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Lower Critical Solution Temperature Behaviors of Aromatic Compounds with Oligo(ethylene glycol) Chains

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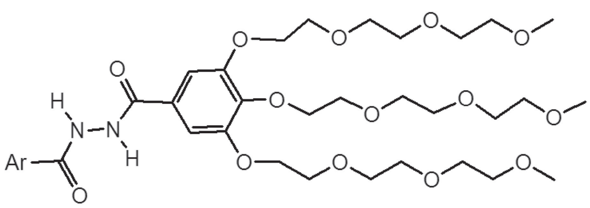
Amphiphilic small molecules comprising aromatic units and amphiphilic oligo(ethylene glycol) side chains were synthesized. These compounds exhibit lower critical solution temperatures (LCST) in aqueous solutions. Control of the LCST has been achieved by changing the solute concentration and adding salts or organic solvents.

The self-assembly of molecules into supramolecular structures is an interesting approach for the development of new nanomaterials.[1] One example of a unique self-assembly phenomenon is lower critical solution temperature (LCST) behavior, wherein a material exhibits a phase transition from a soluble state to an insoluble state when the temperature exceeds the LCST. Recently, such temperature-responsive materials have attracted considerable attention because of their promising applications in many fields such as biomedicine, sensors, catalysts, and molecule isolation.[2] Although materials exhibiting the LCST phenomena have been extensively studied in water-soluble polymers such as poly(*N*-isopropylacrylamide), poly(methyl vinyl ether), and poly(ethylene glycol),[3] few studies have been published on small molecules that exhibit LCST.[4] Thus, we have investigated small molecules with LCST, that can be easily modified to control the aggregation behavior and introduce functional groups. It is generally accepted that an appropriate ratio of hydrophilic–hydrophobic moieties in the molecules is required for LCST behavior to occur.[5] Therefore, we designed hydrophobic aromatic compounds **1**–**4** bearing amphiphilic oligo(ethylene glycol) moieties as materials that are potentially responsive to changes in temperature (Figure 1). In this study, we report the syntheses and solution properties of these novel amphiphilic compounds.

Amphiphilic aromatic compounds **1**–**4** were synthesized as shown in Scheme S1. Methyl gallic acid (**5**) was prepared in 75% yield via the reaction of gallic acid and dry methanol in the presence of concentrated H_2SO_4 as catalyst. Methyl gallic acid (**5**) was reacted with 2-[2-(2-methoxyethoxy)ethoxy]ethoxyl tosylate and the resulting product **6** was further treated with hydrazine to give the corresponding hydrazide derivative **7**[6] in 87% yield. The hydrazide derivative **7** was reacted with benzoyl chloride in the presence of sodium carbonate to give **1** in 73% yield. Similar reactions using 1-naphthalenecarboxylic acid chloride, 9-anthracenecarboxylic acid chloride, and 1-pyrenecarboxylic acid chloride instead of benzoyl chloride gave the corresponding compounds **2**, **3**, and **4**, in 87%, 84%, and 62% yields, respectively.

Compounds **1**, **2**, and **4** were readily soluble in pure water at room temperature, whereas **3** was not soluble in pure water even under heating.[7] In the aqueous solutions, compounds **1**, **2**, and **4** show similar thermal behaviors in response to heat. The aqueous solutions were transparent at room temperature and became turbid on warming, indicating that these compounds exhibited LCST phenomena. This behavior of these compounds **1**, **2**, and **4** was reversible in cycles of warming and cooling and might be caused by entropically favorable dehydration because of the oligo(ethylene glycol) chains.[8]

To determine the transition temperature (T_t) for the LCST phenomena, the transmittance values at 800 nm for the aqueous solutions (concentration: 50 mM) were measured while heating in the temperature range of 10–90 °C. The solutions were clear at low temperature. Upon warming, the transmittance values at 800 nm remained at 100% until a certain temperature and then suddenly decreased, indicating that the solution became turbid. The whole process was thermally reversible and did not show hysteresis (Figure S1). The temperature dependences of transmittance at 800 nm for the different solutions are shown in Figure 2. From the plots of transmittance at 800 nm versus temperature, the values of T_t for **1**, **2**, and **4** were found to be 86,



1: phenyl, **2**: 1-naphthyl, **3**: 9-anthranyl, **4**:1-pyrenyl

Figure 1. Amphiphilic aromatic compounds bearing oligo(ethylene glycol) chains **1**–**4**.

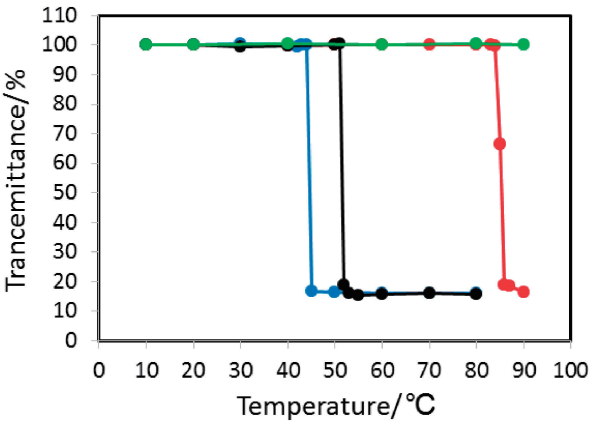


Figure 2. Temperature dependence of light transmittance for 50 mM aqueous solutions of **1** (red line), **2** (blue line), **4** (black line), and **7** (green line).

