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Monosubstituted Phenylboronic Acids, $R-B(OH)_2$ ($R = C_6H_5$, $C_6H_4CH_3$, $C_6H_4NH_2$, C_6H_4OH , and C_6H_4F): A Computational Investigation

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Abstract

Phenylboronic acids (PBAs) are an important class of compounds with diverse applications in synthetic, biological, medicinal, and materials chemistry. In this investigation we report structural and thermochemical parameters for several monosubstituted *ortho*, *meta*, and *para* PBAs, $R-B(OH)_2$ ($R = C_6H_5$, $C_6H_4CH_3$, $C_6H_4NH_2$, C_6H_4OH , and C_6H_4F). Equilibrium geometries of all the PBAs discussed in this article were obtained using second-order Møller-Plesset perturbation theory (MP2) with the Dunning-Woon aug-cc-pVDZ basis set; heats of formation (HOF) were calculated at the Gaussian-3 (G3) level of theory. The *endo-exo* conformers of all the positional isomers of these PBAs were lowest in energy. Using HOF for the monosubstituted PBAs calculated at the G3 level of theory, in conjunction with the experimental HOF for benzene, toluene, aniline, phenol, and fluorobenzene, the values of ΔH_{298}^0 for the transfer processes $C_6H_6 + C_6H_4X-B(OH)_2 \rightarrow C_6H_5X + C_6H_5-B(OH)_2$ ($X = CH_3$, NH_2 , OH , and F) are found to be in good agreement with values of ΔH_{298}^0 calculated at the MP2(FC)/aug-cc-pVTZ//MP2(FC)/aug-cc-pVTZ computational level; the bonding in the reactants and products for these transfer reactions are well-matched and thermochemical calculations at this level are expected to be very accurate, providing checks on the G3 HOF calculations.

TOC image

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Keywords

Monosubstituted Phenylboronic Acids; Second-order Møller-Plesset Perturbation Theory (MP2); Heats of Formation; G3 Level of Theory

Introduction

Phenylboronic acids (PBAs) are a versatile class of compounds with diverse applications covering synthetic, biological, medicinal, and materials chemistry. PBAs are commonly used in cross coupling reactions such as the Suzuki reaction involving organoboron reagents with aryl- or alkenylhalides [1, 2]. They exhibit high affinities towards polar molecules with specific functional groups such as carbohydrates, serving as receptors and sensors for saccharides [3-8]. They also act as transmembrane carriers to selectively transport monosaccharides through lipid bilayers [9]. PBAs' high affinity to carbohydrates have made them excellent candidates as antimicrobial agents [10-12]. In addition, immobilized PBAs have been used as chromatographic supports that selectively retains ribonucleosides, steroids, and proteins [13-19]. Moreover, boronophenylalanine, an PBA containing amino acid, is in clinical trial as a low molecular weight boron delivering agent for boron neutron capture therapy for cancer [20]. Despite increasing interest in these acids – hundreds are currently available commercially – there remains relatively little experimental/computational structural or thermochemical data available in the literature, particularly for the basic monomeric forms of substituted PBAs [21-28].

The position and type of substituent on the ring plays a central role in applications of monosubstituted PBAs. For example, electron withdrawing groups lower the pK_a of the boronic acid, increasing the acidity of the boron hydroxyl groups. Changes in the position of substituents, *i.e.* *ortho*, *para*, *meta*, can alter the performance of a PBA as a fluorophore. Even slight rotations by attached groups can affect hydrogen bonding networks important for modulating the fluorescence of boronic acid containing proteins [29]. The development of boronic acids for traceless delivery of proteins into cells is an emerging frontier. Substituted phenylboronic acids are refined as effective delivery systems to invoke “cell-penetrating peptides” [30].

With the increasing development of boronic acid biochemical applications, we have carried out a computational investigation of monosubstituted phenylboronic acids in order to characterize the effect of substituent variety and placement. Larger macromolecular simulations rely, in part, on parameters derived from quantum mechanical computations. Reliable and consistent parameters for boron are sparse. As a result, we continue our effort to obtain reliable data for a series of fundamental boronic acids through a systematic investigation of the structures and relative energies of several *para*, *meta*, and *ortho* monosubstituted PBAs, $R-B(OH)_2$ ($R = C_6H_5$, $C_6H_4CH_3$, $C_6H_4NH_2$, C_6H_4OH , and C_6H_4F).

Computational Methods

Equilibrium geometries of all the PBAs involved in this article were obtained using second-order Møller-Plesset perturbation theory (MP2) [31] with the frozen core (FC) option, which neglects core-electron correlation; the Dunning-Woon aug-cc-pVDZ and aug-cc-pVTZ basis sets [32-35] were employed in these optimizations. In some cases density functional theory (DFT) calculations using the B3LYP [36], PBE1PBE [37-39], and M06-2X [40] hybrid functionals were carried out for comparison; Pople-style basis sets were used for some of these calculations [41]. The GAUSSIAN 03 [42] and GAUSSIAN 09 [43] suits of programs were used for all the calculations. Frequency analyses were performed analytically for all the PBAs in this investigation at the MP2/aug-cc-pVDZ level to confirm that the optimized structures were local minima on the potential energy surface (PES) and to correct reaction energies to 298.15 K. Heats of formation (HOF) at 298.15K were calculated at the G3 level of theory [44]; this particular extrapolation procedure was chosen based on our experience calculating heats of formation for aliphatic boronic acids [45], where additional experimental/computational data are available for comparison. Atomic charges were obtained from natural population analyses (NPA) and the bonding was analyzed with the aid of natural bond orbitals (NBOs) [46-48].

