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ARTICLE

A New Comonomer Design for Enhancing pH-Triggered LCST Shift of Thermosensitive Polymers

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A Thermosensitive polymers exhibiting a lower critical solution temperature (LCST) can be made responsive to pH change by introducing acid or base comonomer units, and the LCST can be switched between higher and lower temperatures as a result of the polarity change of the comonomer units upon their pH-induced protonation or deprotonation. In the present study, we describe a new comonomer design that aims at increasing the magnitude of the pH-triggered LCST shift. Random copolymers of N-isopropylacrylamide and 4-((2-carboxyallyl)oxy)benzoic acid, denoted as P(NIPAM-*co*-CBA), were synthesized, in which each CBA comonomer unit bears an acrylic acid and a benzoic acid group of similar pKa. With respect to comonomers containing a single acid group, this particular comonomer structure makes it more hydrophobic in the protonated state (pH<pKa) due to the phenyl group and more hydrophilic in the deprotonated state (pH>pKa) due to the doubled charge, which results in larger pH-triggered LCST shift based on the comonomer effect. The demonstrated comonomer design principle, which is general and can also be applied to base comonomers, represents a useful strategy for enhancing the efficiency and sensitivity of the pH-responsiveness of LCST polymers.

Introduction

PH-sensitive polymers have been the focus of a considerable amount of research and development effort. The interest is largely driven by the potential applications of this type of stimuli-responsive polymers in controlled drug delivery.[1–4] Compared to the physiological pH of about 7.4, a wide range of acidic pH values can be found in tumor tissues (pH ~ 6.8) and in the intracellular compartments of cancer cells (pH 4.5-6.5). When a pH–sensitive polymer drug carrier (e.g. micelles), stable at pH 7.4, enters an acidic environment of either tumor tissues or inside cancer cells, with appropriate pKa, the polymer can sense the pH change, and its increased protonation can lead to structural disruption of the carrier and thus allows the drug to be released on the target site. Of the many pH-sensitive polymers that have been studied over the years, a group is particularly interesting. These are thermosensitive polymers whose water solubility features a lower critical solution temperature (LCST), basically being soluble in water at temperatures below LCST (coil chain conformation) and insoluble above LCST (globule).[5–7] Poly(N-isopropylacrylamide) (PNIPAM) is a representative example with a LCST of about 32 °C. This polymer is not pH-sensitive in the homopolymer form, but can be made responsive to pH change by incorporating a number of either acid or base comonomer units into the structure. Since the water solubility of the polymer is influenced by the hydrophilic or hydrophobic nature of the comonomer units, a change in protonation degree of acid or base groups upon pH variation can result in a reversible shift of the LCST. This means that the water solubility can now be controlled by a pH change at a constant temperature. In the drug delivery application context, if the drug carrier is made of such a LCST polymer bearing acid or base comonomer units, a pH decrease can induce a drastic structural disruption, such as contraction of microgel (with acid comonomer) or dissolution of micelles (with base comonomer). Therefore, pH-triggered LCST shift is an important route towards developing pH-responsive polymers, and the comonomer used may play a key role in determining the polymer's sensitivity to pH change, the pH range where the sensitivity manifests as well as the extent of the LCST shift. Again, PNIPAM provides a telling case. For instance, with acrylic acid (pKa 5) units in PNIPAM, pH variation around 4-6 shifts reversibly the LCST over a temperature range generally above the initial LCST of PNIPAM, because acrylic acid in both the protonated neutral (COOH) and the deprotonated ionic form (COO^-) is more hydrophilic than NIPAM,[8–12] with few exceptions.[13] By contrast, with propylacrylic acid, the protonated acid form is more hydrophobic than NIPAM due to the propyl group in the comonomer structure, while the deprotonated form is more hydrophilic than NIPAM; consequently, the pH-triggered LCST shift extends from below to above 32 °C.[9,14] Similar effect was observed with pH-sensitive homopolymers containing side groups of different hydrophobicity.[15]

