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A Computational Investigation of the *Nitrogen-Boron* Interaction in *o*-(*N,N*-Dialkylaminomethyl)arylboronate Systems

Joseph D. Larkin¹, John S. Fossey², Tony D. James³, Bernard R. Brooks¹, and Charles W. Bock^{4,5}

¹The National Institutes of Health, National Heart, Lung, and Blood Institute, Bldg. 50, Bethesda, MD 20851

²School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

³Department of Chemistry, University of Bath, Bath BA2 7AY, UK

⁴Department of Chemistry and Biochemistry, School of Science and Health, Philadelphia University, School House Lane and Henry Avenue, Philadelphia, PA 19144

⁵The Institute for Cancer Research, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111

Abstract

o-(*N,N*-Dialkylaminomethyl)arylboronate systems are an important class of compounds in diol-sensor development. We report results from a computational investigation of fourteen *o*-(*N,N*-dialkylaminomethyl)arylboronates using second-order Møller-Plesset (MP2) perturbation theory. Geometry optimizations were performed at the MP2/cc-pVDZ level and followed by single-point calculations at the MP2/aug-cc-pVDZ(cc-pVTZ) levels. These results are compared to those from density functional theory (DFT) at the PBE1PBE(PBE1PBE-D)/6-311++G(*d,p*)(aug-cc-pVDZ) levels, as well as to experiment. Results from continuum PCM and CPCM solvation models were employed to assess the effects of a bulk aqueous environment. Although the behaviour of *o*-(*N,N*-dialkylaminomethyl) free acid and ester proved to be complicated, we were able to extract some important trends from our calculations: 1) for the free acids the intramolecular hydrogen-bonded B-O-H[⋯]N seven-membered ring conformers **12** and **16** are found to be slightly *lower* in energy than the dative-bonded N→B five-membered ring conformers **10** and **14** while conformers **13** and **17**, with no direct boron-nitrogen interaction, are significantly higher in energy than **12** and **16**; 2) for the esters where no intramolecular B-O-H[⋯]N bonded form is possible, the N→B conformers **18** and **21** are significantly lower in energy than the no-interaction forms **20** and **23**; 3) H₂O insertion reactions into the N→B structures **10**, **14**, **18**, and **21** leading to the seven-membered intermolecular hydrogen-bonded B[⋯]OH₂[⋯]N ring structures **11**, **15**, **19**, and **22** are all energetically favorable.

Supporting Information **Available**: Table 1S and 2S: boron-nitrogen distances for all levels of theory used in this study. Figure 1: Overlaid optimized geometries at the MP2/cc-pVDZ, PBE1PBE/6-31+G(*d*), PBE1PBE/6-311++G(*d,p*), PBE1PBE/cc-pVDZ, and PBE1PBE/aug-cc-pVDZ levels of theory. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Introduction

The so-called coordinative or dative nitrogen-to-boron $N \rightarrow B$ bonds have been studied for many years.¹ The strength of these $N \rightarrow B$ bonds depend greatly on the substituents at both atoms; electron withdrawing groups increase the Lewis acidity of boron, whilst electron donating groups increase the Lewis basicity at nitrogen. In considering $N \rightarrow B$ bond strengths it is necessary to balance these electronic factors against the counteracting steric requirements of the same substituents. An investigation of 144 compounds with $N \rightarrow B$ bonds concluded that steric interactions, as well as ring strain (in the case of cyclic diesters) weaken and elongate the $N \rightarrow B$ bond, which occurs with a concurrent reduction in the tetrahedral geometry of the boron centre.²

The *N*-methyl-*o*-(phenylboronic acid)-*N*-benzylamine **1** system has been investigated separately by a number of groups.^{3–5} Scheme 1 depicts a general model where, at one extreme, the acyclic forms (**1** and **2**) illustrate a separate nitrogen and boron centre and at the other, the cyclic forms (**4** and **5**) illustrate a full $N \rightarrow B$ bond; the species existing in equilibrium in an aqueous environment. Species **3** involves a protonated nitrogen, and this ammonium cation precludes any nitrogen-boron interaction.

The energy of various nitrogen-boron interactions has been calculated from the stepwise formation constants of potentiometric titrations. Based on the relative stabilities of ternary phosphate complexes James and coworkers estimated that nitrogen-boron interactions are approximately between +3.6 and +6.0 kcal/mol in *N*-methyl-*o*-(phenylboronic acid)-*N*-benzylamine.³

The Wang group,⁶ using GGA DFT methodology⁷ and the COSMO implicit solvent model^{8–9} estimated the strength of the $N \rightarrow B$ bond for *o*-(trimethylamino)phenylboronic acids to be +3.1 kcal/mol or less. Based on these results, it appears that the strength of a nitrogen-boron interaction in solution is similar to that of a hydrogen bond in bulk water.^{10–11} While this makes the interaction a weak one it does explain the importance of the $N \rightarrow B$ bond in saccharide sensors. It is the weakness of the $N \rightarrow B$ bond that explains why it is a central feature in many fluorescent PET sensors playing a pivotal role in signalling the binding event.^{12–13} If this interaction were much stronger, then the binding of a diol would not be able to disrupt the nitrogen-boron interaction sufficiently so as to modulate a change in fluorescence. By the same token, if the interaction were much weaker then there would be no significant intramolecular nitrogen-boron interaction to disrupt in the first place.

