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# New L-valine-based hydrogelators: formation of supramolecular hydrogels

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**Abstract**—New L-valine derivatives, which have a positively charged group, function as excellent hydrogelators that can gel pure water, saline, and aqueous solutions containing inorganic acids and salts at 0.2 wt %.

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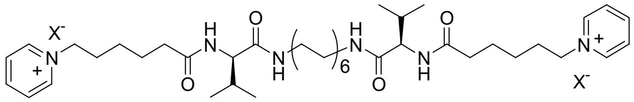
The construction of supramolecular hydrogels and organogels via the self-assembly of low-molecular-weight compounds, hydrogelators, and organogelators, have been considerably explored.[1,2] Organogelators and organogels are used in many industrial fields such as cosmetics, oils, and foods.[2] In contrast, although hydrogels are indispensable for many chemical and biological applications, including superabsorptions, chromatography, drug delivery, biosensing, and tissue engineering,[3] they have been traditionally constructed using hydrophilic polymers that are physically cross-linked through entanglements or chemically cross-linked into a network.

Our challenges regarding the conversion of organogelators into hydrogelators have resulted in the development of L-lysine-based hydrogelators, which are obtained by the introduction of charged groups such as positively charged pyridiniums and imidazoliums as well as negatively charged carboxylate ions into L-lysine type organogelators.[4] Especially, some of the positively charged hydrogelators function as a super-hydrogelator that can gel pure water with less than 0.3 wt %. We now describe the synthesis of new hydrogelators based on L-valine (**1**–**3**) and their hydrogelation abilities for water, saline, and aqueous solutions containing various inorganic salts and acids.



**1**: $X^- = Cl^-$ **2**: $X^- = Br^-$ **3**: $X^- = PF_6^-$

Compounds **1**–**3** were prepared from commercially available *Z*-L-valine as the starting material.† Compound

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† *Dodecamethylene-1,12-bis(N-(6-halohexyl)-L-valine)*: To a dry THF (500 mL) solution of $ValC_{12}Val$ (20 mmol) and triethylamine, 6-halohexanoyl chloride (50 mmol) was slowly added at 0 °C with stirring. After continuous stirring at 0 °C for 1 h and an additional 5 h at room temperature, the resulting solution was evaporated to dryness. The ethanol solution was added to vigorously stirred water (3 L). The white precipitate was filtered, washed with water, and then dried. The product was obtained by recrystallization from ethanol–ether. *Dodecamethylene-1,12-bis(N-(6-pyridiniumhexyl)-L-valine) dihalorides (1)* and *(2)*: A pyridine solution (300 mL) of haloalkanoyl amino acid (20 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 two recrystallizations from ethanol–ether. *Dihexafluorophosphate salt (3)*: Compound **1** (5 mmol) was dissolved in water (300 mL) and then an aqueous solution of $KPF_6$ (20 mmol/10 mL) was added with stirring. The white precipitate was filtered and washed with water. The product was obtained by recrystallization from ethanol–ether.

*Keywords*: Hydrogel; Hydrogelator; L-Valine; Supramolecular chemistry.

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**1** was very water soluble and had no hydrogelation ability for pure water at 50 g/L. When **2** and **3** were dissolved in pure water (30 g/L for **2** and 5 g/L for **3**), these gelators form a transparent hydrogel as shown in Figure 1. Transparent hydrogels are often formed by self-assembled nanofibers with very small diameters.[4c] Superstructures built up with **2** and **3** in hydrogels of pure water were observed by transmission electron microscopy (TEM). As expected, these gelators create a three-dimensional network by the entanglement of self-assembled nanofibers with a diameter of ca. 20 nm (Fig. 1). Very interestingly, the electron micrographs reveal that these gelators self-assembled into numerous intertwined helical fibers. However, the chiralities of the helical nanofibers of these gelators were uncertain in the TEM.

The minimum gel concentrations (MGC, g/L) necessary for hydrogelation of **1**–**3** in various aqueous solutions are listed in Table 1. In pure water, the hydrogelation abilities significantly depended on the counteranions; **1** with $Cl^-$ had no hydrogelation ability at 70 g/L, while **2** and **3** formed hydrogels of pure water; especially, **3** with $PF_6^-$ was able to gel pure water at 2 g/L. Compared with **2**, the hydrogelation ability of **3** was ca. 15 times better. Compound **3** is a super-hydrogelator. Except for $CH_3CO_2H$, the hydrogelation abilities of **1** and **2** increase in the presence of inorganic acids and salts. In particular, the presence of inorganic acids and salts dramatically influences the hydrogelation of **1**; **1** can gel aqueous solutions containing 1 M inorganic salts at 2 g/L in spite of its nonhydrogelation in pure water. For **2**, the hydrogelation abilities in inorganic salt solutions are more than 12 times higher than that in pure water. In the presence of inorganic salts and acids, the electrostatic repulsion between charged groups is reduced and the self-assembly of the hydrogelators is promoted, which leads to a decrease in the MGC values. In contrast, the MGC value of **3** is 2 g/L in most aqueous solutions and the hydrogelation abilities are never affected in the presence of inorganic ions.

