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Review

Interactions between boric acid derivatives and saccharides in aqueous media: Structures and stabilities of resulting esters

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ABSTRACT

The general principles of interaction between bor(on)ic acids and sugars in aqueous media are discussed with a focus on the structural aspects that play a role with respect to the regioselectivity of the interactions and the stability of the resulting adducts. Preorganization and pK_as appear to play important roles. Glucose and sialic acid will be demonstrated to be the promising targets for artificial B-based sensors. These sugars are important markers for diabetes and cancer, respectively.

Abbreviations: B^0, neutral bor(on)ic moiety; B^-, negatively charged bor(on)ate moiety; CEST, chemical exchange saturation transfer; DO3A, 1,4,7,10-tetraazacyclododecane-1,4,7-triacetate; DTPA, diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HPDO3A, 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate; HSA, human serum albumin; Neu5Ac, 5-*N*-acetylneuraminic acid; PBA, phenylboronic acid; sLex, sialyl Lewis X; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance.

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1. Introduction

Borax is an easily accessible ore that is present in large deposits on and near the surface of the earth. Throughout the centuries it has found applications in a large diversity of fields including metallurgy, ceramics and glass, medicine, detergents, insecticides, lubricants, hydraulic fluids for oil exploitation, and catalysis [1]. Many of these applications rely on the interaction of boric acid or its derivatives with polyols, in particular with saccharides. Such interactions are very important in nature as well. Borate-diol esters are present in various natural compounds, for instance in the bacterial antibiotic boromycin and in the rhamnogalacturonan II complex, which strengthens plant cell walls [2]. Furthermore, borates most likely played a crucial role in the prebiotic formation of RNA by stabilizing pentoses like ribose, which were the natural outcome of condensation reactions of formaldehyde and glycolaldehyde [3].

Already in 1890, Magnanini demonstrated, by means of conductivity measurements, that sugars form adducts of boric acid in aqueous solutions [4] and some years later, van't Hoff concluded these adducts to be cyclic esters of boric acid [5]. Böeseken et al. have performed extensive conductivity and polarimetry studies on the interactions between boric acid and carbohydrates, from which a wealth of information on the configurations and conformations of these compounds was obtained [6].

During the last couple of decades, the interest in B-based compounds for medical applications increased significantly. The dipeptide-boronic acid, bortezomib, has entered clinical practice as proteasome inhibitor for treating relapsed multiple myeloma and mantle cell lymphoma [7], whereas other boric acid derivatives emerged as artificial sensors of sugars. Such sensors are usually built up from a boronate-based targeting vector for the molecular recognition of the sugar, a linker, and a reporter unit that provides a signal to the outside world in response to the recognition of the sugar. Many different reporting techniques have been applied [8,9] including pH depression, fluorescence, colorimetry, electrochemistry, and magnetic resonance imaging (MRI) [10]. More recently, drug delivery systems and theranostics with boronate-based targeting vectors have been proposed as well.

Here, a review on the interaction between bor(on)ic acids and sugars in aqueous media and the applications of these phenomena in medicine is presented. The attention will be focused on the structural aspects that play a role with respect to the regioselectivity of the interactions and the stability of the resulting adducts. Since already many excellent reviews have been published on the common reporters in sugar sensing systems [8,9], less attention will be paid to the reporter techniques. The general principles discussed will be applied to demonstrate that glucose and sialic acid are very promising targets for B-based sensors. These sugars are important markers for diabetes and cancer, respectively.

2. Acidity of boric and boronic acids

Boric acid and boronic acids are Lewis acids rather than Brønsted acids. The B-atom in these compounds is sp^2 hybridized and thus planar and trigonal. In aqueous solution, OH^- attacks this electron deficient B-atom converting it into its tetrahedral sp^3-hybridized form (see Fig. 1) [11,12]. The neutral $-B(OH)_2$ function is electron-withdrawing, whereas the anionic $-B(OH)_3^-$ is electron-donating. This difference in electronic properties has been exploited in many sensors.

