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ORIGINAL ARTICLE

Theoretical Study on Ionization of Boric Acid in Aqueous Solution by *Ab Initio* and DFT Methods at T=298.15 K

T=298,15 K'da *Ab İnitio* ve DFT Yöntemleri ile Borik Asidin Sulu Çözeltisinin İyonlaştırılması Üzerine Teorik Bir Çalışma

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ABSTRACT

Objectives: The aim of this research work was to theoretically calculate the pK_a value of boric acid in aqueous solution by theoretical methods at T=298.15 K.

Materials and Methods: Boric acid has antifungal and antiviral properties. It is used in various prescription pharmaceutical products. The *ab initio* and density functional theory (DFT) methods were used in this research work.

Results: To explain the determined acidic dissociation constant, the various molecular conformations and solute-solvent interactions of the species of boric acid were considered. The basis set at the B3LYP/6-31+G (d) level of theory was selected for DFT calculations. We analyzed the formation of intermolecular hydrogen bonds between several species of boric acid and water molecules through Tomasi's method.

Conclusion: The result showed that there was comparable agreement between the experimentally and theoretically determined pK_a values for boric acid.

Key words: Boric acid, acidic dissociation constant, DFT, *ab initio*

ÖZ

Amaç: Bu araştırmanın amacı, borik asidin sulu çözeltisinin pK_a değerini teorik olarak T= 298,15 K'da hesaplamaktır.

Gereç ve Yöntemler: Borik asit antifungal ve antiviral özelliklere sahiptir. Çeşitli reçeteli farmasötik ürünlerde kullanılır. Bu araştırma çalışmasında *ab initio* ve yoğunluk fonksiyonel teorisi (DFT) yöntemleri kullanılmıştır.

Bulgular: Belirlenen asit disosiyasyon sabitini açıklamak için, borik asit türlerinin çeşitli moleküler konformasyonları ve çözünen-çözücü etkileşimleri göz önünde bulunduruldu. B3LYP / 6-31 + G (d) teori düzeyindeki temel set DFT hesaplamaları için seçilmiştir. Tomasi metodu ile çeşitli borik asit türleri ve su molekülleri arasında intermoleküller hidrojen bağlarının oluşumu analiz edildi.

Sonuç: Çalışmanın sonucu, borik asit için deneysel ve teorik olarak belirlenen pK_a değerleri arasında karşılaştırılabilir bir uyum olduğunu göstermiştir.

Anahtar kelimeler: Borik asit, asit disosiyasyon sabiti, DFT, *ab initio*

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INTRODUCTION

Boric acid is a weak acid that forms a white and water-soluble powder.[1] It can be naturally found in seawater, many plants, and most fruits. Boric acid has been used as a mild antiseptic or bacteriostat in eyewashes and mouthwashes. Aqueous solutions of boric acid are topically used for ophthalmic irrigation to cleanse, refresh, and soothe irritated eyes and used for removal of loose foreign material, air pollutants, or chlorinated water.[2]

Boric acid is predominantly eliminated unchanged by the kidney; small amounts are also excreted in sweat, salvia, and feces. Boric acid is concentrated in the brain and liver.[3] Boric acid and its derivatives have been shown to promote riboflavinuria in both animals and humans.[4]

Metabolism of inorganic borates by biological systems is not feasible because excessive energy is required to break the boron-oxygen bond. Inorganic borates, in low concentrations, convert to boric acid at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption.[5]

Studies of the acidity of organic compounds are important and play a very significant role in the evaluation of the activity, reaction mechanisms, and structures of organic compounds.

Equilibrium constants for ionization reactions are usually called ionization constants or acidic dissociation constants (pK_a). pK_a is an important physico-chemical parameter in drug absorption. Many drug compounds include at least one acid and/or basic group, and the ionization state of these groups plays an important role in determining the physico-chemical properties of compounds. Information about the pK_a value of compounds plays a major role in the expansion of drug formulations.[6-8]

Reliable and accurate methods for calculating relative and absolute pK_a values are important for understanding of the effective pK_a values in molecules. Some studies detailing the acid-base properties of compounds in aqueous solutions and in the gas phase are also available.[9] Different experimental procedures are frequently used for the determination of acidity constants. These methods are high-pressure liquid chromatography, liquid-liquid partitioning chromatography, and methods that involve potentiometric titrations or spectrophotometric determination in water or in mixtures of solvents. Manov et al.[10] determined the ionization constant of boric acid and the pH of certain borax-chloride buffer solutions from 0 to 60°C. Arcis et al.[11] determined the ionization of boric acid in water from 298 K to 623 K by AC conductivity and Raman spectroscopy. Dickson carried out emf measurements using the cell: Pt | H2 (g, 101.325 kPa) | borax in synthetic seawater | AgCl; Ag over the temperature range 273.15-318.15 K, and at five salinities from 5 to 45. The obtained results of that research work were used to calculate the stoichiometric (ionic medium) dissociation constant for boric acid in seawater media on the "total" hydrogen ion scale.[12]

