RAPID COMMUNICATION

Water-Soluble Polymers with Tunable Temperature Sensitivity: Solution Behavior*

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INTRODUCTION

Controlled polymer solubility in water is of great interest, with promise of use in applications requiring smart/responsive materials such as sensors and actuators, cell patterning,[1,2] and smart/controlled drug-delivery systems.[3] Temperature-sensitive solubility usually originates from the existence of a lower critical solution temperature (LCST) beyond which the polymer becomes insoluble in water. Such behavior is typical for the polymers that form hydrogen bonds to water.[4–6]

Driven by the high promise for biomedical applications, polymers that exhibit a response in water at about 37 °C are of particular interest. Taylor and Cerankowski[5] predicted that LCST of a water-soluble polymer can be varied by controlling the balance of hydrophilic and hydrophobic segments in the polymer chain. However, most polymers that have been examined are based on a single homopolymer [poly(N-isopropylacrylamide), PNIPAM] that exhibits LCST at 32 °C,[7] and efforts to change its LCST mostly involved modifications through the addition of hydrophobic branches.[6–8] These branched polymers exhibit cloud points (CPs) that do not correlate with the hydrophobic/hydrophilic balance of the polymer.[6] This behavior originates from the branched molecular architecture of these materials that results in a coil to micelle "phase transition" rather than a polymer solution (LCST) phase transition. Bokias et al.[7] showed that increasing the length of the hydrophobic side chains can shift the LCST of PNIPAM, but now the phase transition broadens and occurs over a wide temperature range. Virtanen et al.,[8] who investigated PNIPAM modified with poly(ethylene oxide) (PEO) grafts, also found the same broadening of phase transition that they attributed to the collapsed aggregate formation—a micelle that consists of a PNIPAM/PEO core with a PEO shell. Such coil-to-micelle transitions make it difficult to predict the behavior of branched-modified thermosensitive polymers on the basis of the balance of hydrophilic and hydrophobic molecular segments,[6] thus limiting dramatically the ability to design polymers with tailored temperature response in aqueous solutions.

A sharp LCST transition that is determined by the hydrophobic/hydrophilic balance dictates a linear polymer architecture where the hydrophobic and hydrophilic segments are not lumped together in blocks, which could facilitate the formation of collapsed polymers upon precipitation from solution. This is the driving force for this study that aims to design water-soluble polymers with a controlled temperature response in aqueous solutions and tailor their phase separation through the balance of hydrophilic and hydrophobic segments. For this purpose, we synthesized polymers on the basis of monomers with a controlled stoichiometry of ethylene/(ethylene oxide) with the intention to tailor the polymer LCST by controlling the hydrophobic/hydrophilic balance within the monomer. We report the first experimental results on the solubility phase diagram and the LCST dependence of the monomer composition.

MONOMER DESIGN AND POLYMER SYNTHESIS

Probably the most investigated[4,9−11] biocompatible polymer that exhibits LCST behavior in water is PEO. However, aqueous PEO solutions have an LCST that ranges from 100 to 150 °C depending on molecular weight,[9] a range of temperatures that limits its use as a thermoresponsive polymer for most aqueous applications. A polymer that includes ethylene oxide (EO) parts and hydrophobic parts [e.g., ethylene (EE)] should exhibit a phase transition at lower temperatures than the PEO LCST. Where a linear polymer is used—made of short-enough EO and EE segments to prevent micelle formation—its precipitation from aqueous solution can be envisioned as a sharp LCST transition. Moreover, given the PEO and PE phase behavior in water, a linear-alternating EO-EE copolymer sequence across the polymer should lead to an LCST determined by the hydrophobic/hydrophilic balance, (in the absence of intra- and intermolecular hydrogen bonding). This approach parallels that of Nagasaki et al.[12] who tailored the LCST of poly(dimethylsiloxy-*co*-ethyleneoxide) rubbers by varying the siloxane content of the polymer. The advantages of our approach are twofold. First, the resulting polymers are fully "carbon based;" this involves a more versatile chemistry that can allows for a large range of polymers. Second, the polymers can be made far less susceptible to hydrolysis. Along these lines, we synthesized a series of polymers with a variable EE/EO ratio in the monomer that have the following structure:

$$\text{poly-}[(\text{O}-\text{CH}_2-\text{CH}_2)_m\text{O}-\overset{\displaystyle \text{O}}{\overset{\displaystyle \|}{\text{C}}}-(\text{CH}_2-\text{CH}_2)_n-\overset{\displaystyle \text{O}}{\overset{\displaystyle \|}{\text{C}}}] \tag{1}$$

