Physical Gelation by Low Molecular-weight Compounds and Development of Gelators

Kenji Hanabusa* and Masahiro Suzuki, Interdisciplinary Graduate School of Science and Technology, Shinshu University, Tokida 3-15-1, Ueda, Nagano 386-8567

Received: September 9 2015; E-mail: hanaken@shinshu-u.ac.jp

We discuss low molecular-weight compounds, which occur physical gelation, as gelators. There is a close relationship between crystallization and gelation with respect to the driving forces. Both crystallization and gelation are driven by non-covalent interactions such as hydrogen bonding, van der Waals forces, electrostatic interactions, and π–π interactions. Typical gelators, which include amino acid derivatives, *trans*-1,2-diaminocyclohexane derivatives, and cyclic(dipeptide)s, are discussed. A concept of "gelation-driving segment" has been proposed. Hydrogelators, functional gelators, and polymer-type gelators are developed by using gelation-driving segments.

1. Introduction

Compounds that can physically gel water or organic solvents are called gelators. Gelators are gaining not only academic interest from the perspective of supramolecular chemistry, but also interest due to their practical applications. The first report regarding gelators was in 1942, when Shunichi Yamamoto described the gelator 1,3:2,4-dibenzylidene-D-sorbitol[1]. Few papers on gelators appeared for the next half-century, but research interest increased again during the first half of the 1990s. Combined with advances in the area of supramolecular chemistry, large numbers of papers on gelators have been published annually in recent years[2-16]. However, the number of gelators used in practical applications remains small. The aforementioned 1,3:2,4-dibenzylidene-D-

sorbitol is used as an ingredient in fragrances and cosmetics, 12-hydroxystearic acid[21] is used as an edible-oil solidifying agent, N-lauroyl-L-glutamate-α,γ-bis-n-butylamide are ingredients in fragrances and cosmetics, aromatic diureas are used as ingredients for synthetic oils and greases, and aluminum 2-ethyl hexanoate, which dissolves at room temperature in hydrocarbon solvents and forms a gel-like viscous product, is used as a thickener for ink. Here, the gelation-mechanism, development, and application of gelators are described.

2. Similarity between gelation and crystallization

The physical processes involved in the gelation of low molecular-weight compounds are similar to those in crystallization. Figure 1 shows a comparison of gelation and crystallization. For example, alum can be heated in water to form a homogeneous solution. Cooling of the solution causes the solubility of alum to decrease and the resulting insoluble alum precipitates as crystals, as shown on the left in Figure 1. Crystallization is a common purification technique in synthetic chemistry. On rare occasions, however, certain low molecular-weight compounds may gel instead of crystallize (right side, Figure 1). At this time, compounds forming physical gels are called gelators. Just as heating precipitated crystals with the solvent redissolves the crystals, heating the formed gel redissolves the gel and becomes a homogeneous solution. Crystallization is a phase-separation phenomenon caused by intermolecular interactions. During crystallization, molecules separate from the solvent and become perfectly ordered with three-dimensional regularity. In gelation, a fibrous aggregate forms three-dimensional networks and traps solvent in the networks. Both crystallization and gelation are driven by non-covalent bond interactions such as hydrogen bonding, van der Waals forces, electrostatic interactions, and π-π interactions.

2

Crystallization is considered to be the ultimate stable condition; in contrast, gelation is considered to be a semi-stable condition preceding crystallization.

3. Amino acid based gelators

Strong gelation abilities are found in amino acid derivatives such as an L-isoleucine derivative (**1**)[22] and an L-lysine derivative (**2**)[23] shown in Figure 2. Compound **1** can be easily synthesized in two reaction steps using L-isoleucine as the starting material.

Table 1 shows the solvents gelled by **1** and **2**, ordered by their dielectric constant for compounds from dimethyl sulfoxide to cyclohexane. Compounds **1** and **2** can gel a broad range of liquids, such as highly polar solvents like DMSO and DMF, various alcohols, ketones, esters, aromatic compounds, carbon tetrachloride, hydrocarbons, and silicone, mineral, and edible oils. For example, 1 L of dimethyl sulfoxide can be gelled with 10 g of **1**, and 1 L of silicone oil can be solidified with the addition of 5 g of **1**. However, not all amino acid derivatives with a structure similar to **1** cause gelation. It should be mentioned that the gelation ability strongly depends on the structure of the amino acid. As long as the octadecylamide portion and the benzyloxycarbonyl group were fixed, gelation could be observed for the L-valine and L-isoleucine derivatives. No gelation was observed for other amino acids, such as Gly, L-Ala, racemic D,L-Val, L-Leu, L-tert-Leu, L-Phe, and others. They only crystallize and do not form gels. These results indicate that the expression of gelation ability is limited to the specific structures of L-valine and L-isoleucine.

Gelation by amino acid derivatives is primarily driven by hydrogen bonding. The FT-IR spectrum of kerosene gelled with **1** shows NH stretching vibrations at 3296 cm^{-1}, urethane C=O stretching vibrations at 1688 cm^{-1}, and amide stretching vibrations at 1646 cm^{-1}. These stretching vibrations indicate the formation of hydrogen bonds

between the urethane and amide NH and C=O groups; in addition, almost no non-hydrogen bonded NH and C=O are present. In contrast, chloroform cannot be gelled with **1**. Instead, **1** is miscible in chloroform, and peaks indicative of non-hydrogen-bonding are observed: NH stretching vibrations at 3437 cm^{-1}, urethane C=O stretching vibrations at 1714 cm^{-1}, and amide stretching vibrations at 1671 cm^{-1}. These results led us to conclude that the hydrogen bonding between the amide and urethane is one of driving forces in gelation.

Gelation by low molecular-weight compounds occurs via self-aggregation of molecules driven by non-covalent bonding, resulting in the formation of fibrous aggregates. The fibrous aggregates ultimately form a three-dimensional network structure, in which solvent molecules are trapped. Thus, nano-sized fibrous aggregates inevitably form at the initial stage of gelation. Fibrous aggregates formed by gelators can be readily observed by electron microscopy. TEM images of gels of **1** or **2** negatively stained with osmic acid vapor revealed bundles of massive aggregates formed by numerous fibrous aggregates. The fibrous aggregates have a minimum width of 10 to 30 nm and some of the massive aggregates are linked to each other.

We propose the following mechanism for the gelation of amino acid derivatives **1** and **2**: formation of aggregates by intermolecular hydrogen bonding between the C=O and NH groups of the amide and urethane segments, the growth of the aggregates into massive aggregates, bunching into a tangled network by interactions such as van der Waals forces that mutually inhibit motion and diminish fluidity, and entrapment of solvent within the network.

4. Cyclohexane based gelators

The diamide (**3**)[24] and diurea derivative (**4**)[25] are both synthesized in one step reaction from *trans*-(1*R*, 2*R*)-diaminocyclohexane (Figure 3). Compounds **3** and **4** are excellent gelators comparable to L-isoleucine derivative **1**. Table 2 shows that the gelation abilities of **3** and **4** are quite strong, and a wide range of organic solvents can be gelled at low concentrations. There are three stereoisomers in 1,2-diaminocyclohexane as starting material. The first is the *cis*-isomer, in which the two amino groups are located at axial and equatorial positions, respectively. The others are two enantiomeric trans-isomers, in which two amino groups are located in equatorial positions.

The diamide and diurea derivative of the *cis* form have no gelation ability, nor do compounds synthesized from 1,3-diaminocyclohexane and 1,4-diaminocyclohexane. Molecular models show that two substitution groups for the *trans* forms are at equatorial positions and can form molecular groups through intermolecular hydrogen bonding, but the two substitution groups for the *cis* form are at axial and equatorial positions and cannot form intermolecular hydrogen bonds; therefore, the *cis* form has no gelation ability.

It should be mentioned that the racemate consisting of equimolar mixture of (1*R*, 2*R*) and (1*S*, 2*S*) synthesized as **3**, was able to form gels, but the crystals separated from the gels after several hours. This indicates that the racemate gels are unstable and convert to crystals.

