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New low-molecular weight gelators based on L-valine and L-isoleucine with various terminal groups

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Abstract—New low-molecular weight gelators based on L-valine and L-isoleucine, which have various terminal groups such as ester, carboxyl, and carboxylate, function as a good organogelator that form an organogel in many organic solvents. In addition, the sodium salt compounds form not only organogels but also a hydrogel in the presence of a cationic surfactant.

Low-molecular weight gelators, which form organogels (organogelators) and hydrogels (hydrogelators), have been considerably investigated because of not only their academic interests but also potentially wide applications to industrial fields such as cosmetics, foods, medical science, tissue engineering.[1–4] Though gelators are a small molecule, they create a three-dimensional network by the formation of polymeric superstructures such as nanofibers, nanoribbons, and nanosheets through hydrogen bonding, van der Waals (hydrophobic), and π-stacking interactions. Recently, the nanostructures formed by gelators have been focused and used as organic templates for the fabrication of mesoporous polymers and nano-scaled designed inorganic materials.[5,6] The sol–gel polymerization of various metal alkoxides (Si, Ti, Ta, V, etc.) in solvents containing self-assembled gelators produces hollow nanofibers of metal oxides followed by calcination.[6]

We have developed gelators that are cheaply, simply, and effectively synthesized and environmentally friendly materials (having features such as biodegradation and/or nontoxicity) in addition to a good gelator; especially, L-aminoacid-based gelators are one of the best gelators. Moreover, we have also reported the conversion of organogelators into hydrogelators using L-lysine and L-valine derivatives.[7] The negatively charged L-lysine derivatives can form both hydrogels in aqueous solutions and organogels in organic solvents and oils.[7d] Such an ambidextrous gelation properties should lead to the wide applications of the gelators to industrial fields. We now describe the synthesis of new L-valine- and L-isoleucine-based gelators and their gelation properties.

Gelators **1**–**2** were prepared according to the synthetic procedures using L-valylaminooctadecane and L-isoleucylaminooctadecane [8] as starting materials (Scheme 1).[9] The synthetic procedures of these compounds were very simple and obtained with high yield (total yield > 90%). The gelation abilities of **1**–**2** in various organic solvents and oils are listed in Table 1, where values denote minimum gel concentration (MGC; g/L) necessary for gelation.[10] The methyl esters (**1a**, **2a**) and carboxylic acids (**1b**, **2b**) form organogels in many organic solvents and oils; especially, **1a** and **2b** function as powerful gelators that can gel alkanes, alcohols, esters, cycloethers, aromatic solvents, polar solvents, natural oils, and silicones. **2a** has no gelation abilities for alcohols, while it forms gels in other solvents with low MGC values. In contrast, low organogelation abilities were observed for sodium salt compounds, **1c** and **2c**. Compound **1c** forms organogels in only six solvents and **2c** shows the better organogelation ability than **1c**. This is the reason why the introduction of ionic segment ($-CO_2^-Na^+$) into the organogelator brings about the change in the hydrophilicity–hydrophobicity balance, thus leading to low organogelation abilities.

Keywords: L-Valine; L-Isoleucine; Organogel; Organogelator.

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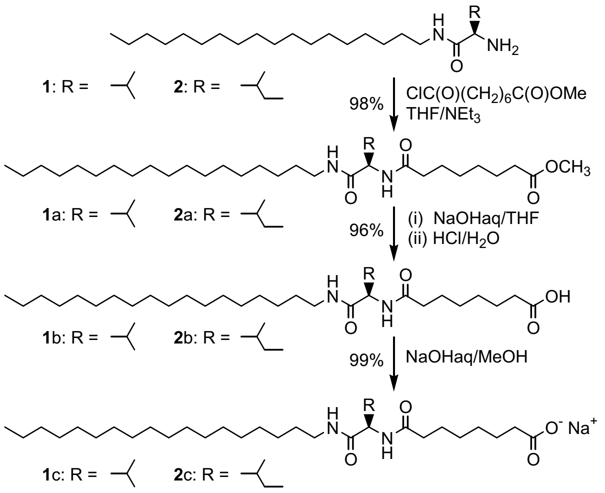

Scheme 1. Synthetic procedure of gelators.

