)−B(1)−O/N(2)	−9(4)	−173.8(17)

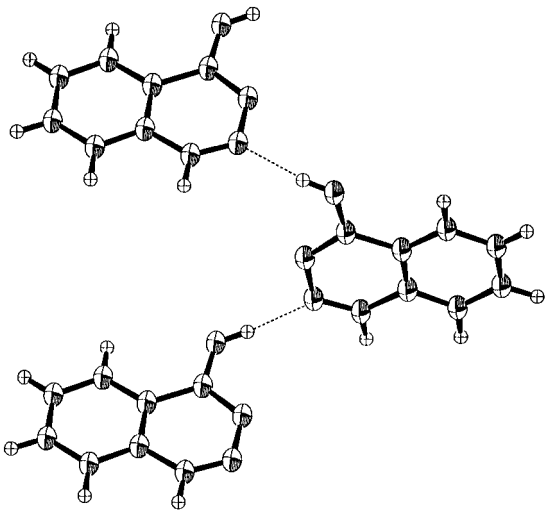
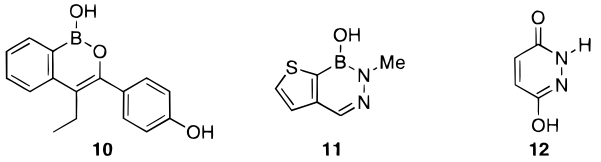


Figure 4. View of intermolecular hydrogen bonding motif of **1**.

1 and **2**, the 6-hydroxypyridazin-3(2*H*)-one (**12**)[31] ambident lactam/lactim of maleic hydrazide is seen to provide valuable comparison data.



Crystalline **1** and **2** are seen to be planar boron heterocycles displaying a distinct deformation of angles at the site of hydroxyl-group ring attachment such that the O1 atom is distanced from the benzene ring. This feature is more pronounced in **2** than in **1** (as it is more so in **11**[30] than in **10**[29]) and cannot be directly related to intermolecular hydrogen-bonding interactions (*vide infra*) as the directionality of the OH group hydrogen bond donation in **1** and **2** differ. A cursory comparison of the three bond angles at the boron reveals that those at **1** and **10** are similar to each other and closely match their counterparts in the lactim fragment of **12**, while those at **2** and **11** are similar to each other and more closely match their counterparts in the lactam fragment of the pyridazinone.

The C4−N3 double-bond length in each heterocycle is typical for endocyclic heterocycle imine moieties, but a striking difference between crystalline **1** and **2** is seen in the position of the 2-heteroatom relative to its neighbors within the 2,3,1-benzodiheteraborine ring. The short (1.388(6) Å) B1−O2 and long (1.419(6) Å) O2−N3 distances in crystalline **1** reveals it to be more naphthalene-like than **2**, wherein the bond length alternation is reversed. In **2**, the B1−N2 distance is long (1.432-(3) Å) and the N2−N3 short (1.373(2) Å). Since the electron-deficient boron center is likely better stabilized by the adjacent nitrogen in **2** than by the endocyclic oxygen in **1** (2,1-azaborines are generally regarded as being more "boroaromatic" than 2,1-oxaborines), it might simply require closer proximity to the 2-heteroatom in the latter. Despite this proximity, though, **1** remains the more Brønsted acidic and also the more chemically reactive under ring transformative conditions.

Both **1** and **2** undergo intermolecular hydrogen-bond association in the solid state, as shown in Figures 4 and 5, respectively. Numerical data for these interactions are shown in Table 6. The B−OH group intermolecular hydrogen bond to N3 in crystalline

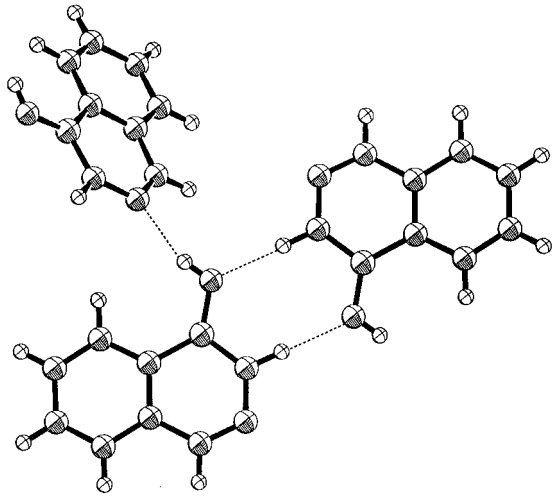


Figure 5. View of intermolecular hydrogen bonding motif of **2**.

