Polymer 40 (1999) 6985–6990

polymer

Lower critical solution temperatures of *N*-substituted acrylamide copolymers in aqueous solutions

H.Y. Liu, X.X. Zhu*

Département de chimie, Université de Montréal, C.P. 6128, succursale Centre-ville, Montreal, Que., Canada H3C 3J7

Received 9 September 1998; received in revised form 20 November 1998; accepted 8 December 1998

Abstract

Several series of copolymers were prepared from *N*-substituted acrylamides by free radical polymerization in solution. We have selected a group of monomers with varying degree of hydrophilicity including acrylamide, *N*-ethylacrylamide, *N*,*N*-dimethylacrylamide, *N*,*N*-diethylacrylamide, and *N*-*tert*-butylacrylamide. The chemical composition in the final copolymers was found to be very close to the original monomer composition in the feed prior to polymerization. In an effort to elucidate the effect of the chemical composition on the phase separations of the aqueous solutions of the copolymers, the lower critical solution temperatures (LCST) of the copolymers in water were determined by differential scanning calorimetry and optical turbidimetry. In principal, the LCST of the copolymers can be adjusted within the freezing and boiling points of the solutions. The copolymers exhibit systematic changes in their LCSTs as a function of their comonomer composition, for which an empirical equation was established. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: *N*-substituted acrylamide copolymers; Lower critical solution temperature

1. Introduction

Certain polymers are soluble in a solvent at low temperatures but become insoluble as the temperature rises above the lower critical solution temperature (LCST). This kind of polymer has recently attracted a great deal of research interest because of its rheological and technological importance [1–6] and potential biomedical applications [7–9]. In particular, the thermosensitivity of poly(*N*-isopropylacrylamide) was extensively studied [10–21]. The aqueous solutions of this polymer can undergo a reversible phase change at ca. 32°C independent of the molar mass or the concentration of the polymer [12]. The thermosensitivity of the polymer makes it especially attractive for various biomedical and pharmaceutical applications. The phase separation behavior for the aqueous solutions of poly(*N*-isopropylacrylamide) and its mechanism were investigated by a variety of experimental techniques including UV turbidimetry [12,14–16,18,20,22], calorimetry [10,15,16,18,20,23], light scattering [13,17], NMR spectroscopy [19,23,24], viscometry [10,11,17] and fluorescence [16,25–29]. The phase transition phenomenon is associated with the temperature dependence of hydrogen bonding and hydrophobic interactions [30–32]. The modification of the LCST of the thermosensitive polymers is of primary interest. This can be achieved by copolymerization or by the addition of salts and surfactants in the aqueous solutions [16,18,22,30,33]. Although LCST was observed for aqueous solutions of many other mono- and di-*N*-substituted acrylamide polymers [22], these polymers have not yet drawn as much attention as poly(*N*-isopropylacrylamide). The structure of the polymers, particularly that of the alkyl group of acrylamide is important to determine the thermosensitivity and solution behavior of the polymers. A better understanding of the properties of *N*-substituted polyacrylamides should help in the development of new thermosensitive hydrogels and to improve the thermosensitivity of the gels.

In an effort to demonstrate how the LCST of the polymers can be varied by adjusting the comonomer composition, we have prepared several series of copolymers from *N*-substituted acrylamides with varying degree of hydrophilicity (or hydrophobicity). The corresponding homopolymers range from insoluble in water to completely soluble at all temperatures. The LCST of the homo- and copolymers was determined and related to the chemical composition of the polymers.

2. Experimental

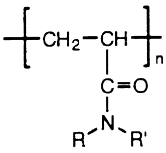
Acrylamide (AA), *N*-*tert*-butylacrylamide (TBA),

---

* Corresponding author. Tel.: 001 514 343 6733; fax: 001 514 343 7586.
E-mail address: zhuj@umontreal.ca (X.X. Zhu)

PII: S0032-3861(98)00858-1

Table 1
Chemical structures and solution properties of selected *N*-alkyl substituted polyacrylamides

	R	R′	Abbreviation	LCST (°C)
Poly(acrylamide)	H	H	PAA	Soluble
Poly(*N*,*N*-dimethylacrylamide)	Me	Me	PDMA	Soluble
Poly(*N*-ethylacrylamide)	H	Et	PEA	82
Poly(*N*-isopropylacrylamide)	H	*i*Pr	PIPA	32[a]
Poly(*N*,*N*-diethylacrylamide)	Et	Et	PDEA	32
Poly(*N*-*tert*-butylacrylamide)	H	*t*Bu	PTBA	Insoluble

[a] Result from Ref. [12].

