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M. Heskins[a]; J. E. Guillet[a]
[a] Department of Chemistry, University of Toronto, Toronto Ontario

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Solution Properties of Poly(N-isopropylacrylamide)

M. HESKINS and J. E. GUILLET

Department of Chemistry
University of Toronto
Toronto, Ontario

SUMMARY

Aqueous solutions of poly(N-isopropyl acrylamide) show a lower critical solution temperature. The thermodynamic properties of the system have been evaluated from the phase diagram and the heat absorbed during phase separation and the phenomenon is ascribed to be primarily due to an entropy effect. From viscosity, sedimentation, and light-scattering studies of solutions close to conditions of phase separation, it appears that aggregation due to formation of nonpolar and intermolecular hydrogen bonds is important. In addition, a weakening of the ordering effect of the water-amide hydrogen bonds as the temperature is raised contributes to the stability of the two-phase system.

INTRODUCTION

Poly(N-isopropylacrylamide) [poly(NIPAM)], when prepared using free-radical initiators, is only soluble in solvents which are capable of forming reasonably strong hydrogen bonds. In aqueous solution, it shows a lower critical solution temperature (LCST) at about 31°C. The latter phenomenon has been observed before in aqueous solutions of polar polymers [1-3] and has been attributed to a negative entropy term affecting the free energy of solution in spite of the unfavorable enthalpy. Such systems are unlikely to fit the simple theories applicable to nonpolar [4, 5] or polar [6] polymer/solvent systems. However, using an empirical expression in the form of the Flory-Huggins equation, an attempt has been made to evaluate the thermodynamic properties near the point of phase separation from the phase diagram and the heat of phase separation on the basis of this entropy effect. It was hoped to obtain some insight into the controlling factors of the phase separation by observing the shape of the polymer chain as the solution approached the LCST by determinations of the frictional properties and by light-scattering measurements.

EXPERIMENTAL

Polymerization

N-isopropylacrylamide (American Cyanamid Co.) was recrystallized from a benzene-hexane mixture. It was polymerized in aqueous solution using a redox catalyst consisting of ammonium persulfate and sodium bisulfite by a method similar to that of Wooten et al.[7]. The polymer used for most of this work was an unfractionated sample with a limiting viscosity number $[\eta] = 2.6$ dl/g in chloroform at 25 deg. C.

Phase Diagram

Two methods were used:

1. Visual observation of the temperature at which the first turbidity appeared in a solution immersed in a water bath as the temperature of the bath was raised at 3°C/hr.
2. Analysis of the two phases: an I.C.C. centrifuge was placed in an oven controlled at the desired temperature. A solution was weighed into a centrifuge, stoppered, and centrifuged for up to 6 hr to separate the phases, which were then analyzed by freeze drying at −5°C. This method was not satisfactory when the two phases had very similar densities, and the phase diagram shown in Fig. 1 is a composite of the results by the two methods.

Heat of Phase Separation

A Perkin-Elmer DSC1B differential scanning calorimeter was used. The method employed was to prepare a weighed aluminum pan fitted with a spacer, add the polymer solution, crimp a second weighed pan on top, and reweigh. The sample was then scanned at 10°C/min over the temperature range of the phase separation at 2 mcal/sec sensitivity against a reference pan containing water. Only one run was carried out with each solution since complete resolution could not be ensured. A typical trace is shown in Fig. 2. The area under the peak between the start of peak and 40°C is a measure of the heat absorbed on phase separation. The response