Table 6. Hydrogen Bonding Parameters (Å or deg) for $C_7H_6BNO_2$ (**1**) and $C_7H_7BN_2O$ (**2**)

	D···A	D−H	H···A	D−H···A
O(1)-H(1)···N(3) in **1**	2.781(4)	0.86(4)	1.95(4)	165(5)
O(1)-H(1)···N(3) in **2**	2.810(2)	0.87(2)	1.97(2)	161(2)
N(2)-H(2)···O(1) in **2**	3.021(2)	0.95	2.07	174

1 is shorter than that in **2**, and in the latter, this group also accepts a hydrogen bond from the N2−H unit of a neighbor. FTIR spectral analyses revealed patterns consistent with the different hydroxyl-centered solid state hydrogen-bonding motifs found in **1** and **2**. The OH stretch in the 3200−2800 cm^{-1} region for **1** (as well as for **3**) is broad, not unlike that of a carboxylic acid dimer even though **1** forms infinite hydrogen-bonded chains and not dimers in the solid state. By contrast, the FTIR spectrum of **2** shows narrow absorbances at 3330 and 3294 cm^{-1} assigned to the OH and NH stretches, respectively. Although the position of the hydrogen atom of the B−OH group in diazaborine **11** had not been located precisely,[30] it is apparent from the molecular orientations in the projection of the crystal's unit cell onto a plane perpendicular to the *a* axis provided in the report that its O1−H1 bond vector orientation is the same as that found for **2** herein. An evaluation of the 2-alkylated 2,3,1-diazaborine **3** by NOESY NMR revealed a through-space spin-interactive proximity of the B−O*H* and H8 protons, thereby providing evidence for such an orientation in solution as well. Interestingly, though, the D···A distance of 2.789(4) Å reported for **11** is closer to that in **1** rather than in **2**.

Solution Hydrogen-Bonding Properties. The coexistence of a Brønsted acidic B1−OH group and a basic site at N3 in **1** and **2** as evidenced by the solution NMR data and the solid state X-ray data discussed above suggested that the heterocyclic peripheries of **1** and **2** would be capable of entering into multiple hydrogen-bond associations with those of the aglycons of certain select natural nucleoside partners. Specifically, the hydrogen-bond complementarity between **1** and guanosine and between **2** and cytidine both appeared reasonable. Experiments with admixtures of the former pair of partners failed to reveal evidence of an associative interaction, but those with an admixture of the latter pair did. VT-NMR spectroscopic analysis[32] (Figure 6 and Figure 7) of a 1:1 admixture (0.4 M in each component) of **2** and 2′,3′,5′-tri-*O*-(methoxymethyl)cytidine in CD_3CN solution was conducted, and the effect of temperature on the chemical shift values for the active hydrogen atoms was

(30) Aurivillius, B.; Löfving, I. *Acta Chem. Scand.* **1974**, *B28*, 989−992.

(31) Cradwick, P. D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1386−1389.

(32) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37−44.

