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Thermosensitive Random Copolymers of Hydrophilic and Hydrophobic Monomers Obtained by Living Cationic Copolymerization[1]

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ABSTRACT: Thermosensitive random copolymers of hydrophilic and hydrophobic monomers are synthesized via living cationic copolymerization. The synthesis starts with the copolymerization of isobutyl vinyl ether (IBVE) and 2-(*tert*-butyldimethylsilyloxy)ethyl vinyl ether (BMSiVE) using the cationogen/$Et_{1.5}AlCl_{1.5}$ initiating system in the presence of an added base to give a copolymer with a narrow molecular weight distribution. The relative reactivities determined by the Fineman−Ross method indicate that the product copolymer has a highly random sequence distribution. Subsequent desilylation gave a well-defined amphiphilic random copolymer of hydrophobic (IBVE) and hydrophilic units (2-hydroxyethyl vinyl ether: HOVE). On heating, an aqueous solution of the product random copolymer undergoes thermally induced phase separation at a critical temperature. This phase separation is quite sensitive and reversible on heating and cooling. The randomness of the sequence distribution is indispensable to realizing such highly sensitive phase separation. For example, diblock copolymers are soluble and form micelles over a wide range of temperature, whereas copolymers with both block and random segments exhibit only slightly sensitive phase separation behavior with hysteresis. The critical temperature of the random copolymer presented here can be controlled by the composition of IBVE and HOVE. In addition to the composition, the structure of the hydrophobic repeating unit is a major factor determining the critical temperature.

Introduction

A range of small molecules and polymers are soluble in water but become insoluble above a certain temperature, known as the lower critical solution temperature (LCST). Among synthetic polymers, poly(*N*-isopropylacrylamide) (PNIPAM)[2] is a typical example exhibiting LCST-type phase separation. Recently, we discovered sharp thermoresponsive behavior in poly(vinyl ether)s with pendant oxyethylene units and ω-alkyl groups (POEVE)[3,4] and poly(4-hydroxybutyl vinyl ether) (poly(OH−Bu))[5] prepared by living cationic polymerization (Scheme 1A). LCST-type phase separation, in general, involves large losses in entropy with both organic compounds[6] and macromolecules.[7] The change in entropy may be affected by the hydrophilic/hydrophobic balance in the polymer, as proposed about 30 years ago.[7] In fact, PNIPAM, POEVE, and poly(OH−Bu) possess repeating units with pendants having appropriate amphiphilicity. If design of the pendant structure in a monomer is indeed a decisive factor in phase separation, efforts in this field must concentrate on monomer synthesis, which will narrow the possibilities for preparation of thermosensitive polymers with various structures.

To synthesize more generalized thermosensitive polymers, an appropriate hydrophilic/hydrophobic balance has to be achieved in a different manner. One facile method would be the preparation of random copolymers of hydrophobic (IBVE, PhOVE, NBVE, OH−He,[5] and AcOVE) and hydrophilic units (HOVE), as shown in Scheme 1B. Thermoresponsiveness has indeed been observed for some of copolymers containing hydrophilic and hydrophobic units such as partially hydrolyzed poly(vinyl acetate),[8,9] poly(diacetone acrylamide-*co*-hydroxyethyl acrylate),[7] poly(*N*-phenylacrylamide-*co*-*N*,*N*-dimethylacrylamide),[10] poly(methyl 2-acetamidoacrylate-*co*-methyl methacrylate)[11] produced by free radical polymerization, as well as methylcelluloses, which can be regarded as copolymers because they have random sequences of hydrophilic and hydrophobic moieties.[12,13] The transitions with these polymers, however, are relatively slow and involve hysteresis between the heating and cooling states stemming from the ill-defined structures.

The thermosensitive poly(vinyl ether)s recently developed by our group feature not only thermosensitivity but controlled molecular weight and sequence.[3−5,14−19] In addition, it was demonstrated in a previous study that random copolymers consisting of water-soluble and water-insoluble alcohol units exhibit highly responsive thermosensitive behavior.[5] These polymers have hydroxy groups in both hydrophilic and hydrophobic units, resulting in complex mechanisms (interactions) leading to phase separation. In this study, therefore, we examined the synthesis and thermoresponsive behavior of amphiphilic random copolymers with hydrophilic units having hydroxy groups and water-insoluble repeating units without protic functions.

There are few examples of living random copolymers in cationic polymerization.[20−22] Thus, the feasibility of the synthesis of random copolymers with a narrow molecular weight distribution (MWD) was first examined by living cationic polymerization in the presence of an added base. The monomers employed in copolymerization were BMSiVE, a would-be water-soluble unit after deprotection, and four different hydrophobic monomers as shown in Scheme 1. The random copolymers prepared here with various combinations of hydrophilic

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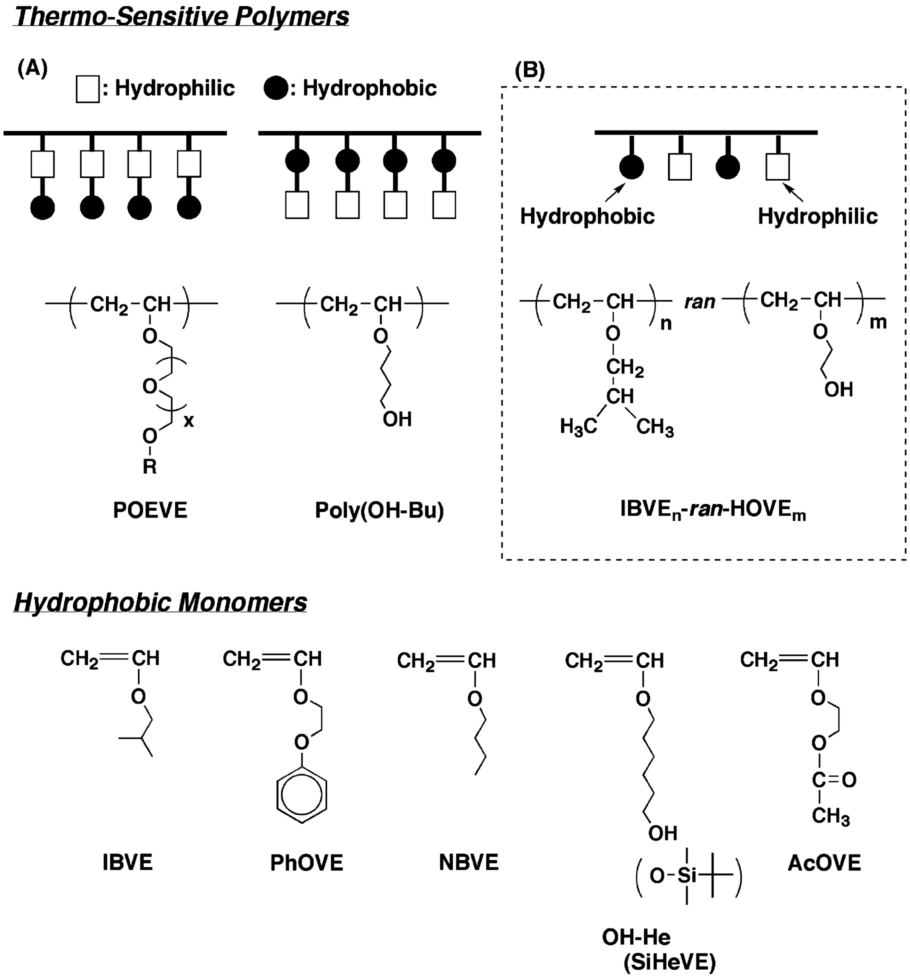
Scheme 1



and hydrophobic units were found to be thermosensitive in water by choosing appropriate compositions.

