Amphiphilic Copolymer Having Acid-Labile Acetal in the Side Chain as a Hydrophobe: Controlled Release of Aldehyde by Thermoresponsive Aggregation−Dissociation of Polymer Micelles

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ABSTRACT: Statistical amphiphilic copolymers of polymethacrylate having a lilial-derived acetal moiety as a hydrophobic side chain and poly(ethylene glycol) (PEG) as a hydrophilic side chain were synthesized with different unit ratios (**3a** (x:y = 100:0), **3b** (x:y = 73:27), and **3c** (x:y = 24:76)). In aqueous media the polymer **3c** (x:y = 24:76) formed its micelles, whose particle diameter was ranged mainly from 10 to 220 nm and averaged diameter was 35 nm. Polymer **3c** in aqueous media exhibited aggregation−dissociation behavior which was dependent sharply and reversibly on temperature in the presence of NaCl. The aggregation of the polymer micelles inhibited hydrolysis of the acid-labile acetal side chain and release of the resulting lilial, while its dissociation removed the inhibition. This responsive behavior by simply heating and cooling could control hydrolysis of the acid-labile acetal side chain and release of the resulting lilial.

Introduction

Polymer systems that enable controlled release of bioactive molecules such as drugs, fragrances, pesticides, and fertilizers have attracted much attention in the fields of pharmaceutical industry,[1] flavor and fragrance industry,[2] and agriculture.[3] The current systems can be categorized into two by their basic strategies, i.e., (1) physical encapsulation and (2) chemical derivation. In the former strategy, molecules are encapsulated by polymeric microcapsule or matrix in order to control their diffusion.[2a,b,3] Besides the controlled releasing ability, the encapsulation strategy with using properly designed polymers enables protection of active molecules against degradation by light, air, microorganism, and moisture. On the other hand, in the latter strategy, active molecules are derived into the corresponding protected forms using various chemical protection methods.[2c,d,4−6] Various kinds of covalent bonds that are labile under specific conditions are used for this strategy, and scission of these chemical bonds is triggered by external stimuli such as pH[5,6] and lights[4c,e,7,8] to release the original molecules in their active forms.

Among various reactions for the chemical derivation strategy applied so far, reactions of diols with aldehydes to obtain the corresponding cyclic acetals have been most popularly used because (1) a wide range of the molecules used as drugs[6] and fragrances[9−12] possess these reactive functional groups and (2) acetal is tolerant under basic conditions but labile under acidic conditions, leading to controlled release of the original molecules with adjusting pH of the environments. Our research interest is attachment of volatile fragrance molecules into side chains of amphiphilic copolymers through acetal linkage, which would have various advantages: (1) The resulting polymeric "pro-fragrance" would have very low vapor pressure which prevents rapid diffusion of the fragrance molecules. (2) Amphiphilic balance of polymers would be easily adjusted by the composition ratio between hydrophilic segment and hydrophobic segment, allowing us to control their self-assemblies.[13] Morishima and co-workers have investigated in detail the assembling behaviors of amphiphilic copolymers having various combinations of hydrophobes and hydrophiles in the polymer side chains in aqueous media.[14] Very recently, Zou and others have developed a thermoresponsive amphiphilic polyacrylamide having acetal pendants as a hydrophobe.[15]

Besides the hydrophobicity, acetal has another aspect as an acid-labile structure, and this nature allows the utilization of acetal in protection−deprotection methodology in various sequences of organic reactions. Recently, Berthier and others described the controlled release of fragrances via retro-Michael addition reaction from amphiphilic polymethacrylates and polystyrene-based β-acyloxy ketones.[9b] This research and the acid-labile acetal prompted us to design a new aqueous system for controlled release of volatile molecules, in which an amphiphilic statistic copolymer having cyclic acetal moieties and hydrophilic poly(ethylene glycol) (PEG) segments in the side chains was used. The acetal was derived from lilial, a volatile aldehyde being one of the most popular fragrance molecules in cosmetics, toiletry, and laundry products, so that the practical aspect of the system would be a new method for controlled release of fragrances. In this case, the acetal moiety was expected to act not only as an acid-labile precursor for lilial but also as a hydrophobic moiety in the polymer side chain to endow the copolymer with an amphiphilic nature, by which the copolymer would have micelle-forming behavior. Herein, we wish to report the synthesis of the copolymer, its micelle formation behaviors in aqueous media, temperature-controlled aggregation−dissociation behaviors of the micelles, and its application as a switching factor to control release of lilial from the aqueous system.

