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Synthesis and Solution Properties of a Novel Thermosensitive Poly(benzyl ether) Dendron with Oligoethyleneoxy Chains at the Periphery

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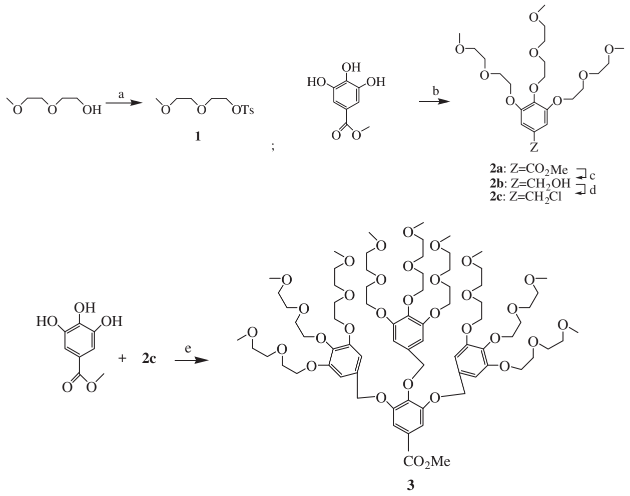
A novel thermosensitive second-generation poly(benzyl ether) dendron with oligoethyleneoxy chains at the periphery was synthesized. Its cloud point (CP) decreased with an increasing concentration over a range of concentrations from 9 to 60 wt %. Fluorescent spectroscopy and AFM studies revealed that the dendron self-assembled into the spherical micelles, about 50 nm in diameter, at concentration over its CMC in an aqueous solution. This dendron has a potential as smart thermosensitive materials.

In recent decades, there has been increased interest in thermosensitive materials due to their promising applications in many fields such as controlled drug release, cell culture, and isolation of molecules.[1–3] These materials exhibit a phase transition from a soluble state to an insoluble state when the temperature is above a lower critical solution temperature (LCST). Because of tunable LCST behavior, poly(ethylene glycol) (PEG)-based polymers have attracted great attention in the last couple of years. Also, PEGs are nontoxic and biocompatible.[4] Short oligo(ethylene glycol) (OEG) groups have been incorporated into not only linear but also dendritic macromolecules.[5] For example, water-soluble polyacrylates and polystyrenics with short pendant OEG groups have been reported.[6] These polymers undergo phase transitions when the temperature is above a critical point. A series of thermosensitive OEG-based dendronized polymers and dendrimers were synthesized.[7] They exhibited sharp phase transitions and negligible hysteresis. But to date, the most studied thermosensitive materials have been polymers. To the best our knowledge, reports of dendrons and small molecules exhibiting the LCST phenomenon are very limited.[8,9] It is generally accepted that an appropriate combination of hydrophilic–hydrophobic balance in the polymer chains is believed to be required for the phase transition to occur.[10] Just like certain thermosensitive amphiphilic OEG-based dendrimers,[5,9] the amphiphilic dendron with the hydrophobic second-generation poly(benzyl ether) branch unit and hydrophilic oligoethyleneoxy peripheries synthesized in this study is potentially a responsive material to temperature change. Indeed, we found that this amphiphilic dendron showed LCST and critical micellization behavior. Here we report on the synthesis and solution properties of this novel amphiphilic dendron.

The synthetic route of first- and second-generation dendrons **2a**, **2b**, **2c**, and **3** are outlined in Scheme 1. The first-generation dendron **2a** was prepared by Williamson etherification of methyl gallate with tosylated di(ethylene glycol) monomethyl ether **1**. **2a** was reduced with lithium aluminum hydride (LAH) to give the first-generation dendron alcohol **2b**. In an earlier paper,[7b] purification of **2a** and **2b** required column chromatography. In this study, the synthetic procedure of **2a** was modified by adjusting the molar ratio of methyl gallate to compound **1** from 1:4 to 1:5 and prolonging the reaction time from 24 to 48 h. As a consequence, **2a** was obtained in sufficient purity only by solvent extraction. Another improvement in this study in comparison with the literature is prolongation of the reaction time of **2a** with LAH from 3 to 16 h. Also the molar ratio of LAH to **2a** was adjusted from 1.5:1 to 2:1. These conditions furnished analytically pure **2b** without column chromatography. Chlorination of **2b** with $SOCl_2$ which is the most attractive reagent for the chlorination of benzyl alcohols because of the short reaction time, low temperature, and low price[11] afforded the corresponding chloride **2c**. The alkylation of methyl gallate with **2c** by using K_2CO_3 as base in DMF generated the new second-generation dendron **3**. The purification of every compound requires only solvent extraction. All these pure products were obtained as oily liquids. The isolated yields were 92.3%, 90.0%, 93.4%, and 91.2% for **2a**, **2b**, **2c**, and **3**, respectively. ^{1}H NMR spectra of **2a** and **2b** was consistent with the literature.[11b] **2b** and **3** were characterized by ^{1}H NMR and ^{13}C NMR spectra. The structure of **3** was further confirmed by IR and ESI-MS (see the Supporting Information).[16]



