JOC Article

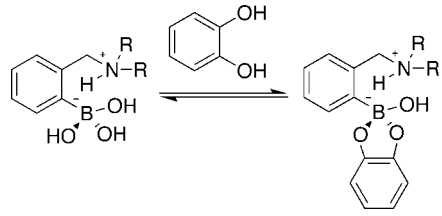
Probing Intramolecular B−N Interactions in *Ortho*-Aminomethyl Arylboronic Acids

Byron E. Collins, Steven Sorey, Amanda E. Hargrove, Shagufta H. Shabbir, Vincent M. Lynch, and Eric V. Anslyn*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas, 1 University Station A5300, Austin, Texas 78712

anslyn@austin.utexas.edu

Received January 29, 2009



This work investigates the interplay between the intramolecular B−N dative bonding and solvent insertion in various *ortho*-methylamino arylboronic acids in protic media. ^{11}B NMR experiments were conducted to study the effect that the degree of substitution of the amine group has on B−N bonding versus solvent insertion. It was found that there is a slight increase in the amount of B−N dative bonding on going from a tertiary to a secondary to a primary amine group, but that solvent insertion dominates in all cases of the boronate esters. A X-ray crystal structure gives further insight into the structure of the solvent-inserted boronate esters, showing that the inserted solvent has its hydrogen primarily on the amine. Lastly, studies of the use of boronate esters as receptors for simple alcohols and carboxylic acids are described.

Introduction

Boronic acids are known to reversibly form boronate esters with various types of 1,2- and 1,3-diols.[1] The covalent, yet quickly reversible, nature of this interaction makes it a desirable binding motif to incorporate into receptors for various hydroxylated targets. For example, in recent years arylboronic acids have been used for the molecular recognition of numerous diol containing targets including catechols,[2−6] α-hydroxy carboxylates,[7−13] peptides,[14] and saccharides.[15−25] Boronic acids have also been used for chromatographic protocols.[26−31] The incorporation of nitrogenous bases in an *ortho*-methyl position to the phenyl boronic acid increases the rate of boronate ester

(1) Kuivila, H. G.; Keough, A. H.; Soboczenski, E. J. *J. Org. Chem.* **1954**, *19*, 780–783.
(2) Yooon, J.; Czarnik, A. W. *Bioorg. Chem.* **1993**, *1*, 267–271.
(3) Secor, K. E.; Glass, T. E. *Org. Lett.* **2004**, *6*, 3727–3730.
(4) Maue, M.; Schrader, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2265–2270.
(5) Paugam, M.-F.; Valencia, L. S.; Bogges, B.; Smith, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 11203–11204.
(6) Paugam, M.-F.; Bien, J. T.; Smith, B. D.; Chrisstoffels, L. A. J.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, *118*, 9820–9825.
(7) Gray, C. W., Jr.; Houston, T. A. *J. Org. Chem.* **2002**, *67*, 5426–5428.
(8) Zhu, L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3676–3677.
(9) Wiskur, S. L.; Lavigne, J. J.; Matzger, A.; Tobey, S. L.; Lynch, V. M.; Anslyn, E. V. *Chem.−Eur. J.* **2004**, *10*, 3792–3804.
(10) Nguyen, B. T.; Wiskur, S. L.; Anslyn, E. V. *Org. Lett.* **2004**, *6*, 2499–2501.
(11) Zhao, J.; Fyles, T. M.; James, T. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 3461–3464.
(12) Zhao, J.; Davidson, M. G.; Mahon, M. F.; Kociok-Kohn, G.; James, T. D. *J. Am. Chem. Soc.* **2004**, *126*, 16179–16186.
(13) Zhu, L.; Zhong, Z.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 4260–4269.
(14) Wright, A. T.; Griffin, M. J.; Zhong, Z.; McCleskey, S. C.; Anslyn, E. V.; McDevitt, J. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6375–6378.
(15) James, T. D.; Linnane, P.; Shinkai, S. *Chem. Commun.* **1996**, 281–288.
(16) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1910–1922.
(17) Wang, W.; Gao, X.; Wang, B. *Curr. Org. Chem.* **2002**, *6*, 1285–1317.
(18) Striegler, S. *Curr. Org. Chem.* **2003**, *7*, 81–102.
(19) Fang, H.; Kaur, G.; Wang, B. *J. Fluoresc.* **2004**, *14*, 481–489.
(20) Phillips, M. D.; James, T. D. *J. Fluoresc.* **2004**, *14*, 549–559.
(21) Cao, H.; Heagy, M. D. *J. Fluoresc.* **2004**, *14*, 569–584.
(22) James, T. D. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 441−479.
(23) Yang, W.; Lin, L.; Wang, B. *Tett. Lett.* **2005**, *46*, 7981–7984.
(24) Gamsey, S.; Miller, A.; Olmstead, M. M.; Beavers, C. M.; Hirayama, L. C.; Pradhan, S.; Wessling, R. A.; Singaram, B. *J. Am. Chem. Soc.* **2007**, *129*, 1278–1286.
(25) Zhang, T.; Anslyn, E. V. *Org. Lett.* **2007**, *9*, 1627–1629.
(26) Weith, H. L.; Wiebers, J. L.; Gillham, P. T. *Biochemistry* **1972**, *9*, 4396–4401.
(27) Rosenberg, M.; Wiebers, J. L.; Gilham, P. T. *Biochemistry* **1972**, *11*, 3623–3628.
(28) Berker, S. A.; Hatt, B. W.; Somers, P. J.; Woodbury, R. R. *Carbohydr. Res.* **1973**, *26*, 55–64.
(29) Reske, K.; Schott, H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 417–418.
(30) Wulff, G.; Vesper, W. *J. Chromatogr.* **1978**, *167*, 171–186.

