



Supramolecular gelation of alcohol and water by synthetic amphiphilic gallic acid derivatives

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ABSTRACT

The supramolecular organogelation of alcohols was observed in relatively hydrophobic amphiphiles with a short oligo(ethylene glycol) unit and three long alkyl chains at room temperature, while the hydrogelation occurred in more hydrophilic gelators with a longer poly(ethylene glycol) unit and two long alkyl chains at various temperatures. When a hot aqueous solution of some of the synthetic hydrogelators was cooled down, the supramolecular hydrogel was formed at room temperature. In some other amphiphiles with less intermolecular interactivity in water at room temperature, a reverse phase transition of sol to gel was observed by elevating the temperature of their aqueous systems, especially below a physiological temperature, 37 °C. The supramolecular hydrogelation at a low or high temperature was dependent on a slight molecular modification of the synthetic amphiphiles.

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1. Introduction

Gels attract much attention as intelligent soft materials with bio-compatible and environmentally friendly aspects. Many polymer-based gelators are commercially available and recently supramolecular gelation of low-molecular-weight compounds has been investigated widely.¹ In the latter systems, gelating molecules self-assembled in a solvent to give stable supramolecules with fibrous structures, which contained a large quantity of solvent molecules. Such low-molecular-weight gelators are easily modified and the properties of their supramolecular gels would be readily affected. Polymer-based gelation of organic solvents as well as aqueous solutions has been reported more frequently than the low-molecular-weight gelation, although the papers for such supramolecular hydrogelation are increasing rapidly.¹

Supramolecular assemblies including gels based on gallic acid (3,4,5-trihydroxybenzoic acid) are available in many reports.² We first reported gallic acid derivatives as easily separable protecting groups with their several other merits including facile preparation at low cost, multi-functionality, high reactivity, and easy detection at the ultraviolet absorption;³ recently Chiba and co-workers applied this concept to other systems.⁴ In the course of preparation of the above protecting groups, we found that the gallic acid derivatives possessing long alkyl chains gelled alcohols: typically,

a purification trial of tris(octadecyloxy)benzoic acid (see Chart 1) by recrystallization from hot 2-propanol gave its organogel at room temperature. Based on this observation, gelation of some gallic acid derivatives was preliminarily reported.⁵ Here we report on gelation of alcohols and water by newly synthesized gallamide possessing an oligo- or poly(ethylene glycol) moiety at the *N*-substituent and long alkyl chains at the *O*-substituents. Especially, the supramolecular hydrogelation was investigated systematically and extensively and transition of sol to gel states was observed during heating of the aqueous systems as well as during normal cooling-down. The reverse temperature dependency was ascribable to a small structural change of the amphiphilic hydrogelators.

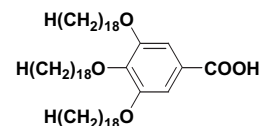


Chart 1. Molecular structure of triply *O*-stearylated gallic acid.

2. Results and discussion

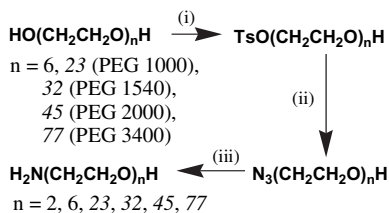
2.1. Synthesis of amphiphilic gallic acid derivatives

Oligo- or poly(ethylene glycol) mono(2-aminoethyl) ethers ($n \geq 6$) were prepared by modification of one terminal hydroxy group of the corresponding diols according to Scheme 1, while 2-(2-aminoethoxy)ethanol ($n=2$) was purchased. Commercially

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available poly(ethylene glycol)s, PEG #, are a mixture of molecules with various polymerization numbers (n). From ^1H NMR spectral analyses of their mono-tosylates, the average values of n were estimated to be 23, 32, 45 and 77 for PEG 1000, 1540, 2000 and 3400, respectively. Here, the average numbers in *italic* are used for the abbreviation of synthetic compounds.