N,*N*-dimethylacrylamide (DMA), acryloyl chloride, ethylamine, and diethylamine were purchased from Aldrich and were used without further purification. 2,2′-Azoisobutyronitrile (AIBN) from Eastman Kodak was recrystallized from methanol and stored in dark bottles in a refrigerator. All solvents were distilled before use.

2.1. Preparation of the monomers

N-ethylacrylamide (EA) and *N*,*N*-diethylacrylamide (DEA) were prepared from the corresponding alkylamines and acryloyl chloride, according to a similar procedure reported by Shea et al. [34]. EA was prepared by adding dropwise a 70 wt.% aqueous ethylamine solution (54.3 ml, 0.67 mol) into a solution of acryloyl chloride (28.8 g, 0.31 mol) in tetrahydrofuran (THF, 500 ml) at −5°C–0°C for 1.5 h. The solution was stirred at room temperature overnight. The aqueous phase was extracted three times with ether. The combined organic phase was dried over $MgSO_4$ and the organic solvents were removed. Distillation under reduced pressure gave a clear oil (22.5 g, 75%, b.p. 59°C–60°C/0.3 mmHg). Literature: b.p. 69°C/93 Pa [35]. ^{1}H NMR in $CDCl_3$ (δ in ppm): 7.28 (^{1}H, br, NH); 6.14 (2H, m, $=CH_2$); 5.47 (^{1}H, m, =CH–); 3.22 (2H, m, CH_2), 1.04 (3H, t, CH_3).

DEA was prepared from acryloyl chloride and diethylamine in dichloromethane. Acryloyl chloride (50 g, 0.54 mol) was slowly added in a dropwise manner into a solution of diethylamine (140 ml, 1.35 mol) in CH_2Cl_2 (400 ml) at 0°C for 3 h. The solution was then stirred at the same temperature for 4 h. The salts formed during the reaction were removed by filtration and washed thoroughly by CH_2Cl_2. The solvent was removed on a rotary evaporator. Distillation of the crude product under reduced pressure yielded a colorless oil (57.4 g, 85%, b.p. 45°C/0.3 mmHg). Literature: b.p. 64°C/250 Pa [35]. ^{1}H NMR in $CDCl_3$ (δ in ppm): 6.18–6.38 (2H, m, $=CH_2$); 5.49 (^{1}H, dd, =CH–); 3.23 (4H, m, CH_2), 1.00 (6H, t, CH_3).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX-300 operating at 300.0 MHz or a Bruker AMX-400 operating at 400.0 MHz for proton in deuterated chloroform or methanol. All chemical shifts are relative to tetramethylsilane (TMS) set at 0 ppm.

2.2. Preparation of the polymers

Poly(*N*,*N*-diethylacrylamide) (PDEA) and poly(*N*-ethylacrylamide) (PEA) homopolymers were prepared by free radical polymerization with 1 mol% AIBN in toluene and THF, respectively, at 60°C for 18–20 h. The solvent was evaporated and the polymer was dissolved in acetone, precipitated in hexane and dried in a vacuum oven. The conversion was between 85% and 95%.

Poly(DEA-co-EA) (20, 40, 60, 80 mol% of EA) and poly(TBA-co-EA) (20, 40, 50, 60, 70, 80 and 90 mol% of EA) were carried out in THF (3 g in 15 ml) with AIBN as the initiator (1 mol%). Dry nitrogen was bubbled through the solution for 15 min prior to polymerization. The temperature was raised gradually during 2 h to 68°C and maintained for ca. 18 h. The mixtures were precipitated in ether or hexane.

Poly(DEA-co-DMA) (10, 20, 30, 40, 50, 60 and 70 mol% of DMA), poly(DEA-co-AA) (20, 30, 40, 45, 50 and 55 mol% of AA) and poly(TBA-co-DMA) (40, 50, 60, 70 and 80 mol% of DMA) were prepared in methanol following a similar procedure as mentioned earlier.