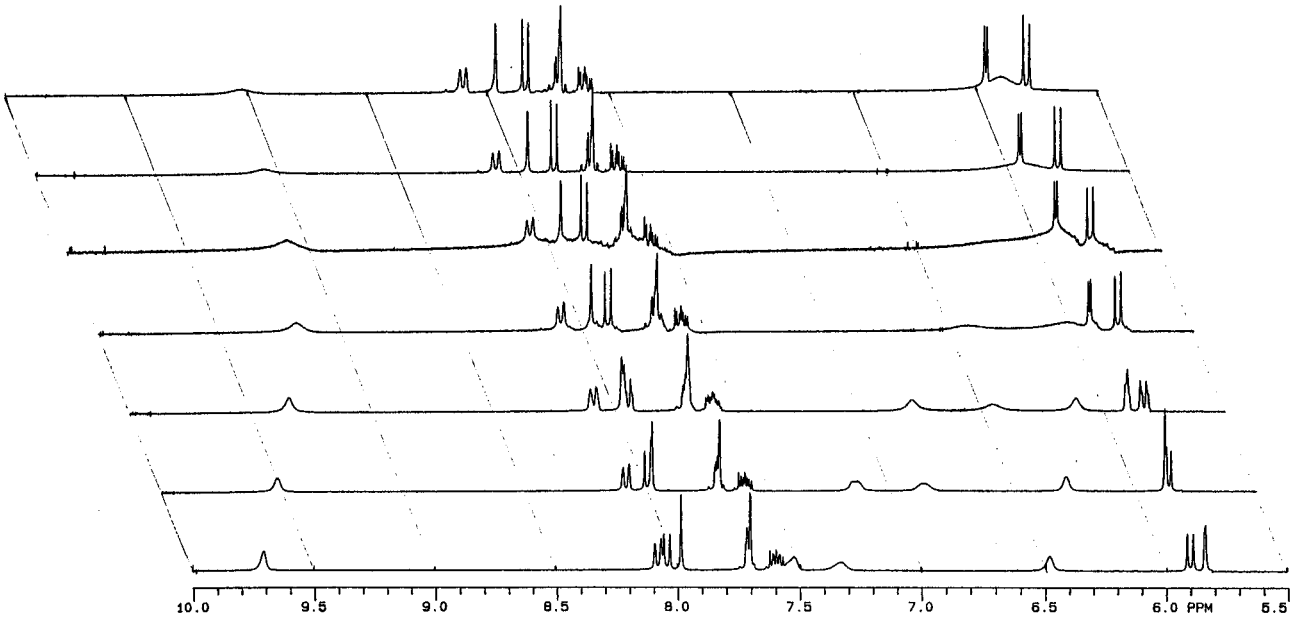


Figure 6. Effect of temperature (60, 50, 40, 23, 0, −20, and −40 °C, from the top) upon the ^{1}H NMR spectrum of a 1:1 (0.4 M) admixture of **2** and 2′,3′,5′-tri-*O*-(methoxymethyl)cytidine in CD_3CN solution.

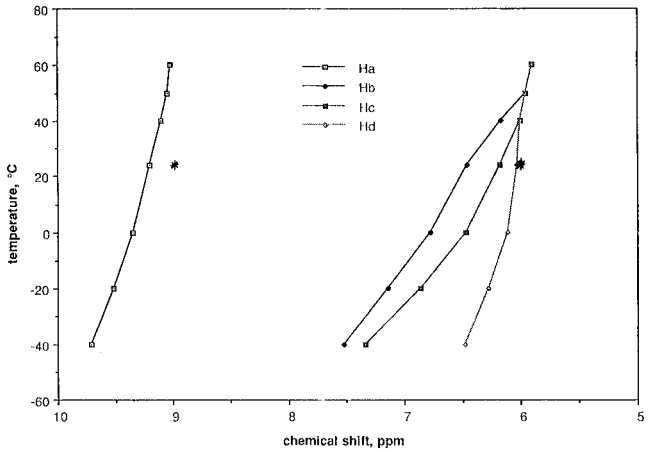
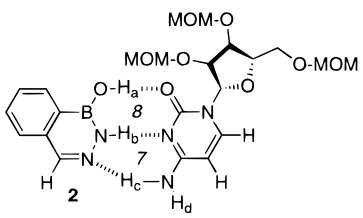


Figure 7. Effect of temperature upon the ^{1}H NMR chemical shifts of the exchangeable protons in a 1:1 (0.4 M) admixture of **2** and 2′,3′,5′-tri-*O*-(methoxymethyl)cytidine in CD_3CN solution. Shift values for the B−OH (δ 8.98) and N2-H (δ 6.00) moieties of uncomplexed **2** and for the 4-NH_2 one of uncomplexed 2′,3′,5′-tri-*O*-(methoxymethyl)-cytidine at room temperature have been marked with an asterisk.

ascertained. By this, evidence of a temperature-dependent multiple hydrogen-bond association was found. The most likely structure of a heterodimeric aggregate of **2** and the cytidine derivative is one in which these partners are held in relative orientation by three hydrogen bonds constituting both an eight- and a seven-membered ring, as shown below. No other binary interactive orientation was deemed to be consistent with the VT-NMR study results.



Conclusions and Implications for Boron Analogue Development

Compounds **1**−**3** maintain an sp^2-hybridized, trigonal planar-substituted, neutral boron center in the solid state and in aqueous and other neutral solution environments, and thus their peripheries are certainly attractive for the development of planar, uncharged boron-containing analogues of nitrogen heterocycle substances. While the B−OH moiety in both **1** and **2** is characterized by a predominant Brønsted acidity, it retains some degree of Lewis acidity and thereby creates an ambidency that is more pronounced in **2** than in **1**. The increased electron deficiency at the boron center of **1** due to its juxtaposition to a ring oxygen, rather than nitrogen atom enhances the Brønsted acidity of the appended hydroxyl group to the extent that significant proton dissociation from this group occurs in neutral aqueous solution. As a consequence of the resulting oxyanion development, the boron center in **1** in this medium becomes *less* electron-deficient due to charge delocalization and consequently is rendered *less* reactive as a Lewis acid toward covalent hydration when compared to that in **2**. In short, the members of the benzo-fused 2,3,1-dihetera subclasses of borine heterocycles display a subtle environment-dependent prototropy so sensitive that certain past difficulties[11j] encountered in attempts to delineate their physicochemical properties now become readily appreciated.

