Synthesis and Volume Phase Transitions of Glucose-Sensitive Microgels

Yongjun Zhang, Ying Guan, and Shuiqin Zhou*

Department of Chemistry and The Center for Engineered Polymeric Materials of College of Staten Island, and The Graduate Center, The City University of New York, 2800 Victory Boulevard, Staten Island, New York 10314

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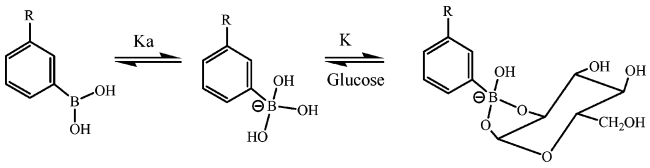
By the functionalization of poly(*N*-isopropylacrylamide-*co*-acrylic acid) microgels with 3-aminophenylboronic acid (APBA) via carbodiimide coupling, nearly monodisperse glucose-sensitive P(NIPAM-PBA) microgels with a diameter of several hundred nanometers were synthesized in aqueous media. Dynamic laser light scattering was used to study the glucose-sensitive and thermosensitive behaviors of the resultant microgels under various conditions. The introduction of the hydrophobic phenylboronic acid (PBA) group significantly decreases the volume phase transition temperature of the resultant microgels. As a result, the P(NIPAM-PBA) microgels with a 10.0 mol % PBA content are in a collapsed state at room temperature. However, the addition of glucose makes the microgels swell dramatically. The glucose-sensitivity of the PBA-containing microgels relies on the stabilization of the charged phenylborate ions by binding with glucose, which can convert more hydrophobic PBA groups to the hydrophilic phenylborate ions. The presence of glucose also induces a two-stage volume phase transition of the P(NIPAM-PBA) microgels, which is explained by the core−shell-like heterogeneous structure of the microgels induced by the formation of the unique glucose−bis(boronate) complex in the "core" area of the microgels. The effects of pH, ionic strength, and PBA content on the glucose sensitivity of the P(NIPAM-PBA) microgels were investigated.

Introduction

Since first being reported in 1986,[1] the thermosensitive poly(*N*-isopropylacrylamide) (PNIPAM) microgels have attracted extensive attention not only due to their theoretical importance,[2−6] but also their potential applications in many fields,[7] such as controlled drug delivery,[8] chemical separation,[9] sensors,[10] and microreactors.[11] The PNIPAM microgels can be readily prepared by precipitation polymerization in water at a temperature above the lower critical solution temperature (LCST) of PNIPAM. The application of PNIPAM-only microgels, however, is limited by the relatively narrow range of physical and chemical properties.[12] The functionalization of PNIPAM microgel can not only control the volume phase transitions, but also introduce other environmental sensitivities. For example, the microgels prepared from the copolymerization of NIPAM monomer with acrylic acid, methacrylic acid, vinylacetic acid, or vinylpyridine are pH responsive.[13−16] Recently, novel photosensitive microgels were synthesized by incorporating dye[17] or gold nanorods[18] to convert light energy to heat. In contrast to the numerous reports on their sensitivity to physical stimuli, their sensitivity to chemical stimuli, that is, a concentration change in particular molecules in the milieu, is rarely studied. Lyon et al. reported that the PNIPAM microgels functionalized with biotin are sensitive to the concentration change of avidin and polyclonal anti-biotin.[19] Some other bioconjugated PNIPAM-based microgels were also reported.[20−23] Here, we report a new type of PNIPAM-based microgels functionalized with a phenylboronic acid (PBA) group, which is sensitive to glucose concentration in the media.

PBA group has long been used as glucose sensing moiety. As shown in Scheme 1, PBA is in equilibrium between the undissociated (or uncharged) and the dissociated (or charged) forms in aqueous solution. Both forms react reversibly with 1,2-*cis*-diols such as glucose. The complexation of the uncharged form with glucose is unstable because it is highly susceptible to hydrolysis, but the binding with glucose causes the thermodynamically more favorable charged form. As a result, the dissociation equilibrium of PBA moves to the right and its pK_a decreases. For a hydrogel modified with PBA group, the binding of 1,2-*cis*-diols increases the degree of ionization on the hydrogel and builds up a Donnan potential for the hydrogel swelling. Based on this property, bulk polymer hydrogels bearing PBA moieties have been prepared to fabricate glucose sensors,[24−28] in which the hydrogels have to be coated on an electrode, constructed as a hologram, or used as a matrix to embed a crystalline colloidal array. On the other hand, Kataoka et al.[29−31] synthesized the phenylboronated PNIPAM gel slab, capillary gels, and gel beads for potential self-regulated insulin delivery through the direct copolymerization of NIPAM with 3-acrylamidophenylboronic acids in DMSO and water/paraffin oil suspension, respectively. However, these gels have to be first transferred to the aqueous phase to get rid of organic solvents. Their swelling curves can only be monitored from the mass change of the gel slabs or diameter change of the gel cylinders or beads under microscope. Furthermore, bulk gels need a long time to reach swelling/collapsing equilibrium.