Scheme 1. Synthesis of oligo- and poly(ethylene glycol) mono(2-aminoethyl) ether: (i) $\text{TsCl}/\text{C}_5\text{H}_5\text{N}$; (ii) $\text{NaN}_3/\text{CH}_3\text{CN}$; (iii) $\text{H}_2\text{-PtO}_2/\text{MeOH}$ ($n \leq 32$), $\text{PPh}_3/\text{C}_5\text{H}_5\text{N}$ ($n \geq 32$).

Methyl gallate was fully and regioselectively alkylated at the three hydroxy groups as shown in steps (i)–(iii) of **Scheme 2**, the methyl esters were saponified (step (iv)), and the carboxylic acids were condensed with the above primary hydroxy-amines, oligo- or poly(ethylene glycol) mono(2-aminoethyl) ethers unprotected at both the ends (step (v)) to give the desired amphiphilic gallamides **1**, **2**, and **4** without formation of the esters.⁶ Similarly, 3,5-dihydroxybenzoic acid and ethyl 3,4-dihydroxybenzoate were transformed to **3** and **5**, respectively. The two numbers in parenthesis just after compound numbers **1**–**5** show the oligomethylation number of their alkoxy chains (the former) and the oligo- or polymerization number of their ethylene glycol units (the latter). Typically, **2**(14,32) is a mono-amide possessing two tetradecyl chains and 32 ethylene glycol units on average. The corresponding mono-ester **2'**(14,32) was also prepared for reference (see **Chart 2**).

Moreover, diamides **6** were synthesized by insertion of an ω -amino acid between the gallamide and ethylene glycol parts in **2** according to **Scheme 3**: the middle number p in the parenthesis indicates the inserted methylene number.

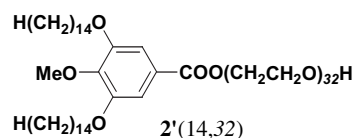
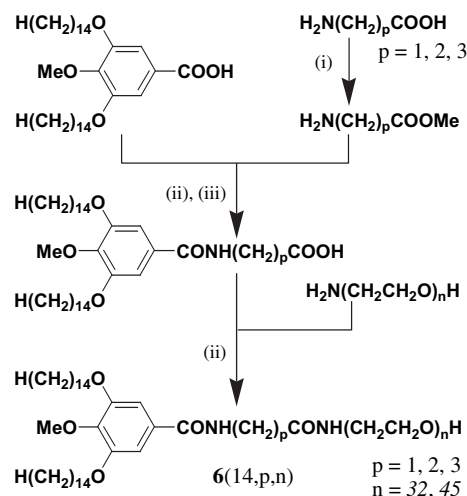
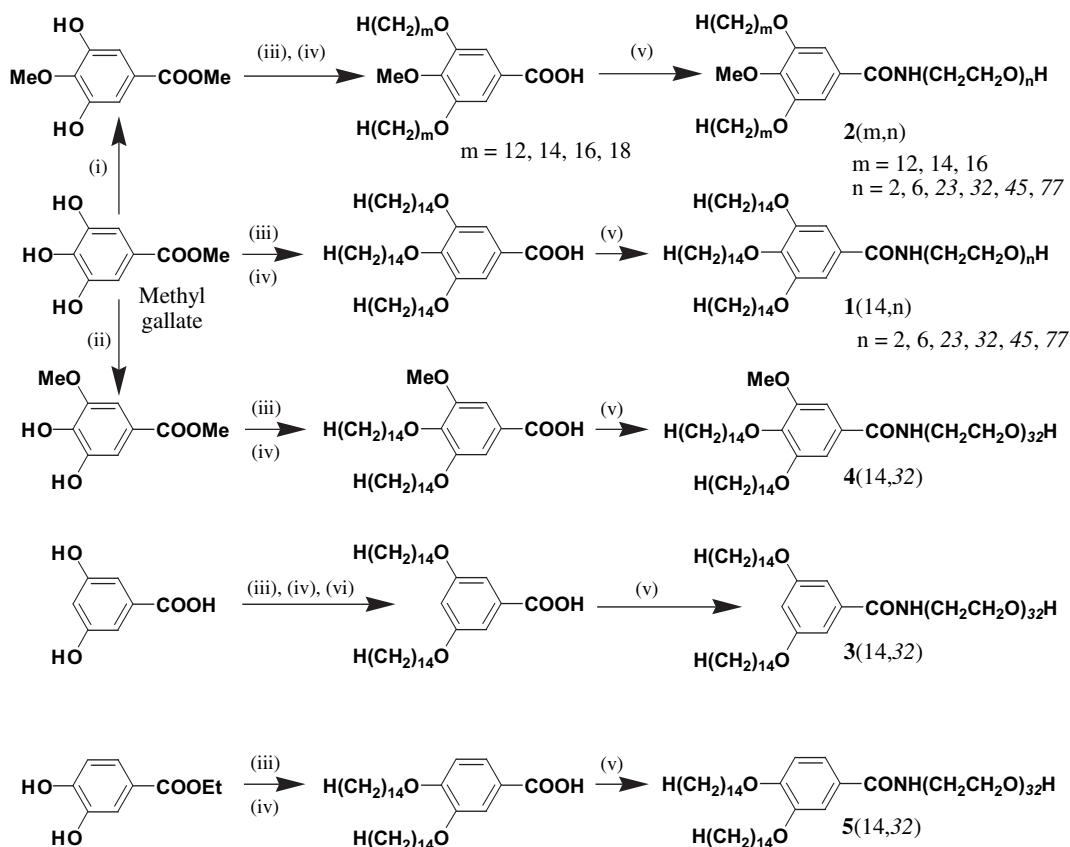


