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Amino Acid Derivatives of Cholesterol as "Latent" Organogelators with Hydrogen Chloride as a Protonation Reagent

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A series of low molecular weight organic gelator (LMOG) gel systems sensitive to alkaline/acidic stimuli was established by employing amino acid derivatives of cholesterol as "latent" gelators, which are cholesteryl glycinate (**1**), cholesteryl L-alaninate, cholesteryl D-alaninate, cholesteryl L-phenyl alaninate, and cholesteryl D-phenyl alaninate. The hydrochloric salts are denoted as **2**, **3**, **4**, **5**, and **6**, respectively. For the 18 solvents tested, one proved to be a weak gelator and gels only two of the solvents. Its gelation ability, however, was greatly improved by bubbling HCl gas, which was produced by reaction of concentrated sulfuric acid with NaCl, through its solution owing to protonation of its amino group. It was demonstrated that the protonated form of it gelled 14 of the solvents tested. Further investigation revealed that the gels changed into solution with addition of any of the amines, including triethylamine (TEA), diethylamine, ethylenediamine, and NH_3. The phase transition could be reversed by further introduction of the acidic gas. SEM measurements showed that **1** self-assembled into different supramolecular structures in different gels. Salt effect studies proved that electrostatic interaction is one of the driving forces for formation of the gels.

1. Introduction

Research in the field of organogels has received increasing attention over the last several years, and the number of low molecular weight organic gelators (LMOGs) is rapidly growing.[1−4] Organogels are materials that consist of an organic liquid and a small amount of a LMOG. Generally speaking, LMOG molecules in a gel self-assemble into crystalline fibers, tapes, strands, or other aggregates with high length-to-width ratios.[5] These elongated objects link each other at "junction zones"[5] to form three-dimensional networks that immobilize solvent by capillary forces and surface tensions.[1,2] Unlike chemical gels, reversible phase transition (solution to gel and gel to solution) in physical gel systems is possible due to the forces maintaining the network being physical in nature. From an application viewpoint, stimuli-responsive phase transition promises accessibility for designing and constructing sensors, actuators, and other molecular devices, etc.[6] To date, most of the reported organogels from LMOGs have been thermoreversible. Actually, formation of some of the organogels can also be controlled by chemical or physical stimuli, such as light,[7] sound,[8] pH,[7c,9] host−guest interaction,[10] charge separation,[11] complexation,[11] oxidative/reductive reactions[12,13] and even a combination of some of them.[13,14] Organogels with stimuli-responsive properties, however, are limited. Recently, examples of chemically reversible LMOGs exhibiting very different gelation properties when in their charged or uncharged states have been reported. For instance, George and Weiss[15] reported that "latent gelators" consisting of structurally simple, uncharged alkylamines or aliphatic amines become rather efficient LMOGs, ammonium carbamates, when CO_2 is introduced. Their further work revealed that not only can CO_2 turn the primary alkylamines into efficient LMOGs, but other neutral triatomic molecules, like NO_2, SO_2, and CS_2 can also turn the amines into efficient LMOGs.[16] Similar to addition of neutral small quadrupolar X = Y = X molecules with large partial positive charges on the Y atom, protonation can also change LMOGs with a primary amino group into charged LMOGs. Pozzo and co-workers[17] reported that some LMOGs with a phenazine moiety form less stable gels and more stable ones when the phenazine is protonated. Surprisingly, to the best of our knowledge, there is no report of LMOGs based on amino acid derivatives of cholesterol, although amino acid derivatives have played significant roles in recent advances of supramolecular hydrogel and organogel preparations.[18] Here we report some

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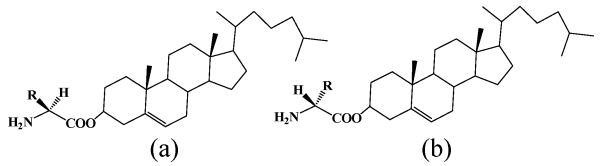
Scheme 1. Compounds Prepared in the Present Work: (a) L-Amino Acid Derivatives of Cholesterol and (b) D-Amino Acid Derivatives of Cholesterol



examples of amino acid derivatives of cholesteryl, a class of "latent gelators", and a series of novel gel systems containing one of the hydrochloric salts of the latent gelators. It was found that the gel formation processes can be controlled by simple introduction and neutralization of HCl gas or its solution or by introducing and driving out the acidic gas.