Comparison of the minimum concentration required for gelation shows that urea derivative **4** at very low concentration can gel various solvents due to hydrogen bonding between the urea bonds; consequently, the urea bond as well as the amide one is useful for the molecular design of gelators.

TEM observation of **3** gelled in acetonitrile revealed a nano-fibrous helical aggregate (Figure 4). The helical aggregate of **3** synthesized from *trans*-(1*R*, 2*R*)-

diaminocyclohexane is always left-spiraled[26], and the helical aggregate for **3** synthesized from *trans*-(1*S*, 2*S*)-diaminocyclohexane is right-spiraled. Since **3** forms asymmetric intermolecular hydrogen bonds, the side with the alkyl group is sterically congested, causing the aggregate to bend, thereby causing the fibers to elongate into spiraled aggregates. In essence, the molecular chirality determines the chirality of the massive aggregate. Circular dichroism spectra were measured to identify the chiral structures. The spectra of *trans*-(1*R*, 2*R*)- and *trans*-(1*S*, 2*S*)-enantiomer in acetonitrile are nearly the same, but the Θ (ellipticity) values are opposite in sign. The observed large induced Θ values suggest the helical aggregates having the opposite helix sense.

The formed gels always show thermally reversible sol-gel transitions due to their non-covalent interactions. Figure 5 shows the sol-gel phase diagram for **3** in toluene, and plots the minimum gel concentration of **3** in toluene at various temperatures. The gel phase is the region above the curve, and the sol phase is below the curve. The thermodynamic parameters calculated for the transition from sol to gel are ΔH = -65 kJ mol^{-1} and ΔS = -160 JK^{-1}mol^{-1}. These parameter values indicate that the enthalpic contribution compensates for the undesirable entropic change. In other words, the enthalpic contribution is of great significance in gelation. In fact, the obtained ΔH value suggests that approximately two hydrogen bonds were formed upon gelation

5. Hydrogelators

Compounds **1** – **4** are insoluble in water even when heated, and therefore cannot gel water. However, low molecular-weight gelators such as **1** – **4** can be converted into hydrogelators by the introduction of hydrophilic groups. Thus, modification of gelation-driving segments, which are discussed later, with hydrophilic groups enables

dissolution in water upon heating and gel formation upon cooling due to non-covalent bond interactions.

Gelator 2^{23} based on L-lysine can be converted to hydrogelators **5** – **8** shown in Figure 6 and carry a positive charge or negative charge.[27-29] Compounds **5** – **8** can be obtained in high yield using commercially available N^ε-lauroyl-L-lysine as the starting material. Compound **8** bears a negative charge and can form a hydrogel at the concentration of 2 wt%. Compounds **5** to **7** bear a positive charge and are effective hydrogelators at the concentration of 0.3 wt%. The concentrations of **5** and **6** required to form hydrogels at a wide range of pH values are shown in Figure 7. Compounds **5** and **6** containing a pyridinium segment can gel saline solution at relatively low concentrations. Compounds **5** and **6** can also gel aqueous solutions containing inorganic salts, acids, alkaline ions, alkaline earth metal ions, and protons (Table 3). Compound **8** bears a negative charge and gels various organic solvents as well as water.

6. Cyclo(dipeptide) gelators and thixotropy

Low molecular-weight gelators should satisfy the following three conditions: (I) Formation of massive fibrous aggregates through intermolecular interactions such as hydrogen bonding; (II) Bond formation leading to the assembly of three-dimensional structures of massive fibrous aggregates; and (III) Physical characteristics that stabilize the gel in a semi-stable state, thereby inhibiting crystallization.

A cyclo(dipeptide) derivative could satisfy all three requirements. Cyclo(dipeptide)s, that is, 2,5-diketopiperazine derivatives are 6-membered rings containing two amide bonds. As shown in Figure 8, cyclo(dipeptide)s are believed to form molecular assemblies through intermolecular hydrogen bonds, thus satisfying requirement (I). Any defect in hydrogen bonding would cause three-dimensional structuring of the fibrous

aggregates as in requirement (II). Finally, random ordering of the R^1 group and R^2 group would inhibit crystallization and stabilize the gelation state, thus satisfying requirement (III).

The cyclo(dipeptide)s **9** – **13** shown in Figure 9 can form gels[30]. Cyclo(dipeptide)s comprising identical amino acid components exhibit good crystallinity but no gelation ability. In contrast, cyclo(dipeptide)s comprising a combination of two amino acids with different characteristics, such as a neutral amino acid (L-valine, L-leucine, and L-phenylalanine) and an acidic amino acid derivative (L-glutamic acid γ-ester or L-aspartic acid β-ester), do act as gelators. Among these, cyclo (L-Asp(OR)-L-Phe), compound **9**, can be synthesized using the artificial sweetener Aspartame® as the starting material. Compound **9** can gel alcohols, esters, ketones, aromatic compounds, soy oil, glycerides and decamethylcyclopentasiloxane, as well as various ionic liquids[31]. The wide range of compounds gelled with **9** suggests that **9** can be used as a lead compound for designing new gelators containing functional groups. For example, designed compounds **10**[32] **- 13** are based on **9** and exhibit gelation ability.

Compound **9** containing a 3,7-dimethyloctyl group is an outstanding gelator. Replacement of the branched alkyl chain with a straight-chain alkyl group such as n-dodecyl causes crystal precipitation and abolishes gelation ability. Gelator **11** containing the hydrophilic 6-hydroxyhexyl group forms thixotropic gels in pure water, alcohol, and aqueous alcohol. Thixotropy refers to transformation of a gel to a liquid sol by stirring or vibration, and subsequent gelation again when left to stand. Thixotropy is observed frequently with high-concentration suspensions such as clays or colloidal dispersions[33], and occurs when three-dimensional cross-linked structures formed by hydrogen bonds or intermolecular interactions are destroyed under shearing stress and then reform when

left to stand. The phenomenon is isothermically reversible and is observed in paints and adhesives. Figure 10 shows a TEM image of fibrous aggregates of **11** formed in toluene.

Gelator **13** containing a poly-dimethylsiloxane segment displays thixotropy in several organic solvents[34,35] such as decane, liquid paraffin, toluene, xylene, mesitylene, isopropyl myristate, and decamethylcyclopentasiloxane. When stirred or vibrated, gels prepared using **11** and **13** promptly convert to sols. After standing for several minutes to several hours at room temperature, the sols revert again to gels. The cycle of the thixotropic behavior of a gel prepared using **13** and decane can be repeated many times as shown in Figure 11. The gel was converted to sol by accelerated shearing from 0 to 100/sec, followed by deceleration from 100-0/sec, generating the first hysteresis loop. The sample was left to stand for 30 minutes and subjected to a second round of accelerating and decelerating shear. The curve obtained during the first round showed a small peak immediately after the start of the measurements, whereas a large peak was observed at the start of the second round. This result indicates the shear stress during shearing acceleration of the second round is larger than that of the first round, and suggests gel reformation during the 30 minutes of standing. Subsequent cycles at 30 minute intervals provided results very similar to those of the second round. Products exploiting the property of multiple cycles of gelation and sol formation could find application in cosmetics and electronics manufacturing. Gelators **11** and **13** are also noteworthy because they form transparent gels with alcohol or silicone oil. Transparency is important for gels used in cosmetics. For example, although silicone oil is frequently used in cosmetics, the formation of a transparent silicone gel has been difficult. Compound **13** can form transparent silicone gels.

7. Concept of gelation-driving segment

The authors have proposed a concept of the gelation-driving segment for the purpose of developing various types of gelators. The extraordinarily strong gelation ability of L-isoleucine derivative **1**[22] has already been described. There are at least three important factors in the gelator **1**. One is the presence of the L-isoleucine residue, and the others are hydrogen bonding sites and the long-chain alkyl group at the C-terminal. Intermolecular hydrogen bonding sites such as amides and urethane as well as a long-chain alkyl group for van der Waals interactions are critical.