Chart 2. Molecular structure of ester **2'**(14,32).



Scheme 3. Synthesis of amphiphilic diamides **6**: (i) SOCl_2 , MeOH ; (ii) $\text{EDC}\cdot\text{HCl}$, $\text{HOBT}\cdot\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$; (iii) $\text{KOH}/\text{EtOH}/\text{H}_2\text{O}$.



Scheme 2. Synthesis of amphiphilic mono-amides **1**–**5**: (i) Me_2SO_4 , $\text{K}_2\text{CO}_3/\text{Me}_2\text{CO}$; (ii) $\text{Na}_2\text{B}_4\text{O}_7\cdot 10\text{H}_2\text{O}$, $\text{Me}_2\text{SO}_4/\text{NaOH}/\text{H}_2\text{O}$; (iii) $\text{H}(\text{CH}_2)_m\text{Br}$, $\text{K}_2\text{CO}_3/\text{DMF}$; (iv) $\text{KOH}/\text{EtOH}/\text{H}_2\text{O}$; (v) $\text{H}_2\text{N}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, $\text{EDC}\cdot\text{HCl}$, $\text{HOBT}\cdot\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$; (vi) $\text{MeONa}/\text{MeOH}/\text{CH}_2\text{Cl}_2$.

2.2. Gelation of alcohols by synthetic amphiphilic gallamides

Synthetic amphiphile **1**(14,2) was dissolved in hot ethanol and the solution (60 mM) was cooled to room temperature to give a white gel (see Fig. 1A). Other low-molecular-weight alcohols including methanol, 1-propanol, 2-propanol, and 1-butanol were gelated by action of 60 mM **1**(14,2) but no more gelation was observed in 1-hexanol to give a colorless solution even after standing overnight. No other organic solvents examined (hexane, toluene, ethyl acetate, and acetone) were gelated under the same conditions (Table 1). Compound **1**(14,6) possessing a longer oligo(ethylene glycol) chain gelated all the C1 to C3 alcohols, but neither alcohols with \geq C4 nor other organic solvents, showing a gelation activity of less than **1**(14,2). More hydrophilic **1**(14,23) did not gelate any organic solvents. These results indicate that gelation of some alcohols by **1**(14,*n*) is dependent upon the length of oligo- or poly(ethylene glycol) chain in a molecule and highly hydrophilic **1** could not function as a gelator for alcohols with a relative low weight molecule.