10.1021/jo900187a CCC: $40.75
Published on Web 04/24/2009

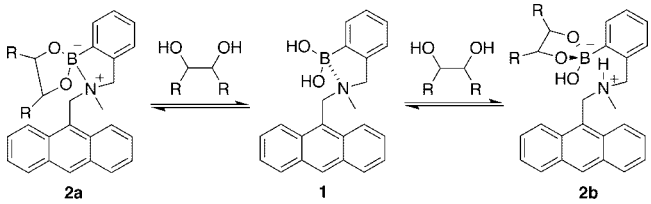


FIGURE 1. Upon formation of a boronate ester, **1** can form either B−N bonded species, **2a**, or a solvated species, **2b**.

formation and diol exchange in neutral aqueous solution.[32] Recent structural and mechanistic investigations have greatly increased our understanding of these interactions.[32−47]

In a landmark study from Shinkai et al., sensor **1** displayed a large fluorescence enhancement upon binding carbohydrates such as glucose or fructose.[46] The observed increase in fluorescence upon analyte binding was attributed to a more favorable B−N dative bonding interaction in the boronate ester over the acid, which interrupted a photoinduced electron transfer (PET) quenching mechanism between the amine and the appended anthracene moiety (Figures 1 and 2a). Subsequently, our own enantioselective sensor designs hinged on the belief that a B−N dative bond is dominant in aqueous media.[48−50]

Recently, however, Wang et al. proposed a hydrolysis mechanism whereby boronate ester formation caused a decrease in the pK_a of the boronic acid along with an increase in the pK_a of the amine group (Figures 1 and 2b).[51,52] According to his study, the change in pK_a triggers the insertion of a solvent molecule, increasing the extent of protonation of the amine. Wang suggested that this change in protonation state would more effectively occupy the nitrogen lone pair involved in PET quenching than would dative bonding.