Results and Discussion

Experimentally it can be difficult to obtain pure samples of some phenylboronic acids that actually have the formula $R-B(OH)_2$ because they often separate from aqueous solutions as hydrates that undergo dehydration to yield boroxines [49, 50]; for example, Rogowska, *et al.* [51] reported recently that their attempts to determine the crystal structure of *p*-fluorophenylboronic acid failed because the system transformed to tris(4-fluorophenyl)boroxine. Furthermore, in the solid state boronic acids usually form hydrogen-bonded networks making it difficult to obtain structural parameters on the isolated monomeric forms [52-54]; an excellent experimental/computational investigation of the impact of intermolecular hydrogen bonding on the structural properties of phenylboronic acid itself has been given by Cyranskia *et al.* [55].

There are three possible orientations of the hydroxyl groups in boronic acids: *endo-exo*, *anti*, and *syn* [54]; these arrangements are illustrated for PBAs in Figure 1; the two possible *ortho* and *meta* positional isomers of monosubstituted PBAs are distinct for the *endo-exo* orientation. In the case of small aliphatic boronic acids, calculations have typically found the *endo-exo* conformers are lowest in energy [56-63], although exceptions have been reported

[64]; energy differences between the *endo-exo* and *anti* conformers are often rather small, while the *syn* conformer is highest in energy. In the case of PBAs, however, substituents on the ring, particularly at the *ortho* positions, are likely to play a significant role in determining the preferred orientation of the hydroxyl groups in the gas-phase monomeric forms. To the authors' knowledge, there are few values of the relative energies for these three conformers for monosubstituted PBAs available in the literature [21, 27, 65-67].

Phenylboronic Acid: $\text{C}_6\text{H}_5\text{-B(OH)}_2$

Planar conformers of PBA with the *endo-exo* and *syn* orientations of the boronic acid moieties, see Figure 1, were found to be local minima on the potential energy surface (PES) at the MP2/aug-cc-pVDZ level; Kua and Iovine [68] found the planar *endo-exo* form to be a local minimum on the B3LYP/6-311+G(*d*) PES. In contrast, the planar *anti* conformer of PBA proved to be a rotational transition state (TS) at the MP2/aug-cc-pVDZ level, presumably a result of adverse steric interactions involving the *ortho* hydrogen atoms on the phenyl ring and the hydroxyl hydrogen atoms of the boronic acid moiety; a nonplanar *anti* form with the boronic acid moiety rotated $\sim 33^\circ$ relative to the phenyl ring was a local minimum on the PES ($\tau_{\text{CCBO}} = \sim 33.0^\circ$ and $\tau_{\text{CBOH}} = \sim 5.7^\circ$ with the hydroxyl hydrogen atoms on opposite sides of the OBO plane), but it was only ~ 0.5 kcal/mol lower in energy than the planar form.

Since PBA is the parent compound in this investigation, it seemed prudent to perform additional optimizations and frequency analyses of the various conformers using several alternative computational levels to confirm the MP2/aug-cc-pVDZ results. DFT optimizations using the hybrid B3LYP [36], PBE1PBE [37-39], and M06-2X [40] functionals with the aug-cc-pVDZ basis set also find that planar *endo-exo* conformers are local minima on the respective PESs; improving the basis set to aug-cc-pVTZ does not change either the MP2 or DFT findings. On the other hand, MP2, B3LYP, and PBE1PBE optimizations using the Pople-style 6-311++G(*d,p*) basis set find planar *endo-exo* conformers to be TSs; reoptimizing $\text{C}_6\text{H}_5\text{-B(OH)}_2$ using nonplanar starting geometries generated local minima on the PESs with small torsional angles ($\tau_{\text{OBCC}} = 1.7^\circ$ and 0.8° at the B3LYP/6-311++G(*d,p*) and PBE1PBE/6-311++G(*d,p*) levels, respectively). This discrepancy appears to be associated with the Pople-style basis set used in these calculations, *e.g.* Rodriguez-Cuamatzi *et al.* [69] also reported nonplanar local minima for the *endo-exo* monomer of PBA at the MP2/6-31G(*d,p*) level. However, a geometry optimized planar structure of PBA proved to be a local minimum at the M06-2X/6-311++G(*d,p*) level and improving the basis set to 6-311++G(2*df,pd*) with the B3LYP and PBE1PBE functions also resulted in planar local minima. Although no direct experimental structural data are available *in vacuo* to resolve this issue for $\text{C}_6\text{H}_5\text{-B(OH)}_2$, these calculations suggest that it is unlikely that there is any significant deviation from planarity for this acid in the gas phase. There are no corresponding discrepancies with calculations for the *syn* or *anti* conformers of PBA. Optimizations using the B3LYP and PBE1PBE functionals with the aug-cc-pVDZ, aug-cc-pVTZ, or 6-311++G(*d,p*) basis sets all found the planar *syn* conformer of PBA to be a local minimum on the PES. Similarly, planar *anti* conformers were found to be TSs, consistent with the MP2(FC)/aug-cc-pVDZ results noted above; nonplanar conformers with τ_{CCBO} torsional angles of ca. 29.5° and 30.4° at the

B3LYP/aug-cc-pVDZ and PBE1PBE/aug-cc-pVDZ levels respectively were found to be local minima on the PESs.

X-ray crystal structure data for the *endo-exo* form of PBA are available at 295K [52] and 100K [55], although these pertain to asymmetric hydrogen-bonded units of two molecules of the acid in the solid state; under these conditions there is some twist of the phenyl rings with respect to the boronic acid moieties (at 295K: 6.6° and 21.4°; at 100K: 6.3° and 21.0° for the two independent molecules). Similar twists have also been observed in the crystal structures of several substituted PBA dimers [28, 53, 70], suggesting a relatively flat rotational potential energy curve around the C–B bond. Indeed, the calculated values of $H^\ddagger$ for internal rotation about the C–B bond for the *endo-exo*, *anti*, and *syn* conformers of the PBA monomer in the gas phase are only 3.0 kcal/mol, 1.3 kcal/mol, and 4.8 kcal/mol respectively at the MP2/aug-cc-pVDZ level.

