Langmuir

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A Novel Glucose/pH Responsive Low-Molecular-Weight Organogel of Easy Recycling

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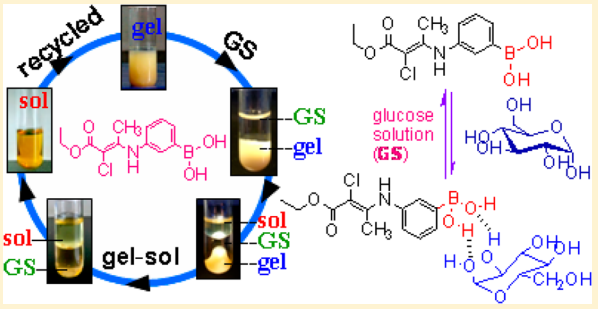
Supporting Information

ABSTRACT: A new phenylboronic acid based gelator was developed to prepare low-molecular-weight organogel (LMOG), which could interact with several solvents to assemble into a three-dimensional nanofiber network. ^{1}H NMR spectroscopy study suggests that the driving force for the gelation includes hydrogen bonding and $\pi-\pi$ stacking. Evaluated by UV-spectroscopy, the gel showed a prompt initial response to glucose at low concentration of 0.012 mmol/mL, which is a critical concentration of venous plasma glucose for diabetes. Significantly, this organogel exhibits excellent sensitivity to glucose among seven sugars tested (i.e., mannitol, galactose, lactose, maltose, sucrose, and fructose). The proposed formation of hydrogen-bonded complexes during the glucose sensing was supported by our energy calculation. Meanwhile, this organogel exhibits pH-response. Importantly, this LMOG could be conveniently recycled and thus be reused.



INTRODUCTION

Stimuli-responsive systems have received considerable attention for their broad potential applications in area such as controlled drug delivery.[1−4] In responding to changes in blood glucose levels, for example, glucose-responsive materials have the capability of regulating insulin release and thus can be used in treating diabetes mellitus, a worldwide health concern.[5−8] Lots of glucose-responsive polymers functionalized with phenylboronic acid (PBA) or enzyme glucose oxidase have been synthesized.[9−13] However, a limited capacity for reversible responses and the lengthy equilibration time for linear polymers limited their practical applications in drug delivery.[14−18] Therefore, there is an urgent need for new materials that could be recycled and could respond rapidly to glucose concentration and that could continuously monitor glucose levels at physiological conditions, which could be applied to a self-tuning controlled-release system that synchronizes release of insulin with elevated glucose concentration.

Comparing to polymer gels, low-molecular-weight organogels (LMOGs) are reversible and more sensitive to changes in their surrounding environment.[19,20] Recently, advances in the production of new LMOGs have attracted considerable attention because of the interesting supramolecular architectures as well as their industrial applications. Various rapid response intelligent LMOGs have recently been developed, which exhibit superfast response to light, electricity, heat, magnetism, pH or to specific molecules.[21−23] The design and modification of LMOGs are easier than those for polymers. In addition, direct drug loading during the organogel preparation makes it possible for a great quantity of drug loading and precise control of drug concentration.[24]

Inspired by these earlier successes, we focused on the design and synthesis of a new type of glucose/pH sensitive LMOG to explore rapid glucose-response, in particular at the glucose levels near the physiological conditions. LMOGs were prepared by introducing the glucose-sensitive phenylboronic acid group into the gel. The PBA-based small molecular mass gelator was designed and synthesized to self-assemble into special organogels. The organogels showed dual sensitivity to both glucose concentration and pH. Moreover, these organogels were reversible and could be reused conveniently. Their response to glucose levels may make them suitable as biosensors of blood glucose levels or for devices involved in the controlled release of insulin.

2. EXPERIMENTAL SECTION

2.1. General Materials and Measurements. All solvents and reagents were commercially available and analytical reagent grade. 3-Aminobenzeneboronic acid was obtained from Shanghai Darui Fine Chemicals Co. Ltd. Neopentyl glycol and diethanolamine were obtained from Shanghai Aladdin Chemistry Co. Ltd. Ethyl 2-chloroacetoacetate were obtained from Alfa Aesar China Co. Ltd. All chemicals were directly used without purification.

^{1}H and ^{13}C NMR spectroscopy were both performed on a Bruker-300 spectrometer operating at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). Tetramethylsilane (TMS) was used as an internal standard, and $CDCl_3$ was used as the solvent. Fourier transform infrared (FT-IR) spectra were recorded on a Bruker EQUINOX 55 spectrometer with the KBr technique. Mass spectrometric analysis was performed on

