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3-Thienylboronic Acid as a Receptor for Diol-Containing Compounds: A Study by Isothermal Titration Calorimetry

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Abstract: The electrochemical activity of 3-thienylboronic acid and its feature to form polymer films makes it a perspective receptor material for sensor applications. The affinity properties of this compound were studied here by isothermal titration calorimetry. A number of different analytes were tested, and the highest binding enthalpy was observed for sorbitol and fructose. An increase of pH in the range of 5.5–10.6 results in the rise of the binding enthalpy with an increase of the binding constant to ~8400 L/mol for sorbitol or ~3400 L/mol for fructose. The dependence of the binding constant on pH has an inflection point at pH 7.6 with a slope that is a ten-fold binding constant per one pH unit. The binding properties of 3-thienylboronic acid were evaluated to be very close to that of the phenylboronic acid, but the electrochemical activity of 3-thienylboronic acid provides a possibility of external electrical control: dependence of the affinity of 3-thienylboronic acid on its redox state defined by the presence of ferro/ferricyanide in different ratios was demonstrated. The results show that 3-thienylboronic acid can be applied in smart chemical sensors with electrochemically controllable receptor affinity.

Keywords: chemical sensors; affinity; isothermal titration calorimetry; 3-thienylboronic acid; diol-containing compounds

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1. Introduction

Ligand-receptor interactions play a key role in many biological processes [1]. This principle was transferred from natural to artificial systems and led to the development of affinity sensors [2] which possess a selective receptor providing binding of specific molecules and a transducer reporting the amount of the bound analyte. The receptor can be of natural origin, like antibodies, defined sequences of nucleic acids or other biomolecules. But already at the beginning of establishing sensor science, the exploitation of artificial receptors for chemical sensors was also introduced. During the last few decades, organic chemists have synthesized a large number of various artificial receptors for chemical sensors possessing different affinity properties. In comparison with biomolecules, artificial receptors have such benefits as high chemical stability, high shelf-life, and low costs. Their production can be scaled up easily. The development of artificial receptors does not include immunization of animals; therefore, they can be principally developed for natural metabolites or highly toxic compounds.

The complex formation due to analyte binding to receptor molecules can be characterized quantitatively by a set of kinetic and thermodynamic parameters [3]. The quantitative data [4] allow one to select artificial receptors with predictable selectivity [5] and detection limit for a particular application. The development of new artificial receptors with high selectivity and required affinity is the top-priority objective in sensor science. Currently, it is performed also by combinatorial approaches [6] using quantitative affinity data as descriptors. A large number of artificial receptors suggested for various compounds include beta-cyclodextrins [7], crown ethers [8], calixarenes [9], spreader-bar stabilized monomolecular layers [10], molecularly imprinted polymers [11], and also boronic acids [12]. The

boronic acid functional group is one of the widely used artificial receptors for the analytes possessing 1,2 or 1,3-diol groups that are Lewis base-containing donors [13]. Boronic acid forms reversible covalent complexes with these moieties in aqueous systems thus leading to the interconversion of boronic acid into corresponding diol-boronate complexes. The interchange between boronic acid and diol moieties depends on the pH of the aqueous environment, pK_a values of boronic acid and analyte, and probably on other factors too [14–16].

The strong but reversible covalent interactions between boronic acid and nucleophile diol moiety make this functional group a well suitable for the development of artificial receptors for chemical sensing [17,18] for saccharides and other practically important molecules containing diols. Such sensors can be based on different transducers, for example: colorimetric [19], fluorescent [20], amperometric [21], potentiometric [22], impedimetric [23], and surface plasmon resonance [24]. The first fluorescent sensor for saccharides recognition by the direct linking binding site of boronic acid with anthracene as a fluorescent unit was reported in the work [25]. The binding with D-fructose at pH 7.4 led to a decrease in fluorescence intensity. Later the design parameters of fluorescent sensors were extended using diboronic acid receptors [26–28].

