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A Computational Investigation of the Oxidative Deboronation of BoroGlycine, $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$, Using H_2O and H_2O_2

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Abstract

We report results from a computational investigation of the *oxidative* deboronation of BoroGlycine, $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$, using H_2O and H_2O_2 as the reactive oxygen species (ROS) to yield aminomethanol, $\text{H}_2\text{N}-\text{CH}_2-\text{OH}$; these results complement our study on the *protodeboronation* of BoroGlycine to produce methylamine, $\text{H}_2\text{N}-\text{CH}_3$ (Larkin *et al.* *J. Phys. Chem. A*, 111, 6489–6500, 2007). Second-order Møller-Plesset (MP2) perturbation theory with Dunning-Woon correlation-consistent (cc) basis sets were used for the calculations with comparisons made to results from Density Functional Theory (DFT) at the PBE1PBE/6-311++G(d,p)(cc-pVDZ) levels. The effects of a bulk aqueous environment were also incorporated into the calculations employing PCM and CPCM methodology. Using H_2O as the ROS, the reaction $\text{H}_2\text{O} + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{H}_2\text{N}-\text{CH}_2-\text{OH} + \text{H}-\text{B}(\text{OH})_2$ was calculated to be endothermic, the value of ΔH_{298}^0 was +12.0 kcal/mol at the MP2(FC)/cc-pVTZ computational level *in vacuo* and +13.7 kcal/mol in PCM aqueous media; the corresponding value for the activation barrier, $H^\ddagger$, was +94.3 kcal/mol relative to the separated reactants *in vacuo* and +89.9 kcal/mol in PCM aqueous media. In contrast, the reaction $\text{H}_2\text{O}_2 + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{H}_2\text{N}-\text{CH}_2-\text{OH} + \text{B}(\text{OH})_3$ was calculated to be highly exothermic with a ΔH_{298}^0 value of –100.9 kcal/mol at the MP2(FC)/cc-pVTZ computational level *in vacuo* and –99.6 kcal/mol in CPCM aqueous media; the highest-energy transition state for the multi-step process associated with this reaction involved the rearrangement of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})(\text{OOH})$ to $\text{H}_2\text{N}-\text{CH}_2-\text{O}-\text{B}(\text{OH})_2$ with a $H^\ddagger$ value of +23.2 kcal/mol *in vacuo* relative to the separated reactants. These computational results for BoroGlycine are in accord with the experimental observations for the deboronation of the FDA approved anti-

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Supporting Information Available: Table 1S contains thermodynamic parameters (kcal/mol) for the reactions of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$ with A.) H_2O and B.) H_2O_2 using the PCM and CPCM implicit solvation Models. Table 2S containing kinetic parameters (kcal/mol) for the Reactions of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$ with A.) H_2O and B.) H_2O_2 using the PCM and CPCM implicit solvation models.

cancer drug Bortezomib (Velcade™, PS-341) where it was found to be the principle deactivation pathway. (Labutti *et al.* Chem. Res. Toxicol., 19, 539–546, 2006).

Keywords

Oxidative Deboronation; BoroGlycine; Second-Order Møller-Plesset Perturbation Theory (MP2); Polarizable Continuum Model (PCM); Density Functional Theory (DFT); Reactive Oxygen Species (ROS)

Introduction

Although boronic acids ($R-B(OH)_2$) have not been found in nature, they have emerged as an important class of compounds with diverse applications in a variety of fields [1–5]. In chemistry and material science, applications include sensors for 1,2 and 1,3-diols [6–14], affinity ligands in chromatographic protocols [15–20], and as submicron-scale devices [21–24]. In synthetic organic chemistry, the properties of boronic acids as mild Lewis acids have made them an attractive class of intermediates [25] that have been widely used in Suzuki cross-coupling reactions [3, 26], Diels-Alder reactions [27], asymmetric synthesis of amino acids [28], selective reduction of aldehydes [29], and carboxylic acid activation [30, 31]. Biochemical and medicinal applications of boronic acids include inhibitors of serine proteases and beta-lactamases [32–34], bioconjugates [35], transmembrane transporters [36–39], anti-HIV drugs [40, 41], substrates for protein immobilization [42], and agents in neutron capture therapy [43–45].