For some time the formation of a $N \rightarrow B$ dative bond between nitrogen and boron was assumed to be responsible for the fluorescence enhancement seen when boronic acids bound diols.^{12–24} This interpretation does, however, raise certain questions. The fluorescence revival in these systems functions as a digital “off-on” response. Fluorescence emission returns to the same maximal value regardless of the observed stability constant (K_{obs}) of the ligand or the $\text{p}K_{\text{a}}'$ of the resulting boronate ester. It is known that the acidity of boron influences the strength of the $N \rightarrow B$ bond.²⁵ Therefore, if a $N \rightarrow B$ bond did modulate PET, we might necessarily expect the fluorescence response to vary as a function of the degree of

acidity or strength of complexation, but this is not the case;²⁶ moreover, numerical values of +3.6 to +6.0 kcal/mol do not agree with the interpretation of a N→B bond.³

The single-crystal X-ray structure of sensor **6**, see Figure 1, in both its bound and unbound state, has recently been published.²⁷ In the case of the unbound receptor the geometry at boron is nearly trigonal planar. This is important, as the absence of minimal deviation from planarity implies that there is little or no direct N→B Lewis base – Lewis acid bond at boron. When bound to tartaric acid, the complex was crystallised from a methanol and dichloromethane solution. In the resulting tartrate complex, two molecules of methanol, one at each boron centre are bound through their oxygen atoms to their respective boron centres. Whilst the hydrogen atoms of methanol could not be directly located in these single-crystal X-ray structures, it is not unreasonable to infer from the geometry that each oxygen atom is dative-bonded to the boron centre and hydrogen-bonded to the adjacent nitrogen atom. Oxygen to boron and oxygen to nitrogen bond distances of around 3.5 and 2.7 Å respectively were reported in this case, see Figure 1.

Whilst speculative, this structural interpretation of the interaction between boronic acid and the proximal tertiary amine through a bound protic solvent molecule (solvent insertion into the N→B bond) corresponds well with contemporary computational and potentiometric titration data, in which the formation of intramolecular seven-membered rings should not be ignored.^{3,28–30} In particular the X-ray crystal structure above and bond strengths determined from potentiometric titrations of between +3.6 and +6.0 kcal/mol are comparable to a hydrogen bonding interaction manifested through a bound solvent molecule at the boron centre.^{3,28–30}

An infrared study into the interaction between nitrogen and boron in a related system indicated that hydrogen bonding to a nitrogen through a bound solvent molecule at the boron centre was possible.³¹ The experimental rationale was based on comparing two emergent peaks in infrared spectra to similar peaks in known model systems. The results indicated that in carbon tetrachloride the interaction between the nitrogen and boron of 8-quinolineboronic acid could be modulated by either water or phenol bound to the boron centre at oxygen, see Figure 2.

Anslyn and coworkers recently performed structural investigations into the nitrogen-boron interaction in *o*-(*N,N*-dialkylaminomethyl)arylboronate systems (*ie o*-(pyrrolidinylmethyl)phenylboronate).^{32–33} From detailed ¹¹B-NMR measurements and X-ray data it was shown that in an aprotic solvent, the N→B bond is usually present. However, in a protic media, solvent insertion into the N→B bond occurs to afford a hydrogen-bonded zwitterionic species. These authors further supported their findings by calculations at the B3LYP/6-31+G(*d,p*)/B3LYP/6-31+G(*d,p*) computational level in a simulated water continuum. Unfortunately, it is well known that the B3LYP functional with a variety of basis sets has significant problems predicting the presence and strength of N→B bonds; thus, some caution needs to be exercised in interpreting these B3LYP computational results.^{29,34–39} Thanks to the experimental and computational investigations by Anslyn^{32–33} and a number of other groups^{3,6,26} it appears from both experimental and computational studies that a variety of structural variations of the nitrogen-boron interaction, *ie* N→B(**4**),

B-O-H $\cdots$ N(**9a**), and B $\cdots$ OHR $\cdots$ N(**9b**), see Scheme 1 and Figure 3, need to be carefully considered for individual boronic acid systems.

In this article we report results from a computational investigation of fourteen *o*-(*N,N*-dialkylaminomethyl)arylboronate systems organized into four groups, see Figure 4. Each group contains a molecule with a N $\rightarrow$ B bond cf compound **10**, a solvent inserted system (B $\cdots$ OH $_2\cdots$ N) cf compound **11**, and an extreme case where the nitrogen and boron centers are separated to a point where no N $\rightarrow$ B bond is possible cf compound **13**. Groups 1 and 2 also contain molecules with intramolecular B-O-H $\cdots$ N cyclic hydrogen bonds, cf **12**. The first group consists of the boronic acids **10**, **11**, **12**, and **13**; the second group consists of the mono methyl ester of boronic acid **14**, **15**, **16** and **17**; the third group consists of the dimethyl boronic esters **18**, **19** and **20**; and the fourth group consists of the cyclic boronic esters **21**, **22** and **23**.

These four groups were chosen for this investigation because they represent a stepwise transition between the free boronic acid (Group 1) and the fully esterified boronic acids (Groups 3 and 4). Including both Groups 3 and 4 in this investigation enabled us to compare the difference between acyclic ester and cyclic ester formation. Using these simple model systems, we employed computational methods to understand the relative energies of N $\rightarrow$ B dative-bonded and B-O-H $\cdots$ N hydrogen-bonded conformers, as well as the thermochemistry of solvent insertion into N $\rightarrow$ B forms that yield structures involving a B $\cdots$ OHR $\cdots$ N linkage. Results from our systematic investigation will provide support for distinguishing which of the three boron-nitrogen coordinated structures is present in *o*-(*N,N*-dialkylaminomethyl)arylboronate systems at neutral pH or in protic media.

