

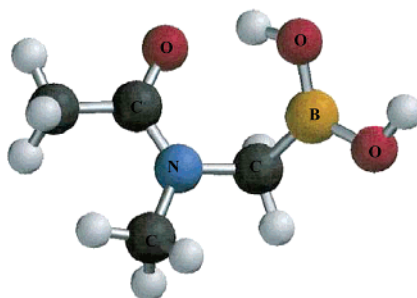
Synthesis and Structural Investigation of Internally Coordinated α -Amidoboronic Acids

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Six new *N*-acyl-boroGly derivatives, along with their *N*-acyl-boroSar analogues, have been synthesized by modification of conventional procedures. Structural characterization of these α -amidoboronic acids was accomplished by extensive use of ^{11}B and ^1H NMR spectroscopy. These compounds were prepared to determine the extent of intramolecular B–O dative bond formation within the context of a five-membered ($:\text{O}=\text{C}-\text{N}-\text{C}-\text{B}$) ring motif. It is shown that the formation of such dative bonds depends on the nature of the substituents at both the acyl carbon and the nitrogen atoms. Computational evidence from second-order Møller–Plesset perturbation theory is provided in support of these findings.

Introduction

Serine proteases constitute a large and functionally diverse class of proteolytic enzymes that have a common catalytic mechanism.^{1–4} They play an important role in the mediation of a number of pathological conditions and, as a consequence, they are targets for inhibition by therapeutic agents.^{5–8} Serine

proteases that are pharmacological targets include the following: elastase,⁵ involved in inflammation and emphysema; thrombin, a blood coagulation enzyme;⁶ and hepatitis C protease,⁷ which is required for viral replication.⁸

Peptide boronic acids, in which the $-\text{B}(\text{OH})_2$ functional group is connected to a peptide or peptidomimetic sequence, form a class of potent and specific inhibitors of serine proteases.^{2,3,9} For example, Bachovchin and co-workers^{10,11} have reported that aminoboronic acid dipeptides of the form L-Xaa-Proline-(2R)-boronic acid (L-Xaa-R-boroPro) are exceptionally potent inhibitors of serine protease dipeptidyl peptidase IV (DPP IV, CD26), an extracellular membrane-bound enzyme; L-Valyl-Proline-(2R)-boronic acid, in particular, has shown both hematopoietic stimulation¹² and antitumor activity.¹³ Interestingly, the dipeptidyl boronic acid derivative Bortezomib (Velcade) has been

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approved recently by the FDA as a proteasome inhibitor and it represents the only new treatment option for multiple myeloma that has become available in more than a decade.¹⁴ The inhibitory mechanism of boronic acid dipeptides utilizes the empty 2p orbital centered on the boron atom. This orbital is believed to interact with the catalytic serine to form a stable “ate” complex,^{15,16} which mimics the transition state for amide hydrolysis.^{17–21} However, dipeptides derived from proline boronic acid such as AlaboroPro and ProboroPro are known to lose their inhibitory activity in aqueous solution at neutral pH. This loss of activity has been shown to be due to the reversible formation of an intramolecular six-membered cyclic species (:N–C–C–N–C–B), analogous to a diketopiperazine, in which an amine nitrogen atom coordinates to the boron.^{22,23} Recently, we found that L-Xaa-boroSar dipeptides represent a new class of DPP IV inhibitors with IC₅₀ values in the submicromolar range.²⁴ Although the biological activity of these dipeptides is typically an order of magnitude lower than that for the analogous boroPro compounds, their tendency for intramolecular, pH-dependent cyclization is also lower, by 1 to 3 orders of magnitude (except for Xaa = Gly, Pro).²⁴ A plausible explanation for the reduced cyclization rate of these boroSar inhibitors is the formation of an intramolecular five-membered (:O=C–N–C–B) ring structure in which the carbonyl oxygen atom coordinates to the boron, effectively stabilizing the active trans conformer of the dipeptide. Such intramolecular five-membered-ring motifs with a B–O dative bond have been observed in esters derived from boronic acids,^{25–27} and postulated as intermediates in the stereoselective reduction of neighboring carbonyl groups.^{28–30} However, relatively little is known about the factors associated with the formation of these intramolecular (:O=C–N–C–B) rings, or their influence on the therapeutic efficacy of potential drugs. It should be mentioned that the presence of intramolecular B–N dative

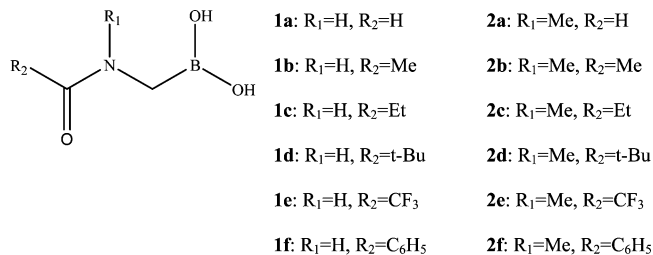


FIGURE 1. Compounds synthesized in this investigation.

bonds has been correlated to some unexpected physiological behavior.^{31–34}

In this article we study intramolecular B–O dative bond formation in some simple α -amidoboronic acids; such acids are also known to be inhibitors of serine proteases.⁴ In particular, we describe the synthesis of six new *N*-acyl-boroGly derivatives and their *N*-acyl-boroSar analogues, see Figure 1.

