Effect of amide moieties for hydrogelators on gelation property and heating-free pH responsive gel-sol phase transition

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Abstract: Two long-chain amidoamine derivatives (C13A2AOH and C17A2AOH) bearing three amide moieties were synthesized and their gelation ability and pH responsivity were compared with a similar, previously reported amidoamine derivative gelator with two amide moieties. C13A2AOH and C17A2AOH gels prepared in water and organic solvents acted as ambidextrous low molecular mass gelators. X-ray diffraction and Fourier transform infrared spectroscopy analyses revealed that C13A2AOH and C17A2AOH formed lamellar-like aggregates in the gels, where the amide moieties were in a strong intermolecular hydrogen-bonding state. The gelation ability, *i.e.*, the molar ratio of solvent to gelator, was significantly dependent on the length of the alkyl chain and the number of amide moieties. In addition, the C13A2AOH and C17A2AOH hydrogels exhibited highly pH-responsive gel-sol transitions. The gel-sol transition for the hydrogels was induced by protonation of the ternary amine and the transition was completely reversible by regulating only the pH without heating.

Key words: low molecular-weight gel, pH- responsive, surfactant, amide, hydrogel

1 INTRODUCTION

Stimuli-responsive materials have been extensively studied due to potential applications including micromachines and pollutant removal materials¹⁾. In particular, pH-responsive materials have attracted significant interest for pharmaceutical applications, due to the presence of pH variations within different tissues and cellular compartments. For instance, cancerous tissues have slightly lower pHs of 6.5-7.2 than that of normal tissue and blood. Basic research on chemical therapy has employed pH sensitive polymers such as poly(*N*-isopropyl acrylamide) copolymers, poly(acrylic acid) copolymers and poly(lactic acid) copolymers as carriers to deliver drugs or bioactive molecules into an affected area with a lower pH²⁾. In recent years, supramolecular assemblies based on low molecular-weight gelators have received increased attraction as alternative materials that are superior to conventional pH sensitive polymers. Low molecular-weight gelators can form long fibril aggregates by self-assembly *via* noncovalent forces, such as hydrogen bonding, and van der Waals or electrostatic interactions³⁾; therefore, high stimuli responsiveness can be installed into the molecular assemblies of the

gelators⁴⁾.

We have previously reported that a long-chain amidoamine derivative (C18AOH, Fig. 1a) bearing two amide groups and terminal hydroxyl groups as the hydrophilic portion can act as an ambidextrous low molecular mass gelator^{5,6)}, in that it has both properties of a hydrogelator and organogelator. It was also demonstrated that the hydrogel has pH responsivity and undergoes a phase transition from gel to a low viscous solution at a pH of ca. 3 when

Fig. 1 Molecular structures of (a) C18AOH, (b) C13A2AOH and (c) C17A2AOH.

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the ternary amine at the bifurcation portion of C18AOH is protonated at a lower pH. However, compared with conventional high-performance hydrogels⁴⁾, the minimum gelation concentration (MGC) of the C18AOH hydrogel is somewhat high; therefore, it is necessary to improve the gelation ability for practical application as a pH-responsive material. In this paper, novel derivatives of C18AOH with an additional amide moiety in the long-chain [C13A2AOH (Fig. 1b) and C17A2AOH (Fig. 1c)] were synthesized and their gelator ability was examined. In addition, the effect of the inserted amide moiety and alkyl-chain length on the pH-responsivity of the C17A2AOH and C13A2AOH hydrogels is discussed.

2 EXPERIMENTAL PROCEDURES

2.1 Materials

All chemicals used were reagent grade and obtained from Aldrich or Kanto Chemicals. Commercially available reagents and solvents were used as-received, without further purification, except methyl acrylate (Kanto Chemicals), which was purified by distillation under reduced pressure in a nitrogen atmosphere, and octadecylamine, which was recrystallized twice from hexane.

2.2 Synthesis of C13A2AOH

2 g (8.3 mmol) of methyl myristate was added to 12.3 g (0.20 mol) of ethylenediamine in 15 mL of dehydrated methanol. The solution was stirred at room temperature for 10 days. Upon removal of the solvent by evaporation and freeze-drying, excess methyl myristate and ethylenediamine were removed by recrystallization from methanol, resulting in tetradecanoic acid (2-amino-ethyl)-amide (C13A2N) in 96% yield.