2. Results and Discussion

Considering the hydrophobic nature of cholesterol, the hydrogen bond forming ability of amino acids, and the fact that a free amino group will remain after reacting an amino acid with cholesterol, it may be of interest to look at the gelation behavior of a compound possessing the two properties and a free amino group. It is expected that the compound could be changed from an uncharged form into a charged form by simple introduction of acidic gas or an acid, like HCl gas or its solution. The gelation behavior of the compound in the two states may be different from each other, and some latent gelators may be created. In addition, the compounds are easily prepared, and the starting reagents are inexpensive. Furthermore, a series of compounds with similar structures can be prepared by simply varying the structure of R and the chirality of the amino acid (L or D, cf. Scheme 1a and b).

According to the strategy described, various amino acid derivatives, including glycine, L-alanine, D-alanine, L-phenyl alanine, and D-phenyl alanine, of cholesterol were prepared. The hydrochloric salts of them are denoted as **2**, **3**, **4**, **5**, and **6**, respectively, and the uncharged cholesteryl glycinate as **1**.

The gelation ability of **1**−**6** was tested for 18 different solvents with 2.5 wt % as a standard concentration. The results are summarized in Table 1. Examination of the table reveals that **1**, **4**, **5**, and **6** are poor gelators. They only gel a few of the solvents tested. However, **2** and **3** gel most of them. In particular, **2** gels 14 of the 18 solvents, in sharp contrast to that of its uncharged form, indicating that protonation of the amino group of **1** is crucial for the gelation process. The poor gelation ability of **1** is further demonstrated by the poor stability of the gels containing it and one of the solvents, 1-butanol or glycol. The gel containing **1** and 1-butanol can only keep its shape at room temperature for less than 2 days and the other one for less than 1 week. In contrast, gels containing **2** are very stable. In fact, no visible changes occur during 3 months preservation of the gel in a closed container at room temperature.

Further examination of the table reveals that the gelation ability of a compound in the table is also dependent upon the chirality of the amino acid moiety in the compound, as shown by the different gelation behavior of **3** and **4**, **5**, and **6** in the same solvent. Details of the conformational effect on the gelation behavior of a given amino acid derivative of cholesterol are under investigation, and results will be reported in the future.

It is to be noted that in gels containing **1** or **2**, only those consisting of **2**/1-octanol, **2**/1-nonanol, **2**/1-decanol, and **2**/glycol are transparent, the others are turbid. To look at the differences between the aggregation mode of the turbid gel and that of the transparent gel, SEM measurements were conducted using

Table 1. Gelation Properties of 2.5 wt % Amino Acid Derivatives of Cholesterol in Various Solvents[a]

solvents	1	2	3	4	5	6
benzene	S	I	I	I	G	PG
formic acid	S	S	S	S	S	S
carbon tetrachloride	S	I	I	I	G	S
trichloromethane	S	TG	S	S	S	S
acetic acid	S	TG	TG	TG	P	TG
propionic acid	S	TG	PG	PG	P	TG
water	I	E	E	E	E	E
methanol	P	PG	S	S	S	S
ethanol	S	TG	TG	S	P	P
1-propanol	S	TG	TG	S	P	P
1-butanol	TG[a]	TG	TG	S	P	S
1-pentanol	S	TG	TG	S	P	S
1-hexanol	S	TG	TG	S	S	S
1-heptanol	S	TG	TG	S	S	S
1-octanol	S	G	TG	S	S	S
1-nonanol	S	G	TG	S	S	S
1-decanol	S	G	TG	S	S	S
glycol	TG[b]	G	E	S	S	TG

[a] S = solution, P = precipitate, I = insoluble, E = emulsion, PG = partial gel, TG = turbid gel, and G = transparent gel. All gels were stable at room temperature in closed tubes for >3 months except a < 2 days and b < 1 week; 3, 4, 5, and 6 denote the hydrochloric salts of cholesteryl L-alaninate, cholesteryl D-alaninate, cholesteryl L-phenylalaninate, and cholesteryl D-phenylalaninate, respectively.

