Conference paper

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Boric acid: a simple molecule of physiologic, therapeutic and prebiotic significance

Abstract: Boric acid, H_3BO_3, is a weak acid and at physiological pH is in the form of an uncharged small molecule. Behaving as a Lewis acid, it forms complexes with amino- and hydroxy acids, carbohydrates, nucleotides and vitamins through electron donor-acceptor interactions. These interactions are believed to be beneficial for human health. Synthetic *bis*-chelate complexes of boric acid with organic biomolecules are therefore considered for nutritional and/or pharmaceutical applications. The use of boric acid for BNCT has gained attention due to the short biological half-life, solubility, plasma circulation and the non-selective soft tissue accumulation properties of this simple molecule. Complexation of boric acid with sugars is of particular importance in understanding the role of boron as a carrier for nucleotides and carbohydrates. A potential and catalytic role of boric acid in peptide and nucleic acid synthesis and in the stabilization of sugar molecules by acting as a complexing agent have been demonstrated. Its possible role as a phosphorylation chaperone in a prebiotic world has been recently suggested. This contribution reviews the highlights in the physiologic, therapeutic and prebiotic significance of boric acid in the last decade.

Keywords: boric acid; borate ester; borate complex; IMEBORON-XV; prebiotic chemistry.

DOI 10.1515/pac-2014-0909

Introduction

Boron was accepted as an essential nutrient for plants nearly a century ago [1] but its exact biological function in animals and humans still remains to be clarified. Research on the requirement of boron as a nutrient and its role in animal and human metabolism has been a growing interest and shows that we do need it.

Inorganic boron in biological systems is present as undissociated orthoboric acid, $B(OH)_3$, or borate ion, $B(OH)_4^-$ [2, 3]. In aqueous solutions, these two forms are in chemical equilibrium (1) and can interconvert in less than a second in favor of one form over the other depending on the pH of the medium. Because the pH of the blood is 7.4, the abundance of these two species in blood should be 98.4 % and 1.6 %, respectively.

$$B(OH)_3 + H_2 \rightleftarrows B(OH)_4^- + H^+ (pKa \sim 9.25) \quad (1)$$

Article note: A collection of invited papers based on presentations at the 15th International Meeting on Boron Chemistry (IMEBORON-XV), Prague, Czech Republic, 24–28 August 2014.

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Boric acid, first mentioned by the Arab chemist Geber in 700 AD, is a weak acid and at physiological pH is largely in the form of an uncharged small molecule with a molecular volume of 71.5 Å^3, which is similar to urea (75.3 Å^3) and other small non-electrolytes [4]. Behaving as a Lewis acid, it forms complexes with hydroxy-group bearing amino- and carboxylic acids, carbohydrates, nucleotides and vitamins through esterification reactions. Partial esterification creates monoesters (1:1 complex) that exist with no charge or a tetrahedral configuration with negative charge. Complete esterification leads to the formation of bicyclic diester (1:2 complex) structures with negatively charged tetrahedral boron anions, as shown in Fig. 1 and Scheme 1. These interactions are pH-dependent and diol binding is favoured at basic pH, while esterification with hydroxy-carboxylic acids is favored in acidic pH ranges [5–11]. The complexes involve covalent interactions that are reversible in aqueous solution. Monoesters are very labile and rapidly hydrolyze to their original components in aqueous solution while diesters are thermodynamically more stable and rarely hydrolytically dissociated in water [12, 13].

As a mild acid, there are many uses of boric acid known to man for thousands of years and many new uses are found every day from medicines to pesticides and industrial products [14]. Synthetic complexes with organic biomolecules are considered for nutritional and/or pharmaceutical applications. Boric acid was used as a first generation BNCT agent in the 1950s but the results were discouraging. After half a century, the use of boric acid for BNCT applications has regained attention due to the biocompatible properties of this simple molecule. Its affinity to sugars is of particular importance in understanding the role of boron in a prebiotic world as a carrier for nucleotides and carbohydrates. This document is intended to review the highlights in the physiologic, therapeutic and prebiotic significance of this simple molecule in the last decade.

