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pK_a Values and Geometries of Secondary and Tertiary Amines Complexed to Boronic Acids—Implications for Sensor Design

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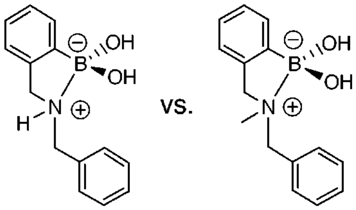
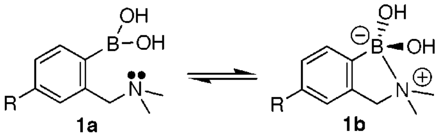
ABSTRACT



The pK_a values and the geometries of secondary and tertiary amines adjacent to boronic acids were determined using potentiometric and ^{11}B NMR titrations. The studies showed that the secondary ammonium ion has a pK_a similar to that of the tertiary ammonium species, which leads to the formation of tetrahedral boron centers at pH values above approximately 5.5. Therefore, secondary amines as well as tertiary amines, when placed proximal to boron centers, can be used to create tetrahedral boronic acids at neutral pH for diol complexation.

The boronic acid functional group is routinely incorporated into synthetic receptors for the complexation of saccharides and other guests that possess 1,2- and 1,3-diol groups.[1−4] The boronic acids form reversible covalent bonds with the diols, creating boronate esters. The kinetics of this interconversion is fast when the boron is tetrahedral, which occurs in basic aqueous media. Since it is not always advantageous to work at a high pH, Wulff has demonstrated that the incorporation of an amine adjacent to the boronic acid creates a tetrahedral sp^3 boron at or near neutral pH. This is shown in the equilibrium between **1a** and **1b** (eq 1),[5] where the lone pair on the nitrogen associates itself



(eq 1)

with the empty p orbital on the boron. It was found that the complex **1b** allowed for rapid boronate ester formation at neutral pH. This boron−nitrogen interaction raises the boronic acid's pK_a from near 9 to near 12[6] and can lower the pK_a of a tertiary ammonium ion from around 9 to near 5. These changes in the hybridization of boron are reflected

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(1) Yoon, J.; Czarnik, A. W. *J. Am. Chem. Soc*. **1992**, *114*, 5874−5875.

(2) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *J. Chem. Soc., Chem. Commun*. **1994**, 477−478.

(3) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed*. **1999**, *38*, 3666−3669.

(4) Ward, C. J.; Patel, P.; Ashton, P. R.; James, T. D. *Chem. Commun*. **2000**, 229−230.

(5) Wulff, G. *Pure Appl. Chem*. **1982**, *54*, 2093−2102.

(6) Julliard, J.; Geugue, N. C. R. *Acad. Paris C* **1967**, *264*, 259−261.

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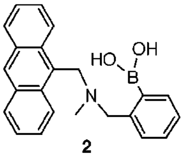
in its chemical shift in ^{11}B NMR. When boron is tetrahedral, its chemical shift is upfield from that of the trigonal planar geometry, where pure sp^3 and sp^2 is approximately 0 and 30 ppm, respectively.[7] Upon formation of the boronate ester, the Lewis acidity of the boron is increased, creating a stronger boron−nitrogen interaction.[8]

Many boronic acid receptors exist that incorporate an adjacent tertiary amine. The intramolecular coordination between a tertiary amine and a boronic acid not only improves the kinetics of exchange but also can be used to modulate photoinduced electron transfer (PET), leading to a sensing application. For example, Shinkai's sugar sensor **2** is a boronic acid linked to an anthracene moiety via a proximal tertiary amine.[2] The amine is able to quench the receptor's fluorescence through PET, even though it is involved in the boron−nitrogen interaction. Upon complexation with a sugar, the fluorescence of the anthracene is regenerated as the formation of the boronate ester increases the Lewis acidity of the boron, decreasing the PET.



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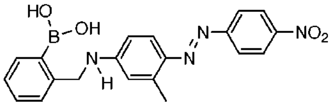

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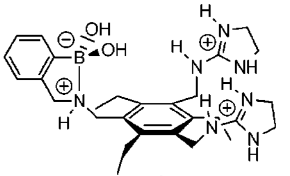

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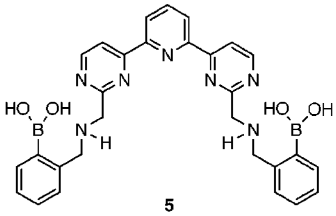