Experimental Section

Materials. Lilial, Amberlyst 15, 4-*tert*-butylcatechol, pyrene, and diethyl ether were purchased from Wako Pure Chemical Industries (Japan) and used as received. 1,4-Dioxane (Wako Pure Chemical Industries, Japan) was distilled over Na wire. 2,2′-Azobis(isobutyronitrile) (AIBN) was purchased from Wako Pure Chemical Industries (Japan) and purified by recrystallization from methanol. Poly(ethylene glycol) methyl ether methacrylate (**2**) was purchased

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Table 1. Results of the Polymerization

run	initial feed ratio (**1**:**2**)	polymer (unit ratio [*x*:*y*])[a]	M_n (M_w/M_n)[b]	conv[a] [%] **1**	conv[a] [%] **2**	yield [%]
1	100:0	**3a** (100:0)	26 500 (3.67)	>99		quantitative[c]
2	75:25	**3b** (73:27)	44 800 (2.27)	>99	>99	90[c]
3	25:75	**3c** (24:76)	32 800 (2.00)	>99	>99	91[d]

[a] Determined by ^{1}H NMR spectrum. [b] Estimated by SEC chromatography. [c] Methanol-insoluble parts. [d] Diethyl ether-insoluble parts.

from Sigma Chemical (St. Louis, MO) and purified by using column packed with inhibitor remover for removing *tert*-butylcatechol (Sigma Chemical, St. Louis, MO) prior to use. Buffer solutions pH = 1.0 (composition: glycine/sodium chloride/hydrogen chloride) and pH = 3.0 (composition: citric acid/ sodium chloride/hydrogen chloride) were purchased from Merck KGaA (Germany). 2,3-Dihydroxypropyl methacrylate was synthesized according to the reported method.[16]

Synthesis of a Methacrylate Monomer Having a Cyclic Acetal Moiety 1. A mixture of 2,3-dihydroxypropyl methacrylate (8.1 mmol), Amberlyst 15 (5 wt % to 2,3-dihydroxypropyl methacrylate), lilial (40.5 mmol), and 4-*tert*-butylcatechol (0.3 mmol) in diethyl ether (60 mL) was refluxed for 24 h with azeotropic removal of water. The solution was dried over anhydride $MgSO_4$ and filtrated to give a crude product. The crude product was concentrated and was purified by silica gel chromatography to obtain **1** (ethyl acetate:hexane = 1:5) (yield = 80%, 2.24 g). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.82−0.99 (d, −CH(C*H*$_3$)-$CH_2C_6H_4C(CH_3)_3$); 1.00−1.39 (s, −CH(CH_3)$CH_2C_6H_4C$(C*H*$_3$)$_3$); 1.87−1.96 (s, CH_2:C(C*H*$_3$)COO−); 1.96−2.14 (m, −C*H*(CH_3)-$CH_2C_6H_4C(CH_3)_3$); 2.29−2.47 and 2.79−2.96 (m, −CH(CH_3)-C*H*$_2C_6H_4C(CH_3)_3$); 3.62−4.00 (m, CH_2:C(CH_3)COOC*H*$_2$CH-(C*H*$_2$O−)O−); 4.11−4.45 (m, CH_2:C(CH_3)COOC*H*$_2$C*H*(CH_2-O−)O−); 4.73−4.92 (dd, −O(−O)C*H*CH(CH_3)$CH_2C_6H_4$C-$(CH_3)_3$); 5.50−5.65 and 6.09−6.17 (C*H*$_2$:C(CH_3)COO−); 7.02−7.36 (aromatic). ^{13}C NMR ($CDCl_3$, 75.4 MHz, δ, ppm): 14.0 (−CH-(*C*H$_3$)$CH_2C_6H_4C(CH_3)_3$); 19.1 (CH_2:C(*C*H$_3$)COO−); 31.9 (−CH-(CH_3)$CH_2C_6H_4$C(*C*H$_3$)$_3$); 35.1 (−CH(CH_3)*C*H$_2C_6H_4C(CH_3)_3$); 37.8 (−CH(CH_3)$CH_2C_6H_4$*C*(CH_3)$_3$); 39.1 (−*C*H(CH_3)$CH_2C_6H_4$C-$(CH_3)_3$); 65.1 (CH_2:C(CH_3)COO*C*H$_2$-); 67.7 (CH_2:C(CH_3)-COOCH_2CH(*C*H$_2$O−)O−); 74.2 (CH_2:C(CH_3)COOCH_2*C*H-(CH_2O−)O−); 108.1 (−O(−O)*C*HCH(CH_3)$CH_2C_6H_4C(CH_3)_3$); 125.8 and 126.8 (*C*H$_2$:C(CH_3)COOCH_2CH(CH_2O−)O−) and (two carbons of methine in aromatic ring); 129.5 (two carbons of methine in aromatic ring); 136.9 and 137.8 (CH_2:*C*(CH_3)COOCH_2-CH(CH_2O−)O−) and (one quaternary carbon in aromatic ring); 149.5 (one quaternary carbon in aromatic ring); 167.5 (CH_2: C(CH_3)*C*OO−).

Synthesis of Polymers 3a,b,c. Polymers **3a**, **3b**, and **3c** were synthesized by copolymerization of **1** and **2** with different initial feed ratios (Table 1, Scheme 2). A typical procedure for synthesizing polymer **3b** is described here. To a solution of **1** (0.26 g, 0.75 mmol) and **2** (0.12 g, 0.25 mmol) in 1,4-dioxane (1.0 mL), AIBN (8.2 mg, 5.0 mol % to total amount of monomers) was added. The resulting solution was degassed by three freeze−evacuate−thaw cycles and heated at 60 °C for 24 h under argon. The mixture was cooled, exposed to air, and poured into methanol (100 mL). The resulting precipitates were filtered with suction and dried under vacuum at ambient temperature for 24 h to obtain the polymer **3b**. For the purification of **3c** diethyl ether was used.