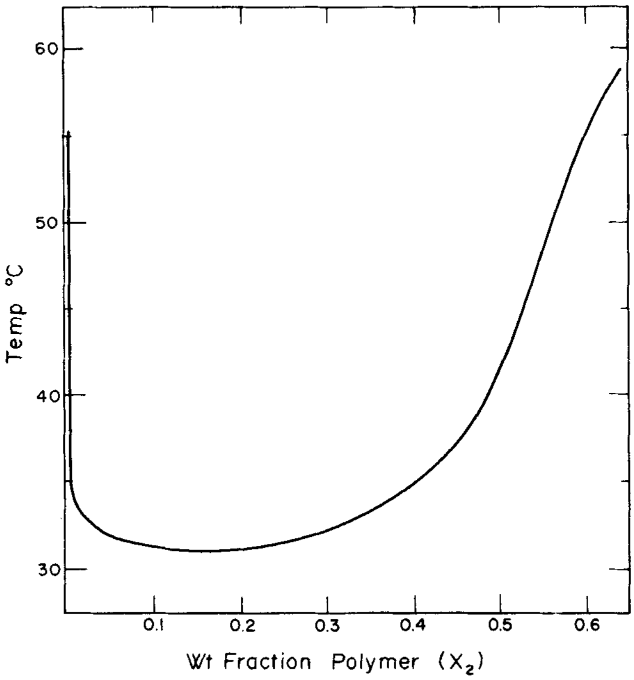

Fig. 1. Phase diagram for poly(N-isopropylacrylamide)/water.

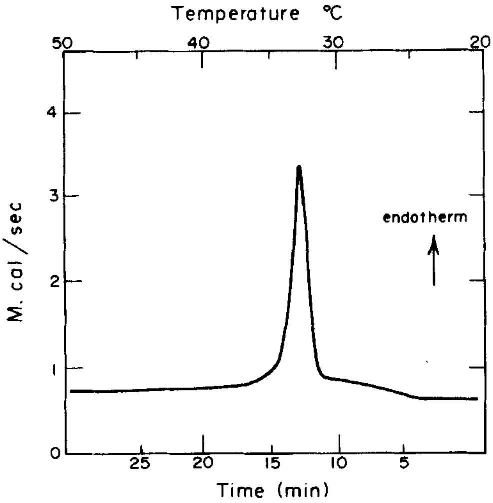

Fig. 2. Calorimeter scan of heat of phase separation of 7.0% w/w solution of poly(NIPAM) in water; weight of sample = 16.6 mg.

Table 1. Heat of Phase Separation

% of polymer by weight	ΔH, cal/g of solution	ΔH, kcal/base mole of polymer
4.6	1.5	3.7
5.0	1.9	4.0
6.8	2.2	3.65
9.8	3.2	3.65
10.6	3.2	3.4
19.8	4.15	2.4
24.1	3.5	1.65

was calibrated with the heat of fusion of a known weight of indium. The results are given in Table 1. Five determinations were carried out at each concentration, the mean error being ±5%.

Specific Volume

This was determined from density measurements with a pyknometer at three temperatures: 15, 25, and 33°C. The apparent specific volume was calculated from the equation

$$\phi_1 = \frac{1}{d_0}\left[\frac{100(d_1 - d_0)}{w_1 d_1} + 1\right]$$

where d_0 = density of solvent

d_1 = density of solution

w_1 = weight of polymer/100 g of water

Then $\overline{V}_1$, the specific volume, was obtained from

$$\overline{V}_1 = \phi_1 + \left(\frac{\partial \phi_1}{\partial w_1}\right) w_1$$

graphically (Table 2). Measurements of the heat of mixing were kindly performed for us by Dr. H. P. Schreiber of Canadian Industries Ltd., McMasterville, Quebec, and are given in Table 3.

Table 2. Partial Specific Volume of Poly-(NIPAM)

Temp., °C	$\overline{V}_1$, cm^3/g
15.0	0.887 ± 0.002
25.0	0.896 ± 0.002
33.0	0.902 ± 0.002

Table 3. Heat of Solution of 0.03% Polymer Solution

Temp., °C	ΔH^M, cal/g of solution
20	+0.051 ± 0.002
25	+0.048 ± 0.002
30	+0.039 ± 0.002