2/ethanol and **2**/1-octanol as examples. The results are shown in Figures 1 and 2, respectively. Examination of the SEM images shown in the figures reveals that the two gels adopt similar rodlike structures with high length-to-width ratios (Figures 1a and 2a). The lengths of the rods can reach several hundred micrometers. Further examination of the images shows that the rods in both of the two gel systems are stacked, but most of them in Figure 1a seem to be cracked. Furthermore, the distinctions in the fine structures of the two gels are also obvious. The "rod" in the turbid gel looks like a hollow prism with a width of about 5 μm (Figure 1b and 1c). In contrast, however, the transparent gel takes ribbonlike fine structures with a width of about 1 μm (Figure 2b and 2c). No hollow structure was observed in this gel. In addition, heterogeneous stacking of the rods in the turbid gel is observed (Figure 1b), which might explain why the bulky gel looks heterogeneous and turbid.[18a,19]

T_{gel} is another parameter denoting gel thermostability. Examination of Figure 3 reveals that the stability of the gel is very dependent upon the concentration of the gelator. For the **2**/1-octanol system, T_{gel} increases linearly along with increasing concentration of **2**. Titration of **2**/1-octanol with triethylamine (TEA) decreases the T_{gel} of the system linearly (cf. Figure 4). In fact, the gel disappears when TEA concentration exceeds a certain value. The observation may be rationalized by considering that **2** reacts with TEA and forms **1** and the hydrochloric salt of TEA (Scheme 2). As indicated earlier, **1** is not an efficient gelator for the solvent, the concentration of the gelator, **2**, decreases along with the titration, and thereby the T_{gel} of the system decreases.

The decrease in the thermostability of the gel must result from several factors since the observed decrease in the figure is significantly faster than what we expected from the decrease in the concentration of **2** alone. On the basis of this consideration, the dilution effect and salt effect on the T_{gel} of the system were studied, and the results are presented in Figure 5. Careful examination of the figure reveals the following. (1) For the system tested, the gel changed into solution with addition of more than

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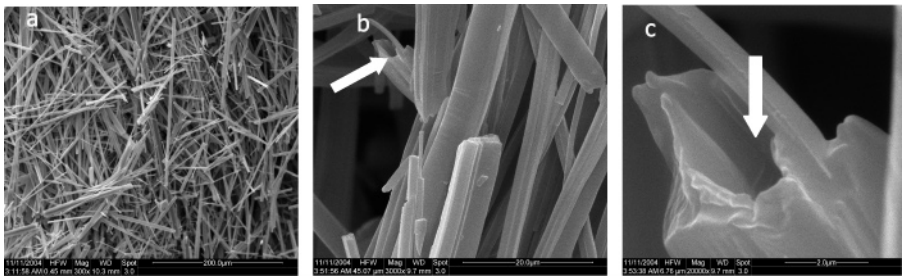


Figure 1. SEM micrographs of the xerogel of **2** from ethanol (turbid gel) (Bar = 200 mm, 20 μm, and 5.0 μm for a, b, and c, respectively).

