Supramolecular Hydrogels Formed by L-Lysine Derivatives

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New hydrogelators based on L-lysine consisting of water-soluble carboxylate and water-insoluble carboxylic acid can gel water below 1 wt %.

Several classes of organogelators have been designed and discovered in recent years, and their main purpose is the formation of gels in organic solvents.[1] In contrast, although low-molecular-weight compounds that can gel water, i.e., hydrogelators, have also been found, there are limited examples compared to organogelators.[2] It is well-known that certain polymers form a hydrogel. Hydrogels have uses in biomedical applications, in areas such as tissue engineering, controlled-release drug delivery systems, and medical implants.[3] We have challenged the conversion of organogelators into hydrogelators and synthesized L-lysine-based hydrogelators by the introduction of charged groups into the organogelators.[4] The positively charged L-lysine-based compounds are excellent hydrogelators that can gel water around 0.3 wt %, while the negatively charged compounds are not necessarily good hydrogelators. In order to increase the hydrogelation ability of negatively charged gelators, many derivatives have been synthesized with different alkali metal cations and alkyl chains. Very interestingly, it was found that the combination of two L-lysine derivatives led to the formation of a hydrogel. We now describe the formation of supramolecular hydrogels using L-lysine derivatives consisting of water-soluble and -insoluble compounds.
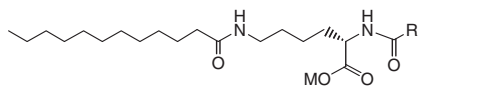

R = C_5H_{11}	R = $C_{11}H_{23}$	R =	R =
1a: M = H	**2a**: M = H	**3a**: M = H	**4a**: M = H
1b: M = Na	**2b**: M = Na	**3b**: M = Na	**4b**: M = Na
1c: M = Li	**2**: 2a/2b = 5:5	**3**: 3a/3b = 5:5	**4**: 4a/4b = 5:5
1d: M = K			
1: 1a/1b = 5:5			
5: 1a/1c = 5:5			
6: 1a/1d = 5:5			

The carboxylic acid compounds, **1a–4a**, are insoluble in water, while the carboxylates, **1b–4b** and **1c–1d**, are readily soluble in water, however, both compounds never gel water. The L-lysine derivatives consisting of a carboxylic acid and carboxylate with a ratio of 5:5, **1–6**, can be dissolved in water by heating, and then the aqueous solutions become a hydrogel at 25 °C. The hydrogelation properties of **1–6** are listed in Table 1. Except for **2b**, **1a–4a**, and **1b–4b** do not have hydrogelation abilities. **2b** functions as a hydrogelator that can gel water at 20 g/L (2 wt %).[4d] **1–6** produced translucent hydrogels after standing at 25 °C for 6 h; particularly, **1**, **5**, and **6** have excellent hydrogelation properties that can gel water below 1 wt %. Furthermore, the counter cations hardly influence their hydrogelation properties. **3** and **4** gen-

Table 1. Hydrogelation properties of **1–6** at 25 °C

	CO_2H:CO_2^-	MGC /g/L[a]	T_{gel}[b]
a	10:0	INS	—
b	0:10	S	—
1	5:5	8	65 °C
2	5:5	30	40 °C
3	5:5	25	65 °C
4	5:5	40	35 °C[c]
5	5:5	7	65 °C
6	5:5	7	65 °C

[a]MGC denotes minimum gel concentration (g/L) necessary for hydrogelation. [b][gelator] = 30 g/L. [c][**4**] = 45 g/L. INS: almost insoluble. S: Solution at 5 wt %.
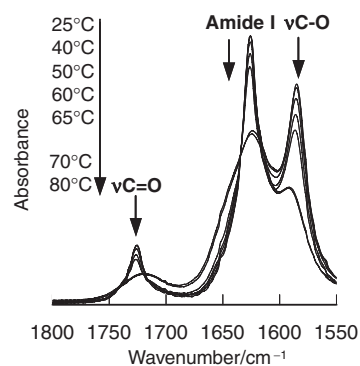
Figure 1. Various temperature FT-IR spectra of **1** (30 g/L) in D_2O at 25–80 °C.

erate the hydrogelation property by a mixture of the acid (**3a** and **4a**) and carboxylate (**3b** and **4b**) which never form a hydrogel, although their abilities are low compared with **1**. In contrast, the hydrogelation ability of **2** is lower than that of **2b**. This is the reason why the combination of **2b** and the more hydrophobic **2a** has broken the suitable hydrophilic–hydrophobic balance for hydrogelation.