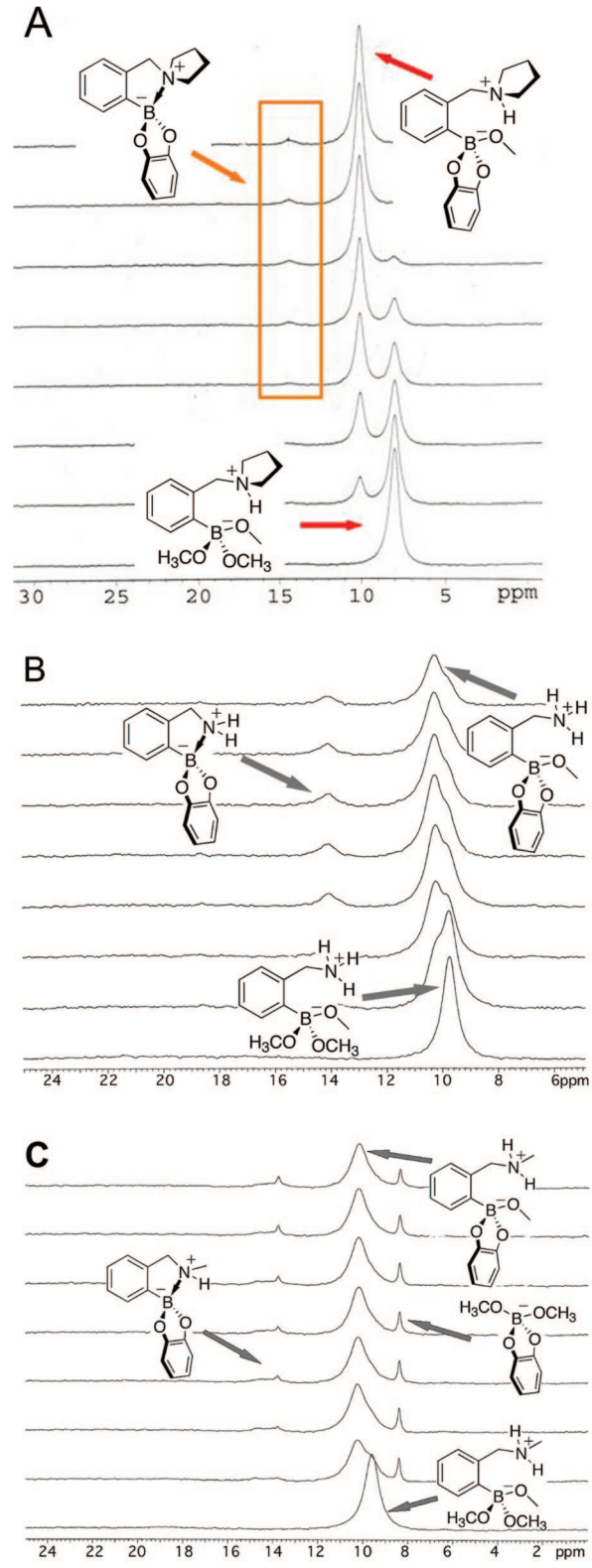
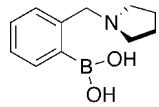


FIGURE 2. ^{11}B NMR spectra of (A) **3**, (B) **4**, and (C) **5**, 10 mM in methanol in the presence of 0, 10, 20, 30, 40, 50, 60, and 80 mM catechol (catechol concentration increases from bottom to top). A is reproduced from our previous report for comparison to B and C.[53]

Our group, prompted by Wang's findings, conducted our own investigation into these two proposed mechanisms via X-ray crystallography, ^{11}B NMR, and pH titrations.[53] Boron NMR experiments were performed by titrating **3** with various guests:

(31) Glad, M.; Ohlson, S.; Hansson, L.; Mansson, M.-O.; Mosbck, K. *J. Chromatogr.* **1980**, *200*, 254–260.
(32) Lauer, M.; Wulff, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 745–749.
(33) Boron-Nitrogen Chemistry: Gould, R. F., Ed. *Advances in Chemistry*; American Chemical Society: Washington, D.C., 1964; Vol. 42.
(34) Burgemeister, T.; Grobe-Einsler, R.; Grotstollen, R.; Mannschreck, A.; Wulff, G. *Chem. Ber.* **1981**, *114*, 3403–3411.
(35) Wulff, G.; Lauer, M.; Bohnke, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 741–742.
(36) Lauer, M.; Bohnke, H.; Grotstollen, R.; Salehnia, M.; Wulff, G. *Chem. Ber.* **1985**, *118*, 246–260.
(37) Wulff, G.; Stellbrink, H. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 216–221.
(38) Norrild, J. C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479–1484.
(39) Bielecki, M.; Eggert, H.; Norrild, J. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 449–455.
(40) Norrild, J. C. *J. Chem. Soc, Perkin Trans. 2* **2001**, 719–726.
(41) Norrild, J. C.; SØtofte, I. *J. Chem. Soc., Perkin Trans. 2* **2001**, 727–732.
(42) Wiskur, S. L.; Lavigne, J. J.; Ait-Haddou, H.; Lynch, V. M.; Chiu, Y. H.; Canary, J. W.; Anslyn, E. V. *Org. Lett.* **2001**, *3*, 1311–1314.
(43) Otsuka, H.; Uchimura, E.; Koshino, H.; Okano, T.; Kataoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 3493–3502.
(44) Ni, W.; Kaur, G.; Springsten, G.; Wang, B.; Franzen, S. *Bioorg. Chem.* **2004**, *32*, 571–581.
(45) Bosch, L. I.; Fyles, T. M.; James, T. D. *Tetrahedron* **2004**, *60*, 11175–11190.
(46) James, T. D.; Sandanayake, K.R.A.S.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 477–478.
(47) Hutin, M.; Bernardinellli, G.; Nitschke, J. R. *Chem.−Eur. J.* **2008**, *14*, 4585–4593.
(48) Zhu, L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3676–3677.
(49) Zhu, L.; Zhong, Z.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 4260–4269.
(50) Zhu, L.; Shabbir, S.; Anslyn, E. V. *Chem.−Eur. J.* **2006**, *13*, 99–104.
(51) Franzen, S.; Ni, W.; Wang, B. *J. Phys. Chem. B* **2003**, *107*, 12942–12948.
(52) Ni, W.; Kaur, G.; Springsteen, G.; Wang, B.; Franzen, S. *Bioorg. Chem* **2004**, *32*, 571–581.
(53) Zhu, L.; Shabbir, S. H.; Gray, M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *J. Am. Chem. Soc.* **2006**, *128*, 1222–1232.