A particularly interesting and relevant example of the use of boronic acids in medicine involves the drug Bortezomib (Velcade™, PS-341) [46, 47], which is a dipeptide boronic acid analogue that is currently FDA approved for the treatment of refractory multiple myeloma, a bone marrow cancer that affects two to three people per 100,000 [46, 47]. Bortezomib, a boronic acid analog of a Phe-Leu dipeptide coupled to a 2-carboxylpyrazine group, see Figure 1, is a selective and highly effective inhibitor of the 26S proteasome, a large multicatalytic protease complex whose function is to regulate a variety of cellular functions by protein ubiquitination and degradation [48, 49]. It is suspected that Bortezomib produces cell death by causing an accumulation of misfolded/damaged proteins, inducing endoplasmic reticulum (ER) stress by overwhelming cellular mechanisms of coping with this buildup (the unfolded protein response, UPR), and triggering a unique pathway of apoptosis [50]. Due to the ability of Bortezomib to induce ER stress it is currently being investigated as a sensitizing agent in therapeutic regimens, *e.g.* for pancreatic cancer, where it apparently induces cell death by an ER stress-dependent mechanism [50]. To a large extent, the potency of Bortezomib is a result of the presence of the boronic acid moiety, which appears to form a tetrahedral intermediate analog with the active site N-terminal threonine residue of the proteasome [51]. Oxidative deboronation has been suggested as a principle route for the metabolism of Bortezomib [52, 53] representing a *deactivation* pathway for this chemotherapeutic agent [53]. Yet, no chemical mechanism has been elucidated for this process.

In the present article we report our results from the first computational study of possible oxidative deboronation mechanisms for BoroGlycine, $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$, using H_2O and H_2O_2 as the reactive oxygen species (ROS). BoroGlycine, a boronic acid analog of the amino acid glycine, serves as a simple model for the boronic component of the anticancer drug Bortezomib, see Figure 1. Furthermore, several derivatives of BoroGlycine, including some isoelectronic and isostructural analogs, have shown promise as chymotrypsin inhibitors [54, 55], and more recently the peptide L- γ -Gly-L-Leu-aminomethyl boronic acid has been shown to be a stronger inhibitor of glutathionyl spermidine synthetase than the phosphonic acid analog, making it an attractive target for the design of anti-parasitic drugs [56] and prompting interest in the properties of BoroGlycine in itself.

Computational Methods

Equilibrium geometries of the molecules involved in this article were obtained using second-order Møller-Plesset perturbation theory (MP2) [57]; the frozen core (FC) option, which neglects core-electron correlation, was employed in all cases. Dunning-Woon cc-pVDZ, aug-cc-pVDZ, cc-pVTZ, and aug-cc-pVTZ basis sets [58–61] were used in the calculations. Frequency analyses were performed analytically to determine whether the optimized structures were local minima or transition states on the PES and to correct reaction energies to 298K. Intrinsic reaction coordinate (IRC) analyses were employed in all cases to unambiguously identify the reactants and products associated with all of the transition states we located [62, 63]. The calculations were performed using the GAUSSIAN 03 suite of programs [64]. Atomic charges were obtained from natural population analyses (NPA) and the bonding was analyzed with the aid of natural bond orbitals (NBOs) [65–68].

Calculations using MP2 methodology with correlation consistent basis sets are not currently practical for investigations of larger boron derivatives of significant chemical interest. On the other hand, density functional theory (DFT) methods, utilizing Pople-style basis sets [69, 70], provides an economical alternative to MP2, but the reliability of specific functional/basis-set combinations for describing the incredibly diverse range of boron chemistry [71] has yet to be fully established [37–40]. Thus, we have compared our MP2/cc-pVDZ, aug-cc-pVDZ, and cc-pVTZ results to those from more computationally-efficient DFT methodologies using the PBE1PBE/6-311++G(*d,p*)(cc-pVDZ) levels [72]; the PBE1PBE functional, in combination with either Pople-style or correlation consistent basis sets, has shown promise in describing a variety of aspects of boron chemistry [73–78]. It should be noted that it is well established that the hybrid B3LYP functional has significant problems in dealing with some aspects of boron chemistry, most notably dative bonding [73–80].