We suppose that L-Ile-NHC$_{18}$H$_{37}$ is one of the gelation-driving segments. In fact, all of the compounds derived from this gelation-driving segment exhibit gelation ability (Figure 12). Functional groups, such as hydroxyl and carboxyl groups, terminal double bond, and halide, are very useful for the synthesis of another functional gelators. The polymer-type gelators described below incorporate a gelation-driving segment into polymer chains.

8. Development of polymer-type gelators

Gels formed with low molecular-weight compounds are in a semi-stable state, therefore, may crystallize if they stand for a long period of time. Gelators used for industrial applications must have predictable stabilities and not crystallize. Polymers and oligomers do not crystallize because of their molecular weight distribution, amorphous structure and molecular motion. The non-crystallizing properties of polymers and oligomers can be exploited to design gelators that form permanently stable gels. The covalent attachment of a gelation-driving segment to a polymer exploits the distinctive amorphous nature of the polymer and enables the development of a polymer-type gelator. It is assumed that polymer-type gelators form non-crystallizing stable gels. Figure 13 shows the reaction scheme for polymer-type gelator **15** by the

10

reaction a gelation-driving segment **14** incorporating racemic D,L-phenylalanine and polydimethylsiloxane.

The gelation ability of polymer-type gelator **15** was investigated using a three component mixed solvent frequently found in cosmetics: glycerol tris-(2-ethyl hexanoate) as polar oil, liquid paraffin as non-polar oil, and decamethylcyclopentasiloxane (D5) as silicone oil. The results of gelation test for compound **15** in the mixed solvent (66 combinations, with weight ratios ranging from 10:0:0 to 0:0:10 of glycerol tris-(2-ethyl hexanoate), liquid paraffin, and D5) are shown in Figure 14. Gelator **15** can form gels at 20 mg/mL with all these mixed solvent combinations. A high ratio of liquid paraffin provided a transparent gel (★), a high ratio of D5 provided an opaque gel (◆), and a high ratio of glycerol tris-(2-ethyl hexanoate), or approximately equal amounts of liquid paraffin and D5, provided translucent gels (●). Transparent gels formed when the solvent contained between 50–70% liquid paraffin. At high D5 concentration the mixed solvent gel became translucent. An opaque gel was formed at very high D5 content.

Phase transition temperatures of the above gels were investigated. The results are shown in Figure 15. The highest phase transition temperatures were recorded for single-component liquid paraffin gel and single-component D5 gel, at 66 to 70˚C. As the concentration of glycerol tris-(2-ethyl hexanoate) as polar oil increased, the phase transition temperature dropped, and the gel reverted to sol at 56 to 60˚C. In contrast, the transition temperature ranged from 61 to 65˚C when the ratio of liquid paraffin and D5 were about the same, even for a small ratio of glycerol tris-(2-ethyl hexanoate). The phase transition temperatures of liquid paraffin gel and D5 gel were about the same, but when the two were mixed, the phase transition temperature dropped.

In addition to polydimethylsiloxane[36], other polymers suited for development of polymer-type gelators include polyethers[37] such as polyethylene glycol or polypropylene glycol, polyesters[37] such as polycaprolactone, and polycarbonates[36].

9. Conclusion

The paper described physical gelation by low-molecular weight compounds, mainly with reference to gelators developed by the authors. The driving forces for physical gelation were non-covalent bonds such as hydrogen bonding, electrostatic interaction, van der Waals interaction, and $\pi-\pi$ interaction. There is a close relationship between crystallization and gelation with respect to non-covalent interactions as driving forces. Amino acid derivatives as typical gelators were discussed. From the results of gelation abilities of amino acid derivatives, we proposed three necessary factors for developing gelators. Cyclo(dipeptide)s satisfying three requirements were designed and developed as gelators. Gelator of cyclo(dipeptide)s showed thixotropic behaviors. On the basis of structures of developed gelators, a concept of "gelation-driving segment" was proposed. Functional gelators and polymer-type gelators were developed by using gelation-driving segments. Polymer-type gelators formed transparent and semi-permanent stable gels. It is important to introduce a gelation-driving segment to highly miscible and flexible polymers such as polysiloxane, polyether, and polycarbonate.

In the future, a variety of industrial applications are expected by utilizing gelators; for example, materials for cosmetics, ink thickeners for inkjet printers, scaffolds for cell growth and proliferation in area of tissue engineering, drug delivery in biomaterials, footholds for producing electronic devices, electrolytes preventing liquid leakage in solar cells and others.