catechols, diols, and α-hydroxy carboxylic acids, in chloroform and methanol. These experiments revealed the dominant species in these solvents as a function of the concentration of added guests. We demonstrated that in methanol the preferred species is the solvated species for both free boronic acids as well as boronate esters. In each crystal structure obtained from methanol, a solvent molecule was seen coordinated between the boron and the nitrogen. However, the ^{11}B NMR spectra often displayed the B−N bonded species as a minor component of the mixtures. The concentrations of the B−N bonding species were pH as well as guest dependent. For example, a solution of **3** with catechol in methanol showed a small detectable peak assigned to B−N bonded boronate ester, while a mixture of **3** with α-hydroxyisobutyric acid in methanol displayed no such species.

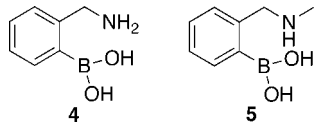


3

In the work presented herein we further explore the dependence of the B−N bond interaction as a function of structure, but we now focus on changes in the structure of the amine. Further, we report a new crystal structure that allows us to elucidate the position of the proton of the solvent this is inserted in the boronate esters. Lastly, we explore the use of boronate esters themselves as receptors for simple alcohols and carboxylic acids.

Results and Discussion

(A) Extent of B−N Bonding as a Function of Sterics. In an effort to further understand the conditions in which B−N bonding is favored, we decided to investigate the effect that the degree of substitution at the *ortho*-aminomethyl group has on B−N dative bonding in protic media. A better understanding of the nature of this interaction could lead to improvements in rationally designed boronic acid−based receptors exploiting PET-based fluorescence quenching.



4 **5**

Our hypothesis was that B−N bonding would be more favorable for 1° amines than 2° amines, which in turn would be more favorable than 3° amines. Our reasoning was that decreased steric bulk on the nitrogen would encourage B−N bond formation. To investigate this hypothesis, we examined boronic acids **4** and **5** using ^{11}B NMR in a manner identical to that used previously with **3**.[53] Compound **4** was commercially available and **5** was synthesized according to known literature procedure via reductive amination with 2-formylphenylboronic acid and methylamine.[54] NMR titrations were performed in methanol with 10 mM boronic acid **4** or **5** and catechol as the guest in concentrations ranging from 0−80 mM. Catechol was chosen because in our previous studies it showed the greatest extent of B−N bond formation when complexed by **3**.

When comparing to the previous results (Figure 2A), Figures 2B and C show that there is a very small increase in the extent

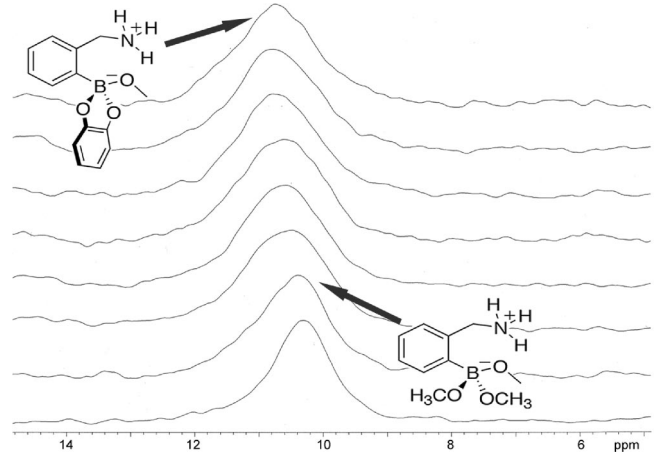


FIGURE 3. Titration of **4** with catechol under the same conditions as in Figure 2 performed on a 300 MHz NMR instrument.