The average molar masses of the polymers and copolymers were determined by size exclusion chromatography (SEC) with 2.5 g/l THF or dimethyl formamide (DMF) solutions on a Waters 410 system. Polystyrene standards were used for calibration and the molar masses of the copolymer was estimated as that of a polystyrene of equivalent elution volume.

2.3. LCST determination

Samples for thermal analysis were prepared by dissolution of different amounts of copolymers in distilled water in an ice water bath. The LCSTs of the polymer solutions were measured on a DSC 2910 differential scanning calorimeter (TA Instruments, New Castle, DE, USA) with a flow of helium at 40 cm^3/min. The samples (ca. 8–12 mg) of different concentrations from 5 to 20 wt.% were placed in sealed capsules in order to prevent water evaporation. The samples were scanned at 5°C/min from 0°C–90°C against an empty reference pan. The phase separation temperatures were determined as the maximum of an exothermic peak of the heating thermogram. The DSC curves were measured for five series of the polymers at 10 wt.% aqueous concentration unless otherwise stated. The glass transition temperatures (T_g) of the polymers were determined by DSC with dried polymer samples at a heating rate of 20°C/min.

For comparison with the DSC measurements, the LCST of selected polymer aqueous solutions was also determined

Table 2
Some physical characteristics of a typical copolymer series poly(DEA-co-DMA)

Copolymer (DEA : DMA)	Monomer conversion (%)	M_n	M_w	M_w/M_n[a]	T_g (°C)
90 : 10	92.9	4.84×10^4	6.34×10^4	1.31	94.4
80 : 20	92.1	5.95×10^4	7.35×10^4	1.23	101.6
70 : 30	97.3	4.42×10^4	6.90×10^4	1.56	101.5
60 : 40	90.3	6.73×10^4	8.02×10^4	1.19	107.8
50 : 50	97.5	5.68×10^4	6.69×10^4	1.17	104.1
40 : 60	97.5	5.41×10^4	7.56×10^4	1.18	103.6
30 : 70	93.3	4.92×10^4	6.03×10^4	1.22	114.5

[a] M_n number-average molar mass; M_w: weight-average molar mass.

by UV turbidimetry on a Varian Cary (1 Bio) UV–VIS Spectrophotometer. The cloud point was observed with the optical transmittance of a 500 nm light beam through a 1 cm sample cell referenced against distilled water at different temperatures. The heating rate was controlled at 0.1°C/min.

3. Results and discussion

3.1. Characterization of the copolymers

Table 1 shows a list of selected *N*-substituted poly(alkylacrylamide)s and their solution properties in water. The copolymers include five series: poly(DEA-co-AA), poly(DEA-co-DMA), poly(DEA-co-EA), poly(TBA-co-EA) and poly(TBA-co-DMA). They were prepared from the corresponding monomers by free radical polymerization in THF or methanol. The choice of the solvent was a matter of convenience, but we have found that the polymers prepared in methanol generally had higher molar mass than those prepared in THF. The conversion from monomers to homo- and copolymers were in the range of 85%–95%. Typical molar masses of the polymers are shown in Table 2 for the poly(DEA-co-DMA) series. In general, the polydispersity index M_w/M_n varied from 1.2 to 2.5. No attempts were made to fractionate these samples except simple precipitations.

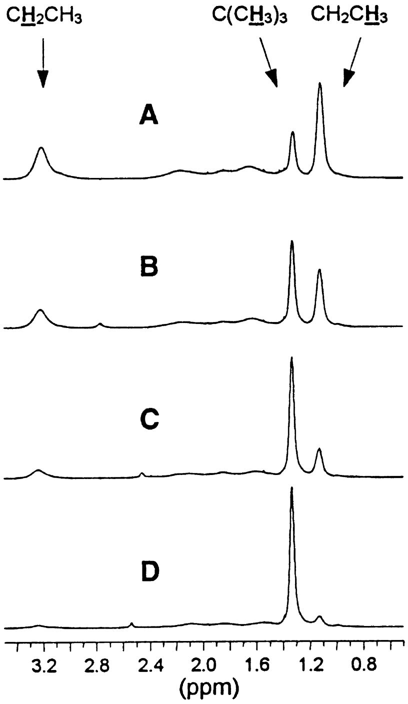


Fig. 1. Proton NMR spectra of poly(TBA-co-EA) in $CDCl_3$ at room temperature showing the NMR signals of interest. Molar ratio of the comonomers (TBA : EA) : (A) 1 : 9; (B) 3 : 7; (C) 5 : 5; (D) 8 : 2.