Computational Methods

Equilibrium geometries for the structures described in this article were obtained using second-order Møller-Plesset (MP2) perturbation theory⁴⁰ with the frozen core (FC) option, which neglects core-electron correlation; the Dunning-Woon correlation-consistent (cc) cc-pVDZ basis set was employed for the initial optimizations;^{41–44} single-point calculations at this MP2/cc-pVDZ geometry were also carried out at the MP2(FC)/aug-cc-pVDZ and MP2/cc-pVTZ computational levels. For comparison, we also performed optimizations at the MP2/6-31+G(*d*) level.⁴⁵ Frequency analyses were performed analytically at the MP2/cc-pVDZ//MP2/cc-pVDZ level to confirm that the optimized structures were local minima on the PES and to correct reaction enthalpies and free energies to 298K. All calculations were carried out using either the GAUSSIAN 03⁴⁶ or GAUSSIAN 09⁴⁷ suite of programs. Bonding was analyzed with the aid of natural bond orbitals (NBOs).^{48–51}

Geometry optimizations using MP2 methodology with augmented correlation-consistent (cc) basis sets are not currently practical for detailed investigations of the larger boron derivatives of primary chemical interest. Density functional theory (DFT) with Pople-style split-valence basis sets^{52–53} provides an economical alternative, but the reliability of specific functional/basis set combinations for describing the incredibly diverse range⁵⁴ of boron chemistry has yet to be fully established. Thus, our MP2 results were compared to those using the hybrid PBE1PBE functional,^{55–56} which makes use of the one-parameter

generalized-gradient approximation (GGA) PBE functional with a 25% exchange and 75% correlation weighting.⁵⁷ Our experience with a variety of PBE1PBE computational levels is that this functional does reasonably well in describing N→B bonds when compared to the corresponding MP2 results;^{29,34–35,39} in contrast, the B3LYP functional does not describe such bonds reliably.^{29,34–39} Additional PBE1PBE calculations that empirically incorporate the effects of dispersion⁵⁸ were performed using QChem 3.2.⁵⁹

Results from continuum solvation models were employed to assess the effects of a bulk aqueous environment on the gas-phase results.⁶⁰ We employed the following implicit solvation models: 1) the IEF Polarizable Continuum Model (PCM) model, developed by Tomasi and coworkers^{61–65} and 2) the conductor-like PCM model (CPCM), introduced by Barone and Cossi.^{66–67} (The UAKS cavity was used for the CPCM solvent model based on the performance indicated by Takano and Houk.⁶⁸) As is well known, such continuum models only provide a description of long-range interactions and have specific limitations in describing protic solvents.^{69–70} Obviously, for the solvent inserted models we investigated it was necessary to include an explicit water molecule in the calculations.

Results and Discussion

In Vacuo

MP2—Calculations were performed on the model *o*-(*N,N*-dialkylaminomethyl)arylboronates **10** to **23** to investigate the factors influencing the balance between the N→B bonded conformers (**10**, **14**, **18** and **21**), the B···OH₂···N solvent inserted forms (**11**, **15**, **19** and **22**), the B-O-H···N intramolecular hydrogen-bonded conformers (**12** and **16**) and those with separated nitrogen and boron centers (**13**, **17**, **20** and **23**), see Figure 4.

As would be expected, the structures with the non-bonded boron and nitrogen centers in all four groups (**13**, **17**, **20** and **23**), were calculated to be consistently higher in energy than the corresponding N→B bonded conformers (**10**, **14**, **18** and **21**); furthermore structures **13** and **17** in groups 1 and 2 were calculated to be higher in energy than the B-O-H···N intramolecular hydrogen-bonded conformers (**12** and **16**). The thermochemistry of the conversions **10**→**13**, **14**→**17**, **18**→**20**, and **21**→**23** at various MP2 levels are listed in Table 1A and provide some measure of the strength of the N→B dative bond in these *o*-(*N,N*-dialkylaminomethyl)arylboronate systems; diffuse functions clearly increase the endothermicity of these processes by some 2 kcal/mol, compare columns 2 and 3. The values of ΔE for these conversions range from +8.3 to +11.9 kcal/mol at the MP2/aug-cc-pVDZ//MP2/cc-pVDZ level and from +6.8 to +9.7 kcal/mol at the MP2/cc-pVTZ//MP2/cc-pVDZ level; thermal corrections calculated at the MP2/6-31+G(*d*)//MP2/6-31+G(*d*) and MP2/cc-pVDZ//MP2/cc-pVDZ levels indicate the values of ΔE are within a few tenths of a kcal/mol of the corresponding values of ΔH_{298}^0 . Interestingly, these computational estimates are significantly higher than previous estimates of the strength of the N→B dative bond in such systems, which range from +3.6 to +6.0 kcal/mol,^{3,28–30} based on the relative stabilities of ternary phosphate complexes in *N*-methyl-*o*-(phenylboronic acid)-*N*-benzylamine.³

There is also general agreement from the MP2 computational results in Table 1A that the B-O-H $\cdots$ N intramolecular hydrogen-bonded conformers of the free acids **12** and **16** are slightly *lower* in energy *in vacuo* than the corresponding dative-bonded N $\rightarrow$ B conformers **10** and **14**, *e.g.* the values of ΔE for the **10** $\rightarrow$ **12** and **14** $\rightarrow$ **16** conversions are -0.7 and -0.9 kcal/mol, respectively, at the MP2/aug-cc-pVDZ//MP2/cc-pVDZ level. This small energy difference suggests that intramolecular N $\rightarrow$ B dative bonds and B-OH $\cdots$ N hydrogen bonds are similar in strength in these *o*-(*N,N*-dialkylaminomethyl)arylboronate systems. The slightly higher energy of the dative-bonded forms might be the result of some strain in the 5-membered N $\rightarrow$ B bonded ring structure.