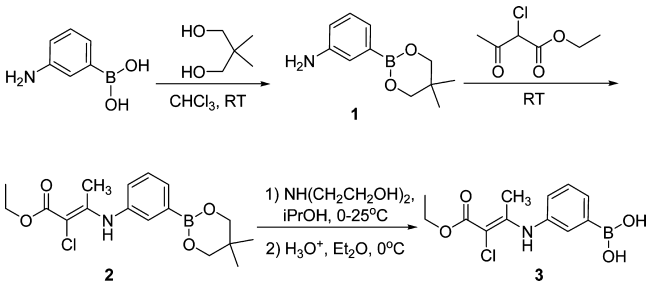
Received: August 30, 2013
Revised: October 1, 2013
Published: October 4, 2013

dx.doi.org/10.1021/la4033578 | Langmuir 2013, 29, 13568−13575

GC-MS analysis (Shimadzu GC-MS-QP2010). Single crystal diffraction was performed on a Bruker Smart APEX CCD. Melting points were uncorrected and recorded on a digital melting point apparatus WRS-1B. Scanning electronic microscopy (SEM) images were taken on a Nova NanoSEM 200 scanning electron microscope. The absorbance was measured with a spectrophotometer (Shimadzu UV-2550).

2.2. Synthesis. The general procedure for synthesis of compound 1, 2, 3 appears in Scheme 1.

Scheme 1. Synthesis of 3-(3-Chloro-4-ethoxy-4-oxobut-2-en-2-ylamino)phenylboronic Acid



Synthesis of Compound 1. A mixture of 3-aminobenzeneboronic acid (1.37 g, 10 mmol), 2, 2-dimethyl-1,3-propanediol (1.04 g, 10 mmol), and chloroform (30 mL) was stirred magnetically at room temperature for 3 h. The mixture was washed with water. The organic phase was separated, dried over anhydrous sodium sulfate, and filtered, and the solvent was evaporated under vacuum to obtain compound **1** (yield: 99%). White crystal. mp 109.5−109.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20−07.27 (m, 1H), 7.15−7.19 (m, 1H), 6.78−6.80 (dd, J = 2.6 1.5 Hz, 1H), 6.75−6.77(dd, J = 2.6 1.5 Hz, 1H), 3.77 (s, 4H), 1.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.38, 128.28, 123.88, 120.11, 117.26, 71.99, 31.56, 21.59. GC-MS (EI, 70 eV): 205 $(M+H)^+$. FT-IR (KBr): 3441.77, 2961.78, 1628.32, 1488.33, 1321.99, 1251.12, 1123.98, 707.62 cm^{-1}.

Synthesis of Compound 2. A mixture of compound **1** (7.0 g, 34 mmol) and ethyl 2-chloroacetoacetate (10 mL) was stirred magnetically at room temperature for 24 h. The solvent was washed with saturated salt solution twice and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, and filtered, and the solvent was evaporated under vacuum. The residue was reprecipitated in 50 mL of isopropanol to obtain compound **2** (yield: 84.2%). White crystal. mp 77.4−77.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.73 (s, 1H), 7.61−7.33 (d, 1H), 7.51 (s, 1H), 7.31−7.36 (t, 1H), 7.11−7.13 (d, 1H), 4.22−4.29 (q, 2H), 3.76 (s, 4H), 2.19 (s, 3H), 1.33−1.38 (t, 3H), 1.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.96, 164.27, 157.03, 138.14, 130.71, 130.19, 128.12, 127.04, 91.89, 72.03, 60.23, 31.58, 21.57, 18.10, 14.19. HR-MS (EI, 70 eV): 352.1497 $(M+H)^+$, $C_{17}H_{23}BClNO_4$ requires 351.1409. FT-IR (KBr): 3440.31, 2963.58, 1636.74, 1313.46, 1253.54, 1122.29, 1072.05, 704.80 cm^{-1}.

Synthesis of Compound 3. A mixture of compound **2** (4.0 g, 12 mmol), diethanolamine (1.26 g, 12 mmol), and isopropanol (50 mL) was stirred at 0 °C for 1 h first and then at room temperature for 5 h. The mixture was filtered. To a solution of the residue in ether (30 mL), sulfuric acid solution (15 mL, 0.005 M) was added. The mixture was allowed to react at 0 °C for 30 min. The organic phase was separated, dried over anhydrous sodium sulfate, and filtered, and the solvent was evaporated under vacuum to obtain compound **3** (yield: 70%). White solid. mp 170.7−171.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.80 (s, 1H), 8.02−8.04(m, 1H), 7.66−7.87 (m, 1H), 7.47−7.52 (m, 1H), 7.11−7.26 (m, 1H), 4.23−4.30 (m, 2H), 2.40 (s, 2H), 2.20 (s, 3H), 1.33−1.38 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ167.09, 164.37, 156.71, 138.49, 132.25, 131.29, 128.82, 128.64, 128.306, 92.42, 60.41, 18.06, 14.14. HR-MS (EI, 70 eV): 284.0854 $(M+H)^+$, $C_{12}H_{15}BClNO_4$ requires 283.0783. FT-IR (KBr): 3456.49, 2365.92, 1641.61, 1435.65, 1374.36, 1255.30, 1016.27, 759.77 cm^{-1}.