Selected structural parameters for $C_6H_5-B(OH)_2$ are shown in Figure 1, and additional values are listed in Supplemental Materials at a variety of computational levels. For comparison, we note that the carbon-carbon bond lengths in isolated benzene are 1.408 Å [1.394 Å] at the MP2/aug-cc-pVDZ [MP2/aug-cc-pVTZ] levels. Clearly, the only carbon-carbon bond lengths in the phenyl ring significantly altered by the presence of the boronic acid moiety involve the carbon atom bound to the boron atom, and these two bond lengths increased by only ca. 0.01 Å; the CC(B)C *ipso* angle is $\sim 2^\circ$ less than the CCC angles in benzene. The calculated boron-carbon bond length in the *endo-exo* conformer of PBA, 1.574 Å [1.567 Å], is just slightly shorter than the boron-carbon bond length in the corresponding conformer of the aliphatic boronic acid $H_3C-B(OH)_2$, 1.581 Å [1.574 Å]. Furthermore, the length of the boron-carbon bond in the rotational TS of the boronic acid moiety in $C_6H_5-B(OH)_2$ (the τ_{CCBO} torsional angles are ca. 90°, orienting the *p*-orbital on boron into the plane of the phenyl ring) is only ~ 0.003 Å longer than in the planar form at the MP2/aug-cc-pVDZ level, and the NPA charge on the boron atom is less than 0.01e more positive in the TS. There is also relatively little effect of the phenyl ring on the structure of the boronic acid moiety. The boron-oxygen bond lengths in the *endo-exo* conformer of PBA, 1.388 Å [1.377 Å] and 1.382 Å [1.371 Å], are quite similar to the corresponding lengths in $H_3C-B(OH)_2$, 1.393 Å [1.378 Å] and 1.382 Å [1.368 Å]. The net charge on the $-B(OH)_2$ moieties in $C_6H_5-B(OH)_2$, +0.36e, and $H_3C-B(OH)_2$, +0.34e, are nearly the same using the MP2/aug-cc-pVDZ density. These results are consistent with the notion that the interaction of the boronic acid moiety and the pi-electron density of the phenyl ring are relatively weak.

In Table 2 we list relative energies for the *endo-exo*, *anti*, and *syn* forms of PBA; the planar *endo-exo* conformer is lowest in energy, presumably a consequence of a weak intramolecular O $\cdots$ H interaction within the boronic acid moiety. Interestingly, the planar *syn* conformer is only ~ 2.0 kcal/mol higher than the *endo-exo* conformer at the MP2/aug-cc-pVTZ level, whereas the nonplanar *anti* conformer is ~ 2.3 kcal/mol higher in energy than the *endo-exo* conformer.

The HOF for PBA calculated at the G3 levels of theory are given in Table 3. To the authors' knowledge there is no direct experimental value available for the HOF of PBA. However, two estimates of $H_f(298.15K)$ have been given in the literature, -151.77 kcal/mol [71] and

–152.26 kcal/mol [71, 72], based on energy decomposition schemes. The calculated G3 values of $H_f(298.15\text{K})$ for the *endo-exo* form, –136.4 kcal/mol, is significantly less negative than the literature estimates, see Table 2. To help assess the merits of the different values, we considered the reaction:

The calculated values of ΔH_{298}^0 for this reaction using the *endo-exo* conformer of PBA are +19.9 kcal/mol and +23.1 kcal/mol at the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ levels, respectively. Experimental heats of formation for benzene, +19.8±0.2 kcal/mol, and water, –57.80±0.01 kcal/mol, are well established [73]; the HOF for boric acid is not as well established experimentally, but high-level calculations by Grant and Dixon [74] predict a value of –239.8±1.5 kcal/mol, in good agreement with the value of –240.0±0.6 kcal/mol estimated by Gurvich *et al.* [75] Using the calculated values of ΔH_{298}^0 for reaction (1), in conjunction with the experimental heats of formation of benzene, water, and boric acid, suggests $H_f(298.15\text{K})$ for PBA is *ca.* –139 kcal/mol, in reasonable agreement with the value predicted from the G3 level of theory.

Monosubstituted Phenylboronic Acids: $\text{C}_6\text{H}_4\text{R}-\text{B}(\text{OH})_2$ (R = CH₃, NH₂, OH, and F)

Methylphenylboronic, aminophenylboronic, hydroxyphenylboronic, and fluorophenylboronic acids are available commercially and are versatile intermediates in organic synthesis. The numbering system we employed for the calculations is shown in Figure 2. Several possible orientations of the CH₃, NH₂, and OH substituents were explicitly explored. Although the –B(OH)₂ group is generally considered *meta* directing, interactions involving the hydroxyl groups and substituents at the *ortho* position play a significant role in determining the relative energies of the possible isomers.