Scheme 1. Complexation Equilibrium between Phenylboronic Acid Derivative and Glucose



* To whom correspondence should be addressed. E-mail: zhoush@mail.csi.cuny.edu.

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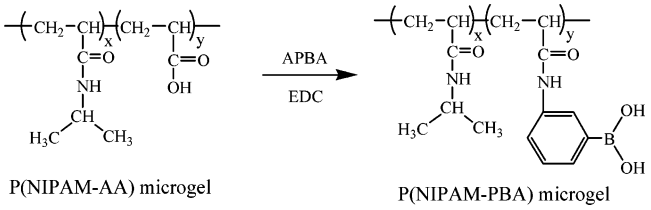
Scheme 2. Synthesis of Glucose-Sensitive P(NIPAM-PBA) Microgels with Pendant Phenylboronic Acids



P(NIPAM-AA) microgel P(NIPAM-PBA) microgel

Microgels have several advantages over bulk gels in some specific applications. First, microgels can undergo a rapid phase transition in response to external stimuli,[10,32] as the rate of volume change is scaled as l^{-2}, where l is the relevant length scale of gel.[33] Second, the monodisperse microgel particles, as building blocks, can be readily assembled to meet various application requirements. Thin microgel films have been easily fabricated through layer-by-layer assembly with a controllable film thickness.[34−36] Highly ordered crystalline colloidal arrays have been assembled from the monodisperse microgel particles at a suitable range of concentration.[5] The optical properties of the crystalline arrays are tunable by controlling the size and concentration of the microgels.[37,38]

In this paper, the monodisperse phenylboronated PNIPAM microgels were synthesized via a two-step procedure. The poly(*N*-isopropylacrylamide-*co*-acrylic acid) [P(NIPAM-AA)] microgels were first synthesized by free radical precipitation polymerization, followed by coupling the 3-aminophenylboronic acid (APBA) to the COOH group of AA units in the microgels. The volume phase transitions of the resultant P(NIPAM-PBA) microgels in response to glucose concentration and temperature change under different pH and ionic strength were investigated by dynamic light scattering. The glucose-sensitive microgels synthesized here have the potential to be used for the fabrication of a glucose sensor and self-regulated insulin release.

Experimental Section

Materials. *N*-Isopropylacrylamide (NIPAM), *N*,*N*′-methylenebis(acrylamide) (BIS), ammonium persulfate (APS), sodium dodecyl sulfate (SDS), acrylic acid (AA), 3-aminophenylboronic acid (APBA), *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride (EDC), and D-fructose were all purchased from Aldrich. D-(+)-Glucose was purchased from ACROS. NIPAM was purified by recrystallization from a hexane/acetone mixture and dried in a vacuum. AA was distilled under reduced pressure.

Microgel Synthesis. The P(NIPAM-AA) microgels were synthesized by free radical precipitation polymerization.[13,14] Briefly, 1.400 g of NIPAM, 0.100 g of AA, 0.033 g of BIS, and 0.057 g of SDS were dissolved in 100 mL of water. The solution was filtered to remove any possible precipitates. The reaction mixture was transferred to a three-necked round-bottom flask equipped with a condenser and a nitrogen inlet and heated to 70 °C under a gentle stream of nitrogen. After 1 h, 5 mL of 0.06 M APS solution was added to initiate the reaction. The reaction was allowed to proceed for 5 h. The resultant microgels were purified by dialysis (cutoff 12 000−14 000) against water for at least 1 week. This P(NIPAM-AA) microgel sample has a feeding AA content of 10.0 mol %. Microgels with AA contents of 5.8 and 2.0 mol % were synthesized using the same procedure but different feeding amounts of AA comonomer.

The phenylboronic acid-functionalized P(NIPAM-PBA) microgels were synthesized as follows. First, 0.233 g of APBA and 0.239 g of EDC were dissolved in 45 mL of water. The solution was cooled in an ice bath, and then 5 mL of purified P(NIPAM-AA) microgels was added. The reaction mixture was kept at about 0 °C for 4 h. The resultant products were purified by dialysis against water. The resulting microgels have a PBA content of 10.0, 5.8, and 2.0 mol %, respectively, according to the AA content of the parent microgels.

