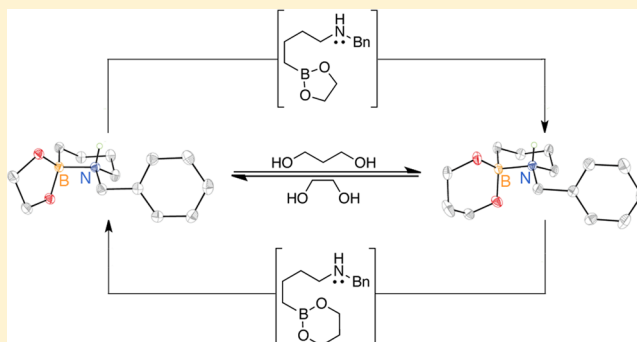


## Thermodynamically Controlled, Dynamic Binding of Diols to a 1,2-BN Cyclohexane Derivative

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## S Supporting Information

**ABSTRACT:** The reversible covalent binding of diols to an *N*-Bn 1,2-BN cyclohexane has been studied by <sup>11</sup>B and <sup>1</sup>H NMR spectroscopy and single-crystal X-ray diffraction analysis. The activation barrier for the reversible B–N Lewis acid–base interaction has been measured by variable-temperature NMR with bound (2*R*,3*R*)-(–)-2,3-butanediol (*T*<sub>c</sub> = –40 °C,  $\Delta G^\ddagger = 11.2 \pm 0.2$  kcal mol<sup>–1</sup>). Deuterium labeling experiments demonstrate that ligand exchange is reversible and rapid at room temperature, and competitive binding studies establish diol association as a thermodynamically controlled process.



Polyhydroxylated molecules play a pivotal role in biochemical processes as signaling compounds. Considerable effort has been devoted to mimic nature's receptors to bind important classes of biomolecules, such as saccharides,<sup>1</sup> nucleosides,<sup>2</sup> and catecholamines.<sup>3</sup> Boron-containing compounds have become attractive targets as small-molecule chemosensors, given their propensity to form reversible, high-affinity covalent interactions with *cis*-diols.<sup>4</sup> For example, the mechanism of action for a family of antibacterial diazaborine compounds relies on formation of a tetrahedral boronate ion by a covalent B–O linkage to the NAD<sup>+</sup> nicotinamide ribose 2'-hydroxyl group.<sup>5a</sup> The significance of this interaction to affect the drug's inhibitory properties was demonstrated by replacement of the diazaborine boron (B)–nitrogen (N) bond with an isoelectronic carbon–carbon unit. Despite similarities in both their chemical and physical properties, the carbonaceous analogue of the diazaborine ring is shown to be biologically inactive.<sup>5b</sup>

Our research group seeks to expand upon the structural diversity achieved in nature through the application-driven synthesis and characterization of BN-containing heterocycles (Figure 1).<sup>6</sup> The BN/CC isosterism strategy has led to the development of compounds possessing unique reactivity profiles<sup>7</sup> and photophysical<sup>8</sup> and biological<sup>9</sup> properties distinct

from those of their all-carbon analogues. In this tradition, we were interested in exploring the potential of 1,2-BN heterocycles as a new class of boron-containing receptors for polyol sensing. Herein, we describe the synthesis and structural characterization of a 1,2-BN cyclohexane derivative chelated to 1,2-, 1,3-, and 1,4-diols. Furthermore, we establish that ligand exchange at boron is rapid and that diol binding is a thermodynamically controlled process.

Our initial efforts to complex 1,2-azaborines with diols in a bidentate fashion proved unsuccessful, presumably due to the aromatic nature of these heterocycles.<sup>10</sup> We therefore shifted our attention toward the all-saturated analogue 1,2-BN cyclohexane.<sup>11</sup> The *N*-benzyl derivative **1**, previously reported by Rona et al.,<sup>12</sup> was envisioned to serve as a versatile precursor for the synthesis of the desired bidentate adduct upon diol addition (Scheme 1). Gratifyingly, addition of 1,3-propanediol proceeded cleanly to afford the air- and moisture-stable complex **2** in 96% isolated yield. Single crystals suitable for X-ray diffraction were grown from a saturated solution in chloroform-*d*, thereby unambiguously confirming bidentate boron coordination and nitrogen protonation. Structural parameters for **2** are consistent with simultaneous boron coordination by the chelating 1,3-diol, as both B–O bond distances are nearly identical in length (B–O(1) = 1.458(3) Å vs B–O(2) = 1.476(3) Å).