Results from continuum solvation models were employed to assess the effects of a bulk aqueous environment on the gas-phase results. We used the following implicit solvation models: **1**) the IEF Polarizable Continuum Model (PCM) model, developed by Tomasi and coworkers [81–86] at the PBE1PBE/6-311++G(*d,p*) and MP2/6-311++G(*d,p*)(cc-pVTZ) computational levels, and **2**) the conductor-like PCM model (CPCM), introduced by Barone and Cossi [87, 88] at the MP2/6-311++G(*d,p*)(cc-pVTZ) computational levels (The UAKS cavity was used for the CPCM solvent model based on the performance indicated by Takano and Houk [89]. Such implicit solvation models, however, only provide a description of long-

range solute-solvent interactions and, as a consequence, have significant limitations in describing protic solvents [90, 91]. Thus, in some cases, explicit water molecules were used to provide a description of the short-range, site-specific effects of an aqueous environment on the hydrogen-bonding or the boron dative-bonding interactions relevant to the oxidative deboronation mechanisms of BoroGlycine that we explored.

Results and Discussion

In this section we present calculated thermodynamic/kinetic data relevant to the oxidative deboronation of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$ with H_2O and HOOH . To a large extent, the oxidative reactivity of the C–B bond is a consequence of the huge difference between the B–O and B–C bond energies[1] [92].

To the authors' knowledge, no experimental data are currently available regarding the structure of BoroGlycine. However, results from a computational investigation of the geometrical structures and relative energies of various conformers of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$, as well as its constitutional isomer $\text{H}_3\text{C}-\text{NH}-\text{B}(\text{OH})_2$, have been reported by Larkin *et al.* [76] in their investigation of possible protodeboronation mechanisms of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$; these results provided a basis for the present study.

Oxidative Cleavage using H_2O

We initially considered H_2O as a possible oxidative agent in order to establish a thermochemical baseline for the conversion of BoroGlycine to aminomethanol. Thermodynamic parameters for the reaction:

are listed in Table 1. This reaction was calculated to be endothermic *in vacuo*, the values of ΔH_{298}^0 are +11.3, +12.0, and +13.3 kcal/mol at the PBE1PBE/6-311++G(*d,p*), MP2/cc-pVTZ and MP2/aug-cc-pVTZ levels respectively. In aqueous media the values of ΔH_{298}^0 for various implicit solvation models were +13.4 kcal/mol at the PCM(PBE1PBE/6-311++G(*d,p*)) level, +13.7 kcal/mol at the PCM(MP2/cc-pVTZ) level, +10.6 kcal/mol at the CPCM(PBE1PBE/6-311++G(*d,p*)) level, and +11.1 at the CPCM(MP2/cc-pVTZ) level, see Table 1S of the Supplementary Materials. Although the corresponding PCM and CPCM values of ΔH_{298}^0 lie on opposite sides of the gas-phase values, neither of these implicit solvation models imply a major role for the long-range effects of an aqueous environment. For comparison, we note that the protodeboronation reaction of BoroGlycine, *i.e.* $\text{H}_2\text{O} + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{B}(\text{OH})_3 + \text{H}_2\text{N}-\text{CH}_3$, was calculated to be substantially exothermic at similar levels *in vacuo*, with values of ΔH_{298}^0 in the –20 to –30 kcal/mol range [76, 93].

Several conformations of transition states (TSs) were obtained for reaction (1), one of which is shown in Figure 2. The calculated activation barrier for this TS was extremely high, the values of $H^\ddagger$ were +85.6 and +94.3 at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels respectively, relative to the separated reactants *in vacuo*, see Table 2. In aqueous media the values of the activation barrier for reaction (1) using several implicit solvation models were +84.2, +88.7, +88.2, and +89.8 at the PCM(PBE1PBE/6-311++G(*d,p*)),

PCM(MP2/6-311++G(*d,p*)), CPCM(PBE1PBE/6-311++G(*d,p*)), and CPCM(MP2/6-311++G(*d,p*)) levels respectively, see Table 2S of the Supplementary Materials. The structure of this TS for reaction (1) clearly identifies the water-oxygen atom as a nucleophile attacking the α -carbon atom of BoroGlycine; the extremely high calculated activation barrier for this reaction is in accord with the nearly complete heterolytic breaking of the carbon-boron bond and the concomitant formation of a boranion and a methaniminium ion, see Figure 2; the MP2/cc-pVTZ NPA charge on the boron atom in this TS was +0.39e, compared to +1.02e and +0.91e in the reactant and product respectively, showing a considerable transfer of electron density to the boron atom from the $\text{H}_2\text{N}-\text{CH}_2$ moiety at the TS. These findings provide computational support for the observation that *oxidative* cleavage of the B–C bond of boronic acid derivatives in air is a kinetically slow process [1]. The corresponding activation barriers for the protodeboronation reaction:

in which the water-oxygen atom attacks the boron atom were found to be much lower, +36.1 and +34.6 kcal/mol *in vacuo* at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels respectively [76].