The hydrogels based on **1**, **3**, **5**, and **6** have good thermal stabilities (Table 1). Their hydrogel-broken temperatures (T_{gel}) are 65 °C at 30 g/L of gelator. In contrast, **2** and **4** form a thermally unstable hydrogel; especially, the hydrogel based on **4** is broken over 35 °C. Such thermal unstabilities should be caused by the unsuitable hydrophilic–hydrophobic balance of **2**. The branched methyl groups in **4** brings about a weak hydrophobic interaction induced by their steric hindrance, which leads to a decrease in the thermal stability. Figure 1 shows the various temperature (VT)-IR spectra of the hydrogel based on **1** at 30 g/L. Up to 65 °C, the IR spectra show absorption bands at 1726 cm⁻¹ (νC=O, CO_2H), 1626 cm⁻¹ (νC=O, amide I), and 1585 cm⁻¹ (νC–O, CO_2^-) and the absorbances slightly decrease with the in-
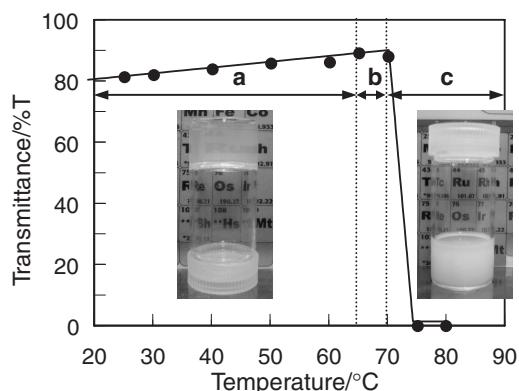
Figure 2. Temperature dependence of transmittance at 600 nm for aqueous solution of **1** (30 g/L). (a) Translucent hydrogel at 25–65 °C; (b) partial gel consisting of translucent gel and opaque solution at 65–70 °C; (c) opaque solution like milk over 70 °C.
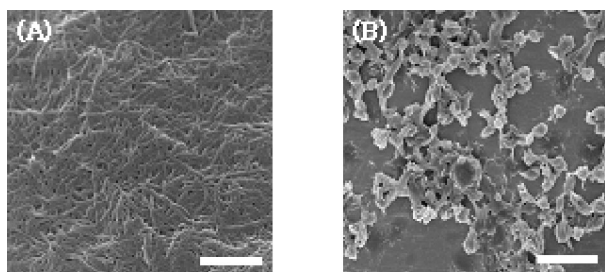

Figure 3. FE-SEM images of aggregates of **1** (10 g/L). (A) Xerogel prepared by freeze-drying of hydrogel at 25 °C. (B) Sample prepared by freeze-drying of aqueous solution at 80 °C. Scale bars are 500 nm for A and 200 nm for B.

creasing temperatures. These absorption bands dramatically change over 65 °C; the absorption bands are broadened and the absorbances decrease. In addition, the absorption bands of the antisynmmetric (ν_{as}) and symmetric (ν_s) CH_2 stretching vibrations of the hydrogel shift to a higher frequency over 65 °C. The temperature is consistent with the *Tgel*; i.e., the IR spectra change when the hydrogel is broken. These results indicate that the gel-to-sol transition is induced by breaking hydrogen bonds and van der Waals interactions, namely, the hydrogel is formed through hydrogen bonding and van der Waals interactions.

We have had an interesting observation for our systems during the heating–dissolution process. Although the aqueous solution of **1** is an opaque solution like milk at 80 °C, the hydrogel is translucent. This behavior is thermally reversible. Figure 2 shows the change in transmittance at 600 nm of an aqueous solution of **1** (30 g/L) at 25–80 °C. The transmittances at 600 nm are more than 80% for the hydrogel and less than 0.4% for the solution at 80 °C. The transmittance increases with the increasing temperature up to 70 °C, and then sharply decreases. Up to 65 °C (region a), a translucent hydrogel is formed. The aqueous solution of **1** produces a partial gel which consists of a translucent gel (87% T) and opaque solution at 65–70 °C (region b), and then becomes completely opaque over 70 °C (region c). These results indicate that the hydrogelators form some aggregates over 70 °C.

In order to evaluate the aggregate, we used FE-SEM. Figure 3 shows the FE-SEM images of samples prepared from

a dried hydrogel (A) and the freeze-drying of the solution at 80 °C.[5] In the hydrogel, **1** self-assembles into nanofibers with a diameter of several tens of nanometers and creates a three-dimensional network. Considering the VT-IR results, the nanofibers are formed through hydrogen bonding and van der Waals interactions. The hydrogel is formed by entrapping water molecules into the spaces of the three-dimensional networks. On the other hand, for a sample of the hot solution, the SEM image is quite different; spherical aggregates and their interconnection are partly observed. This result suggests that the two-component hydrogelators form spherical aggregates around 80 °C.

In summary, we revealed new L-lysine-based hydrogelators prepared by the simple combination of water-soluble carboxylate and -insoluble carboxylic acid compounds that never gel water. Some hydrogels have good thermal stabilities. The VT-IR spectra dramatically change over the *Tgel* and demonstrate that the hydrogel formation takes place through hydrogen bonding and van der Waals interactions. Furthermore, the hydrogelators should form some spherical aggregates at 80 °C.

References and Notes
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5　Samples were prepared as follows: the aqueous solution of **1** (10 mg/mL) in a capped test tube was heated at 80 °C for 2 min until the solution became opaque. The solution was immediately frozen in a dry ice/acetone bath, and then freeze-dried using a vacuum pump for 24 h.