In most cases immobilization of receptors on a surface or their embedding into polymer backbones requires. This led to the high attention to polymerizable monomers possessing boronic acid moiety [29–31]. As reported in [32] co-polymerized with 3-aminophenylboronic acid polyaniline with near-infrared optical response can be used for the detection of different saccharides. The shift in adsorption spectra upon a binding was dependent on saccharide concentration. Sensors with potentiometric signal-transducing were proposed as an alternative for electrochemical sensors based on enzymes and the catalytic ability of the electrode surface [33] due to their technological imperfection. Potentiometric sensors also can be developed by including a boronic acid moiety into the polymer backbone [22,34,35]. Later this approach was upgraded using modified gold nanoparticles into a polymer basis as receptor units transducing a potentiometric signal [36].

The most common and well-studied monomer with integrated boronic acid moiety is phenylboronic acid (PBA). A functionalized derivative of phenylboronic acid is 3-aminophenylboronic acid. It can be considered as substituted aniline–one of the most significant monomers giving conducting polymers after polymerization. Namely, this monomer was used as the first one for the synthesis of polymers with a boronic acid moiety which was applied in photometric sensing of saccharides [32] and later for potentiometric sensing [22]. The common problem of this polymer is the pH sensitivity of its backbone [37]; in the case of analytical applications, it leads to pH interference and requires using of strong buffers. In [38] we have mentioned an unsuccessful attempt to develop a conductometric sensor based on such polymers: the pH interference was so high that it was impossible to get a reliable response to the saccharides.

Along with substituted aniline and some other boronic acid monomers, thiophene functionalized by the boronic acid group has recently attracted attention as a perspective synthetic receptor [23]. In contrast to aniline with integrated boronic acid moiety, a polymerization of thiophene molecules containing a boronic acid side group leads to a polymer that has no basic sites in its backbone. Therefore, one cannot expect any pH influence on its properties due to changes in the backbone protonation, e.g., the sensors based on such material are expected to have a much lower interference with pH changes in comparison with polyaniline backbone. This advantage makes thiophene with boronic acid moieties a promising chemosensitive material for recognizing diol-containing compounds. Recently, we have already reported the preparation of poly-3-thienylboronic acid by electrochemical polymerization of 3-thienylboronic acid (TBA) and discussed the optical, electrochromic, and chemosensitive properties of this new material [38].

In this work, we determine the binding properties of TBA. It has been done using isothermal titration calorimetry (ITC). ITC is a powerful technique allowing one to perform a comprehensive thermodynamic characterization of affinity properties [39,40]. Here we

used this approach to characterize the affinity of TBA toward diol-containing compounds and compared the obtained affinity values with PBA. Additionally, we have demonstrated a possibility for electrochemical control of TBA affinity.

2. Materials and Methods

ITC experiments were performed using an isothermal titration calorimeter Micro Cal PEAQ-ITC from Malvern Instruments. The system has the sample and reference cells made from Hastelloy™ alloy. All experiments were performed at 25 °C. Each experiment involved a series of 18 injections of 2 μL each after the first injection of 0.4 μL. The heat of a ligand dilution was measured in the absence of receptor molecules in separate experiments and subtracted. The resulting titration isotherm was fitted with analysis software of Micro Cal PEAQ-ITC system using the fitting model "One set of sites". Redox potentials were measured using Palm Sens Em Stat^3 potentiostat with the gold electrode as a working electrode and silver/silver chloride reference electrode with double salt bridges (Metrohm) filled with saturated potassium chloride.

D-(−) fructose was purchased from Merck other saccharides (D-(+) glucose, D-(+) galactose, D-sorbitol) as well as lactic acid, R-2-hydroxybutyric acid, polyethylene glycol with molar weight 1500 g/mol, PBA, TBA, potassium ferricyanide and potassium ferrocyanide were from Sigma-Aldrich. For buffer solutions were used potassium hydrogen phosphate, potassium dihydrogen phosphate from Chem Solute (Th. Geyer), sodium carbonate, sodium bicarbonate from Roth, and acetic acid from Sigma-Aldrich. The pH values of buffer solutions were adjusted using 1 M solutions of NaOH or HCl from Roth. Deionized water additionally purified by the system EGLA-classic was applied.