For boric acid, the values of pK_a can be calculated using *ab initio* and density functional theory (DFT) methods.[13-18] These computational methods have an important advantage. In these methods, the important structural properties of molecules, in solution, such as the dihedral angle between the indicated atoms (D); total atomic charge (Mulliken) (q); bond lengths between the indicated atoms (d); and bond angles (A) are calculated. These structural properties can be used in research works as well as in various industries.

In the DFT method, the calculation of electronic structure was performed with DFT and the electrostatic features were modeled through external charge distributions and continuum dielectrics. The polarizable continuum model (PCM) using the integral equation formalism variant PCM is the default self-consistent reaction field (SCRF) method. This method creates the solute cavity via a set of overlapping spheres. It was initially devised by Tomasi and coworkers and Pascual-Ahuir and coworkers. Tomasi's method allowed us to prove that cations, neutral molecules, and anions form intermolecular hydrogen bonds (IHBs) with some molecules of water.[19]

The present paper deals with the influence of factors such as the SCRF model applied, choice of a particular thermodynamic equation, atomic radii used to build a cavity in the solvent (water), optimization of geometry in water, inclusion of electron correlation, and the dimension of the basis set on the solvation free energies and on the calculated pK_a values. The pK_a value of boric acid was calculated in aqueous solution by *ab initio* and DFT methods and temperature of 25°C. We investigated the molecular conformations and solute-solvent interactions of the cation, anion, and neutral species of boric acid to explain the obtained acidic dissociation constants.

MATERIALS AND METHODS

Initially, the structure of species of boric acid was optimized by semiempirical PM3 method in the program HyperChem (CS Chem 3D version 5.0). All calculations about the geometries of the initial and solvated molecules in water were done using the software package Gaussian 09. The DFT calculations were carried out using the hybrid exchange-correlation functional of Becke, Lee, Yang, and Parr (B3LYP) and the Gaussian 6-31G (d) basis set was used.[20]

To analyze the solvent effects on all species involved in the selected ionization reaction, the PCM of Miertus and Tomasi.[21] was used. In this method, the solvent is represented as a structureless polarizable medium characterized by its dielectric constant. Finally, we selected the solvation of the species by means of IHB_S that involve one molecule of the mentioned species and some molecules of water.

RESULTS AND DISCUSSION

The trend of a molecule to lose its H^+ is quantified as pK_a. Boric acid is a weak acid and it has three acid groups. A proton can separate from the hydroxyl group to give an ionized species (Figure 1). This concept of microscopic ionization constant is shown in Equation 1:

$$k=\frac{[H^+][B(OH)_2O^-]}{[B(OH)_3]} \quad \text{Equation} \quad (1)$$

The total free energies (in Hartree and kJ.mol^{-1}) for the single and solvated species of boric acid, in water, were calculated at the B3LYP/6-31+G (d) level of the theory, using Tomasi's method, at T=298.15 K and the results are shown in Table 1. This table shows that the total free energy for various species of boric acid increases with increasing number of water molecules. It shows that the solvation process causes an increase in the total free energy for various species of boric acid. In other words, solvation of the boric acid is an endothermic process. The values of total free energy for various species of boric acid (Table 1) were applied to calculate the pK_a value of boric acid. In addition, these data help us to suggest an appropriate reaction regarding the deprotonation process of boric acid.

Various reactions including the neutral and anion species of boric acid were considered in the program Excel and some of these reactions were not considered further because their equilibrium constants were not comparable with the experimental ones. The selected equation for the deprotonation process of boric acid as well as the experimentally determined and theoretically calculated pK_a is shown in Table 2.

Ionization constant of boric acid

In aqueous solutions, the molecule of boric acid can undergo the below reaction:

$H_3L(H_2O)_4+OH^- \rightleftharpoons H_2L^-(H_2O)_3+2H_2O$ K_c Equation (2)

In the above reaction, $H_3L(H_2O)_4$ (Figure 2A) is the neutral species of boric acid solvated with four molecules of water and $H_2L^-(H_2O)_3$ (Figure 2B) represents the anion species of boric acid solvated with three water molecules.