It should be noted that BoroGlycine is also susceptible to a 1,2-carbon-to-nitrogen migration of the $-\text{B}(\text{OH})_2$ moiety [1, 94–98]. Indeed, this conversion of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$ to $\text{H}_3\text{C}-\text{NH}-\text{B}(\text{OH})_2$ is thermodynamically favored, *e.g.* the calculated values of ΔH_{298}^0 were –18.0 and –19.4 kcal/mol *in vacuo* at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels and the corresponding values of ΔH_{298}^0 in PCM aqueous media were similar [76]. The transition state for this 1,2-migration *in vacuo* and in PCM aqueous media were calculated to involve two very compact 3-centered rings and the activation barriers were computed to be extremely high, the values of $\text{H}^\ddagger$ were ~+70 kcal/mol [76]. In the presence of one explicit water molecule, however, the barrier was dramatically lower, *e.g.* the values of $\text{H}^\ddagger$ were only +27.0 and +28.8 kcal/mol at the PBE1PBE/6-311++G(*d,p*) and MP2/6-311++G(*d,p*) levels respectively [76], emphasizing the importance of the short-range effects of surrounding water molecules on this shift-mechanism.

In vacuo, as well as in the reaction field of water, the above thermochemical results clearly demonstrate that oxidative deboronation of BoroGlycine with a water molecule as the ROS is *not* competitive with the corresponding protodeboronation, or with a 1,2-carbon-to-nitrogen (Matteson) rearrangement of the $-\text{B}(\text{OH})_2$ group. In light of these results, we investigated the oxidative deboronation of BoroGlycine using hydrogen peroxide as the ROS.

Oxidative Cleavage using H_2O_2

As would be expected, calculated thermodynamic parameters for the oxidative deboronation of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2$ using H_2O_2 as the ROS, *i.e.*

show that this reaction is highly exothermic *in vacuo*, *e.g.* the values of ΔH_{298}^0 were -97.7 and -100.9 kcal/mol at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels, see Table 1 and Figure 3; the corresponding values of ΔH_{298}^0 in aqueous media were -96.9 , -100.4 , -96.1 and -99.6 kcal/mol at the PCM(PBE1PBE/6-311++G(*d,p*)), PCM(MP2/cc-pVTZ), CPCM(PBE1PBE/6-311++G(*d,p*)), and CPCM(MP2/cc-pVTZ) levels respectively, see Table 1S (values of ΔH_{298}^0 at other computational levels are also given in this Table), quite similar to the corresponding values *in vacuo*, suggesting a relatively small effect of long-range dielectric interactions with water on the thermodynamics of this reaction.

For comparison, we note that the corresponding protodeboronation reaction:

was also calculated to be significantly exothermic, but the values of ΔH_{298}^0 for the same conformer of $\text{H}_2\text{N} - \text{CH}_2 - \text{B}(\text{OH})_2$, were considerably less negative, -27.4 and -29.4 , kcal/mol *in vacuo* at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels, and -24.5 , -26.9 , -19.9 , and -22.7 kcal/mol in PCM(PBE1PBE/6-311++G(*d,p*)), PCM(MP2(FC)/cc-pVTZ), CPCM(PBE1PBE/6-311++G(*d,p*)), and CPCM(MP2(FC)/cc-pVTZ) levels in aqueous media. Remarkably, these enthalpy changes for the protodeboronation of BoroGlycine using H_2O_2 are only a few kcal/mol more negative than the corresponding changes using H_2O as the ROS [76].