Methylphenylboronic acid: $\text{C}_6\text{H}_4\text{CH}_3-\text{B}(\text{OH})_2$

The five possible structural isomers of methylphenylboronic acid (MPBA) (tolylboronic acid, tolueneboronic acid) were optimized at the MP2/aug-cc-pVDZ level; no symmetry was employed during these optimizations, but the CALCALL option available in GAUSSIAN was employed to help resolve the orientation of the methyl group. The phenyl ring and the boronic acid moiety are essentially coplanar for the 2-, 3-, 4-, and 5-isomers of this conformer, with one of the methyl C–H bonds in the plane of the phenyl ring, whereas for 6-MPBA the OBO and (nominal) ring planes are rotated by *ca.* 30.0° ($\tau_{\text{C}_2\text{C}_1\text{BO}_a} \approx 30.0^\circ$), see Table 1. It should be noted that the methyl C–H bond that is in the plane for the *para*-isomer is on the same side as the O_a–H_a bond, see Figure 2; reoptimizing this isomer with this C–H bond rotated 180° positioning it on the same side as the O_s–H_s bond proved to be a TS, but only 0.01 kcal/mol higher in energy. Additional DFT optimizations and frequency analyses were carried out using the B3LYP and PBE1PBE functionals for this *para* isomer with the ring and boronic acid moiety plane constrained to be coplanar and one of the methyl C–H bonds forced to lie in the same plane on the O_a–H_a side; the resulting structures were indeed local minima on the respective PESs using the aug-cc-pVDZ basis set, in accord with the

corresponding MP2 optimizations, but the structure was a TS using the 6-311++G(*d,p*) basis set. Unconstrained PBE1PBE/6-311++G(*d,p*) optimizations of the two *meta* isomers led to more nonplanar geometries than those from the MP2 and PBE1PBE optimizations using the aug-cc-pVDZ basis set.

Comparing the structural parameters of the *endo-exo* conformer of the various MPBA isomers to those in PBA shows that the effect of the methyl group is minimal, *e.g.* comparable bond lengths consistently change by less than 0.01 Å, and the C6C1C2 (*ipso*) angle, which varies over a narrow range from 117.4° to 118.4°, differs at most by ~0.6°. The presence of the methyl group consistently reduces the CC(CH₃)C ring angle at the point of attachment compared to the corresponding value in PBA. This observation is in agreement with the crystal structure of *para*-MPBA [28]. The reported CC(CH₃)C ring angle is between 117.4° to 118.3°. The corresponding ring angle in unsubstituted PBA is reported to be between 120.0° to 120.3° [52].

The *endo-exo* conformer of *para*-MPBA is the lowest-energy isomer at the MP2/aug-cc-pVDZ level, but the two distinct *meta* isomers are only slightly higher in energy, see Table 2; the two *ortho* isomers are ca. 1.3-1.4 kcal/mol higher in energy, presumably the result of adverse steric interactions involving the proximate methyl and hydroxyl groups. This finding is consistent with the *ortho, para* directing nature of the methyl group. The energy ordering of the MPBA isomers is the same at the PBE1PBE/6-311++G(*d,p*) level as it is at the MP2/aug-cc-pVDZ level. Similar to what we found for PBA, the *syn* conformers of the 3-, 4-, and 5-MPBA isomers are lower in energy than the corresponding *anti* conformers, and ca. 2.0 kcal/mol higher in energy than the corresponding *endo-exo* conformers; the phenyl ring and boronic acid moieties are not coplanar in these *anti* conformers ($\tau_{\text{C2C1BOa}} = 32.4^\circ, 31.6^\circ, \text{ and } 32.4^\circ$ for 3-, 4-, and 5-isomers respectively) which are ca. 0.4 kcal/mol higher in energy than the *syn* conformers. The *anti* conformers of the 2- and 6-MPBA are very nonplanar ($\tau_{\text{C2C1BOa}} \approx 47.2^\circ$) and 0.3 kcal/mol lower in energy than the *syn* conformers, see Table 2. The value of $H^\ddagger$ for the rotational barrier about the C–B bond in the *endo-exo* conformer of *p*-MPBA isomer is 3.7 kcal/mol, slightly higher than this barrier in PBA, 3.0 kcal/mol; this is consistent with the slightly shorter B–C bond length of 1.572 Å in the 4-MPBA.

HOF for the various isomers of MPBA were calculated at the G3 level of theory, see Table 3; for the *endo-exo* conformer of *p*-MPBA the predicted HOF is –144.7 kcal/mol. To help gauge the accuracy of these calculated HOF values, we considered the transfer reaction:

This reaction is well balanced with respect to the bonding types in the reactants and products in the spirit pioneered by George *et al.* [76-78] and clarified by Wheeler *et al.* [79]; calculations at the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ levels are expected to accurately predict its thermochemistry. As would be expected, this reaction is nearly thermoneutral for *p*-MPBA; the calculated values of ΔH_{298}^0 are +0.4 kcal/mol and +0.3 kcal/mol at the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ levels respectively. Experimental HOF for benzene, +19.8±0.2 kcal/mol, and toluene, +12.0±0.26 kcal/mol are available in the

literature [80]. Using the MP2/aug-cc-pVTZ value of ΔH_{298}^0 , in conjunction with the literature HOF values of C_6H_6 and $C_6H_5CH_3$, suggest that the HOF of *p*-MPBA should be ca. 8.1 kcal/mol more negative than the HOF of PBA itself. Indeed, the calculated HOF of *p*-MPBA at the G3 level of theory is 8.25 kcal/mol more negative than the G3 value for PBA, see Table 3.