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Despite the advances achieved in LCST-based pH-sensitive polymers, there is still a need for more studies in order to further improve the ability to tailor or control the pH responsiveness to make the polymers better adaptable to specific uses. As a matter of fact, incorporating stimuli-reactive comonomer units into LCST polymers represents a general strategy to make polymers respond to stimuli such as pH, light or CO_2,[16–19] to name a few. A common fundamental question to address is how to reduce the amount of stimuli-reactive comonomer required to induce a significant responsiveness or, at a given comonomer content, how to increase the magnitude of the LCST shift. For a given LCST polymer, an adequate choice of the comonomer can make the difference. A more effective comonomer can give a greater swing in response to a stimulus by amplifying the shift of LCST over a wider temperature range. This can be important for controlled drug delivery applications. For instance, nanogel carrier can be prepared using a polymer whose LCST decreases upon protonation of acid comonomer units. Upon pH decrease, the LCST needs to shift from above the body temperature (37 °C) to below it in order to allow the nanogel to undergo a volume transition (contraction) that leads to the payload release. It can be expected that a larger LCST decrease should be better than a smaller one, say, between LCST down to 10 °C or 30 °C, because a deeper LCST decrease means greater dehydration of the nanogel particle and thus more straightforward release. Being motivated by these considerations, in the present study, we propose and validate a general pH-reactive comonomer design for enhancing pH-induced LCST shift. A new comonomer bearing two carboxylic acid groups, which is the first of the kind to our knowledge, was synthesized and copolymerized with PNIPAM. We show that very large pH-triggered LCST shift can be obtained as a result of increase in both hydrophobicity and hydrophilicity of the acid groups upon protonation and deprotonation, respectively.

Results and Discussion

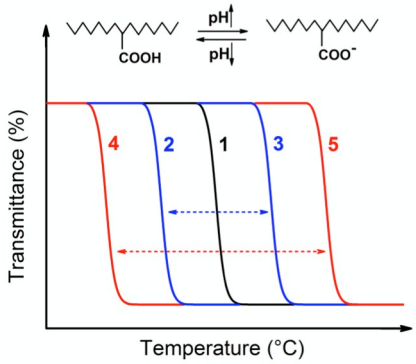
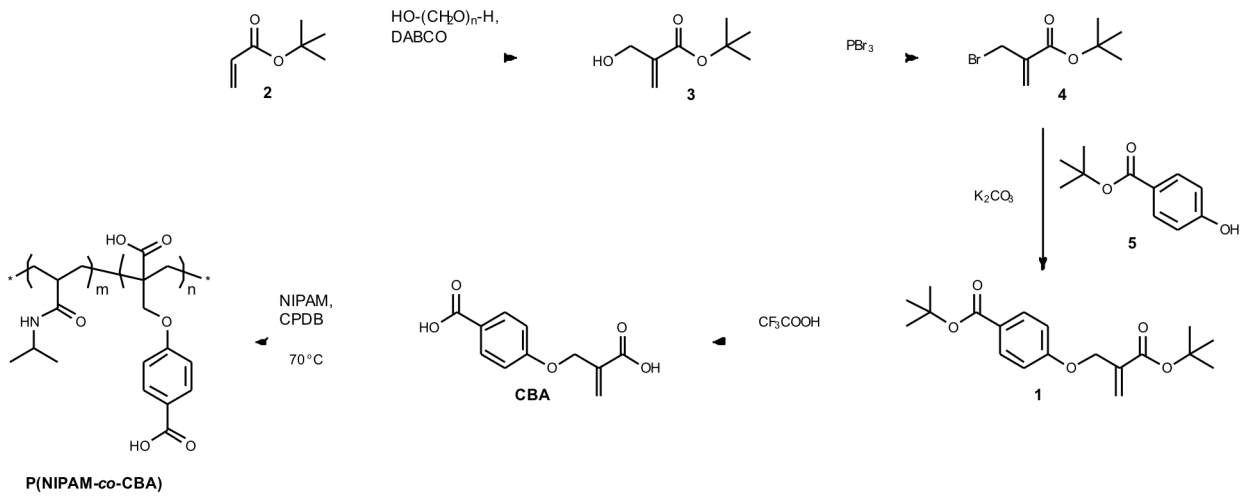


Fig. 1 Schematic Illustration of pH-induced LCST shifts upon protonation and deprotonation of acid comonomer units. Enhanced LCST shift means larger gap between the low and high LCST at the same acid comonomer content.