Polymer **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.68−1.16 (−(CH_2C−(CH_3))$_n$−); 1.16−1.42 (*t*-Bu) and (−CH(CH_3)CH_2-$C_6H_4C(CH_3)_3$); 1.90−2.10 (−C*H*(CH_3)$CH_2C_6H_4C(CH_3)_3$); 2.27−2.46 and 2.73−2.95 (−CH(CH_3)C$H_2C_6H_4C(CH_3)_3$); 3.42−4.15 (−COOCH_2CH(CH_2O−)O−); 4.15−4.43 (−COOCH_2C*H*(CH_2-O−)O−); 4.64−4.89 (−O(−O)C*H*CH(CH_3)$CH_2C_6H_4C(CH_3)_3$); 6.98−7.41 (aromatic).

Polymer **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.68−1.16 (−(CH_2C−(CH_3))$_x$−) and (−(CH_2C−(CH_3))$_y$−); 1.16−1.42 (*t*-Bu) and (−CH(CH_3)$CH_2C_6H_4C(CH_3)_3$); 1.90−2.10 (−C*H*(CH_3)CH_2-$C_6H_4C(CH_3)_3$); 2.27−2.46 and 2.73−2.95 (−CH(CH_3)CH_2C_6-$H_4C(CH_3)_3$); 3.32−3.45 (−$(CH_2CH_2O)_{8.5}CH_3$); 3.45−4.15 (−(CH_2-CH_2O)$_{8.5}CH_3$) and (−COOCH_2CH(CH_2O−)O−); 4.15−4.36 (−COOCH_2C*H*(CH_2O−)O−); 4.64−4.89 (−O(−O)C*H*CH(CH_3)-$CH_2C_6H_4C(CH_3)_3$); 6.98−7.41 (aromatic).

Hydrolysis of 3c in Buffer Solutions. Polymer **3c** (60 mg) was dissolved in buffer solutions (20 mL, pH = 1.0 and 3.0) with and without addition of NaCl (2.3 g). Concentrations of **3c** and NaCl were 3.0 g/L and 2.0 M, respectively. The solutions were heated at 40 or 50 °C. A portion (1.0 mL) of the solution was taken out for the measurement. The amount of released lilial was determined by measuring UV adsorption of the solution dissolving **3c** at λ_{max} 265 nm at 25 °C corresponding to aromatic rings.

Measurements. *1. NMR Spectroscopies.* ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a JEOL AL300 NMR spectrometer in $CDCl_3$, and chemical shifts were determined by using tetramethylsilane (TMS) as an internal standard.

2. Size Exclusion Chromatography (SEC). Number- and weight-average molecular weights (M_n and M_w) were estimated by size exclusion chromatography (SEC) on a Tosoh HLC-8120 system equipped with a refractive index detector and a polystyrene gel column (TSK-GEL Super HM-H, Tosoh Corp.) using THF as an eluent at 40 °C. The system was operated at a flow rate of 0.6 mL/min, and molecular weights were calibrated with using polystyrene standards.

3. UV−vis Spectroscopy. UV−vis spectra were recorded on a JASCO V-570 UV−vis spectrometer equipped with a temperature controller. The spectrometer was used also for measuring transmittance at 500 nm with raising temperature from 25 to 70 °C and lowering from 70 to 25 °C at a rate of 3.0 °C/min.

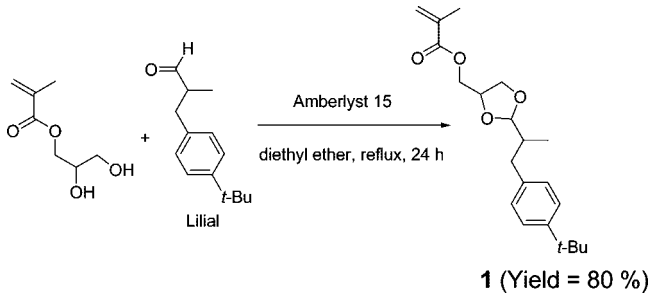
4. Light Scattering. Average particle diameters of micelles of polymer **3c** in aqueous media (3.0 g/L; filtered with Millipore membrane filter (pore size: 0.45 μm)) were measured by an electrophoretic light scattering spectrophotometer (ELS-8000, Otsuka Electronics Co., Ltd.), with vertically polarized incident light at a wavelength of 632.8 nm supplied by He−Ne laser operated at 10 mW and with detecting the corresponding dynamic light scattering (DLS) with a detector set perpendicular (90°) to the incident laser beam.

5. Fluorescence Analysis. Steady-state fluorescence excitation spectra were recorded on a Hitachi F-4500 fluorescence spectrophotometer at ambient temperature. The excitation spectra were monitored at 372 nm, and the slit width was kept at 2.5 nm during the measurements. A pyrene aqueous solution (0.14 μM) was prepared by diluting a pyrene-saturated aqueous solution.[14] To this solution, the polymer was added, and the solution was allowed to stand at ambient temperature for 1 day for equilibration. A series of samples containing pyrene and the polymer with different concentration were analyzed by this method to determine the critical micelle concentration (cmc) of the polymer.