In a finding predictive of the physicochemical properties likely to extend to future 6-hydroxy-1,2,6-oxaza- and 3-hydroxy-1,2,3-diazaborine-containing compounds, the Brønsted acidic B−OH group in **1** and **2** is seen to have an excellent and flexible capability of entering into hydrogen-bonding interactions as a donor, and in **2**, additionally as an acceptor. Both **1** and **2** exhibit solid state intermolecular hydrogen-bonding motifs containing some of the features present in C·G DNA base-pair interactions. The finding that **2** undergoes a hydrogen-bond association with a tri-O-protected cytidine in CD_3CN solution provides further support for the expectation that boron-containing peripheries like those in the boron heterocycles **1** and **2** will serve well as "platforms" for the development of close mimics of biologically derived and/or active nitrogen heterocycle-based compounds such as the 2-aza-3-deazapurines.

Experimental Section

General Procedures, Methods, 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 the adsorbent. Flash column chromatography was performed using 230−400 mesh ASTM Merck silica gel-60. TLC analyses were performed using Analtech 250 μm silica gel GF Uniplates, and visualizations were done with short-wave (254 nm) UV light. Lyophilizations were conducted on a Labconco Lypho-Lock 4.5 L bench-top freeze-dryer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 (300 and 75 MHz) or VXR-500 (500 and 125 MHz) instrument. These spectra were recorded with tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonic acid, sodium salt (DSS) (δ = 0.0 for ^{1}H), and $CDCl_3$ (δ = 77.0 for ^{13}C), $(CD_3)_2SO$ (δ = 39.5 for ^{13}C), CD_3OD (δ = 49.0 for ^{13}C), CD_3CN (δ = 1.3 for ^{13}C), or 1,4-dioxane (δ = 66.5 for ^{13}C) in D_2O as internal reference. Signals from carbons directly attached to a boron atom were not observed due to strong quadrupolar line-broadening although those from ^{15}N isotope-enriched nitrogens in a similar setting were observed. ^{11}B NMR spectra were recorded at 96.2 MHz without field frequency lock on the VXR-300 instrument using nondeuterated solvents and neat external $BF_3{\cdot}(OEt)_2$ (δ = 0.0) as reference. Resonances appearing downfield of the reference signal were assigned positive values. UV spectra were recorded on a Shimadzu UV-160U spectrophotometer. Methanol-d_4 (99%) was purchased from Isotec, Inc. [*formyl*-^{13}C]PhCHO, [$^{15}N_2$]$NH_2NH_2{\cdot}H_2SO_4$, and [^{15}N]$NH_2OH{\cdot}$HCl were purchased from Cambridge Isotope Laboratories. Butyllithium in hexanes was purchased from the Aldrich Chemical Co. and was titrated by the modified Watson−Eastham procedure.[33] Methanol was dried by distillation from $Mg(OMe)_2$ under argon. THF and diethyl ether were dried by distillation from sodium benzophenone ketyl under argon. *N*,*N*,*N*′-Trimethylethylenediamine and trimethylborate were dried over and distilled from CaH_2 and Na, respectively, under argon. Estimation of pK_a values were made by potentiometric measurement of pH. Mass spectral and combustion elemental microanalyses were obtained from the University of Illinois.

Crystallographic Data Collections and Structure Determinations. Data Collection. X-ray quality crystals of **1** were obtained via slow evaporation of an EtOAc solution. Those of **2** were obtained in a similar fashion from CH_3CN. Each suitable crystal was mounted on a glass fiber with epoxy, and data were collected by a Rigaku AFC-5S diffractometer with graphite monchromated Mo Kα radiation. The incident beam collimator was 1.0 mm, the crystal to detector distance was 285 mm, and the detector aperture was 6.0 × 6.0 mm. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections, corresponded to the cells with dimensions listed in Table 2, where details of the data collection are summarized. The weak reflections ($I < 10\sigma(I)$) were rescanned (maximum of four rescans), and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1.