Aminophenylboronic acid: $C_6H_4NH_2-B(OH)_2$

The three conformers of all the constitutional isomers of aminophenylboronic acid (APBA) were optimized at the MP2/aug-cc-pVDZ level; no symmetry constraints were employed during these calculations and several possible orientations of the amino group were considered. As expected the structure in the vicinity of the nitrogen atom is pyramidal for the 3-, 4-, and 5-isomers, where the NH_2 group is relatively distant from the boronic acid moiety; specifically for the para isomer, the three angles around the nitrogen atom are $\angle HNC = 114.2^\circ$, 114.3° and $\angle HNH = 111.0^\circ$ at the MP2/aug-cc-pVDZ level. For all three of these isomers, both N–H bonds optimized to the same side of the (nominal) phenyl ring. There is also some small twisting of the boronic acid moiety and the phenyl ring where $\tau_{C_2C_1BO_a} = 6.0^\circ$, 0.9° , and 2.1° respectively for the 3-, 4-, and 5-isomers, respectively, see Table 1. For the 2- and 6-isomers the structure surrounding the nitrogen atom involves strong $BO_a-H_a \cdots NH_2$ and $NH \cdots O_s-H_s$ interactions respectively linking the $-NH_2$ and $-B(OH)_2$ groups; the $H_a \cdots N$ and $H \cdots O_s$ distances, 1.963[1.980] Å and 2.030[2.020] Å at the MP2/aug-cc-pVDZ[MP2/aug-cc-pVTZ] levels, are relatively short. These distinct interactions lead to the longest and shortest of the C–N bonds we found among these APBA acids: for the 2-isomer the structure in the neighborhood of the nitrogen atom is somewhat tetrahedral ($-NH_2H_a$) and the C–N bond is quite long, 1.442[1.429] Å, whereas for the 6-isomer the structure in the vicinity of the nitrogen atom is more planar ($C=N-H$) and the C–N bond is relatively short, 1.399[1.388] Å; the corresponding C–N bond length in aniline is 1.412[1.401] Å. The *ipso* angle ranges from 117.0° to 118.4° , differing by at most 0.8° from the value in PBA. The presence of the amino group consistently reduces the $CC(NH_2)C$ ring angle at the point of attachment compared to the corresponding value in PBA.

The two *ortho* isomers of APBA are lowest in energy and the 2-isomer is $\sim 0.8[0.4]$ kcal/mol lower in energy than the 6-isomer at the MP2/aug-cc-pVDZ[MP2/aug-cc-pVTZ] levels. The 3-, 4-, and 5-isomers are several kcal/mol higher in energy, see Table 2. In contrast to these results, DFT calculations using the B3LYP and PBE1PBE functionals with the aug-cc-pVDZ basis set find the 2-isomer is 0.8 and 0.6 kcal/mol higher in energy than the 6-isomer; additional PBE1PBE calculations using the aug-cc-pVTZ and 6-311++G(*d,p*) basis sets also find the 2-isomer 0.8 and 0.4 kcal/mol higher in energy. Unfortunately, no experimental evidence is available to resolve this discrepancy. The *anti* conformers of the *ortho* isomers are about 2.9 kcal/mol higher in energy than the *endo-exo* conformers and 0.6 kcal/mol lower in energy than the *syn* conformers at the MP2/aug-cc-pVDZ level, see Table 2; for the other isomers the *anti* conformers are slightly higher in energy than the *syn* conformers. Planar inversion-TSs for the *endo-exo* conformers of the 3-, 4-, and 5-isomers are 1.4, 1.1, and 1.3 kcal/mol respectively higher in energy than the corresponding local minima at the MP2/aug-cc-pVDZ level. For the *para* isomer, the value of $H^\ddagger$ for the amino rotational barrier of the *endo-exo* boronic acid moiety is 4.1 kcal/mol, slightly greater than the value

for methyl substitution at the para position, 3.7 kcal/mol, which is consistent with the shorter B–C bond length for this amino derivative.

Heats of formation for the conformers of the various APBE acids calculated at the G3 level of theory are given in Table 3; for the *endo-exo* conformer of 2-APBE the predicted HOF is –137.5 kcal/mol. The values of ΔH_{298}^0 for the transfer reaction:

are +2.7[+2.4] kcal/mol at the MP2/aug-cc-pVDZ [MP2/aug-cc-pVTZ] levels respectively. Using the HOF of aniline, +20.8±0.21 kcal/mol [73], in conjunction with the HOF for benzene and the MP2/aug-cc-pVTZ value of ΔH_{298}^0 indicates that the HOF for 2-APBE should be about 1.4 kcal/mol more negative than for the corresponding conformer of PBA itself; in good agreement with this finding, the calculated G3 value is ~1 kcal/mol more negative, see Table 3.

Hydroxyphenylboronic acid: $\text{C}_6\text{H}_4\text{OH}-\text{B}(\text{OH})_2$

The five positional isomers of hydroxyphenylboronic acid (HPBE) were optimized at the MP2/aug-cc-pVDZ level. For the *endo-exo* conformers of the 3-, 4-, and 5-isomers, the (C)O–H bond consistently optimized to a position coplanar with the phenyl ring and boronic acid moiety at this level. It should be noted that the H atom of the hydroxyl group attached to the ring can point in two distinct directions in these cases, although calculations showed that energy differences between the two corresponding forms were consistently less than 1 kcal/mol; *e.g.* the form of the *para*-isomer with the H atom on the same side of the structure as O_s-H_s (the HOC4C5 torsional angle is 0.0° , see Figure 2) is ~0.2 kcal/mol lower in energy than the analogous form with the H atom on the opposite side, and both are local minima on the PES. This is in qualitative agreement with a previous study by Sert *et al.* [66] at B3LYP/6-311++G(*d,p*) level. B3LYP and PBE1PBE calculations using either the aug-cc-pVDZ or 6-311++G(*d,p*) basis sets are in accord with the MP2 results for the *para* isomer; for the *meta* isomers frequency analyses at the PBE1PBE/aug-cc-pVDZ level predict planar versions to be local minima on the PESs whereas PBE1PBE/6-311++G(*d,p*) calculations find planar versions to be TSs. Sert *et al.* reported that the lowest energy meta conformer is planar at the B3LYP/6-311++G(*d,p*) level [66]. The *endo-exo* conformers of the 2- and 6-isomers were also planar but involve strong intramolecular $\text{HO}\cdots\text{H}_a-\text{O}_a\text{B}$ and $\text{CO}-\text{H}\cdots\text{O}_s-\text{H}_s$ interactions, see Figure 2; the $\text{H}\cdots\text{O}$ distances are 1.941[1.926] Å and 1.830[1.812] Å respectively at the MP2/aug-cc-pVDZ[MP2/aug-cc-pVTZ] levels. These two different types of interactions lead to significantly different C–O distances: 1.394[1.382] Å in 2-hydroxyphenylboronic acid compared to 1.370[1.358] Å in 6-hydroxyphenylboronic acid; the C–O distance in phenol is 1.381[1.370] Å. The presence of the hydroxyl group typically increases the CC(OH)C ring angle at the point of attachment compared to the corresponding value in PBA.