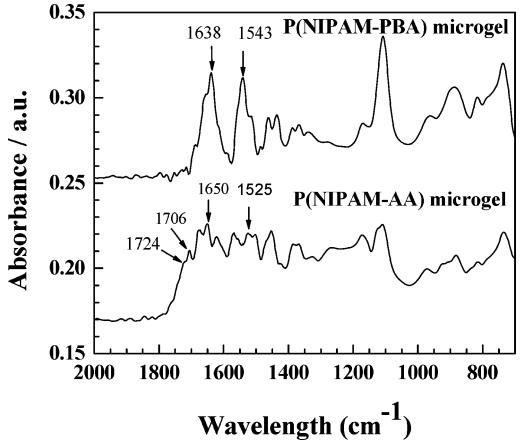


Figure 1. FTIR spectra of P(NIPAM-AA) microgels with an AA content of 10.0 mol % and the corresponding P(NIPAM-PBA) microgels with a PBA content of 10.0 mol %.

Fourier Transform Infrared (FT-IR) Spectroscopy. The microgel suspensions were applied to silica wafer and dried in a vacuum oven. The FTIR spectra were collected using a Fourier transform spectrometer (Nicolet Magna 550) operating at 4 cm^{-1} resolution.

Dynamic Laser Light Scattering (LLS). A standard LLS spectrometer (BI-200SM) equipped with a BI-9000 AT digital time correlator (Brookhaven Instrument Inc.) was used to monitor the size and size distribution of the microgels under different conditions. A He−Ne laser (35 mW, 633 nm) was used as light source. All microgel solutions were passed through Millipore Millex-HV filters with a pore size of 0.45 μm to remove dust before the dynamic LLS measurements. In dynamic LLS, the Laplace inversion of each measured intensity−intensity time correlated function can result in a characteristic line width distribution $G(\Gamma)$.[39] For a purely diffusive relaxation, Γ is related to the translational diffusion coefficient D by $(\Gamma/q^2)_{C\to 0,q\to 0} = D$, where $q = (4\pi n/\lambda)\sin(\theta/2)$ with n, λ, and θ being the solvent refractive index, the wavelength of the incident light in vacuo, and the scattering angle, respectively. $G(\Gamma)$ can be further converted to a hydrodynamic radius (R_h) distribution by using the Stokes−Einstein equation, $R_h = (k_B T/6\pi\eta)D^{-1}$, where T, k_B, and η are the absolute temperature, the Boltzmann constant, and the solvent viscosity, respectively.[40]

Results and Discussion

Synthesis of P(NIPAM-PBA) Microgels. Our strategy to prepare the glucose-sensitive P(NIPAM-PBA) microgels involves the first synthesis of a P(NIPAM-AA) microgel, followed by modification with the glucose-sensing moiety PBA. The preparation of nearly monodisperse P(NIPAM-AA) microgels with well-controlled size and compositions has been well-established from the precipitation polymerization in water.[41−43] It has been reported that the AA contents in the microgels are nearly equal to the feeding ratios of the AA and NIPAM comonomers.[41] Dialysis has been proved to be an effective purification procedure.[42,43] As shown in Scheme 2, the P(NIPAM-AA) microgel could be functionalized with PBA through the coupling of 3-aminophenylboronic acids (APBA) to the AA units in the microgels under EDC catalysis. Figure 1 shows the FTIR spectra of the dried P(NIPAM-AA) microgels (10.0 mol % AA in feeding ratio) and the corresponding P(NIPAM-PBA) microgels. In addition to the absorption maxima of amide I at 1650 cm^{-1} and amide II at 1525 cm^{-1}, the P(NIPAM-AA) microgels present a peak at 1706 cm^{-1} with a shoulder at 1724 cm^{-1}, which was assigned to the stretching of the uncharged

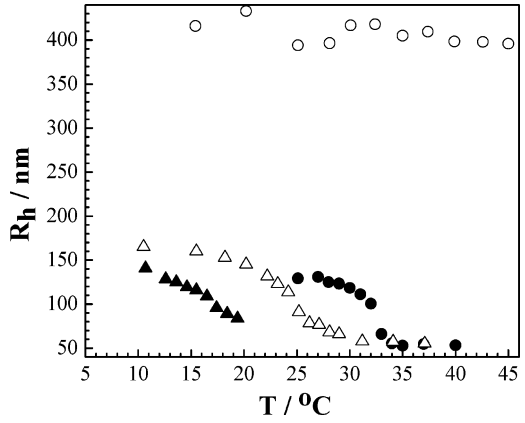


Figure 2. Temperature dependence of the average R_h values of the P(NIPAM-AA) microgels (10.0 mol % AA; circles) and the corresponding P(NIPAM-PBA) microgels (10.0 mol % PBA; triangles), measured at a scattering angle $\theta = 45°$, pH = 3.5 (solid symbols) and 9.1 (hollow symbols), respectively.