Although the methyl esters and carboxylic acids were water-insoluble, **1c** and **2c** dissolved in water; therefore, we examined hydrogelation properties of water-soluble organogelators, **1c** and **2c**. Unfortunately, they never functioned as a hydrogelator and produced slightly viscous solution at 5 wt%. Very interestingly, it was found that **1c** and **2c** formed a hydrogel in the presence of cationic surfactants and the hydrogelation properties significantly depended on the concentration of the surfactants. The hydrogelation properties of **1c** and **2c** under various conditions are listed in Table 2. As mentioned above, **1c** and **2c** did not form a hydrogel in pure water. In the presence of the cationic surfactants, however, they formed a thermo-reversible hydrogel. At low surfactant concentrations, the gelators form the transparent or translucent hydrogels, while they produce a white hydrogel at the high concentrations. Because **1c** and **2c** cannot form a hydrogel in the presence of anionic

Table 1. Gelation properties of **1**–**2** in various solvents at 25 °C[a,b]

	1a	**1b**	**1c**	**2a**	**2b**	**2c**
^{n}Hexane	3	7	INS	5	7	INS
^{c}Hexane	20	12	INS	7	1	—
MeOH	8	20	—	—	12	35
EtOH	15	25	50	—	15	18
^{i}PrOH	30	—	40	—	25	15
AcOEt	5	—	INS	4	25	INS
Acetone	5	8	INS	7	5	INS
^{c}Hexanone	12	30	20	20	12	20
THF	—	—	—	—	30	INS
1,4-Dioxane	12	—	INS	10	8	INS
Ph–CH_3	10	25	—	14	3	—
Ph–Cl	17	30	—	17	5	15
Ph–NO_2	4	12	—	5	3	5
DMF	7	30	—	7	12	10
DMSO	7	20	—	3	3	15
$CHCl_3$	—	—	—	—	—	—
CH_3CN	3	—	INS	5	0.7	INS
Salad oil	10	10	20	8	10	35
Silicone oil	10	50	—	15	50	35
Linseed oil	15	10	20	8	10	40
$(Me_2SiO)_4$[c]	20	—	INS	18	—	INS
$(Me_2SiO)_5$[d]	20	—	INS	15	—	INS
IPM[e]	15	30	10	13	30	40
Coal oil	30	30	—	13	10	—

[a] Values denote minimum gel concentration (MGC; g/L) necessary for gelation.

[b] INS: almost insoluble; —: nongelation at 30 g/L.

[c] $(Me_2SiO)_4$: octamethylcyclotetrasiloxane.

[d] $(Me_2SiO)_5$: decamethylcyclopentasiloxane.

[e] IPM: myristic acid isopropyl ester.

Table 2. Hydrogelation properties of **1c** and **2c** at 25 °C

[G]:[S][a]	S (mM)	DTMACl		HDTMACl	
		1c	**2c**	**1c**	**2c**
5:0[b]	0	—	—	—	—
5:1	3.64	—	—	—	—
5:1.5	5.46	—	GTL	GT	GTL
5:2	7.28	GT	GTL	GTL	GTL
5:10	36.40	GW	GW	GW	GW

[a] [**1c**] = [**2c**] = 18.2 mM (1 wt%).

[b] [**1c**] = [**2c**] = 5 wt%. DTMACl: *n*-dodecyltrimethylammonium chloride. HDTMACl: *n*-hexadecyltrimethylammonium chloride GT: transparent gel; GTL: translucent gel; GW: white gel like milk; —: soluble but no hydrogelation. S: solution; PG: partial gel; VS: viscous solution; P: precipitate.