of B−N bonding on going from a tertiary amine to a secondary or a primary amine. For **3**, **4**, and **5**, the initial boron peak displayed a chemical shift of around 9.8 ppm, which is indicative of the solvated boronate ester. Upon addition of catechol, this peak shifts slightly downfield to 10.2 ppm due to the increased electron withdrawing ability of catechol over methanol. As with **3**, there was also formation of a small amount of dative bonded boronate ester with **4** and **5**. Integration after baseline correction revealed that in **3**, the B−N bound species accounted for about 4% of the boron species present. Comparatively, the B−N bound species in **4** and **5** represented 11 and 10% of the boron in solution (same values within experimental error for NMR integration). The peak at 8.5 ppm in Figure 2C is due to the solvated catechol ester of residual boric acid (see Supporting Information) and was not included in the values presented above. Similar titrations were performed with *meso*-hydrobenzoin and no discernible B−N bond formation was observed.[53] This observation is also in agreement with previous work done with **3**. Finally, in all of the experiments performed, boronate ester formation was complete by the end of the titration, and competition with methanol was not a hindrance.

Notably, when performing titrations with **4** and catechol on a 300 MHz instrument (operating at 96 MHz for ^{11}B), there is only a single boron resonance, which shifts slightly downfield (Figure 3). However, when the same experiment is performed on a 500 MHz instrument (operating at 190 MHz for ^{11}B) a distinct second boron peak indicative of the catechol bound species is seen (Figure 2B). This observation allows us to calculate that, under these conditions, boronate ester exchange takes place at a rate corresponding to a half-life of between 11.1 and 54.7 ms.

(B) X-Ray Analysis. In our previous work, we obtained an X-ray crystal structure of **3** grown from methanol. It showed the presence of a solvent inserted boron species, such as depicted for either **6** or **7** below. In the crystal structure it was apparent that a hydrogen was bound between the pyrrolidine nitrogen and one of the boron bound methoxides. However, we were unable to determine whether that hydrogen was closer to the nitrogen or the oxygen. The position of the hydrogen is a subtle issue, but it defines whether the solvent inserted structure should be best considered as a neutral complexed boronic acid (**6**), or whether the methanol is closer to being fully dissociated creating a zwitterionic structure (**7**).

In the present study, we were able to grow crystals from whose crystal structure we could locate the hydrogen atoms with

(54) Swamy, K. M.; Jang, Y. J.; Park, M. S.; Koh, H. S.; Lee, S. K.; Yoon, Y. J.; Yoon, J. *Tetrahedron Lett.* **2005**, *46*, 3453–3456.

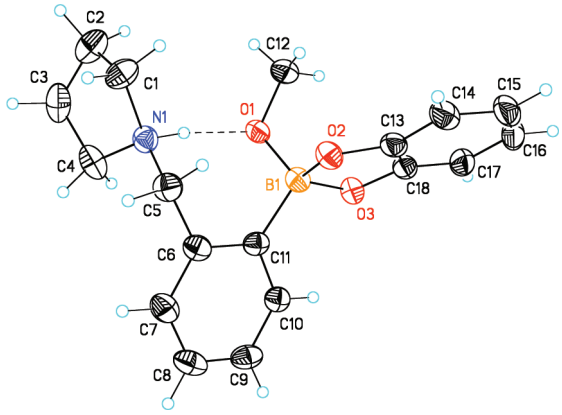
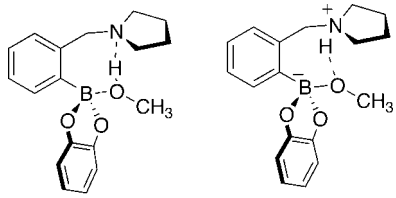


FIGURE 4. View of molecule 1 of **7** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The dashed line is indicative of a H-bonding interaction with geometry: N1−H1N···O1, N···O 2.630(3)Å, H···O 1.69(3)Å, N−H···O 161(2)°.



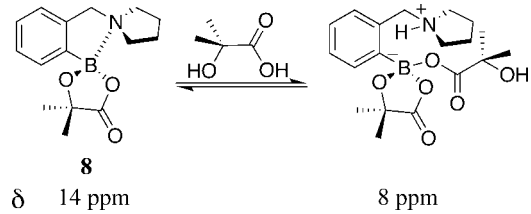
good confidence (Figure 4). These hydrogens were observed in an ΔF map and refined with isotropic displacement parameters. The crystals formed consisted of a three molecule asymmetric unit. In the units analyzed, the hydrogen atoms resided on the nitrogen atoms in all three cases. The three N−H bond distances were found to be 1.02(3), 1.03(3), and 1.04(3)Å. Comparatively, the H−O bond distances were 1.734, 1.693, and 1.668 Å.

