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Facile Phenylboronate Modification of Silica by a Silaneboronate

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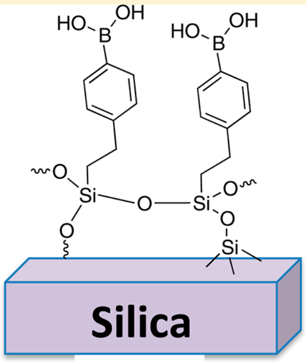
S Supporting Information

ABSTRACT: Macroscopic and colloidal silica surfaces were readily modified with alkoxysilaneboronate, **IV**, yielding silica surfaces with covalently bonded phenylboronic acid groups. XPS and neutron activation confirmed the presence of boron. The ability of these surfaces to specifically interact with polyols was demonstrated with polyol-coated latex and ARS, a dye that specifically couples to boronic acid groups immobilized on colloidal or macroscopic silica. This is a new, direct approach for introduction of phenylboronic acid groups onto silica surfaces.



INTRODUCTION

Polymer- and surface-immobilized phenylboronic acid and related boronates have been extensively reported in the scientific and patent literature, describing a wide range of phenomena and applications, including sensing,[1−4] chromatographic separation,[5,6] pH-dependent gelation,[7] pH-dependent flocculation,[8] and lectin biomimetics.[9] All applications are based upon the ability of organoboronates to condense with diols and polyols.[10,11] The boronate condensation reaction is spontaneous in water under ambient conditions; however, the complexes are weak, pH dependent, and sensitive to the diol/polyol stereochemistry. Indeed, it is the labile, environmentally sensitive nature of these diol−boronate complexes that makes them interesting and useful. Herein, we describe a new, one-step approach to grafting phenylboronic acid groups onto silica

Boronic acid groups immobilized on divinylbenzene beads or silica particles are commercially available.[6] In addition, boronate vinyl monomers for copolymerization[12] and bifunctional organo boronates suitable for bioconjugation are also available. In spite of this wide range of commercial boron-containing reagents, we believe there is no convenient, one-step preparation of boronate-modified silica. In particular, we are interested in modification of small, fragile constructs, such as quartz crystal microbalance sensor surfaces, surface plasmon sensor surfaces and specific locations in microfluidic devices. In addition, we are interested in boronate derivatization of colloidal silica by processes that do not induce colloidal aggregation.

Published approaches to silica−boronate preparation include adsorption of a organoboronate polymer[13,14] or hydrosilylation of a vinyl boronate to silica.[15] One of the easiest and most widely applied approaches to silica surface modification is the reaction with silanes.[16] However, we found only two references to preparation of silanes bearing boronic acid groups. Glad and co-workers prepared *N*-(2-hydroxy-3-[3-(tripropoxysilyl)propoxylpropyl))3-aminobenzene boronic acid propyl ester.[17,18] They described the use of this silane in the preparation of molecularly imprinted materials. More recently, Xu et al. described the use of essentially the same silane for preparing silica monoliths bearing boronic acid groups.[19]

Herein, we describe a one-step procedure for phenylboronate derivatization of silica surfaces with a new silaneboronate (see **IV** in Scheme 1). We demonstrate the approach by modification of quartz crystal microbalance silica sensors and colloidal silica. The resulting surfaces were smooth, uniform, and rich in immobilized phenylboronic acid groups capable of specific interactions with polyols and carbohydrates.

EXPERIMENTAL SECTION

Materials. Triethoxysilane, (+)-dimethyl L-tartrate, 4-vinyl phenylboronic acid, platinum(0)−1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Karstedt's catalyst, $Pt_2[(CH_2{=}CHMe_2Si)_2O]_3$), tetraethyl orthosilicate (TEOS), ammonium hydroxide (28−30%), and alizarin red S (ARS) were all purchased from Sigma-Aldrich. Toluene, dichloromethane, hydrogen peroxide (30%), and molecular sieves type 4A were purchased from Caledon Laboratories Inc. Methylene chloride-d_2 was purchased from Cambridge Isotope Laboratories Inc. Tris(hydroxymethyl)-aminomethane and sodium chloride were purchased from Bioshop Canada Inc. Sodium hydroxide (0.1 N) and hydrochloric acid (0.1 N) were purchased from Labchem Inc.