Results and Discussion

1. Synthesis of an Amphiphilic Polymer Having a Cyclic Acetal Group as a Hydrophobe in the Side Chain. An acetal-containing methacrylate monomer **1** was synthesized by acid-catalyzed acetalization of lilial with 2,3-dihydroxypropyl

Scheme 1



methacrylate (Scheme 1). ^{1}H and ^{13}C NMR spectra of **1** are shown in Figures 1 and 2. The signals assignable to the 1,3-dioxolane ring at 3.62−4.00, 4.11−4.45, and 4.73−4.92 ppm (^{1}H NMR) and at 67.7, 74.2, and 108.1 ppm (^{13}C NMR) were clearly observed, indicating that the methacrylate having a 1,3-dioxolane ring derived from lilial was obtained. The doublet peaks at 4.73−4.92 ppm in the ^{1}H NMR spectrum of **1** exhibit that **1** comprises diastereomeric mixtures, which are *cis*- and *trans*-2,4-disubstituted-1,3-dioxolane isomers. The monomer **1** underwent the radical homopolymerization with using AIBN as an initiator at 60 °C to give the corresponding polymer **3a** (Figure 3). The obtained polymer **3a** was soluble in chloroform, THF, and DMF, but insoluble in methanol and water, confirming the hydrophobicity of the acetal group in the side chain.

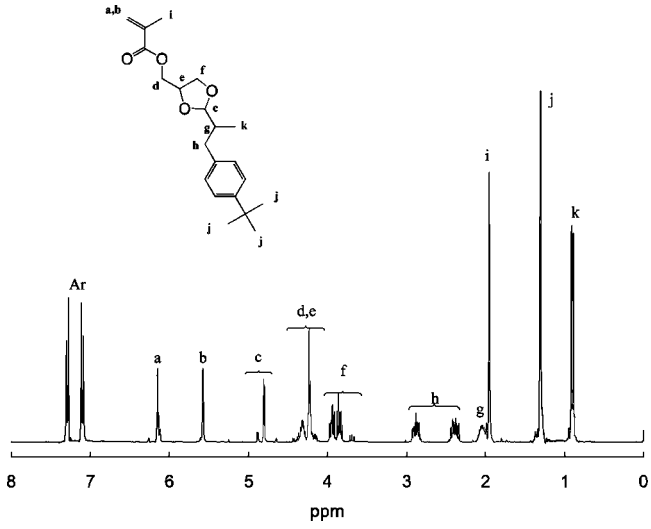


Figure 1. ^{1}H NMR spectrum of **1** in $CDCl_3$.

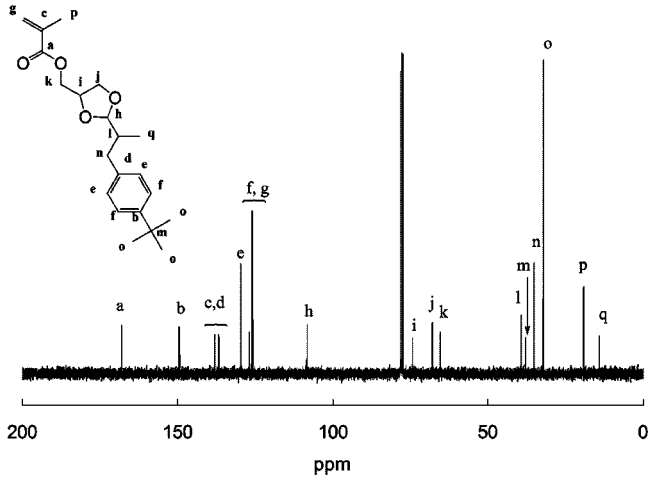


Figure 2. ^{13}C NMR spectrum of **1** in $CDCl_3$.

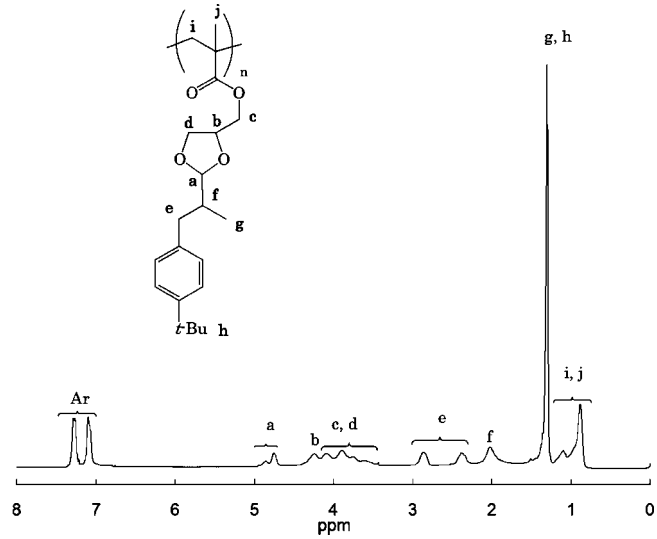
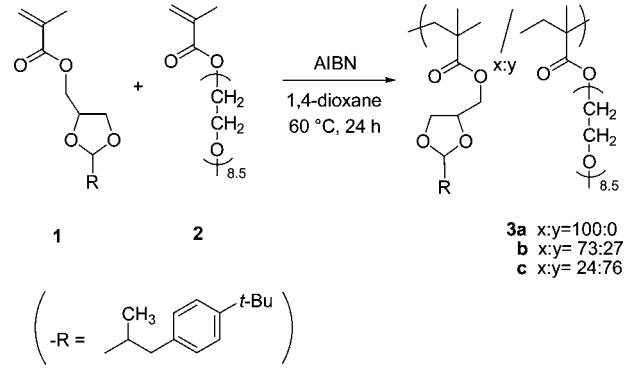


