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Synthesis, self-assembly and characterization of a new glucoside-type hydrogel having a Schiff base on the aglycon

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Abstract—A new hydrogel based on a substituted phenyl glucoside with a Schiff base in the aglycon was synthesized, and the self-assembling characteristics was studied. FTIR spectra, UV–vis absorption spectra and X-ray diffraction (XRD) revealed that π–π interactions between the Schiff base moieties, hydrogen bonds, and the interdigitated interactions between hydrophobic chains had effects on the formation of the self-assembling hydrogel. Scanning electron microscopic (SEM) and transmission electron microscopic (TEM) observation showed that the three-dimensional hydrogel network was constructed from nanotubes with inner diameters of ca. 75 nm and wall of ca. 20 nm.

Keywords: Sugar derivative; Glucoside; Hydrogel; Self-assembly; Nanotubes

1. Introduction

Gels derived from low-molecular-mass compounds have attracted considerable interest in recent years on account of their unique features and potential applications for new organic soft materials,[1] template synthesis,[2] drug delivery,[3] separations and biomimetics.[4] Compounds with wide structural diversities concluding carbohydrates, amino acids, ureas, and cholesterols have been summarized[5] and reported[6–15] to gelatinize organic liquids efficiently. These organogels or hydrogels can self-assemble into nanoscale superstructures such as fibers, rods, ribbons, and tubes. The supramolecular gels are based on the spontaneous, thermoreversible self-assembly of low-molecular-weight molecules under nonequilibrium conditions. Noncovalent interactions give rise to the formation of superstructures, which subsequently entrain and immobilize the solvent inside the interstices of a three-dimensioned network.[16,17] Most organogelators are difficult to dissolve in water on account of their low solubility or insolubility. Therefore, only a limited number of hydrogels composed of such aggregates have been reported, but hydrogels have attracted extensive interest because of their applications for tissue engineering and the development of new materials that reversibly respond to various external stimuli.[18]

Recently, Shinkai and co-workers[6,7] have reported a series of hydrogels comprised of the derivatives of glucose. The mechanism for the formation of the self-assembled structure of those hydrogels have also been extensively discussed. It was found that the hydrogen bonding between the hydroxyl groups of the sugar moiety and the amide groups stabilized the aggregates and determined the overall morphologies. The main morphologies of the hydrogels thus obtained were fibers and twisted ribbons, while only a few tubular structures have been reported.

Hollow tubular structure of nanoscale dimensions may offer a variety of applications in chemistry, biochemistry, and material science. In this work, we synthesized a new compound a phenyl β-D-glucopyranoside

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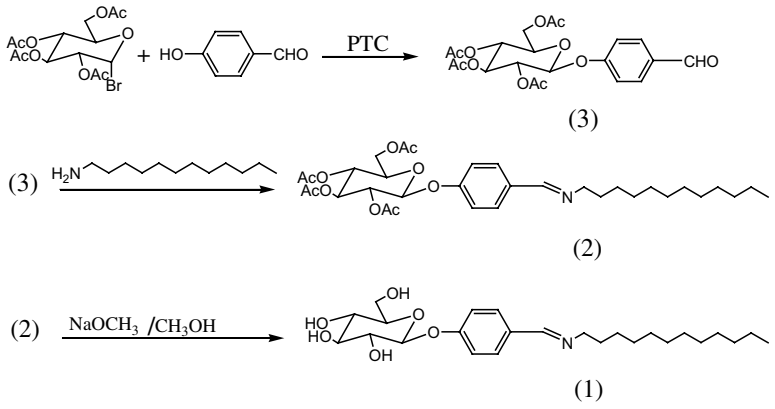

Scheme 1. The synthesis route and structure of compound **1**.

with a Schiff base component on the aglycon (compound **1**, as shown in Scheme 1). Compound **1** was designed as an aqueous gelator to self-assemble into tubular structure. Here, the introduction of conjugated Schiff base units into the glucose derivative replaced the traditional amide groups and serves to increase the rigidity of the molecule, which should be favorable for the molecules to pack into cylindrical structure via π–π interactions. FTIR spectra, UV–vis absorption, and X-ray diffraction (XRD) confirmed that the intermolecular hydrogen bonding, π–π stacking, and interdigitated interactions of hydrophobic chains had an effect on the process of aggregation. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) gave the tubular morphologies of the hydrogel thus obtained.