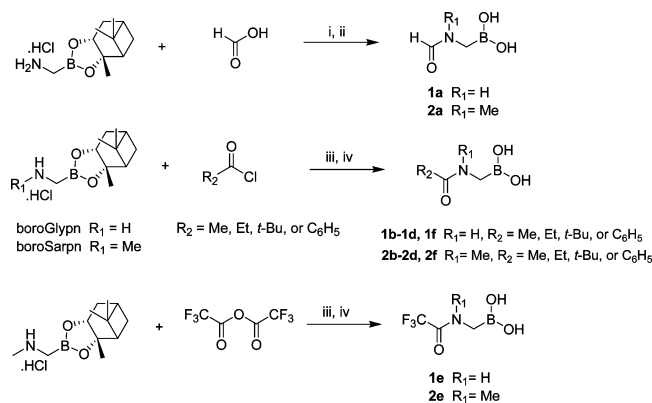
In basic aqueous media, the boron atom in these α -amido-boronic acids is expected to be tetracoordinated, as a result of borate ion formation,^{35–38} and this is indeed observed (vide infra). In acidic media, the boron atom in each of these compounds has the potential to be tetracoordinated via the formation of an intramolecular B–O dative bond in the context of a five-membered (:O=C–N–C–B) ring motif.¹¹ B and ¹H NMR spectroscopy, in conjunction with computational methodology, are used to investigate the extent to which the carbonyl oxygen atom in these α -amidoboronic acids coordinates to the boron. We specifically chose substituents at the acyl carbon atom that do not contain any nitrogen atoms to avoid the competitive formation of intramolecular ring structures involving a B–N dative bond.

Results and Discussion

Synthesis. The syntheses of the *N*-acyl-boroGly derivatives **1a–f** and their corresponding *N*-acyl-boroSar analogues **2a–f** were accomplished by adaptation of the methods described in Scheme 1; detailed procedures are given in the Supporting Information. The pinanediol ester of glycine boronic acid³⁹ was formylated with formic acid⁴⁰ and then deprotected using boron trichloride⁴¹ in methylene chloride at –78 °C to afford the desired compounds **1a** and **2a** as outlined in Scheme

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SCHEME 1^a

^a Reagents and conditions: (i) DIPEA, HATU, DMF; (ii) BCl_3 , CH_2Cl_2 , -78°C , 30% yield for two steps; (iii) DIPEA, CH_2Cl_2 ; (iv) BCl_3 , CH_2Cl_2 , -78°C , 30–50% yield for two steps.

TABLE 1. ^{11}B NMR Chemical Shifts, δ (in ppm), Relative to Boric Acid for Compounds **1a–f** and **2a–f** at High and Low Values of the pH, Recorded in 90% $\text{D}_2\text{O}/\text{H}_2\text{O}$ at 25°C

compd	δ (pH)	δ (pH)	compd	δ (pH)	δ (pH)
1a	+7.6 (1.1)	−17.1 (12.0)	2a	−3.4 (1.2)	−17.0 (12.0)
1b	−5.8 (1.0)	−16.9 (10.0)	2b	−10.8 (1.3)	−16.9 (12.0)
1c	−5.8 (1.5)	−16.7 (10.2)	2c	−10.8 (1.7)	−16.9 (12.0)
1d	−8. (1.2)	−16.9 (12.0)	2d	−11.4 (1.2)	−16.6 (12.0)
					−11.3 (12.0)
1e	+10.6 (1.4)	−17.2 (9.7)	2e	+8.9 (1.9)	−17.8 (12.0)
1f	−3.7 (1.6)	−16.8 (12.5)	2f	−10.1 (1.3)	−16.6 (12.4)

1. Acylation of the pinanediol ester of boroGly or boroSar with acetyl chloride, propanoyl chloride, pivaloyl chloride, or benzoyl chloride, followed by deprotection gave **1b–d**, **1f**, **2b–d**, and **2f** respectively as shown in Scheme 1. Reaction of the pinanediol ester of boroGly or boroSar and trifluoroacetic anhydride with subsequent treatment with boron trichloride gave **1e** and **2e** as depicted in Scheme 1. It should be pointed out that the compounds containing a trifluoroacyl amide moiety are unstable at high pH,^{42–44} because the electron-withdrawing CF_3 group facilitates basic hydrolysis.

Spectroscopic and Computational Results. The ^{11}B and ^1H NMR chemical shifts for the boronic acid derivatives synthesized in this study are listed in Tables 1 and 2, respectively, at both high and low values of the pH.

It is well established that the ^{11}B chemical shifts for tetracoordinated boron species appear at several tens of ppm upfield compared to the corresponding tricoordinated species,^{25,45–48} e.g., for *n*-butylboronic acid at pH values from 1.0 to 7.3, where the boron atom is expected to be entirely tricoordinated, the ^{11}B chemical shift is +13.8 ppm relative to boric acid, whereas at pH 13.4, where the boron is expected to be tetracoordinated as a result of borate ion formation, the shift is −14.7 ppm.²⁴ As can be seen from Table 1, the ^{11}B shifts at

high values of pH (9.7–12.5) for all the boronic acids we synthesized are quite similar, $\delta_{\text{AVE}} = -16.9 \pm 0.4$ ppm, a reflection of their common tetracoordinated borate ion structure in basic media.^{35–38} In contrast, at low values of pH (1.0–1.9), the ^{11}B chemical shifts range from −11.4 to +10.6 ppm, suggesting a variety of different boron environments in this series of related acids.

To understand the structural origin of the different ^{11}B shifts for these related compounds in acidic media, we examined their potential energy surfaces (PESs) using computational methods. Our experience with a variety of boronic acid derivatives,^{49–53} in conjunction with AM1 and PM3^{54–57} potential energy surface scans of **1a–f** and **2a–f**, indicate that the most important conformations of the simple α -amidoboronic acids discussed in this article are those illustrated in Figure 2 for *N*-acetylborosarcosine **2b**; the trans and cis designations refer to rotation (ω) about the $\text{N}_3\text{--C}_4$ bond.

A trans conformation for these compounds is expected to be favored at low pH,⁵⁸ because the potential exists for the carbonyl oxygen atom to interact with the boronic acid group. For example, in the trans-OB conformation the boron and carbonyl oxygen atoms are in relatively close proximity. If a B–O dative bond forms, the increased coordination of the boron atom in the resulting five-membered ring structure will be observed in the ^{11}B spectrum.^{46,47,59} For some of the α -amidoboronic acids in this study, however, computations show that a trans-OB form can be a local minimum on the PES, even though the B–O distance is quite long (>2.4 Å) (vide infra); experimental B–O dative bond lengths in boronate esters are much shorter, 1.56–1.64 Å.^{25–27} In a trans-OB conformer with a long B–O distance, it seems more appropriate to describe the boron–oxygen interaction as an electrostatic attraction between the positively charged boron and the negatively charged oxygen atoms, rather than as a B–O dative bond. In the trans-OH conformation an $\text{H}\cdots\text{O}$ hydrogen bond is part of a seven-membered ring and the boron atom is tricoordinated. This type of motif for a boronic acid has been observed recently by Zhao et al.⁶⁰ in the solid phase and has been predicted by Bhat et al.⁵¹ in computational studies performed in the gas phase; its role on the inhibitory potency of boronic acid dipeptides is not well understood.