Experimental Section

Materials. All monomers but IBVE (Tokyo Kasei, purity >99%) and NBVE (Tokyo Kasei, purity >98%) were prepared from a corresponding hydroxyalkyl vinyl ether or 2-chloroethyl vinyl ether (Maruzen Petrochemical) as reported previously.[5,15,23−26] IBVE and NBVE were washed with aqueous alkaline solution and then with water. These monomers were purified by double distillation over calcium hydride before use. Ethyl acetate (Nacalai tesque) and $ClCH_2COOCH_3$ (Nacalai tesque) were distilled at least twice over calcium hydride. Toluene (Wako) as a polymerization solvent was washed by the usual method and distilled over calcium hydride and then metallic sodium just before use. $Et_{1.5}AlCl_{1.5}$ (Wako; 1.0 M solution in toluene) was used as commercially supplied. Cationogen ($CH_3CH(O\textit{i}Bu)OCOCH_3$, **1)** was prepared from IBVE and acetic acid and was distilled over calcium hydride under reduced pressure.[27] All monomers, the $Et_{1.5}AlCl_{1.5}$ solution, and **1** were stored in a brown ampule under dry nitrogen.

Polymerization Procedures. Polymerization was carried out at 0 °C under a dry nitrogen atmosphere in a glass tube equipped with a three-way stopcock baked at 250 °C for 10 min before use. The reaction was initiated by the addition of $Et_{1.5}AlCl_{1.5}$ solution in toluene into a mixture of a monomer, an added base, and the cationogen **1** in toluene at 0 °C by a dry medical syringe. For *"block-and-random"* copolymerization, a typical example is as follows. BMSiVE (0.64 M, 1.56 mL) was first polymerized in the presence of $ClCH_2COOCH_3$ (1.0 M, 0.88 mL) as an added base ($[\mathbf{1}]_0 = 4.0$ mM; $[Et_{1.5}AlCl_{1.5}]_0 = 20$ mM in toluene). The second monomer, IBVE (0.77 mmol, 0.1 mL, IBVE/BMSiVE = 1/8 molar ratio), was added to the reaction mixture at a given conversion of BMSiVE. When BMSiVE and IBVE had been consumed quantitatively (total 90 s), another feed of IBVE (0.77 mmol, 0.1 mL, IBVE/BMSiVE = 1/8 molar ratio) was added to the solution. After the polymerization was finished (total 100 s), it was quenched with prechilled methanol containing a small amount of aqueous ammonia solution (0.1 wt %). The quenched reaction mixture was diluted with dichloromethane or hexane, then washed with water to remove the initiator residues. The product polymer was recovered from the organic layer by evaporation of the solvents under reduced pressure and vacuum-dried overnight. The conversion of a monomer was determined by gravimetry.

Desilylation of Polymers.[5] A purified copolymer (1 g) was dissolved in THF (45 mL) at 0 °C, and 3.0 N aqueous HCl-EtOH (5 mL) was added. The mixture was stirred at 0 °C for 3 h and then for additional 3 h after EtOH (20 mL) was added into it. The mixtures were neutralized, and water-insoluble residues were filtered off. After removing organic solvents, the polymer was purified by reprecipitation from ethanol into a large excess of hexane and then dissolved in pure water below estimated T_{PS}. The aqueous copolymer solution was dialyzed against pure water for a week using a cellulose tube (Viskase Sales, pore size: 30/32, corresponding to a cutoff molecular weight of 12 000−14 000). These copolymers were recovered by evaporation of water under reduced pressure or a freeze-drying technique and then vacuum-dried overnight (yield > 90%).

Polymer Characterization. The MWD of the copolymers was measured by size exclusion chromatography (SEC) in chloroform at 40 °C on three polystyrene gel columns [TSK gel G-2000H_{XL} (molecular range: 1×10^2 to 1×10^4 (PSt)), 3000H$_{XL}$ (6×10^3 to 6×10^4), and 4000H$_{XL}$ (1×10^4 to 4×10^5); 7.8 mm i.d. × 300 mm each; flow rate 1.0 mL/min] connected to a Tosoh DP-8020 dual pump and a RI-8020 refractive detector. The number-average molecular weight (M_n) and M_w/M_n were calculated from SEC curves on the basis of a polystyrene calibration. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz) and a JEOL JNM-GSX400 (100 MHz), respectively.

Characterization of Aqueous Copolymer Solutions. Aqueous solutions of the copolymers were prepared by dissolving the polymer in Mill-Q water (18 MΩcm) and diluting the sample to those at a desired concentration. The phase separation temperatures of the solutions were measured by monitoring the transmittance of a 500 nm light beam through a 1 cm quartz sample cell at a rate of 1.0 °C/min in heating and cooling scans between 5 and 80 °C. The transmittance was recorded on a JASCO V-500 UV/vis spectrometer equipped with a Peltier-type thermostatic cell holder ETC-505. A phase contrast microscope (IMT-2, Olympus Optical) was used for the observation of coacervate droplets.

A high-sensitivity differential scanning calorimeter (DSC8230, Rigaku) was used to study the endothermic enthalpy. The temperature and heat flow were calibrated using benzoic acid and anisic acid. About 26 mg of polymer samples were placed in stainless pans [resistance to pressure at 50 atm, 3 × 5 o.d. mm for the vessel size] and then carefully sealed. Thermograms were obtained at the rate of 1.0 °C/min in a heating scan between 10 and 90 °C, with water in a stainless pan as a reference.

Apparent hydrodynamic radii (R_h^{app}) of coacervate droplets were determined by dynamic light scattering (DLS) on a FPAR-1000 photometer using fiber optics (Photal Otsuka Electronics) in the range from 20 to 70 °C. The light source was a semiconductor laser ($\lambda_0 = 658$ nm), and correlation function for each solution was obtained at 90°, which gives apparent hydrodynamic radii (R_h^{app}). When the temperature was varied, the measurements were performed after the solution reaches the steady state conditions; typically, the solution was left for 10 min at the temperature in the range near LCST. The time autocorrelation function was fitted using the cumulant method.