Data Reduction. The intensities of three representative reflections were measured after every 100 reflections. No decay correction was applied. The data were corrected for Lorentz and polarization effects.

Structure Determination and Refinement. The structures of **1** and **2** were solved by direct methods and expanded using Fourier techniques. Measured nonequivalent reflections with $I > 1.5\sigma(I)$ were used for the structure determinations. The non-hydrogen atoms were refined with anisotropic displacement factors. Those hydrogen atoms not refined with isotropic displacement factors were included in fixed positions. All calculations were performed using a TEXSAN crystallographic software package of the Molecular Structure Corp.

2-Formylbenzeneboronic Acid. A flask containing magnesium turnings (1.53 g, 63 mmol) was flame-dried under argon and then was charged with 150 mL of THF and 0.1 mL of 1.6 M MeMgBr in THF. 2-(2-Bromophenyl)-1,3-dioxolane[14] (14.2 g, 62 mmol) was then added at room temperature dropwise with stirring. After 30 min, the reaction mixture was heated at reflux for 4 h. The resulting Grignard reagent solution was cooled to 0 °C and was transferred under positive argon pressure to a precooled −78 °C stirred solution of freshly distilled $B(OMe)_3$ (7.27 g, 70 mmol) in THF (150 mL). After 4 h, the mixture was allowed to warm slowly to room temperature and was kept under argon overnight. The solution was then treated with excess 2 M HCl and the layers were separated. The aqueous layer was extracted with ether (3 × 10 mL), and the ether extracts combined with the original THF layer. This organic solution was extracted with 2 M NaOH (3 × 15 mL), and the NaOH extracts were combined before adjustment of the pH to *ca.* 3 (2 M HCl). Finally, this acidified aqueous solution was extracted with ether (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and were rotary evaporated to give 6.3 g (68%) of 2-formylbenzeneboronic acid as a white solid, mp 124−126 °C (lit.[13] 115−123 °C (H_2O); lit.[5d] 118−120 °C (H_2O); lit.[4c] 120−123 °C (H_2O); lit.[5d] dehydrates to anhydride at 110−120 °C, resolidifies at 125−130 °C, (boroxin) melts at 163−165 °C (dec) (H_2O)).

[*formyl*-^{13}C]-2-Formylbenzeneboronic Acid. A solution of *N*,*N*,*N*′-trimethylethylenediamine (0.82 mL, 6.40 mmol) in 16 mL of dry THF at −20 °C was treated dropwise with 4.46 mL of a 1.388 M solution of *n*-BuLi in hexanes (6.2 mmol) under argon while stirring. After 30 min, [*formyl*-^{13}C]benzaldehyde (0.613 mL, 6.0 mmol) was added dropwise. The reaction mixture was stirred at −20 °C for 30 min, and then another 12.97 mL of the *n*-BuLi solution (18.0 mmol) was added dropwise via syringe. After the reaction was stirred for 24 h at −24 °C (freezer), and then trimethylborate (5.45 mL, 48 mmol) freshly distilled from Na was added dropwise at −78 °C via syringe over 15 min. The resulting boronation reaction mixture was kept for 24 h at −78 °C. (After 3 h, it had gelatinized and required brief warming to *ca.* −55 °C.) The mixture was then stirred for 40 min from −70 °C to room temperature, for 40 min at −20 °C, and for 30 min at 0 °C. The reaction mixture was cooled to −70 °C and was quenched by the addition of 1.5 N HCl. The layers of the biphasic mixture were separated, and the top, organic layer was extracted with water. The aqueous extracts were combined with the former bottom, acidified aqueous layer, and this was then extracted with CH_2Cl_2. The organic extracts were rotary evaporated to give a residue that was treated with water and distilled until all of the hydrophobic, oily material had either distilled off or had adhered to the walls of the flask. The aqueous solution was removed by decanting and its volume was reduced to *ca.* 1 mL in a beaker on a hot plate. The yellow precipitate that formed upon cooling was collected by suction filtration and was washed with a small amount of cold water followed by CH_2Cl_2 to give 190 mg (32%) of NMR-pure [*formyl*-^{13}C]formylbenzeneboronic acid: mp 120−123 °C. This sample was used directly for the synthesis of [4-^{13}C,2,3-$^{15}N_2$]-**2**, while the residue (87 mg, 15%) obtained from the aqueous filtrate was used directly for the synthesis of [4-^{13}C,3-^{15}N]**1**.