14.2 g (0.17 mol) of methylacrylate was added to 2.2 g (8.3 mmol) of C13A2N in 15 mL of dehydrated methanol. The solution was stirred at room temperature for 3 days and the solvent and excess methylacrylate were then removed from the solution by rotary evaporation. 3-[(2-methoxycarbonyl-ethyl)-(2-tetradecanoylamino-ethyl)-amino]-propionic acid methyl ester (C13A2OMe) was obtained in 98% yield.

20.2 g (0.33 mol) of 2-aminoethanol and 3.6 g (8.3 mmol) of C13A2OMe were dissolved in 15 mL of dehydrated methanol and the mixture was stirred for 2 weeks at room temperature. Removal of the solvent and 2-aminoethanol by rotary evaporation and freeze-drying produced tetradecanoic acid (2-bis-[2-(2-hydroxy-ethylcarbamoyl)-ethyl]-amino)-ethyl)-amide (C13A2AOH) as a white solid. The crude solid was recrystallized from acetone to give a yield of 95%. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl₃ with a Bruker 400 Ultrashield spectrometer operating at 400 MHz. Mass spectra were re-

corded using a Bruker Daltonics micrOTOF focus mass spectrometer.

¹H-NMR (CDCl₃): δ 0.88 (t, 3H, CH₃), 1.25 (br, 18H, CH₂), 1.27 (br, 2H, CH₂CH₃), 1.56 (quin, 2H, CH₂CH₂CH₂CO), 2.17 (t, 2H, CH₂CH₂CH₂CO), 2.38 (t, 4H, NCH₂CH₂CO), 2.52 (t, 2H, NHCH₂CH₂N), 2.71 (t, 4H, NCH₂CH₂CO), 3.30 (q, 2H, NHCH₂CH₂N), 3.40 (q, 4H, NHCH₂CH₂OH), and 3.69 (q, 4H, CH₂CH₂OH) ppm. High resolution mass spectrometry (HRMS): Calcd for C13A2AOH (M + H⁺) 500.7, Found 501.4.

2.3 Synthesis of C17A2AOH

2.5 g (8.3 mmol) of methyl stearate was added to 12.3 g (0.20 mol) of ethylenediamine in 15 mL of dehydrated methanol. The solution was stirred at room temperature for 10 days. The solvent was removed by evaporation and freeze-drying, and excess methyl stearate and ethylenediamine were removed by recrystallization from methanol to afford octadecanoic acid (2-amino-ethyl)-amide (C17A2N) in 95% yield.

14.2 g (0.17 mol) of methylacrylate was added to 2.7 g (8.3 mmol) of C17A2N in 15 mL of dehydrated methanol. The solution was stirred at room temperature for 3 days followed by removal of the solvent and excess methylacrylate by rotary evaporation to afford 3-[(2-methoxycarbonyl-ethyl)-(2-octadecanoylamino-ethyl)-amino]-propionic acid methyl ester (C17A2OMe) in 95% yield.

20.2 g (0.33 mol) of 2-aminoethanol and 4.2 g (8.3 mmol) of C17A2OMe were dissolved in 15 mL of dehydrated methanol and the mixture was stirred for 2 weeks at room temperature. Removal of the solvent and 2-aminoethanol by rotary evaporation and freeze-drying afforded tetradecanoic acid (2-bis-[2-(2-hydroxy-ethylcarbamoyl)-ethyl]-amino)-ethyl)-amide (C17A2AOH) as a white solid. The crude solid was recrystallized from acetone with 95% yield.

¹H-NMR (CDCl₃): δ 0.88 (t, 3H, CH₃), 1.25 (br, 26H, CH₂), 1.27 (br, 2H, CH₂CH₃), 1.57 (quin, 2H, CH₂CH₂CH₂CO), 2.17 (t, 2H, CH₂CH₂CH₂CO), 2.38 (t, 4H, NCH₂CH₂CO), 2.52 (t, 2H, NHCH₂CH₂N), 2.71 (t, 4H, NCH₂CH₂CO), 3.30 (q, 2H, NHCH₂CH₂N), 3.40 (q, 4H, NHCH₂CH₂OH), and 3.69 (q, 4H, CH₂CH₂OH) ppm. HRMS: Calcd for C17A2AOH (M + H⁺) 557.5, Found 557.5.