(C) α-Amino Methyl Phenyl Boronates as −OH Receptors. During our investigations of structural and solvent effects on B−N interactions in ortho-aminomethyl aryl boronic acids, we often observed a second diol "insertion" when an excess of diol was present in aprotic media. This insertion is analogous to the solvent insertion that is observed in protic solvents that was discussed in the preceding two sections. This interaction was most prominent with α-hydroxycarboxylic acids in chloroform (Scheme 1). Chloroform is a solvent that gives predominantly the B−N dative bonding interaction until an excess of the protic guest species is present.

Observation of this phenomenon led us to hypothesize that it may be possible to exploit this interaction to create monocoordinate receptors for alcohols. To date, there exist only a few receptors for mono-ols, and colorimetric sensing systems capable of alcohol detection are rare.[55] Those that exist are used for the determination of ethanol concentration for quality control purposes. To our knowledge, there are currently no synthetic receptors capable of binding mono-ols at millimolar or lower concentrations. Therefore, alcohol receptors are of both basic scientific interest and have possible practical utility.

To test if a boronate ester of an α-aminomethyl phenyl boronic acid could act as an alcohol receptor, benzyl alcohol

SCHEME 1. Interruption of B−N Bonding by a Carboxylic Acid



SCHEME 2. Benzyl Alcohol Binds Host 9 with a Weak Association Constant

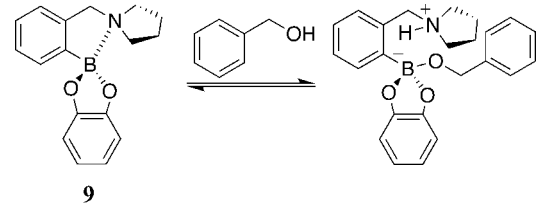


TABLE 1. Various Conditions Used to Investigate Interactions between Either Alcohol or Carboxylate with Boronic Acid Hosts

boronic acid	ester	solvent	guest	K_a (M^{-1})
3	Catechol	$CDCl_3$	Benzyl alcohol	0.3
3	Catechol	$CDCl_3$	Acetic acid	1.3
3	Catechol	DMF	Acetic acid	N/A
3	Catechol	Toluene	Acetic acid	N/A
3	Catechol	Acetonitrile	Acetic acid	7.6
3	4-chlorocatechol	Acetonitrile	Acetic acid	3.3
3	3-methoxycatechol	Acetonitrile	Acetic acid	2.9
3	4-nitrocatechol	Acetonitrile	Acetic acid	9.2
12	4-nitrocatechol	Acetonitrile	Acetic acid	N/A

was titrated into host **9** in deuterochloroform (Scheme 2). Titrations were followed with ^{11}B NMR, and an approximate binding constant (K_a) of 0.3 M^{-1} was measured (Table 1). We were able to measure this small value due to the fact that analyte binding is slow on the NMR time scale and the boron signals for both the B−N bonded and the anionic boron could be measured by integration. As noted above, when methanol is the solvent it is nearly 100% inserted. Of course with a large excess of alcohol that naturally exists when the alcohol is the solvent, even a binding constant near 1 M^{-1} results in near quantitative insertion.

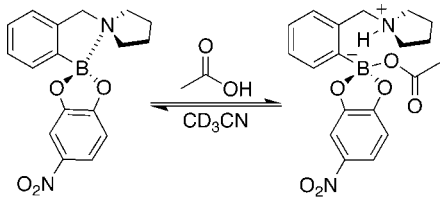
In our previous work, insertion of a guest into a preformed boronate ester (the host) was most prominent with guests possessing acidic functional groups. Therefore, we decided to examine carboxylic acids as guests. When acetic acid was substituted for benzyl alcohol as shown in Scheme 2, an approximate K_a of 1.3 M^{-1} was measured.

We also screened several commercially available deuterated solvents. The results, summarized in Table 1, show that with acetic acid and catechol, acetonitrile is the best solvent for host−guest interaction.