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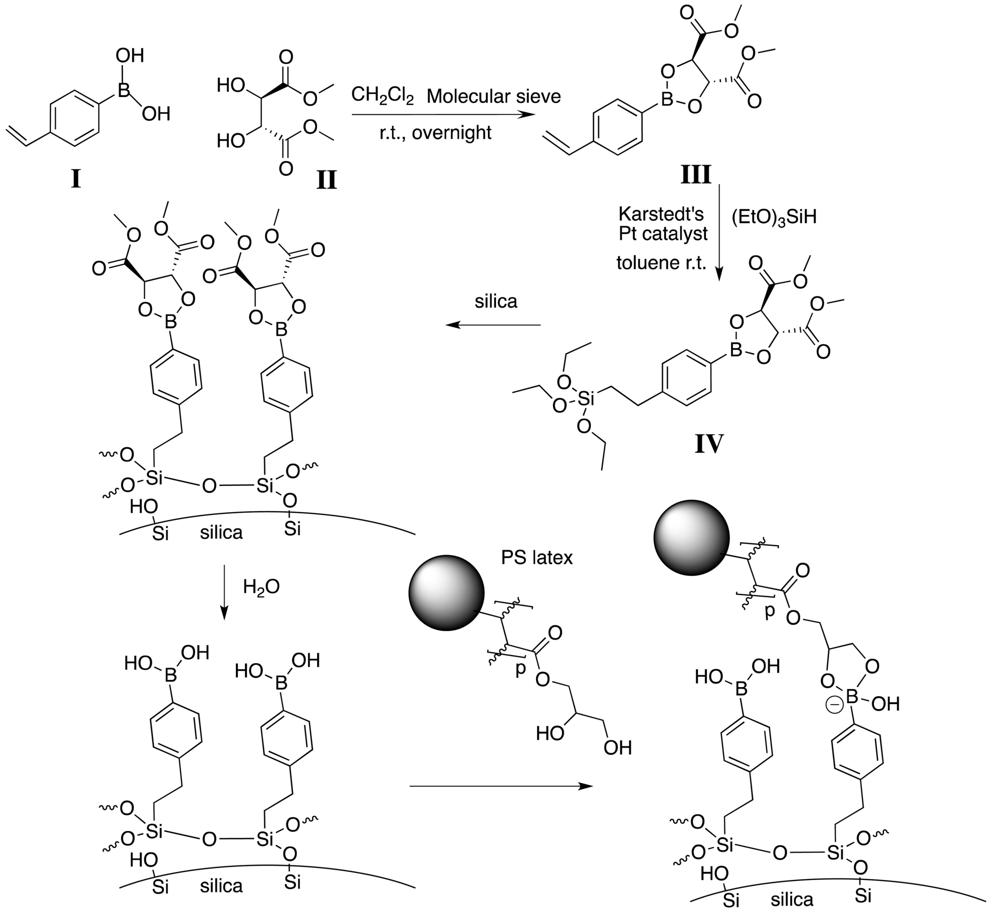
Scheme 1. Synthesis of Dimethyl Tartrate Protected Phenylboronate Silane, Subsequent Reaction with Silica, and Complexation with Polyol-Coated Latex



Poly(glycerol monomethacrylate)-stabilized polystyrene latex (PGMA-PS) was supplied by S. Armes (their designation KLT 156). Latex preparation and characterization was described previously.[20] The hydrodynamic diameter of the particle was of 177 nm, and the electrophoretic mobility was close to zero. The poly(glycerol monomethacrylate) stabilizer chains had a degree of polymerization of 50, and the stabilizer coverage was 3.2 mg m^{-2}.