Scheme 1. Synthesis of compounds **1**, **2a**, **2b**, **2c**, and **3**. Reagents and conditions: (a) 4-methylbenzenesulfonyl chloride, KI, NaOH, THF, H_2O, rt, 4 h; (b) K_2CO_3, KI, DMF, 80 °C, 48 h; (c) LAH, THF, rt, 16 h; (d) $SOCl_2$, DMF, DCM, rt, 2 h; (e) K_2CO_3, DMF, 70 °C, 24 h.

The new dendron **3** is water soluble at room temperature, but a temperature-induced transition from a clear solution to a turbid one was observed for **3** in an aqueous medium at a concentration above the LCST. The effect of the dendron concentration on the cloud point was investigated by turbidity measurements using UV–vis spectrophotometry. As shown in

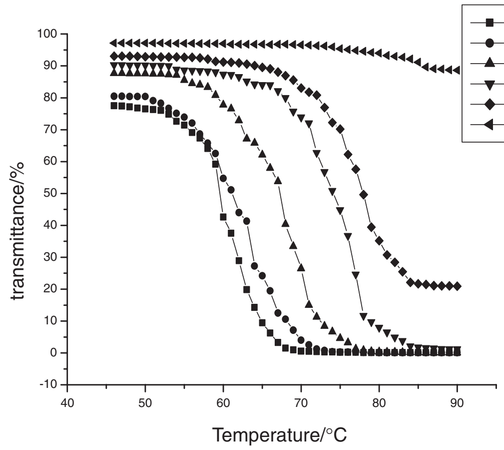


Figure 1. Temperature dependence of light transmittance for aqueous solutions of **3** in the concentration range of 9–60 wt %.

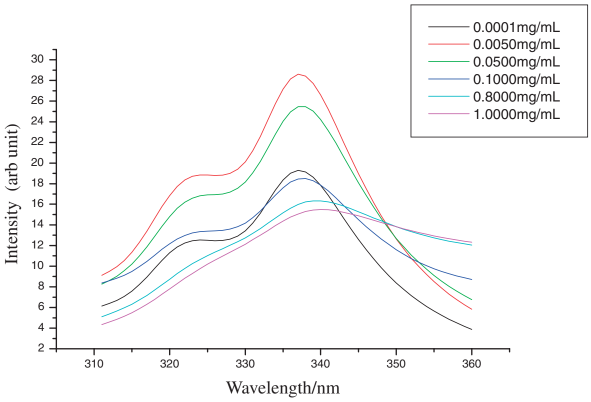


Figure 2. Excitation spectra of pyrene in water at different concentrations of **3**.

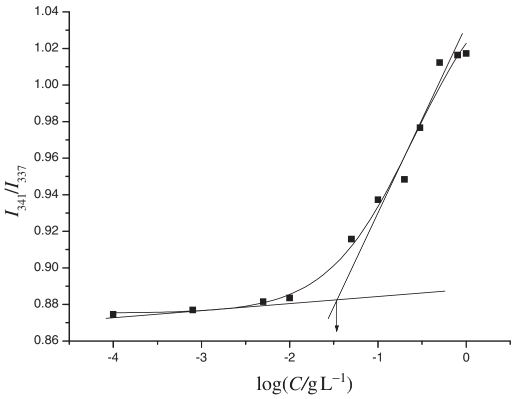


Figure 3. Plot of I_{341}/I_{337} versus logarithm of concentration of **3**.