$$\text{poly-}[\text{CH}_2-(\text{CH}_2-\text{O}-\text{CH}_2)_m\text{CH}_2-\overset{\displaystyle \text{O}}{\overset{\displaystyle \|}{\text{C}}}-\text{O}-(\text{CH}_2-\text{CH}_2)_n-\text{O}-\overset{\displaystyle \text{O}}{\overset{\displaystyle \|}{\text{C}}}] \tag{2}$$
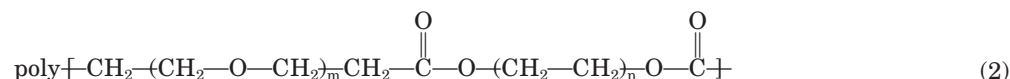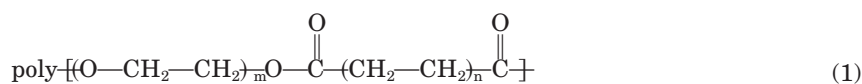
The synthesis of polymers 1 and 2 involved simple polycondensation reactions. For 1 poly(*m*)ethylene glycol (*m* = 4) was reacted with dicarboxychloride poly-(*n*)ethylene (*n* = **3**, suberoyl chloride). For 2 α,ω-bis(carboxymethyl)-poly(*m*)ethyleneoxides (*m* = 5 and 13) were chlorinated and subsequently reacted with α,ω-diol-poly(*n*)ethylenes (*n* = 3 and 6). For both reactions, the dicarboxychlorides were dissolved in tetrahydrofuran (THF), and half of the stoichiometric amount of diol dissolved in THF was added. The remaining part of the diol was added dropwise from a THF solution over 48 h to keep polydispersities small.[13] The reaction was carried out at 150 °C in the presence of NaOH, whereas THF was refluxed. After the reaction, THF was evaporated, and the residue was dissolved in absolute ethanol and filtered; the polymers were recovered from the latter solution after slowly distilling (at about 50 °C) the ethanol away. The combinations of all preceding *m* and *n* resulted in a series of five polymers with a systematic variation of *m/n*, which were all water soluble at room temperature except for the most hydrophobic, that is, polymer 2 with *m* = 5 and *n* = 6.

RESULTS AND DISCUSSION

Solubility Phase Diagram

To get some clues on the phase-transition behavior of our polymers, the phase diagram of one representative polyester (*m/n* = 13/6) is shown in Figure 1, and its phase behavior is compared against the phase diagram of pure PEO [Fig. 1(a)]. In the absence of experimental data for the PEO binodal, at comparable molecular
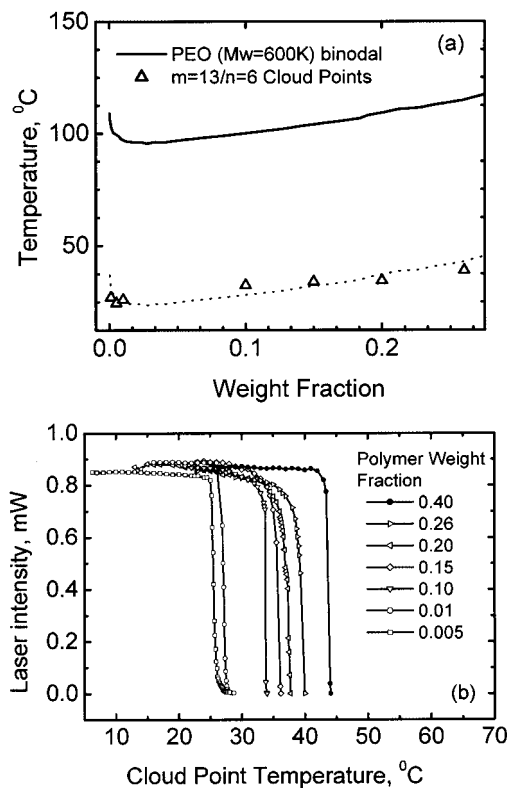

Figure 1. (a) Comparison of the solubility phase diagrams for PEO and for the 13/6 polyester; the dotted line is the PEO bimodal shifted by 72 °C. (b) Experimental turbidity data of the 13/6 polyester for various solution concentrations.

weight as our $m/n = 13/6$ polyester, the calculated phase diagram is given in Fig. 1(a) for weight-average molecular weight $M_w = 600$ K (calculated in the same manner and using the same parameters as described in the literature[14]). In Figure 1(b) the experimental cloud point measurement curves are also provided as a function of the solution concentration. From the experimental data it is obvious that the synthesized polyester has very sharp solubility phase transition, even at high temperatures [Fig. 1(b)]. This suggests that the collapsed coils do not form micelles, as is the case with branched or random/block copolymers,[6] and in contrast to the poly(dimethylsiloxy-*co*-ethyleneoxide) behavior they are less susceptible to hydrolysis.[12] The overall solubility phase diagram is similar to the calculated neat PEO phase diagram but at considerably lower temperatures, as expected by the addition of the hydrophobic ethylene part in the monomer. The sharpness of the phase separation and the similarity to the neat PEO phase diagram suggest that our polymer's solubility is governed by the LCST behavior of EO.

