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New stimuli-responsive copolymers of *N*-acryloyl-*N′*-alkyl piperazine and methyl methacrylate and their hydrogels

L.H. Gan*, G. Roshan Deen, X.J. Loh, Y.Y. Gan

Division of Chemistry, School of Science, Nanyang Technological University, 469, Bukit Timah Road, Singapore, Singapore 259756

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Abstract

Water-soluble copolymers of *N*-acryloyl-*N′*-alkylpiperazine (alkyl: methyl, ethyl) with methyl methacrylate were synthesized and the lower critical solution temperatures (LCSTs) of the copolymers which depend on the compositions and pH of the aqueous solutions are described. The effects of cationic surfactants and simple inorganic salts on the LCSTs are also reported. The influences of pH and temperature on the swelling of the ionizable and thermosensitive hydrogels are studied. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Water-soluble polymers; Piperazine; Lower critical solution temperature

1. Introduction

Water-soluble polymers which show a phase transition in response to external stimuli such as temperature [1,2], pH [3,4], electrolytes [5,6], illumination [7,8], electric field [9], magnetic field [10] have attracted much interest because of their versatile applications such as in the fields of purification of chemicals or as bio-active agents [9], in the development of artificial muscles [9], and in controlled drug delivery systems [11,12]. These polymers are soluble in water at low temperatures but separate from solution when the temperature is raised above the lower critical solution temperatures (LCSTs). Poly(*N*-isopropyl acrylamide) (PNIPAM) is one of the most widely studied thermo-responsive polymer, which undergoes phase separation at around 32°C. Currently, polymer systems that respond to more than one stimulus such as pH and temperature are extensively researched [13–16].

In this paper we report the synthesis of a series of new piperazine-containing copolymers. These copolymers are water-soluble and they exhibit interesting LCST phenomena. The coil-to-globule phase transition of the copolymer is sensitive to pH, temperature, salts and surfactants. The responsive behaviour of the corresponding hydrogels is described.

2. Experimental

2.1. Synthesis of monomers

The synthesis of *N*-acryloyl-*N′*-methyl piperazine (AcrNMP) has been described previously [17]. *N*-Acryloyl-*N′*-ethyl piperazine (AcrNEP) was synthesized using the same procedure and was obtained as a pale yellow liquid with a yield of 60%. ^{1}H NMR (400 MHz in ppm): 0.98–1.04 (C**H**$_3$, t, 3H), 2.36–2.40 (–C**H**$_2$, q, 2H), 3.5 (–N(C**H**$_2$)$_2$–, b, 4H), 3.65 ((C**H**$_2$)$_2$–N–CO–, b, 4H), 6.45–6.52 (yC**H**, q, 1H, $J_{cis} = 16.63$ Hz, $J_{trans} = 10.62$ Hz), 6.15–6.25 (C**H**$_2$y, q, 1H, $J_{cis} = 16.69$ Hz), 5.61–5.63 (C**H**$_2$y, q, 1H, $J_{trans} = 10.63$ Hz). ^{13}C NMR (ppm): 127.6 (*C*H$_2$y), 128.9 (y*C*H), 165.3 (–*C*yO), 41.9 (–CO–N(*C*H$_2$)$_2$r), 45.7 (s(*C*H$_2$)$_2$–N–), 52.2 (sN–*C*H$_2$), 11.8 (–*C*H$_3$).

2.2. Synthesis of copolymers

Copolymers of AcrNMP and AcrNEP with MMA (Scheme 1) were synthesized in dioxane using different monomer feed ratios and AIBN as initiator. The monomer feed ratios are given in Table 1.

2.3. Synthesis of hydrogels

Hydrogels of AcrNMP/MMA and AcrNEP/MMA with various percentage of EGDMA as crosslinkers were prepared by photo-initiation polymerization in bulk (Table 1). The solid transparent pale yellow polymer was immersed in diethyl ether for 3 weeks to remove any unreacted

* Corresponding author. Tel.: +65-4605337; fax: +65-4698928.
E-mail address: lhgan@nie.edu.sg (L.H. Gan).