The Comonomer Design

The rationale of our comonomer design is schematically depicted in Figure 1. The host polymer, i.e., PNIPAM, has an initial LCST (curve 1). As mentioned above, it is known that having acid comonomer units can decrease the LCST at lower pH if the protonated form of the acid is more hydrophobic than the host (curve 2), and increase the LCST at higher pH if the deprotonated form is more hydrophilic (curve 3). Our hypothesis is that if, at a given amount of comonomer units, the protonated form of the acid can be made even more hydrophobic and the deprotonated form even more hydrophilic than the host, both the decrease (curve 4) and increase (curve 5) in LCST would be more prominent, thus further widening the gap between the LCST upon pH change. Scheme 1 shows the chemical structure of the comonomer 4-((2-carboxyallyl)oxy)benzoic acid (CBA) designed to test the assumption. As is seen, the basic idea is to bring two acid groups of similar pKa into the comonomer structure. In the deprotonated form, the number of charges is doubled per



Scheme 1 Synthesis of the comonomer 4-((2-carboxyallyl)oxy)benzoic acid (CBA) and its copolymerization with N-isopropylacrylamide yielding P(NIPAM-*co*-CBA).

comonomer unit, which would increase the hydrophilic power; whereas in the protonated form, the presence of the phenyl group should enhance the hydrophobic character. At this point, needless to emphasize that this comonomer design principle is general; different pairings of acid groups are possible, so are the pairings of two bases. In the latter case, the shift of LCST is simply reversed upon pH change, moving to higher LCST at the protonated state and lower LCST at the deprotonated state.

The Density Functional Theory (DFT) provides the ground state properties of a system knowing its electron density. A DFT analysis (details in Supporting Information) of the new comonomer was performed to reveal the effect of having two acid units in the structure on the solvation (or hydration) propensity in both the protonated and deprotonated state. It should be emphasized that the calculation was not meant to predict the LCST; rather it was used to have some insight into the possible impact of the comonomer on shifting the host polymer's LCST upon pH change. As a simple model, the calculation was focused on the hydration energy and the number of hydrogen bonds that are formed between the comonomer and water molecules. Since the comonomer can be considered as comprising a methacrylic acid (MAA) and a benzoic acid (BA), for the sake of comparison, the same analysis was also carried out on the two corresponding reference molecules, MAA and BA, separately. The main results are summarized in Table 1. In all cases, the deprotonated acid (pH 7) forms H-bonds with higher potential energy than the protonated state (pH 4), meaning greater hydration energy with the ionized carboxylic acid. However, the difference in the hydration energy between the two states is significantly larger for CBA than for MAA or BA, which implies that the new comonomer could indeed be more hydrophobic in the protonated state and become more hydrophilic in the deprotonated state. Furthermore, in order to have a better insight on the polarity and hydrophilicity of the molecules, we also calculated the electrostatic potential (ESP) surfaces and logP that is a measurement of the difference in the Gibbs free energy of solvation in water and in n-octanol for a given compound (definition in Supporting Information). Despite the fact that values of logP stemming from DFT calculations do not agree quantitatively with the experimental data, the same tendency is observed. Roughly, logP of BA is twice that of MAA, due to the presence of aromatic cycle. LogP and ESP surfaces both reveal that the deprotonated state of CBA has much greater polarity and hydrophilicity than deprotonated MAA and BA (Table 1).[20,21] These results are in agreement with the calculated hydration energies. It should be noticed that the dependence of the

Table 1 Hydration Energies, ESP surfaces and logP values from DFT Calculation (units in kJ/mol for hydration energies and ESP surfaces).

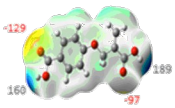
Molecules		CBA (MAA position)	CBA (BA position)	MAA	BA
Protonated state	Hydration energy	-289.6	-288.4	-287.7	-291.0
	ESP surfaces				
	logP	0.61		0.39 (0.93 exp.)[23]	0.72 (1.87 exp.)[24]
Deprotonated state	Hydration energy	-407.7	-441.1	-392.9	-382.4
	ESP surfaces				
	logP	-13.55		-7.33	-5.14
Difference in Hydration Energy between the two forms		118.1	152.7	105.2	91.4

Table 2 Characteristics of Synthesized P(NIPAM-*co*-CBA) Random Copolymers

Sample	CBA in feed (mol%)	CBA in polymer (mol%)[a]	M_n (g/mol)[b]	PDI
P1	1.0	2.1	7490	1.16
P2	2.4	4.3	7530	1.12
P3	4.8	7.6	6850	1.21
P4	7.0	10.0	6360	1.23
P5	13.0	17.3	4590	1.32

[a]Calculated by 1H NMR in d6-DMSO; [b]determined by size exclusion chromatography.