MOLECULAR SHAPE EXPERIMENTS

Light Scattering

The experiments were performed with a Brice-Phoenix instrument, solutions being clarified through a 1.0-μ Millipore filter. Scattering was measured at 5460 Å. The instrument constant was determined by assuming that R_{90} for toluene at 25°C is 1.96×10^{-6}[8]. The value of the incremental refractive index dn/dc for the polymer solutions at 5460 Å was determined using a Brice-Phoenix differential refractometer. At 33°C dn/dc = 0.171 for aqueous solutions. The scattering of aqueous solutions of the polymer was determined for six angles between 30 and 120° and at six concentrations at 33°C. A "Zimm" plot was obtained by plotting Kc/R_θ against $\sin^2 \theta/2 + 200c$. This is shown in Fig. 3.

The scattering of the polymer in ethanol-free chloroform at 90° was measured at 25°C. dn/dc was 0.043 and the assymmetry was small. A plot of Kc/R_{90} against c is shown in Fig. 4.

Viscosity

The intrinsic viscosity or limiting viscosity number $[\eta]$ of the polymer in distilled water was measured at three temperatures

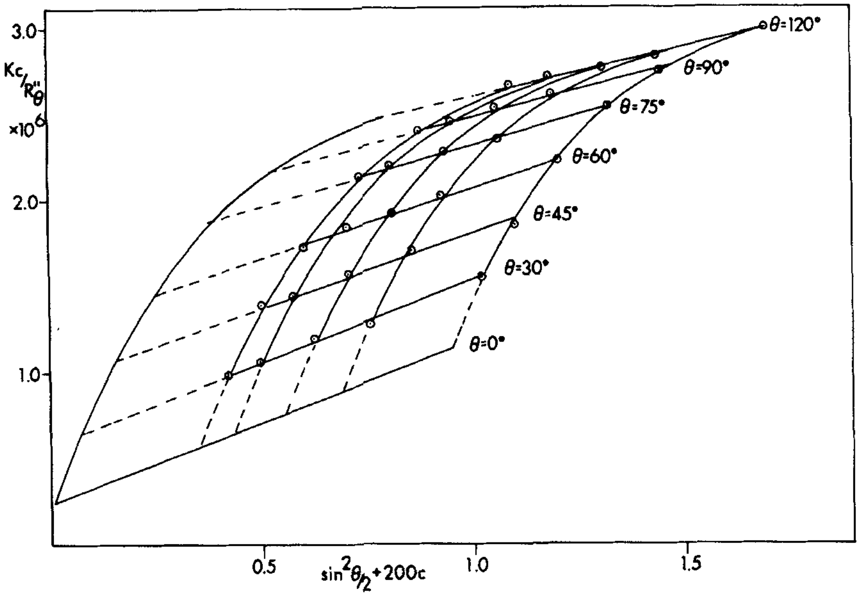

Fig. 3. "Zimm plot" for poly(NIPAM) in water at 33°C.

with a modified Desreux viscometer. Extrapolations to a common intercept at zero concentration from plots of η_{sp}/c and $\ln \eta_r/c$ against c were used to determine $[\eta]$. The results are shown in Table 4.

Table 4. Intrinsic Viscosity of Polymer in Water

Temp., °C	dl/g
15	2.74
25	1.70
33	1.44

Ultracentrifugation

The sedimentation of dilute aqueous solutions was studied with a Spinco Model E ultracentrifuge at six temperatures between 12 and 33°C at 60,000 rpm. The sedimentation was followed by photography of the Schlieren pattern. The sedimentation coefficient was calculated from the slope of the plot of ln r against time, where r