Additionally, reactions involving an explicit water molecule inserted into the N $\rightarrow$ B dative bond, which result in the structures **11**, **15**, **19**, and **22** shown schematically in Figure 4, are calculated to be thermodynamically favored *in vacuo* at all the MP2 levels we considered, see Table 1A; to the authors knowledge this is the first time this has been reported in the gas phase. It is clear from this Table that basis set effects can significantly alter the calculated reaction thermochemistry, *e.g.* the values of ΔE for these insertions at the MP2/cc-pVDZ//MP2/cc-pVDZ level are some 3–4 kcal/mol *more* negative in energy than the MP2/aug-cc-pVDZ//MP2/cc-pVDZ values; the corresponding values at the MP2/cc-pVTZ//MP2/cc-pVDZ are in much better agreement with the MP2/aug-cc-pVDZ//MP2/cc-pVDZ values.

DFT—The number of atoms involved in the *o*-(*N,N*-dialkylaminomethyl)arylboronate model systems we investigated with MP2 methodology severely limited the correlation-consistent basis sets we could employ for the geometry optimization of these structures; specifically our computer resources restricted us to the Dunning-Woon cc-pVDZ basis set for optimizations which does not include any diffuse functions. In view of the role that diffuse functions play in the MP2 thermochemistry of **10**–**23** noted above (see Table 1A), we decided to re-optimize these structures employing the more economical DFT methodology using the PBE1PBE functional with the larger 6–311++G(*d,p*) and aug-cc-pVDZ basis sets which explicitly include diffuse functions.^{29,34–35,39} Interestingly, overlaying the MP2/cc-pVDZ, PBE1PBE/6–311++G(*d,p*), and PBE1PBE/aug-cc-pVDZ optimized structures showed no significant variation in the geometry as a result of altering the computational methodology from MP2 to PBE1PBE and increasing the size of the basis set, see Figure 1S in the Supplementary Materials. Furthermore, the trends observed for the PBE1PBE reaction energetics are generally in accord to those seen at the various MP2 levels we employed, compare Tables 1A and 1B, although some details are different. For example, the predicted values of ΔE at the various PBE1PBE levels for the conformer conversions **10** $\rightarrow$ **13**, **14** $\rightarrow$ **17**, **18** $\rightarrow$ **20**, and **21** $\rightarrow$ **23** suggest that the strength of the N $\rightarrow$ B dative bond in structures **10**, **14**, **18**, and **21** is substantially *less* than the corresponding MP2 estimates, in much closer agreement with the experimental range of $+3.6$ to $+6.0$ kcal/mol.^{3,28–30} Some caution is required here because these GGA calculations do not adequately treat dispersion (see below). Of course, the diminution of the predicted PBE1PBE N $\rightarrow$ B bond strength is reflected in higher exothermicities at this level for the N $\rightarrow$ B to B-O-H $\cdots$ N conversions. The values of ΔE for the hydrogen insertion reactions are all negative at the various PBE1PBE levels and are in reasonable accord with the results from the comparable MP2 calculations.

Considering the well known failure of the more popular hybrid and GGA functionals to properly describe weak Van der Waals interactions,^{71–72} in conjunction with the relatively small energy differences between some conformers of the *o*-(*N,N*-dialkylaminomethyl)arylboronate model systems involved in this investigation, we felt it necessary to perform single-point energy calculations of the PBE1PBE optimized geometries with the PBE1PBE-D functional using the same basis sets, see Table 1C. The PBE1PBE-D functional incorporates the *empirical* dispersion correction of Grimme;⁵⁸ the QChem 3.2 package was employed for these calculations because it is the only code we have access to that has PBE1PBE-D implemented.⁴⁷ In order to avoid possible double-counting of dispersion effects, the energetics of reactions that included an explicit water molecule, *e.g.* **10** + H₂O → **11**, have not been included in the Table. An excellent discussion of this problem has been provided by Barone *et al.*⁷³; our results for these hydration reactions with the PBE1PBE-D functional support their conclusions.

The addition of these empirical dispersion corrections for conformer conversions such as **10** → **12**(**13**) does not qualitatively change the order of the relative energies of the *o*-(*N,N*-dialkylaminomethyl)arylboronates conformers noted in Tables 1A(MP2) or 1B(PBE1PBE). However, as one might anticipate, it drives the PBE1PBE conformer conversion energies closer to those found with the MP2 calculations. The results of these PBE1PBE-D calculations further emphasize the necessity of taking into account N→B dative bonded and B-O-H···N intramolecular hydrogen-bonded conformers when trying to improve the diol-sensor capabilities of *o*-(*N,N*-dialkylaminomethyl)arylboronate systems.

In PCM and CPCM aqueous solvent—To assess the long-range effects an aqueous solvent may play in determining the structures and energetics of the *o*-(*N,N*-dialkylaminomethyl)arylboronate systems **10–23**, all fourteen of the gas-phase structures were re-optimized in the PCM and CPCM reaction fields of water at the MP2/cc-pVDZ//MP2/cc-pVDZ level; these optimizations were followed by single-point calculations at the MP2/aug-cc-pVDZ//MP2/cc-pVDZ and MP2/cc-pVTZ//MP2/cc-pVDZ levels, see Table 2A and 2B. Additional optimizations in these aqueous environments using DFT methodology at the PBE1PBE/6-311++G(*d,p*) and PBE1PBE/aug-cc-pVDZ levels were also performed, see Table 2C and 2D.