Effect of Hydrophobic/Hydrophilic Balance (*n/m*)

The ethylene part of the monomer does make the polymer less soluble in water, but its van der Waals-only interactions with water should facilitate an LCST reduction without significant influence on the overall phase diagram. If this is the case, the phase transition should occur when[5]

$$\left(\frac{\partial^2 S^{ex}}{\partial \phi_{pol}^2}\right)_{T,p} - \left(\frac{\partial^2 H^{ex}}{\partial \phi_{pol}^2}\right)_{T,p} = \frac{RT}{\phi_{pol} \cdot \phi_{water}} \quad (3)$$

where S^{ex} and H^{ex} are the excess entropy and enthalpy, respectively; and ϕ_{pol} and ϕ_{water} are the mole fractions of polymer and water, respectively. The phase separation occurs at the temperature where the enthalpy of hydrophobic interactions is balanced by the enthalpy of hydrogen bonding;[5] beyond that temperature the hydrogen bonds break, and the solution demixes. In a first approximation, this enthalpy balance can be expressed by the ratio of hydrophobic/hydrophilic (H bonding) interactions in the polymer or (in our case) by the balance of hydrophobic/H-bonding interactions within the monomer (Ω)

$$\frac{\text{hydrophobic interaction}}{\text{hydrophilic interaction}}$$

$$\propto \frac{(\# \text{ ethylene}) \, \varepsilon}{(\# \text{ EO}) \, \Delta H_{H\,bond}^{EO} + (\# \text{ ester}) \, \Delta H_{H\,bond}^{ester}} \equiv \Omega \quad (4)$$

where ε is the hydrophobic interaction enthalpy of an ethylene group, and $\Delta H_{H\text{-}bond}^{EO/ester}$ is the hydrogen-bonding enthalpies for an EO and ester group. As defined in eq 4, Ω can be used to quantify the excess enthalpy of solute/solvent interactions per monomer. The phase-
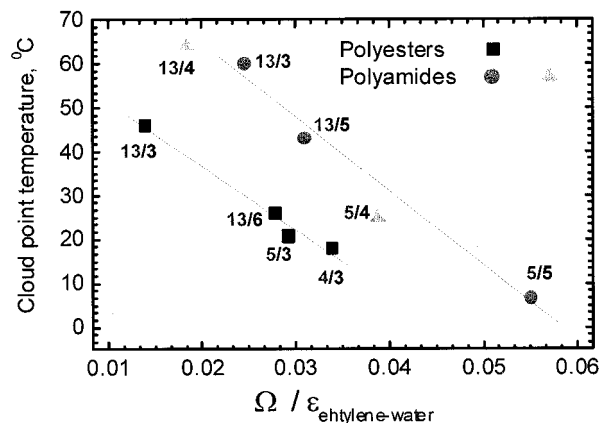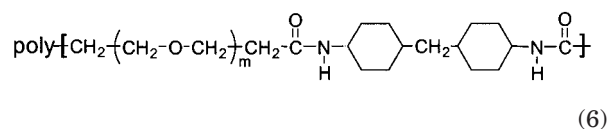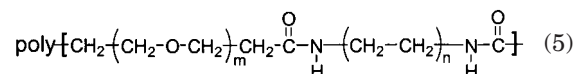

Figure 2. Experimental cloud point temperatures as a function of the monomeric hydrophobic/hydrophilic balance. Several monomer stoichiometries (m/n) are shown for monomers composed of *m*-ethylenoxide and *n*-ethylene parts connected by ester and amide groups.

transition temperature of high-molecular-weight polymers made up of such monomers should also follow the same dependence[5] on the ratio between the enthalpy of hydrophobic EE groups and the enthalpy of hydrogen-bonding (EO and ester) groups in the monomer (Ω).

