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Poly(methyl vinyl ether-*alt*-maleic anhydride) Functionalized with 3-Aminophenylboronic Acid: A New Boronic Acid Polymer for Sensing Diols in Neutral Water

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ABSTRACT: Amidation of poly(methyl vinyl ether-*alt*-maleic anhydride) with 3-aminophenylboronic acid was used to prepare a new boronic acid polymer. The binding of catechol dye, Alizarin Red S to the polymer obtained resulted in getting a stable, colored sensor which was used to establish association constants with different diols in competitive assay. The binding of different diols was readily detected by color change and absorbance values measured at 450 nm were used to calculate the association constants. The polymer obtained formed high-affinity complexes with ribonucleosides, particularly cytidine and uridine. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40778.

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INTRODUCTION

Boronic acids are well known to form complexes with diol-containing compounds through reversible ester formation. The high-affinity interaction between these molecules has been extensively investigated by many researches[1–6] and resulted in application of boronic acids as sensors for saccharides,[7,8] carbohydrate transporters,[9,10] and for separation of carbohydrates and glycoproteins.[11,12] Nevertheless, to understand the properties and stability of boronate ester formed, a method is needed for measurements of association constants of complexes between diols and boronic acid. The easiest and most versatile method is to measure changes in fluorescence or absorption spectra during titration experiments. This method is however limited only to boronic acids that are fluorescent or possess a chromophoric group which is sensitive to binding process. Springsteen and Wang[1,13] have developed a method which allows determination of binding constants even if the boronic acid is not fluorescent or does not contain an appropriate chromophoric group. They have proposed a system consisting of a three-component competitive assay, containing boronic acid, diol compound and Alizarin Red S (ARS) which is anthraquinone dye changing color in response to formation of high-affinity complexes with boronic acids.

Boronic acid polymers have found many applications in medicine, particularly in drug delivery[14–19] and sensing of biologically relevant compounds.[20,21] The main benefits of boronic acid polymers are connected with their increased activity caused by multivalency and the possibility to control drug release by using targeted biodistribution.[22] Moreover, polymers due to their macromolecular structure have increased circulation time in body because their large size slows down the glomerular filtration.[23] In comparison to small molecules they are not as readily detected by mononuclear phagocyte system, which also increases their circulation time.[24] Boronic acid polymers have found application in detection of biologically relevant compounds such as dopamine,[25] glucose,[26–28] diols,[29] ATP,[30] or nucleotides.[31] They also appeared useful in carbohydrate and glycoconjugate purification and identification,[32] preparation of materials of high mechanical[33] and thermal[34–36] stability, synthesis of polyurethane foams[37] and field-flow fractionation/adhesion chromatography.[38]

Saccharide sensing using boronic acid polymers is based on changes in optical or conductivity properties taking place upon binding with a carbohydrate molecule. Optical changes resulting in color shift are especially relevant, because they offer immediate response without need to use any additional apparatus. These polymers are of much interest and numerous examples have been reported in recent studies. Films composed of copolymers of aniline and 3-aminophenylboronic acid have been reported to undergo hypsochromic shift of absorption maximum on addition of saccharides.[39] Translucent boronic acid-carrying nanolatexes with bonded ARS[40] and copolymers with boronic acid residues[41] have been used for selective visual detection of fructose. ARS have been coupled with thermoresponsive

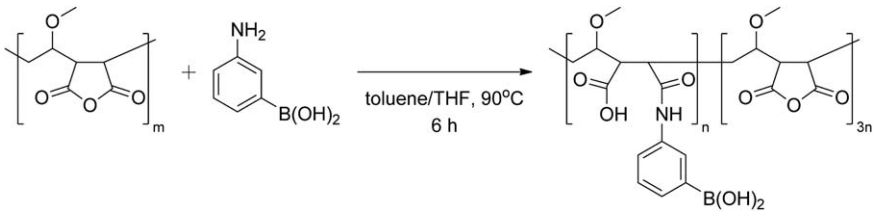

Figure 1. Synthesis of poly(MVE-*alt*-MA-BA).