Physiologic significance of boric acid

Boron exist in the body as undissociated boric acid that does not appear to accumulate in soft tissues but does accumulate in bone. Boric acid is fairly rapidly absorbed and excreted from the body via urine with an average half-life of 1 day [15]. It is of low acute toxicity to mammals when applied to the skin, and moderately toxic if inhaled. There is no evidence that boric acid is metabolized in plants or animals, perhaps due to the large amount of energy required to break the strong B–O covalent bond.

Selected aspects of boric acid action on living systems have been researched but a comprehensive picture has not yet emerged. More is becoming known with substantial evidence for boron being a beneficial food component [16]. Studies have shown that boron appears to affect the mineral (Ca, Mg, P) and vitamin (D) metabolism involved with bone formation and the serum estrogen and possibly testosterone levels thus preventing or treating osteoporosis [17]; increase cognitive functions and psychomotor tasks [18]. The effects of

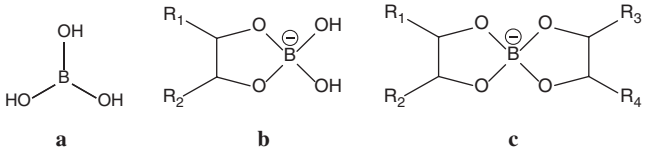

Fig. 1 (a) Boric acid, (b) anionic monoesters and (c) anionic diesters with organic molecules bearing *cis*-hydroxy groups (R=H, alkyl, aryl, acyl).

Scheme 1 Esterification (complexation) reaction of boric acid with organic molecules bearing *cis*-hydroxy groups.

dietary boron on human physiology have been recently reviewed by Hunt, emphasizing its role in calcium metabolism, bone growth and maintenance, insulin metabolism and cognitive functions [19].

In the past few years, several other reports on the physiological effects of boron have been published. The effects of dietary boric acid and borax supplementation on lipid peroxidation (LPO), antioxidant activity and DNA damage in rats have been investigated. Boron supplementation (100 mg/kg) in diet was found to decrease LPO, and enhance the antioxidant defense mechanism and vitamin status [20].

Boric acid is a known inhibitor of several serine proteases, urease and histone deacetylases [21–23]. Studies have shown that it may have a protective role with regard to both prostate and breast cancer [24–26]. At a cellular level, the molecular effects of boric acid lead to an inhibition of protein synthesis, the activation of MAP kinase cascades, an inhibition of cell cycle progression and morphological changes that add up to significant antiproliferative action on certain cancer cell lines [27]. At physiological pH, boric acid enters into the cell and hydrolyzes as borate anion decreasing the intracellular pH [28] making the cell subjected to inhibition and then to apoptosis. The borate ion, not the boric acid, seems to have the physiological activity as i. a cell-signaling molecule, ii. a co-factor of the enzymes it regulates, iii. a non-enzymatic co-factor iv. electron transfer, redox sensing and structural modules and v. a role in cytoskeleton structure, as summarized by Dinca and Scori [29].

Additional findings of interest include studies on the protective effect of boric acid against heavy metal toxicity in human blood [30] and the effect of boric acid exposure on energy homeostasis increasing substrate utilization and ultimately leading to weight loss [31].

Therapeutic significance of boric acid

Traditional medical applications of boric acid include uses as an antiseptic since ancient China and as eye-wash in a very dilute solution since 1700s. Boric acid has anti-bacterial and anti-fungal properties for vaginal yeast infections and other fungal problems as clinically evidenced in 2011 [32]. It is commonly used in contact lens solutions, eye disinfectants, vaginal remedies, baby powder, anti-aging preparations and similar external applications. It is also helpful in treating foul foot odor and in alcohol solution, it can be used to treat some kinds of ear infection (e.g., *otitis externa*) in both humans and animals. Systemic administration has been shown to reduce periodontal inflammation and alveolar bone loss in periodontal disease in rats [33].