dimerized or associated form of carboxylic group of AA units. After modification with APBA, the P(NIPAM-PBA) microgels only present the absorption maxima of amide I at 1638 cm^{-1} and amide II at 1543 cm^{-1}. The disappearance of the peak at 1706 cm^{-1} indicates that the carboxylic groups in the PAA segments are almost completely reacted with APBA. The higher frequency amide I and the lower frequency amide II bands in the P(NIPAM-AA) microgels as compared to the corresponding P(NIPAM-PBA) microgels are due to the hydrogen bonding between PNIPAM and PAA.[44]

Thermosensitive Volume Phase Transitions of the Microgels. The pK_a values of the AA moiety in the P(NIPAM-AA) microgels and the PBA moiety in the P(NIPAM-PBA) microgels are about 4.2[45] and 8.2,[30] respectively. It is expected that the pH value of the media has a great effect on the volume phase transitions of both microgels. Figure 2 shows the temperature-induced volume phase transitions of the two microgels with an AA or PBA content of 10.0 mol % at pH = 3.5 ($<$pK_a) and 9.1 ($>$pK_a), respectively, in terms of the change of hydrodynamic radius (R_h) measured at a scattering angle of $\theta = 45°$. The pH was adjusted by using dilute HCl or NaOH aqueous solutions. At pH = 3.5, when both of the microgels are under the swollen conditions, for example, P(NIPAM-AA) microgels at $T = 25$ °C and P(NIPAM-PBA) microgels at $T = 12$ °C, respectively, they have a similar size because the majority of the AA groups and the PBA groups in the two microgels are in the uncharged form. These results indicate that the modification with PBA group does not change the originally existing morphology of the microgels. However, the hydrophobic PBA groups significantly decrease the volume phase transition temperature (VPTT) of the microgels. For the P(NIPAM-AA) microgels, the incorporation of 10 mol % neutral AA slightly decreases VPTT from ~34 °C for pure PNIPAM microgel to ~32 °C.[2] The slight decrease of the LCST of P(NIPAM-AA) copolymer microgels as compared to the PNIPAM homopolymer microgels might be due to the weak hydrogen bonding between AA and NIPAM units. After modification with APBA, the P(NIPAM-PBA) microgels show a VPTT of ~17 °C, which is about 15 °C lower than that of the unmodified P(NIPAM-AA) microgels. It is well known that the copolymerization with a hydrophilic monomer increases the LCST of PNIPAM, while the copolymerization with a hydrophobic monomer decreases its LCST. The P(NIPAM-PBA) microgels can be considered as a copolymer of NIPAM with 3-acrylamidophenylboronic acid, which is hydrophobic and renders a lower VPTT of the resultant copolymer microgels.

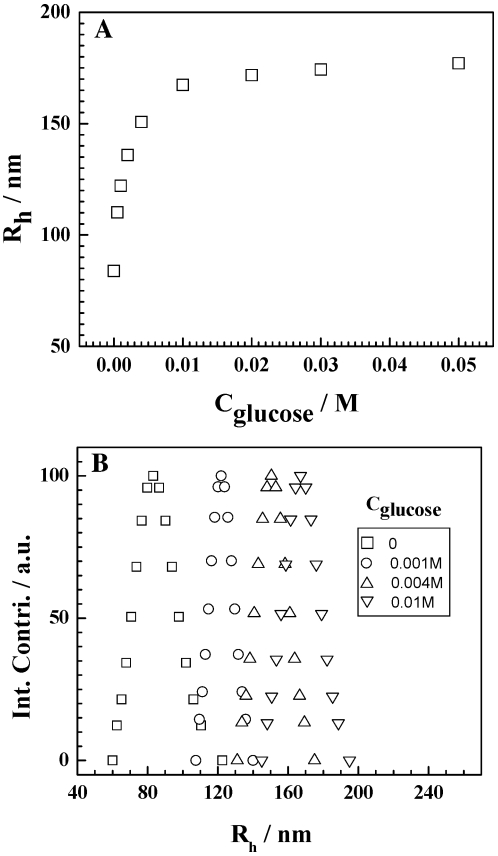


Figure 3. (A) R_h values of the P(NIPAM-PBA) microgels (10.0 mol % PBA) as a function of glucose concentration, measured in 0.005 M phosphate buffer of pH = 9.0 at $T = 25$ °C. (B) Size distributions of the P(NIPAM-PBA) microgels at different glucose concentrations.