Synthesis and solid-state characterization have also been accomplished for the five- and seven-membered chelate ring

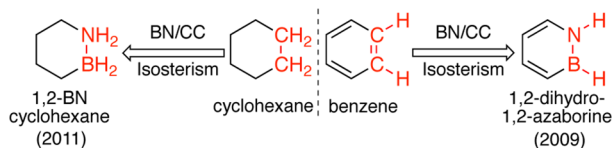


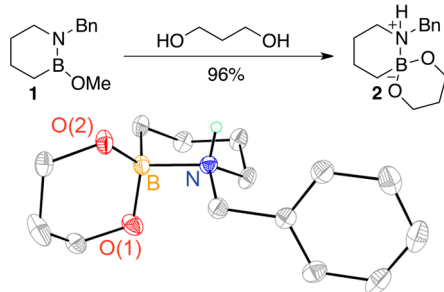
Figure 1. BN/CC isosterism.

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Scheme 1. Synthesis of the 1,3-Diol Complex 2<sup>a</sup>

<sup>a</sup>ORTEP illustration for 2 drawn with thermal ellipsoids at the 35% probability level (hydrogen atoms have been omitted for clarity). Bn = benzyl.

sizes by analogous protocols.<sup>13</sup> Distinct peak separation by <sup>11</sup>B NMR illustrates a convenient method to distinguish among 1,2-, 1,3-, and 1,4-adducts in solution (Table 1). Unexpectedly,

**Table 1. Comparison of Solution (CH<sub>2</sub>Cl<sub>2</sub>) and Solid-State <sup>11</sup>B NMR Chemical Shifts (ppm) for 1,2-, 1,3-, and 1,4-Diol Complexes**

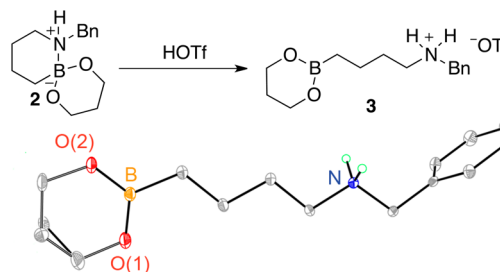
| ring size | solution | solid state |
|-----------|----------|-------------|
| 5         | 9.8      | 8.6         |
| 6         | 25.4     | 3.7         |
| 7         | 6.6      | 6.2         |

the six-membered complex is observed to possess a <sup>11</sup>B resonance at 25.4 ppm in solution, suggesting substantial trigonal-planar character at boron.<sup>14</sup> A comparison with solid-state <sup>11</sup>B NMR reveals a significant discrepancy between solution and solid-state chemical shifts. On the basis of prior investigations by Anslyn and co-workers with *o*-(aminomethyl)-arylboronates, we postulate that the 25.4 ppm <sup>11</sup>B resonance is a time-averaged signal between a tetracoordinate (3.7 ppm) and trigonal-planar (~30 ppm) boron atom.<sup>15</sup> This observation is consistent with the in situ dynamics reported previously for Wulff-type boronic acids, where a dative 1,5-N→B interaction participates in reversible association.<sup>1a,b,16</sup>

This foregoing observation motivated us to perform a series of mechanistic studies to elucidate the strength and nature of the N→B dative bond. Addition of 1 equiv of triflic acid to a −30 °C solution of 2 in methylene chloride afforded a single resonance by <sup>11</sup>B NMR at 31.3 ppm. Unambiguous structural assignment by single-crystal X-ray analysis confirmed the identity of 3 as the acyclic ammonium salt (Scheme 2). Significant contraction of both B–O bond distances is consistent with strengthening of the covalent B–O interaction due to increased electron donation of the oxygen lone pair into the p orbital of boron (B–O(1) = 1.353(2) Å and B–O(2) = 1.364(2) Å).