We consider first the parent compound, *N*-formylglycine boronic acid **1a** ($R_1 = R_2 = \text{H}$), for which the ^{11}B chemical shift relative to boric acid is +7.6 ppm at pH 1.1 compared to −17.1 ppm at pH 12.0, see Table 1; ^1H 300 MHz and ^{11}B 300

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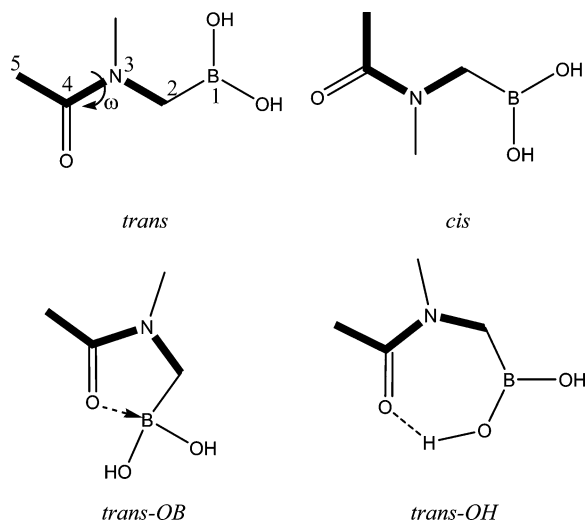
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TABLE 2. ^1H NMR Chemical Shifts, δ (in ppm), for Compounds **1a–f** and **2a–f** at High and Low Values of the pH Recorded in 90% $\text{D}_2\text{O}/10\%$ H_2O at 25 $^\circ\text{C}$

compd	$\alpha\text{-H}$		compd	$\alpha\text{-H}$		N-Me	
	δ (pH)	δ (pH)		δ (pH)	δ (pH)	δ (pH)	δ (pH)
1a	2.66(s) (1.1)	2.20(s) (12.1)	2a	2.41(s) (1.2)	2.41(s) (12.1) 2.38(s) (12.1)	3.11(s) (1.2)	3.01(s) (12.1) 2.87(s) (12.1)
1b	2.36(s) (1.0)	2.14(s) (10.7)	2b	2.39(s) (1.3)	2.80(s) (12.0)	3.14(s) (1.3)	2.91(s) (11.8) 3.07(s) (11.8)
1c	2.34(s) (1.5)	2.14(s) (10.2)	2c	2.41(s) (1.6)	2.39(s) (10.2)	3.13(s) (1.6)	3.16(s) (10.2)
1d	2.31(s) (1.2)	2.13(s) (12.0)	2d	2.49(s) (1.2)	2.45(s) (12.0)	3.31(s) (1.2)	3.30(s) (12.0)
1e	2.60(s) (1.4)	2.31(s) (9.7)	2e	2.70(s) (1.9) 2.63(s) (1.9)	1.97(s) (12.0) 2.28(s) (12.0)	3.23(s) (1.9) 3.04(s) (1.9)	3.20(s) (12.2) 2.68(s) (12.2)
1f	2.60(s) (1.6)	2.38(s) (12.5)	2f	2.65(s) (1.3)	2.48(s) (12.4) 2.70(s) (12.4)	2.90(s) (1.9) 3.27(s) (1.3)	2.60(s) (12.2) 3.00(s) (12.4) 3.14(s) (12.4)

**FIGURE 2.** Conformations of the $:\text{O}=\text{C}-\text{N}-\text{C}-\text{B}$ backbone of *N*-acetylborosarcosine, **2b**.

MHz spectra of **1a** are shown in Figures 1S–3S of the Supporting Information. The fact that this ^{11}B shift is positive at low pH clearly suggests that the boron atom in **1a** is predominantly tricoordinated in acidic media. To further corroborate this conclusion, we optimized the geometry of a *trans*-OB conformer of **1a** in vacuo and in aqueous media using second-order Møller–Plesset (MP2) perturbation theory⁶¹ at the MP2/6-311++G** computational level. The GAUSSIAN 03 suite of programs⁶² was employed for the calculations in this study, and self-consistent reaction field (SCRF) methods with an IEF polarizable continuum model (PCM)^{63–66} were used for the optimizations in aqueous media. Although the optimizations

were initiated with B–O distances consistent with the presence of a dative bond,^{25–27} the resulting B–O distances, 2.56 and 2.71 Å in the gas and aqueous phase, respectively, are quite long, and the boronic acid moiety is essentially planar (sp^2). Thus, we find no evidence for a dative-bonded conformer of **1a**.

Since no data are available concerning the relative stabilities of various conformers of **1a** we also optimized *cis*, *trans*, and *trans*-OH forms, see Figure 2, at the same computational level. The relative energies of the resulting structures, both in vacuo and in aqueous media, along with a few selected geometrical parameters, are listed in Table 3.

Interestingly, the hydrogen-bonded seven-membered-ring *trans*-OH conformer of **1a** has the lowest energy, both in vacuo and in aqueous media.^{51,60} The calculated $\text{O}\cdots\text{H}(\text{O})$ bond lengths, 1.84 and 1.75 Å, respectively, and the corresponding $\text{O}\cdots\text{H}-\text{O}$ bond angles, 154.1° and 158.6° , in this conformer are consistent with a relatively strong hydrogen bond.⁶⁷ Both the *trans* and *trans*-OB conformers are ~ 3.4 kcal/mol higher in energy than the *trans*-OH conformer in the gas phase, and ~ 1.5 kcal/mol higher in solution. Thus, not only is there no B–O dative bond in the *trans*-OB conformer, it is not even the global minimum on the PES.