2.3. Gel Preparation. A weighed amount of the compound **3** in 1.0 mL of organic solvent was placed in a flask fitted with a reflux condenser and heated until complete dissolution of the solid. Compounds that did not dissolve under these conditions were classified as insoluble (I). When cooled to room temperature, the solution was transferred into a closed glass vial. The gelation was simply confirmed by turning the glass vial upside down. The critical gelation concentration (CGC) was determined by measuring the minimum amount of gelator required for the formation of a stable gel at 25 °C. The melting temperature (T_{gel}) of the organogel was determined by an inverted-tube experiment in which the tightly capped vial containing the gel was placed in a water bath and then gradually increasing the temperature at a rate of 1 °C/min. The temperature was noted when the gelated mass started to flow upon tilting of the vial.

2.4. Test of Glucose/pH Sensitive Behavior. The organogels were prepared by gelator (10 mg) in cyclohexane (0.2 mL) and heating at 60 °C until completely dissolved. The gel was obtained by cooling to room temperature to gelate the solvent. Glucose responsiveness of the organogels was carried out by adding glucose solution of different concentration (0, 0.012, 0.024, 0.049, 0.062, 0.123, 0.185, 0.246 mmol/mL) to each organogel. pH-sensitive behavior of the organogels was carried out by adding solution of different pH values to each organogel. The sensitive dynamics curves for the gel were evaluated by online tracking the absorbance of glucose solutions using a UV spectrophotometer.

3. RESULTS AND DISCUSSION

3.1. Self-Assembly and Gelation Behavior. The gelation behavior of the gelator (compound **3**) has been examined in 15 polar and nonpolar solvents (Table 1), which demonstrated

Table 1. Gelation Behavior and CGC in Different Solvents[a]

entry	organic solvent	CGC at 25 °C (mg/mL)
1	cyclohexane	G (24.4 mg/mL)
2	toluene	G (30.0 mg/mL)
3	xylene	G (30.7 mg/mL)
4	dichloromethane	G (100.2 mg/mL)
5	chloroform	G (100.8 mg/mL)
6	tetrachloromethane	G (24.9 mg/mL)
7	diethyl ether	P
8	ethanol	S
9	tetrahydrofuran	S
10	isopropanol	S
11	acetic ether	S
12	acetone	S
13	acetonitrile	S
14	dimethyl sulfoxide	S
15	water	I

[a]G: gel, if the gelator is able to gelate the solvent; S: solution, if the gelator is completely soluble in the solvent; I: insoluble, if the gelator is completely insoluble in the solvent; P: precipitate, if the gelator is soluble in hot solution, but precipitates in cold solution.

that the compound could only gelate in nonpolar solvents such as cyclohexane, dichloromethane, chloroform, tetrachloromethane, toluene, and xylene. Transparent gels as shown in Figure 1f were obtained in dichloromethane or chloroform, whereas translucent or opaque gels were formed in cyclohexane, toluene, xylene or tetrachloromethane. The critical gelation concentration (CGC) was found to depend on the solvent used. For example, the CGC is 2.4 wt % in cyclohexane, and it increases to 10 wt % in chloroform. The gelation process is thermo-reversible, which could be characterized with a gel−sol transition temperature (T_{gel}). The gel in xylene collapsed to

dx.doi.org/10.1021/la4033578 | Langmuir 2013, 29, 13568−13575

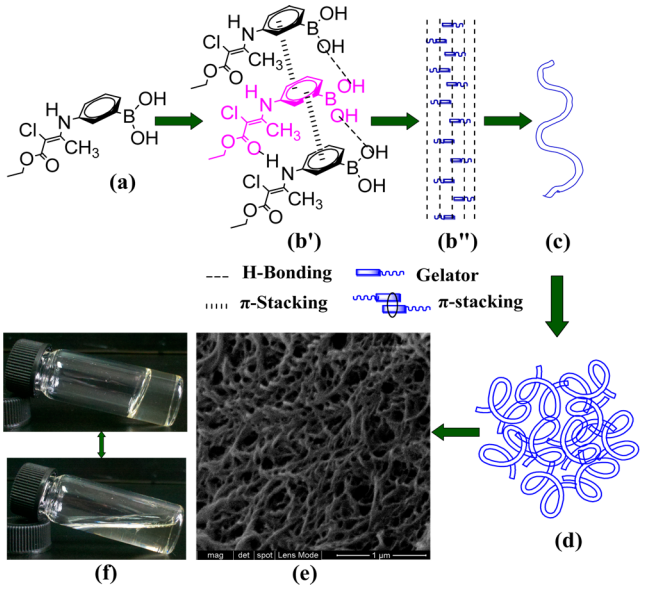


Figure 1. (a) Molecular structure of the gelator; (b′, b″) H-bonding and $\pi-\pi$ stacking interactions between the gelators; (c) self-assembled nanofibers; (d) cross-linked networks of the organogel; (e) SEM image of xerogel; (f) gel−sol transition of compound **3** (50 mg/mL) in cyclohexane.

solution, as the temperature was increased above 60 °C (T_{gel}). The process could be reversed to form gel by cooling to room temperature. Notably, the gelation ability was not affected after numerous cycles, suggesting the good thermo-reversibility. As investigated in the following, this gel−sol transition was a structural transition related to the disruption of noncovalent interactions within the gel network.