1-Hydroxy-1*H*-2,3,1-benzoxazaborine (1). Dewar's modification[4c] of Snyder's procedure[5f] was used to prepare **1** in a 99% yield: mp 262−265 °C (H_2O) (lit.[5f] 150−155 °C (H_2O); lit.[4c] 264−265 °C with slow heating, phase change at 164 °C (H_2O); lit.[5b] 148−150 °C with slow heating, decomposition (bubbling) at 158 °C, then resolidification at 164 °C (H_2O)). Low-resolution ACE-mass spectra: EI, *m/e* 276.1 ([2M − H_2O]$^+$, 86%), 147.1 (M^+, 84%); CI, *m/e* 277.1 ([2M − H_2O]-H^+, 71%), 148.1 (MH^+, 100%). pK_a 4.8.

[4-^{13}C,2-^{15}N]1. A solution of 87 mg (0.6 mmol) of [*formyl*-^{13}C]-formylbenzeneboronic acid in 4 mL of H_2O was treated with 133 mg (1.89 mmol) of [^{15}N]$NH_2OH{\cdot}$HCl and was adjusted to pH 4 by the addition of 1 N NaOH, producing a copious yellow precipitate. The reaction mixture was stirred with heating (steam bath) for 1 h, and upon cooling to room temperature, the precipitate was collected by suction filtration and washed with cold water and then CH_2Cl_2 to afford 130 mg (90%) of [4-^{13}C,2-^{15}N]**1** as a white solid.

1-Methoxy-1*H*-2,3,1-benzoxazaborine (9). A solution of **1** (0.5 g, 3.4 mmol) in 1.5 mL of methanol was heated at reflux for a short time and then was allowed to cool to room temperature. The crystals that deposited were collected by suction filtration to afford 0.45 g (81%) of 1-methoxy-1*H*-2,3,1-benzoxazaborine: mp 90.5−92 °C. ^{1}H NMR ($CDCl_3$): δ 8.40 (s, 1H, CH), 8.05 (d, J = 7.5 Hz, 1H, PhH), 7.76−7.65 (m, 2H, PhH), 7.55 (d, 1H, PhH). Low-resolution ACE-mass spectra: EI, *m/e* 161.7 (M^+, 3%), 146.3 ($M^+ - CH_3$, 100%); CI, *m/e* 162.7 (MH^+, 32%), 147.1 ($MH^+ - CH_3$, 64%), 122.3 (100%). High-resolution EI-mass spectrum: *m/e* 161.064 923 ($C_8H_8B_1NO_2$ requires 161.064 809).

1,2-Dihydro-1-hydroxy-2,3,1-benzodiazaborine (2). The conditions in the literature procedure of Dewar[4c] were modified slightly (95%

(33) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168.

EtOH, reflux, 2 h) to give **2** in an 83% yield: mp 236−238 °C (H_2O) (lit.[4c,d] mp 243−243.5 °C (H_2O), referred to as the anhydride). Low-resolution ACE-mass spectra: EI, *m/e* 274.1 ($[2M - H_2O]^+$, 6%), 146.1 (M^+, 100%); CI, *m/e* 275.2 ($[2M - H_2O]H^+$, 2%), 147.1 (MH^+, 100%). pK_a 7.7.

From 1. A mixture of **1** (100 mg, 0.68 mmol) and NH_2NH_2 (47 μL of 97%, 1.5 mmol) in 10 mL of distilled H_2O was heated at reflux for 8 h, by which time **1** had been consumed (TLC analysis). The clear solution was allowed to cool to room temperature slowly, and the needle-like crystals of **2** (39 mg) that deposited were collected by filtration: mp 235−237 °C. The filtrate was concentrated and the residue obtained was purified by column chromatography using MeOH as eluent to afford an additional 15 mg of **2** as a white solid, for a combined yield of 54%. The ^{1}H NMR spectrum was identical to that of **2** obtained as described above.

From 6. A solution of **6** (100 mg, 0.33 mmol) in 5 mL of 95% ethanol was treated with NH_2NH_2 (22 μL of 97%, 0.7 mmol). The reaction mixture was heated at reflux for 12 h, by which time **6** had been consumed (TLC analysis). The reaction mixture was rotary evaporated to near dryness, and the residue was purified by radial chromatography using 1:3:16 MeOH/hexanes/CH_2Cl_2 as eluent to afford 31 mg (65%) of **2** as a light yellow solid: mp 228−232 °C. The ^{1}H NMR spectrum was identical to that of **2** obtained as described above.