References

1   S. Yamamoto, *J. Chem. Soc. Jpn. Ind. Chem. Soc.* **1943**, *46,* 779; *Chem. Abstr.***1952**, *46*, 7047i.

2   P. Terech, R. G. Weiss, *Chem. Rev*. **1997**, *97*, 3133.

3   J. H. Esch, B. L. Feringa, *Angew. Chem., Int. Ed*. **2000**, *39*, 2263.

4   L. A. Estroff, A. D. Hamilton, *Chem. Rev*. **2004**, *104*, 1201.

5   P. Dastidar, *Chem. Soc. Rev*. **2008**, *37*, 2699.

6   S. Banerjee, R. K. Das, U. Maitra, *J. Mater. Chem.* **2009**, *19*, 6649.

7   M. Suzuki, K. Hanabusa, *Chem. Soc. Rev*. **2009**, *38*, 967.

8   M. Suzuki, K. Hanabusa, *Chem. Soc. Rev*. **2010**, *39*, 455.

9   J.-L. Li, X.-Y. Liu, *Adv. Funct. Mater.* **2010**, *20*, 3196.

10 G. John, B. V. Shankar, S. R. Jadhav, P. K. Vemula, *Langmuir* **2010**, *26*, 17843.

11 H. Svobodová, V. Noponen, E. Kolehmainen, E. Sievänen, *RSC Adv.* **2012**, *2*, 4985.

12 S. S. Babu, S. Prasanthkumar, A. Ajayaghosh, *Angew. Chem., Int. Ed*. **2012**, *51*, 1766.

13 A. Y.-Y. Tam, V. W.-W. Yam, *Chem. Soc. Rev*. **2013**, *42*, 1540.

14 J. Raeburn, A. Z. Cardoso, D. J. Adams, *Chem. Soc. Rev*. **2013**, *42*, 1543.

15 G. Yu, X. Yan, C. Han, F. Huang, *Chem. Soc. Rev*. **2013**, *42*, 6697.

16   M. D, Segarra-Maset, V. J. Nebot, J. F. Miravet, B. Escuder, *Chem. Soc. Rev*. **2013**, *42*, 7086.

17 S. S. Babu, V. K. Praveen, A. Ajayaghosh, Chem. Rev. **2014**, *114*, 1973.

18 D. K. Kumar, J. W. Steed, *Chem. Soc. Rev*. **2014**, *43*, 2080.

19 V. K. Praveen, C. Ranjith, N. Armaroli, *Angew. Chem., Int. Ed.* **2014**, *53*, 365.

20 Y. Lan, M. G. Corradini,aR. G. Weiss, S. R. Raghavanc, M. A. Rogers, *Chem. Soc. Rev.* **2015**, *44*, 6035.

21 T. Tachibana, T. Mori, K. Hori, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1714.

22 K. Hanabusa, K. Hiratsuka, M. Kimura, H. Shirai, *Chem. Mater.* **1999**, *11*, 649.

23 K. Hanabusa, H. Nakayama, M. Kimura, H. Shirai, *Chem. Lett.* **2000**, 1070.

24 K. Hanabusa, M. Yamada H. Shirai, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1949.

25 K. Hanabusa, K. Shimura, K. Hirose, M. Kimura, H. Shirai, *Chem. Lett.* **1996**, 885.

26 J. H. Jung, Y. Ono, K. Hanabusa, S. Shinkai, *J. Am. Chem. Soc.* **2000**, *122*, 5008.

27 M. Suzuki, M. Yumoto, M. Kimura, H. Shirai, K Hanabusa, *Chem. Eur. J.* **2003**, *9*, 348.

28 M. Suzuki, M. Yumoto, M. Kimura, H. Shirai, K. Hanabusa, *New J. Chem.* **2002**, *26*, 817.

29 M. Suzuki, M. Yumoto, M. Kimura, H. Shirai, K. Hanabusa, *Helv. Chim. Acta*, **2004**, *87*, 1.

30 K. Hanabusa, M. Matsumoto, M. Kimura, A. Kakehi, H. Shirai, *J. Colloid Interface Sci.* **2000**, *224*, 231.

31 K. Hanabusa, H. Fukui, M. Suzuki, H. Shirai, *Langmuir* **2005**, *21*, 10383.

32 Y. Yang, M. Suzuki, H. Fukui, H. Shirai, K. Hanabusa, *Chem. Mater.* **2006**, *18*, 1324.

33 H. A. Barnes, *J. Non-Newtonian Fluid Mech.* **1997**, *70*, 1

34 H. Hoshizawa, M. Suzuki, K. Hanabusa, *Chem. Lett.* **2011**, *40*, 1143.

35 H. Hoshizawa, Y. Minemura, K. Yoshikawa, M. Suzuki, K. Hanabusa, *Langmuir* **2013**, *29*, 14666.

36 S. Okabe, K. Ando, K. Hanabusa, M. Shibayama, *J. Polym. Sci. B* **2004**, *42*, 1841.

37 M. Suzuki, C. Setoguchi, H. Shirai, K. Hanabusa, *Chem. Eur. J.* **2007**, *13*, 8193.

Table 1 Minimum gel concentrations (g L^{-1}) of gelators **1** and **2** for typical solvents at 25℃

Solvents	**1**	**2**
Dimethyl sulfoxide	10	25
N,N-Dimethylformamide	20	40
Nitrobenzene	22	17
Methanol	19	30
Ethanol	13	70
Acetone	7	40
Cyclohexanone	35	50
Ethyl acetate	18	25
Chlorobenzene	30	30
Benzene	10	27
Toluene	36	30
Tetrachloromethane	20	80
Cyclohexane	9	30
Silicone oil	5	3
Light oil	10	20
Kerosene	11	30
Salad oil	15	6
Soybean oil	23	6

Table 2 Minimum gel concentrations (g L^{-1}) of gelators **3** and **4** for typical solvents at 25℃

Solvents	**3**	**4**
Dimethyl sulfoxide	12	5
N,N-Dimethylacetamide	11	2
Acetonitrile	5	12
N,N-Dimethylformamide	10	2
Methanol	21	3
Ethanol	33	4
2-Butanone	15	2
Cyclohexanone	11	2
2-Propanol	40	5
Pyridine	25	2
Ethyl acetate	8	insoluble
Chlorobenzene	22	13
Benzene	20	9
Toluene	12	7
Tetrachloromethane	23	15
1,4-Dioxane	12	3
Cyclohexane	11	2
Silicone oil	2	insoluble
Light oil	8	15
Kerosene	7	11
Salad oil	6	30
Soybean oil	7	insoluble

Table 3 Gelation abilities of hydrogelators **5** and **6** for various aqueous solutions at 25°C

	5	**6**
Pure water	0.3	1.2
Saline	0.4	0.7
Hydrochloric acid	0.7	0.1
Sulfuric acid	0.6	0.1
Acetic acid	0.2	1.2
NaCl [a]	0.4	0.4
KCl [a]	0.3	0.4
$MgCl_2$ [a]	0.5	0.6
$CaCl_2$ [a]	0.4	0.9

Values mean minimum gel concentrations (wt-%). [a] [salt] = 0.1 M
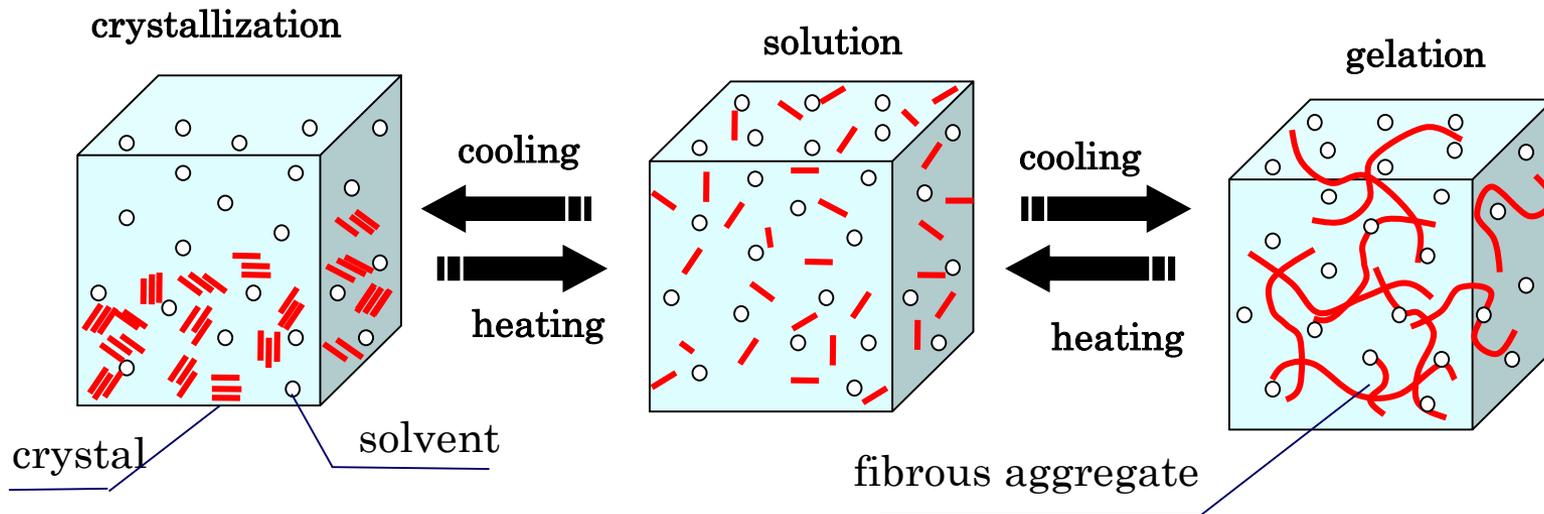
Figure Legends

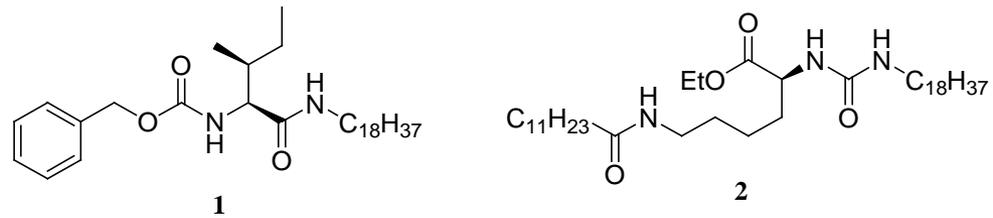Figure 1. Crystallization and gelation of low molecular-weight compounds.

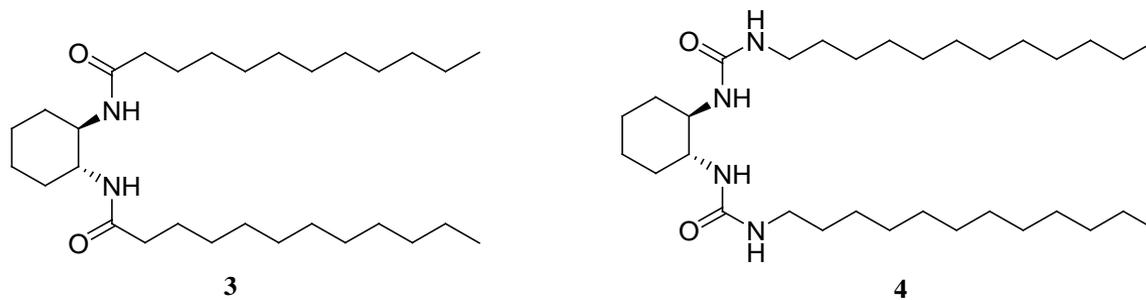Figure 2. Structures of gelators **1** and **2**.