In Figure 2 we summarize all the phase-separation (CP) temperatures as a function of Ω/ε measured for all monomer compositions at 1 wt % polymer solution. For the estimation of Ω the number of EO and EE units are specified by the monomer selection, and the H-bonding enthalpies are well quantified in the literature[15] (the value of the hydrophobic interaction energy ε of the ethylene groups is not known as precisely, but because it is common for all polymers it can be scaled out in Ω/ε. From Figure 2 it is clear that the CP temperature depends linearly on the hydrophobic/hydrophilic balance, as predicted theoretically, and by tuning the stoichiometry of the monomer we could span a temperature range from 15 to 50 °C for the polyesters in eqs 1 and 2. In addition, because this should be a general behavior, we further expanded this series of ester polymers to the comparable series of amides ($m = 13$ or 5, and $n = 3$ or 5) in Structures 1 and 2 and to linear polyamides with a cycloaliphatic hydrophobic group:

$$\text{poly}\left[CH_2\left(CH_2\text{-}O\text{-}CH_2\right)_m CH_2\text{-}\underset{\underset{}{\overset{\overset{O}{\parallel}}{C}}}{}\text{-}\underset{\underset{H}{|}}{N}\text{-}\left(CH_2\text{-}CH_2\right)_n \underset{\underset{H}{|}}{N}\text{-}\overset{\overset{O}{\parallel}}{C}\right] \quad (5)$$

$$\text{poly}\left[CH_2\left(CH_2\text{-}O\text{-}CH_2\right)_m CH_2\text{-}\underset{\underset{H}{|}}{\overset{\overset{O}{\parallel}}{C}\text{-}N}\text{-}\bigcirc\text{-}CH_2\text{-}\bigcirc\text{-}\underset{\underset{H}{|}}{N}\text{-}\overset{\overset{O}{\parallel}}{C}\right]$$

$$(6)$$

The CP temperatures for five of the preceding amides are also depicted in Figure 2 (with the obvious correction in Ω/ε for the enthalpy of an amide H bond instead of an ester). As expected, the polyamide CPs appear at

higher temperatures in comparison with the respective polyesters (because the amide groups can hydrogen bond to water more strongly than the esters). Moreover, the CP temperature dependence on Ω/ε for the polyamides in Structure 1 is parallel to the polyester line (because the phase separation is controlled by the EO/ethylene parts of the monomer, which remain the same). The polyamides of Structure 2 also exhibit a similar Ω/ε dependence; however, addition of their CP temperatures to the Figure 2 plot necessitates the evaluation of a "relative hydrophobicity" of the methyl-dicyclohexane group as compared to the ethylene group (because ε corresponds to the hydrophobic interaction of an ethylene). A relative value of four places the polyamides (Structure 2) in the same line as the polyamides (Structure 1), as estimated and discussed elsewhere.[16]

With the combined polyester/polyamide series of alternating copolymers, it is possible to tune the temperature response of these polymers in the range of 7–70 °C—almost the whole range of temperatures relevant to water at ambient pressure—by simply tailoring the hydrophobic/hydrophilic balance in the monomer. Given the control of the phase separation by the monomer stoichiometry, we believe that the synthesized temperature-sensitive polymers can be a class of materials with much promise for applications in smart/responsive systems, especially in biomedical and/or microfluidic applications.

CONCLUSIONS

A series of linear polymers with a systematically varied hydrophobic/hydrophilic balance in their monomer was synthesized, and their water-solution behavior was explored. Simple scaling arguments have shown that these temperature-responsive polymers obey a linear dependence of the transition temperature on the monomeric hydrophobic/hydrophilic balance. By tailoring the monomer stoichiometry (using short EO and ethylene units connected by ester or amide groups), we were able to achieve transition temperatures from 7 to 70 °C in water at ambient pressures.

EXPERIMENTAL

All reagents were purchased from Sigma–Aldrich in purum grade. Spectroscopic grade THF was purchased from VWR. The water-soluble polymers were characterized by aqueous gel permeation chromatography (GPC), and their characteristics are given in the Table 1. Aqueous GPC measurements were carried out on a Polymer Laboratories GPC, bearing PL Aquagel-OH columns, and calibrated by PEO standards. CP mea-

Table 1. Molecular Weight Characterization of the (1) and (2) Polyesters by Aqueous GPC

Polyester (m/n)	M_{w} (g/mol)	$M_{\mathrm{w}}/M_{\mathrm{n}}$
13/3	377,860	3.04
13/6	575,050	1.33
5/3	247,080	2.06
4/3	300,510	1.83

surements were carried out in a water heat bath, wherein a 2-mL sample vial holding the polymer aqueous solutions was immersed. The temperature was varied at a heating/cooling rate of 0.2 °C/min, and the solution temperature was measured inside the sample vial by a thermocouple. CP was determined by monitoring the transmitted light signal of a red (650 nm) semiconductor laser (2 mW) through a Metrological photodetector with a digital indicator (accuracy of 1 μW).

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