In general, the thermochemical trends noted above for calculations *in vacuo* are also observed in PCM and CPCM aqueous solution, compare corresponding results in Tables 1 and 2, although there is an increase in the conformer conversion and explicit hydration reaction energies when including the effects of these implicit solvation models. Interestingly, for the **10**→**12** and **14**→**16** conformer conversions at the MP2/aug-cc-pVDZ//MP2/cc-pVDZ and MP2/cc-pVTZ//MP2/cc-pVDZ levels suggests that the N→B bonded conformers are slightly *lower* in energy than the B-O-H···N conformers in aqueous solution, contrary to what we found in the gas phase. These calculations show that the description of the intramolecular interaction between nitrogen and boron in *o*-(*N,N*-dialkylaminomethyl)arylboronate systems in aqueous media is quite complex and may involve a combination of N→B, B-O-H···N and B···OH₂···N structures; additional experimental and computational studies need to be performed to establish how to tune this

interaction to enhance the role of one or the other of these structural moieties and to better exploit the pertinent chemical properties of each for various applications.

In contrast to the computational findings from the Anslyn group³² at the B3LYP/6-31+G(*d,p*)/B3LYP/6-31+G(*d,p*) level, our findings on *o*-(*N,N*-dialkylaminomethyl)arylboronic acid **10** in Figure 4 at several MP2 and PBE1PBE levels indicate that the N→B bonded structures are indeed local minima on the PESs for the model *o*-(*N,N*-dialkylaminomethyl)arylboronic acids we considered in this paper (the shortest N···B distance in the *o*-(*N,N*-dialkylaminomethyl)arylboronic acid (*i.e.* *o*-(pyrrolidinylmethyl)phenylboronic acid) structures reported by Anslyn³² was ~2.7 Å, whereas results at the MP2 and PBE1PBE methods of this study predict much shorter distances, 1.768–1.860 Å, see Table 1S and 2S) indicative of a boron-nitrogen dative bond; this difficulty with describing intramolecular N→B bonding in boronic acids appears to be symptomatic of B3LYP methodology.^{29,34–39} On the other hand, there are some areas of agreement with our calculations and those of Anslyn and coworkers³² *e.g.* the boronate ester (formed from the reaction of an *o*-(*N,N*-dialkylaminomethyl)arylboronic acid (*i.e.* *o*-(pyrrolidinylmethyl)phenylboronic acid) with catechol) had a clear N→B dative bond with a N-B distance of 1.80 Å; consistent with our structure **21** which has a calculated range of N-B distances of 1.731–1.790 Å, see Tables 1S and 2S. Other energy minimized structures elucidated by Anslyn and coworkers^{32–33} are comparable to our structures **10**, **11**, **13**, and **23**, see Figure 1S. Although our search of the PESs of these structures established that the Anslyn conformers were indeed local minima, these *o*-(pyrrolidinylmethyl)phenylboronic acids proved to be higher-energy conformers than in our model compounds.

Nitrogen-Boron Distance Comparisons—As a result of the paucity of experimental structural data for *o*-(*N,N*-dialkylaminomethyl)arylboronate systems,^{27,74} we report nitrogen-boron distances in Tables 1S and 2S of the Supplementary Materials. The single-crystal X-ray structure of the *S,S*-diboronic acid (*S,S*-**6**) – L-tartaric acid complex isolated by James and co-workers²⁷ provides a good example of an experimental structure to compare with our calculated structure **11**. All the computational methods we employed perform quite favorably in emulating the two experimental nitrogen-boron distances (3.43 and 3.50 Å) reported for the *S,S*-diboronic acid (*S,S*-**6**) – L-tartaric acid complex, *i.e.* the range of our calculated boron-nitrogen distances for structure **11** is 3.41–3.62 Å (see Tables 1S and 2S). We note that the implicit solvent models tend to predict geometries with contracted nitrogen-boron distances relative to the gas-phase in structures **10**, **14**, **18**, and **21**.

Concluding Remarks

In the development of *o*-(*N,N*-dialkylaminomethyl)arylboronate-based sensors for saccharide detection, it is critical to understand the relative energies of N→B dative-bonded and B-O-H···N hydrogen-bonded conformers, as well as the thermochemistry of solvent inserted forms that yield structures involving a B···OHR···N linkage. The model systems (**10** – **23**) chosen for this investigation represent a transition from the free boronic acid in Group 1 (**10** to **13**), through partial esterification in Group 2 (**14** to **17**), to full esterification in Groups 3 (**18** to **20**) and 4 (**21** to **23**); selection of these particular structures was influenced in part by our available computational resources. These calculations have enabled us to

establish a starting-point from which to determine the role of various nitrogen-boron interactions in *o*-(*N,N*-dialkylaminomethyl)arylboronate-based sensor systems. In general, these findings provide robust thermodynamic evidence^{31,32–33} reiterating that the fluorescence intensity of *o*-(*N,N*-dialkylaminomethyl)arylboronate based sensors requires an understanding of $N \rightarrow B$, $B-O-H \cdots N$ and $B \cdots OH_2 \cdots N$.