Figure 3. Structures of gelators **3** and **4**.

Figure 4. TEM image of acetonitrile gel formed by gelator **3**.
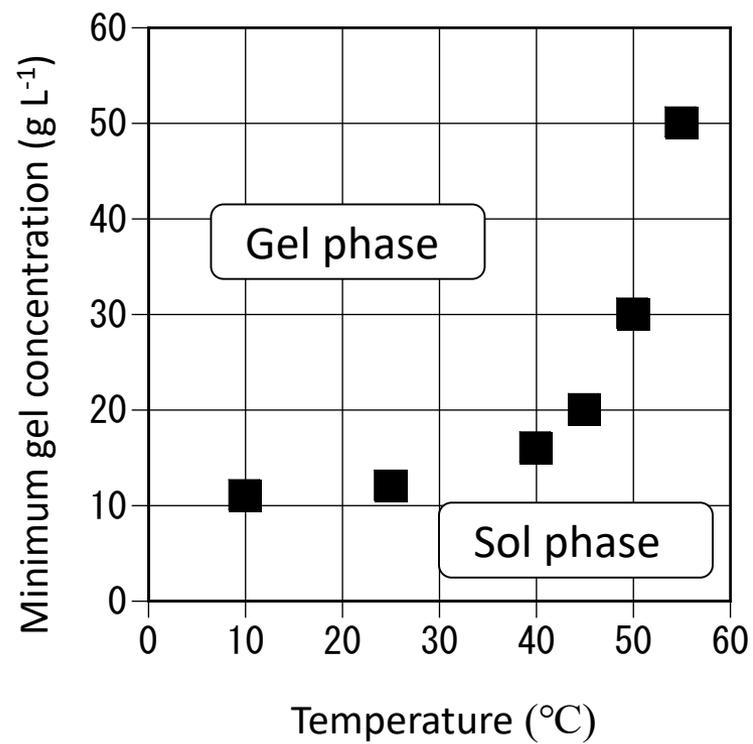
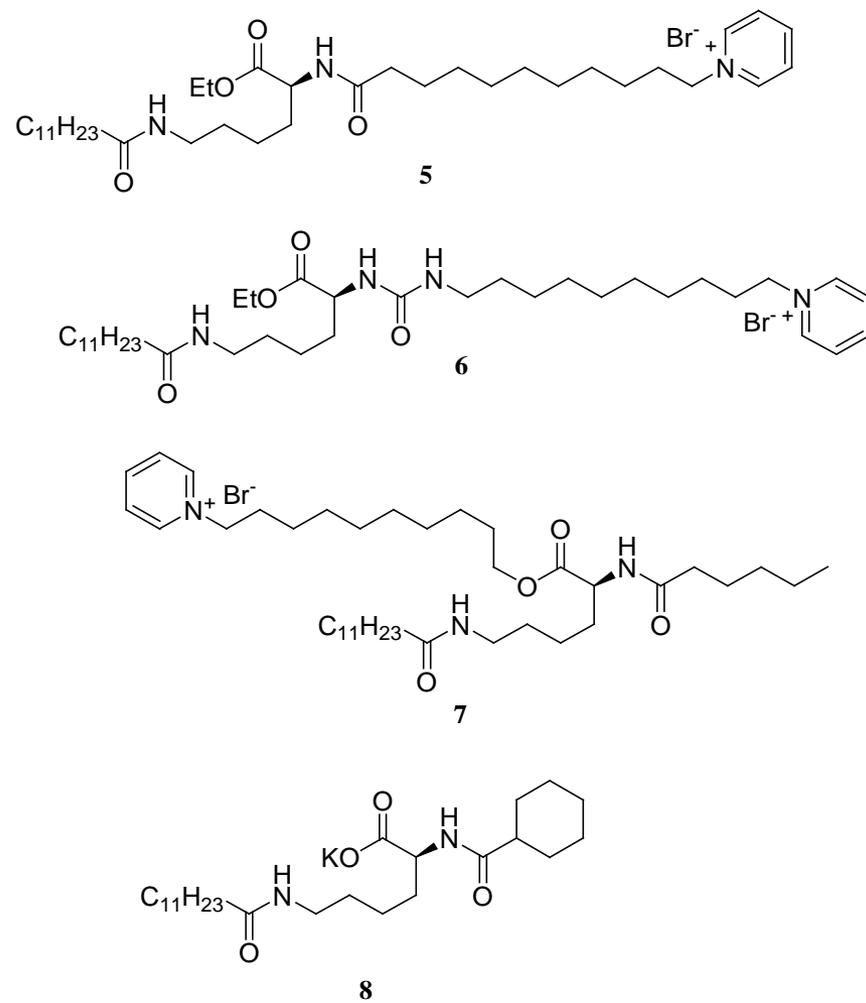Figure 5. Sol-gel phase diagram; the minimum gel concentration of **3** in toluene.
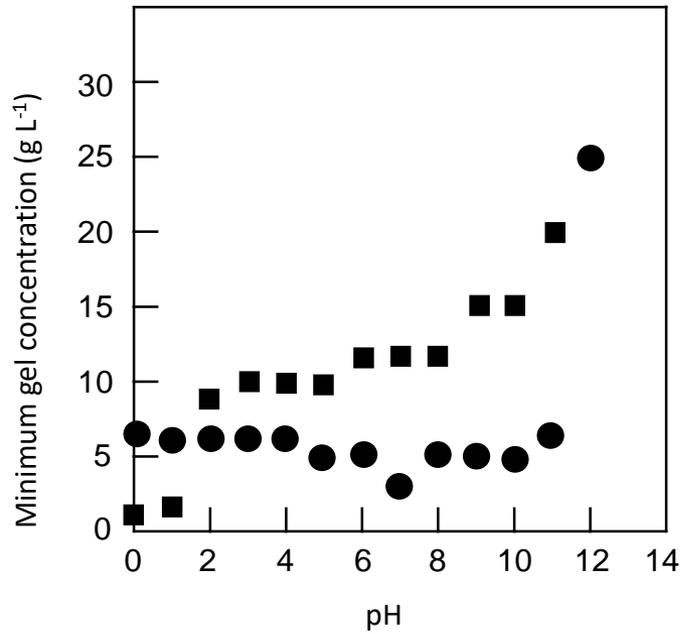
Figure 6. Structures of hydrogelators **5**-**8**.

Figure 7. Minimum gel concentrations of hydrogelators **5** and **6** for various pH solutions.