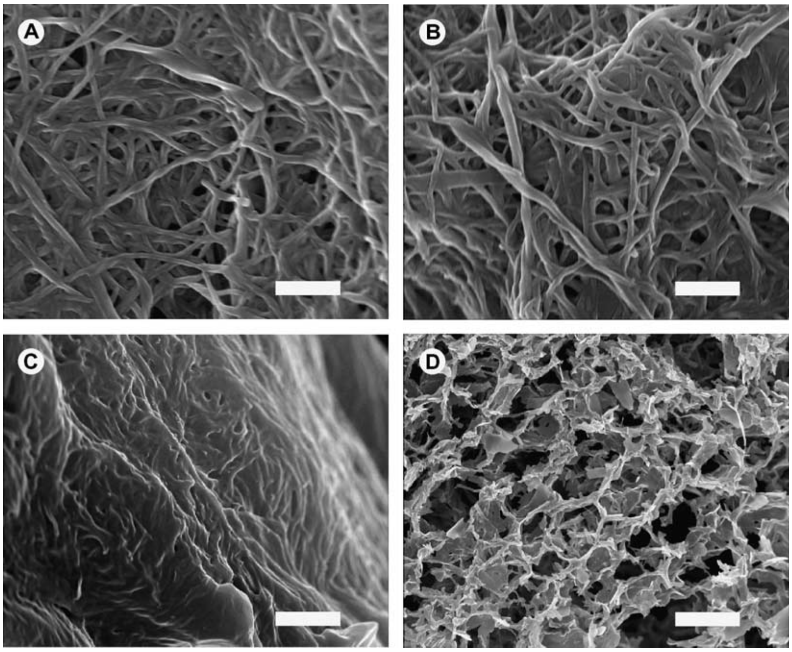

Figure 1. FE-SEM photographs of dried gels prepared from: (A): toluene gel of **1a**; (B): toluene gel of **1b**; (C): hydrogel of **1c**/DTMACl (5:2); (D): hydrogel of **1c**/DTMACl (5:10). Scale bars are 200 nm.

surfactant (SDS), nonionic surfactant (Triton, Tween), and NaCl, sodium salt compounds are a cationic surfactant-triggered hydrogelator.

Such supramolecular gels are often formed by self-assembled nanofibers. Superstructures built up with these gelators in supramolecular gels were observed by a field emission scanning electron microscope (FE-SEM). Figure 1 shows the FE-SEM images of dried gels prepared from organogels and hydrogels. In organogels, the gelators create a three-dimensional network formed by entanglement of self-assembled nanofibers with a diameter of 50–100 nm (images A and B). Similarly, TEM image was observed in a transparent hydrogel (image C). Although a three-dimensional network was observed in a white hydrogel (containing excess cationic surfactant), **1c** self-assembled into nanofibers with a diameter of 200–300 nm (image D).

In order to evaluate the driving forces for gelation, we measured the FT-IR spectra. Figure 2 shows the FT-IR spectra of **2b** in chloroform solution and in cyclohexane gel. In $CHCl_3$ solution (non organogelation), the typical IR bands, arising from non-hydrogen bonded amide groups, were observed at 3432 cm^{-1} (amide A), 1655 cm^{-1} (amide I), and 1510 cm^{-1} (amide II). The IR spectra of cyclohexane gel showed the bands at 3286 cm^{-1} (amide A), 1633 cm^{-1} (amide I), and 1543 cm^{-1} (amide II), characteristics of hydrogen bonded amide groups. In addition, the IR bands of carboxyl group appeared at 1717 cm^{-1} in $CHCl_3$ and 1701 cm^{-1} in cyclohexane gel. Such IR shifts indicate the presence of the intermolecular hydrogen bonding interaction between the amide groups and between the carboxyl groups.[11]

Figure 3 shows the FT-IR spectra of **2c**/DTMACl in D_2O (hydrogel) and **2a** in $CHCl_3$ solution. In hydrogel, the IR spectrum showed the absorption bands at 1627 cm^{-1} (amide I) and 1560 cm^{-1} (amide II), characteristic of the intermolecular hydrogen bonded amide groups. The absorption bands arising from the alkyl