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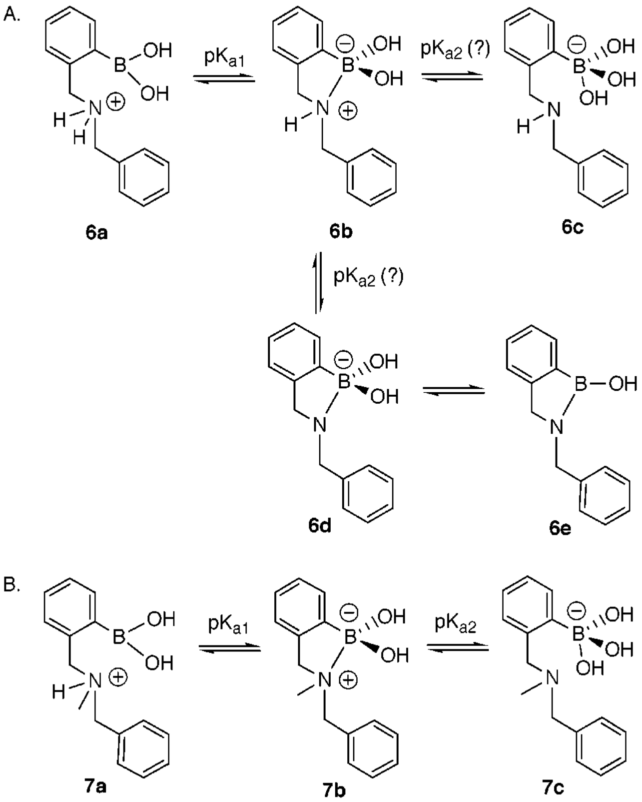
Recently, a secondary amine has been used in a nonfluorescent boronic acid sensor. James has recently synthesized a colorimetric sensor (**3**) for saccharides.[4] The host was generated by covalently attaching an azo dye to a phenyl boronic acid through a proximal secondary amine. The use of an aniline nitrogen gave a color change due to deprotonation upon sugar complexation.

Our lab is currently investigating the incorporation of boronic acids in receptors such as **4** and **5** for recognizing diols found in various natural products.[3,9] Here, dye displacement strategies are being developed to signal the presence of guests[3,10] as compared to the covalently attached signaling moieties of **2** and **3**. In our systems, the role of the secondary amine is both structural and electronic, preorganizing the cavity and enhancing the kinetics of exchange, respectively.

While several examples exist that locate tertiary amines adjacent to boronic acids, for sensing applications, few are available that incorporate secondary amines. The utility of this latter combination raises questions pertaining to the pK_a of the secondary ammonium ion relative to its tertiary counterpart (i.e., the strength of the B−N interaction at neutral pH) as well as the geometry found at the boron and nitrogen centers with varying pH. To address the questions, model compounds **6** and **7** were synthesized. To answer these questions, there are several equilibria to consider. The first pK_a is undoubtedly deprotonation of the ammonium ion in **6a** (Scheme 1A). The second pK_a can be attributed to either another deprotonation of the amine (**6b** to **6d**) or coordination of hydroxide to the boronic acid (**6b** to **6c**). We expect that the pK_a of the amine **6b** should be above that of an alkylammonium since the lone pair has no ability to delocalize and is near a negative charge, yet this needed to be confirmed. If the second deprotonation is of the amine, this could lead to hydroxide elimination to give **6e**, which can be found under dehydrating conditions.[11] This would not be evident in a potentiometric titration since it is formally the elimination of water, although it would be evident in a ^{11}B NMR spectrum. Importantly, if **6e** does dominate at neutral pH, it would not be as effective for binding diols in sensing applications as is a tertiary amine analogue.

Scheme 1



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(7) Nöth, H.; Wrackmeyer, B. Nuclear Magnetic Properties of Boron. In *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; NMR Basic Principles and Progress Series 14; Springer-Verlag: Berlin, 1978; pp 5−14, 287.

(8) Lorand, J. P.; Edwards, J. O. *J. Org. Chem.* **1959**, *24*, 769−774.

(9) Ait Haddou, H.; Anslyn, E. V. University of Texas at Austin, Austin, TX. Unpublished work, 2001.

(10) (a) Metzger, A.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649−652. (b) Niikura, K.; Metzger, A.; Anslyn, E. V. *J. Am. Chem. Soc.* **1998**, *120*, 8533−8534. (c) Niikura, K.; Bisson, A. P.; Anslyn, E. V. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1111−1114. (d) Cabell, L. A.; Monahan, M.-K.; Anslyn, E. V. *Tetrahedron Lett.* **1999**, *40*, 7753−7756.

(11) (a) Hawkins, R. T.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 3863−3866. (b) Hawkins, R. T.; Blackham, A. U. *J. Org. Chem.* **1967**, *32*, 597−600. (c) Lavigne, J. J.; Anslyn, E. V. University of Texas at Austin, Austin, TX. Unpublished work, 2001.

