Temperature-responsive Poly(dehydroalanine)s: Diversifying Phase Transition Temperatures Utilizing α,α-Disubstituted Motif

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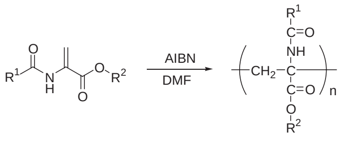
The temperature-responsive poly(dehydroalanine derivative)s having two substituents at the α-position were successfully synthesized. By varying the combination of the structures of the two substituents, the relatively large diversity of their phase transition temperatures could be achieved.

Water-soluble vinyl polymers such as poly(N-alkylacrylamide)s,[1] polyvinylethers,[2] and poly(N-vinylalkylamide)s,[3] that show soluble-to-insoluble phase transition when heated above a critical temperature have received increasing attention in the field of materials science, especially as biomedical materials. These temperature-responsive polymers commonly have both hydrophilic and hydrophobic groups in the monomeric units, and the phase transition temperatures of these polymers are governed by this hydrophilic–hydrophobic balance. The phase transition temperatures of the polymers should be adjusted to satisfy their applications. There are two approaches to control the phase transition temperature; copolymerization[4] and substitution of hydrophobic alkyl groups.[1,3] The copolymerization approach can finely control the phase transition temperature, although the phase transition of the obtained polymer occurs in a relatively broad temperature range based on the inhomogeneity of the copolymerization compositions. On the contrary, the substitution approach can give polymers with a sharp phase transition, although the diversity of the phase transition temperature of the polymers is rather limited. For example, in the case of poly(N-alkylacrylamide)s, only the following three polymers (alkyl group = Et, ^{i}Pr, and ^{n}Pr) show a phase transition temperature. The diversity of the polyvinylethers is still less than poly(N-alkylacrylamide)s; these polymers have phase transition temperatures only when the alkyl group is Me. Therefore, in order to improve the substitution approach, here we have synthesized temperature-responsive polymers bearing two substituents at the α-position; poly(dehydroalanine derivative)s (Scheme 1).[5] These polymers have two amphiphilic groups (alkylamide and alkylester), such that the diversity of the phase transition temperatures increases by varying the combination of these two alkyl groups.



Scheme 1. Polymerization of dehydroalanine derivatives.

The eight monomers **1**–**8** shown in Table 1 were synthesized by following the scheme developed by Mathias and Hermes.[5d] C_{sum} in Table 1 represents the summation of carbon numbers of both alkyl groups (R^1 and R^2) of each monomer. The obtained monomers were polymerized at 60 °C in N,N-dimethylformamide with 2,2′-azobisisobutyronitrile as an initiator. After purification by dialysis against water, the obtained polymer solutions were lyophilized and dissolved in deionized water to provide the measurement solutions.[6] The solution properties of polymers with Me as the R^1 group have been reported by three groups including us.[5a–5c] All of the polymers except for polymer **8** were soluble in water. Figure 1a shows transmittance curves of the polymer solutions, and the corresponding cloud points (T_{c}s) were determined from the curves at the temperature where the transmittance becomes 50%. Although polymer **1** showed no cloud point below 100 °C,[5b] we succeeded to obtain six temperature-responsive polymers from the poly(dehydroalanine derivative)s. The polymers with $C_{\text{sum}} = 3$ have higher T_{c} values (50–60 °C) than those of the polymers with $C_{\text{sum}} = 4$ (20–30 °C). The phase transition behaviors of the polymers are also investigated by differential scanning calorimetry (DSC) using a Seiko Electronics CCS-5200 instrument. The resulting thermograms of the polymers are shown in Figure 1b, and the obtained parameters were summarized in Table 1. Polymers with $C_{\text{sum}} =$ 3 had no detectable peak during the phase transition, while polymers with $C_{\text{sum}} = 4$ had endothermic peaks resulting from dehydration of the polymer chains.

We established three rules to account for the phase transition behavior of the polymers. First, T_{c} values decrease with increasing bulkiness of the alkyl groups. For example, when comparing the T_{c} values of the polymers having Me as the R^1 group (**1**, **2**, **4**,

Table 1. Cloud points and DSC analysis results of polymers

	R^1	R^2	C_{sum}^{a}	M_{w}^{b}	$M_{\text{w}}/M_{\text{n}}$^{b}	T_{c}/°C	T_{min}^{c}/°C	ΔH/(J/g)
1	Me	Me	2	—	—	—^{d}	—	—
2	Me	Et	3	13000	1.6	59	ND^f	ND^f
3	Et	Me	3	12000	1.8	52	ND^f	ND^f
4	Me	^{i}Pr	4	49000	1.4	27	27.3	4.9
5	Et	Et	4	80000	1.6	27	27.5	26.7
6	Me	^{n}Pr	4	26000	1.4	22	22.9	8.5
7	^{i}Pr	Me	4	58000	1.9	19	20.1	31.4
8	^{n}Pr	Me	4	—	—	—^{e}	—	—

[a]Summation of carbon number of R^1 and R^2. [b]Determined by GPC analysis (polystyrene standard). [c]Temperature at endothermic peak minimum. [d]Water soluble up to 100 °C. [e]Water insoluble at 0 °C. [f]Not detected.

