

Rendering Poly(amidoamine) or Poly(propylenimine) Dendrimers Temperature Sensitive

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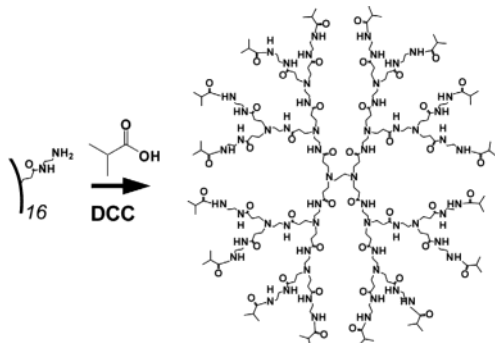
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Many efforts have been made to provide functionalities to dendrimers to increase their usefulness.¹ While the functionalization of dendrimers has been attempted by various strategies, one of the most effective strategies is the modification of the terminal groups at the outer surface of the dendrimer molecule.² In this study, we attempted to provide dendrimers with temperature-sensitive properties using a surface modification strategy. Here, we show that the introduction of isobutyramide (IBAM) groups to the chain ends of poly(amidoamine) (PAMAM) or poly(propylenimine) (PPI) dendrimers could successfully produce a temperature-sensitive water solubility to the dendrimers.

We designed the PAMAM dendrimers having IBAM groups at all the chain ends, because the IBAM group is contained in a temperature-sensitive polymer, poly(*N*-vinylisobutyramide), which exhibits a lower critical solution temperature (LCST) around 39 °C, and is considered to play an important role in the temperature-dependent solubility change in water.³

The PAMAM G2, G3, G4, and G5 dendrimers having an IBAM group at every chain end, which are designated IBAM-G2, IBAM-G3, IBAM-G4, and IBAM-G5, were synthesized according to Scheme 1. The IBAM-G2, IBAM-G3, IBAM-G4, and IBAM-G5 dendrimers possess 16, 32, 64, and 128 terminal IBAM groups, respectively. Figure 1A shows the temperature dependence of the light transmittance of the IBAM-terminated dendrimers dissolved in phosphate-buffered solution of pH 9.0 at 500 nm. The dendrimers were highly soluble in the buffer under low-temperature conditions. The solution of the IBAM-G2 did not change the turbidity over the experimental temperature range. However, for the solutions of the other dendrimers, the turbidity change took place at a specific temperature as the temperature was raised, indicating that the dendrimers became water-insoluble at that temperature. Indeed, no change in the transmittance was observed for the solutions of the unmodified PAMAM dendrimers over the experimental temperature range. In addition, we observed that these dendrimer solutions became transparent again when the temperature of the solutions

Scheme 1. Preparation of IBAM-Terminated PAMAM Dendrimers^a



^a Synthetic route for IBAM-G2 was shown. Other dendrimers were prepared by the same method. DCC, 1,3-dicyclohexylcarbodiimide.

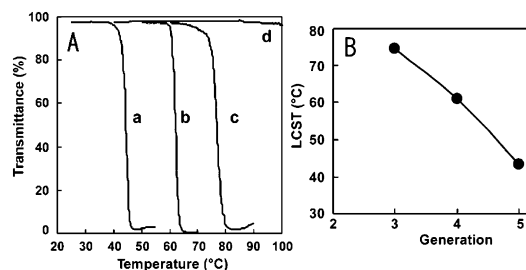


Figure 1. LCST of IBAM-bearing PAMAM dendrimers. (A) Effect of temperature on transmittance of IBAM-G5 (a), IBAM-G4 (b), IBAM-G3 (c), and IBAM-G2 (d) dissolved in 10 mM phosphate-buffered solution (10 mg/mL, pH 9.0). (B) LCST of the IBAM-bearing PAMAM dendrimer as a function of generation.

was decreased below their LCST. Therefore, it is considered that the attachment of the IBAM groups to the chain terminals of the dendrimers provided them a temperature-sensitive water solubility.

Figure 1B represents the LCST of the IBAM-terminated dendrimers as a function of the dendrimer generation. Their LCST remarkably decreased with increasing dendrimer generation. It is known that the LCST of thermosensitive polymers is dependent on the molecular weight. However, the extent of the alteration of the LCST is generally not very significant. For example, Aoshima et al. have shown that the LCST of poly(methoxyethyl vinyl ether) decreased by ca. 5 °C as the number average molecular weight increased from 10 000 to 22 000, but further increase in the molecular weight hardly affected the LCST.⁴ Also, Schild and Tirrell demonstrated that the increase in the average molecular weight of poly(*N*-isopropylacrylamide) from 5400 to 160 000 results in a decrease in LCST by ca. 2 °C.⁵ In contrast, the IBAM-terminated dendrimers exhibit a more remarkable molecular weight dependence; an increase in the molecular weight of ca. 9150 to ca. 37 800 caused a 30 °C decrease in the LCST. It is considered that the overall shape of the PAMAM dendrimers exhibits a structural change from very open, domed shapes at lower generations to a more dense spheroid-like topologies at higher generations.⁶ For the PAMAM dendrimers with the ethylenediamine core, the onset of this structural transition is thought to be at generation 2, and above this generation, the outer dendrimer surface begins to close upon itself with increasing generation, because the terminal groups of the dendrimers are more concentrated on the periphery.⁷ Therefore, it is likely that the density of the terminal IBAM groups near the periphery progressively increases with the increasing generation of the dendrimer. Thus, the interaction of the peripheral IBAM groups would take place more efficiently with the increasing generation. As a result, the dehydration of the terminal IBAM groups might be induced at a lower temperature with increasing generation.