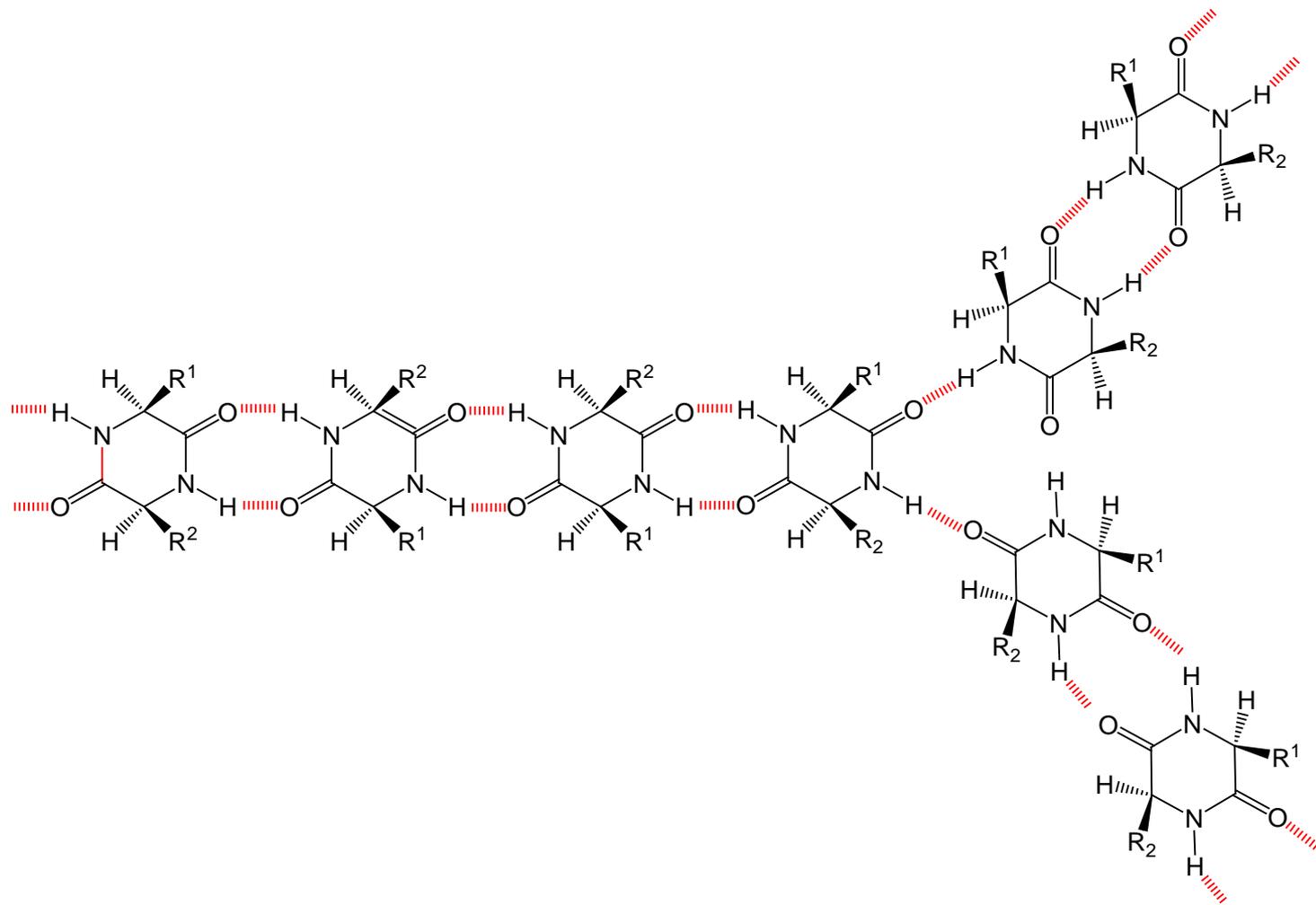Figure 8. Intermolecular hydrogen bonds formed by cyclo(dipeptide).
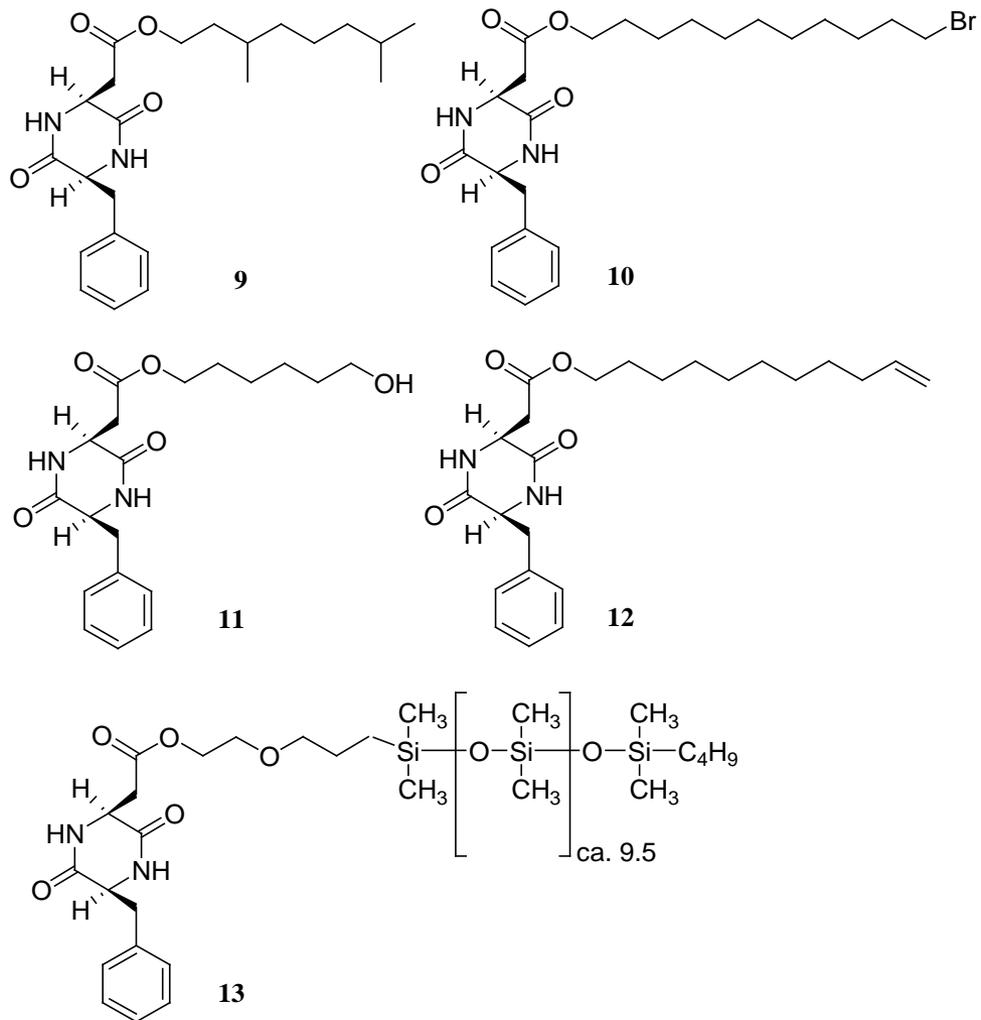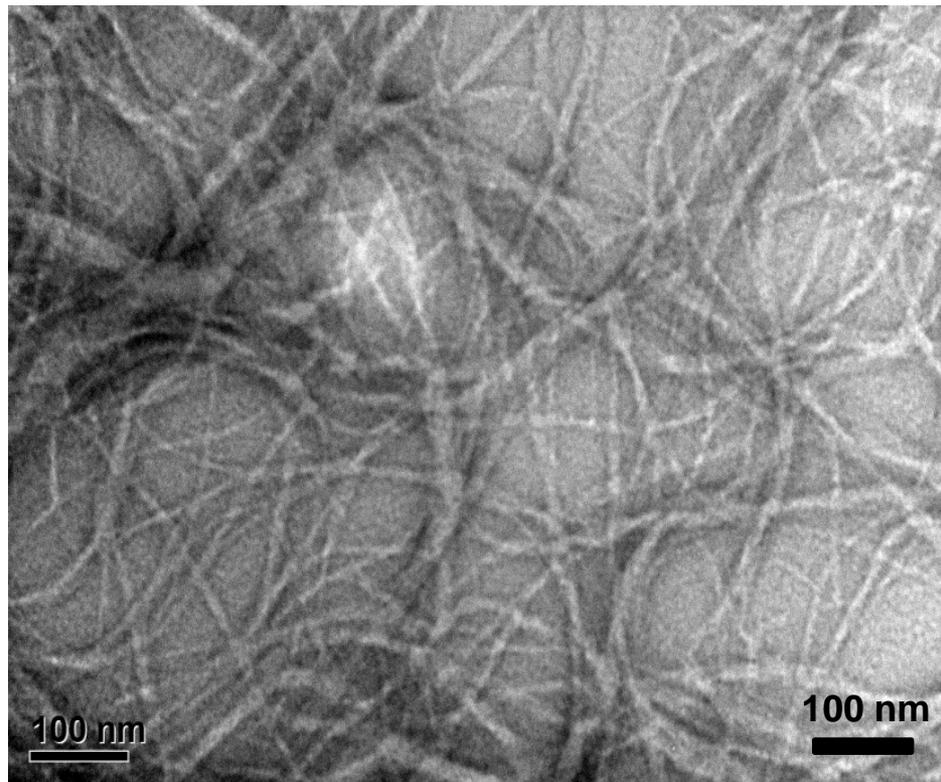
Figure 9. Structures of gelators **9**-**13**.