Results and Discussion

Living Cationic Copolymerization of IBVE and BMSiVE in the Presence of Added Base. Although living cationic polymerization of vinyl ethers with a silyloxy group has been shown to be feasible,[5] their copolymerization with other vinyl ethers remains untested. Thus, cationic copolymerization of IBVE and BMSiVE was carried out using **1**/Et$_{1.5}$AlCl$_{1.5}$ in toluene in the presence of ethyl acetate at 0 °C. Figure 1 shows a typical example of time−conversion curves for the copolymerization of IBVE and BMSiVE (IBVE/BMSiVE = 1/4 molar ratio). Copolymerization occurred without an induction period and was almost completed in 25 h to afford soluble polymers in quantitative yield. The time−conversion plot shows that both monomers were consumed at very similar rates during copolymerization.

Figure 2 plots the molecular weight and M_w/M_n of copolymers of IBVE and BMSiVE (1/4) as a function of monomer conversion. The conversion in this plot represents the total consumed amount of both monomers. The M_n increased in direct proportion to the conversion, and the MWDs of the resulting polymers were quite narrow ($M_w/M_n \leq 1.1$; Figure 2A). ^{1}H NMR analysis confirmed that only vinyl-type polymerization occurred without deprotection of the silyloxy pendants (peaks ***g*** and ***h***) under those conditions as shown in Figure 3A. Table 1 summarizes the effects of monomer feed ratios and added bases on polymerization rate and MWD of product polymers. At any monomer feed ratios, living random copolymerization was achieved to give a polymer with a narrow MWD, regardless of the monomer feed ratio. A weaker added base,[28] ClCH$_2$COOCH$_3$, resulted in a much higher polymerization rate (98% conversion in 90 s), and gave a polymer with a narrow MWD ($M_n = 3.0 \times 10^4$, $M_w/M_n = 1.14$).

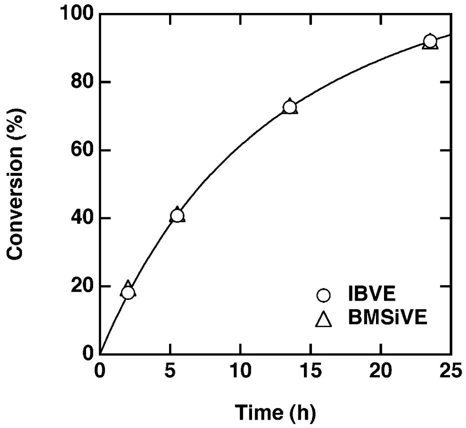


Figure 1. Time−conversion curves for the copolymerization of IBVE and BMSiVE using **1**/Et$_{1.5}$AlCl$_{1.5}$ in toluene in the presence of ethyl acetate at 0 °C: [IBVE]$_0$ = 0.16 M; [BMSiVE]$_0$ = 0.64 M; [**1**]$_0$ = 4.0 mM; [Et$_{1.5}$AlCl$_{1.5}$]$_0$ = 20 mM; [ethyl acetate] = 1.0 M.

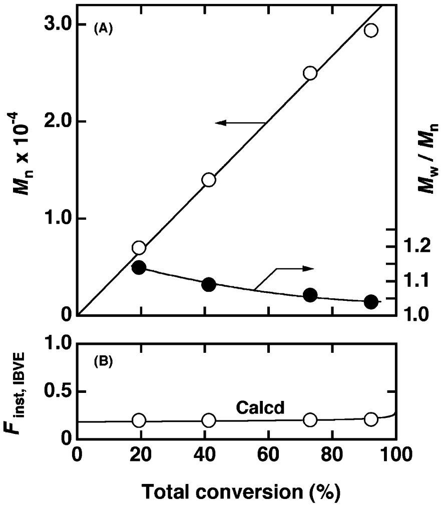


Figure 2. (A) M_n and M_w/M_n of poly(IBVE-*ran*-BMSiVE) obtained using **1**/Et$_{1.5}$AlCl$_{1.5}$ in toluene in the presence of ethyl acetate at 0 °C. (B) The observed instantaneous composition (○) of IBVE ($\boldsymbol{F}_{\text{isnt,IBVE}}$) in the copolymerization of IBVE and BMSiVE using **1**/Et$_{1.5}$AlCl$_{1.5}$ in toluene in the presence of ethyl acetate at 0 °C: [IBVE]$_0$ = 0.16 M; [BMSiVE]$_0$ = 0.64 M; [**1**]$_0$ = 4.0 mM; [Et$_{1.5}$AlCl$_{1.5}$]$_0$ = 20 mM; [ethyl acetate] = 1.0 M. The solid line indicates the calculated instantaneous composition with $r_{\text{IBVE}} = 0.80$ and $r_{\text{BMSiVE}} = 1.06$ assuming that rate constants of the initiation for both monomers are equal.

After the living cationic copolymerization of IBVE and BMSiVE was established, the next issue to be discussed is how the random units are arranged. The relative reactivities for IBVE and BMSiVE were determined by the Fineman−Ross method, giving values of 0.80 ± 0.10 and 1.06 ± 0.08, respectively, indicating that the sequence distribution of the product copolymer is highly random. The instantaneous composition at a given conversion can be calculated from the values of monomer reactivity ratios using the Skeist integral equation[29] (solid line in Figure 2B). This plot fits the residual monomer ratios (open circles in Figure 2B) of IBVE and BMSiVE determined by ^{1}H NMR analysis.