SEM image of the air-dried organogel formed in chloroform (Figure 1e) indicates that the gel consists of nanofibers (50−100 nm wide), which assembles into a three-dimensional network. Generally speaking, the solid phase of the gels is a result of solvent immobilization in a three-dimensional fibrillar network. The gelator (compound **3**) has a large conjugated system, which strengthens intermolecular $\pi-\pi$ stacking as well as the $\pi-\pi$ stacking interactions between the gelator and the solvent to immobilize a large volume of organic solvent in the gel.[25−30] UV spectra of varied concentrations of gelator in cyclohexane (2.19−44.17 μmol/mL) helped to further understand the $\pi-\pi$ stacking (Supporting Information SI-1). Red shifts were observed with an increase in concentration of the gelator. For instance, the λ_{max} was 260 nm with the concentration of 2.19 μmol/mL, which red-shifted to 277 nm when the concentration increased to 44.17 μmol/mL. This result indicated the intermolecular $\pi-\pi$ stacking of gelators. However, the fact that gelator molecules only gelate in nonpolar solvents suggests that $\pi-\pi$ stacking interactions between the gelators and solvent can be easily disturbed or destroyed by polar solvents. Although compound **3** contains amino groups, hydroxyl groups, and carbonyl groups, which act as hydrogen-bond donors and acceptors and therefore normally suppress the self-aggregation of the gelator molecules, the hydrogen-bond interactions seem to play a key role in the three-dimensional self-assembly of the gelators.[31−33] Earlier study suggests that the intermolecular hydrogen-bond interactions alone are not strong enough to maintain the gel structure.[34,35] Therefore, the driving forces for the self-assembly of compound **3** in nonpolar solvents are likely both hydrogen-bond interactions and $\pi-\pi$ stacking interactions (Figure 1).

^{1}H NMR spectra in Figure 2 show the gradual high-field shift of protons upon changing the concentration of compound **3**

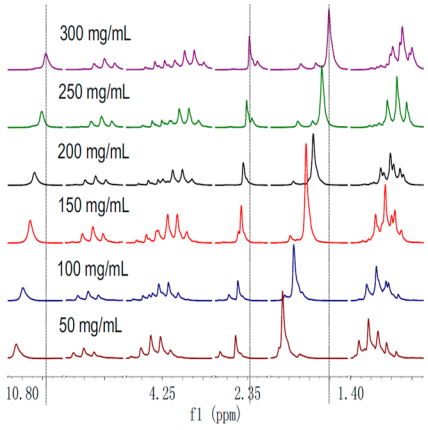


Figure 2. ^{1}H NMR spectra of organogel with different concentrations in $CDCl_3$ (at 25 °C): 50 mg/mL (sol); 100 mg/mL (sol); 150 mg/mL (sol); 200 mg/mL (sol); 250 mg/mL (gel); and 300 mg/mL (gel).

from 50 mg/mL (sol) to 300 mg/mL (gel) in $CDCl_3$. This result implies that hydrogen-bonding exists in the gel phase and such interactions become stronger at a higher concentration. For instance, one proton of a secondary amine at δ = 10.815 ppm at a dilute concentration of 50 mg/mL (sol) high-field shifted to δ = 10.770 ppm at a concentration of 200 mg/mL (gel), and was further high-field shifted to δ = 10.742 ppm at a concentration of 300 mg/mL (gel). The three proton-singlet of the methyl group at δ = 1.356 ppm at a dilute concentration of 50 mg/mL (sol) high-field shifted to δ = 1.273 ppm at the higher concentration of 300 mg/mL (gel).[36−39]

Figure 3 presents the ^{1}H NMR spectra of the gel at different temperatures. At the concentration of 300 mg/mL, the proton in the NH group appeared at δ = 10.752 ppm at 0 °C. As the temperature was increased, the peak became slightly sharp and

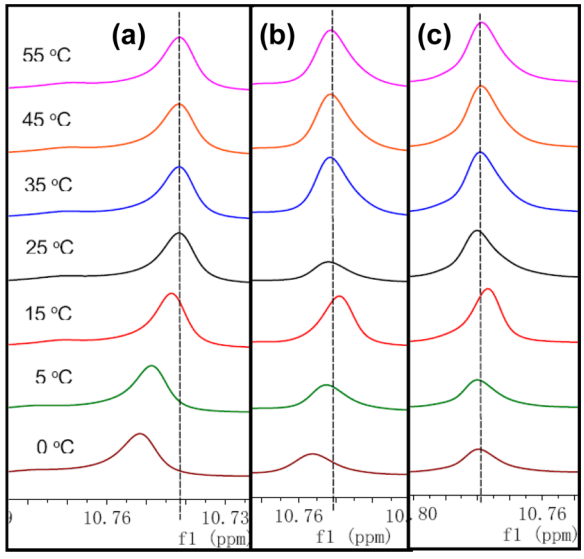


Figure 3. ^{1}H NMR spectra of organogels in $CDCl_3$ at different temperatures, 0−55 °C: (a) 300 mg/mL, (b) 200 mg/mL, and (c) 150 mg/mL.