Figure 10. TEM image of toluene gel formed by gelator **11**.

Figure 11. Hysteresis loop of decane gel formed by gelator **13** (at 25℃, 20 mg/mL).
The 1st round; the measurement with accelerating and reducing shear for 0-100 sec^{-1}
after solubilization by the first shearing.

The 2nd round; the measurement with accelerating and reducing shear for 0-100 sec^{-1} after standing for 30 min after the 1st round.

The 3rd and 4th rounds were done similarly to the 2nd round.

Figure 12. Functional gelators derived from gelation-driving segment (L-Ile-NHC$_{18}$H$_{37}$)

Figure 13. Reaction scheme for polymer-type gelator **15**.

Figure 14. Gelation behavior of polymer type of gelator **15**. Concentration = 20 g/L, Transparent gel (★), Translucent gel (●), Opaque gel (◆)

Figure 15. Sol-gel transition temperature of polymer-type gelator **15** in three-component solvents.

Figure 1   Crystallization and gelation of low molecular weight compounds.

Fig. 2. Structures of gelators 1 and 2.

Figure 3. Structures of gelators **3** and **4**.

Figure 4. TEM image of acetonitrile gel formed by gelator **3**.

Figure 5. Sol-gel phase diagram; the minimum gel concentration of **3** in toluene.

Figure 6. Structures of hydrogelators 5-8.

Figure 7. Minimum gel concentrations of hydrogelators **5** (●) and **6** (·) for various pH solutions.

Figure 8. Intermolecular Hydrogen Bonds Formed by cyclo(dipeptide).

Figure 9. Structures of gelators 9-13.

Figure 10. TEM image of toluene gel formed by gelator **11**.
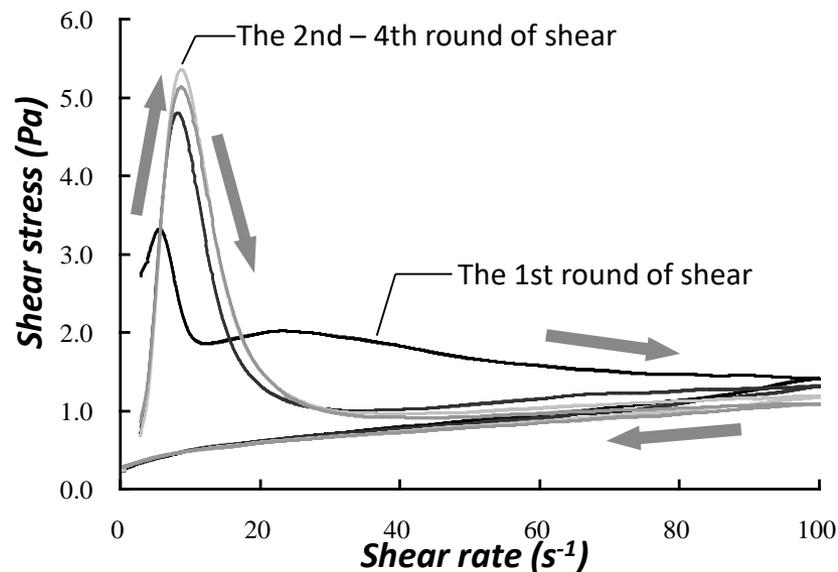
Figure 11. Hysteresis Loop of Decane Gel Formed by Gelator **13** (at 25℃, 20 mg/mL).
The 1st round; the measurement with accelerating and reducing shear for 0-100 sec^{-1} after solubilization by the first shearing.
The 2nd round; the measurement with accelerating and reducing shear for 0-100 sec^{-1} after standing for 30 min after the 1st round.
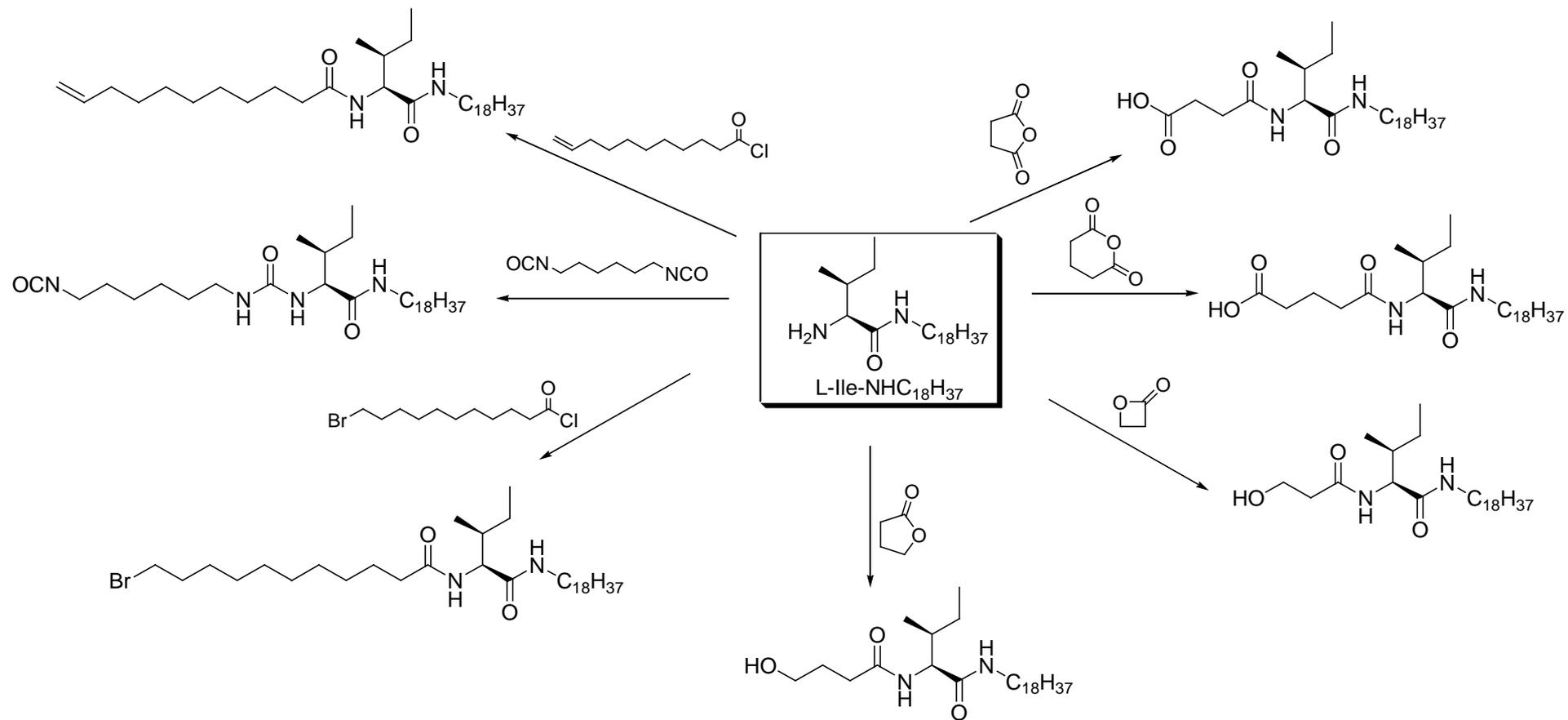The 3rd and 4th rounds were done similarly to the 2nd round.