copolymer[29] or boronic acid terminated polylactide[42] to obtains sensor for the recognition of hydroxyl-containing molecules. Boronic acid-appended azobenzene dye attached to poly(ethyleneimine) showed a significant change in the UV-Vis absorption spectra upon addition of glucose.[43] A porous hydrogel film incorporated with ARS have been used to monitor concentration of glucose in the range from 0.1 to 1 m*M*.[26]

In this article we report the synthesis of new boronic acid polymer and its application in sensing diols in water solutions. The polymer was synthesized by grafting 3-aminophenylboronic acid onto poly(methyl vinyl ether-*alt*-maleic anhydride) by partial amidolysis. The binding of ARS to the boronic acid groups in this polymer gave an optical sensor for diols. It was used to establish the association constants in a competitive assay between diols and the polymer obtained. The binding of diols was readily observed by a color change of the sensor.

EXPERIMENTAL

Materials

All reagents used are commercial products. Poly(methyl vinyl ether-*alt*-maleic anhydride) (poly(MVE-*alt*-MA); average $M_w = 216{,}000$, average $M_n = 80{,}000$), 3-aminophenylboronic acid monohydrate, all carbohydrates, nucleosides, and other diols were purchased from Sigma-Aldrich (St. Louis, MO). All the chemicals were of the analytical grade and used without further purification. Toluene, tetrahydrofuran (THF), diethyl ether and all other solvents were of purity grade p.a., were obtained from POCH (Gliwice, Poland) and were used without further purification.

Synthesis

To a stirred solution of poly(MVE-*alt*-MA) (0.5 g) in toluene (20 mL), 3-aminophenylboronic acid monohydrate (0.44 g, 3.21 mmol) in THF (10 mL) was slowly added. The mixture was refluxed at 90°C for 6 h. After cooling to room temperature, the final product was isolated by filtration, washed thoroughly with toluene, THF, diethyl ether, and dried in vacuo yielding poly(MVE-*alt*-MA-BA) as a white solid (0.59 g). The synthetic scheme is presented in Figure 1.

Apparatus

The FTIR spectra of polymers were recorded on a Bruker IFS 66s spectrometer (Billerica, MA) using KBr pellets (about 1.5 mg of sample in 200 mg of KBr). NMR spectra were recorded on an Agilent 800 MHz NMR spectrometer (Santa Clara, CA) in D_2O at 298 K using residual HDO signal as a reference. Elemental analyses were carried out by a Vario EL III Element Analyzer (Hanau, Germany). Thermal data were obtained by using a Setaram Setsys 1200 (Caluire, France). The thermal stability of polymers was investigated by thermogravimetric analysis and derivative scanning calorimetry in an air stream at a heating rate of 10°C min^{-1}. The pH measurements were performed using Elmetron CP-505 apparatus (Zabrze, Poland) equipped with a combined pH electrode. UV–Vis measurements were made on an Agilent 8453 (Santa Clara, CA) spectrophotometer using 1 cm plastic cuvettes. UV–Vis absorbance spectra were measured at room temperature within 190–1100 nm.

Determination of the Association Constant of ARS with Poly(MVE-*alt*-MA-BA)

A 0.15 m*M* solution of ARS was prepared in 150 m*M* phosphate buffer of pH 6.9 (Solution A). The poly(MVE-*alt*-MA-BA) solution with a concentration of 5.43 mg mL^{-1} (Solution B) was prepared using Solution A as a solvent to avoid dilution of ARS during titration. Because of a long solubility time of poly(MVE-*alt*-MA-BA), determined by partial hydrolysis of anhydride groups, all poly(MVE-*alt*-MA-BA) solutions were prepared 24 h before measurements, in order to obtain clear solutions. 1 mL of ARS solution (Solution A) was placed in a cuvette and treated stepwise with 0–16.29 mg of poly(MVE-*alt*-MA-BA) (0–3.0 mL of solution B). After every addition of the latter solution, the mixture was equilibrated for 3 min and then the spectrum was measured. The UV-Vis curves from the titration of ARS with poly(MVE-*alt*-MA-BA) solution are presented in Figure 2. The association constant was determined using the Benesi-Hildebrand method. For all calculations the absorbance at 450 nm was used, because the changes in absorbance at this wavelength were the highest.