dx.doi.org/10.1021/la4033578 | *Langmuir* 2013, 29, 13568−13575

shifted to δ = 10.742 ppm at 25 °C. The temperature-induced upfield shift of the NH protons is presumably related to the destruction of the H-bonding. The above chemical shifts suggest the presence of H-bonding between amides and carbonyl groups. H-bonding between amides further strengthens the intermolecular interactions. As the temperature was increased further to 55 °C, there was no distinguished shift of the resonance signals, because the gel has already transformed to sol. In addition, the resonance signals corresponding to the aromatic protons of the benzene units were also gradually shifted upfield (Supporting Information SI-2) as the temperature was increased from 0 to 55 °C.[31,40,41] This result implies that the presence of $\pi-\pi$ stacking owing to the benzene units in the gel phase becomes weak at high temperature. To further characterize the effect of temperature on the formation and intermoleculars interaction of organogels, varying temperature UV spectra of the gels were measured (Supporting Information SI-3). Upon an increase in the temperature, blue shifts of the λ_{max} of gelator were observed ranging from 281 nm at 5 °C to 288 nm at 25 °C, whereas the absorbance intensities varied weakly in gel phase. The blue shifts of the λ_{max} of gelator might be attributed to a gradual dissociation of the molecular aggregates and a collapse of the three-dimensional networks within the organogels. It is strong evidence for the $\pi-\pi$ stacking assisted self-assembly of the gelators in combination with the intermolecular hydrogen-bonding interactions in gels.[29,42,43] As for the gel with the concentration of 300 mg/mL, there was a distinct high-field shift of the proton in NH group as the temperature was increased from 0 to 25 °C. However, the upfield shift of the proton was less obvious for the organogel of 250 mg/mL (Supporting Information SI-4), and no evident shift for the gel of 150 mg/mL (Supporting Information SI-5). Gels of compound **3** with high concentration showed a higher sensitivity to temperature. Additionally, the effect of gelation time on the ^{1}H NMR spectra for the gels was characterized systematically (Supporting Information SI-6). The study indicates that all the signals of protons were gradually shifted downfield when the gelation time was increased from 0 to 60 min for the gel of 300 mg/mL prepared both at 0 and 5 °C. However, the downfield shift was not so obvious for the gel at high temperature or with low compound **3** concentration.

3.2. Glucose-Responsive Behavior. A cyclic diagram of glucose response of the above gel shows gel−sol transition as time evolves, with the phase transitions from two-phase to three-phase, then back to two-phase (Figure 4). The gelator could be recycled conveniently, and the recycling rate was higher than 95%, detected via UV spectrophotometer. With these two phases, the pH of the water phase was first regulated to be lower than the pK_{a1} (3.67) of the gelator. Then, the water phase was extracted by the organic phase thoroughly. The organic phase was separated, dried over anhydrous sodium sulfate, and filtered. A certain amount of the gelator supplemented to the organic phase was heated until completely dissolved, and the gel was regained by cooling to room temperature.

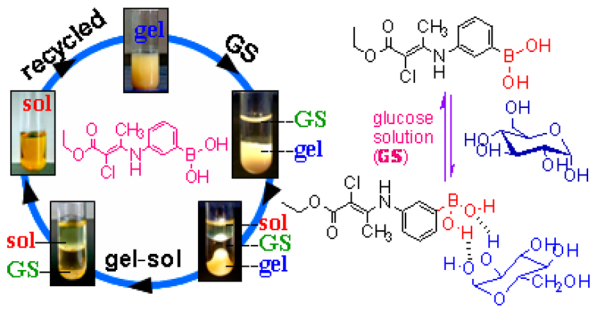


Figure 4. Cyclic diagram of glucose-response and recycling use of the organogel (50 mg of gelator in 1 mL of cyclohexane) in 1 mL of glucose solution (0.185 mmol/mL).

To gain more detailed and accurate information about the glucose-responsive behavior, the glucose-responsive dynamics of the gel was evaluated by online tracking the absorbance of glucose solutions using UV spectroscopy. This analysis is based on the assumption that the achieved glucose response is due to the formation of the PBA−glucose complex, which subsequently prompts the dissolution of the gel. Glucose response of the gel increased with the increasing concentration of glucose, as shown in Figure 5. At a low concentration of 0.012 mmol/mL (critical concentration of venous plasma glucose for diabetes), the gel showed a great sensitivity. The gel had a faster response at higher glucose concentration. The gel also showed much greater response rate as the glucose concentration was increased to 0.185 or 0.246 mmol/mL. The absorbance for both gels has evolved to near the apex after 200 min, where the gels were found to have completely transited to sol. The absorbances for the gel in 0.185 mmol/mL (the molar ratio of glucose/PBA was 1.05:1) and 0.246 mmol/mL (the molar ratio of glucose/PBA was 1.40:1) were similar; therefore, complete PBA−glucose complexes could be generated as the molar ratio of glucose/PBA was greater than 1.0.