2.4 Gelation test

The gelator and solvent were mixed in a test tube and heated until the solid was completely dissolved above ca. 70°C. Note that Krafft points of gelators were 55°C for C18AOH, 49°C for C13A2AOH and 68°C for C17A2AOH. The solution was then left to cool to room temperature. After a few hours, when the solution appeared as a solid-like aggregate, the test tube was turned upside down. The aggregate was considered to be a gel if the solid-like aggregate was completely immobilized. The pH-responsive gela-

tion behavior was observed by adding NaOH or HCl aqueous solution to the gelator solutions and leaving the solution at room temperature without heating or cooling for 1 h.

2.5 Characterization of gels

X-ray diffraction (XRD) measurements were performed with a Rigaku Ultima IV diffractometer using freeze-dried samples of 2 wt% hydrogels.

Fourier transform infrared spectroscopy (FT-IR) was conducted using a spectrometer (Thermo Fisher Scientific Nicolet 6700 FT-IR) equipped with a MCT detector with a resolution of 4 cm^{-1} . A demountable liquid cell with a CaF_2 window was employed for the D_2O solution FT-IR measurements. 1000 scans were recorded and averaged for each spectrum.

Scanning electron microscopy (SEM) was performed using a Jeol JCM-5700 microscope. A tube containing the gel was immersed in liquid nitrogen until the sample was frozen. The frozen sample was then dried in a vacuum and the dry gel (xerogel) was then subjected to Au-Pd sputtering (Hitachi E-1010 sputter coater).

2.6 pH titration

pH titration was conducted using a pH meter (Hanna Instruments HI 1290). The electrode was calibrated with a standard buffer solution prior to use. 0.75 mmol of gelator was dissolved in 30 mL of Millipore water and 4 mL of 0.2 M NaOH solution was added to the solution. Titration was performed by the addition of 0.1 N HCl solution at room temperature.

3 RESULTS AND DISCUSSION

3.1 Gelation ability of C13A2AOH and C17A2AOH

The gelation ability of C13A2AOH and C17A2AOH in some organic solvents and water is summarized in **Table 1** and compared with that of C18AOH⁽⁶⁾. Both C13A2AOH and C17A2AOH formed gels in benzene and water, and exhibited ambidextrous gelation properties. C13A2AOH, which has almost the same molecular length as C18AOH, exhibits gelation capability in apolar solvents such as toluene, benzene, xylene and CCl_4 , as does C18AOH. In contrast, C17A2AOH was precipitated in toluene and CCl_4 , and had poor organogelation ability, but high hydrogelation ability with a small MGC value of 0.3 wt%. The MGC value is strongly affected by not only the gelation ability, but also by the molecular weight of the gelator and solvent; therefore, it is difficult to directly compare their gelation abilities. The calculated gelation numbers (GN: molar ratio of solvent to gelator)⁽⁷⁾ are shown in the bottom column of **Table 1**. The GN value of 3067 to water for C13A2AOH was almost equal to that for C18AOH, while the GN for

Table 1 Gelation properties of C18AOH, C13A2AOH and C17A2AOH.

Solvents	MGC[wt%] (GN[-])		
	C18AOH	C13A2AOH	C17A2AOH
Toluene	0.2 (2522)	0.6 (839)	cryst ^a
Benzene	0.5 (1185)	0.9 (657)	0.9 (731)
CCl_4	0.3 (1080)	0.4 (809)	cryst ^a
H_2O	0.8 (3447)	1.2 (3067)	0.3 (11438)

^acryst: crystallization

C17A2AOH was 3 times larger, which indicates that C17A2AOH has superior hydrogelation ability to the C18AOH and C13A2AOH gelators.