Boric acid was shown to control the proliferation of some types of cancer cells including melanoma, breast and prostate cancer cells ([34] and the references therein). In the 1950s, sodium borate, boric acid and derivatives were utilized as first generation Boron neutron capture therapy (BNCT) agents, but boron concentrations in the tumor were not satisfactory [35]. In the last decade, the use of boric acid for BNCT has regained attention due to the short biological half-life, solubility, plasma circulation and the non-selective soft tissue accumulation properties of this simple molecule. The ability to accumulate in bone would make boric acid a BNCT drug for bone cancer (osteosarcoma) and that it does not accumulate in soft tissues would make it effective for the BNCT of some types of cancer like hepatoma. Recent studies have shown the potential of boric acid-mediated BNCT as a promising therapy for osteosarcoma [36] and liver cancer [37].

Boric acid and other borates have been increasingly used in nutritional supplements as a source of boron. In most of the commercial dietary boron supplements now available, boron is chelated with amino acids or with polyhydroxy acids in combination with a variety of nutrients such as vitamin D, calcium, magnesium, soy isoflavones, chondroitin sulfate, glucosamine and others. However, no information about the exact structures of these chelates are available as they are mostly given in patent formulations. The fructoborate complex (Fig. 2) developed by FutureCeuticals® to promote healthy bones and joints, and to aid in Vitamin D metabolism, prostate health and in the regulation of steroid hormone levels [38, 39] is well characterized.

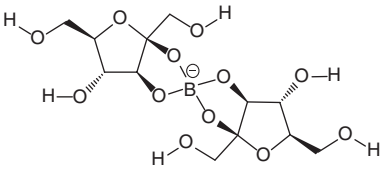

Fig. 2 Chemical structure of the fructo-borate complex anion.

Attempts are underway to prepare new molecular and hybrid materials for potential nutritional and therapeutic uses of boric acid. As natural plant forms of boron or similar synthetic forms are not yet available, complexes of boric acid with biomolecules possess the potential to be used as nutrients or pharmacophores and are therefore of interest. *In vitro* complexation of boric acid with vitamin C (ascorbic acid) [40], vitamin B1(thiamine) and vitamin B6 (pyridoxine) [41] salicylic and glucuronic acids [42–44], citric and malic acids, and mixed combinations of these biomolecules [44] have been described. As shown in Fig. 3, these complexes are in salt form with negatively charged tetrahedral borate anions counterbalanced by bio-active cations (e.g., lithium, sodium, magnesium, calcium), readily soluble in water but slowly undergo hydrolytic dissociation to boric acid and the organic ligand as indicated by solution NMR studies.

High water solubility and slow hydrolysis properties may allow these complexes use in the cumulative treatment of metal ion, boron and biomolecule deficiencies or aid in the metabolic processes where boron is claimed to be active before being completely hydrolysed and excreted from the body (Fig. 4). Thus, these compounds remain central to interesting research topics due to equivocal and relatively unknown useful actions, roles in the treatment of various diseases, and interactions of other elements.