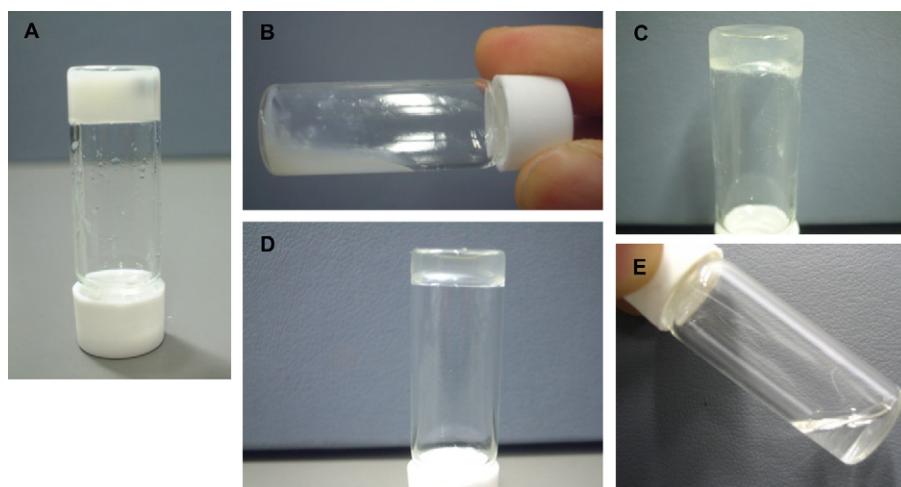


Figure 1. States of ethanol and water containing synthetic amphiphiles (60 mM) at room temperature prepared after cooling their hot solutions: (A) **1**(14,2) in EtOH, (B) **1**(14,32) in H₂O, (C) **1**(14,45) in H₂O, (D) **2**(14,32) in H₂O, and (E) **2**(14,45) in H₂O.

Table 1

Test for organogelation at 60 mM and room temperature^a

Solvent	1 (14,2)	1 (14,6)	1 (14,23)	2 (14,2)	2 (14,6)	2 (14,23)
Methanol	WG	WG	P	P	S	S
Ethanol	WG	WG	P	S	S	S
1-Propanol	WG	WG	—	—	—	—
2-Propanol	WG	WG	—	—	—	—
1-Butanol	WG	S	—	—	—	—
1-Hexanol	S	S	—	—	—	—
Acetone	P	P	P	S	S	S
Ethyl acetate	P	P	P	S	S	S
Toluene	S	S	S	S	S	S
Hexane	P	P	P	P	S	P

^a WG: white gelation; P: precipitation; S: solution.

Doubly tetradecylated amphiphiles **2**(14,2), **2**(14,6) and **2**(14,23) could not gelate any organic solvents including methanol and ethanol. The values of calculated log *P*, C log *P* (*P*=partition coefficient between 1-octanol and aqueous phases) of **1**(14,2), **1**(14,6), **1**(14,23), **2**(14,2), **2**(14,6), and **2**(14,23) were 20.5, 19.9, 17.6, 13.6, 13.1, and 10.8, respectively. Thus, three tetradecyl chains are necessary for the formation of the alcoholic gels and the hydrophobicity would be important for such gelation as mentioned above.

2.3. Hydrogelation by synthetic amphiphilic gallamides

Neither 60 μmol of **1**(14,2) nor **1**(14,6) was completely dissolved in 1 ml of water at 60 °C due to their lower hydrophilicity and no hydrogelation was observed after cooling down to room temperature: their complete dissolution in water could not be observed even after refluxing the suspension for several hours. More hydrophilic **1**(14,23) and **1**(14,32) were dissolved in hot water (60 mM) and the solution was changed to white suspensions after cooling, as recrystallization (see Fig. 1B). Much more hydrophilic **1**(14,45) and **1**(14,77) self-assembled with water solvent under the same conditions to give cloudy white gels (see Fig. 1C). These behaviors are explained as follows. An increase of hydrophilicity of **1**(14,*n*) by elongation of ethylene glycol units enhanced their water-solubility. Moderate hydrophilicity as in **1**(14,23) and **1**(14,32) did not induce enough hydration to the molecules at room temperature to yield large and water-insoluble aggregates through intermolecular hydrophobic interaction of their long tetradecyl chains. Synthetic amphiphiles **1**(14,45) and