3. Results and Discussion

In analogy with the generally-accepted scheme for PBA [41], we can suggest similar reaction pathways for TBA (Figure 1). In an aqueous environment, boronic acid is hydrolyzed with the formation of anionic tetrahedral boronate (2) and releases a hydrogen ion. In the presence of diols, the boronate anion (2) is transformed into its corresponding cyclic boronate ester (3). A direct formation of the trigonal boronic ester (4) from neutral boronic acid (1) is also possible, but this reaction is three-four orders of magnitude slower than the way through anionic tetrahedral boronate (2) [12].

The ratio between the trigonal boronic acid (1) and tetrahedral boronate (2) at a specific pH is defined by the pK_a value of a boronic acid derivative and characterizes its Lewis acidity. The fact that mainly the tetrahedral boronate (2) reacts with diols points to pH influence on the affinity of boronic acid.

All investigated systems possessed a relatively low affinity (Ka < 10^4 L/mol). In contrast to the high affinity systems, which generate binding isotherms of sigmoidal shape, binding isotherms at low-affinity form flat titration curves, which lead to high uncertainties in the measurements of binding constants by using standard ITC analysis procedures. According to the analysis presented in [42], the concentrations of ligands during titration were increased, and the binding stoichiometry was postulated to be equal to 1.0 [43]. The excess of the titrant allowed us to achieve essential receptor saturation by the end of titrations and to extract the values of binding enthalpy and binding constants more exact.

An absence of literature data on the binding of TBA with diols and other potential ligands was the reason to test a number of various compounds: galactose, fructose, sorbitol, polyethylene glycol (PEG), 2-hydroxybutyric acid (HBA), and lactic acid. The integrated titration curves measured at neutral pH are shown in Figure 2. The highest values of the binding enthalpy were observed for sorbitol and fructose. For galactose, lactic acid, HBA, and PEG these values are very low. For the first three compounds also the "slope" of these curves is very low (Figure 2) thus indicating the low-affinity values of TBA to these compounds. A reliable ITC investigation of these interactions is hardly possible. A little more optimistic is the titration curve for polyethylene glycol: the observed saturation within the studied concentration range indicates the value of the binding constant which

may be comparable to that of sorbitol and fructose. However, because of the low value of the binding enthalpy, it was difficult to get credible quantitative values. The reason for so low binding enthalpy of PEG can be a complex behavior of entropy of this polymer during the binding process, such effects were discussed intensively in literature [44]. The binding process is governed by changes in Gibbs energy (ΔG) and entropy (ΔS), but the measurement value is binding enthalpy (ΔH), therefore ITC is not suitable for processes with low enthalpy. One can expect that the PEG–TBA interaction can be characterized quantitatively using other analytical techniques, but in the current work, we had to exclude this important and interesting analyte from a more detailed characterization.