In addition, different catechols were screened for creating different boronate ester hosts (see the second listing in Table 1). It was found that an electron withdrawing group *meta*- to one of the catechol oxygens moderately enhanced binding of acetic acid, while electron donating groups lowered binding affinity. The most successful boronate ester host−guest combination that we uncovered was that of **10** with acetic acid as the guest in acetonitrile.

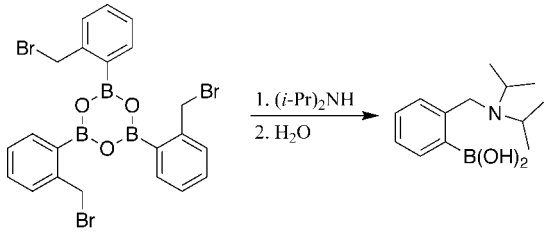
(55) (a) Wick, M. J.; Mihic, S. J.; Ueno, S.; Mascia, P. M.; Trudell, J. R.; Brozowski, S. J.; Ye, Q.; Harrison, N. L.; Haris, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 6504–6509. (b) Mayes, A. G.; Blyth, J.; Kyrölainen-Reay, M.; Millington, R. B.; Lowe, C. R. *Anal. Chem.* **1999**, *71*, 3390–3396. (c) Dubas, S. T.; Iamsamai, c.; Potiyaraj, P. *Sensors Actuators B* **2006**, *113*, 370–375.

SCHEME 3



10

SCHEME 4. Synthesis of 12



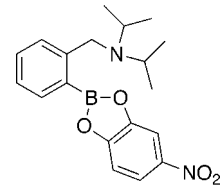
11 **12**

We hypothesized that discouraging B−N bond formation without decreasing the Lewis acidity of the boronic acid could further encourage carboxylic acid association. The pyrrolidine group on **3** was replaced with the more sterically hindered diisopropylamino group. Boronic acid **12** was furnished through nucleophilic substitution on bromomethyl boroxine in diisopropylamine followed by subsequent hydrolysis according to a known literature procedure.[56]

The ^{11}B NMR spectra of **12** with 4-nitrocatechol both in the presence and absence of acetic acid showed the same chemical shift at 12 ppm. The typical shift for a B−N bound boronic acid is 14 ppm and that of an anionic boronate ester bound to three -OR groups is typically 8−10 ppm. Therefore, it seemed likely that there was either a very strong B−N (seemingly unlikely due to sterics) bond or an inserted water. Any tricoordinate B−O species [$-B(OR)_3$] in the boronate ester prior to addition of a guest alcohol, catechol, or carboxylic acid would arise from the water liberated upon initial boronate ester formation.

In order to correctly identify the dominant species, boronate ester **13** was prepared, isolated, and dried using an Abderhalden apparatus. This complex was analyzed by both ^{1}H and ^{11}B NMR. ^{1}H NMR was used to monitor the aromatic hydrogens of the catechol. The dried free boronic acid showed a single peak at 29 ppm, which is indicative of no B−N bond or $-B(OR)_3$ species, while the boronate ester derived from 4-nitrocathechol had a single signal at 11.8 ppm. This means that there is only one boron species present upon addition of 4-nitrocatechol, and that we must have originally isolated a water inserted form of **12**.

The next experiment involved adding two equivalents of 4-nitrocatechol to test if excess catechol would lead to insertion of a second catechol as a guest. Comparison of the ^{1}H NMR spectra of **13** to that of 4-nitrocatechol showed that one of the two hydrogens *ortho*- to the two hydroxyl groups was shifted upfield by 0.3−0.4 ppm while one was only shifted by 0.05 ppm. Most importantly, there were no peaks arising from additional catechol species in **13** that are not present in uncomplexed 4-nitrocatechol alone. Hence, in the presence of excess diol guest, only one catechol species is created in solution with no insertion of a second 4-nitrocatechol. This data lead us to conclude that the increased steric bulk from the diisopropylamine group actually shields the B−N bond, allowing it to remain intact in the presence of guest. This appears to parallel the observation that very hindered boronate esters formed from diols such as pinacol are less hydrolyzable. Thus, the effect of steric bulk on the extent of B−N bond formation and breakage is minimal, which is analogous to the conclusion we reached in part A of this manuscript where substitution on the amino group was found to only have a small influence on B−N bonding.