2. Results and discussion

Hydrogen-bonding-directed self-assembly is a well-studied mechanism for superstructure formation with amphiphiles in an arranged system. In compound **1**, π–π interaction between the Schiff base units may play an important role in directing the formation of the hydrogel, except for the hydrogen bonds between hydroxyl groups. To research the driving forces and mechanism for the self-organization of hydrogel **1** that came from compound **1**, FTIR and UV–vis spectra were measured. In FTIR spectra (not shown), the absorption of ν_{as} (CH_2) and ν_s (CH_2) stretching vibration for alkylene chains were 2921 and 2851 cm^{-1}, respectively, suggesting an all-*trans* conformation of the hydrogel.[19] Furthermore, the appearance of the OH vibration peak at 3412 cm^{-1} confirmed the presence of the intermolecular hydrogen bonding in the glucose.[20] In the UV–vis absorption spectra (as shown in Fig. 1), the λ_{max} for the Schiff base unit of compound **1** in water appeared at 261 nm in the sol phase and at 267 nm in the hydrogel phase. This slight but significant red shift phenomena in the gel phase suggested that the chromophores of the

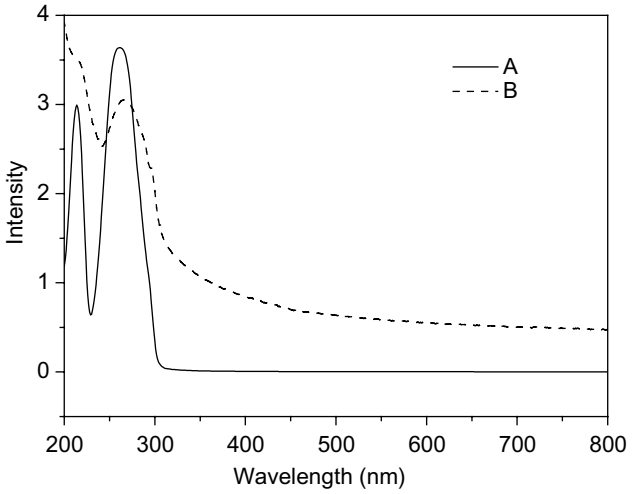

Figure 1. UV–vis absorption spectra: (A) Compound **1** in water in the sol phase [0.05 (wt/vol)%], and (B) compound **1** in water in the hydrogel phase [0.2 (wt/vol)%].

Schiff base assembled into the J-type aggregation mode via π–π stacking.[21] Therefore, the π–π stacking between the Schiff base moieties was favored, and J-type aggregation took place.

To reveal how the molecules packed to the tubular self-assemblies, XRD was investigated (as shown in Fig. 2) for the xerogel obtained from water by a freezing method. The small-angle diffraction comes from the characteristic lattice repeat, that is, the long-range ordering of the hydrogel, whereas the wide-angle region is indicative of hydrocarbon chain packing, that is, the short-range ordering. In Figure 2, the small-angle diffraction pattern of the xerogel showed a series of sharp reflection peaks, indicating the layered organization. The long *d*-spacing of the aggregation obtained by the XRD method was about 4.08, 2.02, and 1.34 nm, which are almost exactly 1:0.5:0.33, and the distance was smaller than twice the extended molecular length of compound **1** (2.5 nm by CPK molecular modeling), but larger than the length of one molecule. It suggested that

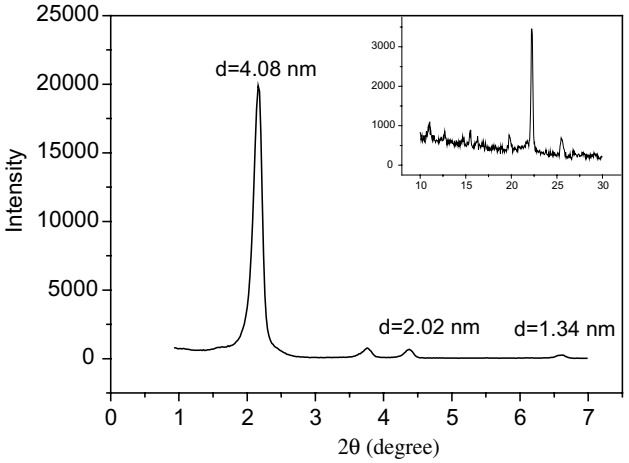

Figure 2. The small-angle XRD pattern of xerogel prepared from hydrogel **1** and wide-angle diffraction (inset).

the self-assembled compound **1** form a bilayer structure with interdigitated lipid chains by a hydrophobic interaction. On the other hand, the diffraction of the wide-angle region also gave a series of sharp peaks, supporting the view that long alkyl chain groups presumably were packed into highly ordered layer packing through the interdigitated hydrophobic interaction.[22] On the basis of XRD, FTIR, and UV–vis results, the hydrogel was found to be stabilized by combination of the hydrogen bonding, π–π interactions, and hydrophobic forces. Therefore, a possible self-assembling mode of the hydrogel based on the bilayered arrangement can be obtained upon the above results (as shown in Fig. 3).