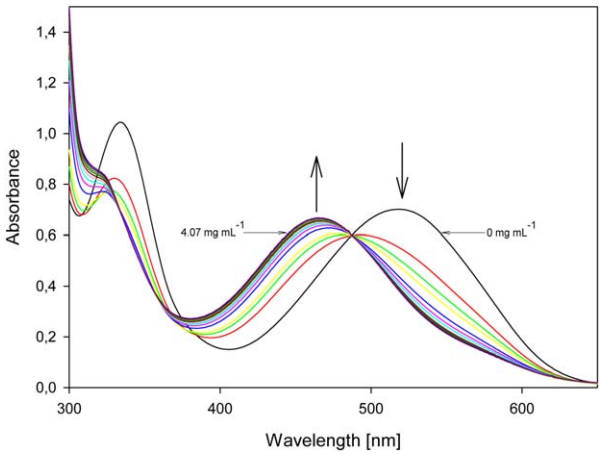

Figure 2. Absorption spectra changes of ARS (0.15 m*M*) with increasing concentration of poly(MVE-*alt*-MA-BA) in phosphate buffer (150 m*M*, pH = 6.9). Concentration of poly(MVE-*alt*-MA-BA) from 0 to 4.07 mg mL^{-1} (indicated in the figure). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

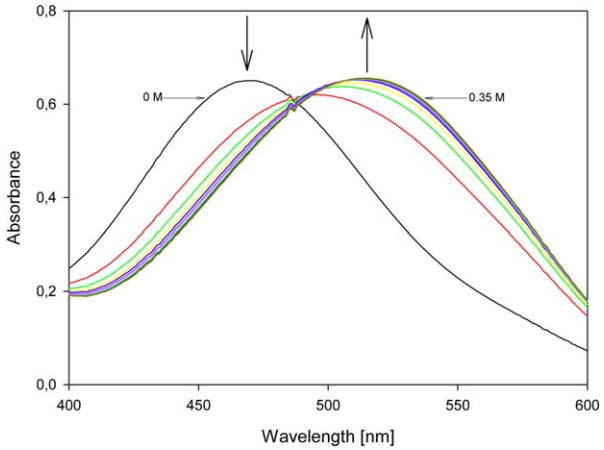

Figure 3. Absorption spectra changes of ARS (0.15 m*M*) and poly(MVE-*alt*-MA-BA) mixture (1.17 mg mL^{-1}) with increasing concentration of fructose in phosphate buffer (150 m*M*, pH = 6.9). Concentration of fructose from 0 to 0.35*M* (indicated in the figure). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Determination of the Association Constants of Diols with Poly(MVE-*alt*-MA-BA)

In the ARS solution (0.15 m*M* in 150 m*M* phosphate buffer of pH 6.9 – Solution A), poly(MVE-*alt*-MA-BA) was dissolved, to the concentration of 1.17 mg mL^{-1} (Solution C). To acquire clear solution, this mixture was prepared 24 h before any measurements. The solutions of diols were prepared using Solution C to avoid dilution during titration. A portion of 1 mL of Solution C was placed in a cuvette and treated stepwise with the diol solution. Arabinose, dopamine hydrochloride, fructose, galactose, glucose, lactose, maltose, mannitol, mannose, ribose, sorbitol, sorbose, sucrose, tagatose, and xylose were used in concentrations from the 0 to 0.35 *M* range. Because of their low solubilities, the concentration ranges of the following compounds are specified after their names: adenosine 0–0.019, catechol 0–0.037, cytidine 0–0.125, galactitol 0–0.121, guanosine 0–0.002, *myo*-inositol 0–0.038, lyxose 0–0.214, and uridine 0–0.131 *M*. After each addition, the mixture was equilibrated for 3 min before the spectrum was measured. For all calculations the absorbance at 450 nm was used. Figure 3 shows an exemplary result of competitive titration of a mixture of poly(MVE-*alt*-MA-BA) and ARS with fructose.