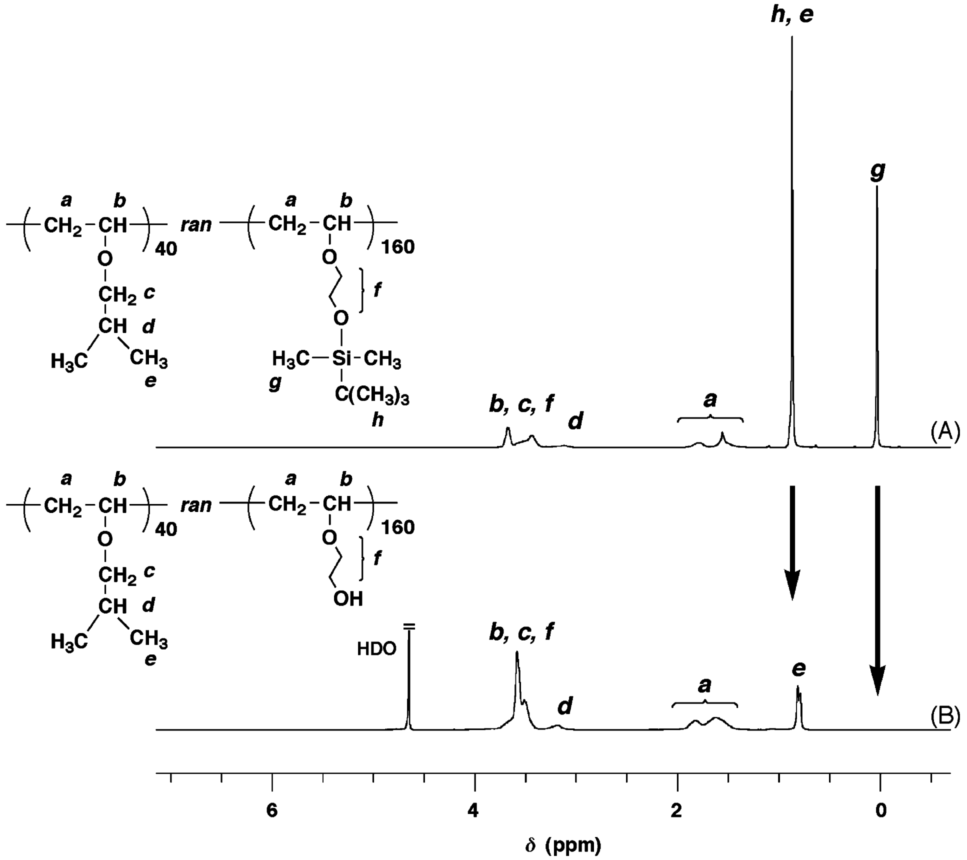


Figure 3. ^{1}H NMR spectra of (A) IBVE$_{40}$-*ran*-BMSiVE$_{160}$ in CDCl$_3$ and (B) IBVE$_{40}$-*ran*-HOVE$_{160}$ in D$_2$O at 30 °C, obtained by desilylation.

Table 1. Copolymerization of IBVE and BMSiVE[a]

added base	IBVE in feed (mole fraction)	polymn time (h)	IBVE in copolymer[b] (mole fraction)	$M_n \times 10^{-4}$ [c]	M_w/M_n[c]
ethyl acetate	0.33	24	0.33	2.7	1.05
	0.23	24	0.23	3.2	1.04
	0.20	24	0.20	2.9	1.04
	0.15	25	0.15	2.8	1.04
	0.12	25	0.12	2.8	1.04
$ClCH_2COOCH_3$	0.20	30 s	0.20	1.8	1.15
	0.20	90 s	0.20	3.0	1.14

[a] Polymerization conditions: [monomers]$_0$ = 0.8 M; [**1**]$_0$ = 4.0 mM; [Et$_{1.5}$AlCl$_{1.5}$]$_0$ = 20 mM; [added base] = 1.0 M, in toluene at 0 °C. Total converstion: 90−100% (except for ClCH$_2$COOCH$_3$ in 30 s, total conversion: 64%). [b] Determined by ^{1}H NMR. [c] Determined by SEC (polystyrene calibration).

To examine whether the sequence distribution affects the phase separation behavior in addition to the total composition, two types of copolymers with the same molecular weight and composition but different sequences were prepared by sequential living cationic polymerization: a diblock copolymer, and a "*block-and-random*" counterpart, which has a section with a random sequence between two different block segments.

The "*block-and-random*" copolymer was prepared, for example, by polymerizing BMSiVE using **1**/Et$_{1.5}$AlCl$_{1.5}$ in toluene in the presence of ClCH$_2$COOCH$_3$ at 0 °C. After 20 s (58.7% conversion for BMSiVE), neat IBVE (IBVE/BMSiVE = 1/8 molar ratio) was added to the reaction mixture. When BMSiVE and IBVE had been consumed quantitatively, another feed of IBVE (the same as the first dose) was added to the solution. Even this third-stage polymerization proceeded smoothly, and all IBVE was consumed in 10 s to give a "*block-and-random*" copolymer. A diblock copolymer of IBVE and BMSiVE was also prepared by polymerizing IBVE and then BMSiVE using **1**/Et$_{1.5}$AlCl$_{1.5}$ under similar reaction conditions.

Figure 4 compares the MWDs of the resulting random, "*block-and-random*", and diblock copolymers (IBVE/BMSiVE = 1/4 molar ratio). All final products (solid lines) have very narrow MWDs ($M_w/M_n \le 1.1$). For the copolymers obtained via sequential polymerization, the MWD curves (solid lines in Figure 4, parts B and C) shifted toward higher molecular weights compared to that of the precursor polymers (dashed and dotted lines). In addition, no tailing was observed in the lower molecular weight region, indicating that neither oligomeric byproducts nor homopolymers were formed (Figure 4, parts B and C).

The total and instantaneous compositions of the copolymers were determined by ^{1}H NMR. Illustrations alongside the MWD curves in Figure 4 depict the instantaneous composition of the copolymers. The width and height of the rectangles represent the normalized chain length and instantaneous composition ($\boldsymbol{F}_{\mathrm{inst,IBVE}}$). The area of the shaded part corresponds to the total composition of IBVE in the copolymer. The composition calculated from the conversion and feed ratio of both monomers is in good agreement with the observed composition, irrespective of the sequence distribution. In the "*block-and-random*" copolymer, 94 and 20 units from both chain ends are BMSiVE and IBVE, respectively, and the middle of the chain consists of a random sequence thereof (86 units, IBVE/BMSiVE = 20/66).

Table 2. Solubility Characteristics of Poly(IBVE), Poly(HOVE), and Various Copolymers of IBVE and HOVE[a]

polymer	water/ temp (°C) 0	20	40	60	80	100	methanol[b]	toluene[b]
poly(IBVE)	×	×	×	×	×	×	×	○
poly(HOVE)	○	○	○	○	○	○	○	×
$IBVE_{40}$-*ran*-$HOVE_{160}$	○	○	○	×	×	×	○	×
$IBVE_{40}$-“*block-and-random*”-$HOVE_{160}$	○	○	○	△	△	△	○	×
$IBVE_{40}$-*block*-$HOVE_{160}$	△	△	△	△	△	△	△	△

[a] Key: (○) soluble; (×) insoluble; (△) slightly turbid. Polymer solubilities were measured on 1.0 wt % solutions ($DP_n \leq 600$). [b] At room temperature.