The initial glucose-response rate of the gel has been investigated in different glucose solutions. The rapid increase in UV-absorbance illustrated the increasing glucose-response rate with glucose concentration. The absorbance change in a blank control liquid was negligible. In contrast, the absorbance increased from 0.09 to 0.16 within 20 min in a 0.012 mmol/mL glucose solution, and it was from 0.28 to 1.14 in 20 min in a 0.185 mmol/mL glucose solution. It confirms that this organogel has good performance in responding to glucose. When the glucose concentration is greater than 0.012 mmol/mL, the gel shows a prompt initial response, which is a very encouraging property for developing rapid and sensitive closed-loop insulin delivery systems. For diabetes management, insulin must be released when venous plasma glucose becomes greater than 0.012 mmol/mL.[44] This glucose concentration is an important discrimination point for insulin administration and is met by this new LMOG gel. In addition, the sustained response time is defined as the time required for the complete gel−sol transition. The gel in a blank control liquid required 20 h sustained response time, as the glucose concentration was increased to 0.246 mmol/mL (the molar ratio of glucose/PBA was 1.4: 1), the sustained response time fell to 130 min. The result indicates that this phenylboronic acid compound has good sensitivity to glucose, since phenylboronic acid forms much more stable cyclic esters with the adjacent diols of saccharides.

In Figure 6, the response of this new LMOG to different saccharides, total of seven saccharides (i.e., mannitol, galactose, lactose, maltose, sucrose, and fructose) with the concentration of 30 mg/mL, was examined. Interestingly, our system was highly sensitive toward glucose in comparison to other saccharides. Moreover, monosaccharides showed a better response rate than disaccharides. The sustained response time

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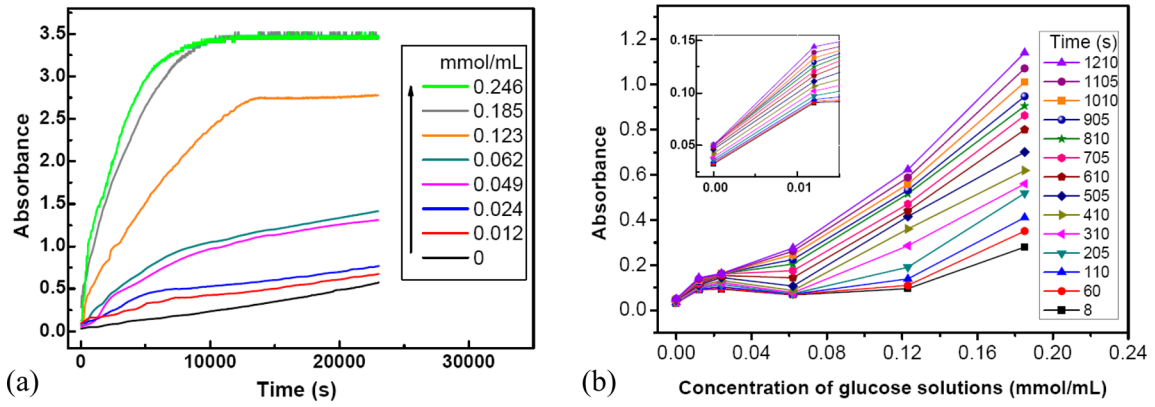


Figure 5. (a) Glucose-response dynamics of the gel in glucose solution (0, 0.012, 0.024, 0.049, 0.062, 0.123, 0.185, 0.246 mmol/mL; 3 mL). (b) Glucose-response speed for the gel in 3 mL different glucose solutions within 20 min. The inset graph is the enlarged part for the gel in 0 and 0.012 mmol/mL glucose solutions. All the gels were made of 20 mg of gelator in 0.4 mL of cyclohexane.

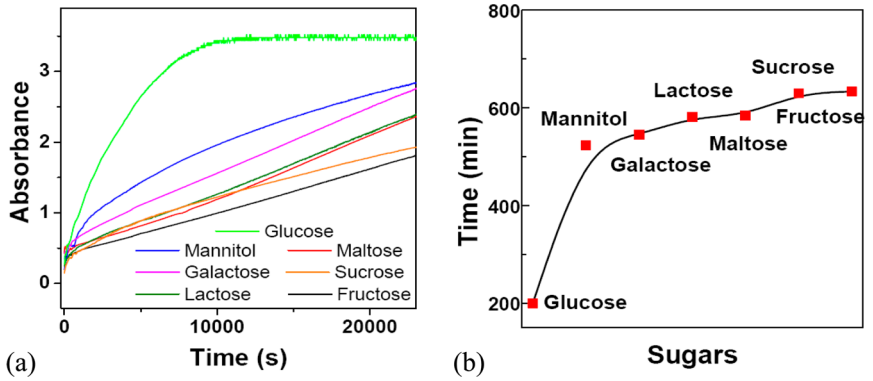
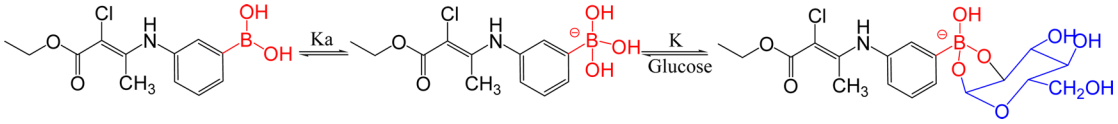


Figure 6. (a) Saccharide response dynamic curve for the gels in saccharide solutions (3 mL, 0.18 mmol/mL). (b) Sustained response time for total gel−sol transition in different seven types of saccharide solutions. All the gels were made of 20 mg gelator in 0.4 mL cyclohexane.