1(14,77) are hydrophilic enough to form fibrous self-aggregates whose surface is poly(ethylene glycol) parts in water. Their fiber networks contained water solvent at room temperature to yield white hydrogels. It is noted that the formation of cloudy gels indicated the partial preparation of extremely large aggregates in the hydrogel. Hydrogelation of **1**(14,*n*) is dependent on the length (*n*) of hydrophilic oligo- or poly(ethylene glycol) chains (see the second column of Table 2).

Table 2

Test for hydrogelation of **1**(14,*n*) and **2**(*m*,*n*) at 60 mM and room temperature^a

<i>n</i>	1 (14, <i>n</i>)	2 (12, <i>n</i>)	2 (14, <i>n</i>)	2 (16, <i>n</i>)
2	p ^b	—	p ^b	—
4	p ^b	—	p ^b	—
23	P	S	P	WG
32	P	S	G	VS
45	WG	S	VS	VS
77	WG	—	G	—

^a G: gelation; WG: white gelation; VS: formation of a viscous sol; P: precipitation; S: formation of a fluid, liquid-like solution.

^b A portion of the total amount remained indissoluble after heating at 60 °C.

Similarly to **1**(14,2) and **1**(14,6) possessing three tetradecyl chains, neither **2**(14,2) nor **2**(14,6) having two tetradecyl substituents gave hydrogels due to their poor water-solubility, in spite of an increase in their hydrophilicity. More hydrophilic **2**(14,23)

was soluble in hot water (60 mM) but gave white precipitates after cooling to room temperature, as in **1**(14,23). In contrast to **1**(14,32) and **2**(14,23), less hydrophobic **2**(14,32) gave a transparent hydrogel under the same conditions as described above [at 60 mM after cooling to room temperature from its hot aqueous solution at 60 °C] (see Fig. 1D). Although **2**(14,45) afforded a highly viscous sol, i.e., a slightly fluid gel (see Fig. 1E), **2**(14,77) yielded a similar clear gel as **2**(14,32); the former is referred to a viscous sol hereafter. As shown in the fourth column of Table 2, hydrogelation of **2**(14,*n*) is dependent on the oligo- or polymerization number (*n*) as is that of **1**(14,*n*). Compared to **1**(14,*n*), even a shorter poly(ethylene glycol) chain as in **2**(14,32) could gelate water and the total balance between hydrophilic and hydrophobic parts in a gelator molecule would be important for the formation of supramolecular hydrogels. It is noteworthy that hydrogels induced by **2**(14,*n*) were clear due to fewer of their large aggregates being formed.

Dodecylated **2**(12,*n*) [*n*=23, 32, and 45] gave no hydrogels under the same conditions, due to their lower hydrophobicity and higher water-solubility (third column of Table 2). Hexadecylated **2**(16,*n*) self-assembled in water (60 mM) to give a white gel at *n*=23 and viscous sols at *n*=32 and 45 (fifth column of Table 2). In **2**(*m*,32), dodecylated compound (*m*=12) was too water-soluble to gelate water, tetradecylated compound (*m*=14) gave a homogeneous hydrogel with transparency due to the good balance of its hydrophilic with hydrophobic substituents and self-aggregates of hexadecylated compound (*m*=16) held water less efficiently to afford a viscous sol (fifth row of Table 2). Hydrophobicity by an increase in the length of alkyl chains is necessary for the formation of hydrogels by self-assemblies of the present synthetic amphiphiles but too long alkyl chains made the hydrogels fluid.