Preparation of Dimethyl Tartrate-Protected Phenylboronate Silane, IV. Our approach was to use hydrosilylation to couple dimethyl tartrate-protected *p*-vinylphenyl boronic acid to triethoxysilane – see Scheme 1. Specifically, a mixture of 4-vinyl phenylboronic acid (**I**) (0.5 g) and (+)-dimethyl L-tartrate (**II**) (0.6019 g) in 100 mL of dichloromethane in the presence of 20 g of 4A molecular sieves was stirred at room temperature overnight to give near quantitative yield of **III**.

To a mixture of **III** and 0.6549 mL of triethoxysilane (1.05 equiv) in 100 mL of toluene was added 2 drops of Karstedt's catalyst. The reaction mixture was heated for 2 h at 50 °C. Finally, the toluene and excess triethoxysilane were removed under vacuum, giving **IV** as a colorless oil; ^{1}H NMR of the product is shown in Figure 1. Analytical data for the new compounds are given below.

Compound III. ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 6H), 5.11 (s, 2H), 5.34 (d, 1H, J = 11.0 Hz), 5.85 (d, 1H, J = 17.6 Hz), 6.75 (dd, 1H, J = 11 and 17.6 Hz), 7.45 (d, 2H, J = 8 Hz), 7.86 (d, 2H, J = 8 Hz). ^{13}C NMR ($CDCl_3$) δ 53.1, 77.9, 115.6, 125.8, 135.5 (very weak), 135.6, 136.7, 141.2, 169.9. ESI-MS (high resolution): 291.1023. Calcd mass: 291.1040.

Compound IV. ^{1}H NMR ($CDCl_3$) δ: 1.13 (m, 2H), 1.24 (t, 9H, J = 7 Hz), 2.72 (m, 2H), 3.81 (m, 12H), 5.09 (s, 2H), 7.23−7.87 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 15.4, 18.2, 29.2, 53.1, 58.9, 77.9, 127.6, 135.5, 149.4, 170.0. ESI-MS: 472.4 (75%, M + NH_4^+), 455.4 (20%, M + 1).

Preparation of Stöber Silica.[21] TEOS (2.4 mL) was added via a syringe into a mixture of 80 mL of ammonia (28%) and 56 mL of methanol under sonication using a Branson 3510R-DTH sonicator (Branson Ultrasonics Corp.). After 30 min, the system was left for 5 h under a nitrogen atmosphere at 30 °C. The resulting particles were first washed with methanol three times and then washed once with acetone. Each washing cycle included dispersing the particles in solvents under sonication and centrifuging at 10 000 rpm using an Allegra 25R centrifuge (Beckman Coulter) to separate the particles from solvents. Particles were dried at 80 °C.

QCM-D Silica Sensor Silane Treatment. A 2.5% (w/v) silane **IV** solution in dry toluene was used to prepare the phenylboronate silane-coated silicone dioxide (SiO_2) sensors. SiO_2 sensors were put in a Spin150-v3 spin coater, and 15 drops of **IV** were placed on top of the sensors. The spin coater was spun at 2000 rpm and then placed in an oven, allowing reaction for 2 h at 50 °C. Sensors were rinsed with dry toluene once and then three times with dichloromethane . Finally, the sensors were dried in an oven at 80 °C.

Stöber Silica Silane Treatment. A 0.05 g amount of Stöber silica (1% w/v) was dispersed (30 min sonication) in toluene to which was added 0.25 g of **IV** (5% w/v) in toluene in a 25 mL one-neck flask. The mixture was heated to 50 °C for 2 h with magnetic stirring. The product was washed once with toluene followed by 3 washers with dichloromethane. Each washing cycle involved dispersing the particles in solvents with sonication and centrifuging at 10 000 rpm. Product was dried at 80 °C.