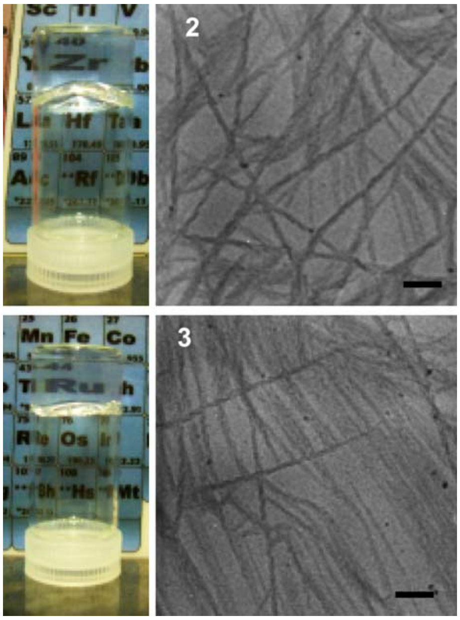

**Figure 1.** Photographs of hydrogels of **2** (3 wt %) and **3** (0.5 wt %) in pure water and TEM images of their dried hydrogels. Scale bar is 100 nm.

The thermal stabilities of the hydrogels were evaluated by determination of the MGC values at various temperatures. The $T_{gel}$s of the hydrogels based on **1**–**3** are listed in Table 2, where the $T_{gel}$ is defined as the hydrogel-destroyed temperature and determined by the inversion-stable method. In pure water, **1** has no hydrogelation, and the hydrogel based on **2** has a low thermal stability; the $T_{gel} = 30\,°C$ at 40 g/L (4 wt %). In contrast, the hydrogel based on **3** is quite thermally stable and the $T_{gel}$ value is 75 °C at 5 g/L (0.5 wt %). The hydrogels based on **1** and **2**, which contain an inorganic acid and salts, have the similar $T_{gel}$ values, and their $MgCl_2$ and $CaCl_2$ hydrogels have good thermal stabilities. Furthermore, the $T_{gel}$s of the hydrogels based on **3** increase in the presence of inorganic salts; particularly, the $MgCl_2$ and $CaCl_2$ hydrogels demonstrated the highest $T_{gel}$ values of 80 °C at 5 g/L (0.5 wt %).

In order to evaluate the difference in the thermal stabilities of the hydrogels, we measured the FT-IR spectra in $D_2O$. Figure 2 shows the FT-IR spectra of hydrogels based on **2** (30 g/L) and **3** (2 g/L) at 25 °C. The typical two absorption bands were observed at 1636 and 1611 $cm^{-1}$ for the hydrogel based on **2**, while the FT-IR spectrum of the hydrogel based on **3** showed the main absorption bands at 1625 $cm^{-1}$ and shoulder bands around 1635 and 1613 $cm^{-1}$. These bands arise from the intermolecular hydrogen bonded amide I. Compared with **2**, **3** undergoes strong hydrogen bonding because the IR peak appears at a lower wavelength. Therefore, the thermal stability of the hydrogels based on **3** arises from a strong intermolecular hydrogen bonding. In addition, the absorption bands of the antisymmetric ($\nu_{as}$) and symmetric ($\nu_s$) $CH_2$ stretching vibrations of the hydrogels based on **2** and **3** appeared at 2920 $cm^{-1}$ ($\nu_{as}$, C–H) and 2851 $cm^{-1}$ ($\nu_s$, C–H), which indicates that the alkyl chains of **2** and **3** have a low fluidity and aggregate through a hydrophobic interaction. These IR results at

**Table 1.** Hydrogelation properties of **1**–**3** at 25 °C[a]

| | $H_2O$[b] | Saline | HCl | AcOH | NaCl | $MgCl_2$ | $CaCl_2$ |
|---|---|---|---|---|---|---|---|
| **1** | S | 30 | 6 | S | 4 | 2 | 2 |
| **2** | 25 | 14 | 3 | 36 | 2 | 2 | 2 |
| **3** | 2 | 2 | 2 | 3 | 2 | 2 | 2 |

[a] Values denote minimum gel concentration (MGC; g/L) necessary for hydrogelation. [Additives] = 1 mol/dm$^3$.