Figure 2 shows the influence of the dendrimer concentration on the LCST of the dendrimer. It is apparent that the IBAM-G5 dendrimer exhibits a reduced concentration dependence of LCST,

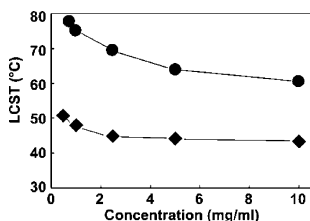


Figure 2. Influence of dendrimer concentration on LCST of IBAM-G4 (●) and IBAM-G5 (◆) in 10 mM phosphate-buffered solution (pH 9.0).

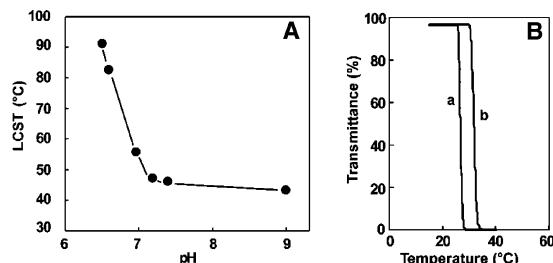


Figure 3. (A) Influence of pH on LCST of IBAM-G5 dissolving in 10 mM phosphate-buffered solution of varying pHs (10 mg/mL). (B) Effect of temperature on transmittance of aqueous solutions of IBAM-terminated DAB-Am-64 (a) and -32 (b) PPI dendrimers (10 mg/mL, pH 12.0).

compared with that of the IBAM-G4 dendrimer. The more densely packed IBAM groups in the periphery of the G5 dendrimer probably enhanced the dehydration caused by the intramolecular interaction of the IBAM groups in addition to the dehydration caused by their intermolecular interaction.

It is expected that the nature of the dendrimer interior may affect the hydrophobicity alteration of the dendrimer surface. Since the PAMAM dendrimers contain tertiary amino groups in their interior, its charge density can be tuned by varying the pH of the solution. Thus, we examined the influence of the pH on the LCST of the IBAM-bearing dendrimer. Figure 3A depicts the pH dependence of LCST of the IBAM-G5 dendrimers. The dendrimer exhibited approximately the same LCST above pH 7.2. However, the LCST significantly increased upon decreasing the pH below 7.2. It has been shown that, in the amine-terminated PAMAM dendrimer, the protonation of the primary amino groups occurs between pHs 7 and 10, whereas the protonation of the tertiary amino groups takes place between pHs 3 and 7.⁸ Apparently, the pH region, where the tertiary amino groups of the dendrimer interior become protonated, agrees well with the pH region where the increase in the LCST of the IBAM-G5 dendrimer was observed. Thus, it is highly likely that the protonation of the dendrimer interior caused the rise in the LCST of the IBAM-bearing dendrimer. Thomas and co-workers proposed that the charge–charge repulsion induced by the protonation of the tertiary amines of the PAMAM dendrimer could cause molecular expansion, as determined from the polarity change in the dendrimer interior.⁹ Therefore, protonation of the interior of the IBAM-G5 dendrimer might induce expansion of the dendrimer and reduce the interaction between the IBAM groups in the periphery of the dendrimer, resulting in an increase in the LCST.

The attachment of IBAM groups to the periphery of the dendrimers gave them a temperature-sensitive property. To know whether this is a general phenomenon or not, we examined the effect of dendrimer interior. We prepared PPI dendrimers with 32 and 64 IBAM groups at the periphery by combining an IBAM group to every chain end of DAB-Am-32 and DAB-Am-64 PPI dendrimers, respectively. As can be seen in Figure 3B, the IBAM-terminated DAB-Am-32 and -64 dendrimers changed water solubility at 31 and 27 °C, respectively. Compared with the PAMAM-based dendrimers having the same number of peripheral IBAM

groups, the PPI-based dendrimers exhibited LCST at much lower temperature, despite their lower molecular weight. Because the PPI dendrimer is much smaller than the PAMAM dendrimer with the same number of the chain ends,^{7b,10} it is likely that the higher density of the peripheral IBAM groups of the PPI dendrimers enhanced interaction between the IBAM groups and caused efficient dehydration at the relatively low-temperature region.

Previously, Kimura et al. prepared the DAB-Am-32 PPI dendrimer having poly(*N*-isopropylacrylamide) arms as a temperature-sensitive host for cobalt phthalocyanins.¹¹ In that case, the temperature sensitivity was given to the dendrimer by conjugation of the temperature-sensitive poly(*N*-isopropylacrylamide) with the dendrimer. In contrast, for the IBAM-terminated dendrimers, the dendrimer itself could achieve temperature-sensitive water solubility.

In this study, we demonstrated that the attachment of IBAM groups to the chain ends of the PAMAM and PPI dendrimers could give them a temperature-sensitive water solubility. Because the terminal moieties of the dendrimers with high generations are known to be densely packed, it is likely that the terminal IBAM groups form a shell that changes the nature of the dendrimer surface between hydrophilic and hydrophobic in response to the ambient temperature. To the best of our knowledge, the IBAM-terminated dendrimers prepared in the present study are the first dendrimers that exhibit temperature-sensitive characteristics. The IBAM-terminated dendrimers have some remarkable features that the conventional thermosensitive polymers do not have, such as a 3-D structure and a precisely controlled molecular size, though efforts have been made to produce linear polymers with a controlled molecular weight and dispersity.¹² The findings obtained in the present study may generate a new family of thermosensitive polymers.

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Supporting Information Available: Experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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