Although the behavior of the *o*-(*N,N*-dialkylaminomethyl)arylboronates model systems we investigated proved to be complicated, several thermochemical trends have been identified: **1)** *in vacuo* the calculated $B-O-H \cdots N$ intramolecular hydrogen-bonded form of the free acid **12** (Group 1) and the partially esterified form **16** (Group 2) are consistently *lower* in energy than the corresponding $B \rightarrow N$ dative bonded structures **10** and **14** respectively, using MP2, PBE1PBE, and PBE1PBE-D methodology with a variety of basis sets, but by only a few kcal/mol, see Table 1; **2)** in PCM and CPCM model solutions, it is clear that the energy difference between the $B-O-H \cdots N$ and $B \rightarrow N$ conformers is less than it is in the gas phase, but which of these structures is lowest in energy is dependent on the computational level to some extent, see Tables 1 and 2, and more computational/experimental work will be necessary to establish unambiguously the factors that can tilt the balance in favor of the $B-O-H \cdots N$ or $B \rightarrow N$ conformers; **3)** *in vacuo*, as well as in PCM and CPCM model aqueous solutions, the conformers in which the boron and nitrogen atoms are far separated are significantly higher in energy than the $B-O-H \cdots N$ or $B \rightarrow N$ conformers for all 4 groups shown in Figure 4; **4)** in comparison to MP2 computations, PBE1PBE does quite well in predicting the reaction energies used to determine the relative stabilities of these *o*-(*N,N*-dialkylaminomethyl)arylboronates, although relatively large basis sets appear to be essential **5)** *in vacuo* and in the long range effects of PCM and CPCM aqueous media, the explicit hydration reactions $N \rightarrow B + H_2O \rightarrow B \cdots OH_2 \cdots N$ in all 4 Groups are exothermic; **6)** the economical cc-pVDZ basis set leads to geometries consistent with calculations performed with larger basis sets, but the energies tend to over-stabilize the hydrogen-bonded conformations; **7)** the PBE1PBE functional, in conjunction with basis sets that include diffuse functions, provides an economical approach to studying these *o*-(*N,N*-dialkylaminomethyl)arylboronate systems; **8)** the PBE1PBE-D functional, which incorporates the *empirical* dispersion correction of Grimme,⁵⁸ generates thermodynamic properties closer to those of MP2 than PBE1PBE using comparable basis sets, although more rigorous testing is required to verify this assertion for other boron systems; **9)** the thermochemical results support the conjecture of Wang⁶ and Anslyn^{32–33} that in protic media the B-N interaction in *o*-(*N,N*-dialkylaminomethyl)arylboronates that modulates the fluorescence response when bound to saccharides involves a $B \cdots OH_2 \cdots N$ form rather than a direct $N \rightarrow B$ dative bond.

Finally, we note that all saccharides displaying 1,2- or 1,3- *cis* diol motifs are expected to bind to mono boronic acids, and the greatest fluorescence responses are for those saccharides having the largest binding constants with these acids. Well established trends for binding constants reveal that fructose has a higher binding constant than glucose with mono boronic acids and as such elicits a greater fluorescence response.⁷⁵ The model systems discussed in this article will help direct the future design of boronic acid based fructose (and glucose) sensors as a result of our identification of the relative energies of the $N \rightarrow B$ dative-

bonded and B-O-H $\cdots$ N hydrogen-bonded conformers, as well as the thermochemistry of solvent insertion into N $\rightarrow$ B forms leading to a B $\cdots$ OHR $\cdots$ N linkage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The single-crystal X-ray structure of the S,S-diboronic acid (S,S-6) – L-tartaric acid complex isolated by James and co-workers.²⁷ Whilst the hydrogen atoms of methanol were not directly located it can be inferred that the geometry between the bound and unbound receptors will be similar, each oxygen atom will therefore concurrently bind to the boron centre and hydrogen bond to the nitrogen atom. Boron to nitrogen bond distances of around 3.5 Å were reported [B(1)···N(1)=3.430 Å and B(2)···N(2)=3.500 Å]; Oxygen to nitrogen bond distances of around 2.7 Å were reported [N(1)···O(1)=2.655 Å and N(2)···O(2)=2.693 Å]. Atoms marked in red represent oxygen, pink boron, grey carbon and blue nitrogen. For clarity hydrogen atoms are not displayed. The red dotted lines represent hydrogen bonds.

Figure 2.

Morrison's proposed complexes of the cis-1,2-cyclopentanediol ester of 8-quinolineboronic acid with solvent water and phenol molecules bridging the nitrogen and boron centres.³¹

Figure 3. The B-O-H $\cdots$ N(**9a**) intramolecular hydrogen-bonded and the B $\cdots$ OHR $\cdots$ N(**9b**) solvent-inserted structures are illustrated.

Figure 4.

The o-(N,N-dialkylaminomethyl)arylboronates **10** to **23** optimized in this investigation.

Scheme 1.

The extent of the interaction between nitrogen and boron is illustrated within the upper and lower bounds of possible contact depicted as the cyclic and acyclic forms.³

Table 1

Reaction Energies, $E(\Delta H_{298}^0)$ (kcal/mol), in *Vacuo* at the **A.** MP2/6-311++G(d)//MP2/6-311+G(d), MP2/6-311++G(d,p), MP2/cc-pVDZ//MP2/cc-pVDZ, MP2/aug-cc-pVDZ//MP2/cc-pVDZ, and MP2/cc-pVTZ//MP2/cc-pVDZ; **B.** PBE1PBE/6-311+G(d)//PBE1PBE/6-311+G(d), PBE1PBE/6-311++G(d,p)//PBE1PBE/6-311++G(d,p), PBE1PBE/cc-pVDZ//PBE1PBE/cc-pVDZ, and PBE1PBE/aug-cc-pVDZ//PBE1PBE/aug-cc-pVDZ; **C.** PBE1PBE-D/6-311+G(d)//PBE1PBE/6-311+G(d,p), PBE1PBE-D/6-311++G(d,p)//PBE1PBE/6-311++G(d,p), PBE1PBE-D/cc-pVDZ//PBE1PBE/cc-pVDZ, and PBE1PBE-D/aug-cc-pVDZ//PBE1PBE/aug-cc-pVDZ Computational Levels.