2.4. Behavior of doubly tetradecylated amphiphiles in water

Since **2**(14,32) is a good hydrogelator as mentioned above, the hydrogelation ability of other related compounds was examined. Removal of the 4-methoxy group from **2**(14,32) as in **3**(14,32) induced the formation of a viscous sol under the same conditions described above. This change from a hydrogel to a viscous sol would be explained by three factors: 1) an increase of the molecular hydrophobicity, 2) an electronic factor to the intermolecularly interactive phenyl and amide groups, and 3) a steric factor to the conformation of the two tetradecoxy chains on the phenyl group. Another amphiphile **4**(14,32) possessing 3,4,5-alkoxy groups, which was regioisomeric to **2**(14,32) gave an aqueous solution but no more hydrogel at room temperature, indicating that the first two factors 1) and 2) could be ruled out. A shift of tetradecoxy group from the 5- to 4-positions on the phenyl group in **3**(14,32) → **5**(14,32) disturbed hydrogelation to give an aqueous solution, which supported that the 3- and 5-tetradecoxy substituents were requisite for the formation of hydrogels at room temperature.

Substitution of amide bond of **2**(14,32) with ester bond as in **2'**(14,32) led to no formation of the hydrogel at room temperature; the amide bond is thus necessary for the hydrogelation. Monomeric **2**(14,32) in dichloromethane gave a vibrational peak at 1658 cm⁻¹ for its amide carbonyl stretching band, while the IR peak for the C=O of its hydrogel was situated at 1647 cm⁻¹. The 11-cm⁻¹ low wavenumber shift by hydrogelation indicated that self-assemblies of **2**(14,32) in the hydrogel were formed by bonding of the amide carbonyl group (probably hydrogen-bonding between amide substituents). After freeze-drying the hydrogel, fibrous networks were observed as shown in a SEM image (see Fig. 2): the fibrous width was about 200 nm and the porous diameter was about 600 nm. Such fibrous self-assemblies of **2**(14,32) would be prepared in its hydrogel and the networks would contain a large amount of water to make the hydrogel. The amphiphilic compounds self-aggregated in water through hydrophobic interaction of the long tetradecyl

chains, π - π stacking of the benzene rings and hydrogen-bonding of the amide groups to form large supramolecules, which self-assembled further to give the fibers as mentioned above.

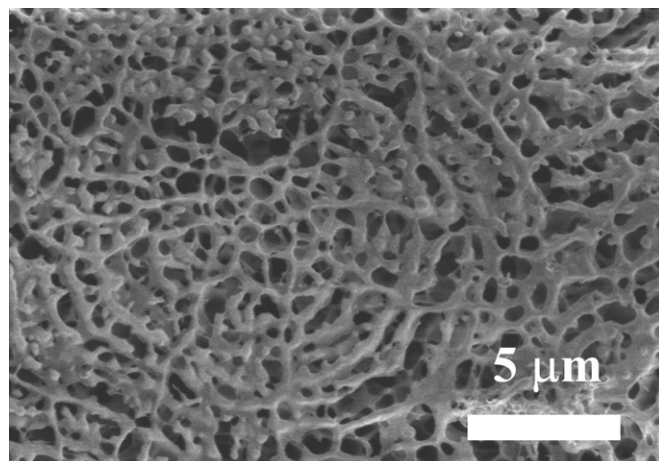


Figure 2. A SEM image of self-assembly of **2**(14,32) after freeze-drying its hydrogel (60 mM, room temperature).

Addition of one more amide bond to **2**(14,32) gave a diamide **6**(14,1,32), which yielded a similar hydrogel. Minimum concentrations for the hydrogel formation of **2**(14,32) and **6**(14,1,32) were 36 and 15 mM, respectively: 15 mM of **6**(14,1,32) was ca. 3%(wt/v). Introduction of an amide bond would strengthen the intermolecular interaction through hydrogen bonding to suppress the minimum concentration. The result also indicates the importance of hydrogen bonding of the amide bonds for hydrogels. Moreover, such intermolecular interaction was supported by the following experiments. Hydrogel of **2**(14,32) was transformed to a sol state by elevating the temperature. The transition temperature (T_{gel}) increased with an increase of concentration: T_{gel} =28, 31, and 43 °C for 36, 40, and 60 mM, respectively. Higher concentration of gelators enhanced the intermolecular interaction in a hydrogel to increase T_{gel} . It is noteworthy that hydrogel by **2**(14,32) at 60 mM was formed under both the acidic and alkaline conditions (at pH=1 and 13).