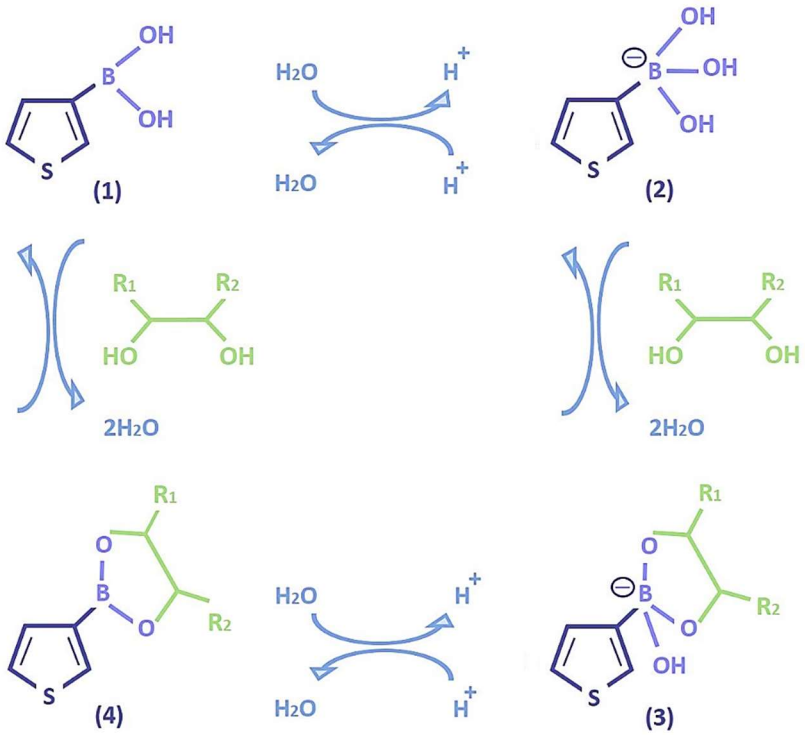

Figure 1. Equilibrium between 3-thienylboronic acid and its ester upon interaction with 1,2- or 1,3-diols in an aqueous solution. The scheme is based on the early suggested scheme for PBA [41].

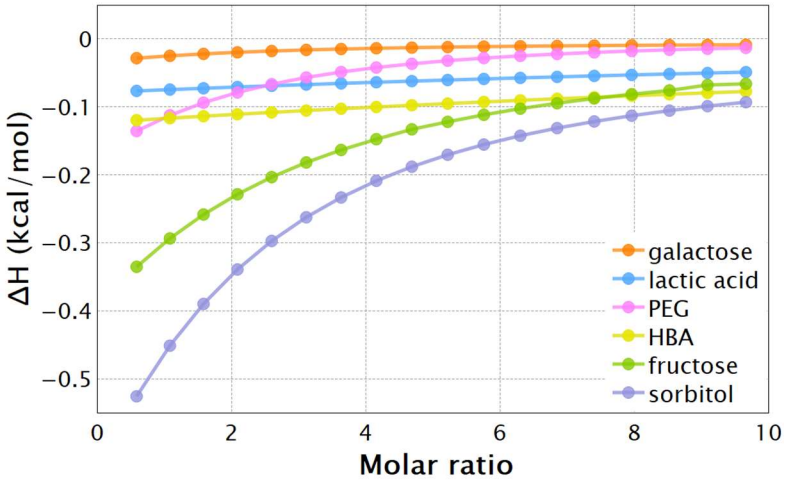

Figure 2. Normalized heat plot measured for binding of different compounds to TBA. Titration conditions: 300 µL of 0.5 mM TBA in the cell and 25 mM of the corresponding compound in the titration syringe, pH 7.4.

A detailed binding analysis was performed for sorbitol and fructose displaying the highest enthalpy effects. The main factor influencing the binding of analytes to boronic acid is pH, therefore the measurements were performed at pH values from 6.0 to 10.6. pH increase leads to the essential increase of the binding enthalpy (Figure 3). This effect becomes especially pronounced in the pH range 7.4–9.2 while a further pH increase has almost no influence.

