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Supramolecular hydrogels containing inorganic salts and acids

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Abstract—L-Lysine-based hydrogelators can form supramolecular hydrogels over a wide pH range and contain inorganic salts and acids, especially, **3** forms hydrogels containing 1 M HCl and H_2SO_4 at 1 g/L.
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Hydrogels have been extensively investigated because of their potential applications for superabsorption, drug delivery materials, and tissue engineering scaffolds and the development of new materials that reversibly respond to various external stimuli.[1,2] They have been traditionally constructed using high molecular weight, hydrophilic polymers that are physically cross-linked through entanglements or chemically cross-linked into a network, and contain a large amount of water that fills the interstitial spaces of the network. Recently, the construction of hydrogels via the self-assembling of low molecular weight compounds (hydrogelators) has been explored.[3] Such hydrogelators self-assemble into nano-scaled superstructures (nanofibers, nanoribbons, nano-tapes, nanosheets, etc.) and then produce gel networks with tunable, responsive properties. We have reported that L-lysine-based hydrogelators with a positively charged terminal group such as pyridiniums and imidazoliums can gel pure water at 3 g/L.[4] In order to use hydrogelators in many fields, the hydrogelation ability should be investigated under the various conditions (e.g., pHs, ionic strengths, etc). We now describe the hydrogelation in aqueous solutions containing inorganic salts and acids and the influence of the additives on the thermal stabilities of the hydrogels.

Compounds **1**–**3** were prepared from commercially available N^ε-lauroyl-L-lysine from the Ajinomoto Co.,

Ltd, according to a synthetically simple approach.[†] The effects of pHs on the hydrogelation of **1**–**3** and the values of the minimum gelation concentration (MGC; g/L) necessary for the hydrogel formation are shown in Table 1. All the compounds could not gel a strong alkali solution. Compound **1** had the smallest MGC value in pure water (pH = 7),[4a] and the hydrogelation ability decreased with the increasing alkalinities and acidities. Namely, **1** can form hydrogels in aqueous solutions with various pH values below pH 11. In contrast, although **2** and **3** had lower hydrogelation abilities in pure water compared with **1**, they showed good hydrogelation abilities at low pH; especially, **3** gelled an aqueous

[†] The synthetic procedure of gelator **1** are described in an earlier publication.[4c] N^ε-*Lauroyl-N^α-(11-bromoundecanoyl)-L-lysine*: N^ε-Lauroyl-L-lysine (60 mmol) was dissolved in water (500 mL) containing NaOH (300 mmol), and ethyl ether (300 mL) was then added. 11-Bromoundecanoyl chloride was added to the ether layer. The biphasic solution was vigorously stirred at 0 °C for 1 h and then at room temperature for 23 h. The resulting solution was acidified by concd HCl (pH≈1). The white precipitate was filtered and washed with water. The product was obtained by two recrystallizations from ethanol–ether (85%). N^ε-*Lauroyl-N^α-(10-bromodecylaminocarbonyl)-L-lysine ethyl ester*: To a dry toluene of N^ε-lauroyl-L-lysine ethyl ester (20 mmol), 10-bromodecyl isocyanate (22 mmol) was added. The mixed solution was heated at 100 °C for 10 min. The resulting solution was evaporated to dryness. The product was obtained by two recrystallizations from ethanol–ether (96%). *Gelators* **2** *and* **3**: A pyridine solution (200 mL) of N^ε-lauroyl-N^α-(11-bromoundecanoyl)-L-lysine or N^ε-lauroyl-N^α-(10-bromodecylaminocarbonyl)-L-lysine ethyl ester (50 mmol) was heated at 100 °C for 24 h under a nitrogen atmosphere. The resulting solution was evaporated to dryness. The product was obtained by recrystallization from ethanol–ether (98%).
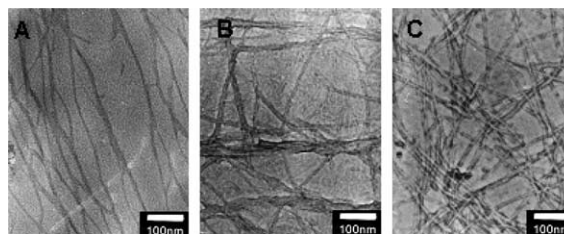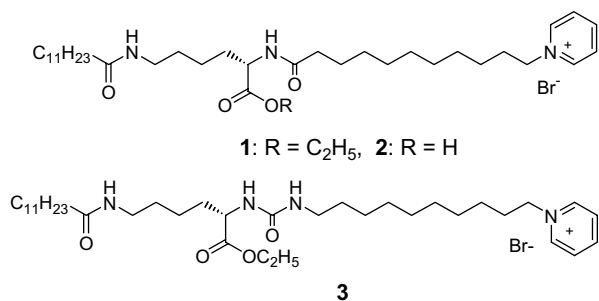
1: R = C$_2$H$_5$, **2**: R = H

3

Figure 1. TEM images of dried gels prepared from **1** (A), **2** (B), and **3** (C) in pure water. [Gelator] = 1.0 wt %.

solution of pH = 0 at 1 g/L, and the hydrogelation ability was ca. 12 times better than that in pure water.