The ^1H NMR spectra of selected poly(TBA-co-EA) samples are shown in Fig. 1. The NMR signals corresponding to each comonomer are well-resolved. The NMR signal at 1.32 ppm corresponds to the protons of the *tert*-butyl group of *N*-*tert*-butylacrylamide and the signals at 1.12 and 3.22 ppm to the ethyl group of *N*-ethylacrylamide. Clearly, the peak intensities at 1.12 and 3.22 ppm increased steadily as the content of the comonomer EA increased in the copolymer. Moreover, the disappearance of the olefinic proton peaks between 5.5 and 6.3 ppm indicates the successful polymerization of the monomers. The integrations of the characteristic peaks are used to calculate their chemical compositions (Table 3). The copolymer compositions are very close to the original monomer compositions in the feed prior to polymerization. The copolymers are expected to be statistically random, also evidenced by the single T_g as determined by DSC (Table 2). The chemical compositions of the copolymers in the other series were determined similarly and, as expected, they are also close to the original monomer composition in the feed.

3.2. LCST of the polymers

The LCSTs of aqueous solutions of PDEA and PEA (5–20 wt.%) were determined to be 32°C and 82°C, respectively, which are different from the values of 25°C and 74°C reported by Taylor and Cerankowski [22]. The difference may arise from the difference in the polymer samples used (molecular weight, concentration, etc.) and/or the conditions used in the measurements of LCST, particularly the heating or cooling rates [20]. A typical turbidimetry experiment and a DSC thermogram are shown in Fig. 2

Table 3
Chemical composition of poly(TBA-co-EA) determined by ^{1}H NMR measurements in $CDCl_3$ on a Bruker AMX-400

Monomer ratio (TBA : EA) in the feed	Monomer ratio (TBA : EA) in the final polymer	Monomer conversion (%)
80 : 20	79.9 : 20.1	87.2
60 : 40	57.9 : 42.1	86.2
50 : 50	48.2 : 51.8	90.4
40 : 60	39.5 : 60.5	89.1
30 : 70	30.1 : 69.9	96.7
20 : 80	20.2 : 79.8	96.6
10 : 90	10.3 : 89.7	98.4

for aqueous PDEA solutions. The phase transition of the polymer is an endothermic process (ca. 23 J/g polymer), corresponding to the disruption of the hydrogen bonds in the solution. As indicated in Fig. 2, the heating rate of 5°C/min in DSC and a heating rate of 0.1°C/min in the UV–VIS measurement gave identical values of LCST (32.2°C) as the heat transfer in the DSC experiment was much more efficient than that in the spectrophotometric technique. We have found that measured LCST of the polymers was quite dependent on the heating rates (especially in the turbidimetry measurements), but much less dependent on the concentration or the molar mass of the polymers. In Fig. 3, the measured LCSTs are plotted as a function of the concentration of poly(DEA-co-EA) (molar ratio 6 : 4) in water. No significant concentration effect on the LCST was detected for this polymer over the concentration range studied (1–20 wt.%). Only a small increase (from 32°C to 33°C) is observed.