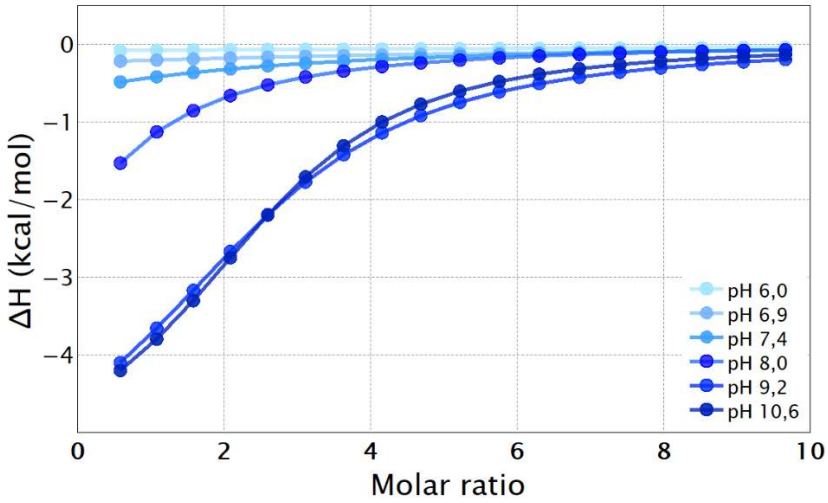

Figure 3. Normalized heat plots for sorbitol binding to TBA at different pH. Titration conditions: 300 μL of 0.5 mM TBA in the cell and 25 mM of sorbitol in the titration syringe.

The high values of binding enthalpy observed for sorbitol and fructose allowed us to perform a quantitative analysis of the affinity of TBA to these compounds. The results are presented in Figure 4 and Table 1. pH increase from 5.5 to 10.6 leads to an increase of the binding constant from ~15 L/mol to ~ 8400 L/mol or from ~50 L/mol to ~3400 L/mol for sorbitol and fructose respectively (Figure 4, Table 1). It corresponds to an increase in the absolute value of binding energy $-\Delta G$ from 3.73 kJ/mol to 21.29 kJ/mol for sorbitol or from 4.24 kJ/mol to 18.9 kJ/mol for fructose. The dependence of the binding constant on pH looks like a classical sigmoid titration curve (Figure 4). In the symmetry point at pH = 7.6, the slope of this curve is exactly 10 times the change in the binding constant per one pH unit. One can suggest that this point corresponds to the pK_a value of any reaction participant. To test, if this pH influence can be explained by the equilibrium between the forms (1) and (2), a pH titration of TBA with NaOH was performed. This has given the pK_a point of TBA~8.1. It is more alkalic value than that of the "appeared pK_a" obtained from the pH dependence of the binding constant (Figure 4). It may indicate an influence on the equilibrium between the forms (3) and (4). Such equilibria were discussed in detail in [45,46]. The fact that boronic acid esters are more acidic than boronic acid explains the observed discrepancy between the pK_a of TBA and pH dependence in Figure 4.

A detailed analysis of pH influence on the complexation of boronic acid with diols was performed in [47]. The authors suggested that the optimal pH for such interaction is in the middle between the pKa values of boronic acid and the corresponding analyte. The pKa values of sorbitol and fructose are 13.6 and 12.06 respectively [45,48]. This gives the optimal pH for sorbitol binding 10.9, and for fructose 10.1. This corresponds to our data (Figure 4) where a permanent increase of the sorbitol binding was observed till the highest measured pH value of 10.6 while the data for fructose demonstrate a saturation at this point.

The binding properties of TBA were compared with PBA which is the most investigated compound with boronic acid moiety (Table 1). The results demonstrate very close values of binding constants. The obtained values of binding constants were validated by "reversible titration" when TBA was in the titration syringe and fructose in the cell. At pH

8.0 the values of binding constants 818 ± 89 L/mol and 513 ± 5 L/mol for PBA and TBA correspondingly were obtained.