Turning to the other boronic acids synthesized in this study, we note that incorporating a methyl group in **1a** at either the acyl carbon, to give *N*-acetylglycine boronic acid **1b**, or the nitrogen, to give *N*-formylborosarcosine **2a**, results in an upfield shift relative to **1a** in the ^{11}B signal at low pH—the resulting values of δ are negative, -5.8 and -3.4 ppm, respectively, see Table 1. Indeed, incorporating a methyl group at both the acyl carbon atom and the nitrogen atom to give *N*-acetylborosarcosine **2b** leads to a further upfield shift—the value of δ is -10.8 ppm; ^{11}B 300 MHz NMR spectra of **2b** are shown in Figures 4S and 5S of the Supporting Information. Lengthening the chain at the carbon in **1b** and **2b** from methyl to ethyl groups, giving **1c** and **2c**, respectively, has virtually no effect on the chemical shift, although increasing the bulky nature of the group at the carbon in **1b** and **2b** from Me to *t*-Bu, giving **1d** and **2d**, respectively, does lead to a small additional upfield shift.

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TABLE 3. MP2(FULL)/6-311++G**//MP2(FULL)/6-311++G** Relative Energies, E_{rel} (kcal/mol), and Selected Structural Parameters^a

compd	compd/conf	vacuo				aqueous media (SCRF)			
		E_{rel}	B–O	τ_{CNCX}	τ_{CNCB}	E_{rel}	B–O	τ_{CNCX}	τ_{CNCB}
1a	cis	+6.52	4.804	0.0	180.0	+3.82	4.800	0.0	176.2 ^b
	trans	+3.34	4.360	180.0	180.0	+1.60	4.384	179.9	179.8
	trans-OB	+3.50	2.561	178.3	41.4	+1.45	2.707	−176.9	47.6
	trans-OH	+0.00	3.164	172.4	64.5	+0.00	3.162	173.2	63.6
1b	cis ^c	+9.24	4.267	−19.6	−66.5	+6.32	4.368	−10.9	−73.1
	trans-OB	+3.26	2.417	179.5	37.4	+0.00	1.661	179.3	4.0
	trans-OH	+0.00	3.133	172.1	66.6	+1.10	3.132	172.8	65.7
2a	cis ^c	+6.19	4.696	−3.6	120.9	+3.87	4.598	1.6	110.1
	trans-OB	+2.81	2.410	177.5	36.3	+0.00	1.675	179.2	3.4
	trans-OH	+0.00	3.150	175.2	70.9	+1.18	3.148	175.2	69.7
2b	cis ^c	+6.03	4.265	−19.4	−75.7	+6.66	4.288	−16.6	−78.5
	trans-OB	+1.29	1.733	177.5	14.8	+0.00	1.640	178.6	4.5
	trans-OH	+0.00	3.099	171.9	75.0	+4.07	3.097	172.4	73.7
1e	cis ^c	+8.19	4.343	−16.6	−74.1	+5.41	4.455	−8.2	−81.4
	trans-OB	+2.50	2.656	−179.1	45.9	+0.31	2.820	179.6	53.0
	trans-OH	+0.00	3.182	174.7	67.1	+0.00	3.193	175.1	67.3
2e	cis ^c	+3.77	4.320	−16.6	−76.6	+1.05	4.389	−12.9	−85.7
	trans-OB	+1.99	2.473	178.9	44.7	+0.00	2.600	178.5	50.0
	trans-OH	+0.00	3.139	174.1	76.2	+0.11	3.146	173.5	75.5

^a The B–O distance is in Å, and the τ_{CNCX} (X = H, C) and τ_{CNCB} torsional angles are in deg.) ^b Frequency analyses at several computational levels using density functional theory suggest that this conformer is a first-order transition state. ^c No trans acyclic form could be found on the PES.

Substitution of a phenyl group at the acyl carbon to give **1f** and **2f** also results in a negative ¹¹B chemical shift. These negative ¹¹B shifts at low pH certainly suggest greater tetra-coordination of the boron atoms in compounds **1b–d**, **1f**, **2a–d**, and **2f** compared to that found in **1a**.

To determine whether calculations also support the presence of a B–O dative bond in the amidoboronic acids discussed above, we optimized the geometry of several conformers of **1b**, **2a**, and **2b** at the MP2/6-311++G** computational level; the relative energies are listed in Table 3. When the optimization of **2b** is initiated from a *trans*-OB geometry, the resulting B–O distances, 1.73 and 1.64 Å in vacuo and in aqueous media, respectively, are much shorter than the corresponding distances in **1a**, and the local environment about the boron atom has significant tetrahedral character as measured by the Höpft index;⁶⁸ the values of THC_{DA} are 52.1% and 65.7% in vacuo and in aqueous media, respectively. Furthermore, the calculated NPA charge distribution in this conformer of **2b** shows a transfer of electron density from the carbonyl oxygen atom to the boron atom, and NBO analyses (HF level) clearly identify a B–O dative bonding orbital. Although in vacuo the *trans*-OB form of **2b** is 2.8 kcal/mol higher in energy than the *trans*-OH form, in aqueous media the *trans*-OB form is 4.1 kcal/mol lower in energy than the *trans*-OH form. Thus, in aqueous media the lowest energy form of **2b** has an intramolecular B–O dative bond, consistent with the observed upfield ¹¹B chemical shifts of **2b** relative to that of **1a**.

In vacuo the calculated B–O distance for the *trans*-OB forms of **1b** and **2a** are quite long (>2.4 Å) and the *trans*-OH form is lower in energy, see Table 3. In contrast, when the optimizations are performed in aqueous media the resulting B–O distances are much shorter (<1.7 Å), consistent with the presence of a B–O dative bond.^{25,27} Furthermore, the *trans*-OB form is lower in energy than the *trans*-OH form. It is interesting that in aqueous solution the length of the B–O dative bond in both **1b** and **2a** is slightly longer than it is in **2b**, which correlates well with the lower upfield ¹¹B chemical shifts of **1b** and **2a** compared to that of **2b**, see Table 1. Thus, in aqueous media

these calculated results provide additional support for our experimental findings.