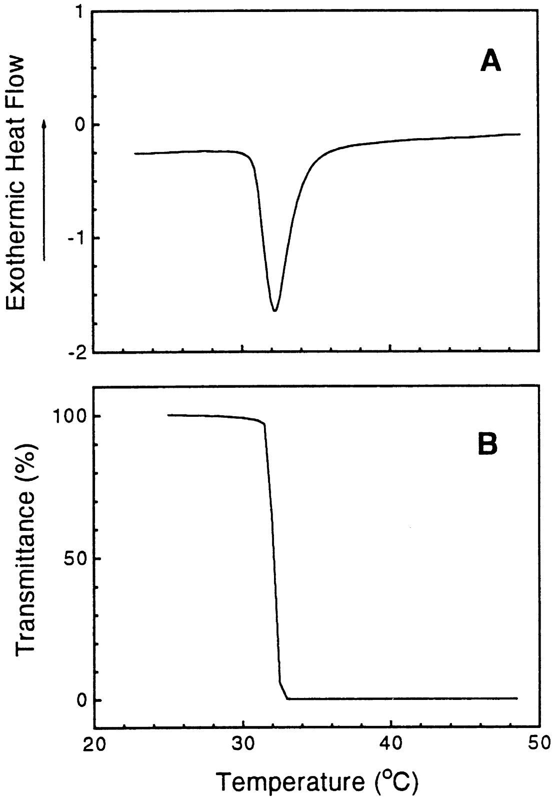


Fig. 2. LCST determination of PDEA by DSC (A) and UV–VIS light transmittance (B) gives the same results (LCST = 32.2°C). (A) 20 wt.% PDEA in water, heating at 5°C/min; (B) 4 wt.% PDEA in water, heating at 0.1°C/min, observation at 500 nm.

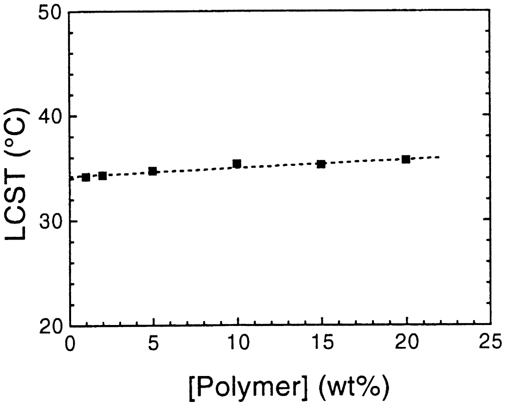


Fig. 3. LCST of poly(DEA-co-EA) (molar ratio 6 : 4) aqueous solutions plotted as a function of the polymer concentration as determined by DSC at a heating rate of 5°C/min.

Fig. 4A shows the LCSTs of poly(DEA-co-EA) and poly(TBA-co-EA) aqueous solutions as a function of the molar fraction of EA in the copolymers. The hydrophilicity of poly(DEA-co-EA) increases with increasing EA content in the copolymers. As expected, the LCSTs of poly(DEA-co-EA) show an increase with increasing EA content. The LCST of the copolymers always lies in between the LCSTs of the two homopolymers. The data can be fitted to the following equation:

$$T = \frac{\mu_1 T_1 + K\mu_2 T_2}{\mu_1 + K\mu_2}, \qquad (1)$$

where μ is the molar fraction of a given monomer (note that $\mu_1 + \mu_2 = 1$), T is the LCST of the corresponding homopolymers and the subscripts 1 and 2 denote comonomers 1 and 2, respectively, and K is a weighting parameter which can be deduced from curve fitting of the experimental results. In the ideal case, K has a value of 1 and the relationship between comonomers 1 and 2 becomes linear. All the curves in our experiments have shown a concave shape with K values less than 1 ranging from 0.51 for poly(TBA-co-EA) (Fig. 4A) to 0.13 for poly(TBA-co-DMA) (Fig. 4C).

The copolymerization with a more hydrophobic monomer will cause a decrease in the LCST of the polymer. For example, when EA is copolymerized with TBA, a more hydrophobic comonomer, the LCST of the copolymer can be lowered significantly with the increasing molar ratio of TBA (Fig. 4A). An extrapolation of the experimental results of LCSTs of the copolymers can lead to a hypothetical LCST value of homopolymer PTBA of ca. −5°C. However, copolymerization with more hydrophilic monomers can increase the LCST of the corresponding homopolymer, as