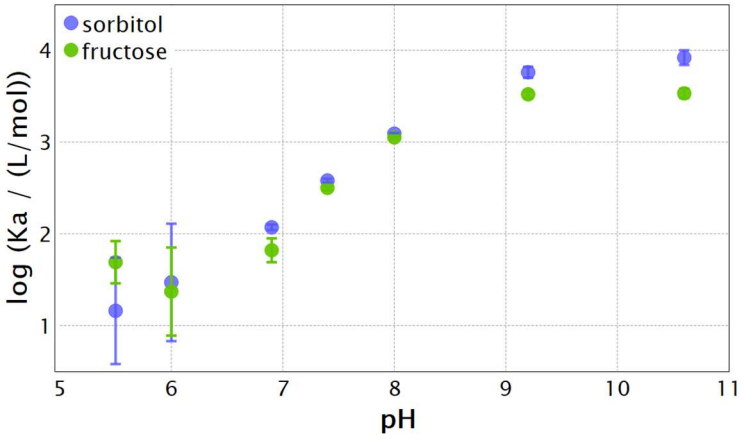

Figure 4. pH dependence of the binding constant of TBA to sorbitol and fructose. Titration conditions: 300 μL of 0.5 mM TBA in the cell and 25 mM of sorbitol in the titration syringe.

Table 1. Binding constants and binding energies for the interaction of fructose with TBA and PBA. Measurement conditions: 300 μL of 1 mM TBA or PBA in the cell, 30 mM of fructose in the titration syringe.

pH	PBA		TBA	
	***Ka* (L/mol)**	**−ΔG (kJ/mol)**	***Ka* (L/mol)**	**−ΔG (kJ/mol)**
7.4	209 ± 4	13.3 ± 0.42	212 ± 10	13.4 ± 0.13
8.0	522 ± 17	15.6 ± 0.08	533 ± 15	15.7 ± 0.08
9.2	3090 ± 222	20.0 ± 0.17	2700 ± 400	19.1 ± 0.84

The obtained values of the binding constant of PBA to fructose are very close to that reported in [47] by competitive fluorescence measurements using Alizarin Red S: 210 L/mol at pH 7.5 or 560 L/mol at pH 8.5. ITC measurements of 3-aminophenylboronic acid [37] give the values which are not dramatically different from that: 137 L/mol at pH 8.0 and 1330 L/mol at pH 9.0.

Very close values of binding constants of TBA and PBA (Table 1) demonstrate that substitution of the phenyl ring by the thiophene one does not influence the absolute value of the affinity of this receptor: the value of the ratio of binding constants of fructose to these compounds at pH 8.0 is 0.98 ± 0.04.

The main feature of TBA in comparison with other similar compounds is its electrochemical activity. Due to this activity, TBA can be electrochemically polymerized forming highly conducting polymer films [38]. It allows us to consider TBA as a promising material for applications in chemical sensors with electrically controlled affinity or in virtual sensor arrays with electrochemical switching of chemosensitive properties [49]. This analytical principle was realized earlier in electrochemical transistors based on polythiophene, polypyrrole, and polyaniline [49–52]. However, in that work, only an intrinsic chemosensitive activity of conducting polymers was exploited. The use of polymerized TBA for this purpose is the way to make such a novel analytical device based on conducting polymer possessing incorporated receptor groups. It was the reason to study the effect of the redox state on the affinity properties. The measurements were performed by ITC in the presence of $K_4Fe(CN)_6/K_3Fe(CN)_6$ at different concentrations and concentration ratios between 0.3 mM and 300 mM. The value of the redox potential of the media was measured in separate experiments with a gold electrode relative to Ag/AgCl electrode with a salt bridge. The results are shown in Figure 5. One can observe an increase in the absolute value of

the binding energy for potential change between 0.13 V and 0.23 V and a decrease of this value for further potential increase till ~0.4 V. The potential value 0.23 V corresponds to the maximal value of the binding constant. Unfortunately, the used method of potential variation did not allow us to study higher potential values at which the main electrochemical activity of this compound is observed [38]. The maximal change in the binding constant between TBA and sorbitol in the studied potential range was 2.75; for the earlier studied electrochemical transistor based on polyaniline and its interaction with trimethylamine this value was 2.47 at the much wider potential range [52].