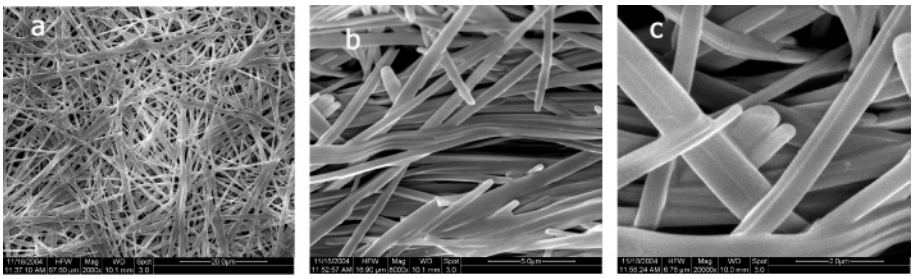


Figure 2. SEM micrographs of the xerogel of **2** from 1-octanol (transpartent gel) (Bar = 20 μm, 5.0 mm, and 2.0 μm for a, b, and c, respectively).

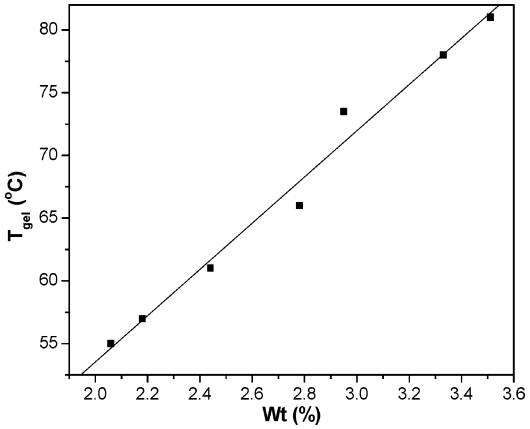


Figure 3. Plot of T_{gel} against the concentration of **2** in 1-octanol.

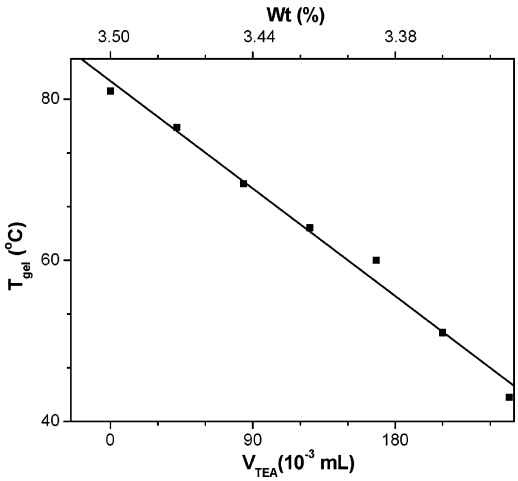


Figure 4. Plot of T_{gel} of **2**/1-octanol gel against the volume of TEA and the concentration of **2**.

43.5 μL of TEA. Further addition of 300 μL of HCl/1-octanol solution to the system, and then heating and cooling, resulted in a gel again. The gel-to-solution and solution-to-gel phase transition processes can be repeated more than three times by alternative addition of TEA and HCl/1-octanol solution. (2) As expected,

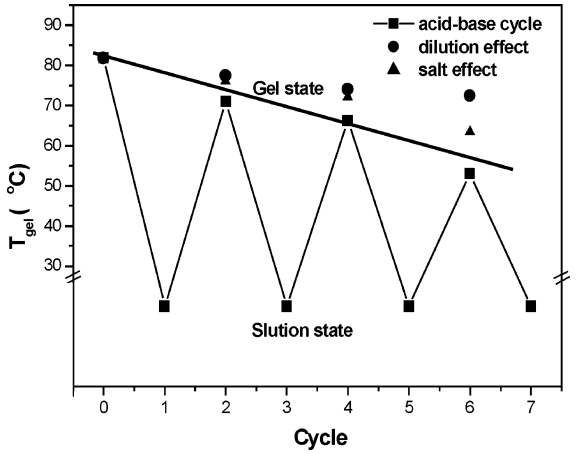
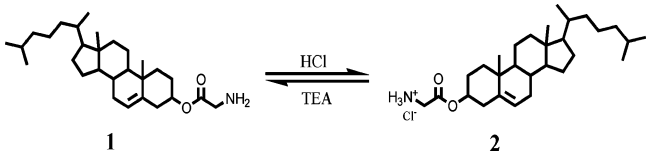


Figure 5. Acid−base cycle of the sol−gel phase transition of **2**/1-octanol gel, and dilution effect and salt effect upon the T_{gel} of the system.