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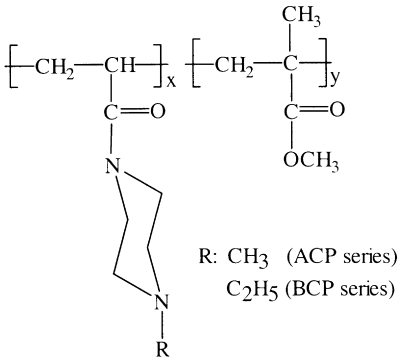

Scheme 1.

components. The gels were then swelled in water and dried to constant weight.

3. Characterization

3.1. Molecular weight determinations

The molecular weights of the polymers were determined by laser light scattering technique in THF solutions. The Brookhaven BI-200SM gonimeter system equipped with a 532 channels BI9000AT digital multiple correlator was used. The light source was a power adjustable vertically polarized argon ion laser with the wavelength of 488 nm. The measured temperature was controlled at 25.0 ^ 0.1°C using a Science/Electronic water bath. Thus the following $\bar{M}_w$ (g mol^{-1}) were obtained: pAcrNMP (1.5×10^5); pAcrNEP (0.78×10^5); ACP1 (2.27×10^5); ACP4 (4.41×10^5); BCP1 (0.89×10^5) and BCP4 (0.87×10^5).

Table 1
Feed composition in the synthesis of copolymers and gels

Copolymers/gels	Mole fraction of monomer in the feed		Mole fraction of monomer in the copolymer	
	AcrNMP	MMA	AcrNMP	MMA
ACP1	0.5452	0.4548	0.4263	0.5737
ACP2	0.6079	0.3921	0.4976	0.5024
ACP3	0.6754	0.3246	0.5514	0.4686
ACP4	0.7583	0.2417	0.6340	0.3660
AG1(2)[a]	0.5451	0.4549	–	–
AG2(2)[a]	0.6572	0.3428	–	–
AG3(2)[a]	0.7529	0.2472	–	–
	AcrNEP	MMA	AcrNEP	MMA
BCP1	0.5200	0.4799	0.4412	0.5588
BCP2	0.6236	0.3764	0.5502	0.4498
BCP3	0.6982	0.3018	0.6017	0.3983
BCP4	0.7618	0.2382	0.6626	0.3374
BG1(2)[a]	0.5329	0.4671	–	–
BG2(2)[a]	0.6612	0.3388	–	–
BG3(2)[a]	0.7552	0.2448	–	–

[a] ACP and BCP series are copolymers, and AG and BG series are gels; values in parentheses are the percentage of crosslinker used.

3.2. LCST measurements

The LCST values were determined by the spectrophotometric method using a Hewlett-Packard UV/Vis spectrometer HP 8452 A with a digital temperature controller. Polymer solutions of 1 wt% were used in all runs.

3.3. Equilibrium swelling experiments

The hydrogel sample was cut into small disc (ca. 0.1 g) and immersed in buffer solutions (sodium acetate–acetic acid for pH 2.6–5.6; sodium hydrogen phosphate–disodium hydrogen phosphate for pH 6.3–9.1) in glass vials at 25°C for 1 week. The sample was then removed from the respective vials, tapped with a Kim-wipe towel to remove excess surface water and weighed. The dry weights were measured after desiccating the gels for 3 days under vacuum at 40°C until constant dry weights were maintained. The swelling ratio (SW) was calculated from the following formula:

$$SW = (W_t - W_d)/W_d$$

where W_t and W_d are, respectively, the wet and dry weights of the sample.

The equilibrium water content (EWC) was calculated from the following expression:

$$EWC(\%) = [(W_t - W_d)/W_t]/100.$$

For the thermal-responsive study, the hydrogels were immersed and equilibrated in de-ionized water at 25°C for 2 days. The vials were then immersed in a constant temperature water bath at specific temperatures.