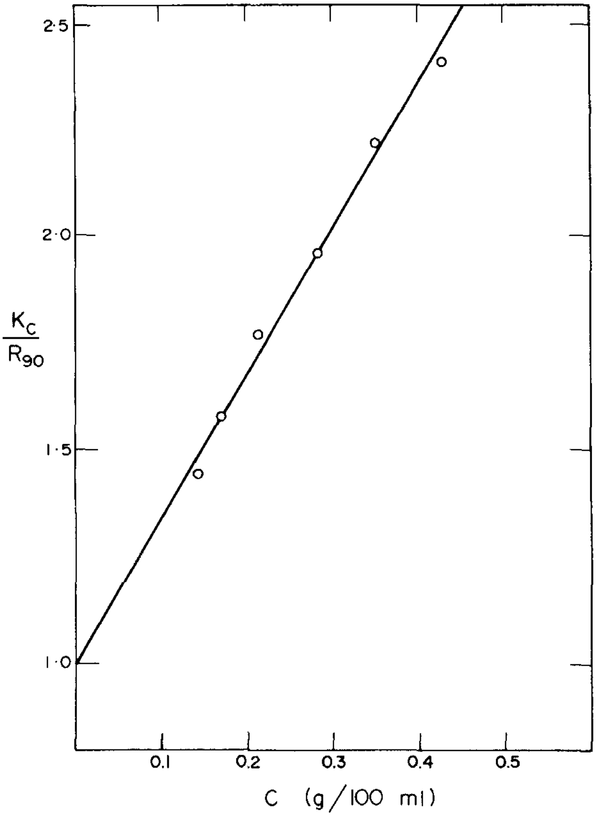

Fig. 4. Light scattering for poly(NIPAM) in chloroform at 25°C.

is the position of the sedimenting peak from the center of rotation. Only two concentrations were used and extrapolations to zero concentration were made using the equation $1/S = 1/S_0(1 + k[\eta]c)$, where k was found to be 0.99 for all temperatures.

No corrections for diffusion or pressure were made. The variation of sedimentation coefficient with temperature is shown in Table 5.

Table 5. Sedimentation Coefficient for Polymer in Water at Various Temperatures

Temp., °C	20	25	27.5	30	32	33
$S_0 \times 10^{13}$ sec^{-1}	2.48	3.04	3.55	4.17	4.76	5.08

Osmometry

The number-average molecular weight was determined in ethanol-free chloroform using a Mechrolab Model 502 membrane osmometer. Regression analysis of the plot of π/c versus c gives a value of $\overline{M}_n$ of 290, 000.

DISCUSSION

The thermodynamic results have been analyzed on the basis of the modified Flory-Huggins equation:

$$\mu_1 = RT[\ln(1-\phi_2) + \left(1+\frac{1}{m}\right)\phi_2 + X_1\phi_2^2 + \nu\phi_2^3] \tag{1}$$

where ϕ_1 = volume fraction of water

ϕ_2 = volume fraction of polymer

m = number of segments in the chain

The first two terms represent the Flory combinational terms, and X_1 is an empirical term which is chosen to be of the form $-\alpha/T + \beta T$, where α represents the enthalpy contribution and β the entropy contribution. ν gives the dependence of X_1 on ϕ_2, $dX_1/d\phi_2$, and is also an adjustable parameter. All the temperature dependence is assumed to be included in the β term in spite of the fact that α may also change with temperature.

The thermodynamic conditions for the occurrence of a critical point are

$$d\mu_1/dn_1 = 0 \qquad \text{and} \qquad d^2\mu_1/dn_1^2 = 0 \tag{2}$$

Applying these to Eq. (1) we obtain

$$\frac{1}{(\phi_2)_c} - \left(1+\frac{1}{m}\right) - 2X_1(\phi_2)_c - \nu(\phi_2)_c^2 = 0 \tag{3}$$

and

$$-\frac{1}{(\phi_2)_c} + 2X_1 + 4(\phi_2)_c = 0 \tag{4}$$

Application of these equations to the system, where $(\phi_2)_c = 0.16$ at $T_c = 31.0$°C, give

$$X_1 = 0.575 \qquad \text{and} \qquad \nu = dX_1/d\phi_2 = 0.25$$

The chemical potential of the two coexisting phases must be equal, i.e., $\mu_1' = \mu_1''$, where the primes represent two phases. This can be applied at temperatures above T_c, and this was done at two temperatures, T = 37°C and T = 40°C, to obtain two further values of X_1 (ν assumed unchanged).