Scheme 2. Reversible Binding of Glucose to Phenylboronic Acid



for glucose is only 200 min, where the time needed for other saccharides ranges from 523 to 633 min. This result illustrates that the newly fabricated organogels have excellent selectivity to glucose.

Glucose response of the above organogel was achieved by incorporating phenylboronic acid functional group into the gelator. The trigonal PBA moiety of the gelator is a Lewis acid. Ionized PBA is in a favorable configuration to undergo bidentate condensation with the cis-diol functional groups of molecules such as glucose (Scheme 2). For the stimuli-sensitive polymer hydrogels, their responsive behavior depends on the swelling of the polymer hydrogel with changes in the physical and chemical parameters of the surrounding environment such as temperature, light, pH, and so on. The reported glucose sensitive materials include polymerized phenylboronic acid materials, such as AAPBA-*co*-(MAH-*β*-CD) copolymer gels, P(NIPAM-AAPBA)-PNIPAM polymer gels, and so on.[45−47] When the PBA groups are anchored to the hydrogel network, the boronate−glucose complex drives the gel swelling response that is proportional to the glucose concentration. In contrast to the polymerized phenylboronic acid gels, the present organogel's response to glucose depends on the disruption of the noncovalent interactions of hydrogen-bonding, *π*−*π* stacking interactions and van der Waals forces within the gel network. The formation of the PBA−glucose complexes destroys the intermolecular physical interactions, thereby breaking the one- to three-dimensional self-assembly of the gelators, which subsequently cause the gelators to dissolve in the organic solvent. Further illustration of the glucose on the assemblies in the nano-microscale was available by comparing the aggregation morphology before and after the addition of glucose solution. The organogel was collected after the addition of glucose solution (0.123 mmol/mL) for 1 h and dried. Compared with the continuous nanofibers of the xeogel with no glucose solution (Figure 1e), the integrity of the fibers was damaged with the addition of glucose solution. Parts of the fibers were surface corroded or fractured (Supporting Information SI-7). This disruption of fibers might be based on the broken of the aggregation between layers. Since the X-ray powder diffraction pattern of the xeogels before and after the addition of glucose solution, both revealed a prominent peak at d = 3.75 Å, which represented typical *π*−*π* stacking interaction in the xerogel (Supporting Information SI-8).[36] This exhibited that the gel

dx.doi.org/10.1021/la4033578 | *Langmuir* 2013, 29, 13568−13575

was directly damaged to be sol exposed to glucose solution, or to be fractured fibers which still kept aggregated layers.

To support the above hypothesis, the energy profile of hydrogen-bonded complexes is calculated in Figure 7 (Gaussian

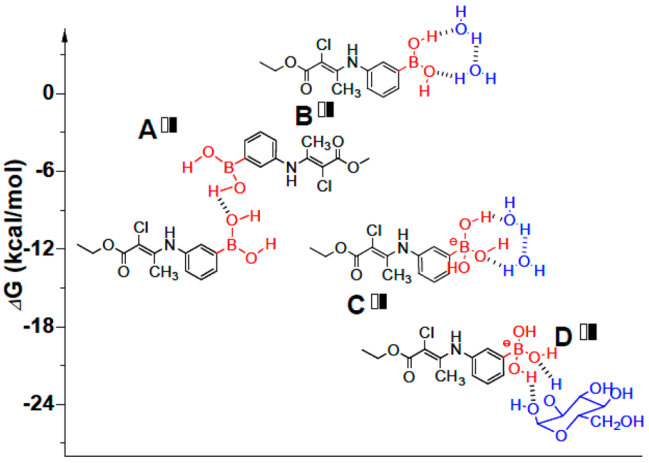


Figure 7. Energy profile (kcal/mol) of hydrogenbonded complexes of A–D.