Figure 4a–e showed the pictures of polarized light microscopy, TEM, and SEM of the hydrogel, and a tubular structure and some slightly coiled tubular structures were obtained. The nanotubes of the self-assembled hydrogel had tens of micrometers of length, inner diameters of ca. 75 nm and wall of ca. 20 nm. And the entangled tubes created a three-dimensional network structure, which indicated that the hydrogel is formed by the entrapment of water (solvent) molecules into the space of the three-dimensional networks. The mechanism of the nanotube formation can be speculated upon the above results (as shown in Fig. 5). The wall of the nanotube is packed by ca. five lipid interdigitated bilayers, and the packed bilayers encircle to form a nanotube.

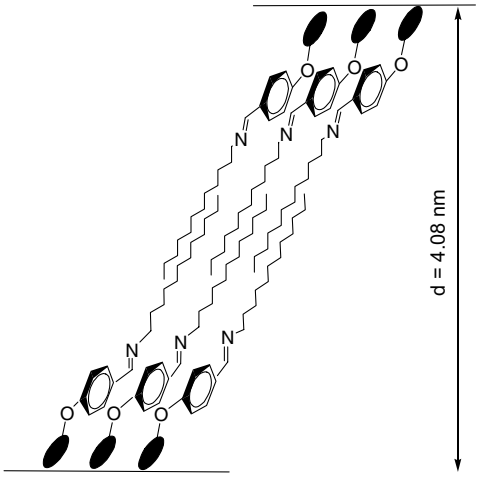

Figure 3. The possible molecular self-assembling packing mode for the hydrogel **1**.

3. Conclusions

In this paper, a new kind of hydrogel, a phenyl glycoside with a Schiff base derivatized aglycon, was synthesized, and the characterization of hydrogel was discussed. Different from the usual hydrogel of glucoamides, the main driving forces for the self-assembly are not only hydrogen bonding, but also π–π interactions between the Schiff base moieties. UV–vis absorption spectra confirmed the interaction of the Schiff base units that could assemble into a J-aggregation via π–π stacking in the hydrogel phase. The XRD pattern revealed three ordered reflection peaks with a long period of 4.08 nm, which suggested a highly ordered bilayered packing with an interdigitated hydrophobic chain. SEM and TEM revealed the tubular morphologies of the self-assembled hydrogel with inner diameters of ca. 75 nm and wall of ca. 20 nm that was stacked by ca. five lipid interdigitated bilayers.

4. Experimental

4.1. Measurements

^{1}H NMR spectra were determined with Varian-300 EX and JEOL JNM-500EX instruments. Electrospray ionization mass spectra (ESIMS, positive-ion mode) were obtained using a Hitachi M-250 mass spectrometer. UV–vis absorption spectra were recorded with a Shimadzu UV-2201 UV–vis spectrophotometer. Fourier-transform infrared (FTIR) spectra were measured at room temperature on a Nicolet Impact 410 FTIR spectrometer. X-ray diffraction (XRD) patterns were obtained on a Japan Rigaku D/max-γA. XRD equipped with graphite monochromatized CuKα radiation ($\lambda = 1.5418$ Å), employing a scanning rate of 0.02°/s in the 2θ range from 0.7° to 10° and 0.05°/s in the 2θ range from 10° to 50°. The measured sample was prepared by casting the hydrogel on silicon and dried at room temperature. Scanning electron microscopy (SEM) was taken with a Japan Hitachi model X-650 San electron microscope. The sample for these measurements was prepared in a 0.5-mL bottle and frozen in liquid nitrogen.