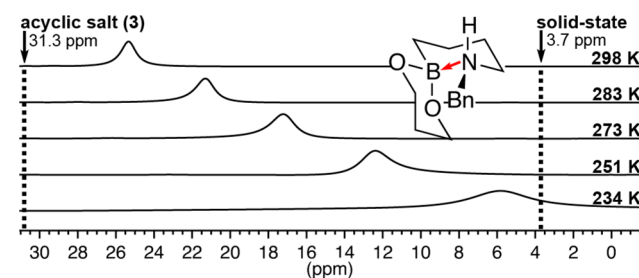
To support our hypothesis that the 25.4 ppm <sup>11</sup>B resonance for 2 is averaged on the NMR time scale, low-temperature <sup>11</sup>B NMR was performed in 10 K increments to 234 K in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 3). Upon gradual temperature depression, an upfield shift toward the 3.7 ppm solid-state resonance is observed. This trend is consistent with increasing sp<sup>3</sup> character at boron, likely resulting from a stronger, more covalent N→B interaction.<sup>14,16a</sup>

We anticipated that the synthesis of chiral complex 4 would allow for the proposed process of reversible N→B association to be observable by variable-temperature <sup>1</sup>H NMR (Scheme 4).

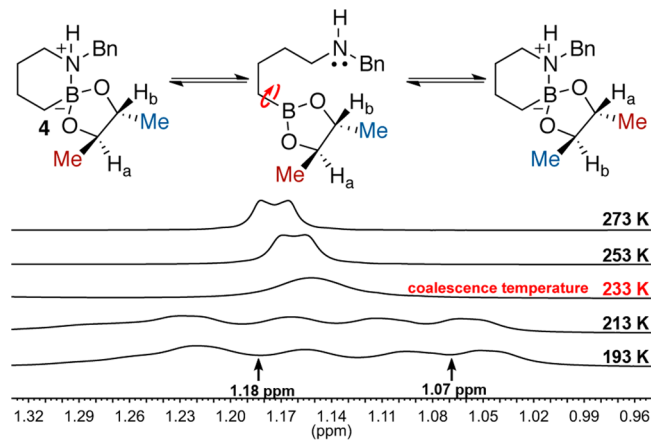
Scheme 2. Synthesis of Acyclic Ammonium Salt 3<sup>a</sup>

<sup>a</sup>ORTEP illustration for 3 drawn with thermal ellipsoids at the 35% probability level. One of the carbon atoms in the six-membered B–O cycle is disordered over two positions in the ratio 0.815/0.185 (hydrogen atoms and triflate counterion have been omitted for clarity). Bn = benzyl, Tf = trifluoromethanesulfonyl.

**Scheme 3. Temperature Dependence of the <sup>11</sup>B Chemical Shift for Complex 2 in CH<sub>2</sub>Cl<sub>2</sub>**



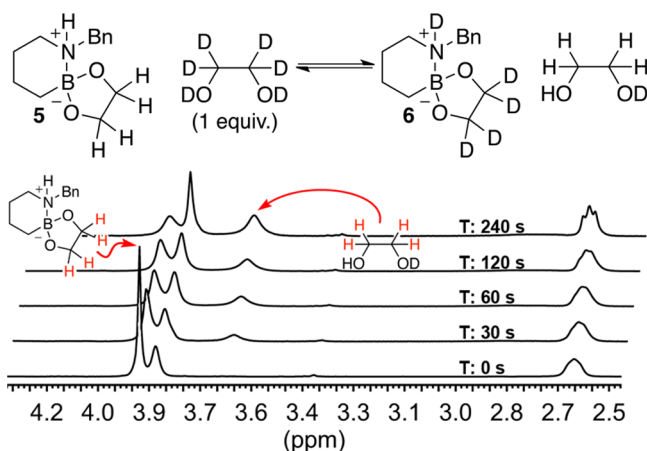
**Scheme 4. Temperature Dependence of the <sup>1</sup>H Signals for the Diastereotopic Methyl Groups in 4 in CD<sub>2</sub>Cl<sub>2</sub>**



A J. Young tube containing 4 in CD<sub>2</sub>Cl<sub>2</sub> was cooled to 273 K, and its <sup>1</sup>H NMR spectrum was recorded in 20 K increments. At 298 K, the diastereotopic methyl groups resonate together as a single, sharp doublet integrating to six protons. When the temperature was lowered to 233 K, the reversible Lewis acid–base interaction became sufficiently slow on the NMR time scale that broadening and distinct signal separation into two sets of doublets was observed. By a modified Arrhenius equation, the activation energy for the proposed dynamic process in Scheme 4 is estimated to be 11.2 ± 0.2 kcal mol<sup>−1</sup> (*T*<sub>c</sub> = −40 °C, Δ*ν* = 33 Hz).<sup>17,18</sup>