Scheme 2. Protonation and Deprotonation of Cholesteryl Glycinate



the T_{gel} of the system decreases along with increasing cycle numbers. Simple addition of a pure solvent, 1-butanol, also resulted in decreasing T_{gel}, indicating that dilution is one of the main reasons responsible for the decrease. The result is also shown in the figure. Similarly, addition of the hydrochloric salt of TEA also resulted in decreases in the T_{gel} values, another important factor affecting the stability of the gel. Considering the measurement error, it may be concluded that it is the deprotonation (Scheme 2), dilution, and salt addition that caused the decrease in the T_{gel} of the system. Furthermore, in addition interactions such as stacking[1,2] and hydrogen bonding,[18] which are the driving forces in self-assembly of the molecules containing cholesterol and amino acid, respectively, exist of salt effect indicates that electrostatic interaction may be one of the driving

forces for the self-assembly of **2** in the system. This tentative conclusion was further evidenced, indirectly, by the result from X-ray analyses of the single crystal of **5**, which was made from its ethanol solution (see Supporting Information). Clearly, an increase in the concentration of the salt must increase the ionic strength of the system and thereby screen the electrostatic interaction between different gelator molecules and thus decrease the stability of the gel. It is to be noted, however, that the **2**/1-octanol gel can be also destroyed by driving out HCl, which can be realized by either heating the gel at a temperature above 100 °C in an open vial for several minutes or bubbling N_2 through the heated gel. The gel can be formed again by simple introduction of HCl/1-octanol. This gel formation/dissolution cycle can be repeated more than three times.

The gelation ability of the cholesterol-based gelator, **1**, can also be tuned using HCl gas and NH_3 gas as reagents. It was demonstrated that the values of T_{gel} for the gel systems corresponding to the mother, the first, the second, and the third cycles of the gelation/dissolution process are 81, 78, 70, and 65 °C, respectively. Clearly, the decrease in T_{gel} may be rationalized by considering the salt (NH_4Cl) effect as discussed above.

It is to be noted that it might be possible to turn the latent gelators reported in this article into efficient gelators using neutral triatomic molecules, such as CO_2, NO_2, SO_2, and CS_2, etc., as activating reagents because they can react with the primary amines and result in charge separation, which may enhance intermolecular interaction between different molecules of the gelators.[15a]

3. Conclusion

A novel alkaline−acidic responsive LMOG gel system was established utilizing cholesterol glycinate as a "latent gelator" with HCl as a protonation reagent. The gel systems containing other amino acid derivatives of cholesterol showed similar behaviors, but the gelling performances of these amino acid derivatives depend on the chirality of the compounds.

4. Experimental Section

Gelation Test. A known weight of potential gelator and a measured aliquot of liquid were placed into a sealed test tube, and the system was heated in an oil bath until the solid was dissolved; then, the solution was cooled slowly to room temperature in a water bath, and finally the test tube was turned upside down to see at if the solution inside could still flow. A positive test is obtained if the flow test is negative. It is to be noted that some of the obtained gels are turbid (TG) and some transparent (G). In some cases, solution and solidlike gel may coexist within a system. This kind of system has been referred to as "partial gels (PG)". For systems in which only solution remained until the end of the tests, they were referred to as nongelling systems (S). The system in which the potential gelator could not be dissolved even at the boiling point of the solvent was called an insoluble system (I). In a few cases, emulsions (E) were also observed.