[4-^{13}C,2,3-$^{15}N_2$]2. An ice-cooled, stirred solution of 100 mg (2.52 mmol) of NaOH in 0.5 mL of H_2O was treated sequentially with 167 mg (1.26 mmol) of $[^{15}N]NH_2NH_2 \cdot H_2SO_4$, 3 mL of EtOH, and 95 mg (0.629 mmol) of [*formyl*-^{13}C]formylbenzeneboronic acid. The reaction mixture was heated at reflux for 3 h and was then diluted by the addition of 4 mL of H_2O. The volume of solution was then reduced to *ca.* 1 mL, and upon cooling to room temperature a white solid was produced. This solid was collected by suction filtration and was washed successively with cold water and CH_2Cl_2 afforded 80 mg (86%) of [4-^{13}C,2,3-$^{15}N_2$]**2**.

1,2-Dihydro-1-hydroxy-2-methyl-2,3,1-benzodiazaborine (3). Dewar's procedure[4c] was used to prepare **3** in a 79% yield: mp 159−161 °C (aqueous EtOH) (lit.[4c] 154−156 °C with resolidification and remelting at 168 °C (aqueous EtOH)). pK_a 8.1. Compound **3** in $(CD_3)_2$SO solution was analyzed by COSY and NOE NMR, permitting the following spectral assignments to be made: 8.51 (s, 1H, OH), 8.27 (d, 1H, H8), 8.00 (s, 1H, H4), 7.74−7.68 (m, 2H, H5 and H6), 7.59 (t, 1H, H7), 3.52 (s, 3H, NMe). COSY interactions included H4/H5, H6/H7, and H7/H8; NOE ones included OH/H8 and H4/H5.

Bis-(8-B-4)-1,3,5-tris[2-[(dimethylhydrazono)methyl]phenyl]-boroxin (5) and (8-B-4)-[2-[(Dimethylhydrazono)methyl]phenyl]-dihydroxyboron (4). A solution of 2-formylbenzeneboronic acid (500 mg, 3.3 mmol) and 1,1-dimethylhydrazine (0.42 mL, 5.4 mmol) in 2.0 mL of 95% EtOH was treated with concentrated HCl (0.1 mL). The reaction mixture was stirred at room temperature for 5 h, and the white crystalline product that deposited was collected and was washed successively with water, 95% EtOH, Me_2CO, and then Et_2O to give 500 mg (88%) of **5**: mp 227−229 °C (Me_2CO). Low-resolution ACE-mass spectrum: EI, *m/e* 522.4 (40%, M^+), CI, *m/e* 522.4 (100%, M^+).

A stirred suspension of **5** in D_2O kept at 25 °C for 24 h produced (8-B-4)-[2-[(dimethylhydrazono)methyl]phenyl]dihydroxyboron (**4**) by ^{1}H NMR. A sample of **5** in H_2O heated at reflux for 24 h produced $B(OH)_3$ (^{11}B NMR) and PhCH═NNMe$_2$ (^{1}H NMR and TLC).

1,2-Dihydro-1-hydroxy-2-(4-methylbenzenesulfonyl)-2,3,1-benzodiazaborine (6). A dry (Abderhalden, P_2O_5, 110 °C, 3 d) sample of the *p*-toluenesulfonylhydrazone of 2-bromobenzaldehyde was subjected to conditions of Sharp and Skinner[16] to afford **6** in a 93% yield: mp 159−161 °C (lit.[34] 156−158 °C).

1,2-Dihydro-1,1-dihydroxy-3-methyl-1*H*-2,3,1-benzoxazaborine (7). A mixture of 2-formylbenzeneboronic acid (200 mg, 2.0 mmol) and MeNHOH·HCl (167 mg, 2.0 mmol) in 10 mL of 50% aqueous EtOH was adjusted to pH 7 by the addition of 1 N NaOH, and the reaction mixture was kept at room temperature for 12 h. The solvent was then removed by rotary evaporation at 50 °C to give an oil which was dissolved in 5 mL of MeOH and suction filtered to remove insolubles. Rotary evaporation gave a residue which was dissolved in 5 mL of water and rotary evaporated again to give a white solid. This solid was washed several times with $(CH_3)_2CO$ and dried in air to give 320 mg (99%) of **7**: mp 245−246 °C (lit.[18] 239 °C). The solid was dried in vacuo (Abderhalden, P_2O_5, 56 °C). pK_a 5.1. ^{1}H NMR (D_2O): δ 8.51 (s, 1H, H4), 7.76−7.45 (m, 4H, PhH), 3.91 (s, 3H, 3-Me); ^{13}C NMR (D_2O): δ 150.7 (C4), 138.5, 133.0, 132.8, 131.0, 130.0, 51.9 (3-Me). An aqueous solution of 50 mg of the dry solid in 2 mL of H_2O was lyophilized to furnish a white powdery solid: mp 241−243 °C. ^{1}H NMR ($(CD_3)_2$SO): δ 8.79 (s, 1H, H4), 8.04−7.35 (m, 4H, PhH). ^{1}H NMR ($CDCl_3$): δ 8.19 (s, 1H, H4), 7.97−7.33 (m, 4H, PhH).