Figure 3. ^{1}H NMR spectrum of **3a** in $CDCl_3$.

Scheme 2



In order to obtain an amphiphilic polymer, monomer **1** was copolymerized with a hydrophilic monomer **2**, a methacrylate having PEG chain (Scheme 2). Both of the monomers were consumed quantitatively, giving the corresponding polymers **3b** and **3c** with different unit ratios in a good yields (Table 1). The ^{1}H NMR spectrum of **3b** showed clearly the signals assignable to the protons of PEG and the 1,3-dioxolane moieties (Figure 4). The composition ratios (*x*:*y*) were calculated with using these signals. M_n and M_w were estimated by SEC. Solubilities of the obtained polymers are summarized in Table 2. All the polymers were soluble in common organic solvents such as chloroform, THF, and DMF at room temperature but completely insoluble in *n*-hexane. Polymer **3c** was partially soluble in methanol and soluble in water.

2. Micelle Formation Behavior of the Amphiphilic Polymer 3c. When water was added to the polymer **3c**, the mixture became a solution apparently, i.e., transparent to visible light. In order to clarify whether the polymer **3c** was really dissolved in water or underwent self-association into its micelles having a diameter smaller than wavelength of visible light, DLS was measured at a polymer concentration of 3.0 g/L at 25 °C. This concentration was eventually higher than the critical micelle-forming concentration (vide infra). Figure 5 shows the corresponding spectrum, supporting the formation of micelles. The particle diameter ranged mainly from 10 to 220 nm, and the corresponding average value was 35 nm.

Further detailed investigation on the micelle forming behaviors was studied by fluorescence spectroscopy with using pyrene as a probe. Figure 6 shows a series of the fluorescence excitation spectra of pyrene in the presence of the polymer **3c** with various

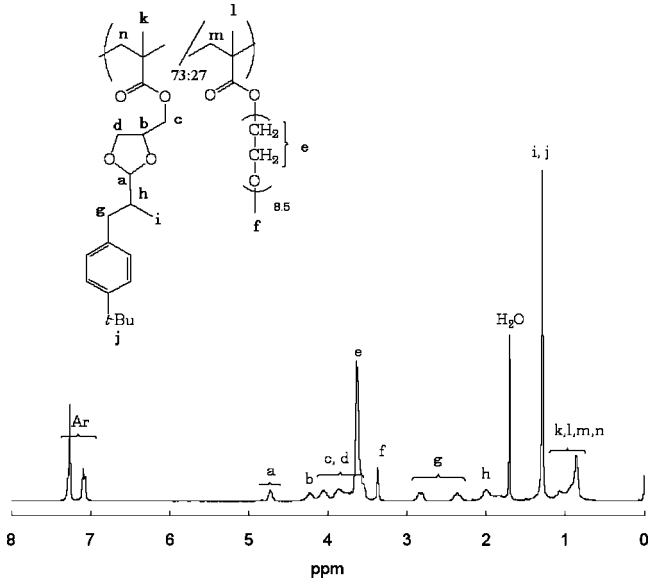


Figure 4. ^{1}H NMR spectrum of **3b** in $CDCl_3$.

Table 2. Solubility of 3[a]

run	polymer (*x*:*y*)[b]	*n*-hexane	$CHCl_3$	THF	DMF	MeOH	H_2O
1	**3a** (100:0)	+	++	++	++	−	−
2	**3b** (73:27)	−	++	++	++	−	+
3	**3c** (24:76)	−	++	++	++	+	++

[a] THF = tetrahydrofuran; DMF = *N,N*-dimethylformamide; ++ = soluble; + = partially soluble; − = insoluble. Concentration: 1 mg/mL, room temperature. [b] Determined by ^{1}H NMR spectrum.

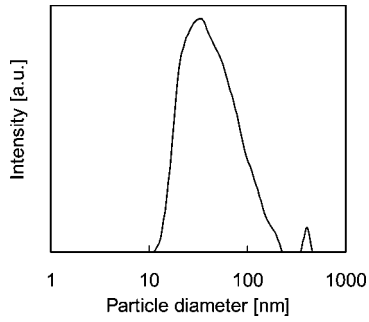


Figure 5. Particle size distribution measured by DLS for the micelles of the polymer **3c** formed in water: [**3c**] = 3.0 g/L.