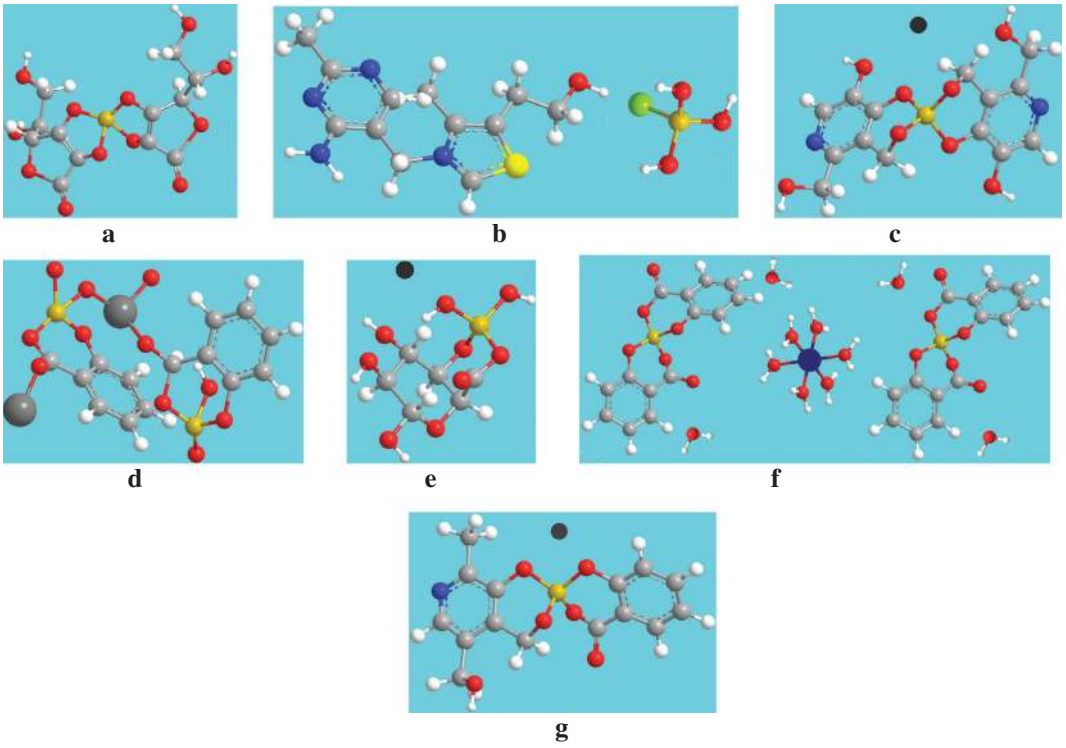

Fig. 3 Structures of boric acid complexes with some biomolecules (a) bis(ascorbato)borate [40], (b) thiamine chloroborate [41], (c) bis(pyridoxine)borate [41], (d) lithium salicylatoborate [42], (e) magnesium bis(salicylato)borate [43], (f) glucuronatoborate [42], (g) glucuronatosalicylatoborate [44]. Color definition of balls: white: H; gray: C; red: O; dark yellow: B; blue: N; yellow: S; black: Na, dark blue: Mg, dark gray: Li.

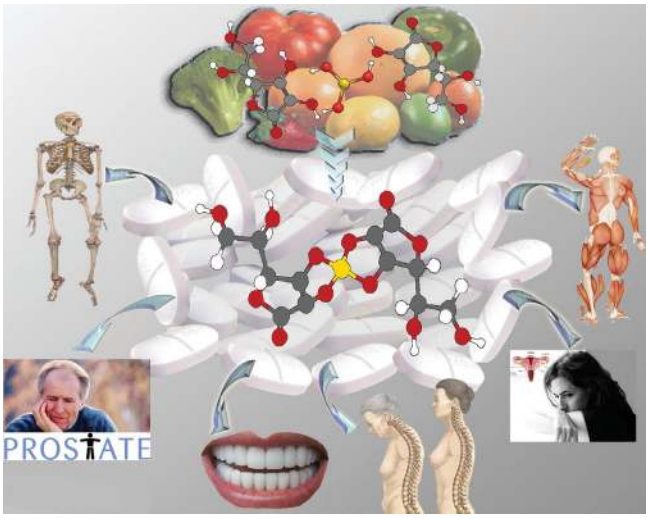

Fig. 4 Beneficial effects of organic biomolecule-borate complexes.