The equilibria available to the analogous tertiary model (**7**) is more straightforward (Scheme 1B). Deprotonation of the ammonium ion (**7a** to **7b**) and coordination of hydroxide (**7b** to **7c**) can be assigned to the first and second pK_a, respectively.[5] Given the equilibria presented in Scheme 1, we performed potentiometric titrations and ^{11}B NMR versus pH studies on **6** and **7** to probe the pK_a values and the geometries at boron as a function of pH.

Secondary model **6** was prepared in one step through a reductive amination between benzylamine and 2-formylbenzene boronic acid. Tertiary model **7** was prepared by protecting the boronic acid of 2-methylbenzene boronic acid with neopentyl glycol. The methyl group was then brominated and subsequently displaced through nucleophillic substitution by *N*-methyl benzylamine. The boronic acid was deprotected by hydrolysis on silica gel.[12]

Potentiometric titrations were performed to determine the first pK_a values associated with **6a** and **7a**. The pK_a of an ammonium generally ranges between 9 and 10, but a boronic acid adjacent to an ammonium will lower that significantly. The titration curves for both models are shown in Figure 1.

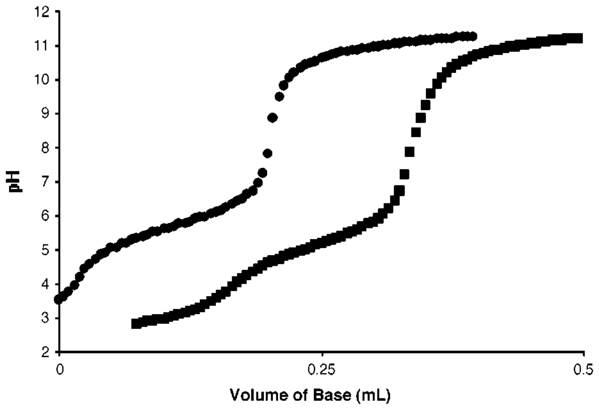

Figure 1. pH profile of **6** (■) and **7** (●) upon addition of base (0.15 M NaCl in water, 0.1 M NaOH, and 4.5 mM (initial) **6** and **7**). The titration of **6** started with a higher concentration of acid, and the first few data points were excluded.

From these curves, a pK_a of 5.7 was found for **7a**, which is comparable to the known value of 5.2 for a dimethylammonium ion adjacent to a boronic acid.[5] The titration of the secondary model **6a** produced a value of 5.3 for its pK_a. Hence, the pK_a values determined from the potentiometric titrations of **6a** and **7b** are quite similar.[13]

In an effort to better understand the geometry at boron, the ^{11}B NMR spectra of **6** and **7** were recorded as a function of pH (Figure 2).[14] In our studies, both compounds **6** and **7** showed shifts from approximately 30 to 10 ppm as the pH was raised. This indicates that the boron centers in both the secondary and the tertiary model compounds are trigonal planar at low pH and upon increasing the pH they become tetrahedral, with pK_a values of 5.2 and 5.8, respectively. These values are in agreement with those determined by potentiometric titrations. Further, at neutral pH the chemical shifts found for **6** and **7** are nearly identical. Since we are confident in the assignment of form **7b** at neutral pH for the tertiary model, it indicates that the proper form for the secondary counterpart is **6b** at this pH. These data therefore indicate that the dominant forms of the secondary and tertiary compounds near neutral pH are **6b** and **7b**, respectively.

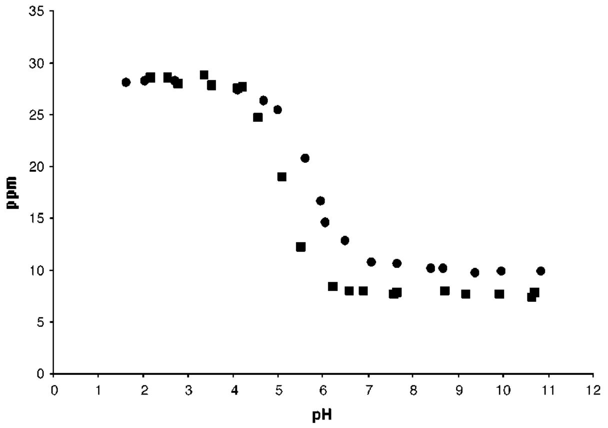

Figure 2. ^{11}B NMR chemical shifts of model compounds **6** (■) and **7** (●) with increasing pH (10% d_4-methanol in water, 40 mM **6** and **7**, 40 mM NaCl). Referenced to $Et_2O{\cdot}BF_3$ in toluene as zero.