LCSTs of charged PNIPAM-based copolymers on their charge fraction was investigated previously by an analytical theory on a macroscopic thermodynamic level.[22]

pH-induced LCST Shift

As mentioned above, to experimentally test the effect of the new comonomer CBA on the pH-induced LCST shift, a series of random copolymer P(NIPAM-*co*-CBA) with various contents of CBA, were synthesized using RAFT polymerization. Table 2 summarizes the characteristics of the samples. As is seen, the copolymerization proceeds in a controlled way, yielding polymers with reasonably low polydispersity index (M_w/M_n) and general agreement between the feed and ^{1}H NMR-determined molar content of CBA units in the copolymers. The average molecular weights, as determined by SEC using PMMA standards, are relatively low for all samples. The effect of pH on the LCST was investigated by measuring the cloud points of P(NIPAM-*co*-CBA) solutions under the same conditions. Unless otherwise stated, each solution was prepared by dissolving the polymer (0.2 wt%) in cold PBS (stirring in the ice-water bath), and the solution transmittance (at 500 nm) was recorded as a function of temperature upon heating the solution at a rate of 0.5 °C/min. For a given polymer solution, the pH was adjusted by using HCl or NaOH, ranging from 4.0 to 7.0 with an interval of 0.5.

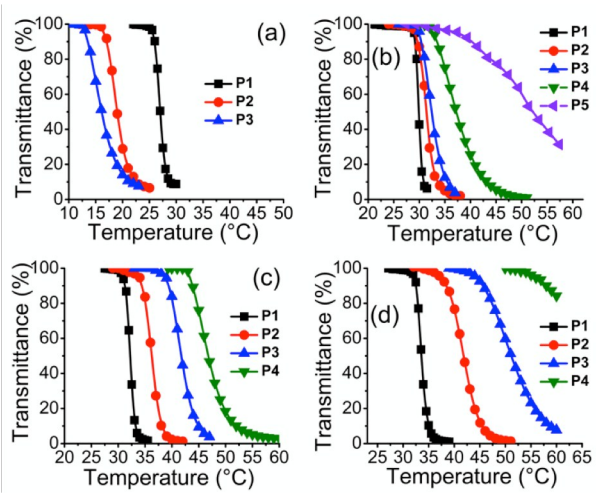


Fig. 2 Plots of transmittance vs. temperature for the solutions of different P(NIPAM-*co*-CBA) samples obtained at: a) pH 4.5, b) pH 5.0, c) pH 5.5 and d) pH 6.0.

Figure 2 shows the plots of transmittance vs. temperature for the solutions of all P(NIPAM-*co*-CBA) samples, measured at four different pH values: 4.5, 5.0, 5.5 and 6.0. In case no data are shown for a given P(NIPAM-*co*-CAB) sample, it means that at that particular pH no transmittance drop (cloud point) could be detected over the temperature range used for the measurements (10-60 °C), i.e., the polymer remains either soluble (below LCST, P5 in Figs. 2c and 2d) or insoluble (above LCST, P4 and P5 in Fig.2a). At pH 4.5 (Fig.2a), all samples display a cloud point below 30 °C, which decreases with increasing the CBA content. This result indicates that at this pH, the acid comonomers are essentially protonated (pH<pKa) and the CBA exerts a hydrophobic comonomer effect on PNIPAM, bringing down the LCST. With pH up to 5.0 (Fig.2b), the situation is drastically reversed, as more acid comonomer groups are deprotonated (pH approaching pKa). While all samples see their cloud points shifted to higher temperatures, the magnitude of increase is greater with increasing the CBA content, so that the actual cloud points are in the ascending order of the CBA content. At this point, the cloud points of P2 and P3 are only slightly above that of P1, suggesting counterbalance between the hydrophobic and hydrophilic comonomer effects. With pH further raised to 5.5 and 6.0, the cloud points of all samples continue to increase in a pace proportional to the CBA content, widening their differences in cloud point. At these two pH values, the acid groups are mainly deprotonated (pH>pKa) and CBA acts predominantly as hydrophilic comonomer whose effect raises the LCST of P(NIPAM-*co*-CBA).