Because of the strong hydrophobicity of the PBA group, the P(NIPAM-PBA) microgels start to aggregate severely at ~19.5 °C before they reach the fully collapsed state.

When the pH value of the media increases to 9.1, AA groups are totally deprotonated, resulting in the increase in osmotic pressure and Coulombic repulsion. To induce the P(NIPAM-AA) chain to collapse, a higher temperature needs to be provided. No volume phase transition was detected in our experimental temperature window ($<$45 °C), which is consistent with the previous report that the P(NIPAM-AA) microgels with 10 mol % AA have a VPTT around 56 °C.[43] At pH = 9.1, the size of the P(NIPAM-PBA) microgels in the swollen state is smaller than that of the P(NIPAM-AA) microgels due to the incomplete ionization of the PBA group. However, the partial ionization of PBA group still dramatically increases the size and VPTT of the microgels in comparison with the uncharged form at pH = 3.5. More importantly, the partial ionization of the P(NIPAM-PBA) microgels at pH = 9.1 stabilizes the particles during the collapsing process. As a result, the microgels reach the equilibrated collapsing limit without aggregation.

Glucose Sensitivity of P(NIPAM-PBA) Microgels. The introduction of PBA group makes the resultant microgels glucose-sensitive. Figure 3A shows the R_h values of the P(NIPAM-PBA) microgels in a 0.005 M phosphate buffer of pH = 9.0 with different glucose concentrations measured at 25 °C. With the increase in glucose concentration, the particle size expands dramatically. In the absence of glucose, the average R_h was only 84 nm; however, the particle size is doubled when glucose concentration is at 0.01 M. The R_h−[glucose] plot flats off when the glucose concentration is above 0.01 M where the microgel network chains stretch to nearly a maximum.

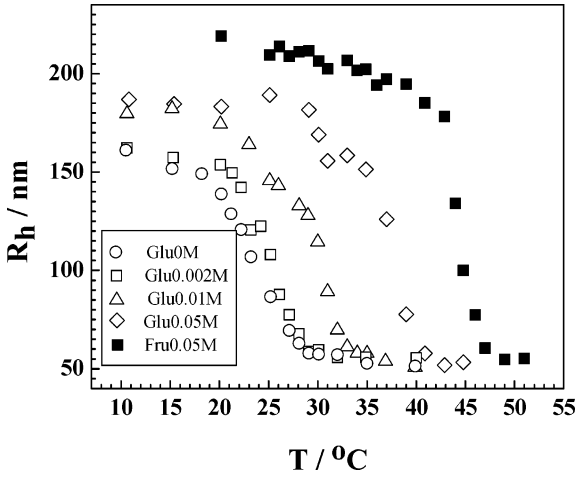


Figure 4. Temperature-induced R_h change of the P(NIPAM-PBA) microgels (10 mol % PBA) in the 0.005 M phosphate buffer of pH = 9.0 with various glucose or fructose concentrations.

Figure 3B shows the size distributions of the P(NIPAM-PBA) microgels at various glucose concentrations. The swelling of the particles with the increase in glucose concentration is clearly presented. In addition, these microgels are nearly monodisperse regardless of their swollen states.

While the glucose can induce a dramatic size expansion of the P(NIPAM-PBA) microgels at room temperature, Figure 4 shows the effect of glucose concentration on the thermosensitive volume phase trantions of these microgels. As expected, the addition of glucose in the milieu significantly increases the VPTT of the P(NIPAM-PBA) microgels. For example, the presence of 0.05 M glucose results in a VPTT increase of ~15 °C. Obviously, this effect is due to the stabilization of the charged phenylborates by complexing with glucose, which converts more hydrophobic uncharged PBA group to hydrophilic charged phenylboronate group (Scheme 1). The continuous volume phase transitions of the P(NIPAM-PBA) microgels are different from the discontinuous volume phase transitions observed in the phenylborated PNIPAM bulk gels,[29,31] which is attributed to the shear modulus, which keeps the shape of a bulk gel until its internal stress builds to a certain point that the shear module can no longer maintain the shape of the gel.[2]