Ellipsometry. The thickness of the dry films on the sensors was measured using an Exacta 2000AP self-nulling ellipsometer, with a laser wavelength of 632.8 nm, at an incident angle of 70° at room temperature. An ellipsometric measurement gives two parameters, polarizer and analyzer, using the Exacta 2000AP Start-up software.

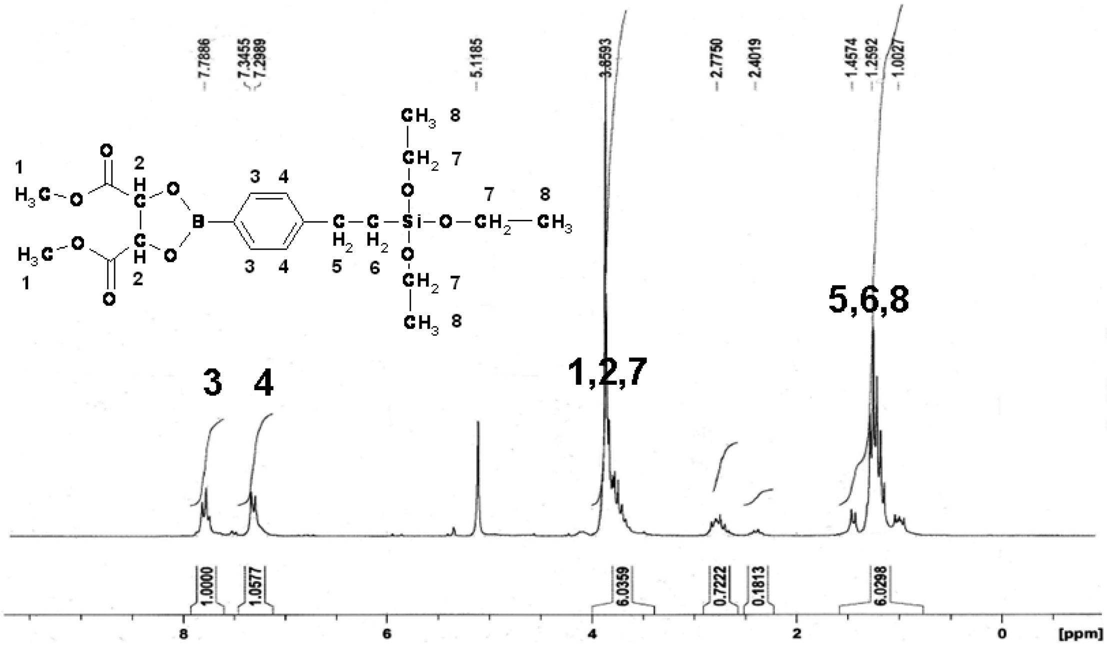


Figure 1. ^{1}H NMR of dimethyl tartrate-protected phenylboronate silane.

Film thickness and refractive index were calculated using a uniform film model in the Exacta 2000AP Sit software.

XPS. QCM-D sensors were placed in a Quantera II imaging XPS Spectrometer (PHI Physical Electronics Inc.). Samples were irradiated with a monochromatic Al Kα X-ray source at a takeoff angle of 45°, a spot size of 100 μm, and a power of 25 W. For most measurements three data were collected from three locations on the surface.

QCM-D. Deposition measurements were performed with a Q-Sense quartz crystal microbalance (E4 model from Q-Sense, Sweden) fitted with the QCM E4 module holding QSX 303 silica sensors with and without silane coatings. Solutions were injected into the sensors with an IPC-N935 tubing pump with planetary drive from Ismatec. Frequency and dissipation changes of the 1st−13th overtones were monitored using Qsoft401 software version 2.5.2. Qtools software version 3.0.7 was used to analyze the data. All experiments were conducted at 22 °C.

Scanning Electron Microscopy. QCM-D surfaces were examined with a Tescan Vega II LSU scanning electron microscope (Tescan USA, PA) operating at 20 kV. Sensors were mounted onto grids and sputter coated with gold.