4. Results and discussion

4.1. Copolymer composition and solubility

The composition of the copolymers was determined from the nitrogen content obtained by elemental analysis. The reactivity ratio of the AcrNMP/MMA system has previously been studied [18]. The compositions of the copolymers and gels prepared in this study are shown in Table 1. Copolymers containing AcrNMP above 42 mol% and AcrNEP above 44 mol% were all soluble in water. Homopolymers pAcrNMP and pAcrNEP were very soluble in water and no LCST behaviour was observed. It should be noted that the piperazine-based monomers possess an amide and a tertiary amine group. There are relatively few studies on the thermal-responsive poly(amido-amine). One of the better-studied systems is poly(*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA) [14,19].

4.2. Effect of pH

The effect of pH on the phase transition for ACP1 is shown in Fig. 1. The LCST values, obtained from the maxima of first derivatives of the percentage

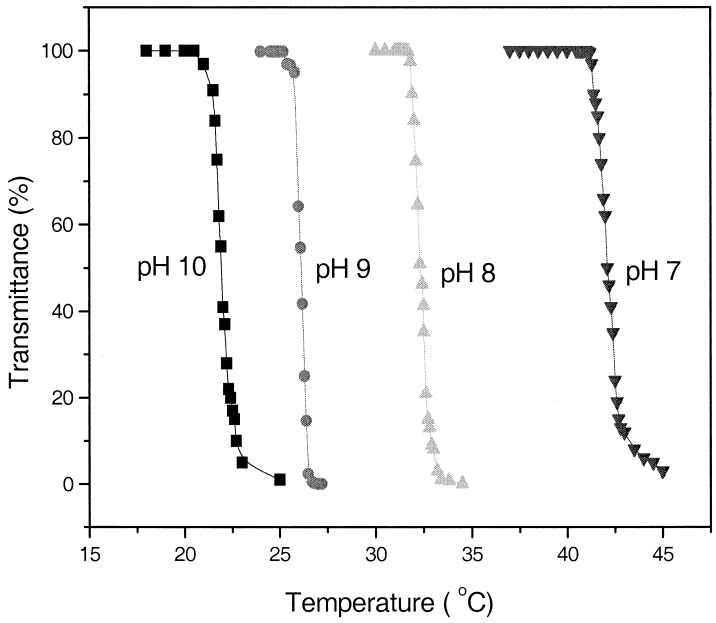

Fig. 1. Change of percentage transmittance with temperature for the copolymer ACP1 at $\lambda = 459$ nm.

transmittance–temperature curves are presented in Table 2. The results clearly show that the copolymers are highly sensitive to pH. A mere change of 0.8 pH scale from pH 6.3 to 7.1 has resulted in a 33°C difference in LCST for ACP1. The effect of pH was obviously due to the various degrees of protonation on the basic amino group in the piperazine molecules. Protonation gave rise to electrostatic repulsion [20] among the piperazinium side groups, thereby increasing the phase transition temperature.

4.3. Effect of monomer content

At a fixed pH, the LCST increased with increasing piperazine-based monomer content, in line with the more hydrophilic nature of the AcrNMP and AcrNEP monomer units. At the same composition, the ethyl substituted AcrNEP copolymer had lower LCST than the corresponding AcrNMP copolymer. For example, comparing copolymers ACP3 with BCP2, both of which contained the same piperazine monomer at ~55 mol%, the LCST was 72°C for ACP3 against 39°C for BCP2 at pH 7.1. The effect of monomer content was found to be greater for the more hydrophilic AcrNMP. A difference of ~46°C was observed for AcrNMP content in the copolymers varying from 42.6 to 63.4 mol%. The differences were almost invariant to pH. A smaller difference of ~25°C at almost the same composition range of 44.1–66.3 mol% was recorded for AcrNEP copolymers. In addition to the critical balance between the hydrophobic–hydrophilic characters in the polymer chain which influences the LCST, the pK_b values of the basic monomer units must also be a factor. The charge density will affect the LCST for polymers containing a chargeable monomer unit. Feil et al. [22] in their study of a terpolymer, p(NiPAAm-*co*-BMA-*co*-DEAEMA) reported that for all the polymer systems studied, roughly the same amount of monomer units of approximately 4 mol%, were charged at each LCST.