The two *ortho* isomers of the *endo-exo* conformers of $\text{C}_6\text{H}_4\text{OH}-\text{B}(\text{OH})_2$ are lowest with the 6-isomer 0.6[0.7] kcal/mol lower in energy at the MP2/aug-cc-pVDZ[MP2/aug-cc-pVTZ]

levels, see Table 2; the energy differences using the PBE1PBE functional with the aug-cc-pVDZ and 6-311++G(*d,p*) basis sets yield comparable values, 1.2 and 1.0 kcal/mol respectively. The other isomers of this conformer are more than 4 kcal/mol higher in energy than the 6-isomer. As a result of a favorable CO–H $\cdots$ O_s–H_s interaction, the *syn* conformer of the *ortho* isomers are only 2.6 kcal/mol higher in energy than the corresponding *endo-exo* conformer at the MP2/aug-cc-pVDZ level, whereas the corresponding *anti* conformer of these isomers are 4.3 kcal/mol higher in energy. For the *para* isomer, the value of $H^\ddagger$ for the rotational barrier of the *endo-exo* boronic acid moiety is 3.5 kcal/mol.

Heats of formation for the conformers of HPBA calculated at the G3 level of theory are given in Table 3; for 6-HPBA the predicted HOF for the *endo-exo* conformer is –183.60 kcal/mol. The transfer reaction

is found to be slightly endothermic as a result of the intramolecular O–H $\cdots$ O_s–H_s interaction; the values of ΔH_{298}^0 are +4.7[+4.8] kcal/mol at the MP2/aug-cc-pVDZ[MP2/aug-cc-pVTZ] levels. Using the experimental HOF of phenol, –23.05±0.15 kcal/mol[73], along with benzene and the calculated MP2/aug-cc-pVTZ reaction energy, predicts that the HOF of 6-HPBA is ca. 47.6 kcal/mol more negative than that of PBA; this difference calculated at the G3 level is 47.2 kcal/mol, see Table 3.

Fluorophenylboronic acid: C₆H₄F–B(OH)₂

The five planar isomers of the *endo-exo* conformer of fluorophenylboronic acid (FPBA) were optimized at the MP2/aug-cc-pVDZ level and frequency analyses showed that the 2-, 3-, 4-, and 5-isomers were local minima on the PES. Planar 6-FPBA proved to be a rotational TS, a result of an adverse interaction involving the proximate negatively-charged fluorine (–0.35e) and oxygen (–0.92e) atoms; the calculated F $\cdots$ O distance was 2.726 Å. Reoptimizing a nonplanar *endo-exo* conformer of 6-FPBA resulted in a stable structure with a C2C1BO_a torsional angle of ~35.8° (the F $\cdots$ O distance increased to 2.908 Å) as shown in Table 1. Planar *anti* conformers of the 3-, 4-, and 5-isomers are rotational TSs on the PES.

The crystal structure of 5-FPBA has been reported by Wu *et al.* [25]; note that the numbering system used by these authors is different than the one adopted in this article; this conformer is labeled 3-FPBA in their numbering system. As expected in the solid state, hydrogen-bonded dimers are formed. Differences in bond lengths and angles for 3-FPBA from the crystal structure and the corresponding gas phase parameters calculated at various levels are attributed to crystal packing forces.

As can be seen from the data in Table 2, the *endo-exo* conformer of 2-FPBA is lowest in energy. This was to be expected as the structure has a strong F $\cdots$ H_a–O_a interaction; the F $\cdots$ H distance is 2.020[2.010] Å at the MP2/aug-cc-pVDZ[MP2/aug-cc-pVTZ] levels. The remaining conformers are all at least 3 kcal/mol higher in energy. Erdogdu *et al.* [22] reported that the *endo-exo* conformer of 2-FPBA is 5.7 kcal/mol lower in energy than *endo-exo* conformer of 6-FPBA, as well as 4.8 and 6.9 kcal/mol lower in energy than the *anti* and

syn forms of 2-FPBA respectively at the B3LYP/6-31++G(*d,p*) level. Silla *et al.* [27] reported that the *endo-exo* conformer of 2-FPBA is 3.8 and 5.8 kcal/mol lower in energy than the *anti* and *syn* forms of 2-FPBA at B3LPY/aug-cc-pVDZ level as well as 2.4 kcal/mol lower in energy than the *endo-exo* conformer of 4-FPBA. Karabacak *et al.* [21] reported that the *exo-endo* conformer of 5-FPBA is 0.09 kcal/mol lower in energy than 3-FPBA as well as 1.9 and 4.1 kcal/mol lower in energy than the *anti* and *syn* forms of 5-FPBA at B3LYP/6-311++G(*d,p*) level. All studies are in qualitative agreement with our MP2/aug-cc-pVDZ level calculations, see Table 2.

The values of $H^\ddagger$ for the rotational barriers about the C–B bonds in the *endo-exo*, *anti*, and *syn* conformers of 4-FPBA are 3.1, 1.3, and 5.1 kcal/mol, respectively, at the MP2/aug-cc-pVDZ level. The values of $H^\ddagger$ for rotations of the –B(OH)₂ group that lead to the conversions: 3-FPBA → 5-FPBA and 2-FPBA → 6-PBAI respectively.