A close examination of the deswelling curves reveals an interesting phenomenon: the microgels present a two-stage volume phase transition in the presence of glucose, while the size distribution of the microgels remains very narrow under all of the conditions. Upon heating, the P(NIPAM-PBA) microgels undergo a small degree of collapse, followed by a second transition with a large volume change. The intermediate plateau becomes more pronounced as the glucose concentration increases. The mechanism of the glucose-induced two-stage phase transition is not quite clear. A similar two-stage transition was reported when a certain amount of sodium dodecyl sulfate (SDS) is present in the PNIPAM microgel suspensions.[46] The authors thought that the first step involves the breaking up of micelles and expelling SDS from the gel network and the second step represents the collapse of the surfactant-free gel network. This explanation cannot be applied to the glucose-induced two-stage transition because glucose interacts with the microgel in a different way from that of SDS. A distinct two-step volume phase transition has also been observed from the core−shell microgels with PNIPAM (LCST = 34 °C) as core and poly(*N*-isopropylmethacrylamide) (LCST = 45 °C) as shell.[47] The two transitions represent the collapse of the core and the shell, respectively. We speculate that the glucose-induced two-stage volume phase transitions of the P(NIPAM-PBA) microgels are also related to a core−shell-like structure. The structural heterogeneity of the PNIPAM microgels prepared from batch polymerization has been widely studied.[48−51] It is well known that the cross-linker BIS is statistically incorporated faster than the monomer NIPAM, resulting in a radial distribution of cross-linkers in the microgels when cross-linking density is less than 7 mol %.[51] In our case, the overall cross-linking density is 1.5 mol %. Therefore, the microgels involved in the present study can be considered to have an internal core−shell-type structure with respect to cross-linking density, where the core represents the relatively densely cross-linked center and the shell represents the relatively loosely cross-linked periphery. However, no two-stage deswelling has been observed from these microgels in the absence of glucose because the VPTT difference between the core and the shell is not significant. Nevertheless, the addition of glucose can induce a distinct core−shell-like structure of the microgels. It is known that in the alkaline aqueous solutions, besides the glucose−mono(boronate) complex shown in Scheme 1, a glucose−bis(boronate) complex can be also formed, in which one glucose molecule is complexed with two PBA group.[52,53] For the formation of glucose−bis(boronate) complex, the two PBA groups must be close enough, so it is more favorable for their formation in the "core" area with a relatively high cross-link density. The formation of glucose−bis(boronate) complex increases the cross-linking density but does not change the pK_a of the PBA group.[54] As a result, the VPTT of the core is lower than that of the shell, and a two-transition deswelling curve can be presented when the temperature increases gradually.

The hypothesis is supported by the one-stage transition of the microgels in the presence of 0.050 M fructose (solid square curve in Figure 4). It has been suggested that, while glucose can form both the glucose−mono(boronate) complexes and the glucose−bis(boronate) complexes with the PBA group, other sugars, including fructose, can only form mono(boronate) complexes with PBA group.[54] Therefore, the fructose molecules react with the PBA group in the "core" and the "shell" area of the microgels in the same way, and only one transition was observed. In contrast, when the glucose molecules react with the microgels, the formation of glucose−bis(boronate) complexes is more favorable in the "core" area than in the "shell" area. The amount of glucose−bis(boronate) complex increases with increasing glucose concentration, which makes the VPTT difference between the "core" and the "shell" more significant. As a result, the intermediate plateau between the two transitions becomes more pronounced as the glucose concentration increases. It is noteworthy that the size of the swollen microgels in the fructose solution is larger than that in the glucose solution at the same concentration because fructose has a higher association constant (~4370) with the PBA group than does glucose (~110).[55] The VPTT is also higher than that of glucose.

Effects of pH, Ionic Strength, and PBA Content on the Glucose-Sensitivity of the P(NIPAM-PBA) Microgels. The pH value of the media has a great effect on the glucose-sensitivity of the hydrogels modified with PBA group. It was found that the glucose sensors made from the phenylborated polyacrylamide hydrogels embedded with crystalline colloid array are only responsive to glucose concentration change in the pH range of 7.0 < pH < 9.5.[25] At pH < 7.0, the majority of PBA groups are in the uncharged form, while at pH > 9.5, almost all of the PBA groups are transferred to the charged form. As a result, the PBA-based glucose-sensors lose their responsibility under these conditions. Figure 5A shows the effect of