A. MP2					
Reaction/Level	MP2/6-31+G(d)//MP2/6-31+G(d)	MP2/6-311++G(d,p)//MP2/6-31+G(d)	MP2/cc-pVDZ//MP2/cc-pVDZ	MP2/aug-cc-pVDZ//MP2/cc-pVDZ	MP2/cc-pVTZ//MP2/cc-pVDZ
$\Delta E(\Delta H_{298}^0)$ (kcal/mol)					
10 + H ₂ O → 11	-3.1 (-1.2)	-2.6	-6.9 (-5.6)	-2.4	-3.2
10 → 12	-1.0 (-0.4)	-1.2	-3.3 (-2.7)	-0.7	-1.9
10 → 13	+9.5 (+9.7)	+8.8	+7.5 (+7.7)	+9.6	+8.0
14 + H ₂ O → 15	-6.3 (-3.7)	-3.2	-7.9 (-6.7)	-3.5	-3.6
14 → 16	-1.9 (-1.3)	-1.9	-3.8 (-3.2)	-0.9	-1.2
14 → 17	+8.2 (+8.5)	+7.8	+6.8 (+7.1)	+9.0	+8.5
18 + H ₂ O → 19	-9.2 (-6.8)	-6.4	-11.3 (-10.0)	-6.8	-8.0
18 → 20	+7.7 (+7.7)	+7.0	+6.8 (+6.8)	+8.3	+6.8
21 + H ₂ O → 22	-6.0 (-3.6)	-2.8	-7.3 (-5.9)	-2.7	-4.4
21 → 23	+10.8 (+11.0)	+10.0	+9.2 (+9.3)	+11.9	+9.7

B. PBE1PBE			
Reaction/Level	PBE1PBE/6-31+G(d)//PBE1PBE/6-31+G(d)	PBE1PBE/6-311++G(d,p)//PBE1PBE/6-311++G(d,p)	PBE1PBE/cc-pVDZ//PBE1PBE/cc-pVDZ
10 + H ₂ O → 11	-5.8 (-3.8)	-3.3 (-1.7)	-2.6 (-1.0)
10 → 12	-5.1 (-4.6)	-4.8 (-4.3)	-4.3 (-3.8)
10 → 13	+5.2 (+5.3)	+4.8 (+5.0)	+5.0 (+5.1)
14 + H ₂ O → 15	-6.5 (-4.5)	-4.1 (-2.5)	-3.2 (-1.7)
14 → 16	-6.3 (-5.8)	-6.4 (-5.9)	-5.2 (-4.9)
14 → 17	+3.9 (+4.0)	+3.5 (+3.7)	+3.9 (+3.9)

B. PBE1PBE				
Reaction/Level	PBE1PBE/6-31+G(d)//PBE1PBE/6-31+G(d)	PBE1PBE/6-311++G(d,p)//PBE1PBE/6-311++G(d,p)	PBE1PBE/cc-pVDZ//PBE1PBE/cc-pVDZ	PBE1PBE/aug-cc-pVDZ//PBE1PBE/aug-cc-pVDZ
18 + H ₂ O → 19	−9.7 (−7.8)	−7.2 (−5.7)	−13.9 (−12.9)	−6.2 (−4.8)
18 → 20	+2.3 (+2.3)	+2.0 (+2.0)	+2.7 (+2.7)	+2.5 (+2.5)
21 + H ₂ O → 22	−6.5 (−4.7)	−4.1 (−2.7)	−10.5 (−9.5)	−3.1 (−1.7)
21 → 23	+4.4 (+4.5)	+4.1 (+4.2)	+4.0 (+4.0)	+4.8 (+4.8)

C. PBE1PBE-D ^a				
Reaction/Level	PBE1PBE-D/6-31+G(d)//PBE1PBE/6-31+G(d)	PBE1PBE-D/6-311++G(d,p)//PBE1PBE/6-311++G(d,p)	PBE1PBE-D/cc-pVDZ//PBE1PBE/cc-pVDZ	PBE1PBE-D/aug-cc-pVDZ//PBE1PBE/aug-cc-pVDZ
10 → 12	−3.8	−3.6	−4.0	−2.9
10 → 13	+8.0	+7.5	+7.5	+7.9
14 → 16	−4.0	−3.8	−4.2	−3.0
14 → 17	+7.5	+7.2	+7.3	+7.6
18 → 20	+6.9	+6.6	+7.0	+7.3
21 → 23	+8.7	+8.6	+8.4	+9.2

^aThese calculations were all performed with QChem 3.2 using a grid with 75 radial shells and 302 angular points.

Table 2

Reaction Energies, $E(\Delta H_{298}^0)$ (kcal/mol), in PCM and CPCM Implicit Aqueous Media at the **A.** PCM(MP2): MP2/cc-pVDZ//MP2/cc-pVDZ, MP2/cc-pVDZ//MP2/cc-pVDZ, and MP2/cc-pVTZ//MP2/cc-pVDZ; **B.** CPCM(MP2) MP2/cc-pVDZ//MP2/cc-pVDZ, MP2/cc-pVDZ//MP2/cc-pVDZ, and MP2/cc-pVTZ//MP2/cc-pVDZ; **C.** PCM(PBE1PBE): PBE1PBE/6-31+G(d), PBE1PBE/6-311++G(d,p), PBE1PBE/cc-pVDZ, and PBE1PBE/aug-cc-pVDZ; **D.** CPCM(PBE1PBE): PBE1PBE/6-31+G(d), PBE1PBE/cc-pVDZ, and PBE1PBE/aug-cc-pVDZ Computational Levels.