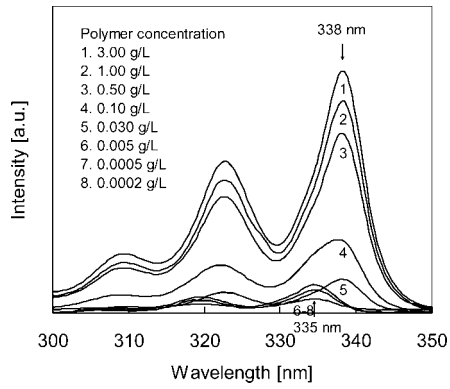


Figure 6. Steady-state fluorescence excitation spectra monitored at 372 nm for pyrene in aqueous media of **3c**: [pyrene] = 1.4×10^{-7} M.

concentrations. By increasing the concentration of **3c** from 2.00×10^{-4} to 3.00 g/L, the absorption at 335 nm decreased and that at 338 nm increased accordingly to suggest that the environment of the pyrene molecules would have changed from a hydrophilic one into a hydrophobic one.[17] The hydrophobic environment could be created by self-association of the polymer in water into the corresponding micelles, with directing the hydrophobic acetal moieties inside into the micelles. With using the adsorption intensities at 335 and 338 nm (represented as I_{335} and I_{338}, respectively), the dependence of the ratio I_{335} and I_{338} on the polymer concentration is plotted in Figure 7a. In the low concentration region (<0.02 g/L), a plateau was observed. Upon increasing the polymer concentration over 0.02 g/L, I_{338}/I_{335} abruptly increased to reach a next plateau in the high concentration region (>0.5 g/L). The I_{338}/I_{335} ratios at the first plateau and the second plateau were defined as I_{min} and I_{max}, respectively. With using these data, we calculated the ratio between concentrations of pyrene in the micellar phase $[Py]_m$ and in the bulk water phase $[Py]_w$ according to the following equation reported: $[Py]_m/[Py]_w = (I_{338}/I_{335} - I_{min})/(I_{max} - I_{338}/I_{335})$. The ratio is plotted as a function of the polymer concentration in Figure 7b to find that the critical micelle-forming concentration (cmc) was 0.035 g/L.

3. Aggregation Behavior of the Micelles. Next, we investigated aggregation behavior of the micelles under various conditions. Amphiphilic polymers bearing oligo(ethylene glycol) in the side chains exhibit the thermoresponsive behavior due to the formation and cleavage of hydrogen bond between water molecules and hydrophilic oligo(ethylene glycol).[18] In general, ionic strength is one of the dominating parameter in various aqueous systems containing polymers. We prepared four kinds of aqueous systems containing the polymer **3c** with four different concentrations of NaCl (0, 1.0, 2.0, and 3.0 M). In all cases, concentration of **3c** was 3.0 g/L, which was much higher concentration than the cmc to ensure the micelle formation. These four systems were heated at 25 to 70 °C and then cooled at 70 to 25 °C, with monitoring transmittance of a 500 nm visible light. The corresponding temperature dependence of the transmittance is shown in Figure 8. In the absence of NaCl, nearly 100% transmittance was maintained in the temperature range, suggesting the intrinsic high stability of the micelles. Other research groups reported that oligo(ethylene glycol)-based copolymer micelles exhibited a higher transition temperature in pure water than that of homopolymer having oligo(ethylene glycol) in the side chains at around 80 °C, suggesting that the transition temperature of polymer **3c** in pure water would be higher than 70 °C.[19] In contrast, the systems containing NaCl exhibited sharp responses of transmittance on temperature. Upon heating the 1.0 M aqueous NaCl solution system, the corresponding transmittance started to decrease at 56 °C and became 0 at 59 °C, suggesting that the micelles would have started aggregation into larger particles. This transition temperature was successfully controlled by concentration of NaCl; i.e., by increasing concentration of NaCl, the transition temperature became lower accordingly. These results can be explained by the salt effects described in other papers, which is the salt cleaves the hydrogen bond between the polymer and water molecules, and the hydrophobic interaction occurs between the polymers.[20] The resulting emulsions were stable above the transition temperatures, and no sedimentation occurred. In addition, by cooling these emulsions below the transition temperatures, they became transparent again, indicating that the polymer micelles would be liberated from the aggregation.

4. Effects of Micelle Aggregation on Hydrolysis of the Acetal in the Side Chain. Polymer **3c**, which could form its micelles in aqueous media, showed interesting reaction behaviors; i.e., the rate of hydrolysis of the side-chain acetal largely depended on the aggregation behavior of the micelles. To confirm that the hydrolysis of **3c** releases lilial to the outside of water, we first examined the hydrolysis of **3c** in two-phase solutions (water phase dissolving **3c** and hexane phase) to