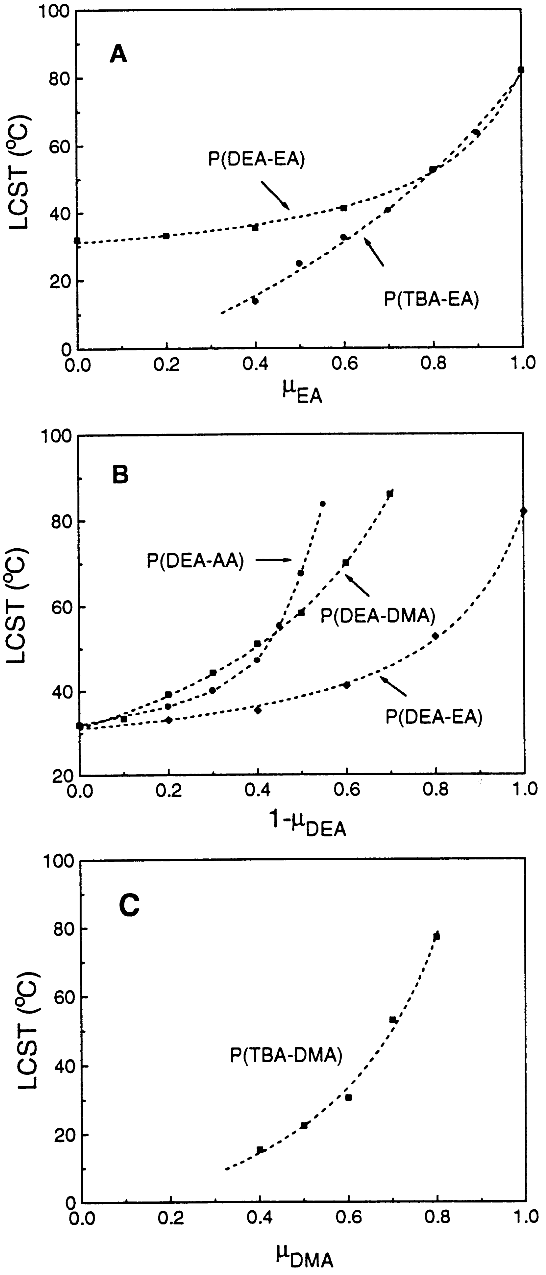


Fig. 4. LCST of the different series of copolymers in water plotted as a function of their chemical compositions (molar fractions). Dashed lines represent fittings to Eq. (1). (A) Copolymer series poly(X-co-EA), where X = DEA or TBA; (B) Copolymer series poly(DEA-co-X), where X = AA, DMA or EA; (C) poly(TBA-co-DMA).

shown in Fig. 4B, where the LCSTs of three series of copolymers, poly(DEA-co-AA), poly(DEA-co-DMA) and poly(DEA-co-EA), are plotted as a function of the molar fraction of EA, AA and DMA, respectively. It is clear that the LCSTs of poly(DEA-co-AA) and poly(DEA-co-DMA) are systematically higher than those of poly(DEA-co-EA). The increase in LCST is especially drastic for poly(DEA-co-AA) with increased amount of AA in the copolymer. A hypothetical LCST for the homopolymer PDMA can be obtained by extrapolation (>200°C) by the use of Eq. (1). However no such hypothetical LCST can be obtained for PAA. Based on the substitution groups of the acrylamide, the hydrophilicity of the monomers is expected to follow the order: AA > DMA > EA > DEA > TBA. The real and hypothetical LCST values of the homopolymers confirm the order of hydrophilicity of the *N*-substituted acrylamide monomers and hence their homopolymers.

The change in hydrophilicity or hydrophobicity by modifying the comonomer composition is the key in the changes of LCST of the polymers. At low temperatures, the strong hydrogen bonding between the hydrophilic groups of the polymer (amide groups) and water helps in the dissolution of the polymer in water. With increasing temperature, hydrogen bonding weakens, while hydrophobic interactions among the side groups strengthen [20]. Interactions between hydrophobic groups become dominant at temperatures above the LCST, leading to an entropy-driven collapse of the polymer chains and hence phase separation. The process is evidenced by the endothermic phase separation shown in the DSC experiments (Fig. 2A). The correlation of LCST and the hydrophobicity of the polymer is obvious.

We know that, within the freezing and boiling points of the aqueous solutions, PDMA is soluble in water and PTBA is practically insoluble in water. As one may expect from our results in Figs. 4A and B, we can predict that it is possible to obtain copolymers from these two monomers with LCST in water. The results for poly(TBA-co-DMA) in Fig. 4C, just as predicted, show the changes of LCST as a function of the comonomer composition, which can be fitted to Eq. (1). This means that we can obtain copolymers with LCSTs in water simply by balancing the hydrophilicity–hydrophobicity of the final polymer.