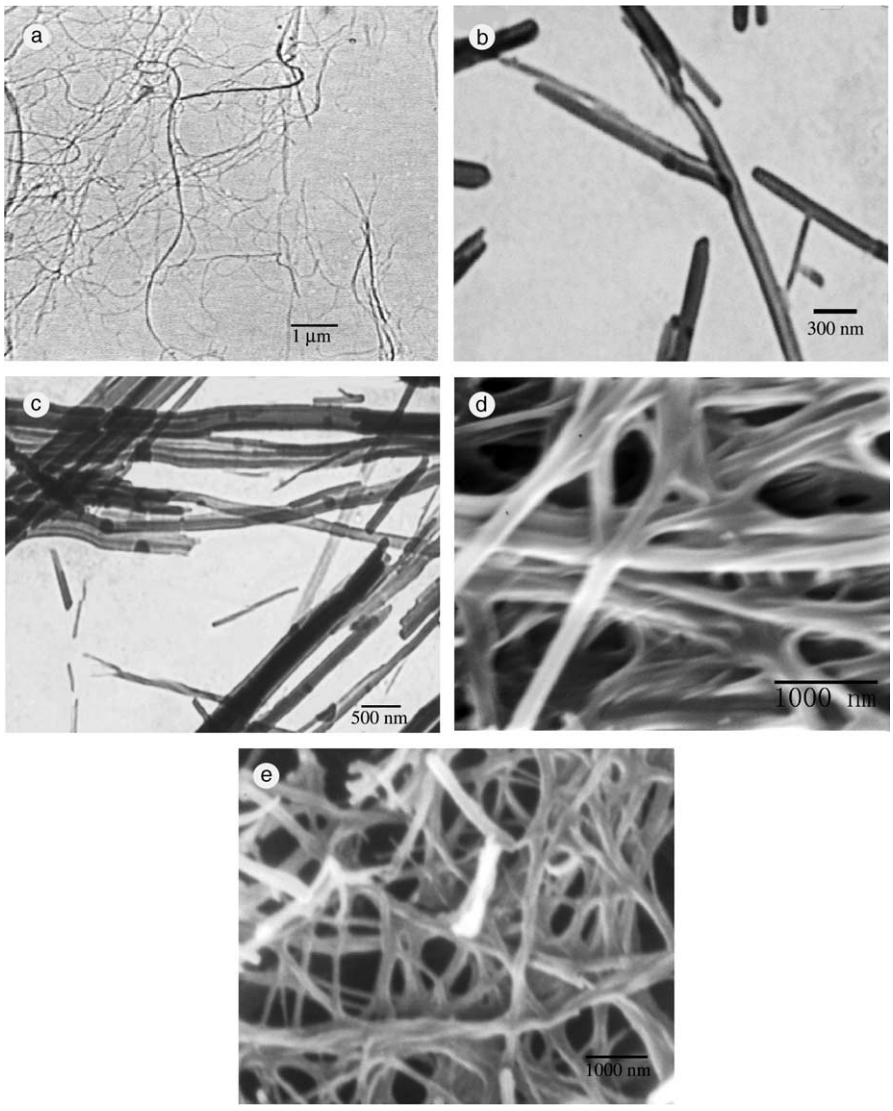

Figure 4. The morphological pictures of hydrogel **1** [0.2 (wt/vol) %]: (a) polarized light microscopy, (b and c) TEM, and (d and e) SEM.

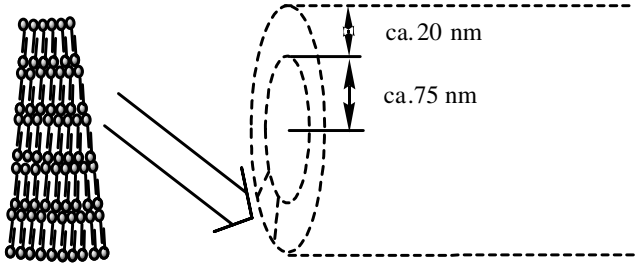

Figure 5. The aggregation model of the tubular hydrogel **1**.

The frozen specimens were evaporated by a vacuum pump, and then the dry samples were coated by gold. Transmission electron microscopy (TEM) was taken with a Hitachi modes H600A-2 apparatus by wiping the gel onto a 200-mesh copper grid, followed by naturally evaporating the solvent.

4.2. Materials

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide was prepared according to the standard literature procedures[23] and identified by FTIR and ^{1}H NMR spectral evidence. The completed process of the synthesis is shown in Scheme 1.