Electrophoretic Mobility. The electrophoretic mobility of the Stöber silica and phenylboronate silane-coated silica particles was measured using a Brookhaven Zetaplus zeta-potential analyzer operating in electrophoretic light-scattering mode with BIC Zetaplus software (version 2.5). A total of 10 runs (15 cycles per run) were performed at 25 °C.

Dynamic Light Scattering (DLS). The average diameters of silica and phenylboronate silane-coated silica particles were measured using a Brookhaven dynamic light-scattering instrument with a BI-9000AT autocorrelator and 35 mW laser with a wavelength of 632.8 nm at a scattering angle of 90°. Sample data were acquired using BIC dynamic light-scattering software 9kdlsw32 (version 3.34). The cumulative statistical method was used to analyze the data. Sample temperature was controlled at 25 ± 1 °C using a NESLAB water bath.

Neutron Activation Analysis. Neutron activation analysis was used to determine the mass percentage of boron in silane-coated silica particles. In a typical experiment, 10−20 mg samples (in a precleaned high-density polyethylene vial and heat sealed) were irradiated for 600 s in a beam port site (nominal neutron flux 5×10^7 neutron/cm^2·s) and simultaneously counted. Gamma spectra were collected with a hyperpure germanium detector (efficiency 20%, fwhm 1.9 at 1332 keV) on a PC-based multichannel analyzer. The photopeak at 477.6 keV was integrated to give a measure of the boron content with a detection limit for boron of 10 ppm.

Fluorescence Microscopy. Silane-treated SiO_2 sensors were immersed in 7.3×10^{-4} M ARS at pH 11 in 5 mM NaCl buffer. A wet sensor was placed under an Olympus BX51 optical and fluorescence microscope fitted with a Q-Imaging Retiga EXi digital camera: ImagePro software was used for acquiring images and data.

Fluorescence Spectroscopy. Mixtures of silane-coated silica particles and ARS were prepared in 0.1 M PBS buffer (pH 7.4) with a final silica particles concentration of 0.05 g/L and ARS concentration of 0.05−125 ppm. Fluorescence intensities were measured with a Safire fluorescence spectrophotometer running XFLUOR4 software version V4.30 to acquire data. The excitation wavelength was 468 nm, and the emission wavelength was 517 nm. All measurements were conducted at room temperature.

■ RESULTS AND DISCUSSION

Synthesis of Tartrate-Protected Silaneboronate. Scheme 1 summarizes our approach to the synthesis of the silaneboronate, **IV**; the proton NMR data of the final product is shown in Figure 1. The tartrate protecting group was necessary; otherwise, the unprotected boronic acid interfered with the hydrosilylation catalyst. Note that hydrosilylation produces two isomers. The dominant isomer is **IV**; however, NMR indicates the minor presence of the variation of **IV** where the silicon is bonded to the benzylic carbon.

Two types of silica surfaces were treated with the silane, silica-coated QCM-D sensor surfaces and Stöber colloidal silica. In both cases the silica was exposed to the protected silaneboronate in dry toluene at 50 °C.

Silaneboronate-Treated QCM-D Silica Sensor. Table 1 summarizes the properties of the silaneboronate coating on the silica surface before contact with liquid water. Ellipsometry gave an average thickness of 231 nm and Sauerbrey mass of 280 mg/m^2. Assuming the density of fully condensed silane was close to that of silica (2.2 g/mL), the pore volume of the silane layer was 45%. Modified sensors were first exposed to water in the QCM-D, resulting a frequency gain corresponding to a Sauerbrey weight loss of 5 mg/m^2, which we attributed to tartrate removal.