Gel-to-Sol Transition Temperature (T_{gel}) Measurement. Temperatures of gel to solution (T_{gel}) were measured using a conventional falling ball method.[20] In the test a small glass ball ($d \approx 3$ mm) was placed on top of the gel in the test tube ($d = 10$ mm). The tube was slowly heated in a thermostated water bath until the ball fell from the surface of the gel to the bottom of the tube. The two specific temperatures corresponding to the starting point of the falling process and the ending of it were recorded. The average of the two temperatures was taken as the T_{gel} of the system.

SEM Observation. SEM pictures of the xerogel were taken on a Quanta 200 Scanning Electron Microscopy spectrometer (Philips-FEI). The accelerating voltage was 15 kV, and the emission was 10 mA. The xerogel was prepared by freezing the gel in liquid nitrogen, and it was then freeze dried.

Preparation of 2. Step a: 0.175 g (1 mmol) of Boc-glycin and 0.387 g (1 mmol) of cholesterol were dissolved in 40 mL of dichloromethane. The solution was maintained at 0 °C using an ice bath. A 0.206 g (1 mmol) amount of dicyclohexylcarbodimide (DCC) and 0.012 g (1 mmol) of *N*,*N*-dimethylaminopyridine (DMAP) were then added, and the reaction mixture was stirred for 4 h at 0 °C. After reaction, the mixture was filtered and the filtrate washed with 0.001 mol L^{-1} hydrochloric acid (30 mL × 3), 0.001 mol L^{-1} sodium hydroxide aqueous solutions (30 mL × 3), and pure water (30 mL × 3). The organic layer was evaporated to dryness. The residue was purified by a silica gel column eluting with THF/*n*-hexane (1:6, v/v) to give cholesteryl Boc-glycinate in 64% yield as a white solid. Step b: 0.544 g (1 mmol) of cholesteryl Boc-glycinate was dissolved in 100 mL of dichloromethane and then bubbled with dry HCl gas for 30 min. The mixture was filtered, and the residue was washed with dichloromethane and dried in a vacuum to give the desired product in 90% yield as a white crystal. ^{1}H NMR ($CDCl_3$/Me_4Si): δ (ppm) 5.37 (1H, alkenyl), 4.66−4.69 (1H, m, oxycyclohexyl), 3.98 (2H, d, CH_2CO, $J = 1.26$ Hz), 2.31−2.34 (2H, d, CH_2, $J = 7.68$ Hz), 0.67−1.85 (42H, m, cholesteryl protons). FT-IR (cm^{-1}): 3478 (NH), 2945, 2861 (CH), 1744 (CO), 1611 (NH), 1246 (−C−O). Anal. Calcd for $C_{29}H_{52}O_3NCl$: C, 69.95; H, 10.84; N, 2.81. Found: C, 70.21; H, 10.46; N, 2.58.