2.5. Temperature dependency for hydrogelation

As mentioned above, 60 mM of **2**(14,32) in water gave a clear hydrogel in the range from room temperature to 43 °C, above which the normal gel was transformed to the viscous sol. Similar transformation was observed by rheological technique. During heating the hydrogel of **2**(14,32) from 0 °C, storage modulus G' was larger than loss modulus G'' below 53 °C and G' was smaller than G'' in the range between 53 and 69 °C (see Fig. 3A). The elastic modulus data indicate that T_{gel} from gel to sol states was 53 °C, which was higher than the above value from fluidity checked by the eye: the difference might be ascribable to the observation techniques. Such temperature-dependent gels are often observed because thermal energy could collapse the gel network. In contrast, the viscous sol induced by **3**(14,32) at room temperature (60 mM) was changed to a hydrogel at 60 °C (see also Table 3). Such a reverse dependency is sometimes observed in a hydrogel by polymeric gelators including PEG and poly(*N*-isopropylacrylamide) derivatives.⁷ During the heating of aqueous 60 mM of **4**(14,32), transformation of solution to gel states was similarly observed at 52 °C. Even with heating, no state transformation occurred in **5**(14,32) to make it an aqueous solution due to its weaker intermolecular interaction (vide supra). It is noted that the resulting

hydrogels of **3**(14,32) and **4**(14,32) at higher temperatures were changed to their original and clear viscous sol and solution, respectively, after cooling down to room temperature.

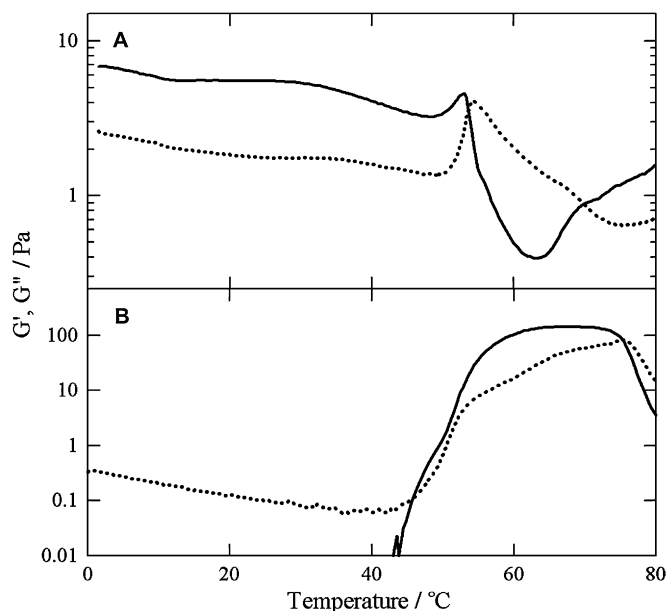


Figure 3. Temperature dependence of the dynamic moduli of aqueous solutions (60 mM) of (A) **2**(14,32) and (B) **2**(14,45); storage modulus G' (solid) and loss modulus G'' (dotted). In (B), G' below 43 °C could not be measured due to being values lower than 0.01.

Table 3

Test for hydrogelation of **2–5**(14,32) and **2**(14,45) at 60 mM^a

Compound	State	
	At room temperature	At higher temperature ($T_{gel}/^{\circ}\text{C}$) ^b
2 (14,32)	G	VS (43)
3 (14,32)	VS	G (60)
4 (14,32)	S	G (52)
5 (14,32)	S	S
2 (14,45)	VS	G (46)

^a G: gelation; VS: formation of a viscous sol; S: formation of a fluid, liquid-like solution.

^b T_{gel} is a transformation temperature, determined from fluidity measurements checked by the eye.