Analyzing the data in Figure 2, it becomes already clear that the width of LCST shift upon protonation and deprotonation of CBA units is proportional to the content of the comonomer. To better illustrate this result, Figure 3 shows the plots of

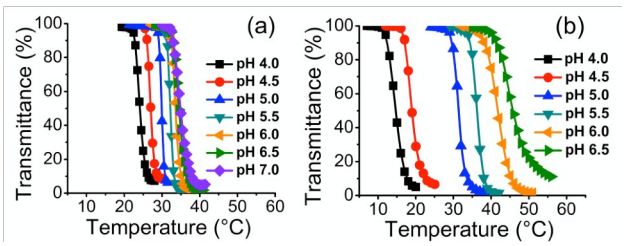


Fig. 3 Plots of transmittance vs. temperature obtained at different pH values for the solutions of two P(NIPAM-co-CBA) samples: a) P1 and b) P2.

Table 3 Cloud Points (°C) of Various Copolymer Solutions

pH	Cloud Points (°C)				
	P1	**P2**	**P3**	**P4**	**P5**
4.0	24.1	14.6	a	a	a
4.5	26.9	18.9	15.8	a	a
5.0	29.9	31.4	32.3	36.9	51.3
5.5	32.2	36.2	41.7	46.6	b
6.0	33.6	41.7	50.8	b	b
6.5	34.5	45.3	b	b	b
7.0	34.8	b	b	b	b

a < 10 °C; b > 60 °C

transmittance vs. temperature for two samples, P1 and P2, over the pH range 4-7 at an interval of 0.5. Data of the cloud points for all samples over this pH range are collected in Table 3. With P1, the sample having the lowest CBA content of 2.1 mol%, the cloud point difference between pH 4 and 7 is about 10 °C (Fig3.a). By contrast, P2 has a higher CBA content of 4.3 mol%, the variation of cloud point reaches about 32 °C (Fig.3b). The effect of the comonomer content on the LCST shift is understandable. A higher content of CBA means greater switch between "hydrophobic" and "hydrophilic" comonomer effect on LCST in response to the switch between the neutral (protonated) and ionic (deprotonated) forms of the acid comonomer. Obviously, the efficiency of acid comonomers for shifting LCST over pH-induced protonation and deprotonation should be compared at the same comonomer content. Such a comparison with comonomers investigated in the literature is difficult to make due to often different comonomer contents as well as different experimental conditions used to measure the cloud point (polymer concentration, heating rate, etc.). Nevertheless, the 32 °C cloud point shift obtained at CBA content of 4.3 mol% and polymer concentration of 2 mg/mL is among the largest variation,[8–14] indicating the high efficiency of CBA for the targeted comonomer effect. For instance, Stayton et al. investigated pH-induced LCST (cloud point) shift of random copolymers of NIPAM and propylacrylic acid, P(NIPAM-*co*-PAA) under basically the same conditions as those used in the present study.[14] At the comonomer content PAA of about 2.6 mol%, the largest cloud point shift is about 18 °C over pH rage 5.0-7.0. With the PAA content at 9 mol%, the shift is about 17 °C over pH 5.0-6.5. For comparison, with our P(NIPAM-*co*-CBA), the sample P4, having about 10 mol% CBA, displays cloud point shift of larger than 50 °C over pH range 4.5-6.0 (Table 3).

Comparing different carboxylic acid comonomers, in addition to their different pH-induced LCST shift efficiencies, they may also impart different pH sensitivities to the LCST polymers. In other words, the question of interest is how small is the pH

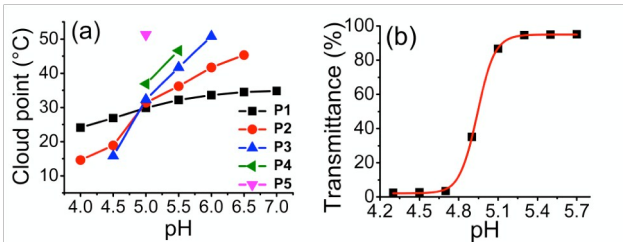


Fig. 4 a) Plots of cloud point vs. pH for the solutions of different (NIPAM-*co*-CBA) samples. b) Transmittance change as a function of pH for the solution of P5 measured at 37 °C.