Preparation of 3, 4, 5, and 6. The preparation procedures used for the preparation of **3**, **4**, **5**, and **6** are similar to that for **2**. Satisfactory results were obtained. For **3**: ^{1}H NMR ($CDCl_3$/Me_4Si) δ (ppm) 8.67 (3H, NH_3), 5.36 (1H, alkenyl), 4.61−4.65 (1H, m, oxycyclohexyl), 4.20−4.22 (1H, m, $CH(CH_3)CO$), 2.31−2.33 (2H, d, CH_2, $J = 5.7$ Hz), 0.67−1.87 (44H, m, methyl, cholesteryl protons). FT-IR (cm^{-1}): 3437 (NH), 2941, 2867 (CH) 1741 (−C═O), 1259 (−C−O). Anal. Calcd for $C_{30}H_{52}NO_2Cl$: C, 72.95; H, 10.54; N, 2.84. Found: C, 72.53; H, 10.51; N, 2.60. For **4**: ^{1}H NMR ($CDCl_3$/Me_4Si) δ (ppm) 8.67 (3H, NH_3), 5.36 (1H, alkenyl), 4.61−4.65 (1H, m, oxycyclohexyl), 4.20−4.22 (1H, m, $CH(CH_3)CO$), 2.31−2.33 (2H, d, CH_2, $J = 7.68$ Hz), 0.67−1.87 (44H, m, methyl, cholesteryl protons). FT-IR (cm^{-1}): 3437 (NH), 2941, 2867 (CH), 1741 (−C═O), 1259 (−C−O). Anal. Calcd for $C_{30}H_{52}NO_2Cl$: C, 72.95; H, 10.54; N, 2.84. Found: C, 72.39; H, 10.63; N, 2.71. For **5**: ^{1}H NMR ($CDCl_3$/Me_4Si) δ (ppm) 8.78 (3H, NH_3), 7.24−7.31 (5H, m, benzyl), 5.30 (1H, alkenyl), 4.53 (2H, m, oxycyclohexyl), 4.36 (2H, m, $CH_2(C_6H_5)CO$), 3.31−3.47 (2H, m, $CH_2(C_6H_5)$), 0.66−2.10 (43H, m, cholesteryl protons). FT-IR (cm^{-1}): 3440 (NH), 2936, 2868 (CH), 1748 (−C═O), 1281 (−C−O), 846, 798, 755 (C_6H_5). Anal. Calcd for $C_{36}H_{57}NO_2Cl$: C, 75.86; H, 9.83; N, 2.46. Found: C, 75.26; H, 9.45; N, 2.70. For **6**: ^{1}H NMR ($CDCl_3$/Me_4Si) δ (ppm) 8.78 (3H, NH_3), 7.24−7.31 (5H, m, benzyl), 5.30 (1H, alkenyl), 4.36−4.54 (3H, m, oxycyclohexyl, $CH_2(C_6H_5)CO$), 3.33−3.49(2H, m, $CH_2(C_6H_5)$), 0.66−2.25 (43H, m, cholesteryl protons). FT-IR (cm^{-1}): 3438 (NH), 2941, 2868 (CH), 1744 (−C═O), 1244 (−C−O), 844, 803, 787 (C_6H_5). Anal. Calcd for $C_{36}H_{57}NO_2Cl$: C, 75.86; H, 9.83; N, 2.46. Found: C, 75.24; H, 9.89; N, 2.45.

TEA Titration Test. A 44.0 μL amount of TEA/1-octanol solution (v/v = 1:9) was added to a solution of 0.1499 g of **2** in 5 mL of 1-octanol, and the T_{gel} of the system was measured. Another 44.0 μL of TEA solution was added to the system already containing some TEA, and the T_{gel} of the system was measured again. The process was repeated several times. In this way, the TEA titration curve was obtained (cf. Figure 4).

Acid/Base Cycle Studies. The T_{gel} of the gel system formed from 0.1503 g (0.0003 mol) of **2** and 5 mL of 1-octanol was measured first. Then (1) 43.5 μL (0.0003 mol) of TEA was added to the system, and a transparent solution was obtained after heating and then cooling. (2) To the obtained solution, 300 μL of HCl/1-octanol solution (1.0 mol/L) was added. If a gel was formed after heating and cooling, then T_{gel} was measured. After repeating steps 1 and 2 several times, some of the data shown in Table 1 was obtained. The data for the dilution effect was obtained by simply repeating the above process using pure 1-octanol instead of the TEA solution and the acid solution.

(20) Takahashi, A.; Sakai, M.; Kato, T. *Polym. J.* **1980**, *12*, 335−341.

The acid/base cycle was also conducted using HCl gas and NH_3 gas instead of HCl/1-octanol solution and TEA, respectively. The details of the experiment are similar to that described above. The acid/base cycle was repeated three times.

Salt Effect Study. A varying amount, 0.044 g (0.0003 mol), 0.088 g (0.0006 mol), and 0.132 g (0.0009 mol), of the hydrochloric salt of TEA was added to the mother gel system used for the acid/base cycle test, and the T_{gel} of each system was measured. The result is also shown in Table 1.

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Supporting Information Available: X-ray analyses results and experimental procedures for making a single crystal of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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