To assess the effect of introducing an electron-withdrawing group on the formyl carbon atom, we synthesized trifluoroacetyl glycine boronic acid, **1e**, and its sarcosine analogue, **2e**, in which the appropriate hydrogen atom in **1a** and **2a** was replaced by a trifluoromethyl group; the ¹H 300 MHz spectrum of **2e** is shown in Figure 6S of the Supporting Information. At low values of the pH, the observed ¹¹B shifts are positive, +10.6 and +8.9 ppm, respectively, see Table 1. This suggests that there is no intramolecular B–O dative bond present in either of these compounds. We also optimized the geometries of several conformers of **1e** and **2e** at the MP2/6-311++G** computational level. The *trans*-OB forms have very long B–O distances, 2.66 Å in vacuo and 2.82 Å in aqueous solution for **1e**, and 2.47 and 2.60 Å for **2e**. Furthermore, in aqueous media the *trans*-OB conformer of **1e** not the global minimum on the MP2 PES and for **2e** the *trans*-OB and *trans*-OH conformers are very close in energy. Thus, these computational results are in accord with our experimental observations.

Finally, to illustrate the complex acid–base equilibria involved with an α -amidoboronic acid containing an intramolecular B–O dative bond, a set of 1D 300 MHz ¹H NMR spectra of **2b** in 90% H₂O/10% D₂O at 25 °C and at different values of the pH were recorded, see Figure 3A; the corresponding 2D ¹H/¹H NOESY spectrum is shown in Figure 3B. At low values of the pH, 2D ¹H/¹H COSY and ¹H/¹H NOESY spectra indicate that the species labeled **A** in Figure 3A has a *trans* C₂–N₃–C₄–C₅ linkage. Although it is not possible to unambiguously identify the specific *trans* conformer(s) involved from these experiments, the large upfield ¹¹B chemical shift observed for **2b** at low pH, in conjunction with the results of our MP2 optimizations, strongly suggests that the *trans*-OB conformer is present. Of course, as the pH increases above ~9, boronate ion formation becomes a competitive process. There is an upfield shift in the signal from the N–CH₃ protons of **A**, a result of the rapid exchange between **A** and a *trans* form, **B**, of the associated boronate ion, see Scheme 2. Furthermore, a *cis* form of this borate ion, **C**, is also evident in Figure 3A; **C** is in slow

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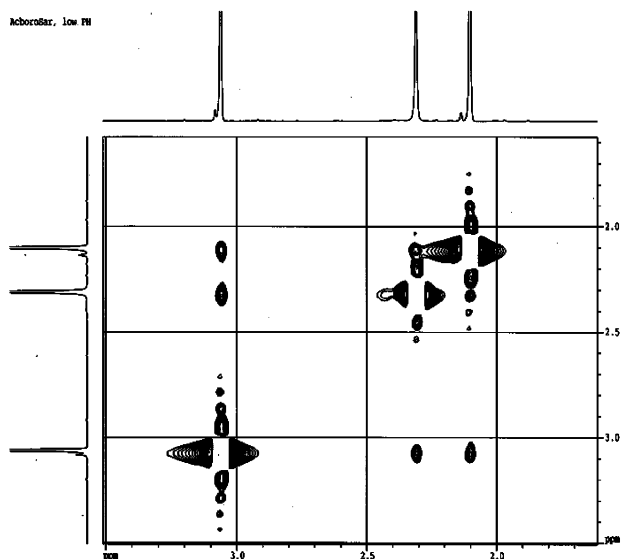
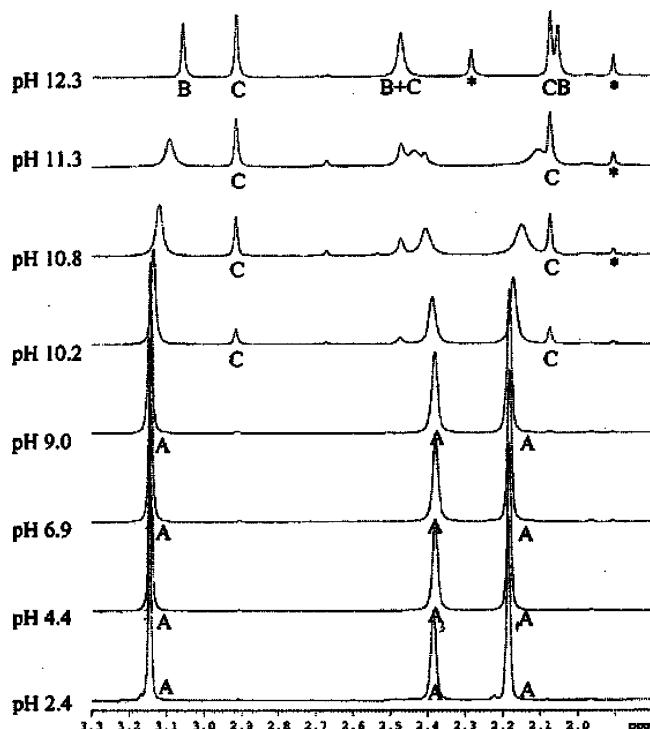
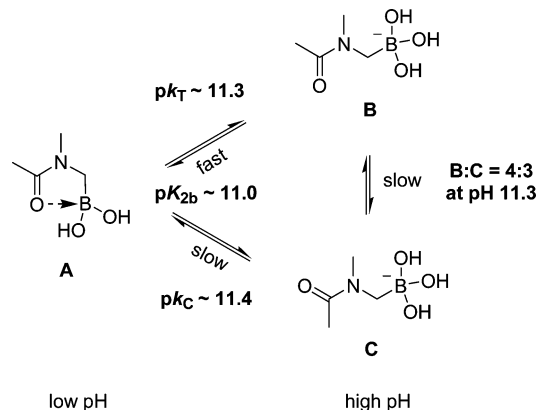


FIGURE 3. (A) Stack plot of 1D ^1H 300 MHz NMR spectra of **2b** in 90% H_2O /10% D_2O at 25 $^\circ\text{C}$ and various values of the pH. Forms **A**, **B**, and **C** are described in the text; decomposition products are indicated with an asterisk. (B) 2D $^1\text{H}/^1\text{H}$ NOESY spectrum of **2b** at pH ~ 2 . The NOE peaks between H-b and H-c indicate a trans conformer.