Despite an extensive search, no single-step mechanism for reaction (3) could be found *in vacuo* or in aqueous media [99]; thus our attention turned to possible multi-step mechanisms, see Figure 3. It appears that the initial step in this reaction involves the conversion of BoroGlycine to aminomethyl peroxy borinic acid [100, 101], *i.e.*

which was calculated to be just slightly exothermic, *e.g.* the values of ΔH_{298}^0 *in vacuo* were -2.0 and -1.5 kcal/mol at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels, see Table 1 (results at other levels are also listed in this Table); the values of ΔH_{298}^0 in implicit solvent were $+0.2$, $+0.5$, $+4.1$, and $+4.2$ kcal/mol at the PCM(PBE1PBE/6-311++G(*d,p*)), PCM(MP2/cc-pVTZ), CPCM(PBE1PBE/6-311++G(*d,p*)), and CPCM(MP2/cc-pVTZ) levels, respectively. The calculated values of the activation enthalpy for reaction (5) were $+18.0$ and $+15.1$ kcal/mol *in vacuo* at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels respectively, relative to the separated reactants, see Table 2 and Figure 3. Using implicit solvation models, the activation enthalpies for reaction (5) were somewhat higher relative to the isolated reactants compared to the gas-phase results: PCM: PBE1PBE/6-311++G(*d,p*) = $+24.2$ kcal/mol and MP2/cc-pVTZ = $+17.9$ kcal/mol; CPCM: PBE1PBE/6-311++G(*d,p*) = $+25.2$ and MP2/cc-pVTZ = $+22.6$ kcal/mol.

The second step in the mechanism for reaction (3) above involves the rearrangement of $\text{H}_2\text{N} - \text{CH}_2 - \text{B}(\text{OH})(\text{OOH})$ to $\text{H}_2\text{N} - \text{CH}_2 - \text{O} - \text{B}(\text{OH})_2$, see Figure 3. This isomerization is highly exothermic, *e.g.* the computed values of ΔH_{298}^0 were -96.3 and -101.4 kcal/mol *in*

vacuo at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels; the corresponding values in aqueous media were: PCM: PBE1PBE/6-311++G(*d,p*) = −95.4 and MP2/cc-pVTZ = −100.6 kcal/mol; CPCM: PBE1PBE/6-311++G(*d,p*) = −96.4 kcal/mol and MP2/cc-pVTZ = −101.4 kcal/mol respectively. In the presence of an explicit water molecule oriented initially to play an active role in the process, see Figure 3, the values of $H^\ddagger$ for this rearrangement were calculated to be +18.2 and +23.2 kcal/mol *in vacuo* relative to $H_2N-CH_2-B(OH)(OOH)$ and H_2O at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels respectively; the corresponding values relative to the isolated reactants, H_2O_2 and $H_2N-CH_2-B(OH)_2$, were +16.2, and +21.7 kcal/mol. In the reaction field of water the values of $H^\ddagger$ were +21.6, +25.9, +21.9, and +34.8 kcal/mol using PCM(PBE1PBE/6-311++G(*d,p*)), PCM(MP2/cc-pVTZ), CPCM(PBE1PBE/6-311++G(*d,p*)), and CPCM(MP2/cc-pVTZ) methodology.

In the final step of this mechanism, $H_2N-CH_2-O-B(OH)_2$ is converted to $H_2N-CH_2(OH)$ and $B(OH)_3$, see Figure 3. This reaction, $H_2O + H_2N-CH_2-O-B(OH)_2 \rightarrow H_2N-CH_2(OH) + B(OH)_3$, is nearly thermoneutral where the values of ΔH_{298}^0 are +0.6 and +1.9 kcal/mol *in vacuo* at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels respectively; the value of ΔH_{298}^0 in PCM (CPCM) implicit solvent at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels of theory are +0.1 (+1.4) and −2.8 (−1.5). The transition state for this process was also located and the value of $H^\ddagger$ is +20.6 and +18.6 kcal/mol *in vacuo* relative to isolated $H_2N-CH_2-O-B(OH)_2$ and H_2O at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels; the corresponding values in aqueous media were: PCM: PBE1PBE/6-311++G(*d,p*) = +21.6 kcal/mol and MP2/cc-pVTZ = +21.0 kcal/mol; CPCM: PBE1PBE/6-311++G(*d,p*) = +21.9 kcal/mol (our attempts to locate a transition state at the CPCM: MP2/cc-pVTZ level failed).

Concluding Remarks

Boronic acids have emerged as an important class of compounds in chemistry, biochemistry, synthesis, medicine, and material science [1–35, 37–55, 76, 102] but much remains to be learned about their geometrical structures, thermodynamics, and kinetics *in vacuo* and in a variety of solvents, as well as the reliability of various computational methods for describing the diverse range of boron chemistry [71]. In this article we discussed our computational findings for the oxidative deboronation of BoroGlycine, $H_2N-CH_2-B(OH)_2$, using H_2O and H_2O_2 as the ROS *in vacuo* and in the reaction field of water.