Table 1. Properties of the Silaneboronate Film on a QCM-D Silica Sensor before Immersion into Water

property	value	source
boron content	2 wt %	XPS
thickness	231.1 nm	ellipsometry
refractive index	1.1299 ± 0.0047	ellipsometry
mass coverage	280 mg/m^2	QCM Sauerbrey mass
density	1.21 g/mL	QCM + ellipsometry
pore fraction	45%	assumed density of solid, fully hydrolyzed and condensed silaneboronate was 2.2 g/mL

In previous work we have shown that latex particles stabilized by surface polyol layers will selectively deposit onto cellulose surfaces bearing phenylboronate groups.[22] The poly(glycerol monomethacrylate) surfaces chains are excellent colloidal stabilizers, and the only explanation for their pH-dependent deposition onto the modified cellulose was that deposition was driven by formation of boronate ester linkages. Therefore, we believe that the PGMA-coated particles are an excellent probe for boronate-rich surfaces.

PGMA-coated latex deposition was monitored by quartz crystal microbalance measurements. The QCM-D frequency shift results are shown in Figure 2A at pH 7.4 and Figure 2B at pH 4. At neutral pH, the latex showed strong adsorption onto the silaneboronate sensor whereas there was little deposition on the control silica sensor. At low pH, where boronate ester formation should not occur, there was little deposition. The surfaces of the QCM-D sensors were examined at the end of experiments by SEM. Sample micrographs are shown in Figure 2C−F. The highest coverage corresponded to the silaneboronate sensor at neutral pH, in agreement the QCM-D frequency data. There was limited latex deposition on the untreated silica (Figure 2E and 2F) sensors. There was slightly more deposition at pH 4 compared to pH 7.4, possibly reflecting the lower degree of silanol dissociation at lower pH.

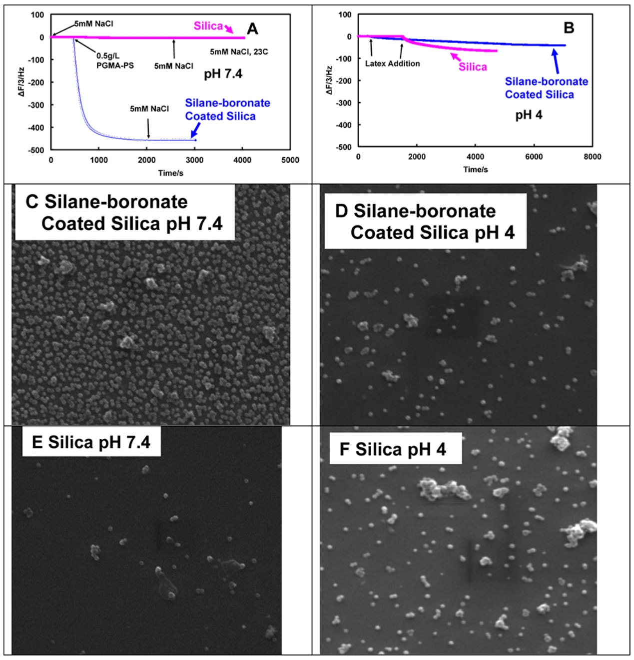


Figure 2. PGMA-PS deposition onto silica QCM-D sensors before and after silaneboronate treatment. SEMs micrographs show images of QCM-D sensor surfaces after the deposition experiment.

Silaneboronate-Treated Stöber Silica. Table 2 summarizes the properties of Stöber silica before and after silaneboronate treatment. The diameter increase suggests the presence of a 5 nm silaneboronate layer. The electrophoretic mobility of the treated particles was significantly less than the starting particles, confirming that the surface silanols were covered by the silaneboronate.

Table 2. Properties of Stöber Silica and Silaneboronate-Coated Silica in 5 mM NaCl at pH 8.5[a]

property	Stöber silica	silaneboronate-treated Stöber silica
average diameter/nm	188.9 ± 1.6	202.2 ± 1.9
electrophoretic mobility, 10^{-8} m^2 V^{-1} s^{-1}	−6.23 ± 0.09	−2.34 ± 0.06
boron (w/w) if 100% conversion		3.5%
boron (w/w) from neutron activation	0.042%	1.1%
boron (w/w) from DLS[b]		0.91%
boron (w/w) from XPS[c]		2% ± 1.1%
boron (w/w) from ARS binding, see Figure 3		1.9%

[a] Example calculations are given in the Supporting Information. [b] Assuming core and shell densities were 1.82 g mL^{-1}.[23] [c] On the basis of 3 measurements.