RESULTS AND DISCUSSION

Synthesis and Characterization of Poly(MVE-*alt*-MA-BA)

The new boronic acid polymer was synthesized by partial amidolysis of maleic anhydride groups of poly(methyl vinyl ether-*alt*-maleic anhydride) in the reaction with 3-aminophenylboronic acid. Poly(MVE-*alt*-MA) is known to react with amines or alcohols to produce polymers with functional side chains. Nevertheless, not all anhydride groups undergo amidation or alcoholysis and even under excess of amine or alcohol some of them remain unreacted.[44,45] To assess how many functional groups were introduced into polymer structure it is necessary to use additional experimental techniques.

The ^{1}H-NMR poly(MVE-*alt*-MA-BA) spectrum (Figure 4), the polymer was allowed dissolve in D_2O for 24 h and the water signals were suppressed with selective presaturation. The signals at 1.1–1.3 ppm come from residual -C**H**$_3$ and -C**H**$_2$- protons, those at 1.4–2.3 ppm come from the main chain -C**H**$_2$- protons, those at 2.3–3.8 ppm come from -O-C**H**, -C**H**(COOH)- and -C**H**(CONHR)- protons. In the aromatic part of the spectra, the signals at 6.9–7.8 ppm can be attributed to Ph-**H** protons of phenylboronic acid moiety. The ratio of intensities of the NMR signals assigned to aromatic protons (introduced into polymer in the reaction with 3-aminophenylboronic acid) to those assigned to alkyl protons, whose amount has not changed during functionalization process, is 11 : 88. This clearly indicates

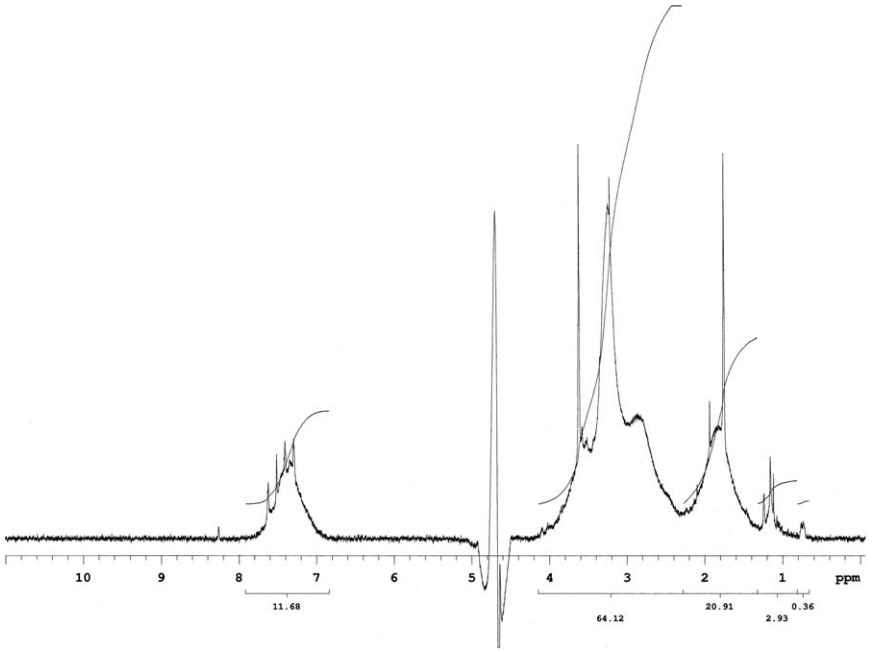

Figure 4. ^{1}H-NMR spectrum of poly(MVE-*alt*-MA-BA).