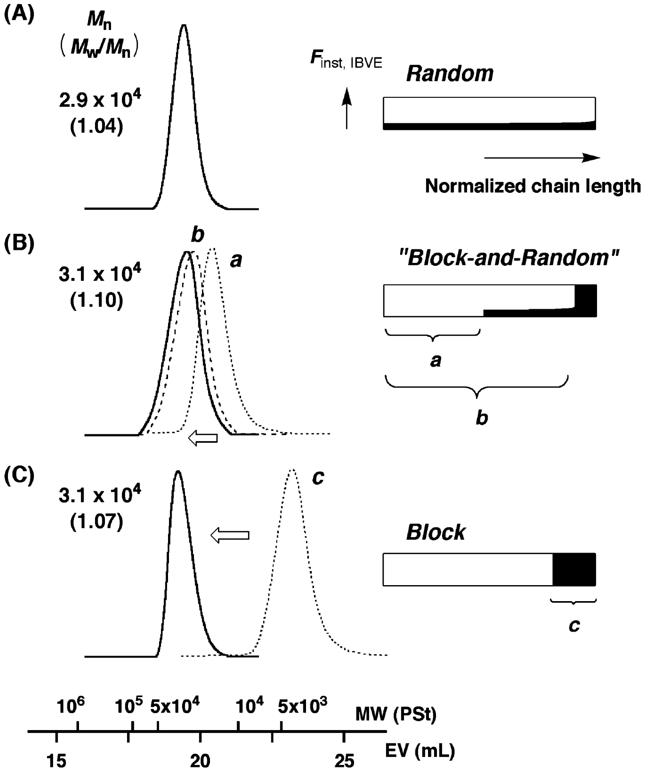


Figure 4. Molecular weight distribution curves of various $IBVE_{40}$-*co*-$BMSiVE_{160}$ with different sequence distributions obtained using **1**/$Et_{1.5}AlCl_{1.5}$ in toluene in the presence of an added base at 0 °C: $[\mathbf{1}]_0 = 4.0$ mM; $[Et_{1.5}AlCl_{1.5}]_0 = 20$ mM; [added base] = 1.0 M. (A) $IBVE_{40}$-*ran*-$BMSiVE_{160}$; (B) $IBVE_{40}$-“*block-and-random*”-$BMSiVE_{160}$ and its precursors (peak ***a***, $BMSiVE_{94}$: $M_n = 1.7 \times 10^4$, $M_w/M_n = 1.16$, peak ***b***, copolymer $BMSiVE_{94}$-*block*-($IBVE_{20}$-*ran*-$BMSiVE_{66}$): $M_n = 2.7 \times 10^4$, $M_w/M_n = 1.14$); (C) $IBVE_{40}$-*block*-$BMSiVE_{160}$ and its precursor (peak ***c***, $IBVE_{40}$: $M_n = 4.0 \times 10^3$, $M_w/M_n = 1.12$). Added base: ethyl acetate (A and C); $ClCH_2COOCH_3$ (B).

Desilylation of the copolymers was carried out with the addition of aqueous HCl-EtOH in THF at 0 °C. Quantitative desilylation was confirmed by the disappearance of the ^{1}H NMR signals at 0.1 ppm (s, 6H, Si−CH_3) and 0.9 ppm (s, 9H, Si−C−CH_3) of the *tert*-butyldimethylsilyl group as shown in Figure 3B.

Thermally-Induced Phase Separation of $IBVE_{40}$-*ran*-$HOVE_{160}$ in Water. Table 2 summarizes the solubility characteristics of poly(HOVE), poly(IBVE), and various copolymers (random, “*block-and-random*”, and diblock) of IBVE and HOVE (IBVE/HOVE = 1/4 molar ratio).[30] Poly(HOVE) ($DP_n = 400$, $M_w/M_n = 1.04$) is soluble in water in the range from 0 to 100 °C,[31] whereas poly(IBVE) is insoluble in water. $IBVE_{40}$-*ran*-$HOVE_{160}$ is soluble in water at room temperature similar to poly(HOVE), as it contains more hydrophilic components than hydrophobic components. Interestingly, the aqueous solution transformed into an opaque liquid when warmed to above 41 °C, as monitored by the transmittance at 500 nm (middle line in Figure 5). Upon warming a 1.0 wt % solution, the transmittance decreased sharply at 41 °C, indicating that the phase separation was highly sensitive. When the phase-separated solution was cooled, it returned to the homogeneous state. Neither the molecular weight ($DP_n = 30-600$) nor polydispersity (M_w/M_n: 1.04 vs 1.61)[32] appeared to have any effect on this phase separation.

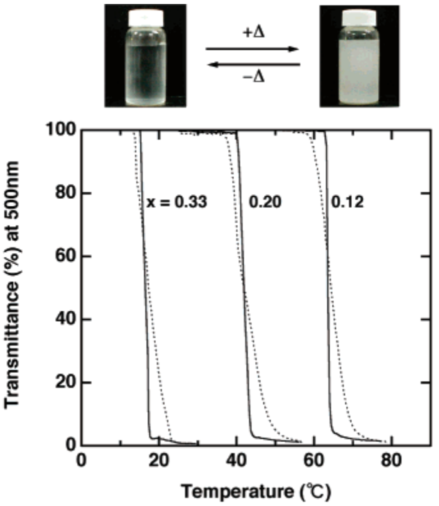


Figure 5. Temperature dependence of the transmittance at 500 nm of 1.0 wt % aqueous solutions of random copolymers $(IBVE_x\text{-}ran\text{-}HOVE_{1-x})_{200}$ ($x = 0.33$, 0.20, and 0.12; $M_w/M_n \leq 1.05$): rate 1.0 °C/min, heating (—) and cooling (- - -). The inset is a photograph of 1.0 wt % aqueous solution of $IBVE_{40}$-*ran*-$HOVE_{160}$ at room temperature (left) and 55 °C (right).

Figure 5 also shows the effect of composition (x: mole fraction of IBVE in random copolymer) on the temperature dependence of the transmittance of aqueous solutions of random copolymers, $(IBVE_x\text{-}ran\text{-}HOVE_{1-x})_{200}$, upon heating and cooling. Phase separation occurred with a similar sensitivity in all cases, irrespective of the ratio of IBVE to HOVE. The mole fraction, x, however, was found to determine the temperature of phase separation (T_{PS}), varying from 16 °C at $x = 0.33$ to 65 °C at $x = 0.12$ for a 1.0 wt % aqueous solution. Figure 6 shows the relationships between the hydrophilic/hydrophobic balance and the T_{PS} for the random copolymers (Figure 6A) and POEVE (Figure 6B). With POEVE, the number of the oxyethylene units in the pendant affects the T_{PS} (Figure 6B), which, in turn, means that monomer synthesis is required to vary T_{PS}. By contrast, the T_{PS} can be controlled only by regulating the composition in a copolymer of common monomers.