Five independent approaches were used to estimate the boron content of the treated silica particles, and the results are summarized in Table 2. If the all added silane ended up on the particle surfaces, the theoretical maximum mass fraction of boron is 3.5%. Neutron activation analysis gave a boron content of 1.11 ± 0.04%. The corresponding estimate from dynamic light scattering was 0.91% assuming complete hydrolysis of the silane and assuming both the silica core and the silica boronate shell densities were equal to 1.82 g/mL, the reported value for Stöber silica.[23]

XPS measurements were performed on QCM-D silica sensors with adsorbed colloidal silaneboronate-treated Stöber silica giving a mean value of 2% but with a broad distribution.

Springsteen and Wang have shown that alizarin red S (ARS) condenses with boronate ions to give fluorescent products.[10] ARS fluorescence characterization of the silaneboronate-treated Stöber silica was preformed two ways: (1) the silaneboronate-treated Stöber silica was deposited onto QCM-D surfaces, and fluorescence microscopy confirmed that the surfaces were

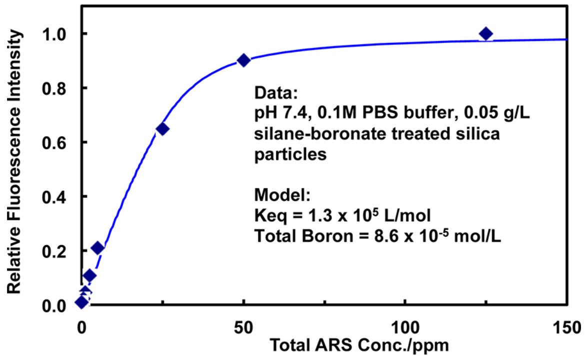


Figure 3. ARS binding to silaneboronate-treated silica. Theoretical curve was fit by varying the boronate−ARS binding constant. Incident wavelength was 468 nm, and fluorescence intensity was measured at 517 nm.

fluorescent (example images are in the Supporting Information file); (2) fluorescence of the silaneboronate-treated Stöber silica dispersions was measured as a function of the added ARS dosage. Results are shown in Figure 3 together with a curve calculated with a single binding constant model. An approximate "best fit" was obtained with a binding constant of 1.3 × 10^5 L/mol, which is 100 times greater than Springsteen's value for ARS binding to phenylboronic acid in solution at the same pH and ionic strength; see calculations in the Supporting Information.[10] The content of boron accessible to ARS was 1.9%, which was more than the value from neutron activation but less than the theoretical maximum (Table 2). In view of the high binding constant required in our calculation, we have limited confidence in the boron contents estimates from ARS binding. Therefore, of the five independent estimates of boron contents in Table 2, we have the most confidence in the neutron activation result, particularly as it did not rely on assumptions.

■ CONCLUSIONS

The dimethyl tartrate-protected phenylboronate silane **IV** (see Scheme 1) readily condenses onto silica surfaces, yielding a porous silica coating decorated with phenylboronic acid groups. Our silaneboronate-treated surfaces demonstrated specific binding of polyol-coated latex (QCM-D surface) and ARS dye (colloidal silica), as expected for a surface bearing phenylboronic acid groups. In our experiments, the coatings thicknesses ranged from 6 nm for the colloidal silica to 231 nm on the macroscopic the QCM-D silica sensor. There are no obvious barriers to achieving thinner coatings. Indeed, we anticipate that our silaneboronate could effectively functionalize a wide variety of silane-active substrates, including microfluidic devices, optical fibers, and metal oxide sensor surfaces.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Fluorescent microscope images of silaneboronate-treated Stöber silica and MathCad modeling ARS binding to silaneboronate-treated silica. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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