In order to separate X_1 into its entropy and enthalpy terms, the heat of phase separation can be used. To do this, it is convenient to express the thermodynamic quantities in terms of a new concentration variable corresponding to the composition of the concentrated phase and pure water. From Fig. 1 the composition of the concentrated phase at 40°C corresponds to a weight fraction of water of 0.52. Defining new concentration variables ϕ_3 and ϕ_4, the volume fraction of water and concentrated phase, respectively, ϕ_4 will be given by

$$\phi_4 \equiv 2.2mn_2/(n_1 + mn_2) = 2.2\phi_2$$

and n_3, the number of moles of water $\equiv n_1 + 1.2mn_2$. The heat of phase separation should be equal in magnitude to the heat of solution of the two phases (initially at 40°C) but opposite in sign. As a first approximation in this case we assume a regular solution and can therefore write the heat of solution as

$$\Delta H = RTn_3\phi_4X_3 \tag{5}$$

where X_3 is now the empirical enthalpy term expressed in the new concentration variables. From this

$$\Delta H = 2.2RT(n_1 + mn_2)\phi_2X_3 \tag{6}$$

and

$$h_1 = \partial\, \Delta H/\partial n_1 = 2.2(\phi_2^2 + 1.2\phi_2^2\, mn)X_3 \tag{7}$$

The value of h_1 was obtained by determination of the intercept of the tangent to the plot of H, the measured heat of phase separation against ϕ_2, and from this the value of X_3 may be determined at any temperature between 31 and 40°C. X_1 is written in the form

$$X_1 = (\alpha/T) + \beta T \tag{8}$$

and from the values of X_3 and X_1 at 37 and 40°C one may estimate the value of $\alpha = 470$ cal and $\beta = 8.8 \times 10^{-3}$ cal/deg^2 at 40°C. This permits the calculation of X_1 for a single phase solution at any other temperature by substitution in Eq. (8). The thermodynamic functions can then be calculated from the integrated form of the modified Flory-Huggins equation for the free energy of mixing:

$$\Delta G = RT[n_1 \ln \phi_1 + n_2 \ln \phi_2 + n_1\phi_2 X_1] \tag{9}$$
$$= RT\{n_1 \ln \phi_1 + n_2 \ln \phi_2 + n_1\phi_2[(\alpha/T) + \beta T]\}$$

$$\Delta H = Rn_1\phi_2\alpha \tag{10}$$

$$\Delta S = -R[n_1 \ln \phi_1 + n_2 \ln \phi_2 + n_1\phi_2\beta T] \tag{11}$$

Plots of these ΔG, ΔH, and T ΔS for the single solution (dashed lines) and the two-phase system (solid lines) at 40°C are shown in Fig. 5.