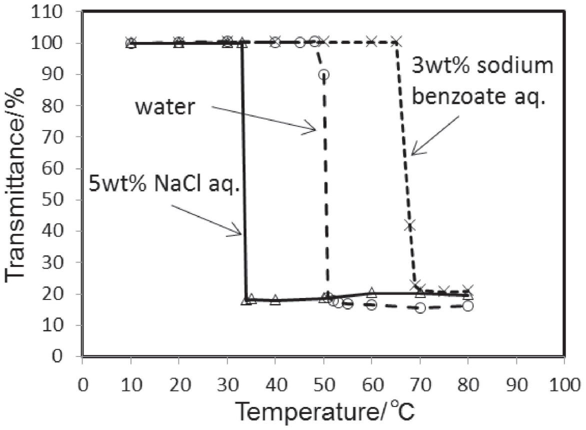


Figure 3. Temperature dependence of light transmittance for pure water, 5 wt % NaCl aqueous solution, and 3 wt % sodium benzoate aqueous solution of **2** ($c = 10$ mM).

43, and 52 °C, respectively. In contrast, the hydazide derivative **7**, which lack an aromatic unit, did not exhibit any LCST behavior.

To investigate the solute concentration dependence of T_t, the transmittance at 800 nm was also measured at different solution concentrations. The transmittance at 800 nm versus temperature plots at various concentrations for **1**, **2**, and **4** are shown in Figure S2. The T_t values for these three compounds shifted to higher temperature with decreasing concentration (**1**: 86 °C at 50 mM, 80 °C at 100 mM; **2**: 50 °C at 10 mM, 43 °C at 50 mM; **4**: 55 °C at 1 mM, 52 °C at 3–50 mM). The critical concentrations of LCST behavior of **1**, **2**, and **4** shift to lower values with increasing hydrophobicity of the aromatic unit (**1**: 50 mM, **2**: 10 mM, **4**: 1 mM) as shown in Figure S2, indicating that the hydrophobic components play an important role in the LCST phenomena.

To investigate the effect of added salt on the LCST behavior, sodium chloride or sodium benzoate was added to the aqueous solutions of **1**, **2**, and **4**. The addition of sodium chloride decreased the T_t values of all three compounds. Conversely, the addition of sodium benzoate increased the T_t values (Figures 3 and S3). Furthermore, these salt effects were enhanced by increasing the salt concentration. These behaviors indicate that sodium chloride has a salting-out effect, whereas sodium benzoate has a salting-in effect.[9,10]

The aqueous solution of **4** exhibits LCST behavior even in the presence of organic solvents. Therefore, we investigated the LCST behavior of **4** in mixed water/organic solvents with a wide range of concentrations (1–100 mM) and mixed solvent compositions (ϕ_{H_2O} (proportion of H_2O in solvent mixture): 0–100%). These solutions were examined at both low and high temperature allowing the observation of two types of behavior: transparent solution and opaque state. The LCST phenomena were observed as the proportion of H_2O in the solvent mixture increased. When ethanol was used as the organic solvent, a clearly demarcated boundary region emerged between the transparent solution and the opaque state, as shown in Figure 4. When methanol was used as organic cosolvent, the boundary line shifted toward a lower proportion of water compared to when ethanol was used: in contrast, the use of 1-propanol shifted the boundary line toward higher proportion of water (Figure S4). These obtained results indicated that increasing the hydrophobicity of the organic cosolvent depresses LCST behavior.

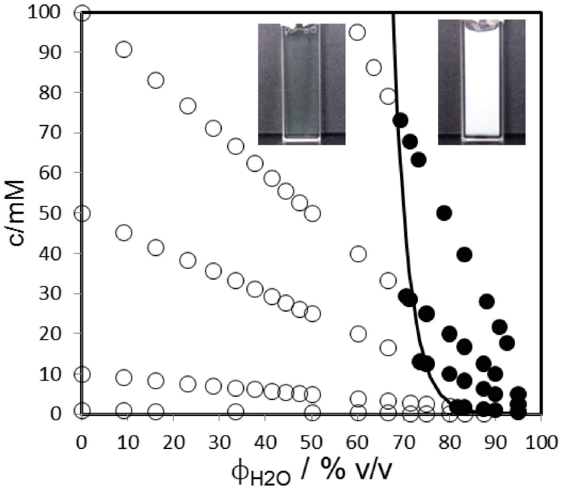


Figure 4. Concentration (c)–composition (ϕ_{H_2O}) phase diagram for **4** in ethanol/water mixture (open circles: non LCST behavior, filled circles: LCST behavior).