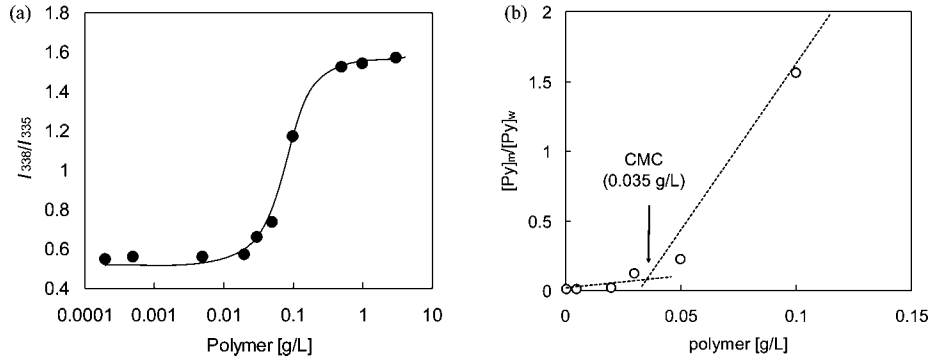


Figure 7. (a) Concentration of **3c** vs I_{338}/I_{335} ratio. The I_{335} and I_{338} represent the intensity of fluorescence excitation spectra at 335 and 338 nm in Figure 6, respectively. (b) Concentration of **3c** vs $[Py]_m/[Py]_w$ ratio calculated from the I_{338}/I_{335} ratio.

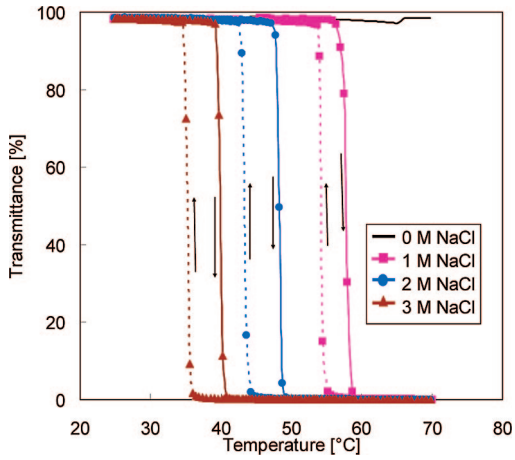


Figure 8. Dependence of thermoresponse of the polymer **3c** (the initial concentration = 3.0 g/L) in aqueous media on concentration of NaCl: solid line: 25 to 70 °C; broken line: 70 to 25 °C.

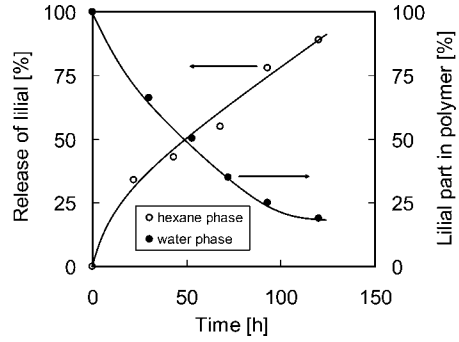


Figure 9. Time vs release of aldehyde from **3c** (the initial concentration = 3.0 g/L) in two-phase solutions (pH 1.0 buffer solution phase and hexane phase) at 50 °C.

measure UV adsorption of the hexane phase containing lilial released as well as that of the water phase containing **3c** remained. During the two-phase system, hexane and water phases were gently stirred not to mix each other. As shown in Figure 9, the released amount of the resulting lilial extracted in the hexane phase increased with the decrease of the amount of lilial part in **3c** in the water phase. Accordingly, the released amount of lilial was determined by measuring the remaining amount of **3c** in aqueous media for further investigation on its hydrolysis.

For the investigation on the hydrolysis, the NaCl-free system that exhibited no transition temperature and the 2.0 M aqueous NaCl solution system that exhibited the transition temperature at 47 °C were employed. The pH of the systems was adjusted and maintained at 3.0 by using a buffer solution. These systems

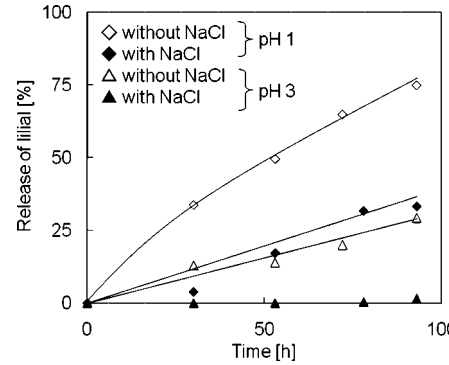


Figure 10. Time vs release of aldehyde from **3c** (the initial concentration = 3.0 g/L) in buffer solutions at 50 °C in the presence and absence of NaCl (2.0 M).

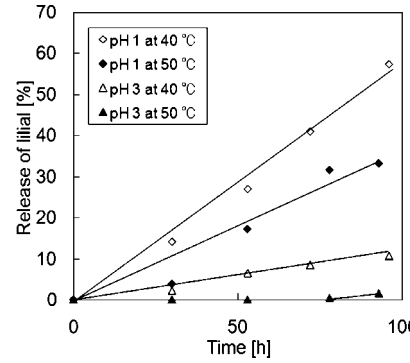


Figure 11. Time vs release of aldehyde from **3c** (the initial concentration = 3.0 g/L) in buffer solutions at 40 and 50 °C in the presence of NaCl (2.0 M).