2′,3′,5′-Tri-*O*-(methoxymethyl)cytidine. This compound was prepared from cytidine in a 68% yield according to a method[35] developed for the preparation of the corresponding tri-*O*-protected uridine: mp 140−140.5 °C. ^{1}H NMR ($(CD_3)_2$SO): δ 7.73 (d, J = 7.45 Hz, 1H, H6), 7.22 (m, exchanges with D_2O, 2H, NH_2), 5.88 (d, J = 4.05 Hz, 1H, H1′), 5.74 (d, J = 7.45 Hz, 1H, H5), 4.7−4.6 (m, 6H, three CH_2-OCH_3), 4.2−4.1 (m, 3H, H2′, H3′, and H4′), 3.70 (m, 2H, 5′-CH_2), 3.3 (s, 6H, two CH$_2$OCH_3), 3.28−3.21 (2s, 3H, CH$_2$OCH_3). ACE-mass spectrum: CI, *m/e* 376.2 (MH^+). Anal. Calcd for $C_{15}H_{25}N_3O_8$: C, 48.00; H, 6.71; N, 11.19. Found: C, 47.71; H, 6.80; N, 11.63.

Isotope Acquisition by 1 and 2 from $H_2{}^{18}O$. A solution of 5 mg of **1** or **2** in 0.5 mL of dry CH_3CN was treated with 0.1 mL of $H_2{}^{18}O$, and the clear solution was kept at 69−75 °C under argon for 12 h. The solution was allowed to cool to room temperature, and the volatiles were removed by slow evaporation under a gentle argon flow. The yellow crystalline solids obtained were analyzed by low-resolution ACE-MS. The spectra of material derived from **1** revealed little ^{18}O isotope incorporation, but that from **2** showed essentially complete incorporation: EI, *m/e* 148.1 ([^{18}O]**2** M^+, 100%); CI, *m/e* 149.1 ([^{18}O]-**2** MH^+, 100%). When another 5 mg sample of **1** was subjected to the above conditions for 36 h, low-resolution ACE-MS analysis of the derived material revealed *ca.* 50% isotope incorporation: EI, *m/e* 149 ([^{18}O]**1** M^+, 84%), 147.1 (**1** M^+, 81%); CI, *m/e* 150 ([^{18}O]**1** MH^+, 100%), 148.1 (**1** MH^+, 89%). A careful analysis of the low intensity (1%) $[2M - H_2O]^+$ peaks present in the 274−280 amu region revealed a similar degree of isotope incorporation in the anhydro dimer species, thereby eliminating the possibility that the single isotopic enrichment in **1** was due to the hydrolysis of a singly isotope-enriched anhydro dimer by propitious unenriched water during handling.

Acknowledgment. This work was supported by grant GM44819 from the National Institutes of Health. Mr. John M. Merrill, an Undergraduate NIGMS Summer Scholar in 1993, prepared some of the boron heterocycles for this study. Ms. Colleen Lawler, another Undergraduate researcher, prepared and characterized the 2′,3′,5′-tri-*O*-(methoxymethyl)cytidine. This article is dedicated to Dr. Nelson J. Leonard, California Institute of Technology, Pasadena, CA, on the occasion of his 80th birthday.

Supporting Information Available: Selected FTIR data for **1**−**3** and **5**, multisolvent UV data for **1**−**5**, full crystal data and data collection parameters, and positional and thermal parameters for **1** and **2** (3 pages). See any current masthead page for ordering and Internet access instructions.

JA963784I

(34) Müller, B. W. *Helv. Chem. Acta* **1978**, *61*, 325−327.

(35) Groziak, M. P.; Koohang, A. *J. Org. Chem.* **1992**, *57*, 940−944.