Table 2
LCST values of 1 wt% copolymer solutions at various pH

Copolymer	LCST (°C)/pH				
	6.3	7.1	8.0	9.0	10.1
ACP1	75.12	42.18	32.20	26.08	22.00
ACP2	–	56.11	41.90	31.02	25.14
ACP3	–	72.01	60.00	49.98	40.05
ACP4	–	88.11	75.06	69.10	61.99
BCP1	69.80	34.71	23.14	20.80	19.60
BCP2	74.51	39.00	26.60	22.53	20.90
BCP3	86.10	48.30	39.95	32.87	25.60
BCP4	92.30	61.11	51.24	43.92	35.62

4.4. Effect of simple salts and cationic surfactants

The effects of simple inorganic salts, NaCl, NaBr, KI and KCl on the LCST of ACP1 and BCP1 are presented in Table 3. The salts of bromide and chloride were found to exert a salting-out effect whereas iodide produced a salting-in effect.

The effects of cationic surfactants, dodecyl trimethylammonium bromide (DTAB), tetradecyl ammonium bromide (TTAB), hexadecyl trimethylammonium bromide (HTAB), and hexadecyl trimethylammonium chloride (HTAC) on the LCST of ACP1 are shown in Table 4. Long chain surfactant molecules are known to form polymer–surfactant complexes through the hydrophobic interactions between the alkyl tail and the polymer backbone. In very dilute

Table 3
Effect of simple salts on LCST values of 1 wt% copolymer solutions

	LCST (°C)					
[Salt] (M)	NaCl		NaBr		KI	
Copolymer	ACP1	BCP1	ACP1	BCP1	ACP1	BCP1
0	42.18	34.71	42.18	34.71	42.18	34.71
0.005	37.21	25.20	26.61	20.51	29.60	22.52
0.01	37.00	23.31	29.12	21.50	30.41	26.03
0.05	36.52	22.10	29.43	21.42	34.60	27.94
0.1	36.01	21.52	30.74	22.00	37.35	28.91
0.5	33.00	21.01	32.50	24.52	48.40	37.31
1.0	27.10	16.00	33.62	25.73	56.33	42.66

Table 4
LCST values of 1 wt% ACP1 solutions with various concentrations of cationic surfactants

Concentration ($\times 10^4$) (M)	LCST (°C)			
	DTAB	TTAB	HTAB	HTAC
0	42.18	42.18	42.18	42.18
2.5	27.50	37.23	46.15	39.10
10.0	29.41	38.14	51.94	55.00
30.0	41.11	58.62	84.22	67.67
50.0	42.32	–	–	–

solutions, the cationic surfactants behaved like simple electrolytes and exerted a salting-out effect on the polymers, hence the LCST values decreased initially. Above the critical aggregation concentration (cac), the polymer–surfactant complexes were formed. The charged head groups of the surfactant molecules binding to the polymers gave rise to the electrostatic repulsion and this stabilized the polymer chains, thus the LCST increased. The minima for the three surfactants in the LCST–concentration relationships signified the onset of the surfactant–polymer binding, and these occurred at concentrations lower than the cmc of the respective surfactants, i.e. DTAB (1.6×10^{-2} mol dm^{-3}); TTAB (3×10^{-3} mol dm^{-3}); HTAC (1×10^{-3} mol dm^{-3}) [21]. No minimum was observed for the surfactant HTAB as the cac was expected to be very low because of the low cmc of HTAB at 8×0^{-4} mol dm^{-3}.