3.2 Characterization of hydrogels

XRD analysis of the C13A2AOH and C17A2AOH hydrogels was conducted to evaluate the network structures of the gels. The XRD patterns in **Fig. 2** show four periodic reflection peaks at 2.17° , 4.28° , 6.41° , 8.56° for the C13A2AOH hydrogel, and at 1.91° , 3.76° , 5.73° , 7.51° for the C17A2AOH hydrogel. The appearance of the periodic peaks indicates that both hydrogels have aggregates with lamellar structures (**Fig. 2c**). The structures of the C13A2AOH and C17A2AOH hydrogels were the same as that for the C18AOH hydrogel⁽⁸⁾. On the basis of the first peak, the d spacing of the lamellar structure was evaluated to be 4.05 nm for C13A2AOH and 4.72 nm for C17A2AOH. The hydrocarbon chains in the lamellar structures of C13A2AOH and C17A2AOH were interdigitated, because the evaluated spacings were longer than the corresponding molecular length, but shorter than double the length. It was previously reported⁽⁶⁾ that C18AOH having almost the same molecular length as C13A2AOH showed a shorter d spacing of 3.47 nm, which indicates that both gelators have interdigitated states, but the degree of penetration of the alkyl-chain portions in C13A2AOH is lower than that in C18AOH.

FT-IR spectra of the C18AOH, C13A2AOH and C17A2AOH hydrogels in D_2O were measured and the results are shown in **Fig. 3**. The bands observed at 2921, 2850 and 1627 cm^{-1} for the C17A2AOH and C13A2AOH hydrogels (**Fig. 3**) are assigned to the antisymmetric and symmetric CH_2 stretching and amide I bands, respectively. The peak positions of the CH_2 stretching bands appear at a higher wavenumber than the corresponding positions at 2918 and 2849 cm^{-1} for the C18AOH hydrogel with the all-trans methylene chain. This result indicates that the alkyl-

Fig. 2 XRD patterns of (a) C13A2AOH and (b) C17A2AOH hydrogels. (c) Lamellar structures of the C13A2AOH and C17A2AOH hydrogels.

chains of C13A2AOH and C17A2AOH are not in the all-trans conformation, but contain some gauche conformations, such as the liquid crystal state of surfactant-water systems⁹. The observed bands at 2921 and 2850 cm^{-1} are in agreement with those observed for conventional hydrogels¹⁰.

However, the amide I band of the C13A2AOH and C17A2AOH hydrogels appears at a lower wavenumber of 1627 cm^{-1} , compared with 1635 cm^{-1} for C18AOH. The amide I band is a very sensitive monitor for the hydrogen state of the amide groups, and the shift to a lower wavenumber indicates that the degree of hydrogen bonding between the amide moieties in C13A2AOH and C17A2AOH is stronger than that in C18AOH. Thus, the introduction of an additional amide moiety into the chemical structure of

Fig. 3 FT-IR spectra of the C18AOH, C13A2AOH and C17A2AOH hydrogels in D_2O .

C18AOH causes the formation of a strong intermolecular hydrogen bonded network, which has a strong influence on the gelation ability.

3.3 pH-responsive behavior of hydrogels

Fig. 4 shows the photographs of the C13A2AOH and C17A2AOH hydrogels at various pHs and at room temperature. Both C13A2AOH and C17A2AOH in water undergo a gel-sol phase transition from the hydrogel (gel) at a high pH to a low viscosity transparent solution (sol) at a low pH, while an opaque dispersion with precipitates (suspension) is evident at a medium pH. SEM images of freeze-dried

Fig. 4 Photographs of the pH-responsive gel-sol transition of the (a) C13A2AOH and (b) C17A2AOH hydrogels at room temperature.

Fig. 5 SEM images of the C17A2AOH hydrogel at (a) pH 9.0 (gel phase), (b) pH 4.2 (suspension phase) and (c) pH 2.0 (sol phase).

samples of the gel, suspension and sol phases are shown in Fig. 5. Fiber-like aggregates are observed in the gel phase, and the amount of fiber aggregates is decreased in the suspension phase, while the fiber aggregates are absent in the sol phase.

FT-IR spectra of the gelators in the gel and sol phases were measured to obtain information on the molecular states. Table 2 shows the antisymmetric and symmetric CH_2 stretching and amide I bands at pH 9 (gel phase) and pH 2 (sol phase). The antisymmetric CH_2 stretching mode and amide I mode peaks are shifted to higher wavenumbers of ca. 2924 and 1638 cm^{-1} with decrease in the pH, which corresponds to melting of the alkyl chains and the weak hydrogen bonding state of the amide group, respectively^{9, 10}, when the gelators are completely dissolved in water at a lower pH. This conclusion is consistent with the transparency of the gelator solutions. Thus, the pH-responsive gel-sol transition was induced by a change in the solubility of the gelators.