A. PCM(MP2)				
Reaction/Level	PCM: MP2/cc- pVDZ// MP2/cc-pVDZ	PCM: MP2/aug-cc- pVDZ// MP2/cc-pVDZ	PCM: MP2/cc- pVTZ// MP2/cc-pVDZ	
	$\Delta E(\Delta H_{298}^0)$ (kcal/mol)			
10 + H ₂ O → 11	-5.5 (-3.3)	-3.5		-3.4
10 → 12	+0.2 (+0.2)	+3.3		+2.0
10 → 13	+11.1 (+10.9)	+13.8		+12.1
14 + H ₂ O → 15	-7.5 (-5.3)	-3.5		-4.8
14 → 16	-0.7 (-0.6)	+2.7		+0.9
14 → 17	+10.3 (+12.6)	+12.9		+11.4
18 + H ₂ O → 19	-11.2 (-8.8)	-7.2		-8.5
18 → 20	+9.4 (+9.3)	+10.8		+9.3
21 + H ₂ O → 22	-7.4 (-5.1)	-3.0		-4.8
21 → 23	+12.5 (+12.3)	+15.5		+13.3

B. CPCM(MP2)			
Reaction/Level	CPCM: MP2/cc-pVDZ//MP2/cc-pVDZ	CPCM: MP2/aug-cc-pVDZ//MP2/cc-pVDZ	CPCM: MP2/cc-pVTZ//MP2/cc-pVDZ
	$\Delta E(\Delta H_{298}^0)$ (kcal/mol)		
10 + H ₂ O → 11	-4.3 (-1.7)	-1.5	-2.2
10 → 12	-1.0 (-1.2)	+2.1	+0.8
10 → 13	+7.9 (+7.4)	+11.6	+10.0
14 + H ₂ O → 15	-7.7 (-5.7)	-2.9	-4.3
14 → 16	-1.4 (-1.7)	+2.3	+0.6
14 → 17	+8.9 (+8.4)	+11.6	+9.9

B. CPCM(MP2)			
Reaction/Level	CPCM: MP2/cc-pVDZ//MP2/cc-pVDZ	CPCM: MP2/au ^g -cc-pVDZ//MP2/cc-pVDZ	CPCM: MP2/cc-pVTZ//MP2/cc-pVDZ
18 + H ₂ O → 19	−10.9 (−8.7)	−6.4	−7.9
18 → 20	+8.7 (+8.3)	+10.2	+8.7
21 + H ₂ O → 22	−7.2 (−5.1)	−2.4	−4.4
21 → 23	+11.5 (+11.1)	+14.4	+12.3

C. PCM(PBE1PBE)				
Reaction/Level	PCM: PBE1PBE/6-31+G(d)//PBE1PBE/6-31+G(d)	PCM: PBE1PBE/6-311++G(d,p)//PBE1PBE/6-311++G(d,p)	PCM: PBE1PBE/ccpVDZ//PBE1PBE/ccpVDZ	PCM: PBE1PBE/au ^g -cc-pVDZ//PBE1PBE/au ^g -cc-pVDZ
10 + H ₂ O → 11	−5.4 (−2.8)	−3.0 (−0.6)	−8.4 (−6.2)	−3.1 (−0.7)
10 → 12	−1.5 (−1.6)	−1.3 (−1.5)	−2.3 (−2.3)	−0.8 (−1.1)
10 → 13	+9.0 (+8.8)	+8.6 (+8.4)	+8.1 (+7.9)	+8.9 (+8.6)
14 + H ₂ O → 15	−6.0 (−3.4)	−3.8 (−1.5)	−10.8 (−8.7)	−3.8 (−1.5)
14 → 16	−3.1 (−3.1)	−2.9 (−3.0)	−3.8 (−3.8)	−2.3 (−2.4)
14 → 17	+6.9 (+6.7)	+6.9 (+6.7)	<i>a</i>	+7.2 (+7.0)
18 + H ₂ O → 19	−9.5 (−6.7)	−7.0 (−4.5)	−15.2 (−14.0)	−7.0 (−4.6)
18 → 20	+4.8 (+4.6)	+4.6 (+4.4)	<i>a</i>	+5.1 (+4.9)
21 + H ₂ O → 22	−6.5 (−4.0)	−4.2 (−1.9)	−10.9 (−8.9)	−4.1 (−1.9)
21 → 23	+8.2 (+8.0)	+7.9 (+7.8)	+7.4 (+7.3)	+8.3 (+8.1)

D. CPCM(PBE1PBE)			
	CPCM: PBE1PBE/6-31+G(d)//PBE1PBE/6-31+G(d)	CPCM: PBE1PBE/6-311++G(d,p)//PBE1PBE/6-311++G(d,p)	CPCM: PBE1PBE/cc-pVDZ//PBE1PBE/cc-pVDZ
10 + H ₂ O → 11	−4.4 (−1.7)	−1.9 (+0.5)	−2.0 (+0.4)
10 → 12	−2.4 (−2.7)	−2.4 (−2.7)	−1.9 (−2.4)
10 → 13	+6.8 (+6.2)	+5.7 (+5.1)	+8.2 (+7.2)
14 + H ₂ O → 15	−5.3 (−2.8)	−3.9 (−1.6)	−3.0 (−0.7)
14 → 16	−3.1 (−3.3)	−4.0 (−4.3)	−2.5 (−2.8)
14 → 17	+5.2 (+4.7)	+4.9 (+4.4)	+7.9 (+6.9)
18 + H ₂ O → 19	−8.9 (−6.3)	−6.4 (−4.0)	−6.2 (−3.8)
18 → 20	+4.0 (+3.7)	+3.8 (+3.4)	+4.6 (+4.2)
21 + H ₂ O → 22	−6.1 (−3.7)	−3.7 (−1.5)	−3.5 (−1.4)

D. CPCM(PBE1PBE)				
	CPCM: PBE1PBE/6-31+G(d)/PBE1PBE/6-31+G(d)	CPCM: PBE1PBE/6-311+G(d,p)//PBE1PBE/6-311+G(d,p)	CPCM: PBE1PBE/cc-pVDZ//PBE1PBE/cc-pVDZ	CPCM: PBE1PBE/ang-cc-pVDZ//PBE1PBE/ang-cc-pVDZ
21 → 23	+7.1 (+6.7)	+6.8 (+6.3)	-4.0 (-5.0)	+8.5 (+7.2)

^d All attempts at computing geometric minima for structures **17** and **20** were unsuccessful.