were heated at 50 °C, with monitoring the UV absorption at 265 nm corresponding to the aromatic rings of lilial part in the polymer **3c**, by which the time dependences of amount of the released lilial were clarified (Figure 10). When lilial was released from **3c**, the UV adsorption of **3c** at 265 nm decreased. From the NaCl-free system, which was transparent to a 500 nm visible light at 50 °C, lilial was gradually released, and the total amount reached 29% after 93 h. On the other hand, from the system containing NaCl, which was turbid at 50 °C due to the aggregation of the micelles, only a negligible amount of lilial was released. This suppression effect of the presence of NaCl on release of lilial was also observed at lower pH. At pH = 1, lilial was smoothly released from the NaCl-free system, as was expected from the acid labile nature of acetals, while release of lilial was significantly suppressed in the 2.0 M aqueous NaCl solution system. These results suggested that the aggregation of the polymer micelles would lead to growth of highly

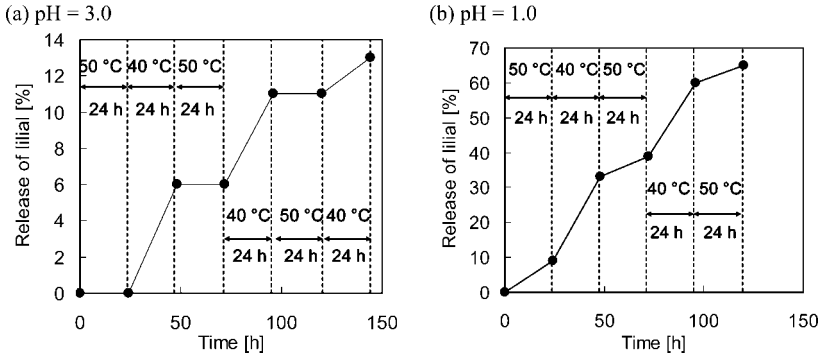


Figure 12. Controlled release of lilial from **3c** (the initial concentration = 3.0 g/L) in buffer solution (pH = 3.0 and 1.0) in the presence of NaCl (2.0 M) by thermo-switching at 40 and 50 °C.

hydrophobic domains, by which the acid labile acetal moieties were protected from their contact with acidic water and the consequent hydrolysis.

5. Thermally Controlled Release of Aldehyde. As was demonstrated in the previous section, aggregation of the micelles, which was induced by addition of NaCl, inhibited the release of aldehyde significantly. Another interesting feature of this aggregation discussed in section 3 was its reversible response to temperature; i.e., the aggregation collapsed by cooling while it recovered by heating. In addition, the thermo response was very sharp so that the thermal switching was achieved in a narrow temperature range within 5 deg. This thermo-switching behavior prompted us to apply it to thermally controlled release of lilial.

We prepared an aqueous system containing the polymer **3c** and NaCl. The concentrations of **3c** and NaCl were 3.0 g/L and 2 M, respectively. The pH of the system was adjusted to 3 with using a buffer solution. As can be expected from the results shown in Figure 8, the system was transparent at 40 °C, below the transition temperature for the aggregation of the corresponding polymer micelles. Under these conditions, the side-chain acetal was gradually hydrolyzed, leading to a slow release of lilial from the system (Figure 11). In contrast, release of lilial was significantly suppressed at 50 °C: At this temperature, the aqueous system was turbid due to the aggregation of the polymer micelles. In this aggregated state, release of lilial was not detectable for 70 h.

We next investigated lilial-releasing behaviors of the system under much more acidic conditions at pH 1. At 40 °C, the system was transparent, and the higher acidity of the media efficiently accelerated the hydrolysis of the acetal in the side chain, leading to a much faster release of lilial than that at pH 3. On the other hand, at 50 °C, the system became turbid due to the aggregation of the micelles, and this aggregation moderated the release of lilial.

The sharp switching behavior of the system between 40 and 50 °C prompted us to perform a programmed multistep retaining and releasing of lilial (Figure 12). Polymer **3c** was dissolved in a pH 3.0 buffer solution containing 2.0 M NaCl and was heated to 50 °C to make the system heterogeneous, in which the micelle of **3c** was aggregated. As shown in Figure 12a, in the first step with maintaining the temperature at 50 °C, release of lilial was successfully suppressed for 24 h. In the second step, the system was cooled to 40 °C to liberate the micelle from its aggregation. As a result, release of lilial was successfully initiated and was continued for 24 h. The third step was a period for successful suppression of release of lilial by heating the system at 50 °C, and the fourth step was that for releasing lilial again by maintaining the temperature at 40 °C. Application of the same thermal program to the system at pH 1.0 resulted in successful deceleration and acceleration of releasing lilial (Figure 12b).

Summary

A new amphiphilic polymethacrylate having a lilial-derived acetal moiety as a hydrophobic side chain was synthesized. The copolymer could undergo self-association in aqueous media to form its micelles, of which aggregation−dissociation responded sharply and reversibly on temperature in the presence of NaCl. Based on the responsive behavior, hydrolysis of the acid-labile acetal side chain and release of the resulting lilial were inhibited upon switching the aggregation on by heating, while this inhibition was removed upon switching the aggregation off by cooling. The present simple and versatile concept for thermally controlled release based on utilization of a reactive amphiphilic copolymer would give us a great opportunity to design and develop a wide variety of systems for intelligent products for medical and other applications.

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