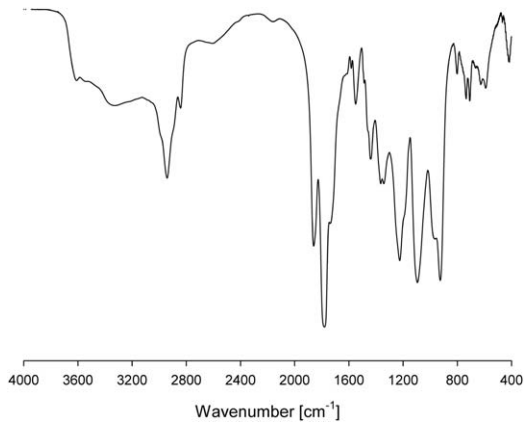

Figure 5. FTIR spectrum of poly(MVE-*alt*-MA-BA).

that statistically there is one anhydride group that has undergone amidation reaction per three unreacted anhydride groups. This information allowed the calculation of molar concentration of boronic acid moieties ([P] parameter) in poly(MVE-*alt*-MA-BA) solution, that were further used to calculate K_{ars} and K_a values. For 5.43 mg mL^{-1} solution of poly(MVE-*alt*-MA-BA), the concentration of boronic acid moieties was 7.13 m*M*, whereas for 1.17 mg mL^{-1} solution of poly(MVE-*alt*-MA-BA) it was 1.54 m*M*.

Elemental analysis of poly(MVE-*alt*-MA-BA) gave the following results (%): C, 53.48; H, 5.21; N, 1.67. To calculate theoretical amounts of each element, the model structure proposed by ^{1}H-NMR spectroscopy was used. Calculated elemental analysis gave the result (%): C, 53.63; H, 5.30; N, 1.84 which was in good agreement with experimental result. This confirms that during functionalization with 3-aminophenylboronic acid, one per four anhydride groups has undergone amidation reaction.

The FTIR spectrum of poly(MVE-*alt*-MA-BA) is presented in Figure 5. The structure of poly(MVE-*alt*-MA-BA) is confirmed by the appearance of the following characteristic absorption bands (cm^{-1}): at 3340 (medium broad peak for ν BO—H overlapped with carboxylic ν O—H and amide ν N—H), 2945 (ν C—H in CH_2 and CH_3), 2842 (ν C—H in CH_2 chain backbone of MVE unit), 1863 (ν C=O in anhydride groups), 1781 (ν C=O in anhydride groups), 1738 (ν C=O in carboxyl groups), 1630 (ν NH—C=O partially overlapped with ν C=O), 1550 (ν C=C), 1440 (δ CH_3, CH_2), 1366 and 1343 (δ CH_3 in CH_3—O), 1226 (ν C—O), 1095 (ν C—B overlapped with ν C—O—C), 923 (γ C—O), 735 and 710 (γ CH_2).[46]

The thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) results for poly(MVE-*alt*-MA-BA) are presented in Figure 6. In the temperature range 40–245°C, only a small loss of mass is observed. It can be attributed to the physisorbed residual water or solvent molecules as well as evaporation of volatile organic components. The polymer undergoes a three step decomposition process. The first step starts at 245°C and ends at 280°C and is probably related to decomposition and oxidation of the most reactive part of the polymer. The total mass loss at this step is 24.5%. The second step starts at 280°C and ends at 500°C. In this relatively long step, the polymer is slowly decomposed and oxidized with the total mass loss of 29.7%. The last step start at 500°C, ends at 620°C and is related to complete oxidation of all organic material. The residual mass is ~1.4%. The DSC curve presents two exothermic effects, both corresponding to the first and third decomposition steps. The second decomposition step is very slow therefore it is not represented by any peaks in the DSC curve.

Binding of ARS to Poly(MVE-*alt*-MA-BA)

Alizarin Red S displays a significant change in color in response to complex formation with boronic acid. This property was used for determination of association constants in competitive assays, between boronic acids and other diol-containing compounds.[1] The ARS binding to poly(MVE-*alt*-MA-BA) permitted a construction of an optical sensor of diols employing the reversible boronate ester formation.