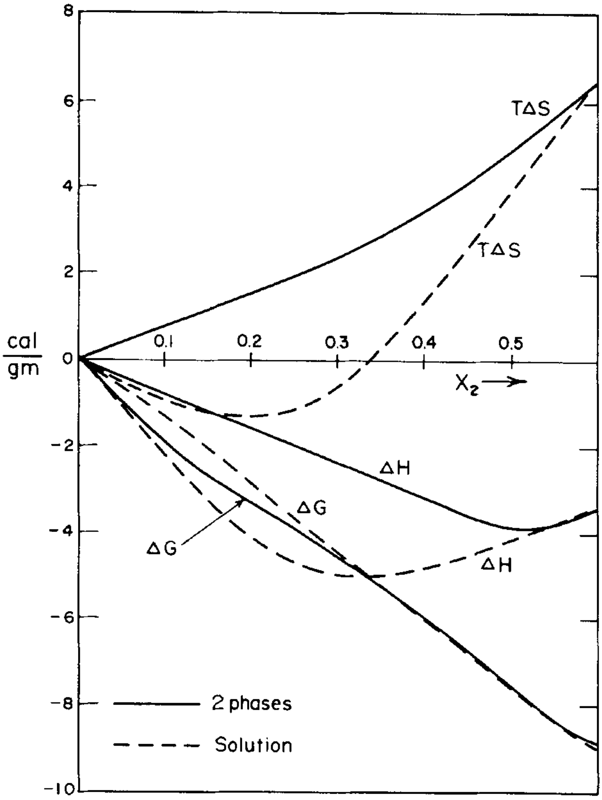

Fig. 5. Thermodynamic functions ΔG, ΔH, and T ΔS of poly(NIPAM) in water at 40°C for the single solution phase (dashed line) and the two-phase system (solid line).

It can be seen that the free-energy term is favorable (more negative) for the two-phase system up to a mole fraction of polymer of about 0.35, after which the value becomes indistinguishable from that of the single-phase system. Inspection of the enthalpy and T ΔS terms indicate clearly that although the enthalpy term is less favorable, the major factor is the entropy term and it is this which makes the two phases thermodynamically favored. Similar calculations at 37°C show comparable results and we may assume that this will be true for all temperatures above 31°C. It appears then that the reason for the lower critical solution temperature in this case is the large positive entropy difference between the system involving two phases as compared with a single homogeneous solution. Possible explanations for this behavior will be discussed after consideration of studies of the molecular shape.

DETERMINATION OF MOLECULAR SHAPE

From osmometry and light scattering in chloroform the number and weight averages of the molecular weight of the polymer sample used in these studies were found to be

$$\overline{M}_n = 290{,}000$$

$$\overline{M}_w = 1{,}000{,}000$$

The polydispersity ratio $\overline{M}_w/\overline{M}_n$ is 3.5, which indicates a fairly broad distribution.

It is possible to analyze the results from sedimentation and viscosity to determine whether a flexible-coil model or a rod-like model is best capable of representing the polymer at the point of phase separation.

From the equivalent sphere model the radius of gyration of a random coil is given by [9]

$$(R_G)^{3/2} = [\eta]M/6^{2/3}\,\phi \qquad (12)$$

where $\phi = 3.6 \times 10^{21}$ and $[\eta]$ is the intrinsic viscosity. The radius of gyration may also be calculated from ultracentrifuge data from the relation [9]

$$R_G = M(1 - \overline{V}_2\rho)/NPs_0\eta_0 \qquad (13)$$

where s_0 = sedimentation constant extrapolated to infinite dilution

η_0 = viscosity of the solvent

ρ = density of the solution

P = constant having a value of 8.5 in many cases

Estimates of R_G may also be made using the prolate ellipsoid model. In principle this requires a knowledge of the degree of solvation, but if this is small (as indicated by NMR studies), the hydrodynamic volume will be given by

$$V_h = (M\,\overline{V}_2/N) = 4\pi ab^2/3 \tag{14}$$

The hydrodynamic volume is related to the intrinsic viscosity $[\eta]$ by the equation $[\eta] = \nu V_h$, and from the value of ν the axial ratio a/b may be determined by the method of Simha [10]. From the axial ratio and Eq. (14), the value of a, the long axis of the prolate ellipsoid, is determined, from which R_G is determined from the relation

$$R_G = \sqrt{a^2/12} \tag{15}$$

The axial ratio may also be determined from centrifuge data using Perrin's equations [11], which relate a/b to the diffusion coefficient ratio D_0^{max}/D_0, where

$$D_0 = \frac{s_0RT}{M(1-\overline{V}_2\rho)} \quad \text{and} \quad D_0^{max} = \frac{kT}{6\pi\eta_0(3M\overline{V}_2/4\pi N)^3} \tag{16}$$

From these equations, R_G for the two models have been calculated using

$M = 1.0 \times 10^6$

$[\eta] = 1.44$ dl/g

$s_0 = 5.08 \times 10^{-13}$ sec

T = 33°C

These are given in Table 6. It can be seen that the agreement between the results for the flexible coil model is much better than those of the rod-like model.