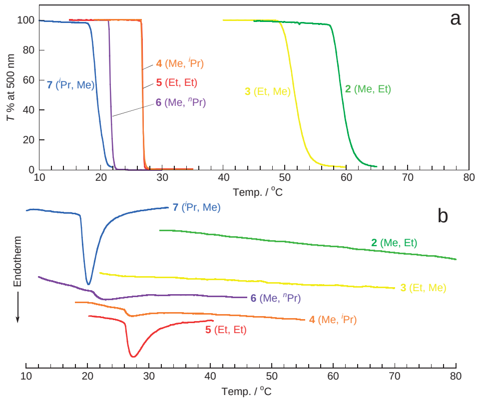


Figure 1. (a) Transmittance curves and (b) DSC thermograms of polymer solutions. Polymer concentrations were 5.0 and 50 g/L for a and b, respectively. The alkyl substituent of each polymer was described as (R^1, R^2). Heating rates were 1.0 and 0.5 for a and b, respectively.

and **6**), the T_c values of the polymers decreased depending on the bulkiness of the R^2 group as follows; Me > Et > ^{i}Pr > ^{n}Pr. In the polymers having Et as the R^1 group (**3** and **5**), the T_c of **3** (R^2 = Me) was higher than that of **5** (R^2 = Et). These results indicate that the hydrophobic hydration becomes entropically less favorable with increasing size of the hydrophobic groups, so that the polymers either become insoluble or their T_c values decrease. This same dependence of the T_c values on the alkyl structure was observed when comparing the polymers having the same R^2 group; R^2 = Me (**1**, **3**, **7**, and **8**), and Et (**2** and **5**), respectively. A similar effect of alkyl size on the cloud point of the polymer was also reported in poly(*N*-alkylacrylamide)[1] and poly(*N*-vinyl alkylamide).[3] As a second rule, comparing the polymers with the same combination of two alkyl groups (**2**/**3**, **4**/**7**, and **6**/**8**), polymers having Me as R^1 have higher T_c values than those having Me as R^2. For example, both polymers **2** and **3** have combinations of Me and Et, while the T_c value of **2** (59 °C) was higher than that of **3** (52 °C).

Third, the transition heats (ΔH) of the polymers increase with increasing bulkiness of the alkyl groups. For example, comparing the two polymers having Me as R^1 (**2**, **4**, and **6**), the transition heats decreased depending on the bulkiness of the R^2 group in the following order; ^{n}Pr > ^{i}Pr > Et. Similar results were obtained when R^1 = Et (**3** and **5**), R^2 = Me (**3** and **7**), and Et (**2** and **5**). The larger transition heat with increasing alkyl size can be explained by the following two reasons; (1) the number of water molecules which participate in hydration of the alkyl groups became larger with increasing size of the alkyl group, (2) the phase transition of the polymers with larger alkyl groups occurred in the lower temperature range so that the energy of the hydrogen bonding between the water molecules and the polymer would be larger.[7] It is important to note that there was a large difference in the transition heats of polymers **4** and **7**, despite these polymers having the same combination of alkyl groups (Me and ^{i}Pr), indicating that it is not only the size of the hydrophobic group, but also the chemical nature of the neighboring hydrophilic group (amide or ester), which affected the transition heats and phase transition temperatures of the polymers.[8]

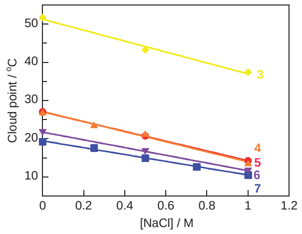


Figure 2. Effect of NaCl addition on the cloud points of aqueous polymer solutions (polymer conc. = 5.0 g/L).

Figure 2 shows the NaCl concentration dependence of the T_c value of each polymer. The T_c values of the polymers linearly decreased with increasing NaCl concentration. The slopes of the lines are almost constant irrespective of the structures of the alkyl substituents. This independence of the alkyl structures on the slope was also observed in poly(*N*-alkylacrylamide).[6]

In conclusion, we have synthesized eight poly(dehydroalanine derivative)s by taking advantage of the *α*,*α*-disubstituted structures of the dehydroalanine monomer, and have successfully obtained six temperature-responsive polymers from these candidates. The phase transition temperatures and transition heats of the polymers were systematically changed depending on the bulkiness of the alkyl substituents.

References and Notes

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6 Polymer **8** was purified by reprecipitation using diethyl ether/petroleum ether mixture.
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8 Neighboring hydrophilic groups would perturb the degree of hydration of the side groups (hydrogen-bond strength and number of hydrating H_2O), so that the ΔH and the T_c values will be changed.
9 Supporting Information (the hysteresis of the transmittance curves and the polymer concentration dependence of the cloud points) is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.