09 software package, M06/6-31G*(LANL2DZ) method, the relative energies are the free energy in the gas phase (ΔG_{298})). Here, only the hydrogen-bonded complexes of boric acid group were considered in order to simplify the calculation process. Nevertheless, it allows us to examine the thermodynamic parameters related to the glucose-responsive behavior of the organogel.[48] Complex A (ΔG = −2.4812 kcal/mol) is prevalent in the gel, forming through hydrogen-bonding interactions between boric acid groups of the gelator molecule itself. However, with the addition of an aqueous solution of glucose to the gel, the hydrogen-bonded complexes of boric acid groups undergo changes. Three kinds of hydrogen-bonded complexes may be produced, that is, complex B (ΔG = −1.3222 kcal/mol) formed between boric acid and water molecules, complex C (ΔG = −16.1433 kcal/mol) formed between ionized boric acid and water molecules, and complex D (ΔG = −18.4777 kcal/mol) formed between ionized boric acid and glucose molecule. Judging from the energy profile, the hydrogen-bonded complexes of C and D of ionized boric acid groups have much lower energy than those of A and B. ΔG values that are large and negative indicate that the formation of such a specific complex is favored. Thus, the formation of complex B is least favored for this process, which coincides with the relative stability of the gel in a blank solution. Complexes C and D have the largest values of ΔG, and are negative. The addition of glucose solution into the gel or adjusting the pH may prompt the boric acid ionization and then the breakage of hydrogen bonds in complex A, producing the lower energy complexes C and D. This system is thermodynamically oriented.

3.3. pH Sensitivity Behavior. pH-sensitive behavior of the above gel was evaluated in Figures 8. The study was performed with an online UV spectroscopy. These experiments show that the organogel has the greatest sensitivity in pH = 11 and pH = 13 solutions. On the other hand the pH-response is near the same within the pH range of 5 to 9, i.e. a stable organogel could be obtained within such pH range. Such a feature may be associated with the pK_a of the gelator (pKa1=3.67, pKa2=10.01). Further investigation on the initial pH-response rate in different pH solutions was carried out (Supporting Information SI-9). The rapid increase in UV-absorbance suggests the increasing pH-response rate at higher pH. Specifically, the absorbance in a blank liquid was nearly constant, whereas the absorbance increased from 0.1966 to 1.6812 within 1320 s in a pH = 11 solution, and raised from 0.6544 to 2.9599 within 1320 s in a pH = 13 solution. The above studies confirm that this organogel had good performance in pH-response. The rapid response of the gel at high pH may be attributed to the PBA ionization and acceleration of hydrogen-bonding destruction, which might favor the gel to sol transition.[17,49] Therefore, the sustained response time of the organogel in pH = 13 solution is less than 55 min, compared with 864 min of the sustained response time at pH = 7.

4. CONCLUSIONS

In summary, we developed a new phenylboronic acid based low molecular gelator which can interact with several nonpolar solvents to assemble into a three-dimensional network. ^{1}H NMR spectroscopy study suggests that the driving forces of the aggregation are hydrogen-bonding and π–π stacking interactions. These PBA based organogels show sensitivity to both glucose and pH, which could be potentially applied as functionally stimuli-responsive materials. This work provides a completely new glucose-sensitive low molecular weight organogel besides glucose-sensitive polymer gel. These LMOGs might

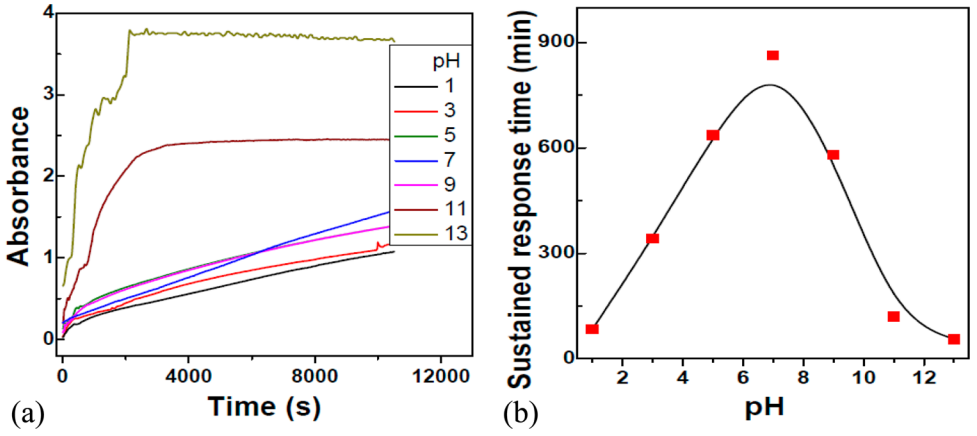


Figure 8. (a) pH-response dynamic curve for gel in 3 mL solutions with different pH values(1, 3, 5, 7, 9, 11, 13). (b) Sustained response time for total gel–sol transition in 3 mL different pH solutions. All the gels were made of 20 mg of gelator in 0.4 mL of cyclohexane.

dx.doi.org/10.1021/la4033578 | Langmuir 2013, 29, 13568–13575

overcome the defects of glucose-sensitive polymer gels, due to the distinguished difference between them in gel formation and gel performance. We expect a better application in areas such as a new kind of smart sensors or devices for the insulin self-tuning controlled release system, after more research on improving and optimizing the characteristics of glucose-sensitive LMOGs.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental details. 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.

■ ACKNOWLEDGMENTS

This work was supported by grants from the National Natural Science Foundation of China (No. 21272176, 21202122), the Science and Technology Project of Zhejiang Province (No. 2013C33188), and the Fresh Talent Program of Zhejiang Province (No. 2011R424046).

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