Prebiotic significance of boric acid

A number of hypotheses have been proposed about the origin of life on primitive earth. The most widespread ones, including the "Peptide World" and "RNA World," have been overviewed by Fitz et al. [45]. The consideration of oligomerization of amino acids toward a possible "peptide world" is one of the most discussed topics for the evolutionary scenario. The formation of peptides in aqueous solution is a rather unfavorable reaction, both thermodynamically and kinetically, as the condensation of amino acids to peptides requires the removal of water from the reaction partners. A potential and catalytic role of boric acid in peptide and nucleic acid synthesis has been demonstrated [46]. The effects of boric acid on the polymerization of glycine was studied. Some cyclic and linear oligopeptides were obtained and spontaneous binding of amino acids to RNA with boric acid was suggested.

The RNA world hypothesis [47] assumes that the basic building blocks (e.g., amino acids, hydroxy acids, sugars, purines, pyrimidines and fatty acids) of RNA were readily available on the prebiotic earth. It has been suggested that the minerals available on the surface of the earth and in the oceans could have played a crucial role in the prebiotic synthesis of RNA by concentrating these organic species on their reactive surfaces and catalyzing the polymerization reactions as reviewed by Ferris [48], Hazen and Sverjensky [49] and Hashizume et al. [50].

A wide array of sugars, including ribose, can be formed from formaldehyde (formose reaction) under possible prebiotic conditions, however, ribose has no selectivity and is rather unstable [51]. Boric acid and borate minerals have been suggested to play a crucial role in transforming the prebiotic organic molecules to give ribose in a stable form by acting as a complexing agent. It is well known that boric acid and borate complexes with 1,2-diol and 2,3-diol compounds and the cyclic form of ribose presents two hydroxyl groups in a *cis* configuration for complexation with boron. Benner and co-workers demonstrated that ribose formation from formaldehyde and glycolaldehyde is stabilized in the presence of borate [52]. da Silva and co-workers showed possible clues on the roles of borate ions, alkaline and earth alkaline ions in the synthesis and stabilization of ribose during the pre-RNA period [53].

It is generally assumed that in reactions carried out around the pKa of boric acid (and above), the reactive species is borate, while the trigonal boron is responsible for the reactivity at lower pH values. Depending on the prebiotic pH alterations, complexation of boric acid with sugars might be of importance in understanding the role of boron as a carrier for nucleotides [54]. Mono-chelate (mono-ester) and bis-chelate (di-ester) anionic complexes of boric acid with L-ascorbic acid, a sugar acid with the same furanose ring as ribose, have

been isolated from aqueous solutions in salt form with Li^+, Na^+ and Ca^{2+} ions [40]. The bis-chelate complexes were found to have remarkably higher thermal and hydrolytic stabilities than their mono-chelate analogs. The hydrolytic dissociation of the 1:2 Ca-complex in 9 h at pH = 7.6 was about 50 % indicating that the sugar ring can be stabilized long enough for further chemical transformations.

Recent studies have presented plausible suggestions to the i. "the water problem," ii. "selectivity of ribose," iii. "chirality" and iv. "prebiotic phosphorylation" issues that the RNA world hypothesis carries difficulties to explain, by considering the possible inclusion of boron in prebiotic chemistry. Many bonds in RNA are thermodynamically unstable with respect to hydrolysis in water. In 2012, a geological model has been introduced for the "water problem," proposing the synthesis of RNA in a prebiotic dry valley which receives high pH run-off, rich in eroding borate minerals, formamide, ammonium formate and other necessary species, where borate moderates the formose reaction in strongly dehydrating conditions [55]. An approach to the "selectivity problem" was reported in 2013, verifying that borate selectively increases the stability of ribose over other aldopentoses sequestering from isomerization and decomposition reactions [56].