Table 6. Radius of Gyration Calculated from Sedimentation and Viscosity at 33°C

Model	Viscosity, Å	Axial ratio	Sedimentation, Å	Axial ratio
Flexible coil	390	1	400	1
Prolate ellipsoid	585	46	700	65

The temperature dependence of the viscosity-average molecular weight was determined from the intrinsic viscosity and sedimentation coefficient at various temperatures using the Flory-Mandelkern equation [9]. These are given in Table 7. These results suggest that the polymer is associating as the temperature approaches the LCST.

Table 7. Effect of Temperature on Viscosity-Average Molecular Weight

Temp., °C	$\overline{M}_V \times 10^{-6}$
20	0.69
25	0.67
27.5	0.83
30	0.93
32	1.05
33	1.14

This association results in a much larger increase in $\overline{M}_W$, as measured by light scattering. In water at 33°C, the value of $\overline{M}_W$ was 4.5×10^6. From the slope of Kc/R_θ at zero concentration, the Z-average radius of gyration can be calculated. This was found to be 3000 Å. If it is assumed that the segment distribution in the aggregates is the same as in a coil of molecular weight 4.5×10^6, an estimate of the extension of that coil can be obtained from the Kuhn statistical segment length A_M [12] defined by

$$\langle \overline{h^2} \rangle^{1/2} = (P \cdot l \cdot A_M)^{1/2} \tag{17}$$

where P is the degree of polymerization, l is the length of a monomer unit, and $\langle \overline{h^2} \rangle^{1/2}$ is root-mean-square end-to-end distance, which for random coils equals $\sqrt{6}\,\langle r^2 \rangle^{1/2}$.

This gives $A_M = 550$ Å, which is very high compared with poly(vinyl alcohol) in water (16 Å) [12]. This is due in part to the use of the Z-average radius of gyration, correction for which will reduce A_M by at least a factor of 2. However, such a consideration is unlikely to reduce A_M to values typical of other vinyl polymers. Values of A_M of 200-300 Å have been observed for cellulose derivative [13] and alginic acid [14] in water, in which these polymers are known to be extended in solution. It may be concluded from this that although the molecule appears to be a random coil, it is highly extended in solution, which leads to the large statistical segment length A_M.

CONCLUSION

We have suggested that the phase separation of poly(NIPAM) can be attributed to an entropy effect, and it is of interest to examine the experimental results to see whether they give an insight into the reasons for this. One factor is the formation of hydrophobic bonds, which have been postulated in protein-water systems [15]. These bonds are due to the affinity of nonpolar groups for one another because of their incompatibility with water. The tendency for the formation of such bonds is also enhanced by the destabilization of ice-like structure in water when nonpolar solutes aggregate. Association of polymer molecules with increasing temperature has been taken as evidence of hydrophobic bond formation in similar systems [16], and our results are also consistent with this explanation.

It seems likely, therefore, that phase separation takes place by association of the polymer molecules into larger aggregates formed by intermolecular hydrogen bonding and nonpolar bonds. The endothermic heat of phase separation is probably due to the breaking of the hydrogen bonds with water. This implies that not many new water-water bonds are formed when the polymer precipitates.

Alternatively, it is also possible to ascribe this phenomenon to the fact that the polymer is more ordered in dilute solution than in the concentrated phase and that this ordering is due to the relatively strong hydrogen bonds formed between water and the polymer. As the temperature is raised, these hydrogen bonds become weaker and the solution becomes unstable. This mechanism would require that the polymer should have an open structure in solution. The evidence for this is not unequivocal but the low asymmetry in chloroform compared to that in water indicates that water has extended the coil considerably.

It seems, therefore, that the conditions for phase separation by both these mechanisms is fulfilled, and it is possible that both have an influence on the observation of an LCST in this system.

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