4.3. Synthesis

4.3.1. Synthesis of *p*-formylphenyl (2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranoside (3). The method of phase-transfer catalysis was applied in this synthesis. Tetrabutylammonium bromide (Aldrich) (1.2898 g, 4 mmol) was dissolved in 1:1 water–chloroform (20 mL), and the mixture was stirred and heated to 40 °C. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (8.22 g, 0.02 mol) was dissolved in $CHCl_3$ (15 mL, designated as solution

A) and *p*-hydroxylbenzaldehyde (Aldrich) (2.44 g, 0.02 mol) was dissolved in water (20 mL) containing 6.9 g of K_2CO_3 (designated as solution B). Then solutions A and B were simultaneously dropped into the above mixture, and the system was heated to 60 °C and stirred vigorously. After 6 h, the organic phase was separated and washed with NaOH (10 mL, 5%) three times. The solution thus obtained was dried with anhyd Na_2SO_4. The solvent was evaporated under reduced pressure and the solid was recrystallized in ethanol. The white crystalline product (5.0 g, 55%) was collected and dried in a vacuum: mp 142–143 °C; FTIR: 2963.5, 2746.8, 1750.5, 1737.6, 1692.6, 1601.0, 1222.3 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.933 (s, 1H, CHO), 7.861 (d, 2H, ArH), 7.106 (d, 2H, ArH), 5.157–5.343 (m, 4H, CH), 4.159–4.331 (m, 2H, CH), 3.926–3.961 (m, 1H, CH), 2.081 (s, 3H, CH_3CO), 2.070 (s, 3H, CH_3CO), 2.067 (s, 3H, CH_3CO), 2.052 (s, 3H, CH_3CO). ESIMS: Calcd for $C_{21}H_{24}O_{11}$ m/z 452.13; found m/z 453.1 [M+H].

4.3.2. Synthesis of 4-(*N*-dodecylimino)methylphenyl (2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranoside (2). A mixture of compound **3** (0.30 g, 0.66 mmol), dodecylamine (0.12 g, 0.66 mmol) and a drop of HOAc in 15 mL of EtOH were refluxed for 3 h. The solution was filtered after cooling to room temperature, and the filtrate was dried in a vacuum evaporator to give a product (0.38 g, 93%): mp 112–116 °C; FTIR: 2921.4, 2850.7, 1746.7, 1647.22, 1607.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.204 (s, 1H, CH=N), 7.712 (d, 2H, ArH), 7.032 (d, 2H, ArH), 5.124–5.316 (m, 4H, CH), 4.148–4.306 (m, 2H, CH), 3.886–3.919 (m, 1H, CH), 3.591 (t, 2H, NCH_2), 2.087 (s, 3H, CH_3CO), 2.066 (s, 3H, CH_3CO), 2.060 (s, 3H, CH_3CO) 2.045 (s, 3H, CH_3CO), 1.251–1.324 (m, 20H, CH_2), 0.878 (t, 3H, CH_3). ESIMS: Calcd for $C_{33}H_{49}N_4O_{10}$ m/z 619.34; found m/z 620.3 [M+H].

4.3.3. Synthesis of 4-(*N*-dodecylimino)methylphenyl β-D-glucopyranoside (1). Compound **2** (0.3 g) was refluxed in MeOH (10 mL), and 0.2 mL of MeOH containing 0.2 mol/L $NaOCH_3$ was added. After refluxing for 1 h, the solvent was evaporated under reduced pressure, and the solid that was obtained was purified by column chromatography on silica gel with 1:9 MeOH–$CHCl_3$ to give pure **1** (0.20 g, 96%). FTIR: 3334.7, 2921.8, 2851.7, 1642.8, 1606.4 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 8.25 (s, 1H, CH=N), 7.65 (d, 2H, ArH), 7.06 (d, 2H, ArH), 5.37 (s, 1H, OH), 5.15 (s, 1H, OH), 5.07 (s, 1H, OH), 4.92 (d, 1H, CH), 4.58 (s, 1H, OH), 3.17–3.68 (m, 6H, CH), 3.25 (m, 2H, NCH_2), 1.23–1.58 (m, 20H, CH_2), 0.85 (t, 3H, CH_3). ESIMS: Calcd for $C_{21}H_{24}O_{11}$ m/z 451.3; found m/z 452.1 [M+H].

4.4. Formation of hydrogel

Compound **1** (1 mg) and 0.5 mL of water containing a trace amount of EtOH (0.05 mL) were put in a septum-capped sample tube and heated until the solid was dissolved. The solution was cooled at room temperature for 5 h and the gel was formed.

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