Although a growing literature exists about the stabilization of ribose with boron, conjugation of ribose with a base to make a nucleoside or add phosphate to make a nucleotide still remains an open question. Complexation of boric acid with sugars and nucleosides could allow the approach and fixation of a phosphate group to the sugars and polymerization of phoshoribose to polyphosphoribose. Holm and co-workers proposed that brucite mineral [solid $Mg(OH)_2$] may scavenge borate and phosphate from sea water. Brucite with adsorbed phosphate may catalyze the synthesis of pyrophosphate from orthophosphate, high pH conditions promote the abiotic formation of ribose and ribose can be stabilized by borate leaving available positions for phosphorylation [57]. da Silva and Holm later argued that borophosphates and siliphosphates, possibly existing in hydrogel forms under prebiotic environments, could play a role in "prebiotic phosphorylation" and emerging "homochirality" [58]. Anionic borophosphates could stabilize ribose like inorganic borate adjusting the phosphate group to be reactive. Depending on the alterations in composition and temperature, chiral crystalline derivatives of these hydrogels could lead to the enantiometric enrichment of the racemic ribose on surface which then determines the chirality of amino acids. Our recent work [59] provides experimental evidence in favor of this hypothesis. We examined possible formation of –C–O–B–O–P– linkages in aqueous media by adding orthophosphate to solutions of boric acid and some biomolecules (Fig. 5). Species containing ortho- to tri-phosphate groups attached to the borate esters of salicylic, ascorbic and citric acids were obtained and structurally defined by a number of chemical and physical methods. Analytical results indicated the presence of –C–O–B–O–P– linkages with the attached phosphate groups varying between orthophosphate and triphosphate, depending on the starting material. While no details of the mechanism are yet available to us, the biomolecules that we studied may serve as models in the B–P-organic system. We further demonstrated that under melt-quench conditions these organic-mediated B–O–P bonded materials convert to bioactive glasses with quasicrystalline regions on the surface. The bioactivity tests in synthetic

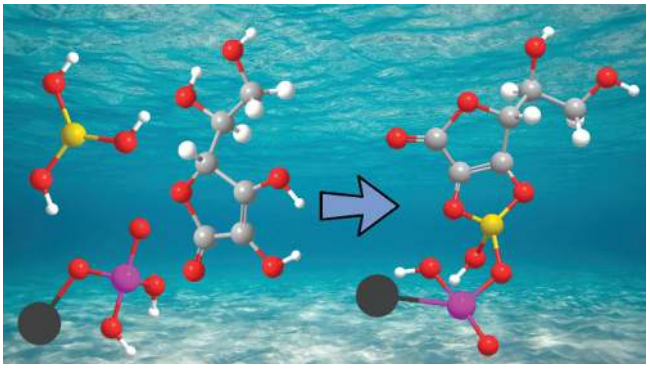

Fig. 5 A schematic representation of the interaction of boric acid with inorganic phosphate and ascorbic acid in water producing the borophosphate ester of the organic molecule.

body fluid (SBF) solutions showed instant formation of amorphous calcium phosphates as apatite precursors [60], indicating that C–O–B–O–P bonded skeletons might play some role in biomineralization, with another possible contribution of boron to the evolution of life.

The current discussions outlined above suggest a possible role for boric acid in stabilizing sugars and linking biomolecules to inorganic phosphate providing that the appropriate prebiotic conditions (e.g., concentration, pH, temperature) requirements are established. These studies provide supporting evidence in favour of a positive response to the question "Is boric acid the missing link in prebiotic chemistry?" posed by Prieur in 2001 [61].

Conclusions

Boric acid is one of the most used and studied boron containing chemicals since ancient times. Though important progress has been achieved regarding the physiologic, therapeutic and prebiotic significance of this small molecule, further research is required to clarify the mechanisms operating in these areas.

Complexation of boric acid with organic *cis*-diol-functionalized molecules appears to be the most probable chemical mechanism in understanding *i*. the occurrence of boron complexes in biological systems, *ii*. the sugar binding properties of boron, and *iii*. the involvement of boron in the evolution of the living world.

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