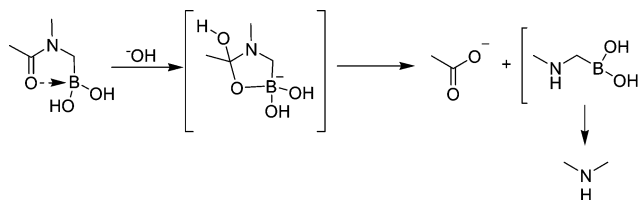
exchange with **A**, and the ratio of the species **A** to **C** decreases as the pH increases; the ratio of **B**:**C** is 4:3 at pH 11.3.

The microscopic equilibrium constant, pK_T , was obtained by measuring the *N*-methyl chemical shifts in the interval between **B** and **A**. At pH 11.3 the *N*-methyl shifts were at their titration midpoint, which leads to a value of 11.3 for pK_T . Knowing that forms **B** and **C** are in the ratio of 4:3 at that pH leads to a microscopic equilibrium constant, pK_C , of 11.4, which is larger than pK_T by log 0.1. The sum of microscopic equilibrium constants k_T and k_C leads to a macroscopic constant, K_{2b} , for which pK_{2b} is 11.0.

SCHEME 2. Summary of the Microscopic (pK_T and pK_C) and Macroscopic (pK_{2b}) Acid–Base Equilibrium Constants and pH-Dependent Structural Changes Involved with **2b**



SCHEME 3. Proposed Mechanism for Alkali Hydrolysis of **2b**



Interestingly, **2b** was readily hydrolyzed and deboronated into acetic acid and dimethylamine at high pH, as confirmed by ^1H NMR (data not shown). On the basis of the rate of the disappearance of the *N*-methyl peaks and the appearance of acyl methyl peaks in the ^1H NMR spectra, the half-life of decomposition is ~ 48 h at room temperature. The instability of **2b** at high pH suggests that the dative-bonded *trans*-OB conformer plays a catalytic role in enhancing the rate of amide hydrolysis via the mechanism shown in Scheme 3.

Conclusions

A collection of simple *N*-acyl-boroGly derivatives and their boroSar analogues have been synthesized, characterized by ^{11}B and ^1H NMR spectroscopy, and studied computationally with second-order Møller–Plesset perturbation theory. Each of these α -amidoboronic acids is amenable to the formation of an intramolecular B–O dative bond in the context of a five-membered ($:\text{O}=\text{C}-\text{N}-\text{C}-\text{B}$) ring motif. The ^{11}B chemical shifts observed for the compounds in this study at high values of pH, $\delta_{\text{AVE}} = -16.9 \pm 0.4$ ppm, reflect their common tetracoordinated borate ion structure in basic media,^{35–38} whereas at low values of pH, the corresponding chemical shifts range from -11.4 to $+10.6$ ppm, suggesting a variety of possible boron environments in acidic media. For the parent compound, *N*-formylglycine boronic acid **1a**, and the trifluoro derivatives **1e** and **2e**, positive ^{11}B chemical shifts indicate that there are no B–O dative-bonded conformers present in acidic media. Calculations at the MP2(FULL)/6-311++G** computational level in vacuo and in aqueous media also find no evidence for a dative-bonded conformer on the PES. However, substitution of electron donating groups on the acyl carbon and/or nitrogen atoms leads to compounds with upfield ^{11}B shifts in acidic media, indicating tetracoordination of the boron atom as a result of intramolecular B–O dative bond formation. Calculations in aqueous media find similar results.

In vacuo, our MP2(FULL)/6-311++G** calculations consistently find that the seven-membered hydrogen-bonded ring structure, *trans*-OH, is the lowest energy conformer of the α -amidoboronic acids in this study. In aqueous media, however, when a B–O dative bond forms, it is the five-membered *trans*-OB conformer that is often lowest in energy, although the SCRF energy differences between the *trans*-OB and *trans*-OH conformers in these cases is usually quite small. The competition between *trans*-OH and *trans*-OB forms and its influence on the inhibitory potency of boronic acid dipeptides need to be further addressed.

Experimental Section

N-Formyl-boroGly 1a. To a stirred solution of (+)-pinanediol-1-(*N*-methylamino)-1-methyl boronate hydrochloride (H-boroGly-pn·HCl) (245 mg, 1 mmol) and formic acid (60 mg, 96%, 1.2 mmol) in anhydrous DMF (3 mL) was added HATU (400 mg, 1.05 mmol) at 0 °C under argon atmosphere. To this solution was added *N,N*-diisopropylethylamine (DIPEA, 0.4 mL, 99.5%, 2.3 mmol) and the mixture was stirred overnight. DMF was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 mL), washed sequentially with KHSO₄ (0.1 M, 3 × 15 mL), NaHCO₃ (5%, 3 × 10 mL), and brine (3 × 10 mL), and dried (MgSO₄). Removal of solvent afforded the crude HCO-boroGly-pn, which was used without further purification. To the crude HCO-boroGly-pn dissolved in anhydrous dichloromethane (5 mL), cooled to –78 °C, was added a solution of boron trichloride (2 mL, 1.0 M) in dichloromethane (2 mL) and the mixture was then stirred for 1 h. The reaction mixture was evaporated to dryness under reduced pressure and coevaporated with anhydrous methanol (2 × 5 mL). The residue was then partitioned between water (20 mL) and ether (30 mL) and the product was isolated as a white powder (yield: 25%), using HPLC from the aqueous layer after lyophilization. ¹H NMR (D₂O, pH 1.02) δ 2.66 (2H, s, –NCH₂B–), 8.05 (1H, s, HCO–); ¹³C NMR (D₂O) δ (u) 29.9, 167.7; ¹¹B NMR (D₂O, pH 1.06) δ 10.4; LC-MS (ESI+) for C₂H₆BNO₃ *m/z* (rel intensity) 256.0 ([3 × (M – H₂O) + H]⁺, 100), 171.1 ([2 × (M – H₂O) + H]⁺, 99), 86.3 ([M – H₂O + H]⁺, 84); *tr* = 3.4 min.