variation required for turning the polymer from soluble to insoluble state in water or vice versa. A comonomer like CBA exhibiting greater switch between hydrophobic and hydrophilic states associated with the protonation-deprotonation transition would give rise to higher sensibility. To better illustrate this feature, Figure 4a plots the cloud points (LCST) vs. pH for the solutions of all P(NIPAM-*co*-CBA) samples (graphical presentation of data in Table 3). The apparent slope, d*LCST*/d*pH*, around pH 4.5-5.0 increases with the content of CBA in the copolymer (as stated above, the cloud point at pH 4.5 for samples P4 and P5 could not be measured for being below 10 °C). This result implies that with increasing the content of CBA, the required pH variation for switching the polymer water solubility became increasingly smaller. As an example, Figure 4b shows the change in transmittance of the solution of P5 (0.2 mg/mL) at 37 °C as a function of pH at an interval of 0.2. The copolymer is soluble at pH 5.1 but becomes insoluble at pH 4.8, meaning that a pH variation of about 0.3 unit is enough to switch the water solubility. In the context of possible drug delivery applications, if nanogel is made with this polymer, it should remain stable even at pH5.1, and the volume transition (collapse) of the nanogel would take place only inside intracellular compartments with a pH below 5.[3] In principle, this feature can be exploited for payload release specifically within a narrow range of acidic pHs.

Finally, it should be mentioned that the present study focuses on only pH-induced LCST shift. Reversely, since the polymer undergoes a phase transition between hydrated and dehydrated state, the dielectric constant of the local environment surrounding the acid groups may change, resulting in change in the actual pKa. In other words, the pH responsiveness of the polymer may be affected by the changing thermosensitivity.

Experimental

Materials

Unless otherwise stated, all chemicals were purchased from Aldrich and used as received. The monomer, N-isopropylacrylamide (NIPAM), was recrystallized from hexane

prior to use; whereas the designed comonomer, 4-((2-carboxyallyl)oxy)benzoic acid (CBA), was synthesized according to Scheme 1 (details below). The reversible addition fragmentation chain transfer (RAFT) agent, 2-(2-cyanopropyl) dithiobenzoate (CPDB), was synthesized using a reported method.[23] The initiator, 2,2'-azobis(2-methylpropionitrile) (AIBN), was purified by recrystallizations from ethanol.

Synthesis of the Comonomer CBA

The fully *t*-butyl protected monomer **1** was prepared following a three-step sequence amenable to the preparation of large quantities if necessary (Scheme 1). The allylic alcohol **3** was synthesized following a Baylis-Hillman procedure from *t*-butyl acrylate **2** and in 75% yield.[24,25] The alcohol **3** was then transformed into its corresponding allylic bromide **4** by means of PBr3 (75%).[25] **4** was used as an alkylating agent for the phenolate ion of commercially available or easily prepared phenol **5**.[26] Thus, treatment of **5** with potassium carbonate followed by addition of **4** in acetone under reflux yielded the methacrylate derivative **1** (yield: 86%), which was readily converted to the comonomer CBA upon hydrolysis of the two ester groups. More details are given in Supporting Information.

Synthesis of the Random Copolymer P(NIPAM-*co*-CBA)

RAFT polymerization was utilized to prepare the random copolymer P(NIPAM-*co*-CBA) having different CBA contents. Using the copolymer containing about 2.1 mol% CBA as example, the synthetic details are as follows. A 10 mL round-bottom flask was charged with NIPAM (0.5 g, 4.4 mmol), CBA (9.8 mg, 0.044 mmol), AIBN (1.5 mg), CPDB (9.8 mg, 0.044 mmol) and dioxane (1 mL). The mixture was degassed by three times freeze-thaw cycles; then it was placed into an oil bath preheated to 80 ^{o}C. The polymerization was allowed to proceed for 2.5 h with the mixture under stirring. After polymerization, the mixture was cooled to room temperature and precipitated into ethyl ether. The purification was repeated three times. The final product was dried to constant weight under vacuum.