A different feature of $(IBVE_x\text{-}ran\text{-}HOVE_{1-x})_{200}$ and POEVE is the way in which the phase separates above T_{PS}. With the random copolymer, no precipitation was observed at a higher temperature, but the solution remained opaque over a longer period unlike POEVE,

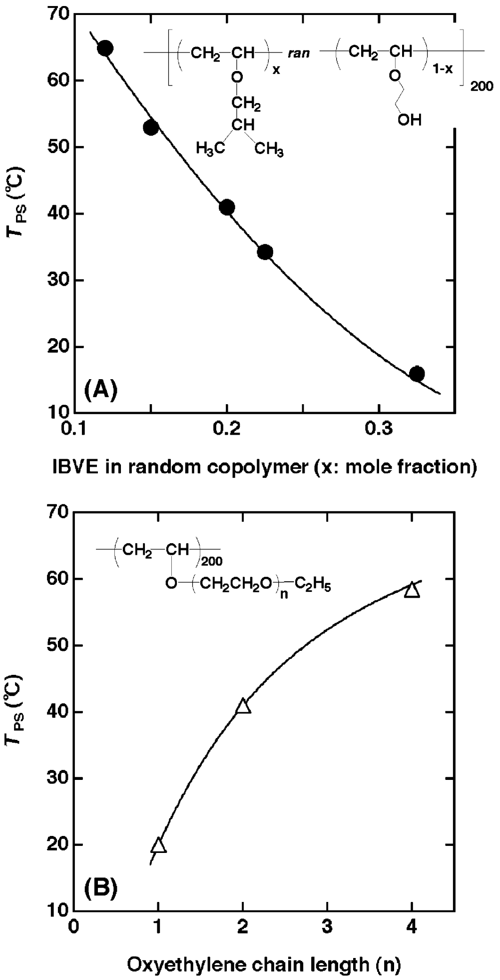


Figure 6. (A) Relationships between T_{PS} in water and the composition of random copolymers (IBVE$_x$-*ran*-HOVE$_{1-x}$)$_{200}$. (B) Effect of oxyethylene chain length on T_{PS} of POEVE:[3] DP$_n$ $\sim$ 200; M_w/M_n < 1.1; [polymer] = 1.0 wt %.

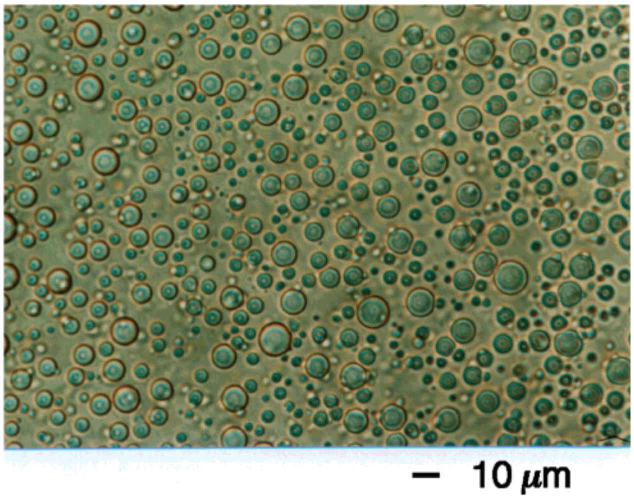


Figure 7. Micrograph of a 1.0 wt % aqueous solution of IBVE$_{40}$-*ran*-HOVE$_{160}$ at 55 °C.

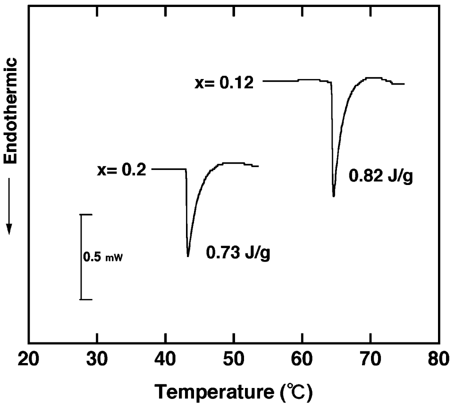


Figure 8. DSC thermograms of 1.0 wt % aqueous solutions of random copolymers (IBVE$_x$-*ran*-HOVE$_{1-x}$)$_{200}$ ($x = 0.20$ and 0.12; $M_w/M_n \leq 1.05$): heating rate 1.0 °C/min.

which precipitated above its T_{PS}. Droplets (coacervates) were observed in the micrograph of the opaque solution (1.0 wt %) at 55 °C (Figure 7). The formation of droplets instead of precipitates may be attributed to the degree of dehydration. Thus, the heat of transition (ΔH) was calculated by DSC analysis as shown in Figure 8. The transition temperature determined calorimetrically is consistent with that obtained by UV analysis. The ΔH of the 1.0 wt % aqueous solution for IBVE$_{40}$-*ran*-BMSiVE$_{160}$ was 0.73 J/g, endothermic, which is smaller than that (1.14 J/g) for poly(2-ethoxyethyl vinyl ether) (DP$_n$ = 200, $M_w/M_n = 1.07$), a thermosensitive polymer exhibiting a sharp transition due to abrupt dehydration at T_{PS}.[16] The smaller ΔH with the transition suggests that the dehydration from a random copolymer at T_{PS} will be incomplete. These data suggest that the "partially" dehydrated polymers would aggregate through hydrophobic interaction above a critical temperature to form droplets containing water.

Effects of Sequence Distribution. Figure 9 compares the thermally induced phase separation behavior of the three different copolymers in water as monitored by UV (500 nm) and DLS measurements. The phase separation for the random copolymer was highly sensitive and reversible with little hysteresis, as demonstrated by the sharp change in transmittance and by R_h^{app} upon heating and cooling (Figure 9, parts A and D).

Upon warming a 1.0 wt % aqueous solution of the "*block-and-random*" copolymer, which would form only a small aggregate at a lower temperature, phase separation occurred, but only gradually and with large hysteresis between heating and cooling cycles (Figure 9B). Accordingly, the R_h^{app} gradually became larger with increasing temperature, also with hysteresis (Figure 9E). As shown in Figure 9, parts C and F, on the other hand, the block copolymer had little effect on transmittance and R_h^{app} with varying temperature, indicative of no thermosensitivity. Judging from R_h^{app}, the IBVE$_{40}$-*block*-HOVE$_{160}$ chains are likely to assemble to form a micelle in the temperature range examined here.

Thus, the randomness and evenness of the sequence distribution in a copolymer has a significant effect on the sensitivity of phase separation. Copolymers with an uneven distribution exhibit phase separation but with appreciable hysteresis, as may be the case with aqueous solution of commercially available methylcellulose.[13] The forthcoming article will describe a further detailed investigation of the phenomena of "*block-and-random*" and block copolymers.