General Procedure for the Preparation of 1b–1d and 1f. To an ice-cold solution of H-boroGly-pn·HCl (245 mg, 1 mmol) and RCOCl (R = CH₃, C₂H₅, CMe₃ or C₆H₅) in anhydrous dichloromethane (10 mL) was added *N,N*-diisopropylethylamine (0.4 mL, 99.5%, 2.3 mmol) under argon and the solution was stirred for 3 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with KHSO₄ (0.1 M, 3 × 15 mL), NaHCO₃ (5%, 3 × 10 mL), and brine (3 × 10 mL), dried (MgSO₄), and concentrated to dryness to afford the crude RCO-boroGly-pn. The crude product was dissolved in anhydrous dichloromethane (5 mL), the solution was cooled to –78 °C, and boron trichloride in dichloromethane (5 mL, 5 mmol) was added. The reaction mixture was stirred for 1 h. It was then evaporated to dryness and coevaporated by adding anhydrous methanol (2 × 5 mL). The residue was partitioned between water (20 mL) and ether (30 mL). The product RCO-boroGly-OH was isolated from the aqueous layer as a white powder after lyophilization with HPLC.

N-Acetyl-boroGly 1b. ¹H NMR (D₂O) δ 2.10 (3H, s, CH₃CO–), 2.36 (2H, s, –NCH₂B–); ¹³C NMR (D₂O) δ (u) 19.1, 37.5, 179.7; ¹¹B NMR (D₂O, pH 0.99) δ –5.6; LC-MS (ESI+) for C₃H₈BNO₃ *m/z* (rel intensity) 298.1 ([3 × (M – H₂O) + H]⁺, 100), 199.2 ([2 × (M – H₂O) + H]⁺, 79), 100.4 ([M – H₂O + H]⁺, 51); *tr* = 4.2 min; HRMS calcd for C₃H₇BNO₂ [MH⁺ – H₂O] 100.0570, found 100.0571.

N-Propionyl-boroGly 1c. ¹H NMR (D₂O, pH 1.49) δ 1.14 (3H, t, *J* = 7.6 Hz, CH₃CH₂–), 2.34 (2H, s, –NCH₂B–), 2.41 (2H, q, *J* = 7.6 Hz, CH₃CH₂–); ¹³C NMR (D₂O) δ (u) 11.1, 26.8, 36.7, 182.9; ¹¹B NMR (D₂O, pH 1.49) δ –5.8; LC-MS (ESI+) for C₄H₁₀BNO₃ *m/z* (rel intensity) 340.2 ([3 × (M – H₂O) + H]⁺,

50), 227.1 ([2 × (M – H₂O) + H]⁺, 82), 114.3 ([M – H₂O + H]⁺, 100); *tr* = 4.8 min; HRMS calcd for C₄H₉BNO₂ [MH⁺ – H₂O] 114.0726, found 114.0730.

N-(2,2-Dimethyl-propionyl)-boroGly 1d. ¹H NMR (D₂O) δ 1.21 (9H, s, –CMe₃), 2.31 (2H, s, –NCH₂B–); ¹³C NMR (D₂O) δ (u) 28.3, 37.5, 38.0, 188.0; ¹¹B NMR (D₂O, pH 1.76) δ –7.9; LC-MS (ESI+) for C₆H₁₄BNO₃ *m/z* (rel intensity) 424.3 ([3 × (M – H₂O) + H]⁺, 2), 283.2 ([2 × (M – H₂O) + H]⁺, 31), 142.2 ([M – H₂O + H]⁺, 100); *tr* = 9.6 min; HRMS calcd for C₆H₁₃BNO₂ [MH⁺ – H₂O] 142.1039, found 142.1044.

N-Benzoyl-boroGly 1f. ¹H NMR (D₂O) δ 2.60 (2H, s, –NCH₂B–), 7.64 (2H, dd, *J* = 7.3, 7.6 Hz, Ar–H), 7.71 (1H, d, *J* = 7.3 Hz, Ar–H), 7.88 (2H, d, *J* = 7.6 Hz, Ar–H); ¹³C NMR (D₂O) δ (u) 36.7, 130.0, 130.5, 131.4, 136.4, 174.6; ¹¹B NMR (D₂O, pH 1.58) δ –3.7; LC-MS (ESI+) for C₈H₁₀BNO₃ *m/z* (rel intensity) 323.1 ([2 × (M – H₂O) + H]⁺, 16), 162.1 ([M – H₂O + H]⁺, 100); *tr* = 12.9 min; HRMS calcd for C₈H₉BNO₂ [MH⁺ – H₂O] 162.0726, found 162.0726.

N-2,2,2-Trifluoroacetyl-boroGly 1e. To an ice cold solution of H-boroGly-pn·HCl (245 mg, 1 mmol) and trifluoroacetic anhydride (210 mg, 99+%, 1 mmol) in anhydrous dichloromethane (10 mL) was added DIPEA (0.4 mL, 99.5%, 2.3 mmol) under argon and then the solution was stirred for 3 h. The reaction mixture was concentrated to a small volume (2–3 mL) and the product TFAC-boroGly-pn was isolated by column chromatography on silica gel with ethyl acetate–methanol (5:1) as eluant.

The above product was dissolved in anhydrous dichloromethane (5 mL) then cooled to –78 °C, and BCl₃ in dichloromethane (2 mL, 1.0 M) was added; the reaction mixture was stirred for 1 h. It was then evaporated to dryness under reduced pressure and coevaporated with anhydrous methanol (2 × 5 mL), and the residue was partitioned between water (20 mL) and ether (30 mL). The product TFAC-boroGly-OH was isolated as a white powder from the aqueous layer with HPLC (yield: 32%). ¹H NMR (D₂O) δ 2.60 (2H, s, –NCH₂B–); ¹¹B NMR (D₂O, pH 1.44) δ 10.6; LC-MS (ESI+) for C₃H₅F₃BNO₃ *m/z* (rel intensity) 307.0 ([2 × (M – H₂O) + H]⁺, 18), 154.0 ([M – H₂O + H]⁺, 100); *tr* = 7.0 min.