[b] In pure water. S: solution at 50 g/L.

**Table 2.** $T_{gel}$ (°C) of hydrogels based on **1**–**3**[a]

| | $H_2O$[b] | Saline | HCl | AcOH | NaCl | $MgCl_2$ | $CaCl_2$ |
|---|---|---|---|---|---|---|---|
| **1**[c] | — | — | 50 °C | — | 55 °C | 60 °C | 60 °C |
| **2**[c] | — | — | 45 °C | — | 55 °C | 55 °C | 60 °C |
| **3**[c] | 75 °C | 75 °C | 75 °C | 70 °C | 70 °C | 80 °C | 80 °C |

[a] [Additives] = 1.0 mol/dm$^3$.

[b] In pure water.

[c] [**1**] = [**2**] = 10 g/L (1 wt%) and [**3**] = 5 g/L (0.5 wt%).

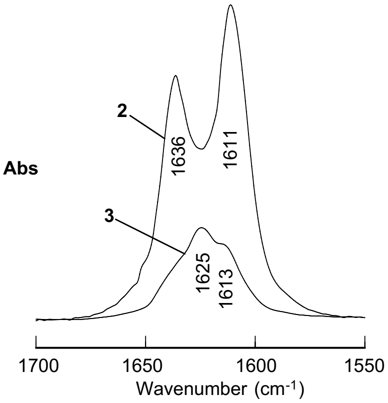

**Figure 2.** FT-IR spectra of hydrogels based on **2** (30 g/L) and **3** (2 g/L) in $D_2O$.

room temperature imply that **2** and **3** self-assemble into nanofibers through hydrogen bonding between the amide groups and hydrophobic interactions between the alkyl groups.

Figure 3 shows the various temperature (VT) FT-IR spectra of the hydrogels based on **2** (30 g/L) and **3** (2 g/L), in which their $T_{gel}$ values are 40 and 55 °C. The IR bands in the amide I region slightly decrease below the $T_{gel}$s, and then they dramatically change to over the $T_{gel}$s.

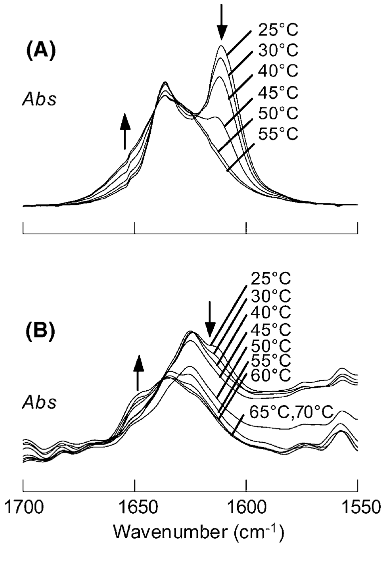

**Figure 3.** Various temperature FT-IR spectra of **2** (A; 30 g/L) and **3** (B; 2 g/L) in $D_2O$.

It is noteworthy that, at high temperature, similar IR spectra are obtained for both **2** (55 °C) and **3** (70 °C), indicating that **2** and **3** are dispersed in the hot $D_2O$ solution. Furthermore, the absorption bands of the antisymmetric ($\nu_{as}$) and symmetric ($\nu_s$) $CH_2$ stretching vibrations shift from 2920 to 2927 cm$^{-1}$ and from 2851 to 2857 cm$^{-1}$. Such a higher frequency shift is induced by an increase in the fluidity of the alkyl chains in **3**.[5] These results indicate that the hydrogen bonding and hydrophobic interactions are broken over $T_{gel}$s, leading to the destruction of the hydrogels.

In summary, we revealed the formation of supramolecular hydrogels based on new L-valine derivatives **1**–**3** in aqueous solutions containing inorganic salts and acids and the thermal properties of their hydrogels. These hydrogelators can form hydrogels containing inorganic salts and acids. The VT-FT-IR spectrum measurements demonstrate that the $T_{gel}$ is consistent with the temperatures at which the hydrogen bonding and van der Waals interactions are broken. Detailed studies of the influence of acids and salts on the hydrogelation and helical nanostructures of the hydrogelators are now in progress.

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