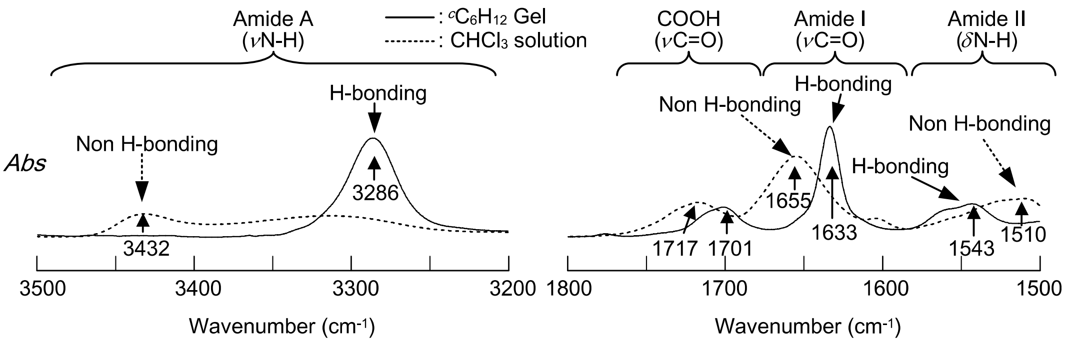

Figure 2. FT-IR spectra of **2b** in chloroform solution (dashed line) and cyclohexane gel (solid line). [**2b**] = 20 mg/mL.

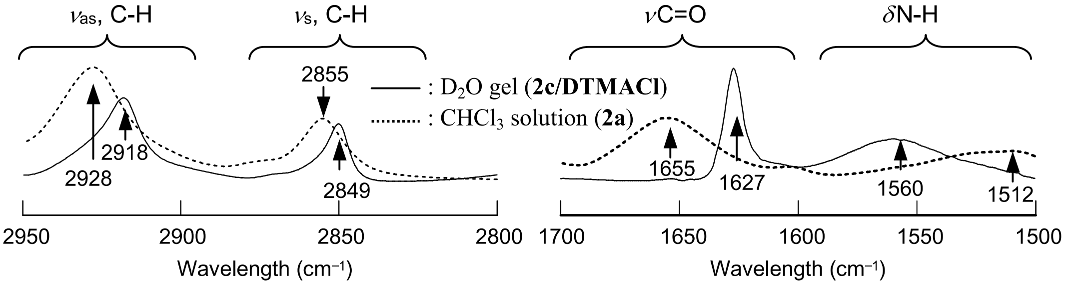

Figure 3. FT-IR spectra of **2c** in D_2O containing DTMACl (hydrogel, solid line) and **2a** in $CHCl_3$ (solution, dashed line). [**2c**] = [**2a**] = 10 mg/mL (18.2 mM), [DTMACl] = 7.28 mM in D_2O.

chains, antisymmetric (ν_{as}, C–H) and symmetric (ν_s, C–H) stretching vibrations, appeared at the low wavenumbers, 2918 cm^{-1} and 2849 cm^{-1}, compared with those of **2a** in $CHCl_3$ solution. Such IR shift implies that the fluidity of the alkyl chains decreases in hydrogel because of a strong hydrophobic interaction. Therefore, the driving forces for the formation of a hydrogel are mainly hydrophobic interaction and complementarily hydrogen bonding. In addition, a cationic surfactant plays a very important role in the hydrogelation. In the presence of a cationic surfactant, the ion exchange reaction between **1c** and surfactant takes place. The **1c**/surfactant may self-assemble into nanofibers with involving **1c** and create a three-dimensional network, consequently leading to hydrogelation.

In summary, we revealed the synthesis of new gelators based on L-valine and L-isoleucine and their gelation properties. The ester compounds, **1a** and **2a**, and the carboxyl compounds, **1b** and **2b**, function as an excellent organogelator that form the organogels in many organic solvents at relatively low concentration. In contrast, the organogelation abilities of the sodium salt compounds, **1c** and **2c**, decrease compared with other gelators, however, they are water-soluble organogelator and cationic surfactant-triggered hydrogelator.