HOF for the conformers of FPBA calculated at the G3 level of theory are given in Table 3. For the lowest-energy *endo-exo* conformer, 2-FPBA, the HOF is –187.4 kcal/mol at the G3 level; the corresponding value for 4-FPBA is –184.4 kcal/mol. To the authors' knowledge there are no direct experimental or estimated values available in the literature for the HOF of FPBA. To help assess these calculated values, we considered the reaction:

The calculated values of ΔH_{298}^0 are +16.7[+20.0] kcal/mol for 2-FPBA at the MP2/aug-cc-pVDZ [MP2/aug-cc-pVTZ] levels. The HOF of fluorobenzene is known, -27.7 ± 0.5 kcal/mol [81, 82]. Using the MP2/aug-cc-pVTZ calculated value of ΔH_{298}^0 in conjunction with the literature HOF values of C₆H₅F, B(OH)₃, and H₂O, gives a value *ca.* –189.7 kcal/mol for DH_f(298 K) for this conformer C₆H₄F–B(OH)₂ in reasonable agreement with the above G3 value. We also considered the transfer reaction:

where the bonding types are well balanced in the reactants and products and calculations are expected to accurately predict the reaction thermochemistry. For the *endo-exo* conformer of 2-FPBA, this reaction is slightly endothermic as a result of the F··H_a–O_a interaction – the calculated values of ΔH_{298}^0 are +3.2[+3.1] kcal/mol at the MP2/aug-cc-pVDZ [MP2/aug-cc-pVTZ] levels. (Using 4-FPBA, reaction (6) is nearly thermoneutral – the corresponding MP2/aug-cc-pVDZ value of ΔH_{298}^0 is +0.3 kcal/mol). Using the experimental HOF of benzene and fluorobenzene, and the MP2/aug-cc-pVTZ calculated enthalpy for reaction (6), +3.1 kcal/mol, the HOF of 2-FPBA is expected to be 50.6 kcal/mol more negative than that of C₆H₅–B(OH)₂; the calculated HOF for the *endo-exo* conformer of 2-FPBA at the G3 level of theory, –187.4 kcal/mol, is 51.0 kcal/mol more negative than that for the *endo-exo* conformer of PBA, see Table 3.

Concluding Remarks

Structural and thermochemical data for the monomeric forms of PBAs are relatively scarce. In this article we have calculated geometries and energies for the *endo-exo*, *anti*, and *syn* conformers of the five positional isomers of R–B(OH)₂ (R = C₆H₅, C₆H₄CH₃, C₆H₄NH₂, C₆H₄OH, and C₆H₄F) at a variety of computational levels; HOF were obtained at the G3 level of theory. We have shown the following: **1)** The *endo-exo* conformer of monomeric Ph–B(OH)₂ is planar and lower in energy than the *anti* and *syn* conformers; the G3 estimate of its HOF is –136.4 kcal/mol, somewhat less negative than the values currently in the literature based on energy decomposition schemes. **2)** For the monosubstituted PBAs we considered, the *endo-exo* conformers were also lowest in energy for all the positional isomers at each of the computational levels we employed. **3)** For R = C₆H₄NH₂, C₆H₄OH, and C₆H₄F the lowest energy *endo-exo* conformers are for *ortho* positional isomers, where there are strong BO_a–H_a⋯NH₂, NH⋯O_s–H_s, BO_a–H_a⋯O–H, CO–H⋯O_s–H_s, or BO_a–H_a⋯F interactions; the relative strengths of competing donor-acceptor interactions in the case of R = C₆H₄NH₂ proved to be somewhat dependent on the computational level. **4)** For R = C₆H₄CH₃ the lowest energy *endo-exo* conformer is for the *para*-isomer. **5)** Rotational barriers for the boronic acid moiety of the PBAs in this study are relatively low, *e.g.* the values of H[†] are 3.0, 3.7, 4.1, 3.5 and 3.1 kcal/mol for the *para* isomers of the *endo-exo* conformers of R–B(OH)₂ (R = C₆H₅, C₆H₄CH₃, C₆H₄NH₂, C₆H₄OH, and C₆H₄F) respectively; in view of this finding, it is not surprising that different computational method/basis set combinations lead to some minor discrepancies with respect to the co-planarity of the phenyl ring and boronic acid moiety. **6)** Using calculated HOF for the monosubstituted PBAs at the G3 level of theory, in conjunction with the experimental HOF of benzene, toluene, aniline, phenol, and fluorobenzene yield reaction energies for the transfer reactions C₆H₆ + C₆H₄X–B(OH)₂ → C₆H₅X + C₆H₅–B(OH)₂ (X = CH₃, NH₂, OH, and F) that are consistent with the calculated values of ΔH₂₉₈⁰ at the MP2/aug-cc-pVTZ computational level; the bonding in the reactants and products for these reactions are well-matched and thermochemical calculations at this level should be quite accurate, providing some level of confidence for the G3 calculations.

Supplementary Material

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Figure 1.

Geometries of the planar *Endo-Exo*, *Anti*(TS), and *Syn* Conformers of Phenylboronic Acid $C_6H_5-B(OH)_2$; Distances (Å) and Angles (°) are from MP2(FC)/aug-cc-pVDZ//MP2(FC)/aug-cc-pVDZ [MP2(FC)/aug-cc-pVTZ//MP2(FC)/aug-cc-pVTZ] Geometry Optimizations.

Figure 2.
Numbering System for the Monosubstituted Phenylboronic Acids.