Characterizations

^{1}H NMR spectra were recorded on a Bruker AC 400, using DMSO-d_6 as the solvent. The spectra of the monomer CBA and the random copolymer P(NIPAM-*co*-CBA) are shown in Figures S1 and S2, respectively. The compositions of the various copolymer samples were determined from the ^{1}H NMR spectra by comparing the integral of peak *h* (3.8 ppm, from the tertiary carbons of NIPAM side groups) with the integral of either peak *e* (7.8 ppm, from the aromatic protons of CBA) or peak *c* (4.0 ppm, assigned to ethyl groups of CBA); similar results were obtained from the different resonance signals. The increased intensity of peaks *e* and *c* with respect to peak *h* reflects the increased percentage of CBA in the samples P1-P5. Size exclusion chromatography (SEC) was performed on Tosoh EcoSEC GPC system, equipped with three TSK-GEL Super AWM-H columns (6x150mm). The measurements were conducted at 50 ^{o}C using dimethylformamide (DMF) containing 1 g/L of LiBr as the eluent (flow rate: 0.5 mL/min) and poly(methyl methacrylate) (PMMA) as standards. The cloud points of P(NIPAM-*co*-CBA) solutions at a polymer concentration of 0.2 wt% were measured using an Agilent Cary Series UV-Vis-NIR spectrophotometer by monitoring the solution transmittance (measured at wavelength of 500 nm) as a function of temperature upon heating at a rate of 0.5°C/min. The transmittance curves were normalized to 100% for clarity. The cloud point of a given solution was taken as the temperature corresponding to the inflection point of the changing transmittance that was graphically determined from the maximum value of the first derivative of the heating curve. For the cloud point measurements of the solutions at different pH values, P(NIPAM-*co*-CBA) samples were first dissolved in 0.15 mol L^{-1} phosphate-buffered saline (PBS) (pH 7.4, under stirring in the ice-water bath), with the solution pH then adjusted to a desired value by adding NaOH (0.1N, 1N) or HCl (0.1N, 1N). The pH was measured using a Fisher Scientific Accumet AB 15 pH Meter with 13-620-223A Accumet glass pH electrode.

Conclusions

We have reported the design and synthesis of a polymerizable compound bearing two carboxylic acid groups of similar pKa in the structure, and showed that using it as comonomer in PNIPAM could enlarge the reversible shift of LCST upon pH change. Both the cloud point measurement and DFT calculations suggest that the wide swing of LCST is due to the comonomer structure that can increase both the hydrophobicity and hydrophilicity with protonated and deprotonated acid groups, respectively. Having two (or even more) acid or base groups in the comonomer structure may present a general approach to increasing the sensitivity and efficiency of pH-induced water solubility switch for thermosensitive polymers like PNIPAM. Obtaining the same shift of LCST with a lower content of the comonomer may be regarded as an amplification mechanism, and it is of interest for different reasons. First, it allows fine-tuning of the phase (or volume) transition temperature of the polymer in response to pH change. With respect to a constant solution (or body) temperature, a deeper decrease below or greater increase above for the LCST means different dehydration or hydration state of the polymer, respectively, which would result in different degrees of disruption for nanocarriers (e.g., nanogel or micelle) built with the polymer. Secondly, it may give rise to great pH sensitivity of the polymer water solubility. As shown, for the P(NIPAM-*co*-CBA) sample containing 17.3 mol% CBA, a pH change of about 0.3 unit is sufficient for switching the polymer between soluble and insoluble state. Thirdly, the ability of reducing the amount of comonomer while retaining the pH-induced LCST shift may be beneficial depending on the sought applications. This would be desirable in case the comonomer causes toxicity. Moreover, by limiting the structural and chemical perturbation of the thermosensitive polymer, it would be possible to diminish the comonomer's

effect of slowing down the thermal phase transition, which is noticeable with P5 (Fig.2b).

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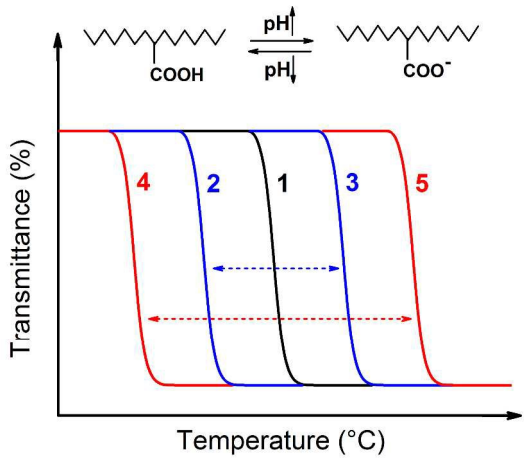
Graphic for Table of content



A rational comonomer design leads to large pH-induced LCST shift.