To further confirm the geometry of **6** near neutral pH, we wanted to obtain a crystal structure, but our attempts to grow crystallographic quality crystals were unsuccessful. However, the geometry was clear from X-ray crystallography on crystals of the polyaza compound **5** (Figure 3).[9,15] Importantly, the boron is tetrahedral, as is the coordinated nitrogen, and the B−N bond lengths are 1.669 Å.[16] ^{11}B NMR of the crystals provide a chemical shift of 9.4 ppm, consistent with our assignment of form **6b** at neutral pH.

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(12) Lavigne, J. J. Ph.D. Dissertation, University of Texas at Austin, 2000.

(13) Potentiometric studies were conducted with a Brinkmann Titrino 702 autotitrator. A Metrohm combined pH glass electrode (Ag/AgCl) with 3 M NaCl internal filling solution was used. Measurements were taken at 25 °C under nitrogen. About 100 data points were collected for each titration, and the analysis was carried out as described by Martell (see below). Equilibrium constants were calculated using the program BEST. All constants were determined using at least two independent titrations. Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants*; VCH Publishers: New York, 1992.

(14) ^{11}B NMR spectra were obtained with a Bruker AMX-500 spectrometer. Quartz NMR tubes were used to limit background noise. The pH values of the solutions were adjusted between 1.6 and 11 and measured with an Orion 720A pH meter.

(15) Toyota, S.; Futawaka, T.; Asakura, M.; Ikeda, H.; Oki, M. *Organometallics* **1998**, *17*, 4155−4163.

(16) Crystal data for **4**. $C_{33}H_{37}B_2N_7O_4$, $M = 617.32$, monoclinic, space group $C2/c$ (No. 15), $a = 21.7733(9)$, $b = 16.3103(9)$, $c = 8.9580(3)$ Å, $\beta = 99.049(3)°$, $V = 3141.7(2)$ Å^3, $Z = 4$, $D_c = 1.30$ g/cc, $\mu = 0.087$ mm^{-1}. Data were collected at 123(2) K on a Nonius Kappa CCD using graphite monochromatized Mo Kα radiation (0.71073 Å). A total of 5976 reflections were collected, 3535 were unique ($R_{int} = 0.028$). The structures were refined on F^2 to a wR2 = 0.119 with an R1 [for 2497 reflections with $F_o > 4(\sigma(F_o))$] = 0.0549 and a goodness of fit = 1.05. The molecule lies on a crystallographic 2-fold rotation axis passing through the central pyridine ring.

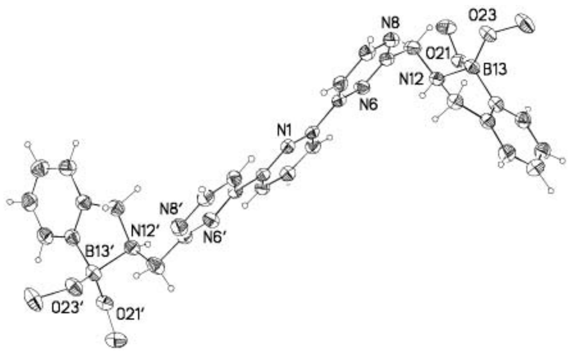

Figure 3. View of **5** showing a partial atom labeling scheme. Thermal ellipsoids are scaled to the 50% probability level. Hydrogen atoms shown are drawn to an arbitrary scale. The molecule lies on a crystallographic 2-fold rotation axis bisecting the pyridine ring and passing through N1. Atoms with labels appended by ′ are related by $-x$, y, $1/2 - z$. The protons on the amines were located and refined in the crystal structure.

In conclusion, we have determined that the pK_a values of secondary ammoniums adjacent to boronic acids are comparable to those of the analogous tertiary ammoniums. Further, at neutral pH, form **6b** dominates. Therefore, secondary amines can be used to coordinate boronic acids for sensor applications with geometries appropriate for the complexation of 1,2- and 1,3-diols, just as is now routinely done with tertiary amines. Undoubtedly there will be a difference in the extent of PET between a tertiary and second amine that can be exploited for sensor applications,[17] but the use of secondary and tertiary amines are essentially the same with regards to complexation geometry and pH dependence.

Acknowledgment. This work has been supported by the Welch Foundation and the National Institutes of Health.

Supporting Information Available: Experimental procedures and characterization for compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Bissel, R. A.; de Silva, A. P.; Gunaratne, H. Q. N.; Lynch, P. L. M.; Maguire, G. E. M.; McCoy, C. P.; Sandanayake, K. R. A. S. *Top. Curr. Chem.* **1993**, *168*, 223−264.