Figure 6 shows pH titration curves for the hydrogels. The plateau regions were observed at pHs 4, 5 and 3.5 for C18AOH, C13A2AOH and C17A2AOH. Ottaviani et al¹¹ reported the pK_b values of poly(amidoamine) starburst dendrimers and showed that protonation of the external layer of the amine occurred at pH 7, whereas protonation of more internal amines occurred at pH 4. Consequently, it is reasonable to consider that the pH titration curve plateaus result from protonation of the internal ternary amines of the gelators. Furthermore, the amine acidity is generally affected by the electron density on the N atom, *i.e.*, the functional group and alkyl chain length of the molecular structure^{12, 13}. Thus, the difference in the pH of the plateau regions between the gelators is probably caused by the electron density variation on the N atom of the ternary amine, which is derived from the different chain lengths and the introduction of an additional amide moiety.

Figure 7 shows phase diagrams of the C18AOH, C13A2AOH and C17A2AOH hydrogels. The pHs at the boundary between the sol and suspension phases in Fig. 7 are almost equal to the corresponding pHs at the plateau region, which indicates that the sol-suspension transition is

Table 2 FT-IR spectral bands of the hydrogels at various pHs.

Gelators		CH_2 stretching band [cm^{-1}]		Amide I band [cm^{-1}]
		antisymmetric	symmetric	
C18AOH	pH 9	2917.6	2848.5	1635.1
	pH 2	2924.1	2853.1	1642.0
C13A2AOH	pH 9	2921.6	2850.3	1626.6
	pH 2	2924.6	2854.0	1637.7
C17A2AOH	pH 9	2920.5	2849.6	1627.0
	pH 2	2923.8	2852.7	1637.9

Fig. 6 pH titration curves of the C18AOH, C13A2AOH and C17A2AOH hydrogels.

Fig. 7 Phase diagrams for the pH-responsive behavior of C18AOH, C13A2AOH and C17A2AOH in water.

Fig. 8 Photographs of the pH-responsive gel-sol transition of the C18AOH, C13A2AOH and C17A2AOH hydrogels.

induced by the complete protonation of the ternary amine of the gelator. On the other hand, the boundaries between the gel and suspension phases correspond to the onset of protonation.

Finally, we discuss the sensitivity and reversibility of the pH-responsive gel-sol transitions. It would be advantageous to detect a slight pH change by the reversible gel-sol transition of a pH-responsive gel material. **Figure 7** shows that the C18AOH hydrogel has a broad suspension phase region of pHs 4-6, while C13A2AOH and C17A2AOH have narrow suspension phase regions of pHs 5-6 and pHs 3.5-4.5, respectively. Here, the suspension phases have quite low viscosity, because the networks of the fiber-like aggregates shorten due to the modest solubility of the gelators. In addition, the phase transition from suspension to gel cannot be achieved by simply increasing the pH without heating (**Fig. 8**), because the fiber-network of the gelator can not be constructed effectively from the precipitates. Thus, the suspension-gel phase transition of the C18AOH hydrogel by a change in the pH is an irreversible process. To obtain highly sensitive and reversible pH-responsive gel materials, it is necessary to avoid the suspension phase. **Figures 7 and 8** indicate that the C13A2AOH and C17A2AOH hydrogels, which have narrow suspension phase regions, would be suitable to cause a reversible gel-sol transition by a slight change in pH without heating or cooling.

4 CONCLUSION

We have demonstrated that both low molecular mass C13A2AOH and C17A2AOH gelators with three amide moieties have ambidextrous gel properties, and that C17A2AOH is the more favorable for hydrogel. The additional amide moiety in the alkyl chain plays an important role to improve the intermolecular hydrogen bonding. The molecular structure of the gelators, such as the amide moiety or the alkyl chain length influences the pH responsiveness of the gel-sol transition. The C17A2AOH and C13A2AOH hydrogels exhibit highly sensitive and revers-

ible pH responsivity that results in a gel-sol transition by a slight change in the pH.

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