The equilibrium in the solution of boronic acid polymer (P) and ARS dye (A) can be described as:

$$P + A \overset{K_{ars}}{\longleftrightarrow} PA$$

where K_{ars} $[M^{-1}]$ is the association constant of PA complex formation and P symbolizes one boronic acid residue of the polymer chain. The Benesi-Hildebrand[47] analysis of K_{ars} involves the measurements of absorbance as a function of $[P]$ when $[P] >> [A]$. Using the Benesi-Hildebrand equation:

$$\frac{[A]_0}{Abs} = \left(\frac{1}{[P]}\right)\left(\frac{1}{\varepsilon K_{ars}}\right) + \frac{1}{\varepsilon} \quad (1)$$

one can plot $x = 1/[P]$ vs. $y = [A]_0/Abs$ to receive the y-intercept $= 1/\varepsilon$ and slope $= (1/K_{ars}\varepsilon)$. The parameters of the equations are the following: $[A]_0$ (mol L^{-1}) is the total concentration of ARS dye, [P] (mol L^{-1}) is the total concentration of boronic groups from poly(MVE-*alt*-MA-BA) (varied), *Abs* is the absorbance measured at 450 nm, and ε is the molar absorptivity.

After addition of poly(MVE-*alt*-MA-BA) the color of a buffered solution of ARS changed from burgundy to orange indicating formation of boronate ester. The maximum amount of ARS that poly(MVE-*alt*-MA-BA) is capable to bond was established to be 1.31 m*M* per gram of polymer. By using titration monitored by UV-Vis spectroscopy at 450 nm it was possible to

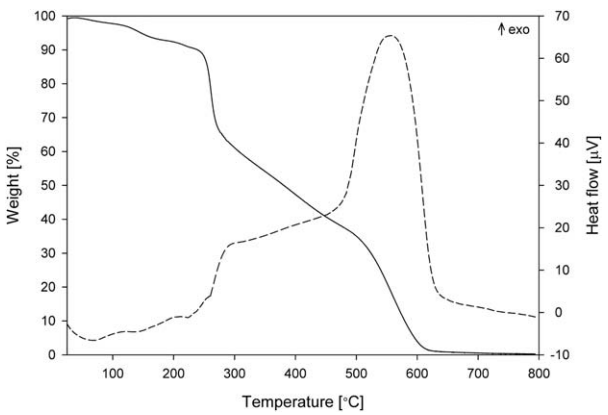

Figure 6. TGA (solid line) and DSC (dashed line) results for poly(MVE-*alt*-MA-BA).

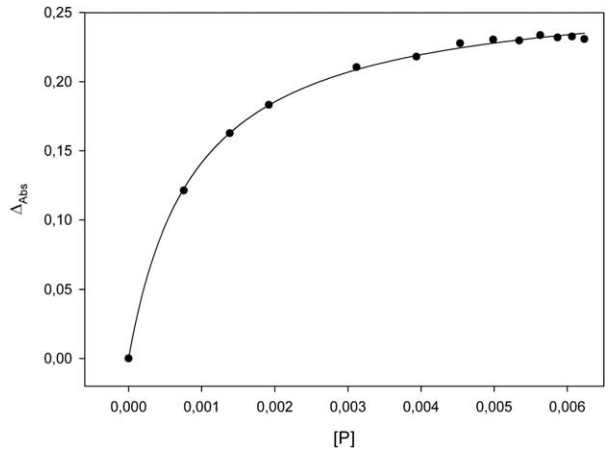

Figure 7. Plot of Δ_{Abs} (at 450 nm) versus $[P]$ for ARS (0.15 m*M*) upon titration with poly(MVE-*alt*-MA-BA) (concentrations from 0 to 4.07 mg mL^{-1}) in phosphate buffer (150 m*M*, pH = 6.9) where $[P]$ is the total concentration of boronic groups from poly(MVE-*alt*-MA-BA).

establish K_{ars} value of 1080 M^{-1}. The titration curve obtained by plotting Δ_{Abs} vs. $[P]$ is presented in Figure 7. Although the color change was almost immediate, after every titration step the mixture was stirred for 3 min to equilibrate all boronic acid moieties that were built-in into the polymer structure. The measured K_{ars} value was smaller than for phenylboronic acid itself (1500 M^{-1} at pH 7.0)[1] which can be attributed to substitution of phenylboronic ring by amide group and to additional steric effects that have occurred in the polymer structure.