The pK_a values of boric acid (**1**) and phenylboronic acid (**2**) are 9.24 and 8.70, respectively (25 °C, ionic strength 0.0) [13,14]. Obviously, the acidity of boronic acids depends on the charge density at the B-atom; electron-withdrawing groups increase the acidity, whereas electron-donating groups decrease it. This has been

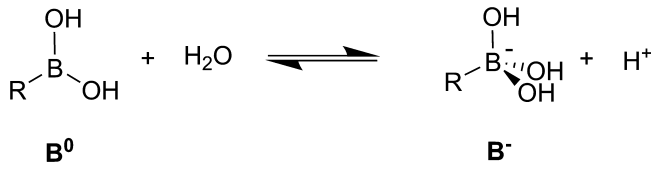

Fig. 1. The acid–base equilibrium of boric acid (R = OH) and boronic acids (R = alkyl or aryl).

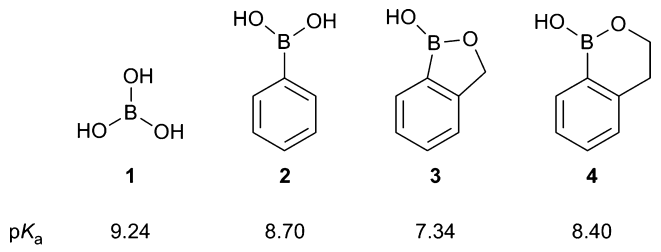

Fig. 2. Boric acid and some phenylboronic acids and their pK_a values in water at 25 °C.

corroborated by a plot of pK_as of 3- and 4-substituted phenylboronic acids versus the Hammet σ-values of the substituents, which is a straight line with a positive slope (ρ = 2.17) [15]. Phenylboronic acid endowed with a 2-hydroxymethyl function spontaneously closes to the corresponding benzoxaborole (**3**, see Fig. 2) under neutral and basic conditions [16,17]. In contrast to phenylboronic acid (**2**), this compound is water-soluble and has a considerably lower pK_a (7.34) than its parent **2** [18,19]. This can be explained by the relative large ring strain around the sp^2 B-atom of **3**, which is relieved largely upon conversion to the basic form having an sp^3 B-atom. In homolog, **4**, the difference in ring strain between the acid and conjugated base is considerably less as reflected in its pK_a, which is close to that of **2** [18]. The pK_a values of 3- or 4-substituted derivatives of compound **3** also obey the Hammett equation with a ρ-value (2.10) that is almost the same as that for derivatives of **2**.

Derivatives of the corresponding 2-aminomethyl phenylboronic acid behave differently; they often form a dative bond between the B and N atoms in crystal structures [20] and in aprotic solvents [21,22]. However in protic solvents such as water, an equilibrium of acyclic (**6**, **7**) and cyclic forms (**8**, **9**) as depicted in Fig. 3 occurs [14,21,22]. The extent of B—N bond formation and the strength of this bond depend on the nature of the substituents on the B and N atoms and on the pH. (Dialkylamino)arylboronic acids in protic solvents predominantly follow a pathway of solvent insertion

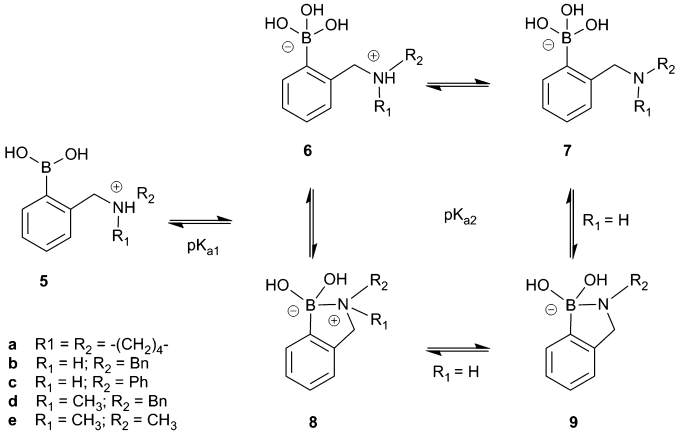

Fig. 3. Protonation equilibria of 2-aminomethyl substituted phenylboronic acids.