Figure 1, the cloud point decreased with increasing solution concentration in the range 9–60 wt % of the dendron, but it was found to be almost independent at higher concentrations. The chemical structure of the dendron **3** possesses hydrophilic oligoethyleneoxy chains and hydrophobic poly(benzyl ether) units. The main mechanism of the thermally induced phase separation is thought to be due to hydrogen bonds and hydrophobic interaction.[12] Below the LCST, the predominantly hydrogen-bonding interactions between the hydrophilic groups and water molecules lead to dissolution of the dendron in water. As the temperature is raised, the hydrogen-bonding interactions weaken and hydrophobic interactions among hydrophobic groups begin to predominate. Once, the hydrophobic interactions reach a critical level at the LCST, the dendron precipitate from solution. A higher concentration may cause the interactions between the dendron and water to decrease, thus less thermal energy is needed to break the water structure, resulting in a lower LCST. Interestingly, the first-generation dendron **2a** did not exhibit any sharp transition point that resembles an LCST behavior. These results suggest that the thermoresponsive character of the dendrons is dependent on the generation as observed for thermosensitive biaryl-based dendrimers with a penta(ethylene glycol) monomethyl ether and a decyl chain.[9] Compared with poly(ethylene oxide)–poly(propylene oxide) block copolymers,[13] this newly synthesized OEG-based dendron showed a lower LCST with a stronger temperature dependence because of the shorter oligo(ethylene oxide) terminal chains.

Pyrene is hydrophobic and exhibits low solubility in water (6×10^{-7} M). When the environment of pyrene changes from polar to apolar, its emission and excitation spectra are altered.[14] Therefore, steady-state fluorescence spectra of the dendron **3** solution with a pyrene probe were used to study the association behavior of **3** in aqueous solution. In the pyrene excitation spectra, the peak at 337 nm in water red-shifts to 341 nm as concentration of **3** increases (Figure 2). This change is due to the transfer of pyrene from water to the hydrophobic core of the micelles. It is premised that the peak would be moved to 341 nm when pyrene is totally surrounded into the micelles.[15] So the intensity ratio at 341 versus 337 nm (I_{341}/I_{337}) is plotted as a function of concentrations of **3** in Figure 3. We can observe from Figure 3 that when the concentration of **3** is lower, the ratio of I_{341}/I_{337} was almost unchanged. It suggests that pyrene is dispersed in the water in molecular form. The ratio of I_{341}/I_{337} rapidly increases with increasing concentrations of **3**. The concentration at the abrupt increase in the ratio of I_{341}/I_{337} represents a critical micelle concentration (CMC) value. The CMC of **3** was determined to be 0.034 mg mL^{-1}.

To further determine the micelle morphology of compound **3**, its self-aggregation was investigated by AFM. As seen in Figure 4, spherical micelles about 50 nm in diameter formed from the aqueous solution of **3** above the CMC after air-drying.

In conclusion, the efficient synthesis of a novel thermosensitive second-generation poly(benzyl ether) dendron with oligoethyleneoxy chains at the periphery was described. The synthetic method of the first dendron and corresponding alcohol was improved in order to obtain the product with high yields and easy purification. The second-generation dendron exhibits concentration-dependent LCST behavior. Its cloud point increased with a decrease in the compound concentration in water. Studies of the association behavior of the dendron in aqueous solution revealed that the formation of spherical micelles of the dendron with about 50 nm in diameter took place over its CMC. This dendron has potential as a smart thermosensitive material.

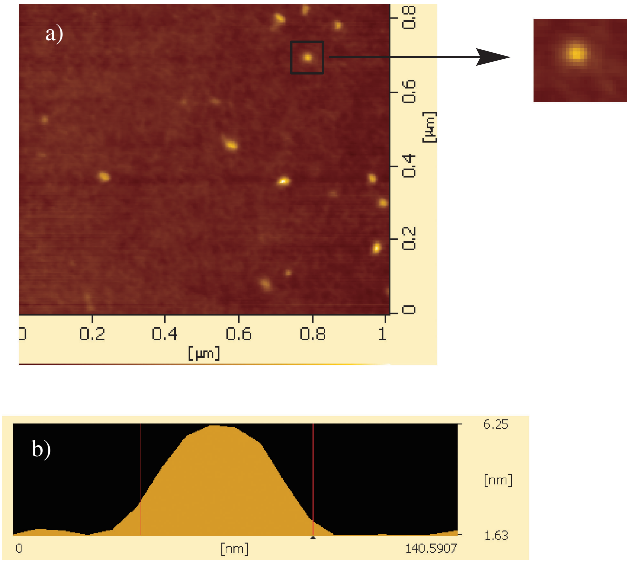


Figure 4. AFM images of aggregates from dendron **3**.

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16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.