Binding of Diols to Poly(MVE-*alt*-MA-BA)

The solution of poly(MVE-*alt*-MA-BA) was used to bind and measure association constants with various diols in competitive assays. In competitive assay the reporter (ARS) and the receptor (boronic acid polymer) associate under the measurement conditions. The complex of the receptor and the reporter dissociates in the presence of a guest (diol).

The two equilibriums in the complex solution during titration of boronic acid polymer (P) and ARS dye (A) with a diol substrate (D) are:

$$\mathrm{P+A} \overset{K_{ars}}{\longleftrightarrow} \mathrm{PA}$$

$$\mathrm{P+D} \overset{K_a}{\longleftrightarrow} \mathrm{PD}$$

where K_a $[M^{-1}]$ is the association constant for PD complex formation. The association constant K_a can be calculated from the following eqs. (2–4):

$$Q = \frac{[A]}{[PA]} = \frac{Abs_{PA} - Abs}{Abs - Abs_A} \tag{2}$$

where Abs is absorbance measured, Abs_{PA} is the initial absorbance of ARS – poly(MVE-*alt*-MA-BA) solution and Abs_A is the absorbance of ARS;

$$L = [p]_0 - \frac{1}{QK_{Ars}} - \frac{[A]_0}{Q+1} \tag{3}$$

where $[A]_0$ (mol L^{-1}) is the total concentration of ARS and $[P]_0$ (mol L^{-1}) is the total concentration of boronic groups from poly(MVE-alt-MA-BA);

$$\frac{[D]}{L} = \frac{K_{ars}}{K_a} Q + 1 \tag{4}$$

where $[D]$ (mol/L) is the diol concentration (varied). To obtain K_a value one must plot $x = Q$ vs. $y = [D]/[L]$ to receive a slope = K_{ars}/K_a. The y-intercept should be 1, but we obtained its different values. This is however in accordance with the results of other groups also reporting to have obtained different values of the y-intercept.[1,2] The values of the association constants measured are presented in Table I.

The binding of diols to poly(MVE-*alt*-MA-BA) results in release of free ARS which is connected with color change of the solution from orange to burgundy. Titration with increasing concentration of appropriate diol allows measurements of the association constants by monitoring the decrease in absorption at 450 nm by UV-Vis spectroscopy. The measured association constants are generally in good agreement with the values reported by Springsteen and Wang.[1] For all compounds they are lower than those measured for phenylboronic acid, which can be explained by the same factors that are responsible for the low binding constant with ARS: additional substitution of phenylboronic ring and steric effects that are present in polymer structure. Springsteen and Wang have shown that the values of association constants continue to decrease in the following order: ARS > sorbitol > fructose > tagatose > mannitol = sorbose. In our studies this order of decrease in K_a values is similar: ARS > sorbitol > fructose > mannitol > tagatose > sorbose. The difference in K_a value between mannitol and tagatose is very small (9 in our studies, 10 reported by Springsteen, and Wang) therefore, the change in the above presented order is acceptable and is probably related to small changes in binding properties of boronic residues in polymer structure. More surprising is the relatively big difference in K_a values between tagatose and sorbose (according to Springsteen and Wang the K_a value for these

Table I. Association Constants (K_a) with Poly(MVE-*alt*-MA-BA) at pH 6.9, 150 m*M* Phosphate Buffer