We examined the viability of ligand exchange from complex 5 using deuterium labeling (Scheme 5). When 1 equiv of ethylene glycol-*d*<sub>6</sub> was added to a CD<sub>2</sub>Cl<sub>2</sub> solution containing 5, a decrease in the relative intensity of the 3.93 ppm signal

Scheme 5.  $^1\text{H}$  NMR Analysis of Ligand Exchange for Complex 5 in  $\text{CD}_2\text{Cl}_2$



corresponding to the four glycol protons was observed. In tandem, a new resonance emerged at 3.66 ppm, confirmed by spiking experiments to be consistent with ejected ethylene glycol.<sup>13</sup> Within 4 min, the integrated areas of free and bound ethylene glycol were approximately equal, and no further change in the NMR spectrum was observed ( $K_{\text{eq}} \approx 1$ ). The reverse process, beginning with a solution containing deuterated complex 6, was shown to be consistent with these results.<sup>13</sup>

We used  $^{11}\text{B}$  and  $^1\text{H}$  NMR spectroscopy to determine trends in preferential polyol complexation by quantifying the equilibrium constant for the exchange reaction illustrated in Table 2. The observed  $K_{\text{eq}}$  values demonstrate that binding of

Table 2. Equilibrium Constants Calculated by Competitive Exchange Starting with 5<sup>a</sup>

|                 |       |      |      |
|-----------------|-------|------|------|
|                 |       |      |      |
| Ring Size       | 5     | 2    | 7    |
| $K_{\text{eq}}$ | 1.00  | 0.31 | 0.04 |
|                 |       |      |      |
| Geometry        | 8     | 9    | 10   |
| $K_{\text{eq}}$ | >100  | 1.26 | 0.27 |
|                 |       |      |      |
| Electronics     | 11    | 12   |      |
| $K_{\text{eq}}$ | 34.28 | 2.24 |      |

<sup>a</sup>Experimental procedure adapted from ref 20. Equilibrium constants measured in  $\text{CD}_2\text{Cl}_2$ .

1,3-propanediol (2) and 1,4-butanediol (7) is energetically unfavorable relative to formation of the 1,2-glycol complex 5. The  $K_{\text{eq}}$  data for systems 8–10 show that preorganization of the ligand into a *cis* geometry can improve the binding strength. Complex 9, in which a 1,3-diol is geminally disubstituted at the C(2) position, exhibits a nearly 4-fold increase in  $K_{\text{eq}}$  relative to

2. We attribute this result to a Thorpe–Ingold effect, where a dimethyl repulsion contracts the inner  $\angle\text{C}–\text{C}–\text{C}$  of the 2,2-dimethyl-1,3-propanediol ligand to promote *cis* chelation.<sup>19</sup> Notably, the conformational rigidity imparted by a *cis*-olefin relays a significant increase in the association constants for 8 and 10 relative to 5 and 7, respectively. Finally, the substantial difference in the binding constants between 11 and 12 illustrates that an increase in the acidity of the chelating ligand has a marked impact on the strength of diol association. This observation is consistent with the conclusions reported by Pizer and co-workers for related binding studies on boronic acids.<sup>4c</sup> The data for 8 and 11 reveal that, among the parameters studied, the most significant consideration for high-affinity binding is the diminished  $\text{p}K_{\text{a}}$  value of the complexing diol ligand.

To conclude, we have synthesized a new class of polyol complexes derived from the 1,2-BN cyclohexane framework. Diol binding is shown to be a high-affinity process that affords air- and moisture-stable bidentate complexes in near-quantitative yield.  $^{11}\text{B}$  NMR is used as a technique to conveniently distinguish among five-, six-, and seven-membered diol complexes in solution. Molecular dynamics analysis by VT NMR reveals an activation barrier of approximately  $11.2 \pm 0.2$  kcal mol<sup>−1</sup> for the reversible Lewis acid–base  $\text{N} \rightarrow \text{B}$  interaction. Deuterium labeling experiments established that ligand exchange is reversible and rapid at room temperature. We have also shown through competitive binding experiments that the 1,2-BN cyclohexane framework possesses an inherent thermodynamic preference for a five-membered chelate ring size, *cis*-binding geometry, and acidic diol ligands.

## ■ ASSOCIATED CONTENT

### Supporting Information

Text, figures, tables, and CIF files giving experimental procedures, spectroscopic data, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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