Similarly to **3**(14,32), a viscous sol induced by **2**(14,45) at room temperature (60 mM) was heated and changed to a hydrogel at 46 °C, supported by rheological measurements (see Fig. 3B): T_{gel} from sol to gel=45 °C. The reverse T_{gel} was dependent on the concentration and a lower concentration of the gelator slightly increased values of the T_{gel} : 46, 49, and 50 °C for 60, 56, and 45 mM, respectively. The same hydrogels with reverse temperature dependency were observed in **6**(14,*p*,45) [$p=1-3$]: transformation of a viscous sol to a hydrogel above 46–47 °C at 60 mM. After standing at 37 °C for 1 h, **2**(14,45) possessing one amide bond still gave a viscous sol but all of the three amphiphiles **6**(14,*p*,45) [$p=1-3$] having two amide bonds gave hydrogels. More intermolecular interaction was gradually formed in viscous sols by additional hydrogen bonds to give hydrogels at a lower temperature.

3. Concluding remarks

Amphiphilic compounds were easily and systematically prepared from inexpensive gallic acid (a connector), PEG (a hydrophilic part) and alkyl bromide (a hydrophobic component). One of the synthetic amphiphiles **2**(14,32) self-aggregated in water at room

temperature through intermolecular interaction including hydrophobic interaction of its myristyl (tetradecyl) chains and hydrogen bond of its amide substituents to give a supramolecular hydrogel above 36 mM [ca. 7%(wt/v)]. The resulting gel was stable below 43 °C at 60 mM and also in the range of pH=1–13. The phase transition temperature (gel to sol) was dependent on the concentration and decreased to 28 °C at 36 mM. In contrast, more hydrophilic compound **2**(14,45) gave a sol state in water at room temperature and changed to a hydrogel above 46 °C at 60 mM. Insertion of one amide moiety to **2**(14,45) as in **6**(14,*p*,45) [$p=1-3$] induced also the formation of hydrogels with reverse temperature dependency and gave stable supramolecular gels at 37 °C (physiological temperature) after standing for 1 h. The present synthetic amphiphiles gave three temperature-dependent supramolecular hydrogels: 1) a gel at both room and physiological temperatures, 2) a gel at room temperature and a sol at physiological temperature and 3) a sol at room temperature and a gel at physiological temperature. Therefore, the present hydrogels are promising for biomedical application including as useful media for culturing, storing, and transporting bioactive cells, although the molecular interpretation of such unique supramolecular gelation has not been revealed yet.

4. Experimental

4.1. Apparatus

FTIR spectra were measured with a Shimadzu IRAffinity-1 spectrophotometer. Solution samples in CH_2Cl_2 were measured in a KBr cell with a transmission mode and gels were on an aluminum-coated glass and measured with a reflection mode using a Shimadzu AIM-8000R microscope. A SEM image was obtained by a JEOL JSM-6301F FE-SEM. Rheological measurements of aqueous samples were conducted by a TA Instruments AR-G2 rheometer, and the storage modulus G' and the loss modulus G'' were measured on heating at 3 °C/min with an oscillatory frequency of 1 Hz.

4.2. Materials

Amphiphilic amides **1–6** were prepared according to Schemes 1–3. Their synthetic details as well as that of an amphiphilic ester **2'** are described in Supplementary data.

4.3. Gelation

A solvent (1 ml) was added to a synthetic amphiphilic compound (usually 60 μmol) in a sample tube with a 15-mm diameter and heated to 50–60 °C in a water bath. Distilled water was used for the hydrogelation test. The hot mixture was stirred with a Vortex mixer and/or sonicated with an ultrasonic cleaning apparatus, then cooled to room temperature. The resulting aqueous mixture was heated at 1 °C/min and the gelation was checked by upside-down method. The pH of an aqueous solution was controlled by addition of HCl or NaOH and measured with a Horiba EX-20 pH meter.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at [doi:10.1016/j.tet.2010.01.002](https://doi.org/10.1016/j.tet.2010.01.002).

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