13

Summary

In summary, we have investigated the effect of amine substitution on B−N dative bonding in *ortho*-aminomethyl aryl boronic acids. Our results show that while the degree of substitution does have a minor effect on the extent of B−N bonding, the solvated species still dominates in protic media. Also, the ^{11}B NMR experiments provided qualitative insight into the rate of boronate ester exchange. Further, we have shown that while the presence of an excess amount of diol can interrupt a B−N bond in boronate esters in nonprotic solvent, the binding affinities that boronate esters have toward mono-ols and carboxylic acids are very low. Moreover, increasing the steric bulk around the *ortho*-aminomethyl group appears to sterically shield the system from insertion of an hydroxy containing guest. Finally, X-ray crystal data has provided greater structural understanding of the solvated boronate esters indicating ionization of the O−H group and the formation of a zwitterion.

Experimental Section

***N*-Isopropyl-*N*-(2-(5-nitrobenzo[*d*][1,2,3]dioxaborol-2-yl)benzyl)proban-2-amine (13).** *o*-(Diisopropylaminomethyl)phenylboronic acid (70 mg, 0.3 mmol) and 4-nitrocatechol (46.3 mg, 0.3 mmol) were stirred in dry chloroform (50 mL) at room temperature form 20 min. Magnesium sulfate (50 mg, 0.4 mmol) was added, and the reaction was stirred overnight. The reaction mixture was filtered, and the filtrate was washed with chloroform (2 × 5 mL). Solvent was removed under reduced pressure to provide **13** as a yellow powder. The product was dried further using an abderhalden apparatus with refluxing toluene in the presence of phosphorus pentaoxide for 12 h. This gave **13** as a yellow solid (105 mg, 98% yield). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) = 1.34−1.38 (d, 12H, CH_3), 3.52−3.6 (m, 2H, CH), 4.41−4.44 (t, 2H, CH_2), 6.55−6.58 (d, 1H, phenyl-H), 7.2−7.33 (m, 4H, phenyl-H), 7.57−7.59 (d, 1H, phenyl-H), 7.62−7.65 (dd, 1H, phenyl-H). ^{13}C NMR (500 MHz, CD_3CN) δ (ppm) = 18.9, 52.2, 52.3, 103.5, 107.5, 127.7, 129.2, 132.4, 133.4, 133.6, 140.2, 154.3, 161.8. HRMS (ESI+): calcd. for $C_{19}H_{23}BN_2O_4$ $[M + H]^+$ 355.1824; found *m*/*z*: 355.1829. mp 117−121 °C.

Crystal Structure Data. X-Ray Experimental for $C_{18}H_{22}BNO_3$. Crystals grew as colorless prisms by slow evaporation from methanol. The data crystal was a prism that had approximate dimensions; 0.35 × 0.17 × 0.09 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochro-

(56) Lauer, M.; Böhnke, H.; Grotstollen, R.; Salehnia, M.; Wulff, G. *Chem. Ber.* **1985**, *118*, 246–260.

mator with Mo Kα radiation ($\lambda = 0.71073$Å). A total of 525 frames of data were collected using ω-scans with a scan range of 0.8° and a counting time of 153 s per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S1. Data reduction were performed using DENZO-SMN.[57] The structure was solved by direct methods using SIR97[58] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[50] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2 × Ueq of the attached atom (1.5 × Ueq for methyl hydrogen atoms). The hydrogen atoms on the nitrogen atoms were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0332*P)^2 + (2.7466*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.122, with $R(F)$ equal to 0.0558 and a goodness of fit, S, = 1.01. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given in the Supporting Information. The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[60] All figures were generated using SHELXTL/PC.[61] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in Tables S1−S7, Supporting Information.

Acknowledgment. We acknowledge the work of Dr. Lee Daniels of Rigaku America, The Woodlands, Texas for work on the X-ray crystal structures presented herein. This work was supported by the National Science Foundation (CHE-0616467) as well as the Welch Foundation.

Supporting Information Available: Necessary NMR spectra, and complete crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900187A

(57) DENZO-SMN: Otwinowski Z.; Minor W. *Methods in Enzymology, 276: Macromolecular Crystallography part A*; Carter, C. W., Jr., Sweets, R. M., Eds; Academic Press: New York, 1997; pp 307−326.

(58) SIR97: A program for crystal structure solution: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

(59) Sheldrick, G. M. *SHELXL97. Program for the Refinement of Crystal Structures*; University of Gottingen: Germany, 1994.

(60) *International Tables for X-ray Crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic Press: Boston, 1992; Vol C, Tables 4.2.6.8 and 6.1.1.4.

(61) Sheldrick, G. M. *SHELXTL/PC*, version 5.03; Siemens Analytical X-ray Instruments, Inc.: Madison, WI, 1994.