Table 2 lists the hydrogelation properties of **1–3** in saline and aqueous solutions containing various acids and inorganic salts. The hydrogelation ability of **1** in saline and aqueous solutions containing 1 M CH$_3$CO$_2$H, NaCl, and KCl nearly equaled that in pure water, while it decreased in aqueous acid solutions. On the other hand, **2** and **3** showed good hydrogelation abilities for aqueous solutions of acids and salts[5]; in addition, **3** could also gel the aqueous solution containing 4 M HCl less than 1 wt % (data not shown). In other words, **2** and **3** are acid- and salt-triggered hydrogelators. Practically, 10 g/L (1 wt %) aqueous solutions of **2** or **3** immediately gel by injection of aqueous solutions containing inorganic salts and acids.

Figure 1 shows the TEM photographs of the hydrogels of **1**, **2**, and **3** prepared in pure water. In pure water, **1** and **3** create a three-dimensional network entangled by the self-assembled nanofibers with a diameter of ca. 10–40 nm. In contrast, the self-assembled nanofibers of **2** have larger diameter (10–90 nm) than other nanofibers, although **2** also creates a three-dimensional network.

Compounds **1** and **3** self-assemble into the nanofibers through a 1D hydrogen bonding, while the nanofibers of **2** are probably formed through 2D or 3D hydrogen bonding because of its carboxylic acid group. The carboxylic acid group capable of hydrogen bonding might play a role in the entanglement of the nanofibers, resulting in the formation of large nanofibers.

The strength of hydrogels based on the gelators is one of the important properties of the gels. We measured the strength of the hydrogels.[6] Table 2 lists the strength of hydrogels based on **1–3** at 15 g/L. Compared with the hydrogels of pure water, the strength of the hydrogels containing acids and salts increased, and **2** formed the rigid hydrogels compared with **1** and **3** in all solutions. The gel strength will correspond to the rigidity of self-assembled nanofibers; namely, the hydrogel formed by rigid nanofibers shows high gel strength. Therefore, the nanofibers based on **2** is relatively rigid, being supported by the fact that the nanofibers have large diameter in TEM photograph. In addition, the presence of inorganic salts and acids accelerates the formation of rigid nanofibers due to the reduction of electrostatic repulsion between pyridinium groups, resulting in high gel strength.

Table 1. Effects of pH on hydrogelation of **1–3**[a]

	pH[b]														
	0	1	2	3	4	5	6	7[c]	8	9	10	11	12	13	14
1	7	6	6	6	6	5	5	3[d]	5	5	5	6	25	S	S
2	3	6	7	12	15	15	15	15	17	17	17	17	25	S	S
3	1	2	9	10	10	10	12	12	12	15	15	20	VS	VS	S

[a] Values denote minimum gelation concentration necessary for hydrogel formation (g/L).
[b] pH values were calculated from the amount of added HCl (pH 1–6) and NaOH (pH = 8–14).
[c] In pure water.
[d] Ref. 4a. VS: viscous solution at 3 wt %. S: solution at 3 wt %.

Table 2. Hydrogelation properties of **1–3** in water, saline, and aqueous solutions containing inorganic salts and acids (1 M) and gel strengths at 25 °C

	MGC[a]							Gel strength (kPa)[b]						
	H$_2$O	Saline	HCl	H$_2$SO$_4$	AcOH	NaCl	KCl	H$_2$O	Saline	HCl	H$_2$SO$_4$	AcOH	NaCl	KCl
1	3[c]	4	7	6	2	4	3	0.54	1.08	3.23	4.66	31.02	1.26	1.31
2	15	15	3	3	15	2	3	6.10	35.3	19.36	19.57	11.74	41.9	42.1
3	12	7	1	1	12	4[d]	4[d]	0.18	5.56	16.32	16.47	1.11	4.48[d]	4.51[d]

[a] MGC is minimum gel concentration necessary for hydrogel formation (g/L).
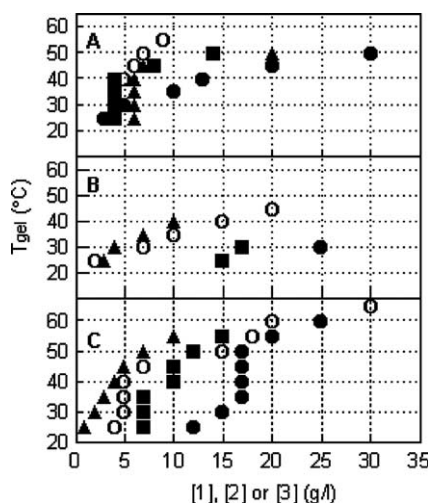[b] [Gelator] = 15 g/L.
[c] Ref. 4a.
[d] [NaCl] = [KCl] = 0.1 M.

Figure 2. T_{gel} for **1** (A), **2** (B), and **3** (C) in pure water (●), saline (■), 1 M H$_2$SO$_4$ aq (▲), and 1 M or 0.1 M NaCl aq (○).