4. Conclusion

The LCST of the mono- and di-*N*-substituted acrylamide polymers can be modified easily by copolymerization with other monomers. By copolymerization with a more hydrophilic monomer, even hydrophobic polymers can be made to possess an LCST. Similarly, water-soluble polymers can be made to possess an LCST by copolymerization with a hydrophobic monomer. An increase in the overall hydrophobicity of the copolymer lowers the LCST, leading in some cases to a polymer insoluble in water. Likewise, an increase in the hydrophilicity of the copolymers can raise the LCST and may result in a hydrophilic polymer freely soluble at all temperatures. Given a chemical composition, the LCST of the copolymer can be estimated by the use of Eq. (1). Similarly, copolymers with more than two comonomers can also be made for the purpose of altering the LCST. Only acrylamide-based copolymers are studied here, but the general rule may be applicable also for other copolymers. Moreover, these and other *N*-substituted acrylamide copolymers may serve as interesting alternatives for the well-known poly(*N*-isopropylacrylamide).

Acknowledgements

Financial support from the Natural Sciences and Engineering Research Council (NSERC) of Canada and from Fonds FCAR of the Province of Quebec is gratefully acknowledged. The authors wish to thank Mr. L. Masaro, Ms. A. Benrebouh and Mr. D. Avoce for their assistance in the characterization of the polymers.

References

[1] Schild HG. Prog Polym Sci 1992;17:163.
[2] Kokufuta E. Adv Polym Sci 1993;110:157.
[3] Okano T. Adv Polym Sci 1993;110:179.
[4] Gehrke SH. Adv Polym Sci 1993;110:81.
[5] Saito S, Konno M, Inomata H. Adv Polym Sci 1993;11:207.
[6] Lowe JS, Chowdhry BZ, Parsonage JR, Snowden MJ. Polymer 1998;39:1207.
[7] Bae YH, Okano T, Hsu R, Kim SW. Makromol Chem, Rapid Commun 1987;8:481.
[8] Chen G, Hoffman AS. Bioconjugate Chem 1993;4:509.
[9] Chen G, Hoffman AS. Macromol Rapid Commun 1995;16:175.
[10] Heskins M, Guillet JE. Bioconjugate Chem 1968;A2:1441.
[11] Fujishige S. Polymer J 1987;19:297.
[12] Fujishige S, Kubota K, Ando I. J Phys Chem 1989;93:3311.
[13] Kubota K, Fujishige S, Ando I. J Phys Chem 1990;94:5154.
[14] Irie M. Adv Polym Sci 1993;110:49.
[15] Schild HG, Tirrell DA. J Phys Chem 1990;94:4352.
[16] Schild HG, Tirrell DA. Langmuir 1991;7:665.
[17] Kubota K, Fujishige S, Ando I. Polymer J 1990;22:15.
[18] Cho CS, Jung JH, Sung YK, Lee YM. Macromol Rapid Commun 1994;15:727.
[19] Zeng F, Tong Z, Feng H. Polymer 1997;38:5539.
[20] Boutris C, Chatzi EG, Kiparissides C. Polymer 1997;38:2567.
[21] Huglin MB, Liu Y, Velada JL. Polymer 1997;38:5785.
[22] Taylor LD, Cerankowski LD. J Polym Sci, Polym Chem Ed 1975;13:2551.
[23] Ohta H, Ando I, Fujishige S, Kubota K. J Polym Sci, Polym Phys Ed 1991;29:963.
[24] Tokuhiro T, Amiya T, Mamada A, Tanaka T. Macromolecules 1991;24:2936.
[25] Winnik FM. Macromolecules 1990;23:233.
[26] Winnk FM, Ringsdorf H, Venzmer J. Langmuir 1991;7:905.
[27] Winnk FM, Ringsdorf H, Venzmer J. Langmuir 1991;7:912.
[28] Schild HG, Tirrell DA. Langmuir 1990;6:1676.
[29] Schild HG, Tirrell DA. Langmuir 1991;7:1319.
[30] Feil H, Bae YH, Feijen J, Kim SW. Macromolecules 1993;26:2496.
[31] Inomata H, Goto S, Saito S. Macromolecules 1990;23:4887.
[32] Volpert E, Selb J, Candau F. Polymer 1998;39:1025.
[33] McPhee W, Tam KC, Pelton R. J Colloid Interface Sci 1993;156:24.
[34] Shea KJ, Stoddard GJ, Shavelle DM, Wakui F, Choate RM. Macromolecules 1990;23:4497.
[35] Benešová O, Plaisner V, Ulbrich K, Šprincl L. Polym in Medicine 1979;9:63.