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9. L-Valylaminooctadecane (L-$C_{18}ValNH_2$) and L-isoleucylaminooctadecane (L-$C_{18}IleNH_2$) were prepared according to the literature.[8] **1a**: To a dry THF solution of L-$C_{18}ValNH_2$ (20 mmol) and NEt_3 (10 mL), a freshly distilled suberoyl chloride monomethyl ester was slowly added at 0 °C with stirring and then the reaction mixture was stirred at room temperature for 12 h. The resulting solution was filtered and the filtrate was evaporated to dryness. The products were obtained by recrystallization from methanol–ether (yield: 98%). IR (KBr) ν: 3291 cm^{-1} (νN–H), 1737 cm^{-1} (νC=O), 1634 cm^{-1} (νC=O), 1541 cm^{-1} (δN–H); ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): $\delta = 0.88$ (t, $J = 6.6$ Hz, 3H; CH_3), 0.93–0.95 (m, 6H; $CH(CH_3)_2$), 1.25–1.35 (m, 34H; alkyl), 1.45–1.51 (m, 2H; $NHCH_2CH_2$), 1.61–1.63 (m, 4H; $OCOCH_2CH_2$, $NHCOCH_2CH_2$), 2.00–2.09 (m, 1H; $(CH_3)_2CH$), 2.21 (t, $J = 7.5$ Hz, 2H; CH_2CON), 2.29 (t, $J = 7.6$ Hz, 2H; $CH_2CO_2CH_3$), 3.10–3.17 (m, 2H; $NHCH_2$), 3.66 (s, 3H; OCH_3), 4.21 (t, $J = 8.6$ Hz, 1H; NHCHCO), 6.31 (d, $J = 8.8$ Hz, 1H; CONHCH), 6.34 (t, $J = 5.6$ Hz, 1H; $CONHCH_2$); elemental analysis calcd (%) for $C_{32}H_{62}N_2O_4$ (538.85): C, 71.33; H, 11.60; N, 5.20. Found: C, 71.39; H, 11.98; N, 5.21. **1b**: **1a** (10 mmol) was dissolved in THF (300 mL) and 1 M aq NaOH (50 mL) was added. After heating the reaction mixture at 60 °C for 24 h, the resulting solution was evaporated to dryness. The solid was dissolved in water (600 mL) and then the aqueous solution was acidified by conc HCl (pH = 1). White precipitate was filtered, washed with water, and then