Figure 3. VT-FT-IR spectra of **3** in pure water (3.0 wt%).

Very interestingly, we found that the hydrogels containing salts had better thermal stabilities than those of pure water. Figure 2 shows the dependence of T_{gel} on the concentration of **1**, **2**, and **3** in pure water, saline, 1 M H$_2$SO$_4$, and 1 M NaCl.[7] At $T_{gel} = 50$ °C, **1** forms hydrogels at 30 g/L in pure water, 14 g/L in saline, 20 g/L in 1 M H$_2$SO$_4$, and 7 g/L in 1 M NaCl. At $T_{gel} = 55$ °C, **3** forms hydrogels at 20 g/L in pure water, 15 g/L in saline, 10 g/L in 1 M H$_2$SO$_4$, and 18 g/L in 1 M NaCl. These results indicate that the hydrogels formed by **3** have better thermal stabilities than those of **1**. Moreover, it is surprising that the 0.1 M NaCl hydrogel form by **3** shows $T_{gel} = 65$ °C at 30 g/L. Generally, the gelators possessing urea groups form bifurcated hydrogen bonds in the nanofibers with thermal stability.[8] Therefore, the high thermal stabilities of the hydrogels based on **3** are caused by strongly bifurcated hydrogen bonding through the urea groups. In contrast, the hydrogels based on **2** were thermally unstable ($T_{gel} = 30$ °C at 25 g/L in pure water, $T_{gel} = 30$ °C at 17 g/L in saline, $T_{gel} = 40$ °C at 10 g/L in 1 M H$_2$SO$_4$, and $T_{gel} = 45$ °C at 20 g/L in 1 M NaCl). According to a recent report by Shinkai and co-workers,[9] a 2D and 3D hydrogen bonded network produce a thermally unstable gel. Therefore, the hydrogels based on **2** are thermally weak, though they have mechanical strength.

Figure 3 shows the various temperature (VT) FT-IR spectra of **3** in pure water (3.0 wt%). At 25 °C (hydrogel), the absorption bands of the amide I (vC=O) and urethane carbonyl appear at 1634 and 1607 cm^{-1}. With increasing temperature up to 60 °C, the IR band of the amide I shows slight decrease in intensity and no frequency shift, while that of the urethane carbonyl slightly decreases and shifts to a lower wavelength (1607 cm^{-1} → 1613 cm^{-1}). The hydrogel state is maintained. At 65 °C, the hydrogel is broken, and the IR spectra show a sharp decrease in the amide I band as well as the urethane carbonyl band disappearing, giving one broad IR band. In addition, the absorption around 1650 cm^{-1} corresponding to the nonhydrogen bonded amide I increases. The absorption bands of the anti-
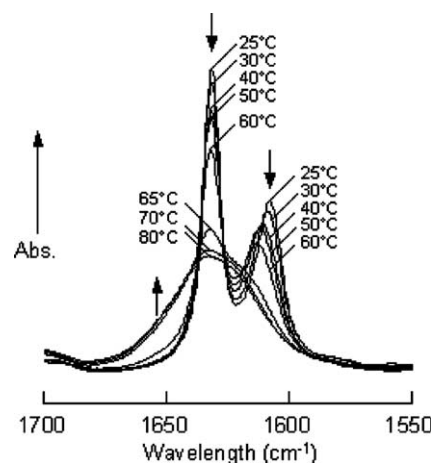
symmetric (v_{as}) and symmetric (v_s) CH$_2$ stretching vibrations of **3** appeared at 2922 cm^{-1} (v_{as}, C–H) and 2850 cm^{-1} (v_s, C–H) up to 60 °C, while over 60 °C, they shifted to 2927 and 2857 cm^{-1}. Such a higher frequency shift is induced by an increase in the fluidity of the alkyl chains in **3**.[10] These results indicate that the gel-to-sol transition is induced by breaking hydrogen bonds and van der Waals interaction.

In summary, we revealed the formation of supramolecular hydrogels of **1**–**3** in aqueous solutions containing inorganic salts and acids, the strength of the hydrogels, and the thermal properties of their hydrogels. These hydrogelators can form hydrogels containing inorganic salts and acids. The hydrogels based on **2** have highly mechanical strength, but not thermal stabilities compared with **1** and **3**. This result indicates that **2** self-assembles into nanofibers through 2D and 3D hydrogen bonding. The VT-FT-IR spectrum measurements demonstrate that the T_{gel} is consistent with the temperatures that the hydrogen bonding and van der Waals interactions are broken. Detailed study of the role of the hydrogel structures on the gel strength and the influence of acids and salts on hydrogelation are in progress.

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5. Compound **3** was not dissolved in 1 M salt solutions.

6. The strength of hydrogels was measured using a Sun Science RHEO TEX SD-305 and evaluated as the strength necessary to sink a cylinder bar ($0.547\,cm^2$ in area) 4 mm deep in the hydrogel.

7. For **3**, 0.1 M NaCl aqueous solution.

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