During the reaction of Equation 2, the autopyrolysis of two water molecules, in pure water, can occur as shown below:

$2H_2O \rightleftharpoons OH^-+H_3O^+$ $K_w=1.008\times10^{-14}$ Equation (3)

The very low amount of K_w shows that a few water molecules are ionized in pure liquid water.

The reaction of Equation 4 can be obtained by combining Equation 2 and 3:

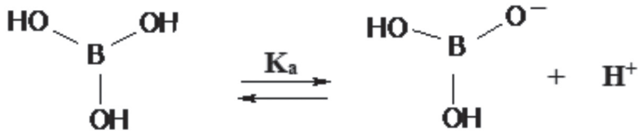
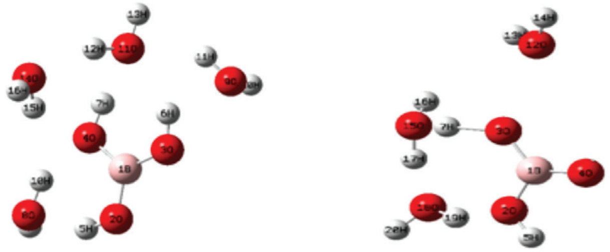


Figure 1. The scheme of deprotonation of boric acid



(A): $H_3L(H_2O)_4$ **(B)**: $H_2L^-(H_2O)_3$

Figure 2. The calculated structure for the neutral (A) and cation (B) species of boric acid solvated with four and three water molecules, respectively, obtained at the B3LYP/6-31+G(d) level of theory and using Tomasi's method at 298.15 K

$H_3L(H_2O)_4 \rightleftharpoons H_2L^-(H_2O)_3+H_3O^+$ K_a Equation (4)

It is clear that the value of K_a can be calculated using K_c and K_w as below:

$K_a=K_c\times K_w$ Equation (5)

Equation 5 was applied to calculate the values of the ionization constant of boric acid, K_a, in water at T=298.15 K. The theoretically calculated value of pK_a for boric acid at T=298.15 K is shown in Table 2. As can be seen in this table, there is good agreement between the experimentally determined (pK_a=9.237)[22] and theoretically calculated pK_a values of boric acid at this temperature.

Table 3 shows the optimized values of structural properties for the anion and neutral species of boric acid, in water, obtained at the B3LYP/6-31+G (d) level of theory with Tomasi's method at T=298.15 K.

As can be seen in Table 3, for boric acid, the values of q_{O4} for $HL^-(H_2O)_3$ and $H_2L(H_2O)_4$ are -1.104481 and -0.907847, respectively. It shows that the absolute value of electrical charge around the O_4 atom in $HL^-(H_2O)_3$, compared to that in $H_2L(H_2O)_4$, increases and it can imply H^+ separates from the O_4 atom during the deprotonation process of boric acid in water.

Table 1. The calculated total free energy (G^o_{sol}) using Tomasi's method at the B3LYP/6-31+G (d) level of theory for neutral and cationic species of boric acid at 298.15 K

No	Species	G^o_{sol} (Hartree)	$G^o_{sol/molecule}$ (kJ.mol^{-1})
0	H_2L^-	-252.913276	-664023.7424
1	H_2L^- (H_2O)	-329.373889	-432385.5313
2	H_2L^- $(H_2O)_2$	-405.824119	-355163.7074
3	H_2L^- $(H_2O)_3$	-482.272605	-316551.6507
4	H_2L^- $(H_2O)_4$	-558.723888	-293385.8854
0	HL	-252.517526	-662984.7009
1	$H_3L(H_2O)$	-328.959459	-431841.4884
2	$H_3L(H_2O)_2$	-405.403531	-354795.6228
3	$H_3L(H_2O)_3$	-481.843749	-316270.1604
4	$H_3L(H_2O)_4$	-558.291915	-293159.0564
0	H_3O^+	-76.862	-201801.1616
0	H_2O	-76.434	-200677.4477
0	OH^-	-75.952	-199411.9569

Table 2. The value of pK_a for the deprotonation of boric acid obtained using the Tomasi's method at the B3LYP/6-31+G (d) level of theory, at 298.15 K

Species	Selected equations	pK_a (calculated)	pK_a (experimental)
Boric acid	$H_3L(H_2O)_4 \rightleftharpoons H_2L^-(H_2O)_3+H_3O^+$	9.36436	9.237