Thermosensitive Random Copolymer with Various Hydrophobic Units. Similar thermosensitive random copolymers of hydrophilic HOVE and hydrophobic units were prepared by living cationic polymerization using **1**/Et$_{1.5}$AlCl$_{1.5}$ in toluene in the presence of ethyl acetate at 0 °C, as shown in Table 3. We

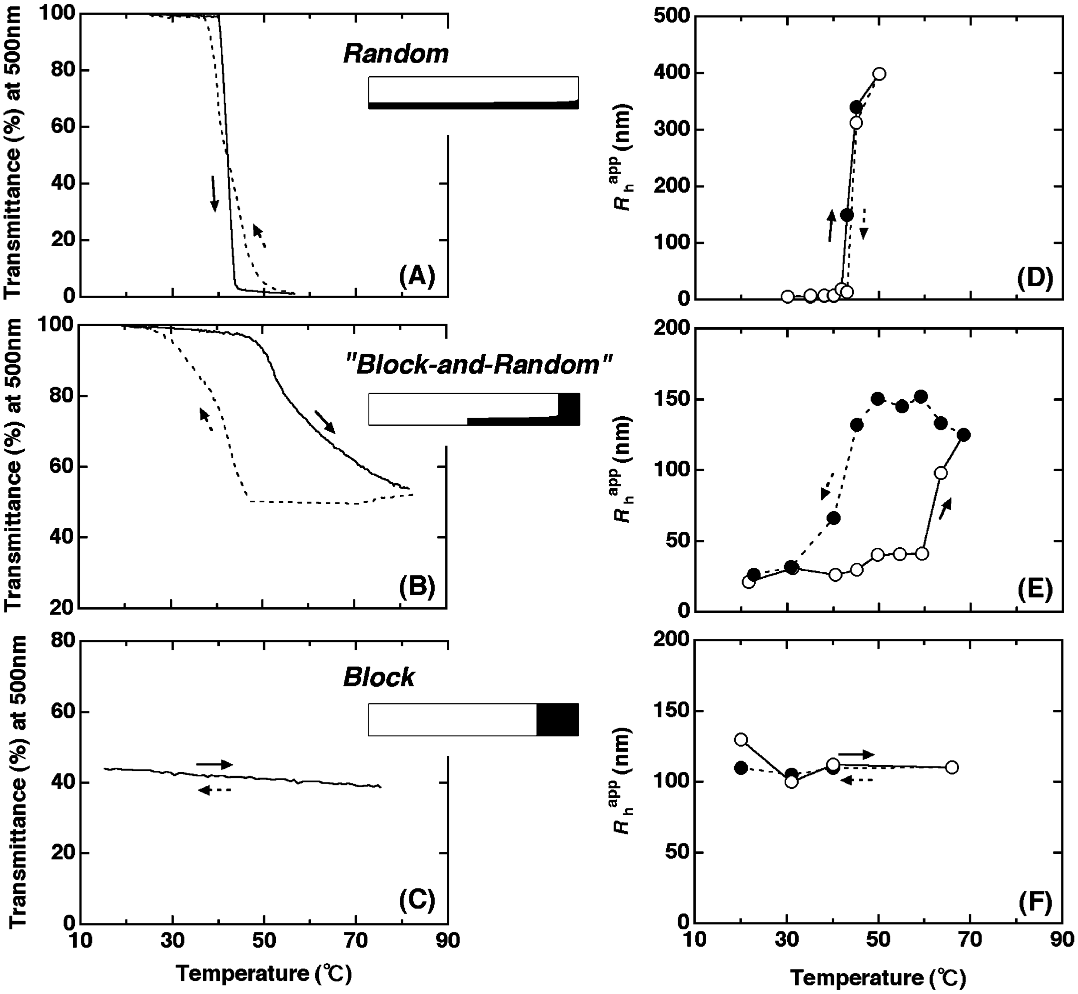


Figure 9. Effects of sequence distribution on phase separation behavior with various copolymers of IBVE and HOVE. The transmittance at 500 nm (A–C) of 1.0 wt % aqueous solutions and the apparent hydrodynamic radii (R_h^{app}) of the polymers in the same solutions (D–F): heating (—) and cooling (- - -). The rate on UV measurements was 1.0 °C/min.

Table 3. Typical Copolymerization of Hydrohobic Monomer and BMSiVE[a]

hydrophobic monomer (M_1)	M_1 in feed (mole fraction)	polymn time (h)	M_1 in copolymer[b] (mole fraction)	$M_n \times 10^{-4}$ [c]	M_w/M_n[c]
PhOVE	0.10	22	0.10	3.5	1.12
NBVE	0.20	24	0.20	3.0	1.04
SiHeVE[d]	0.25	24	0.25	3.4	1.06
AcOVE	0.59	70	0.57	2.3	1.14

[a] Polymerization conditions: $[\text{monomers}]_0 = 0.8$ M; $[\mathbf{1}]_0 = 4.0$ mM; $[\text{Et}_{1.5}\text{AlCl}_{1.5}]_0 = 20$ mM; [ethyl acetate] = 1.0 M, in toluene at 0 °C. Total converstion: 90–100%. [b] Determined by ^{1}H NMR. [c] Determined by SEC (polystyrene calibration). [d] *tert*-Butyldimethylsilyl-protected OH–He.

Table 4. Relative Reactivities[a] **for Copolymerization with Various Hydrophobic Units**[b]

monomer 1	monomer 2	r_1	r_2
PhOVE	BMSiVE$_{(\text{HOVE})}$	1.05 ± 0.01	0.96 ± 0.02
IBVE		0.80 ± 0.10	1.06 ± 0.08
NBVE		0.99 ± 0.04	0.71 ± 0.08
SiHeVE$_{(\text{OH-He})}$		0.97 ± 0.14	1.08 ± 0.03
AcOVE		0.48 ± 0.01	1.99 ± 0.06

[a] Determined by the Fineman–Ross method. [b] Polymerization conditions: $[\mathbf{1}]_0 = 4.0$ mM; $[\text{Et}_{1.5}\text{AlCl}_{1.5}]_0 = 20$ mM; [ethyl acetate] = 1.0 M, in toluene at 0 °C.

employed several monomers having different types of hydrophobic groups such as phenyl (PhOVE), alkyl (NBVE), hydroxyl alkyl (OH–He), and ester (AcOVE) groups. The product copolymers obtained from various combinations of monomers had very narrow MWDs ($M_w/M_n \leq 1.1$). Table 4 lists the relative reactivities determined by the Fineman–Ross method. All monomers except AcOVE were consumed at very similar rates relative to BMSiVE.

Figure 10 shows their phase separations by the transmittance at 500 nm and their instantaneous compositions of the copolymer (calculated by both total conversion 90% and relative reactivities shown in Table 4). Interestingly, for all combinations, aqueous copolymer solutions exhibited sensitive phase separation on heating. This shows that a wide range of hydrophobic units can be used to obtain thermoresponsive random copolymers with hydroxy groups. Figure 11 plots T_{PS} in water, determined from the transmittance at 500 nm, of 1.0 wt % aqueous solutions of random copolymers with various functional groups against the mole fraction of hydrophobic units. The T_{PS} of random copolymers decreased monotonically with the number of hydrophobic units. When a hydrophobic monomer having a polar group (hydroxyalkyl group or ester) was employed, the T_{PS} shifted to higher temperatures. Moreover, the T_{PS} can be controlled by regulating the ratio of hydrophilic and hydrophobic units, independently of the structure of the hydrophobic form.