N-Formyl-boroSar 2a. This compound was prepared following the same procedure as described for **1a** but with H-boroSar-pn·HCl as the starting material. ¹H NMR (D₂O) δ 2.41 (2H, s, –NCH₂B–), 3.11 (3H, s, –NCH₃), 7.92 (1H, s, HCO–); ¹³C NMR (D₂O) δ (u) 38.8, 42.9, 167.8; ¹¹B NMR (D₂O, pH 1.17) δ –3.4; LC-MS (ESI+) for C₃H₈BNO₃ *m/z* (rel intensity) 298.1 ([3 × (M – H₂O) + H]⁺, 53), 199.1 ([2 × (M – H₂O) + H]⁺, 100), 100.3 ([M – H₂O + H]⁺, 32); *tr* = 4.4 min; HRMS calcd for C₃H₉BON₃ [MH⁺] 118.0675, found 118.0672.

General Procedures for the Preparation of 2b–d and 2f. These compounds were prepared following the same procedure that was used for **1b–d** and **1f** but with H-boroSar-pn·HCl as the starting material.

N-Acetyl-boroSar 2b. ¹H NMR (D₂O) δ 2.18 (3H, s, CH₃CO–), 2.39 (2H, s, –NCH₂B–), 3.14 (3H, s, –NCH₃); ¹³C NMR (D₂O) δ (u) 17.1, 38.7, 47.7, 177.6; ¹¹B NMR (D₂O, pH 1.30) δ –10.80; LC-MS (ESI+) for C₄H₁₀BNO₃ *m/z* (rel intensity) 340.1 ([3 × (M – H₂O) + H]⁺, 100), 227.1 ([2 × (M – H₂O) + H]⁺, 98), 114.3 ([M – H₂O + H]⁺, 98); *tr* = 4.8 min; HRMS calcd for C₄H₉BNO₂ [MH⁺ – H₂O] 114.0726, found 114.0731.

N-Propionyl-boroSar 2c. ¹H NMR (D₂O) δ 1.14 (3H, t, *J* = 7.6 Hz, CH₃CH₂–), 2.41 (2H, s, –NCH₂B–), 2.51 (2H, q, *J* = 7.6 Hz, CH₃CH₂–), 3.13 (3H, s, –NCH₃); ¹³C NMR (D₂O) δ (u) 10.8, 24.0, 38.2, 48.0, 180.8; ¹¹B NMR (D₂O, pH 1.26) δ –10.8; LC-MS (ESI+) for C₅H₁₂BNO₃ *m/z* (rel intensity) 382.2 ([3 × (M – H₂O) + H]⁺, 48), 255.1 ([2 × (M – H₂O) + H]⁺, 74), 128.2 ([M – H₂O + H]⁺, 100); *tr* = 5.9 min; HRMS calcd for C₅H₁₁BNO₂ [MH⁺ – H₂O] 128.0883, found 128.0884.

N-(2,2-Dimethylpropionyl)-boroSar 2d. ¹H NMR (D₂O) δ 1.31 (9H, s, (CH₃)₃C–), 2.49 (2H, s, –NCH₂B–), 3.31 (3H, s, –NCH₃); ¹³C NMR (D₂O) δ (u) 28.9, 37.9, 40.3, 52.6, 184.6; ¹¹B NMR (D₂O, pH 1.22) δ –11.4; LC-MS (ESI+) for C₇H₁₆BNO₃ *m/z* (rel

intensity) 466.3 ($[3 \times (M - H_2O) + H]^+$, 5), 311.2 ($[2 \times (M - H_2O) + H]^+$, 24), 156.1 ($[M - H_2O + H]^+$, 100); tr = 12.3 min; HRMS calcd for $C_7H_{15}BNO_2$ [$MH^+ - H_2O$] 156.1196, found 156.1201.

N-Benzoyl-boroSar 2f. 1H NMR (D_2O) δ 2.65 (2H, s, $-NCH_2B-$), 3.27 (3H, s, $-NCH_3$), 7.64–7.70 (5H, m, Ar-H); ^{13}C NMR (D_2O) δ (u) 40.5, 49.2, 129.1, 131.0, 131.5, 135.4, 175.3; ^{11}B NMR (D_2O , pH 1.34) δ -10.0; LC-MS (ESI+) for $C_9H_{12}BNO_3$ m/z (rel intensity) 351.1 ($[2 \times (M - H_2O) + H]^+$, 7), 216.0 ($[M + Na]^+$, 4), 176.0 ($[M - H_2O + H]^+$, 100); tr = 12.8 min; HRMS calcd for $C_9H_{11}BNO_2$ [$MH^+ - H_2O$] 176.0883, found 176.0889.

N-2,2,2-Trifluoroacetyl-boroSar 2e. This compound was prepared by using the same procedure that was used for **1e** but with H-boroSar-pn·HCl. 1H NMR (D_2O) δ two isomers, 2.63 (2H, s, $-NCH_2B-$), 2.90 (3H, s, $-NCH_3$); and 2.70 (2H, s, $-NCH_2B-$), 3.23 (3H, s, NCH_3); ^{11}B NMR (D_2O , pH 1.87, δ) 8.9; LC-MS

(ESI+) for $C_4H_7F_3BNO_3$ m/z (rel intensity) 502.1 ($[3 \times (M - H_2O) + H]^+$, 4), 335.1 ($[2 \times (M - H_2O) + H]^+$, 100), 168.4 ($[M - H_2O + H]^+$, 55); tr = 12.1 min; HRMS calcd for $C_4H_6F_3BNO_2$ [$MH^+ - H_2O$] 168.0444, found 168.0451.

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Supporting Information Available: General analytical chemical procedures, characterization data of all target compounds **1a–f**, **2a–f** (1H NMR, ^{13}C NMR, ^{11}B NMR, LC-MS), selected stack-plot NMR spectra, and pdb files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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