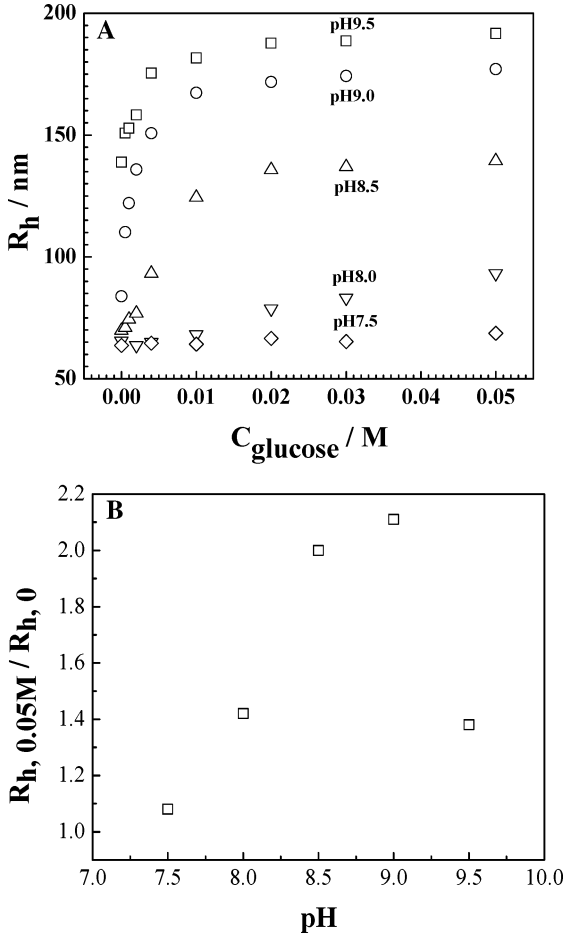


Figure 5. (A) R_h values of P(NIPAM-PBA) microgels (10.0 mol % PBA) as a function of glucose concentration, measured in 0.005 M phosphate buffers of different pH values at $T = 25$ °C. (B) $R_{h,0.05M}/R_{h,0}$, the ratio of the particle size in the presence of 0.050 M glucose and that in the absence of glucose, as a function of pH value.

pH on the glucose-induced swelling behavior of the P(NIPAM-PBA) microgels. At pH = 7.5, the glucose-induced size expansion is negligible. In the pH range of 8.0−9.5, the glucose-induced swelling is significant, indicating the microgels are glucose-sensitive under these conditions. The swelling ratio of the microgels in the presence of 0.050 M glucose as compared to that in the absence of glucose, $R_{h,0.05M}/R_{h,0}$, has been plotted against pH in Figure 5B. This plot more clearly reflects the pH effect on the overall glucose-sensitivity of the P(NIPAM-PBA) microgels. The glucose-sensitivity of the microgels increases with the increase in pH, reaches a maximum at pH = 9.0, and then decreases at higher pH. The glucose-sensitivity of the microgel at lower glucose concentrations shows the same trend.

The glucose-sensitivity of the P(NIPAM-PBA) microgels is based on the increased ionization of PBA group in the presence of glucose. Therefore, ionic strength should have a great effect on the glucose-induced swelling of the P(NIPAM-PBA) microgels. Figure 6 shows the glucose-induced R_h change of the P(NIPAM-PBA) microgels in phosphate buffers of two ionic strengths at $T = 25$ °C. In both buffers, the P(NIPAM-PBA) microgels exhibit glucose-induced size expansion; however, a smaller size in the 0.050 M buffer is found than that in the 0.005 M buffer at all glucose concentrations, which can be explained by the weakening of Donnan potential. Although the particle swelling is depressed by high ionic strength, the P(NIPAM-PBA) microgels still show good glucose sensitivity in the 0.050 M buffer. The overall sensitivity measurement, $R_{h,0.05M}/R_{h,0}$, just decreases slightly from 2.11 in the 0.005 M buffer to 1.89 in the 0.050 M buffer. It is noteworthy that the ionic strength of the 0.050 M phosphate buffer is close to that of human blood, which implies that the P(NIPAM-PBA) microgels have potential to work at physiological ionic strength.

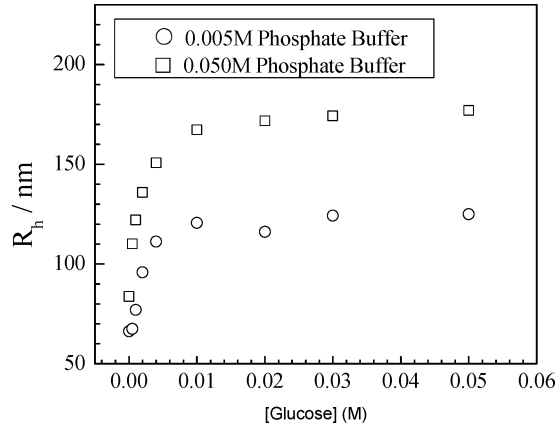


Figure 6. Glucose-induced R_h increase of P(NIPAM-PBA) microgels in 0.005 and 0.050 M phosphate buffers at pH = 9.0 and $T = 25$ °C.