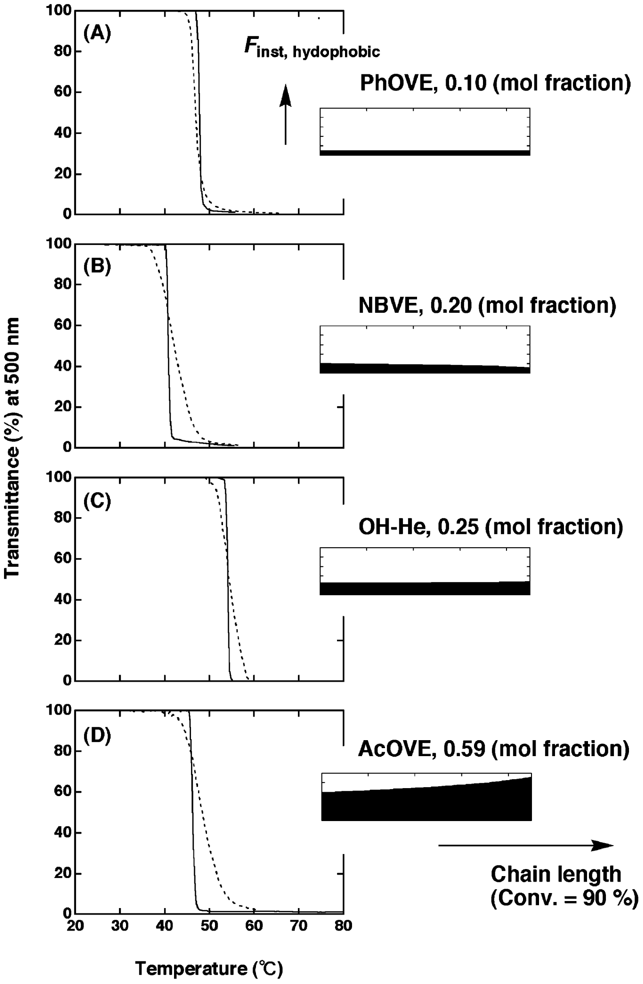


Figure 10. Temperature dependence of the transmittance at 500 nm of 1.0 wt % aqueous solution and instantaneous composition (conversion: 90%) by Skeist integral equation of random copolymers of HOVE and various hydrophobic units: (A) PhOVE (feed mole fraction: 0.1); (B) NBVE (0.20); (C) OH−He (0.25); (D) AcOVE (0.59) [polymerization conditions (before desilylation): see Table 3].

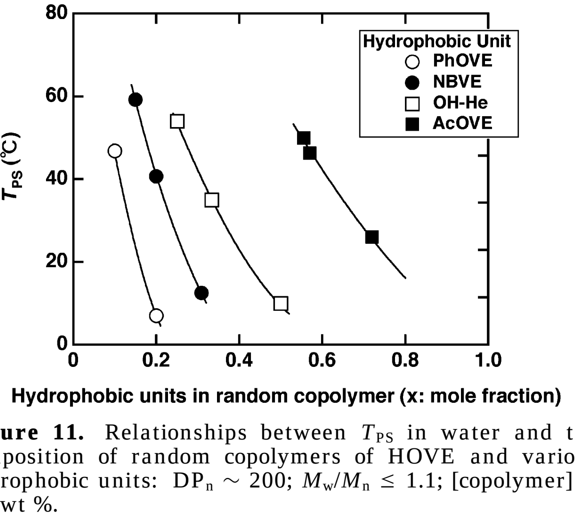


Figure 11. Relationships between T_{PS} in water and the composition of random copolymers of HOVE and various hydrophobic units: $DP_n \sim 200$; $M_w/M_n \leq 1.1$; [copolymer] = 1.0 wt %.

Conclusion

Thermosensitive random copolymers with hydrophilic and hydrophobic units were prepared by living cationic polymerization using the **1**/$Et_{1.5}AlCl_{1.5}$ initiating system in the presence of an added base. This study demonstrated that an appropriate hydrophilic/hydrophobic balance along the polymer main chain induces sensitive phase separation (LCST-type) behavior in water. To fulfill such a balance, a copolymer consisting of a certain hydrophobic monomer with specific monomer composition and even sequence distribution is required, which cannot be achieved without living polymerization. To the best of the authors' knowledge, this is the first example of thermosensitive amphiphilic random copolymers with well-defined structures.

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References and Notes

(1) This work was presented in part at the following meetings: (a) 51th Annual Meeting of the Society of Polymer Science, Japan, Yokohama, May 2002; paper ID10. Sugihara, S.; Aoshima, S. *Polym. Prepr., Jpn.* **2002**, *51*, 153. (b) 51th Symposium on Macromolecules, the Society of Polymer Science, Japan, Kitakyushu, Oct 2002; paper IB14. Sugihara, S.; Kanaoka, S.; Aoshima, S. *Polym. Prepr., Jpn.* **2002**, *51*, 1193.
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(30) The steric structure (diad) of the random copolymer was relatively meso-rich; meso/racemo = 64/36, as determined from the peak intensity of the methylene carbon in the main chain by ^{13}C NMR (see, Hatada, K.; Kitayama, T.; Natsuo, N.; Yuki, H. *Polym. J.* **1983**, *15*, 719). This is almost identical to the structures of poly(2-methoxyethyl vinyl ether)[3] and poly(OH−Bu),[5] which exhibit phase separation in water.

(31) The dissolution of poly(HOVE) without aggregation was supported by the fact that its hydrodynamic radii ranged from 6.5 to 7.0 nm in the range from 15 to 50 °C, which are consistent with the size of a single chain for that DP_n. No aggregation of the poly(HOVE) chain was also confirmed by the observation of single relaxation regarding to their translational diffusion in the correlation function of dynamic light scattering measurement.[18]

(32) The random copolymer with relatively broad MWD (M_w/M_n = 1.61) was prepared by simply mixing three random copolymers prepared with living system of the same condition [(1) $M_n = 7.0 \times 10^3$, $M_w/M_n = 1.14$, (2) $M_n = 1.4 \times 10^4$, $M_w/M_n = 1.09$, and (3) $M_n = 2.9 \times 10^4$, $M_w/M_n = 1.04$ (before desilylation)] (polymerization conditions: see the caption for Figure 2). Therefore, both polymers (M_w/M_n: 1.04 and 1.61) are very similar in sequence distribution.

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