Table 1

Rotation Angle (°) of Phenyl Ring with Respect to Boronic Acid Moieties, $\tau_{C2C1BOa}$, for the *endo-exo* Conformers of the Positional Isomers of the Boronic Acids, R-B(OH)₂, (R = C₆H₅, C₆H₄CH₃, C₆H₄NH₂, C₆H₄OH, and C₆H₄F) Calculated at the MP2(FC)/aug-cc-pVDZ/MP2(FC)

R-	(<i>ortho</i>) 2-	(<i>meta</i>) 3-	(<i>para</i>) 4-	(<i>meta</i>) 5-	(<i>ortho</i>) 6-
CH ₃	0.0	0.0	0.0	0.0	30.0
NH ₂	11.9	6.0	0.9	2.1	18.3
OH	0.0	0.0	0.0	0.0	0.0
F	0.0	0.0	0.0	0.0	35.8

Table 2

Relative Energies, E (kcal/mol) of the *endo-exo*, *anti*, and *syn* Conformers of the Positional Isomers of the Boronic Acids, $R-B(OH)_2$, ($R = C_6H_5$, $C_6H_4CH_3$, $C_6H_4NH_2$, C_6H_4OH , and C_6H_4F) Calculated at the MP2(FC)/aug-cc-pVDZ/MP2(FC)/aug-cc-pVDZ [MP2(FC)/aug-cc-pVTZ/MP2(FC)/aug-cc-pVTZ] Levels; all energies listed are relative to the lowest-energy form.

$R-B(OH)_2$			
	E (kcal/mol)		
R	Conformer		
	<i>endo-exo</i>	<i>anti</i>	<i>syn</i>
C_6H_5			
	0.00 [0.00]	+2.56 [+2.30]	+1.94 [+1.98]
$C_6H_4CH_3$			
2-CH ₃ <i>ortho</i>	+1.34	+3.34	+3.62
3-CH ₃ <i>meta</i>	+0.15	+2.55	+2.13
4-CH ₃ <i>para</i>	0.00 [0.00]	+2.49	+2.05
5-CH ₃ <i>meta</i>	+0.04 [+0.06]	+2.55	+2.13
6-CH ₃ <i>ortho</i>	+1.37	+3.34	+3.62
$C_6H_4NH_2$			
2-NH ₂ <i>ortho</i>	0.00 [0.00]	+2.89	+3.54
3-NH ₂ <i>meta</i>	+3.02	+5.05	+4.77
4-NH ₂ <i>para</i>	+2.05	+4.59	+4.14
5-NH ₂ <i>meta</i>	+2.43	+5.05	+4.77
6-NH ₂ <i>ortho</i>	+0.80 [+0.35]	+2.89	+3.54
C_6H_4OH			
2-OH <i>ortho</i>	+0.60 [+0.71]	+4.28	+2.63
3-OH <i>meta</i>	+4.66	+7.16	+6.24
4-OH <i>para</i>	+4.03	+6.80	+5.99
5-OH <i>meta</i>	+4.05	+7.16	+6.24
6-OH <i>ortho</i>	0.00 [0.00]	+4.28	+2.63
C_6H_4F			

R–B(OH)₂			
	E (kcal/mol)		
R	Conformer		
	<i>endo-exo</i>	<i>anti</i>	<i>syn</i>
2-F <i>ortho</i>	0.00 [0.00]	+3.84	+6.31
3-F <i>meta</i>	+3.39	+6.05	+4.96
4-F <i>para</i>	+3.06 [+2.91]	+5.92	+4.65
5-F <i>meta</i>	+3.25	+6.05	+4.96
6-F <i>ortho</i>	+4.70	+3.84	+6.31

Table 3

Heats of Formation, $H_f(298.15K)$ (kcal/mol), of the Boronic Acids, $R-B(OH)_2$, ($R = C_6H_5$, $C_6H_4CH_3$, $C_6H_4NH_2$, C_6H_4OH , and C_6H_4F) Calculated at the G3 Level of Theory.

$R-B(OH)_2$			
	$H_f(298.15K)$ (kcal/mol)		
R	Conformer		
	<i>endo-exo</i>	<i>anti</i>	<i>syn</i>
C_6H_5	-136.41	-133.93	-134.70
$C_6H_4CH_3$			
2- CH_3 <i>ortho</i>	-142.68	-140.79	-140.81
3- CH_3 <i>meta</i>	-144.41	-142.09	-142.61
4- CH_3 <i>para</i>	-144.66	-142.19	-142.84
5- CH_3 <i>meta</i>	-144.50	-142.09	-142.61
6- CH_3 <i>ortho</i>	-142.90	-140.79	-140.81
$C_6H_4NH_2$			
2- NH_2 <i>ortho</i>	-137.47	-134.84	-135.11
3- NH_2 <i>meta</i>	-135.06	-133.17	-133.46
4- NH_2 <i>para</i>	-136.45	-133.84	-134.62
5- NH_2 <i>meta</i>	-135.62	-133.17	-133.46
6- NH_2 <i>ortho</i>	-137.51	-134.84	-135.11
C_6H_4OH			
2-OH <i>ortho</i>	-183.02	-179.29	-181.17
3-OH <i>meta</i>	-178.33	-176.30	-177.27
4-OH <i>para</i>	-179.60	-176.77	-177.87
5-OH <i>meta</i>	-179.30	-176.30	-177.27
6-OH <i>ortho</i>	-183.60	-179.29	-181.17
C_6H_4F			
2-F <i>ortho</i>	-187.39	-183.61	-181.39
3-F <i>meta</i>	-184.04	-181.46	-182.64

R–B(OH)₂			
	H_f(298.15K) (kcal/mol)		
R	Conformer		
	<i>endo-exo</i>	<i>anti</i>	<i>syn</i>
4-F <i>para</i>	–184.45	–181.60	–183.02
5-F <i>meta</i>	–184.18	–181.46	–182.64
6-F <i>ortho</i>	–182.86	–183.61	–181.39