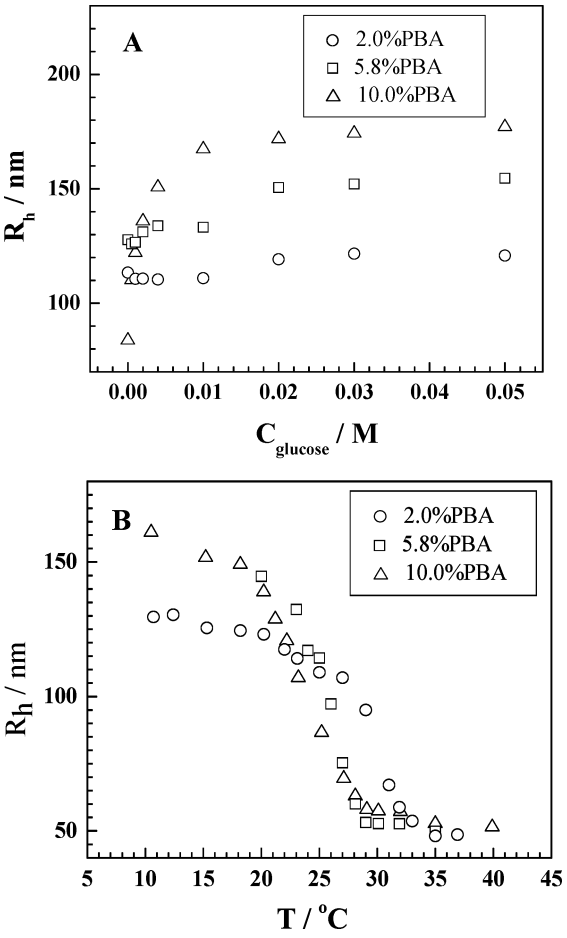


Figure 7. (A) Effect of the PBA content on the glucose sensitivity of P(NIPAM-PBA) microgels in 0.005 M phosphate buffer of pH = 9.0 at $T = 25$ °C. (B) Thermosensitive volume phase transition curves of P(NIPAM-PBA) microgels with different PBA contents in terms of R_h change measured in 0.005 M phosphate buffer of pH = 9.0.

The P(NIPAM-PBA) microgels involved in the above studies have a PBA content of 10.0 mol %. Based on the mechanism shown in Scheme 1, the glucose sensitivity of the P(NIPAM-PBA) microgels should increase with the increase in the PBA content. Figure 7A shows the glucose-induced size change of three P(NIPAM-PBA) microgels with PBA content of 2.0, 5.8,

and 10.0 mol % (according to the feedings of AA comonomers), respectively, in the 0.005 M phosphate buffer of pH = 9.0 at $T = 25$ °C. With a low PBA content of 2.0 and 5.8 mol %, the addition of glucose only expands the microgel network to a small degree. In contrast, the addition of glucose can induce a dramatic expansion for the P(NIPAM-PBA) microgels with a 10.0 mol % PBA content. The low glucose sensitivity of the two microgels with low PBA contents can be explained from their volume phase transition curves. Figure 7B shows the effect of PBA content on the thermosensitive behavior of the P(NIPAM-PBA) microgels. As expected, VPTT of the P(NIPAM-PBA) microgels decreases with the increase in the content of the hydrophobic PBA group. At 25 °C, the two P(NIPAM-PBA) microgels with low PBA contents are in a fully swollen state or close to a fully swollen state; therefore, the addition of glucose can only induce a limited further expansion. In contrast, the P(NIPAM-PBA) microgels with a 10.0 mol % PBA content are close to their fully collapsed state at 25 °C. This result suggests that the P(NIPAM-PBA) microgels must contain a certain high level of PBA group to be potentially used as glucose sensors at room temperature. It can be expected that a high glucose-sensitivity will be observed when the measurement is carried out near the collapsing temperature.

Conclusion

Nearly monodisperse glucose-sensitive P(NIPAM-PBA) microgels with a diameter of a few hundred nanometers were successfully synthesized from the functionalization of P(NIPAM-AA) microgels with 3-aminophenylboronic acid via EDC coupling in water. The introduction of the hydrophobic PBA moieties significantly reduces the VPTT of the resultant P(NIPAM-PBA) microgels; however, the collapsed microgels swell in the presence of glucose in alkaline solutions at room temperature because the ionization degree of the PBA group increases as a result of the stabilization of the phenylboronate ions by complexing with glucose. The presence of glucose not only increases the VPTT of the P(NIPAM-PBA) microgels, but also induces a two-stage volume phase transition. The glucose-sensitivity of the P(NIPAM-PBA) microgels depends on pH, ionic strength, and the PBA content of microgels. To observe a remarkable glucose-induced swelling of the microgels at room temperature, the P(NIPAM-PBA) microgels should have a certain high PBA content. Maximum sensitivity was observed at pH = 9.0 and low ionic strength; however, the microgels still show significant glucose-sensitivity at physiological ionic strength.

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