Using H_2O as the ROS, the oxidative reaction: $H_2O + H_2N-CH_2-B(OH)_2 \rightarrow H_2N-CH_2-OH + H-B(OH)_2$, was calculated to be endothermic, the values of ΔH_{298}^0 are +11.3, +12.0, and +13.3 kcal/mol at the PBE1PBE/6-311++G(*d,p*), MP2/cc-pVTZ and MP2/aug-cc-pVTZ computational levels respectively, see Table 1; the corresponding values for the protodeboronation reaction: $H_2O + H_2N-CH_2-B(OH)_2 \rightarrow B(OH)_3 + H_2N-CH_3$, were found to be exothermic at similar levels, with values in the −20 to −30 kcal/mol range [76]. The values for the oxidative activation enthalpy, $H^\ddagger$, were predicted to be extremely high relative to the separated reactants, +85.6 and +94.3 kcal/mol, using PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels. Computed effects from implicit solvation models proved to be minimal on the thermodynamics of this oxidative mechanism.

Using H_2O_2 as the ROS, the oxidative reaction: $\text{H}_2\text{O}_2 + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{H}_2\text{N}-\text{CH}_2-\text{OH} + \text{B}(\text{OH})_3$, was calculated to be highly exothermic, the values of ΔH_{298}^0 were -97.7 and -100.9 kcal/mol at the PBE1PBE/6-311++G(*d,p*) and MP2/cc-pVTZ levels respectively; the corresponding protodeboronation reaction: $\text{H}_2\text{O}_2 + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{H}_2\text{N}-\text{CH}_3 + \text{B}(\text{OH})_2(\text{OOH})$, was also calculated to be exothermic, but the values of ΔH_{298}^0 were considerably less negative -29.9 and -25.9 kcal/mol. This oxidative process proved to involve several steps, see Figure 3; the highest-energy transition state for the multi-step process involved the rearrangement of $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})(\text{OOH})$ to $\text{H}_2\text{N}-\text{CH}_2-\text{O}-\text{B}(\text{OH})_2$ and the value of $H^\ddagger$ was $+18.2$ and $+23.2$ kcal/mol relative to the separated reactants at the PBE1PBE/6-311++G** and MP2/cc-pVTZ levels. These results provide computational support for the experimental results of Labutti *et al.*[53] that H_2O_2 mediated deboronation energetically favors an oxidative approach. Our results further suggest this occurs *via* a multi-step mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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93. In the absence of experimental data for reaction (1), it seemed wise to establish the reliability of our calculations as best we could. The enthalpy for the hydrolysis reaction of methylboronic acid, $\text{H}_3\text{C}-\text{B}(\text{OH})_2$: $\text{H}_3\text{C}-\text{B}(\text{OH})_2 + \text{H}_2\text{O} \rightarrow \text{CH}_4 + \text{B}(\text{OH})_3$, has been reported to be -26.8 kcal/mol, based on published heat-of-formation data (298°K) for the molecules in this reaction [97]. The calculated values of ΔH for this hydrolysis in vacuo were -27.9 , -27.8 , -21.5 , -30.5 , and -29.4 kcal/mol at the PBE1PBE/6-311++G(d,p), MP2/cc-pVDZ, MP2/aug-cc-pVDZ, MP2/cc-pVTZ and BPV86/tzvp levels respectively; the corresponding value of ΔH at the BPV86/tzvp level in a COSMO aqueous medium was -24.2 kcal/mol, ~ 5 kcal/mol lower than the value in vacuo. It is of interest to note that the calculated values of ΔH for the analogous hydrolysis reaction of BoroGlycine: $\text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{N}-\text{CH}_3 + \text{B}(\text{OH})_3$, were -29.2 , -31.9 , -26.1 , -30.8 , and -30.3 kcal/mol; the COSMO value at the BPV86/tzvp level was -26.0 kcal/mol. Thus, the presence of a basic primary amine group in the α -position appears to play a relatively minor role in the thermodynamics of this hydrolysis.
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FIGURE 1.
Structures of Bortezomib (A) and BoroGlycine (B).