Table 5
The EWC as a function of pH and temperature

Gels	EWC (%)/25°C		EWC (%)/pH 7		
	pH 2.6	pH 7	10°C	25°C	50°C
AG1 (2)	85	64	68	64	50
AG2 (2)	88	70	72	70	55
AG3 (2)	92	72	78	72	58
BG1 (2)	87	55	59	55	36
BG2 (2)	89	60	62	59	39
BG3 (2)	95	66	67	63	42

4.5. Effect of pH and temperature on the swelling of hydrogels

The gels had low swelling at high pH and high swelling at low pH as expected. At low pH, the tertiary amino groups in the piperazine ring were mostly protonated. Electrostatic repulsion between the charged groups and the osmostic pressure generated by the counter ions are considered to be the two main factors for the enhanced expansion of polylectrolyte gels [22]. The swellings were highest for the two gels made from the homopolymers pAcrNMP and pAcrNEP with 2% EDGMA crosslinker. In comparison, the swelling of pAcrNEP gel was slightly higher than the pAcrNMP gel due to the more bulky ethyl substituent. The equilibrium

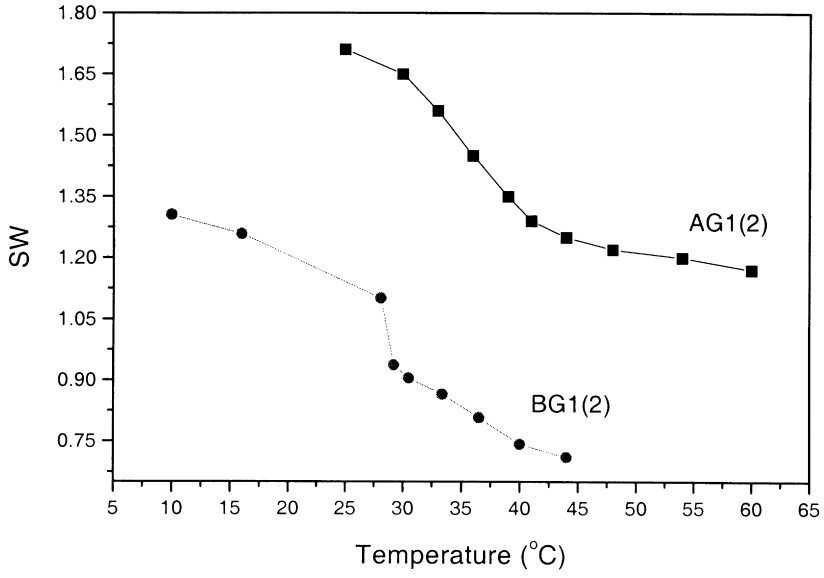

Fig. 2. Effect of temperature on the swelling of gels AG1 and BG1.

water contents for the two series of gels at pH 2.6 and pH 7 are presented in Table 5.

The effects of temperature on the swelling of gels, exemplified by samples AG1 and BG1 are shown in Fig. 2. The gels exhibited a reversible thermoshrinking behaviour. The inflection points for the transitions from the low to high swelling roughly coincided with the LCST values of the respective non-crosslinked copolymers, i.e. ACP1 and BCP1. The AG1 gel showed a continuous volume change, while the BG1 gel exhibited a slight discontinuous volume change around the region of the LCST, indicating different alkyl substituents in the piperazine ring could influence the transition behaviour. The EWC of all the copolymer gels as a function of temperature are presented in Table 5.

5. Conclusions

This study presented two series of new stimuli-responsive polymeric systems containing piperazine-based monomers. The new copolymers displayed the LCST phenomena. The LCSTs could be controlled by varying the composition of the copolymers and it was highly sensitive to pH, salts and cationic surfactants. The corresponding hydrogels also showed thermal and pH sensitivity. The study for the potential applications of these systems such as in controlled drug release is currently in progress.

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