Figure 12. Functional gelators derived from gelation-driving segment (L-Ile-NHC$_{18}$H$_{37}$)
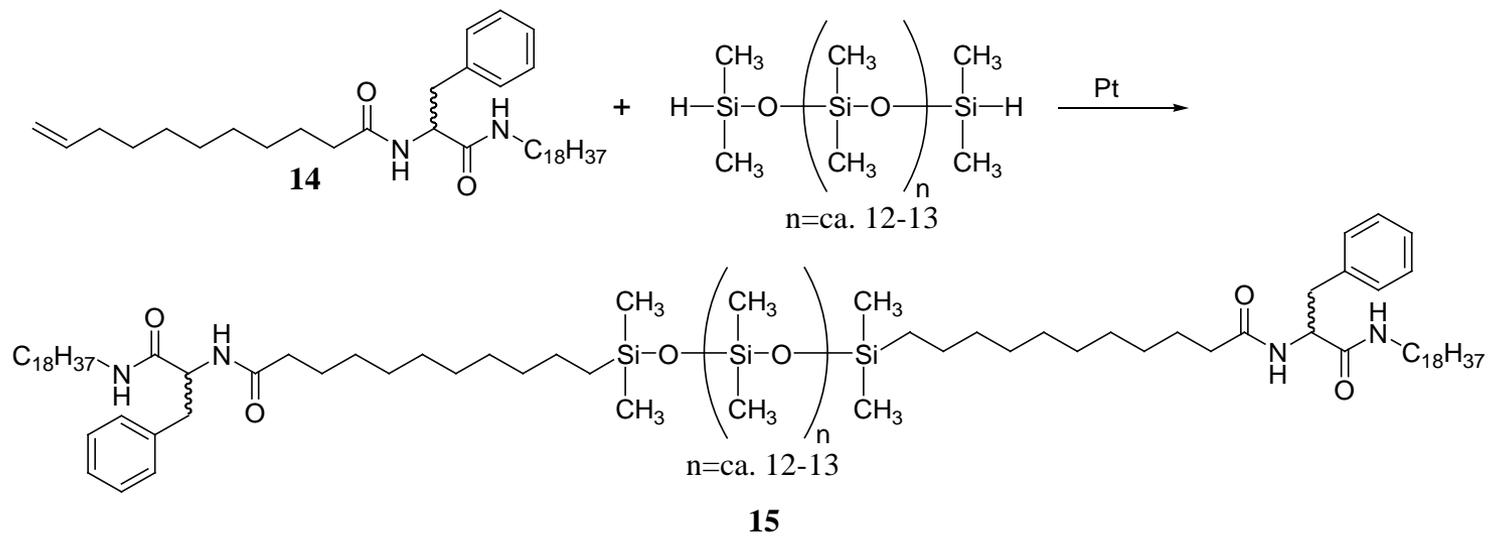
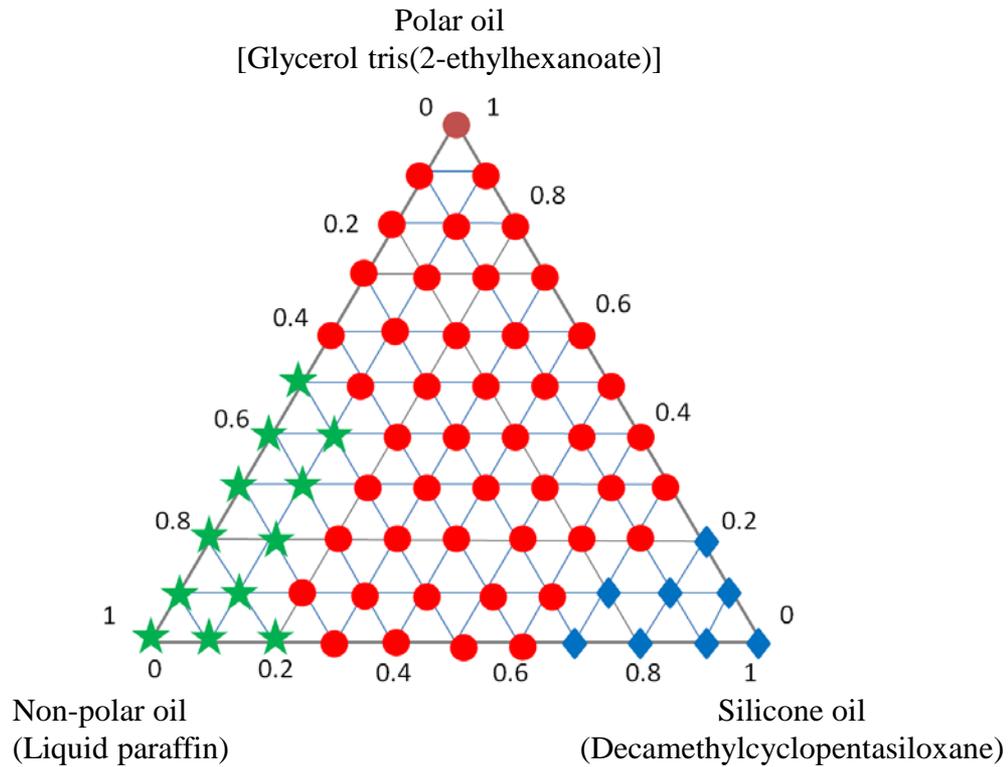Figure 13. Reaction scheme for polymer-type gelator 15.

Figure 14. Gelation behavior of polymer type of gelator **15**. Concentration = 20 g/L, Transparent gel (★), Translucent gel (●), Opaque gel (◆)
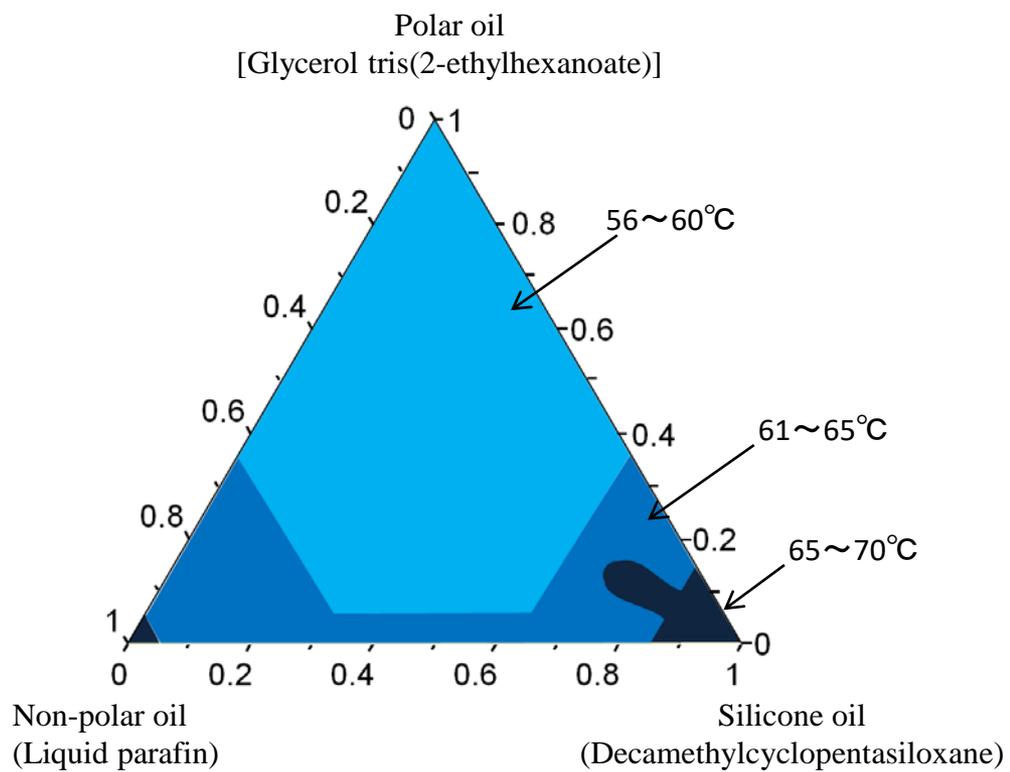
Figure 15. Sol-gel transition temperature of polymer-type gelator **15**
in three-component solvents.

Physical Gelation by Low Molecular-weight Compounds and Development of Gelators

Kenji Hanabusa* and Masahiro Suzuki

Gelators are compounds that can cause physical gelation. The driving forces for the physical gelation are non-covalent bonds. The formation of fibrous aggregates is an important factor responsible for gelation. Aggregation of gelator molecules can be often observed by electron microscopy.