PBE1PBE/6-311++G(*d,p*)
 PCM(PBE1PBE/6-311++G(*d,p*))
 CPCM(PBE1PBE/6-311++G(*d,p*))
 MP2/cc-pVTZ
 PCM(MP2/cc-pVTZ)
 CPCM(MP2/cc-pVTZ)

FIGURE 2.

Mechanism for the Reaction: $\text{H}_2\text{O} + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{H}_2\text{N}-\text{CH}_2-\text{OH} + \text{HB}(\text{OH})_2$.

FIGURE 3.

Mechanism for the Reaction: $\text{H}_2\text{O}_2 + \text{H}_2\text{N}-\text{CH}_2-\text{B}(\text{OH})_2 \rightarrow \text{H}_2\text{N}-\text{CH}_2-\text{OH} + \text{B}(\text{OH})_3$.

Table 1Thermodynamic Parameters (kcal/mol) for the Reactions of $\text{H}_2\text{N-CH}_2\text{-B(OH)}_2$ with **A.** H_2O and **B.** H_2O_2 .

	<u>PBE1PBE/</u>	<u>MP2(FC)/</u>		
	<u>6-311++G(d,p)</u>	<u>cc-pVDZ</u>	<u>aug-cc-pVDZ</u>	<u>cc-pVTZ</u>
A. H_2O				
$\text{H}_2\text{N-CH}_2\text{-B(OH)}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{N-CH}_2\text{-OH} + \text{HB(OH)}_2$				
E	+11.0	+9.8	+14.1	+11.6
ΔH_{298}^0	+11.3	+10.2	+14.4	+12.0
ΔG_{298}^0	+11.1	+9.7	+14.1	+11.7
B. H_2O_2				
$\text{H}_2\text{N-CH}_2\text{-B(OH)}_2 + \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{N-CH}_2\text{-OH} + \text{B(OH)}_3$				
E	-98.9	-100.2	-100.3	-102.4
ΔH_{298}^0	-97.7	-98.6	-98.9	-100.9
ΔG_{298}^0	-96.4	-97.6	-97.6	-100.1
$\text{H}_2\text{N-CH}_2\text{-B(OH)}_2 + \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{N-CH}_2\text{-B(OH)(OOH)} + \text{H}_2\text{O}$				
E	-1.4	-0.1	-2.3	-0.9
ΔH_{298}^0	-2.0	-0.7	-2.9	-1.5
ΔG_{298}^0	-1.6	-0.1	-2.0	-1.4
$\text{H}_2\text{N-CH}_2\text{-B(OH)(OOH)} \rightarrow \text{H}_2\text{N-CH}_2\text{-O-B(OH)}_2$				
E	-97.7	-100.6	-100.9	-103.0
ΔH_{298}^0	-96.3	-98.9	-99.2	-101.4
ΔG_{298}^0	-94.6	-97.9	-97.6	-99.4

Table 2Kinetic Parameters (kcal/mol) for Reactions of $\text{H}_2\text{N-CH}_2\text{-B(OH)}_2$ with **A.** H_2O and **B.** H_2O_2 .

<u>PBE1PBE//</u>	<u>MP2(FC)//</u>			
<u>6-311++G(<i>d,p</i>)</u>	<u>cc-pVDZ</u>	<u>aug-cc-pVDZ</u>	<u>cc-pVTZ</u>	
A. H₂O				
H₂N-CH₂-B(OH)₂ + H₂O → TS → H₂N-CH₂-OH + HB(OH)₂				
E [‡]	+87.3	+97.1	+92.0	+95.5
H [‡]	+85.6	+95.9	+90.6	+94.3
G [‡]	+95.3	+104.9	+100.0	+103.6
B. H₂O₂				
H₂N-CH₂-B(OH)₂ + H₂O₂ → TS → H₂N-CH₂-B(OH)(OOH) + H₂O				
E [‡]	+20.0	+15.3	+16.8	+16.9
H [‡]	+18.0	+13.5	+14.8	+15.1
G [‡]	+30.4	+26.5	+27.7	+27.8
H₂N-CH₂-B(OH)(OOH) + H₂O → TS → H₂N-CH₂-O-B(OH)₂ + H₂O				
E [‡]	+18.9	+20.8	+24.3	+23.7
H [‡]	+18.2	+20.4	+23.8	+23.2
G [‡]	+31.2	+33.6	+36.7	+36.5