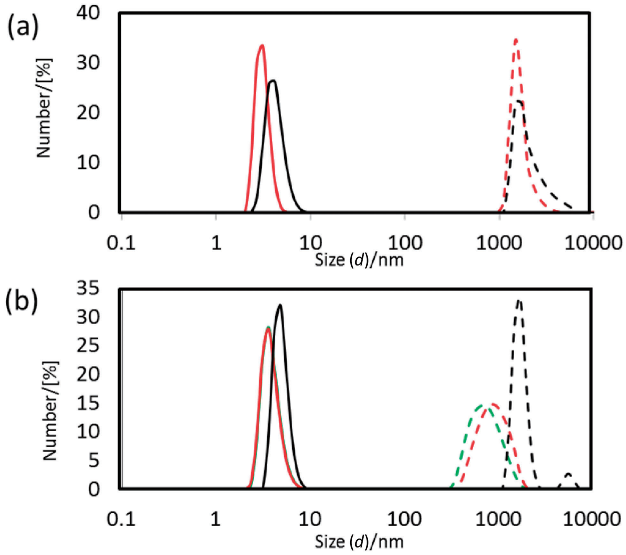


Figure 5. Size distributions in DLS in aqueous solutions of (a) **2** at 25 °C (red line: 10 mM, black line: 50 mM), red dotted line (60 °C, 10 mM), black dotted line (50 °C, 50 mM); (b) **4** at 25 °C (green line: 5 mM, red line: 10 mM, black line: 50 mM) and at 60 °C (green dotted line: 5 mM, red dotted line: 10 mM, black dotted line: 50 mM).

To examine the size distributions of the aggregates of compounds **2** and **4**, dynamic light scattering (DLS) measurements were carried out below and above T_t (Figure 5). Below T_t, scattering peaks of **2** and **4** were observed for sizes of less than 10 nm, whereas above T_t, the observed peaks corresponded to size larger than 1000 nm. The obtained hydrodynamic diameter (D_h) values below and above T_t were significantly different, indicating that the molecules predominantly existed as large assemblies above T_t. Similar behavior was observed in the presence of salts (sodium chloride and sodium benzoate) as shown in Figure S5.

Variable-temperature (VT) ^{1}H NMR measurements were carried out on 50 mM solution of **1** in D_2O. In the spectrum of **1** below T_t (30 °C), all signals were sharp and no peak broadening was observed. In contrast, all the proton signals became broader above T_t (70 °C). This observation supports the idea that the phase separation of **1** occurs along with the suppression of the molecule movements.[11] Similar signal changes were observed for the analogous compounds **2** and **4** at elevated temperature (Figure S6).

The gelation abilities of compounds **1**–**4** were also examined in thirty organic solvents. Gel formation was determined using the "stable to inversion of the test-tube" method.[12] Compounds **1**–**4** did not form organogels in any of the tested organic solvents (Table S1). We also investigated the gelation abilities using water/organic solvent mixtures: compound **3** formed a gel when methanol or ethanol was used as the organic cosolvent (Table S2). The results led us to conduct a detailed examination of the gelation behavior of **3** in water/ethanol mixtures with different compositions. Compound **3** could be dissolved in solvent mixtures containing 0%–60% (by volume) water, however, gelation was not observed. Conversely, compound **3** formed a gel in solvent mixtures containing 70%–80% water, and yielded suspensions or remained insoluble in mixtures containing more than 90% water. As shown in Figure S7, the solutions of **3** in mixed water/ethanol solvents containing 0%–60% water were slightly fluorescent under UV light, whereas the gel states in solvents containing 70%–80% water were highly fluorescent. The fluorescence spectra of **3** in solution and gel states were collected in water/ethanol solvent mixtures (Figure S8). Gelation-induced fluorescence enhancement was observed for **3** in water/ethanol mixture containing 70%–80% water.[13] The self-assembled gel structure of the xerogel of **3** was examined by scanning electron microscopy (SEM). The SEM image of the gel formed in the mixture containing 80% water indicated that the gel had sheet-like aggregates with thicknesses of approximately several hundred nm (Figure S9).

In summary, we have prepared amphiphilic aromatic compounds **1**–**4** with tri(ethylene glycol) side chains and examined their LCST behaviors in aqueous solutions. Compounds **1**, **2**, and **4** exhibited LCST behavior in pure water (and in water/organic solvent mixture for **4**), and the values of T_t increased with a decreasing solution concentration. Compounds **1**, **2**, and **4** also exhibited decreased or increased T_t values in the presence of added salts, indicating salting-out and salting-in effects. The temperature-dependent aggregation behaviors were also supported by DLS and VT ^{1}H NMR measurements. Compound **3** formed a gel in 70–80% water/ethanol mixtures and exhibited gelation-induced fluorescence enhancement. These amphiphilic aromatic compounds **1**–**4** show thermosensitive properties making them potential temperature-responsive materials.

Supporting Information is available electronically on J-STAGE.

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