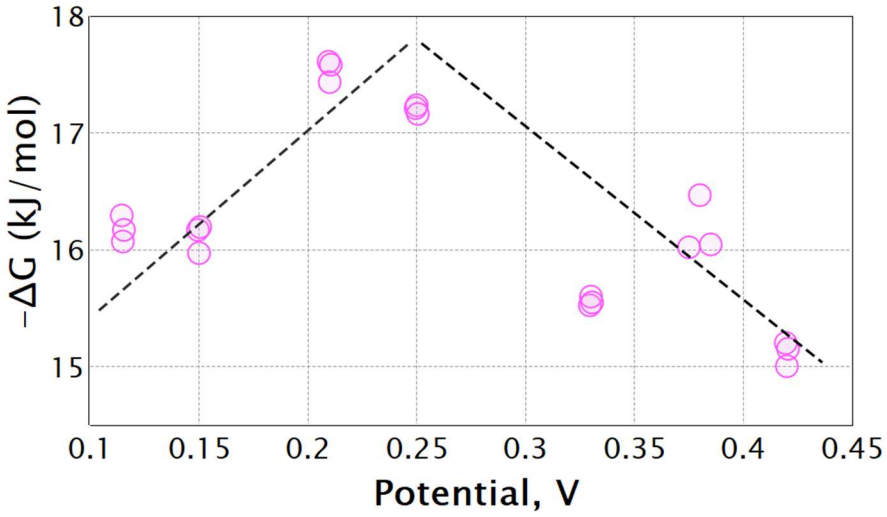

Figure 5. Influence of redox potential on the binding constant of TBA to sorbitol at pH 8.0. Titration conditions: 300 μL of 0.5 mM TBA and 0.3–300 mM of mixtures of $K_4[Fe(CN)_6]$ and $K_3[Fe(CN)_6]$ at various ratios; 25 mM of sorbitol in the titration syringe. The redox potential is indicated vs. Ag/AgCl(sat). The dash lines are drawn to indicate the trend of the data dependence.

4. Conclusions

We have described a new artificial receptor based on thiophene with an incorporated boronic acid moiety that provides its chemical sensitivity to diol-containing compounds. The material demonstrates a pronounced affinity toward some saccharides, for example, sorbitol and fructose. The maximal value of the binding constant is ~8000 M^{-1} for sorbitol at strongly alkalic pH. In relation to applications in chemical sensors it means that in combination with a transducer providing a signal/noise ratio of ~1000, one can achieve the limit of detection of ~1 μM. To important features of this material belong its electrochemical activity and the formation of conducting polymers. Analytical properties of chemical sensors based on this material in the polymeric form will be presented later (this work is in progress) while in the current manuscript we have performed an investigation of the affinity of this material in its monomeric form–TBA.

We have demonstrated that the affinity can be electrochemically controlled, therefore this material can be applied in chemical sensors with electrically switched affinity profiles, like electrochemical chemotransistors [49,50,52]. In this study, we modified redox conditions by introducing redox-active compounds. According to our knowledge, it is the first application of this approach in ITC. Such a combination of ITC with the control of electrochemical conditions of studied compounds can be useful in the investigation of each redox-active analyte or receptor molecules. In integrated electrochemical chemotransistors [53] the control of the redox state of chemosensitive material is performed by the application of electrical potential. To make ITC-measurements with electrochemical control more convenient and to provide a wider potential range, a development of ITC instruments with integrated redox- and reference electrodes is required; in many experiments the metallic cell wall of the device can operate as the redox electrode.

The affinity properties of TBA are very similar to that of other known materials which do not allow applications in chemical sensors with controllable affinity (for example, PBA), therefore even without using electrochemical control the application range of TBA is not smaller than that of PBA. One can expect that an exploiting of ideas that were applied successfully for other compounds with boronic acid moieties for TBA improvement is the way to further increase its binding constant and selectivity for desired analytes. For example, one can make a design and chemical synthesis of corresponding polymerizable dimers with a required position of boronic acids for effective analyte binding [54].

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Conflicts of Interest: The authors declare no conflict of interest.

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