Table 3. The calculated structural properties for the neutral and cation species of boric acid using Tomasi's method at the B3LYP/6-31+G (d) level of theory at 298.15 K

Species	Calculated magnitudes	
Boric acid	$H_2L(H_2O)_4$	$HL^-(H_2O)_3$
K_c	2313964803	-
K_a	2.2956E+23	-
qB_1	1.311027	1.174291
qO_2	-1.018240	-0.947905
qO_3	-1.132647	-0.912080
qO_4	-0.907847	-1.104481
qH_7	0.650111	0.605440
qO_9	-1.093296	-
qH_{11}	0.549604	-
qH_{13}	0.562297	0.557999
qH_{16}	0.637048	0.539621
qH_{19}	-	0.599065
qH_{20}	-	0.558377
dO_2B_1	1.382044	1.357259
dO_3B_1	1.384941	1.366905
dO_4B_1	1.355540	1.412990
dH_5O_2	0.971181	0.979039
dH_6O_3	0.991077	-
dH_7O_3	-	0.977600
dH_7O_4	0.967252	-
dO_8O_4	2.788456	-
dO_9O_3	3.841056	-
$dH_{11}O_9$	0.973583	-
$dH_{13}O_{12}$	-	0.968626
dH_6O_9	2.124582	-
$dH_{19}O_2$	-	2.098563
$AO_3B_1O_2$	114.708261	119.682443
$AO_4B_1O_2$	118.806632	118.757031
$AH_5O_2B_1$	111.895234	112.464635
$AH_6O_3B_1$	121.477128	-
$AH_7O_3B_1$	-	111.480812
$AO_9O_3B_1$	144.288763	-
$AH_{10}O_9O_3$	115.173761	-
$AH_{11}O_9O_3$	139.273690	-
$AH_{13}O_{12}O_3$	-	147.569337
$AH_{16}O_{15}O_3$	-	130.127543
$DO_4B_1O_2O_3$	-179.779914	-178.510094
$DH_5O_2B_1O_4$	3.701327	-177.469800
$DH_6O_3B_1O_4$	14.750747	-
$DH_7O_3B_1O_4$	177.137823	-171.677912
$DH_{10}O_9O_3B_1$	-18.098064	-
$DH_{13}O_{12}O_3B_1$	-	147.569337
$DH_{16}O_{15}O_3B_1$	-	130.127543

K_C: Equilibrium constant of equation, K_a: Acidic dissociation constants of species in water, D: Dihedral angle between the indicated atoms (Å), : Total atomic charge (Mulliken) (au), d: Bond lengths between the indicated atoms, A: Angles (°)

Study on H-bonding between selected species of boric acid and water

The structural properties of a species, solved in water, can help us to understand the interaction between this species and water (H-bonding). One of the most important of these structural properties is the bond length between the indicated atoms from solute and solvent (water) molecules (in Å). These data, for neutral and cation species of boric acid, are listed in Table 3. The power of hydrogen bonds can be classified as strong (bond length is between 1.2 Å and 2.2 Å and the angle is between 175° and 180°), moderate (bond length is between 1.5 Å and 2.2 Å and the angle is between 130° and 180°), and weak (bond length is between 2.2 Å and 3.2 Å and the angle is between 90° and 150°).[23] As can be seen in Table 3, for $H_2L(H_2O)_4$, the bond length between atom H_6, from boric acid, and O_9, from water, is 2.124582 (dH_6O_9=2.124582). In addition, for $H_2L^-(H_2O)_3$, the bond length between atom O_2, from boric acid, and H_{19}, from water, is 2.098563 ($dH_{19}O_2$=2.098563). These data show that for boric acid the power of H-bonding between $H_2L(H_2O)_4$ and water and also between $H_2L^-(H_2O)_3$ and water are classified as moderate. It must be noted that IHBs data can be used in the design of benefit and help us to predict nano drugs.[7]

CONCLUSION

In this research work, we showed the feasibility of a theoretical method, DFT and *ab initio*, to calculate the ionization constants of boric acid at T=298.15 K. As a result, we selected various acid-base reactions that include the solvation of the hydrogen, hydroxyl ions, and other anions or neutral molecules in protic solvents such as water, which possess a high hydrogen-bond-donor capability. The calculations performed at the B3LYP/6-31+G (d) levels of theory using Tomasi's method allowed us to prove that neutral molecules and anions form IHBs with some molecules of water. In addition, the comparison between experimentally determined and theoretically calculated pK_a, for boric acid, shows that there is good agreement between them at 298.15 K.

Conflicts of interest: No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

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