Diol	K_a $[M^{-1}]$	Diol	K_a $[M^{-1}]$
ARS	1080	maltose	0[a]
cytidine	130	mannose	0[a]
uridine	81	sucrose	0[a]
sorbitol	46	adenosine	–[b]
fructose	40	guanosine	–[b]
mannitol	34	arabinose	–[c]
tagatose	25	catechol	–[c]
sorbose	9	dopamine	–[c]
galactitol	0[a]	galactose	–[c]
glucose	0[a]	lyxose	–[c]
myo-inositol	0[a]	ribose	–[c]
lactose	0[a]	xylose	–[c]

[a] The values were too low to be accurately measured with this method.
[b] The solubility of those compounds was too low to allow measurement of association constant.
[c] The compounds reacted with ARS which was indicated by a change in solution color to reddish brown.

compounds was identical) but the reason for this effect has not been established yet. Unfortunately, we were unable to measure accurately K_a values for glucose, lactose, maltose, mannose, and sucrose because there were no significant differences in their absorption spectra during titration, therefore the K_a value was established as 0 for these compounds. According to Springsteen and Wang, the K_a values for these carbohydrates are in the range 13–0.67. We observed K_a values generally lower than those measured by Springsteen and Wang, therefore K_a value of 0 is consistent with our expectations.

Measurements of K_a for all aldopentoses (arabinose, lyxose, ribose, and xylose), galactose, catechol, and dopamine (which is a catecholamine) has not given any satisfactory results. The color of solution instead of changing into burgundy (the color of free ARS) changed into reddish brown. The assumption that this change in color is connected with reaction of ARS with examined diol molecules was confirmed by mixing buffered ARS solution (without poly(MVE-*alt*-MA-BA)) with these diols. The new absorption band that is produced interferes with the band at 450 nm which is used to calculate K_a values, so it was impossible to obtain accurate K_a values. The fact that aldopentoses as well as catechol and its derivative react with ARS is not surprising. All these compounds possess reactive groups that can undergo reduction–oxidation reactions leading to products with different absorption properties. Unfortunately, we were unable to explain why from among all aldohexoses studied only galactose underwent a reaction that led to unusual change in color. It is worth noting that this reaction is not instant at low concentrations, used in fluorescence measurements, it can take more time than needed to accomplish titration procedure. This is probably the reason why Springsteen and Wang and other researchers that used ARS method to establish association constants have not reported this unusual change in color.

Measurements of K_a for ribonucleosides (adenosine, cytidine, guanosine, uridine) indicated that cytidine and uridine produce high-affinity complexes with boronic acid moieties. The measured K_a values were 130 and 81 M^{-1} respectively, so much higher than for any other carbohydrates. Unfortunately we were unable to measure K_a values for adenosine and guanosine, because of their too low solubility that made them inapplicable for this method. Investigation of boron with nucleosides and nucleic acid has recently been a subject of profound interest because of a wide range of their potential medicinal, biotechnological or analytical applications.[48] In view of the above, the synthesis of boronic acid polymer that can form high-affinity complexes with nucleosides is a substantial achievement.

CONCLUSIONS

A new boronic acid polymer was prepared by amidation of anhydride groups of poly(MVE-*alt*-MA) with 3-aminophenylboronic acid. The resulting polymer was characterized by chemical and spectroscopic methods. It was established that 25% of anhydride groups underwent amidation reaction. After solubilization in phosphate buffered solution this polymer was associated with ARS to produce colored optical sensor that was further used to measure the association constants with different diols in competitive assays. Generally, all K_a values were lower than those measured for phenylboronic acid. The poly(MVE-*alt*-MA) polymer showed higher affinity to ribonucleosides, particularly cytidine and uridine, than to any carbohydrate examined.

With different amines or alcohols the presented procedure can be used to prepare a variety of boron-containing diol-responsive polymers. The ARS method allows easy measurements of association constant between boronic acid residue of the polymer chain and a particular diol. Owing to the reversible binding properties and high water solubility, boronic acid polymers of this type can find applications in biology or medicine for example for carbohydrate detection, drug delivery or isolation of nucleosides.

ACKNOWLEDGMENTS

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