dried. The product was obtained by recrystallization from MeOH–ether (yield: 96%) IR (KBr) *v*: 3287 cm^{-1} (*v*N–H), 1710 cm^{-1} (*v*C=O), 1635 cm^{-1} (*v*C=O), 1545 cm^{-1} (*δ*N–H); ^{1}H NMR (400 MHz, CDCl$_3$, TMS, 25 °C):*δ* = 0.88 (t, *J* = 6.6 Hz, 3H; CH_3), 0.92–0.95 (m, 6H; CH(CH_3)$_2$), 1.25–1.27 (m, 34H; alkyl), 1.47–1.51 (m, 2H; NHCH$_2$CH_2), 1.59–1.68 (m, 4H; OCOCH$_2$CH_2, NHCOCH$_2$CH_2), 1.99–2.06 (m, 1H; (CH$_3$)$_2$CH), 2.22 (t, *J* = 7.6 Hz, 2H; CH_2CON), 2.33 (t, *J* = 7.1 Hz, 2H; CH_2CO$_2$H), 3.11–3.35 (m, 2H; NHCH_2), 4.18 (t, *J* = 8.6 Hz, 1H; NHCHCO), 6.44 (t, *J* = 5.6 Hz, 1H; CONHCH$_2$), 7.03 (d, *J* = 9.1 Hz, 1H; CONHCH); elemental analysis calcd (%) for $C_{31}H_{60}N_2O_4$ (524.82): C, 70.94; H, 11.52; N, 5.34. Found: C, 71.14; H, 11.84; N, 5.34. **1c**: **1b** (10 mmol) was dissolved in MeOH (200 mL) and then 1 M aq NaOH (10 mL) was added. After stirring at room temperature for 20 min, the resulting solution was evaporated to dryness. The product was obtained by recrystallization from MeOH–ether (yield: 99%). IR (KBr) *v*: 3287 cm^{-1} (*v*NH), 1636 cm^{-1} (*v*C=O), 1562 cm^{-1} (*δ*N–H); elemental analysis calcd (%) for $C_{31}H_{59}N_2O_4Na$ (546.80): C, 68.09; H, 10.88; N, 5.12. Found: C, 68.21; H, 11.04; N, 5.12. **2a**–**c** were prepared by the same procedures as **1a** and **1c**. **2a**: IR (KBr) *v*: 3291 cm^{-1} (*v*N–H), 1735 cm^{-1} (*v*C=O), 1634 cm^{-1} (*v*C=O), 1541 cm^{-1} (*δ*N–H); ^{1}H NMR (400 MHz, CDCl$_3$, TMS, 25 °C): *δ* = 0.86–0.92 (m, 9H; CH_3), 1.25–1.35 (m, 36H; alkyl), 1.45–1.65 (m, 6H; alkyl), 1.80–1.84 (m, 1H; (CH$_3$)(CH$_3$CH$_2$)CH), 2.20 (t, *J* = 7.6 Hz, 2H; CH_2CON), 2.29 (t, *J* = 7.6 Hz, 2H; CH_2CO$_2$CH$_3$), 3.12–3.33 (m, 2H; NHCH_2), 4.20 (t, *J* = 8.1 Hz, 1H; NHCHCO), 6.02 (t, *J* = 5.1 Hz, 1H; CONHCH$_2$), 6.15 (d, *J* = 8.8 Hz, 1H; CONHCH); elemental analysis calcd (%) for $C_{33}H_{64}N_2O_4$ (552.87): C, 71.69; H, 11.67; N, 5.07. Found: C, 71.73; H, 11.84; N, 5.08. **2b**: IR (KBr) *v*: 3289 cm^{-1}(*v*N–H), 1710 cm^{-1} (*v*C=O), 1635 cm^{-1} (*v*C=O), 1543 cm^{-1} (*δ*N–H); ^{1}H NMR (400 MHz, CDCl$_3$, TMS, 25 °C): *δ* = 0.86–0.90 (m, 9H; CH_3), 1.25–1.34 (m, 34H; alkyl), 1.475–1.51 (m, 2H; CONHCH$_2$CH_2), 1.58–1.67 (m, 4H; NHCOCH$_2$CH_2, OCOCH$_2$CH_2), 1.78–1.83 (m, 1H; (CH$_3$)$_2$CH), 2.20 (t, *J* = 6.6 Hz, 2H; CH_2CON), 2.33 (t, *J* = 6.8 Hz, 2H; CH_2CO$_2$CH$_3$), 3.12–3.33 (m, 2H; NHCH_2), 4.22 (t, *J* = 8.81 Hz, 1H; NHCHCO), 6.43 (t, *J* = 5.6 Hz, 1H; CONHCH$_2$), 7.05 (d, *J* = 9.1 Hz, 1H; CONHCH); elemental analysis calcd (%) for $C_{32}H_{62}N_2O_4$ (538.85): C, 71.33; H, 11.60; N, 5.20. Found: C, 71.35; H, 11.98; N, 5.21. **2c**: IR (KBr) *v*: 3289 cm^{-1} (*v*NH), 1635 cm^{-1} (*v*C=O), 1560 cm^{-1} (*δ*N–H); elemental analysis calcd (%) for $C_{32}H_{61}N_2O_4Na$ (560.83): C, 68.53; H, 10.96; N, 5.00. Found: C, 68.71; H, 11.11; N, 5.01.

10. The gelation test was carried out as follows: a mixture of weighed gelator in solvents in a sealed test tube was heated until a clear solution appeared. After allowing the solution to stand at 25 °C for 4 h, their state was evaluated by the so-called ‘stable to inversion of a test tube’ method.[7]
11. Similar IR shifts of the amide groups were observed for **1a** and **2a**.